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Synthesis of the Pentacyclic Core of Citreamicin η

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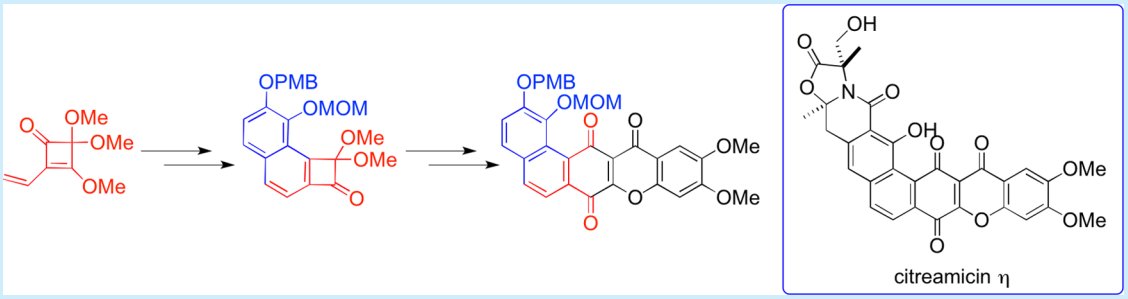
Supporting Information



ABSTRACT: The citreamicins comprise a novel class of polycyclic xanthone natural products that have not yet yielded to total synthesis. A concise 11-step synthesis of the pentacyclic core of citreamicin η is now reported that features the use of a general approach for the synthesis of 1,4-dioxygenated xanthones. The synthesis also showcases improved techniques for effecting regioselective bromination of certain substituted phenols and coupling of acetylides with hindered ketones.

The citreamicins comprise a subclass of polycyclic xanthone natural products,[1] the first member of which was isolated from a culture of *Micromonospora citrea* taken from lake Manyara in Tanzania, Africa in 1989 by Lechevalier.[1a] Additional members of this family have since been isolated and structurally characterized by Carter[1b] and others.[1c,d] Virtually all of the citreamicins display potent inhibitory activity against a spectrum of Gram-positive aerobic and anaerobic bacteria, but of particular interest is their activity toward multidrug-resistant *Staphylococcus aureus* (MDRSA) and vancomycin-resistant *Enterococcus faecalis* (VRE).[1c] Citreamicin η (**1**) is one of the most potent members of the family having a MIC of 26 nM against several Gram-positive strains of bacteria (Figure 1).[1b] In addition to their potent antibiotic activity, several citreamicins exhibit cytotoxic activity against HeLa and Hep62 cells.[1e] What distinguishes the citreamicins from other polycyclic xanthone natural products such as cervinomycin A_2 (**2**),[2] IB-00208 (**3**),[3] or kibdelone C (**4**)[4] is the dihydrooxazolo-[3,2-*b*]-isoquinolinone moiety that is embodied in the GAB ring subunit (Figure 1). Despite the potent biological activities of the citreamicin antibiotics, none has yet succumbed to synthesis. In contrast, successful total syntheses of the cervinomycins[5] and kibdelones[6] have been reported, and we recently disclosed the synthesis of the aglycone of IB-00208 (**3**).[7] Synthetic efforts directed toward a number of other polycyclic xanthones have also been described.[8]

We have had an ongoing interest in developing a general strategy for the synthesis of polycyclic xanthone natural products, so the potent biological activity and the structural complexity of citreamicin η (**1**) captured our attention. Drawing upon our experience in inventing a novel approach to 1,4-dioxygenated xanthones that we applied to the synthesis of IB-00208 aglycone,[7,9] we developed a plan for preparing

