Towards a Total Synthesis of the Antibiotic Lysolipin I**

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Dedicated to Professor Oskar Jeger

The original objective of total syntheses was the ultimate proof of structures of natural products. Since this is now much more efficiently done by X-ray analysis, the scientific significance of such work should be shifted to the preparative aspect, which is based on good strategies and progress of synthetic methodology. This report summarizes our efforts directed to a total synthesis of the heptacyclic antibiotic lysolipin I. The crucial point of our synthetic strategy is the use of a cyclohexanone as precursor for the phenolic ring F. In addition to several other advantages, this saturated ring allows a stepwise build-up of steric strain and controls the diastereoselectivity by virtue of additional asymmetric centers relating the configurations of isolated centers of chirality. The scope and limitations of the access to 2-aryl-cyclohexanone derivatives by Michael-addition to p-quinones has been evaluated on a broad basis. A regioselective monoprotection of substituted hydroquinones could be achieved by reductive phosphorylation of p-quinones with phosphites. In relation to a different approach, a new method for the preparation of nitroaromatic compounds by cyclocondensation has been devised.

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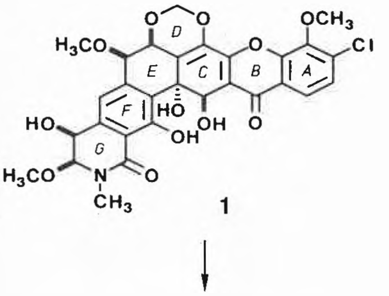
1. Introduction

In 1975 *Drautz, Keller-Schierlein,* and *Zähner* reported the isolation of two new antibiotics, lysolipin X (**1**) and lysolipin I (**2**), from cultures of a *Streptomyces violaceoniger* strain[1]. The metabolite **1** is readily transformed by heat or light to the biologically more active derivative **2.** Both compounds inhibit very efficiently the growth of Gram-positive and Gram-negative bacteria by complexation with the carrier lipids of mureine intermediates. This interference with the cell-wall biosynthesis causes the lysis of the microorganisms. The structure of lysolipin I (**2**), which has been determined by X-ray analysis (relative configuration)[2a][*], is closely related to the structures of albofungin (**3**) and chloralbofungin (**4**)[3], metabolites of a *Streptomyces albus* strain[4]. According to *Fukushima* et al.[5] the antibiotic P-42-1, isolated from an *Actinomyces tumemacerans* strain, as well as kanchanomycin (BA-180285A) from an unidentified Streptomyces culture[6] are closely related, most probably even identical with albofungin (**3**). In addition to high activity against Gram-positive bacteria and fungi, P-42-1[5] and kanchanomycin[6] were found to be cytotoxic to *Hela* cell-cultures and exhibited antitumor activity. Interestingly, lysolipin I (**2**) has also some potential for antitumor activity, as it inhibits the RNA-synthesis in vivo[1].



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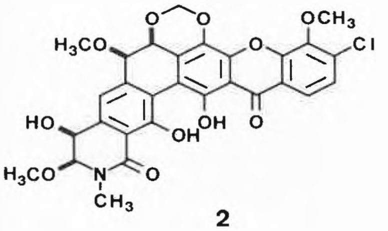

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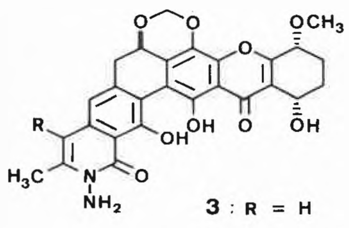
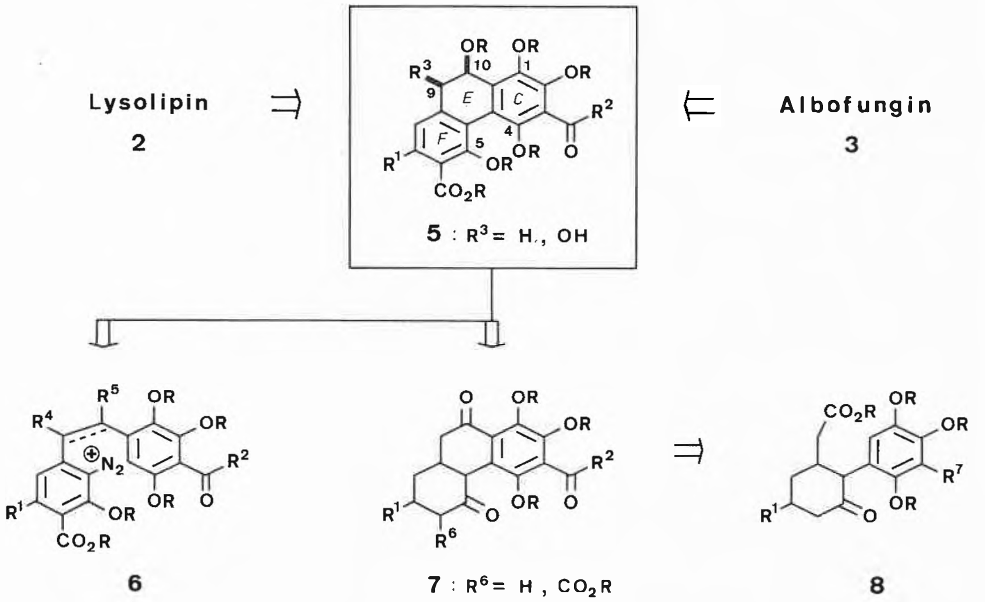


3 : R = H

4 : R = Cl

The antibiotics lysolipin (**1, 2**) and albofungin (**3, 4**) represent an entirely new class of natural products. Their clinical application is, however, precluded by their toxicity and by the inefficiency of the microbial production[*]. A ready access by synthesis could eventually allow the preparation of analogues with more specific, either cytotoxic or antimicrobial, biological activity. It should, however, be said, that the major thrill connected with the total synthesis of such novel structures is still caused by the solution of unprecedented problems.

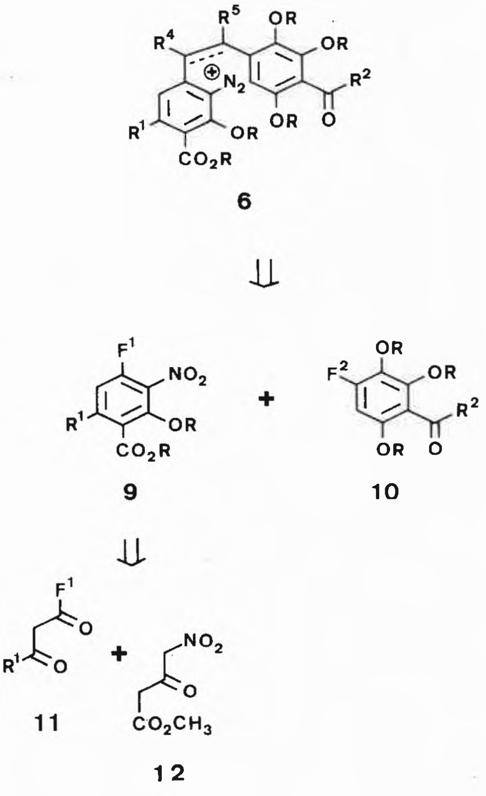


Scheme 1. R: protecting group, R^i: suitable substituents.

