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Note

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Bioinspired Asymmetric Synthesis of (–)-Gymnothelignan V

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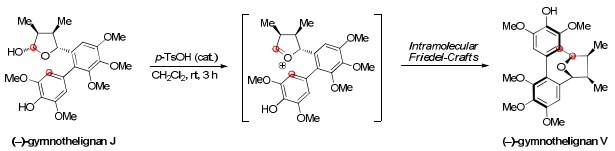
ABSTRACT:

Bioinspired asymmetric total synthesis of structurally unique sub-type of lignan namely (–)-gymnothelignan V was achieved. The key synthetic sequences involved reduction of eupomatilone skeleton leading to (–)-gymnothelignan J followed by the formation of the corresponding oxocarbenium ion and stereoselective intramolecular Friedel-Crafts reaction. Our synthetic approach provides the information to support the plausible biosynthetic pathway of this structurally unusual lignan. On a similar basis, other structurally related natural and non-natural gymnothelignans including (–)-gymnothelignan D, 6,9-bis-*epi*-gymnothelignan V, and 5-*epi*-gymnothelignans D and J were readily prepared.



Lignans are a large group of natural products derived from the dimerization of two phenylpropanoid (C6–C3) units. The enormous structural diversity of lignans stems from various linkage patterns between C6–C3 units, the difference of C6 groups, and a variety of relative orientations of the substituents attaching in their molecules.[1] Gymnothelignans are structurally novel subclass of lignans bearing tetrahydrofuran (THF) ring with variable conformations and stereochemistries across the THF ring. Gymnothelignans A–O isolated from *Gymnotheca chinensis* Decne (*G. chinensis*), a Chinese's traditional herbal medicine used for treatment of contusions and strains, were reported in 2012.[2] The gymnothelignans A–O could be classified to belong to three potentially related lignan skeletons including eupomatilone[3] (gymnothelignans A–K), dibenzocyclooctadiene[4] (gymnothelignans L, M, and V) and eupodienone[5] skeletons (gymnothelignans N and O) (Figure 1). Up to date, more than twenty-three gymnothelignans including gymnothelignans P−Y were isolated and identified.[2,6] Despite their interesting structural frameworks and potential biological activities, only a few syntheses of gymnothelignans have been reported.[4d-g,5c]

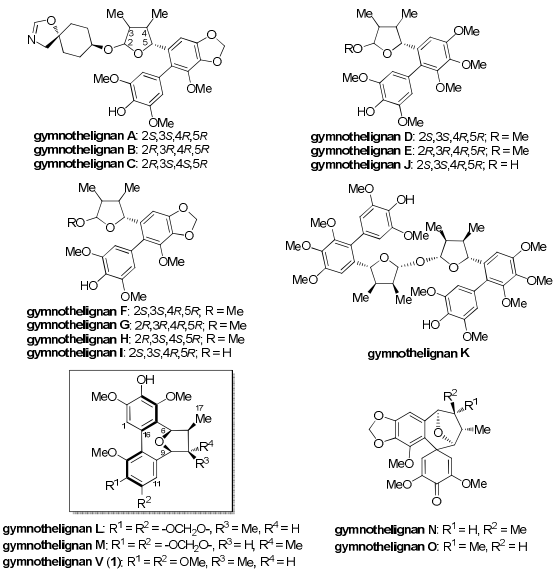
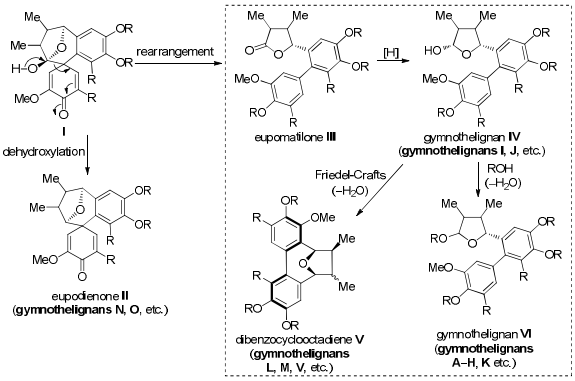


Figure 1. Structures of selected examples of gymnothelignans

(–)-Gymnothelignan V [(–)-**1**] and related derivatives bearing unique dibenzocyclooctadiene structural framework and stereochemistries attracted our attention to develop their asymmetric synthesis on the basis of biomimetic approach.[7] Biosynthetic pathway of gymnothelignans *via* spirohemiketal **I** was first proposed by Xu and Zhou.[2a,3a] An alternative biosynthetic pathway starting from 2,5-diaryltetrahydronfuran lignans was recently proposed by She.[5c] Beside the previously described biosynthetic routes, we speculated that three unique skeletons of gymnothelignans may biogenetically be derived *via* spirohemiketal **I** derived from the corresponding hydroxy ketone precursor[3a] (Scheme 1). Therefore, dehydroxylation of the hemiketal **I** could give eupodienone skeleton **II** (gymnothelignans N and O, etc.). On the other hand, the hemiketal **I** could undergo rearrangement to form eupomatilone skeleton **III** (eupomatilones 1–6)[3] which could further undergo reduction to provide the corresponding gymnothelignan of types **IV** (gymnothelignans I and J, etc.).[8] The dibenzocyclooctadiene skeleton **V** [(–)-**1**, etc.] was proposed to be accessed by an intramolecular Friedel−Crafts reaction through an oxocarbenium cation intermediate derived from **IV**. Finally, intermolecular

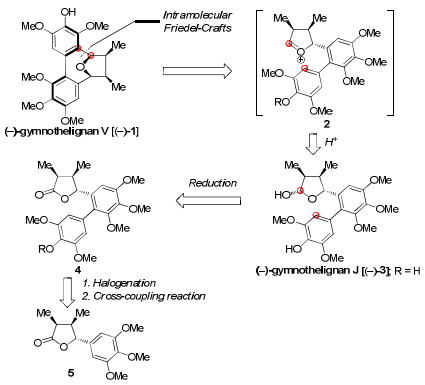
nucleophilic addition through an oxocarbenium cation intermediate derived from **IV** should deliver gymnothelignan of types **VI** (gymnothelignans A–H, and K, etc.) with diverse substituents and contiguous stereochemistries across the THF ring. In the present work, the synthetic conversions of **III** to **V** *via* **IV** will be described (Scheme 1).

