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First total synthesis of Boehmenan

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Abstract. The first total synthesis of dilignan Boehmenan has been achieved. A biomimetic oxidative coupling of the ferulic acid methyl ester in the presence of silver oxide is the crucial step in the synthesis sequence, generating the dihydrobenzofuran skeleton. Hydroxyl group was protected with DHP and reducted with $LiAlH_4$ to afford the intermediate diol. The diol was condensated with the derivative of ferulic acid, then removed the protecting groups, to get Boehmenan. Meanwhile, a study on the ring-opening reaction of the intermediate dihydrobenzofuran neolignan under base conditions was described.

Keywords. Boehmenan; dihydrobenzofuran neolignan; dilignan; biomimetic oxidative coupling; ring-opening reaction mechanism.

1. Introduction

The structurally novel lignan Boehmenan (**1**) was first isolated in 2001 by Seca *et al*. from the bark of Kenaf (*Hibiscus cannabinus*), which is an annual dicotyledonous herbaceous plant and well-known in Asia and Africa.[1] In 2005, Wu *et al*. reported that Boehmenan was isolated from the stems of *Hibiscus taiwanensis*, co-occurring with a structurally diverse set of natural products.[2] Rudiyansyah *et al*. isolated it together with another nine compounds by the phytochemical exploration of a wood bark extract from *Durio zibethinus* in 2006.[3] Cytotoxicity-guided fractionation of the stems of *Helicteres hirsuta*, led to the isolation and identification of Boehmenan by Chin *et al*. in the same year.[4] In addition, Sasaki *et al*. extracted it from the whole plants of *Sambucus adnata* and reported the evaluation of the PTP1B inhibitory activities of it in 2011. The kinetic analysis indicated that Boehmenan in hibits PTP1B activity in a competitive manner.[5]

Boehmenan, with a dihydrobenzofuran skeleton, is formed by polymerization of four phenylpropanoid units. This compound belongs to the very interesting class of dilignan on account of their great number of structural possibilities. Dilignan family are found in all part of plants[6,7] and display biological activities including antioxidant[8] and antituberculosis activities[9] and inhibitory effects on the growth of dicotyledons.[10] Although many dilignans with broad application prospect have been found in nature, only a few have been synthesized. In 2010, our team developed a novel synthetic route of dilignan *threo*-(±)-diferuloysecoisolariciresinol. The method involved two Stobbe reactions to construct the skeleton of lignan, and then condensed with ferulaic acid to give *threo*-(±)-diferuloysecoisolariciresinol.[11]

Here, we report the first total synthesis of another dilignan Boehmenan. The synthesis was based on a strategy involving biomimetic oxidative coupling to give the key intermediate dihydrobenzofuran neolignan, and then treated with derivative of ferulic acid to obtain the natural product Boehmenan as shown in scheme 1. Furthermore, the reaction conditions of biomimetic oxidative coupling are described, and the possible ring-opening reaction mechanisms of dihydrobenzofuran compound are discussed in this paper.

2. Experimental

2.1 *Materials and apparatus*

The reagents and the solvents used in this study were of analytical grade and were used without further purification. Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked by TLC on silica gel GF254 plates using UV/Iodine as visualizing agent and silica gel (200–300 mesh) was used for column chromatographic purification. The ^{1}HNMR and ^{13}CNMR spectra were recorded

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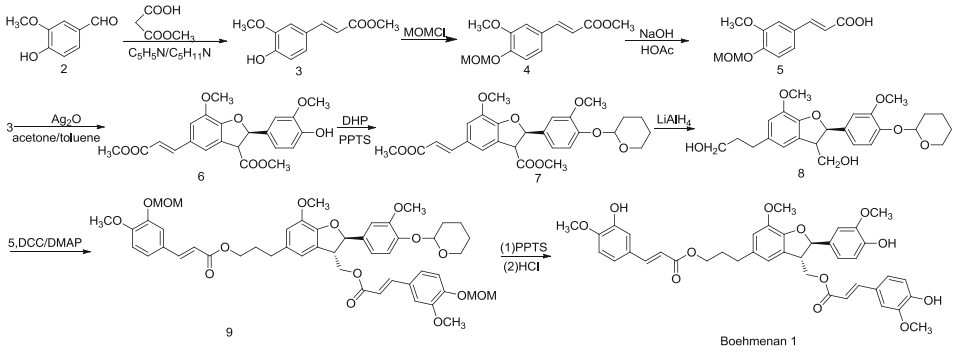


Scheme 1. Synthesis of Boehmenan.

on a Brucker *AM-500* MHz spectrometers. HRMS were obtained on a Bruker Daltonics APEXII47e spectrometer.