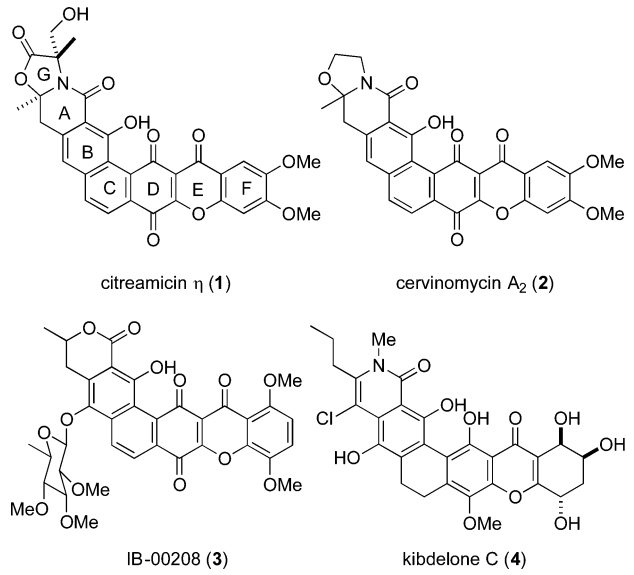


Figure 1. Polycyclic xanthone natural products.

citreamicin η (**1**) that is outlined in retrosynthetic format in Scheme 1. We envisioned final assembly of **1** by a late-stage annelation of the G and A rings onto the hexacyclic precursor **5** by a thermodynamically controlled, diastereoselective condensation with (*S*)-α-methylserine.[10] Formation of **5** from **6** requires a cross-coupling to introduce the ester group and the introduction of an *ortho*-acetonyl group. Compound **6** can be

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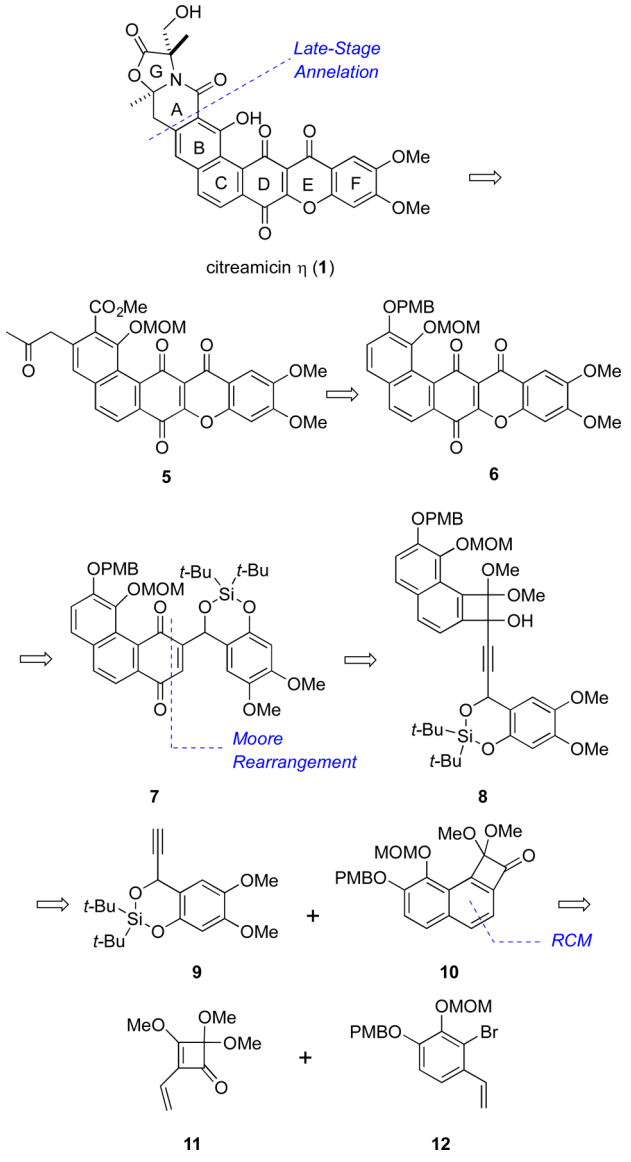
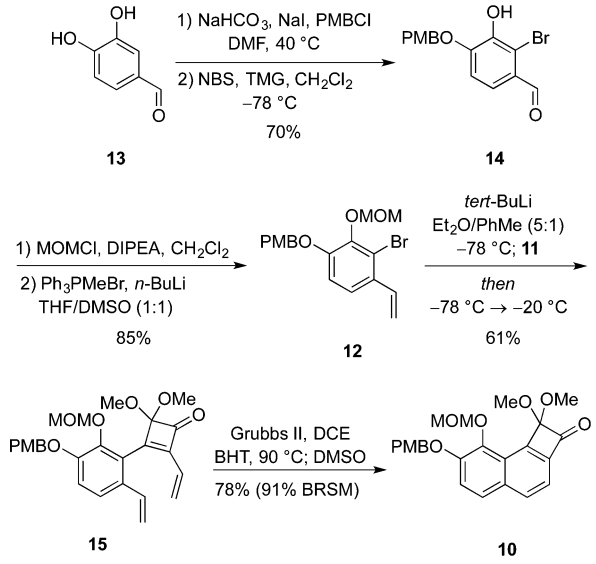
Scheme 1. Retrosynthetic Analysis of Citreamicin *η*



