Biomimetic Synthesis of Deca- and Dodecaketide-Derived Quinone Antibiotics

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Two ketide side chains are positioned in vicinal position on a planar aromatic or quinoid core in the biomimetic-type synthesis of ketide-derived quinone antibiotics, described in this article. The close proximity of electrophilic and nucleophilic sites in the side chains restricts the large number of theoretically possible non-enzymatic aldol reactions of the lateral ketide chains during the cyclization. Usually only two cyclization modes are observed: the "linear" or "angular" fashion. An anthraquinone core serves both in the synthesis of the linearly condensed anthracyclinones and the angularly arranged benzo[*a*]naphthacenequinones. Naphthalenes or naphthoquinones are best suited for the construction of angucyclinones. An advantage of the biomimetic approach to polyketide antibiotics is that all functional groups are "automatically" positioned correctly on the hydroaromatic part. In addition, this approach allows a great flexibility in the kind and location of substituents on the aromatic core.

Introduction

The term "biomimetic" is used in different contexts and meanings in the chemical literature, and so it is reasonable to analyze how the term is used in a representative number of recent journal articles.

There are 171 hits produced for the search term "biomimetic" in the combined 1994−2000 electronic file of ChemInform.[1] The term is used in quite different ways, ranging from "biomimetic transformations",[2] "biomimetic oxidations",[3] or "biomimetic catalysis",[4] etc. to descriptions designating relationships with biological processes, as expressed in, for instance, the title "Biomimetic Chemistry of Nickel".[5]

The combined search terms "Biomimetic" and "Synthesis" produced 31 hits.

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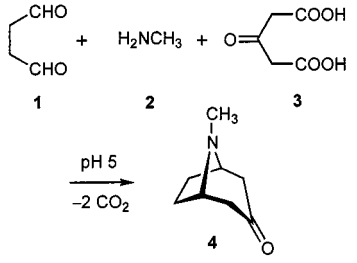
Two different aspects are usually connected with the term. One relates to mild "physiological" reaction conditions. The other, more frequently used in recent publications, involves the relating of synthetic strategies to the pathways of biosynthesis. The nature of that relating may be close to putative or experimentally established biosynthesis, or it may be less so, and analysis of the relevant publications reveals that the authors make rather liberal use of the term. The term "biomimetic" is used in this sense throughout this personal review on polyketide-derived quinone antibiotics.

A few selected examples (see also ref.[6]) may give an idea of how the term "biomimetic" has been used in syntheses that have played an important role in the history of natural products. A classical example from the field of alkaloid synthesis is the combination at ambient temperature and pH = 5 of the simple starting materials succinaldehyde (**1**), methylamine (**2**), and acetonedicarboxylic acid (**3**) to yield tropinone (**4**) (Scheme 1). The reaction, first investigated by Robinson[7] and later improved by Schöpf and Lehmann[8]

Karsten Krohn was born in 1944 and graduated from the university of Kiel in 1968. He obtained his PhD in 1971 under the supervision of Professor A. Mondon with a thesis on the isolation and synthesis of alkaloids (narciclasin and lycoricidin) from daffodils. He spent his postdoctoral work first with Professor Mondon and then with Professor Winterfeldt as a DFG stipendiary, working on the synthesis of camptothecin. In 1975 he moved to the University of Hamburg, where he started his work on quinone antibiotics (in particular the anthracyclines) and achieved his Habilitation in 1979. He became Associate Professor at the Technical University of Braunschweig in 1981 and Full Professor in 1991 at the Universität−Gesamthochschule in Paderborn. In 1984 he was Visiting Professor in Madison, Wisconsin and in 1996 in Nancy (France). His research interests are in the isolation and synthesis of natural products, synthesis of quinone antibiotics (anthracyclines, angucyclines), and the chemistry of sugars (C-glycosides, O-glycosides, conversion of sugars into useful chiral building blocks).

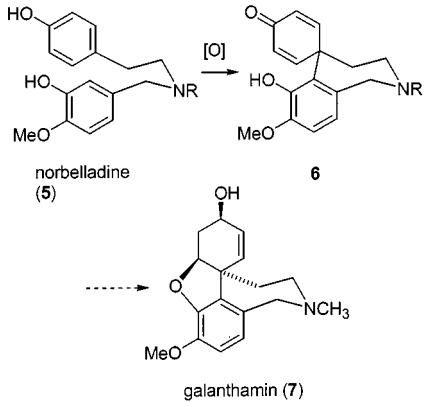
MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

by use of a buffered solution at ambient temperature, is also an early example of the multi-component reactions that play an eminent role in modern combinatorial chemistry. It is the textbook example of reactions that occur at nearly "physiological" conditions. However, it is less appropriate for a demonstration of the relating of synthetic strategies to the pathway of the compound's biosynthesis, which starts from ornithine and arginine, with *N*-methylpyrrolidine as an intermediate.[9]



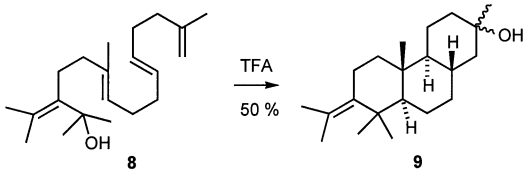
Scheme 1. "Biomimetic" synthesis of tropinone (**4**) by Robinson[7] and Schöpf[8]

Another prominent example from alkaloid chemistry is Barton's pioneering biomimetic synthesis of galanthamine (**7**)[10] (Scheme 2). In the key step, norbelladine (**5**) is cyclized by a phenol coupling reaction to afford the cyclodienone derivative **6** (see reviews on biomimetic alkaloid synthesis[11–13] and phenol oxidation[14,15]).



Scheme 2. Biomimetic synthesis of galanthamine (**7**) by phenol oxidation[10]

Biomimetic polyalkene cyclizations have found numerous applications in the synthesis of terpenoids and steroids (see review[16]). In 1955, Stork[17] and Eschenmoser[18] independently published the hypothesis that polyalkenes react in defined conformations, which should allow the relative stereochemistry of the cyclization products to be predicted. Thus, the stereochemistry of the starting materials [(*E*) or (*Z*) double bonds] is transferred to the cyclization products. This is an extremely important prerequisite for the feasibility of biomimetic chemical synthesis, as the stereochemical outcome of the cyclizations thus does not depend entirely on pre-folding of the substrate in the active sites of the enzymes. (This general problem of reaction at specific sites in solution chemistry, in contrast to enzyme-catalyzed transformations, has been addressed by Breslow and coworkers.[19,20] One of the solutions proposed by this group is the strategy of specific tethers.) In biomimetic polyalkene cyclizations, appropriate initiating groups (easily transformable into reactive cations), terminating sites, and the synthesis of stereochemically defined (*E*) or (*Z*) double bonds had to be achieved in the laboratory. This was achieved in the pioneering work of Johnson (see reviews[21,22]). One simple example from the Johnson group is shown in Scheme 3; the three six-membered rings of the terpenoid **9** are formed simultaneously in 50% yield by treatment of the polyolefin **8** with trifluoroacetic acid.



