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Total synthesis of radulanin H and proposed structure of radulanin E

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ABSTRACT

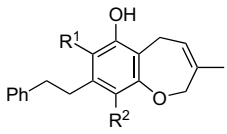
The total synthesis of radulanin H and the proposed structure of radulanin E have been achieved utilizing an intramolecular condensation, sequential regioselective C- and O-allylations, and ring closing metathesis as the key steps.

1. Introduction

Radulanins H (**1**)[1] and E (**2**),[2] isolated by Asakawa et al. from the liverwort *Radula perrottetii* and *Radula variabilis*, are 3-methyl-2,5-dihydro-1-benzoxepin derivatives[3] (Fig. 1). It has been reported that radulanin H (**1**) exhibits significant calmodulin and cyclooxygenase inhibitory activities,[4] and the structures of **1** and **2** containing a highly functionalized benzene ring with a seven-membered cyclic ether moiety have attracted considerable synthetic interest.[5] There have been reports on the total syntheses of **1** and **2** only by Yamaguchi, in which an intramolecular Mitsunobu cyclization was used for the construction of the seven-membered ring.[6,7] Herein, we describe concise total synthesis of radulanin H (**1**) and the proposed structure of radulanin E (**2**), utilizing an intramolecular condensation, sequential regioselective allylations, and ring closing metathesis as the key steps.

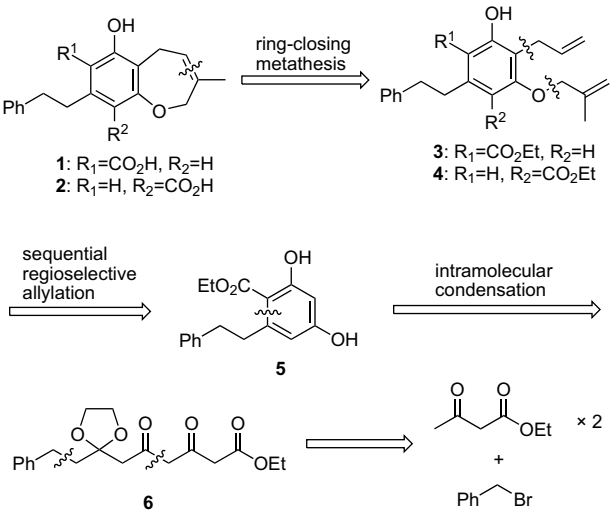
2. Results and discussion

Our strategy for the radulanins H (**1**) and E (**2**) is embodied in the retrosynthetic analysis shown in Scheme 1. We anticipated that the seven-membered cyclic ether moiety could be constructed by the ring closing metathesis of **3** and **4**, each of which would be prepared from a common synthetic intermediate **5** by sequential regioselective C- and O-allylations. The substituted resorcinol **5** would be constructed by an intramolecular condensation of the diketoacetal **6**, derived from ethyl acetoacetate and benzyl bromide.



radulanin H (**1**) : R_1=CO_2H, R_2=H
radulanin E (**2**) : R_1=H, R_2=CO_2H

Figure 1. Structure of radulanins H and E.



Scheme 1. Retrosynthetic analysis.

The preparation of the substituted resorcinol **5** was performed as shown in Scheme 2. The addition of the dienolate of ethyl acetoacetate to benzyl bromide and subsequent protection of the ketone moiety with ethylene glycol in the presence of TsOH furnished the acetal **7** in 81% yield for the two steps. The diketoacetal **6** was obtained likewise by addition of the dienolate to the resulting **7**. When **6** was subjected to the reaction with $NaClO_4$ in AcOH,[8] the

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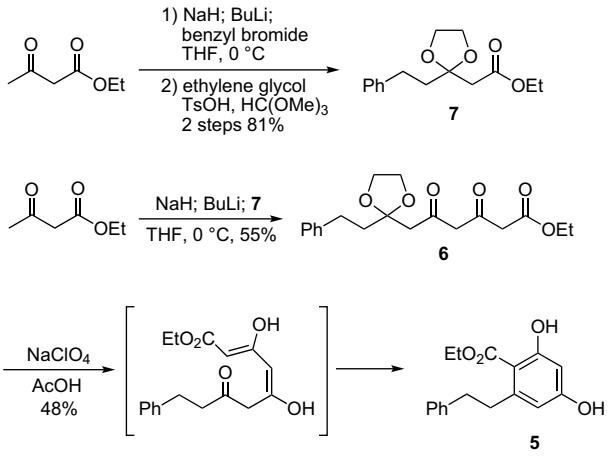
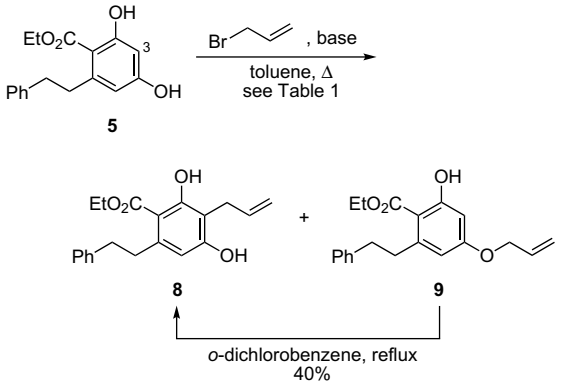


Scheme 2. Synthesis of resorcinol **5**.



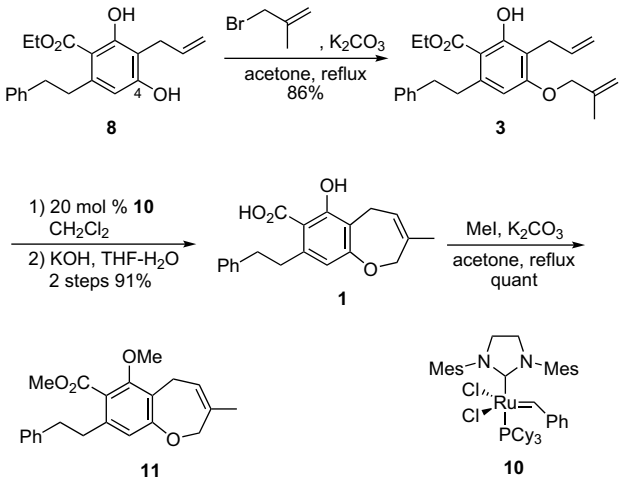
Scheme 3. Regioselective allylation of **5**.

desired intramolecular condensation occurred to afford the substituted resorcinol **5** in 48% yield.

