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Enantioselective Total Synthesis of (−)-Kibdelone C

John R. Butler, Chao Wang, Jianwei Bian, and Joseph M. Ready*

Department of Biochemistry, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75390-9038, United States

Supporting Information

ABSTRACT: The kibdelones are aromatic polyketide natural products featuring isoquinolinone and tetrahydroxanthone ring systems. They display potent cytotoxicity toward a range of human cancer cell lines. Here, we present an enantioselective total synthesis of kibdelone C that utilizes a Shi epoxidation to establish the absolute and relative stereochemistry, an acid-catalyzed cyclization to form the tetrahydroxanthone, and a C−H arylation to complete the hexacyclic skeleton.

The kibdelones (**1**−**3**, Scheme 1) are aromatic polyketides recently isolated from a soil actinomycete by the Capon group.[1] A distinguishing characteristic of the kibdelones is their propensity to interconvert by way of aerobic oxidation and disproportionation. Thus, structures **1**−**3** differ by virtue of the oxidation states of their B- and C-rings. Upon standing in MeOH, purified **2** or **3** evolves to an equilibrium mixture of **1**:**2**:**3** in approximately a 3:1:2 ratio. Kibdelones possess potent nematocidal and antibiotic activity. Additionally, they are impressive anticancer agents, displaying GI_{50}'s in the low nanomolar range against a panel of human cancer cell lines. Screening against the National Cancer Institute's 60-cell panel suggested a novel mode of action, although their curved, helical, and amphiphilic character is reminiscent of natural products known to bind nucleic acids or nucleic acid-binding proteins.[2]

Structurally, the kibdelones present a hexacyclic skeleton featuring two fully substituted aryl rings and two fully substituted heteroaryl rings. The F-ring contains three stereogenic centers, while the A-ring is halogenated. Overall, these natural products share structural features with other biologically active polyketides, including simaomicin α,[3] cervinomycin,[4] the kigamicins,[5] and SCH 54445.[6] Interestingly, among these, only the kibdelones display significant anticancer activity as single agents.[7] Taken together, the combination of potent cytotoxicity and structural complexity has engendered excitement in the synthetic community. Indeed, the Porco group reported an elegant approach to the ABCD-ring system[8] and has recently completed a total synthesis of (+)-**3**.[9] Furthermore, other aromatic polyketides have succumbed to total synthesis through a number of instructive strategies.[10] Here we report our successful efforts to develop a convergent enantioselective synthesis of kibdelone C (**3**).

We envisioned assembling the AB-DEF-ring system **4** from an isoquinolinone and a tetrahydroxanthone fragment (Scheme 1). In turn, these substructures would both arise from two simpler precursors (**5**−**8**). We anticipated forming the C-ring through a C−H arylation strategy to construct the full carbon skeleton of the natural products. We hoped that such a convergent approach would lend efficiency to the synthesis and ultimately allow access to diverse derivatives for biological testing.

The isoquinolinone fragment of the kibdelones was assembled starting with an amidation of amino alcohol **5**[11] with benzoic acid **6**[12] under Schotten−Baumann conditions (Scheme 2). Subsequent TEMPO oxidation[13] provided aldehyde **9** in good yield. BCl_3 effected cyclization and selective removal of one *O*-methyl group;[14] dehydration yielded the isoquinolinone ring system **10**. Other Lewis and Bronsted acids proved ineffective, while BBr_3 provided mainly doubly demethylated material. Finally, Sonogashira coupling[15] and desilylation gave the terminal alkyne **11**, a substrate for a second Sonogashira coupling with the tetrahydroxanthone fragment (see below).