Scheme 3. Acid-catalyzed biomimetic polyalkene cyclization of **8** to terpenoid **9**[23]

In the context of polyenes, mention must be made of the outstanding biomimetic synthesis of prostaglandins by Corey et al.,[24] involving hydroperoxides and endoperoxides of unsaturated fatty acids. These few examples may suffice to introduce the reader to the specific features of biomimetic synthesis; for other important classes of biomimetic natural product synthesis, see reviews on porphyrinoids,[25] alkaloids,[11,12,26,27] pericyclic key reactions,[28] and polycyclic ether natural products.[29]

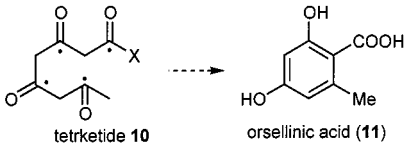
In the following sections, deca- and dodecaketide-derived biomimetic-type syntheses of quinone antibiotics developed in our laboratory are described.

Aromatic Biomimetic Polyketide Synthesis

The reactive thioester acetyl CoA and its carboxylation product malonyl CoA are the pivotal starting materials both for primary and for secondary metabolism. Fatty acids, for example, are formed by linear conjoining of this C_2 repeating unit (see review[30]). If reduction and subsequent elimination of the β-oxo esters are disregarded, the result is hypothetical highly reactive oligomeric β-oxo esters, which are processed to the aromatic polyketides by Polyketide Synthetase complex II (PKS II). The important macrolide antibiotics are products of the PKS I complex, with occasional incorporation of other fatty acids (e.g., methylmalonyl CoA) such as propionate (for the discovery of new polyketide pathways in plants, see ref.[31] and in bacteria, see ref.[32]).

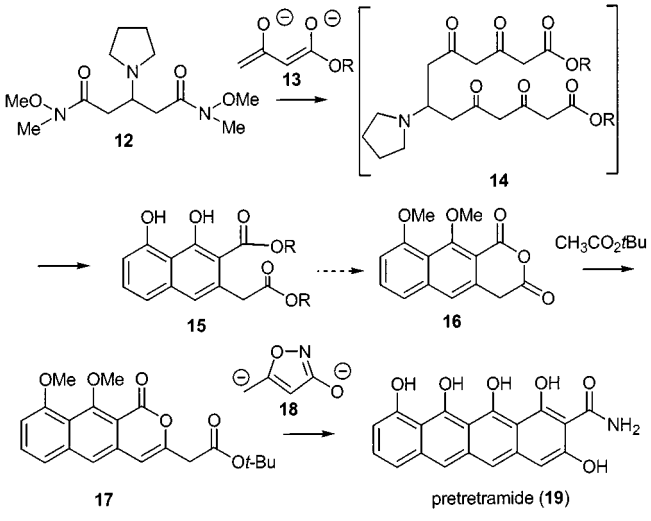
The repeating [CH_2–CO] unit in many natural products was recognized as early as 1907 by Collie,[33] but polyketide origination in its present form was postulated later, by Birch.[34] It involves appropriate folding and condensation, mostly to six-membered ring systems, and very often in-

cluding aromatic and chiral nonaromatic parts. The simplest example is the biosynthesis of orsellinic acid (**11**) from the tetraketide **10**, as shown in Scheme 4 (see reviews on polyketide biosynthesis[35,36]).



Scheme 4. Biosynthesis of orsellinic acid

The "mimicking" of polyketide biosynthesis through the use of synthetic oligoketides and their derivatives was pioneered by Harris and co-workers[37] and later extended by Yamaguchi's group[38] and others. The biomimetic synthesis of the simple naturally occurring anthraquinones emodine[39] or chrysophanol[40] became textbook examples of biomimetic synthesis. The principles are demonstrated in Scheme 5, with the biomimetic pretetramide synthesis,[41,42] a recent example more closely related to our work. The bis(*N*-methoxy-*N*-methylamide) **12**, with two highly reactive electrophilic sites, was treated with 2 equiv. of the acetoacetate dianion **13** to yield the symmetric heptaketide intermediate **14**. The molecule is depicted in such a way as to convey the desired Claisen and aldol condensations (accompanied by the elimination of pyrrolidine) to form the naphthalenediol **15**. It is important to note that the pyrrolidine residue was positioned in such a fashion as to direct the outcome of the cyclization to the desired naphthalene. The elimination removes the "corner" phenolic hydroxy group present in − for instance − emodine. To preserve this hydroxy group, a ketal group had to be placed at that position.[39]



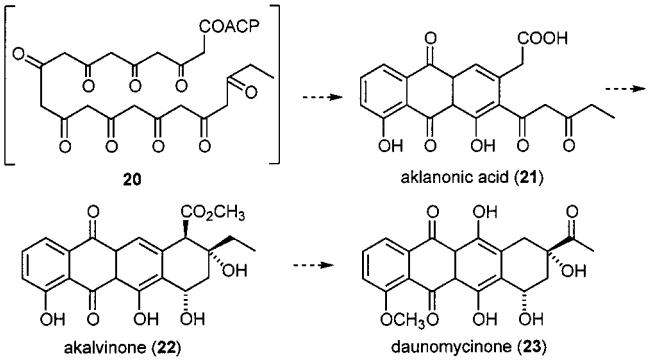
Scheme 5. Biomimetic synthesis of pretetramide (**19**)[41,42]

The next steps in the synthesis of **19** involved its transformation into the dimethoxy anhydride **16**. In this molecule, the "aliphatic" ester is more reactive, and the "bottom" chain is extended upon reaction with the acetic ester anion to form **17**. The heterocyclic dianion **18** proved to be a good choice for extension of the "top" chain. Further condensation and processing then provided pretetramide (**19**).

Biomimetic Synthesis of Anthracyclines

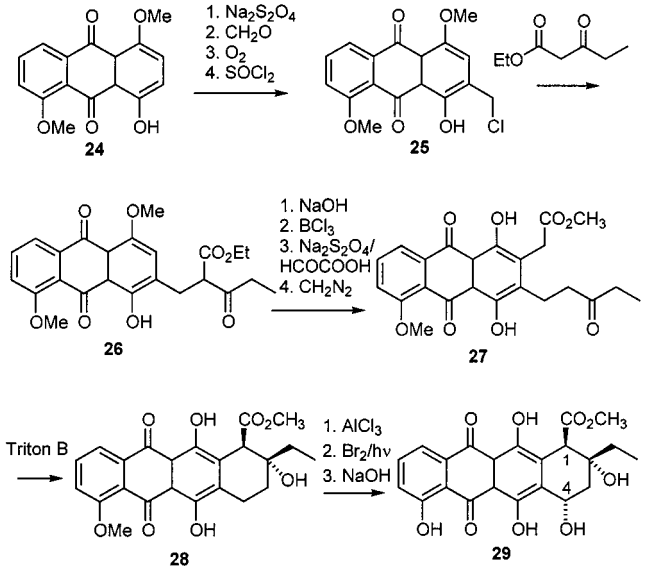
In the adroit work of Harris et al., a naphthalene core with two functions for chain extension was constructed from simple open-chain polyketides. In our work, related to biomimetic synthesis in the anthracycline and angucycline series, we have often used an approach less closely related to biosynthesis in the first steps, by using preformed aromatic cores. This has allowed more flexibility in the placement of substituents on the core, and also in the synthesis of non-naturally occurring substitution patterns. In contrast to the biomimetic emodine or pretetramide syntheses, our work has focussed on the construction of *nonaromatic* rings attached to the aromatic/quinoid nucleus. Thus, the emphasis has been on the stereoselective construction of substituted cyclohexane rings in the last biomimetic-type aldol reactions. En route to the precursor oligoketides, carefully tuned reactions have had to be used for ketide chain extension to prevent prior unwanted condensations and to direct the desired mode of cyclization (such as linear versus angular, vide infra).

