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# Stereoselective Construction of Tetra-Substituted Tetrahydrofuran Compounds from Benzylic Hemiacetal in the Presence of $H_2$ and a Pd Catalyst: Stereoselective Synthesis of a Stereoisomer of (−)-Virgatusin and Its Antimicrobiological Activity

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**Tetra-substituted tetrahydrofuran compounds were stereoselectively prepared from benzylic hemiacetal in the neutral condition by employing the simple reagent, $H_2$, and a Pd catalyst. The stereoselective conversion of benzylic hemiacetal to two different stereoisomers of the tetrasubstituted tetrahydrofuran compound was observed. One of these tetrahydrofuran compounds was converted to the virgatusin stereoisomer to estimate its antimicrobiological activity.**

**Key words:** virgatusin; tetrahydrofuran lignan; antimicrobiological activity

The tetrahydrofuran structure is widely distributed and is a synthetic target for organic chemists. The reduction of hemiacetal has been employed to obtain tetrahydrofuran compounds. Although stereoselectivity is required in synthetic studies of natural products, the stereocontrolled synthesis of a tetra-substituted tetrahydrofuran compound is difficult because of the existence of four chiral centers. In previous studies, stereocontrolled reduction of the benzylic hemiacetal to a substituted tetrahydrofuran compound using Lewis acid[1–7] and hydride[8] has been reported. However, there is a possibility of epimerization of the benzylic stereocenter of benzyl ether under the Lewis acid condition because of the occurrence of the benzyl cation. In some cases, neutral conditions for the reduction of benzylic hemiacetal would be important to obtain a tetrahydrofuran compound bearing the desired stereochemistry. In this present study, stereoselective reduction of benzylic hemiacetal using the simple reagent, $H_2$ gas, and a Pd catalyst was tried. To achieve this objective, silyloxy ketone **1** was prepared, and then unstable benzylic hemiacetal **2** converted from **1** was used for this study (Scheme 1). Resulting tetrahydrofuran compound **3** or **4** contained two benzylic chiral centers on a benzyl ether. It could be assumed that the neutral condition was better for the reduction of hemiacetal **2** to avoid epimerization of the benzylic chiral center. This article describes the stereoselective reduction of benzylic hemiacetal under the neutral condition using $H_2$ and a Pd catalyst, giving a tetra-substituted tetrahydrofuran derivative.

## Results and Discussion

The preparation of ketone **9** is shown in Scheme 2. Lactone **5** was prepared from (1*S*,2*R*)-2-allyl-1-(3,4-methylenedioxyphenyl)-1,3-propanediol[9] by tritylation of the primary hydroxy group, oxidative cleavage of the olefin, and oxidation to the lactone. Lactone **5** was subjected to the aldol reaction with 3,4-dimethoxybenzaldehyde to give the corresponding aldol product (*erythro*/*threo* = 4/1). Pure *erythro*-form **6** was obtained by protection of the resulting benzyl alcohol as a TIPS ether. This lactone **6** was treated with $LiBH_4$ to give the corresponding diol, which was converted to a diacetate, before detritylation was performed under a formic acid-ether system to give **7**. Detritylation without acetylation was accompanied by desilylation. Deacetylation followed by protection of the primary hydroxy groups as pivaloates gave **8**, before oxidation of benzyl alcohol **8** gave ketone **9**.

After desilylation of ketone **9**, resulting unstable benzylic hemiacetal **10** was treated with $H_2$ and a Pd catalyst (Table 1). In entry 1, hemiacetal **10** was reacted with $H_2$ and $Pd(OH)_2$ in EtOAc. Unexpectedly, this reaction predominantly gave **11**,[10] which was a 2,5-*cis*, 3,4-*trans*-tetra-substituted tetrahydrofuran compound. Two reaction mechanisms could be assumed, one being

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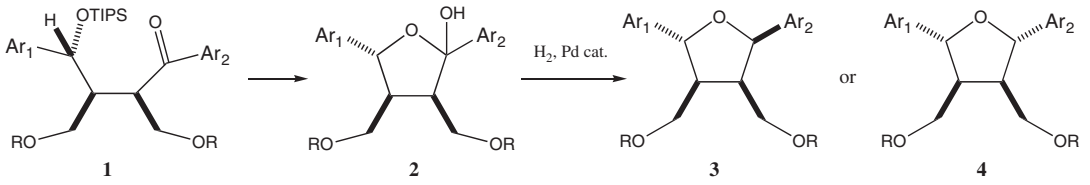
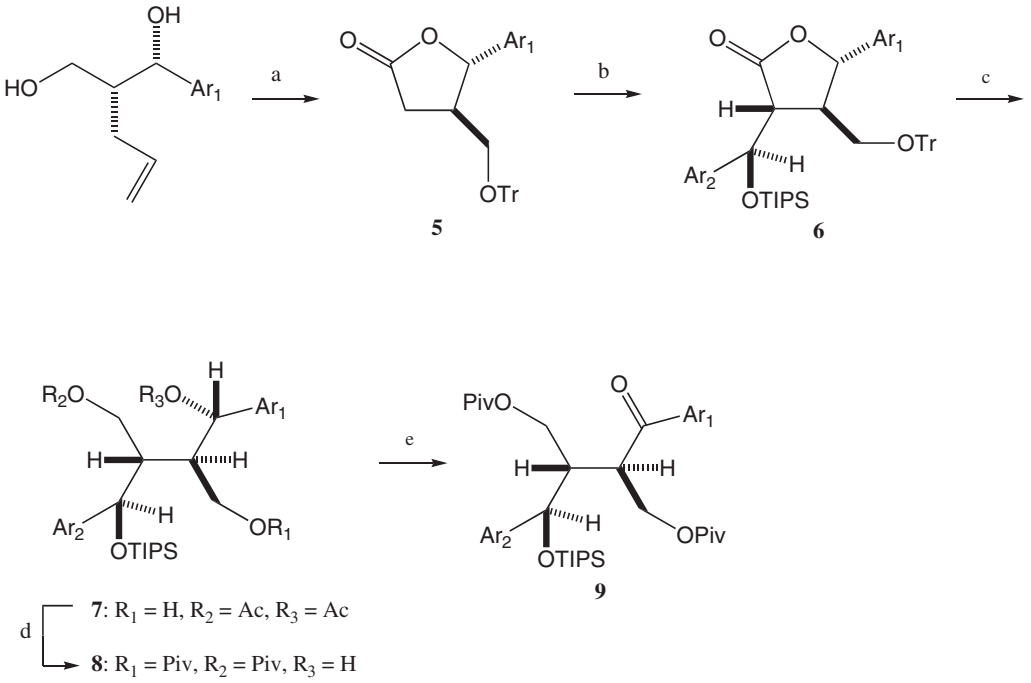