We wanted to exploit the pseudo-C_2 symmetry within the F-ring that related the two diols to one another. To that end, diene **12** was subjected to Shi epoxidation conditions[16] to yield a diepoxide that was immediately reduced with borane (Scheme 3). This sequence, invented by Myers and co-workers,[17] generated doubly protected, C_2-symmetric tetraol **14** as a single diastereomer in >95:5 enantiomer ratio. Selective monotosylation provided secondary alcohol **15**. ^{1}H NMR analysis indicated that the adjacent tosyloxy and silyloxy substituents adopt a *trans*-diaxial relationship. Presumably, the steric bulk of the equatorially disposed silyloxy group favors monosulfonylation. Swern oxidation with trifluoroacetic anhydride yielded a ketone that underwent elimination under the basic reaction conditions.[18] Subsequent iodination and Luche reduction secured a vinyl iodide (**16**) corresponding to the F-ring of the kibdelones.

Deprotonation of alcohol **16** with CH_3Li followed by lithiation with *t*-BuLi generated a vinyllithium reagent that could participate in a nucleophilic addition to aldehyde **18**. This aldehyde, prepared as shown in Scheme 4, is both hindered and electron rich; therefore, it displays minimal electrophilicity. Improved reactivity was observed with dianionic organometallic reagents lacking a C-10 protecting group (e.g., **16**) compared to *O*-alkyl or *O*-silyl analogues. Similar observations were made by Nicolaou's group in the context of their synthesis of diversonol.[19] Dess−Martin oxidation generated an enedione that, upon treatment with acidic acetone and *t*-BuOH, shed three protecting groups and cyclized to construct the tetrahydroxanthone, protected as an acetonide (**21**, Scheme 5).[19] This transformation may involve condensation of the D-ring phenol with the F-ring ketone to give conjugated oxonium **20**. Conducting this reaction in the absence of acetone yielded the unprotected xanthone as a mixture of C-10 epimers, while omitting *t*-BuOH resulted in the incorporation of

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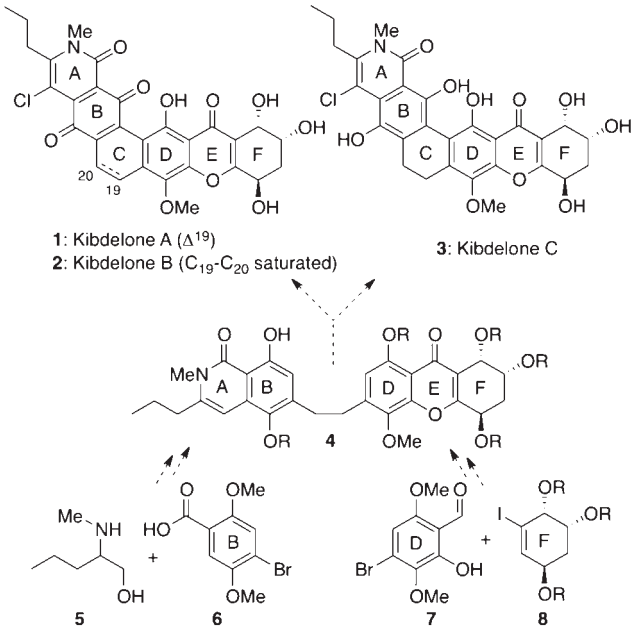
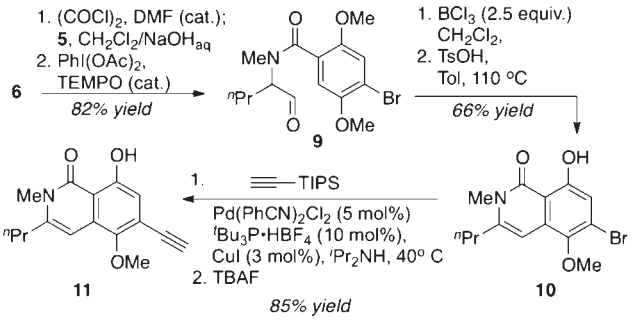
Scheme 1. Synthetic Strategy toward the Kibdelones