formed from the quinone **7** via an oxidation/cyclization cascade, whereas generation of **7** features a Moore rearrangement of **8**,[11] which is the product of the union of the acetylide **9** and the naphthocyclobutenone **10**. The synthesis of **10** would then require the coupling of bromostyrene **12** with the known vinyl squarate **11** followed by a ring closing metathesis (RCM) that creates the arene ring.

The initial stage of the synthesis involved preparation of the napthocyclobutenone **10**. Accordingly, the C4 phenolic moiety in 4,5-dihydroxybenzaldehyde (**13**) was first selectively protected as its *p*-methoxybenzyl (PMB) ether,[12] followed by an amine-mediated, regioselective bromination *ortho* to the phenol at the 6-position to furnish **14** in 70% overall yield (Scheme 2).[13] The bromination step proved somewhat troublesome as use of *tert*-$BuNH_2$[13b] or $(i\text{-Bu})_2NH$[13a] with a variety of brominating agents and solvents provided mixtures of 6- and 3-brominated products. Inasmuch as a *N*-bromoamine is arguably the putative brominating agent in these reactions, we hypothesized that the identity of the amine might have a profound effect on the selectivity of the reaction. We thus screened a series of amines and sources of electrophilic bromine

Scheme 2. Synthesis of Cyclobutanone 10

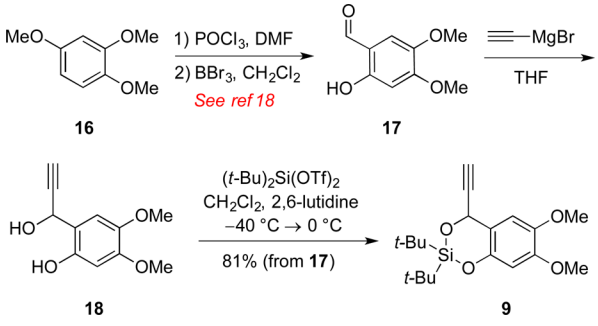


and discovered that the combination of tetramethylguanidine (TMG) and *N*-bromosuccinimide (NBS) served admirably to furnish **14** in 84% yield with >20:1 selectivity on multigram scale. Protection of the C5 phenolic hydroxy group as a methoxymethyl (MOM) ether followed by a Wittig olefination provided bromostyrene **12** in 85% yield for the two steps.[14]

