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Use of the Benzyl Mesylate for the Synthesis of Tetrahydrofuran Lignan: Syntheses of 7,8-*trans*, 7′,8′-*trans*, 7,7′-*cis*, and 8,8′-*cis*-Virgatusin Stereoisomers

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The benzyl mesylate was employed to construct the tetrasubstituted tetrahydrofuran lignan with avoiding Friedel-Crafts type of reaction. The optically pure 7,8-*trans*, 7′,8′-*trans*, 7,7′-*cis*, and 8,8′-*cis*-virgatusin stereoisomers were synthesized. The enantiomeric excess was ≫99%.

Key words: lignan; virgatusin; tetrahydrofuran lignan

Lignans with different biological activities[1,2] possess two or three phenylpropanoid units as an important structural feature and are widely distributed in many plants. The bonding type of these phenylpropanoid units and oxidation positions on the lignan structure are presumed to be responsible for their biological activities. The many kinds of biological activity and structure of lignan have attracted the attention of synthetic and biological chemists.[2,3] One of the difficulties of a synthetic study on lignan is constructing the chiral center. In the field of natural products chemistry, stereoisomers are of high interest for research about the structure-activity relationship, and the collation of stereoisomer libraries has proceeded.[4]

The 4-substituted tetrahydrofuran lignan, (−)-virgatusin (**1**),[5] has been isolated and a total synthesis achieved.[6–8] Anti-virus activity has been anticipated.[9] The antifungal activity of **1**[10] and antibacterial activity of **2**[11] were discovered in the course of our biological studies (Fig. 1). To continue these studies, syntheses of the stereoisomers of virgatusin having four chiral centers are important. The attractive structure of the stereoisomers of virgatusin and potent anti-microbiological activity make them suitable synthetic targets. The stereoselective construction of a 2,5-diaryltetrahydrofuran moiety is important in this synthetic study, and the use of unstable benzyl mesylate **3** has been considered. A Friedel-Crafts type of reaction of the benzyl mesylate giving an aryl-benzyl carbon bond has previously been reported.[12] To obtain desired 2,5-diaryltetrahydrofuran **4**, etherification between the benzylic oxygen at the 7′ position and the benzylic position (7 position) of benzyl mesylate **3** is needed (Scheme 1). The Friedel-Crafts type of cyclization reaction between the 6′ position and benzylic 7 position of **3** is not desirable in this synthesis. When intramolecular etherification of benzyl mesylate **3** occurs prior to the Friedel-Crafts type of reaction, SN1 etherification would occur to give stable **4** because of the existence of a benzyl cation at the 7 position. Thus, the 7′ oxygen would attack the 7-position from the opposite side of the 8 and 8′ substituents. The stereoselective synthesis of stereoisomer **4** requires one benzylic position (the 7′ position) to be stereoselectively constructed before attempting this benzylic oxygen-benzyl mesylate etherification. On the other hand, stereoselective construction of the stereochemistry at the 7 position is unnecessary. An aldol condensation, using potassium enolate,[13] was employed to obtain single stereochemistry at the 7′-benzylic position in this study. To avoid etherification between the primary oxygen and the benzylic position of the mesylate (the 7 position) or another benzylic position (the 7′ position) of **3**, appropriate protective groups for the benzyl alcohol and the primary alcohol of compound **3** need to be selected.

This article describes using the benzyl mesylate to synthesize 2,5-diaryltetrahydrofuran-type lignan **5** with avoiding the Friedel-craft type of reaction.

Results and Discussion

Substrate **9** for the intramolecular cyclization was prepared from lactone **6**[14] (Scheme 2). The aldol condensation of lactone **6** with 3,4-dimethoxybenzaldehyde, using potassium bis(trimethylsilyl)amide, stereoselectively gave *erythro* aldol product **7** (*erythro*/*threo* =

