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Synthesis of Two Naturally Occurring 3-Methyl-2,5-dihydro-1-benzoxepin Carboxylic Acids

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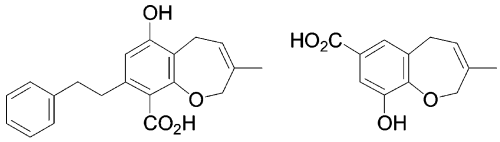

Radulanin E (**1**) (**2**)

Two naturally occurring 3-methyl-2,5-dihydro-1-benzoxepin carboxylic acids, 6-hydroxy-3-methyl-8-(phenylethyl)-2,5-dihydro-1-benzoxepin-9-carboxylic acid (radulanin E) (**1**) and 9-hydroxy-3-methyl-2,5-dihydro-1-benzoxepin-7-carboxylic acid (**2**), were synthesized using Stille coupling followed by Mitsunobu cyclization.

Many compounds having a 3-methyl-2,5-dihydro-1-benzoxepin structure have been isolated from various kinds of plants.[1a−o] As shown in Scheme 1, they might be biogenetically derived from *o*-prenylphenols; an oxidative seven-membered cyclization gives corresponding 3-methyl-2,5-dihydro-1-benzoxepins, while a similar five- or six-membered cyclization gives corresponding 2-isopropenyl-2,3-dihydrobenzofurans or 2,2-dimethyl-2*H*-chromenes.

Our recent interests have been focused on the effective preparation of naturally occurring 3-methyl-2,5-dihydro-1-benzoxepin derivatives. Now, in this paper, the first syntheses of two naturally occurring 3-methyl-2,5-dihydro-1-benzoxepin carboxylic acids, shown in Figure 1, 6-hydroxy-3-methyl-8-(phenylethyl)-2,5-dihydro-1-benzoxepin-9-carboxylic acid (radulanin E) (**1**),[1e,f] isolated from *Radula* sp. (Hepaticae), and 9-hydroxy-3-methyl-2,5-dihydro-1-benzoxepin-7-carboxylic acid (**2**),[1l] isolated from *Hemizonia lobbii* (Composiate), are described.

As shown in Scheme 2, only two procedures were reported for the preparation of 3-methyl-2,5-dihydro-1-benzoxepins; the first one was a ring-closing metathesis, reported by Stefinovic et al.,[2] and the other one was Stille coupling of ortho-O-protected benzyl bromide with 3-(2-tetrahydropyranyl)oxy-2-methyl-1(*Z*)-propenyltrimethylstannane (**3**) following Mitsunobu seven-membered cyclization, as reported in our previous paper.[3]

Our previous studies[4,5] on the Vilsmeier formylations of 2-isopropenyl-2,3-dihydrobenzofurans show, as depicted in Scheme 3, that 2-isopropenyl-2,3-dihydrobenzofuran and its 7-methoxy derivative gave the corresponding 5-carbaldehydes, the 4-methoxy derivative gave a mixture of 5-carbaldehyde and 7-carbaldehyde, and 2-isopropenyl-2,3-dihydrobenzofuran-5-carboxylic acid was prepared by oxidation of the corresponding 5-carbaldehyde with Ag_2O.

This implied a new approach for three naturally occurring 3-methyl-2,5-dihydro-1-benzoxepin carboxylic acids, as shown in Scheme 4; radulanin E (**1**) and radulanin H might be synthesized from 3-methyl-6-(protected)oxy-8-(phenylethyl)-2,5-dihydro-1-benzoxepin (**6**) by Vilsmeier formylation followed by respective oxidation via 9-carbaldehyde (**4**) and 7-carbaldehyde (**5**), and 9-hydroxy-3-methyl-2,5-dihydro-1-benzoxepin-7-car-

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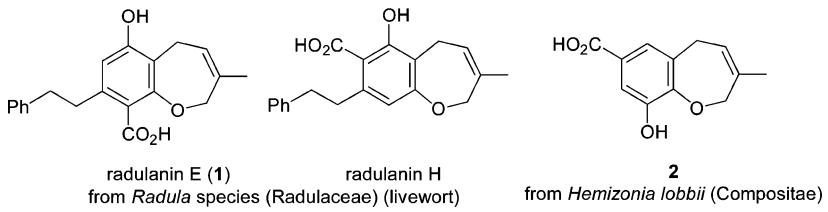
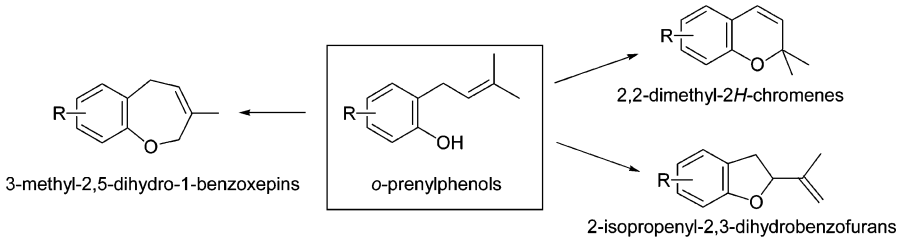
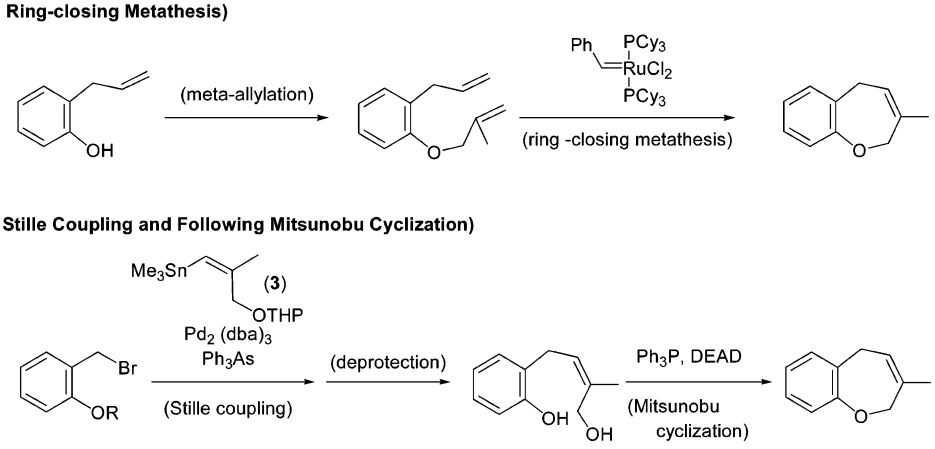


FIGURE 1. Natural 3-methyl-2,5-dihydro-1-benzoxepin carboxylic acids as the synthetic targets.

