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Synthesis and Biological Evaluation of ABCD Ring Fragments of the Kibdelones**

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The kibdelones A-C (**1-3**) and their isomeric metabolites (*cf.* isokibdelone C **4)** are hexacyclic tetrahydroxanthone natural products recently isolated by Capon and coworkers from the rare Australian actinomycete *Kibdelosporangium* sp. (Figure 1).[1] An interesting property is the facile equilibration of kibdelones B **2**, and C **3** to a mixture of **1**-**3***via* keto/enol tautomerizations followed by quinone/hydroquinone redox reactions.[1] Related natural products include simaomicin α **5** which has been shown to sensitize cancer cells to cytotoxic agents including bleomycin at nanomolar concentrations and to exhibit potent antimalarial and anticoccidial activities. [2] Evaluation of the kibdelones in the NCI 60-cell panel of human cancer cell lines revealed that they are active at low nanomolar concentrations against a number of human tumor cell lines. For example, kibdelone A has a GI_{50} of 1.2 nm against a SR (leukemia) tumor cell line and <1 nm (GI_{50}) against SN12C (renal) cell carcinoma.[1] In addition, the kibdelones were shown to display novel COMPARE analysis profiles for cancer cell growth inhibition.

There has been substantial work towards the synthesis of the polycyclic xanthones including cervinomycin A_2 **6**, but more limited studies on the synthesis of the corresponding tetrahydroxanthones.[3] Our initial strategy to construct the ABCD ring fragment **7** involved Diels-Alder cycloaddition of heterocyclic quinone **8** and hydroxystyrene **9** (Scheme 1). Literature reports have described [4+2] cycloadditions of styrenes and quinones including applications in natural product synthesis.[4] We envisioned that the cycloaddition may

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proceed through the hydrogen-bonded assembly **A** (*exo* cycloaddition geometry shown). There are literature precedents in which intermolecular hydrogen-bonding has been utilized to accelerate and control the stereochemistry of Diels-Alder cycloadditions.[5] In this Communication, we report our efforts directed towards this approach which ultimately led to the serendipitous discovery of a novel Pt(IV)-catalyzed arylation to assemble the ABCD ring fragment of the kibdelones.

The synthesis of the requisite isoquinoline **8** began with condensation of homophthalic acid **10**[6] with butanoic anhydride and pyridine. Treatment of the resulting isocoumarin with methylamine in THF and dehydration afforded isoquinolinone **11**.[7] Demethylation of **11** with BBr_3 followed by oxidation with Ag_2O afforded the heterocyclic quinone **12.** To access hydroxystyrene **9**, commercially available bromovanillin **13** was demethylated with $AlCl_3$ in pyridine and selectively methylated with Li_2CO_3 and MeI in DMF [8] which was followed by silyl protection to afford aldehyde **14** (55% yield, 3 steps). Dakin oxidation of **14** with *m*-CPBA,[9] followed by hydrolysis of the intermediate formate, provided a phenol intermediate which was directly subjected to Stille coupling with vinyl tributylstannane to afford hydroxystyrene **9** (63%, 3 steps).[10]

Unfortunately, attempted thermal and catalyzed Diels-Alder cycloaddition of quinone **12** and hydroxystyrene **9** were unsuccessful, largely due to instability and decomposition of the quinone **12**. To improve the stability and handling of the AB quinone reaction partner, we targeted preparation of the corresponding quinone monoketal **16** (Scheme 3). Moreover, we reasoned that **16** may be a candidate for ionic Diels-Alder cycloaddition with styrene **9** under Lewis-acidic conditions.[11] Selective demethylation of isoquinolinone **11** with BCl_3, followed by oxidation with iodosobenzene diacetate (PIDA) in methanol, provided quinone monoketal **15** in 90% yield (2 steps). Compound **15** proved to be a suitable substrate for chlorination with catalytic triphenylphosphine (PPh_3) and *N*-chlorosuccinimide [12] enabling access to quinone monoketal **16** in 72% yield.

