Synthesis of the Tetracyclic Framework of Polycyclic Spiro Lignan Natural Products

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ABSTRACT: Polycyclic spiro lignans are a new family of lignan natural products recently isolated from Gymnotheca involucrata. The first synthesis of two model substrates of this rare family of natural products was achieved in six steps. An efficient strategy that features Suzuki coupling and Friedel–Crafts acylation was employed to construct the ABC tricyclic fluorene framework. Subsequently, Grignard reaction followed by acid-mediated cyclization furnished the spiro cyclic ether ring D.

INTRODUCTION

Gymnothespirolignans A–F (Figure 1) belong to a novel and rare family of lignan natural products that has been named polycyclic spiro lignans.1,2 They were isolated in 2014 and 2016 from the herbaceous flowering plant Gymnotheca involucrata collected from the southwestern region of China. Gymnothespirolignan A and B showed modest antiviral activities against respiratory syncytial virus with IC50 values of 31.87 and 17.51 μM, respectively.3 Gymnothespirolignan C demonstrated moderate insecticidal activity against the banded cucumber beetle Diabrotica balteata at 500 ppm in an artificial diet assay.4 Furthermore, structurally related synthetic polycyclic spiro-tetrahydrofurans have been reported as serotonin (5-HT) receptor ligands.5 The synthesis of this type of scaffold has also been pursued using a variety of strategies.4–7 Our interest in these compounds arose from their conformational-restricted structure that provides a fixed spatial orientation of functional groups that may be exploited for efficient and defined binding modes with biomolecular targets, as we previously demonstrated with aporphine alkaloids.8

All six currently known members of the gymnothespiolignan family contain a highly substituted fluorene motif as well as a spiro-disubstituted tetrahydrofuran with three adjacent stereocenters. They are structurally related to sacidumlignan D (Figure 1)—a known member of the related class of lignans that was identified as a rearranged tetrahydrofuran lignan.9 Gymnothespirolignan A–F and sacidumlignan D have a common disubstituted tetrahydrofuran. However, they differ in terms of the connectivity and substitutions of the aromatic rings. In this study, we report a synthetic approach for polycyclic spiro lignans using two model substrates 1a and 1b (Figure 1).

Four racemic10–13 and two enantioselective12,14 syntheses have been described for sacidumlignan D. In all those syntheses, the di-substituted tetrahydrofuran was indirectly...
prepared through the formation of butyrolactones followed by reduction to a diol and subsequent acid-mediated cyclization to form the ether linkage. In this report, a concise and direct route for the construction of the spiro tetrahydrofuran with the formation of the ether linkage without employing butyrolactones is presented, thus avoiding subsequent ring opening and cyclization during lactone reduction.

The new strategy is outlined in the retrosynthetic analysis in Figure 2. We envisioned four key transformations with late-stage ether linkage construction via acidic cyclization of diols A. The diols would arise from Grignard addition to fluorenones B that would be obtained via Friedel–Crafts acylation of carboxylic acids C. The later materials would be accessed from Suzuki coupling of the known bromo-containing substrates D and the commercially available boronic acid E.

**RESULTS AND DISCUSSION**

The synthesis commenced with the construction of fluorenone 7a (Scheme 1) over three steps from the known bromo-containing derivative 3a (synthesized by the methylation of 2-bromo-3-hydroxybenzaldehyde, 2a, according to a reported method15). Suzuki coupling between substrate 3a and 3,4,5-trimethoxyphenyl boronic acid, 4, using 5 mol % Pd(Ph3P)4 efficiently generated biaryl 5a in 95% yield. Pinnick oxidation of aldehyde 5a gave the corresponding carboxylic acid 6a, albeit in 50% yield. However, oxidation using 30% hydrogen peroxide and 15% aqueous sodium hydroxide according to a procedure by Koyama and Kamikawa16 provided the desired carboxylic acid 6a in 98% yield. Warning: caution should be exercised when conducting this oxidation reaction as vigorous effervescence has occurred! We were able to mitigate this issue by conducting the reaction on relatively small scale (e.g. ≤150 mg of 5a). Finally, Friedel–Crafts acylation17 utilizing
trifluoroacetic anhydride (TFAA) at 0 °C for 30 min furnished the required fluorenone 7a in 93% yield.

