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Stereoselective Trimerization of [(S)*R*]-[(*p*-Tolylsulfinyl)methyl]-*p*-quinols and *p*-Quinamines

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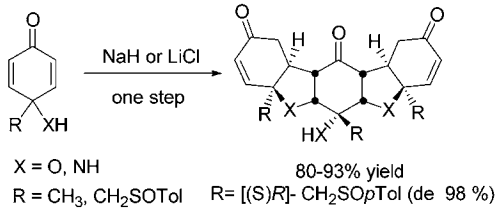
ABSTRACT



The asymmetric synthesis of pentacyclic derivatives was achieved in a single step starting from enantiopure [(S)*R*]-[(*p*-tolylsulfinyl)methyl]-*p*-quinols or the nitrogen analogue, through a domino sequence involving four conjugate additions in excellent yields. Eight new stereogenic centers were created in one step and in a highly diastereoselective manner.

Dimerization of quinols has been postulated to occur in the biosynthetic pathways of several natural products such as bisorbicillinoids[1] and trichodimerol.[2a] Reactions such as Diels−Alder[3] or Michael-type additions[3] seems to be involved. The complex structure and interesting biological properties of these compounds have stimulated chemical[4] and biomimetic[2a,5] total syntheses of the natural products and synthetic analogues. Both *ortho*- and *para*-quinols are involved in these sequences.

As a part of an ongoing program devoted to asymmetric synthesis mediated by sulfoxides, we synthesized enantiomerically pure [(S)*R*]-[(*p*-tolylsulfinyl)methyl]-*p*-quinols[6] such as **1** and showed their reactivity as dienophiles[6b,d] in Diels−Alder reactions and as Michael-type acceptors.[6a,c] More recently, we found that the sulfinyl *p*-quinols and also the nitrogen analogues [(S)*R*]-[(4-amino-4-[(*p*-tolylsulfinyl)-methyl]-2,5-cyclohexadienone[7] **2** are excellent substrates in domino reactions. We demonstrated that they are able to act as both acceptor and donor in successive conjugate additions.[8,9]

Having in mind the reported biomimetic approaches to bisorbicillinoids and the interest of finding enantiopure and stable analogues of quinols, which could be used as substrates in biomimetic synthesis, we decided to explore if sulfinyl

(1) Evidence supporting the real intermediacy of quinols in such biosynthetic routes has been recently reported: Abe, N.; Sugimoto, O.; Tanji, K.; Hirota, A. *J. Am. Chem. Soc*. **2000**, *122*, 12606−12607.

(2) (a) Trifonov, L. S.; Bieri, J. H.; Prewo, R.; Dreiding, A. S.; Hoesch, L.; Rast, D. M. *Tetrahedron* **1983**, *39*, 4243−4256. (b) Trifonov, L. S.; Dreiding, A. S.; Hoesch, L.; Rast. D. M. *Helv. Chim. Acta* **1981**, *64*, 1843−1846. (c) Andrade, R.; Ayer, W. A.; Trifonov, L. S. *Can. J. Chem*. **1996**, *74*, 371−379. (d) Abe, N.; Murata, T.; Hirota, A. *Biosci. Biotechnol. Biochem*. **1998**, *62*, 661−666.

(3) (a) Nicolaou, K. C.; Jautelat, R.; Vassilikogiannakis, G.; Baran, P. S.; Simonsen, K. B. *Chem. Eur. J*. **1999**, *5*, 3651−3665. (b) Nicolaou, K. C.; Simonsen, K. B.; Vassilikogiannakis, G.; Baran, P. S.; Vidali, V. P.; Pitsinos, E. N.; Couladouros, E. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3555−3559.

(4) Barnes-Seeman, D.; Corey, E. J. *Org. Lett*. **1999**, *1*, 1503. (b) Wood, J. L.; Thompson, B. D.; Yusuff, N.; Pflum, D. A.; Matthäus, M. S. P. *J. Am. Chem. Soc*. **2001**, *123*, 2097−2098.

(5) Nicolaou, K. C.; Vassilikogiannakis, G.; Simonsen, K. B.; Baran, P. S.; Zhong, Y.-L.; Vidali, V. P.; Pitsinos, E. N.; Couladouros, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 3071−3079.

