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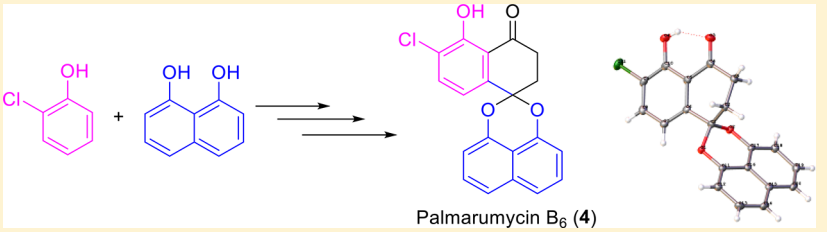
Total Synthesis and Structure Revision of Palmarumycin B_6

Xinlei Liu,[†] Weiwei Wang,[†] Yu Zhao,[†] Daowan Lai,[‡] Ligang Zhou,[‡] Zhilong Liu,[§] and Mingan Wang*[,†]

[†]Department of Applied Chemistry, College of Sciences, [‡]Department of Plant Pathology, and [§]Department of Entomology, College of Plant Protection, China Agricultural University, Beijing 100193, People's Republic of China

Supporting Information



ABSTRACT: Palmarumycin B_6 and its regioisomer were synthesized *via* 7- and 13-step routes using 2-chlorophenol and 4-chlorophenyl methyl ether as the starting materials in overall yields of 2.7% and 12%, respectively. Their structures were characterized by ^{1}H and ^{13}C NMR, HRESIMS, and X-ray diffraction data. The structure of palmarumycin B_6 was revised as 6-chloropalmarumycin CP_{17}. The bioassay results showed that the larvicidal activity of palmarumycin B_6 with an LC_{50} value of 32.7 μM was significantly higher than that of its 8-chloro isomer, with an LC_{50} value of 227.3 μM.

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The outbreak of the Zika fever epidemic in Brazil in 2015 has raised concerns that the mosquitoes of the genus *Aedes* (such as *A. aegypti* and *A. albopictus*) might be the vectors of the Zika virus. This issue has stimulated a renewed interest to develop sustainable vector control systems.[1,2] The resistance of the mosquitoes to traditional insecticides has developed quickly in recent years;[3−6] therefore a search for novel drugs, especially those derived from natural products, to overcome this serious problem is important. Palmarumycins CP_{17}, B_6, and C_8 (Figure 1) were isolated from the endophytic fungus *Berkleasmium* sp., which was purified from the medicinal plant *Dioscorea zingiberensis* C. H. Wright. These compounds exhibited excellent larvicidal activity against the mosquito *A. albopictus* and antibacterial activity against several bacteria.[7,8] Palmarumycin B_6, with an LC_{50} value of 32.7 μM against *A. albopictus*, is a member of the spirobisnaphthalene family that showed broad bioactivities, such as antifungal, antimicrobial, antitumor, anticancer, antiparasitic, anti-inflammatory, and cytotoxic activity.[9−12] Many reports related to the total synthesis, structure modification, and biological activity evaluation of the spirobisnaphthalene natural products have appeared in recent years.[13−32] The syntheses of palmarumycin CP_{17} and its analogues were completed, and the bioassay results showed that they have antifungal activity against several phytopathogens.[33] Because of the interesting larvicidal activity of palmarumycin B_6 against *A. albopictus*, its limited access in the fermentation extract of the endophytic fungus *Berkleasmium* sp., and the importance of the halogen atom in the A-ring,[7,8] the total synthesis and structure confirmation of palmarumycin B_6 were assessed in order to gain insight into the structure−activity relationships of spirobisnaphthalene compounds and explore their modes of action.

RESULTS AND DISCUSSION

The retro-synthetic analysis of palmarumycin B_6 (**2**) is shown in Scheme 1. Palmarumycin B_6 can be synthesized from ketal (**9**) by oxidation with pyridinium dichromate (PDC) and *t*-BuOOH, followed by a demethylation of the methoxy group. Ketal (**9**) could be obtained from a ketalization of 8-chloro-5-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**7**) with 1,8-dihydroxynaphthalene in a similar process to that in the synthesis of palmarumycin CP_{17}.[33] 8-Chloro-5-methoxy-3,4-dihydronaphthalen-1(2H)-one (**7**) could be derived from 4-chlorophenyl methyl ether, a commercially available starting material, *via* Friedel−Crafts acylation, carbonyl reduction, and acid-catalyzed cyclization.[34]

The synthesis of palmarumycin B_6 (**2**) started with 4-chlorophenyl methyl ether as shown in Scheme 2. Compound **5** was obtained via acylation reaction of 4-chlorophenyl methyl ether using succinic anhydride and anhydrous $AlCl_3$ in dichloromethane (DCM) at room temperature in a 60% yield. Reduction of the carbonyl group with trifluoroacetic acid (TFA) and Et_3SiH at room temperature afforded **6** in a 98% yield. Compound **6** was subjected to an intramolecular cyclization catalyzed by polyphosphoric acid (PPA) at 80 °C to afford 8-chloro-5-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**7**) in 74% yield. Although the core spiroketal compound **9** could be generated from a direct ketalization, the resulting yield was too low. The yield was significantly improved by forming enol ether **8** with trimethyl orthoformate. When **8** reacted with 1,8-dihydroxynaphthalene, compound **9** was

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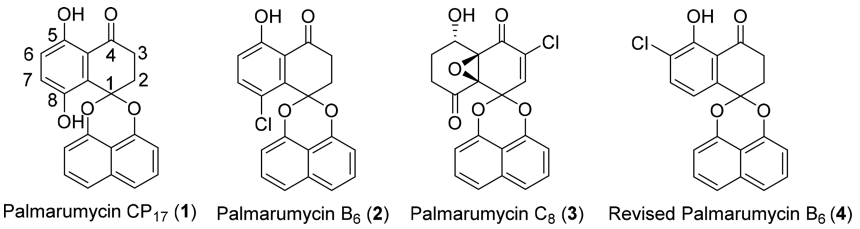
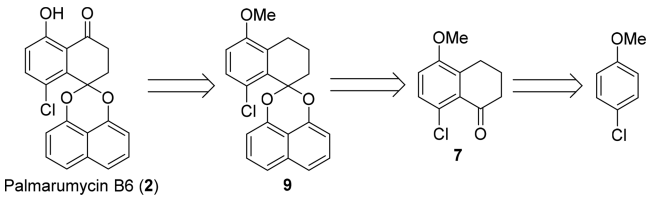


Figure 1. Structures of palmarumycins **1**−**4**.

