# 137. Experiments on the Total Synthesis of Lysolipin I

Part I

## On Configuration and Conformation of 5-Substituted 1,2,3,4,4a,9,10,10a-Octahydrophenanthrene-4,9-diones[1])

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*Summary*

The substituted 1,2,3,4,4a,9,10,10a-octahydrophenanthrene-4,9-dione **2**, synthesized from the cyclohexanone **8** and quinone **11** *(Scheme 2)*, was found by X-ray analysis and $^1$H-NMR studies to be the isomer with *cis*-junction of the saturated rings. The *cis*-fusion could also be determined from the $^1$H-NMR data of the related compound **17** *(Scheme 4)*, which was previously considered to be *trans*-fused. In contrary to previous argumentations, the interaction of the C(4)-carbonyl O-atom of *trans*-fused octahydrophenanthrenes is more severe with a 5-methoxy than with a 5-methyl substituent.

The main problem of a total-synthetic approach to Lysolipin I (**1**), an interesting antibiotic with an unusual heptacyclic structure [2][4]), is the construction of a highly substituted 9,10-dihydrophenanthrene-4,5-diol **a** *(Scheme 1)*. Confronted with this problem, we reasoned, that a octahydrophenanthrene-4,9-dione **b** would be an ideal precursor for **a**, since, contrarily to the preparation of phenanthrenes and 9,10-dihydrophenanthrenes, which is seriously hampered by substituents at C(4) and C(5), the preparation of the more flexible octahydro derivatives **b** by cyclization of (2'-arylcyclohexyl)acetic acids **c** is hardly affected by 4,5-substitution [4] *(Scheme 1)*. The transformation of **b** to **a**, involving the introduction of an aroyl substituent at C(6) and of a carboxy group at C(3), $OsO_4$ oxidation of a derivative with 9,10-double bond, and aromatization of ring *A*, appears to be straightforward. Besides the advantage of introducing chirality in an earlier stage of the synthesis, the additional asymmetric centers of **b** (C(2), C(4a), and C(10a)) could be very helpful for relating the asymmetric centers C(9) and C(10) with the remote asymmetric centers of the C(2)-substituent ($R^1$) of **a**.

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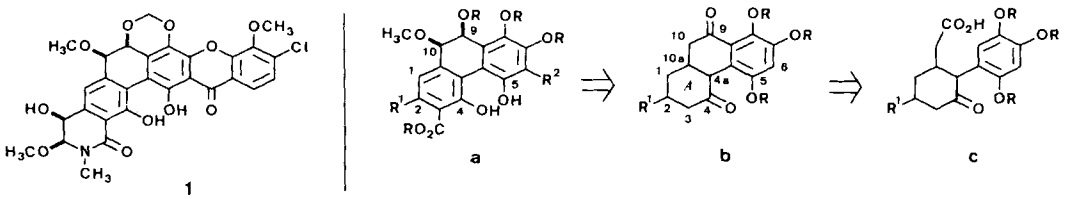
[1]) These results are partly included in the Ph.D. thesis of *V. Sch.* [1] and are part of the projected Ph.D. thesis of *Ch. H.* In addition, they have been presented in part at the 'Herbstversammlung der Schweizerischen Chemischen Gesellschaft', October 16, 1981, in Bern.

[2]) These authors have carried out the X-ray analysis.

[3]) Institut für Kristallographie und Petrographie der Eidgenössischen Technischen Hochschule, CH–8092 Zürich.

