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First enantioselective synthesis of (−)- and (+)-virgatusin, tetra-substituted tetrahydrofuran lignan

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The first highly enantioselective syntheses of tetra-substituted tetrahydrofuran lignan, (−)- and (+)-virgatusin, were achieved. Hemiacetal **15** was stereoselectively obtained from Evans's *syn*-aldol product **8** as a single isomer. This hemiacetal **15** was converted to (−)-virgatusin *via* hydrogenolysis. (+)-Virgatusin was also synthesized through the same process. The enantiomeric excess of the both enantiomers was determined as more than 99% ee.

Introduction

(−)-Virgatusin, a tetra-substituted tetrahydrofuran lignan, was isolated from *Phylanthus amarus*[1] with other lignans. This plant has been used by natives as a herbal drug for liver. The plant extract from this species exhibited inhibition of the endogenous DNA polymerase of the hepatitis B virus.[2] Because lignans cover a wide spectrum of biological activity,[3–5] nothing is definitively known regarding the biological activity of (−)-virgatusin. Recently, related compounds have been isolated.[6–9] Lignans are widely distributed among many kinds of plant. Research on the biological activity of lignans is very important for the effective utilization of this bioresource.

Since some lignans are biosynthesized as an enantiomeric mixture,[10] the synthetic study of lignans would contribute to biological research. (−)-Virgatusin has four chiral centers on the tetrahydrofuran ring. There is a considerable interest in the synthesis of highly substituted tetrahydrofuran rings. In the case of other types of tetra-substituted tetrahydrofuran lignans, racemic syntheses are known.[11–14] Only Yoda and coworkers reported the synthesis of (−)-virgatusin utilizing resolution of the starting material.[15] Our challenge is the first enantioselective synthesis of virgatusin to give enantiomerically pure (−)- and (+)-virgatusin, respectively. This project will lead to the precise determination of biological activity.

A key step is the construction of an ethereal bond between two benzylic positions. The S_N1 cyclization by benzylic cation produced at the 7′ position of **2** will predominately give the undesired steric configuration. On the other hand, S_N2 cyclization of the secondary benzyl mesylate derived from **2** will fail because of a Friedel–Craft type reaction.[16] Yoda and coworkers succeeded in the conversion of an α,β-mixture of hemiacetal **3** to **4** by using Et_3SiH and $TiCl_4$ by control of the temperature.[15] Without temperature control, the benzylic positions would be epimerized under this condition. If the stereoselective preparation of hemiacetal **5** is possible, the tetra-substituted tetrahydrofuran **6** could be obtained as a single isomer by treatment of **5** with H_2 and catalyst (Fig. 1). It could be expected that H_2 would add to the 7′C and oxygen of the hemiacetal, giving desired configuration as a hydrogenolysis product. It is important for this project to get stereoselectively the C7′ position of hemiacetal **5**.

This article describes the first highly enantioselective synthesis of (−)- and (+)-virgatusin. In this work, the stereoselective construction of the tetra-substituted tetrahydrofuran ring was achieved by a new method.

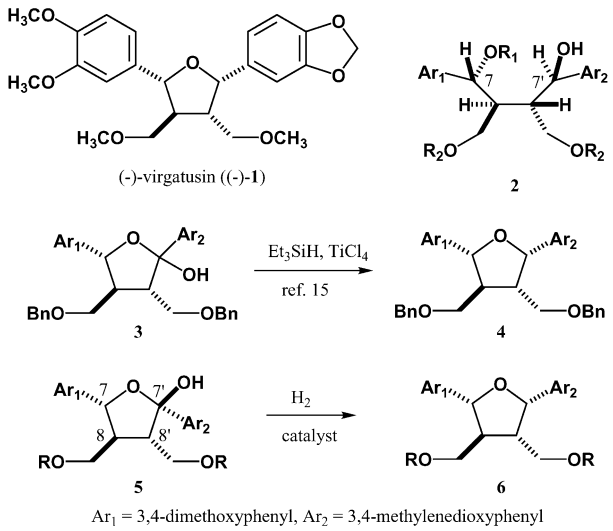

Fig. 1

Results and discussion

According to the procedure by Evans,[17] *syn*-aldol product **8** was obtained from (*R*)-acyl oxazolidinone **7** and 3,4-dimethoxybenzaldehyde in 93% yield. After protection of the benzylic hydroxy group as the triisopropylsilyl ether by treatment with triisopropylsilyl triflate and 2,6-lutidine (100% yield), the auxiliary was reductively removed to give the primary alcohol **10** in 62% yield. Oxidative cleavage of the olefin by employing OsO_4 and $NaIO_4$ gave the hemiacetal, which was exposed to pyridinium chlorochromate oxidation to afford lactone **11** in 73% yield through 3 steps. The aldol condensation of lactone **11** with piperonal by using KHMDS as base gave aldol product **12** in 93% yield. Though the major product was the *erythro* isomer,[18] the *threo* isomer could been seen in the NMR spectrum (*erythro* : *threo* = 9 : 1). Lactone **12** was reduced to the corresponding diol by $LiBH_4$, which led to dipivaloyl ester **13** as a single isomer by using pivaloyl chloride and pyridine in 69% yield through 2 steps. The resulting benzyl alcohol was converted to ketone **14** by pyridinium chlorochromate oxidation in 94% yield (Scheme 1).