The first early examples were the biomimetic-type syntheses of anthracyclines of the rhodomycinone or aklavinone types, the biosynthetic precursors of the well-known antitumor antibiotics daunorubicin (**23**) and doxorubicin. A few important steps of the biosynthesis, regarding only the aglycone part of the molecules, are shown in Scheme 6 (see reviews[43,44]). The first isolable intermediate from the putative decaketide **20** is aklanonic acid **21**. Interestingly, with this compound, a partially cyclized intermediate could be isolated from certain mutants, and this could be microbially converted into cinerubin by *Streptomyces galilaeus*.[45] Trisaccharides of aklavinone (**22**), the aklacinomycins, have been used as anticancer drugs in Japan as so-called second-generation anthracycline antibiotics.[46]



Scheme 6. Some late steps in biosynthesis of anthracyclines antibiotics[44]

Our general strategy was based on the use of preformed anthraquinones as the starting materials for anthracycline synthesis. Three of the four linearly condensed rings of the anthracyclines are already assembled in the anthraquinone part. For successful transformation into ε-rhodomycinone (**29**) and related compounds, however, the problem of regioselective attachment of the appropriate side chains in vicinal positions had to be solved. Two solutions to this important problem of regioselectivity have been published, both making use of 1-hydroxy-4,5-dimethoxy-9,10-anthraquinone (**24**) as a key intermediate.[47−49] Selective attachment of different side chains onto **24** was possible by use of the Marschalk reaction.[50] French chemists developed a very elegant method for the alkylation of the very unreactive anthraquinones, and this found widespread application in anthracycline chemistry.[51] The inert, electron-deficient anthraquinones are first reduced to the corresponding highly nucleophilic hydroquinones, which are treated with aldehydes as the electrophiles to afford specific alkylation at the position *ortho* to the phenolic group. Reaction at higher temperatures results in elimination of a hydroxy group through an intramolecular redox process,[50] while at low temperatures the initially formed hydroxyalkyl products can be isolated.[52,53] Both versions are useful in anthracycline synthesis, as demonstrated in Scheme 7 for ε-rhodomycinone (**29**).[54] The leuko form of **24** was prepared by sodium dithionite reduction; treatment of the dihydroquinone with formaldehyde gave the hydroxymethylation product, which was chlorinated with thionyl chloride to provide **25**. Alkylation of 3-oxovaleric ester with **25** then afforded oxo ester **26**. Decarboxylation and ether cleavage of **26** gave a bis(phenol), which was subjected to a second Marschalk reaction to yield the oxo ester **27** after methylation with diazomethane. In this case, the initially obtained benzylic hydroxy group was removed thermally in the intramolecular redox reaction.

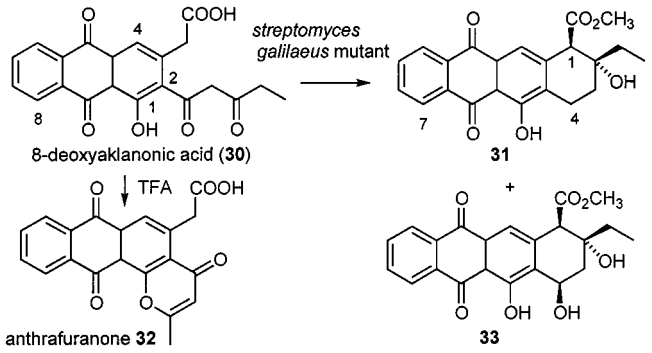


Scheme 7. ε-Rhodomycinone (**29**) synthesis using the Marschalk reaction[54]

The biomimetic-type cyclization of oxo ester **27** to yield 4-deoxy-ε-rhodomycinone (**28**) could be effected by treatment with simple bases. Stirring a solution of **27** with Triton B in protic solvents stereoselectively gave the *trans*-hydroxy ester **28**. The corresponding *cis*-ester was obtained by the use of lithium amides in an aprotic solvent such as THF. Separable diastereomers were isolated by use of chiral menthol esters, but the degree of asymmetric induction was very low. The benzylic hydroxy group at C-4, originating from a polyketide oxygen atom, was introduced by bromination and displacement of the bromine atom by a hydroxy group. The deoxyamino sugars, essential for the antitumor activity of the anthracycline antibiotics, are usually attached to the C-4 hydroxy group of the aglycones. The introduction of the 4-hydroxy group was highly stereoselective, because the incoming hydroxy was directed by neighboring group participation by the hydroxy group at C-2. In addition to the rhodomycinones, many non-natural[55,56] − and also natural − anthracyclinones with an ester group at C-1 − such as aklavinone,[57−63] auramycinone derivatives,[56,64] feudomycinones,[65] and nogalamycinones[66] − have been prepared by employment of this biomimetic-type oxo ester cyclization as outlined in Scheme 7.

