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The diversity and utility of arylthiazoline and aryloxazoline siderophores: challenges of total synthesis

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Siderophores are unique ferric ion chelators produced and secreted by some organisms like bacteria, fungi and plants under iron deficiency conditions. These molecules possess immense affinity and specificity for Fe^{3+} and other metal ions, which attracts great interest due to the numerous possibilities of application, including antibiotics delivery to resistant bacteria strains. Total synthesis of siderophores is a must since the compounds are present in natural sources at extremely small concentrations. These molecules are extremely diverse in terms of molecular structure and physical and chemical properties. This review is focused on achievements and developments in the total synthesis strategies of naturally occurring siderophores bearing arylthiazoline and aryloxazoline units.

1 Introduction

Iron is an exceptionally versatile cofactor that is indispensable for a plethora of biochemical reactions in both mammalian hosts and pathogenic microorganisms. Its acquisition and regulation is crucial for efficacious microbial growth and survival. Deficiency can hinder vital cellular processes such as respiration and proliferation, while an excess may cause toxic effects by inducing oxidative damage through reactive oxygen species produced in the Fenton and Haber–Weiss reactions.[1] In the pre-oxygen era, microorganisms were able to exploit highly soluble Fe(II). Although iron is still abundant in the Earth's crust, in the aerobic environment Fe(III) exists as insoluble ferric hydroxide, largely inaccessible to microorganisms.

To supply and regulate iron, microorganisms have evolved sophisticated iron acquisition and trafficking systems.[2,3] Under iron depleted conditions, bacteria and fungi produce siderophores,[4] low molecular weight (MW under 1500 Da) molecules with high binding affinity for ferric iron, capable of solubilizing the ferric hydroxide polymers and sequestering iron from a host's proteins and ligands. Low iron concentrations trigger a "signal" to start biosynthesis of the appropriate siderophores and the proteins involved in siderophore uptake machinery. As soon as sufficient amount of iron is transported and accumulated inside the cell, its acquisition system is turned off.[5]

Since the early 1950s, when the first three siderophores were isolated and identified as growth factors of bacteria, 270 different siderophores have been structurally characterized (from over 500 identified) and this number is growing.[6]

The process of isolation of siderophores from natural sources is very tedious, inefficient, and thus expensive. The unique chemical structure diversity and numerous applications both in medicine and industry, prompted scientists to prepare these molecules by total synthesis (more in Sections 3.1 and 3.2). Over the last decades only two reviews concerning the synthesis of naturally occurring siderophores were published.[7,8]

Total synthesis allows for obtaining analogs of naturally occurring siderophores – mimics, which are extremely important in biomedical applications, for example in the Trojan horse strategy (antibiotic therapy). This approach allows for a deeper investigation of the relationship between structure and metal complexing properties or bioactive function. In the retrosynthetic analysis essential to plan the total synthesis of siderophores, genetic and biochemical knowledge of siderophore biosynthesis is extremely useful. Siderophore retrosynthesis is based on finding the structure of target

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compound synthons that would correspond to the following stages of biosynthesis.[8,9]

The review covers total synthesis strategies of naturally occurring siderophores with arylthiazoline and aryloxazoline subunits. The keynote of this work is to present known strategies for preparation of this particular group of siderophores with a detailed analysis of the newest and most efficient approaches. This overview allows tracking the progress in this area made over the years, and identifying the possibilities for further development. In addition, the review describes the synthesis of analogues of some siderophores with arylthiazoline and aryloxazoline subunits, thus showing the impact of structural variations on the activity of these compounds.

Main classification of naturally occurring siderophores is based on the type of functional groups involved in the chelation of iron ions includes three basic groups such as catecholate, hydroxamate, and α-hydroxycarboxylate (Fig. 1).[10] To date more than 100 siderophores bearing analogs of this type of donors have been isolated.[11] In our review, we would like to focus on siderophores that have an aromatic phenolate and/or catecholate fragment in their structure linked directly to a thiazoline/oxazoline moiety, which will be called arylthiazolines/aryloxazolines (this nomenclature is not commonly used in siderophores classification).

Numerous reviews have been published in the literature describing the types of siderophores produced by microbes, their properties, functions, as well as their acquisition machineries; for a comprehensive discussion, the readers are referred to selected reviews and the references therein.[3–12] Arylthiazoline and aryloxazoline-type siderophores, so far have been only rarely discussed as a group,[8,13] showing the diversity of the structures and the total synthesis approach, all illustrated by most prominent examples.

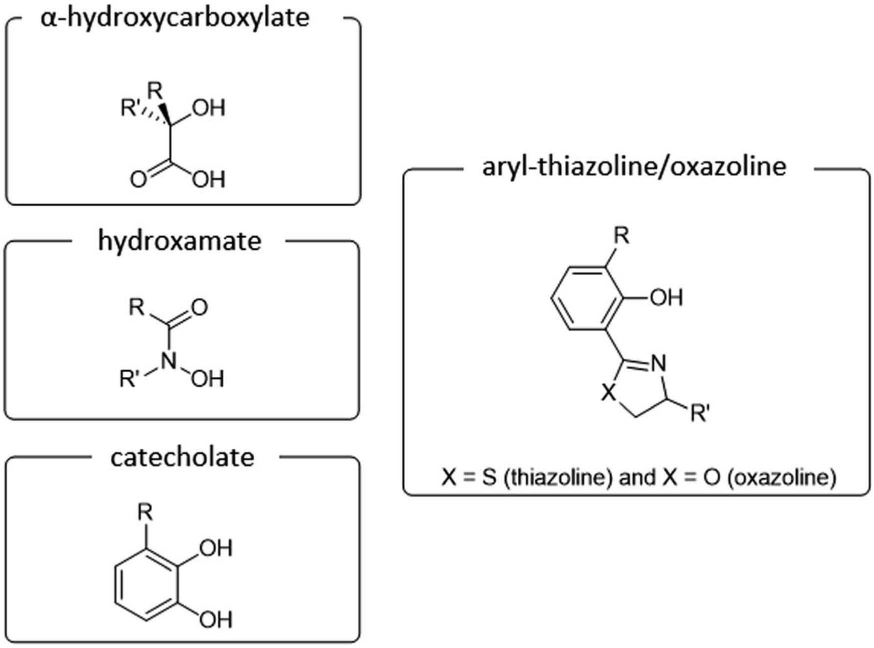


Fig. 1 The iron-binding moieties in various types of siderophores.

2 Origins and total synthesis of arylthiazoline and aryloxazoline siderophores and analogues

2.1 Arylthiazoline siderophores: origin and total synthesis

The group of arylthiazoline-based siderophores are characterized by the presence of a 2-thiazoline framework in the structure of a substituted aromatic ring and two or three linearly connected heterocyclic subunits. Phenolic hydroxyl group, the nitrogen atom of the thiazoline ring and usually a terminal carboxyl group are involved in iron coordination. The group members differ mainly in substituents of the phenolic ring, and modifications of the terminal thiazolidine fragment. Moreover, the configuration of the stereogenic centres should be also taken into account (Fig. 2).

2.1.1 Pyochelin. Pyochelin is a prototype of arylthiazoline-based siderophores. It was first isolated in 1978 from iron-deficient cultures of *Pseudomonas aeruginosa* ATCC 15692 by Liu and Shokrani.[14] Cox and co-workers were pioneers in studying pyochelin properties,[15,16] and established its structure in 1981.[17]

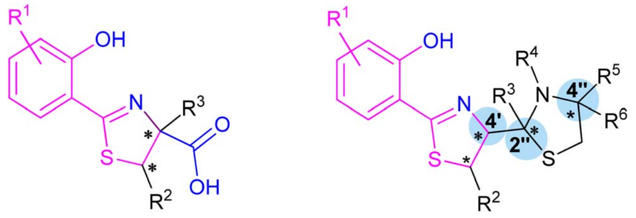


Fig. 2 Two typical structures of thiazoline-based siderophores. Fragments involved in iron coordination marked blue. Stereogenic centres indicated by asterisks.

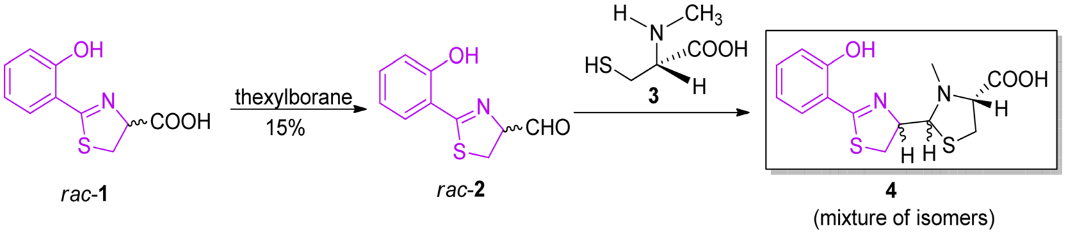
Pyochelin is produced mainly by Gram-negative *Pseudomonas*[18] and *Burkholderia*,[19] highly aggressive opportunistic pathogenic bacteria that are common causative agents for severe respiratory infections affecting patients with compromised immunity. Moreover, *P. aeruginosa* is responsible for highly lethal hospital-acquired infections as it is unaffected by many disinfecting agents and its strains are often resistant to the majority of antibiotics.[20] However, pyochelin was also isolated from Gram-positive bacteria, *Streptomyces*.[21]

This unusual siderophore is built of one phenol moiety connected to thiazoline ring which is attached to thiazolidine part with a methyl-substituted nitrogen atom and a carboxylic group attached to the adjacent position. It has three chiral centres at positions C-4′, C-2″ and C-4″ with absolute configurations (*R*,*R*,*R*) (pyochelin I), but the C-2″-centre readily isomerizes to the (*S*) form (pyochelin II) yielding a equimolar mixture of two epimers.[22] On the other hand, Schalk *et al.*[23] reported about four diastereoisomers which were obtained by organic synthesis: pyochelin I (4′*R*,2″*R*,4″*R*), pyochelin II (4′*R*,2″*S*,4″*R*), neopyochelin I (4′*S*,2″*R*,4″*R*) and neopyochelin II (4′*S*,2″*S*,4″*R*) with varying proportions depending on starting compound (Fig. 2).

