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Studies on the synthesis of biphenylneolignans. Part 1: Enantioselective synthesis of (*S*,*S*)- and (*R*,*R*)-2,2′-dimethoxy-4-(3-hydroxy-1-propenyl)-4′-(1,2,3-trihydroxypropyl)diphenyl ether

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Abstract—Two *erythro*-isomers of 2,2′-dimethoxy-4-(3-hydroxy-1-propenyl)-4′-(1,2,3-trihydroxypropyl)diphenyl ether, (7′*S*, 8′*S*)-**9** and (7′*R*, 8′*R*)-**9**, were synthesized in seven steps, in which an improved method for the synthesis of the key intermediate **3** was developed. The absolute configuration of the target molecules was also confirmed. © 2002 Published by Elsevier Science Ltd.

1. Introduction

The biphenyl ether framework is often found in natural products, among which biphenyl ether lignans show various bioactivities.[1] Two enantiomers of 2,2′-dimethoxy-4-(3-hydroxy-1-propenyl)-4′-(1,2,3-trihydroxypropyl)diphenyl ethers were isolated from the famous folk medicines of south east Asia, namely *Eurycoma longifolia*.[2] To date, no report on the synthesis of these compounds is known. Herein, we report a convenient route in which **3** was synthesized through a milder microwave-accelerated[3] S_NAr reaction. In the reaction, phenol is directly coupled with the electron-deficient aryl framework to construct the biphenyl ether link.[4]

2. Results and discussion

As shown in Scheme 1, compound **1** and vanillin **2** were smoothly converted to biphenyl ether **3** under microwave irradiation and solvent-free conditions in 91% yield. When the mixture was heated, the formation of byproducts increased with the prolonged reaction time. The S_NAr reaction can also be carried out under the normal reaction conditions such as CsF in DMF or K_2CO_3 in DMF, but the workup process is troublesome. Compound **3** reacted with monoethyl malonate[5] in the presence of pyridine and piperidine[6] to give an unsaturated ester **4** in 81% yield. After reduction and diazotization, the nitro group in compound **4** was transformed to the desired phenol **6**. Compound **6** was heated under reflux with MeI and K_2CO_3 in acetone to afford the important intermediate **7**. Reduction of **7** with $LiAlH_4/AlCl_3$ in THF gave the corresponding unsaturated alcohol **8**.[7] On the basis of our previous work,[8] asymmetric dihydroxylation of **8** with AD-mix-α afforded (7′*S*,8′*S*)-**9** in 92% e.e. and 86% yield. Similarly, asymmetric dihydroxylation reaction of **8** using AD-mix-β afforded (7′*R*,8′*R*)-**9** in good yield.

Advantages of the synthetic approach included: (i) The application of microwave radiation to construct the biphenyl link under solvent-free conditions. This method is rapid, clean and affords an easier workup of the final material. (ii) It avoids the poor regioselectivity of traditional oxidative couplings of phenol.[9]

3. Conclusion

In summary, two natural biphenylneolignans (7′*S*,8′*S*)-**9**, (7′*R*,8′*R*)-**9** were synthesized for the first time. Their

