ORGANIC LETTERS

2003
Vol. 5, No. 6
843−844

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

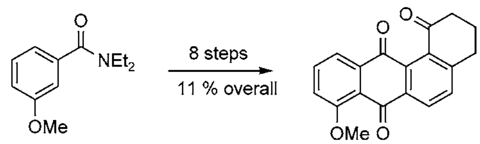
Aris Kalogerakis and Ulrich Groth*

Fachbereich Chemie, Universität Konstanz, Fach M-720, Universitaetsstrasse 10, 78457 Konstanz, Germany

ulrich.groth@uni-konstanz.de

Received December 18, 2002

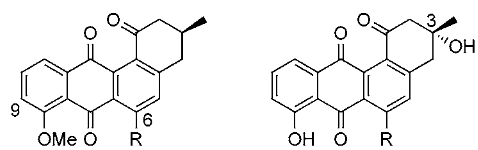
ABSTRACT



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 B_2 **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 vinylcyclohexene[6] or on biomimetic-type reactions[7] by employing polyketide condensations.



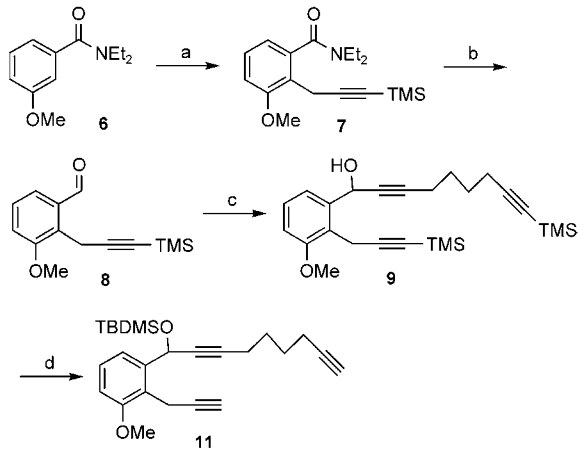
(+)-rubiginone B_2 R=H **1**
(+)-hatomarubigin A R=OH **2**
(-)-tetrangomycin R=H **3**
(-)-rabelomycin R=OH **4**

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]-cycloaddition[8] 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 $RhCl(PPh_3)_3$ and $RuCl_2({=}CHPh)(PCy_3)_2$, which

(1) (a) Rohr, J.; Thiericke, R. *Nat. Prod. Rep.* **1992**, 103−137. (b) Krohn, K.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 127−195.
(2) Oka, M.; Kamei, H.; Hamagishi, Y.; Omita, K.; Miyaki, T.; Konish, M.; Oki, T. *J. Antibiot.* **1990**, *43*, 967−976.
(3) Hayakawa, Y.; Ha, S.-C.; Kim, Y. L.; Furihata, K.; Sato, H. *J. Antibiot.* **1991**, *44*, 1179−1186.
(4) Kunstmann, M. P.; Mitscher, L. A. *J. Org. Chem.* **1996**, *31*, 2920−2925.
(5) Liu, W.-C.; Parker, W. L.; Slusarchyk, D. S.; Greenwood, G. L.; Graham, S. F.; Meyers, E. *J. Antibiot.* **1970**, *23*, 437−441.
(6) (a) Carreño, M. C.; Urbano, A.; Vitta, C. D. *Chem. Commun.* **1999**, 817−818. (b) Carreño, M. C.; Urbano, A.; Vitta, C. D. *Chem. Eur. J.* **2000**, *6*, 906−913. (c) Larsen, D. S.; O'Shea, M. D.; Brooker, S. *Chem. Commun.* **1996**, 203−204. (d) Boyd, V. A.; Sulikowski, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 8472−8473.
(7) (a)Yamaguchi, M.; Okuma, T.; Horiguchi, C.; Ikeura, C.; Minami, T. *J. Org. Chem.* **1992**, *57*, 1647−1649. (b) Krohn, K.; Böker, N.; Flörke, U.; Freund, C. *J. Org. Chem.* **1997**, *62*, 2350−2356.
(8) (a) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539−644. (b) Malacria, M. *Chem. Rev.* **1996**, *96*, 289−306.
(9) Transition Metal Catalyzed Reactions in Organic Synthesis, Part 3. For Part 2, see: Fischer, S.; Groth, U.; Jung, M.; Schneider, A. *Synlett* **2002**, 2023−2026.