Conversion of ketone **14** to hemiacetal **15** was achieved by employing tetra-*n*-butylammonium fluoride and acetic acid in 87% yield (Scheme 1). Fortunately, this hemiacetal **15** was

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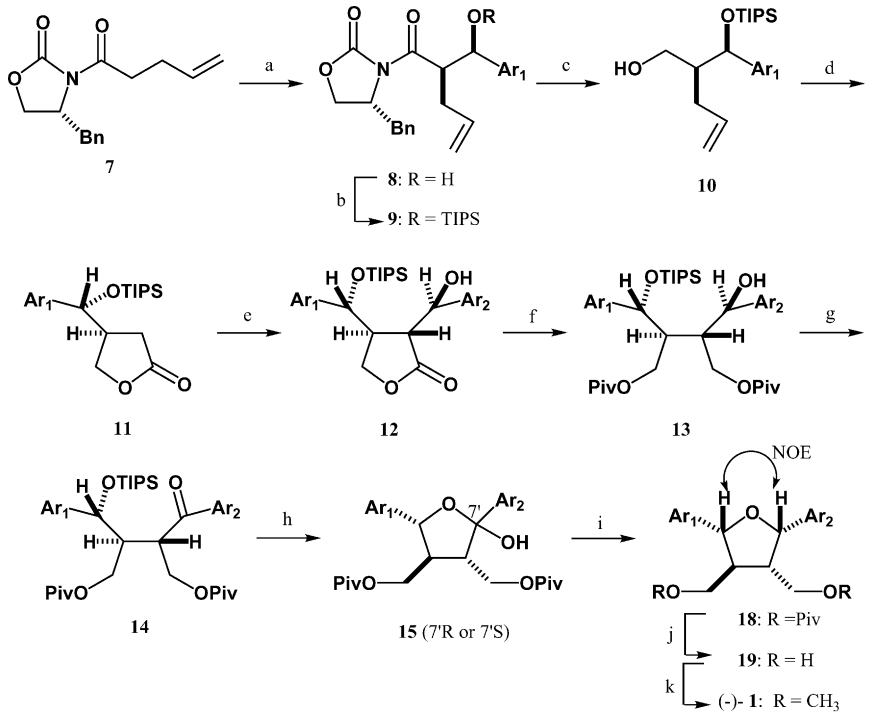


Ar_1 = 3,4-dimethoxyphenyl, Ar_2 = 3,4-methylenedioxyphenyl

Scheme 1 Synthesis of (−)-virgatusin (a) $(n\text{-Bu})_2$BOTf, Et_3N, 3,4-dimethoxybenzaldehyde, CH_2Cl_2, −78 to 0 °C, 1 h (93% yield); (b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt, 1 h (100% yield); (c) $LiBH_4$, MeOH, THF, rt, 16 h (62% yield); (d) (1) OsO_4, NMO, aq. acetone, *tert*-BuOH, rt, 48 h, (2) $NaIO_4$, MeOH, rt, 16 h, (3) PCC, CH_2Cl_2, rt, 16 h (73% yield, 3 steps); (e) KHMDS, piperonal, THF, −70 °C, 1 h (93% yield, 90% de); (f) (1) $LiBH_4$, THF, −78 to 0 °C, 24 h, (2) PivCl, pyridine, rt, 30 min (69% yield, 2 steps); (g) PCC, MS 4 Å, CH_2Cl_2, rt, 16 h (94% yield); (h) $(n\text{-Bu})_4NF$, AcOH, THF, rt, 16 h (87%); (i) H_2, $Pd(OH)_2/C$, EtOAc, rt, 1 h (79% yield); (j) NaOH, aq. EtOH, rt, 20 h (85% yield); (k) NaH, CH_3I, THF, rt, 5 h (88% yield).

obtained as a single isomer. The stereochemistry at the 7′ position could not be determined in this work. In the case of hemiacetal **17**, a mixture of 7′*R* : *S* isomer (1 : 1) was obtained from di(*tert*-butyldiphenylsilyloxy)(triethylsilyloxy) ketone **16** by employing 2% HF in CH_3CN (Scheme 2). This ketone **16** was prepared from alcohol **8** by the almost same process. The benzylic hydroxy group of **8** was prepared as the TES ether. The two primary hydroxy groups were protected as TBDPS ethers instead of dipivaloyl esters. Treatment of this hemiacetal **17** with Et_3SiH and $BF_3.OEt_2$ or $TiCl_4$[15] did not give desired tetrahydrofuran derivative, but many unidentified compounds were obtained. Since hemiacetal **15** was unstable giving a highly polar compound, the next step had to be started immediately. The conversion of hemiacetal **15** to tetrahydrofuran derivative **18** by using Et_3SiH and $BF_3{\cdot}OEt_2$ or $TiCl_4$[15] also failed. However, hydrogenolysis in the presence of $Pd(OH)_2/C$ gave tetrahydrofuran derivative **18** as a single isomer in 79% yield. The benzylic ethereal bonds on the main structure were not cleaved in this work. Though the selective hydrogenolysis of phenolic benzyl ether was reported,[19,20] this is a first report of the selective hydrogenolysis of a hemiacetal. A differential NOE experiment between 7-H and 7′-H confirmed this relative configuration. The mesylation of the benzyl hydroxy group of **13** by using methanesulfonyl chloride and triethylamine gave many unidentified products. This fact means that S_N2 etherification to construct the tetrahydrofuran ring was not suitable in this case.

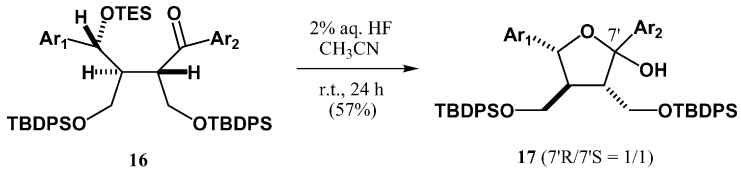
After hydrolysis of pivaloyl ester **18** by exposure to aqueous NaOH solution (85% yield), methylation of the resulting diol by using methyl iodide and NaH gave (−)-virgatusin ((−)-**1**) in 88% yield. The enantiomeric excess of the synthesized pivaloyl ester **18** and (−)-virgatusin ((−)-**1**) was determined as more than 99% ee by a chiral column.

(+)-Virgatusin was also synthesized from (*S*)-acyl oxazolidinone and 3,4-dimethoxybenzaldehyde through the same procedure. The enantiomeric excess was also determined as more than 99% ee.

