Construction of the Cyclopenta[1,3]cyclopropa[1,2-*b*]naphthalene System in a One-Pot Domino Reaction☆

Karsten Krohn*, Christian Freund, and Ulrich Flörke

Fachbereich Chemie und Chemietechnik der Universität–GH Paderborn,
Warburger Straße 100, D-33098 Paderborn, Germany
Fax: (internat.) + 49(0)5251/603245
E-mail: kk@chemie.uni-paderborn.de

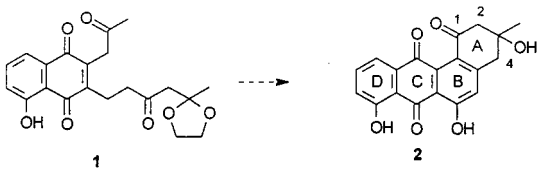
Received June 27, 1998

Keywords: Domino reactions / Spirocyclization / Michael additions / β-Dicarbonyl compounds / Nucleophilic substitution

Base treatment of the angucycline oligoketide precursor **6** unexpectedly afforded the spirocyclization product **7**. An additional step in the domino cyclization process was observed starting from the quinoid bromo diketone **3b** to yield stereospecifically the condensed tetracycle **8** with the benzo-annelated skeleton of the cubebol-type sesquiterpenes. The structure of **8** was confirmed by X-ray structure analysis. Further extension of the domino sequence by reaction of the dibromide **10** with acetonedicarboxylic ester **11** gave the cyclization/condensation products **12**, **13**, or **14**, depending on the reaction conditions.

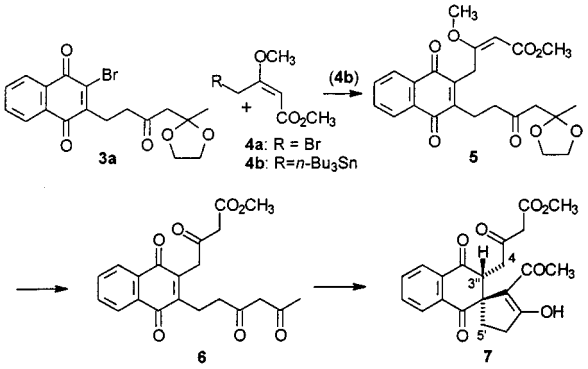
In a preceding communication we described the biomimetic-type synthesis of angucyclines such as rabelomycin (**2**) by sequential cyclization of the open-chain ketide **1** (Scheme 1,[1] see review[2]). The method was limited to the class of angucyclines with aromatic ring B since the first aldol product derived from **1** could not be cyclized to hydroaromatic precursors of the SS-228Y- or SF-2315-type (review on angucyclines: ref.[3]).

Scheme 1



Insufficient acidity of the terminal methyl group of the top side-chain in the oligoketide **1** could be one reason for the failure of the second cyclization step in the hydroaromatic series. The acidity of this position could be increased by addition of a terminal ester group as shown in the β-oxo ester **6** (Scheme 2). The ketide **6** is also more related to possible biosynthetic precursors of the angucycline antibiotics (reviews: refs.[2][3]). Surprisingly, and in contrast to the behavior of ketone **1**, the oxo ester **6** did *not* give the six-membered aldol cyclization product but the spiro compound **7** upon treatment with a mild base (potassium carbonate in 2-propanol). This interesting Michael-type reaction to spiro compounds, discovered by serendipity, initiated an investigation of the domino reactions of the multifunctional electrophile **10** with the bifunctional nucleophile acetonedicarboxylic ester **11**. We now report on the results of these reactions culminating in the one-pot synthesis of the tetracyclic ring systems **8** or **14**.

Scheme 2



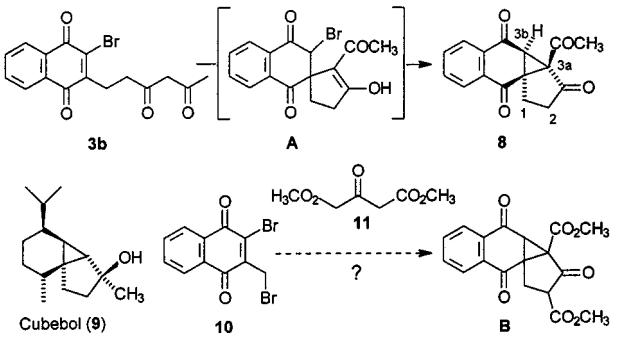
The requisite oxo ester **6** was prepared by attachment of a C_4 side-chain on the bromonaphthoquinone **3a**[4] by a Stille reaction[5] with the allylstannane **4b** (Scheme 2). The new allylstannane **4b** was obtained by coupling the corresponding bromide **4a** with tri-*n*-butylstannyl chloride with activated zinc and ultrasound irradiation (91%). The Stille reaction afforded the unsaturated ester **5** (88%) which was hydrolyzed in one step to the pentaoxo ester **6** (81%) and cyclized to the spiro compound **7** (60%) by treatment with potassium carbonate in 2-propanol. Only one diastereoisomer was formed, and the relative stereochemistry was established by NOE experiments as shown in formula **7**. Irradiation at the resonance of the acetyl methyl group showed a strong NOE enhancement (11%) of the signal for the proton at C-3′′ and the *cis* orientation of the methylene groups at C-4 and C-5′ was further confirmed by NOE interaction. The ^{1}H-NMR spectrum also indicated the almost

  1434−193X/98/1212−2713 $ 17.50+.50/0

entire enolization of the cyclic 1,3-diketone moiety of the molecule.

