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Approaches to Polycyclic 1,4-Dioxygenated Xanthones. Application to Total Synthesis of the Aglycone of IB-00208

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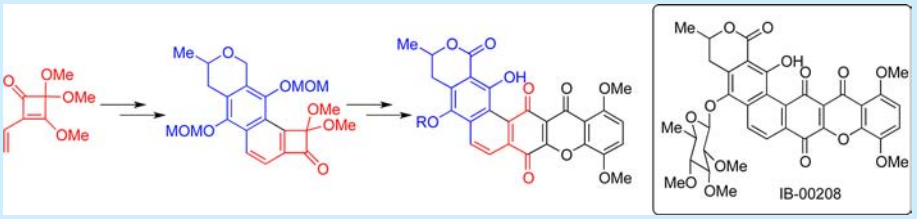
Supporting Information



ABSTRACT: Hexacyclic xanthone natural products such as IB-00208 present a formidable challenge in organic synthesis. A new approach to polycyclic 1,4-dioxygenated xanthones from benzocyclobutenones has been developed and applied to the first total synthesis of the aglycone of IB-00208. The 22-step synthesis features an acetylide stitching process that joins an aryl aldehyde with an angularly fused benzocyclobutenone, which was prepared by a ring-closing metathesis reaction. The resulting acetylenic benzocyclobutenone diol underwent a Moore rearrangement to give an intermediate that was further elaborated to the aglycone of IB-00208 as a mixture of hydroquinone−quinone tautomers.

The polycyclic, xanthone antibiotic IB-00208 (**1**) (Figure 1) was isolated by Romero and co-workers in 2003 from the culture broth of *Actinomadura* sp.[1] This novel compound exhibits potent cytotoxic activity (MIC = 1 nM) against several tumor cell lines including P388D1, A-549, HT-29, and SK-MEL-28, as well as strong antibiotic activity against several Gram-positive bacteria. The hexacyclic core of IB-00208 contains a 1,4-dioxygenated xanthone subunit and is structurally related to citreamicin α (**2**),[2] kibdelone A (**3**),[3] and cervinomycin A_2 (**4**),[4] all of which exhibit significant biological activities (Figure 1). The relative stereochemistry of the sugar moiety in IB-00208 (**1**) was established by analysis of spin−spin coupling constants and supported by NOESY experiments; however, the absolute stereochemistry at C(3) of **1** is not known.

Owing to the complex polycyclic structures and potent biological activities of **1**−**4**, there has been considerable interest in the total synthesis of these and other polycyclic xanthones,[5−7] but neither IB-00208 nor citreamicin α has yet succumbed to total synthesis. A key structural subunit embedded in many of these natural products is a 1,4-dioxygenated xanthone, which itself presents significant challenges to synthesis.[8] In the context of our interest in these and other polycyclic xanthone natural products, we recently developed a concise route to 1,4-dioxygenated xanthones that features a novel extension of the Moore cyclization,[9,10] and we now report the application of this general entry to xanthones to the first total synthesis of the aglycone of IB-00208.

Our approach to IB-00208 (**1**) is outlined in a retrosynthetic format in Scheme 1. We reasoned that the late stage intermediate **5** could be converted into **1** via benzylic oxidation,

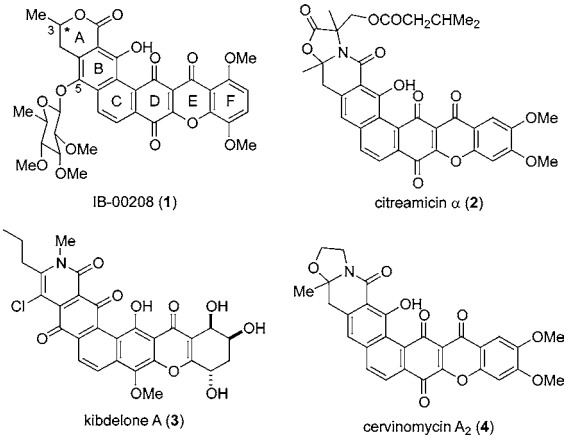


Figure 1. IB-00208 and related polycyclic, 1,4-dioxygenated xanthone-derived natural products.