Scheme 1. Retrosynthetic Analysis of Palmarumycin B_6 (2)



formed in an overall yield of 50% over the two steps. Oxidation of compound **9** with PDC and *t*-BuOOH in benzene gave compound **10** in 74% yield, which was demethylated with Me_3SiI to afford the target palmarumycin B_6 (**2**) in 73% yield. After completion of the synthesis of palmarumycin B_6 (**2**), it was found that its ^1H and ^{13}C NMR data were not consistent with those of the reported palmarumycin B_6.[7,8] The ^1H and ^{13}C NMR chemical shifts at C-5, C-6, C-7, C-8, and C-8a (Table 1, Figure 2) are different. It was hypothesized that the correct structure of palmarumycin B_6 was actually as depicted in compound **4** (Figure 1).

Given that palmarumycin B_6 may actually be compound **4**, the 6-chloro derivative of palmarumycin CP_{17}, the synthesis of compound **4** was undertaken. The retrosynthetic analysis of **4** is shown in Scheme 3, and it parallels the synthesis of compound **2**. However, the starting material should be 2-chlorophenol or 2-chlorophenyl methyl ether based upon the difference of the regiochemistry of the A-ring.[35,36]

The reaction of 2-chlorophenyl methyl ether with succinic anhydride and anhydrous $AlCl_3$ in DCM at room temperature gave 4-(3-chloro-4-methoxyphenyl)-4-oxobutanoic acid in 98% yield, an unwanted regioisomer.[37] Therefore, 2-chlorophenol was selected as the raw material. The synthetic route of 6-chloropalmarumycin CP_{17} (**4**) started with 2-chlorophenol as shown in Scheme 4. Compound **12** was prepared *via* the Fries rearrangement of 2-chlorophenyl acetate, following the reported procedures.[35,36] Compound **16** was obtained following protection of **12**, bromination of **13**, and alkylation of **14** with diethyl malonate, and hydrolysis and decarboxylation of **15**. The same protocol was utilized to accomplish the total synthesis of 6-chloropalmarumycin CP_{17} (**4**) from **16** as was used to synthesize compound 8-chloropalmarumycin CP_{17} (**2**). The ^1H and ^{13}C NMR data of **4** were identical with the reported data of palmarumycin B_6 (Table 1, Figure 2).[7,8] The structure of **4** was also characterized by X-ray diffraction analysis and is depicted in Figure 3. Therefore, the correct structure of palmarumycin B_6 is revised to **4**, 6-chloropalmarumycin CP_{17}.

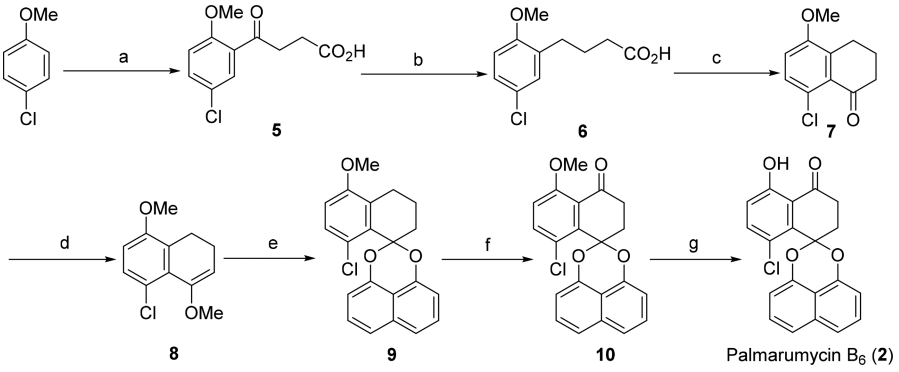
The larvicidal activity of palmarumycin B_6 (**4**) and its 8-chloro isomer (**2**) was evaluated using the bioassay protocols described in the previous report.[8] The preliminary results showed that the larvicidal activity of palmarumycin B_6 (**4**) with an LC_{50} value of 32.7 μM was significantly higher than that of its 8-chloro isomer with an LC_{50} value of 227.3 μM, which indicated that the location of the chlorine atom plays a crucial role for the larvicidal activity against *A. albopictus*.

In summary, the 6- and 8-chloro derivatives of palmarumycin CP_{17} were synthesized. Their structures were characterized by ^1H and ^{13}C NMR and HRESIMS data. The revised structure of palmarumycin B_6 was confirmed by X-ray crystallographic data (CCDC 1834663). The larvicidal activity of palmarumycin B_6 (**4**) was significantly higher than that of its 8-chloro isomer (**2**).