Having obtained fluorenone 7a, the construction of the spiro tetrahydrofuran was pursued (Scheme 2). The reaction between fluorenone 7a and the Grignard reagent derived from commercially available (3-bromopropoxy)methyl)benzene, 8, in diethyl ether18 generated alcohol 9a in 65% yield. Debenzylation of 9a using 10% Pd/C under an atmosphere of hydrogen for 24 h formed diol 10a in 84% yield. Finally, acid-mediated cyclization using two equivalents of trifluoroacetic acid (TFA) at 0 °C for only 2 min formed the ether linkage generating the gymnothespirolignan model substrate 1a in 89% yield.

Encouraged by the successful synthesis of the model substrate 1a, the preparation of a second model substrate 1b, which has all of the aromatic substituents as naturally occurring gymnothespirolignans A−C and F, was pursued. The synthesis started with the generation of fluorenone 7b. Bromo-containing substrate 3b was prepared using the method reported by Alam et al.19 from commercially available methyl 3,4,5-trihydroxybenzoate, 2b. Suzuki coupling of 3b with boronic acid 4 following a reported method20 with a slight modification generated biaryl derivative 5b in 92% yield. The basic hydrolysis of methyl ester 5b with lithium hydroxide in a 1:1 mixture of THF and MeOH with heating at 70 °C overnight furnished the desired carboxylic acid 6b in 94% yield. The treatment of 6b with TFAA-generated fluorenone 7b in 90% yield. The reaction of fluorenone 7b and the Grignard reagent derived from 8 in diethyl ether or tetrahydrofuran or a mixture of these solvents, unfortunately, gave only trace amounts of the desired product 9b. This likely resulted from poor solubility of 7b in diethyl ether or tetrahydrofuran. However, conducting the reaction in a mixture of 1,4-dioxane and diethyl ether (1:4) gave the desired tertiary alcohol 9b in 70% yield along with approximately 10% of the inseparable fluorenol 11. Performing the reaction in a mixture of dimethoxyethane and 1,4-dioxane (1:1) provided the required product 9b in 85% yield accompanied with only a trace amount of 11, which did not affect the next reaction. The hydrogenolysis of the benzyl protecting group of 9b generated diol 10b in 80% yield. Finally, the treatment of 10b with TFA at 0 °C furnished model substrate 1b in 74% yield.

■ CONCLUSIONS

In summary, a synthetic approach to polycyclic spiro lignans was established. Model substrates 1a and 1b were prepared in six steps and overall yields of 42 and 39% starting from the known bromo-containing substrates 3a or 3b, respectively. The synthetic route started by synthesizing fluorenone 7a and 7b via Suzuki coupling to install the biaryl bond followed by Friedel−Crafts acylation. Additionally, the spiro cyclic ether ring was concisely constructed utilizing Grignard reactions to synthesize diols 10a and 10b, which were subjected to acid-mediated cyclization to form the ether linkage. Currently, the illustrated strategy for the construction of the model substrates is being applied to the syntheses of naturally occurring gymnothespirolignans.

