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Total Synthesis of Thelephantin O, Vialinin A/Terrestrin A, and Terrestrins B–D

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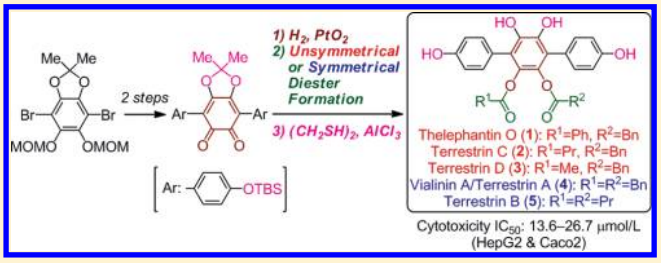
Supporting Information

ABSTRACT: The first total synthesis of natural, unsymmetrical 2′,3′-diacyloxy-*p*-terphenyls, thelephantin O (**1**) and terrestrins C and D (**2** and **3**, respectively), was achieved via a practical route which was also applicable to the synthesis of the symmetrical diesters vialinin A/terrestrin A (**4**) and terrestrin B (**5**). Compounds **1**–**5** exhibited cytotoxicity against cancer cells (HepG2 and Caco2) with IC_{50} values of 13.6–26.7 μmol/L.



Thelephantin O (**1**)[1] (Figure 1) was recently isolated by Norikura as a novel, naturally occurring 2′,3′-diacyloxy-*p*-terphenyl compound from the fungus *Thelephora aurantiotincta*, collected in Aomori Prefecture, Japan, along with vialinin A/terrestrin A (**4**), previously isolated from other fungi of *Thelephora* genus, *T. vialis*,[2] and *T. terrestris*.[3] Compounds **1** and **4** were also reported to show cytotoxicity against human hepatocellular carcinoma cells (HepG2) and human colonic carcinoma cells (Caco2).[1] We are interested in the biological properties of other members of the 2′,3′-diacyloxy-*p*-terphenyl family, such as terrestrins B, C, and D (**5**, **2**, and **3**, respectively),[3,4] of which the bioactivity has not been investigated so far. Therefore, we aimed to synthesize all of these compounds for biological evaluation.

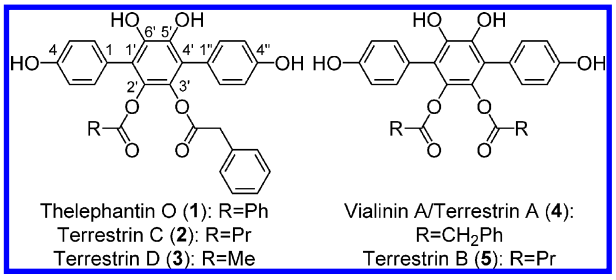
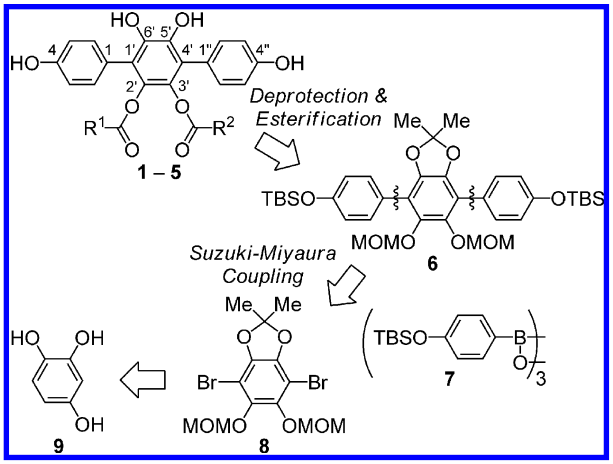


Figure 1. Thelephantin O (**1**), vialinin A/terrestrin A (**4**), and terrestrins B, C, and D (**5**, **2**, and **3**, respectively).

Vialinin A/terrestrin A (**4**) and terrestrin B (**5**) were first synthesized by Takahashi et al.[5,6] The synthetic path was followed later by Fujiwara to prepare a reference compound for identification of **4** isolated from *T. aurantiotincta*.[1] Because the path included some technical and poorly reproducible steps due to the oxidation-sensitive middle ring of the *p*-terphenyl skeleton,[7] the steps were modified to obtain a reasonable amount of **4**.[8] Furthermore, we explored more efficient routes to related compounds, particularly to unsymmetrical diesters **1**–**3**. Here, the first total synthesis of **1**–**3** via a new practical route, which is also applicable to symmetrical diesters **4** and **5**, is described along with the cytotoxicity of synthetic **1**–**5** against HepG2 and Caco2 cells.

Our synthesis of 2′,3′-diacyloxy-*p*-terphenyl compounds **1**–**5**, outlined in Scheme 1, employed an isopropylidene acetal group, instead of the methylene acetal group in the previous synthesis,[1,5] for protection of the 1,2-diol of the central benzene ring, with the aim of simultaneously removing it and the TBS

Scheme 1. Outline of Synthesis Method for 1–5



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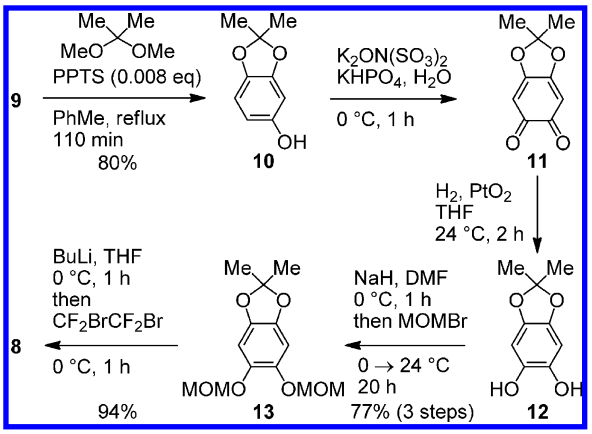
ethers of the terminal benzene rings under acidic conditions at the final stage. The installation of unsymmetrical or symmetrical diester was scheduled after the construction of the *p*-terphenyl skeleton by Suzuki-Miyaura coupling[9] of triarylboroxine **7**[10] and dibromide **8**, derived concisely from commercially available benzene-1,2,4-triol (**9**). Our synthesis also relied on careful selection of reaction conditions for the steps generating an unstable intermediate. In such cases, a clean, catalytic reaction with no byproduct was employed, and the unstable product was used immediately, without isolation, in the next step.

