Total Synthesis of the Spiroketal Naphthoquinone (±)-Diepoxin σ

Peter Wipf* and Jae-Kyu Jung

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received December 3, 1998

Due to their extraordinary level of oxygenation and the presence of highly electrophilic oxiranyl ketone functionalities, spiroketal naphthodecalins of the preussomerin, palmarumycin, and diepoxin type present challenging targets for total synthesis (Figure 1). We have recently established efficient approaches toward palmarumycin CP_1 and (±)-deoxypreussomerin A (palmarumycin C_2).[1] Independently, total syntheses of palmarumycin CP_1, CP_2, and the related CJ-12,371 have also been disclosed by Barett et al. and Taylor et al.[2,3] The structure of the more highly oxygenated diepoxin σ (Sch 49209) was reported in 1993 by Schlingmann et al. from American Cyanamid and in 1994 by Chu et al. from Schering-Plough.[4,5] The absolute stereochemistry of diepoxin σ was assigned in 1996 by exciton-coupled CD.[6] Diepoxin σ shows considerable antifungal activity and MIC's against a panel of selected bacteria in the range of 4−32 μg/mL.[4] The Schering group also reported potent in vitro activity in the antitumor invasion assay, with an IC_{50} of 0.75 μM against HT 1080 human fibrosarcoma cells.[5] Furthermore, in vivo this compound demonstrated a significant reduction in the size of primary tumors and the number of metastases.[5]

As a continuation of our program toward the synthesis and mechanistic evaluation of the reactivity pattern of epoxyketone natural products such as aranorosin and manumycins,[7] we reported the first synthetic strategy toward diepoxins in 1997.[8] In a demonstration of the use of long-range dipole effects in chiral auxiliary design, we were able to obtain enantiomerically pure model compound **2** in eight steps and 8.3% overall yield from **1** (Scheme 1).[8] However, after selective monohydrolysis of the trifluoromethyl acetal and hydroxy-group directed bis-epoxidation followed by removal of the chiral auxiliary from **3** to give diketone **4**, we were unable to introduce naphthodiol to gain access to spiroketal **5**. Therefore, we modified our retrosynthetic strategy to diepoxin σ as shown in Scheme 2.

Introducing the naphthodiol acetal before enone epoxidation by spirocyclization[1] to quinone **6** was envisioned to solve the problems encountered in the acetalization stage of our first generation approach shown in Scheme 1. The biaryl ether precursor to **6** could be conveniently derived by Ullmann ether coupling of protected hydroquinone **8** with 8-iodo-1-methoxynaphthalene (**7**).[1] During the entire course of the synthesis, the enone alkene moiety in the target molecule was going to be protected as the Diels−Alder

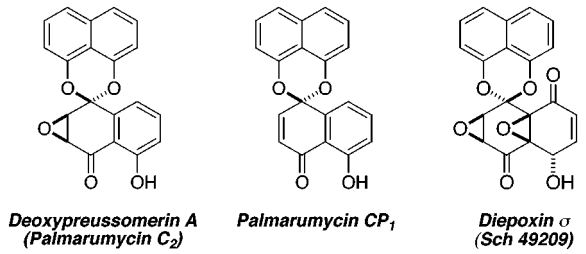
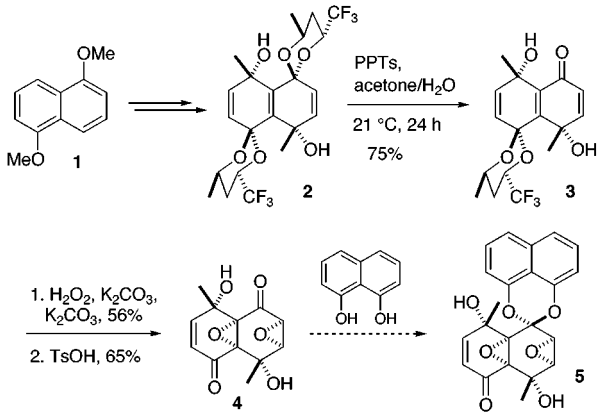
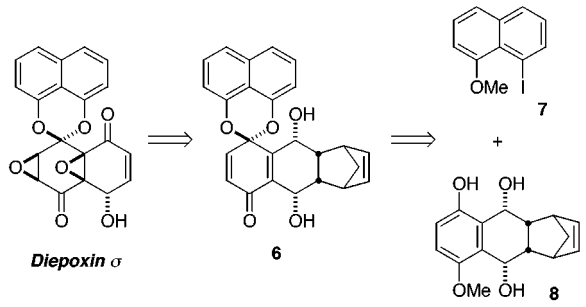


Figure 1.

