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Synthesis and biological evaluation of deoxypreussomerin A and palmarumycin CP_1 and related naphthoquinone spiroketals

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Abstract—Oxidative cyclization of bis-hydroxynaphthyl ethers allows concise total syntheses of palmarumycin CP_1 and deoxypreussomerin A in 8-9 steps and 15–35% overall yield from 5-hydroxy-8-methoxy-1-tetralone (**8**). Polymer-bound triphenyl phosphine was found to be a superior reagent for the rapid preparation of a small library of palmarumycin analogs. Preliminary biological evaluation of naphthoquinone spiroketals against MCF-7 and MDA-MB-231 human breast cancer cells revealed several low-micromolar growth inhibitors.

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1. Introduction

The novel antifungal metabolites preussomerins A–F were identified in 1990 by Gloer and coworkers during the course of an investigation of chemical agents involved in interspecies competition among coprophilous (dung-colonizing) fungi (Fig. 1).[1] In addition to these early reports from *Preussia isomera* Cain samples, preussomerins were later also discovered in the endophytic fungus *Harmonerna dematioides* by Polishook and coworkers.[2] Another report of an epoxy naphthalenediol spiroketal compound, bipendensin, was published in 1990 by Connolly.[3] The latter natural product was isolated in very small amounts from wood samples of the African tree *Afzelia bipendensis*. A compound having the same gross structure as bipendensin was isolated in 1994 from an unidentified *Coniothyium* fungus collected from forest soil on West Borneo, and was named palmarumycin C_{11} by Krohn and coworkers.[4]

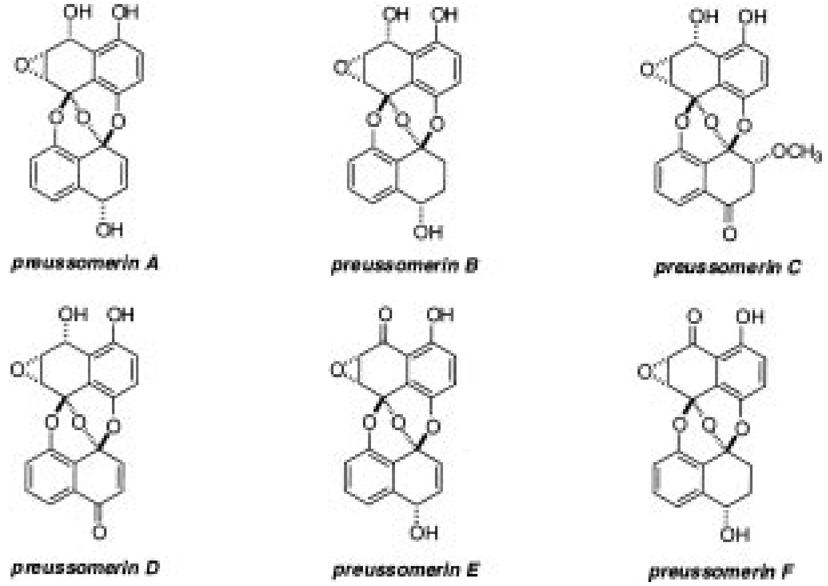

Figure 1. Preussomerins isolated from *Preussia isomera*.

Keywords: spirocyclization; naphthoquinone; palmarumycin; deoxypreussomerin; total synthesis; polymer-bound reagent; iodobenzenediacetate; phenol oxidation; cytotoxicity; breast cancer cell line.

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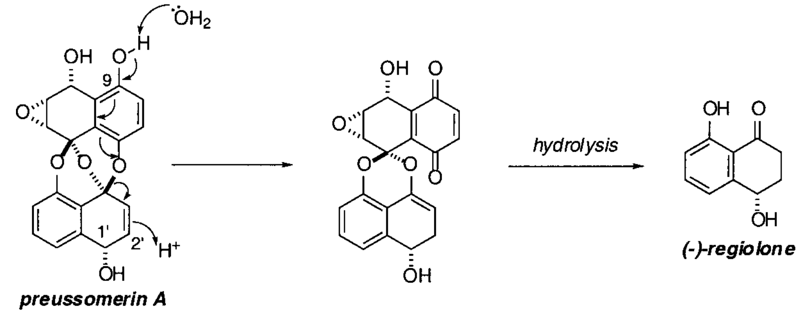


Figure 2. Acidic degradation of preussomerin A.

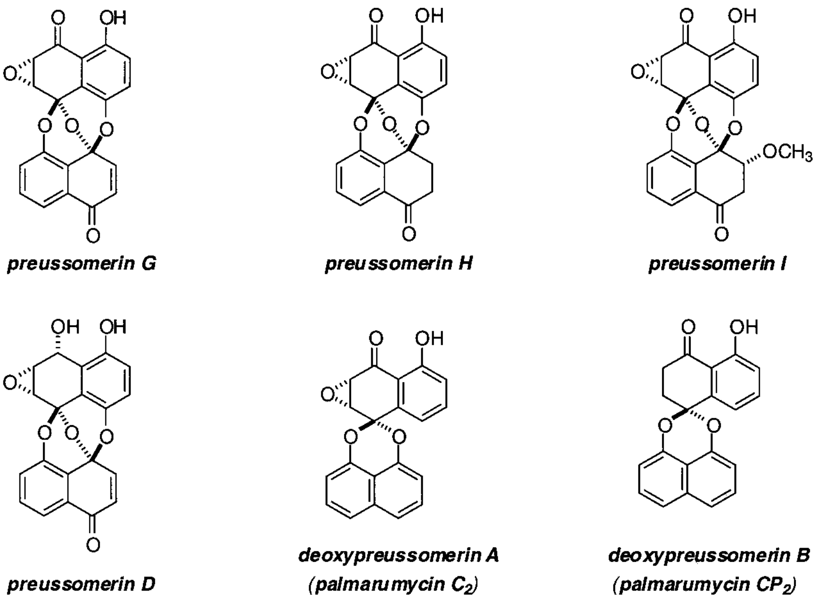
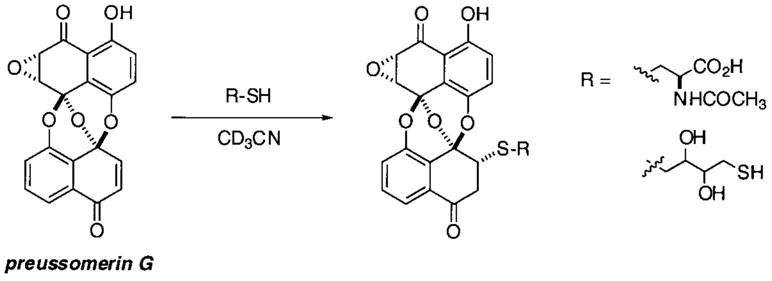


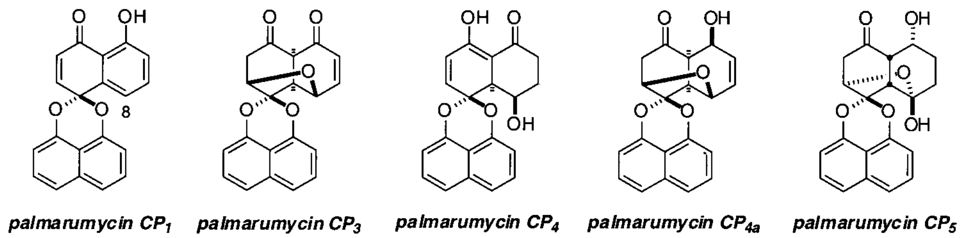
Figure 3. Preussomerins and deoxypreussomerins isolated from a coelomycetes fungus.

The absolute stereochemistry of preussomerins was assigned as shown in Fig. 1 on the basis of the isolation of known (−)-regiolone as a degradation product.[1b] Although the ketal linkages were resistant to acid hydrolysis at room temperature, vigorous cleavage conditions (6 M HCl/acetone, 1:1, 100°C, 12 h) afforded (−)-regiolone[5] as the major product. Conservation of the stereochemistry at the C-1′ position could be rationalized by a mechanism involving protonation at the C-2′ position during the decomposition process followed by loss of the 9-OH proton and formation of an enol ether (Fig. 2). Hydrolysis of the remaining ketal linkage would then account for the formation of regiolone without loss of stereochemical integrity at the hydroxylated benzylic carbon.

Even though preussomerin A exhibited only low-micromolar cytotoxicity toward a mammalian cell line,[1b] a Merck group reported that preussomerins and deoxypreussomerins showed promising effects as novel ras farnesyl-protein transferase (FTPase) inhibitors.[6] Preussomerin G–I and deoxypreussomerin A and B, accompanied by preussomerin D, were isolated from the fermentation broth of an unidentified coelomycetes fungus collected in Bajo Verde, Argentina (Fig. 3). IC_{50}'s of FTPase inhibitory activities of preussomerins, deoxypreussomerins and derivatives of preussomerin G range between 1–20 μM. Preussomerin G and preussomerin D were the most active. Interestingly, deoxypreussomerins, which possibly are biosynthetic precursors of preussomerins,[6] had equal or