Dibromide **8** was synthesized from **9** in five steps (Scheme 2). Purified **9**[11] was reacted with 2,2-dimethoxypropane, which was added portionwise to the reaction system in the presence of a catalytic amount of PPTS in refluxing toluene with azeotropic removal of methanol to produce **10** in 80% yield.[12] When a strong acid catalyst, such as TsOH, or an increased amount of PPTS was used in the reaction, significant amounts of byproduct were obtained due to aromatic substitution.

Scheme 2. Synthesis of Compound 8

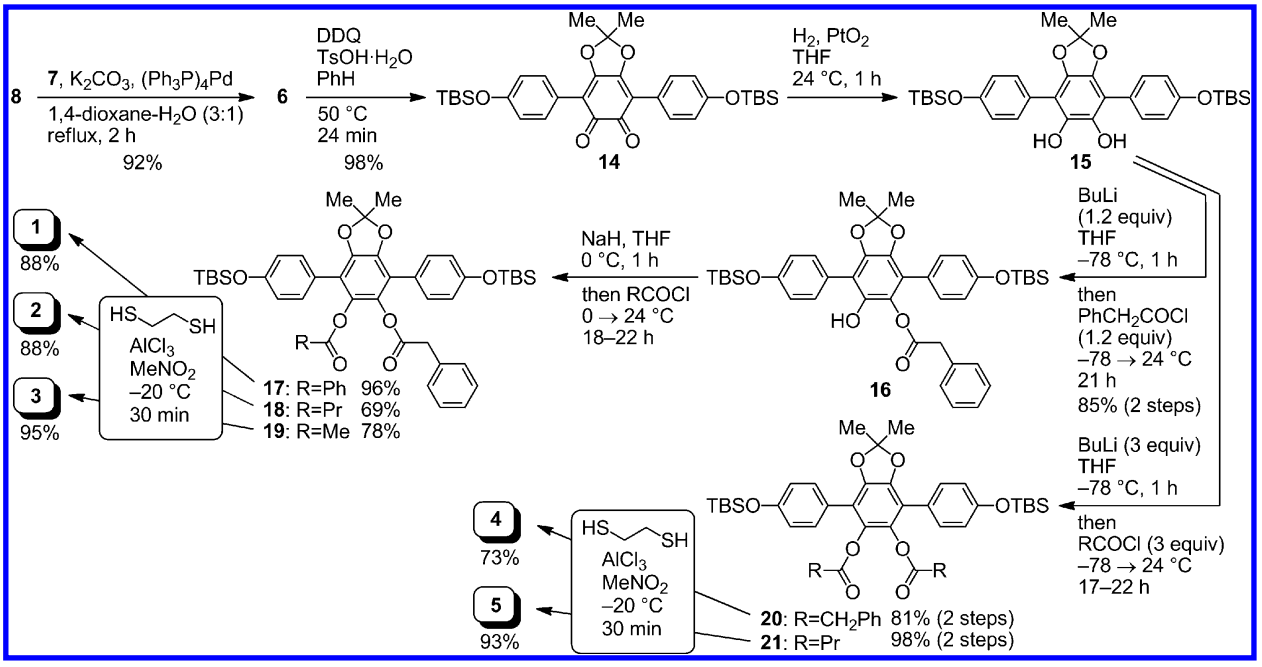


Treatment of **10** with Frémy's salt produced water-soluble *o*-quinone **11**,[13] which was isolated quantitatively in an almost pure form by continuous extraction with EtOAc. The *o*-quinone was reduced in THF by catalytic hydrogenation with PtO_2 to give air-sensitive **12**,[14] which was used immediately without purification in the next reaction with MOMBr to produce **13** in 77% yield over three steps. The ortho-lithiation of **13** with BuLi, followed by reaction with 1,2-dibromo-1,1,2,2-tetrafluoroethane, afforded **8** in 94% yield.

The *p*-terphenyl skeleton was constructed from **8** by Suzuki–Miyaura cross-coupling under standard conditions (Scheme 3). The reaction of **8** with **7** in the presence of $(Ph_3P)_4Pd$ and K_2CO_3 in refluxing aqueous 1,4-dioxane successfully afforded *p*-terphenyl **6** (92%), of which the MOM groups were oxidatively removed with DDQ in the presence of $TsOH{\cdot}H_2O$, according to the Takahashi procedure,[5,15] to give *o*-quinone **14** (98%).

Next, the formation of unsymmetrical diester was examined. As benzo[*d*][1,3]dioxole-5,6-diol derivative **15**, derived from **14** by hydrogenation with PtO_2 catalyst in THF,[14] was extremely unstable in air, it was used in situ for the subsequent esterification reaction. Our first attempt at unsymmetrical diesterification via a dianion, generated from **15** with 2 equiv of BuLi, by one-pot sequential addition of phenylacetyl chloride and benzoyl chloride resulted in moderate yield of diester **17** (up to 51%) with significant byproduction of symmetrical diesters. This may be attributable to a small difference in reactivity between the dianion of **15** and the monoanion generated by monoesterification of the dianion during the reaction. Therefore, we explored a stepwise route for diesters. Monodeprotonation of diol **15**, generated in situ, with 1.2 equiv of BuLi followed by reaction with phenylacetyl chloride selectively afforded monoester **16** as a fairly stable compound in 85% yield over two steps from **14**.[16] Monoester **16** was deprotonated with NaH, and the resulting phenoxide was treated with benzoyl chloride to successfully produce unsymmetrical diester **17** in 96% yield. The esterification of **16** with

Scheme 3. Total Synthesis of Thelephantin O (1), Vialinin A/Terrestrin A (4), and Terrestrins B, C, and D (5, 2, and 3, respectively)



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butanoyl chloride and acetyl chloride under the same conditions also gave diesters **18** (69%) and **19** (78%), respectively.

Symmetrical diesters **20** and **21** were synthesized via diesterification of the dianion of **15**, in line with Takahashi's method,[5] in good yield (81% and 98%, respectively, over two steps).

