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Total Synthesis of (−)-Sacidumlignans B and D

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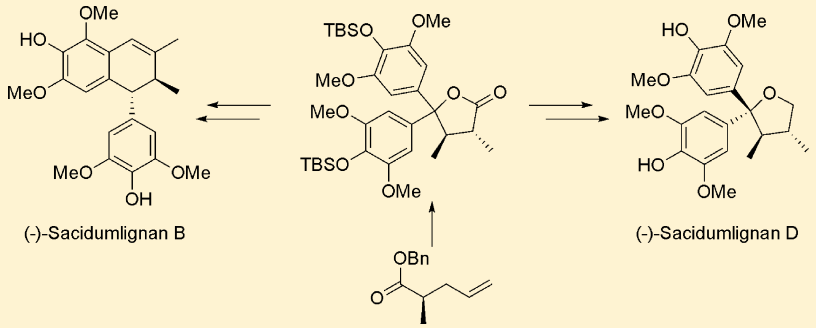
Supporting Information



ABSTRACT: The first total synthesis of naturally occurring sacidumlignans A (**1**), B (**2**), and D (**4**) was executed and the absolute configuration of **2** and **4** was determined. A diastereoselective α- methylation of a lactone was used as the key step for the control of the chiral centers of the central lignan core. An acid mediated dehydrative cyclization of an aldehyde to construct the dihydronaphthalene unit of **2** and the aromatization of the intermediate dihydronaphthalene derivative to synthesize **1** are the key reactions employed in this regard.

In 2005, Yue and co-workers reported the isolation of four new lignans **1**−**4** (named respectively as sacidumlignans A−D) from the plant *Sarcostemma acidum* (Roxb).[1a] The plant *S. acidum* is one among the known 10 species of the genus *Sarcostemma* and used in folklore medicine as a remedy for chronic cough and postnatal hypogalactia in China. With the help of extensive 2D NMR experiments, the structures of sacidumlignans A−D and their relative configuration were proposed (Figure 1). The structures of sacidumlignans A−D are closely related (Figure 1) and indicate that they all originate from a common precursor. The three sacidumlignans A, B, and C contain naphthalene and di- and tetrahydronaphthalene rings, respectively, and the sacidumlignan D was identified as a rearranged tetrahydrofuran lignan with an unprecedented skeleton. The isolation of a natural product viz. orthosilignin having the constitution of the sacidumlignan B was reported in 2002; however, its relative stereochemistry has not been investigated.[1b]

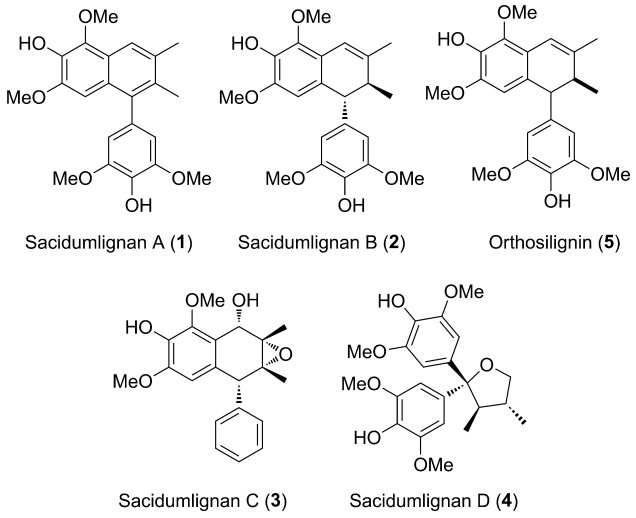


Figure 1. Structures of sacidumlignans A−D (**1**−**4**) and of related orthosilignin (**5**).

Inspired by its unprecedented structure, the (±)-sacidumlignan D has been synthesized in our group which led to the confirmation of its proposed relative configuration.[2] In continuation, we have been interested in developing an asymmetric synthesis of sacidumlignan D to elucidate its absolute configuration, thereby devising an approach that would enable the synthesis of other sacidumlignans.

To this end, retrosynthetic analyses of the sacidumlignans B and D were done, leading to an advanced intermediate **6** (Scheme 1) from which either of **2** and **4** could be made. For the synthesis of **4**, the previously established synthetic route will be followed from **6**, whereas the synthesis of **2** will feature a dehydrative cyclization of γ-aryl aldehyde[3] (a carbon variant of Pomeranz−Fritsch isoquinoline/isoquinolinone synthesis[4]) leading to the dihydronaphthalene core **8** and subsequent TBS-ether deprotection. To the best of our knowledge, this reaction has been not used in the synthesis of aryldihydronaphthalene lignans.[5] The synthesis of sacidumlignan A (**1**) was

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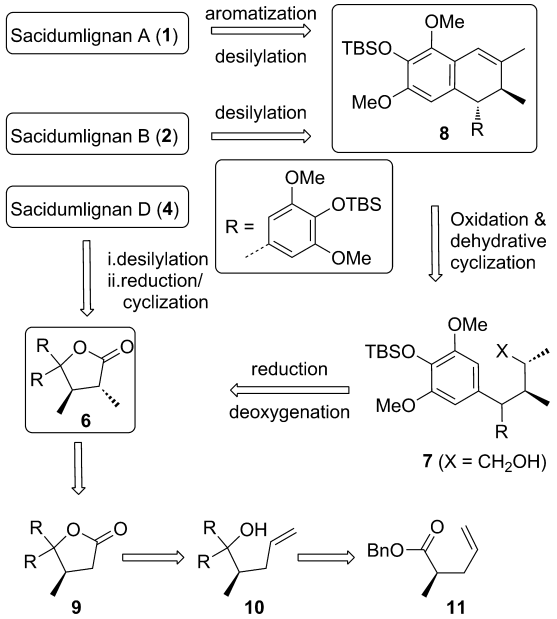
Scheme 1. Retrosynthetic Disconnections for Sacidumlignans A, B, and D