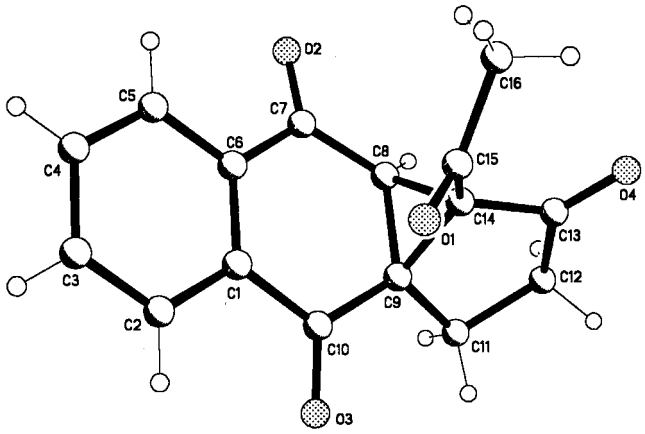
Encouraged by this interesting spirocyclization, we next studied the reactivity of the related bromo diketone **3b**. Whereas the top oxo ester side-chain in the dialkylated naphthoquinone **6** did not play any evident role in the spirocyclization to **7**, a different behavior was expected from the reaction of the related bromo diketone **3b**. The vinylic bromine in **3b** is unreactive in normal S_N-type substitution reactions. However, a highly reactive sp^3-α-oxo bromide is generated after initial spirocyclization to the intermediate **A** and the condensed cyclopenta[1,3]cyclopropa[1,2-*b*]naphthalene ring system may now be formed in a domino displacement reaction. The experiment showed that our assumption was indeed correct and the highly functionalized tetracycle **8** was isolated as a single diastereoisomer in 68% in the two-step one-pot domino reaction (Scheme 3). The relative stereochemistry of the ring system with three stereoselectively generated chiral centers was established by X-ray analysis as shown in the stereoplot of the molecule in the crystal (Figure 1).[6] Inspection of models confirmed that the system with the *cis*-annelated five- and six-membered rings is relatively unstrained, except from the usual strain in the cyclopropane ring. The related (not benzoannelated) tricyclo[4.4.0.$0^{1,5}$] decane ring system with identical stereochemistry is found in many naturally occurring sesquiterpenes such as cubebol (**9**) isolated from *Piper cubeba*[7] (synonyms 4-cubebanol, β-D-galactopyranoside: arvoside A). A synthesis of this class of natural products may potentially be achieved starting from monocyclic analogs of the dibromide **10**.

Scheme 3



In the next step of our investigation, we tried to extend the domino sequence further by an additional reaction. The challenge was the construction of the entire tetracyclic ring system **B** in a one-pot reaction by simply mixing the dibromide **10** with bifunctional β-oxo esters such as acetonedicarboxylic ester **11** and potassium carbonate as shown in Scheme 3. This goal was in fact realized by a careful choice of proper reaction conditions (see Scheme 5). However, even simple multifunctional substrates such as **10** and **11** dispose of a variety of reaction pathways as demonstrated by the condensation products **12** and **13** isolated in our first experiments. Thus, addition of diester **11** to a suspension of dibromide **10** and potassium carbonate/18-crown-6 in dry

Figure 1. Structure of **8** in the crystal



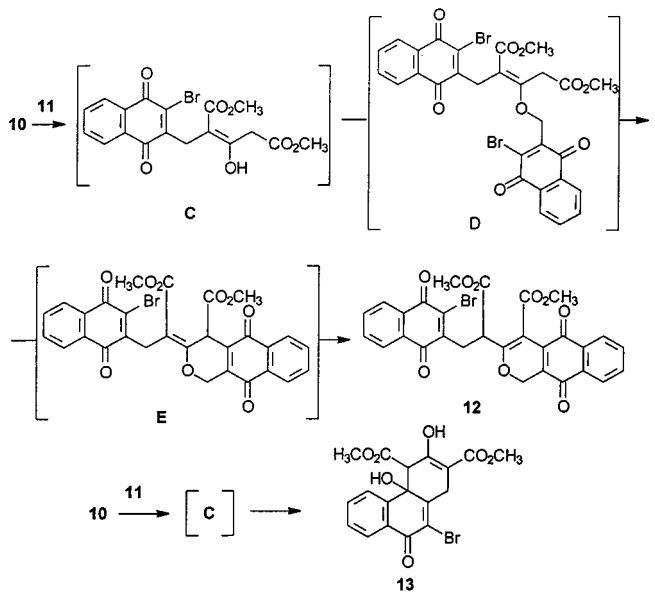
THF led to the formation of the substituted benzo[*g*]isochromene **12**. The formation of **12** can be rationalized by initial alkylation of the β-oxo ester **11** with the highly reactive "benzylic" bromide **10** to yield intermediate **C**, *O*-alkylation of this intermediate with another molecule of bromide **10** to form intermediate **D**, followed by intramolecular Michael addition and HBr elimination to yield the benzoisochromene **E** (Scheme 4). The double bond is finally isomerized under the basic reaction conditions to the more stable intramolecular position to yield the final product **12**. The particular sequence of the events may perhaps be exchanged but we believe that intermediates of this kind plausibly explain the formation of **12**.

Next we tried to change the nature of the base by replacing potassium carbonate with sodium hydride. The only isolable product under these conditions was the tetrahydrophenanthrene system **13** (26%). The analogy to the angucycline systems (see **1**) and in particular to the difficult non-aromatic types[2] is evident. Of particular value is the generation of the tertiary hydroxy group at C-4 common to all SS-228Y and aquayamycin types[3] and this approach certainly merits further investigation in connection with the synthesis of hydroaromatic angucyclines.

