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Total Syntheses of Cladoacetals A and B: Confirmation of Absolute Configurations

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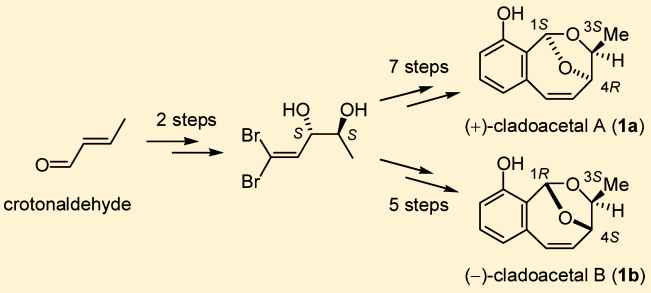
Supporting Information

ABSTRACT: The first enantioselective syntheses of cladoacetals A (**1a**, overall yield: 16%) and B (**1b**, overall yield: 34%) from crotonaldehyde in nine and seven steps, respectively, have been accomplished. Sharpless asymmetric dihydroxylation, Suzuki coupling, and acid-catalyzed intramolecular acetalization were the key steps in the syntheses. The absolute configuration of natural (+)-cladoacetal A was affirmed to be 1*S*,3*S*,4*R*, whereas that of (−)-cladoacetal B was affirmed to be 1*R*,3*S*,4*S*.



INTRODUCTION

Cladoacetals A (**1a**) and B (**1b**) have been previously isolated from solid-substrate fermentation cultures of an unidentified fungicolous isolate (NRRL 29097) that resembles *Cladosporium* sp.[1] The relative configurations displayed in Figure 1 were determined by NMR spectroscopy. Cladoacetals possess a benzo-fused dioxabicyclo[4.2.1]nonene framework. Although **1a** and **1b** vary only in the relative configuration at C-3, their absolute configurations have not yet been determined. Compound **1a** shows antibacterial activity, whereas the biological activity of **1b** has not been investigated. In this paper, we report the first enantioselective syntheses of **1a** and **1b**, and the determination of their absolute configurations.

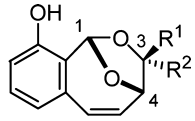
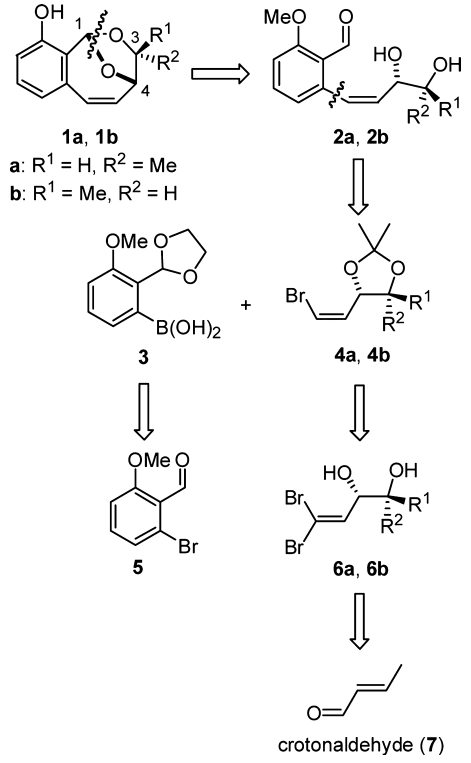


Figure 1. Structure of cladoacetals A and B.

A retrosynthetic analysis suggested that the desired cladoacetals A and B could be synthesized from acetal precursors **2** via intramolecular acetalization (Scheme 1). The key intermediates **2** could be obtained by the Suzuki coupling of boronic acid **3** and *Z*-vinyl bromides **4**. Boronic acid **3** could be prepared from bromoaldehyde **5** through protection of the aldehyde and subsequent replacement of the bromide group with boronic acid. On the other hand, **4** could be obtained from diols **6** via protection of the 1,2-diols followed by selective hydrogenolysis; **6** could be prepared from commercially available crotonaldehyde in two steps, one-carbon homologation and subsequent Sharpless asymmetric dihydroxylation of the resulting 1,1-dibromoalkene intermediate.

Scheme 1. Retrosynthetic Analysis



RESULTS AND DISCUSSION

Preparation of Boronic Acid 3. The boronic acid fragment **3** was prepared from **5**[2] through a two-step sequence, as shown in Scheme 2. Protection of the aldehyde with ethylene glycol

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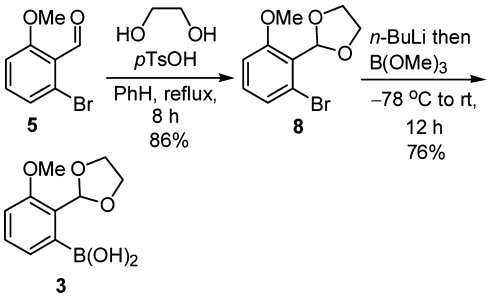
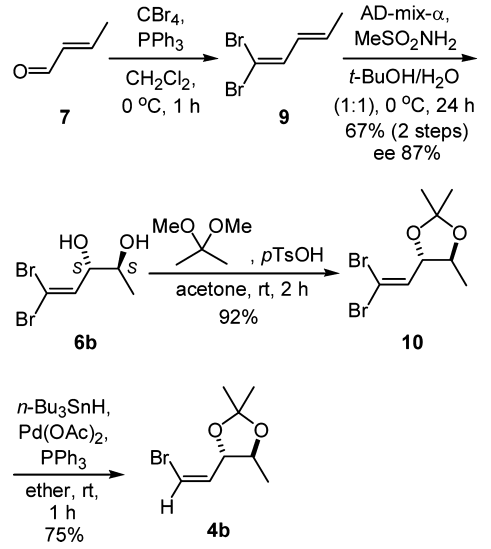
Scheme 2. Preparation of Boronic Acid 3



afforded **8**, which upon lithium–halogen exchange and subsequent treatment with trimethyl borate gave the desired product **3** in 78% yield.

Preparation of *Z*-Vinyl Bromide 4b. With the necessary boronic acid fragment in hand, we turned our attention to the synthesis of the *Z*-vinyl bromide fragments. We first focused on the synthesis of **1b** because the necessary C-3 and C-4 stereocenters could be obtained directly by Sharpless asymmetric dihydroxylation. To this end, the known (2*S*,3*S*)-diol **6b**[3] was obtained in 67% yield and with 87% enantiomeric excess (ee) from crotonaldehyde (**7**) via one-carbon homologation[4] and the Sharpless asymmetric dihydroxylation[5] of **9** with AD-mix-α[3] (Scheme 3). The resulting diol was then protected as its

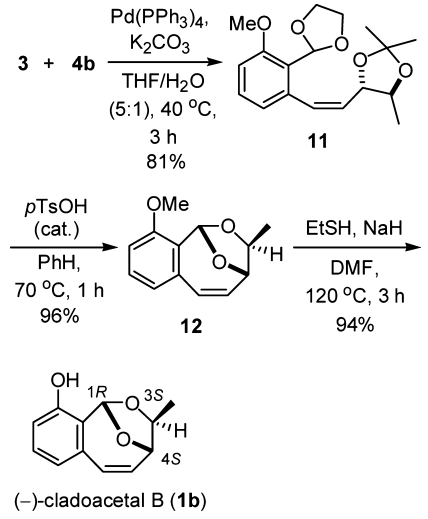
Scheme 3. Preparation of *Z*-Vinyl Bromide 4b



isopropylidene acetal to afford dibromoalkene **10**.[6] Stereoselective hydrogenolysis of **10** by a palladium-catalyzed *n*-Bu_3SnH reduction[7] afforded **4b** in 75% yield.

