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Synthesis of 3-Methylobovatol

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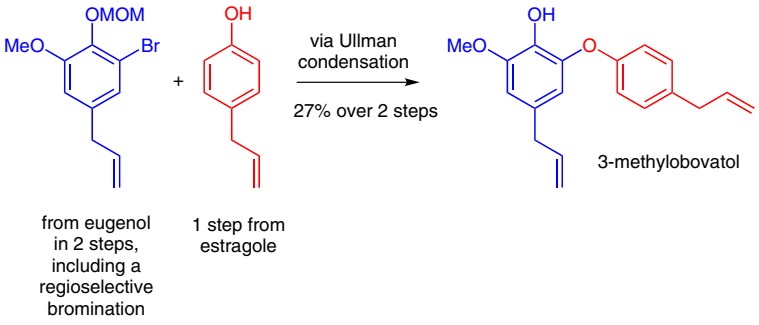

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Abstract Biphenyl lignans are rare compounds that exhibit a broad range of biological activities. The first total synthesis of natural biphenyl ether lignan, 3-methylobovatol, has been achieved in four steps. This synthesis allows for modification of the C-2 phenol and in doing so, will facilitate various structure–activity relationship studies into these bioactive compounds.

Key words synthesis, lignin, biphenyl ether, obovatol, Ullmann condensation

Biphenyl-type lignans are rare compounds from within the lignan class (Figure 1). These compounds are biosynthesized through the radical coupling of phenolic substrates, resulting in compounds with either a C–C linkage between aryl units [as in magnolol (**1**) and honokiol (**2**)], or with a C–O ether linkage [as seen in obovatol (**3**) and obovatal (**4**)]. Magnolianin (**5**) is a novel 1,4-benzodioxane lignan, isolated from the bark of *Magnolia obovata* and is a trilignan derived from two molecules of obovatol (**3**, red) and one of magnolol (**1**, blue).[1]

The most well-known biphenyl ether lignan is obovatol (**3**), which was first isolated alongside its oxidized derivative obovatal (**4**) from the bark of *Magnolia obovata*, a material commonly used in Japan and China for the treatment of gastrointestinal issues and neurosis.[2,3] Obovatol (**3**) has been reported to have a range of biological activities including inhibition of chitin synthase 2,[4] inhibition of NO production,[5] displays antiplatelet effects,[6] and also exhibits antitumor and anti-inflammatory activities through inhibition of the transcription factor, NF-κB.[7] Analogues of **3** have shown activity against colon and prostate cancer[8] whilst **3**

