Recent progress in the total synthesis of naphthyridinomycin and lemonomycin tetrahydroisoquinoline antitumor antibiotics (TAAs)

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In this *tutorial review*, which should be of general interest to synthetic organic chemists at large, recent progress in the total synthesis of the tetrahydroisoquinoline antitumor antibiotics cyanocycline A, naphthyridinomycin, bioxalomycin α_2, and lemonomycin is highlighted in detail and some biological background information is given as well. Preparations of truncated derivatives and uncompleted synthetic approaches are also described. The literature coverage includes the newest research results through the year 2008.

Introduction

The family of tetrahydroisoquinoline alkaloids (TAAs) can be classified into different subgroups depending on their structural properties.[1] The saframycin family is the largest of these subgroups, which contains the saframycins, safracins, renieramycins, and ecteinascidins, whose common structural features are a core ring fragment containing five condensed six-membered rings, two of which are present as either quinones and/or hydroquinones, a tetrahydroisoquinoline moiety and a piperazine subunit as shown in Fig. 1.

Another important group is the naphthyridinomycin family. Its congeners exhibit a main carbon frame of mostly six condensed rings, four of them six-membered, and a five-membered bridged ring system. The eponymous tetrahydroisoquinoline system, whose aromatic part can also be present as a quinone moiety, as well as a piperazine ring system are common elements in all representatives of this family of natural products. A labile oxazolidine fragment forms the last five-membered ring, present in 14 of 15 congeners of the naphthyridinomycin alkaloids (Fig. 2). The third important group of natural products containing the tetrahydroisoquinoline ring system is the quinocarcin family, which contains compounds that exhibit the bicyclic isoquinoline frame and a piperazine moiety with a condensed five-membered ring system. The hydroquinone ring system can also be found in its oxidized form as quinone. In several members of this family

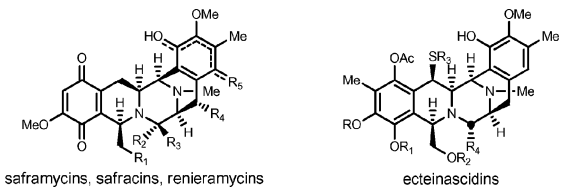

Fig. 1 Saframycin tetrahydroisoquinolines.

Fig. 2 Naphthyridinomycin alkaloids.

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Prof. Johann Mulzer received his PhD in 1974 under the supervision of Rolf Huisgen before he joined the group of E. J. Corey at Harvard as a postdoctoral fellow. Currently he holds a position as full professor and Head of the Institute of Organic Chemistry at the University of Vienna. His main research interests are the total synthesis of structurally and physiologically interesting natural products.

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Uwe Rinner studied chemistry at the Technical University in Graz. He moved to Florida to pursue graduate studies under the guidance of Prof. Hudlicky and received his PhD in 2003. After a postdoctoral stay in Canada, he joined the group of Prof. Mulzer at the University of Vienna. His research focuses on the synthesis of diterpenes and other biologically interesting natural products.

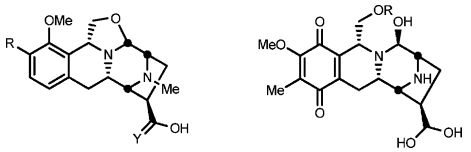


Fig. 3 Quinocarcin family.

an oxazolidine ring is present in the structure as well. The main representatives of this alkaloid family are quinocarcin and quinocarcinol, tetrazomine and lemonomycin (Fig. 3). Many of the above-mentioned natural products can be classified as broad spectrum antibiotics, which exhibit strong antitumor activity in extraordinarily low concentrations. Therefore, the tetrahydroisoquinoline antitumor antibiotics are important targets for medicinal chemists in their steady quest for potent lead structures. In this tutorial review, chemistry, biology, and syntheses of representative members of the naphthyridinomycin and lemonomycin families are discussed. As much of the earlier work has been reviewed comprehensively,[1] special emphasis will be placed on recent advances in the total synthesis of (+)-cyanocycline A and (−)-lemonomycin.

Naphthyridinomycin family

Isolation and structure elucidation

Naphthyridinomycin (**1**, Fig. 4) was first isolated in 1974 by Kluepfel and co-workers from the fermentation broth of AYB-1026, as a labile, red, crystalline compound which shows a tendency to decomposition.[2,3] The structure elucidation was achieved by single crystal X-ray diffraction analysis.[3,4] Two years later, SF-1739 HP (**2**) was isolated by the research groups of Watanabe and Itoh.[5,6]

The highly functionalized naphthyridinomycin features an unprecedented hexacyclic framework containing such labile functionalities as an oxazolidine ring, a quinone moiety and a hemiaminal function. Extraordinary are also the three contiguous nitrogen bearing stereogenic centers. By treatment with sodium cyanide, naphthyridinomycin was converted into cyanonaphthyridinomycin,[7] which was proven to be identical with cyanocycline A (**3**), isolated shortly thereafter by Hayashi and co-workers from a strain of *Streptomyces flavogriseus*.[8] The structure of **3** could be elucidated by X-ray diffraction analysis together with the crystal structure of cyanocycline F (**4**).[9] Originally, the absolute configuration of cyanocycline A was wrongly assigned; however, the asymmetric total synthesis by Fukuyama in 1992 revealed that the (+)-enantiomer of cyanocycline A is the natural one.[10]

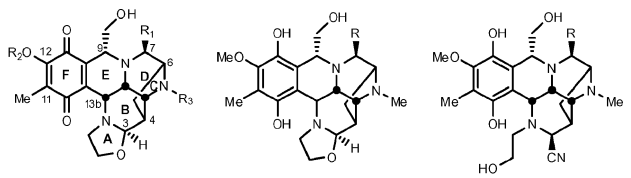


Fig. 4 Naphthyridinomycin and cyanocyclines.

In 1993, Gould and co-workers isolated three other TAAs from the fermentation broth of *Streptomyces lusitanus*.[11] These highly unstable alkaloids were derivatized by cyanation to furnish the new stable cyanocyclines B (**5**) and C (**7**), along with cyanocycline D (**9**). Their original structures were assigned to be **6** and **8**, respectively (Fig. 4). One year later, the research group of Ellestad isolated four new products from the fermentation broth of *Streptomyces viridostaticus* ssp. *litoralis*.[12,13] These natural compounds were given the names bioxalomycin α_1, α_2, β_1, and β_2, **10–13** (Fig. 5), and by reviewing the original article of the structure elucidation of naphthyridinomycin (**1**), these results raised considerable doubt about possible artefact formation during isolation. Therefore, the authors resubmitted a fermentation broth of *S. lusitanus* to new and milder isolation conditions, and could indeed obtain bioxalomycin β_2 instead of naphthyridinomycin.[13] Even on repeating the original naphthyridinomycin isolation procedure only bioxalomycin β_2 was isolated, which led to the assumption that naphthyridinomycin might only be a degradation product of bioxalomycin β_2. The latest members of the naphthyridinomycin family are the dnacins **14** and **15**, as well as the aclindomycins, **16** and **17** (Fig. 6). The first of these natural products was already isolated in 1980, by Tanida *et al*. from *Actinosynnema pretiosum* C-14482,[14,15] but the structure could not be elucidated before 1994.[16] Their only difference from naphthyridinomycin lies in the substitution pattern of the quinone ring system. Aclindomycins A and B can be numbered among the bioxalomycins and were isolated in 2001 from *Streptomyces halstedii* by Yoshimoto *et al*.[17] These alkaloids contain a very unusually hydroxylated quinone system with a quinomethide double bond between C-9 and C-9a. The C-3a configuration is inverted with respect to all other members of the naphthyridinomycin family. So

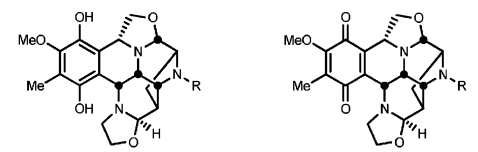


Fig. 5 Bioxalomycins.

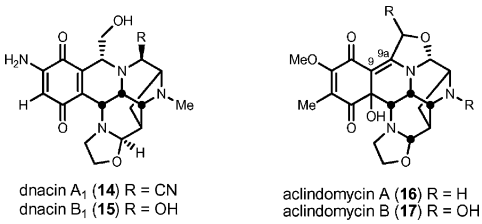


Fig. 6 Dnacins and aclindomycins.

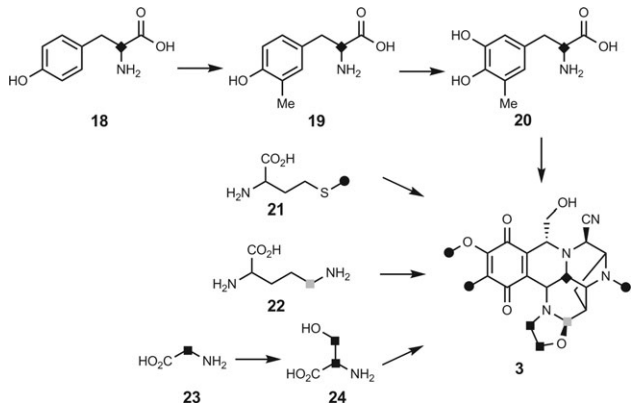


Fig. 7 Biosynthesis of cyanocycline A.

far, no synthetic approaches toward these compounds have been reported.

