Total synthesis of (±)-agastinol

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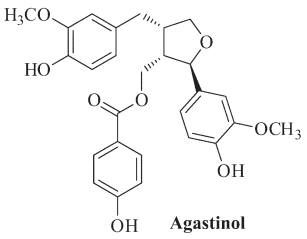
A synthesis of the tetrahydrofuran lignan (±)-agastinol, starting from the cheap Vanillin, has been developed based on Stobbe reaction with diethyl succinate to give the skeleton of lignan, which was then reduced to afford *meso*- and *threo*-(±)-secoisolanciresinol. *threo*-(±)-Secoisolanciresinol was treated with DDQ in acetic acid to give the 2-aryl tetrahydrofuran lignan, and which was then condensed with ferulic acid to give (±)-agastinol for the first time.

Keywords: synthesis, lignan, agastinol, Stobbe reaction

Lignans are a class of secondary plant metabolites produced by the oxidative dimerisation of two phenylpropanoid units. Although their backbone consists of only two phenylpropane (C_6–C_3) units, lignans show an enormous structural diversity.[1–3] Natural products of the lignan family display interesting and diverse biological activities, including anti-spasmodic, anticancer, anti-inflammatory activity.[4–7] In 2002, the lignan compound agastinol (**1**) isolated from *Agastache rugosa*, was shown to inhibit etoposide-induced apoptosis in U937 cells with IC_{50} values of 15.2 and 11.4 μg mL^{-1}, respectively. From these results, agastinol seems to be a worthy candidate for further research as a potential anti-apoptotic agent.[8]

Agastinol is a tetrahydrofuran lignan, whose core is a 2,3,4-trisubstituted tetrahydrofuran. The majority of the tetrahydrofuran lignan which have the substituents arranged with 2,3-*trans*, 3,4-*cis* stereochemistry, exhibit greater biological activity. There is a growing interest in the synthesis of tetrahydrofuran lignans due to applications in various pharmacological effects.[9] Several efficient methods for their synthesis have been reported. Meyer introduced the stereoselective synthesis of all-*cis*-2,3,5-trisubstituted tetrahydrofurans by the Lewis acid-mediated condensation of aldehydes with 7-substituted 1-oxa-2-silacyclohept-4-enes.[10] Miles preferred reagent-controlled stereoselective synthesis of lignan-related tetrahydrofurans. The reaction of ring-closing metathesis-derived cyclic allylsiloxanes with aldehydes in the presence of a Lewis acid gave 2,3,4-trisubstituted tetrahydrofurans related to the tetrahydrofuran lignan family of natural producs.[11] Maiti developed a route involving a radical cyclisation step which proceeds with high stereoselectivity.[12,13]

We now provide full details of the total synthesis of agastinol. The synthesis involved a Stobbe reaction to construct the skeleton of lignan (C_6–C_4–C_6) and resolution of *threo*- and *meso*-isomers. Treatment with DDQ in acetic acid then gave the 2-aryl tetrahydrofuran lignan. The 2-aryl tetrahydrofuran lignan was condensed with 4-hydroxybenzoic acid to give the natural product, agastinol.

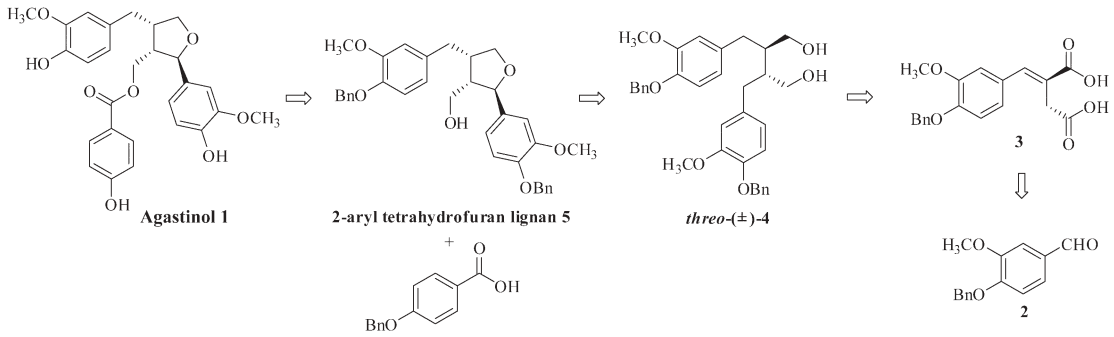


Scheme 1

Results and discussion

Our approach to the synthesis of agastinol is outlined in Scheme 2. It was anticipated that condensation of **2** with ethyl succinate would furnish **3**, which after the second condensation of with **2** into *threo*-(±)-**4** and subsequent treatment with DDQ would provide the desired key intermediate **5**. The acylation of **5** give the agastinol **1**.