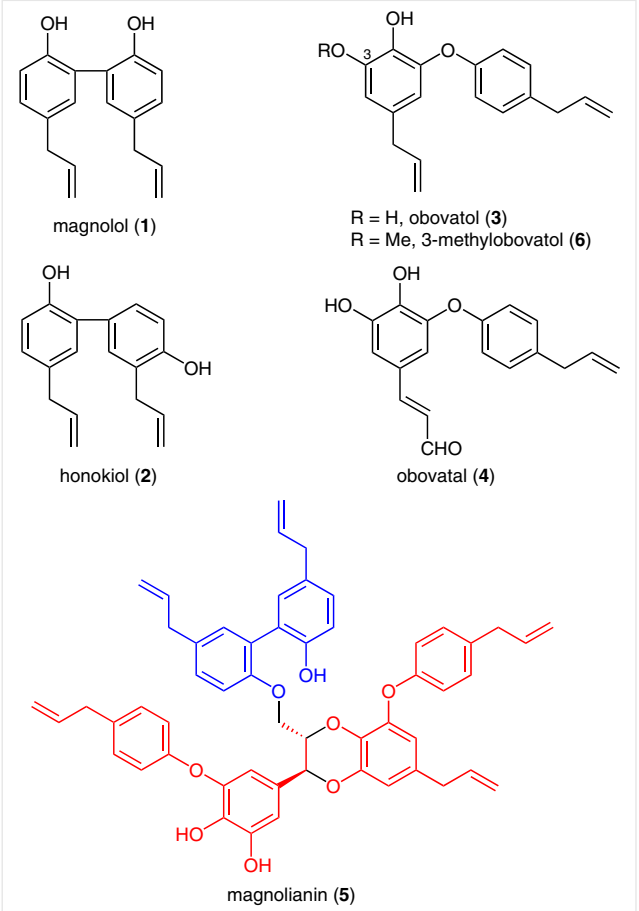


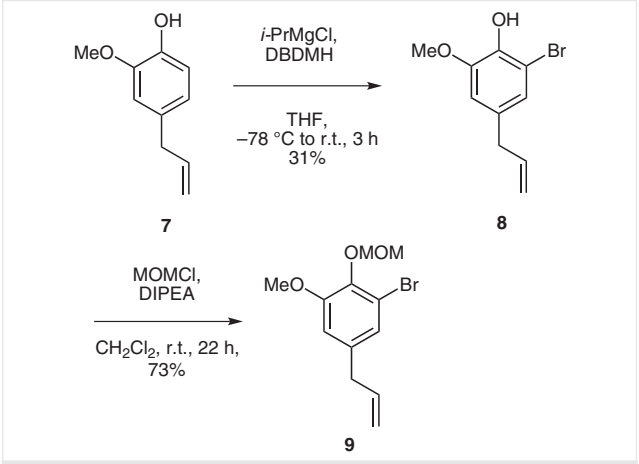
Figure 1 Naturally occurring biphenyl lignans and magnolianin (**5**), a trilignan

and closely related compounds **1**, **2**, and **4** have been screened for their antibacterial activity against *Streptococcus mutans*.[2]

Kijjoa et al. first isolated 3-methylobovatol (**6**) from *Magnolia henryi*, and it has subsequently been isolated from *Illicium lanceolatum*, a plant known for its anti-inflammatory activity.[9,10] Like obovatol (**3**), **6** was found to inhibit NO production, in a dose-dependent manner, with an IC_{50} of 26.59 μg/mL; this inhibitory effect was determined to not be attributable to its nonspecific cell toxicity.[10]

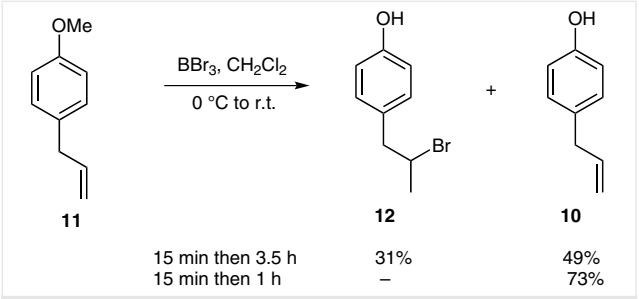
In our continuing work on *O*-aryl-linked lignans,[11–14] we sought to prepare 3-methylobovatol (**6**) using methods that could later allow for the preparation of obovatol analogues for further study into the broad range of activities that are displayed by **3** or could be used to prepare magnolianin (**5**) using our previously reported methods for 1,4-benzodioxane lignan construction.[11–13]

The synthesis began with the selective bromination of eugenol (**7**), using *i*-PrMgCl and dibromodimethylhydantoin (DBDMH).[15] *i*-PrMgCl is used to form the corresponding phenoxide, increasing the nucleophilicity at the carbon *ortho* to the phenol for bromination (Scheme 1). Using this method after three hours, bromide **8** was produced in 31% yield.[16] If the reaction was left for longer in an effort to increase the yield of **8**, polybrominated compounds were obtained which were inseparable from desired **8**. Following this, phenol **8** was protected in 73% yield, to provide MOM ether **9** for the required Ullmann condensation reaction.[17]



