Tetrahedron Vol. 46, No. 2, pp. 291–318, 1990
Printed in Great Britain.

0040-4020/90 $5.00 + .00

TETRAHEDRON REPORT NUMBER 267

SYNTHESIS OF ANTHRACYCLINONES BY ELECTROPHILIC AND NUCLEOPHILIC ADDITION TO ANTHRAQUINONES

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(*Received* 11 *January* 1989)

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1. INTRODUCTION

The importance currently attributed to the chemistry of anthracyclinones stems from their outstanding antitumour activity.[1] Very few compounds pass the stringent requirements as drugs for antitumour chemotherapy. It is estimated that the selection of about 40 drugs currently in clinical use have been selected from over 600,000 compounds tested *in vitro*.[2] Among these are several natural, semisynthetic and synthetic anthracyclines.[3] In fact, anthracyclines have played an ever increasing role since their introduction by the Farmitalia and Rhône Poulenc groups[3] and are today the most commonly used drugs in combination anticancer chemotherapy. The anthracyclines are extremely helpful in the treatment of acute leukaemia in children; about 90% of the sufferers can be cured.[3] However, many kinds of tumours (especially solid tumours) resist the treatment or show only initial remission. Much work still has to be done to improve the therapeutic effect and reduce the toxicity of anticancer drugs.

Fundamental research into the isolation and structural elucidation of anthracyclines began much earlier than their use in chemotherapy; most of the basic aglycone structures were known from the work of Ollis[4] and Brockmann[5] (for further important contributions, see references 6, 7–10). The biosynthesis of pyrromycinone was shown to proceed via a polyketide pathway by successive condensation of nine malonate units to a propionate starter.[11] The polyketide origin, and additionally insights into further details of subsequent hydroxylation and glycosidation steps was later

confirmed for many other members of the anthracyclinone family (daunomycine **1**,[12-14] nogalamycine **2**,[15] steffimycin B **3**,[15] aclacinomycin A **4**[16,17]). The neutral sugars were usually derived from glucose,[15] while the methyl groups attached to oxygen or nitrogen came from methionine.[15]

The structural variety of anthracyclines is demonstrated by four typical representatives: daunorubicin (**1**), nogalamycin (**2**), steffimycin B (**3**) and aclacinomycin A (**4**) (for reviews on structure, see references 3, 5, 9, 18–21). Three types of structural differences are found: (i) the substitution pattern of the anthraquinone ring system, (ii) the stereochemistry and type of substituents of the hydroaromatic ring A and (iii) the structure and number of sugars attached glycosidically at position C-7 or C-10, or occasionally C-glycosidically at ring D as seen in nogalamycin (**2**). A common element to all anthracyclines is the linearly condensed tetracyclic ring system. This is expressed in their characteristic name coined by Brockmann[5] from *anthra*quinones and tetra*cyclines*.

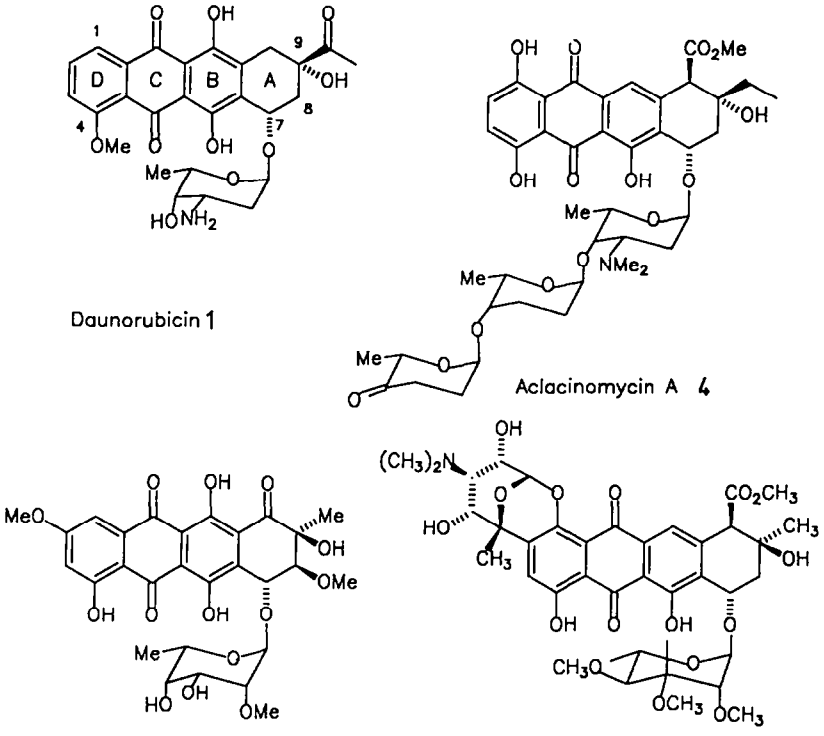


Chart 1. Different structures of some anthracyclines.

It is not surprising that the similarity to anthraquinones stimulated the use of these precursors, which are cheaply available from dyestuff production, for the synthesis of anthracyclinones. A great number of other approaches allow good control of the regio- and stereochemical problems associated with anthracyclinone chemistry (for recent reviews see references 3, 21–30). However, a challenge consisted in the controlled incorporation of the already prefabricated three rings of anthraquinone into anthracyclines. A number of very efficient solutions to these problems, including enantioselectivity, have recently been found. In addition, some interesting new reactivities of the seemingly unreactive anthraquinones were discovered in the course of these investigations (for reviews on anthraquinones, see references 31, 32).

The success of the 'anthraquinone approach' to anthracyclinones is probably attributable to the

fact that at least three mechanistically different types of reaction allow the attachment of various side chains to anthraquinones. Electrophilic additions or substitutions and nucleophilic additions occur at different oxidation states of anthraquinones and the reactions are complementary from a preparative viewpoint. In addition, Claisen rearrangements are also possible and different results can be obtained from the two stable oxidation states (hydroquinone or quinone).[33-41] In the course of their investigations chemists have learned to control the introduction of required functionalities, as well as regio- and stereochemistry. This review summarizes the results of these reactions in anthracyclinone chemistry.

2. ELECTROPHILIC ADDITIONS

By far the most important reaction for anthracyclinone synthesis using anthraquinones as starting materials is the reaction of aldehydes with anthrahydroquinones. The name "Marschalk reaction" proposed by Brockmann[42] in honour of the inventor seems to be generally accepted today. The use of the Marschalk reaction for anthracyclinone synthesis was simultaneously investigated by Sih *et al.*,[43,44] by our group[45,46] and by Morris and Brown.[47] Ten years of experience have demonstrated the scope and limitations of the Marschalk reaction for the introduction of various side chains on the anthraquinone nucleus. In the following sections, general aspects, based on the present knowledge of the Marschalk reaction, will be described.

2.1. *Scope and limitation of the Marschalk reaction*

In an attempted reductive methylation of a diaminoanthraquinone sulfonic acid with formaldehyde and sodium hydrosulphite Marschalk *et al.*[48] obtained a new product of unknown structure. In order to elucidate the structure of these new products, a systematic investigation of the reaction of aldehydes with anthrahydroquinones was carried out. A new type of reaction was discovered that enabled the direct attachment of alkyl side chains to hydroxy- or aminoanthraquinones, which were otherwise completely resistant to the conditions of Friedel–Crafts reactions. It was important to conduct the reaction at elevated temperatures and by these methods a variety of aliphatic and aromatic aldehydes could be linked to anthraquinones.

A number of important observations can be summarized from the work of Marschalk *et al.*[48]

(i) With the exception of 1,3-dihydroxyanthraquinones[49] reduction to the corresponding hydroquinones is necessary prior to the reaction with aldehydes.

(ii) Formaldehyde is most reactive and a second vicinal hydroxymethyl or methyl group (e.g. conversion of quinizarin to 2,3-dimethylquinizarin) can be introduced using this aldehyde.

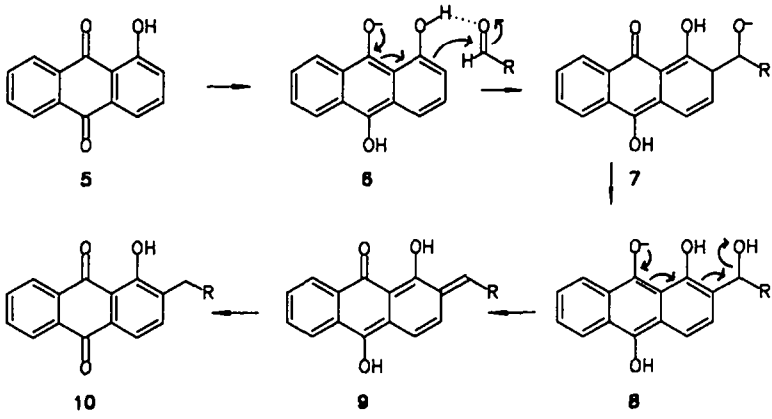
(iii) A second vicinal alkyl group cannot be introduced by reaction with higher aliphatic or aromatic aldehydes under normal reaction conditions. Thus, selective monoalkylation of 1,4-dihydroxyanthraquinones (e.g. quinizarin) is possible.

(iv) The alkyl side chain is *always* introduced *ortho* to a free phenolic hydroxy group.

In the reduction step the electron deficient anthraquinone system is converted into an electron rich, highly nucleophilic polyhydroxy anthracene. This process can be termed 'redox umpolung'. The process is illustrated in Scheme 1, showing the conversion of 1-hydroxy-9,10-anthraquinone (**5**) to the hydroquinone **6** and the reaction with aldehydes. The remarkable *ortho*-selectivity of the Marschalk reaction contrasts with the condensation of phenol with formaldehyde, which leads to an *ortho*- and *para*-bridged polymeric network. A possible explanation might be the hydrogen bonding of the aldehyde to the phenolic group as shown in Scheme 1. This idea is supported by the observation of Shaw[50] and our group that the reaction is sometimes faster in less protic solvent systems (e.g. THF versus H_2O) which favour hydrogen bridging. However, no systematic investigations have yet been conducted to elucidate this point.

In the further reactions of Scheme 1 the primary adduct **7** is isomerized to the hydroxyalkylated

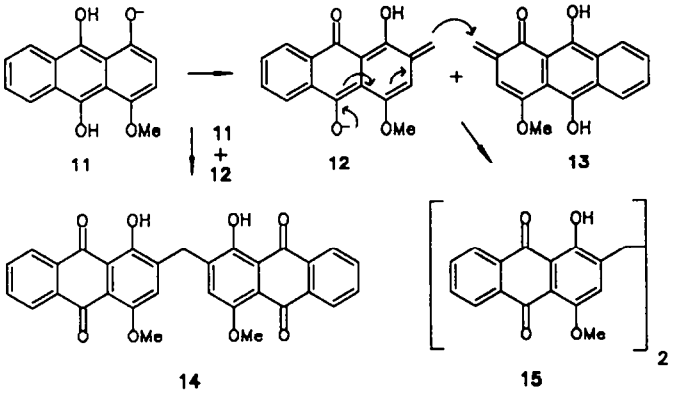
anthrahydroquinone anion **8**. The important discovery of Marschalk[48] was the thermal elimination of the hydroxyl group in **8** to yield directly the methylated anthraquinone **10**. This process is typical of hydroxylated anthraquinones and bridged naphthoquinones[51] (*vide infra*). Based on polarographic studies,[53,89] the intramolecular redox process is believed to proceed via quinone methides such as **9**. The elimination of the hydroxyl group is mechanistically related to a retro Michael reaction. Intermediate *ortho* quinone methides such as **9** are well characterized intermediates in the metabolism of anthracyclines, in which the sugar is eliminated after biological reduction of the anthraquinone system.[54,55] The process can also be exploited to remove and isolate the oligosaccharide units from anthracyclines by mild hydrogenation or microsomal NADPH reduction.[9] A noteworthy exception to the retro Michael type elimination is the 1,5-dihydroxy-2-hydroxymethyl-9,10-anthraquinone system.[56] The special arrangement of the phenolic hydroxy groups seem to favour *ortho*-quinoid tautomeric structures, which make the elimination process more difficult.