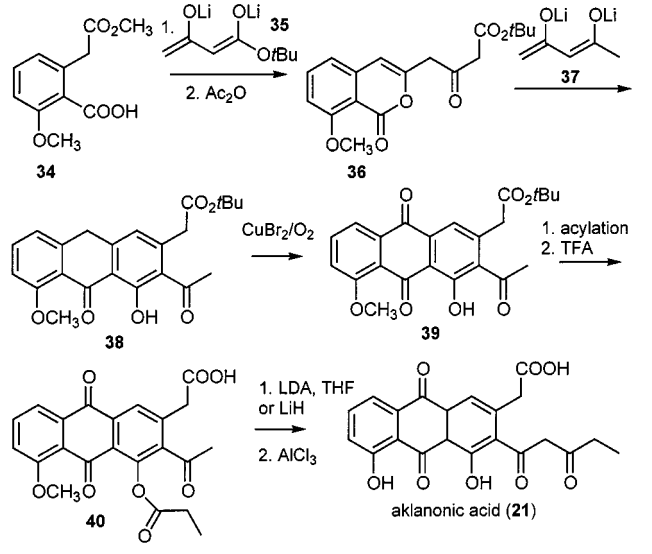
No enantioselective version with chiral esters or bases as the catalyst had yet succeeded, though. However, Kishi and co-workers found a solution to the problem, placing an alkoxy group at the benzylic position by starting from a precursor with an enantiomerically pure chiral acetal group at that position.[67,68] As mentioned above, it was shown by researchers in Jena that aklanonic acid (**21**) was converted into anthracyclines by the enzyme system present in *Streptomyces* mutants.[45] We wondered whether closely related but non-natural analogues could also be cyclized in an enantioselective manner by the enzyme system of the microorganism. For that purpose we prepared 4-deoxyaklanonic acid (**30**)[69,70] and incubated that compound in a fermentation broth of a *Streptomyces galilaeus* mutant strain.[71] In fact, this achiral non-natural precursor **30** was converted in good yield (56%) into 4,7-deoxyaklavinone (**31**) and smaller amounts of 4-epi-7-deoxyaklavinone (**33**) (Scheme 8). Not surprisingly, both compounds were produced in enantiomerically pure form, verified by HPLC analysis on a chiral column (racemic material was available for comparison[56]). This experiment can also be viewed as an early example of target-directed biosynthesis. In addition, phenolic anthraquinones with a dicarbonyl side chain, as in 8-deoxyaklanonic acid (**30**), can undergo cyclization involving the phenolic hydroxy group to yield anthrafuranone antibiotics such as **32** (pluramycines[72,73]) through the use of trifluoroacetic acid.[74]

The synthesis of aklanonic acid[70,71] is instructive, as it uses some of the dianion chemistry introduced to biomimetic polyketide synthesis by Harris in combination with the Baker−Venkataraman rearrangement[75,76] for ketide chain extension (Scheme 9). The Baker−Venkataraman rearrangement is an *intra*molecular acyl transfer to the neighboring acetyl group, as exemplified in the transformation of **40** into **21** in Scheme 9. In the synthesis, the



Scheme 8. Enantioselective cyclization of 4,7-deoxyaklavinone (**31**) by a *Streptomyces galilaeus* mutant strain[71]

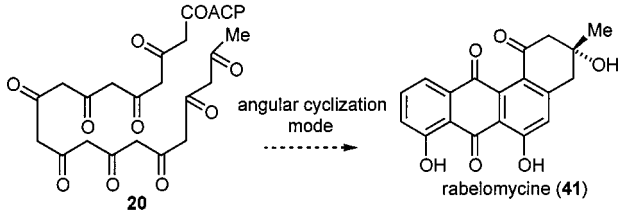
homophthalate half-ester **34** was treated with the dianion of acetoacetate **35** to yield the isocoumarin **36**. Attack of the acetylacetone dianion **37** on the lactone group of **36** afforded anthrone **38** in a one-pot multistep reaction. Air oxidation in the presence of catalytic amounts of copper bromide gave the anthraquinone oxo ester **39**, which was acylated with propionyl chloride, and that ester was then cleaved with trifluoroacetic acid to provide **40**. Baker–Venkataraman intramolecular acylation gave good yields of the chain-extended product aklanonic acid (**21**) after cleavage of the methyl ether. The Baker–Venkataraman reaction had to be conducted at the acid stage to prevent unwanted cyclization. The same reaction was also useful in some of the biomimetic-type angucyclinone syntheses described in the next section.



Scheme 9. Synthesis of aklanonic acid using the Baker–Venkataraman reaction[70]

Biomimetic-Type Angucyclinone Syntheses

In the previous section, examples of the linear cyclization mode, giving rise to the anthracycline antibiotics, were presented. In addition to condensation to linearly arranged systems, angular folding gives rise to the "angucyclines", a suitable name coined by Zeeck and Rohr[77] for a large group of recently discovered antibiotics.[78,79] The cyclization mode producing the angucyclinone rabelomycin (**41**) is shown in Scheme 10. In the angucycline series, no partially cyclized intermediates corresponding to aklanonic acid (**21**) in the linear anthracyclines are known.

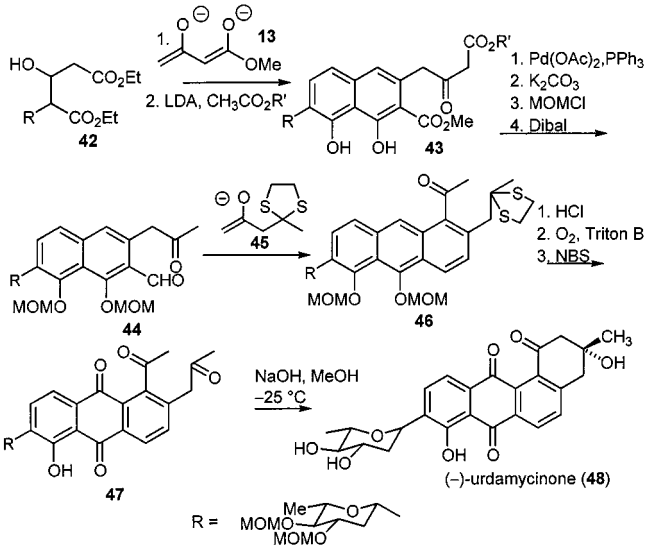


Scheme 10. Angular cyclization mode of dekaketide **21** to afford rabelomycin (**41**)[78]

A wide range of linearly and angularly condensed polycyclic aromatic ketide derivatives was prepared by Yamaguchi and co-workers, as compiled in their review.[38] The authors extensively used the condensation of esters with the acetoacetate dianion (Weiler reaction). The biomimetic-type synthesis of (−)-urdamycinone B (**48**) by polyketide condensation, shown in Scheme 11, is particularly noteworthy.[80] On the basis of their earlier investigations on biomimetic-type condensations of dianions to afford aromatic systems,[81] they prepared the naphthalenediol **43** by successive condensation of glutaric ester **42** with the acetoacetate and acetate anions. The aldehyde **46** was then prepared by a sequence of palladium-catalyzed dealkoxydecarbonylation, base-catalyzed ring-closure, protection as a MOM ether, and DIBAL reduction. An important step was the chain-extension of the aldehyde with lithiated acetylacetone monothioacetal (**45**). The intermediate diketoalcohol spontaneously cyclized with concomitant elimination and aromatization to **46**. The dithioacetal protecting group prevented further uncontrolled cyclization steps. Acid-catalyzed deprotection, base-catalyzed oxidation with air to the anthraquinone, and removal of the dithiane protecting group then generated the crucial dioxo intermediate **47**. Base-catalyzed cyclization afforded the non-natural (−)-urdamycinone B (**48**) (34%), together with the diastereomer (37%) (Scheme 11). Thus, no asymmetric induction by the remote sugar on the newly formed chiral center at C-3 could be observed.

