

First total synthesis of (\pm) Maackin[†]Yi Yang^a, Pingyan Bie^a, Chenglu Zhang^{a, b} and Xinfu Pan^{a*}^aDepartment of Chemistry, National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P.R.. China^bHeilongjiang August First Land Reclamation University, Mishan, 158308, P.R. China

(\pm) Maackin **6** was synthesised from the readily available material 3,5-dihydroxybenzoic acid and 3,4-dihydroxybenzaldehyde, using a coupling reaction as a key step.

Keywords: Maackin, Wittig reaction, Dimerisation

(\pm) Maackin **6** was isolated from *Maackia amurensis*¹ and the structure was assigned by spectroscopic methods. It was reported that compounds which contained the structure of 1,4-benzodioxane ring may have cytotoxic, hepatoprotective² and other biological activity.³ Until now, no synthesis of compound **6** has appeared. We now report a simple synthesis.

Kayser *et al.*⁴ reported that a neighbouring group had great effect on the regioselectivity of Wittig reactions. During their study, they found that methoxyl group participated the Wittig reaction and resulted in good regioselectivity (>90%). In our studies, a MEM ether in compound **2** was found to play a key role in determining the geometry. When the Wittig reaction was used, the single product had the trans configuration because of the steric effect. A plausible mechanism for the formation of the product **2** is outlined in Scheme 2.

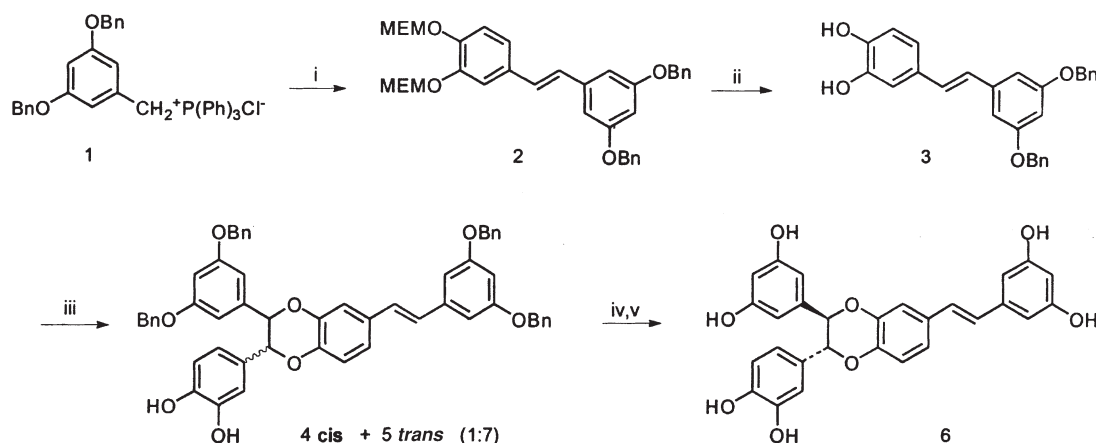
As shown in Scheme 1, 3,4-bis[(methoxyethoxy)methoxy]benzaldehyde (prepared from 3,4-dihydroxybenzaldehyde) was reacted with the phosphonium **1** (prepared from 3,5-dihydroxybenzoic acid) to afford compound **2**. No *cis* isomer was detected by HPLC analysis. After treatment with TFA in chloroform, the MEM protecting group was removed. Based on an earlier report,⁵ compound **3** was oxidised by Ag₂O to afford a mixture of isomer (**4** *cis*: **5** *trans* ca. 1:7 by ¹HNMR). The isomers (**4** and **5**) were stirred in dry DMF with anhydrous K₂CO₃ for 1h, and the *cis*-isomer **4** was converted into *trans* configuration **5**. Finally compound **5** was treated with K/ *t*-BuNH₂/ *t*-BuOH/ THF /18-crown-6 to obtain compound **6**.⁶

Experimental

Melting points were measured on a Kofler apparatus and were uncorrected. Mass spectra were recorded on a ZAB-HS spectrometer. Elemental analyses were performed on a Carlo-Erba 1106 instrument. IR spectra were recorded on a Nicolet 170 SXFT-IR spectrometer. ¹H NMR spectra were recorded on a Bruker AC-80 and AM-400 instrument. Chemical shifts are referenced to Me₄Si on the δ scale. *J* values are in Hz. Standard flash chromatography was employed to purify the crude reaction mixture using *ca* 200–300 mesh silica gel under positive nitrogen pressure.