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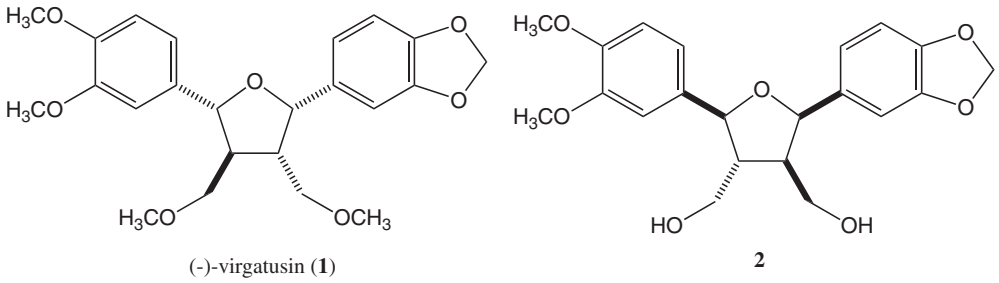
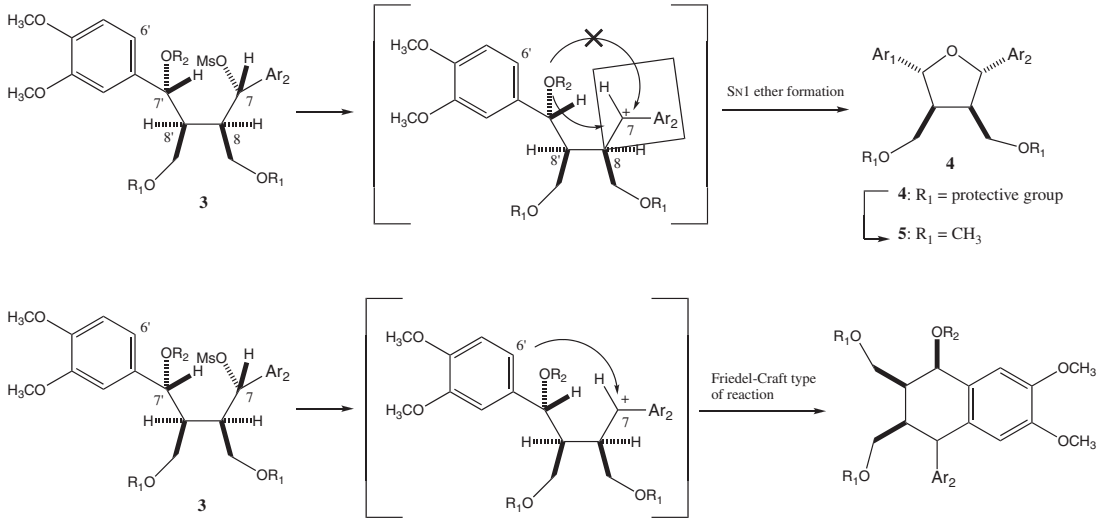
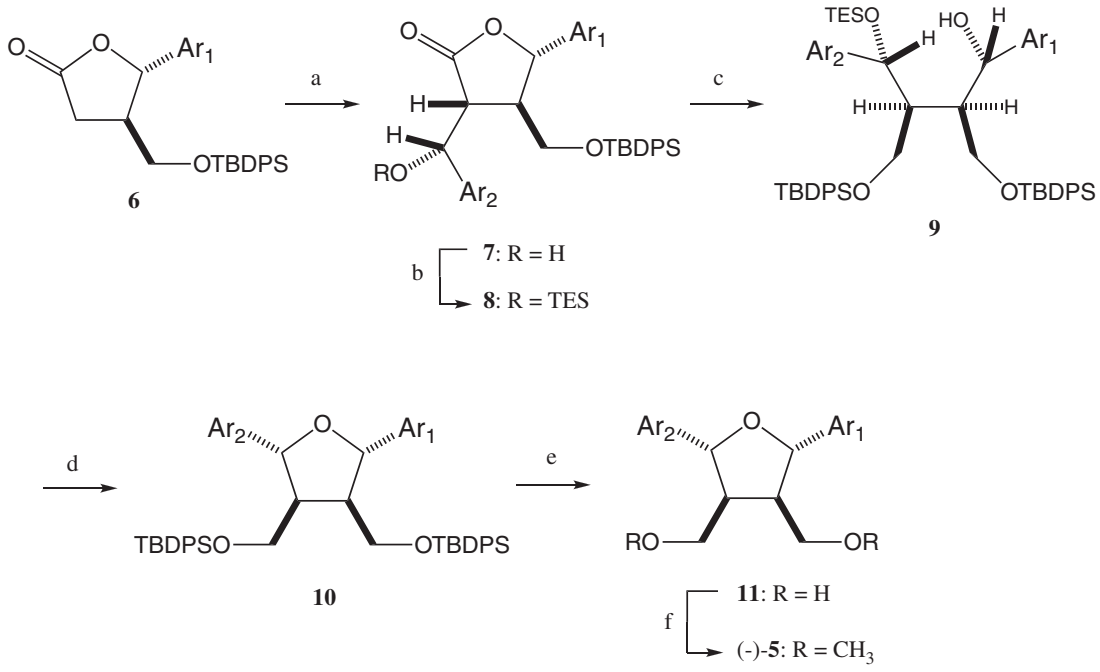


Fig. 1. (−)-Virgatusin and Its Related Compounds.

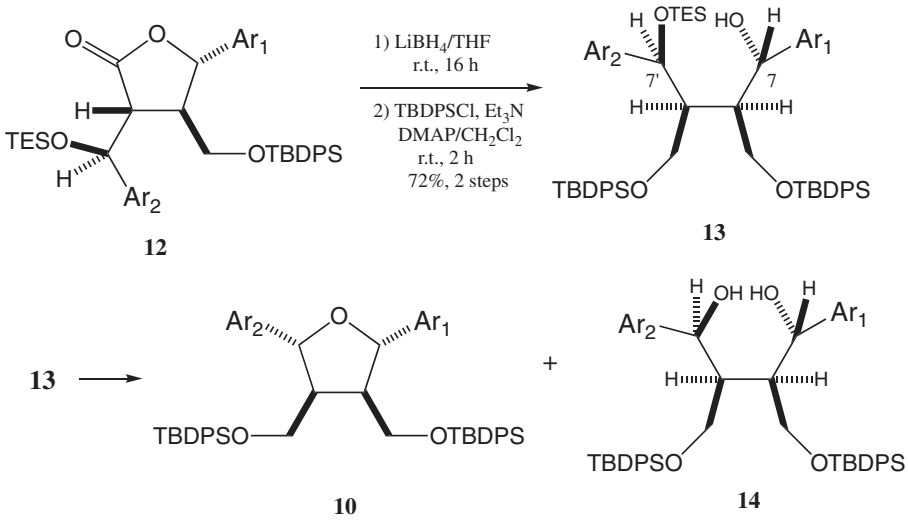


Scheme 1. Intramolecular SN1 Ether Formation and Friedel-Crafts Type Reaction of Benzyl Mesylate **3**. Ar_1, 3,4-methylenedioxyphenyl; Ar_2, 3,4-dimethoxyphenyl



Scheme 2. Synthesis of Stereoisomer of Virgatusin (−)-**5**.

(a) KHMDS, 3,4-dimethoxybenzaldehyde, THF, −70 °C, 1 h (94% yield, containing 5% of the *threo* isomer); (b) TESOTf, 2,6-lutidine, CH_2Cl_2, r.t., 1 h (78% yield); (c) (1) $LiBH_4$, THF, r.t., 16 h; (2) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, r.t., 2 h (69% yield); (d) MsCl, Et_3N, CH_2Cl_2, r.t., 2 h (98% yield); (e) *n*-Bu_4NF, THF, r.t., 2 h (62% yield); (f) NaH, CH_3I, THF, r.t., 16 h (92% yield). Ar_1, 3,4-methylenedioxyphenyl; Ar_2, 3,4-dimethoxyphenyl