Biosynthesis

A biosynthetic pathway was published by Zmijewski *et al*. in 1982, who demonstrated *via* ^{14}C-labeling that cyanocycline A is assembled from (*S*)-methionine (**21**), (*S*)-tyrosine (**18**), glycine (**23**), and D,L-ornithine (**22**) (Fig. 7).[18] In 1985, the same research group showed that ^{15}N-labeled glycine was transformed into serine and then used for the construction of the oxazolidine ring of cyanocycline A.[19,20] The biosynthetic formation of the aromatic part of cyanocycline A does not proceed *via* DOPA, but *via* tyrosine (**18**), which was incorporated into the natural product. It could be proven that **18** was methylated and later hydroxylated to the corresponding catechol, prior to incorporation into the title compound.[21]

Biological activity

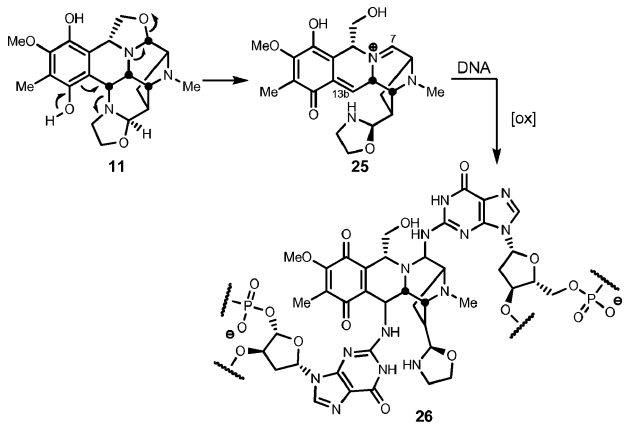
Naphthyridinomycin is a strong antibiotic against both Gram-positive and Gram-negative bacteria.[2,22] At low naphthyridinomycin concentrations, the incorporation of ^{14}C-thymidine into the DNA of *Escherichia coli* was inhibited;[22] at higher concentrations also RNA and protein synthesis were inhibited. Also, the inhibition of DNA became irreversible. In extensive studies Zmijewski *et al*. showed that ^{3}H-naphthyridinomycin binds to DNA in small amounts *via* a covalent bond.[23] If the alkaloid is reduced with DTT (dithiothreitol), DNA binding occurs to a much higher extent and irreversibly, in contrast to the natural quinoid compound. Experiments to resolve the sequence specificity of DNA alkylation by poly(dG)–poly(dC) and poly(dA)–poly(dT) polydeoxyribonucleic acids showed that naphthyridinomycin promotes binding to GC-rich regions. If guanine is replaced by inosine, no significant alkylation takes place, leading to the assumption that naphthyridinomycin alkylates the primary amino group of guanine.[23]

Whereas the biological activities of naphthyridinomycin and cyanocycline A are about equal, bioxalomycin α_2 (**11**) is extraordinarily effective against Gram-positive bacteria[12] (Table 1). Bioxalomycin α_2 shows cross-linking to duplex DNA by double alkylation of the N-2 of guanine, presumably at the C-7 and C-13b positions. Probably this occurs *via* an *o*-quinone methide intermediate **25**.[24,25] In addition, the bis-DNA adduct again undergoes oxidation to the corresponding quinone **26** (Scheme 1).

Table 1 Antimicrobial activities of bioxalomycin α_2 (**11**) against Gram-positive isolates[19]

Tested bacteria[a]	MIC[b]/μg mL^{-1}
Bacillus cereus [1]	0.12
Enterococcus faecalis VS [4]	≤0.002–0.25
Enterococcus faecium VR [2]	0.03–0.06
Methicillin-resistant *Staphylococcus aureus* [33]	0.004–0.015
Methicillin-sensitive *Staphylococcus aureus* [4]	≤0.002–0.015
Coagulase-negative *Staphylococci* [6]	≤0.002–0.004
Staphylococcus haemolyticus [1]	≤0.002
Streptococcus pyogenes [1]	≤0.002
Streptococcus agalactiae [1]	≤0.002
Streptococcus pneumoniae [1]	0.015

[a] The number of strains are shown in brackets. [b] Minimum inhibitory concentrations.

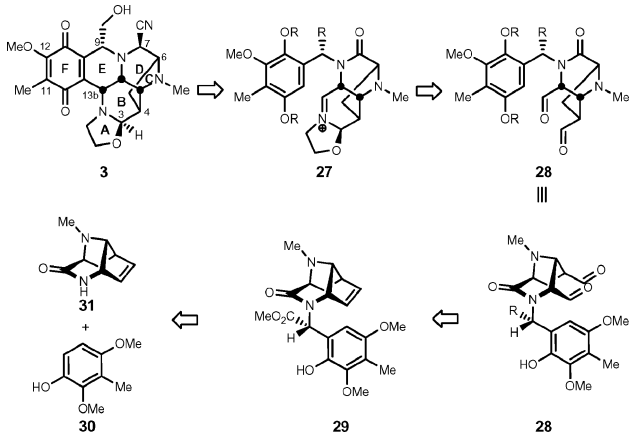


Scheme 1 Interstrand cross-linking between bioxalomycin α_2 and DNA.

It was also shown that bioxalomycin α_2 (**11**), just like the TAAs quinocarcin and tetrazomine, spontaneously converts dioxygen to superoxide in a Cannizarro-like mechanism. In this respect, **11** is several orders of magnitude more effective than any other member of the TAA family, probably due to the presence of two oxazolidine moieties and the redox-labile hydroquinone ring.

Total syntheses of cyanocycline A

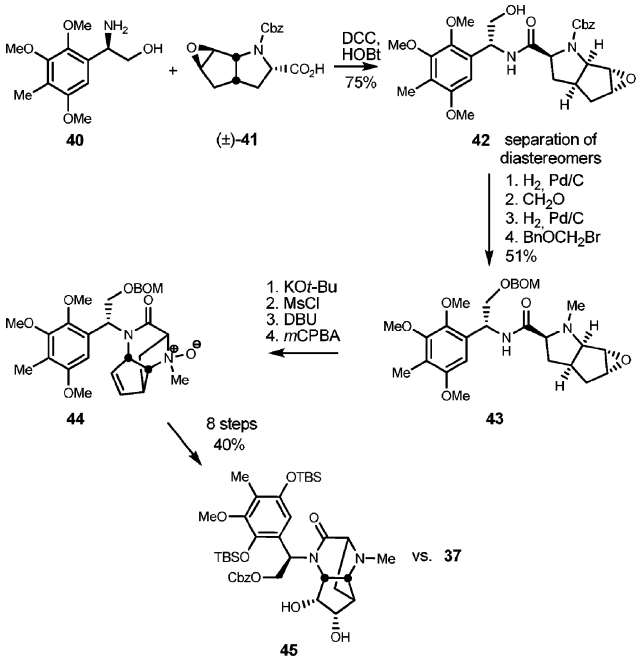
Three total syntheses of cyanocycline A have been published to date. The first one, by Evans *et al*. aimed for racemic material and follows the retrosynthetic strategy outlined in Scheme 2. Thus, ring E was envisaged to be formed *via* a Pictet–Spengler cyclization of iminium ion **27** which was to be generated regioselectively from dialdehyde **28** and TBS-ethanolamine. Dialdehyde **28** is accessible from oxidative cleavage of olefin **29**, which is formed from **30** and **31**, respectively. Tosylate **33** (Scheme 3)[26] was obtained by hydrolysis of β-lactam **32**, LAH reduction, cyano-Mannich reaction, and protection of the hydroxyl and amino moieties. Upon treatment with base, this material cyclized and after epimerization to the desired diastereomer was converted to **34** after stereoselective epoxidation and basic hydrolysis. Cbz-removal, Eschweiler–Clarke methylation and base catalyzed cyclization



Scheme 2 Evans' retrosynthetic analysis of cyanocycline A.

furnished the hydroxylated tricyclic lactam **35**. Elimination of the secondary alcohol *via* the selenoxide gave the desired tricyclic amide **31** in high yield. This intermediate was treated with methyl glyoxylate followed by thionyl chloride.[27] Upon Friedel–Crafts alkylation of the resulting chloroamide with stannous tetrachloride and phenol **30**, amino ester **29** was obtained in moderate yield which was efficiently converted to quinone **36**. In three steps primary alcohol **36** was acetylated, the quinone moiety was again reduced to the corresponding hydroquinone, protected as a silyl-ether and dihydroxylated with osmium tetroxide to provide *cis*-diol **37** as stable intermediate. Glycol cleavage generated bis-aldehyde **28** which was treated with TBS-ethanolamine to give aminodiol **38**. Treatment with trifluoroacetic acid led, presumably *via* **27**, to the formation of rings A and E in a high yielding one pot procedure.[28]

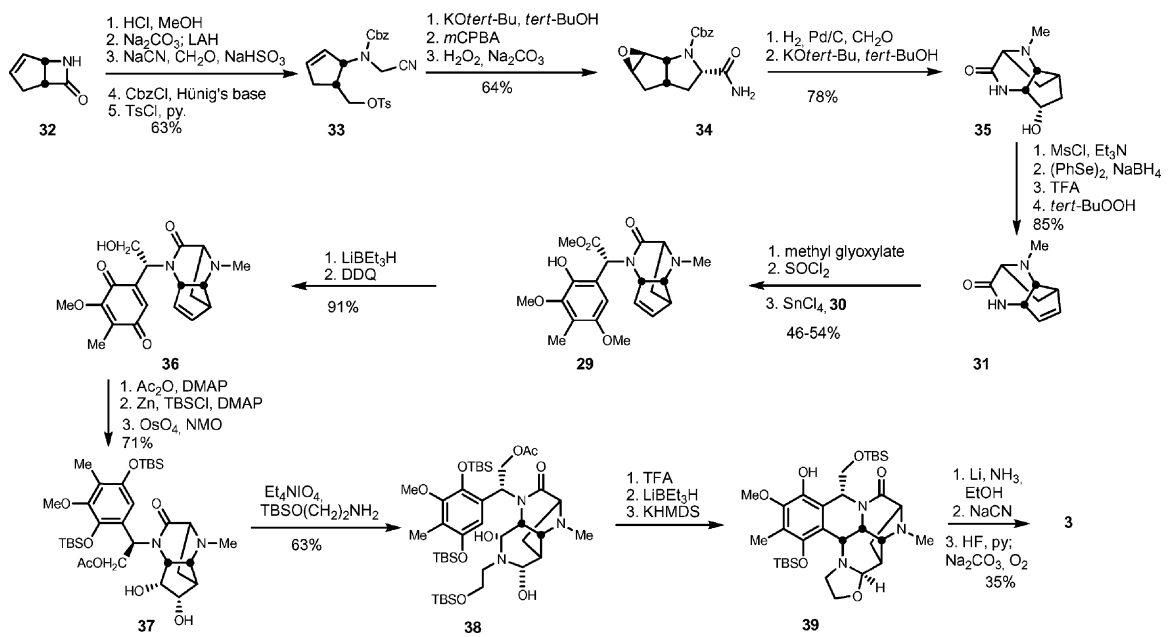
Reductive cleavage of the acetate protecting group and base-induced phenol–carbinol *O*-silyl migration furnished **39** as a single product. The amide was reduced under Birch



Scheme 4 Evans' total synthesis of (+)-cyanocycline A.

conditions to the aminal, which was trapped by sodium cyanide to establish the characteristic nitrile function. Removal of the remaining silyl ether group led to cyanocycline A hydroquinone. Oxidation to the quinone completed the first racemic total synthesis of target compound **3**.