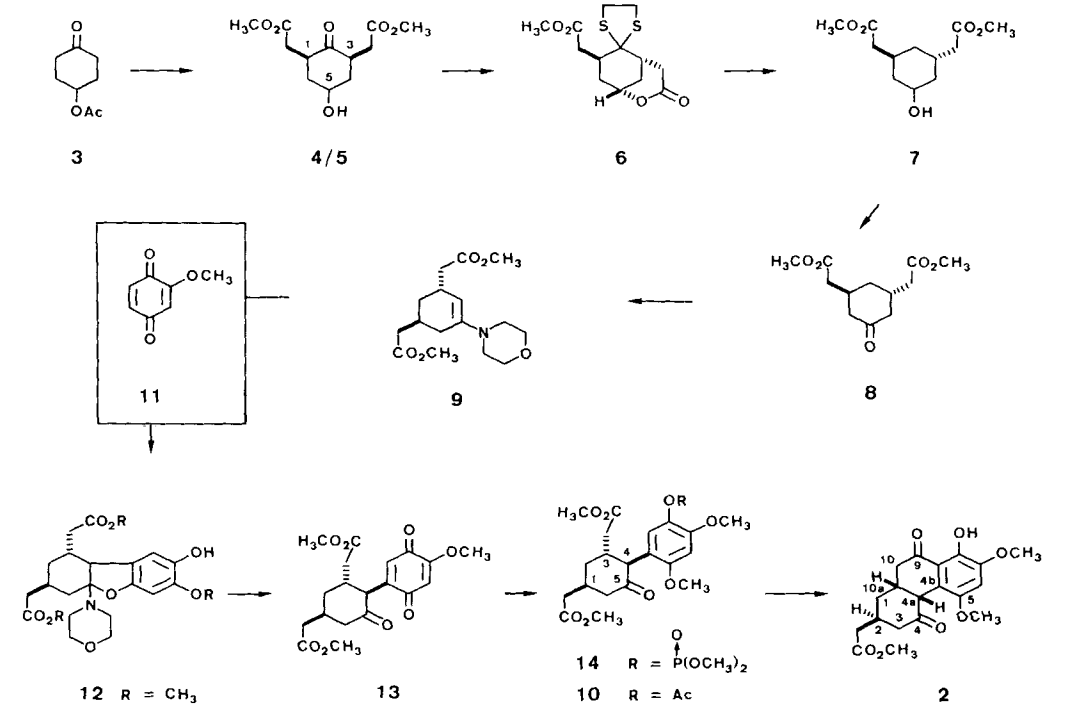
[4]) Similar structures were determined for the antibiotics Albofungin and Chloroalbofungin [3].

*Scheme 1*



The octahydrophenanthrenedione **2** could be prepared from 4-oxocyclohexyl acetate (**3**) in 12 steps (*ca.* 12% overall yield) as depicted in *Scheme 2*[5]). Alkylation of the pyrrolidine-enamine derived from **3** with bromoacetate/diisopropylethylamine according to [5] followed by alcoholysis of the acetate gave a mixture of the C(5)-epimers **4** and **5** (68% after distillation). The main product of thioacetalization, lactone **6**, was isolated in 70% yield by crystallization and flash chromatography of the mother liquor. Desulfurization with *Raney*-Ni and cleavage of the lactone by heating in MeOH/$MeSO_3H$ gave 70% of alcohol **7**, which was converted to cyclohexanone **8** (97%) by *Jones* oxidation. The enamine **9** could be converted in *ca.* 50% overall yield to the cyclohexanone **10** by applying a previously developed method [6]. *Michael* addition of

*Scheme 2*



[5]) A full account of these experiments will be given later (see also [1]).

enamine **9** (1.8-fold excess) to methoxy-*p*-benzoquinone (**11**)[6]) and oxidation of the adduct **12** with $FeCl_3$ gave quinone **13**, which yielded phosphate **14** (72% based on **11**, 76% based on converted **8**) on reduction with $P(OMe)_3$ [6] [7]. Cleavage of the phosphate (trimethylsilyl bromide followed by hydrolysis at pH 4 [6])[7]) and acetylation gave **10**, isolated in 70% yield by crystallization. The intramolecular acylation affording **2** in 78% yield could be effected without prior hydrolysis of the methyl ester, simply by treating **10** with neat $MeSO_3H$ [8] at 55° (2 h)[7]).