■ EXPERIMENTAL SECTION

General Information. All oxygen- or moisture-sensitive reactions were carried out under an argon atmosphere in oven-dried glassware with rubber septa and magnetic stirring. An oil bath was used as the heat source for reactions that required heating. All commercially available chemicals and solvents were used directly without further purification. Reactions were monitored by thin-layer chromatography on Baker-flex silica gel plates IB2-F. Visualization was accomplished with UV light (254 nm) or a visualizing agent (phosphomolybdic acid stain). Flash chromatography was conducted on a silica gel (40−60 μm). Melting points were measured using the Thomas Hoover UNI-MELT capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a 600 MHz spectrometer at room temperature. All 1H NMR spectra were measured in parts per million (ppm, δ) relative to the signal of tetramethylsilane (0.0 ppm). Data for 13C NMR were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad), coupling constant (Hz), and integration. All 13C NMR spectra were recorded on a 151 MHz spectrometer and were reported in ppm relative to CDCl3 (77.0 ppm). High resolution mass spectra (HRMS)
were performed by the University of Texas Mass Spectrometry facility using electrospray ionization (ESI) or chemical ionization (CI) and analyzed using the quadrupole time-of-flight (Q-TOF) mass spectrometer. The spectra were reported as \( m/z \) (relative intensity) for the molecular ion \([M]\). 2-Bromo-3-methoxybenzaldehyde (3a)\(^{15}\) and methyl 6-bromo-7-methoxybenzo[d][1,3]dioxole-5-carboxylate (3b)\(^{15}\) were prepared according to the literature procedures. All new compounds were characterized by \(^1\)H and \(^13\)C NMR spectroscopies and high-resolution mass spectrometry (HRMS). Known compounds were characterized by \(^1\)H and \(^13\)C NMR spectroscopies, and the spectra were compared with the reported data.

3',4',5',6-Tetramethoxy-[1,1'-biphenyl]-2-carboxaldehyde (5a). To a suspension of \( \text{Pd(PPh}_3\text{)$_2$Cl}_2 \) (346.6 mg, 0.33 mmol, 5 mol %) in anhydrous DME (6 mL) under an argon atmosphere was added a solution of 2-bromo-3-methoxybenzaldehyde 3a\(^{15}\) (1.29 g, 6 mmol, 1 equiv) in anhydrous DME (24 mL), and the resulting solution was stirred at room temperature for 15 min. A solution of \((3,4,5\text{-trimethoxyphenyl})\text{boronic acid} \) (4.14 g, 6.6 mmol, 1 equiv) in ethanol (4 mL) was added and the resulting mixture was stirred at room temperature for 10 min. Aqueous 2 M \( \text{Na}_2\text{CO}_3 \) (7 mL) was added and the resulting mixture was heated under reflush for 24 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The resulting residue was acidiﬁed with 3 N aqueous HCl. The aqueous layer was extracted with DCM (3 × 150 mL). The combined organic extracts were washed with saturated aqueous NaHCO\(_3\) and brine, dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The reported data.

3',4',5',6-Tetramethoxy-[1,1'-biphenyl]-2-carboxylic Acid (6a). To a solution of 5a (100 mg, 0.33 mmol, 1 equiv) in methanol (10 mL) in a 250 mL round bottom flask at 60 °C was added a mixture of 15% aqueous sodium hydroxide (5 mL) and 30% hydrogen peroxide (5 mL). After 1 min, additional 30% hydrogen peroxide (11 mL) was added. Caution should be exercised when conducting this reaction as vigorous efervescence has occurred! We were able to mitigate this issue by conducting the reaction on relatively small scale (e.g. ≤150 mg of 5a). The round bottom flask was ﬁtted with a condenser open to the air, and the resulting mixture was heated at 60 °C for 10 min, then at 80 °C for 20 min, and then at 90 °C for 1 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was washed with diethyl ether (discarded). The residue was then acidiﬁed with 3 N HCl (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure to give the crude carboxylic acid 6a that was judged pure from \(^1\)H NMR and used in the next step without further puriﬁcation. (103 mg, 98%); pale yellow solid; mp 167–170 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 7.44 (d, \( J = 8.4 \) Hz, 1H), 7.38 (t, \( J = 8.1 \) Hz, 1H), 7.12 (d, \( J = 8.4 \) Hz, 1H), 6.51 (s, 2H), 3.89 (s, 3H), 3.81 (s, 6H), 3.78 (s, 3H) ppm; \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \( \delta \) 173.0, 156.9, 152.6, 137.1, 132.2, 131.5, 130.9, 128.5, 121.7, 114.4, 106.9, 60.8, 56.1, 56.0 ppm; HRMS (Cl) \( m/z \) calculated for C\(_{17}\)H\(_{18}\)O\(_6\) [M]+: 318.1103; found, 318.1098.

