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Efficient Total Synthesis of (±)-Isoguaiacin and (±)-Isogalbulin

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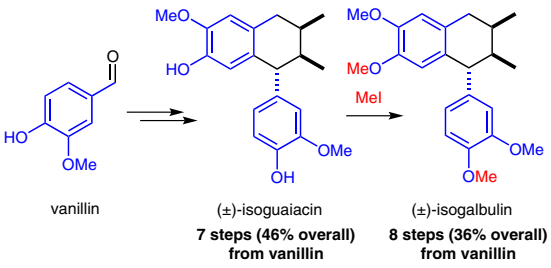

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Abstract 1-Arylnaphthalene lignans such as (–)-isoguaiacin and (–)-isogalbulin have been reported to exhibit notable biological properties. While (–)-isoguaiacin has not been previously synthesized, syntheses of (–)-isogalbulin are generally long and produce a mixture of stereoisomers. We herein present the efficient total synthesis of (±)-isoguaiacin and (±)-isogalbulin in seven and eight steps with an overall yield of 46% and 36%, respectively. The reported approach harnesses a hydrogenolysis reaction in acidic conditions, to convert a furan into an arylnaphthalen structure.

Key words lignan, 1-arylnaphthalene, synthesis, Paal–Knorr, cyclization

1-Arylnaphthalene (aryl tetralin) lignan natural products, including (–)-isoguaiacin (**1**) and (–)-isogalbulin (**2**, Figure 1), have received considerable attention owing to their notable and varied biological properties. 1-Arylnaphthalene lignans have been shown to possess antitumour and anti-HIV activities,[1] as well as indications of activity against Parkinson's and Alzheimer's disease, along with numerous others.[2]

First isolated in 1964 from *Guaiacum officinale*[3] and since then from a range of natural sources including *Larrea tridentate*,[4] *Machilus thunbergii*,[5–8] *Calyptranthes pallens*,[9]

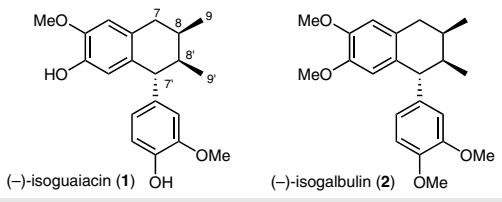


Figure 1 Structures of 8,8′-*syn*-1-arylnaphthalen lignan natural products.

(–)-isoguaiacin (**1**) specifically has been shown to exhibit antioxidant,[5] hepaprotective,[5] neuroprotective,[6] antiproliferative,[7,9] and increased osteoblast differentiation.[8] (–)-Isogalbulin (**2**) has been isolated from *Virola sebifera*[10] and has not been shown to exhibit such a wide range activities, but has demonstrated an increase in osteoblast differentiation.[8] Lignans (–)-**1** and (–)-**2** have the less common 8,8′-*syn* stereochemistry; compounds with a *trans* relationship have been more commonly found and synthesised.

While the synthesis of (±)-isoguaiacin (**1**) has not been previously reported, (+)-**2** has previously been synthesised. Some of these syntheses involve the conversion of other natural products[4,11,12] and typically provide aryltetralins in low overall yields and as mixtures of stereoisomers.[13,14] Whitby et al. reported the synthesis of (±)-**2** using zirconium chemistry in 21% overall yield,[15] and Wang et al. successfully produced (±)-**2**, albeit in a lengthy, nonselective synthesis of 12 steps,[16] while the first enantioselective syntheses of (+)-**2** was reported by Xie et al., in 10 steps utilising a Sharpless epoxidation as the enantiodetermining step.[17]

During the course of our investigation into the synthesis of various lignans,[18–32] we have noted various rearrangement reactions, particularly in the synthesis of tetrahydrofuran natural products. To further explore the possibility of stereoselectively synthesising the 1-arylnaphthalene natural product scaffold through the hydrogenation of furanoid compounds,[33,34] we attempted to explore an efficient, selective synthetic route to both (±)-**1** and (±)-**2**.