Scheme 1. Proposed pathway of the Marschalk reaction.

The reactive quinone methides can also undergo reactions other than tautomerization to the methyl anthraquinones **10**. For instance, nucelophiles such as sulphur compounds can be added in a Michael type reaction.[57] This reactivity has been discussed in connection with the mode of biological action[58] involving bioreductive alkylation.[59] A second type of reaction is anthrone formation. Anthrones have recently been isolated as metabolites[54] and also in the Marschalk reaction conducted under more vigorous conditions.[60] Another common reaction of the quinone methides such as **9** is dimerization, in which one molecule acts as a nucleophile and the other as an electrophile. The dimer formation can be observed on reduction of anthracyclinones with *in vitro* systems;[55,61,62] they can also be isolated as minor components from natural sources[9] or in the Marschalk reaction of 1-amino-9,10-anthraquinone with formaldehyde.[52] Interestingly, dimer formation occurs more readily with systems containing one free phenolic group[63] and is difficult to achieve with 1,4-dihydroxyanthraquinones (quinizarin system). The principle of the dimerization process of *ortho*-quinone methides is the same in glycosidic anthracyclines and more simple systems such as **9**. Scheme 2 illustrates dimer formation in the reaction of leucoquinizarin monomethyl ether (**11**) with formaldehyde.[64] The quinone methide **12** is formed after hydroxymethylation of **11** and elimination of the hydroxyl group. Coupling to another molecule of **12**, represented by the tautomeric form **13**, leads to a dihydro precursor of the dimer **15**. In the intermediate, one half of the molecule is reduced and the other part is oxidized to the anthraquinone state. Oxidative workup (air) rapidly leads to the bisquinone **15**. The intermediate quinone methide **12** can also couple to a molecule of the leuco form **11** to afford the methylene bridged compound **14**. It is noteworthy that these coupling

reactions occur in relatively dilute solution in competition with the addition of the surrounding nucleophilic solvent. The dimerization even in relatively dilute solution can be rationalized by the formation of associated forms (perhaps charge transfer complexes) that assist the approach of the molecules in the right position prior to covalent bonding. However, dimers similar to **14** formed in the Marschalk reaction of 1-aminoanthraquinone can be converted to 1-amino-2-methylanthraquinone by reaction with excess formaldehyde and prolonged heating.[52]

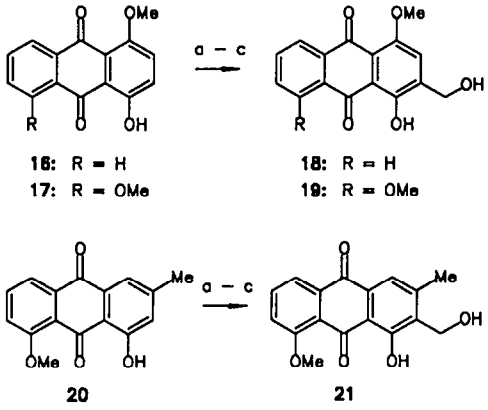


Scheme 2. Formation of dimers in the Marschalk reaction.

Coupling products such as **14** and **15** are easily detected by TLC, because of their lower rates of migration compared with the monomeric products. The dimers are normally quite insoluble in many solvents but their complete removal by crystallization is sometimes quite difficult. The dimers are unpleasant side products in anthracyclinone synthesis and we have attempted to avoid their formation. The quinone methides such as **12** represent oxidized species and the simultaneous presence of oxidized and reduced molecules (leading to charge transfer complexes) has to be carefully avoided. During the course of the reaction this can be effected by the presence of a slight excess of the reducing agent. However, during the oxidative workup in an alkaline medium the reaction mixture passes through a partially oxidized state. We have observed that dimer formation occurred mainly at this period if the reaction mixture is simply stirred in the presence of air. The yield of the monomeric Marschalk products is much better if the reaction mixture is slowly poured into a rapidly stirred solution of dilute hydrogen peroxide, which immediately oxidizes the leuco forms to quinones.[63] As mentioned earlier, this precaution in workup is not required in the hydroxyalkylation of quinizarin type anthraquinones (1,4-dihydroxy groups).

Good yields of alkylanthraquinones employing normal Marschalk conditions (heating under reflux) are obtained because of the irreversible elimination of benzylic leaving groups, including various water soluble coupling products, by the reducing agent (sulphite or dithionite). However, the preservation of the initially formed benzylic hydroxyl groups after addition of the aldehydes would be of great value in anthracyclinone synthesis. Many anthracyclines (e.g. β-rhodomycinone) have two benzylic hydroxy groups that could be generated synthetically by intermolecular or intramolecular Marschalk reactions. Furthermore, the benzylic functionality could be used for the elaboration of side chains with various functional groups needed for further transformation to anthracyclinones. The hydroxymethylation and aminomethylation of 1-hydroxy-9,10-anthraquinone or quinizarin has been realized by Bredereck *et al.*[65,66,89] by reoxidizing the reaction mixture after a very short reaction time (0.5 min). We found this method impractical for large scale preparations. Systematic investigations[46,67] revealed that the intramolecular redox process via the retro Michael reaction proceeded at a much slower rate than the addition of the aldehyde. Con-

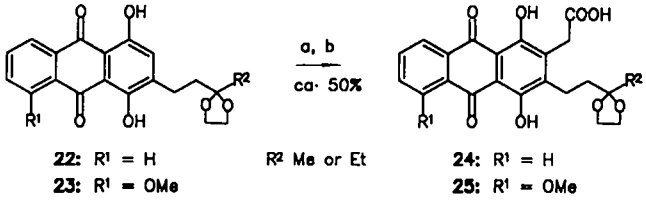
ducting the reaction at 0–10°C (depending on the substitution pattern of the anthrahydroquinone) and employing the rapid reoxidation procedure normally gave good yields (60–90%) of hydroxyalkyl anthraquinones. Typical examples are the hydroxymethylation of 1-hydroxy-4-methoxy-9,10-anthraquinone (**16**)[40,68–70] and 1-hydroxy-4,8-dimethoxy-9,10-anthraquinone (**17**)[60,64,69–72] to the corresponding products **18** and **19** (Scheme 3).



Scheme 3. Hydroxymethylation of monohydroxy anthraquinones.
a: NaOH, $Na_2S_2O_4$; **b**: CH_2O; **c**: dilute H_2O_2.

The hydroxymethyl anthraquinone **19** serves as a starting material for the synthesis of α-, β- and γ-rhodomycinones (*vide infra*). The presence of a vicinal methyl group in **20** does not disturb the hydroxymethylation and the important precursor **21** of 11-deoxyanthracyclinones can be isolated in about 70% yield.[73,74] Two hydroxymethyl groups can be introduced if the phenolic hydroxy groups are in different rings A and C.[56]

In the reaction of 1,4-dihydroxyanthrahydroquinone with higher aliphatic aldehydes only mono-addition takes place under normal conditions. The addition is distinctly slower and the elimination of the hydroxy group becomes more important, leading to mixtures of hydroxyalkylated and alkylated quinizarins even at low reaction temperatures.[46] A second side chain can be introduced by employing more vigorous conditions (prolonged reflux) and a large excess of reactive aldehydes. The selective and sequential introduction of a second side chain by reaction of the quinizarin derivatives **22** and **23** with glyoxylic acid afforded the acetic acid derivatives **24** and **25** which were the basis of the syntheses of 4-demethoxy-ε-rhodomycinone[45] and ε-rhodomycinone.[60,71]

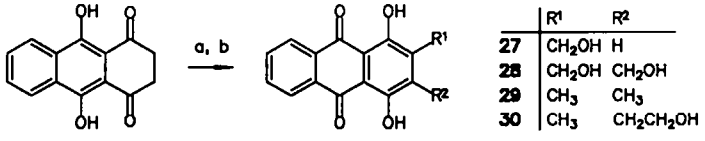


Scheme 4. Marschalk reaction of substituted anthraquinones with glyoxylic acid.[60]
a: NaOH, $Na_2S_2O_4$, CHOCOOH, ca 80°C; **b**: reoxidation.

A two-fold alkylation of leucoquinizarin (**26**) can also be brought about in boiling isopropanol in the presence of piperidine acetate (conditions of Lewis[75]). These conditions have found application

in rhodomycinone synthesis,[69,76] but no general rules can be given as to which method is best for a particular transformation.

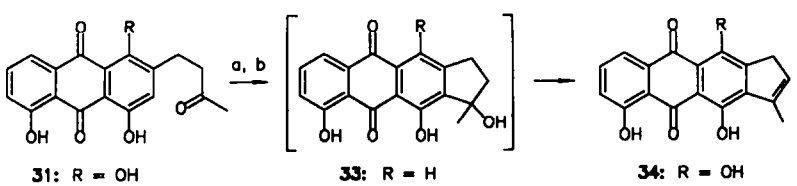
The reaction of formaldehyde with leucoquinizarin, which exists in the diketo form **26** in neutral solution according to NMR measurements,[77] merits special comment (Scheme 5). The reactivity of formaldehyde can lead to some side reactions. At low reaction temperatures incomplete conversion of **26** yields the monohydroxymethylated product **27** which can be isolated in up to 50% yield.[46] The polar bishydroxymethyl compound **28** is also formed on using a large excess of formaldehyde. The original Marschalk conditions (reflux) lead to the dimethyl compound **29**, which can be used as a convenient starting material for deoxydaunomycinones.[78,79] Careful investigation[46,80] revealed a number of side products such as the hydroxyethyl compound **30**. The formation of the hydroxyethyl compound **30** can be explained by quinone methide addition to formaldehyde (compare Scheme 2). In fact, the complex mixture in the reaction of leucoquinizarin (**26**) with formaldehyde yielded products with almost all the combinations of the substituents R^1 and R^2 (**27–30**).[80]



Scheme 5. Hydroxymethylation of quinizarin (**26**).
a: CH_2O; **b**: reoxidation.

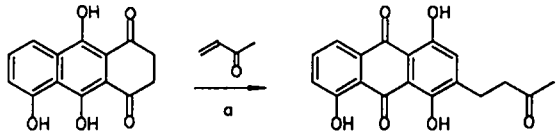
Can electrophiles other than aldehydes (such as esters, ketones, α,β-unsaturated carbonyl compounds or halides react to form new C–C double bonds? So far, to the best of our knowledge, esters have not yet been subjected to a Marschalk type of reaction, even intramolecularly. After unsuccessful attempts to induce the cyclization of anthraquinone esters, Sih *et al.*[44,81] reduced the ester to the aldehyde stage, which underwent Marschalk cyclization in the predicted manner. Another solution was found by Whitlock *et al.*,[82,83] who methylated a bromoanthraquinone system reductively giving a bromo-9,10-dimethoxy-anthracene. Cyclization then proceeded with a carboxyl group in the side chain after lithiation of the bromo anthracene.

