ORGANIC LETTERS

2006
Vol. 8, No. 25
5873−5876

First Enantioselective Total Synthesis and Structure Determination of the Anthrapyran Metabolite γ-Indomycinone

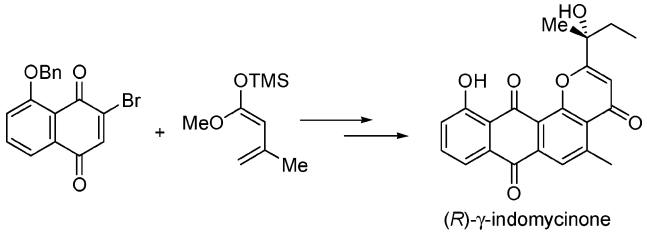
Lutz F. Tietze,* Ramakrishna Reddy Singidi, and Kersten M. Gericke

Institute of Organic and Biomolecular Chemistry, Georg-August-University, Tammannstr. 2, D-37077 Göttingen, Germany

ltietze@gwdg.de

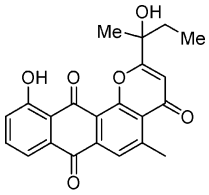
Received October 10, 2006

ABSTRACT



The first total synthesis of (*R*)-γ-indomycinone has been achieved which allowed the determination of the configuration of the stereogenic center of natural γ-indomycinone as (*S*). The approach stands out for its generality and efficiency.

γ-Indomycinone (**1**) has recently been isolated as a new member of the pluramycin class of antibiotics from the culture broth of an actinomycete identified as *Streptomyces* sp.[1,2] [marine (B5543) and terrestrial (GW3/1130)] along with the known compounds rubiflavinone C-1[3] and β-indomycinone.[4] These antibiotics contain a 4*H*-anthra[1,2-*b*]pyran-4,7,12-trione nucleus, typical for the pluramycin antibiotics,[5] which are known for their potent anticancer activity due to a specific alkylation at N-7 of the guanine base in the DNA. However, they differ from the pluramycin group antibiotics by the absence of an aminosugar moiety attached to the chromophore by a C-glycosidic bond.



1

Figure 1. Proposed structure of γ-indomycinone (**1**).

The constitution of γ-indomycinone (**1**) (Figure 1) was established by spectroscopic methods, but its absolute configuration remains unknown so far. Because it was isolated in only minute amounts, a chemical total synthesis was needed for the determination of the configuration of the stereogenic center as well as of its bioactivity.

Despite the excellent work of Hauser,[6a,b] Uno,[6c,d] Krohn,[6e] McDonald,[6f] and their co-workers, a general approach to the anthrapyran antibiotics, especially those with stereogenic centers in the side chain, has only recently been accomplished within the total synthesis of the natural product AH-1763 IIa.[7]

(1) Schumacher, R. W.; Davidson, B. S.; Montenegro, D. A.; Bernan, V. S. *J. Nat. Prod.* **1995**, *58*, 613−617.

(2) Laatsch, H.; Abdelfattah, M. New Secondary Metabolites from Bacteria: Seitomycin with high Anti-*Helicobacter pylori* Activity, Exfoliazone B, new Steffimycinones, Espicufolin B, Flavomarine A and B, and BS-46 with a Novel Carbon Skeleton, Ph.D. thesis, University of Göttingen, Göttingen, 2004.

(3) Nadig, H.; Séquin, U. *Helv. Chim. Acta* **1987**, *70*, 1217−1228.

