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Enantioselective formal total synthesis of aplysin utilizing a palladium-catalyzed addition of an arylboronic acid to an allenic alcohol—Eschenmoser/Claisen rearrangement

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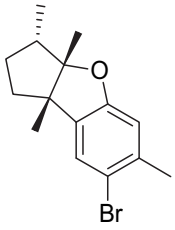
ABSTRACT

The enantioselective formal total synthesis of aplysin has been achieved utilizing a palladium-catalyzed addition of arylboronic acid to the allenic alcohol followed by the Eschenmoser/Claisen rearrangement as the key steps.

1. Introduction

Aplysin (**1**), isolated from the sea hare *Aplysia kurodai*,[1] is representative of a class of halogenated sesquiterpenoids, which exhibits antifeedant properties to protect the host mollusks from raptorial advances. The sterically congested structure of **1**, containing two consecutive quaternary carbon stereocenters, has attracted considerable synthetic interest (Fig. 1).[2]



aplysin (**1**)

Figure 1. Structure of aplysin (**1**).

Recently, we have developed an addition of arylboronic acids to allenic alcohols using a palladium catalyst,[3] in which aryl-substituted allylic alcohols having an *E*-olefin were obtained regio- and stereoselectively. Furthermore, it was found that a quaternary carbon center can be stereospecifically created by the Claisen-type rearrangement[4] of the resulting allylic alcohol (Scheme 1), and the methodology was successfully applied to the enantioselective synthesis of the enokipodins A and B.[5] Since our methodology would potentially provide valuable building blocks for the syntheses of natural products having a quaternary carbon center,[6] we envisioned such an application of this methodology for the synthesis of aplysin (**1**). Herein, we describe the enantioselective formal total synthesis of **1**, utilizing the palladium-catalyzed addition of an arylboronic acid to an allene followed by the Eschenmoser/Claisen rearrangement.

2. Results and discussion

Our strategy for aplysin (**1**) is shown in the retrosynthetic analysis in Scheme 2. We expected that the dihydrobenzofuran **2**, Fukumoto's intermediate for the synthesis of **1**,[2d] could be synthesized from the cyclopentenone **3** via an intramolecular oxymercuration. Compound **3** would be obtained by the formation of a five-membered ring from the amide **4**, which would be prepared by the palladium-catalyzed addition of the arylboronic acid **6** to the optically active allenic alcohol **5** followed by the Eschenmoser/Claisen rearrangement.

The synthesis of the intermediate **4** was carried out as shown in Scheme 3. Enantioselective reduction of the alkynyl ketone **7** with the (*S*)-CBS reagent[7] and BH_3 followed by the reaction of the resulting alcohol **8** with $LiAlH_4$ gave the optically active allenic alcohol **5** in 83% yield with 99% ee.[8] When compound **5** was treated with the arylboronic acid **6** in the presence of 5 mol% of $[Pd_2(OH)_2(PPh_3)_4][BF_4]_2$ and 5 equiv of Et_3N in dioxane/H_2O (20:1) at 80 °C,[3] the desired aryl-substituted allylic alcohol **9** was produced in 74% yield with 95% ee.[9] We next examined the Eschenmoser/Claisen rearrangement of **9** to construct the quaternary asymmetric center. The reaction successfully proceeded to afford the corresponding amide **4** having a quaternary asymmetric center in 84% yield. The enantiomeric excess of **4** was 95%, which indicates

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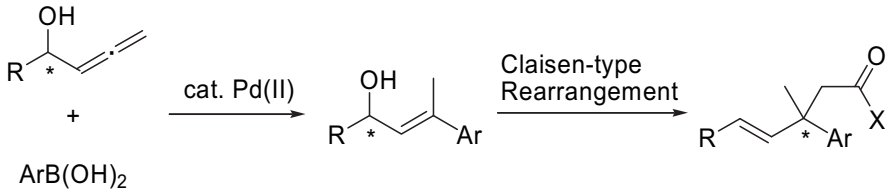
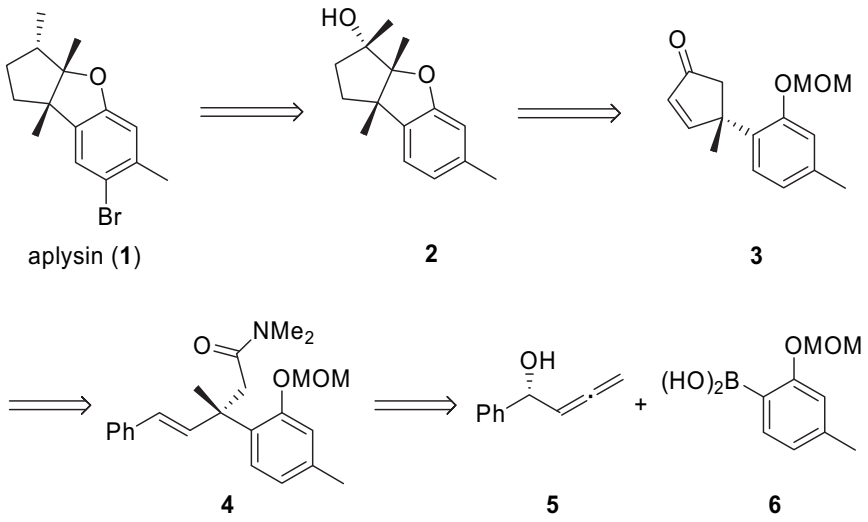


