# A Novel Synthetic Approach to Biphenyls

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Two novel biphenyls, 2,2'-bis(1-hydroxyethyl)-3,3',5,5'-tetramethylbiphenyl **(7)** and 2,2'-bis(1-hydroxyethyl)-4,4',6,6'-tetramethylbiphenyl **(13)** were synthesized through Wittig reaction, photochemical oxidative cyclization, and ozonolysis, using xylene and mesitylene as starting materials. The novel approach is applicable to both symmetrical and unsymmetrical biphenyls.

The chemical constituents of the heartwood of Taxus species have been investigated earlier.[1,2] Recently Liu[3] studied the methanol extracts of the heartwood of *Taxus mairei* from Taiwan and isolated among others a minor component identified as 2,2'-bis(hydroxyethyl)-3,3',5,5'-tetramethylbiphenyl **(7)** based on its IR and NMR spectra. Since this is a new compound, we now report the synthesis of this novel biphenyl and its isomeric compound 2,2'-bis(1-hydroxyethyl)-4,4',6,6'-tetramethylbiphenyl **(13)**.

For the synthesis of 2,2'-bis(1-hydroxyethyl)-3,3',5,5'-tetramethylbiphenyl **(7)**, the Ullmann coupling reaction between two appropriate aryl bromides was tried first but was found to be unsuccessful. A novel approach to the biphenyl **7** is described in Scheme A.

Chloromethylation of *m*-xylene gave 2,4-dimethylbenzyl chloride **(2)** in 63% yield, which was allowed to undergo a Sommelet reaction to afford 2,4-dimethylbenzaldehyde **(3)** in 88% yield. Compounds **2** and **3** were reacted together to form (*E*)-2,2',4,4'-tetramethylstilbene **(4)** (72% yield). Photochemical oxidative cyclization of **4** led to 1,3,6,8-tetramethylphenanthrene **(5)** in 51% yield. Ozonolysis of compound **5** followed by reduction by potassium iodide afforded dialdehyde **6** in 67% yield. The biphenyl **7** was obtained by treating **6** with methylmagnesium iodide.

There are three chiral centers in compound **7**, these include the central bond connecting the two aryl groups. As both rings are

Scheme B

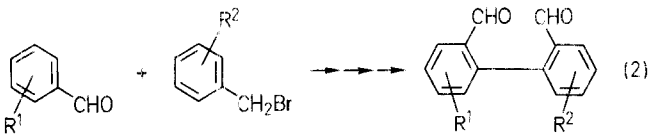
symmetrically substituted, there are three diastereomers, each of which is a racemic mixture. Three diastereomers were indeed isolated (see experimental).

The Grignard reaction can be carried out either by adding the Grignard reagent to the dialdehyde or by adding the dialdehyde to the Grignard reagent. Both procedures gave three diastereomers, but in the former procedure **7a** (see experimental) was isolated as the major product, and in the latter **7b** and **7c** were isolated as the major products. The reason for the selectivity is probably due to the chelation between magnesium and oxygen atom. The exact stereochemical course will be revealed by single crystal X-ray studies of the three diastereomers.

Similarly the isomeric biphenyl 2,2′-bis(1-hydroxyethyl)-4,4′,6,6′-tetramethylbiphenyl **(13)** can be obtained starting with the side chain bromination of mesitylene by NBS and following the same sequence of reactions as for the preparation of **7** (Scheme **B**).

Compound **13** is expected to have three diastereomers. Only two diastereomers were isolated pure, **13a** and **13b**. The $^1$H-NMR spectrum indicated that the other diastereomer is contaminated with impurities and difficult to purify.

This novel approach to the synthesis of biphenyl is applicable both to symmetrical and unsymmetrical biphenyls. In contrast, the conventional Ullmann coupling can only provide the symmetrical biphenyls in good yields, with unsymmetrical biphenyls the yield is at most 50%.



(2)

IR were recorded with a JASCO model IRA-1 spectrometer. NMR spectra were recorded on Varian EM-390 90 MHz spectrometer or Joel JMN-FX-100 spectrometer. The chemical shifts in $^1$H-NMR spectra were referred to TMS. Mass spectra were taken with a Joel JMS-3000 mass spectrometer on a Hitachi-RMS-4 spectrometer operating at an ionization voltage of 70 eV. TLC was carried out on Merck silica gel or aluminum oxide TLC plates (5550). Separations by column chromatography were carried out on silica gel (Merck, Kieselgel 60, 70–230 mesh). Melting points were recorded on a Yanagimoto micromelting point apparatus and were uncorrected. Ozone generator was Fisher model 501 Perkin-Elmer 240C EA analyzer. Preparative photolysis was carried out under a nitrogen atmosphere using Hanovia 450-W medium pressure mercury lamp in a water-cooled pyrex lamp well. Solutions were analyzed for product formation with a dual flame ionization Hitachi 163 gas chromatograph using a SE-30 (1 m) column.