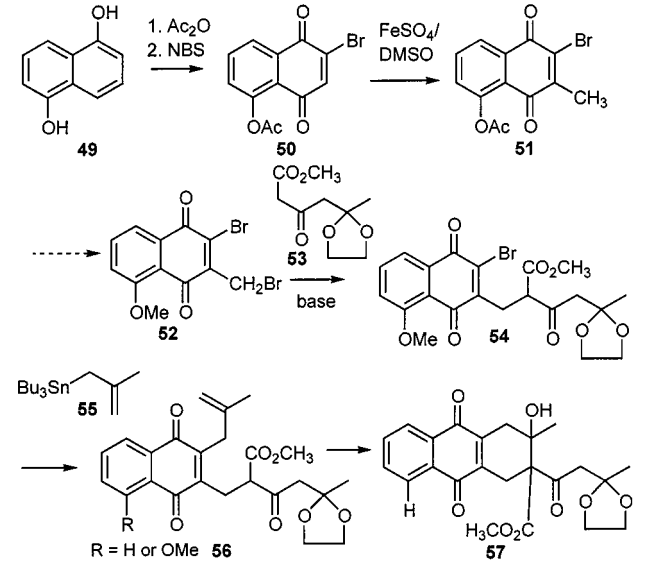
The example shows that the nucleophilic centers have to be correctly opposed to corresponding electrophilic carbonyl groups. In compound **47**, the acidity of the hydrogen atoms on the acetyl group directly attached to the anthraquinone core is certainly much higher than that of those in the "bottom" side chain. This is not necessarily the case if the ring is not aromatic, in which case a cyclization product of different regiochemistry might result (see below).

In our work we decided to construct the naphthalene core by a different route. The naphthoquinone dibromide starting material **52** can easily be prepared from 1,5-dihydroxynaphthalene (**49**), followed by acetylation and bromination to give 5-acetoxy-2-bromo-1,4-naphthoquinone



Scheme 11. Biomimetic-type synthesis of (−)-urdamycinone B (**48**)[80]

(**50**)[83] (Scheme 12). Radical methylation with dimethyl sulfoxide, catalyzed by Fenton's reagent, gave the methylation product **51** in 62% yield.[83] Ester cleavage and methylation, followed by NBS bromination, then afforded the dibromide **52** (compare ref.[84]). The vinylic bromide serves two purposes; it sterically prevents unwanted premature Michael addition of the oxo ester to the quinone double bond and it activates the vinylic position for the attachment of the second side chain (see below).



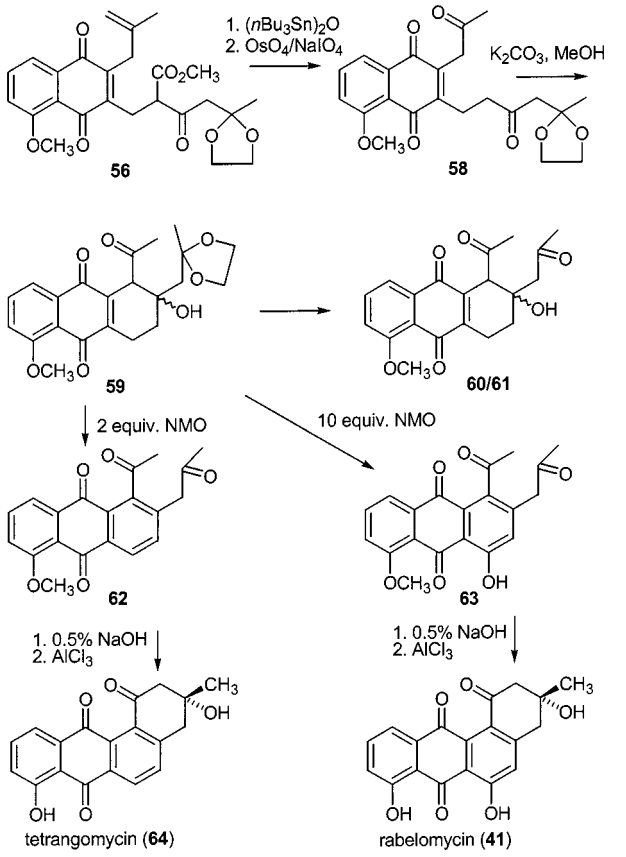
Scheme 12. Attachment of two side chains on the 1,4-naphthoquinone core and linear cyclization of oxo ester **57**[85]

The attachment of a C_5 side chain at the intended benzylic position by S_N2 alkylation with the protected oxo ester **53** as the nucleophile proceeded reliably and in good yields to form the alkylated oxo ester **54**.[85] The second chain could be coupled very efficiently by treatment of the vinylic bromide **54** with the allyltin compound **55** in a palladium-catalyzed Stille reaction[86] (see review[87]) to afford the dialkylated naphthoquinone **56**. Halonaphthoquinones had previously been coupled in a palladium/copper-catalyzed reaction by Echavarren et al.[88]

The reaction sequence was also conducted with other substituents on the naphthoquinone ring (OMe in **52** replaced by OH or H, for example). The next step in our synthetic plan was the cleavage of the double bond in the side chain. Ozonolysis gave irreproducible results, but the Lemieux-Johnson reaction ($OsO_4/NaIO_4$) cleaved the double bond of the side chain without affecting the quinone. The ester **56** was a good model with which to study the cyclization mode. On treatment with the Lemieux-Johnson reagent, direct conversion into the linearly condensed system **57** (R = H) was observed. Evidently, the highly acidic position of the β-oxo ester immediately adds to the electrophilic carbonyl group generated by double bond cleavage in the opposite side chain.[85] To induce an angular cyclization mode, the ester group responsible for the high C−H acidity had to be removed first.

Methoxydecarbonylation of **56** [the reaction was also conducted with related derivatives (R in **56**: H, OMe, OH)] under neutral conditions with bis(*n*-tributyltin) oxide[89] gave the protected triketone **58**. Subjection of **58** to treatment with a very mild base (K_2CO_3 in methanol) resulted in a mixture of the inseparable *cis* and *trans* cyclization products **59**. Clean cleavage of the ketal in **59** furnished the expected two stereoisomeric aldol products **60** and **61** (one in crystalline form), in which ring B of the angucycline was established and the substituents were positioned so as to form the angularly condensed ring A (Scheme 13).[85]

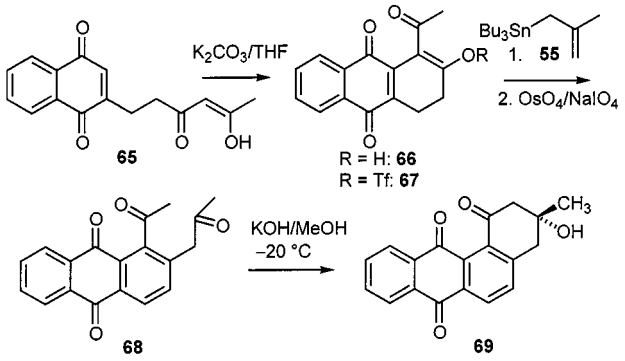
With the primary cyclization products **60/61** in hand, the cyclization to produce ring A of the angucyclines was next investigated. In principle, aldol reaction of these intermediates should directly yield products of the SF-2315 angucycline type. However, we were initially unable to cyclize these hydroaromatic precursors. Cyclization should be easier, as demonstrated by Yamaguchi et al.,[80] if the side chains are attached to a flat aromatic ring in which the reactive centers of the chains are forced to be much closer together, in addition to the increased C−H acidity of the "top" acetyl side chain. Interestingly, and contrary to expectations, the aldol products **60/61** proved to be quite resistant to β-elimination. Finally, NMO was tried on **60/61** as an oxidative reagent. This reaction produced not only the aromatization product **62**, but − very interestingly − also the corresponding phenol **63** (Scheme 13). The yield of phenolic product clearly depended on the amount of NMO employed, and up to 80% of the phenol **63** was isolated with the use of 10 equiv. of NMO! The reagent was first used in this context by Sulikowski et al.,[90] and quinonemethide tautomers are assumed to act as reactive intermediates for NMO addition. The mild base-catalyzed aldol cyclization of diketones of structure **62** or **63** is demonstrated in Scheme 13 for the synthesis of tetrangomycin (**64**) and rabelomycin (**41**), but *all* of the aromatic angucyclines were available by this biomimetic-type methodology by use of two successive aldol reactions.[85]



