Total Synthesis of Angucyclines, 12[+]

Biomimetic-Type Synthesis of the Racemic Non-Aromatic Angucyclinones of the SF 2315 and SS 228Y Types

Karsten Krohn,*[a] Ulrich Flörke,[a] Christian Freund,[a] and Nasir Hayat[a]

Dedicated to Prof. Wolf Walter on the occasion of his 80th birthday

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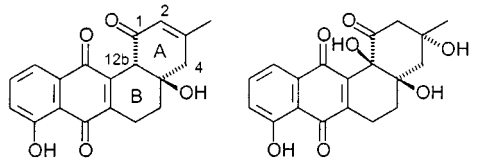
The biomimetic-type aldol reaction of the tricyclic (*E*)-configured precursors **6a/b** gave the racemic nonaromatic angucycline derivatives **11**–**13** of the SF 2315 and SS 288Y types. Chelate controlled conditions in the cyclization of **6b** led to the regioisomeric product **10**.

Introduction

The class of the angularly condensed angucyclines with the benz[*a*]anthracenequinone skeleton has grown to more than 250 structurally defined representatives.[1,2] They exhibit a variety of interesting biological activities, such as antibacterial,[3–5] antifungal,[6–8] antitumor,[9,10] and vincristine-cytotoxicity potentiating activity,[11] platelet aggregation inhibition,[12,13] activity as endothelin receptor antagonists,[14] and inhibition of prolyl,[15] tyrosine,[16] or dopamine hydrolases.[17] The biological activity is most often linked (with the exception of antitumor and weak antibacterial activity) to a nonaromatic ring B and one or more glycosidic connections to deoxy sugars. One or two hydroxyl groups are located at the angular positions connecting the rings A and B, named SF 2315-type,[18,19] [example SF 2315 A (**1**), Scheme 1] [18] or SS 228Y-type,[20,21] [example WP 3688–2 (**2**)][22] (for review see ref.[1]).



Scheme 1. Examples of angucyclines of the SF 2315 and SS 288Y types

In previous studies the stereocontrolled assembly of the SF 2315B ring system was reported by Sulikowski et al.[23] and our group[24,25] using Diels–Alder reactions. We now report on an alternative approach, in which the substitution pattern originally generated by the biosynthetic pathway is constructed in only two successive base-catalyzed aldol reactions of an appropriate oligoketide precursor.

Results and Discussion

The starting materials **4a/b** and **5a/b** (natural pattern a: R = OH, nonnatural pattern b: R = H) were prepared as described previously[26] by an aldol reaction of the open-chain diketone **3** yielding the diastereoisomeric mixtures **4a/5a** and **4b/5b** (both ratios ca. 1:1.8 by NMR spectroscopy) in 88 and 94% yield, respectively. In the preceding communication,[26] only the synthesis of the ring B aromatic angucyclines was reported and separation of the (*E*)- and (*Z*)-isomers **4** and **5** was not required for that purpose. By contrast, the stereochemistry of the vicinal side chains played a major role in the construction of nonaromatic derivatives and the stereoisomers had to be separated. The chromatographic separation of the stereoisomers **4** and **5** could be achieved at the stage of the ketals **4/5** but was carried out more conveniently with the corresponding diketones **6/7**. The best method for ketal cleavage proved to be the procedure of Huet et al.[27] using dilute sulfuric acid adsorbed on silica gel in dichloromethane to yield the mixture of **6/7** almost quantitatively starting from **4/5**. Separation of the diketones by preparative TLC chromatography on silica gel afforded the pure (*E*)-stereoisomers **6a** and **6b** and the (*Z*) isomers **7a** and **7b**. The unambiguous assignment by NMR spectroscopy proved to be difficult in view of the absence of relevant protons at the stereogenic centers, for application of the Karplus rules, or NOE effects. Fortunately, single crystal X-ray analysis of the more polar compound revealed the (*Z*)-stereochemistry of **7a** as shown in Figure 1.

The stage was now set to study the cyclization by mild-base-catalyzed aldol reaction. Preliminary studies at room

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[a] Fachbereich Chemie und Chemietechnik,
University of Paderborn,
Warburger Strasse 100, D-33098 Paderborn, Germany
Fax: (internat.) + 49-5251/603-245
E-mail: kk@chemie.uni-paderborn.de