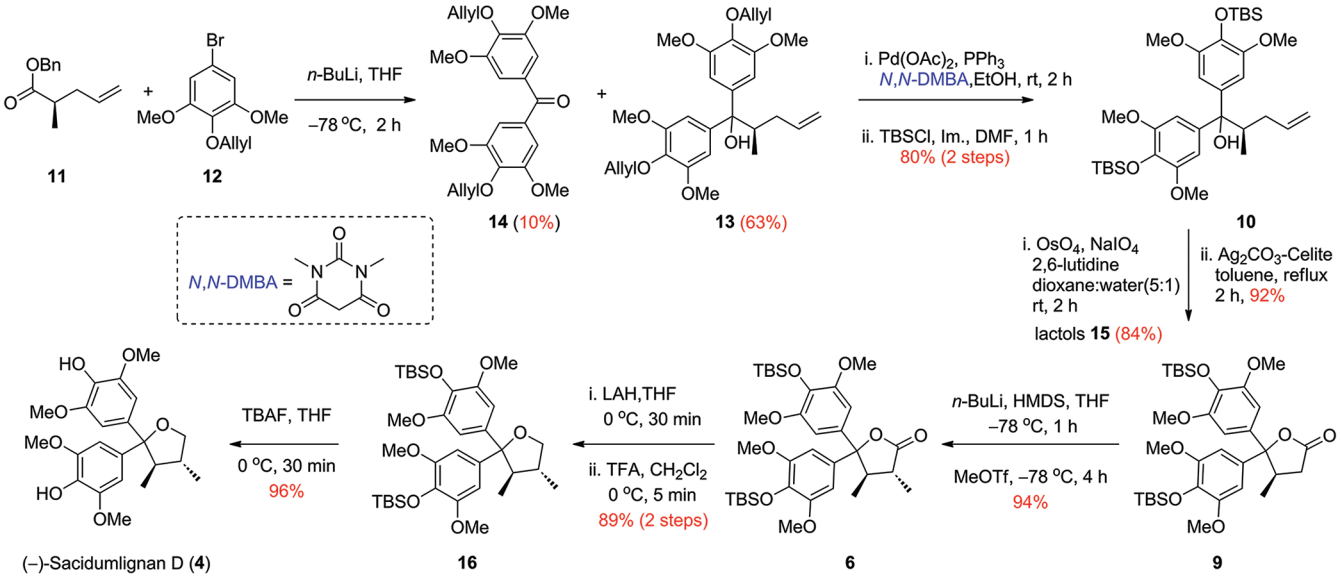
planned via the aromatization[6] of the dihydronaphthalene derivative **8** prior to deprotection. Scheme 1 saliently presents the key retrosynthetic disconnections. In our previous synthesis of (±)-sacidumlignan D,[2] the synthesis of (±)-**6** involved the reverse Wacker oxidation of a homoallylic alcohol which, in turn, was prepared by using Zn-mediated Barbier crotylation of a benzophenone derivative. To have a fixed absolute configuration at C(3), we have opted for the preparation of the intermediate lactone **9** from the oxidative olefin cleavage of a pent-4-en-1-ol derivative **10** which, in turn, was planned via the addition of an aryllithium to the corresponding (2*R*)-benzyl 2-methylpent-4-enoate (**11**), tentatively proposing an *R*-configuration at C(3) in **2** and **4**.

The synthesis of lactone **6** (Scheme 2) commenced with the lithiation of the bromo derivative **12** followed by its addition to the known benzyl ester **11**[7] to afford the required diaryl addition product **13** in 63% yield. The moderate yield was accounted for by the identification of the formation of a dehalogenated compound and the corresponding benzophenone **14** (10%) as the side products. The benzophenone side product is assumed to occur as a result of elimination of a carbanion.[8]

Subsequently, compound **13** was subjected to deallylation using the palladium(II) acetate, triphenylphosphine, and *N*,*N*′-dimethylbarbituric acid as the allyl scavenger.[9] The resulting product was found to be unstable in $CDCl_3$ solution and thus was subjected for phenolic O-TBS protection using TBSCl and imidazole in DMF to obtain the intermediate **10**. The next key intermediate lactone **9** was obtained from **10** in 77% yield by a two-stage sequence involving a one-pot osmium tetroxide catalyzed dihydroxylation−sodium periodate mediated diol cleavage,[10] followed by the oxidation of intermediate lactols **15** with Celite-supported silver carbonate[11] in toluene at reflux.[12] The diastereoselective α-methylation of lactone **9** was carried out under the established conditions (HMDS, *n*-BuLi, MeOTf) and gave the key intermediate lactone **6** in 94% yield. The latter served as the starting point for the synthesis of sacidumlignans B and D. As has been established in the synthesis of (±)-sacidumlignan D, the LAH reduction of **6** followed by TFA treatment of the crude diol gave the di-*O*-TBS protected sacidumlignan D (**16**), which upon TBS deprotection afforded the (−)-sacidumlignan D (**4**). The chiral-HPLC analysis of racemic and optically active sacidumlignans revealed the ee as 96%. The physical and spectral data of synthetic (−)-sacidumlignan D (**4**) were in full agreement with the data reported for the natural product and the similarity in the sign and magnitude of the optical rotation [$[\alpha]^{25}_D$ = −138.2 (*c* 1.37, acetone); lit.[1] $[\alpha]^{25}_D$ = −115 (*c* 1.14, acetone)] revealed that the naturally occurring sacidumlignan D indeed had been synthesized.