**Scheme 1.** Reduction of the Benzylic Hemiacetal.

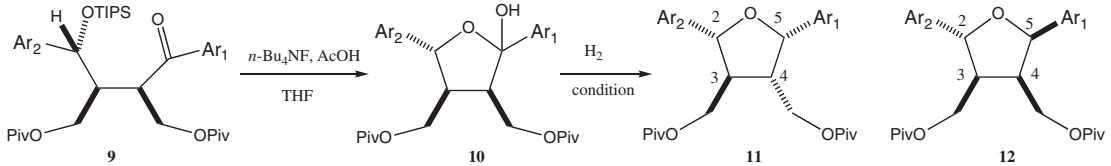



**Scheme 2.** Preparation of Ketone **9**.

(a) (1) TrCl, 4-DMAP, pyridine, r.t., 1 h (92% yield); (2) $OsO_4$, NMO, aq. acetone, *tert*-BuOH, r.t., 13 h; (3) $NaIO_4$, MeOH, r.t., 2 h (85%, 2 steps); (4) PCC, $CH_2Cl_2$, MS 4A, r.t., 13 h (90% yield); (b) (1) KHMDS, 3,4-dimethoxybenzaldehyde, THF, $-70\,^{\circ}C$, 1 h (68% yield, mixture of *erythro*/*threo* = 4/1); (2) TIPSOTf, 2,6-lutidine, $CH_2Cl_2$, r.t., 2 h (46% yield, 2 steps); (c) (1) $LiBH_4$, THF, $60\,^{\circ}C$, 14 h; (2) $Ac_2O$, pyridine, DMAP, r.t., 13 h; (3) $HCO_2H$, $Et_2O$, $0\,^{\circ}C$ 1 h (53% yield, 3 steps); (d) (1) $K_2CO_3$, MeOH, r.t., 12 h; (2) PivCl, pyridine, r.t., 11 h (85%, 2 steps); (e) PCC, MS 4A, $CH_2Cl_2$, r.t., 16 h (83% yield). $Ar_1$, 3,4-methylenedioxyphenyl; $Ar_2$, 3,4-dimethoxyphenyl.

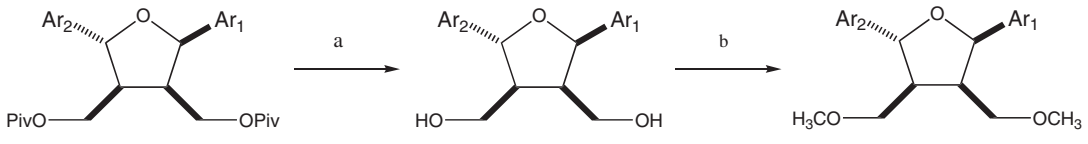
**Table 1.** Reaction of Benzylic Hemiacetal **10** with $H_2$ and a Pd Catalyst

$Ar_1$, 3,4-methylenedioxyphenyl; $Ar_2$, 3,4-dimethoxyphenyl




| Entry | Catalyst | Solvent | Time (min) | **11** (%) | **12** (%) |
|---|---|---|---|---|---|
| 1 | $Pd(OH)_2/C$ | EtOAc | 5 | 44 | 0 |
| 2 | Pd/C | THF | 30 | 0 | 0 |
| 3 | $Pd(OH)_2/C$ | THF | 60 | 0 | 0 |
| 4 | Pd | EtOAc | 5 | 3 | 26 |
| 5 | $Pd(OH)_2/C$ | EtOAc, AcOH (4 eq) | 10 | 20 | 17 |
| 6 | $Pd(OH)_2/C$ | EtOAc, AcOH (23 eq) | 10 | 39 | 16 |
| 7 | $Pd(OH)_2/C$ | EtOH | 15 | 0 | 28 |
| 8 | $Pd(OH)_2/C$ | EtOAc-EtOH (1:1) | 15 | 0 | 25 |
| 9 | $Pd(OH)_2/C$ | EtOAc-EtOH (1:1) | 4 | 0 | 53 |

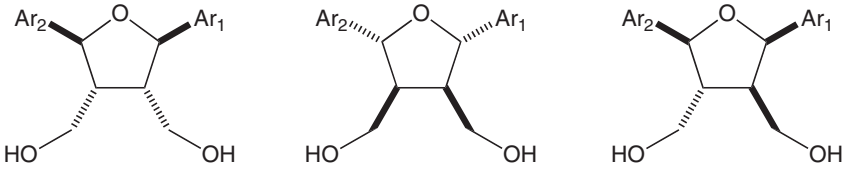
production of a dihydrofuran, and the other being epimerization at the 4 position. It could be assumed that the dihydrofuran had been formed from hemiacetal **10** by dehydration, and then hydrogenation occurred from the opposite side of the aryl group at the 2 position ($Ar_2$).[11] To ascertain the validity of this reaction




