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Enantioselective Total Synthesis of (*S*)-Bisoranjidiol, an Axially Chiral Bisanthraquinone

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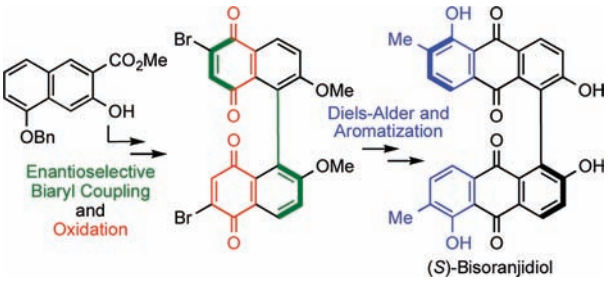
ABSTRACT



The first enantioselective total synthesis of the bisanthraquinone (*S*)-bisoranjidiol and an unnatural regioisomer has been accomplished. Key features of the synthesis include the asymmetric oxidative biaryl coupling of a hindered 8-substituted 2-naphthol, selective *para*-quinone formation, and regioselective tandem Diels–Alder/aromatization reactions.

(*S*)-Bisoranjidiol [(*S*)-**1**, Figure 1] is a photosensitizing bisanthraquinone capable of interacting with molecular oxygen to generate electronically excited singlet oxygen and the ground state radical anion upon irradiation with light.[1] These photosensitizing properties are responsible for the phototoxicity of the shrub *Heterophyllaea pustulata* (genera Rubiaceae), from which it was isolated in 2006.[2] Native to the Andean Mountains of Argentina and Bolivia, the plant poses a danger to grazing livestock. Ingestion of the plant and exposure to sunlight causes dermatitis, keratoconjunctivitis (which may lead to blindness), and behavioral changes, such as restlessness and photophobia.[3,4] The photosensitizing properties of (*S*)-**1** make it an interesting natural product with potential applications in photodynamic therapy.[5] Recently, it has been reported to be a good antibacterial agent[6] and photodynamically active toward cancer cells.[7] To date, neither asymmetric syntheses of bisanthraquinones nor any synthesis of **1** has been achieved. In this letter, we report the first total synthesis of (*S*)-bisoranjidiol (**1**) via a route that would allow analog generation to optimize biological properties.

Bisoranjidiol (**1**) is a member of a larger class of axially chiral symmetrical bisanthraquinone natural products possessing a biaryl linkage at the 1,1′-positions (see Figure 1). Spectroscopic analyses and chemical methods established the structure and configuration of **1**.[2] Bisoranjidiol (**1**) is unique compared to the other bisanthraquinone natural products (**2**) as it lacks the 4,4′-hydroxyl groups and the *meta*-substitution pattern of the distal rings shared by the other congeners.

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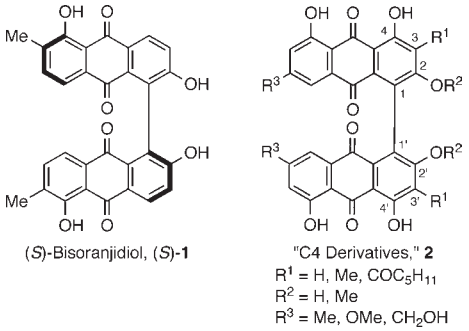
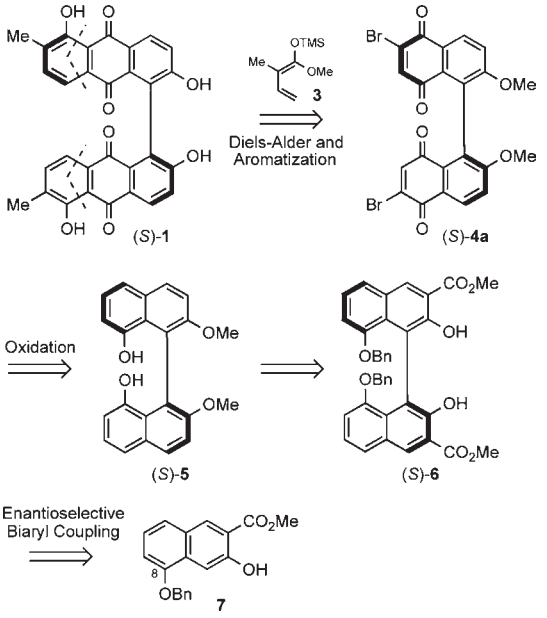


Figure 1. Bisanthraquinone natural products.

