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SESQUITERPENE LACTOLS FROM *LASERPITIUM HALLERI*

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Abstract—Three new pairs of anomeric sesquiterpene lactols have been isolated from the roots of *Leserpitium halleri*. They were obtained in pure form only after methylation of the hemiacetalic hydroxyl group, which resulted in the exclusive formation of only one methyl ketal from each pair of anomers. The stereochemistry at the ketalic centre of the methyl derivatives was assessed by correlation with methylhallerin, a compound of known configuration.

INTRODUCTION

As a part of an investigation on alpine plants, we reported the isolation of hallerin (**1a, b**), a mixture of anomeric sesquiterpene lactols, from the roots of *Laserpitium halleri* Crantz subsp. *halleri* [1].

Inspection of the high-field ^{1}H NMR spectra of crude samples of hallerin showed that, besides the expected resonances for **1a, b**, three other sets of split signals were present, accounting for *ca* 10% of the material, and most probably representing other pairs of anomeric lactols. We present here the structural elucidation of these minor products.

RESULTS AND DISCUSSION

The separation of the mixture of lactols was simplified by treatment with methyl iodide and silver(I) oxide in dry dichloromethane, since exclusively one methylketal was formed from each pair of anomers. Furthermore, the methyl derivative of hallerin (**1c**), representing the most abundant constituent of the mixture, is a highly crystalline compound, and most of it could be removed by crystallization from hexane. By column chromatography of the mother liquors, it was thus possible to obtain pure **2c**, and a mixture of **3c** and **4c**, which could be further separated on $AgNO_3$-coated silica gel.

Compound **2c** is the methyl derivative of a mixture of anomeric elemanes (isohallerin **2a, b**), previously prepared by Cope rearrangement of hallerin [1], while **3c** and **4c** are the methyl derivatives of anomeric eudesmane lactols (**3a, b**; **4a, b**).

The stereochemistry at the ketalic centre of methylhallerin (**1c**) was established as *S* (β-OMe) by an X-ray diffraction study [2]. That of the other methyl ketals was assessed by correlation with methylhallerin [1]. Cope rearrangement of **1c** gave **2c**, while transannular cyclization of **1c** under controlled conditions (see Experimental) afforded **3c** and **4c**, showing that the stereochemistry at the ketalic centre is the same in all these compounds.

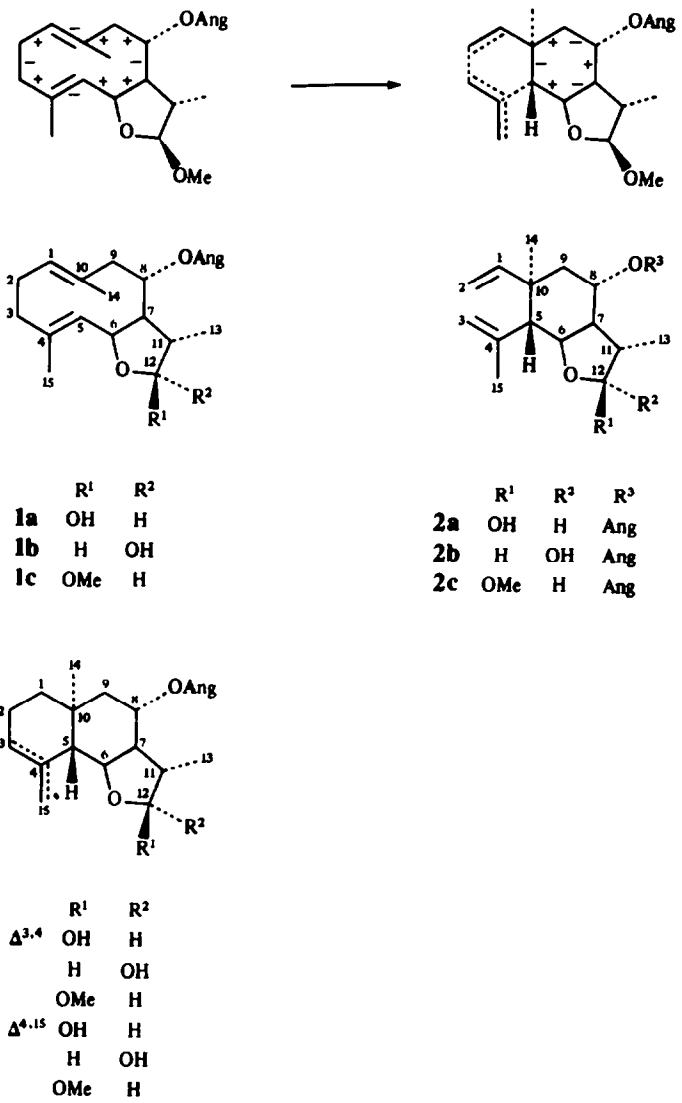
Comparison of the ^{1}H NMR spectra of **1c** and **2c–4c** shows that Cope rearrangement to **2c** and transannular cyclization to **4c** are accompanied by inversion of the fragment C-6–C-10, which results in flipping from a boat to a chair conformation of the cyclohexane ring bound to the γ-lactol ring. These changes are outlined in Fig. 1 according to the torsion angle notation [3]. Interestingly, the conformation of ring B is different in the eudesmane **4c** and **3c**, as shown by the different splitting pattern of H-8 (*q*, J = 7.0 Hz in **3c**; *br s*, in **4c**). Although it is difficult to derive the geometry of ring B in **3c** from simple inspection of the coupling constants around the ring, the pattern is similar to that reported for isosilerolide [4], in which ring B adopts a twist–boat conformation, at least in the solid state [5]. These differences are difficult to rationalize, and