quinone formation, deprotection, and stereo- and regioselective glycosylation of the sterically less encumbered phenolic group. In our original plan, we had envisioned that electrocyclic ring opening of **7** would generate the acetylenic vinyl ketene **6** in accord with the findings of Moore.[9] Simple analogs of **6** can cyclize via a radical pathway, a reaction manifold that our group leveraged in a concise total synthesis of cribrostatin 6,[11] but compound **6** is also suitably substituted to undergo cyclization via an ionic pathway to give **5** in a process inspired by a related transformation reported by Fuganti.[12] Intermediate **7** would be

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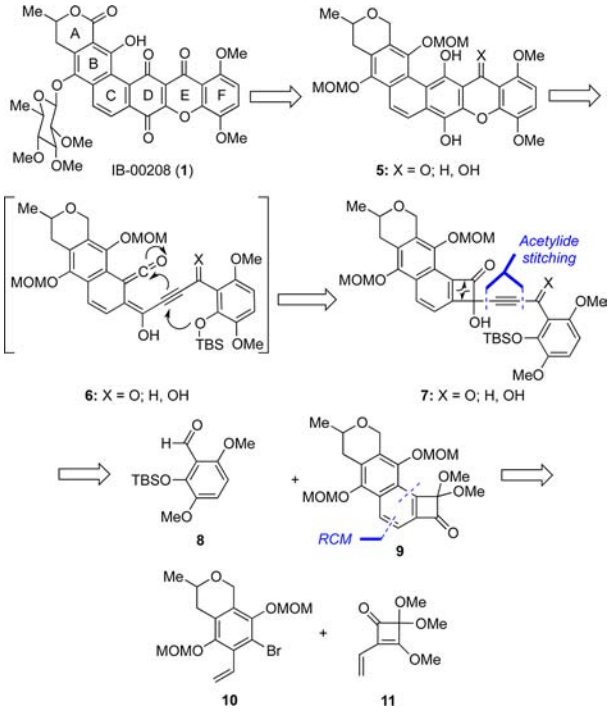
Scheme 1. Overview of Retrosynthetic Analysis of IB-00208

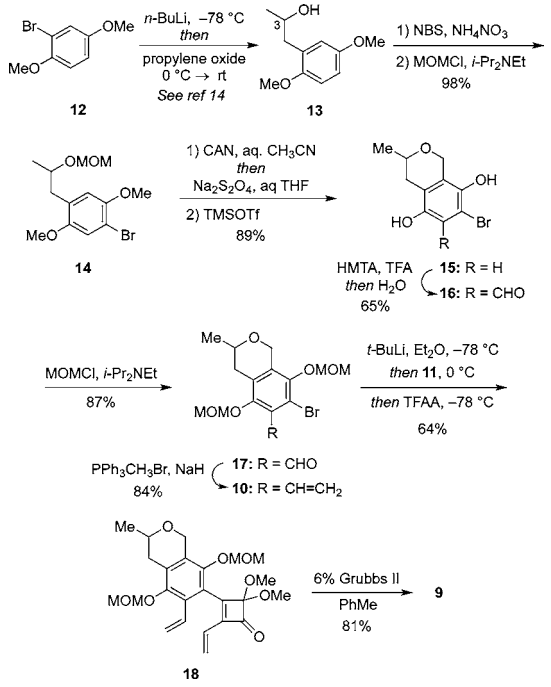


accessed by union of the aldehyde **8** and the key intermediate fused-cyclobutenone **9** by an acetylide stitching sequence. When we initiated this project, angular, polycyclic cyclobutenedione derivatives such as **9** were unknown, but we reasoned **9** might be accessible from coupling of **10** and the known vinyl squarate **11**,[13] followed by ring closing metathesis (RCM) to form the benzene ring in **9**.

Toward preparing the fused cyclobutenedione **9**, commercially available 2-bromo-1,4-dimethoxybenzene (**12**) was treated with *n*-BuLi, and the resulting aryllithium reagent was allowed to react with propylene oxide to yield the racemic secondary alcohol **13** (Scheme 2).[14] Although the absolute stereochemistry at C(3) of **1** is unknown, both enantiomers of propylene oxide are commercially available, so it is possible to prepare either enantiomer of **13**, and hence of the aglycone of **1**, via this approach. Regioselective bromination of **13** by NBS in the presence of a catalytic amount of ammonium nitrate (NH_4NO_3),[15] followed by installation of a MOM group, which served the dual roles of being a protecting group and the source of a carbon atom in the A-ring, gave **14** in excellent yield. The hydroquinone protecting groups were easily removed by a redox process, and a TMSOTf-induced oxa-Pictet–Spengler cyclization generated the dihydropyran ring of **15**.[16] A Duff reaction of **15** with hexamethylenetetramine (HMTA)[17] gave **16** in 58% overall yield from **14**. Protection of the hydroquinone moiety in **16** as its bis-MOM ether, followed by Wittig olefination, furnished **10** in 73% overall yield. The aryllithium reagent derived from **10** by metal–halogen exchange was then coupled with vinyl squarate **11** following a procedure reported by Moore[13] to give **18** in 64% yield.[18] RCM of **18** in the presence of Grubbs II catalyst afforded cyclobutenone **9** in 81% yield.

