Efficient Synthesis of Cylindol A and the Proposed Structure of Cylindol B: The Structure of Cylindol B Still in Question

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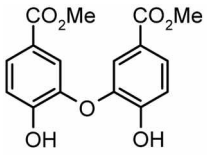
Received February 19, 2008

Highly efficient syntheses of cylindol A (**1**) and the proposed structure of cylindol B (**2**) have been accomplished using common synthetic transformations from symmetrical starting materials **7** and **11**, respectively. The latter synthesis revealed that the proposed structure of the natural cylindol B was assigned incorrectly. Isomers of **2** such as **15** and **16** were synthesized as a possible candidate of the natural cylindol B. However, their spectral data also did not match that of the natural cylindol B. Therefore, the structure of the natural cylindol B is yet to be resolved.

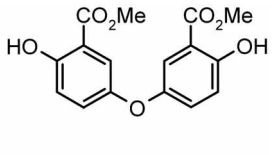
Key Words : Cylindol A, Cylindol B

Introduction

In pursuit of natural products having 5-lipoxygenase inhibitory effect as an anti-inflammatory agent, Ohizumi et al. isolated cylindol A (**1**) and B (**2**) from the rhizomes of *Imperata cylindrica* which was used in Chinese medicine as diuretic and anti-inflammatory agents.[1] The structure of cylindol A (**1**) was unambiguously determined by its independent total synthesis, whereas the structure of cylindol B (**2**) was determined solely by spectroscopic analysis. For further investigation on their activities towards other indications, it was prerequisite to devise a more efficient and common synthetic routes towards cylindol A (**1**) as well as towards the proposed structure of cylindol B (**2**). Herein, we describe highly efficient synthesis of cylindol A (**1**) and the proposed structure of cylindol B (**2**) and disclose the wrong structural assignment of cylindol B.

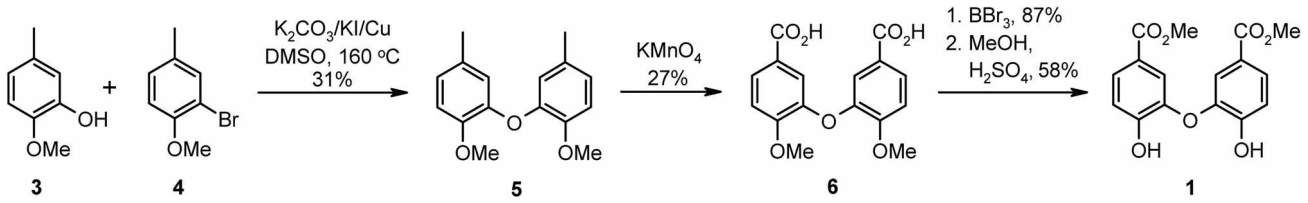


Cylindol A (1)

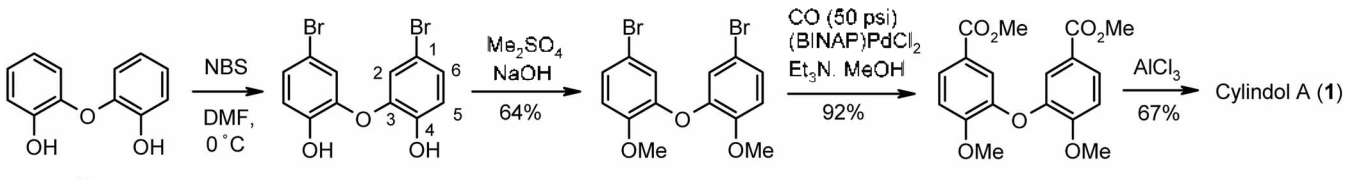


The proposed structure of Cylindol B (2)