Regioselective C-allylation of **5** was next attempted (Scheme 3). We initially examined the reaction according to Fürstner's procedure,[9] in which the C-allylation of resorcinols proceeded regioselectively. When **5** was treated with allyl bromide and NaH in toluene at 80 °C, the desired C-3 allylated product **8** was produced in 38% yield (Table 1, entry 1). Further examination revealed that the use of Ag_2CO_3 at 140 °C afforded the *O*-allylated product **9** as the major product in 60% yield (entry 2). The ratio of **8** to **9** was altered depending on the base (entries 2–6), and it was found that the desired product **8** was obtained in 57% yield along with the production of **9** (33% yield) when the reaction was carried out in the presence of K_2CO_3 (entry 6). The byproduct **9** was able to be converted to **8** by the Claisen rearrangement in refluxing *o*-dichlorobenzene.

Table 1
Examination of the regioselective allylation of **5**

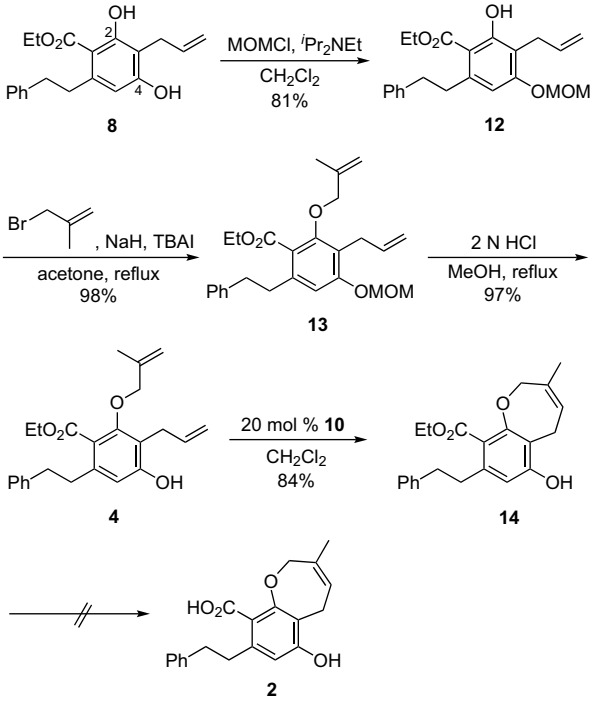
Entry	Base	Temp (°C)	Time (h)	Yields (%)	
				8	**9**
1	NaH	80	13	38	—
2	Ag_2CO_3	140	24	15	60
3	NaOH	140	27	41	23
4	K_3PO_4	140	18	33	37
5	Na_2CO_3	140	48	21	17
6	K_2CO_3	140	3	57	33



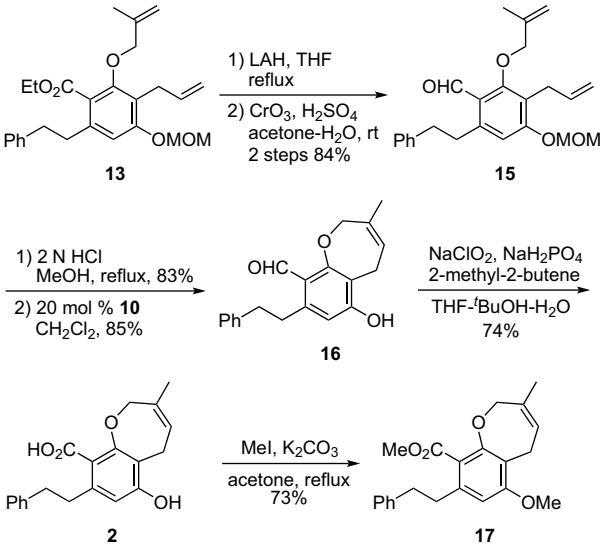
Scheme 4. Completion of the synthesis of radulanin H (**1**).

Our approach toward the synthesis of radulanin H (**1**) is described in Scheme 4. When the allyl resorcinol **8** was treated with β-methallyl bromide and K_2CO_3, the regioselective β-methallylation of the C-4 phenolic oxygen proceeded to give the diene **3** in 86% yield. Finally, ring closing metathesis of **3** using Grubbs second generation catalyst **10**, followed by hydrolysis of the ethyl ester moiety in aqueous KOH solution produced radulanin H (**1**) in 91% yield for the two steps. The structure of the synthesized **1** was confirmed by preparation of the methyl ester derivative **11**.[1] Thus, treatment of **1** with MeI and K_2CO_3 in acetone produced the methyl ester **11**. The ^1H NMR data of synthetic **11** were completely identical with that of the compound derived from the natural radulanin H.

We next focused on the synthesis of radulanin E (**2**). To achieve the synthesis, it is necessary to introduce the β-methallyl moiety on the less reactive C-2 hydroxyl group in **8**. We therefore examined initially the protection of the more reactive C-4 hydroxyl group (Scheme 5). When the intermediate **8** was subjected to the reaction



Scheme 5. Attempts toward the synthesis of radulanin E (**2**).



Scheme 6. Completion of the total synthesis of radulanin E (**2**).

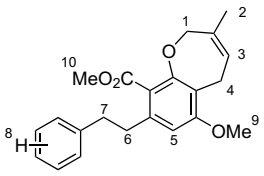


Figure 3. Structure of **17**.

Table 2
Comparison of the ^{1}H NMR data of reported[2] and synthesized **17**

^{1}H number	Reported (90 MHz)	Synthesized (400 MHz)	$\Delta\delta$[a]
1	4.47 (br s)	4.47 (s)	—
2	1.57 (br s)	1.53 (s)	+0.04
3	5.65 (m)	5.56–5.58 (m)	+0.08
4	3.45 (m)	3.40 (d)	+0.05
5	6.77 (s)	6.37 (s)	+0.40
6,7	2.92 (s)	2.89 (s)	+0.03
8	7.30 (s)	7.17–7.21 (m), 7.27–7.30 (m)	+0.06
9	3.78 (s)	3.73 (s)	+0.05
10	3.95 (s)	3.91 (s)	+0.04

[a] Chemical shifts in parts per million.

with MOMCl and ^{i}Pr$_2$NEt, the corresponding MOM ether **12** was regioselectively obtained in 81% yield. The β-methallylation of **12** at the C-2 hydroxyl group proceeded successfully using NaH and TBAI[10] to produce the diene **13** in 98% yield. Deprotection of the MOM group under acidic conditions (97% yield) followed by ring closing metathesis using **10** gave radulanin E ethyl ester (**14**) (84% yield). Finally, we examined the hydrolysis or reduction–oxidation of the ester moiety of **14** under various conditions. However, all attempts failed presumably because of the steric hindrance around the ester moiety.

