New 6/8/6-Taxanes Isolated from the Heartwood of *Taxus cuspidata*

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Two new natural taxanes were isolated from the heartwood of *Taxus cuspidata*. The structures were established as *rel*-(2*α*,5*α*,7*β*,9*α*,10*β*,12*α*)-7,9-bis(acetyloxy)-2-(benzoyloxy)-11,12-epoxy-1,5-dihydroxy-10-[(hydroxyacetyl)oxy]tax-4(20)-en-13-one (**1**), and (2*α*,5*α*,10*β*,14*β*)-taxa-4(20),11-diene-2,5,10,14-tetrol 2-acetate (**2**) on the basis of spectroscopic analysis.

Introduction. – Plants of the genus *Taxus* (Taxaceae) are a rich source of biologically active diterpenoids belonging to the unique structure class of taxoids [1–3]. Paclitaxel (*Taxol*®) is one of the most potent anticancer drugs, initially isolated from the bark of Pacific (western) yew *Taxus brevifolia*, currently on the market as drug for ovarian and breast cancers and showing also promising effects for a variety of other cancers such as neck, lung, gastrointestinal, and bladder cancer. Extensive chemical investigations on the plants of the genus *Taxus* has resulted in the isolation of more than 550 taxane-type diterpenes to date, and some of them were found to possess interesting anticancer activity [1–6]. These studies have established a database and will offer interesting clues to track the biogenesis pathway of taxanes. The Japanese yew, *Taxus cuspidata*, is a low trailing shrub or tall tree mainly distributed in the northeast of China, Korea, and Japan. This yew was developed for ornamental purposes and is very popular as a decorating plant in gardens and yards in Japan and North America. Previous chemical investigations on this yew have led to the identification of more than 120 taxanes including various skeletons, but there are still new taxanes being isolated [1–3]. In our continuing search for bioactive taxanes, we have isolated previously a series of new taxanes with various skeletons from the needles of the Japanese yew [3][7]. Further investigation on the hardwood of this plant harvested in a different region in

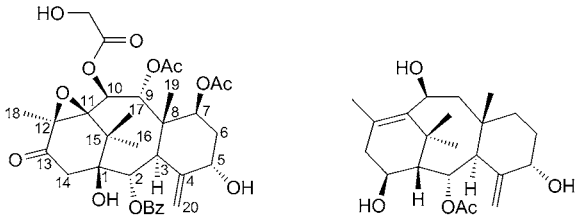

Figure. *Taxanes* **1** *and* **2** *isolated from the heartwood of* Taxus cuspidate

Japan resulted in the isolation of the two new taxanes **1** and **2** (*Fig.*[1])). A discussion of the isolation and structure characterization of these components is presented in this communication.