2,4-Dimethylbenzyl chloride **(2)** was prepared by chloromethylation[4] of *m*-xylene in 63% yield. 2,4-Dimethylbenzaldehyde **(3)** was prepared from **2** by Sommelet[5] reaction (88%). 3,5-Dimethylbenzyl bromide **(8)** was prepared from mesitylene using NBS and benzoyl peroxide[6] (72%). 3,5-Dimethylbenzaldehyde **(9)** was prepared from **8** using hexamethylenetetramine[5] (87%).

**(*E*)-2,2′,4,4′-Tetramethylstilbene (4):**
Compound **2** (16.2 g, 0.105 mol) is dissolved in triethyl phosphite (18.1 g, 52 mmol) and heated to 140°C. The mixture is refluxed for 1 h and the temperature is raised to 190°C. After cooling, DMF (50 mL) and NaOMe (7.1 g) are added. The mixture is stirred for 15 min and **3** (14.1 g, 0.105 mol) in DMF (50 mL) is added. The mixture is stirred for another 30 min and poured onto water (100 mL). The off-white solid is collected and chromatographed on silica gel using *n*-hexane as eluent to give white solid. Recrystallization from ethanol gives pure **4**; yield: 17.1 g (72%); m.p. 107–109°C.

| | | | |
|---|---|---|---|
| $C_{18}H_{20}$ | calc. | C 91.45 | H 8.53 |
| (236.4) | found | 91.49 | 8.45 |

MS: *m/e* = 236 ($M^+$).

IR (KBr): $\nu$ = 3010, 2920, 1660, 1605, 1500, 1480, 965 cm$^{-1}$.

$^1$H-NMR ($CCl_4$): $\delta$ = 2.27 (s, 6H); 2.33 (s, 6H); 6.85 (br s, 2H); 6.95 (d, 2H, $J$ = 9 Hz); 7.00 (s, 2H); 7.35 (d, 2H, $J$ = 9 Hz).

**(*E*)-3,3′,5,5′-Tetramethylstilbene (10):**
This is prepared analogously using the same procedure as for **4**; yield: 80%. The crude product is recrystallized from ethanol to give pure **10** in needles; m.p. 139–140°C (Lit.[7] m.p. 140–141°C).

MS: *m/e* = 236 ($M^+$).

IR (KBr): $\nu$ = 3050, 1600, 1580, 1450, 960 cm$^{-1}$.

$^1$H-NMR ($CCl_4$): $\delta$ = 2.28 (s, 12H); 6.75 (br s, 2H); 6.87 (s, 2H); 6.97 (br s, 4H).

**1,3,6,8-Tetramethylphenanthrene (5):**
To a Pyrex photochemical reaction vessel is added **4** (10 g, 42.4 mmol) and iodine (0.552 g, 22 mmol) in cyclohexane (950 mL). The solution is irradiated with a medium-pressure mercury lamp for 24 h.[8] The extent of reaction is monitored by GC to be greater than 95%. The residual iodine is reduced by adding 10% sodium bisulfite solution. The organic solution is dried ($MgSO_4$) and evaporated; yield: 5.10 g (51%). Recrystallization from ethanol affords pure **5**; m.p. 151–153°C (Lit.[9] 152.5–153.5°C).

| | | | |
|---|---|---|---|
| $C_{18}H_{18}$ | calc. | C 92.30 | H 7.78 |
| (234.3) | found | 92.28 | 7.71 |

MS: *m/e* = 234 ($M^+$).

IR (KBr): $\nu$ = 3050, 2970, 1600, 1500, 1460, 850 cm$^{-1}$.

$^1$H-NMR ($CCl_4$): $\delta$ = 2.57 (s, 6H); 2.70 (s, 6H); 7.15 (s, 2H); 7.75 (s, 2H); 8.27 (s, 2H).

**2,4,5,7-Tetramethylphenanthrene (11):**
The title compound is prepared from **10** using the same procedure as for **5**. The crude **11** is recrystallized from ethanol; yield: 62%; m.p. 112–114°C (Lit.[7] 111–113°C).

MS: *m/e* = 234 ($M^+$).

IR (KBr): $\nu$ = 3030, 2950, 1605, 1580, 1450 cm$^{-1}$.