Having been unable to convert the ester **14** to radulanin E, we chose to adopt the transformation of the ester moiety prior to the construction of the seven-membered ring (Scheme 6). Thus, the ester **13** was reduced with LAH, and the resulting primary alcohol was oxidized using Jones reagent. We expected to obtain the corresponding carboxylic acid, but the aldehyde **15** was actually generated in 84% yield. After cleavage of the MOM group under acidic conditions (83% yield), the resulting phenolic diene was converted to **16** by ring closing metathesis with **10** (85% yield). The structure of **16** was unambiguously confirmed by an X-ray crystallographic analysis (Fig. 2).[11] Although **16** was previously reported as the synthetic intermediate for radulanin E by Yamaguchi,[7] its ^{1}H NMR spectra showed significant differences from that of the reported one.[12] When oxidation of compound **16** using $NaClO_2$ was carried out, the synthesis of radulanin E (**2**) was achieved in 74% yield. The infrared absorption data of synthetic **2** showed agreement with that of the compound derived from the natural radulanin E.[2] The synthesized **2** was further converted to the methyl ester derivative **17**, whose ^{1}H NMR data were compared to the reported one, which was derived from the natural product (Fig. 3 and Table 2).[2] Although most of the signals showed good agreement, the singlet signal of the aromatic proton was not identical (^{1}H number 5 in Table 2).[13] Based on the structural confirmation of **16** by X-ray crystallographic analysis, we are confident that the structure of our synthesized **2** is correct. On the other hand, the assigned structure of radulanin E is reasonable from the viewpoint of the biosynthesis, in which both radulanin H and E would be derived from 2-carboxy-3,5-dihydroxy-4-(3-methyl-2-butenyl)bibenzyl (**18**)[3e] (Scheme 7). From these matters, it is strongly assumed that the signal (6.77 ppm) in the reported **17** would be the typographical error, and the assigned structure of radulanin E (**2**) is correct.

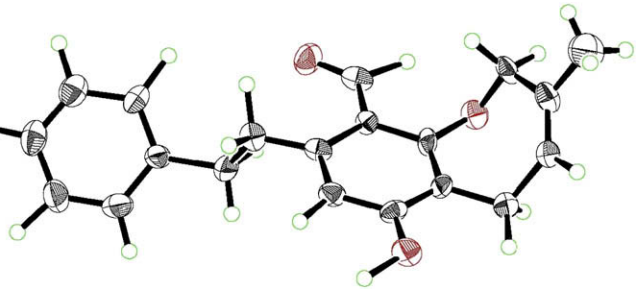
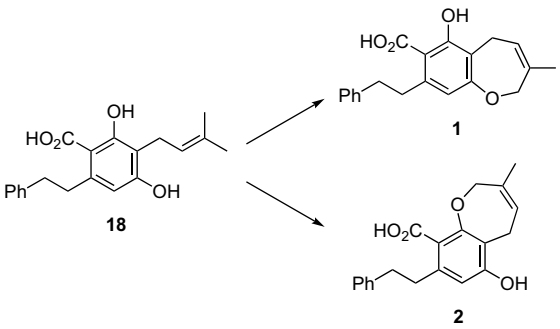


Figure 2. ORTEP drawing of **16**.



Scheme 7. Proposed biosynthetic pathway for radulanin H (**1**) and E (**2**).

3. Conclusion

We have completed the total synthesis of radulanin H and the proposed structure of radulanin E. A part of ^{1}H NMR data of the methyl ester of synthetic radulanin E was not identical with that of the compound derived from the natural radulanin E, but it is suggested that the assigned structure of radulanin E (**2**) is correct.

4. Experimental

4.1. General

All nonaqueous reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise indicated. Materials were obtained from commercial suppliers and used

without further purification except when otherwise noted. Solvents were dried and distilled according to the standard protocols. The phrase 'residue upon workup' refers to the residue obtained when the organic layer was separated and dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure.

4.2. (2-Phenethyl-[1,3]dioxolan-2-yl)-acetic acid ethyl ester (7)

To a stirred suspension of NaH (0.61 g, 25.2 mmol) in THF (50 mL) was added dropwise ethyl acetoactate (2.66 mL, 21.0 mmol) at 0 °C. After stirring was continued for 10 min, a 2.67 M solution of BuLi in hexane (7.9 mL, 21.0 mmol) was added dropwise at the same temperature. After further stirring was continued for 20 min, benzyl bromide (2.75 mL, 23.1 mmol) in THF (3.0 mL) was added dropwise to this mixture and stirring was continued for 1 h at the same temperature. The reaction mixture was quenched with aqueous HCl and extracted with Et_2O. The combined extracts were washed with brine and the residue upon workup was used in the next step without purification. Thus, to a stirred solution of this crude, trimethylorthoformate (6.90 mL, 63.1 mmol) and ethylene glycol (5.86 mL, 105.2 mmol) was added *p*-TsOH (0.40 g, 2.10 mmol) at rt and stirring was continued for 6 h. The reaction mixture was quenched with aqueous NaH_2PO_4 solution and extracted with Et_2O. The combined extracts were washed with brine and the residue upon workup was chromatographed on silica gel with hexane–AcOEt (80:20 v/v) as eluent to give acetal **7** (4.49 g, 81% in two steps) as a colorless oil. IR (neat) cm^{-1} 2980, 2889, 1734, 1045; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, t, J=7.2 Hz), 2.13–2.17 (2H, m), 2.70 (2H, s), 2.71–2.76 (2H, m), 3.99–4.07 (4H, m), 4.16 (2H, q, J=7.2 Hz), 7.16–7.22 (3H, m), 7.26–7.29 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 29.7 (CH_2), 39.5 (CH_2), 42.7 (CH_2), 60.5 (CH_2), 65.2 (CH_2), 108.9 (Cq), 125.7 (CH), 128.3 (CH), 141.8 (Cq), 169.4 (Cq); HRMS (ESI) m/z calcd for $C_{15}H_{20}O_4Na$ $[M+Na]^+$ 287.1259, found 287.1253.

