Juglorescein, Juglocombins and Juglochromans: Structure of Juglomycin Dimers from Streptomycetes

H. Lessmann, R. P. Maskey, S. Fotso, H. Lackner, and H. Laatsch

Department of Organic and Biomolecular Chemistry, University of Göttingen, Tammannstraße 2, D-37077 Göttingen, Germany

Reprint requests to Prof. Dr. H. Laatsch. Fax: +49(0)551-399660. E-mail: hlaatsc@gwdg.de

Z. Naturforsch. **60b,** 189 – 199 (2005); received June 22, 2004

Dedicated to Professor Dr. A. de Meijere on the occasion of his 65th birthday

Novel juglomycin derivatives with a C_{28} skeleton were isolated from the *Streptomyces* strains 815 and GW4184. Juglorescein (**1a**) and juglocombin A (**2a**) and B (**3a**) are C,C dimers of juglomycin C (**10**) with a five membered ring between the two monomeric moieties. In the juglochromans A – D (**4a**, **5a**, **6a**, **6c**), two juglomycin C (**10**) units are connected by C,C and C,O bonds forming a central isochroman or a chroman system. The structures of the new natural products were elucidated by detailed spectra analyses, by comparison of the NMR data with those of related compounds and by biosynthetic considerations. The new natural products were antimicrobially inactive.

Key words: Juglomycin, Dimeric Quinones, *Streptomycetes*

Introduction

Several new juglomycins, broadband antibiotics with a 5-hydroxynaphthoquinone chromophore and a C_4-side chain at C-2, were isolated from the culture broth of terrestrial *Streptomyces* strains and described previously [1 – 3]. 2,3-Dihydrojuglomycin A (**7**) is supposed to be their biosynthetic precursor [1a, 3]. Additionally, the *Streptomyces* sp. 815 and GW4184 produced a very polar, deeply red juglomycin dimer with a unique C_{28}-skeleton, the juglorubin (**11**), which was assumed to be a dimerisation product of juglomycin C (**10**) [3, 4]. Furthermore, from the strain 815 a series of mainly yellowish dimers were isolated [3] and named juglorescein (**1a**), juglocombin A (**2a**) and B (**3a**) and juglochroman A – D (**4a**, **5a**, **6a**, **6c**). Recently, juglorescein (**1a**) and traces of some of the other dimers were also found in cultures of the new strain GW4184. These new dimers support the hypothetic pathway from juglomycin C (**10**) to juglorubin (**11**) [4]. Here we report the structure elucidation of these novel natural products; the separation and isolation is described in the previous paper [2].

Results and Discussion

*Juglorescein (***1a***)*

Juglorescein (**1a**), isolated as long colourless needles, was quantitatively transformed with diazomethane into its dimethyl ester $C_{30}H_{28}O_{14}$ (**1b**), which gave a molecular weight of *m/z* 612 (DCI MS). Accordingly, the initial NMR data of **1a** indicated the presence of two carboxylic acid groups, and a later ESI HR mass spectrum afforded the molecular formula $C_{28}H_{24}O_{14}$ (585.1238 $[M+H]^+$).

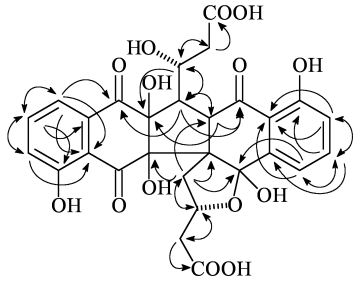
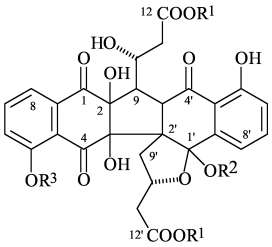
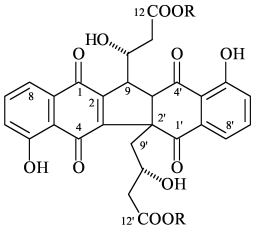


Fig. 1. Structure of juglorescein (**1a**) derived by H,H COSY (↔), HMQC (not shown) and selected HMBC (→) couplings.

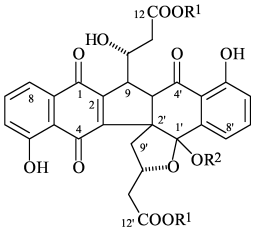
The molecular and the NMR data suggested that **1a** was a dimer of juglomycin C (**10**). The ^{1}H NMR spectrum showed signals of four CH and three CH_2 groups and two sets of each three consecutive aromatic protons. Consistent with the molecular formula, the ^{13}C NMR spectrum exhibited 28 signals, twelve of them from aromatic carbons (6 CH ands 6 C_q-O groups). The number of sp^2 carbons and the missing colour indicated that the quinone systems were



1	a	b	c	d
R^1	H	CH_3	CH_3	CH_3
R^2	H	H	H	CH_3
R^3	H	H	$COCH_3$	H



2a: R = H
2b: R = CH_3



3a: $R^1 = R^2 = H$
3b: $R^1 = CH_3$; $R^2 = H$
3c: $R^1 = R^2 = CH_3$

reduced, which was confirmed by similarities in the UV/vis spectra (λ_{max} 343 nm) of **1a**/**1b** and of 2,3-dihydrojuglomycin A (**7**; λ_{max} 339 nm). As only three ^{13}C signals of conjugated ketones ($\delta = 206.6$, 204.0 and 193.8) were observed, the fourth keto group was assumed to form a ketal or hemiketal. This was supported by an acetal carbon signal at $\delta = 101.8$. The final structure of juglorescein was determined *via* H,H COSY, HMQC and HMBC correlations of the dimethyl ester **1b** [3] and recently confirmed by ESI HRMS data and a direct NMR analysis of **1a** (Fig. 1) isolated from strain GW4184.

The formation of a hemiketal could occur between CO-1' and one of the four aliphatic OH groups, which were identified by NMR. The H,H COSY spectrum of **1b** in DMSO showed a coupling between the CH proton at $\delta = 4.82$ (10-H) and an OH proton at $\delta = 5.40$ (10-OH). In the COLOC spectrum (DMSO), the OH signals at $\delta = 6.55$ (1'-OH) and 5.95 (3-OH) depicted couplings with the neighbouring carbon atoms, thus leaving only C-1'/C-10' or the strained C-1'/C-2 cyclisation as alternatives. As a long range coupling ($J = 1$ Hz) between 9-H and 2-OH was observed, also visible in the H,H COSY spectrum, and because of the similarity in the ^{13}C NMR data of C-2 ($\delta = 88.7$) and C-3 (89.4), the ketalization *via* the OH group at C-2 was ruled out. Accordingly, C-10' ($\delta = 73.6$) showed a downfield shift as compared with C-10 ($\delta = 68.0$), which is similar to that in the juglomycins C (**10**) and D with open side chains. HMBC cross peaks of 8'-H, 9'-H and C-1' proved the position of the acetal carbon atom. Hence, the carbonyl-1' is ketalised by 10'-OH and the structure of juglorescein is **1a**.

*Juglocombin A/B (***2a**/**3a***)*

While the juglocombins A/B (**2a**/**3a**) were obtained as a mixture difficult to purify, methylation with diazomethane/methanol delivered the dimethyl esters **2b**/**3b**, which (*via* **3c**) gave pure samples for spectroscopic studies. The UV/vis spectrum exhibited two maxima (λ_{max} 418 and 339 nm), which irreversibly shifted to 540 and 434 nm in alkaline solution. Thus, it was expected that **2b**/**3b** and finally **2a**/**3a** might contain two independent chromophores, a juglon system as in juglomycin C (**10**, $\lambda_{max} = 418$ nm) and a 2,3-dihydrojuglon system as in 2,3-dihydrojuglomycin A (**7**, $\lambda_{max} = 339$ nm) or in **1a**. The DCI mass spectrum of **2b**/**3b** showed *quasi*-molecular ion peaks at *m/z* 598 ($[M+H_2 +NH_4]^+$) and 596 ($[M+NH_4]^+$), which determined the molecular weight to be *m/z* 578.

The ^1H NMR spectrum of **2b**/**3b** exhibited complex aromatic signals, and also the aliphatic region depicted peaks of four methoxy groups and far more signals than expected for the molecular weight. The ^{13}C spectrum delivered 60 signals, which was twice as many as for a dimeric juglomycin structure. This led to conclude the presence of two interconvertable compounds. With the aid of H,H COSY and HMQC cross peaks, the side chains and the aromatic parts were derived; however, the complete structure could not be elucidated without ambiguity from these data.

The existence of two compounds in equilibrium was confirmed by treatment of **2b**/**3b** with MeOH/10% conc. HCl, which delivered a pure C_{31}-methylketal (**3c**) in very good yield (82%). On hydrolysis with 1 N HCl, **3c** yielded a product with ^1H NMR data identical to those of **2b**/**3b**. In alkaline solution, the yellow colour of **3c** changed first to violet and then to brown red with an irreversible shift of the UV/vis maxima at 325 and 416 to 350 and 515 nm, respectively. DCI MS determined the *quasi*-molecular peak to be *m/z* 610 and led to the molecular formula $C_{31}H_{28}O_{12}$ (**3c**), which ultimately gave $C_{28}H_{22}O_{12}$ for the free acids **2a**/**3a**.