Synthesis of (−)-Cladoacetal B (1b). Suzuki–Miyaura coupling[8] of **4b** and **3** yielded the desired product **11** in 81% yield (Scheme 4). The next step was to construct the tricyclic core structure of **1b** by intramolecular acetalization. Treament of **11** with a catalytic amount of *p*TsOH in refluxing benzene directly gave the desired tricyclic compound **12** in 96% yield. By deprotection with EtSNa,[9] **12** was easily converted into the target molecule **1b** in 94% yield. Initial attempts to deprotect the methyl ether by using BBr_3 were unsuccessful, and only a complex mixture was obtained. Spectroscopic data recorded for the synthetic molecule were found to be in good agreement with those reported for the natural product **1b**.[10] However, the

Scheme 4. Completion of the Total Synthesis of (−)-Cladoacetal B (1b)



recorded optical rotation ($[\alpha]^{25}_D = -173$ (*c* 1.4, MeOH)) and the literature value[1] ($[\alpha]^{22}_D = -135$ (*c* 0.6, MeOH)) were identical in sign but different in magnitude. To determine whether such a difference resulted from some technical error, the optical rotation values for different synthetic samples were recorded, but similar values were observed in all cases. Because of the rigid tricyclic ring system in cladoacetals, the relative configuration at C-1 and C-4 should be 1*R** and 4*S**, respectively. Accordingly, we believed that only one isomer would be formed in the acid-catalyzed intramolecular acetalization of **11**. Thus, the aforementioned discrepancy in the optical rotation is presumably due to the relatively small amount (0.9 mg) of natural **1b** isolated in previous studies and the corresponding higher margin of error. The structure of **1b** was further confirmed by single-crystal X-ray diffraction analysis (Figure 2),[11] and the

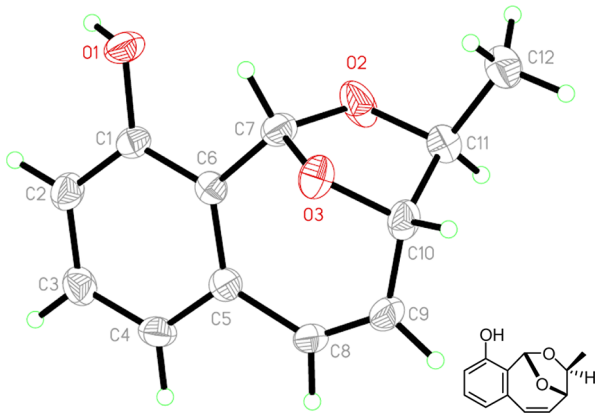


Figure 2. ORTEP plot of the crystal structure of cladoacetal B (**1b**) (numbering is arbitrary).

absolute configuration at C-1, C-3, and C-4 was affirmed to be 1*R*, 3*S*, and 4*S*.

Preparation of *Z*-Vinyl Bromide 4a. Next, we focused our attention on the synthesis of **1a**. Because the only difference between **1a** and **1b** is the relative configuration at the C-3 stereocenter, we chose (4*S*,5*R*)-**15** as our target intermediate for the synthesis of **1a**. This synthesis, as shown in Scheme 5, also

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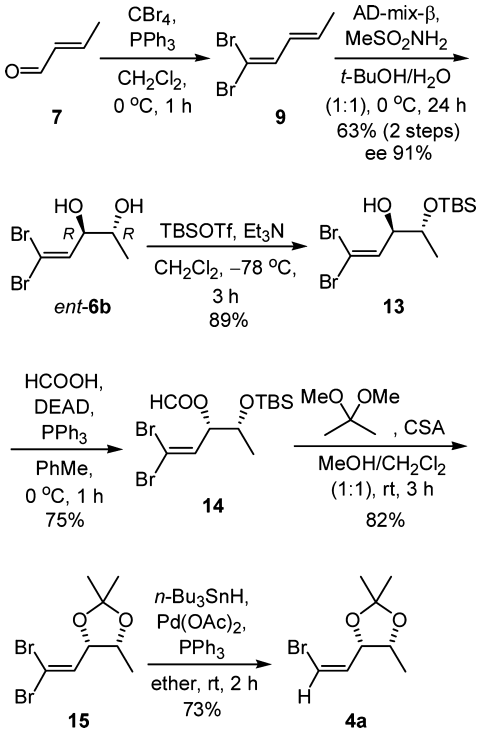
Scheme 5. Preparation of *Z*-Vinyl Bromide 4a

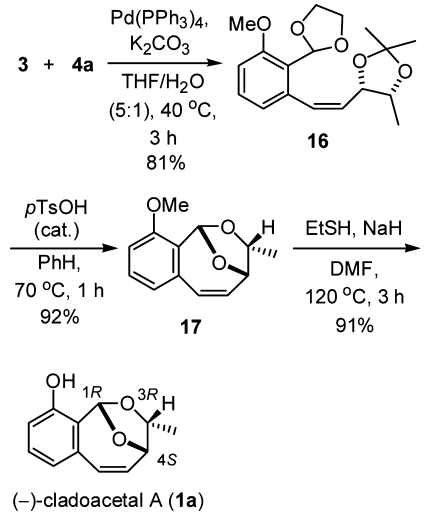


began with **7**. One-carbon homologation and Sharpless asymmetric dihydroxylation using AD-mix-β furnished (2*R*,3*R*)-diol *ent*-**6b** in 63% yield and with 91% ee.[12] Next, inversion of the allylic hydroxyl group in *ent*-**6b** was achieved by selective protection[13] of the hydroxyl group at C-2, followed by the application of Mitsunobu conditions,[13] to give the desired product (2*R*,3*S*)-**14**. The best selectivity in the regioselective protection of the hydroxyl group at C-2 in *ent*-**6b** was observed when using TBSOTf as the silylation agent at −78 °C. Poor selectivity was observed when the reaction was carried out at a higher temperature or used TBSCl as the silylation agent. Then, transformation of the formyl and TBS protecting groups in **14** into isopropylidene acetal under acidic conditions[14] and subsequent treatment with *n*-Bu_3SnH in the presence of a palladium catalyst gave **4a** in 73% yield.

Synthesis of (−)-Cladoacetal A (1a). Once **4a** was obtained, it was coupled with fragment **3** under Suzuki−Miyaura conditions to yield the desired product **16** in 81% yield (Scheme 6). Intramolecular acetalization of **16** under acidic conditions led to the formation of benzo-fused dioxabicyclo[4.2.1]nonene **17** in 92% yield. Finally, deprotection of the methyl ether with EtSNa afforded **1a** in 91% yield. The spectroscopic data of the synthetic molecule were found to be in good agreement with those reported for the natural product **1a**.[10] However, the specific rotation of the synthetic molecule ($[\alpha]^{25}_D = -250$ (*c* 1.4, MeOH)) was found to be opposite to that of the natural product[1] ($[\alpha]^{22}_D = +266$ (*c* 1.4, MeOH)). Thus, the absolute configuration of natural cladoacetal A at C-1, C-3, and C-4 should be 1*S*, 3*S*, and 4*R*.

