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Synthesis of Unsymmetrical Biphenyl Lignans, Honokiol and Related Compounds, Utilizing Quinol-acetates as Reactive Intermediates

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An unsymmetrical biphenyl lignan, honokiol (**1a**), a constituent of *Magnoliaceae*, and related compounds were synthesized by the reaction of the quinol-acetates **3** with the Grignard reagent **4** followed by Claisen rearrangement.

Keywords——synthesis; unsymmetric biphenyl; lignan; honokiol; quinol-acetate; Grignard reagent

Quinol derivatives are considered to be not only versatile intermediates for organic synthesis, but also intermediates in the biosynthesis of various natural products, and a number of applications of quinols as synthons for the synthesis of natural products have been reported.[1] Several biphenyl lignans, for example, honokiol (**1a**) and magnolol (**1c**), isolated from *Magnoliaceae*,[2] are known. It is also known that **1a** and **1c** possess antimicrobial activity against Gram-positive and acid-fast bacteria and fungi,[3] and central depressant effects.[4] This paper reports the first synthesis of an unsymmetrical biphenyl lignan, honokiol (**1a**), and related compounds utilizing the quinol-acetates **3a** and **3b** as reactive intermediates.

Although several methods are available for the synthesis of biphenyls, namely, Ullmann reaction, Scholl reaction, Grignard coupling reaction, oxidative coupling reaction, *etc.*, the present synthetic plan to construct the biphenyl lignans consists of direct coupling of the quinol-acetate **3a** or **3b** with phenol ether or its equivalent. This approach is attractive because of the simplicity of the reaction and its possible involvement in biosynthesis.

The quinol-acetates **3a** and **3b** were synthesized from the corresponding phenols **2a** and **2b** by oxidation with $Pb(OAc)_4$ in AcOH. Though direct C–C bond formation between the quinol-acetates **3** and allyloxybenzene (**8**) or 2-allylphenol (**9**) in the presence of Lewis acids (BF_3OEt_2, $SnCl_4$, *etc.*) in CH_2Cl_2 or CH_3NO_2 was unsuccessful,[5] the biphenyls **6a** and **6b** were obtained by the reactions of the quinol-acetates **3a** and **3b** with the Grignard reagent **4** in yields of 67% from **3a** and 34.9% from **2b**. Formation of the alternative compound **7a** or **7b** is possible in this reaction. The structures of the biphenyls obtained were established by the following spectroscopic analyses.

The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectral data of **6a**, **6b**, **1a**, and **1b**, the assignments of which were aided by off-resonance decoupling and by comparison with the spectra of **2a**, **2b**, **8**, and **9**, are shown in Chart 2 and Table I. Differences of the carbon signals between the biphenyl **6a** and the reference compounds **2a** and **8** were observed only at the C-1′ and C-1 carbons. That is, the C-1′ and C-1 signals (at 127.69 and 129.63 ppm) were observed at lower field than the corresponding signals, 115.4 and 120.8 ppm, of **2a** and **8**. This result shows reasonable agreement with the previous report,[6] which indicated that the signal of C-1′ in the biphenyl **6a** may be shifted *ca.* 13 ppm to lower field than that of C-2 of **2a**. Thus, the alternative structure **7a** can be excluded.

