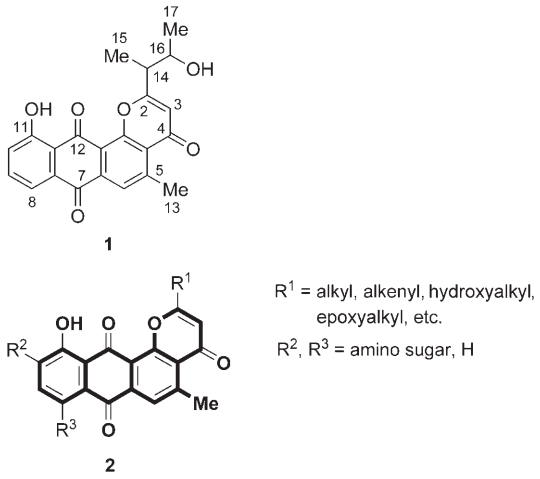

Figure 1. Proposed structure of AH-1763 IIa (**1**) and the structural core **2** of 4*H*-anthra[1,2-*b*]pyran-4,7,12-trione natural products.

Anthrapyran Natural Products

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Enantioselective Total Synthesis and Structure Determination of the Antiherpetic Anthrapyran Antibiotic AH-1763 IIa**

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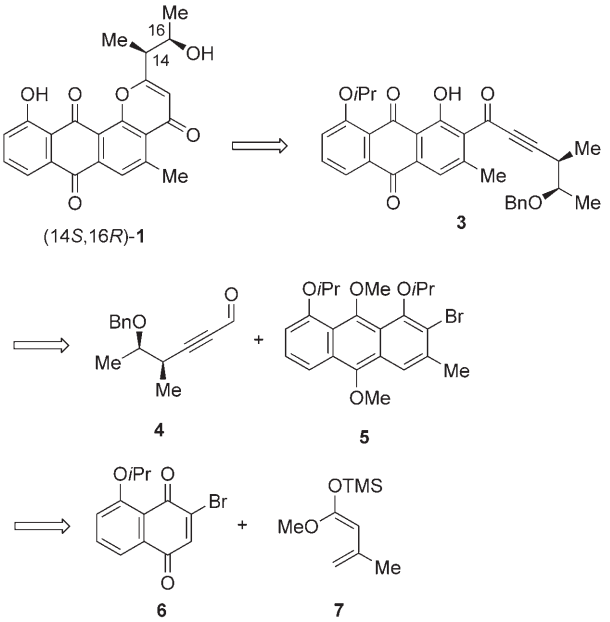
Dedicated to Professor Siegfried Blechert on the occasion of his 60th birthday

The anthrapyran antibiotic AH-1763 IIa (**1**) was isolated in 1997 by Uyeda et al.[1] from a culture broth of *Streptomyces cyaneus*. Compound **1** contains the 4*H*-anthra[1,2-*b*]pyran-4,7,12-trione nucleus **2** found in the pluramycin antibiotics (Figure 1).[2] These antibiotics, first described in 1956 by Umezawa et al.,[3] are most commonly isolated from terrestrial *Streptomyces* sp. and are known for their potent anticancer activity arising from the specific alkylation at N7 of the guanine base in DNA. Pluramycin antibiotics[2] have amino sugars typically attached at the C8 and C10 positions, which, however, are not found in AH-1763 IIa (**1**). This compound exhibits a remarkable inhibitory activity against Gram-positive bacteria like *Bacillus subtilis* and *Staphylococcus aureus*.[1] Moreover, it has a very strong antiherpetic activity ($EC_{50} = 2.1\ \mu g\,mL^{-1}$ against HSV-1), which has so far not been observed for any other compound of the anthrapyran natural products.[1,4]

Despite the excellent work from the research groups led by Hauser,[5a,b] Uno,[5c,d] Krohn,[5e] and McDonald,[5f] there is still no general approach to the anthrapyran antibiotics, especially those with stereogenic centers in the side chain.

