Total Synthesis of Palmarumycin CP_1 and (±)-Deoxypreussomerin A

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Received March 30, 1998

Since the isolation of the spiroketal MK3018 by Ogishi et al. in 1989[1] and the bis-ketal decalin preussomerin A by Weber et al. in 1990,[2] many structurally related fungal metabolites have been reported (Figure 1).[3] In addition to general antitumor and antibiotic activities,[3] selective inhibition of Ras farnesyl-protein transferase with an IC_{50} of ≥1.2 μM has been detected with these compounds.[4]

Recently, Krohn et al. reported the first semisynthetic generation of the palmarumycin spiroacetal framework by oxidative cyclization of a fungal metabolite.[5] As a part of our program toward the synthesis and mechanistic study of epoxy ketone natural products,[6,7] we have recently embarked on the total synthesis of diepoxin σ.[8] In this paper, we describe our progress toward a general route for the construction of the spiroketal naphthodecalins and, specifically, the first total syntheses of palmarumycin CP_1 and (±)-deoxypreussomerin A. These natural products were isolated from *Coniothyrium palmarum*[3f] and an unidentified ceolomycetes (MF 5916),[4] respectively, and are representative for the structural features of many naturally occurring naphthoquinone dimers. Deoxypreussomerin A was also isolated (and named palmarumycin C_2) from *C. palmarum*, and the structure was further confirmed by X-ray analysis.[3g] We envisioned that both compounds as well as ultimately diepoxin σ could be derived from *p*-quinone ketal **1**, which

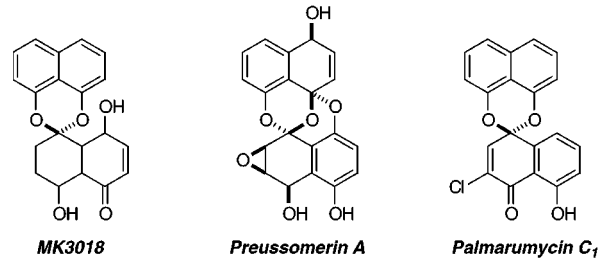
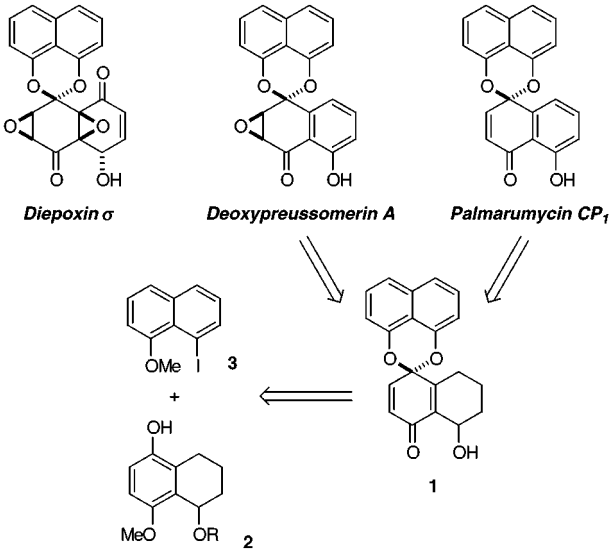


Figure 1. Representative spiroketal naphthodecalin natural products.

Scheme 1



should be available by Ullmann ether coupling of phenol **2** and iodide **3** followed by oxidative spirocyclization (Scheme 1).

Our first attempts for an Ullmann coupling[9] between the readily available[10] tetralone **4** and 8-iodo-1-methoxynaphthalene (**3**)[11] failed, possibly due to the lack of nucleophilicity of the deactivated tetralone under the standard Ullmann reaction conditions. After protection of the carbonyl group in **4** with ethylene glycol, the resulting acetal was now successfully converted to the biaryl ether **5** in 78% yield in refluxing pyridine in the presence of 0.2 equiv of Cu_2O and 1 equiv of K_2CO_3 (Scheme 2). When 1 equiv of Cu_2O was used, the coupling yield dropped to <60%.

