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TOTAL SYNTHESIS AND THE CONFIRMATION OF THE REVISED STRUCTURES OF BOTCININS A AND B

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Abstract – The stereoselective total syntheses of botcinins A (**1**) and B (**2**), and homobotcinin E (**4**), a homologue of botcinin E (**3**), have been achieved starting from a polyoxygenated tetrahydropyran intermediate **15** via formation of botcinic acid (**12**) and botcineric acid (**13**). Through the total syntheses, three actual relationships are revealed, that is, (i) the structure of botcinin A (**1**) is identical with the revised structure of the natural compound, which was formerly assumed to be 3-*O*-acetyl-2-epibotcinolide (**5**), (ii) the structure of botcinin B (**2**) is identical with the revised structure of the natural compound, which was supposed to be 3-*O*-acetyl-2-epihomobotcinolide (**6**), and (iii) the structure of the natural compound formerly assumed to be 2-epihomobotcinolide (**8**) must be revised to that of homobotcinin E (**4**).

Botcinins A, B and E (**1**, **2** and **3**) were isolated from *Botrytis cinerea* (strain AEM 211) as antifungal metabolites against *Magnaporthe grisea*, a pathogen of the rice blast disease, by Nakajima *et al*. in 2005-6.[1,2] Before the isolation of these compounds by Nakajima, Cutler *et al*.[3-5] and Collado *et al*.[6,7] independently extracted several natural metabolites from *B. cinerea*, which have significant phytotoxicity to a variety of plants, including three related compounds, called 3-*O*-acetyl-2-epibotcinolide (**5**),[6] 3-*O*-acetyl-2-epihomobotcinolide (**6**),[7] and 2-epibotcinolide (**7**).[6] By a detailed comparison of the spectroscopic data of the natural products by Nakajima, it was proposed that the structural revision of the reported compounds assumed to be **5** and **7** should be done by replacing them with those of **1** and **3**, respectively,[2] as shown in **Figure 1**.

This paper is dedicated to the memory of Dr. John William Daly.

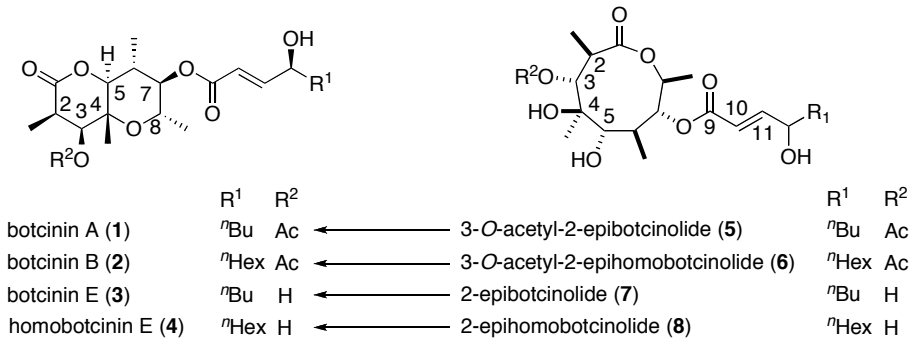
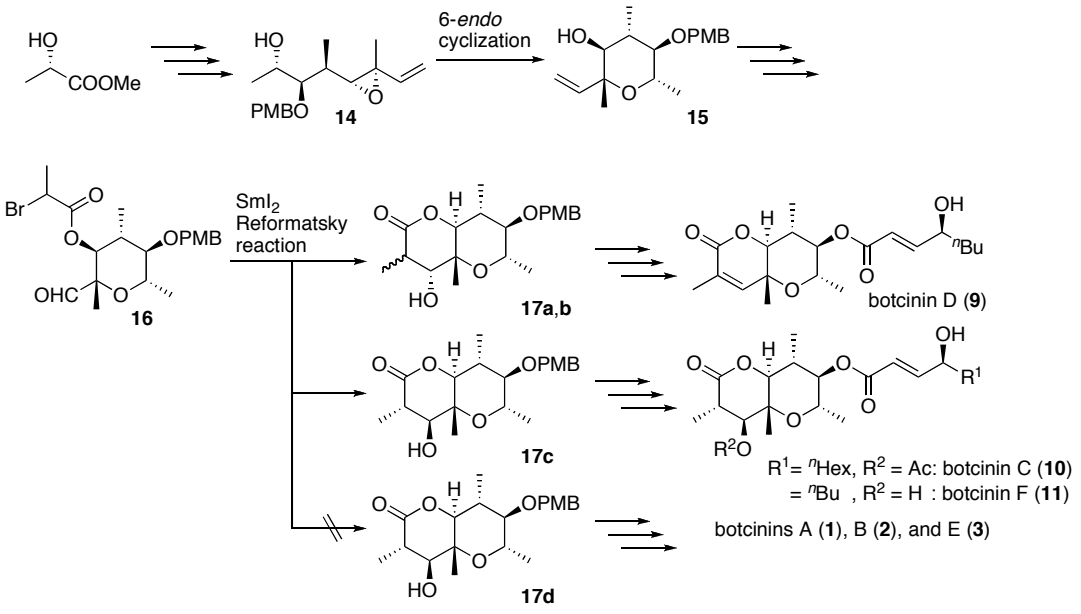