Here we describe the enantioselective total syntheses of (14*S*,16*R*)- and (14*R*,16*R*)-AH-1763 IIa (**1** and **28**, respectively). Our work allowed us to determine the previously unknown relative and absolute configuration of the natural product and also provides a general synthetic entry to the anthrapyran antibiotics. The retrosynthetic analysis of (14*S*,16*R*)-AH-1763 IIa (**1**) is outlined in Scheme 1. The first



Scheme 1. Retrosynthetic analysis of (14*S*,16*R*)-AH-1763 IIa (**1**). Bn = benzyl, TMS = trimethylsilyl.

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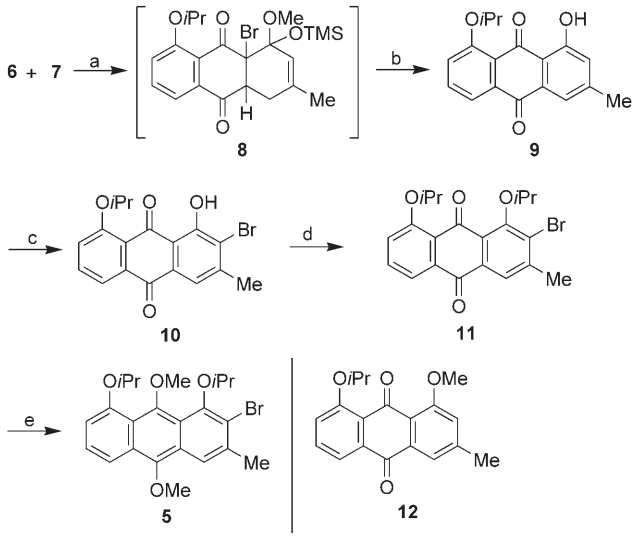
Supporting information for this article (experimental procedure for the synthesis of **1** and its diastereomer **28**) is available on the WWW under http://www.angewandte.org or from the author.

disconnection in the pyrone ring moiety envisions an intramolecular 6-*endo*-digonal cyclization of the ynone **3**, which in turn should result from a nucleophilic attack of an aryl lithium species generated from the bromodimethoxyanthracene derivative **5** on the propargylic aldehyde **4**. The stereogenic centers of the propargylic aldehyde **4** could be constructed using the well-established Evans aldol methodology,[6] and **5** should be accessible from a Diels–Alder reaction of fragments **6** and **7**.

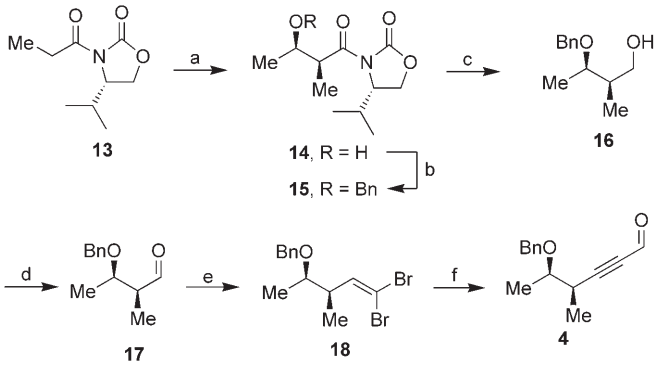
The Diels–Alder reaction of **6**[7] and **7**[8] in benzene yielded the primary cycloadduct **8**, which was converted without further isolation into the thermodynamically more stable anthraquinone derivative **9** by treatment with silica gel as a mild acid (Scheme 2). The bromine atom acts as a



Scheme 2. Reagents and conditions: a) Benzene, RT, 6 h; b) SiO_2, CH_2Cl_2, RT, 24 h, 94% overall yield for two steps; c) NBS, cat. iPr_2NH, CH_2Cl_2, RT, 12 h, 97%; d) Cs_2CO_3, *i*PrI, acetone/DMF (3:1), reflux, 12 h, 94%; e) $Na_2S_2O_4$, TBABr, KOH, H_2O, $DMSO_4$, THF, RT, 4 h, 98%. DMF = *N*,*N*-dimethylformamide, $DMSO_4$ = dimethyl sulfate, NBS = *N*-bromosuccinimide, TBABr = tetrabutylammonium bromide.