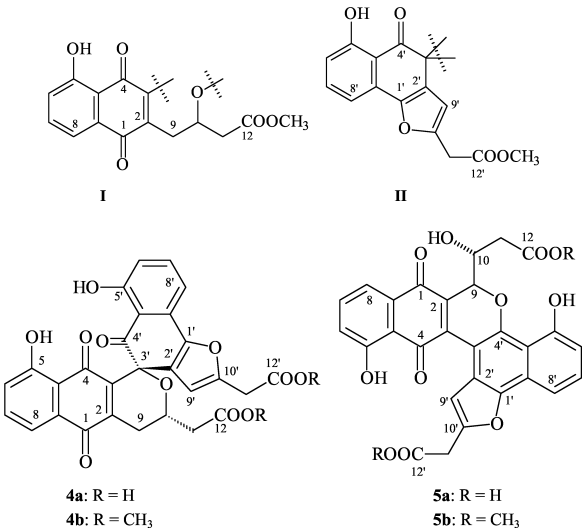
The ^1H NMR spectrum of **3c**, similar to that of juglorescein (**1a**) and its ester **1b**, also depicted signals for two sets of each three adjacent aromatic protons.

The aliphatic region showed four CH and three CH_2 signals comparable to those of the analogous protons in **1a** and **1b**. Three of the four methines and a methylene group gave the coupling sequence of a CH_2-CH-CH-CH fragment (11-H_2/10-H/9-H/3'-H), and 9'-H_2/10'-H/11'-H_2 formed a sequence of another β-hydroxybutyric acid side chain. – By comparison with those of **1a**, the ^{13}C NMR data of **3c** could be completely assigned. The spectrum showed 31 carbon signals, two of them at $\delta = 104.5$ and $\delta = 203.4$ assigned to a ketal carbon (C-1') and a chelated aromatic ketone (C-4'), respectively. Carbon C-2' ($\delta = 65.5$) forms the junction to the second juglone moiety, so that the right half of the molecule is identical to that of juglorescein (**1a**), as confirmed by comparable ^1H and ^{13}C NMR data. The left half represents a 3-substituted juglomycin C (**10**), similar to juglomycin Z [5], with characteristic signals of two quinone carbonyls ($\delta = 189.5$ and 183.5) and the two aromatic quarternary carbons C-2 and C-3 ($\delta = 151.1$, 152.0). The resulting structure of the methyl derivative is **3c** and leads finally to the structures **2a** and **3a** for the juglocombins A and B.

*Juglochroman A (**4a**)*

Juglochroman A gave a yellow amorphous dimethyl ester (**4b**), the molecular weight of which was determined to be *m/z* 558 (DCI MS), and indicated the molecular formula $C_{30}H_{22}O_{11}$. The UV/vis maxima were at 328 (weak) and 414 nm and, in alkaline solution, at 334, 408 and 530 nm. The molecular formula of the free acid ($C_{28}H_{18}O_{11}$) and the characteristic UV/vis data indicated again a juglon and a dihydrojuglon chromophore in the molecule. The IR spectrum denoted signals at 1741 (ester) and 1646, 1619 cm^{-1} for the chelated and non-chelated carbonyls of a quinone system.

The ^1H NMR spectrum displayed signals of two chelated OH groups ($\delta = 11.83$ and 11.34), two sets of three consecutive aromatic protons (as in **1b**–**3b**), an aromatic sp^2 proton at $\delta = 6.77$, a methine group bearing oxygen and three methylene groups. The protons 9-H_2/10-H/11-H_2 formed another spin system. The striking allylic coupling between the CH_2 ($\delta = 3.85$) and the sp^2 protons ($\delta = 6.77$, $J = 0.8$ Hz) was comparable to that in **9**, the thermolysis product of dihydrojuglomycin A (**7**). The ^{13}C spectrum delivered 30 peaks as expected, two of them ($\delta = 188.3$ and 183.1) pointed at a juglon system and one ($\delta = 200.3$) at a chelated aromatic ketone (C-4'). The absence of the fourth carbonyl peak indicated a further modification at this group.



In the COLOC spectrum, the quinonoid carbonyl C-1 coupled with the 9-H_a proton and the *peri*-proton 8-H ($\delta = 7.68$). Furthermore, 5-OH coupled with C-4a, C-5 and C-6, and 7-H coupled with C-8a. With the $^3J_{CH}$ correlations and by comparison of the NMR data with those of the related part of **3c** and juglomycin Z [5], the substructure I was developed.

With the remaining three consecutive aromatic protons, a chelated OH group, an sp^2 proton (singlet) and a methylene group, and by comparison of all NMR data with those of the 1,4,5-trihydroxynaphthalene moiety of 1,4-dihydro-juglomycin A and **9** (Table 1 and 2; exp.) [3], the substructure II could be formed. Structure II was also supported by the chelation of 5'-OH, couplings from 5'-OH to C-4a', C-5' and C-6', from 9'-H to C-1', C-2' and C-10' and from the aromatic protons to the neighbouring carbons. I and II possess each two open valencies, and the aliphatic quaternary carbon C-3' in II ($\delta = 75.5$) must be connected to oxygen. The only possible way to connect both substructures yields an unusually substituted isochroman-quinone system with a spiro-bridge. Hence, juglochroman A dimethyl ester and juglochroman A have the structures **4b** and **4a**, respectively.

The absolute configuration at C-10 as (S) could be derived from the juglomycins A-D [1], and that of C-3' from the differential NOE spectrum. Irradiation of the 10-H signal showed a clear NOE effect of the 9'-H and 11'-H_2 protons, which can be explained only by the (R)-configuration at C-3'.

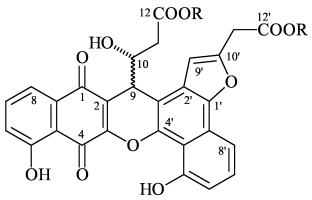
*Juglochroman B (***5a***)*

Juglochroman B (**5a**) was also isolated as its dimethyl ester **5b**, dark green needles (m.p. 192 °C) which were sparingly soluble in chloroform, methanol and acetone. MS methods like EI, FD and FAB failed, but DCI MS fixed the molecular weight at *m/z* 558 ($C_{30}H_{22}O_{11}$). In spite of the unusual dark green colour ($\lambda_{max} = 580$ nm) as compared to other mono- and dimeric juglomycins, **5b** could also be identified as a juglomycin dimer due to the ^{1}H and ^{13}C NMR data and the molecular formula of $C_{28}H_{18}O_{11}$ (free acid).

The ^{1}H NMR spectrum depicted again signals of two aromatic ABC systems and two methoxy groups and showed the allylic coupling of the naphthofuran proton 9'-H ($\delta = 6.82$, t, $J = 0.8$ Hz) with the methylene protons 11'-H_2 ($\delta = 3.96$, d) as in **4b**. Only one chelated phenolic OH ($\delta = 11.98$) was observed, whereas the second OH absorbed at $\delta = 9.46$. A further OH proton (10-OH) gave a doublet at $\delta = 3.41$ ($J = 4.4$ Hz), and 10-H ($\delta = 4.40$, m) coupled with 11-H_2 and a lowfield methine proton at $\delta = 5.76$ (9-H), thus indicating the β-hydroxybutyric acid side chain of juglomycin C or Z with a further oxygen at C-9. The ^{13}C NMR spectrum supported the dimeric structure by carbonyl signals at $\delta = 188.7/181.9$, typical of the 5-hydroxy-naphthoquinone system, and by a signal pattern of a naphthofuran substructure similar to that of **9**. By detailed analysis of all NMR data, a 2,3-substituted juglon and a naphthofuran moiety with free valencies at C-3/C-9 and C-3'/C-4, respectively, were derived. These can be connected in two different ways. But, as the C-9 and C-4' signals are lowfield shifted due to an oxygen bridge, the carbons C-3 and C-3' must be connected, too. This leads to the benzoisochromanquinone structure **5b** for the juglochroman B dimethyl ester and **5a** for juglochroman B, which also explains its green colour originating from the two coplanar and directly interacting chromophores.

*Juglochroman C (***6a***) and D (***6c***)*

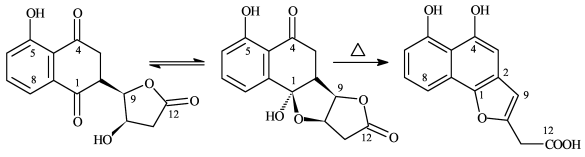
Two further juglomycin dimers, juglochroman C (**6a**) and D (**6c**), were isolated from the culture of the *Streptomyces* strain 815 as their dimethyl esters **6b** and **6d**. These delivered identical DCI mass spectra pointing at the molecular weight of *m/z* 558. The UV/vis and NMR spectra were nearly identical as well, suggesting **6b**/**d** to be diastereomers. Both proton NMR spectra exhibited signals of two sets of each three consecutive aromatic protons, of two methoxy groups and of an



6a: R = H
6b: R = CH_3
6c: diastereomer of **6a**
6d: diastereomer of **6b**

aromatic CH with an allylic coupling, as well as of two methylene and two methine protons. The allylic couplings in **6b** ($\delta = 7.26$, 4.09) and **6d** ($\delta = 6.88$, 3.96) pointed at a naphthofuran system as in **5a**/**b**, which was confirmed by comparison of the NMR data with those of **9** (Table 1 and 2, exp.). The remaining signals were assigned to a 2,3-substituted naphthoquinone system, *i.e.* **6b** and **6d** possess the same substructures as **5b**. In contrast to the latter, the ^{13}C NMR spectra of **6b** and **6d** indicated each only *one* aliphatic CH carbon bearing oxygen ($\delta_{C\text{-}10} = 71.4$ and 70.9, respectively), and instead of the second CH-O signal, a further oxygen-free methine group at $\delta = 37.1$ (**6b**) and 37.2 (**6d**) was found (C-9). The similar chemical shifts of the two quinone carbonyls in **6b** ($\delta = 183.1$, 182.6) and in **6d** ($\delta = 183.3$, 181.9) indicated the presence of oxygen at C-3 of the juglon unit as in juglomycin D [1], thus proving a C-3/C-4' oxygen bridge. This alternative connection of the two substructures results in the final structures of the juglochroman C/D dimethyl esters (**6b**/**d**) and hence in the structures **6a** and **6c** for juglochroman C and D, respectively.

