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Selective Oxidation of 8,8′-Hydroxylated Binaphthols to Bis-spironaphthalenones or Binaphtho-*para*- and Binaphtho-*ortho*-quinones

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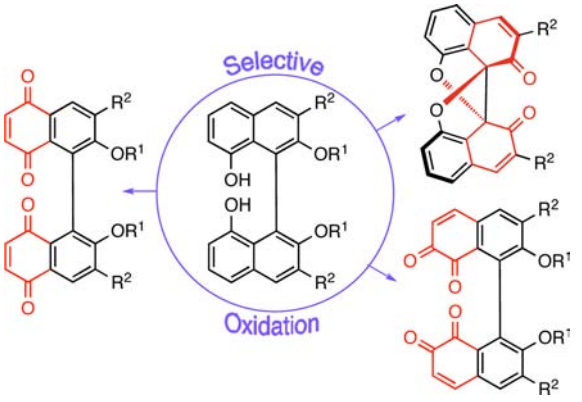
ABSTRACT



The selective oxidation of a series of functionalized 8,8′-hydroxylated binaphthols to binaphtho-*para*- and binaphtho-*ortho*-quinones has been realized using either a Co-salen catalyst or *ortho*-iodoxybenzoic acid. A unique spirocyclic bis-spironaphthalenone was also obtained in good yield via a phenyliodonium diacetate promoted oxidative dearomatization.

Naphthoquinones are prominent naturally occurring pigments and metabolites found in a variety of lifeforms, including animals, plants, fungi, and microorganisms.[1] While most of the structures are monomeric, there are several examples of natural products displaying an axially chiral binaphtho-*para*-quinone unit (**2**, Figure 1) as part of their architecture. These compounds include the binaphtho-*para*-quinones maritinone,[2] hypocrellin D,[3] and the alterporriols,[4] as well as numerous bisanthraquinones, such as bisoranjidiol[5] and skyrin.[6] The bioactivity of those biaryls and related axially or helically chiral natural products makes them attractive synthetic targets, leading to a need for efficient entries to binaphthoquinones. For example, the first total synthesis of (*S*)-bisoranjidiol was accomplished through the use of an axially chiral binaphtho-*para*-quinone as the dieneophile in a Diels–Alder reaction.[7] In addition, binaphtho-*ortho*-quinones have been used as intermediates for the synthesis of the

(1) Thomson, R. H. *Naturally Occurring Quinones III: Recent Advances*, 3rd ed.; Chapman and Hall: New York, 1987.
(2) Tezuka, M.; Takahasi, C.; Kuroyanagi, M.; Satake, M.; Yoshihira, K.; Natori, S. *Phytochemistry* **1973**, *12*, 175–183.
(3) Fang, L.-Z.; Qing, C.; Shao, H.-J.; Yang, Y.-D.; Dong, Z.-J.; Wang, F.; Zhao, W.; Yang, W.-Q.; Liu, J.-K. *J. Antibiot.* **2006**, *59*, 351–354.
(4) (a) Ohnishi, K.; Suemitsu, R.; Kubota, M.; Matano, H.; Yamada, Y. *Phytochemistry* **1991**, *30*, 2593–2595. (b) Debbab, A.; Aly, A. H.; Edrada-Ebel, R.; Wray, V.; Müller, W. E. G.; Totzke, F.; Zirrgiebel, U.; Schächtele, C.; Kubbutat, M. H. G.; Lin, W. H.; Mosaddak, M.; Proksch, P.; Ebel, R. *J. Nat. Prod.* **2009**, *72*, 626–631. (c) Debbab, A.; Aly, A. H.; Edrada-Ebel, R.; Wray, V.; Proksch, A.; Pescitelli, G.; Kurtan, T.; Proksch, P. *Eur. J. Org. Chem.* **2012**, 1351–1359. (d) Zheng, C.-J.; Shao, C.-L.; Guo, Z.-Y.; Chen, J.-F.; Deng, D.-S.; Yang, K.-L.; Chen, Y.-Y.; Fu, X.-M.; She, Z.-G.; Lin, Y.-C.; Wang, C.-Y. *J. Nat. Prod.* **2012**, *75*, 189–197.
(5) Núñez Montoya, S. C.; Agnese, A. M.; Cabrera, J. L. *J. Nat. Prod.* **2006**, *69*, 801–803.
(6) Howard, B. H.; Raistrick, H. *Biochem. J.* **1954**, *56*, 56–65.
(7) Podlesny, E. E.; Kozlowski, M. C. *Org. Lett.* **2012**, *14*, 1408–1411.