The synthesis of pyochelin was first described in 1988 by Cox and co-workers in a three-step non-stereoselective procedure.[16] The acid intermediate **1** was prepared by method of Mathur *et al.*[24] and converted to the corresponding aldehyde **2**, which was condensed further with L-*N*-methylcysteine **3**, providing a mixture of pyochelin isomers **4**, with an overall yield of approximately 5% (Scheme 1).

In a following paper,[25] by optimising the reaction conditions, the overall yield was improved to 65%. The performed synthesis allowed to obtain four out of eight possible stereoisomers in the 4 : 1 : 1 : 4 ratio (Fig. 3). Based on the comparison of NMR spectra to the one of 4-methylpyochelin I methyl ester, whose structure was resolved by X-ray crystallography, Cox assigned the absolute configuration of four stereoisomers, *i.e.*, pyochelins I and II and neopyochelins I and II.

An improved synthesis of pyochelin was described by Zamri and Abdallah, who proposed a stereocontrolled synthetic pathway and obtained a mixture of four diastereoisomers in the 2 : 1 : 2 : 5 ratio (Scheme 2).[26,27] In the new proposed synthesis, the method of Mathur *et al.*[24] for acid preparation (**1**, Scheme 2) was replaced by a protocol described by Bergeron *et al.* to avoid epimerization of the C-4′ stereogenic centre.[28] The acid **1** was converted to *N*-methoxy-*N*-methyl hydroxamate intermediate **7**; *N*,*O*-dimethylhydroxylamine was coupled to compound **1** using diethyl cyanophosphonate (DECP) as coupling reagent, providing hydroxamate **7** in excellent yield (94%); reduction of



Scheme 1 Non-stereoselective synthesis of pyochelin.[16]

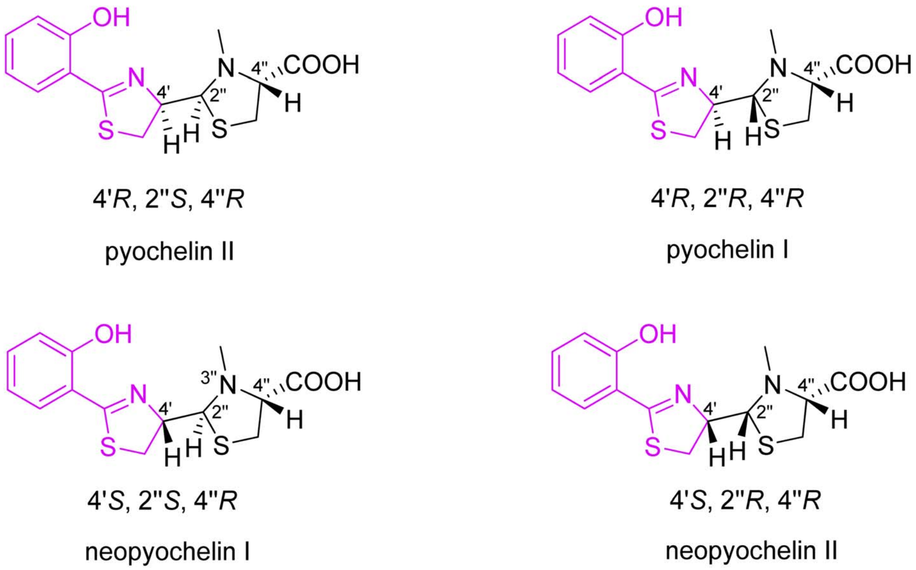
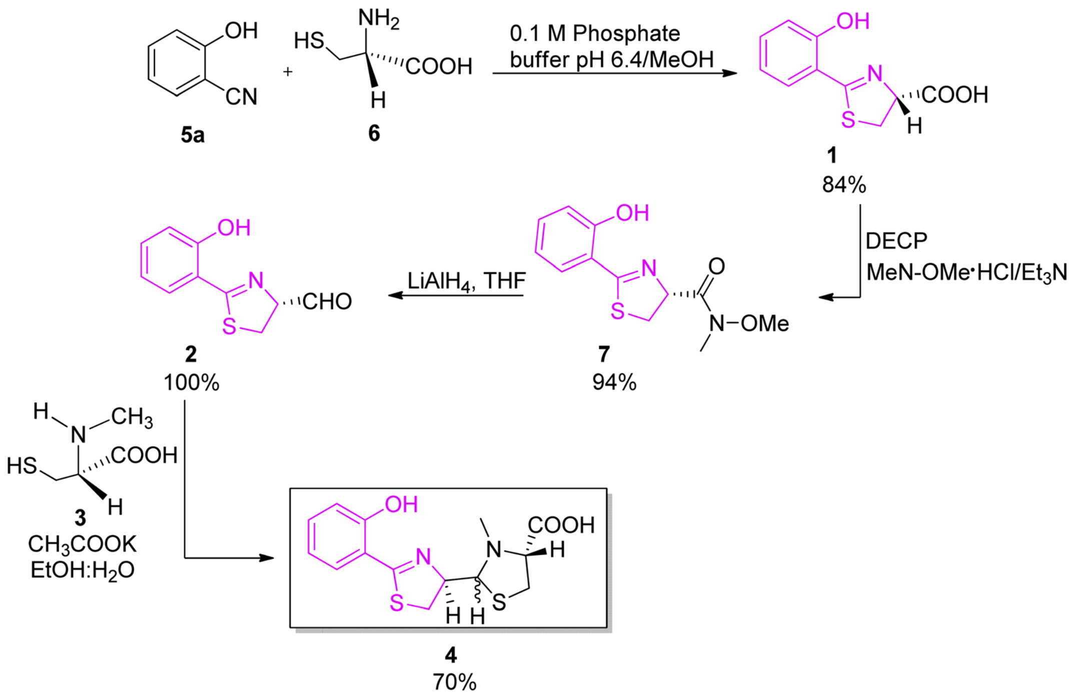


Fig. 3 Synthesized stereoisomers of pyochelin **4**.[25]

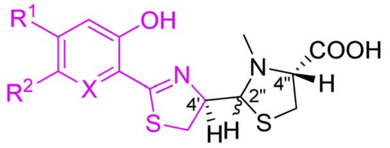


Scheme 2 Stereoselective synthesis of pyochelin proposed by Zamri and Abdallah.[26,27]

the hydroxamate **7** by excess $LiAlH_4$ afforded an aldehyde **2**. The final condensation step was accomplished by the known methodology between aldehyde **2** and L-*N*-methylcysteine hydrochloride **3** in a 4 : 1 mixture of ethanol and water in the presence of potassium acetate, and yielded 70% of pyochelin **4** as a mixture of four diastereoisomers. In natural pyochelin, the absolute configurations are (4′*R*) and (4″*R*). During the synthesis of pyochelin, partial epimerization occurs at C-4′ while the absolute configuration at C-4″ remains unaffected thus providing a mixture of pyochelin isomers: pyochelin I and II, and neopyochelin I and II.

Synthetic analogs of pyochelin can enrich the library of biologically active molecules, to tune the chemical or physical properties of the pyochelin, as well as to provide a tool for the investigation of the structure–function relationship of the transporters. An appropriate architecture of ligands and the geometry of complexes allow a control of efficient iron coordination and bacterial recognition. However, the epimerization at the C-2″ chiral centre shows the difficulty in preparing enantiopure synthetic pyochelin analogs.

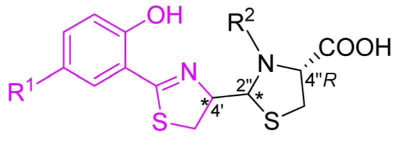
The first pyochelin analogs were only accessed by mutasynthesis (Fig. 4).[29] The mutasynthetic pyochelin analogs as mixtures of two rapidly interconverting isomers I (4′*R*,2″*R*,4″*R*) and II (4′*R*,2″*S*,4″*R*) were compared to pyochelin in their ability to transport iron in *P. aeruginosa*. Isomeric forms were transformed into methyl esters and separated (in case of **8c** only one form I was obtained). 4-Methylpyochelins **8b** and *epi*-**8b** were more active than pyochelin in ^{55}Fe(III) transport, while the other two analogs 5-fluoropyochelin **8a** and *epi*-**8a** and 6-azapyochelin **8c** demonstrated a decreased iron uptake.



8a R^1 = H, R^2 = F, X = CH (4′*R*, 2″*R*, 4″*R*)
epi-**8a** R^1 = H, R^2 = F, X = CH (4′*R*, 2″*S*, 4″*R*)
8b R^1 = CH_3, R^2 = H, X = CH (4′*R*, 2″*R*, 4″*R*)
epi-**8b** R^1 = CH_3, R^2 = H, X = CH (4′*R*, 2″*S*, 4″*R*)
8c R^1 = H, R^2 = H, X = N (4′*R*, 2″*R*, 4″*R*)

Fig. 4 Pyochelin analogs accessed by mutasynthesis.[29]

Extensive work in the field of synthetic pyochelin analogs was performed by the group of Schalk, Mislin and their coworkers. The Schalk group focused on studying the properties of several biologically active analogs and conjugates of pyochelin **9a–c**, as will be described on several examples. In the first generation, the effect of the configuration on bacterial uptake was tested (Fig. 7).[30] Uptake rates of ^{55}Fe(III), tested on *P. aeruginosa* (ATCC 15692) as well on its pyoverdine defective mutant CDC5 (pPVR2), suggested that the configuration at carbon C-4′ has no effect on the biological properties of pyochelin. Zinc complexation of the mixture (4′*R*,2″*R*,4″*R*) and (4′*R*,2″*S*,4″*R*) pyochelins provided exclusively (2″*R*) diastereomer, which indicated template direction effect. Moreover, substitution in the aromatic part (R^1, Fig. 7) or amine group in thiazolidine part (R^2, Fig. 5) did not affect dramatically the biological properties of the corresponding analogs compared to pyochelin.



