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Total Syntheses of HMP-Y1, Hibarimicinone, and HMP-P1

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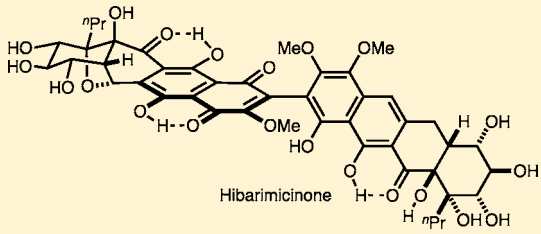
Supporting Information

ABSTRACT: Total syntheses of HMP-Y1, atrop-HMP-Y1, hibarimicinone, atrop-hibarimicinone, and HMP-P1 are described using a two-directional synthesis strategy. A novel benzyl fluoride Michael−Claisen reaction sequence was developed to construct the complete carbon skeleton of HMP-Y1 and atrop-HMP-Y1 via a symmetrical, two-directional, double annulation. Through efforts to convert HMP-Y1 derivatives to hibarimicinone and HMP-P1, a biomimetic mono-oxidation to desymmetrize protected HMP-Y1 was realized. A two-directional unsymmetrical double annulation and biomimetic etherification was developed to construct the polycyclic and highly oxidized skeleton of hibarimicinone, atrop-hibarimicinone, and HMP-P1. The use of a racemic biaryl precursor allowed for the synthesis of both hibarimicinone atropisomers and provides the first confirmation of the structure of atrop-hibarimicinone. Additionally, this work documents the first reported full characterization of atrop-hibarimicinone, HMP-Y1, atrop-HMP-Y1, and HMP-P1. Last, a pH-dependent rotational barrier about the C2−C2′ bond of hibarimicinone was discovered, which provides valuable information necessary to achieve syntheses of the glycosylated congeners of hibarimicinone.



INTRODUCTION

Background. Hibarimicins A−G are complex pseudodimeric type-II polyketides isolated from the culture broth of the rare actinomycete *Microbispora rosea* subsp. *hibaria* TP-A0121.[1] These metabolites inhibit proliferation and induce differentiation of numerous human cancer cell lines. In particular, hibarimicin B (**1**, Figure 1), which is identical to angelmicin B,[1b,c] has the most potent antiproliferative activity in HL-60 cells (IC_{50} = 58 nM).[1h] The cellular target and biological mechanism of action of **1** remain undetermined. The hibarimicins are among the most complex and largest type-II polyketides known. Hibarimicins A−G share an unprecedented highly oxidized aglycon, hibarimicinone (**2a**, Scheme 1). The C_2-symmetry of **2a** is broken by oxidation of the B-, C-, and D-rings relative to the G-, F-, and E-rings, respectively. More specifically, the B-ring contains a cyclic ether bridging C8′ and C13′, the C-ring contains a hydroxyl group at C6′, and the D-ring is a quinone. Furthermore, **2a** exhibits axial chirality about its highly congested C2−C2′ bond and is isolated as a single atropisomer.[1i,2] Altogether, the hibarimicins and hibarimicinone (**2a**) are challenging targets that have resisted total synthesis[3] until earlier this year when Tatsuta et al. reported the first total synthesis of **2a**.[4] Herein, we report enantioselective total syntheses of hibarimicinone (**2a**) and atrop-hibarimicinone (**2b**), and the first total syntheses of the biosynthetically related natural product aglycons HMP-Y1 (**3a**), atrop-HMP-Y1 (**3b**), and HMP-P1 (**6**) (Scheme 1).

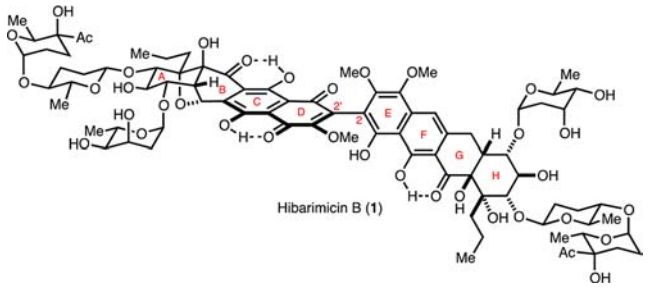


Figure 1. Structure of hibarimicin B (**1**).

Biosynthesis Hypothesis. Mutagenesis of *Microbispora rosea* subsp. *hibaria* TP-A0121 led to the identification of novel metabolites, including HMP-Y1 (**3a**), HMP-P1 (**6**), and their glycosylated derivatives (Scheme 1).[1f] Through ^{13}C-acetate labeling studies, it was discovered that C_2-symmetric **3a** is a precursor to **2a**, which is subsequently glycosylated to yield hibarimicins A−G. Ostensibly, this conversion (**3a** → **2a**) proceeds by breaking the C_2-symmetry of **3a** via oxidation of the B-, C-, and D-rings and demethylation of the C4′−OMe methyl group. We postulated that a single desymmetrizing oxidation of the C-ring of **3a** to hypothetical quinone **4** would be sufficient to relay oxidation to the B- and D-rings. This could be achieved via (1) tautomerization of quinone **4** to C8′-*ortho*-quinone methide **5** with subsequent oxy-Michael addition of the C13′−OH to install the B-ring cyclic ether, (2) reoxidation of the C-ring, and (3) transposition of the C-ring quinone to the D-ring with concomitant demethylation to give **2a**. HMP-P1 (**6**) arises from **2a** via cyclization of C1−OH onto C3′ of the D-ring quinone and subsequent expulsion of methanol.[1f]

