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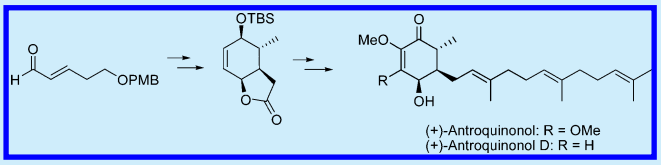
Total Synthesis of (+)-Antroquinonol and (+)-Antroquinonol D

Rohidas S. Sulake and Chinpiao Chen*

Department of Chemistry, National Dong Hwa University, Hualien 97401, Taiwan

Supporting Information

ABSTRACT: The first total synthesis of (+)-antroquinonol and (+)-antroquinonol D, two structurally unique quinonols with a sesquiterpene side chain, is described. The route features an iridium-catalyzed olefin isomerization−Claisen rearrangement reaction (ICR), lactonization, and Grubbs olefin metathesis. The requisite α,β-unsaturation was achieved via the selenylation/oxidation protocol and elimination of β-methoxy group to provide two natural products from a common intermediate.



Antrodia camphorata has a long history as a medicinal fungus. *A. camphorata* is widely used in traditional folk medicines for alcohol detoxification, treatment of cancer, hypertension, fatigue, viral infection, and liver diseases.[1] Important bioactive compounds isolated from *A. camphorata* include polysaccharides, maleic/succinic acid derivatives, benzenoids, and benzoquinone derivatives.[2] Antroquinonol and antroquinonols B−D (Figure 1) are isolated from very expensive and rarely found mycelia and fruiting bodies of *A. camphorata*.[3] These compounds are characterized by a unique, unstable quinonol framework with a sesquiterpene side chain.

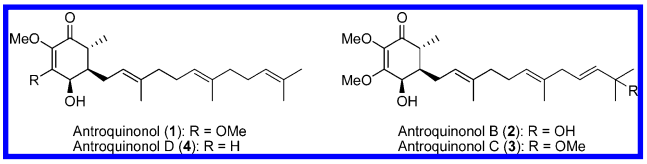


Figure 1. Quinolic derivatives isolated from *A. camphorata*.

The use of antroquinonol for the treatment of multiple forms of cancer has been tested in vivo. The compound has shown promising inhibition of cell growth for at least three kinds of cancer cell lines (NSCLC, liver, and breast cancer).[4a] Antroquinonol (Hocena) capsule was recognized as breakthrough anticancer drug and received the approval from US FDA for clinical trial phase II study. Antroquinonol D is also a potent anticancer agent and was identified as a new DNMT1 inhibitor, which induced DNA demethylation, and reversed the silencing of multiple tumor suppressor genes, induced cancer cell death, and inhibited cell migration.[3c] Despite owning impressive therapeutic profiles,[4] detailed biological studies of these compounds are hampered due to the rare availability and high cost of natural sources. Its low natural abundance makes total synthesis of (+)-antroquinonol particularly important for the preparation of sufficient quantities for further biological evaluation and to determine the absolute configuration. In the course of these efforts, total synthesis of (±)-antroquinonol D was achieved through the Michael addition on cyclohexadienone followed by a diastereoselective reduction of cyclohexenone and the synthesis of the sesquiterpene side chain.[5] Herein, we report the first total synthesis of (+)-antroquinonol and (+)-antroquinonol D which features a Claisen rearrangement and ring-closing metathesis followed by a lactonization for the development of three stereogenic centers.

Quinonol compounds under several conditions readily aromatize through enolization followed by dehydration to generate a more stable aromatic ring,[5,6] which makes the synthesis of this type of compound more challenging. In order to rule out the potential labile nature of β-methoxy group of enone and the possibility of aromatization we focused on the installment of α,β-unsaturated ketone at the final stages. Retrosynthetically, (+)-antroquinonol (**1**) and antroquinonol D (**4**) could be synthesized from cyclohexanone **5** through α,β-unsaturation and elimination of β-methoxy group, respectively. The sesquiterpene side chain could be accessed by olefination of the lactol derived from lactone **6**. The *syn* configuration between C_4−OH and sesquiterpene side chain could be generated through lactonization of the corresponding acid available from cyclohexene **7**. Claisen rearrangement of bis-allyl ether **8** followed by allylation and ring-closing metathesis could provide cyclohexene **7**. Finally a key starting material bis-allyl ether **8** could arise from catalytic asymmetric diethylzinc addition followed by allylation of known (*E*)-5-(4-methoxybenzyloxy)pent-2-enal (Figure 2).[7]

