THREE NEW REARRANGED TAXANE DITERPENOIDS FROM THE BARK OF *TAXUS CHINENSIS* VAR. *MAIREI* AND THE NEEDLES OF *TAXUS CUSPIDATA*

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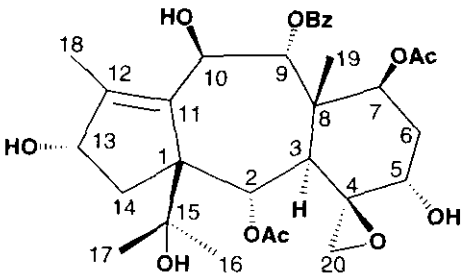
Abstract-Three new rearranged taxane diterpenoids with 5/7/6–membered ring system were isolated from the bark of *Taxus chinensis* var. *mairei* (**1** and **2**) and the needles of *T. cuspidata* (**3**). The structures of them were established as 2α,7β-diacetoxy-5α,10β,13α,15-tetrahydroxy-4β(20)-epoxy-9α-benzoyloxy-11(15→1)*abeo*tax-11-ene (**1**), 2α,4α-diacetoxy-7β-benzoyloxy-5β,20-epoxy-9α,10β,13α,15-tetrahydroxy-11(15→1)*abeo*tax-11-ene (**2**), and 4α,7β-diacetoxy-2α-benzoyloxy-5β,20-epoxy-9α,10β,13α,15-tetrahydroxy-11(15→1)*abeo*tax-11-ene (**3**) on the basis of spectral data including 2D NMR spectroscopies.

In view of the demonstrated clinical effectiveness of paclitaxel in ovarian, breast and other carcinomas, there have been intensive efforts to search for other members of the taxane group, which may either be directly active, or serve as precursors for the semisynthesis of other active analogs. This situation led more than 200 taxane diterpenoids to be isolated[1-4] and there are still great number of new taxoids be isolated.[5-9] *Taxus chinensis* var. *mairei* as a tall tree distributed in the south-east of China. In the previous studies we reported several new taxoids isolated from the bark and needles of *T. chinensis* var. *mairei*,[10-12] our continuing investigation on the bark of *Taxus chinensis* var. *mairei* and the needles of *Taxus cuspidata* resulted in the isolation of three new 11(15→1)*abeo*taxanes. A discussion of the isolation and structural characterization of these components is presented in this communication.

Compound (**1**) was isolated as a white amorphous solid in a 0.00033 % yield. IR absorptions at 3350, 1720, and 1700 cm^{-1} suggested that **1** had free hydroxy and acetoxy groups. FAB–MS gave the ion peaks at *m/z* 611 $(M+Na)^+$. HR-FAB-MS gave the formula of $C_{31}H_{40}O_{11}Na$ (611.2465; calcd 611.2466). From combined analyses of the MS, and subsequent works on the ^{1}H-NMR and ^{13}C-NMR spectra, the molecular



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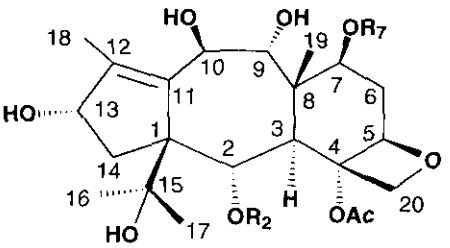

