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Assignment and Stereocontrol of Hibarimicin Atropoisomers

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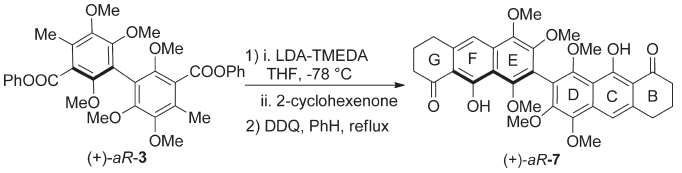
ABSTRACT



A stereochemical feature of the hibarimicins is a central biaryl (HMP-Y6) or aryl-quinone (hibarimicinone) incorporated as a single atropodiastereomer. Herein, a chiral resolution and deracemization process to access optically enriched biaryls *aR*-3 and *aS*-3 is described. From these atropoenantiomers the BCD-EFG ring system of HMP-Y6 is constructed [(+)-*aR*-7]. Comparison of CD spectra of *aR*-7 to HMP-Y6 leads to the assignment of HMP-Y6 and hibarimicin B atropoisomers as *aR* and *aS*, respectively.

The hibarimicins were isolated from the soil microbe *Microbispora rosea* during the course of screening natural product extracts for tyrosine kinase inhibitors.[1,2] Structural studies on hibarimicins A, B, C, D, and G concluded that the five metabolites shared a common aglycone [hibarimicinone (Figure 1)] conjugated to six deoxy sugars located at C10/C12 and C10′/C12′.[1b] The relative stereochemistry of the aglycone hibarimicinone was assigned as shown in Figure 1 with the configuration of the C13 tertiary alcohol (H ring) tentative. Kajiura and co-workers later reported on biosynthetic studies using blocked mutants of the hibarimicin producer *Microbispora rosea* subsp. *hibaria* TP-A0121 that proved the C13 (H ring) and C13′ (A ring) stereochemistry were identical.[3] Key to clarification of C13 stereochemistry was the isolation of HMP-Y6 (Figure 1),[3c] a glycosylated C_2-symmetric shunt metabolite, derived from the oxidative homocoupling of an aromatic undecaketide followed by glycosylation. Acidic methanolysis of HMP-Y6 resulted in release of C10/C12 and C10′/C12′ deoxy sugars to provide the aglycone (HMP-Y1, Figure 1). Comparison of the core biaryl substitution pattern of HMP-Y6 to known atropisomeric natural products such as biphyscion[4] supports an

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(1) (a) Kajiura, T.; Furumai, T.; Igarashi, Y.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot*. **1998**, *51*, 394–401. (b) Hori, H.; Igarashi, Y.; Kajiura, T.; Furumai, T.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot*. **1998**, *51*, 402–417.

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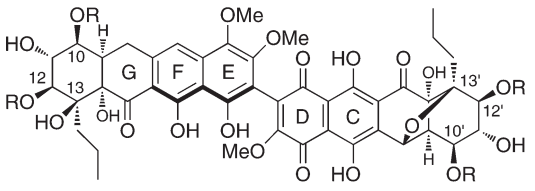
atropodiastereoslective oxidative homocoupling followed by oxidation of the BCD ring system leading to hibarimicinone with retention of atropo configuration.[5] In connection with our pursuit of a total synthesis of hibarimicinone[6] we describe here a deracemization method providing atropo-stereocontrol and assignment of configuration of the central biaryl carbon–carbon bond of HMP-Y6 and hibarimicin B by spectroscopic correlation further supported by computational studies.



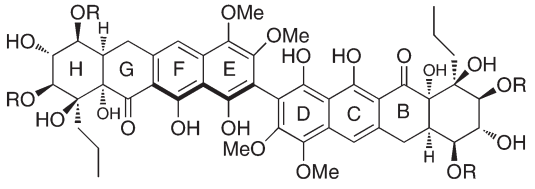


Figure 1. Structures of hibarimicinone, hibarimicins A-D, HMP-Y6, and HMP-Y1.

A variety of naturally occurring dimeric quinones, biaryls, and binaphthoquinones have been identified and the subject of synthetic investigations.[7] In general two approaches have been utilized in their assembly: oxidative biomimetic homocouplings[8] and two-directional annulations[9] (Figure 2). Nonenzymatic biomimetic homocouplings of 2-naphthols have provided diastereoselectivity under substrate control, but diastereoselective homocouplings of 1-naphthols, as required for HMP-Y1 (Figure 2), have not been reported.[10] Müller and Steglich[9a,b] have employed two-directional Michael–Dieckmann cyclizations of optically active biaryl *o*-toluate esters obtained by resolution. For the purpose of assigning absolute stereochemistry of the central biaryl bond of HMP-Y1 our studies began with a two-directional annulation strategy starting from single atropoenantiomers of bis-*o*-tolyl phenyl benzoate.