Results and Discussion. – Compound **1** was obtained as a colorless amorphous solid. The molecular composition of **1**, $C_{33}H_{40}O_{13}$, was established from the combined analysis of high-resolution FAB-MS (*m/z* 683.2109 ($[M+K]^+$)) and the ^{13}C-NMR spectrum (*Table 1*). The ^{1}H-NMR spectrum of **1** (*Table 1*) exhibited the three-H-atom signals due to the four tertiary Me groups at δ(H) 0.91, 1.09, 1.79, and 2.13, and two acetyl groups at relatively low field (δ(H) 2.04 and 2.05), which was verified by the observation of ^{13}C-NMR signals at δ(C) 20.7 and 169.2, and 20.7 and 169.4. A benzoyl group was indicated by the signals at δ(H) 8.01 (*d*, $J = 8.4$ Hz, 2 H), 7.47 (*t*, $J = 7.9$ Hz, 2 H), and 7.61 (*t*, $J = 7.5$ Hz, 1 H) as well as the signals at δ(C) 166.0, 130.0, 128.4, and 133.5. The presence of a (hydroxyacetyl)oxy group was also suggested by the NMR data at δ(H) 4.21 (*d*, $J = 17.2$ Hz), and 4.04 (*dd*, $J = 17.2$ and 3.8 Hz) with a large coupling constant, and δ(H) 2.38 (*d*, $J = 3.8$ Hz) as well as the signals at δ(C) 171.4 and 60.2. A couple of an isolated *AB* system with a large coupling constant was also observed at δ(H) 6.12 (*d*, $J = 11.2$ Hz, 1 H) and 5.68 (*d*, $J = 11.2$ Hz, 1 H). These signals indicated that **1** had a taxane-type skeleton [1–4]. The connectivity of the H-atoms at the taxane skeleton of **1** were determined by analysis of the ^{1}H,^{1}H-COSY plot. Interpretation of the ^{1}H- and ^{13}C-NMR and HMBC spectra permitted the positional assignment of all the functional groups. The signals at δ(H) 5.31 (*s*, 1 H) and 4.94 (*s*, 1 H), together with δ(C) 141.8 and 118.4, and δ(H) 3.37 (*d*, $J = 5.9$ Hz, 1 H), are the characteristics of an exocyclic CH_2= group and the C(3) ring junction H-atom in a taxane with a C(4)=C(20) bond [1–4]. With H–C(3) as a starting point, the connectivity from C(3) to C(2) was deduced from the ^{1}H,^{1}H-COSY experiment. The signal at δ(H) 4.36 (*dd*, $J = 2.9$ Hz, 1 H) was assigned to H–C(5). Similarly, with H–C(5) as a starting point, the spin system from C(5) to C(6) to C(7) was readily interpreted from the analysis of the ^{1}H,^{1}H-COSY data. The chemical shift of H–C(5) suggested that a free OH group was attached at C(5) [1–4]. The ^{13}C-NMR signal at δ(C) 205.3 suggested the presence of a keto group at C(13) of the taxane skeleton [1–4]. According to this, CH_2(14) displayed an *AB* system with a large coupling constant, $J_{gem} = 19.6$ Hz. The splitting pattern of CH_2(14) and the chemical shift of C(1) in the

[1]) Trivial atom numbering; for systematic names, see *Exper. Part.*

Table 1. *^{1}H- and ^{13}C-NMR Data* ($CDCl_3$, 500 and 125 MHz, resp.) *of* **1**[1]). *d* in ppm, *J* in Hz.

Position	δ(H)	δ(C)[a])	HMBC	NOESY[b])
C(1)	–	**78.8**		
H–C(2)	6.06 (*d*, *J* = 5.9)	71.0	C(1), C(8), Ph*C*OO	H–C(9)^s, Me(19)^s, Me(16)^s
H–C(3)	3.37 (*d*, *J* = 5.9)	41.1	C(1), C(5), C(8), Me(19)	H–C(7)/H–C(10)^s, H_α–C(14)^s, Me(18)^m
C(4)	–	**141.8**		
H–C(5)	4.36 (*dd*, *J* = 2.9)	74.9		H_α–C(6)^s, H_β–C(6)^s, H_a–C(20)^s
H_α–C(6)	1.97 – 2.01 (*m*)	37.0		H–C(5)^s, H–C(7)^s
H_β–C(6)	1.71 – 1.74 (*m*)			H–C(5)^s, Me(19)^s
H–C(7)	5.70 (*dd*, *J* = 11.5, 5.4)	68.6	C(5), Me(19), *C*OO–C(7)	H–C(3)^s, H_α–C(6)^s
C(8)	–	**47.1**		
H–C(9)	6.12 (*d*, *J* = 11.2)	74.8	C(7), C(8), C(10), Me(19), *C*OO–C(9)	H–C(2)^s, Me(16)^s, Me(19)^s
H–C(10)	5.68 (*d*, *J* = 11.2)	72.9	C(9), C(11), C(12), C(15), *C*OO–C(10)	H–C(3)^s, H–C(7)^s, Me(18)^s
C(11)	–	**64.4**		
C(12)	–	**62.4**		
C(13)	–	**205.3**		
H_α–C(14)	3.01 (*d*, *J* = 19.6)	47.2	C(1), C(2), C(13), C(15), C(1), C(12)	H–C(3)^s, H_β–C(14)^s
H_β–C(14)	2.51 (*d*, *J* = 19.6)			H_α–C(14)^s, Me(17)^s
C(15)	–	**44.0**		
Me(16)	1.79 (*s*)	20.2	C(1), C(11), C(15), Me(17)	H–C(2)^s, H–C(9)^s, Me(17)^s
Me(17)	0.91 (*s*)	24.5	C(1), C(11), C(15), Me(16)	H_β–C(14)^s, Me(16)^s
Me(18)	2.13 (*s*)	14.3	C(11), C(12), C(13)	H–C(3)^m, H–C(10)^s
Me(19)	1.09 (*s*)	13.2	C(3), C(7), C(8), C(9)	H–C(2)^s, H_β–C(6)^s, H–C(9)^s
H_a–C(20)	5.31 (*s*)	118.4	C(3)	H–C(5)^s, H_b–C(20)^s
H_b–C(20)	4.94 (*s*)		C(3), C(4), C(5)	Me(19)^m, H_a–C(20)^s
*Me*COO–C(9)	2.05 (*s*)	20.7, **169.4**	*C*OO–C(9)	
*Me*COO–C(7)	2.04 (*s*)	20.7, **169.2**	*C*OO–C(7)	
PhCOO–C(2): CO		**166.0**		
C(1)		n.d.[c])		
H–C(2′,6′)	8.01 (*d*, *J* ≈ 8.4))	130.0		
H–C(3′,5′)	7.47 (*t*, *J* ≈ 7.9)	128.4		
H–C(4′)	7.61 (*t*, *J* ≈ 7.5)	133.5		
$OHCH_2COO$–C(10): CO		**171.4**		
CH_2O	4.21 (br. *d*, *J* = 17.2, H_a), 4.04 (br. *dd*, *J* = 17.2, 3.8, H_b)	60.2		$H_b(CH_2O)^s$, OH^w, H_a–CH–O^s, OH^w
OH	2.38 (br., *d*, *J* = 3.8)			CH_2O