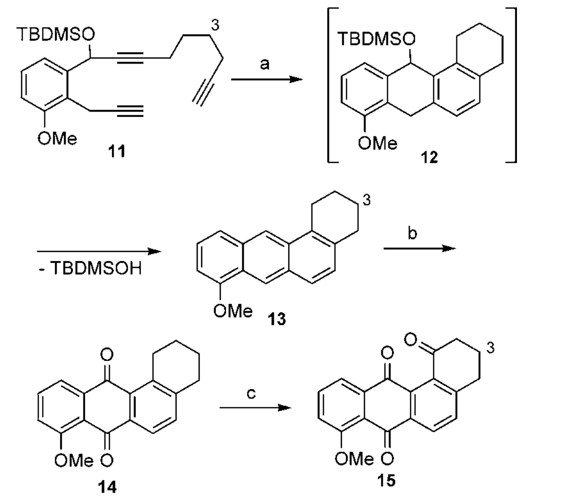
10.1021/ol0274920 CCC: $25.00
Published on Web 02/27/2003

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) CuCN•2LiCl, −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) NH_4F/Bu_4NHSO_4, CH_2Cl_2, 48 h, (ii) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 25 °C, 2 h (95%).

Scheme 2[a]



[a] Reagents and conditions: (a) 5% CpCo(ethene)$_2$, Et_2O, −80 °C to room temperature, 18 h, or 5% CpCo(CO)$_2$, toluene, reflux, *hν*, 4 h (66%). (b) 8 equiv of [Ag(Py)$_2$]MnO_4, CH_2Cl_2, 25 °C, 18 h (63%). (c) *hν*, air, $CHCl_3$, 25 °C, 18 h (61%).

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 CuCN•2LiCl 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-octadiyne[14] to this aldehyde, the triple bonds of the resulting triyne **9** were deprotected with NH_4F[15] (deprotection with TBAF in THF led to decomposition of the triyne **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 CpCo(ethene)$_2$[17]and the commercially available CpCo(CO)$_2$. Reaction of **11** with 5% CpCo(ethene)$_2$ succeeded under mild conditions at low temperature. Surprisingly we observed the loss of the TBDMSO-group with concomitant aromatization to the anthracene **13** (55% yield and 16% isolated starting material). In the case of CpCo(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 [Ag(Py)$_2$]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.

Acknowledgment. The authors are grateful to the Fonds der Chemischen Industrie and the EU-Comission, Directorate XII, for financial support.

Supporting Information Available: Experimental procedures and analytical data for all compounds, ^{1}H 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.

OL0274920

(10) (a) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2426−2430. (b) Neeson, S. J.; Stevenson, P. J. *Tetrahedron* **1989**, *45*, 6239−6248. (c) Blechert, S.; Peters, J. U. *Chem. Commun.* **1997**, 1983−84.

(11) Brimble, M. A.; Robinson, S. G. *Tetrahedron* **1996**, *52*, 9553−9562.

(12) (a) Kreye, P. Ph. D Thesis, University of Goettingen (F.R.G.), 1996. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 0, 879−933. (c) Singer, P. D.; Knochel, P. *Chem. Rev.* **1993**, *93*, 2117−2188.

(13) Kim, S.; Ahn, K. H. *J. Org. Chem.* **1984**, *49*, 1717−1724.

(14) Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856−5866.

(15) Herold, P. *Helv. Chim. Acta* **1986**, *71*, 354−356.

(16) Corey, E. J.; Cho, H.; Ruecker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *36*, 3455−3458.

(17) (a) Jonas, K.; Deffense, E.; Habermann, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 716. (b) Eichberg, M. J.; Dorta, R. L.; Lamottke, K.; Vollhardt, K. P. C. *Org. Lett.* **2000**, *16*, 2479−2481. (c) Eichberg, M. J.; Dorta, R. L.; Grotjahn, D. B.; Lamottke, K.; Schmidt, M.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **2001**, *123*, 9324−9337. (d) Cammack, J. K.; Jalisatgi, S.; Matzger, A. J.; Negrón, A.; Vollhardt, K. P. C. *J. Org. Chem.* **1996**, *61*, 4798−4800.

(18) Tius, M. A.; Galeno, J. G.; Gu, X.; Zaid, J. H. *J. Am. Chem. Soc.* **1991**, *113*, 5775−5783.

(19) (a) Krohn, K.; Ballwanz, F.; Baltus, W. *Liebigs Ann. Chem.* **1993**, 911−913. (b) Krohn, K.; Micheel, J.; Zukowski, M. *Tetrahedron* **2000**, *56*, 4753−4758. (c) Caygill, G. B.; Larsen, D. S.; Brooker, S. *J. Org. Chem.* **2001**, *66*, 7427−7431. (d) Mal, D.; Roy, H. N. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3167−3171. (e) Carreño, M. C.; Ribagorda, M.; Somoza, A.; Urbano, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 2755−2757.