9a (4'*S*) R^1 = H, R^2 = H
9b (4'*S*) R^1 = H, R^2 = Boc
9c (4'*R*, *S*) R^1 = NHBoc, R^2 = CH_3

Fig. 5 Structure of first generation of synthetic pyochelin analogs.[30]

In an additional series of pyochelin analogs, the thiazoline ring was replaced by a thiazole moiety (Fig. 6).[31] The series was prepared using the synthetic protocol for pyochelin analogs through Weinreb amide intermediate,[32] and tested for ^{55}Fe uptake by *P. aeruginosa*, strains PAO1 and PAD07. As phenol function is crucial for the coordination of Fe(III),[33] analogs bearing a methylated hydroxyl group failed to transport Fe(III), and only analogs **10a**, **10c**, **10e** and **10f** were able to transfer iron inside the bacteria.

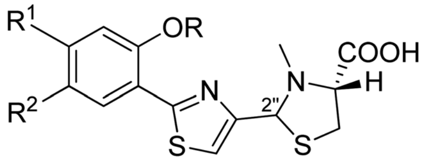
2.1.2 Yersiniabactin, micacocidin and piscibactin.

Micacocidin belongs to a well-known family of zinc-containing metallophores.[34] It was isolated from *Pseudomonas* culture primarily as Zn(II) complex together with Cu(II) and Fe(III) analogs, and extensively studied by the Aburahi Laboratories.[35] The micacocidin structure was determined by single crystal X-ray crystallographic analysis of its Zn(II) complex,[36] which indicated the presence of an aliphatic side chain on the aromatic ring and a methyl substituent in the nitrogen atom in the thiazolidine ring. This metabolite is also produced by the economically relevant plant infecting bacterium *Ralstonia solanacearum* (which produces staphyloferrin B as main siderophore),[37,38] and shows strong activity against *Mycoplasma pneumoniae*, a pathogen responsible for community-acquired pneumonia.[34]

Total synthesis of micacocidin was performed by Ino and co-workers.[39–41] There are five stereogenic carbon atoms in its structure. Cysteine was utilised as a chiral source for C-9, C-12 and C-18 centres, and for generation of the (*S*) secondary alcohol on C-14 by a stereoselective reduction of ketone. C-10 chirality was generated at a final stage by formation of a Zn complex.

Arylthiazoline part was synthesised starting from 3-methoxy-*N*,*N*-dimethylbenzylamine **11** which was converted to intermediate **12** in 5 steps and a total yield of 70%, using the procedure described by Kamikawa.[42] Next, condensation of **12** with *p*-methoxybenzyl (PMB)-protected D-cysteine provided compound **13** which was cyclized using PCl_5 to obtain thiazoline derivative in 95% yield. Methyl deprotection of both ether and ester using boron tribromide provided carboxylic acid **14**, which was subsequently converted to Weinreb amide **15** using bis(2-*oxo*-3-oxazolidinyl)phosphinic chloride (BOP-Cl) coupling reagent. Following phenol protection by *tert*-butyldiphenylsilyl (TBDPS) group, the Weinreb amide was reduced by $LiAlH_4$ to afford aldehyde **16**, the desired segment of micacocidin (Scheme 3).

The second synthon[41] was prepared starting from thiazolidine **18** which could be obtained from L-cysteine hydrochloride **17** in a two-step route,[43] followed by the reaction with carbonyldiimidazole (CDI) and a subsequent condensation with methyl isobutyrate, leading to keto-ester **19**. Reduction of the ketone function and construction of an oxazolidinone ring provided compound **20.** Condensation of **20** with 2-methyl-(*S*)-cysteine methyl ester hydrochloride using CDI yielded **21.** Reaction with TFA in refluxing toluene resulted in cyclization of



10a-h
6 - 52 %

10a R = H, R^1 = H, R^2 = H (2"*R*)
10b R = Me, R^1 = H, R^2 = H (2"*R,S*)
10c R = H, R^1 = OH, R^2 = H (2"*R,S*)
10d R = Me, R^1 = OH, R^2 = H (2"*R,S*)
10e R = H, R^1 = NH_2, R^2 = H (2"*R,S*)
10f R = H, R^1 = H, R^2 = NH_2 (2"*R,S*)
10g R = Me, R^1 = H,R^2 = NH_2 (2"*R,S*)
10h R = Me, R^1 = H, R^2 = F (2"*R,S*)

Fig. 6 Pyochelin analogs based on the thiazole ring.[31]

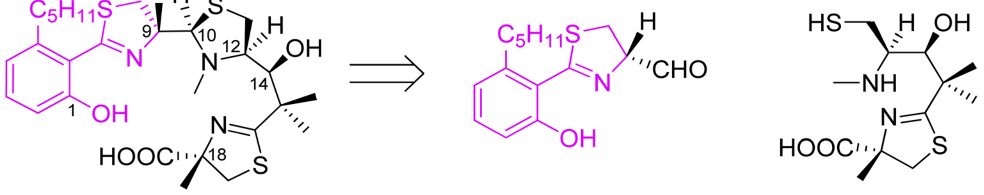
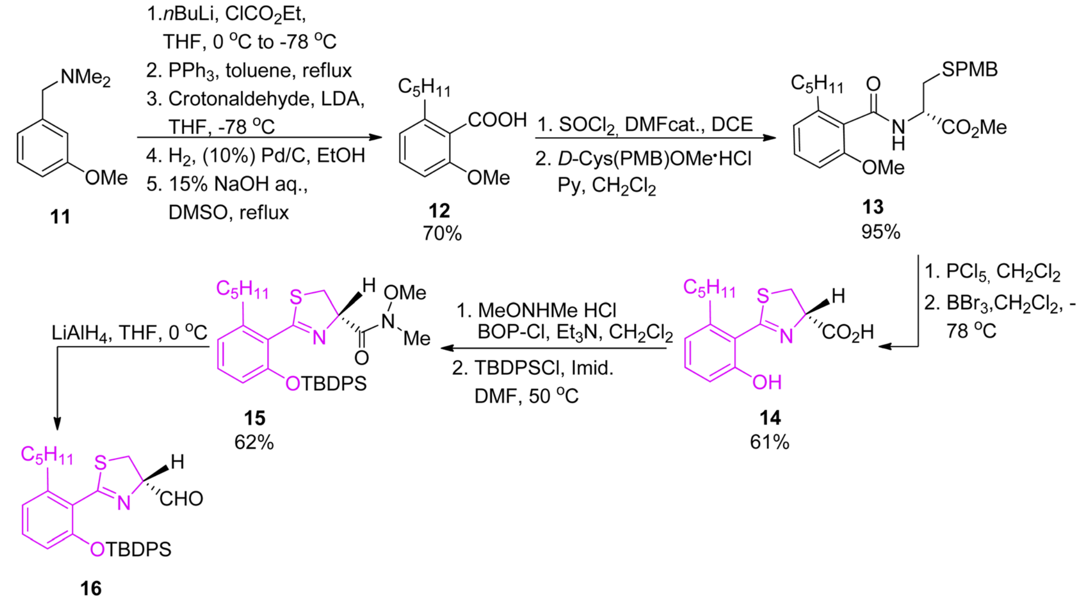


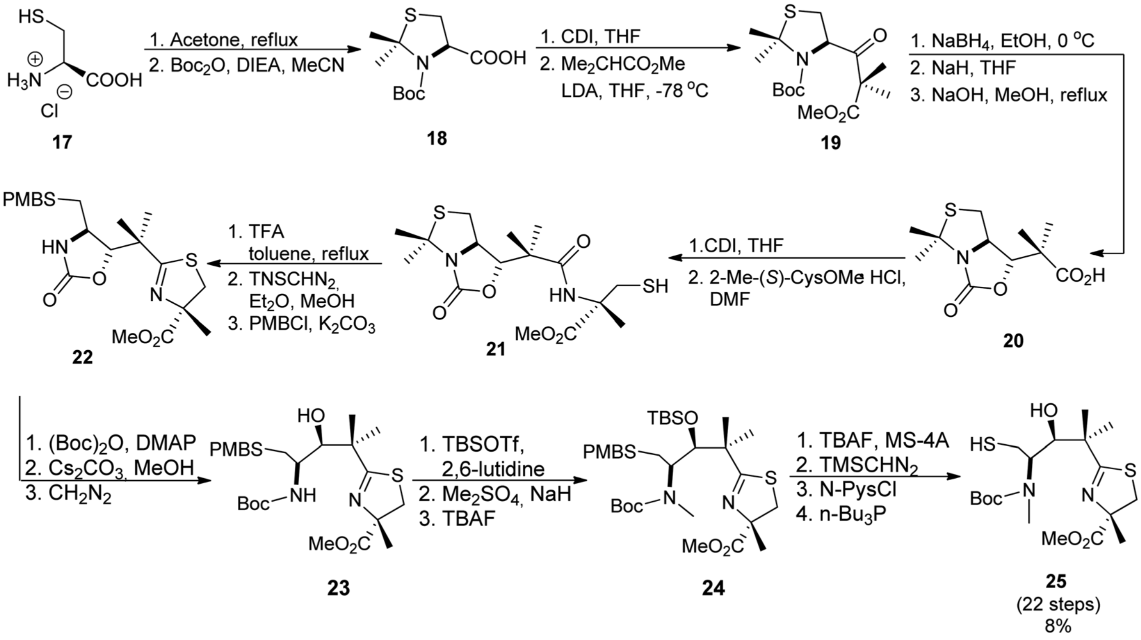
Fig. 7 Retrosynthetic analysis of micacocidin.[39–41]