[a]) The δ(C) were extracted from the HMQC experiment (± 0.2 ppm). The bold-type values are those of quaternary C-atoms who's chemical shifts were obtained from the HMBC experiment (± 0.2 ppm).[b]) NOESY intensities are marked by superscripts as strong (s), medium (m), and weak (w).[c]) Not detected.

^{13}C-NMR spectrum suggested that an OH group was positioned at C(1). However, the downfield chemical shift of C(13) and the lack of further olefinic C-atoms in the ^{13}C-NMR spectrum indicated that the endocyclic C(11)=C(12) bond which usually occurrs in most taxoids [1–4], was either oxidized or reduced. The ^{13}C-NMR spectrum of **1** showed two oxygenated tertiary C-atoms at δ(C) 64.4 and 62.4, and these two signals were assigned to C(11) and C(12), respectively, from the HMBC spectrum. Judging from the ^{13}C-NMR spectrum and molecular formula, only one O-atom and one insaturation equivalent were left as required by the molecular composition, thus the presence of an epoxy group at C(11) and C(12) was suggested [1–4]. The unusual upfield shift of H–C(10) was caused by the magnetic anisotropy effect of the 11,12-epoxy ring. H–C(10) in 11,12-epoxytaxanes is similar to H–C(5) in 4,20-epoxytaxanes, both of them are dramatically upfield-shifted comparing with the corresponding H-atoms in taxa-4(20),11-dienes [1–4]. The 11,12-epoxytaxanes, unlike other 4,20-epoxytaxanes, are rare in the nature. Chemical epoxidation of the C(11)=C(12) bond is more difficult than that of C(4)=C(20) [8]; the isolation of an 11,12-epoxytaxane with a C(4)=C(20) bond indicated that there are some selective enzymes in the biosynthesis of taxanes in the plants. The relative configuration of **1** was established by the NOESY data, chemical shifts, and their coupling constants. Thus the coupling constant between H–C(9) and H–C(10) ($J = 11.2$ Hz) and the observed NOESY correlations H–C(2)/H–C(9) and H–C(9)/Me(16) established a chair-boat conformation for ring *B*, which is the typical conformation of natural taxoids. The β-orientation of H–C(2) and H–C(9) were assigned by the NOESY correlations H–C(2)/Me(19), Me(19)/H_b–C(20), and H–C(9)/Me(16). The α-orientation of H–C(10) was confirmed by the NOESY correlation H–C(10)/Me(18). OH–C(5) was supposed to be α-oriented from the viewpoint of biosynthesis, as in most natural taxoids [1–4]. The β-orientation of the epoxy group at C(11) and C(12) was established by the NOESY correlations Me(18)/H–C(3) and H–C(10). The upfield chemical shift of Me(17) due to the presence of the 11,12-epoxy ring and the γ-effect between C(16) and C(12) also suggested that the epoxy group had the β-orientation [4]. From these data, the structure of **1** was established as *rel*-(2α,5α,7β,9α,10β,12α)-7,9-bis(acetyloxy)-2-(benzoyloxy)-11,12-epoxy-1,5-dihydroxy-10-[(hydroxyacetyl)oxy]tax-4(20)-en-13-one[1]).

