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Synthetic studies directed toward the AB decalin common to HMP-Y1 and hibarimicinone

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ABSTRACT

Efforts toward the synthesis of the decalin ring system common to the hibarimicin shunt metabolite HMP-Y1 and parent aglycone hibarimicinone are reported herein. An intramolecular Diels–Alder cyclization rapidly generated the decalin framework. Two approaches toward completion of the AB decalin were vetted. Incorporation of a phenylsulfonyl leaving group β- to both a ketone and a γ-lactone followed by base-induced elimination of sulfinate led to the undesired α,β-unsaturated lactone. Methanolysis of the γ-lactone followed by elimination produced the unexpected bridged cyclic ether by way of an intramolecular oxy-Michael addition of the endo oriented C13 alcohol.

Hibarimicin B (**1**) was isolated from the soil bacterium *Microbispora rosea* in 1998, and its structure was proven identical to the previously reported angelmicin B (Fig. 1).[1–4] The hibarimicins were reported to modestly inhibit *src* tyrosine kinase (hibarimicin A, IC_{50} = 5.8 μM, hibarimicin B, IC_{50} = 23 μM) and exhibited cytotoxicity against B16–F10 (murine melanoma) and HCT-116 (human colon carcinoma) cells at concentrations ranging from 0.41 to 1.1 μM. The 100-fold concentration difference between in vitro kinase inhibition and cancer cell growth inhibition (HL-60, IC_{50} = 57 nM) suggests further studies into their mode of action is warranted.[5] Biosynthetic and structural studies demonstrated the aglycon hibarimicinone (**2**) to precede the hibarimicins, and arise from oxidation of a C_2-symmetric precursor termed HMP-Y1 (**3**).[6–8]

The symmetric structure of hibarimicinone is suggestive of a two-directional synthetic strategy, of which our laboratory[9–12] and others[13–16] have employed recently culminating in two total syntheses.[17–19] With this strategy in mind we planned to utilize a biaryl D–D′ ring surrogate **4** of defined configuration in a bis-annulation reaction with a suitable unsaturated decalin **5** (Scheme 1). Furthermore, our ability to access **4** as a single atropisomer through our previously reported deracemization protocol avoids the necessity for separation of atropisomeric mixtures en route to the natural hibarimicinone isomer.[12]

At the time we initiated a synthetic route to the AB decalin **5** the absolute stereochemistry of hibarimicinone was unknown.

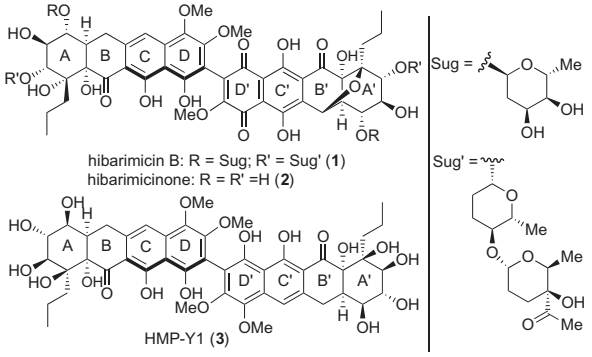
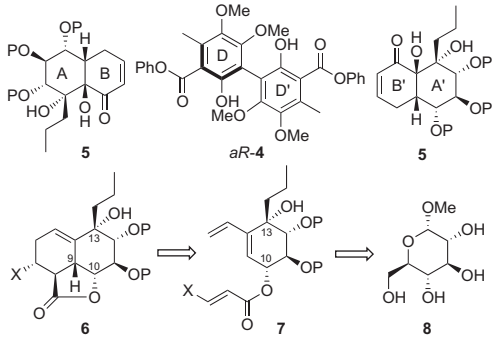


Figure 1. Hibarimicin B (**1**), hibarimicinone (**2**) and HMP-Y1 (**3**).



Scheme 1. Two-directional strategy and analysis of AB decalin **5**.

