ORGANIC LETTERS

2007
Vol. 9, No. 24
5019−5022

Direct Stereocontrolled Synthesis of Polyoxygenated Hydrobenzofurans and Hydrobenzopyrans from *p*-Peroxy Quinols

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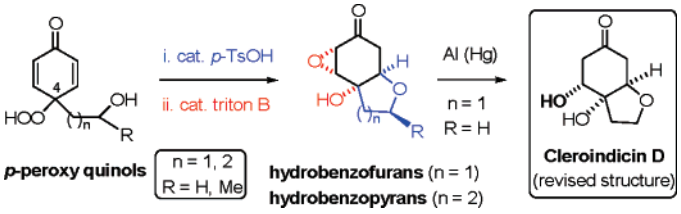
Received September 12, 2007

ABSTRACT



An acidic−basic tandem catalytic process on *p*-peroxy quinols with hydroxy alkyl chains at C-4 allowed the one-pot synthesis of hydrobenzofuran and hydrobenzopyran tricyclic epoxides. In this transformation, two new cycles and four new stereogenic centers are created in a highly stereocontrolled manner. The usefulness of the strategy is illustrated with the first total synthesis and structural revision of natural product Cleroindicin D.

Stereoselective approaches to hydrobenzofurans and hydrobenzopyrans continue to attract considerable attention due to the widespread appearance of these structural motifs in natural products.[1] Although different strategies have been applied for the construction of these fused heterocycles[2] when dealing with highly substituted systems, multistep syntheses have been reported. Thus, new methodologies[3] allowing short and stereocontrolled routes to such naturally occurring moieties are necessary to achieve high efficiency and atom economy.[4]

We have recently reported a practical method for the simple and selective oxidative dearomatization of *p*-alkyl phenols into *p*-peroxy quinols and *p*-quinols using Oxone and $NaHCO_3$ as a source of singlet oxygen (Scheme 1).[5] For example, the reaction of *p*-(2-hydroxyethyl)phenol (**1**) with Oxone afforded *p*-peroxy quinol **2**, and if this reaction was followed by the addition of $Na_2S_2O_3$, phenol **1** directly furnished rengyolone (**4**), a natural *cis*-fused hydrobenzofuran, formed by intramolecular conjugate addition of the hydroxy ethyl chain into the cyclohexadienone framework of the initially formed *p*-quinol **3**. Taking into account this result, as well as the presence of the hydroperoxide function in *p*-peroxy quinol **2**, we decided to investigate the use of

(1) Hydrobenzofurans: (a) Wu, Q.-H.; Liu, Ch.-M.; Chen, Y.-J.; Gao, K. *Helv. Chim. Acta* **2006**, *89*, 915−922. (b) Shibano, M.; Okuno, A.; Taniguchi, M.; Baba, K.; Wang, N.-H. *J. Nat. Prod.* **2005**, *68*, 1445−1449. Hydrobenzopyrans: (c) Isaka, M.; Tanticharoen, M.; Kongsaeree, P.; Thebtaranonth, Y. *J. Org. Chem.* **2001**, *66*, 4803−4808. (d) Delgado, G.; Olivares, M. S.; Chávez, M. I.; Ramírez-Apan, T.; Linares, E.; Bye, R.; Espinosa-García, F. J. *J. Nat. Prod.* **2001**, *64*, 861−864.

(2) Hydrobenzopyrans: Recent review: (a) Tang, Y.; Oppenheimer, J.; Song, Z.; You, L.; Zhang, X.; Hsung, R. P. *Tetrahedron* **2006**, *62*, 10785−10813. Hydrobenzofurans: Recent work: (b) Yamashita, M.; Ohta, N.; Shimizu, T.; Matsumoto, K.; Matsuura, Y.; Kawasaki, I.; Tanaka, T.; Maezaki, N.; Ohta, S. *J. Org. Chem.* **2003**, *68*, 1216−1224. (c) Clive, D. L. J.; Fletcher, S. P. *Chem. Commun.* **2003**, 2464−2465.