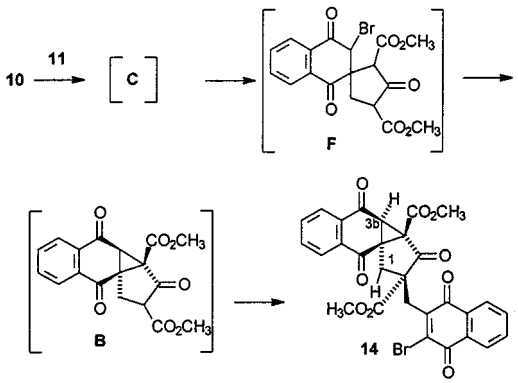
Finally, the inverse addition of the reaction components (addition of dibromide **10** to a stirred suspension of the diester **11** and potassium carbonate in THF) reproducibly led to the anticipated cyclopenta[1,3]cyclopropa[1,2-*b*]naphthalene system **14**. The product **14** is formed by an alkylation of the CH-acidic position in **B** which is generated via the intermediates **C** and **F** (Scheme 5). The stereochemistry of the upper four-membered ring system is identical to that of the analog **8** as shown by the almost superimposible NMR spectra for that part of the molecule. The configuration of the additional stereogenic center at C-2 formed by the alkylation with the bromide **10** was unambiguously established by NOE experiments. Significant NOE enhancements (5%) were observed between the methyl group of the ester at C-2 with the β-proton at C-1 and also with the proton at C-3b confirming the *cis* configuration of these groups as shown in formula **14**.

We believe that the reactions described here are typical for the general principles of domino reactions. The five elec-

Scheme 4



Scheme 5



trophilic centers in the dibromide **10** undergo a very subtle change of reactivity during the course of the reaction path. Initially, only the quasi-benzylic bromine on the methyl group is reactive in nucleophilic displacement reactions to form intermediate **C**. The second vinylic bromine effectively protects the quinoid system from unwanted *intermolecular* Michael addition. However, in intermediate **C**, the *intramolecular* Michael reaction is possible to form the spiro compound **F**. In the spirocyclization, the initially unreative vinylic bromine is transformed to a highly reactive sp^3-α-bromo ketone. The cyclization to form the cyclopropane ring in **B** is probably a very rapid reaction as confirmed by the absence of any intermediate in the TLC monitoring of the reaction. From a synthetic viewpoint, domino reactions starting from simple precursors as described here, may lead very economically to interesting complex systems that merit further research (review for domino reactions: ref.[8]).

Experimental Section

For general methods and instructions see ref.[9].

X-ray Crystallographic Study of **8**:[6] Crystal data: $C_{16}H_{12}O_4$, M_r = 268.26, triclinic, space group $P-1$, a = 7.966(2), b = 10.994(2), c = 15.629(2) Å, α = 89.27(1), β = 88.48(1), γ = 69.79(1)°, V = 1284.0(4) Å^3, Z = 4, D_c = 1.388 Mg/m^3. Data collection: AXS Bruker P4 diffractometer, Mo-K_α radiation, λ = 0.71073 Å, graphite monochromator, crystal size 0.31 × 0.42 × 0.44 mm, T = 293(2) K, ω scan, 2.4° ≤ Θ ≤ 25°, 0 ≤ h ≤ 9, −12 ≤ k ≤ 13, −14 ≤ l ≤ 14, 4532 reflections collected, 4218 independent reflections (R_{int} = 0.025), μ = 0.100 mm^{-1}. Structure solution by direct methods, full-matrix least-squares refinement based on 4218 F^2 values and 364 parameters, hydrogen atoms located from difference map and refined with "riding model", all but hydrogen atoms refined anisotropically, max (Δ.σ) < 0.001, Goof = 1.047, $R1$ [I > 2 σ(I)] = 0.039, w$R2$ (all data) = 0.114, min/max height in final ΔF map −0.147/0.202 e/Å^3. Program used: SHELXTL V5.[10]

Methyl 3-Methoxy-4-tributylstannyl-2-butenecarboxylate (**4b**): A suspension of freshly activated zinc dust (3.0 g, 45 mmol) in dry THF (45 ml) was treated under argon at 25°C with tributyltin chloride (10.20 g, 31.50 mmol) and iodine (30 mg, 0.12 mmol). The suspension was sonicated until the brown color disappeared (ca. 3 min) and methyl 4-bromo-3-methoxy-2-butenecarboxylate (**4a**,[11] 7.85 g, 37.50 mmol) was added dropwise. Sonication of the suspension was continued for 2 h and the mixture was then poured with stirring into an emulsion of 0.2 N HCl (107 ml) and Et_2O (100 ml). The aqueous phase was extracted twice with Et_2O (40 ml) and the combined organic phases were washed with water (75 ml) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue purified by bulb-to-bulb distillation (135°C/0.1 Torr) to afford the colorless liquid stannane **4b** (12.06 g, 91%). − IR (film): $\tilde{\nu}$ = 2931 cm^{-1} (C−H), 2849 (C−H), 1702 (C=O), 1584 (C=C), 1433, 1412, 1355, 1265 (C−O). − UV (methanol): λ_{max} (lg ε) = 271 nm (3.46). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.85−0.96 (m, 15 H, 3 × $SnCH_2$ and 3 × butyl-CH_3), 1.20−1.69 (m, 12 H, 3 × $SnCH_2CH_2CH_2CH_3$), 2.55 (s, 2 H, 4-H), 3.60, 3.64 (2 × s, 6 H, 2 × OCH_3), 4.82 (s, 1 H, 2-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.09 (t, 3 × $SnCH_2$), 13.43 (q, 3 × butyl-CH_3), 17.24 (t, C-4), 27.03 (t, 3 × $SnCH_2CH_2CH_2CH_3$), 28.62 (t, 3 × $SnCH_2CH_2CH_2CH_3$), 50.11, 54.68 (2 × q, 2 × OCH_3), 84.54 (d, C-2), 168.60, 179.44 (2 × s, C-1 and C-3). − MS (EI); *m/z* (%) (for ^{120}Sn): 420 (< 1) [M$^+$], 349 (16), 313 (100), 269 (96), 213 (22), 199 (28), 177 (56) [M$^+$ − 2 × *n*Bu − $CH_2C(OCH_3)$=$CHCO_2CH_3$], 155 (23), 121 (25), 57 (40) [*n*Bu$^+$]. − $C_{18}H_{36}O_3Sn$ (419.17): calcd. C 51.58, H 8.66; found C 51.48; H 8.48.