Table 1. ^{13}C NMR data for compounds **1c**, **2a**, **2b**, **2c** (50 MHz, $CDCl_3$, TMS internal standard

C	1c	2a	2b	2c
1	129.17 *s*	147.46 *d*	147.90 *d*	147.99 *d*
2	25.88 *t*	114.32 *t*	113.87 *t*	113.73 *t*
3	39.63 *t*	110.80 *t*	110.69 *t*	110.66 *t*
4	134.07 *s**	143.20 *s*	143.84 *s*	143.84 *s*
5	127.33 *d*	46.76 *d*	50.44 *d*	50.40 *d*
6	76.30 *d*	77.43 *d*	78.15 *d*	78.48 *d*
7	53.32 *d*	53.75 *d*	54.13 *d*	53.35 *d*
8	72.05 *d*	69.77 *d*	70.64 *d*	69.93 *d*
9	44.88 *t*	41.04 *t*	43.08 *t*	38.61 *t*
10	133.95 *s**	39.92 *s*	40.32 *s*	40.21 *s*
11	42.33 *d*	41.04 *d*	43.08 *d*	42.95 *d*
12	109.71 *d*	98.48 *d*	104.87 *d*	19.76 *d*
13	17.90 *q*†	15.72 *q*	11.94 *q*	16.47 *q*
14	16.78 *q*	20.61 *q*	19.35 *q*	19.44 *q*
15	21.00 *q*†	25.35 *q*	24.49 *q*	25.16 *q*
OMe	54.46 *q*			56.58 *q*

The ^{13}C signals for the angelate group were almost identical in **1c**, **2a**, **2b** and **2c**. Those observed in **1c** are given as representative: C-1′ 166.71 *s*, C-2′ 128.64 *s*, C-3′ 136.44 *d*, C-4′ 15.52 *q*, C-5′ 20.52 *q*.

*†Interchangeable signals.



	R^1	R^2
1a	OH	H
1b	H	OH
1c	OMe	H

	R^1	R^2	R^3
2a	OH	H	Ang
2b	H	OH	Ang
2c	OMe	H	Ang

		R^1	R^2
3a	$\Delta^{3,4}$	OH	H
3b		H	OH
3c		OMe	H
4a	$\Delta^{4,15}$	OH	H
4b		H	OH
4c		OMe	H

Scheme 1. Top, conformational changes during Cope rearrangement and transannular cyclization of **1c**.

were not observed in α- and β-cyclohallerin lactones, the 1-hydroxylated γ-lactones corresponding to **3c** and **4c** [1].

The stereochemical outcome of the methylation of hallerin and related mixtures of anomeric lactols has been discussed elsewhere [2]. It is interesting to note that substitution of dichloromethane for DMF allows the selective methylation of the more acidic hemiacetalic hydroxyl in the presence of alcoholic hydroxyls [1].