2 R_2=Ac R_7=Bz
3 R_2=Bz R_7=Ac

formula was confirmed as $C_{31}H_{40}O_{11}$. The ^{1}H-NMR spectrum of **1** showed the characteristic signals of taxoids, including singlets for four methyl groups at δ 1.07, 1.25, 1.50 and 1.71 ppm. The upfield signals of δ 2.21 (1H, d, J = 5.24 Hz) and δ 3.41 (lH, d, J = 5.24 Hz) ppm appeared as an AB system, indicative of a terminal methylene group of the epoxide ring of baccatin I type,[14] which was further verified by two ^{13}C-NMR signals at δ 59.50 and δ 49.67 ppm. **1** also showed two methylene groups, one methine group, six oxymethine groups, two quaternary carbons, two oxy-quaternary carbons, two acetyl groups, one benzoyl group and two fully substituted olefinic carbons in the ^{1}H- and ^{13}C-NMR spectra. The skeleton of compound (**1**) was deduced as an 11(15→1)*abeo*taxane, *i. e.* brevifoliol type taxane by the careful observation of the signals in the ^{1}H-NMR spectrum.[15] Two key results further supported the brevifoliol skeleton for **1**. One was that the C-1 and C-15 signals resonated at unusual positions. The signal at δ 76.65 ppm in the ^{13}C-NMR was assigned to C-15, which was confirmed by correlation with the protons of H-2 and H-14 in the HMBC spectrum. The downfield nature of this signal indicated that C-15 must be oxygenated. On the other hand, the C-1 signal, which correlated with H-3, H-10 and H-13 in the HMBC spectrum, resonated at unusually lower field (δ 65.83 ppm) than that of the normal taxane (*ca.* δ 43 ~46 ppm). These two signals in the ^{13}C-NMR spectrum were used to distinguish 11(15→1)*abeo*taxane from the normal taxane. The other one was lacking a diagnostic three-bond correlations from H-16 and H-17 to C-11 and this fact also eliminated the normal taxane structure from consideration.[16] The doublet signal at δ 5.95 ppm, which correlated with the signal at δ 3.17 ppm, a characteristic signal of H-3, indicated the δ 5.95 ppm signal was H-2. This lower field resonance of H-2 suggested an acetyl group

Table 1. ^{1}H-NMR Spectral Data of Compounds (**1**, **2**, and **3**) ($CDCl_3$, ppm, 500 MHz).

	1		**2**		**3**	
position	^{1}H	*J* (Hz)	^{1}H	*J* (Hz)	^{1}H	*J* (Hz)
2	5.95 d	6.53	5.83 d	7.57	6.11 d	7.46
3	3.17 d	6.53	3.10 d	7.57	3.13 d	7.46
5	3.12 br s		4.96 d	7.57	4.89 d	7.69
6α	1.89 br d	13.04	2.72 m		2.58 m	
6β	2.04 m		2.00 m		2.83 m	
7	5.45 dd	5.03, 11.54	5.52 t	7.94	5.34 t	8.10
9	6.05 d	5.52	4.21 br d	10.01	4.29 br d	9.89
10	4.72 d	5.52	4.59 br d	10.01	4.60 br d	9.89
13	4.62 br s		4.50 br d	7.08	4.58 t	8.21
14α	1.63 dd	7.54, 14.25	1.48 dd	15.14, 7.08	1.72 dd	16.10, 7.22
14β	2.27 dd	6.03, 14.25	2.18 m		2.27 m	
16	1.25 s		1.06 s		1.08 s	
17	1.50 s		1.01 s		1.04 s	
18	1.71 s		2.17 s		1.98 s	
19	1.07 s		1.96 s		1.94 s	
20a	2.21 d	5.24	4.56 d	6.32	4.50 d	7.50
20b	3.41 d	5.24	4.42 d	6.32	4.13 d	7.50
o-Ph	8.00 d	7.53	8.04 br d	7.81	8.02 d	7.42
m-Ph	7.45 t	7.53	7.44 m		7.45 m	
p-Ph	7.56 t	9.05	7.55 m		7.60 m	
2-AcO	2.04 s		2.16 s			
4-AcO			2.00 s		2.21 s	
7-AcO	2.05 s				2.06 s	

attached to this position. The proton resonated at δ 4.62 ppm correlated with H-14α, H-14β and 18-CH_3 in the ^{1}H-^{1}H COSY spectrum was H-13 and a hydroxyl group located at C-13. The signal at δ 6.05 ppm (1H, d, J = 5.52 Hz) was assigned to H-9 from the observation of long–range couplings to C-3 and C-11 in the HMBC spectrum, therefore, we established the signal at δ 4.72 ppm (1H, d, J = 5.52 Hz) to H-10 owing to the presence of a direct coupling to H-9 in the ^{1}H-^{1}H COSY spectrum and a hydroxy group attached to C-10. Benzoyl group was attached to C-9 as shown in the HMBC spectrum. Much smaller coupling constant between H-9 and H-10 (J = 5.52 Hz) revealed the B/C rings had chair/boat conformation.[13] The signal at δ 5.45 ppm (1H, dd, J = 5.03, 11.54 Hz) was assigned to H-7, which correlated with C-9 and a carbonyl carbon of an acetyl group in the HMBC experiment. H-5 resonated at δ 3.12 ppm (1H, br s) suggested that the epoxidic oxygen was β-oriented and *cis* to H-5. This shielding effect on H-5 was in good agreement with the observed chemical shift. Actually, all naturally occurring