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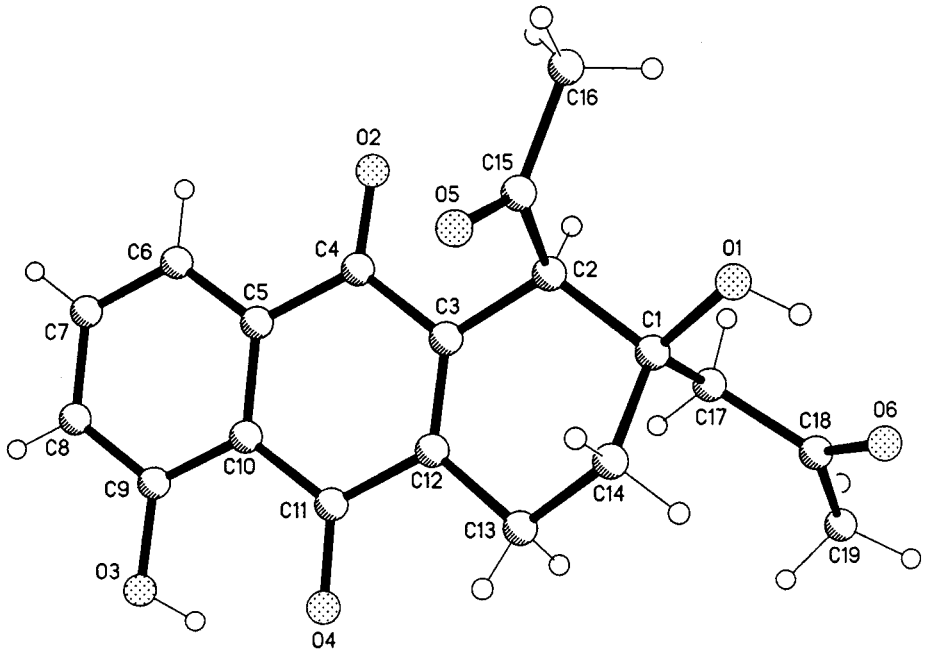
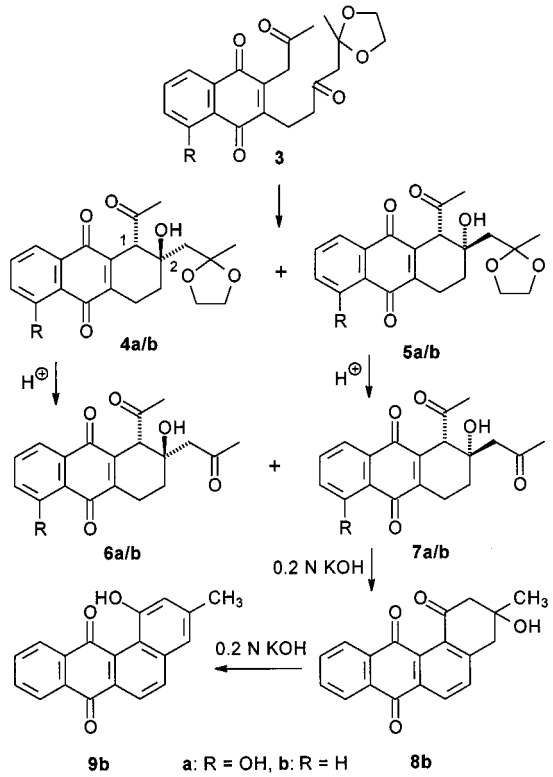


Figure 1. The structure of the (*Z*)-isomer **7a** in the crystal

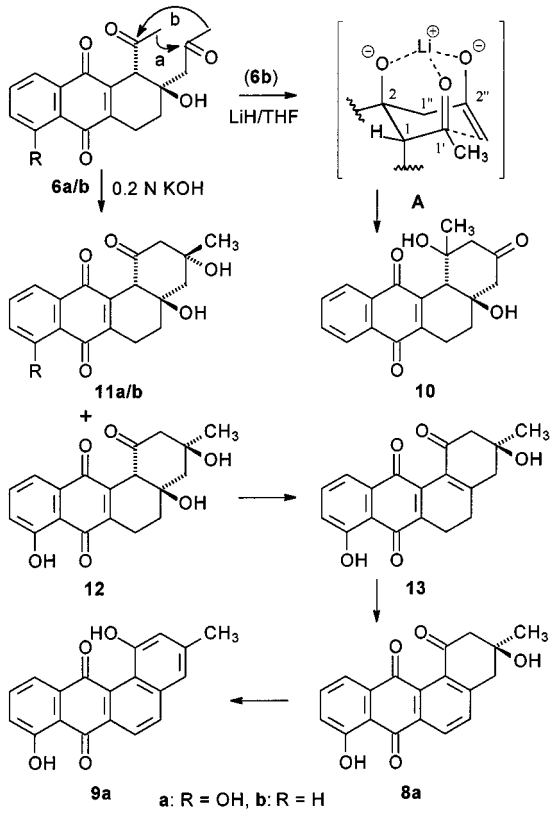


Scheme 2. Starting materials for aldol cyclizations and reaction of the (*Z*)-isomer **7b**

temperature of either isomer **6** or **7** always led to decomposition, or complete aromatization to benzo[*a*]anthraquinones by twofold water elimination. We therefore decided to test the reaction at much lower temperatures (–25 to –60 °C). The reaction of the (*Z*)-isomer **7b**, with two *trans*-configured ketide chains attached to C-1 and C-2, was studied first. Virtually no reaction occurred below –35 °C and a very slow conversion was observed above –25 °C in 0.2 N methanolic KOH. This yielded only the aromatic angucyclines 8-deoxytetrangomycin (**8b**) and 8-deoxytetrangulol (**9b**), identical with samples from previous biomimetic[26] and Diels–Alder reactions[28] (Scheme 2).