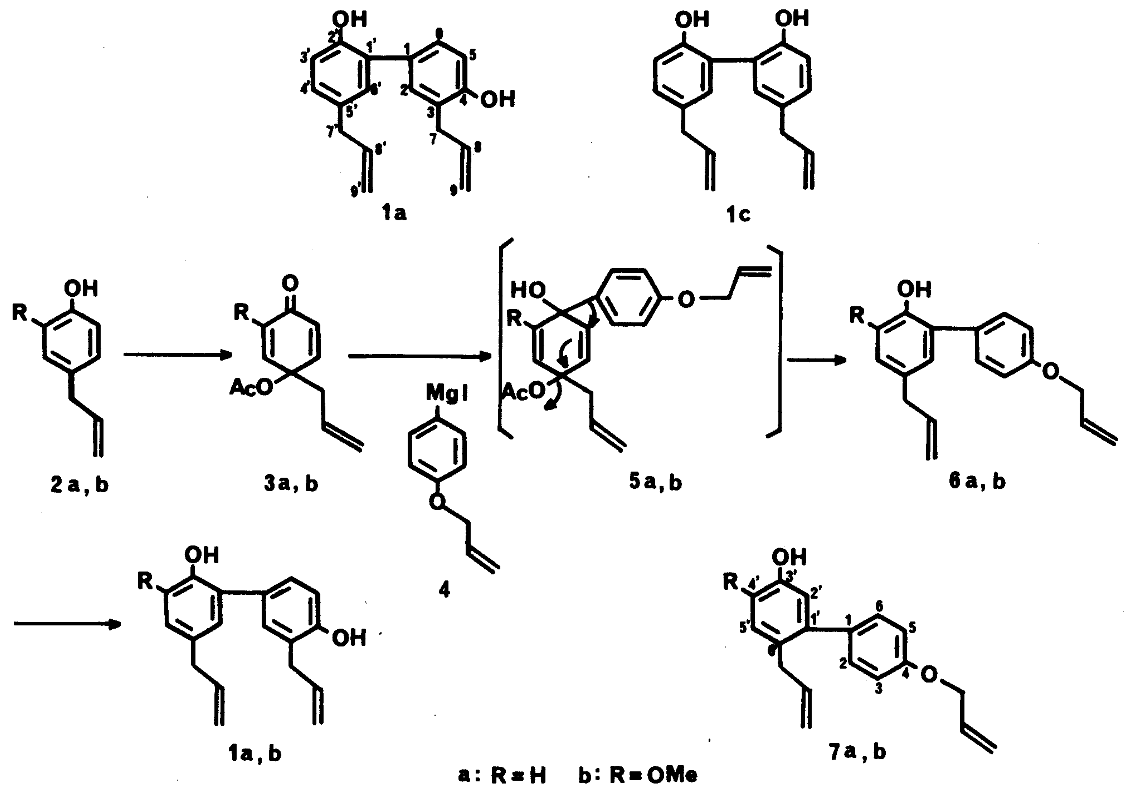

Chart 1

The structure of **6b** was confirmed by the proton nuclear magnetic resonance spectrum (^{1}H-NMR), as summarized in Table II, in addition to the ^{13}C-NMR analysis. The proton signals of C-4′ and C-6′ of **6b** were observed at 6.66 and 6.77 ppm (doublet in each case, J=1.95 Hz). This result suggests the presence of *meta* coupling protons. Therefore, the alternative structure **7b** can be excluded.

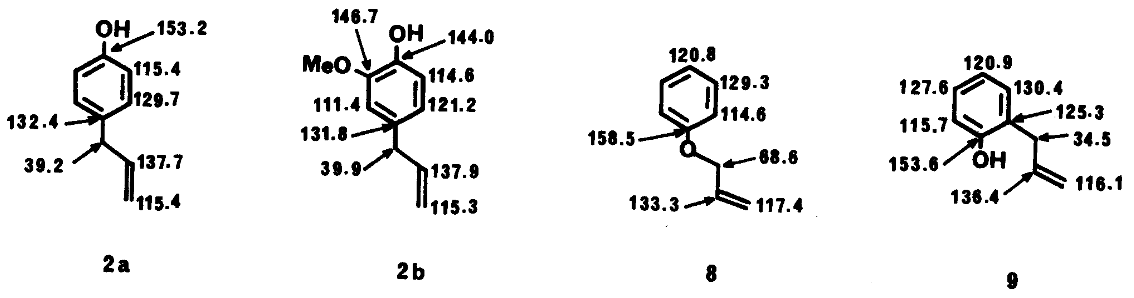

Chart 2

^{13}C-NMR spectra of **2a**, **2b**, **8** and **9** were measured in CDCl$_3$ at 25 °C (25 MHz).

Two reaction paths, namely, (i) through the elimination of the acetoxyl group followed by addition of the Grignard reagent and (ii) through the formation of an intermediate such as **5**, are possible for the formation of **6a** or **6b** by the reaction of **3a** or **3b** with **4**. This reaction may occur by the latter path because the presence of an intermediate such as **5** was observed during the thin-layer chromatography (TLC) checks of reaction progress. Therefore, the formation of **6a** or **6b** can be assumed to occur as follows. Reaction of **3** with the Grignard reagent **4** may give an intermediate **5a** or **5b**,[1b,7] followed by elimination of the acetoxyl group and aryl 1,2-shift in a concerted manner to yield **6**. Claisen rearrangement by treatment of **6a**

TABLE I. ^{13}C-NMR Spectral Data for **6a**, **6b**, **1a** and **1b**[a)]