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perylenequinones[8] and for a reported binaphthalenetetrol natural product.[9]

Aside from their applications in total synthesis, binaphthoquinones, such as targets **1** and **2** (Figure 1), represent interesting BINOL analogs and scaffolds for the development of chiral electron-poor ligands for asymmetric catalysis and redox active ligands.[10] Axially chiral binaphthoquinones may also lead to the development of organic oxidants, along the lines of benzoquinone, with the ability to effect asymmetric oxidations.

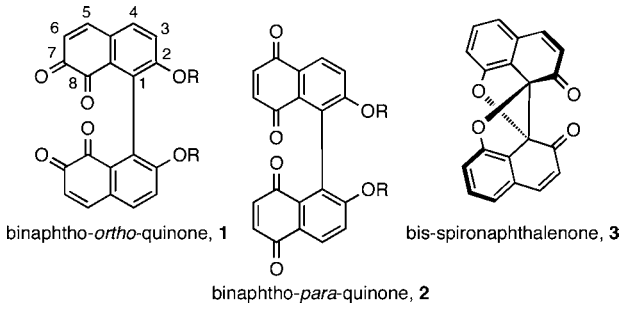
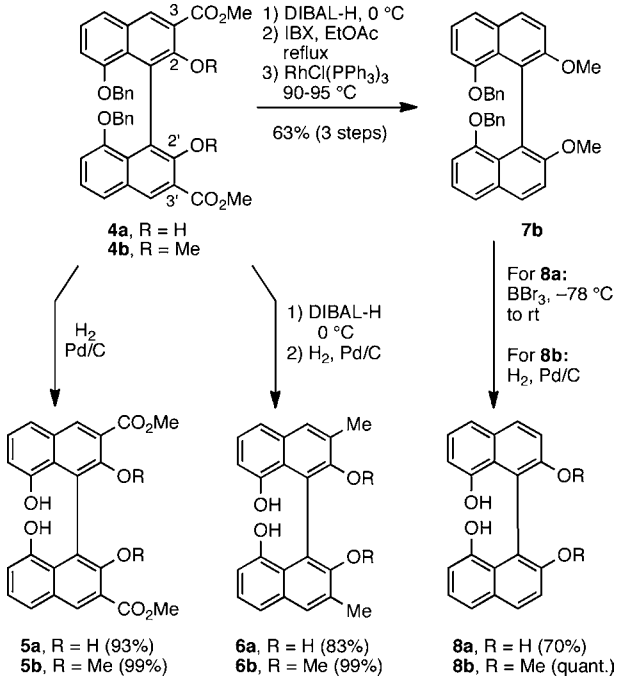


Figure 1. Targets of selective oxidation.

Previous syntheses of binaphtho-*para*-quinones, containing various linkages, have been reported via nonstereoselective oxidative dimerizations.[11] However, the selective oxidation to either the binaphtho-*ortho*- or binaphtho-*para*-quinone (**1** vs **2**, Figure 1) had not been described. Investigation of this oxidation with an 8,8′-hydroxylated binaphthol also led to exploration of a third structure, a unique bis-spironaphthalenone (**3**).

To explore selective quinone formation, three series of 8,8′-hydroxylated binaphthols were synthesized (Scheme 1), in which the functionality at the 3,3′-positions was varied and the hydroxyl at the 2,2′-positions was either free or protected. These six binaphthols were formed from common intermediate **4a** and its methylated version **4b**.[7] The first set of 3,3′-diester biaryls, **5a** and **5b**, were easily generated from **4a** and **4b** by hydrogenolysis of the benzyl groups. Likewise, the 3,3′-dimethyl biaryls, **6a** and **6b**, were produced in good yield over two steps by reduction of the methyl ester and hydrogenolysis of the resultant benzylic alcohols as well as the benzyl protecting groups. For the final set, the esters of **4b** could be removed via a three-step sequence, followed by hydrogenolysis of the benzyl groups to produce **8b**.[7] The corresponding tetrol was then formed by a global deprotection of **7b** with BBr_3 to give **8a** in 70% yield.