The analytical data of **2** and of the intermediates **4**–**14** are fully consistent with the structures shown in *Scheme 2*. The *cis*-junction of the saturated rings of **2**, in particular, is indicated by the $^1$H-NMR spectrum exhibiting a 5.5 Hz coupling constant between the bridgehead protons H–C(4a) and H–C(10a). Since the *trans*-fused system has been assumed to be the thermodynamically favored isomer of such octahydro-5-methoxyphenanthrene-4,9-diones [4] [10], the structure of **2** was proved by X-ray analysis (see *Fig.*)[8]). The *cis*-junction is affirmed by the dihedral angle of 52° between the H–C(4a) and H–C(10a) bonds; the favored conformation **2a** *(Scheme 3)* is given by the dihedral angle of 76° formed by the C(4)–C(4a) and C(4b)–C(5) bonds, and by the

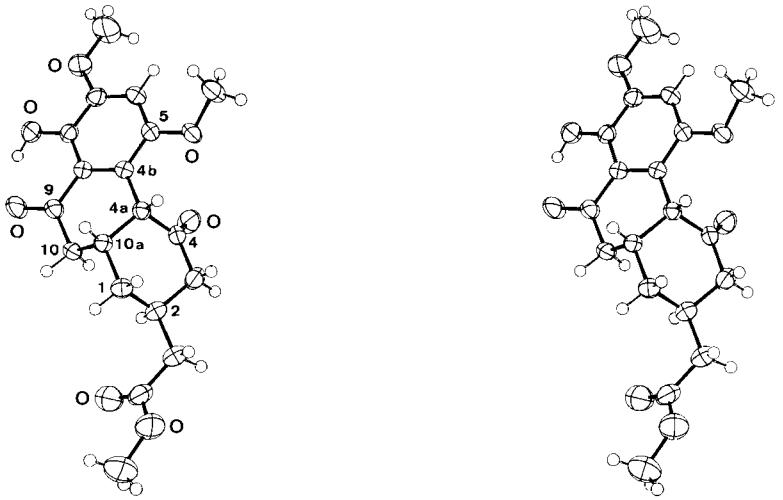



Figure. *Stereoscopic view of* **2** *drawn by ORTEP* [9]. Thermal vibrational ellipsoids at the 50% probability level.

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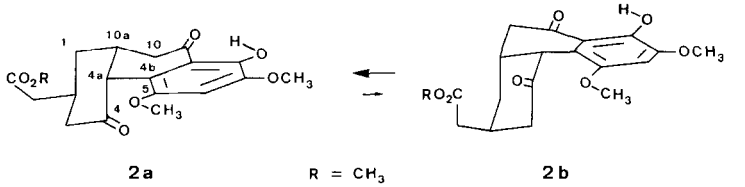
[6]) The *cis*-epimer of **9** does not add to quinone **11** [1].

[7]) Methyl carboxylate groups which were partially hydrolyzed by this procedure have been restituted by treatment with ethereal $CH_2N_2$.

[8]) Triclinic space group $P\bar{1}$: $a = 8.458$, $b = 9.978$, $c = 11.733 \pm 0.001$ Å; $\alpha = 90.25$, $\beta = 95.80$, $\gamma = 115.19 \pm 0.01°$; $Z = 2$, $d$(calc) = 1.36 g/cm$^3$. Intensity measurements at r.t. were made with a *Syntex-P2$_1$* diffractometer (graphite monochromator, Mo$K\alpha$ radiation, $\lambda = 0.7107$ Å). The structure was solved by direct methods from 3130 independent reflexions ($\theta \leq 25°$) with SHELX-84 (test version of a new program for crystal structure analysis) and refined by full-matrix-least-squares analysis, using 2412 reflexions ($I > 3\sigma(I)$; SHELX-76 [11], XRAY-72 [12]). H-Atoms were located at an intermediate stage and included in the refinement with isotropic vibrational parameters (other atoms anisotropic). The final $R$-value was 0.039 ($R_W = 0.041$). Atomic parameters have been deposited with the *Cambridge Crystallographic Data Centre*, Lensfield Road, Cambridge CB2 1EW, England.

antiperiplanar position of $H_\alpha$–C(10) and H–C(10a). The $^1$H-NMR data of **2** show that the conformer **2a** is favored in solution as well: in addition to the coupling with H–C(4a) ($J$ = 5.5 Hz), the signal of H–C(10a) is split by coupling with 2H–C(1) ($J \approx 4$ and 3.5 Hz) and 2H–C(10) ($J \approx 12$ and 6 Hz).