12 (+)-**13** (+)-**14**

**Scheme 3.** Synthesis of Virgatusin Stereoisomer (+)-**14**.
(a) aq. NaOH, EtOH, r.t., 5 h (63% yield); (b) NaH, MeI, r.t., 5 h (66% yield). $Ar_1$, 3,4-methylenedioxyphenyl; $Ar_2$, 3,4-dimethoxyphenyl

**Table 2.** Antibacterial Activity [MIC values (mM)] of (+)- and (−)-**13**, (+)- and (−)-**15**, and (+)-**17**
$Ar_1$, 3,4-methylenedioxyphenyl; $Ar_2$, 3,4-dimethoxyphenyl




(+)-**15** (-)-**15** (+)-**17**

| | (+)-**13** | (−)-**13** | (+)-**15** | (−)-**15** | (+)-**17** |
|---|---|---|---|---|---|
| *Bacillus subtilis* NBRC 13719$^T$ | >50 | >50 | >50 | >50 | 12.5 |
| *Listeria denitrificans* JCM 11481 | >50 | 25 | 50 | 12.5 | >50 |
| *Staphylococcus aureus* subsp. *aureus* NBRC 14462 | >50 | >50 | >50 | >50 | >50 |

mechanism, hemiacetal **10** was treated with $Pd(OH)_2/C$ in EtOAc under $N_2$ gas; however, the hemiacetal was recovered and no products were yielded. The unstable dihydrofuran, which was easily transformed to a high polar compound, was prepared from hemiacetal **10** by treating with mesyl chloride and $Et_3N$. The reaction of this dihydrofuran with $H_2$ and $Pd(OH)_2$ in EtOAc did not give **11**. The reaction mechanism giving **11** could consequently not be determined.

The reaction conditions were examined to obtain the other stereoisomer. Although the reaction conditions of $H_2$, Pd/C-THF and $H_2$, and $Pd(OH)_2$/C-THF did not yield any product (entries 2 and 3), employing Pd-black in EtOAc under $H_2$ gas gave different stereoisomer **12** together with **11** (**11**/**12** = 1/9, entry 4). In this case, 2,5-*trans*, 3,4-*cis* form **12** was favored. For the next step, a reaction under acidic conditions was examined. In entries 5 and 6, the selectivity between **11** and **12** was decreased. Complete selectivity for stereoisomer **12** was achieved by employing $Pd(OH)_2$ in ethanol as a protic solvent under $H_2$ gas (entry 7). The application of the EtOAc-EtOH solvent also gave only **12** as a single isomer (entry 8), and the yield was increased by a shorter reaction time (entry 9). The stereochemistry of **12** was confirmed by a differential NOE experiment. Upon irradiation at 5-H, NOEs were observed at 3-H and 4-H. Hemiacetal **10** did not give any product by treatment with $Pd(OH)_2/C$ and $N_2$ in EtOAc and EtOH. The unstable dihydrofuran prepared from hemiacetal **10** could not be converted to a tetrahydrofuran compound by a reaction with $Pd(OH)_2/C$ and $H_2$ in EtOAc-EtOH. The reaction mechanism could not be determined in this experiment.

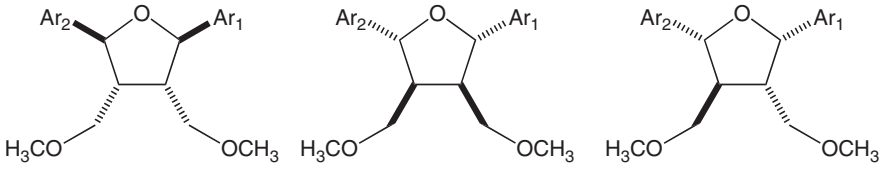
Compound **12** was converted to virgatusin stereoisomer (+)-**14** by hydrolysis followed by methylation (Scheme 3). Enantiomer (−)-**14** was also synthesized from (1*R*,2*S*)-2-allyl-1-(3,4-methylenedioxyphenyl)-1,3-propanediol by the same synthetic method as that just described. The optical purity was determined as being more than 99% ee. Stereoisomer **11** has been reported as an important synthetic intermediate to (−)-virgatusin.[10] The highly stereoselective syntheses of the two tetrasubstituted tetrahydrofuran compounds were achieved by using the simple reagent, $H_2$, and a Pd catalyst in a suitable solvent.

The antimicrobiological activity of synthesized (+)- and (−)-**13** and of (+)- and (−)-**14** was examined with previously synthesized (+)- and (−)-**15** and (+)- and (−)-**16**.[12] The antibacterial activity of (+)-**17** against *Bacillus subtilis* has been reported in our previous study (MIC of 12.5 mM).[13] Compounds (−)-**13**, (+)-**15** and (−)-**15** showed antibacterial activity against *Listeria denitrificans* instead of *Bacillus subtilis*, the activity of (−)-**15** being strongest (Table 2). The activity of (−)-**16** against *Colletotrichum lagenarium* was observed in the antifungal test (growth %: 80.9 ± 3.06), although the activity was weaker than that of natural (−)-virgatusin (**18**; growth %: 49.4 ± 3.92)[14] (Table 3).

