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Flexible Route to Palmarumycin CP_1 and CP_2 and CJ-12.371 Methyl Ether

Karsten Krohn,*[a] Si Wang,[a] Ishtiaq Ahmed,[a] Sultan Altun,[a] Abdulselam Aslan,[a] Ulrich Flörke,[a] Ines Kock,[a] and Stefanie Schlummer[a]

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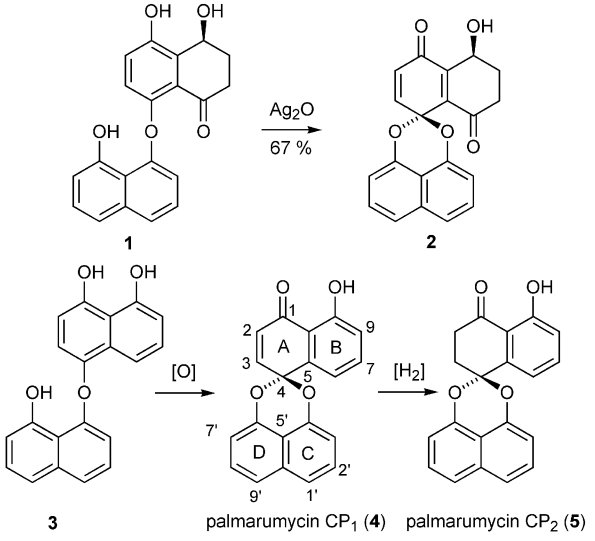
The total synthesis of palmarumycin CP_1 (**4**) and CP_2 (**5**) and racemic CJ-12.371 methyl ether (**17**) is described using the Diels–Alder reaction of benzoquinone 1,8-dihydroxynaphthalene acetal (**10**) with 1-methoxy-1,3-butadiene under neat reaction conditions. The stereochemistry of adduct **15** was confirmed by single-crystal X-ray analysis. The transformation of **15** into target products **4**, **5**, and **17** involved dehydrogenation, methyl ether cleavage, and reduction and oxidation steps.

Introduction

The palmarumycins belong to the group of spirodioxynaphthalene fungal metabolites. The first representative, named bipendensin, was isolated from *Afzelia bipendensis*, an African plant.[1] However, it is most probable that the compound was produced by a fungus living in this plant, as later suggested by Prajoubklang et al.[2] A few years later, a large number of these spiro compounds were isolated mostly from endophytic fungi, and they were named diepoxines,[3] "Sch-plus number",[4–6] "CJ-plus number",[7] cladosporins,[8–10] palmarumycins,[11–15] sphaerolones,[16] decaspirones,[17] and deoxypreussomerin (palmarumycin CP_1).[18] Almost 100 different compounds have been characterized in the meantime, and the "dimeric" 1,8-dihydroxynaphthalenes are amongst the polyketide natural products that show the greatest diversity (review:[19]). An interesting observation was made with the isolation of open intermediate **1**, which could be oxidized by silver oxide to palmarumycin derivative **2** (Scheme 1), suggesting the biosynthesis from monomeric 1,8-dihydroxynaphthalene, biaryl ether formation, and enzyme-catalyzed phenol oxidation.[20] The biosynthetic origin from 1,8-dihydroxy "monomeric" units was confirmed by feeding experiments by Zeeck and Bode.[21]

Alcohol **2** is not the simplest derivative, and palmarumycin CP_1 (**4**) and CP_2 (**5**),[12] generated by phenol oxidation from bisnaphthol **3**, may be called the "mother" compounds from which all the other derivatives may be deduced by simple chemical transformations (Scheme 1).

The spirodioxynaphthalenes show a great variety of biological activity ranging from antifungal and antibacterial,[3,11,12,17] antimitotic,[22] and antileishmanial[23] to antitumor activity.[22,24] The antitumor and antimitotic activity may be linked to phospholipase D inhibition,[6,25,26] DNA gyrase inhibition,[7] or the inhibition of the thioredoxin-reductase system.[27–29] These biological activities combined with the interesting structure has stimulated many synthetic groups to synthesize these spiro naphthalenes. Two major routes, including the synthesis of palmarumycin CP_1 and CP_2, have been developed for this purpose. In the first route, mainly used by the groups of Barrett[30,31] and Taylor,[32,33] an acetalization procedure of tetralones and 1,8-dihydroxynaphthalene was applied. As a result of the poor nucleophilicity of 1,8-dihydroxynaphthalene, forced conditions had to be used, but the yields were generally good. In the second method, the "biomimetic" oxidation of phenolic