The first highly enantioselective synthesis of (−)- and (+)-virgatusin was accomplished by employing Evans's *syn*-aldol condensation and stereoselective construction of the hemiacetal, followed by hydrogenolysis through 14 steps in 13% overall yield.

Experimental

Melting point (mp) data are uncorrected. NMR data were measured by a JNM-EX400 spectrometer, IR spectra were determined with a Shimadzu FTIR-8100 spectrophotometer, EIMS data were measured with a JMS-MS700V spectrometer, and optical rotation values were evaluated with a HORIBA SEPA-200 instrument. The silica gel used was Wakogel C-300 (Wako, 200–300 mesh). HPLC analyses were performed with Shimadzu LC-6AD and SPD-6AV instruments. The numbering of compounds was changed to follow IUPAC nomenclature rules.



Ar_1 = 3,4-dimethoxyphenyl, Ar_2 = 3,4-methylenedioxyphenyl

Scheme 2 Conversion of di(*tert*-butyldiphenylsilyloxy)(triethylsilyloxy) ketone **16** to hemiacetal **17**.

(4*R*)-4-Benzyl-3-{(2*R*)-2-[(*R*)-(3,4-dimethoxyphenyl)(hydroxy)-methyl]-4-pentenoyl}-2-oxazolidinone 8

To a solution of (*R*)-oxazolidinone **7** (11.6 g, 0.045 mol) in CH_2Cl_2 (100 ml) was added dibutylboron triflate (49.2 ml, 1 M in CH_2Cl_2, 0.049 mol) and Et_3N (7.20 ml, 0.052 mol) at below 0 °C. After cooling to −65 °C, a solution of 3,4-dimethoxybenzaldehyde (8.33 g, 0.050 mol) in CH_2Cl_2 (20 ml) was added. The reaction solution was stirred at −65 °C for 20 min, and then warmed to 0 °C. After stirring at 0 °C for 1 h, phosphate buffer pH 7 (100 ml), MeOH (140 ml), and 2 : 1 MeOH : 30% H_2O_2 (140 ml) were added. The mixture was stirred at below 10 °C for 1 h, and then evaporated at 30 °C. The resulting residue was dissolved in CH_2Cl_2 and H_2O. The organic solution was separated, washed with sat. aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). After concentration, the residue was applied to silica gel column chromatography (EtOAc : hexane = 1 : 3) to give aldol product **8** (17.7 g, 0.042 mol, 93%) as a colorless oil, $[a]_D^{20} = -93$ (*c* 1.8, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3675, 3013, 2967, 1779, 1692, 1516, 1385, 1264, 1238, 1196, 1140, 1028, 909; $\delta_H(CDCl_3)$ 2.58–2.72 (3H, m, C*H*HAr, CH_2CH=CH$_2$), 2.60 (1H, d, *J* 2.4 Hz, OH), 3.21 (1H, dd, *J* 13.4, 3.2 Hz, CH*H*Ar), 3.81 (1H, d, *J* 9.3 Hz, 5-*H*H), 3.85 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.02 (1H, dd, *J* 9.3, 2.4 Hz, 5-H*H*), 4.38 (1H, m, O=CCH), 4.51 (1H, m, 4-H), 4.89 (1H, dd, *J* 6.6, 2.4 Hz, ArC*H*OH), 5.04 (1H, m, CH=C*H*H), 5.12 (1H, m, CH=CH*H*), 5.80–5.91 (1H, m, C*H*=CH$_2$), 6.80 (1H, d, *J* 8.3 Hz, ArH), 6.90 (1H, dd, *J* 8.3, 2.0 Hz, ArH), 6.99 (1H, d, *J* 2.0 Hz, ArH), 7.16–7.18 (2H, m, ArH), 7.24–7.33 (3H, m, ArH); $\delta_C(CDCl_3)$ 32.5, 38.0, 49.4, 55.5, 55.86, 55.91, 65.8, 74.6, 109.4, 110.8, 117.2, 118.7, 127.3, 128.9, 129.3, 134.0, 135.20, 135.24, 148.6, 148.9, 153.1, 174.5 (Found: C, 67.55; H, 6.48; N, 3.30. $C_{24}H_{27}O_6N$ requires C, 67.75; H, 6.40; N, 3.29%). (+)-**8**: $[a]_D^{20} = +93$ (*c* 1.9, $CHCl_3$).

(4*R*)-4-Benzyl-3-{(2*R*)-2-[(*R*)-(3,4-dimethoxyphenyl)-(triisopropylsilyloxy)methyl-4-pentenoyl]}-2-oxazolidinone 9

To an ice-cooled solution of alcohol **8** (12.7 g, 0.030 mol), 2,6-lutidine (5.92 ml, 0.051 mol) in CH_2Cl_2 (100 ml) was added TIPSOTf (10.3 ml, 0.038 mol). After the reaction solution was stirred at room temperature for 1 h, sat. aq. $NaHCO_3$ solution was added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After concentration, the residue was applied to silica gel column chromatography (EtOAc : hexane = 1 : 3) to give silyl ether **9** (17.5 g, 0.030 mol, 100%) as a colorless oil, $[a]_D^{20} = -73$ (*c* 1.1, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2948, 1779, 1686, 1510, 1466, 1385, 1262, 1238, 1102; $\delta_H(CDCl_3)$ 1.01–1.02 (20H, m, *iso*-Pr), 1.15 (1H, m, *iso*-Pr), 2.59 (1H, dd, *J* 13.7, 9.8 Hz, PhC*H*H), 2.67 (1H, m, C*H*HCH=CH$_2$), 2.85 (1H, m, CH*H*CH=CH$_2$), 3.09 (1H, dd, *J* 13.7, 2.9 Hz, PhCH*H*), 3.47 (1H, dd, *J* 8.3, 7.8 Hz, 5-*H*H), 3.82 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.87 (1H, dd, *J* 8.3, 2.0 Hz, 5-H*H*), 4.10 (1H, m, O=CCH), 4.51 (1H, m, 4-H), 4.83 (1H, d, *J* 8.3 Hz, ArCHOTIPS), 5.03 (1H, m, CH=C*H*H), 5.13 (1H, m, CH=CH*H*), 5.83–5.93 (1H, m, C*H*=CH$_2$), 6.71 (1H, d, *J* 8.3 Hz, ArH), 6.78 (1H, dd, *J* 8.3, 2.0 Hz, ArH), 7.00 (1H, d, *J* 2.0 Hz, ArH), 7.13–7.14 (2H, m, ArH), 7.22–7.33 (3H, m, ArH); $\delta_C(CDCl_3)$ 12.5, 12.7, 17.9, 18.0, 34.3, 37.9, 51.9, 55.7, 55.8, 55.9, 65.6, 77.2, 109.94, 109.99, 110.1, 116.8, 119.3, 127.2, 128.8, 129.4, 135.28, 135.34, 135.7, 148.5, 152.8, 173.8 (Found: C, 68.05; H, 8.08; N, 2.50. $C_{33}H_{47}O_6NSi$ requires C, 68.12; H, 8.14; N, 2.41%). (+)-**9**: $[a]_D^{20} = +73$ (*c* 0.89, $CHCl_3$).