2.2 *Synthesis of (E)- ferulic acid methyl ester (**3**)*

A mixture of vanillin (8.58 g, 56.4 mmol), methyl hydrogen malonate (13.32 g, 112.8 mmol) and piperidine (0.72 g, 8.5 mmol) in pyridine (13 mL) were heated at 100°C for 4 h. The residue was poured into diluted hydrochloric acid solution which was cooled at 0°C. After three days, the crude product obtained was filtered and recrystallized from ethanol to give compound **3** (10.40 g).

2.2a *(E)- ferulic acid methyl ester (**3**)*: This compound was obtained as a white solid, mp: 63–64°C; 89% yield; HRMS calcd for $C_{11}H_{12}O_4$ 208.0737, found 208.0751; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69 and 3.91 (s, 6H, 2 × OCH_3), 6.39 (d, 1H, J = 16.0 Hz, ArCH=CH), 6.87–7.30 (m, 3H, ArH), 7.59 (d, 1H, J = 16.0 Hz, ArCH=CH), 8.11 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.49, 56.36, 111.42, 115.55, 116.06, 123.75, 127.42, 145.66, 148.67, 149.98, 167.87 (C=O). The data are consistant with the literature.[12]

2.3 *Synthesis of methyl (E)-4-methoxymethyl-3-methoxycinnamate (**4**)*[13,14]

2.3a *The preparation of MOMCl*: In a 1 L round-bottomed flask fitted with a stopper carrying a reflux condenser and a glass tube reaching nearly to the bottom of the flask are placed methyl alcohol (100.00 g, 3.1 mol) and formaldehyde (72.00 g, 2.4 mol). A rapid stream of hydrogen chloride is run into the mixture, which is cooled with running water. In about two hours a layer of chloromethyl ether begins to appear. The stream of hydrogen chloride is continued for two or three hours longer until the solution is saturated. The layer of chloromethyl ether is then separated. The water layer is saturated with calcium chloride, and more ether separates. This is added to the main portion, which is then dried over calcium chloride and fractionally distilled. The yield of MOMCl boiling at 55–60°C is about 150 g.

2.3b *The synthesis of methyl (E)-4-methoxymethyl-3-methoxycinnamate (**4**)*: A mixture of compound **3** (2.81 g, 13.5 mmol), potassium carbonate (5.59 g, 40.5 mmol) in acetone (20 mL), was stirred for 1 h at room temperature. Then, MOMCl (2.18 g, 27.1 mmol) was added drop-wise. Stirring was continued for 3 h and the reaction mixture was then quenched with aqueous ammonium chloride. The mixture was extracted with ethyl acetate, dried over $MgSO_4$, concentrated under vacuum to give **4** (3.15 g).

2.3c *Methyl (E)-4-methoxymethyl-3- methoxycinnamate (**4**)*: This compound was obtained as a colourless oil, 93% yield; HRMS calcd for $C_{13}H_{16}O_5$ 252.0998, found 252.1004; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.46 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 5.23 (s, 2H, OCH_2O), 6.43 (d, 1H, J = 16.5 Hz, ArCH=CH), 6.80–7.10 (m, 3H, ArH), 7.52 (d, 1H, J = 16.5 Hz, ArCH=CH).

2.4 *Synthesis of (E)-4-methoxymethyl-3-methoxycinnamic acid (**5**)*

To the compound **4** (0.94 g, 3.7 mmol) in ethanol (20 mL), 20 mL aqueous solution of NaOH (0.18 g, 4.5 mmol) were added, then the mixture was heated under reflux for 3 h. After that the reaction mixture was cooled and poured in acetic acid, which has been cooled

in an ice bath. The solid product obtained was filtered and recrystallised (petroleum/acetic ether = 1/15) to give the compound **5** (0.84 g).

2.4a *(E)-4-methoxymethyl-3-methoxycinnamic acid (**5**)*: This compound was obtained as a white solid, mp: 135–137°C; 95% yield; HRMS calcd for $C_{12}H_{14}O_5$ 238.0841, found 238.0848; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.52 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.28 (s, 2H, OCH_2O), 6.33 (d, 1H, J = 16.0 Hz, ArCH=CH), 7.10–7.28 (m, 3H, ArH), 7.71 (d, 1H, J = 16.0 Hz, ArCH=CH).