There are examples of ketones adding intramolecularly to anthrahydroquinones under Marschalk conditions.[67] An instructive example was found by Sutherland *et al.*;[84] the ketone **31** underwent cyclization and subsequent dehydration giving **34**. A 8-deoxy-analogue of **34**, synthesized in a different manner, was used as a precursor for 8-nordaunomycinone by Tu *et al.*[85] In addition to **34**, the corresponding dihydro-compound was formed, but the alcohol related to the primary cyclization product **33** was not isolated. Our investigation of the cyclization of a number of similar ketones such as **32** showed that the hydroxy group *ortho* to the alkyl side chain was not required for the cyclization. In this case the *tert*-alcohol **33** was isolated as an intermediate in addition to the dehydration product **35**.[56]



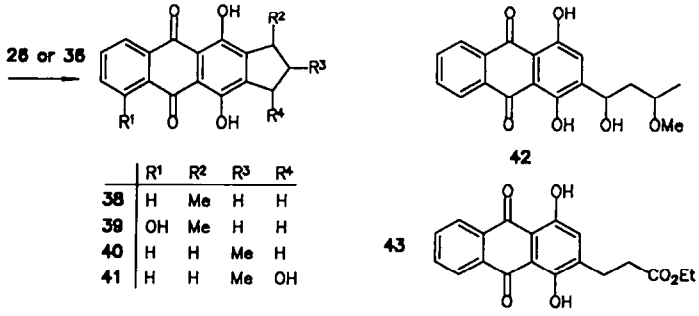
Scheme 6. Intramolecular Marschalk reaction of ketones.[56,84]
a: NaOH, $Na_2S_2O_4$; **b** reoxidation.

A number of examples of the reactions of quinizarin type anthraquinones with α,β-unsaturated carbonyl compounds are described in the literature. For the synthesis of ε-rhodomycinone we needed 3-oxoalkyl-quinizarins of the type **37** (compare Scheme 4). The alkylation of **36** posed a regiochemical problem but a literature report described the preferred attack at C-3 using piperidine acetate as a catalyst[86] (Lewis condition[75]). Piperidine acetate did not work but boron trifluoride successfully catalysed the addition of methylvinyl ketone to leuco-5-hydroxyquinizarin **36**[56] at C-3 (Scheme 7). This reaction demonstrated that the 1,4-addition of anthrahydroquinones to Michael acceptors is possible, but the yields were low in this case and a stepwise synthesis of **37** was later preferred (*vide infra*).



Scheme 7. Regioselective Michael addition of 5-hydroxy-leucoquinizarin (**36**) to methylvinyl ketone.
a: $BF_3 \cdot Et_2O$.

Crotonaldehyde reacted in relatively low yield with leucoquinizarin (**26**)[45] or **36**[87] to form the cyclic products **38** and **39**. This involved an initial Michael addition followed by intramolecular Marschalk reaction of the intermediate aldehyde. Methacrolein, presenting less steric hindrance at the α-position, reacted rapidly and a 1 : 1 mixture of the cyclopentaanthraquinones **40** and **41** were isolated in high yield.[56] If the reaction of crotonaldehyde with leucoquinizarin (**26**) was conducted in methanol, the β-methoxy alcohol **42** was formed.[56] Evidently, a Michael type addition of methanol to crotonaldehyde took place first and this was followed by a Marschalk reaction of the resulting β-methoxy aldehyde. A number of unsaturated esters and nitriles have been added to leucoquinizarin (**26**) in a similar manner giving adducts of type **43** in about 50% yield. The isolation of open chain products exclusively demonstrates that esters and nitriles do not undergo the Marschalk reaction, even intramolecularly.



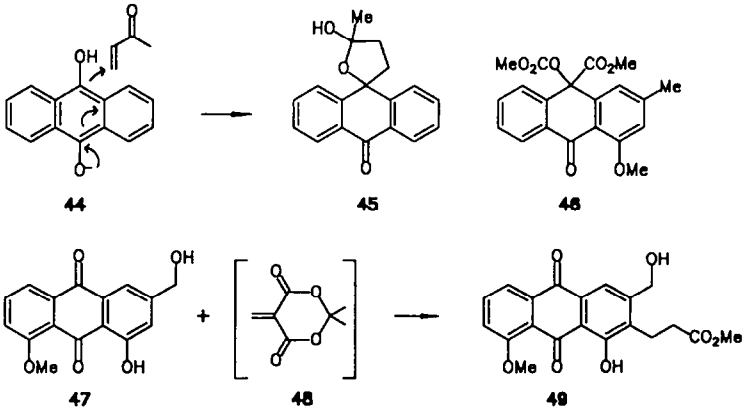
	R¹	R²	R³	R⁴
38	H	Me	H	H
39	OH	Me	H	H
40	H	H	Me	H
41	H	H	Me	OH

Chart 2. Marschalk reaction of **26** of **36** with α,β-unsaturated carbonyl compounds leading to cyclic or acyclic adducts.

A totally different picture presented itself in the reaction of unsaturated carbonyl compounds with anthrahydroquinones which did not possess hydroxyl groups at C-1 and C-4. A number of differently substituted anthrahydroquinones were tested and in all cases C-9 was the nucleophilic centre that added to a number of different Michael acceptors.[88] Phenolic hydroxyl groups were not needed, as shown in the typical example of the reaction of anthrahydroquinone **44** with methyl vinyl ketone to form the spiro-hemiacetal structure **45** (Scheme 8). Other electrophiles can add in a similar

manner, as in the reaction of ethyl chloroformate with the corresponding anthrahydroquinone to form the adduct **46**.[74] Even aldehydes may initially add in a similar manner, but in this case the addition is reversible[65,89] and the reaction is terminated by the formation of stable Marschalk products. A similar course might be followed in the reaction of the aloe-emodin derivative **47** with the methylenemalonate **48** prepared from Meldrum's acid.[90] The intermediate C-9 adduct could rearrange to the stable C–C coupling product **49** during the long reaction time (14–16 h) at elevated reaction temperature (90°C) (Scheme 8).

Adducts resulting from attack at C-9 are also formed in the Michael addition of anthrahydroquinone with quinone methides derived from lignin.[91] This process is of great commercial importance in the anthrahydroquinone-catalysed delignification of wood.

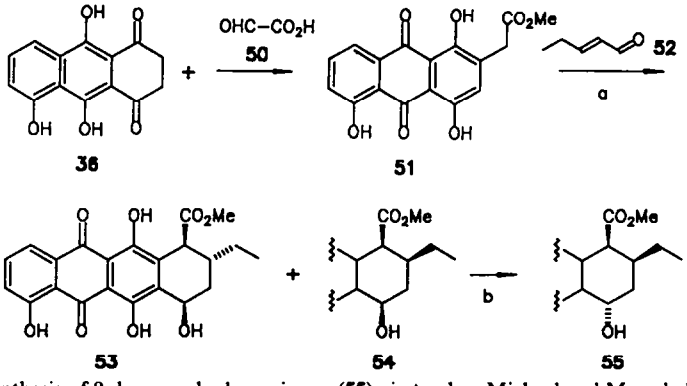


Scheme 8. Michael additions at C-9[88] or C-2[90] of anthrahydroquinones.

2.2. *Keto-ester cyclizations*

In the following sections selected applications of the Marschalk reaction in anthracycline synthesis are presented. The first problem lies in the attachment of appropriately functionalized side chains that allow the construction of the substituted ring A with defined stereochemistry. The Marschalk reaction can be applied twice if two nucleophilic centres are present, as in leucoquinizarins **26** or **36**. Ring A can be closed either in the course of the second Marschalk reaction or by C–C bond formation of two functionalized vicinal side chains.

The first reaction mode is demonstrated in the synthesis of the 9-deoxy-ε-rhodomycinones **55**[92,93] shown in Scheme 9. The Marschalk reaction of **36** with glyoxylic acid (**50**) afforded predominantly

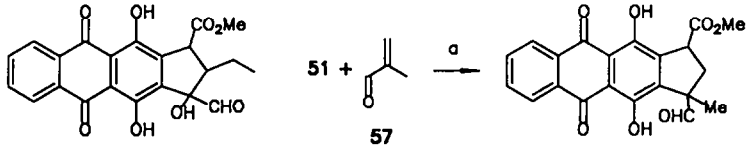


Scheme 9. Synthesis of 9-deoxy-ε-rhodomycinone (**55**) via tandem Michael and Marschalk reactions.

a: NaH, DMF, 20°C; **b**: CF_3COOH/CH_2Cl_2.

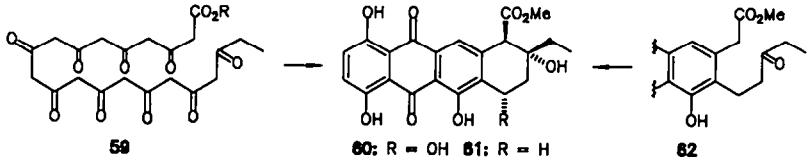
(ratio ca 7 : 1) a C-2 adduct, which was esterified to **51**[93] (compare[86]). The synthetic idea was the construction of ring A in tandem Michael and Marschalk reactions of the activated ester **51** with α,β-unsaturated aldehydes such as pentenal (**52**). The multistep one-pot reaction afforded a mixture of the tetracyclic isomers **53** and **54** in a combined yield of 40–50%. Interestingly, both isomers showed a *cis*-orientation of the ester and the hydroxy group at C-7. 9-Deoxy-ε-rhodomycinone **55** of natural relative configuration was obtained by equilibration of the benzylic alcohol of **53**.[92]

No reducing agent was added to the reaction mixture, and the example of Scheme 9 seems to be a contradiction of the statement that only anthrahydroquinones are able to add to aldehydes. However, the course of the reaction was better understood when a side product **56** (Scheme 10) was isolated. An 82% yield of a related aldehyde **58** was obtained in the reaction of **51** with methacrolein (**57**)[92] (Scheme 10). Evidently, the intermediate anion formed in the initial Michael reactions reacted in a nucleophilic addition to the anthraquinone producing anthrahydroquinones. The byproduct **56** was formed in a subsequent hydroxylation of the acidic position. The hydroquinones thus formed are in equilibrium with other quinonoid systems so that the primary Michael adduct can eventually cyclize in a Marschalk reaction forming **53**/**54**.



Scheme 10. Michael addition of unsaturated aldehydes followed by nucleophilic addition.[92]
a: NaH, DMF.

