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Synthesis of 8-*Epi*-9-*epi*-isolactarorufin, the First *trans* Fused Rings Isolactarane Sesquiterpene

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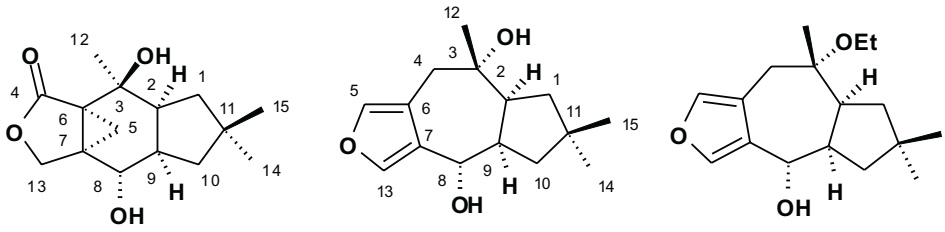
8-*Epi*-9-*epi*-isolactarorufin, the first *trans* fused rings isolactarane sesquiterpene was synthesized. Its stereochemistry was determined by ^{1}H NMR spectroscopy and X-ray analysis.

Key words: isolactarorufin, sesquiterpenes, *trans* fused rings isolactarane sesquiterpene, Meerwein-Ponndorf-Verley reduction

Isolactarorufin (**1**) is so far the only known isolactarane sesquiterpene isolated from *Lactarius* species. It was at first discovered in an EtOH extract of *Lactarius rufus* [1] and later also in *Lactarius vellereus* and *Lactarius necator* [2].

Natural isolactarorufin, as well as natural lactarane sesquiterpenes have *cis* fused six and five, and seven and five membered rings, respectively [3]. Until now, there was no report of synthetic *trans* fused six and five membered rings in isolactarane sesquiterpenes [4], however the syntheses of *trans* fused lactarane sesquiterpenes are known and are described for furandiol (**2**) [5] and 3-*O*-ethylfurandiol (**3**) [6] (Fig. 1).

The preparation of *trans* fused ring compounds within isolactarane skeleton became important as it was found that N-tertbutoxycarbonylphenylisoserinate of 8-*epi*-9-*epi*-isolactarorufin showed interesting antitumor properties [7]. In case of furane lactaranes the transformation of the ring junction involved the oxidation of 8-hydroxyl group to a ketone **4**, its equilibration through enolization in methanolic sodium hydroxide solution to **4b** followed by sodium borohydride reduction [5] which gave in almost 100% the 8-*epi*-9-*epi*-derivative 5 (Scheme 1).



1 **2** **3**

Figure 1.

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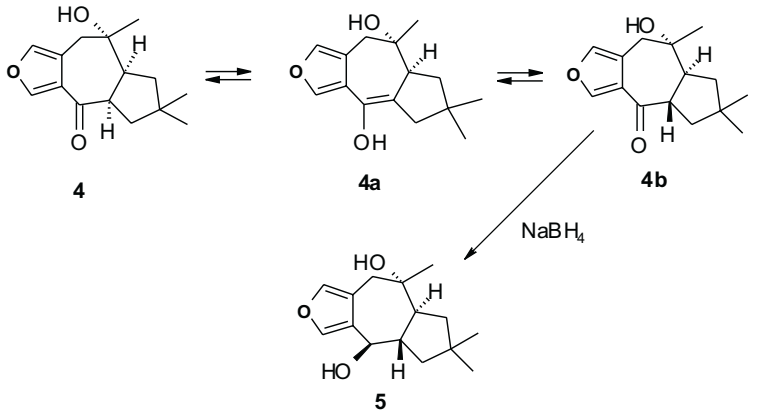
Scheme 1