2.5 *Synthesis of methyl (E)-3-[2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methoxycarbonyl-2, 3-dihydro-1-benzofuran-5-yl]-prop-2-enoate (**6**)*[15–17]

Fresh silver oxide (1.56 g, 6.7 mmol) was added to a solution of compound **3** (2.81 g, 13.5 mmol) in dry acetone (20 mL) and toluene (30 mL) under a nitrogen atmosphere at −20°C. After stirring for 30 h, the mixture was filtered and evaporated under reduced pressure. The residue was purified by a short silica gel column chromatography (petroleum/acetic ether = 3/1) to give the compound **6** (1.27 g).

2.5a *Methyl (E)-3-[2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methoxycarbonyl-2,3-dihydro-1- benzofuran-5-yl]-prop-2-enoate (**6**)*: This compound was obtained as a white crystals, mp: 151–152 °C; 45% yield; HRMS calcd for $C_{22}H_{22}O_8$ 414.1315, found 414.1328; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 and 3.82 (s, 6H, 2 × OCH_3), 3.83 and 3.94 (s, 6H, 2 × OCH_3), 4.49 (d, 1H, J = 8.0 Hz, H-8), 6.03 (d, 1H, J = 8.0 Hz, H-7), 6.46 (d, 1H, J = 16.0 Hz, H-8′), 6.85–7.34 (m, 5H, ArH), 7.64 (d, 1H, J = 16.0 Hz, H-7′) 7.69 (s, 1H, OH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.67, 53.07, 55.92, 56.35, 56.54, 87.54, 110.97, 113.46, 116.03, 116.29, 119.02, 120.19, 127.36, 129.42, 131.81, 145.50, 145.80, 148.21, 148.75, 151.01, 167.86 (C=O), 171.73 (C=O). The data are consistant with the literature.[12]

2.6 *Synthesis of methyl (E)-3-{2-[4-(tetrahydro-2H-pyran-2-yloxy)-3-methoxyphenyl]-7-methoxy-3-methoxycarbonyl-2,3-dihydro-1-benzofuran-5-yl}-prop-2-enoate (**7**)*[18,19]

A 25 mL dried round-bottom flask containing anhydrous dichloromethane 5 mL was charged with compound **6** (0.83 g, 2.0 mmol), PPTS (0.05 g, 0.2 mmol) and DHP (0.21 g 2.5 mmol). After the mixture was stirred for 4 h at room temperature, the reaction completed. The residue was chromatographed on a silica gel column (petroleum/acetic ether = 4/1) to give the compound **7** (0.85 g).

2.6a *Methyl (E)-3-{2-[4-(tetrahydro-2H-pyran-2-yloxy)-3-methoxyphenyl]-7- methoxy-3-methoxycarbonyl-2, 3-dihydro-1-benzofuran-5-yl}-prop-2-enoate (**7**)*: This compound was obtained as a pale yellow oil, 85% yield; HRMS calcd for $C_{27}H_{30}O_9$ 498.1889, found 498.1995; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.59–1.94 (m, 6H, $CH_2CH_2CH_2$), 3.56–3.73 (m, 2H, OCH_2), 3.72 and 3.84 (s, 6H, 2 × OCH_3), 3.88 and 3.92 (s, 6H, 2 × OCH_3), 4.35 (d, 1H, J = 8.0 Hz, H-8), 5.39 (t, 1H, OCHO), 6.12 (d, 1H, J = 8.0 Hz, H-7), 6.30 (d, 1H, J = 16 Hz, H-8′), 6.77–7.19 (m, 5H, ArH), 7.63 (d, 1H, J = 16 Hz, H-7′). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.79, 25.23, 30.28, 51.65, 52.90, 55.45, 55.62, 56.16, 62.12, 87.33, 97.02, 110.37, 112.18, 115.57, 117.80, 117.97, 118.80, 125.74, 128.64, 133.65, 144.45, 144.78, 146.63, 150.02, 150.52, 167.63 (C=O), 170.77 (C=O).