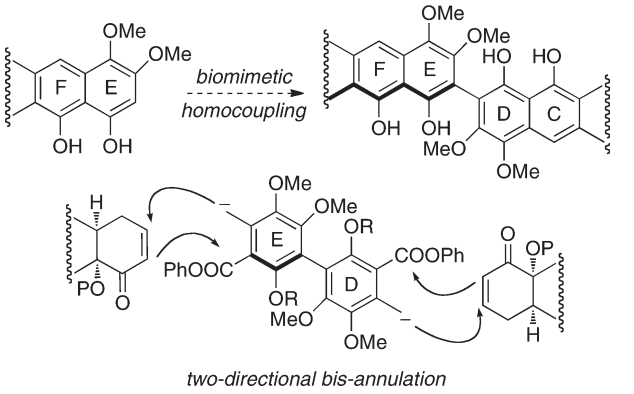


Figure 2. Biomimetic and two-directional strategies directed toward HMP-Y1.

Despite the importance of biaryl atropisomers as chiral ligands and their frequent occurrence in nature, control of axial chirality remains challenging and no general methods are currently available to directly produce the required bis-*o*-tolyl phenyl benzoate enantioselectively (Figure 2).[11] For this reason we considered chiral resolution as it would provide access to both enantiomers and assist in assigning the absolute stereochemistry of HMP-Y1. To begin we examined the Spring oxidative organocuprate homocoupling starting from a series of protected phenols (**1a**–**c**) (Scheme 1).[12] Lithiation, cupration, and oxidation of methyl ether **1a** provided biaryl **2a** in yields ranging from 51 to 63%, while cuprates derived from MOM (**1b**) and benzyl (**1c**) ethers oxidatively coupled in slightly lower yields. Phenyl ester **3** was derived from biaryl **2a** by bromination followed by a lithium–halogen exchange and phenyl chloroformate quench. We examined the resolution of biaryl intermediates en route to **3** and bis-phenyl ester **3** by chiral LC using several chiral solid supports. Resolution of enantiomers was observed only with bis-phenyl ester **3**, which could be separated on preparative scale. In order to assign the absolute stereochemistry of (+)- and (−)-phenyl benzoate **3**, bis-phenol (±)-**4** [from either MOM ether **2b** (HCl, MeOH) or benzyl ether **2c** (H_2, Pd/C)] was condensed with an excess of (*S*)-Mosher acid to give diastereomers *aR*-**5** and *aS*-**6**. The latter diastereomer was recrystallized from ether–dichloromethane and subject to single-crystal X-ray analysis allowing unambigous assignment of stereochemistry. Phenol *aS*-**4** was derived from Mosher ester *aS*-**6** by LAH reduction and advanced to *aS*-**3** by a three-step reaction

(7) (a) Bringmann, G.; Mortimer, A.; Keller, P.; Gresser, M.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384–5427. (b) Bringmann, G.; Tasler, S. *Tetrahedron* **2001**, *57*, 331–343. (c) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563–639.

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(10) For examples of stereoselective 2-naphthol homocouplings, see: (a) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193–3207. (b) Young, S.; Grove, C.; Gozalez, M.; Urgaonkar, S.; Fettinger, J.; Shaw, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 3730–3733.

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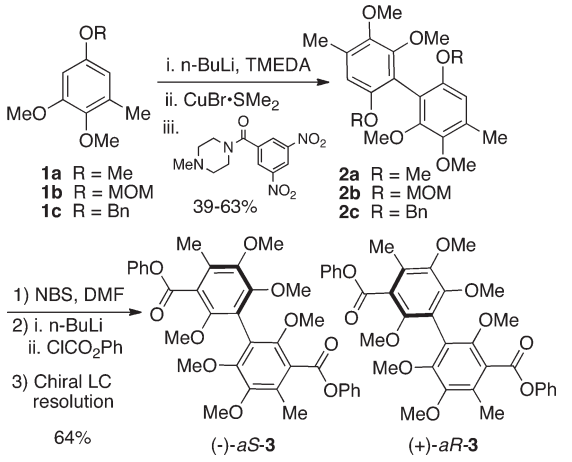
sequence (Scheme 2). Atropoenantiomer *aS*-**3** correlated with the slower eluting enantiomer in the chiral-LC resolution of biaryl (±)-**3** described above.