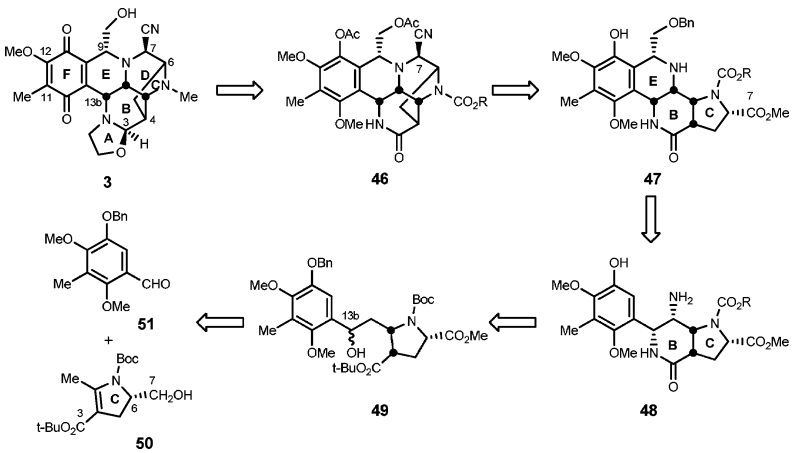
In 1987, Evans and Illig performed a chiral switch of this synthesis by developing an asymmetric approach to a derivative of lactam **37** (Scheme 4).[28,29] *Via* an auxiliary based strategy, amino alcohol **40** was prepared in enantiomerically enriched form and added to racemic epoxy acid **41**, a close analog of the previous intermediate **34**. The diastereomeric amides were separated and the synthesis was carried on with



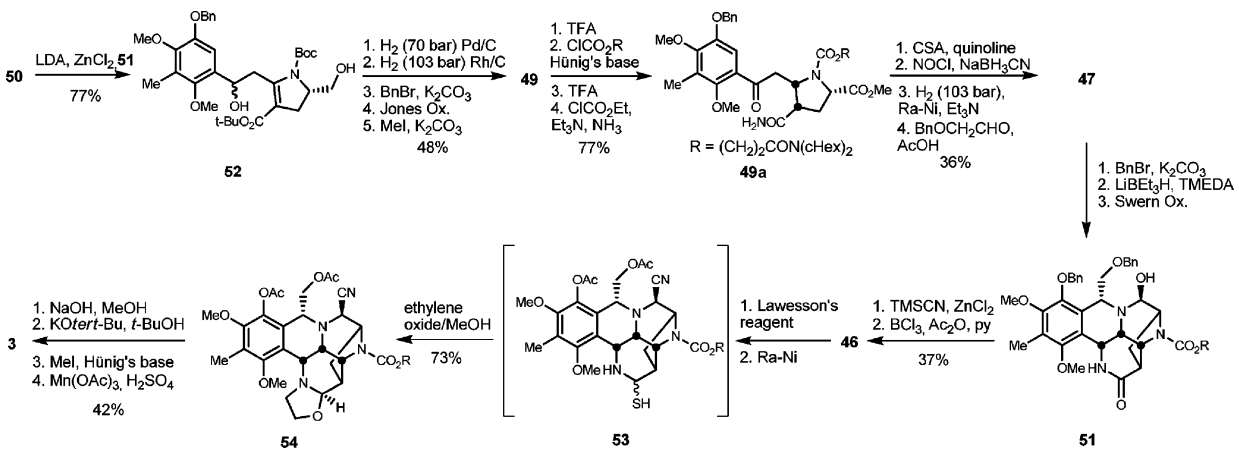
Scheme 3 Evans' total synthesis of *rac*-cyanocycline A.

diastereomer **42**. Hydrogenolytic liberation of the amine function, reductive *N*-methylation and benzyloxymethyl (BOM) protection of the primary alcohol function gave **43**. Transannular N–C-cyclization was achieved with potassium *tert*-butoxide as before to generate the tricyclic lactam. *O*-Mesylation, elimination and oxidation of the methylated nitrogen with *meta*-chloroperbenzoic acid furnished *N*-oxide **44** as the only product. In eight more synthetic operations this advanced intermediate was transformed into intermediate **45**, which, apart from the *O*-Cbz protecting group, is identical to intermediate **37** in the racemic synthesis of (±)-cyanocycline A. From **45**, optically active **3** was prepared in analogy with the racemic precedent, and the absolute configuration was confirmed by comparison of the optical rotations of the synthetic and the natural product. However, these results were never published, but only disclosed in a PhD thesis.[29]

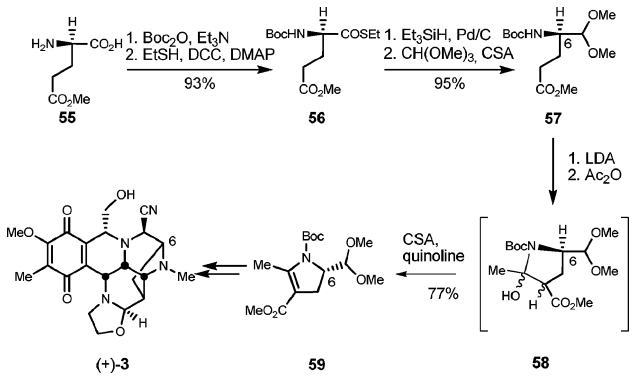
In 1987, Fukuyama and co-workers published the second synthesis of racemic cyanocycline A.[30] This approach focuses on an early connection of the aromatic portion and the preformed pyrrolidine C-ring **50** to form hydroxy ester **49**, from which ring B in tricycle **48** is developed. Pictet–Spengler cyclization is used to close ring E in **47**, whose ester group at C-7 is later reduced to the aldehyde and serves to close ring D in **46**. Finally, oxazolidine ring A is annulated to ring B with ethylene oxide (Scheme 5). As outlined in Scheme 6, dihydropyrrole **50** was coupled to the aromatic aldehyde **51** to furnish secondary alcohol **52** as an epimeric mixture. Hydrogenation with two different metal catalysts first led to cleavage of the benzylic protecting group and under more harsh conditions to the stereoselective reduction of the enamine. Reprotection of the phenolic position and oxidation furnished intermediate **49**. The *N*-Boc group was cleaved selectively and the amine was reprotected with an unusual carbamate, which is stable to a very broad spectrum of reaction conditions and was developed by the Fukuyama group especially for this synthesis. Cleavage of the *tert*-butyl ester and conversion to the amide led to compound **49a**. Acid catalyzed cyclization gave an enamine which was reductively nitrosylated to furnish the corresponding oxime. Hydrogenation of this material with Raney nickel led to the amine and removed the phenolic OBn group. Pictet–Spengler cyclization with benzyloxy acetaldehyde to establish **47** in which rings C–F are correctly installed was followed by reprotection of the phenol group, reduction of the methyl ester to the corresponding aldehyde which immediately cyclized to hemiaminal **51**, thus closing ring D. Conversion into the amino nitrile and replacement of the benzyl protecting groups by acetates gave pentacycle **46**. Formation of the oxazolidine ring A was achieved in a three step sequence to afford **54** in good overall yield. The total synthesis of (±)-**3** was completed by the cleavage of the N- and



Scheme 5 Fukuyama's retrosynthetic analysis of cyanocycline A.



Scheme 6 Fukuyama's total synthesis of *rac*-cyanocycline A.



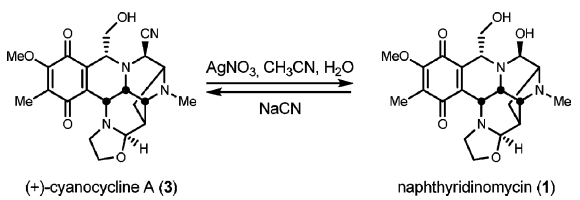
Scheme 7 Fukuyama's total synthesis of (+)-cyanocycline A.

O-protecting groups, introduction of the methyl function at the free amine and cautious oxidation to the quinone.

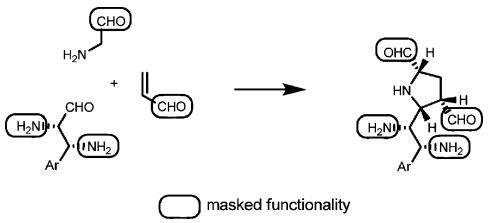
In 1992, Fukuyama modified this racemic sequence to an enantioselective one (Scheme 7).[10] As the C-6 stereocenter controls all the other stereogenic centers, it was sufficient to synthesize dihydropyrrole **59** in non-racemic form. L-Glutamic acid methyl ester **55** was converted into the corresponding protected thioester **56**. Reduction to the aldehyde and acetalization furnished compound **57** which was treated with LDA and acetic anhydride and converted in an aldol type cyclization to **58**. This material was dehydrated to establish the dihydropyrrole ring **59** in an enantioselective manner and used to perform the total synthesis of cyanocycline A by repeating the reaction sequence known from the racemic synthesis. This work allowed the structural proof of the absolute configuration of (+)-cyanocycline A (**3**), thus officially confirming Evans' unpublished result (*vide supra*).