4,20-epoxy taxanes have been formulated as β-epoxide.[3] In this kind of compounds, the β-epoxy oxygen causes an upfield shift of H-5β as compared to the corresponding △4(20)-olefinic taxanes. On the basis of the above analysis, the structure of **1** was established as 2α,7β-diacetoxy-9α-benzoyloxy-4β(20)-epoxy-5α,10β,13α,15-tetrahydroxy-11(15→1)*abeo*tax-11-ene. The HMBC spectrum totally supported the whole carbon framework. This was the second example of the 11(15→1)*abeo*taxane with an epoxidic ring at C-4 (20).[17] One interesting feature of both ^{1}H- and ^{13}C-NMR spectra observed in **1** was that the signals were very broad when the spectra were obtained at ambient temperature. Decreasing the temperature to 0℃, however, displayed normal sharp resonances and well-resolved spin systems, indicating that line broadening was due to a slow equilibrium between two or more conformational isomers. This behavior has been observed previously in taxoids that were subsequently shown to have the brevifoliol skeleton.[16,18,19] Compound (**1**) has little activity in the brine shrimp test at the following conditions: 10, 50 and 100 μg/mL at 30℃ for 24 hours and 48 hours, whereas taxol showed the activity at 10 μg/mL at the same conditions.

The molecular formula of compound (**2**), $C_{31}H_{40}O_{11}$, was established by the analysis of HR-FAB-MS at *m/z* 611.2464 ($[M+Na]^+$) (△+ 0.1 mmu). The IR spectrum had absorptions at 3400 and 1730 cm^{-1}, characteristic of hydroxyl and ester groups, respectively. The ^{1}H-NMR spectrum of **2** exhibited the proton signals due to four methyl groups at δ 1.06, 1.01, 2.17, and 1.96 ppm, two acetyl groups at relative lower field (δ 2.16 and 2.00 ppm), and a benzoyl group at down field. These suggested that **2** has a taxane-type skeleton. The chemical shift of the characteristic proton resonances due to the oxetane moiety were virtually identical with a doublet at δ 4.96 ppm for H-5α, and signals for an AB system at δ 4.56 and 4.42 ppm for the C-20 methylene bridge.[20] Assignment of these and other groups on the taxane skeleton was made by an analysis of the ^{1}H-^{1}H COSY, ^{13}C-NMR, HMBC, and HMQC spectra. Starting with H-3α, which was a characteristic signal of the taxane skeleton, the coupling pattern with H-2 (δ 5.83 ppm) established H-2 as β-oriented. Similarly, H-5α (δ 4.96 ppm) was correlated with the one proton multiplet of H-6α (δ 2.72 ppm), which also shared a geminal coupling with the one proton multiplet of H-6β (δ 2.00 ppm). Both H-6α and H-6β shared a cross-peak with the triplet at δ 5.52 ppm (J = 7.94 Hz) assigned to H-7α. The isolated double of doublets at δ 4.59 and δ 4.21 ppm were assigned to H-10α and H-9β, respectively. The vicinal coupling between H-9β and H-10α, with the coupling constants of J = 10.01 Hz indicated their *trans*-orientation in the molecule. The double of doublets at δ 1.48 ppm and the multiple at δ 2.18 ppm