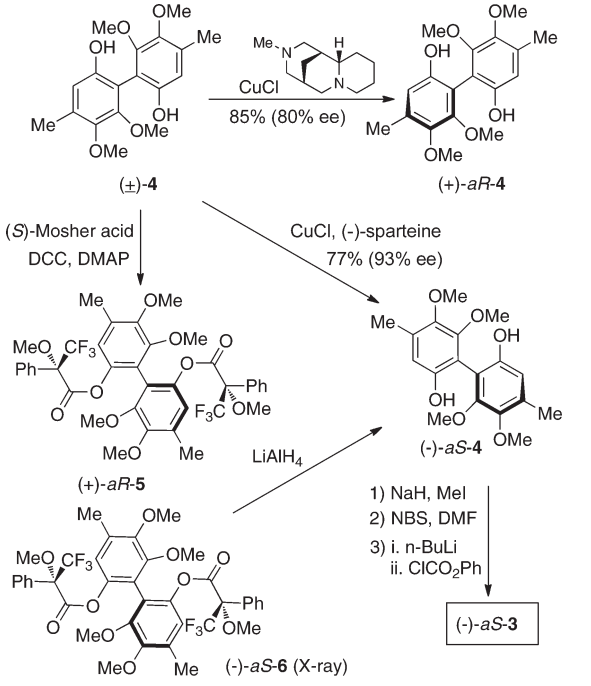
Scheme 1. Preparation and Resolution of Biaryl **3**



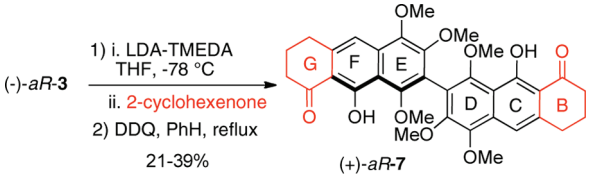
Having assigned the absolute configuration of (−)-*aS*-**3** and (+)-*aR*-**3**, we turned our attention to developing a method of accessing enantiomerically enriched **3** not relying on a chiral resolution. We were drawn to reports describing copper(II)−diamine complexes to deracemize C_2-symmetric ligands including BINOL, VAPOL, and VANOL.[13] Typically deracemization is accomplished by in situ generation of copper(II)−(−)-sparteine by the aerobic sonication of CuCl and (−)-sparteine followed by exposure of this complex to the racemic biaryl. While this method has been applied to chiral ligands[13a,b] and oligonaphthalenes[14] no report of reagent-controlled deracemization in the context of a natural product synthesis has appeared.[15] We were pleased to observe exposure of racemic biphenol **4** to the copper(II)−(−)-sparteine complex resulted in isolation of (−)-*aS*-**4** in 93% ee[16] and 77% yield. When (±)-**4** was treated with copper(II) complexed to O'Briens diamine[17] [(+)-sparteine surrogate], (+)-*aR*-**4** was produced in 80% ee (85% yield).

In order to evaluate the proposed bis-annulation (Figure 2) we optimized conditions for the generation of

Scheme 2. Absolute Configuration Assignment and Deracemization Route to (+)-*aS*-**3**



Scheme 3. Bis-annulation Leading to BCDEFG Ring System



the bis-*o*-toluate anion[18] derived from **3** using a series of deprotonation conditions followed by a D_2O quench.[19] Interestingly, no deprotonation was observed using 1 or 2 equiv of the LDA−TMEDA complex; however use of 4 equiv of LDA−TMEDA resulted in generation of the bis-toluate anion as demonstrated by near complete deuterium incorporation. Addition of 2 equiv of cyclohexenone to the bis-toluate anion derived from (+)-*aR*-**3** followed by DDQ oxidation provided (+)-*aR*-**7** (Scheme 3). Subsequently racemic (±)-**7** was resolved using chiral-LC on a preparative scale to give optically pure (−)-*aS*-**7** and (+)-*aR*-**7**.

Biaryl dimers (−)-*aS*-**7** and (+)-*aR*-**7** constitute the BCD-EFG substructure of HMP-Y6 (Figure 1). Furthermore, since **7** incorporates the chromophore of HMP-Y6 we anticipated that the quantum chemical predictions of ECD spectra for single enantiomers of **7** and comparison of the CD spectrum of HMP-Y6 to *aS*-**7** and *aR*-**7** would

(13) (a) Zhang, Y.; Yeung, S.-M.; Wu, H.; Heller, D. P.; Wu, C.; Wulff, W. D. *Org. Lett.* **2003**, *5*, 1813–1816. (b) Hu, G.; Holmes, D.; Gendhar, B. F.; Wulff, W. D. *J. Am. Chem. Soc.* **2009**, *131*, 14355–14364. (c) Lee, W. K.; Park, Y. S.; Beak, P. *Acc. Chem. Res.* **2009**, *42*, 224–234.