Scheme 13. Biomimetic-type synthesis of tetrangomycin (**64**) and rabelomycin (**41**)[85]

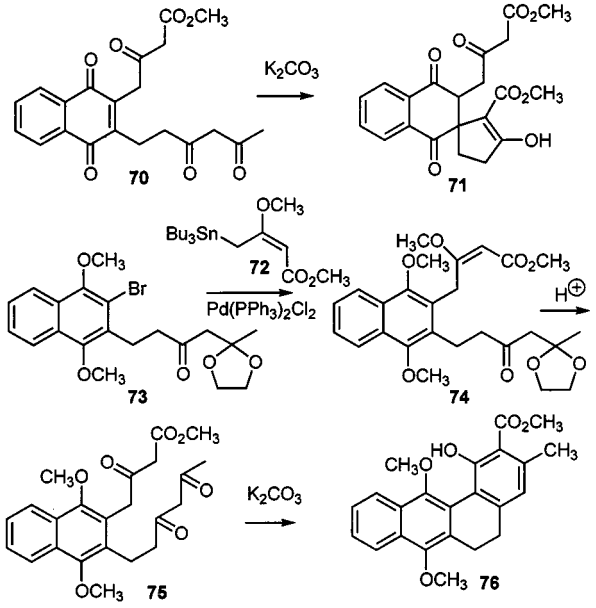
In an alternative and also very efficient approach, 8-deoxytetrangomycin (**69**) was prepared from the dioxonaphthoquinone starting material **65** (Scheme 14).[91,92] This open-chain naphthoquinone derivative underwent facile cyclization under mild basic conditions (K_2CO_3/18-crown-6) in THF solution to give the dihydroanthraquinone **66**. It is well known that 1,2-dihydroanthraquinones of type **66** undergo very rapid dehydrogenative aromatization under basic conditions, but only traces of the corresponding aromatic anthraquinone could be detected by TLC. The cyclization product **66** existed exclusively in the keto-enol form, and our synthetic scheme anticipated its conversion into the corresponding triflate **67** for attachment of side chains at this position by use of the Stille reaction. The attachment of the methallyl side chain proceeded without aromatization in 86% yield. This compound was identical with a sample prepared by the route described above[85] and could be cleaved by the Lemieux-Johnson procedure[93] to afford **68**. Intramolecular aldol reaction at low temperature then afforded the non-natural angucycline 8-deoxytetrangomycin (**69**).

As outlined in Scheme 6, the putative decaketide precursor **20** is attached to the acyl carrier protein through a thioester linkage. In the biomimetic cyclizations described above, this ester group was omitted, since most of the angucyclines lack the ester group. However, it would be very interesting to study the behavior and cyclization mode of



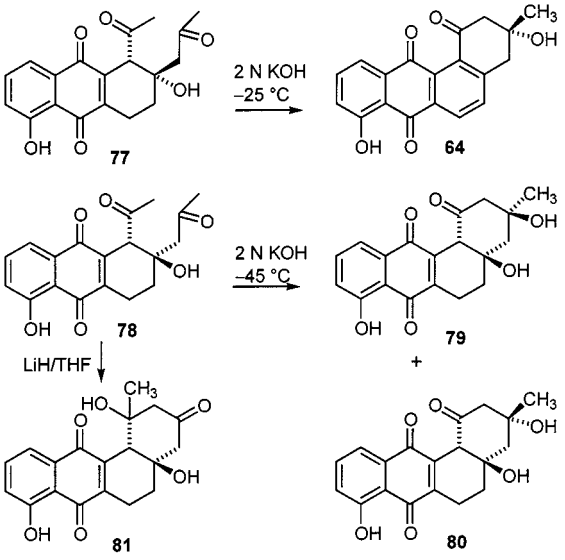
Scheme 14. Alternative route to 8-deoxytetrangomycin (**69**)[91]

oligoketides possessing this ester group. The first compound studied in this context was the trioxo ester **70**. Unexpectedly, the spiro compound **71** was formed in good yield after base treatment of **70** (Scheme 15).[94] Thus, the presence of the potent quinoid Michael acceptor had to be avoided in base-catalyzed reactions, and so our attention turned to the corresponding hydroquinone dimethyl ethers, such as **73**. The target compound **74** was prepared in a Stille reaction between bromide **73** and the stannane **72**. Treatment of the product **74** with hydrochloric acid simultaneously cleaved the enol ether and the ketal to give the trioxo ester **75** in 58% overall yield. The aldol reaction of **75** was studied using the mild base potassium carbonate in 2-propanol. In a smooth reaction, only one of the two possible cyclization modes[95] was effected, to afford the phenolic ester **76** in 66% yield.[96] The sequence comprises two successive aldol reactions and elimination of two molecules of water. This biomimetic-type reaction has great potential for the construction of the landomycin or elmycin aglycones[78] with nonaromatic B rings.



Scheme 15. Cyclization modes in the presence of an ester group[94,96]