We next proceeded with the total synthesis of sacidumlignans A (**1**) and B (**2**) (Scheme 3). The main concern in the proposed retrosynthetic strategy was the deoxygenation of the benzylic-OH group without cyclization, using triethylsilane in the presence of $BF_3{\cdot}Et_2O$.[13] This reaction had been optimized

Scheme 2. Total Synthesis of (−)-Sacidumlignan D (4)



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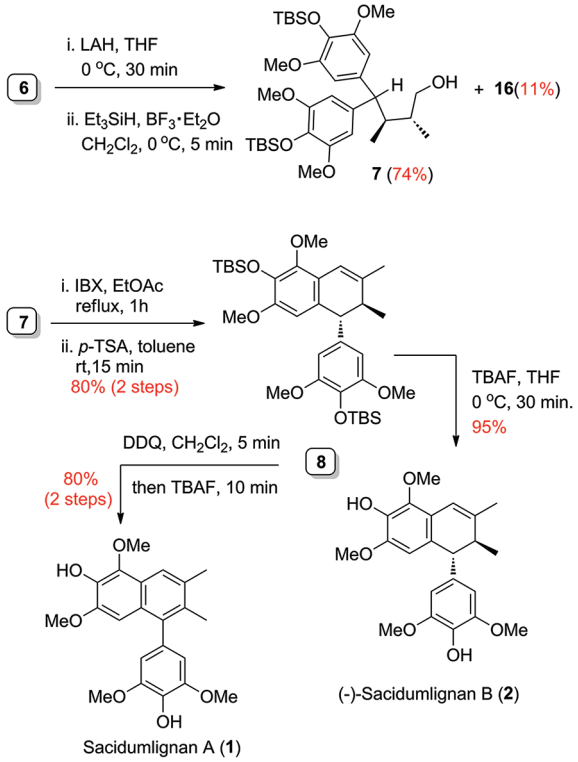
Scheme 3. Total Synthesis of Sacidumlignans A (1) and B (2)



using the crude diol resulting from the LAH reduction of lactone **6**. The optimized conditions involve the addition of diol to a solution of triethylsilane in CH_2Cl_2 at 0 °C followed by the slow addition of $BF_3{\cdot}Et_2O$ and quenching of the reaction after 5 min of addition. Under these conditions, the requisite alcohol **7** was obtained in 74% yield along with the cyclization product **16** in 11% yield. Decreasing the reaction temperature was found to favor the formation of the cyclization product, and at −78 °C, the cyclization product **16** was predominantly obtained. With the increase in temperature, the monoalcohol became less prominent in competition with the TBS deprotection. Oxidation of the alcohol **7** with 2-iodoxybenzoic acid (IBX)[14] followed by *p*-TSA-mediated cyclization cum elimination[3,4] in toluene at room temperature gave the di-*O*-TBS-sacidumlignan **8** in excellent yields and with more than 99% diastereoselectivity without any damage to the protecting group. Here, the cyclization occurred in a manner such that the methyl and aromatic groups became *anti* to each other, thus making the central dihydronaphthalene skeleton of the sacidumlignan B. The final desilylation of **8** with TBAF completed the synthesis of (−)-sacidumlignan B (**2**). The similarity in the spectral and optical rotation data of **2** [$[\alpha]^{25}_D$ = −65.9 (*c* 0.8, acetone); lit.[1] $[\alpha]^{25}_D$ = −116 (*c* 1.44, acetone)] with that of the natural product confirmed the assigned relative configuration and established the absolute configuration of sacidumlignan B.

Finally, subjecting the dihydronaphthalene intermediate **8** to a one-pot aromatization with DDQ in CH_2Cl_2 and desilylation by adding TBAF gave the sacidumlignan A (**1**) in 80% yield. The spectral data of **1** are in complete agreement with the data reported for the natural product, except for the appearance of extra phenolic OH peaks, which were confirmed by deuterium exchange studies.

In summary, the total synthesis of naturally occurring sacidumlignans B and D was completed, and their relative and/or absolute configurations were established. Furthermore, we have also executed the synthesis of sacidumlignan A from an intermediate used in the synthesis of sacidumlignan B. For the total synthesis of the sacidumlignan B, a dehydrative cyclization of a γ-aryl aldehyde leading to the aryldihydronaphthalene units has been used, which is the first of its kind. The adopted strategy employed a single advanced intermediate for all the targets executed.