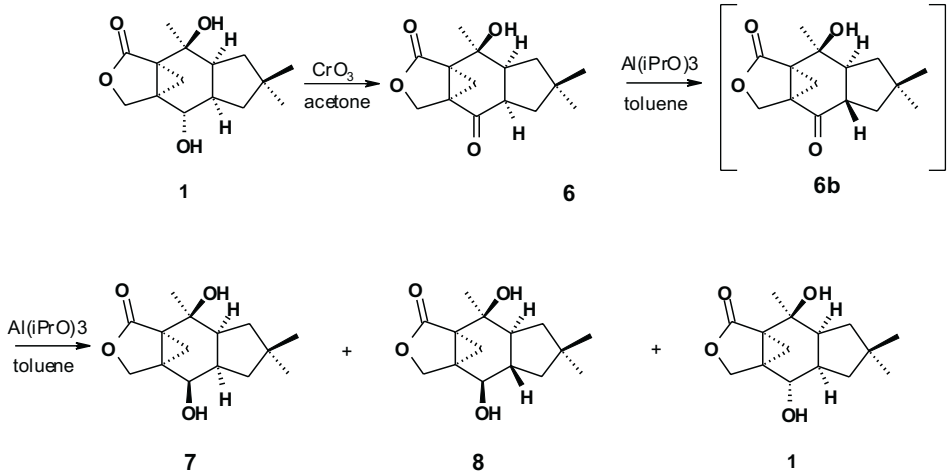


RESULTS AND DISCUSSION

Analogous reaction in case of lactones such as isolactarorufin (**1**) is impossible, because attempts of equilibration in strong alkaline solution would result in opening of the lactone ring and different relactonization upon acidification [6]. Thus, in order to carry the transformation we decided to reduce the ketone group in slightly alkaline medium. At first, we oxidized isolactarorufin (**1**) to ketone **6** using the described procedure [11] and then we used the Meerwein-Ponndorf-Verley method for reduction. This reaction is slow, so we expected that ketone **6** would transform mainly into thermodynamically more stable **6b**, *trans* fused derivative which was not isolated (Scheme 2).

We obtained three isomers after the reduction: 8-*epi*-isolactarorufin (**7**), 8-*epi*-9-*epi*-isolactarorufin (**8**) and isolactarorufin (**1**) with yield: 12%, 45% and 10%, respectively (Scheme 2).

Scheme 2



Since the ^{1}H NMR spectrum of **8** was inconclusive the stereochemistry of **8** was determined by X-ray analysis. Suitable crystals were prepared and X-ray diffraction measurements were performed at room temperature at the Nonius BV MACH3 diffractometer for crystal obtained from methanol solution. Unit cell dimensions were obtained by refinement of setting angles for 25 reflections in θ-range 22.49–43.27°. The structure was solved by the SHELXS97 [9] and refined by the SHELXL97 programs [10]. Hydrogen atom positions were inserted geometrically and refined in riding mode; these for OH groups were found from $\Delta\rho$ maps and refined. In general, the molecule is characterized by large thermal motions. Perhaps for this reason absolute structure could not be refined with the collected set of data [Flack parameter – 0.5(3)]. Relative configurations of the stereogenic centers are shown in Fig. 1. Interestingly, hydrogen bonding involves only hydroxyl but not lactone group (see Table 2). Details of data collection and structure refinement are collected in Table 1.

Table 1. Crystal data and structure refinement for **8**.

Empirical formula	$C_{60}H_{88}O_{16}$
Formula weight	1065.30
Temperature	293(2) K
Wavelength (Å)	1.54184
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions (Å, °)	a = 7.4301(2)
	b = 12.4880(6)
	c = 15.7781(8)
Volume (Å^3)	1464.99(5)
Z, Calculated density (Mg m^{-3})	1, 1.208
Absorption coefficient (mm^{-1})	0.705
F(000)	576
Crystal size (mm)	0.77×0.63×0.52
θ-range for data collection (°)	4.52 to 74.67
Limiting indices	$0 \le h \le 9, 0 \le k \le 15, -19 \le l \le 19$
Reflections collected / unique	1472 / 1472 [R(int) = 0.0000]
Completeness to theta = 74.67	84.7 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1472 / 0 / 181
Goodness-of-fit on F^2	1.057
Final R indices [$I>2\sigma(I)$]	R_1 = 0.0356, wR_2 = 0.1043
R indices (all data)	R_1 = 0.0356, wR_2 = 0.1043
Absolute structure parameter	–0.5(3)
Extinction coefficient	0.0072(8)
$\Delta\rho$ (e Å^{-3})	0.144 and –0.103

Table 2. Hydrogen bonds for **1** [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
O(2)–H(2)...O(1)#1	0.88(3)	1.90(3)	2.735(2)	158(3)
O(1)–H(1)...O(2)#2	0.83(4)	1.95(4)	2.741(2)	159(3)

Symmetry transformations used to generate equivalent atoms:
#1 x-1/2,-y+1/2,-z+1 #2 x+1,y,z

Supplementary material: Crystallographic data for the structure reported in this paper have been deposited at Cambridge Crystallographic Data Center. Number CCDC 212160. These data can be obtained free of charge *via* www.ccdc.cam. ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

The ORTEP diagram showing molecular conformation of **8** is shown in Fig. 2. Thermal ellipsoids are shown at 30% probability level.