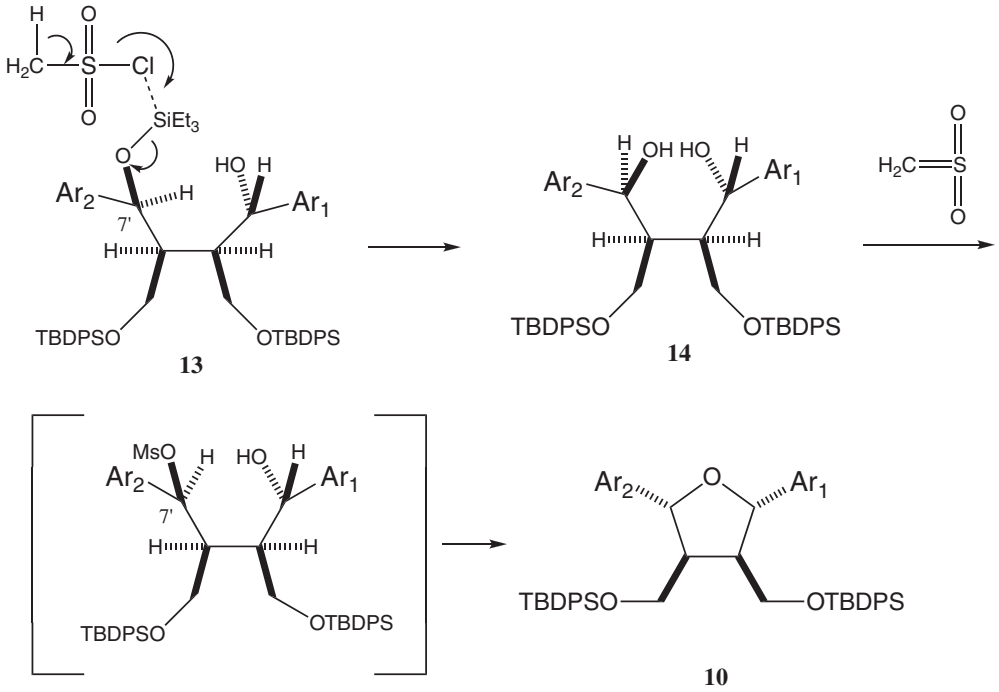
Reaction conditions to **13**	**10**	**14**	recovered **13**
MsCl (1.1 eq.), Et_3N (1.1 eq.), CH_2Cl_2, r.t., 1 h	0%	52%	33%
MsCl (1.1 eq.), Et_3N (1.1 eq.), CH_2Cl_2, r.t., 16 h	40%	0%	0%
Ms_2O, Et_3N, CH_2Cl_2 r.t., 1 h	17%	29%	32%
Ms_2O, Et_3N, CH_2Cl_2 r.t., 16 h	98%	0%	0%

Scheme 3. Mesylation of Benzyl Alcohol **13**.
Ar_1, 3,4-methylenedioxyphenyl; Ar_2, 3,4-dimethoxyphenyl

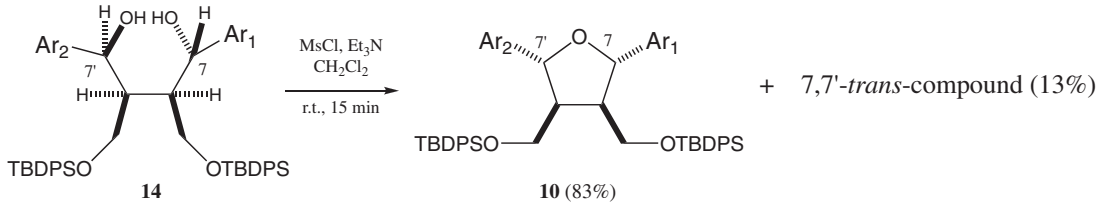
95/5). While some of the *threo* isomer of **7** could be separated in this stage, the *erythro* product was completely separated after triethylsilylating the benzylic hydroxy group. After $LiBH_4$ reduction of lactone **8** to the corresponding butanol derivative, the primary hydroxy group was selectively protected as a *tert*-butyldiphenylsilyl ether, giving substrate **9** for the intramolecular cyclization reaction. The benzylic triethylsilyl ether would be selectively cleaved in the presence of the *tert*-butyldiphenylsilyl ether before intramolecular cyclization of **9** occurred.

Substrate **9** was treated with methanesulfonyl chloride in CH_2Cl_2 in the presence of triethylamine. Although the benzyl mesylate was not obtained, cyclization product **10** was obtained as a single isomer in this step in a high yield (98%). It could be assumed that the benzyl mesylate was produced as a first step, followed by the emergence of a benzyl cation. The benzylic oxygen in the triethylsilyl ether attacked this resulting benzyl cation to stereoselectively give tetrahydrofuran ring **10**. Under theses conditions, the Friedel-Crafts type of reaction[12] between the aryl carbon and benzylic carbon of the benzyl mesylate did not occur. The stereochemistry of tetrahydrofuran derivative **10** was determined by a comparison with the literature data.[2] Even if the reaction was carried out at a lower temperature (−10 °C), the benzyl mesylate could not be isolated, the use of pyridine or *N*,*N*-diisopropylethylamine instead of triethylamine giving the same result.

Benzyl alcohol **13** was prepared from minor silylated *threo* aldol product **12** (Scheme 3). Unexpectedly, treating **13** with methanesulfonyl chloride in the presence of triethylamine also gave tetrahydrofuran derivative **10** (40%) as a single isomer after a 16-h reaction, indicating that the benzyl cation at the 7′ position had been produced instead of at the 7 position. A 1-h reaction enabled diol **14** (52%) to be obtained, together with the recovery of benzyl alcohol **13** (33%). To determine the stereochemistry of **14**, the *threo* isomer of lactone **7** was subjected to $LiBH_4$ reduction and subsequent *tert*-butyldiphenylsilylation to give **14**, whose NMR data agreed with those of **14** which had been obtained after treating benzyl alcohol **13** with methanesulfonyl chloride. The stereoisomer of benzyl alcohol **13** was not isolated from this reaction mixture. It could be assumed from these results that mesylation to the benzylic hydroxy group of **13** did not occur in this reaction. When benzyl alcohol **13** was treated only with



Scheme 4. Proposed Mechanism for the Production of Diol **14** and Tetrahydrofuran Derivative **10** from Benzyl Alcohol **13**. Ar_1, 3,4-methylenedioxyphenyl; Ar_2, 3,4-dimethoxyphenyl