Finally, the optimal conditions for removal of TBS and the isopropylidene acetal groups were determined after intensive exploration. As the treatment of **17** with methanolic HCl at 50 °C removed only the TBS groups, and the isopropylidene acetal remained intact, the combination of a Lewis acid and ethane-1,2-dithiol was employed for deprotection. Among several Lewis acids examined, $SnCl_4$ and $AlCl_3$ were found to cleave both the isopropylidene acetal and TBS groups of **17**. However, $SnCl_4$ formed firm a chelate complex with product **1**, and hence the desired **1** was isolated at low yield. On the other hand, $AlCl_3$ cleanly produced **1**. Thus, after optimization of the reaction conditions, deprotection of **17** was achieved on treatment with ethane-1,2-dithiol and $AlCl_3$ in nitromethane at −20 °C to give **1** at 88% yield. Compounds **18**, **19**, **20**, and **21** were also deprotected under the same conditions to produce **2** (88%), **3** (95%), **4** (73%), and **5** (93%), respectively, in good yield.

The spectral data for synthetic **1**, **2**, **3**, **4**, and **5** were identical to those for natural thelephantin O,[1] terrestrin C,[3] terrestrin D,[3] vialinin A/terrestrin A,[2,3] and terrestrin B,[3,5b] respectively.

The cytotoxicity of the synthetic compounds against HepG2 and Caco2 was then investigated. Compounds **1**,[17,18] **2**, **3**, **4**,[17] and **5** exhibited inhibitory activity against HepG2/Caco2 growth, with IC_{50} values of 16.3/24.1, 13.6/24.1, 15.5/26.5, 14.1/23.7, and 20.7/26.7 μmol/L, respectively. Thus, the cytotoxic effects of terrestrins B−D on cancer cells were confirmed.

In conclusion, the first total synthesis of natural, unsymmetrical 2′,3′-diacyloxy-*p*-terphenyls, thelephantin O (**1**), and terrestrins C and D (**2** and **3**, respectively), was achieved via a practical route, which was also applicable to the synthesis of symmetrical diesters, vialinin A/terrestrin A (**4**) and terrestrin B (**5**). *p*-Terphenyl compounds **1**−**5** exhibited cytotoxicity against cancer cells (HepG2 and Caco2) with IC_{50} values of 13.6−26.7 μmol/L.

EXPERIMENTAL SECTION

General experimental methods are provided in the Supporting Information.

2,2-Dimethylbenzo[*d*][1,3]dioxol-5-ol (10). In a two-necked flask, equipped with a distillation apparatus in one neck and a stopcock in the other, were added benzene-1,2,4-triol (**9**) (purified by silica gel column chromatography, 629.2 mg, 4.989 mmol), pyridinium *p*-toluenesulfonate (1.0 mg, 0.004 mmol), and anhydrous toluene (50 mL), and the mixture was stirred and heated to reflux with slow distillation of the solvent (ca. 0.7 mL/min). To the mixture was added 2,2-dimethoxypropane portionwise through the stopcock every 15 min (0.15 mL × 4 and 0.10 mL × 3: total 0.90 mL, 7.3 mmol). During the reaction, toluene (10 mL) was also added every 15 min to compensate for the loss of solvent. After 110 min from the start of the reaction, the reaction mixture was cooled to 24 °C and was directly subjected to column chromatography (silica gel, hexane/EtOAc = 10 → 1) to give **10** (664.4 mg, 3.998 mmol, 80%) as a colorless oil along with recovered **9** (97.2 mg, 7.71 mmol, 15%). **10**: IR (neat) ν 3369, 3073, 3054, 2991, 2937, 1636, 1618, 1496, 1476, 1386, 1377, 1275, 1221, 1152, 1116, 1074, 980, 946, 835, 787, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.65 (6H, s), 4.70−4.99 (1H, brs, OH), 6.21 (1H, dd, *J* = 2.6, 8.3 Hz), 6.34 (1H, d, *J* = 2.6 Hz), 6.55 (1H, d, *J* = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7 (CH_3 × 2), 98.1 (CH), 106.0 (CH), 107.9 (CH), 118.2 (C), 141.5 (C), 148.0 (C), 150.1 (C); EI-HRMS (*m*/*z*) calcd for $C_9H_{10}O_3$ [M^+] 166.0630, found 166.0657.

5,6-Bis(methoxymethoxy)-2,2-dimethylbenzo[*d*][1,3]dioxole (13). To an ice-cooled, vigorously stirred suspension of KH_2PO_4 (1.552 g, 11.40 mmol) and potassium nitrosodisulfonate (6.067 g, 70% purity, 15.82 mmol) in H_2O (45 mL) was added dropwise a solution of **10** (1.246 g, 7.498 mmol) in MeOH (3 mL), and the mixture was stirred for 60 min at the same temperature. Then, the mixture was saturated with NaCl (24 g) and subjected to continuous extraction with EtOAc overnight. The extract was concentrated under reduced pressure to give 2,2-dimethylbenzo[*d*][1,3]dioxole-5,6-dione (**11**) (yellow needles, 1.360 g) in an almost pure form. **11**: mp 180 °C (sublimed); IR (KBr) ν 3088, 3027, 3001, 2926, 2853, 1659, 1633, 1403, 1390, 1284, 1229, 1214, 1146, 1083, 985, 870, 837, 661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.80 (6H, s), 5.94 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1 (CH_3 × 2), 101.1 (CH × 2), 124.0 (C), 161.0 (C × 2), 177.8 (C × 2); EI-HRMS (*m*/*z*) calcd for $C_9H_8O_4$ [M^+] 180.0423, found 180.0454. To a suspension of the above **11** (1.360 g) in THF (50 mL) was added PtO_2 (17.7 mg, 0.0779 mmol), and the mixture was stirred under H_2 atmosphere at 24 °C. After being stirred for 2 h, the reaction mixture turned to a clear pale yellow solution. Then, the solvent was removed under the reduced pressure, and the residue (crude 2,2-dimethylbenzo[*d*][1,3]dioxole-5,6-diol, **12**) was immediately dissolved in DMF (38 mL). To the solution was added NaH (60% in mineral oil, 1.267 g, 31.68 mmol) at 0 °C, and the mixture was stirred for 1 h. To the resulting dark blue solution was added dropwise bromomethyl methyl ether (2.5 mL, 31 mmol) at 0 °C, and the mixture was stirred at 24 °C for 20 h. The reaction was quenched with H_2O, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 12) to give **13** (1.557 g, 5.760 mmol, 77% over three steps) as a colorless oil. **13**: IR (neat) ν 3122, 3086, 3062, 2991, 2953, 2936, 2903, 2827, 1494, 1386, 1377, 1244, 1215, 1151, 1083, 1045, 980, 922, 877, 844, 787 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.64 (6H, s), 3.52 (6H, s), 5.09 (4H, s), 6.66 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7 (CH_3 × 2), 56.1 (CH_3 × 2), 96.8 (CH_2 × 2), 100.7 (CH × 2), 118.3 (C), 141.4 (C × 2), 142.4 (C × 2); EI-HRMS (*m*/*z*) calcd for $C_{13}H_{18}O_6$ [M^+] 270.1103, found 270.1137.