2.7 *Synthesis of 3-{2-[4-(Tetrahydro-2H-pyran-2-yloxy)-3-methoxyphenyl]-3-hydroxymethyl-7-methoxy-2,3-dihydro-1-benzofuran-5-yl}propan-1-ol (**8**)* [12,20]

In a 50 mL dried three-necked flask, $LiAlH_4$ (0.19 g, 5.0 mmol) was dissolved in 30 mL of dry THF, and compound **7** (0.50 g, 1.0 mmol) was added slowly. The mixture was stirred at 0°C under a nitrogen atmosphere for 3 h. H_2O (0.19 mL) was added, followed by treatment with HCl, and the mixture was extracted with AcOEt (3 × 10 mL). Then the organic phase was washed with saturated NaCl solution (20 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column (petroleum/acetic ether = 1/1) to give the compound **8** (0.34 g).

2.7a *3-{2-[4-(Tetrahydro-2H-pyran-2-yloxy)-3-methoxyphenyl]-3-hydroxymethyl-7-methoxy-2,3- dihydro-1-benzofuran-5-yl}propan-1-ol (**8**)*: This compound was obtained as a yellow oil, 77% yield; HRMS calcd for $C_{25}H_{32}O_7$ 444.2148, found 444.2156; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60–1.96 (m, 6H, $CH_2CH_2CH_2$), 1.86–2.08 (m, 2H, H-8′), 2.56 (t, 2H, H-7′), 3.50–3.53 (m, 2H, OCH_2), 3.55–3.56 (d, 1H, J = 7.0 Hz, H-8), 3.70 (t, 2H, H-9′), 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.03–4.09 (m, 2H, H-9), 5.30 (t, 1H, OCHO), 5.47 (d, 1H, J = 7.0 Hz, H-7), 6.59-7.01 (m, 5H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.85,

25.22, 30.28, 31.91, 34.48, 53.85, 56.01, 56.12, 60.87, 62.36, 63.91, 87.60, 97.60, 109.92, 110.38, 116.39, 118.03, 118.62, 128.20, 135.40, 135.84, 143.97, 145.28, 145.92, 150.27.

2.8 *Synthesis of 2-[4-(tetrahydro-2H-pyran-2-yloxy)-3-methoxyphenyl]-5-[3-(4-methoxymethyl-3-methoxycinnamoyloxy)propyl]-3-[(4-methoxymethyl-3-methoxycinnamoyloxy)propyl]-7-methoxybenzodihydrofuran (**9**)*[21]

Under a nitrogen atmosphere, a 50 mL, oven dried, round-bottom flask containing anhydrous dichloromethane (20 mL) was charged with acid **5** (0.119 g, 0.5 mmol), compound **8** (0.111 g, 0.25 mmol), dicyclohexyl carbodiimide (DCC, 0.105 g, 0.5 mmol), and 4-dimethylaminopyridine (DMAP, 0.021 g, 0.165 mmol) at 0°C. The ice bath was removed after the addition was completed, and the resulting solution was stirred for 6 h at room temperature. The reaction mixture was filtrated and the solvent was distilled off. The residue was purified by flash column chromatography to afford compound **9** (0.103 g).

2.8a *2-[4-(Tetrahydro-2H-pyran-2-yloxy)-3-methoxyphenyl]-5-[3-(4-methoxymethyl-3-methoxcinnamoyloxy) propyl]-3-[(4-methoxymethyl-3-methoxcinnamoyloxy) propyl]-l-7-methoxybenzodihydrofuran (**9**)*: This compound was obtained as a yellow oil, 47% yield; HRMS calcd for $C_{49}H_{56}O_{15}$ 884.3619, found 884.3628; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54–2.17 (m, 6H, $CH_2CH_2CH_2$), 1.92–2.04 (m, 2H, H-2‴), 2.72 (t, 2H, H-1‴), 3.49 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.60–3.64 (m, 2H, OCH_2), 3.75 (m, 1H, H-3), 3.85 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.05 (dd, 1H, J = 7.0 and 12.0 Hz, H-1″), 4.43 (dd, 1H, J = 7.0 and 12.0 Hz, H-1″), 4.84 (t, 2H, J = 6.5 Hz, H-3‴), 5.07 (s, 1H, OCHO), 5.27 (s, 4H, 2 × OCH_2O), 5.60 (d, 1H, J = 6.5 Hz, H-2), 6.27 (d, 1H, J = 16.0 Hz, H-a), 6.35 (d, 1H, J = 16.0 Hz, H-a′), 6.67–7.16 (m, 11H, ArH), 7.50 (d, 1H, J = 16.0 Hz, H-b), 7.61 (d, 1H, J = 16.0 Hz, H-b′). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.19, 24.96, 25.21, 30.27, 33.91, 50.51, 55.94 (2 × OCH_3), 56.16 (2 × OCH_3), 56.34 (2 × OCH_3), 62.12, 63.78, 65.27, 88.72, 95.14, 97.50, 104.20, 110.25, 110.45, 110.86, 115.60, 115.64, 115.91, 116.23, 116.24, 117.75, 118.85, 121.36, 122.28, 122.51, 127.76, 128.49, 128.86, 134.44, 134.75, 144.19, 144.82, 145.33, 145.53, 146.37, 148.22, 148.51, 148.74, 149.74, 149.88, 166.89 (C=O), 167.01 (C=O).

