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Total Synthesis of (−)-8-*O*-Methyltetrangomycin (MM 47755)

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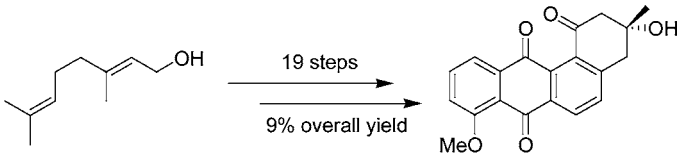
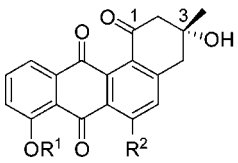
ABSTRACT



A stereoselective total synthesis of the natural antibiotic (−)-8-*O*-methyltetrangomycin 1 is reported. The essential steps for this convergent synthesis are the transformation of a geraniol epoxide into a chiral octadiyne derivative, which was converted into a triyne. The cobalt-mediated [2+2+2] cycloaddition of the triyne led to a benz[*a*]anthracene system, which was oxidized with $Ag(Py)_2MnO_4$ to a benz[*a*]anthraquinone. Deprotection with aqueous HF in acetonitrile and photooxidation afforded the desired product (−)-1.

(−)-8-*O*-Methyltetrangomycin belongs to the angucyclinone antibiotics,[1] which are mainly isolated from certain strains of *Streptomyces* bacteria. The angucyclinones exhibit a broad range of biological properties such as antiviral, antibacterial, and antitumor activities, whereby (−)-8-*O*-methyltetrangomycin **1** (or MM 47755) shows mainly activity against gram-positive organisms such as *Bacillus subtilis* (MIC: 32 μg/mL).[2]

Besides its angular benz[*a*]anthraquinone framework, one unique feature of (−)-8-*O*-methyltetrangomycin **1** is its chiral tertiary hydroxy function at the C3 position in the A ring, which is also found in other representatives of the angucyclinone family such as (−)-tetrangomycin **2**[3] and (−)-rabelomycin **3**[4] (Figure 1).



(-)-MM 47755 R^1=Me, R^2=H **1**
(-)-tetrangomycin R^1=H, R^2=H **2**
(-)-rabelomycin R^1=H, R^2=OH **3**

Figure 1. 3-Hydroxy-angucyclinones.

Although there are already some familiar methods for the construction of the stereogenic center at C3 with moderate to good enantiomeric excess,[5,6] we wanted to demonstrate the fundamental viability of our methodology[7] utilizing a chiral monoprotected diyne as a building block for the synthesis of angucyclinones.

The stereoselective total synthesis of **1** was successfully accomplished with an overall yield of 9% over 19 linear steps

(1) (a) Rohr, J.; Thiericke, R. *Nat. Prod. Rep.* **1992**, 103−137. (b) Krohn, K.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 127−195. (c) Carreno, M. C.; Urbano, A. *Synlett* **2005**, *1*, 1−25.

(2) (a) Shigahara, Y.; Koizumi, Y.; Tamamura, T.; Homma, Y.; Isshiki, K.; Dobashi, K.; Naganawa, H.; Takeuchi, T. *J. Antibiot.* **1988**, *41*, 9, 1260−1264. (b) Gilpin, M. L.; Balchin, J.; Box, S. J.; Tyler, J. W. *J. Antibiot.* **1989**, *42*, 4, 627−628. (c) Grabley, S.; Hammann, P.; Hütter, K.; Kluge, H.; Thiericke, R.; Wink, J. *J. Antibiot.* **1991**, *44*, 6, 670−673.

(3) (a) Dann, M.; Lefemine, D. V.; Barbatschi, F.; Shu, P.; Kunstmann, M. P.; Mitscher, L. A.; Bohonos, N. *Antimicrob. Agents Chemother*. **1965**, 832−835. (b) Kunstmann, M. P.; Mitscher, L. A. *J. Org. Chem.* **1966**, *31*, 2920−2925.

(4) Liu, W.-L.; Parker, W. L.; Slusarchyk, D. S.; Greenwood, G. L.; Graham, S. F.; Meyers, E. *J. Antibiot.* **1970**, *23*, 437−441.