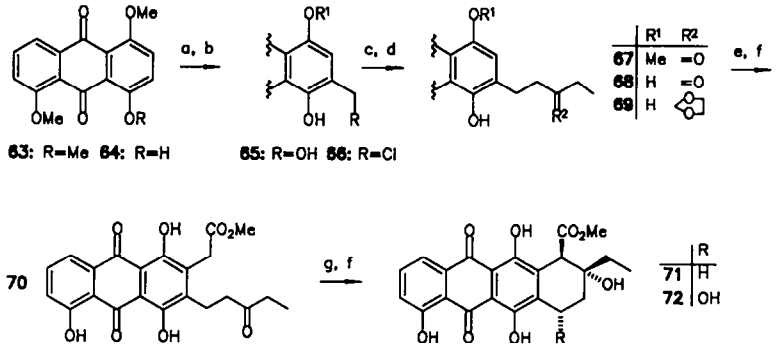
The 9-deoxy-ε-rhodomycinones were obtained in just two reaction steps from **36**. However, the introduction of the tertiary hydroxy group at C-9, which is essential for biolocal activity,[3] was difficult to introduce this way and we had to modify our plans. The analysis of the biosynthesis of pyrromycinone (**60**), first studied by Ollis *et al.*,[4] revealed that ring A was formed in an aldol type of reaction of the keto-ester part of the hypothetical polyketide **59** (Scheme 11). Another hint was the base catalysed recyclization of the thermolysis product **62** of ε-pyrromycinone (**61**).[5]



Scheme 11. Biosynthesis of pyrromycinone (**60**)[4] and biomimetic aldol cyclization.[5]

A model keto-ester obtained from quinizarin was used for our initial studies of a biomimetic rhodomycinone synthesis. The additional problems of regioselectivity were addressed in the first total synthesis of ε-rhodomycinone (**72**) outlined in Scheme 12.[60,71] A 7 : 1 preference for the C-3 adduct was observed in the direct alkylation of the unsymmetrically substituted 1,4,5-trihydroxy-9,10-anthraquinone under Lewis conditions.[86] However, traces of the wrong isomer are often difficult to remove in the anthraquinone series and we decided to begin with isomerically pure

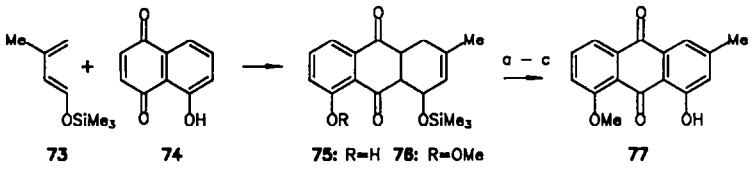
starting materials obtained by selective protection. The dimethyl ether **64** was initially prepared by a kinetically controlled boroacetate formation with 1,4,5-trihydroxy-9,10-anthraquinone,[64] a reaction first studied by Dimroth and Faust.[95] Later we applied the shorter method of Preston *et al.*[96] using boron trifluoride etherate for the selective C-4 ether cleavage of **63** to afford over 70% of the isomerically pure monophenol **64**. The free phenolic function permitted regioselective Marschalk hydroxymethylation to **65**. The side chain was attached via chlorination to form **66**: alkylation with 3-oxovalerate followed by saponification and decarboxylation yielded the 3-oxoalkyl anthraquinone **67** in over 90% yield. A selective methyl ether cleavage with boron trichloride[97] liberated the phenol at C-1 and then the keto-group in **68** was protected by acetalization giving **69**. A second side chain was introduced in a Marschalk reaction with glyoxylic acid. Esterification and simultaneous methyl ether and acetal cleavage with aluminum trichloride gave the desired keto-ester **70**. The thermodynamically more stable *trans*-hydroxy ester **71** was preferentially formed in the cyclization using Triton B as catalyst in pyridine. The corresponding *cis*-hydroxy ester was formed with lithium amide at −70°C in THF and the latter result presumably reflects kinetically controlled conditions. Finally, the benzylic hydroxy group at C-7 was introduced by a bromination solvolysis reaction sequence giving the 7,9-*cis*-diol **72** (ε-rhodomycinone) with high stereoselectivity.



Scheme 12. Total synthesis of racemic ε-rhodomycinone (**72**).[60]

a: hydroxymethylation; **b**: $SOCl_2$; **c**: base, 3-oxovalerate; **d**: BCl_3, ethyleneglycol, H^+; **e**: CHOCOOH, CH_2N_2; **f**: $AlCl_3$; **g**: Triton B; **h**: Br_2, hν; NaOH.

Aclacinomycine A (**4**) has been developed into an effective second generation antitumour agent in Japan.[19] Great efforts were made to synthesize the corresponding aglycone aklavinone (**83**) and other 11-deoxyanthracyclinones with ester groups at C-10. Most of these syntheses use the ketoester cyclization developed for the ε-rhodomycinones.[74,98–108] However, because the phenolic hydroxy group at C-11 is missing, a Marschalk reaction cannot be used to introduce the ester functionality and we had to modify our synthetic scheme for the synthesis of aklavinone.[107] We decided to use an anthraquinone with a methyl group at C-3 with the intention of chain elongation to an ester. The starting material was prepared in a regioselective Diels–Alder reaction[111] of juglone (**74**) with the silyloxy diene **73**[109] as shown in Scheme 13. The regiochemistry of Diels–Alder reactions of juglone have been studied experimentally[110–113] as well as theoretically.[114] The chelated hydroxyl group of juglone dominates the stereochemical outcome so that both oxygen functions are located as in the product **75**. A Marschalk reaction at C-2 was later planned and therefore the phenolic hydroxyl group at C-8 was blocked by methylation giving **76**. Cleavage of the allylic silyl ether and oxidation with pyridinium chlorochromate gave the selectively blocked chrysophanol derivative **77** in high yield. This method was recently extended by Brassard *et al.*[115] to Diels–Alder adducts with halogenated quinones.

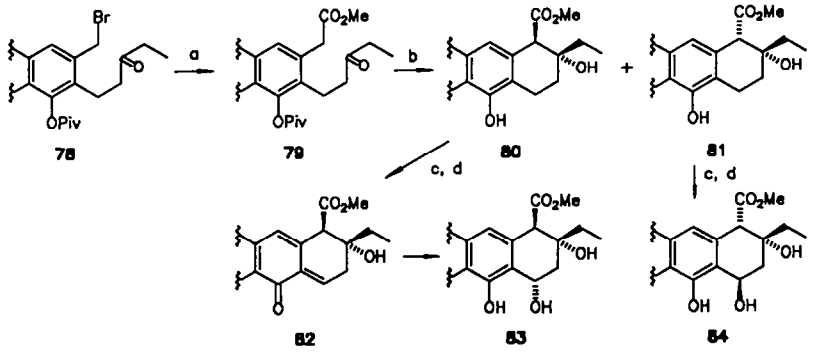


73 74 75: R=H 76: R=OMe 77

Scheme 13. Synthesis of chrysophanol monomethyl ether (77) via Diels–Alder reaction.[107,111]
a: CH_3I, Ag_2O; **b**: H^+, CH_3OH; **e**: pyridinium chlorochromate (PCC).

Conversion to aklavinone included chain elongation similar to that shown in Scheme 12. An essential step was the regioselective monobromination at the methyl group to **78**. The alternative benzylic position was effectively shielded by the neighbouring pivaloate group. The bromide was converted to an acetic ester derivative **79** using the Arndt–Eistert homologation procedure. This methodology was also used by Boeckman *et al.*[99] and Gesson *et al.*[116] in their aklavinone and auramycinone syntheses.

The keto-ester cyclization of **79** gave a 3.3:1 mixture of the hydroxy-esters **80** and **81** in methanolic solvent with Triton B as catalyst. Hydroxylation at C-7 was performed by radical bromination and solvolysis with dilute alkali. The 7,9-*cis*-diol aklavinone (**83**) resulted from the *trans*-hydroxy ester **80** (ratio ca 9 : 1), whereas the *cis*-compound **81** gave predominantly the *trans*-diol **84** (ratio ca 7 : 1). The relative configuration of nogalamycin (**2**) corresponds to that of **84** and the information about the stereochemical course of cyclization and hydroxylation was later exploited in a synthesis of the nogalamycin aglycone (*vide infra*).[104] The highly selective *cis*-hydroxylation was rationalized to proceed by an elimination addition process via the quinone methide **82**.[117] The axial hydroxyl group at C-9 directs the incoming hydroxide anion by hydrogen bonding. The hydroxyl group of the corresponding *cis*-hydroxyl ester **81** is engaged in a hydrogen bond with the neighbouring carbonyl group of the ester group so the hydroxide anion comes towards the less hindered face to afford the 7,9-*trans*-diol **84**.[104,107]

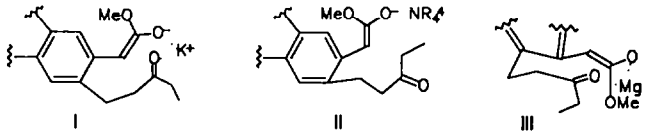


78 79 80 81 82 83 84

Scheme 14. Synthesis of aklavinone.[107]
a: seven steps (via Arndt–Eistert); **b**: Triton B; **c**: Br_2, CCl_4 hν; **d**: H_2O, $NaCO_3$.

The stereochemical course in the cyclization of the keto-ester **79** also merits some comment. Two contradictory models have been proposed to explain the stereochemical outcome in 11-deoxy-keto-esters as shown in Chart 3. Boeckman *et al.*[99] suggest that a chelated transition state such as I leads predominantly to the *cis*-hydroxy ester, whereas transition state II with a non-chelation counter ion or reaction in chelate breaking protic solvents gives the *trans*-compounds. However,

Hauser and Mal[100] found that the formation of the *cis*-hydroxy ester prevails in the presence of magnesium salts and proposed transition state model III. In fact, the design of such models is complicated by the fact that two parameters (conformation of ester enolate and carbonyl group) can be changed simultaneously. According to our own observation, kinetically controlled conditions (very low temperatures or weak bases) favour the formation of the *cis*-compound **81**. With stronger bases and higher temperatures equilibration takes place to the more stable *trans*-adducts **80**. This does of course not exclude the influence of strongly chelating counter ions such as magnesium in model III. We used potassium carbonate in THF as base in our synthesis of the noglamycinone aglycone (ratio 80:81 = 21:66).[104] The *cis*-hydroxy-ester was subsequently hydroxylated at C-7 giving the 7,9-*trans*-diol **84** in 58% yield.

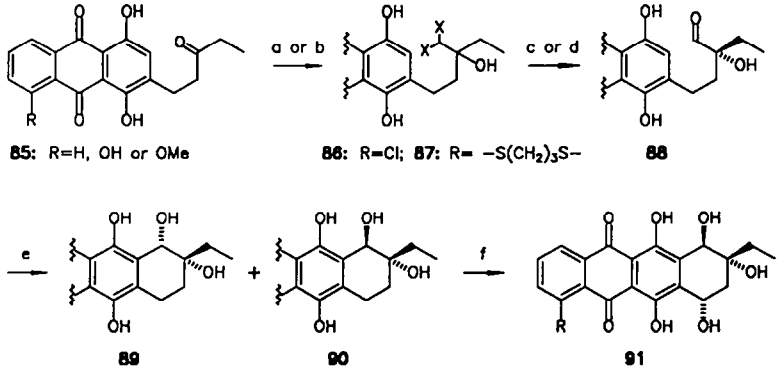


I II III

Chart 3. Transition state models for the stereochemical outcome of the ketoester cyclization (I and II[99]; III[100]).