4,7-Dibromo-5,6-bis(methoxymethoxy)-2,2-dimethylbenzo-[*d*][1,3]dioxole (8). To a solution of **13** (141.9 mg, 0.5250 mmol) in THF (2.1 mL) was added dropwise BuLi (1.65 mol/L in hexane, 0.95 mL, 1.6 mmol) at 0 °C, and the mixture was stirred for 1 h. To the resulting suspension was added dropwise 1,2-dibromo-1,1,2,2-tetrafluoroethane (0.20 mL, 1.7 mmol) at 0 °C, and the mixture was stirred for 1 h. To the mixture was added H_2O, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 15) to give **8** (211.0 mg, 0.4929 mmol, 94%) as a colorless solid. **8**: mp 149−151 °C; IR (KBr) ν 2992, 2963, 2935, 2923, 2831, 1452, 1377, 1362, 1309, 1251, 1222, 1162, 1088, 1054, 1018, 987, 965, 934, 922, 855, 806, 749, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.76 (6H, s), 3.66 (6H, s), 5.10 (4H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0 (CH_3 × 2), 58.3 (CH_3 × 2), 96.9 (C × 2), 99.7 (CH_2 × 2), 120.6 (C), 142.0 (C × 2), 142.6 (C × 2); EI-HRMS (*m*/*z*) calcd for $C_{13}H_{16}O_6{}^{79}Br_2$ [M^+] 425.9314, found 425.9322.

4,7-Bis[4-(*tert*-butyldimethylsilyloxy)phenyl]-5,6-bis-(methoxymethoxy)-2,2-dimethylbenzo[*d*][1,3]dioxole (6). To a mixture of **8** (1.193 g, 2.787 mmol), tris[4-(*tert*-butyldimethylsilyloxy)-phenyl]boroxine (**7**) (2.947 g, 4.195 mmol), K_2CO_3 (2.319 g, 16.80 mmol), $Pd(PPh_3)_4$ (163.8 mg, 0.1417 mmol) was added a 3:1 mixture of 1,4-dioxane and H_2O (30 mL) at 24 °C, and the mixture was refluxed for 2 h. The mixture was cooled to 24 °C, and satd aq NH_4Cl (30 mL) was added to the mixture. The mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under

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reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 100 → 50) to give **6** (1.756 g, 2.571 mmol, 92%) as a colorless solid. **6**: mp 166−169 °C; IR (KBr) ν 3040, 2992, 2956, 2930, 2896, 2858, 2826, 1608, 1517, 1472, 1463, 1438, 1398, 1376, 1363, 1298, 1262, 1217, 1170, 1160, 1102, 1080, 1043, 1013, 973, 950, 915, 838, 804, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.22 (12H, s), 1.00 (18H, s), 1.66 (6H, s), 3.01 (6H, s), 4.84 (4H, s), 6.88 (4H, d, J = 8.6 Hz), 7.45 (4H, d, J = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.4 (CH_3 × 4), 18.2 (C × 2), 25.7 (CH_3 × 6), 26.0 (CH_3 × 2), 57.0 (CH_3 × 2), 99.2 (CH_2 × 2), 117.3 (C × 2), 117.8 (C), 119.6 (CH × 4), 125.7 (C × 2), 131.6 (CH × 4), 141.1 (C × 2), 141.3 (C × 2), 154.9 (C × 2); FD-HRMS (m/z) calcd for $C_{37}H_{54}O_8Si_2$ [M^+] 682.3357, found 682.3378.

4,7-Bis[4-(*tert*-butyldimethylsilyloxy)phenyl]-2,2-dimethylbenzo[*d*][1,3]dioxole-5,6-dione (14). To a solution of **6** (1.756 g, 2.571 mmol) in benzene (30 mL) were added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (883.5 mg, 3.892 mmol) and TsOH·H_2O (253.4 mg, 1.318 mmol) at 24 °C, and the mixture was heated to 50 °C for 24 min with stirring. The reaction was quenched with satd aq $NaHCO_3$, and the mixture was extracted with $CHCl_3$ several times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5) to give **14** (1.497 g, 2.524 mmol, 98%) as red needles. **14**: mp 258−261 °C; IR (KBr) ν 3072, 3043, 2994, 2956, 2930, 2895, 2886, 2858, 1672, 1636, 1603, 1511, 1472, 1463, 1389, 1381, 1342, 1299, 1277, 1268, 1225, 1178, 1153, 1075, 1034, 1011, 918, 843, 823, 811, 784, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.23 (12H, s), 1.00 (18H, s), 1.83 (6H, s), 6.88 (4H, d, J = 8.7 Hz), 7.53 (4H, d, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.4 (CH_3 × 4), 18.1 (C × 2), 25.6 (CH_3 × 6), 26.3 (CH_3 × 2), 112.7 (C × 2), 119.6 (CH × 4), 121.6 (C), 122.2 (C × 2), 130.9 (CH × 4), 155.6 (C × 2), 156.0 (C × 2), 176.8 (C × 2); FD-HRMS (m/z) calcd for $C_{33}H_{44}O_6Si_2$ [M^+] 592.2676, found 592.2682.