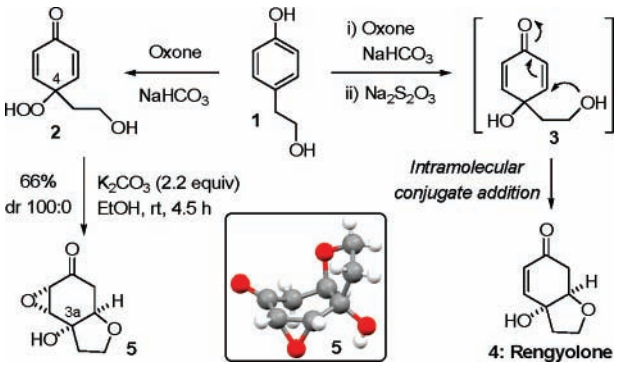
(3) Hydrobenzopyrans: (a) Gómez-Arrayás, R.; Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1816−1825. Hydrobenzofurans: (b) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552−2553.

(4) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281.

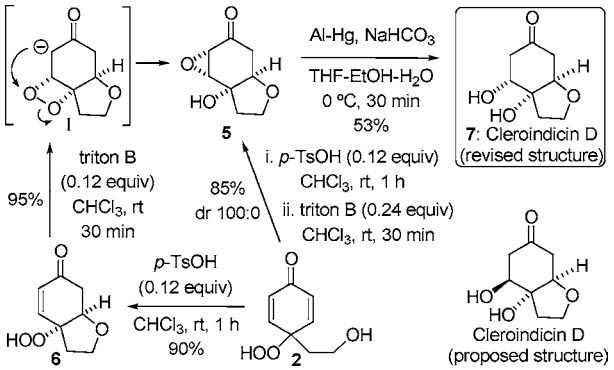
(5) Carreño, M. C.; González-López, M.; Urbano, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 2737−2741.

10.1021/ol702236e CCC: $37.00
Published on Web 11/01/2007

Scheme 1. Stereocontrolled Synthesis of Tricyclic Epoxide **5** from *p*-Peroxy Quinol **2** under Basic Conditions



Scheme 2. Diastereoselective Synthesis of Hydrobenzofurans **5** and **6** and Completion of the Synthesis of Cleroindicin D



such readily accessible starting materials in the synthesis of polyoxygenated fused heterocyclic derivatives.

Herein, we describe a one-pot diastereoselective access to polyoxygenated hydrobenzofurans and hydrobenzopyrans from *p*-peroxy quinols, using an efficient tandem acidic−basic catalytic process. The usefulness of the method is illustrated with the first synthesis and structure revision of natural hydrobenzofuran Cleroindicin D.

Initially, we chose *p*-peroxy quinol **2**, lacking stereogenic centers to avoid added stereochemical complexities, as a model substrate to test the key bond-forming reactions under basic conditions (Scheme 1). After trying several bases ($NaHCO_3$, K_2CO_3, Na_2CO_3, Triton-B) and solvents (H_2O, MeOH, EtOH, CH_2Cl_2), the best results were achieved by treatment of *p*-peroxy quinol **2** with 2.2 equiv of K_2CO_3 in EtOH. Under these conditions, diastereomerically pure tricyclic epoxide **5** was obtained in 66% yield. Compound **5** resulted from the domino process[6] including intramolecular cyclization of the 2-hydroxy ethyl chain at C-4 to the cyclohexadienone moiety of **2** and epoxidation. It is noteworthy that two new rings and four new stereogenic centers were created in only one step in a complete diastereoselective manner. The *cis* junction[7] between the six- and five-membered rings and the *syn* orientation of the epoxide with respect to the angular OH at C-3a were demonstrated after X-ray analysis of **5**.[8]