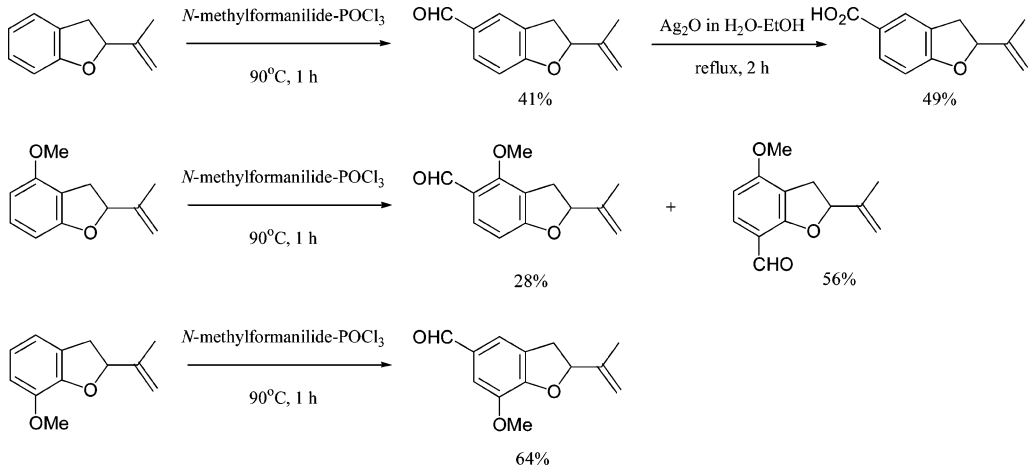
SCHEME 1. Biogenetic Oxidative Cyclization of *o*-Prenylphenols



SCHEME 2. Reported Preparative Procedures of 3-Methyl-2,5-dihydro-1-benzoxepins



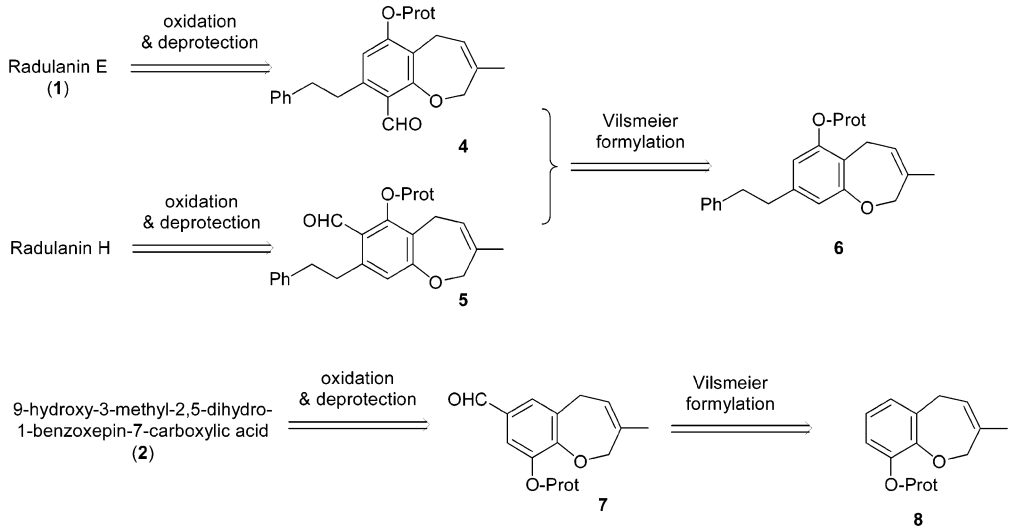
SCHEME 3. Vilsmeier Formylation of Isopropenyldihydrobenzofurans



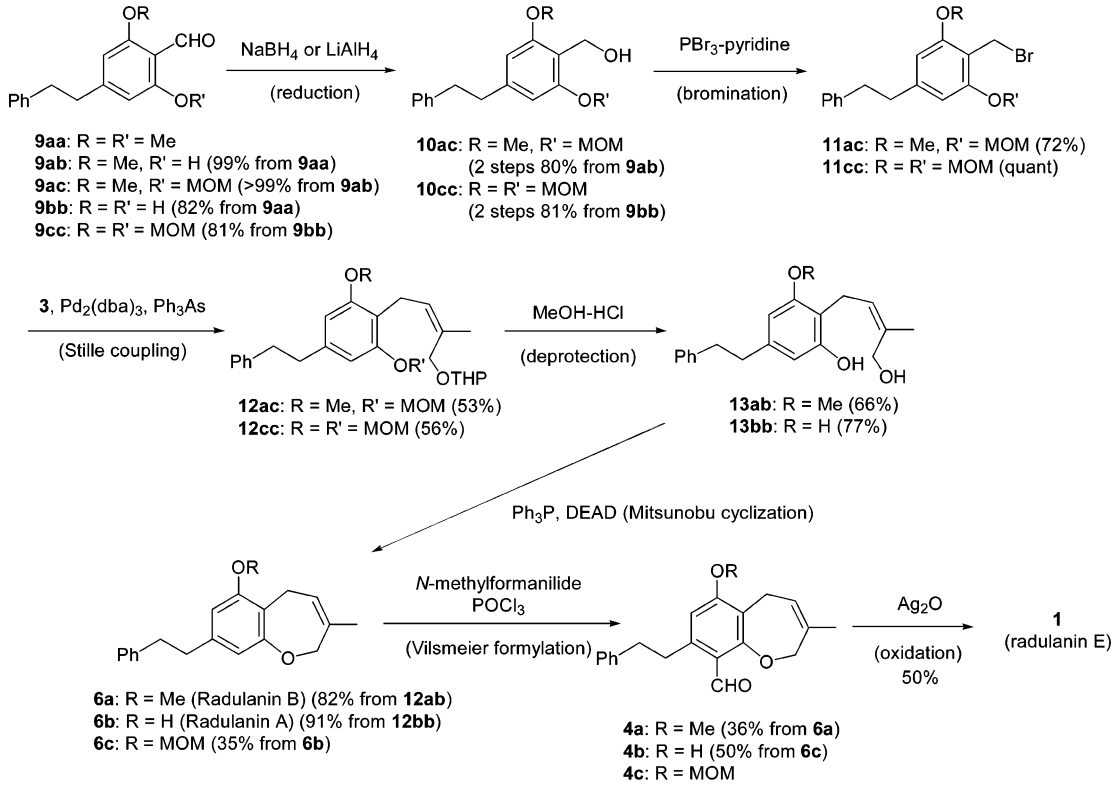
boxylic acid **2** might be synthesized from 3-methyl-9-(protected)oxy-2,5-dihydro-1-benzoxepin (**8**) by Vilsmeier formylation followed by oxidation via 7-carbaldehyde (**7**).