Initial attempts to effect the addition of the aryllithium reagent derived from the metal−halogen exchange of **12** to the vinyl squarate **11** led primarily to debrominated **12**. However, performing the metal−halogen exchange in an empirically determined mixture of Et_2O and toluene (5:1), followed by adding **11** at −78 °C and rapidly warming the reaction mixture to −20 °C, suppressed the various side reactions and led to the isolation of **15** in 61% yield. Although trifluoroacetic anhydride (TFAA) or $BF_3{\cdot}Et_2O$ are often used to promote elimination of the intermediate adduct to form the cyclobutenone moiety,[15] the transformation of **12** to **15** required no such acidic quenches. In analogy with a similar transformation developed during our synthesis of IB-00208, we found that heating **15** in degassed dichloroethane in the presence of Grubbs II catalyst delivered the napthocyclobutenone **10** in 78% (91% BRSM) yield.[16,17]

With **10** in hand, the next task was the synthesis of the acetylene **9**. In the event, 1,2,5-trimethoxybenzene (**16**) was converted to the known aldehyde **17** via a literature procedure involving Vilsmeier−Hack formylation, followed by selective *O*-demethylation with BBr_3 (Scheme 3).[18] Addition of ethynyl

Scheme 3. Synthesis of Acetylide 9



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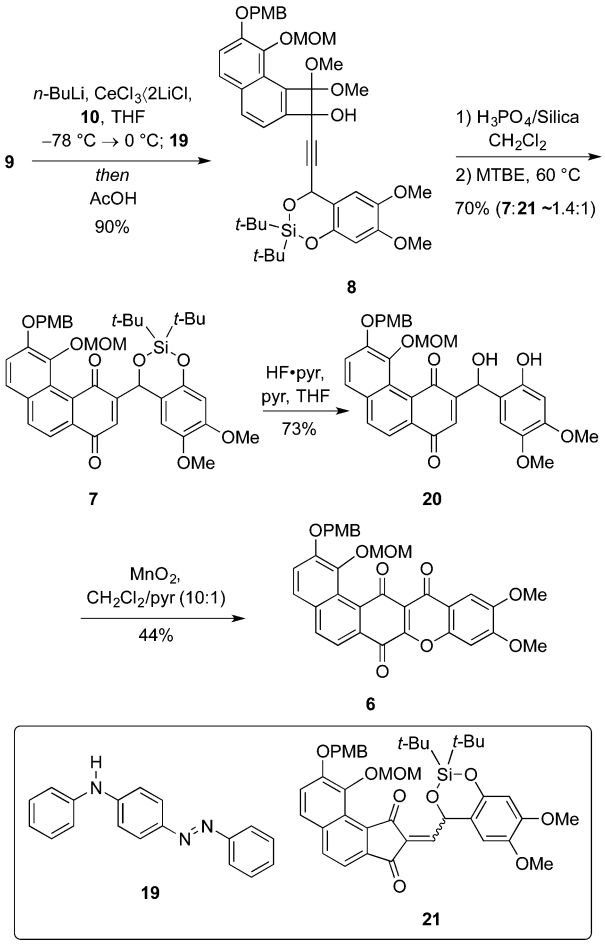
magnesium bromide to **17** furnished the benzyl alcohol **18**, which was prone to various decomposition pathways in the presence of acids or by heating, so it was immediately converted to the stable cyclic silyl ether **9** in 81% yield from **16**.[9b]

Initial attempts to couple acetylide **9** with **10** using tetramethylpiperidine magnesium bromide (TMPMgBr) as a base to deprotonate **9** as previously developed for our synthesis of IB-00208 aglycone provided **8** in only 30−40% yield (Scheme 4).[7] Use of a number of other Li, Na, or K bases also