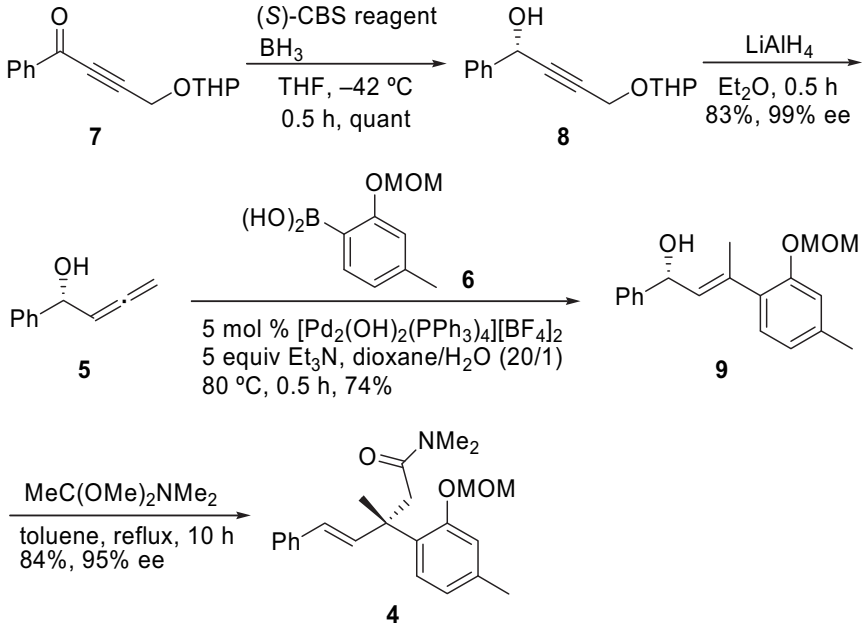
Scheme 1. Palladium-catalyzed addition of an arylboronic acid to an allenic alcohol—Eschenmoser/Claisen rearrangement.



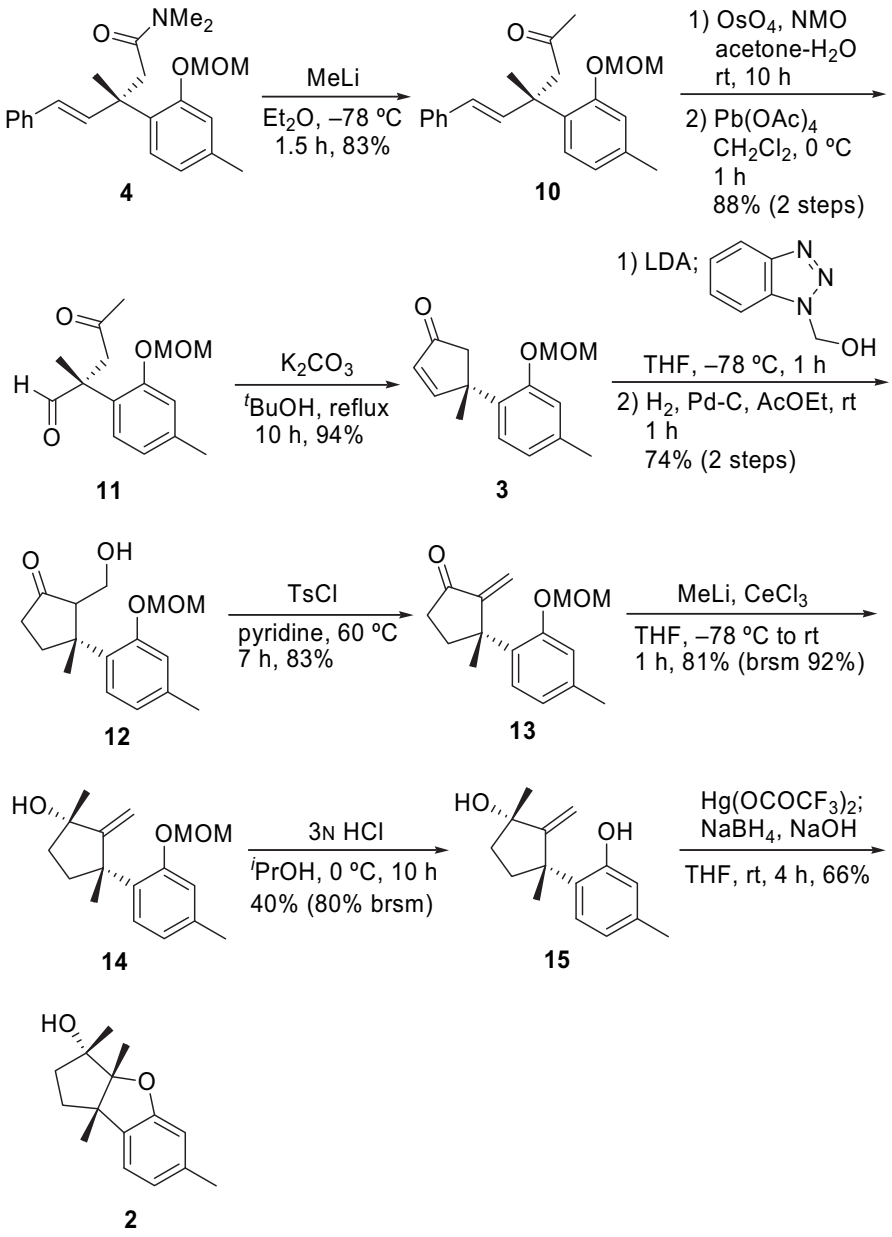
Scheme 2. Retrosynthetic analysis of aplysin (**1**).