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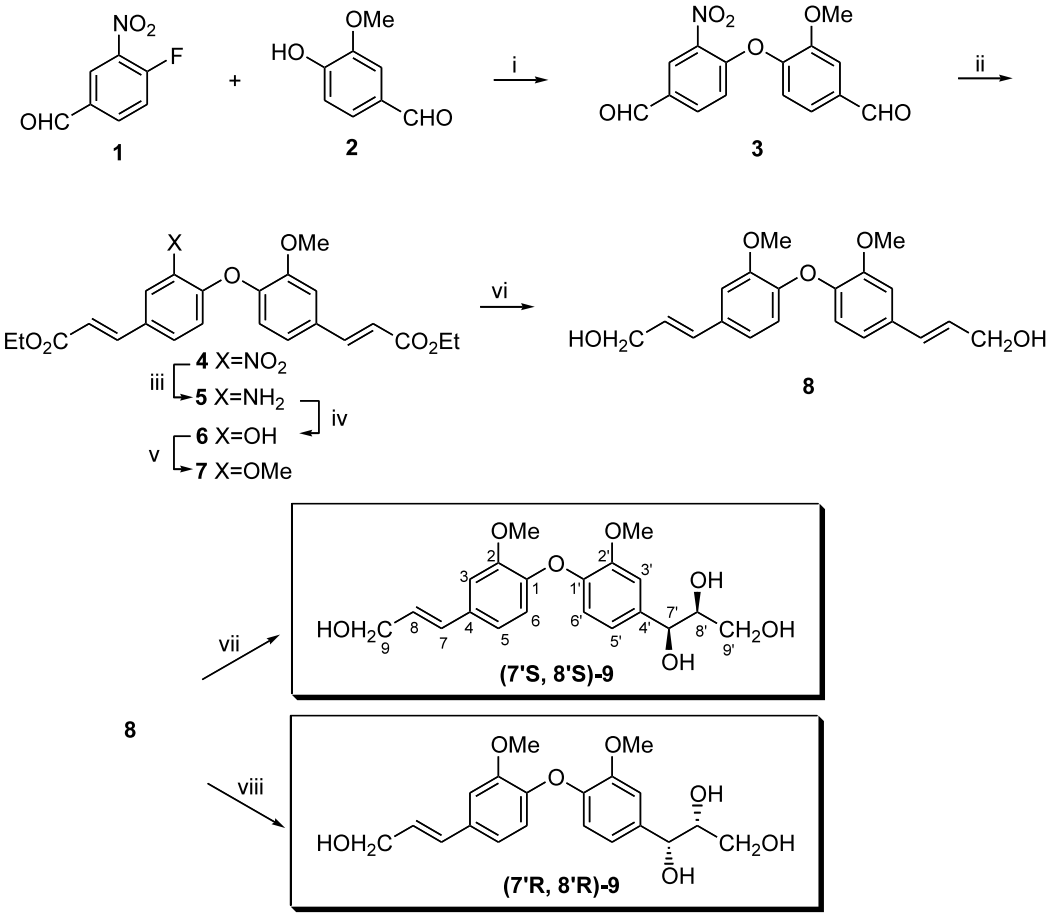

Scheme 1. *Reagents and conditions*: (i) K_2CO_3, $NBu_4^+Cl^-$, M.W., 200 W, 5 min, 91%; (ii) $HCO_2CH_2CO_2Et$, pyridine, piperidine, reflux, 6 h, 81%; (iii) Fe–$FeSO_4$, 92%; (iv) 1. H_2SO_4, $NaNO_2$, 2. H_2SO_4, Na_2SO_4, boiling water, 84%; (v) 1. MeI, K_2CO_3, 98%; 2. KOH, acetone–water, 95%; (vi) LAH, $AlCl_3$, THF, 0.5 h, 94%; (vii) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0°C, 20 h, 92% e.e., 86%; (viii) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0°C, 20 h, 92% e.e., 86%.

spectroscopic and specific rotation data are in agreement with the literature.[1] The synthetic route that we have developed here could also be applied to the conveniently synthesis of many other biphenylneolignans.

4. Experimental

4.1. General

Melting points were measured on a Kofler apparatus and were uncorrected. AD-mix-α and AD-mix-β were purchased from Aldrich. The microwave oven used for the reaction was a Samsung® MW610WA. ^1H and ^{13}C NMR data were recorded with Avance DRX-200 MHz spectrometers. Chemical shifts are referenced to TMS on the 'δ' scale. Mass spectra were recorded on a VG ZAB-HS spectrometer. IR spectra were recorded on a Nicolet 170 SXFT-IR spectrometer. Optical rotations were determined on a Perkin–Elmer 341 polarimeter. Chiral analysis was performed on Varian Dynamax SD-300 using chiralcel column CDMPC (150×4.6 mm D) with hexane/isopropyl alcohol (20:1, 0.5 mL/min, 25°C) as eluent. Flash column chromatography was generally performed on silica gel (200–300 mesh) eluting with petroleum ether:ethyl acetate and TLC inspections on silica gel GF_{254} plates with petroleum ether: ethyl acetate, if not noted especially below.

4.2. 4-(4-Formyl-2-methoxyphenoxy)-3-nitrobenzaldehyde, 3

4-Fluoro-3-nitrobenzaldehyde **1** (2 g, 12 mmol) and vanillin **2** (1.8 g, 12 mmol) were mixed with tetrabutylammonium chloride (556 mg, 2 mmol), K_2CO_3 (1.65 g, 12 mmol) with a pestle and mortar. The reaction mixture was then irradiated in a microwave oven (operating at 200 W) for 5 min. On completion of the reaction (monitored by TLC), the mixture was cooled and quenched with ice water, and then extracted with ethyl acetate. After removal of the solvent, the crude product was purified by flash chromatography using petroleum ether and ethyl acetate (4:1, v/v) as eluent. The solvent was evaporated to yield biphenyl ether **3** as yellow solid (3.3 g, 91%). Mp 127–129°C. MS (EI): 301(M^+,43), 273(25), 254(13), 211(14), 183(161), 167(90), 151(100). ^1H NMR (200 MHz, $CDCl_3$): 3.84 (s, 3H), 6.94 (d, $J=8.5$ Hz, 1H), 7.34 (d, $J=1.8$ Hz, 1H), 7.54 (d, $J=8.6$ Hz, 1H), 7.56 (dd, $J=8.5$, 1.8 Hz, 1H), 7.98 (dd, $J=8.6$, 2 Hz, 1H), 8.50 (d, $J=2$ Hz, 1H), 9.99