Prior syntheses of symmetrical bisanthraquinones possessing a 1,1′-biaryl linkage include biomimetic coupling of an anthraquinone or anthrone monomer,[8] the Ullman reaction between brominated anthraquinones,[9] and double addition of an isobenzofuran-1,3-dione to a biphenyl intermediate.[10] However, the only bisanthraquinone natural products synthesized include skyrin (0.28−35% yield, $R^{1,2}$ = H, R^3 = Me; Figure 1) and hinakurin (≤58% yield, R^1 = H, $R^{2,3}$ = Me; Figure 1), which were formed via biomimetic syntheses[8] and an Ullman reaction, respectively.[9a] The total syntheses of related bisanthraquinones, biphyscion, 2,2′-*epi*-cytoskyrin A, and rugulosin have also been reported; however, biphyscion contains a 2,2′-biaryl linkage,[11] and the latter two possess a cage-like "skyrane" motif.[12]

Retrosynthetic analysis of (*S*)-**1** revealed a different, nonbiomimetic approach to this structural subtype that hinges on the much simpler prospect of forming a bisnaphthol via oxidative coupling rather than the more difficult oxidative coupling of an oxidation resistant anthraquinone. Specifically, a double Diels−Alder reaction between a binaphtho-*para*-quinone [(*S*)-**4a**] and vinyl ketene acetal **3**, followed by aromatization, would readily reveal the core bisanthraquinone structure (Scheme 1). The Diels−Alder reaction of 1,4-naphthoquinones with vinylketene acetals, followed by aromatization, is well-known.[13] Alkyl trimethylsilyl- or bis(trimethylsilyl)vinyl ketene acetals, also referred to as Brassard dienes,[13] are typically employed in these types of reactions although less ornate dienes such as Danishefsky's diene[14] have also been used.

Scheme 1. Retrosynthetic Analysis



The key binaphtho-*para*-quinone (*S*)-**4a** would, in turn, require a selective oxidation of (*S*)-**5**, a heretofore unexplored undertaking. Enantioselective oxidative binaphthol coupling of **7**, containing substitution at the 8-position, with our 1,5-diaza-*cis*-decalin copper catalyst,[15] followed by ester and protecting group removal would provide key intermediate (*S*)-**6**. This asymmetric coupling reaction has been an integral part of the syntheses of several other axially or helically chiral naphthalene-based natural products from our group.[16,17]

Coupling precursor **7** was effectively prepared from **8** via a Fischer esterification and selective benzylation of the less hindered phenol (Scheme 2). The enantioselective biaryl coupling of substrate **7** with (*R,R*)-**9** proceeded

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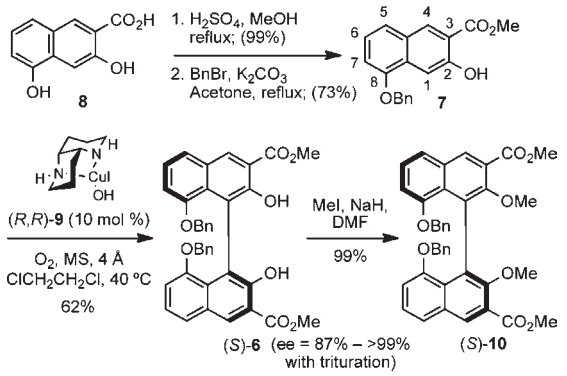
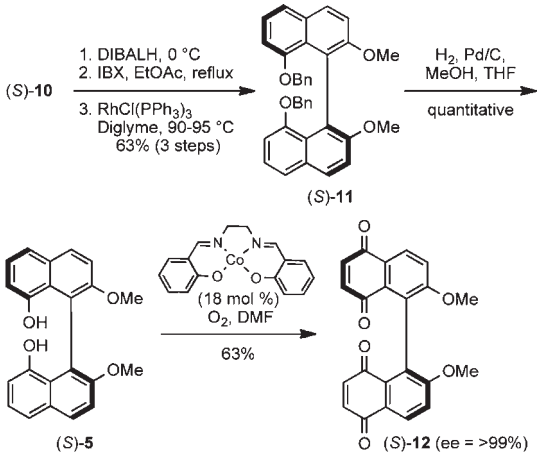
surprisingly smoothly even with the C8-substitution, which provides considerable steric hindrance to the coupling at C1. As a result, (*S*)-**6**[18] was obtained in 62% yield and 87% ee (61% yield, 92% ee with (*S,S*)-**9**). After one trituration, material of >99% ee was readily obtained. To the best of our knowledge, the only reported enantioselective binaphthol coupling reaction with substitution in the hindered 8-position is the coupling of naphtho[2,1-*b*]furan-8-ol in 50% yield and 75% ee.[19]