Cyanocycline A was also treated with silver nitrate in a mixture of acetonitrile and water (Scheme 8). The product formed was very unstable, and any effort to purify or isolate a clean sample only led to decomposition. Crude ^{1}H-NMR and mass analysis gave an unambiguous hint that the product was naphthyridinomycin. In fact, the new compound could easily be re-converted into cyanocycline A with sodium cyanide.[10]

The latest synthesis of (+)-cyanocycline A was carried out by Garner and Kaniskan.[31] Their retrosynthetic concept was very much modelled after Fukuyama's precedent by going back to intermediates **60–62**. However, the novel contribution lies in the formation of intermediate **63**. In earlier model studies, Garner developed a metal catalyzed multicomponent protocol for the stereoselective synthesis of highly functionalized pyrrolidines as outlined in Scheme 9 [32] This [C + NC + CC] coupling protocol is perfectly suited for the elaboration of key intermediate **63** and in continuation of earlier studies, they applied a 1,3-dipolar cycloaddition to form pyrrolidine **63** by connecting aldehyde **66** L-glycylsultam (**64**; with X^L being Oppolzer's L-camphorsultam)



Scheme 8 Conversion of cyanocycline A into naphthyridinomycin and *vice versa*.



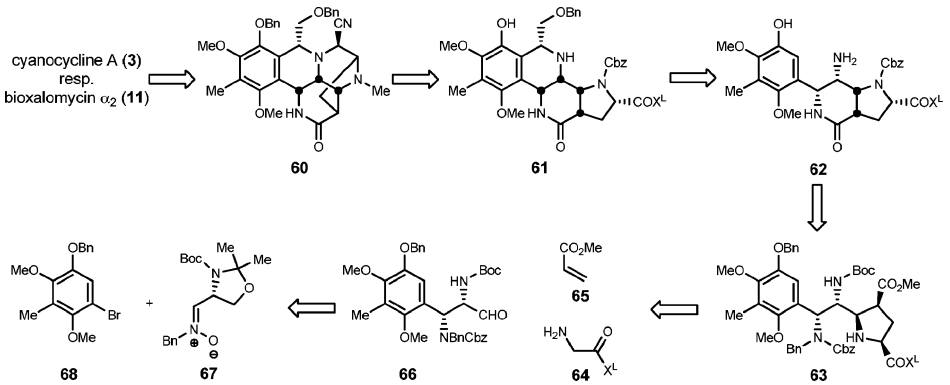
Scheme 9 Garner's key [C + NC + CC] coupling reaction.

and methyl acrylate (**65**) under mediation with 10 mol% silver acetate (Scheme 10). This [3 + 2] cycloaddition reaction provides the desired material with complete enantiocontrol. It was suggested that this cycloaddition proceeds *via* formation of an azomethinylide–silver complex **69** which adds methyl acrylate *via* an *endo* transition state (Scheme 11).

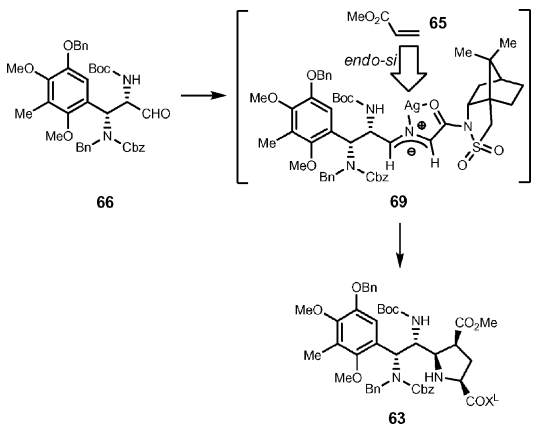
The synthesis of key aldehyde **66** started with the addition of the aromatic Grignard reagent prepared from bromide **68** to nitrone **67** and provided *anti*-hydroxylamine **70** as sole product (Scheme 12). Reduction of the hydroxylamine moiety with zinc followed by carbamate protection of the secondary amine, cleavage of the acetonide and Dess–Martin periodinane oxidation furnished amino aldehyde **66**. The cycloaddition was performed as outlined above to form the pyrrolidine ring **63** in which five out of the eight stereocenters present in cyanocycline A are established correctly. The endgame started with palladium-catalyzed hydrogenolysis of **63** to give a phenolic lactam. The free secondary amine was protected as the benzyloxy carbamate, and the acid sensitive *N*-Boc group was removed to set the stage for a Pictet–Spengler reaction with benzyloxy acetaldehyde. By this sequence, tetracycle **61** was obtained in a relatively short and efficient synthesis. Key intermediate **61** is closely related to compound **47**, Fukuyama's intermediate (Scheme 5), the only difference being protecting groups on functionalities on the C-ring. Therefore, the synthesis of (+)-**3** was completed by reducing the sultam and the Cbz groups in **62** to obtain alcohol **61a**. Next (Scheme 13) this alcohol was oxidized to the aldehyde which immediately cyclized to form the pentacyclic intermediate **60**. The lactam was reduced to imine **71** which was then used to annulate the isoxazolidine ring in **72**. Removal of the benzyl protecting groups furnished **73**, which was identical with the penultimate intermediate in Fukuyama's synthesis. (*cf.* Scheme 6). The first racemic total synthesis by Evans *et al.* was performed with a total of 31 synthetic operations, counting the longest linear sequence, starting from commercially available, simple starting materials. The second total synthesis by Fukuyama was only somewhat shorter, counting 29 synthetic operations and led to racemic material as well. The enantioselective second generation total syntheses of cyanocycline A were longer and required 31 and 35, respectively, synthetic transformations. The newest total synthesis of (+)-cyanocycline A by Garner and Kaniskan exhibits by far the shortest reaction sequence with 22 operations counting the longest sequence, but its overall yield is lower than that of the previous approaches.

Uncompleted synthetic approaches toward the naphthyridinomycin family

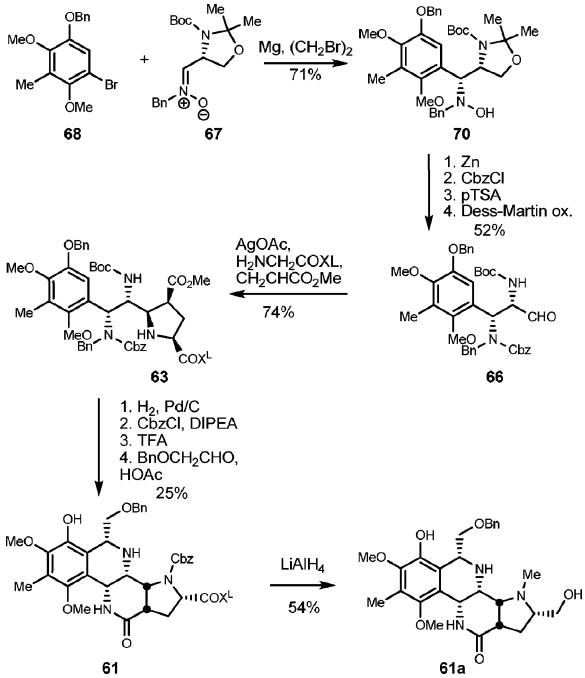
Several synthetic approaches toward members of the naphthyridinomycin alkaloid family have been reported



Scheme 10 Garner's retrosynthetic analysis of (+)-cyanocycline A or (+)-bioxalomycin α_2.

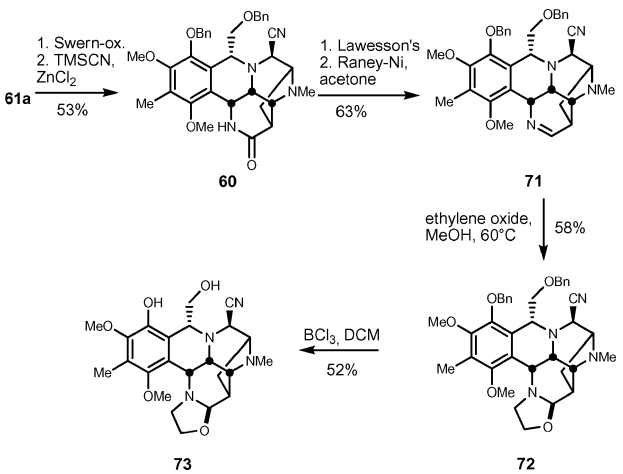


Scheme 11 Proposed mechanism for the *endo-si* azomethinylide–acrylate cycloaddition.



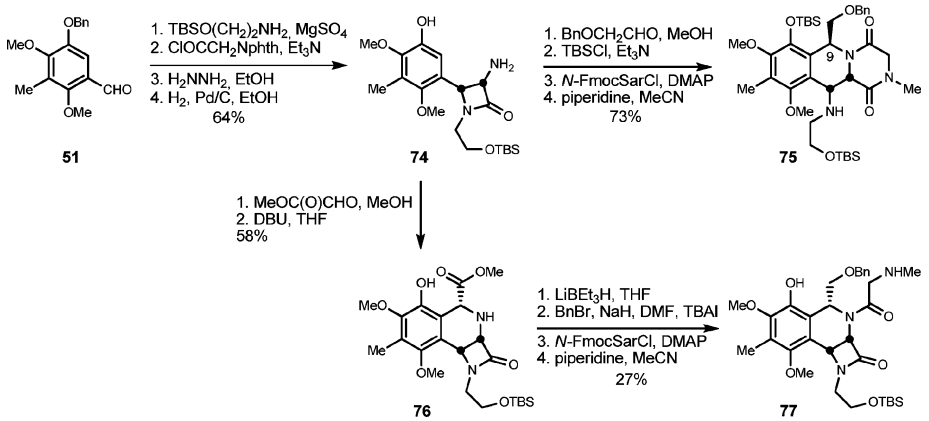
Scheme 12 Garner's total synthesis of (+)-cyanocycline A (part 1).

during the past two decades. In the years between 1984 and 1994 the research groups of Parker (1984),[33] Danishefsky (1984),[34,35] Joule (1987),[36] and Garner (1988 and 1997)[37–41]