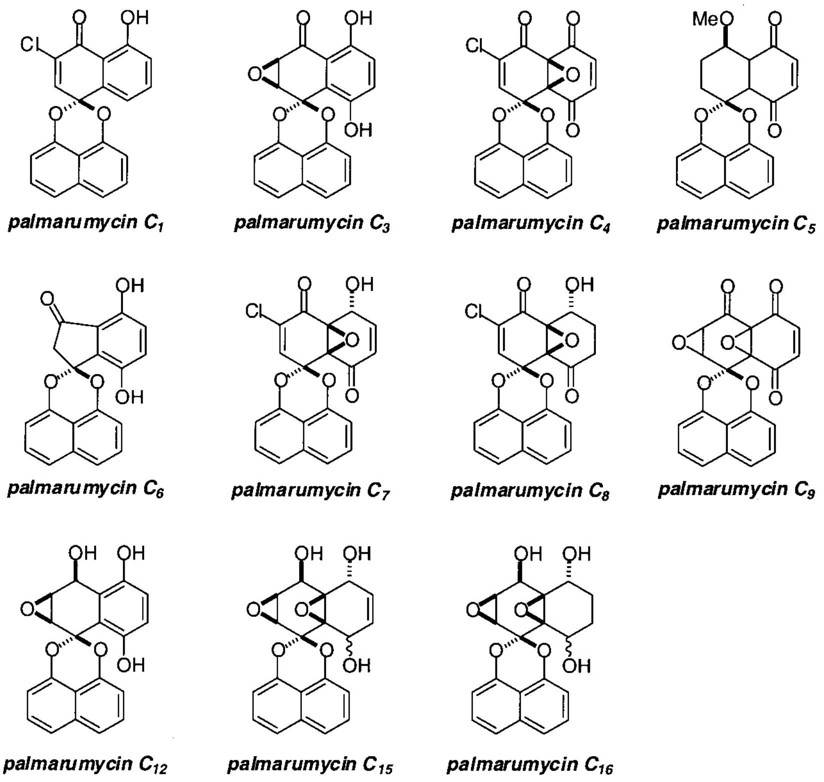


Scheme 1.



palmarumycin CP_1 palmarumycin CP_3 palmarumycin CP_4 palmarumycin CP_{4a} palmarumycin CP_5

Figure 4. Palmarumycins from *Coniothyrium palmarium*.



palmarumycin C_1 palmarumycin C_3 palmarumycin C_4 palmarumycin C_5

palmarumycin C_6 palmarumycin C_7 palmarumycin C_8 palmarumycin C_9

palmarumycin C_{12} palmarumycin C_{15} palmarumycin C_{16}

Figure 5. Palmarumycins from an unidentified *Coniothyrium* species (relative configurations are shown).

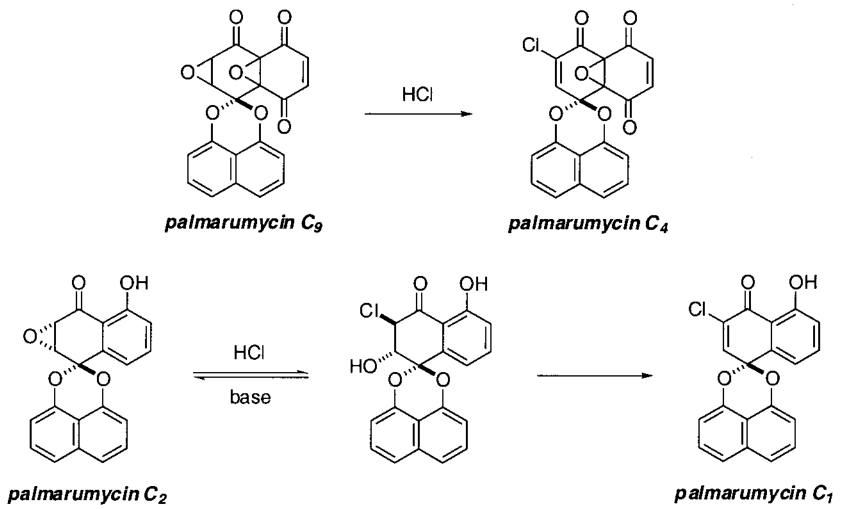
better activities than preussomerins H and I. Deoxypreussomerin A and B were also reported independently as antifungal agents and named palmarumycin C_2 and CP_2, respectively.[4,7]

Preussomerin G reacted with strong nucleophiles in a highly stereospecific Michael fashion to give a quantitative yield of the C-3′ adduct (Scheme 1). Presumably, steric hindrance makes the top face of preussomerin G inaccessible to nucleophiles, and thus Michael addition takes place exclusively from the more accessible α-face.

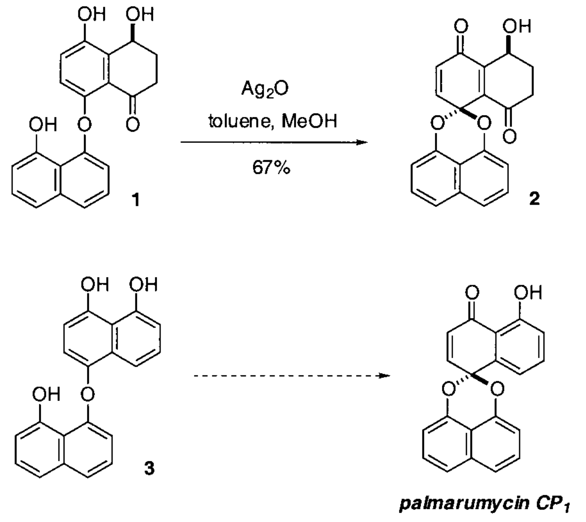
Additional naphthalenediol spiroketals of the palmarumycin family have been reported by Krohn and coworkers.[4,7,8] These metabolites were produced by two strains of the endophytic fungi *Coniothyrium palmarium* and an unidentified *Coniothyrium* species (Figs. 4 and 5).

Palmarumycin CP_3, CP_4, C_3, C_{10} and C_{12} show high antifungal activity. Apparently, the introduction of an oxygen function into the 8-position significantly increases the antifungal effect. The chloroepoxide palmarumycin C_4 and palmarumycin C_9, isolated as an isomeric mixture of epoxides, completely inhibited germination and growth of garden cress. In most palmarumycins, only the relative configuration was elucidated, except for palmarumycin CP_{4a} and CP_5. The absolute configurations of the latter compounds were elucidated by CD calculations. After computation of the CD spectra of six low energy conformers, Boltzmann-weighted addition and comparison of the resulting averaged spectrum with the experimental data allowed the assignment of the absolute configuration of palmarumycin CP_{4a} and CP_5 as shown in Fig. 4.[8]

Krohn and coworkers proposed a biosynthesis of palmarumycin CP_1 based on a 1,8-dihydroxynaphthalene or a suitable phenolic derivative precursor.[4,9] According to their hypothesis, coupling could occur via a phenol oxidation as often encountered in polyketide biosynthesis,[10] and the chlorinated palmarumycins could be derived from addition of chloride ions to epoxides. In order to probe this mechanism, palmarumycin CP_2 and palmarumycin C_9 were treated with methanolic hydrochloric acid (Scheme 2). As expected, formation of chlorinated palmarumycin C_4 from



Scheme 2.



Scheme 3.

palmarumycin C_9 could be detected by TLC. For the reaction of palmarumycin C_2, an intermediate chlorohydrin was identified as the major isomer. This chlorohydrin slowly decomposed to palmarumycin C_1 upon standing in chloroform solution. Palmarumycin C_2 was recovered upon treatment with base. These experiments established a possible pathway to the chlorinated palmarumycins. They also highlighted the unexpected stability of the naphthalenediol spiroketal that was not even affected by heating in acetic acid at 100°C.[4]

Interestingly, Krohn and coworkers isolated the open chain compound **1** from *Coniothyrium palmarum*.[11] This isolation offered the chance to probe the biosynthetic hypothesis involving phenol oxidation. Upon exposure to silver(II) oxide, the binaphthyl ether **1** cyclized to give quinone ketal **2** (Scheme 3). However, **2** could not be detected in the fermentation broth of *Coniothyrium palmarum*. It is possible that a total synthesis of palmarumycins based on the phenolic oxidation of binaphthyl ethers could be

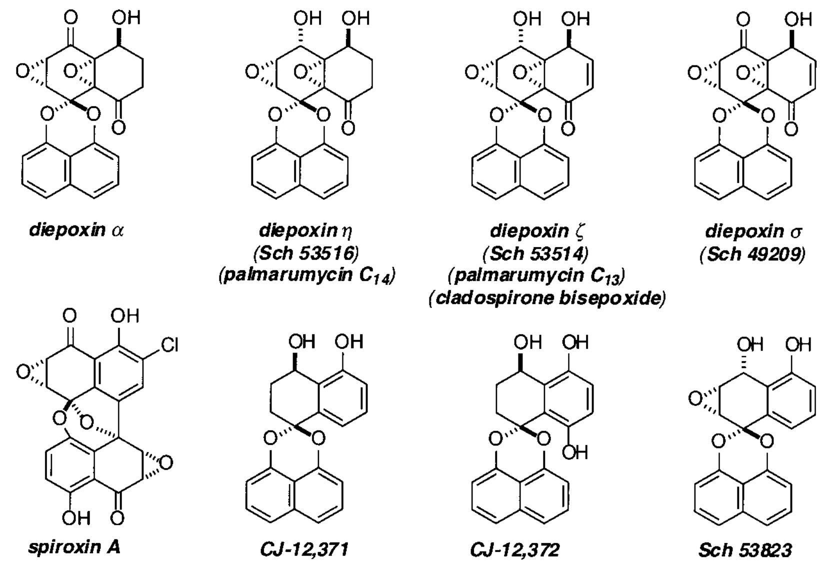
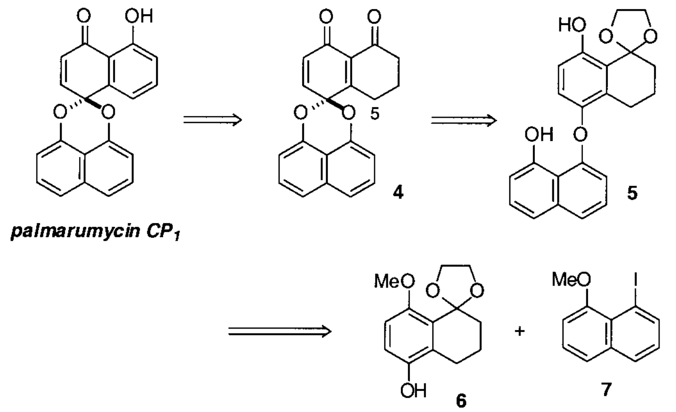
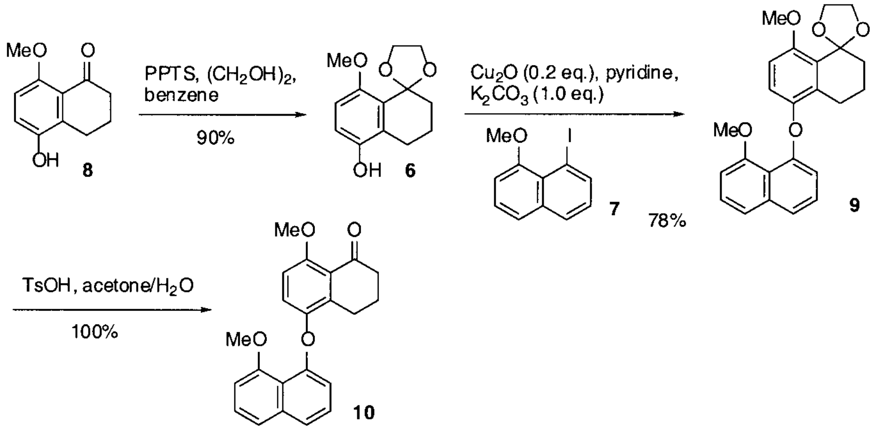


Figure 6. Representative structurally related fungal metabolites.