We already reported the preparation of 3-methyl-8-(phenylethyl)-2,5-dihydro-1-benzoxepin-6-ol (radulanin A)(**6b**) and its methoxy derivative (radulanin B) (**6a**). According to the reported procedure, as shown in Scheme 5,[3] **6a** and **6b** were prepared from 2,6-dimethoxy-4-(phenylethyl)benzaldehyde **9aa**. The starting material **9aa** was prepared from 1,3-dimethoxy-5-(phenylethyl)-benzene by formylation by treatment with *n*-BuLi−DMF (91%) and then converted to **9ab** or **9bb** by demethylation with MgI_2 or boron tribromide. 2-Methoxy-6-(methoxymethyloxy)-4-(phenylethyl)benzaldehyde **9ac** and 2,6-bis-(methoxymethyloxy)-4-(phenylethyl)benzaldehyde **9cc** were prepared by the respective MOM protection with

SCHEME 4. Synthetic Strategy for 3-Methy-2,5-dihydro-1-benzoxepincarboxylic Acids via Vilsmeier Formylation and Oxidation



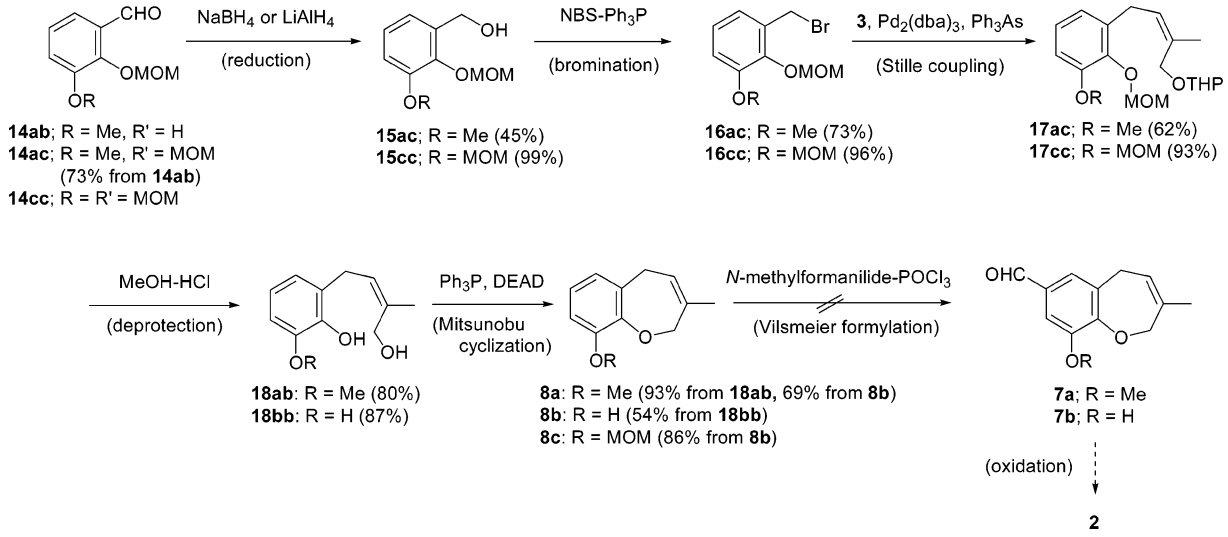
SCHEME 5. Approach for Radulanin E (1) via 3-Methyl-8-(pheylethyl)-2,5-dihydro-1-benzoxepin-6-ol Derivatives 6b,c and 4b



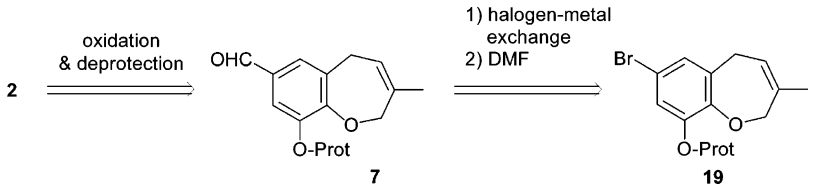
MOMCl−NaH. The benzaldehydes **9ac**,**cc**, thus prepared, were then converted to the corresponding benzyl bromides **10ac**,**cc** by reduction with $NaBH_4$ or $LiAlH_4$ followed by bromination with PBr_3−pyridine. Stille coupling of **10ac**,**cc** with vinylstannane **3** using $Pd_2(dba)_3$−Ph_3As gave corresponding coupling products (**11ac**,**cc**), which were converted to corresponding diol **12a** or triol **12b** by acidic deprotection. Mitsunobu cyclizations of **12a**,**b** by treatment with Ph_3P and DEAD gave the corresponding benzoxepins, 6-methoxy-3-methyl-8-(phenylethyl)-2,5-dihydro-1-benzoxepin (radulanin B) (**6a**) and 3-methyl-8-(phenylethyl)-2,5-dihydro-1-benzoxepin-6-ol (radulanin A) (**6b**). Then, **6b** was converted to the corresponding MOMoxy derivative **6c**.