(5) (a) Kim, K.; Boyd, V. A.; Sobti, A.; Sulikowski, G. A. *Isr. J. Chem.* **1997**, *37*, 3−22. (b) Boyd, V. A.; Sulikowski, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 32, 8472−8473.

(6) (a) Landell, J. S.; Larsen, D. S.; Simpson, J. *Tetrahedron Lett.* **2003**, *44*, 5193−5196. (b) Carreno, M. C.; Urbano, A.; Di Vitta, C. *Chem.−Eur. J.* **2000**, *6*, 906−913.

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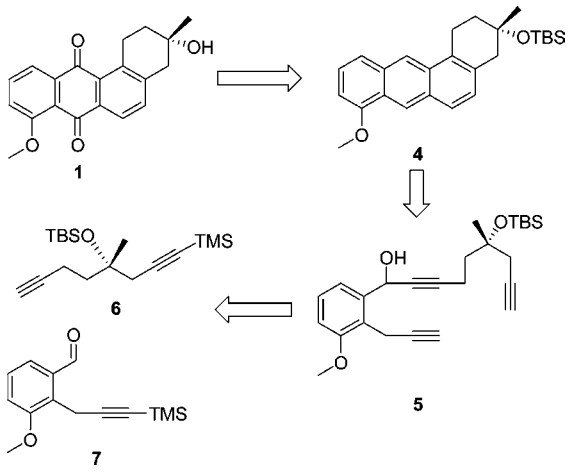
and an enantiomeric excess of ≥91%. The stability of the protected alcohol **19** (Scheme 4) under the conditions of the cobalt-mediated [2+2+2] cycloaddition was shown by the racemic synthesis of **1** with 11% overall yield comprising nine linear steps.

On the basis of previous work of our group,[7] we designed the following retrosynthetic way for **1** which is shown in Scheme 1.

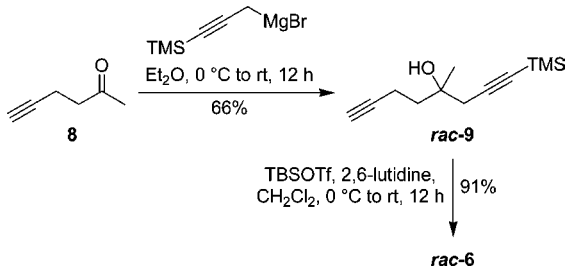
Scheme 1



The idea was to synthesize (−)-**1** via the chiral benz[*a*]-anthracene **4** which should be accessible by the cobalt-mediated [2+2+2] cycloaddition of chiral triyne **5**. Triyne **5** should result from the addition of the chiral octadiyne **6** to the substituted benzaldehyde **7**[8] and successive selective deprotection of both trimethylsilyl groups under basic conditions.

Our synthesis of the racemic diyne ***rac*-6** (Scheme 2) started with the addition of 3-(trimethylsilyl)-propargylmagnesium-bromide to hex-5-yn-2-one **8**[9] which gave the diynol ***rac*-9** in 66% yield. The tertiary hydroxy function was then protected with TBSOTf and 2,6-lutidine as its TBS-ether ***rac*-6**.

