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Studies Toward the Total Synthesis of Angelmicin B (Hibarimicin B): Synthesis of a Model CD–D′ Arylnaphthoquinone

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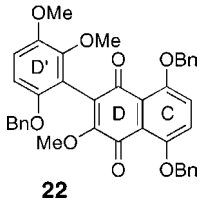
ABSTRACT



22

A synthesis of arylnaphthoquinone 22 corresponding to the CD–D′ unit of angelmicin B via the Suzuki coupling of the D′ arylboronic acid 15 with the CD bromonaphthoquinone 21 is described. The mild conditions for the Suzuki cross-coupling leading to 22 may prove to be useful for the eventual late-stage coupling of the two highly functionalized halves of angelmicin B.

Angelmicins A and B were isolated from *Microbispora rosea* by Uehara and co-workers in 1993.[1,2] Initially, these compounds were reported to be highly specific inhibitors of protein tyrosine kinase involved in oncogenic *src* signal transduction, while no effect was observed on protein kinases A and C.[2] Later, angelmicin B was also shown to inhibit the growth of tumor cells and induce differentiation in human myeloid leukemia (HL-60) cell lines.[3] However, these activities do not appear to be directly related since the effective concentration of angelmicin B (the most active member of the family) in *src* tyrosine kinase inhibition is about 100-fold higher than that required for cell growth suppression. This suggests that the angelmicins may be involved in the modulation of more than one physiological pathway.[4] Several members of the same class of natural products (subsequently named hibarimicins) were later isolated from a different subspecies of *Microbispora rosea*.[4]

It has been speculated that the hibarimicins' activity as cancer cell growth inhibitors may arise from topoisomerase II inhibition.[3a] Biosynthetic studies on the hibarimicins indicate that cyclization of a polyacetate precursor to generate an aglycone monomer, followed by oxidative dimerization, gives rise to the aglycone (hibarimicinone).[5]

It is interesting to note that while hibarimicinone is a strong tyrosine kinase inhibitor, it has no effect on HL-60 cells.[5b]

The novel structure of angelmicin B (**1**, Figure 1), together with its significant biological properties, defines this compound as an important synthetic target.[6] Angelmicin B is

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(2) For structure elucidation, see: (a) Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *Tetrahedron Lett.* **1996**, *37*, 2785. (b) Kajiura, T.; Furumai, T.; Igarashi, Y.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **1998**, *51*, 394.

(3) (a) Yokoyama, A.; OkabeKado, J.; Uehara, Y.; Oki, T.; Tomoyasu, S.; Tsuruoka, N.; Honma, Y. *Leuk. Res.* **1996**, *20*, 491. (b) Showalter, H. D. H.; Kraker, A. J. *Pharmacol. Ther.* **1997**, *76*, 55.

(4) (a) Kajiura, T.; Furumai, T.; Igarashi, Y.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **1998**, *51*, 394. (b) Cho, S. I.; Fukazawa, H.; Honma, Y.; Kajiura, T.; Hori, H.; Igarashi, Y.; Furumai, T.; Oki, T.; Uehara, Y. *J. Antibiot.* **2002**, *55*, 270.

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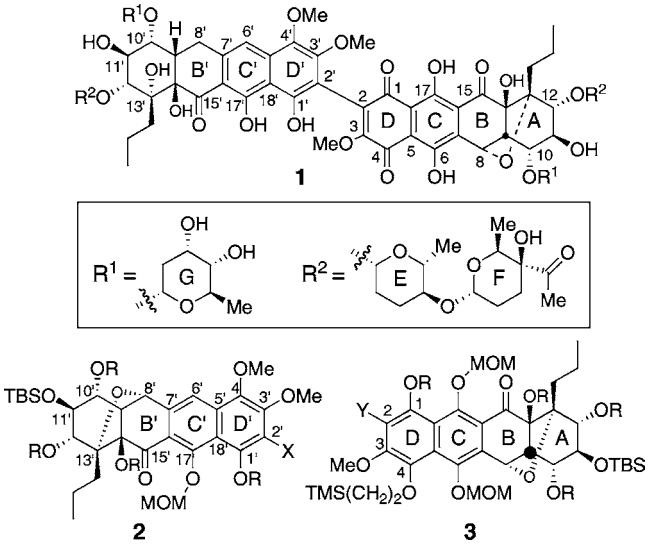
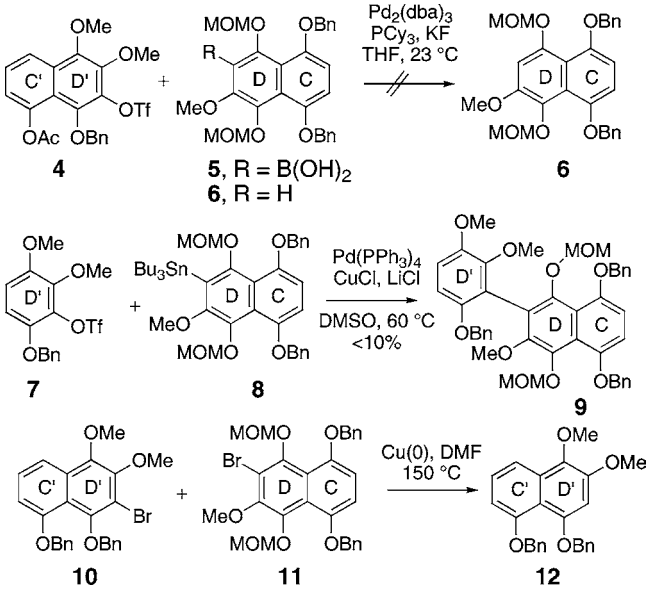