2.3. *Synthesis of racemic β-rhodomycinones*

The ester group of ε-rhodomycinone (**72**), originating from the cyclization of polyketo esters such as **59** is replaced by a hydroxyl group in the β-rhodomycinones. In other cases the ester is replaced by a hydrogen atom (daunomycinones) or by a carbonyl group (steffimycinones). These types of anthracyclinones demand special methods for their synthesis. The easy access to regioselectively substituted anthraquinones such as **67–69** (see Scheme 12) was exploited in the synthesis of β-rhodomycinone type anthracyclinones. The missing carbon atom in ketone **85** can be introduced by reaction with formyl anion equivalents such as lithiated 1,3-dithiane[68] or dichloromethane[64,70,72] to afford the adducts **86** and **87**. Anthracyclinones with different side chains (methyl, ethyl, propyl) can be prepared by simply changing the β-keto ester in the alkylation step with the benzyl chloride **66**.[72] In addition, the substituent at C-4 can be changed from R = H (4-deoxy-β-rhodomycinones)[68,70] to R = OH (β-rhodomycinone)[64,72] or to R = OMe (feudomycinones).[70] The example shown in Scheme 15 demonstrates the reaction principle with the most common naturally



85: R=H, OH or OMe **86**: R=Cl; **87**: R= $-S(CH_2)_3S-$ **88**

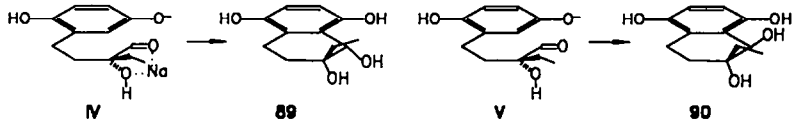
89 **90** **91**

Scheme 15. Synthesis of β-rhodomycinone **91** via Marschalk reaction of α-hydroxy aldehyde **88**.

a: $LiCHCl_2$, −100°C; **b**: Li-1,3-dithiane, −20°C; **c**: hν, O_2, then H^+, CH_3OH; **d**: NaOH; **e**: $Na_2S_2O_4$, CH_2Cl_2, Triton B; **f**: $(CF_3CO)_2O$, then Br_2, hν, NaOH.

occurring ethyl side chain. The unmasking of the latent aldehyde function of **86** and **87** yields the relatively stable α-hydroxy aldehyde **88**. The use of mercury salt could be avoided in the deprotection of **87** by photochemical oxidation to the monosulfoxide of **87** and transacetylation under acidic conditions. The lithio dichloromethane reagent developed by Köbrich[118] proved to be even more satisfactory. Stepwise saponification of the α-hydroxy dichloride **86** via intermediate epoxides to the α-hydroxy aldehyde **88** and subsequent Marschalk cyclization could be conducted in one single reaction flask. The stereochemical outcome can be directed by the reaction conditions (see Scheme 16 below). The desired *trans*-diol **90** was stereoselectively hydroxylated via the usual bromination-solvolysis sequence, affording β-rhodomycinone **91** (80% yield). As a rule, hydroxylation at C-7 is easy if the other benzylic position at C-10 is substituted by ester, keto or hydroxyl groups. If both benzylic positions are free, competitive dibromination may lead to substantial aromatization in the subsequent solvolysis step. In the daunomycinone series this can be inhibited by increasing the steric hindrance at C-10 by ketalization of the acetyl side chain.[119]

The stereochemical outcome of the Marschalk cyclization can be rationalized in terms of chelation versus non-chelation control as depicted in Scheme 16. The *cis*/*trans* ratio ranges from 3 : 1 in NaOH/THF via 1 : 3 in $NaOH/H_2O$[64,72] to 1 : 10–15 under phase transfer conditions using Triton B as catalyst.[70] Less protic conditions (e.g. THF) favour a chelated transition state IV leading to the *cis*-diol **89**. The sodium ion in model IV is presumably surrounded by many solvent molecules that make attack of the nucleophile towards this face of the molecule more difficult. In contrast, chelate breaking solvents such as water or non-chelating counter ions such as Triton B result in a transition state V, leading to predominant formation of the desired natural *trans*-configuration **90**.

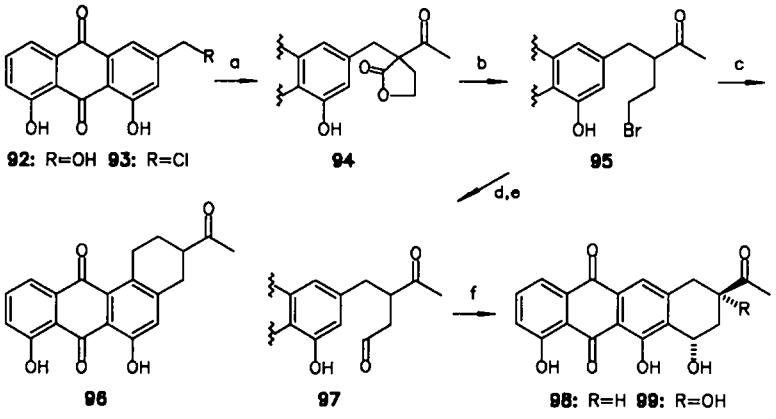


Scheme 16. Transition state models of the α-hydroxy aldehyde cyclization.

2.4. 11-*Deoxycarminomycinone via Marschalk reaction*

Aloe-emodin is an ideal starting material for 11-deoxy-anthracyclinones. The product is easily available by oxidative workup of aloin,[120] a constituent of cheap aloe powder. However, in attempts to attach side chains *inter*molecularly, the less hindered position at C-7 is always attacked preferentially. For reaction at C-2 of the anthraquinone **92** the phenolic group at C-8 has to be protected but this cannot be done selectively.[121] The difficulty can be overcome by *intra*molecular reactions using the hydroxymethyl group at C-3 for chain elongations. One example is the synthesis of 11-deoxycarminomycinone (**99**) shown in Scheme 17. Alkylation of acetyl butyrolactone with the benzyl chloride **93** affords the product **94** quantitatively. Bromination with simultaneous decarboxylation to **95** is achieved by treatment of the lactone **94** with hydrogen bromide in acetic acid (76% yield). Surprisingly, after ketalization to prevent cyclopropane formation and reduction with dithionite, the angularly condensed system **96** was formed (74% yield).[94] The cyclization of **95** to **96** is the first example of reaction with a halide in a Marschalk type reaction. The *para*-selectivity can be explained by the lack of hydrogen bonding that is possible with aldehydes (compare Scheme 1). In terms of hard and soft nucleophiles the soft bromide reacts preferentially with the softer *para*-position.[122] The reaction also provides easy access to substituted tetrahydrobenz[*a*]anthracene systems, which form the skeleton of a large group of antibiotics named angucyclines.[123] In order to see if the linear anthracycline systems could be obtained, the aldehyde **97** was prepared by treatment of **95** with silver acetate in acetic acid followed by PCC oxidation. Marschalk reaction of **97** gave exclusively the linear anthracyclinone system **98**.[124] Hydroxylation of the acidic position at C-7 next to the

acetyl side chain by the method of Gardner[125] and equilibration of the benzylic hydroxy group with trifluoroacetic acid (*cis/trans* = 8 : 1) completed the synthesis of 11-deoxy-carminomycinone **99**.[124] A number of 11-deoxyanthracyclines have been isolated by the Farmitalia group from *Microspora peucetica*.[8] They showed good to excellent cytostatic properties *in vitro* but *in vivo* neurotoxicity unfortunately prevented their further development into anticancer drugs.[126]

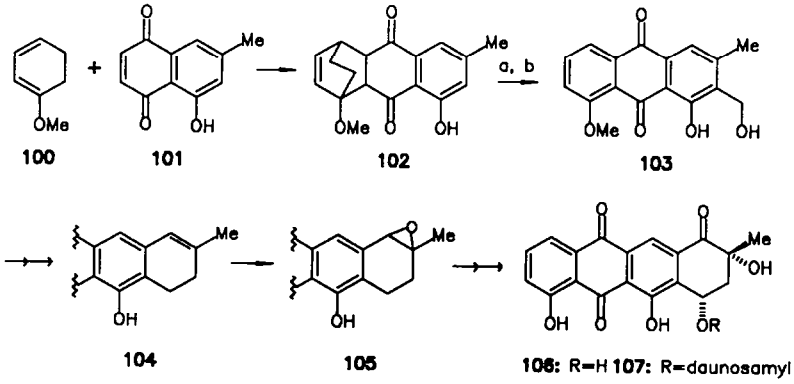


Scheme 17. Synthesis of the angucycline system **96** and of 11-deoxycarminomycinone (**99**) from aloe emodin (**92**).[94,124]

a: NaH/DMF, acetyl butyrolactone; **b**: HBr/HOAc, 3 h reflux; **c**: ethyleneglycol, H^+, then NaOH, $Na_2S_2O_4$; **d**: AgOAc, HOAc; **e**: PCC; **f**: NaOH, $Na_2S_2O_4$; **g**: hydroxylation at C-9, then CF_3COOH.

2.5. 8-*Demethoxy-aranciamycinone: naphthoquinones in the Marschalk reaction*

The Marschalk reaction has been used in the synthesis of 11-deoxyanthracyclines in yet another way. Steffimycinone B (**3**) and the related 2-demethoxy compound aranciamycinone (**106**)[127] are examples of 10-oxoanthracyclinones. 8-Demethoxy-aranciamycinone (**106**) and the corresponding daunosamyl glycoside (**107**) were synthesized in two different ways. In the first method chrysophanol monomethyl ester (**77**) was used to prepare the dihydronaphthacene quinone precursor **104**.[73] Better overall yields were obtained in the conversion of the mechanistically interesting *naphtho*-hydroquinone equivalent **102** in a Marschalk type reaction.[128] The dione **102** was obtained in the Diels–Alder reaction of 7-methyljuglone (**101**) with 1-methoxy-1,3-cyclohexadiene **100**. Enolization

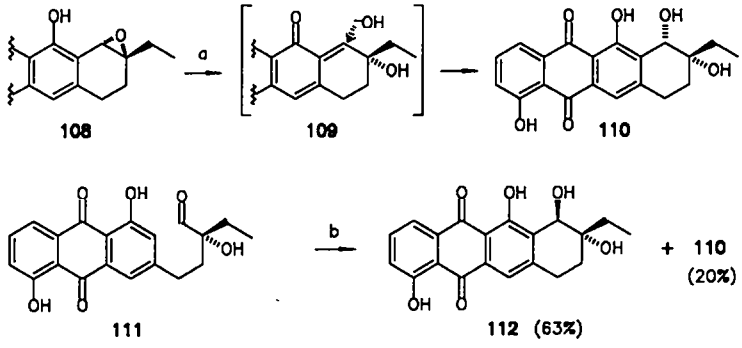


Scheme 18. Synthesis of 8-demethoxyaranciamycinone (**106**) by the Marschalk reaction with naphtho-hydroquinones.[128]

a: NaOH, CH_2O, then O_2; **b**: 104°C.

of **102** to a naphthohydroquinone takes place under the alkaline conditions of the Marschalk reaction and addition to formaldehyde yields the hydroxymethyl-anthraquinone **103** after oxidation and retro-diene reaction. Another application of naphthohydroquinones is the conversion of Diels–Alder adducts from naphthazarin to digitopurpone and islandicin.[51] The necessary functional groups at C-9 and C-10 for the aranciamycinone synthesis were introduced by epoxidation of **104** followed by epoxide opening to the corresponding *trans*-diol. Chiral oxoperoxomolybdenum lactamide complexes could be used in an asymmetric epoxidation of **104**. An enantiomeric excess of 53% at $-20°C$[129] and of 72%[56] at $-78°C$ was obtained which is among the highest values obtained, for *non*functionalized olefins. Further steps in the conversion to **106** involved the usual *cis*-hydroxylation at C-7 and glycosidation of the benzylic hydroxy group with daunosamyl chloride and silver triflate.[128]

The expected *trans*-diol resulted from the epoxide opening of **105**. However, in our synthesis of γ-citromycinone (**112**),[130] in which the hydroxyl group at C-6 is transferred to C-11, a *cis*-diol **110** resulted from the treatment of **108** with dilute alkali, as shown in Scheme 19. Evidently, a quinone methide intermediate **109** (related to **82**) postulated for the hydroxylation at C-7 (compare Scheme 14) is responsible for this remarkable inversion of the usual stereochemistry in epoxide opening. The compound of the desired natural *trans*-configuration was obtained in the Marschalk cyclization of the hydroxy aldehyde **111** to yield 63% of the *trans*-diol **112** (γ-citromycinone) and 20% of the *cis*-diol **110**.[130] It should be mentioned that the introduction of hydroxy groups at C-7 via bromination/solvolysis gives only low yields in 6-deoxyanthracyclinones.[131] A better strategy in this case is the coupling with fully functionalized AB building blocks.[41,132]



Scheme 19. *cis*-Opening of an epoxide and synthesis of γ-citromycinone.[130]
a: 0.3 N NaOH; **b**: NaOH, $Na_2S_2O_4$, the O_2.