2.9 *Synthesis of 2-(4-hydroxy-3-methoxyphenyl)-5-[3-(4-hydroxy-3-methoxycinnamoyloxy) propyl]-3-(4-hydroxy-3-methoxycinnamoyloxmethyl)-7-methoxybenzodihydrofuran (**Boehmenan**)*

In a 25 mL round-bottom flask, a mixture of **9** (0.097 g, 0.11 mmol) and PPTS (2.52 g, 0.011 mmol) in anhydrous ethanol (8 ml) were stirred for 2 h at 55°C. The solvent was removed *in vacuo* to give a crude product. To the residue of 25 ml (round-bottomed flask), hydrochloric acid (4 ml) in THF solution was added. Then the mixture was stirred for 0.5 h at room temperature and it was concentrated *in vacuum*. The crude product was purified by flash chromatography to afford **Boehmenan** (59.05 mg).

2.9a *2-(4-Hydroxy-3-methoxyphenyl)-5-[3-(4-hydroxy-3-methoxcinnamoyloxy)propyl]-3-hydroxymethyl-7-methoxybenzodihydrofuran (**Boehmenan**)*: This compound was obtained as yellow oil, 75% yield; HRMS calcd for $C_{40}H_{40}O_{12}$ 712.2520, found 712.2536; 1H NMR (500 MHz, $CDCl_3$) δ 1.97–2.06 (m, 2H, H-2‴), 2.71 (t, 2H, J = 7.6 Hz, H-1‴), 3.83 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.93 (s, 6H, 2 × OCH_3), 3.84–3.93 (m, 1H, H-3), 4.23 (t, 2H, J = 6.5 Hz, H-3‴), 4.43 (dd, 1H, J = 7.7 and 11.2 Hz, H-1″), 4.59 (dd, 1H, J = 5.1 and 11.2 Hz, H-1″), 5.50 (d, 1H, J = 7.8 Hz, H-2), 5.65 (s, 1H, OH), 5.91 (s, 1H, OH), 5.92 (s, 1H, OH), 6.23 (d, 1H, J = 15.9 Hz, H-a), 6.30 (d, 1H, J = 15.9 Hz, H-a′), 6.69–7.09 (m, 11H, ArH), 7.49 (d, 1H, J = 15.9 Hz, H-b), 7.61 (d, 1H, J = 15.9 Hz, H-b′). ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.71, 32.13, 50.67, 55.90 (2 × OCH_3), 56.01 (2 × OCH_3), 63.68, 65.42, 88.89, 108.76, 109.32, 109.39, 112.38, 114.21, 114.71, 114.72, 114.73, 115.37, 116.12, 119.71, 122.97, 123.14, 126.67, 126.94, 127.43, 132.50, 134.89, 144.08, 144.92, 145.48, 145.66, 146.23, 146.64, 146.71, 146.73, 147.94, 148.12, 167.02 (C=O), 167.34 (C=O). The data are consistant with the literature.[1]

2.10 *The formation of the dihydrobenzofuran neolignan (**10–12**)*

2.10a *The formation of methyl (E,E)-4,4′-dihydroxy-3,5′-dimethopxy-ß-3′-bicinnamate (**10**)*: The compound **6** (82.9 mg, 0.2 mmol) was dissolved in acetone (10 ml) with KOH (22.4 mg, 0.4 mmol) and stirred at room temperature for 4 h. The solution was acidified with HCl and partitioned between EtOAc and saturated NaCl. The organic layer was dried over $MgSO_4$, and

then crystallized (petroleum/acetic ether = 2/1) to give compound **10** (62.1 mg).