Disappointingly, no trace of the more interesting nonaromatic cyclization products could be detected. The low reactivity and the total absence of hydroaromatic intermediates suggested that water elimination preceded the aldol reaction. How can this behavior be explained? From model considerations, the steric requirements of the transition states leading to a *trans*-decalin system should be comparable to those leading to the *cis*-decalin arrangement of rings A and B. However, there are electronic effects to rationalize the high activation energy for cyclization of **7b** to nonaromatic cyclization products. The ketide side chains necessarily have to assume a bisequatorial configuration for six-membered ring formation. Consequently, the negatively charged oxygen of the enolate of the C-1 acetyl group has to approach the oxygen carbonyl of the naphthoquinone for formation of the regioisomers of type **8** or **9** which were isolated in the reaction. Presumably, this electrostatic repulsion prevents cyclization to hydroaromatic products, and side reactions such as base-catalyzed water elimination can take place. Remarkably, to the best of our knowledge, in nature there are no known angucyclines with a *trans* fusion of rings A and B.[29]

In the next series, the influence of catalytic amounts of base on the (*E*)-isomers **6a/b** with *cis*-alkyl chains at C-1 and C-2 was studied. In the previous experiment with the (*Z*)-isomer **7b**, chelate-breaking alkaline methanolic conditions were employed. To study the influence of the reaction conditions on the regio- and stereochemical outcome, we now employed chelate-controlled conditions (LiH in THF).



Scheme 3. Cyclization of **6a/b** under chelate-breaking and chelate-controlled conditions

Surprisingly, the regioisomer **10** resulting from cyclization mode (b) in **6b** was isolated as the major product (55%) in addition to minor amounts (13%) of the 8-deoxytetrangomycin **8b**. It was not possible to elucidate the relative configuration of **10** by analysis of the NMR spectra. However, there was no doubt about the configuration of the regioisomer **10**, which was in agreement with the NMR spectroscopic data. In addition, the structure was confirmed by chemical evidence. This regioisomer failed to undergo acid-catalyzed aromatization to **9b**, a rapid and infallible test for formation of benz[*a*]anthracenequinone with a phenolic hydroxyl group at C-1 [cyclization mode (a) in **6**]. The preference of cyclization mode (b) under the chelation-controlled conditions can be rationalized by a modified Zimmerman-Traxler transition state A, in which an optimal chelation of the lithium cation with three oxygens is possible (Scheme 3).

Finally, the most promising cyclization experiments were performed with the (*E*)-isomers **6a** and **6b** under chelate-breaking conditions at –45 to –55 °C in 0.2 N methanolic KOH. The slow emergence of a polar cyclization product in the reaction of **6b** could be observed by TLC. At longer reaction times (ca. 2 days), the previously observed aromatization products 8-deoxytetrangomycin **8b** (30%) and trace amounts of 8-deoxytetrangulol **9b** were also isolated in addition to the major nonaromatic product **11b** (63%) (at 48% conversion). Again, the elucidation of the relative configuration at the two quaternary centers at C-3 and C-4a of **11b** was difficult by NMR methods. However, it was possible to achieve an X-ray single crystal analysis proving the *trans* arrangement of the respective hydroxyl groups of **11b** as shown in Figure 2.

A similar base-catalyzed aldol reaction at –55 °C was performed with the diketone **6a** (R = OH) leading to products with the natural substitution pattern. Interestingly, in this experiment, two additional polar cyclization products were formed. Again, the most polar constituent corresponded to the *trans*-diol **11a** (24%) as verified by comparison of the NMR spectra of **11b** which was almost identical in the relevant parts. Essential parts of the data of **11a** were also very similar to those of the natural product **2**, isolated by Gould and Cheng in 1993 from *Streptomyces phaeochromogenes* WP 3688.[22] The racemic synthetic material **11a** can thus be named 4a-deoxy WP 3688–2 and it is also related to SF 2315 A (**1**), the product of water elimination from **11a**. In the biosynthesis, the hydroxyl group at C-12a present in WP 3688–2 does not originate from the common 1,3-oxygen pattern of the polyketide precursors. The oxygen is intro-

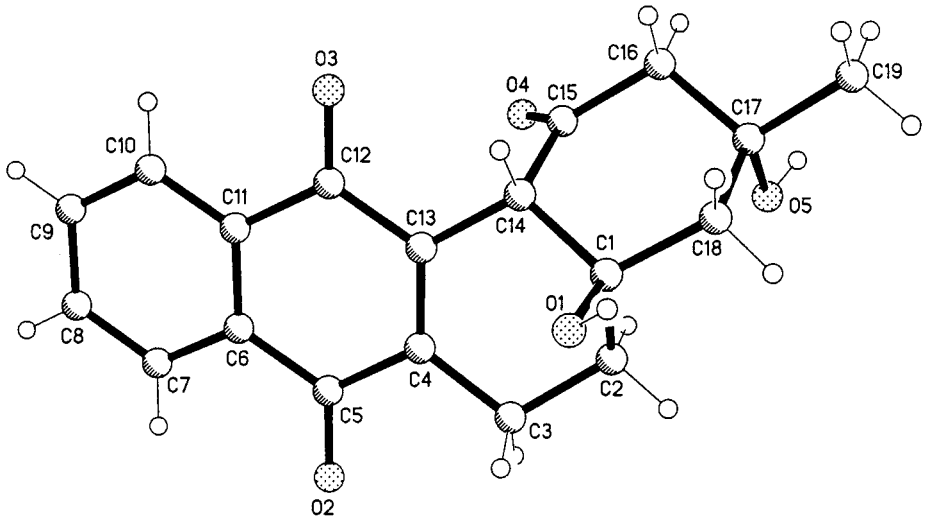


Figure 2. The structure of the *trans*-diol **11b** in the crystal

duced by later oxygenation with atmospheric oxygen as established by the elegant work of Rohr et al.[30] Although **11a** or its 5,6-desaturation product is postulated as one of the early intermediates in the biosynthesis of the largest group of nonaromatic angucyclines, it has not yet been isolated from natural sources.