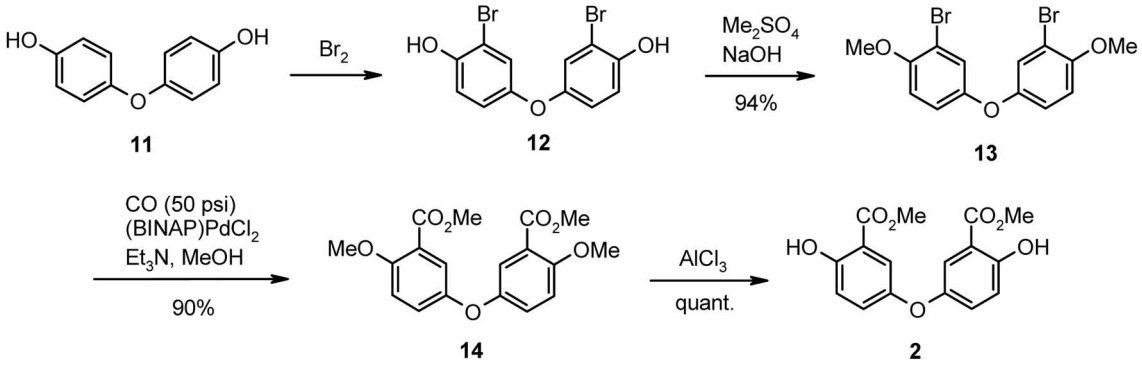
Since the reported synthesis of cylindol A is not practical (overall 4.5% yield) particularly due to low yields of 31 and 27%, respectively at the stage of Ullmann type coupling of **3** and **4** and at the stage of the oxidation of the methyl group of **5** to the carboxylic acid functionality (Scheme 1), we devised a practical route which features simultaneous and common functionalization of the symmetrical starting materials **7** for cylindol A (**1**) (Scheme 2) and **11** for the proposed structure of cylindol B (**2**) (Scheme 3). Thus, bromination reaction of 2,2'-dihydroxy diphenyl ether (**7**) using NBS[2] provided para-substituted dibromide **8**, the regioselectivity of which was confirmed by the coupling pattern of ^{1}H NMR spectrum: 6-H (dd, J = 6.2, 2.5 Hz) coupled with 2-H (d, J = 2.5 Hz) in long-range fashion and with 5-H (d, J = 6.2 Hz) vicinally (Scheme 2). After methylation of the phenol group of **8**, methoxycarbonylation in the presence of (BINAP)PdCl$_2$ in methanol under 50 psi



Scheme 1



Scheme 2



Scheme 3

of carbon monoxide[3] gave diester **10**, which was demethylated selectively by aluminum chloride[4] to provide cylindol A (**1**) in excellent overall 39% yield. Its spectroscopic data was consistent completely with that of the reported value.

The same sequence of reactions used in the synthesis of cylindol A (**1**) was applied to **11**: bromination, methylation, methoxycarbonylation under carbon monoxide atmosphere in the presence of palladium catalyst, and final selective demethylation afforded the proposed structure of cylindol B (**2**) (Scheme 3). The connectivity of the synthetic cylindol B (**2**) was confirmed by HMBC spectra and its mass spectrum also matched the proposed structure. However, the spectral data of the synthetic cylindol B (**2**) did not match the reported value as evidenced in the comparison between the regenerated ^{1}H and ^{13}C spectra from the reported data of the natural cylindol B and those of synthetic materials (Figure 1).

Since the natural cylindol B could not be available at our hand,[5] we attempted to synthesize possible isomers of **2** such as **15** and **16**, which would have similar ^{1}H NMR pattern to the reported data of the natural cylindol B on the basis of empirical correlation with related compounds.[6] To this end, compound **7** was acetylated to give **17**, which was treated with bromine to provide **18** regioselectively. Direct methoxycarbonylation of **18** was failed to result in only the deprotection of the acetyl groups. Accordingly, we changed the acetyl group to the methyl group as in **19**, which underwent smooth methoxycarbonylation to give **20**. Selective demethylation by aluminum chloride afforded isomer **15**. In the same manner, another isomer **16** was prepared starting from **11**. However, contrary to our expectation, their