(6) (a) Carreño, M. C.; Pérez González, M.; Ribagorda, M.; Houk, K. N.; *J. Org. Chem*. **1998**, *63*, 3687−3693. (b) Carreño, M. C.; Pérez González, M.; Houk, K. N. *J. Org. Chem*. **1997**, *62*, 9128−9137. (c) Carreño, M. C.; Pérez González, M.; Ribagorda, M.; Fischer, J. *J. Org. Chem*. **1996**, *61*, 6758−6759. (d) Carreño, M. C.; Pérez González, M.; Fischer, J. *Tetrahedron Lett*. **1995**, *36*, 4893−4896.

(7) By analogy with *p*-quinols, we use the name *p*-quinamines for the 4-amino analogues. This name was proposed in 1928: Fries, K.; Ohemes, G. *Justus Liebigs Ann Chem.* **1928**, *462*, 1.

(8) Carreño, M. C.; García Luzón, M. C.; Ribagorda, M. *Chem. Eur. J.* **2002**, *8*, 208−216.

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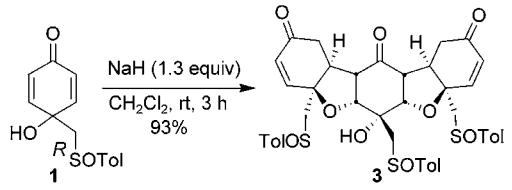
p-quinol **1** and *p*-quinamine **2** could behave like the natural quinol metabolites in a dimerization process. It is known that free *ortho*-quinols, which are extremely reactive, dimerize instantaneously,[10] but there is not evidence of such behavior in *p*-quinols.[11] We report herein our findings on the stereoselective synthesis of trimeric and dimeric species based on highly stereoselective Michael-type domino reactions.

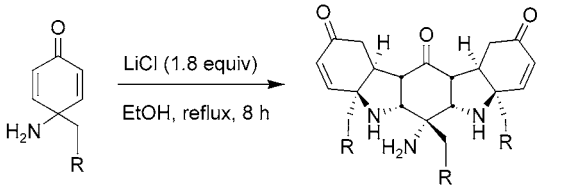
Initial experiments were carried out with [(S)*R*]-[(4-hydroxy-4-[(*p*-tolylsulfinyl)methyl]-2,5-cyclohexadienone **1** in the presence of NaH in a CH_2Cl_2 solution at room temperature. We found that after 3 h, the reaction led to the formation of the trimeric derivative **3** as a unique diastereomer with an excellent isolated yield (93%). Thus, in a single-step reaction, four new bonds and up to eight new stereogenic centers were formed generating a pentacyclic system.

Scheme 1



When the same reaction conditions (NaH, CH_2Cl_2, rt) were used with the nitrogen analogue [(S)*R*]-4-[(*p*-tolylsulfinyl)-methyl]-2,5-cyclohexadienone **2**, the *p*-quinamine remained unaltered. On the other hand, when **2** was refluxed in ethanol in the presence of LiCl, the trimer **4** was obtained in 80% isolated yield (Scheme 2).[12] To learn whether the sulfoxide

Scheme 2



of the starting material played an important role in the formation of the pentacyclic structure, we carried out the reaction on 4-amino-4-methyl-2,5-cyclohexadienone **5**, lacking the sulfoxide. Thus, upon treatment of **5** in refluxing EtOH with LiCl, compound **6** could be isolated as pure diastereomer in 42% yield (Scheme 2). The low yield obtained suggested a significant role of the sulfoxide in the process. This result is in accordance with our previous studies related to 1,4-conjugate additions on both 4-sulfinylmethyl *p*-quinols[6a,b] and *p*-quinamines,[8] where we demonstrated that the presence of the sulfoxide significantly increased the electrophilicity of the cyclohexadienone moiety.

The structures of compounds **3**, **4**, and **6** were determined by ^{1}H, ^{13}C, and mass spectroscopic techniques. The absolute configuration of the stereogenic carbons in diastereomers **3** and **4** and the relative configuration of **6** could be assigned on the basis of a comparative analysis of their ^{1}H NMR parameters as well as a chemical correlation with the trisulfone **7** resulting from the *m*-CPBA oxidation of **3**.