$^1$H-NMR ($CCl_4$): $\delta$ = 2.45 (s, 6H); 2.50 (s, 6H); 7.08 (br s, 2H); 7.25 (br s, 4H).

**2,2′-Diformyl-3,3′,5,5′-Tetramethylbiphenyl (6):**
Ozone is passed into a solution of **5** (1.90 g, 8.1 mmol) in dry MeOH (50 mL) at −30°C until **5** has completely reacted.[10] Then iodine (5 g) and glacial acetic acid (5 mL) are added and the solution is left standing for 1 h. The iodine is reduced by 10% sodium sulfite solution, and methanol is removed by evaporation. The mixture is extracted with EtOAc (3 × 30 mL) and evaporated to give a crude product which is chromatographed on silica gel using hexane/EtOAc (9:1) as eluent to afford pure **6**; yield: 1.40 g (67%); m.p. 96–97°C.

| | | | |
|---|---|---|---|
| $C_{18}H_{18}O_2$ | calc. | C 81.19 | H 6.81 |
| (266.3) | found | 80.77 | 6.85 |

MS: *m/e* = 266 ($M^+$).

IR (KBr): $\nu$ = 3030, 2920, 2870, 2780, 1670, 1600, 1570, 1430, 1380, 865 cm$^{-1}$.

$^1$H-NMR ($CDCl_3$): $\delta$ = 2.36 (s, 6H); 2.63 (s, 6H); 6.91 (br s, 2H); 7.08 (br s, 2H); 9.82 (s, 2H).

**2,2′-Diformyl-4,4′,6,6′-Tetramethylbiphenyl (12):**
Compound **11** is converted to **12** by the same procedure as for **6**. The crude product is chromatographed on silica gel using hexane/EtOAc (8:2) as eluent to give pure **11**; yield: 62%; m.p. 117–119°C.

MS: *m/e* = 266 ($M^+$).

IR (KBr): $\nu$ = 3030, 2960, 2860, 2760, 1690, 1600, 1570 cm$^{-1}$.

$^1$H-NMR ($CDCl_3$): $\delta$ = 1.93 (s, 6H); 2.44 (s, 6H); 7.36 (s, 2H); 7.69 (s, 2H); 9.55 (s, 2H).

**Grignard Reaction of Methylmagnesium Iodide with Biphenyldials:**[11]
A. *With* **6**: To **6** (500 mg, 1.88 mmol) in dry ether (10 mL) is added, under nitrogen and at −10°C, 1 molar THF solution of methylmagnesium iodide (5 mL, 5 mmol), and the temperature is raised gradually to 40°C within 1 h. The reaction is stopped by adding ice (10 g) followed by 2 normal $H_2SO_4$ (10 mL). The mixture is extracted with ether (3 × 10 mL), the combined ethereal layer is washed with 10% $NaHCO_3$ solution (10 mL) and water (10 mL). The solvent is removed to afford a solid which is chromatographed on silica gel using hexane/$CHCl_3$ (8:2) as eluent to give **7a**; yield: 335 mg (60%); m.p. 133–135°C.

MS: *m/e* = 298 ($M^+$).

IR (KBr): $\nu$ = 3400, 1605, 1500, 1460, 1095 $cm^{-1}$.

$^1$H-NMR ($CDCl_3$): $\delta$ = 0.99 (d, 6H, $J$ = 7 Hz); 2.35 (s, 12H); 5.30 (q, 2H, $J$ = 7 Hz); 6.98 (s, 2H); 7.08 (s, 2H).

$^{13}$C-NMR ($CDCl_3$): $\delta$ = 20.2 ($CH_3$); 21.1 ($CH_3$); 22.1 ($CH_3$); 69.6 (CH); 128.6 (CH); 130.6 (CH); 134.5 (C); 136.9 (C); 137.0 (C); 148.8 (C).

*Isolation of Diastereoisomers of* **7a**:

To dry magnesium turnings (0.22 g, 9 mmol) in dry ether (10 mL), under nitrogen, is added methyl iodide (0.56 mL, 9 mmol) in dry ether (10 mL). The mixture is refluxed until all the magnesium has disappeared. Compound **6** (0.8 g, 3 mmol) in dry ether (10 mL) is added and the mixture is refluxed for 1 h. Ice (10 g) and 2 normal $H_2SO_4$ (10 mL) is added and the mixture is extracted with EtOAc (3 × 20 mL). The organic layer is washed with 10% NaOH solution (30 mL), dried ($MgSO_4$) and evaporated. The crude product is chromatographed on silica gel using hexane/EtOAc/$CHCl_3$ (5:1:1) as eluent to give diastereomers **7b** and **7c**.