that a highly enantiospecific [3,3]-sigmatropic rearrangement had proceeded.

The synthetic sequence toward the key intermediate **2** from **4** is outlined in Scheme 4. Transformation of the amide **4** to the methyl ketone **10** with MeLi followed by the oxidative cleavage of the double bond successfully afforded the ketoaldehyde **11**. The cyclopentenone **3** was obtained in 94% yield by the intramolecular aldol condensation of **11** with K_2CO_3. After hydroxymethylation of **3** using LDA and benzotriazole/methanol,[10] the resulting product was successively hydrogenated to give the β-hydroxy ketone **12** (74% yield, two steps). Treatment of **12** with TsCl in pyridine caused the dehydration to afford the methylenecyclopentanone **13** (83% yield), which was subjected to the reaction with MeLi in the presence of $CeCl_3$ leading to the methylated product **14** in 81% yield. The final stage of the synthesis involves the deprotection of the MOM group of **14** followed by the cyclization. However, mainly decomposition



Scheme 3. Synthesis of the intermediate **4**.



Scheme 4. Synthesis of the dihydrobenzofuran **2**.

of **14** was observed in most of the acidic deprotective conditions, presumably due to the instability of the tertiary allylic alcohol moiety. After several attempts, the desired product **15** was obtained in 40% yield (80% yield based on recovered starting material) when 3 N HCl was used in ^{i}PrOH at 0 °C for 10 h. The cyclization of **15** was conducted by the oxymercuration/reduction procedure producing the dihydrobenzofuran **2** in 66% yield. The spectroscopic data of our sample of synthetic **2** were completely identical with those previously reported.[2d]

3. Conclusion

In conclusion, we have completed the enantioselective formal total synthesis of aplysin, in which the enantioselective construction of the quaternary carbon center using a palladium-catalyzed addition of an arylboronic acid to an allene followed by an Eschenmoser/Claisen rearrangement has been successfully applied.

4. Experimental

4.1. General

All nonaqueous reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise indicated. Materials were obtained from commercial suppliers and used without further purification except when otherwise noted. Solvents were dried and distilled according to standard protocols. The phrase 'residue upon workup' refers to the residue obtained when the organic layer was separated and dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. Column chromatography was performed on silica gel, and flash column chromatography was performed on silica gel using the indicated solvent.

*4.1.1. (S)-1-Phenyl-4-(tetrahydropyran-2-yloxy)-but-2-yn-1-ol (**8**).* To a stirred solution of 1-phenyl-4-(tetrahydropyran-2-yloxy)-but-2-yn-1-one **7** (6.34 g, 25.8 mmol) in THF (100 mL) was added

dropwise 1.0 M solution of (*S*)-2-methyl-CBS-oxazaborolidine in toluene (25.8 mL, 25.8 mmol) at rt. After stirring was continued for 10 min at −42 °C, 1.0 M solution of BH_3 in THF (118 mL, 129 mmol) was added dropwise to the reaction mixture at the same temperature. After stirring was continued for 30 min, the reaction mixture was quenched with EtOH. The residue upon evaporation was chromatographed on silica gel with hexane/AcOEt (75:25 v/v) as eluent to give (*S*)-propargylic alcohol **8** (6.35 g, quant) as a yellow oil; $[\alpha]_D^{27}$ −9.67 (*c* 1.0 in $CHCl_3$). Other spectral data coincides with those of the enantiomer of **8**.[5]

