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Total Synthesis of the Novel NF-κB Inhibitor (−)-Cycloepoxydon

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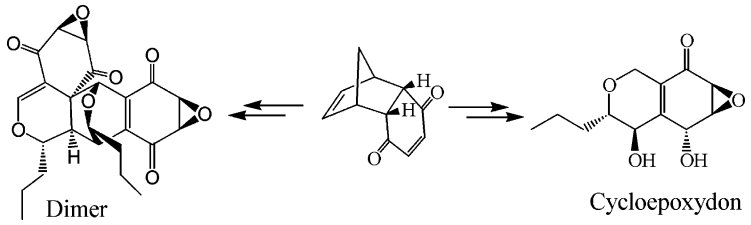
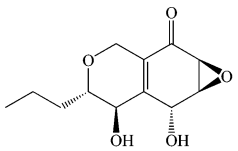
ABSTRACT



An enantioselective total synthesis of the novel, biologically active epoxyquinone natural product (−)-cycloepoxydon has been accomplished from the readily available Diels−Alder adduct of cyclopentadiene and *p*-benzoquinone. A new cycloepoxydon related heptacyclic dimer has been prepared and characterized.

Polyketide-derived natural products, embodying an epoxyquinone core, are surfacing with increasing frequency from diverse natural sources, and have been found to exhibit promising, wide-ranging biological activity.[1] Cycloepoxydon **1** from a *deuteromycete* strain,[1c] jesterone **2** from the fungal species *P. jesteri*,[1f] panepoxydone **3** from basidiomycete *Lentinus* crinitus,[1b] and yanuthone A **4** from a marine isolate of *Aspergillus niger*[1d] constitute representative recent examples of the monomeric epoxyquinones encountered in nature. Among these, cycloepoxydon **1** has been shown to inhibit activation of NF-κB, an inducible, ubiquitous transcription factor that regulates the expression of various cellular genes involved in immune and inflammation responses and apoptosis.[1c]



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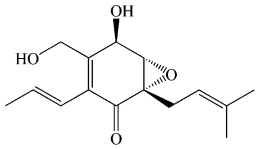

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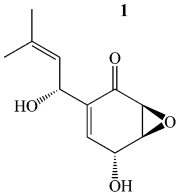

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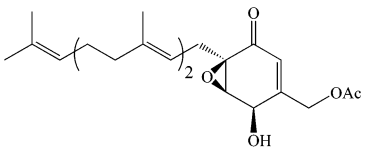

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Thus, **1** and its analogues have the potential for broad applications as novel therapeutic agents. As a result, synthetic protocols providing access to **1** through simple, flexible strategies from readily available building blocks hold special appeal. The research group of Porco has recently accomplished[2] the first total synthesis of (−)-cycloepoxydon **1** in which tartrate-mediated asymmetric epoxidation through nucleophilic addition was an important step. As part of our ongoing interest[3] in the synthesis of epoxyquinone natural products, we describe here a total synthesis of (−)-cycloepoxydon **1**.

Recently, we have achieved convenient access to (+)-**5** via enzymatic desymmetrization of **6**,[4] which in turn has been prepared from the readily available Diels−Alder adduct **7** of cyclopentadiene and benzoquinone.[3a] Our synthetic pursuit

(1) (a) Oloigosporons: Anderson, M. G.; Jarman, T. B.; Rickards, R. W. *J. Antibiot.* **1995**, *48*, 391. (b) Panepoxydon: Erkel, G.; Anke, T.; Sterner, O. *Biochem. Biophys. Res. Commun.* **1996**, *226*, 214. (c) Cycloepoxydon: Gehrt, A.; Erkel, G.; Anke, H.; Anke, T.; Sterner, O. *Nat. Prod. Lett.* **1997**, *9*, 259. Gehrt, A.; Erkel, G.; Anke, T.; Sterner, O. *J. Antibiot.* **1998**, *51*, 455. (d) Yanuthones: Bugni, T. S.; Abbanat, D.; Bernan, V. S.; Maiese, W. M.; Greenstein, M.; Van Wagoner, R. M.; Ireland, C. M. *J. Org. Chem.* **2000**, *65*, 7195. (e) Ambuic acid: Li, J. Y.; Harper, J. K.; Grant, D. M.; Tombe, B. O.; Bashyal, B.; Hess, W. M.; Strobel, G. A. *Phytochemistry* **2001**, *56*, 463. (f) Jesterone: Li, J. Y.; Strobel, G. A. *Phytochemistry* **2001**, *57*, 261.

