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SESQUITERPENE LACTONES OF *ONOPORDON TAURICUM**

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Key Word Index—*Onopordon tauricum*, Compositae; sesquiterpene lactones, germacranolides, elemanolides, eudesmanolides

Abstract—The chloroform extract of the leaves of *Onopordon tauricum* yielded 10 sesquiterpene lactones, including a new elamanolide and four new eudesmanolides. The structures of the new compounds were elucidated by chemical transformations and modern spectral methods.

INTRODUCTION

Onopordopicrin (**1**), an antitumour lactone [1], is the major constituent of all previously studied species of *Onopordon* (subtribe Carduinae, tribe Cynareae,) [2–4], including one European population of *O. tauricum* Willd [5]. Our chemical examination of a second population of this latter species from the Marmara region of Turkey [6], afforded five known and five new sesquiterpene lactones. While this population also yielded onopordopicrin, the main sesquiterpene lactone was onopordopicrin's 2′,3′-dihydro derivative, arctiopicrin (**2**).

RESULTS AND DISCUSSION

The known germacranolides of the chloroform extract of the leaves of *O. tauricum* were identified as onopordopicrin (**1**) [3], arctiopicrin (**2**) [7, 8] and 4′-desoxoarctiopicrin (**4**) [3] based on a comparison of their published spectral and physical properties. Here we present previously unreported ^{1}H NMR and other spectral data for arctiopicrin, its diacetate derivative (**3**) and 4′-desoxarctiopicrin (**4**) (see Table 1 and Experimental).

The known elemanolide, melitensin (**5**), was also readily identified by comparison of its spectral data with those reported previously [9]. The ^{1}H NMR (Table 1) and 2D homonuclear COSY spectra of the new elemanolide (**6**), $C_{19}H_{24}O_6$ (EIMS), showed close similarity in most respects to those recorded for melitensin. The main differences between the ^{1}H NMR spectrum of melitensin (**5**) and that of **6** were the presence of an aldehyde signal at δ9.46 (*s*) for **6** instead of a C-15 hydroxymethylene signal for **5** and more downfield chemical shifts of the H-3a and H-3b protons (at δ6.29, 6.27, both *s*) for **6**. These small differences indicated that the C-15 hydroxymethylene group of melitensin (**5**) had been oxidized to an aldehyde group in **6**. Except for the side chain signals, the ^{1}H NMR spectrum of the 2′,3′-dehydro analogue of **6**, which is known from *Onopordon leptolepis* [10], is almost identical to that of **6**. Finally, active manganese dioxide oxidation of melitensin (**5**) yielded **6** which is therefore 15-dehydromelitensin.

The other five lactones isolated from *O. tauricum* were eudesmanolides and differed from each other by their acyl groups, oxidation stages at the C-1 and C-15 positions, as well as the stereochemistry of the C-4 substituent. The first compound of this series **7** was the known lactone 8-α-(4′-hydroxymethacryloyloxy)-sonchucarpolide [11].

The ^{1}H NMR spectrum of the new eudesmanolide **8** (Table 1), $C_{19}H_{26}O_7$ (CIMS), clearly indicated the presence of the same lactone skeleton as **7**, differing only in the side chain at C-8. The side chain of **8** was readily identified from characteristic ^{1}H NMR signals (see Table 1) and EIMS fragment ([4-hydroxyisobutyrate acylium]$^+$ at *m/z* 87) as a 4-hydroxybutyrate. Therefore, **8** is the 8-α-(4′-hydroxybutyroyloxy) derivative of sonchucarpolide.

The next new C-14 aldehydic eudesmanolide, 8-*O*-(4′-hydroxybutyroyl)-onopordaldehyde (**9**), was closely related to **8**. The similarity of the ^{1}H NMR spectra of these two compounds, except for the absence of the C-1 hydroxyl geminal proton signal in the ^{1}H NMR spectrum of **9**, indicated that **9** must be the C-1 desoxo derivative of **8**. In accord with this observation, the CIMS of **9** displayed a molecular ion at *m/z* 351 $[M+H]^+$, that is 16 mass units less than that of **8**.