4-[(E)-2-(3,5-[bis(benzyloxy)phenyl]vinyl)-1,2-bis[(2-methoxyethoxy)methoxy]benzene (2): To a solution of compound **1** (1g, 1.7 mmol) in THF 20 ml, *n*-Butyl lithium (1.4 mol/l, 1.2 ml) was added dropwise and the mixture was stirred for 30 min under a stream of argon at room temperature. 3,4-Bis[(methoxyethoxy)methoxy]benzaldehyde (0.64 g, 2 mmol) in THF 5 ml was added to the above solution and stirred for 3 h. Then brine was added to quench the reaction. It was extracted with ethyl acetate and dried over Na₂SO₄. The solvent was evaporated and the crude product was purified by flash chromatography using petroleum ether and ethyl acetate (3:1, v/v) as eluent to afford a white solid **2** (0.82 g, 81%). M.p. 131–133°C; ¹H NMR (400MHz, CDCl₃): δ 3.41(s, 3H, -OCH₃), 3.42 (s, 3H, -OCH₃), 3.61(m, 4H, -CH₂O-), 3.90 (m, 4H, -CH₂O-), 5.10 (s, 4H, -CH₂-Ar), 5.36 (s, 2H, -OCH₂O-), 5.40 (s, 2H, -OCH₂O-), 6.56 (d, 1H, *J*=2 Hz, Ar-H), 6.81 (d, 2H, *J*=2 Hz, Ar-H), 6.97 (d, 1H, *J*=16 Hz, -CH=CH-), 7.03 (d, 1H, *J*=16Hz, -CH=CH-), 7.12 (dd, 1H, *J*=1.8 and 8.3 Hz, Ar-H), 7.23 (d, 1H, *J*=8.3 Hz, Ar-H), 7.35 (d, 1H, *J*=1.8 Hz, Ar-H), 7.39–7.44 (m, 10H, Ar-H). EI-MS (*m/z*): 600 (M⁺, 16), 523 (25), 446 (57), 436 (23), 388 (26), 360 (44), 316 (11), 277 (96), 224 (11), 180 (55), 121(100), 89 (45), 59 (73). Anal. calcd for C₃₆H₄₀O₈: C, 71.98; H, 6.71. Found: C, 72.05; H, 6.80.

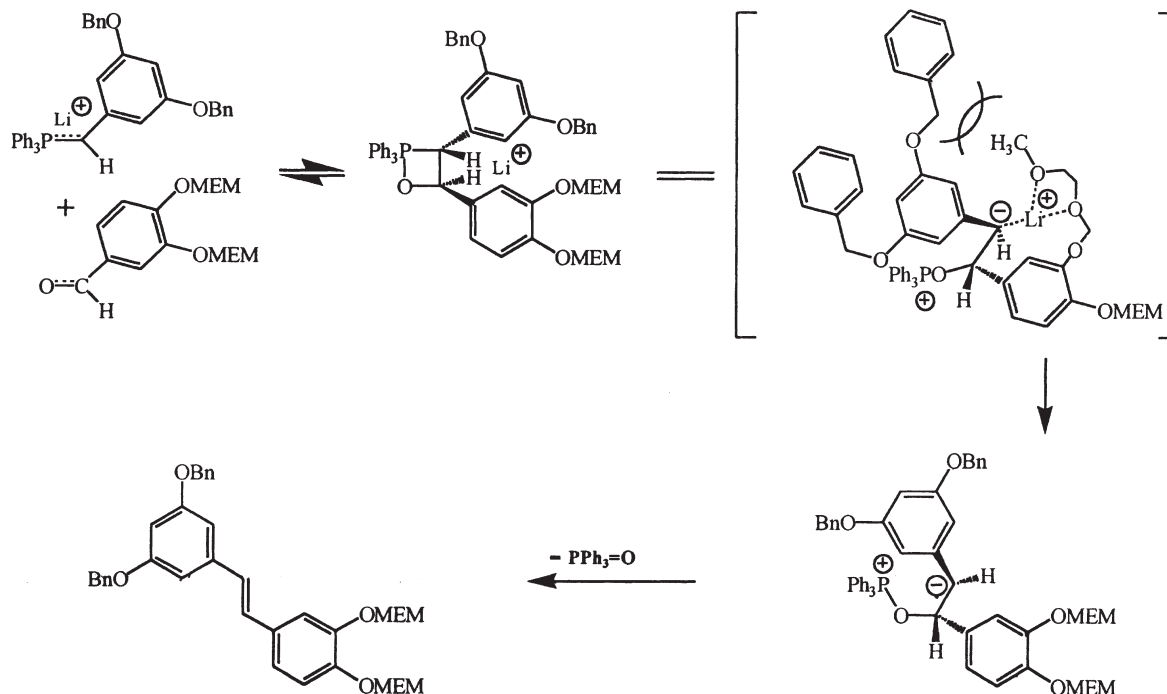
4-[(E)-2-(3,5-[bis(benzyloxy)phenyl]vinyl)-1,2-dihydroxy benzene (3): To the solution of compound **2** (0.826 g, 1.3 mmol) in 10ml chlo-



Scheme 1 Reagents and conditions: (i) *n*-BuLi, 3,4-bis[(methoxyethoxy)methoxy]benzaldehyde, THF, 81%; (ii) TFA, CHCl₃ 85%; (iii) Ag₂O, benzene / acetone (5:1, v/v) 46%; (iv) K₂CO₃, DMF; v) K/ *t*-BuNH₂/ *t*-BuOH/ THF / 18-crown-6, 72%.