2.6. *Synthesis of enantiomerically pure rhodomycinones*

The Marschalk reaction has been used in a number of additional ways to attach side chains on the way to anthracyclinones.[36,41,43,44,47,63,133–137] However, it is perhaps even more important that the methodology developed for racemic rhodomycinones can easily be adapted for the synthesis of enantiomerically pure compounds. In contrast to the many elegant methods for asymmetric synthesis of the daunomycinone group of anthracyclines (for a review see reference 29) the Marschalk reaction opened the door to optically active rhodomycinones and related compounds. Chiral building blocks derived from the chiral pool of natural precursors are incorporated. The advantage of this 'chiron' approach[138] is that starting materials of known absolute configuration and 100% optical purity can be used. With a few exceptions the optical yields in asymmetric inductions are very substrate-dependent so that the enantiomeric excess is not always satisfactory if known procedures are applied to slightly different cases (compare[139]). The challenge of the 'chiron' approach for anthracyclinones

lies in the construction of suitable building blocks with masked 1,4-dialdehyde functionality and a chiral tertiary alcohol group. Compounds with this special arrangement are not directly available from natural sources.

The pathway for racemic rhodomycinones outlined in Scheme 15 can be simplified for the enantioselective synthesis. A retrosynthetic analysis shown in Chart 4 reveals that two different reaction modes are possible: cyclization of α-hydroxy aldehydes (mode I) and of β-hydroxy aldehydes (mode II).[76,140] Both modes were realized experimentally and the respective advantages and stereochemical consequences are discussed below.

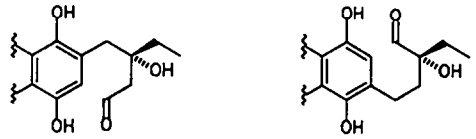
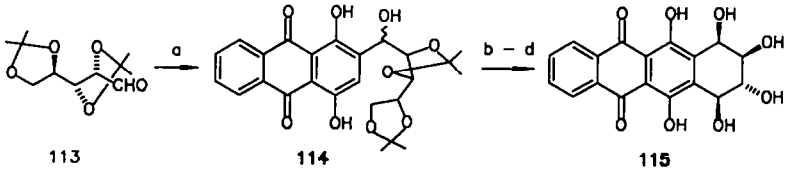


Chart 4. Reaction modes in the Marschalk cyclization of α-hydroxy aldehydes.

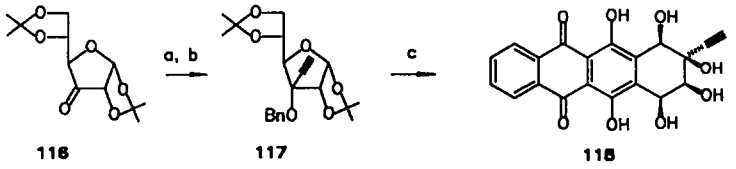
2.6.1. *Sugars as chiral templates.* In a series of papers Shaw *et al.*[50,141-144] explored the possibility of linking sugars to anthrahydroquinones. An aldehyde function is hidden in the cyclic hemiacetalic furanoside or pyranoside form of aldoses. However, Shaw *et al.*[142] found that a number of hexopyranoses (D-glucose, D-xylose, D-glucosamine) did not react with leucoquinizarin under the conditions of the Marschalk reaction. Evidently, the aldehyde group had to be fixed in some kind of open chain form. Thus, the D-arabino aldehyde **113**, easily available from glucose, was coupled to leucoquinizarin (**26**) to afford the adduct **114**.[143] Selective deprotection and glycol cleavage liberated the aldehyde for a second Marschalk reaction to form a tetracyclic product with a configuration of the hydroxy groups as shown in **115**. The stereochemical outcome of the newly generated stereogenic centres at C-7 and C-10 depended greatly on the nature of the protective groups.



Scheme 20. Synthesis of anthracyclines without side chain.[143]

a: Marschalk reaction,[48] 0°C; **b**: $AcOH/H_2O$; **c**: $NaIO_4$; **d**: second Marschalk reaction.

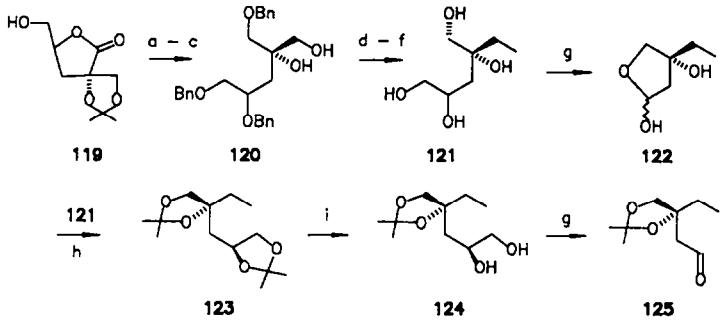
Side chains can be introduced into anthracyclines if branched sugars such as **117** are used. The acetylene **117** can be obtained from the widely used keto sugar building block **116**. Further standard transformations are necessary to obtain the tetracyclic ethynyl compound **118**.[144]



Scheme 21: Incorporation of the branched sugar **117** into the anthracycline **118**.[144]

a: ethynylmagnesium bromide; **b**: benzylation; **c**: five steps.

Monneret, Florent *et al.*[76,145,146] used α-D-isosaccharino-1,4-lactone (**119**) as versatile starting material for incorporation into anthracyclines. The building blocks were also used for the construction of chiral AB fragments that were condensed to tetracycles.[147,148] In this context only the direct attachment to anthrahydroquinones is discussed. Initially, only products with hydroxymethyl side chain that came from the sugar carbon skeleton were synthesized.[145,146] Key reactions in the conversion to the required building blocks **122** and **125** with ethyl side chain are shown in Scheme 22. α-D-Isosaccharino-1,4-lactone (**119**) was reduced with lithium aluminium hydride, protected by benzylation, and selectively cleaved to afford the diol **120**. The hydroxymethyl group was then converted into the ethyl group by mesylation of the primary hydroxyl group and displacement with lithium dimethyl cuprate (65%). The benzyl ethers were then cleaved to the tetraol **121** by hydrogenation and glycol cleavage of the vicinal hydroxyl groups with periodate liberating the latent aldehyde functionality to yield **122** represented in the cyclic hemiacetal form. However, the adduct in the condensation with leucoquinizarin (**26**) was isolated in only 10% yield. We observed a similar result with an analogous benzylated furanoside.[149] Thus, sugars cannot be coupled to anthrahydroquinones in good yield if they can form cyclic hemiacetals either as pyranosides[142] or furanosides.[76,149] To improve the yields in the coupling reaction, sugars which are fixed in the open chain form have to be prepared. This could be achieved by acetalization of **121** to give **123**, followed by selective acetal cleavage to **124** and periodate cleavage to **125** as shown in Scheme 22. The yield in the reaction with leucoquinizarin (**26**) was improved to 40%.[76] In order to prepare the tetracyclic anthracyclinones, the acetal in the adduct of **26** and **125** had to be cleaved and the primary alcohol oxidized to the aldehyde followed by a second Marschalk reaction (compare Scheme 23).

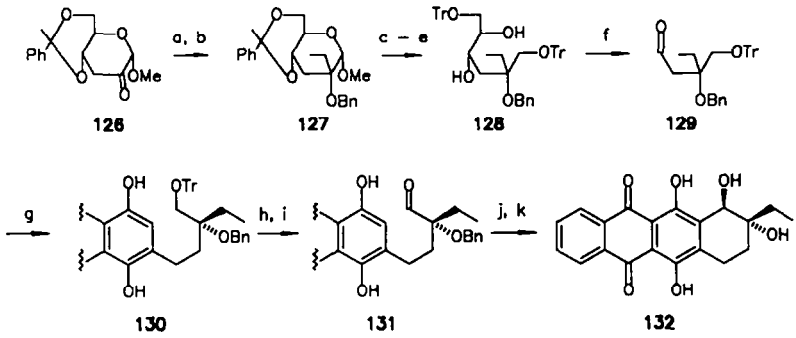


Scheme 22. Building blocks **122** and **125** from α-D-isosaccharino-1,4-lactone (**119**) for γ-rhodomycinone synthesis.[76]

a: LAH; **b**: NaH, BnBr; **c**: H^+, **d**: MsCl/Py; **e**: Me_2CuLi (65%); **f**: H_2/Pd—C; **g**: $NaIO_4$; **h**: dimethoxypropane, H^+; **i**: MeOH, 10% HOAc, 12 h, r.t.

We have used carbohydrates in a quite different way, as shown in Scheme 23. The carbon skeleton of the carbohydrate was not totally incorporated, but the chiral information inherent in the pyranoside methyl glycosides was used to introduce side chains in a highly selective manner. Initially, we studied the Grignard reaction with 2-deoxy-3-oxo-sugars derived from α-D-mannopyranoside. The investigations were useful in elucidating the stereochemistry of the addition reaction but products of inverse absolute configuration were obtained.[150] Products of correct natural configuration were prepared from 3-deoxyhexopyranoside (**126**), which was obtained in four steps from the cheap methyl α-D-glucopyranoside. The addition of the ethylmagnesium bromide yielded a crystalline adduct in over 90% yield, which was benzylated to **127**; no stereoisomer could be detected.[150] Further transformations involved deprotection, acetolysis of the methyl glycoside, borohydride reduction and tritylation to give **128**. The tritylation avoided the hemiacetal formation

that resulted in low yields in the subsequent Marschalk reaction. Glycol cleavage afforded the aldehyde **129**, which was coupled to leucoquinizarin to give **130** in over 60% yield.[149] The trityl ether was cleaved and the primary alcohol oxidized to the aldehyde **131** using the Pfitzner Moffat procedure. Marschalk cyclization and debenzylation yielded the desired *trans*-configurated 4-deoxy-γ-rhodomycinone **133** (Scheme 23). The almost exclusive formation of the *trans*-α-hydroxy benzyl ether in the Marschalk cyclization is in good agreement with the non-chelation model as depicted in transition state IV (Scheme 16).