A key compound for the structure elucidation of the juglochromans **4**–**6** was the naphthofuran **9** which is not a natural product. However, it was easily obtained by a careful thermolysis of 2,3-dihydrojuglomycin A (**7**) at 140 °C [3]. It is plausible that primarily the hemiacetal **8a** is formed, which in spite of the unfavourable *cis* orientation of 1-OH and 2-H looses water and forms the aromatic compound **9**. The structure was confirmed by its origin, the molecular weight and the typical NMR pattern of the adjacent protons, two



7 **8a** **9**

8b: 1-OMe instead of 1-OH

aromatic singlets and an aliphatic methylene group. The latter showed an allylic coupling of 0.7 Hz with 9-H ($\delta = 6.77$). The ^{13}C NMR spectrum, also in agreement with **9**, indicated five CH groups, four quaternary carbons bearing oxygen and only one sp^3 carbon (see Table 1 and 2, exp.).

Conclusion

The structures of the new dimerisation products of juglomycin C (**10**, Fig. 2), which were isolated from two *Streptomyces* strains of quite different origin, confirmed the proposals [3, 4] concerning the formation of the deeply red, structurally unique juglorubin (**11**) (Fig. 2). As the metabolites were also gained on very different experimental ways and were stable during work-up, the probability of producing isolation artifacts was rather low.

Off course, it remained uncertain to what extent the various products had been created by intracellular processes or by subsequent reactions in the cultivation medium. The various dimers can be arranged in a coherent scheme (Fig. 2), which includes some plausible intermediates (**I**–**V**): The condensation of the two juglomycin C units (**10**) seems to occur on two different pathways and starts (**A**) with the formation of a C-9/C-3' or (**B**) of a C-3/C-3' bond. Comparable reactions are known from the literature [6]. The first one should be an addition of the extended enolate of juglomycin C (Fig. 2) to C-3' of the partner, quite in parallel to the dimerisation of plumbagin (2-methyljuglone) to zeylanone [6a]. Next, the resulting anion **I** should cyclise in a tandem Michael addition to form the C-3/C-2' bond and thus juglocombin A (**2a**). The formation of a C-3-O-C-4' bridge is also possible and leads to the diastereomeric juglochromans C and D (**6a**, **6c**). The hemiketal of **2a**, isolated as juglocombin B (**3a**), can be enzymatically oxidised (probably *via* the epoxide) to yield the juglorescein (**1a**). Pathway **A** continues from **2a**/**3a** *via* the extended enole of **IV** to the dehydratable intermediate **V**. This undergoes a C-1'/C-2' bond cleavage resulting in the formation of the nine-membered lactone ring, which, together with the conjugated benzindenylide-quinone system, forms the unique structure of juglorubin (**11**) [3, 4].

The initial intermediate **II** on pathway **B** is first dehydrated (probably *via* a mono-hemiketal in analogy of **7** → **9**) leading to a naphthofuran compound like **III**, which can react from different mesomeric structures. The cyclisation *via* C-9/4'-O delivers juglochroman B (**5a**), while the formation of a C-10-O-C-3' bridge results in the *spiro*-compound juglochroman A (**4a**). All juglochromans contain the typical naphthofuran system being connected in different ways to the juglomycin C partner.

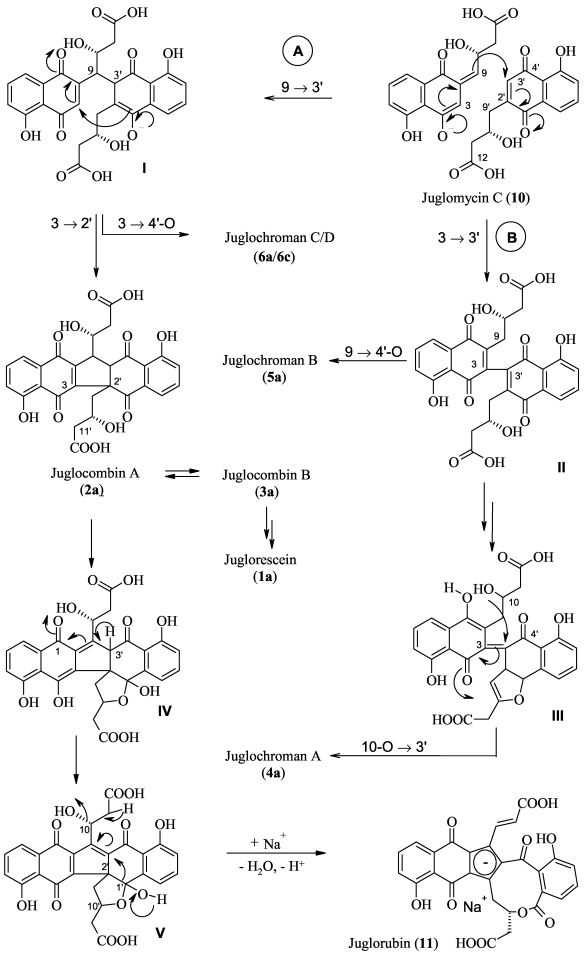


Fig. 2. Schematic survey of the isolated dimerisation products of juglomycin C (**10**) and the hypothetical intermediates **I**–**V**.

During the formation of **1a**, **2a** or **3a** up to six new stereocentres are generated; their determination by CD measurements or by comparison with similar diol structures, *e.g.* in tetracenomycin C [7], was not unambiguously possible. Only very few microbial metabolites display a structural similarity with **1a** and **2a**/**3a**, *e.g.* momofulvenone A [8] or the microbial degradation products shikometabolin A and B [9]. The ebony constituent zeylanone [6a] is, however, the closest analogue.

The production of monomeric juglomycins and in parallel 1-methylanthraquinones and benzoisochromanquinones isolated from the same culture broths is understandable on a common biosynthetic basis [1–3]. The condensation of the monomeric juglomycins or their precursors under formation of various dimerisation products (Fig. 2) can be summarized in a comprehensive scheme of complex interactions demonstrating the variability of the fermentation products of juglomycin-producing *Streptomyces* strains.

Experimental Section

For materials and methods, fermentation of the strains and isolation of the metabolites from various crude products and fractions: see ref. [2]. As most of the NMR-analytical studies were done with the methyl esters (improved solubility, resolution etc.), we supply the data of the metabolites and the derivatives.

*Juglorescein (***1a***)*

Streptomyces sp. 815 (fraction C-4) and GW4184: Colourless needles from $CHCl_3$/MeOH/C_6H_{12}, m.p. 142–145 °C (dec. at ≈ 120 °C), yellow colouration with NH_3. – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) = 344$ (3.97), 251 (sh, 4.18), 230 (4.46) nm. – IR (KBr): $\nu = 3406$ (OH), 2925, 1718, 1636, 1456, 1352, 1252, 1168, 1053, 808, 738, 668 cm^{-1}. – $[\alpha]_D^{20} = -107.4$ (c = 0.29, MeOH). – ^{1}H NMR (500 MHz, acetone-d_6): $\delta = 12.37$ (s, H/D exch., 1 H, 5'-OH), 11.02 (s br, H/D exch., 1 H, 5-OH), 7.77 (dd, $J = 8.4/7.4$ Hz, 1 H, 7-H), 7.57 (dd, $J = 7.4/1.2$ Hz, 1 H, 8-H), 7.55 (dd, $J = 8.2/7.7$ Hz, 1 H, 7'-H), 7.38 (dd, $J = 7.7/1.2$ Hz, 1 H, 8'-H), 7.29 (dd, $J = 8.4/1.2$ Hz, 1 H, 6-H), 6.90 (dd, $J = 8.2/1.2$ Hz, 1 H, 6'-H), 6.62 (s br, H/D exch., 1 H, 2-OH), 6.55 (s br, H/D exch., 1 H, 1'-OH), 5.96 (s br, H/D exch., 1 H, 3-OH), 4.90 (s br, H/D exch., 1 H, 10-OH), 4.88 (dddd, $J = 8.6/7/7/6.6$ Hz, 1 H, 10'-H), 4.84 (ddd, $J = 9.1/3.7/2.4$ Hz, 1 H, 10-H), 3.65 (dd, $J = 4.8/2.4$ Hz, 1 H, 9-H), 3.49 (d, $J = 4.8$ Hz, 1 H, 3'-H), 3.21 (dd, $J = 13.9/8.6$ Hz, 1 H, 9'-H_a), 3.06 (dd, $J = 17.2/3.7$ Hz, 1 H, 11-H_a), 2.89 (dd, $J = 17.2/9.1$ Hz, 1 H, 11-H_b), 2.82 (dd, $J = 17/7$ Hz, 1 H, 11'-H_a), 2.72 (dd, $J = 17/7$ Hz, 1 H, 11'-H_b), 2.45 (dd, $J = 13.9/6.6$ Hz, 1 H, 9'-H_b). – ^{13}C NMR (125.7 MHz, acetone-d_6): $\delta = 206.3$ (C-4'), 203.4 (C-4), 192.6 (C-1), 173.9 (C-12), 172.2 (C-12'), 163.3 (C-5), 162.0 (C-5'), 144.8 (C-8a'), 138.3 (C-7), 137.5 (C-7'), 136.6 (C-8a), 124.3 (C-6), 119.8 (C-8), 118.4 (C-8'), 118.3 (C-4a), 117.6 (C-6'), 115.2 (C-4a'), 101.3 (C-1'), 89.5 (C-3), 88.3 (C-2), 73.1 (C-10'), 67.9 (C-10), 64.2 (C-2'), 56.1 (C-3'), 47.1 (C-9), 41.6 (C-11), 40.9 (C-11'), 40.4 (C-9'). – (+)-ESI-MS: m/z (%) = 1191 ($[2M+Na]^+$, 72), 607 ($[M+Na]^+$, 100); (-)-ESI-MS: m/z (%) = 1167 ($[2M-H]^-$, 39), 605 ($[2M+Na-2H]^-$, 12), 583 ($[M-H]^-$, 100); ESI-HRMS: $m/z = 585.1238$ $[M+H]^+$ (calcd. 585.1239 for $C_{28}H_{25}O_{14}$); 607.1061 $[M+Na]^+$ (calcd. 607.1058 for $C_{28}H_{24}NaO_{14}$).