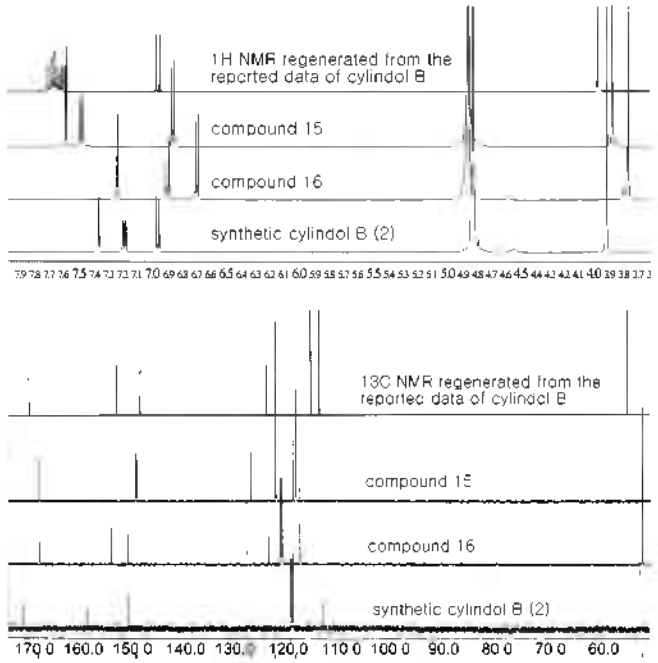
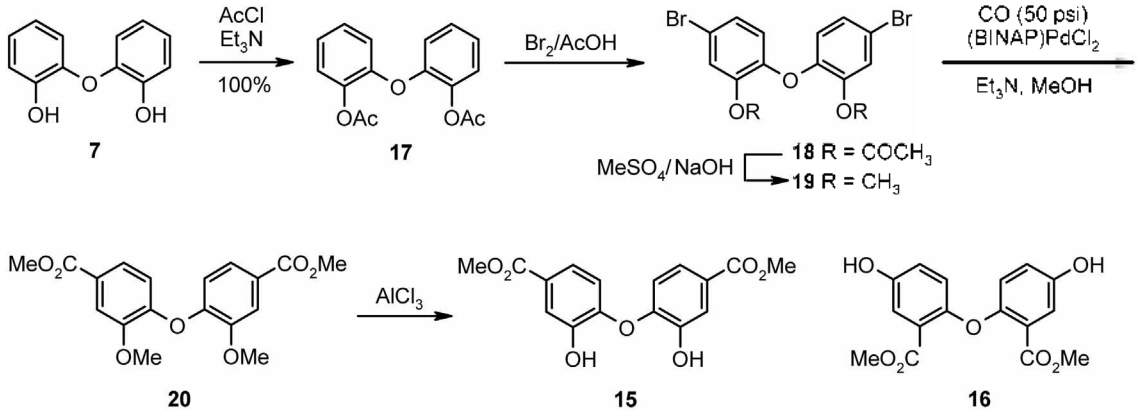


Figure 1. Comparison of the ^{1}H and ^{13}C NMR spectra regenerated from the reported data of natural cylindol B with those of the synthetic cylindol B (**2**) and its isomers, **15** and **16**.



Scheme 4

spectral data also did not match with those of the natural cylindol B (Figure 1).

In summary, we have accomplished very efficient syntheses of cylindol A (**1**) and the proposed structure of cylindol B (**2**), from which we found that the structure of the natural cylindol B was elucidated wrong. As a possible candidate for the natural cylindol B, isomers of **2** such as **15** and **16** were synthesized. However, their spectral data also did not match that of the natural cylindol B. Therefore, the structure of the natural cylindol B is yet to be resolved.

Experimental Section

Solvents and reagents were obtained from commercial sources and used without further purification. NMR spectra were obtained on a Jeol 500 MHz spectrometer. GC analyses were carried out on an Agilent 6890N network GC system and an FID detector. HPLC analyses were carried out on a Hewlett-Packard 1100 system and a Waters 490E detector and 616 pump system. Mass spectra were collected using a Finnigan LCQ mass spectrometer system and a Jeol JMX-700 mass spectrometer.