Compound **2** was obtained as amorphous solid. The molecular composition of **2**, $C_{22}H_{34}O_5$, was established from the combined analysis of high-resolution FAB-MS (*m*/*z* 417.2044 ($[M+K]^+$)) and the ^{13}C-NMR spectrum (*Table 2*). Seven indices of H-atom deficiency were calculated from the molecular formula. The ^{1}H-NMR spectrum of **2** (*Table 2*) exhibited four three-H-atom signals due to the four quaternary Me groups at δ(H) 0,79, 1.21, 1.69, and 1.96, two of them (δ(H) 1.21 and 1.69) being COSY-related as geminal Me groups; and one acetyl group at δ(H) 2.07. The latter was verified by the C=O groups at δ(C) 169.6 and the Me group at δ(C) 21.6. These signals, together with its plant-origin consideration, suggested that **2** was a taxane derivative [1–3]. Analysis of the ^{1}H-, ^{13}C-, and 2D-NMR data of **2** disclosed 22 C-atom signals due to one acetyl, four oxymethines, two CH, and four CH_2 groups, to two *sp*-hybridized quaternary C-atoms and four *sp* (three fully substituted olefinic) C-atoms, and to four Me groups attached to quaternary C-atoms. These observations indicated that **2** contained three rings. The assignments of functional groups at the taxane skeleton were made on the basis of ^{1}H,^{1}H-COSY and HMBC cross-peaks, starting with the signals at δ(H) 3.14 (*d*,

Table 2. *^{1}H- and ^{13}C-NMR Data* ($CDCl_3$, 500 and 125 MHz, resp.) *of* **2**. δ in ppm, J in Hz.

Position	δ(H)	δ(C)[a])	HMBC	NOESY[b])
H–C(1)	1.72 (*d*, *J* = *2.0*)	63.4		H–C(2)^s, Me(17)^s
H–C(2)	5.40 (*dd*, *J* = 6.0, 2.0)	71.4		H–C(1)^s, H_β–C(9)^s, Me(19)^s
H–C(3)	3.14 (*d*, *J* = 6.0)	40.0	C(2), C(8), Me(19)	H_α–C(7)^w, H–C(14)^s, Me(18)^m
C(4)	–	n.d.[c])		
H–C(5)	4.17 (*dd*, *J* = 2.7)	76.5	C(3), C(20)	H_a–C(20)^s
CH_2(6)	1.68–1.72 (*m*)	31.2		
H_α–C(7)	2.00–2.03 (*m*)	33.0		H–C(3)^w, H_β–C(7)^s, H–C(10)^s
H_β–C(7)	1.05–1.09 (*m*)			H_α–C(7)^s
C(8)	–	**39.8**		
H_α–C(9)	1.60–1.63 (*m*)	47.0		H–C(2)^s, H_α–C(9)^s, Me(16)^s, Me(19)^s
H_β–C(9)	2.29 (*dd*, *J* = 14.6, 11.7)			H_β–C(9)^s, H–C(10)^s
H–C(10)	5.13 (*dd*, *J* = 11.7, 5.6)	67.5	C(9), C(12), C(15)	H_α–C(7)^w, H_β–C(9)^w, H_α–C(9)^s, Me(18)^s
C(11)	–	**137.8**		
C(12)	–	**133.9**		
H_α–C(13)	2.63 (*dd*, *J* = 18.5, 9.3)	42.1	C(1), C(14), C(11), C(12), Me(18)	H–C(3)^w, H_β–C(13)^s, H–C(14)^s, Me(18)^w
H_β–C(13)	2.43 (br. *dd*, *J* = 18.5, 5.5)			H_α–C(13)^s, Me(16)^s
H–C(14)	4.09 (*dd*, *J* = 9.3, 5.5)	67.9	C(2), C(15)	H–C(3)^s, H_α–C(13)^s
C(15)	–	**37.8**		
Me(16)	1.69 (*s*)	25.7	C(1), C(11), C(15), Me(17)	H_β–C(9)^s
Me(17)	1.21 (*s*)	31.9	C(1), C(11), C(15), Me(16)	H–C(1)^s, H_β–C(13)^s
Me(18)	1.96 (*s*)	21.1	C(11), C(12), C(13)	H–C(3)^m, H–C(10)^s, H_α–C(13)^w
Me(19)	0.79 (*s*)	22.2	C(3)/C(8), C(7), C(9)	H–C(2)^s, H_α–C(7)^w, H_β–C(9)^s, Me(16)^s, H_b–C(20)^w
H_a–C(20)	5.09 (br. *s*)	113.2		H–C(5)^s, H_b–C(20)^s
H_b–C(20)	4.78 (br. *s*)			Me(19)^w, H_a–C(20)^s
*MeCO*O–C(2)	2.07 (*s*)	21.6, **169.6**	*C*OO–C(2)	