7-Methoxy-6-(3,4,5-trimethoxyphenyl)benzo[d][1,3]dioxole-5-carboxylic Acid (6b). An aqueous LiOH solution (1 M, 52 mL, 52 mmol, 8 equiv) was added to a solution of ester 5b (2.446 g, 6.5 mmol, 1 equiv) in 1:1 mixture of THF/MeOH (40 mL). The resulting solution was then heated at 70 °C overnight. The reaction mixture was cooled to 0 °C and then was quenched with a 1 N aqueous HCl solution. The aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure to give the crude carboxylic acid 6b that was judged pure from \(^1\)H NMR and used in the next step without further puriﬁcation. (2.214 g, 95% yield); pale yellow solid; mp 187–188 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 7.16 (s, 1H), 6.43 (s, 2H), 6.07 (s, 2H), 3.89 (s, 3H), 3.81 (s, 6H), 3.78 (s, 3H) ppm; \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \( \delta \) 173.0, 152.6, 152.5, 141.2, 140.9, 137.2, 131.5, 131.5, 124.0, 106.9, 105.2, 102.1, 60.9, 56.1, 56.0 ppm; HRMS (Cl) \( m/z \) calculated for C\(_{17}\)H\(_{18}\)O\(_6\) [M]+: 385.0948; found, 385.0947.

General Procedure of Friedel–Crafts Acylations to Synthesize Fluorenones 7a or 7b. To a suspension of carboxylic acid 6a or 6b (6 mmol, 1 equiv) in anhydrous DCM for 6a or anhydrous CHCl\(_3\) for 6b (22 mL) under an argon atmosphere at 0 °C was added TFAA (2.5 mL, 18 mmol, 3 equiv). The resulting solution was stirred at the same temperature for 30 min before quenching with water (100 mL). The aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure to give the crude carboxylic acid 6b that was judged pure from \(^1\)H NMR and used in the next step without further puriﬁcation. (2.214 g, 94%); off-white solid; mp 187–188 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 7.16 (s, 1H), 6.43 (s, 2H), 6.07 (s, 2H), 3.89 (s, 3H), 3.81 (s, 6H), 3.78 (s, 3H) ppm; \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \( \delta \) 171.4, 152.6, 148.2, 141.2, 140.9, 137.2, 131.5, 131.5, 124.0, 106.9, 105.2, 102.1, 60.9, 56.0, 56.0 ppm; HRMS (ESI) \( m/z \) calculated for C\(_{17}\)H\(_{18}\)O\(_6\) [M + Na]+: 385.0984; found, 385.0907.
J = 7.2, 1.8 Hz, 1H), 4.11 (s, 3H), 3.98 (s, 3H), 3.96 (s, 3H), 3.86 (s, 3H) ppm; 13C NMR (151 MHz, CDCl₃): δ 190.6, 158.8, 154.7, 153.2, 141.5, 141.0, 136.8, 130.1, 129.1, 117.3, 116.9, 115.9, 104.3, 61.9, 61.3, 56.3, 55.6 ppm; HRMS (Cl) m/z: calcd for C₁₂H₁₉O₄ [M⁺], 300.0998; found, 300.0993.

6,7,8-Tetramethoxy-9H-fluoren-2,3-di(1,3)diol-9-one (7b). It was obtained as an orange solid (1.86 g, 90% yield); mp 153–154 °C; 1H NMR (600 MHz, CDCl₃): δ 7.07 (s, 1H), 6.76 (s, 1H), 5.99 (s, 2H), 4.10 (s, 3H), 4.08 (s, 3H), 3.95 (s, 3H), 3.84 (s, 3H) ppm; 13C NMR (151 MHz, CDCl₃): δ 189.1, 158.6, 152.9, 149.7, 141.2, 140.9, 140.6, 139.3, 130.5, 128.2, 117.7, 103.5, 101.9, 99.4, 61.9, 61.3, 59.5, 56.2 ppm; HRMS (ESI) m/z: calcd for C₁₅H₁₂O₆ [M + Na]⁺, 357.0788; found, 357.0780.