Such oxidation allowed the formation of a single compound **7** in 70% yield. The ^{1}H NMR spectrum of **7** appeared drastically simplified in comparison with that of its precursor **3**. This suggested the existence of a plane of symmetry in **7** not present in **3** due to the chirality of the sulfinyl groups. The exclusive formation of one diastereomer **7** also verified the formation of a unique diastereomer in the reaction leading to **3**. The most significant ^{1}H NMR parameters for this configurational assignment are displayed in Figure 1. Upon

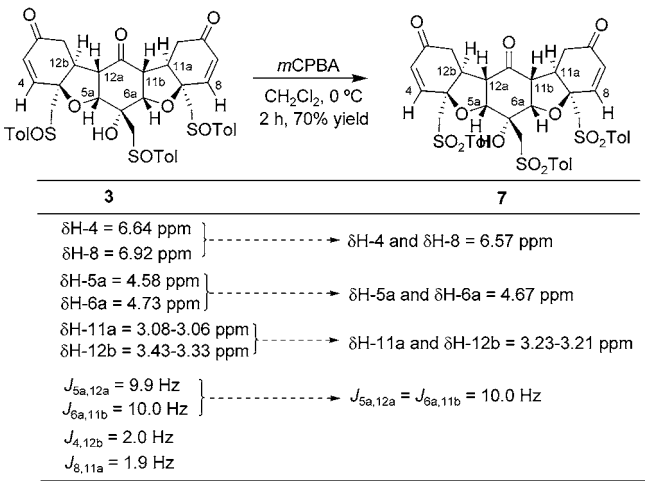


Figure 1. *m*-CPBA oxidation of **3** and significant ^{1}H NMR parameters for configurational assignment of **3** and **7**.

oxidation, olefinic H-8 and H-4 hydrogens appearing at 6.92 and 6.64 ppm in the sulfinyl derivative **3** collapse to a single signal appearing at 6.57 ppm in sulfone **7**. The same was observed for the methine groups H-12b and H-11a and H-6a and H-5a. A similar collapse was observed in the ^{1}H NMR parameters of pentacyclic nitrogen derivatives **4** and **6**. Once more, the lack of the sulfinyl group in **6** clearly simplified the ^{1}H NMR spectrum (see Supporting Information for details). The cis relationship between H_{5a} and H_{12a}, as well as H_{6a} and H_{11b}, in the central six-membered ring was deduced from the value of their coupling constants (J = 9.9

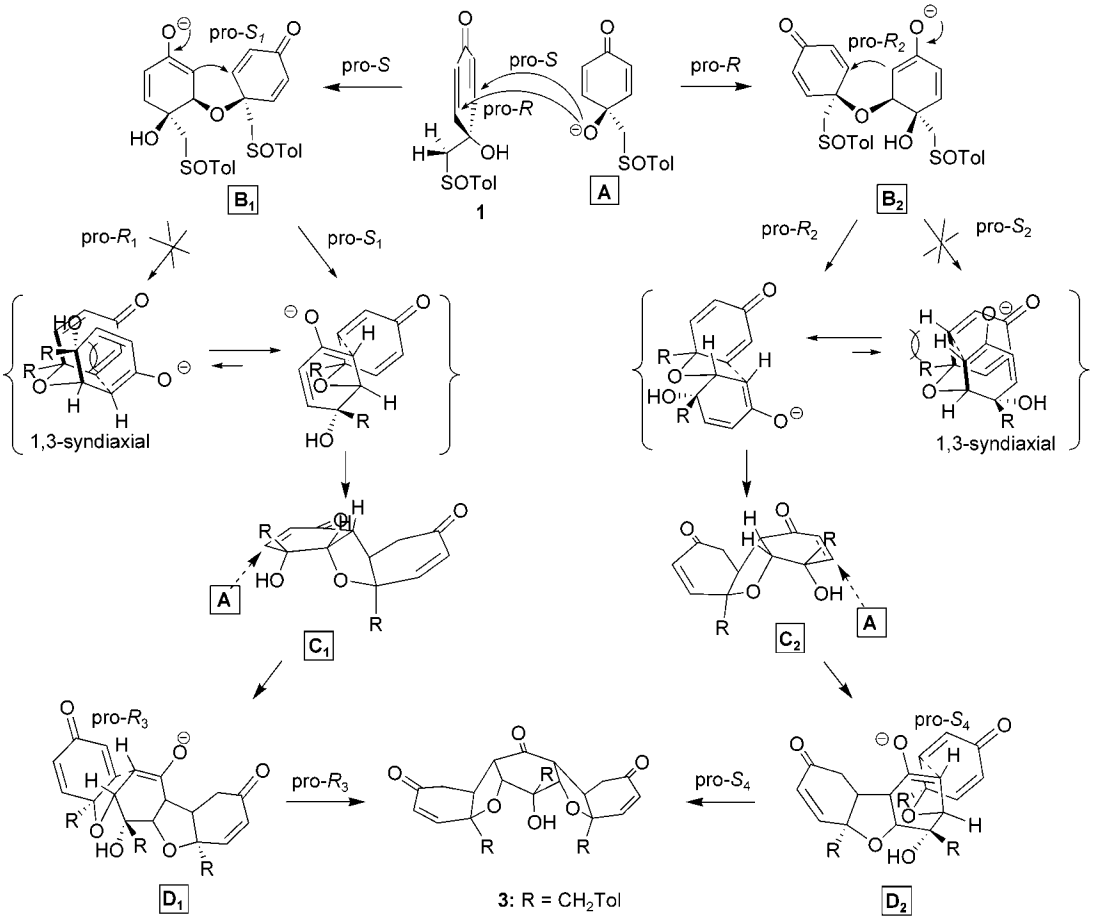
(9) Carreño, M. C.; Posner, G. H.; Ribagorda, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 2753−2755.