*4.1.2. (R)-1-Phenyl-2,3-butadiene-1-ol (**5**).* To a stirred suspension of $LiAlH_4$ (1.17 g, 30.7 mmol) in Et_2O (150 mL) was added dropwise a solution of (*S*)-propargylic alcohol **8** (6.31 g, 25.6 mmol) in Et_2O (50 mL) at 0 °C. After being refluxed for 30 min, the reaction mixture was treated with minimum amount of cold water and filtered through a pad of Celite. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (85:15 v/v) as eluent to give allenic alcohol **5** (3.12 g, 83%, 99% ee) as a colorless oil; $[\alpha]_D^{27}$ −34.1 (*c* 1.2 in $CHCl_3$). Enantiomeric excess was determined by HPLC analysis [CHIRALCEL OD-H column, 10% isopropanol/hexane, 0.5 mL/min, λ=254 nm, retention times 16.9 min (*R*), and 20.3 min (*S*)]. Other spectral data coincides with those of the enantiomer of **5**.[5]

*4.1.3. 2-Methoxymethoxy-4-methylphenylboronic acid (**6**).* To a stirred solution of 1-(methoxymethoxy)-3-methylbenzene (484 mg, 3.18 mmol) in Et_2O (20 mL) and TMEDA (0.57 mL, 3.82 mmol) was added dropwise 0.45 M solution of ^{s}BuLi in hexane (8.5 mL, 3.82 mmol) at −78 °C. After stirring was continued for 2 h, trimethyl borate (0.71 mL, 6.36 mmol) was added dropwise to this reaction mixture at the same temperature and stirring was continued for 21 h at rt. The reaction mixture was quenched with 2 N HCl to pH 6 and extracted with AcOEt. The combined extracts were washed with brine, and the residue upon workup was recrystallized from hexane/AcOEt to give boronic acid **6** (268 mg, 43%) as white needles; mp 77.6–80.1 °C (recrystallized from AcOEt/hexane); IR (KBr): 3398, 1609, 1157, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (3H, s), 3.51 (3H, s), 5.29 (2H, s), 6.04 (2H, s), 6.90 (1H, d, *J*=7.6 Hz), 6.95 (1H, s), 7.73 (1H, d, *J*=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9 (CH_3), 56.5 (CH_3), 94.6 (CH_2), 114.1 (CH), 123.1 (CH), 136.6 (CH), 142.8 (Cq), 143.6 (Cq), 162.5 (Cq); HRMS (ESI) *m*/*z* calcd for $C_9H_{13}O_4NaB$ $[M+Na]^+$ 219.0805, found 219.0806.

*4.1.4. (R)-3-(2-Methoxymethoxy-4-methylphenyl)-1-phenylbut-2-en-1-ol (**9**).* To a stirred solution of allenic alcohol **5** (2.00 g, 13.7 mmol) in 1,4-dioxane/water (20:1) (105 mL) were added arylboronic acid **6** (3.49 g, 17.8 mmol), Et_3N (9.53 mL, 68.4 mmol), and $[Pd_2(OH)_2(PPh_3)_4][BF_4]_2$ (1.01 g, 0.684 mmol) at rt. After stirring was continued for 30 min at 80 °C, the reaction mixture was diluted with AcOEt and dried over $MgSO_4$. After filtration of the mixture through a pad of silica gel, the residue upon evaporation of the solvent was chromatographed on silica gel with hexane/AcOEt (85:15 v/v) as eluent to give allylic alcohol **9** (3.03 g, 74%, 95% ee) as a yellow oil; $[\alpha]_D^{27}$ +7.08 (*c* 1.1 in $CHCl_3$); IR (neat): 3388, 3028, 1610 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (1H, d, *J*=2.4 Hz), 2.14 (3H, d, *J*=0.8 Hz), 2.32 (3H, s), 3.42 (3H, s), 5.11 (1H, d, *J*=6.8 Hz), 5.14 (1H, d, *J*=6.8 Hz), 5.63 (1H, dd, *J*=2.4 and 8.8 Hz), 5.71 (1H, dd, *J*=0.8 and 8.8 Hz), 6.77 (1H, d, *J*=7.6 Hz), 6.89 (1H, s), 7.03 (1H, d, *J*=7.6 Hz), 7.28 (1H, t, *J*=7.6 Hz), 7.36 (2H, t, *J*=7.6 Hz), 7.47 (2H, d, *J*=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8 (CH_3), 21.3 (CH_3), 56.1 (CH_3), 70.7 (CH), 94.6 (CH_2), 115.5 (CH), 122.5 (CH), 126.1 (CH), 127.4 (CH), 127.4 (Cq), 128.4 (CH), 129.3 (CH), 131.7 (CH), 137.2 (Cq), 138.5 (Cq), 143.7 (Cq), 154.0 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{19}H_{23}O_3$ $[M+H]^+$ 299.1647, found 299.1643. Enantiomeric excess was determined by HPLC analysis [CHIRALCEL AS-H column, 10% isopropanol/hexane, 0.5 mL/min, λ=254 nm, retention times 17.7 min (*R*), and 20.9 min (*S*)].

