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Total Synthesis and Absolute Stereochemical Assignment of Kibdelone C

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Abstract

The kibdelones are hexacyclic tetrahydroxanthenes and potent anticancer agents isolated from an Australian microbe. Herein, we describe the synthesis of a chiral, non-racemic iodocyclohexene carboxylate EF ring fragment of the kibdelones employing an intramolecular iodo halo-Michael aldol reaction and its merger with an ABCD ring fragment to afford the congener kibdelone C.

The polycyclic xanthone natural products are a diverse family of polyketides characterized by their highly oxygenated, hexacyclic frameworks (Figure 1). Kibdelones A–C (**1–3**, Figure 1) are hexacyclic tetrahydroxanthone^{1b} natural products which were isolated by Capon and coworkers from the rare Australian microbe *Kibdelosporangium sp.* along with isomeric metabolites including isokibdelone A **4**.^{1a} During their isolation, it was found that methanol solutions of **2** and **3** equilibrated to a mixture of **1–3**,^{1b} likely through keto/enol tautomerizations followed by quinone/hydroquinone redox reactions. The kibdelones also display potent nanomolar activity in variety of human tumor cell lines. For example, kibdelone C **3** has a GI₅₀ of <1 nM against a SR (leukemia) tumor cell line and <1 nM (GI₅₀) against SN12C (renal) cell carcinoma. There are numerous related hexacyclic xanthone natural products (*cf.* **5–9**, Figure 1).² Overall, the class of molecules exhibits a diverse range of biological activities, including potent antimalarial, antibiotic, anticoccidial, and anticancer properties.²

Despite extensive synthetic efforts towards polycyclic xanthenes such as the cervinomycins **5**,^{3c–g} there have been limited reports describing synthetic efforts^{3a,b,h} towards hexacyclic tetrahydroxanthone natural products, in part due to the challenge in constructing the polyhydroxylated F ring moiety. In our retrosynthetic analysis, we envisioned that the congener kibdelone C **3** may be obtained from merger of ABCD fragment **12**⁴ and 2-iodo-1-cyclohexenecarboxylate fragment **13**. In order to access the tetrahydroxanthone ring-system, we envisioned use of an *oxa*-Michael/retro-Michael⁵ Friedel-Crafts annulation sequence. This approach has been utilized in the literature for the synthesis of xanthenes from biaryl-ethers,^{3d,6} but has not previously been used to access tetrahydroxanthone ring systems. Fragment **12** may be derived from Pt(IV)-catalyzed arylation of quinone monoketal **10** and hydroxystyrene **11**.⁴ We envisioned that the chiral EF ring fragment **13** may be obtained from diastereoselective, intramolecular halo-Michael aldol reaction of aldehyde ynoate **14**,

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Supporting Information Available: Experimental procedures, and characterization data for all new compounds described herein, including CIF files for compound **22** and **25**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

the latter derived from protected diol **15**. There are numerous literature reports describing intermolecular reactions of preformed β -iodoallenoates reacting with aldehydes⁷ including a recent report by Frontier and coworkers describing an intramolecular variant with an alkynone substrate.⁸

The synthesis of the requisite EF ring fragment **13** began with Dess-Martin-periodinane oxidation of the commercially available, enantiopure alcohol **15**.⁹ Zinc-acetylide, chelation-controlled addition to aldehyde **16**, followed by benzylation with NaH in THF and desilylation with TBAF, provided the 1,3 *anti*-protected propargylic alcohol **17** (60%, 3 steps).¹⁰ Alcohol **17** was oxidized to a carboxylic acid in a two step sequence using IBX in ethyl acetate¹¹ followed by Pinnick oxidation. Further treatment with H₂SO₄ in MeOH provided both the derived methyl ester and deprotected propargylic diol **18** (73%, three steps). Selective benzylation of the secondary alcohol of **18** was achieved through benzylidene formation with benzaldehyde dimethylacetal and *p*-TsOH in toluene which was followed by reduction with sodium cyanoborohydride and TMSCl in CH₃CN to provide *bis*-benzyl ether **19** (76%, two steps).¹² Primary alcohol **19** was finally oxidized with IBX to afford the requisite ynoate aldehyde **14** (90%).¹¹

