Further New Secoatisane Diterpenoids from the Chinese Mangrove *Excoecaria agallocha* L.

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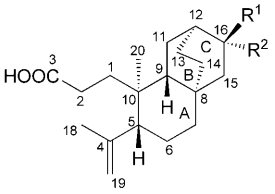
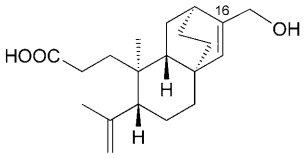
Four new 3,4-seco-*ent*-atisane diterpenoids, agallochaols G–J (**1–4**), were isolated from the stems and leaves of the Chinese mangrove *Excoecaria agallocha* L. Their structures were established on the basis of detailed spectroscopic analysis, chemical evidence, and by comparison with the literature data of related compounds.

Introduction. The mangrove *Excoecaria agallocha* L.(Euphorbiaceae) is a rich source of diterpenoids with different skeletons [1–5]. We previously reported the isolation and structure elucidation of the new compounds agallochaols A–F from the title plant [6][7]. During our continuing search for medicinal agents from mangroves, we now report the isolation and structure elucidation of four additional new minor diterpenoids, agallochaols G–J (**1–4**).



	R^1	R^2
1	Me	OH
2	CH_2OH	OH
3	CH_2OH	H
5	OH	CH_2OH
6	OH	Me



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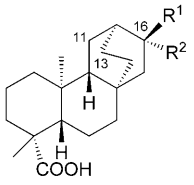
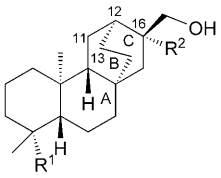
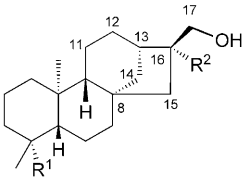


	R^1	R^2
7	Me	OH
8	OH	Me



	R^1	R^2
9	CHO	OH
11	COOH	H



	R^1	R^2
10	CHO	OH
12	COOH	H

Results and Discussion. – The usual workup [6] of the AcOEt-soluble fraction of the MeOH extract of the stems and leaves of *E. agallocha* yielded the new compounds **1**–**4**. All of them demonstrated considerable spectroscopic analogy with the previously reported agallochaol C (**5**) [7] and excoacarin V3 (**6**) [7][8], which possess a common seco-*ent*-atisane skeleton, and differing from each other only by either the oxidation or reduction at C(16). The NMR spectra of **1**–**4** displayed each a set of typical signals due to COOH and isopropenyl groups, characteristic for secoatisane diterpenoids. The *ent* configuration of compounds **1**–**4** was tentatively assumed to be the same as in **5** [7] and **6** [8] from the co-occurrence and close similarity of their structures and based on their negative sign of optical rotation.

Agallochaol G (**1**) was isolated as a colorless oil, and its molecular formula was deduced to be $C_{20}H_{32}O_3$ from the ESI-MS quasi-molecular ion peak at *m/z* 343 ($[M+Na]^+$), and based on the ^{1}H- and ^{13}C-NMR spectra (*Tables 1* and *2*, resp.). The IR spectrum showed absorption bands assignable to an OH (3427) and a C=O group (1708 cm^{-1}), as well as a 1,1-disubstituted alkene (1640, 806 cm^{-1}). The presence of a COOH and an isopropenyl group was also evident from the ^{1}H- and ^{13}C-NMR data. The COOH group was further confirmed by treatment of **1** with diazomethane affording the corresponding methyl ester. Furthermore, the 3- and 5-positions of the COOH and the isopropenyl group, respectively, were secured by the HMBC correlations (*Figure*) between the C=O resonance at δ(C) 179.6 and CH_2(2) at δ(H) 2.16/2.37; between C(4) at δ(C) 147.3 and Me(18) at δ(H) 1.74, H–C(5) at 1.90, and CH_2(19) at 4.67/4.86, respectively; and between C(5) at δ(C) 51.2 and H–C(9) at δ(H) 1.10, Me(20) at 0.97, and Me(18) at 1.74, respectively. In addition, other long-range correlations for the quaternary C-atoms C(8), C(10), and C(16), and for the tertiary ones (C(9) and C(12)), were observed in the HMBC spectrum.