(2) Li, C.; Pace, E. A.; Liang, M.-C.; Lobkovsky, E.; Gilmore, T. D.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 11308.

(3) (a) Mehta, G.; Islam, K. *Tetrahedron lett*. **2003**, *44*, 3569. (b) Mehta, G.; Ramesh, S. S. *Tetrahedron Lett*. **2004**, *45*, 1985.

(4) Mehta, G.; Islam, K. To be submitted for publication.

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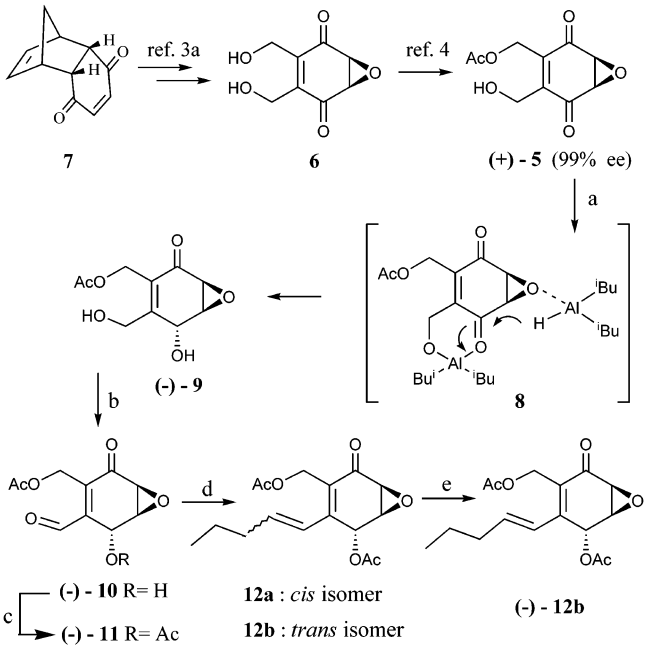
of **1** emanated from the enantiomerically pure epoxyquinone (+)-**5**, which had two strategically placed and chemodifferentiated sidearms on the epoxyquinone core.

Dibal-H reduction in (+)-**5** was both regio- and stereoselective to furnish (−)-**9** through a chelation-controlled process involving the intermediacy of an aluminum chelate[5] **8** and hydride delivery from the same face as the epoxide ring (Scheme 1).[6] TEMPO-mediated oxidation[7] in (−)-**9** was chemoselective and exclusively furnished the aldehyde (−)-**10**[6] through the oxidation of the allylic primary hydroxyl group. The secondary hydroxy group in (−)-**10** was protected at this stage to give diacetate (−)-**11** (Scheme 1). Four-carbon Wittig olefination in (−)-**11** was chemoselective and engaged only the allylic aldehyde group but the stereoselectivity in this reaction was unsatisfactory and led to a cis:trans mixture of diastereomers **12a**,**b** (2.6:1) (Scheme 1). Since only the trans-isomer **12b** was considered serviceable for further elaboration to the natural product **1**, considerable effort was expended toward improving the stereoselectivity of the Wittig reaction but without much success. However, a solution to this problem was devised by exploiting the possibility of photochemical cis−trans isomerization of the disubstituted double bond in the dienone chromophore present in **12a**,**b**. When the mixture of diastereomers **12a**,**b** was irradiated from a 450-W Hg lamp through Pyrex in the presence of iodine, it cleanly and quantitatively furnished the desired trans-isomer (−)-**12b** (Scheme 1).[6]

Scheme 1 [a]



[a] Reagents and conditions: (a) DIBALH (2 equiv), THF, −78 °C, 74%; (b) TEMPO, O_2, CuCl, DMF, rt, 77%; (c) Ac_2O, pyridine, DMAP, DCM, 0 °C, 71%; (d) *n*-$C_4H_9PPh_3Br$, *t*-BuOK, THF, 0 °C, 54%; (e) *hν*, 450 W (Hanovia), I_2, $CDCl_3$, 2 h, quant.