Initial attempts at fragment coupling of **9** and **16** using established ionic Diels-Alder conditions (*e.g.* TMSOTf in CH_3CN) did not lead to observable cycloaddition products. However, under these conditions arylation product **17** was unexpectedly isolated in 15% yield. A report by Sartori and coworkers described use of stoichiometric amounts of Et_2AlCl to afford biaryls from quinone monoketals and phenols.[13] Unfortunately latter conditions did not effect conversion of **9** and **16** to biaryl product **17**. Since the desired B-D ring connection was established *via* this unexpected coupling, we conducted an extensive screen of both Brønsted and Lewis acids to improve the yield of the transformation.[6] Following evaluation of reaction conditions, we identified Pt(IV), Au(III), and In(III) catalysts for the arylation (Table 1). $AuCl_3$ and $InCl_3$ provided modest yields (20-25%) of the biaryl product (entries 1-2). Chloroplatinic acid (H_2PtCl_6-$6H_2O$), bromoplatinic acid (H_2PtBr_6-$9H_2O$), and $PtCl_4$ (entries 3-5) provided moderate yields of arylation product **17** (25-35%). Ultimately, $PtBr_4$ was found to be optimal providing 2-vinyl biphenyl **17** in yields up to 55% on a multigram scale (Table 1). Interestingly, we also isolated by-product **18**, a dimer of the quinone-monoketal, from arylation reactions in 4-6% yield and as the sole product when $SnCl_4$ was employed as a Lewis-acid.[6] The structure of dimer **18** was determined by single X-ray crystal structure analysis [14] (Figure 2).

Additional evaluation of the $PtBr_4$ arylation conditions revealed that the presence of water was necessary for catalytic activity. [15] Kobayashi and co-workers have also reported *aza*-Michael additions of carbamates to enones catalyzed by the platinum *aqua* complex $PtCl_4$-$5H_2O$.[16] A survey of water stoichiometry using $PtBr_4$ as catalyst and freshly distilled acetonitrile revealed the optimal catalyst:water ratio to be 2:1.[6] A literature report of Pt(IV) carbohydrate complexes indicates that the pKa of water molecules complexed with platinum

metal centers can decrease by as much as 13 orders of magnitude.[17b] In addition, a crystal structure of a *cis*-diaqua-Pt(IV) complex with 18-crown-6 shows that the Pt(IV)-bound water molecules may hydrogen bond to ether oxygens.[17c]

Based on the water requirement for the reaction, we envision two possible activated quinone-monoketal intermediates as shown in Figure 3. In the first case (**B**), hydrogen bond activation of the ketal may be followed by S_N2' addition to the activated acetal.[18] In the second case (**C**), dual **π**-activation of the quinone monoketal by platinum and **σ**-activation of the quinone monoketal *via* hydrogen bonding from the platinum-aqua complex may lead to arylation.[19,20] Alternatively, Pt(IV)-aqua complexes may dissociate a water molecule and activate the ketal by direct coordination to Pt(IV).[17a] We believe the regioselectivity of the arylation is influenced by steric bulk of the TBDPS protecting group as formation of the undesired regioisomer is not observed.

With 2-vinyl biphenyl **17** in hand, we achieved the synthesis of the ABCD ring fragment *via* photoelectrocyclization[21] in cyclohexane. Silyl-deprotection of the photocyclization product afforded **19** in 61% yield (two steps) (Scheme 3). The structure of dihydrophenanthrene **19** was confirmed by single X-ray crystal structure analysis [22] (Figure 4). We also isolated the corresponding phenanthrene **20** from a gram scale photocyclization in an immersion well in 5% yield. Attempts to conduct the photocyclization of **17** in the presence of oxygen have thus far failed to produce **20** in higher yield. Analysis of molecular models of **17** revealed that the low-energy biaryl conformers are bisected.[6] Optimization of the photocyclization conditions showed higher conversions when the reaction was conducted at room temperature or above. The increased reactivity at elevated temperature may arise from overcoming the rotational barrier of biaryl **17**. [21]