4.3. 3,5-Dioxo-6-(2-phenethyl-[1,3]dioxolan-2-yl)-hexanoic acid ethyl ester (6)

To a stirred suspension of NaH (7.0 g, 0.29 mol) in THF (800 mL) was added dropwise ethyl acetoacetate (30.7 mL, 0.24 mol) at 0 °C. After stirring was continued for 10 min, a 2.80 M solution of BuLi in hexane (86.6 mL, 0.24 mol) was added dropwise at the same temperature. After further stirring was continued for 20 min, acetal **7** (15.4 g, 58.1 mmol) in THF (200 mL) and $BF_3{\cdot}OEt_2$ (11.5 mL, 93.0 mmol) were added successively to this mixture at −78 °C and stirring was continued for 1 h at 0 °C. The reaction mixture was quenched with water and extracted with AcOEt. The combined extracts were washed with saturated aqueous $NaHCO_3$ solution and brine. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (70:30 v/v) as eluent to give diketoester **6** (11.1 g, 55%) as a yellow oil; IR (neat) cm^{-1} 2981, 2892, 1738, 1604, 1033; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, t, J=7.2 Hz), 2.03–2.07 (2H, m), 2.66 (2H, s), 2.70–2.75 (2H, m), 2.88 (0.33H, s), 3.35 (2H, s), 3.55 (0.33H, s), 3.83 (0.33H, s), 4.02 (4H, s), 4.19 (2H, q, J=7.2 Hz), 5.72 (1H, s), 7.16–7.20 (3H, m), 7.26–7.29 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 29.6 (CH_2), 39.8 (CH_2), 45.3 (CH_2), 45.8 (CH_2), 61.4 (CH_2), 65.2 (CH_2), 102.0 (CH_2), 109.5 (Cq), 125.8 (CH), 128.3 (CH), 128.3 (CH), 141.6 (Cq), 167.3 (Cq), 187.6 (Cq), 187.9 (Cq); HRMS (ESI) m/z calcd for $C_{19}H_{24}O_6Na$ $[M+Na]^+$ 371.1471, found 371.1481.

4.4. 2,4-Dihydroxy-6-phenethyl-benzoic acid ethyl ester (5)

To a stirred solution of diketoester **6** (1.0 g, 2.87 mmol) in acetic acid (70 mL) was added $NaClO_4$ (1.76 g, 14.4 mmol) at rt. After stirring was continued for 7 h, the reaction mixture was diluted with water and extracted with AcOEt. The combined extracts were washed with water, saturated aqueous $NaHCO_3$ solution and brine. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (70:30 v/v) as eluent to give resorcinol **5** (0.40 g, 48%) as colorless crystals; mp: 86.4–87.6 °C (recrystallized from AcOEt/hexane); IR (KBr) cm^{-1} 3298, 2985, 1647, 1599; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, t, J=7.2 Hz), 2.87 (2H, t, J=7.6 Hz), 3.20 (2H, t, J=7.6 Hz), 4.43 (2H, q, J=7.2 Hz), 5.78 (1H, s), 6.18 (1H, d, J=2.4 Hz), 6.31 (1H, d, J=2.4 Hz), 7.16–7.22 (3H, m), 7.25–7.31 (2H, m), 11.86 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 38.0 (CH_2), 38.3 (CH_2), 61.5 (CH_2), 101.7 (CH), 105.3 (Cq), 111.0 (CH), 126.0 (CH), 128.2 (CH), 128.4 (CH), 141.7 (Cq), 147.5 (Cq), 160.1 (Cq), 165.4 (Cq), 171.3 (Cq); HRMS (ESI) m/z calcd for $C_{17}H_{18}O_4Na$ $[M+Na]^+$ 309.1103, found 309.1110.

4.5. 3-Allyl-2,4-dihydroxy-6-phenethyl-benzoic acid ethyl ester (8) and 4-allyloxy-2-hydroxy-6-phenethyl-benzoic acid ethyl ester (9)

To a stirred suspension of resorcinol **5** (104 mg, 0.36 mmol) and K_2CO_3 (60.4 mg, 0.44 mmol) in toluene (6 mL) was added allyl bromide (0.16 mL, 1.82 mmol) at rt. After stirring was continued for 3 h at 130 °C in sealed tube, the reaction mixture was filtrated through Celite. The residue upon evaporation of the solvent was chromatographed on silica gel with hexane–AcOEt (80:20 v/v) as eluent to give allyl resorcinol **8** (67.5 mg, 57%) and *o*-allyl ether **9** (39.2 mg, 33%). Compound **8**: colorless crystals, mp 88.5–89.6 °C (recrystallized from AcOEt/hexane); IR (KBr) cm^{-1} 3350, 3074, 1618, 1279; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, t, J=7.2 Hz), 2.87 (2H, t, J=5.6 Hz), 3.18 (2H, t, J=5.6 Hz), 3.48 (2H, d, J=6.0 Hz), 4.44 (2H, q, J=7.2 Hz), 5.11–5.18 (2H, m), 5.38 (1H, s), 6.00 (1H, ddt, J=16.8, 10.0, and 6.0 Hz), 6.22 (1H, s), 7.17–7.22 (3H, m), 7.27–7.31 (2H, m), 12.17 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 27.2 (CH_2), 38.0 (CH_2), 38.2 (CH_2), 61.5 (CH_2), 105.0 (Cq), 110.4 (Cq), 110.8 (CH), 115.8 (CH_2), 125.9 (CH), 128.2 (CH), 128.3 (CH), 135.8 (CH), 141.8 (Cq), 144.8 (Cq), 158.9 (Cq), 162.8 (Cq), 171.8 (Cq); HRMS (ESI) m/z calcd for $C_{20}H_{22}O_4Na$ $[M+Na]^+$ 349.1416, found 349.1419. Compound **9**: colorless oil, IR (neat) cm^{-1} 2982, 1650, 1614, 1577, 1254, 1175; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, t, J=7.2 Hz), 2.87 (2H, t, J=5.6 Hz), 3.20 (2H, t, J=5.6 Hz), 4.43 (2H, q, J=7.2 Hz), 4.50 (2H, d, J=5.6 Hz), 5.29 (1H, dd, J=10.4 and 1.2 Hz), 5.39 (1H, dd, J=17.2 and 1.2 Hz), 6.00 (1H, ddt, J=17.2, 10.4, and 5.6 Hz), 6.28 (1H, d, J=2.4 Hz), 6.36 (1H, d, J=2.4 Hz), 7.17–7.22 (3H, m), 7.27–7.31 (2H, m), 11.84 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 38.0 (CH_2), 38.4 (CH_2), 61.4 (CH_2), 68.6 (CH_2), 100.0 (CH), 104.9 (Cq), 111.3 (CH), 118.1 (CH_2), 125.9 (CH), 128.2 (CH), 128.3 (CH), 132.4 (CH), 141.8 (Cq), 146.7 (Cq), 162.8 (Cq), 165.5 (Cq), 171.4 (Cq); HRMS (ESI) m/z calcd for $C_{20}H_{22}O_4Na$ $[M+Na]^+$ 349.1426, found 349.1423.

