160. The Relative Stabilities of Substituted *cis*- and *trans*-1,2,3,4,4a,9,10,10a-Octahydrophenanthrenes, Including Configurational Corrections in the *Elad-Ginsburg* Morphine Synthesis

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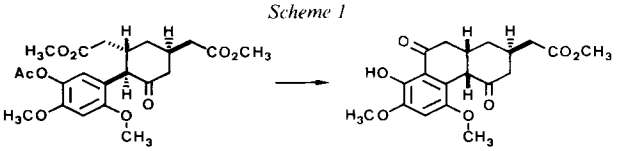
The relative configuration of the title compounds has been determined by ^{1}H-NMR measurements at 300 MHz. In contradistinction to prevailing opinion, it was found that 4-oxo derivatives prefer the *cis*-configuration. While the *cis*/*trans* ratio is 82:18 for the parent 1,2,3,4,4a,9,10,10a-octahydrophenanthrene-4,9-dione, the *trans*-isomers of C(5)-substituted derivatives cannot be detected under the conditions of equilibration. The *cis*-configuration is retained upon acetalization of the 4-oxo derivative. A warning is issued regarding the assigned configurations of certain intermediates in the *Elad-Ginsburg* synthesis of morphine.

The cycloacylation of 2'-aryl-cyclohexylacetic acids affording 1,2,3,4,4a,9,10,10a-octahydrophenanthrene systems has found numerous applications, especially in connection with natural-product syntheses [1]. Whereas the configuration of the product is generally given by the configuration of the precursor, a possible isomerization of C(4a) has to be taken in account for 1,2,3,4,4a,9,10,10a-octahydrophenanthrene-4-ones. While it was assumed that such an isomerization does not occur during cyclization of bicyclic intermediates to give these products [2], it could be shown recently, that cyclization of the

Scheme 1



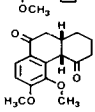
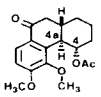
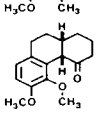
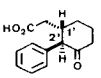
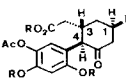
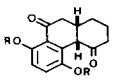
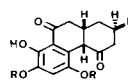
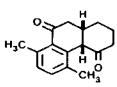
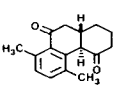
1 2

3 4

[1]) Present address: *Ciba-Geigy AG*, CH-4002 Basel.

cyclohexanone derivative **1** with *trans*-substitution at C(3) and C(4) leads to the *cis*-octahydrophenanthrene **2** [3] *(Scheme 1)*. Instigated by this result based on an X-ray diffraction analysis, the closely related 5,8-dimethoxy derivative **3** was analyzed by ^{1}H-NMR

Table. *Structures and ^{1}H-NMR Data* (300 MHz) *of 1,2,3,4,4a,9,10,10a-Octahydrophenanthrenes*[2])

Compound	No.	Ref.	J(4a,10a) [Hz]/ δ(H–C(10a)) [ppm]	Compound	No.	Ref.	J(4a,10a) [Hz]/ δ(H–C(10a)) [ppm]
	**5**	[2] [6]	5.0/2.96		**6**		11.5/2.35
	**7**[a]) R, R = Phthaloyl	[7]	5.5/3.92		**8**[b]) R, R = Phthaloyl	[7]	12.0/3.28
	**9**	[2] [7]	4.5/2.68		**17**	[12]	7.0/3.21[c])
	**10**[d])	[7]	5.0/3.02		**18**	[2] [9] [10]	–/–[e])
	**11**	[8]	5.0/2.92		**19**[f])	[2]	11.0/*ca.* 1.5
	**12**	[8]	4.5/2.66		**20**[g])	[11]	11.0/–
	**13**	[2]	5.0/2.90		**21**[h])	[2]	11.5/2.08
	**14**	[2]	5.0/*ca.* 2.45		**22**	[2] [6] [13]	12.0/–[i])
	**15**	[2]	4.5/2.53		**1**	[3]	11.5/–[k])
	**3** R = CH_3	[4]	5.5/2.92		**2** R = CH_3, R^1 = $CH_2CO_2CH_3$	[3]	5.5/2.94
	**4**	[4]	5.3/2.99		**16**	[4]	11.5/*ca.* 2.2

[a]) J(10, 10a) = 13.5 Hz. [b]) J(10,10a) = 12.5 Hz. [c]) J(3a,9a)/δ(H–C(9a)). [d]) J(10,10a) = 13.5 Hz. [e]) J(4,4a) could not be determined due to the overlapping signals of H–C(4a) and H_{eq}–C(4); its *trans*-configuration has, however, been proven unambiguously before [2][9][10]. [f]) The assignment of the H_{eq}–C(4) and H–C(4a) signals has been achieved by ^{1}H, ^{13}C decoupling experiments. [g]) J(4,4a) = < 5 Hz. [h]) J(4,4a) = 10 Hz. [i]) J(1',2'). [k]) J(3,4).