Scheme 4.



Scheme 5.

achieved as shown for **3**; however, no further studies along these lines have been reported. Taylor and coworkers also investigated a biomimetic cyclization approach with little success.[12]

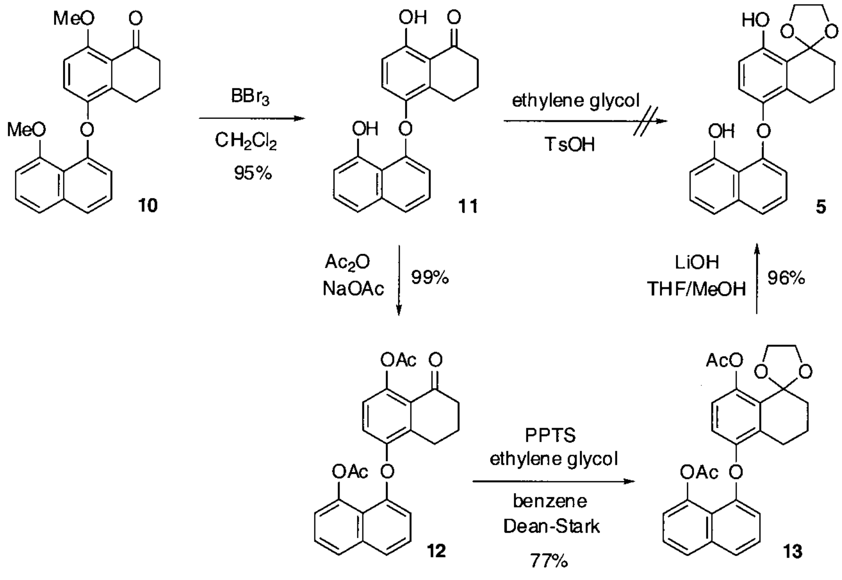
Deoxypreussomerins and palmarumycins are structurally closely related to the more recently isolated diepoxins,[13] CJ-12,371 and CJ-12,372,[14] and spiroxins[15] (Fig. 6).[16] Antimicrobial, antifungal, and some anticancer activities were identified for diepoxins and spiroxins. A Pfizer research group isolated the novel fungal metabolites CJ-12,371 and CJ-12,372 from a fermentation broth of an unidentified fungus N983-46. These compounds showed DNA gyrase inhibitory activity. The phospholipase D inhibitor Sch 53823 has the same gross structure as palmarumycin C_{11}, however, the melting point and optical rotation are different, suggesting that palmarumycin C_{11} and Sch 53823 are stereoisomers.[16b]

The combination of attractive biological activities and novel structural features in the spirobisnaphthalene family of natural products has attracted considerable interest from the synthetic organic community. In addition to pioneering total syntheses of palmarumycin CP_1 and deoxypreussomerin A,[12,17–19] innovative approaches toward diepoxin σ,[20] preussomerins G and I,[21] palmarumycin CP_2,[18,19] palmarumycin C_{11},[18] and CJ-12,371[18,19] have been reported since 1997.

In the course of our approaches toward the total synthesis of diepoxin σ,[20,22] we also devised a potential synthetic strategy toward palmarumycin CP_1 and deoxypreussomerin A (Scheme 4).[17] In a preliminary retrosynthetic analysis, naphthalenediol spiroketal **4** was derived from binaphthyl ether **5**, and dehydrogenation at C(5) and C(6) in **4** should be facilitated by the presence of the enone moiety. Compound **5** would be easily prepared by an Ullmann ether coupling reaction with 1-iodo-8-methoxynaphthalene (**7**)[23] and the tetraline derivative **6**. In the present work, we report our investigations along these lines and the realization of concise synthetic routes toward the natural products as well as a series of analogs for biological testing.

2. Results and discussion

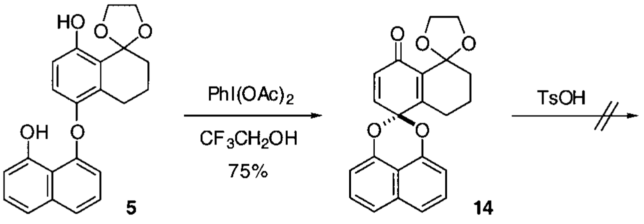
5-Hydroxy-8-methoxy-1-tetralone (**8**, Scheme 5) was prepared by a modified literature procedure.[22,24] Attempts for an Ullmann ether coupling between **8** and 8-iodo-1-methoxynaphthalene (**7**) failed, quite likely due to the deactivating effect of the tetralone carbonyl group. Coupling with ketal **6** was more successful and resulted in a 78% yield of naphthyl ether **9** which was further converted to ketone **10**. While we failed to demethylate ketal **9** with NaSEt in DMF or with BBr_3, demethylation of ketone **10** using BBr_3 smoothly afforded compound **11** in 95% yield. The presence of a ketone function in **11** was likely to retard



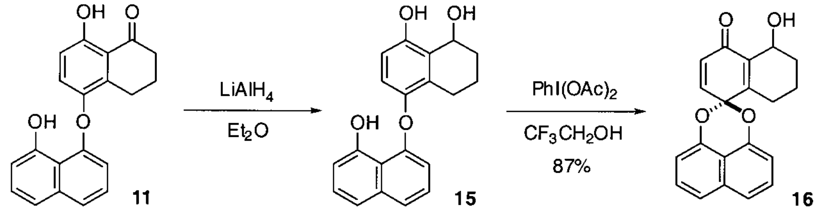
Scheme 6.

the subsequent oxidative cyclization which involves a very electron deficient transition state. Since the ketone function in **11** was unreactive to acetalization conditions, the phenolic hydroxyl groups were first acetylated, and ketal **13** was subsequently saponified to afford the oxidative cyclization precursor **5** in good overall yield (Scheme 6).

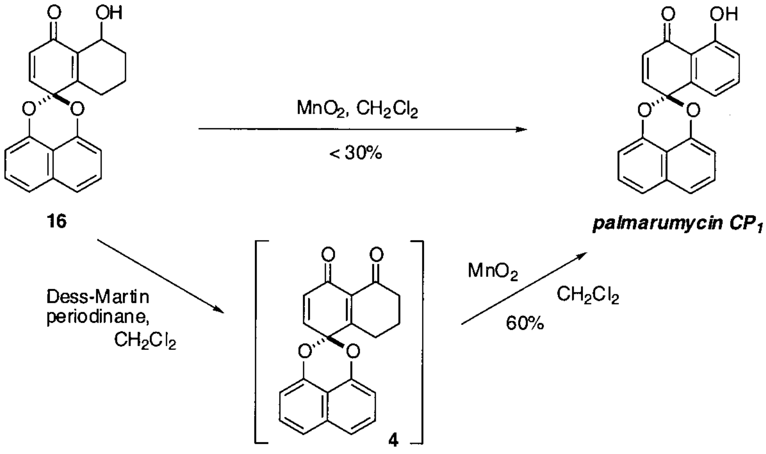
Oxidative cyclization of ketal **5** with PhI(OAc)$_2$ in trifluoroethanol afforded bisketal **14** in 75% yield (Scheme 7).



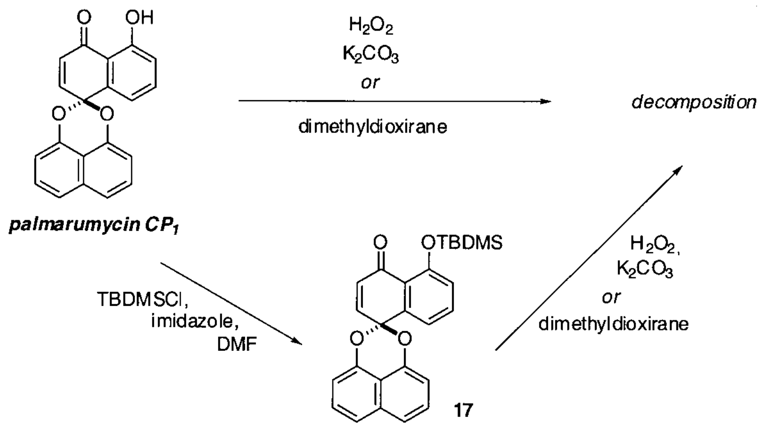
Scheme 7.



Scheme 8.



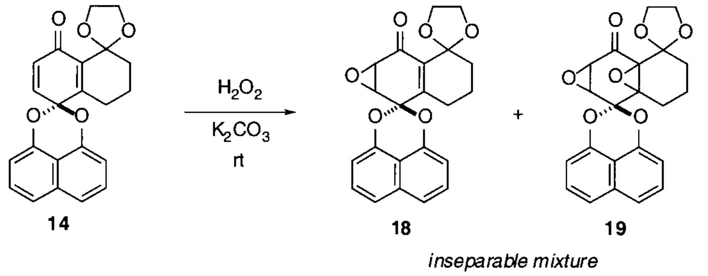
Scheme 9.