[a]) – [c]) See *Footnotes a – c* in *Table 1*.

$J = 6.0$ Hz, 1 H), which is typical of the H_α–C(3) ring-junction H-atom in the taxane diterpenes [1–4]. Accordingly, the signal at δ(H) 5.40 (*dd*, $J = 6.0$, 2.0 Hz, 1 H) was assigned to H–C(2). The chemical shift of H–C(2) suggested that an acetyloxy group was located at C(2); therefore, the signal at δ(H) 1.72 (*d*, $J = 2.0$ Hz, 1 H) was attributed to H–C(1). Continuing this spin system, the signals at δ(H) 4.09 (*dd*, $J = 9.3$, 5.5 Hz, 1 H), 2.63 (*dd*, $J = 18.5$, 9.3 Hz, 1 H), and 2.43 (*dd*, $J = 18.5$, 5.5 Hz, 1 H) were readily assigned to H–C(14) and H_α- and H_β–C(13), respectively, from the ^{1}H,^{1}H-COSY experiment. The chemical shift of H–C(14) implied that a free OH group was positioned at C(14). Similarly, the signal at δ(H) 4.17 (*dd*, $J = 2.7$ Hz, 1 H) was the characteristic signal of H_β–C(5) of a taxane, which showed three-bond correlations with C(3) and C(20) in the HMBC experiment [1–4]. The chemical shift of H_β–C(5) implied that a free OH group was connected to C(5). With H_β–C(5) as reference, the spin system from H–C(5) to H–C(6) and H–C(7) was readily deduced from the ^{1}H,^{1}H-COSY data. The signal at δ(H) 5.13 (*dd*, $J = 11.7$, 5.6 Hz, 1 H), which exhibited a long-range correlation with C(9), C(12), and C(15), was assigned to H–C(10) and a free OH group was connected to C(10). With H–C(10) as reference, H_α- and H_β–C(9) were easily assigned. The remaining coupling system of an exocyclic CH_2= group at δ(H) 5.09 and 4.78 (2 br. *s*, each 1 H) was attributed to H_a–C(20) and H_b–C(20), respectively. The assignments of the C-atoms were achieved by analysis of the HMQC and HMBC spectra. The configuration of **2** was determined on the basis of coupling constants and NOESY data. The structure of **2** was thus elucidated as (2α,5α,10β,14β)-taxa-4(20),11-diene-2,5,10,14-tetrol 2-acetate. The characteristics of 14-substituted taxanes is that C(1) resonates at an unusual downfield shift (δ(C) 59–65) [9] compared corresponding 13-substituted taxanes (δ(C) < 52). Compound **2** was reported as the chemical reaction product of (2α,5α,10β,14β)-taxa-4(20),11-diene-2,5,10,14-tetrol tetraacetate with $NaHCO_3$ in MeOH [9].

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Experimental Part

General. Flash column chromatography (CC): Silica gel *60* (SiO_2, 230–400 mesh; *EM Science*). TLC: Silica gel *60* F_{254} (SiO_2, 0.25 mm or 0.5 mm; *EM Science*). Prep. HPLC: *Waters Delta Prep 3000*, *Waters UV 486* tunable absorbance detector (210 nm), and *Whatman Partisil 10 ODS-2 Mag-9* (9.4 × 250 mm); t_R in min Optical rotation: *Jasco DIP-370*. NMR Spectra: *Bruker Avance-500*; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Vacuum Generators ZAB-HS*; in *m*/*z*.