The Vilsmeier formylation of the 6-methoxy derivative (radulaninn B) **6a** gave a 9:1 mixture of corresponding 9-carbaldehyde (**4a**) and 7-carbaldehyde (**5a**) in 40% yield after being treated with *N*-methylformanilide and phosphoryl chloride at 90 °C for 1 h. In addition, the similar Vilsmeier formylation of 6-MOMoxy derivative (**6c**) gave a single formylated compound, 6-hydroxy-3-(phenylethyl)-2.5-dihydro-1-benzoxepin-9-carbaldehyde (**4b**). The 9-carbaldehyde **4b** was then oxidized with Ag_2O to give the corresponding 9-carboxylic acid **1**, which was identical

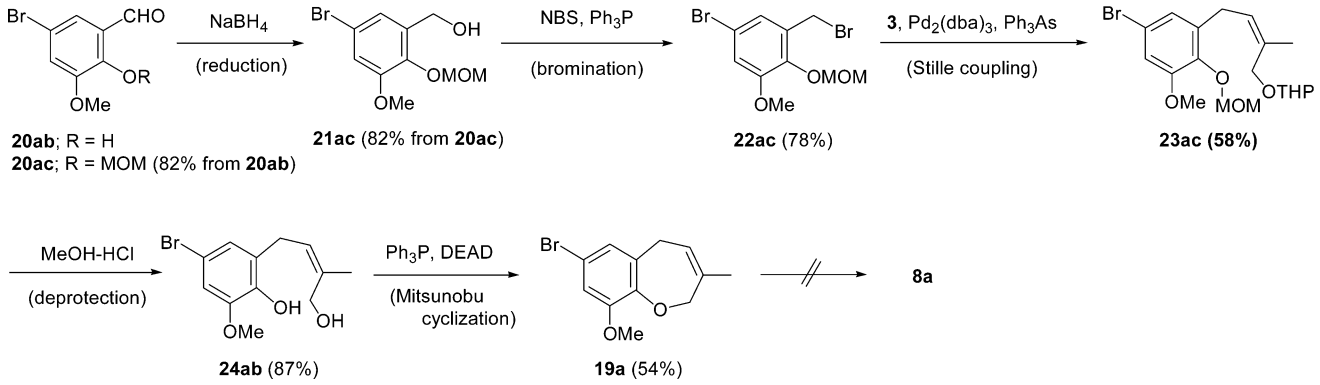
SCHEME 6. Approach A for 9-Hydroxy-3-methyl-2,5-dihydro-1-benzoxepin-7-carboxylic Acid 2 via Vilsmeier Formylation of 3-Methyl-9-(MOMoxy)-2,5-dihydro-1-benzoxepin 8c



SCHEME 7. New Plan (B) for Benzoxepin-7-carboxylic Acid 1 Using Halogen−Metal Exchange in 7-Bromo-3-methyl-9-(protected oxy)-2,5-dihydro-1-benzoxepin 19



SCHEME 8. Approach (B) for 7a or 2 via Halogen−Metal Exchange in 7-Bromo-9-methoxy-3-methyl-2,5-dihydro-1-benzoxepin 19a

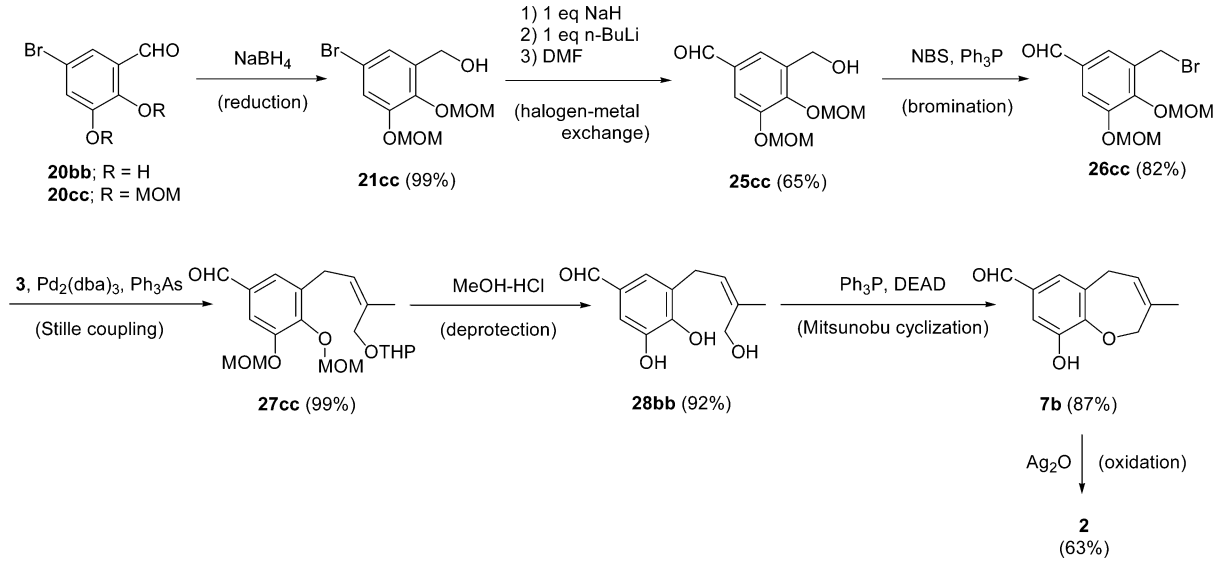


with natural radulanin E.[1e] The Vilsmeier formylation showed none of the formation of 7-carbaldehyde, and another approach was required for natural radulanin H.

