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First Asymmetric Synthesis of Orthoquinone Monoketal Enantiomers via Anodic Oxidation

Stéphane Quideau,* Isabelle Fabre, and Denis Deffieux

Institut Européen de Chimie et Biologie, 2 rue Robert Escarpit, 33607 Pessac Cedex, France, and Centre de Recherche en Chimie Moléculaire, Laboratoire de Chimie des Substances Végétales, Université Bordeaux 1, 351 cours de la Libération, 33405 Talence Cedex, France

s.quideau@iecb.u-bordeaux.fr

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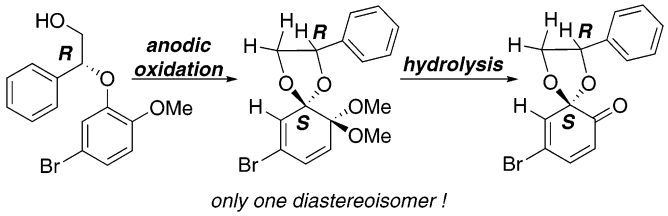
ABSTRACT

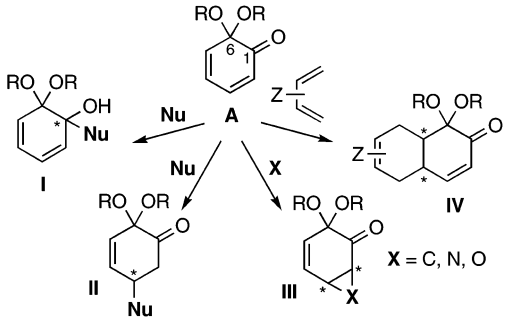


An asymmetric synthesis of orthoquinone monoketals was accomplished using anodic oxidation to convert aryl methyl ethers bearing a chiral ethanol unit into orthoquinone bisketals, followed by monohydrolysis of their dimethyl ketal unit. All four possible stereoisomers were generated in a diastereoselective manner by varying the attachment point of the chiral *pro*-ketal alcoholic auxiliary to the starting arene. A preliminary screening of subsequent nucleophilic addition reactions confirmed the potential utility of these synthons in asymmetric synthesis.

Orthoquinone monoketals, 6,6-dialkoxycyclohexa-2,4-dienone derivatives (e.g., **A**), are synthetically useful species, for their dienone unit and adjacent oxygen functions, which are displayed on a six-membered ring system, render them ideally suited for a large variety of chemical transformations, including 1,2- and 1,4-additions, as well as a variety of cycloadditions (Scheme 1). Several such utilizations have been elegantly implemented in the total synthesis of complex natural products.[1]

However, the lack of control over the chemistry of these systems has hindered the general use of orthoquinone monoketals as synthons in organic chemistry. Three drawbacks to their preparation include (1) their overwhelming tendency toward [4 + 2] dimerization,[2] (2) rearomatization under acidic and reductive conditions,[1b,3] and (3) the lack of stereocontrol over the C-6 ketal center concerning subsequent diastereoselective transformations. While the first two problems have found satisfactory solutions in the use of appropriate substitution patterns and reaction conditions,[1b,4] no

Scheme 1. Selection of Synthecially Useful Chemical Transformations of Orthoquinone Monoketals A into Functionalized Six-Membered Ring Systems **I**−**IV**



(1) For recent reviews on synthetic applications of orthoquinone monoketals, see: (a) Quideau, S. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002; pp 539−573. (b) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383−1429.

(2) Liao, C.-C.; Chu, C.-S.; Lee, T.-H.; Rao, P. D.; Ko, S.; Song, L.-D.; Shia, H.-C. *J. Org. Chem.* **1999**, *64*, 4102−4110.