Synthesis of optically pure bis-allyl ether **8** was considered as the most crucial step in the synthesis, as the Claisen rearrangement reactions are highly stereospecific and enantiomerically enriched starting materials provide products of high optical purity. The enantioselective addition of diethylzinc to the known aldehyde **9** with catalytic (+)-MIB (morpholino isoborneol) in pentane and toluene as solvent followed by allylation with NaH in THF provided the requisite bis-allyl ether **8** with a 93% ee (Scheme 1).[8] Claisen rearrangement of allyl vinyl ether offered direct access to the aldehyde.[9] A survey

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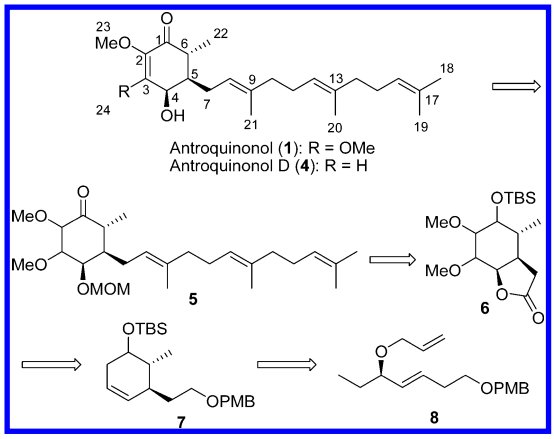
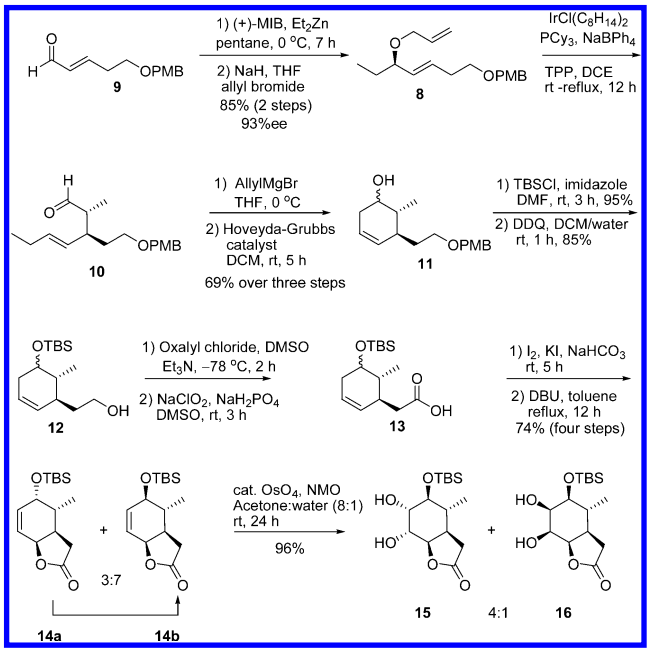


Figure 2. Retrosynthetic analysis of (+)-antroquinonol and (+)-antroquinonol D.