(10) (a) Barton, D. H. R.; Magnus, P. D.; Rosenfeld, M. N. *J. Chem. Soc., Chem. Commun.* **1975**, 301−301. (b) Barton, D. H. R.; Magnus, P. D.; Quinney, J. C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1610−1614.

(11) *p*-Quinols are sufficiently stable to be isolated and stored. See, for instance: Wipf, P.; Jung, J.-K. *Chem. Rev.* **1999**, *99*, 1469−1480.

(12) Conditions were chosen in accordance with previous results obtained with *p*-quinamine **2**; see ref 9.

Scheme 3



and 10 Hz, respectively). The long-distance coupling observed between H_4-H_{12b} and H_8-H_{11a} ($J = 2.0$ and 1.9 Hz) is a characteristic of the W spatial disposition between both pairs of protons (Figure 2).

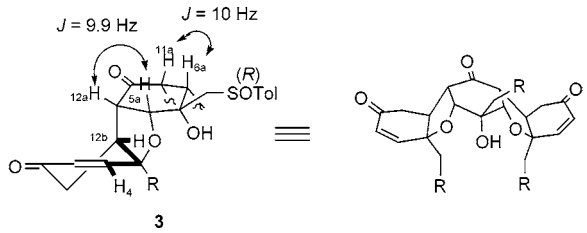


Figure 2. Geometry of pentacyclic compound **3** based on the symmetry of its oxidation product **7** and the cis and long-distance (W) coupling constants observed.

The synthesis of the pentacyclic compound **3** is assumed to proceed via the reaction sequence shown in Scheme 3. Initial 1,4-addition of the alkoxide **A**, resulting from NaH reaction with **1**,[13] to both conjugate positions of a second equivalent of *p*-quinol **1**, is followed by three successive 1,4-additions on each resulting diastereomer, which evolve in a diastereoconvergent way to the final pentacyclic derivative, after incorporating a second equivalent of **1**.