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points (uncorrected) were measured on a WRX-4 microscopic melting point apparatus (Shanghai Yi Ce Instrument Factory). All ^1H and ^{13}C NMR

Scheme 2. Synthesis of 8-Chloropalmarumycin CP_{17} (2)[a]



[a]Reagents and conditions: (a) succinic anhydride, $AlCl_3$, DCM, rt, 24 h, 60%; (b) Et_3SiH, TFA, rt, 6 h, 98%; (c) PPA, 90 °C, 2 h, 74%; (d) $(CH_3O)_3CH$, PPTs, MeOH, 60 °C, 12 h, 72%; (e) 1,8-dihydroxynaphthalene, TsOH, toluene, reflux, 72 h, 70%; (f) PDC, Celite, *t*-BuOOH, benzene, rt, 24 h, 74%; (g) TMSI, $CHCl_3$, 0 °C, 12 h, 73%.

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Table 1. NMR Data of 2, 4, and Palmarumycin B_6[7,8] in $CDCl_3$ (300 MHz)

	^{1}H NMR (δ, J in Hz)			^{13}C NMR (δ)		
position	palmarumycin B_6[7,8]	**2**	**4**	palmarumycin B_6[7,8]	**2**	**4**
1				98.2	99.1	98.2
2	2.49, t (6.5)	2.54, t (6.3)	2.49, t (6.2)	29.5	30.3	29.5
3	2.88, t (6.5)	2.83, t (6.3)	2.88, t (6.2)	34.3	34.3	34.3
4				203.4	202.9	203.4
4a				116.3	117.0	116.3
5				158.1	161.3	158.1
6	7.42, d (8.3)	7.08, d (9.0)		117.2	121.2	117.2
7	7.70, d (8.3)	7.63, d (9.0)	7.70, d (8.2)	137.1	140.5	137.1
8			7.42, d (8.2)	124.2	124.4	124.1
8a				139.6	135.8	139.5
1′				147.3	146.9	147.3
2′	6.97, d (7.5)	6.99, d (7.4)	6.97, d (7.5)	109.6	109.5	109.6
3′	7.46, dd (7.5, 8.3)	7.46, dd (7.4, 8.4)	7.46, dd (7.5, 8.4)	127.7	127.6	127.7
4′	7.54, d (8.3)	7.54, d (8.4)	7.54, d (8.4)	121.2	120.9	121.2
4a′				134.4	134.4	134.3
5′	7.54, d (8.3)	7.54, d (8.4)	7.54, d (8.4)	121.2	120.9	121.2
6′	7.46, dd (7.5, 8.3)	7.46, dd (7.4, 8.4)	7.46, dd (7.5, 8.4)	127.7	127.6	127.7
7′	6.97, d (7.5)	6.99, d (7.4)	6.97, d (7.5)	109.6	109.5	109.6
8′				147.3	146.9	147.3
8a′				113.4	112.6	113.4
OH	13.01, s	12.57, s	13.02, s			

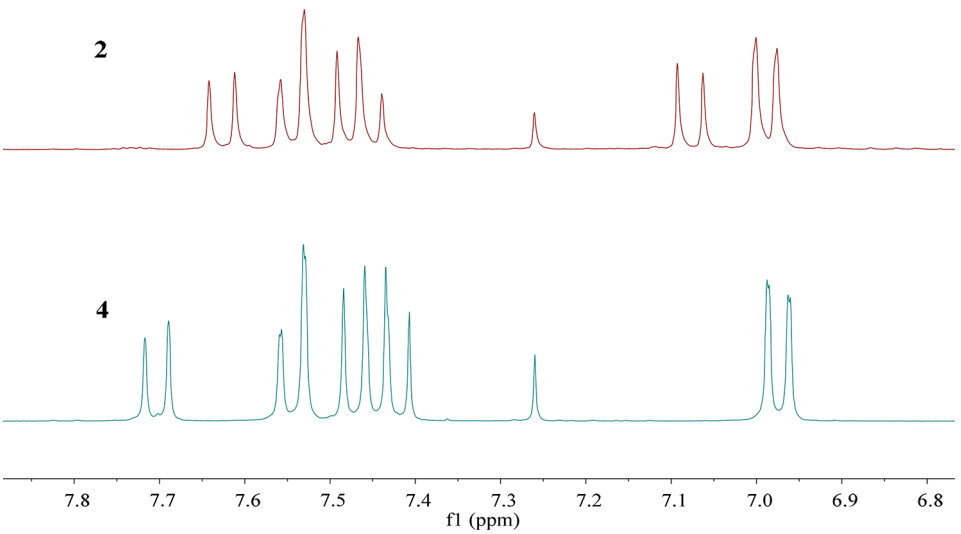
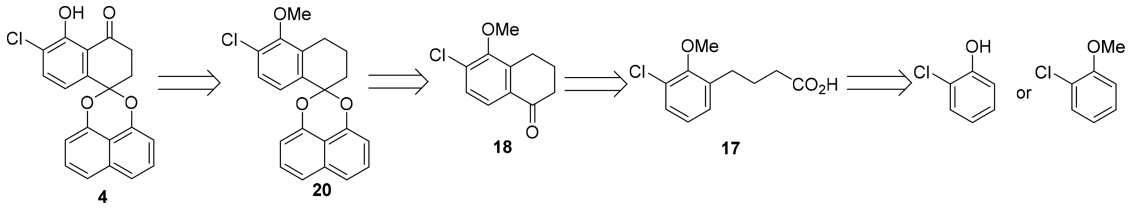


Figure 2. Comparison of ^{1}H NMR spectra of compounds **2** and **4** in the low-field region.

Scheme 3. Retrosynthetic Analysis of Compound 4



spectra were obtained on a Bruker DPX 300 spectrometer with $CDCl_3$ and DMSO-d_6 as solvents and tetramethylsilane (TMS) as an internal standard. HRESIMS spectra were analyzed on a Bruker Apex II mass spectrometer. All reactions were performed under a N_2 atmosphere with magnetic stirring. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Organic solutions were concentrated under reduced pressure using a rotary evaporator or oil pump. Flash column chromatography was performed using Qingdao Haiyang silica gel (200−300 mesh) and neutral Al_2O_3. The crystal structure was analyzed with a Thermo Fisher ESCALAB 250 four-circle X-ray diffractometer (Xcalibur, Eos, Gemini).