A retrograde synthetic analysis of lysolipin I (**2**) or albofungin (**3**) immediately leads to a polysubstituted 9,10-dihydrophenanthrene **5**, representing the central carbocyclic rings *C, E,* and *F* of these heptacyclic structures (Scheme 1). Besides problems of regio- and stereoselectivity, difficulties due to the interacting C(4)- and C(5)-hydroxy-substituents have to be considered for a synthesis of **5.** An extensive literature search led to the conclusion that such strained systems should be accessible by the Pschorr-cyclization of a stilbene or a dihydrostilbene **6**[7,8]. A very attractive alternative approach uses octahydrophenanthrenes **7** as precursors of **5.** Part of the strain is thus built up in the course of the aromatization of **7,** and the access to **7** by cyclization of a (2'-aryl-3'-oxocyclohexyl) acetic acid **8** should proceed with excellent yield (Scheme 1)[9]. Judged by literature reports other approaches like the Diels-Alder-cycloaddition of styrenes and *p*-quinones[10] or the photocyclization of stilbenes[11] appear less suited for the synthesis of phenanthrene **5.**

2. Construction of Highly Substituted Nitroaromatic Systems by Cyclocondensation

The approach to lysolipin I (**2**) via Pschorr-cyclization of a stilbene **6** (Scheme 1) requires the highly substituted aromatics **9** and **10** as precursors for **6.** The idea of preparing the 3-nitrosalicylate **9** by cyclocondensation of a *β*-dicarbonyl compound **11** and 4-nitro-acetoacetate **12** was considered especially appealing (Scheme 2). After a considerable amount of experimentation with derivatives of 4-bromo-



Scheme 2. R: protecting group, R^i: suitable substituents, F^i: suitable functionalities for bond formation.

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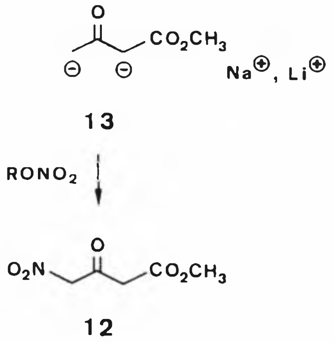
[*] The structure of the labile lysolipin X (**1**) has been determined later by spectroscopic analysis[2b].

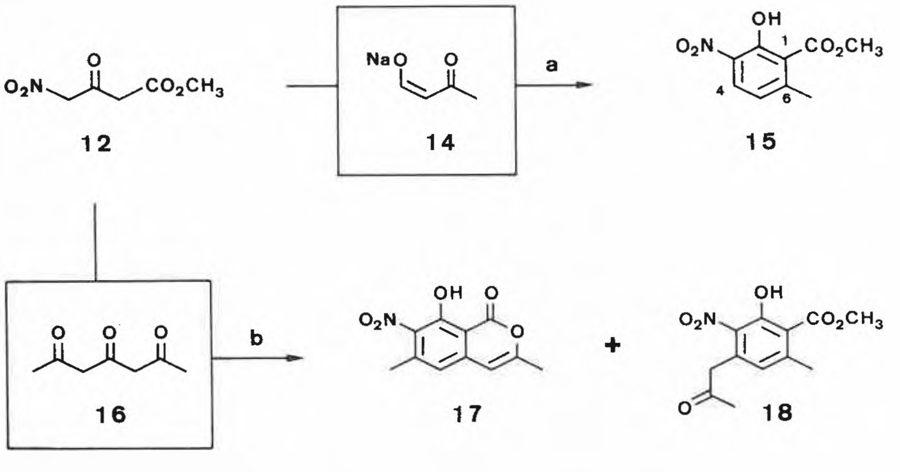
[*] At a concentration of 10 ± 5 mg of lysolipin (**1,2**) per liter of culture medium the production is stopped by lysis of the cells[1].

acetoacetate, it was found that the unknown γ-nitro-β-ketoester **12** can be conveniently obtained by reacting the acetoacetate-dianion **13**[12] with half an equivalent of an alkyl nitrate. The ester **12**, a stable distillable liquid obtained in ca. 60% yield, is susceptible to base- or acid-catalyzed cleavage into malonic acid derivatives and nitromethane (Scheme 3)[13].



Scheme 3.

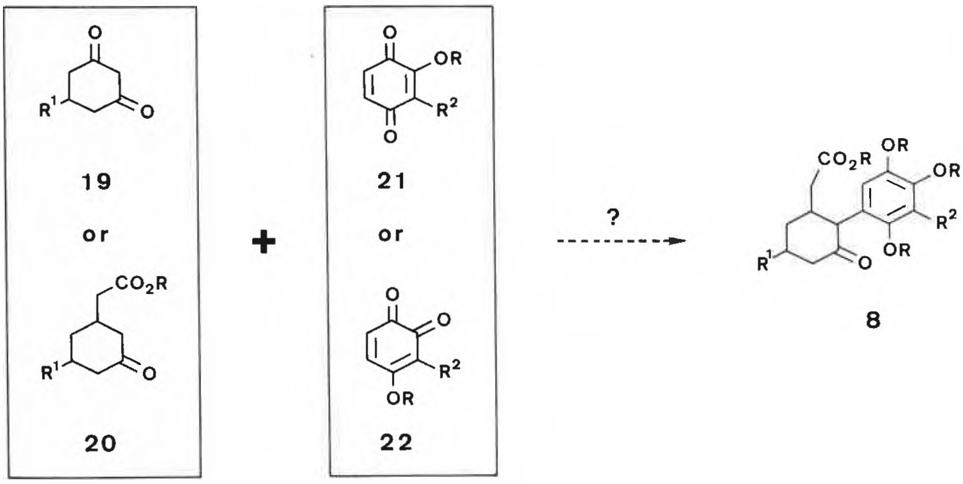
Cyclocondensations with **12** had therefore to be carried out under aprotic conditions. Reaction with a 1.5-fold excess of a β-dicarbonyl compound **11** in dry tetrahydrofurane (THF) using a tertiary amine or amidine as catalyst and molecular sieves as water-adsorbent afforded the desired 3-nitrosalicylates **9** in yields ranging from 20 to 80%[14].



Scheme 4. a: Di-2-propyl-ethylamine · HCl; b: 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

While the cyclocondensation with β-keto-aldehydes proceeded with high regioselectivity, the major product from the reaction of **12** with the Na-salt of formylacetone **14** was the 6-methyl-salicylate **15** (40%), this was not observed for unsymmetrical diketones. As an example 2,4,6-heptanetrione (**16**) afforded 20% of isocoumarine **17** and 5% of products derived from the regioisomer **18** (Scheme 4). This example also shows, that with complex substrates such condensations tend to be inefficient, due to side reactions. The influence of the β-dicarbonyl-structure on the reaction with 4-nitro-acetoacetate **12** appears to be similar to the effects which have been observed for the analogous condensation with 3-oxo-glutarates[15]: while enhanced reactivity results with electron-withdrawing substituents, the condensation is impeded by too many and especially by bulky alkyl-groups.

3. Preparation of 2-Arylcyclohexanone-Derivatives by 1,4-Addition to Quinones

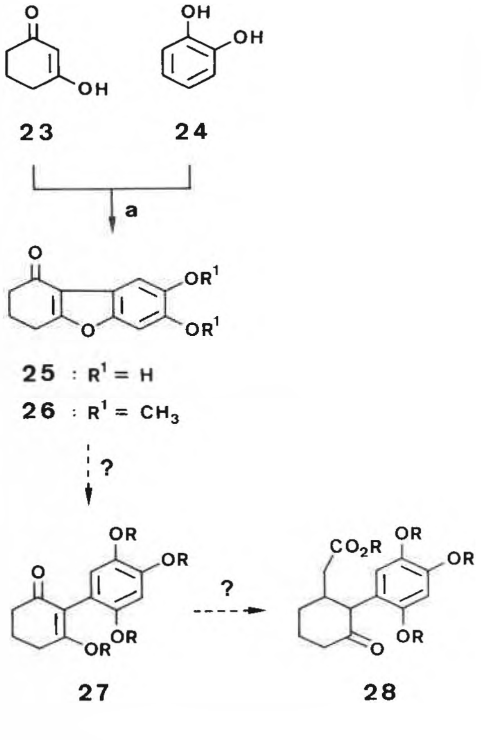


Scheme 5.