(2*S*)-2-[(*R*)-(3,4-Dimethoxyphenyl)(triisopropylsilyloxy)methyl]-4-penten-1-ol 10

To an ice-cooled solution of $LiBH_4$ (0.90 g, 0.041 mol) in THF (100 ml) was added MeOH (1.49 ml) and acyloxazolidinone **9** (9.76 g, 0.017 mol) in THF (80 ml), and then the resulting reaction solution was stirred at room temperature for 16 h before addition of sat. aq. NH_4Cl solution. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration and subsequent silica gel column chromatography (EtOAc : hexane = 1 : 3) gave alcohol **10** (4.50 g, 0.011 mol, 62%) as a colorless oil, $[a]_D^{20} = +15$ (*c* 0.85, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3461, 2946, 1516, 1464, 1260, 1157, 1142, 1049, 1028, 884, 818; $\delta_H(CDCl_3)$ 0.96–1.08 (20H, m, *iso*-Pr), 1.15 (1H, m, *iso*-Pr), 1.75 (1H, m, 3-*H*H), 1.95 (1H, m, 3-H*H*), 2.27 (1H, m, 2-H), 3.28 (1H, m, OH), 3.48 (1H, m, 1-*H*H), 3.62 (1H, m, 1-H*H*), 3.88 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.97 (1H, d, *J* 3.9 Hz, ArCHOTIPS), 5.02–5.08 (2H, m, CH=CH_2), 5.81 (1H, m, C*H*=CH$_2$), 6.79–6.83 (2H, m, ArH), 6.98 (1H, d, *J* 1.5 Hz, ArH); $\delta_C(CDCl_3)$ 12.1, 17.9, 18.0, 32.6, 46.8, 55.76, 55.79, 63.3, 77.9, 110.3, 110.4, 116.6, 119.5, 133.2, 136.8, 148.3, 148.5 (Found: C, 67.61; H, 9.76. $C_{23}H_{40}O_4Si$ requires C, 67.60; H, 9.87%). (−)-**10**: $[a]_D^{20} = -15$ (*c* 0.98, $CHCl_3$).

(3*S*)-3-[(*R*)-(3,4-Dimethoxyphenyl)(triisopropylsilyloxy)methyl]-4-butanolide 11

A reaction solution of olefin **10** (3.65 g, 8.93 mmol), 4-methylmorpholine *N*-oxide (1.29 g, 11.0 mmol), and OsO_4 (aq. 2% solution, 1 ml) in acetone (80 ml), *tert*-BuOH (20 ml), and H_2O (20 ml) was stirred at room temperature for 48 h before addition of $Na_2S_2O_3$ (1 g). After the mixture was concentrated, the residue was dissolved in EtOAc and H_2O. The organic solution was evaporated, washed with brine, and dried (Na_2SO_4). Evaporation gave crude glycol. A reaction mixture of the crude glycol and $NaIO_4$ (2.35 g, 11.0 mmol) in MeOH (30 ml) was stirred at room temperature for 16 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). Concentration and subsequent silica gel column chromatography (EtOAc : hexane = 1 : 1) gave hemiacetal (3.38 g, 8.23 mmol, 92%) as a colorless oil. A reaction mixture of hemiacetal (3.38 g, 8.32 mmol) and PCC (2,13 g, 9.88 mmol) in CH_2Cl_2 (30 ml) containing MS 4 Å (0.5 g) was stirred at room temperature for 16 h before addition of dry ether. After filtration, the filtrate was concentrated. The residue was applied to silica gel column chromatography (5% EtOAc in toluene) to give lactone **11** (2.67 g, 6.53 mmol, 79%) as colorless crystals, mp 91–92 °C (*iso*-Pr$_2$O), $[a]_D^{20} = +49$ (*c* 0.55, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2948, 1775, 1514, 1466, 1260, 1176, 1154, 1140, 1094, 1026, 1013, 909, 884; $\delta_H(CDCl_3)$ 0.96–1.03 (21H, m, *iso*-Pr), 2.55 (1H, dd, *J* 17.6, 9.0 Hz, 2-*H*H), 2.66 (1H, dd, *J* 17.6, 7.8 Hz, 2-H*H*), 2.87 (1H, ddddd, *J* 9.0, 7.8, 7.8, 6.8, 6.2 Hz, 3-H), 3.88 (6H, s, OCH_3), 4.10 (1H, dd, *J* 9.3, 6.8 Hz, 4-*H*H), 4.15 (1H, dd, *J* 9.3, 7.8 Hz, 4-H*H*), 4.72 (1H, d, *J* 6.2 Hz, ArCHOTIPS), 6.78 (1H, dd, *J* 8.3, 2.0 Hz, ArH), 6.81 (1H, d, *J* 8.3 Hz, ArH), 6.87 (1H, d, *J* 2.0 Hz, ArH); $\delta_C(CDCl_3)$ 12.4, 17.9, 18.0, 31.0, 44.6, 55.8, 69.7, 75.5, 109.2, 110.7, 118.7, 134.5, 148.8, 149.1, 176.8 (Found: C, 64.61; H, 8.96. $C_{22}H_{36}O_5Si$ requires C, 64.67; H, 8.88%). (−)-**11**: $[a]_D^{20} = -49$ (*c* 0.98, $CHCl_3$).