The remaining two eudesmanolides, 8-(4′-hydroxybutyroyl)-onopordic acid (**10**), $C_{19}H_{26}O_7$, and 8-(4′-hydroxybutyroyl)-1-β-hydroxyonopordic acid (**11**), $C_{19}H_{26}O_8$, exhibited ^{1}H NMR spectral data (see Table 1) similar to those of **9** and **8**, respectively. The absence of the C-15 aldehydic proton signal and the coupling constant of the H-5 signals were the main differences between the ^{1}H NMR spectra of **9** and **10**; the spectra of **8** and **11** also differed in the same way. Therefore, the C-15 aldehyde group of **9** and **8** is substituted by a carboxyl group in **10** and **11** as indicated by their IR and CIMS spectra (i.e. absorption band at 1720 cm^{-1} and $[M+H]^+$ at *m/z* 367 for **10** and at *m/z* 383 for **11**). On the other hand, the coupling constant differences of the H-5

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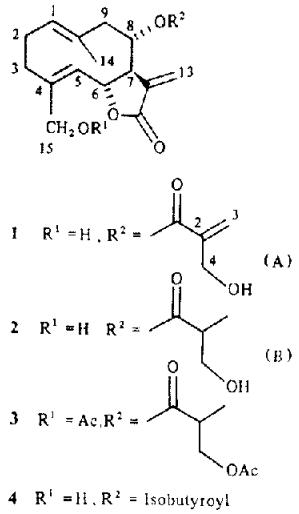
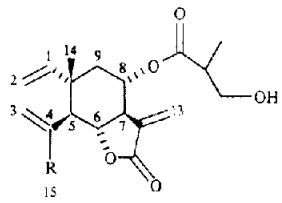


1 R^1 = H, R^2 = (A)

2 R^1 = H R^2 = (B)

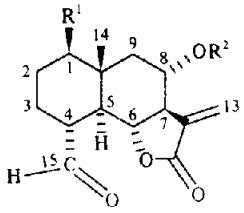
3 R^1 = Ac, R^2 =

4 R^1 = H, R^2 = Isobutyroyl



5 R = CH_2OH

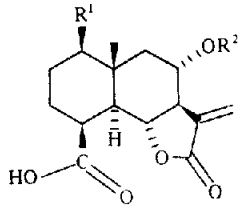
6 R = CHO



7 R^1 = OH R^2 = A

8 R^1 = OH R^2 = B

9 R^1 = H, R^2 = B



10 R^1 = H R^2 = B

11 R^1 = OH, R^2 = B

signal observed in the ^{1}H NMR spectrum of **9** compared to the spectrum of **10**, and the spectrum of **8** compared to that for **11**, should be related to the β-stereochemistry of the C-4 carboxyl group of the latter compounds, i.e. **10** and **11**. In order to assign the total stereochemistry of **10** and **11**, following the complete chemical shift assignment of the signals for the protons of **11** by high resolution 2D homonuclear COSY, **11** was subjected to a series of NOE differences spectroscopy experiments (Fig. 1). Since the stereochemistry of the H-7 proton in eudesmanolides is accepted as α on biogenetic grounds [12], the relative stereochemistry of the other asymmetric centres of **11** to the C-7 centre should establish the absolute stereochemistry of **11**. The NOE irradiation of the H-7 signal markedly enhanced the H-5 signal and to some extent the H-9α signal but not the H-6 and H-8 signals. The H-5 and H-9α signals were also affected by the NOE irradiation of the H-1 signal. These experiments clearly indicated an α stereochemistry for H-1 and H-5, and a β stereochemistry for H-6 and H-8. The NOE irradiation of the H-8 signal only affected the H-6 signal, whereas the NOE irradiation of the H-6 signal enhanced both the H-8 and the C-14 methyl signals. However, the H-4 and H-5 signals were not affected by either of these two irradiations. The last two irradiations confirmed a β stereochemistry for H-6, H-8 and the C-14 methyl group.

The C-15 carboxylated lactones (i.e. compounds **10** and **11**) distinguish this population of *O. tauricum* from other species of *Onopordon*, as well as members of other related genera of the tribe Cynareae, such as *Jurinea*, *Centaurea*, *Arctium* and *Cnicus*. Furthermore, in contrast to the previously studied *Onopordon* species which mainly exhibit 8-(4′-hydroxymethacrylate) side chain-containing lactones, the sesquiterpene lactone chemistry of this population is dominated by 8-(4′-hydroxybutyrate) esterified lactones.