The cyclization of an (2′-aryl-cyclohexyl)acetic acid **8** offers probably a more attractive access to lysolipin I (**2**) or albofungin (**3**) than the Pschorr-cyclization (cf. Scheme 1). While aryl-cyclohexyl-derivatives are generally prepared by the addition of an aryl-Grignard or an aryl-lithium reagent to a cyclohexanone[9], we reasoned that 1,4-addition of a cyclohexanone-derivative (**19** or **20**) to a *para-* or *ortho-*quinone (**21** or **22**) would be a more direct access to **8** (Scheme 5). The regioselectivity of this bond-formation is controlled electronically for the quinones[16] and can be circumvented by choosing symmetrical cyclohexane-diones **19** or 3,5-disubstituted cyclohexanes **20** (R^1 = CH_2CO_2R).

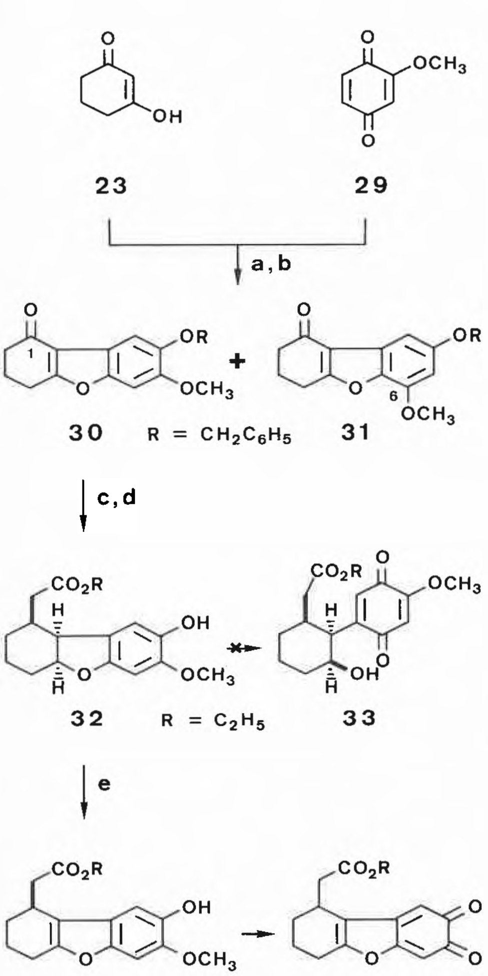
3.1. Transformation of 1,2,3,4-Tetrahydrodibenzofuran-1-ones

The outset of these studies was given by the ready access to 1,2,3,4-tetrahydrodibenzofuran-1-one **25** by reaction of cyclohexane-1,3-dione (**23**) and catechol (**24**) under oxidizing conditions[17]. It was planned to arrive at a 2-aryl-cyclohexanone **28** by a sequence involving furan-ring cleavage and alkylation of the resulting cyclohexanedione-derivative **27** (Scheme 6). Replacement of dione **23** by a dione **19**, substituted at C-5, should lead to the target-compound **8** (R^2 = H) (Scheme 5).



Scheme 6. R: protecting group; a: $K_3[Fe(CN)_6]$ or anodic oxidation.

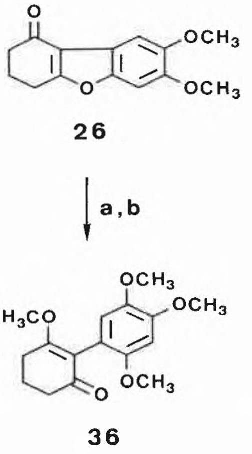
When we found, that the yield of tetrahydrodibenzofuranone prepared according to *Wanzlick* et al.[17a] was quite low (22% of **26** after *O*-methylation)[18,19][*], an alternative access to such dibenzofurans was sought for. $ZnCl_2$-catalyzed reaction[20] of dione **23** with methoxy-*p*-quinone (**29**) followed by benzylation interestingly gave in addition to 25% of the dibenzofuranone **30**, corresponding to the regiocontrol expected for a methoxy-substituted quinone[16], a small amount (6%) of the 6-methoxy-isomer **31** (Scheme 7)[18,19]. Compared to the preparation of **26**, this variant is not a major improvement, but we hoped that the regioselective *O*-protection of **30** would allow a furan-ring cleavage by oxidation to a *p*-quinone.



Scheme 7. a: $ZnCl_2$(t-BuOH/CH_2Cl_2); b: $C_6H_5CH_2Br/K_2CO_3$; c: Li-ethoxyacetylide; d: H_2/5% Pd-C; e: $HIO_4 \cdot 2\ H_2O$.

When this could not be achieved with several derivatives of **30**, we decided to replace the C(1)-oxygen-function by an alkyl-group. Alkylation with Li-ethoxyacetylide, hydrolysis, and catalytic hydrogenation afforded the hexahydrodibenzofuryl-acetic ester **32** in 46% overall yield. The desired cleavage to the *p*-quinone **33** was, however, intercepted by dehydrogenation to the tetrahydrodibenzofuran **34**, which was further oxidized to the labile *o*-quinone **35** (Scheme 7)[18,19].

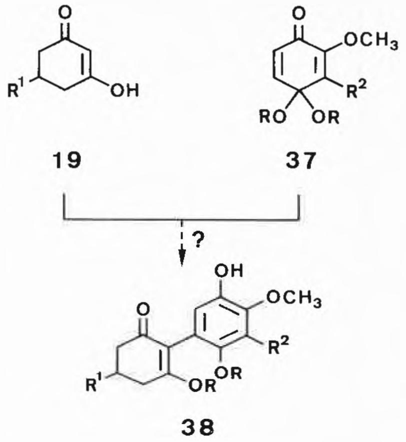
In order to realize the sequence depicted in Scheme 6, the furan-ring of the tetrahydrodibenzofuran-1-one-system had to be cleaved hydrolytically. After many unsuccessful tries[18,19], it was discovered only recently that this transformation can be effected by heating a solution of **26** in NaOH/EtOH-H_2O according to *Royer* et al.[21]. Alkylation with CH_3I gives the 2-aryl-cyclohexane-1,3-dione-derivative **36** in 67% yield (Scheme 8)[19][*].



Scheme 8. a: NaOH/EtOH-H_2O; b: CH_3I/K_2CO_3.

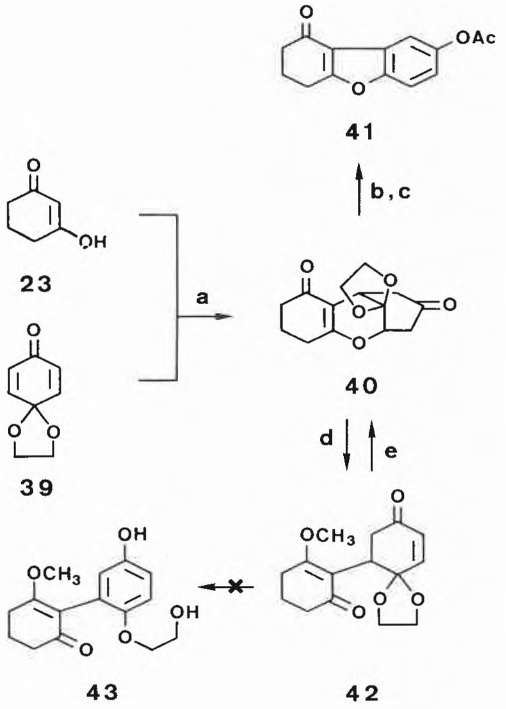
3.2. Experiments with Quinone-Acetals

The chemistry of quinone-acetals is one of the vastly growing fields of synthetic organic chemistry[22]. Encouraged by several reports on the 1,4-addition of active methylene-compounds to quinone-monoacetals[23], we expected that the reaction of a cyclohexane-1,3-dione **19** and a monoacetal **37** would open a better access to 2-aryl-1,3-cyclohexanedione-derivatives **38** than the analogous process with free *p*-quinones (Scheme 9).