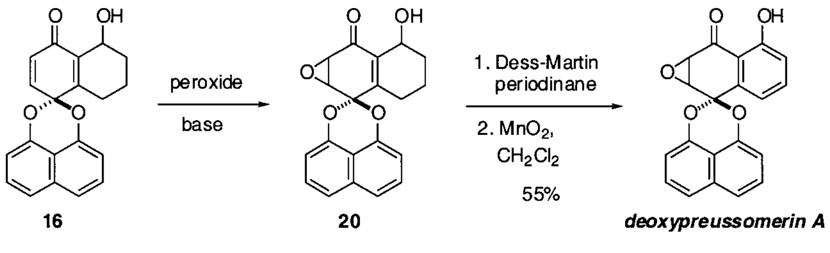
Scheme 10.

Unfortunately, deprotection of **14** under acidic conditions led to complex mixtures.

Diol **11** was quantitatively reduced to triol **15**, which was oxidatively cyclized using $PhI(OAc)_2$ in trifluoroethanol to afford naphthalenediol spiroketal **16** in 87% yield (Scheme 8). Further oxidation of the alcohol function of **16** was attempted with PCC and $BaMnO_4$ under buffered conditions but failed to provide the desired ketone in acceptable yields. In contrast, when **16** was treated with activated MnO_2 at room temperature, a clean conversion to the natural product palmarumycin CP_1 was effected (Scheme 9). For complete conversion of **16** to palmarumycin CP_1, a large excess (more than 50 equiv.) of MnO_2 was required, and a considerable amount of product remained adsorbed on MnO_2 and could not be recovered. When the reaction was performed in dry benzene at reflux, the amount of MnO_2 required for the complete conversion of **16** was decreased to ~10 equiv., but the resulting palmarumycin CP_1 was contaminated with a inseparable byproduct. We therefore resorted to a two-step protocol. Oxidation of **16** with Dess–Martin periodinane, purification of the intermediate ketone by column chromatography on SiO_2, and treatment with 10 equiv. of MnO_2 in dry methylene chloride for 2 d at room temperature

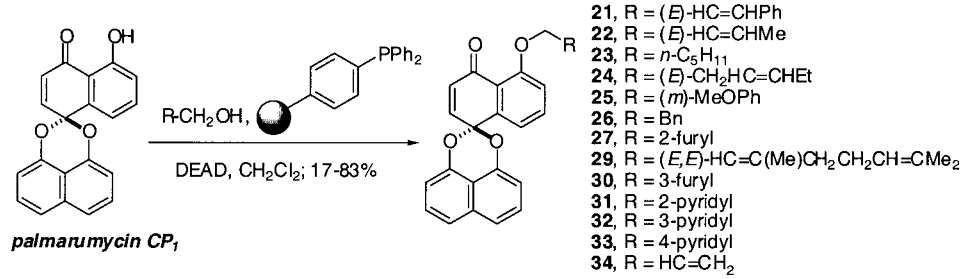


Scheme 11.

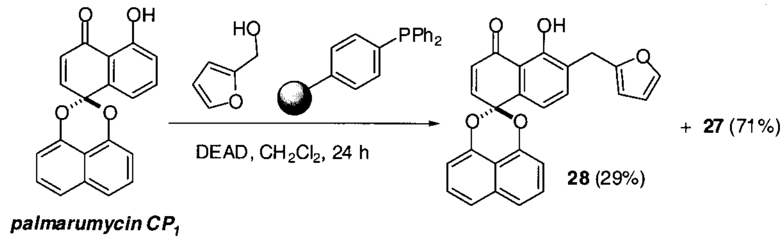


Peroxide	Base	Temperature	Yield of **20**
Hydrogen peroxide	K_2CO_3	rt	25%
t-Butyl hydroperoxide	NaOH	0 °C	31%
Cumene hydroperoxide	NaOH	0 °C	40%
Cumene hydroperoxide	NaH	0 °C	45%
Cumene hydroperoxide	NaH	-20 °C	47%

Scheme 12.



Scheme 13.



Scheme 14.

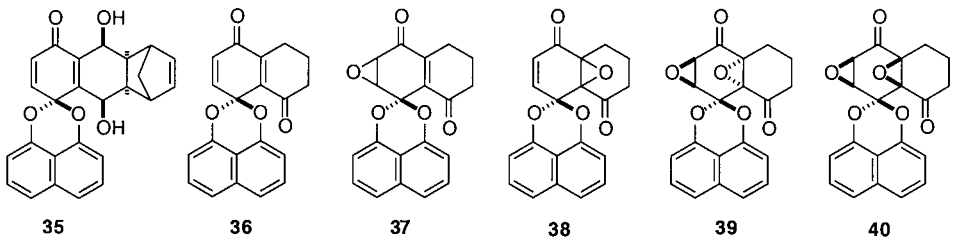


Figure 7. Deoxypreussomerin A and diepoxin σ analogs.

afford the target molecule in 60% yield. Palmarumycin CP_1 was thus obtained in 35% overall yield in 8 steps from the known tetralone **8**.

In consideration of the close structural similarity between palmarumycin CP_1 and the farnesyl-protein transferase inhibitor deoxypreussomerin A, an epoxidation reaction of palmarumycin CP_1 was attempted. However, treatment with hydrogen peroxide anion led to decomposition instead of epoxidation, and a mild epoxidizing agent, dimethyldioxirane also provided only decomposed products. Even after protection of the phenol function of palmarumycin CP_1 as the TBDMS ether, no synthetically useful epoxidation could be realized (Scheme 10). Therefore, we had to resort to earlier, more extensively protected synthetic intermediates.

When compound **14** was treated with excess hydrogen peroxide anion, monitoring of the reaction progress was difficult due to the overlap of products with the starting material **14** on TLC. The reaction mixture was thus quenched before complete consumption of **14**. ^1H NMR analysis of the crude product showed that mono- and diepoxides were formed in a ratio of about 1:1 with ~10% remaining starting material (Scheme 11). This result demonstrated that a regioselective epoxidation of the disubstituted double bond of **14** in the presence of the internal tetrasubstituted double bond was unlikely to succeed.

In contrast, treatment of allylic alcohol **16** with hydrogen peroxide anion resulted in the isolation of the desired monoepoxide **20** in 25% yield (Scheme 12). The relative configuration of the epoxide and the hydroxyl group was not

Table 1. IC_{50} values [μM] in 2 cancer cell lines

Compound	MCF-7	MDA-MB-231
21	7.6	3.6
22	5.5	1.4
23	13.4	13.6
24	43.4	9.2
25	2.3	2.7
26	3.9	4.6
27	1.1	2.5
28	2	6.5
29	4.6	2
30	2	2
31	2	2.8
32	1.5	1.4
33	8	7.3
34	2	2.7
Diepoxin σ	1.5	2
Palmarumycin CP_1	0.9	2.4
35	1.3	2.1
36	3.8	6.4
37	4.6	23
38	1.3	3.4
39	4.6	8.2
40	2.8	2.9

determined. Peroxides and bases were screened to optimize the epoxidation reaction. When cumene hydroperoxide and NaH were used at −20°C, the epoxidation yield increased to 47%. The two step oxidation protocol developed for the synthesis of palmarumycin CP_1 converted epoxy alcohol **20** to the desired natural product in 55% yield. (±)-Deoxypreussomerin A was thus synthesized in 15% overall yield and 9 steps from the known **8**.

The successful development of efficient synthetic strategies for the preparation of palmarumycin CP_1 and deoxypreussomerin A allowed us to prepare analogs and investigate the biological SAR of this class of compounds in more detail. A small library of palmarumycin analogs was obtained by Mitsunobu reaction of the natural product using polystyrene-bound triphenylphosphine (Scheme 13). A total of 13 alcohols were used for the coupling reaction, and yields and ease of purification were greatly improved by the use of the polymer-bound reagent. In the treatment of palmarumycin CP_1 with 2-furyl methanol, the ether product **27** was accompanied by the C-alkylated phenol **28** (Scheme 14). All other reactions produced a single isomer. In addition to these palmarumycin analogs, several diepoxin σ derivatives[20,22] were subjected to biological testing (Fig. 7).

Two widely used human breast cancer cell lines were evaluated for their sensitivity to the cytotoxic effects of the naphthoquinone spiroketals. MCF-7 cells were originally derived from an adenocarcinoma of the breast and retain several characteristics of differentiated mammary epithelium including the ability to process estradiol via cytoplasmic estrogen receptors. MCF-7 cells express the tumor suppressor gene product p53, which is required for the programmed cell death or apoptosis caused by many agents.[25] MDA-MB-231 cells, which were also derived from an adenocarcinoma of the breast, are less differentiated than the MCF-7 cells and fail to express functional p53 or estrogen receptors. This class of tumor cells are important targets for new therapies, because loss of estrogen receptor expression is associated with poor patient prognosis.[26] All cells were tested for 72 h with six concentrations of compounds ranging from 0.1 to 30 μM to determine the concentration required for 50% growth inhibition (IC_{50}). We extrapolated to determine the IC_{50} for compounds with little cytotoxicity at 30 μM, the highest concentration tested. As indicated in Table 1, 45% of the compounds (10/22) had an $IC_{50}<3$ μM in both cell types. Half of the compounds showed no selectivity to either human tumor cell type, while 32% of the compounds were more cytotoxic to MCF-7 compared with MDA-MB-231 cells. This included **37**, which was 5-fold more cytotoxic to MCF-7 cells (IC_{50} 4.6 vs 23 μM). The enhanced sensitivity of MCF-7 to these compounds may be due to the expression of p53 in these cells. The assay used in our studies, however, did not specifically measure apoptosis and this could be examined in the future. Studies to be published elsewhere indicate that at least one compound, **27**, can arrest mammalian cells in the G2/M phase of the cell cycle. The five fold enhanced sensitivity of MDA-MB-231 cells to **24** compared to MCF-7 cells is of interest, because the MDA-MB-231 cells lack both functional estrogen receptors and p53.