EXPERIMENTAL

Plant material. Leaves of *Onopordon tauricum* Willd. were collected from the Marmara region of Turkey between Kirklareli and Luleburgaz in June 1980. A voucher specimen is deposited in Herbarium, Faculty of Pharmacy, University of Istanbul (ISTE 44591).

Extraction and isolation of the compounds. Air-dried and unground leaves of *O. tauricum* (890 g) were extracted with $CHCl_3$ for 20 min. The extract was concd to a syrup, then the concentrate was taken up in MeOH and diluted with H_2O until an 80% MeOH soln (*ca* 1 l) was obtained. The resulting soln was filtered, and then partitioned against C_6H_6 (2 × 200 ml). The alcohol fraction was concentrated until only H_2O remained and the resulting soln was extracted with CH_2Cl_2 (3 × 200 ml). The combined CH_2Cl_2 extract was dried with dry $MgSO_4$ and then concd to a light yellow gum (7·9 g) *in vacuo*. The gum (3·5 g) was dissolved in a minimum amount of MeOH–CH_2Cl_2 (3:1) and the soln was chromatographed over a Sephadex LH-20 column (4 × 60 cm) packed in the same solvent. One hundred 30 ml fractions were collected and each was monitored by TLC. Sesquiterpene lactone-enriched fractions were combined (2·4 g) and redissolved in a minimum amount of cyclohexane–CH_2Cl_2–EtOH (7:4:1) and then the resulting soln was chromatographed on a Sephadex LH-20 column (3 × 50 cm) packed in same solvent system. Final purification of the compounds was made by silica gel prep. TLC, 2 mm layer thickness, which were eluted with CH_2Cl_2–C_6H_6–EtOAc–MeCN (4:4:2:1, 3:3:2:1 and 2:2:2:1).

Arctiopicrin (**2**). Gum (1·45 g), EIMS (probe, 70 eV) *m/z* (rel. int.): 350 $[M]^+$ (0·2), 247 $[M - C_4H_8O_3 + H]^+$ (2·21), 228 [M

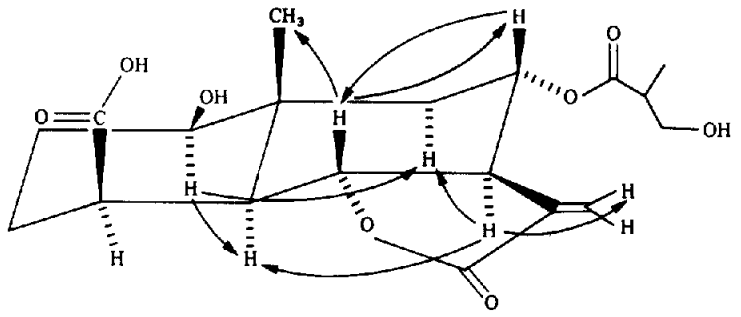


Fig 1

Table 1 ^{1}H NMR spectra of compounds **2–4, 6, 8–11** (200 MHz, $CDCl_3$, TMS as int standard, J in Hz in parentheses)