Scheme 4. Coupling and Completion of the Pentacyclic Core



provided **8** in low yields. The cerium acetylide that was generated from the addition of *n*-BuLi to a mixture of **8** and $CeCl_3 \cdot 2LiCl$[19] reacted cleanly with **10**, but adventitious proton sources necessitated the use of excess base and **9**, which produced either the *n*-butyl adduct of **10** or incomplete conversion. In part to address problematic experimental situations such as this, we recently developed 4-(phenylazo)-diphenylamine (PDA) (**19**) as a universal indicator to titrate a variety of strong bases.[20] PDA served admirably as an internal indicator and allowed us to easily generate the cerium acetylide of **9** stoichiometrically *in situ*. Indeed, using this technique to avoid excess amounts of *n*-BuLi enabled us to produce **8** in 90% yield on gram scales.[21] Although conditions (*p*-TsOH, acetone) we had previously used to hydrolyze the dimethyl acetal moiety in compounds related to **8** were unsuccessful,[22] we discovered that transformation of **8** to the corresponding ketone occurred smoothly with H_3PO_4-impregnated silica.[23] Preliminary experiments to effect the Moore rearrangement of this intermediate naphthocyclobutenone provided mixtures (1:1) of the desired quinone **7** and the side product **21** in low yields. Formation of compounds such as **21** by Moore rearrangements are known,[11] but we had not previously isolated such compounds in significant quantities, so this outcome came as a surprise. Toward enhancing the combined yield and favor **7** over **21**, a variety of solvents were screened for the Moore rearrangement, and we found that degassed methyl *tert*-butylether (MTBE) furnished a separable mixture (ca. 1.4:1) of **7** and **21** in an average of 41% and 29% yields, respectively. Deprotection of the cyclic silyl ether moiety of **7** with HF·pyridine buffered with additional amounts of pyridine then provided **20** in 73% yield. The transformation of **20** to **6** proved difficult because **20** was unstable to acids and bases, and based upon evidence from LCMS data, **20** seemed to oligomerize in the presence of a variety of oxidants. We eventually discovered MnO_2 that had been "tamed" with pyridine to "poison" the active sites on the solid MnO_2 was a suitable oxidant.[24] In the event, treating **20** with MnO_2 in a mixture (10:1) of CH_2Cl_2 and pyridine provided **6** in 44% yield, thereby completing the synthesis of the pentacyclic core substructure of citreamicin η.

In summary, we have completed a short 11-step synthesis of the pentacyclic core of citreamicin η. The route, which was inspired by our previous methodological work[9] and our synthesis of the aglycone of IB-00208,[7] features a novel application of the Moore rearrangement followed by a cyclization of the intermediate quinone to form the xanthone ring subunit of the natural product. We again exemplified our previous approach for the synthesis of angular naphthocyclobutendione derivatives by the RCM of styryl cyclobutenones such as **15**. The discovery that TMG enhances the selectivity in the amine-promoted *ortho*-bromination of phenols with NBS may prove to be generally useful. We also showed that PDA can be exploited as an internal indicator to enable the quantitative generation of cerium acetylides uncontaminated with excess nucleophilic bases. Current efforts toward the annelation of the GA rings onto **6** are underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03760.

Complete experimental procedures, full characterization of new compounds, and copies of ^1H and ^{13}C spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Citreamicin α (originally called LL-E19085α): Maiese, W. M.; Lechevalier, M. P.; Lechevalier, H. A.; Korshalla, J.; Goodman, J.; Wildey, M. J.; Kuck, N.; Greenstein, M. *J. Antibiot.* **1989**, *42*, 846−851. (b) Citreamicins β, γ, ζ, and η: Carter, G.; Nietsche, J. A.; Williams, D. R.; Borders, D. B. *J. Antibiot.* **1990**, *43*, 504−512. (c) Citreamicins δ and ε: Hopp, D. C.; Milanowski, D. J.; Rhea, J.; Jacobsen, D.; Rabenstein, J.; Smith, C.; Romari, K.; Clarke, M.; Francis, L.; Irigoyen, M.; Luche, M.; Carr, G. J.; Mocek, U. *J. Nat. Prod.* **2008**, *71*, 2032−2035. (d) Neocitreamicins I and II: Peoples, A. J.; Zhang, Q.; Millett, W.; Rothfeder, P. M. T.; Pescatore, B. C.; Madden, A. A.; Ling, L. L.; Moore, C. M. *J. Antibiot.* **2008**, *61*, 457−463. (e) Citreamicins ε and B: Liu, L.-L.; He, L.-S.; Xu, Y.; Han, Z.; Li, Y.-X.; Zhong, J.-L.; Guo, X.-R.; Zhang, X.-X.; Ko, K. M.; Qian, P.-Y. *Chem. Res. Toxicol.* **2013**, *26*, 1055−1063.