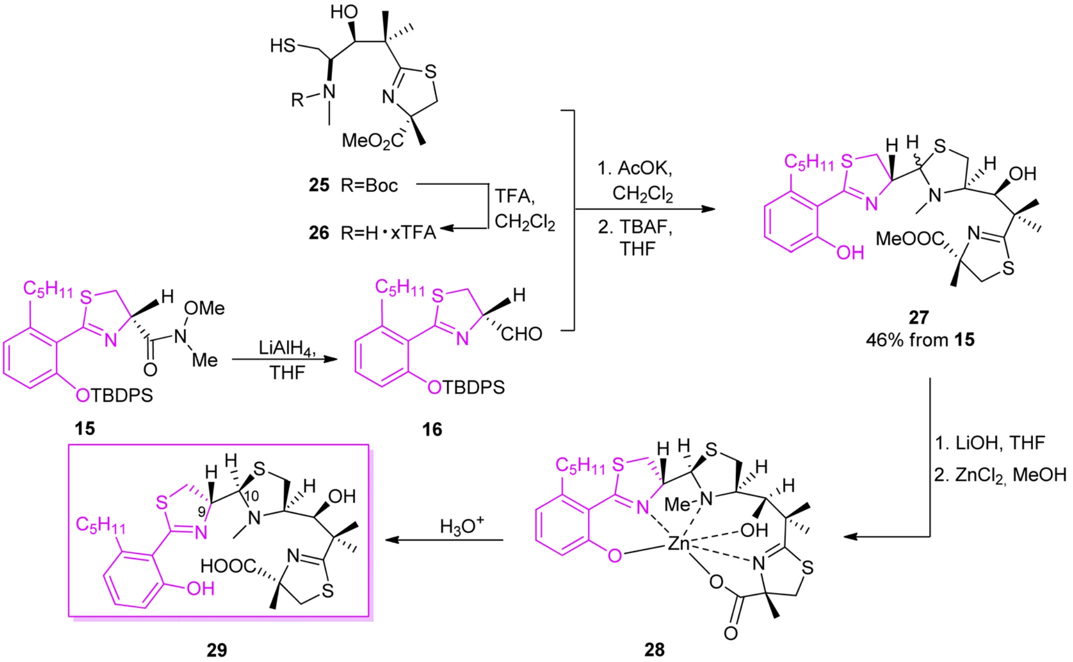
Scheme 3 Synthesis of the thiazoline synthon of micacocidin.[39,40]

the *N*-acylcysteine. Treatment with (trimethylsilyl)diazomethane restored the methyl ester moiety which was hydrolyzed during the reaction and provided **22**. Cleavage of the oxazolidinone ring was achieved in several steps and provided Boc-protected segment **23**. A subsequent hydroxyl group protection and *N*-methylation led to intermediate **24**, which was further deprotected yielding building block **25** with free hydroxyl and thiol residues (Scheme 4). Hydrolysis provided compound **26** which was condensed with the first synthon **16** as shown in Scheme 5. The TBDPS-protected aryl thiazoline fragment **16** was fairly labile, it was stored as Weinreb amide **15** which was treated with LiAlH$_4$ shortly prior the condensation with **16**. Desilylation with TBAF afforded micacocidin methyl ester **27** as a mixture of diastereomers. Hydrolysis of the terminal ester **27** by LiOH provided the corresponded acid. Treatment with zinc chloride resulted in isomerisation at C-10 and provided the desired micacocidin **29** (Scheme 5).

To understand structure-antymicoplasma activity relationship of micacocidin, Ino and co-workers prepared several derivatives by modifying hydroxyl and carboxylic groups in the

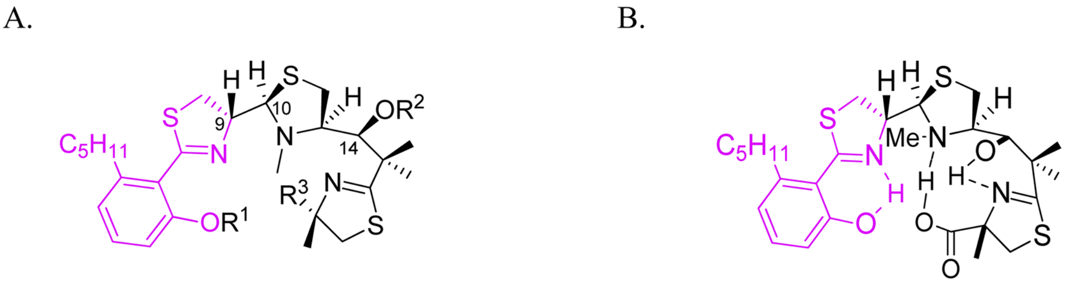


Scheme 4 Synthesis of second building block of micacocidin.[39,41]



Scheme 5 Final assembly of the two segments of micacocidin.[39,41]

skeleton of the siderophore isolated from the fermentation of *Pseudomonas* sp. No. 57-250 (Fig. 8).[44] MIC values were determined for three strains: *Mycoplasma gallisepticum*, *M. pneumoniae*, *M. hyopneumoniae*. Compounds **27** and **30g** were active, while a bulky ester group PCB **30a**, amide derivatives **30b–d** as well as methyl or MOM derivatives at the phenolic position **30f–h, 30j–k** resulted in a reduced activity. According to the authors, the lack of bulky groups and the presence of hydrogen bonds



Folded conformation of **29**

27 $R^1 = H, R^2 = H, R^3 = CO_2Me$
28 $R^1 = Zn, R^2 = H, R^3 = CO_2Zn$
29 $R^1 = H, R^2 = H, R^3 = CO_2H$
30a $R^1 = H, R^2 = H, R^3 = CO_2PCB$
30b $R^1 = H, R^2 = H, R^3 = CONH_2$
30c $R^1 = H, R^2 = H, R^3 = CONHMe$
30d $R^1 = H, R^2 = H, R^3 = CONMe$
30e $R^1 = H, R^2 = H, R^3 = CH_2OH$
30f $R^1 = Me, R^2 = H, R^3 = CO_2H$
30g $R^1 = H, R^2 = Me, R^3 = CO_2H$
30h $R^1 = Me, R^2 = H, R^3 = CO_2Me$
30i $R^1 = H, R^2 = H, R^3 = CO_2MOM$
30j $R^1 = H, R^2 = MOM, R^3 = CO_2MOM$
30k $R^1 = MOM, R^2 = MOM, R^3 = CO_2MOM$

MOM: methoxymethyl
PCB: p-chlorobenzyl

Fig. 8 (A) Structural variations of micacocidin analogs, (B) a proposed folded conformation of micacocidin.[44]

are required for activity, and the active derivatives have to possess a similar spatial conformation. The relationship between configuration and activity was examined as well. Regardless of the C-9 configuration, C-10 (*R*) isomers presented a similar activity to micacocidin **29**, while C-10 (*S*) isomers exhibited a reduced activity. These results supported the authors' proposal that the potency of siderophores depends on the ability of the derivatives to adopt a folded conformation.

In an additional work,[45] micacocidin analogs **31a–f** were generated by exploiting precursor-directed biosynthesis approach. The series varied in alkyl side chain, thus did not induce significant changes in the spatial folding. Almost all gallium complexes showed promising activities against *M. pneumoniae* ATCC 29342, and comparable to the native micacocidin. Derivative **31b** was an exception, and exhibited a significantly reduced activity. A minimum alkyl chain length might be important for the interaction with the biological target (Fig. 9).

Yersiniabactin was first isolated from *Yersinia* bacterial strain, a causative agent of a broad range of diseases such as plague, bowel infections and reactive arthritis.[46] Afterwards it was found that this strong chelating agent is not limited to one particular bacteria species and can be utilized by different kinds of microbes such as Enterobacteriaceae (*E. coli* and *S. enterica*).[47–49] The yersiniabactin system is the most frequently carried, genetically non-conserved siderophore system in uropathogenic *E. coli*.[50] The siderophore contains a phenol and a thiazolidine ring, as well as two thiazoline rings. Its stereochemistry is striking for the existence of five chiral centres, with a mixture of two C-10 epimers being isolated during structure elucidation studies.[37,38]

Following the preparation of micacocidin, Ino and coworkers accomplished a total synthesis of yersiniabactin (Fig. 10).[51]

The first building block was prepared starting from condensation of Weinreb amide **32** (ref. 52) and 2-methoxybenzoyl chloride **33**, which provided ester **34**. Next, in a 5-step route thioamide **36** was obtained which was converted to **7** by the reaction with the Burgess reagent. Further hydroxyl group protection and reduction of Weinreb amide **7** yielded aldehyde **37** (Scheme 6).

The second synthon for yersiniabactin was prepared according to the reaction conditions used in the total synthesis of micacocidin (Scheme 4).[41] Compound **23** which was an intermediate in the synthesis of micacocidin was fully deprotected to provide derivative **38**, and condensation with the first building block **37** afforded thiazolidine **39**. Ester **39** hydrolysis provided the desired yersiniabactin siderophore **40** (Scheme 7).