The *cis*-diol structure **12** (8.5%) was assigned to the second most polar product as deduced from the NMR spectra, the HRMS spectrum, and the chemical transformation to tetrangomycin **8a** and tetrangulol **9a**. The *cis*-diol **12** was very unstable relative to the *trans* isomer **11a**. A solution of **12** in $CDCl_3$ decomposed by water elimination on standing for a few hours. This elimination product was also formed in the alkaline reaction mixture as the third most polar compound. On standing in solution, it was further transformed by dehydrogenation to the natural product tetrangomycin **8a**, isolated in 9% yield from the aldol reaction mixture. Several possible olefinic structures, but most plausibly **1** and **13**, can be postulated as being formed by loss of one molecule of water from **12**. An assignment in favor of **13** could be made unambiguously by the absence of the proton at C-12b and the presence of two new quaternary carbons C-4a and C-12b in the NMR spectra. The isolation of the intermediate **13** from natural sources has not yet been reported. The instability of the *cis* isomer **12** when compared to the *trans* isomer **11a** can perhaps be explained by the enhanced leaving-group capability of 4a-OH in **12** by chelation with the neighboring hydroxyl group at C-3.

In conclusion, a biomimetic-type aldol reaction of **6a/b**, with *cis* orientated side chains at C-1 and C-2, with methanolic KOH at low temperature led, for the first time, to the isolation of nonaromatic angucycline derivatives **11**–**13** of the SF 2315 and SS 288Y types. Under chelate controlled conditions the regioisomeric cyclization product **10** was formed.

Experimental Section

For general methods and instrumentation see ref.[31]

Cleavage of the Ketals 4a/5a: A suspension of silica gel (800 mg) in CH_2Cl_2 (9 mL) was treated with 15% aqueous H_2SO_4 (80 mg) and stirred for ca. 15 min. A mixture of **4a/5a**[26] (208 mg, 0.54 mmol) was then added, the suspension was stirred for 4 h at 20 °C (TLC monitoring), filtered, and the filtrate washed with water (10 mL). The organic phase was dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was separated by preparative TLC chromatography on silica gel (CH_2Cl_2/MeOH, 100:1) to afford the nonpolar (*E*)-isomer **6a** (20 mg, 34%) m.p. 158−160 °C and the polar (*Z*)-isomer **7a** (36 mg, 60%) m.p. 160−162 °C as yellow solids.

(*E*)-1-Acetyl-2,5-dihydroxy-2-(2-oxopropyl)-1,2,3,4-tetrahydroanthraquinone (6a): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.91−1.95 (m, 2 H, 3-H), 2.29 (s, 3 H, 3′′-H), 2.51 (s, 3 H, 2′-H), 2.72−2.87 (m, 4 H, 4-H and 1′′-H), 4.36 (s, 1 H, 1-H or OH), 4.42 (s, 1 H, 1-H or OH), 7.24−7.25 (m, 1 H, 6-H), 7.58−7.61 (m, 2 H, 7-H and 8-H), 12.01 (s, chel. OH). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.04, 29.27 (2 × t, C-3 and C-4), 31.90, 33.23 (2 × q, C-2′ and C-3′′), 49.97 (t, C-1′′), 56.66 (d, C-1), 70.66 (s, C-2), 115.30 (s, C-8a or C-10a), 119.46, 124.70 (2 × d, C-6 and C-7), 132.18 (s, C-8a or C-10a), 136.06 (d, C-8), 142.95, 146.62 (2 × s, C-4a and C-9a), 161.82 (d, C-5), 184.76, 189.98 (2 × s, C-9 and C-10), 208.14 (s, C-1′), 210.89 (s, C-2′′).

(*Z*)-1-Acetyl-2,5-dihydroxy-2-(2-oxopropyl)-1,2,3,4-tetrahydroanthraquinone (7a): UV (CH_2Cl_2): λ_{max} (lg ε) = 425 nm (3.63), 304 (3.24), 273 (4.03), 256 (3.97). − IR (KBr): $\tilde{\nu}$ = 3454 cm^{-1} (OH), 2941 (CH), 2916 (CH), 2850 (CH), 1712 and 1695 (C=O), 1658 and 1633 (C=O), 1608, 1458, 1350, 1287, 1178, 1137, 954, 779, 707. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.68−1.96 (m, 1 H, 3-H or 4-H), 2.02−2.10 (m, 1 H, 3-H or 4-H), 2.20 (s, 3 H, 3′′-H), 2.30−2.49 (m, 1 H, 3-H or 4-H), 2.48 (s, 3 H, 2′-H), AB-system: [δ_A = 2.62 (d), δ_B = 2.74 (d), *J* = 18.0 Hz, 2 H, 1′′-H), 2.94−3.04 (m, 1 H, 3-H or 4-H), 4.17 (s, 1 H, 1-H), 4.50 (s, 1 H, OH), 7.21−7.28 (m, 1 H, 6-H), 7.54−7.62 (m, 2 H, 7-H and 8-H), 12.00 (s, 1 H, chel. OH). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.92, 29.03 (2 × t, C-3 and C-4), 32.25, 33.70 (2 × q, C-2′ and C-3′′), 49.85 (t, C-1′′), 55.04 (d, C-1), 115.60 (s, C-10a), 119.60, 124.85 (2 × d, C-6 and C-7), 132.09 (s, C-8a), 136.75 (d, C-8), 143.18, 145.47 (2 × s, C-4a and C-9a), 161.86 (s, C-5), 183.85, 189.84 (2 × s, C-9 and C-10), 207.23, 210.70 (2 × s, C-1′ and C-2′′). − MS (EI, 159 °C): *m*/*z* (%) = 342 (6) [M^+], 300 (8) [$M^+ + 1 - COCH_3$], 282 (73) [$M^+ + 1 - COCH_3 - H_2O$], 240 (58), 225 (23) 43 (100) [$C_2H_3O^+$]. − $C_{19}H_{18}O_6$ (342.35): calcd. C 66.66, H 5.30; found C 64.78, H 4.19.