3. Conclusions

Oxidative cyclization of bis-hydroxynaphthyl ethers with hypervalent iodine reagents allows a ready access to structurally novel naphthoquinone spiroketal natural products. We have achieved concise total syntheses of palmarumycin CP_1 and deoxypreussomerin A in 8-9 steps and 15–35% overall yield from 5-hydroxy-8-methoxy-1-tetralone (**8**). Polymer-bound triphenylphosphine was found to be a superior reagent for the rapid preparation of a small library of palmarumycin analogs. Preliminary biological evaluation of 22 naphthoquinone spiroketals against two human breast cancer cell lines revealed several potent and selective growth inhibitors. In view of this favorable profile, further biological studies of this series are continuing.

4. Experimental

4.1. General

All moisture-sensitive reactions were performed under an atmosphere of N_2 or Ar and all glassware was dried in an oven at 140°C prior to use. THF and Et_2O were dried by distillation over Na/benzophenone under a nitrogen atmosphere. Dry CH_2Cl_2 was obtained by distillation from CaH_2. Dry DMF was obtained by distillation from alumina under reduced pressure. Dry CF_3CH_2OH was obtained by distillation from $CaSO_4$. Unless otherwise noted, solvents or reagents were used without further purification. NMR spectra were recorded at either 300 MHz/75 MHz ($^1H/^{13}C$ NMR) or 500 MHz/125 MHz ($^1H/^{13}C$ NMR) in $CDCl_3$ unless stated otherwise.

4.2. Antiproliferative Assay

The antiproliferative actions of our compounds were examined using a colorimetric assay described previously[27] with two human breast cancer cell lines: the p53 replete, estrogen-receptor positive MCF-7 and the p53 deficient, estrogen-receptor negative MDA-MB-231 cells (American Type Culture Collection, Manassas, VA). Briefly, cells were seeded (6000/well) in 96-well plates that contained Eagle's minimum essential medium (MCF-7) or RPMI-1640 medium (MDA-MB-231) and 10% fetal bovine serum and placed in a humidified 37°C incubator maintained at 5% CO_2. Cells were allowed to attach overnight and treated with vehicle or compounds (0.1–30 μM) for 72 h. The medium was then replaced with serum free medium containing 0.1% of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide. Plates were incubated for 3 h in the dark and the total cell number was calculated by colorimetric determination at 540 nm of the formazane metabolic product as previously described.[27]

4.2.1. 5-Hydroxy-8-methoxy-1,2,3,4-tetrahydronaphthalene-1-spiro-2′-dioxolane (6). To a solution of **8** (4.8 g, 25 mmol) and ethylene glycol (3.1 g, 50 mmol) in benzene (700 mL) was added pyridinium *p*-toluenesulfonate (PPTs) (0.3 g). The reaction mixture was heated at reflux for 30 h in a flask equipped with a Dean–Stark apparatus, washed with 5% $NaHCO_3$ solution (2×200 mL) and brine (300 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography on

SiO_2 (hexanes/EtOAc, 2:1) gave 5.32 g (90%) of **6** as a solid: mp 139–140°C; IR (heat) 3359, 2928, 1583, 1468, 1327, 1244, 1159, 1118, 1064, 1008, 945, 924, 864, 794, 716 cm^{-1}; ^{1}H NMR δ 6.55 (d, 1H, J=8.8 Hz), 6.54 (d, 1H, J=8.8 Hz), 5.42 (s, 1H, OH), 4.25 (t, 2H, J=6.6 Hz), 4.07 (t, 2H, J=6.6 Hz), 3.75 (s, 3H), 2.57 (t, 2H, J=6.0 Hz), 1.93–1.80 (m, 4H); ^{13}C NMR δ 152.6, 146.9, 128.3, 125.8, 115.2, 110.7, 108.1, 65.5, 56.6, 35.9, 24.0, 20.1; MS (EI) *m/z* (rel intensity) 236 (M^+, 94), 208 (100), 193 (19), 175 (11), 164 (19), 149 (11), 134 (20), 121 (10), 106 (10), 99 (20), 77 (10), 65 (9), 55 (13); HRMS (EI) calcd for $C_{13}H_{16}O_4$ 236.1049, found 236.1052.

4.2.2. 8-Methoxy-5-(8′-methoxynaphthalene-1′-yloxy)-3,4-dihydro-2*H*-naphthalen-1-one (10). To a solution of **6** (4.72 g, 0.02 mol) and **7** (8.52 g, 0.03 mol) in degassed pyridine (150 mL) were added K_2CO_3 (2.76 g, 0.02 mol) and Cu_2O (286 mg, 0.002 mol). This reaction mixture was heated at reflux for 12 h under a nitrogen atmosphere. After addition of additional Cu_2O (286 mg, 0.002 mol) to the solution, heating was continued for 12 h. Pyridine was removed under reduced pressure and the residue was redissolved in EtOAc (300 mL). It was washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 2:1) gave 6.14 g (78%) of **9** as an oil. This oil was treated with TsOH (100 mg) in a mixture of acetone/water (7:1, 50 mL) for 7 h at room temperature. The reaction mixture was concentrated in vacuo and the residue was diluted with EtOAc (300 mL), washed with water (2×100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 1:1) gave 5.44 g (100%) of **10** as a colorless solid: mp 152–153°C; IR(neat) 2952, 1696, 1581, 1484, 1387, 1272, 1245, 1183, 1095, 980, 838, 821, 759 cm^{-1}; ^{1}H NMR δ 7.59 (dd, 1H, J=8.2, 0.8 Hz), 7.45 (dd, 1H, J=8.2, 1.0 Hz), 7.37 (q, 2H, J=7.9 Hz), 6.87 (dd, 1H, J=7.6, 0.8 Hz), 6.81 (dd, 1H, J=7.6, 0.8 Hz), 6.72 (d, 1H, J=8.9 Hz), 6.67 (d, 1H, J=9.1 Hz), 3.84 (s, 3H), 3.74 (s, 3H), 3.05 (t, 2H, J=6.2 Hz), 2.67 (t, 2H, J=6.3 Hz), 2.11 (p, 2H, J=6.4 Hz); ^{13}C NMR δ 197.9, 156.2, 155.4, 152.7, 149.3, 137.6, 136.4, 126.7, 126.4, 124.1, 123.1, 121.7, 120.7, 118.8, 115.9, 110.1, 106.1, 56.3, 56.0, 40.9, 24.1, 22.5; MS (EI) *m/z* (rel intensity) 348 (M+, 100), 319 (7), 305 (10), 291 (14), 261 (8), 218 (7), 189 (12), 174 (24) 158 (45), 127 (34), 115 (29), 101 (10), 77 (15), 63 (8); HRMS (EI) calcd for $C_{22}H_{20}O_4$ 348.1361, found 348.1361.

4.2.3. 8-Hydroxy-5-(8′-hydroxynaphthalen-1′-yloxy)-3,4-dihydro-2*H*-naphthalen-1-one (11). To a solution of **10** (3.92 g, 11.3 mmol) in CH_2Cl_2 (120 mL) was added a 1 M solution of BBr_3 in CH_2Cl_2 (40 mL, 40 mmol) at −78°C. The reaction mixture was warmed to room temperature, stirred for 12 h, poured into ice water (200 g) and extracted with CH_2Cl_2 (2×300 mL). The combined organic layers were washed with brine (200 mL), dried (Na_2SO_4) and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 8:1) gave 3.44 g (95%) of **11** as a colorless solid: mp 165–166°C; IR (neat) 3403, 2947, 1624, 1449, 1387, 1343, 1289, 1213, 1167, 1024, 808, 749 cm^{-1}; ^{1}H NMR δ 12.46 (s, 1H, OH), 9.02 (s, 1H, OH), 7.50–7.32 (m, 4H), 7.18 (t, 1H, J=8.0 Hz), 6.98 (dd, 1H, J=7.2, 1.1 Hz), 6.93 (d, 1H, J=8.9 Hz), 6.40 (d, 1H, J=7.7 Hz), 2.85 (t, 2H, J=6.0 Hz), 2.70 (t, 2H, J=6.3 Hz), 2.06 (p, 2H, J=6.4 Hz); ^{13}C NMR δ 204.7, 161.1, 155.4, 154.0, 141.8, 137.2, 137.1, 131.1, 128.1, 125.5, 123.1, 119.3, 117.4, 117.1, 114.9, 111.0, 107.4, 38.7, 23.6, 22.1; MS (EI) *m/z* (rel intensity) 320 (M^+, 100), 287 (6), 263 (10), 247 (7), 177 (9), 159 (25), 144 (38), 131 (29), 115 (34), 103 (15), 89 (10), 77 (23), 65 (14); HRMS (EI) calcd for $C_{20}H_{16}O_4$ 320.1049, found 320.1044.