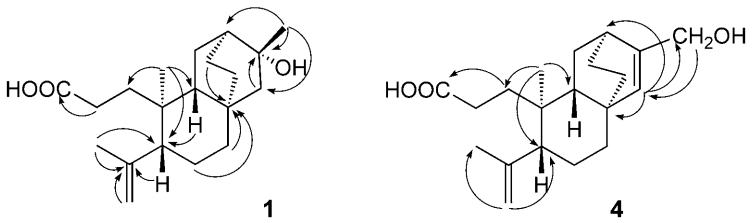


Figure. *Key HMBC correlations for* **1** *and* **4**

The above-mentioned evidence clearly suggested that **1** is a secoatisane-type diterpene. Comparison of the ^{1}H- and ^{13}C-NMR data revealed strong similarities between **1** and the co-occurring excoacarin V3 (**6**) [7][8]. In fact, **1** was found to differ from **6** only by the configuration at C(16) (epimers). The ^{13}C-NMR resonances for C(11) and C(13) of **1** were shifted upfield (from δ(C) 23.3 to 21.8) and downfield (from 23.8 to 25.3), respectively, relative to those of the corresponding C-atoms of **6**. These differences could be rationalized by the γ-gauche effect due to the Me group at C(16) [9]. The epimeric relationship between **1** and **6** was further confirmed by comparison of their ^{13}C-NMR data with those of the model epimers **7** and **8** [9].

Table 1. *^{1}H-NMR Data of Compounds* **1**–**4**. At 400 MHz; δ in ppm. Assignments based on ^{1}H,^{1}H-COSY, HMQC, HMBC, and NOESY experiments (see text).

Position	**1**[a])	**2**[b])	**3**[a])	**4**[a])
H_a–C(1)	1.53–1.55 (*m*)	1.44–1.46 (*m*)	1.55–1.57 (*m*)	1.54–1.57 (*m*)
H_b–C(1)	1.53–1.55 (*m*)	1.44–1.46 (*m*)	1.55–1.57 (*m*)	1.54–1.57 (*m*)
H_a–C(2)	2.15–2.18 (*m*)	2.07–2.09 (*m*)	2.21–2.24 (*m*)	2.14–2.17 (*m*)
H_b–C(2)	2.36–2.39 (*m*)	2.26–2.29 (*m*)	2.39–2.41 (*m*)	2.38–2.41 (*m*)
H–C(5)	1.89–1.92 (*m*)	1.88–1.90 (*m*)	1.92–1.94 (*m*)	2.02–2.04 (*m*)
H_α–C(6)	1.32–1.35 (*m*)	1.28–1.30 (*m*)	1.32–1.34 (*m*)	1.33–1.35 (*m*)
H_β–C(6)	1.77–1.80 (*m*)	1.88–1.90 (*m*)	1.73–1.75 (*m*)	1.54–1.56 (*m*)
H_α–C(7)	1.34–1.38 (*m*)	1.34–1.36 (*m*)	1.30–1.32 (*m*)	1.77–1.80 (*m*)
H_β–C(7)	1.06–1.10 (*m*)	1.05–1.08 (*m*)	1.10–1.12 (*m*)	1.59–1.61 (*m*)
H–C(9)	1.08–1.10 (*m*)	1.00–1.03 (*m*)	1.30–1.32 (*m*)	1.15–1.17 (*m*)
H_α–C(11)	1.33–1.35 (*m*)	1.28–1.30 (*m*)	1.32–1.34 (*m*)	1.34–1.36 (*m*)
H_β–C(11)	2.02–2.05 (*m*)	1.95–1.97 (*m*)	1.66–1.68 (*m*)	1.80–1.83 (*m*)
H–C(12)	1.53–1.55 (*m*)	1.74–1.76 (*m*)	1.70–1.72 (*m*)	2.49–2.51 (*m*)
H_α–C(13)	1.53–1.55 (*m*)	1.46–1.47 (*m*)	1.46–1.48 (*m*)	1.48–1.51 (*m*)
H_β–C(13)	1.68–1.38 (*m*)	1.28–1.30 (*m*)	1.26–1.28 (*m*)	1.33–1.35 (*m*)
H_α–C(14)	1.83–1.85 (*m*)	1.85–1.87 (*m*)	1.86–1.88 (*m*)	2.00–2.02 (*m*)
H_β–C(14)	1.06–1.08 (*m*)	1.06–1.08 (*m*)	0.87–0.86 (*m*)	0.82–0.85 (*m*)
H_α–C(15)	1.20–1.23 (*m*)	0.96–0.98 (*m*)	0.77–0.79 (*m*)	–
H_β–C(15)	1.37–1.40 (*m*)	1.18–1.20 (*m*)	1.30–1.32 (*m*)	–
H–C(15)	–	–	–	5.85 (br. *s*)
H–C(16)	–	–	1.86–1.88 (*m*)	–
Me(17)	1.29 (*s*)	–	–	–
H_a–C(17)	–	3.47 (*d*, $J=11.4$)	3.52 (*d*, $J=7.1$)	4.15 (br. *s*)
H_b–C(17)	–	3.32 (*d*, $J=11.4$)	3.53 (*d*, $J=7.1$)	4.15 (br. *s*)
Me (18)	1.74 (*s*)	1.70 (*s*)	1.74 (*s*)	1.75 (*s*)
H_a–C(19)	4.67 (br. *s*)	4.64 (br. *s*)	4.67 (br. *s*)	4.69 (br. *s*)
H_b–C(19)	4.86 (br. *s*)	4.78 (br. *s*)	4.85 (br. *s*)	4.86 (br. *s*)
Me(20)	0.97 (*s*)	0.94 (*s*)	0.97 (*s*)	1.00 (*s*)