(2*R*,3*S*)-3-[(*R*)-(3,4-Dimethoxyphenyl)(triisopropylsilyloxy)-methyl]-2-[(*R*)-(hydroxy)(3,4-methylenedioxyphenyl)methyl]-4-butanolide 12

To a solution of KHMDS (8.47 ml, 0.5 M toluene solution, 4.24 mmol) in THF (20 ml) was added a solution of lactone **11** (1.44 g, 3.52 mmol) in THF (10 ml) at −70 °C. After stirring at −70 °C for 15 min, piperonal (0.58 g, 3.86 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 aldol product **12** (1.84 g, 3.29 mmol, 93%, a mixture of *erythro* : *threo* = 9 : 1) as a colorless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3497, 2946, 1759, 1516, 1256, 1240, 1042; $\delta_H(CDCl_3)$ 0.87–1.00 (21H, m, *iso*-Pr), 2.73 (1H, d, *J* 4.4 Hz, OH), 2.79 (1H, dd, *J* 5.4, 2.9 Hz, 2-H), 2.88

(1H, dddd, *J* 8.3, 5.4, 4.6, 3.9 Hz, 3-H), 3.78 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.33 (1H, dd, *J* 8.8, 4.6 Hz, 4-*H*H), 4.40 (1H, dd, *J* 8.8, 8.3 Hz, 4-H*H*), 4.65 (1H, d, *J* 3.9 Hz, ArCHOTIPS), 5.20 (1H, dd, *J* 4.4, 2.9 Hz, ArC*H*OH), 5.96 (1H, s, OC*H*HO), 5.97 (1H, s, OCH*H*O), 6.48 (1H, d, *J* 2.0 Hz, ArH), 6.54 (1H, dd, *J* 8.3, 1.5 Hz, ArH), 6.60 (1H, d, *J* 1.5 Hz, ArH), 6.65–6.71 (3H, m, ArH); $\delta_C(CDCl_3)$ 12.5, 17.90, 17.94, 43.0, 48.8, 55.58, 55.62, 70.0, 72.5, 75.5, 101.2, 105.9, 107.8, 109.1, 110.4, 118.6, 133.3, 135.0, 147.0, 147.7, 148.3, 148.6, 178.5 (Found: C, 64.35; H, 7.62. $C_{30}H_{42}O_8Si$ requires C, 64.49; H, 7.58%).

(2*S*,3*S*)-2-[(*R*)-(3,4-Dimethoxyphenyl)(triisopropylsilyloxy)-methyl]-3-[(*R*)-(hydroxy)(3,4-methylenedioxyphenyl)methyl]-tetramethylene dipivaloate 13

To a solution of $LiBH_4$ (0.59 g, 27.1 mmol) in THF (10 ml) was added a solution of lactone **12** (1.96 g, 3.51 mmol) in THF (10 ml) at −10 °C. After the reaction solution was stirred at 0 °C for 24 h, sat. aq. NH_4Cl solution was added at below 0 °C, and then concentrated. The residue was dissolved in EtOAc and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave crude diol. To an ice-cooled solution of crude diol in pyridine (5 ml) was added PivCl (0.56 ml, 4.53 mmol), and then the reaction mixture was stirred at room temperature for 30 min. After additions of CH_2Cl_2 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). Evaporation and subsequent silica gel column chromatography (EtOAc : hexane = 1 : 5) gave pivaloyl ester **13** (1.77 g, 2.42 mmol, 69%) as a colorless oil, $[\alpha]_D^{20} = +58$ (*c* 0.57, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3629, 2975, 1723, 1626, 1254, 1157, 1042, 930; $\delta_H(CDCl_3)$ 0.97–1.02 (21H, m, *iso*-Pr), 1.21 (9H, s, Piv), 1.24 (9H, s, Piv), 2.12 (1H, m, 2-H), 2.46 (1H, m, 3-H), 2.77 (1H, d, *J* 4.4 Hz, OH), 3.76 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.17 (1H, dd, *J* 11.2, 8.3 Hz, PivOC*H*H), 4.24 (1H, dd, *J* 11.2, 3.4 Hz, PivOCH*H*), 4.38–4.43 (2H, m, $PivOCH_2$), 4.80 (1H, dd, *J* 4.4, 3.5 Hz, 1-H), 4.99 (1H, d, *J* 4.4 Hz, ArCHOTIPS), 5.91 (1H, d, *J* 8.8 Hz, OC*H*HO), 5.92 (1H, d, *J* 8.8 Hz, OCH*H*O), 6.40 (1H, s, ArH), 6.52 (1H, s, ArH), 6.58–6.65 (3H, m, ArH), 6.80 (1H, d, *J* 8.3 Hz, ArH); $\delta_C(CDCl_3)$ 12.7, 18.1, 27.2, 27.3, 38.75, 38.81, 41.7, 43.8, 55.4, 55.7, 63.3, 63.4, 73.0, 74.8, 101.0, 106.1, 107.6, 109.0, 110.3, 118.5, 118.7, 135.6, 136.6, 146.4, 147.5, 148.0, 148.5, 178.3, 178.7 (Found: C, 65.96; H, 8.58. $C_{40}H_{62}O_{10}Si$ requires C, 65.72; H, 8.55%). (−)-**13**: $[\alpha]_D^{20} = -58$ (*c* 1.4, $CHCl_3$).