Scheme 1. Synthesis of 8,8′-Hydroxylated Binaphthols



For selective *para*-quinone formation, a Co-salen catalyzed oxidation[12] was found to provide the optimal results. Each of the diols **5b**, **6b**, and **8b** were selectively oxidized to the corresponding binaphtho-*para*-quinones **9b**, **11b**, and **10b** in 57−63% yield (Scheme 2). Approximately 19−23% of an unsymmetrical binaphtho-*ortho*,*para*-quinone was also generated in each case, but was easily removed upon purification. Other oxidants such as CAN, DDQ, phenyliodonium diacetate (PIDA), or phenyliodonium bis(trifluoroacetate) either led to complex mixtures or were inefficient. PIDA, in particular, was the most selective oxidant, providing only the desired binaphtho-*para*-quinones, but with consistently lower yields compared to Co-salen. In addition to *para*-quinone formation, the corresponding binaphtho-*ortho*-quinones could be formed selectively from the same intermediate with IBX (*o*-iodoxybenzoic acid).[13] For example, the use of 2 equiv of IBX led to the formation of **12b** in 74% yield (Scheme 2).

As removal of the protecting groups at the 2,2′-positions generally led to decomposition, selective oxidation of the

(8) (a) Merlic, C. A.; Aldrich, C. C.; Albaneze-Walker, J.; Saghatelian, A.; Mammen, J. *J. Org. Chem.* **2001**, *66*, 1297–1309. (b) Mulrooney, C. A.; Morgan, B. J.; Li, X.; Kozlowski, M. C. *J. Org. Chem.* **2010**, *75*, 16–29.

(9) Podlesny, E. E.; Kozlowski, M. C. *J. Nat. Prod.* **2012**, *75*, 1125–1129.

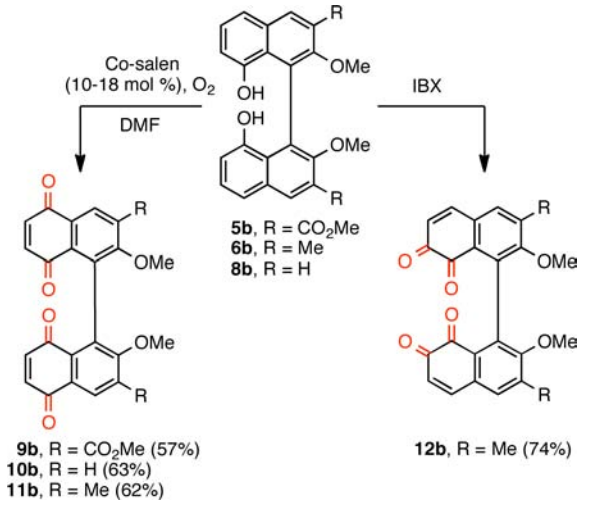
(10) For a review, see: Chirik, P. J.; Wieghardt, K. *Science* **2010**, *327*, 794–795.

(11) (a) Cameron, D. W.; Chan, H. W.-S. *J. Chem. Soc. C* **1966**, 1825–1832. (b) Cameron, D. W.; Chan, H. W.-S.; Hildyard, E. M. *J. Chem. Soc. C* **1966**, 1832–1836. (c) Blackburn, G. M.; Cameron, D. W.; Chan, H. W.-S. *J. Chem. Soc. C* **1966**, 1836–1842. (d) Banks, H. J.; Cameron, D. W.; Crossley, M. J.; Samuel, E. L. *Aust. J. Chem.* **1976**, *29*, 2247–2256. (e) Laatsch, H. *Liebigs Ann. Chem* **1985**, 2420–2442. (f) Okamoto, I.; Doi, H.; Kotani, E.; Takeya, T. *Tetrahedron Lett.* **2001**, *42*, 2987–2989. (g) Takeya, T.; Doi, H.; Ogata, T.; Okamoto, I.; Kotani, E. *Tetrahedron* **2004**, *60*, 9049–9060. (h) Takeya, T.; Otsuka, T.; Okamoto, I.; Kotani, E. *Tetrahedron* **2004**, *60*, 10681–10693.