2-Bromo-3-(3,5-dioxohexyl)[1,4]naphthoquinone (**3b**): A suspension of silica gel (1.2 g) in CH_2Cl_2 (3 ml) was stirred for 15 min in diluted sulfuric acid (15%, 120 mg, 0.18 mmol) and acetal **3a**[4] (300 mg, 0.76 mmol) was added. Stirring was continued until the acetal was cleaved (ca. 30 min, TLC control), the suspension was filtered, the solvent was removed under reduced pressure, and the residue purified by filtration through a short column of silica gel to yield the diketone **3b** as yellow crystals (254 mg, 95%); m.p. 126°C. − IR (KBr): $\tilde{\nu}$ = 3312 cm^{-1} (OH), 2940 (C−H), 1671 (C=O), 1639 (C=O), 1586, 1572, 1407, 1326, 1271 (C−O), 1207. − UV (methanol): λ_{max} (lg ε) = 272 nm (3.67), 311 (3.43). − ^{1}H NMR (200 MHz, $CDCl_3$) (enol form): δ = 2.06 (s, 3 H, 6′-H), 2.54−2.62 (m, 2 H, 2′-H), 2.78−2.86 (m, 2 H, 1′-H), 5.56 (s, 1 H, 4′-H), 7.71−7.82 (m, 2 H, 6-H and 7-H), 8.09−8.18 (m, 2 H, 5-H and 8-H), 15.26 (br s, 1 H, chel. OH). − ^{13}C NMR (50 MHz, $CDCl_3$) (enol): δ = 24.91 (q, CH_3), 28.04 (t, C-1′), 36.27 (t, C-2′), 100.20 (d, C-4′), 127.59 (d, C-5, C-8), 127.99 (d, C-5, C-8), 131.51 (s, C-4a, C-8a), 131.87 (s, C-4a, C-8a), 134.46 (d, C-6, C-7), 134.69 (d, C-6, C-7), 139.90 (s, C-2), 150.66 (s, C-3), 177.90 (s, C-1, C-4), 181.84 (s, C-1, C-4), 190.38 (s, C-3′, C-5′), 193.30 (s, C-3′, C-5′). − MS (EI/250°C); *m/z* (%): 348/350 (11) [M$^+$], 290/292 (52) [M$^+$ − H_3CCOCH_2 − H$^+$], 269 (100) [M$^+$ − Br], 266 (72), 264 (83),

227 (94) [$M^+ - Br - H_3CCO + 1$], 211 (54) [$M^+ - Br - H_3CCOCH_2 - H^+$], 183 (45) [$M^+ - Br - H_3CCOCH_2CO - H^+$], 128 (42), 85 (95) [$H_3CCOCH_2CO^+$], 43 (95) [$COCH_3^+$]. – HRMS: $C_{16}H_{13}{}^{79}BrO_4$: calcd. 347.99972; found 347.999 ± 3 ppm.

Methyl 3-Methoxy-4-{3-[4-(2-methyl[1,3]dioxolan-2-yl)-3-oxobutyl]-1,4-dioxo-1,4-dihydronaphthalen-2-yl}-2-butenecarboxylate (**5**): A mixture of naphthoquinone **3a** (300 mg, 0.764 mmol), $Pd(PPh_3)_4$ (46 mg, 0.038 mmol), CuBr (120 mg, 0.83 mmol), and stannane **4b** (646 mg, 1.54 mmol) in dry 1,4-dioxane (5 ml) was refluxed for 1.5 h (TLC control). The crude mixture was filtered through a short column of silica gel (Et_2O), the solvent was removed under reduced pressure, and the residue purified by chromatography on silica gel (1. PE; 2. CH_2Cl_2/MeOH, 100:2) to yield the dialkylated naphthoquinone **5** (298 mg, 88%) as yellow crystals, m.p. 122°C. – IR (KBr): $\tilde{\nu}$ = 2988 cm^{-1} (C–H), 2938 (C–H), 2888 (C–H), 1707 (C=O), 1664 (C=O), 1616 (C=O), 1599 (C=C). – UV (methanol): λ_{max} (lg ε) = 272 nm (4.50), 330 (3.87). – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3 H, dioxolane-CH_3), 2.67–2.88 (m, 6 H, 1′′-H, 2′′-H and 4′′-H), 3.55 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.96 (s, 4 H, OCH_2CH_2O), 4.38 (s, 2 H, 4-H), 5.13 (s, 1 H, 2-H), 7.68–7.72 (m, 2 H, 6-H and 7-H), 8.06–8.10 (m, 2 H, 5-H and 8-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.49 (t, C-4), 24.25 (q, dioxolane-CH_3), 28.52 (t, C-1′′), 42.50 (t, C-2′′), 50.82 (q, OCH_3), 51.44 (t, C-4′′), 55.70 (q, OCH_3), 64.41 (t, OCH_2CH_2O), 90.93 (d, C-2), 107.65 (s, dioxolane-OCO), 126.04, 126.35 (2 × d, C-5′ and C-8′), 131.78, 131.98 (2 × s, C-4a′ and C-8a′), 133.24 , 133.34 (2 × d, C-6′ and C-7′), 142.88 (s, C-2′), 147.69 (s, C-3′), 167.64, 171.31 (2 × s, C-1 and C-3), 183.95, 184.52 (2 × s, C-1′ and C-4′), 205.33 (s, C-3′′). – MS (EI/140°C); *m/z* (%): 442 (19) [M^+], 383 (43) [$M^+ - CO_2CH_3$], 356 (12) [$M^+ - CH_3(OCH_2CH_2O)C + 1$], 297 (10) [$M^+ - CO_2CH_3 - CH_3(OCH_2CH_2O)C + 1$], 281 (40) [$M^+ - CO_2CH_3 - CH_3(OCH_2CH_2O)C - CH_3$], 239 (20), 221 (5), 152 (4), 87 (100) [$CH_3(OCH_2CH_2O)C^+$], 43 (20). – $C_{24}H_{26}O_8$ (442.16): calcd. C 65.15, H 5.92; found C 64.87, H 5.69.

