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Application of Carbohydrate-Templated Asymmetric Diels–Alder Reaction to the Syntheses of *ent*-Penicillones A and B

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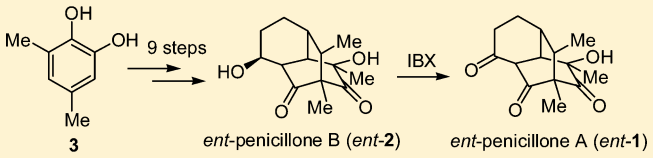
Supporting Information

ABSTRACT: Total syntheses of *ent*-penicillones A (*ent*-**1**) and B (*ent*-**2**) from 3,5-dimethylcatechol (**3**) were accomplished in 10 and 9 synthetic steps, respectively. A carbohydrate-templated asymmetric intramolecular Diels–Alder reaction of a masked *o*-benzoquinone (MOB) **9** and an aqueous acid-catalyzed intramolecular aldol reaction are the key synthetic steps. In addition, the absolute configurations of the bicyclo[2.2.2]oct-5-en-2-one core obtained from the per-*O*-benzylated α-D-glucopyranosyl as a carbohydrate template in the intramolecular Diels–Alder reaction of MOBs were revised.



Penicillones A (**1**) and B (**2**), possessing a novel tricyclo[5.3.1.0^{3,8}]undecane skeleton (Figure 1), were

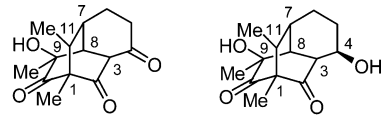


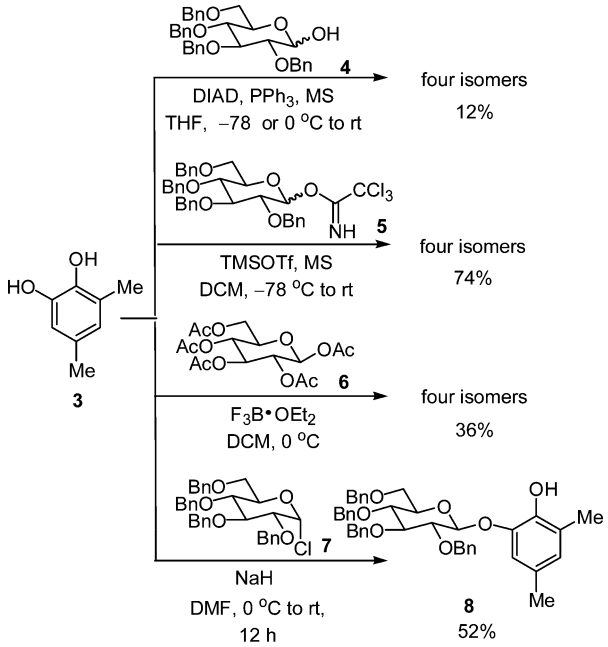
Figure 1. Structures of pencillones A (**1**) and B (**2**).

isolated from a fungus *Penicillium terrestre* obtained from marine sediments of Jiaozhou Bay, Qingdao.[1] Penicillone A (**1**) shows cytotoxicity against P-388 and A-549 cancer cell lines, while penicillone B (**2**) was inactive against P-388. The absolute configuration of (−)-**2** has been determined by Mosher's ester analysis. A comparison of CD absorptions of (+)-**1** and (−)-**2** suggested that these two compounds have the same absolute configuration. Therefore, the absolute configurations of (+)-**1** and (−)-**2** were concluded to be 1*R*,3*S*,7*R*,8*S*,9*S*,11*R* and 1*R*,3*S*,4*R*,7*R*,8*S*,9*S*,11*R*, respectively.

Masked *o*-benzoquinones (MOBs) have been demonstrated as valuable intermediates in organic synthesis.[2] We have accomplished several natural product syntheses employing MOB intermediates,[3,4] including (±)-penicillones A and B.[5] Recently, Hung reported a three-step synthesis of optically pure bicyclo[2.2.2]oct-5-en-2-ones via carbohydrate-templated asymmetric intramolecular Diels–Alder reactions of MOBs.[6] Thus, we decided to use this strategy to synthesize optically pure penicillones A and B.

The synthesis of optically pure **1** and **2** started from 3,5-dimethylcatechol (**3**).[7] Better diastereoselectivity has been observed when using per-*O*-benzylated β-D-glucopyranosyl as the carbohydrate template in the oxidative coupling of phenol with allyl alcohols.[6] Thus, installation of the carbohydrate template in catechol **3** was first carried out via coupling 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**4**) with **3** using a Mitsunobu-type glycosylation.[8] Unfortunately, this reaction gave four regio- and stereoisomers in low yield (Scheme 1). We turned our attention to using D-glucopyranose trichloroacetimidate (**5**) in the *O*-glycosylation under Lewis acidic conditions.[9] Although the yield increased to 74%, the regio- and stereoselectivity were

Scheme 1. *O*-Glycosylation of Catechol 3



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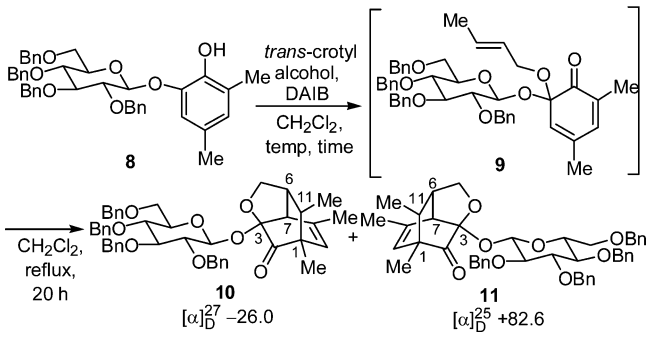
still poor. We noted that, in certain cases, the stereochemical outcome of the glycosylation reaction was affected by the type of protecting group employed at the 2-position in the glycosyl donor. A participating group, typically one containing a carboxyl group, can result in the predominant formation of a β-glycoside. Thus, D-glucopyranose derivative **6** was used in the *O*-glycosylation.[10] However, neighboring group participation was not observed in this glycosylation, and the stereoselectivity still was not improved. To our delight, a solution was found by treating catechol **3** with D-glucopyranose derivative **7**[11] under basic conditions to give a single β-form product **8**. The exclusive β-form product was obtained via an S_N2 replacement of the less hindered hydroxyl group in **3** with chloride. The stereochemistry of the acetal moiety in **8** was assigned using its proton coupling constant.