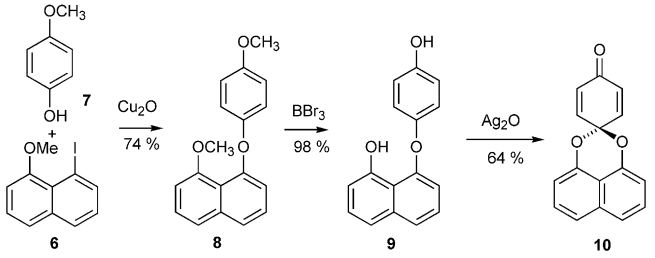
Scheme 1. Biomimetic oxidation of open precursor **1** to palmarumycin derivative **2** and biosynthesis of palmarumycin CP_1 (**4**) and CP_2 (**5**) by phenol oxidation of bisnaphthol ether **3**.

[a] Department of Chemistry, University of Paderborn, Warburger Straße 100, 33098 Paderborn, Germany
Fax: +49-5251-60-3245
E-mail: k.krohn@uni-paderborn.de

naphthalene ethers into the spiro bisnaphthalenes was applied by Wipf et al.[34–36]

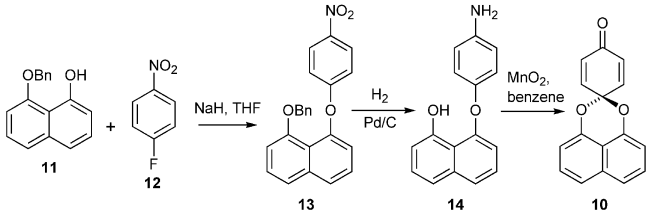
Results and Discussion

We wanted to try a flexible route allowing the addition of different dienes to benzoquinone acetal **10** to yield a variety of palmarumycin derivatives. Benzoquinone acetal **10** was prepared by Ullmann coupling of 8-iodo-1-methoxynaphthalene (**6**)[37] with 4-methoxyphenol (**7**) to yield mixed benzyl ether **8** in 74% yield. The dimethyl ether was cleaved with the use of boron tribromide to give bisphenol **9**, which was oxidized with silver oxide to **10** in 64% yield (Scheme 2).



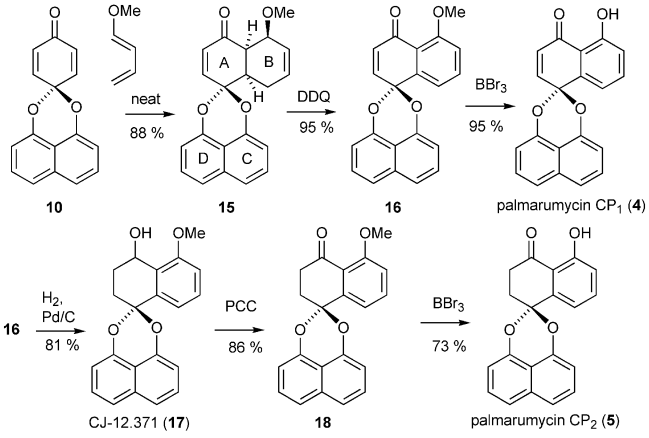
Scheme 2. Synthesis of benzoquinone naphthalenedioxy acetal **10** by a biomimetic approach.

During our work,[38] a paper of Coutts et al.[39] appeared, describing the synthesis of **10** by using an aromatic nucleophilic substitution of 4-fluoro-1-nitrobenzene (**12**) with 8-benzyloxy-1-hydroxynaphthalene (**11**) to afford benzyl ether **13** (Scheme 3). Hydrogenation of **13** afforded amine **14** and oxidation with manganese dioxide gave benzoquinone acetal **10**. Although the yields of our approach were good to acceptable, the Sandmeyer reaction to yield iodide **6**[37] was not amenable to large-scale production of **10**, and we later used the procedure of Coutts et al. to produce larger amounts of benzoquinone acetal **10**.