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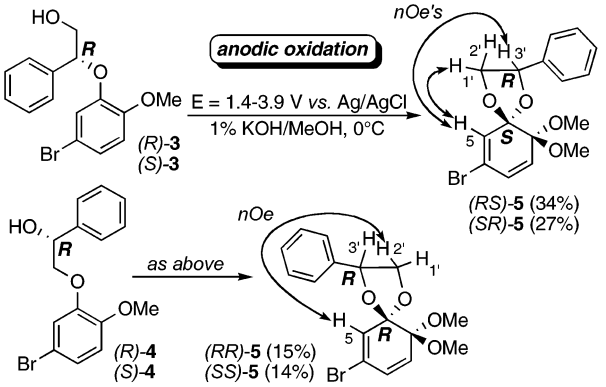
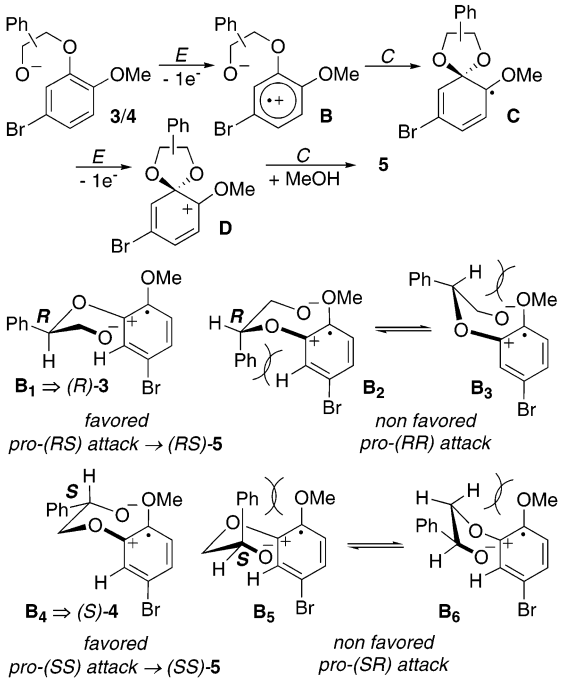
Scheme 2. Diastereoselective Anodic *spiro*-Cyclization of Chiral Primary and Secondary Alcoholic Phenyl Alkyl Ethers **3** and **4** into the Four Possible Orthoquinone Bisketal Enantiomers **5**



Scheme 3. Proposed Transition State Models for the Rationalization of the Diastereoselectivity Observed in the Anodic *spiro*-Cyclization of Chiral Primary and Secondary Alcoholic Phenyl Alkyl Ethers **3** and **4** into Orthoquinone Bisketal Enantiomers **5**



asymmetric preparation of orthoquinone monoketals has been described in the benzoid series.[5] As Pettus recently wrote,[1b] the development of such methods is a worthy goal in organic chemistry considering the potential of these entities for enantioselective synthesis. Herein we report for the first time a promising and environmentally benign approach to this challenge.

Our interest in the oxidative dearomatization of 2-alkoxyphenols into such cyclohexa-2,4-dienone derivatives led us to envisage asymmetric versions of the reactions we are investigating.[6] We found inspiration in the work done on cyclohexa-2,5-dienones equipped with chiral cyclic ketal moieties.[7,8] These compounds are usually generated via mild acid-mediated transketalization reactions by heating together paraquinone dimethyl monoketals and enantiopure diols.[7] These conditions are not suitable for the targeted cyclohexa-2,4-dienones, which are sensitive to both acids and heat. In this study, we instead relied on anodic oxidation to generate orthoquinone bisketals from phenyl methyl ethers bearing a chiral ethanol unit O-tethered to the phenyl ring next to the methyl ether group (Scheme 2). The two enantiomers of both phenyl methyl ethers **3** and **4** were generated by a Williamson-type reaction between 5-bromoguaiacol (**1**) and (*S*)-2-chloro-1-phenylethanol (**2**) or its enantiomer (*R*)-**2** (see Supporting Information for details on these preparations). The chirality of their ethanol unit was thus anticipated to induce asymmetry at the aromatic carbon center undergoing the $sp^2 \rightarrow sp^3$ geometry change during anodic *spiro*-cyclization (Schemes 2 and 3). The 5-bromo substituent on guaiacol is needed to hinder dimerization of the product (Scheme 4).[4a] All four enantiopure alcohols were then individually electrolyzed, under the conditions developed by Dolson and Swenton,[9] to furnish the desired bisketals **5** (Scheme 2).