Synthesis of (+)-Cladoacetal A (1a). To further confirm the absolute configuration of natural cladoacetal A, we decided to synthesize (+)-cladoacetal A from (2*S*,3*S*)-diol **6** using the same reagents and procedures shown in Schemes 5 and 6. Thus, selective protection of the hydroxyl group at C-2 in **6b** was followed by the inversion of the allylic hydroxyl group under Mitsunobu conditions to give (2*S*,3*R*)-*ent*-**14** in 77% yield

Scheme 6. Completion of the Total Synthesis of (−)-Cladoacetal A (1a)



(Scheme 7). Transformation of the formyl and TBS protecting groups in *ent*-**14** into isopropylidene acetal under acidic conditions and subsequent treatment with *n*-Bu_3SnH in the presence of a palladium catalyst gave *Z*-vinyl bromide *ent*-**4a**. Coupling of **3** and *ent*-**4a** under Suzuki−Miyaura conditions gave the desired product *ent*-**16** in 78% yield. Acid-catalyzed intramolecular acetalization of *ent*-**16** afforded the tricyclic compound *ent*-**17**. Finally, deprotection of the methyl ether with EtSNa afforded the final product in 89% yield. The specific rotation of this synthetic molecule ($[\alpha]^{25}_D = +255$ (*c* 2.7, MeOH)) was found to be in good agreement with that of the natural product[1] ($[\alpha]^{22}_D = +266$ (*c* 1.4, MeOH)). Thus, the absolute configuration of natural cladoacetal A at C-1, C-3, and C-4 was confirmed to be 1*S*, 3*S*, and 4*R*.

CONCLUSION

In conclusion, we have accomplished the enantioselective syntheses of cladoacetals A (overall yield: 16%) and B (overall yield: 34%) from crotonaldehyde in nine and seven steps, respectively. The absolute configuration of natural (+)-cladoacetal A was confirmed to be (1*S*,3*S*,4*R*), whereas that of (−)-cladoacetal B was confirmed to be (1*R*,3*S*,4*S*).

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 developing agent. Merck silica gel 60 (particle size 0.04−0.063 mm) was employed for flash chromatography. Melting points are uncorrected. IR spectra were recorded as films on KBr plates. ^{1}H NMR spectra were obtained in $CDCl_3$ unless otherwise noted at 400 MHz. ^{13}C NMR spectra were obtained at 100 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 ESI or EI source.

2-(2-Bromo-6-methoxyphenyl)-1,3-dioxolane (8). *p*-Toluenesulfonic acid monohydrate (43 mg, 0.23 mmol) and ethylene glycol (1.00 g, 16.1 mmol) were added to a solution of **5** (500 mg, 2.3 mmol) in benzene (20 mL) at room temperature. The reaction mixture was heated under reflux for 8 h in a Dean−Stark apparatus. The contents

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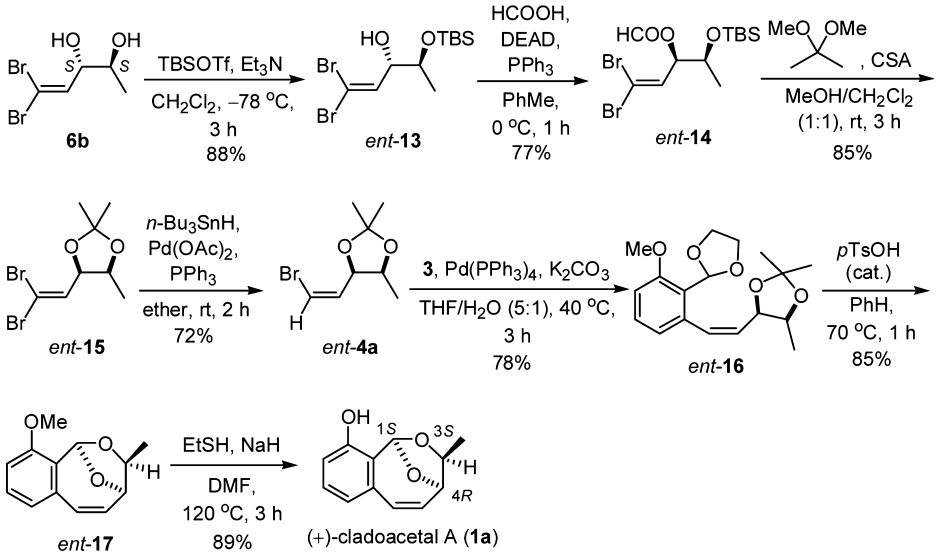
Scheme 7. Total Synthesis of (+)-Cladoacetal A (1a)



were cooled to room temperature and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with EtOAc. The combined organic extracts were washed successively with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes = 1:10) to afford **8** (0.52 g, 86%) as a pale yellow solid: mp 68–69 °C; IR (neat) ν_{max} 2891, 1589, 1574, 1463, 1405, 1264, 1211, 1092, 1066, 1033, 959, 778, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, J = 8.0, 1.2 Hz, 1H), 7.14 (dd, J = 8.0, 8.0 Hz, 1H), 6.86 (dd, J = 8.0, 1.2 Hz, 1H), 6.46 (s, 1H), 4.28–4.24 (m, 2H), 4.04–4.01 (m, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 131.0, 126.3, 124.0, 123.6, 110.9, 101.3, 65.9, 56.1; MS (EI) m/z (% base peak) 260 (14), 258 (M^+, 14), 232 (32), 230 (33), 215 (62), 213 (65), 186 (14), 149 (10), 91 (37), 73 (100); HRMS (EI) calcd for $C_{10}H_{11}{}^{79}BrO_3$ 257.9892, found 257.9898.

2-(1,3-Dioxolan-2-yl)-3-methoxyphenylboronic Acid (3). To a stirred solution of **8** (100 mg, 0.38 mmol) in THF (5 mL) was added *n*-BuLi (0.48 mL, 0.76 mmol, 1.6 M solution in hexane) at −78 °C. After it was stirred at −78 °C for 30 min, trimethyl borate (0.09 mL, 0.76 mmol) was added. The resulting mixture was allowed to stir vigorously at room temperature for 12 h. The reaction mixture was quenched with water and separated the organic layer. The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give **3** (65.4 mg, 76%): mp 86–88 °C; IR (neat) ν_{max} 3417, 2954, 2929, 2898, 1574, 1458, 1336, 1261, 1068, 947, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J = 8.8, 7.2 Hz, 1H), 7.16 (d, J = 7.2 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.18 (s, 1H), 5.15 (br s, 2H), 4.21–4.17 (m, 2H), 4.04–4.00 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 130.6, 126.1, 124.7, 111.7, 99.0, 64.9, 55.7; MS (EI) m/z (% base peak) 224 (M^+, 3), 159 (21), 139 (4), 115 (5), 103 (100), 73 (31); HRMS (EI) calcd for $C_{10}H_{13}BO_5$ 224.0856, found 224.0857.