Figure 1. The Structure of Botcinins (1, 2, 3, and 4) and Corresponding Botcinolides (5, 6, 7, and 8)

Recently, we synthesized botcinins C-F (**10**, **9**, **3**, **11**),[8,9] botcinic acid (**12**),[9] and botcineric acid (**13**),[9] and confirmed that the structure of the natural compound assumed to be 2-epibotcinolide (**7**) is incorrect[10] and should be revised to that of the corresponding structure of botcinin E (**3**) as predicted by Nakajima. During the synthetic studies of **3**, we noted that the true form of the natural compound supposed to be 3-*O*-acetyl-2-epihomobotcinolide (**6**) should also be identified as that of botcinin B (**2**) (**Figure 1**). Furthermore, it was additionally anticipated that the structure of the natural metabolite, called 2-epihomobotcinolide (**8**), should be revised to that of homobotcinin E (**4**) although **4** was not isolated by other groups.

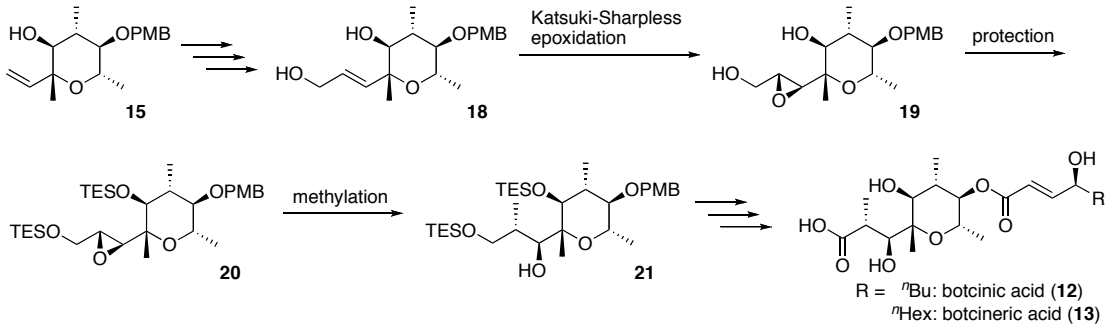
In this communication, we report the total syntheses of botcinins A (**1**) and B (**2**), and homobotcinin E (**4**), and updated the proposed structures of the botcinolides in order to show the true forms of these natural products.



Scheme 1. Syntheses of Botcinins C (10), D (9), and F (11)[8]

As shown in **Scheme 1**, the synthetic route is summarized for the preparation of botcinins D (**9**), C (**10**), and F (**11**) from the corresponding lactones **17a**-**c**.[8] These precursors were generated from a highly substituted tetrahydropyran ring **15** via the SmI_2-mediated Reformatsky reaction of 2-bromoester **16**, which includes formyl part at a suitable position. On the other hand, we accomplished the total synthesis of botcinic acid (**12**) and botcineric acid (**13**) through the alternative synthetic route using the six-membered ether **15** as a key intermediate (**Scheme 2**).[9]