4.2.4. Acetic acid 8-(4′-acetoxy-5′-oxo-5′,6′,7′,8′-tetrahydronaphthalen-1′-yloxy)-naphthalen-1-yl ester (12). To a solution of **11** (487 mg, 1.52 mmol) in acetic anhydride (2 mL) was added sodium acetate (100 mg). The reaction mixture was heated to 95°C, stirred for 4 h and cooled to room temperature. The mixture was poured into ice water (100 g), stirred for 1 h and extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 2:1) gave 607 mg (99%) of **12** as an oil: IR (neat) 3059, 2951, 1765, 1686, 1601, 1573, 1460, 1367, 1258, 1202, 1115, 1025, 898, 825, 760, 735 cm^{-1}; ^{1}H NMR δ 7.77 (d, 1H, J=7.9 Hz), 7.58 (d, 1H, J=8.0 Hz), 7.50 (t, 1H, J=8.0 Hz), 7.29 (t, 1H, J=7.7 Hz), 7.18 (t, 1H, J=7.4 Hz), 7.16 (d, 1H, J= 7.6 Hz), 6.97 (d, 1H, J=8.7 Hz), 6.58 (dd, 1H, J=7.7, 0.7 Hz), 2.91 (t, 2H, J=5.7 Hz), 2.62 (t, 2H, J=6.2 Hz), 2.40 (s, 3H), 2.19 (s, 3H), 2.07 (p, 2H, J=6.4 Hz); ^{13}C NMR δ 196.3, 170.3, 170.0, 153.1, 150.8, 146.8, 146.0, 138.3, 137.1, 126.6, 126.4, 126.3, 126.2, 125.8, 123.3, 123.1, 120.0, 119.4, 111.8, 40.1, 23.8, 22.0, 21.2, 21.1; MS (EI) *m/z* (rel intensity) 404 (M^+, 23), 362 (30), 320 (100), 202 (10), 149 (21), 115 (12), 91 (33), 69 (18), 57 (28); HRMS (EI) calcd for $C_{24}H_{20}O_6$ 404.1260, found 404.1266.

4.2.5. 8-Hydroxy-5-(8′-hydroxynaphthalene-1′-yloxy)-1,2,3,4-tetrahydronaphthalene-1-spiro-2″-dioxolane (5). To a solution of **12** (240 mg, 0.593 mmol) and ethylene glycol (1.10 g, 17.79 mmol) in benzene (20 mL) was added PPTS (75 mg, 0.297 mmol). The reaction mixture was heated at reflux for 62 h in a flask equipped with a Dean–Stark apparatus, cooled to room temperature, diluted with benzene (100 mL), washed with 5% $NaHCO_3$ solution (2×50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 1:1) gave 205 mg (77%) of **13** as on oil. To a solution of **13** (175 mg, 0.39 mmol) in degassed THF/MeOH (15 mL, 2/1) was added lithium hydroxide monohydrate (41 mg, 0.98 mmol) at 0°C. The reaction mixture was stirred for 2 h in an ice bath, neutralized with saturated ammonium chloride solution and extracted with ethyl acetate (2×100 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 2:1) gave 137 mg (96%) of **5** as a solid: mp 174–175°C; IR (neat) 3405, 3318, 3057, 2959, 2904, 1608, 1581, 1469, 1402, 1365, 1301, 1253, 1220, 1182, 1157, 1121, 1035, 944, 928, 878, 818, 759 cm^{-1}; ^{1}H NMR δ 9.18 (s, 1H, OH), 8.13 (s, 1H, OH), 7.46–7.34 (m, 3H), 7.17 (t, 1H, J=8.0 Hz), 7.10 (d, 1H, J=8.8 Hz), 6.96 (dd, 1H, J=7.2, 1.1 Hz), 6.85 (d, 1H, J=8.8 Hz), 6.45 (d, 1H, J=7.6 Hz), 4.34–4.17 (m, 4H), 2.68 (t, 2H, J=6.3 Hz), 1.99–1.95 (m, 2H), 1.91–1.83 (m, 2H); ^{13}C NMR δ 155.5, 154.8, 154.2, 143.3, 137.0, 133.5, 127.8, 125.7, 124.4, 122.6, 120.6, 119.1, 116.1, 114.9, 110.6, 109.8, 107.3, 63.9, 31.3, 23.5, 19.2; MS (EI) *m/z* (rel intensity) 364 (M^+, 100), 320 (55), 159 (11), 144 (24), 131 (14), 115 (22), 77 (7), 55 (8); HRMS (EI) calcd for $C_{22}H_{20}O_5$ 364.1311, found 364.1311.

4.2.6. 1-Oxo-1,4,5,6,7,8,-hexahydronaphthalene-4-spiro-2′-naphtho[1″,8″-de][1′,3′]dioxin-8-spiro-2‴-dioxolane (14). To a suspension of **5** (58 mg, 0.159 mmol) in trifluoroethanol (20 mL) was added Phl(OAc)$_2$ (62 mg, 0.191 mmol). The reaction mixture was stirred for 2 h at room temperature and $NaHCO_3$ (32 mg, 0.382 mmol) was added. The resulting mixture was concentrated in vacuo and the residue was diluted with EtOAc (50 mL), washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 4:1) gave 43 mg (75%) of **14** as an oily solid: IR (neat) 3059, 2949, 2897, 1680, 1651, 1608, 1584, 1412, 1396, 1302, 1271, 1144, 1096, 1052, 1031, 949, 825, 814, 757 cm^{-1}; ^{1}H NMR δ 7.52 (d, 2H, *J*=8.1 Hz), 7.43 (t, 2H, *J*=7.9 Hz), 6.93 (d, 2H, *J*=7.1 Hz), 6.76 (d, 1H, *J*=10.3 Hz), 6.08 (d, 1H, *J*=10.4 Hz), 4.41–4.36 (m, 2H), 4.08–4.04 (m, 2H), 2.75–2.65 (m, 2H), 1.95–1.85 (m, 4H); ^{13}C NMR δ 182.4, 154.1, 146.8, 136.4, 134.1, 134.0, 130.6, 127.6, 121.2, 112.9, 109.7, 105.9, 92.8, 66.1, 35.6, 24.5, 19.5; MS (EI) *m/z* (rel intensity) 362 (M^+, 100), 319 (39), 306 (16), 262 (15), 234 (9), 204 (10), 178 (16), 131 (13), 115 (17), 99 (13), 84 (22), 55 (13); HRMS (EI) calcd for $C_{22}H_{18}O_5$ 362.1154, found 362.1160.

4.2.7. (±)-8-Hydroxy-1-oxo-1,4,5,6,7,8-hexahydronaphthalene-4-spiro-2′-naphtho[1″,8″-de][1′,3′]dioxin (16). To a solution of **11** (1.51 g, 4.72 mmol) in Et_2O (70 mL) was added in portions solid $LiAlH_4$ (358 mg, 9.44 mmol) at 0°C. The solution was stirred for 2 h at 0°C, warmed to room temperature and stirred for an additional 2 h. The reaction mixture was carefully quenched with 5% sodium bisulfate solution in an ice bath. After adding 40 mL of 5% sodium bisulfate solution, the product was extracted with Et_2O (2×150 mL). The combined ether layers washed with brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. The resulting solid was added to dry trifluoroethanol (150 mL) and stirred until a fine suspension was obtained. After addition of PhI(OAc)$_2$ (1.67 g, 5.19 mmol), the mixture was stirred for 30 min at room temperature, $NaHCO_3$ (1.0 g, 12 mmol) was added. The solution was concentrated in vacuo and the resulting residue was diluted with EtOAc (300 mL), washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 2:1) gave 1.32 g (87%) of **16** as a yellow solid: mp 199–200°C; IR (neat) 3434, 2945, 1673, 1642, 1630, 1600, 1409, 1374, 1263, 1080, 944, 757 cm^{-1}; ^{1}H NMR δ 7.54 (d, 2H, *J*=8.0 Hz), 7.45 (td, 2H, *J*=7.4, 2.2 Hz), 6.95 (td, 2H, *J*=7.6, 0.7 Hz), 6.90 (d, 1H, *J*=10.4 Hz), 6.19 (d, 1H, *J*=10.4 Hz), 4.82 (t, 1H, *J*=4.9 Hz), 3.31 (bs, 1H, OH), 2.78–2.51 (m, 2H), 1.98–1.90 (m, 3H), 1.82–1.72 (m, 1H); ^{13}C NMR δ 185.8, 151.6, 146.8, 139.3, 135.6, 134.1, 129.1, 127.7, 127.6, 121.3, 112.9, 109.8, 109.7, 92.6, 62.7, 29.6, 24.2, 17.7; MS (EI) *m/z* (rel intensity) 320 (M^+, 100), 304 (30), 265 (35), 247 (21), 235 (10), 219 (11), 197 (18), 169 (24), 160 (32), 144 (35), 133 (35), 115 (50), 103 (16), 88 (13), 77 (28), 63 (17); HRMS (EI) calcd for $C_{20}H_{16}O_4$ 320.1049, found 320.1039.

4.2.8. 8-Hydroxy-1-oxo-1,4-dihydronaphthalene-4-spiro-2′-naphtho[1″,8″-de][1′,3′]dioxin (palmarumycin CP$_1$). To a solution of **16** (32 mg, 0.1 mmol) in CH_2Cl_2 (5 mL) was added Dess–Martin periodinane (64 mg, 0.15 mmol) at room temperature. The reaction mixture was stirred for 2 h and diluted with EtOAc (30 mL). It was washed with 5% $NaHCO_3$ solution (10 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 2:1) gave 32 mg of a yellow residue which was treated with MnO_2 (Aldrich, 85% activated, 102 mg, 1 mmol, dried over P_2O_5 just before use) in dry CH_2Cl_2 (5 mL) for 2 d at room temperature. The reaction mixture was filtered through celite and washed with CH_2Cl_2 (10 mL). The combined solutions were concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 4:1) gave 19 mg (60%) of palmarumycin CP$_1$ as a yellow solid: mp 170°C (dec.); IR (neat) 3053, 1659, 1602, 1449, 1409, 1372, 1341, 1269, 1237, 1110, 1073, 942, 822, 746 cm^{-1}; ^{1}H NMR δ 12.17 (s, 1H, OH), 7.67 (t, 1H, *J*=8.0 Hz), 7.58 (d, 2H, *J*=8.5 Hz), 7.47 (t, 2H, *J*=7.9 Hz), 7.46 (d, 1H, *J*=7.8 Hz), 7.14 (dd, 1H, *J*=8.2, 1.1 Hz), 7.02 (d, 1H, *J*=10.9 Hz), 6.98 (d, 2H, *J*=7.7 Hz), 6.37 (d, 1H, *J*=10.9 Hz); ^{13}C NMR δ 188.8, 161.9, 147.2, 139.7, 138.8, 136.7, 134.2, 129.8, 127.7, 121.4, 119.7, 119.4, 113.8, 113.0, 109.9, 92.9; MS (EI) *m/z* (rel intensity) 316 (M^+, 100), 288 (12), 287 (19), 259 (8), 175 (11), 114 (45), 88 (11), 63 (9); HRMS (EI) calcd for $C_{20}H_{12}O_4$ 316.0736, found 316.0730.