[2]) For a detailed spectral description, *cf. Exper. Part.*

[3a]. In contrast to previous reports, in which the *trans*-configuration was assigned, wholesale but through an erroneous generalization, to all 1,2,3,4,4a,9,10,10a-octahydrophenanthrenes, except the 5,8-dimethyl-4,9-dione **4** [4] *(Scheme 1)*, the 5,8-dimethoxy compound **3** was found to have the *cis*-configuration as well [3a]. An inspection of the premises, which apparently led to erroneous assignments in the *Elad-Ginsburg* morphine synthesis [5], was necessary. This synthesis [5] was successful, and it eventually led to products of correct configuration. Nevertheless, it should presumably have been based upon correct configurational assignments and transformations of such octahydrophenanthrene systems. To answer the questions raised, we decided to determine the relative configuration of these intermediates and model compounds ([2–13]) by NMR analysis. The structures **1–22** with their appropriate relative configurations, based upon the magnitude of the coupling constant between H–C(4a) and H–C(10a), J(4a,10a) = 4.5–5.5 Hz for *cis*-, J(4a,10a) = 11–12 Hz for *trans*-anelated isomers, are listed in the *Table*[2]).

Surprisingly, not only compounds with C(5)-substitution as well as a C(4)-oxo function (see **2**, **3**, **4**, **13**, **14**) and respective acetal derivatives (**15**) had the *cis*-configuration; this list also includes derivatives without C(5)-substituent (see **5**, **7**, **9**, **10**, **11**, **12**), which turned out to be *cis* or epimer mixtures with the *cis*-isomer as the major component. With a J(3a,9a) value of 7 Hz, the 1,2,3,3a,8,9,9a-hexahydroindene-3,8-dione (**17**) [12] is the *cis*-isomer as well. The *trans*-configuration of the 2′-aryl-cyclohexylacetic-acid precursors was found to be retained in octahydrophenanthrenes without oxo function at C(4) (see **18**, **19**, **20**, **21**) *(Table)*. Since the 2′-cyclohexylacetic acids were obtained from intermediates containing the corresponding carbonyl group, it is reassuring to know that *Barton*'s conformational tenets, regarding stability of the *trans*-1,2-diequatorial isomer, hold here as well.

To obtain an estimate of the energy difference between the tricyclic *cis*- and the *trans*-system, equilibration of the parent 1,2,3,4,4a,9,10,10a-octahydrophenanthrene-4,9-dione (obtained as a 82.5:17.5 mixture of *cis*- and *trans*-isomers **5** and **6** by hydrolysis of acetal **9**) was studied. The pure isomers could be obtained and characterized by HPLC separation of the mixture. According to the physical data, either the *cis*-isomer **5** or an equilibrated mixture of **5** and **6** correspond to the material described previously [2] [6][3]). Heating solutions of either pure **5** or pure **6** in toluene/EtOH containing a catalytic amount of CH_3SO_3H led to the same mixture of 82% *cis*-isomer **5** and 18% *trans*-isomer **6**[4]). This ratio, therefore, reflects the thermodynamic equilibrium of **5** and **6**. The 10-phthalimidooctahydrophenanthrene-4,9-dione, obtained by two independent methods [7], turned out to be an 8:2 mixture of *cis*-isomer **7** and *trans*-epimer **8** as well. In this case, however, no separation was attempted.

It is interesting to note, that in the case of 1,2,3,4,4a,9,10,10a-octahydrophenanthrenes with a C(1)- or a C(10)-oxo function the *trans*-isomers **23** and **24** are energetically favored as compared to the *cis*-isomers **25** and **26** (**23**/**25** = 4:1 [14]; **24**/**26** = 61:39 [15],

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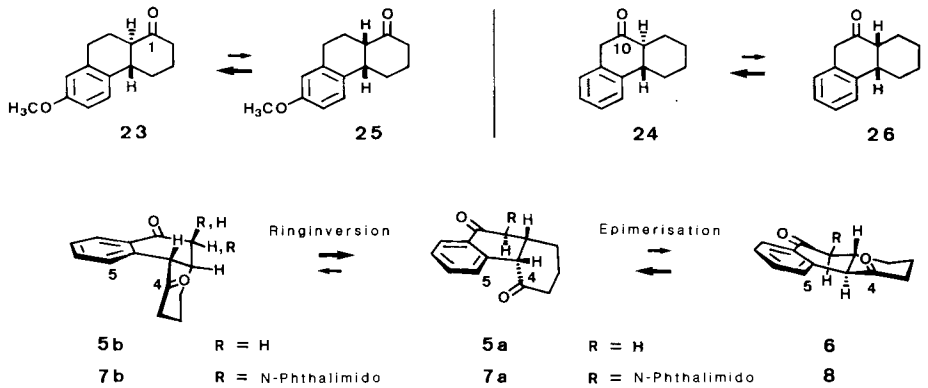
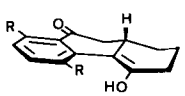
[3]) Recrystallization from CH_2Cl_2/Et_2O/hexane gives a melting point of 80–82° for the *cis*-isomer **5** and 109–112° for the *trans*-isomer **6**. In the case of **5**, redetermination of the melting point, after the material had resolidified, gave a higher reading (94–97°) which is close to the reported value (94–95°, either from BuOH [2] or from dilute AcOH [6]). It was not verified, whether this higher melting point is due to a different crystal modification or to *cis*/*trans*-isomerization.