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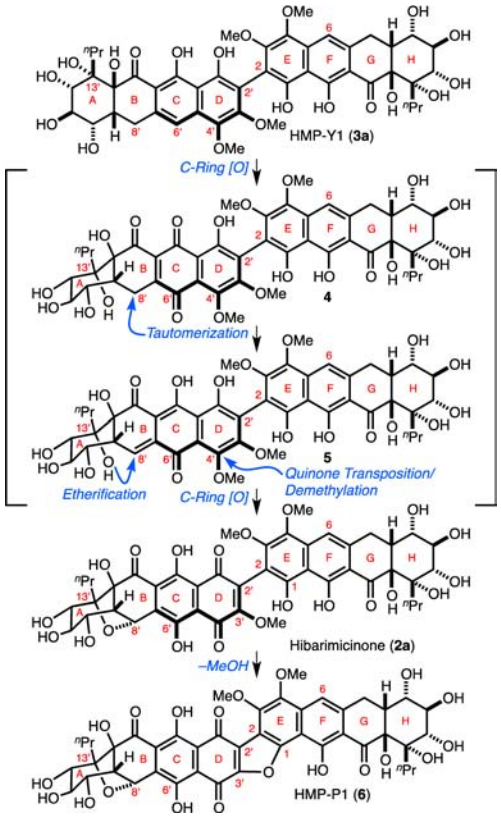
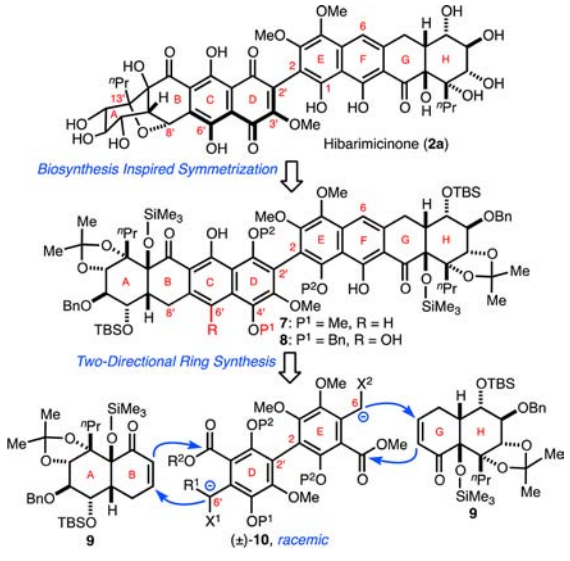
Scheme 1. Proposed Biosynthetic Conversion of HMP-Y1 (3a) to Hibarimicinone (2a) and HMP-P1 (6)



RESULTS AND DISCUSSION

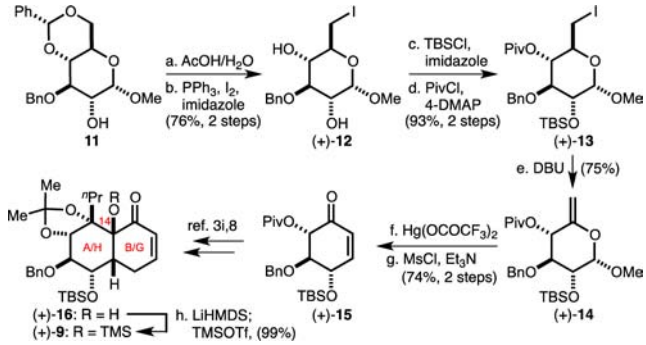
Synthesis Plan. Inspired by our proposed biosynthetic relay oxidation scheme, we envisioned that a similar set of biomimetic retrosynthetic disconnections could simplify **2a** to two plausible precursors, C_2-symmetric octacycle **7** and pseudo-C_2-symmetric octacycle **8** (Scheme 2). Targeting **7** was attractive for two reasons: (1) global deprotection would yield HMP-Y1 (**3a**), and (2) it would allow direct assessment of the feasibility of a biomimetic mono-oxidation to access a quinone analogous to **4**. In contrast to **7**, the C_2-symmetry of **8** is perturbed by the presence of a benzyl group[5] and the C6′–OH (both highlighted in red), the latter of which would facilitate chemoselective C-ring oxidation to a quinone. The most noteworthy feature shared by both **7** and **8** is the degeneracy of the AB- and HG-ring systems that results from the retrosynthetic excision of the B-ring cyclic ether bond. Next, it was envisioned that both octacyclic systems could be constructed in a single operation via a two-directional double annulation,[6] where the dianion of biaryl **10** would react with two equivalents of the AB-/HG-enone (+)-**9**. The use of a symmetric biaryl annulation donor would lead to **7**, whereas the employment of an unsymmetrical variant, with additional oxidation at C6′, would result in **8**. Both of these strategies are convergent and circumvent the need to construct the hindered C2–C2′ bond at a late stage. Efforts by the Roush group to form the C2–C2′ bond in simple model systems via cross-coupling were met with difficulty.[3d] At the outset of our study, the configuration of the stereochemical axis about the C2–C2′ bond of hibarimicinone (**2a**) was ambiguous.[1i] Consequently, we elected to proceed with racemic biaryl annulation donor **10** to prepare and characterize both atropisomers of HMP-Y1 (**3a**) and hibarimicinone (**2a**).

Scheme 2. Biosynthesis-Inspired Retrosynthesis of HMP-Y1 (3a), Hibarimicinone (2a), and HMP-P1 (6)



Synthesis of the AB-/HG-Enone (+)-9. We previously reported a gram-scale enantiospecific synthesis of the AB-/HG-ring system corresponding to the unnatural enantiomer of **2a**.[3i] The AB-/HG-enone (+)-**16** (Scheme 3), with stereochemistry corresponding to the natural enantiomer of **2a**, was prepared from key intermediate cyclohexenone (+)-**15** following an analogous series of diastereoselective transformations. Notably, both enantiomers of (+)-**15** were accessed from α-D-methyl-glucopyranoside by taking advantage of its latent C_2-symmetry. The AB-/HG-enone synthesis commenced with AcOH-mediated deprotection of benzylidene acetal **11** followed by selective iodination of the resultant primary hydroxyl group to provide diol (+)-**12**. Next, chemoselective monosilylation of (+)-**12** with TBSCl was accomplished by exploiting a subtle steric difference between its two secondary hydroxyl groups. The remaining secondary hydroxyl group was then pivaloylated under forcing conditions to furnish differentially protected

Scheme 3. Synthesis of the AB-/HG-enone (+)-9[a]



[a]Conditions: (a) $AcOH/H_2O$, 80 °C; (b) PPh_3, I_2, imidazole, PhMe/CH_2Cl_2, room temperature → 45 °C, 76% (two steps); (c) TBSCl, imidazole, CH_2Cl_2, 0 °C → room temperature, 99%; (d) PivCl, 4-DMAP, $ClCH_2CH_2Cl$, 50 °C, 94%; (e) DBU, MeCN, 80 °C, 75%; (f) 30 mol % $Hg(OCOCF_3)_2$, Me_2CO/H_2O; (g) MsCl, Et_3N, CH_2Cl_2, 0 °C → room temperature, 74% (two steps); (d) LiHMDS, THF, 0 °C; then TMSOTf, 0 °C → room temperature, 99%.