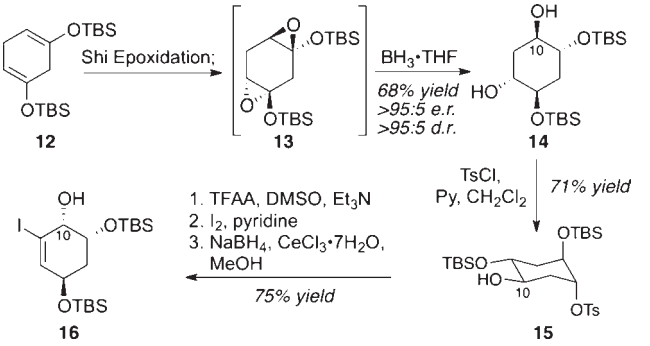
Scheme 2. Synthesis of Isoquinolinone 11



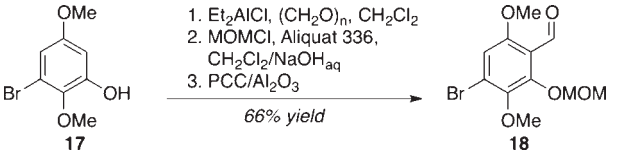
a methylene acetal spanning the C-10 and C-11 alcohols. The proclivity of this diol to trap formaldehye would re-emerge later in the synthesis.[20]

Sonogashira coupling with alkyne **11** required Cu-free conditions and slow addition of the alkyne to avoid oxidative dimerization.[21] Next, hydrogenation yielded the pentacyclic structure **22**, which contains all the carbons of the kibdelones. A serendipitously discovered Cu-catalyzed iodination led to a substrate for C−H arylation (**23**) en route to the C-ring of the natural products.[22] In this context, the coupling of C−H bonds with aryl halides has been studied extensively, although we are aware of no applications in such a complex setting.[18] Extensive optimization revealed that every parameter was critical for the success of this cyclization to form the kibdelone skeleton (**24**): other phosphines, buffers, solvents, metals, temperatures, or atmospheric make-ups proved inferior to the conditions shown. Likewise, the Boc group proved critical for obtaining synthetically useful yields. The free phenol or alkyl ethers cyclized less efficiently, and esters were cleaved under the reaction conditions. The most common side products under all conditions were de-iodinated materials and, at higher temperatures, substances with aromatized F-rings.

Scheme 3. Enantioselective Synthesis of the F-Ring



Scheme 4. Synthesis of the D-Ring



The endgame of our synthesis proved complicated. For example, chlorination with hexachlorodieneone **25** was rapid, although initially problematic. Thus, reducing unreacted **25** ($Na_2S_2O_4$) and extracting the resultant pentachlorophenol prior to concentrating the crude reaction mixture proved critical to avoid decomposition of the chlorinated product.[24] Even so, we isolated the expected chlorinated product **26**, along with materials possessing masses consistent with hydration of the isoquinolinone ring.[25] Furthermore, these hydrates were formed as diastereomeric mixtures and, along with compound **26**, exist as atropisomers at room temperature. Deprotection of this mixture under acidic conditions removed the Boc group and converted the aforementioned A-ring hydrates to the isoquinolinone. Next, oxidation with $PhI(OAc)_2$ gave a mixture of kibdelone B methyl ether (**27**) and two derivatives containing either a MOM group (**28**) or a methylene acetal (**29**), presumably arising from formaldehyde generated during removal of the MOM group. If these quinones were reduced to the hydroquinone, they underwent aerobic oxidation back to the quinone in a matter of minutes. Fortunately, **27**−**29** could all be converted to the natural product by treatment with BCl_3 to remove the C-6 methyl ether and the acetals that remained in **28** and **29**. Crude reaction mixtures contained both kibdelones B and C according to HPLC/MS analysis. This mixture produced a brown, sparingly soluble residue upon concentration, possibly as a result of spontaneous oxidation. Nonetheless, as predicted by the isolation report,[1] reduction of the crude reaction products with dithionite yielded kibdelone C (**3**). In our hands, the final product was subject to oxidation and ill-defined decomposition. Careful purification by HPLC provided the natural product in >90% purity.[26] The synthetic material displayed ^1H and ^{13}C NMR spectra and molecular weight identical to those reported by Capon and co-workers. The optical rotation of synthetic **3** was equal in magnitude but opposite in sign to that reported for the natural product, establishing the absolute configuration of the kibdelones as enantiomeric to what is shown in Schemes 1 and 5.