This anodic *spiro*-cyclization afforded the bisketals in only low yields when starting from the secondary alcohols (*R*)- and (*S*)-**4**, whereas the less encumbered primary alcohols (*R*)- and (*S*)-**3** were both converted into the desired products in ca. 30% yield. Off course, these isolated yields still deserve to be further optimized to expand the preparative value of this methodology, but the fact that, in each of the four cases, a different stereoisomer was isolated as the sole *spiro*-ketal product shows the remarkable potential of this unprecedented anodic oxidation approach to chiral orthoquinone ketals. The configuration at the newly generated *spiro*-centers was determined via two-dimensional NOE spectroscopy (Scheme 2). Thus, (*R*)-**3** led to the bisketal (*RS*)-**5** as indicated by the observation of two NOE correlations between each of the two *spiro*-ketal protons $H_{1'}$ and $H_{3'}$ and the aromatic proton H_5. A similar couple of correlations were observed for (*SR*)-**5** that was generated from the primary alcohol (*S*)-**3**. In the case of the other enantiomeric pair of bisketals (*RR*)- and

(3) Quideau, S.; Looney, M. A.; Pouységu, L.; Ham, S.; Birney, D. M. *Tetrahedron Lett.* **1999**, *40*, 615−618.

(4) (a) Lai, C.-H.; Shen, Y.-L.; Wang, M.-N.; Rao, K.; Liao, C.-C. *J. Org. Chem.* **2002**, *67*, 6493−6502. (b) Andersson, G. *Acta Chem. Scand.* **1976**, *B 30*, 403−406.

(5) For an example of chiral naphthoid orthoquinone monoketals, see: (a) Fujioka, H.; Annoura, H.; Murano, K.; Kita, Y.; Tamura, Y. *Chem. Pharm. Bull.* **1989**, *37*, 2047−2052.

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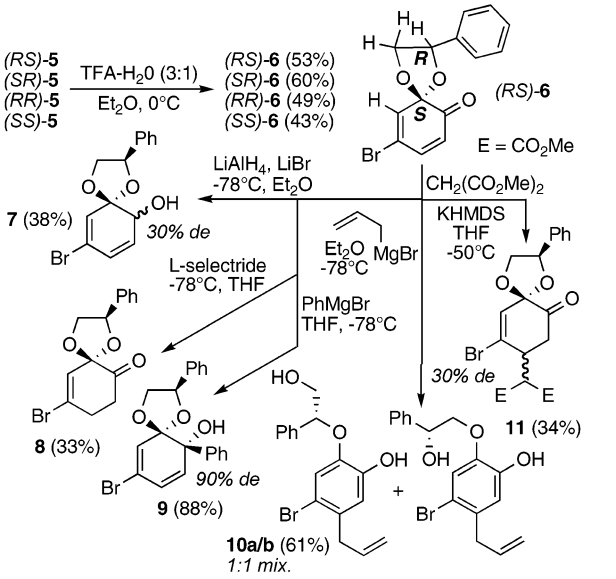
(7) (a) Corey, E. J.; Wu, L. I. *J. Am. Chem. Soc.* **1993**, *115*, 9327−9328. (b) de March, P. ; Escoda, M.; Figueredo, M.; Font, J.; Alvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1995**, *60*, 3895−3897. (c) Hu, Y.; Li, C.; Kulkarni, B. A.; Strobel, G.; Lobkovsky, E.; Torczynski, R. M.; Porco, J. A., Jr. *Org. Lett.* **2001**, *3*, 1649−1652. For another approach, see: (d) Wipf, P.; Jung, J.-K. *Angew. Chem., Int. Ed.* **1997**, *37*, 7764−767.

(8) For a related example of an enantioselective access to paraquinols, see: Mejorado, L. H.; Hoarau, C.; Pettus, T. R. R. *Org. Lett.* **2004**, *6*, 1535−1538.

(9) Dolson, M. G.; Swenton, J. S. *J. Org. Chem.* **1981**, *46*, 177−179.