X-ray Structure Analysis of 7a:[32] $C_{19}H_{18}O_6$, crystal size 0.22 × 0.28 × 0.47 mm, M_r = 342.3, triclinic, space group *P*1(bar), *a* = 6.925(1), *b* = 8.066(1), *c* = 14.922(2) Å, α = 88.58(2), β = 88.56(1), γ = 85.44(2)°, *V* = 830.4(2) Å^3, *Z* = 2, $D_{calcd.}$ = 1.369 g cm^{-3}, μ = 0.10 mm^{-1}, *F*(000) = 360. Data collection was performed on a Siemens P4 diffractometer using graphite monochromated Mo-K_α radiation, ω-scan, 5 < 2Θ < 50°; –8 ≤ *h* ≤ 1, –9 ≤ *k* ≤ 9, –17 ≤ *l* ≤ 17, 3720 reflections collected, 2928 unique reflections, R_{int} = 0.022, LP correction. Structure solved by direct and conventional Fourier synthesis, full-matrix least-squares refinement based on F^2 and 231 parameters, all but H-atoms refined anisotropically, H-atoms refined with riding model. Refinement converged at *R*1 = 0.054, *wR*2 (all data) = 0.134, Goof = 1.018, min/max height in final ΔF map –0.16/0.17 eÅ^{-3}, max(δ/σ) = 0.001. Programs used: SHELXTL.[33]

Cleavage of the Ketals 4b/5b: A mixture of **4b/5b**[26] (200 mg, 0.54 mmol) was treated as described for **6a/7a** to afford the nonpolar (*E*)-isomer **6b** (59.5 mg, 34%) m.p. 177.5 °C and the polar (*Z*)-isomer **7b** (108.5 mg, 62%) m.p. 154 °C as yellow solids.

(1*R,2*S**)-1-Acetyl-2-hydroxy-2-(2-oxopropyl)-1,2,3,4-tetrahydroanthraquinone (6b):** ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.79−1.99 (m, 2 H, 3-H), 2.25 (s, 3 H, 3′′-H), 2.49 (s, 3 H, 2′-H), 2.69−2.84 (m, 4 H, 4-H and 1′′-H), 4.34 (s, 1 H, 1-H or OH), 4.43 (s, 1 H, 1-H or OH), 7.67−7.72 (m, 2 H, 6-H and 7-H), 7.98−8.10 (m, 2 H, 5-H and 8-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.61, 29.54 (2 × t, C-3 and C-4), 31.95, 33.26 (2 × q, C-2′ and C-3′′), 49.90 (t, C-1′′), 56.72 (d, C-1), 70.83 (s, C-2), 126.68, 126.79 (2 × d, C-5 and C-8), 132.18, 132.41 (2 × s, C-8a and C-10a), 134.02, 134.19 (2 × d, C-6 and C-7), 141.90, 146.19 (2 × s, C-4a and C-9a), 184.76, 185.15 (2 × s, C-9 and C-10), 208.53 (s, C-1′), 211.00 (s, C-2′′).

(1*R,2*R**)-1-Acetyl-2-hydroxy-2-(2-oxopropyl)-1,2,3,4-tetrahydroanthraquinone (7b):** ^{1}H NMR (200 MHz, $CDCl_3$): δ = AB-system: [δ_A = 1.78−1.84 (m), δ_B = 2.02−2.14 (m), 2 H, 3-H], 2.20 (s, 3 H, 3′′-H), AB-system: [δ_A = 2.34−2.44 (m), δ_B = 2.93−3.05 (m), 2 H, 4-H], 2.50 (s, 3 H, 2′-H), AB-system: [δ_A = 2.63 (d), δ_B = 2.75

(d), ^2J = 17.8 Hz, 2 H, 1′′-H], 4.19 (s, 1 H, 1-H), 4.51 (s, 1 H, OH), 7.68−7.75 (m, 2 H, 6-H and 7-H), 7.97−8.09 (m, 2 H, 5-H and 8-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.46, 29.10 (2 × t, C-3 and C-4), 32.26, 33.72 (2 × q, C-2′ and C-3′′), 49.86 (t, C-1′′), 54.97 (d, C-1), 72.17 (s, C-2), 126.77 (2 × d, C-5 and C-8), 132.12, 132.36 (2 × s, C-8a and C-10a), 134.18, 134.34 (2 × d, C-6 and C-7), 142.05, 145.55 (2 × s, C-4a and C-9a), 184.63, 184.73 (2 × s, C-9 and C-10), 207.54 (s, C-1′), 210.83 (s, C-2′′).