Methyl 4-[1,4-Dioxo-3-(3,5-dioxohexyl)-1,4-dihydronaphthalene-2-yl]-3-oxobutanoate (**6**): A solution of **5** (199 mg, 0.45 mmol) in CH_2Cl_2 (22 ml) was treated at 20°C with conc. HCl (37% in H_2O, 8 drops) and stirred for 1.5 h (TLC control). The solution was poured into water, the aqueous phase was extracted twice with CH_2Cl_2 (50 ml), and the combined organic phases were washed with water (30 ml) and dried (Na_2SO_4). The solvent was removed at reduced pressure and the residue purified by crystallization from CH_2Cl_2/Et_2O to afford the ketide **6** (140 mg, 81%) as yellow crystals, m.p. 116°C. – IR (KBr): $\tilde{\nu}$ = 3415 cm^{-1} (OH), 2976 (C–H), 2924 (C–H), 1747 (C=O), 1714 (C=O), 1659 (C=O), 1625 (C=O), 1593 (C=C). – UV (methanol): λ_{max} (lg ε) = 297 nm (4.24). – ^1H NMR (200 MHz, $CDCl_3$) (enol): δ = 2.02 (s, 3-H, 6′′-H), 2.51–2.93 (m, 4 H, 1′′-H and 2′′-H), 3.70 (s, 2 H, 2-H), 3.79 (s, 3-H, OCH_3), 4.04 (s, 2 H, 4-H), 5.49 (s, 1 H, 4′′-H), 7.70–7.74 (m, 2 H, 6′-H and 7′-H), 8.03–8.07 (m, 2 H, 5′-H and 8′-H), 15.23 (br s, 1 H, chel. OH). – ^{13}C NMR (50 MHz, $CDCl_3$) (enol form): δ = 23.88 (t, C-1′′), 24.75 (q, C-6′′), 37.80 (t, C-4), 41.38 (t, C-2′′), 49.71 (t, C-2), 53.00 (q, OCH_3), 100.49 (d, C-4′′), 126.93 (2 × d, C-5′ and C-8′), 132.08, 132.51 (2 × s, C-4a′ and C-8a′), 141.50 (s, C-2′), 138.54 (s, C-3′), 167.74 (s, C-1), 184.53, 184.74 (2 × s, C-1′ and C-4′), 189.95 (s, C-5′′), 193.93 (s, C-3′′), 198.77 (s, C-3). – MS (EI/200°C); *m/z* (%): 384 (26) [M^+], 366 (37), 352 (41) [$M^+ - OCH_3 + 1$], 325 (12) [$M^+ - CO_2CH_3$], 323 (16), 284 (95) [$M^+ - COCH_2CO_2CH_3 + 1$], 252 (58), 227 (44), 226 (82) [$M^+ - CH_2CO_2CH_3 - COCH{=}C(OH)CH_3$], 224 (46), 198 (100) [$M^+ - COCH_2CO_2CH_3 - COCH{=}C(OH)CH_3$], 141 (21), 101 (21), 85 (40) [$COCH{=}C(OH)CH_3^+$], 59 (25) [$CO_2CH_3^+$], 43 (36) [$COCH_3^+$]. – $C_{21}H_{20}O_7$ (384.38): calcd. C 65.62, H 5.24; found C 65.52, H 5.41.