Scheme 1. Proposed biosynthetic pathway to gymnothelignans



Guided by the plausible biosynthetic pathway (Scheme 1), the synthetic plan to access (–)-**1** was proposed as depicted in Scheme 2. The dibenzocyclooctadiene skeleton of (–)-**1** was planned to be constructed *via* the intramolecular Friedel–Crafts reaction of an oxocarbenium cation intermediate **2**[9] which should be readily generated from (–)-gymnothelignan J [(–)-**3**] upon treatment with an acid. Lignan **3** should be obtained *via* a stereoselective reduction of eupomatilone scaffold**4** which in turn should be readily synthesized from (3*S*,4*R*,5*R*)-γ-butyrolactone **5** by halogenation reaction followed by cross-coupling reaction.

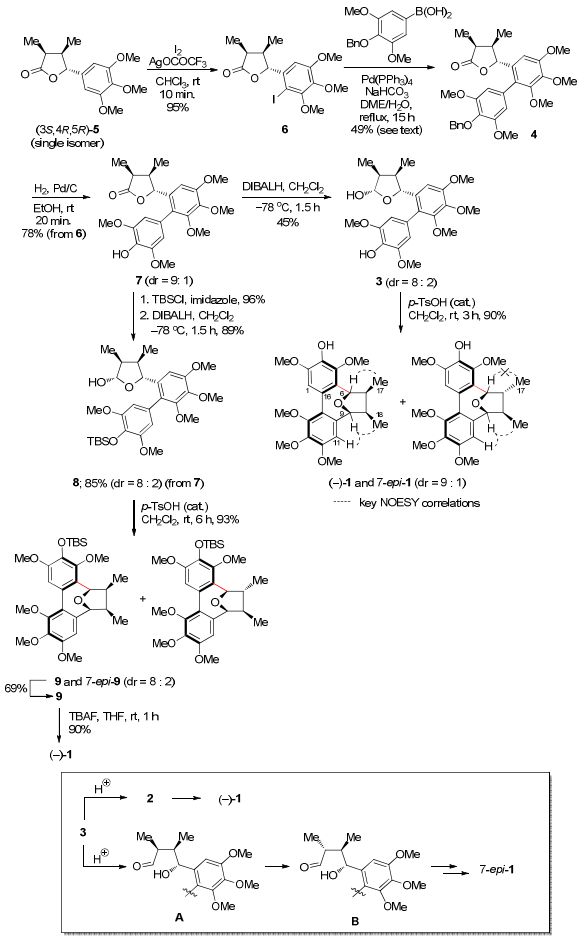
Scheme 2. Synthetic plan to (–)-gymnothelignan V [(–)-1]



The stereoselective construction of eupomatilone scaffold **4** was accomplished in a straightforward manner starting from (3*S*,4*R*,5*R*)-**5**.[3f,3i,7] Thus, iodination of (3*S*,4*R*,5*R*)-**5** (single isomer) using molecular iodine and silver trifluoroacetate ($AgOCOCF_3$) in $CHCl_3$ was readily completed within 10 min (TLC analysis) providing **6** in 95% yield (Scheme 3). The Suzuki-Miyaura coupling[3f,10] of **6** with [4-(benzyloxy)-3,5-dimethoxyphenyl]boronic acid using $Pd(PPh_3)_4$ as a catalyst in the presence of $NaHCO_3$ in a mixture of DME and H_2O as the solvents at refluxing temperature for 15 h gave the corresponding eupomatilone product **4**[11] which proved to be difficult to be isolated from aromatic by-products. Fortunately, partial separation could be achieved providing **4** in 49% yield upon careful purification of the crude mixture of **4** on silica gel. In a straightforward synthesis, the crude mixture of **4** (dr = 9 : 1), without purification, was subsequently subjected to debenzylation (H_2, Pd/C, EtOH, rt, 20 min.) to yield the corresponding product **7** (78% yield, dr = 9 :1, from **6**). The reduction of a keto group of **7** using DIBALH in CH_2Cl_2 at −78 °C for 1.5 h provided lignan **3** as a mixture of two diastereomers (45% yield, dr = 8 : 2). It is believed that the reduction reaction should proceed with high diastereoselectivity from the less hindered face of the carbonyl moiety of **7**. Isomerization could be originated from the equilibration of the ring-opening and ring-closing of the lactol moiety of **3**. Although (–)-**3** could be partially separated and fully characterized (see the Supporting Information), in the synthetic point of view, both diastereomers of **3** yielded the same oxocarbenium cation. Thus,

upon treatment of **3** (dr = 8 : 2) with a catalytic amount of *p*-TsOH in CH_2Cl_2 at room temperature, a complete consumption of **3** was observed (TLC monitoring) after 3 h. The corresponding oxocarbenium cation derived from **3** readily underwent stereoselective intramolecular Friedel-Crafts cyclization with highly oxygenated biphenyl moiety to give the desired product (–)-**1** together with its isomer, 7-*epi*-**1**,[12] as an inseparable mixture in 90% yield (dr = 9 : 1). The formation of 7-*epi*-**1** was proposed to proceed through the lactol ring-opening under acidic conditions followed by epimerization at the α carbon of the resulting aldehyde **A** to form **B** leading to 7-*epi*-**1** as depicted in Scheme 3. Gratifyingly, the overall yield of (–)-**1** can be improved by the followings; a phenolic moiety of **7** was protected as a silyl ether followed by the reduction of keto group (DIBALH, CH_2Cl_2, −78 °C, 1.5 h) providing a diastereomeric mixture of **8** in 85% yield (dr = 8 : 2) (from **7**). Without purification, intramolecular Friedel-Crafts cyclization of **8** gave a mixture of **9** and 7-*epi*-**9** in 93% yield (dr = 8 : 2). Upon careful chromatographic purification (SiO_2), analytical pure **9** could be separated in 69% yield. Finally, desilylation of **9** with TBAF gave (–)-**1** in 90% yield. The relative stereochemistry of (–)-**1** was confirmed on the basis of NOESY experiments. The spectroscopic characteristics of (–)-**1** and (–)-**3** are in good agreement with those reported in the literature (see the Supporting Information).