Piscibactin, a siderophore isolated from subspecies *Piscidia* of *Photobacterium damselae*, is known as a causative agent of fish pseudotuberculosis, a malady that causes large economic losses in marine environment.[53] High mortality rate and wide geographical distribution makes it a major problem in the mediterranean fishing industry. Synthesis of piscibactin is also considered as a virulence factor in other bacteria, such as *Yersinia enterocolitica* responsible for severe enteric inflammation in humans.[53] Piscibactin isolation was first reported in 2012 together with an additional metabolite, prepiscibactin, presumably a possible intermediate of piscibactin biosynthesis.[53] The piscibactin structure was determined by Souto *et al.*[53] and the studies performed allowed to establish the stereochemistry of piscibactin as (9*R*,10*S*,12*R*,13*S*).

A successful approach for piscibactin synthesis (close analogue of yersiniabactin) was accomplished by Jiminez *et al.* in 2021.[54] Before, Segade and co-workers proposed a total synthesis of prepiscibactin.[55,56] Retrosynthetic analysis of piscibactin was based on three synthons, and in all three cysteine was utilized as starting material (Fig. 11).

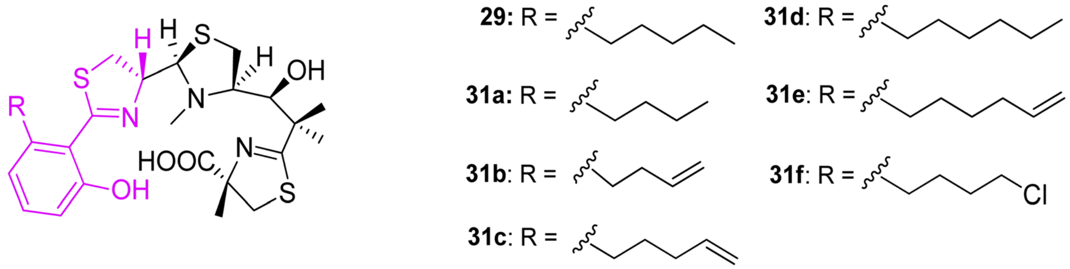


Fig. 9 Structural variations of micacocidin analogs, prepared by precursor-directed biosynthesis method.[45]

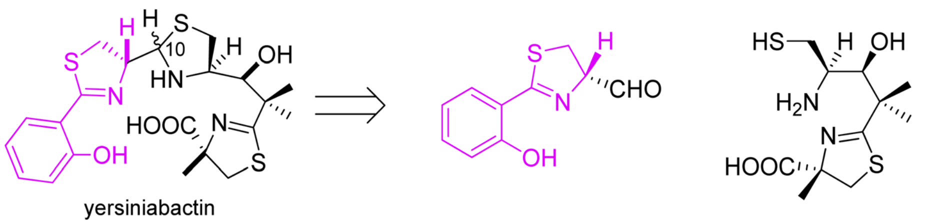
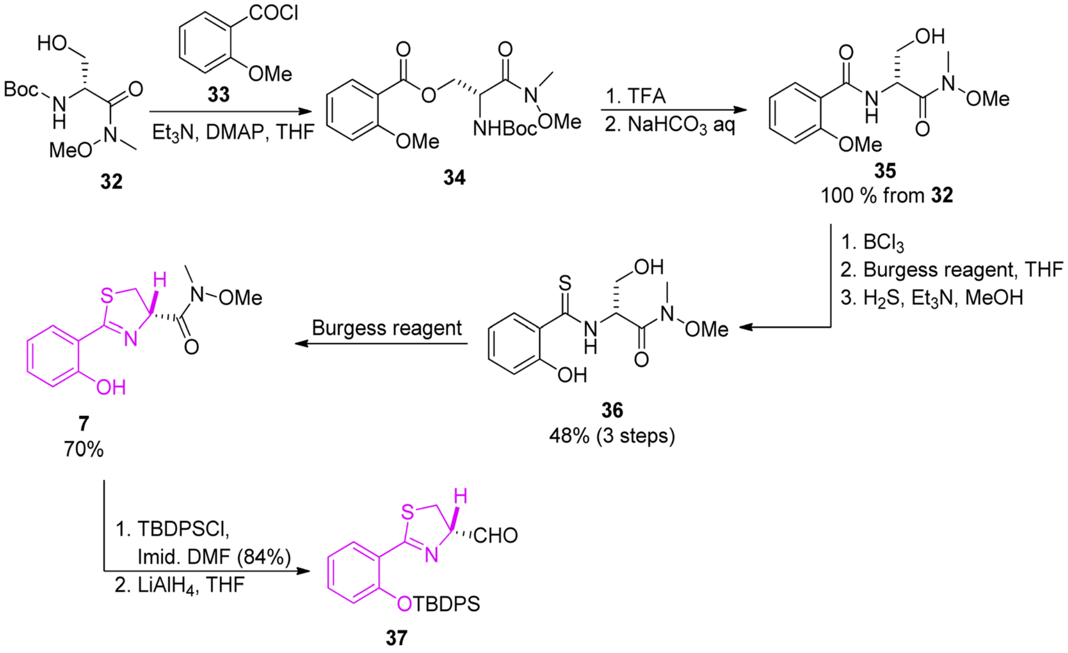


Fig. 10 Retrosynthetic analysis of yersiniabactin.[51]

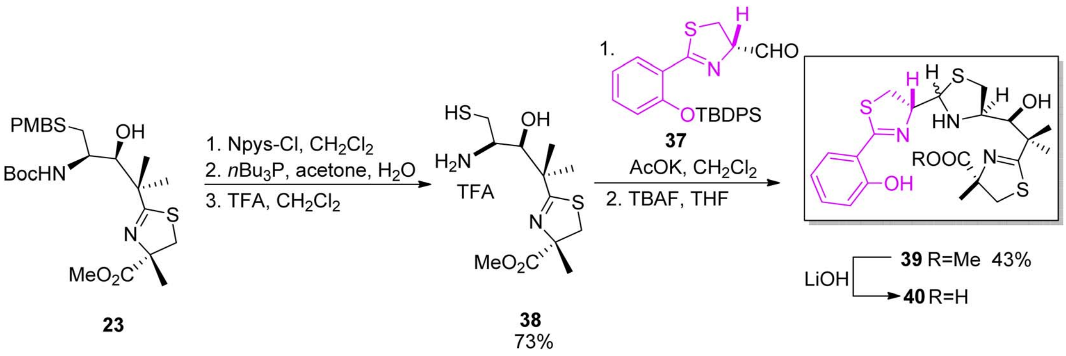


Scheme 6 Synthesis of thiazoline part of yersiniabactin.[51]

Piscibactin was prepared from two key synthons, and D- and L-cysteine were used as chiral sources for C-9 (*S*) and C-12 (*S*), respectively (Fig. 11). Applying a similar methodology as for pyochelin preparation,[26] the first synthon was obtained through the formation of Weinreb amide, and reduction of the resulting hydroxamic ester with $LiAlH_4$ (Scheme 2).

The second synthon, thiazoline based amino thiol was prepared utilizing multi-functionalized carboxylic acid **41** and (*S*)-α-azido-methylcysteine.[57] Synthetic route for full protected carboxylic acid **41** was accomplished through protection of L-cysteine **6** and a subsequent transformation in a stereoselective manner leading to final building block formation **41** in 20% of overall yield (8 steps). For preparation of thiazoline fragment **46** it was necessary to couple the activated acid of the protected statine **39** with a freshly prepared thiol **42** using EDCl. In the Staudinger reduction and a subsequent intramolecular *aza*-Wittig reaction, thioester **41** was transformed into the thiazoline **44** in good yield. Further deprotection of amino thiol **44** led to the second building block **46** in 42% yield. Condensation of thiazolinic aldehyde **2** with thiazoline **46** in dichloromethane afforded an epimeric mixture of methyl esters of piscibactin which were hydrolyzed and submitted without purification to complexation with gallium using $Ga(acac)_3$. Final HPLC separation gave piscibactin Ga^{3+} complex **47** and its 9*S* epimer in ratio 2 : 1 and 10% yield (Scheme 8).

2.1.3 Anguibactin. Anguibactin was first isolated in 1986 from marine bacterial strain *Vibrio anguillarum* 775 by Actis *et al.*[58] It is a common fish pathogen responsible for vibriosis, a deadly haemorrhagic septicaemic disease affecting various marine and freshwater fish. The disease has high morbidity and mortality rates and causes severe economical loses in the fish industry.[59] This siderophore was of particular interest for scientists for one more reason. Its structure resembles very closely another iron carrier compound, namely the oxazoline-



Scheme 7 Final assembly of the two segments of yersiniabactin **40**.[51]