*4.1.5. (S)-3-(2-Methoxymethoxy-4-methylphenyl)-3-methyl-5-phenylpent-4-enoic acid dimethylamide (**4**).* To a stirred solution of allylic alcohol **9** (2.50 g, 8.38 mmol) in toluene (90 mL) was added *N*,*N*-dimethylacetamide dimethylacetal (12.3 mL, 83.8 mmol) at rt. After being refluxed for 10 h, the solvent was removed in vacuo. The residue was chromatographed on silica gel with hexane/AcOEt (75:25 v/v) as eluent to give amide **4** (2.55 g, 84%, 95% ee) as a yellow oil; $[\alpha]_D^{27}$ −13.0 (*c* 1.0 in $CHCl_3$); IR (neat): 2933, 1649, 1014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (3H, s), 2.31 (3H, s), 2.85 (3H, s), 2.92 (3H, s), 3.06 (1H, d, *J*=14.4 Hz), 3.14 (1H, d, *J*=14.4 Hz), 3.39 (3H, s), 5.11 (1H, d, *J*=6.8 Hz), 5.14 (1H, d, *J*=6.8 Hz), 6.24 (1H, d, *J*=16.4 Hz), 6.80 (1H, dd, *J*=0.8 and 8.0 Hz), 6.84 (1H, d, *J*=16.4 Hz), 6.92 (1H, d, *J*=0.8 Hz), 7.16 (1H, t, *J*=7.2 Hz), 7.20–7.30 (3H, m), 7.34 (2H, d, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (CH_3), 25.8 (CH_3), 35.4 (CH_3), 37.7 (CH_3), 41.9 (CH_2), 42.6 (Cq), 56.1 (CH_3), 94.6 (CH_2), 115.6 (CH), 122.4 (CH), 125.9 (CH), 126.0 (CH), 126.7 (CH), 127.9 (CH), 128.4 (CH), 132.3 (Cq), 137.7 (Cq), 138.0 (Cq), 139.1 (CH), 155.2 (Cq), 171.3 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$ 368.2226, found 368.2223. Enantiomeric excess was determined by HPLC analysis [CHIRALCEL AS-H column, 10% isopropanol/hexane, 0.5 mL/min, λ=254 nm, retention times 33.1 min (*R*), and 44.5 min (*S*)].

*4.1.6. (S)-4-(2-Methoxymethoxy-4-methylphenyl)-4-methyl-6-phenylhex-5-en-2-one (**10**).* To a stirred solution of amide **4** (656 mg, 1.79 mmol) in Et_2O (20 mL) was added dropwise 2.5 M solution of MeLi in diethoxymethane (0.86 mL, 2.14 mmol) at −78 °C. After stirring was continued for 1.5 h at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with Et_2O. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel with hexane/AcOEt (91:9 v/v) as eluent to give ketone **10** (500 mg, 83%) as a colorless oil; $[\alpha]_D^{27}$ −44.5 (*c* 1.0 in $CHCl_3$); IR (neat): 2916, 1703, 1503 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (3H, s), 1.91 (3H, s), 2.31 (3H, s), 3.08 (1H, d, *J*=14.8 Hz), 3.38 (1H, d, *J*=14.8 Hz), 3.42 (3H, s), 5.13 (1H, d, *J*=6.4 Hz), 5.16 (1H, d, *J*=6.4 Hz), 6.26 (1H, d, *J*=16.4 Hz), 6.68 (1H, d, *J*=16.4 Hz), 6.79 (1H, dd, *J*=0.8 and 7.6 Hz), 6.93 (1H, d, *J*=0.8 Hz), 7.15–7.21 (1H, m), 7.18 (1H, t, *J*=7.2 Hz), 7.27 (2H, t, *J*=7.2 Hz), 7.34 (2H, d, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (CH_3), 25.8 (CH_3), 31.5 (CH_3), 42.1 (Cq), 52.7 (CH_2), 56.2 (CH_3), 94.5 (CH_2), 115.6 (CH), 122.4 (CH), 126.1 (CH), 126.2 (CH), 126.9 (CH), 127.9 (CH), 128.5 (CH), 131.2 (Cq), 137.8 (Cq), 138.0 (Cq), 138.7 (CH), 155.3 (Cq), 208.0 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{22}H_{27}O_3$ $[M+H]^+$ 339.1960, found 339.1962.