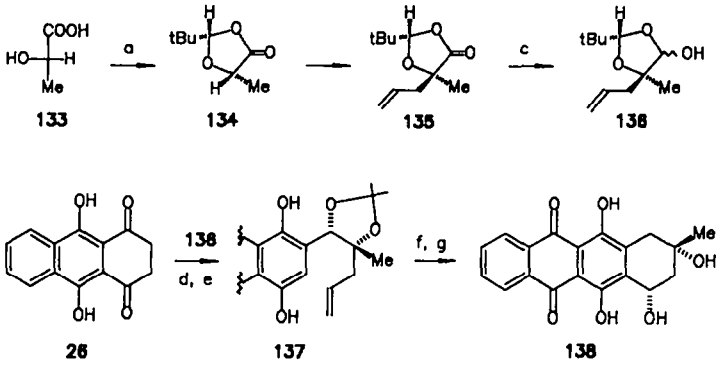
Scheme 23. Synthesis of tritylated aldehyde **129** and coupling with **26** to 4-deoxy-rhodomycinone.[149,150]
a: EtMgBr; **b**: NaH, BnBr; **c**: H^+, then $Ac_2O/BF_3 \cdot Et_2O$; **d**: $NaBH_4$; **e**: NaH, TrCl; **f**: $NaIO_4$; **g**: Marschalk reaction with **26**; **h**: CF_3COOH, **i**: DMSO-oxidation, **j**: second Marschalk reaction; **k**: debenzylation.

The Marschalk cyclization of the α-hydroxy aldehyde **131** (shown in Scheme 23) represents an example of reaction mode II (see Chart 4). The stereochemistry of the newly generated chiral centre at C-10 is effectively controlled to yield the desired *trans*-product **132**. In addition, the stereoselective *cis*-hydroxylation at C-7 can be achieved in the same manner as shown in Scheme 15 for the racemic series. The situation is different with reaction mode I (Chart 4). The benzylic hydroxy group at C-7 is generated during the cyclization step, but *cis*/*trans* mixtures are generally obtained if the tertiary hydroxyl group at C-9 is free. Blocking of this hydroxyl group as an ether or as an acetal leads predominantly to the 7,9-*cis*-diols.[76,140]

2.6.2. *α-Hydroxy acids as chiral templates.* (*S*)-Lactic acid,[140] (*S*)-malic acid[151,152] and 2-(*R*)-hydroxybutyric acid[69] have been utilized successfully in our group to synthesize feudomycinones, daunomycinones and rhodomycinones in enantiomerically pure forms. In all cases the side chains of the starting materials were incorporated into the anthracyclinones. One carbonyl group of malic acid was used to generate the acetyl side chain of the daunomycinones. With few exceptions (e.g. citramalic acid) the naturally occurring α-hydroxy acids are secondary alcohols. The chemical challenge to use these building blocks for anthracyclines consists in the conversion to tertiary alcohols without loss of chirality. In addition, the necessary functional groups for the attachment to anthraquinones have to be introduced. Fortunately, after the development of our racemic syntheses, Seebach *et al.*[153] introduced their concept of "self-reproduction of chirality", which could be adopted for our purpose to generate the tertiary alcohol of the building blocks for anthracyclinone synthesis.

(*S*)-Lactic acid (**133**) was used for the synthesis of 4-demethoxy-feudomycinone C as shown in Scheme 24.[140] Treatment of **133** with pivalaldehyde provided the *cis*-acetal **134** as the major product, which was purified by crystallization. Alkylation of **134** with allyl bromide produced compound **135** in 98% diastereomeric excess, because of the steric hindrance of the bulky *tert*-butyl group. The lactone **135** was reduced with diisobutylaluminium hydride (DIBAL-H) to the lactol **136** that was

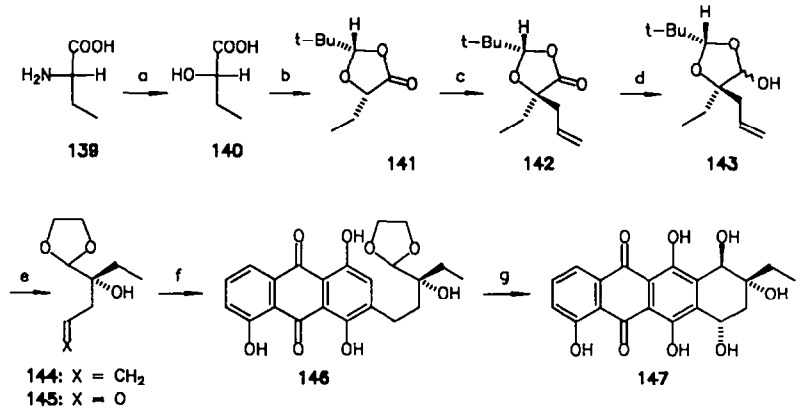
coupled with leucoquinizarin (**26**) under the conditions of Lewis[75] or Marschalk[48] to give a mixture of diols that were converted to the acetonide **137**. The masked aldehyde function of **136** could be liberated by treatment with acid but the deprotection also took place spontaneously under the reaction conditions. Ozonolysis of the olefinic acetonide **137** followed by Marschalk cyclization afforded the 7,9-*cis*-diol **138** (4-demethoxy-feudomycinone C) in 51% yield.[140] The benzylic substituent at C-10 was reductively removed in the course of the Marschalk reaction because the alkoxy group is a better leaving group than a hydroxyl group under alkaline conditions. In addition, a remarkable 7,9-*cis*-selectivity in this cyclization mode I was observed.



Scheme 24. Chiral building blocks from (*S*)-lactic acid (**133**) and conversion to 4-demethoxy-feudomycinone C (**138**).[140]

a: *t*-BuCHO, H^+; **b**: LDA, allylbromide, −20°C; **c**: DIBAL/THF, −78°C; **d**: Marschalk reaction with **136**; **e**: acetone, H^+; **f**: O_3; **g**: $Na_2S_2O_4$, then O_2.

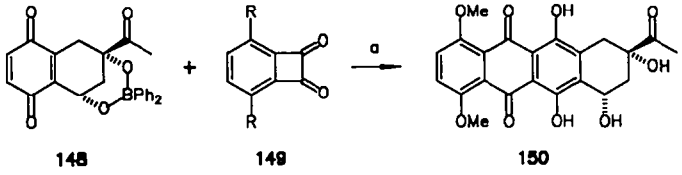
The experience with (*S*)-lactic acid showed that the Marschalk reaction[48] is a very powerful tool for attaching chiral side chains in the synthesis of optically active anthracyclinones. However, the incorporation of lactic acid derivatives gave only anthracyclinones with methyl side chains. The use of (*S*)-2-hydroxybutyric acid (**140**) gave the pharmacologically more interesting rhodomycinones with ethyl side chain [e.g. β-rhodomycinone (**147**)].[69] Since (*S*)-2-hydroxybutyric acid (**140**) is not commercially available, it was prepared from (*S*)-2-aminobutyric acid (**139**) by known procedures.[154] Acetalization with pivalaldehyde produced a mixture of *cis*- and *trans*-acetals, from which the major *cis*-acetal **141** was crystallized in pure form. Alkylation with allyl bromide gave the diastereomer **142** as the major product (de >95%), as shown in Scheme **25**. An anomeric mixture of the lactols **143** was obtained by DIBAH reduction and transacetalization with ethylene glycol converted the unstable lactols to the acetal **144** in high yield. Ozonolysis unmasked the hidden aldehyde functionality of the terminal α-double bond. In fact, the partially protected 1,4-dialdehyde **145** and the corresponding dimethylacetal (unpublished results, K. Krohn and H. Linoh) are ideal building blocks for double Marschalk reaction with anthrahydroquinones. Coupling of the aldehyde **145** with leucoquinizarin (**26**) under Marschalk conditions and subsequent transformations afforded 4-deoxyrhodomycinones.[69] However, it was known from the work of Sutherland[86,133] that a C-3 selective coupling with the unsymmetrically substituted 1,4,5-trihydroxyanthraquinone under Lewis conditions[75] was possible. This enabled the first total synthesis of enantiomerically pure β-rhodomycinone (**147**). Alkylation under Lewis conditions produced a mixture (7 : 1) of regioisomeric alkylated quinones, from which the major isomer **146** was isolated in 44% yield by crystallization. Further highly stereoselective steps similar to those used for the racemic series[72] converted **146** into the natural β-rhodomycinone (**147**). A number of optical antipodes were prepared similarly from the cheap (*R*)-aminobutyric acid *ent*-**139**.



Scheme 25. First total synthesis of (*R*)-β-rhodomycinone (**147**) by incorporation of (*S*)-2-hydroxybutyric acid.[69]

a: See ref.[154]; **b**: pivalaldehyde, H^+; **c**: LDA, allyl bromide; **d**: DIBAH/THF, −20°C; **e**: ethyleneglycol, H^+; **f**: 1,4,5-trihydroxyanthrahydroquinone, isopropanol, piperidine acetate;[75] **g**: 3 steps, compare ref.[72]

(*S*)-Malic acid was used in a similar way to synthesize the enantiomerically pure AB building block (−)-(**148**).[151] A Diels–Alder reaction was employed to couple the optically active naphthoquinone **148** in a single step with bisketenes generated photochemically from benzocyclobutadienones (**149**) (R = H, Me; OMe). The example of Scheme 26 shows the reaction to give enantiomerically pure 1-methoxy-daunomycinone (**150**).[152]



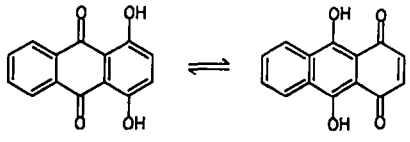
Scheme 26. Coupling of the optically active AB-fragment with bisketenes from **149** to 1-methoxy-daunomycinone.[151,152]

a: hν, deprotection.

3. NUCLEOPHILIC ADDITIONS

Examples of nucleophilic additions to anthraquinones have already been mentioned in Section 2.2. The Michael additions of α,β-unsaturated aldehydes with the quinizarin ester **51** gave the anthracyclopentane derivatives **56** and **58** (see Scheme 10). Perhaps the first observation of nucleophilic addition to anthraquinones in the context of anthracyclinone synthesis was a similar addition product with methylvinyl ketone.[67] These reactions have potential for the synthesis of 7- or 10-nor-anthracyclinones, but the biological activity of related compounds was disappointing[85,155] so the method was not developed further. All these *intra*molecular additions occurred with quinizarin structures with phenolic hydroxyl groups at C-1 and C-4. Later investigations confirmed that nucleophilic additions to quinizarin type molecules are particularly easy: they also occur in *inter*-molecular fashion. This behaviour can be rationalized by tautomerization of **151a** to **151b** with an external quinone function, as depicted in Scheme 27. The equilibrium is certainly strongly shifted towards **151a**, but the possibility of Diels–Alder reactions with quinizarin boroacetate demonstrates

the existence of such tautomers.[156] Thus, nucleophilic additions to **151** may be understood mechanistically as Michael additions to the tautomeric quinone **151b** with simultaneous conversion to the hydroquinone state. However, nucleophilic additions can also occur with anthraquinones lacking the 1,4-dihydroxy-arrangement of quinizarin. Only *intra*molecular versions are known with these anthraquinones and vigorous reaction conditions or additional activation by electron withdrawing substituents are often necessary to promote cyclization.

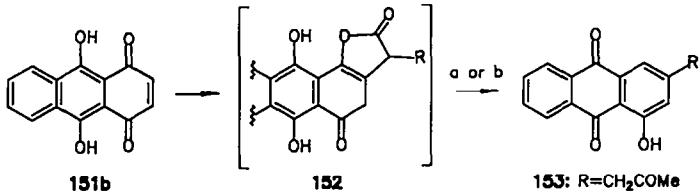


151a **151b**

Scheme 27. Tautomeric forms of quinizarin **151**.

