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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 co-workers 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]

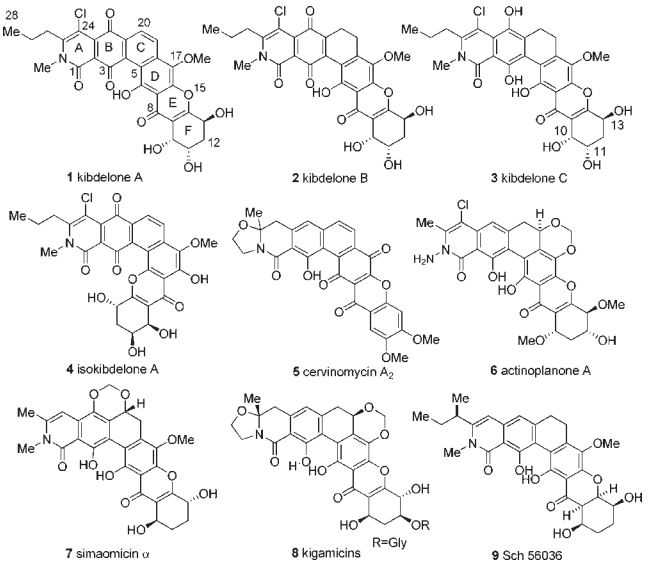


Figure 1. Kibdelones and related hexacyclic xanthone natural products.

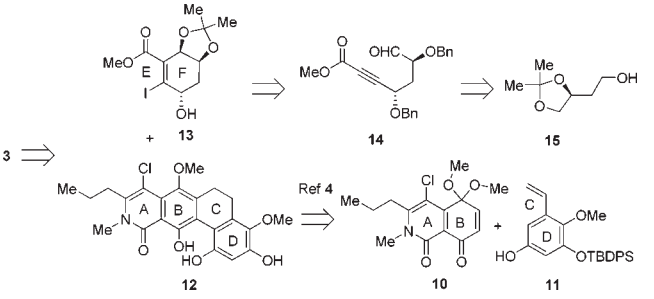


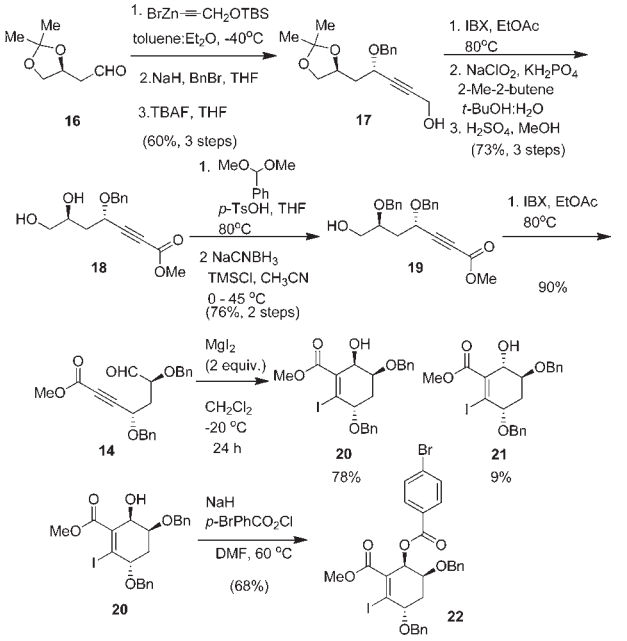
Figure 2. Retrosynthetic analysis for kibdelone C.