regiochemical control element in the Diels–Alder reaction.[9] This method is operationally simpler and gives higher yields (94%) than the procedure developed by Brassard and Savard[8] for the preparation of the anthraquinone building block **9**, which is a common precursor also of other naturally occurring anthraquinone antibiotics. The *O*-methyl ether **12**, which was a major side product in the synthesis by Brassard[8] and has been proven to be worthless for further transformations (see also Reference [5e]), did not form. The subsequent regioselective bromination of anthraquinone **9** was feasible owing to the strong *ortho*-directing effect of the hydroxy group. Thus, treatment of **9** with NBS in dichloromethane in the presence of a catalytic amount of a secondary amine[10] gave after purification by column chromatography the monobromoanthraquinone **10** in nearly quantitative yield (97%). The regioselectivity of both the bromination and the Diels–Alder reaction was unambiguously deduced from HMBC ^{1}H NMR experiments. To complete the synthesis of the building block **5**, both the hydroxy group and the quinone moiety had to be protected. Following an orthogonal protecting-group strategy, the hydroxy group of bromoanthraquinone **10** was protected by treatment with *i*PrI and Cs_2CO_3 in a mixture of acetone and *N*,*N*-dimethylformamide to give its isopropyl ether **11** (94% yield).[11] Finally, reductive methylation[12] of the quinone moiety in **11** was realized by using aqueous sodium dithionite to furnish the corresponding air-sensitive hydroquinone, which underwent methylation upon treatment with KOH and dimethylsulfate to provide the bromodimethoxyanthracene **5** in an excellent overall yield of 98%.

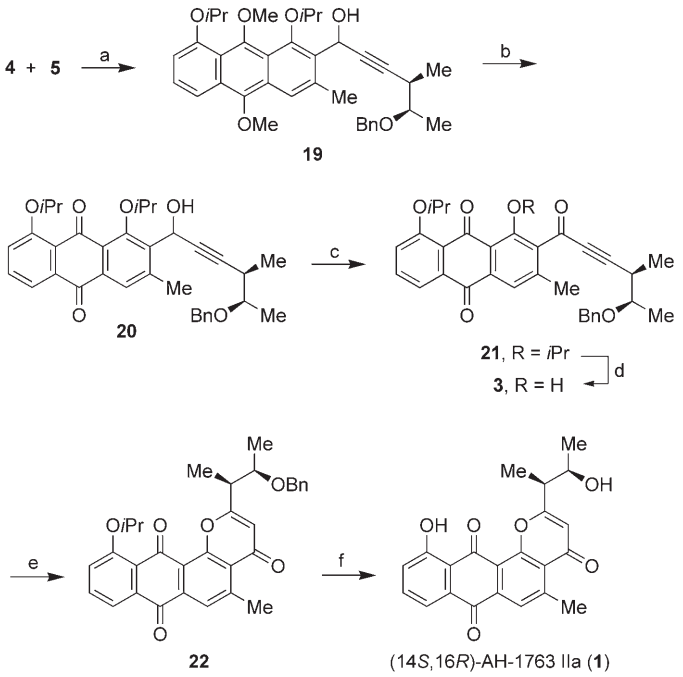
The synthesis of the side-chain unit started from the known aldol product **14**,[13] which was obtained from **13**[14] and protected as its benzyl ether **15** using benzyltrichloroacetimidate (Scheme 3).[15] Reductive removal of the chiral auxiliary



Scheme 3. Reagents and conditions: a) 1. nBu_2BOTf, Et_3N, CH_2Cl_2, −3°C, 1 h; 2. acetaldehyde, −78°C→0°C, 4.5 h, 3. phosphate buffer, MeOH, H_2O_2 (30%), 0°C, 45 min, 87%; b) benzyltrichloroacetimidate, cat. TfOH, cyclohexane/CH_2Cl_2 (2:1), RT, 1 h, 85%; c) $LiBH_4$, Et_2O, 0°C, 4 h, 92%; d) IBX, CH_2Cl_2, DMSO, RT, 2 h, 95%; e) PPh_3, CBr_4, Zn, CH_2Cl_2, RT, 12 h, 90%; f) *n*BuLi, THF, DMF, −78°C→0°C, 4 h, 90%. IBX = 2-iodoxybenzoic acid, DMSO = dimethyl sulfoxide, TfOH = trifluoromethanesulfonic acid.