## Experimental

Optical rotation values were measured with a Horiba SEPA-200 instrument. NMR data were obtained with a JNM-EX400 spectrometer, and EIMS data were measured with a JMS-MS700V spectrometer. The silica gel used was Wakogel C-300 (Wako, 200-300 mesh). HPLC

**Table 3.** Antifugal Activity (growth % against control) of (+)- and (−)-**14**, (+)- and (−)-**16**, and (−)-Virgatusin (**18**) against *C. lagenarium*
$Ar_1$, 3,4-methylenedioxyphenyl; $Ar_2$, 3,4-dimethoxyphenyl




(+)-**16** (-)-**16** (-)-virgatusin (**18**)

| (+)-**14** | (−)-**14** | (+)-**16** | (−)-**16** | (−)-Virgatusin (**18**) |
|---|---|---|---|---|
| >1 mM | >1 mM | >1 mM | 0.25 mM<br>80.9 ± 3.06 (growth %) | 0.25 mM<br>49.4 ± 3.92 (growth %) |

analyses were performed with Shimadzu LC-6AD and SPD-6AV instruments. The numbering of compounds follows IUPAC nomenclatural rules.

*(3R,4S)-4-(3,4-Methylenedioxyphenyl)-3-trityloxymethyl-4-butanolide (**5**).* A reaction solution of (1*S*,2*R*)-2-allyl-1-(3,4-methylenedioxyphenyl)-1,3-propanediol[9] (4.40 g, 18.6 mmol), trityl chloride (5.19 g, 18.6 mmol), and 4-DMAP (0.10 g) in pyridine (25 ml) was stirred at room temperature for 1 h before additions of $H_2O$ and EtOAc. The organic solution was separated, washed with sat. aq. $CuSO_4$ solution, sat. aq. $NaHCO_3$ solution, and brine, and dried ($Na_2SO_4$). After evaporation, the organic residue was applied to silica gel column chromatography (EtOAc-hexane = 93:7) to give trityl ether (7.20 g, 17.2 mmol, 92%) as a colorless oil, $[\alpha]^{20}_D = -3.1$ (*c* 2.8, $CHCl_3$); $\delta_H(CDCl_3)$ 1.98 (1H, m, $CH_2$=CHC$H_2$C*H*), 2.13–2.17 (2H, m, $CH_2$=CHC$H_2$), 3.10 (1H, s, OH), 3.19 (2H, d, *J* 4.9 Hz, $CH_2$OTr), 4.82–4.90 (3H, m, ArC*H*(OH), C$H_2$=CH), 5.58 (1H, m, C*H*=$CH_2$), 5.88 (2H, s, $OCH_2O$), 6.67 (2H, s, ArH), 6.75 (1H, s, ArH), 7.20–7.30 (9H, m, ArH), 7.40–7.42 (6H, m, ArH); $\delta_C(CDCl_3)$ 30.4, 45.7, 63.9, 75.5, 87.3, 100.8, 106.9, 107.7, 116.3, 119.5, 127.0, 127.8, 128.6, 136.6, 136.9, 143.7, 146.4, 147.4. *Anal*. Found: C, 79.93; H, 6.42. Calcd. for $C_{32}H_{30}O_4$: C, 80.31; H, 6.32%. (+)-Trityl ether: $[\alpha]^{20}_D = +3.0$ (*c* 1.1, $CHCl_3$) A reaction solution of trityloxy olefin (7.20 g, 17.2 mmol), 4-methylmorpholine *N*-oxide (2.40 g, 20.5 mmol), and $OsO_4$ (aq. 2% solution, 1.5 ml) in acetone (140 ml), *tert*-BuOH (35 ml), and $H_2O$ (35 ml) was stirred at room temperature for 13 h before addition of sat. aq. $Na_2S_2O_3$ solution. After the mixture was concentrated, the residue was dissolved in EtOAc and $H_2O$. The organic solution was separated, washed with brine, and dried ($Na_2SO_4$). Evaporation gave crude glycol. A reaction mixture of the crude glycol and $NaIO_4$ (4.32 g, 20.2 mmol) in MeOH (70 ml) was stirred at room temperature for 2 h before concentration. The residue was dissolved in EtOAc and $H_2O$. The organic solution was separated, washed with brine, and dried ($Na_2SO_4$). Evaporation and subsequent silica gel column chromatography (EtOAc-hexane = 1:4) gave hemiacetal (7.01 g, 14.6 mmol, 85%) as a colorless oil. A reaction mixture of this hemiacetal (7.01 g, 14.6 mmol) and PCC (4.03 g, 18.7 mmol) in $CH_2Cl_2$ (20 ml) containing MS 4A (0.3 g) was stirred at room temperature for 13 h before addition of dry ether. After filtration, the resulting filtrate was concentrated. The residue was applied to silica gel column chromatography (EtOAc-hexane = 1:9) to give lactone **5** (6.33 g, 13.2 mmol, 90%) as a colorless oil, $[\alpha]^{20}_D = +0.9$ (*c* 2.0, $CHCl_3$); $\delta_H(CDCl_3)$ 2.56 (1H, m, 3-H), 2.61–2.73 (2H, m, 2-$H_2$), 3.22 (1H, dd, *J* 9.8, 3.9 Hz, TrOC*H*H), 3.27 (1H, dd, *J* 9.8, 5.4 Hz, TrOCH*H*), 5.24 (1H, d, *J* 7.3 Hz, 4-H), 5.94 (2H, s, $OCH_2O$), 6.60 (1H, dd, *J* 7.8, 2.0 Hz, ArH), 6.68 (1H, d, *J* 2.0 Hz, ArH), 6.71 (1H, d, *J* 7.8 Hz, ArH), 7.22–7.31 (9H, m, ArH), 7.37–7.39 (6H, m, ArH); $\delta_C(CDCl_3)$ 31.8, 44.7, 61.8, 83.5, 86.9, 101.2, 106.3, 108.2, 119.7, 127.2, 127.9, 128.5, 132.4, 143.4, 147.8, 148.1, 175.8. *Anal*. Found: C, 77.51; H, 5.71. Calcd. for $C_{31}H_{26}O_5$: C, 77.81; H, 5.48%. (3*S*,4*R*)-**5**: $[\alpha]^{20}_D = -1.0$ (*c* 1.1, $CHCl_3$).