EXPERIMENTAL SECTION

All of the moisture- and air-sensitive reactions were carried out in anhydrous solvents under argon atmosphere. The commercially available reagents were used without further purification except boron trifluoride etherate and hexamethyldisilazane, which were distilled prior to use. The reactions were monitored by TLC plate under UV light and anisaldehyde solution for charring purpose. Purifications were carried out by column chromatography using 100−200 mesh (0.075−0.150 mm) and 230−400 mesh (0.037−0.063 mm) silica gel. The NMR spectra of all of the compounds were recorded on 200, 400, and 500 MHz spectrometers in $CDCl_3$ or in acetone-d_6 solutions using TMS as internal standard. The signal multiplicities are abbreviated as s = singlet, d = doublet, t = triplet, q = quartet, st = sextet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dddd = doublet of doublet of doublet of doublet, ddt = doublet of doublet of triplet, ddq = doublet of doublet of quartet, tq = triplet of quartet, m = multiplet and br = broad.

(*R*)-1,1-Bis(4-(allyloxy)-3,5-dimethoxyphenyl)-2-methylpent-4-en-1-ol (13). At −78 °C, a solution of **12** (2.94 g, 10.8 mmol) in THF (15 mL) was treated with *n*-BuLi in hexane (6.43 mL, 10.3 mmol). After 1 h of vigorous stirring at −78 °C, a solution of the ester **11** (1.0 g, 4.9 mmol) in THF (15 mL) was added drop by drop, and stirring was continued at the same temperature for 2 h. The reaction mixture was quenched with satd NH_4Cl solution and warmed to rt. The reaction mixture was partitioned between water/CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (100−200 silica gel, 20% EtOAc in petroleum ether) to procure **13** (1.49 g, 63%) as a low melting solid and the ketone **14** (200 mg, 10%) as byproduct. **13**: R_f = 0.3 (25% EtOAc in petroleum ether); mp 73−75 °C; $[\alpha]^{25}_D$ = −13.6 (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) ν 3501, 2935, 2854, 1589, 1504, 1463, 1415, 1320, 1237, 1124, 988, 923, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.73 (s, 2H), 6.69 (s, 2H), 6.09 (2 x dddd, *J* = 17.2, 10.3, 8.1, 6.1 Hz, 2H), 5.86 (dddd, *J* = 16.9, 10.2, 8.0, 6.3 Hz, 1H), 5.29 (ddt, *J* = 17.2, 3.5, 1.6 Hz, 2H), 5.17 (br d, *J* = 10.3 Hz, 2H), 5.03−4.97 (m, 2H), 4.50−4.48 (m, 4H), 3.82 (br s, 12H), 2.58 (tq, *J* = 6.8, 2.5 Hz, 1H), 2.23 (br.dd, *J* = 13.8, 5.6 Hz, 1H), 2.14 (s, 1H), 1.84 (br dt, *J* = 13.8, 8.9 Hz, 1H), 0.90 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (q), 36.2 (t), 40.8 (d), 56.1 (q, 4C), 74.0 (t, 2C), 81.0 (s), 103.1 (d, 2C), 103.2 (d, 2C), 116.1 (t), 117.4 (t), 117.5 (t), 134.5 (d, 2C), 135.2 (s), 135.3 (s), 137.4 (d), 141.8 (s, 2C), 152.9 (s, 2C), 153.0 (s, 2C) ppm; HRMS (*m*/*z*) calcd for $C_{28}H_{36}O_7Na$ 507.2359, found 507.2317.

(*R*)-1,1-Bis(4-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethoxyphenyl)-2-methylpent-4-en-1-ol (10). To a solution of PPh_3 (13 mg, 0.05 mmol) in EtOH (5 mL) was added $Pd(OAc)_2$ (6 mg, 0.025 mmol) followed by 1,3-dimethylbarbituric acid (213 mg, 1.36 mmol), and the contents were stirred at rt. After 10 min of stirring, the color of the solution was changed to orange. At that time, **13** (300 mg, 0.62 mmol) in ethanol (10 mL) was introduced, and stirring was continued for additional 2 h. As the reaction proceeded, the color of the solution was changed to red and to blood red. The ethanol was evaporated and the crude was purified by column chromatography (100−200 silica gel, 40% EtOAc in petroleum ether) to procure compound intermediate triol (210 mg, 84%) as a pale yellow syrup (R_f = 0.3, 50% EtOAc in petroleum ether) which was used for the next reaction without any characterization.

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To an ice-cooled solution of above triol (500 mg, 1.24 mmol) in anhydrous DMF (5 mL) were added imidazole (340 mg, 4.9 mmol) and TBSCl (470 mg, 3.1 mmol), and the mixture was stirred for 1 h at rt. After the completion of reaction as indicated by TLC, the reaction mixture was partitioned between water−EtOAc and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude was purified by column chromatography (100−200 silica gel, 10% EtOAc in petroleum ether) to obtain **10** (750 mg, 96%) as yellow liquid: R_f = 0.8 (30% EtOAc in petroleum ether); $[\alpha]^{25}_D$ = −5.8 (*c* 2.8, acetone); IR ($CHCl_3$) ν 3525, 2933, 2857, 1587, 1511, 1463, 1415, 1328, 1249, 1186, 1131, 914, 838, 782, 753 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.66 (s, 2H), 6.63 (s, 2H), 5.85 (dddd, *J* = 16.2, 10.8, 7.9, 6.4 Hz, 1H), 5.01−4.93 (m, 2H), 3.75−3.74 (br s, 12H), 2.52 (tq, *J* = 6.7, 2.6 Hz, 1H), 2.26 (dd, *J* = 13.5, 5.8 Hz, 1H), 2.03 (s, 1H), 1.79 (ddd, *J* = 13.5, 7.9, 4.0 Hz, 1H), 1.00 (s, 18H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.11 (br s, 12H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.7 (q, 4C), 14.2 (q), 18.7 (s, 2C), 25.8 (q, 6C), 36.5 (t), 41.0 (d), 55.8 (q, 4C), 81.1 (s), 103.7 (d, 2C), 103.8 (d, 2C), 115.9 (t), 132.9 (s), 133.0 (s), 137.8 (d), 138.9 (s, 2C), 151.0 (s, 2C), 151.1 (s, 2C) ppm; HRMS (*m*/*z*) calcd for $C_{34}H_{56}O_7Si_2Na$ 655.3462, found 655.3469.