Plant Material. The heartwood of *Taxus cuspidata* was collected in the autumn of 1997 in Toyama Prefecture in the west of Japan. The botanical identification was made by Prof. *T. Oritani* at Toyama Prefectural University, Toyama, Japan. Several voucher specimens have been deposited with the laboratory of applied bioorganic chemistry, Graduate School of Agricultural Sciences, Tohoku University, Japan. The access number is 1997-10-1.

Extraction, Isolation, and Purification of Taxanes. The air-dried heartwood of *Taxus cuspidata* was chipped (5.74 kg) and extracted with 18 l of MeOH for two weeks at r.t. The plant residue was filtered and extracted again with fresh solvent (12 l of MeOH, total 20 l) for one week. The combined org. extracts were concentrated. H_2O (3 l) was added, and lipids were removed by stirring the mixture with hexane (3×3 l). The aq. phase was then salted (NaCl, 200 g) and extracted with CH_2Cl_2 (4×3 l). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated dark extract (55 g). A portion of the CH_2Cl_2 extract (35 g) was absorbed onto 50 g of SiO_2 and packed on a wet CC. Successive elution with MeOH/CH_2Cl_2 5 → 45% (total 15 l) yielded *Fr. D-1* to *Fr. D-44*. The *Fr. D-20* to *Fr. D-25* were combined (2.2 g) according to their TLC behavior and subjected to CC (SiO_2 (100 g), hexane/acetone): *Fr. D-20-1* to *Fr. D-20-9*. The combined *Fr. D-20-8* and *Fr. D-20-9* (0.33 g) were applied to prep. HPLC (within 50 min, linear gradient MeCH/H_2O 25 → 100%, 3 ml/min): **1** (1.8 mg, t_R 33.4). The combined *Fr. D-30* to *Fr. D-33* (4 g) were subjected to CC (SiO_2 (150 g), hexane/acetone): *Fr. D-30-1* to *Fr. D-30-12*. The combined *Fr. D-30-10* and *Fr. D-30-11* (0.56 g) were applied to prep. HPLC (within 50 min, linear gradient MeCN/H_2O (25 → 100%, 3 ml/min): **2** (2.1 mg, t_R 23.4).

rel-*(2α,5α,7β,9α,10β,12α)-7,9-Bis(acetyloxy)-2-(benzoyloxy)-11,12-epoxy-1,5-dihydroxy-10-[(hydroxyacetyl)oxy]tax-4(20)-en-13-one* (=*2-Hydroxyacetic Acid* rel-*(1a*R,*4*R,*5*R,*5a*S,*7*R,*9*R,*9a*R,*10*S,*11*R,*11a*S*)-9,10-Bis(acetyloxy)-5-(benzoyloxy)dodecahydro-4,7-dihydroxy-1a,9a,12,12-tetramethyl-6-methylene-2-oxo-3*H-*4,11a-methanobenzo[5,6]cyclodec[1,2-*b*]oxiren-11-yl Ester*; **1**): White amorphous solid. $[\alpha]_D = +23$ ($c = 0.050$, MeOH). NMR: *Table 1*. HR-FAB-MS: 683.2109 ($[M+K]^+$, $C_{33}H_{40}KO_{13}^+$; calc. 683.2106).

(2α,5α,10β,14β)-Taxa-4(20),11-diene-2,5,10,14-tetrol 2-Acetate (=*(3*S,*4a*S,*5*S,*6*S,*7*S,*11*S,*12a*S*)-1,2,3,4,4a,5,6,7,8,11,12,12a-Dodecahydro-9,12a,13,13-tetramethyl-4-methylene-6,10-methanobenzocyclodecene-3,5,7,11-tetrol 5-Acetate*; **2**). White amorphous solid. $[\alpha]_D = +21$ ($c = 0.050$, MeOH). NMR: *Table 2*. HR-FAB-MS: 417.2044 ($[M+K]^+$, $C_{22}H_{34}KO_5^+$; calc. 417.2043).

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