Cyclization of the (*E*)-Isomer 6a: To a solution of KOH in dry methanol (0.2 M, 30 mL) was added the dione **6a** (30 mg, 0.077 mmol) under argon at –55 °C and the mixture was stirred for ca. 72 h at this temperature (TLC monitoring). The mixture was then acidified by addition of 1 M HCl (8 mL) and a saturated aqueous solution of NH_4Cl (35 mL). The aqueous phase was extracted three times with CH_2Cl_2 (15 mL), the combined organic phases were washed with water (15 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was separated by preparative TLC on silica gel (1 mm, (CH_2Cl_2/MeOH, 100:3) to afford the starting material **6a** (10.5 mg, 35%), the *trans*-diol **11a** (5.1 mg, 24%), the *cis*-diol **12** (1.8 mg, 8.5%), the olefin **13** (5.1 mg, 25.5%), tetrangomycin **(8a)** (1.8 mg, 9%) and tetrangulol (**9a**) (0.5 mg, 2.6%).

(3*S,4a*S**,12b*R**)-3,4,4a,5,6,12b-Hexahydro-3,4a,8-trihydroxy-3-methyl-2*H*-benz[*a*]anthracene-1,7,12-trione (11a)**: m.p. 210 °C (dec.). – UV (CH_2Cl_2): λ_{max} (lg ε) = 422 nm (3.71), 271 (4.13), 250 (4.04). − IR (KBr): $\tilde{\nu}$ = 3494 cm^{-1} (OH), 3408 (OH), 2962 (CH), 2925 (CH), 1708 (C=O), 1640 and 1633 (C=O), 1612. − ^{1}H NMR (200 MHz, [D_6]acetone): δ = 1.28 (s, 3 H, CH_3), 1.54−1.65 (m, 1 H, 5-H), 2.04−2.15 (m, 2 H, 2-H or 5-H), 2.19−2.37 (m, 2 H, 4-H), 2.47−2.57 (m, 2 H, 2-H or 6-H), 2.77−2.84 (m, 1 H, 6-H), 3.71 (s, 1 H, C-3-OH), 3.89 (s, 1 H, 12b-H), 4.03 (s, 1 H, C-4a-OH), 7.13−7.17 (dd, J = 7.2 Hz, J = 1.1 Hz, 1 H, 9-H), 7.41−7.44 (m, J = 7.2 Hz, 1 H, 10-H), 8.31 (m, J = 7.6 Hz, 1 H, 11-H), 11.99 (s, 1 H, C-8-OH). − ^{13}C NMR (75 MHz, [D_6]acetone): δ = 20.45 (t, C-6), 31.25 (t, C-5), 31.53 (q, CH_3), 51.87 (t, C-4), 54.00 (t, C-2), 56.28 (d, C-12b), 71.53 (s, C-3), 72.07 (s, C-4a), 115.28 (s, C-7a), 118.87 (d, C-9), 123.77, (d, C-10), 132.75 (s, C-11a), 136.71 (d, C-11), 142.68, 145.34 (2 × s, C-12a and C-6a), 161.41 (s, C-8), 183.28, 190.40 (2 × s, C-12 and C-7), 204.69 (s, C-1). − MS (EI, 240 °C): *m*/*z* (%) = 343 (15) [M^+], 324 (15) [$M^+ - H_2O$], 307 (10) [$M^+ - 2\ H_2O$], 265 (20) 240 (100), 225 (19), 43 (22) [$C_2H_3O^+$], 18 (9) [H_2O^+]. − HRMS ($C_{19}H_{18}O_6$): calcd. 342.1103; found 342.1097.

(3*R,4a*S**,12b*R**)-3,4,4a,5,6,12b-Hexahydro-3,4a,8-trihydroxy-3-methyl-2*H*-benz[*a*]anthracene-1,7,12-trione (12):** m.p. 150−152. – UV (CH_2Cl_2): λ_{max} (lg ε) = 422 nm (3.62), 273 (4.04), 250 (3.99). − IR (KBr): $\tilde{\nu}$ = 3475 cm^{-1} (OH), 3441 (OH), 2950 (CH), 2929 (CH), 1708 (C=O), 1666 (C=O), 1645 (C=O), 1462, 1366, 1300, 1270, 1237, 1195, 1141, 762. − ^{1}H NMR (200 MHz, [D_6]acetone): δ = 1.13 (s, 3 H, CH_3), 1.65−1.83 (m, 2 H, 4-H), 1.97−2.00 (s, 1 H, 2-H), 2.13−2.38 (m, 2 H, 5-H or 6-H), 2.60−2.66 (m, 2 H, 5-H or 6-H), 2.40 (s, 1 H, 2-H), 3.71 (s, 1 H, 12b-H), 4.45 (s, 1 H, C-3-OH), 4.58 (s, 1 H, C-4a-OH), 7.13−7.17 (dd, J = 8.4 Hz, 1 H, 9-H), 7.38−7.42 (m, J = 7.5 Hz, 1 H, 10-H), 7.55−7.63 (m, J = 8.2 Hz, 1 H, 11-H), 11.90 (s, 1 H, C-8-OH). − ^{13}C NMR (75 MHz, [D_6]acetone): δ = 21.58 (t, C-6), 30.55 (q, CH_3), 33.53 (t, C-5), 47.42 (t, C-4), 53.60 (t, C-2), 57.96 (d, C-12b), 73.59, 73.84 (2 × s, C-3 and C-4a), 115.28 (s, C-7a), 119.21 (d, C-9), 124.27 (d, C-10), 133.60 (s, C-11a), 136.71 (d, C-11), 142.84 (s, C-12a), 145.89 (s, C-6a), 161.80 (s, C-8), 183.36, 184.41 (2 × s, C-12 and C-7), 206.67 (s, C-1). − MS (EI, 200 °C): *m*/*z* (%) = 343 (12) [M^+], 324 (60) [$M^+ - H_2O$], 306 (100) [$M^+ - 2H_2O$], 265 (30), 264 (77), 240 (90), 225 (19), 43 (22) [$C_2H_3O^+$], 18 (32) [H_2O^+]. − HRMS ($C_{19}H_{18}O_6$): calcd. 342.1103; found 342.1097.