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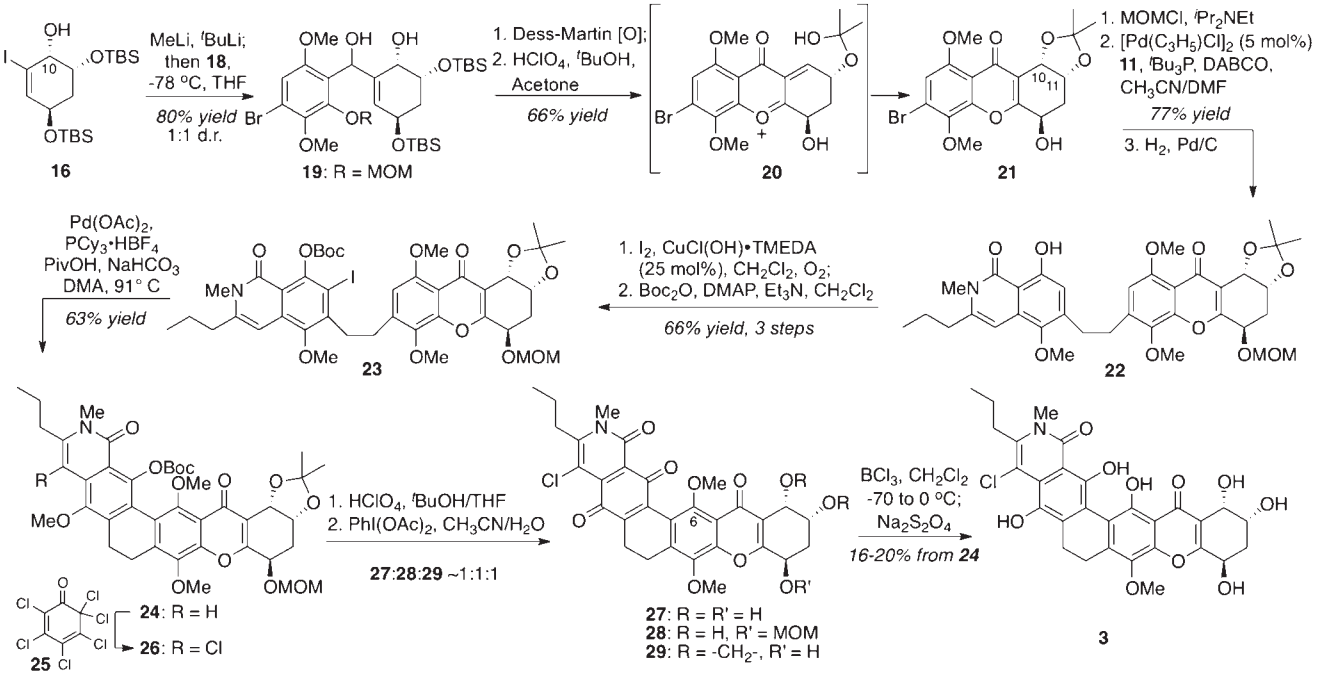
Scheme 5. Synthesis of Kibdelone C (3)



In summary, we have developed a convergent, enantioselective synthesis of the kibdelones. Since the absolute stereochemistry was established using asymmetric catalysis, we will have access to the natural configuration by using the opposite Shi catalyst. These characteristics should allow us to prepare and evaluate diverse derivatives of these potent anticancer agents.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
joseph.ready@utsouthwestern.edu

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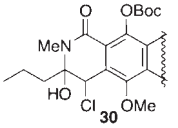
(24) Other chlorination reagents including NCS and PPh_3/NCS performed similarly.
(25) Mass spectrometry and ^1H NMR data are consistent with **30**.



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A similar product was identified during the isolation of **1**−**3**. See ref 1.

(26) See Supporting Information for full experimental details.