Scheme 2. Synthesis of Biaryl



After methylation of (*S*)-**6**, the esters were effectively removed in 63% yield via a three-step sequence involving DIBALH reduction to the alcohol, IBX promoted oxidation to the aldehyde, and decarbonylation with $RhCl(PPh_3)_3$ (Scheme 3). In this instance, this combination was found to be more efficient and reliable than decarboxylation. Hydrogenolysis of the benzyl groups followed by a selective salcomine catalyzed oxidation yielded the binaphtho-*para*-quinone (*S*)-**12** in 63% yield without loss of enantiopurity. Approximately 23% of an unsymmetrical binaphtho-*ortho, para*-quinone was also isolated. This side product could be avoided by using (diacetoxyiodo)benzene, but yields were much lower.

Scheme 3. Synthesis of Binaphtho-*para*-quinone



Abbreviations: IBX, *o*-iodoxybenzoic acid

With (*S*)-**12** in hand, the remaining key step was transformation of the binaphtho-*para*-quinone into a bisanthraquinone via regioselective tandem Diels–Alder/aromatization reactions. Initial investigations revealed that the use of Lewis acids, such as $ZnCl_2$, provided control over the regioselectivity of the cycloaddition, however, side reactions and decomposition of the quinone consistently resulted in low yields. Aside from Lewis acids, halogens are often used as directing groups when working with vinyl ketene acetals and *para*-quinones.[20] Subsequent investigations on a monomeric system indicated that halogen directing groups provided superior yields and complete regiocontrol in the cycloaddition reaction.

To install the desired bromine directing group, (*S*)-**12** was brominated with Br_2, followed by dehydrohalogenation in acetic acid (Scheme 4). This procedure provided a mixture of bromoquinones in 95% yield. The mixture was comprised of the 6,6′-, 6,7′-, and 7,7′-dibrominated regioisomers. Approximately equal ratios of the 6,6′- and 6,7′-dibromoquinones [(*S*)-**4a** and (*S*)-**4b**; Scheme 4] were obtained, plus 10% of the 7,7′-dibromoquinone [(*S*)-**4c**]. The production of (*S*)-**4a** and (*S*)-**4b** was seen as an opportunity to produce both a significant amount of bisoranjidiol precursor [(*S*)-**13a**] and an unnatural bisanthraquinone regioisomer. Due to the directing ability of the halogen in the cycloaddition reaction, we expected the ratio of regioisomers **4a**–**c** to be reflected in the product bisanthraquinones. When diene **14**[21] was used in a test reaction with a substrate analogous to **4a**–**c**,[22] this result did occur, but interestingly, with diene **3**[23] and **4a**–**c**, the process was very selective for (*S*)-**13a**. It appeared that (*S*)-**4b** and (*S*)-**4c** were either not reacting as well as (*S*)-**4a** and/or were decomposing. To evaluate the reasons for the selectivity, the regioisomers (*S*)-**4a** and (*S*)-**4b** were separated and treated separately with diene **3**. The key intermediate to bisoranjidiol, (*S*)-**4a**, reacted completely with diene **3** in 2 days to afford the "out–out" bisanthraquinone (*S*)-**13a** in 80% yield, following aromatization over silica (Scheme 4). Dibromoquinone (*S*)-**4b**, on the other hand, stalled at the monocycloadduct stage and required 5–6 days to reach completion, with noticeably more decomposition over the course of the reaction compared to (*S*)-**4a**. Aromatization over silica provided "out–in" (*S*)-**13b** in 46–71% yield. This was deprotected to give the regioisomer of bisoranjidiol (Scheme 4). The minor isomer

(18) The absolute configuration was assigned based upon analogy to other binaphthols formed by the diaza-*cis*-decalin copper catalyst. This coupling reaction has been demonstrated to be highly stereoregular. See refs 15 and 16.

(19) Upadhyay, S. P.; Karnik, A. V. *Tetrahedron Lett.* **2007**, *48*, 317–318.