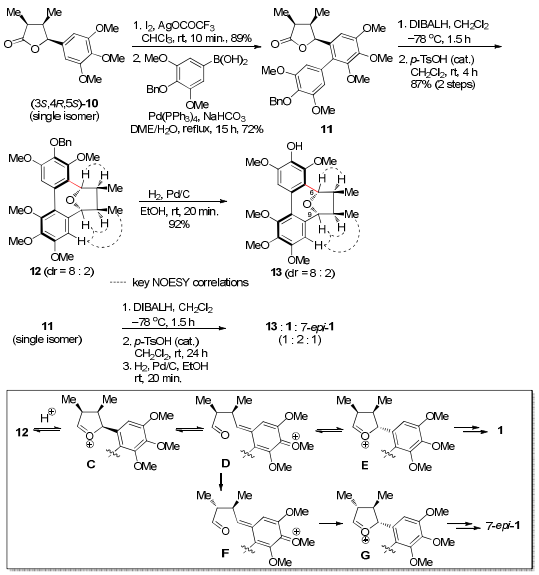
Scheme 3. Synthesis of (–)-gymnothelignan V [(–)-1] and (–)-gymnothelignan J [(–)-3]



In order to demonstrate the viability of our biomimetic approach to access structurally complex lignans, eupomatilone derivative **11** bearing all-*syn* stereochemistries was synthesized from γ-butyrolactone (3*S*,4*R*,5*S*)-**10** (single isomer)[3e] in 64% yield (two steps). Reduction of **11** gave the corresponding lactol which was further treated with *p*-TsOH (CH_2Cl_2, rt, 4 h) to promote intramolecular Friedel-Crafts cyclization providing the corresponding dibenzocyclooctadiene **12** in 87% yield (dr = 8 : 2) after a two-steps reaction (Scheme 4). Debenzylation of **12** gave 6,9-bis-*epi*-gymnothelignan V (**13**) (92% yield, dr = 8 : 2).[13] Interestingly, dibenzocyclooctadiene skeletons were found to be sensitive to acid conditions and readily underwent epimerization under prolonged reaction time. It was found that the reaction between the lactol derived from **11** with a catalytic amount of *p*-TsOH in CH_2Cl_2 at room temperature for 24 h led to the formation

of **13**, **1**, and 7-*epi*-**1** with a ratio 1 : 2 : 1 (^{1}H NMR analysis) after debenzylation. Since **12** (dr = 84 : 16) could be obtained when the reaction was carried out at room temperature for 4 h (TLC monitoring), it was hypothesized that, under acidic conditions, **12** underwent ring-opening reaction to form cationic intermediates **C** and **D**. Cyclization of **D** preferably took place to give **E** with *anti*-orientation between the methyl group at C-4 and the aromatic ring at C-5 in order to minimize the steric interaction between the two groups. Subsequent intramolecular Friedel-Crafts cyclization of **E** then gave **1** after debenzylation. On the other hand, epimerization at the α carbon of **D** led to 7-*epi*-**1** via **F** and **G**, respectively. Noteworthy, the epimerization was also observed when **1** was treated with a catalytic amount of *p*-TsOH (CH_2Cl_2, rt, 24 h) providing a mixture of **1**, 7-*epi*-**1** and **13** with a ratio 1 : 1 : 1 (^{1}H NMR analysis).

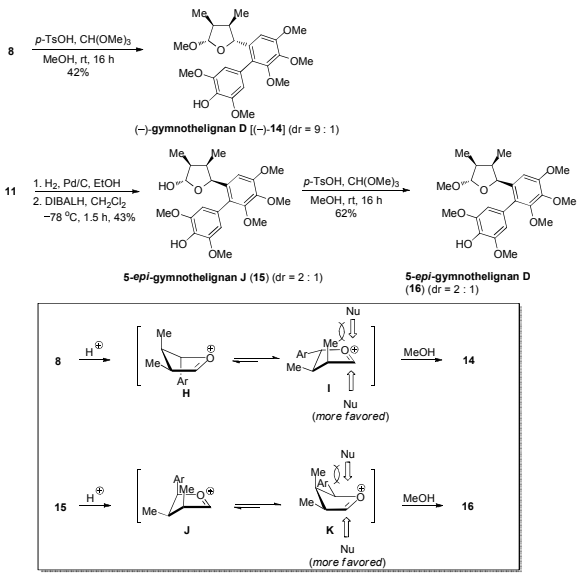
Scheme 4. Synthesis of 6,9-bis-*epi*-gymnothelignan V (13)



The synthesis of other structurally related natural and non-natural gymnothelignans, such as (–)-gymnothelignan D [(–)-**14**], 5-*epi*-gymnothelignan J (**15**), and 5-*epi*-gymnothelignan D (**16**) was also demonstrated (Scheme 5). Thus, treatment of **8** with a catalytic amount of *p*-TsOH in the

presence of trimethyl orthoformate in dry MeOH at room temperature overnight (16 h) promoted the formation of the oxocarbenium cation followed by the intermolecular nucleophilic substitution together with desilylation providing **14** in 83% yield (dr = 71 : 16 : 13) in a single operation. Compound (–)-**14** (42% yield, dr = 9 : 1) could be separated upon careful chromatographic purification (SiO_2). The spectroscopic characteristics of (–)-**14** are in agreement with those reported in the literature (see the Supporting Information). Similarly, 5-*epi*-gymnothelignan J (**15**) and 5-*epi*-gymnothelignan D (**16**) could be synthesized in 43% (dr = 2 : 1) and 62% yields (dr = 2 : 1), respectively. The observed diastereoselectivity for the nucleophilic addition was proposed to occur through the attack of the nucleophile on the less sterically hindered faces of favorable conformers **I** and **K** derived from **8** and **15**, respectively.[14] The stereochemistries of **15** and **16** were established on the basis of NOESY experiments (see the Supporting Information).

Scheme 5. Synthesis of (–)-gymnothelignan D [(–)-14], 5-*epi*-gymnothelignan J (15) and 5-*epi*-gymnothelignan D (16)



In conclusion, on the basis of the proposed biosynthetic pathway, we reported the first asymmetric total synthesis of (–)-gymnothelignan V, the structurally novel dibenzocyclooctadiene gymnothelignan. Reduction of the eupomatilone skeleton to give (–)-gymnothelignan J, the formation of the corresponding oxocarbenium ion followed by the intramolecular Friedel-Crafts reaction were the key reactions employed. Our work provides the information to support the plausible biosynthetic pathway of gymnothelignans which is in accordance with She's proposal. The viability of the synthetic approach proved to be practicable for the synthesis of various structurally related gymnothelignans including (–)-gymnothelignan D, 6,9-bis-*epi*-gymnothelignan V, 5-*epi*-gymnothelignan J, and 5-*epi*-gymnothelignan D. Asymmetric synthesis of other members of gymnothelignans and related structures is in progress.