With phenol **8** in hand, the next step was the asymmetric intramolecular Diels–Alder reaction of the masked *o*-benzoquinone, which was generated from phenol **8** and diacetoxyiodobenzene (DAIB) in the presence of *trans*-crotyl alcohol (Table 1).[12] The reaction was first carried out at −30 °C for 6 h to form MOB **9** before the reaction mixture was heated under reflux for 20 h. The intramolecular Diels–Alder reaction of **9** proceeded smoothly at reflux to generate desired tricyclic β,γ-enones **10** and **11** in 58% total yield and a 2:1 ratio (entry 1). Compounds **10** and **11** were easily separated by silica-gel chromatography. Better diastereoselectivity was observed when the oxidation was carried out at −50 °C (entry 2). However, an attempt to improve the diastereoselectivity using an even lower temperature (−78 °C) was unsuccessful (entry 3). We reasoned that the poor selectivity in this reaction was attributed to the poor solubility of DAIB in CH_2Cl_2 at −78 °C and the oxidation not proceeding very well at this temperature. When the reaction mixture was heated to reflux, the oxidation and cyclization occurred simultaneously, giving a 1:1 mixture of the products. The best diastereoselectivity was observed when the oxidation was carried out at −78 °C and then warmed up slowly to −50 °C (entry 4). The absolute configurations of the bicyclo[2.2.2]oct-5-en-2-one cores in **10** and **11** were assigned by comparing their specific rotations with similar structures of known compounds.[6] Accordingly, a negative specific rotation indicated an absolute configuration of 1*S*,3*R*,6*S*,7*S*,10*S* in the bicyclo[2.2.2]oct-5-en-2-one core, while a positive specific rotation indicated an absolute configuration of 1*R*,3*S*,6*R*,7*R*,10*R*. Therefore, the synthesis of natural penicillones was started from **11**.

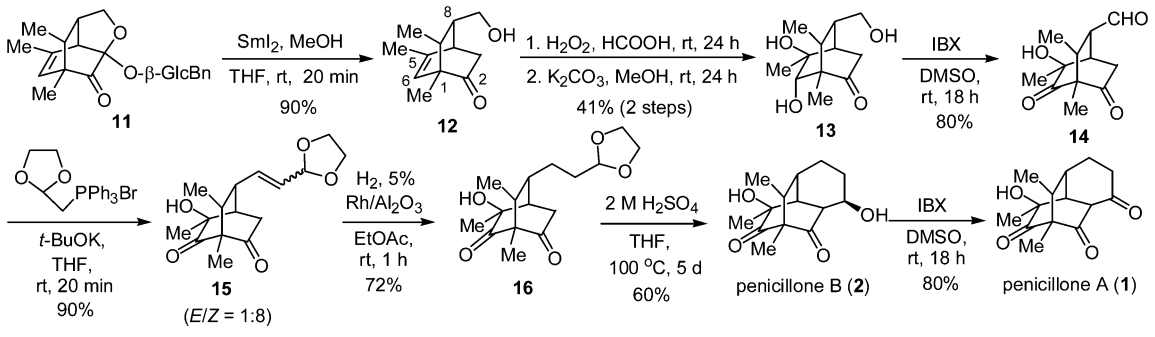
Table 1. DAIB-Oxidized Intramolecular [4 + 2] Cycloaddition of Phenol 8 with *trans*-Crotyl Alcohol



entry	DAIB (equiv)	temp (°C)	time (h)	yield (%)	**10:11**
1	3	−30	6	58	2:1
2	10	−50	20	60	2.3:1
3	10	−78	20	39	1:1
4	10	−78 to −50	20	53	3.3:1

To complete the total synthesis, ketone **11** was first reduced with samarium diiodide[13] in THF in the presence of MeOH to furnish alcohol **12** in 90% yield (Scheme 2). Compound **12** could then be converted to penicillones according to a literature procedure.[5] Thus, stereocontrolled installation of the C-5 hydroxyl group was achieved via sequential epoxidation, epoxide ring-opening, and saponification.[14] The next stage was a two-carbon homologation of the C-8 hydroxymethyl side chain, accomplished by oxidizing the primary and secondary alcohols to an aldehyde and ketone, respectively, simultaneously with IBX[15] and then treating with (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide[16] and *t*-BuOK[17] to give unsaturated dioxolane intermediate **15** as an *E*/*Z*-mixture (*E*/*Z* = 1:8). Replacing *t*-BuOK with *n*-BuLi as a base in the Wittig reaction was unsuccessful. Hydrogenation of the unsaturated dioxolane **15** over 5% Rh on alumina[18] afforded aldol precursor **16**. Finally, aqueous acid-catalyzed hydrolysis and an aldol reaction were carried out in refluxing THF with 2 M H_2SO_4 to generate the desired product, penicillone B (**2**) as an only epimer. The reason for the formation of a single *endo*-epimer is presumably due to the 1,3-diaxial interaction present in the *exo*-epimer.[5,19] Oxidation of penicillone B (**2**) with IBX furnished penicillone A (**1**). Spectra for these products were fully consistent with the literature data[1] and our synthesized racemic penicillones.[5] However, the specific rotation of synthetic penicillone B ($[\alpha]_D^{25}$ +12.6 (*c* 0.2, MeOH)) was found to have the opposite sign to that of the natural product ($[\alpha]_D^{20}$ −13.7 (*c* 0.2, MeOH)) (Scheme 3). Moreover, the specific rotation of synthetic penicillone A ($[\alpha]_D^{25}$ −140.5 (*c*

Scheme 2. Final Steps of the Total Synthesis of Penicillones A (1) and B (2)