*(2R,3R,4S)-2-[(R)-(3,4-Dimethoxyphenyl)(triisopropylsilyloxy)methyl]-4-(3,4-methylenedioxyphenyl)-3-trityloxymethyl-4-butanolide (**6**).* To a solution of KHMDS (18.0 ml, 0.5 M toluene solution, 9.00 mmol) in THF (20 ml) was added a solution of lactone **5** (3.33 g, 6.96 mmol) in THF (10 ml) at −70 °C. After stirring at −70 °C for 15 min, 3,4-dimethoxybenzaldehyde (1.35 g, 8.12 mmol) in THF (5 ml) was added, and then the reaction solution was stirred at −70 °C for 1 h before addition of sat. aq. $NH_4Cl$ solution. The organic solution was separated, washed with brine, and dried ($Na_2SO_4$). After evaporation, the residue was applied to silica gel column chromatography (EtOAc-hexane = 1:3) to give a diastereomeric mixture of aldol product (*erythro*/*threo* = 4/1, 3.04 g, 4.72 mmol, 68%) as a colorless oil. To an ice-cooled solution of this diastereomeric mixture of aldol product (3.04 g, 4.72 mmol), 2,6-lutidine (1.37 ml, 11.8 mmol) in $CH_2Cl_2$ (20 ml) was added TIPSOTf (1.58 ml, 5.88 ml). After the reaction solution was stirred at room temperature for 2 h, sat. aq. $NaHCO_3$ solution was added. The organic solution was separated, washed with sat. aq. $CuSO_4$ solution, sat. aq. $NaHCO_3$ solution, and brine, and dried ($Na_2SO_4$). After concentration, the residue was applied to silica gel column chromatography

(1% EtOAc in toluene) to give pure *erythro* product **6** (2.54 g, 3.17 mmol, 46%, 2 steps) as a colorless oil, $[\alpha]^{20}_D = +64$ (*c* 1.8, $CHCl_3$); $\delta_H(CDCl_3)$ 1.01–1.06 (18H, m, $CH(CH_3)_2$), 1.08–1.17 (3H, m, $CH(CH_3)_2$, 2.80 (1H, dd, *J* 9.8, 4.9 Hz, C*H*HOTr), 2.86 (1H, dd, *J* 9.8, 2.4 Hz, CH*H*OTr), 3.03 (1H, m, 3-H), 3.26 (1H, dd, *J* 9.8, 2.0 Hz, 2-H), 3.77 (3H, s, $OCH_3$), 3.85 (3H, s, $OCH_3$), 4.90 (1H, d, *J* 8.8 Hz, 4-H) 5.67 (1H, d, *J* 2.0 Hz, ArC*H*OTIPS), 5.93 (2H, s, $OCH_2O$), 6.30 (1H, dd, *J* 8.3, 2.0 Hz, ArH), 6.57 (1H, d, *J* 2.0 Hz, ArH), 6.63 (1H, d, *J* 7.8 Hz, ArH), 6.67 (1H, d, *J* 8.3 Hz, ArH), 6.89–6.91 (2H, m, ArH), 7.10–7.15 (6H, m, ArH), 7.19–7.22 (9H, m, ArH); $\delta_C(CDCl_3)$ 12.6, 18.0, 18.1, 43.1, 51.4, 55.6, 55.8, 59.9, 72.6, 82.0, 86.5, 101.1, 107.1, 107.7, 108.4, 110.8, 117.7, 120.8, 127.0, 127.7, 128.5, 132.9, 135.2, 143.3, 147.7, 147.9, 148.2, 148.8, 176.6. *Anal*. Found: C, 73.18; H, 6.94. Calcd. for $C_{49}H_{56}O_8Si$: C, 73.47; H, 7.05%. (−)-**6**: $[\alpha]^{20}_D = -64$ (*c* 0.7, $CHCl_3$).