Synthesis of 8-Chloropalmarumycin CP_{17} (Palmarumycin B_6, 2). *4-(5-Chloro-2-methoxyphenyl)-4-oxobutanoic acid (**5**).* To succinic anhydride (200 mg, 2 mmol, 1 equiv), 4-chloroanisole (285 mg, 2 mmol), and DCM (10 mL) in a 25 mL round-bottom flask, was

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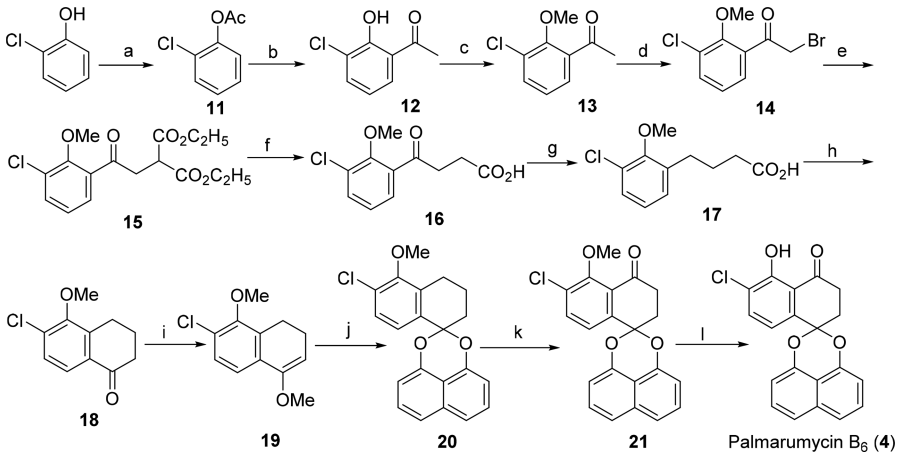
Scheme 4. Synthesis of 6-Chloropalmarumycin CP_{17} (4)[a]



[a]Reagents and conditions: (a) acetyl chloride, Et_3N, DCM, rt, 4 h, 97%; (b) $AlCl_3$, 1,2-dichlorobenzene, 110 °C, 3 h, 32%; (c) CH_3I, K_2CO_3, acetone, reflux, 4 h, 94%; (d) Br_2, Et_2O, rt, 1 h, 78%; (e) diethyl malonate, NaH (60%), THF, rt, 1 h, 75%; (f) (i) NaOH, THF/H_2O, 60 °C, 1 h; (ii) HCl, dioxane/H_2O, reflux, 8 h, 97%; (g) (i) Et_3SiH, TFA, rt, 6 h, 96%; (ii) $PdCl_2$, Et_3SiH, THF, rt, 1 h, 82%; (h) PPA, 90 °C, 2 h, 78%; (i) $(CH_3O)_3CH$, PPTs, MeOH, 60 °C, 12 h; (j) 1,8-dihydroxynaphthalene, TsOH, toluene, reflux, 72 h, 46%; (k) PDC, Celite, *t*-BuOOH, benzene, rt, 24 h, 73%; (l) TMSI, $CHCl_3$, 0 °C, 12 h, 81%.

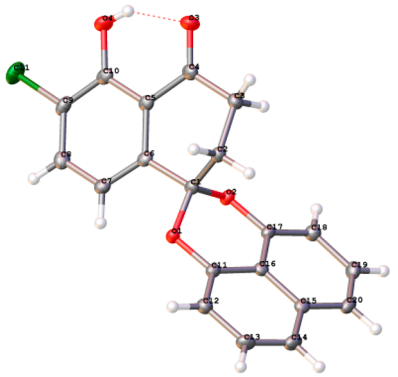


Figure 3. ORTEP drawing of palmarumycin B_6 (4).

added $AlCl_3$ (373 mg, 2.8 mmol, 1.4 equiv) portionwise in an ice bath. The mixture was stirred for 24 h at room temperature and monitored by TLC. The reaction was quenched with crushed ice and 1 M HCl (5 mL), and the organic phase was washed with brine solution. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 3:1) to give compound **5** (292 mg, 60%) as a white solid: mp 117−119 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.13 (1H, brs), 7.60 (1H, dd, J = 8.7, 2.7 Hz), 7.52 (1H, d, J = 2.7 Hz), 7.23 (1H, d, J = 8.7 Hz), 3.89 (3H, s), 3.14 (2H, t, J = 6.6 Hz), 2.53 (2H, t, J = 6.6 Hz); ESIMS, m/z 243 $[M + H]^+$. The data were consistent with the reported data.[34]

*4-(5-Chloro-2-methoxyphenyl)butanoic acid (**6**).* Et_3SiH (1.74 g, 15 mmol, 3 equiv) was added into a TFA (12 mL) solution of **5** (1.213 g, 5 mmol) in a 25 mL round-bottom flask at room temperature. The mixture was stirred at room temperature for 6 h. The solvent was removed under reduced pressure, diluted with EtOAc (20 mL), and washed with water until the pH was >4. The solution was treated with 1 M KOH (3 × 20 mL), the aqueous phase was combined, and the pH was adjusted to 1 with 1 M HCl. The aqueous phase was extracted with EtOAc (3 × 20 mL), and the organic phase was dried over anhydrous Na_2SO_4. The solvent was removed, and the residue was recrystallized from DCM to afford compound **6** (1.116 g, 98%) as a white solid: mp 80−82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.00 (1H, brs), 7.15−7.08 (2H, m), 6.75 (1H, d, J = 8.7 Hz), 3.79 (3H, s), 2.64 (2H, t, J = 7.2 Hz), 2.37 (2H, t, J = 7.2 Hz), 1.97−1.80 (2H, m); ESIMS, m/z 229 $[M + H]^+$. The data were identical with the published data.[34]