Scheme 3. Synthesis of benzoquinone acetal **10** according to Coutts et al.[39]

Unfortunately, Coutts et al. could not prepare palmarumycin derivatives, because the decarboxylation of the corresponding 3-methoxy-2-pyrone adduct failed. For the Diels–Alder reaction of **10** with 3-methoxy-2-pyrone, high pressure had to be used. Benzoquinone acetals are known to be poor pure dienophiles.[40] To avoid the high pressure conditions (12–14 kbar[39]), several methods may be applied to increase the reaction rate. First of all, donor (oxygen)-substituted dienes could be used to decrease the HOMO–LUMO distance of the reactants. Fortunately, these oxygen functions are present in most palmarumycin derivatives, including palmarumycin CP_1 and CP_2. Secondly, either high temperatures or high concentrations of the reactants would help to increase the reaction rate. On the other hand, twofold subsequent additions to the double bonds in **10** had to be avoided, and therefore, the reaction conditions should be sufficiently mild. After some experimentation, we found that "neat" conditions were optimal to obtain mono adduct **15** in 88% yield after chromatographic purification. The benzoquinone acetal was dissolved in a fivefold excess amount of 1-methoxy-1,3-butadiene, easily prepared in large amounts from crotonaldehyde.[41] This mixture was stirred for at least 3 d at room temperature (Scheme 4). As expected, Diels–Alder product **15** formed a single stereoisomer that was isolated as slightly yellow crystals. The relative configuration with *cis*-configured hydrogen atoms and a *trans*-oriented methoxy group was confirmed by single-crystal X-ray analysis (Figure 1). The central C-1 atom lies 0.483(2) Å above the aromatic ring moiety, and the geometry around C-1 is almost tetrahedral with angles in the range 104.9(2)–113.2(2)°.



Scheme 4. Conversion of benzoquinone acetal **10** into palmarumycin CP_1 (**4**) and CP_2 (**5**).

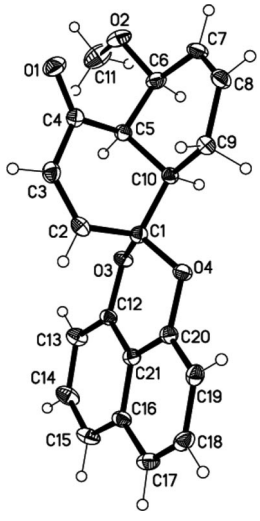


Figure 1. Molecular structure of Diels–Alder product **15**. Anisotropic displacement ellipsoids are shown at the 50% probability level.

The next task was the dehydrogenation of ring B without elimination of the methoxy group. 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) proved to be the reagent of choice, and palmarumycin CP_1 methyl ether (**16**) was isolated in 95% yield by gentle heating in toluene. The only remaining step to palmarumycin CP_1 (**4**) was the cleavage of the methyl ether. The cyclic acetal of the spirodioxynaphthalenes was surprisingly stable, but it was possible to use the strong Lewis acid boron tribromide for methyl ether cleavage to form **4** in 73% yield (Scheme 4).

The synthesis of palmarumycin CP_2 (**5**) required selective reduction of the double bond. This was easily performed in a two-step procedure involving hydrogenation to afford alcohol **17** followed by oxidation with pyridinium chlorochromate (PCC) to give ketone **18**. Again, BBr_3 was used to cleave the methyl ether to form palmarumycin CP_2 (**5**) in 73% yield. More direct methods of selective hydrogenation of enone **16** to ketone **18** are available; however, our route provided another palmarumycin derivative, the methyl ether of CJ-12.371 (**17**).[7] The biological activity of natural products **4** and **5** against a panel of microorganisms and one alga [bacteria (*Bacillus megaterium, Escherichia coli*), fungi (*Ustilago violacea, Mycotypha microspora, Fusarium oxysporum, Eurotium repens*), alga (*Chlorella fusca*)] was reported in a previous communication.[11]

Experimental Section

General Experimental Procedures: Melting points were determined with a Gallenkamp melting point apparatus. Optical rotations were measured with a Perkin–Elmer 241 MC polarimeter. The IR spectra were recorded with a Nicolet-510P spectrometer. NMR spectra were recorded with a Bruker Avance-500 NMR spectrometer with TMS as internal standard. EI mass spectra were obtained with an MAT 8200 mass spectrometer. CD spectra were recorded with a J-810 spectropolarimeter. Silica gel (70–230 mesh) was used for column chromatography.