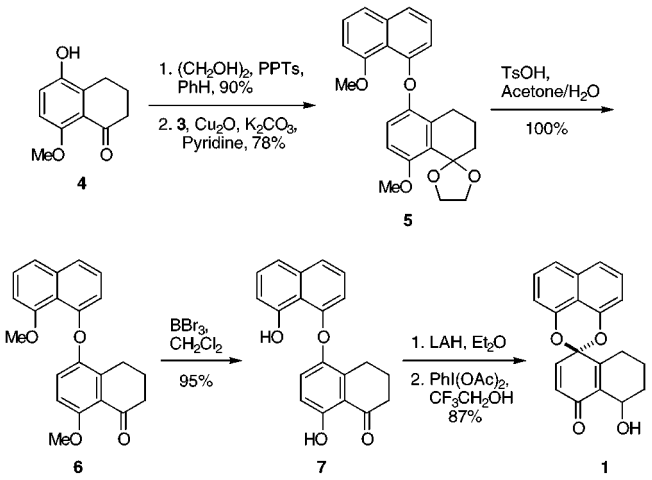
O-Demethylation in the presence of the dioxolane protective group was not clean; however, stepwise cleavage of the acetal in aqueous acetone with TsOH followed by double demethylation with BBr_3 gave **7** in 95% overall yield. After considerable experimentation, we found that the oxidative spirocyclization of phenol **7** was best performed after reduction of the tetralone with LAH by treatment with $PhI(OAc)_2$ in trifluoroethanol for 10 min.[6,8,12] The linchpin spiroketal intermediate **1** was thus obtained in high overall yield.

For the preparation of palmarumycin, spiroketal **1** was oxidized with Dess−Martin reagent,[13] followed by aromati-