Scheme 13 Garner's total synthesis of (+)-cyanocycline A (part 2).

published synthetic approaches to more or less advanced intermediates toward a total synthesis of cyanocycline and its congeners, respectively. In connection with a planned synthesis of racemic bioxalomycin α_2, Williams and co-workers reported a synthesis of the tricyclic tetrahydroisoquinoline **75**, (Scheme 14).[42] The key step is a [2 + 2]-cycloaddition/Pictet–Spengler reaction sequence. Aldehyde **51** is converted into an imine by reaction with a silyl-protected ethanolamine. [2 + 2]-Cycloaddition of the ketene formed *in situ* from phthalimidoacetyl chloride furnished the desired β-lactam. After hydrazinolysis of the phthalimide and hydrogenolysis of the benzyl ether, amine **74** was isolated. Pictet–Spengler reaction followed by transamidation of the β-lactam with sarcosin furnished diketopiperazine **75**. As C-9 was formed with the wrong configuration the authors tried to rectify the situation by generating ester **76** in the Pictet–Spengler step. Now C-9 could be equilibrated with DBU; however, the transamidation failed and β-lactam **77** was obtained instead. Aiming for a synthesis of non-racemic naphthyridinomycin, the Fukuyama group reported the stereoselective synthesis of tetracyclic compound **88**.[43] Key steps were the Ugi 4-CC reaction, an intramolecular Mizoroki–Heck reaction, and a Pictet–Spengler cyclization. (*R*)-Aryl glycinol **81** was prepared *via* a Mannich-type reaction of phenol **30** with chiral iminolactone **78** to provide **79** with high diastereoselectivity. Protection of the phenol, reductive ring opening and selective



Scheme 14 Williams' synthetic approach toward bioxalomycin α_2.

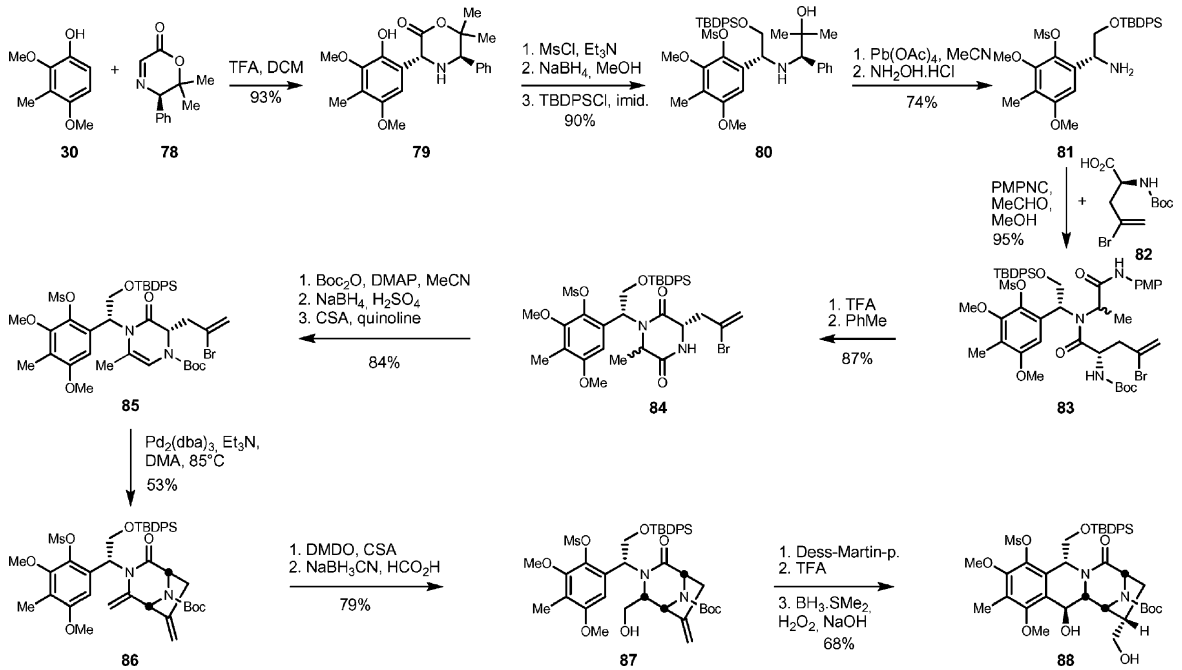
silylation of the primary alcohol furnished **80**. Oxidative removal of the chiral auxiliary afforded the desired aryl glycinol **81**. An Ugi 4-CC reaction including **81**, **82**, acetaldehyde and *p*-methoxyphenylisonitrile followed by removal of the Boc-protecting group generated diketopiperazine **84**. After formation of the endocyclic olefin **85**, the pyrrolidine ring was closed under Mizoroki–Heck conditions to give **86**, whose exocyclic enamine double bond was converted into the primary alcohol **87**. Oxidation to the aldehyde, acid-catalyzed cyclization and hydroboration/oxidation of the remaining olefin gave tetracyclic diol **88** under complete stereocontrol (Scheme 15).

The most recently published work toward the diazabicyclo[3.2.1]octane core of the naphthyridinomycin alkaloids dates to 2006 and was released by Wipf *et al.*[44] The key transformation in this reaction sequence is an intramolecular palladium-catalyzed allylic alkylation (Scheme 16). Starting from aldehyde **89**, acid **90** could be synthesized in four synthetic operations. It was then coupled with *N*-(2,5-dimethoxy)benzylglycine ethylester (**91**) and alkylated with ethyl chloroformate to furnish compound **92**. Desilylation with TBAF and conversion of the free alcohol into a benzoate function provided **93** as a useful precursor for the π-allyl palladium promoted intramolecular cyclization reaction. This transformation proceeded successfully in the presence of 20 mol% Pd_2dba_3 (dba = dibenzylidene acetone) and DBU to furnish the desired bicycle **94** present in the naphthyridinomycins.

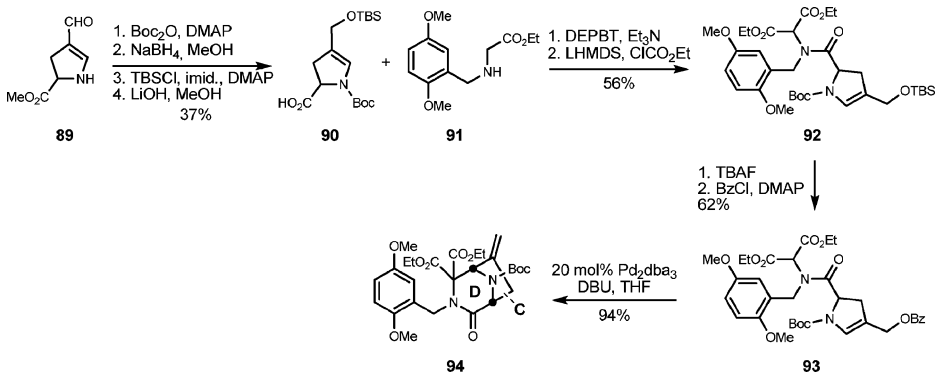
Lemonomycin

Isolation and structure elucidation

Lemonomycin (**95**, Fig. 8) was first isolated in 1964 from *Streptomyces candidus* (LL-AP191).[45] Despite its early isolation, the structure of this complex alkaloid remained unsolved until 2000, when He *et al.* succeeded in its elucidation.[46] Lemonomycin contains the typical tetracyclic core system known from the quinocarcin alkaloid family, whereas the



Scheme 15 Fukuyama's synthesis of tetracyclic key intermediate **88**.



Scheme 16 Wipf's π-allyl palladium approach.

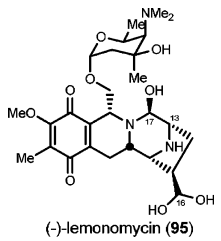


Fig. 8 (−)-Lemonomycin.

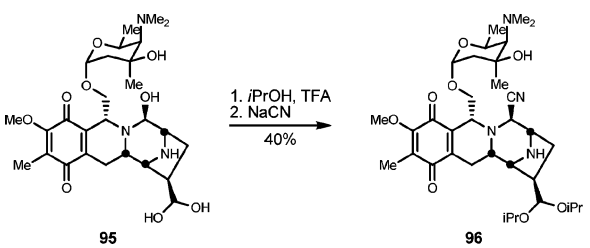
substitution pattern of the quinone ring is identical to the one in the naphthyridinomycins. The non-methylated nitrogen in the pyrrolidine substructure is new to this class of antibiotics, and the unit containing the carbons C-16 to C-13 and C-17 is possibly biosynthetically derived from glutamic acid. Another interesting feature of **95** is the high stability of the hydrate moiety formed at the C-16 aldehyde function. In addition, the 2,6-dideoxo-4-amino sugar is rare in nature, and the 3-hydroxy-3-methyl substitution pattern is exclusively found in **95**. In the same publication a semisynthetic analog (**96**) of **95** was described. Upon treatment with 2-propanol in trifluoroacetic acid followed by cyanation with sodium cyanide **95** was converted into its cyano-analog **96** as shown in Scheme 17.