Then, we tried to perform the cyclization process under acidic conditions. To our delight, the treatment of *p*-peroxy quinol **2** with 0.12 equiv of *p*-TsOH in $CHCl_3$ at rt (Scheme 2) promoted the fast and diastereoselective intramolecular conjugate addition of the primary OH, affording in 90% yield hydrobenzofuran **6**,[7] still bearing an enone fragment and the hydroperoxide group. Upon treatment with 0.12 equiv of Triton-B in $CHCl_3$, bicyclic hydroperoxide **6** provided tricyclic epoxide **5** as the unique diastereomer in an excellent 95% yield (Scheme 2). The formation of the epoxide took place exclusively on the same face of the cyclohexenone bearing the OOH group of derivative **6** probably through the evolution of a dioxetane intermediate such as **I**,[9] formed after intramolecular conjugate addition of the hydroperoxide anion to the cyclohexenone moiety, under the basic conditions. This result evidenced that compound **6** must be an intermediate in the one-pot synthesis of **5** from *p*-peroxy quinol **2** under basic conditions (Scheme 1).

With a synthetic improvement in mind, we thought of performing the transformation of *p*-peroxy quinol **2** into tricyclic epoxide **5**, without isolating the bicyclic hydroperoxide intermediate **6**, in a tandem catalytic process.[10] Thus, we treated sequentially *p*-peroxy quinol **2** with *p*-TsOH (0.12 equiv) and Triton-B (0.24 equiv), observing the exclusive formation of tricyclic epoxide **5**, out of the four possible diastereoisomers (Scheme 2). This tandem process including an acid-catalyzed intramolecular conjugate addition and a base-catalyzed epoxide formation improved the yield of **5** obtained in the direct base-promoted synthesis (85 vs 66% yield).

With compound **5** in hand, we undertook the regioselective opening of the epoxide ring en route to the *cis*-diol **7** (Scheme 2), an isomer of the natural product Cleroindicin D, isolated by Sun et al. from the aerial parts of *Clerodendrum indicum* in 1997,[11] to which a *trans* disposition for the diol moiety was initially assigned. After much experimentation, we found that treatment of epoxide **5** with Na−Hg in EtOH[12] furnished diol **7** in 53% yield. All ^1H and ^{13}C NMR data of synthetic **7** matched exactly with those published by Sun.[11,13] Then, in accordance with the stereochemical course of our synthetic approach, the structure of natural Cleroindicin D should be revised to **7**, with the two OH groups in a *cis* disposition.

We were also interested in the diastereoselective approach to the parent hydrobenzopyrans starting from the correspond-

(6) Tietze, L. F.; Brasche, G.; Gericke, K. M. In *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006.

(7) The *cis* junction was deduced from the small coupling constants (J = 1.8−5.5 Hz) shown by the angular hydrogen next to the heterocyclic oxygen, indicating an equatorial disposition for this proton.

(8) CCDC 655110, 655111, and 655112 for **5**, **21**, and **27**, respectively, contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(9) Hu, Y.; Floss, H. G. *J. Am. Chem. Soc.* **2004**, *126*, 3837−3844.

(10) Chapman, Ch. J.; Frost, Ch. G. *Synthesis* **2007**, 1−21.

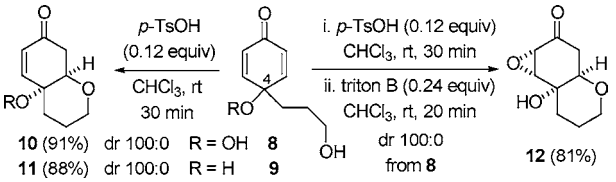
(11) Tian, J.; Zhao, Q.-S.; Zhang, H.-J.; Lin, Z.-W.; Sun, H.-D. *J. Nat. Prod.* **1997**, *60*, 766−769.

(12) Honzumi, M.; Ogasawara, K. *Tetrahedron Lett.* **2002**, *43*, 1047−1049.