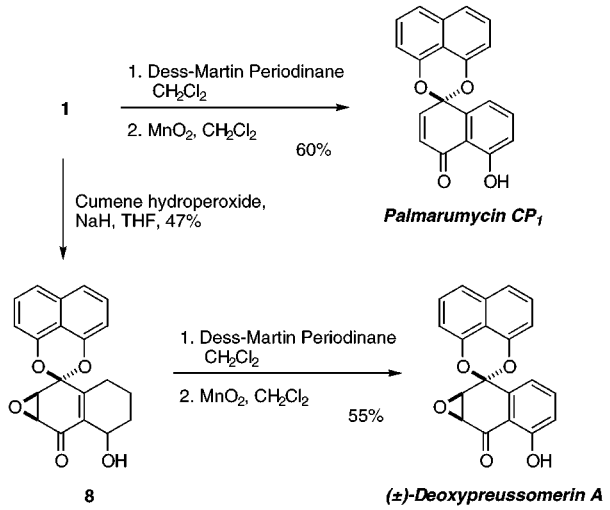
(1) Ogishi, H.; Chiba, N.; Mikawa, T.; Sasaki, T.; Miyaji, S.; Sezaki, M. *JP 01,294,686*, 1989; *Chem. Abstr.* **1990**, *113*, 38906q.
(2) Weber, H. A.; Baenziger, N. C.; Gloer, J. B. *J. Am. Chem. Soc.* **1990**, *112*, 6718.
(3) (a) Preussomerins A−F: Weber, H. A.; Gloer, J. B. *J. Org. Chem.* **1991**, *56*, 4355. (b) Diepoxins: Schlingmann, G.; West, R. R.; Milne, L.; Pearce, C. J.; Carter, G. T. *Tetrahedron Lett.* **1993**, *34*, 7225. (c) Schlingmann, G.; Matile, S.; Berova, N.; Nakanishi, K.; Carter, G. T. *Tetrahedron* **1996**, *52*, 435. (d) SCH 49210, SCH 53514, and SCH 53156: Chu, M.; Truumees, I.; Patel, M. G.; Gullo, V. P.; Blood, C.; King, I.; Pai, J.-K.; Puar, M. S. *Tetrahedron Lett.* **1994**, *35*, 1343. (e) SCH 49211 and SCH 49212: Chu, M.; Truumees, I.; Patel, M. G.; Gullo, V. P.; Pai, J.-K.; Das, P. R.; Puar, M. S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1539. (f) Palmarumycins CP_1−CP_4: Krohn, K.; Michel, A.; Flörke, U.; Aust, H.-J.; Draeger, S.; Schulz, B. *Liebigs Ann. Chem.* **1994**, 1093. (g) Palmarumycins C_1−C_{16}: Krohn, K.; Michel, A.; Flörke, U.; Aust, H.-J.; Draeger, S.; Schulz, B. *Liebigs Ann. Chem.* **1994**, 1099. (h) CJ-12,371 and CJ-12,372: Sakemi, S.; Inagaki, T.; Kaneda, K.; Hirai, H.; Iwata, E.; Sakakibara, T.; Yamauchi, Y.; Norcia, M.; Wondrack, L. M.; Sutcliffe, J. A.; Kojima, N. *J. Antibiot.* **1995**, *48*, 134. (i) SCH 49209: Chu, M.; Truumees, I.; Patel, M. G.; Gullo, V. P.; Puar, M. S.; McPhail, A. T. *J. Org. Chem.* **1994**, *59*, 1222. (j) Cladospirone bisepoxide: Thiergardt, R.; Rihs, G.; Hug, P.; Peter, H. H. *Tetrahedron* **1995**, *51*, 733. (k) SCH 50673 and SCH 50676: Chu, M.; Truumees, I.; Patel, M.; Blood, C.; Das, P. R.; Puar, M. S. *J. Antibiot.* **1995**, *48*, 329. (l) SCH 53823 and SCH 53825: Chu, M.; Patel, M. G.; Pai, J.-K.; Das, P. R.; Puar, M. S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 579. (m) Palmarumycin CP_{4a} and CP_5: Krohn, K.; Beckmann, K.; Flörke, U.; Aust, H.-J.; Draeger, S.; Schulz, B.; Busemann, S.; Bringmann, G. *Tetrahedron* **1997**, *53*, 3101.
(4) Singh, S. B.; Zink, D. L.; Liesch, J. M.; Ball, R. G.; Goetz, M. A.; Bolessa, E. A.; Giacobbe, R. A.; Silverman, K. C.; Bills, G. F.; Pelaez, F.; Cascales, C.; Gibbs, J. B.; Lingham, R. B. *J. Org. Chem.* **1994**, *59*, 6296.
(5) Krohn, K.; Beckmann, K.; Aust, H.-J.; Draeger, S.; Schulz, B.; Busemann, S.; Bringmann, G. *Liebigs Ann./Recueil* **1997**, 2531.
(6) Aranorosin: Wipf, P.; Kim, Y. *J. Org. Chem.* **1993**, *58*, 1649. Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, *58*, 7195. LL-C10037α: Wipf, P.; Kim, Y. *J. Org. Chem.* **1994**, *59*, 3518. Wipf, P.; Kim, Y.; Jahn, H. *Synthesis* **1995**, 1549. Asukamycin and manumycin A: Wipf, P.; Xu, W.; Takahashi, H.; Jahn, H.; Coish, P. D. G. *Pure Appl. Chem.* **1997**, *69*, 639. Wipf, P.; Coish, P. D. G. *Tetrahedron Lett.* **1997**, *38*, 5073.
(7) Wipf, P.; Jeger, P.; Kim, Y. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 351.
(8) Wipf, P.; Jung, J.-K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 764.
(9) Moroz, A. A.; Shvartsberg, M. S. *Russ. Chem. Rev.* **1974**, *43*, 679.
(10) Newhall, W. F.; Harris, S. A.; Holly, F. W.; Johnston, E. L.; Richter, J. W.; Walton, E.; Wilson, A. N.; Folkers, K. *J. Am. Chem. Soc.* **1955**, *77*, 5646.
(11) Graybill, B. M.; Shirley, D. A. *J. Org. Chem.* **1966**, *31*, 1221.
(12) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677.
(13) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