We next evaluated the intramolecular halo-Michael aldol reaction. Treatment of **14** with of magnesium iodide^{7f-g} (2 equiv.) at -20 °C in CH₂Cl₂ afforded 2-iodo-1-cyclohexenecarboxylate **20** in 78% yield (19% overall yield from **15**) on a multigram scale along with minor diastereomer **21** (9%). The stereochemistry of the major diastereomer was confirmed by X-ray crystal structure analysis of the derived *p*-bromobenzoate **22**.¹³ A proposed mechanism for the transformation is shown in Figure 3. We envision reversible^{7f} formation β -iodoallenoate diastereomers **A** and **B**, the former which may undergo cyclization through transition state **C** to major diastereomer **20** and the latter which may react thru assembly **D** to afford minor diastereomer **21**. The preference for **C** vs. **D** leading to major diastereomer **20** may be due to stabilizing chelation of the α -benzyl ether and aldehyde with MgI₂.^{7a,b,d,g,14} Alternatively, it is possible that the relative thermodynamic stability of products **20** and **21** may be reflected in the product ratio if epimerization by a retro-halo-Michael aldol process¹⁵ can occur under the reaction conditions.

Initial attempts at fragment coupling of **12** with benzyl-protected iodoacrylate **20** proved to be unsuccessful under a variety of basic, palladium, and copper-catalyzed conditions.¹⁶ Accordingly, we decided to target the benzyl-deprotected acetone **13** (Scheme 2) as reaction partner with the expectation that an unprotected, allylic hydroxyl should impart greater reactivity in *oxa*-Michael reactions.^{5b} Numerous conditions for debenylation of **20** were attempted, including hydrogenolysis and various Lewis acids (*e.g.* AlCl₃, ZrCl₄, and TMSI).¹³ Unfortunately, most conditions led to either degradation or formation of complex aggregates and emulsions upon aqueous workup. Fortunately, treatment of **20** with BCl₃¹⁷ effected smooth conversion to a triol which was reprotected by treatment with 2,2-dimethoxypropane under acidic conditions to afford **13** (87%, two steps, Scheme 2).

Initial base-catalyzed *oxa*-Michael reactions of ABCD ring fragment **12** and iodocyclohexene carboxylate **13** included evaluation of NaH, K₂CO₃, Cs₂CO₃, (*n*-Bu)₄NOH, and KOtBu as bases in either CH₃CN or DMF at temperatures from 25–100 °C. However, these conditions failed to produce any detectable coupling products. We next evaluated a variety of copper and palladium-catalyzed methods, including conditions reported by Buchwald and coworkers for C-O bond formation using Cu(I), picolinic acid, and K₃PO₄ as base in DMSO (Scheme 2).^{16c} In light of the latter precedent for coupling of sterically hindered and electron rich nucleophiles, we believed that this would be an effective condition for fragment coupling of **12** and **13**. Further experimentation revealed that copper (I) was not required for the transformation. Dimethyl sulfoxide proved to be an

optimal solvent, presumably due to its ability to dissolve phenolate(s) derived from dihydrophenanthrene **12** at reduced temperatures. The base was also found to be important, as little to no conversion was observed with NaH, K₂CO₃, Cs₂CO₃, and KO^tBu. Moreover, the workup procedure was found to be crucial due to acid sensitivity of vinylogous carbonate **23**. Careful workup at 0° C with 0.5 N KHSO₄ (pH = 2) was found to be optimal for protonation of the phenolates and to minimize degradation of the newly formed vinylogous carbonate linkage. ¹H NMR comparison of the phenol chemical shifts of dihydrophenanthrene **12** and vinylogous carbonate **23** strongly supported the desired connectivity of the *oxa*-Michael product.¹³

Initially we believed that the lack of reactivity seen in iodoacrylate **20** versus **13** may be due to the steric bulk imparted by the allylic, benzyl ether moiety. Accordingly, conformer searches of both **13** and **20** were performed using Spartan '08 calculated at a semi-empirical level of theory using an AM1 basis set. In the low energy conformer of dibenzyl ether **20**, the allylic ether substituent appears to be in an axial orientation. In contrast, in the low energy conformer of successful substrate **13**, the hydroxyl moiety resides in an equatorial orientation (Figure 4). Accordingly, the lone-pair of the benzyl ether may raise the LUMO of the acrylate system by an σ - π^* interaction which may also contribute to the low reactivity observed for **20**.¹⁸