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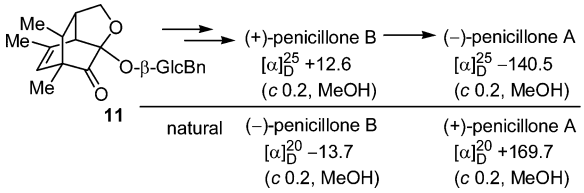
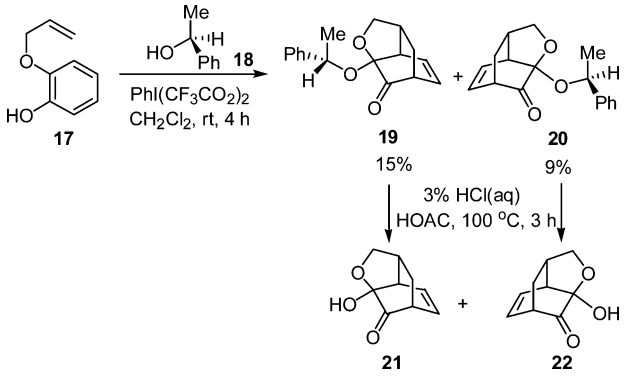
Scheme 3. Comparison of the Optical Rotations of Natural and Synthetic Penicillones A and B



0.2, MeOH)) also had the opposite sign to that of the natural product ($[\alpha]_D^{20}$ +169.7 (*c* 0.2, MeOH)).

As the optical rotations of synthetic and natural penicillones were opposites, we examined the procedure used to determine the absolute configurations of the bicyclo[2.2.2]oct-5-en-2-one core in literature.[6] According to the literature, although the absolute configurations of **19** and **20** were determined by single-crystal X-ray diffraction analysis, their optical rotations were unreported. Moreover, **21** and **22** were not obtained directly from the hydrolysis of **19** and **20**, respectively, which were obtained from the hydrolysis of the corresponding per-*O*-benzylated *β*-D-glycopyranosyl bicyclo[2.2.2]oct-5-en-2ones. Thus, we decided to revise the determination of the absolute configurations of **10** and **11**. The reaction of 2-allyloxyphenol (**17**) with (*S*)-1-phenylethanol (**18**) in the presence of $PhI(OCOCF_3)_2$ furnished diastereomers **19** and **20** in 15% and 9% yields, respectively (Table 2). The absolute

Table 2. Comparison of the Optical Rotations of 21 and 22



	published $[\alpha]_D^T$[a]	synthetic $[\alpha]_D^T$[a]
19	–[b]	$[\alpha]_D^{25}$ +242.5
20	–[b]	$[\alpha]_D^{28}$ −354.3
21	$[\alpha]_D^{24}$ −287.5	$[\alpha]_D^{28}$ +454.9
22	$[\alpha]_D^{25}$ +257.2	$[\alpha]_D^{29}$ −453.9

[a]In $CHCl_3$. [b]Unreported.

configuration of **19** was confirmed by single-crystal X-ray diffraction analysis (Figure 2). Hydrolysis of the ketal moiety in **19** and **20** under acidic aqueous conditions afforded hemiketals **21** and **22**. We then compared the optical rotations of **21** and **22** with the literature data and found their values to be quite different from those reported (Table 2). The specific rotation of synthetic **21** ($[\alpha]_D^{28}$ +454.9 (*c* 1.5, $CHCl_3$)) was found to have the opposite sign and different magnitude compared to that reported ($[\alpha]_D^{24}$ −287.5 (*c* 1.3, $CHCl_3$)). The same pattern was also found for **22** ($[\alpha]_D^{29}$ −453.9 (*c* 0.8, $CHCl_3$)) compared with its reported value ($[\alpha]_D^{25}$ +257.2 (*c* 0.5, $CHCl_3$)). Due to these differences in optical rotation values between the synthetic and reported compounds, we believed

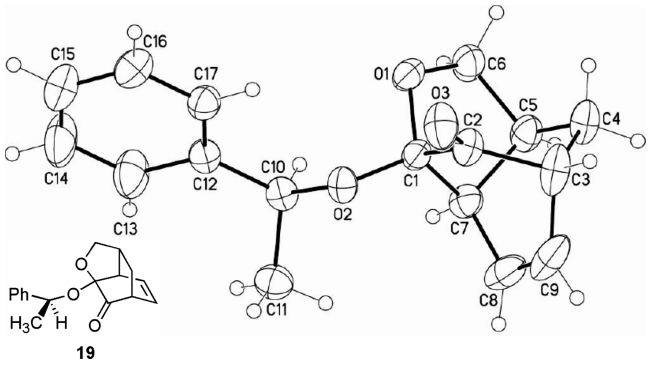
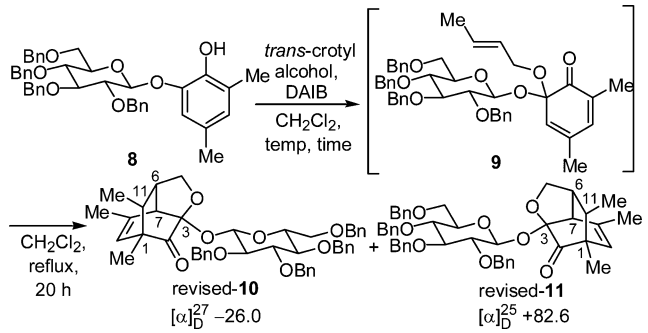


Figure 2. ORTEP plot of the crystal structure of **19** (numbering is arbitrary). Ellipsoid contour percent probability level is 50%.

that the absolute configurations of tricyclic cores in **10** and **11** were opposite to each other. Therefore, the absolute configurations of **10** and **11** in the bicyclo[2.2.2]oct-5-en-2-one cores should be 1*R*,3*S*,6*R*,7*R*,10*R* and 1*S*,3*R*,6*S*,7*S*,10*S*, respectively. The structures of **10** and **11** in Table 1 are revised to revised-**10** and revised-**11**, respectively, as shown in Table 3. Furthermore, since the structure of **11** has been revised to revised-**11**, other structures in Scheme 2 should also be revised to their enantiomers and shown in Scheme 4.