Biological activity

Lemonomycin exhibits antimicrobial activity against a number of microorganisms (Table 2). The natural product **95** and its cyano derivative **96** also show strong *in vitro* cytotoxicity against the human colon cell line (HTC116) with IC_{50}s of 0.36 and 0.26 μg mL^{-1}, respectively.[46]

Total synthesis of (−)-lemonomycin

Only one total synthesis of **95** has been completed to date, by the Stoltz group in 2003.[47] The alkaloid was synthesized in

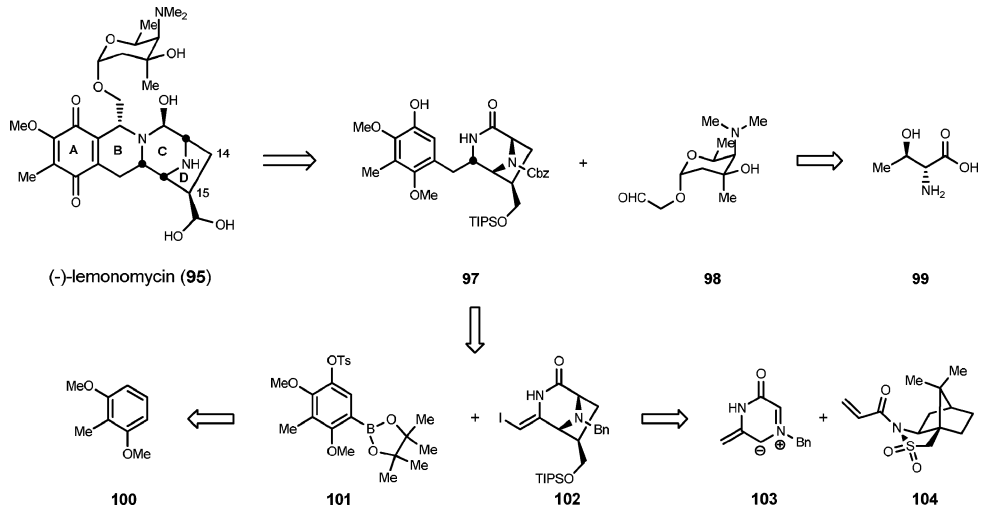


Scheme 17 Semisynthesis of a lemonomycin analog.

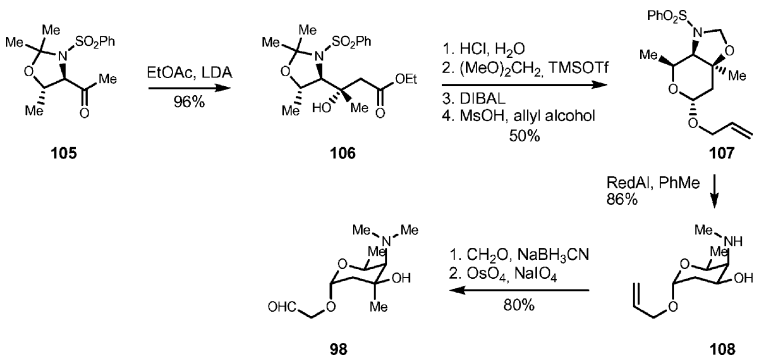
Table 2 Antimicrobial activities of lemonomycin (**95**)

Test organisms	MIC/μg mL^{-1}
Bacillus subtilis	0.05
Enterococcus faecium	0.2
MR*Staphylococcus aureus*	0.4
Staphylococcus aureus	0.2

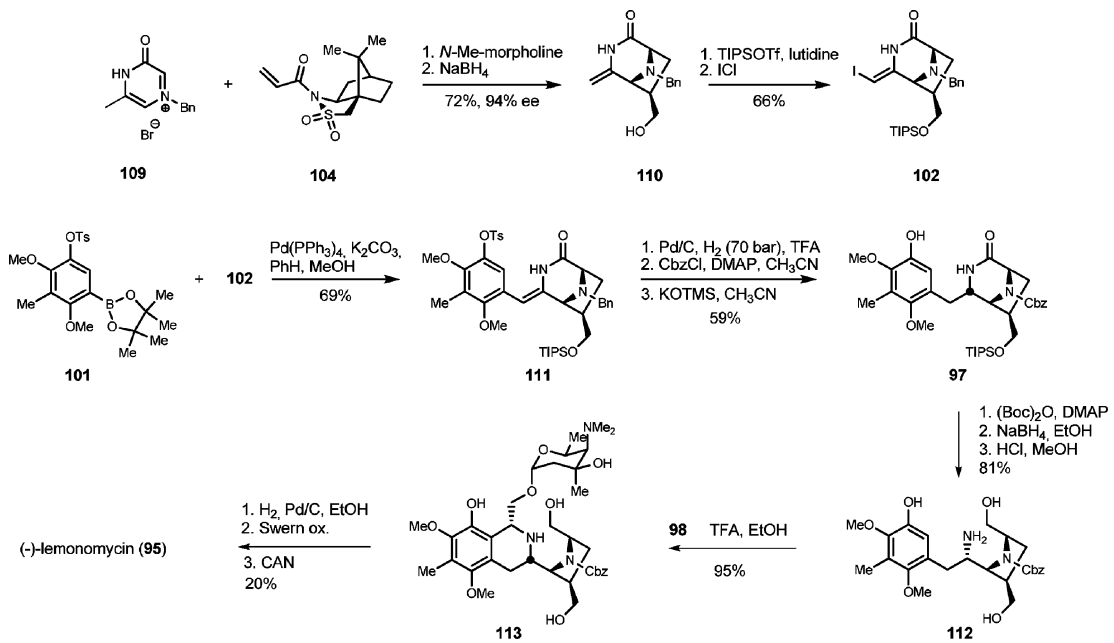
15 steps from readily accessible starting materials. Retrosynthetically (Scheme 18), a Pictet–Spengler reaction that incorporates the aminosugar moiety directly into the target compound without any glycosylation reaction or protection group leads back to aglycon **97**. A Suzuki coupling is used to disconnect **97** into vinyliodide **102** and arylboronate **101**. For the synthesis of **102**, which contains rings C and D, an asymmetric *exo*-selective Joule-type 1,3-dipolar cycloaddition[40] between azomethinylide **103** and Oppolzer's sultam **104** is applied. The aminopyranose subunit **98** was synthesized from the D-threonine derived ketone **105** (Scheme 19). A Felkin–Anh controlled addition of lithiated ethyl acetate furnished hydroxy ester **106** as a single diastereomer, which was converted into a δ-lactone on acid-mediated cleavage of the acetonide function. Then an oxazolidine ring was formed with dimethoxymethane. Diastereoselective reduction to the lactol and formation of the allyl glycoside led to bicycle **107** which was converted into amino alcohol **108** and, finally into aldehyde **98**. The synthesis of the *Z*-iodoenamide **102** was performed in four synthetic operations (Scheme 20). Deprotonation of oxidopyrazinium bromide **109** with *N*-methyl morpholine generated azomethinylide **103**, whose *in situ* addition to acrylamide **104** furnished, upon reduction with sodium borohydride, bicycle **110**. Silyl protection of the primary alcohol and iodination provided the desired precursor **102** for the Suzuki coupling reaction with **101** to furnish **111**, which was then stereoselectively reduced to the amine under high pressure conditions, with concomitant cleavage of the benzylic protection group. Cbz protection of the amine and cleavage of the sulfonic ester group furnished lactam **97**. As the reactivity of this amide was quite low, it was converted into the more reactive amine **112**, which successfully underwent Pictet–Spengler cyclization with aminopyranose acetaldehyde **98** to give tetrahydroisoquinoline **113** stereoselectively. After removal of the *N*-Cbz group, formation of the aldehyde hydrate and oxidation to the quinone, natural (−)-lemonomycin (**95**) was obtained.



Scheme 18 Stoltz's retrosynthetic analysis of (−)-lemonomycin.



Scheme 19 Stoltz's synthesis of lemonomycin—preparation of aminosugar **98**.



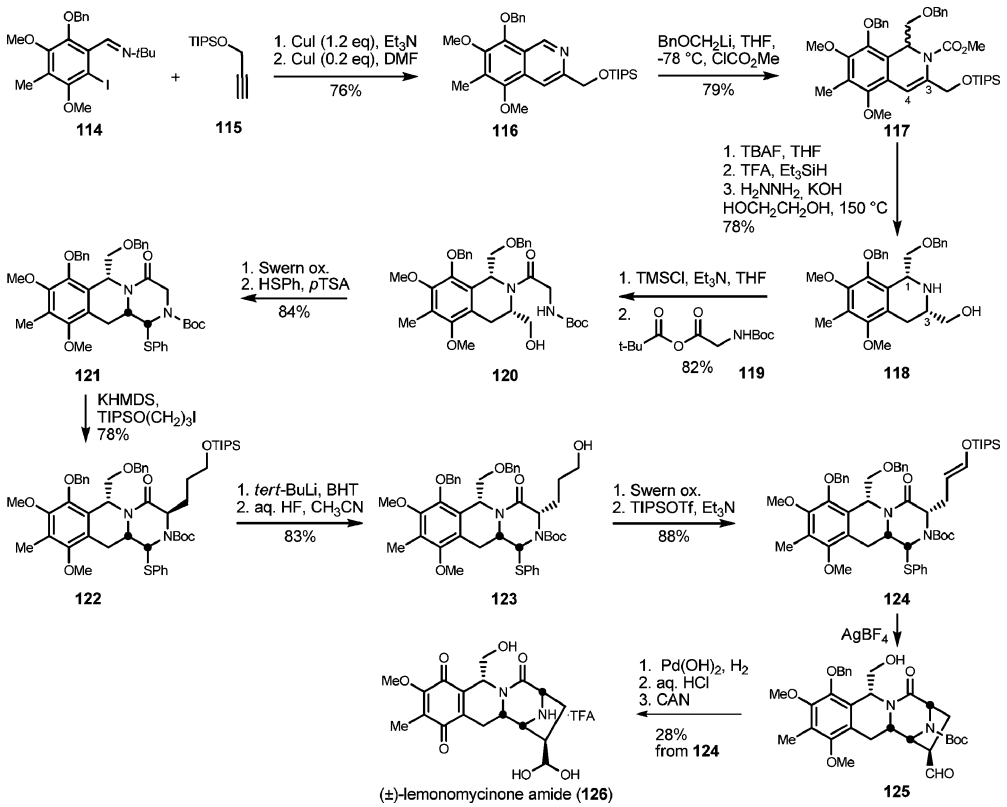
Scheme 20 Stoltz's total synthesis of (−)-lemonomycin.

In conclusion, the natural product was obtained in 15 steps, counting the longest linear sequence, in an overall yield of 3.1%.