Scheme 2



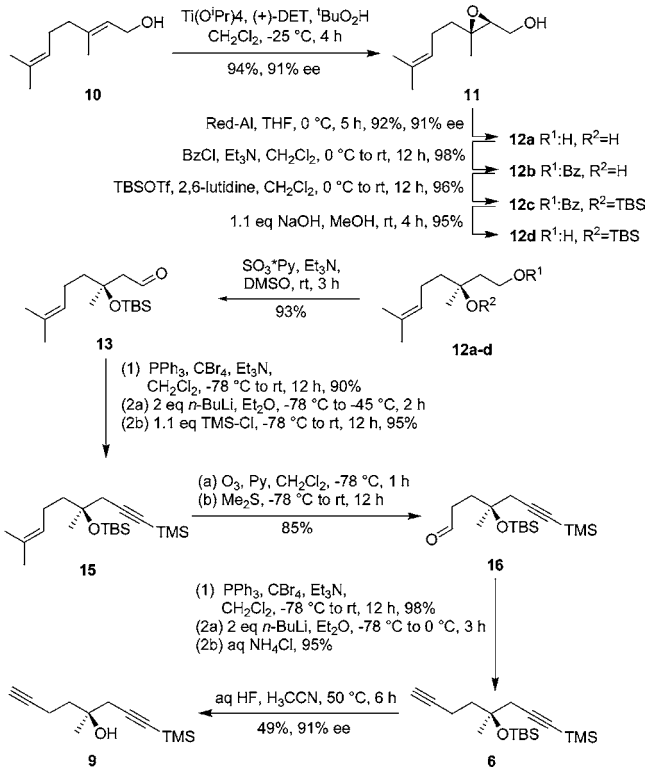
(8) For the synthesis of the substrate benzaldehyde **7**, see ref 7.

(9) Hex-5-yn-2-one was synthesized according to: Eglington, G.; Whiting, M. C. *J. Chem. Soc.* **1953**, *607*, 3052−3059.

With the achiral diyne ***rac*-6** in hand, we performed the total synthesis as shown in Scheme 4 with ***rac*-6** instead of **6** as the starting material. After we had proven that the expected way to synthesize (±)-8-*O*-methyltetrangomycin ***rac*-1**, in nine steps with an overall yield of 11%, works as described, we developed an asymmetric synthesis of the chiral octadiyne **6** as the starting material for an enantioselective approach toward the total synthesis of (−)-**1**.

The synthesis of **6** (Scheme 3) was started with a Sharpless epoxidation[10] of geraniol **10** giving us the epoxide **11**. A

Scheme 3



reductive ring opening of **11** with Red−Al according to the protocol of Sharpless et al.[11] led us to the chiral diol **12a**. The reductive ring opening was tested under various conditions with Red−Al, $LiAlH_4$,[12] and DIBAl−H, whereby it could be shown that only Red−Al gave the diol **12a** without any loss of optical purity. Interestingly, the reduction of the epoxide **11** with $LiAlH_4$ led to a significant decrease of the optical purity down to 57% ee, whereas reduction with DIBAl−H led to no isolable amounts of the desired diol. The enantiomeric excess of the diol **12a** was determined to be ≥91% via chiral GC analysis.[13] Protection of the primary hydroxy function of **12a** with benzoyl chloride, protection of the tertiary alcohol with TBSOTf, and successive saponi-

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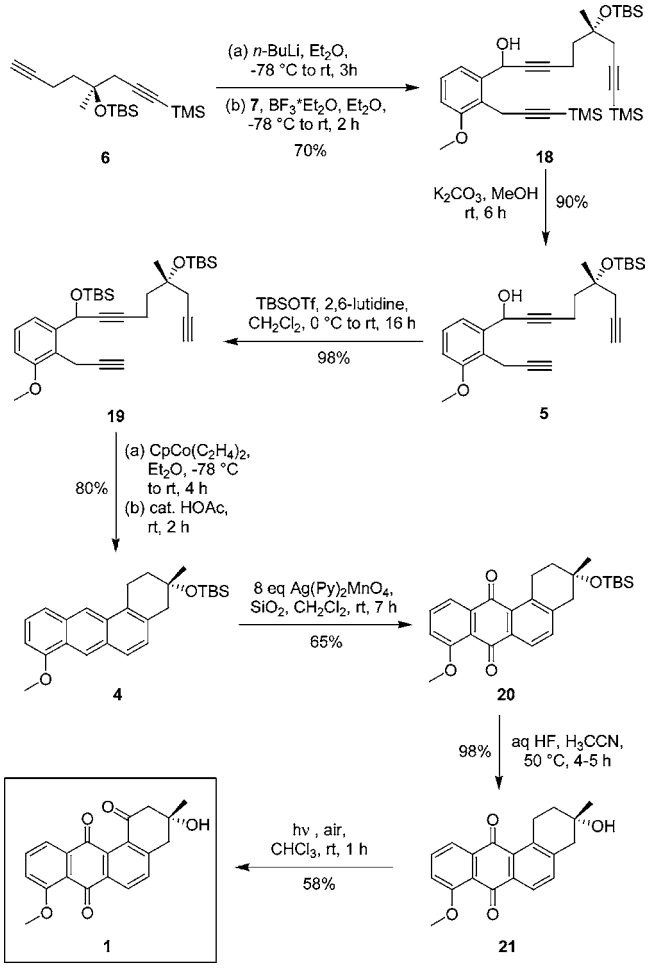
(12) Jung, M. E.; MacDougall, J. M. *Tetrahedron Lett.* **1999**, *40*, 35, 6339−6342.