(2) (a) Omura, S.; Iwai, U.; Hinotozawa, K.; Takahashi, O.; Kato, J.; Nakagawa, A. *J. Antibiot.* **1982**, *35*, 645−652. (b) Omura, S.; Nakagawa, A. *J. Am. Chem. Soc.* **1986**, *108*, 6088−6089.

(3) Malet-Cascon, L.; Romero, F.; Espliego-Vazquez, F.; Gravalos, D.; Fernandez-Puentes, J. L. *J. Antibiot.* **2003**, *56*, 219−225.

(4) (a) Ratnayake, R.; Lacey, E.; Tennant, S.; Gill, J. H.; Capon, R. J. *Chem. - Eur. J.* **2007**, *13*, 1610−1619. (b) Ratnayake, R.; Lacey, E.; Tennant, S.; Gill, J. H.; Capon, R. J. *Org. Lett.* **2006**, *8*, 5267−5270.

(5) For synthesis of the cervinomycins, see: (a) Kelly, T. R.; Jagoe, C. T.; Li, Q. *J. Am. Chem. Soc.* **1989**, *111*, 4522−4524. (b) Rao, A. V. R.; Yadav, J. S.; Reddy, K. K.; Upender, V. *Tetrahedron Lett.* **1991**, *32*, 5199−5202. (c) Mehta, G.; Shah, S. R.; Venkateswarlu, Y. *Tetrahedron* **1994**, *50*, 11729−11742. (d) Yadav, J. S. *Pure Appl. Chem.* **1993**, *65*, 1349−1356. Partial work: (e) Rao, A. V. R.; Reddy, K. K.; Yadav, J. S.; Singh, A. K. *Tetrahedron Lett.* **1988**, *29*, 3991−3992. (f) Mehta, G.; Shah, S. R. *Tetrahedron Lett.* **1991**, *32*, 5195−5198.

(6) For synthesis of the kibdelones, see: (a) Butler, J. R.; Wang, C.; Bian, J.; Ready, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 9956−9959. (b) Sloman, D. L.; Bacon, J. W.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2011**, *133*, 9952−9955. (c) Winter, D. K.; Endoma-Arias, M. A.; Hudlicky, T.; Beutler, J. A.; Porco, J. A., Jr. *J. Org. Chem.* **2013**, *78*, 7617−7626. Partial work: (d) Sloman, D. L.; Mitasev, B.; Scully, S. S.; Beutler, J. A.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 2511−2515. (e) Endoma-Arias, M. A.; Hudlicky, T. *Tetrahedron Lett.* **2011**, *52*, 6632−6634.

(7) Yang, J.; Knueppel, D.; Cheng, B.; Mans, D.; Martin, S. F. *Org. Lett.* **2015**, *17*, 114−117. Knueppel, D.; Yang, J.; Cheng, B.; Mans, D.; Martin, S. F. *Tetrahedron* **2015**, *71*, 5741−5757.