H	**2** (d_5-Pyridine)	**3**	**4**	**6**	**8** [$(CD_3)_2$ CO + $CDCl_3$]	**9**	**10**	**11** (500 MHz)
1a	5.03 *br dd* (4, 10 7)	5 06*	4.95* *br*	5.17 *dd* (10 7, 17 4)	3 39 *dd* (4 1, 11 2)		1 6–	3 95 *dd* (4 8, 11 4)
1b								
2a	2 78* *m*	2 51**m*	2 58**m*	4.95 *d* (10.7)		1.3–		2 18 *m*
2b	2 28 *m*	1 95–	1 9–	4.83 *d* (17.4)	1.5–		2 1 *m*	1 86 *m*
3a	2 12 *m*	2 28 *m*	2.3 *m*	6 29 *s*	1 9 *m*	1 9 *m*	2 45 *m*	2 50 *dt* (7.4, 13.9)
3b	1 92 *br dt* (5 4, 11 8)			6 27 *s*				2 39 *ddd* (1.7, 5 8, 13 9)
4					2 51 *m*	2 49 *m*		1.60 *m*
5	4 91 *br d* (9 6)	4 92*	4.80 *br d* (9 9)	3.18 *d* (12 1)	2 02 *t* (11.3)	1.89 *t* (11.3)	2 72* *d* (10.9)	2.64 *d* (10 9)
6	5.42** *t* (9 6)	4 87** *t* (9 7)	5 08** *t* (9.9)	4.39 *dd* (11.3, 12 1)	4 1 *t* (11.2)	3 87 *t* (11.2)	4 15 *t* (11 1)	4 19 *t* (11 1)
7	3 23 *m*	3 06 *m*	3 02 *m*	2 92 *tt* (3, 11 1)	2 96 *m*	2 84 *m*	2 79 *m*	2 76 *tt* (3, 11)
8	5 48** *m*	4 98** *m*	4 98** *m*	5 28 *dt* (4 3, 10 9)	5 26 *dt* (4 4, 10 8)	5 46 *dt* (4 4, 10 8)	5.22 *dt* (4 5, 10 7)	5 20 *dt* (4 5, 10 8)
9a	2 74* *br d* (11 9)	2 51*	2 52*	2 01 *dd* (4 3, 12.6)	2 46 *dd* (4 4, 12.8)	2 06 *dd* (4 4, 12 8)	2 15 *dd* (4 5, 12 7)	2 43 *dd* (4 5,12.6)
9b	2.53 *br t* (11 9)	2 42 *br t* (11 8)	2 38 *br t* (11 6)	1 68 *dd* (10 8; 12 6)	1.32 *br dd* (11 1, 12 8)	1 28 *br dd* (11 1, 12 8)	1 52 *br dd* (11 1, 12 7)	1.42 *dd* (11 2, 12 6)
13a	6 52 *d* (3 4)	6 35 *d* (3 5)	6 32 *d* (3 5)	6 15 *d* (3 1)	6 06 *d* (3 1)	6 11 *d* (3 15)	6 12 *d* (3 1)	6 12 *d* (3 1)
13b	6 31 *d* (2 6)	5 87 *d* (2 7)	5 83 *d* (2 6)	5 73 *d* (2 8)	5 81 *d* (3 0)	5 66 *d* (2 9)	5 67 *d* (2 9)	5.66 *d* (2 95)
14	1 58 *br s*	1 50 *br s*	1 49 *br s*	1.08 *s*	1 02 *s*	1 04 *s*	0 95 *s*	0 91 *s*
15a	4 52 *d* (14)	4 60 *br s*	4 28 *d* (13 9)	9.46 *s*	9 57 *d* (4)	9 64 *d* (4 2)		
15b	4 37 *d* (14)		4 06 *d* (13 9)					
2′	2 93 *m*	2 81 *m*	2 52** *m*	2 72 *m*	2.68 *m*	2 72 *m*	2.73* *m*	2 70 *m*
3′	1 30 *d* (7 1)	1 22 *d* (7 2)	1 20 *d* (7 1)	1 19 *d* (7 2)	1 15 *d* (7 1)	1 18 *d* (7.2)	1.19 *d* (7.2)	1 17 *d* (7.2)
4′a	4 13† *dd* (7 8, 10.4)	4 25† *dd* (8.7, 11)	4.15 *d* (7 1)	3 77 *d* (6 1)	3 72 *dd*† (7 6, 10 6)	3 76 *d* (6.1)	3.76 *d* (6 1)	3 75 *d* (6 1)
4′b	3.95† *dd* (5 2, 10.4)	4 1† *dd* (5 1, 11)			3 66 *dd*† (5 2, 10 6)			
–OAc		2 1, 2.03						

*,** Overlapping signals

†Centre of the A or B part of ABX signal.