Scheme 1. Synthesis of Lactone

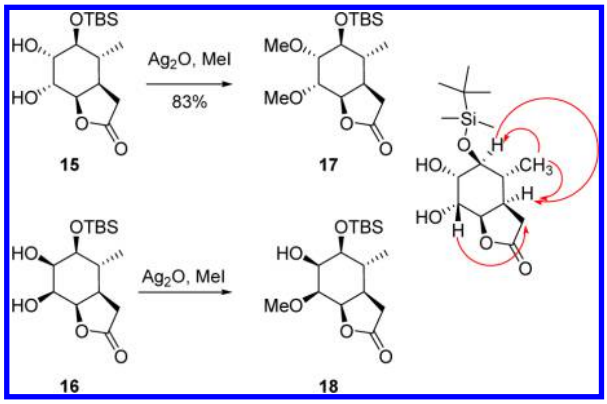


for the isomerization of allyl ether to vinyl ether revealed that the iridium-based complex developed by Nelson is highly efficient and stereoselective.[10] When optimized reaction conditions (IrCl, PCy_3, $NaBPh_4$, dichloroethane) were applied, allyl vinyl ether was generated from bis-allyl ether **8** and then it was subjected to Claisen rearrangement by refluxing in dichloroethane to provide aldehyde **10** as a mixture of diastereomers (92:8). Allylation of the aldehyde **10** with allylmagnesium bromide in THF followed by ring-closing metathesis of the intermediate diene with Grubbs−Hoveyda catalyst afforded the hexenol **11** in a good yield. The resulting secondary alcohol was protected as the corresponding OTBS ether and then deprotection of the PMB group with DDQ in DCM/water furnished primary alcohol **12**.

The resultant primary alcohol **12** was oxidized to aldehyde and further Pinnick oxidation using $NaClO_2$ in DMSO under buffer conditions[11] afforded the acid **13**. Iodolactonization of the acid **13** under standard conditions[12] followed by dehydroiodination with DBU in toluene provided a separable diastereomeric mixtures of the lactone **14a** and **14b** (3:7). To avoid the complexity in the following synthesis, the minor diastereomer **14a** was converted to **14b** through deprotection of TBS ether, Mitsunobu inversion, and again TBS protection. Cyclohexene **14b** was oxidized with cat. OsO_4 and NMO in acetone/water to afford a diastereomeric mixture of diols **15** and **16** (4:1) in 96% yield (confirmed by NOESY spectrum). Even though the bulky TBS group and the lactone ring in the cyclohexene **14b** are on the same side, 1,3-diaxial interactions due to the α-methyl group affected the stereoselectivity of dihydroxylation.

Dimethylation of the diol **15** was achieved with a mild and neutral Purdie reagent such as Ag_2O and methyl iodide in a sealed tube, affording the desired lactone **17** in 83% yield (Scheme 2). However, due to the steric resistance of the bulky

Scheme 2. Methylation and NOE Effects Observed for Diol 15



TBS group in the diol **16**, dimethylation at a higher temperature, or addition of any catalyst failed to deliver dimethylated product and gave monomethyl lactone **18**.

With the requisite lactone **17** in hand, we next turned our attention to the attachment of the sesquiterpene side chain. Our initial attempts to couple lactol **19** generated from the lactone **17** by DIBAL-H with the sulfones **20** or **21** through Julia olefination conditions [base (LiHMDS, KHMDS, LDA, BuLi), solvent system (THF, HMPA, ether), anion stabilizer (crown ethers)] were unsuccessful.

After several abortive attempts with Julia olefination, homologation was executed through Wittig olefination. Condensation of the lactol **19** with ylide $Ph_3PC(Me)CO_2Et$ in benzene provided the *trans*-olefin **23** in 95% yield (Scheme 3). The resultant secondary alcohol group was protected as MOM ether and subsequent DIBAL-H reduction of the ester provided allylic alcohol **24**. Bromination of the allylic alcohol under Appel reaction conditions (CBr_4/PPh_3, DCM, 0 °C) provided the allylic bromide **25** in 94% yield. Construction of the sesquiterpene side chain was achieved through coupling of the allylic bromide **25** with the carbanion derived from geranyl phenyl sulfide[13] **26** in the presence of TMEDA to provide the sulfide intermediate, which was subjected to desulfurization[14] using lithium in liquid ammonia to afford the required sesquiterpene side chain of antroquinonol. With the side chain installed, deprotection of the TBS group with TBAF in THF followed by oxidation with PCC afforded the cyclohexanone **28** in 82% yield.