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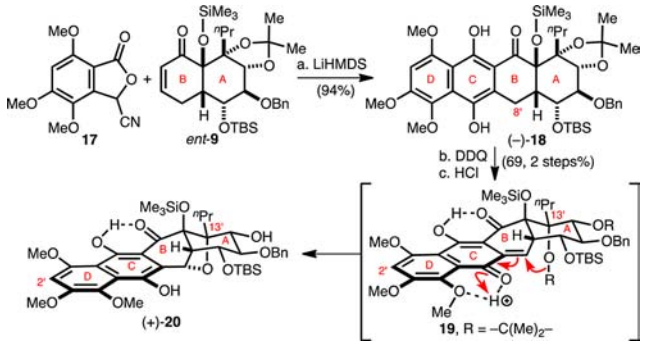
pyranose (+)-**13**. Exposure of (+)-**13** to DBU promoted elimination of the primary iodide to generate exocyclic enol ether (+)-**14**, which underwent type-II Ferrier rearrangement upon treatment with catalytic $Hg(OCOCF_3)_2$.[7] The resultant β-hydroxy-cyclohexanone was dehydrated to provide (+)-**15**. Following our previous procedures,[3i] (+)-**15** was converted to (+)-**16**,[8] and the tertiary C14−OH was ultimately TMS-protected to give annulation acceptor (+)-**9**.

Demonstration of a Biomimetic Etherification on a Model ABCD-Ring System. A key transformation in our synthesis plan is a late-stage biomimetic etherification that retrosynthetically symmetrizes hibarimicinone (**2a**) and HMP-P1 (**6**). Consequently, a model ABCD-ring system was first investigated to test the viability of this proposed reaction. Kraus annulation[9] of cyanophthalide **17**[10] with *ent*-AB-/HG-enone *ent*-**9**[8] under rigorously oxygen-free conditions gave ABCD-tetracycle (−)-**18** (Scheme 4). Deoxygenation was critical for

Scheme 4. Synthesis of an ABCD-Pentacyclic Model System[a]



[a]Conditions: (a) LiHMDS, THF, −78 → 0 °C, 94%; (b) DDQ, CH_2Cl_2, −20 °C; (c) HCl, CH_2Cl_2, 0 °C, 69% (two steps).

the success of the annulation, as adventitious oxygen caused decomposition. (−)-**18** was then oxidized with DDQ to the corresponding C-ring quinone, which upon exposure to anhydrous HCl led to clean formation of pentacyclic ether (+)-**20**. This transformation presumably occurs through the intermediacy of *ortho*-quinone methide **19**,[11] which is trapped by the proximal acetonide oxygen with concomitant acetonide cleavage. Notably, this acid-mediated etherification required high dilution to avoid formation of (−)-**18** and decomposition products, potentially via intermolecular processes.[11c] We propose that acetonide cleavage is triggered by its proximity to the reactive *ortho*-quinone methide intermediate due to the failure to isolate any acetonide cleavage products that lack the cyclic ether bond. This concept is further validated by later observations on the dimeric system, where only the acetonide of the A-ring is cleaved, whereas the G-ring acetonide remains intact (vide infra). Overall, the model oxidation-etherification sequence afforded excellent precedence for our subsequent studies.

Development of a Benzyl Fluoride Michael−Claisen Reaction Sequence to Achieve the First Total Syntheses of HMP-Y1 (3a) and atrop-HMP-Y1 (3b). Our synthesis plan for HMP-Y1 (**3a**) involved a symmetric two-directional double annulation to generate C_2-symmetric octacycle **7**, which could potentially be desymmetrized through a biomimetic mono-oxidation to access hibarimicinone (**2a**) and HMP-P1 (**6**). Such a double annulation strategy is ambitious due to the lack of robust annulation sequences to generate naphthols (1-hydroxynaphthalenes rather than 1,4-dihydroxynaphthalenes, i.e., hydroquinones),[12] and thus necessitated a flexible synthesis of symmetric biaryl annulation donors in which different substituents at C6/C6′ could be introduced. Our biaryl synthesis began with 5-methylvanillin **21**[13] (Scheme 5), which was converted to trialkoxytoluene **22** through a three-step process involving: (1) *O*-methylation, (2) Dakin oxidation followed by in situ formate methanolysis, and (3) MOM protection of the resultant phenol. Next, regioselective *ortho*-lithiation of **22** at C2′ and $FeCl_3$-mediated oxidative dimerization of the resultant aryllithium species delivered biaryl (±)-**23**. Carbomethoxy groups were then installed in a two-step sequence involving bromination and lithium−halogen exchange followed by acylation to afford bis-*ortho*-toluate (±)-**24**.

The reaction kinetics and ultimate success of Michael−Claisen reaction sequences[14] hinge on numerous factors. These include, but are not limited to: (1) the stability and nucleophilicity of the reacting carbanion,[15] (2) the stability of the electrophilic acceptor to the base required to deprotonote the donor,[16] and (3) the steric bulk of the donor (substituents at C6/C6′ and the ester side chain) and of the acceptor. Furthermore, the slow step of the tandem reaction sequence will change based on the particular donor and acceptor used. We found that (±)-**24** could be deprotonated twice by LiTMP and that the corresponding dianion underwent two-directional bis-Michael−Claisen reaction sequence with various 2-cyclohexenones, including the AB-/HG-enone *ent*-**9**. However, the slow rate of both the Michael and the Claisen reactions[17] of the sequence with sterically encumbered *ent*-**9** versus simpler 2-cyclohexenones, coupled with the finite lifetime of the dianion of (±)-**24**, led to very low yields (<10%) of the desired octacyclic dihydronaphthalene products. Attempts to facilitate the Claisen step of the reaction sequence by utilizing activated ester analogues (i.e., phenyl and 2,2,2-trifluoroethyl) were particularly problematic since the bulkier activated esters slowed the initial Michael reaction and the respective dianions were more prone to decomposition. Most importantly, aromatization of the C-/F-rings of the octacyclic products was met with difficulty and led us to consider alternative approaches.[18] Benzyl sulfoxide[19]- and benzyl sulfone[20]-substituted *ortho*-toluates were also evaluated to achieve the desired naphthol annulation with (+)-**9** or *ent*-**9**, but ultimately proved unsuccessful in the context of a two-directional double annulation (vide infra).