The acid lability of **23** proved to be disappointing, as in our initial plan for formation of the tetrahydroxanthone ring system we envisioned treatment of ester **23** with either sulfuric acid,^{19a} Eaton's reagent,^{19b} or PPA (polyphosphoric acid),^{19c} known reagents for intramolecular Friedel-Crafts annulation of esters. A report describing a mild, intramolecular Friedel-Crafts cyclization using cyanuric chloride and AlCl₃ led us to target the carboxylic acid derived from ester **23**.²⁰ Fortunately, we were able to saponify **23** by treatment with LiOH in dioxane. In this reaction, some cleavage of the vinylogous carbonate linkage to afford **12** was observed (LC/MS). Fortunately, we were able to carry on the crude acid mixture (contained approx. 10% of **12**) directly into cyclization *via* treatment with cyanuric chloride and pyridine in DCE (75° C) which afforded tetrahydroxanthone **24** (39%, two steps, Scheme 3).²⁰ The fact that AlCl₃ was not required for the transformation led us to propose the mechanism shown in Figure 5. Activation of the carboxylic acid may afford an intermediate such as **E** which can further react to form the highly reactive α -*oxo*-ketene^{21,22} intermediate **F**, the latter which may further undergo 6 π -electrocyclization and rearomatization to form the requisite tetrahydroxanthone **24**. As the reaction was conducted with excess pyridine, it is conceivable that intermediate **E** is an acyl pyridinium²³ rather than an acid chloride.

In the final stages of the synthesis, we found that compound **24** was a poor substrate for oxidative demethylation.¹³ Accordingly, the acetonide was removed *via* treatment with 3N HCl in THF to provide triol **25** in 95% yield (Scheme 4). X-ray crystal analysis of **25** showed two molecules in the asymmetric unit and served to confirm the hexacyclic tetrahydroxanthone framework (Figure 6).¹³ Due to the known instability of kibdelone B **2**,^{1b} we envisioned an oxidative demethylation/*in-situ* reduction sequence to access kibdelone C.²⁴ Attempted oxidations using ceric ammonium nitrate (CAN) were found to be both pH and temperature sensitive. Reaction of **25** with 2.0 equiv. of CAN in pH 7.0 buffer afforded mixtures of B and D ring-oxidized products, as well a compound showing a mass for both B and D ring hydroquinones. Reaction of **25** with CAN in water led to a 3:2 mixture of B vs. D ring oxidized products. Fortunately, treatment of **25** with CAN (2.2 equiv.) and 10 equivalents of AcOH at rt for 2 minutes, followed by a reductive quench with excess sodium dithionite, provided a ~ 5:1 mixture of kibdelone C and a doubly demethylated product. In this case, we believe that protonation of the xanthone carbonyl with acetic acid may produce a DE ring benzopyrylium species^{13,25} which should reduce the propensity for

oxidation of the D ring. Alternatively, it is conceivable that the more selective oxidant cerium (IV) acetate may be formed under the reaction conditions.²⁶ Proton, carbon, UV/VIS and optical rotation ($[\alpha]_D^{23} = +48^\circ$ synthetic, $+49^\circ$ natural ($c = 0.5$, CHCl_3)) for synthetic **3** were found to be identical in all aspects to the natural product.¹ The absolute stereochemical assignment of natural kibelone C was accordingly assigned as 10*R*, 11*S*, 13*S* as shown in structure **3** (Figure 1).

In summary, a convergent total synthesis of kibelone C has been achieved. A diastereoselective halo Michael/aldol reaction sequence was utilized for construction of the highly functionalized 2-iodo-1-cyclohexenecarboxylate EF ring fragment **13**. The ABCD dihydrophenanthrene fragment **12** was reacted through a site-selective *oxa*-Michael reaction to afford a sensitive vinylogous carbonate precursor **22**. The acid lability of **22** was overcome utilizing cyanuric chloride to mildly activate a derived carboxylic acid to afford the tetrahydroxanthone ring system. A precursor to kibelone C, methyl ether **24**, was synthesized and found to be very stable in relation to the highly oxidizable **3**. Further studies concerning the synthesis and biological evaluation of additional kibelone congeners and additional tetrahydroxanthone natural products are currently in progress and will be reported in due course.

Supplementary Material

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Acknowledgments

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Figure 1.
Kibdelones and Related Hexacyclic Xanthone Natural Products

Figure 3.
Proposed Mechanisms for Formation of **20** and **21**

Figure 4.
AM1 low energy conformers for **20** and **13**

Figure 5.
Proposed Mechanism for Xanthone Formation

Figure 6.
X-Ray Crystal Structure of kibelone C methyl ether **25**

Scheme 1.
Synthesis of the EF ring fragment

Scheme 2.
Fragment Coupling

Scheme 3.
Xanthone Formation and Elaboration to kibdelone C