(8) For synthetic work on other polycyclic xanthones, see: (a) (−)-Simaomicin α: Wang, Y.; Wang, C.; Butler, J. R.; Ready, J. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 10796−10799. (b) FD-594 Aglycon: Masuo, R.; Ohmori, K.; Hintermann, L.; Yoshida, S.; Suzuki, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3462−3465. (c) Studies toward lysolipin I: Duthaler, R. O.; Wegmann, U. H.-U. *Helv. Chim. Acta* **1984**, *67*, 1755−1766. (d) Duthaler, R. O.; Scherrer, V. *Helv. Chim. Acta* **1984**, *67*, 1767−1775. (e) Duthaler, R. O.; Mathies, P.; Petter, W.; Heuberger, C.; Scherrer, V. *Helv. Chim. Acta* **1984**, *67*, 1217−1221. (f) Duthaler, R. O.; Heuberger, C.; Wegmann, U. H.-U.; Scherrer, V. *Chimia.* **1985**, *39*, 174−182. (g) Studies toward Sch 56036: Walker, E. R.; Leung, S. Y.; Barrett, A. G. M. *Tetrahedron Lett.* **2005**, *46*, 6537−6540.

(9) (a) Nichols, A. L.; Zhang, P.; Martin, S. F. *Org. Lett.* **2011**, *13*, 4696−4699. (b) Nichols, A. L.; Zhang, P.; Martin, S. F. *Tetrahedron* **2012**, *68*, 7591−7597.

(10) For an example of a similar condensation, see: Hosokawa, S.; Fumiyama, H.; Fukuda, H.; Fukuda, T.; Seki, M.; Tatsuta, K. *Tetrahedron Lett.* **2007**, *48*, 7305−7308.

(11) (a) Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392−3393. (b) Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975−989.

(12) Plourde, G. L.; Spaetzel, R. R. *Molecules* **2002**, *7*, 697−705.

(13) (a) Fujisaki, S.; Eguchi, H.; Omura, A.; Okamoto, A.; Nishida, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1576−1579. (b) Pearson, D. E.; Wysong, R. D.; Breder, C. V. *J. Org. Chem.* **1967**, *32*, 2358−2360.

(14) The addition of DMSO as a cosolvent suppressed undesired Cannizzaro side reactions. See: Gupta, A. K. S. *Tetrahedron Lett.* **1968**, *9*, 5205−5206.

(15) Gayo, L. M.; Winters, M. P.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 6896−6899.

(16) DMSO was used to aid in the removal of Ru from the product. See: Ahn, Y. M.; Yang, K. L.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411−1413.

(17) BHT was found to improve the yield and prevent decomposition of the starting material under the reaction conditions. For the effect of phenols on olefin metathesis, see: Forman, G. S.; McConnell, A. E.; Tooze, R. P.; Janse van Rensburg, W.; Meyer, W. H.; Kirk, M. M.; Dwyer, C. L.; Serfontein, D. W. *Organometallics* **2005**, *24*, 4528−4542.

(18) (a) Lin, Y.-L.; Wu, C.-S.; Lin, S.-W.; Huang, J.-L.; Sun, Y.-S.; Yang, D.-Y. *Bioorg. Med. Chem.* **2002**, *10*, 685−690. (b) Marion, F.; Williams, D. E.; Patrick, B. O.; Hollander, I.; Mallon, R.; Kim, S. C.; Roll, D. M.; Feldberg, L.; Van Soest, R.; Andersen, R. J. *Org. Lett.* **2006**, *8*, 321−324.

(19) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 497−500.

(20) Blumberg, S.; Martin, S. F. *Tetrahedron Lett.* **2015**, *56*, 3674−3678.

(21) AcOH quench was necessary to prevent the formation of ring-opened material. See also ref 9b.

(22) Using a cyclic silyl ether to simultaneously protect both the phenol and benzyl alcohol groups of **8** was essential to prevent acid-catalyzed ionization of the benzylic alcohol moiety. Other protecting group strategies such as those previously employed in our synthesis of the aglycone of IB-00208 (see ref 7) were ineffective.

(23) Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, *1978*, 63−65.

(24) Lewis bases as well as water and polar aprotic solvents such as DMF and acetone are also known to modulate the activity of MnO_2. For a review see: Fatiadi, A. J. *Synthesis* **1976**, *1976*, 65−104.

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Org. Lett. XXXX, XXX, XXX−XXX