**General Procedure of Grignard Reactions to Synthesize Alcohols 9a or 9b.** A round bottom flask was charged with magnesium turnings (136 mg, 5.6 mmol, 3.5 equiv with respect to 8) and anhydrous diethyl ether (1 mL) and placed in an atmosphere of argon. A reagent solution was stirred for an additional 1 h at 30 °C. After 10 min, the solution became cloudy, and then the remaining mixture of 8 and dibromoethane (11 μL, 0.028 mmol, 0.08 equiv with respect to 7a) was dissolved in diethyl ether (2 mL), and then cooled to room temperature. The ambient temperature Grignard solution was added dropwise over 30 min. After complete addition, the Grignard reagent solution was stirred until cloudy, and then the remaining mixture of 8 and dibromoethane was added dropwise over 30 min. After complete addition, the Grignard reagent solution was stirred for an additional 1 h at 30 °C and then cooled to room temperature. The ambient temperature Grignard solution was added dropwise via cannula to a stirred solution of 7a (120 mg, 0.4 mmol, 1 equiv) in diethyl ether (1 mL) or to a stirred solution of 7b (138 mg, 0.4 mmol, 1 equiv) in DME/1,4-dioxane (1:1) (2 mL) at 0 °C under an atmosphere of argon. The resulting reaction mixture was allowed to gradually warm to room temperature over 1 h before quenching with a saturated aqueous NH₄Cl solution. The aqueous phase was extracted with EtOAc (3 × 50 mL), and the combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with EtOAc/hexane (50:50) to afford 10a or with EtOAc/hexane (60:40) to give 10b.

9-(3-Hydroxypropyl)-1,2,3,5-tetramethoxy-9H-fluoren-9-ol (9a). It was obtained as a white solid (65 mg, 80% yield); mp 184–187 °C; 1H NMR (600 MHz, CDCl₃): δ 7.22 (s, 1H), 6.70 (s, 1H), 5.96 (s, 2H), 4.12 (s, 3H), 4.03 (s, 3H), 3.92 (s, 3H), 3.86 (s, 3H), 3.46 (br s, 2H), 2.55 (s, 1H), 2.48–2.43 (m, 1H), 2.20–2.15 (m, 1H), 1.35 (s, 1H), 1.11–1.06 (m, 2H) ppm; 13C NMR (151 MHz, CDCl₃): δ 154.7, 150.1, 149.4, 143.6, 140.5, 139.1, 136.5, 134.9, 130.8, 124.0, 102.5, 101.3, 98.7, 82.8, 82.6, 61.1, 60.9, 59.6, 56.2, 34.9, 27.8 ppm; HRMS (ESI) m/z: calcd for C₁₅H₁₂O₆ [M⁺], 360.1573; found, 360.1575.

9-(3-Hydroxypropyl)-4,6,7,8-tetramethoxy-9H-fluorene-2,3-di(1,3)diol-9-ol (10a). It was obtained as a white solid (65 mg, 80% yield); mp 184–187 °C; 1H NMR (600 MHz, CDCl₃): δ 7.22 (s, 1H), 6.70 (s, 1H), 5.96 (s, 2H), 4.12 (s, 3H), 4.03 (s, 3H), 3.92 (s, 3H), 3.86 (s, 3H), 3.46 (br s, 2H), 2.55 (s, 1H), 2.48–2.43 (m, 1H), 2.20–2.15 (m, 1H), 1.35 (s, 1H), 1.11–1.06 (m, 2H) ppm; 13C NMR (151 MHz, CDCl₃): δ 154.7, 150.1, 149.4, 143.6, 140.5, 139.1, 136.5, 134.9, 130.8, 124.0, 102.5, 101.3, 98.7, 82.8, 82.6, 61.1, 60.9, 59.6, 56.2, 34.9, 27.8 ppm; HRMS (ESI) m/z: calcd for C₁₅H₁₂O₆ [M⁺], 427.1363; found, 427.1374.

**General Procedure of Acid Mediated Cyclizations to Synthesize 1a or 1b.** To a solution of 10a or 10b (0.05 mmol, 1 equiv) in chloroform (2 mL) at 0 °C under an atmosphere of argon was added TFA (7.5 μL, 0.075 mmol, 10% Pd/C (20 wt %). Additional 0.5 mL of methanol was added to wash the wall of the flask. The reaction mixture was stirred under an atmosphere of H₂ at room temperature for 24 h for 9a and 5 h for 9b. The reaction mixture was then filtered through Celite and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with EtOAc/hexane (50:50) to afford 1a or with EtOAc/hexane (60:40) to give 1b.