$-C_4H_8O_3-H_2O]^+$ (5.45), 150 (21 1), 147 (49 4), 105 (34 2), 91 (64 5), 87 $[C_4H_7O_2]^+$ (15 6) Acetylation of 100 mg of 2 in 2 ml of $Ac_2O-C_5H_5N$ (1 1) at room temperature, overnight gave arctiopicrin diacetate (**3**) (115 mg), gum, IR ν_{max}^{NaCl} cm^{-1} 2980, 2960, 2950, 1780, 1740 (*br*), 1460, 1365, 1260 (sh), 1235, 1185, 1148 (sh), 1130, 1040 EIMS (probe, 70 eV) *m/z* (rel. int) 306 $[M-C_6H_9O_3+H]^+$ (0 4), 289 $[M-C_6H_{10}O_4+H]^+$ (1), 247 $[M-C_6H_9O_3-Ac+2H]^+$ (11 5), 229 $[M-C_6H_{10}O_4-HOAc+H]^+$ (32 1), 214 (12 6), 148 (49 4), 128 (100), 120 (90 2), 105 (22 8), 91 (48 6), 43 (94 3) CIMS (isoC$_4$H$_{10}$, 0 5 torr, direct probe) *m/z* (rel int) 433 $[M-H]^+$ (10 54), 349 $[M+H-2\times Ac]^+$ (4 37), 307 $[M+H-C_6H_9O_3+H]^+$ (6 8), 289 $[M+H-C_6H_{10}O_4]^+$ (28 06), 229 $[M+H-C_6H_{10}O_4-HOAc]^+$ (100)

8-O-*Isobutyroylsalonitenolide* (**4**) Gum (16 mg), IR ν_{max}^{NaCl} cm^{-1} 3495, 2980, 2940, 2875, 1768, 1735, 1655, 1470, 1450, 1390, 1290, 1265, 1195, 1150, 1025, 1000, 955, 815 EIMS (probe, 70 eV) *m/z* (rel int) 334 $[M]^+$ (0 2), 247 $[M-C_4H_8O_2+H]^+$ (13 1), 229 $[M-C_4H_8O_2-H_2O+H]^+$ (22 2), 148 (52 3), 120 (100), 106 (28 9), 91 (62 4), 71 $[C_4H_7O_2]^+$ (65 6)

15-*Dehydromelitensin* (**6**) Gum (12 mg), IR ν_{max}^{NaCl} cm^{-1} 3520, 3092, 2980, 2950, 2880, 2710, 1775, 1735, 1695, 1640, 1460, 1410, 1260, 1180, 1130, 1050, 1020, 970, 880, 860, 818, 760 EIMS (probe, 70 eV) *m/z* (rel int) 348 $[M]^+$ (0 46), 269 $[M-C_4H_7O_2+H]^+$ (1 92), 244 $[M-C_4H_8O_3]^+$ (13 36), 226 $[M-C_4H_8O_3-H_2O]^+$ (9 15), 215 $[M-C_4H_8O_3-CHO]^+$ (24 52), 198 (27 0), 147 (79 31), 119 (100), 105 (17 23), 91 (49 28), 87 $[C_4H_7O_2]^+$ (27 88)

Oxidation of melitensin (**5**) Melitensin (15 mg) was dissolved in CH_2Cl_2 (5 ml), active MnO_2 (150 mg) was added in small portions and the suspension stirred at room temp for 1 hr The reaction mixture was filtered through a small celite pad and the CH_2Cl_2 was evapd *in vacuo* to yield 11 mg gum Spectral properties of the product were found to be identical with **6**

8-α-(4′-*hydroxybutyroyloxy*)-*Sonchucarpolide* (**8**) White amorphous powder (11 mg), IR ν_{max}^{NaCl} cm^{-1} 3450, 3100, 3020 (sh), 2940, 2880, 2740, 1770, 1725 (*br*), 1680 (sh), 1460, 1400, 1260, 1180, 1125, 970 EIMS (probe, 70 eV) *m/z* (rel int) 280 $[M-C_4H_7O_2+H]^+$ (0 6), 262 $[M-C_4H_8O_3]^+$ (1 4), 252 $[280-CHO+H]^+$ (52 2), 234 $[M-C_4H_8O_3-CHO+H]^+$ (8 26), 216 $[M-C_4H_8O_3-CHO-H_2O+H]^+$ (35 04), 201 (17 94), 188 (41 34), 141 (38 06), 131 (39 35), 123 (87 55), 105 (39 22), 87 $[C_4H_7O_2]^+$ (19 85) CIMS (isoC$_4$H$_{10}$, 0 5 torr, direct probe) *m/z* (rel int) 367 $[M+H]^+$ (11 20), 349 $[M+H-H_2O]^+$ (13 03), 339 $[M+H-CHO+H]^+$ (6 47), 337 $[M-CHO]^+$ (10 63), 281 $[M+H-C_4H_7O_2+H]^+$ (26 88), 263 $[M+H-C_4H_8O_3]^+$ (100), 245 $[M+H-C_4H_8O_3-H_2O]^+$ (60 86), 217 $[M+H-C_4H_8O_3-H_2O-CHO+H]^+$ (26 04)