[a]) In $CDCl_3$, referencing to $CHCl_3$ (δ(H) 7.26). [b]) In $CD_3OD/CDCl_3$, referencing to CH_3OH (δ(H) 3.30).

From the above data, the structure of agallochaol G (**1**) was determined as 16-*epi*-excoacarin V3, which corresponds to 16α-hydroxy-3,4-seco-*ent*-atis-4(19)-en-3-oic acid.

Agallochaol H (**2**) was assigned the molecular formula $C_{20}H_{32}O_4$ by HR-ESI-MS (*m/z* 359.2204 ($[M+Na]^+$)), the same as for compound **5**. In the ^{1}H-NMR spectrum of **2**, signals were present for two Me groups (δ(H) 1.70, 0.94 (2*s*)), an OCH_2 function (δ(H) 3.32, 3.47 (2*d*, $J=11.4$ Hz each)), and two olefinic H-atoms (δ(H) 4.64, 4.78 (2 br. *s*)). The ^{13}C-NMR (DEPT) spectra showed the presence of two Me, ten CH_2, and three CH groups, as well as five quaternary C-atoms (*Table 2*). By comparison of the ^{13}C-NMR data of **2** with those of **5**, only C(11) was found to differ in chemical shift (δ(C) 21.3 for **2** *vs.* 24.5 for **5**). Again, this difference was attributed to the γ-gauche effect, in this case exerted by the β-oriented CH_2OH group at C(16) on C(11). Therefore, these two compounds only differed in the configuration at C(16), the other parts being identical.

From the above data, the structure of agallochaol H (**2**) was derived as 16-*epi*-agallochaol C, which corresponds to 16α,17-dihydroxy-3,4-seco-*ent*-atis-4(19)-en-3-oic acid.

Table 2. *^{13}C-NMR Data of Compounds* **1**–**6**, **9**, and **11**. At 100 MHz; δ in ppm. Assignments based on ^{1}H,^{1}H-COSY, HMQC, and HMBC experiments.