Our investigations began with cheap vanillin as the starting material. The 4-hydroxyl group of vanillin was protected with benzyl chloride to afford the product **2**. Compound **2** underwent Stobbe condensation with diethyl succinate in the presence of sodium ethoxide in ethanol to produce compound **3**. The *trans*-(*E*)-configuration of the olefinic double bond was evident from the appearance of the deshielded vinylic proton at δ 7.87 in its ^{1}H NMR spectrum. Compound **3** was methylated with diazomethane in methanol to yield the diester **6**. QA second Stobbe condensation of **6** with **2** in methanol in the presence of sodium methoxide yielded compound **7**. The deshielded vinylic proton at δ 7.96 in the ^{1}H NMR spectrum of **7** indicated the *trans*-(*E*)-configuration for both the olefinic double bonds.[14] Compound **7** was again methylated to produce a diester **8**. Treatment of **8** with $LiAlH_4/AlCl_3$ afforded the unsaturated diol **9**. This was followed by hydrogenation over a 10% palladium on charcoal catalyst to produce a readily separable mixture (approximate 1:1) of the diols *meso*-secoisolariciresinol **(10a)** and *threo*-(±)-secoisolariciresinol (**10b**).



Scheme 2

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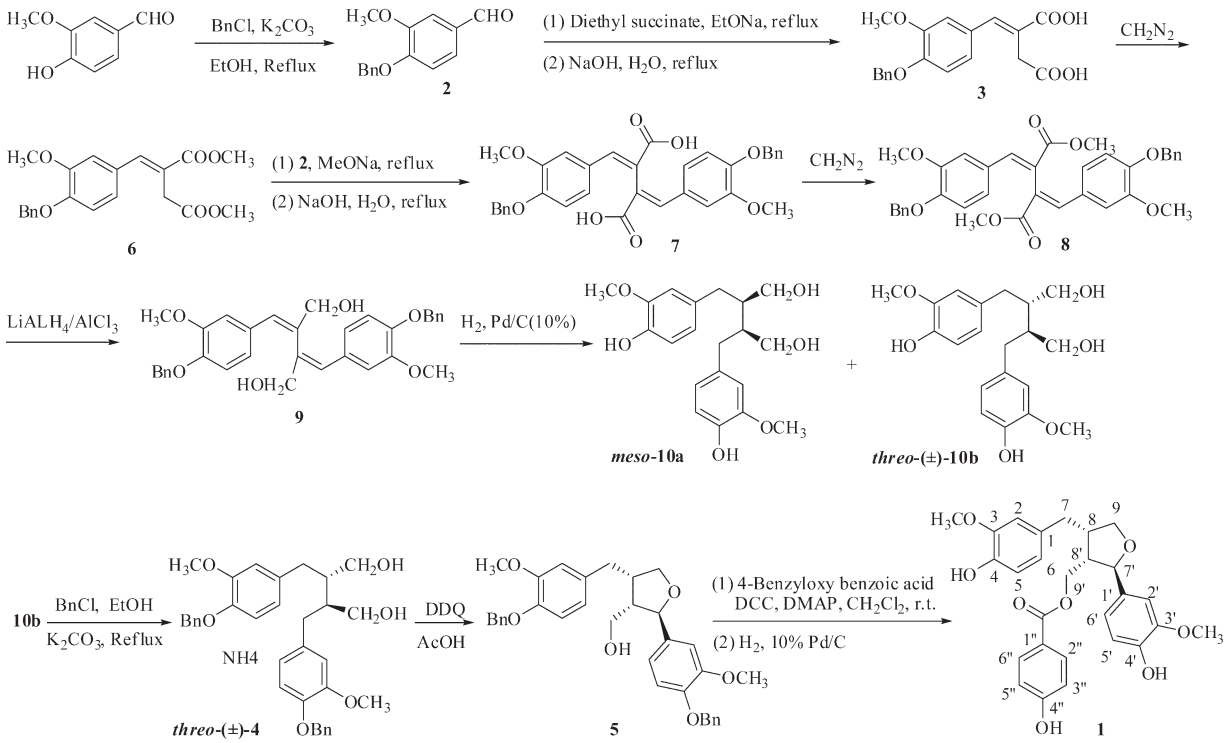