Scheme 5. Reaction of Diol **14** with Methanesulfonyl Chloride. Ar_1, 3,4-methylenedioxyphenyl; Ar_2, 3,4-dimethoxyphenyl

triethylamine, no reaction occurred. It might be assumed from this that interaction between the Si atom and Cl atom took place by the treatment with methanesulfonyl chloride, desilylation occurring to give diol **14** having the same stereochemistry. Since the stereochemistry of diol **14** was not changed and no salt was produced in this reaction, it could be assumed that direct mesylation to 7-OH did not occur. Selective mesylation to the 7′-hydroxy group of diol **14** then took place to give the benzyl mesylate which was subsequently transformed to tetrahydrofuran derivative **10** by SN1 intramolecular cyclization (Scheme 4). The Friedel-Crafts type of reaction product did not result in this reaction. The reaction of benzyl alcohol **13** with methanesulfonic anhydride was also tried. In a short reaction (1 h), tetrahydrofuran derivative **10** (17%) and diol **14** (29%) were obtained, together with the recovery of benzyl alcohol **13** (32%). A longer reaction (16 h) gave tetrahydrofuran derivative **10** in a higher yield (98%) than the reaction using methanesulfonyl chloride (Scheme 3). Mesylation to diol **14** was examined by using methanesulfonyl chloride (Scheme 5), the reaction proceeding quickly to give tetrahydrofuran derivative **10** (83%) and the 7,7′-*trans*-compound (13%). Although selective mesylation to the 7′-hydroxy group of diol **14** was also observed, the selectivity was decreased. The presence of the triethylsilyl ether increased this selectivity, meaning that *erythro* or *threo* selectivity in the aldol condensation of lactone **6** was not necessary to give the stereochemistry of **10**.

Tetrahydrofuran derivative **10** was converted to stereoisomer of virgatusin **5** by desilylation and subsequent methylation of the resulting hydroxy groups. The enantiomer of **5** was also synthesized by employing the same synthetic method. The optical purity of both (+)-**5** and (−)-**5** was determined as ≫99%ee by using a chiral column.

The 7,8-*trans*,7′,8′-*trans*,7,7′-*cis*,8,8′-*cis*-virgatusin stereoisomers were stereoselectively synthesized by an SN1 intramolecular cyclization reaction of benzyl mesylate, avoiding the Friedel-Crafts type of reaction. This is a new example of the use of benzyl mesylate.

Experimental

Optical rotation values were measured by 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), and the HPLC analysis was performed with Shimadzu LC-6AD and SPD-6AV instruments. The numbering of compounds follows the IUPAC nomenclatural rules.

*(2R,3R,4S)-3-[(tert-Butyldiphenylsilyloxy)methyl]-2-[(R)-(hydroxy)(3,4-dimethoxyphenyl)methyl]-4-(3,4-methylenedioxyphenyl)-4-butanolide (**7**).* To a solution of KHMDS (50.1 ml, 0.5 M in toluene, 0.025 mol) in THF (150 ml) was added a solution of lactone **6** (7.69 g, 0.016 mol) in THF (50 ml) at −70 °C. After the mixture was stirred at −70 °C for 15 min, a solution of 3,4-dimethoxybenzaldehyde (2.94 g, 0.018 mol) in THF (20 ml) was added. The resulting 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). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/4) gave aldol product **7** (9.30 g, 0.015 mol, 94%) containing 5% of the *threo* isomer as a colorless oil. δ_H ($CDCl_3$) 1.01 (9H, s, *tert*-BuSi), 2.78 (1H, m, 3-H), 2.98 (1H, dd, *J* 10.7, 3.9 Hz, 2-H), 3.23 (1H, d, *J* 9.8 Hz, C*H*HOSi), 3.43 (1H, dd, *J* 9.8, 2.4 Hz, CH*H*OSi), 3.75 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 5.07 (1H, d, *J* 8.8 Hz, 4-H), 5.56 (1H, br. s, ArC*H*OH, d, *J* = 2.2 Hz, by D_2O exchange), 5.81 (2H, s, OCH_2O), 6.30 (1H, d, *J* 7.8 Hz, ArH), 6.53 (1H, d, *J* 7.8 Hz, ArH), 6.63 (1H, s, ArH), 6.72 (1H, d, *J* 8.3 Hz, ArH), 6.90 (1H, d, *J* 8.3 Hz, ArH), 6.93 (1H, s, ArH), 7.27–7.38 (8H, m, ArH), 7.54–7.56 (2H, m, ArH); δ_C ($CDCl_3$) 18.9, 26.7, 45.3, 49.0, 55.48, 55.54, 59.8, 69.8, 81.4, 100.8, 106.8, 107.5, 108.0, 110.8, 117.0, 120.6, 127.5, 127.6, 127.7, 129.6, 129.8, 132.3, 132.4, 132.5, 133.8, 135.2, 135.3, 148.0, 148.8, 177.3. *Anal.* Found: C, 69.37; H, 6.36. Calcd. for $C_{37}H_{40}O_8Si$: C, 69.35; H, 6.29%. Some of *threo* isomer was purified to give a colorless oil, $[\alpha]^{20}_D = +99$ (*c* 1.6, $CHCl_3$). δ_H ($CDCl_3$) 1.06 (9H, s, *tert*-Bu), 2.16 (1H, m, 2-H), 2.94 (1H, dd, *J* 10.9, 3.6 Hz, C*H*HOTBDPS), 3.25 (1H, dd, *J* 10.8, 2.5 Hz, CH*H*OTBDPS), 3.35 (1H, dd, *J* 10.1, 8.5 Hz, 2-H), 3.81 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.50 (1H, d, *J* 1.9 Hz, OH), 4.91 (1H, dd, *J* 8.2, 1.9 Hz, ArC*H*OH), 5.07 (1H, d, *J* 8.9 Hz, 4-H), 5.91 (2H, s, OCH_2O), 6.09 (1H, d, *J* 8.1 Hz, ArH), 6.28 (1H, s, ArH), 6.54 (1H, d, *J* 8.1 Hz, ArH), 6.73 (1H, d, *J* 8.2 Hz, ArH), 6.82 (1H, d, *J* 8.2 Hz, ArH), 7.00 (1H, s, ArH), 7.29–7.47 (6H, m, ArH), 7.56–7.58 (4H, m, ArH); δ_C ($CDCl_3$) 19.2, 26.9, 47.9, 49.2, 55.7, 55.8, 59.5, 74.5, 81.4, 101.2, 106.2, 108.0, 109.3, 110.8, 119.1, 120.1, 127.7, 128.0, 130.0, 130.2, 131.6, 132.48, 132.52, 132.6, 135.5, 135.8, 147.8, 148.0, 149.2, 149.4, 178.3.