Scheme 4. Selective Monohydrolysis of Bisketals **5** into Enantiopure Orthoquinone Monoketals **6** and Evaluation of the Capability of (*RS*)-**6** to Induce Asymmetry in Subsequent Reactions



(*SS*)-**5** that were respectively generated from the secondary alcohols (*R*)- and (*S*)-**4**, only one *spiro*-ketal proton should point toward the side of the molecule bearing the aromatic proton H_5. This was indeed verified in their NOESY spectra (Scheme 2 and Supporting Information). Thus, all four possible bisketal stereoisomers are independently accessible thanks to the apparent diastereospecificity of this anodic *spiro*-ketalization reaction.

A rationalization of this stereochemical control can be made on the basis of the transition state models proposed in Scheme 3. Assuming that the reaction performed in 1% KOH/MeOH follows a classical ECEC mechanistic sequence,[10] *spiro*-ketalization (**B** → **C**) is very likely the first chemical (*C*) event. Our transition state (TS) models are hence derived from the radical cation alkoxide intermediate **B**. No major torsional or steric impediment appears in the intramolecular *pro*-(*RS/SR*) attack of the primary alkoxide onto the *β*-face of the cationic center as depicted in the *pro*-(*RS*) envelope $\mathbf{B_1}$-TS derived from (*R*)-**3**, whereas the corresponding *pro*-(*RR*) attack suffers from a bad interaction between the phenyl group and the benzoid radical cation unit in the $\mathbf{B_2}$-TS. This interaction can be released by positioning the phenyl-bearing out-of-plane carbon of the envelope on the other side of this plane, but the resulting *pseudo*-boat $\mathbf{B_3}$-TS would then display a van der Waals interaction between the benzylic hydrogen atom and the methoxy group. An analogous examination of the secondary alcohol *spiro*-cyclization shows that, this time, a *pro*-(*SS/RR*) attack of the alkoxide onto the α-face of the cationic center should be preferred, as depicted in the *pro*-(*SS*) envelope $\mathbf{B_4}$-TS derived from (*S*)-**4**. The alternative *pro*-(*SR*) $\mathbf{B_5}$- and $\mathbf{B_6}$-TSs both suffer from interactions involving the methoxy group of the benzoid radical cation unit (Scheme 3). Overall, this simple analysis does provide an adequate model to rationalize the diastereoselectivity observed in these *spiro*-cyclizations.

All four bisketals **5** were then individually treated with a 1:3 H_2O−TFA mixture in Et_2O at 0 °C. Under these conditions, selective hydrolysis of their dimethylketal unit furnished the four orthoquinone *spiro*-monoketals **6** in reasonable yields (Scheme 4). As expected, the 4-bromine substituent does retard their dimerization long enough to conveniently carry out further transformations. The capability of their chirality to induce asymmetry in subsequent reactions was then briefly examined using (*RS*)-**6** (Scheme 4). Treatment with LAH/LiBr[5] at −78 °C furnished the cyclohexa-2,4-dienols **7** in only 30% de and the use of the bulkier hydride reagent L-selectride led to a 1,4-reduction into the ketone **8** in 33% yield. However, an excellent induction of asymmetry was obtained using PhMgBr at −78 °C to furnish the tertiary alcohol **9** in 88% yield and 90% de. Addition of allylMgCl proceeded in a 1,4-fashion with concomitant rearomatization and opening of the *spiro*-ketal unit to furnish a 1:1 mixture of the two phenols **10a**/**b**. However, the KHMDS-mediated 1,4-addition of dimethylmalonate at −50 °C in THF gave the ketones **11** in 34% yield and 31% de. This excess is only moderate but nevertheless remarkable, since it resulted from a 1,4-asymmetry induction from the *spiro*-center. The fact that ketones are here obtained in contrast to the case of the allyl addition is probably due to a rapid quench of the initial enolate adduct from the remaining malonate acidic α-proton.

In conclusion, the work described therein constitutes the first example of an asymmetric preparation of orthoquinone monoketals in the benzoid series and shows that intramolecular additions to electrochemically generated arene radical cations have the capacity to undergo in situ diastereoselective reactions. By simply varying the attachment point of the chiral *pro*-ketal auxiliary to the starting arene, all four possible monoketal diastereomers are accessible. A preliminary screening of their synthetic applications did confirm their potential utility in asymmetric nucleophilic 1,2- and 1,4-addition reactions.

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Supporting Information Available: Detailed experimental procedures and ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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