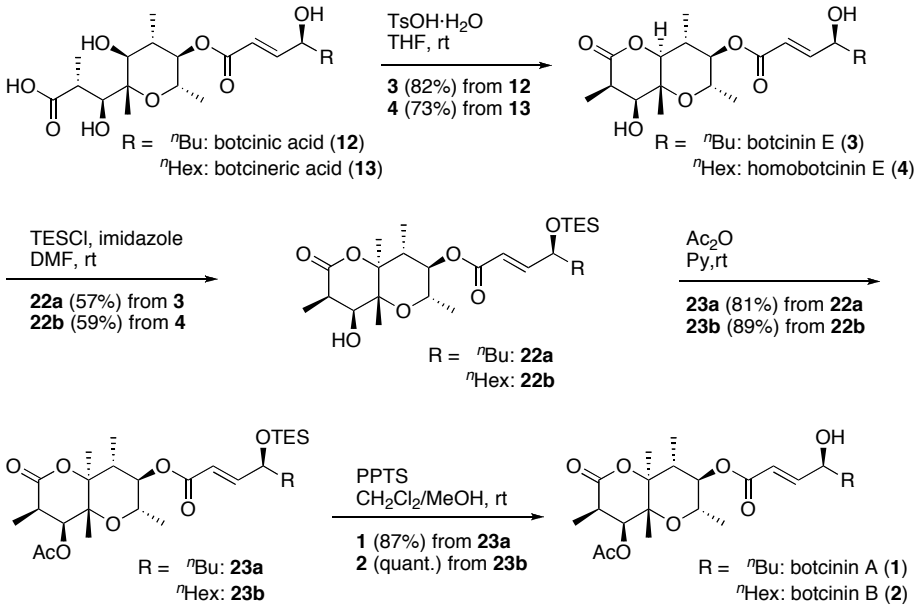
In the previous paper,[9] we also succeeded to transform botcinic acid (**12**) into botcinin E (**3**) by the acidic treatment. Because botcinins A (**1**) and B (**2**) might have the same stereochemistries at the C-2 and -3 positions to those of **3**, it is postulated that **1** and **2** could be synthesized from **12** and **13**, respectively.



Scheme 2. Syntheses of Botcinic Acid (12) and Botcineric Acid (13) [9]

First, botcineric acid (**13**) was converted into homobotcinin E (**4**)[11] according to the same procedure for the preparation of botcinin E (**3**) from botcinic acid (**12**) as shown in **Scheme 3**. Next, the hydroxyl groups at the allylic positions in **3** and **4** were selectively protected with TES group, and the remaining hydroxyl groups of **22a** and **22b** were acetylated using acetic anhydride with pyridine. Botcinin A (**1**)[12] and botcinin B (**2**)[13] were finally produced by the deprotection of the TES group in **23a** and **23b**, respectively, under acidic conditions using PPTS in CH_2Cl_2/MeOH at rt.

The spectroscopic data of the synthetic **1** and **2** well corresponded with those of the isolated **1** and **2**. As Nakajima reported that the structure of the natural compound, assumed to be 3-*O*-acetyl-2-epibotcinolide (**5**), should be revised to that of **1**, we could also predict that the true structure of the natural compound formerly assumed to be 3-*O*-acetyl-2-epihomobotcinolide (**6**) should be replaced by that of **2**. The compared spectroscopic data of **2** with **6** are depicted in **Table 1** and these data are well corresponded, therefore, it is apparently concluded that the true structure of the natural compound, assumed to be **6**, is identical to that of **2**.



Scheme 3. Syntheses of Botcinin A (1) and Botcinin B (2)

Homobotcinin E (**4**) is a deacetylated compound of botcinin B (**2**), and the structure of the natural compound assumed to be 3-*O*-acetyl-2-epihomobotcinolide (**6**) had been revised to that of **2** as shown above; therefore, we postulated that **4** should be the true structure of the natural metabolite formerly assumed to be 2-epihomobotcinolide (**8**).

Homobotcinin E (**4**) is also a homologue of botcinin E (**3**) with an extra two-carbon in the side chain as well as a relationship between 2-epihomobotcinolide (**8**) and 2-epibotcinolide (**7**). In accordance with this correlation, Nakajima reported that the structure of the natural metabolite, which was supposed to be **7**, should be identical to that of **3** because the NMR data of **7** and **3** are almost identical; however, there are some exceptional resonances in the NMR spectra that should be clarified by the advanced investigations.