2,2'-Dihydroxy-5,5'-dibromo-diphenyl ether (8). To a solution of 2,2'-dihydroxy diphenyl ether (**7**, 1.0 g, 4.95 mmol) in 5 mL of DMF was added slowly NBS (1.98 g, 2.25 equiv in 5 mL of DMF) at 0 °C. After 1 h, GC analysis showed the completion of the reaction. After cooling to ca. 5 °C, the reaction mixture was quenched with 10 mL of water and extracted with 20 mL of MTBE. The separated aqueous layer was re-extracted with 10 mL of MTBE. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$. After concentration, the residue (2.13 g) was column chromatographed (silica gel, ethyl acetate/hexane = 1/2) to give 1.9 g of the product as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (dd, J = 6.2, 2.5 Hz, 1H x 2), 6.98 (d, J = 2.5 Hz, 1H x 2), 6.92 (d, J = 6.2 Hz, 1H x 2), 5.83 (br, 1H x 2).

2,2'-Dimethoxy-5,5'-dibromo-diphenyl ether (9). To a clear yellow solution of dibromo-diphenol (**8**, 1.78 g, 4.95 mmol) in 5 mL of ethanol was added Me_2SO_4 (3.0 g, 4.4 equiv). To the mixture was added 33 wt% NaOH (6.0 equiv) dropwise at *ca.* 5 °C and the mixture was heated at reflux for 4 h. After cooling to room temperature, the volatile was evaporated in vacuo and the residue was extracted with ethyl acetate (5 mL × 10). The combined extracts were concentrated in vacuo and the crude residue (2.7 g) was purified by column chromatography (ethyl acetate/hexane = 1/3) to give 1.23 g of the product as a white solid (64.1% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.2 (dd, J = 8.0, 2.5 Hz, 1H x 2), 6.93 (d, J = 2.5 Hz, 1H x 2), 6.84 (d, J = 8.0 Hz, 1H x 2), 3.85 (s, 3H x 2).

2,2'-Dimethoxy-5,5'-dimethoxycarbonyl-diphenyl ether (10). Dibromide (**9**, 1.23 g, 3.12 mmol) and triethylamine (0.83 g, 2.6 equiv) were dissolved in 20 mL of methanol and 3 mL of DMF. To the solution was added (BINAP)$PdCl_2$ (164 mg, 6 mol%). The mixture was flushed with nitrogen three times and charged with carbon monoxide (50 psi), and then heated to 100 °C. After 19 h, the mixture was cooled to room temperature and the mixture was micro-filtered to remove precipitates. The filtrate was concentrated in vacuo and the residue was diluted in ethyl acetate/hexane (1/2) to precipitate insoluble materials. The mixture was filtered and the filtrate was concentrated and purified by column chromatography (ethyl acetate/hexane =1/2) to give **10** as a yellow solid (1.0 g, 91.8%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, J = 8.5, 1.8 Hz, 1H x 2), 7.48 (d, J = 1.8 Hz, 1H x 2), 7.0 (d, J = 8.5 Hz, 1H x 2), 3.92 (s, 3H x 2), 3.85 (s, 3H x 2).

Cylindol A (1). A solution of dimethoxy diphenyl ether (**10**, 1.0 g, 2.89 mmol) in 7 mL of dichloromethane was added to a cold mixture of $AlCl_3$ (3.13 g, 8.1 equiv) in 10 mL of dichloromethane. After 6 h at room temperature, the mixture was heated at reflux for 24 h. The mixture was cooled to *ca.* 5 °C and quenched with water (20 mL) to cause precipitation of the product. The mixture was filtered and the filter cake was slurried in 5 mL of methanol with stirring. The precipitate was filtered, washed with 1 mL of methanol, and dried to give **1** as a beige powder (0.61 g, 66.4%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.70 (dd, J = 7.9, 1.8 Hz, 1H x 2), 7.43 (d, J = 1.8 Hz, 1H x 2), 6.98 (d, J = 7.9 Hz, 1H x 2), 3.81 (s, 3H x 2); ^{13}C NMR (125 MHz, CD_3OD) δ 168.1, 154.5, 145.6, 127.8, 122.9, 121.2, 117.7, 52.5; MS (ESI) m/z 317 $[M - H]^-$; HRMS (ESI) Calcd for $C_{16}H_{13}O_7$: 317.0666, Found: 317.0668.