(13) See Supporting Information.

Scheme 4



fication of the benzoate gave the monoprotected diol **12d**. Parikh−Doering oxidation[14] was the method of choice for the oxidation of the primary alcohol **12d** to gain access to aldehyde **13**. Oxidizing the primary alcohol **12d** with some classical methods such as PCC and PDC (low or no observable conversion) or Dess−Martin periodinane (decomposition, even with additional pyridine to buffer the acetic acid) failed. **13** was then converted according to a Corey−Fuchs protocol[15] into the dibromide **14**. Noteworthy is that standard Corey−Fuchs conditions did not give the dibromide **14**, and the starting material remained unchanged. Further experiments showed that the use of triethylamine was essential for the feasibility of this reaction, as well as the quality of the tetrabromocarbon.[16]

Elimination of dibromide **14** with 2 equiv of *n*-BuLi led after quenching with TMS−Cl to compound **15**.

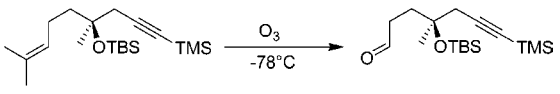
Ozonolysis[17] of the enyne **15** in dichloromethane and pyridine at −78 °C gave the aldehyde **16**, whereby the classical conditions failed to deliver the expected aldehyde **16** (see Table 1). Ozonolysis with CH_2Cl_2/MeOH (9:1) as

(14) (a) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507. (b) Tidwell, T. T. *Synthesis* **1990**, 857−869.

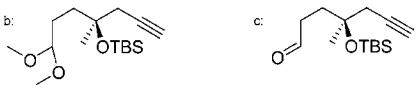
(15) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1997**, *62*, 4313−4320.

(16) The CBr_4 from Merck Company KG Darmstadt gave the best results.

Table 1. Ozonolysis of Compound **15** under Various Conditions



entry	reaction conditions	yield (%) of **16**[a]
1	CH_2Cl_2/MeOH (9:1)	47
2	CH_2Cl_2/MeOH (9:1), 1.5 equiv of KHCO3	30
3	CH_2Cl_2, 2 equiv of HOAc	16
4	CH_2Cl_2	66
5	CH_2Cl_2, 1 equiv of pyridine	64−69
6	CH_2Cl_2, 2.5 equiv of pyridine	85



[a] The given yields are after workup with dimethyl sulfide and column chromatography over silica gel.

solvent gave the dimethylacetal with loss of the TMS protecting group. By adding $KHCO_3$ to the reaction, we were able to prevent the formation of the acetal, but the TMS group was still cleaved. Only the addition of 2.5 equiv of abs pyridine gave the desired aldehyde **16** in an acceptable yield. Conversion of **16** by the above-mentioned modified Corey−Fuchs reaction finally gave the chiral octadiyne **6** with the dibromide **17** as an isolable but unstable intermediate.