Position	**1**[a])	**2**[b])	**3**[c])	**4**[c])	**5**[c])	**6**[a])	**9** [10]	**11** [10]
1	33.4 (*t*)	33.4 (*t*)	33.3 (*t*)	34.4 (*t*)	35.5 (*t*)	33.0 (*t*)	39.8 (*t*)	40.7 (*t*)
2	28.6 (*t*)	28.5 (*t*)	28.6 (*t*)	28.0 (*t*)	30.1 (*t*)	27.6 (*t*)	18.5 (*t*)	19.1 (*t*)
3	179.6 (*s*)	177.0 (*s*)	179.6 (*s*)	178.8 (*s*)	179.0 (*s*)	177.7 (*s*)	34.4 (*t*)	37.8 (*t*)
4	147.3 (*s*)	147.2 (*s*)	147.5 (*s*)	147.3 (*s*)	149.5 (*s*)	147.5 (*s*)	48.5 (*s*)	43.7 (*s*)
5	51.2 (*d*)	50.7 (*d*)	51.1 (*d*)	51.0 (*d*)	52.6 (*d*)	50.4 (*d*)	56.7 (*d*)	57.0 (*d*)
6	24.5 (*t*)	24.3 (*t*)	24.6 (*t*)	26.8 (*t*)	26.4 (*t*)	24.6 (*t*)	18.4 (*t*)	22.4 (*t*)
7	38.3 (*t*)	38.0 (*t*)	38.9 (*t*)	36.3 (*t*)	40.0 (*t*)	38.1 (*t*)	42.0 (*t*)	41.6 (*t*)
8	33.6 (*s*)	32.4 (*s*)	31.0 (*s*)	37.2 (*s*)	34.5 (*s*)	33.5 (*s*)	44.6 (*s*)	44.8 (*s*)
9	42.7 (*d*)	42.5 (*d*)	43.3 (*d*)	44.7 (*d*)	44.7 (*d*)	41.9 (*d*)	55.4 (*d*)	55.3 (*d*)
10	39.6 (*s*)	39.4 (*s*)	39.7 (*s*)	39.3 (*s*)	41.2 (*s*)	39.3 (*s*)	40.7 (*s*)	39.6 (*s*)
11	21.8 (*t*)	21.3 (*t*)	21.3 (*t*)	24.8 (*t*)	24.5 (*t*)	23.3 (*t*)	20.2 (*t*)	18.9 (*t*)
12	37.7 (*d*)	31.5 (*d*)	25.9 (*d*)	31.9 (*d*)	33.7 (*d*)	37.5 (*d*)	45.5 (*d*)	38.2 (*d*)
13	25.3 (*t*)	24.2 (*t*)	28.9 (*t*)	28.4 (*t*)	24.7 (*t*)	23.8 (*t*)	37.5 (*t*)	37.2 (*t*)
14	26.9 (*t*)	27.3 (*t*)	28.4 (*t*)	27.7 (*t*)	28.7 (*t*)	26.8 (*t*)	26.1 (*t*)	31.4 (*t*)
15	57.3 (*t*)	51.7 (*t*)	43.5 (*t*)	136.3 (*d*)	53.9 (*t*)	56.1 (*t*)	53.2 (*t*)	45.0 (*t*)
16	72.3 (*s*)	74.0 (*s*)	38.9 (*d*)	143.8 (*s*)	75.5 (*s*)	73.3 (*s*)	81.8 (*s*)	43.3 (*d*)
17	30.7 (*q*)	68.4 (*t*)	66.6 (*t*)	64.1 (*t*)	70.1 (*t*)	30.1 (*q*)	66.4 (*t*)	67.5 (*t*)
18	23.4 (*q*)	23.5 (*q*)	23.5 (*q*)	23.4 (*q*)	24.6 (*q*)	23.7 (*q*)	24.3 (*q*)	29.0 (*q*)
19	113.5 (*t*)	113.1 (*t*)	113.4 (*t*)	113.5 (*t*)	114.4 (*t*)	113.2 (*t*)	205.7 (*s*)	183.7 (*s*)
20	17.6 (*q*)	17.4 (*q*)	17.7 (*q*)	17.8 (*q*)	18.9 (*q*)	17.9 (*q*)	n.r.[d])	15.6 (*q*)

[a]) In $CDCl_3$; referencing to $CDCl_3$ (δ(C) 77.0). [b]) In $CD_3OD/CDCl_3$; referencing to CD_3OD (δ(C) 49.0). [c]) In CD_3OD; referencing to CD_3OD (δ(C) 49.0). [d]) Not reported.