Scheme 9. R: protecting group, R^i: suitable substituents.

This process was first studied with unsubstituted model compounds. Under optimized conditions the reaction between dione **23** and the spiroacetal **39** gave the cycloadduct **40** in 85% yield (Scheme 10)[24,25]. While acid-catalyzed hydrolysis of **40** and acetylation not unexpectedly gave the tetrahydrodibenzofuranone **41** in high yield (91%), all attempts to convert **40** into a 2-aryl-1,3-cyclohexanedione (e.g. **43**) failed. The product **42**, corresponding to the primary Michael-adduct of **23** with **39**, could, however, be obtained in excellent yield (94%) from **40** by *β*-elimination. Due to its congested structure, **42** was found to be rather labile, returning to **40** under a variety of very mild conditions like slow chromatography on silica gel. Aromatization of **42** under several conditions was again accompanied by cyclization to the dibenzofurane **41**. The desired 2-aryl-1,3-cyclohexanedione **43** could not be obtained (Scheme 10)[24,25].



Scheme 10. a: t-BuOK/t-BuOH; b: 6N HCl/dioxane; c: Ac_2O/pyridine; d: $(CH_3O)_2SO_2/K_2CO_3$; e: silica gel.

While the reaction of the dimethyl-monoacetal **44** (R = H) with dione **23** catalyzed by *t*-BuOK proceeded similarly as the reactions of spiroacetal **39**[24,25], unexpected observations were made with the

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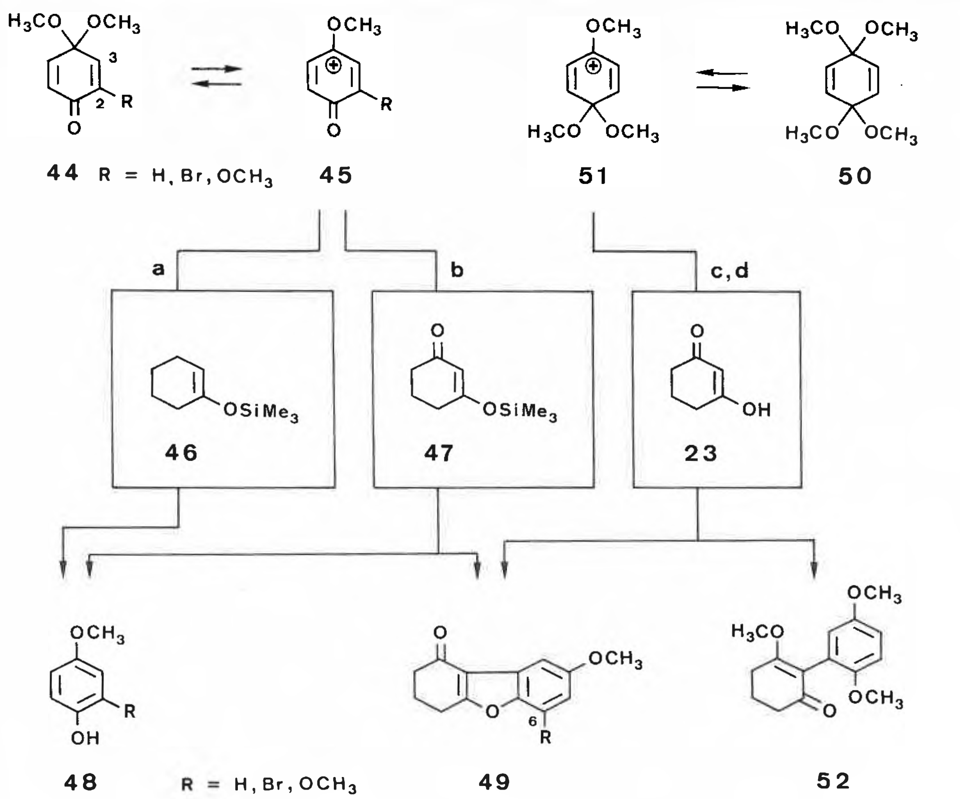
[*] Problems arise from the sensitivity of the product **25**, a catechol, to the oxidizing agent.

[*] Quite unexpectedly, careful acidification before alkylation allows the isolation of unprotected 2-aryl-cyclohexane-1,3-dione[19]. It has also to be noted that acyclic 2-aryl-1,3-diones, obtained from 3-acyl-2-alkylbenzofurans, undergo *retro*-Claisen-reaction under these conditions[21].

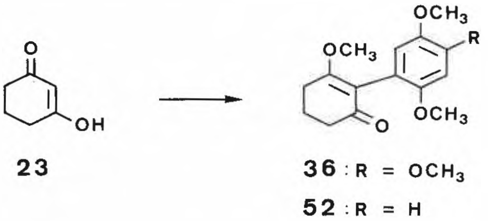


Scheme 11. a: $TiCl_4$(-78°C) or neat without catalyst (200°C); b: $[Bu_4N]F$/THF (reflux); c: $ZnCl_2$/dioxane (reflux); d: $(CH_3O)_2SO_2/K_2CO_3$.

silyl-enolethers **46** and **47** (Scheme 11). When fluoride was used as a catalyst the reactions were sluggish. A considerable increase of rates could, however, be induced at higher temperature or by adding Lewis-acids. Under such conditions the dimethylmonoacetals **44** presumably react via the oxycarbenium-ions **45**. With trimethyl-siloxycyclohexene (**46**) only direct reduction of **45** to the hydroquinone-monomethylether **48** was observed (61% by $TiCl_4$-catalysis, quantitative from the thermal process at 200°C)[24,25]. The fluoride-catalyzed reactions of the cyclohexanedione-derivative **47** on the other hand afforded in addition to some hydroquinone **48** variable amounts (16–50%) of 6-substituted dibenzofuranones **49**. Interestingly, quinone-monoacetals substituted at C-3 did not react with **47** under these conditions[24,25]. It had been demonstrated that a variety of nucleophiles add in 1,4-fashion to the oxycarbenium-ion **51** generated by acid-catalysis from quinone-bisacetal **50**[26]. This method was indeed successful with the dione **23** as well, and after *O*-methylation the 2-aryl-cyclohexanedione-derivative **52** was isolated in 57% yield together with 21% of dibenzofuranone **49** (R = H) (Scheme 11)[24,25].

3.3. Addition of Enamines to p-Quinones

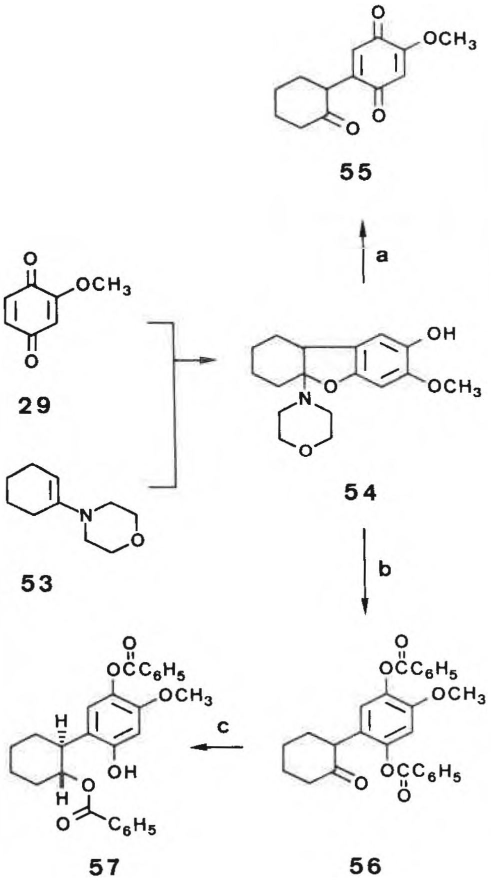
In the previous sections it has been disclosed that 2-aryl-1,3-cyclohexanediones are accessible from 1,3-cyclohexanedione (**23**) by two methods: 1) from 1,2,3,4-tetrahydrodibenzofuran-1-ones by hydrolytic furan-ring cleavage (→**36**, Scheme 8), 2) by $ZnCl_2$-catalyzed addition to quinone-bisacetal **50** (→**52**, Scheme 11). Both approaches suffer, however, from severe disadvantages. The appropriate dibenzofuranones are formed in low yield from the free quinones (Scheme 6 and 7)[18,19], and the very efficient access to **41** via the spiro-monoacetal **39** (Scheme 10) failed with the corresponding methoxy-substituted quinone-monoacetal[24,25]. Based on theoretical considerations, reaction of a methoxy-substituted quinone-bisacetal would lead to the regioisomer of **36** (Scheme 12).