To elaborate protected dihydrophenanthrene **21** to a B-ring quinone, we first attempted selective demethylation using standard conditions, (*e.g.* BBr_3, BCl_3, TMSI, and $AlCl_3$) (Scheme 4). Unfortunately, these conditions were found to be unselective, with mixtures of both B and C ring demethylated products observed. Fortunately compound **21** could be selectively acylated in aprotic solvents due to the strongly hydrogen bonded B-ring phenol. Oxidative cleavage with CAN in acetonitrile/pH 7.0 buffer followed by desilylation afforded the tetracyclic quinone **22**. Oxidation of the B *vs.* D ring was confirmed by HMBC experiments.[6] Further experiments revealed that **23** was sensitive to basic deacylation conditions. Fortunately, treatment of **23** with Otera's distannoxane catalyst[23] in toluene/methanol afforded tetracycle **23**, a compound bearing the ABCD core of kibdelone B in 85% yield. In the presence of aqueous sodium dithionite, the B ring of **23** was cleanly reduced to afford hydroquinone **24** in 90% yield, a compound analogous to the ABCD ring structure of kibdelone C **3**.

Compounds **19**, **20**, **23**, and **24** were evaluated in the NCI 60-cell screen.[24] Compounds **19** and **20** were judged to be inactive, with mean cell growth of 82% and 93% of control, respectively, at 10 μM. Compounds **23** and **24** passed the criteria for testing in dose-response format, with mean cell growths of 63% and 54%, respectively. In dose-response format, both **23** and **24** bearing the ABCD functionalities of kibdelones B and C, respectively, showed mean GI_{50} values of 4.5 μM while having no selectivity. In comparison, kibdelone C (**3**), the most potent of the natural products in the kibdelone series, had a mean GI_{50} of 2.4 nM, with 100-fold selectivity between the most and least sensitive cell lines tested. Thus, it is apparent that the contribution of the E and F rings of the kibdelone structure is highly important for cytotoxic activity.

In summary, a proposed Diels-Alder cycloaddition to construct the ABCD ring structure of the kibdelones led to the discovery of a novel Pt(IV)-mediated arylation of quinone

monoketals to produce a complex 2-vinyl biphenyl adduct. Photocycloaddition and further oxidation of this compound was used to access ABCD analogs of the kibdelones. Analogs were evaluated for initial biological activity in the NCI 60-cell screen and were found to be ~2000 times less active in comparison to kibdelones B and C, suggesting that the tetrahydroxanthone structure of the kibdelones may be crucial for cytotoxicity. Studies towards the completion of the total synthesis of the kibdelones, as well as mechanistic studies and substrate scope of the Pt(IV) arylation of quinone monoketals, is ongoing and will be reported in due course.

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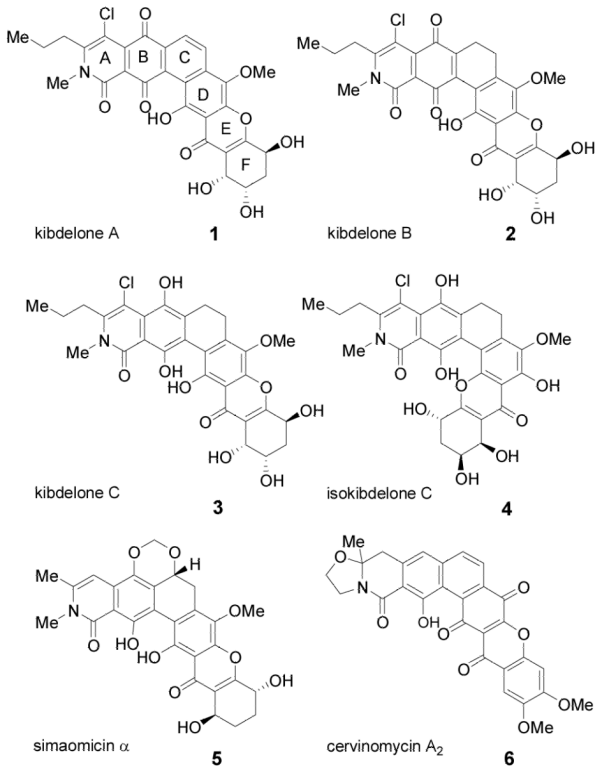