Carbon No.	**6a**[b)]	**6b**[b)]	**1a**[b,8)]	**1b**[b)]
1′ or 1	127.69 s	126.99 s	127.81 s	127.22 s
2′	150.77 s	140.96 s	150.53 s	140.84 s
3′	115.72 d	146.72 s	116.36 d	146.78 s
4′	128.69 d	109.67 d	128.75 d	109.79 d
5′	132.16 s	131.22 s	132.33 s	131.33 s
6′	128.69 d	122.24 d	129.57 d	122.35 d
7′	39.39 t	39.92 t	39.34 t	39.98 t
8′	137.73 d	137.67 d	137.73 d	137.73 d
9′	115.48 t	115.54 t	115.54 t	115.60 t
1 or 1′	129.63 s	130.16 s	130.28 s	130.39 s
2	130.16 d	130.16 d	131.04 d	131.10 d
3	115.31 d	114.42 d	126.52 s	125.23 s
4	158.11 s	157.75 s	153.64 s	153.29 s
5	115.31 d	114.42 d	115.66 d	115.60 d
6	130.16 d	130.16 d	128.40 d	128.58 d
7	68.81 t	68.81 t	34.87 t	35.44 t
8	133.09 d	133.39 d	136.03 d	136.44 d
9	117.71 t	117.36 t	116.66 t	116.36 t
3′-OMe		56.07 q		56.19 q

a) δ in CDCl$_3$; ^{13}C, 25 MHz at 25 °C. *b*) These assignments were aided by off-resonance decoupling and by comparison with the spectrum of **2a**, **2b**, **8**, and **9**. s, singlet; d, doublet; t, triplet; q, quartet.

TABLE II. ^{1}H-NMR Spectral Data for **6a**, **6b**, **1a** and **1b**[a)]

Proton	**6a**	**6b**	**1a**	**1b**
2	7.38 (d, *J*=9.03)	7.53 (d, *J*=8.79)	7.20 (d, *J*=2)	7.33 (br s)
6			7.19 (dd, *J*=8.79, 2)	7.37 (d, *J*=8.79)
3	7.01 (d, *J*=9.03)	6.97 (d, *J*=8.79)		
5			6.88 (d, *J*=8.79)	6.82 d, *J*=8.79)
4′	7.03 (dd, *J*=8.79, 2)	6.66 (d, *J*=1.95)	7.06 (dd, *J*=8.79, 1.95)	6.65 (d, *J*=1.95)
6′	7.02 (d, *J*=2)	6.77 (d, *J*=1.95)	7.01 (br s)	6.75 (d, *J*=1.95)
3′	6.88 (d, *J*=8.79)		6.88 (d, *J*=8.79)	
8,8′	5.78—6.28 (m)	5.79—6.23 (m)	5.77—6.23 (m)	5.78—6.19 (m)
9,9′	4.95—5.54 (m)	4.95—5.67 (m)	4.98—5.26 (m)	5.00—5.29 (m)
7	4.58 (d, *J*=5.1)	4.57 (d, *J*=5.1)	3.44 (d, *J*=6.4)	3.44 (d, *J*=6.35)
7′	3.34 (d, *J*=6.4)	3.35 (d, *J*=6.8)	3.34 (d, *J*=6.6)	3.34 (d, *J*=6.59)
3′-OMe		3.91 (s)		3.89 (s)

a) δ in CDCl$_3$; ^{1}H-NMR at 100 MHz (*J*=Hz).

and **6b** with BCl$_3$ at −15 °C gave honokiol (**1a**), mp 84—86 °C and **1b**, mp 36—36.5 °C, in yields of 80% and 95%, respectively. All physical data of synthetic honokiol (**1a**) were identical with those of the natural product.[2b,d,3b,8)]

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 260-10 spectrometer, ^1H and ^{13}C-NMR spectra with a JEOL JNM-FX 100 spectrometer (with tetramethylsilane as internal standard; $CDCl_3$ sol.) and mass spectra (MS) with a JEOL JMS-D 300 spectrometer. Elementary analyses were done by Ms. A. Sakamoto and Ms. M. Takeda, Kissei Pharmaceutical Company, Matsumoto, Japan. Wako Silica gel C-200 (200 mesh) and Merck Kieselgel 60 F_{254}, and Merck Aluminiumoxid 90 (activity II—III, 70-230 mesh ASTM) were used for column chromatography and TLC, respectively.