4.6. 3-Allyl-2-hydroxy-4-(2-methylallyloxy)-6-phenethyl-benzoic acid ethyl ester (3)

To a stirred suspension of allyl resorcinol **8** (40.0 mg, 0.12 mmol) and K_2CO_3 (25.4 mg, 0.18 mmol) in acetone (1 mL) was added β-methallyl bromide (0.015 mL, 0.15 mmol) at rt. After stirring was continued for 4 h under reflux condition, the reaction mixture was filtrated through Celite. The residue upon evaporation of the solvent was chromatographed on silica gel with hexane–AcOEt (97:3 v/v) as eluent to give diene **3** (40.2 mg, 86%) as a colorless oil; IR (neat) cm^{-1} 2978, 2925, 1649, 1281; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, t, J=7.2 Hz), 1.80 (3H, s), 2.88 (2H, t, J=7.6 Hz), 3.22 (2H, t, J=7.6 Hz), 3.44 (2H, d, J=6.4 Hz), 4.34 (2H, s), 4.43 (2H, q, J=7.2 Hz), 4.94–5.06 (4H, m), 6.00 (1H, ddt, J=17.2, 10.0, and 6.4 Hz), 6.13 (1H, s), 7.15–7.21 (3H, m), 7.27–7.30 (2H, m), 11.87 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 19.4 (CH_3), 27.1 (CH_2), 38.1 (CH_2),

38.7 (CH_2), 61.4 (CH_2), 71.5 (CH_2), 105.3 (Cq), 107.0 (CH), 112.5 (CH_2), 113.6 (Cq), 114.2 (CH_2), 125.9 (CH), 128.3 (CH), 128.4 (CH), 136.3 (CH), 140.5 (Cq), 141.8 (Cq), 144.2 (Cq), 160.3 (Cq), 162.1 (Cq), 171.6 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{24}H_{28}O_4Na$ $[M+Na]^+$ 403.1885, found 403.1882.

4.7. 6-Hydroxy-3-methyl-8-phenethyl-2,5-dihydro-benzo[*b*]oxepine-7-carboxylic acid (radulanin H) (1)

To a stirred solution of diene **3** (9.4 mg, 0.025 mmol) in degassed CH_2Cl_2 (2.5 mL) was added second generation Grubbs' catalyst **10** (4.2 mg, 4.9 μmol) at rt. After stirring was continued for 2 h, the residue upon evaporation of the solvent was quickly chromatographed on silica gel with hexane–AcOEt (95:5 v/v) as eluent to give radulanin H ethyl ester. To a stirred solution of this radulain H ethyl ester in THF–water (1:2) (3 mL) was added KOH (12.7 mg, 0.23 mmol) at rt and stirring was continued for 12 h at 50 °C. The reaction mixture was quenched with aqueous HCl and extracted with CH_2Cl_2. The combined extracts were washed with brine and the residue upon workup was chromatographed on silica gel with hexane–AcOEt (50:50 v/v) as eluent to give radulanin H (**1**) (6.7 mg, 91% in two steps) as colorless crystals; mp 125.5–126.4 °C (recrystallized from AcOEt/hexane); IR (KBr) cm^{-1} 3024, 1635, 1254; ^1H NMR (400 MHz, $CDCl_3$) δ 1.64 (3H, s), 2.89 (2H, t, *J*=7.6 Hz), 3.22 (2H, t, *J*=7.6 Hz), 3.52 (2H, d, *J*=4.4 Hz), 4.50 (2H, s), 5.72 (1H, t, *J*=4.4 Hz), 6.41 (1H, s), 7.18–7.21 (3H, m), 7.27–7.31 (2H, m), 11.70 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6 (CH_3), 21.6 (CH_2), 38.1 (CH_2), 38.6 (CH_2), 72.9 (CH_2), 105.6 (Cq), 116.0 (CH), 119.5 (Cq), 122.7 (CH), 126.0 (CH), 128.4 (CH), 128.4 (CH), 134.1 (Cq), 141.8 (Cq), 145.7 (Cq), 162.3 (Cq), 164.2 (Cq), 175.8 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{20}O_4Na$ $[M+Na]^+$ 347.1259, found 347.1258.

4.8. 6-Methoxy-3-methyl-8-phenethyl-2,5-dihydro-benzo[*b*]oxepine-7-carboxylic acid methyl ester (radulanin H methyl ester methyl ether) (11)

To a stirred suspension of radulanin H (**1**) (24.6 mg, 0.076 mmol) and K_2CO_3 (31.4 mg, 0.23 mmol) in acetone (10 mL) was added MeI (0.24 mL, 3.80 mmol) at rt. After stirring was continued for 18 h under reflux condition, the reaction mixture was filtrated through Celite. The residue upon evaporation of the solvent was chromatographed on silica gel with hexane–AcOEt (85:15 v/v) as eluent to give methyl ester **11** (27.5 mg, quant) as a colorless oil; IR (neat) cm^{-1} 2942, 1730, 1302, 1268; ^1H NMR (400 MHz, $CDCl_3$) δ 1.54 (3H, s), 2.79–2.90 (4H, m), 3.40–3.42 (2H, m), 3.74 (3H, s), 3.91 (3H, s), 4.40 (2H, s), 5.59–5.63 (1H, m), 6.70 (1H, s), 7.16–7.21 (3H, m), 7.26–7.30 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0 (CH_3), 22.3 (CH_2), 35.6 (CH_2), 37.6 (CH_2), 52.2 (CH_3), 62.9 (CH_3), 74.2 (CH_2), 118.1 (CH), 120.2 (CH), 124.4 (Cq), 126.1 (CH), 127.9 (Cq), 128.4 (CH), 134.3 (Cq), 139.0 (Cq), 141.5 (Cq), 154.5 (Cq), 160.4 (Cq), 168.7 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{22}H_{24}O_4Na$ $[M+Na]^+$ 375.1572, found 375.1571.