2.10b *Methyl (E,E)-4,4′-dihydroxy-3,5′-dimethopxy-ß-3′-bicinnamate (**10**)*: This compound was obtained as pale yellow solid, 75% yield; mp. 148–149 °C; HRMS calcd for $C_{22}H_{22}O_8$ 414.1315, found 414.1326; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.50 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 5.74 (s, 1H, OH), 6.00 (s, 1H, OH), 6.26 (d, 1H, J = 16.0 Hz, H-8′), 6.57–7.07 (m, 5H, Ar-H), 7.56 (d, 1H, J = 16.0 Hz, H-7′), 7.83 (s, 1H, H-7). ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.02, 52.06, 55.22, 56.62, 110.59, 113.47, 115.58, 115.73, 124.53, 125.19, 125.63, 125.66, 126.13, 126.22, 140.68, 145.07, 147.58, 147.66, 148.72, 148.78, 167.02 (C=O), 167.40 (C=O).

2.10c *The formation of (E,E)-4,4′-dihydroxy-3,5′-dimethopxy-ß-3′-bicinnamic acid (**11**)*: The compound **6** (82.9 mg, 0.2 mmol) was dissolved in 10% NaOH (10 ml) and stirred at room temperature for 4 h. The mixture was acidified with HCl and partitioned between EtOAc and saturated NaCl. The organic layer was dried over $MgSO_4$, and then crystallized (petroleum/acetic ether = 2/1) to give compound **11** (70.3 mg).

2.10d *(E,E)-4,4′-dihydroxy-3,5′-dimethopxy-ß-3′-bicinnamic acid (**11**)*: This compound was obtained as pale yellow oil, 91% yield; HRMS calcd for $C_{20}H_{18}O_8$ 386.1002, found 386.1013; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.37 (d, 1H, J = 16.0 Hz, H-8′), 6.71–7.37 (m, 5H, Ar-H), 7.60 (d, 1H, J = 16.0 Hz, H-7′), 7.82 (s, 1H, H-7), 12.15 (s, 2H, 2 × COOH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.93, 56.45, 110.27, 113.27, 116.24, 125.14, 125.62, 126.34, 126.37, 127.26, 127.59, 141.81, 145.81, 147.85, 148.02, 148.96, 149.12, 155.64, 168.56 (C=O), 169.18 (C=O). The data are consistant with the literature.[22]

2.10e *The formation of (E)-4-hydroxy-3-(2-[(E)-4-hydroxy-3-methoxystyryl]-}5-methoxycinnamic acid (**12**)*: The compound **6** (82.9 mg, 0.2 mmol) was dissolved in 10% NaOH (10 ml) and stirred for 4 h under reflux. Then the reaction solution was cooled and concentrated. The mixture was acidified with HCl and partitioned between EtOAc and saturated NaCl. The organic layer was dried over $MgSO_4$, and then crystallized (petroleum/acetic ether = 2/3) to give compound **12** (36.9 mg).

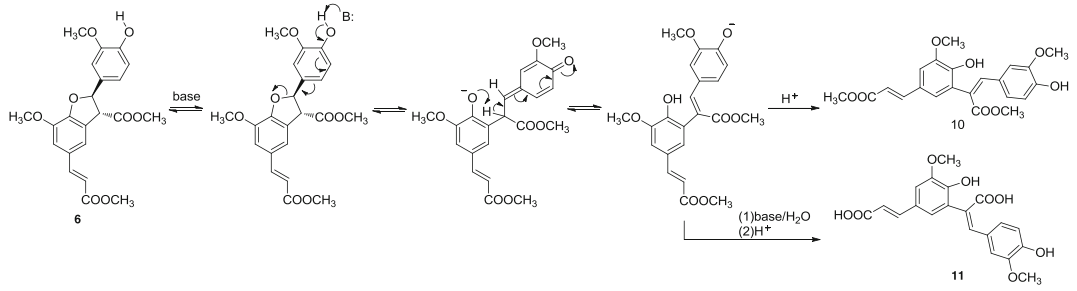
2.10f *(E)-4-hydroxy-3-(2-[(E)-4-hydroxy-3-methoxystyryl]-}5-methoxycinnamic acid (**12**)*: This compound was obtained as pale yellow oil, 54% yield; HRMS calcd for $C_{19}H_{18}O_6$ 342.1103, found 342.1109; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (s, 3H, OCH_3), 3.83(s, 3H, OCH_3), 6.46 (d, 1H, J = 15.5 Hz, H-8′), 6.76–7.52 (m, 5H, Ar-H), 7.21(d, 1H, J = 15.5 Hz, H-7), 7.22(d, 1H, J = 15.5 Hz, H-8), 7.53(d, 1H, J = 15.5 Hz, H-7′), 9.14 (s, 1H, Ph-OH), 9.40 (s, 1H, Ph-OH), 12.20 (s, 1H, COOH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.06, 56.56, 109.55, 110.26, 116.17, 116.70, 119.95, 120.09, 120.37, 125.09, 125.90, 129.60, 129.89, 145.19, 146.37, 147.11, 148.32, 148.58, 168.50 (C=O). The data are consistant with the literature.[22]