3,8-Dihydroxy-3-methyl-3,4,5,6-tetrahydro-2*H*-benz[*a*]anthracene-1,7,12-trione (13): m.p. 187 (dec.). − UV (CH_2Cl_2): λ_{max} (lg ε) = 421 nm (3.15), 300 (3.26), 233 (3.69). − IR (KBr): $\tilde{\nu}$ = 3420 cm^{-1} (OH), 2960 (C–H), 2924 (C–H), 1729 (C=O), 1673 (C=O), 1655 (C=O). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.29 (s, 3 H, CH_3), 2.45−3.54 (m, 2 H, 5-H or 6-H), 2.73−3.92 (m, 2 H, 5-H or 6-H), 2.82 (s, 2 H, 2-H or 4-H), 2.85 (s, 2 H, 2-H or 4-H), 3.62 (s, C-3-OH), 7.23−7.26 (m, 1 H, 9-H), 7.60−7.63 (m, 2 H, 10-H and 11-H), 12.03 (s, 1 H, C-8-OH). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.71 (t, C-6), 29.24 (t, C-5), 29.35 (q, CH_3), 45.46 (t, C-4), 52.20 (t, C-2), 71.49 (s, C-3), 114.89 (s, C-7a), 119.08 (d, C-9), 123.44 (d, C-10), 129.78 (s, C-11a and 6a), 132.94 (s, C-8a), 136.06 (d, C-11), 141.27, 141.70 (2 × s, C-12a and C-12b), 160.00, 160.90, (2 × s, C-4a and C-8), 182.12, 188.40 (2 × s, C-7 and C-12), 193.34 (s, C-1). − MS (EI, 188 °C): *m*/*z* (%) = 324 (12) [M^+], 306 (60) [$M^+ - H_2O$], 266 (100) [$M^+ - H_2O + 3 - C_2H_3O$], 264 (20), 237 (18), 225 (19), 43 (7) [$C_2H_3O^+$], 18 (18) [H_2O^+]. − HRMS ($C_{19}H_{16}O_5$): calcd. 324.0997; found 324.0995.

Cyclization of the (*E*)-Isomer 6b: The dione **6b** (25 mg, 0.077 mmol) was treated for ca. 90 h at –40 to –50 °C with 0.2 M methanolic KOH, as described above for **6a**, to afford the starting material (13.1 mg, 52%), the diol **11b** (7.5 mg, 63%) m.p. 201 °C (dec.), 8-deoxytetrangomycin[26] (**8b**) (3.4 mg, 30%) m.p. 214 °C and 8-deoxytetrangulol (**9b**) (0.5 mg, 2.6%).[26] Compounds **8b** and **9b** were also formed by similar treatment of **7b** at –25 °C.

(3*S,4a*S**,12b*R**)-3,4,4a,5,6,12b-Hexahydro-3,4a-dihydroxy-3-methyl-2*H*-benz[*a*]anthracene-1,7,12-trione (11b):** IR (KBr): $\tilde{\nu}$ = 3492 cm^{-1} (OH), 3411 (OH), 2960 (C–H), 2930 (C–H), 1702 (C=O), 1661 (C=O), 1644 (C=O), 1589 (C=C). − UV (methanol): λ_{max} (lg ε) = 270 nm (3.52), 331 (2.74). − ^{1}H NMR (600 MHz, [D_6]acetone): δ = 1.42 (s, 3 H, CH_3), AB-system: [δ_A = 1.72 (m), δ_B = 2.24 (m), 2 H, 5-H], AB-system: [δ_A = 2.22 (dd), δ_B = 2.44 (d), ^2J = 14.1 Hz, ^4J = 2.5 Hz, 2 H, 4-H], AB-system: [δ_A = 2.37 (dd), δ_B = 2.94 (d), ^2J = 12.8 Hz, ^4J = 2.5 Hz, 2 H, 2-H], 2.59−2.74 (m, 2 H, 6-H), 3.77 (s, 1 H, C-3-OH), 4.04 (s, 1 H, 12b-H), 4.08 (s, 1 H, C-4a-OH), 7.77−7.86 (m, 2 H, 9-H and 10-H), 7.98−8.11 (m, 2 H, 8-H and 11-H). − ^{13}C NMR (75 MHz, [D_6]acetone): δ = 21.45 (t, C-6), 31.09 (t, C-5), 32.04 (q, CH_3), 52.52 (t, C-4), 54.52 (t, C-2), 56.74 (d, C-12b), 72.00 (s, C-3), 72.60 (s, C-4a), 126.69, 126.76 (2 × d, C-8 and C-11), 134.09 (2 × s, C-7a and C-11a), 134.42 (2 × d, C-9 and C-10), 141.76 (s, C-12a), 145.83 (s, C-6a), 184.48 (s, C-12), 185.00 (s, C-7), 205.19 (s, C-1). − MS (DCI negative, NH_3, 8 mA/s): *m*/*z* (%) = 326 (100) [M^+], 308 (37) [$M^+ - H_2O$], 290 (23) [$M^+ - 2H_2O$]. − HRMS ($C_{19}H_{18}O_5$): calcd. 326.11542; found 326.11571.

