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Total Synthesis and Absolute Stereochemical Assignment of Kibdelone C

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Supporting Information

ABSTRACT: Kibdelones are hexacyclic tetrahydroxanthones and potent anticancer agents isolated from an Australian microbe. Herein, we describe the synthesis of a chiral, nonracemic 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.

Polycyclic xanthone natural products are a diverse family of polyketides characterized by their highly oxygenated hexacyclic frameworks. Kibdelones A−C (**1**−**3**, Figure 1) are hexacyclic tetrahydroxanthone[1b] natural products isolated by Capon and coworkers from the rare Australian microbe *Kibdelosporangium sp.* along with isomeric metabolites including isokibdelone A (**4**, Figure 1).[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 a variety of human tumor cell lines. For example, **3** has a GI_{50} of <1 nm against both an SR (leukemia) tumor cell line and 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 toward polycyclic xanthones such as the cervinomycins **5**,[3c−g] there have been limited reports on synthetic efforts[3a,b,h] toward 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** (Figure 2). To access the tetrahydroxanthone ring system, we envisioned use of an *oxa*-Michael/retro-Michael[5] Friedel−Crafts annulation sequence. This approach has been utilized in the literature for the synthesis of xanthones 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**, the latter derived from protected diol **15**. Numerous literature reports describe intermolecular reactions of preformed β-iodoallenoates reacting with aldehydes,[7] including a recent report by Frontier and co-workers on an intramolecular variant with an alkynone substrate.[8]

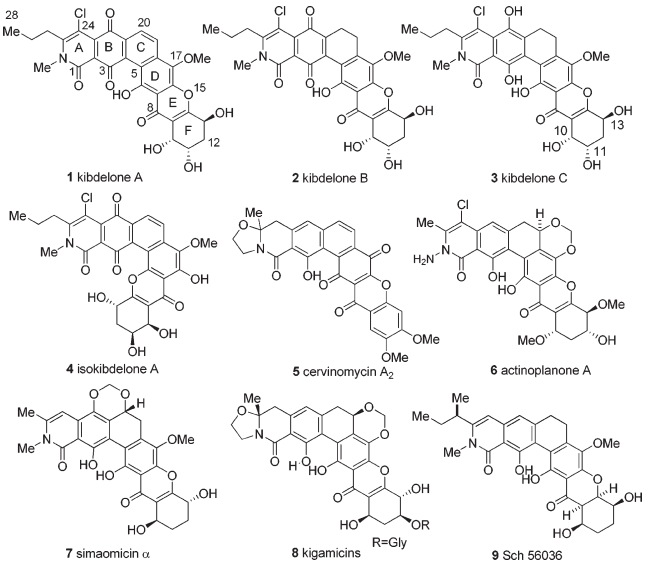

Figure 1. Kibdelones and related hexacyclic xanthone natural products.

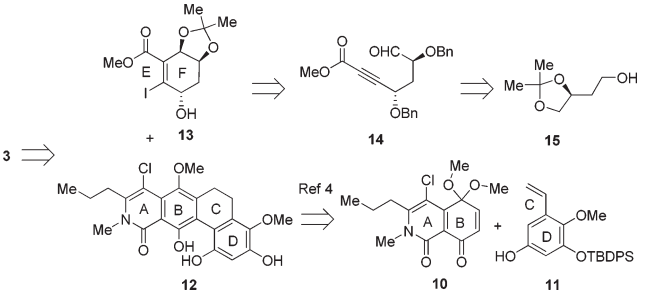

Figure 2. Retrosynthetic analysis for kibdelone C.

The synthesis of 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%, three steps, Scheme 1).[10] **17** was oxidized to a carboxylic acid in a two-step sequence using IBX in ethyl acetate[11] followed by Pinnick oxidation. Further treatment with H_2SO_4 in MeOH provided both the derived methyl ester and deprotected propargylic diol **18** (73%,