(s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 56.1, 111.6, 118.3, 122.2, 125.2, 127.8,131.0, 134.0, 135.2, 139.9, 147.1, 151.6, 154.9, 188.5, 190.5.

4.3. (2-Nitro-2′-methoxy-4,4′-diacrylic acid ethyl ester)diphenyl ether, 4

Monoethyl malonate (1.523 g, 11.54 mmol) was added to a solution of compound **3** (1.74 g, 5.77 mmol) in pyridine (15 mL) and piperidine (0.25 mL). The mixture was heated under reflux at 120°C for 6 h, and then the solvent was evaporated. The crude product was dissolved in ethyl acetate and the resulting solution was washed with 5% sodium bicarbonate and water, dried over Na_2SO_4. The solvent was distilled off and the residue was purified by flash chromatography using petroleum ether and ethyl acetate (3:1, v/v) as eluent. Compound **5** was obtained as a white solid (1.93 g, 81%). Mp 136–138°C. MS (EI): 441 (M^+, 55), 396(39), 304(63), 287(39), 221(100). ^{1}H NMR (200 MHz, $CDCl_3$): 1.29 (t, $J=6.5$ Hz, 3H), 1.31 (t, $J=6.5$ Hz, 3H), 3.78 (s, 3H), 4.23 (q, $J=6.5$ Hz, 2H), 4.25 (q, $J=6.5$ Hz, 2H), 6.36 (d, $J=15.6$ Hz, 1H), 6.38 (d, $J=15.6$ Hz, 1H), 6.82 (dd, $J=8$, 2.2 Hz, 1H), 7.07(d, $J=8$ Hz, 1H), 7.09 (d, $J=8.4$ Hz, 1H), 7.12 (d, $J=2.2$ Hz, 1H), 7.59 (dd, $J=8.4$, 2 Hz, 1H), 7.61(d, $J=15.6$ Hz, 1H), 7.63 (d, $J=15.6$ Hz, 1H), 8.09 (d, $J=2$ Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): 14.2, 56.0, 60.6, 112.0, 118.5, 118.7, 119.7, 121.6, 121.9, 124.9, 129.3, 132.8, 133.1, 140.0, 141.1, 143.3, 144.4, 151.3, 152.0, 166.1, 166.5.

4.4. (2-Amino-2′-methoxy-4,4′-diacrylic acid ethyl ester)diphenyl ether, 5

To the suspension of compound **4** (1 g, 2.25 mmol) in 50 mL boiling H_2O was added Fe (1.26 g, 22.5 mmol) and $FeSO_4$ (340 mg, 2.25 mmol). The reaction mixture was heated under reflux for 3 h, filtered through Celite, and washed thoroughly with CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by flash chromatography using CH_2Cl_2 and MeOH (30:1, v/v) as eluent to afford **5** as slightly yellow solid (850 mg, 92%). Mp 92–94°C. MS (EI): 411 (M^+,53), 368(49), 353(20), 339(21), 313(32), 285(33), 190(38), 155(45), 57(100). ^{1}H NMR (200 MHz, $CDCl_3$): 1.30 (t, $J=6.2$ Hz, 3H), 1.32 (t, $J=6.2$ Hz, 3H), 3.78 (s, 3H), 3.97(br, 2H), 4.24 (q, $J=6.2$ Hz, 2H), 4.26 (q, $J=6.2$ Hz, 2H), 6.35 (d, $J=15.6$ Hz, 1H), 6.37 (d, $J=15.6$ Hz, 1H), 6.76 (d, $J=8.3$ Hz, 1H), 7.04 (d, $J=8.5$ Hz, 1H),7.06 (dd, $J=8.3$, 2 Hz, 1H), 7.08 (d, $J=1.5$ Hz, 1H),7.11(d, $J=2$ Hz, 1H) 7.54 (dd, $J=8.3$, 1.5 Hz, 1H), 7.55 (d, $J=15.6$ Hz, 1H), 7.57 (d, $J=15.6$ Hz, 1H).