*(2R,3R,4S)-3-[(tert-Butyldiphenylsilyloxy)methyl]-2-[(R)-(3,4-dimethoxyphenyl)(triethylsilyloxy)methyl]-4-(3,4-methylenedioxyphenyl)-4-butanolide (**8**) and (2R,3R,4S)-3-[(tert-butydiphenylsilyloxy)methyl]-2-[(S)-(3,4-dimethoxyphenyl)(triethylsilyloxy)methyl]-4-(3,4-methylenedioxyphenyl)-4-butanolide (**12**).* To an ice-cooled solution of aldol product **7** (4.01 g, 6.26 mmol) containing 5% of *threo* isomer and 2,6-lutidine (1.46 ml, 12.5 mmol) in CH_2Cl_2 (100 ml) was added TESOTf (1.55 ml, 6.85 mmol). The reaction solution was stirred at room temperature for 1 h before addition of sat. aq. NH_4Cl solution. The organic solution was separated, washed with sat. aq. $CuSO_4$ solution, sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/7) gave TES ether **8** (3.71 g, 4.91 mmol, 78%) as a colorless oil, $[\alpha]^{20}_D = +19$ (*c* 0.9, $CHCl_3$); δ_H ($CDCl_3$) 0.60–0.67 (6H, m, $(CH_3CH_2)_3Si$), 0.93 (9H, t, *J* 7.8 Hz, $(CH_3CH_2)_3Si$), 0.97 (9H, s, *tert*-BuSi), 2.83 (1H, m, 3-H), 2.91 (1H, dd, *J* 10.7, 3.9 Hz, 2-H), 3.18 (1H, dd, *J* 9.8, 2.0 Hz, C*H*HOSi), 3.27 (1H, dd, *J* 9.8, 2.0 Hz, CH*H*OSi), 3.79 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.06 (1H, d, *J* 8.8 Hz, 4-H), 5.56 (1H, d, *J* 2.0 Hz, ArCHOSi), 5.93 (2H, s, OCH_2O), 6.36 (1H, dd, *J* 7.8, 1.5 Hz, ArH), 6.61 (1H, d, *J* 7.8 Hz, ArH), 6.65 (1H, d, *J* 1.5 Hz, ArH), 6.72 (1H, d, *J* 8.8 Hz, ArH), 6.84–6.86 (2H, m, ArH), 7.21–7.23 (2H, m, ArH), 7.29–7.47 (6H, m, ArH), 7.51–7.53 (2H, m, ArH); δ_C ($CDCl_3$) 4.7, 6.8, 19.1, 26.8, 45.1, 50.2, 55.67, 55.70, 60.2, 71.6, 81.2, 101.1, 106.8, 107.8, 108.0, 110.8, 117.2, 120.6, 127.6, 127.8, 129.8, 129.9, 132.5, 132.8, 133.1, 134.8, 135.4, 135.7, 147.7, 147.9, 148.1, 148.9, 176.7. *Anal.* Found: C, 68.70; H, 7.32. Calcd. for $C_{43}H_{54}O_8Si_2$: C, 68.40; H, 7.21%. (−)-**8**: $[\alpha]^{20}_D = -19$ (*c* 1.4, $CHCl_3$). *Threo* isomer **12** (0.18 g, 0.24 mmol, 4%) was obtained as a colorless oil, $[\alpha]^{20}_D = -20$ (*c* 2.5, $CHCl_3$). δ_H ($CDCl_3$) 0.48–0.60 (6H, m, $Si(CH_2CH_3)_3$), 0.87 (9H, t, *J* 7.8 Hz, $Si(CH_2CH_3)_3$), 1.08 (9H, s, *tert*-BuSi), 3.38 (1H, m, 3-H), 3.39 (1H, dd, *J* 8.8, 3.9 Hz, 2-H), 3.72 (1H, dd, *J* 10.5, 2.7 Hz, C*H*HOSi), 3.77 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.88 (1H, dd, *J* 10.5, 4.9 Hz, CH*H*OSi), 5.07 (1H, d, *J* 7.8 Hz, 4-H), 5.46 (1H, d, *J* 4.4 Hz, ArCHOSi), 5.74 (1H, d, *J* 2.0 Hz, ArH), 5.85 (1H, d, *J* 5.9 Hz, OC*H*HO), 5.86 (1H, d, *J* 5.9 Hz, OCH*H*O), 5.97 (1H, dd, *J* 8.1, 2.0 Hz, ArH), 6.47 (1H, d, *J* 8.3 Hz, ArH), 6.79 (1H, d, *J* 8.3 Hz, ArH), 6.84–6.88 (2H, m, ArH), 7.37–7.42 (4H, m, ArH), 7.44–7.48 (2H, m, ArH), 7.61–7.63 (4H, m, ArH); δ_C ($CDCl_3$) 4.6, 6.8, 19.3, 26.9, 46.7, 50.6, 55.76, 55.80, 62.6, 72.8, 81.6, 101.0, 106.2, 107.6, 109.9, 110.7, 118.9, 119.9, 127.7, 127.8, 129.86, 129.94, 132.98, 133.01, 133.1, 133.2, 135.6, 135.7, 147.4, 147.7, 148.6, 148.7, 175.9. *Anal.* Found: C, 68.68; H, 7.30. Calcd. for $C_{43}H_{54}O_8Si_2$: C, 68.40; H, 7.21%.