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[†] This is a Short Paper, there is therefore no corresponding material in *J. Chem. Research (M)*.



Scheme 2 A mechanism for MEM participation in the Wittig reaction.

reform, trifluoroacetic acid (0.3ml) in 5ml chloroform was added dropwise. After stirring for 3h at room temperature, brine was added, and the solution was extracted with chloroform and dried over Na_2SO_4 . The solvent was evaporated off and the crude product was purified by flash chromatography using petroleum ether and ethyl acetate (3:1, v/v) as an eluent to afford a white solid **3** (0.47 g, 85%). M.p. 116–118°C; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.09 (s, 4H, $-\text{CH}_2-\text{Ar}$), 6.58 (d, 1H, $J=1.8$ Hz, Ar-H), 6.67 (d, 2H, $J=1.8$ Hz, Ar-H), 6.86 (d, 1H, $J=16$ Hz, $-\text{CH}=\text{CH}-$), 6.95 (d, 1H, $J=16$ Hz, $-\text{CH}=\text{CH}-$), 7.07 (m, 3H), 7.38–7.45 (m, 10H, Ar-H). EI-MS (m/z): 424 (22), 242 (34), 227 (5), 212 (9), 207 (4), 128 (8), 91(100), 65 (11), 57 (85). Anal. calcd for $\text{C}_{28}\text{H}_{24}\text{O}_4$: C, 79.22; H, 5.70. Found: C, 79.18; H, 5.73.

Tetrabenzyl ether of Maackin (5): Silver oxide (0.22g, 1 mmol) was added to a solution of compound **3** (0.4g, 1mmol) in benzene/acetone (5:1, v/v, 25ml). The solution was stirred vigorously for 7 h at 55–60°C. It was then filtered. The filtrate was evaporated in vacuum and the residue was stirred with K_2CO_3 in DMF at room temperature for 12 h, and then extracted with ethyl acetate, and washed with water. After removal of solvent, the crude product was purified by flash chromatography using petroleum ether and ethyl acetate (3:1, v/v) as eluent to afford a yellow solid **5** (0.18g, 46%). M.p. 124–126°C; IR ν/cm^{-1} (KBr): 3350, 1583, 1675, 965; $^1\text{H NMR}$ (400MHz, CDCl_3): δ 5.11 (s, 8H, $-\text{CH}_2\text{Ph}$), 5.26 (d, 1H, $J=7.9$ Hz, Ar-CH-O-Ar), 5.31(d, 1H, $J=7.9$ Hz, Ar-CH-O-Ar), 6.91–7.41(m, 34H, Ar-H and $-\text{CH}=\text{CH}-$). FAB-MS (m/z): 846 (M^+ , 27), 723 (24), 623 (91), 543 (41), 466 (11), 435 (25), 424 (28), 307 (19), 289 (23), 180 (52), 107 (89). Anal. calcd for $\text{C}_{56}\text{H}_{46}\text{O}_8$: C, 79.41; H, 5.47. Found: C, 79.49; H, 5.41.

Maackin (6): To a stirred solution of tetrabenzyl ether of Maackin (**5**) (0.2g, 0.24mmol) in 10ml THF, the solution of $t\text{-BuNH}_2$ (70 mg), $t\text{-BuOH}$ (70 mg), and 18-crown-6 (50mg) in 1 ml THF was added. After stirring for a few minutes, 400 mg potassium was added in portions. Stirring was continued for 3 h, HCl (10ml, 2M) was added, and the solution was extracted with ethyl acetate and dried over Na_2SO_4 .

The solvent was evaporated and the crude product was purified by flash chromatography using MeOH and ethyl acetate (1:3, v/v) as eluent to afford a pale yellow solid **6** (41mg, 72%). M.p. 172–173°C; IR ν/cm^{-1} (KBr): 3388, 1608, 1507; $^1\text{H NMR}$ (400MHz, CD_3OD): δ 4.86 (d, 1H, $J=8$ Hz, Ar-CHO-Ar), 4.92(d, 1H, $J=8$ Hz, $-\text{CHO}-$), 6.08 (s, 3H, Ar-H), 6.12(t, 1H, Ar-H), 6.41 (d, 2H, $J=2$ Hz, Ar-H), 6.49(dd, 1H, $J=2$ Hz and 8 Hz, Ar-H), 6.65(d, 1H, $J=2$ Hz, Ar-H), 6.59–6.97 (m, 4H, Ar-H and $-\text{CH}=\text{CH}-$), 7.11 (dd, 1H, $J=2$ and 8 Hz, Ar-H), 7.20(d, 1H, $J=2$ Hz, Ar-H). FAB-MS (m/z): 486 (M^+ , 12), 468(21), 422 (26), 375 (24), 244 (87), 137 (74), 91 (27), 71 (53), 57 (81), 43 (100). Anal. calcd for $\text{C}_{28}\text{H}_{22}\text{O}_8$: C, 69.13; H, 4.56. Found: C, 69.20; H, 4.51. The spectral data were in good agreement with those reported.¹

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