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

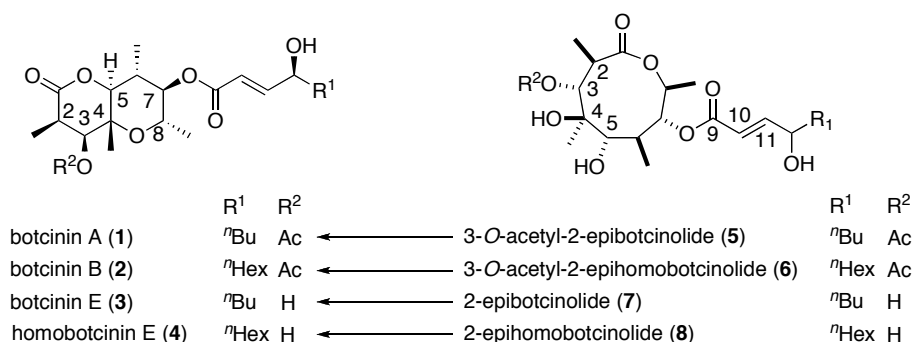
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**Abstract** – The stereoselective total syntheses of botcinins A (**1**) and B (**2**), and homobotcinin E (**4**), a homologue of botcinin E (**3**), have been achieved starting from a polyoxygenated tetrahydropyran intermediate **15** via formation 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**).

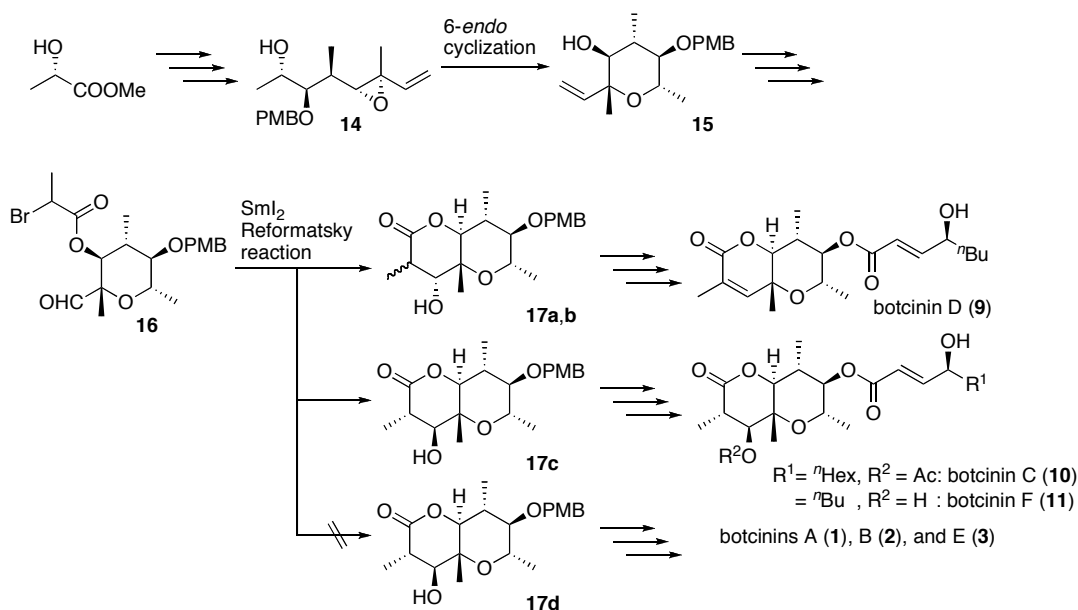
Botcinins A, B and E (**1**, **2** and **3**) were isolated from *Botrytis cinerea* (strain AEM 211) as antifungal metabolites against *Magnaporthe grisea*, a pathogen of the rice blast disease, by Nakajima *et al.* in 2005-6.<sup>1,2</sup> Before the isolation of these compounds by Nakajima, Cutler *et al.*<sup>3-5</sup> and Collado *et al.*<sup>6,7</sup> 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**),<sup>6</sup> 3-*O*-acetyl-2-epihomobotcinolide (**6**),<sup>7</sup> and 2-epibotcinolide (**7**).<sup>6</sup> 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,<sup>2</sup> as shown in **Figure 1**.