X-ray Structure Analysis of 11b:[32] $C_{19}H_{18}O_5$, crystal size 0.06 × 0.07 × 0.58 mm, M_r = 326.3, monoclinic, space group $P2_1/n$, a = 5.7780(4), b = 19.885(6), c = 13.319(6) Å, β = 100.37(3)°, V = 1505.8(1) Å^3, Z = 4, $D_{calcd.}$ = 1.439 g cm^{-3}, μ = 0.10 mm^{-1}, F(000) = 688. Data collection as before, $4 < 2\Theta < 50°$, $-6 \le h \le 0$, $-23 \le k \le 0$, $-15 \le l \le 15$, 2876 reflections collected, 2622 unique reflections, R_{int} = 0.053, LP correction. Structure solved by direct and conventional Fourier synthesis, full-matrix least-squares refinement based on F^2 and 220 parameters, all but H-atoms refined anisotropically, H-atoms at calculated positions refined with riding model. Refinement converged at $R1$ = 0.069, $wR2$ (all data) = 0.175, Goof = 1.002, min/max height in final ΔF map –0.23/0.23 eÅ^{-3}, max(δ/σ) = 0.001. Programs as before.[33]

(1*RS*,4a*S,12b*S**)-1,4a-Dihydroxy-1-methyl-1,4,4a,5,6,12b-hexahydro-2*H*-benz[*a*]anthracene-3,7,12-trione (10):** The (*E*)-isomer **6b**

was added under argon at −25 °C to a suspension of LiH (4 mg, 0.50 mmol) in dry THF (10 mL). The mixture was stirred for 4 days at −25 °C (TLC monitoring) and was then acidified by addition of 1 M HCl (6 mL) and saturated NH_4Cl solution (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), washed with water (10 mL), dried (Na_2SO_4), and the solvent removed under reduced pressure. Chromatographic separation by TLC (1 mm, silica gel) (CH_2Cl_2/MeOH, 100:5) afforded the starting material **6b** (3 mg, 16%), **9b** (2 mg, 13%) and **10** (9 mg, 55%) as a yellow solid, m.p. 211 °C (dec.). − IR (KBr): $\tilde{\nu}$ = 3444 cm^{-1} (OH), 3384 (OH), 2966 (C–H), 2925 (C–H), 1699 (C=O), 1659 (C=O), 1643 (C=O), 1626 (C=C), 1592 (C=C). − UV (methanol): λ_{max} (lg ε) = 237 nm (3.09), 270 (3.66), 329 (2.89). − ^{1}H NMR (200 MHz, [D$_6$]acetone): δ = 1.18 (s, 3 H, CH_3), 1.62−1.64 (m, 1 H, 5-H_a), 2.30−2.55 (m, 3 H, 2-H_a, 4-H_a and 5-H_b), 2.64−2.66 (m, 2 H, 6-H), 2.85−2.99 (m, 2 H, 2-H_b and 4-H_b), 3.74 (s, 1 H, 12b-H), 3.84 (s, 1 H, OH), 4.04 (br s, 1 H, OH), 7.80−7.84 (m, 2 H, 9-H and 10-H), 8.04−8.07 (m, 2 H, 8-H and 11-H). − ^{13}C NMR (50 MHz, $CDCl_3$/[D$_4$]MeOH, 9:1): δ = 21.44 (t, C-6), 29.59 (t, C-5), 31.17 (q, CH_3), 47.58 (d, C-12b), 55.03, 55.56 (2 × t, C-2 and C-4), 72.29, 73.83 (2 × s, C-1 and C-4a), 126.03, 126.29 (2 × d, C-8 and C-11), 132.03, 132.15 (2 × s, C-7a and C-11a), 133.38, 133.45 (2 × d, C-9 and C-10), 141.54, 147.78 (2 × s, C-6a and C-12a), 184.60, 185.36 (2 × s, C-7 and C-12), 208.28 (s, C-3). − MS (DCI negative, NH_3, 8 mA/s): *m/z* (%) = 326 (100) [M^+], 268 (<1), 226 (<1), 147 (<1). − HRMS ($C_{19}H_{18}O_5$): calcd. 326.11542; found 326.11603.

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[32] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-137358 for **7a** and CCDC-137359 for **11b**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].
[33] SHELXTL NT, Ver. 5.10, Bruker Analytical X-ray Systems, Madison, Wisconsin, USA.

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