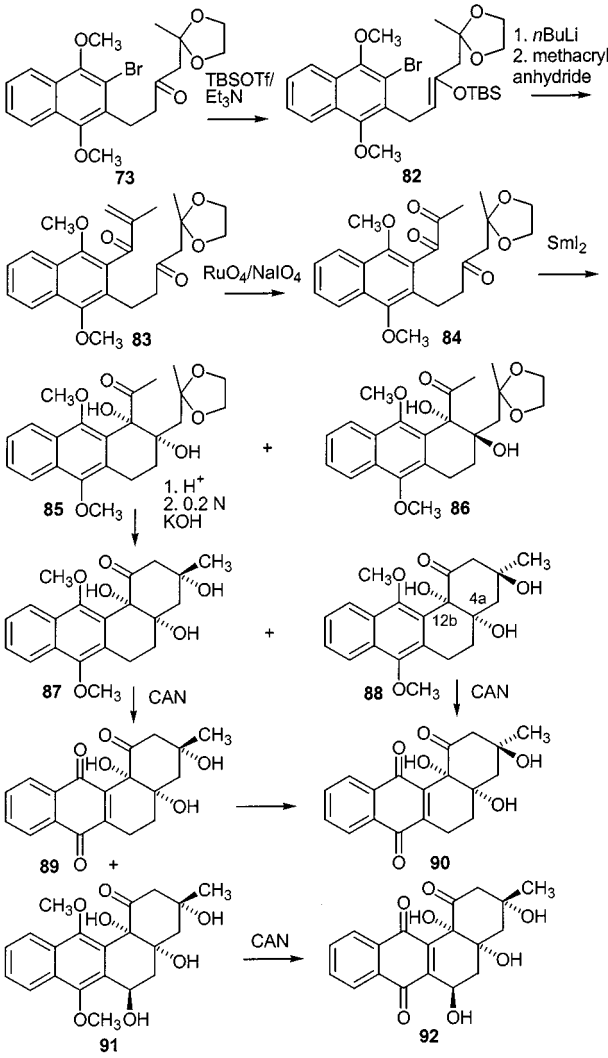
A challenging problem was the synthesis of nonaromatic angucyclines of the SF 2315A, WP 3688-2 or aquayamycin types.[78,79] For a long time, the base-catalyzed cyclizations of diketones such as **60/61** (Scheme 13) had remained unsuccessful, due to decomposition and aromatization of the starting materials. The desired nonaromatic angucylines were finally isolated when the reaction temperature was lowered to −45 to −60 °C.[97] The reaction behavior of the (*Z*) isomer **77**, with two *trans*-configured ketide chains attached to C-1 and C-2, was studied first. Virtually no reaction occurred below −35 °C, while very slow conversion was observed above −25 °C in 0.2 N methanolic KOH. This mainly yielded the aromatic angucyclines tetrangomycin (**64**) and some tetrangulol (Scheme 16). Evidently, *trans* elimination of water and subsequent dehydrogenation rapidly result in aromatization. *Interestingly, neither is there a single known nonaromatic angucycline with a trans configuration of rings A and B in nature!*



Scheme 16. Aldol reactions of the *trans*- and *cis*-diketones **77** and **78** under chelation-controlled and chelate-breaking conditions[97]

In the next series, the influence of catalytic amounts of bases on the (*E*) isomer **78**, with *cis*-alkyl chains at C-1 and C-2, was studied. In the first experiment, chelate-controlled conditions (LiH in THF) were employed. Surprisingly, the result was the regioisomer **82**, together with minor amounts of the tetrangomycin (**64**). Cyclization experiments with the (*E*) isomers **78** under chelate-breaking conditions at −45 to −55 °C in 0.2 N methanolic KOH (ca. 2 d) afforded the two stereoisomeric nonaromatic cyclization products **79** and **80**, corresponding to nonaromatic angucycline derivatives of the SF-2315[98] and SS 288Y[99] types, respectively.

Of particular importance are those angucycline antibiotics bearing two *cis*-hydroxy groups at the ring junction positions at C-4a and C-12b (numbering, see **88**, Scheme 17), such as aquayamycin and WP 3688-2.[99] Remarkably, the tertiary hydroxy group at C-12b does not originate from the polyketide chain but rather from air oxygen, as shown by Rohr et al.[100] The *C*-glycosidic aquayamycin is known to be a potent inhibitor of tyrosine[101] and dopamine hydrolases.[102] With the exception of model studies,[103,104] only one synthesis, by Suzuki et al.,[105] of the entire benz[*a*]anthracene system including the two hydroxy groups at C-4a and C-12b was known.



Scheme 17. Synthesis of angucyclines with hydroxy groups at C-4a and C-12a, with a SmI_2-mediated coupling as the key step[106,110]

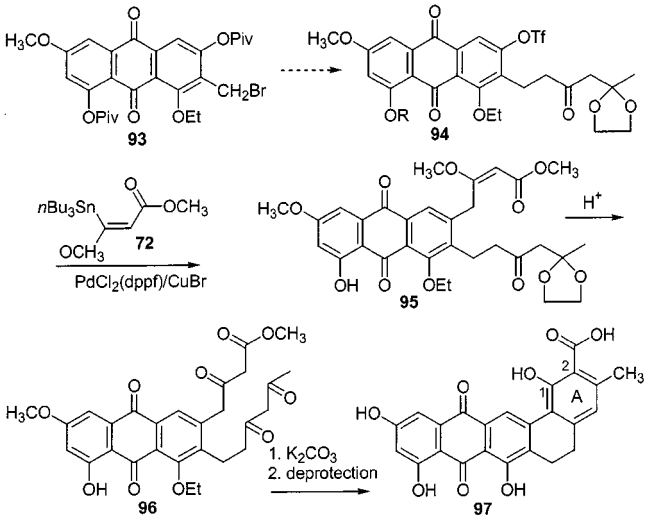
In our biomimetic-type approach,[106] lithiation of **82** (derived from **73**, Scheme 15) and treatment with methacrylic anhydride afforded the unsaturated acylation product **83** (Scheme 17). The reactive ruthenium tetroxide[107] was employed in conjunction with sodium periodate to cleave the electron-deficient double bond to the triketone **84**. SmI_2-mediated cyclization, initially explored on a series of model compounds, gave the *cis*- and *trans*-diols **85** and **86** in 83% yield. Interestingly, a high degree of dependence of the isomer ratio on the reaction temperature was observed. At −100 °C, the *trans*-diol **86** predominated (2:1), whereas at 18 °C the desired *cis*-diol **85** was favored (9:1). Model stud-

ies suggested that this reaction was ionic and not a ketyl radical dimerization. It represents a novel intramolecular C−C bond-forming reaction between 1,2-diones and ketones to yield 1,2-diol-3-ones.

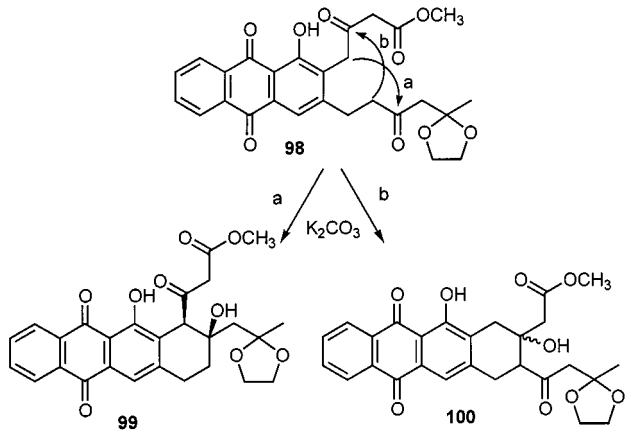
The acid-catalyzed cleavage of the *cis*-diol **85** on silica gel by the procedure of Huet et al.[108] proceeded without decomposition, to give the corresponding dione (the *trans*-diol **86** decomposed to a naphthopyran). This dione was treated with dilute alkali in methanol similarly to as described above (see Scheme 13), and a very clean reaction giving three compounds was observed. The major compounds were the desired tetracyclic 3,4a-*cis*- and 3,4a-*trans*-triols **87** and **88**, formed in a ca. 1.7:1 ratio while the minor constituent was the benzylic hydroxylation product **91**. CAN oxidation of the quinone dimethyl ethers by use of the modification of Tanoue and Tarada[109] afforded the quinones **89** and **90**, corresponding stereochemically to the aquayamycin- and WP 388-2-type angucycline antibiotics. Similarly, the hydroxylation product **92** was oxidized by CAN to yield 8-deoxyurdamycinone F (**92**),[110] an angucycline first isolated by Rohr and Zeeck et al.[111]