*Juglorescein-dimethylester (***1b***)*

Methylation of 100 mg juglorescein (**1a**) with diazomethane/MeOH yielded 98 mg (93%) **1b**, which after PTLC (see exp. in ref [2]) crystallized as thin colourless needles from $CHCl_3$/MeOH/C_6H_{12} (m.p. 134–137 °C, dec.). – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) = 345$ (3.87), 252 (4.07), 230 (4.33), 214 (sh, 4.26), 203 (4.31) nm; (MeOH/NaOH): $\lambda_{max}(\lg\varepsilon) = 410$ (3.82), 338 (3.59), 261 (4.05), 238 (4.18), 217 (4.41) nm. – IR (KBr): $\nu = 3389$, 2956, 1717, 1637/1606, 1450, 1350/1322, 1250, 1161, 1078, 1050, 806, 739 cm-^{1}. – $[\alpha]_D^{20} = -86.5$ (c = 0.17, acetone); CD (MeOH): $\lambda_{extr}([\theta]^{22}) = 357$ (−18020), 324 (+13510), 302 (sh., +3320), 276 (-39340), 265 (sh., −37790), 235 (+21350), 216 (−32030) nm. – ^{1}H NMR (500 MHz, acetone-d_6): $\delta = 12.34$ (s, H/D exch., 1 H, 5'-OH), 11.02 (s br, H/D exch., 1 H, 5-OH), 7.76 (dd, $J = 8.0/7.5$ Hz, 1 H, 7-H), 7.56 (dd, $J = 7.5/1.4$ Hz, 1 H, 8-H), 7.54 (dd, $J = 8.4/8.0$ Hz, 1 H, 7'-H), 7.36 (ddd, $J = 8.0/1.4/ < 1$ Hz, 1 H, 8'-H), 7.28 (dd, $J = 8.0/1.4$ Hz, 1 H, 6-H), 6.86 (dd, $J = 8.4/1.4$ Hz, 1 H, 6'-H), 6.62 (d, $J =< 1$ Hz, H/D exch., 1 H, 2-OH), 6.55 (d, $J =< 1$ Hz, H/D exch., 1 H, 1'-OH), 5.95 (s, H/D exch., 1 H, 3-OH), 5.40 (dd, $J = 3.8/0.5$ Hz, H/D exch., 1 H, 10-OH), 4.86 (dddd, $J = 8.6/7/7/6.6$ Hz, 1 H, 10'-H), 4.82 (dddd, $J = 9.1/3.7/2.4/ < 1$ Hz, 1 H, 10-H), 3.73 (s, 3 H, 12-OMe), 3.64 (s, 3 H, 12'-OMe), 3.64 (dd br, $J = 5.0/2.4/ < 1$ Hz, 1 H, 9-H), 3.47 (d, $J = 5.0$ Hz, 1 H, 3'-H), 3.20 (dd, $J = 13.5/8.6$ Hz, 1 H, 9'-H_a), 3.06 (dd, $J = 17.0/3.7$ Hz, 1 H, 11-H_a), 2.89 (dd, $J = 17.0/9.1$ Hz, 1 H, 11-H_b), 2.83 (dd, $J = 16.6/7$ Hz, 1 H, 11'-H_a), 2.74 (dd, $J = 16.6/7$ Hz, 1 H, 11'-H_b), 2.45 (dd, $J = 13.5/6.6$ Hz, 1 H,9'-H_b). – ^{13}C NMR (125.7 MHz, acetone-d_6): $\delta =$ 206.3 (C-4'), 203.4 (C-4), 192.6 (C-1), 172.7 (C-12), 171.6 (C-12'), 163.4 (C-5), 161.9 (C-5'), 144.8 (C-8a'), 138.3 (C-7), 137.5 (C-7'), 136.6 (C-8a), 124.4 (C-6), 118.3 (C-8'), 118.2 (C-4a), 117.6 (C-6'), 115.2 (C-4a'), 101.3 (C-1'), 89.4 (C-3), 88.3 (C-2), 73.0 (C-10'), 67.9 (C-10), 64.1 (C-2'), 56.0 (C-3'), 51.9 (12-OCH_3), 51.7 (12'-OCH_3), 47.1 (C-9), 42.1 (C-11), 40.9 (C-11'), 40.3 (C-9'); MS (DCI/NH_3): $m/z = 630.3$ ($[M+NH_4]^+$). – $C_{30}H_{28}O_{14}$ (612.54): calcd. C 58.83, H 4.61; found C 58.65, H 4.67.

*5-O-Acetyl-juglorescein-dimethyl ester (***1c***)*

Juglorescein-dimethyl ester (**1b**, 30 mg, 0.05 mmol), acetic acid anhydride (0.2 ml) and Na_2CO_3 (200 mg) in $CHCl_3$ (5 ml) were stirred for 12 h at 22 °C and the excess of Ac_2O decomposed by MeOH (1 ml) and water. The precipitate was filtered off and the residue purified by PTLC ($CHCl_3$/2% MeOH, developed twice) to get 22 mg (68%)

1c as colourless amorphous powder, m.p. 128 °C (dec.). – ^{1}H NMR (200 MHz, acetone-d_6): $\delta = 12.38$ (s, H/D exch., 1 H, 5'-OH), 8.00 (dd, $J = 7.6/1.4$ Hz, 1 H, 8-H), 7.87 (dd, $J = 8.1/7.6$ Hz, 1 H, 7-H), 7.54 (dd, $J = 8.3/7.9$ Hz, 1 H, 7'-H), 7.52 (dd, $J = 8.1/1.4$ Hz, 1 H, 6-H), 7.35 (dd, $J = 7.9/1.2$ Hz, 1 H, 8'-H), 6.62[a] (s, H/D exch., 1 H, 2-OH), 6.35[a] (s br, H/D exch., 1 H, 1'-OH), 5.79[a] (s, H/D exch., 1 H, 3-OH), 5.37[a] (s br, H/D exch., 1 H, 10-OH), 4.88 (m, 1 H, 10'-H), 4.84 (m, 1 H, 10-H), 3.72 (s, 3 H, 12-OMe), 3.65 (overlapped, 1 H, 9-H), 3.61 (s, 3 H, 12'-OMe), 3.41 (d, $J = 4.8$ Hz, 1 H, 3'-H), 3.25 (dd, $J = 14.0/8.6$ Hz, 1 H, 9'-H_a), 3.04 (dd, $J = 17/3.7$ Hz, 1 H, 11-H_a), 2.88 (overlapped, 1 H, 11-H_b), 2.75 (d, $J = 6.8$ Hz, 2 H, 11'-H_2), 2.39 (dd, $J = 14.0/6.6$ Hz, 1 H, 9'-H_b), 2.37 (s, 3-H, 5-COMe); [a] assignment may be exchanged. – ^{13}C NMR (50.3 MHz; acetone-d_6,): $\delta = 196.0$ (C-4), 169.6 (-O*CO*Me), 152.2 (C-5), 137.6 (C-8a), 136.1 (C-7), 130.9 (C-6), 127.4 (C-4a), 126.0 (C-8), 90.0 (C-3), 21.0 (-OCO*Me*), further signals similar to **1b**.

*1'-O-Methyl-juglorescein-dimethylester (***1d***)*

Juglorescein-dimethyl ester (**1b**, 15 mg, 0.025 mmol) was stirred for 2 h with 1 g molecular sieve (3 Å) and 5 mg *p*-toluene sulphonic acid monohydrate in 5 ml absolute MeOH. The evaporation residue was extracted three times with each 5 ml $CHCl_3$. PTLC ($CHCl_3$/2% MeOH, developed twice) of the residue yielded 9 mg (0.014 mmol, 59%) of **1d** as a light yellow amorphous solid with m. p. 118 °C (dec.). – $[\alpha]_D^{20} = +35.5°$ (c = 0.11, MeOH). – ^{1}H NMR (200 MHz, acetone-d_6): δ11.84 (s, H/D exch., 1 H, 5'-OH), 11.30 (s br, H/D exch., 1 H, 5-OH), 7.70 (dd, $J = 8.3/7.5$ Hz, 1 H, 7-H), 7.64 (dd, $J = 8.3/7.7$ Hz, 1 H, 7'-H), 7.56 (dd, $J = 7.5/1.3$ Hz, 1 H, 8-H), 7.26 (dd, $J = 8.3/1.3$ Hz, 1 H, 6-H), 7.24 (dd, $J = 7.7/1.0$ Hz, 1 H, 8'-H), 6.95 (dd, $J = 8.3/1$ Hz, 1 H, 6'-H), 6.64 (s br, H/D exch., 1 H, 2-OH), 5.46 (s, H/D exch., 1 H, 3-OH), 5.40 (m, 1 H, 10'-H), 5.10 (s, H/D exch., 1 H, 10-OH), 4.80 (m, 1 H, 10-H), 4.05 (dd, $J = 4.1/2.6$ Hz, 1 H, 9-H), 3.71 (s, 3 H, COOMe), 3.69 (s, 3 H, COOMe), 3.50 (dd, $J = 13.3/5.6$ Hz, 1 H, 9'-H_a), 3.45 (d, $J = 4.1$ Hz, 1 H, 3'-H), 3.32 (s, 1'-OMe), 2.87 (dd, $J = 16.5/3.6$ Hz, 1 H, 11-H_a), 2.85 (overlapped, 1 H, 9'-H_b), 2.80 (dd, $J = 16.0/5.6$ Hz, 1 H, 11'-H_a), 2.69 (dd, $J = 16.0/7.8$ Hz, 1 H, 11'-H_b), 2.68 (dd, $J = 16.5/9.3$ Hz, 1 H, 11-H_b).