4,7-Bis[4-(*tert*-butyldimethylsilyloxy)phenyl]-6-hydroxy-2,2-dimethylbenzo[*d*][1,3]dioxol-5-yl Phenylacetate (16). To a solution of **14** (253.2 mg, 0.4271 mmol) in THF (4.2 mL) was added PtO_2 (4.8 mg, 0.021 mmol), and the mixture was stirred under H_2 atmosphere at 24 °C. After being stirred for 1 h, the red reaction solution turned to a clear pale yellow solution. Then, the solution (including 4,7-bis[4-(tert-butyldimethylsilyloxy)phenyl]-2,2-dimethylbenzo[*d*][1,3]dioxole-5,6-diol (**15**)) was placed under Ar atmosphere, and cooled to −78 °C. To the solution were added BuLi (1.62 mol/L in hexane, 0.316 mL, 0.512 mmol) and the mixture was stirred at −78 °C for 1 h. Then, to the mixture was added phenylacetyl chloride (0.0678 mL, 0.512 mmol) at −78 °C, and the mixture was warmed to 0 °C and stirred for 21 h. Then, the mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/toluene/EtOAc = 50/50/1) followed by recrystallization (EtOH, several times) to give **16** (257.5 mg, 0.3611 mmol, 85%) as a colorless solid. **16**: mp 189−191 °C; IR (KBr) ν 3429, 3089, 3063, 3034, 2984, 2956, 2930, 2896, 2886, 2858, 1766, 1736, 1609, 1521, 1472, 1442, 1392, 1376, 1329, 1262, 1215, 1173, 1128, 1058, 1009, 916, 840, 805, 781, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.23 (6H, s), 0.24 (6H, s), 1.00 (9H, s), 1.02 (9H, s), 1.64 (6H, s), 3.67 (2H, s), 4.72 (1H, s, OH), 6.80 (2H, d, J = 8.5 Hz), 6.91 (2H, d, J = 8.5 Hz), 7.18 (2H, brd, J = 7.8 Hz), 7.21−7.28 (3H, m), 7.29 (2H, d, J = 8.5 Hz), 7.41 (2H, d, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.4 (CH_3 × 2), −4.3 (CH_3 × 2), 18.1 (C), 18.2 (C), 25.62 (CH_3 × 3), 25.63 (CH_3 × 3), 25.8 (CH_3 × 2), 40.9 (CH_2), 110.9 (C), 116.2 (C), 118.0 (C), 119.6 (CH × 2), 120.2 (CH × 2), 123.8 (C), 124.6 (C), 127.2 (CH), 128.6 (CH × 2), 129.1 (C), 129.3 (CH × 2), 130.7 (CH × 2), 131.1 (CH × 2), 133.3 (C), 138.4 (C), 139.1 (C), 142.7 (C), 155.1 (C), 155.5 (C), 169.6 (C); FD-HRMS (m/z) calcd for $C_{41}H_{52}O_7Si_2$ [M^+] 712.3252, found 712.3219.

4,7-Bis[4-(*tert*-butyldimethylsilyloxy)phenyl]-2,2-dimethyl-6-(phenylacetoxy)benzo[*d*][1,3]dioxol-5-yl Benzoate (17). To a solution of **16** (73.1 mg, 0.103 mmol) in THF (2.0 mL) was added NaH (60% in mineral oil, 15.4 mg, 0.385 mmol) at 0 °C, and the mixture was stirred for 1 h. To the mixture was added benzoyl chloride (0.024 mL, 0.21 mmol) at 0 °C, and the mixture was stirred at 24 °C for 22 h. The reaction was quenched with satd aq NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 50 → 20) to give **17** (80.6 mg, 0.0986 mmol, 96%) as a colorless solid. **17**: mp 78−79 °C; IR (KBr) ν 3089, 3064, 3034, 2956, 2930, 2896, 2887, 2858, 1768, 1748, 1609, 1520, 1463, 1440, 1392, 1377, 1258, 1219, 1173, 1112, 1080, 1066, 1046, 1025, 1006, 914, 841, 805, 782, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.11 (6H, s), 0.24 (6H, s), 0.91 (9H, s), 1.01 (9H, s), 1.71 (6H, s), 3.42 (2H, s), 6.74 (2H, d, J = 8.6 Hz), 6.80 (2H, d, J = 8.6 Hz), 6.92 (2H, brd, J = 8.0 Hz), 6.99−7.08 (3H, m), 7.32 (2H, d, J = 8.6 Hz), 7.37 (2H, d, J = 8.6 Hz), 7.39 (2H, brt, J = 7.8 Hz), 7.56 (1H, brt, J = 7.5 Hz), 7.92 (2H, brd, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5 (CH_3 × 2), −4.4 (CH_3 × 2), 18.1 (C), 18.2 (C), 25.58 (CH_3 × 3), 25.64 (CH_3 × 3), 26.0 (CH_3 × 2), 40.7 (CH_2), 116.3 (C), 116.4 (C), 118.9 (C), 119.6 (CH × 2), 119.7 (CH × 2), 124.1 (C), 124.2 (C), 126.9 (CH), 128.3 (CH × 2), 128.4 (CH × 2), 128.8 (C), 129.1 (CH × 2), 130.1 (CH × 2), 130.7 (CH × 2), 130.8 (CH × 2), 132.7 (C), 133.4 (C), 134.36 (C), 134.40 (C), 142.8 (C), 142.9 (C), 155.2 (C), 155.3 (C), 164.3 (C), 169.1 (C); FD-HRMS (m/z) calcd for $C_{48}H_{56}O_8Si_2$ [M^+] 816.3514, found 816.3477.

4,7-Bis[4-(*tert*-butyldimethylsilyloxy)phenyl]-2,2-dimethyl-6-(phenylacetoxy)benzo[*d*][1,3]dioxol-5-yl Butanoate (18). In the same manner as **17**, compound **18** was synthesized as a colorless solid (57.6 mg, 0.0736 mmol, 69%) from **16** (75.4 mg, 0.106 mmol), NaH (60% in mineral oil, 10.3 mg, 0.258 mmol), and butanoyl chloride (0.0221 mL, 0.212 mmol). **18**: mp 157−159 °C; IR (KBr) ν 3088, 3067, 3035, 2959, 2932, 2899, 2888, 2861, 1770, 1605, 1518, 1468, 1441, 1396, 1264, 1176, 1126, 1110, 1011, 917, 841, 807, 785, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.20 (6H, s), 0.24 (6H, s), 0.74 (3H, t, J = 7.4 Hz), 0.98 (9H, s), 1.01 (9H, s), 1.37 (2H, sx, J = 7.4 Hz), 1.68 (6H, s), 1.91 (2H, t, J = 7.4 Hz), 3.57 (2H, s), 6.80 (2H, d, J = 8.6 Hz), 6.82 (2H, d, J = 8.6 Hz), 7.19 (2H, brd, J = 8.0 Hz), 7.21−7.31 (3H, m), 7.30 (4H, d, J = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.4 (CH_3 × 2), −4.3 (CH_3 × 2), 13.5 (CH_3), 18.0 (CH_2), 18.2 (C × 2), 25.7 (CH_3 × 6), 26.0 (CH_3 × 2), 35.2 (CH_2), 40.9 (CH_2), 116.2 (C), 116.4 (C), 118.9 (C), 119.7 (CH × 4), 124.2 (C), 124.3 (C), 127.2 (CH), 128.6 (CH × 2), 129.4 (CH × 2), 130.8 (CH × 2), 130.9 (CH × 2), 133.0 (C), 134.2 (C × 2), 142.7 (C), 142.9 (C), 155.3 (C × 2), 168.9 (C), 171.0 (C); FD-HRMS (m/z) calcd for $C_{45}H_{58}O_8Si_2$ [M^+] 782.3670, found 782.3658.