*(1S,2R,3S)-3-[(R)-(3,4-Dimethoxyphenyl)(triisopropylsilyloxy)methyl]-2-hydroxymethyl-1-(3,4-methylenedioxyphenyl)tetramethylene diacetate (**7**).* To a solution of $LiBH_4$ (1.41 g, 6.47 mmol) in THF (40 ml) was added a solution of silyloxy lactone **6** (2.54 g, 3.17 mmol) in THF (10 ml) at room temperature. After the reaction solution was stirred for 14 h at 60 °C, sat. aq. $NH_4Cl$ solution was added, and then the mixture was concentrated. The residue was dissolved in EtOAc and $H_2O$. The organic solution was separated, washed with brine, and dried ($Na_2SO_4$). After evaporation, the residue was dissolved in pyridine (2.4 ml) and $Ac_2O$ (2.4 ml) containing 4-DMAP (20 mg). After the reaction solution was stirred at room temperature for 13 h, ice was added. The mixture was stood at room temperature for 6 h, and then the mixture was dissolved in EtOAc and $H_2O$. The organic solution was separated, washed with 6 M aq. HCl solution, sat aq. $NaHCO_3$ solution, and brine, and dried ($Na_2SO_4$). Evaporation gave crude diacetate. To a solution of this crude diacetate in ether (90 ml) was added formic acid (135 ml) at below 0 °C. The resulting reaction solution was stirred at below 0 °C for 1 h before addition of $CHCl_3$. The organic solution was separated, washed with sat. aq. $NaHCO_3$ solution and brine, and dried ($Na_2SO_4$). Concentration and subsequent silica gel column chromatography (EtOAc-hexane = 1:5) gave hydroxy diacetate **7** (1.09 g, 1.68 mmol, 53%, 3 steps) as a colorless oil. (+)-**7**: $[\alpha]^{20}_D = +3.7$ (*c* 0.9, $CHCl_3$); $\delta_H(CDCl_3)$ 1.02–1.03 (21H, m, *iso*-Pr), 1.91 (3H, s, Ac), 2.03 (3H, s, Ac), 2.38 (1H, m, OH), 2.51 (1H, m, CH), 2.63 (1H, m, CH), 3.36 (1H, m, C*H*HOH), 3.50 (1H, m, CH*H*OH), 3.88 (3H, s, $OCH_3$), 3.89 (3H, s, $OCH_3$), 3.98 (1H, dd, *J* 11.5, 6.1 Hz, C*H*HOAc), 4.06 (1H, dd, *J* 11.5, 7.6 Hz, CH*H*OAc), 5.06 (1H, d, *J* 7.8 Hz, ArCHOTIPS), 5.68 (1H, d, *J* 10.7 Hz, ArCHOAc), 5.95 (2H, s, $OCH_2O$), 6.75–6.79 (3H, m, ArH), 6.83–6.85 (2H, m, ArH), 6.92 (1H, s, ArH); $\delta_C(CDCl_3)$ 12.7, 18.07, 18.10, 20.8, 21.4, 44.9, 47.6, 55.8, 55.9, 63.2, 63.7, 75.9, 76.2, 101.1, 107.2, 108.2, 109.7, 110.5, 119.3, 121.0, 133.7, 135.5, 147.3, 147.8, 148.7, 149.0, 169.3, 170.9. *Anal*. Found: C, 63.74; H, 7.96. Calcd. for $C_{34}H_{50}O_{10}Si$: C, 68.13; H, 7.79%. (−)-**7**: $[\alpha]^{20}_D = +3.8$ (*c* 1.3, $CHCl_3$).

*(2R,3S)-3-[(R)-(3,4-Dimethoxyphenyl)(triisopropylsilyloxy)methyl]-2-[(S)-(hydroxy)(3,4-methylenedioxyphenyl)methyl]tetramethylene dipivaloate (**8**).* A reaction mixture of alcohol **7** (1.09 g, 1.68 mmol) and $K_2CO_3$ (0.54 g, 3.91 mmol) in MeOH (10 ml) was stirred for 12 h at room temperature before additions of $CHCl_3$ and $H_2O$. The organic solution was separated, washed with brine, and dried ($Na_2SO_4$). Evaporation gave crude triol. To an ice-cooled solution of the crude triol in pyridine (7 ml) was added PivCl (0.44 ml, 3.57 mmol), and then the reaction mixture was stirred at room temperature for 11 h. After additions of EtOAc and $H_2O$, the organic solution was separated, washed with 1 M aq. HCl solution, sat. aq. $NaHCO_3$ solution, and brine, and dried ($Na_2SO_4$). After evaporation, the residue was applied to silica gel column chromatography (EtOAc-hexane = 1:5) to give dipivaloate **8** (1.04 g, 1.42 mmol, 85%, 2 steps) as a colorless oil, $[\alpha]^{20}_D = +44$ (*c* 1.1, $CHCl_3$); $\delta_H(CDCl_3)$ 1.04–1.14 (21H, m, *iso*-Pr), 1.04 (9H, s, Piv), 1.24 (9H, s, Piv), 2.38 (1H, m, CH), 2.42 (1H, m, CH), 3.40 (1H, dd, *J* 11.2, 3.9 Hz, CH*H*OPiv), 3.61 (1H, dd, *J* 11.2, 7.3 Hz, C*H*HOPiv), 3.88 (3H, s, $OCH_3$), 3.93 (3H, s, $OCH_3$), 4.36 (1H, dd, *J* 11.2, 8.8 Hz, CH*H*OPiv), 4.45 (1H, d, *J* 8.8 Hz, ArC*H*OH), 4.59 (1H, dd, *J* 11.2, 5.4 Hz, C*H*HOPiv), 5.29 (1H, d, *J* 3.9 Hz, ArCHOTIPS), 5.36 (1H, s, OH), 5.92 (2H, s, $OCH_2O$), 6.71 (2H, s, ArH), 6.82–6.85 (3H, m, ArH), 7.01 (1H, s, ArH); $\delta_C(CDCl_3)$ 12.5, 18.0, 27.0, 27.2, 38.5, 38.7, 42.6, 47.3, 55.7, 55.8, 62.9, 65.9, 71.6, 74.8, 100.9, 106.7, 108.0, 109.8, 110.9, 118.8, 120.4, 134.8, 137.1, 147.2, 147.9, 148.4, 148.7, 177.9. *Anal*. Found: C, 65.93; H, 8.55. Calcd. for $C_{40}H_{62}O_{10}Si$: C, 65.72; H, 8.55%. (−)-**8**: $[\alpha]^{20}_D = -44$ (*c* 1.6, $CHCl_3$).