4.9. 3-Allyl-2-hydroxy-4-methoxymethoxy-6-phenethyl-benzoic acid ethyl ester (12)

To a stirred solution of allyl resorcinol **8** (0.37 g, 1.14 mmol) and $^iPr_2NEt$ (0.40 mL, 2.27 mmol) in CH_2Cl_2 (12 mL) was added MOMCl (0.13 mL, 1.70 mmol) at rt. After stirring was continued for 8 h at the same temperature, the reaction mixture was diluted with water and extracted with AcOEt. The combined extracts were washed with brine and the residue upon workup was chromatographed on silica gel with hexane–AcOEt (90:10 v/v) as eluent to give ether **12** (0.34 g, 81%) as a colorless oil; IR (neat) cm^{-1} 2979, 1650, 1274; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, t, *J*=7.2 Hz), 2.88 (2H, t, *J*=7.2 Hz), 3.22 (2H, t, *J*=7.2 Hz), 3.43 (2H, d, *J*=6.0 Hz), 3.43 (3H, s), 4.44 (2H, q, *J*=7.2 Hz), 4.94–5.02 (2H, m), 5.12 (2H, s), 5.97 (1H, ddt, *J*=17.2, 10.0, and 6.0 Hz), 6.37 (1H, s), 7.15–7.21 (3H, m), 7.26–7.30 (2H, m), 11.87 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3), 27.1 (CH_2), 38.1 (CH_2), 38.6 (CH_2), 56.2 (CH_3), 61.4 (CH_2), 93.7 (CH_2), 106.0 (Cq), 108.6 (CH), 114.2 (Cq), 114.2 (CH_2), 125.9 (CH), 128.3 (CH), 128.3 (CH), 136.2 (CH), 141.7 (Cq), 144.2 (Cq), 158.9 (Cq), 162.2 (Cq), 171.6 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{22}H_{26}O_5Na$ $[M+Na]^+$ 393.1678, found 393.1675.

4.10. 3-Allyl-4-methoxymethoxy-2-(2-methylallyloxy)-6-phenethyl-benzoic acid ethyl ester (13)

To a stirred suspension of ether **12** (44.0 mg, 0.12 mmol), NaH (5.7 mg, 0.24 mmol), and β-methallyl bromide (0.018 mL, 0.18 mmol) in THF (1.5 mL) was added TBAI (87.7 mg, 0.24 mmol) at 0 °C. After stirring was continued for 3 h at rt, the reaction mixture was quenched with water and extracted with Et_2O. The combined extracts were washed with brine and the residue upon workup was chromatographed on silica gel with hexane–AcOEt (90:10 v/v) as eluent to give diene **13** (50.4 mg, 98%) as a colorless oil; IR (neat) cm^{-1} 2977, 2935, 1721, 1270; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, t, *J*=7.2 Hz), 1.81 (3H, s), 2.87 (4H, br s), 3.40 (2H, d, *J*=6.0 Hz), 3.43 (3H, s), 4.29 (2H, s), 4.35 (2H, q, *J*=7.2 Hz), 4.94–5.00 (3H, m), 5.10–5.14 (3H, m), 5.98 (1H, ddt, *J*=17.6, 9.6, and 6.0 Hz), 6.64 (1H, s), 7.16–7.21 (3H, m), 7.26–7.30 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3), 19.4 (CH_3), 28.1 (CH_2), 35.9 (CH_2), 37.7 (CH_2), 56.1 (CH_3), 61.2 (CH_2), 78.6 (CH_2), 94.2 (CH_2), 110.7 (CH), 111.7 (CH_2), 114.7 (CH_2), 120.6 (Cq), 122.7 (Cq), 125.9 (CH), 128.3 (CH), 128.5 (CH), 136.7 (CH), 139.0 (Cq), 141.3 (Cq), 141.5 (Cq), 155.2 (Cq), 156.8 (Cq), 168.4 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{32}O_5Na$ $[M+Na]^+$ 447.2147, found 447.2154.

4.11. 3-Allyl-4-hydroxy-2-(2-methylallyloxy)-6-phenethyl-benzoic acid ethyl ester (4)

To a stirred solution of ether **13** (29.8 mg, 0.070 mmol) in MeOH (1 mL) was added aqueous HCl at rt. After stirring was continued for 1.5 h under reflux condition, the reaction mixture was diluted with water and extracted with AcOEt. The combined extracts were washed with saturated aqueous $NaHCO_3$ solution and brine. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (80:20 v/v) as eluent to give phenol **4** (26.0 mg, 97%) as colorless crystals; mp 57.1–58.0 °C (recrystallized from AcOEt/hexane); IR (KBr) cm^{-1} 3313, 2978, 2941, 1678; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, t, *J*=7.2 Hz), 1.81 (3H, s), 2.81–2.90 (4H, m), 3.45 (2H, d, *J*=5.6 Hz), 4.26 (2H, s), 4.35 (2H, q, *J*=7.2 Hz), 4.94 (1H, s), 5.10 (1H, s), 5.14–5.18 (2H, m), 5.23 (1H, s), 6.02 (1H, ddt, *J*=16.4, 10.8, and 5.6 Hz), 6.49 (1H, s), 7.17–7.21 (3H, m), 7.28–7.30 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3), 19.4 (CH_3), 28.1 (CH_2), 35.5 (CH_2), 37.5 (CH_2), 61.3 (CH_2), 78.8 (CH_2), 112.0 (CH_2), 112.8 (CH), 116.4 (CH_2), 116.8 (Cq), 121.7 (Cq), 126.0 (CH), 128.3 (CH), 128.4 (CH), 136.0 (CH), 139.7 (Cq), 141.1 (Cq), 141.5 (Cq), 155.5 (Cq), 156.4 (Cq), 168.5 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{24}H_{28}O_4Na$ $[M+Na]^+$ 403.1885, found 403.1884.