Scheme 12.

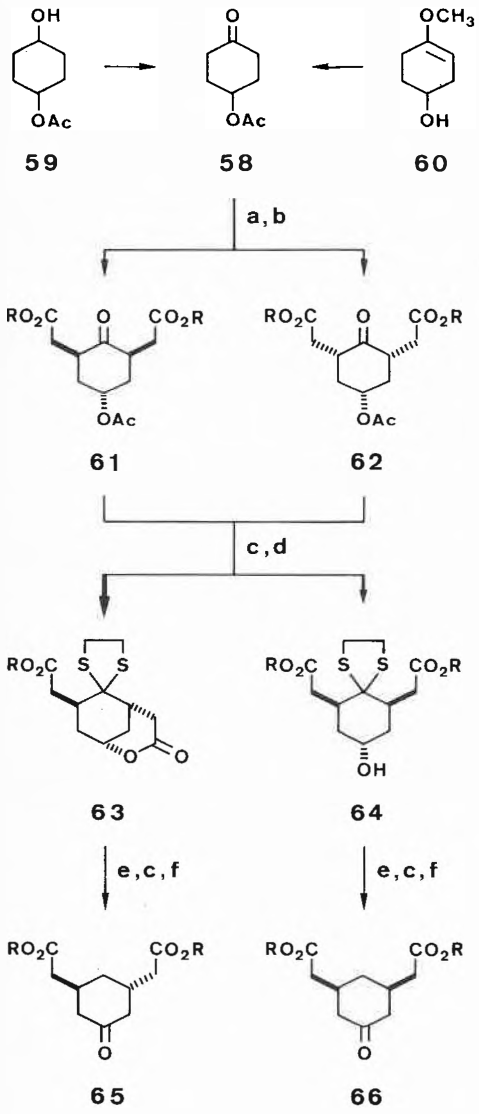
For this reason the alternative approach, addition of a symmetrically 3,5-disubstituted cyclohexanone **20** to quinones **21** or **22** (Scheme 5), was also pursued.

Since enamines are excellent nucleophiles for 1,4-additions to *p*-quinones[27,28], we decided to study this reaction with 1-morpholino-cyclohexene (**53**) as a model-compound. Reaction with methoxy-*p*-quinone (**29**) gave the hexahydrodibenzofurane **54**, which could be opened to quinone **55** by oxidation with $FeCl_3$[28] (84% overall yield, Scheme 13)[18,29,30]. The cleavage of the furan-ring, a very important point for our purposes, could also be effected by heating **54** in a mixture of benzoyl chloride and pyridine according to *Brannock* et al.[31]. The dibenzoate **56** was thereby isolated in 69% yield[18]. Unexpectedly, an elegant method allowing the protection against furan-ring formation was discovered, when **56** was reduced with $NaBH_4$. An intramolecular acyl-shift led to the phenol **57**, which could be *O*-methylated with $(CH_3O)_2SO_2$ (61% yield, Scheme 13)[18].



Scheme 13. a: $FeCl_3/CH_3OH$-H_2O; b: benzoyl chloride/pyridine; c: $NaBH_4$/2-propanol.

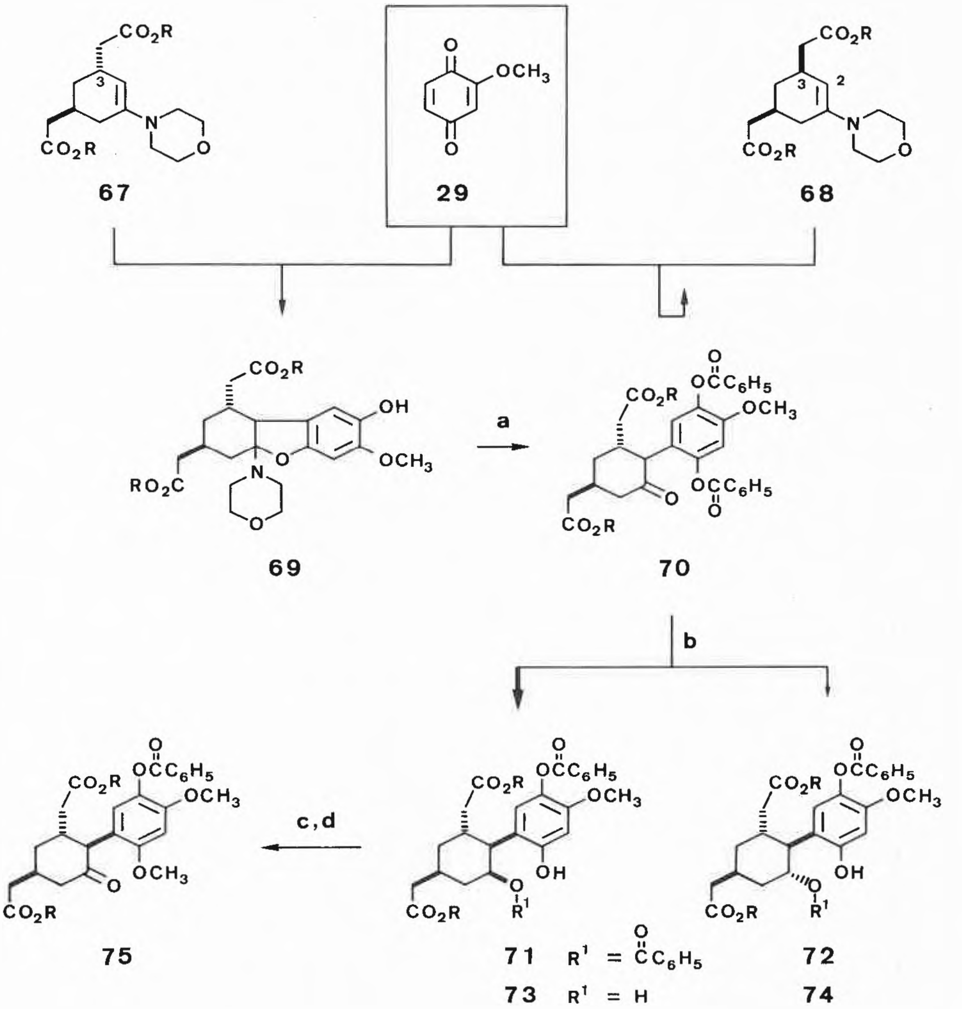
The next problem which had to be solved was the synthesis of a suitable 3,5-disubstituted cyclohexanone **20** (Scheme 5). Starting with 4-acetoxycyclohexanone **58**, which could be readily prepared either by Jones-oxidation of monoacetate **59**[32], or by acetylation and hydrolysis of enolether **60**[33], the isomeric 1,3-cyclohexanediyl-diacetic esters **65** and **66** have been prepared as depicted in Scheme 14[18,19]. Conversion of ketone **58** to the pyrrolidine-enamine and alkylation with bromoacetate according to *Marshall* and *Flynn*[34] gave a 55:45 mixture of the epimeric α,α'-*cis*-dialkylated ketones **61** and **62**



Scheme 14. R = CH_3, C_2H_5; *a: pyrrolidine*(−H_2O); *b:* $BrCH_2CO_2R$/*di-2-propyl-ethylamine; c:* ROH/CH_3SO_3H; *d: ethane-dithiol*/$BF_3 \cdot Et_2O$; *e: Raney-Ni*/H_2; *f:* CrO_3/H_2SO_4/*acetone*-H_2O.