We next envisaged a benzyl fluoride Michael−Claisen reaction sequence to generate naphthalenes after subsequent dehydrohalogenation.[21] Although there was no precedence for such a strategy, a benzyl fluoride annulation donor was attractive for several reasons: (1) the electronegative fluorine atom should stabilize the biaryl dianion, (2) the small atomic radius of fluorine should provide minimal steric hindrance to the initial Michael reaction, (3) the strength of C−F bonds would disfavor α-elimination and S_N2 displacement of fluoride, and (4) despite the strength of C−F bonds, elimination of the benzyl fluoride under appropriate conditions could lead to C- and F-ring aromatization.[22] The dianion of (±)-**24** was brominated with $(BrCF_2)_2$ to yield the bis-benzyl bromide, which upon heating with TBAT[23] afforded bis-benzyl fluoride (±)-**25**. After significant experimentation, the desired protected HMP-Y1 derivatives (−)-**27a** and (+)-**27b**[24] were accessed from (+)-**9** and (±)-**25** in a two-step procedure involving: (1) a

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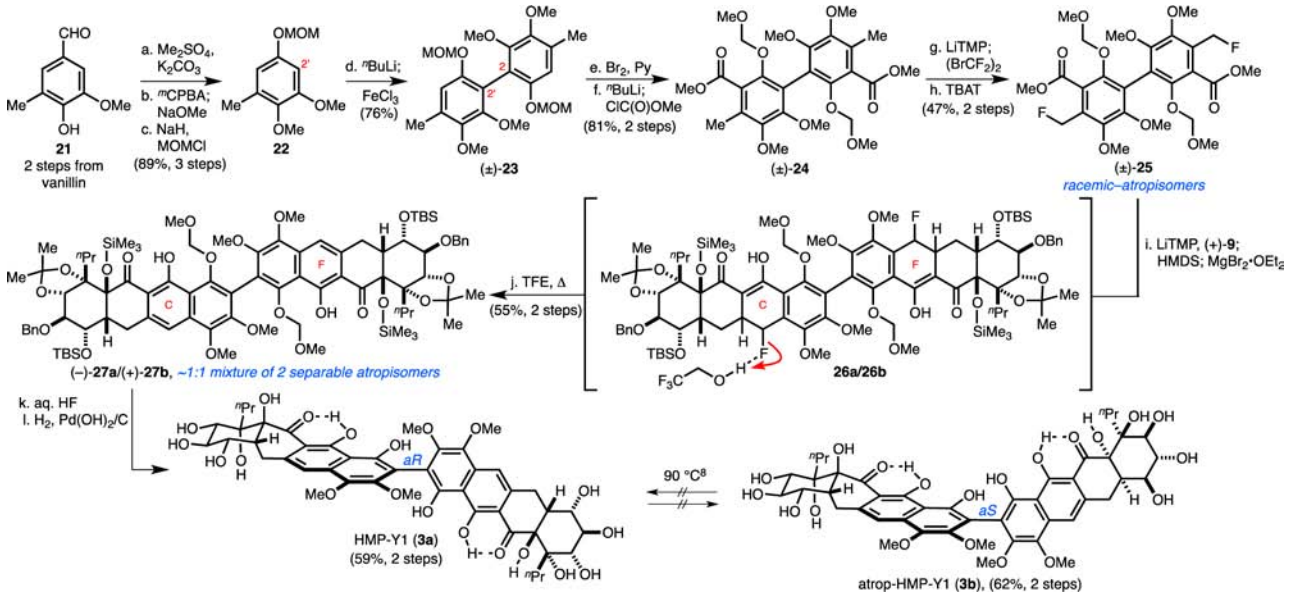
Scheme 5. Synthesis of HMP-Y1 (3a) and atrop-HMP-Y1 (3b) via a Benzyl Fluoride Michael–Claisen Reaction Sequence[a]



[a]Conditions: (a) Me_2SO_4, K_2CO_3, Me_2CO, 98%; (b) ^{m}CPBA, $NaHCO_3$, CH_2Cl_2; then Na_2CO_3, MeOH; (c) NaH, MOMCl, DMF, 0 °C → room temperature, 91% (two steps); (d) ^{n}BuLi, TMEDA, THF, −78 → 0 °C; then $FeCl_3$, 0 °C → room temperature, 76%; (e) Br_2, Py, CH_2Cl_2, 0 °C, 91%; (f) ^{n}BuLi, THF, −78 °C; then ClC(O)OMe, −78 °C → room temperature, 89%; (g) LiTMP, THF, −78 °C; then $(BrCF_2)_2$, −78 °C, 62%; (h) TBAT, MeCN, 82 °C, 75%; (i) (+)-**9**, LiTMP, THF, −78 °C; then HMDS, −78 → −35 °C; then $MgBr_2{\cdot}OEt_2$, −35 → 0 °C; (j) CF_3CH_2OH/H_2O, $NaHCO_3$, 80 °C, 55% (two steps); (k) aq HF, MeCN/THF, 50 °C; (l) H_2, $Pd(OH)_2/C$, THF; for **3a**, 59% (two steps); for **3b**, 62% (two steps).

bis-Michael–Claisen reaction sequence promoted by LiTMP and $MgBr_2{\cdot}OEt_2$ to afford octacycles **26a** and **26b** and (2) the formal elimination of HF by heating the unpurified reaction product in 2,2,2-trifluoroethanol (TFE) to achieve aromatization of the C- and F-rings and provide atropisomers (−)-**27a** and (+)-**27b**, which were readily separated and carried forward independently. Several features of this sequence deserve comment. As we had hoped, the use of a bis-benzyl fluoride (±)-**25** allowed for the initial bis-Michael addition to occur at −78 °C, thus minimizing decomposition of the dianion intermediate and of (+)-**9**. Addition of $MgBr_2{\cdot}OEt_2$ mid annulation sequence was critical to promote the final intramolecular Claisen reactions and obviated the need to use an activated ester analogue. This discovery should help expand the substrate scope of the Michael–Claisen reaction sequence. Finally, the unique ability of TFE to promote the desired elimination is presumably due to its ability to strongly hydrogen bond with fluorine, and thus activate it for mild solvolysis. Indeed, use of ethanol in place of TFE only led to trace elimination. The employment of a benzyl fluoride annulation-elimination sequence to generate naphthalene derivatives is without precedence and may prove to be a general method for the synthesis of naphthols.