**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),<sup>8,9</sup> botcinic acid (12),<sup>9</sup> and botcineric acid (13),<sup>9</sup> and confirmed that the structure of the natural compound assumed to be 2-epibotcinolide (7) is incorrect<sup>10</sup> 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.

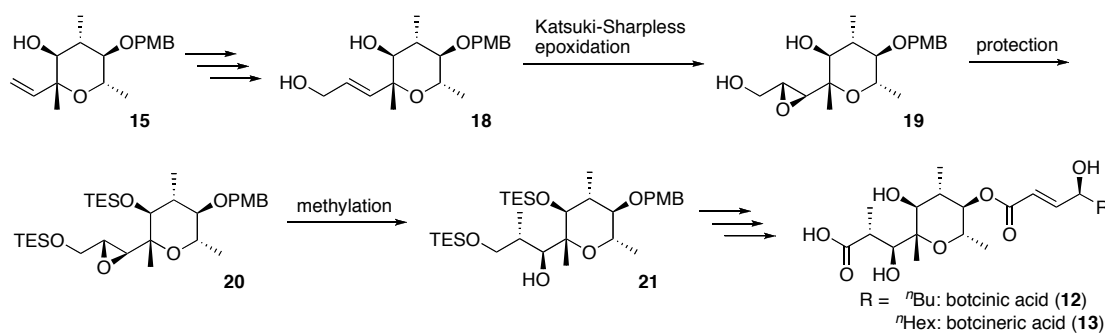
In this communication, we report the total syntheses of botcinins A (1) and B (2), and homobotcinin E (4), and updated the proposed structures of the botcinolides in order to show the true forms of these natural products.



**Scheme 1. Syntheses of Botcinins C (10), D (9), and F (11)<sup>8</sup>**

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**.<sup>8</sup> These precursors were generated from a highly substituted tetrahydropyran ring **15** via the SmI<sub>2</sub>-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**).<sup>9</sup>

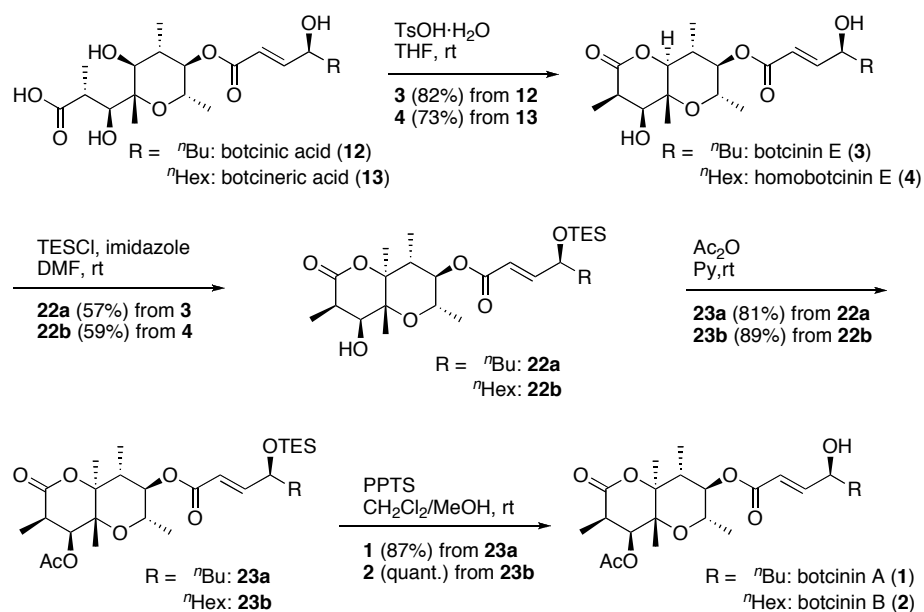
In the previous paper,<sup>9</sup> we also succeeded to transform botcinic acid (**12**) into botcinin E (**3**) by the acidic treatment. Because botcinins A (**1**) and B (**2**) might have the same stereochemistries at the C-2 and -3 positions to those of **3**, it is postulated that **1** and **2**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