Figure 1.
Representative Polycyclic Xanthone Natural Products

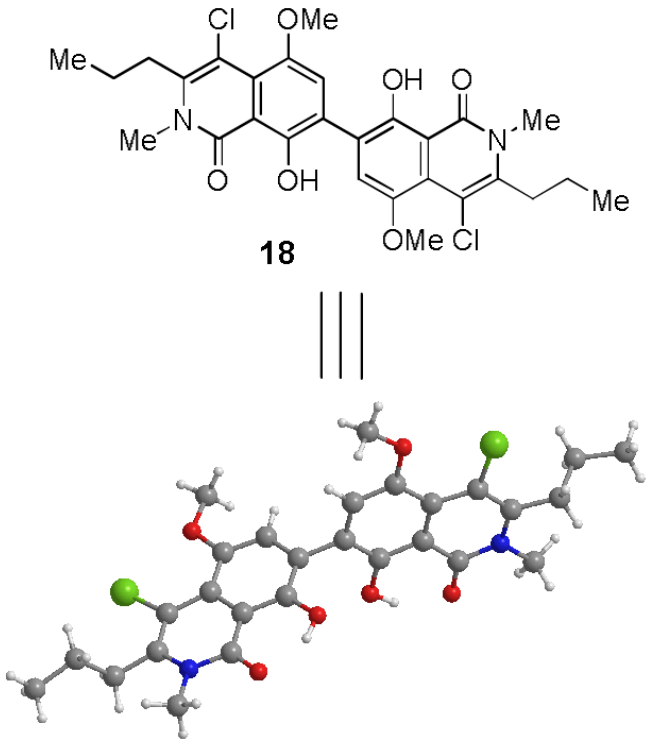


Figure 2.
X-Ray Structure of Biaryl Dimer **18**

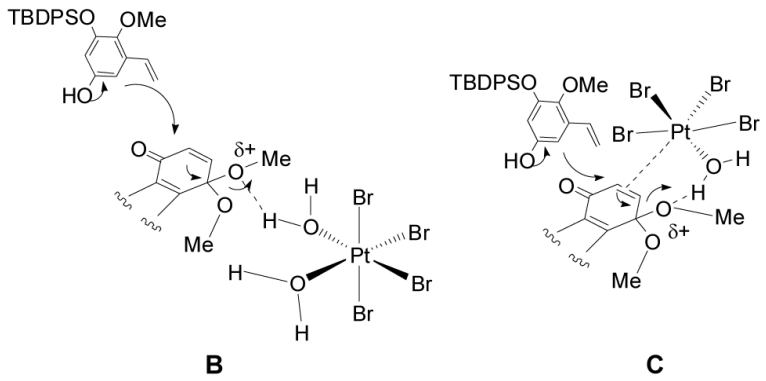


Figure 3.
Possible Active Intermediates for Pt(IV)-mediated Arylation

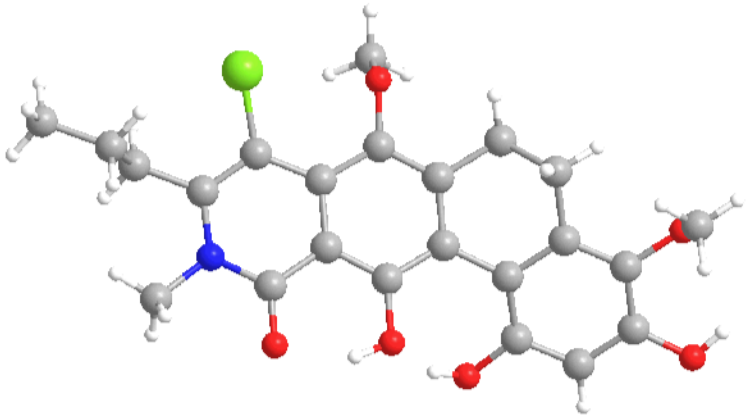