(68%)[*]. Crucial for the success of this approach was the reduction of the keto-function by thioacetalization and Raney-Ni desulfurization. The steric strain imposed by the spiro-anellated 1,3-dithiolane ring is the reason why the isomer with *trans*-configurated side-chains was the favored product of thioacetalization. If the acetate of **61**/**62** was cleaved prior to the acetalization, the main product was the lactone **63** (69%), most of which (52%) could be isolated by crystallization. Desulfurization, alcoholysis of the lactone-ring, and Jones-oxidation finally gave the *trans*-configurated cyclohexanone **65** in 32% overall yield from **58**. Flash-chromatography of the mother-liquor from the crystallization of lactone **63** afforded more **63** (17%) and the *cis*-configurated thioacetal **64** in variable yield. The isomeric ketone **66** was then obtained from **64** by an analogous reaction-sequence.

The sequence illustrated by Scheme 14 gives thus an efficient access to the 3,5-*trans*-disubstituted cyclohexanone **65**. We were therefore pleased, when the morpholine-enamine **67** derived from **65** added smoothly to the methoxy-*p*-quinone (**29**) affording the hexahydrodibenzofuran **69**, while the isomeric enamine **68** derived from the less readily available ketone **66** did not react with **29** (Scheme 15)[18]. This difference in reactivity of **67** and **68** is due to the acetic acid side-chain at C-3. The conformer with an axial C(3)-substituent is easily accessible for the *trans*-configurated isomer **67** but very high in energy for **68**.



Scheme 15. a: benzoyl chloride/pyridine; b: $NaBH_4$; *c:* $(CH_3O)_2SO_2/K_2CO_3$; *d:* CrO_3/H_2SO_4/*acetone*-H_2O.

An equatorial substituent at C-3 obviously impedes a pseudo-axial attack from C-2 of **68** to the quinone **29**. In analogy to the model study (Scheme 13), the adduct **69** was then converted to the dibenzoate **70** (54% based on **29**). Reduction with $NaBH_4$ was again accompanied by a benzoyl-shift. In 2-propanol ca. 20% of the alcohols **73** and **74** were isolated in addition to 72% of the dibenzoates **71** and **72**. The product-distribution could be changed to ca. 59% of **73**/**74** and variable amounts (18–29%) of dibenzoate **71** by using 2-propanol-H_2O (60:40) as solvent for this reduction[*]. The desired ketone **75** was finally obtained in 51% overall yield from **70** by *O*-methylation of the phenols **73**/**74** and Jones-oxidation (Scheme 15)[18].

4. Reductive Phosphorylation of *p*-Quinones

Looking for a still better access to 2-aryl-cyclohexanones, the possibility to arrive at regioselectively protected compounds by reaction of cyclohexyl-substituted *p*-quinones like **55** (Scheme 13) with phosphites was envisaged. This redox-process leading to *O*-phosphorylated/*O*-alkylated hydroquinones had been reported by

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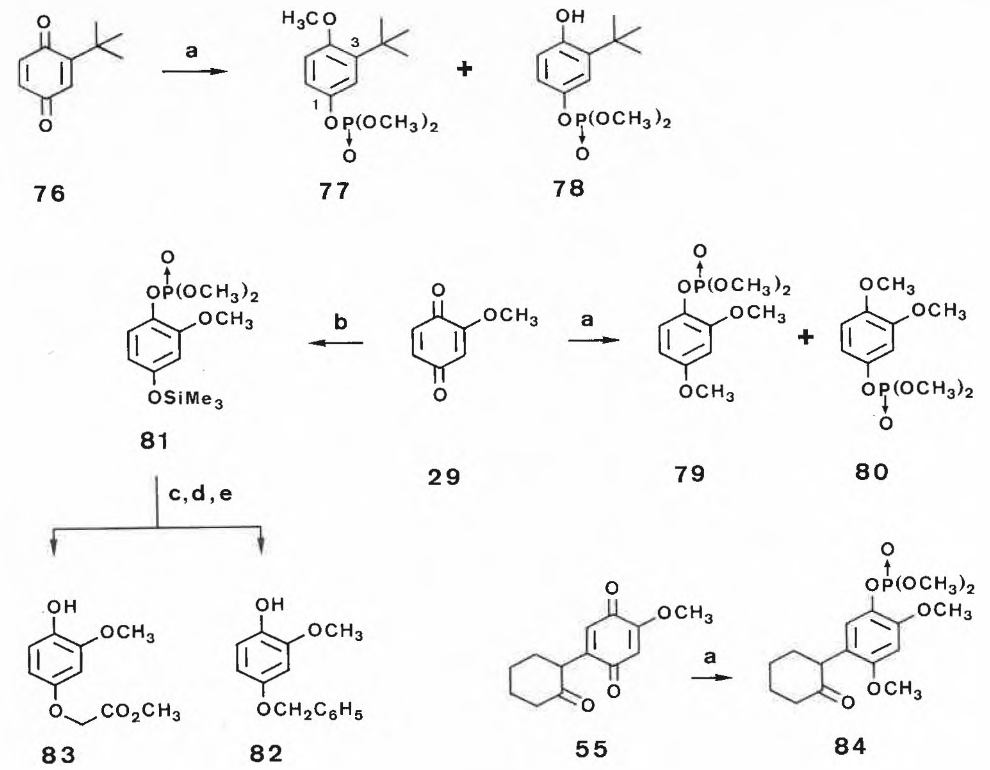
[*] This sequence was carried out with the methyl[29] and the ethyl ester[18].

[*] In contrary to the reduction of **56**, where only the equatorial alcohol **57** was observed (Scheme 13), the axial epimer **71** and **73**, respectively, was the major product isolated from reductions of **70** (**71**/**73**:**72**/**74** ca. 3:1). Treatment of **71**/**72** with $NaBH_4$ interestingly did not afford the alcohols **73**/**74**.