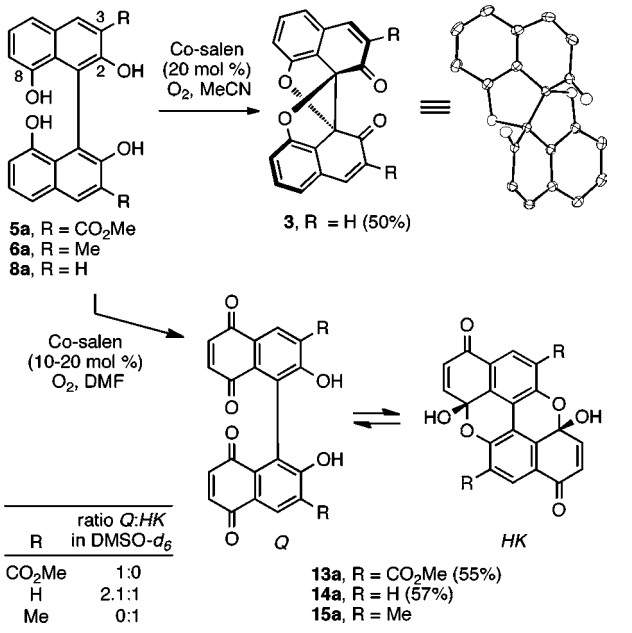
(12) (a) Wakamatsu, T.; Nishi, T.; Ohnuma, T.; Ban, Y. *Synth. Commun.* **1984**, *14*, 1167–1173. (b) Uliana, M. P.; Vieira, Y. W.; Donatoni, M. C.; Corrêa, A. G.; Brocksom, U.; Brocksom, T. J. *J. Braz. Chem. Soc* **2008**, *19*, 1484–1489.

(13) Magdziak, D.; Rodriguez, A. A.; Van De Water, R. W.; Pettus, T. R. R. *Org. Lett.* **2002**, *4*, 285–288.

Scheme 2. Oxidation to Binaphtho-*para* or Binaphtho-*ortho*-quinones



Scheme 3. Oxidation to Binaphtho-*para*-quinone or Bis-spironaphthalenone



unprotected tetrols **5a**, **6a**, and **8a** was explored. Using the standard conditions of Co-salen in DMF under oxygen, each of the tetrols was selectively oxidized to the corresponding binaphtho-*para*-quinone (**13a**–**15a**, Scheme 3). Interestingly, two of these binaphtho-*para*-quinones (Q) were observed via ^{1}H NMR to exist in equilibrium with their corresponding bishemiketals (HK), characterized by a nearly planar hexacyclic array compared to the axial chiral binaphtho-*para*-quinones (Q) with a 70°–80° dihedral angle between the two naphthoquinone units. This behavior has been reported to occur with a bisanthraquinone, but only upon treatment with acid.[14] The formation of HK was confirmed by trapping **14a** as the bisketal, via methylation using Ag_2O and MeI. The structure of the resultant bisketal was confirmed via X-ray crystallography.[15]

The ratio of bisquinone to bishemiketal (Q/HK) is dependent on both the substituents at the 3,3′-positions and the solvent. In DMSO-d_6, **13a**, with electron-withdrawing groups at the 3,3′-positions, exists exclusively as the binaphtho-*para*-quinone, **14a** is a 2.1:1 mixture, and the more electron-rich 3,3′-dimethyl binaphtho-*para*-quinone (**15a**) is almost completely the bishemiketal (Scheme 3). For compound **14a**, changing the solvent to THF-d_8 shifts the equilibrium to the bishemiketal (1:2.8).

While screening other oxidation conditions with the tetrol substrates, significantly different reactivity was observed. Specifically, by switching the solvent from DMF to MeCN for the Co-salen catalyzed oxidation, a unique spirocyclic compound, **3**, was isolated as the major product (Scheme 3). An X-ray structure determination identified the compound as the architecturally complex bis-spironaphthalenone, which formed by an intramolecular oxidative cyclization resulting in dearomatization. A search of the literature did not reveal any synthetic or naturally occurring compounds with the same type of spirocyclic structure as **3**. There are, however, some structurally relevant natural products that contain one of the spirofurans. These natural products include grandidone D[16] and the spiroxins A–E.[17] In addition, compounds containing a carbonyl adjacent to a spirodihydrobenzofuran have been reported, which include calixarenes[18] and spironaphthalenones.[19] Due to the unusual structure of **3**, derivatization and investigation of its reactivity were pursued.