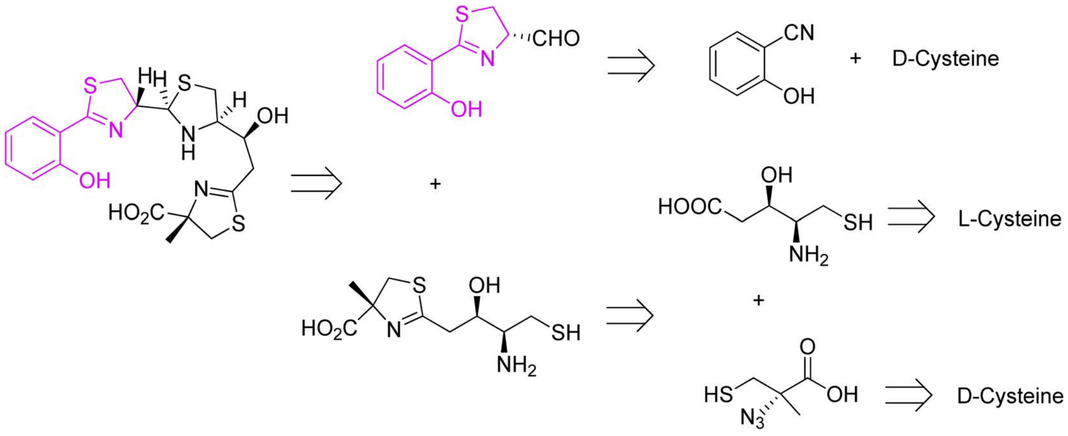
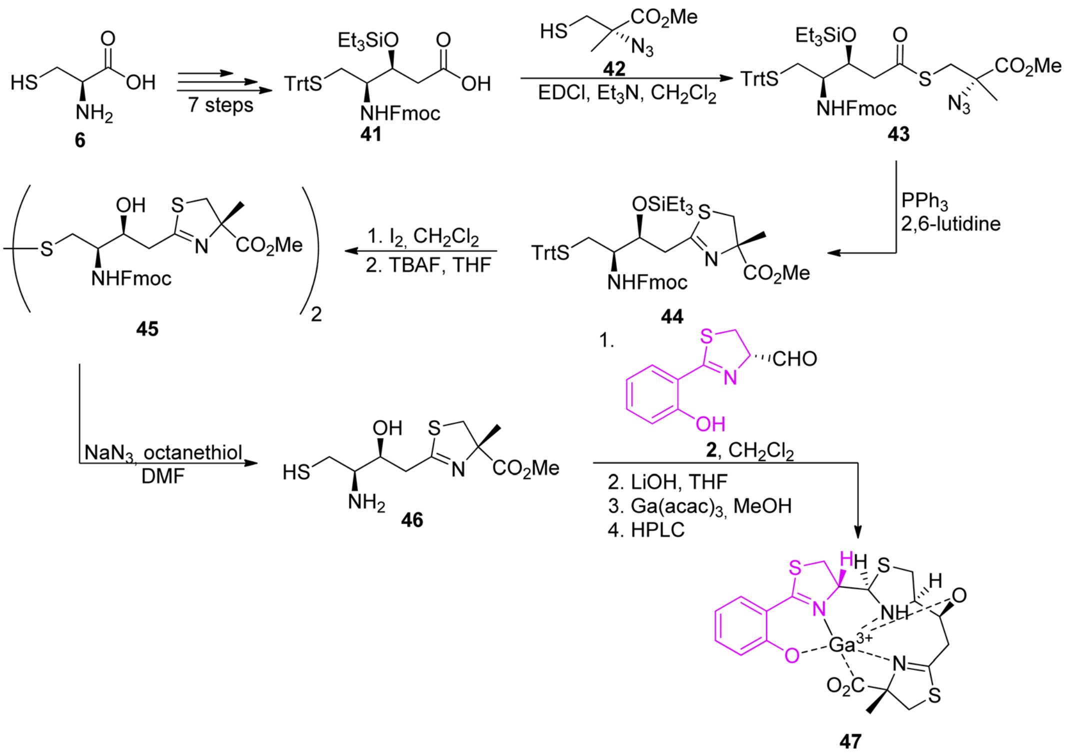


Fig. 11 Rethrosynthetic analysis of piscibactin.

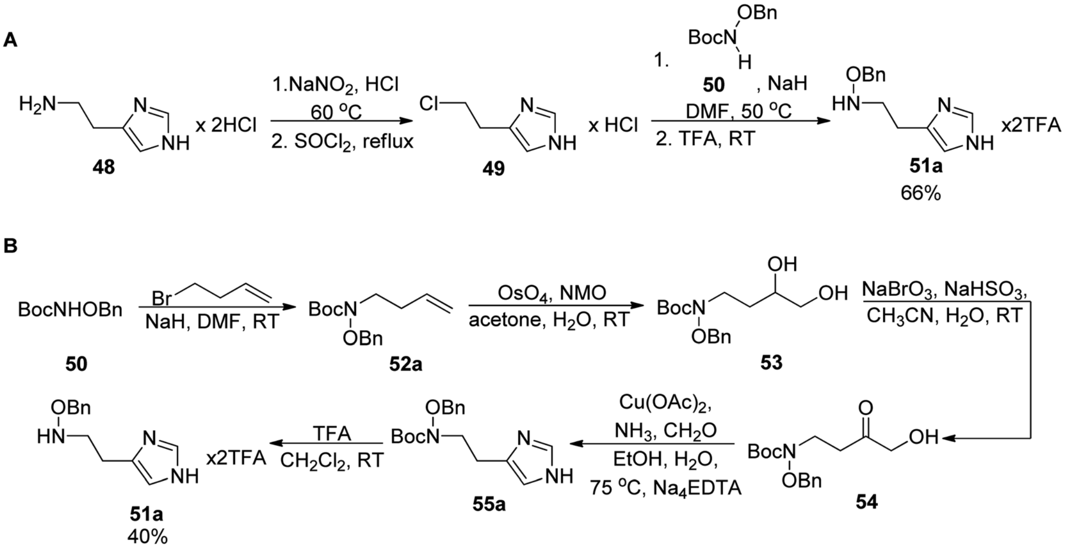
derived acinetobactin (*vide infra*) utilized by multidrug-resistant *Acinetobacter baumannii*, an opportunistic pathogen responsible for many lethal hospital-acquired infections.[60] Acinetobactin was found to be unstable and readily converted to its isoxazolidinone form while anguibactin was proven to be resistant to isomerization.

The structure of anguibactin can be described as being built of two planar sections, one containing the phenyl-thiazole system with its substituents and another with the imidazole ring. It was first elucidated in 1986,[58] and the initial suggestion was later confirmed by van der Helm *et al.* solving an X-ray structure in 1989.[61]

The total synthesis of angiubactin was carried out using a convergent approach.[60] It was initiated by preparation of the phenylthiazole core in a similar synthetic pathway as for pyochelin,[26] by condensation of L-cysteine and aryl nitrile **5a** (Scheme 2). The imidazole fragment **49a** was prepared in two ways. In 2010 Takeuchi *et al.*[62] proposed its synthesis through histamine dihydrochloride **48** transformations into 4-(2-chloroethyl)imidazole hydrochloride **49** using $SOCl_2$ and a subsequent coupling reaction with *N-tert*-butoxycarbonyl (Boc)-*O*-benzyloxyamine **50**,[63] followed by deprotection,[64] yielding *O*-benzyloxyhistamine **51a** in 66% total yield (Scheme 9, part A). In the second approach proposed in 2015 by Kim *et al.*,[65]



Scheme 8 Total synthesis of enantiomerically pure piscibactin gallium complex 47.



Scheme 9 Two synthetic routes for the formation of the imidazole part **51a**: (A) from histamine hydrochloride,[62] (B) from *N*-Boc-*O*-benzyloxyamine and 4-bromobut-1-ene.[65]

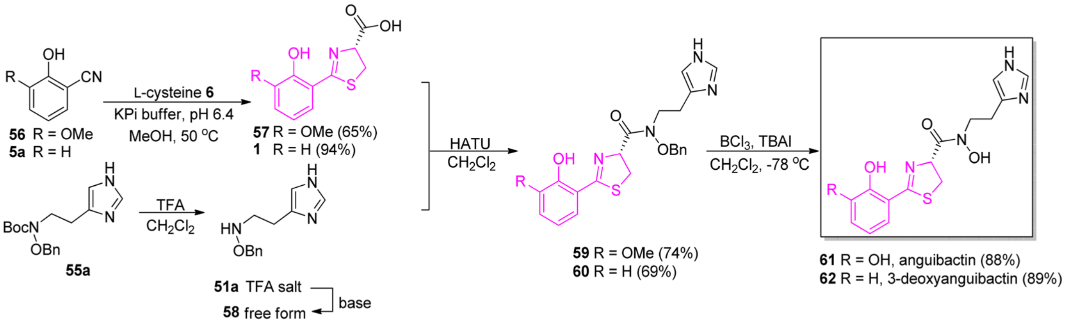
a terminal olefin **52a** was first synthesized from *N*-Boc-*O*-benzyloxyamine **50** and 4-bromobut-1-ene. Dihydroxylation under Ujohn conditions afforded diol **53** which was transformed into α-hydroxyketone **54** through the selective oxidation of the secondary hydroxyl group with $NaBrO_3/NaHSO_3$.[66] In the final step, the Cu(II)-promoted imidazole formation with ammonia and formaldehyde was performed followed by deprotection with TFA which resulted in desired histamine *N*-oxide derivative **51a** in 40% overall yield (Scheme 9, part B).

A stereoselective coupling of the intermediate **57** to a free amine of *N*,*O*-imidazole **58** mediated by HATU in dichloromethane provided product **59** (er = 98 : 2). The use of tetrabutylammonium iodide (TBAI) and boron trichloride (BCl_3) led to a clean removal of both benzyl and methyl groups and successfully generated compound **61**. Along with **61**, its 3-deoxy derivative **62** was also prepared in an analogous manner (Scheme 10).