EXPERIMENTAL SECTION

General information. ^{1}H NMR spectra were recorded on 400 or 500 MHz spectrometer and are reported in ppm. Proton-decoupled ^{13}C NMR spectra were recorded on 75, 100, or 125 MHz spectrometer and are reported in ppm. Reactions were monitored by thin-layer chromatography (TLC) and visualized by UV and a solution of $KMnO_4$. Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled over calcium hydride and stored over activated molecular sieves (4 Å). Ethanol (EtOH) and methanol (MeOH) were distilled over Mg turning. Other common solvents [CH_2Cl_2, hexanes, ethyl acetate (EtOAc), MeOH, and acetone] were distilled before use. All glassware and syringes were oven-dried and kept in a desiccator before use. Purification of the reaction products were carried out

by column chromatography or preparative thin-layer chromatography plates on silica gel. Compounds **5** and **10** were synthesized according to the literature.[3,7]

Synthesis of compound 4: To a solution of **5** (280 mg, 1 mmol) in $CHCl_3$ (10 mL) was added $AgOCOCF_3$ (221 mg, 1 mmol, 1 equiv.) in one portion under argon. Iodine (254 mg, 1 mmol, 1 equiv.) was added to the resulting suspension. The progress of the reaction was monitored by TLC analysis. After stirring for 10 min., the reaction mixture was filtered through a Celite pad and washed with $CHCl_3$ (40 mL). The filtrate was washed with saturated aqueous $NaHSO_3$ and dried over anhydrous Na_2SO_4. Purification by column chromatography (30% EtOAc in hexanes) gave compound **6** (386 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 (s, 1H), 5.24 (d, J = 2.2 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 2.80–2.70 (m, 1H), 2.60–2.50 (m, 1H), 1.28 (d, J = 7.2 Hz, 3H), 1.17 (d, J = 7.3 Hz, 3H). The ^{1}H NMR data of this sample were identical with those reported.[3f] A round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a reflux condenser was charged with **6** (41 mg, 0.1 mmol), [4-(benzyloxy)-3,5-dimethoxyphenyl]boronic acid (43 mg, 0.15 mmol, 1.5 equiv.), $NaHCO_3$ (29 mg, 0.35 mmol, 3.5 equiv.), $Pd(PPh_3)_4$ (6 mg, 5 mol%), DME (3.5 mL), and H_2O (0.35 mL). The resulting mixture was heated to reflux for 15 h. After cooling down to room temperature, the mixture was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. Purification by column chromatography (40% EtOAc in hexanes) gave a mixture of **4** with aromatic by-products. Careful purification by preparative thin-layer chromatography (30% EtOAc in hexanes, multiple runs) gave **4** (26 mg, 49% yield) as a pale yellow oil. $[\alpha]^{27}_D$ = –27 (c 0.36, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52–7.48 (m, 2H), 7.38–7.27 (m, 3H), 6.66 (s, 1H), 6.45 (s, 1H), 6.40 (s, 1H), 5.10 (s, 2H), 5.01 (d, J = 4.5 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.81 (s, 3H), 3.80

(s, 3H), 3.66 (s, 3H), 2.80–2.70 (m, 1H), 2.43–2.34 (m, 1H), 1.06 (d, J = 7.5 Hz, 3H), 0.62 (d, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.8, 153.6, 153.5, 153.1, 151.6, 142.1, 137.7, 136.1, 132.5, 131.0, 128.6, 128.1, 128.0, 127.9, 108.3, 106.8, 103.8, 82.9, 74.9, 61.3, 60.9, 56.3, 56.2, 41.6, 37.1, 13.4, 9.8; IR (neat): ν_{max} 1773, 1583, 1489, 1458, 1405, 1313, 1236, 1126, 1102 cm^{-1}; MS: *m/z* (%) relative intensity 431 (M^+–Bn, 100), 399 (22), 343 (24), 331 (11); HRMS (ESI-TOF) calcd for $C_{30}H_{34}O_8Na$ $[M+Na]^+$: 545.2151, found: 545.2150.

Compound 7: A round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a reflux condenser was charged with **6** (36 mg, 0.09 mmol), [4-(benzyloxy)-3,5-dimethoxyphenyl]boronic acid (39 mg, 0.14 mmol, 1.5 equiv.), $NaHCO_3$ (28 mg, 0.3 mmol, 3.5 equiv.), $Pd(PPh_3)_4$ (6 mg, 5 mol%), DME (2 mL), and H_2O (0.2 mL). The resulting mixture was heated to reflux for 15 h. After cooling down to room temperature, the mixture was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with water, brine, and dried over anhydrous Na_2SO_4 to give a crude mixture of **4**. A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with the crude mixture of **4**, Pd/C (10% w/w, 24 mg), and dry EtOH (2 mL). The argon inlet was replaced by a H_2 balloon, and the reaction mixture was stirred at room temperature for 20 min. After filtration through a Celite pad, the crude mixture was purified by column chromatography (60% EtOAc in hexanes) to yield **7** (30 mg, 78% yield) (from **6**) as a white solid. mp. = 136–140 ^{o}C (60% EtOAc in hexanes); $[\alpha]^{26}_{D}$ = –46 (c 0.98, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (s, 1H), 6.47 (s, 1H), 6.43 (s, 1H), 5.63 (br s, 1H), 5.03 (d, J = 4.8 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.87 (s, 6H), 3.65 (s, 3H), 2.85–2.70 (m, 1H), 2.50–2.35 (m, 1H), 1.07 (d, J = 7.5 Hz, 3H), 0.68 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9, 153.0, 151.7, 147.0, 146.9, 142.0, 134.0, 132.6, 128.2, 126.3, 107.7, 106.2,

103.7, 82.9, 61.2, 60.9, 56.4, 56.2, 41.6, 37.3, 13.3, 9.9; IR (neat): ν_{max} 3442, 1762, 1598, 1460, 1404, 1104 cm^{-1}; MS: *m/z* (%) relative intensity 432 (M^+, 63), 358 (10), 331 (100); HRMS (ESI-TOF) calcd for$C_{23}H_{28}NaO_8$ $[M+Na]^+$: 455.1682, found: 455.1698.