A literature search revealed that, formally, the rings *A*–*C* of **2** correspond to those of the known compound **9**, a metabolite previously isolated from *Trewia nudiflora* [10]. However, careful comparison of their NMR data revealed apparent differences. In fact, the ^{13}C-NMR resonances for C(8), C(9), C(12), C(13), and C(16) of **2** and those of **9** are quite different (*Table 2*). This finding raises the question as whether the proposed structure of **9** is correct. It was reported that the ^{13}C-NMR resonance of C(16) is characteristic for distinguishing *ent*-kaurane and *ent*-atisane diterpenes [9]. Generally, C(16) resonates at δ(C) 78–82 for the former, and at 72–75 ppm for the latter. In the light of this empirical data, it seems that **9** should be revised as **10**, with an *ent*-kaurane skeleton instead of an atisane framework.

Agallochaol I (**3**) had the molecular formula $C_{20}H_{32}O_3$, as established by ESI-MS and ^{13}C-NMR experiments; this is 16 mass units less than in the case of **2**. Careful comparison of the ^{13}C-NMR data of **3** with those of **2** indicated that an oxygenated quaternary C-atom, assignable to C(16) in **2**, was replaced by a methine group at δ(C) 38.9 in **3**. Further, two signals resonating at δ(C) 25.9 and 43.5, assignable to C(12) and C(15), were consequently shifted upfield. From these data, the structure of compound **3** was determined as 17-hydroxy-3,4-seco-*ent*-atis-4(19)-en-3-oic acid.

Interestingly, like for compound **2**, the ^{13}C-NMR signals for C(8), C(9), C(12), C(13) and C(16) of **3** were obviously different from those of 17-hydroxy-*ent*-atisan-19-oic acid (**11**) (*Table 2*) although formally sharing the same partial structure (rings *A*–*C*) [10].

This clearly suggests that, as in the case of **2** *vs.* **9**, the structure of **11** should be depicted as **12** (*i.e.*, 17-hydroxy-*ent*-kaurane-19-oic acid).

Agallochaol J (**4**) displayed a HR-ESI-MS peak at *m/z* 341.2088 ($[M+Na]^+$), two mass units lower than in the case of **3**. The ^{1}H- and ^{13}C-NMR spectra of **4** (*Tables 1* and *2*, resp.) revealed a close relationship with **3**. An overall comparison of the pertinent NMR data revealed that the main difference between these two compounds was at ring *C*. The ^{13}C-NMR (DEPT) experiment implied an unsaturation at C(15) (trisubstituted C=C bond), as deduced by the HMBC correlations between H–C(15) at δ(H) 5.85 (br. *s*) and C(8), C(12), and C(17) (δ(C) 37.2, 31.9, and 64.1, resp.); and between CH_2(17) at δ(H) 4.15 (br. *s*) and both C(15) and C(16) (δ(C) 136.3 and 143.8, resp.) (see *Figure*). The presence of the $\Delta^{15(16)}$ unsaturation was inferred from the downfield shifts of C(8) (from δ(C) 31.0 to 37.2) and C(12) (from 25.9 to 31.9). From these data, agallochaol J (**4**) was identified as 17-hydroxy-3,4-seco-*ent*-atis-15-en-3-oic acid.

The cytotoxic activities of agallochaol H-J (**1**–**4**) against the growth of tumor cell lines HL-60 (human acute myeloid leukemia) and A549 (human lung adenocarcinoma) were evaluated. Unfortunately, all tested compounds were inactive at a concentration of 20 μg/ml. Other tests such as antifungal and antibiotic assays of these new compounds are currently ongoing.

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Experimental Part

General. Column chromatography (CC): silica gel (100–200 and 200–300 mesh; *Qing Dao Hai Yang Chemical Group Co.*). TLC: precoated silica-gel plates (*G60 F_{254}*; *Yan Tai Zi Fu Chemical Group Co.*). Optical rotation: *Perkin-Elmer-341 Polarimeter*. IR spectra: *Nicolet Magna FT-IR 750* spectrometer; KBr pellets; in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker DRX-400* spectrometer; at 400 or 100 MHz for ^{1}H and ^{13}C resp.; chemical shifts δ in ppm rel. to residual $CHCl_3$ (δ(H) 7.26, δ(C) 77.0) or CD_3OD (δ(H) 3.30, δ(C) 49.0), coupling constants *J* in Hz; all assignments were supported by ^{1}H,^{1}H-COSY, HMQC, and HMBC experiments. ESI- and HR-ESI-MS: *Q-TOF Micro LC-MS-MS* spectrometer; in *m/z*.