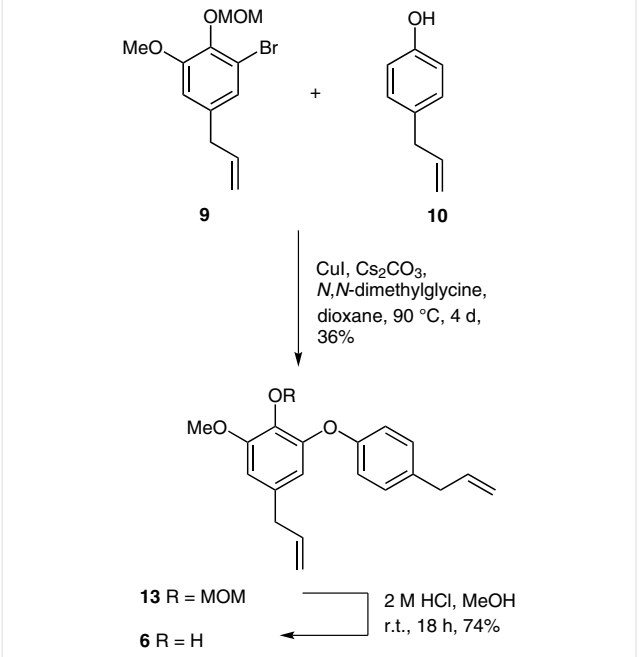
Scheme 1 Synthesis of bromide **9**

The second coupling partner for the Ullmann condensation was 4-allylphenol (**10**) which was thought to be easily produced through the previously reported demethylation of estragole (**11**).[18] The reaction was first attempted by adding a solution of BBr_3 at 0 °C, and then allowing the reaction to warm to room temperature and stir for 3.5 hours, a shorter time than has been previously reported (Scheme 2).[18] Unfortunately, it was found that a mixture of desired product **10** (49%) and bromide **12** (31%) was produced, with **12** most likely formed by the addition of HBr to the terminal alkene in **10**.[19] Shortening the reaction time to one hour provided 4-allylphenol (**10**) in 73% yield, with no evidence of bromide **12** being produced.[20]



Scheme 2 Synthesis of 4-allylphenol (**10**)

The Ullmann condensation between bromide **9** and phenol **10** was attempted using conditions reported by Kwak et al., which used a combination of CuI and Cs_2CO_3 with *N*,*N*-dimethylglycine used as the ligand. However, using the reported time of two days gave the desired diaryl ether **13** in a poor yield of 16% (Scheme 3).[21] Increasing the reaction time from two to four days improved the yield of **13** to 36% (with 52% of **9** returned unreacted), and no observed isomerization of the terminal alkene, an effect commonly observed.[21,22] It has previously been reported that MOM groups are unstable in the basic Ullmann condensation conditions.[23] Our result demonstrates that the above conditions for Ullmann condensations are compatible with MOM groups.



Scheme 3 Synthesis of 3-methylobovatol (**6**)

Unreacted starting material **9** and the desired diaryl ether **13** were inseparable using standard flash chromatography. However, using the classical, but infrequently applied method of employing silver impregnated silica,[24,25] the dialkene-containing product **13** was able to be easily separated from monoalkene aryl bromide **9**. Finally, deprotection of the MOM ether using 2 M HCl in methanol provided the natural product **6** in 74% yield.[26]

The ^{1}H NMR spectra for synthetic **6** was in close agreement with the literature values reported for the natural product, with slight differences in values for H-7, H-7′, and OMe groups.[9] This led us to speculate that the isolated natural compound could be an alternate methylated derivative of obovatol, that being 2-methylobovatol. That compound has been prepared by others via methylation of obovatol (**3**),[27] and its NMR data show significant differences in the aromatic proton signals when compared to reported data for isolated **6** and our prepared synthetic sample. This indicates that the natural product is not 2-methylobovatol and most likely is the 3-methyl isomer **6**. Unfortunately, no ^{13}C NMR data were reported when **6** was isolated.

In conclusion the synthesis of 3-methylobovatol (**6**) in four steps has been achieved. This synthesis demonstrates the compatibility of MOM ether protecting groups for alcohols in Ullmann condensation reactions, as well as the effective usage of silver-impregnated silica to separate mono- and dialkene-containing products that would otherwise be inseparable. This synthesis also allows for further modification of the C-2 phenol for further study into the effect of this group and other functionalities that could be added there, on the activities of these compounds.