*Juglocombin A dimethyl ester (***2b***) and Juglocombin B dimethyl ester (***3b***)*

Methylation (CH_2N_2/MeOH, 0 °C) of fraction B4 (380 mg) [2] and PTLC afforded 62 mg of a slightly impure mixture of the dimethyl esters **2b**/**3b**. For preparing a pure sample, 40 mg of **3c** were treated with 2N HCl (5 ml) for 1 h at 50 °C. The suspension was then diluted with water (40 ml), neutralized with diluted NaOH and extracted twice with each 20 ml of $CHCl_3$. The organic phase was dried over Na_2SO_4 and the residue purified by PTLC (impr. silica gel [2], C_6H_{12}/EtOAc, 3:1) to obtain 32 mg (82%) of pure **2b**/**3b**, m.p. 87 °C. – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) =$ 426 (3.63), 344 (3.69), 246 (4.22), 228 (4.36), 211 (4.63); (MeOH/NaOH)[b]: $\lambda_{max}(\lg\varepsilon) = 558$ (3.79), 266 (4.35), 223 (4.55) nm; [b] decomp. – IR (KBr): $\nu = 3440$ (OH), 2911, 1733 (ester), 1710/1700 (w), 1665 (w), 1655, 1633/1608 (C=O), 1453, 1257, 1167, 1067 cm^{-1}. – ^{1}H NMR (500 MHz, acetone-d_6): **2b**/**3b**: $\delta = 12.24$ (s, H/D exch., 1 H, OH), 12.14 (s, H/D exch., 1 H, OH), 11.92 (s, H/D exch., 1 H, OH), 11.30 (s, H/D exch., 1 H, OH), 3.65, 3.64, 3.59 and 3.56 (4s, 4 × 3 H, 4 OMe); **2b**: 7.72 (dd, $J = 8.3/7.5$ Hz, 1 H, 7-H), 7.71 (dd br, 1 H, 7'-H), 7.53 (dd br, 1 H, 8'-H), 7.44 (dd, $J = 7.5/1.1$ Hz, 1 H, 8-H), 7.29 (dd br, 1 H, 6'-H), 7.25 (dd, $J = 8.3/1.1$ Hz, 1 H, 6-H), 4.85 (m, 1 H, 10-H), 4.66 (s br, H/D exch., 1 H, 10-OH), 4.22 (m, 1 H, 10'-H), 4.21 (d br, H/D exch., 1 H, 10'-OH), 3.58 (overlapped, 1 H, 3'-H or 9-H), 3.54 (overlapped, 1 H, 9-H or 3'-H), 3.11 (dd, $J = 14/2.6$ Hz, 1 H, 9'-H_a), 2.81 (dd, $J = 16/7.9$ Hz, 1 H, 11-H_a), 2.78 (dd, $J = 16/5.9$ Hz, 1 H, 11-H_b), 2.50 (dd, $J = 15.2/4.3$ Hz, 1 H, 11'-H_a), 2.46 (dd, $J = 15.2/7.3$ Hz, 1 H, 11'-H_b), 2.37 (dd, $J = 14/11.1$ Hz, 1 H, 9'-H_b); **3b**: 7.72 (dd, $J = 8.3/7.5$ Hz, 1 H, 7-H), 7.55 (dd, $J = 8.4/7.8$ Hz, 1 H, 7'-H), 7.44 (dd, $J = 7.5/1.1$ Hz, 1 H, 8-H), 7.37 (dd, $J =$ 7.8/1.0 Hz, 1 H, 8'-H), 7.25 (dd, $J = 8.3/1.1$ Hz, 1 H, 6-H), 6.92 (dd, $J = 8.4/1.0$ Hz, 1 H, 6'-H), 6.53 (s br, H/D exch., 1 H, 1'-OH), 5.04 (m, 1 H, 10'-H), 5.01 (m, 1 H, 10-H), 4.75 (d, H/D exch., $J = 5.5$ Hz, 1 H, 10-OH), 4.22 (d, $J = 7.1$ Hz, 1 H, 3'-H), 3.81 (d br, 1 H, 9-H), 3.45 (dd, $J = 13.8/8.1$ Hz, 1 H, 9'-H_a), 2.90 (dd, $J = 16/8.3$ Hz, 1 H, 11-H_a), 2.85 (dd, $J = 16/5.6$ Hz, 1 H, 11-H_b), 2.64 (d br, $J = 6.7$ Hz, 2 H, 11'-H_2), 2.33 (dd (br), $J = 13.8/5.2$ Hz, 1 H, 9'-H_b); – ^{1}H NMR (200 MHz, $CDCl_3$): **2b**/**3b** $\delta = 12.13$, 12.07, 11.70 und 11.48 (4s, H/D exch., 4 × 1 H, 4x OH), 7.76 – 7.50 (m, 9 H), 7.34 – 7.26 (m, 2 H), 7.00 (dd, 1 H), 6.84 (s, H/D exch., 1 H, OH), 4.92 (m br, 2 H), 4.86 (d br, H/D exch., 1 H, OH), 4.26 (m br, 1 H), 4.16 (d, 1 H), 4.12 (d, 1 H), 3.79, 3.78, 3.70 and 3.69 (4s, 4*x* × 3 H, 4 OMe), 3.63 – 3.30 (m, 6 H), 3.08 – 2.40 (m, 10 H). – ^{13}C NMR (125.7 MHz, acetone-d_6): **2b**/**3b**: $\delta = 172.5$, 172.3, 172.1 and 171.5 (4 *CO*OMe), 162.7, 162.5, 162.3 and 161.2 (phenolic C), 51.7 (COO*Me*); **2b**: $\delta = 204.4$ (C-4'), 195.7 (C-1'), 189.4 (C-4), 182.8 (C-1), 151.7 (C-3), 149.1 (C-2), 137.8 (C-7), 137.6 (C-7'), 136.4 (C-8a'), 133.9 (C-8a), 125.2 (C-6), 123.8 (C-6'), 119.3 (C-8), 119.3 (C-8'), 116.3 (C-4a), 67.5 (C-10), 66.3 (C-10'), 65.2 (C-2'), 57.0 (C-3'), 56.3 (C-9), 43.6 (C-11'), 42.8 (C-9'), 40.6 (C-11); **3b**: $\delta = 204.8$ (C-4'), 190.9 (C-4), 183.5 (C-1), 153.8 (C-3), 149.5 (C-2), 144.2 (C-8a'), 137.9 (C-7), 137.1 (C-7'), 133.9 (C-8a), 125.4 (C-6), 119.7 (C-8), 118.4 (C-8'), 118.1 (C-6'), 116.9 (C-4a), 116.8 (C-4a'), 102.5 (C-1'), 73.6 (C-10'), 67.6 (C-10), 65.5 (C-2'), 56.0 (C-9), 53.7 (C-3'), 44.8 (C-9'), 40.7 (C-11'), 40.6 (C-11). – ^{13}C NMR (50.3 MHz, $CDCl_3$):

2b/**3b**: δ = 203.3, 202.4, 194.9, 190.4, 187.9, 183.0, 181.6, 173.7, 173.1, 172.9, 170.9, 162.6, 162.1, 161.7, 161.1, 154.3, 149.9, 149.3, 146.7, 141.2, 137.5, 137.4, 137.3, 136.2, 134.9, 132.5, 132.4, 125.6, 125.4, 124.0, 120.1, 119.4; 119.3, 118.3, 117.8, 117.0, 116.0, 115.6, 115.0, 101.3, 72.0, 67.1, 66.6, 65.4, 65.0, 63.9, 56.4, 55.5, 55.1, 52.8, 52.1, 51.9, 43.6, 41.3, 41.1, 40.0, 39.4, 39.2. – MS (DCI, NH_3): *m/z* (%) = 598 ($[M+2H+NH_4]^+$, 100), 596 ($[M+NH_4]^+$, 68). – $C_{30}H_{26}O_{12}$ (578.52): calcd. C 62.28, H 4.53; found C 62.36, H 4.64.