(4*R*)-5,5-Bis(4-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethoxyphenyl)-4-methyltetrahydrofuran-2-ol (15). To a suspension of compound **10** (250 mg, 0.39 mmol), 2,6-lutidine (0.1 mL, 0.79 mmol), and $NaIO_4$ (127 mg, 0.59 mmol) in dioxane (5 mL)−water (1 mL) was added a solution of OsO_4 (2 mg) in toluene (10 μL) and stirred at rt for 2 h. After completion, the reaction mixture was partitioned between water and CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Purification of the crude product by silica gel column chromatography (100−200, 20% EtOAc in petroleum ether) gave **15** (210 mg, 84%) as a colorless syrup: R_f = 0.2 (20% EtOAc in petroleum ether); $[\alpha]^{25}_D$ = −82.5 (*c* 2.1, acetone); IR ($CHCl_3$) ν 3418, 2932, 2857, 1587, 1514, 1463, 1455, 1415, 1337, 1249, 1130, 910, 838, 782, 756 cm^{-1}.

Major isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 6.67 (s, 1.4H), 6.29 (s, 1.4H), 5.79 (br t, *J* = 4.9 Hz, 0.7H), 3.76 (s, 4.5H), 3.68 (s, 4.1H), 3.27 (tq, *J* = 12.8, 6.9 Hz, 0.8H), 2.46 (d, *J* = 4.9 Hz, 0.7H), 2.08 (ddd, *J* = 12.8, 6.5, 1.4 Hz, 0.7H), 1.94 (ddd, *J* = 12.8, 9.8, 5.0 Hz, 0.7H), 1.00 (s, 10.3H), 0.99 (s, 8.1H), 0.83 (d, *J* = 6.9 Hz, 2.3H), 0.12 (s, 6.2H), 0.10 (s, 5.6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7 (q, 2C), −4.6 (q, 2C), 17.0 (q), 18.7 (s, 2C), 25.8 (q, 6C), 39.0 (d), 42.0 (t), 55.7 (q, 2C), 55.9 (q, 2C), 91.6 (s), 98.0 (d), 104.4 (d, 2C), 104.5 (d, 2C), 132.9 (s), 133.5 (s), 136.1 (s), 139.5 (s), 150.6 (s, 2C), 151.0 (s, 2C) ppm.

Minor isome:r. ^1H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 0.6H), 6.60 (s, 0.5H), 5.61 (dd, *J* = 9.9, 4.7 Hz, 0.3H), 3.75 (s, 1.5H), 3.70 (s, 1.9H), 3.22 (d, *J* = 4.7 Hz, 0.2H), 2.99 (br st, 0.3H), 2.29 (ddd, *J* = 13.0, 6.9, 5.6 Hz, 0.3H), 1.77 (ddd, *J* = 13.0, 7.6, 4.9 Hz, 0.3H), 1.00 (s, 10.3H), 0.99 (s, 8.1H), 0.89 (dd, *J* = 6.9 Hz, 1H), 0.12 (s, 6.2H), 0.1 (s, 5.6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7 (q, 2C), −4.6 (q, 2C), 17.6 (q), 18.7 (s, 2C), 25.8 (q, 6C), 40.1 (d), 41.0 (t), 55.7 (q, 2C), 55.9 (q, 2C), 91.9 (s), 97.9 (d), 104.2 (d, 2C), 104.9 (d, 2C), 132.9 (s), 133.5 (s), 136.3 (s), 139.5 (s), 150.5 (s, 2C), 151.0 (s, 2C) ppm; HRMS (*m*/*z*) calcd for $C_{33}H_{54}O_8Si_2K$ 673.2994, found 673.2996.

(*R*)-5,5-Bis(4-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethoxyphenyl)-4-methyldihydrofuran-2(3*H*)-one (9). To a solution of lactols **15** (70 mg, 0.11 mmol) in toluene (5 mL) was added silver carbonate on Celite (152 mg, 0.55 mmol contains 1 mmol of Ag_2CO_3 per 0.57 g of prepared reagent). The reaction mixture was refluxed at 130 °C for 2 h in the dark. The reaction mixture was cooled and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (100−200 silica gel, 15% EtOAc in petroleum ether) to afford **9** (64 mg, 92%) as a colorless solid: R_f = 0.5 (30% EtOAc in petroleum ether); mp 145−146 °C; $[\alpha]^{25}_D$ = −97.2 (*c* 3.1, acetone); IR ($CHCl_3$) ν 2997, 2933, 2895, 2857, 1767, 1587, 1514, 1463, 1417, 1336, 1249, 1129, 972, 920, 839, 783, 760, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.66 (s, 2H), 6.38 (s, 2H), 3.78 (s, 6H), 3.71 (s, 6H), 3.34−3.26 (m, 1H), 2.75 (dd, *J* = 17.2, 7.5 Hz, 1H), 2.34 (dd, *J* = 17.2, 5.0 Hz, 1H), 1.0 (s, 9H), 0.99 (s, 9H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.12 (s, 6H), 0.11 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7 (q, 4C), 17.2 (q), 18.6 (s, 2C), 25.7 (q, 6C), 37.7 (t), 38.3 (d), 55.7 (q, 2C), 56.0 (q, 2C), 92.7 (s), 103.1 (d, 2C), 104.1 (d, 2C), 133.1 (s), 133.5 (s), 134.4 (s), 135.1 (s), 151.1 (s, 2C), 151.3 (s, 2C), 176.1 (s) ppm; HRMS (*m*/*z*) calcd for $C_{33}H_{52}O_8Si_2Na$ 655.3099, found 655.3107.