(2*S*,3*S*)-2-[(*R*)-(3,4-Dimethoxyphenyl)(triisopropylsilyloxy)-methyl]-3-(3,4-methylenedioxybenzoyl)tetramethylene dipivaloate 14

A reaction mixture of benzyl alcohol **13** (0.51 g, 0.70 mmol), PCC (0.19 g, 0.88 mmol), and MS 4 Å (0.2 g) in CH_2Cl_2 (20 ml) was stirred at room temperature for 16 h before addition of dry ether. After concentration of the filtrate, the residue was applied to silica gel column chromatography (5% EtOAc in toluene) to give ketone **14** (0.48 g, 0.66 mmol, 94%) as a colorless oil, $[\alpha]_D^{20} = +14$ (*c* 0.80, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3021, 1725, 1676, 1516, 1443, 1256, 1157, 1042; $\delta_H(CDCl_3)$ 0.99–1.04 (21H, m, *iso*-Pr), 1.19 (18H, s, Piv), 2.52 (1H, m, 3-H), 3.79 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.97 (1H, dd, *J* 11.7, 4.9 Hz, C*H*HOPiv), 4.13 (1H, dd, *J* 11.7, 4.4 Hz, CH*H*OPiv), 4.13–4.18 (1H, m, 2-H), 4.45 (1H, dd, *J* 10.7, 9.8 Hz, C*H*HOPiv), 4.53 (1H, dd, *J* 10.7, 3.4 Hz, CH*H*OPiv), 4.95 (1H, d, *J* 6.4 Hz, 4-H), 6.05 (2H, s, OCH_2O), 6.66 (1H, dd, *J* 8.3, 2.0 Hz, ArH), 6.75 (1H, d, *J* 8.3 Hz, ArH), 6.80 (1H, d, *J* 8.3 Hz, ArH), 6.87 (1H, d, *J* 2.0 Hz, ArH), 7.36 (1H, d, *J* 1.5 Hz, ArH), 7.46 (1H, dd, *J* 8.3, 1.5 Hz, ArH); $\delta_C(CDCl_3)$ 12.5, 18.0, 18.1, 27.0, 27.1, 38.5, 38.7, 43.7, 46.7, 55.7, 55.9, 61.5, 62.8, 73.7, 101.9, 107.8, 108.4, 109.8, 110.6, 119.1, 124.9, 131.2, 134.8, 148.3, 148.7, 148.9, 151.9, 177.8, 178.0, 197.6 (Found: C, 65.65; H, 8.30. $C_{40}H_{60}O_{10}Si$ requires C, 65.90; H, 8.30%). (−)-**14**: $[\alpha]_D^{20} = -14$ (*c* 0.82, $CHCl_3$).

(2*R*,3*S*,4*S*,5*S*)-2-(3,4-Dimethoxyphenyl)-5-(3,4-methylenedioxyphenyl)-3,4-bis(pivaloyloxymethyl)-tetrahydrofuran 18

To an ice-cooled solution of silyl ether **14** (0.98 g, 1.23 mmol) in THF (20 ml) was added AcOH (93 µl) and $(n\text{-}Bu)_4NF$ (1.48 ml, 1 M THF solution, 1.48 mmol). The reaction solution was stirred at room temperature for 16 h before addition of sat. aq. $NaHCO_3$ solution. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration and subsequent silica gel column chromatography (EtOAc : hexane = 3 : 1) gave unstable hemiacetal **15** (0.61 g, 1.07 mmol, 87%) as a colorless oil; $\delta_H(CDCl_3)$ 1.196 (9H, s, Piv), 1.203 (9H, s, Piv), 3.34 (1H, m, 4-H), 3.87 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.81–3.91 (1H, m, 3-H), 4.26 (1H, dd, *J* 11.2, 6.8 Hz, C*H*HOPiv), 4.36 (1H, dd, *J* 11.2, 4.2 Hz, CH*H*OPiv), 4.77 (1H, d, *J* 12.7 Hz, C*H*HOPiv), 4.83 (1H, d, *J* 12.7 Hz, CH*H*OPiv), 5.33 (1H, d, *J* 4.4 Hz, 5-H), 5.99 (2H, s, OCH_2O), 6.83–6.86 (2H, m, ArH), 6.90–6.92 (2H, m, ArH), 7.08 (1H, d, *J* 1.5 Hz, ArH), 7.12 (1H, dd, *J* 8.3, 1.5 Hz, ArH); $\delta_C(CDCl_3)$ 27.1, 27.2, 38.8, 54.1, 55.8, 55.9, 59.8, 65.0, 84.1, 101.3, 102.2, 107.9, 108.3, 108.6, 111.2, 117.8, 122.0, 123.9, 134.6, 147.7, 148.6, 148.9, 149.2, 178.3, 178.5. A reaction mixture of hemiacetal (0.39 g, 0.68 mmol) and $Pd(OH)_2$ (0.30 g) in EtOAc (10 ml) was stirred at ambient temperature under H_2 gas for 1 h. After filtration, the filtrate was concentrated. The residue was applied to silica gel column chromatography (EtOAc : hexane = 3 : 1) to give tetra-substituted tetrahydrofuran **18** (0.30 g, 0.54 mmol, 79%) as a colorless oil, $[\alpha]_D^{20} = -19$ (*c* 0.82, $CHCl_3$), more than 99% ee (HPLC, DAICEL chiral column OD-H, detected at 280 nm, 1 ml min^{-1}, 10% *iso*-PrOH in hexane, t_R 16 min); $\nu_{max}(CHCl_3)/cm^{-1}$ 2966, 1721, 1524, 1262, 1160, 1043; $\delta_H(CDCl_3)$ 1.17 (9H, s, Piv), 1.18 (9H, s, Piv), 2.37 (1H, m, 3-H), 2.73 (1H, m, 4-H), 3.79–3.86 (2H, m, 4-CH_2OPiv), 3.89 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.21 (1H, dd, *J* 11.2, 5.1 Hz, 3-C*H*HOPiv), 4.29 (1H, dd, *J* 11.2, 4.4 Hz, 3-CH*H*OPiv), 4.67 (1H, d, *J* 8.3 Hz, 2-H), 5.12 (1H, d, *J* 7.3 Hz, 5-H), 5.95 (2H, s, OCH_2O), 6.78 (1H, d, *J* 7.8 Hz, ArH), 6.84–6.91 (3H, m, ArH), 7.00–7.01 (2H, m, ArH); $\delta_C(CDCl_3)$ 27.06, 27.15, 38.6, 38.9, 45.5, 50.4, 55.9, 56.0, 63.7, 64.7, 81.2, 82.8, 101.0, 106.9, 108.1, 109.8, 111.2, 119.1, 119.6, 131.7, 132.4, 147.0, 147.7, 149.0, 149.2, 178.2, 178.3 (Found: C, 66.56; H, 7.20. $C_{31}H_{40}O_9$ requires C, 66.89; H, 7.24%). (+)-**18**: $[\alpha]_D^{20} = +19$ (*c* 1.1, $CHCl_3$), more than 99% ee (t_R 12 min).

