

Synthesis of the Benz[*a*]anthraquinone Core of Angucyclinone Antibiotics

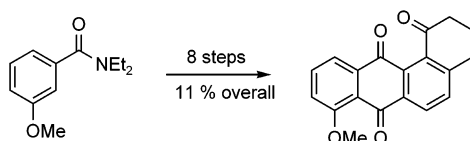
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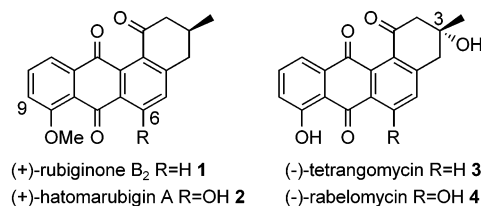
ABSTRACT



A general method for the synthesis of benz[*a*]anthraquinones is reported. The key step is a catalytic cobalt-mediated [2+2+2]-cycloaddition of a triyne, which affords an angularly substituted tetracycle. Oxidation of this core gives the typical structure of angucyclinone antibiotics.

The angucyclines are a large class of antibiotics isolated from several strains of *Streptomyces*. They display a broad spectrum of biological properties including antiviral, antifungal, antitumor, and enzyme inhibitor activity.¹ Most of these antibiotics feature a unique benz[*a*]anthraquinone structure either with or without a 9-*C*-glycosidic moiety. Members of this class of angucyclines without a glycosidic moiety, the angucyclinones, have the benz[*a*]anthraquinone structure either without a hydroxy group at C-6 such as (+)-rubiginone B₂ **1**² or with a hydroxy group at C-6 such as (+)-hatomarubigin A **2**.³ Some members of this class feature a tertiary hydroxy group at C-3 such as (–)-tetrangomycin **3**⁴ and (–)-rabelomycin **4**.⁵

Most general strategies for the construction of the angucyclinone framework are based on Diels–Alder reaction of a naphthoquinone with a vinylcyclohexene⁶ or on biomimetic-type reactions⁷ by employing polyketide condensations.



Herein we would like to present the first synthesis of the benz[*a*]anthraquinone structure of the angucyclinone antibiotics via an intramolecular cobalt-mediated [2+2+2]-cycloaddition⁸ of a triyne. The cyclization of triynes is a powerful synthetic method to form several carbon–carbon bonds in one step and provides access to polycyclic systems with a newly formed highly substituted benzene nucleus. We were able to synthesize a triyne-precursor **11** (Scheme 1) which, after cobalt-mediated [2+2+2]-cycloaddition, gave the anthracene structure **13** (Scheme 2).⁹ Cyclization experiments with RhCl(PPh₃)₃ and RuCl₂(=CHPh)(PCy₃)₂, which

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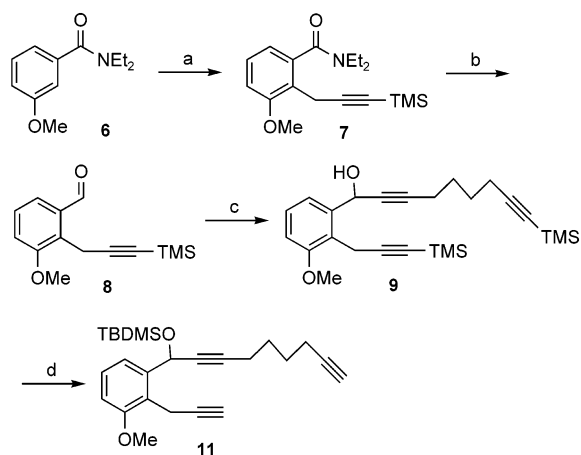
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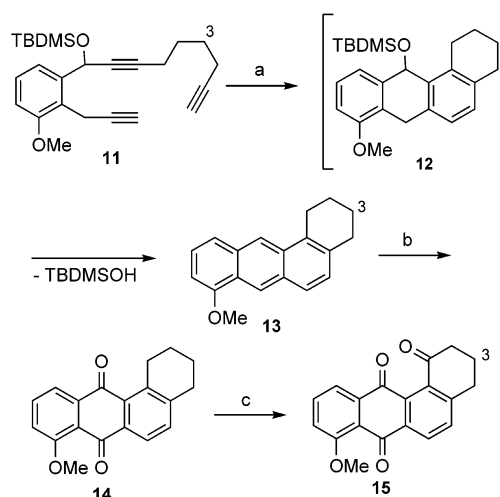
Scheme 1^a