We envisioned one of the pivotal transformations in the synthesis of aryl tetralins would be the conversion of a furan structure, which could be synthesised through a Paal–Knorr synthesis of the corresponding diketone (Figure 2). The diketone structure itself could be formed from the dimerisation of related, substituted benzaldehyde derivatives. Owing to their aforementioned promising biological prop-

erties and to synthesise (±)-**1** for the first time and improve the efficiency of the synthesis of (±)-**2**, we identified (±)-isoguaiacin (**1**) as our primary synthetic target, which could then be methylated to provide (±)-isogalbulin (**2**).

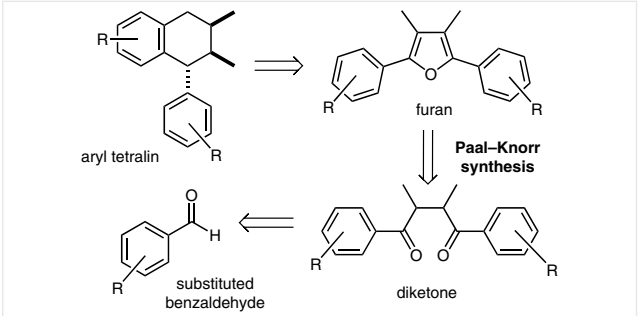
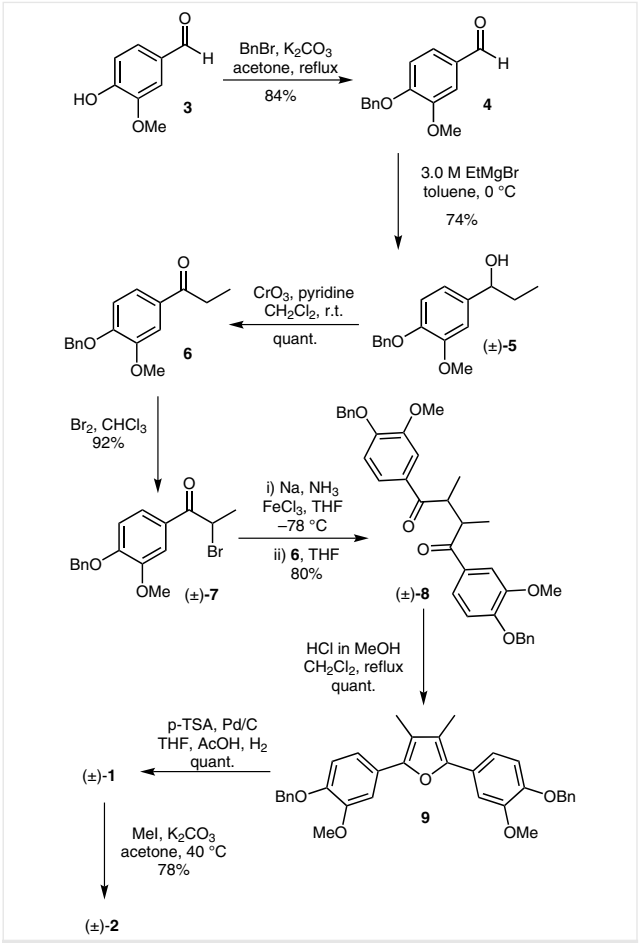


Figure 2 Retrosynthetic analysis towards 8,8′-*syn*-1-arylnaphthalenes

As we envisioned the key transformation to involve a catalytic hydrogenation reaction, we decided that a benzyl moiety would be an appropriate protecting group for the phenols in **1**, thus vanillin (**3**) was benzyl-protected to give benzaldehyde **4** in 84% yield (Scheme 1).[35] In order to extend the carbon chain by two carbon atoms, EtMgBr was added to benzaldehyde **4** to provide alcohol **5** which was then oxidised in quantitative yield to ketone **6** following Collins oxidation procedures.[35] With the successful preparation of ketone **6**, one of the two intermediates required for the dimerisation reaction, the next step was bromination of **6** to produce the other key intermediate **7**. Following procedures by Adler et al., **6** was brominated using Br_2 in $CHCl_3$ at room temperature, giving bromoketone **7** in 92% yield.[36]

With ketone **6** and α-bromoketone **7** in hand, 1,4-diketone **8** was synthesised by the reaction of these two units using methodology reported by Perry et al. and Schneiders and Stevenson.[37,38] That is, the treatment of ketone **6** with sodamide, prepared by the mixing of ferric chloride and sodium metal in liquid ammonia at –78 °C, followed by the addition of α-bromoketone **7** to the reaction mixture. Once synthesised, 1,4-diketone **8**[39] was then converted into quantitative yield to the furan **9** by treatment with HCl. Finally, furan **9**[40] was hydrogenated, catalysed by Pd/C in the presence of *p*-toluenesulfonic acid monohydrate in THF/AcOH;[41] pleasingly, a reaction time of 15 hours provided the desired product (±)-isoguaiacin (**1**) in quantitative yield.[42] The NMR data of synthetic **1** was identical to reported values.