Acetate hydrolysis in (−)-**12b** led to the diol (−)-**13** and the primary hydroxyl group was selectively protected as the TBS derivative (−)-**14** (Scheme 2).[6] Epoxidation of the trans double bond in the side chain with *m*-chloroperbenzoic acid in aqueous buffer was stereoselective and occurred exclusively from the face opposite to the neighboring secondary hydroxyl group to deliver the *γ*,*δ*-epoxyenone (−)-**15**,[6] an outcome along the lines previously observed by Porco et al.[2] When (−)-**15** was exposed to 40% HF in acetonitrile to remove the TBS protecting group, concomitant hydroxy-mediated *endo*-epoxide opening was also encountered to furnish (−)-cycloepoxydon **1** as the predominant product.[6,8] Our synthetic (−)-**1** had spectral data (^{1}H and ^{13}C NMR) identical with that reported in the literature[1c] for the natural product and had an $[\alpha]_D$ value of −135° ($CHCl_3$−CH_3OH 90:10), lit. $[\alpha]_D$ −145° ($CHCl_3$−CH_3OH 95:5).[1c]

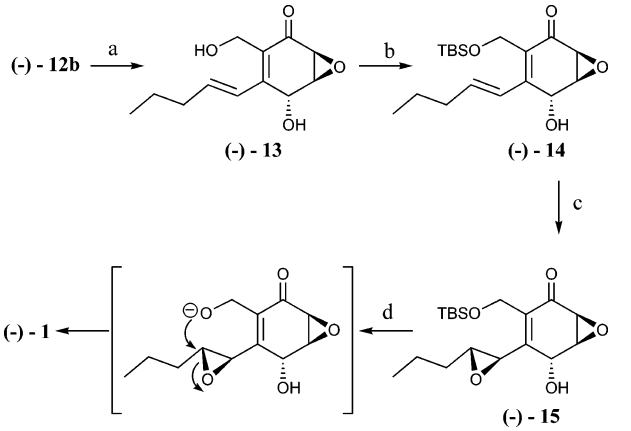
It has been demonstrated recently that dimeric products derived from epoxyquinones, both of natural as well as synthetic origin, exhibit a notable and sometimes enhanced

(5) Kiyooka, S.-I.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009.