(2*S*,3*S*)-5,5-Dibromopent-4-ene-2,3-diol (6b). To a solution of tetrabromomethane (9.47 g, 28.6 mmol) in CH_2Cl_2 (40 mL) was added PPh_3 (15 g, 57.2 mmol) at 0 °C, and the bright orange mixture was stirred at 0 °C for 15 min. A solution of crotonaldehyde (**7**) (1 g, 14.3 mmol) in CH_2Cl_2 (20 mL) was added to the bright orange mixture and stirred for 1 h. The reaction mixture was diluted with hexanes and filtered through neutral silica gel. The filtrate was carefully concentrated in vacuo to give dibromoalkene **9** as a yellow oil, which was used immediately for the next step. To a flask containing AD-mix-α (20.00 g) in *tert*-butyl alcohol (65 mL) and water (65 mL) at room temperature was added methanesulfonamide (1.34 g, 14.3 mmol). The mixture was cooled to 0 °C, and then dibromoalkene **9** was added in one portion. The heterogeneous slurry was stirred vigorously at 0 °C for 24 h. Sodium sulfite (20.00 g) was added at 0 °C, and the reaction mixture was allowed to warm to room temperature. After stirring for 1 h, the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes = 1:3) to afford diol **6b** (2.47 g, 67% over 2 steps) as a pale yellow solid: ee = 87% (HPLC column Chiralcel OD; injection amount 30 μL; sample concentration 2 mg of diol/1 mL of mobile phase solvent; mobile phase hexane/2-propanol (95/5 v/v); flow rate 1 mL/min); $[\alpha]^{25}{}_D$ = −5.3 (c 28.8, $CHCl_3$); mp 48–49 °C; IR (neat) ν_{max} 3376, 2976, 1613, 1451, 1133, 1035, 924, 785 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.49 (d, J = 8.2 Hz, 1H), 4.14–4.10 (m, 1H), 3.76–3.73 (m, 1H), 2.55 (br s, 1H), 2.36 (br s, 1H), 1.24 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 93.4, 76.7, 69.8, 18.8; MS (EI) m/z (% base peak) 260 (0.07), 258 (M^+, 0.06), 217 (24), 215 (50), 213 (27), 181 (7), 179 (8), 137 (88), 135 (100), 133 (13), 107 (26), 105 (25), 55 (35); HRMS (EI) calcd for $C_5H_8{}^{79}Br_2O_2$ 257.8891, found 257.8894.

(4*S*,5*S*)-4-(2,2-Dibromovinyl)-2,2,5-trimethyl-1,3-dioxolane (10). To a solution of **6b** (1.00 g, 3.85 mmol) in acetone (7 mL) at room temperature was added *p*-toluenesulfonic acid monohydtre (73 mg, 0.39 mmol) and 2,2-dimethoxypropane (7 mL, 58 mmol). After stirring at room temperature for 2 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes = 1:20) to afford **10** (1.06 g, 92%) as a colorless oil: $[\alpha]^{25}{}_D$ = 2.3 (c 30.8, $CHCl_3$); IR (neat) ν_{max} 2985, 2932, 1625, 1456, 1380, 1242, 1173, 1092, 1038, 862, 811, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.43 (d, J = 8.2 Hz, 1H), 4.23 (dd, J = 8.2, 8.2 Hz, 1H), 3.88 (dq, J = 8.2, 6.0 Hz, 1H), 1.42 (s, 3H), 1.38 (s, 3H), 1.33 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 109.3, 93.8, 82.1, 75.9, 27.2, 26.7, 17.0; MS (EI) m/z (% base peak) 298 (M^+, 0.2), 287 (13), 285 (26), 283 (14), 258 (24), 256 (49), 254 (27), 177 (45), 175 (46), 96 (100); HRMS (ESI) calcd for $C_8H_{13}{}^{79}Br_2O_2$ (M^+ + H) 298.9277, found 298.9274.

(4*S*,5*S*)-(*Z*)-4-(2-Bromovinyl)-2,2,5-trimethyl-1,3-dioxolane (4b). To a flame-dried flask were added palladium acetate (75 mg, 0.33 mmol) and triphenylphosphine (350 mg, 1.32 mmol) in Et_2O (10 mL). The resulting solution was stirred for 30 min, and then a solution of **10** (1.00 g, 3.3 mmol) in Et_2O (10 mL) and tributyltin hydride (1 mL, 3.7 mmol) ws added. The reaction mixture was stirred for 1 h and then diluted with water. The aqueous layer was separated and extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on alumina (hexanes) to afford **4b** (552 mg, 75%) as a colorless oil: $[\alpha]^{25}{}_D$ = 13.1 (c 10.0, $CHCl_3$); IR (neat) ν_{max} 2923, 2852, 1630, 1459, 1378, 1261, 1091, 858, 803, 755, 694 cm^{-1}; ^1H NMR

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(400 MHz, $CDCl_3$) δ 6.42 (dd, J = 7.3, 1.4 Hz, 1H), 6.13 (dd, J = 8.1, 7.3 Hz, 1H), 4.50 (dd, J = 9.2, 8.1 Hz, 1H), 3.84 (dq, J = 9.2, 6.4 Hz, 1H), 1.44 (s, 3H), 1.40 (s, 3H), 1.34 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 111.6, 109.1, 80.0, 76.4, 27.3, 26.8, 16.9; MS (EI) m/z (% base peak) 222 (1), 220 (M^+, 1), 207 (26), 205 (27), 178 (21), 176 (21), 165 (9), 163 (9), 137 (10), 135 (13), 116 (100), 97 (58); HRMS (EI) calcd for $C_8H_{13}{}^{79}BrO_2$ 220.0099, found 220.0098.

(4*S*,5*S*)-(*Z*)-4-[2-(1,3-Dioxolan-2-yl-)3-methoxystyryl]-2,2,5-trimethyl-1,3-dioxolane (11). A mixture of palladium acetate (6 mg, 0.027 mmol) and triphenylphosphine (28 mg, 0.1 mmol) in THF (3 mL) was stirred at room temperature for 30 min. A solution of **4b** (30 mg, 0.13 mmol) in THF (1 mL), **3** (90 mg, 0.4 mmol) in THF (1 mL), and a solution of K_2CO_3 (76 mg, 0.55 mmol) in water (1 mL) were added to the above mixture. The reaction mixture was then heated to 40 °C for 3 h. After cooling to room temperature, the mixture was diluted with water. The aqueous layer was separated and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes = 1:10) to afford **11** (35.1 mg, 81%) as a pale yellow oil: $[\alpha]^{25}{}_D$ = −181.6 (c 8.4, $CHCl_3$); IR (neat) ν_{max} 2981, 2931, 2892, 1579, 1473, 1404, 1378, 1264, 1086, 1025, 957, 860, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, J = 8.4, 7.4 Hz, 1H), 7.05 (d, J = 11.3 Hz, 1H), 6.87 (d, J = 7.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.29 (s, 1H), 5.56 (dd, J = 11.3, 9.5 Hz, 1H), 4.17−4.08 (m, 3H), 3.98−3.95 (m, 2H), 3.84 (s, 3H), 3.83−3.79 (m, 2H), 1.43 (s, 3H), 1.36 (s, 3H), 1.11 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 138.0, 135.1, 129.8, 126.7, 123.0, 122.6, 110.6, 108.2, 99.6, 78.9, 77.1, 65.5, 65.3, 55.9, 27.3, 27.2, 16.5; MS (EI) m/z (% base peak) 320 (M^+, 17), 276 (18), 245 (22), 205 (43), 186 (100), 174 (53), 161 (44), 146 (24), 115 (38), 73 (61); HRMS (EI) calcd for $C_{18}H_{24}O_5$ 320.1624, found 320.1621.