4-Acetoxy-4-allyl-2,5-cyclohexadien-1-one (3a)——Lead tetraacetate (979 mg, 2.2 mmol) was added at once to a stirred solution of 4-allylphenol (201 mg, 1.5 mmol) in AcOH (5 ml) and the whole was stirred at room temperature for 15 min. The reaction mixture was poured into ice-water and then extracted with ether. The organic layer was washed with sat. $NaHCO_3$ and purified water, dried and concentrated. The residue was subjected to alumina column chromatography. The eluate with hexane–chloroform (1 : 1, v/v) gave 84 mg (29.2%) of **3a** as an oil. IR (film) cm^{-1}: 1740, 1660, 1620. ^1H-NMR ($CDCl_3$) δ: 2.07 (3H, s, OAc), 2.58 (2H, d, $J=7.1$ Hz, $-CH_2-CH=CH_2$), 5.01—5.22 (2H, m, $-CH=CH_2$), 5.50—5.91 (1H, m, $-CH=CH_2$), 6.27 (2H, d, $J=10.1$ Hz, C-2 and C-6 H), 6.84 (2H, d, $J=10.1$ Hz, C-3 and C-5 H). MS *m/e*: Calcd for $C_{11}H_{12}O_3$ (M^+): 192.0787. Found: 192.0788.

4-Acetoxy-4-allyl-2-methoxy-2,5-cyclohexadien-1-one (3b)——Compound **3b** (an oil), was synthesized from eugenol by a procedure similar to that used for **3a**, and was used without further purification for the next step. IR (film) cm^{-1}: 1740, 1670, 1640, 1620. ^1H-NMR ($CDCl_3$) δ: 2.07 (3H, s, OAc), 2.70 (2H, d, $J=8.0$ Hz, $CH_2-CH=CH_2$), 3.60 (3H, s, OMe), 4.95—5.20 (2H, m, $-CH=CH_2$), 5.42—5.95 (1H, m, $-CH=CH_2$), 5.80 (1H, $J=2.5$ Hz, C-3 H), 6.25 (1H, d, $J=10.0$ Hz, C-6 H), 6.90 (1H, dd, $J=10.0$, 2.5 Hz, C-5 H).

5′-Allyl-4-allyloxy-2′-hydroxybiphenyl (6a)——A solution of a small amount of 4-allyloxyiodobenzene and methyl iodide in dry ether was added to a stirred mixture of Mg turnings (165.2 mg, 6.77 mmol) in dry ether (20 ml) under a nitrogen atmosphere, and the mixture was refluxed for *ca.* 1 h. Then, the remaining halide solution (1.35 g, 5.19 mmol) in dry ether (20 ml) was added dropwise and the mixture was refluxed for 4 h until the magnesium turnings disappeared. A solution of **3a** (250 mg, 1.3 mmol) in dry ether was added dropwise to the Grignard reagent thus prepared under a nitrogen atmosphere at −15 °C, and the whole was stirred under the same conditions for 30 min. The resultant solution was poured into sat. NH_4Cl in ice-water, and then extracted with ether. The ether layer was washed with H_2O, dried and concentrated. The residue was subjected to silica gel column chromatography. The eluate with AcOEt–chloroform (3 : 1, v/v) gave 232 mg (67%) of **6a** as an oil. IR (film) cm^{-1}: 3450, 1640, 1600. MS *m/e*: Calcd for $C_{18}H_{18}O_2$ (M^+): 266.1304. Found: 266.1283.

5′-Allyl-4-allyoxy-2′-hydroxy-3′-methoxybiphenyl (6b)——Compound **6b** (an oil), was synthesized from **3b** by a procedure similar to that used for **6a** in 34.9% yield from eugenol. IR (film) cm^{-1}: 3500, 1640, 1600. MS *m/e*: Calcd for $C_{19}H_{20}O_3$ (M^+): 296.1410. Found: 296.1405.

3,5′-Diallyl-4,2′-dihydroxybiphenyl (1a)——A solution of **6a** (80 mg, 0.3 mmol) in chlorobenzene (2 ml) was added slowly to a solution of BCl_3 (35.2 mg, 0.3 mmol) in chlorobenzene (4 ml) under a nitrogen atmosphere at −15 °C, and the whole was stirred under the same conditions for 1 h. The reaction mixture was poured into ice-MeOH, and then extracted with ether. The organic layer was washed with sat. $NaHCO_3$ and H_2O, dried and concentrated. The residue was subjected to silica gel column chromatography. The eluate with hexane–AcOEt (10 : 3, v/v) gave 68 mg (80%) of honokiol (**1a**) as colorless crystals (benzene–hexane), mp 84—86 °C. IR (KBr) cm^{-1}: 3300, 1640, 1610, 1500. MS *m/e*: Calcd for $C_{18}H_{18}O_2$ (M^+): 266.1304. Found: 266.1311. *Anal.* Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.23; H, 6.73.