4.12. 6-Hydroxy-3-methyl-8-phenethyl-2,5-dihydro-benzo[*b*]oxepine-9-carboxylic acid ethyl ester (14)

To a stirred solution of phenol **4** (19.1 mg, 0.050 mmol) in degassed CH_2Cl_2 (3 mL) was added second generation Grubbs' catalyst **10** (8.5 mg, 0.010 mmol) at rt. After stirring was continued for 3 h, the residue upon evaporation of the solvent was chromatographed on silica gel with hexane–AcOEt (90:10 v/v) as eluent to give radulanin E ethyl ester (**14**) (14.9 mg, 84%) as a colorless oil; IR (neat) cm^{-1} 3378, 2978, 2929, 1696, 1609; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, t, *J*=7.2 Hz), 1.53 (3H, d, *J*=0.8 Hz), 2.82–2.87 (4H, m), 3.38 (2H, d, *J*=4.0 Hz), 4.39 (2H, q, *J*=7.2 Hz), 4.47 (2H, s), 5.16

(1H, s), 5.56–5.59 (1H, m), 6.34 (1H, s), 7.15–7.21 (3H, m), 7.28–7.29 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4 (CH_3), 19.9 (CH_3), 21.5 (CH_2), 35.4 (CH_2), 37.6 (CH_2), 61.1 (CH_2), 74.2 (CH_2), 112.3 (CH), 119.8 (CH), 120.4 (Cq), 121.9 (Cq), 126.0 (CH), 128.4 (CH), 134.1 (Cq), 138.9 (Cq), 141.5 (Cq), 153.2 (Cq), 156.9 (Cq), 168.2 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{22}H_{24}O_4Na$ $[M+Na]^+$ 375.1572, found 375.1572.

4.13. 3-Allyl-4-methoxymethoxy-2-(2-methylallyloxy)-6-phenethyl-benzaldehyde (15)

To a stirred suspension of LAH (0.11 g, 3.0 mmol) in THF (3 mL) was added dropwise diene **13** (25.5 mg, 0.060 mmol) in THF (0.5 mL) at rt. After stirring was continued for 1 h under reflux condition, and the reaction mixture was quenched with water and extracted with AcOEt. The combined extracts were washed with brine and the residue upon workup was used in the next step without purification. Thus, to a stirred solution of this crude in acetone (1 mL) was added Jones reagent (prepared from 2.7 g of CrO_3 and 2.3 mL of concentrated H_2SO_4 in 7.7 mL of water) at rt and stirring was continued for 1 min. The reaction mixture was filtrated through Celite and the residue upon evaporation of the solvent was chromatographed on silica gel with hexane–AcOEt (80:20 v/v) as eluent to give aldehyde **15** (22.9 mg, 84% in two steps) as a colorless oil; IR (neat) cm^{-1} 2922, 2861, 1681, 1595, 1562, 1060; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (3H, s), 2.85 (2H, t, *J*=7.6 Hz), 3.25 (2H, t, *J*=7.6 Hz), 3.42–3.43 (2H, m), 3.44 (3H, s), 4.29 (2H, s), 4.96–5.02 (3H, m), 5.15 (2H, s), 5.18 (1H, s), 5.98 (1H, ddt, *J*=16.4, 10.4, and 7.6 Hz), 6.62 (1H, s), 7.16–7.20 (2H, m), 7.24–7.30 (3H, m), 10.41 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5 (CH_3), 27.7 (CH_2), 36.7 (CH_2), 37.4 (CH_2), 56.3 (CH_3), 80.5 (CH_2), 93.9 (CH_2), 112.4 (CH), 112.8 (CH_2), 114.8 (CH_2), 120.6 (Cq), 121.7 (Cq), 125.7 (CH), 128.2 (CH), 128.7 (CH), 136.3 (CH), 140.4 (Cq), 141.9 (Cq), 145.4 (Cq), 160.0 (Cq), 163.4 (Cq), 191.2 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{24}H_{28}O_4Na$ $[M+Na]^+$ 403.1885, found 403.1885.

4.14. 3-Allyl-4-hydroxy-2-(2-methylallyloxy)-6-phenethyl-benzaldehyde

To a stirred solution of aldehyde **15** (22.9 mg, 0.060 mmol) in MeOH (1 mL) was added aqueous HCl at rt. After stirring was continued for 2 h at under reflux condition, the reaction mixture was diluted with water and extracted with AcOEt. The combined extracts were washed with saturated aqueous $NaHCO_3$ solution and brine. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (80:20 v/v) as eluent to give phenol (16.9 g, 83%) as colorless crystals; mp: 112.8–113.0 °C (recrystallized from AcOEt/hexane); IR (KBr) cm^{-1} 3070, 2924, 1657, 1593, 1427; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (3H, s), 2.83 (2H, t, *J*=7.6 Hz), 3.22 (2H, t, *J*=7.6 Hz), 3.48 (2H, d, *J*=5.6 Hz), 4.27 (2H, s), 5.02 (1H, s), 5.13–5.18 (3H, m), 5.92 (1H, br s), 6.03 (1H, ddt, *J*=17.2, 10.4, and 7.6 Hz), 6.48 (1H, s), 7.16–7.20 (2H, m), 7.25–7.30 (3H, m), 10.37 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5 (CH_3), 27.7 (CH_2), 36.4 (CH_2), 37.3 (CH_2), 80.6 (CH_2), 113.0 (CH_2), 114.8 (CH), 116.0 (CH_2), 117.6 (Cq), 120.6 (Cq), 125.8 (CH), 128.2 (CH), 128.5 (CH), 135.8 (CH), 140.3 (Cq), 141.8 (Cq), 146.1 (Cq), 160.8 (Cq), 164.5 (Cq), 191.8 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{22}H_{24}O_3Na$ $[M+Na]^+$ 359.1623, found 359.1620.