(1*R*,10*S*,11*S*)-3-Methoxy-11-methyl-12,13-dioxatricyclo-[8.2.1.0^{2,7}]trideca-2(7),3,5,8-tetraene (12). To a stirred solution of **11** (35 mg, 0.11 mmol) in benzene (10 mL) was added *p*-toluenesulfonic acid monohydrate (6 mg, 0.033 mmol) at 70 °C for 1 h. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was separated 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 flash chromatography on silica gel (EtOAc/hexanes = 1:10) to afford **12** (23 mg, 96%) as a colorless solid. Analytically pure **12** was obtained by crystallization from CH_2Cl_2−hexane: mp 133−134 °C; $[\alpha]^{25}{}_D$ = −78.0 (c 10.0, $CHCl_3$); IR (neat) ν_{max} 2965, 1580, 1466, 1269, 1243, 1196, 1058, 1016, 945, 871, 805, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, J = 8.6, 7.6 Hz, 1H), 6.91 (s, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 6.36 (d, J = 11.7 Hz, 1H), 6.10 (dd, J = 11.7, 5.1 Hz, 1H), 4.58 (dq, J = 6.1, 1.3 Hz, 1H), 4.44 (dd, J = 5.1, 1.3 Hz, 1H), 3.85 (s, 3H), 1.32 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 135.7, 132.7, 130.9, 129.4, 127.8, 125.2, 110.8, 99.5, 85.3, 80.0, 56.0, 20.2; MS (EI) m/z (% base peak) 218 (M^+, 2), 174 (100), 159 (20), 146 (52), 131 (46), 115 (8), 103 (26), 77 (15); HRMS (EI) calcd for $C_{13}H_{14}O_3$ 218.0943, found 218.0938.

(−)-Cladoacetal B (1b). A suspension of NaH (7 mg, 0.29 mmol) in DMF (2 mL) was cooled to 0 °C, and EtSH (12 mg, 0.19 mmol) was added. After stirring at 0 °C for 30 min, the **12** (20 mg, 0.09 mmol) in DMF (2 mL) was added. The solution was heated to 120 °C for 3 h and then cooled to room temperature. The reaction mixture was quenched with water. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with saturated aqueous $Na_2S_2O_7$, brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes = 1:6) to afford cladoacetal B (**1b**) (17.6 mg, 74%) as a pale yellow solid. Analytically pure **1b** was obtained by crystallization from CH_2Cl_2−hexane: mp 220−221 °C; $[\alpha]^{25}{}_D$ = −173.1 (c 1.4, MeOH); IR (neat) ν_{max} 3296, 2970, 2925, 2853, 1581, 1464, 1290, 1118, 1054, 990, 958, 861, 806, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (dd, J = 8.0, 7.6 Hz, 1H), 6.88 (s, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.60 (d, J = 8.0 Hz, 1H), 6.36 (d, J = 11.7 Hz, 1H), 6.08 (dd, J = 11.7, 5.1 Hz, 1H), 5.19 (br s, 1H), 4.60 (dq, J = 6.4, 1.2 Hz, 1H), 4.46 (dd, J = 5.1, 1.2 Hz, 1H), 1.32 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 136.2, 132.5, 130.9, 129.3, 126.0, 125.5, 115.7, 99.4, 85.3, 80.0, 20.2; MS (EI) m/z (% base peak) 204 (M^+, 4), 161 (12), 160 (100), 132 (68), 131 (51), 103 (14), 91 (4), 77 (16); HRMS (EI) calcd for $C_{12}H_{12}O_3$ 204.0786, found 204.0780.

(2*R*,3*R*)-5,5-Dibromopent-4-ene-2,3-diol (*ent*-6b). To a solution of tetrabromomethane (9.47 g, 28.6 mmol) in CH_2Cl_2 (40 mL) was added PPh_3 (15 g, 57.2 mmol) at 0 °C, and the bright orange mixture was stirred at 0 °C for 15 min. A solution of crotonaldehyde (7) (1 g, 14.3 mmol) in CH_2Cl_2 (20 mL) was added to the bright orange mixture and stirred for 1 h. The reaction mixture was diluted with hexanes and filtered through neutral silica gel. The filtrate was carefully concentrated in vacuo to give dibromoalkene **9** as a yellow oil, which was used immediately for the next step. To a flask containing AD-mix-β (20.00 g) in *tert*-butyl alcohol (65 mL) and water (65 mL) at room temperature was added methanesulfonamide (1.34 g, 14.3 mmol). The mixture was cooled to 0 °C, and then dibromoalkene **9** was added in one portion. The heterogeneous slurry was stirred vigorously at 0 °C for 24 h. Sodium sulfite (20.00 g) was added at 0 °C, and the reaction mixture was allowed to warm to room temperature. After stirring for 1 h, the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes = 1:3) to afford diol *ent*-**6b** (2.34 g, 63% over 2 steps) as a pale yellow solid: ee = 91% (HPLC column Chiralcel OD; injection amount 30 μL; sample concentration 2 mg of diol/1 mL of mobile phase solvent; mobile phase hexane/2-propanol (95/5 v/v); flow rate 1 mL/min); mp 54−55 °C; $[\alpha]^{25}{}_D$ = 5.4 (c 19.0, $CHCl_3$); IR (neat) ν_{max} 3365, 2976, 2925, 1618, 1373, 1265, 1132, 1036, 924, 870, 785 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (d, J = 8.6 Hz, 1H), 4.12 (dd, J = 8.6, 6.6 Hz, 1H), 3.74 (dq, J = 6.6, 6.4 Hz, 1H), 2.50 (br s, 2H), 1.23 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 93.3, 76.7, 69.8, 18.7; MS (EI) m/z (% base peak) 258 (M^+, 24), 256 (49), 254 (25), 243 (15), 217 (18), 215 (41), 213 (26), 199 (13), 177 (48), 175 (49), 137 (64), 135 (79), 119 (32), 117 (32), 96 (100), 58 (88); HRMS (EI) calcd for $C_5H_8{}^{79}Br_2O_2$ 257.8891, found 257.8894.

(3*R*,4*R*)-1,1-Dibromo-4-[(*tert*-butyldimethylsilyl)oxy]pent-1-en-3-ol (13). To a stirred solution of *ent*-**6b** (1.0 g, 3.8 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added triethylamine (1.6 mL, 11.5 mmol) and TBSOTf (1.0 mL, 4.3 mmol). After stirring at −78 °C for 3 h, the reaction mixture was diluted with water. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Mg_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on alumina (EtOAc/hexanes = 1/30) to afford **13** (1.28 g, 89%) as a colorless oil: $[\alpha]^{25}{}_D$ = −19.2 (c 25.4, $CHCl_3$); IR (neat) ν_{max} 3464, 2930, 1619, 1471, 1377, 1257, 1067, 957, 836 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (d, J = 8.1 Hz, 1H), 4.07−4.02 (m, 1H), 3.83−3.80 (m, 1H), 2.60 (d, J = 6.0 Hz, 1H), 1.21 (d, J = 6.0 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 91.6, 76.5, 70.8, 25.8, 20.0, 18.0, −4.3, −4.9; MS (ESI) m/z (% base peak) 375 (50), 373 (100), 371 (M^+ − H, 53); HRMS (ESI) calcd for $C_{11}H_{21}{}^{79}Br_2O_2Si$ (M^+ − H) 370.9678, found 370.9689.