Table 3. Revised Structures of DAIB-Oxidized Intramolecular [4 + 2] Cycloaddition of Phenol 8 with *trans*-Crotyl Alcohol



entry	DAIB (equiv)	temp (°C)	time (h)	yield (%)	**10**:**11**
1	3	−30	6	58	2:1
2	10	−50	20	60	2.3:1
3	10	−78	20	39	1:1
4	10	−78 to −50	20	53	3.3:1

The diastereoselectivity of oxidative coupling of phenol **8** with *trans*-crotyl alcohol is proposed from examination of the possible reactive conformations of the oxocarbenium intermediate that is presumably formed during the formation of the ketal with *trans*-crotyl alcohol (Figure 3). The conformation **23** not only has a higher steric hindrance between the phenyl ring and cationized cyclohexadienone but also possesses a stronger dipole−dipole interaction between the carbonyl group and the C1′−O bond in the pyranosyl ring. These effects presumably result in a preference for conformer **24** which can be attacked by *trans*-crotyl alcohol from the *α*-face.

CONCLUSION

In summary, we accomplished the total synthesis of *ent*-penicillones A (*ent*-**1**) and B (*ent*-**2**) from 3,5-dimethylcatechol

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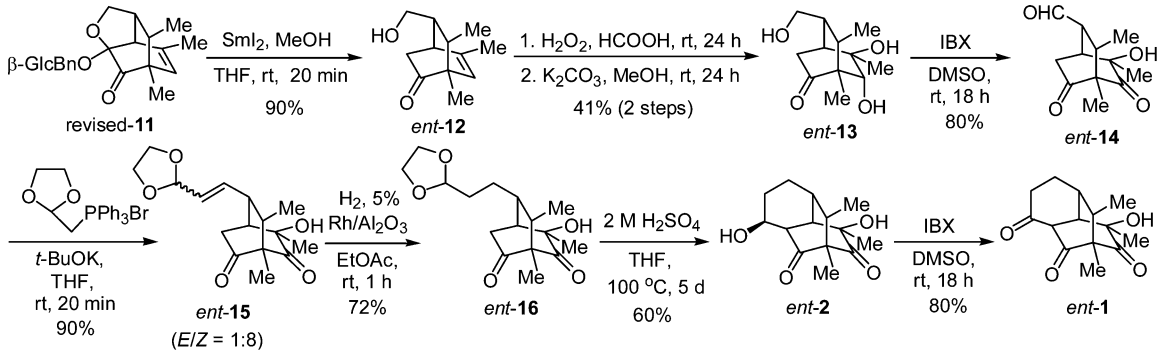
Scheme 4. Revised Structures in the Total Synthesis of *ent*-Penicillones A (*ent*-1) and B (*ent*-2)



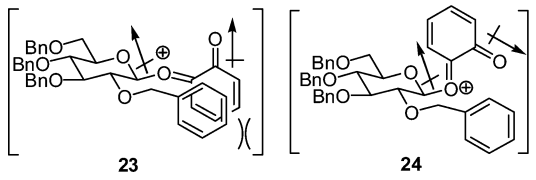


Figure 3. Possible conformations of the oxocarbenium intermediate.

(3) in 10 and 9 synthetic steps, respectively, using a carbohydrate-templated MOB strategy. We also revised the absolute configurations of the bicyclo[2.2.2]oct-5-en-2-one core obtained from per-*O*-benzylated α-D-glucopyranosyl as the carbohydrate template in the intramolecular Diels–Alder reaction of MOBs.

EXPERIMENTAL SECTION

General Information. Unless stated otherwise, reagents were obtained from commercial sources and used without further purification. All reactions were performed under a nitrogen atmosphere in anhydrous solvents, which were dried prior to use following standard procedures. Reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254) using 7% ethanolic phosphomolybdic acid as the developing agent. Standard column chromatography was conducted using 70–230 mesh silica gel from E. Merck. Flash column chromatography was performed using 230–400 mesh silica gel from E. Merck. IR spectra were recorded as films on NaCl plates. ^{1}H NMR spectra were obtained in $CDCl_3$ unless otherwise noted at 400 or 600 MHz. ^{13}C NMR spectra were obtained at 100 or 150 MHz. Chemical shifts were reported in δ (ppm) using solvent resonance as the internal reference. High resolution mass spectra (HRMS) were obtained on a TOF MS instrument with an EI or ESI source.

3,5-Dimethyl-2-hydroxyphenyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (8). A mixture of NaH (0.16 g, 4.02 mmol, 60% in w/w oil) and **3** (0.37 g, 2.68 mmol) in DMF (27 mL) was stirred at 0 °C for 10 min. A solution of **7** (1.00 g, 1.79 mmol) in DMF (9 mL) was added to the reaction mixture. After stirring at room temperature for 12 h, the mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica-gel chromatography (hexane/EtOAc/CH_2Cl_2 = 5:1:1) to give **8** (0.61 g, 52%) as a colorless oil. $[\alpha]_D^{25}$ −31.0 (*c* 1.0, $CHCl_3$); IR (neat) ν 3454, 3032, 2935, 2879, 1644, 1496, 1454, 1359, 1310, 1070, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.15 (m, 18H), 7.10–7.05 (m, 2H), 6.65 (s, 1H), 6.63 (s, 1H), 6.59 (brs, 1H), 4.92 (d, *J* = 10.8 Hz, 1H), 4.85 (d, *J* = 11.0 Hz, 1H), 4.81 (d, *J* = 11.0 Hz, 1H), 4.77 (d, *J* = 11.0 Hz, 1H), 4.74 (d, *J* = 10.8 Hz, 1H), 4.63 (d, *J* = 7.2 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 10.8 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 3.65–3.57 (m, 5H), 3.38 (m, 1H), 2.13 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.6 (C), 144.3 (C), 138.4 (C), 137.94 (C), 137.92 (C), 137.8 (C), 128.7, (C), 128.5–127.4 (CH × 20), 125.6 (C), 118.9 (CH), 116.9 (CH), 105.3 (CH), 84.7 (CH), 81.6 (CH), 77.5 (CH), 75.6 (CH_2), 75.3 (CH_2), 75.2 (CH), 75.0 (CH_2), 73.5 (CH_2), 68.5 (CH_2), 20.5 (CH_3), 15.8 (CH_3); HRMS (ESI, (M + Na)$^+$) calcd for $C_{42}H_{44}O_7Na$ 683.2985, found 683.2994.