A similar approach for natural 9-hydroxy-3-methyl-2,5-dihydro-1-benzoxepin-7-carboxylic acid **2** was planned as shown in Scheme 5. 3-Methoxy-2-(methoxymethyloxy)-benzaldehyde (**14ac**) was prepared by MOM protection of commercially available *o*-vanilin (**14ab**) and 2,3-bis-(methoxymethyloxy)benzaldehyde (**14cc**) was prepared by MOM protection of catechol followed by formylation by treatment with *n*-BuLi−DMF, and they were converted to the corresponding benzyl bromide **15ac** by reduction with $NaBH_4$ followed by bromination with *N*-bromosuccimide-triphenyl phosphine. According to the reported procedure,[3] Stille coupling of **16ac**,**cc** with vinylstannane **3** using $Pd_2(dba)_3$−Ph_3As effectively gave the corresponding coupling products (**17ac**,**cc**); subsequent deprotection readily gave the corresponding diol (**18ab**) and triol (**18bb**), and Mitsunobu cyclizations of **18ab**,**bb** gave the corresponding 3-methyl-2,5-dihydro-1-benzoxepins (**8a**,**b**). The 9-hydroxy derivative **8b** was converted to the corresponding 9-methoxy derivative **8a** or 9-methoxymethyloxy derivative **8c** by treating it with MeI−K_2CO_3 or MOMCl−NaH. However, both Vilsmeier formylations of **8a**,**c** were unsuccessful in all conditions and showed recovery of **8a** or deprotected **8b** (from **8c**). It was very interesting that the seven-membered 9-methoxy-3-methyl-2,5-dihydro-1-benzoxepin **8a** showed the different reactivity for Vilsmeier formylations from the five-membered 2-isopropenyl-2,3-dihydrobenzofuran.

So, another new approach (B) for **2** was planned via halogen−metal exchange of 7-bromo-3-methyl-9-(protected)oxy-2,5-dihydro-1-benzoxepins **19** and a subsequent carboxylation or formylation, as shown in Scheme 7.

SCHEME 9. Successful Approach (C) for Benzoxepin-7-carboxylic Acid 2 Using Halogen−Metal Exchange in 5-Bromo-2,3-bis(methoxymethyloxy)benzyl Alcohol 21cc



As shown in Scheme 8, 7-bromo-9-methoxy-3-methyl-2,5-dihydro-1-benzoxepin (**19a**) was prepared and subjected to the conversion via halogen−metal exchange. 5-Bromo-3-methoxy-2-(methoxymethyloxy)benzaldehyde (**20ac**) was prepared from 2-hydroxy-5-bromo-3-methoxybenzaldehyde (**20ab**), prepared by bromination of *o*-vanilin **14ab**,[6] and then converted to the corresponding benzyl bromide (**22ac**) by reduction with $NaBH_4$ giving (**21ac**), followed by bromination with NBS−PPh_3. Stille coupling of **22ac** with vinylstannane **3** gave the corresponding coupling product **23ac**, which was then converted to the corresponding 7-bromo-9-methoxybenzoxepin (**19a**) by acidic deprotection with HCl−MeOH, giving **24ab** followed by Mitsunobu cyclization with Ph_3P−DEAD. Metalation of **19a** was unsuccessful in all procedures (with alkyllithiums or Grignard reagents) and only showed recovery of **19a**. Thus, the conversion from 7-bromo-9-(methoxymethyloxy)-3-methyl-2,5-dihydro-1-benzoxepin (**19c**) to the corresponding 7-carbaldehyde **7c** or **2** would likely be fruitless.

At last, we found a new successful approach (C) for 9-hydroxy-3-methyl-2,5-dihydro-1-benzoxepin-7-carboxylic acid **2**, as shown in Scheme 9. This approach used the halogen−metal exchange in bromo benzyl alcohol (**21cc**), which was prepared from 5-bromo-3-hydroxy-2-methoxybenzaldehyde (**20ab**) in three steps: (1) demethylation with BBr_3 (92%) giving **20bb**, (2) MOM protection with MOMCl−NaH (73%), giving 5-bromo-2,3-bis(methoxymethyloxy)benzaldehyde (**20cc**), and (3) reduction with $NaBH_4$. The halogen−metal exchange in **21cc** was effective using metalation by treatment with *n*-BuLi followed by formylation by treatment with DMF to give 5-formyl-2,3-bis(methoxymethyloxy)benzyl alcohol (**25cc**). The formyl benzyl alcohol **25cc** was then converted to the corresponding benzyl bromide (**26cc**) by bromination with NBS−Ph_3P. Stille coupling of **26cc** with vinylstannane **3** using $Pd_2(dba)_3$−Ph_3As gave the corresponding coupling product (**27cc**), which was then converted to the corresponding diol (**28bb**) by deprotection with HCl−MeOH. Mitsunobu cyclization of **28bb** gave 9-hydroxy-3-methyl-2,5-dihydro-1-benzoxepin-7-carbaldehyde (**7b**), and the oxidation of **7b** with Ag_2O gave 9-hydroxy-3-methyl-2,5-dihydro-1-benzoxepin-7-carboxylic acid **2**, which was identical with natural acid in all spectral data.[11]

Experimental Section

Methods and Materials. All reactions requiring anhydrous conditions were conducted in well dried glassware under an argon atmosphere. Solvents were distilled immediately before use: THF and Et_2O from Na/benzophenone; benzene, pyridine, and DMF from calcium hydride (DMF; under reduced pressure); and MeOH from $Mg(OMe)_2$. CH_2Cl_2, was distilled first from P_2O_5 and then from CaH_2. Organic solutions were concentrated by a rotary evaporator below 45 °C in vacuo. Analytical TLC was carried out using 0.25 mm Merck silica gel plates (60F-254) using UV light as plates, and column chromatography was performed with 230−400 mesh Merck silica gel 60 for flash chromatography. Melting points were taken on a micro melting point apparatus and are uncorrected. IR spectra were obtained in liquid films or KBr disks on an FT/IR spectrometer, and ^1H NMR spectra were obtained in a $CDCl_3$ solution on a 400 MHz spectrometer. ^1H NMR data are reported in parts per million (δ) downfield from internal TMS; coupling constants are given in hertz. Elemental analyses were determined on a micro CHN analyzer. Mass spectra were recorded under electron ionization (EI) conditions on a mass spectrometer.