It has been reported that under certain conditions silver(I) ions can catalyse the interconversion of elemane and eudesmane derivatives possibly via the corresponding germacrane derivatives [6]. However no reaction of this type was observed by treatment of pure **1c** and **2c** with Ag_2O in dichloromethane.

Lactols **1a, b–4a, b** are structurally related to lactones isolated from the Laserpitieae tribe of the Umbelliferae from which they differ, apart the ester moiety, only in the absence of an oxygenated function at C-11. It is not clear, however, if sesquiterpene lactols in the Laserpitieae tribe are involved in the biogenesis of sesquiterpene lactones, of which they might represent the ultimate precursors. Sesquiterpene lactones, were not isolated from the roots of *Lasepitium halleri*, whereas investigation of the fruits gave only sesquiterpenoids with an unoxidized C-7 side-chain [7].

EXPERIMENTAL

Silica gel 60 (70–230 mesh, Merck) was used for CC; $AgNO_3$-coated silica gel was prepared by suspending silica gel (TLC-grade, 100 g) in a 5% soln of $AgNO_3$ in MeCN (200 ml), and removing the solvent under vacuum. The material prepared in this way was activated before use by heating at 120° for 2 hr. Crude hallerin was obtained from the roots of *Laserpitium halleri* as described in ref. [1].

Methylation of the mixture of lactols. A 2.0 g sample of crude hallerin (6.2 mmol) was dissolved in 25 ml CH_2Cl_2 (distilled from P_2O_5) and 1.60 g Ag_2O was added, followed by an excess (2 ml, 39 mmol) of MeI. The suspension was stirred at room temp. for 6 hr, and then filtered and evapd. A solid material was obtained, which was crystallized from hexane to give pure methylhallerin (**1c**, 1.40 g). The mother liquors were chromatographed on silica

gel (20 g, hexane–EtOAc, 6:1) to give pure **2c** (160 mg), an additional 200 mg of **1c** and 95 mg of a mixture of **3c** and **4c**, which was further separated by CC on silver-coated silica gel (20 g, hexane–EtOAc, 9:1) to give 20 mg **3c** and 32 mg **4c**.

Methylhallerin (**1c**). Leaflets from hexane, mp 91°, $[\alpha]_D^{25}$ −9 ($CHCl_3$; *c* 0.95); IR ν_{max}^{KBr} cm^{-1}: 2900, 1720, 1660, 1460, 1390, 1240 and 1160; EI-MS 70 eV, *m/z* (rel. int.): 348 $[M]^+$ ($C_{21}H_{32}O_4$) (3), 83 $[C_5H_7O]^+$ (100); ^1H NMR ($CDCl_3$ 200 MHz, TMS as internal standard) [the resonance values of the protons of the angelate were constant in all the compounds reported here: those for **1c** are given as representative: δ 5.98 (1H, *qq*, *J* = 7.0, 1.5 Hz, H-3'), 1.97 (3H, *dq*, *J* = 7.0, 1.5 Hz, H-4'), 1.89 (3H, *q*, *J* = 1.5 Hz)]: δ 5.26 (1H, *dq*, *J* = 10.4, 9.8, 5.0 Hz, H-8), 5.15 (1H, *tq*, *J* = 8.0, 8.0, 1.2 Hz, H-1), 4.92 (2H, *m*, H-5, H-6 overlapped signals), 4.48 (1H, *d*, *J* = 1.3 Hz, H-12), 3.23 (3H, *s*, –OMe), 2.85 (1H, *ddd*, *J* = 5.0, 12, 1.5 Hz, H-9), 2.65 (1H, *qt*, *J* = 7.2, 1.3, 1.3 Hz, H-11), 1.67 (3H, *d*, *J* = 1.5 Hz, H-14), 1.43 (3H, *d*, *J* = 1.5 Hz, H-15), 1.13 (3H, *d*, *J* = 7.2 Hz, H-13).