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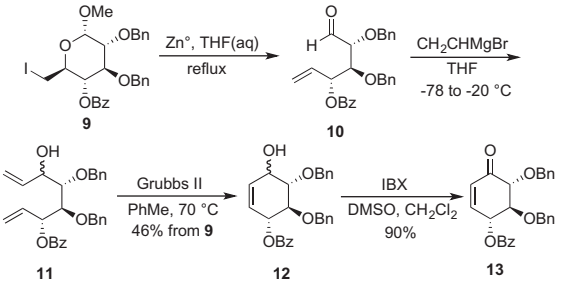
Therefore, although **2** represents the now-defined absolute stereochemistry of hibarimicinone, we initially targeted the opposite absolute stereochemistry due to perceived ready access to the A-ring triol starting from methyl-α-D-gluco-pyranoside (**8**). Based on earlier studies of an intermolecular Diels–Alder approach[10] to decalin **5** that failed to deliver the desired C9 ring fusion stereochemistry we elected to pursue an intramolecular Diels–Alder (IMDA) reaction employing **7** as the key Diels–Alder substrate. We anticipated triene **7** to be conveniently prepared starting from inexpensive methyl glucopyranoside **8**.

Our synthesis of triene **7** proceeded by way of cyclohexenone **13** (Scheme 2). The multi-gram preparation of **13** started with a published five-step conversion of D-glucose **8** to the 6-iodo derivative **9**.[20,21] The latter was then subjected to a Vasella fragmentation by treatment with zinc dust in refluxing THF/H_2O (Scheme 2).[22] Due to instability upon concentration, aldehyde **10** was subjected without purification to a solution of vinylmagnesium bromide to afford an inconsequential mixture of secondary alcohols **11**. Next, ring closing metathesis of **11** provided cyclohexenol **12** in good yield (46% over three steps). Finally, IBX oxidation of **12** in a solution of 1:1 DMSO/CH_2Cl_2 afforded enone **13** in 90% yield.

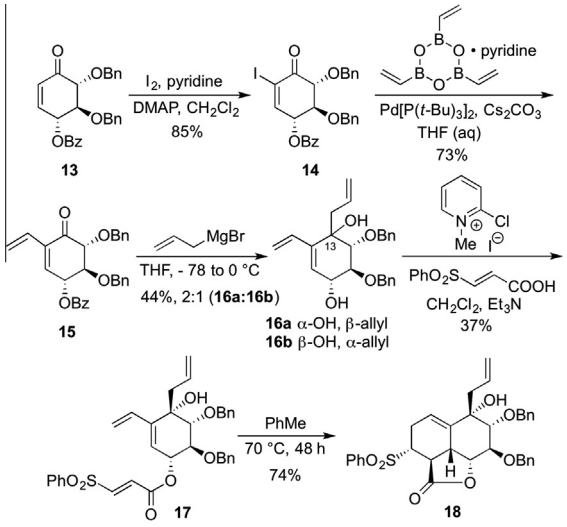
Iodination of cyclohexenone **13** using the Johnson–Uskokovic protocol[23] provided iodoenone **14**, a key intermediate en route to IMDA substrate **7** incorporating an orthogonally protected C10 hydroxyl group, keto group poised for introduction of the C13 tertiary alcohol, and a C14 halide for vinylation. Suzuki cross coupling of **14** with the cyclic vinyl boronate provided dienone **15** in good yield (Scheme 3).[24–26] We then turned our attention to installation of the C-13 stereocenter by addition of a 3-carbon allyl Grignard reagent to the keto group accompanied by C10 benzoate removal. Unfortunately, despite examination of numerous reaction conditions and reagents, this reaction suffered from low yield and diastereoselectivity, producing an optimized 2:1 mixture of inseparable diastereomers (**16a** and **16b**) in 44% yield. The isomers were subject to esterification with β-phenylsulfonylacrylic acid, a dienophile chosen for its reactivity, and ready introduction of B ring unsaturation following base-mediated sulfinate elimination of the anticipated cycloadduct.[27] To this end, Mukaiyama's esterification conditions[28] afforded ester **17** in 37% yield following separation of the minor diastereomeric ester derived from **16b**. Upon heating a solution of **17** in toluene (0.02 M) over two days, we were pleased to observe clean conversion of **17** to decalin **18** as a single diastereomer. The assigned stereochemistry of **18** was based on the analysis of NOESY spectroscopy correlations.