(1*S*,3*S*,6*R*,7*R*,10*R*)-3-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-1,8,10-trimethyl-4-oxatricyclo[4.3.1.0^{3,7}]dec-8-en-2-one (revised-10) and (1*R*,3*R*,6*S*,7*S*,10*S*)-3-(2,3,4,6-Tetra-*O*-benzyl-β-D-gluco-pyranosyl)-1,8,10-trimethyl-4-oxatricyclo[4.3.1.0^{3,7}]-dec-8-en-2-one (revised-11). To a mixture of **8** (0.58 g, 0.88 mmol) and *trans*-crotyl alcohol (58 mL) and in CH_2Cl_2 (12 mL) was added $PhI(OAc)_2$ (0.85 g, 2.64 mmol) at −30 °C. After being stirred at −30 °C for 6 h, the reaction mixture was heated to reflux for 16 h. The solution was cooled to room temperature, and the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash silica-gel chromatography (hexane/EtOAc/CH_2Cl_2 = 8:1:8) to give revised-**10** (247 mg, 39%) and revised-**11** (124 mg, 19%). Revised-**10**: $[\alpha]_D^{27}$ −26.0 (*c* 2.0, $CHCl_3$); IR (neat) ν 3065, 3030, 2868, 1745, 1497, 1454, 1360, 994, 738, 698 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39–7.34 (m, 2H), 7.26–7.15 (m, 16H), 7.07–7.05 (m, 2H), 5.30 (s, 1H), 5.15 (d, *J* = 10.8 Hz, 1H), 4.91 (d, *J* = 10.9 Hz, 1H), 4.91 (d, *J* = 7.8 Hz, 1H), 4.73 (d, *J* = 10.8 Hz, 1H), 4.67 (d, *J* = 10.8 Hz, 1H), 4.66 (d, *J* = 10.8 Hz, 1H), 4.43 (d, *J* = 10.8 Hz, 1H), 4.41 (d, *J* = 10.8 Hz, 1H), 4.38 (d, *J* = 10.8 Hz, 1H), 4.05 dd, *J* = 7.8, 3.4 Hz, 1H), 3.74 (d, *J* = 8.1 Hz, 1H), 3.64–3.58 (m, 2H), 3.52–3.38 (m, 4H), 3.09 (dd, *J* = 4.2, 1.8 Hz, 1H), 1.88 (m, 1H), 1.81 (s, 3H), 1.71 (q, *J* = 7.1 Hz, 1H), 1.16 (s, 3H), 0.84 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.5 (C), 138.9 (C), 138.6 (C), 138.3 (C), 138.0 (C), 137.8 (C), 129.2–127.5 (CH × 20), 124.5 (CH), 100.1 (C), 96.5 (CH), 84.4 (CH), 80.9 (CH), 77.5 (CH), 75.7 (CH_2), 75.3 (CH_2), 74.8 (CH), 74.5 (CH_2), 74.2 (CH_2), 73.4 (CH_2), 69.4 (CH_2), 50.3 (C), 48.6 (CH), 45.4 (CH), 42.0 (CH), 16.5 (CH_3), 15.2 (CH_3), 14.2 (CH_3); HRMS (ESI, (M + Na)$^+$) calcd for $C_{46}H_{50}O_8Na$ 753.3403, found 753.3404. Revised-**11**: $[\alpha]_D^{25}$ +82.6 (*c* 6.5, $CHCl_3$); IR (neat) ν 3066, 3028, 2933, 2872, 1736, 1454, 1066, 1028, 736 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39–7.36 (m, 2H), 7.34–7.20 (m, 16H), 7.18–7.15 (m, 2H), 5.38 (s, 1H), 5.02 (d, *J* = 11.1 Hz, 1H), 4.93 (d, *J* = 7.8 Hz, 1H), 4.90 (d, *J* = 10.8 Hz, 1H), 4.80 (d, *J* = 10.8 Hz, 1H), 4.74 (d, *J* = 10.8 Hz, 1H), 4.69 (d, *J* = 10.8 Hz, 1H), 4.59 (d, *J* = 10.8 Hz, 1H), 4.52 (d, *J* = 10.8 Hz, 1H), 4.52 (d, *J* = 10.8 Hz, 1H), 4.07 (dd, *J* = 7.8, 3.2 Hz, 1H), 3.81–3.54 (m, 7H), 3.11 (dd, *J* = 4.2, 1.8 Hz, 1H), 2.00 (m, 1H), 1.87 (s, 3H), 1.80 (q, *J* = 7.1 Hz, 1H), 1.20 (s, 3H,), 0.89 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.4 (C), 138.6 (C × 2), 138.3 (C), 138.2 (C), 137.8 (C), 128.4–127.4 (CH × 20), 125.0 (CH), 100.1 (C), 98.9 (CH), 84.7 (CH), 82.0 (CH), 77.7 (CH), 75.6 (CH_2), 75.0 (CH), 74.9 (CH_2), 74.6 (CH_2), 73.6 (CH_2), 73.2 (CH_2), 68.7 (CH_2), 50.9 (C), 50.0 (CH), 46.4 (CH), 42.5 (CH), 21.1 (CH_3), 16.6 (CH_3), 15.2 (CH_3); HRMS (ESI, (M + Na)$^+$) calcd for $C_{46}H_{50}O_8Na$ 753.3403, found 753.3407.

(1*R*,4*S*,7*S*,8*S*)-8-Hydroxymethyl-1,5,7-trimethylbicyclo-[2.2.2]oct-5-en-2-one (*ent*-12). To a stirred solution of revised-**11** (0.56 g, 0.77 mmol) in methanol (2 mL) was added SmI_2 (0.1 M in