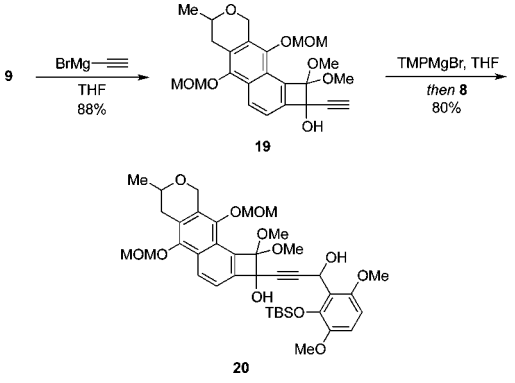
The next stage of the synthesis involved an acetylide stitching process to assemble a compound related to **7**. Accordingly, **9** was converted into propargyl alcohol **19** in 88% yield (Scheme 3). Double deprotonation of **19** using an excess of the strong,

Scheme 2. Synthesis of Cyclobutenone 9



non-nucleophilic base bromomagnesium 2,2,6,6-tetramethylpiperidide (TMPMgBr) generated a dianion that was coupled with aldehyde **8**, which was prepared via silylation[19] of the corresponding known phenol,[20] to deliver **20** in 80% yield.

Scheme 3. Preparation of 20 by Acetylide Stitching



At this juncture, the key sequence of electrocyclic ring opening and subsequent cyclizations was at hand. In model studies with an analog of **20** lacking the A-ring, we were unable to selectively oxidize the acetylenic-benzylic alcohol moiety to give a ketone. In view of this unfavorable precedent, the ketal group in **20** was removed to deliver **21** (Scheme 4), which upon heating in DMSO (0.005 M) at 100 °C gave **22** in 54% overall yield from **20**. No hexacyclic product related to **5** that would have arisen from cyclization of a putative acetylenic vinyl ketene as expected from the work of Fuganti[12] was observed under any of the conditions examined. Rather, **21** simply underwent a Moore rearrangement to give exclusively benzoquinone **22**.[9,10]

Completing the synthesis of IB-00208 (**1**) from **22** required selective oxidations of the secondary alcohol at C(15) and the methylene group at C(1) as well as cyclization to form the

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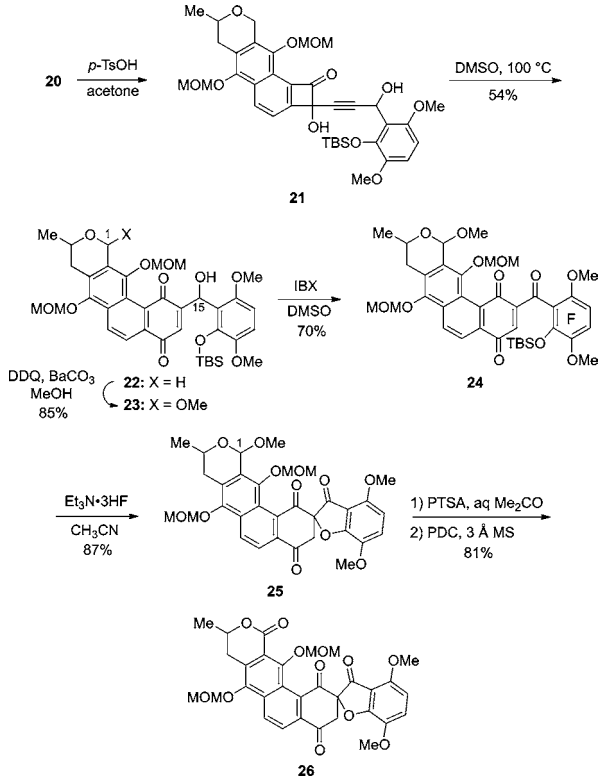
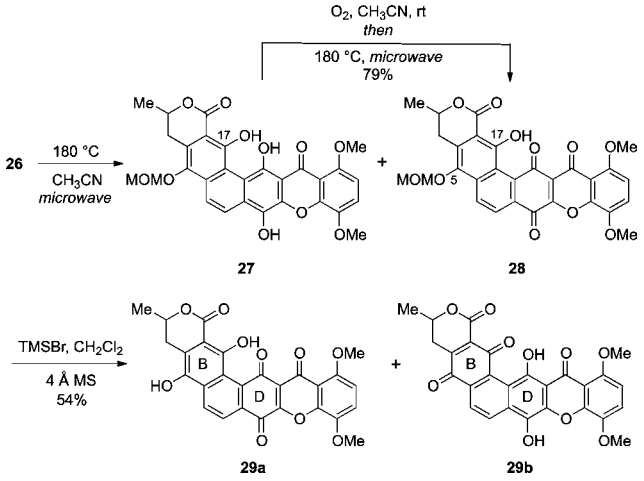
Scheme 4. Sequential Rearrangement and Cyclizations of 21