Figure 1. Angelmicin B (**1**, also known as hibarimicin B) and proposed functionalized A′B′C′D′ (**2**) and ABCD (**3**) monomers (R = H or protecting group).

Scheme 1. Representative Unsuccessful Cross-Coupling Strategies



pseudodimeric with respect to the D−D′ biaryl bond; the two halves differ only in the oxidation states of the B/B′, C/C′, and D/D′ rings. The absolute configurations of the sugar units (E, F, and G), the configuration of the C13′ stereocenter, and the relative stereochemistry between distal rings A and A′ are unknown at present. In addition, it is unclear if the barrier to rotation about the D−D′ bond is high enough to allow the existence of atropisomers and, if so, what the stereochemistry is about this linkage.[7]

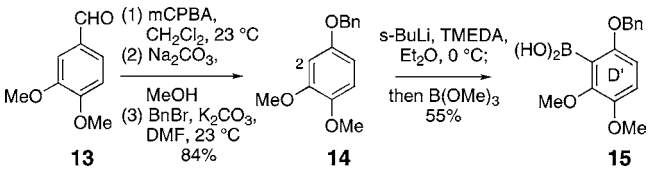
We have focused on a synthetic strategy that involves the late-stage coupling of functionalized ABCD and A′B′C′D′ monomers (see **2** and **3**, Figure 1), to exploit the near symmetry of **1** in earlier stages of the synthesis. While the convergence of this approach is attractive, late-stage construction of the D−D′ biaryl bond is expected to be challenging due to the tetra-ortho substitution about the biaryl linkage; a considerable steric barrier would have to be overcome in the bond-forming step. In addition, the problem of axial chirality remains to be addressed.[6b,7]

In a series of extensive preliminary studies, we evaluated cross-couplings of CD metal derivatives (aryl boronates, stannanes, and zinc derivatives) such as **5** and **8** with C′D′ electrophiles (bromides, iodides, and triflates) such as **4**, **7**, and **10** (Scheme 1).[8] However, all experiments along these lines were ultimately unproductive due to the lack of reactivity of the electron-rich aromatic electrophiles (cf. **4**, **7**, and **10**) as well as the relative instability of CD arylmetal derivatives (cf., **5** and **8)**. In most cases, demetalated products such as **6** were recovered along with unreacted aryl halide/triflate, while only traces of coupled biaryl product (see **9**) were observed. Attempted couplings of fragments such as **10** and **11** under Ullmann conditions were also unsuccessful, giving rise instead to dehalogenated products (**12**).

We speculated that the highly electron-rich nature of the aryltriflate/arylbromide fragments such as **4**, **7**, **10**, and **11**, along with a significant steric congestion around C(2), contributes to the poor reactivity of these (potentially) electrophilic coupling partners. In view of these difficulties, we considered the possibility that a bromoquinone could be used as the electrophilic coupling partner in the cross-coupling sequence.[9] This led to the development of a concise synthesis of a model CD−D′ fragment of angelmicin B, which is reported herein.