*(1S,2R,3S,4R)-2,3-Bis[(tert-butyldiphenylsilyloxy)methyl]-4-(3,4-dimethoxyphenyl)-1-(3,4-methylenedioxyphenyl)-4-triethylsilyloxy-1-butanol (**9**).* To an ice-cooled solution of $LiBH_4$ (1.08 g, 0.050 mol) in THF (10 ml) was added a solution of lactone **8** (3.77 g, 4.99 mmol) in

THF (10 ml), and then the reaction solution was stirred at room temperature for 16 h before addition of sat. aq. NH_4Cl solution. After the mixture was concentrated, the residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, dried (Na_2SO_4), and concentrated to give crude diol. A reaction solution of this crude diol, Et_3N (0.89 ml, 6.39 mmol), DMAP (29 mg, 0.24 mmol), and TBDPSCl (1.48 ml, 5.69 mmol) in CH_2Cl_2 (10 ml) was stirred at room temperature for 2 h before additions of H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/7) gave diTBDPS ether **9** (3.43 g, 3.44 mmol, 69%) as a colorless oil, $[\alpha]^{20}_D = +36$ (*c* 1.0, $CHCl_3$). δ_H ($CDCl_3$) 0.40–0.55 (6H, m, $(CH_3CH_2)_3Si$), 0.82 (9H, t, *J* 8.1 Hz, $(CH_3CH_2)_3Si$), 0.90 (9H, s, *tert*-BuSi), 1.08 (9H, s, *tert*-BuSi), 2.33 (1H, m, CH), 2.67 (1H, m, CH), 3.17 (1H, m, C*H*HOSi), 3.43 (1H, m, CH*H*OSi), 3.70–3.80 (2H, m, CH_2OSi), 3.80 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.34 (1H, br. s, OH), 5.15 (1H, br. s, ArC*H*OH), 5.82 (2H, s, OCH_2O), 5.83 (1H, d, *J* 7.3 Hz, ArCHOSi), 6.45–6.51 (2H, m, ArH), 6.57–6.62 (2H, m, ArH), 6.74 (1H, d, *J* 6.8 Hz, ArH), 6.93 (1H, s, ArH), 7.24–7.44 (16H, m, ArH), 7.59–7.64 (4H, m, ArH); δ_C ($CDCl_3$) 4.5, 6.7, 19.0, 19.2, 26.8, 26.9, 46.9, 55.5, 55.8, 63.1, 71.2, 74.0, 100.6, 106.7, 107.5, 109.8, 110.7, 119.2, 119.8, 127.3, 127.4, 127.6, 127.7, 129.4, 129.5, 129.6, 133.3, 133.4, 133.47, 133.54, 135.4, 135.47, 135.50, 135.6, 138.2, 146.3, 147.4, 148.1, 148.6. *Anal.* Found: C, 71.34; H, 7.89. Calcd. for $C_{59}H_{76}O_8Si_3$: C, 71.04; H, 7.68%. (−)-**9**: $[\alpha]^{20}_D = -36$ (*c* 2.5, $CHCl_3$).

*(2R,3S,4R,5S)-3,4-Bis[(tert-butyldiphenylsilyloxy)methyl]-2-(3,4-dimethoxyphenyl)-5-(3,4-methylenedioxyphenyl)tetrahydrofuran (**10**).* To an ice-cooled solution of benzyl alcohol **9** (0.72 g, 0.72 mmol) and Et_3N (0.11 ml, 0.79 mmol) in CH_2Cl_2 (4 ml) was added MsCl (62 µl, 0.80 mmol). The reaction solution was stirred at room temperature for 2 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). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/7) gave tetrahydrofuran compound **10** (0.61 g, 0.71 mmol, 98%) as a colorless oil, $[\alpha]^{20}_D = -3$ (*c* 1.1, $CHCl_3$). δ_H ($CDCl_3$) 0.97 (9H, s, *tert*-BuSi), 0.98 (9H, s, *tert*-BuSi), 2.53 (2H, m, 3, 4-H), 3.79 (3H, s, OCH_3), 3.82–3.97 (4H, m, 3,4-CH_2OSi), 3.87 (3H, s, OCH_3), 4.90 (1H, d, *J* 6.8 Hz, ArCH), 4.95 (1H, d, *J* 6.4 Hz, ArCH), 5.93 (1H, d, *J* 5.4 Hz, OC*H*HO), 5.94 (1H, d, *J* 5.4 Hz, OCH*H*O), 6.68–6.71 (2H, m, ArH), 6.76–6.81 (2H, m, ArH), 6.83–6.87 (2H, m, ArH), 7.25–7.33 (10H, m, ArH), 7.37–7.40 (4H, m, ArH), 7.54–7.57 (6H, m, ArH); δ_C ($CDCl_3$) 19.06, 19.10, 26.8, 51.0, 51.3, 55.7, 55.9, 61.8, 61.9, 82.8, 82.9, 100.9, 107.0, 107.9, 109.7, 111.0, 118.7, 120.3, 127.6, 127.7, 129.6, 133.2, 133.3, 134.7, 135.50, 135.53, 135.6, 136.0, 146.9, 147.7, 148.4, 148.8; FAB *m/z* (%) 865 ($M^+ + 1$, 2%), 197 (53), 135 (100). HRFABMS ($M^+ + 1$): Calcd. for $C_{53}H_{61}O_7Si_2$, 865.3956. Found: 865.3956. (+)-**10**: $[\alpha]^{20}_D = +3$ (*c* 1.8, $CHCl_3$).

*(2R,3S,4R,5S)-3,4-Bis(hydroxymethyl)-2-(3,4-dimethoxyphenyl)-5-(3,4-methylenedioxyphenyl)tetrahydrofuran (**11**).* A reaction solution of diTBDPS ether **10** (0.39 g, 0.45 mmol) and *n*-Bu_4NF (0.99 ml, 1 M in THF, 0.99 mmol) in THF (5 ml) was stirred at room temperature for 2 h before additions of sat. aq. NH_4Cl 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 = 1/9 and 1/4) gave diol **11** (0.11 g, 0.28 mmol, 62%) as a colorless oil, $[\alpha]^{20}_D = -5$ (*c* 0.66, $CHCl_3$). δ_H ($CDCl_3$) 2.53 (2H, m, 3,4-H), 3.63 (2H, br. s, OH), 3.71–3.78 (2H, m, C*H*$_2$OH), 3.82–3.90 (2H, m, C*H*$_2$OH), 3.87 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.60 (1H, d, *J* 7.3 Hz, ArCH), 4.61 (1H, d, *J* 7.3 Hz, ArCH), 5.95 (2H, s, OCH_2O), 6.77–6.80 (2H, m, ArH), 6.84–6.88 (2H, m, ArH), 6.94–6.97 (2H, m, ArH); δ_C ($CDCl_3$) 51.6, 51.8, 55.89, 55.91, 60.06, 60.15, 82.1, 101.0, 106.7, 108.1, 109.7, 111.1, 118.8, 120.0, 133.6, 135.0, 147.3, 147.9, 148.8, 149.1. *Anal.* Found: C, 64.57; H, 6.33. Calcd. for $C_{21}H_{24}O_7$: C, 64.94; H, 6.23%. (+)-**11**: $[\alpha]^{20}_D = +5$ (*c* 1.2, $CHCl_3$).