4.15. 6-Hydroxy-3-methyl-8-phenethyl-2,5-dihydro-benzo[*b*]oxepine-9-carbaldehyde (16)

To a stirred solution of phenol (18.8 mg, 0.056 mmol) in degassed CH_2Cl_2 (3 mL) was added second generation Grubbs' catalyst **10** (9.5 mg, 0.011 mmol) at rt. After stirring was continued for 2 h at the same temperature, the reaction mixture was evaporated and residual oil was directly chromatographed on silica gel with hexane–AcOEt (90:10 v/v) as eluent to give **16** (14.6 mg, 85%) as colorless crystals; mp: 169.7–170.3 °C (recrystallized from AcOEt/hexane); IR (KBr) cm^{-1} 3147, 2924, 1658, 1577, 1309; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (3H, d, *J*=1.2 Hz), 2.82 (2H, t, *J*=7.6 Hz), 3.20 (2H, t, *J*=7.6 Hz), 3.43 (2H, d, *J*=4.0 Hz), 4.53 (2H, d, *J*=1.2 Hz), 5.62–5.66 (1H, m), 5.87 (1H, s), 6.36 (1H, s), 7.15–7.20 (2H, m), 7.24–7.29 (3H, m), 10.46 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8 (CH_3), 21.2 (CH_2), 36.3 (CH_2), 37.3 (CH_2), 74.7 (CH_2), 114.4 (CH), 120.0 (Cq), 120.4 (CH), 122.0 (Cq), 125.9 (CH), 128.3 (CH), 128.6 (CH), 133.6 (Cq), 141.9 (Cq), 144.9 (Cq), 157.3 (Cq), 165.5 (Cq), 191.1 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{20}O_3Na$ $[M+Na]^+$ 331.1310, found 331.1313.

4.16. X-ray crystallographic analysis of compound 16[11]

A colorless block crystal having approximate dimensions of 0.70×0.50×0.30 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo Kα radiation. The structure was solved by direct methods (SIR97) and expanded using Fourier techniques (DIRDIF99). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on *F* was based on 31,136 observed reflections ($I>0.00\sigma(I)$) and 912 variable parameters and converged (largest parameter shift was 8.20 times its esd) with unweighted and weighted agreement factors of R=0.064 and R_w=0.199. Crystal data for **16**: $C_{20}H_{20}O_3$, M=308.38, monoclinic, space group $P2_1$, a=7.2514(3) Å, b=15.3163(8) Å, c=29.364(1) Å, b=90.0000°, V=3261.3(3) Å^3, Z=8, D_c=1.256 g/cm^3, $F(000)$=1312.00, μ(Mo Kα)=0.83 cm^{-3}.

4.17. 6-Hydroxy-3-methyl-8-phenethyl-2,5-dihydro-benzo[*b*]oxepine-9-carboxylic acid (proposed structure of radulanin E) (2)

To a stirred solution of **16** (29.8 mg, 0.10 mmol), NaH_2PO_4 (92.8 mg, 0.77 mmol), and 2-methyl-2-butene (0.56 mL, 5.3 mmol) in THF–^{t}BuOH–water (1:3:5) (5 mL) was added $NaClO_2$ (61.2 mg, 0.68 mmol) at rt and stirring was continued for 15 h. The reaction mixture was quenched with aqueous HCl and extracted with CH_2Cl_2. The combined extracts were washed with brine and the residue upon workup was chromatographed on silica gel with hexane–AcOEt (50:50 v/v) as eluent to give the proposed structure of radulanin E (**2**) (23.2 mg, 74%) as colorless crystals; mp 150.6–151.2 °C (recrystallized from AcOEt/hexane); IR ($CHCl_3$) cm^{-1} 3170, 1716, 1603, 1583, 1504, 874, 744; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (3H, s), 2.89 (2H, t, *J*=7.2 Hz), 3.16 (2H, t, *J*=7.2 Hz), 3.43 (2H, d, *J*=4.0 Hz), 4.60 (2H, s), 5.50 (1H, br s), 5.62–5.65 (1H,m), 6.45 (1H, s), 7.16–7.29 (5H, m), 10.73 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7 (CH_3), 21.4 (CH_2), 37.0 (CH_2), 37.7 (CH_2), 74.8 (CH_2), 114.7 (CH), 115.0 (Cq), 120.3 (CH), 121.9 (Cq), 125.9 (CH), 128.3 (CH), 128.6 (CH), 132.9 (Cq), 141.8 (Cq), 144.1 (Cq), 154.7 (Cq), 158.8 (Cq), 167.5 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{20}O_4Na$ $[M+Na]^+$ 347.1259, found 347.1256.

4.18. 6-Methoxy-3-methyl-8-phenethyl-2,5-dihydro-benzo[*b*]oxepine-9-carboxylic acid methyl ester (17)

To a stirred suspension of (**2**) (12.8 mg, 0.039 mmol) and K_2CO_3 (16.4 mg, 0.12 mmol) in acetone (4 mL) was added MeI (0.12 mL, 1.97 mmol) at rt. After stirring was continued for 1 h under reflux condition, the reaction mixture was filtrated through Celite. The residue upon evaporation of the solvent was chromatographed on silica gel with hexane–AcOEt (90:10 v/v) as eluent to give methyl ester **17** (10.2 g, 73%) as a colorless oil; IR (neat) cm^{-1} 2947, 1731, 1604, 1577, 1452; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (3H, s), 2.89 (4H, s), 3.40 (2H, d, *J*=4.0 Hz), 3.73 (3H, s), 3.91 (3H, s), 4.47 (2H, s), 5.56–5.58 (1H, m), 6.37 (1H, s), 7.17–7.21 (3H, m), 7.27–7.30 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9 (CH_3), 21.1 (CH_2), 36.2 (CH_2), 37.9

(CH_2), 52.0 (CH_3), 55.7 (CH_3), 74.1 (CH_2), 107.8 (CH), 120.0 (CH), 120.1 (Cq), 123.6 (Cq), 126.0 (CH), 128.4 (CH), 128.5 (CH), 134.1 (Cq), 138.9 (Cq), 141.6 (Cq), 156.4 (Cq), 156.8 (Cq), 168.5 (Cq); HRMS (ESI) m/z calcd for $C_{22}H_{24}O_4Na$ $[M+Na]^+$ 375.1572, found 375.1572.

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Supplementary data

^1H and ^{13}C spectra for all compounds can be found in the Supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.05.027.

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11. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 724435. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
12. We checked the Yamaguchi's NMR chart of **16**, which was provided by Prof. Yamaguchi, and it was found that his sample contained many impurities. It is assumed that the Yamaguchi's data have been misassigned because of the impurity peaks.
13. A NMR chart of **17**, which was prepared by Asakawa could not be obtained because the data were measured more than 30 years ago.