Scheme 3. *Conformational Equilibrium of Octahydrophenanthrene* **2**

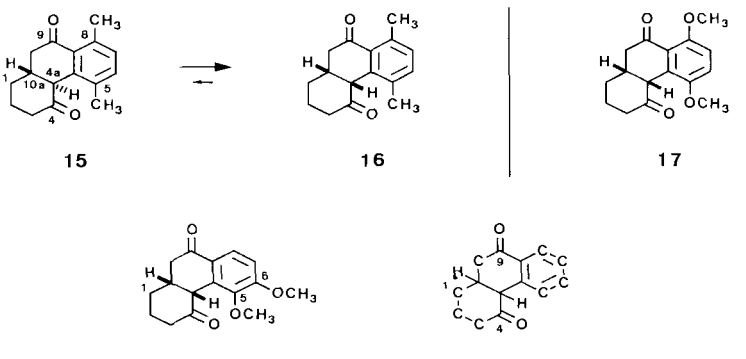



**2a** R = $CH_3$ **2b**

In order to determine, whether the epimerization observed upon cyclization of **10** is due to the methoxycarbonylmethyl substituent at C(2), which is equatorial in conformer **2a** but axial in **2b** and in the C(4a)-epimer of **2** with *trans*-fused rings, the known octahydrophenanthrene-4,9-diones **15**, **16**, and **17** *(Scheme 4)* were prepared [4c][9]) and analyzed by $^1$H-NMR (300 MHz). The couplings between the bridgehead H-atoms ($J$ = 11.5 Hz for **15** with *trans*-fused rings, but 5.3 Hz for **16** and 5.5 Hz for **17**) show, that the previous assignment was correct in the case of the epimers **15** and **16**. However, the 5,8-dimethoxy derivative **17** is the *cis*-fused compound and not the *trans*-isomer as has been stated before [4c] [10].

It is reasonable to assume that for **16** a conformation is preferred which is analogous to **2a** (see [10]). Judging by the similarity of the $^1$H-NMR spectra of **16** and **17**, a conformation such as **2a** can be deduced for **17** as well. A particular feature of the $^1$H-NMR spectra of the *cis*-isomers **2**, **16**, and **17** is the low-field shift of H–C(10a): 2.93 ppm for **2**, 2.99 ppm for **16**, and 2.92 ppm for **17**. The corresponding signal of the *trans*-epimer **15** is located within a multiplet at 2.15–2.35 ppm.

*Scheme 4*




**15** **16** **17**

**18** **d**

[9]) The published procedure was modified inasmuch as $MeSO_3H$ [8] was used for the final cyclizations instead of the hazardous HF(liq.). Under these conditions **15** and **16** were equilibrated *(Scheme 4)*.

It can be concluded, that the epimer with *cis*-fused rings is the thermodynamically favored form of 5-methoxy-substituted octahydrophenanthrene-4,9-diones. The 5,6-dimethoxy derivative **18**, a key-intermediate of the morphine synthesis by *Ginsburg & Elad* [4c] [13], who did not have the means for a configurational determination at that time, is most probably also the *cis*-isomer *(Scheme 4)*[10]).

In contrary to previous reasonings [4c] [10], the interaction of the non-bonding electrons of the O-atoms at C(4) and C(5) must be more severe than the interaction of $O$=C(4) with $CH_3$–C(5), since the *trans*-epimer of compound **17** could not be detected under conditions which allow the isolation of **15** [4c].

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[10]) A *Chemical Abstract Service* literature search (March 23, 1984), using the substructure **d** *(Scheme 4)*, afforded no additional reports on octahydro-5-methoxyphenanthrene-4,9-diones.