*(2R,3S,4R,5S)-3,4-Bis(methoxymethyl)-2-(3,4-dimethoxyphenyl)-5-(3,4-methylenedioxyphenyl)tetrahydrofuran (**5**).* To an ice-cooled suspension of NaH (22 mg, 60% in oil, 0.55 mmol) in THF (1 ml) was added a solution of diol **11** (0.10 g, 0.26 mmol) in THF (2 ml). The resulting mixture was stirred at room temperature for 30 min before addition of CH_3I (40 ml, 0.64 mmol). The resulting reaction solution was stirred at room temperature for 16 h before additions of EtOAc and H_2O. 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 stereoisomer of virgatusin **5** (0.10 g, 0.24 mmol, 92%) as a colorless oil, $[\alpha]^{20}_D = -10$ (*c* 0.81, $CHCl_3$), ≫99%ee (HPLC, DAICEL OD-H chiral column, detected at 280 nm, 1 ml min^{-1}, 10% *iso*-PrOH in hexane, t_R 32 min. δ_H ($CDCl_3$) 2.56 (2H, m, 3,4-H), 3.34 (6H, s, OCH_3), 3.48–3.52 (2H, m, C*H*$_2$$OCH_3$), 3.54–3.58 (2H, m, C*H*$_2$-OCH_3), 3.88 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.81 (1H, d, *J* 6.8 Hz, ArCH), 4.82 (1H, d, *J* 6.8 Hz, ArCH), 5.94 (2H, s, OCH_2O), 6.78 (1H, d, *J* 7.8 Hz, ArH), 6.85 (1H, d, *J* 7.8 Hz, ArH), 6.90 (1H, dd, *J* 7.8, 1.7 Hz, ArH), 6.96–7.00 (3H, m, ArH); δ_C ($CDCl_3$) 49.1, 49.3, 55.8, 55.9, 58.83, 58.85, 70.53, 70.54, 82.9, 100.9, 106.9, 108.0, 109.8, 111.0, 118.7, 119.9, 134.5, 136.0, 147.0, 147.7, 148.5, 148.9; EIMS *m/z* (%): 416 (M^+, 88), 224 (86), 208 (97), 192 (82), 189 (94), 173 (98), 84 (100). HREIMS (M^+): Calcd. for $C_{23}H_{28}O_7$, 416.1835. Found: 416.1834. (+)-**5**: $[\alpha]^{20}_D = +10$ (*c* 0.94, $CHCl_3$), ≫99%ee (t_R 20 min).

*(1S,2R,3S,4S)-2,3-Bis[(tert-butyldiphenylsilyloxy)methyl]-4-(3,4-dimethoxyphenyl)-1-(3,4-methylenedioxyphenyl)-4-triethylsilyloxy-1-butanol (**13**).* Colorless oil, $[\alpha]^{20}_D = -18$ (*c* 0.9, $CHCl_3$). δ_H ($CDCl_3$) 0.37–0.43 (6H, m, $Si(CH_2CH_3)_3$), 0.78 (9H, t, *J* 7.9 Hz, $Si(CH_2CH_3)_3$), 0.95 (9H, s, *tert*-BuSi), 1.03 (9H, s, *tert*-BuSi), 2.05 (1H, m, CH), 2.46 (1H, m, CH), 3.32 (1H, dd, *J* 7.4, 6.4 Hz, C*H*HOSi), 3.41 (1H, dd, *J* 7.4, 7.4 Hz, CH*H*OSi), 3.65 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.88 (1H, dd, *J* 10.4, 4.6 Hz, C*H*HOSi), 4.01 (1H, dd, *J* 10.4, 8.2 Hz, CH*H*OSi), 4.26 (1H, d, *J* 2.3 Hz, OH), 4.77 (1H, dd, *J* 8.2, 2.3 Hz, ArC*H*OH), 5.00 (1H, d, *J* 5.9 Hz, ArCHOSi), 5.89 (2H, s OCH_2O), 6.57–6.72 (5H, m, ArH), 6.78 (1H, d, *J* 8.2 Hz, ArH), 7.21–7.31 (8H, m, ArH), 7.34–7.39 (4H, m, ArH), 7.42–7.44 (4H, m, ArH), 7.54 (2H, d, *J* 6.8 Hz, ArH), 7.60 (2H, d, *J* 6.6 Hz, ArH); δ_C ($CDCl_3$) 4.7, 6.8, 19.06, 19.10, 26.8, 26.9, 47.5, 49.5, 55.5, 55.7, 62.4, 63.9, 72.9, 75.6, 100.7, 106.9, 107.7, 109.9, 110.4, 119.3, 119.8, 127.4, 127.5, 127.56, 127.61, 129.4, 129.57, 129.62, 133.1, 133.2, 133.5, 133.6, 135.38, 135.41, 135.6, 135.7, 135.8, 138.2, 146.4, 147.5, 147.9, 148.3. *Anal.* Found: C, 71.26; H, 7.78. Calcd. for $C_{59}H_{76}O_8Si_3$: C, 71.04; H, 7.68%.