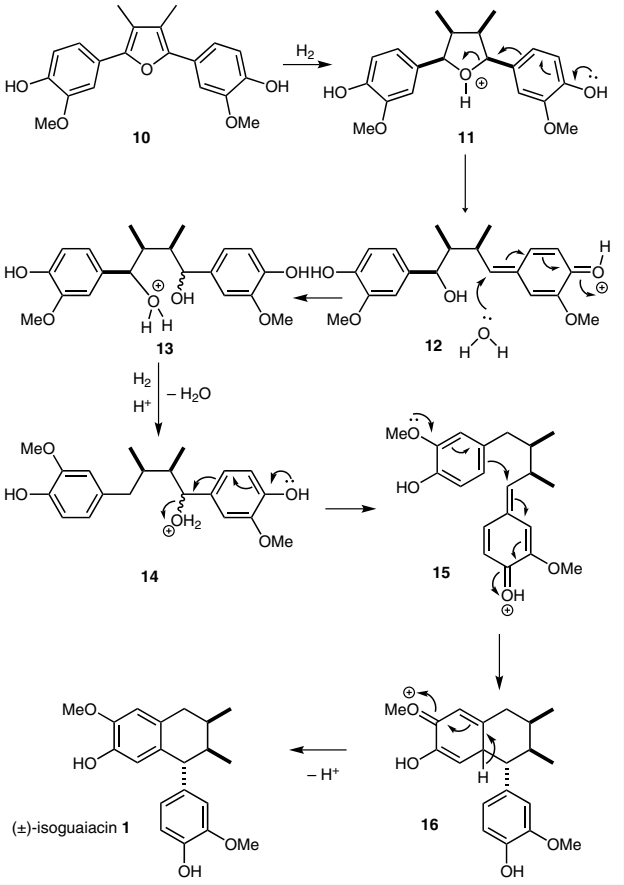
We hypothesise that (±)-isoguaiacin (**1**) is formed according to the mechanism shown (Scheme 2). Following the benzyl deprotection of **9**, the formed furan **10**[43] then undergoes selective hydrogenation to tetrahydrofuran **11** with all *syn* stereochemistry. Electron donation from the *para* hydroxy group, in the acidic conditions, allows for ring opening and resultant formation of a quinone methide **12** which then undergoes attack by water to give dihydroxyl species **13**. Further hydrogenolysis, leads to intermediate **14** which undergoes elimination of water to give quinone methide **15**. Intramolecular cyclisation of **15** gives **16**, which rearomatises to give aryl tetralin, (±)-**1**.[44]



Scheme 1 Synthesis of (±)-isoguaiacin (**1**) and (±)-isogalbulin (**2**)

Once synthesised, (±)-isoguaiacin (**1**) was then methylated using methyl iodide in acetone to give (±)-isogalbulin (**2**) in 78% yield, which was again spectroscopically identical to reported data.[45]

Overall, (±)-isoguaiacin (**1**) and (±)-isogalbulin (**2**) were synthesised over 7 steps and 8 steps in 46% and 36% yields, respectively, presenting this as an efficient, high-yielding, and convenient method to generate these naturally occurring aryl tetralin natural products and associated products. These methods provide an easy synthesis of these natural products allowing greater biological investigation without relying on natural sources.