6-Acetoxy-4,7-bis[4-(*tert*-butyldimethylsilyloxy)phenyl]-2,2-dimethylbenzo[*d*][1,3]dioxol-5-yl Phenylacetate (19). In the same manner as **17**, compound **19** was synthesized as a colorless solid (23.9 mg, 0.0317 mmol, 78%) from **16** (29.0 mg, 0.0407 mmol), NaH (60% in mineral oil, 12.0 mg, 0.300 mmol), and AcCl (0.007 mL, 0.1 mmol). **19**: mp 157−160 °C; IR (KBr) ν 3088, 3067, 3035, 2955, 2930, 2895, 2858, 1772, 1609, 1520, 1472, 1464, 1440, 1394, 1376, 1368, 1300, 1263, 1217, 1196, 1172, 1110, 1020, 914, 839, 805, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.21 (6H, s), 0.24 (6H, s), 0.98 (9H, s), 1.01 (9H, s), 1.65 (3H, s), 1.68 (6H, s), 3.58 (2H, s), 6.82 (2H, d, J = 8.6 Hz), 6.83 (2H, d, J = 8.6 Hz), 7.20−7.32 (5H, m), 7.307 (2H, d, J = 8.6 Hz), 7.315 (2H, d, J = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.4 (CH_3 × 2), −4.3 (CH_3 × 2), 18.2 (C × 2), 19.9 (CH_3), 25.6 (CH_3 × 6), 26.1 (CH_3 × 2), 41.0 (CH_2), 116.22 (C), 116.25 (C), 118.9 (C), 119.7 (CH × 4), 124.1 (C), 124.2 (C), 127.2 (CH), 128.7 (CH × 2), 129.4 (CH × 2), 130.74 (CH × 2), 130.78 (CH × 2), 133.1 (C), 134.1 (C), 134.2 (C), 142.81 (C), 142.84 (C), 155.3 (C × 2), 168.5 (C), 168.9 (C); FD-HRMS (m/z) calcd for $C_{43}H_{54}O_8Si_2$ [M^+] 754.3357, found 754.3337.

4,7-Bis[4-(*tert*-butyldimethylsilyloxy)phenyl]-2,2-dimethylbenzo[*d*][1,3]dioxole-5,6-diyl Bis(phenylacetate) (20). To a solution of **14** (100.0 mg, 0.1687 mmol) in THF (3.4 mL) was added PtO_2 (1.9 mg, 0.0084 mmol), and the mixture was stirred under H_2 atmosphere at 24 °C. After being stirred for 1 h, the red reaction solution turned to a clear pale yellow solution. Then, the solution

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(including **15**) was placed under Ar atmosphere, and cooled to −78 °C. To the solution were added BuLi (1.65 mol/L in hexane, 0.307 mL, 0.506 mmol) and the mixture was stirred at −78 °C for 1 h. Then, to the mixture was added phenylacetyl chloride (0.067 mL, 0.51 mmol) at −78 °C, and the mixture was warmed to 0 °C and stirred for 17 h. Then, the mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 50 → 15) to give **20** (113.9 mg, 0.1370 mmol, 81% over two steps) as a colorless solid. **20**: mp 174−175 °C; IR (KBr) ν 3088, 3064, 3033, 2955, 2930, 2887, 2858, 1772, 1609, 1520, 1471, 1463, 1440, 1391, 1376, 1263, 1219, 1172, 1125, 1106, 1011, 915, 841, 806, 782, 730, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.23 (12H, s), 1.00 (18H, s), 1.67 (6H, s), 3.29 (4H, s), 6.75 (4H, d, J = 8.5 Hz), 7.09 (4H, brd, J = 8.0 Hz), 7.20−7.29 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.3 (CH_3 × 4), 18.1 (C × 2), 25.6 (CH_3 × 6), 26.0 (CH_3 × 2), 40.4 (CH_2 × 2), 116.3 (C × 2), 118.8 (C), 119.6 (CH × 4), 124.0 (C × 2), 127.2 (CH × 2), 128.5 (CH × 4), 129.4 (CH × 4), 130.7 (CH × 4), 133.1 (C × 2), 134.1 (C × 2), 142.8 (C × 2), 155.2 (C × 2), 168.8 (C × 2); FD-HRMS (m/z) calcd for $C_{49}H_{58}O_8Si_2$ [M^+] 830.3670, found 830.3690.

4,7-Bis[4-(*tert*-butyldimethylsilyloxy)phenyl]-2,2-dimethylbenzo[*d*][1,3]dioxole-5,6-diyl Bis(butanoate) (21). In the same manner as **20**, compound **21** was synthesized as a colorless solid (116.8 mg, 0.1589 mmol, 98% over two steps) from **14** (96.1 mg, 0.162 mmol), PtO_2 (≤1.0 mg, ≤ 0.0044 mmol), H_2, BuLi (1.62 mol/L in hexane, 0.30 mL, 0.49 mmol), and butanoyl chloride (0.0508 mL, 0.486 mmol). **21**: mp 164−168 °C; IR (KBr) ν 3066, 3041, 2958, 2930, 2898, 2885, 2859, 1771, 1608, 1520, 1471, 1464, 1440, 1394, 1377, 1362, 1299, 1263, 1221, 1169, 1141, 1109, 1094, 1077, 1017, 1010, 916, 837, 805, 782 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.22 (12H, s), 0.82 (6H, t, J = 7.4 Hz), 0.99 (18H, s), 1.53 (4H, sx, J = 7.4 Hz), 1.68 (6H, s), 2.26 (4H, t, J = 7.4 Hz), 6.84 (4H, d, J = 8.6 Hz), 7.33 (4H, d, J = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.4 (CH_3 × 4), 13.5 (CH_3 × 2), 18.17 (C × 2), 18.21 (CH_2 × 2), 25.6 (CH_3 × 6), 26.0 (CH_3 × 2), 35.7 (CH_2 × 2), 116.4 (C × 2), 118.8 (C), 119.7 (CH × 4), 124.4 (C × 2), 130.9 (CH × 4), 134.3 (C × 2), 142.8 (C × 2), 155.3 (C × 2), 171.1 (C × 2); FD-HRMS (m/z) calcd for $C_{41}H_{58}O_8Si_2$ [M^+] 734.3670, found 734.3683.