(13) We thank Prof. Sun for providing us with ^1H and ^{13}C NMR spectra of natural Cleroindicin D (see Supporting Information).

ing *p*-peroxy quinol **8** or *p*-quinol **9**, bearing a 3-hydroxypropyl chain at C-4 (Scheme 3). When we submitted these

Scheme 3. Diastereoselective Synthesis of Hydrobenzopyrans **10**−**12** from *p*-Peroxy Quinol **8** and *p*-Quinol **9**



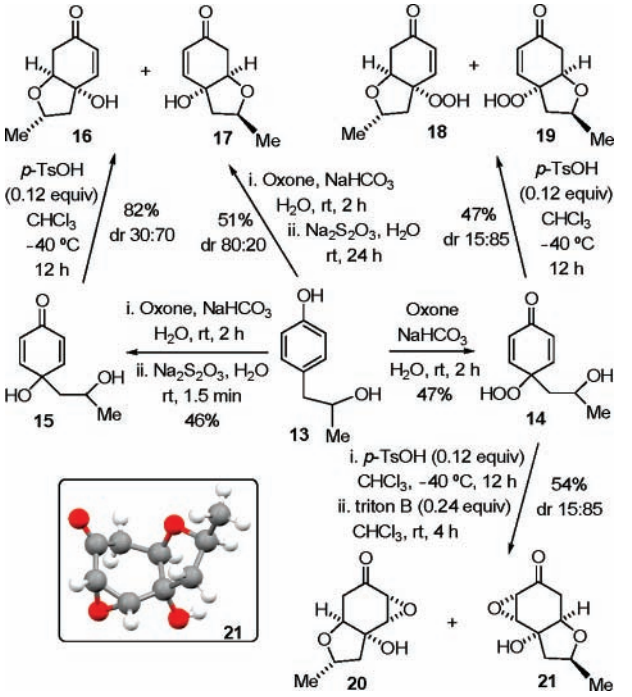
compounds to reaction with K_2CO_3 in EtOH, complex reaction mixtures containing unreacted starting material were observed. Fortunately, under catalytic acidic conditions, *p*-peroxy quinol **8** evolved into bicyclic hydroperoxide **10**[7] with an excellent 91% yield. The *p*-quinol **9**, in the presence of *p*-TsOH, afforded hydrobenzopyran **11**[7] with 88% yield.[14] Moreover, when *p*-peroxy quinol **8** was submitted to the tandem catalytic process, *p*-TsOH followed by Triton-B, tricyclic epoxide **12**,[7] bearing four stereogenic centers, was exclusively obtained in 81% yield.

Once we optimized the conditions for the diastereoselective intramolecular cyclization process, we turned our attention to the synthesis of *p*-peroxy quinols and *p*-quinols bearing a stereogenic center at the hydroxy alkyl chain at C-4 in order to study the influence of such a stereocenter on the intramolecular differentiation of the two diastereotopic double bonds of the cyclohexadienone system.

As depicted in Scheme 4, the oxidative dearomatization of phenol **13** with Oxone/$NaHCO_3$ in H_2O afforded in 47% yield *p*-peroxy quinol **14**, bearing a 2-hydroxypropyl chain at C-4. The sequential treatment of **13** with Oxone and $Na_2S_2O_3$ gave the *p*-quinol **15** in 46% yield when the reaction was quenched immediately after the addition of $Na_2S_2O_3$ (1.5 min). When longer reaction times were used (24 h), phenol **13** evolved directly into an 80:20 mixture of hydrobenzofurans **16**[7,15] and **17**[7,15] (51% yield), resulting from the intramolecular conjugate addition of the 2-hydroxypropyl chain at C-4 to both conjugate positions of the cyclohexadienone moiety of the presumed intermediate **15**. The major formation of diastereoisomer **16** indicated that an efficient intramolecular differentiation of the two diastereotopic double bonds in such systems was possible.