*1'-O-Methyljuglocombin B dimethyl ester (***3c***)*

50 mg **2b**/**3b** in 5 ml methanol / conc. HCl (9:1) were stirred for 24 h at 22 °C, diluted with 30 ml $CHCl_3$ and washed twice with each 20 ml of 10% $NaHCO_3$ solution and then with H_2O. PTLC (impr. silica gel, C_6H_{12}/EtOAc, 3:1) yielded 42 mg of amorphous, yellow **3c** with m.p. 88 °C. Further 105 mg of **3c** were obtained from the HCl/MeOH-treated fraction C-5 [2]. – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) = 422$ (3.65), 256 (4.16), 212 (4.68); (MeOH/NaOH): $\lambda_{max}(\lg\varepsilon) =$ 519 (3.61), 354 (3.75), 281 (4.03), 264 (4.05), 220 (4.62) nm. – IR (KBr): ν = 3511 (OH), 2933, 2844, 1733 (ester), 1656 (w), 1639/1611 (quinone), 1457, 1250, 1200, 1161, 1067, 839, 811, 772, 733 cm^{-1}. – $[\alpha]_D^{20} = -133.3$ (c = 0.2, acetone); CD (MeOH): $\lambda_{extr.}([\theta]^{22}) = 440$ (+1100), 360 (−18100), 319 (sh., −3100), 298 (+6310), 274 (−27870), 246 (−21100) nm. – ^{1}H NMR (200 MHz, acetone-d_6): δ = 12.33 (s, H/D exch., 1 H, 5'-OH), 11.24 (s, H/D exch., 1 H, 5-OH), 7.74 (dd, *J* = 8.3/7.4 Hz, 1 H, 7-H), 7.68 (dd, *J* = 8.3/7.6 Hz, 1 H, 7'-H), 7.60 (dd, *J* = 7.4/1.3 Hz, 8-H), 7.42 (dd, *J* = 7.6/1.1 Hz, 1 H, 8'-H), 7.33 (dd, *J* = 8.3/1.3 Hz, 1 H, 6-H), 7.03 (dd, *J* = 8.3/1.1 Hz, 1 H, 6'-H), 5.42 (dddd, *J* = 8.5/7.3/7.2/6.5 Hz, 1 H, 10'-H), 4.92 (dddd, *J* = 9/4.4/3.7/1.7 Hz, 1 H, 10-H), 4.51 (d, *J* = 4.4 Hz, H/D exch., 1 H, 10-OH), 3.93 (dd, *J* = 3.8/1.7 Hz, 1 H, 9-H), 3.72 (d, *J* = 3.8 Hz, 1 H, 3'-H), 3.67 (s, 3 H, COO*Me*), 3.66 (s, 3 H, COO*Me*), 3.18 (dd, *J* = 14/7.2 Hz, 1 H, 9'-H_a), 2.91 (s, 3 H, 1'-O*Me*), 2.76 (dd, *J* = 15.5/3.7 Hz, 1 H, 11-H_a), 2.73 (dd, *J* = 15.0/6.5 Hz, 11'H_a), 2.64 (dd, *J* = 15.5/9 Hz, 1 H, 11-H_b), 2.51 (dd, *J* = 15.0/7.3 Hz, 11'-H_b), 2.34 (dd, *J* = 14/8.5 Hz, 1 H, 9'-H_b). – ^{13}C NMR (50.3 MHz, acetone-d_6): δ203.4 (C-4'), 189.5 (C-4), 183.5 (C-1), 172.3 (C-12), 171.6 (C-12'), 162.6 (C-5), 161.1 (C-5'), 152.0[a] (C-2), 151.1[a] (C-3), 142.9 (C-8a'), 137.0[b] (C-7'), 136.8[b] (C-7), 133.8 (C-8a), 125.3 (C-6), 119.9[c] (C-8), 119.0[c] (C-8'), 118.2[c] (C-6'), 117.0[d] (C-4a), 116.8[d] (C-4a'), 75.9 (C-10'), 67.8 (C-10), 65.5 (C-2'), 55.1 (C-3'), 52.4 (C-9), 51.8 (12-OMe), 51.7 (12'-OMe), 47.0 (C-9'), 42.3 (C-11), 40.9 (C-11'); [a,b,c,d] assignment may be exchanged. – MS (DCI, NH_3): m/z = 610.4 ($[M + NH_4]^+$); $C_{31}H_{28}O_{12}$ (592.56).

*Juglochroman A dimethylester (***4b***)*

Juglochroman A dimethylester (22 mg, **4b**) was obtained as yellow amorphous powder (m.p. 86 °C, dec.) from fraction C-5 after treatment with methanol / conc. HCl (9:1, 1 h, r.t.) and separation by PTLC (SS-7, [2]). – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) = 411$ (3.84), 328 (3.49), 257 (4.42), 211 (4.59); (MeOH/NaOH): $\lambda_{max}(\lg\varepsilon) = 530$ (3.61), 408 (3.77), 334 (3.53), 262 (4.39), 209 (4.63) nm. – IR (KBr): ν = 3446, 2926, 1741, 1646, 1619, 1456, 1278, 1164, 1000, 810, 744 cm^1. – $[\alpha]_D^{20} = +33.8$ (c = 0.12, MeOH). – ^{1}H NMR (200 MHz, acetone-d_6): δ = 11.83 (s, H/D exch., 1 H, H/D exch., 5'-OH), 11.34 (s, H/D exch., 1 H, 5-OH), 7.78 (dd, *J* = 8.3/7.5 Hz, 1 H, 7-H), 7.71 (dd, *J* = 8.5/7.5 Hz, 1 H, 7'-H), 7.68 (dd, *J* = 7.5/1.3 Hz, 1 H, 8-H), 7.28 (dd, *J* = 8.3/1.3 Hz, 1 H, 6-H), 7.23 (dd, *J* = 7.5/1.0 Hz, 1 H, 8'-H), 6.93 (dd, *J* = 8.5/1.0 Hz, 1 H, 6'-H), 6.77 (t, *J* = 0.8 Hz, 1 H, 9'-H), 4.63 (dddd, *J* = 9.5/7.5/5.5/3.2 Hz, 1 H, 10-H), 3.85 (d, *J* = 0.8 Hz, 2 H, 11'-H_2), 3.67 (s, 3 H, OCH_3), 3.53 (s, 3 H, OCH_3), 3.16 (dd, *J* = 19.2/3.2 Hz, 9-H_a), 2.80 (dd, *J* = 16.1/5.5 Hz, 11-H_a), 2.63 (dd, *J* = 16.1/7.5 Hz, 11-H_b), 2.57 (dd, *J* = 19.2/9.5 Hz, 9-H_b). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.80 (s, H/D exch., 1 H, 5'-OH), 11.30 (s, H/D exch., 1 H, 5-OH), 7.67 (dd, *J* = 7.4/1.0 Hz, 1 H, 8-H), 7.60 (dd, *J* = 8.0/7.4 Hz, 1 H, 7-H), 7.55 (dd, *J* = 8.5/7.5 Hz, 1 H, 7'-H), 7.20 (dd, *J* = 8.0/1.0 Hz, 1 H, 6-H), 7.20 (dd, *J* = 7.5/1.0 Hz, 1 H, 8'-H), 6.90 (dd, *J* = 8.5/1.0 Hz, 1 H, 6'-H), 6.31 (t, *J* = 0.8 Hz, 1 H, 9'-H), 4.49 (m, 1 H, 10-H), 3.75 (d, *J* = 0.8 Hz, 2 H, 11'-H_2), 3.73 (s, 3 H, 12'-OCH_3), 3.62 (s, 3 H, 12-OCH_3), 3.12 (dd, *J* = 19.4/3.1 Hz, 9-H_a), 2.73 (dd, *J* = 16.2/6.5 Hz, 11-H_a), 2.64 (dd, *J* = 16.2/6.6 Hz, 11-H_b), 2.56 (dd, *J* = 19.4/10.6 Hz, 9-H_b). – ^{13}C NMR (50.3 MHz, acetone-d_6): δ = 200.3 (C-4'), 188.3 (C-4), 183.1 (C-1), 170.1 and 169.6 (*CO*OMe), 164.5 (C-5'), 162.2 (C-5), 151.0 (C-10'), 147.5* (C-1'), 147.1* (C-3), 143.4 (C-2), 139.4 (C-7), 138.0 (C-7'), 132.8 (C-8a), 131.3 (C-8a'), 125.2 (C-6), 124.5 (C-2'), 120.0 (C-8), 118.1 (C-6'), 115.2 (C-4a), 112.4 (C-8'), 111.0 (C-9'), 110.9 (C-4a'), 75.5 (C-3'), 67.6 (C-10), 52.5 and 51.7 (COO*Me*), 40.6 (C-11), 34.2 (C-11'), 28.1 (C-9); * assignment may be reversed. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 198.8 (C-4'), 186.7 (C-4), 182.5 (C-1), 170.3 (C-12), 168.9 (C-12'), 163.7 (C-5'), 161.6 (C-5), 149.2 (C-10'), 146.9 (C-1'), 145.3 (C-3), 143.1 (C-2), 138.1 (C-7), 136.6 (C-7'), 131.5 (C-8a), 130.5 (C-8a'), 124.8 (C-6), 122.2 (C-2'), 119.6 (C-8), 117.8 (C-6'), 114.4 (C-4a), 111.9 (C-8'), 110.2 (C-4a'), 109.3 (C-9'), 74.5 (C-3'), 66.4 (C-10), 52.5 (12'-OCH_3), 51.8 (12-OCH_3), 40.2 (C-11), 33.4 (C-11'), 27.4 (C-9) – MS (DCI, NH_3): m/z = 576 ($[M+NH_4]^+$); $C_{30}H_{22}O_{11}$ (558.50).