*4.1.7. (R)-2-(2-Methoxymethoxy-4-methylphenyl)-2-methyl-4-oxopentanal (**11**).* To a stirred solution of ketone **10** (499 mg, 1.47 mmol) in acetone/water (6:1) (21 mL) were added a catalytic amount of OsO_4 and NMO (181 mg, 1.62 mmol) at rt. After stirring was continued for 10 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ solution and extracted with AcOEt. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel with hexane/AcOEt (20:80 v/v) as eluent to give diol (549 mg) as a colorless oil. To a stirred solution of this diol (549 mg) in CH_2Cl_2 (15 mL) was added $Pb(OAc)_4$ (654 mg, 1.47 mmol) at 0 °C. After stirring was continued for 1 h at the same temperature, the reaction mixture was filtrated through a pad of Celite. The residue upon evaporation of the solvent was chromatographed on silica gel with hexane/AcOEt (86:14 v/v) as eluent to give ketoaldehyde **11** (342 mg, 88%, two steps) as a colorless oil; $[\alpha]_D^{27}$ −116 (*c* 1.1 in $CHCl_3$); IR (neat): 2937, 1715, 1612 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (3H, s), 1.97 (3H, s), 2.33 (3H, s), 3.08 (1H, d, *J*=16.4 Hz), 3.17 (1H, d, *J*=16.4 Hz), 3.46 (3H, s),

5.13 (1H, d, J=6.4 Hz), 5.16 (1H, d, J=6.4 Hz), 6.85 (1H, dd, J=0.8 and 7.6 Hz), 6.96 (1H, d, J=0.8 Hz), 7.13 (1H, d, J=7.6 Hz), 9.61 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1 (CH_3), 21.3 (CH_3), 31.2 (CH_3), 48.6 (CH_2), 50.0 (Cq), 56.4 (CH_3), 94.3 (CH_2), 114.8 (CH), 122.8 (CH), 126.6 (Cq), 127.9 (CH), 139.3 (Cq), 154.2 (Cq), 202.7 (Cq), 207.0 (Cq); HRMS (ESI) m/z calcd for $C_{15}H_{21}O_4$ $[M+H]^+$ 265.1440, found 265.1435.

*4.1.8. (S)-4-(2-Methoxymethoxy-4-methylphenyl)-4-methyl-2-cyclopentenone (**3**).* To a stirred solution of ketoaldehyde **11** (342 mg, 1.29 mmol) in ^{t}BuOH (30 mL) was added K_2CO_3 (894 mg, 6.47 mmol) at rt. After being refluxed for 10 h, the reaction mixture was diluted with Et_2O and filtered through a pad of Celite. The residue upon evaporation of the solvent was chromatographed on silica gel with hexane/AcOEt (87:13 v/v) as eluent to give cyclopentenone **3** (298 mg, 94%) as a colorless oil; $[\alpha]_D^{27}$ −65.3 (c 1.1 in $CHCl_3$); IR (neat): 2922, 1714, 1015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (3H, s), 2.32 (3H, s), 2.58 (1H, d, J=18.8 Hz), 2.78 (1H, d, J=18.8 Hz), 3.46 (3H, s), 5.15 (1H, d, J=6.8 Hz), 5.18 (1H, d, J=6.8 Hz), 6.17 (1H, d, J=5.6 Hz), 6.77 (1H, d, J=8.0 Hz), 6.95 (1H, s), 7.06 (1H, d, J=8.0 Hz), 7.79 (1H, d, J=5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0 (CH_3), 27.2 (CH_3), 46.8 (Cq), 50.1 (CH_2), 56.1 (CH_3), 93.7 (CH_2), 115.0 (CH), 121.8 (CH), 126.3 (CH), 130.1 (Cq), 131.0 (CH), 138.2 (Cq), 154.9 (Cq), 170.7 (CH), 209.8 (Cq); HRMS (ESI) m/z calcd for $C_{15}H_{19}O_3$ $[M+H]^+$ 247.1334, found 247.1336.