Global deprotection of (−)-**27a** and (+)-**27b** with aqueous HF followed by hydrogenolysis afforded HMP-Y1 (**3a**) and atrop-HMP-Y1 (**3b**), respectively.[25] Heating **3a** or **3b** to 90 °C led to no detectable isomerization about the C2–C2′ bond.[8] With no authentic CD spectra for natural **3a** available, synthetic **3a** and **3b** were designated by comparing their CD spectra with the CD spectrum of the glycosylated derivative of **3a**, HMP-Y6.[8] The axial stereochemistry of HMP-Y1 (**3a**) has not been rigorously determined, although model studies and the CD-spectra of HMP-Y6 and hibarimicinone (**2a**) suggest **3a** possesses the *aR* configuration by the CD exciton chirality method.[2,26] Additionally, **3a**, **2a**, and hibarimicin A–G are all isolated as single atropisomers.[26] We show that the axial stereochemistry of **3a** and **2a** is not the result of thermodynamic equilibration (vide infra), and thus their biosynthetic relationship also argues that they possess the same relative configuration about the C2–C2′ bond. Therefore, **3a** can be assigned the *aR* configuration since the axial chirality of **2a** was unambiguously determined.[4]

Biomimetic Mono-Oxidation of Protected HMP-Y1. With a route to HMP-Y1 (**3a**) and atrop-HMP-Y1 (**3b**) established, we next attempted the biomimetic mono-oxidation of protected HMP-Y1 derivatives. We discovered that the desired oxidation of binaphthol *ent*-**27a** to the C-ring quinone (−)-**29** could be achieved in low yield with CAN (Scheme 6), demonstrating the plausibility of our proposed biomimetic desymmetrizing oxidation. We speculate that the congested biaryl may sterically occlude the approach of oxidants to the otherwise easily oxidized D-/E-ring system,[27] allowing oxidation of the more electron-deficient C-/F-rings. Despite this initial success, our attempts to optimize the CAN oxidation were met with difficulty due to bis-oxidation and formation of nitrated byproducts. A survey of other oxidants also proved fruitless.

Nevertheless, with naphthazarin (−)-**29** in hand, we next investigated the desired biomimetic etherification reaction. Unfortunately, exposure of (−)-**29** to the optimized conditions developed on our model system led to no observable etherification but rather only rapid MOM group cleavage. A screen of various acids and conditions also proved unsuccessful. The resistance of (−)-**29** to undergo the desired etherification in contrast to the C-ring quinone derivative of (−)-**18** was surprising. Because the major difference between the two systems is the lability of the MOM groups of (−)-**29** relative to the methyl group of (−)-**18**, we postulated that a free phenol at C1′ might disfavor either acetonide decomposition or formation of the necessary *ortho*-quinone methide intermediate.

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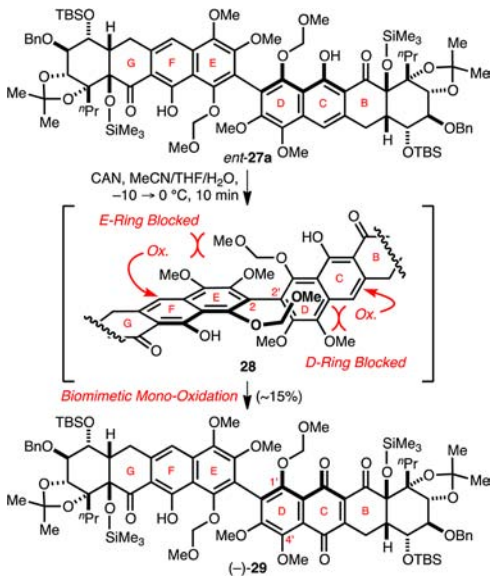
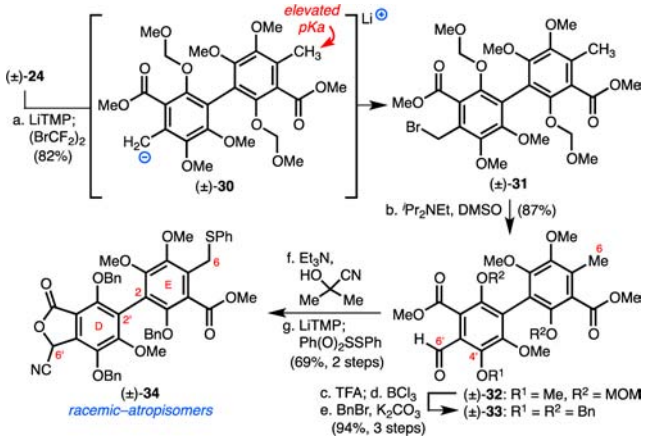
Scheme 6. Biomimetic Mono-Oxidation of Protected HMP-Y1



This prompted us to replace the MOM group with a more acid-stable protecting group.

Additionally, our current biomimetic strategy would inevitably require a late-stage demethylation of the C4′−OMe methyl group. Ideally, one would remove the C4′−OMe methyl group as late in an eventual synthesis of hibarimicin B (**1**) as possible to protect the sensitive and stereochemically labile binaphthyl core (vide infra). However, the acidic conditions necessary to effect demethylation would be incompatible with the sensitive 2-deoxy- and 2,3-dideoxyglycosides of **1**. The aforementioned reasons prompted us to investigate our alternative strategy for the synthesis of hibarimicione (**2a**) and HMP-P1 (**6**) utilizing an unsymmetrical two-directional annulation reaction with biaryl (±)-**34** (Scheme 7).

Scheme 7. Synthesis of Unsymmetrical Biaryl (±)-34 via a Selective Mono-Deprotonation of (±)-24[a]



[a]Conditions: (a) LiTMP, THF, −78 °C; then $(BrCF_2)_2$, 82%; (b) $^iPr_2NEt$, DMSO, 70 °C, 87%; (c) TFA, CH_2Cl_2, 0 °C → room temperature; (d) BCl_3, CH_2Cl_2, −78 → 0 °C; (e) BnBr, K_2CO_3, DMF, 0 → 60 °C, 94% (three steps); (f) $Me_2C(OH)CN$, Et_3N, $CHCl_3$, 97%; (g) LiTMP, THF, −78 °C; then $Ph(O)_2SSPh$, 71%.