(3*R*,4*R*)-5,5-Bis(4-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethoxyphenyl)-3,4-dimethyldihydrofuran-2(3*H*)-one (6). At −78 °C, a solution of freshly distilled hexamethyldisilazane (0.09 mL, 0.44 mmol) in anhydrous THF (1 mL) was treated with *n*-BuLi (0.21 mL, 0.33 mmol) and the mixture stirred for 30 min at the same temperature. To this was introduced a solution of **9** (70 mg, 0.11 mmol) in THF (1 mL). After 1 h of stirring, MeOTf (0.02 mL, 0.17 mmol) was added, and the contents were stirred for an additional 4 h at −78 °C. The reaction was quenched with satd NH_4Cl solution and allowed to warm to rt. The contents were partitioned between water−EtOAc. The organic layer was separated, and the aqueous layer extracted with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude was purified (230−400 silica gel, 10% EtOAc in petroleum ether) to procure lactone **6** (67 mg, 94%) as colorless solid by column chromatography: R_f = 0.5 (20% EtOAc in petroleum ether), mp 116−117 °C; $[\alpha]^{25}_D$ = −60.9 (*c* 2.3, acetone); IR ($CHCl_3$) ν 2934, 2857, 1776, 1588, 1514, 1463, 1338, 1249, 1207, 1131, 914, 839, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.62 (s, 2H), 6.20 (s, 2H), 3.77 (s, 6H), 3.67 (s, 6H), 2.86 (dq, *J* = 11.8, 6.7 Hz, 1H), 2.43 (dq, *J* = 11.8, 7.0 Hz, 1H), 1.29 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 6.7, 3H), 1.01 (s, 9H), 0.99 (s, 9H), 0.13 (s, 6H), 0.11 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7 (q, 4C), 13.2 (q), 16.2 (q), 18.6 (s), 18.7 (s), 25.7 (q, 6C), 41.1 (d), 46.2 (d), 55.7 (q, 2C), 56.0 (q, 2C), 91.0 (s), 104.1 (d, 2C), 104.7 (d, 2C), 132.7 (s), 133.7 (s), 134.5 (s), 135.4 (s), 150.9 (s, 2C), 151.2 (s, 2C), 178.7 (s) ppm; HRMS (*m*/*z*) calcd for $C_{34}H_{54}O_8Si_2Na$ 669.3255, found 669.3254.

((((3*R*,4*R*)-3,4-Dimethyltetrahydrofuran-2,2-diyl)bis(2,6-dimethoxy-4,1-phenylene))bis(oxy))bis(*tert*-butyldimethylsilane) (16). To an ice-cooled solution of lactone **6** (32 mg, 0.05 mmol) in THF (1 mL) was added LAH (6 mg, 0.15 mmol) slowly and the mixture stirred for 30 min at rt. Subsequently, the reaction mixture was quenched with satd NH_4Cl solution and filtered through Celite pad, and the filtrate was partitioned between water−CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting crude diol was directly utilized in the next step without further purification.

A solution of above crude residue in CH_2Cl_2 (1 mL) was cooled to 0 °C and treated with 7 μL of TFA. Within 5 min, the reaction was quenched with satd $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, and the resulting residue was purified by column chromatography (100−200 silica gel, 5% EtOAc in petroleum ether) to afford **16** (28 mg, 89%, two steps) as a colorless solid: R_f = 0.2 for reduction (20% EtOAc in petroleum ether), 0.8 for cyclization (20% EtOAc in petroleum ether); mp 72−74 °C; $[\alpha]^{25}_D$ = −114.2 (*c* 1.8, acetone); IR ($CHCl_3$) ν 2957, 2930, 2857, 1586, 1511, 1463, 1412, 1333, 1249, 1183, 1130, 1040, 915, 838, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.61 (s, 2H), 6.31 (s, 2H), 4.30 (t, *J* = 7.8 Hz, 1H), 3.76 (s, 6H), 3.67 (s, 6H), 3.48 (dd, *J* = 10.5, 8.3 Hz, 1H), 2.37 (dq, *J* = 10.6, 6.8 Hz, 1H), 2.03 (ddq, *J* = 13.6, 10.6, 7.1 Hz, 1H), 1.02 (d, *J* = 7.0 Hz, 3H), 1.01 (s, 9H), 0.99 (s, 9H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.13 (s, 6H), 0.09 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7 (q, 2C), −4.7 (q, 2C), 14.4 (q), 15.5 (q), 18.7(s), 18.7 (s), 25.8 (q, 6C), 40.6 (d), 49.6 (d), 55.6 (q, 2C), 55.9 (q, 2C), 73.9 (t), 90.9 (s), 104.7 (d, 2C), 105.0 (d, 2C), 132.8 (s), 133.4 (s), 137.7 (s), 139.4 (s), 150.4 (s, 2C), 151.0 (s, 2C) ppm; HRMS (*m*/*z*) calcd for $C_{34}H_{56}O_7Si_2H$ 633.3643, found 633.3628.