*4.1.9. (2R,3R) and (2S,3R)-2-Hydroxymethyl-3-(2-methoxymethoxy-4-methylphenyl)-3- methylcyclopentanone (**12**) (ratio of 1:1).* To a stirred solution of ^{i}Pr$_2$NH (0.085 mL, 0.609 mmol) in THF (3 mL) was added dropwise 1.5 M solution of ^{n}BuLi in hexane (0.41 mL, 0.609 mmol) at −78 °C. After stirring was continued for 1.5 h, cyclopentenone **3** (50.0 mg, 0.203 mmol) in THF (2 mL) was added dropwise to this reaction mixture at the same temperature. After stirring was continued for 2 h, benzotriazole/methanol (150 mg, 1.02 mmol) was added to this reaction mixture, and further stirring was continued for 1 h at the same temperature. The reaction mixture was quenched with water and extracted with Et_2O. The combined extracts were washed with brine, and the residue upon workup was diluted with AcOEt (5 mL) and treated with Pd/C (5.6 mg, 10%) at rt. After stirring was continued under a hydrogen atmosphere for 1 h, the reaction mixture was filtered through a pad of Celite. The residue upon evaporation was chromatographed on silica gel with hexane/AcOEt (80:20 v/v) as eluent to give β-hydroxy ketone **12** (42.0 mg, 74% as a 1:1 mixture, two steps) as a colorless oil; $[\alpha]_D^{27}$ +50.3 (c 1.1 in $CHCl_3$); IR (neat) 3458, 2953, 1731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (1.5H, s), 1.44 (1.5H, s), 2.04 (0.5H, br s), 2.11−2.18 (0.5H, m), 2.28−2.57 (3.5H, m), 2.33 (3H, s), 2.76 (0.5H, dd, J=4.0 and 8.4 Hz), 2.93 (0.5H, br s), 3.20 (0.5H, dd, J=4.0 and 8.4 Hz), 3.35−3.43 (0.5H, m), 3.49 (1.5H, s), 3.50 (1.5H, s), 3.45−3.55 (0.5H, m), 3.72 (0.5H, ddd, J=2.4, 8.4, and 11.2 Hz), 3.90 (0.5H, ddd, J=2.8, 8.4, and 11.2 Hz), 5.16 (0.5H, d, J=6.8 Hz), 5.20 (0.5H, d, J=6.8 Hz), 5.25 (1H, s), 6.80 (0.5H, dd, J=0.8 and 8.0 Hz), 6.82 (0.5H, dd, J=0.8 and 8.0 Hz), 6.95 (0.5H, d, J=0.8 Hz), 6.98 (0.5H, d, J=0.8 Hz), 7.13 (0.5H, d, J=8.0 Hz), 7.16 (0.5H, d, J=8.0 Hz); HRMS (ESI) m/z calcd for $C_{16}H_{23}O_4$ $[M+H]^+$ 279.1596, found 279.1594.

*4.1.10. (S)-3-(2-Methoxymethoxy-4-methylphenyl)-3-methyl-2-methylenecyclopentanone (**13**).* To a stirred solution of β-hydroxy ketone **12** (453 mg, 1.63 mmol) in pyridine (20 mL) was added TsCl (1.55 g, 8.14 mmol) at rt. After stirring was continued for 7 h at 60 °C, the reaction mixture was diluted with water and extracted with AcOEt. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel with hexane/AcOEt (90:10 v/v) as eluent to give enone **13** (353 mg, 83%) as a colorless oil; $[\alpha]_D^{27}$ −156 (c 1.0 in $CHCl_3$); IR (neat): 2960, 1722, 928 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (3H, s), 1.79−1.88 (1H, m), 2.31 (3H, s), 2.45 (2H, t, J=8.0 Hz), 2.51−2.60 (1H, m), 3.40 (3H, s), 5.01 (1H, d, J=0.8 Hz), 5.04 (1H, d, J=6.8 Hz), 5.12 (1H, d, J=6.8 Hz), 5.97 (1H, s), 6.77 (1H, dd, J=0.8 and 8.0 Hz), 6.92 (1H, d, J=0.8 Hz), 7.20 (1H, d, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (CH_3), 28.0 (CH_3), 34.0 (CH_2), 36.2 (CH_2), 45.5 (Cq), 56.1 (CH_3), 93.9 (CH_2), 115.2 (CH), 115.6 (CH_2), 121.6 (CH), 126.6 (CH), 133.2 (Cq), 138.0 (Cq), 154.4 (Cq), 155.0 (Cq), 207.7 (Cq); HRMS (ESI) m/z calcd for $C_{16}H_{21}O_3$ $[M+H]^+$ 261.1491, found 261.1492.