with $LiBH_4$ in wet Et_2O[16] gave the primary alcohol **16** in 92% yield. Subsequent oxidation utilizing the very mild IBX[17] reagent furnished aldehyde **17** in very good yield (95%). Corey–Fuchs homologation[18] of **17** afforded the vinyl dibromide **18** in 90% yield. Subsequent treatment of **18** with *n*BuLi followed by formylation with *N*,*N*-dimethylformamide[19] furnished the desired propargylic aldehyde **4** in 90% yield with 99% *ee* and d.r. > 99:1.

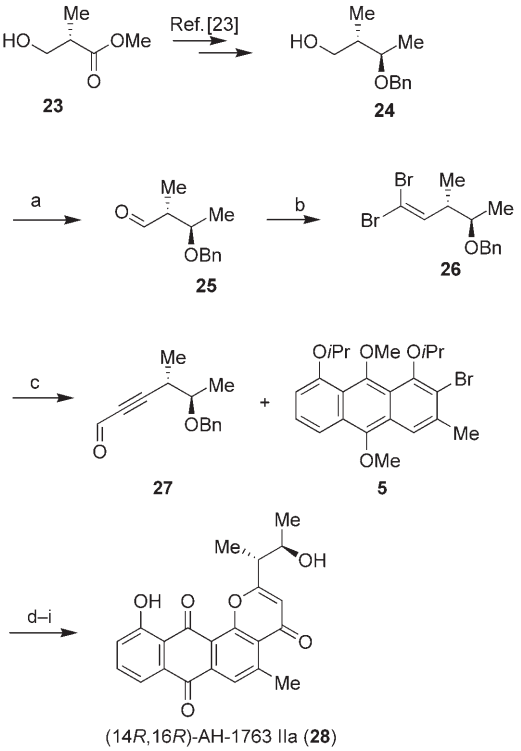
Having successfully synthesized both the building blocks **4** and **5** in a convenient and highly efficient manner, we focused on coupling these intermediates. After conversion of **5** into the corresponding lithium derivative by bromine–lithium exchange using *n*BuLi at low temperature, the subsequent reaction with the propargylic aldehyde **4** proceeded smoothly to give alcohol **19** in 75% yield as a 1:1 mixture of the two possible diastereomers (Scheme 4). The yields were best when the aldehyde was added immediately after generation of the organolithium compound. Oxidative demethylation of the anthracene derivative **19** using $Ag^{II}O/HNO_3$[20] gave anthraquinone **20** in 90% yield. Compound **20** was subsequently subjected to IBX oxidation[17] to afford the ynone



Scheme 4. Reagents and conditions: a) *n*BuLi, THF, −78 °C, 10 min, 75 %; b) $Ag^{II}O$, dioxane, 4 N HNO_3, RT, 30 min, 90 %; c) IBX, CH_2Cl_2, DMSO, RT, 5 h, 97 %; d) AcOH, cat. H_2SO_4, 60 °C, 10 min, 88 %; e) Cs_2CO_3, acetone, RT, 30 min, 71 %; f) $TiCl_4$, CH_2Cl_2, −78 °C→0 °C, 4 h, 90 %.

derivative **21** in 97 % yield. It was expected that the deprotection of phenolic hydroxy group at C12b and the proposed intramolecular 6-*endo*-dig cyclization could be done in one step under acidic conditions. However, treatment of **21** in acetic acid at 50 °C with a catalytic amount of sulfuric acid only led to cleavage of the isopropyl ether at C12b probably because of activation by the adjacent carbonyl groups.[21] Neither raising the temperature nor increasing the reaction time resulted in cyclization but resulted in an undesired elimination of the benzyloxy group in the side chain. The pyron ring was finally achieved under basic conditions. Thus, treatment of **3** in acetone with Cs_2CO_3 yielded the tetracycle **22** in 71 % yield.[5c,d,22] In the final steps in the synthesis of (14*S*,16*R*)-AH-1763 IIa (**1**) the isopropyl and benzyl protecting groups were removed by treating **22** with $TiCl_4$ in CH_2Cl_2 at −78 °C and then allowing the reaction mixture to warm slowly to 0 °C (yield of **1**: 90 %).[10d]