The stereochemistry of the overall process could be rationalized as summarized in Scheme 3. According to previous results on conjugate additions on *p*-quinol derivatives,[6,14] the initial attack of the alkoxide **A** was expected to occur from the less hindered face of **1**, which is the one supporting the OH, with complete π-facial diastereoselectivity. In such an initial 1,4-conjugate addition, both prochiral electrophilic positions of the cyclohexadienone moiety of **1** react, giving rise to two diastereoisomeric intermediate enolates $\mathbf{B_1}$ (attack at the pro-*S* position) and $\mathbf{B_2}$ (attack at the pro-*R* position). The subsequent intramolecular 1,4-addition of the enolates $\mathbf{B_1}$ and $\mathbf{B_2}$ took place with total π-facial diastereoselection at the pro-S_1 and pro-R_2 prochiral electrophilic positions of their cyclohexadienone moiety, respectively, giving rise to the new intermediates $\mathbf{C_1}$ and $\mathbf{C_2}$. The origin of such a high diastereoselectivity can be found in the existence of a 1,3-syn diaxial destabilizing interaction

(13) Mechanism and stereochemical outcome of the formation of **4** and **6** from *p*-quinamines **2** and **5** are assumed to be similar with the NH_2 group instead of the alkoxide acting as nucleophile and with enols instead of enolates as intermediates due to the ethanolic medium.

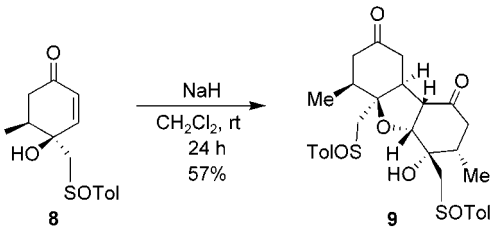
(14) (a) Swiss, K. A.; Liotta, D. C.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 9393−9394. (b) Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678−11688.

in the transition states[15,9] represented in Scheme 3 for the pro-R_1 double-bond attack in the intermediate $\mathbf{B_1}$ and the pro-S_2 double-bond attack in $\mathbf{B_2}$. The third conjugate addition of a new molecule of the alkoxide **A** on $\mathbf{C_1}$ and $\mathbf{C_2}$ took place on the OH free enone moiety from the less hindered face containing the OH substituent (Scheme 3). The resulting enolate, suffers a fourth intramolecular conjugate addition, with a high diastereoselection due to the preferred attack to the conjugate pro-R_3 electrophilic position of the new cyclohexadienone fragment existent in the intermediate, through a transition state represented as $\mathbf{D_1}$. The most favored evolution of the diastereomeric analogue $\mathbf{D_2}$, proceeding from $\mathbf{C_2}$, corresponds to the attack at the pro-S_4 conjugate position. In both cases, the intramolecular attack to the pro-S_3 alternative conjugate position of $\mathbf{D_1}$ and pro-R_4 position of $\mathbf{D_2}$ (not represented), is strongly disfavored due to the existence of destabilizing 1,3-syn diaxial interactions. Such selective domino reactions result in a diastereoconvergent synthesis of the final compound **3**.

Finally, we have examined the behavior of a system bearing a single enone. Thus, reaction of 4-hydroxy-4-[(*p*-tolylsulfinyl)methyl]-5-methylcyclohexenone[6] **8** with NaH in CH_2Cl_2 gave compound **9** through two successive conjugate additions. The tricyclic derivative was isolated in 57% yield as a single diastereoisomer (Scheme 4), showing that the domino conjugate additions occurring from the alkoxides of a 4-(*p*-tolylsulfinyl)methyl-4-hydroxy-substituted cyclohexenone moiety occur in a highly stereoselective, efficient, and general manner.

In summary, we have found that 4-[(*p*-tolylsulfinyl)-methyl]-*p*-quinols and *p*-quinamines behave like natural quinol metabolites, giving rise to a domino sequence of four conjugate additions when treated with NaH or LiCl. Pentacyclic derivatives **3** and **4** have been synthesized in a highly efficient process, wherein four new bonds and eight stereogenic centers are formed in a highly diastereoselective manner (up to 98% de and ee). A dimeric structure **9** was formed after two conjugate additions, when a single γ-hydroxy-γ-(*p*-tolylsulfinyl)methyl cyclohexenone moiety is present in the starting material **8**. The presence of the sulfoxide in the starting materials is essential not only for the sake of optical activity but also to increase the electrophilicity of the enone moiety. Interest of these reactions in the biomimetic enantioselective synthesis of natural products is evident since differently substituted *p*-quinols and *p*-quinamines, as well as the 4-hydroxy-4-*p*-(tolylsulfinyl)-methyl-2-cyclohexenones, are easily accessible in enantiomerically pure form.[6,8,9]

Scheme 4



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Supporting Information Available: Experimental procedures and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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