[4]) The ratio was determined from the ^{1}H-NMR spectra by integration of the H–C(4a) signals.

Scheme 2



Scheme 2). Probably, the preference of the *cis*-epimers **5** and **7** over the *trans*-isomers **6** and **8** is due to the oxo group at C(4), whose steric interaction wit C(5) is less severe for the conformers **5a**/**7a** than for the conformers **5b**/**7b** or the *trans*-isomers **6**/**8** *(Scheme 2)*. This strain increases for C(5)-substituted derivatives, and in these cases (see **2**, **3**, **4**, **13**, **14**, *Table*), the *trans*-isomers cannot be detected in equilibrated mixtures. In general, the acidic conditions applied for the cyclization of *trans*-substituted 2′-aryl-3′-oxocyclohexylacetic acids (*e.g.* **1**, **22**, *Table*) suffice for complete equilibration[5]). A notable exception is, however, 2′-(2″,5″-dimethylphenyl)-3′-oxocyclohexylacetic acid, which affords a mixture of *trans*- and *cis*-octahydrophenanthrenes **16** and **4**, respectively, with the thermodynamically less stable *trans*-isomer **16** predominating upon cyclization with liquid HF [4]. The kinetic stability of **16** must, therefore, be due to the steric strain of the enol intermediate **27**, which is higher in energy than the unsubstituted or MeO-substituted derivatives **28** and **29**.



27 R = CH_3
28 R = H
29 R = OCH_3

As shown before by X-ray and ^{1}H-NMR analysis [3a], *cis*-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-4,9-diones prefer the chair/chair conformation represented by the formulae **5a**/**7a** *(Scheme 2)*. This is fully confirmed by the NMR spectra of the C(10)-substituted compounds **7** and **10** of this study. The J(10,10a) value of 13.5 Hz corresponds to an *anti-periplanar* (trans-diaxial) relation, which is only possible for the conformer **7a** with an equatorial *exo*-substituent R *(Scheme 2)*. The δ(H–C(10a)) value listed in the *Table* is another characteristic feature of these ^{1}H-NMR data, which is of analytical importance for those octahydrophenanthrenes, whose configuration cannot be determined by J(4a,10a). By comparing the epimeric pairs **5**/**6**, **7**/**8**, **4**/**16**, it can be seen that δ(H–C(10a)) is shifted by *ca.* 0.6 ppm to lower field for the *cis*-isomers **5**, **7**, and **4**. Further, δ(H–C(10a)) is influenced by substituents at C(10) (compare **5** and **7**, **9** and **10**, **6** and **8**) and by the C(9)-oxo group (compare **5** and **9**, **11** and **12**, **13** and **15**).

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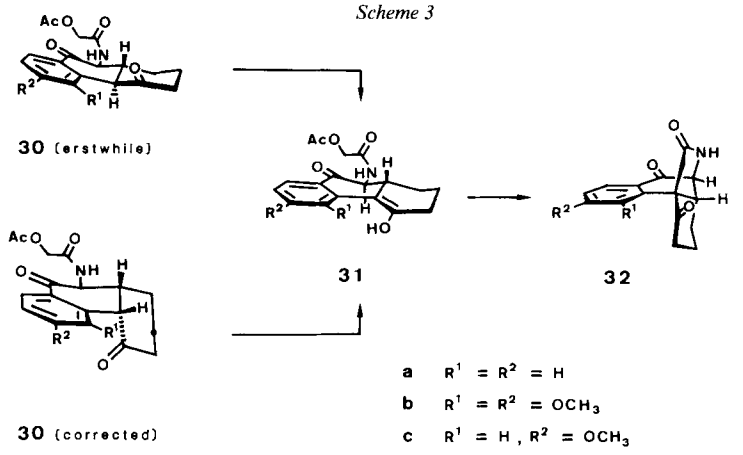
[5]) It is here that *Ginsburg* and *Pappo* [2] made a wrong assumption continued for the MeO-substituted analogs [5].