Methyl 4-(2-Acetyl-3,1′,4′-trioxo-3′,4′-dihydro-1′H-spiro[cyclopentane-1,2′-naphthalen]-3′-yl)-3-oxobutanoate (**7**): A solution of ketide **6** (60 mg, 0.16 mmol) in dry 2-propanol (10 ml) was treated with K_2CO_3 (324 mg, 2.34 mmol) and stirred for 1.5 h at 20°C (TLC control). The mixture was then quenched by pouring into 0.3 N HCl (30 ml). The mixture was extracted twice with CH_2Cl_2 (40 ml), the organic phase was dried (Na_2SO_4), filtered, and the solvent evaporated at reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2/MeOH, 100:4) to yield from the main fraction the spiro compound **7** (36 mg, 60%) as faintly yellow microcrystalline powder; m.p. 128.5°C. – IR (KBr): $\tilde{\nu}$ = 3436 cm^{-1} (OH), 2945 (C–H), 1751 (C=O), 1751 (C=O), 1718 (C=O), 1698 (C=O), 1620, 1595 (C=C). – UV (methanol): λ_{max} (lg ε) = 299 nm (4.22). – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.82–1.93 (m, 2 H, 5′-H), 2.03 (s, 3-H, $COCH_3$), 2.38–2.57 (m, 3 H, 4′-H, 4-H_a, 4-H_b), 3.34 (dd, 1 H, ^2J = 16.9 Hz, ^3J = 9.2 Hz, 4-H_a, 4-H_b), AB system: [δ_A = 3.62 (d), δ_B = 3.73 (d), ^2J = 15.5 Hz, 2 H, 2-H], 3.77 (s, 3 H, OCH_3), 4.26 (dd, 1 H, ^3J = 2.6 and 9.1 Hz, 3′′-H), 7.75–7.85 (m, 2 H, 6′′-H and 7′′-H), 8.00–8.05 (m, 1 H, 5′′-H, 8′′-H), 8.15–8.19 (m, 1 H, 5′′-H, 8′′-H), 15.05 (br s, 1 H, chel. OH). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.03 (q, $COCH_3$), 28.03 (t, C-4′, C-5′), 34.18 (t, C-4′, C-5′), 38.12 (t, C-4), 50.05 (t, C-2), 52.68 (d, C-3′′), 52.97 (q, OCH_3), 60.96 (s, C-2′′), 110.16 (s, C-2′), 127.23 (d, C-5′′, C-8′′), 128.76 (d, C-5′′, C-8′′), 133.72 (s, C-4a′′ and C-8a′′), 135.09 (d, C-6′′, C-7′′), 135.19 (d, C-6′′, C-7′′), 167.70 (s, C-1), 187.56 (s, C-3′), 196.22 (s, C-1′′, C-4′′), 197.13 (s, C-1′′, C-4′′), 199.29 (s, C-3, *C*OCH_3), 200.89 (s, C-3, *C*OCH_3). – MS (EI/130°C); *m/z* (%): 384 (10) [M^+], 366 (33), 341 (17) [$M^+ - COCH_3$], 323 (34), 292 (9), 269 (100) [$M^+ - CH_2COCH_2CO_2CH_3$], 251 (40), 227 (71) [$M^+ - COCH_3 - CH_2COCH_2CO_2CH_3 + 1$], 224 (32), 223 (19), 133 (7), 115 (6) [$CH_2COCH_2CO_2CH_3^+$], 104 (10), 77 (14), 59 (4) [$CO_2CH_3^+$], 43 (17) [$COCH_3^+$]. – $C_{21}H_{20}O_7$ (384.38): calcd. C 65.62, H 5.24; found C 65.70, H 5.03.

3a-Acetyl-1,2,3a,3b-tetrahydrocyclopenta[1,3]cyclopropa[1,2-b]naphthalene-3,4,9-trione (**8**): A solution of bromonaphthoquinone **3b** (100 mg, 0.29 mmol) in dry 2-propanol (15 ml) was treated with potassium carbonate (352 mg, 2.55 mmol) and stirred for 15 min (TLC control). The reaction was quenched by pouring into a mixture of 1 N HCl (9.5 ml) and a saturated aqueous solution of NH_4Cl (30 ml) and CH_2Cl_2 (30 ml). The aqueous phase was extracted twice with CH_2Cl_2 (60 ml), the combined organic phases were dried (Na_2SO_4), filtered, and the solvent removed at reduced pressure. The residue was purified by chromatography on silica gel (CH_2Cl_2). Crystallization from CH_2Cl_2/Et_2O afforded the tetracycle **8** (52 mg, 68%) as faintly yellow crystals; m.p. 118°C. – IR (KBr): $\tilde{\nu}$ = 3025 cm^{-1} (C–H), 2925 (C–H), 1741 (C=O), 1704 (C=O), 1680 (C=O), 1594. – UV (methanol): λ_{max} (lg ε) = 269 nm (3.63), 303 (3.33). – ^1H NMR (200 MHz, $CDCl_3$): δ = 2.13 (s, 3 H, $COCH_3$), 2.18–2.36 (m, 1 H, 1-H_a, 1-H_b), 2.45–2.56 (m, 2 H, 2-H), 3.16 (s, 1 H, 3b-H), 3.20–3.31 (m, 1 H, 1-H_a, 1-H_b), 7.72–7.76 (m, 2 H, 6-H and 7-H), 8.02–8.09 (m, 2 H, 5-H and 8-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.16 (t, C-1), 30.79 (q, $COCH_3$), 32.58 (t, C-2), 40.11 (d, C-3b), 48.45 (s, C-9a), 61.75 (s, C-3a), 127.12 (d, C-5, C-8), 127.22 (d, C-5, C-8), 133.62 (s, C-4a, C-8a), 134.01 (s, C-4a, C-8a), 134.92 (d, C-6, C-7), 135.13 (d, C-6, C-7), 188.00 (s, C-4, C-9), 189.12 (s, C-4, C-9), 196.99 (s, C-3), 204.84 (s, *C*OCH_3). – MS (EI/80°C); *m/z* (%): 268 (100) [M^+], 253 (22) [$M^+ - CH_3$], 226 (38), 225 (34) [$M^+ - COCH_3$], 212 (48), 198 (44), 197 (63) [$M^+ - COCH_3 - CO$], 169 (25) [$M^+ - COCH_3 - COCH_2CH_2$], 141 (27), 115 (26), 104 (14), 86 (16), 84 (23), 76

(25), 43 (56) [$COCH_3^+$]. − $C_{16}H_{12}O_4$ (268.27): calcd. C 71.64, H 4.51; found C 71.48, H 4.38.