With access to the required sesquiterpene side chain and cyclohexanone core, the synthesis could be completed by the introduction of α,β-unsaturation and the removal of MOM protecting group. The total synthesis of antroquinonol D was

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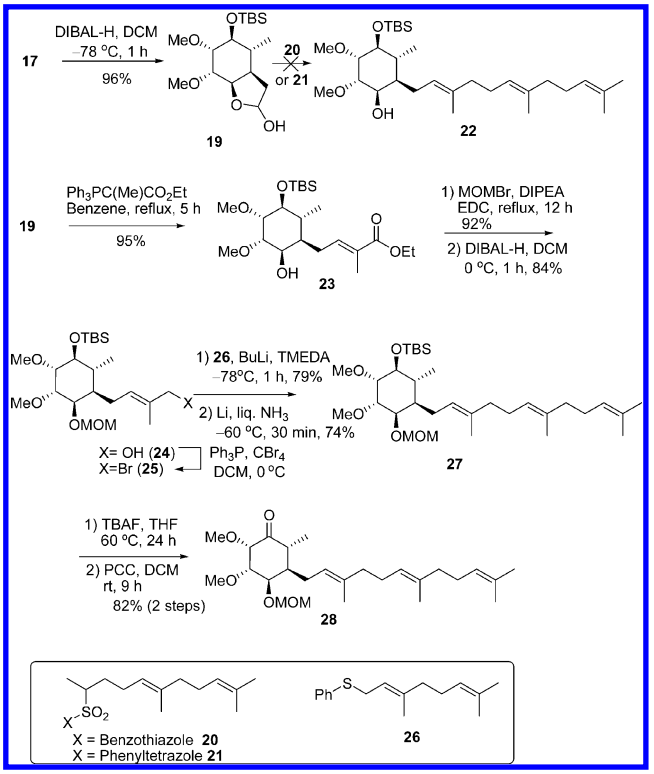
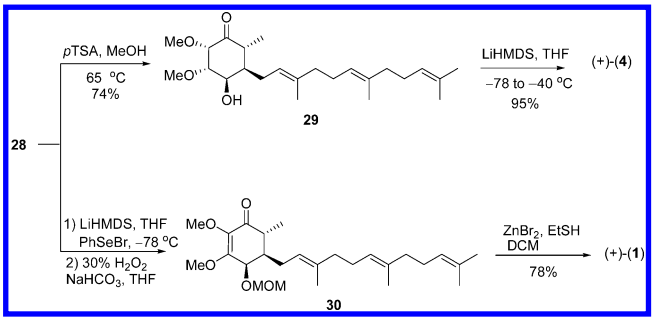
Scheme 3. Construction of Sesquiterpene Side Chain



accomplished through the deprotection of the MOM group with *p*TSA in MeOH followed by the elimination of *β*-methoxy group by deprotonation using LiHMDS in THF (Scheme 4).

Scheme 4. Synthesis of Antroquinonol and Antroquinonol D



In order to complete the synthesis of antroquinonol, the regioselective phenylselenation of ketone **28** was achieved with LiHMDS in THF at −78 °C and then oxidative elimination using 30% H_2O_2 provided *α,β*-unsaturated ketone **30**. The final stage of the synthesis of antroquinonol required deprotection of MOM ether. Most of the conditions[15] tested for the cleavage of this group turned out unreactive or led to the decomposition of starting material. Deprotection of the MOM group of **30** was effected efficiently with $ZnBr_2$ and ethanethiol in DCM to furnish (+)-antroquinonol in good yield.[16]

The spectroscopic data of synthesized (+)-antroquinonol (**1**) and (+)-antroquinonol D (**4**) were consistent with those reported for the natural product in all respect.[3] The measured optical rotation indicated that the synthetic material possessed the same absolute stereochemistry as the natural product and thus confirms the structure as well as the proposed configurations for these natural products; isolated (+)-**4**: $[\alpha]_D$ +52.2, *c* 0.5, MeOH;[3c] this work (+)-**4**: $[\alpha]_D$ +48.6, *c* 0.5, MeOH; isolated (+)-**1**: $[\alpha]^{18}_D$ +72.7, *c* 0.28, $CHCl_3$;[3a,17] this work (+)-**1**: $[\alpha]^{25}_D$ +42.5, *c* 1.2, $CHCl_3$.