After screening various hydrogenation conditions we determined the allyl group of **18** could be selectively saturated under one atmosphere of hydrogen in a 3:2 mixture of heptane and ethyl acetate over 5% Pd/C (20 min) to provide **19** in 86% yield (Scheme 4). Ketohydroxylation of the C14–C15 alkene was accomplished using RuO_4 in the presence of excess Oxone resulting in the stereoselective installation of the C14 hydroxyl group.[29] The stereoselectivity of this oxidation presumably results from a combination of steric (convex approach) and electronic (allylic alcohol) effects.[30,31] Despite examining various conditions, all attempts to purify ketone **20** resulted in decomposition. However, having finally arrived at an AB decalin incorporating all six stereocenters we subjected crude **20** to base-mediated (DBU, CH_2Cl_2) sulfinate elimination. Unfortunately, we observed exclusive formation of α,β-unsaturated lactone **21**, an intermediate which proved unworkable in advancing to decalin **5**. We reasoned the resistance of the double bond occupying the desired C16–C17 position arose from strain imparted from the fused γ-lactone, and thus we moved to relieve that strain prior to sulfinate elimination.[32]

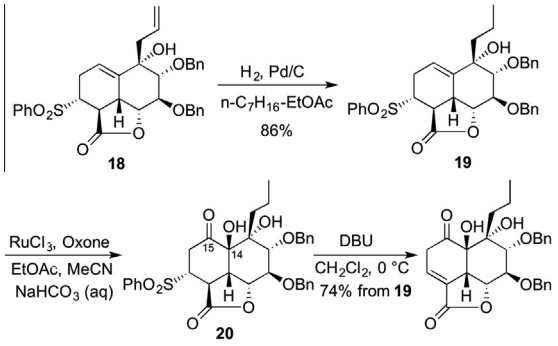
Treatment of lactone **19** with K_2CO_3 in methanol at a low temperature followed by TES protection of the released secondary alcohol afforded methyl ester **22** in 82% yield (Scheme 5). Oxidation of the C14–C15 trisubstituted olefin with RuO_4 proceeded in good yield and stereoselectivity to afford α-hydroxyketone **23**, a compound once again unstable to silica gel chromatography as experienced with α-hydroxyketone **20**. When treated with DBU at a low temperature the former underwent sulfinate elimination and isomerization to bridged ether **24**. This isomerization arises by way of base-mediated intramolecular Michael addition of the proximal C-13 tertiary alcohol. Notably, we observed no scrambling of the methyl ester stereocenter, possibly indicating the Michael addition perhaps proceeded by way of the desired α,β-unsaturated enone. Efforts to protect the C-13 alcohol and circumvent the undesired cyclization were unsuccessful.



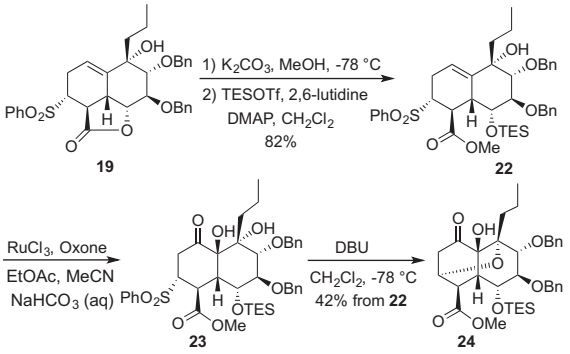
Scheme 2. Preparation of cyclohexenone **13** from glucopyranoside **9**.



Scheme 3. Synthesis of decalin **18**.



Scheme 4. Attempted B-ring enone formation through sulfone elimination.



Scheme 5. Alternate route to B-ring enone leads to bridged ether formation.

In summary, during the course of our investigations to assemble an AB-decalin structure (**5**) to be employed in a two-directional approach to HMP-Y1, we encountered the unanticipated isomerization of **20**–**21** and enone interception of the C13 tertiary hydroxyl group (**23**–**24**). Workers successful in the total synthesis of HMP-Y1 and/or hibarimicinone avoided these obstacles by early protection of the C13 hydroxyl group. However, we demonstrated stereocontrolled decalin formation by way of a highly functionalized IMDA substrate (**7**), and we employed a novel method for installation of the essential β-hydroxyketone.

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Supplementary data

Supplementary data (experimental procedures and compound spectral data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.069.

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