Formic Acid (*R*)-3,3-Dibromo-1-{(*S*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl}allyl Ester (14). To a stirred mixture of **13** (700 mg, 1.87 mmol) and triphenylphosphine (982 mg, 3.74 mmol) in toluene (10 mL) was added a solution of diethyl azodicarboxylate (DEAD) (0.6 mL, 3.74 mmol) and formic acid (0.14 mL) in toluene (10 mL) dropwise at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes = 1:30) to afford **14** (565 mg, 75%) as a colorless oil: $[\alpha]^{25}{}_D$ = 34.3 (c 30.4, $CHCl_3$); IR (neat) ν_{max} 2930, 2857, 1733, 1627, 1471, 1377, 1256, 1156, 1040, 940, 838, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 6.51 (d, J = 8.7 Hz, 1H), 5.39 (dd, J = 8.7, 3.7 Hz, 1H), 4.02 (dq, J = 6.5, 3.7 Hz, 1H), 1.16 (d, J = 6.5 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 133.1, 95.3, 77.2, 68.8, 25.9, 25.7, 25.6, 19.5, 18.0, −4.7, −4.8; MS (EI) m/z (% base peak) 400 (M^+, 0.1), 353 (5), 250 (8), 205 (87), 189 (11), 176

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(100), 161 (29), 147 (18), 133 (47), 118 (28), 104 (23), 91 (22), 77 (23); HRMS (EI) calcd for $C_{12}H_{22}{}^{79}Br_2O_3Si$ 399.9705, found 399.9708.

(4*S*,5*R*)-4-(2,2-Dibromovinyl)-2,2,5-trimethyl-1,3-dioxolane (15). To a solution of **14** (500 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) and MeOH (10 mL) at room temperature was added camphorsulfonic acid (CSA) (289 mg, 1.2 mmol) and 2,2-dimethoxypropane (6 mL, 48 mmol). After stirring at room temperature for 3 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes = 1:20) to afford **15** (306 mg, 82%) as a colorless oil: $[\alpha]^{25}{}_D = -3.8$ (*c* 40.0, $CHCl_3$); IR (neat) ν_{max} 2985, 2933, 1613, 1455, 1380, 1218, 1174, 1092, 1040, 859, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (d, *J* = 8.7 Hz, 1H), 4.72 (dd, *J* = 8.7, 6.0 Hz, 1H), 4.40 (dq, *J* = 6.6, 6.0 Hz, 1H), 1.47 (s, 3H), 1.36 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 108.9, 92.0, 79.2, 73.5, 28.1, 25.5, 15.2; MS (EI) *m*/*z* (% base peak) 287 (10), 285 (20), 283 ($M^+ - 15$, 10), 258 (17), 256 (34), 254 (18), 243 (7), 213 (5), 199 (6), 177 (35), 175 (36), 135 (6), 119 (19), 117 (20), 96 (82), 58 (100); HRMS (EI) calcd for $C_8H_{12}{}^{79}Br_2O_2$ 297.9204, found 297.9203.

(4*S*,5*R*)-(*Z*)-4-(2-Bromovinyl)-2,2,5-trimethyl-1,3-dioxolane (4a). To a flame-dried flask was added palladium acetate (22.4 mg, 0.1 mmol) and triphenylphosphine (105 mg, 0.4 mmol) in Et_2O (5 mL). The resulting solution was stirred for 30 min, and then a solution of **15** (300 mg, 1.0 mmol) in Et_2O (5 mL) and tributyltin hydride (0.3 mL, 1.1 mmol) was added. The reaction mixture was stirred for 2 h and then diluted with water. The aqueous layer was separated and extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on alumina (hexanes) to afford **4a** (161 mg, 73%) as a colorless oil: $[\alpha]^{25}{}_D = 29.3$ (*c* 10.0, $CHCl_3$); IR (neat) ν_{max} 2985, 1621, 1455, 1380, 1259, 1085, 853, 802, 653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.37 (dd, *J* = 7.3, 1.4 Hz, 1H), 6.19 (dd, *J* = 7.8, 7.3 Hz, 1H), 4.99 (ddd, *J* = 7.8, 6.4, 1.4 Hz, 1H), 4.44 (dq, *J* = 6.4, 6.1 Hz, 1H), 1.49 (s, 3H), 1.38 (s, 3H), 1.17 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.2, 110.2, 108.5, 77.2, 73.6, 28.2, 25.6, 15.6; MS (EI) *m*/*z* (% base peak) 220 (M^+, 0.02), 207 (9), 205 (9), 178 (7), 176 (7), 165 (3), 163 (3), 135 (2), 119 (1), 97 (23), 58 (100); HRMS (EI) calcd for $C_8H_{13}{}^{79}BrO_2$ 220.0099, found 220.0098.

(4*S*,5*R*)-(*Z*)-4-[2-(1,3-Dioxolan-2-yl)-3-methoxystyryl]-2,2,5-trimethyl-1,3-dioxolane (16). A mixture of palladium acetate (6 mg, 0.027 mmol) and triphenylphosphine (28 mg, 0.1 mmol) in THF (3 mL) was stirred at room temperature for 30 min. A solution of **4a** (20 mg, 0.09 mmol) in THF (1 mL), **3** (80 mg, 0.36 mmol) in THF (1 mL), and a solution of K_2CO_3 (36.4 mg, 0.27 mmol) in water (1 mL) were added to the above mixture. The reaction mixture was then heated to 40 °C for 3 h. After cooling to room temperature, the mixture was diluted with water. The aqueous layer was separated and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes = 1:10) to afford **16** (23.5 mg, 81%) as a pale yellow oil: $[\alpha]^{25}{}_D = -39.2$ (*c* 3.0, $CHCl_3$); IR (neat) ν_{max} 2982, 2933, 2889, 1579, 1472, 1379, 1263, 1215, 1065, 1024, 957, 853, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 8.3, 7.6 Hz, 1H), 6.98 (d, *J* = 11.5 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.28 (s, 1H), 5.67 (dd, *J* = 11.5, 9.8 Hz, 1H), 4.66 (dd, *J* = 9.8, 6.1 Hz, 1H), 4.21 (dq, *J* = 6.3, 6.1 Hz, 1H), 4.15–4.08 (m, 2H), 3.99–3.95 (m, 2H), 3.84 (s, 3H), 1.50 (s, 3H), 1.29 (s, 3H), 1.19 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 138.2, 132.9, 129.9, 126.6, 122.8, 122.7, 110.6, 107.9, 99.7, 75.0, 74.3, 65.5, 65.4, 55.9, 28.5, 25.7, 15.9; MS (EI) *m*/*z* (% base peak) 320 (M^+, 40), 276 (32), 245 (23), 233 (24), 205 (59), 186 (100), 174 (74), 161 (64), 146 (34), 115 (48), 73 (75); HRMS (EI) calcd for $C_{18}H_{24}O_5$ 320.1624, found 320.1627.

(1*R*,10*S*,11*R*)-3-Methoxy-11-methyl-12,13-dioxatricyclo-[8.2.1.0^{2,7}]trideca-2(7),3,5,8-tetraene (17). To a stirred solution of **16** (20 mg, 0.06 mmol) in benzene (10 mL) was added *p*-toluenesulfonic acid monohydrate (4 mg, 0.023 mmol) at 70 °C for 1 h. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was separated 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 flash chromatography on silica gel (EtOAc/hexanes = 1:10) to afford **17** (13 mg, 92%) as a pale yellow solid. Analytically pure **17** was obtained by crystallization from CH_2Cl_2–hexane: mp 103–105 °C; $[\alpha]^{25}{}_D = -172.2$ (*c* 6.0, $CHCl_3$); IR (neat) ν_{max} 2932, 1577, 1464, 1383, 1270, 1196, 1104, 1063, 966, 805, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.80 (s, 1H), 6.48 (d, *J* = 11.8 Hz, 1H), 5.84 (dd, *J* = 11.8, 5.0 Hz, 1H), 4.63 (dd, *J* = 5.0, 4.6 Hz, 1H), 4.42 (dq, *J* = 6.2, 4.6 Hz, 1H), 3.82 (s, 3H), 1.34 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 135.9, 132.4, 130.1, 129.5, 127.5, 125.5, 111.1, 98.7, 84.9, 78.0, 56.0, 13.6; MS (EI) *m*/*z* (% base peak) 218 (M^+, 2), 174 (100), 159 (12), 146 (35), 131 (29), 115 (22), 103 (23), 91 (9), 77 (12); HRMS (EI) calcd for $C_{13}H_{14}O_3$ 218.0943, found 218.0939.