In summary, we have accomplished the first total synthesis of (+)-antroquinonol and (+)-antroquinonol D, which confirmed the absolute stereostructures assigned for these natural products. The present synthesis is based on iridium-catalyzed isomerization/Claisen rearrangement, Grubbs olefin metathesis, and lactonization to form the three required streogenic centers of quinonol. The common intermediate could be converted to two members of this class of compounds. This strategy allows for the preparation of sufficient quantities of the natural product for detailed biological studies.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all reactions and products, including ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chinpiao@mail.ndhu.edu.tw.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Geethangili, M.; Tzeng, Y.-M. *Evidence-Based Complementary Altern. Med.* **2011**, 216641. (b) Ao, Z. H.; Xu, Z. H.; Lu, Z. M.; Xu, H. Y.; Zhang, X. M.; Dou, W. F. *J. Ethnopharmacol.* **2009**, *121*, 194−212. (c) Lu, Z. M.; Tao, W. Y.; Xu, H. Y.; Ao, Z. H.; Zhang, X. M.; Xu, Z. H. *Nat. Prod. Res.* **2011**, *25*, 684−695. (d) Huang, C. H.; Chang, Y. Y.; Liu, C. W.; Kang, W. Y.; Lin, Y. L.; Chang, H. C.; Chen, Y. C. *J. Agric. Food Chem.* **2010**, *58*, 3859−3866. (e) Hsiao, G.; Shen, M. Y.; Lin, K. H.; Lan, M. H.; Wu, L. Y.; Chou, D. S.; Lin, C. H.; Su, C. H.; Sheu, J. R. *J. Agric. Food Chem.* **2003**, *51*, 3302−3308. (f) Hseu, Y.-C.; Chang, W.-C; Hseu, Y.-T.; Lee, C.-Y.; Yech, Y.-J.; Chen, P.-C.; Chen, J.-Y.; Yang, H.-L. *Life Sci.* **2002**, *71*, 469−482. (g) Song, T. Y.; Yen, G. C. *J. Agric. Food Chem.* **2002**, *50*, 3322−3327. (h) Lee, I. H.; Huang, R. L.; Chen, C. T.; Chen, H. C.; Hsu, W. C.; Lu, M. K. *FEMS Microbiol. Lett.* **2002**, *209*, 63−67.

(2) Shi, L. S.; Chao, C. H.; Chen, C. H.; Liao, Y. R.; Wu, S. J.; Leu, Y. L.; Shen, Y. C.; Kuo, Y. H. *Bioorg. Med. Chem.* **2011**, *19*, 677−683.

(3) (a) Lee, T.-H.; Lee, C.-K.; Tsou, W.-L.; Liu, S.-Y.; Kuo, M.-T.; Wen, W.-C. *Planta Med.* **2007**, *73*, 1412−1415. (b) Liu, S.-Y.; Wen, W.-C.; Kuo, M.-T. EP2233463 A1, 2010. (c) Wang, S.-C.; Lee, T.-H.; Hsu, C.-H.; Chang, Y.-J.; Chang, M.-S.; Wang, Y.-C.; Ho, Y.-S.; Wen, W.-C.; Lin, R.-K. *J. Agric. Food Chem.* **2014**, *62*, 5625−5635.

(4) (a) Liu, S.-Y.; Wen, W.-C.; Tsou, W.-L.; Kuo, M.-T.; Huang, C.-H.; Fok, K.-H.; Li, Y.-Y.; Chang, C.-C. US 7342137 B1, 2008. (b) Lu, M.-C.; Mohamed, E.-S.; Wu, T.-Y.; Du, Y.-C.; Chang, T.-T.; Chen, C.-F.; Hsu, Y.-M.; Lai, K.-H.; Chiu, C.-P.; Chang, F.-R; Wu, Y.-C. *Pharmacol. Ther.* **2013**, *139*, 124−156. (c) Chiang, P.-C.; Lin, S.-C.; Pan, S.-L.; Kuo, C.-H.; Tsai, I.-L.; Kuo, M.-T.; Wen, W.-C.; Guh, J.-H. *Biochem. Pharmacol.* **2010**, *79*, 162−171. (d) Liu, S.-Y.; Kuo, M.-T.; Wen, W.-C. US 7411003, 2008. (e) Bharath Kumar, V.; Yuan, T.-C.; Liou, J.-W.; Yang, C.-J.; Sung, P.-J.; Weng, C.-F. *Mutat. Res.* **2011**, *707*, 42−52. (f) Hsu, C.-Y.; Sulake, R. S.; Huang, P.-K.; Shih, H.-Y.; Sie, H.-