*Juglochroman B dimethylester (***5b***)*

Blackish-green needles (4 mg) were obtained after repeated crystallization ($CHCl_3$/MeOH/C_6H_{12}) of the impure product obtained from fraction C-5 [2], m.p. 192 °C (dec.). – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) = 580$ (3.26), 430 (3.69), 358 (3.74), 269 (4.39), 257 (sh, 4.47), 240 (sh, 4.44),

	4b	5b[a]	6b	6d	9	THN
5'-OH	11.83	9.58	9.18	9.06	10.30	10.0
6'-H	6.93 (8.5/1.1)	6.88 (7.2/1.6)	7.00 (7.8/1.1)	7.05 (7.7/1.2)	6.83 (7.7/1.1)	6.78 (7.6/1.0)
7'-H	7.71 (8.5/7.5)	7.68 – 7.83 m	7.54 (8.1/7.8)	7.49 (8.3/7.7)	7.44 (8.3/7.7)	7.29 (8.5/7.6)
8'-H	7.23 (7.5/1.1)	7.68 – 7.83 m	7.36 (8.1/1.1)	7.31 (8.3/1.2)	7.66 (8.5/1.1)	7.66 (8.5/1.0)
9'-H	6.77 (0.8)	7.00 br	7.26 (0.8)	6.88 (0.7)	6.77 (0.7)	–
11'-H_2	3.85 (0.8)	4.03 (0.7)	4.09 (0.8)	3.96 (0.7)	3.97 (0.7)	–

Table 1. ^{1}H NMR data of the naphthofuran moiety of juglochroman esters, the 1,4,5-trihydroxy-naphthalene(THN) system of 1,4-dihydro-juglomycin A and **9** in acetone-d_6. [a] $CDCl_3/CD_3OD$.

214 (4.39) nm; (MeOH/NaOH): $\lambda_{max}(\lg\varepsilon) = 570$ (3.57), 371 (3.66), 268 (sh, 4.31), 252 (4.38), 207 (4.62) nm. – IR (KBr): $\nu = 3407$, 2955/2925, 1734, 1637, 1595, 1560, 1458/1438, 1372/1342, 1287/1260, 1173, 1024, 970, 807, 763, 669 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 11.98$ (s, H/D exch., 1 H, 5-OH), 9.46 (s, H/D exch., 1 H, 5'-OH), 7.68 (m, 3 H, 7-H/8-H/8'-H), 7.53 (dd, $J = 8.1/7.8$ Hz, 1 H, 7'-H), 7.36 (m, 1 H, 6-H), 6.95 (dd, $J = 7.8/1.2$ Hz, 1 H, 6'-H), 6.82 (t, $J = 0.8$ Hz, 1 H, 9'-H), 5.76 (d, $J = 8.5$ Hz, 1 H, 9-H), 4.40 (m, 1 H, 10-H), 3.96 (d, $J = 0.8$ Hz, 2 H, 11'-H_2), 3.78 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 3.41 (d, $J = 4.4$ Hz, H/D exch., 1 H, 10-OH), 2.65 (dd, $J = 17.0/9.3$ Hz, 1 H, 11-H_a), 2.36 (dd, $J = 17.0/2.8$ Hz, 11-H_b). – ^{1}H NMR (200 MHz, acetone-d_6): $\delta = 11.94$ (s, H/D exch., 1 H, 5-OH), 9.58 (s br, H/D exch., 1 H, 5'-OH), 7.83 (dd, $J = 8.2/1.3$ Hz, 1 H, 8-H), 7.68 – 7.51 (m, 3 H, 7'-H/8-H/8'-H), 7.38 (dd, $J = 8.2/1.3$ Hz, 1 H, 6-H), 7.00 (s br, 1 H, 9'-H), 6.88 (dd, $J = 7.2/1.6$ Hz, 1 H, 6'-H), 5.78 (d, $J = 7.5$ Hz, 1 H, 9-H), 4.80 (d, $J = 6.3$ Hz, H/D exch., 1 H, 10-OH), 4.50 (m, 1 H, 10-H), 4.03 (d, $J = 1.7$ Hz, 2 H, 11'-H_2), 3.73 (s, 3 H, OCH_3), 3.50 (s, 3 H, OCH_3), 2.60 (m, 2 H, 11-H_2). – ^{13}C NMR (50.3 MHz, $CDCl_3/CD_3OD$); $\delta = 187.7$ (C-4), 181.9 (C-1), 172.2 (C-12), 169.9 (C-12'), 161.7 (C-5), 155.8 (C-5'), 149.7 (C-4'), 149.6 (C-10'), 147.2 (C-1'), 136.9 (C-7), 136.5[a] (C-2), 133.5 (C-3), 131.7[a] (C-8a), 131.4 (C-7'), 125.4[b] (C-8a'), 125.0 (C-6), 120.6[b] (C-2'), 119.3 (C-8), 115.5[b] (C-3'), 112.3 (C-4a), 111.8[c] (C-6', C-8'), 109.3[c] (C-9'), 107.4 (C-4a'), 74.9 (C-9), 64.7 (C-10), 52.6 (OCH_3), 52.1 (OCH_3), 37.8 (C-11), 34.5 (C-11'); [a,b,c] assignment may be reversed. – ^{13}C NMR (50.3 MHz, acetone-d_6): $\delta = 188.7$ (C-4), 182.6 (C-1), 171.7 (C-12), 169.9 (C-12'), 162.3 (C-5), 157.2 (C-5'), 151.1 (C-4'), 150.8 (C-10'), 147.2 (C-1'), 137.6 (C-7), 137.1[a] (C-2), 135.1[a] (C-3), 132.9[a] (C-8a), 131.9 (C-7'), 125.8[b] (C-3'), 125.1 (C-6), 122.0[b] (C-2'), 119.3 (C-8), 116.6[b] (C-8a'), 113.0 (C-4a), 112.1[c] (C-6'), 111.6[c] (C-8'), 110.4[c] (C-9'), 108.4 (C-4a'), 76.3 (C-9), 66.6 (C-10), 52.5 (OCH_3), 51.7 (OCH_3), 39.1 (C-11), 34.6 (C-11'); [a,b,c] assignment may be reversed. – MS (DCI, NH_3): $m/z = 576.1$ ($[M + NH_4]^+$); $C_{30}H_{22}O_{11}$ (558.50).

*Juglochroman C/D dimethyl ester (***6b**/**6d***)*

From the methylated fraction C-5, juglochroman C-dimethyl ester (5.5 mg, **6b**) and juglochroman D-dimethyl ester (7 mg, **6d**) with very similar characteristics were obtained after difficult separations [2].

Table 2. ^{13}C NMR data of the naphthofuran moiety of juglochromans, the 1,4,5-trihydroxynaphthalene (THN) system of 1,4-dihydro-juglomycin A and **9** in acetone-d_6.

	4b	5b[a]	6b	6d	9	THN
C-1'	147.5	147.2	147.7	148.3	145.7	143.1
C-2'	124.5	120.6	122.3	122.2	125.4	118.7
C-3'	75.5	115.5	119.9	113.7	106.5	108.5
C-4'	200.3	149.7	143.7	143.8	151.0	147.6
C-4a'	110.9	107.4	101.1	107.4	113.0	115.8
C-5'	164.5	155.8	153.9	153.6	156.1	155.4
C-6'	118.1	111.8	110.8	111.6	109.8	110.0
C-7'	138.0	131.4	128.7	129.3	128.8	127.2
C-8'	112.4	111.8	112.0	112.9	111.7	111.7
C-8a'	131.3	125.4	122.5	122.8	124.2	129.3
C-9'	111.0	109.3	105.3	105.0	101.4	–
C-10'	151.0	149.6	152.1	151.4	152.6	–

6b: Grey-brown solid with m.p. 211 °C (dec.). – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) = 422$ (3.68), 346 (3.67), 330 (3.66), 310 (sh, 3.80), 297 (sh, 3.88), 286 (3.92), 248 (4.67), 207 (4.53); (MeOH/NaOH): $\lambda_{max}(\lg\varepsilon) = 517$ (3.76), 350 (3.91), 332 (3.88), 288 (4.22), 255 (sh, 4.65), 245 (4.70), 219 (sh, 4.73), 208 (4.75) nm. – IR (KBr): $\nu = 3478$, 2954, 1734, 1628, 1595, 1457, 1379, 1255, 1203, 1063, 1027, 761 cm^{-1}. – ^{1}H NMR (500 MHz, acetone-d_6): $\delta = 9.18$ (s br, H/D exch., 1 H, 5'-OH), 7.84 (dd br, $J = 8.4/7.7$ Hz, 1 H, 7-H), 7.73 (dd br, $J = 7.7/1.0$ Hz, 1 H, 8-H), 7.70 (dd, $J = 8.1/1.1$ Hz, 1 H, 8'-H), 7.54 (dd, $J = 8.1/7.8$ Hz, 1 H, 7'-H), 7.37 (dd br, $J = 8.4/1.0$ Hz, 1 H, 6-H), 7.26 (t, $J = 0.8$ Hz, 1 H, 9'-H), 7.00 (dd, $J = 7.8/1.1$ Hz, 1 H, 6'-H), 4.79 (s br, 1 H, 9-H), 4.65 (s br, H/D exch., 1 H, 10-OH), 4.48 (ddd, $J = 8.4/5.6/2.4$ Hz, 1 H, 10-H), 4.09 (d, $J = 0.8$ Hz, 2 H, 11'-H_2), 2.68 (dd, $J = 16.3/5.6$ Hz, 11-H_a), 2.35 (dd, $J = 16.3/8.4$ Hz, 11-H_b); 5-OH not visible. – ^{13}C NMR (125.7 MHz, acetone-d_6): $\delta = 183.1$ (C-4), 182.6 (C-1), 171.5 (C-12), 168.9 (C-12'), 161.5 (C-5), 153.9 (C-5'), 152.7 (C-3), 152.1 (C-10'), 147.7 (C-1'), 143.7 (C-4'), 137.5 (C-7), 132.2 (C-8a), 128.7 (C-7'), 123.8 (C-6), 122.5[a] (C-3'), 122.4[a] (C-2'), 119.9[a] (C-2), 119.2 (C-8), 114.0[b] (C-8a'), 112.0[c] (C-6'), 110.8[b/c] (C-4a/C-8'), 110.2[b] (C-4a'), 105.3 (C-9'), 70.9 (C-10), 50.7 (2 C, OCH_3), 38.7 (C-11), 37.1 (C-9), 33.7 (C-11'); [a,b,c] assignment may be reversed. – MS (DCI, NH_3): $m/z = 576.1$ ($[M + NH_4]^+$); $C_{30}H_{22}O_{11}$ (558.50).