Biomimetic-Type Synthesis of Benzo[*a*]naphthacenequinones

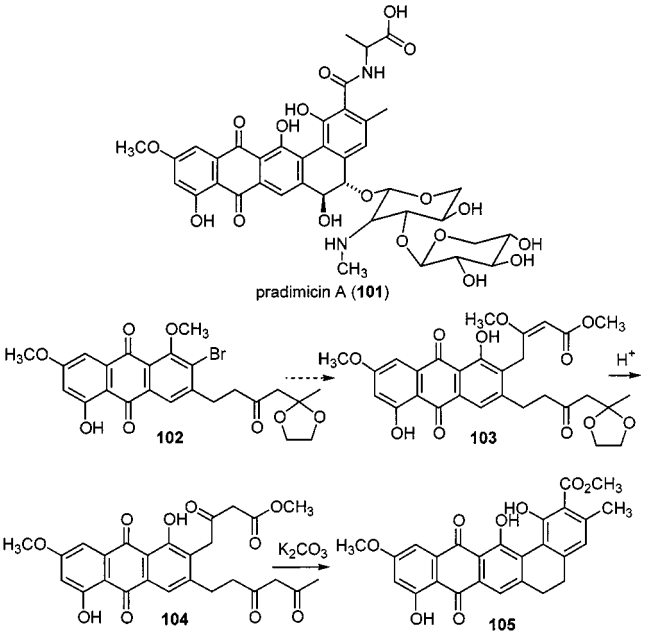
The number of known antibiotics with the benzo[*a*]naphthacenequinone skeleton has grown to more than 20 compounds. The simplest representatives, G-2N and G-2A,[112] and also derivatives of madurahydroxylactone,[113] have antibacterial properties. The structurally more complex *O*-glycosidic pradimicins [pradimicin A (**101**), Scheme 20] and benanomicins show remarkable in vivo antifungal activity (see reviews[114,115]). The related benanomicin A also inhibits infection of T-cells by Human Immunodeficiency Virus (HIV).[116]



Scheme 18. Synthesis of G-2A (**97**) by base-catalyzed cyclization of trioxo ester **96**[119]



Scheme 19. Angular and linear cyclization modes starting from diketo ester **100**[95]



Scheme 20. Synthesis of pradinone (**105**) by base-catalyzed cyclization of trioxo ester **104**[95]

The required anthraquinone **93**, allowing later attachment of the ketide side chains, was prepared by means of a Diels−Alder reaction, followed by NBS bromination. Chain-extension proceeded as described above, by alkylation of methyl 5,5-diethylenedioxo-3-oxo-hexanecarboxylate[39] with the benzylic bromide **93**, followed by demethoxycarbonylation and conversion into the triflate **94**. Despite steric hindrance, the triflate **95** reacted cleanly with the allylstannane **72**,[94] with [1,1-bis(diphenylphosphanyl)-ferrocene]dichloropalladium [$PdCl_2$(dppf)][118] as the catalyst, to yield the (*E*)-vinyl ether **95** (82%). The vinyl ether **95** was cleaved quantitatively to give the corresponding trioxo ester **96**, and the stage was set for the crucial cyclization experiments. In fact, mild basic treatment of **96** with potassium carbonate in 2-propanol initiated the aldol reac-

tions as shown in Scheme 18 to afford *one single* benzo[*a*]-naphthacenequinone. No products resulting from a "linear" cyclization product resulted, as shown similarly for a tetracyclic case in Scheme 15. In addition, the successive aldol reactions of the trioxo ester **96** were followed by water elimination and aromatization to the protected form of **97**. Interestingly, ring A is aromatic in all natural products possessing an ester group at C-2! Evidently, in contrast to angucyclines lacking this ester group, the high C−H acidity of the initially formed β-oxo ester aldol product very easily undergoes β-elimination of water.

The synthesis of the natural pigment was completed by cleavage of the protecting groups by means of a short melt in $AlCl_3$/NaCl at 150 °C to yield the natural product G-2A (**97**).

The angular cyclization mode is not necessarily the only possible pathway. This was confirmed in cyclization experiments with the partially deprotected ketal **98**. The ketal **98** gave a mixture of the "angularly" substituted naphthacenequinone **99** (Scheme 19, path a) and "linearly" substituted (path b) cyclization product **100** in a ca. 2−3:1 ratio.[95] No significant effect on the "angular/linear" product ratio was observed when the corresponding methyl ether was subjected to the basic reaction conditions.

The pradimicin- and benanomicin-type benzo[*a*]naphthacenequinone antibiotics have glycosidically attached deoxy sugars at 5-OH and short peptide chains bound to the carboxylic acid at C-2 [see pradimicin A (**101**), Scheme 20]. The aglycon has recently been synthesized by Suzuki's group.[120] In our biomimetic-type synthesis of the corresponding dideoxy compound pradinone (**105**), we used a trioxo ester cyclization of an appropriately substituted anthraquinone precursor.[95] A somewhat different strategy, as described for the synthesis of **96**, had to be employed to arrive at the precursor **103**. The bromide **102** was used instead of a triflate **94** for the Stille coupling with stannane **72**, to afford the pentasubstituted anthraquinone **104**. Again, only one, single, orange/red-colored, nonpolar cyclization product was isolated from base-catalyzed cyclization of **104** and pradinone (**105**) was isolated in 70% yield in a one-pot reaction.

Concluding Remarks

A large number of deca- and dodecaketide-derived quinone antibiotics are easily accessible synthetically by biomimetic-type approaches. By starting from precursors with a 1,3-arrangement of carbonyl groups on the ketide side chains, attached to a quinoid or aromatic core, the naturally occurring 1,3-oxygen pattern of polyketide-derived natural products is generated automatically. The vicinal placement of the side chains on the rigid core restricts the large number of aldol reactions possible with open-chain oligoketides. The remaining "linear" (anthracyclines) and "angular" (angucyclines, pradimicines) cyclization modes can be controlled by appropriate protection or by fine-tuning of carbonyl reactivity. By careful choice of reaction conditions, β-elimination and subsequent aromatization can be prevented and partially nonaromatic aglycones, not previously accessible by this approach, can be synthesized. A microbial enzyme system has successfully been used in enantioselective aldol cyclization of a ketide precursor. However, the general use of chiral bases during the aldol reactions to mimic the enantioselectivity of enzymatic reactions remains a future challenge in biomimetic polyketide synthesis.

Acknowledgments

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