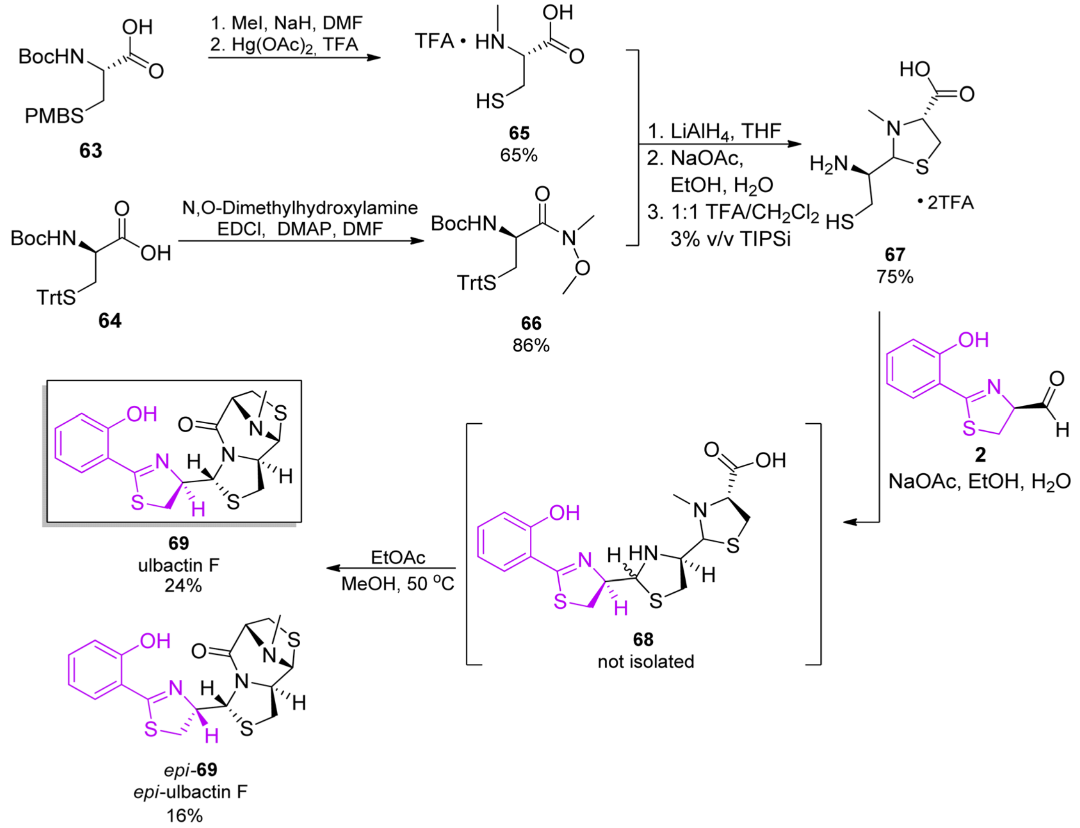
2.1.4 Ulbactin.

Ulbactin is a natural siderophore which was isolated in two epimeric forms (ulbactin F and G, in the ratio 17 : 1, respectively) from marine bacterial genus of *Brevibacillus*[67] extracted from an unidentified sponge found near Iwate, Japan. Although *Brevibacillus* sp. is not considered to be a dangerous microbe, the structures of identified compounds are captivating because its core is also shared by *Pseudomonas aeruginosa* siderophore pyochelin, though a peculiar tricyclic ring system is present.

The compounds possess an unusual heterocyclic structure in which two thiazolidine rings are fused to form a tricyclic ring system. After successful isolation and chromatographic purification, ulbactin F was obtained as pale yellow crystals and its structure was elucidated by Igarashi *et al.*[67] A series of studies on the structure of ulbactin F allowed its identification and determination of the absolute configuration as (4′*R*,3″*R*,6″*R*,9″*R*, and 9″*R*). Ulbactin G with the same molecular composition is the epimeric form of ulbactin F with absolute configuration (4′*R*,3″*S*,6″*R*,9″*R*, and 9″*R*).[68] A peculiar feature of ulbactin F and G, namely the 6,9-imino-1*H*,3*H*,5*H*-thiazolo[4,3-*c*][1,4]thiazepin-5-one tricyclic ring system containing two sulfur atoms and two nitrogen atoms makes it very intriguing. This ring system, but lacking *N*-methyl group, was also reported for ulbactin D.[67]



Scheme 10 Total synthesis of angiubactin **61** and its analog **62**.[60]



Scheme 11 Total synthesis of ulbactin **69**.[68]

As ulbactin F is the major metabolite (*vide supra*), this diastereomer was targeted in the total synthesis.[68] Convergent synthetic pathways were applied, with several building blocks prepared. Synthesis of the phenylthiazolidine core followed the pathway used for pyochelin, converting salicylnitril to aldehyde **2**.[26] The thiazolidine synthons were prepared from protected enantiomeric cysteines. Reaction of the two fragments in ethanol/water with NaOAc, and then heating in an ethyl acetate/methanol mixture, provided the product **69** in total yield of 12% and its epimer, *epi*-**69**, as a side product (Scheme 11).

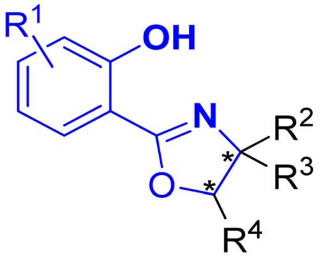


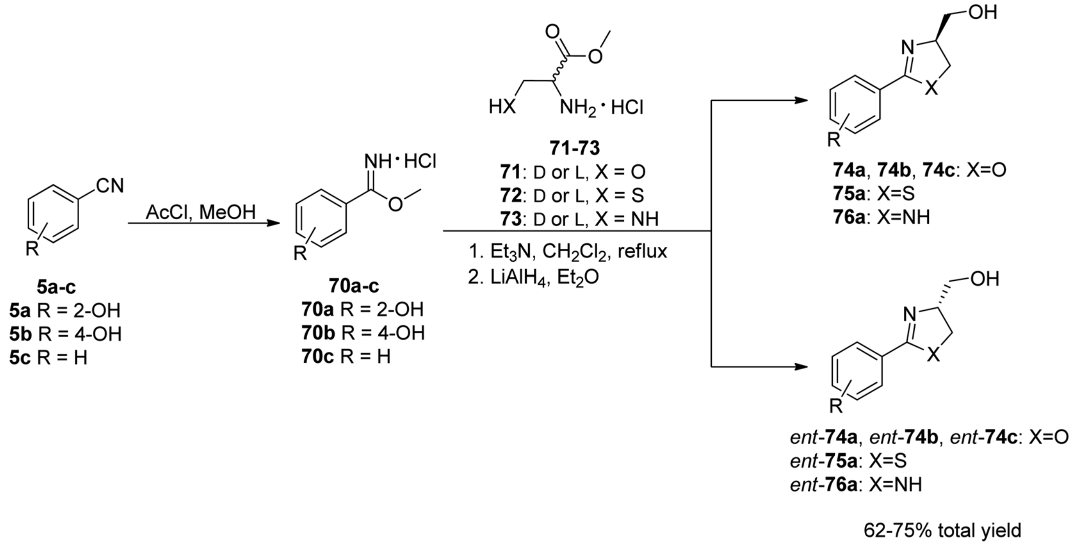
Fig. 12 A general structure of oxazoline-based siderophores. Fragments involved in iron coordination are marked in bold.

2.2 Aryloxazoline siderophores: origin and total synthesis

Oxazolines are a large family of heterocyclic imino ethers possessing a five-membered ring structure. Within the oxazoline family, 2-oxazolines have been most extensively studied so far and found broad applications in various fields. This is an important structural motif and pharmacophore of natural products and bioactive compounds (including siderophores, Fig. 12).[69] The aryloxazoline/oxazole moiety is present in many siderophores and plays a crucial role in coordination mode and iron transport machinery in microorganisms.

2.2.1 (−)-Yanglinmycin, spoxazomicins and madurastatins. In 2013, Zhang's group isolated (−)-yanglingmycin, 2-aryl-substituted 4,5-dihydrooxazole derivative from the fermentation broth of *Streptomyces djakartensis*.[70] Though it was not clearly stated in the original paper, this compound is an (*S*) enantiomer of spoxazomicin C. Due to the presence of various functionalities and its biological activities, yanglingmycin has been considered as a potential component of pharmaceutical drugs, polymeric materials, insecticides and so on.[71,72]

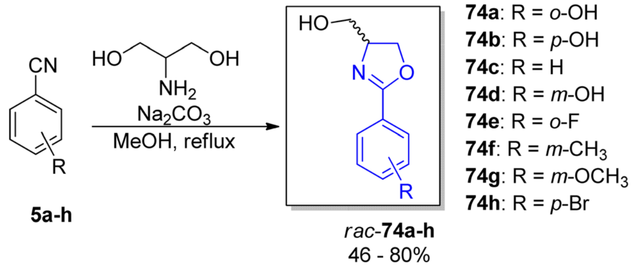
To investigate the bactericidal activities of yanglingmycin, the Zhang group[70] decided to synthesize this molecule and its analogs. In order to achieve the intended goal, an efficient synthetic pathway for the preparation of 2-aryl/heteroaryloxazolines from nitriles under metal- and catalyst-free condition was used.[73] Benzonitrile and its substituted analogs **5a–c** were applied as the starting materials. In the initial step, a Pinner reaction was performed to afford the corresponding methyl benzimidate hydrochlorides **70a–c**,[74] which were then reacted with various amino acid methyl ester hydrochlorides **71–73**.[75] The final products were obtained by an



Scheme 12 The synthetic route to yanglingmycin enantiomers and its analogs.[76]

efficient reduction of esters into alcohols using $LiAlH_4$, yielding (−)-yanglingmycin **74a** and its analogs **74b–c**, *ent*-**74a–c**, **75**, *ent*-**75**, **76** and *ent*-**76** in total yields of 62% and 52–65%, respectively (Scheme 12).[76]

For a deeper exploration of the antibacterial potency, a series of hydroxyl ester *rac*-**77a–z** and hydroxyl ether *rac*-**78a–o** derivatives of the racemic (±)-yanglingmycin and its phenyl substituted analogs *rac*-**74a–h** were prepared (Schemes 13 and 14).[77] To obtain 2-aryl-substituted 4,5-dihydrooxazole analogs *rac*-**74a–h**, arylnitriles **5a–h** were reacted with serinol in the presence of sodium carbonate (Scheme 13). Hydroxyl ester derivatives of (±)-yanglingmycin *rac*-**77a–z** were synthesized through esterification reactions using a catalytic amount of EDC, and hydroxyl ether derivatives **74a–o** were obtained by etherifications of the alcoholic hydroxyl group in the presence of a base. Additionally, a fluorinated analog *rac*-**77** was afforded *via* (±)-yanglingmycin *rac*-**74a** treatment with DAST (68% yield) (Scheme 14). *In vitro* antibacterial studies against four Gram-negative and three Gram-positive bacteria strains revealed that some derivatives are more active than (±)-yanglingmycin *rac*-**74a**. Structure–activity relationship analysis clearly showed that antimicrobial activity was lost after most derivatizations of alcoholic hydroxyl group and in the absence of phenolic hydroxyl substituent. On the other hand, incorporation of a short-chain ester group, an electron-deficient ether moiety and fluorination of alcoholic hydroxyl group were found beneficial for the antibacterial potency.