*8-Chloro-5-methoxy-3,4-dihydronaphthalen-1(2H)-one (**7**).* A mixture of compound **6** (1.062 g, 4.64 mmol) was added to polyphosphoric acid (30 mL) in a 100 mL round-bottom flask at 90 °C. The mixture was stirred for 2 h, quenched with ice/water, and extracted with EtOAc (3 × 20 mL). The organic phase was combined, washed with a saturated $NaHCO_3$ solution (3 × 20 mL), and dried over anhydrous Na_2SO_4. The solvent was removed, and the residue was recrystallized from DCM to provide compound **7** (726 mg, 74%) as a yellow solid: mp 47−49 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (1H, d, J = 8.7 Hz), 6.90 (1H, d, J = 8.7 Hz), 3.85 (3H, s), 2.89 (2H, t, J = 6.3 Hz), 2.66 (2H, t, J = 6.3 Hz), 2.13−2.04 (2H, m); ESIMS, m/z 211 $[M + H]^+$. The data were identical with the published data.[34]

*5-Chloro-4,8-dimethoxy-1,2-dihydronaphthalene (**8**).* Compound **7** (2.152 g, 10.2 mmol) and Pyridinium 4-toluenesulfonate (PPTs) (513 mg, 2.05 mmol, 0.2 equiv) were added into a MeOH (60 mL) solution of trimethyl orthoformate (30 mL) in a 250 mL round-bottom flask at room temperature. The mixture was heated at reflux for 12 h, Et_3N (0.5 mL) was added, and the solvent was removed under reduced pressure. The residue was diluted with EtOAc (50 mL), the solution was washed with brine, and the organic phase was dried over anhydrous Na_2SO_4. The solvent was removed, and the crude product was purified by flash column chromatography on neutral Al_2O_3 (petroleum ether/EtOAc, 20:1) to afford compound **8** (1.655 g, 72%) as a colorless, viscous liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, J = 8.7 Hz), 6.71 (1H, d, J = 8.7 Hz), 5.20 (1H, t, J = 5.4 Hz), 3.80 (3H, s), 3.68 (3H, s), 2.68 (2H, t, J = 6.3 Hz), 2.20−2.14 (2H, m); ESIMS, m/z 225 $[M + H]^+$.

*8-Chloro-5-methoxy-3,4-dihydro-2H-spiro[naphthalene-1,2′-naphtho[1,8-de][1,3]dioxine] (**9**).* Compound **8** (1.655 g, 7.39 mmol), 1,8-dihydroxynaphthalene (1.317 g, 8.23 mmol, 1.11 equiv), *p*-toluenesulfonic acid (254 mg, 1.34 mmol, 0.18 equiv), and toluene (80 mL) were added into a 250 mL round-bottom flask, and the mixture was stirred and heated at reflux under a N_2 atmosphere for 3 days. After completion of the reaction, Et_3N (0.5 mL) was added, the solution was diluted with EtOAc (100 mL) and washed with brine, and the organic phase was dried over anhydrous Na_2SO_4. The solvent was removed, and the crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 20:1) to give compound **9** (1.81 g, 70%) as a yellow solid: mp 144−146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.39 (4H, m), 7.32 (1H, d, J = 8.7 Hz), 6.92 (2H, dd, J = 7.2, 1.0 Hz), 6.81 (1H, d, J = 8.7 Hz), 3.84 (3H, s), 2.78 (2H, t, J = 6.0 Hz), 2.19−2.15 (2H, m), 1.89−1.80 (2H,

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m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.59, 147.66, 134.35, 132.42, 130.76, 129.94, 127.50, 126.20, 120.21, 112.98, 111.31, 109.14, 100.67, 55.89, 33.01, 24.39, 18.85; HRESIMS, m/z $C_{21}H_{18}ClO_3$ $[M + H]^+$, calcd 353.0939, found 353.0936.

*8-Chloro-5-methoxy-2,3-dihydro-4H-spiro[naphthalene-1,2′-naphtho[1,8-de][1,3]dioxin]-4-one (**10**).* Compound **9** (348 mg, 0.99 mmol) and PDC (1.123 g, 3 mmol, 3 equiv) were added to a 100 mL round-bottom flask containing Celite (2.8 g) and benzene (30 mL) in an ice−water bath, the mixture was stirred, and 5−6 M *t*-BuOOH (8 mL) was injected into the mixture with a syringe over 15 min. The ice−water bath was removed, and the mixture was stirred at room temperature for 24 h. The mixture was diluted with EtOAc (50 mL), and the solids were filtered off. The organic phase was washed with 0.2 M HCl (2 × 50 mL) solution and brine and dried over anhydrous Na_2SO_4. The organic phase was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 10:1) to afford compound **10** (266 mg, 74%) as a white solid: mp 196−198 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (1H, d, J = 8.7 Hz), 7.51 (2H, dd, J = 7.2, 1.0 Hz), 7.45 (2H, t, J = 7.8 Hz), 7.07 (2H, d, J = 8.7 Hz), 6.96 (2H, dd, J = 7.5, 1.0 Hz), 3.95 (3H, s), 2.79−2.74 (2H, m), 2.56−2.51 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.02, 158.08, 146.92, 137.84, 137.64, 134.33, 127.59, 125.98, 123.63, 120.79, 115.05, 112.64, 109.41, 99.57, 56.79, 36.97, 31.50; HRESIMS, m/z $C_{21}H_{16}ClO_4$ $[M + H]^+$, calcd 367.0732, found 367.0735.