S0022-3263(98)00576-3 CCC: $15.00
Published on Web 05/12/1998

Scheme 2



Scheme 3



zation of the resulting decalin dione with activated MnO_2 (Scheme 3). This two-step protocol provided significantly higher yields than simple exposure of **1** to an excess of MnO_2, particularly since the product was difficult to remove from this reagent. Synthetic palmarumycin, which was spectroscopically in all aspects identical to the data reported for the fermented compound,[14] was thus obtained in 35% overall yield in eight steps from tetralone **4**. The same strategy provided (±)-deoxypreussomerin A after epoxidation of **1** with cumene hydroperoxide anion in THF in 15% overall yield based on a nine-step conversion from **4**.[15]

The structural features of many dimeric naphthoquinone natural products are deceptively simple. In particular, the actual introduction of the spiroketal moiety by dehydration of a *p*-quinone or transacetalization of a semiquinone precursor with 1,8-naphthalenediol has, in our hands, so far been unsuccessful. The use of the Ullmann ether coupling followed by oxidative spirocyclization, however, provides a high-yielding access to the intermediate **1**, which should be useful for the preparation of gram quantities of many spiroketal naphthodecalin metabolites. Specifically, we have achieved the first total syntheses of palmarumycin CP_1 and deoxypreussomerin A, two representative members of this class of natural products. Our work provides further support for the intermediacy of phenolic binaphthyl ethers related to **6** or **7** in the biosynthesis of naphthoquinone natural products, as first postulated by Krohn et al.[3g,5] We are currently extending our biomimetic strategy toward the enantioselective synthesis of diepoxin *σ*.

Acknowledgment. This work was supported by the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Supporting Information Available: Experimental details and characterization for **1**, **6**, **7**, palmarumycin CP_1, and (±)-deoxypreussomerin A (16 pages).

JO980576V

(14) Spectroscopic data for synthetic palmarumycin CP_1: mp 170 °C dec; IR (neat) 3053, 1659, 1602, 1449, 1409, 1372, 1341, 1269, 1237, 1110, 1073, 942, 822, 746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 12.17 (s, 1 H, OH), 7.67 (t, 1 H, J = 8.0 Hz), 7.58 (d, 2 H, J = 8.5 Hz), 7.47 (t, 2 H, J = 7.9 Hz), 7.46 (d, 1 H, J = 7.8 Hz), 7.14 (dd, 1 H, J = 8.2, 1.1 Hz), 7.02 (d, 1 H, J = 10.9 Hz), 6.98 (d, 2 H, J = 7.7 Hz), 6.37 (d, 1 H, J = 10.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 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.

(15) Spectroscopic data for synthetic (±)-deoxypreussomerin A (palmarumycin C_2): 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}; ^1H NMR (300 MHz, $CDCl_3$) δ 11.37 (s, 1 H, OH), 7.65 (t, 1 H, J = 8.0 Hz), 7.60 (d, 1 H, J = 8.6 Hz), 7.57 (d, 1 H, J = 8.0 Hz), 7.53 (t, 1 H, J = 8.3 Hz), 7.45 (t, 1 H, J = 7.4 Hz), 7.44 (d, 1 H, J = 7.9 Hz), 7.19 (dd, 1 H, J = 7.6, 0.8 Hz), 7.14 (dd, 1 H, J = 8.6, 0.8 Hz), 6.92 (dd, 1 H, J = 7.6, 0.7 Hz), 4.09 (d, 1 H, J = 4.1 Hz), 3.68 (d, 1 H, J = 3.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 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.