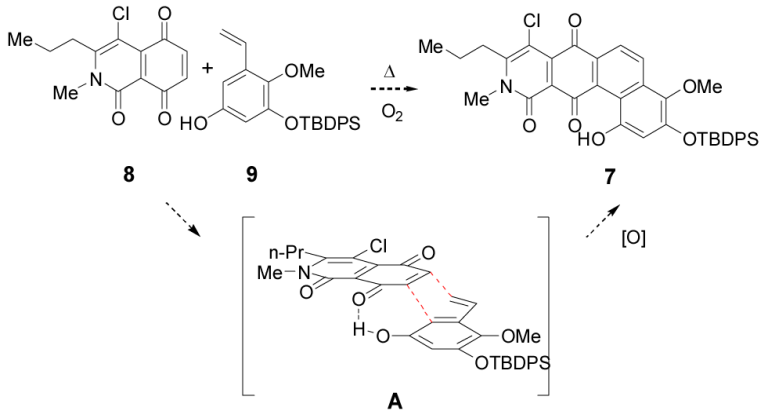
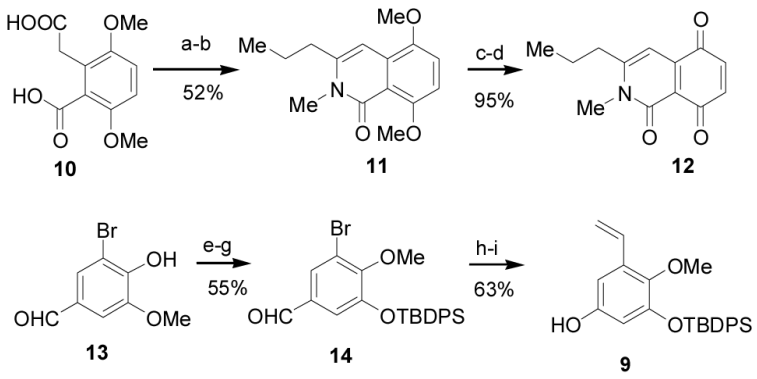


Figure 4.
X-ray crystal structure of **19**

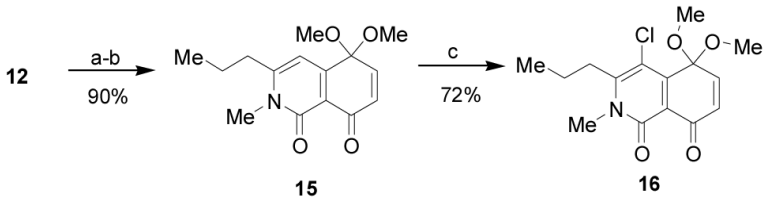


Scheme 1.
Proposed cycloaddition of heterocyclic quinone **8** and styrene **9**



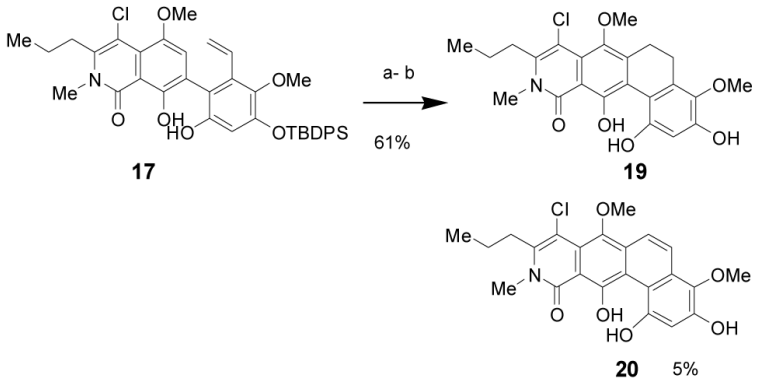
Scheme 2.