(–)-Gymnothelignan J [(–)-3]: Compound **7** (44 mg, 0.1 mmol) was dissolved in dry CH_2Cl_2 (1 mL) and the resulting solution was cooled at −78 °C. A solution of DIBALH (1 M in hexanes) (0.4 mL, 0.4 mmol, 5 equiv.) was added dropwise. The reaction was allowed to stir at −78 °C for 1.5 h then it was quenched with MeOH at −78 °C, allowed to warm to room temperature, and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with water, brine, and dried over anhydrous Na_2SO_4. Purification by column chromatography (75% EtOAc in hexanes) gave **3** (20 mg, 45% yield, dr = 81 : 19) as a pale yellow oil. (–)-(**3**) (8 mg, 18% yield) could be partially separated using preparative thin-layer chromatography (50% EtOAc in hexanes, multiple runs). $[\alpha]^{27}_D$ = –31 (c 0.76, acetone) {lit.[2a] $[\alpha]^{20}_D$ = −4 (c 0.10, acetone)}; ^{1}H NMR (400 MHz, acetone-d_6): δ 7.41 (s, 1H), 6.49–6.43 (m, 2H), 5.07 (d, *J* = 2.0 Hz, 1H), 4.54 (d, *J* = 7.7 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 9H), 3.58 (s, 3H), 2.45–2.35 (m, 1H), 2.15–2.05 (m, 1H), 0.78 (d, *J* = 7.3 Hz, 3H), 0.69 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 153.7, 151.6, 148.2, 148.1, 142.1, 138.3, 135.8, 129.8, 127.8, 110.0, 108.4, 108.2, 104.4, 83.9, 61.3, 60.8, 56.8, 56.2, 45.0, 44.4, 12.4, 11.4; IR (neat): ν_{max} 3398, 1599, 1519, 1489, 1100 cm^{-1}; MS: m/z (%) relative intensity 434 (M^+, 38), 416 (100); HRMS (ESI-TOF) calcd for $C_{23}H_{30}O_8Na$ $[M+Na]^+$: 457.1838, found: 457.1839. The spectral data of this sample were identical with those reported.[2a]

(–)-Gymnothelignan V [(–)-1] and 7-*epi*-1: A solution mixture of **3** (dr = 81 : 19, 15 mg, 0.03 mmol) and a catalytic amount of *p*-TsOH in dry CH_2Cl_2 (1 mL) was allowed to stir at room

temperature for 3 h. The progress of the reaction was monitored by TLC. After complete consumption of **3**, the reaction mixture was quenched with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (40% EtOAc in hexanes) gave a mixture of (–)-**1** and 7-*epi*-**1** (13 mg, 90% yield, dr = 9 : 1) as a yellow gum. ^{1}H NMR (400 MHz, acetone-d_6, integrated equally for (–)-**1** and 7-*epi*-**1**, signals of (–)-**1** marked*): δ 7.69* (s, 1H), 7.55 (s, 1H), 7.48* (s, 1H), 6.70 (s, 1H), 6.68* (s, 1H), 5.50 (d, *J* = 6.1 Hz, 1H), 5.12* (d, *J* = 1.8 Hz, 1H), 4.54* (d, *J* = 5.4 Hz, 1H), 4.44 (d, *J* = 6.1 Hz, 1H), 3.88* (s, 3H), 3.85* (s, 3H), 3.83 (s, 3H), 3.82* (s, 3H), 3.81* (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.47* (s, 3H), 3.42 (s, 3H), 2.45–2.35* (m, 1H), 2.35–2.20* (m, 1H), 1.11 (d, *J* = 6.7 Hz, 3H), 1.07* (d, *J* = 7.0 Hz, 3H), 1.06* (d, *J* = 7.0 Hz, 3H), 0.66 (d, *J* = 6.8 Hz, 3H). Some peaks of 7-*epi*-**1** overlap with those of (–)-**1**; ^{13}C NMR (100 MHz, acetone-d_6, signals of (–)-**1** marked*): δ 154.8*, 152.6*, 147.3*, 145.0*, 143.5*, 142.4*, 139.3*, 131.5*, 124.7*, 124.5*, 113.9, 113.5*, 108.4, 108.3*, 92.0, 91.4*, 85.8*, 83.1, 61.6*, 61.5*, 60.9*, 60.8, 57.0*, 56.7*, 54.6, 49.8*, 46.4, 43.4*, 17.6, 14.6*, 14.4*, 13.1. Some peaks of 7-*epi*-**1** overlap with those of (–)-**1**.

Compound 8: Compound **7** (43 mg, 0.1 mmol) was dissolved in dry CH_2Cl_2 (2 mL) and then imidazole (14 mg, 0.2 mmol) and a solution of TBSCl (30 mg, 0.2 mmol) in dry hexanes (0.5 mL) were added. The reaction mixture was allowed to stir at room temperature overnight and then quenched with a saturated aqueous $NaHCO_3$ solution (10 mL). The organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (30% EtOAc in hexanes) gave the corresponding silylated product of **7** (52 mg, 96% yield) as a white solid. mp. = 88–90 ^{o}C (30% EtOAc in hexanes); $[\alpha]^{25}_D$ = –36 (c 0.32,