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THF, 31 mL, 3.1 mmol) at room temperature under an Ar atmosphere. After the mixture was stirred for 20 min, the solvent was evaporated. The residue was dissolved in water and 2 M HCl and extracted with EtOAc. The combined extracts were washed successively with saturated aqueous $NaHCO_3$, saturated aqueous $Na_2S_2O_3$, and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash silica-gel chromatography (hexane/EtOAc = 1:1) to give *ent*-**12** (134 mg, 90%) as a white solid. Analytically pure *ent*-**12** was obtained by crystallization from Et_2O−hexane: mp 100−101 °C; $[\alpha]_D^{25}$ +269.4 (*c* 1.8, $CHCl_3$); IR (neat) ν 3414, 3029, 2966, 2921, 2817, 1717, 1651, 1455, 1379, 1166, 1090, 1047, 999, 782 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.29 (s, 1H), 3.75 (ddd, *J* = 10.8, 9.8, 5.4 Hz, 1H), 3.49 (ddd, *J* = 10.8, 9.8, 5.4 Hz, 1H), 2.65 (m, 1H), 2.24 (dd, *J* = 18.7, 2.0 Hz, 1H), 1.99 (ddd, *J* = 18.7, 3.3, 1.9 Hz, 1H), 1.85 (d, *J* = 1.6 Hz, 3H), 1.44 (m, 1H), 1.37 (m, 1H), 1.17 (m, 1H), 1.08 (s, 3H), 0.89 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 213.9 (C), 147.3 (C), 123.6 (CH), 63.5 (CH_2), 52.7 (C), 48.5 (CH), 37.7 (CH), 37.5 (CH), 33.9 (CH_2), 19.9 (CH_3), 17.6 (CH_3), 15.1 (CH_3); MS (EI, 70 eV) *m*/*z* (% base peak) 194 (M^+, 8), 176 (3), 163 (2), 152 (22), 121 (100), 105 (10), 91 (11), 79 (7); HRMS (EI) calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1309.

(1*R*,4*S*,5*R*,6*R*,7*S*,8*S*)-5,6-Dihydroxy-8-hydroxymethyl-1,5,7-trimethylbicyclo[2.2.2]octan-2-one (*ent*-13). A mixture of *ent*-**12** (0.51 g, 2.62 mmol) and 35% H_2O_2 (0.51 g, 5.24 mmol) in 90% formic acid (5 mL) was stirred at room temperature for 24 h. The solvent was removed in vacuo, the residue was then dissolved in MeOH (4 mL), and K_2CO_3 (0.72 g, 5.24 mmol) was added. The mixture was stirred at room temperature for 24 h. The reaction mixture was filtered through a short pad of silica gel, and the solvent was removed in vacuo. The crude product was purified by flash silica-gel chromatography (EtOAc/MeOH = 20:1) to give *ent*-**13** (244 mg, 41%) as a white solid. Mp 163−164 °C; $[\alpha]_D^{25}$ +9.0 (*c* 0.8, MeOH); IR (neat) ν 3382, 2974, 2932, 2878, 1721, 1557, 1454, 1416, 1374, 1099, 1055, 988, 897 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 3.76 (s, 1H), 3.47 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.37 (dd, *J* = 11.1, 8.8 Hz, 1H), 3.25 (s, 1H), 2.36 (dd, *J* = 19.5, 2.9 Hz, 1H), 2.22 (m, 1H), 2.14 (ddd, *J* = 19.5, 3.2, 1.8 Hz, 1H), 1.99 (m, 1H), 1.21 (s, 3H), 1.11 (m, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 217.9 (C) 79.1 (CH), 76.1 (C), 64.5 (CH_2), 54.8 (C), 43.1 (CH), 41.3 (CH), 37.5 (CH), 36.4 (CH_2), 23.6 (CH_3), 15.4 (CH_3), 14.7 (CH_3); MS (EI, 70 eV) *m*/*z* (% base peak) 228 (M^+, 4), 210 (54), 192 (39), 179 (18), 167 (60), 156 (34), 149 (35), 137 (39), 133 (100), 121 (82), 112 (47), 107 (35), 97 (65), 85 (83), 83 (45); HRMS (EI) calcd for $C_{12}H_{20}O_4$ 228.1362, found 228.1360.

(1*S*,2*S*,3*S*,4*S*,6*R*)-6-Hydroxy-3,4,6-trimethyl-5,8-dioxo-bicyclo[2.2.2]octane-2-carbaldehyde (*ent*-14). A mixture of *ent*-**13** (0.31 g, 1.35 mmol) and IBX (1.13 g, 4.05 mmol) in DMSO (12 mL) was stirred at room temperature for 18 h. The reaction mixture was quenched with water and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash silica-gel chromatography (hexane/EtOAc = 1:2) to give *ent*-**14** (243 mg, 80%) as a white solid. Mp 82−83 °C; $[\alpha]_D^{25}$ +108.5 (*c* 0.9, $CHCl_3$); IR (neat) ν 3476, 2983, 2934, 2877, 2730, 1744, 1716, 1455, 1377, 1141, 1055, 990, 929, 880 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.78 (brs, 1H), 3.06 (ddd, *J* = 8.1, 1.9, 1.9 Hz, 1H), 2.85 (brs, 1H), 2.81 (m, 1H), 2.58 (dm, *J* = 19.8 Hz, 1H), 2.54 (m, 1H), 2.40 (dd, *J* = 19.8, 2.7 Hz, 1H), 1.26 (s, 3H), 1.12 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.5 (C), 205.1 (C), 200.6 (CH), 75.1 (C), 65.6 (C), 52.7 (CH), 37.6 (CH), 37.1 (CH_2), 34.6 (CH), 22.9 (CH_3), 17.1 (CH_3), 9.1 (CH_3); MS (EI, 70 eV) *m*/*z* (% base peak) 224 (M^+, 34), 196 (20), 181 (15), 163 (19), 153 (50), 135 (54), 125 (85), 123 (90), 108 (24), 107 (30), 97 (14), 83 (100), 55 (48); HRMS (EI) calcd for $C_{12}H_{16}O_4$ 224.1049, found 224.1050.