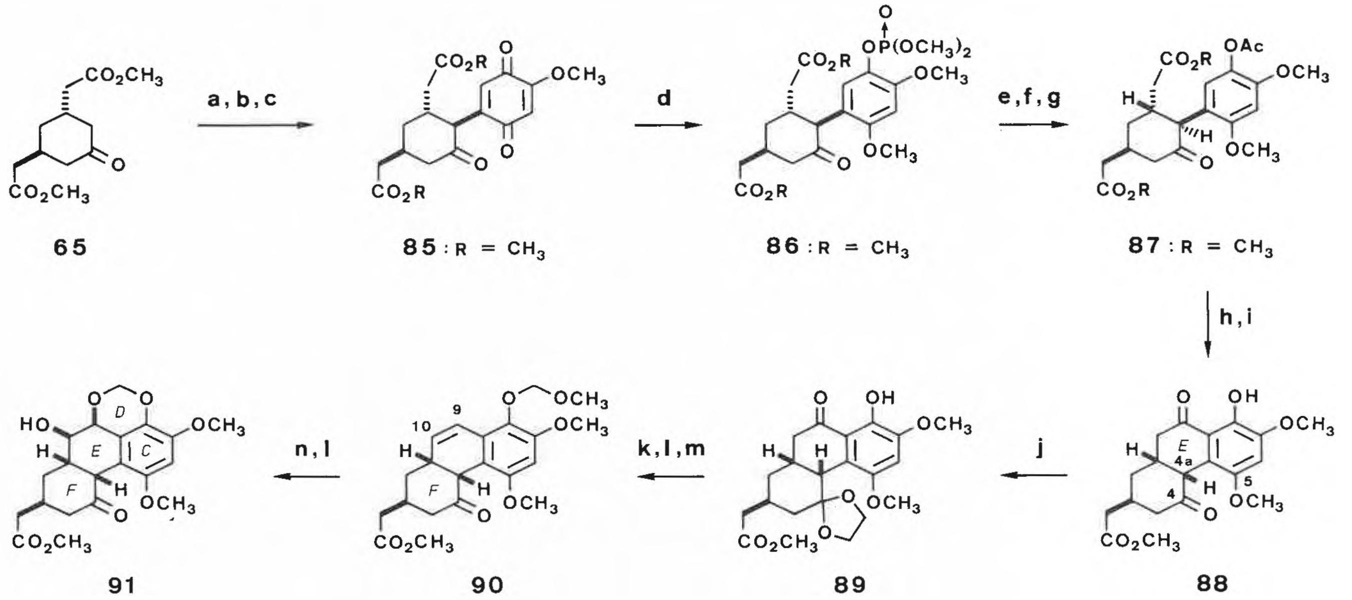


Scheme 16. a: $P(OCH_3)_3$; b: $P(OCH_3)_3/(CH_3)_3SiCl$; c: $H^{\oplus}/ROH$; d: RBr/K_2CO_3; e: CsF/ROH or $(CH_3)_3SiBr$ and acetate-buffer (pH 4)/dioxane (reflux).

Ramirez et al. some time ago[35]. As the mechanism of this reaction studied by *Ramirez* et al.[36] and *Boeckestein* and *Buck*[37] appeared too complex in order to make any conclusive predictions concerning the regiocontrol, we investigated this point with a representative series of mono-substituted *p*-benzoquinones[29,30]. While most substituents have only a small to intermediate influence on the regioselectivity, pronounced effects have been found for bulky substituents and for the methoxy-group[*]. *tert*-Butyl-*p*-benzoquinone (**76**), as an example, reacts with exclusive formation of the 3-*tert*-butyl-substituted phenyl phosphates **77** (72%) and **78** (13%) (Scheme 16). Very important for our synthetic plans was the result of the reaction with methoxy-*p*-quinone (**29**). The desired product, phosphate **79**, was isolated in 79% yield, while only 3% of the regioisomer **80** were formed. Modification of this reaction by employing an excess of trimethylsilyl chloride in addition to the phosphite turned out to be a versatile method for the preparation of mono-*O*-alkylated hydroquinones[29,30]. With methoxy-*p*-quinone (**29**) the main product, the phenyl-silyl-ether **81**, can be hydrolyzed to the crystalline *p*-hydroxyphenyl phosphate. *O*-Alkylation and phosphate-cleavage[*] gave the 2,4-dialkoxyphenols **82** and **83**, respectively, in excellent yield (Scheme 16)[24,25,29,30]. The model-compound **55**, finally, with a bulky cyclohexyl-substituent and a methoxy-group both directing the phosphorylating agent to the same carbonyl-target, afforded the phosphate **84** (77%) without detectable amounts of the regioisomer[29,30].

5. Synthesis of an Intermediate Incorporating Rings *C*, *D*, *E*, and *F* of Lysolipin I

Based on the success with model-quinone **55** (Scheme 16), the reduction by phosphites was applied to the substituted system (Scheme 17)[29,41]. The adduct of the morpholine-enamine derived from the dimethyl ester **65** to methoxy-*p*-quinone (**29**) (corresponding to **69**, Scheme 15) was oxidized with $FeCl_3$ to quinone **85**, which was reduced by $P(OCH_3)_3$ affording phosphate



*Scheme 17. a: morpholine($-H_2O$); b: methoxy-p-quinone (**29**); c: $FeCl_3$; d: $P(OCH_3)_3$; e: $(CH_3)_3SiBr/CH_3CN$; f: acetate-buffer (pH 4)/dioxane (reflux); g: Ac_2O/pyridine; h: CH_3SO_3H (50°C); i: CH_2N_2; j: glycol/mesitylene-SO_3H; k: $NaBH_4$; l: mesitylene-SO_3H; m: $ClCH_2OCH_3$/di-2-propyl-ethylamine; n: OsO_4.*

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[*] Quinones substituted with π-acceptors are *C*-phosphorylated by phosphites.

[*] Optimal conditions for the phosphate-cleavage have been found to be either dealkylation with $(CH_3)_3SiBr$[38] followed by hydrolysis at pH 4[39] or CsF-catalyzed alcoholysis[40].

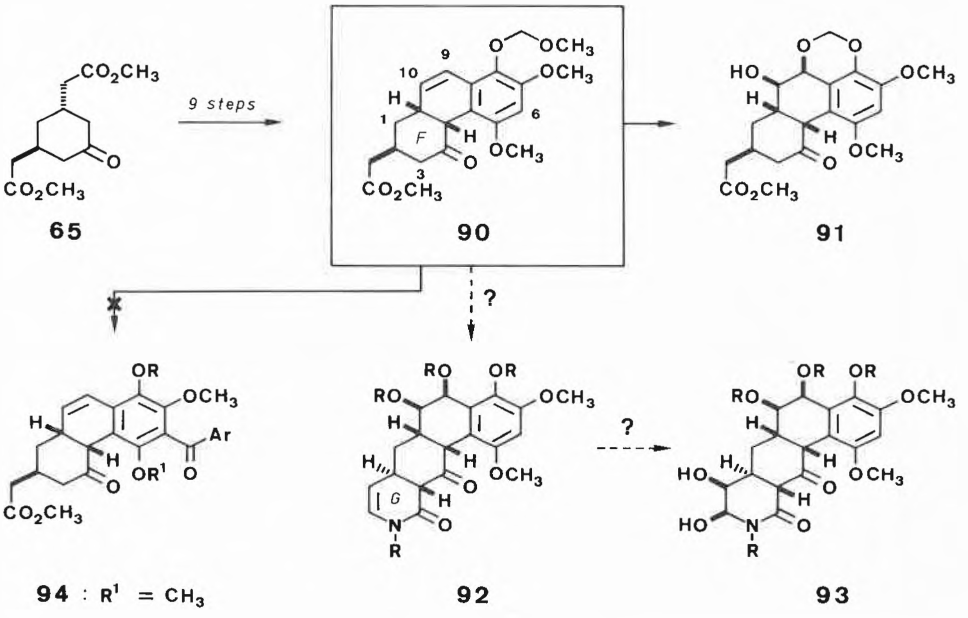
86. Phosphate-cleavage, CH_2N_2-treatment (re-esterification of partially hydrolyzed methyl esters), and acetylation gave the crystalline 2-aryl-cyclohexanone **87** in 50% yield based on converted **65**[*]. Compared to the previous method affording ca. 27% of benzoate **75** (Scheme 15)[18], this new variant represents a real improvement.

For the next step, cyclization of the diester **87** or **75**, we first proceeded in the usual way: protection of the ketone by acetalization before saponification of the ester-functions. The following cycloacylation with BF_3-gas or polyphosphoric acid and esterification gave, however, the octahydrophenanthrene-dione **88** only in low yield (16%)[18]. It was then discovered that **87** can be converted directly to **88** in 78% yield by neat CH_3SO_3H at 50 °C (Scheme 17)[18,29][**]. The ^{1}H-NMR-spectrum and a X-ray-analysis of the octahydrophenanthrene-4,9-dione **88** showed that the saturated rings are *cis*-anellated[29,41]. An epimerization of the benzylic position α to the keto-function (C-4a of **88**) must therefore have occurred in the course or after the cyclization. This finding is in contrast to previous reports, assigning the *trans*-ring-junction to similar 5-substituted octahydrophenanthrene-4,9-diones[9b].