1,2,3,5-Tetramethoxy-4,5'-dihydro-3'H-spirofluorene-9,9'-furan (1a). It was obtained as a semisolid (15 mg, 89% yield); 1H NMR (600 MHz, CDCl₃): δ 7.37 (s, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 4.31–4.25 (m, 2H), 3.98 (s, 3H), 3.95 (s, 3H), 3.94 (s, 3H), 3.90 (s, 3H), 2.68–2.63 (m, 1H), 2.48–2.31 (m, 2H), 2.28–2.20 (m, 1H) ppm; 13C NMR (151 MHz, CDCl₃): δ 154.9, 154.5, 154.0, 150.2, 141.6, 134.9, 132.5, 128.7, 126.1, 115.3, 110.6, 103.7, 90.2, 69.8, 61.1, 60.9, 56.2, 55.4, 35.9, 27.8 ppm; HRMS (ESI) m/z: calcd for C₂₁H₂₁O₃ [M⁺], 342.1467; found, 342.1461.
4,6,7,8-Tetramethoxy-4',5'-dihydro-3'H-spiro[fluroene-[2,3-d][1,3]dioxole-9,2'-furan] (1b). It was obtained as a white solid (13.6 mg, 74% yield); mp 145 °C; 1H NMR (600 MHz, CDCl3): 6.72 (s, 1H), 6.62 (s, 1H), 5.94 (d, J = 7.2 Hz, 2H), 4.27–4.21 (m, 2H), 4.10 (s, 3H), 3.96 (s, 3H), 3.92 (s, 3H), 3.88 (s, 3H), 2.66–2.61 (m, 1H), 2.38–2.32 (m, 1H), 2.32–2.24 (m, 1H), 2.19–2.15 (m, 1H) ppm; 13C NMR (151 MHz, CDCl3): δ 154.5, 150.1, 149.2, 146.6, 141.0, 139.0, 136.3, 135.0, 132.7, 123.2, 102.6, 98.7, 89.8, 69.7, 61.1, 61.0, 59.6, 56.2, 35.9, 27.8 ppm; HRMS (ESI) m/z: calcd for C21H22O7 [M + Na]+, 409.1258; found, 409.1270.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c00976.

Copies of the 1H and 13C NMR spectra for 1a−b, 5a−b, 6a−b, 7a−b, 9a−b, and 10a−b are provided (PDF).

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Notes

The authors declare no competing financial interest.

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**REFERENCES**

(1) Xiao, S.-J.; Lei, X.-X.; Xia, B.; Xu, D.-Q.; Xiao, H.-P.; Xu, H.-X.; Chen, F.; Ding, L.-S.; Zhou, Y. Two novel polycyclic spiro lignans from Gymnotheca involucrata. *Tetrahedron Lett.* 2014, 55, 5949–5951.

(2) Xiao, S.-J.; Guo, D.-L.; Xia, B.; Allen, S.; Gu, Y.-C.; Chen, F.; Ding, L.-S.; Zhou, Y. Polycyclic spiro lignans and biphenyl tetrahydrofurane lignans from Gymnotheca involucrata. *Planta Med.* 2016, 82, 723–728.

(3) Moritomo, A.; Yamada, H.; Matsuowa-Nomura, T.; Watanabe, T.; Itahana, H.; Oku, M.; Akuzawa, S.; Okada, M. Synthesis and pharmacological evaluation of optically pure, novel carbonyl guanidine derivatives as dual S-HT3 and S-HT3 receptor antagonists. *Biorg. Med. Chem.* 2014, 22, 6026–6038.

(4) Yoshida, S.; Kasai, M.; Kimura, T.; Akiba, T.; Takahashi, T.; Sakamoto, S. Development of a Practical and Scalable Synthesis of a Potent Selective Dual Antagonist for S-HT3B and S-HT7 Receptors. *Org. Process Res. Dev.* 2012, 16, 654–663.