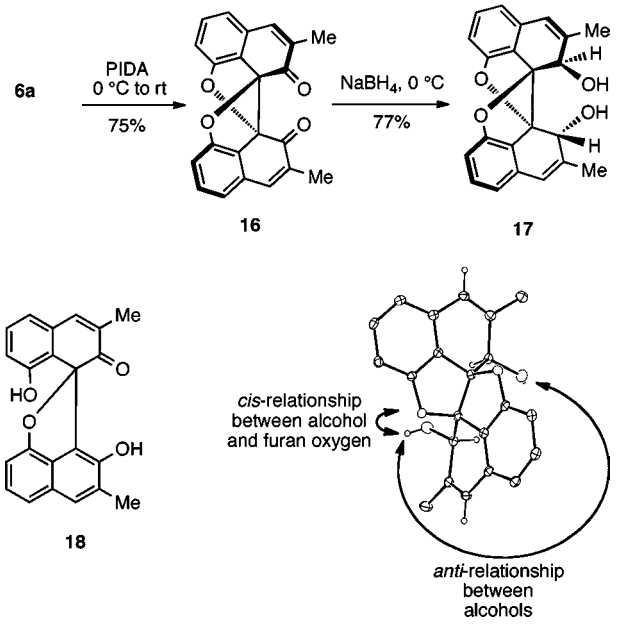
Aside from Co-salen, PIDA was found to be an efficient oxidant to promote formation of the bis-spironaphthalenone. Using this hypervalent iodide reagent, **16** was synthesized in 75% yield (Scheme 4). The carbonyls of spiro compound **16** were diastereoselectively reduced with $NaBH_4$ to give diol **17** in 77% yield. An X-ray crystal structure confirmed the *anti* relationship between the two newly formed alcohols and the *cis* relationship between the alcohols and furan oxygens (Scheme 4). Attempts to functionalize **16** or **17** further were unsuccessful due to favorable elimination of the furan oxygens and rearomatization to regenerate **6a** or the partially rearomatized product, **18**. Preliminary work with alkyl lithiums, such

(14) Tanaka, O. *Chem. Pharm. Bull.* **1958**, *6*, 203–208.
(15) See Supporting Information for crystal structure.

(16) (a) Uchida, M.; Miyase, T.; Yoshizaki, F.; Bieri, J. H.; Rüedi, P.; Eugster, C. H. *Helv. Chim. Acta* **1981**, *64*, 2227–2250. (b) Rüedi, P.; Uchida, M.; Eugster, C. H. *Helv. Chim. Acta* **1981**, *64*, 2251–2256.
(17) McDonald, L. A.; Abbanat, D. R.; Barbieri, L. R.; Bernan, V. S.; Discafani, C. M.; Greenstein, M.; Janota, K.; Korshalla, J. D.; Lassota, P.; Tischler, M.; Carter, G. T. *Tetrahedron Lett.* **1999**, *40*, 2489–2492.
(18) (a) Litwak, A. M.; Grynszpan, F.; Aleksiuk, O.; Chen, S.; Biali, S. E. *J. Org. Chem.* **1993**, *58*, 393–402. (b) Georghiou, P. E.; Ashram, M.; Clase, H. J.; Bridson, J. N. *J. Org. Chem.* **1998**, *63*, 1819–1826.
(19) (a) Kasturi, T. R.; Sattigeri, J. A.; Pragnacharyulu, P. V. P. *Tetrahedron* **1995**, *51*, 3051–3060. (b) Khoramabadi-zad, A.; Yavari, I.; Shiri, A.; Bani, A. *J. Heterocyclic Chem.* **2008**, *45*, 1351–1358.

as MeLi, did show addition to the carbonyl, but a large number of side products were observed.

Scheme 4. Synthesis and Selective Reduction of a Bis-spironaphthalenone



In summary, 8,8′-hydroxylated binaphthols have been oxidized selectively to either the binaphtho-*para*-quinones or the binaphtho-*ortho*-quinones, which are BINOL analogs potentially useful as asymmetric ligands or oxidants. Binaphtho-*para*-quinones with unprotected hydroxyls undergo intramolecular cyclization to generate the corresponding bishemiketals. The ratio of bisquinone/bishemiketal is dependent on both the solvent and the electronic nature of the ring substituents. The oxidative dearomatization of binaphthalenetetrols provides a strained and architecturally unique bis-spironaphthalenone containing two quaternary centers and a continuous hexacyclic array.

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Supporting Information Available. Experimental procedures, characterization data, NMR spectra, crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.