Based on the above examinations, we attempted to compare the spectroscopic data of ^{1}H and ^{13}C NMR on **7**, **3**, **8**, and **4** in detail in order to determine the exact structures of natural products (**Table 2**). From **Table 2**, we found that the resonances of the ^{1}H NMR of **7** appeared at a 0.1 ppm lower field compared to those of the isolated and synthetic **3**. It was apparently discordant that the chemical shift of H-11 in **7** was observed at δ 7.91 ppm in the former report by Collado's group,[6] but they assigned δ 7.02 ppm to the corresponding proton peak of **8** in the later paper.[7] Furthermore, H-11 of our synthetic **3** and **4** appeared at δ 7.02 ppm, and Nakajima also assigned the chemical shift of H-11 in the isolated **3** to δ 7.03 ppm. Therefore, we can expect that the resonance of H-11 in **7** should be observed at around δ 7.02 ppm, and

Table 1. The ^{1}H and ^{13}C NMR Data of 2 and 6 in $CDCl_3$

	6*		**2** (isolated)		**2** (synthetic)	
position	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1	173.2	–	173.2	–	173.2	–
2	37.2	3.14	37.2	3.16	37.3	3.17
3	74.2	5.39	74.3	5.40	74.3	5.42
4	75.2	–	75.2	–	75.2	–
5	78.5	3.79	78.5	3.80	78.6	3.81
6	35.3	2.17	35.4	2.18	35.4	2.18
7	76.0	4.51	76.0	4.52	76.1	4.54
8	68.4	3.66	68.4	3.67	68.4	3.68
9	165.7	–	165.7	–	165.7	–
10	118.9	6.04	119.0	6.05	119.0	6.07
11	151.9	7.03**	151.8	7.00	151.8	7.02
12	71.0	4.31	71.0	4.32	71.1	4.36-4.33
13	36.6	1.57	36.6	1.53-1.65	36.7	1.64-1.54
14	25.1	1.27	25.2	1.25-1.50	25.2	1.45-1.30
15	29.0	1.27	29.0	1.25-1.50	29.1	1.45-1.30
16	31.6	1.27	31.6	1.25-1.50	31.7	1.45-1.30
17	22.5	1.27	22.5	1.25-1.50	22.5	1.45-1.30
18	14.0	0.86	14.0	0.87	14.0	0.89
2-Me	10.1	1.10	10.2	1.11	10.2	1.13
4-Me	11.9	1.24	11.9	1.25	11.9	1.27
6-Me	13.6	1.04	13.6	1.05	13.7	1.07
8-Me	18.1	1.07	18.2	1.08	18.2	1.10
Ac-CO	170.0	–	170.1	–	170.1	–
Ac-Me	20.5	2.10	20.5	2.11	20.6	2.13

* In the original paper, it was described that these spectroscopic data had been recorded in CD_3OD, however, the attached spectra in the paper showed that this experiment had been obviously carried out in $CDCl_3$.[7]

** In the original paper, it was described that the resonance had been observed at δ 6.03 ppm, however, the attached spectra in the paper showed that this resonance had undoubtedly appeared at around δ 7.0 ppm.[7]

Collado's group might have made a typographic error in the preparation of their paper. The resonance at δ 170.1 ppm for C-9 in **7** in CD_3OD might also be an error in the preparation of the paper because the corresponding C-9 signals in the isolated and synthetic **3** were observed at δ 165.8 ppm. Consequently, we now suggest that homobotcinin E (**4**) should be the true form of the natural product, which was first isolated as 2-epihomobotcinolide (**8**), in the same way as the structure of the natural compound formerly assumed to be 2-epibotcinolide (**7**) had been revised to that of botcinin E (**3**).[9,10]