Surprisingly, upon acidic catalysis at −40 °C, *p*-quinol **15** also gave a mixture of **16** and **17** (82% yield), but with the opposite diastereoselection (**16**/**17** = 30:70). This difference could be a consequence of a kinetic (*p*-TsOH, −40 °C) versus thermodynamic control ($NaCO_3H$, rt). The *p*-peroxy quinol **14** also suffered the cyclization process in the

Scheme 4. Oxidative Dearomatization of Phenol **13** and Diastereoselective Synthesis of Racemic 2-Methyl-Substituted Hydrobenzofurans



presence of *p*-TsOH, giving rise to a 15:85 mixture of peroxy hydrobenzofurans **18**[7,15] and **19**[7,15] in 47% yield. A similar diastereoselection was observed in the sequential treatment of *p*-peroxy quinol **14** with catalytic amounts of *p*-TsOH and Triton-B. In this case, a 15:85 mixture of epoxy hydrobenzofurans **20**[7,15] and **21**[7,15] was directly formed in 54% yield after the intramolecular conjugate addition/epoxidation process. The relative configuration of compound **21** was confirmed by X-ray analysis (Scheme 4).

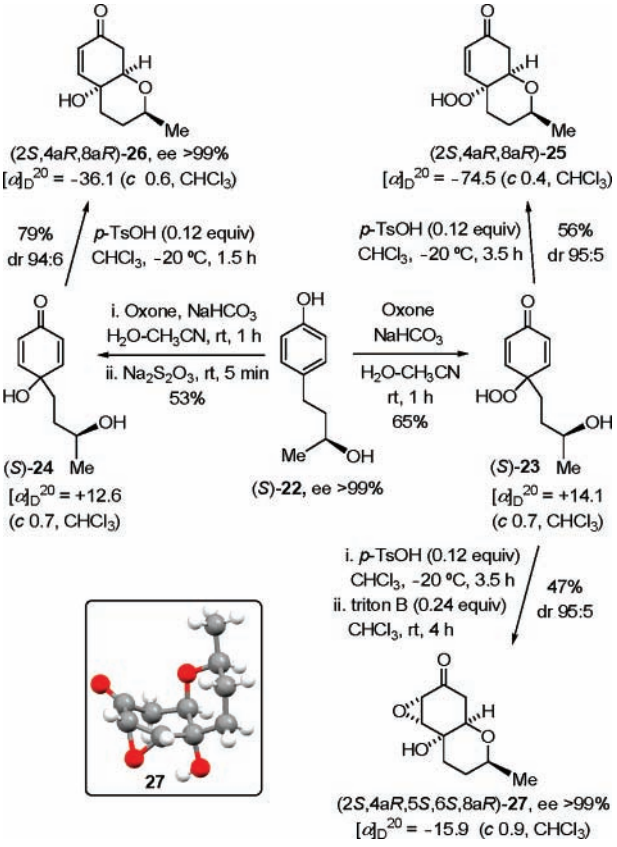
More interesting and synthetically useful results were obtained in the analogous reactions carried out from *p*-peroxy quinol **23** and *p*-quinol **24**, bearing a 3-hydroxybutyl chain at C-4 (Scheme 5). In this case, we decide to use nonracemic starting materials en route to enantiopure hydrobenzopyrans. Thus, when (+)-Rhododendrol (*S*)-**22** (ee >99%), obtained by enzymatic resolution of the racemic derivative,[16] was reacted with Oxone in a mixture of H_2O and CH_3CN, *p*-peroxy quinol (*S*)-**23** was obtained in 65% yield. The corresponding *p*-quinol (*S*)-**24** was directly synthesized from (*S*)-**22** after the Oxone/$Na_2S_2O_3$ sequential treatment in 53% yield. Reaction of *p*-peroxy quinol (*S*)-**23** under the acid-catalyzed conditions (0.12 equiv of *p*-TsOH, $CHCl_3$, −20 °C) afforded bicyclic hydroperoxide (2*S*,4a*R*,8a*R*)-**25**[7,15] in 56% yield after chromatographic separation of the initially formed 95:5 mixture. When *p*-quinol (*S*)-**24** was submitted to the same experimental conditions, hydrobenzopyran (2*S*,4a*R*,8a*R*)-**26**[7,15] was obtained in an excellent 94:6 diastereoisomeric mixture, being isolated pure, after flash

(14) The only similar example found in the literature for this type of acid-promoted cyclization in derivatives lacking the angular OH group afforded bicycles with a *trans* junction under thermodynamic control: Duhamel, P.; Deyine, A.; Dujardin, G.; Plé, G.; Poirier, J.-M. *J. Chem Soc., Perkin Trans. 1* **1995**, 2103−2114.