Conversion of (1*S*,2*R*,3*R*)-2,3-bis[(*tert*-butyldiphenylsilyloxy)-methyl]-1-(3,4-dimethoxyphenyl)-3-(3,4-methylenedioxybenzoyl)-1-(triethylsilyloxy)propane 16 to hemiacetal 17

To an ice-cooled solution of alcohol **8** (21.8 g, 0.051 mol) and 2,6-lutidine (11.8 ml, 0.10 mol) in CH_2Cl_2 (200 ml) was added TESOTf (17.1 ml, 0.076 mol). The reaction solution was stirred in ice bath for 1 h before addition of sat. aq. $NaHCO_3$ solution. The organic solution was separated, washed with brine, and dried (Na_2SO_4). The organic solution was evaporated, and then the residue was applied to silica gel column chromatography (EtAOc : hexane = 1 : 3) to give oxazolidinone-TES ether (24.7 g, 0.046 mol, 90%) as a colorless oil. To an ice-cooled solution of $LiBH_4$ (4.00 g, 0.18 mol) in THF (200 ml) containing MeOH (3.79 ml) was added a solution of the oxazolidinone-TES ether (24.7 ml, 0.046 mol) in THF (50 ml). After the reaction solution was stirred at room temperature for 12 h, sat. aq. NH_4Cl solution was added. The mixture was concentrated, and then the residue was dissolved in EtOAc and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After the solution was evaporated, the residue was purified with silica gel column chromatography (EtOAc : hexane = 1 : 4) to give olefin-alcohol (6.52 g, 0.019 mol, 41%) as a colorless oil. A reaction solution of the olefin-alcohol (6.52 g, 0.019 mol), NMO (2.77 g, 0.024 mol), and 2% OsO_4 (3.5 ml) in acetone (140 ml), *tert*-BuOH (35 ml), and H_2O (35 ml) was stirred at room temperature for 20 h before addition of $Na_2S_2O_3$. 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 $NaIO_4$ (4.95 g, 0.023 mol) in MeOH (100 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). Concentration gave crude hemiacetal. A reaction mixture of the crude hemiacetal, PCC (4.15 g, 0.019 mol), and MS 4 Å (0.3 g) in CH_2Cl_2 (80 ml) was stirred at room temperature for 16 h before addition of dry ether. After filtration, the filtrate was concentrated. The residue was applied to silica gel column chromatography (EtOAc : hexane = 1 : 3) to give lactone (3.77 g, 0.010 mol, 53%, 3 steps) as a colorless oil. To a solution of KHMDS (24.7 ml, 0.5 M toluene solution, 0.012 mol) was added a solution of the lactone (3.77 g, 10.0 mmol) in THF (25 ml) at −70 °C. After 15 min, a solution of piperonal (1.72 g, 0.011 mol) in THF (10 ml) was added. 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 concentration, the residue was applied to silica gel column chromatography (EtOAc : hexane = 1 : 3) to give aldol product (4.69 g, 9.08 mmol, a mixture of *erythro* : *threo* = 9 : 1) as a colorless oil. To a solution of $LiBH_4$ (1.54 g, 70.7 mmol) in THF (50 ml) was added a solution of the aldol product (4.69 g, 9.08 mmol) in THF (20 ml) at below 0 °C. The resulting reaction solution was stirred at 0 °C for 16 h before addition of sat. aq. NH_4Cl solution. After concentration, the residue was dissolved in EtOAc and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave crude triol. A reaction solution of the resulting crude triol, Et_3N (3.01 ml, 21.6 mmol), DMAP (94 mg, 0.77 mmol), and TBDPSCl (4.64 ml, 17.8 mmol) in CH_2Cl_2 (10 ml) was stirred at room temperature for 4 h before additions of sat. aq. $NaHCO_3$ solution and CH_2Cl_2. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Evaporation and silica gel column chromatography (5% EtOAc in hexane) gave diTBDPSoxy-benzyl alcohol (7.02 g, 7.03 mmol, 77%, 2 steps) as a colorless oil. A reaction mixture of the benzyl alcohol (2.03 g, 2.03 mmol), PCC (0.48 g, 2.23 mmol), and MS 4 Å (0.2 g) in CH_2Cl_2 (40 ml) was stirred at room temperature for 48 h at 0 °C. After filtration, the filtrate was concentrated. The residue was applied to silica gel column chromatography (1% EtOAc in toluene) to give ketone **16** (0.40 g, 0.40 mmol, 20%) as a colorless oil, $[\alpha]_D^{20} = +44$ (*c* 1.2, $CHCl_3$); $\delta_H(CDCl_3)$ 0.36 (6H, q, *J* 8.3 Hz, $SiCH_2CH_3$), 0.78 (9H, t, *J* 8.3 Hz, $SiCH_2CH_3$), 0.85 (9H, s, *tert*-Bu), 0.96 (9H, s, *tert*-Bu), 2.15 (1H, m, 2-H), 3.48 (1H, dd, *J* 10.8, 4.2 Hz, C*H*HOTBDPS), 3.62 (1H, dd, *J* 10.8, 6.6 Hz, CH*H*OTBDPS), 3.67 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.05–4.13 (3H, m, C*H*HOTBDPS, 2-H), 4.18 (1H, dd, *J* = 9.6, 9.6 Hz, CH*H*OTBDPS), 5.01 (1H, d, *J* 5.4 Hz, 1-H), 6.01 (2H, s, OCH_2O), 6.53 (1H, d, *J* 6.8 Hz, ArH), 6.61 (1H, d, *J* 7.8 Hz, ArH), 6.69–6.71 (2H, m, ArH), 7.20–7.40 (15H, m, ArH), 7.41–7.49 (3H, m, ArH), 7.55–7.57 (3H, m, ArH), 7.72 (1H, d, *J* 8.8 Hz, ArH); $\delta_C(CDCl_3)$ 19.0, 19.1, 26.6, 26.9, 46.3, 50.3, 55.6, 55.8, 60.9, 62.9, 73.3, 101.5, 107.4, 108.7, 109.6, 110.5, 118.9, 124.7, 127.5, 129.3, 129.4, 129.5, 132.5, 133.3, 133.47, 133.55, 133.9, 135.5, 135.6, 135.7, 136.3, 147.7, 148.0, 148.6, 151.0, 199.3 3 (Found: C, 71.08; H, 7.41. $C_{59}H_{74}O_8Si_3$ requires C, 71.19; H, 7.49%). A reaction solution of TES ether **16** (90 mg, 0.090 mmol) in MeCN (5 ml) containing 2% HF (1 ml) was stirred at room temperature for 24 h before additions of H_2O and EtOAc. The organic solution was separated, washed with sat. aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). After concentration, the residue was applied to silica gel column chromatography (EtOAc : hexane = 1 : 6) to give unstable hemiacetal **17** (45 mg, 0.051 mmol, 57%) as a colorless oil. Hemiacetal **17** gave complicated spectrum data. The ratio of 7′*R* : 7′*S* was determined by 5.30 (0.5H, d, *J* 9.3 Hz, 7-H) and 5.56 (0.5H, d, *J* 4.4 Hz, 7-H).