1-Methoxy-8-(4-methoxyphenoxy)naphthalene (8): A solution of *p*-methoxyphenol (**7**; 0.35 g, 2.8 mmol) and 8-iodo-1-methoxynaphthalene (**6**;[37] 0.40 g, 1.4 mmol) in pyridine (5 mL) was treated with Cu_2O (0.20 g, 1.4 mmol), and the suspension was heated under reflux for 22 h. HCl (6 N, 10 mL) was added, and the organic material was extracted with ethyl acetate (2 × 5 mL). The combined organic phase was washed with water and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 9:1) to afford a faint yellow solid of biaryl ether **8** (0.29 g, 74%). M.p. 83 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.81 (s, 6 H, 2 OCH_3), 6.84–6.91 (m, 5 H, 7-H, 2′-H, 3′-H, 5′-H, 6′-H), 7.10 (d, J = 7.5 Hz, 1 H, 2-H), 7.40–7.54 (m, 3 H, 3-H, 5-H, 6-H), 7.68 (d, J = 8.2 Hz, 1 H, 4-H) ppm. ^{13}C NMR (50 MHz, DMSO): δ = 56.1 (q, C-10), 56.5 (q, C-9), 106.6 (d, C-7), 115.0 (2 d, C-2′, C-6′), 118.1 (d, C-2), 118.2 (2 d, C-3′, C-5′), 120.1 (s, C-8a), 121.2 (d, C-6), 124.7 (d, C-3), 126.9 (d, C-5), 127.0 (d, C-4), 138.0 (s, C-4a), 153.3 (s, C-4′), 154.0 (s, C-8), 154.9 (s, C-1′), 156.7 (s, C-1) ppm. MS (70 eV): *m*/*z* (%) = 280 (100) $[M]^+$, 265 (24) $[M - CH_3]^+$, 250 (28) $[M - 2CH_3]^+$, 237 (51), 209 (51), 194 (37), 165 (24), 129 (17), 95 (26), 77 (28), 64 (13), 41 (15). IR (film): $\tilde{\nu}$ = 3055 (CH), 2999 (CH), 2933 (CH), 2834 (CH), 1577 (CH), 1500 (Ar), 1271 (CO), 130 (CO) cm^{-1}. $C_{18}H_{16}O_3$ (280.32): calcd. C 77.12, H 5.75; found C 76.00, H 5.66.

8-(4-Hydroxyphenoxy)naphthalen-1-ol (9): A solution of methyl ether **8** (0.28 g, 1 mmol) in dichloromethane (DCM, 5 mL) was treated with a solution of BBr_3 (1.0 M in DCM, 1.91 mL) as described for **4** (see below) to afford phenol **9** (245 mg, 98%). M.p. 94 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.58 (dd, J = 7.5, 1.0 Hz, 1 H, 2-H), 6.89 (td, J = 8.5, 2.5/3.5 Hz, 2 H, 3′-H, 5′-H), 6.96 (dd, J = 7.5, 1.5 Hz, 1 H, 7-H), 7.09 (td, J = 8.5, 2.5/3.5 Hz, 2 H, 2′-H, 6′-H), 7.21 (t, J = 7.5 Hz, 1 H, 3-H), 7.35 (dd, J = 7.5, 1.5 Hz, 1 H, 5-H), 7.38 (t, J = 7.5 Hz, 1 H, 6-H), 7.47 (dd, J = 7.5, 1.5 Hz, 1 H, 4-H), 9.13 (s, 1 H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 109.3 (d, C-2), 110.6 (d, C-7), 115.5 (s, C-8a), 116.7 (d, C-3′, C-5′), 119.2 (d, C-6), 122.5 (d, C-2′, C-6′), 123.6 (d, C-4), 125.5 (d, C-3), 127.7 (d, C-5), 136.9 (s, C-4a), 147.8 (s, C-4′), 153.2 (s, C-1′), 153.8 (s, C-8), 156.0 (s, C-1) ppm. IR (ATR): $\tilde{\nu}$ = 3409, 1608, 1581, 1501, 1448, 1191, 1025, 842, 813, 752, 531 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 252 (92) $[M]^+$, 195 (7), 131 (22), 115 (35), 84 (100), 35 (28). HRMS (EI, 70 eV): calcd. for $C_{16}H_{12}O_3$ 252.07864; found 252.07686.