6d: Bronze coloured solid, m.p. 234 °C (dec.). – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) = 422$ (3.66), 346 (3.67), 330 (3.73),

310 (sh, 3.88), 298 (sh, 3.97), 288 (4.00), 253 (sh, 4.66), 249 (4.69), 207 (4.56); (MeOH/NaOH): $\lambda_{max}(\lg\varepsilon) = 517$ (3.73), 350 (3.91), 333 (3.93), 313 (sh, 4.11), 288 (4.26), 256 (sh, 4.68), 248 (4.72), 222 (4.68) nm. – IR (KBr): $\nu = 3489$, 2954, 1735, 1654/1640/1625, 1594, 1458, 1376, 1279/1253, 1204, 1065, 1023, 815, 759, 703 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3/CD_3OD$): $\delta = 11.50$ (s br, H/D exch., 1 H, 5-OH), 9.06 (s, H/D exch., 1 H, 5'-OH), 7.73 (dd, $J = 8.3/1.2$ Hz, 1 H, 8'-H), 7.72 (dd, 7.4/1.2 Hz, 1 H, 8-H), 7.68 (dd, $J = 8.2/7.4$ Hz, 1 H, 7-H). 7.49 (dd, $J = 8.3/7.7$ Hz, 1 H, 7'-H), 7.31 (dd, $J = 8.2/1.2$ Hz, 1 H, 6-H), 7.05 (dd, $J = 7.7/1.2$ Hz, 1 H, 6'-H), 6.88 (t, $J = 0.7$ Hz, 1 H, 9'-H), 4.68 (d, $J = 3.8$ Hz, 1 H, 9-H), 4.38 (ddd, $J = 9.9/3.8/3.3$ Hz, 1 H, 10-H), 3.96 (d br, $J = 0.7$ Hz, 2 H, 11'-H_2), 3.79 (s, 3 H, OCH_3), 3.56 (s, 3 H, OCH_3), 2.50 (dd, $J = 15.7/3.3$ Hz, 1 H, 11-H_a), 2.40 (dd, $J = 15.7/9.9$ Hz, 1 H, 11-H_b). – ^{13}C NMR (125.7 MHz, $CDCl_3/CD_3OD$): $\delta = 183.3$ (C-4), 181.9 (C-1), 172.2 (C-12), 169.2 (C-12'), 161.9 (C-5), 153.6 (C-5'), 152.1 (C-3), 151.4 (C-10'), 148.3 (C-1'), 143.8 (C-4'), 137.6 (C-7), 131.8 (C-8a), 129.3 (C-7'), 124.7 (C-6), 122.8[a] (C-3'), 122.2[a] (C-2'), 121.0[a] (C-2), 120.1 (C-8), 113.7[b] (C-8a'), 112.9[c] (C-6'), 111.6[c] (C-8'), 111.1[b] (C-4a), 107.4 (C-4a'), 105.0 (C-9'), 71.4 (C-10), 52.6 (OMe), 51.9 (OMe), 38.7 (C-11), 37.2 (C-9), 34.5 (C-11'); [a,b,c] assignment may be reversed. – MS (DCI, NH_3): $m/z = 576.1$ ($[M + NH_4]^+$); $C_{30}H_{22}O_{11}$ (558.50).

*(1aR,4aR,4bS,10bR)-Tetrahydro-7-hydroxy-10b-methoxyfuro[3,2-b]naphtho[2,1-d]-furan-3,6(2H,5H)-dione (***8b***) [10]*

100 mg (0.36 mmol) **7** and 25 mg *p*-toluenesulfonic acid in 5 ml methanol were stirred for 1 h at 20 °C. PTLC afforded 96 mg (92%) **8b** which crystallised from $CHCl_3$/methanol/cyclohexan as compact colourless prisms with m.p. 126 °C (dec.). – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) = 332$ (3.27), 288 (sh, 3.51), 256 (3.97), 219 (4.55) nm; (methanol/NaOH): $\lambda_{max}(\lg\varepsilon) = 560$ (3.93), 303 (4.33), 220 (4.57) nm. – IR (KBr): $\nu = 3433$ (OH), 2987/2984 (aliph. CH), 1784/1768 (lactone), 1643 (C=O, chel.), 1612 (C=C), 1454, 1328, 1294, 1225, 1177, 1156, 1121, 1053, 1045, 1005, 964, 930, 885, 814, 736, 663, 622 cm^{-1}. – $[\alpha]_D^{20}$: −182.20 (c = 0.21, acetone). – CD (methanol): $\lambda_{extr}([\theta]^{22}) = 352$ (sh, +1480), 345 (+1550), 255 (−22020), 223 (−14560) nm. – ^{1}H NMR (200 MHz, DMSO-d_6): $\delta =$ 12.14 (d, $J = 0.4$ Hz, 1 H, 5-OH), 7.55 (dd, $J = 8.3/7.7$ Hz, 1 H, 7-H), 7.09 (dd, $J = 7.7/1.1$ Hz, 1 H, 8-H), 6.89 (ddd, $J = 8.3/1.1/0.4$ Hz, 1 H, 6-H), 5.20 (ddd, $J = 4.8/4.5/0.3$ Hz, 1 H, 9-H), 5.04 (ddd, $J = 6.4/4.5/0.7$ Hz, 1 H, 10-H), 3.32 (ddd, $J = 7.1/4.8/2.4$ Hz, 1 H, 2-H), 3.11 (ddd, $J =$ 18.3/7.1/0.3 Hz, 1 H, 3-H_a), 2.95 (dd, $J = 18.3/2.4$ Hz, 1 H, 3-H_b), 2.78 (dd, $J = 18.6$x/6.4 Hz, 1 H, 11-H_a), 2.21 (dd, $J =$ 18.6/0.7 Hz, 1 H, 11-H_b). – ^{13}C NMR (50.3 MHz, DMSO-d_6): δ202.2 (C-4), 174.2 (C-12), 159.9 (C-5), 142.9 (C-8a), 136.6 (C-7), 117.8 (C-8), 115.1 (C-4a), 117.1 (C-6), 104.4 (C-1), 84.9 (C-9), 76.7 (C-10), 49.7 (C-2), 36.3 (C-3), 34.2 (C-11). – MS (EI, 70 eV): *m/z* (%) = 290 (36, $[M]^+$), 259 (100, $[M - OCH_3]^+$); HRMS: 290.0790 (calcd. 290.0790 for $C_{15}H_{14}O_6$). – $C_{15}H_{14}O_6$ (290.27): calcd. C 62.07, H 4.86; found C 61.87, H 4.76.

*2-(5,6-Dihydroxynaphtho[1,2-b]furan-2-yl)acetic acid (***9***)*

20 mg of **7** were heated for 5 min to 140 °C and then dissolved in 1 ml acetone. 10 ml phosphate buffer (pH 7.4) were added and nonpolar side products and starting material extracted twice with each 5 ml of $CHCl_3$. Finally, **9** was extracted twice at pH 3 with each 10 ml $CHC1_3$. Crystallisation from $CHCl_3$/MeOH/cyclohexane yielded 11 mg (57%) of **9** as colourless needles with m.p. 196 °C. – UV/vis (Methanol): $\lambda_{max}(\lg\varepsilon) = 353$ (4.19), 336 (4.02), 322 (3.82), 298 (sh, 3.88), 257 (4.76), 202 (4.39); (Methanol/NaOH): $\lambda_{max}(\lg\varepsilon) = 363$ (4.24), 347 (4.11), 330 (3.95), 261 (sh, 4.73), 253 (4.77), 205 (4.71) nm. – IR (KBr): $\nu = 3546$, 3406, 3072, 1690, 1647, 1607, 1405, 1251, 1180, 1046, 962, 938, 904, 844, 806, 762 cm^{-1}. – ^{1}H NMR (200 MHz, acetone-d_6): δ10.3 (s br, 2 H, 4-,5-OH), 7.66 (dd, $J =$ 8.3/1.1 Hz, 1 H, 8-H), 7.44 (dd, $J = 8.3/7.7$ Hz, 1 H, 7-H), 6.98 (s, 1 H, 3-H), 6.83 (dd, $J = 7.7/1.1$ Hz, 1 H, 6-H), 6.77 (t, $J = 0.7$ Hz, 9-H), 3.97 (d, $J = 0.7$ Hz, -CH_2-COOH), 3.3 (s br, OH). – ^{13}C NMR (50.3 MHz, acetone-d_6): δ170.4 (CH_2-*C*OOH), 156.1 (C_q-5), 152.6* (C_q-10), 151.0* (C_q-4), 145.7 (C_q-1), 128.8 (C-7), 125.4# (C_q-2), 124.2# (C_q-8a), 113.0 (C_q-4a), 111.7 (C-8), 109.8 (C-6), 106.6 (C-3), 101.4 (C-9), 34.7 (-*C*H_2-COOH); * and # may be exchanged. $C_{14}H_{10}O_5$ (258.23).

Acknowledgements

We thank R. Machinek and his team for the NMR measurements, G. Remberg and H. Frauendorf for the mass spectra and Mrs. N. Sieck and Mrs. M. Lackner for technical and microbiological support. This work was supported by grants from the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and the Bundesministerium für Bildung und Forschung (BMBF, grant 03F0346A).

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