Scheme 3



The key-sequence of the *Elad-Ginsburg* synthesis of morphine [5] is depicted in *Scheme 3* according to [5], but we now must correct the structure of **30** as a result of the data presented herein. Cyclization of **30a** in model studies for the morphine synthesis were interpreted to proceed *via* the enol **31a** (*cf.* [2] [8]); it was no surprise, that **32a** was correlated with *N*-methylmorphinan (of *cis*-configuration) rather than with *N*-methylisomorphinan, the *trans*-isomer thereof. In fact, the then believed *trans*-configuration in the intermediate octahydrophenanthrenes [2] [7] never caused any worry, since eventually the tetracyclic systems constructed (*e.g.* **32a, b** [5]) were expected to have the *cis*-configuration (after epimerization *via* **31a, b**), which *Nature* has produced in morphine and codeine. *Stork* has proposed an ingenious mechanism for the unprecedented cyclization **30** to **32** *cum* epimerization through **31** [16]. The crucial point for the correct stereochemical outcome of this synthesis is, however, the relative configuration at C(10) and C(10a) of **30**. The rationalization given by *Stork* [16] for a *trans*-configurated intermediate – *'the amino group at C(10) must be equatorial, since its adjacency to a ketone allows it to epimerize to the more stable configuration after its formation'* – is valid for the *cis*-configurated octahydrophenanthrenes as well, only because this system prefers the ψ-chair-chair conformation **5a** depicted in *Scheme 2* and not the ring-inverted ψ-chair-chair conformation **5b** (*cf.* [3a]).

Finally, we must issue a warning. Unfortunately, we cannot include *all* of the intermediates in the *Elad-Ginsburg* morphine synthesis [5] and similar work cited herein. We measured the ^{1}H-NMR spectra of a random sampling of intermediates, but we cannot *guarantee* that *not one* of the tricyclic compounds involved there does not retain *trans*-configuration. If any of these intermediates is prepared again, there are now available two formidable tools, X-ray structure analysis and ^{1}H-NMR spectroscopy, to check correct configuration.

Postscript: No responsability for whatever errors exist in [2] [5] [7] is to be attributed to the late *D. Elad* or to *R. Pappo*. It is solely that of one of us *(D.G.)*.

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Experimental Part

1. Separation and Isomerization of *cis*- and *trans*-1,2,3,4,4a,9,10,10a-Octahydrophenanthrene-4,9-dione (5 and 6, respectively). – a) *Separation.* A mixture **5**/**6** (100 mg, **5**/**6** = 82.5:17.5) was separated by HPCL (silica gel, hexane/CH_2Cl_2/Et_2O 5:5:1, 25 bar, 20 ml/min flow rate, UV detection at 250 nm) giving 10 mg of (4a*R**,10a*S**)-epimer **6** (*trans*, $Vol._{ret.}$ = 356 ml, m.p. 109–112° from CH_2Cl_2/Et_2O/hexane) and 69 mg of (4a*S**,10a*S**)-epimer **5** (*cis*, $Vol._{ret.}$ = 428 ml, m.p. 80–82° from CH_2Cl_2/Et_2O/hexane, remelting at 94–97° after resolidification).

b) *Isomerization of* **6** *(trans).* A soln. of **6** (*ca.* 3.5 mg) in 0.4 ml of toluene and 25 µl of 2% CH_3SO_3H in EtOH was stirred under reflux for 1¾ h at 100°. Workup with Et_2O and chromatography (silica gel, hexane/CH_2Cl_2/Et_2O 9:9:2) gave 2.7 mg of **5**/**6** (82.2:17.8 according to ^{1}H-NMR, integration of H–C(4a)).

c) *Isomerization of* **5** *(cis).* A soln. of **5** (*ca.* 8 mg) in 1.5 ml of toluene and 75 µl of 2% CH_3SO_3H in EtOH was stirred under reflux at 100° for 1¾ h. Workup and purification as above gave 6 mg of **5**/**6** (82:18 according to ^{1}H-NMR, integration of H–C(4a)).

2. NMR Spectra of 1–22 (*cf.* the *Table*). The following spectra have been measured on a *Bruker WM-300* spectrometer at 300 MHz (^{1}H) and 75.4 MHz (^{13}C).

*Dimethyl (1*R**,3*S**,4*R**)-4-(5'-Acetoxy-2',4'-dimethoxyphenyl)-5-oxocyclohexane-1,3-diacetate* (**1**) [3]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.82 (*ddd, J* = 14, 12, 4.5), 1.98 (*d, J* = 14, *further split,* $w_{½} \approx 8$) (2 H–C(2)); 2.14 (*dd, J* = 16, 8.5), 2.30 (*dd, J* = 16, 4), 2.46 (*ddd, J* = 15, 3.5, 2), 2.47 (*d, J* = 8, *further split,* $w_{½} \approx 2$), and 2.61 (*dd, J* = 15, 5.5, *further split,* $w_{½} \approx 2$) (2 H–C(6), 2 $CH_2CO_2CH_3$); 2.27 (*s,* CH_3CO_2–C(5')); 2.67–2.87 (*m,* H–C(1), H–C(3)); 3.43 (*d, J* = 11.5, *further split,* $w_{½} \approx 2$, H–C(4)); 3.57, 3.70, 3.79, 3.83 (4*s,* 4 CH_3O); 6.53 (*m,* $w_{½} \approx 1.5$, H–C(3')); 6.70 (*s,* H–C(6')).