Table 2. The ^{1}H and ^{13}C NMR Data of 3, 4, 7, and 8 in CD_3OD

	7		**3** (isolated)		**3** (synthetic)		**8**		**4** (synthetic)	
position	^{13}C	and ^{1}H	^{13}C	and ^{1}H	^{13}C	and ^{1}H	^{13}C	and ^{1}H	^{13}C	and ^{1}H
1	173.2	—	174.0	—	174.0	—	177.4	—	177.4	—
2	38.4	3.10	38.4	3.21	38.3	3.20	39.6	3.20	39.5	3.20
3	74.1	3.97	74.0	4.09	74.0	4.08	75.0	4.08	75.0	4.08
4	76.3	—	*	—	77.2	—	78.9	—	78.1	—
5	78.5	3.83	78.4	3.95	78.4	3.94	79.7	3.94	79.6	3.94
6	35.6	2.10	35.6	2.22	35.6	2.25-2.17	36.8	2.21	36.8	2.21
7	77.2	4.40	76.2	4.51	76.2	4.50	78.1	4.50	77.9	4.50
8	68.5	3.66	68.4	3.79	68.4	3.78	69.6	3.77	69.5	3.78
9	**170.1**	—	**165.8**	—	**165.8**	—	**167.6**	—	**167.6**	—
10	119.2	5.94	119.1	6.06	119.1	6.05	119.9	6.05	119.8	6.05
11	151.7	**7.91**	151.8	**7.03**	151.8	**7.02**	154.0	**7.02**	154.1	**7.02**
12	71.1	4.13	71.1	4.26	71.1	4.27-4.23	71.6	4.25	71.6	4.25
13	36.4	1.45	36.4	1.63-1.50	36.4	1.62-1.49	37.5	1.49	37.5	1.62-1.49
14	27.3	1.25	27.4	1.47-1.33	27.4	1.40-1.26	26.4	1.31	26.4	1.46-1.26
15	22.5	1.25	22.5	1.47-1.33	22.5	1.40-1.26	32.9	1.31	32.9	1.46-1.26
– /16	—	—	—	—	—	—	23.6	1.17	23.6	1.46-1.26
– /17	—	—	—	—	—	—	30.2	1.17	30.3	1.46-1.26
16/18	13.9	0.81	13.9	0.93	13.9	0.92	14.3	0.89	14.4	0.90
2-Me	10.3	1.02	10.3	1.15	10.3	1.14	10.4	1.13	10.3	1.14
4-Me	10.9	1.06	11.0	1.19	11.0	1.17	11.5	1.17	11.8	1.18
6-Me	13.7	0.90	13.7	1.03	13.7	1.01	13.9	1.07	13.8	1.02
8-Me	18.2	0.96	18.2	1.08	18.2	1.07	18.6	1.11	18.6	1.07

* not observed.

In conclusion, we achieved the first asymmetric total syntheses of botcinins A (**1**) and B (**2**), and homobotcinin E (**4**) via stereocontrolled reactions. As a result of the synthetic efforts, we determined that the true structure of the natural compound, assumed to be 3-*O*-acetyl-2-epibotcinolide (**5**), should be corrected to that of **1**, and the structures of the natural extracts, assumed to be 3-*O*-acetyl-2-epihomobotcinolide (**6**) and 2-epihomobotcinolide (**8**), should also be revised to those of **2** and **4**, respectively.

ACKNOWLEDGEMENTS

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11. Homobotcinin E (**4**): $[\alpha]_D^{26}$ –64.7 (*c* 0.57, EtOH), $[\alpha]_D^{24}$ –70.7 (*c* 1.26, $CHCl_3$) [lit.,[7] $[\alpha]_D^{35}$ –34 (*c* 2.0, $CHCl_3$)]; IR (neat): 3437, 2930, 2857, 1727 cm^{-1}; ^1H NMR (CD_3OD): δ 7.01 (dd, *J* = 15.5, 5.0 Hz, 1H), 6.07 (d, *J* = 15.5 Hz, 1H), 4.52 (dd, *J* = 10.5, 9.8 Hz, 1H), 4.37-4.31 (m, 1H), 4.14 (d, *J* = 9.5 Hz, 1H), 3.73 (dq, *J* = 9.8, 5.8 Hz, 1H), 3.70 (d, *J* = 11.0 Hz, 1H), 3.05 (dq, *J* = 9.5, 7.3 Hz, 1H), 2.18 (ddq, *J* = 11.0, 10.5, 6.0 Hz, 1H), 1.63-1.54 (m, 2H), 1.48-1.25 (m, 8H), 1.23 (s, 3H), 1.28 (d, *J* = 7.3 Hz, 1H), 1.11 (d, *J* = 5.8 Hz, 1H), 1.05 (d, *J* = 6.0 Hz, 3H), 0.88 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (CD_3OD): δ 177.4, 167.6, 154.1, 119.8, 79.6, 78.1, 77.9, 75.0, 71.6, 69.5, 39.5, 37.5, 36.8, 32.9, 30.3, 26.4, 23.6, 18.6, 14.4, 14.0, 11.6, 10.5; HR MS: calcd for $C_{22}H_{36}O_7Na$ ($M + Na^+$) 435.2353, found 435.2332.
12. Botcinin A (**1**): $[\alpha]_D^{23}$ –39.3 (*c* 0.72, EtOH) [lit.,[1] $[\alpha]_D^{25}$ –33 (*c* 0.50, EtOH)]; IR (neat): 3440, 2922, 1733 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.01 (dd, *J* = 15.8, 4.5 Hz, 1H), 6.06 (dd, *J* = 15.8, 2.0 Hz, 1H), 5.41 (d, *J* = 9.8 Hz, 1H), 4.53 (dd, *J* = 9.8, 9.8 Hz, 1H), 4.36-4.32 (m, 1H), 3.80 (d, *J* = 10.3 Hz, 1H), 3.63 (dq, *J* = 9.5, 6.0 Hz, 1H), 3.16 (dq, *J* = 10.3, 7.0 Hz, 1H), 2.20 (ddq, *J* = 10.0, 9.5, 6.0 Hz, 1H), 2.21 (s, 3H), 1.66-1.54 (m, 2H), 1.44-1.33 (m, 4H), 1.18 (s, 3H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 6.3 Hz, 3H), 1.02 (d, *J* = 6.0 Hz, 3H), 0.90 (t, *J* = 6.5 Hz, 3H); ^1H NMR (CD_3OD): δ 7.01 (dd, *J* = 15.5,