(5) Li, D. Y.; Jiang, L. L.; Chen, S.; Huang, Z. L.; Dang, L.; Wu, X. Y.; Liu, P. N. Cascade Reaction of Alkynols and 7-Oxabenzonorbornadienes Involving Transient Hemiketal Group Directed C–H Activation and Synergistic RhIII/ScIII Catalysis. *Org. Lett.* 2016, 18, 5134–5137.

(6) Kirmse, W.; Lelgemann, R.; Friedrich, K. Carben-Reaktionen mit Oxetan und mit Oxetan/Methanol-Gemischen. *Chem. Ber.* 1991, 124, 1853–1863.

(7) Degrand, C.; Gasquez, F.; Compagnon, P.-L. Electroreduction of (benzophenone)tricarbonylchromium and (flurorene)-tricarbonylchromium in the presence of electrophiles. *J. Organomet. Chem.* 1985, 280, 87–94.

(8) Xu, A. F.; Cuny, G. D. Discovery of 7-hydroxyaporphines as conformationally restricted ligands for beta-1 and beta-2 adrenergic receptors. *MedChemComm* 2018, 9, 353–356.

(9) Gan, L.-S.; Yang, S.-P.; Fan, C.-Q.; Yue, J.-M. Lignans and their degraded derivatives from Sarcostemum acidum. *J. Nat. Prod.* 2005, 68, 221–225.

(10) Pandey, S. K.; Ramana, C. V. Total Synthesis of (±)-Sacidumlignan B. *J. Org. Chem.* 2011, 76, 2315–2318.

(11) Zhang, J.-J.; Yan, C.-S.; Peng, Y.; Luo, Z.-B.; Xu, X.-B.; Wang, Y.-W. Total synthesis of (±)-Sacidumlignans D and A through Ueno-Stork radical cyclization reaction. *Org. Biomol. Chem.* 2013, 11, 2498–2513.

(12) Xie, C.; Bai, D.; Huang, S.-H.; Jia, X.; Hong, R. Kinetic resolution of diols via etherification catalyzed by a chiral phosphoric acid: Concise synthesis of (±)-Sacidumlignan D. *Asian J. Org. Chem.* 2014, 3, 277–280.

(13) Ha, T. M.; Chatalova-Sazepin, C.; Wang, Q.; Zhu, J. Copper-catalyzed formal [2+2+1] heteroannulation of alkenes, alkynitriles, and water: Method development and application to a total synthesis of (±)-Sacidumlignan D. *Angew. Chem., Int. Ed.* 2016, 55, 9249–9252.

(14) Rout, J. K.; Ramana, C. V. Total synthesis of (±)-Sacidumlignans B and D. *J. Org. Chem.* 2012, 77, 1566–1571.

(15) Zhao, G.; Xu, G.; Qian, C.; Tang, W. Efficient enantioselective syntheses of (±)-dalesconol A and B. *J. Am. Chem. Soc.* 2017, 139, 3360–3363.

(16) Koyama, H.; Kamikawa, T. Total syntheses of O4,O9-dimethylthiathins A and C 1. *J. Chem. Soc., Perkin Trans. 1* 1998, 203–210.

(17) Sargent, M. V. The structure and synthesis of the novel orchid pigments dengibsin and dengibsinin. *J. Chem. Soc., Perkin Trans. 1* 1997, 2553–2563.

(18) Reichau, S.; Parker, E. J. Active site plasticity of a critical enzyme from Mycobacterium tuberculosis. *RSC Adv.* 2013, 3, 3209–3212.

(19) Alam, A.; Takaguchi, Y.; Ito, H.; Yoshida, T.; Tsuboi, S. Multi-functionalization of gallic acid towards improved synthesis of α- and β-DDB. *Tetrahedron* 2005, 61, 1909–1918.

(20) Rainka, M. P.; Mäne, J. E.; Buchwald, S. L. Dynamic kinetic resolution of αβ-unsaturated lactones through asymmetric copper-catalyzed conjugate reduction: Application to the total synthesis of eupomatiline-3. *Angew. Chem., Int. Ed.* 2005, 44, 6177–6180.