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(15) Nelson and Meyers were the first to report on the copper(II)-mediated deracemization of biaryls under substrate control; see: Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 3259–3262.

(16) Enantiomeric excess was determined by analysis of the derived bis-menthyl carbonate. See Supporting Information for details.

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(18) (a) Charest, M.; Lerner, C.; Brubaker, J.; Siegel, D.; Myers, A. *Science* **2005**, *308*, 395–398. (b) Mal, D.; Pahari, P. *Chem. Rev.* **2007**, *107*, 1892–1918.

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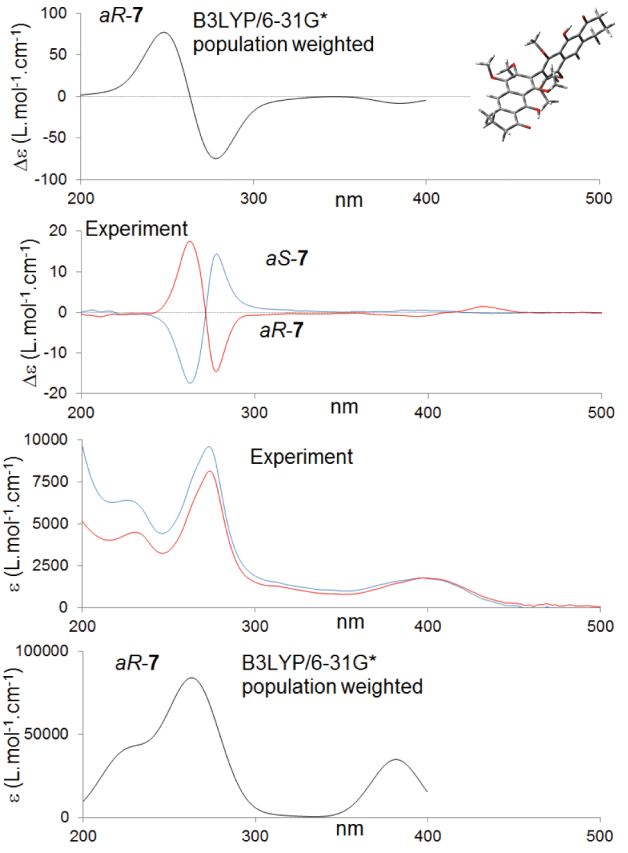

Figure 3. ECD and absorption spectra of **7**. Top panel: quantum chemical prediction of ECD spectrum for a*R*-**7** at the B3LYP/6-31G* level; Middle two panels: experimental ECD and absorption spectra of a*S*-**7** (blue) and a*R*-**7** (red); Bottom panel: quantum chemical prediction of absorption spectrum for a*R*-**7**. The inset in the top panel shows the structure of lowest energy conformation of a*R*-**7** at the B3LYP/6-31G* level.

allow assignment of configuration of the HMP-Y6 atropisomer. The experimental electronic circular dichroism (ECD) spectra of *aS*-**7** and *aR*-**7**, along with a quantum chemical prediction for *aR*-**7**, are shown in Figure 3. A bisignate negative ECD couplet (negative ECD band on the long wavelength side and positive ECD band on the short wavelength side) was observed, as also predicted, for *aR*-**7**. The negative ECD couplet predicted by the quantum chemical calculations for negative torsional angle between the planes of two biaryl moieties in *aR*-**7** is in agreement with the same relation predicted for the transition dipole moments by the empirical exciton coupling model.[20] Finally, the CD spectrum of HMP-Y6[21] correlates with *aR*-**7** with both having a negative torsional angle between the planes of two biaryl moieties.

In summary, the axial chirality of HMP-Y6 has been assigned the *aR* configuration, and assuming the configuration is retained upon oxidation to hibarimicin, the latter can be assigned the *aS* configuration.[22] To date, all isolated hibarimicins share the same UV and CD spectrum indicating they also possess the *aS* configuration. Heating a methanol solution of hibarimicinone in methanol (60 °C) resulted in isomerization to the unnatural *aR* isomer, indicating the hibarimicinone atropodiastereomer *aS* is not a thermodynamic product. This observation will need to be taken into account when designing a total synthesis of hibarimicinone or HMP-Y1.

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

(20) Harada, N.; Nakanishi, K. *Circular dichroic spectroscopy: Exciton coupling in organic stereochemistry*; University Science Books: Mill Valley, CA, 1983.

(21) See Supporting Information.

(22) Note the difference in configurational assignment between HMP-Y1 (*aR*) and hibarimicinone (*aS*) results from a switch in group priorities in accord with the Cahn–Ingold–Prelog sequence rules.