General Method for Stille Coupling.[3] Under an argon atmosphere, $Pd_2(dba)_3$−$CHCl_3$ (53 mg, 0.054 mmol) and triphenylarsine (126 mg, 0.41 mmol) were added to dry deoxygenated DME (3 mL), and the suspension was stirred at room temperature for 15 min. A solution of benzyl bromide **16ac**,**cc**, **22ac**, or **26cc** (1.00 mmol) and vinylstannane **3** (366 mg, 1.15 mmol) in dry deoxygenated DME (7 mL) was added to the suspension, and the mixture was heated at 85 °C for 24 h. After cooling, the mixture was diluted with diethyl ether and filtered through a thin pad of anhydrous magnesium sulfate. The ethereal filtrate was washed with a 10% aqueous potassium fluoride solution, a saturated aqueous ammonium chloride solution, and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified on a silica gel column, eluted with 10% ethyl acetate in hexane, to give a corresponding coupled product **17ac**,**cc**, **23ac**, or **27cc**. The yields of the Stille coupling are summarized in Table 1.

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TABLE 1. Stille Coupling of Benzyl Bromides 11ac,cc, 16ac,cc, 22ac, and 26cc with Vinylsatnanne 3[a]

benzyl bromide	coupling product (yield)
11ac	**12ac** (53%)[3]
11cc	**12cc** (56%)[3]
16ac	**17ac** (62%)
16cc	**17cc** (93%)
22ac	**23ac** (58%)
26cc	**27cc** (99%)

[a] Conditions: benzyl bromide (1 mol), vinylstannane 3 (1.2 mol), $Pd_2(dba)_3$ (5 mol %), ph_3As (40 mol %); reaction time, 24 h; reaction temp, 85 °C.

TABLE 2. Mitsunobu Cyclization of Diols 13ab, 18ab, and 24ab or Triols 13bb, 18bb, and 28bb[a]

substrate	reaction time	benzoxepin (yield)
13ab	15 min	**6a** (82%)[3]
13bb	30 min	**6b** (91%)[3]
18ab	2 h	**8a** (93%)
18bb	1.5 h	**8b** (54%)
24ab	1.5 h	**19a** (54%)
28bb	30 min	**7b** (87%)

[a] Conditions: substrate (1 mol), Ph_3P (2 mol), DEAD (2 mol); reaction temp, rt.

17ac: 73%; pale yellow oil; ^{1}H NMR δ 1.53−1.76 (m, 6H), 1.82 (br s, 3H), 3.54 (br t, J = 7.4 Hz, 2H), 3.59 (s, 3H), 3.84 (s, 3H), 3.90 (dt, J = Hz, 2H), 4.22 (d, J = 11.7 Hz, 1H), 4.23 (d, J = 11.7 Hz, 1H), 4.64 (t, J = 4.0 Hz, 1H), 5.10 (s, 2H), 5.56 (t, J = 7.4 Hz, 1H), 6.79 (d, J = 7.7 Hz, 2H), 7.01 (t, J = 7.7 Hz, 1H). Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.57; H, 8.29.

17cc: 93%; pale yellow oil; ^{1}H NMR δ 1.55−1.76 (m, 6H), 1.82 (br s, 3H), 3.50−3.52 (m, 2H), 3.50 (s, 3H), 3.59 (s, 3H), 3.45−3.56 (m, 1H), 3.86−3.92 (m, 1H), 4.18−4.25 (m, 2H), 4.63 (t, J = 3.2 Hz, 1H), 5.11 (s, 2H), 5.18 (s, 2H), 5.54 (t, J = 7.3 Hz, 1H), 6.83 (dd, J = 2.3 and 7.1 Hz, 1H), 6.95−7.01 (m, 2H). Anal. Calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.27; H, 8.23.

23ac: 58%; pale yellow oil; ^{1}H NMR δ 1.55−1.76 (m, 6H), 1.82 (br s, 3H), 3.50−3.52 (m, 2H), 3.56 (s, 3H), 3.81 (s, 3H), 3.45−3.56 (m, 1H), 3.86−3.92 (m, 1H), 4.18 (br s, 2H), 4.62 (t, J = 3.1 Hz, 1H), 5.05 (s, 2H), 5.48 (t, J = 7.3 Hz, 1H), 6.88 (d, J = 2.2 Hz, 1H), 6.92 (d, J = 2.2 Hz, 1H). Anal. Calcd for $C_{19}H_{27}O_5Br$: C, 54.94; H, 6.55. Found: C, 54.81; H, 6.33.

27cc: 99%; yellow oil; IR ν 1697 cm^{-1}; ^{1}H NMR δ 1.52−1.81 (m, 6H), 1.85 (br s, 3H), 3.50−3.52 (m, 2H), 3.51 (s, 3H), 3.59 (s, 3H), 3.45−3.56 (m, 1H), 3.86−3.92 (m, 1H), 4.10−4.15 (m, 2H), 4.64 (t, J = 3.8 Hz, 1H), 5.23 (s, 2H), 5.25 (s, 2H), 5.55 (t, J = 7.4 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.64 (d, J = 2.0 Hz, 1H), 9.86 (s, 1H). Anal. Calcd for $C_{21}H_{30}O_7 \cdot 1/2H_2O$: C, 62.51; H, 7.76. Found: C, 62.53; H, 7.69.

General Method for Acidic Deprotection. Under an argon atmosphere, to a solution of **17ac**,**cc**, **23ac**, or **27cc** in methanol was added a catalytic amount of concentrated hydrochloric acid, and the mixture was refluxed for 30 min. After cooling, the mixture was concentrated in vacuo, and the mixture was treated with a saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified on a silica gel column, eluted with 50% ethyl acetate in hexane, to give the corresponding deprotected diols **18ab**, **24ab** or triols **18bb**, **28bb**.

18ab: 80%; pale yellow oil; IR ν 3420 cm^{-1}; ^{1}H NMR δ 1.85 (br s, 3H), 3.46 (d, J = 7.7 Hz, 2H), 3.91 (s, 3H), 4.27 (br s, 2H), 5.45 (t, J = 7.7 Hz, 1H), 6.77 (m, 2H), 6.83 (t, J = 7.7 Hz, 2H); MS *m/z* 208 (M$^+$). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.13; H, 7.63.