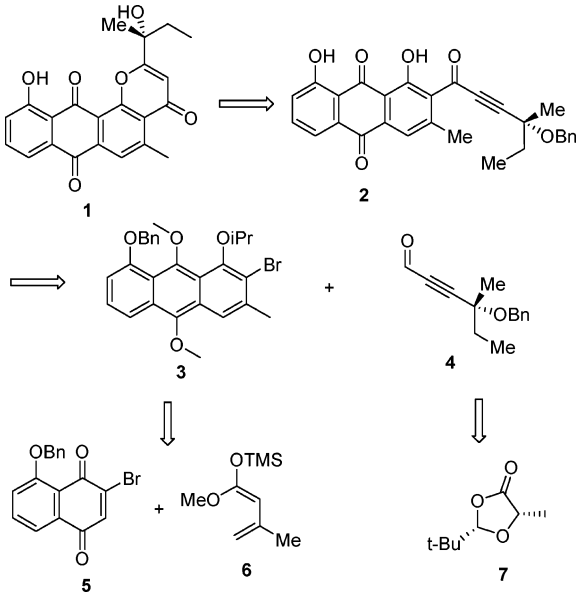
(4) Brockmann, H. *Angew. Chem.* **1968**, *7*, 493; *Angew. Chem., Int. Ed.* **1968**, *39*, 481.

(5) (a) Eckardt, K. Quinones and Other Carbocyclic Antitumor Antibiotics in Antitumor Compounds of Natural Origin. In *Chemistry and Biology*; Aszalos, A., Ed.; CRC Press: Boca Raton, 1981; Vol. II. (b) Séquin, U. The Antibiotics of the Pluramycin Group (4*H*-Anthra[1,2-*b*]pyran Antibiotics) In *Progress in the Chemistry of Organic Natural Products*; Zechmeister, L., Ed.; Springer, Wien: New York, 1986; Vol. 50, pp 58−122.

10.1021/ol062492b CCC: $33.50
Published on Web 11/15/2006

Here, we describe the first enantioselective total synthesis of (*R*)-γ-indomycinone (*R*-**1**), which also allowed us to determine the stereochemistry of the natural compound. Its retrosynthetic analysis is outlined in Scheme 1. The first

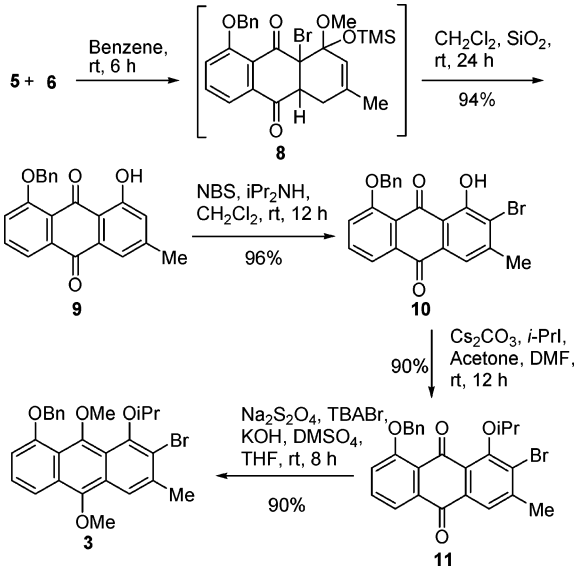
Scheme 1. Retrosynthetic Analysis of (*R*)-γ-Indomycinone (*R*-**1**)



disconnection in the pyrone ring moiety envisions an intramolecular 6-*endo*-dig cyclization of the chiral ynone **2**, which in turn should result from a nucleophilic attack of an aryl lithium species generated from the bromodimethoxyanthracene derivative **3** on the enantiopure propargylic aldehyde **4**. Compound **3** should be accessible from the two fragments **5** and **6** employing a Diels−Alder reaction, and the aldehyde **4** could be obtained from the enantiopure dioxolanone **7**.