(6) All new compounds were fully characterized on the basis of spectral data (IR, ^{1}H and ^{13}C NMR, mass). Selected spectral data: (−)-**9**: $[\alpha]^{23}_D$ (−)176 (*c* 4.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 4.99 (1H, s), 4.88 (1H, d, *J* = 12.3 Hz), 4.77 (1H, d, *J* = 12.0 Hz), 4.55 (2H, br s), 4.04 (1H, s), 3.84 (1H, s), 3.56 (1H, s), 3.46 (1H, s), 2.02 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 193.2, 171.6, 154.5, 127.5, 64.3, 61.2, 56.6, 56.1, 52.6, 20.8; HRMS (ES) *m*/*z* calcd for $C_{10}H_{12}NaO_6$ [M + Na]$^+$ 251.0532, found 251.0536. (−)-**10**: $[\alpha]^{24}_D$ (−)305 (*c* 2.36, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 10.33 (1H, s), 5.21 (1H, d, *J* = 12.6 Hz), 5.20 (1H, s), 5.14 (1H, d, *J* = 12.6 Hz), 3.88 (1H, d, *J* = 3.9 Hz), 3.66 (1H, d, *J* = 3.6 Hz), 2.05 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 194.5, 192.7, 170.4, 144.0, 134.7, 60.8, 55.7, 54.8, 52.8, 20.6; HRMS (ES) *m*/*z* calcd for $C_{10}H_{10}NaO6$ [M + Na]$^+$ 249.0375, found 249.0369. (−)-**12b**: $[\alpha]^{24}_D$ (−)194 (*c* 1.09, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 6.44 (1H, d, *J* = 15.9 Hz), 6.35 (1H, s), 6.29−6.21 (1H, m), 5.02 (1H, d, *J* = 11.7 Hz), 4.85 (1H, d, *J* = 11.7 Hz), 3.75 (1H, m), 3.57 (1H, d, *J* = 3.9 Hz), 2.21 (2H, q, *J* = 7.2 Hz), 2.13 (3H, s), 2.05 (3H, s), 1.47 (2H, sextate, *J* = 7.2 Hz), 0.92 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 193.1, 170.7, 169.9, 145.7, 142.5, 128.2, 125.0, 63.2, 56.4, 53.0, 52.0, 35.9, 21.9, 20.8, 20.7, 13.5; HRMS (ES) *m*/*z* calcd for $C_{16}H_{20}NaO_6$ [M + Na]$^+$ 331.1158, found 331.1161. (−)-**13**: $[\alpha]^{24}_D$ (−)231 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 6.56−6.48 (2H, m), 5.04 (1H, s), 4.37 (2H, s), 3.87 (1H, dd, *J* = 1.2, 3.6 Hz), 3.5 (1H, dd, *J* = 0.6, 3.6 Hz), 2.29−2.21 (2H, m), 1.51 (2H, sextate, *J* = 7.2 Hz), 0.95 (1H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 196.2, 148.9, 143.4, 129.5, 125.2, 63.1, 55.8, 55.5, 52.4, 36.0, 22.0, 13.7; HRMS (ES) *m*/*z* calcd for $C_{12}H_{16}NaO_4$ [M + Na]$^+$ 247.0946, found 247.0950. (−)-**15**: $[\alpha]^{23}_D$ (−)-140 (*c* 0.72, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 4.64 (1H, d, *J* = 12.6 Hz), 4.43 (1H, d, *J* = 12.3 Hz), 4.36 (1H, br s), 3.97 (1H, d, *J* = 2.4 Hz), 3.78 (1H, dd, *J* = 1.5, 3.6 Hz), 3.53 (1H, dd, *J* = 0.6, 3.6 Hz), 3.19−3.15 (2H, m), 1.79−1.73 (1H, m), 1.68−1.46 (3H, m), 0.99 (3H, t, *J* = 7.2 Hz), 0.86 (9H, s), 0.02 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 192.2, 150.4, 134.3, 61.5, 60.2, 56.4, 55.6, 55.5, 52.7, 33.9, 25.8 (3 C), 19.1, 18.2, 13.8, −5.2, −5.4; HRMS (ES) *m*/*z* calcd for $C_{18}H_{30}NaO_5Si$ [M + Na]$^+$ 377.1760, found 377.1743. (−)-**1**: $[\alpha]^{23}_D$ (−)135 (*c* 0.55, $CHCl_3$:MeOH 90:10); ^{1}H NMR [300 MHz, $CDCl_3$:MeOH-d_4 90:10] *δ* 4.92 (1H, s), 4.51 (1H, dd, *J* = 2.1, 17.1 Hz), 4.07−4.04 (2H, m), 3.77 (1H, dd, *J* = 1.2, 3.6 Hz), 3.40 (1H, dd, *J* = 0.9, 3.6 Hz), 3.30 (1H, m), 1.72 (1H, m), 1.52 (1H, m), 1.44−1.32 (2H, m), 0.9 (3H, t, *J* = 7.2 Hz); ^{13}C NMR [75 MHz, $CDCl_3$:MeOH-d_4 90:10] 191.9, 150.5, 129.3, 77.7, 64.9, 62.0, 59.9, 57.0, 52.2, 33.9, 18.5, 13.9• (−)-**19**: $[\alpha]^{25}_D$ (−)159 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 6.61−6.51 (1H, m), 6.31 (1H, d, *J* = 16.2 Hz), 4.57 (1H, dd, *J* = 6.9, 12.9 Hz), 4.44 (1H, dd, *J* = 5.1, 12.6 Hz), 3.89 (1H, d, *J* = 4.2 Hz), 3.86 (1H, d, *J* = 3.9 Hz), 2.40 (1H, t, *J* = 6.3 Hz), 2.23 (2H, q, *J* = 7.2 Hz), 1.88 (2H, sextate, *J* = 7.2 Hz), 0.94 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 193.8, 192.9, 147.4, 141.6, 137.0, 120.5, 57.3, 54.0, 53.7, 36.5, 21.8, 13.7; HRMS (ES) m/z calcd for $C_{12}H_{14}NaO_4$ [M + Na]$^+$ 245.0790, found 245.0779. (+)-**24**: $[\alpha]^{23}_D$ (+)144 (*c* 0.90, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.89 (1H, s), 5.68 (1H, s), 4.37 (1H, q, *J* = 4.8 Hz), 4.18 (1H, t, *J* = 6.3 Hz), 3.88 (1H, d, *J* = 3.6 Hz), 3.84 (1H, d, *J* = 4.2 Hz), 3.82 (1H, d, *J* = 3.6 Hz), 3.67 (1H, d, *J* = 3.6 Hz), 3.28 (1H, s), 2.64 (1H, d, *J* = 2.7 Hz), 1.35−1.17 (8H, m), 0.89−0.83 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) 199.9, 187.7, 187.6, 187.0, 159.3, 145.0, 143.5, 112.3, 81.4, 71.4, 69.5, 60.6, 55.7, 54.6, 54.2, 49.9, 38.8, 36.9, 36.4, 35.0, 18.9, 18.5, 13.8, 13.4; HRMS (ES) *m*/*z* calcd for $C_{24}H_{24}NaO_8$ [M + Na]$^+$ 463.1369, found 463.1360.