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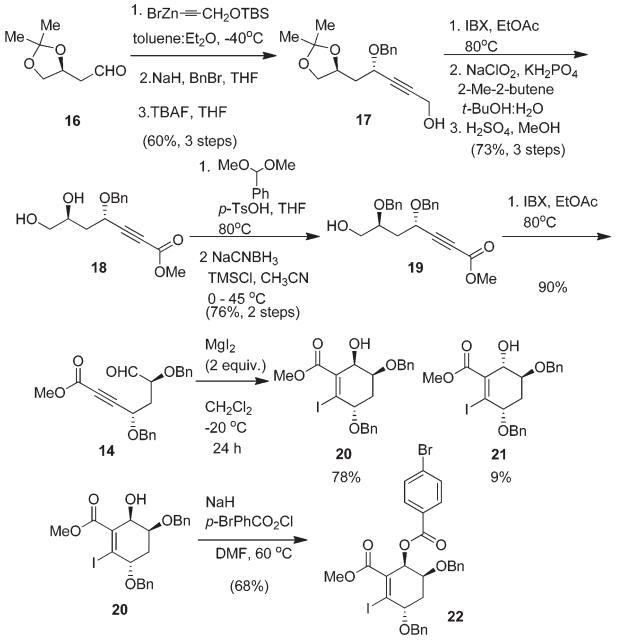
Scheme 1. Synthesis of the EF-Ring Fragment



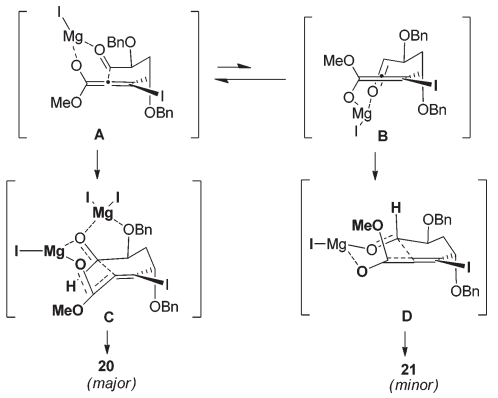
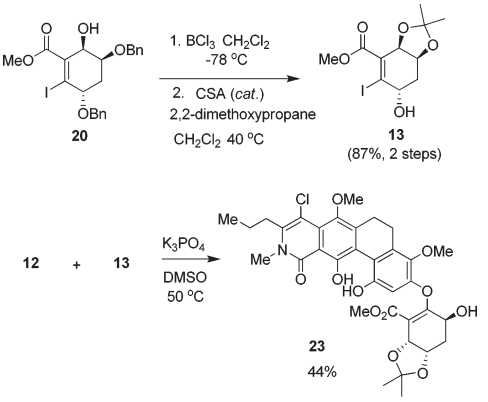


Figure 3. Proposed mechanisms for formation of **20** and **21**.

three steps). Selective benzylation of the secondary alcohol of **18** was achieved through benzylidene formation with benzaldehyde dimethylacetal and *p*-TsOH in toluene followed by reduction with sodium cyanoborohydride and TMSCl in CH_3CN to provide bis-benzyl ether **19** (76%, two steps).[12] Primary alcohol **19** was finally oxidized with IBX to afford the 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 CH_2Cl_2 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 of β-iodoallenoate diastereomers **A** and **B**; the former may undergo cyclization through transition state **C** to give **20**, and the latter may react through assembly **D** to afford **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 MgI_2.[7a,b,d,g,14] Alternatively,

Scheme 2. Fragment Coupling



it is possible that the relative thermodynamic stability of **20** and **21** may be reflected in the product ratio if epimerization by a retro-halo-Michael aldol process[15] 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] We therefore decided to target the benzyl-deprotected acetonide **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 debenzylation of **20** were attempted, including hydrogenolysis and various Lewis acids (e.g., $AlCl_3$, $ZrCl_4$, and TMSI).[13] Most conditions led to either degradation or formation of complex aggregates and emulsions upon aqueous workup. However, treatment of **20** with BCl_3[17] effected smooth conversion to a triol which was reprotected by treatment with 2,2-dimethoxypropane under acidic conditions to afford **13** (87%, two steps).

Initial base-catalyzed *oxa*-Michael reactions of ABCD-ring fragment **12** and iodocyclohexene carboxylate **13** included evaluation of NaH, K_2CO_3, Cs_2CO_3, $(n\text{-Bu})_4NOH$, and KO*t*Bu as base in either CH_3CN or DMF at temperatures from 25 to 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 co-workers for C−O bond formation using Cu(I), picolinic acid, and K_3PO_4 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 Cu(I) was not required for the transformation. DMSO 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 or no conversion was observed with NaH, K_2CO_3, Cs_2CO_3, and KO*t*Bu. 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 $KHSO_4$ (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. Conformer searches of both **13** and **20** were performed using Spartan '08, calculated at a semiempirical level of theory using an AM1 basis set. In the low-energy conformer of