Synthesis of the Unsymmetrical Biaryl Annulation Donor (±)-34. The unsymmetrical fully substituted biaryl (±)-**34** presents unique synthesis challenges that are shared with the hibarimicins; cross-coupling technology to form such sterically hindered biaryls from electron-rich arenes is limited.[3d] In contrast, dimerization reactions to form hindered biaryls are robust and reliable (e.g., **22** → (±)-**23**). Thus, we imagined that a practical synthesis approach to (±)-**34** would necessitate the desymmetrization of (±)-**24**. A strategy to monofunctionalize (±)-**24** involving radical bromination would inevitably result in an inefficient statistical mixture of benzylic bromides. However, we hypothesized that selective monodeprotonation of (±)-**24** would be feasible since the initial carbanion would elevate the pK_a of the remaining *ortho*-toluate due to a field effect. Indeed, we found that selective monodeprotonation of (±)-**24** at C6′ could be achieved with 1.25 equiv of LiTMP (Scheme 7). The resultant anion (±)-**30** was then brominated with $(BrCF_2)_2$ to give benzyl bromide (±)-**31** in 82% yield. This single element of asymmetry was sufficient to introduce the remaining differential functionality of (±)-**34**. (±)-**31** was oxidized to aldehyde (±)-**32**,[28] which was then converted to tribenzyl-protected biaryl (±)-**33** by (1) acid-promoted removal of the MOM groups, (2) chemoselective cleavage of the C4′−OMe methyl group with BCl_3, and (3) global reprotection with BnBr. Treatment of (±)-**33** with a controlled source of hydrogen cyanide afforded a cyanophthalide intermediate.[29] Finally, double deprotonation of this intermediate with LiTMP followed by a short exposure to *S*-phenyl benzenethiosulfonate chemoselectively installed the phenyl sulfide moiety[21] at C6 to provide biaryl (±)-**34**. The observed chemoselectivity in this reaction is a result of the much higher reactivity of the *ortho*-toluate anion relative to the cyanophthalide anion.

Completion of Hibarimicinone (2a) and atrop-Hibarimicinone (2b) via an Unsymmetrical Two-Directional Double Annulation. We anticipated that reaction of the lithiated cyanophthalide of (±)-**34** with (+)-**9** would directly construct the C-ring hydroquinone via a Kraus annulation, and reaction of the lithiated benzyl phenyl sulfide of (±)-**34** with a second equivalent of (+)-**9** would lead to the F-ring via a Michael−Claisen reaction sequence. We found that the desired transformations could be achieved by treating a mixture of (±)-**34** and (+)-**9** with LiHMDS followed by subsequent addition of KHMDS mid annulation sequence under rigorously oxygen-free conditions to yield octacycle (−)-**35a** and (+)-**35b** as a ∼1.3:1 mixture of atropisomers (Scheme 8). The addition of KHMDS was crucial to facilitate the final intramolecular Claisen reaction to construct the F-ring.[30] At this stage, atropisomers (−)-**35a** and (+)-**35b** were separated and carried forward independently. Elimination of the C6-benzylic phenyl sulfide was accomplished with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) to yield binaphthalenes (−)-**36a** and (+)-**36b**. It is worth reiterating at this point that the corresponding C6-benzyl sulfoxide and sulfone derivatives of (±)-**34** ultimately proved unsuccessful,[31] highlighting the difficulty to achieve naphthol annulations in the context of complex molecule synthesis. To the best of our knowledge, this is the first example of a benzyl sulfide Michael−Claisen reaction sequence to generate naphthalenes, and together with the benzyl fluoride Michael−Claisen reaction sequence reported herein offers two new alternatives to approach challenging naphthol annulations.

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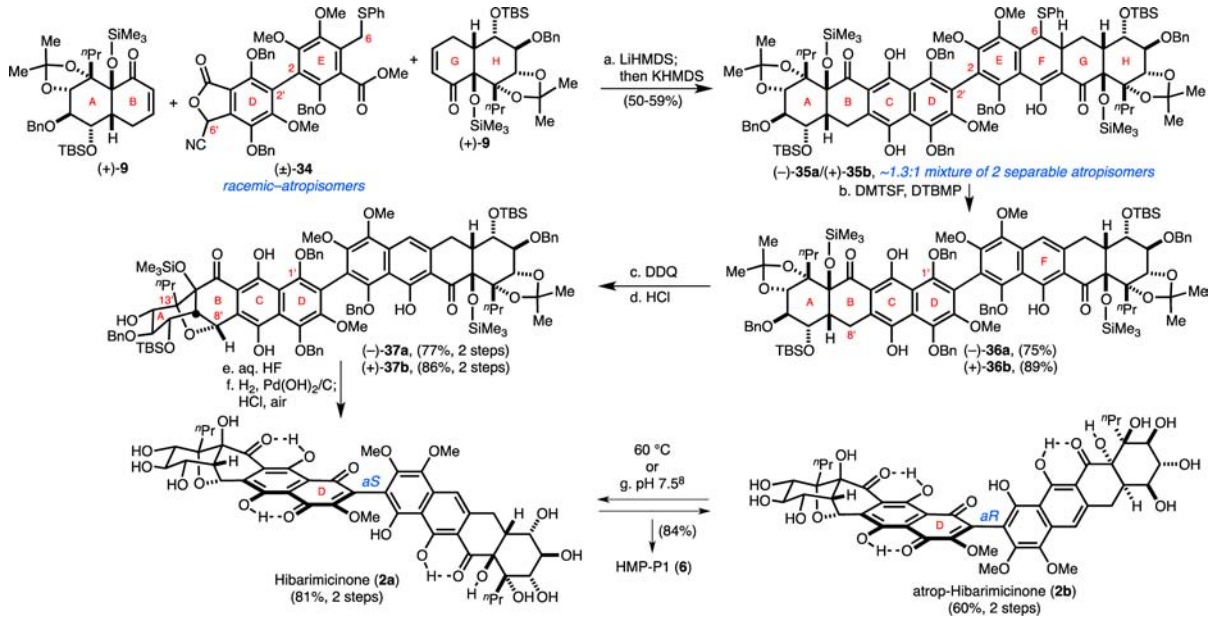
Scheme 8. Completion of Hibarimicinone (2a), atrop-Hibarimicinone (2b), and HMP-P1 (6)[a]



[a]Conditions: (a) LiHMDS, THF, −78 → 0 °C; then KHMDS, 0 °C → room temperature, 50−59%; (b) DMTSF, DTBMP, MeCN, 0 °C → room temperature; for (−)-**35a**, 75%; for (+)-**35b**, 89%; (c) for (−)-**36a**, DDQ, PhMe, 0 °C; for (+)-**36b**, DDQ, PhMe, 0 °C → room temperature; (d) HCl, $ClCH_2CH_2Cl$, 5 °C; for (−)-**37a**, 77% (two steps); for (+)-**37b**, 86% (two steps); (e) aq HF, MeCN/THF; (f) H_2, $Pd(OH)_2$/C, EtOAc; then HCl, MeOH, air; for **2a**, 81% (two steps); for **2b**, 60% (two steps); (g) aq pH 7.5 NaH_2PO_4/NaOH buffer, MeOH, room temperature; from **2a**, 84%; from **2b**, 84%.