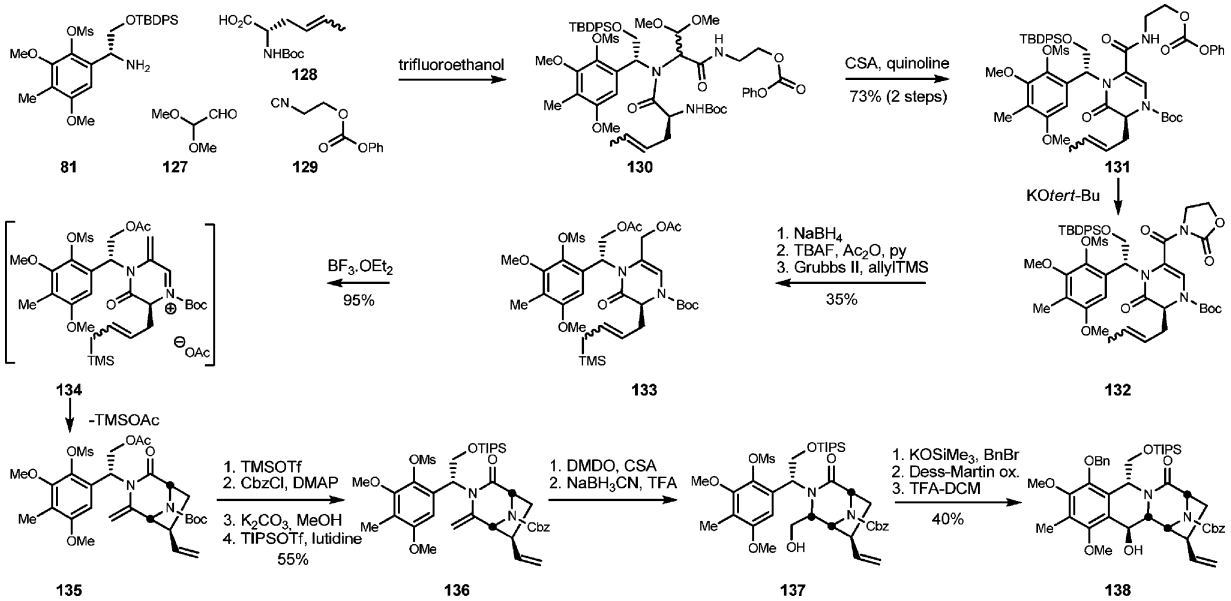
Uncompleted synthetic approaches toward lemonomycin

During the past three years no less than five uncompleted approaches to lemonomycin were disclosed. Thus, in 2005, Magnus and Matthews reported the racemic total synthesis of lemonomycinone amide **126**, an aglycon derivative that contains the characteristic tetracyclic core of lemonomycin.[48] The synthesis starts with the construction of rings A/B in form of isoquinoline **116** *via* a modified Larock synthesis by connecting *o*-iodoimine **114** with TIPS protected propargylic alcohol **115** under Castro conditions, followed by a copper catalyzed cyclization. Addition of benzyloxymethyl lithium to the imine function followed by trapping of the free amine with chloroformate provided 1,2-dihydroisoquinoline **117**. The primary alcohol function was deprotected, which directly led to the formation of an oxazolidinone. Stereoselective reduction of the 3,4-olefin by hydrogenation under ionic conditions gave the 1,3-*cis*-substituted tetrahydroisoquinoline. The carbamate was removed with hydrazine to provide amino alcohol **118**. Silyl-activated amide formation with **119** furnished intermediate **120**, which was converted into the corresponding hemiaminal by Swern oxidation as a 3 : 2 mixture of diastereomers. The synthesis of ring A–C fragment **121** was completed by a stereocontrolled formation of the *N*,*S*-acetal with thiophenol. The annulation of ring D started with an alkylation of amide **121** with (3-iodopropoxy)triisopropylsilane to give **122** as a single diastereomer. The undesired configuration at C-13 was inverted by deprotonation with *tert*-butyl lithium and reprotonation with BHT (2,6-di-*tert*-butyl-4-methyl phenol). Primary alcohol **123** was isolated after removal of the silyl protecting group. Swern oxidation and subsequent silyl enol ether formation furnished **124** as a suitable substrate for attaching ring D, which was achieved *via* a Mukaiyama type aldol addition of the silyl enol ether on a preformed *N*-acyliminium cation. Aldehyde **125** was obtained as a single diastereomer. Removal of the *O*-Bn and *N*-Boc protecting groups by aqueous hydrochloric acid furnished the corresponding amino aldehyde, which was present entirely in its hydrated form. Quinone formation with ceric ammonium nitrate gave (±)-lemonomycinone amide (**126**) as its trifluoroacetate (Scheme 21).

In 2005, Fukuyama and co-workers published the synthesis of a (−)-lemonomycin key intermediate (**138**).[49] The tetracyclic backbone of lemonomycin was assembled *via* key steps such as the Ugi 4-CC reaction, developed earlier (Scheme 15), but now with the novel isocyanide **129**, a cross-metathesis with an allyl silane and an intramolecular Hosomi–Sakurai type reaction to establish the bicyclo[3.2.1]octane framework **135** with complete stereoselectivity (Scheme 22). The synthesis starts with the Ugi 4-CC reaction between two amino acid derivatives **81** and **128** which were connected with isonitrile **129** and glyoxyaldehyde dimethylacetal **127** to provide dipeptide **130**. The formation of the cyclic enamide **131** was achieved by treatment with camphorsulfonic acid and quinoline. Potassium *tert*-butoxide was used as a strong base to close an oxazolidinone ring, which was subsequently reduced to the primary alcohol. Desilylation, followed by acetylation and



Scheme 21 Magnus' synthesis of (±)-lemonomycinone amide.



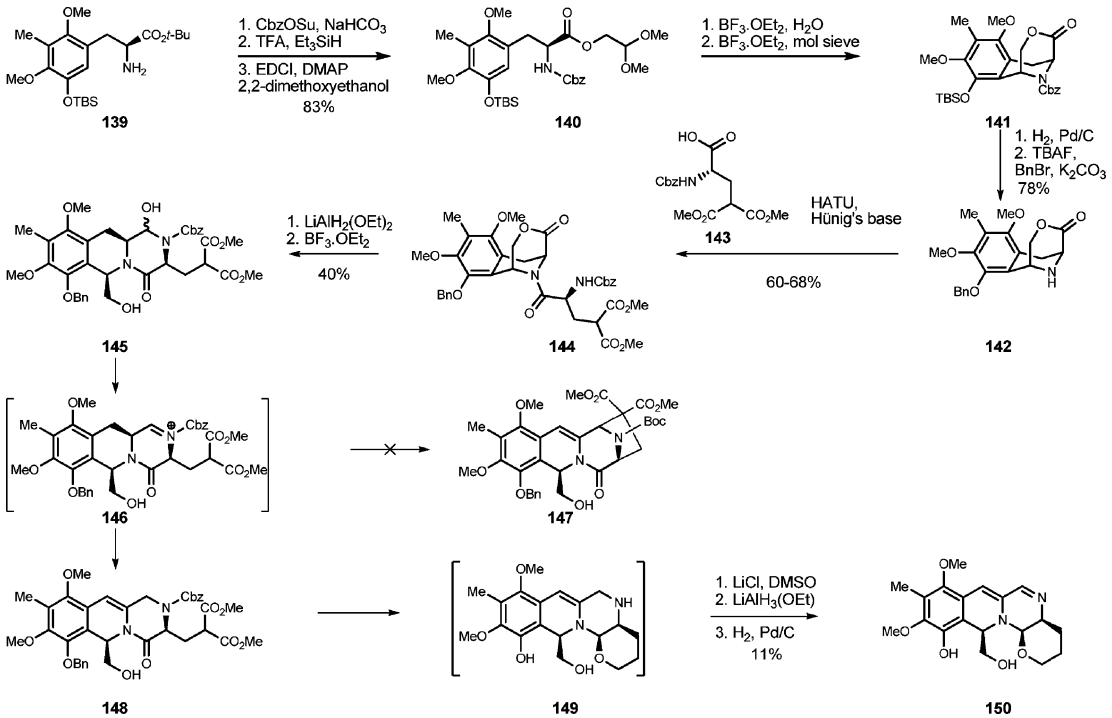
Scheme 22 Fukuyama's synthesis of lemonomycin precursor **146**.

cross-metathesis with allyl-TMS-silane, furnished cyclization precursor **133**. Acetate 1,4-elimination with boron trifluoride etherate generated the conjugated acyliminium cation **134**, which was intramolecularly trapped by the allylsilane to provide the tricyclic product **135** with complete stereocontrol. After manipulation of the N- and O-protecting groups, cyclic enamide **136** was obtained. DMDO (dimethyldioxirane) epoxidation of the exocyclic double bond furnished an acyliminium cation which was reduced from the less hindered *exo*-face to generate alcohol **137** selectively. The aromatic OMs group was exchanged for OBn. Finally, oxidation of the primary alcohol to the aldehyde followed by a cyclization closely related to the one shown in Scheme 15 provided tetracycle **138**.