Acknowledgment

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(16) **4-Bromoeugenol (8)**[28]
To a solution of eugenol (**7**, 1.00 g, 6.09 mmol) in dry THF (20 mL) at –78 °C was added *i*-PrMgCl (2.0 M in THF, 3.05 mL, 6.09 mmol), and the mixture was stirred for 30 min at –78 °C. A solution of DBDMH (1.39 g, 4.87 mmol) in dry THF (10 mL) was then added, and the mixture stirred at –78 °C for 3 h. Sat. aq NH_4Cl (25 mL) was then added along with EtOAc (20 mL) and the two layers separated. The aqueous layer was further extracted with EtOAc (2 × 20 mL), and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and the solvent removed in vacuo. The crude product was purified by flash chromatography (*n*-hexanes–EtOAc, 9:1) to yield the title product **8** (0.360 g, 31%) as a yellow oil. R_f = 0.42 (*n*-hexanes–EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): δ = 3.29 (2 H, d, *J* = 6.4 Hz, H-7), 3.87 (3 H, s, OMe), 5.07–5.10 (2 H, m, H-9), 5.80 (1 H, br s, OH), 5.86–5.97 (1 H, m, H-8), 6.63 (1 H, s, H-5), 6.92 (1 H, s, H-3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.5 (C-7), 56.2 (OMe), 109.8 (C-2), 110.4 (C-5), 116.2 (C-9), 124.3 (C-3), 132.7 (C-4), 136.9 (C-8), 141.3 (C-1), 147.1 (C-6). The ^{1}H NMR and ^{13}C NMR data were in agreement with the literature values.
(17) **5-Allyl-1-bromo-3-methoxy-2-(methoxymethoxy)benzene (9)**
To phenol **8** (0.200 g, 0.82 mmol) in CH_2Cl_2 (5 mL) at r.t., under an atmosphere of nitrogen, was added DIPEA (0.18 mL, 1.03 mmol) followed by MOMCl (0.18 mL, 1.65 mmol), and the mixture was stirred at r.t. for 22 h. Sat. aq NH_4Cl (5 mL) was added and the organic layer separated. The aqueous layer was further extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography (*n*-hexanes–EtOAc, 9:1) to yield the title product **9** (0.176 g, 73%) as a pale yellow oil. R_f = 0.61 (*n*-hexanes–EtOAc, 4:1). IR (film): ν_{max} = 3078, 2939, 2842, 1596, 1567, 1487, 1464, 1414, 1269, 1159, 1078, 1046, 959, 843, 815, 684 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): δ = 3.30 (2 H, d, *J* = 6.4 Hz, H-7), 3.65 (3 H, s, OCH_2OCH_3), 3.83 (3 H, s, OMe), 5.08–5.13 (2 H, m, H-9), 5.14 (2 H, s, OCH_2OCH_3), 5.86–5.96 (1 H, m, H-8), 6.67 (1 H, s, H-4), 6.98 (1 H, s, H-6). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.6 (C-7), 56.0 (OCH_2OCH_3), 57.9 (OMe), 98.6 (OCH_2OCH_3), 112.1 (C-4), 116.5 (C-9), 117.6 (C-1), 124.8 (C-6), 136.5 (C-8), 137.4 (C-5), 153.0 (C-2), 162.3 (C-3). MS (ESI$^+$): *m/z* (%) = 311 (100) [^{81}BrMNa$^+$], 309 (98) [^{79}BrMNa$^+$], 233 (10) and 199 (5). HRMS (ESI$^+$): *m/z* calcd for $C_{12}H_{15}{}^{81}BrNaO_3$: 311.0077; found [MNa$^+$]: 311.0076; *m/z* calcd for $C_{12}H_{15}{}^{79}BrNaO_3$: 309.0097; found [MNa$^+$]: 309.0094.
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(19) **4-(2-Bromopropyl)phenol (12)**
To a solution of methyl ether **11** (100 mg, 0.674 mmol) in CH_2Cl_2 (5 mL) under an atmosphere of nitrogen and cooled to 0 °C was added dropwise a solution of BBr_3 (0.190 mL, 2.0 mmol) in CH_2Cl_2 (1 mL). The resulting solution was stirred at 0 °C for 15 min and then let warm to r.t. and stirred for 3.5 h. The mixture was then cooled to 0 °C and quenched with H_2O (10 mL). The