(7) Semmelhack, M. F.; Schmid, C. R.; Cortes, D. A.; Chou, C. S. *J. Am. Chem. Soc*. **1984**, *106*, 3374.

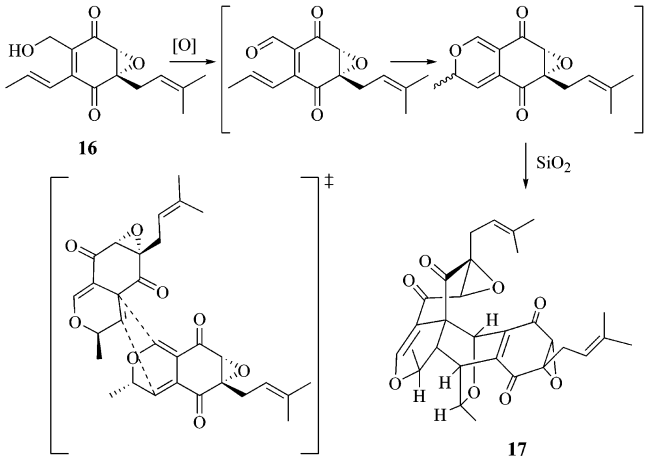
Scheme 2 [a]



[a] Reagents and conditions: (a) LiOH, MeOH, 0 °C, 66%; (b) TBSCl, imidazole, DMAP, DCM, 0 °C, 92%; (c) MCPBA, DCM, pH 7, rt, 86%; (d) 40% HF, CH_3CN, 0 °C, 2 h, 69%.

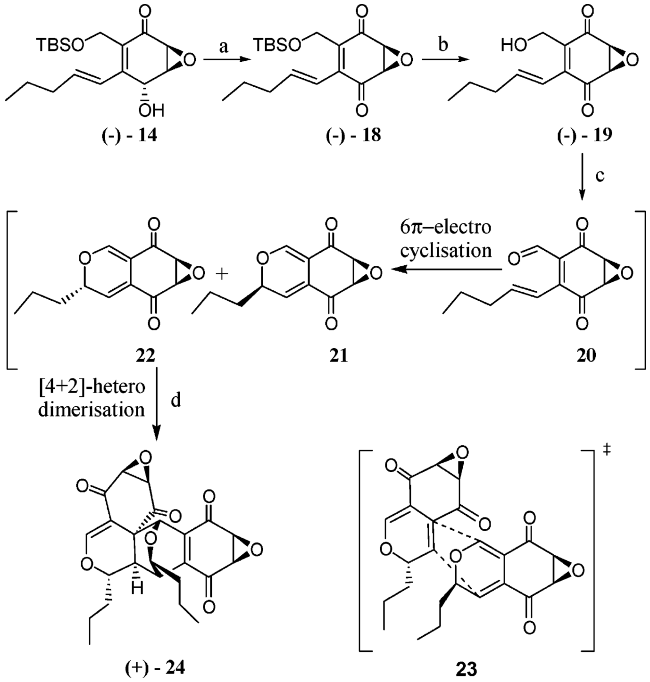
biological activity profile.[9] For example, a "jesterone dimer" **17**, prepared from epoxyquinone **16** via a 6π electrocyclization, [4+2]-cycloaddition cascade (Scheme 3), has been