(2*R*,3*S*,4*S*,5*S*)-2-(3,4-Dimethoxyphenyl)-3,4-bis(hydroxymethyl)-5-(3,4-methylenedioxyphenyl)tetrahydrofuran 19

A reaction solution of pivaloyl ester **18** (0.29 g, 0.52 mmol) in EtOH (6 ml) and 1 M aq. NaOH solution (4 ml) was stirred at room temperature for 20 h before additions of $CHCl_3$ and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration and subsequent silica gel column chromatography (EtOAc : hexane = 6 : 1) gave diol **19** (0.17 g, 0.44 mmol, 85%) as a colorless oil, $[\alpha]_D^{20} = -31$ (*c* 0.85, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500, 3000, 1515, 1258, 1031; $\delta_H(CDCl_3)$ 2.22 (1H, m, 3-H), 2.54 (1H, m, 4-H), 3.11 (1H, dd, *J* 10.3, 10.3 Hz, 4-C*H*HOH), 3.31 (1H, dd, *J* 10.3, 4.6 Hz, 4-CH*H*OH), 3.55 (1H, dd, *J* 10.3, 8.8 Hz, 3-C*H*HOH), 3.71 (1H, dd, *J* 10.3, 3.9 Hz, 3-CH*H*OH), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.46 (1H, d, *J* 9.8 Hz, 2-H), 5.08 (1H, d, *J* 8.8 Hz, 5-H), 5.95 (2H, s, OCH_2O), 6.76–6.82 (2H, m, ArH), 6.86–6.88 (2H, m, ArH), 6.88–7.01 (2H, m, ArH); $\delta_C(CDCl_3)$ 50.9, 55.1, 55.9, 62.8, 63.6, 81.2, 82.5, 101.0, 107.0, 108.0, 110.0, 111.1, 119.1, 119.8, 132.3, 132.8, 147.0, 147.6, 149.0, 149.1; *m/z* (EI) 388 (M^+, 74%), 222 (37), 207 (72), 189 (92), 174 (100), 149 (41), 135 (55), 115 (31) [Found (HRMS): M^+, 388.1521. $C_{21}H_{24}O_7$ requires M^+, 388.1522]. (+)-**19**: $[\alpha]_D^{20} = +31$ (*c* 0.38, $CHCl_3$).

(2*R*,3*S*,4*S*,5*S*)-2-(3,4-Dimethoxyphenyl)-3,4-bis-(methoxymethyl)-5-(3,4-methylenedioxyphenyl)tetrahydrofuran ((−)-virgatusin (1))

To an ice-cooled suspension of NaH (29 mg, 60% oil suspension, 0.73 mmol) in THF (5 ml) was added a solution of diol **19** (0.13 g, 0.33 mmol) in THF (10 ml). After the resulting solution was stirred at 0 °C for 30 min, MeI (1.00 ml, 16.1 mmol) was added, and then the reaction solution was stirred at room temperature for 5 h before addition of sat. aq. HN_4Cl solution and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After concentration, the residue was applied to silica gel column chromatography (EtOAc : hexane = 2 : 1) to give (−)-virgatusin ((−)-**1**) (0.12 g, 0.29 mmol, 88%) as a colorless oil, $[\alpha]_D^{20} = -19$ (*c* 0.48, CH_2Cl_2), more than 99% ee (HPLC, DAICEL chiral column OD-H, detected at 280 nm, 1 ml min^{-1}, 10% *iso*-PrOH in hexane, *t*R 14 min), Lit.[1]: $[\alpha]_D^{20} = -12.7$ (*c* 0.5, CH_2Cl_2). The spectral data agreed with those of the natural product. (+)-virgatusin: $[\alpha]_D^{20} = +19$ (*c* 0.32, CH_2Cl_2), more than 99% ee (t_R 16 min).

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