Methyl 3-[2-(3-Bromo-1,4-dioxo-1,4-dihydronaphthalene-2-yl)-1-methoxycarbonylethyl]-5,10-dioxo-5,10-dihydro-1H-benzo[g]isochromene-4-carboxylate (**12**): A mixture of 2-bromo[1,4]naphthoquinone **10**[12] (500 mg, 1.52 mmol) in dry THF (20 ml), dry potassium carbonate (2.13 g, 15.41 mmol), and 18-crown-6 (20 mg, 76 μmol) was treated at 0°C under argon with a solution of dimethyl acetonedicarboxylate **11** (315 mg, 1.81 mmol) in dry THF (5 ml). The mixture was stirred for 1.5 h (TLC control for disappearance of starting material), quenched by pouring into a mixture of 1 N HCl (32 ml), saturated NH_4Cl (70 ml) and Et_2O (40 ml). The aqueous phase was extracted twice with Et_2O (60 ml), dried (Na_2SO_4), filtered, and the solvent removed at reduced pressure. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 100:3) to yield an orange-red solid (83 mg, 19%), m.p. 197°C. − IR (KBr): $\tilde{\nu}$ = 2935 cm^{-1} (C−H), 1744 (C=O), 1719 (C=O), 1673 (C=O), 1652 (C=O), 1591 (C=C), 1569, 1561. − UV (methanol): λ_{max} (lg ε) = 272 nm (4.19), 316 (3.76), 418 (3.29). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.45 (s, 3 H, OCH_3 of C-4-CO_2CH_3), 3.51−3.63 (m, 2 H, C-1′-CH_2), 3.78 (s, 3 H, OCH_3 of C-1′-CO_2CH_3), 4.62 (dd, ^3J = 4.6 and 10.4 Hz, 1 H, 1′-H), AB system [δ_A = 5.13 (d), δ_B = 5.32 (d), ^2J = 14.5 Hz, 2 H, 1-H], 7.66−8.18 (m, 8 H, arom. H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.66 (t, C-1′-CH_2), 45.19 (d, C-1′), 52.67 (q, C-4-CO_2CH_3), 53.42 (q, C-1-CO_2CH_3), 64.10 (t, C-1), 108.42 (s, C-4), 126.48 (d, arom. C-H), 127.20 (d, arom. C-H), 127.58 (d, arom. C-H), 127.63 (s, C-4a, C-10a), 128.03 (d, arom. C-H), 131.37 (s, C-9a, C-5a, C-4a′′, C-8a′′), 131.94, 132.23 (3 × s, C-10a, C-5a, C-4a′′, C-8a′′), 134.27, 134.38, 134.42, 134.67 (4 × d, arom. C-H), 136.58 (s, C-4a, C-10a), 141.08 (s, C-3′′), 148.17 (s, C-2′′), 164.24 (s, C-3), 166.24 (s, C-4-CO_2CH_3), 169.86 (s, C-1′-CO_2CH_3), 177.68 (s, C-4′′, C-5), 181.01 (s, C-4′′, C-5), 181.88 (s, C-1′′), 182.29 (s, C-10). − MS (EI/120°C); *m/z* (%): 592/590 (6) [M^+], 560/558 (12) [M^+ − $HOCH_3$], 528/526 (31), 447 (37), 419 (26), 364 (21), 342 (59) [M^+ − Br − H_2C-(1,4-dioxo-1,4-dihydronaphthalene)], 251 (44), 211 (19), 149 (20), 101 (40), 84 (28), 57 (30). − HRMS: $C_{29}H_{19}{}^{81}BrO_9$: calcd. 592.019; found 592.019 ± 3 ppm.

Dimethyl 10-Bromo-3,4a-dihydroxy-9-oxo-1,4,4a,9-tetrahydrophenanthrene-2,4-dicarboxylate (**13**): Dimethyl acetonedicarboxylate (**11**) (315.0 mg, 1.81 mmol) was added dropwise with stirring at 0°C under argon to a suspension of NaH (47.5 mg, 1.98 mmol) in dry THF (5 ml). Stirring was continued for 10 min at 0°C. The mixture was added dropwise to a cooled (−20°C) solution of bromo[1,4]naphthoquinone **10** (500.0 mg, 1.52 mmol) in dry THF (10 ml). The mixture was stirred for 5 h and the temperature was allowed to rise to 10°C (TLC monitoring for starting material **10**). The reaction was quenched as usual [NH_4Cl solution (50 ml) and HCl (1 N, 4 ml)], the aqueous phase was extracted twice with Et_2O (80 ml), washed with water (50 ml), dried (Na_2SO_4), and the solvent removed at reduced pressure. The residue was dissolved in CH_2Cl_2 (10 ml) and **13** (162 mg, 26%) precipitated as a yellowish solid; m.p. 199.5°C (decomp.). − IR (KBr): $\tilde{\nu}$ = 3423 cm^{-1} (OH), 2950 (C−H), 1738 (C=O), 1681 (C=O), 1649 (C=O), 1632, 1597, 1450, 1380, 1303, 1266 (C−O) − UV (methanol): λ_{max} (lg ε) = 273 nm (4.13). − ^{1}H NMR (200 MHz, [D_6]DMSO): δ = 3.16 (s, 3 H, C-4-CO_2CH_3), AB system [δ_A = 3.49 (d), δ_B = 3.80 (d), 2 H, 1-H], 3.85 (s, 3 H, C-2-CO_2CH_3), 4.15 (s, 1 H, 4-H), 6.99 (br s, 1 H, C-4a-OH), 7.45−8.17 (m, 4 H, arom. H), 11.88 (s, 1 H, C-3-OH). − ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 31.54 (t, C-1), 53.17 (2 × q, 2 × OCH_3), 59.97 (d, C-4), 71.72 (s, C-4a), 97.41 (s, C-2), 124.36 (s, C-10), 127.06 (d, C-5, C-8), 128.32 (d, C-5, C-8), 129.10 (s, C-4b, C-8a), 130.01 (d, C-6, C-7), 143.79 (s, C-4b, C-8a), 155.28 (s, C-10a), 163.95 (s, C-3), 168.17 (s, C-4-CO_2Me), 171.74 (s, C-2-CO_2Me), 177.44 (s, C-9). − MS (EI/200°C); *m/z* (%): 424 (< 1)/422 (< 1) [M^+], 406 (22)/404 (21) [M^+ − H_2O], 374 (27), 372 (26), 343 (100) [M^+ − Br], 311 (84), 251 (26), 211 (20), 183 (18), 150 (12), 101 (18), 59 (28) [$CO_2CH_3^+$], 15 (14) [CH_3^+]. − HRMS: $C_{18}H_{15}{}^{79}BrO_7$: calcd. 422.0001; found 421.9916.