*8-Chloro-5-hydroxy-2,3-dihydro-4H-spiro[naphthalene-1,2′-naphtho[1,8-de][1,3]dioxin]-4-one (**2**) (Palmarumycin B_6, 8-chloropalmarumycin CP_{17}).* TMSI (0.3 mL, 2.1 mmol) was added into a $CHCl_3$ (2 mL) solution of compound **10** (78 mg, 0.21 mmol) in a 10 mL round-bottom flask in an ice−water bath. The mixture was stirred at 0 °C for 12 h. The solution was extracted with saturated aqueous $Na_2S_2O_3$ (2 × 30 mL) solution. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was subjected to flash column chromatography on silica gel and eluted with petroleum/EtOAc(20:1) to afford compound **2** (55 mg, 73%) as a light yellow solid: mp 129−131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.57 (1H, s), 7.63 (1H, d, J = 8.7 Hz), 7.56−7.43 (3H, m), 7.07 (1H, d, J = 8.7 Hz), 6.98 (2H, d, J = 7.5 Hz), 2.85−2.81 (2H, m), 2.57−2.52 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.91, 161.31, 146.89, 140.47, 135.79, 134.39, 127.65, 124.43, 121.22, 120.94, 117.04, 112.65, 109.46, 99.11, 34.32, 30.28; HRESIMS, m/z $C_{21}H_{16}ClO_4$ $[M + H]^+$, calcd 367.0732, found 367.0735.

Synthesis of 6-Chloropalmarumycin CP_{17} (Revised palmarumycin B_6, 4). *2-Chlorophenyl acetate (**11**).* 2-Chlorophenol (12.861 g, 100 mmol) and Et_3N (24.2 mL, 3 equiv) were added into a 250 mL round-bottom flask containning DCM (100 mL). Acetyl chloride (8.49 mL, 1.2 equiv) was added dropwise into the solution at 0 °C, and the mixture was stirred at room temperature for 2 h. The mixture was washed with 1 M HCl (1 × 100 mL) and brine. The organic phase was dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 20:1) to afford compound **11** (16.61 g, 97%) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (1H, dd, J = 7.8, 1.8 Hz), 7.31−7.25 (1H, m), 7.22−7.16 (1H, m), 7.13 (1H, dd, J = 7.8, 1.8 Hz), 2.36 (3H, s); ESIMS, m/z 171 $[M + H]^+$. These data were identical with the reported data.[35,36]

*2-Chloro-6-acetylphenol (**12**).* $AlCl_3$ (3.231 g, 24 mmol, 1.2 equiv) was added to a 50 mL round-bottom flask containing 2-chlorophenyl acetate (3.443 g, 20.2 mmol) and 1,2-dichlorobenzene (10 mL). The mixture was heated to 100−110 °C in an oil bath for 4 h. The reaction was quenched by crushed ice and extracted with EtOAc (2 × 50 mL). The organic phase was washed with brine twice, the solvent was removed under vacuum, and the crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 10:1) to give compound **12** (1.111 g, 32%) as a yellow solid: mp 54−56 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.85 (1H, brs), 7.68 (1H, dd, J = 7.8, 1.8 Hz), 7.57 (1H, dd, J = 7.8, 1.8 Hz), 6.87 (1H, t, J = 7.8 Hz), 2.66 (3H, s); ESIMS, m/z 171 $[M + H]^+$. These data were consistent with the published data.[35,36]

*2-Chloro-6-acetylphenyl methyl ether (**13**).* Compound **12** (4.671 g, 27.4 mmol) was dissolved in acetone (60 mL) in a 200 mL round-bottom flask. K_2CO_3 (7.575 g, 54.79 mmol, 2 equiv) was added to the solution, and the mixture was stirred. CH_3I (5.56 mL, 4 equiv) was added to the stirred mixture, and the reaction mixture heated at reflux for 3 h. The mixture was cooled to room temperature, and the solid was removed. The solvent was evaporated under vacuum, and the residue was diluted with EtOAc (50 mL). The crude product was washed with saturated aqueous $Na_2S_2O_3$ (2 × 30 mL) solution and brine, and the organic phase dried over anhydrous Na_2SO_4. The organic solution was concentrated under reduced pressure to give compound **13** (4.728 g, 94%) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (1H, dd, J = 7.8, 1.8 Hz), 7.51 (1H, dd, J = 7.8, 1.8 Hz), 7.12 (1H, t, J = 7.8 Hz), 3.89 (3H, s), 2.63 (3H, s); ESIMS, m/z 185 $[M + H]^+$. These data were identical with the reported data.[35,36]

*2-Chloro-6-bromoacetylphenyl methyl ether (**14**).* Compound **13** (7.544 g, 40.89 mmol) was added to a 250 mL round-bottom flask containing Et_2O (80 mL). Bromine (2.1 mL, 1 equiv) was added dropwise, and the solution was stirred for 8 h. The reaction was quenched with water (60 mL) and extracted with Et_2O (2 × 30 mL). The organic phase was washed with saturated aqueous Na_2CO_3 (20 mL) solution and brine and dried over anhydrous Na_2SO_4. The solvent was removed, and the crude product was purified by column chromatography on silica gel (DCM/petroleum ether, 1:15) to afford compound **14** (8.304 g, 78%) as a white wax solid: mp 40−42 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (2H, d, J = 8.1 Hz), 7.16 (1H, t, J = 8.1 Hz), 4.56 (2H, s), 3.95 (3H, s); ESIMS, m/z 263 $[M + H]^+$.