Scheme 1



Scheme 2



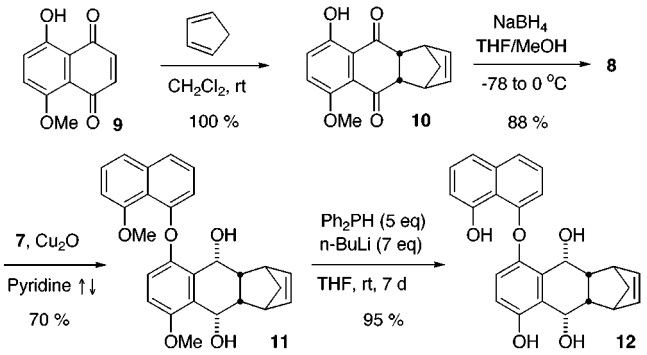
adduct with cyclopentadiene.[9,10] Despite the risk involved in a high-temperature retro Diels−Alder reaction on the densely functionalized diepoxin core, this strategy proved successful for the first preparation of this highly oxygenated natural product.

[4 + 2] Cycloaddition between *O*-methylnaphthazarin (**9**)[11] and cyclopentadiene followed by syn-reduction of naphthoquinone **10** readily provided the desired phenol **8** (Scheme 3). Ullmann coupling of this triol with iodide **7**[12] in the presence of stoichiometric copper(I) oxide[13] led to the biaryl ether **11** in 70% yield. Demethylation of **11** proved to be a very challenging reaction due to the acid/base lability of the two benzylic alcohols. After considerable experimentation

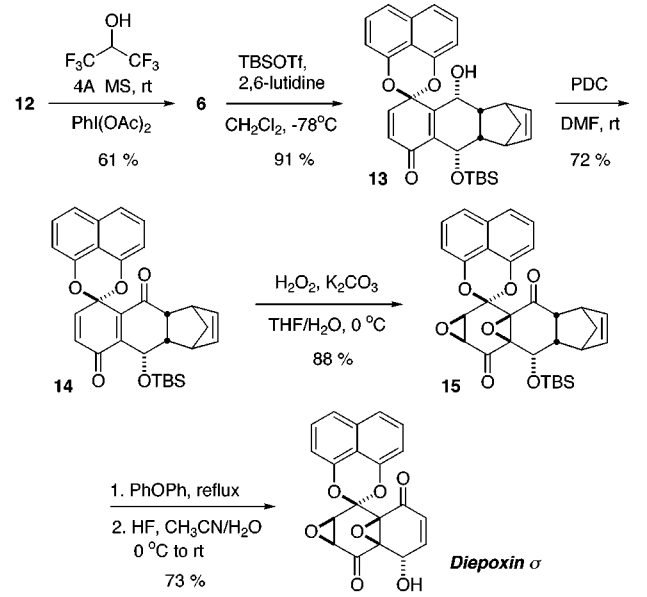
(1) Wipf, P.; Jung, J.-K. *J. Org. Chem.* **1998**, *63*, 3530.
(2) Barrett, A. G. M.; Hamprecht, D.; Meyer, T. *Chem. Commun.* **1998**, 809.
(3) Ragot, J. P.; Alcarez, M.-L.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 4921.
(4) Schlingmann, G.; West, R. R.; Milne, L.; Pearce, C. J.; Carter, G. T. *Tetrahedron Lett.* **1993**, *34*, 7225.
(5) Chu, M.; Truumees, I.; Patel, M. G.; Gullo, V. P.; Puar, M. S.; McPhail, A. T. *J. Org. Chem.* **1994**, *59*, 1222.
(6) Schlingmann, G.; Matile, S.; Berova, N.; Nakanishi, K.; Carter, G. T. *Tetrahedron* **1996**, *52*, 435.
(7) (a) Wipf, P.; Kim, Y. *J. Org. Chem.* **1993**, *58*, 1649. (b) Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, *58*, 7195. (c) Wipf, P.; Kim, Y. *J. Org. Chem.* **1994**, *59*, 3518. (d) Wipf, P.; Kim, Y.; Jahn, H. *Synthesis* **1995**, 1549.
(8) Wipf, P.; Jung, J.-K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 764.
(9) In an earlier approach, we had failed to introduce this unsaturation by Saegusa−Ito or related schemes: Wipf, P.; Jung, J.-K. Unpublished results.
(10) For other applications of the Diels−Alder protective group strategy, see: (a) Ichihara, A.; Kimura, R.; Oda, K.; Sakamura, S. *Tetrahedron Lett.* **1976**, 4741. (b) Kamikubo, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1996**, 1679.
(11) Compound **9** was prepared in 46% yield from 1,5-dimethoxynaphthalene by bisformylation with Cl_2CHOCH_3 and $TiCl_4$, oxidative removal of formyl groups with *m*-CPBA and LiOH, and oxidation with $FeCl_3$. See ref 8 and Laatsch, H. *Liebigs Ann. Chem.* **1990**, 1151.
(12) Graybill, B. M.; Shirley, D. A. *J. Org. Chem.* **1966**, *31*, 1221.
(13) Moroz, A. A.; Shvartsberg, M. S. *Russ. Chem. Rev.* **1974**, *43*, 679.