*Methyl [(2*R**,4a*S**,10a*S**)-1,2,3,4,4a,9,10,10a-Octahydro-8-hydroxy-5,7-dimethoxy-4,9-dioxophenanthrene-2-yl]acetate* (**2**) [3]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.92–1.99 (*m, 4 main signals,* 2 H–C(1)); 2.35–2.63 (*m,* 7 H); 2.94 (*dtt, J* ≈ 12, 6, 3.5, H–C(10a)); 3.71, 3.76, 3.92 (3*s,* 3 CH_3O); 4.15 (*d, J* = 5.5, H–C(4a)); 6.81 (*m,* $w_{½} \approx 2$, H–C(6)); 12.02 (*d, J* ≈ 0.5, OH).

*(4a*S**,10a*R**)-1,2,3,4,4a,9,10,10a-Octahydro-5,8-dimethoxyphenanthrene-4,9-dione* (**3**) [3a] [4]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.76–2.21 (*m,* 4 H); 2.37–2.65 (*m,* 2 H); 2.40 (*ddd, J* = 16, 4.5, 1.5, H_{exo}–C(10)); 2.59 (*tdd, J* = 13, 6, 1, H_{ax}–C(3)); 2.92 (*d, J* ≈ 13.5, *further split,* $w_{½} \approx 12$, H–C(10a)); 3.75, 3.86 (2*s,* 2 CH_3O); 4.27 (*d, J* ≈ 5.5, *further split,* $w_{½} \approx 3$, H–C(4a)); 6.89, 7.04 (2*d, J* = 9, H–C(6), H–C(7)).

*(4a*S**,4a*R**)-1,2,3,4,4a,9,10,10a-Octahydro-5,8-dimethylphenanthrene-4,9-dione* (**4**) [3a] [4]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.86 (*d, J* ≈ 14, *further split,* $w_{½} \approx 7$, 1 H); 1.92–2.25 (*m,* 3 H); 2.14 (*s,* CH_3–C(5)); 2.43 (*ddd, J* = 16, 5.5, 1.5, H_{eq}–C(10)); 2.49–2.64 (*m,* 3 H); 2.95 (*s,* CH_3–C(8)); 2.99 (*d, J* = 14, *further split,* $w_{½} \approx 13$, H–C(10a)); 4.06 (*d, J* = 5.3, *further split,* $w_{½} \approx 3$, H–C(4a)); 7.08, 7.24 (2*d, J* ≈ 8, H–C(6), H–C(7)).

*(4a*S**,10a*S**)-1,2,3,4,4a,9,10,10a-Octahydrophenanthrene-4,9-dione* (**5**) [2] [6]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.70–1.88 (1 H), 1.92–2.10 (3 H) (2*m,* 2 H–C(1), 2 H–C(2)); 2.38–2.55 (*m,* 2 H–C(3)); 2.55–2.65 (*m,* 2 H–C(10)); 2.90–3.04 (2.96) (*m,* H–C(10a)); 3.98 (*d, J* = 5, *further split, m,* $w_{½} \approx 2$, H–C(4a)); 7.10 (*d, J* ≈ 7.5, *further split, m,* $w_{½} \approx 3$, H–C(5)); 7.40 (*t, J* ≈ 7.5, *further split, m,* $w_{½} \approx 3$), 7.54 (*td, J* ≈ 7.5, 1.5) (H–C(6), H–C(7)); 8.08 (*dd, J* ≈ 7.5, 1.5, H–C(8)).

*(4a*R**,10a*S**)-1,2,3,4,4a,9,10,10a-Octahydrophenanthrene-4,9-dione* (**6**). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.75–2.05 (3 H), 2.15–*ca.* 2.3 (1 H) (2*m,* 2 H–C(1), 2 H–C(2)); *ca.* 2.25–2.45 (*m,* H–C(10a)); 2.60 (*dd, J* = 16, 13), 2.79 (*dd, J* = 16, 3.5) (2 H–C(10)); 2.53–2.71 (*m,* 2 H–C(3)); 3.89 (*d, J* = 11.5, *further split, m,* $w_{½} \approx 3$, H–C(4a)); 7.38 (*t, J* ≈ 7.5, *further split, m,* $w_{½} \approx 4$, H–C(7)); 7.5–7.65 (*m,* H–C(5), H–C(6)); 8.05 (*d, J* ≈ 7.5, *further split, m,* $w_{½} \approx 3$, H–C(8)).