aqueous mixture was extracted with CH_2Cl_2 (10 mL), and then the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and the solvent removed in vacuo. The crude product was purified by flash chromatography (*n*-hexanes–EtOAc, 9:1) to yield the title product **12** (44.4 mg, 31%) as a colorless oil. R_f = 0.39 (*n*-hexanes–EtOAc, 4:1). IR (film): ν_{max} = 3316, 2969, 2921, 1612, 1598, 1512, 1443, 1377, 1223, 1171, 1057, 999, 847, 820, 772 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, Me_4Si): δ = 1.67 (3 H, d, *J* = 6.4 Hz, CH_3), 2.97 (1 H, q, *J* = 3.2 Hz, $ArCH_aH_b$), 3.12 (1 H, q, *J* = 3.2 Hz, $ArCH_aH_b$), 4.21 (1 H, sext, *J* = 6.4 Hz, CHBr), 5.40 (1 H, br s, OH), 6.78 (2 H, d, *J* = 8.4 Hz, H-2), 7.06 (2 H, d, *J* = 8.4 Hz, H-3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5 (CH_3), 46.6 (CH_2), 51.1 (CHBr), 115.3 (C-2), 130.4 (C-3), 130.8 (C-4), 154.4 (C-1). MS (ESI$^+$): *m/z* (%) = 215 (50) [^{81}BrM – H]$^+$, 213 (50) [^{79}BrM – H]$^+$, 181 (100). HRMS (ESI$^+$): *m/z* calcd for $C_9H_{10}{}^{81}BrO$: 214.9900; found [M – H]$^+$: 214.9894. *m/z* calcd for $C_9H_{10}{}^{79}BrO$: 212.9921; found [M – H]$^+$: 212.9922. In a separate fraction, 4-allylphenol (**10**, 43.8 mg, 49%) was isolated as a colorless oil.

(20) **4-Allylphenol (10)**[29]

To a solution of methyl ether **11** (1.00 g, 6.74 mmol) in CH_2Cl_2 (18 mL) under an atmosphere of nitrogen and cooled to 0 °C was added dropwise a solution of BBr_3 (0.96 mL, 10 mmol) in CH_2Cl_2 (18 mL). The resulting solution was stirred at 0 °C for 15 min and then let warm to r.t. and stirred for 1 h. The mixture was then cooled to 0 °C and quenched with H_2O (20 mL). The aqueous mixture was extracted with CH_2Cl_2 (20 mL), and then the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and the solvent removed in vacuo. The crude product was purified by flash chromatography (*n*-hexanes–EtOAc, 9:1) to yield the title product **10** (0.66 g, 73%) as a colorless oil. R_f = 0.45 (*n*-hexanes–EtOAc, 4:1). ^1H NMR (400 MHz, $CDCl_3$, Me_4Si): δ = 3.33 (2 H, d, *J* = 6.8 Hz, $ArCH_2$), 5.05–5.10 (2 H, m, CH=CH_2), 5.53 (1 H, br s, OH), 5.92–6.02 (1 H, m, C*H*=CH_2), 6.78 (1 H, dd, *J* = 2.0, 6.4 Hz, H-2), 7.06 (1 H, dd, *J* = 2.0, 6.4 Hz, H-3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.3 ($ArCH_2$), 115.3 (C-2), 115.4 (CH=*C*H_2), 129.7 (C-3), 132.2 (C-4), 137.8 (*C*H=CH_2), 153.7 (C-1). The ^1H NMR and ^{13}C NMR data were in agreement with the literature values.

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(22) **5-Allyl-1-(4′-allylphenoxy)-3-methoxy-2-(methoxymethoxy)benzene (13)**