Scheme 2 Proposed mechanism for the generation of (±)-isoguaiacin (**1**)

Acknowledgment

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(39) **(±)-2′,3′-Bis(4-benzyloxy-3-methoxybenzoyl)butane (8)**
To liquid NH_3 (20 mL) at –78 °C was added $FeCl_3$ (0.002 g) and Na (0.092 g, 3.95 mmol) and the mixture stirred for 2.5 h. To the dark-grey suspension of sodamide was added a solution of **6** (0.464 g, 1.72 mmol) in THF (6 mL), dropwise over 10 min and stirred for 40 min. A solution of **7** (0.600 g, 1.72 mmol) in THF (18 mL) was then added dropwise over 30 min. After the mixture was stirred for a further 2.5 h, NH_4Cl (0.500 g) was added, and the mixture warmed to r.t. to remove the NH_3. The mixture was then filtered, washed with EtOAc, and concentrated in vacuo to give the crude product which was then purified using flash chromatography (9:1 *n*-hexanes–EtOAc) to give the title product (0.742 g, 80%) as a colorless semisolid. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27 (6 H, d, *J* = 6.6 Hz, 2′-CH_3 and 3′-CH_3),

3.87–3.96 (8 H, m, 2 × OCH_3, H-2′ and H-3′), 5.23 (4 H, s, 2 × $ArCH_2$), 6.91 (2 H, d, *J* = 8.4 Hz, H-5, H-5‴), 7.31 (2 H, tt, *J* = 1.2, 7.2 Hz, H-4, H-4‴), 7.35–7.40 (4 H, m, H-3″, H-5″, H-3⁗, H-5⁗), 7.42–7.44 (4 H, m, H-2″, H-6″, H-2⁗, H-6⁗), 7.50 (2 H, d, *J* = 2.0 Hz, H-2, H-2‴), 7.61 (2 H, dd, *J* = 2.0, 8.4 Hz, H-6, H-6‴). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0 (2′-CH_3 and 3′-CH_3), 43.3 (C-2′ and C-3′), 56.0 (2 × OCH_3), 70.8 (2 × OCH_2), 111.2 (C-2 and C-2‴), 112.3 (C-5 and C-5‴), 122.9 (C-6 and C-6‴), 127.2 (C-2″, C-6″, C-2⁗ and C-6⁗), 128.1 (C-4″ and C-4⁗), 128.7 (C-3″, C-5″, C-3⁗, and C-5⁗), 129.5 (C-1 and C-1‴), 136.4 (C-1″, C-1⁗), 149.5 (C-3 and C-3‴), 152.4 (C-4 and C-4‴), 203.0 (C-1′ and C-4′). The ^1H NMR and ^{13}C NMR data were consistent with those reported in literature.[46]

(40) **3,4-Dimethyl-2,5-bis(4′-benzyloxy-3′-methylphenyl)furan (9)**

To a solution of diketone **8** (0.300 g, 0.557 mmol) in CH_2Cl_2 (5.5 mL) was added a solution of aq methanolic HCl (9.45 mL, 4.8% HCl in MeOH) and stirred at 80 °C at reflux for 2.75 h. The mixture was then cooled to r.t. to give the title product (0.29 g, quant.) as a white solid; mp 155 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.20 (6 H, s, 3-CH_3 and 4-CH_3), 3.95 (6 H, m, 2 × OCH_3), 5.20 (4 H, s, 2 × $ArCH_2$), 6.94 (2 H, d, *J* = 8.4 Hz, H-5, H-5‴), 7.14 (2 H, dd, *J* = 1.6, 8.4 Hz, H-6′, H-6‴), 7.24 (2 H, d, *J* = 1.6 Hz, H-2′, H-2‴), 7.31 (2 H, t, *J* = 7.2 Hz, H-4″, H-4⁗), 7.38 (4 H, t, *J* = 7.2 Hz, H-3″, H-5″, H-3⁗, H-5⁗), 7.46 (4 H, d, *J* = 7.2 Hz, H-2″, H-6″, H-2⁗, H-6⁗). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.9 (3-CH_3 and 4-CH_3), 56.1 (2 × OCH_3), 71.2 (2 × OCH_2), 109.8 (C-2 and C-2‴), 114.2 (C-5 and C-5‴), 118.1 (C-3 and C-4), 118.4 (C-6′ and C-6‴), 125.7 (C-1 and C-1‴), 127.3 (C-2″, C-6″, C-2⁗, and C-6⁗), 127.9 (C-4″ and C-4⁗), 128.6 (C-3″, C-5″, C-3⁗, and C-5⁗), 137.2 (C-1″ and C-1⁗), 146.9 (C-2 and C-5), 147.2 (C-4′ and C-4⁗), 149.7 (C-3′, C-3⁗).