Plant Material. *Excoecaria agallocha* was collected in Guangxi Province, P. R. China, in 1999, and identified by Associate Prof. *Jin-Gui Shen*, Shanghai Institute of Materia Medica, Chinese Academy of Sciences (SIMM-CAS). A voucher specimen (No. 99PL-05) was deposited at SIMM-CAS.

Extraction and Isolation. The dried ground stems and leaves (4.0 kg) of *E. agallocha* were extracted with MeOH (3 × 5 l), and the MeOH extract was concentrated *in vacuo*. The resulting residue (410 g) was dissolved in H_2O (1 l) and extracted, in this order, with petroleum ether (PE), AcOEt, and BuOH. The AcOEt extract was evaporated *in vacuo* to give a residue (100 g), which was separated by CC (SiO_2, 100–200 mesh, 1.5 kg; PE/AcOEt 90 : 10, 80 : 20, 70 : 30, 60 : 40, 50 : 50, then Me_2CO). The eluted material was combined to yield 16 fractions (*Fr.*) on the basis of TLC evidence. *Fr. 9* and *10* were further purified by CC (1. SiO_2, $CHCl_3$/MeOH; 2. *Sephadex LH-20*, MeOH) to yield pure **1** (11 mg), **2** (10 mg), **3** (7 mg), **4** (3 mg).

Agallochaol G (=*16α-Hydroxy-3,4-seco*-ent-*atis-4(19)-en-3-oic Acid*; **1**). Colorless oil. $[\alpha]_D^{20} = -17$ ($c = 0.7$, $CHCl_3$). IR: 3427, 2929, 1708, 1640, 806. ^{1}H- and ^{13}C-NMR: see *Tables 1* and *2*, resp. ESI-MS: 343 ($[M+Na]^+$).

Methyl 16α-Hydroxy-3,4-seco-ent-*atis-4(19)-en-3-oate.* Compound **1** (2.0 mg) was treated under standard conditions with CH_2N_2 at r.t. to afford the corresponding Me ester (1.8 mg) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.96 (*s*, Me(20)); 1.29 (*s*, Me(17)); 1.58 (br. *s*, Me(18)); 2.12–2.16 (*m*, H_a–C(2)); 2.35–2.38 (*m*, H_b–C(2)); 3.65 (br. *s*, MeO); 4.67 (br. *s*, H_a–C(19)); 4.86 (br. *s*, H_b–C(19)). ESI-MS: 357 ($[M+Na]^+$).

Agallochaol H (=*16α,17-Dihydroxy-3,4-seco*-ent-*atis-4(19)-en-3-oic Acid*; **2**). Colorless oil. $[\alpha]_D^{20} = -7$ ($c = 0.38$, MeOH/$CHCl_3$ 4:1). IR: 3409, 2954, 1708, 1637, 891. ^{1}H- and ^{13}C-NMR: see *Tables 1* and *2*, resp. ESI-MS: 359 ($[M+Na]^+$), 695 ($[2M+Na]^+$). HR-ESI-MS: 359.2204 ($[M+Na]^+$; $C_{20}H_{32}NaO_4^+$; calc. 359.2207).

Agallochaol I (=*17-Hydroxy-3,4-seco*-ent-*atis-4(19)-en-3-oic Acid*; **3**). Colorless oil. $[\alpha]_D^{20} = -7.1$ ($c = 0.33$, $CHCl_3$). IR: 3410, 2952, 1708, 1456, 892, 757. ^{1}H- and ^{13}C-NMR: see *Tables 1* and *2*, resp. ESI-MS: 319 ($[M-H]^-$), 639 ($[2M-H]^-$).

Agallochaol J (=*17-Hydroxy-3,4-seco*-ent-*atis-15-en-3-oic Acid*; **4**). Colorless oil. $[\alpha]_D^{20} = -14$ ($c = 0.23$, $CHCl_3$). IR: 3423, 2924, 1705, 1637, 893. ^{1}H- and ^{13}C-NMR: see *Tables 1* and *2*, resp. ESI-MS: 341 ($[M+Na]^+$). HR-ESI-MS: 341.2088 ($[M+Na]^+$, $C_{20}H_{32}NaO_3^+$; calc. 341.2093).

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