Scheme 3



shown to exhibit impressive anti-cancer activity against human breast and leukemia cell lines.[10] In light of such observations, it was of interest to prepare a cycloepoxydon-related dimer. Consequently, (−)-**14** was oxidized with TPAP to the epoxyquinone (−)-**18** and the TBS deprotection led to (−)-**19** (Scheme 4).[6] Dess−Martin oxidation[11] furnished the intermediate aldehyde **20,** which underwent concomitant 6π electron cyclization to **21** and **22** and further endo-selective intermolecular Diels−Alder heterodimerization (see **23**) led to the "cycloepoxydon dimer" (+)-**24** (Scheme 4).[6] The stereostructure of (+)-**24** follows from similar endo-dimerizations documented in the literature[12−14] wherein the two alkyl chains are positioned to minimize steric interactions.

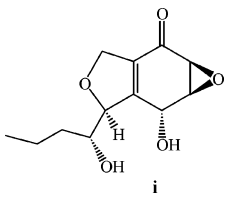
Scheme 4 [a]



[a] Reagents and conditions: (a) TPAP, NMMO, mol. Sieve, DCM, rt, 82%; (b) HF·Py, CH_3CN, 0 °C, 91%; (c) Dess−Martin periodinane, DCM, rt; (d) SiO_2, DCM, rt, 70% (in two steps).

In summary, we have achieved a simple and effective enantioselective synthesis of the novel epoxyquinone natural

(8) Porco et al.[2] have reported the formation of **1** and regioisomeric exo-cyclized product isocycloepoxydon **i** in a ratio of 3:2 during the hydroxyl-mediated opening of the epoxide closely related to (−)-**15**. However, in our case, employing (−)-**15** and slightly different reaction conditions, **1** was obtained as the major product with isocycloepoxydon **i** constituting about 10% of the reaction mixture.



i

(9) (a) Torreyanic acid: Lee, J. C.; Strobel, G. A.; Lobkovsky, E.; Clardy, J. *J. Org. Chem.* **1996**, *61*, 3232. (b) Epoxyquinol A: Kakeya, H.; Onose, R.; Koshino, H.; Yoshida, A.; Kobayashi, K.; Kageyama, S.-I.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124*, 3496. (c) Epoxyquinol B: Kakeya, H.; Onose, R.; Yoshida, A.; Koshino, H.; Osada, H. *J. Antibiot.* **2002**, *55*, 829. (d) Panepophenanthrin: Sekiizawa, R.; Ikeno, S.; Nakamura, H.; Naganawa, H.; Matsui, S.; Iinuma, H.; Takeuchi, T. *J. Nat. Prod.* **2002**, *65*, 1491.

(10) (a) Hu, Y.; Li, C.; Kulkarni, B. A.; Strobel, G.; Lobkovsky, E.; Torczynski, R. M.; Porco, J. A., Jr. *Org. Lett.* **2001**, *3*, 1649. (b) Liang, M.-C.; Bardhan, S.; Li, C.; Pace, E. A.; Porco, J. A., Jr.; Gilmore, T. D. *Mol. Pharmacol.* **2003**, *64*, 123.

(11) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(12) Li, C.; Johnson, R. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 5095−5106.

(13) Transition state calculations[12,14] for the Diels−Alder dimerization of several model epoxyquinones related to **21** and **22**, as well as mechanistic studies, support the assignment of endo-anti dimeric structure (+)-**24**.

(14) Shoji, M.; Kishida, S.; Kodera, Y.; Shiina, I.; Kakeya, H.; Osada, H.; Hayashi, Y. *Tetrahdron. Lett.* **2003**, *44*, 7205.

product (−)-cycloepoxydon from the readily available Diels−Alder adduct of cyclopentadiene and *p*-benzoquinone. A cycloepoxydone related dimer with biological potential has also been prepared.

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