8-O-(4′-*hydroxybutyryol*)-*Onopordaldehyde* (**9**) Gum (7 mg), IR ν_{max}^{NaCl} cm^{-1} 3500, 3100, 2980 (sh), 2940, 2870, 2730, 1778, 1740 (sh), 1725, 1675 (sh), 1460, 1390, 1260, 1180, 1120, 1025, 965, 865, 815 EIMS (probe, 70 eV) *m/z* (rel int) 350 $[M]^+$ (0 2), 264 $[M-C_4H_7O_2-H]^+$ (1 1), 246 $[M-C_4H_8O_3]^+$ (3 86), 236 $[264-CHO+H]^+$ (36 2), 218 $[M-C_4H_8O_3-CHO-H]^+$ (24 8), 174 (27 3), 146 (19 8), 134 (22 4), 126 (100), 105 (29 8), 87 $[C_4H_7O_2]^+$ (19 9) CIMS (isoC$_4$H$_{10}$, 0 5 torr, direct probe) *m/z* (rel int) 351 $[M+H]^+$ (64 09), 265 $[M+H-C_4H_7O_2+H]^+$ (50 36), 247 $[M+H-C_4H_8O_3]^+$ (100), 236 $[M+H-C_4H_7O_2-CHO+H]^+$ (20 56), 229 $[M+H-C_4H_8O_3-H_2O+H]^+$ (49 19)

8-O-(4′-*hydroxybutyroyl*)-*Onopordic acid* (**10**) Gum (12 mg), IR ν_{max}^{NaCl} cm^{-1} 3500, 3100, 2980, 2940, 2880, 1772, 1740 (sh), 1720, 1460, 1258, 1200, 1180, 1118, 1030, 982, 813 EIMS (probe, 70 eV) *m/z* (rel int) 280 $[M-C_4H_7O_2+H]^+$ (0 85), 262 $[M-C_4H_8O_3]^+$ (1 14), 232 $[M-C_4H_8O_3-CH_2O]^+$ (31 62), 217 $[M-C_4H_8O_3-COOH]^+$ (54 69), 204 $[M-C_4H_8O_3-C_2H_2O_2]^+$ (82 81), 199 (36 51), 189 (50 62), 161 (43 61), 122 (100), 105 (34 81), 87 $[C_4H_7O_2]^+$ (17 74) CIMS (CH_4, 0 5 torr, direct probe) *m/z* (rel int) 367 $[M+H]^+$ (2 1), 337 $[M+H-CH_2O]^+$ (84 6), 251 $[M+H-C_4H_7O_2-CH_2O+H]^+$ (100), 233 $[M+H-C_4H_8O_3-CH_2O]^+$ (53 42)

1-β-*Hydroxy*-8-O-(4′-*hydroxybutyroyl*)-*onopordic acid* (**11**) Gum (9 mg), IR ν_{max}^{NaCl} cm^{-1} 3450, 3105, 3020, 2980, 2940, 2880, 1770, 1730, 1720 (sh), 1670 (sh), 1455, 1260, 1180, 1120, 1090, 1020, 975, 815 EIMS (probe, 70 eV) *m/z* (rel int) 279 $[M-C_4H_8O_3+H]^+$ (1 34), 277 $[M-C_4H_7O_2-H_2O]^+$ (1 19), 248 $[M-C_4H_8O_3-CH_2O]^+$ (27 38), 230 $[M-C_4H_8O_3-CH_2O-H_2O]^+$ (22 31), 215 (19 43), 186 (100), 161 (42 33), 105 (35 89), 87 $[C_4H_7O_2]^+$ (26 34) CIMS (isoC$_4$H$_{10}$, 0 5 torr, direct probe) *m/z* (rel int) 383 $[M+H]^+$ 1 22, 353 $[M+H-CH_2O]^+$ (100), 267 $[M+H-C_4H_7O_2-CH_2O+H]^+$ (59 19), 249 $[M+H-C_4H_8O_3-CH_2O]^+$ (34 48)

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