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(42) **(±)-Isoguaiacin (1)**

To furan **9** (0.100 g, 0.192 mmol) in a solution of THF (5.5 mL) and AcOH (2.3 mL) was added *p*-toluenesulfonic acid monohydrate (0.010 g, 10 % w/w) and Pd/C (0.100 g, 100 % w/w). The mixture was stirred under and atmosphere of hydrogen for 15 h and was then filtered through Celite. To the filtrate was added water (4 mL), and the mixture was extracted with water (2 mL), followed by brine (2 mL), dried ($MgSO_4$), and concentrated in vacuo to afford the title product (0.065 g, quant.) as an orange-brown solid; mp 147–149 °C (lit. 149 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89–0.90 (6 H, m, H-9 and H-9′), 1.92–1.95 (1 H, m, H-8′), 2.02–2.04 (1 H, m, H-8), 2.46 (1 H, dd, *J* = 7.2, 16.0 Hz, H-7_b), 2.90 (1 H, dd, *J* = 5.6, 16.0 Hz, H-7_a), 3.59 (1 H, d, *J* = 6.4 Hz, H-7′), 3.81 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 5.35 (br s, OH), 5.47 (br s, OH), 6.41 (1 H, s, H-5), 6.49 (1 H, dd, *J* = 2.0, 8.1 Hz, H-6′), 6.55 (1 H, d, *J* = 2.0 Hz, H-2′), 6.57 (1 H, s, H-2), 6.78 (1 H, d, *J* = 8.1 Hz, H-5′). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8 and 15.9 (C-9 and C-9′), 29.3 (C-8), 35.3 (C-7), 40.6 (C-8′), 50.5 (C-7′), 55.9 (3-OCH_3 and 3′-OCH_3), 110.6 (C-2), 111.5 (C-2′), 113.8 (C-5′), 116.1 (C-5), 122.0 (C-6′), 127.6 (C-6), 130.9 (C-1), 139.0 (C-1′), 143.5 (C-4), 143.7 (C-4′), 145.0 (C-3), 146.2 (C-3′). The ^1H NMR and ^{13}C NMR data were consistent with that reported in literature.[44]

(43) Hydrogenation of **9** for one hour leads to complete removal of the benzyl groups to give **10** only; an extended reaction time is required to transform **10** into (±)-**1**.

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(45) **(±)-Isogalbulin (2)**

To a stirred solution of **1** (0.025 g, 0.076 mmol) in acetone (3 mL) was added K_2CO_3 (0.053 g, 0.38 mmol), followed by MeI (0.024 mL, 0.38 mmol) and the mixture stirred at 40 °C for 3 d. The reaction mixture was then filtered and the to give the title product (0.0205 g, 78%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90–0.93 (6 H, m, H-9 and H-9′), 1.92–1.96 (1 H, m, H-8′), 2.00–2.05 (1 H, m, H-8), 2.46 (1 H, dd, *J* = 8.0, 16.0 Hz, H-7_b), 2.87 (1 H, dd, *J* = 5.6, 16.0 Hz, H-7_a), 3.67 (3 H, s, OCH_3), 3.67–3.69 (1 H, m, H-7′), 3.80 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 6.35 (1 H, s, H-5), 6.50 (1 H, dd, *J* = 2.0, 8.0 Hz, H-6′), 6.57 (1 H, d, *J* = 2.0 Hz, H-2′), 6.60 (1 H, s, H-2), 6.74 (1 H, d, *J* = 8.0 Hz, H-5′). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.2 and 16.5 (C-9 and C-9′), 28.6 (C-8), 34.7 (C-7), 40.8 (C-8′), 50.9 (C-7′), 55.69 (OCH_3), 55.74 (OCH_3), 55.78 (OCH_3), 55.83 (OCH_3), 110.6 (C-5′), 111.0 (C-2), 112.2 (C-2′), 113.3 (C-5), 121.3 (C-6′), 128.4 (C-6), 129.5 (C-1), 139.8 (C-1′), 147.1 and 147.2 (C-3, C-4, C-4′), 148.6 (C-3′). The ^1H NMR and ^{13}C NMR data were consistent with those reported in literature.[17]

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