Scheme 3

Threo-(±)-**10b** had consistently larger R_f values than those of the corresponding *meso*-**10a**, and each pair were easily separated by flash column chromatography over silica gel. The data for the configuration of *threo*-(±)-**10b** was in agreement with that reported in the literature.[15]

The 4-hydroxyl group of *threo*-(±)-**10b** was protected with benzyl chloride to afford the compound **4**. *Threo*-(±)-**4** was treated with DDQ in acetic acid to give the 2-aryl-tetrahydrofuran lignan **5**.[16] After acylation of **5** with 4-benzyloxybenzoic acid, and then hydrogenation, natural product agastinol **1** was obtained (Scheme 3). The spectroscopic data of agastinol was in agreement with the literature.[8]

In summary, we have developed an efficient and practical synthesis of a tetrahydrofuran lignan based on Stobbe reaction to construct the skeleton of lignan, oxidation with DDQ to give the tetrahydrofuran ring. Agastinol, a potential anti-apoptotic agent, was obtained for the first time by this route.

Experimental

Melting points were taken on Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet NEXUS 670 FT–IR. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker AM–500 MHz spectrometers. Mass spectra were recorded on a ZAB–HS spectrometer. HRMS were obtained on a Bruker Daltonics APEXII47e spectrometer. Flash column chromatography was performed on silica gel (200–300 mesh) and TLC inspections on silica gel GF_{254} plates.

Threo-(±)-Secoisolariciresinol(**10b**) was synthesised according to the procedure which has been described previously.[17]

Threo-(±)-2,3-bis(4′-benzyloxy-3′-methoxybenzyl)-1,4-butanediol (**4**): Following the procedure described for the preparation of **2**, and starting with the diester **10b** (3.6 g, 10 mmol), compound **4** was obtained as a yellow oil (4.8 g, 89%). IR (KBr/cm^{-1}): 3383, 2921, 1521, 1245, 1037, 928. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.85–1.95 (m, 2H, 2 × ArCH$_2$C*H*), 2.62–2.67 (m, 4H, 2 × ArC*H*$_2$CH), 3.54–3.56 (m, 2H, C*H*$_2$OH), 3.60–3.62 (m, 2H, C*H*$_2$OH), 3.80 (s, 6H, 2 × OCH_3), 5.13 (s, 4H, 2 × ArCH$_2$O), 6.61–6.71 (m, 6H, ArH), 7.27–7.37 (m, 10H, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 35.9 (C-3, C-4), 45.0 (C-7′, C-7″), 56.1 (2 × OCH_3), 63.4 (C-1, C-4), 71.3 (2 × ArCH$_2$O), 113.0 (C-2′, C-2″), 114.4 (C-5′, C-5″), 121.0 (C-6′, C-6″), 127.3, 127.8, 128.5, 133.9 (C-1′, C-1″), 137.4, 146.7 (C-4′, C-4″), 149.8 (C-3′, C-3″). HRMS Calcd for $C_{34}H_{42}NO_6$(M+NH_4^+): 560.3007. Found: 560.3012.