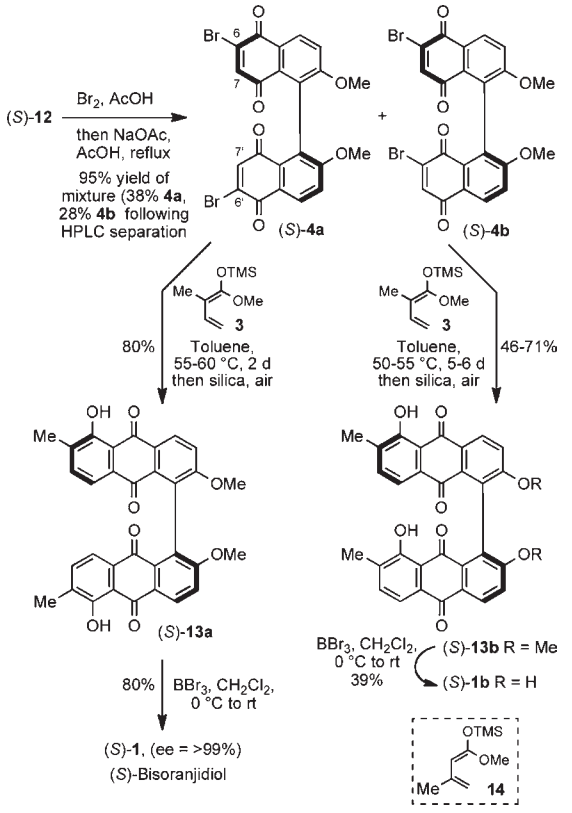
(20) For examples, see: (a) Cameron, D. W.; Riches, A. G. *Aust. J. Chem.* **1999**, *52*, 1165–1171. (b) Tietz, L. F.; Gericke, K. M.; Schuberth, I. *Eur. J. Org. Chem.* **2007**, 4563–4577. (c) Danishefsky, S. J.; Uang, B. J.; Quallich, G. *J. Am. Chem. Soc.* **1985**, *107*, 1285–1293.

(21) Tietz, L. F.; Gericke, K. M.; Singidi, R. R.; Schuberth, I. *Org. Biomol. Chem.* **2007**, *5*, 1191–1200.

(22) The test reaction was carried out with a mixture of the "out", "out-in", and "in" bromoquinones, analogous to **4a**–**c**, but containing 3,3′-methyl esters and 2,2′-hydroxyls

(23) Kim, G. T.; Wenz, M.; Park, J. I.; Hasserodt, J.; Janda, K. D. *Bioorg. Med. Chem.* **2002**, *10*, 1249–1262.

Scheme 4. Synthesis of (*S*)-Bisoranjidiol and an Unnatural Regioisomer



(*S*)-**4c** mostly led to decomposition. Presumably, the formation of the "in" Diels–Alder adduct with the phenolic substituent disposed to the hindered bay region of the structure is highly disfavored on steric grounds.

Finally, deprotection of (*S*)-**13a** with excess BBr_3 provided (*S*)-bisoranjidiol, (*S*)-**1**, in 80% yield with no erosion of the enantiomeric excess (Scheme 4). Both the chemical shifts and splitting patterns from the ^1H and ^{13}C NMR data of the synthetic material were in accord with the published spectroscopic data for the natural product.[2] Using an authentic sample of the natural product kindly provided by Dr. Cabrera,[2] we undertook chiral HPLC analysis to confirm the original stereochemical assignment as *S*.[2] Surprisingly, the authentic sample showed only 5% ee of the (*S*)-enantiomer. Since the ee is small, it is also possible that the natural sample is racemic. Concurrently, we discovered that the enantiopurity of bisoranjidiol eroded in MeOH (25 °C, $t_{1/2}$ = 3.8 months; 80 °C, $t_{1/2}$ = 1.8 h). As the isolation conditions involved refluxing solvent (benzene) and exposure to base and acid,[2] it is not unreasonable that significant erosion of the enantiopurity occurred during isolation and subsequent handling of the material.

In summary, the first total synthesis of (*S*)-bisoranjidiol has been completed in 12 steps and 4% overall yield from commercially available **8**. This synthesis also represents the most selective coupling of a 2-naphthol with substitution in the hindered 8-position, as well as the first enantioselective synthesis of a 1,1′-linked bisanthraquinone. This approach represents a more efficient entry into this natural product series and also permits flexibility in the generation of further analogs for study.

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

The authors declare no competing financial interest.