Methylisohallerin (**2c**). Colourless oil, $[\alpha]_D^{25}$ +30 ($CHCl_3$; *c* 1.83); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1640, 1460, 1390 and 1230; EI-MS 70 eV, *m/z* (rel. int.): 348 $[M]^+$ ($C_{21}H_{32}O_4$) (6), 83 $[C_5H_7O]^+$ (100); ^1H NMR ($CDCl_3$, 200 MHz, TMS as internal standard): δ 5.74 (1H, *dd*, *J* = 17.0, 11.0 Hz, H-1), 5.22 (1H, *td*, *J* = 4.0, 4.0, 2.2 Hz, H-8), 5.02 (1H, *m*, H-3a), 4.90 (1H, *dd*, *J* = 11.0, 1.0 Hz, H-2a), 4.86 (1H, *dd*, *J* = 17.0, 1.0 H-2b); 4.74 (1H, *br s*, H3b), 4.57 (1H, *d*, *J* = 4.0 Hz, H-12), 4.43 (1H, *dd*, *J* = 11.0, 6.5 Hz, H-6), 3.68 (3H, *s*, –OMe); 2.33 (1H, *d*, *J* = 11.0 Hz, H-5); *ca* 2.12 (1H, *m*, H-11); 1.78 (3H, *br s*, H-15); 1.57 (1H, *dd*, *J* = 16.0, 4.0 Hz, H-9a), 1.21 (3H, *d*, *J* = 6.4 Hz, H-13); 1.08 (3H, *s*, H-14).

Methyl-α-cyclohallerin (**3c**). Gum, $[\alpha]_D^{25}$ −140 ($CHCl_3$; *c* 0.51); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1460, 1390, 1240–1220; EI-MS 70 eV, *m/z* (rel. int.): 348 $[M]^+$ ($C_{21}H_{32}O_4$) (4), 83 $[C_5H_7O]^+$ (100); ^1H NMR ($CDCl_3$, 200 MHz, TMS as internal standard): δ 5.40 (1H, *br s*, H-3); 5.10 (1H, *q*, *J* = 7.0 Hz, H-8), 4.80 (1H, *d*, *J* = 5.0 Hz, H-12), 4.18 (1H, *dd*, *J* = 10.5 and 7.5 Hz, H-6); 3.36 (3H, *s*, –OMe); 1.83 (3H, *br s*, H-15); 1.12 (3H, *d*, *J* = 6.2 Hz, H-13); 0.96 (3H, *s*, H-14).

Methyl-β-cyclohallerin (**4c**). Colourless oil, $[\alpha]_D^{25}$ +8 ($CHCl_3$; *c* 0.60); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1650, 1450, 1390, 1240–1210; EI-MS 70 eV, *m/z* (rel. int.): 348 $[M]^+$ ($C_{21}H_{32}O_4$) (3), 83 $[C_5H_7O]^+$ (100); ^1H NMR ($CDCl_3$, 200 MHz, TMS as internal standard): δ 5.14 (1H, *br s*, H-8), 4.94 (1H, *br s*, H-15a), 4.83 (1H, *br s*, H-15b); 4.62 (1H, *d*, *J* = 3.0 Hz, H-12); 4.45 (1H, *dd*, *J* = 10.5 and 6.0 Hz, H-6), 3.30 (3H, *s*, –OMe); 1.24 (3H, *d*, *J* = 6.2 Hz, H-13); 0.88 (3H, *s*, H-14).

Cope rearrangement of methylhallerin (**1c**). A 1.10 g sample of **1c** was heated under vacuum (water pump) at 180° in a Kugelrohr apparatus for 5 min. A yellowish oil was obtained, which was filtered on a short column of silica gel (4 g) to give 996 mg of **2c** as a colourless oil, having spectral data (^1H NMR, IR) identical to those of **2c** obtained from the methylation of the mixture of lactols from *L. halleri*.

Transannular cyclization of methylhallerin (**1c**). A 100 mg sample of **1c** was dissolved in 0.5 ml of $CDCl_3$ in an NMR tube, and 5 mg of *p*-toluensulphonic acid were added. The course of the reaction was followed by ^1H NMR (60 MHz). After 10 min. all of **1c** had reacted, and the reaction was quenched by addition of 0.7 ml of a saturated $NaHCO_3$ soln. The contents of the tube was poured into CH_2Cl_2 (10 ml), and the tube was rinsed × 3 with the same solvent. After separation of the phases and drying ($MgSO_4$), 91 mg of a yellow oil were obtained. After 2 separations on silver-coated silica gel (hexane–EtOAc 9:1 as eluent), 12 mg of **3c** and 21 mg of **4c** were obtained, identical (^1H NMR, 200 MHz) with the eudesmanes obtained from the methylation of the mixture of lactols from *L. halleri*.

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