*(2S,3R)-2-[(R)-(3,4-Dimethoxyphenyl)(triisopropylsilyloxy)methyl]-3-(3,4-methylenedioxybenzoyl)tetramethylene dipivaloate (**9**).* A reaction mixture of benzyl alcohol **8** (1.13 g, 1.55 mmol), PCC (0.41 g, 1.90 mmol), and MS 4A (50 mg) in $CH_2Cl_2$ (10 ml) was stirred at room temperature for 16 h before addition of dry ether. The mixture was filtered, and then the filtrate was concentrated. The residue was applied to silica gel column chromatography (EtOAc-hexane = 1:6) to give ketone **9** (0.94 g, 1.29 mmol, 83%) as a colorless oil, $[\alpha]^{20}_D = +36$ (*c* 0.8, $CHCl_3$); $\delta_H(CDCl_3)$ 0.92–0.93 (21H, m, *iso*-Pr), 0.98 (9H, s, *tert*-Bu), 1.02 (9H, s, *tert*-Bu), 2.37 (1H, m, 2-H), 3.85 (3H, s, $OCH_3$), 3.89 (3H, s, $OCH_3$), 4.03 (1H, m, 3-H), 4.26 (1H, dd, *J* 11.9, 6.8 Hz, C*H*HOPiv), 4.35 (1H, dd, *J* 10.5, 8.3 Hz, C*H*HOPiv), 4.41 (1H, dd, *J* 10.5, 6.6 Hz, CH*H*OPiv), 4.51 (1H, dd, *J* 11.9, 4.1 Hz, CH*H*OPiv), 5.07 (1H, d, *J* 3.9 Hz, ArCHOTIPS), 6.03 (2H, s, $OCH_2O$), 6.81–6.83 (3H, m, ArH), 6.93 (1H, s, ArH), 7.42 (1H, d, *J* 2.1 Hz, ArH), 7.51 (1H, dd, *J* 8.3, 2.1 Hz, ArH); $\delta_C(CDCl_3)$ 12.4, 17.89, 17.93,

26.90, 26.94, 38.5, 38.6, 42.1, 47.9, 55.7, 55.9, 62.2, 64.9, 73.8, 101.8, 107.7, 108.3, 109.6, 110.7, 118.6, 124.9, 132.5, 135.3, 148.2, 148.3, 148.7, 151.8, 177.9, 178.0, 197.9. *Anal*. Found: C, 65.77; H, 8.21. Calcd. for $C_{40}H_{60}O_{10}Si$: C, 65.90; H, 8.30%. (−)-**9**: $[\alpha]^{20}_D = -36$ (*c* 1.6, $CHCl_3$).

*(2R,3S,4S,5S)-2-(3,4-Dimethoxyphenyl)-5-(3,4-methylenedioxyphenyl)-3,4-bis(pivaloyloxymethyl)tetrahydrofuran (**11**).* To an ice-cooled solution of silyloxy ketone **9** (0.80 g, 1.10 mmol) in THF (20 ml) containing AcOH (0.22 ml) was added TBAF (8.80 ml, 1 M in THF, 8.80 mmol). The reaction solution was stirred at room temperature for 30 min before addition of sat. aq. $NaHCO_3$ solution and EtOAc. The organic solution was separated, washed with brine, and dried ($Na_2SO_4$). Concentration followed by silica gel column chromatography (EtOAc-hexane = 1:3) gave unstable hemiacetal **10** (0.55 g, 0.96 mmol, 87%) as a colorless oil. The reaction mixture of unstable hemiacetal **10** (50 mg, 0.087 mmol) and 20% $Pd(OH)_2/C$ (50 mg) in EtOAc (20 ml) was stirred at ambient temperature under $H_2$ gas for 5 min. After filtration, the resulting filtrate was concentrated. The residue was applied to silica gel column chromatography (EtOAc-hexane = 1:7) to give tetrahydrofuran derivative **11** (21 mg, 0.038 mmol, 44%) as a colorless oil, $[\alpha]^{20}_D = -20$ (*c* 0.3, $CHCl_3$). NMR data agreed with those in the literature.[10)]