$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (s, 1H), 6.43 (br s, 1H), 6.39 (d, J = 1.1 Hz, 1H), 5.08 (d, J = 4.2 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.78 (s, 6H), 3.61 (s, 3H), 2.80–2.70 (m, 1H), 2.45–2.35 (m, 1H), 1.05 (d, J = 7.5 Hz, 3H), 1.20 (s, 9H), 0.66 (d, J = 7.1 Hz, 3H), 0.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.0, 152.9, 151.7, 151.6, 151.5, 142.0, 133.7, 132.7, 128.3, 127.7, 108.2, 106.6, 103.6, 83.0, 61.2, 60.9, 56.2, 55.9, 55.8, 41.6, 37.1, 29.7, 25.8, 13.5, 9.7, –4.7; IR (neat): ν_{max} 1779, 1582, 1456, 1404, 1314, 1259 cm^{-1}; MS: m/z (%) relative intensity 547 (M^+, 1), 489 (100); HRMS (ESI-TOF) calcd for $C_{29}H_{42}O_8SiNa$ $[M+Na]^+$: 569.2547, found: 569.2548. The obtained silylated product of **7** (37 mg, 0.07 mmol) was dissolved in dry CH_2Cl_2 (1 mL) under an argon atmosphere, and the resulting solution was cooled at −78 °C. A solution of DIBALH (1 M in hexanes) (0.14 mL, 0.14 mmol, 2 equiv.) was added dropwise. After stirring at −78 °C for 1.5 h, the reaction mixture was quenched with MeOH (2 mL) at −78 °C, allowed to warm to room temperature, and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (40% EtOAc in hexanes) gave **8** (33 mg, 89% yield) as a mixture of diastereomers (83 : 17). The crude mixture of **8** was further used in the next step without purification. ^{1}H NMR (400 MHz, acetone-d_6): δ 7.41 (s, 1H), 6.50–6.40 (m, 2H), 5.45–5.35 (m, 1H), 5.12–5.06 (m, 1H), 4.53 (d, J = 7.4 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.59 (s, 3H), 2.43–2.33 (m, 1H), 2.15–2.05 (m, 1H), 1.03 (s, 9H), 0.79 (d, J = 7.3 Hz, 3H), 0.69 (d, J = 7.1 Hz, 3H), 0.15 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 153.8, 152.0, 151.9, 151.6, 142.1, 138.3, 133.9, 130.2, 129.7, 109.6, 108.2, 107.9, 104.6, 84.0, 61.3, 60.8, 56.3, 56.2, 44.9, 44.4, 26.3, 19.4, 12.6, 11.3, 1.5, –4.3; HRMS (ESI-TOF) calcd for $C_{29}H_{44}O_8SiNa$ $[M+Na]^+$: 571.2703, found: 571.2706.

(–)-Gymnothelignan V [(–)-1]: A solution mixture of **8** (15 mg, 0.03 mmol) and a catalytic amount of *p*-TsOH in dry CH_2Cl_2 (1 mL) was allowed to stir at room temperature for 6 h. The progress of the reaction was monitored by TLC analysis. Then, the reaction mixture was quenched with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 to provide a mixture of **9** and 7-*epi*-**9** (13.5 mg, 93% yield, dr = 8 : 2). Careful purification of the mixture of **9** and 7-*epi*-**9** using preparative thin-layer chromatography on silica gel (20% EtOAc in hexanes, multiple runs) provided **9** in 69% yield (10 mg). $[\alpha]^{26}_{D}$ = –8.6 (c 0.45, CH_2Cl_2); ^{1}H NMR (400 MHz, acetone-d_6): δ 7.50 (s, 1H), 6.69 (s, 1H), 5.11 (d, *J* = 1.9 Hz, 1H), 4.57 (d, *J* = 5.0 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 6H), 3.81 (s, 3H), 3.48 (s, 3H), 2.43–2.33 (m, 1H), 2.33–2.23 (m, 1H), 1.08 (d, *J* = 2.2 Hz, 3H), 1.06 (d, *J* = 2.3 Hz, 3H), 1.04 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6): δ 154.5, 152.4, 150.1, 148.9, 143.1, 141.9, 137.5, 131.1, 126.6, 123.9, 113.4, 107.8, 91.0, 85.1, 61.1, 61.0, 60.7, 56.2, 55.7, 48.8, 43.6, 26.2, 19.2, 14.1, 13.9, –4.3, –4.4; HRMS (ESI-TOF) calcd for $C_{29}H_{43}O_7Si$ $[M+H]^+$: 553.2778, found: 531.2777.

Treatment of **9** with a solution of TBAF in THF for 1 h gave (–)-**1** (7 mg, 90% yield) as a yellow gum after purification by column chromatography (30% EtOAc in hexanes). $[\alpha]^{26}_{D}$ = –9.3 (c 0.67, MeOH) {lit.[2d] $[\alpha]^{20}_{D}$ = –19 (c 0.31, MeOH)}; ^{1}H NMR (400 MHz, acetone-d_6): δ 7.67 (s, 1H), 7.48 (s, 1H), 6.68 (s, 1H), 5.12 (d, *J* = 1.5 Hz, 1H), 4.54 (d, *J* = 5.3 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.49 (s, 3H), 2.43–2.33 (m, 1H), 2.33–2.25 (m, 1H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 154.3, 152.1, 146.8, 144.5, 143.0, 141.9, 138.8, 131.0, 124.2, 124.1, 113.0, 107.8, 90.9, 85.2, 61.1, 61.0, 60.4, 56.5, 56.2, 49.3, 42.9, 14.1, 13.9; IR (neat): ν_{max} 3364, 1593, 1447, 1296, 1098 cm^{-1}; MS: m/z

(%) relative intensity 416 (M^+, 100), 371 (10), 358 (23); HRMS (ESI-TOF) calcd for $C_{23}H_{28}O_7Na$ $[M+Na]^+$: 439.1733, found: 439.1732.

The spectral data of this sample were identical with those reported.[2d]