4.5. (2-Hydroxy-2′-methoxy-4,4′-diacrylic acid ethyl ester)diphenyl ether, 6

Under salt–ice bath cooling, compound **5** (600 mg, 1.44 mmol) was added into H_2SO_4 (5 mL, 6 N), after a few minutes, sodium nitrite (100 mg, 1.44 mmol) in water (2.5 mL) was added drop-wise, keep the temperature of the acid solution at 5°C for 1 h. Then the diazonium solution was added dropwise into the boiling mixture of water (10 mL), H_2SO_4 (10 mL) and Na_2SO_4 (15 g). The solution was continuously boiled for 5 min and then allowed to cool to rt. After it was stored overnight in a refrigerator, the solid was filtrated and recrystallized from ethyl acetate to afford **6** as a yellow solid (497 mg, 84%). Mp 102–103°C. MS (EI): 412 (M^+, 26) 390(38), 350(98), 304(87), 221(43), 167(25), 44(100). ^{1}H NMR (200 MHz, $CDCl_3$): 1.31 (t, $J=6.2$ Hz, 3H), 1.32 (t, $J=6.2$ Hz, 3H) 3.85 (s, 3H), 4.25 (q, $J=6.2$ Hz, 2H), 4.27 (q, $J=6.2$ Hz, 2H), 6.47 (d, $J=15$ Hz, 1H), 6.49 (d, $J=15$ Hz, 1H), 6.81(d, $J=8.3$ Hz, 1H), 7.01(d, $J=8.3$ Hz, 1H), 7.03 (dd, $J=8.3$, 2 Hz, 1H), 7.05 (dd, $J=8.3$, 1.7 Hz, 1H),7.18 (d, $J=1.7$ Hz, 1H), 7.21(d, $J=2$ Hz, 1H), 7.24 (d, $J=15$ Hz, 1H), 7.26 (d, $J=15$ Hz, 1H).

4.6. (2,2′-Dimethoxy-4,4′-diacrylic acid ethyl ester)diphenyl ether, 7

A mixture of compound **6** (300 mg, 0.74 mmol), MeI (0.5 mL) and anhydrous potassium carbonate (300 mg) in acetone (5 mL) was heated under reflux for 6 h. After general work up, the crude products were dissolved in water and then extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was distilled off and the residue was purified by flash chromatography using petroleum ether and ethyl acetate (3:1, v/v) as eluent. The product **7** was obtained as white solid (296 mg, yield 94%). Mp 80–81°C. MS (EI): 426 (M^+, 36), 381(22), 354(56), 337(41), 323(82), 167(100). ^{1}H NMR (200 MHz, $CDCl_3$): 1.29 (t, $J=6.1$ Hz, 6H), 3.85 (s, 6H), 4.23 (q, $J=6.1$ Hz, 4H), 6.47 (d, $J=15$ Hz, 2H), 6.81(d, $J=8$ Hz, 2H), 7.06 (dd, $J=8$, 1.4 Hz, 2H), 7.18 (d, $J=1.4$ Hz, 2H), 7.25 (d, $J=15$ Hz, 2H).

4.7. (2,2′-Dimethoxy-4,4′-dipropenyl alcohol)diphenyl ether, 8

To a suspension of $LiAlH_4$ (80 mg, 2.118 mmol) in dry THF (50 mL), $AlCl_3$ (95 mg, 0.706 mmol) was added portionwise at rt. After stirring for 10 min, a solution of compound **7** (300 mg, 0.706 mmol) in dry THF was added dropwise to the mixture. The reaction mixture was stirred at rt for 0.5 h. Then the reaction was quenched with ice-water, extracted with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4. The solvent was distilled off and the residue was purified by flash chromatography using petroleum ether and ethyl acetate (2:1, v/v) as eluent. Compound **8** was obtained as a white solid (227 mg, 94%). Mp 96–97°C. MS (EI): 342 (M^+, 5), 251(26), 219(63), 191(78), 182(100). ^{1}H NMR (200 MHz, $CDCl_3$): 3.83 (s, 6H), 4.29 (d, $J=5.5$ Hz, 4H), 6.47 (dt, $J=15$, 5.5 Hz, 2H), 6.81(d, $J=8.3$ Hz, 2H), 7.08 (dd, $J=8.3$, 1.6 Hz, 2H), 7.17 (d, $J=1.6$ Hz, 2H), 7.24 (d, $J=15$ Hz, 2H).