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Org. Lett. XXXX, XXX, XXX−XXX

W.; Lai, Y.-K.; Chen, C.; Weng, C.-F. *Br. J. Pharmacol.* **2015**, *172*, 38−49.
(5) Sulake, R. S.; Jiang, Y.-F.; Lin, H.-H; Chen, C. *J. Org. Chem.* **2014**, *79*, 10820−10828.
(6) During deprotection of MOM group of antroquinonol under several conditions we observed a facile aromatization.
(7) (a) Mikami, K.; Takahashi, K.; Nakai, T. *Tetrahedron Lett.* **1987**, *28*, 5879−5882. (b) Sugiura, M.; Yanagisawa, M.; Nakai, T. *Synlett* **1995**, 447−448. (c) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **2000**, *122*, 3785−3786. (d) May, J. A.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 12426−12427. (e) Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978−4979. (f) Pohjakallio, A.; Pihko, P. M. *Chem.—Eur. J.* **2009**, *15*, 3960−3964.
(8) (a) Wu, Z.-L.; Wu, H.-L.; Wu, P.-Y.; Uang, P.-Y. *Tetrahedron: Asymmetry* **2009**, *20*, 1556−1560. (b) Cheng, K.; Kelly, A. R.; Kohn, R. A.; Dweck, J. F.; Walsh, P. J. *Org. Lett.* **2009**, *11*, 2703−2706.
(9) Nonoshita, K.; Maruoka, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 541−545.
(10) (a) Nelson, S. G.; Bungard, C. J.; Wang, K. J. *J. Am. Chem. Soc.* **2003**, *125*, 13000−13001. (b) Nelson, S. G.; Wang, K. *J. Am. Chem. Soc.* **2006**, *128*, 4232−4233. (c) Stevens, B. D.; Bungard, C. J.; Nelson, S. G. *J. Org. Chem.* **2006**, *71*, 6397−6402.
(11) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567−569.
(12) Bergner, E. J.; Helmchen, G. *Eur. J. Org. Chem.* **2000**, 419−423.
(13) (a) Fukuda, T.; Irie, R.; Katsuki, T. *Tetrahedron* **1999**, *55*, 649−664. (b) Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **1999**, *121*, 6792−6797.
(14) (a) Coates, R. M.; Ley, D. A.; Cavender, P. L. *J. Org. Chem.* **1978**, *43*, 4915−4922. (b) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *J. Org. Chem.* **1990**, *55*, 5088−5107.
(15) (a) Auerbach, J.; Weinreb, S. M. *Chem. Commun.* **1974**, 298−299. (b) Meyers, A. I.; Durandetta, J. L.; Munavu, R. J. *J. Org. Chem.* **1975**, *40*, 2025−2029. (c) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635−648. (d) Boehlow, T. R.; Harburn, J. J.; Spilling, C. D. *J. Org. Chem.* **2001**, *66*, 3111−3118. (e) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933−2935. (f) Deville, J. P.; Behar, V. *J. Org. Chem.* **2001**, *66*, 4097−4098. (g) Khupse, R. S.; Erhardt, P. W. *Org. Lett.* **2008**, *10*, 5007−5010.
(16) (a) Sohn, J.-H.; Waizumi, N.; Zhong, H. M.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 7290−7291. (b) Han, J. H.; Kwon, Y. E.; Sohn, J.-H.; Ryu, D. H. *Tetrahedron* **2010**, *66*, 1673−1677.
(17) The reported optical rotation value of antroquinonol is $[\alpha]^{18}_{D}$ +72.7, *c* 0.28, $CHCl_3$. However, when we remeasured the optical rotation of authentic sample available from biotech department (after purification by column chromatography), we observed the optical rotation value of +43.5 (in $CHCl_3$: *c* 1.2 or 0.28), comparable to our synthetic material (+42.5 in $CHCl_3$: *c* 1.2). The difference in optical rotation might be due to the low concentration measured for the original sample.

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