*4.1.11. (1S,3R)-3-(2-Methoxymethoxy-4-methylphenyl)-1,3-dimethyl-2-methylenecyclopentanol (**14**).* To a stirred suspension of $CeCl_3$ (142 mg, 0.576 mmol) in THF (6 mL) was added dropwise 1.0 M solution of MeLi in Et_2O (0.58 mL, 0.576 mmol) at −78 °C. After stirring was continued for 1 h, enone **13** (30.0 mg, 0.115 mmol) in THF (4 mL) was added dropwise at the same temperature. After stirring was continued for 1 h at the same temperature, the reaction mixture was quenched with water and extracted with Et_2O. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel with hexane/AcOEt (88:12 v/v) as eluent to give alcohol **14** (25.7 mg, 81%) as a colorless oil and some starting material was recovered (3.7 mg, 12%); $[\alpha]_D^{28}$ −66.1 (c 0.85 in $CHCl_3$); IR (neat): 3558, 2966, 927 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (3H, s), 1.47 (3H, s), 1.52−1.64 (1H, m), 1.88−1.99 (2H, m), 2.32 (3H, s), 2.44−2.53 (1H, m), 3.34 (1H, s), 3.47 (3H, s), 4.66 (1H, s), 5.14 (1H, d, J=6.8 Hz), 5.18 (1H, s), 5.22 (1H, d, J=6.8 Hz), 6.81 (1H, dd, J=0.8 and 8.0 Hz), 6.92 (1H, d, J=0.8 Hz), 7.35 (1H, d, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (CH_3), 27.0 (CH_3), 28.5 (CH_3), 36.7 (CH_2), 40.1 (CH_2), 48.8 (Cq), 56.7 (CH_3), 78.7 (Cq), 94.5 (CH_2), 106.8 (CH_2), 115.4 (CH), 122.1 (CH), 127.83 (CH), 133.4 (Cq), 137.6 (Cq), 154.2 (Cq), 166.4 (Cq); HRMS (ESI) m/z calcd for $C_{17}H_{24}O_3$ $[M]^+$ 276.1725, found 276.1728.

*4.1.12. (1S,3R)-3-(2-Hydroxy-4-methylphenyl)-1,3-dimethyl-2-methylidenecyclopentanol (**15**).* To a stirred solution of MOM ether **14** (5.4 mg, 0.020 mmol) in ^{i}PrOH (2 mL) was added 3 N HCl (0.5 mL) at 0 °C. After stirring was continued for 30 h at the same temperature, the reaction mixture was extracted with Et_2O and washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (88:12 v/v) as eluent to give phenol **15** (1.8 mg, 40%) as a colorless oil and some starting material was recovered (2.7 mg, 50%); $[\alpha]_D^{28}$ −66.1 (c 0.85 in $CHCl_3$); IR (neat): 3354, 2966, 910 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (3H, s), 1.50−2.35 (3H, m), 1.57 (3H, s), 2.28 (3H, s), 2.44−2.55 (1H, m), 4.83 (1H, s), 5.23 (1H, s), 6.68 (1H, s), 6.69 (1H, d, J=8.0 Hz), 7.26 (1H, d, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7 (CH_3), 26.2 (CH_3), 28.9 (CH_3), 36.1 (CH_2), 39.4 (CH_2), 47.8 (Cq), 80.2 (Cq), 108.9 (CH_2), 118.5 (CH), 120.1 (CH), 126.9 (CH), 129.9 (Cq), 138.0 (Cq), 153.9 (Cq), 164.0 (Cq); HRMS (ESI) m/z calcd for $C_{15}H_{21}O_2$ $[M+H]^+$ 233.1542, found 233.1543.

*4.1.13. (3S,3aR,8bS)-(−)-2,3,3a,8b-Tetrahydro-3-hydroxy-3,3a,6,8b-tetramethyl-1H-cyclopenta[b]benzofuran (**2**).* To a stirred solution of phenol **15** (10 mg, 0.044 mmol) in THF (5 mL) was added Hg$(OCOCF_3)_2$ (19 mg, 0.044 mmol) at rt. After stirring was continued for 4 h, the reaction mixture was treated with aqueous 10% NaOH (0.6 mL) and $NaBH_4$ (8.8 mg, 0.23 mmol) successively, and saturated with NaCl. This mixture was diluted with AcOEt and filtrated through silica gel. The residue upon evaporation of the solvent was chromatographed on silica gel with hexane/AcOEt (90:10 v/v) as eluent to give dihydrobenzohuran **2** (6.7 mg, 66%) as a colorless oil; $[\alpha]_D^{28}$ −8.0 (c 0.60 in $CHCl_3$) [lit., $[\alpha]_D^{25}$ −6.6 (c 0.56 in $CHCl_3$)];[2d] IR (neat): 3568, 2954, 1500 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, s), 1.25 (3H, s), 1.36 (3H, s), 1.52−1.79 (4H, m), 2.30 (3H, s), 2.77 (1H, d, J=0.8 Hz), 6.57 (1H, t, J=0.8 Hz), 6.71 (1H, dq, J=0.8 and 7.6 Hz), 6.93 (1H, d, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5 (CH_3), 21.4 (CH_3), 22.0 (CH_3), 23.6 (CH_3), 37.7 (CH_2), 39.9 (CH_2), 51.8 (Cq), 80.9 (Cq), 99.4 (Cq), 109.8 (CH), 121.7 (CH), 122.5 (CH), 133.9 (Cq), 138.3 (Cq), 157.2 (Cq); HRMS (ESI) m/z calcd for $C_{15}H_{20}O_2Na$

$[M+Na]^+$ 255.1361, found 255.1365. The spectroscopic data of our sample of synthetic **2** were completely identical with those previously reported.[2d]

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.04.134.

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