5.0 Hz, 1H), 6.07 (d, *J* = 15.5 Hz, 1H), 4.52 (dd, *J* = 10.5, 9.8 Hz, 1H), 4.37-4.31 (m, 1H), 4.14 (d, *J* = 9.5 Hz, 1H), 3.73 (dq, *J* = 9.8, 5.8 Hz, 1H), 3.70 (d, *J* = 11.0 Hz, 1H), 3.05 (dq, *J* = 9.5, 7.3 Hz, 1H), 2.18 (ddq, *J* = 11.0, 10.5, 6.0 Hz, 1H), 1.63-1.54 (m, 2H), 1.48-1.25 (m, 4H), 1.25 (s, 3H), 1.12 (d, *J* = 7.0 Hz, 1H), 1.09 (d, *J* = 6.0 Hz, 1H), 1.06 (d, *J* = 6.0 Hz, 3H), 0.91 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 173.1, 170.1, 165.7, 151.8, 119.1, 78.5, 76.1, 75.2, 74.3, 71.1, 68.4, 37.3, 36.3, 35.4, 27.3, 22.5, 20.6, 18.2, 13.9, 13.7, 11.9, 10.2; HR MS: calcd for $C_{22}H_{34}O_8Na$ ($M + Na^+$) 449.2146, found 449.2146.

13. Botcinin B (**2**): $[\alpha]_D^{25}$ –27.5 (*c* 0.76, EtOH) [lit.,[1] $[\alpha]_D^{25}$ –35 (*c* 0.50, EtOH)]; IR (neat): 3480, 2928, 1731, 1652 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.01 (dd, *J* = 15.5, 4.5 Hz, 1H), 6.06 (d, *J* = 15.5 Hz, 1H), 5.42 (d, *J* = 10.0 Hz, 1H), 4.54 (dd, *J* = 10.5, 9.9 Hz, 1H), 4.36-4.33 (m, 1H), 3.81 (d, *J* = 10.3 Hz, 1H), 3.68 (dq, *J* = 9.9, 6.5 Hz, 1H), 3.17 (dq, *J* = 10.3, 7.3 Hz, 1H), 2.19 (ddq, *J* = 10.5, 10.0, 6.3 Hz, 1H), 2.13 (s, 3H), 1.65-1.54 (m, 2H), 1.45-1.30 (m, 4H), 1.27 (s, 3H), 1.13 (d, *J* = 7.3 Hz, 3H), 1.10 (d, *J* = 6.3 Hz, 3H), 1.07 (d, *J* = 6.5 Hz, 3H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 173.2, 170.1, 165.7, 151.8, 119.0, 78.6, 76.1, 75.2, 74.3, 71.1, 68.4, 37.3, 36.7, 35.4, 31.7, 29.1, 25.2, 22.5, 20.6, 18.2, 14.0, 13.7, 11.9, 10.2; HR MS: calcd for $C_{24}H_{38}O_8Na$ ($M + Na^+$) 477.2459, found 477.2448.