8-(Benzyloxy)-1-(4′-nitrophenoxy)naphthalene (13): A solution of 1-benzyloxy-8-hydroxynaphthalene (**11**; 25.00 g, 0.10 mol) and 1-fluoro-4-nitrobenzene (**12**; 16.92 g, 0.12 mol) in dry THF (300 mL) and DMSO (75 mL) was treated with NaH (2.88 g, 0.12 mol). The reaction mixture was stirred under reflux for 3 h under an atmosphere of nitrogen with TLC monitoring [petroleum ether (PE)/EtOAc, 4:1]. The solvent was removed under reduced pressure, the residue was neutralized by addition of 1 N HCl (300 mL), and the mixture was extracted with EtOAc (3 × 300 mL). The combined organic phase was repeatedly washed with water to remove the DMSO and then dried with Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography (*n*-hexane). The biaryl ether crystallized by addition of *n*-pentane/diethyl ether as a slightly yellow solid (30.43 g, 82%, ref.[39] 75–85%). M.p. 121–123 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.88 (s, 2 H, CH_2), 6.51 (d, J = 9.1 Hz, 2 H, 2′-H, 6′-H), 6.90 (d, J = 7.8 Hz, 1 H, 2-H), 7.01 (d, J = 7.7 Hz, 2 H, 2′′-H, 6′′-H), 7.14 (d, J = 7.5 Hz, 1 H, 7-H), 7.25 (t, J = 7.8 Hz, 2 H, 3′′-H, 5′′-H), 7.33 (t, J = 7.4 Hz, 1 H, 4′′-H), 7.43 (t, J = 7.8 Hz, 1 H, 3-H), 7.50 (t, J = 7.5 Hz, 1 H, 6-H), 7.52 (d, J = 8.2 Hz, 1 H, 4-H), 7.78 (d, J = 8.2 Hz, 1 H, 5-H), 7.89 (d, J = 9.1 Hz, 2 H, 3′-H, 5′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 71.0 (t, CH_2), 107.2 (d, C-7), 115.2 (d, C-2′, C-6′), 119.6 (s, C-8a), 119.8 (d, C-2), 119.7 (d, C-5′), 121.0 (d, C-5), 125.5 (d, C-4), 126.2 (d, C-2′, C-6′), 126.5 (d, C-3), 127.8 (d, C-6), 128.0, 128.2, 128.3, 128.8, 129.0 (d, C-2′′, C-3′′, C-4′′, C-5′′, C-6′′), 136.0 (s, C-4a), 137.6 (s, C-1′′), 141.3 (s, C-4′), 149.3 (s, C-1), 154.5 (s, C-8), 165.0 (s, C-1′) ppm.

1-(4′-Aminophenyloxy)-naphthalen-8-ol (14): 1-(Benzyloxy)-8-(4-nitrophenoxy)naphthalene (**13**; 18.60 g, 0.05 mol) was dissolved in dry ethanol (250 mL) and hydrogenated by stirring under an atmosphere of hydrogen at ambient pressure over 10% Pd/C (1.0 g) for 3 d. Care had to be taken to avoid the formation of a partially reduced 4-amino-8-benzyl ether (TLC monitoring; PE/EtOAc, 2:1). The suspension was filtered to afford amino phenol **14** as a slightly brown solid (8.16 g, 65%, ref.[39] 95%). M.p. 108–110 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.47 (br. s, 2 H, NH_2), 6.59 (d, J = 7.5 Hz, 1 H, 2-H), 6.75 (dd, J = 8.6, 2.7 Hz, 2 H, 3′-H, 5′-H), 6.96 (d, J = 7.5 Hz, 1 H, 7-H), 7.17 (dd, J = 8.6, 2.7 Hz, 2 H, 2′-H, 6′-H), 7.20 (t, J = 7.9 Hz, 2 H, 3-H, 6-H), 7.37 (m, 2 H, 4-H, 5-H), 9.2 (s, 1 H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.8 (d, C-2), 110.5 (d, C-7), 115.4 (s, C-8a), 116.2 (d, C-2′, C-6′), 119.0 (d, C-

3′, C-5′), 122.4 (d, C-4), 122.6 (d, C-5), 125.5 (d, C-3), 127.7 (d, C-6), 136.9 (s, C-4a), 144.2 (s, C-1′), 146.1 (s, C-1), 154.1 (s, C-4′), 156.4 (s, C-8) ppm.

Benzoquinone Acetal (10)

Oxidation with Active MnO_2 (Method A): A solution of 1-(4′-aminophenyloxy)-8-naphthol (**14**; 10.05 g, 0.04 mol) in dry toluene (100 mL) was treated with active manganese dioxide (17.40 g, 0.20 mol), and the mixture was stirred overnight at room temperature under an atmosphere of argon. The suspension was filtered, the toluene was removed at reduced pressure, and the residue was purified by silica gel chromatography to yield benzoquinone acetal **10** as faintly yellow crystals (7.50 g, 75%, ref.[39] 70–80%). M.p. 115 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.33 (d, J = 10.3 Hz, 2 H, 3-H, 5-H), 6.96 (d, J = 10.3 Hz, 2 H, 2-H, 6-H), 6.98 (dd, J = 8.0, 1.5 Hz, 2 H, 2′-H, 7′-H), 7.46 (dd, J = 8.0, 1.5 Hz, 2 H, 4′-H, 5′-H) 7.56 (t, J = 8.0 Hz, 2 H, 3′-H, 6′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 92.0 (s, C-1), 109.7 (d, C-2′, C-7′), 113.1 (s, C-4a′), 121.3 (d, C-4′, C-5′), 127.9 (d, C-3′, C-6′), 129.9 (d, C-3, C-5), 134.1 (s, C-8a′), 140.1 (d, C-2, C-6), 146.4 (d, C-1′, C-8′), 184.5 (s, C-4) ppm.