The published ^{1}H NMR spectrum of the compound isolated by Uyeda et al.[1] and that of our synthetic (14*S*,16*R*)-AH-1763 IIa (**1**) were identical in all respects, including chemical shifts and coupling constants. In addition, the ^{13}C NMR spectra deviated by at most 0.1 ppm. However, the optical rotation of the synthetic compound was measured to be $[\alpha]_D = -28.6$ ($c = 0.1$, $CHCl_3$), in contrast to the reported value of $[\alpha]_D = +6.6$ ($c = 0.1$, $CHCl_3$)[1] for the natural product. For that reason we also synthesized the (14*R*,16*R*)-AH-1763 IIa diastereomer **28** in order to compare the analytical data. Compound **28** was prepared from bromodimethoxyanthracene **5** and the propargylic aldehyde **27** following the synthetic route established for the synthesis of **1** (Scheme 5). For the synthesis of the aldehyde **27** the commercially available ester **23** was transformed into the primary alcohol **24** by a known procedure.[23] Oxidation of **24** using IBX[17] followed by treatment with the Corey–Fuchs



Scheme 5. Reagents and conditions: a) IBX, CH_2Cl_2, DMSO, RT, 2 h, 93 %; b) PPh_3, CBr_4, Zn, CH_2Cl_2, RT, 12 h, 92 %; c) *n*BuLi, THF, DMF, −78 °C→0 °C, 4 h, 88 %; d) *n*BuLi, THF, −78 °C, 10 min, 72 %; e) $Ag^{II}O$, dioxane, 4 N HNO_3, RT, 30 min, 90 %; f) IBX, CH_2Cl_2, DMSO, RT, 5 h, 97 %; g) AcOH, cat. H_2SO_4, 60 °C, 10 min, 86 %; h) Cs_2CO_3, acetone, RT, 30 min, 70 %; i) $TiCl_4$, CH_2Cl_2, −78 °C→0 °C, 4 h, 90 %.

reagent produced dibromoalkene **26**,[18] which was converted into the desired propargylic aldehyde **27** by successive treatment with *n*BuLi and *N*,*N*-dimethylformamide.[19] Finally reaction of **27** and **5** under the conditions optimized in the synthesis of **1** gave (14*R*,16*R*)- AH-1763 IIa (**28**).

Comparison of the ^{1}H and ^{13}C NMR spectroscopic data of synthetic **28** with those reported for isolated AH-1763 IIa (**1**) clearly indicate that the two compounds are not enantiomers but diastereomers. Thus, 14H and 16H in **28** give rise to signals at $\delta = 2.78$ and $\delta = 4.17$ ppm, respectively, with the coupling constant $J_{H14,H16} = 8.3$ Hz. In contrast, the signals for 14H and 16H in the isolated AH-1763 IIa (**1**) are found at $\delta = 2.88$ and $\delta = 4.32$ ppm, respectively, with $J_{H14,H16} = 3.3$ Hz. From these data we conclude that the relative stereochemistry of natural AH-1763 IIa (**1**) is identical to that of the synthetic material (14*S*,16*R*)-**1**. However, the sign of the $[\alpha]_D$ value of the two compounds is opposite. We therefore assume the absolute stereochemisty of the isolated natural product is 14*R*,16*S* even though the value of the optical rotation of (14*S*,16*R*)-AH-1763 IIa (**1**) is higher than that reported for the natural product. Unfortunately, direct comparison of the two com-

pounds was not possible since we did not have a sample of the natural material.

In conclusion, we have developed a new general strategy for the synthesis of anthrapyran antiobotics which resulted in the first enantioselective total synthesis of (14*S*,16*R*)-AH-1763 IIa (**1**) and in addition the determination of the relative and absolute stereochemistry of the natural product **1**.

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