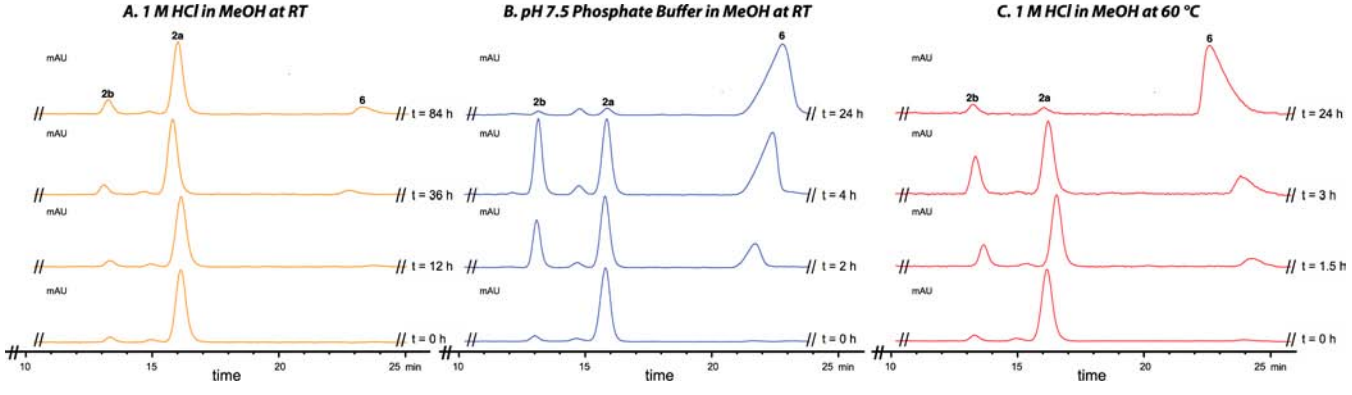


Figure 2. (A) Upon standing in acidic methanol (1 M HCl) at room temperature, hibarimicinone (**2a**) and atrop-hibarimicinone (**2b**) underwent minor interconversion and minimal conversion to HMP-P1 (**6**) (orange HPLC traces). (B) Exposure of **2a** to pH 7.5 aqueous phosphate buffer at room temperature (blue HPLC traces) or (C) acidic methanol (1 M HCl) at 60 °C (red HPLC traces) resulted in isomerization to **2b** and eventual formation of **6**. See the Supporting Information for HPLC time-courses starting with **2b**.

Oxidation of (−)-**36a** and (+)-**36b** with DDQ produced the corresponding C-ring quinones. Exposure of the respective quinones to anhydrous HCl promoted the desired biomimetic etherification to yield nonacycles (−)-**37a** and (+)-**37b**. This successful etherification of the benzyl protected naphthazarins, in contrast to MOM-protected (−)-**29**, confirmed our suspicion that the C1′-phenol has far-reaching stereoelectronic effects on this system. With the complete skeletons of **2a** and **2b** in hand, all that remained to complete the syntheses was global deprotection and oxidation of the D-ring. Deprotection of the acid-labile protecting groups was accomplished upon exposure to aqueous HF. Finally, the benzyl groups were removed via hydrogenolysis, and after addition of acidic methanol, filtering, and exposure to air, hibarimicinone (**2a**) and atrop-hibarimicinone (**2b**) were formed. All of the spectroscopic data for **2a** and **2b** match those reported[4,8,26] and thereby confirmed the structure of **2b**.

Discovery of a pH-Dependent Rotational Barrier about the C2−C2′ Bond in Hibarimicinone (2a) and atrop-Hibarimicinone (2b). The addition of acidic methanol prior to aerobic oxidation was crucial to prevent isomerization between **2a** and **2b** and formation of HMP-P1 (**6**).[25,32] Upon prolonged handling or standing at ambient temperatures in acidic methanol (1 M HCl), we observed only minor interconversion between **2a** and **2b**, and minimal formation of **6** (Figure 2A). However, simple exposure of **2a** and **2b**, independently, to pH 7.5 aqueous phosphate buffer in methanol led to the formation of **6** in 84% yield in both cases (Scheme 8). Monitoring these transformations by HPLC revealed that nearly complete isomerization about the C2−C2′ bond (**2a** ↔ **2b**) had occurred within 4 h, while formation of **6**

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was almost complete after 24 h (Figure 2B).[8] Together, these observations suggest that the rotational barriers about C2−C2′ for **2a** and **2b** are pH-dependent.

These findings are particularly interesting due to prior observations that heating **2a** in neutral methanol at 60 °C leads to nearly complete interconversion to **2b** in 30 min and ultimately complete cyclization to yield **6** after 90 min.[1i,2,26] However, we found that heating either **2a** or **2b** to 60 °C in acidic methanol (1 M HCl) led to only partial interconversion between **2a** and **2b** and minor conversion to **6** after 90 min (Figure 2C). This suggests that the observed rapid rotation at 60 °C in neutral methanol has less to do with providing the necessary thermal energy to surpass the intrinsic activation barrier about C2−C2′ in the uncharged forms of **2a**/**2b** (**38a**/**38b** in Figure 3), but rather enables access to the deprotonated

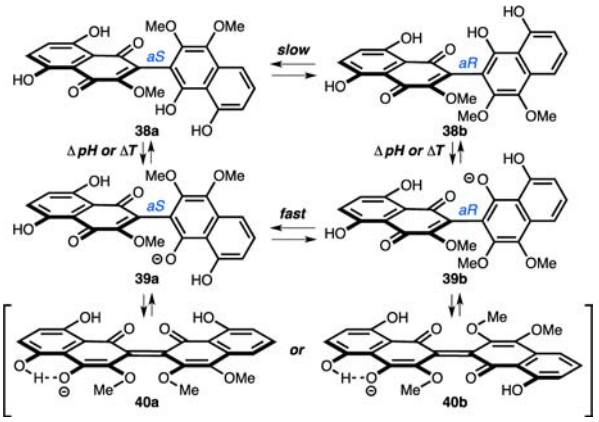

Figure 3. A proposed model to explain the pH-dependent rotational barrier about the C2−C2′ bond of **2a** and **2b**. Only the CDEF-ring system is depicted for brevity.