A mixture of bromide **9** (189 mg, 0.658 mmol), phenol **10** (132 mg, 0.987 mmol), Cs_2CO_3 (429 mg, 1.32 mmol), CuI (12.5 mg, 0.066 mmol), and *N*,*N*-dimethylglycine hydrochloride (28.0 mg, 0.197 mmol) in dioxane (3 mL) in a sealed tube under an atmosphere of nitrogen was heated at 90 °C for 4 d. The solution was removed from the heat and allowed to cool to r.t. The cooled mixture was partitioned between EtOAc (2 mL) and H_2O (2 mL), and the organic layer was separated. The aqueous layer was further extracted with EtOAc (2 × 2 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was purified by flash chromatography (*n*-hexanes–EtOAc, 9:1) with silver impregnated silica to yield the title product **13** (80.0 mg, 36%) as a pale yellow oil. R_f = 0.61 (*n*-hexanes–EtOAc, 4:1) 0.61. IR (film): ν_{max} = 2967, 2839, 1565, 1504, 1487, 1463, 1269, 1216, 1156, 1078, 1045, 952, 815, 774 682 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, Me_4Si): δ = 3.26 (2 H, d, *J* = 6.8 Hz, H-7), 3.34 (2 H, d, *J* = 6.8 Hz, H-7′), 3.51 (3 H, s, OCH_2OCH_3), 3.86 (3 H, s, OMe), 5.03–5.08 (4 H, m, H-9 and H-9′), 5.09 (2 H, s, OCH_2OCH_3), 5.86–5.99 (2 H, m, H-8 and H-8′), 6.41 (1 H, d, *J* = 2.0 Hz, H-6), 6.54 (1 H, d, *J* = 2.0 Hz, H-4), 6.88 (2 H, d, *J* = 8.0 Hz, H-2′ and H-6′), 7.09 (2 H, d, *J* = 8.0 Hz, H-3′ and H-5′). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.4 (C-7′), 40.0 (C-7), 55.9 (OMe), 56.9 (OCH_2OCH_3), 98.2 (OCH_2OCH_3), 108.0 (C-4), 113.1 (C-6), 115.6 (C-9′), 116.0 (C-9), 117.4 (C-2′ and C-6′), 129.5 (C-3′ and C-5′), 134.2 (C-4′), 135.6 (C-2), 136.4 (C-5), 136.8 (C-8), 137.5 (C-8′), 149.8 (C-1), 153.7 (C-3) and 155.9 (C-1′). MS (ESI$^+$): *m/z* (%) = 363 (100) [MNa$^+$], 265 (5), 207 (5). HRMS (ESI+): *m/z* calcd for $C_{21}H_{24}NaO_4$: 363.1567; found: [MNa$^+$]: 363.1578. In a separate fraction, bromide **9** (98 mg, 0.381 mmol) was isolated as a colorless oil.

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(26) **5-Allyl-1-(4′-allylphenoxy)-3-methoxyphenol (6) or 3-Methylobovatol (6)**

To a solution of methoxymethyl ether **13** (50.0 mg, 0.15 mmol) in MeOH (5 mL) was added 2 M HCl (0.5 mL), and the resultant mixture was stirred at r.t. for 18 h. 1 M NaOH was added until the solution was pH 5, and then the solution was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography (*n*-hexanes–EtOAc, 9:1) to give the title product **6** (32.0 mg, 74%) as a yellow oil. R_f = 0.42 (*n*-hexanes–EtOAc, 4:1). IR (film): ν_{max}: 3507, 2976, 2915, 2844, 1600, 1504, 1453, 1433, 1312, 1220, 1168, 1058, 994, 914, 823 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, Me_4Si): δ = 3.25 (2 H, d, *J* = 6.8 Hz, H-7), 3.34 (2 H, d, *J* = 6.8 Hz, H-7′), 3.90 (3 H, s, OMe), 5.02–5.09 (4 H, m, H-9 and H-9′), 5.45 (1 H, br s, OH), 5.81–6.01 (2 H, m, H-8 and H-8′), 6.43 (1 H, d, *J* = 2.0 Hz, H-6), 6.53 (1 H, d, *J* = 2.0 Hz, H-4), 6.90 (2 H, d, *J* = 8.0 Hz, H-2′ and H-6′), 7.10 (2 H, d, *J* = 8.0 Hz, H-3′ and H-5′). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.4 (C-7′), 39.9 (C-7), 56.2 (OMe), 107.3 (C-4), 113.0 (C-6), 115.7 (C-9′), 115.8 (C-9), 117.3 (C-2′ and C-6′), 129.6 (C-3′ and C-5′), 131.4 (C-5), 134.4 (C-4′), 135.6 (C-2), 137.3 (C-8), 137.5 (C-8′), 143.0 (C-1), 147.8 (C-3), 155.8 (C-1′). MS (ESI$^+$): *m/z* (%) = 319 (100) [MNa$^+$], 227 (80), 158 (20). HRMS (ESI$^+$): *m/z* calcd for $C_{19}H_{20}NaO_3$ [MNa$^+$]: 319.1305; found: 319.1304. The ^1H NMR data were in agreement with the literature values.[9]

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