4.2.9. (±)-2,3-Epoxy-8-hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalene-4-spiro-2′-naphtho[1″,8″-de][1′,3′]dioxin [(±)-deoxypreussomerin A]. To a solution of **16** (54.5 mg, 0.17 mmol) in THF (5 mL) was added cumene hydroperoxide (157 μL, 0.85 mmol) and NaH (60%, 6.5 mg, 0.17 mmol) at −20°C. The reaction mixture was stirred for 4 h at −20°C, and diluted with EtOAc (40 mL) and brine (5 mL). The separated organic layer was washed with an additional brine(20 mL), dried(Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 3:1) gave 27 mg (47%) of monoepoxide **20**. To a solution of this epoxide in CH_2Cl_2 (4 mL) was added Dess–Martin periodinane (51 mg, 0.12 mmol) at room temperature. The reaction mixture was stirred for 2 h, diluted with EtOAc (30 mL), washed with 5% $NaHCO_3$ solution (10 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 2:1) gave 27 mg of a yellow residue which was treated with MnO_2 (Aldrich, 85% activated, 82 mg, 0.8 mmol, dried over P_2O_5 just before use) in dry CH_2Cl_2 (5 mL) for 37 h at room temperature. The mixture was filtered through celite and washed with CH_2Cl_2 (10 mL). The combined solutions were concentrated in vacuo. Chromatography on SiO_2 (hexanes/EtOAc, 3:1) gave 14.5 mg (26% from **16**) of (±)-deoxypreussomerin A as a colorless solid: mp 200–201°C; IR (neat) 3050, 1651, 1605, 1455, 1409, 1380, 1330, 1266, 1239, 1173, 1110, 1061, 963, 920, 878, 820, 809, 759, 720 cm^{-1}; ^{1}H NMR δ 11.37 (s, 1H, OH), 7.65 (t, 1H, *J*=8.0 Hz), 7.60 (d, 1H, *J*=8.6 Hz), 7.57 (d, 1H, *J*=8.0 Hz), 7.53 (t, 1H, *J*=8.3 Hz), 7.45 (t, 1H, *J*=7.4 Hz), 7.44 (d, 1H, *J*=7.9 Hz), 7.19 (dd, 1H, *J*=7.6, 0.8 Hz), 7.14 (dd, 1H, *J*=8.6, 0.8 Hz), 6.92 (dd, 1H, *J*=7.6, 0.7 Hz), 4.09 (d, 1H, *J*=4.1 Hz), 3.68 (d, 1H, *J*=3.9 Hz); ^{13}C NMR δ 196.6, 161.9, 146.9, 146.7, 137.8, 136.9, 134.2, 127.9, 127.7, 121.5, 121.4, 120.1, 119.1, 112.8, 112.3, 110.2, 109.4, 96.0, 53.3; MS (EI) *m/z* (rel intensity) 332 (M+, 100), 316 (28), 303 (11), 287 (19), 173 (15), 145 (23), 132 (12), 114 (27), 89 (13), 74 (14), 63 (12), 57 (7); HRMS(EI) calcd for $C_{20}H_{12}O_5$ 332.0685, found 332.0688.

4.3. General procedure for Mitsunobu reactions

4.3.1. (*E*)-8-(3-Phenyl-allyloxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2′-naphtho[1″,8″-de][1′,3′]dioxin (21). A solution of palmarumycin CP_1 (7.4 mg, 0.023 mmol), diphenylphosphino-polystyrene (82.1 mg, 1.41 mmol/g, 0.116 mmol) and cinnamyl alcohol (15.5 μL, 0.118 mmol) in dry CH_2Cl_2 (0.4 mL) was stirred for 30 min at room temperature and cooled to 0°C. Diethyl azodicarboxylate (DEAD) (18.0 μL, 0.114 mmol) was added to the reaction mixture at 0°C and stirring was continued for 24 h at room temperature. The reaction mixture was washed with 5% aqueous KOH solution (0.5 mL), followed by 5% HCl (0.5 mL). The methylene chloride extract was filtered, the resin was washed further with CH_2Cl_2 (2×0.5 mL) and the solvent was concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 9:1) gave 1.8 mg (24%) of palmarumycin CP_1 and 5.0 mg (52%) of **21** as a colorless oil: ^{1}H NMR δ 7.70 (t, 1H, *J*=8.0 Hz), 7.60–7.56 (m, 3H), 7.50–7.45 (m, 4H), 7.37–7.20 (m, 4H), 6.99 (d, 2H, *J*=7.3 Hz), 6.93 (bs, 1H), 6.87 (d, 1H, *J*=10.5 Hz), 6.49 (dt, 1H, *J*=5.2, 16.0 Hz), 6.31 (d, 1H, *J*=10.5 Hz), 4.93 (d, 2H, *J*=5.2 Hz); HRMS(EI) calcd for $C_{29}H_{20}O_4$ 432.1362, found 432.1362.

4.3.2. (*E*)-8-(But-2-enyloxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2′-natphtho[1″,8″-de][1′,3′]dioxin (22). According to the general procedure, palmarumycin CP_1 (2.4 mg, 0.008 mmol), diphenylphosphino-polystyrene (28.2 mg, 1.41 mmol/g, 0.040 mmol), 2-buten-1-ol (3.3 μL, 0.038 mmol) and DEAD (6.0 μL, 0.038 mmol) in dry CH_2Cl_2 (0.2 mL) provided after 24 h 2.5 mg (88%) of **22** as a colorless oil: ^{1}H NMR δ 7.68 (t, 1H, *J*=8.0 Hz), 7.60–7.55 (m, 3H), 7.49 (d, 1H, *J*=7.7 Hz), 7.46 (d, 1H, *J*=8.2 Hz), 7.17 (d, 1H, *J*=8.6 Hz), 6.98 (d, 2H, *J*=7.4 Hz), 6.85 (d, 1H, *J*=10.5 Hz), 6.29 (d, 1H, *J*=10.5 Hz), 6.03 (dq, 1H, *J*=15.3, 6.5 Hz), 5.85–5.75 (m, 1H), 4.69 (d, 2H, *J*=5.4 Hz), 1.80 (d, 3H, *J*=6.2 Hz); HRMS(EI) calcd for $C_{24}H_{18}O_4$ 370.1205, found 370.1214.

4.3.3. 8-Hexyloxy-1-oxo-1,4-dihydronaphthalene-4-spiro-2′-naphtho[1″,8″-de][1′,3′]dioxin (23). According to the general procedure, palmarumycin CP_1 (2.0 mg, 0.006 mmol), diphenylphosphino-polystyrene (31.3 mg, 1.41 mmol/g, 0.044 mmol), hexyl alcohol (4.0 μL, 0.031 mmol) and DEAD (5.0 μL, 0.032 mmol) in dry CH_2Cl_2 (0.1 mL) provided after 43 h 1.3 mg (50%) of **23** as a colorless oil: ^{1}H NMR δ 7.66 (t, 1H, *J*=8.3 Hz), 7.57–7.50 (m, 3H), 7.48–7.42 (m, 2H), 7.14 (d, 1H, *J*=8.3 Hz), 6.96 (d, 2H, *J*=7.5 Hz), 6.82 (d, 1H, *J*=10.4 Hz), 6.26 (d, 1H, *J*=10.4 Hz), 4.10 (t, 2H, *J*=5.9 Hz), 2.30–1.20 (m, 11H).

4.3.4. (*E*)-8-(Hex-3-enyloxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2′-naphtho[1″,8″-de][1′,3′]dioxin (24). According to the general procedure, palmarumycin CP_1 (2.1 mg, 0.007 mmol), diphenylphosphino-polystyrene (23.9 mg, 1.41 mmol/g, 0.034 mmol), *trans*-3-hexen-1-ol (4.2 μL, 0.034 mmol) and DEAD (5.2 μL, 0.033 mmol) in dry CH_2Cl_2 (0.1 mL) provided after 67 h 1.3 mg (43%) of **24** as a colorless oil: ^{1}H NMR δ 7.68 (t, 1H, *J*=8.3 Hz), 7.60–7.45 (m, 5H), 7.16 (d, 1H, *J*=8.4 Hz), 6.97 (d, 2H, *J*=7.5 Hz), 6.85 (d, 1H, *J*=10.5 Hz), 6.28 (d, 1H, *J*=10.4 Hz), 5.66–5.60 (m, 1H), 5.45–5.30 (m, 1H), 4.15 (t, 2H, *J*=6.9 Hz), 2.7–2.6 (m, 2H), 2.4–2.3 (m, 2H), 1.00 (t, 3H, *J*=6.4 Hz).

4.3.5. 8-(3-Methoxy-benzyloxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2′-naphtho[1″,8″-de][1′,3′]dioxin (25). According to the general procedure, palmarumycin CP_1 (2.0 mg, 0.006 mmol), diphenylphosphino-polystyrene (22.8 mg, 1.41 mmol/g, 0.032 mmol), 3-methoxybenzyl alcohol (4.0 μL, 0.032 mmol) and DEAD (5.0 μL, 0.032 mmol) in dry CH_2Cl_2 (0.1 mL) provided after 45 h 1.6 mg (67%) of **25** as a colorless oil: ^{1}H NMR δ 7.68–7.54 (m, 4H), 7.45 (t, 2H, *J*=7.7 Hz), 7.24–7.10 (m, 4H), 6.97 (d, 2H, *J*=7.5 Hz), 6.9–6.8 (m, 2H), 6.30 (d, 1H, *J*=10.4 Hz), 5.29 (s, 2H), 3.86 (s, 3H).

