Published in final edited form as:

Tetrahedron Lett. 2012 March 14; 53(11): 1345–1346. doi:10.1016/j.tetlet.2011.12.126.

Cascade assembly of the benzo[a]anthraquinone ring system common to the angucycline antibiotics

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Abstract

A benzo[a]anthraquinone ring system, common to a group of angucycline antibiotics, has been prepared by a unique cascade of reactions. The reaction sequence was initiated by a Suzuki-Miyaura cross-coupling between a bromoquinone and vinyl boronic anhydride. The reaction product is proposed to undergo a 6π -electron cyclization triggered by reductive activation of the quinone. The reaction process is proposed to be autocatalytic.

Keywords

Cascade reaction; Quinone; Electrocyclization; Suzuki-Miyaura coupling; Reductive activation

The structural feature common to the angucycline antibiotics is a benz[a]anthraquinone aglycone that varies in oxidation state within the AB ring sub-structure (Figure 1).¹ Since the identification tetrangomycin in 1965 a large number of angucycline metabolites have been identified with associated biological activity ranging from antitumor to antifungal. These discoveries have stimulated interest in the total synthesis of this sub-class of aromatic polyketide natural products.² The Diels-Alder and Hauser type annulations have figured prominently among synthetic strategies leading to the chemical synthesis of a variety of angucyclinones. Moore^{3a-c} and others^{3d-f} have employed a cascade of pericyclic reactions starting from benzocyclobutenes to construct the central quinone (C ring) in order to complete benzoanthraquinone ring assembly (**1**, **2**, Scheme 1). In the course of studies on aromatic polyketides unrelated to the angucyclines we have uncovered a new route to access the angucycline ring system by apparent rearrangement of vinyl quinone **4** to construct the corner B ring. The synthesis of quinone **4** required access to uniquely functionalized protected hydroquinone **3**. Herein, we detail the results of this serendipitous discovery and a brief discussion of mechanistic implications of the key rearrangement.

Our synthetic studies started from dibromonaphthazarin **6** prepared by the Brazzard annulation reaction.⁴ Reduction of quinone **6** to the corresponding dihydroquinone was followed by immediate phenol protection with MOMCl using Adogen 464 as a phase-transfer reagent.⁵ At this point we required a bromine exchange resulting in

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Supplementary Material

Supplementary data associated with this article can be found in the online version, at doi:XXXXX.

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desymmetrization of dibromide **7**. The required metalation relied upon an initial lithium-halogen exchange that under standard conditions provided a mixture of distannane **9** and proton quenched products **10** and **11**. A solution to this undesired reaction outcome was found in a publication by Yoshida and co-workers^{6a} who studied the mono lithium-halogen using 1,2-dibromobenzene.⁶ Yoshida's studies indicated a rapid quench with stannyl chloride was critical to the success of the reaction. Indeed, when addition of n-butyllithium to dibromide **7** was followed by the addition of trimethylstannyl chloride after 50 seconds we were gratified to isolate bromostannane **8** in a reproducible 80–85% yield.

Stille cross-coupling of bromostannane **8** with 2-iodocyclohexenone proceeded smoothly using reaction conditions reported by Porco in his synthesis of (–)-kinamycin C.⁷ Oxidation of MOM protected dihydroquinone **13** with CAN in acetonitrile led to bromoquinone **14** now activated to engage in a Suzuki-Miyaura cross-coupling. In the event reaction of **14** with vinyl boronic anhydride did not lead to the expected vinyl quinone but unexpectedly angular quinone **16** (29%). When the coupling was carried out with vinyl boronate **15** quinone **17** was produced in 48% yield.

The cross-coupling of **14** with vinyl boronic anhydride likely delivers vinyl quinone **18a**, less clear is the pathway by which **18a** proceeds to the observed product quinone **16**. The most direct pathway proceeds by way of a 6 π -electrocyclic ring closure to **19** followed by isomerization to hydroquinone **20** followed by oxidation to **16**. However, the pericyclic rearrangement of **18a** to **19** would likely be a high-energy transformation requiring a reaction temperature significantly higher than observed.⁸ An alternate explanation would be anion-accelerated process by way of either semiquinone **18b** or two-electron reduction product **18c**.⁹ Interestingly, many quinone containing natural products including mitomycin, dynemycin and anthracyclines utilize quinone reductive activation to trigger chemical transformations leading to reactive intermediates poised to modify biomolecules such as DNA.¹⁰ When accompanied by subsequent oxidation rearrangement of **18b/18c** leads to dihydroquinone **20** by way of quinone **19**. Finally, oxidation of **20** would account for the observed production of angular quinone **16**. The final oxidation of **20** could be achieved by conversion of quinone **18a** to dihydroquinone **18c**. Overall, the proposed reaction pathway shown in Scheme 4 is reductive rendering the process autocatalytic.¹¹

In conclusion, we have discovered a new synthetic route to access the core tetracyclic structure common to members of the angucycline group of antibiotics. Interestingly, this transformation may take advantage of quinone reduction as a means of reaction acceleration, and when combined with a final oxidation step constitutes an autocatalytic process.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by the National Institutes of Health (CA 059515) and the Vanderbilt Institute of Chemical Biology. We also acknowledge Dr. Weidong Zhang for early studies on the conversion of dibromide **7** to arylstannane **8**.

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Figure 1.
Select angucycline antibiotics.

Scheme 1.
Pericyclic reactions leading to benz[a]anthraquinone core.

Scheme 2.
Desymmetrization of dibromonaphthazarin.

Scheme 3.
Preparation of benz[a]anthraquinone.

Scheme 4.
Proposed reaction pathway from **18** to **16**.