**Scheme 2. Syntheses of Botcinic Acid (12) and Botcineric Acid (13)**<sup>9</sup>

First, botcineric acid (**13**) was converted into homobotcinin E (**4**)<sup>11</sup> 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**)<sup>12</sup> and botcinin B (**2**)<sup>13</sup> were finally produced by the deprotection of the TES group in **23a** and **23b**, respectively, under acidic conditions using PPTS in CH<sub>2</sub>Cl<sub>2</sub>/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  $^1\text{H}$  and  $^{13}\text{C}$  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  $^1\text{H}$  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  $\delta$  7.91 ppm in the former report by Collado's group,<sup>6</sup> but they assigned  $\delta$  7.02 ppm to the corresponding proton peak of 8 in the later paper.<sup>7</sup> Furthermore, H-11 of our synthetic 3 and 4 appeared at  $\delta$  7.02 ppm, and Nakajima also assigned the chemical shift of H-11 in the isolated 3 to  $\delta$  7.03 ppm. Therefore, we can expect that the resonance of H-11 in 7 should be observed at around  $\delta$  7.02 ppm, and

**Table 1. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR Data of **2** and **6** in  $\text{CDCl}_3$** 

position	<b>6</b> *		<b>2</b> (isolated)		<b>2</b> (synthetic)	
	$^{13}\text{C}$	$^1\text{H}$	$^{13}\text{C}$	$^1\text{H}$	$^{13}\text{C}$	$^1\text{H}$
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  $\text{CD}_3\text{OD}$ , however, the attached spectra in the paper showed that this experiment had been obviously carried out in  $\text{CDCl}_3$ .<sup>7</sup>

\*\* In the original paper, it was described that the resonance had been observed at  $\delta$  6.03 ppm, however, the attached spectra in the paper showed that this resonance had undoubtedly appeared at around  $\delta$  7.0 ppm.<sup>7</sup>

Collado's group might have made a typographic error in the preparation of their paper. The resonance at  $\delta$  170.1 ppm for C-9 in **7** in  $\text{CD}_3\text{OD}$  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  $\delta$  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**).<sup>9,10</sup>

**Table 2. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR Data of 3, 4, 7, and 8 in  $\text{CD}_3\text{OD}$** 

position	<b>7</b>		<b>3 (isolated)</b>		<b>3 (synthetic)</b>		<b>8</b>		<b>4 (synthetic)</b>	
	$^{13}\text{C}$	and $^1\text{H}$	$^{13}\text{C}$	and $^1\text{H}$	$^{13}\text{C}$	and $^1\text{H}$	$^{13}\text{C}$	and $^1\text{H}$	$^{13}\text{C}$	and $^1\text{H}$
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	<b>170.1</b>	—	<b>165.8</b>	—	<b>165.8</b>	—	<b>167.6</b>	—	<b>167.6</b>	—
10	119.2	5.94	119.1	6.06	119.1	6.05	119.9	6.05	119.8	6.05
11	151.7	<b>7.91</b>	151.8	<b>7.03</b>	151.8	<b>7.02</b>	154.0	<b>7.02</b>	154.1	<b>7.02</b>
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<sub>3</sub>) [lit.,<sup>7</sup>  $[\alpha]_D^{35} -34$  (*c* 2.0, CHCl<sub>3</sub>)]; IR (neat): 3437, 2930, 2857, 1727 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD): 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); <sup>13</sup>C NMR (CD<sub>3</sub>OD): 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<sub>22</sub>H<sub>36</sub>O<sub>7</sub>Na (M + Na<sup>+</sup>) 435.2353, found 435.2332.
12. Botcinin A (**1**):  $[\alpha]_D^{23} -39.3$  (*c* 0.72, EtOH) [lit.,<sup>1</sup>  $[\alpha]_D^{25} -33$  (*c* 0.50, EtOH)]; IR (neat): 3440, 2922, 1733 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): 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); <sup>1</sup>H NMR (CD<sub>3</sub>OD): 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);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  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  $\text{C}_{22}\text{H}_{34}\text{O}_8\text{Na}$  ( $\text{M} + \text{Na}^+$ ) 449.2146, found 449.2146.

13. Botcinin B (**2**):  $[\alpha]_{\text{D}}^{25} -27.5$  ( $c$  0.76, EtOH) [lit.,<sup>1</sup>  $[\alpha]_{\text{D}}^{25} -35$  ( $c$  0.50, EtOH)]; IR (neat): 3480, 2928, 1731, 1652  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  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);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  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  $\text{C}_{24}\text{H}_{38}\text{O}_8\text{Na}$  ( $\text{M} + \text{Na}^+$ ) 477.2459, found 477.2448.