(−)-Cladoacetal A (1a). A suspension of NaH (5 mg, 0.21 mmol) in DMF (2 mL) was cooled to 0 °C, and EtSH (9 mg, 0.14 mmol) was added. After it was stirred at 0 °C for 30 min, **17** (15 mg, 0.07 mmol) in DMF (2 mL) was added. The solution was heated to 120 °C for 3 h and then cooled to room temperature. The reaction mixture was quenched with water. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with saturated aqueous $Na_2S_2O_7$, brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes = 1:4) to afford cladoacetal A (**1a**) (12.8 mg, 91%) as a colorless solid. Analytically pure **1a** was obtained by crystallization from CH_2Cl_2–hexane: mp 161–162 °C; $[\alpha]^{25}{}_D = -250.4$ (*c* 1.4, MeOH); IR (neat) ν_{max} 3310, 2953, 2924, 2853, 1583, 1463, 1292, 1097, 957, 808, 749, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.77 (s, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.48 (d, *J* = 12.0 Hz, 1H), 5.83 (dd, *J* = 12.0, 4.8 Hz, 1H), 5.24 (br s, 1H), 4.65 (dd, *J* = 4.8, 4.6 Hz, 1H), 4.43 (dq, *J* = 6.0, 4.6 Hz, 1H), 1.35 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 136.3, 132.4, 129.9, 129.4, 125.8, 125.7, 115.9, 98.7, 84.7, 77.9, 13.6; MS (EI) *m*/*z* (% base peak) 204 (M^+, 2), 161 (11), 160 (100), 132 (55), 131 (32), 103 (10), 77 (12); HRMS (EI) calcd for $C_{12}H_{12}O_3$ 204.0786, found 204.0789.

(3*S*,4*S*)-1,1-Dibromo-4-[(*tert*-butyldimethylsilyl)oxy]pent-1-en-3-ol (*ent*-13). To a stirred solution of **6b** (1.0 g, 3.8 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added triethylamine (1.6 mL, 11.5 mmol) and TBSOTf (1.0 mL, 4.3 mmol). After stirring at −78 °C for 3 h, the reaction mixture was diluted with water. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Mg_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on alumina (EtOAc/hexanes = 1/30) to afford *ent*-**13** (1.26 g, 88%) as a colorless oil: $[\alpha]^{25}{}_D = 17.5$ (*c* 28.0, $CHCl_3$); IR (neat) ν_{max} 3428, 2956, 2887, 2859, 1622, 1462, 1257, 1143, 957, 785 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.44 (d, *J* = 8.0 Hz, 1H), 4.04 (dd, *J* = 8.0, 4.8 Hz, 1H), 3.81 (dq, *J* = 6.0, 4.8 Hz, 1H), 2.57 (br s, 1H), 1.20 (d, *J* = 6.0 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 91.6, 76.5, 70.7, 25.7, 20.0, 18.0, −4.3, −4.9; MS (EI) *m*/*z* (% base peak) 372 (M^+, 0.01), 357 (13), 319 (46), 317 (51), 315 (46), 215 (48), 159 (60), 139 (35), 115 (49), 75 (100); HRMS (EI) calcd for $C_{11}H_{22}{}^{79}Br_2O_2Si$ 371.9756, found 371.9756.

Formic Acid (*S*)-3,3-Dibromo-1-{(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl}allyl Ester (*ent*-14). To a stirred mixture of *ent*-**13** (500 mg, 1.33 mmol) and triphenylphosphine (701 mg, 2.7 mmol) in toluene (10 mL) was added a solution of diethyl azodicarboxylate (DEAD) (0.4 mL, 2.7 mmol) and formic acid (0.10 mL) in toluene (10 mL) dropwise at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes = 1:30) to afford *ent*-**14** (414 mg, 77%) as a colorless oil: $[\alpha]^{25}{}_D = -39.8$ (*c* 21.6, $CHCl_3$); IR (neat) ν_{max} 2960, 2929, 2856, 1732, 1627, 1456, 1407, 1374, 1254, 1171, 1105, 1039, 940, 835, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 6.51 (d, *J* = 8.7 Hz, 1H), 5.39 (dd, *J* = 8.7, 3.7 Hz, 1H), 4.02 (dq, *J* = 6.5, 3.7 Hz, 1H), 1.16 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR

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(100 MHz, $CDCl_3$) δ 159.7, 133.1, 95.4, 77.2, 68.8, 25.9, 25.7, 19.6, 18.0, −4.6, −4.8; MS (EI) m/z (% base peak) 400 (M^+, 0.2), 383 (1), 353 (1), 251 (2), 207 (3), 191 (2), 177 (16), 161 (2), 133 (53), 117 (7), 103 (19), 89 (100), 73 (27); HRMS (EI) calcd for $C_{12}H_{22}{}^{79}Br_2O_3Si$ 399.9705, found 399.9709.

(4*R*,5*S*)-4-(2,2-Dibromovinyl)-2,2,5-trimethyl-1,3-dioxolane (*ent*-15). To a solution of *ent*-**14** (402 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) and MeOH (10 mL) at room temperature was added camphorsulfonic acid (CSA) (232 mg, 1.0 mmol) and 2,2-dimethoxypropane (5 mL, 40 mmol). After stirring at room temperature for 3 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes = 1:20) to afford *ent*-**15** (255 mg, 85%) as a colorless oil: $[\alpha]^{25}{}_D = 7.6$ (c 26.2, $CHCl_3$); IR (neat) ν_{max} 2991, 2937, 1623, 1458, 1379, 1217, 1089, 1043, 860, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (d, J = 8.6 Hz, 1H), 4.71 (dd, J = 8.6, 6.1 Hz, 1H), 4.40 (dq, J = 6.4, 6.1 Hz, 1H), 1.47 (s, 3H), 1.35 (s, 3H), 1.21 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 108.8, 92.0, 79.2, 73.5, 28.1, 25.5, 15.2; MS (EI) m/z (% base peak) 298 (M^+, 4), 285 (12), 279 (12), 256 (14), 191 (10), 177 (18), 175 (11), 167 (24), 149 (100), 135 (8), 119 (12), 117 (12), 96 (27), 83 (24); HRMS (EI) calcd for $C_8H_{12}{}^{79}Br_2O_2$ 297.9204, found 297.9206.