The synthesis of D′ arylboronic acid **15** is summarized in Scheme 2. Veratraldehyde (**13**) was converted to trialkoxy-

Scheme 2. Synthesis of the D′ Arylboronic Acid **15**



benzene derivative **14** in 84% yield by Bayer−Villiger oxidation of the aldehyde followed by hydrolysis of the intermediate formate and benzylation of the resultant phenol. Subsequently, selective ortho-lithiation of the 2 position of **14** by using *s*-BuLi/TMEDA[10] followed by addition of

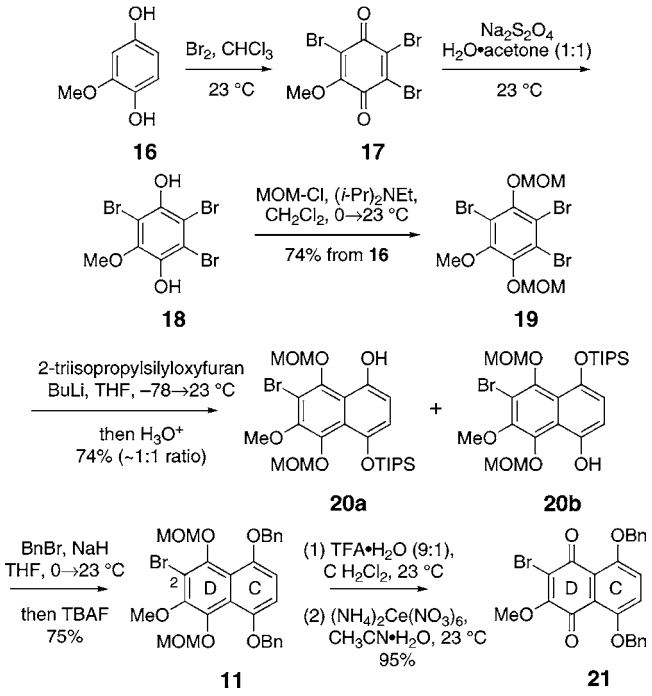
(7) Using MM2 calculations, we estimated the barrier to rotation about the biaryl axis to be about 20 kcal/mol. While this barrier is generally sufficient for atropisomers to be resolvable at 23 °C, the atropisomer situation in angelmicin is uncertain in view of the studies by Sulikowski (ref 6b). However, the model D−D′ biaryl system studied by Sulikowski has fewer substituents in the positions flanking the 2−2′ biaryl bond than in angelmicin B itself, and it is unclear if the rapid atropisomerism (via tautomerization pathways) noted by Sulikowski will be relevant to the natural product itself.

(8) Full details of these studies will be reported elsewhere.

trimethylborate afforded arylboronic acid **15** in 55% yield. Arylboronic acid **15** proved to be somewhat unstable, undergoing protodeboronation to **14** in the presence of aqueous acid (e.g., under standard acidic workup conditions).[11]

The CD bromonaphthoquinone **21** was synthesized from methoxyhydroquinone (**16**) as shown in Scheme 3. Thus,

Scheme 3. Synthesis of CD Naphthoquinone Bromide **12**

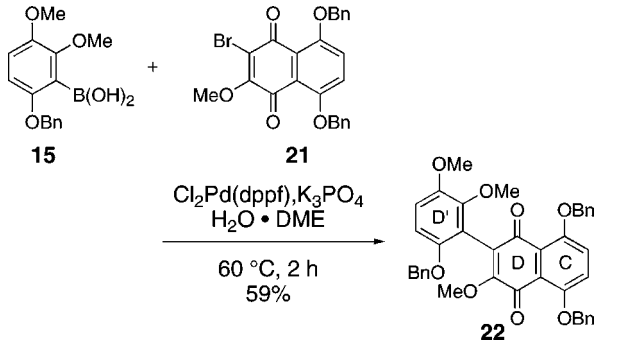


bromination of **16** was performed according to a literature method.[12] While this procedure has been reported to provide tribromoquinone **17** in 90% yield, we always obtained a mixture of **17** and hydroquinone **18**. This mixture was directly subjected to dithionite reduction[13] to afford hydroquinone **18**. Treatment of **18** with MOM-Cl in the presence of Hünig's base afforded bis-methoxymethyl ether **19** in 74% yield over three steps. We found it necessary to add the Hünig's base to a cooled mixture of **18** and MOM-Cl. If, however, the base was added first, up to 45% of a monodebrominated hydroquinone was isolated as its bis-methoxymethyl ether (**19** lacking one of the bromine substituents). Furthermore, **17**, **18**, and **19** were found to be fairly unstable, giving rise to debrominated materials upon storage (neat, −20 °C) for several weeks.