Recently, we have shown that anthraquinones can be obtained in an operationally simple way via a regioselective Diels−Alder reaction,[7] which is highly advantageous compared to the known procedure. Thus, cycloaddition of 3-bromojuglone benzyl ether **5**[8] as a dienophile and 1-methoxy-3-methyl-1-trimethylsiloxy-1,3-butadiene **6**[9] as a diene led to adduct **8**, which without isolation yielded the anthraquinone **9** by treatment with silica gel as a mild acid in 94%. The bromo atom at C-3 in **5** acts as a regiochemical control element directing the carbon−carbon bond formation during the Diels−Alder reaction.[10] The following regioselective ortho-bromination of anthraquinone **9** was feasible due to the strong ortho-directing effect of the hydroxyl group. Thus, treatment of **9** with NBS in dichloromethane in the presence of a catalytic amount of a secondary amine[11] gave the monobromoanthraquinone **10** in nearly quantitative yield. To complete the synthesis of the building block **3** (Scheme 2),

Scheme 2. Synthesis of the Building Block **3**



both the hydroxyl group and the quinone moiety had to be protected. Following an orthogonal protecting-group strategy, the hydroxyl group of bromoanthraquinone **10** was protected as its isopropyl ether **11** in 90% yield by treatment with *i*-PrI and Cs_2CO_3 in a mixture of acetone and *N*,*N*-dimethylformamide.[12] Finally, reductive methylation of the quinone moiety in **11** using the phase-transfer method[13] with aq sodium dithionite followed by treatment with KOH and dimethyl sulfate led to the desired dimethoxyanthracene **3** in 90% overall yield. **3** is sensitive to light in the presence of air. Under these conditions, a partial formation of the corresponding anthraquinone takes place. The building block **3** has the advantage, over the already used corresponding building block with two isopropyl ether moieties as protecting groups,[7] that deprotection as one of the last steps does not cause any problems.

(6) (a) Hauser, F. M.; Rhee, R. P. *J. Am. Chem. Soc.* **1979**, *101*, 1628−1629. (b) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1980**, *45*, 3061−3068. (c) Uno, H.; Sakamoto, K.; Honda, E.; Ono, N. *Chem. Commun*. **1999**, 1005−1006. (d) Uno, H.; Sakamoto, K.; Honda, E.; Fukuhara, K.; Ono, N.; Tanaka, J.; Sakanaka, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 229−238. (e) Krohn, K.; Vitz, J. *Eur. J. Org. Chem*. **2004**, 209−219. (f) Fei, Z.; McDonald, F. E. *Org. Lett.* **2005**, *7*, 3617−3620.

(7) Tietze, L. F.; Gericke, K. M.; Singidi, R. R. J. *Angew. Chem*. **2006**, *118*, 7146−7150; *Angew. Chem., Int. Ed*. **2006**, *45*, 6990−6993.

(8) (a) Takeya, T.; Kajiyama, M.; Nakumara, C.; Tobinaga, S. *Chem. Pharm. Bull.* **1999**, *47*, 209−219. (b) Wheeler, A. S; Naiman, B. *J. Am. Chem. Soc.* **1922**, *44*, 2331−2334. (c) Thomson, R. H. *J. Org. Chem*. **1948**, *13*, 377−383. (d) Hannan, R. L.; Barber, R. B.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 2153−2158. (e) Tietze, L. F.; Güntner, C.; Gericke, K. M.; Schuberth, I.; Bunkoczi, G. *Eur. J. Org. Chem*. **2005**, 2459−2467.

(9) Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455−3464.

(10) Grunwell, J. R.; Karipides, A.; Wigal, C. T.; Heinzman, S. W.; Parlow, J.; Surso, J. A.; Clayton, L.; Fleitz, F. J.; Daffner, M.; Stevens, J. E. *J. Org. Chem.* **1991**, *56*, 91−95.