18bb: 87%; pale yellow oil; IR ν 3381 cm^{-1}; ^{1}H NMR δ 1.80 (br s, 3H), 2.51 (br s, 1H), 3.43 (d, J = 8.1 Hz, 2H), 4.32 (br s, 2H), 5.44 (t, J = 8.1 Hz, 1H), 5.80 (br s, 1H), 6.66 (dd, J = 7.3 and 2.0 Hz, 1H), 6.72−6.79 (m, 2H), 7.60 (br s, 1H); MS *m/z* 194 (M$^+$). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.27; H, 7.29.

24ab: 87%; orange crystals, mp 105−107 °C; IR ν 3438, 3266 cm^{-1}; ^{1}H NMR δ 1.82 (br s, 3H), 3.38 (d, J = 7.8 Hz, 2H), 3.78 (s, 3H), 4.23 (br s, 2H), 5.39 (t, J = 7.8 Hz, 1H), 6.85 (d, J = 2.8 Hz, 1H), 6.88 (d, J = 2.8 Hz, 1H); MS *m/z* 286 and 288 (M$^+$). Anal. Calcd for $C_{12}H_{15}O_3Br$: C, 50.19; H, 5.27. Found: C, 50.26; H, 5.32.

28bb: 92%; yellow crystals, mp 164−166 °C (recrystallized from ethanol); IR ν 3456 cm^{-1}; ^{1}H NMR δ 1.74 (br s, 3H), 3.32 (s, 2H), 4.04 (s, 2H), 4.61 (br s, 1H), 5.32 (t, J = 7.0 Hz, 1H), 7.42 (br, 1H), 8.28 (br, 1H), 9.41 (br s, 1H), 9.43 (br s, 1H), 9.86 (s, 1H), 9.88 (br s, 1H), 9.90 (br s, 1H); MS *m/z* 204 (M$^+$), 189 (M$^+$ − H_2O − CH_3). Anal. Calcd for $C_{12}H_{14}O_4 \cdot 1/4H_2O$: C, 63.57; H, 6.46. Found: C, 63.81; H, 6.39.

General Method for Mitsunobu Cyclization.[3] Mitsunobu cyclizations of diol **13ab** and triol **13bb** giving radulanin A (**6b**) and radulanin B (**6a**) were already reported in our previous paper.[3] Diols **18ab**, **24ab** or triols **18bb**, **28bb** were subjected to the similar Mitsunobu cyclizations, according to the reported procedure. [3]

Under an argon atmosphere, to a solution of diols **18ab**, **24ab** or triols **18bb**, **28bb** (0.500 mmol) and triphenylphosphine (285 mg, 1.09 mmol) in dry THF (3 mL) at room temperature was added a 40% DEAD toluene solution (461 mg, 1.06 mmol) in dry THF (2.5 mL), and the mixture was stirred for 1.5 h. The mixture was diluted with water and extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified on a silica gel column, eluted with 10% ethyl acetate in hexane, to give the corresponding 3-methyl-2,5-dihydro-1-benzoxepin **8a**,**b**, **19a**, or **7b**. The yields in the Mitsunobu cyclization are summarized in Table 2.

6a: 93%; colorless oil; ^{1}H NMR δ 1.52 (br s, 3H), 3.36 (br d, J = 3.9 Hz, 2H), 4.45 (br s, 2H), 5.61−5.65 (br t, J = 3.9 Hz, 1H), 5.72 (s, 1H), 6.59−6.61 (m, 1H), 6.83−6.92 (m, 2H); MS *m/z* 190 (M$^+$), 175 (M$^+$ − CH_3). The sample was identical with that prepared from **6b** by methylation using methyl iodide−potassium carbonate (69%).

6b: 54%; pale yellow oil; IR ν 3424 cm^{-1}; ^{1}H NMR δ 1.57 (br s, 3H), 3.40 (br d, J = 3.9, 2H), 4.45 (br s, 2H), 5.61−5.65 (m, 1H), 5.72 (s, 1H), 6.59−6.61 (m, 1H), 6.83−6.92 (m, 2H); MS *m/z* 176 (M$^+$).

19a: 54%; red crystals; mp 68−70 °C (recrystallized from hexane); ^{1}H NMR δ 1.52 (br s, 3H), *3.34* (br d, J = 3.9 Hz, 2H), 3.85 (s, 3H), 4.40 (br s, 2H), 5.50−5.66 (br t, J = 3.9 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 6.93 (d, J = 2.1 Hz, 1H); MS *m/z* 270 and 268 (M$^+$). Anal. Calcd for $C_{12}H_{13}O_2Br$: C, 53.55; H, 4.87. Found: C, 53.65; H, 5.00.

7b: 87%; colorless needles; mp 100−101 °C (recrystallized from cyclohexane−diethyl ether); IR ν 3367, 1691 cm^{-1}; ^{1}H NMR δ 1.64 (br s, 3H), 3.45 (br d, J = 3.9 Hz, 2H), 4.55 (br s, 2H), 5.60−5.80 (br t, J = 3.9 Hz, 1H), 5.86 (s, 1H), 7.17 (d, J = 2.1 Hz, 1H), 7.35 (d, J = 2.1 Hz, 1H), 9.84 (s, 1H); MS *m/z* 204 (M$^+$), 189 (M$^+$ − CH_3). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.68; H, 6.03.

MOM Protection of 6b, 8b. Under an argon atmosphere, a solution of **6b** or **8b** (0.15 mmol) in dry THF (5 mL) was carefully treated with a suspension of 60% oily sodium hydride (33 mg, 1.4 mmol) in dry THF (3 mL) at room temperature, and the mixture was stirred at room temperature for 30 min. Chloromethyl methyl ether (3.9 mL, 40 mmol) was added dropwise to the mixture, and the mixture was stirred at room temperature for 2 h. The mixture was treated with cold water and extracted with ethyl acetate. The organic layer was washed with a 5% aqueous sodium hydroxide solution and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified on a silica gel

column, eluted with 5% ethyl acetate in hexane, to give the corresponding MOM ether **6c** or **8c**.