N-*[(4a*S**,10*S**,10a*R**)- and* N-*[(4a*R**,10*S**,10a*R**)-1,2,3,4,4a,9,10,10a-Octahydro-4,9-dioxophenanthrene-10-yl]phthalimide* (**7** and **8**, respectively) [7]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.75–2.3 (*m,* 2 H–C(1'), 2 H–C(2')); 2.5–2.75 (*m,* 2 H–C(3')); 3.2–3.36 (3.28) (*m,* H–C(10a'), *(4a'*R**)-epimer*); 3.86–3.99 (3.92) (*m,* H–C(10a'), *(4a'*S**)-epimer*); *ca.* 4.12 (*d, J* ≈ 12, H–C(4a'), *(4a'*R**)-epimer*); 4.15 (*d, J* = 5.5, H–C(4a'), *(4a'*S**)-epimer*); 4.94 (*d, J* = 13.5, H–C(10'), *(4a'*S**)-epimer*); 5.05 (*d, J* = 12.5, H–C(10'), *(4a'*R**)-epimer*); 7.1–7.25, 7.35–7.5, 7.5–7.7 (3*m,* H–C(5'), H–C(6'), H–C(7')); 7.7–7.8 (2 H), 7.8–7.95 (2 H) (2*m,* H–C(3), H–C(4), H–C(5), H–C(6)); 8.05–8.15 (*m,* H–C(8')).

*(4a*S**,10a*S**)-1,2,3,4,4a,9,10,10a-Octahydrophenanthrene-4-spiro-2'-(1',3'-dioxolane)-9-one* (**9**) [2] [7]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.56–1.95 (*m,* 2 H–C(1), 2 H–C(2), 2 H–C(3)); 2.35 (*ddd, J* = 18, 5.5, 1), 3.19 (*dd, J* = 18, 14) (2 H–C(10)); 2.61–2.75 (2.68) (*m,* H–C(10a)); 2.90–3.02 (1 H), 3.16–3.27 (1 H), 3.57–3.72 (2 H) (3*m,* 2 H–C(4'), 2 H–C(5')); 3.15 (*d, J* ≈ 4.5, H–C(4a)); 7.27–7.38 (1 H), 7.40–7.48 (2 H) (2*m,* H–C(5), H–C(6), H–C(7)); 8.04 (*d, J* ≈ 7.5, *further split, m,* $w_{½} \approx 3$, H–C(8)).

Ethyl [(4aS,10S*,10aR*)-1,2,3,4,4a,9,10,10a-Octahydro-9-oxophenanthrene-4-spiro-2'-(1',3'-dioxolane)-10-yl]carboxylate* (**10**) [7]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.31 (*t*, *J* = 7, CH_3CH_2O); 1.57–1.78 (4 H), 1.78–1.98 (2 H) (2*m*, 2 H–C(1'), 2 H–C(2'), 2 H–C(3')); 2.92–3.02 (1 H), 3.14–3.23 (1 H), 3.58–3.74 (2 H) (3*m*, 2 H–C(4''), 2 H–C(5'')); 2.95–3.08 (3.02) (*m*, H–C(10a')); 3.22 (*d*, *J* = 5, H–C(4a')); 4.22, 4.28 (2*dq*, *J* = 11, 7, CH_3CH_2O); 4.30 (*d*, *J* = 13.5, H–C(10')); 7.32–7.40 (*m*, *3 main signals*, H–C(7')); 7.40–7.53 (*m*, H–C(5'), H–C(6')); 8.04 (*d*, *J* = 8, *further split*, *m*, $w_{1/2} \approx 3$, H–C(8')).

(4aS,10aS*)-1,2,3,4,4a,9,10,10a-Octahydro-6-methoxyphenanthrene-4,9-dione* (**11**) [8]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.7–1.85 (1 H), 1.88–2.1 (3 H) (2 H–C(1), 2 H–C(2)); 2.4–2.5 (*m*, 2 H–C(3)); 2.5–2.63 (*m*, 2 H–C(10)); 2.85–2.98 (*m*, H–C(10a)); 3.83 (*s*, CH_3O); 3.94 (*d*, *J* = 5, H–C(4a)); 6.54 (*d*, *J* ≈ 2.5, *further split by a small coupling*, H–C(5)); 6.90 (*dd*, *J* = 8.5, 2.5, *further split by a small coupling*, H–C(7)); 8.05 (*d*, *J* = 8.5, H–C(8)).