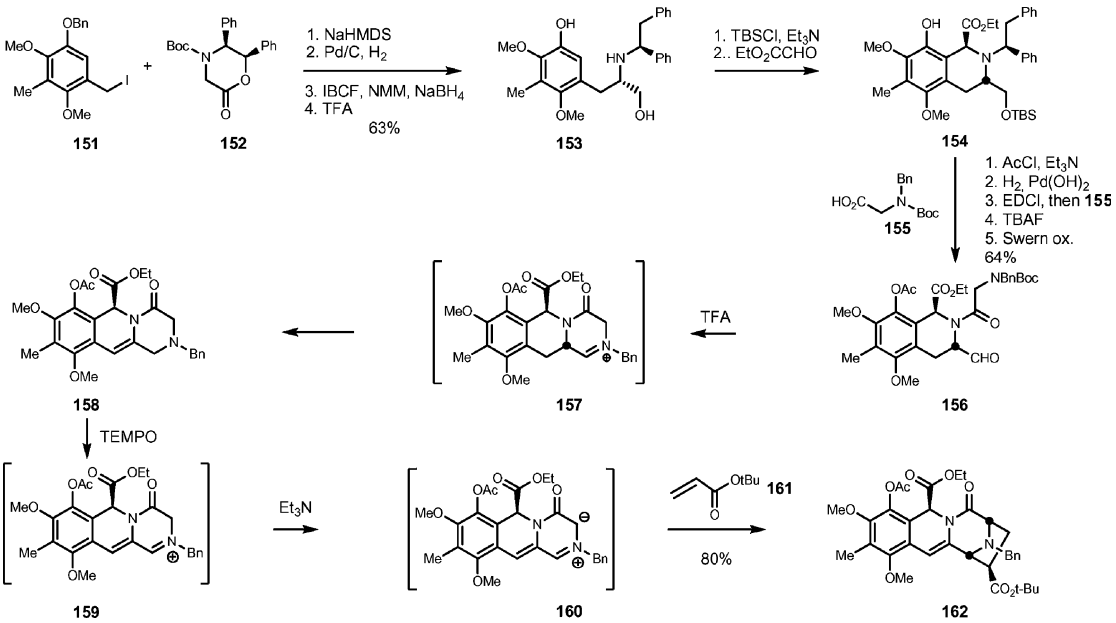
In 2006, Zhu *et al*. reported their work toward lemonomycin, which was terminated on reaching the tetracyclic compound **150** (Scheme 23).[50] The key step is a Mukaiyama-type cyclization of acetal **140** to **141** to close ring B. This strategy is similar to the one used by Fukuyama (Schemes 15 and 22). Amino-ester **139** was first converted into ester **140**. Chemoselective hydrolysis of the dimethoxy acetal furnished the desired aldehyde, which cyclized under Lewis acid catalysis to form the bridged tetrahydroisoquinoline **141**. Removal of the Cbz group and exchanging the phenolic TBS for a Bn group generated amino lactone **142**, which was coupled with L-5,5′-dimethyl-*N*-Cbz-4-carboxyglutamate (**143**) to give amide **144**. Reduction with $LiAlH_2(OEt)_2$ generated a lactol which upon treatment with boron trifluoride etherate generated aminal **145**. Under further effect of the Lewis acid acyliminium cation **146** was generated. Unfortunately, the desired formation of **147** *via* intramolecular malonate/acyliminium addition failed, most probably because of steric hindrance. Instead, an isomerization to enamine **148** was observed. Decarboxylation of **148** under Krapcho conditions[51] afforded a monoester. Reduction of ester and amide generated a cyclic aminal. Hydrogenolytic removal of the Cbz and the Bn groups gave unstable amine **149**, which upon purification underwent autoxidation to furnish imine **150** as the most stable conjugated product.

Another uncompleted approach to lemonomycin was reported in 2007 by Williams *et al*.[52] The key step is based on a diastereo- and regiocontrolled Joule-type 1,3-dipolar cycloaddition between *tert*-butyl acrylate and azomethine ylide **160** (Scheme 24), similar to the one used by Stoltz (Scheme 20). For the enantiocontrolled synthesis of tetrahydroisoquinoline **154** the authors used their own methodology by alkylating the chiral glycine derived template **152** with benzyl iodide **151**. Reductive transformations, followed by cleavage of the *N*-*tert*-butoxycarbamate group gave amino alcohol **153**, which was *O*-silylated and subjected to a Pictet–Spengler cyclization with ethyl glyoxylate to afford tetrahydroisoquinoline **154** as a single diastereomer in high yield though with the wrong configuration at the benzylic position. Acetylation of the phenolic OH group, followed by hydrogenolytic removal of the dihydrostilbene appendage furnished the free amine function, which was acylated with 2-(benzyl(Boc)amino)acetic acid (**155**). Cleavage of the silyl protecting group and Swern oxidation afforded amino aldehyde **156** as a precursor for azomethine ylide **160**. Removal of the *N*-Boc group with trifluoroacetic acid induced cyclization to iminium cation **157**, which rapidly tautomerized to the thermodynamically favored conjugated enamine **158**. Oxidation of this intermediate with tetramethyl piperidine oxyl (TEMPO) afforded the fully conjugated iminium ion which was deprotonated to give azomethine ylide **160**. Cycloaddition with the acrylate led to compound **162** as a single diastereomer.

Recently, Mulzer and co-workers completed a stereocontrolled synthesis of compound **172** which contains the entire tetracyclic core framework of (−)-lemonomycin.[53] Their strategy is based on the generation of a highly oxygenated tetrahydroisoquinoline **167**, which was coupled with Myers' cyanohydrin side-chain (**168**) in a Strecker-like amino alkylation. For the synthesis of intermediate **167** (Scheme 25), aryl bromide **68** was lithiated and coupled with Fmoc–Garner's aldehyde **163** to provide secondary alcohol **164a**/**b** as a mixture of diastereomers. After an oxidation–reduction sequence,

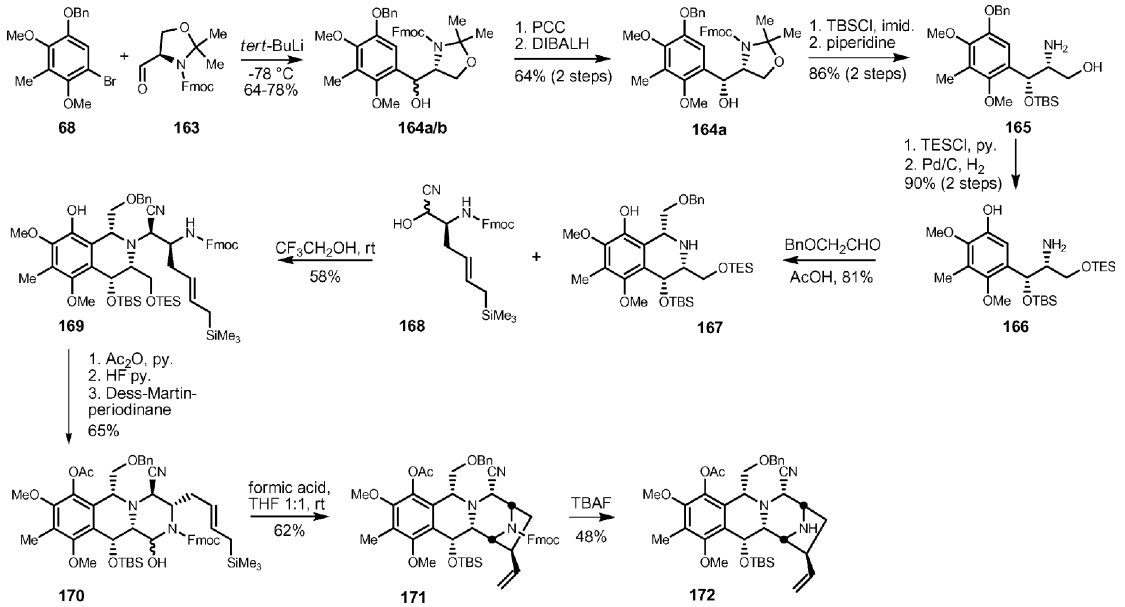


Scheme 23 Zhu's synthesis of a tetracyclic enamide intermediate.

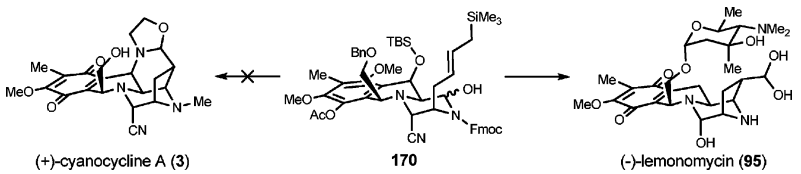


Scheme 24 Williams' synthetic approach towards lemonomycin.

syn-diastereomer **164a** was obtained as the only product. TBS protection followed by simultaneous removal of the Fmoc and acetonide protecting groups furnished amino alcohol **165**. TES protection of the primary OH group followed by debenzylation of the phenol gave **166** which was converted into **167** *via* a Pictet–Spengler cyclization with benzyloxy acetaldehyde in an acidic medium. As outlined before, key intermediate **167** was successfully connected with silylated cyanohydrin side-chain **168** in a Strecker-type reaction to provide compound **169**. Acetylation of the free phenol, liberation of the primary alcohol, and Dess–Martin periodinane promoted oxidation generated the aldehyde which was trapped by the Fmoc-protected nitrogen to yield an epimeric mixture of carbinolamines **170**. Treatment of this mixture with formic acid led to an *N*-acyliminium cyclization. At the same time, the nitrile group was isomerized into the equatorial position to furnish cyclized product **171**. Upon treatment with TBAF the desired tetracyclic compound **172** was isolated.



Scheme 25 Mulzer's approach toward a tetracyclic key intermediate.



Scheme 26 Stereochemical consequences of the acyliminium cyclization.

Conclusions

Despite long-lasting and widespread activity, only three independent syntheses have been completed of cyanocycline A, and only one of lemonomycin. This observation underlines the complexity of the targets and the problems encountered in following the various strategies. It is also remarkable that cyanocycline A and lemonomycin, despite their obvious similarity, require different strategies to install the pyrrolidine D-ring. This discrepancy is obviously due to the opposite configuration at C-15 (lemonomycin) and C-4 (cyanocycline A) in the pyrrolidine bridge (Scheme 26). In lemonomycin this stereochemical problem is readily solved either by the Joule cycloaddition or by acyliminium cyclizations, which, as observed for intermediate **170**, place the 15-16-appendage automatically into the less hindered *exo*-position. In the cyanocycline core, however, this would mean that the C-3 aldehyde could not be used for forming rings B and A. Thus, the pyrrolidine ring has to be assembled with the correct configuration at C-4 prior to its incorporation in the larger framework. This little detail may serve as an illustration how, in both cases, an intriguing fine-tuning of synthetic methodology had to be applied, which makes this synthetic area a particularly attractive test ground for the development of new ideas.

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