were assigned to the H-14α and H-14β, respectively, on the basis of their geminal coupling (J = 15.14 Hz) and coupling with the H-13β. All of the proton-bearing carbons were assigned by an analysis of the HETCOR spectrum. Seven oxygen-containing carbons (C-2, C-5, C-7, C-9, C-10, C-13, and C-20) were correlated with their corresponding proton signals. The signal at δ 27.50 ppm and δ 22.45 ppm corresponding to C-16 and C-17 (methyl groups), respectively, showed cross-peaks with two three proton signals at δ 1.06 and δ 1.01 ppm. An analysis of the HMBC spectrum permitted an unambiguous assignment of the C-18 and C-19 signals, the ester functions, and quaternary carbons. The signal at δ 78.66 ppm (C-9) showed a three-bond coupling with the C-19 methyl group (δ 1.96 ppm) and at the same time, H-3α (δ 3.10 ppm) and H-9β signals displayed a cross-peak with an up-field signal at δ 13.40 ppm (assigned to C-19) and with the resonance at δ 43.29 ppm (assigned to C-8). The H-9β, H-10α, and H-13β signals did not showed cross-peaks with carbonyl carbons, and these, along with their up-field positions (δ 4.21, 4.59, and 4.50 ppm, respectively), strongly indicated that free hydroxyl groups attached to C-9, C-10, and C-13. Proton resonances at δ 8.04 ppm, 2.16 and 2.00 ppm, assigned for the *ortho*-proton of the benzoate, and the acetate protons, showed three-bond coupling with the carbon signals at δ 165.63, 170.61, and 171.35 ppm, respectively, thus indicating that these resonances were due to the C=O carbon of the benzoate and the two acetate groups. At the same time, resonances at δ 165.63 (benzoate C=O) and 170.61 ppm displayed cross-peaks with the proton signals at δ 5.52 (H-7α) and 5.83 ppm (H-2β), respectively, and strongly indicated an attachment of the benzoate function at C-7, and one acetate (δ 2.16 ppm corresponding to the acetate methyl signal) at C-2. The second acetate methyl signal did not show a cross-peak with any proton except with the singlet at δ 2.00 ppm, and this indicated that the second acetate function was located at the C-4 carbon. The signal for the C-4 carbon was assigned by its correlation with H-3α, H-5α, and H-20 signals. The H-10α signal showed cross-peaks with the resonances at δ 136.71, 147.76 and 67.50 ppm, which were assigned for C-11, C-12, and C-1, respectively. The C-11 and C-12 carbon signals showed cross-peaks with the H-14β resonance, which indicated that both C-11 and C-12 are three bonds apart from H-14β. This mean that the A ring is a cyclopentene as in an 11(15→1)*abeo*taxane structure.[21] The carbon signal at δ 78.80 ppm, assigned to the hydroxyl-bearing C-15, displayed a cross-peak with the C-16 and C-17 methyl resonances at δ 1.06 and 1.01 ppm. The C-1 signal (δ 67.50 ppm), apart from H-10α, also showed three-bond coupling with the H-3α and C-16, C-17 methyl signals. Since no cross-peak was observed between C-16, C-17 (methyl) signals and the C-11 olefinic carbon in the HMBC spectrum further supported the 11(15→1)*abeo*taxane skeleton for **2**.[22] The C-11 and C-12 carbon signals also showed coupling with a three-proton resonance at δ 2.17 ppm, assigned

Table 2. ^{13}C-NMR Spectral Data of Compounds (**1**, **2**, and **3**) ($CDCl_3$, ppm, 125 MHz).

position	1	2	3	position	1	2	3
1	65.83	67.50	68.21	17	29.69	22.45	24.76
2	69.89	75.08	71.81	18	11.13	11.37	11.32
3	37.27	44.67	44.50	19	14.10	13.40	13.07
4	59.50	79.99	80.04	20	49.67	75.08	68.60
5	75.80	85.28	84.36	*o*-Ph	128.39	128.42	129.94
6	29.67	29.69	34.75	*m*-Ph	129.77	129.65	128.61
7	68.90	72.13	71.80	*p*-Ph	133.00	133.01	133.53
8	44.48	43.29	42.87	*i*-Ph	130.29	130.52	130.90
9	81.10	78.66	78.76	PhC=O	167.70	165.63	165.98
10	66.98	68.33	77.78	2-AcO		21.64	
11	138.37	136.71	137.10			170.61	
12	145.84	147.76	147.53	4-AcO	21.63	22.97	22.46
13	75.62	77.73	74.93		169.69	171.35	171.12
14	40.23	39.80	39.91	7-AcO	21.52		21.76
15	76.65	78.80	76.01		171.69		170.36
16	27.92	27.50	27.66				

to the C-18 methyl. Since the carbon signal at δ 13.40 ppm was assigned to the C-19 methyl, the remaining carbon signal in the methyl region at δ 11.38 ppm must be assigned to C-18 methyl. Thus, the structure of **2** is shown to be 2α,4α-diacetoxy-7β-benzoyloxy-5β,20-epoxy-9α,10β,13α,15-tetrahydroxy-11(15→1)*abeo*tax-11-ene (2-debenzoyl-2-acetyl taxayuntin B[23]).