Oxidation of Bisphenol 9 with Silver Oxide (Method B): A similar oxidation of **9** with silver oxide afforded 64% of benzoquinone acetal **10**.

Oxidation with PIDA (Method C): The oxidation of **14** (1.00 g, 4.00 mmol) in dry dichloromethane (30 mL) with phenyliodine diacetate (PIDA; 1.93 g, 6.00 mmol) at room temperature under an atmosphere of argon afforded **10** (0.23 g, 23%) after chromatographic purification.

5-Methoxy-4a,5,8,8a-pentahydrospiro[naphthalene-1,2′-naphtho[1,8-*de*][1,3]dioxin]-4-one (15): A suspension of benzoquinone acetal **10** (2.50 g, 0.01 mol) in 1-methoxy-1,3-butadiene (4.20 g, 0.05 mmol) was stirred under an atmosphere of argon at room temperature for 4–5 d (TLC monitoring). After completion of the reaction, the excess amount of 1-methoxy-1,3-butadiene was evaporated under high vacuum, and the residue was filtered through a pad of silica gel to afford white crystals of Diels–Alder mono adduct **15** (3.17 g, 95%). M.p. 143–144 °C. IR (KBr): $\tilde{\nu}$ = 3418, 3059, 2977, 2923, 2819, 1694, 1634, 1607, 1585, 1520, 1416, 1378, 1275, 1183, 1117, 824, 758 cm^{-1}. UV (MeOH): λ (log ε) = 327 (3.55), 312 (3.68), 301 (3.78), 297 (3.77) nm. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.27 (m, 1 H, 8-H), 2.39 (m, 1 H, 8-H), 2.97 (m, 1 H, 8a-H), 3.46 (s, 3 H, OCH_3), 3.68 (m, 1 H, 4a-H), 4.13 (m, 1 H, 5-H), 6.19 (d, J = 11.0 Hz, 1 H, 6-H), 6.25 (m, 1 H, 7-H), 6.34 (d, J = 10.0 Hz, 1 H, 3-H), 6.79 (d, J = 10.0 Hz, 1 H, 2-H), 6.87 (dd, J = 10.0, 3.0 Hz, 2 H, 2′-H, 7′-H), 7.54 (t, J = 8.1 Hz, 2 H, 3′-H, 6′-H), 7.53 (d, J = 8.1 Hz, 2 H, 4′-H, 5′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.4 (t, C-8), 42.2 (d, C-8a), 45.3 (d, C-4a), 57.0 (q, OCH_3), 77.3 (s, C-5), 99.9 (s, C-1), 109.6 (d, C-7′), 110.1 (d, C-2′), 113.7 (s, C-8a′), 121.3 (d, C-5′), 121.5 (d, C-4′), 125.4 (d, C-3), 127.9 (d, C-3′, C-6′), 128.8 (d, C-7), 132.2 (d, C-6), 134.6 (s, C-4a′), 138.7 (d, C-2), 146.7 (s, C-8′), 147.5 (s, C-1′), 196.4 (s, C-4) ppm. MS (EI): m/z (%) = 334 (55) [M]$^+$, 319 (2), 302 (3), 263 (5), 247 (5), 197 (58), 196 (13), 159 (18), 115 (62), 105 (105), 71 (21), 57 (11), 28 (100). $C_{21}H_{18}O_4$ (334.371): calcd. C 75.37, H 5.42; found C 74.64, H 5.18.