*Diethyl 2-[2-(3-chloro-2-methoxyphenyl)-2-oxoethyl]malonate (**15**).* NaH (60%) (586 mg, 14.65 mmol, 1.05 equiv) was suspended in dry tetrahydrofuran (THF) (10 mL) in a 100 mL round-bottom flask. A solution of diethyl malonate (2.273 g, 14.2 mmol, 1 equiv) in dry THF (10 mL) was added dropwise at 0 °C under a N_2 atmosphere. The solution was stirred at 0 °C for 10 min until it turned clear. Then a solution of compound **14** (3.743 g, 14.2 mmol) in dry THF (20 mL) was added. The mixture was warmed to room temperature and stirred for 2 h under a N_2 atmosphere. The reaction was quenched with a saturated aqueous NH_4Cl (20 mL) solution at 0 °C, and the THF was removed under reduced pressure. The reaction mixture was poured into water and extracted with EtOAc (3 × 20 mL). The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 10:1) to give compound **15** (3.662 g, 75%) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56−7.52 (2H, m), 7.12 (1H, t, J = 8.1 Hz), 4.21 (4H, t, J = 7.5 Hz), 4.02 (1H, t, J = 7.2 Hz), 3.93 (3H, s), 3.61 (2H, d, J = 7.2 Hz), 1.28 (6H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.73, 168.54, 154.80, 133.97, 133.60, 128.54, 128.00, 124.60, 61.91, 61.36, 47.07, 41.50, 13.68; HRESIMS, m/z $C_{16}H_{20}ClO_6$ $[M + H]^+$, calcd 343.0943, found 343.0946.

*4-(3-Chloro-2-methoxyphenyl)-4-oxobutanoic acid (**16**).* Compound **15** (2.232 g, 6.5 mmol) was added to a 100 mL round-bottom flask with a LiOH solution (1.642 g, 39.1 mmol, 6 equiv) in THF (30 mL) and water (30 mL), and the mixture stirred and heated at 60 °C for 1 h. The THF was removed under reduced pressure, and the aqueous solution was acidified with HCl (1 M) to pH = 1. The aqueous solution was extracted with EtOAc (3 × 20 mL), and the organic phase was combined and washed with brine twice, dried over anhydrous Na_2SO_4, and concentrated under vacuum to afford the intermediate diacid. This intermediate was dissolved in 1,4-dioxane (30 mL), and 2 M HCl (30 mL) was added. The mixture was heated at reflux for 8 h, the solution cooled, and 1,4-dioxane removed under reduced pressure. The solution was extracted with EtOAc (3 × 20 mL), and the organic phase was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to afford compound **16** (1.533 g, 97%) as a yellow solid: mp 40−42 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (1H, dd, J = 8.1, 1.8 Hz), 7.56 (1H, dd, J = 7.8, 1.8 Hz), 7.25

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(1H, t, J = 7.8 Hz), 3.81 (3H, s), 3.16 (1H, t, J = 7.2 Hz), 2.57 (2H, t, J = 7.2 Hz); HRESIMS, m/z $C_{11}H_{12}ClO_4$ $[M + H]^+$, calcd 243.0419, found 243.0415. These data were consistent with the reported data.[37]

*4-(3-Chloro-2-methoxyphenyl)butanoic acid (**17**).* Et_3SiH (2.899 g, 24.52 mmol, 3 equiv) was added to a TFA (24 mL) solution of compound **16** (1.982 g, 8.17 mmol) in a 50 mL round-bottom flask at room temperature. The mixture was stirred at room temperature for 6 h, the solvent removed under vacuum, and the residue diluted with EtOAc (50 mL) and washed with water until pH > 4. The organic phase was treated with 1 M KOH (3 × 20 mL). The aqueous phase was combined, and the pH adjusted to <1 with 1 M HCl. Then the aqueous phase was extracted with EtOAc (2 × 30 mL), and the organic phase was concentrated under reduced pressure to afford 4-(3-chloro-2-methoxyphenyl)-4-hydroxybutanoic acid (1.695 g, 96%) as a colorless liquid.

$PdCl_2$ (119 mg, 0.63 mmol, 0.12 equiv) was added to a solution of the 4-hydroxybutanoic acid (1.329 g, 5.44 mmol) and Et_3SiH (1.899 g, 16.4 mmol, 3 equiv) in THF (30 mL) at room temperature under a N_2 atmosphere. The mixture solution was stirred for 2 h, and the solvent removed under reduced pressure. The residue was diluted with EtOAc (50 mL), and the solution was washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to give compound **17** (1.018 g, 82%) as a yellow solid: mp 75−77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (1H, dd, J = 7.8, 1.8 Hz), 7.08 (1H, dd, J = 7.8, 1.8 Hz), 6.98 (1H, t, J = 7.8 Hz), 3.85 (3H, s), 2.72 (2H, t, J = 7.5 Hz), 2.41 (2H, t, J = 7.5 Hz), 2.00−1.90 (2H, m); HRESIMS, m/z $C_{11}H_{14}ClO_3$ $[M + H]^+$, calcd 229.0626, found 229.0624.

*6-Chloro-5-methoxy-3,4-dihydronaphthalen-1(2H)-one (**18**).* A mixture of P_2O_5 (3 g) and phosphoric acid (4.5 mL; 85%) was stirred in a 25 mL round-bottom flask at 90 °C for 2 h to obtain the polyphosphoric acid. Compound **17** (321 mg, 1.4 mmol) was added into the polyphosphoric acid at 90 °C, and the mixture stirred for 2 h, quenched with crushed ice, and extracted with EtOAc (3 × 20 mL). The organic phase was combined, washed with a saturated aqueous $NaHCO_3$ solution, and dried over anhydrous Na_2SO_4. The crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 10:1) to afford compound **18** (229 mg, 78%) as a white solid: mp 82−84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (1H, d, J = 8.4 Hz), 7.32 (1H, d, J = 8.4 Hz), 3.85 (s), 2.99 (2H, t, J = 6.0 Hz), 2.63 (2H, t, J = 6.0 Hz), 2.16−2.08 (2H, m); HRESIMS, m/z $C_{11}H_{12}ClO_2$ $[M + H]^+$, calcd 211.0520, found 211.0522.