3. Results and discussion

The analytic and spectroscopic data of Boehmenan and the intermediate products are given in experimental section.

Our approach to the synthesis of natural product Boehmenan **1** is outlined in scheme 2. Vanillin was used as starting material. Compound **3** was formed through Knoevenagel condensation between vanillin and methyl hydrogen malonate. The 4-hydroxyl group of **3** was protected with MOMCl to afford the product **4**, which was hydrolysed to form compound **5**.

The preparation of compound **6** from ferulic acid methyl ester **3** by biomimetic oxidative coupling with Ag_2O to construct the skeleton of dihydrobenzofuran lignan was the key step in our method. The reaction gave different yield dependent on the reaction conditions. As shown in table 1, freshly prepared Ag_2O was used in the reaction into compound **7** with higher yield than that of conventional Ag_2O and recycling Ag_2O. The solvent system had only small effect on the yield of **7**, but the reaction temperature and time had significant influence in the reaction. A decrease in the reaction temperature increased the yield of compound **6**, while the by product was decreased. Moreover, in the process of the reaction, the yield increased to a maximum and began to decrease as the time increased further. The optimum reaction conditions were obtained as follows: freshly prepared Ag_2O, dry acetone (20 mL) and toluene (30 mL), 30 h and −20 °C. Under above conditions, the yield of compound **6** was 45%.[23,24]



Scheme 2. Formation of the stilbene **10** and diacid **11** from diester **6**.

Conversion of **6** into intermediate **8** was carried out by two steps: protection of dimers **6** with THP group and reduction of the resulting compound **7** with $LiAlH_4$.

The protection of hydroxyl group as MOM ether is a commonly used transformation in synthetic organic chemistry. So the methoxymethyl chloride was firstly chosen as a protecting reagent for free hydroxyl in the presence of dry K_2CO_3 and acetone, but no reaction occurred. When treated with KOH in THF, compound **6** was transformed to ring-opening product **10**. Finally, the target products **7** was gained by using DHP with PPTS as protecting reagent. Thus, to research the ring-openning reaction of compound **6** in the presence of acid and base, various conditions, such as certain base, solvent, temperature and time, were tested.

The results from table 2 show that the ring-openning compound **10** was obtained in the condition of entry 1–6. When strongly basic with H_2O was used as solvent, the diacid **11** was formed at room temperature with 91% yield (entry 11), while at reflux, the monoacid **12** was gained (entry 12). Treatment of the diester **6** with weak base K_2CO_3 in the conditions (entry 7–9) did not produce any product, but at reflux in H_2O, the compound **6** was transformed into **11** with 83% yield (entry 10).

The formation of **10** and **11** is proposed by the mechanism presented in scheme 2. At basic conditions, the attack of the nucleophile at the hydroxy-H seems to initiate the opening of the dihydrobenzofuran ring to a quinone methide intermediate, subsequent elimination of H-proton and restoration of the aromatic ring system, followed by the formation of the compound **10** after acidification at room tempreture in organic solvent. But in H_2O, the saponified products **11** is obtained.

The mechanism for the formation of compound **12** is shown in scheme 3. In aqueous sodium hydroxide solution under heating, the hydrolysis of diester **6** results in the cyclic diacid. After the decarboxylation, the acyclic products **12** is obtained with the openning of the dihydrobenzofuran ring.