(4aS,10aS*)-1,2,3,4,4a,9,10,10a-Octahydro-6-methoxyphenanthrene-4-spiro-2'-(1',3'-dioxolane)-9-one* (**12**) [8]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.55–1.94 (*m*, 2 H–C(1), 2 H–C(2), 2 H–C(3)); 2.30 (*ddd*, *J* = 18, 5.5, *ca.* 1), 3.15 (*dd*, *J* = 18, 14) (2 H–C(10)); 2.59–2.72 (*m*, H–C(10a)); 2.98–3.07 (1 H), 3.3–3.4 (1 H), 3.6–3.76 (2 H) (2 H–C(4'), 2 H–C(5')); 3.1 (*d*, *J* = 4.5, H–C(4a)); 3.85 (*s*, CH_3O); 6.86 (*dd*, *J* = 8.5, 2.5, H–C(7)); 6.94 (*d*, *J* = 2.5, H–C(5)); 8.01 (*d*, *J* = 8.5, H–C(8)).

(4aS,10aS*)-1,2,3,4,4a,9,10,10a-Octahydro-5,6-dimethoxyphenanthrene-4,9-dione* (**13**) [2]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.75–1.87 (*m*, H_{eq}–C(1)); 1.9–2.2 (*m*, 2 H–C(2), H_{ax}–C(1)); 2.37–2.65 (*m*, 2 H–C(3), 2 H–C(10)); 2.84–2.97 (*m*, H–C(10a)); 3.76, 3.93 (2*s*, 2 CH_3O); 4.26 (*d*, *J* = 5, H–C(4a)); 6.96 (*d*, *J* = 8.5, H–C(7)); 7.88 (*d*, *J* = 8.5, H–C(8)).

(4aS,10aS*)-1,2,3,4,4a,9,10,10a-Octahydro-5,6-dimethoxyphenanthrene-4-one* (**14**) [2]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.56–1.68 (2 H), 1.74–1.87 (1 H), 1.87–2.14 (3 H) (3*m*, 2 H–C(1), 2 H–C(2), 2 H–C(10)); 2.35–2.58 (*m*, 2 H–C(9), H–C(10a)); 3.73, 3.83 (2*s*, 2 CH_3O); 4.00 (*d*, *J* = 5, *further split*, $w_{1/2} \approx 2$, H–C(4a)); 6.80 (*s*, H–C(7), H–C(8)).

(4aS,10aS*)-1,2,3,4,4a,9,10,10a-Octahydro-5,6-dimethoxyphenanthrene-4-spiro-2'-(1',3'-dioxolane)-9-one* (**15**) [2]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.55–2.0 (*m*, 2 H–C(1), 2 H–C(2), 2 H–C(3)); 2.28 (*ddd*, *J* = 18, 7, *ca.* 1), 3.04 (*dd*, *J* = 18, 13) (2 H–C(10)); 2.47–2.60 (*m*, H–C(10a)); 2.97–3.05 (1 H), 3.18–3.27 (1 H), 3.6–3.72 (2 H) (2 H–C(4'), 2 H–C(5')); 3.66 (*d*, *J* = 4.5, H–C(4a)); 3.90, 3.92 (2*s*, 2 CH_3O); 6.92 (*d*, *J* = 8.5, H–C(7)); 7.78 (*d*, *J* = 8.5, H–C(8)).

(4aR,10aS*)-1,2,3,4,4a,9,10,10a-Octahydro-5,8-dimethylphenanthrene-4,9-dione* (**16**) [4]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.79–2.07 (*m*, 3 H); 2.04 (*s*, CH_3–C(5)); 2.14–2.33 (*m*, 2 H); 2.49–2.79 (*m*, 4 H); 2.57 (*s*, CH_3–C(8)); 3.99 (*d*, *J* = 11.5, *further split*, $w_{1/2} \approx 2.5$, H–C(4a)); 7.09, 7.26 (2*d*, *J* ≈ 8, H–C(6), H–C(7)).

(3aS,9aS*)-1,3,3a,8,9,9a-Hexahydrobenz[e]inden-3,8-dione* (**17**) [12]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.85–1.98, 2.17–2.32 (2*m*, 2 H–C(1)); 2.33–2.58 (*m*, 2 H–C(2)); 2.55 (*dd*, *J* = 16, 10.5), 2.81 (*dd*, *J* = 16, 5.5, *further split*, *m*, $w_{1/2} \approx 2$) (2 H–C(9)); 3.14–3.28 (3.21) (*m*, H–C(9a)); 3.58 (*d*, *J* ≈ 7, *further split*, *m*, $w_{1/2} \approx 3$, H–C(3a)); 7.32–7.45, 7.54–7.64 (2*m*, *3 main peaks each*, H–C(5), H–C(6)); 7.47–7.54 (*m*, *2 main peaks*, H–C(4)); 7.99 (*dd*, *J* ≈ 8, 1, H–C(7)).