(−)-Sacidumlignan D (4). At 0 °C, a solution of **16** (36 mg, 0.06 mmol) in THF (1 mL) was treated with TBAF (37 mg, 0.14 mmol)

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and stirred for 30 min. The reaction was quenched with satd NH_4Cl solution and extracted with EtOAc. The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (100−200 silica, 40% EtOAc in petroleum ether) to obtain (−)-sacidumlignan D (**4**) (22 mg, 96%) as a white amorphous solid: R_f = 0.3 (50% EtOAc in petroleum ether); mp 150−152 °C; $[\alpha]^{25}_D$ = −138.2 (*c* 1.37, acetone); IR ($CHCl_3$) ν 3535, 3429, 3009, 2962, 2936, 2873, 2840, 1614, 1515, 1455, 1327, 1215, 1115, 1050, 1008, 912, 840, 753, 666 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.17 (s, 1H), 7.06 (s, 1H), 6.78 (s, 2H), 6.53 (s, 2H), 4.26 (t, *J* = 7.7 Hz, 1H), 3.80 (s, 6H), 3.73 (s, 6H), 3.33 (dd, *J* = 10.1, 8.2 Hz, 1H), 2.42 (dq, *J* = 9.6, 6.9 Hz, 1H), 2.04−1.94 (m, 1H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, acetone-d_6) δ 15.4 (q), 17.0 (q), 42.3 (d), 51.1 (d), 56.9 (q, 2C), 57.0 (q, 2C), 74.2 (t), 91.5 (s), 106.0 (d, 2C), 106.4 (d, 2C), 135.7 (s), 136.2 (s), 137.1 (s), 139.4 (s), 148.0 (s, 2C), 148.4 (s, 2C) ppm; HRMS (*m*/*z*) calcd for $C_{22}H_{28}O_7H$ 405.1913, found 405.1900.

(2*R*,3*S*)-4,4-Bis(4-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethoxyphenyl)-2,3-dimethylbutan-1-ol (7). The reduction of lactone **6** with LAH was carried out according to the procedure used for the preparation of compound **16**. After that, the crude residue was directly employed in the next step without further purification. At 0 °C, a solution of the above crude product (55 mg) in CH_2Cl_2 (1 mL) was treated slowly with Et_3SiH (0.07 mL, 0.43 mmol) followed by $BF_3{\cdot}Et_2O$ (0.03 mL, 0.25 mmol) and stirred for 5 min before quenching with satd $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, and the crude was purified by column chromatography (100−200 silica gel, 25% EtOAc in petroleum ether) to afford the alcohol **7** (40 mg, 74%) as colorless oil and the compound **16** (6 mg, 11%): R_f = 0.4 for **7**, 0.7 for **16** (20% EtOAc in petroleum ether); $[\alpha]^{25}_D$ = −16.7 (*c* 3.4, acetone); IR ($CHCl_3$) ν 3450, 2956, 2934, 2857, 1588, 1508, 1465, 1421, 1330, 1248, 1127, 1037, 913, 834, 784 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.50 (s, 2H), 6.47 (s, 2H),3.76 (s, 12H), 3.47 (dd, *J* = 10.6, 8.4 Hz, 1H), 3.44 (dd, *J* = 10.6, 6.4 Hz, 1H), 3.42 (d, *J* = 11.4 Hz, 1H), 2.50 (ddq, *J* = 11.4, 6.8, 2.1 Hz, 1H), 1.77−1.69 (m, 1H), 1.64 (br s, 1H), 0.99 (br s, 18H), 0.75 (d, *J* = 6.9 Hz, 3H), 0.65 (d, *J* = 6.8 Hz, 3H), 0.11 (br s, 6H), 0.10 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6 (q, 2C), − 4.7 (q, 2C), 9.8 (q), 11.8 (q), 18.7 (s, 2C), 25.8 (q, 6C), 36.2 (d), 36.3 (d), 55.8 (q, 2C), 55.9 (q, 2C), 56.7 (d), 67.0 (t), 105.3 (d, 2C), 105.4 (d, 2C), 132.6 (s, 2C), 136.9 (s), 137.4 (s), 151.2 (s, 2C), 151.3 (s, 2C) ppm; HRMS (*m*/*z*) calcd for $C_{34}H_{58}O_7Si_2Na$ 657.3619, found 657.3571.