Compound (**3**) was isolated as a colorless gummy substance from the needles of Japanese yew, *Taxus cuspidata*. The composition $C_{31}H_{40}O_{11}$ of **3** was deduced from the HR-FAB-MS spectrum. The ^{1}H- and ^{13}C-NMR spectra of compound (**3**), shown in Tables 1 and 2, gave indications of a 5,20-oxetane ring (^{1}H signals for H-20 at δ 4.50 and 4.13 ppm, doublet signals at δ 4.89 ppm for H-5), two acetyl groups and a benzoyl group. The presence of signals due to H-13 at δ 4.58 ppm and H-2 at δ 6.11ppm, as well as the diagnostic signals for C-1 and C-15, suggested that a 5/7/6-membered ring system as in brevifoliol was presented. This was further confirmed by observing the HMBC experiment. In the HMBC spectrum, correlations between C-15 and H-16, H-17, and C-1 and H-10 were observed, whereas a correlation between C-15 and H-10, always observed in taxoids with the 6/8/6-membered ring system, was not observed. The correlations between C-11, C-12, and H-14α were also observed, whereas only a correlation between C-12 and H-14α can be observed in taxoids with 6/8/6-membered ring system. The general structural assignments were made on the basis of ^{1}H-^{1}H COSY and HETCOR spectra. In order to

confirm the location of the benzoate group, an HMBC spectrum was run. Long range interaction was observed between the *ortho*-protons of the benzoate (δ 8.02 ppm) and corresponding carbonyl signal at δ 165.98 ppm, which in turn, interacted with the H-2 (δ 6.11 ppm). Thus the location of the benzoate group was established at C-2. One of the acetyl groupa was attached to C-7 as indicated by the HMBC spectrum, another acetyl group was suggested at C-4 (except a methyl group at 2.21 ppm, no proton correlated with the signal at 171.12 ppm in the HMBC spectrum) as in the case of all the other taxoids ever isolated[2-4]. Thereby making **3** as a new member of this group, its structure was determined to be 2α-benzoyloxy-5β.20-epoxy-9α,10β,13α,15-tetrahydroxy-4α,7β-diacetoxy-11(15→1)*abeo*tax-11-ene (13-deacetyl-9,10-debenzoyl-tachinin C[24]).

The configurations of compounds (**2** and **3**), which were deduced from the NOESY experiments and the coupling constants, were the same as those of their analogous.

EXPERIMENTAL

Melting points were measured with a MRK micro-melting point apparatus and are uncorrected. Optical rotations were recorded on a Horiba SEPA-300 digital polarimeter. UV spectrum was recorded on a Shimadzu UV–1600 spectrophotometer. IR spectra were obtained on a Jasco IR–810 instrument. MS were measured on a Jeol JMS-700 spectrometer using EI modes. ^{1}H- and ^{13}C-NMR spectra were run on a Varian Unity Inova 500 spectrometer in $CDCl_3$ at 20℃. Chemical shifts are reported in ppm scale relative to that of tetramethylsilane (δ = 0) as an internal standard, and coupling constants are given in Hertz. Open column chromatography was performed using Merck silica gel 60 (100-200 mesh). Thin layer chromatographies were carried out with precoated Merck silica gel 60 F_{254} plates. Preparative TLC were performed using the same type of plates as used for TLC but using 0.85 mm thickness, and the spots were detected under UV (254 nm) and/or by spraying with 10% sulfuric acid and then heating on a hot plate.

Plant material: The bark of *T. chinensis* var. *mairei* was collected from Ziping town, Jiangxi Province, the People's Republic of China, in the autumn of 1995. The plant material was authenticated by Professor R. L. Liu of Zhangzhou Forestry School, where a voucher specimen has been deposited.

The needles of *T. cuspidata* were collected from Sendai, in the north-east of Japan, in the autumn of 1996. The botanical identification was made by Prof. T. Oritani, Toyama Prefectural University. A voucher specimen has been deposited in our laboratory of Graduate School of Agricultural Science, Tohoku University, Japan.

Extraction and Isolation: Air dried bark (13.25 kg) was extracted twice with MeOH (45 L) at rt for one week. The extracts were treated with activated charcoal and concentrated to a syrup (350 g) under reduced pressure. This syrup was diluted with water and the aqueous solution was extracted with EtOAc successively. The combined EtOAc extract, upon evaporation, gave a dark syrup (88 g), which was adsorbed by silica gel and subjected to a normal phase silica gel open column chromatography. Elution with hexane and hexane–EtOAc (2:1, 1:1, 1:2, 1:4 and EtOAc) gave six fractions. Frs. 2 and 3 were further purified by column chromatography and preparative TLC, finally afforded the compound (**1**) (4.5 mg) and (**2**) (2.0 mg). Air dried needles (7.0 kg) were extracted with MeOH (20 L) twice at rt. for one week. The MeOH extracts were concentrated to residue under reduced press. This residue (300 g) was diluted with water and the aqueous solvent was extracted with EtOAc three times. The combined EtOAc extract, upon evaporation, yielded a dark syrup (90 g). A part (60 g) of above concentrate was subjected to a silica gel column chromatography, eluted with $CHCl_3$-EtOAc (20:1, 10:1, 5:1, 2:1 and EtOAc), five fractions were obtained. Fr. 3 was repeatedly chromatographed on silica gel column and plates, eluted or developed with hexane-acetone, hexane-EtOAc, and $CHCl_3$-MeOH, finally afforded compound (**3**) (2.3 mg).