(15) The relative configuration of 2-methyl hydrobenzofurans and hydrobenzopyrans synthesized was deduced after NOESY experiments. The mixtures **16**/**17**, **18**/**19**, and **20**/**21** could not be separated.

(16) Yuasa, Y.; Shibuya, S.; Yuasa, Y. *Synth. Commun.* **2003**, *33*, 1469−1475.

Scheme 5. Oxidative Dearomatization of Phenol (*S*)-**22** and Stereoselective Synthesis of Enantiopure 2-Methyl-Substituted Hydrobenzofurans **25**−**27**



chromatography, in 79% yield and >99% ee.[17] These results indicated an excellent stereocontrol of the process since almost only one out of the four possible diastereoisomers was obtained in enantiomerically pure form.

In an even more efficient way, the *p*-TsOH−Triton-B tandem catalytic process on *p*-peroxy quinol (*S*)-**23** furnished, out of the eight possible isomers, enantiopure[17] tricyclic epoxide (2*S*,4a*R*,5*S*,6*S*,8a*R*)-**27**[7,15] after separation of the initially formed 5:95 mixture in 47% yield. The relative configuration of the five stereocenters of compound **27** was demonstrated after X-ray analysis.

The excellent diastereoselectivity achieved in the synthesis of hydrobenzopyrans **25**−**27** was defined in the formation of the tetrahydropyran ring by the acid-catalyzed intramolecular conjugate addition process, through the efficient differentiation of the two diastereotopic faces and the two diastereotopic double bonds (four possible diastereoisomers) of the cyclohexadienone moiety of *p*-peroxy quinol **23** and *p*-quinol **24**. As depicted in Figure 1, the intramolecular

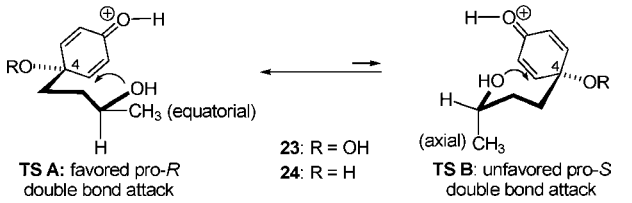


Figure 1. Proposed model for the acid-catalyzed intramolecular conjugate addition of *p*-peroxy quinol **23** and *p*-quinol **24**.

nucleophilic attack of the OH of the 3-hydroxybutyl chain must occur from the opposite face of the OR group at C-4 to avoid destabilizing electrostatic interactions between both oxygens to give exclusively the *cis*-fused heterocycles. The differentiation of the two double bonds of the cyclohexadienone framework is due to the stereoselective intramolecular conjugate attack of the hydroxy alkyl chain at C-4 on the pro-*R* double bond of the system (represented as **TS-A** in Figure 1), which is favored over that on the pro-*S* bond (**TS-B**) due to the preferred equatorial disposition of the methyl substituent in the chair-like tetrahydropyran forming ring **TS-A** if compared with the axial arrangement of the same group in **TS-B**, thus justifying the observed diastereoselection.

In summary, we have described a new, short, and efficient protocol for the stereoselective preparation of polysubstituted hydrobenzofurans and hydrobenzopyrans with up to five stereogenic centers. Applying this strategy, we achieved the first total synthesis and structural revision of natural Clerodindicin D in three steps and 36% overall yield from a commercially available phenol.

Acknowledgment. We thank MCYT (Grant CTQ2005-02095/BQU) and UAM-CAM (Grant CCG07-UAM/PPQ-1451) for financial support. S.B. and A.L. wish to thank MEC, and M.G.-L. thanks CAM for fellowships.

Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The enantiomeric purities were determined by chiral HPLC (see Supporting Information).