*Reaction of benzyl alcohol **13** with methanesulfonyl chloride.* Reaction for 1 h: recovered **13** (33%) and diol **14** (52%) as a colorless oil, $[\alpha]^{20}_D = +7$ (*c* 0.8, $CHCl_3$). δ_H ($CDCl_3$) 0.99 (9H, s, *tert*-BuSi), 1.04 (9H, s, *tert*-BuSi), 2.17 (1H, m, CH), 2.56 (1H, m, CH), 3.33 (1H, dd, *J* 10.3, 4.3 Hz, C*H*HOSi), 3.55 (1H, dd, *J* 10.3, 7.6 Hz, CH*H*OSi), 3.75 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.97 (1H, dd, *J* 11.0, 3.7 Hz, C*H*HOSi), 4.09 (1H, dd, *J* 11.0, 7.0 Hz, CH*H*OSi), 4.67 (1H, d, *J* 8.9 Hz, ArC*H*OH), 5.19 (1H, d, *J* 5.3 Hz, ArC*H*OH), 5.89 (2H, s, OCH_2O), 6.50 (1H, d, *J* 7.9 Hz, ArH), 6.57 (1H, d, *J* 7.9 Hz, ArH), 6.63 (1H, s, ArH), 6.75 (1H, d, *J* 8.2 Hz, ArH), 6.89 (1H, s, ArH), 6.92 (1H, d, *J* 8.2 Hz, ArH), 7.26–7.49 (16H, m, ArH), 7.56 (2H, d, *J* 6.9 Hz, ArH), 7.62 (2H, d, *J* 6.9 Hz, ArH); δ_C ($CDCl_3$) 19.08, 19.10, 26.9, 46.7, 48.6, 55.7, 55.9, 62.1, 64.3, 73.7, 75.3, 100.8, 106.8, 107.8, 109.5, 110.8, 118.5, 120.0, 127.57, 127.59, 127.69, 127.73, 129.64, 129.76, 129.81, 132.6, 132.8, 132.9, 133.0, 135.46, 135.51, 135.6, 136.3, 136.9, 146.9, 147.7, 147.8, 148.6; EIMS *m/z* (%): 882 (M^+, 4), 448 (39), 253 (47), 199 (100), 135 (90). HREIMS (M^+): Calcd. for $C_{53}H_{62}O_8Si_2$, 882.3980. Found: 882.3977. Reaction for 16 h: tetrahydrofuran derivative **10** (40%).

*Reaction of benzyl alcohol **13** with methanesulfonic anhydride.* To an ice-cooled solution of benzyl alcohol **13** (41 mg, 0.041 mmol) and Et_3N (7 µl, 0.050 mmol) in CH_2Cl_2 (2 ml) was added Ms_2O (8 mg, 0.046 mmol). After the reaction solution was stirred at room temperature for 1 h, H_2O and CH_2Cl_2 were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9 and 1/3) gave tetrahydrofuran derivative **10** (6 mg, 0.0069 mmol, 17%), diol **14** (11 mg, 0.012 mmol, 29%), and recovered **13** (13 mg, 0.013 mmol, 32%). In the case of 16 h reaction, tetrahydrofuran derivative **10** (35 mg, 0.040 mmol, 98%) was obtained.

*Determination of the stereochemistry of diol **14**.* To an ice-cooled solution of $LiBH_4$ (48 mg, 3.58 mmol) in THF (10 ml) was added a solution of the *threo* isomer of **7** (0.13 g, 0.20 mmol) in THF (10 ml). The resulting reaction mixture was stirred at 0 °C for 13 h before addition of sat. aq. NH_4Cl solution. After concentration, the residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave a crude triol. After a reaction solution of this crude triol, TBDPSCl (10 µl, 0.038 mmol), Et_3N (6.0 ml, 0.043 mmol), and DMAP (0.2 mg, 0.0016 mmol) in CH_2Cl_2 (2 ml) was stirred at room temperature for 30 min, H_2O and CH_2Cl_2 were added. 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 **14** (0.10 g, 0.11 mmol, 55%).

*Treatment of diol **14** with methanesulfonyl chloride.* To an ice-cooled solution of diol **14** (16 mg, 0.018 mmol) and Et_3N (3 ml, 0.022 mmol) in CH_2Cl_2 (2 ml) was added MsCl (23 ml, 0.30 mmol). After stirring at room temperature for 15 min, H_2O and CH_2Cl_2 were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9) gave tetrahydrofuran derivative **10** (13 mg, 0.015 mmol, 83%) and 7,7′-*trans*-compoud (2 mg, 0.0023 mmol, 13%) as a colorless oil. 7,7′-*trans*-compound, $[\alpha]^{20}_D = -36$ (*c* 0.1, $CHCl_3$). δ_H ($CDCl_3$) 0.91 (9H, s, *tert*-Bu), 0.93 (9H, s, *tert*-Bu), 2.33 (1H, m, 4-H), 2.68 (1H, m, 3-H), 3.49 (2H, d, *J* 5.2 Hz, $CH_2OTBDPS$), 3.66 (3H, s, OCH_3), 3.79–3.84 (1H, overlapped, C*H*HOTBDPS), 3.84 (3H, s, OCH_3), 4.02 (1H, dd, *J* 10.3, 6.2 Hz, CH*H*OTBDPS), 5.13 (1H, d, *J* 6.7 Hz, ArCH), 5.37 (1H, d, *J* 6.0 Hz, ArCH), 5.93 (1H, s, OC*H*HO), 5.96 (1H, s, OCH*H*O), 6.66 (1H, d, *J* 8.3 Hz, ArH), 6.72–6.78 (3H, m, ArH), 6.81 (1H, s, ArH), 6.85 (1H, s, ArH), 7.20–7.42 (16H, m, ArH), 7.48–7.71 (4H, m, ArH); δ_C ($CDCl_3$) 18.95, 19.04, 26.77, 26.84, 47.8, 53.5, 55.6, 55.8, 60.5, 62.6, 82.2, 83.3, 100.9, 106.7, 108.0, 109.1, 110.8, 118.1, 119.6, 121.3, 122.3, 127.45, 127.48, 127.58, 127.59, 129.46, 129.52, 129.6, 132.3, 133.1, 133.2, 133.5, 135.4, 135.48, 135.50, 135.56, 137.7, 147.7, 148.6. EIMS *m/z* (%) 864 (M^+, 0.3%), 433 (49), 252 (52), 199 (100). HREIMS (M^+): Calcd. for $C_{53}H_{60}O_7Si_2$, 864.3878. Found, 864.3881.

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