4,4′-Dibenzyloxy-3,3′-dimethoxybenzyl-9-hydroxy-7,9′-epoxylignan (**5**): DDQ (0.9 g, 4 mmol) was added to a solution of compound **4** (1.1 g, 2 mmol) in glacial acetic acid. The mixture was stirred for 5 h. The reaction mixture was poured onto crushed ice and extracted with EtOAc (20 mL). The organic layer was washed with a saturated solution of $NaHSO_3$ (3 × 20 mL) and a saturated solution of $NaHCO_3$ (3 × 20 mL). The extract was dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography of the residue gave (±)-dihydrosesamin **5** as a colourless oil (0.5 g, 46%). IR (KBr/cm^{-1}): 3448, 2936, 1595, 1512, 1456, 1226, 1023. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.76 (dd, 1H, *J* = 13.0, 11.0 Hz, H-7α), 2.76–2.87 (m, 1H, H-8′), 3.01–3.09 (m, 1H, H-8), 3.22 (dd, 1H, *J* = 13.5, 5.5 Hz, H-7β), 3.80 (s, 6H, 2 × OCH_3), 4.06 (dd, 1H, *J* = 8.5, 6.5 Hz, H-9α), 4.17 (dd, 1H, *J* = 11.0, 6.5 Hz, H-9′α), 4.25 (dd, 1H, *J* = 11.0, 7.0 Hz, H-9′β), 4.30 (dd, 1H, *J* = 8.5, 6.5 Hz, H-9β), 5.15 (s, 4H, 2 × ArCH$_2$O), 5.28 (d, 1H, *J* = 6.0 Hz, H-7′), 6.90–7.45 (m, 16H, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 33.1 (C-9), 42.3 (C-8), 52.5 (C-8’), 56.0 (2 × OCH_3), 60.8 (C-9’), 71.2 (ArCH$_2$), 72.7 (C-7), 82.5 (C-7’), 108.7, 111.2, 112.1, 112.4, 117.9, 120.5, 127.1, 127.7, 128.4, 132.3, 134.9, 137.3, 147.4, 148.2, 148.8, 148.9. HRMS Calcd for $C_{34}H_{40}NO_6$ (M+NH_4^+):558.2851. Found: 558.2847.

Agastinol (**1**): A solution of **5** (0.54 g, 1 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise to a solution of 4-benzyloxybenzoic acid (0.23 g, 1 mmol), DCC (2.1 g, 10 mmol) and DMAP (0.13 g, 1 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C for 2 h under nitrogen. After stirring the mixture overnight at room temperature, the reaction mixture was filtered and the solvent was distilled. The residue was dissolved in 20 mL MeOH and was stirred under a hydrogen atmosphere for 7 h in the presence of 10% Pd/C (0.6 g). The reaction mixture was filtered through a pad of Celite, and then the solvent was removed *in vacuo*. Flash column chromatography of the residue gave an amorphous powder of Agastinol **1** (0.42 g, 87%) (no melting point). IR (KBr, cm^{-1}) *v*: 3452, 2918, 1720, 1590, 1507, 1455, 1152. ^{1}H NMR (CD_3OD, 500 MHz) δ: 2.62 (dd, 1H, *J* = 13.5, 10.5 Hz, H-7α), 2.65–2.73 (m, 1H, H-8′), 2.81–2.89 (m, 1H, H-8), 2.93 (dd, 1H, *J* = 13.5, 5.5 Hz, H-7β), 3.74 (dd, 1H, *J* = 8.5, 6.5 Hz, H-9α), 3.77 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.02 (dd, 1H, *J* = 8.5, 6.5 Hz, H-9β), 4.38 (dd, 1H, *J* = 11.0, 6.5 Hz, H-9′α), 4.60 (dd, 1H, *J* = 11.0, 7.5 Hz, H-9′β), 4.85 (d, 1H, *J* = 6.5 Hz, H-7′), 6.70–7.83 (m, 10H, ArH). ^{13}C NMR (CD_3OD,

125 MHz) δ: 33.9 (C-9), 43.9 (C-8), 50.5 (C-8′), 56.4 ($2 \times OCH_3$), 63.7 (C-9′), 73.3 (C-7), 84.1 (C-7′), 110.6, 111.5 (C-3″, C-5″), 113.2, 115.2, 115.8, 119.6, 122.0, 122.5(C-1″), 132.6 (C-2″, C-6″), 132.8, 135.7, 145.8, 146.8, 148.4, 148.5, 162.9 (C-4′′), 166.5 (C=O). HRMS Calcd for $C_{27}H_{32}NO_8$ ($M+NH_4^+$): 498.2123. Found: 498.2125. The data are consistent with the literature.[8]

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