**7b**: yield: 65%; m.p. 143–145 °C.

| | | | |
|---|---|---|---|
| $C_{20}H_{26}O_2$ | calc. | C 80.54 | H 8.72 |
| (298.4) | found | 79.98 | 8.69 |

MS: $m/e$ = 298 ($M^+$).

IR (KBr): $\nu$ = 3400, 3000, 1600, 1575, 1450, 1080, 860 $cm^{-1}$.

$^1$H-NMR ($CDCl_3$): $\delta$ = 1.27 (d, 3H, $J$ = 7 Hz); 1.33 (d, 3H, $J$ = 7 Hz); 2.23 (s, 6H); 2.34 (s, 3H); 2.53 (s, 3H); 4.67 (q, 1H, $J$ = 7 Hz); 4.98 (q, 1H, $J$ = 7 Hz); 6.60 (s, 1H); 6.70 (s, 1H); 6.91 (s, 2H).

$^{13}$C-NMR ($CDCl_3$): $\delta$ = 20.2 ($CH_3$); 20.4 ($CH_3$); 20.7 ($CH_3$); 21.3 ($CH_3$); 24.2 ($CH_3$); 68.2 (CH); 68.3 (CH); 127.8 (CH); 129.6 (CH); 130.9 (C); 132.3 (CH); 135.3 (C); 136.6 (C); 137.1 (C); 138.1 (C); 140.2 (C); 141.0 (C).

**7c**: yield: 13%; m.p. 137–139 °C.

MS: $m/e$ = 298 ($M^+$).

IR (KBr): $\nu$ = 3400, 3000, 1605, 1580, 1500, 1460, 1090, 1070 $cm^{-1}$.

$^1$H-NMR ($CDCl_3$): $\delta$ = 1.30 (d, 6H, $J$ = 7 Hz); 2.26 (s, 6H); 2.51 (s, 6H); 3.48 (br s, 2H); 4.68 (q, 2H, $J$ = 7 Hz); 6.63 (s, 2H); 6.93 (s, 2H).

$^{13}$C-NMR ($CDCl_3$): $\delta$ = 20.6 ($CH_3$); 20.9 ($CH_3$); 22.3 ($CH_3$); 67.8 (CH); 127.8 (CH); 132.2 (CH); 135.6 (C).

B. *With* **12**:

To dry magnesium (0.22 g, 9 mmol) in dry ether (10 mL), under nitrogen, is added slowly methyl iodide (0.56 mL, 9 mmol) in dry ether (10 mL), and the mixture is refluxed until the magnesium has disappeared. Compound **12** (0.80 g, 3 mmol) in dry ether is added and the solution is refluxed for 1 h. The reaction is quenched by adding ice (10 g) and 2 normal $H_2SO_4$ (10 mL) and the mixture is extracted with EtOAc (3 × 20 mL). The combined organic layer is washed with 5% NaOH solution (10 mL), dried ($MgSO_4$) and evaporated to give a crude mixture which is separated by TLC on silica gel using hexane/$CHCl_3$ (3:1) as eluent to give three diastereomers.

**13a**: yield: 490 mg (55%); m.p. 119–121 °C.

MS: $m/e$ = 280 ($M^+$-$H_2O$).

IR (KBr): $\nu$ = 3040, 2970, 1605, 1460, 1080 $cm^{-1}$.

$^1$H-NMR ($CDCl_3$): $\delta$ = 1.38 (d, 6H, $J$ = 7 Hz); 2.08 (s, 6H); 2.33 (s, 6H); 3.94 (q, 2H, $J$ = 7 Hz); 6.95 (s, 4H).

**13b:** yield: 130 mg (15%); m.p. 135–137 °C.

MS: $m/e$ = 280 ($M^+$-$H_2O$).

IR (KBr): $\nu$ = 3400, 3040, 2970, 1605, 1460, 1080, 1060 $cm^{-1}$.

$^1$H-NMR ($CDCl_4$): $\delta$ = 0.64 (d, 3H, $J$ = 7 Hz); 1.38 (d, 3H, $J$ = 7 Hz); 2.07 (s, 6H); 2.30 (s, 3H); 2.33 (s, 3H); 4.18 (q, 1H, $J$ = 7 Hz); 4.64 (q, 1H, $J$ = 7 Hz); 6.75 (s, 1H); 6.94 (s, 3H).

**13c:** yield: 130 mg, contains impurities and hence could not be purified.

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