^a Reagents and conditions: (a) (i) *s*-BuLi/TMEDA, THF, -80°C , 1 h, (ii) ZnCl_2 , -80°C , 1 h, (iii) $\text{CuCN}\cdot 2\text{LiCl}$, -80°C , 1 h, (iv) (3-bromoprop-1-ynyl)trimethylsilane **5**, -80°C to room temperature (85%). (b) DIBAL/BuLi, THF, 25°C , 18 h (68%). (c) BuLi/1-TMS-1,7-octadiyne, THF (82%). (d) (i) $\text{NH}_4\text{F}/\text{Bu}_4\text{NHSO}_4$, CH_2Cl_2 , 48 h, (ii) TBDMSOTf, 2,6-lutidine, CH_2Cl_2 , 25°C , 2 h (95%).

can also promote alkyne trimerization,¹⁰ were not successful in our systems. Two-step oxidation of **13** led then to the angucyclinone core **15**.

The amide **6**¹¹ was at first selectively ortho-lithiated with *s*-BuLi/TMEDA.^{12b} It was then transmetalated with ZnCl_2 and then $\text{CuCN}\cdot 2\text{LiCl}$ and allowed to react with (3-bromoprop-1-ynyl)trimethylsilane **5** to give the propynylamide **7**.^{12c} This was directly reduced to benzaldehyde **8** with the DIBAL/BuLi complex.¹³ After addition of lithiated 1-TMS-1,7-octadiyne¹⁴ to this aldehyde, the triple bonds of the resulting triene **9** were deprotected with NH_4F ¹⁵ (deprotection with TBAF in THF led to decomposition of the triene **9**). The hydroxy group was then transformed into its silyl ether **11** with the aid of TBDMSOTf.¹⁶

For the cyclization of **11** we used $\text{CpCo}(\text{ethene})_2$ ¹⁷ and the commercially available $\text{CpCo}(\text{CO})_2$. Reaction of **11** with 5% $\text{CpCo}(\text{ethene})_2$ succeeded under mild conditions at low temperature. Surprisingly we observed the loss of the TBDMSO-group with concomitant aromatization to the

Scheme 2^a

^a Reagents and conditions: (a) 5% $\text{CpCo}(\text{ethene})_2$, Et_2O , -80°C to room temperature, 18 h, or 5% $\text{CpCo}(\text{CO})_2$, toluene, reflux, $h\nu$, 4 h (66%). (b) 8 equiv of $[\text{Ag}(\text{Py})_2]\text{MnO}_4$, CH_2Cl_2 , 25°C , 18 h (63%). (c) $h\nu$, air, CHCl_3 , 25°C , 18 h (61%).

anthracene **13** (55% yield and 16% isolated starting material). In the case of $\text{CpCo}(\text{CO})_2$ the reaction had been carried out in toluene under reflux and irradiation with a tungsten lamp (66% yield). Oxidation of **13** with the aid of the mild reagent $[\text{Ag}(\text{Py})_2]\text{MnO}_4$ gave the anthraquinone **14** (63% yield).¹⁸ We have also been trying to oxidize with CrO_3 in AcOH, but these conditions led to decomposition of the anthracene. The introduction of the C-1 carbonyl was achieved by photooxidation, a general method for the angucyclinones developed by Krohn.¹⁹ Exposure of **14** to visible light (tungsten lamp) gave the typical structure **15** of the angucyclinone antibiotics (61% yield).

In conclusion, the angucyclinone framework **15** was synthesized from benzamide **6** in 8 steps and 11% yield overall. This method provides a new access toward the angucyclinone antibiotics, which do not have a hydroxy group at C-6. The stereocenter at C-3 is not involved in the [2+2+2]-cycloaddition, therefore this methodology offers a good strategy for the enantioselective synthesis of this class of antibiotics.

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Supporting Information Available: Experimental procedures and analytical data for all compounds, ^1H NMR and ^{13}C NMR spectra for **13**, **14**, and **15**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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