To determine the enantiomeric excess of **6** by chiral GC, the TBS-protecting group had to be removed. Aqueous hydrofluoric acid in acetonitrile proved to be the reagent of choice, leaving the acetylenic TMS-protecting group untouched. The enantiomeric purity of **9** was determined by chiral GC analysis in comparison with the achiral diynol ***rac*-9** to be >91% ee.[18]

Addition of the lithiated diyne **6** to a mixture of the substituted benzaldehyde **7**[8] and an equivalent borontrifluoride gave the bis-TMS-protected cyclization precursor **18** with 70% yield. Without the use of borontrifluoride, the addition showed a much lower yield of only 25%. Removal of the trimethylsilyl groups under basic conditions with potassium carbonate in methanol led to the TBS-protected triyne **5**. Protection of the secondary hydroxy function with TBSOTf and 2,6-lutidine gave the triyne **19** which is the direct precursor for the intramolecular cobalt-mediated [2+2+2] cycloaddition.[19] Cyclization of triyne **19** was performed under different conditions (see Table 2), but the equimolar use of $CpCo(C_2H_4)_2$[20] led to the best yields in

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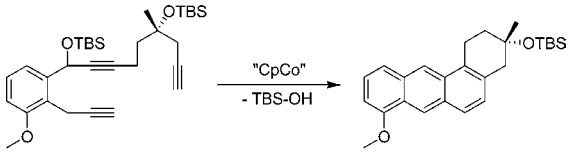
(18) See Supporting Information.

Table 2. Cobalt-Mediated [2+2+2] Cycloaddition under Different Reaction Conditions



19 4

entry	reaction conditions	yield (%) of **4**[a]
1	10 mol % of $CpCo(CO)_2$, toluene, reflux, 40 h	23[b]
2	20 mol % of $CpCo(CO)_2$, toluene, hν, reflux, 8 h	44[b]
3	40 mol % of $CpCo(CO)_2$, toluene, hν, reflux, 4 h	33
4	100 mol % of $CpCo(CO)_2$, toluene, hν, reflux, 4 h	64
5	20 mol % of CpCo(COD), toluene, hν, rt, 4 h	
6	40 mol % of $CpCo(C_2H_4)_2$, Et_2O, −78 °C to rt, 4 h	45[c]
7	100 mol % of $CpCo(C_2H_4)_2$, Et_2O, −78 °C to rt, 4 h	80[c]

[a] The given yields are after workup and column chromatography over silica gel. [b] The catalyst was added slowly via syringe pump to the starting material **19** in refluxing toluene (see also ref 22). [c] Before the workup was done, 5 drops of acetic acid were added to the solution and stirred at room temperature for 2 h.

comparison with the $CpCo(CO)_2$ and the CpCo(COD)[21] catalysts. Application of the recently published syringe pump technique[22] (Table 2, entries 1 and 2) also showed interesting results, although these results could not match the yields achieved by the use of equivalent amounts of the "Jonas" catalyst $CpCo(C_2H_4)_2$.

The chiral tetrahydrobenz[*a*]anthracene **4** was then oxidized with an excess of a 1:2 mixture of $Ag(Pyr)_2MnO_4$[23] and silica gel in dry dichloromethane, which gave the tetrahydrobenz[*a*]anthraquinone **20** in 65% yield. The deprotection of the tertiary alcohol at C3 proved to be difficult: the usual methods such as TBAF, HF*Pyr, or NH_4F failed completely. Only concentrated aqueous HF in acetonitrile at elevated temperatures (∼50 °C) showed an efficient conversion. Finally, regioselective photooxidation[24] at C1 of the completely deprotected tetrahydrobenz[*a*]anthraquinone **21** in $CHCl_3$ gave (−)-8-*O*-methyltetrangomycin **1** in 58% yield.

The structure of **1** was determined by one- and two-dimensional NMR, mass, and IR spectroscopy. All recorded data were in accordance with the corresponding published data. The enantiomeric excess of (−)-8-*O*-methyltetrangomycin **1** was determined to be ≥91% by comparing its optical rotation with the data reported earlier.[2,6]

Acknowledgment. We wish to thank Dr. Barbara Heller, IfOK Rostock, for her kind supply of the CpCo(COD) catalyst. Furthermore, the authors are grateful to Merck Company KG and Wacker Chemie AG for valuable starting material.

Supporting Information Available: Detailed experimental procedures and full characterization of compounds **4**−**6**, **9**, **11**, **13**−**21**, and **1** are given, as well as ^1H and ^{13}C NMR spectra for compounds **4**, **6**, **9**, **19**−**21**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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