Dimethyl 2-(3-Bromo-1,4-dioxo-1,4-dihydronaphthalen-2-ylmethyl)-3,4,9-trioxo-2,3,4,9-tetrahydro-1 H,3bH-cyclopenta[1,3]cyclopropa[1,2-b]naphthalene-2,3a-dicarboxylate (**14**): A mixture of dimethyl acetonedicarboxylate (**11**) (525 mg, 3.01 mmol), potassium carbonate (2.60 g, 18.81 mmol), and 18-crown-6 (20 mg, 76 μmol) in dry THF (10 ml) was stirred for 15 min at 20°C. A solution of bromo[1,4]naphthoquinone **10** (500 mg, 1.52 mmol) in dry THF (20 ml) was then added dropwise within 1 h. The mixture was stirred for further 15 min (TLC control for disappearance of **10**) and then quenched by pouring into a mixture of 1 N HCl (40 ml) and aqueous saturated NH_4Cl (100 ml) and Et_2O (40 ml). The aqueous phase was extracted twice with Et_2O (80 ml), the combined organic phases were dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure. The residue was separated by chromatography on silica gel (Et_2O/PE; 5:1) to yield **14** (203 mg, 45%) as a yellow solid; m.p. 207.5°C. − IR (KBr): $\tilde{\nu}$ = 3012 cm^{-1} (C−H), 2955 (C−H), 1762 (C=O), 1731 (C=O), 1688 (C=O), 1651 (C=O), 1589 (C=C), 1570, 1433. − UV (methanol): λ_{max} (lg ε) = 275 nm (4.17), 336 (3.50). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.04 (s, 1 H, 3b-H), AB system [δ_A = 2.83 (d), δ_B = 3.56 (d), ^2J = 14.5 Hz, 2 H, 1-H], 3.30 (s, 3 H, OCH_3), AB system [δ_A = 3.32 (d), δ_B = 3.83 (d), ^2J = 13.4 Hz, 2 H, C-2-CH_2], 3.85 (s, 3 H, OCH_3), 7.69−8.21 (m, 8 H, arom. H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.95 (t, C-2-CH_2, C-1), 38.08 (t, C-2-CH_2, C-1), 39.09 (d, C-3b), 44.70 (s, C-9a), 53.72 (q, OCH_3), 54.59 (q, OCH_3), 54.99 (s, C-3a, C-2), 57.97 (s, C-3a, C-2), 127.18, 127.23, 127.84, 128.16 (4 × d, arom. C-H), 131.39, 131.72, 132.95, 133.24 (4 × s, C-8a, C-4a, C-4a′, C-8a′), 134.67, 134.90, 135.16 (4 × d, arom. C-H), 143.12 (s, C-2′, C-3′), 147.13 (s, C-2′, C-3′), 162.84 (s, CO_2CH_3), 169.95 (s, CO_2CH_3), 177.56 (s, C-1′, C-4′), 182.13 (s, C-1′, C-4′), 186.55 (s, C-4, C-9), 187.83 (s, C-4, C-9), 197.35 (s, C-3). − MS (EI/300°C); *m/z* (%): 592/590 (3) [M^+], 561/559 (13) [M^+ − OCH_3], 560 (22), 558 (19), 512 (46), 511 (100) [M^+ − Br], 480/478 (11), 479 (34) [M^+ − Br − $HOCH_3$], 447 (13), 420 (16), 419 (28), 341 (14), 309 (59) [M^+ − Br − H_2C-(1,4-dioxo-1,4-dihydronaphthalene) − $HOCH_3$], 225 (9), 104 (7), 76 (7). − $C_{29}H_{19}O_9Br$ (591.37): calcd. C 58.90, H 3.24; found C 58.77, H 3.14.

☆ Dedicated to Professor *Eckehardt Dehmlow* on the occasion of his 65th birthday.

[1] K. Krohn, N. Böker, C. Freund, *J. Org. Chem.* **1997**, 2350−2356.
[2] K. Krohn, J. Rohr, *Top. Curr. Chem.* **1997**, *188*, 128−195.
[3] J. Rohr, R. Thiericke, *Nat. Prod. Rep.* **1992**, *9*, 103−137.
[4] K. Krohn, N. Hayat, *J. Prakt. Chem./Chem.-Ztg.* **1998**, *340*, 171−174.
[5] J. K. Stille, *Angew. Chem.* **1986**, *98*, 504−519; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508−523.
[6] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101863. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].
[7] [7a] Isolation: F. Vonasek, V. Herout, F. Sorm, *Coll. Czech. Chem. Commun.* **1960**, *25*, 919−926. − [7b] Synthesis: S. Torii, T. Okamoto, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 771−774. − [7c]

Synthesis and Stereochemistry: A. Tanaka, R. Tanaka, H. Ude, A. Yoshikoshi, *J. Chem. Soc., Perkin Trans. 1* **1972**, 1721−1727.
[8] L. F. Tietze, U. Beifuß, *Angew. Chem.* **1993**, *105*, 137−170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131−164.
[9] K. Krohn, A. Michel, U. Flörke, H.-J. Aust, S. Draeger, B. Schulz, *Liebigs Ann. Chem.* **1994**, 1093−1097.
[10] Siemens, *SHELXTL*, Version 5; Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA, **1995**.
[11] S. M. Weinreb, J. Auerbach, *J. Am. Chem. Soc.* **1975**, *97*, 2503−2506.
[12] K. Krohn, N. Böker, A. Gauhier, G. Schäfer, F. Werner, *J. Prakt. Chem./Chem.-Ztg.* **1996**, *338*, 349−354.

[98287]