Compound 11: According to the procedure for the synthesis of **4**, iodination of **10** (56 mg, 0.2 mmol) using I_2 (52 mg, 0.2 mmol, 1 equiv.) and $AgOCOCF_3$ (45 mg, 0.2 mmol, 1 equiv.) in $CHCl_3$ (3 mL) gave the corresponding aryl iodide (72 mg, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (s, 1H), 5.55 (d, *J* = 5.0 Hz, 1H), 3.88 (s, 6H), 3.87 (s, 3H), 3.35–3.25 (m, 1H), 3.10–3.00 (m, 1H), 1.21 (d, *J* = 7.2 Hz, 3H), 0.49 (d, *J* = 7.3 Hz, 3H). The ^{1}H NMR data of this sample were identical with those reported.[3f] Cross-coupling reaction of the obtained aryl iodide (35 mg, 0.08 mmol) using [4-(benzyloxy)-3,5-dimethoxyphenyl]boronic acid (39 mg, 0.13 mmol), $NaHCO_3$ (27 mg, 0.32 mmol), $Pd(PPh_3)_4$ (7 mg, 5 mol%), DME (3.5 mL), and H_2O (0.35 mL) gave **11** (32.5 mg, 72% yield) after purification by column chromatography (30% EtOAc in hexanes). $[\alpha]^{31}_D$ = –27 (c 0.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54–7.46 (m, 2H), 7.40–7.25 (m, 3H), 6.83 (s, 1H), 6.42 (d, *J* = 2.2 Hz, 1H), 6.31 (d, *J* = 2.2 Hz, 1H), 5.33 (d, *J* = 6.5 Hz, 1H), 5.11 (s, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.67 (s, 3H), 2.73–2.60 (m, 1H), 2.13–2.00 (m, 1H), 1.11 (d, *J* = 9.6 Hz, 3H), 0.53 (d, *J* = 9.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.7, 153.6, 153.4, 152.9, 151.2, 141.6, 137.7, 135.9, 131.2, 129.9, 128.5, 128.0, 127.8, 126.7, 107.6, 106.1, 104.9, 80.4, 74.8, 61.3, 60.9, 56.3, 40.7, 38.8, 9.9, 9.7; IR (neat): ν_{max} 1776, 1582, 1126, 1104 cm^{-1}; MS: *m/z* (%) relative intensity 522 (M^+, 36), 431 (100); HRMS (ESI-TOF) calcd for $C_{30}H_{34}NaO_8$ $[M + Na]^+$: 545.2151, found: 545.2152.

Compound 12: Compound **11** (25 mg, 0.05 mmol) was dissolved in dry CH_2Cl_2 (1 mL) and the resulting solution was cooled at −78 °C. A solution of DIBALH (1 M in hexanes) (0.1 mL, 0.1 mmol, 2 equiv.) was added dropwise. The reaction was allowed to stir at −78 °C for 1.5 h then it

was quenched with MeOH at −78 °C, allowed to warm to room temperature, and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine, and dried over anhydrous Na_2SO_4. The obtained crude mixture was dissolved in dry CH_2Cl_2 (1 mL) and a catalytic amount of *p*-TsOH was added. The reaction mixture was allowed to stir at room temperature for 4 h, quenched with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (30% EtOAc in hexanes) gave **12** (21 mg, 87% yield, after two steps) as a pale yellow oil. $[\alpha]^{25}_D$ = +0.3 (c 0.68, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6): δ 7.58–7.53 (m, 2H), 7.51 (s, 1H), 7.43–7.29 (m, 3H), 6.53 (s, 1H), 5.12 (d, *J* = 5.8 Hz, 1H), 5.09 (s, 2H), 5.05 (d, *J* = 6.2 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.47 (s, 3H), 2.16–2.08 (m, 1H), 1.88–1.78 (m, 1H), 1.18 (d, *J* = 6.7 Hz, 3H), 0.58 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ 154.5, 152.5, 152.2, 150.8, 143.0, 140.3, 139.3, 135.1, 132.8, 129.5, 129.1, 128.9, 128.6, 124.9, 115.4, 108.2, 88.2, 82.2, 75.4, 62.4, 61.5, 61.2, 56.6, 56.3, 53.7, 46.2, 17.6, 13.9; IR (neat): ν_{max} 1264, 1128, 1100 cm^{-1}; MS: m/z (%) relative intensity 506 (M^+, 40), 415 (100); HRMS (ESI-TOF) calcd for $C_{30}H_{35}O_7$ $[M + H]^+$: 507.2383, found: 507.2381.

6,9-Bis-*epi*-gymnothelignan V (13): Debenzylation of **12** (15 mg, 0.03 mmol) using H_2 balloon, Pd/C (10% w/w, 3 mg), and dry EtOH (1 mL) for 20 min and filtration through a Celite pad followed by purification by column chromatography (60% EtOAc in hexanes) gave **13** (11 mg, 92% yield) as a pale yellow oil. $[\alpha]^{25}_D$ = +0.5 (c 0.62, EtOAc); ^{1}H NMR (400 MHz, acetone-d_6): δ 7.64 (s, 1H), 7.47 (s, 1H), 6.50 (s, 1H), 5.11 (d, *J* = 5.8 Hz, 1H), 5.03 (d, *J* = 6.2 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.46 (s, 3H), 2.15–2.05 (m, 1H), 1.90–1.80 (m, 1H), 1.18 (d, *J* = 6.7 Hz, 3H), 0.57 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ

154.2, 152.0, 147.0, 145.0, 142.9, 138.7, 134.7, 132.9, 125.3, 124.3, 114.5, 108.2, 88.3, 82.2, 61.5, 61.4, 61.2, 56.8, 56.3, 53.6, 46.3, 17.7, 13.9; IR (neat): ν_{max} 3378, 1596, 1490, 1463, 1260 cm^{-1}; MS: m/z (%) relative intensity 416 (M^+, 100), 347 (29); HRMS (ESI-TOF) calcd for $C_{23}H_{28}NaO_7$ $[M + Na]^+$: 439.1733, found: 439.1732.

(–)-Gymnothelignan D [(–)-14]: A solution of **8** (15 mg, 0.03 mmol) in dry MeOH (1.5 mL) and $CH(OMe)_3$ (0.1 mL) was treated with *p*-TsOH (cat.). After stirring at room temperature overnight (16 h), the reaction mixture was quenched with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (25% CH_2Cl_2:25% EtOAc in hexanes) gave a diastereomeric mixture of **14** (10 mg, 83% yield, dr = 71 : 16 : 13) as pale yellow oil. Careful chromatographic purification using preparative thin-layer chromatography on silica gel (20% EtOAc in hexanes, multiple runs) provided (–)-**14** in 42% yield (5 mg). $[\alpha]^{26}_D$ = −14.5 (c 0.87, $CHCl_3$) {lit.[2a] $[\alpha]^{20}_D$ = −12 (c 0.03, MeOH)}; ^{1}H NMR (400 MHz, acetone-d_6): δ 7.22 (s, 1H), 7.09 (s, 1H), 6.45 (br s, 2H), 4.59 (s, 1H), 4.58 (d, *J* = 8.5 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.59 (s, 3H), 3.44 (s, 3H), 2.46–2.35 (m, 1H), 2.22–2.12 (m, 1H), 0.78 (d, *J* = 7.3 Hz, 3H), 0.74 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6): δ 153.9, 151.7, 148.3, 148.2, 142.3, 137.5, 136.0, 130.3, 127.6, 111.7, 110.1, 108.5, 107.6, 84.2, 61.2, 60.8, 56.8, 56.7, 56.1, 55.1, 44.5, 44.2, 11.9, 11.3; IR (neat): ν_{max} 3414, 1600, 1490, 1461, 1099 cm^{-1}; MS: m/z (%) relative intensity 448 (M^+, 74), 376 (100); HRMS (ESI-TOF) calcd for $C_{24}H_{32}O_8Na$ $[M+Na]^+$: 471.1995, found: 471.1999. The spectral data of this sample were identical with those reported.[2a]