10.1021/jo9823691 CCC: $18.00
Published on Web 01/28/1999

Scheme 3



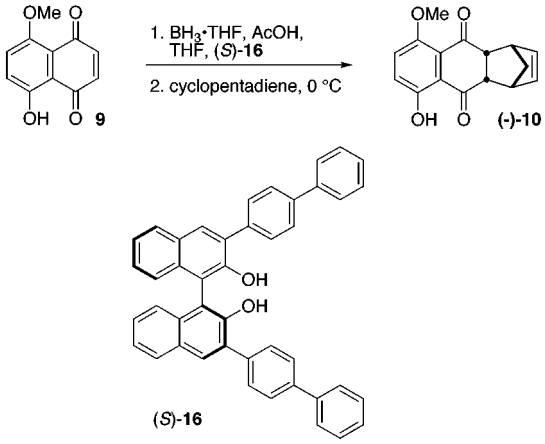
Scheme 4



with various methyl aryl ether cleavage protocols, we found that lithiated diphenylphosphine[14] was very well suited to convert **11** into tetrol **12** in near-quantitative yield.

Oxidative acetalization[1] of tetrol **12** with iodobenzene diacetate[15] in hexafluoro-2-propanol provided the naphthoquinone **6** in 61% yield (Scheme 4). In contrast, oxidation in trifluoroethanol or methylene chloride/acetonitrile failed to give a satisfactory yield (only 25−30% of **6** could be isolated). After regioselective protection of the less hindered alcohol and oxidation with pyridinium dichromate, bis-epoxidation from the convex face of dienedione **14** led to the advanced intermediate **15** in 88% yield. Traces of a stereoisomeric side

Scheme 5



product were observed at room temperature, but only a single diepoxide was isolated when the reaction was run at 0 °C. Despite the high temperatures required for the retro Diels−Alder reaction of compound **15**, the use of diphenyl ether at 250−260 °C reflux temperatures smoothly converted the pentacyclic **15** to the corresponding γ-silyloxy enone, which provided the desired (±)-diepoxin σ after deprotection with aqueous HF. The synthetic compound was obtained in 10 steps and 15% overall yield from naphthoquinone **9** and was spectroscopically identical to data reported for the natural sample.[16]

This methodology establishes, for the first time, a successful synthetic strategy toward the highly oxygenated diepoxin family of naphthaline dimers. We are also able to obtain enantiomerically highly enriched material from an asymmetric version of the Diels−Alder reaction of *O*-methylnaphthazarin and cyclopentadiene (Scheme 5). In the presence of 2 equiv of chiral ligand **16**,[17] (−)-**10** was isolated in 70% ee.[18] Further progress toward the asymmetric total syntheses of diepoxins will be reported in due course.

Acknowledgment. This work was supported by the National Science Foundation and the Sloan and Camille Dreyfus Foundations.

Supporting Information Available: Experimental details and characterization for all new compounds. Copies of ^{1}H and ^{13}C NMR spectra.

JO9823691

(14) (a) Mann, F. G.; Pragnell, M. J. *J. Chem. Soc.* **1965**, 4120. (b) Ireland, R. E.; Walba, D. M. *Org. Synth.* **1977**, *56*, 44.

(15) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677.

(16) Mp 230−235 °C dec; ^{1}H NMR δ 7.57 (d, 1 H, J = 8.0 Hz), 7.56 (d, 1 H, J = 8.2 Hz), 7.50 (t, 1 H, J = 7.5 Hz), 7.45 (t, 1 H, J = 7.9 Hz), 7.17 (d, 1 H, J = 7.6 Hz), 6.99 (d, 1 H, J = 7.5 Hz), 6.65 (dd, 1 H, J = 10.6, 5.3 Hz), 6.05 (d, 1 H, J = 10.5 Hz), 5.18 (d, 1 H, J = 5.3 Hz), 3.86 (d, 1 H, J = 3.9 Hz), 3.52 (d, 1 H, J = 3.9 Hz), 3.6−3.4 (bs, 1 H, OH); ^{13}C NMR δ 197.8, 185.4, 145.0, 139.8, 134.3, 128.0, 127.8, 127.5, 121.5, 121.4, 112.0, 110.0, 109.3, 93.6, 66.5, 65.5, 62.0, 58.1, 54.8; HRMS (EI) calcd for $C_{20}H_{12}O_7$ 364.0583, found 364.0597.

(17) Simonsen, K. B.; Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 7536.

(18) The enantioselectivity of this reaction was determined by chiral HPLC analysis (Chiralcel OD) of (−)-**10**.