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%,

Received: April 20, 2011
Published: June 07, 2011

dx.doi.org/10.1021/ja203642n | *J. Am. Chem. Soc.* 2011, 133, 9952–9955

Scheme 1. Synthesis of the EF-Ring Fragment



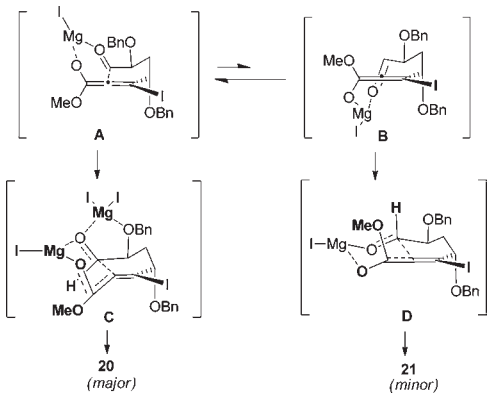
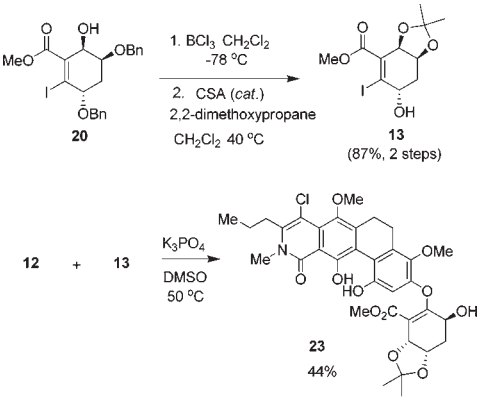


Figure 3. Proposed mechanisms for formation of **20** and **21**.

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. ^{1}H 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

dx.doi.org/10.1021/ja203642n |*J. Am. Chem. Soc.* 2011, 133, 9952–9955

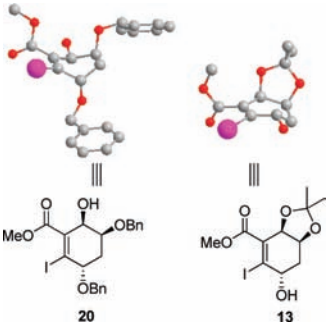
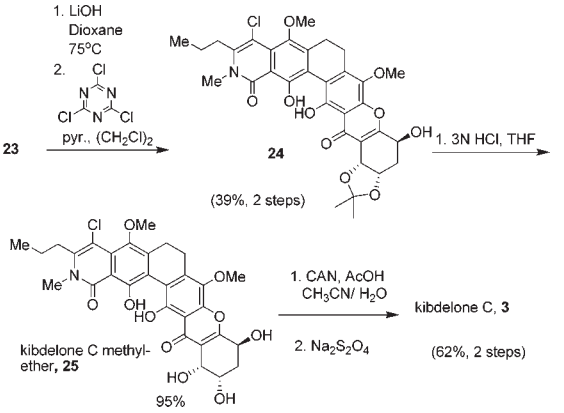


Figure 4. AM1 low-energy conformers for **20** and **13**.

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

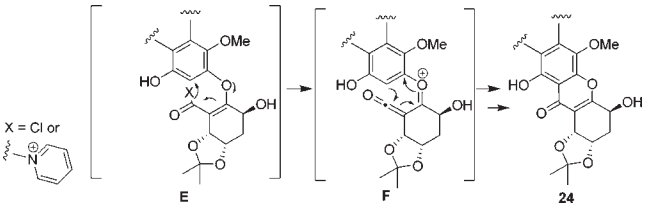


Figure 5. Proposed mechanism for xanthone formation.

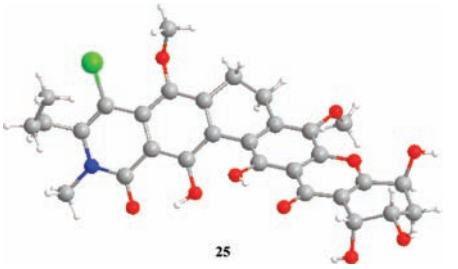


Figure 6. X-ray crystal structure of kibdelone C methyl ether **25**.

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.

dx.doi.org/10.1021/ja203642n |*J. Am. Chem. Soc.* 2011, 133, 9952–9955

■ 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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■ ACKNOWLEDGMENT

We thank the National Institutes of Health (R01 CA137270) and Merck Research Laboratories for research support, Drs. Emil Lobkovsky (Cornell) and Bruce Noll (Bruker) for X-ray crystal structure analyses and refinement assistance, and Dr. Paul Ralifo (Boston University) for NMR assistance. We thank Andrew Little, Stephen Scully, and Dr. Branko Mitasev (Boston University) for extremely helpful and stimulating discussions. We also thank Prof. Robert J. Capon (University of Queensland) for kindly providing a natural sample and ^{1}H and ^{13}C NMR spectra for kibdelone C and Prof. Joseph Ready (University of Texas Southwestern Medical Center) for sharing details of their synthesis prior to publication.

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