***tert*-Butyl(((5*R*,6*S*)-5-(4-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethoxyphenyl)-1,3-dimethoxy-6,7-dimethyl-5,6-dihydronaphthalen-2-yl)oxy)dimethylsilane (8).** A suspension of **7** (35 mg, 0.06 mmol) and IBX (24 mg, 0.08 mmol) in EtOAc (5 mL) was refluxed for 1 h. The reaction mixture was cooled to room temperature and was filtered through Celite. The resulting aldehyde was dissolved in toluene (1 mL) and treated with *p*-TSA (0.5 mg, 0.002 mmol, 5 mol %). After being stirred at rt for 15 min, the reaction mixture was concentrated, and the residue was purified by column chromatography (100−200 silica gel, 5% EtOAc in petroleum ether) to afford **8** (27 mg, 80% in two steps) as a colorless syrup: R_f = 0.6 (10% EtOAc in petroleum ether); $[\alpha]^{25}_D$ = −45.1 (*c* 0.4, acetone); IR ($CHCl_3$) ν 2956, 2928, 2851, 1585, 1456, 1410, 1333, 1248, 1193, 1127, 1100, 941, 916, 834, 776 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.42 (d, *J* = 1.2 Hz, 1H), 6.29 (s, 1H), 6.23 (s, 2H), 3.78 (s, 3H), 3.67 (br s, 9H), 3.60 (d, *J* = 4.3 Hz, 1H), 2.38 (dq, *J* = 7.0, 4.3 Hz, 1H), 1.78 (d, *J* = 1.2 Hz, 3H), 1.05 (d, *J* = 7.0 Hz, 3H), 1.02 (s, 9H), 0.99 (s, 9H), 0.15 (d, *J* = 1.1 Hz, 6H), 0.10 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7 (q, 2C), −4.6 (q, 2C), 18.5 (q), 18.6 (s), 18.7 (s), 22.4 (q), 25.8 (q, 6C), 41.7 (d), 51.9 (d), 55.3 (q), 55.6 (q, 2C), 60.7 (q), 104.9 (d, 2C), 108.6 (d), 115.3 (d), 121.1 (s), 128.6 (s), 132.3 (s), 136.6 (s), 137.7 (s), 138.4 (s), 147.0 (s), 150.1 (s), 151.1 (s, 2C) ppm; HRMS (*m*/*z*) calcd for $C_{34}H_{54}O_6Si_2K$ 653.3096, found 653.3093.

Synthesis of (−)-Sacidumlignan B (2). The procedure used in the preparation of compound **4** was followed for the silyl deprotection of **8** (20 mg). Usual workup and purification by column chromatography gave (−)-sacidumlignan B (**2**) (12 mg, 95%) as a colorless solid: R_f = 0.5 (50% EtOAc in petroleum ether); $[\alpha]^{25}_D$ = −65.9 (*c* 0.8, acetone); IR ($CHCl_3$) ν 3510, 3439, 2956, 2928, 2846, 1722, 1613, 1514, 1459, 1314, 1209, 1111, 757, 661 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.31 (s,1H), 6.95 (s, 1H), 6.50 (s, 1H), 6.46 (d, *J* = 1.2 Hz, 1H), 6.42 (s, 2H), 3.81 (s, 3H), 3.74 (s, 3H), 3.71 (s, 6H), 3.67 (d, *J* = 3.0 Hz, 1H), 2.41 (dq, *J* = 7.0, 3.0, 1H), 1.82 (d, *J* = 1.2 Hz, 3H), 1.05 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, acetone-d_6) δ 18.9 (q), 22.7 (q), 42.5 (d), 52.0 (d), 52.0 (q), 56.4 (q, 2C), 60.9 (q), 105.9 (d, 2C), 109.4 (d), 116.1 (d), 121.4 (s), 127.1 (s), 135.1 (s), 137.1 (s), 138.8 (s), 139.1 (s), 143.9 (s), 147.8 (s), 148.3 (s, 2C) ppm; HRMS (*m*/*z*) calcd for $C_{22}H_{26}O_6Na$ 409.1627, found 409.1639.

Sacidumlignan A (1). A solution of **8** (8 mg, 0.013 mmol) and DDQ (5 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) were stirred at room temperature and under argon atmosphere. After 5 min, TBAF (9 mg, 0.032 mmol) was added and the mixture stirred for 10 min and then quenched with satd NH_4Cl solution. Usual workup followed by chromatographic purification (100−200 silica gel, 25% EtOAc in petroleum ether) gave sacidumlignan A (**1**) (4 mg, 80%) as a colorless solid: R_f = 0.5 (50% EtOAc in petroleum ether); IR ($CHCl_3$) ν 3543, 3439, 2957, 2925, 2853, 1722, 1611, 1518, 1464, 1288, 1215, 1116, 911, 759 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.77 (s, 1H), 7.73 (s, 1H), 7.32 (s, 1H), 6.58 (s, 1H), 6.49 (s, 2H), 3.97 (s, 3H), 3.84 (s, 6H), 3.67 (s, 3H), 2.45 (s, 3H), 2.11 (s, 3H) ppm; ^{13}C NMR (100 MHz, acetone-d_6) δ 17.6 (q), 21.4 (q), 55.9 (q), 56.7 (q, 2C), 60.7 (q), 101.8 (d), 106.2 (d, 2C), 120.5 (d), 123.9 (s), 127.4 (s), 131.7 (s), 131.8 (s), 133.7 (s), 135.7 (s), 138.1 (s), 138.7 (s), 140.7 (s), 148.9 (s, 2C), 149.1 (s) ppm; HRMS (*m*/*z*) calcd for $C_{22}H_{24}O_6Na$ 407.1471, found 407.1442.

■ ASSOCIATED CONTENT

Supporting Information

^1H, ^{13}C, DEPT NMR and LR-/HRMS of all new compounds, LC chromatograms for (−)-sacidumlignan D (**4**) and (±)-sacidumlignan D, and COSY and NOESY of (−)-sacidumlignan B (**2**). This material is available free of charge via the Internet at http://pubs.acs.org

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