*(2R,3S,4R,5R)-2-(3,4-Dimethoxyphenyl)-5-(3,4-methylenedioxyphenyl)-3,4-bis(pivaloyloxymethyl)tetrahydrofuran (**12**) and conversion to (2R,3S,4R,5R)-3,4-bis(hydroxymethyl)-2-(3,4-dimethoxyphenyl)-5-(3,4-methylenedioxyphenyl)tetrahydrofuran (**13**).* A reaction mixture of unstable hemiacetal **10** (0.41 g, 0.72 mmol) and 20% Pd $(OH)_2/C$ (0.50 g) in EtOAc (60 ml) and EtOH (60 ml) was stirred at ambient temperature under $H_2$ gas for 4 min. After filtration, the resulting filtrate was concentrated. The residue was applied to silica gel column chromatography (EtOAc-hexane = 1:6) to give unstable tetrahydrofuran **12** (0.21 g, 0.38 mmol, 53%) as a colorless oil, $[\alpha]^{20}_D = +22$ (*c* 1.8, $CHCl_3$); $\delta_H(CDCl_3)$ 1.09 (9H, s, Piv), 1.17 (9H, s, Piv), 2.83 (1H, m, 4-H), 2.95 (1H, m, 3-H), 3.88 (3H, s, $OCH_3$), 3.89–3.94 (2H, overlapped, $CH_2OPiv$), 3.90 (3H, s, $OCH_3$), 4.22 (1H, dd, *J* 11.6, 7.2 Hz, C*H*HOPiv), 4.27 (1H, dd, *J* 11.6, 7.7 Hz, CH*H*OPiv), 5.04 (1H, d, *J* 9.2 Hz), 5.51 (1H, d, *J* 5.6 Hz), 5.94 (2H, s, $OCH_2O$), 6.77 (1H, d, *J* 8.0 Hz, ArH), 6.84–6.94 (5H, m, ArH); $\delta_C(CDCl_3)$ 27.0, 27.2, 38.5, 45.5, 50.2, 55.9, 56.0, 61.0, 62.2, 82.7, 82.8, 101.0, 106.6, 108.2, 109.1, 111.2, 118.6, 119.1, 132.3, 134.7, 146.9, 147.7, 148.9, 149.3, 178.1. (−)-**12**:, $[\alpha]^{20}_D = -22$ (*c* 1.6, $CHCl_3$). A reaction solution of unstable pivaloyl ester **12** (0.21 g, 0.38 mmol) in EtOH (4.3 ml) and 1 M aq. NaOH solution (5.5 ml) was stirred at room temperature for 5 h before additions of $CHCl_3$ and $H_2O$. The organic solution was separated, washed with brine, and dried ($Na_2SO_4$). After evaporation, the resulting residue was applied to silica gel column chromatography (EtOAc-hexane = 1:1) to give corresponding diol **13** (94 mg, 0.24 mmol, 63%) as a colorless oil, $[\alpha]^{20}_D = +74$ (*c* 1.0, $CHCl_3$); $\delta_H(CDCl_3)$ 2.70 (2H, m, 3-H, 4-H), 2.93 (1H, s, OH), 3.29 (1H, m, OH), 3.58–3.69 (2H, m, C$H_2$OH), 3.73–3.86 (2H, m, C$H_2$OH), 3.86 (3H, s, $OCH_3$), 3.88 (3H, s, $OCH_3$) 4.91 (1H, d, *J* 8.9 Hz), 5.42 (1H, d, *J* 4.9 Hz), 5.94 (2H, s, $OCH_2O$), 6.79 (2H, s, ArH), 6.81–6.85 (2H, m, ArH), 6.89 (1H, dd, *J* 8.2, 1.8 Hz, ArH), 6.93 (1H, d, *J* 1.8 Hz, ArH); $\delta_C(CDCl_3)$ 48.3, 54.0, 55.8, 55.9, 59.6, 59.7, 80.9, 82.9, 100.9, 106.2, 108.1, 108.9, 111.1, 118.3, 118.7, 132.9, 134.7, 146.7, 147.7, 148.6, 149.1. EIMS *m/z* (%): 388 (88), 207 (93), 194 (100), 189 (97), 151 (61). HREIMS ($M^+$): calcd. for $C_{21}H_{24}O_7$, 388.1522; found, 388.1522. (−)-**13**: $[\alpha]^{20}_D = -74$ (*c* 0.9, $CHCl_3$).

*(2R,3S,4R,5R)-3,4-Bis(methoxymethyl)-2-(3,4-dimethoxyphenyl)-5-(3,4-methylenedioxyphenyl)tetrahydrofuran (**14**).* To an ice-cooled suspension of NaH (25 mg, 60% oil suspension, 0.63 mmol) in THF (4 ml) was added a solution of (+)-diol **13** (50 mg, 0.13 mmol) in THF (5 ml). After the resulting solution was stirred at 0 °C for 30 min, MeI (0.50 ml, 8.03 mmol) was added, and then the reaction mixture was stirred at room temperature for 5 h before additions of sat. aq. $NH_4Cl$ solution and EtOAc. The organic solution was separated, washed with brine, and dried ($Na_2SO_4$). After concentration, the resulting residue was applied to silica gel column chromatography (EtOAc-hexane = 1:2) to give virgatusin stereoisomer **14** (36 mg, 0.086 mmol, 66%) as a colorless oil, $[\alpha]^{20}_D = +42$ (*c* 0.8, $CHCl_3$); $\delta_H(CDCl_3)$ 2.68 (1H, m, 3-H), 2.75 (1H, m, 4-H), 3.12 (1H, dd, *J* 9.8, 5.4 Hz, C*H*HOCH$_3$), 3.13 (3H, s, $OCH_3$), 3.22 (1H, d, *J* 9.8, 4.3 Hz, CH*H*OCH$_3$), 3.31 (3H, s, $OCH_3$), 3.44 (1H, dd, *J* 9.3, 5.8 Hz, C*H*HOCH$_3$), 3.62 (1H, dd, *J* 9.3, 8.4 Hz, CH*H*OCH$_3$), 3.87 (3H, s, $OCH_3$) 3.89 (3H, s, $OCH_3$), 4.99 (1H, d, *J* 8.3 Hz, 2-H), 5.42 (1H, d, *J* 6.0 Hz, 4-H), 5.95 (2H, s, $OCH_2O$), 6.79 (1H, d, *J* 8.1 Hz, ArH), 6.83–6.86 (2H, m, ArH), 6.91–6.96 (3H, m, ArH); $\delta_C(CDCl_3)$ 46.0, 51.4, 55.8, 55.9, 58.5, 58.8, 69.2, 70.4, 82.6, 83.4, 100.8, 107.0, 107.7, 109.2, 110.9, 118.3, 119.4, 133.7, 135.7, 146.4, 147.4, 148.4, 149.0; *m/z* (EI) 416 (40), 384 (32), 224 (53), 189 (100), 165 (55), 149 (53). HREIMS ($M^+$): calcd. for $C_{23}H_{28}O_7$, 416.1835; found, 416.1832. ≫99% ee (HPLC, DAICEL OD-H chiral column, detected at 280 nm, 1 ml $min^{-1}$, 10% *iso*-PrOH in hexane, *t*R 24 min). (−)-**14**: $[\alpha]^{20}_D = -42$ (*c* 0.6, $CHCl_3$), ≫99% ee (*t*R 19 min).

*Antibacterial and antifungal activity test.* The antimicrobiological test was performed by the same method as that previously described.[13,14)]

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