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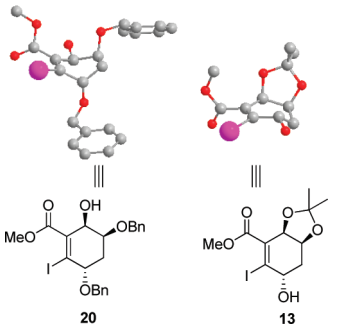
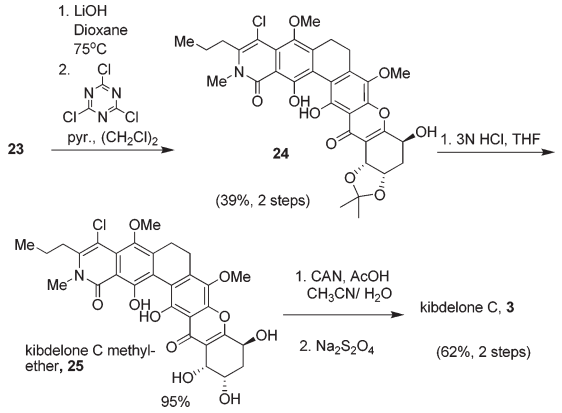


Figure 4. AM1 low-energy conformers for **20** and **13**.

Scheme 3. Xanthone Formation and Elaboration to 3



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). The lone pair of the benzyl ether may raise the LUMO of the acrylate system by a $\sigma-\pi^*$ 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 sulfuric acid,[19a] Eaton's reagent,[19b] or 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 $AlCl_3$ led us to target the carboxylic acid derived from ester **23**.[20] 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). We carried the crude acid mixture (containing ~10% of **12**) directly into cyclization via treatment with cyanuric chloride and pyridine in DCE (75 °C) to afford tetrahydroxanthone **24** (39%, two steps, Scheme 3).[20] The fact that $AlCl_3$ 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 may further undergo 6π-electrocyclization and re-aromatization to form **24**. As the reaction was conducted with excess pyridine, it is conceivable that intermediate **E** is an acyl pyridinium[23] rather than an acid chloride.

In the final stages of the synthesis, we found that **24** was a poor substrate for oxidative demethylation.[13] The acetonide was removed via treatment with 3 N HCl in THF to provide triol **25** in 95% yield (Scheme 3). X-ray crystal analysis of **25** showed

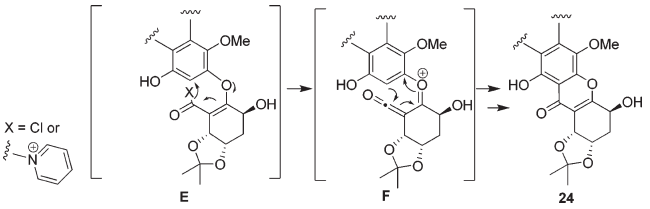


Figure 5. Proposed mechanism for xanthone formation.

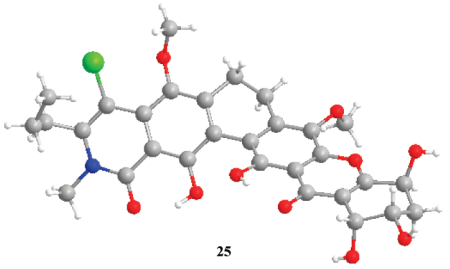


Figure 6. X-ray crystal structure of kibdelone C methyl ether **25**.

two molecules in the asymmetric unit, confirming 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 (**3**).[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 as 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. Treatment of **25** with CAN (2.2 equiv) and 10 equiv of AcOH at room temperature for 2 min, followed by a reductive quench with excess sodium dithionite, provided a ~5:1 mixture of 3 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 possible that the more selective oxidant cerium(IV) acetate may be formed under the reaction conditions.[26] ^1H and ^{13}C NMR and UV/vis spectra and optical rotation ($[\alpha]_D^{23}$ = +48° synthetic, +49° natural (c = 0.5, $CHCl_3$)) for synthetic **3** were identical in all aspects to those of the natural product.[1] The absolute stereochemical assignment of natural kibdelone C was thus assigned as 10*R*,11*S*,13*S* as shown in structure **3** (Figure 1).

In summary, a convergent total synthesis of kibdelone C has been achieved. A diastereoselective halo-Michael/aldol reaction sequence was used to construct 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 kibdelone 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 kibdelone congeners and additional tetrahydroxanthone natural products are currently in progress and will be reported in due course.

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■ ASSOCIATED CONTENT

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

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