form of **2a** and **2b** (**39a**/**39b** in Figure 3) via inter- or intramolecular proton transfer. Rapid interconversion between **37a** and **37b** can then follow through a transition state that is stabilized by π-electron overlap,[3b,33] as depicted in cross-conjugated resonance structures **40a** and **40b**. Consequently, variables that affect the equilibrium between **38a** and **39a**, and **38b** and **39b**, will affect the rate of isomerization. The addition of acid to the media inhibits access to species **39a** and **39b** by driving the equilibrium toward **38a** and **38b**, and thus disfavors isomerization. In contrast, heat (60 °C) should promote equilibration between the protonation states and thus facilitate isomerization. Our discovery of the pH-dependent barrier demonstrates the delicate nature of the C2−C2′ axis, which must be accommodated in an eventual synthesis of hibarimicin B (**1**).[32]

CONCLUSION

Enantioselective total syntheses of hibarimicinone (**2a**) and atrop-hibarimicionone (**2b**), and the first total syntheses of HMP-Y1 (**3a**), atrop-HMP-Y1 (**3b**), and HMP-P1 (**6**), have been accomplished. The complete carbon skeleton of each natural product was assembled via a convergent two-directional annulation strategy. The use of a racemic biaryl in conjunction with the two-directional annulation strategy enabled both atropisomers of the natural products to be separately constructed and fully characterized, thus providing the first reported full characterization of **2b**, **3a**, **3b**, and **6**. Additionally, during the pursuit of this annulation strategy, we encountered numerous challenges when conducting naphthol annulation reactions. Consequently, we developed two valuable Michael−Claisen reaction sequences to construct complex naphthols that might find use as general methods. The mild conditions needed to dehydrohalogenate the benzyl fluoride intermediates are particularly noteworthy given the strength of C−F bonds.

The plausibility of our proposed biosynthesis was also validated by the demonstration that a desymmetrizing mono-oxidation of the C-ring can be conducted on a protected HMP-Y1 derivative. Overoxidation to the bis-C-/F-ring quinone was also observed, but natural products corresponding to such a double oxidation have not been isolated in nature or during mutagenesis studies. This perhaps suggests that an enzyme mediates this key biosynthetic transformation, but how **3a** is only mono-oxidized remains unclear.

After the key two-directional annulations, only three and five steps were needed to complete HMP-Y1 (**3a**) and hibarimicinone (**2a**), respectively. In the case of **2a**, these steps include a biomimetic etherification to install the B-ring cyclic ether via an *ortho*-quinone methide intermediate. The success of this reaction required an acid-stable protecting group to mask the C1′-phenol owing to subtle yet far-reaching stereoelectronic effects imparted by the naphthazarin-naphthalene system. The peculiarities and sensitivity of this system are also highlighted by our discovery of the pH-dependent rotational barrier about the C2−C2′ bond. These particular observations provide crucial information that will facilitate an eventual synthesis of hibarimicin B (**1**).

Last, the intermediate (−)-**37a** will be highly useful in an eventual total synthesis of **1**; it is suitably protected with orthogonal protecting groups to allow for the sequential installation of the 2-deoxy- and 2,3-dideoxyglycosides prior to deprotection of the sensitive binaphthyl core of the molecule. Future studies toward the total synthesis of **1** will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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(15) (a) *ortho*-Toluate and related carbanions will suffer from competitive bimolecular self-condensation reactions with the ester moiety if the Michael addition is not fast enough. For an interesting discussion on the stability of *ortho*-toluate and related carbanions, see: Brubaker, J. D. Ph.D. Thesis, Harvard University, 2007 and references therein. (b) In the case of a single annulation process, the instability of the deprotonated annulation donor can often be circumvented through the use of excess donor. However, due to the inherent stoichiometry of the two-directional double annulation, the biaryl donor is used as the limiting reactant, and thus the stability of its dianion is critical to the success of the reaction.

(16) We observed that *ent*-**9** is stable to LiTMP and LDA at −78 °C, and LiHMDS at 0 °C in THF. At higher respective temperatures for prolonged reaction times, significant decomposition occurred.

(17) Simple 2-cyclohexenones will undergo the Michael addition within seconds at −78 °C and eventual Claisen reaction at −10 °C with the *ortho*-toluate carbanion corresponding to the D-/E-ring. In contrast, *ent*-**9** underwent Michael addition after approximately 1 h, and the Claisen reaction was never driven to completion when the dianion of (±)-**24** was employed.

(18) DDQ or PhSeCl with pyridine could successfully be employed to aromatize dihydronaphthalenes of simple BCD-ring model systems but proved unsuccessful on binaphthyl systems.

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(21) Benzyl phenyl sulfide substituted *ortho*-toluates were concurrently found to be useful partners for naphthol annulations and were ultimately employed in our synthesis of **2a** and **6** due to the inability to construct the C6-benzyl fluoride analogue of (±)-**34**.

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(24) (a) For brevity, each atropisomer is depicted as a single structure lacking stereochemistry about the C2−C2′ bond. See the Supporting Information for full details. (b) The regioisomer of the enolized 1,3-diketone was undetermined and is arbitrarily depicted.

(25) No NMR or CD spectra for **3a** and **6** have been previously recorded according to ref 26. See the Supporting Information for full details.

(26) Described in a personal communication with Professor Y. Igarashi and Professor H. Hori.

(27) (a) Preferential oxidation of the D-ring occurs in simpler BCD-ring model systems. (b) The ^{1}H NMR signal of the methoxymethyl groups of *ent*-**27a** and *ent*-**27b** is shifted over 0.6 ppm upfield relative to the corresponding monomer, suggesting that they are positioned over the naphthyl ring systems and subject to anisotropic magnetic field effects.

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(31) The small coupling constant between the C6′ and C7′ hydrogen atoms of (−)-**35a** and (+)-**35b** suggests a *syn* relationship of the hydrogen atoms with respect to the ring system. This relative stereochemistry would preclude *syn*-elimination to aromatize the F-ring. Indeed, one diastereomer of the corresponding sulfoxide of (±)-**34** underwent two-directional annulation but failed to eliminate to aromatize the F-ring.

(32) The carbohydrates of the hibarimicin natural products are cleaved with acidic methanol (1 M HCl, 30 °C). These conditions are similar to those we employ during the benzyl deprotection and oxidation of (−)-**37a** and (+)-**37b**. However, milder acidic conditions (i.e., aq pH 3.5 phosphate buffer) in methanol may potentially be substituted during the analogous deprotection and oxidation of **1** because these conditions are employed in the HPLC purification of **1** and hibarimicin related natural products. See ref 1f, g for the conditions used for carbohydrate cleavage and purification of the hibarimicin natural products.

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