Reagents and conditions: a) 2:1 pyridine: butyric-anhydride reflux; b) 2.0M $MeNH_2$THF RT, CSA, toluene, 85 °C; c) BBr_3, THF −78 °C-rt; d) Ag_2O, $CHCl_3$; e) $AlCl_3$, pyridine, CH_2Cl_2 ; f) Li_2CO_3, MeI, DMF 45 °C; g) TBDPS-Cl, DMAP, TEA, CH_2Cl_2; h) MCPBA CH_2Cl_2, $NaHCO_3$, MeOH 0 °C; i) vinyl tributyltin, $Pd(PPh_3)_4$, toluene 85 °C. ; THF = tetrahydrofuran, CSA = camphor sulfonic acid, DMAP = 4-dimethylaminopyridine, MCPBA = *m*-chloroperoxybenzoic acid.



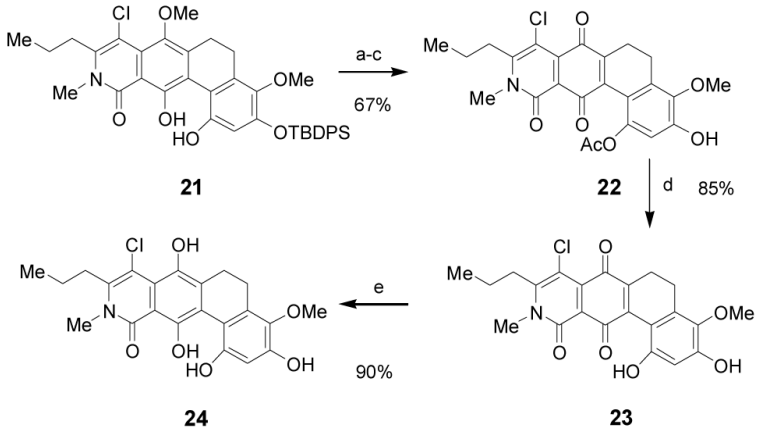
Scheme 3.

Reagents and conditions: a) BCl_3, THF −78 °C-RT b) PIDA, MeOH 0 °C-RT c) NCS, PPh_3, DMA. PIDA = Iodobenzene diacetate, NCS = *N*-chloro-succinimide, DMA =dimethylformamide.



Scheme 4.

Reagents and conditions: a) *hν* (Pyrex filter), cyclohexane; b) TBAF, THF 0 °C. TBAF = tetrabutylammonium fluoride.



Scheme 5.

Reagents and conditions: a) acetyl chloride, DIEA $CH_2Cl_2$0 °C; b) CAN, CH_3CN/ pH 7 buffer 0 °C; c) HF-pyrdine, THF 0 °C d) Otera's catalyst, 2:1 toluene:MeOH 70 °C; e) $Na_2S_2O_4$ H_2O:EtOAc. DIEA = disopropylethylamine, THF = tetrahydrofuran CAN = ceric ammonium nitrate.

Table 1

Evaluation of Conditions for Pt (IV) Arylation

Entry	Catalyst [a]	time [b]	Yield [c]
1	$AuCl_3$ (10)	6	25
2	$InCl_3$ (10)	12	27
3	H_2PtCl_6-$6H_2O$ (5)	6	23
4	H_2PtBr_6-$9H_2O$ (5)	6	25
5	$PtCl_4$* (5)	6	33
6	$PtBr_4$ * (5)	4	55

[a](mol %)

*[b]*hrs

*[c]*Isolated yield (%) All reactions run in CH3CN at 65 °C * with 10 mol % water