(4aR,10aS*)-1,2,3,4,4a,9,10,10a-Octahydrophenanthrene-9-one* (**18**) [2] [9] [10]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.20–1.61 (4 H), 1.72–1.93 (3 H), 1.93–2.04 (1 H) (3*m*, 2 H–C(1), 2 H–C(2), 2 H–C(3), H_{ax}–C(4), H–C(10a)); 2.37 (*dd*, *J* = 17, 13), 2.68 (*dd*, *J* = 17, 3.5) (2 H–C(10)); 2.49–2.62 (*m*, H_{eq}–C(4), H–C(4a)); 7.32 (*t*, *J* = 7.5, *further split*, $w_{1/2} \approx 3$, H–C(7)); 7.43 (*d*, *J* ≈ 8, *further split*, $w_{1/2} \approx 3$, H–C(5)); 7.52 (*t*, *J* = 7.5, *further split*, $w_{1/2} \approx 3$, H–C(6)); 8.06 (*dd*, *J* = 8, 1.5, H–C(8)).

(4aR,10aS*)-1,2,3,4,4a,9,10,10a-Octahydro-5,6-dimethoxyphenanthrene-9-one* (**19**) [2]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.05–1.23 (*m*, H_{ax}–C(4)); 1.3–1.65 (3 H), 1.75–2.0 (4 H) (2 H–C(1), 2 H–C(2), 2 H–C(3), H–C(10a)); 2.33 (*dd*, *J* = 15, 13.5), 2.45 (*dd*, *J* = 15, 3) (2 H–C(10)); 2.71 (*td*, *J* = 11, 3, H–C(4a)); 3.19 (*dq*, *J* = 13, *ca.* 3, H_{eq}–C(4)); 3.79, 3.91 (2*s*, 2 CH_3O); 6.89 (*d*, *J* = 8.5, H–C(7)); 7.86 (*d*, *J* = 8.5, H–C(8)). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.2, 27.3 (C(2), C(3)); 30.3 (C(4): *t*, off-res. ^{1}H-dec., *d*, *upon selective ^{1}H-decoupling at 957 Hz/3.19 ppm*); 33.8 (C(1)); 40.8 (C(10a)); 43.7 (C(4a): *d*, off-res. ^{1}H-dec., *s*, *upon selective ^{1}H-decoupling at 813 Hz/2.71 ppm*); 45.4 (C(10)); 55.7, 59.9 (2 CH_3O); 110.1 (C(7)); 124.1 (C(8)); 127.3 (C(5a)); 139.4 (C(8a)); 147.6 (C(5)); 157.4 (C(6)); 196.8 (C(9)).

(4R,4aS*,10aS*)-1,2,3,4,4a,9,10,10a-Octahydrophenanthrene-4-yl Acetate* (**20**) [11]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.1–1.3 (1 H), 1.4–1.75 (4 H), 1.77–1.96 (3 H), 2.05–2.2 (1 H, *not H–C(10a), presumably H–C(3)*) (4*m*, 2 H–C(1), 2 H–C(2), 2 H–C(3), 2 H–C(10), H–C(10a)); 1.86 (*s*, CH_3COO–C(4)); 2.55 (*d*, *J* ≈ 11, *further split*, *m*, $w_{1/2} \approx 5$, H–C(4a)); 2.75–3.0 (*m*, 2 H–C(9)); 5.82 (*m*, $w_{1/2} \approx 7$, H–C(4)); 7.02–7.15 (3 H), 7.15–7.25 (1 H) (2*m*, H–C(5), H–C(6), H–C(7), H–C(8)).

(4S,4aS*,10aS*)-1,2,3,4,4a,9,10,10a-Octahydro-5,6-dimethoxy-9-oxophenanthrene-4-yl Acetate* (**21**) [2]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.16–1.54 (3 H), 1.73–1.95 (2 H), 2.32–2.43 (1 H) (3*m*, 2 H–C(1'), 2 H–C(2'),

H–C(3')); 2.02 (*s*, CH_3COO–C(4')); 2.08 (*qt*, $J \approx 12$, 4.5, H–C(10a')); 2.32 (*dd*, $J = 18$, 12), 2.76 (*dd*, $J = 18$, 4.5) (2 H–C(10')); 2.81 (*dd*, $J \approx 11.5$, 10, H–C(4a')); 3.71, 3.91 (2*s*, 2 CH_3O); 5.28 (*td*, $J \approx 10$, 4.5, H–C(4')); 6.88 (*d*, $J = 8.5$, H–C(7')); 7.81 (*d*, $J = 8.5$, H–C(8')).

[(1S,2R*)-3-Oxo-2-phenylcyclohexyl]acetic Acid* (**22**) [2] [6] [13]. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.58–1.75 (1 H), 1.75–1.94 (1 H), 2.08–2.24 (2 H) (3*m*, 2 H–C(5'), 2 H–C(6')); 2.10 (*dd*, $J = 16$, 9), 2.23 (*dd*, $J = 16$, 4) (2 H–C(2)); 2.37–2.63 (*m*, 2 H–C(4'), H–C(1')); 3.40 (*d*, $J = 12$, H–C(2')); 7.03–7.12 (2 H), 7.20–7.38 (3 H) (2*m*, Ph); 7.2–8.7 (br., COOH).

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