4.8. (*S*,*S*)-2,2′-Dimethoxy-4-(3-hydroxy-1-propenyl)-4′-(1,2,3-trihydroxypropyl)diphenyl ether, (7′*S*, 8′*S*)-9

To a stirred solution of *t*-BuOH (1.1 mL) and H_2O (1.1 mL), AD-mix-α (307 mg) and $MeSO_2NH_2$ (21 mg) were added. The mixture was stirred at rt until both phases were clear, and then cooled to 0°C. Compound **8** (75 mg, 0.22 mmol) was added to the mixture immediately. Stirred vigorously at 0°C until TLC revealed the absence of **8**. The reaction was quenched with Na_2SO_3 (330 mg) at 0°C, then warmed to rt and stirred for 0.5 h. The mixture was extracted with ethyl acetate (3×5 mL). The combined organic layer was washed with 2N KOH, water and dried over Na_2SO_4. The solvent was distilled off and the residue was purified by flash chromatography using petroleum ether and ethyl acetate (1:3, v/v) as eluent. (7′*S*,8′*S*)-**9** (71 mg, 86%, 92% e.e.) was obtained as a yellow solid. Mp 53–56°C $[\alpha]_D^{25}$ +0.7 (*c* 1.0, MeOH). HRMS: calcd for $C_{20}H_{24}O_7$+H 377.1522. Found $(M+H)^+$ 377.1536. ^{1}H NMR (200 MHz, pyridine-d_5): δ 3.72 (s, 3H), 3.74 (s, 3H), 4.41(dd, J=11.7, 3.9 Hz, 1H), 4.55 (dd, J=11.7, 5.4 Hz, 1H), 4.56 (d, J=5.4 Hz, 2H), 5.04 (ddd, J=5, 5, 5 Hz, 1H), 5.61(d, J=5.1 Hz, 1H), 6.55 (dt, J=15.9, 5.4 Hz, 1H), 6.85 (d, J=15.8 Hz, 1H), 7.05 (dd, J=8.3, 1.9 Hz, 1H), 7.14 (d, J=1.9 Hz, 1H), 7.24 (d, J=8.0 Hz, 1H), 7.37 (d, J=8.3 Hz, 1H), 7.38 (dd, J=8.0, 2.0 Hz, 1H), 7.59 (d, J=2.0 Hz, 1H). ^{13}C NMR (50 MHz, pyridine-d_5): 55.8, 55.9, 61.8, 62.9, 73.6, 86.2, 110.9, 112.1, 116.0, 117.8, 119.9, 120.6, 129.4, 129.7, 131.9, 134.5, 147.4, 148.4, 148.7, 151.2. IR (KBr/cm^{-1}): 3450, 1520, 1270, 1130, 1030, 860.

4.9. (*R*,*R*)-2,2′-Dimethoxy-4-(3-hydroxy-1-propenyl)-4′-(1,2,3-trihydroxypropyl)diphenyl ether, (7′*R*, 8′*R*)-9

By a procedure similar to the preparation of (*S*,*S*)-**9**, the reaction of **8** (60 mg, 0.175 mmol), AD-mix-β (245 mg), *t*-BuOH (0.9 mL) and H_2O (0.9 mL), gave (7′*R*,8′*R*)-**9** (57 mg, 86%, 92% e.e.) as a yellow solid. Mp 57–60°C. $[\alpha]_D^{25}$ −1.4 (*c* 1.0, MeOH). HRMS: calcd for $C_{20}H_{24}O_7$+H 377.1522. Found $(M+H)^+$ 377.1507. ^{1}H NMR (200 MHz, pyridine-d_5): δ 3.75 (s, 3H), 3.78 (s, 3H), 4.10 (dd, J=11.8, 5.6 Hz, 1H), 4.40 (dd, J=11.8, 3.6 Hz, 1H), 4.58 (d, J=5.2 Hz, 2H), 4.98 (ddd, J=5.6, 5.6, 5.6 Hz, 1H), 5.61 (d, J=5.6 Hz, 1H), 6.58 (dt, J=15.8, 5.2 Hz, 1H), 6.89 (d, J=15.8 Hz, 1H), 7.07 (dd, J=8.3, 1.2 Hz, 1H), 7.19 (d, J=1.2 Hz, 1H), 7.27 (d, J=7.8 Hz, 1H), 7.42 (dd, J=7.8, 1.7 Hz, 1H), 7.50 (d, J=8.3 Hz, 1H), 7.59 (d, J=1.7 Hz, 1H). ^{13}C NMR (50 MHz, pyridine-d_5): δ 55.8, 55.9, 61.8, 62.9, 73.4, 87.3, 110.9, 111.9, 116.0, 117.9, 120.0, 120.6, 129.4, 129.8, 132.0, 134.0, 147.5, 148.4, 149.2, 151.1. IR (KBr/cm^{-1}): 3450, 1510, 1130, 1030, 860.

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