4.3.6. 8-(2-Phenyl-ethoxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2′-naphtho[1″,8″-de][1′,3′]dioxin (26). According to the general procedure, palmarumycin CP_1 (2.0 mg, 0.006 mmol), diphenylphosphino-polystyrene (23.4 mg, 1.41 mmol/g, 0.033 mmol), phenethyl alcohol (3.8 μL, 0.032 mmol) and DEAD (5.0 μL, 0.032 mmol) in dry CH_2Cl_2 (0.2 mL) provided after 24 h 1.0 mg (33%) of **26** as a colorless oil: ^{1}H NMR δ 7.67–7.1 (m, 12H), 6.98 (d, 2H, *J*=7.5 Hz), 6.86 (d, 1H, *J*=10.5 Hz), 6.30 (d, 1H, *J*= 10.6 Hz), 4.33 (t, 2H, *J*=7.0 Hz), 3.27 (t, 2H, *J*=7.0 Hz).

4.3.7. 8-(Furan-2-ylmethoxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2′-naphtho[1″,8″-de][1′,3′]dioxin (27) and 7-(furan-2-ylmethyl)-8-hydroxy-1-oxo-1,4-dihydronaphthalene-4-spiro-2′-naphtho[1″,8″-de][1′,3′]dioxin (28). According to the general procedure, palmarumycin CP_1 (2.1 mg, 0.007 mmol), diphenylphosphino-polystyrene (22.5 mg, 1.41 mmol/g, 0.032 mmol), furfuryl alcohol (2.8 μL, 0.032 mmol) and DEAD (5.0 μL, 0.032 mmol) in dry CH_2Cl_2 (0.2 mL) provided after 5 d 2.0 mg (71%) of **27** and 1.0 mg (29%) of **28** as colorless oils. **27**: ^{1}H NMR δ 7.70–7.45 (m, 6H), 7.29–7.26 (m, 2H), 7.05–6.95 (m, 2H), 6.86 (d, 1H, *J*=10.5 Hz), 6.55 (bs, 1H), 6.41 (bs, 1H), 6.28 (d, 1H, *J*=10.5 Hz), 5.23 (s, 2H). **28**: ^{1}H NMR δ 12.67 (s, 1H), 7.61 (d, 2H, *J*=8.2 Hz), 7.62–7.44 (m, 4H), 7.11 (d, 1H, *J*=8.8 Hz), 7.00–6.92 (m, 3H), 6.35 (d, 1H, *J*=10.4 Hz), 6.26 (t, 1H, *J*=2.4 Hz), 5.91 (d, 1H, *J*=3.2 Hz), 4.26 (s, 2H).

4.3.8. (*E,E*)-8-(3,7-Dimethyl-octa-2,6-dienyloxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2′-naphtho[1″,8″-de]-[1′,3′]dioxin (29). According to the general procedure, palmarumycin CP_1 (2.0 mg, 0.006 mmol), diphenylphosphino-polystyrene (23.1 mg, 1.41 mmol/g, 0.033 mmol), geraniol (5.6 μL, 0.032 mmol) and DEAD (5.0 μL, 0.032 mmol) in dry CH_2Cl_2 (0.2 mL) provided after 29 h 2.1 mg (83%) of **29** as a colorless oil: ^{1}H NMR δ 7.67 (t, 1H, *J*=8.2 Hz), 7.59–7.55 (m, 3H), 7.50–7.44 (m, 2H), 7.16 (d, 1H, *J*=8.2 Hz), 6.98 (d, 2H, *J*=7.4 Hz), 6.85 (d, 1H, *J*=10.5 Hz), 6.28 (d, 1H, *J*=10.5 Hz), 5.56 (t, 1H, *J*=6.0 Hz), 5.10 (bs, 1H), 4.79 (d, 2H, *J*=6.2 Hz), 2.11 (bs, 4H), 1.78 (s, 3H), 1.69 (s, 3H), 1.62 (s, 3H).

4.3.9. 8-(Furan-3-ylmethoxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2′-naphtho[1″,8″-de][1′,3′]dioxin (30). According to the general procedure, palmarumycin CP_1 (2.0 mg, 0.006 mmol), diphenylphosphino-polystyrene (23.4 mg, 1.41 mmol/g, 0.033 mmol), 3-furanmethanol (2.8 μL, 0.032 mmol) and DEAD (5.0 μL, 0.032 mmol) in dry CH_2Cl_2 (0.2 mL) provided after 3 d 1.2 mg (50%) of **30** as a colorless oil: ^1H NMR δ 7.63–7.45 (m, 5H), 7.42–7.35 (m, 3H), 7.16 (d, 1H, J=8.2 Hz), 6.89 (d, 2H, J=7.4 Hz), 6.77 (dd, 1H, J=10.5, 1.3 Hz), 6.51 (bs, 1H), 6.20 (dd, 1H, J=10.5, 1.3 Hz), 5.08 (s, 2H); HRMS(EI) calcd for $C_{25}H_{16}O_5$ 396.0998, found 396.0997.

4.3.10. 8-(Pyridin-2-ylmethoxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2′-naphtho[1″,8″-de][1′,3′]dioxin (31). According to the general procedure, palmarumycin CP_1 (2.2 mg, 0.007 mmol), diphenylphosphino-polystyrene (29.7 mg, 1.41 mmol/g, 0.042 mmol), 2-pyridylcarbinol (3.4 μL, 0.035 mmol) and DEAD (5.5 μL, 0.035 mmol) in dry CH_2Cl_2 (0.2 mL) provided after 4 d 0.2 mg (9%) of palmarumycin CP_1 and 1.2 mg (43%) of **31** as a colourless oil: ^1H NMR δ 8.50 (bs, 1H), 8.16 (bs, 1H), 7.88 (bs, 1H), 7.77–7.50 (m, 4H), 7.51–7.45 (m, 3H), 7.4–7.3 (m, 1H); 6.99 (d, 2H, J=7.7 Hz), 6.92 (bd, 1H, J=10.5 Hz), 6.33 (d, 1H, J=10.5 Hz), 5.42 (bs, 2H); HRMS(EI) calcd for $C_{26}H_{17}NO_4$ 407.1158, found 407.1139.

4.3.11. 8-(Pyridin-3-ylmethoxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2′-naphtho[1″,8″-de][1′,3′]dioxin (32). According to the general procedure, palmarumycin CP_1 (2.1 mg, 0.007 mmol), diphenylphosphino-polystyrene (23.8 mg, 1.41 mmol/g, 0.034 mmol), 3-pyridylcarbinol (3.3 μL, 0.033 mmol) and DEAD (5.2 μL, 0.033 mmol) in dry CH_2Cl_2 (0.2 mL) provided after 5 d 0.3 mg (14%) of palmarumycin CP_1 and 0.9 mg (29%) of **32** as a colorless oil: ^1H NMR δ 8.8–8.5 (m, 2H), 8.29 (d, 1H, J=7.9 Hz), 7.74–7.40 (m, 8H), 7.25–7.20 (m, 1H), 6.97 (d, 1H, J=7.1 Hz), 6.88 (d, 1H, J=10.5 Hz), 6.30 (d, 1H, J=10.4 Hz), 5.32 (s, 2H); HRMS(EI) calcd for $C_{26}H_{17}NO_4$ 407.1158, found 407.1152.

4.3.12. 8-(Pyridin-4-ylmethoxy)-1-oxo-1,4-dihydronaphthalene-4-spiro-2′-naphtho[1″,8″-de][1′,3′]dioxin (33). According to the general procedure, palmarumycin CP_1 (2.0 mg, 0.006 mmol), diphenylphosphino-polystyrene (22.4 mg, 1.41 mmol/g, 0.032 mmol), 4-pyridylcarbinol (7.6 mg, 0.069 mmol) and DEAD (5.0 μL, 0.032 mmol) in dry CH_2Cl_2 (0.2 mL) provided after 7 d 0.6 mg (30%) of palmarumycin CP_1 and 0.5 mg (17%) of **33** as a colorless oil: ^1H NMR δ 8.9–8.5 (m, 2H), 8.10 (bs, 1H), 7.78–7.1 (m, 7H), 7.00 (d, 2H, J=7.4 Hz), 6.94 (d, 1H, J=10.5 Hz), 6.34 (d, 1H, J=10.5 Hz), 5.40 (bs, 1H), 4.80 (bs, 2H).

4.3.13. 8-Allyloxy-1-oxo-1,4-dihydronaphthalene-4-spiro-2′-naphtho[1″,8″-de][1′,3′]dioxin (34). According to the general procedure, palmarumycin CP_1 (2.1 mg, 0.007 mmol), diphenylphosphino-polystyrene (23.5 mg, 1.41 mmol/g, 0.033 mmol), allyl alcohol (2.3 μL, 0.034 mmol) and DEAD (5.2 μL, 0.033 mmol) in dry CH_2Cl_2 (0.2 mL) provided after 3 d 0.6 mg (33%) of palmarumycin CP_1 and 1.8 mg (71%) of **34** as a colorless oil: ^1H NMR δ 7.69 (t, 1H, J=8.1 Hz), 7.62–7.56 (m, 2H), 7.49 (d, 1H, J=7.5 Hz), 7.46 (d, 1H, J=8.3 Hz), 7.17 (d, 1H, J=8.3 Hz), 6.98 (d, 2H, J=7.0 Hz), 6.86 (d, 1H, J=10.5 Hz), 6.29 (d, 1H, J=10.7 Hz), 6.20–6.06 (m, 1H), 5.68 (dd, 1H, J=17.2, 1.5 Hz), 5.38 (dd, 1H, J=10.8, 1.5 Hz), 4.77–4.74 (m, 2H); HRMS(EI) calcd for $C_{23}H_{16}O_4$ 356.1049, found 356.1064.

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