5-Methoxyspiro[naphthalene-1,2′-naphtho[1,8-*de*][1,3]dioxin]-4-one (16): A solution of Diels–Alder adduct **15** (1.50 g, 4.49 mmol) in dry toluene (20 mL) was treated under an atmosphere of nitrogen with DDQ (1.52 g, 6.73 mmol). The reaction mixture was stirred for 24 h at 85 °C [TLC monitoring, dichloromethane (DCM)]. After cooling, the reaction mixture was filtered, the solvent was removed at reduced pressure, and the residue was purified by column chromatography over silica gel (DCM) to afford palmarumycin CP_1 methyl ether **16** (1.41 g, 95%). M.p. 203–204 °C (ref.[31] m.p. 204 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.99 (s, 3 H, OCH_3), 6.28 (d, J = 10.5 Hz, 1 H, 3-H), 6.85 (d, J = 10.5 Hz, 1 H, 2-H), 6.97 (d, J = 7.6, Hz, 2 H, 2′-H, 7′-H), 7.17 (d, J = 8.5 Hz, 1 H, 6-H), 7.46 (t, J = 7.5 Hz, 2 H, 3′-H, 6′-H), 7.56 (d, J = 8.4 Hz, 2 H, 4′-H, 5′-H), 7.59 (d, J = 7.7 Hz, 1 H, 8-H), 7.70 (t, J = 8.2 Hz, 1 H, 7-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 56.4 (q, OCH_3), 93.4 (s, C-1), 109.8 (d, C-2′, C-7′), 113.55 (d, C-8a′), 114.2 (s, C-6), 119.0 (s, C-4a), 120.2 (d, C-8), 121.2 (s, C-4′, C-5′), 127.6 (d, C-3′, C-6′), 132.2 (d, C-3), 134.2 (s, C-4a′), 134.9 (d, C-7), 135.2 (d, C-2), 141.1 (s, C-8a), 147.4 (s, C-1′, C-8′), 159.9 (s, C-5), 182.9 (s, C-4) ppm.

5-Hydroxyspiro[naphthalene-1,2′-naphtho[1,8-*de*][1,3]dioxin]-4-one, Palmarumycin CP_1 (4): A solution of methyl ether **16** (330 mg, 1.0 mmol) in dry DCM (5 mL) was treated dropwise at –78 °C under an atmosphere of nitrogen with a solution of BBr_3 (1.0 M in DCM, 1.91 mL). During the addition, the color of the solution turned from slightly yellow to red. The solution was warmed to –30 °C and water (15 mL) was added, and the mixture was stirred for 5 h. The mixture was extracted with DCM (3 × 15 mL), the organic phase was dried with $MgSO_4$, and the solvent was removed at reduced pressure to yield **4** (300 mg, 95%). M.p. 171–172 °C. The data of the synthetic product were identical to those of the natural product.[11,31]

CJ-12.371 Methyl Ether (17): A solution of **16** (102 mg, 0.31 mmol) in ethyl acetate (7.0 mL) was treated with Pd/C (10%, 30 mg), and the suspension was stirred under hydrogen (atmospheric pressure) for 12 h. The catalyst was filtered off, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography over silica gel (3.0 g) to afford **17**[8] methyl ether (83 mg, 81%) as a resin. IR (KBr): $\tilde{\nu}$ = 3534, 3053, 2929, 2836, 1765, 1615, 1589, 1460, 1413, 1377, 1258, 1062, 963, 824, 767 cm^{-1}. UV (MeOH): λ (log ε) = 327 (3.64), 313 (3.79), 300 (3.92), 286 (3.90) nm. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.39 (t, J = 8.0 Hz, 1 H, 2-H), 2.10 (t, J = 8.0 Hz, 1 H, 3-H), 3.07 (m, 1 H, 4-H), 5.10 (s, 1 H, 4-OH), 6.93 (d, J = 7.8 Hz, 1 H, 6-H), 7.48 (t, J = 7.8 Hz, 1 H, 7-H), 7.44 (d, J = 7.8 Hz, 1 H, 8-H), 7.03 (dd, J = 8.1, 1.5 Hz, 2 H, 2′-H, 7′-H), 7.56 (t, J = 8.1 Hz, 2 H, 3′-H, 6′-H), 7.50 (dd, J = 8.1, 1.5 Hz, 2 H, 4′-H, 5′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 100.46 (C-1), 26.78 (C-2), 26.27 (C-3), 63.15 (C-4), 129.91 (C-4a), 157.57 (C-5), 111.76 (C-6), 128.27 (C-7), 119.84 (C-8), 134.60 (C-8a), 148.44 (C-1′), 109.86 (C-2′), 127.89 (C-3′), 120.83 (C-4′), 136.63 (C-4a′), 126.76 (C-5′), 127.77 (C-6′), 109.67 (C-7′), 148.36 (C-8′), 114.04 (C-8a′) ppm. MS (EI): m/z (%) = 334 (42) [M]$^+$, 316 (100), 311 (45), 284 (21), 256 (8), 221 (35), 178 (18), 115 (31), 84 (78). HRMS (EI): calcd. for $C_{21}H_{18}O_4$ [M]$^+$ 334.1205; found 334.1204.