Thelephantin O (1). To a solution of **17** (28.2 mg, 0.0345 mmol) and ethane-1,2-dithiol (0.0322 mL, 0.345 mmol) in $MeNO_2$ (0.7 mL) was added $AlCl_3$ (40.0 mg, 0.300 mmol) at −20 °C, and the mixture was stirred for 30 min. To the solution were added satd aq potassium sodium tartrate, H_2O, and EtOAc, and the mixture was stirred at 24 °C for 1 h. Then, the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, $CHCl_3$/MeOH = 20) to give **1** (16.7 mg, 0.0304 mmol, 88%) as a colorless solid. **1**: mp 246−247 °C; IR (KBr) ν 3432, 3036, 2919, 2850, 1738, 1632, 1613, 1526, 1452, 1429, 1263, 1173, 1107, 1059, 1024, 973, 833, 711, 699, 544 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 3.32 (2H, s), 6.70 (2H, d, J = 8.8 Hz), 6.79 (2H, brd, J = 7.9 Hz), 6.81 (2H, d, J = 8.8 Hz), 6.94−7.03 (3H, m), 7.16 (2H, d, J = 8.8 Hz), 7.20 (2H, d, J = 8.8 Hz), 7.41 (2H, brdd, J = 7.5, 8.4 Hz), 7.59 (1H, brtt, J = 1.3, 7.5 Hz), 7.80 (2H, brdd, J = 1.3, 8.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 41.3 (CH_2), 115.9 (CH × 2), 116.1 (CH × 2), 123.88 (C), 123.95 (C), 124.82 (C), 124.84 (C), 127.9 (CH), 129.3 (CH × 2), 129.6 (CH × 2), 130.04 (CH × 2), 130.08 (C), 130.9 (CH × 2), 132.55 (CH × 2), 132.61 (CH × 2), 134.2 (C), 134.7 (CH), 134.83 (C), 134.92 (C), 142.6 (C × 2), 157.9 (C), 158.1 (C), 166.1 (C), 171.3 (C); UV−vis (MeOH) λ (log ε) 208 (4.83), 231 (4.66), 261 (4.44) nm; FD-HRMS (m/z) calcd for $C_{33}H_{24}O_8$ [M^+] 548.1471, found 548.1463.

Terrestrin C (2). In the same manner as **1**, compound **2** was synthesized as a pale brown solid (8.5 mg, 0.017 mmol, 88%) from **18** (14.7 mg, 0.0188 mmol), ethane-1,2-dithiol (0.016 mL, 0.19 mmol), and $AlCl_3$ (21.2 mg, 0.159 mmol). **2**: mp 91−93 °C; IR (neat) ν 3414, 3090, 3065, 3033, 2976, 2935, 2876, 1767, 1751, 1703, 1613, 1592, 1526, 1496, 1456, 1429, 1384, 1365, 1269, 1230, 1173, 1147, 1108, 1077, 983, 834, 730, 697 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.70 (3H, t, J = 7.4 Hz), 1.30 (2H, brsx, J = 7.4 Hz), 1.86 (2H, t, J = 7.3 Hz), 3.48 (2H, s), 6.796 (2H, d, J = 8.7 Hz), 6.800 (2H, d, J = 8.7 Hz), 7.06 (2H, dd, J = 1.8, 7.6 Hz), 7.12 (2H, d, J = 8.7 Hz), 7.13 (2H, d, J = 8.7 Hz), 7.18−7.27 (3H, m); ^{13}C NMR (100 MHz, CD_3OD) δ 13.7 (CH_3), 19.0 (CH_2), 36.1 (CH_2), 41.5 (CH_2), 115.97 (CH × 2), 116.10 (CH × 2), 123.86 (C), 123.93 (C), 124.91 (C), 124.98 (C), 128.1 (CH), 129.6 (CH × 2), 130.4 (CH × 2), 132.62 (CH × 2), 132.67 (CH × 2), 134.71 (C), 134.76 (C), 134.80 (C), 142.49 (C), 142.61 (C), 158.2 (C × 2), 171.2 (C), 173.1 (C); UV−vis (MeOH) λ (log ε) 204 (4.76, shoulder), 227 (4.38), 262 (4.30) nm; FD-HRMS (m/z) calcd for $C_{30}H_{26}O_8$ [M^+] 514.1628, found 514.1617.

Terrestrin D (3). In the same manner as **1**, compound **3** was synthesized as a pale brown solid (15.9 mg, 0.0327 mmol, 95%) from **19** (25.9 mg, 0.0343 mmol), ethane-1,2-dithiol (0.029 mL, 0.35 mmol), and $AlCl_3$ (37.4 mg, 0.280 mmol). **3**: mp 118−120 °C; IR (KBr) ν 3425, 3061, 3031, 2958, 2924, 2855, 1757, 1701, 1613, 1526, 1457, 1426, 1369, 1340, 1214, 1173, 1106, 1014, 980, 903, 834, 730, 696, 592, 536 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.61 (3H, s), 3.50 (2H, s), 6.80 (4H, d, J = 8.7 Hz), 7.08 (2H, dd, J = 1.6, 7.7 Hz), 7.12 (2H, d, J = 8.7 Hz), 7.14 (2H, d, J = 8.7 Hz), 7.19−7.28 (3H, m); ^{13}C NMR (100 MHz, CD_3OD) δ 20.0 (CH_3), 41.5 (CH_2), 115.96 (CH × 2), 116.10 (CH × 2), 123.80 (C), 123.86 (C), 124.89 (C), 124.96 (C), 128.2 (CH), 129.6 (CH × 2), 130.4 (CH × 2), 132.56 (CH × 2), 132.62 (CH × 2), 134.71 (C), 134.80 (C), 134.82 (C), 142.55 (C), 142.57 (C), 158.12 (C), 158.18 (C), 170.5 (C), 171.2 (C); UV−vis (MeOH) λ (log ε) 204 (4.80), 224 (4.42), 263 (4.39) nm; FD-HRMS (m/z) calcd for $C_{28}H_{22}O_8$ [M^+] 486.1315, found 486.1331.