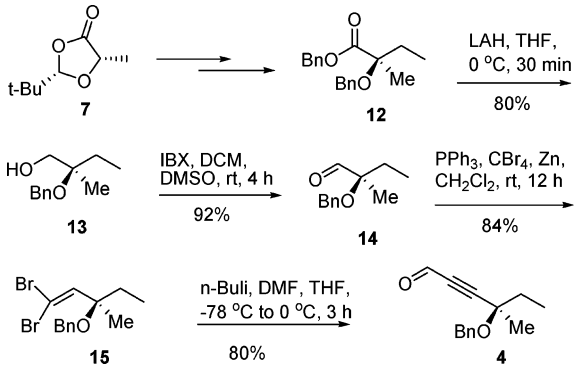
(11) (a) Fujisaki, S.; Eguchi, H.; Omura, A.; Okamoto, A.; Nishida, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1576−1579. (b) Krohn, K.; Bernhard, S.; Floerke, U.; Hayat, N. *J. Org. Chem.* **2000**, *65*, 3218−3222. (c) Nicolaou, K. C.; Gray, D.; Tae, J. *Angew. Chem.* **2001**, *113*, 3791−3795; *Angew. Chem., Int. Ed*. **2001**, *40*, 3679−3683. (d) Bringmann, G.; Menche, D.; Kraus, J.; Mühlbacher, J.; Peters, K.; Peters, E.-M.; Brun, R.; Bezabih, M.; Abegaz, B. M. *J. Org. Chem.* **2002**, *67*, 5595−5610.

(12) Winters, R. T.; Sercel, A. D.; Showalter, H. D. *Synthesis* **1988**, 712−714.

(13) Allevi, P.; Anastasia, M.; Bingham, S.; Ciuffreda, P.; Pierangela, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, *3*, 575 -582.

The synthesis of the needed propargylic aldehyde **4** (Scheme 3) started from the ester **12**, which is easily

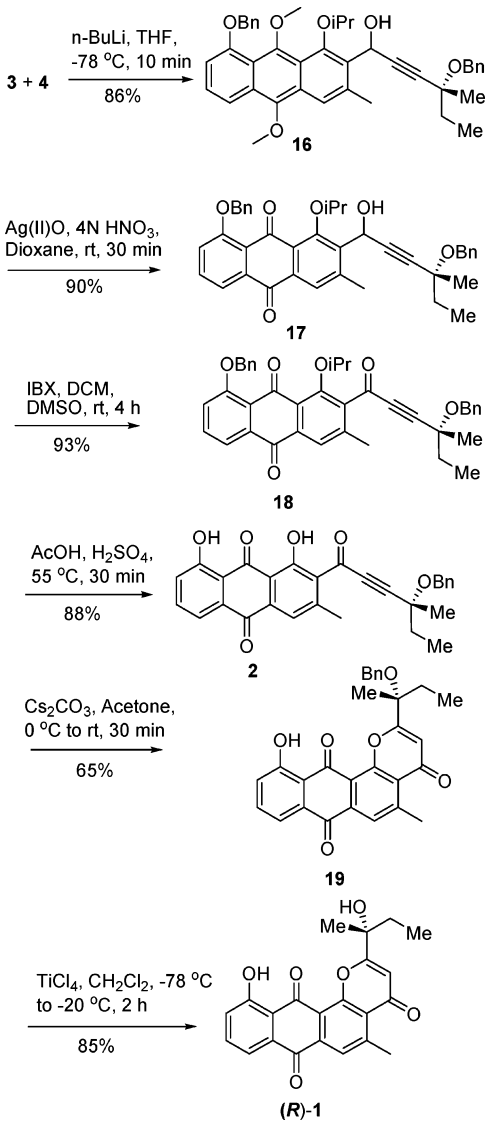
Scheme 3. Synthesis of the Propargylic Aldehyde **4**



accessible from enantiomerically pure dioxolanone **7** according to a known procedure.[14] Reduction of **12** with LAH yielded the primary alcohol **13** in 80% yield, which on oxidation utilizing the very mild IBX[15] reagent furnished the aldehyde **14**. Finally, a Corey−Fuchs homologation[16] to give **15** was followed by treatment with *n*-BuLi and *N*,*N*-dimethylformamide[17] to furnish the desired propargylic aldehyde **4** in 80% yield.