5-Hydroxyspiro[naphthalene-1,2′-naphtho[1,8-*de*][1,3]dioxin]-2,3-dihydro-4-one (18): A solution of **17** (75 mg, 0.22 mmol) in dry DCM (2.0 mL) was treated with pyridinium chlorochromate (119 mg, 0.55 mmol) at room temperature. The mixture was stirred until the starting material was consumed (TLC monitoring). The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography over silica gel (3.6 g; hexane/ethyl acetate, 95:5→8:2) to afford ketone **18** (palmarumycin CP_2 methyl ether; 64 mg, 86%) as yellow crystals. M.p 153–155 °C (ref.[31] m.p. 154–156 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.51 (t, J = 8.0 Hz, 1 H, 2-H), 2.81 (t, J = 8.0 Hz, 1 H, 2-H), 7.16 (dd, J = 8.0, 1.7 Hz, 1 H, 6-H), 7.68 (t, J = 8.0 Hz, 1 H, 7-H), 7.44 (dd, J = 8.0, 1.7 Hz, 1 H, 8-H), 6.98 (dd, J = 7.5, 2.0 Hz,

2 H, 2′-H, 7′-H), 7.64 (t, J = 7.5 Hz, 2 H, 3′-H, 6′-H), 7.54 (dd, J = 7.5, 2.0 Hz, 2 H, 4′-H, 5′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 99.27 (C-1), 25.82 (C-2), 29.84 (C-3), 195.81 (C-4), 143.41 (C-4a), 160.36 (C-5), 114.02 (C-6), 121.39 (C-7), 118.21 (C-8), 135.32 (C-8a), 147.96 (C-1′, 8′), 113.88 (C-8a′), 109.81 (C-2′, 7′), 127.93 (C-3′, 6′), 121.19 (C-4′, 5′), 134.60 (C-4a′) ppm.

Palmarumycin CP$_2$ (5): To a solution of **18** (25 mg, 0.074 mmol) in dry dichloromethane (2.0 mL) was added dropwise at –78 °C a solution of BBr_3 (1.0 M in DCM, 0.15 mL). The initially pale yellow solution turned red as the addition proceeded. The cooling bath was removed, and the mixture was warmed to –30 °C. The reaction mixture was quenched by addition of water (5.0 mL), and the mixture was stirred for 5 h at room temperature. The mixture was extracted with dichloromethane (3 × 10 mL). The combined organic phase was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography over silica gel (2.5 g; hexane/ethyl acetate, 98:2→90:10) to afford **5** (16 mg, 63%). M.p. 169–170 °C. The data of the synthetic material were identical to those of the natural product.[11,31]

Crystal Structure Determination of 5-Methoxy-4a,5,8,8a-pentahydrospiro[naphthalene-1,2′-naphtho[1,8-*de*][1,3]dioxin]-4-one (15):[42] $C_{21}H_{18}O_4$, M_r = 334.4, orthorhombic, space group $Pna2_1$, a = 13.5156(9) Å, b = 12.5095(8) Å, c = 9.6532(6) Å, V = 1632.1(2) Å^3, Z = 4, D_x = 1.361 g cm^{-3}, F(000) = 704, T = 120(2) K. Bruker-AXS SMART APEX CCD, graphite monochromator, λ(Mo-K_α) = 0.71073 Å, μ = 0.094 mm^{-1}, colorless crystal, size 0.22 × 0.18 × 0.14 mm, 12751 intensities collected $2.2 < \theta < 28.3°$, $-18 < h < 18$, $-16 < k < 13$, $-12 < l < 12$. Structure solved by direct methods,[43] full-matrix least-squares refinement[43] with 4031 independent reflections based on F^2 and 227 parameters, all but H atoms refined anisotropically, H atoms from difference Fourier maps refined with riding model on idealized positions with U = 1.5 U_{iso}(methyl-C) or 1.2 U_{iso}(C). Compound **15** crystallizes in the noncentrosymmetric space group $Pna2_1$; however, in the absence of significant anomalous scattering effects, the Flack[44] parameter is essentially meaningless. Accordingly, Friedel pairs were merged. Refinement converged at $R_1[I > 2\sigma(I)]$ = 0.048, wR_2(all data) = 0.110, S = 1.02, max(δ/σ) < 0.001, min/max height in final ΔF map –0.24/0.24 e Å^{-3}. Figure 1 shows the molecular structure.

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