A mixture of tribromide **19** and 2-triisopropylsilyloxyfuran was treated with *n*-BuLi in THF at −78 °C. The benzyne intermediate generated from **19** under these conditions readily combined with the furan derivative.[14] Upon mild acidic workup, naphthols **20a**,**b** were directly obtained as a nearly 1:1 mixture. This mixture was quickly taken on to the subsequent step, since naphthols **20a**,**b** were found to be extremely susceptible to air oxidation. For instance, a sample of **20a**,**b** left on the benchtop readily decomposed to unidentified quinone products within several hours. Thus, treatment of the **20a**,**b** mixture with NaH and benzyl bromide, followed by addition of TBAF, effected its direct conversion to bis-benzyl ether **11** (75% yield). Due to the instability of the intermediate naphthols, this three-step sequence comprising of benzyl protection, TIPS ether cleavage, and reprotection as the benzyl ether was best accomplished in a one-pot protocol. If the same set of transformations was carried out stepwise, less than 25% yield of **11** was obtained.

As previously noted, attempts to effect cross-coupling reactions with highly electron-rich, highly substituted aryl halides and triflates (see Scheme 1) were consistently unsuccessful. Indeed, all attempts to effect the cross-coupling of **15** and **11** met with failure. We envisaged that quinone **21** would be a much more electrophilic coupling partner and therefore be able to undergo oxidative addition of Pd(0) at a much faster rate than **11**. Accordingly, deprotection of the MOM ethers of **11** with TFA·water afforded a stable 1,4-hydroquinone derivative, which was oxidized to naphthoquinone **21** with either silver(I) oxide or ceric ammonium nitrate.[15] After exploring a number of reaction conditions, we were pleased to find that the cross-coupling of arylboronic acid **15** with bromonaphthoquinone **21** could be accomplished using $Cl_2Pd(dppf)$ in dimethoxyethane−water, with K_3PO_4 as the base (Scheme 4). This provided the model CD−D′ biaryl unit **22** in 59% yield.

Scheme 4. Synthesis of Aryl-quinone **22** via Cross-Coupling of Arylboronic Acid **15** with Bromonaphthoquinone **21**



The coupling reaction depicted in Scheme 4 is noteworthy, because the highly substituted, polyoxygenated D′ and CD rings could be coupled in an efficient manner. This is in

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contrast to previous reports, where cross-couplings to form aryl-quinone derivatives containing four ortho substituents flanking the biaryl bond were found to be inefficient or unsuccessful.[10] Moreover, the use of a suitable chiral ligand in the Suzuki reaction would potentially allow asymmetric induction in the biaryl coupling step.[16] Finally, the conditions developed for the hindered biaryl coupling in angelmicin B may prove to be useful in the synthesis of other biaryl-containing natural products.[17]

With a model D′−CD ring system in hand, we sought to gain some experimental insight regarding the atropisomer situation in angelmicin B. The methylene protons of the D′ ring benzyl ether in **22** appear as an AB quartet ($\Delta\upsilon = 21.4$ Hz; $J_{AB} = 12.6$ Hz), indicating that an element of asymmetry is present in the molecule. Accordingly, we performed variable-temperature ^{1}H NMR studies in order to determine the barrier to rotation about the D′−D bond. Even at 150 °C (the upper limit of our measurement), the AB pattern was discernible, indicating that free rotation about the biaryl axis was not possible at this temperature. Using this information, the energy barrier for atropisomerization in **22** must be greater than 22 kcal/mol.[18] Using MM2 calculations, we estimated the energy barrier in **23** (a simplified version of **22**) to be 25.6 kcal/mol (Figure 2). Although **22** with three benzyl ethers represents a derivatized version of the D′−CD ring system of angelmicin B, the high barrier to rotation suggests that the natural product could exist as a single atropisomer.[7]

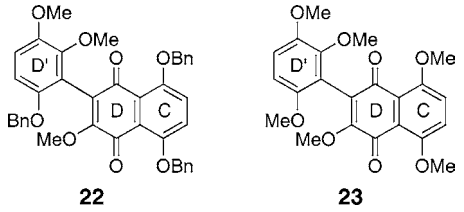

Figure 2. Comparison of measured and calculated energy barriers for atropisomerization in compounds related to angelmicin B. Experimental energy barrier for **22**: >22 kcal/mol. Calculated energy barrier for **23**: 25.6 kcal/mol.

In conclusion, we have synthesized a model D′−CD ring system of angelmicin B via the Suzuki reaction of D′ arylboronic acid **15** with CD bromonaphthoquinone **21**. This cross-coupling proceeds under mild conditions, which should allow for this reaction to be used in a planned late-stage coupling of two highly functionalized halves of angelmicin B. Further progress toward the total synthesis of angelmicin B will be reported in due course.

Acknowledgment. We thank the National Institutes of Health (BM 38907) for support of this work. S.N. thanks the Department of Chemistry, University of Michigan, for a Margaret and Herman Sokol Graduate Fellowship.

Supporting Information Available: Experimental details and spectroscopic data for compounds **11**, **14**, **15**, **17**−**19**, **21**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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