The intermediate **8** was condensated with compound **5** in the presence of DCC and DMAP at room temperature to form compound **9**. The removal of the protecting groups using PPTS and HCl at room temperature afforded the target product **Boehmenan**.

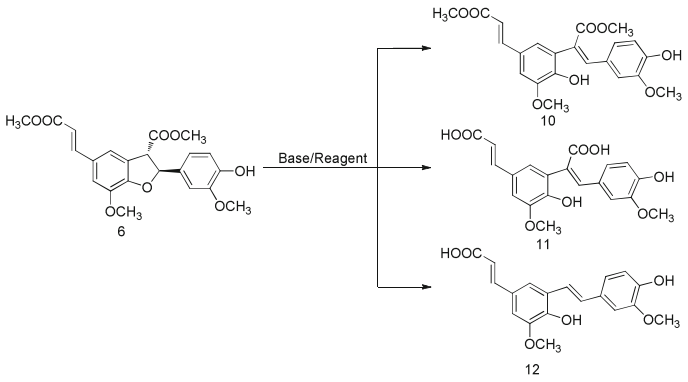
4. Conclusion

In summary, we have developed an efficient synthesis strategy of **Boehmenan** which was based on biomimetic oxidative coupling to construct the skeleton of lignan. The synthetic method has the advantages of

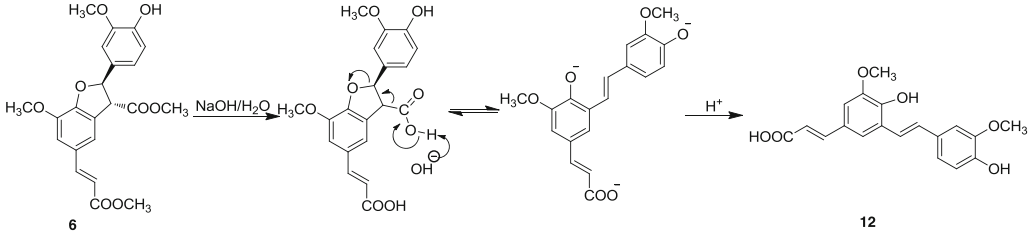
Table 1. Comparison of different reaction conditions and oxidant effect.

Entry	Preparation of Ag_2O	Solvent	T (°C)	Time (h)	Yield (%)
1	Freshly prepared Ag_2O	Acetone/toluene	25	8	21
2	Freshly prepared Ag_2O	Acetone/toluene	25	24	41
3	Freshly prepared Ag_2O	Acetone/toluene	25	32	33
4	Recycling Ag_2O	Acetone/toluene	25	24	17
5	Conventional Ag_2O	Acetone/toluene	25	24	21
6	Freshly prepared Ag_2O	CH_2Cl_2	25	24	37
7	Freshly prepared Ag_2O	Acetone/toluene	0	28	43
8	Freshly prepared Ag_2O	Acetone/toluene	0	34	39
9	Freshly prepared Ag_2O	Acetone/toluene	−25	30	45
10	Freshly prepared Ag_2O	Acetone/toluene	−25	36	38

Table 2. The ring-opening reaction of compound **6** under different conditions.



Entry	Base	Reagent	T (°C)	Time (h)	Product	Yield (%)
1	KOH	Acetone	r.t	4	10	75
2	KOH	C_2H_5OH	r.t	4	10	72
3	KOH	DMF	r.t	4	10	65
4	NaH	THF	r.t	4	10	87
5	NaH	DMF	r.t	4	10	86
6	C_2H_5ONa	C_2H_5OH	r.t	4	10	94
7	K_2CO_3	Acetone	56	4	–	–
8	K_2CO_3	C_2H_5OH	78	4	–	–
9	K_2CO_3	H_2O	r.t	4	–	–
10	K_2CO_3	H_2O	100	4	11	83
11	NaOH	H_2O	r.t	4	11	91
12	NaOH	H_2O	100	4	12	65
13	PPTS	$CHCl_3$	r.t	4	–	–
14	HCl	–	r.t	4	–	–
15	CH_3COOH	–	r.t	4	–	–



Scheme 3. Formation of the compound **12** from compound **6**.

easy availability of starting materials and simple operation. So it has considerable practical value. By this route, natural compound **Boehmenan** was synthesized in 8 steps, with an yield of 8% for the first time. In addition, the ring-openning reaction of dihydrobenzofuran neolignan intermediate was discussed in this paper.

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