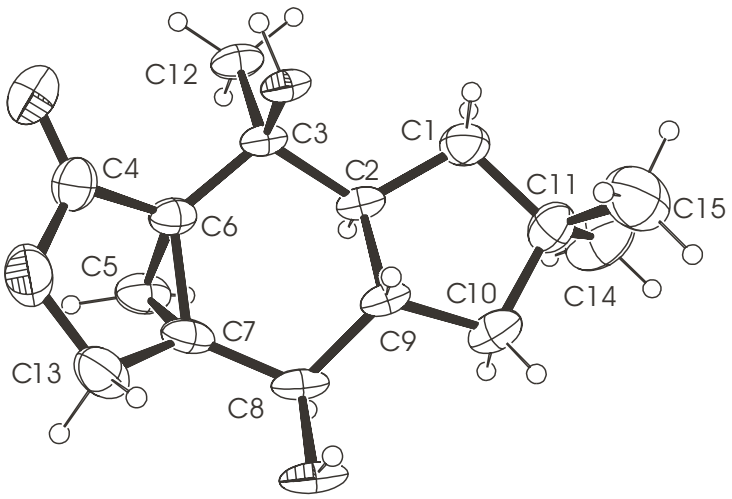


Figure 2.

EXPERIMENTAL

Chromatographies were carried out on Kieselgel 60, 230–400 mesh (Merck No. 9385) and were monitored by TLC. Melting points were determined with a Kriometr Boetius Franz Küstner (Dresden) melting point apparatus and are uncorrected. UV spectra were obtained in ethanolic solution with Varian CARY 1E spectrometer. IR spectra were measured with Perkin Elmer FT-IR 1600 spectrometer. NMR spectra were measured in $CDCl_3$ solutions, using Bruker ADVANCE 500 instrument, with TMS as internal standard. Mass spectra were obtained using ADM 604 Inectra GmbH mass spectrometer. X-ray analysis was obtained with monocrystalline diffractometer MACH 3 Nonius BV.

8-Ketoisolactarorufin (6). Isolactarorufin (1; 1.0 g, 4 mmol) was oxidized by excess of Jones reagent according to the procedure described in [11]. Thus from **1** (1.0 g, 4 mmol) **6** (932 mg, 94%) was obtained.

8-*Epi*-9-*epi*-isolactarorufin (8). 8-Ketoisolactarorufin (**6**; 500 mg; 1.9 mmol) was dissolved in toluene (25 ml) and isopropanol (5 ml). Subsequently aluminium isopropanolate (1.9 mmol) was added to the solution and the reaction mixture was refluxed (*ca.* 10 hours) until **6** disappeared (TLC, CH_2Cl_2 – iPrOH 95:5). Subsequently the reaction mixture was washed with tartaric acid solution, dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by column chromatography on silica gel (hexane – CH_2Cl_2 – acetone, gradient) and the following compounds were isolated: 8-*epi*-isolactarorufin (**7**; 60 mg; 12%), 8-*epi*-9-*epi*-isolactarorufin (**8**; 227 mg; 45%), isolactarorufin (**1**; 51 mg; 10%).

8-*Epi*-9-*epi*-isolactarorufin (8). M.p. 145–148°C; UV (EtOH) λ_{max} 223 nm; ε_{max} 4430; IR (film) ν_{max}: 3316, 2928, 2860, 1729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.00 (d, J = 5.5 Hz, 1H, H-5); 1.05 (s, 3H, H-14 or H-15); 1.06 (s, 3H, H-14 or H-15); 1.11 (d, J = 5.5 Hz, 1H, H-5); 1.10–1.12 (m, 1H, H-10); 1.33–1.46 (m, 2H, H-1 and H-2); 1.47 (s, 3H, H-12); 1.69 (dd, J = 12.2, 10.2 Hz, 1H, H-1); 1.79 (dd, J = 12.5, 7.2 Hz, 1H, H-10); 2.13 (m, 1H, H-9); 3.70 (d, J = 9.9 Hz, 1H, H-8); 4.13 (d, J = 9.7 Hz, 1H, H-13); 4.58 (d, J = 9.7 Hz, 1H, H-13); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.17 (C5); 25.62 (C12); 31.23; 31.85 (C14 and C15); 34.04 (C11, C6 or C7); 37.87 (C11, C6 or C7); 37.96 (C1); 39.32 (C11, C6 or C7); 45.17 (C10); 45.24 (C9); 47.27 (C2); 67.52 (C3); 69.17 (C13); 74.35 (C8); 176.33 (C4); ESI (MeOH) m/z: 289 $(M+Na)^+$; HR-MS 289.1410 calculated for $C_{15}H_{22}O_4Na$, found 289.1413.

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