3.1. *Intermolecular additions to quinizarin systems*

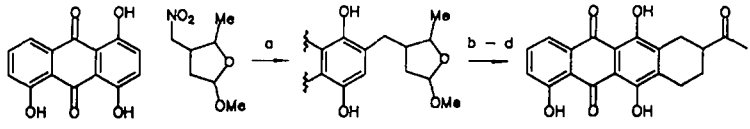
Sutherland and Towers[84] observed the unexpected formation of the deoxygenated adduct **153** in the reaction of quinizarin **151** with a five-fold excess of sodium methoxide and a ten-fold excess of ethyl acetoacetate in boiling methanol. The reaction can be understood mechanistically as a Michael addition of the acetoacetate anion to **151b**, lactonization to the intermediate **152** and elimination with regeneration of the quinone followed by decarboxylation to **153** (Scheme 28). We found a similar conversion to the ester **154** which is an interesting precursor of aklavinone,[157] by substituting malonate for acetoacetate.[56] The deoxygenation in this formal *cine*-substitution is surprising but not without precedence when anthrahydroquinones are involved.[40,42]



151b **152** **153**: R=CH_2COMe **154**: R=CH_2CO_2Me

Scheme 28. Nucleophilic *cine*-substitution of quinizarin with acetoacetate or malonate.[56,84]
a: acetoacetate, MeOH, MeONa, reflux; **b**: malonate, MeOH, MeONa, reflux.

Other stabilized carbanions derived from acetylacetone or nitro compounds have also been added intermolecularly to anthraquinones.[84] A sophisticated combination of a nucleophilic addition and a Marschalk reaction elaborated by Sutherland *et al.*[158,159] led to a regiospecific synthesis of 7,9-bisdeoxycarminomycinone (**158**) as shown in Scheme 29. The anion of the nitro compound **156**



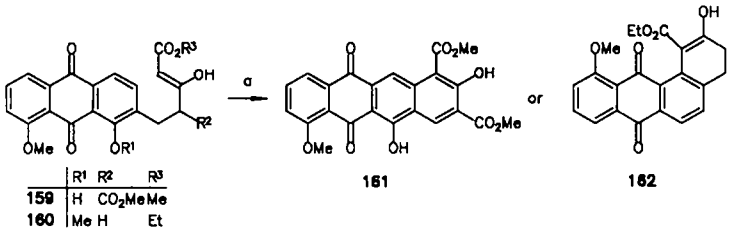
155 **156** **157** **158**

Scheme 29. Combination of nitronate addition and Marschalk reaction in the synthesis of **158**.[158,159]
a: MeONa, MeOH, reflux (67%); **b**: 1 N HCl; **c**: NaOH, $Na_2S_2O_4$, 90°C; **d**: PCC (56% overall).

(prepared in five steps from ethyl laevulinate) added regiospecifically to 5-hydroxy-quinizarin **155** to afford the adduct **157**. Acidic cleavage of the cyclic acetal liberated the aldehyde function that was used in the subsequent Marschalk cyclization. Oxidation of the Marschalk product afforded the ketone **158**.

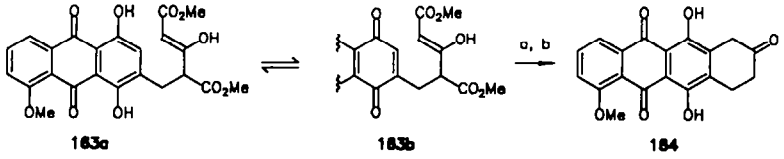
3.2. *Intramolecular nucleophilic additions to anthraquinones*

An instructive example of the different reactivity of quinizarin and chrysazine derivatives to nucleophilic reaction is shown in Scheme 30.[160] The acetonedicarboxylic ester **159** was cyclized by treatment with sodium hydride in DMF at 80°C to the napthacene **161**. The primary cyclization product was completely aromatized under the drastic basic reaction conditions. Dihydronaphthacenes (in this case as enolate intermediates) are generally dehydrated in the presence of strong bases, even in the absence of oxygen. This can be mechanistically understood by deprotonation of the benzylic position and isomerization to a naphthacenhydroquinone anion followed by rapid oxidation on workup to a naphthacenequinone. Another interesting reaction related to this kind of cyclization was the formation of an angularly condensed product **162** starting from the corresponding methyl ether **160**.[160] We are currently investigating this new reaction for the total synthesis of angucycline antibiotics.



Scheme 30. Cyclization of chrysazine ketoesters to linearly or angularly condensed systems.[160]
a: NaH, DMF, 3 h, 80°C.

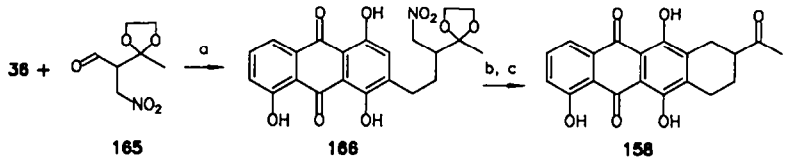
The corresponding quinizarin analogue to **159** behaved quite differently and provided a very short regioselective route to the important intermediate **164**, used in the early daunomycinone total synthesis of Kende.[161] Potassium carbonate/crown ether in THF at room temperature was sufficient to induce the cyclization of **163**. The ease of the addition may again be explained by a tautomeric equilibrium of **163a** and **163b** as shown in Scheme 31.[162] Stronger base or higher reaction temperatures led to rapid aromatization but acidic saponification and decarboxylation afforded the ketone **164** in 54% overall yield.



Scheme 31. Synthesis of the daunomycinone precursor **164** by nucleophilic cyclization of **163**.[162]
a: K_2CO_3, 18-crown-6, 20°C (>70%); **b**: $AcOH/H_2O/H_2SO_4$, 90°C, 5 h (77%).

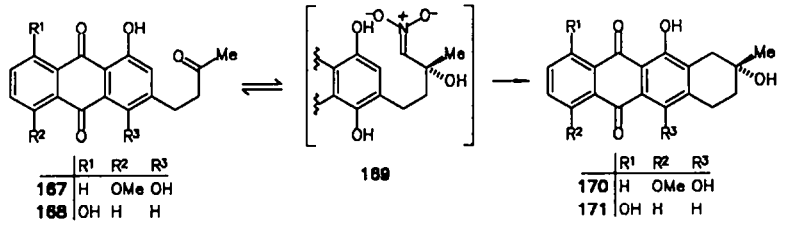
An intramolecular nitronate addition was used in a second synthesis of 7,9-bisdeoxycarminomycinone (**158**) by Sutherland *et al.* (Scheme 32).[159,163] The sequence of Marschalk and nucleophilic addition was reversed and the Lewis conditions[75] were used to condense the aldehyde

165 with **36** to afford a 5:1 mixture of adducts (66%). Crystallization gave the pure regioisomer **166** (40% yield) and the usual conditions for nitronate addition afforded a tetracyclic ketal that was cleaved to the known ketone **158**. Regioselectivity in the first alkylation step is not as high as in the nitronate addition shown in Scheme 29, but the reaction sequence is two steps shorter than in the first synthesis. It must be noted that in both reactions the nitro group is eliminated from an intermediate hydroquinone adduct. In principle, this reaction is related to the reductive removal of benzylic hydroxyl groups in the Marschalk reaction.



Scheme 32. 7,9-Bisdeoxycarminomycinone (**158**) via intramolecular nitronate addition.[159,163]
a: Isopropanol, piperidinium acetate, reflux[75]; **b**: MeONa, MeOH, reflux (85%); **c**: CF_3COOH/H_2O (95%).

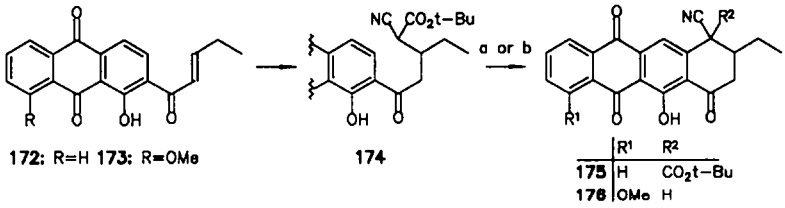
A limitation of the syntheses of Sutherland *et al.*[159] is the missing hydroxy group at C-9 in the cyclization product **150**. A subsequent hydroxylation of this position is only possible with the activating acetyl side chain present only in the daunomycinone family. We have used a transient nitronate **169** in a one-step anthracyclinone synthesis with a hydroxy group at C-9 and alkyl side chains (Scheme 33)[164] starting from readily available 3-oxoalkylanthraquinones such as **167** or **168**. These precursors had already been used previously in our α-hydroxy aldehyde Marschalk cyclizations (see Scheme 15). The missing C-10-carbon atom for the conversion to anthracyclinones was introduced by reaction with nitromethane and sodium methanolate in boiling methanol. The intermediate and presumably reversibly formed nitronate adduct **169** adds in the usual Michael addition followed by elimination of a nitrite anion to afford the anthracyclinones **170** and **171** in 81% yield. The one step cyclization is generally applicable with a variety of 1,4-dihydroxy anthraquinones. Compounds without a hydroxy group *ortho* to the side (e.g. **171**) react equally well, but the presence of the phenolic group in the *meta* position seems to be necessary.[164]



Scheme 33. One step nitronate cyclization to anthracyclinones.[164]
a: CH_3NO_2, MeOH, MeONa, 1–2d reflux (81%).

Aklavinone analogues derived from chrysazine were prepared by Cava *et al.*[35,165,166] Ring B of the future anthracyclinone has only one hydroxy group and no tautomerism such as shown in Scheme 27 is possible. However, an additional electron withdrawing benzylic carbonyl group in **172** and **173** facilitates the double Michael addition sequence shown in Scheme 34. The unsaturated ketones were prepared from chrysazine, involving Claisen rearrangements. The first Michael addition of **172** with *tert*-butyl cyanoacetate occurs more rapidly than addition to the anthraquinone

nucleus and the intermediate open chain adduct **174** can be isolated after short reaction times. Prolonged reaction in DMSO provides the tetracyclic cyanoester **175** in 67% yield.[35,165] The *tert*-butyl ester group can be removed by acidic cleavage and decarboxylation. However, the sequence to the cyanide **176** could be shortened by reaction of **173** with phenylthio acetonitrile, the phenyl sulphide anion being eliminated.[35,166]



Scheme 34. Aklavinone analogues via double Michael addition to **172** and **173**.[166]

a: $NCCH_2CO_2t$-Bu, DMF, NaH, 1 h (53%); **b**: $NCCH_2CO_2t$-Bu, NaH, DMSO, 2.5 h (67%); **c**: $PHCH_2CN$, NaH, DMSO, 1 h (83%).

4. CONCLUDING REMARKS

Diels–Alder reactions have predominated in the condensation of different fragments in the synthesis of daunomycinone type anthracyclinones.[28,30] With few exceptions the synthesis of enantiomerically pure derivatives was achieved by anionic condensation with chiral AB fragments.[29] In contrast, the best methods discovered only recently for the preparation of optically active rhodomycinones involve the incorporation of chiral aldehydes using the Marschalk reaction with anthraquinones. Natural products (and also derivatives not occurring naturally) with a wide variety of substituents can thus be prepared in optically pure form. The Marschalk reaction also proved very useful in the preparation of anthraquinone ketoesters which are excellent precursors for racemic anthracyclinones with an ester group at C-10. However, the ketoester cyclization still lacks enantioselectivity.

The nucleophilic additions to anthraquinones have introduced, preparatively and also mechanistically, interesting new aspects into anthraquinone chemistry. However, no complete and only two formal total syntheses have been published using this methodology. This may change in the future.

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