5-*epi*-Gymnothelignan J (15): Debenzylation of **11** (17 mg, 0.03 mmol) using H_2 balloon, Pd/C (10% w/w, 3 mg), and dry EtOH (1 mL) for 20 min followed by reduction of the resulting

product using DIBALH (1 M in hexanes) (0.1 mL, 0.1 mmol, 2 equiv.) gave **15** (6 mg, 43% yield, dr = 2 : 1) as pale yellow oil. ^{1}H NMR (400 MHz, acetone-d_6, integrated equally for both diastereomers, major isomer marked*): δ 7.23 (s, 1H), 7.01* (s, 1H), 6.47* (d, J = 1.2 Hz, 1H), 6.45 (d, J = 1.4 Hz, 1H), 6.38* (d, J = 1.2 Hz, 1H), 6.37 (d, J = 1.4 Hz, 1H), 5.25 (d, J = 5.2 Hz, 1H), 5.15* (d, J = 4.5 Hz, 1H), 5.11* (d, J = 5.9 Hz, 1H), 4.91 (d, J = 6.1 Hz, 1H), 3.85* (s, 3H), 3.84 (s, 3H), 3.83 (s, 6H), 3.82 (s, 3H), 3.81* (s, 6H), 3.79* (s, 3H), 3.59 (s, 3H), 3.58* (s, 3H), 2.25-2.15 (m, 1H), 2.10-2.00* (m, 1H), 1.95-1.85 (m, 2H), 0.96 (d, J = 6.9 Hz, 3H), 0.94* (d, J = 7.1 Hz, 3H), 0.67 (d, J = 7.5 Hz, 3H), 0.49* (d, J = 7.4 Hz, 3H). Some peaks of minor isomer overlap with those of major isomer; ^{13}C NMR (125 MHz, acetone-d_6, major isomer marked*): δ 152.3*, 152.2, 151.3*, 151.0, 141.1*, 140.9*, 135.6, 135.0, 134.2*, 127.4*, 127.3, 127.1, 126.9*, 108.3*, 108.2, 107.5, 107.0*, 106.9, 106.3*, 103.0*, 98.9, 82.2, 80.0*, 60.4*, 59.9, 55.9*, 55.8, 55.4*, 55.3, 45.7*, 42.0, 40.9*, 39.4, 11.3*, 9.4*, 9.3. Some peaks of minor isomer overlap with those of major isomer; IR (neat): ν_{max} 3416, 1720, 1599, 1489, 1099 cm^{-1}; MS: m/z (%) relative intensity 434 (M^+, 37), 416 (100); HRMS (ESI-TOF) calcd for $C_{23}H_{30}O_8Na$ $[M+Na]^+$: 457.1838, found: 457.1833.

5-*epi*-Gymnothelignan D (16): A solution of **15** (14 mg, 0.03 mmol) in dry MeOH (1 mL) and $CH(OMe)_3$ (0.1 mL) was treated with *p*-TsOH (cat.). After stirring at room temperature overnight (16 h), the reaction mixture was quenched with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (25% CH_2Cl_2:25% EtOAc in hexanes) gave **16** (9 mg, 62% yield, dr = 2 : 1) as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, integrated equally for both diastereomers, major isomer marked*): δ 6.97* (s, 2H), 6.45* (s, 2H), 6.31* (s, 2H), 5.54* (s, 2H), 5.08* (d, J = 4.6 Hz, 1H), 4.98 (d, J = 6.2 Hz, 1H), 4.78 (d, J = 5.3 Hz, 1H), 4.71*

(d, J = 5.2 Hz, 1H), 3.93* (s, 3H), 3.92 (s, 3H), 3.90 (s, 3H), 3.89* (s, 6H), 3.88 (s, 3H), 3.86* (s, 3H), 3.85* (s, 3H), 3.65 (s, 3H), 3.64* (s, 3H), 3.52 (s, 3H), 3.42* (s, 3H), 2.30-2.20 (m, 1H), 2.20-2.10* (m, 1H), 1.95-1.80* (m, 2H), 0.98* (d, J = 7.2 Hz, 3H), 0.95 (d, J = 7.2 Hz, 3H), 0.63 (d, J = 7.5 Hz, 3H), 0.50* (d, J = 7.4 Hz, 3H); Some peaks of minor isomer overlap with those of major isomer; ^{13}C NMR (125 MHz, $CDCl_3$, major isomer marked*): δ 152.3, 151.2*, 146.8*, 146.6*, 140.9*, 140.7, 133.7*, 133.6, 133.5*, 127.6, 127.4*, 127.2*, 110.4*, 107.2*, 107.1, 106.7, 106.4, 106.0*, 106.0, 105.8*, 82.8, 80.5*, 61.3, 61.2*, 60.9*, 56.4, 56.3, 56.2*, 56.1*, 55.7*, 55.6, 44.1*, 41.9, 40.3*, 39.2, 12.3*, 11.8, 10.1*, 9.5. Some peaks of minor isomer overlap with those of major isomer; IR (neat): ν_{max} 3402, 1599, 1459, 1099 cm^{-1}; MS: m/z (%) relative intensity 448 (M^+, 60), 376 (100); HRMS (ESI-TOF) calcd for $C_{24}H_{32}NaO_8$ $[M+Na]^+$: 471.1995, found: 471.2016.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Copies of ^{1}H and ^{13}C NMR spectra of characterized compounds, NOESY spectra of compounds **4**, (–)-**1**, **11**, **12**, **13**, **14**, **15**, and **16**

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(13) The observed variation of coupling constants between protons H-6/H-7 and H-8/H-9 of compounds **1**, **9**, **12**, and **13** is possibly the results from the H-C-C-H dihedral angles in a rigid [4.1.2]-bridged bicyclic system.

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