3,5′-Diallyl-4,2′-dihydroxy-3′-methoxybiphenyl (1b)——Compound **1b**, mp 36—36.5 °C, was synthesized from **6b** by a procedure similar to that used for **1a** in 95% yield from **6b**. IR (KBr) cm^{-1}: 3400, 1600. MS *m/e*: Calcd for $C_{19}H_{20}O_3$ (M^+): 296.1411. Found: 296.1411. *Anal.* Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.81; H, 6.88.

References and Notes

1) *a)* S. Fujita, *Yuki Gosei Kagaku Kyokai Shi* (a review), **40**, 307 (1982); *b)* J. S. Swenton, *Acc. Chem. Res.*, **16**, 74 (1983).

2) *a)* M. Fujita, H. Itokawa, and Y. Sashida, *Chem. Pharm. Bull.*, **20**, 212 (1972); *b) Idem, Yakugaku Zasshi*, **93**, 422 (1973); *c)* Y. Sugii, *ibid.*, **50**, 183 (1930); *d)* F. S. El-Feraly and W.-S. Li, *Lloydia*, **41**, 442 (1978).

3) *a)* A. M. Clark, F. S. El-Feraly, and W.-S. Li, *J. Pharm. Sci.*, **70**, 951 (1981); *b)* K. Ito, T. Iida, K. Ichino, M. Tsunezuka, M. Hattori, and T. Namba, *Chem. Pharm. Bull.*, **30**, 3347 (1982); *c)* T. Namba, M. Tsunezuka, M. Hattori, S. Kadota, and T. Kikuchi, *Proc. Symp. Wakan-Yaku*, **15**, 179 (1982); *d)* T. Namba, M. Tsunezuka, and M. Hattori, *Journal of Medicinal Plant Research*, **44**, 100 (1982).

4) *a)* K. Watanabe, H. Watanabe, Y. Goto, M. Yamaguchi, N. Yamamoto, and K. Hagino, *Journal of Medicinal*

Plant Research, **49**, 103 (1983); *b*) H. Watanabe, K. Watanabe, and K. Hagino, *J. Pharmacobio-Dyn.*, **6**, 184 (1983); K. Watanabe, H. Watanabe, Y. Goto, N. Yamamoto, and M. Yoshizaki, *Jpn. J. Pharmacol.*, **25**, 605 (1975).

5) *a*) B.-T. Groebel, E. Konz, H. Millauer, and R. Pistorius, *Synthesis*, **1979**, 605; *b*) D. A. Evans, P. A. Cain, and R. S. Wong, *J. Am. Chem. Soc.*, **99**, 7083 (1977); *c*) S. Harusawa, M. Miki, J. Hirai, and T. Kurihara, *Chem. Pharm. Bull.*, **33**, 899 (1985).

6) G. L. Nelson, G. C. Levy, and J. D. Cargioli, *J. Am. Chem. Soc.*, **94**, 3089 (1972).

7) *a*) D. R. Henton, K. Anderson, M. J. Manning, and J. S. Swenton, *J. Org. Chem.*, **45**, 3411 (1980); *b*) D. A. Evans, J. M. Hoffman, and L. K. Truesdale, *J. Am. Chem. Soc.*, **95**, 5822 (1973); *c*) D. A. Evans and J. M. Hoffman, *ibid.*, **98**, 1983 (1976).

8) The ^{13}C-NMR spectra of the natural and synthetic honokiol **1a** were identical, but some of the signal assignments by previous workers[3b)] differ from our analysis. That is, the previous report described the signals at 130.3 and 128.8 ppm as doublet and singlet, respectively. In this paper, we assigned the corresponding signals as singlet and doublet. Further, previous workers assigned the signals at 128.8 and 126.5 ppm to C-3 and C-1, respectively. On the other hand, we assigned the signals at 130.28 and 126.52 ppm to C-1 or C-1′ and C-3 based on the analyses of the related compounds **6a**, **6b**, and **1b**.