Compound (**1**). mp 155-156℃ (EtOAc). $[\alpha]_D^{24}$ -8° (c 0.02, $CHCl_3$); UV λ_{max}^{MeOH} nm: 228 (ε 1940); IR ν_{max} ($CHCl_3$, film) cm^{-1} : 3350, 2920, 1740, 1720, 1700, 1365, 1278, 1225, 1062, 934, 750 and 708. FAB-MS *m/z*: 611 $(M+Na)^+$, 589 $(M+H)^+$, 571 $(M+H-H_2O)^+$, 553 $(M+H-2H_2O)^+$, 545 $(M-COCH_3)^+$, 529 $(M+H-HOAc)^+$, 511 $(M+H-H_2O-AcOH)^+$, 493 $(M+H-2H_2O-AcOH)^+$, 451 $(M+H-H_2O-2AcOH)^+$, 433 $(M+H-2H_2O-2AcOH)^+$, 331, 185, 149, 93, 75, and 57. HR-FAB-MS *m/z*: 611.2465 ($C_{31}H_{40}O_{11}Na$, requires: 611.2466). ^1H- and ^{13}C-NMR data: see Tables 1 and 2.

Compound (**2**). gum, $[\alpha]_D^{24}$ -6° (c 0.01, $CHCl_3$); IR ν_{max} ($CHCl_3$, film) cm^{-1} : 3400, 2960, 2910, 2860, 1730, 1600, 1580, 1450, 1380, 1250, 1180, 1120, 1070, 1020, 980, 940, 840, 750 and 710. FAB-MS *m/z*: 611 $(M+Na)^+$, 589 $(M+H)^+$, 571 $(M+H-H_2O)^+$, 553 $(M+H-2H_2O)^+$, 511 $(M+H-H_2O-AcOH)^+$, 493 $(M+H-2H_2O-AcOH)^+$, 433 $(M+H-2H_2O-2AcOH)^+$, 149, 105, 93, 77, and 55. HR-FAB-MS *m/z*: 611.2469 ($C_{31}H_{40}O_{11}Na$, requires: 611.2466). ^1H- and ^{13}C-NMR data: see Tables 1 and 2. NOESY correlations ($CDCl_3$, H/H): 2/17, 2/9, 2/19, 3/7, 3/10, 3/14α, 5/6α, 5/6β, 10/14α, 13/17.

Compound (**3**). gum, $[\alpha]_D^{24}$ -11° (c 0.015, $CHCl_3$); IR (film) ν_{max} ($CHCl_3$) cm^{-1} : 3400, 2930, 1720, 1700, 1600, 1580, 1450, 1360, 1278, 1250, 1070, 940, 760 and 708. FAB-MS *m/z*: 611 $(M+Na)^+$, 589

$(M+H)^+$, 571 $(M+H-H_2O)^+$, 553 $(M+H-2H_2O)^+$, 545 $(M-COCH_3)^+$, 529 $(M+H-HOAc)^+$, 511 $(M+H-H_2O-AcOH)^+$, 493 $(M+H-2H_2O-AcOH)^+$, 451 $(M+H-H_2O-2AcOH)^+$, 433 $(M+H-2H_2O-2AcOH)^+$, 331, 185, 149, 93, 75, and 57. HR-FAB-MS *m/z*: 611.2468 (calcd for $C_{31}H_{40}O_{11}Na$, 611.2466), *m/z*: 589.2650 ($C_{31}H_{41}O_{11}$, requires: 589.2646). ^1H- and ^{13}C-NMR data: see Tables 1 and 2. NOESY correlations ($CDCl_3$, H/H): 2/17, 2/9, 2/19, 3/7, 3/10, 3/14α, 5/6α, 5/6β, 10/14α, 13/17.

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