(1*S*,3*R*,4*S*,7*S*,8*R*)-8-[2-(1,3-Dioxolan-2-yl)-vinyl]-3-hydroxy-1,3,7-trimethylbicyclo[2.2.2]octane-2,6-dione (*ent*-15). To a suspension of (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide (211 mg, 0.49 mmol) in THF (1.2 mL) was added *t*-BuOK (1 M in THF, 0.45 mL, 0.45 mmol) at room temperature under an Ar atmosphere. After the mixture was stirred for 30 min, aldehyde *ent*-**14** (50 mg, 0.22 mmol) in THF (1.6 mL) was added, followed by stirring for another 20 min. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash silica-gel chromatography (hexane/EtOAc = 2:3) to give *ent*-**15** (59 mg, 90%) as a white solid. $[\alpha]_D^{25}$ +69.7 (*c* 1.2, $CHCl_3$); IR (neat) ν 3446, 2976, 2936, 2887, 1740, 1714, 1556, 1472, 1375, 1135, 1113, 987, 936 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.73 (dd, *J* = 10.8, 10.8 Hz, 1H), 5.59 (dd, *J* = 10.8, 7.2 Hz, 1H), 5.54 (d, *J* = 7.2 Hz 1H), 4.00−3.87 (m, 4H), 3.12 (m, 1H), 2.78 (dd, *J* = 19.7, 2.7 Hz, 1H), 2.76 (brs, 1H), 2.55 (ddd, *J* = 19.7, 3.4, 1.8 Hz, 1H), 2.24 (m, 1H), 1.71 (m, 1H), 1.18 (s, 3H), 1.08 (s, 3H), 0.89 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.3 (C), 206.8 (C), 137.0 (CH), 129.4 (CH), 98.7 (CH), 76.2 (C), 65.6 (C), 65.0 (CH_2 × 2), 43.8 (CH), 43.3 (CH), 37.9 (CH), 36.1 (CH_2), 23.0 (CH_3), 15.4 (CH_3), 9.1 (CH_3); MS (EI, 70 eV) *m*/*z* (% base peak) 294 (M^+, 1), 266 (20), 223 (10), 204 (2), 179 (5), 161 (5), 149 (4), 121 (5), 99 (8), 83 (100), 73 (22); HRMS (EI) calcd for $C_{15}H_{22}O_4$ (M^+ − 28) 266.1518, found 266.1515.

(1*S*,3*R*,4*S*,7*S*,8*S*)-8-[2-(1,3-Dioxolan-2-yl)-ethyl]-3-hydroxy-1,3,7-trimethylbicyclo[2.2.2]octane-2,6-dione (*ent*-16). A mixture of *ent*-**15** (47 mg, 0.16 mmol) and 5% Rh/Al_2O_3 (47 mg) in EtOAc (1 mL) was stirred under a hydrogen balloon at room temperature for 1 h. Filtration and concentration in vacuo gave a residue, which was purified by flash silica-gel column chromatography (hexane/EtOAc = 2:3) to give *ent*-**16** (34 mg, 72%) as a white solid. Analytically pure *ent*-**16** was obtained by crystallization from CH_2Cl_2−hexane: mp 93−94 °C; $[\alpha]_D^{25}$ +20.5 (*c* 1.5, $CHCl_3$); IR (neat) ν 3435, 2975, 2935, 2879, 1736, 1714, 1455, 1413, 1142, 1025, 935 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.86 (dd, *J* = 4.5, 4.4 Hz, 1H), 3.82−3.95 (m, 4H), 2.72 (dd, *J* = 19.7, 2.7 Hz, 1H), 2.68 (brs, 1H), 2.51 (ddd, *J* = 19.7, 3.3, 1.9 Hz, 1H), 2.22(m, 1H), 1.98 (m, 1H), 1.77−1.44 (m, 5H), 1.19 (s, 3H), 1.05 (s, 3H), 0.89 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.8 (C), 207.3 (C), 104.0 (CH), 75.7 (C), 66.2 (C), 64.9 (CH_2 × 2), 43.8 (CH), 40.6 (CH), 38.8 (CH), 36.0 (CH_2), 31.9 (CH_2), 26.8 (CH_2), 23.5 (CH_3), 16.3 (CH_3), 9.3 (CH_3); MS (EI, 70 eV) *m*/*z* (% base peak) 296 (M^+, 1), 268 (22), 225 (45), 206 (4), 191 (3), 163 (91), 135 (52), 123 (15), 107 (9), 99 (16), 83 (13), 73 (100); HRMS (EI) calcd for $C_{15}H_{24}O_4$ (M^+ − 28) 268.1675, found 268.1678.

***ent*-Penicillone B (*ent*-2).** A mixture of *ent*-**16** (67 mg, 0.23 mmol) and 2 M H_2SO_4 (1 mL) in THF (2 mL) was stirred at 100 °C for 5 d. After being cooled to room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash silica-gel chromatography (CH_2Cl_2/Et_2O = 3:1) to give *ent*-**2** (34 mg, 60%) as a white solid. Analytically pure *ent*-**2** was obtained by crystallization from acetone: mp 192−193 °C; $[\alpha]_D^{25}$ +12.6 (*c* 1.3, MeOH); IR (neat) ν 3520, 3318, 2956, 2921, 1733, 1694, 1458, 1411, 1261, 1161, 1093, 1053, 1028, 951, 915 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 4.75 (brs, 1H), 3.72 (m, 1H), 3.56 (d, *J* = 9.7 Hz, 1H), 2.79 (m, 1H), 2.35 (m, 1H), 2.04 (m, 1H), 1.83 (m, 1H), 1.73 (m, 1H), 1.65 (dq, *J* = 7.1, 3.9 Hz, 1H), 1.58 (tt, *J* = 13.7, 3.9 Hz, 1H), 1.31 (m, 1H), 1.27 (s, 3H), 0.99 (d, *J* = 7.1 Hz, 3H), 0.98 (s, 3H); ^{13}C NMR (150 MHz, acetone-d_6) δ 213.0 (C), 210.3 (C), 74.1 (C), 72.9 (CH), 68.1 (C), 51.5 (CH), 47.0 (CH), 40.8 (CH), 34.3 (CH), 29.3 (CH_2), 28.5 (CH_2), 22.6 (CH_3), 18.1 (CH_3), 10.3 (CH_3); MS (EI, 70 eV) *m*/*z* (% base peak) 252 (M^+, 26), 224 (89), 209 (30), 191 (22), 178 (10), 163 (50), 149 (77), 135 (38), 128 (45), 121 (100), 107 (28), 83 (29); HRMS (EI) calcd for $C_{14}H_{20}O_4$ 252.1362, found 252.1366.