With this sufficiently efficient method for the preparation of the key intermediate **88** in hand[***], we decided to proceed with the further elaboration in direction of lysolipin I (**2**). After selective acetalization of the C(4)-ketone (→**89**), the functionality of the middle ring was modified by $NaBH_4$-reduction of the C(9)-ketone, H_2O-elimination, acetal cleavage, and alkylation of the C(8)-phenol with chlormethyl-methyl-ether affording the hexahydrophenanthrene **90** in 63% overall yield from **88** (Scheme 17). The following oxidation with OsO_4 proceeded with high diastereoselectivity, the reagent attacking from the less hindered *exo*-face of the molecule (83% yield). Acid-catalyzed transacetalization finally effected the cyclization of ring *D*, affording the tetracyclic compound **91** in moderate yield (39%, Scheme 17)[29]. The problems encountered in this last step are due to the steric strain of the dioxin-ring, and in part to the sensitivity of the benzylic position C-9. Less difficulties are to be expected, when this step will be transposed to a later stage of the synthesis, to an intermediate with aromatic ring *F* and an electron-withdrawing substituent at C-6.

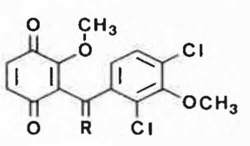
6. Prospects and Concluding Remarks

The main tasks remaining for the completion of this total synthesis are the anellation of rings *A*, *B*, and *G*, the stereocontrolled introduction of the oxygen-substituents of rings *E* and *G*, and the aromatization of ring *F*. It could already be demonstrated (Scheme 17) that oxidation of the hexahydrophenanthrene **90**, available in 9 steps (26%) from cyclohexanone **65**, affords selectively **91**. It is then planned to convert **90** into the tetracyclic derivative **92** by an appropriate sequence involving reduction of the methyl ester, carboxylation of C-3, and oxidation of the 9,10-double bond (Scheme 18). Another OsO_4-oxidation is expected to afford **93** with the correct relative configuration of the four hydroxy-groups, provided that the dihydropyridone-ring *G* is *trans*-anellated.

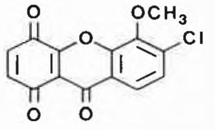


Scheme 18. R: protecting group.

The anellation of rings *A* and *B* involves introduction of an aroyl-substituent at C-6 of **90** and cyclization to the xanthone. After some unsuccessful attempts to acylate **90** and other derivatives with *o*-chlorbenzoyl chloride (**94**, Scheme 18)[27], we decided to introduce this substituent in an earlier stage of the synthesis, replacing the methoxy-*p*-quinone (**29**, Schemes 15 and 17) by a disubstituted quinone, **95** or **96**, or by the xanthoquinone **97**.



95 : R = H,H
96 : R = O



97

A synthetic approach to such compounds is illustrated by Scheme 19[24]. Regioselective lithiation[44] of the methoxymethyl-ether **98**, obtained from 2,5-dihydroxy-benzaldehyde[24], with *n*-Butyllithium/*N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) at −78 °C[*] and addition of the phenyllithium **99** to the acid chloride **100**, prepared from 2,6-dichloro-*m*-cresol[24], afforded the benzophenone **101**, albeit in very low yield (3–12%)[**]. The xanthone **102**, representing rings *A*, *B*, and *C* of lysolipin I (**2**), was finally obtained by cyclization with NaOH in boiling EtOH

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[*] In order to minimize the amount of side-products from redox-processes between product and quinone **29**, only 0.55 equivalents of **29** were added to the enamine derived from **65**; 40% of **65** could be recovered by flash-chromatography of the mixture containing the polar phosphate **86**.

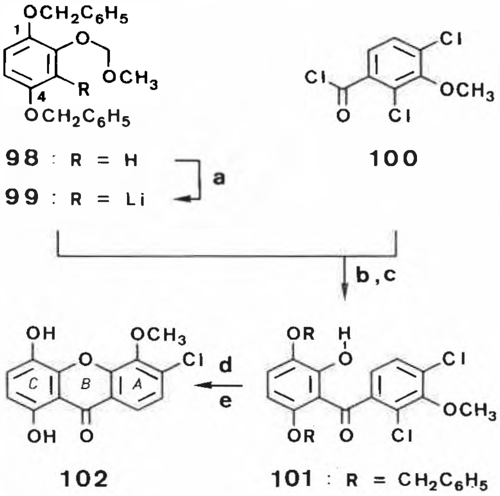
[**] Methanesulfonic acid is an efficient reagent for cycloacylations of free carboxylic acids[42]. To our knowledge the intramolecular acylation reported by *Brossi* and *Gerecke*[43] is so far the only known example of an aromatic acylation by an ester without concomitant ester hydrolysis. It has to be noted that in the course of the conversion of **87** to **88** only a small portion of the second non-acylating methyl ester is cleaved. Instead of the phenyl acetate **87**, the corresponding phenol or the benzoate **75** (Scheme 15), but not the phosphate **86**, could be cyclyzed to **88** as well[18,29].

[***] The reaction sequence depicted in Schemes 14 and 17 affords **88** in 11 steps from 4-acetoxycyclohexanone **58** (ca. 12% overall yield).

[*] The lithio-derivative **99** proved to be more sensitive than similar compounds[45]. Metallation at 0 °C without TMEDA led to extensive debenzylation of the C(4)-phenyl-ether.

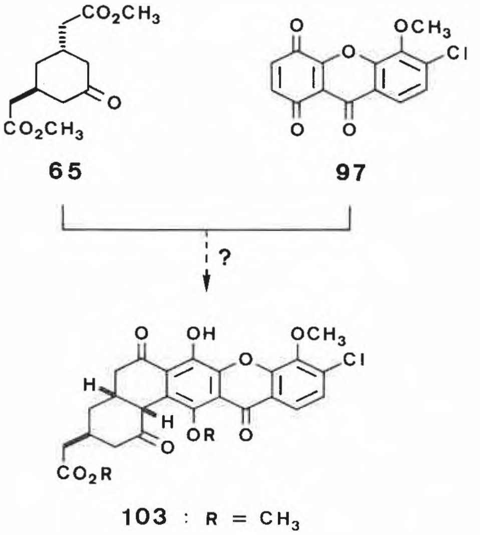
[**] Addition of the acid chloride **100** to **99**, the usual procedure, led to intractable product mixtures. A dark-red coloration during this reaction is probably indicative for single-electron-transfer-processes[24].

and hydrogenolysis of the benzyl ethers (Scheme 19)[24][*].



Scheme 19. a: n-BuLi/TMEDA; b: addition of **99** *to* **100***; c:* CH_3SO_3H/CH_3OH*; d: NaOH/EtOH; e:* H_2*/10% Pd-C.*

In analogy to the synthetic scheme used with methoxy-*p*-quinone **29** (Scheme 17) the pentacyclic compound **103** should be accessible from the cyclohexanone **65** and the quinone **97** (Scheme 20). According to theoretical considerations by *Houk* et al.[16], the nucleophilic addition to quinone **97** should occur with the desired regioselectivity. Provided that **103** can be obtained in this way, it is planned to proceed with the synthesis as outlined in Scheme 18.



Scheme 20.

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[*] It should be possible to improve the synthesis of **102** by minor modifications, e.g. replacing the acid chloride **100** by another electrophile, and by using transition-metal-catalysts for the cyclization of **101**.