pyranone E-ring. In the event, benzylic oxidation at C(1) of **22** proceeded selectively with DDQ in the presence of MeOH[21] to produce the acetal **23** in 85% yield (Scheme 4). Oxidation of the alcohol at C(15) using IBX gave **24**, and subsequent fluoride-ion induced removal of the TBS group gave spirocycle **25** via spontaneous cyclization of the intermediate phenoxide. The regiochemical outcome of this cyclization to form a spirocyclic ring system rather than the desired 1,4-dioxygenated xanthone is consistent with previous observations from our laboratory that the substitution pattern on the F-ring of **24** governs the regioselectivity.[10] Hydrolysis of the C(1) acetal followed by oxidation of the intermediate hemiacetal with pyridinium dichromate (PDC) in the presence of 3 Å molecular sieves gave lactone **26** in 81% overall yield from **25**.[22]

We have shown that simpler spirocyclic ketones related to **26** undergo rearrangement to give xanthones,[10] so we were gratified to discover that heating **26** at 180 °C in a microwave reactor gave a mixture of hydroquinone **27** and quinone **28**, both of which lacked the phenolic MOM protecting group at C(17) (Scheme 5). Although oxidation of **27** to **28** occurred slowly upon exposure of **27** to air under ambient conditions, continued heating of a mixture of **27** and **28** in the presence of oxygen led to the exclusive formation of **28** in 79% yield from **26**. Initial attempts to remove the C(5) phenolic MOM protecting group of **28** under acidic conditions gave complex mixtures. However, reaction of **28** with freshly distilled TMSBr,[23] followed by workup and partial purification by fractional precipitation, furnished a mixture (~2:1) of compounds for which the LC-HRMS and ^{1}H NMR spectral data (see Supporting Information) are consistent with those expected for **29a**, the aglycone of **1**, and its isomer **29b**, which is produced by tautomerization of the initially formed **29a**. It was perhaps not unexpected that the hydroquinone−quinone tautomers **29a** and **29b** were obtained upon deprotection of **28**,

Scheme 5. Synthesis of the Aglycone of IB-00208 (1)



because the redox potentials of the B- and D-rings would be predicted to be similar, so **29a** and **29b** should be of comparable stability. Unfortunately, the tautomers **29a** and **29b** were somewhat prone to decomposition, so we were not able to separate or purify either of them for further characterization and elaboration.

In summary, we completed the first total synthesis of racemic **29a**, the aglycone of IB-00208 (**1**), together with its hydroquinone−quinone tautomer **29b**. The longest linear sequence in the synthesis required 22 steps from commercially available starting materials. Preparation of key intermediate **9** via an RCM reaction represented a potentially general route to polycyclic benzocyclobutenedione derivatives, and an acetylide stitching process was exploited to couple **9** with an aryl aldehyde leading to ketone **21**. Our initial plan to form the hexacyclic framework of IB-00208 by a one-pot, electrocyclic ring-opening/cyclization cascade from **21** could not be implemented, but an alternative approach was adopted successfully that led to **28**, the monoprotected aglycone of IB-00208. Deprotection of **28** gave a mixture of the tautomeric aglycones **29a** and **29b**.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, full characterization of new compounds, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) See Supporting Information for experimental details.

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