Having successfully synthesized both the building blocks **3** and **4** in a convenient and highly efficient manner, we focused on the coupling of these intermediates as the next task. After conversion of **3** into the lithium derivative by metalation using *n*-BuLi, the subsequent reaction with the propargylic aldehyde **4** proceeded smoothly to give the corresponding alcohol **16** in 86% yield as a mixture of both possible diastereomers in a ratio of 1:1 (Scheme 4) according to the NMR spectra of the product. The missing selectivity has no consequences because the formed stereogenic center is later removed by oxidation. However, it should be noted that the aldehyde should be added in one batch immediately after generation of the organolithium compound to get good results. Oxidative cleavage of the 7,12-dimethoxy groups present in **16** was accomplished in 90% yield using silver(II) oxide in dilute nitric acid[18] to give the anthraquinone derivative **17**, which was subsequently subjected to IBX oxidation[15] to afford the ynone **18** in 93% yield. First, we had planned to remove the protecting groups at the anthraquinone moiety and perform the ring closure under acidic conditions in a domino process.[19] However, treatment of **18** in acetic acid at 55 °C with a catalytic amount of sulfuric

Scheme 4. Synthesis of (*R*)-γ-Indomycinone (*R*-**1**) from **3** and **4**



acid led only to a cleavage of the benzyl and isopropyl ethers at the anthraquinone to give **2**, but not to a cyclization. Both raising the temperature and increasing the reaction time did not provide the desired product but induced an elimination of the benzyloxy group in the side chain. However, an efficient formation of the γ-pyrone ring system was possible by an intramolecular 6-*endo*-dig cyclization of **2** under basic conditions. Thus, treatment of **2** in acetone with Cs_2CO_3 yielded the tetracycle **19** in 65% yield.[20] Formation of a furanone was not detected. The final step in the synthesis of (*R*)-γ-indomycinone (*R*-**1**) was the removal of the benzyl protecting group in the side chain, which was effected in 85% yield by treatment of **19** with $TiCl_4$ in CH_2Cl_2 at −78 °C and then by slow warming to −20 °C.[11d]

The ^{1}H NMR spectra of the isolated natural product[1,2] and synthetic compound **1** are identical in all respects, including

(14) (a) Seebach, D.; Naff, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313−1324. (b) Lee, M.; Kim, D. H. *Bioorg. Med. Chem.* **2000**, *8*, 815−823.

(15) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537−4538.

(16) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769−3772.

(17) Ohno, H.; Anzai, M.; Toda, A.; Ohishi, S.; Fujii, N.; Tetsuaki, T.; Takemoto, Y.; Ibuka, T. *J. Org. Chem.* **2001**, *66*, 4904−4914.

(18) (a) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227−231. (b) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1980**, *45*, 3061−3068.

(19) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006, (ISBN: 3-527-29060-5).

(20) Mzhel'skaya, M. A.; Moroz, A. A.; Shvartsberg, M. S. *Seriya Khimicheskaya* **1991**, *7*, 1469−1472.

chemical shifts as well as coupling constant values. The absolute configuration of the stereogenic center in the natural product was determined by comparison of the optical rotation. The $[\alpha]^{25}_D$ value of the synthetic compound (*R*)-**1** was determined as +4.0 (*c* 0.1, DMSO), which is opposite in sign to a natural sample with $[\alpha]_D = -5.5$ (c 0.11, DMSO), which was provided by Prof. Laatsch at the University of Göttingen.[2] This clearly indicates that natural γ-indomycinone has an (*S*)-configuration at the stereogenic center.

In conclusion, we have developed a new general strategy for the synthesis of anthrapyran antibiotics, which resulted in the first enantioselective total synthesis of (*R*)-γ-indomycinone (*R*-**1**) and which allowed us to determine the natural γ-indomycinone as (*S*)-**1**.

Acknowledgment. The authors are grateful to the Fonds der Chemischen Industrie for supporting this work, and R.R.S. thanks the Alexander von Humboldt Foundation for a postdoctoral grant.

Supporting Information Available: Full experimental procedures and detailed spectral data of all key compounds are reported. Copies of ^{1}H and ^{13}C spectra are additionally provided, along with HRMS data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062492B