(4*R*,5*S*)-(*Z*)-4-(2-Bromovinyl)-2,2,5-trimethyl-1,3-dioxolane (*ent*-4a). To a flame-dried flask was added palladium acetate (22.4 mg, 0.1 mmol) and triphenylphosphine (105 mg, 0.4 mmol) in Et_2O (4 mL). The resulting solution was stirred for 30 min, and then a solution of *ent*-**15** (300 mg, 1.0 mmol) in Et_2O (3 mL) and tributyltin hydride (0.3 mL, 1.1 mmol) was added. The reaction mixture was stirred for 2 h and then diluted with water. The aqueous layer was separated and extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on alumina (hexanes) to afford *ent*-**4a** (159 mg, 72%) as a colorless oil: $[\alpha]^{25}{}_D = -27.6$ (c 7.8, $CHCl_3$); IR (neat) ν_{max} 3092, 2974, 2929, 1375, 1214, 1027, 857, 647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.37 (d, J = 7.4 Hz, 1H), 6.19 (dd, J = 7.7, 7.4 Hz, 1H), 4.99 (dd, J = 7.7, 6.2 Hz, 1H), 4.44 (dq, J = 6.2, 6.2 Hz, 1H), 1.49 (s, 3H), 1.38 (s, 3H), 1.17 (d, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.2, 110.1, 108.5, 77.2, 73.6, 28.2, 25.5, 15.6; MS (EI) m/z (% base peak) 221 (M^+ + H, 0.3), 207 (2), 205 (2), 193 (4), 191 (3), 167 (5), 165 (4), 163 (3), 149 (28), 127 (10), 125 (13), 123 (11), 111 (29), 97 (23), 83 (60), 57 (100); HRMS (EI) calcd for $C_8H_{13}{}^{79}BrO_2$ 220.0099, found 220.0098.

(4*R*,5*S*)-(*Z*)-4-[2-(1,3-Dioxolan-2-yl)-3-methoxystyryl]-2,2,5-trimethyl-1,3-dioxolane (*ent*-16). A mixture of palladium acetate (10 mg, 0.045 mmol) and triphenylphosphine (47 mg, 0.18 mmol) in THF (3 mL) was stirred at room temperature for 30 min. A solution of *ent*-**4a** (50 mg, 0.22 mmol) in THF (2 mL), **3** (102 mg, 0.45 mmol) in THF (2 mL), and a solution of K_2CO_3 (94 mg, 0.68 mmol) in water (1.2 mL) were added to the above mixture. The reaction mixture was then heated to 40 °C for 3 h. After cooling to room temperature, the mixture was diluted with water. The aqueous layer was separated and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes = 1:10) to afford *ent*-**16** (56.6 mg, 78%) as a pale yellow oil: $[\alpha]^{25}{}_D = 37.5$ (c 2.6, $CHCl_3$); IR (neat) ν_{max} 2981, 2890, 1581, 1463, 1260, 1073, 951, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, J = 8.4, 7.6 Hz, 1H), 6.98 (d, J = 11.6 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.28 (s, 1H), 5.67 (dd, J = 11.6, 9.8 Hz, 1H), 4.66 (dd, J = 9.8, 6.1 Hz, 1H), 4.21 (dq, J = 6.4, 6.1 Hz, 1H), 4.15–4.08 (m, 2H), 3.99–3.95 (m, 2H), 3.83 (s, 3H), 1.50 (s, 3H), 1.28 (s, 3H), 1.19 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 138.1, 132.9, 129.9, 126.6, 122.8, 122.6, 110.5, 107.8, 99.6, 74.9, 74.3, 65.5, 65.4, 55.8, 28.5, 25.7, 15.8; MS (EI) m/z (% base peak) 320 (M^+, 12), 276 (9), 245 (11), 233 (11), 205 (34), 186 (100), 174 (51), 161 (45), 146 (16), 115 (30), 73 (59); HRMS (EI) calcd for $C_{18}H_{24}O_5$ 320.1624, found 320.1622.

(1*S*,10*R*,11*S*)-3-Methoxy-11-methyl-12,13-dioxatricyclo-[8.2.1.0^{2,7}]trideca-2(7),3,5,8-tetraene (*ent*-17). To a stirred solution of *ent*-**16** (50 mg, 0.16 mmol) in benzene (15 mL) was added *p*-toluenesulfonic acid monohydrate (6 mg, 0.03 mmol) at 70 °C for 1 h. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was separated 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 flash chromatography on silica gel (EtOAc/hexanes = 1:10) to afford *ent*-**17** (29 mg, 85%) as a pale yellow solid. Analytically pure *ent*-**17** was obtained by crystallization from CH_2Cl_2–hexane: mp 108–109 °C; $[\alpha]^{25}{}_D = 177.2$ (c 9.6, $CHCl_3$); IR (neat) ν_{max} 2961, 2921, 2866, 1578, 1464, 1381, 1269, 1101, 805 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, J = 8.1, 7.6 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 6.80 (s, 1H), 6.48 (d, J = 12.0 Hz, 1H), 5.84 (dd, J = 12.0, 5.0 Hz, 1H), 4.63 (dd, J = 5.0, 4.6 Hz, 1H), 4.42 (dq, J = 6.0, 4.6 Hz, 1H), 3.83 (s, 3H), 1.34 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 135.9, 132.4, 130.1, 129.5, 127.5, 125.5, 111.1, 98.7, 84.9, 78.0, 56.0, 13.6; MS (EI) m/z (% base peak) 218 (M^+, 0.7), 174 (100), 159 (23), 146 (86), 131 (56), 115 (29), 103 (30), 91 (1), 77 (8); HRMS (EI) calcd for $C_{13}H_{14}O_3$ 218.0943, found 218.0945.

(+)-Cladoacetal A (1a). A suspension of NaH (8 mg, 0.33 mmol) in DMF (2 mL) was cooled to 0 °C and added EtSH (12 mg, 0.19 mmol). After stirring at 0 °C for 30 min, *ent*-**17** (20 mg, 0.09 mmol) in DMF (2 mL) was added. The solution was heated to 120 °C for 3 h and then cooled to room temperature. The reaction mixture was quenched with water. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with saturated aqueous $Na_2S_2O_7$, brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc/hexanes = 1:4) to afford cladoacetal A (**1a**) (16.7 mg, 89%) as a colorless solid. Analytically pure **1a** was obtained by crystallization from CH_2Cl_2–hexane: mp 159–160 °C; $[\alpha]^{25}{}_D = 255.2$ (c 2.7, MeOH); IR (neat) ν_{max} 3485, 2955, 2925, 1583, 1456, 1323, 1239, 1096, 956, 808, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (dd, J = 8.1, 7.6 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.77 (s, 1H), 6.55 (d, J = 8.1 Hz, 1H), 6.48 (d, J = 11.9 Hz, 1H), 5.83 (dd, J = 11.9, 5.0 Hz, 1H), 5.27 (br s, 1H), 4.65 (dd, J = 5.0, 4.7 Hz, 1H), 4.43 (dq, J = 6.4, 4.7 Hz, 1H), 1.35 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 136.3, 132.4, 129.8, 129.4, 125.7, 125.6, 115.9, 98.7, 84.7, 78.0, 13.6; MS (EI) m/z (% base peak) 204 (M^+, 0.7), 167 (5), 160 (100), 149 (11), 132 (50), 112 (6), 104 (6), 77 (4); HRMS (EI) calcd for $C_{12}H_{12}O_3$ 204.0786, found 204.0789.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray crystallographic data and CIF file for **1b**, copies of ^1H and ^{13}C NMR for compounds **1**, **3**, **4**, **6**, **8**, and **10**–**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) Comparison tables of the ^{1}H and ^{13}C NMR data for natural and synthetic cladoacetals are summarized in the Supporting Information.
(11) CCDC 885995 contains the supplementary crystallographic data for **1b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Also see the Supporting Information.
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