*6-Chloro-5-methoxy-3,4-dihydro-2H-spiro[naphthalene-1,2′-naphtho[1,8-de][1,3]dioxine] (**20**).* Compound **18** (209 mg, 1 mmol) and PPTs (51 mg, 0.2 mmol, 0.2 equiv) were added to a MeOH solution (30 mL) of trimethyl orthoformate (10 mL) in a 100 mL flask at room temperature. The mixture was heated at reflux for 12 h, Et_3N (0.5 mL) added, the solvent removed, and the residue purified by flash column chromatography on neutral Al_2O_3 (petroleum ether/EtOAc, 20:1) to afford compound **19** as a white solid.

A mixture of compound **19**, 1,8-dihydroxynaphthalene (194 mg, 1.2 mmol, 1.2 equiv), and p-toluenesulfonic acid (38 mg, 0.2 mmol, 0.2 equiv) in toluene (30 mL) in a 50 mL round-bottom flask was stirred and heated for 72 h at reflux under a N_2 atmosphere. The solution was diluted with EtOAc (60 mL), washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed, and the crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 30:1) to produce compound **20** (160 mg, 46% for two steps) as a light yellow solid: mp 179−181 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (1H, d, J = 8.4 Hz), 7.52−7.36 (5H, m), 6.92 (2H, dd, J = 7.2, 1.2 Hz), 3.88 (3H, s), 2.92 (2H, t, J = 6.3 Hz), 2.15−2.11 (2H, m), 1.98−1.91 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.32, 148.09, 135.64, 134.31, 134.19, 128.93, 128.51, 127.52, 124.33, 120.58, 113.70, 109.50, 100.26, 60.19, 30.55, 23.94, 19.11; HRESIMS, m/z $C_{21}H_{18}ClO_3$ $[M + H]^+$, calcd 353.0939, found 353.0938.

*6-Chloro-5-methoxy-2,3-dihydro-4H-spiro(naphthalene-1,2′-naphtho[1,8-de][1,3]dioxin)-4-one (**21**).* Compound **20** (393 mg, 1.11 mmol) and PDC (1.235 g, 3.34 mmol, 3 equiv) were added to a 100 mL round-bottom flask with Celite (4 g) and benzene (30 mL) in an ice−water bath. To the stirred solution was added 5−6 M t-BuOOH (9 mL) *via* syringe in 15 min. The ice−water bath was removed, and the mixture stirred at ambient temperature for 24 h. The solution was diluted with EtOAc, and the solid was removed. The organic phase was washed with 1 M HCl solution (25 mL) and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue subjected to flash column chromatography on silica gel (petroleum ether/EtOAc, 10:1) to give compound **21** (296 mg, 73%) as a yellow solid: mp 115−117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (2H, s), 7.53 (2H, d, J = 8.4 Hz), 7.45 (2H, t, J = 8.1 Hz), 6.96 (2H, d, J = 7.2 Hz), 3.99 (3H, s), 2.78 (2H, t, J = 6.9 Hz), 2.47 (2H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.39, 155.86, 147.43, 140.99, 135.19, 134.32, 132.09, 127.67, 127.22, 122.63, 121.11, 113.50, 109.59, 98.50, 62.08, 35.44, 29.46; HRESIMS, m/z $C_{21}H_{16}ClO_4$ $[M + H]^+$, calcd 367.0732, found 367.0736.

*6-Chloro-5-hydroxy-2,3-dihydro-4H-spiro[naphthalene-1,2′-naphtho[1,8-de][1,3]dioxin]-4-one (**4**) (revised palmarumycin B_6).* TMSI (1.242 mL, 8.73 mmol, 10 equiv) was added to a $CHCl_3$ (10 mL) solution of compound **21** (320 mg, 0.87 mmol) in a 25 mL flask in an ice−water bath. The mixture was stirred at 0 °C for 12 h, the solvent removed under vacuum, and the residue subjected to flash column chromatography on silica gel and eluted with petroleum/EtOAc (10:1) to afford compound **4** (249 mg, 81%) as a light yellow solid: mp 190−192 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.02 (1H, s), 7.70 (1H, d, J = 8.1 Hz), 7.54 (2H, dd, J = 8.4, 1.0 Hz), 7.46 (2H, t, J = 8.1 Hz), 7.42 (1H, d, J = 8.1 Hz), 6.97 (2H, dd, J = 7.2, 1.0 Hz), 2.88 (2H, t, J = 6.6 Hz), 2.49 (2H, t, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.36, 158.12, 147.32, 139.55, 137.07, 134.34, 127.69, 124.14, 121.16, 117.19, 116.30, 113.38, 109.61, 98.16, 34.31, 29.49; HRESIMS, m/z $C_{20}H_{14}ClO_4$ $[M + H]^+$, calcd 353.0575, found 353.0578.

X-ray Diffraction Analysis of Palmarumycin B_6 (4). Colorless plate-like crystals of palmarumycin B_6 (**4**) were obtained from a slowly evaporating CH_2Cl_2/n-hexane solution. A 0.40 × 0.35 × 0.30 mm^3 crystal was selected for analysis. The parameters and structure information for compound **4** have been deposited at the Cambridge Crystallographic Data Centre. CCDC ID 1834663 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

■ ASSOCIATED CONTENT

Supporting Information

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Additional information (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +86-10-62734093. E-mail: wangma@cau.edu.cn.

ORCID

Xinlei Liu: 0000-0002-2630-7751

Ligang Zhou: 0000-0003-4681-191X

Notes

The authors declare no competing financial interest.

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