***ent*-Penicillone A (*ent*-1).** A mixture of *ent*-**2** (20 mg, 0.08 mmol) and IBX (44 mg, 0.16 mmol) in DMSO (0.55 mL) was stirred at room temperature for 18 h. The reaction mixture was quenched with water and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash silica-gel chromatography (hexane/EtOAc = 1:1) to give *ent*-**1** (16 mg, 80%) as a white solid. Analytically pure *ent*-**1** was obtained by crystallization from acetone: mp 190−191

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°C; $[\alpha]_D^{25}$ −140.5 (*c* 1.0, $CHCl_3$); IR (neat) ν 3401, 2970, 2941, 2872, 1739, 1714, 1692, 1450, 1377, 1141, 1090, 1025, 908, 800 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.47 (m, 1H), 2.66 (brs, 1H), 2.55 (m, 1H), 2.49 (m, 1H), 2.45−2.40 (m, 2H), 2.03 (m, 1H), 1.97 (m, 1H), 1.91 (m, 1H), 1.21 (s, 3H), 1.15 (s, 3H), 1.06 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.4 (C), 201.7 (C), 201.3 (C), 73.9 (C), 67.3 (C), 62.6 (CH), 46.7 (CH), 41.0 (CH), 34.8 (CH_2), 33.5 (CH), 28.1 (CH_2), 22.6 (CH_3), 17.9 (CH_3), 9.8 (CH_3); MS (EI, 70 eV) *m*/*z* (% base peak) 250 (M^+, 22), 232 (13), 222 (51), 204 (14), 179 (75), 161 (13), 149 (37), 135 (100), 121 (59), 107 (17), 91 (15), 83 (20); HRMS (EI) calcd for $C_{14}H_{18}O_4$ 250.1205, found 250.1209.

(3*S*,3a*R*,6*R*,7a*R*)-3,6-Methanobenzofuran-7(6*H*)-1,2,3,3a,7a-tetrahydro-7a-[(1*S*)-1-phenylethoxy] (19) and (3*R*,3a*S*,6*S*,7a*S*)-3,6-Methanobenzofuran-7(6*H*)-1,2,3,3a,7a-tetrahydro-7a-[(1*S*)-1-phenylethoxy] (20). To a mixture of (*S*)-1-phenylethanol (**18**) (2 mL) and $PhI(OCOCF_3)_2$ (186 mg, 0.58 mmol) in CH_2Cl_2 (3 mL) was slowly added a solution of 2-allyloxyphenol (**17**) (60 mg, 0.40 mmol) in CH_2Cl_2 (4 mL). After being stirred at room temperature for 4 h, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica-gel chromatography (hexane/EtOAc = 5:1) to give **19** (16 mg, 15%) and **20** (10 mg, 9%). Analytically pure **19** and **20** were obtained by crystallization from CH_2Cl_2−hexane. **19**:[6] $[\alpha]_D^{25}$ +242.5 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.2 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 6.26 (dt, *J* = 8.1, 1.6 Hz, 1H), 6.07 (ddd, *J* = 8.1, 6.3, 1.2 Hz,1H), 5.04 (q, *J* = 6.6 Hz, 1H), 4.03 (dd, *J* = 8.1, 1.6 Hz, 1H), 3.96 (d, *J* = 8.0 Hz, 1H), 3.21 (ddd, *J* = 6.3, 4.3, 1.6 Hz,1H), 3.12 (m, 1H), 2.39 (m, 1H), 1.81−1.71 (m, 2H), 1.48 (d, *J* = 6.6 Hz, 3H). **20**:[6] $[\alpha]_D^{28}$ −354.3 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.21 (m, 5H), 6.18 (dd, *J* = 8.0, 6.7, 1.6 Hz, 1H), 5.55 (dd, *J* = 8.0, 6.5 Hz, 1H), 5.11 (q, *J* = 6.6 Hz, 1H), 4.05 (dd, *J* = 8.0, 3.5 Hz, 1H), 3.73 (d, *J* = 8.0 Hz, 1H), 3.12 (ddd, *J* = 6.5, 3.1, 2.2 Hz,1H), 2.94 (m, 1H), 2.30 (m, 1H), 1.81−1.68 (m, 2H), 1.49 (d, *J* = 6.6 Hz, 3H).

(3*S*,3a*R*,6*R*,7a*S*)-3,6-Methanobenzofuran-7(6*H*)-one,2,3,3a,7a-tetrahydro-7a-hydroxy (21). A mixture of **19** (25 mg, 0.09 mmol) and 3% HCl (0.3 mL) in HOAc (2 mL) was stirred at 100 °C for 3 h. After being cooled to room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica-gel chromatography (EtOAc/hexanes = 1:3) to give **21** (14 mg, 91%) as a white solid. Analytically pure **21** was obtained by crystallization from CH_2Cl_2−hexane:[6] $[\alpha]_D^{28}$ +454.9 (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.29 (dt, *J* = 13.0, 1.8 Hz, 1H), 6.23 (dt, *J* = 13.0, 1.3 Hz, 1H), 4.18 (dd, *J* = 8.0, 3.2 Hz, 1H), 3.99 (brs, 1H), 3.71 (d, *J* = 8.0 Hz,1H), 3.31−3.22 (m, 2H), 2.52−2.46 (m, 1H), 1.98−1.82 (m, 2H).

(3*R*,3a*S*,6*S*,7a*R*)-3,6-Methanobenzofuran-7(6*H*)-one,2,3,3a,7a-tetrahydro-7a-hydroxy (22). A mixture of **20** (13.0 mg, 0.048 mmol) and 3% HCl (0.3 mL) in HOAc (2 mL) was stirred at 100 °C for 3 h. After being cooled to room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica-gel chromatography (EtOAc/hexanes = 1:3) to give **22** (7.4 mg, 93%) as a white solid. Analytically pure **22** was obtained by crystallization from CH_2Cl_2−hexane:[6] $[\alpha]_D^{29}$ −453.9 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.29 (dt, *J* = 13.0, 1.8 Hz, 1H), 6.22 (dt, *J* = 13.0, 1.3 Hz, 1H), 4.18 (dd, *J* = 8.0, 3.2 Hz, 1H), 4.09 (brs, 1H), 3.70 (d, *J* = 8.0 Hz,1H), 3.31−3.22 (m, 2H), 2.51−2.45 (m, 1H), 1.90−1.79 (m, 2H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02055.

X-ray crystallographic data for **19**; copies of ^1H and ^{13}C NMR for compounds *ent*-**1**−**2**, **8**, revised-**10**−**11**, and *ent*-**12**−**16**; copies of ^1H NMR for compounds **19**−**22** (PDF)

Crystallographic data for **19** (CIF)

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Notes

The authors declare no competing financial interest.

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