Vialinin A/Terrestrin A (4). In the same manner as **1**, compound **4** was synthesized as a colorless solid (11.3 mg, 0.0201 mmol, 73%) from **20** (22.9 mg, 0.0276 mmol), ethane-1,2-dithiol (0.0236 mL, 0.283 mmol), and $AlCl_3$ (36.7 mg, 0.275 mmol). **4**: mp 211−213 °C; IR (KBr) ν 3427, 3088, 3064, 3033, 2925, 2853, 1760, 1613, 1525, 1496, 1455, 1428, 1384, 1343, 1229, 1173, 1126, 985, 835, 731, 696, 588, 538, 513 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 3.36 (4H, s), 6.83 (4H, d, J = 8.7 Hz), 7.02 (4H, brd, J = 8.1 Hz), 7.12 (4H, d, J = 8.7 Hz), 7.19−7.28 (6H, m); ^1H NMR (400 MHz, CD_3OD) δ 3.25 (4H, s), 6.77 (4H, d, J = 8.7 Hz), 6.96 (4H, brd, J = 8.1 Hz), 7.09 (4H, d, J = 8.7 Hz), 7.17−7.26 (6H, m); ^{13}C NMR (100 MHz, acetone-d_6) δ 40.6 (CH_2 × 2), 115.9 (CH × 4), 123.1 (C × 2), 124.4 (C × 2), 127.7 (CH × 2), 129.2 (CH × 4), 130.2 (CH × 4), 132.3 (CH × 4), 134.6 (C × 2), 134.7 (C × 2), 141.7 (C × 2), 157.8 (C × 2), 169.6 (C × 2); ^{13}C NMR (100 MHz, CD_3OD) δ 41.1 (CH_2 × 2), 116.1 (CH × 4), 123.9 (C × 2), 124.8 (C × 2), 128.1 (CH × 2), 129.6 (CH × 4), 130.4 (CH × 4), 132.6 (CH × 4), 134.68 (C × 2), 134.72 (C × 2), 142.6 (C × 2), 158.1 (C × 2), 171.2 (C × 2); UV−vis (MeOH) λ (log ε) 209 (4.68, shoulder), 230 (4.31), 261 (4.20) nm; FD-HRMS (m/z) calcd for $C_{34}H_{26}O_8$ [M^+] 562.1628, found 562.1607.

Terrestrin B (5). In the same manner as **1**, compound **5** was synthesized as a pale yellow solid (6.0 mg, 0.013 mmol, 93%) from **21** (10.2 mg, 0.0139 mmol), ethane-1,2-dithiol (0.012 mL, 0.14 mmol), and $AlCl_3$ (28.2 mg, 0.211 mmol). **5**: mp 182−184 °C; IR (KBr) ν 3425, 2968, 2934, 2875, 1745, 1639, 1632, 1614, 1598, 1526, 1461, 1385, 1250, 1172, 1104, 978, 832 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.76 (6H, t, J = 7.4 Hz), 1.43 (4H, brsx, J = 7.3 Hz), 2.16 (4H, t, J = 7.1 Hz), 6.82 (4H, d, J = 8.6 Hz), 7.15 (4H, d, J = 8.6 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 13.8 (CH_3 × 2), 19.2 (CH_2 × 2), 36.4 (CH_2 × 2), 116.0 (CH × 4), 123.9 (C × 2), 125.0 (C × 2), 132.7 (CH × 4), 134.8 (C × 2), 142.5 (C × 2), 158.2 (C × 2), 173.1 (C × 2); UV−vis (MeOH) λ (log ε) 204 (4.71), 226 (4.38), 263 (4.35) nm; FD-HRMS (m/z) calcd for $C_{26}H_{26}O_8$ [M^+] 466.1628, found 466.1629.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental methods, the assay method for cytotoxicity against HepG2 and Caco2 cells, and copies of ^1H and ^{13}C NMR spectra of all new compounds as well as synthetic thelephantin O, vialinin A/terrestrin A, and terrestrins

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B–D. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) When **9** was used as obtained from commercial sources, we often found that the reaction proceeded without acid catalyst. It may be attributable to acidic contamination in the commercial reagent because purified **9** did not react with 2,2-dimethoxypropane in the absence of acid catalyst.

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(14) Sodium dithionite ($Na_2S_2O_4$), regularly used for the reduction of related *o*-quinones to catechols, often produces sulfur during workup, and it makes isolation/purification of catechols difficult. Hydrogenation of **11** and **14** with a small amount of PtO_2 catalyst cleanly produced **12** and **15**, respectively, without any byproducts, and hence **12** and **15** were able to be used in the next reaction without purification and even removal of catalyst. See: Reinaud, O.; Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1985**, *26*, 3993.

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(16) The monoacylation step was also examined with pyridine (2 equiv) and phenylacetyl chloride (1.1 equiv) in CH_2Cl_2 after in situ hydrogenation of *o*-quinone **14**: the reaction produced a 12:1 mixture of monoester **16** and diester **20** (total 77% yield) along with a small amount of recovered **14**. However, the separation of the mixture of **16** and **20** proved to be difficult. Therefore, esterification of a monoanion of diol **15**, which gave monoester **16** almost exclusively, was employed.

(17) In the previous report,[1] the inhibition rate of cell viability in HepG2/Caco2 by natural thelephantin O and vialinin A (terrestrin A) at 8 μmol/L concentration showed 53.91 ± 3.34%/67.74 ± 2.34% and 38.85 ± 5.14%/55.41 ± 0.92%, respectively. Synthetic vialinin A also exhibited 44.23 ± 3.54% inhibition against HepG2 at 8 μmol/L concentration.

(18) In this work, the inhibitory activity of natural thelephantin O against HepG2 and Caco2 was remeasured, and the IC_{50} values were determined to be 15.8 (HepG2) and 15.2 μmol/L (Caco2).