3,3'-Dibromo-4,4'-dihydroxy diphenyl ether (12). To a solution of diphenyl ether (**11**, 1.0 g, 4.95 mmol) in 10 mL of dichloromethane was added bromine (1.3 g, 3.3 equiv). After keeping overnight, all the volatile was removed by nitrogen purge to give the dibromide as a solid, which was used for the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, J = 2.5 Hz, 1H x 2), 6.98 (d, J = 8.5 Hz, 1H x 2), 6.88 (dd, J = 8.5, 2.5 Hz, 1H x 2), 5.35 (br s, 1H x 2).

3,3'-Dibromo-4,4'-dimethoxy diphenyl ether (13). To a solution of the dibromide (**12**, 4.95 mmol) in 5 mL of ethanol was added Me_2SO_4 (1.8 mL, 3.75 equiv) and aqueous NaOH (0.75 g/1.5 mL water, 3.8 equiv) in sequence. After 4 h at reflux, the mixture was cooled to room temperature. The mixture was concentrated in vacuo and the residue was diluted with 10 mL of dichloromethane and 10 mL of 1 N HCl. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated to give **13** as a pale yellow oil (1.8 g, 94% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, J = 2.5 Hz, 1H x 2), 6.92 (dd, J = 8.5, 2.5 Hz, 1H x 2), 6.86 (d, J = 8.5 Hz, 1H x 2), 3.88 (s, 3H x 2).

3,3'-Dimethoxycarbonyl-4,4'-dimethoxy diphenyl ether (14). Dibromide (**13**, 0.2 g, 0.52 mmol), (BINAP)$PdCl_2$ (25 mg, 6 mol%) and triethylamine (93 L, 1.3 equiv) were dissolved in 3.5 mL of methanol. The mixture was flushed with nitrogen three times and charged with carbon monoxide (50 psi), and then heated to 100 °C. After 2 d, the reaction mixture was concentrated and the residue was chromatographed to give 0.16 g of the diester (**14**, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 1.8 Hz, 1H x 2), 7.10 (dd, J = 9.2, 1.8 Hz, 1H x 2), 6.95 (d, J = 9.2 Hz, 1H x 2), 3.90 (s, 3H x 2,), 3.87 (s, 3H x 2).

The proposed structure of cylindol B (2). A solution of the dimethyl ether (**14**, 0.16 g, 0.46 mmol) in 1.0 mL of dichloromethane was added to a mixture of $AlCl_3$ (0.37 g, 6 equiv) in 3.7 mL of dichloromethane at room temperature. After 2 h, the mixture was concentrated and the residue was quenched with 4 mL of water and extracted with ethyl acetate. The separated organic phase was concentrated to give **2** (147 mg) in quantitative yield. ^{1}H NMR (500 MHz, CD_3OD) δ 7.35 (d, J = 1.8 Hz, 1H x 2), 7.18 (dd, J = 8.5/1.8 Hz, 1H x 2), 6.95 (d, J = 9.2 Hz, 1H x 2), 3.90 (s, 3H x 2); ^{13}C NMR (125 MHz, CD_3OD) δ 171.1, 158.8, 151.0, 128.2, 120.0, 119.6, 113.8, 49.2; MS (ESI) m/z 317 $[M-H]^-$; HRMS (ESI) Calcd for $C_{16}H_{13}O_7$: 317.0666, Found: 317.0670.

Supporting Information Available. Experimental procedures for the synthesis of **15** and **16**. ^{1}H and/or ^{13}C NMR spectra of all compounds, and HMBC spectra of the proposed structure of cylindol B (**2**) are available at *http://www.kcsnet.or.kr/bkcs* or from the corresponding author.

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