6c: 35%; yellow oil; ^{1}H NMR δ 1.53 (br s, 3H), 2.82−2.92 (m, 4H), 3.45 (br d, J = 3.8 Hz, 2H), 3.48 (s, 3H), 4.40 (br s, 2H), 5.12 (s, 2H), 5.16 (br t, J = 3.8 Hz, 1H), 6.37 (d, J = 1.2 Hz, 1H), 6.68 (d, J = 1.2 Hz, 1H), 7.18−7.23 (m, 3H), 7.26−7.30 (m, 2H).

8c: 86%; pale pink oil; ^{1}H NMR δ 1.52 (br s, 3H), 3.36 (br d, J = 3.8 Hz, 2H), 3.86 (s, 3H), 4.43 (br s, 2H), 5.60 (br t, J = 3.8 Hz, 1H), 6.93−7.02 (m, 3H), 10.37 (s, 1H).

Vilsmeier Formylation of 6a,c.[4,5] Under an argon atmosphere, *N*-methylformanilide (98 mg, 0.73 mmol) was treated with phosphoryl chloride (80 mg, 0.53 mmol), and the mixture was heated at 90 °C for 20 min. A solution of benzoxepin **6a**,**c** (0.01 mmol) in *N*-methylformanilide (1.5 mL) was added to the mixture, and the mixture was heated at the same temperature for 40 min. After cooling, the mixture was poured on a saturated aqueous sodium hydrogencarbonate solution and extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified on a silica gel column, eluted with 5% ethyl acetate in hexane, to give a mixture of 9-carbaldehyde **4a** and 7-carbaldehyde **5a** (from **6a**) or a pure 9-carbaldehyde **4b** (from **6c**). The ratio of **4a** and **5a** was determined from the ^{1}H NMR spectrum of the mixture.

4a: 36% determined by ^{1}H NMR; yellow oil; IR ν 1678 cm^{-1}; ^{1}H NMR δ 1.55 (br s, 3H), 2.85 (dd, J = 5.9 and 7.8 Hz, 2H), 3.27 (dd, J = 5.9 and 7.8 Hz, 2H), 3.42−3.43 (br d, J = 3.9 Hz, 2H), 3.77 (s, 3H), 4.51 (br s, 2H), 5.58−5.64 (br t, J = 3.9 Hz, 1H), 6.36 (s, 1H), 7.17−7.22 (m, 3H), 7.27−7.31 (m, 2H), 10.49 (s, 1H).

6-Methoxy-3-methy-8-(phenylethyl)-2,5-dihydro-1-benzoxepin-7-carbaldehyde 5a: 4% determined by ^{1}H NMR; yellow oil; IR ν 3367, 1691 cm^{-1}; ^{1}H NMR δ 1.55 (br s, 3H), 2.91 (br d, J = 3.9 Hz, 2H), 3.20 (m, 2H), 3.42−3.43 (m, 2H), 3.80 (s, 3H), 4.51 (br s, 2H), 5.58−5.64 (br t, J = 3.9 Hz, 1H), 6.11 (s, 1H), 7.17−7.12 (m, 3H), 7.27−7.31 (m, 2H), 10.36 (s, 1H).

4b: 50% from **6c**; yellow oil; IR ν 3411, 1665 cm^{-1}; ^{1}H NMR δ 1.55 (br s, 3H), 2.78−2.90 (br d, J = 3.9 Hz, 2H), 3.38−3.49 (m, 2H), 4.42 (br s, 2H), 5.58−5.64 (br t, J = 3.9 Hz, 1H), 6.38 (s, 1H), 6.53 (s, 1H), 7.17−7.22 (m, 3H), 7.27−7.31 (m, 2H), 8.48 (s, 1H).

General Method for Oxidation with Ag_2O.[4] Fresh silver oxide was prepared by treating a solution of silver nitrate (34 mg, 0.20 mmol) with 1 M aqueous sodium hydroxide solution (0.40 mL), and the suspension was stirred at room temperature for 30 min. A solution of carbaldehyde **4b** or **7b** (0.100 mmol) in a 1 M sodium hydroxide aqueous solution was added to the suspension of silver oxide, and the mixture was refluxed gently for 30 min. After cooling, the mixture was filtered to remove metallic Ag, and the aqueous alkaline filtrate was washed once with diethyl ether, acidified with 10% hydrochloric acid, and extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified on a silica gel column, eluted with 30% ethyl acetate in hexane, to give a corresponding carboxylic acid **1** or **2**.

1: 50%; IR ν 3411, 1665 cm^{-1}; ^{1}H NMR δ 1.55 (br s, 3H), 2.78−2.90 (br d, J = 7.0 Hz, 2H), 3.38−3.49 (m, 2H), 4.42 (br s, 2H), 5.58−5.64 (br t, J = 7.0 Hz, 1H), 6.38 (s, 1H), 6.53 (s, 1H), 7.17−7.22 (m, 3H), 7.27−7.31 (m, 2H), 8.48 (s, 1H). The spectral data were identical with those of natural radulanin H, obtained from *Radula* species.[1k]

2: 63%; yellow crystals; IR ν 3500−2500, 1695 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.51 (br s, 3H), 3.33 (br d, J = 7.3 Hz, 2H), 4.35 (br s, 2H), 5.56−5.62 (br t, J = 7.3 Hz, 1H), 7.17 (d, J = 2.1 Hz, 1H), 7.30 (d, J = 2.1 Hz, 1H), 8.30 (s, 1H), 9.44 (s, 1H); MS *m/z* 220 (M^+), 1695 ($M^+ - CH_3$). The spectral data were identical with those of natural 9-hydroxy-3-methyl-2,5-dihydro-1-benzoxepin-7-carboxylic acid, obtained from *Hemizonia lobbii*.[11]

Supporting Information Available: Preparative procedures and spectral data of benzaldehydes **9ac**,**cc**, **14ac**,**cc**, and **20ac**,**cc**, benzyl alcohols **10ac**,**cc**, **15ac**,**cc**, **21ac**,**cc**, and **25cc**, and benzyl bromides **11ac**,**cc**, **16ac**,**cc**, **22ac**, and **26cc**. This material is available free of charge via the Internet at http://pubs.acs.org.

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