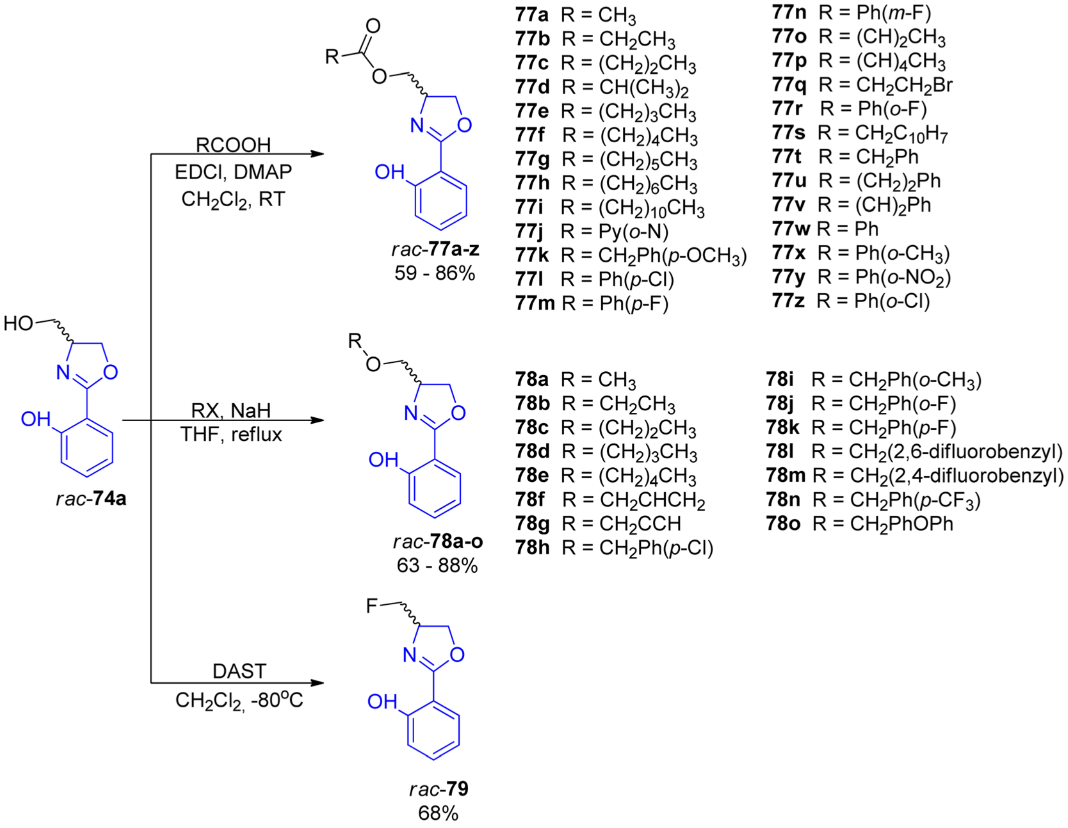


Scheme 13 Synthesis of (±)-yanglingmycin and its phenyl-substituted analogs.[77]

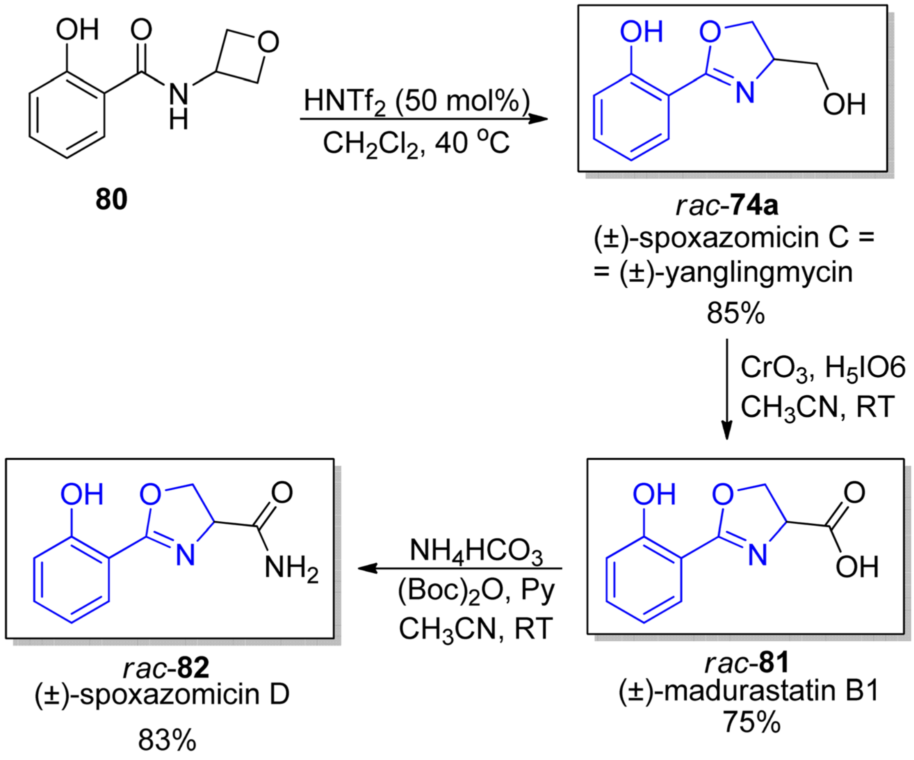
In 2019 Sun *et al.* proposed a mild catalytic approach to 2-oxazolines *via* oxetane ring-opening reaction (a model substrate was synthetized by acylation of commercially available 3-amino oxetane).[78] This synthetic protocol is a useful tool for preparation of a diverse family of natural products with 2-oxazoline unit including spoxazomycin C *rac*-**74a** and its analogs, such as spoxazomycin D **82** and madurastatin B1 **81** in racemic form (Scheme 15). It is worth emphasizing that 2-aryl-substituted 4,5-dihydrooxazole derivatives are crucial building blocks in total syntheses of many natural products such as mycobactin type siderophores *etc.*

2.2.2 Acinetobactin, pseudomonine and fimsbactin.

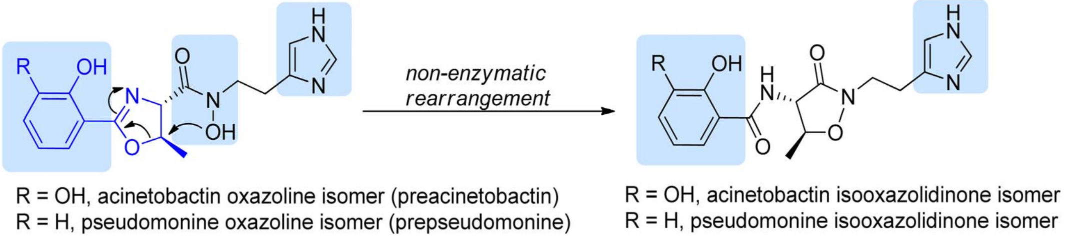
Acinetobactin is a siderophore which contains catechol-oxazoline moiety, hydroxamate unit and imidazole ring. It was first described as the siderophore of highly resistant human pathogen *A. baumannii*,[79] and later on to be also produced by the fish pathogen *Aeromonas salmonicida* subsp. *salmonicida*[80,81] (a Gram-negative γ-proteobacteria identified as the causative agent of furunculosis, a devastating disease affecting cultured and wild fish worldwide). The structure of acinetobactin was initially proposed,[79] but further research revealed facile and spontaneous rearrangement from oxazolinyl hydroxamate into isooxazolidinone form.[82,83] This phenomenon is similar to the previously observed conversion of prepseudomonine to pseudomonine, another siderophore produced by *Pseudomonas fluorescens* with salicylate-oxazoline moiety in the structure (Scheme 16).[84] The isooxazolidinone of pseudomonine is generated through the rearrangement of a preceeding oxazoline hydroxamate condensation product (prepseudomonine). Walsh *et al.* revealed that the mode of heterocyclization for N–O–C



Scheme 14 Synthesis of esterified, etherified and fluorinated analogs of (±)-yanglingmycin *rac*-**77a–z**, *rac*-**78a–o** and *rac*-**79**.[77]



Scheme 15 New catalytic protocol for synthesis of oxazolines from oxetanes.[78]



Scheme 16 Structures of isomeric siderophores produced by *A. baumannii* and *P. fluorescens*.[86] Potential iron chelating motifs are highlighted using blue background.

bond formation follows the intramolecular S_N2 mechanism and the oxygen of a hydroxamate intermediate attacks the β-carbon of the Thr-derived oxazoline leading to isooxazolidinone formation. This S_N2 rearrangement reaction involves an inversion of configuration at the β-carbon of Thr side chain.[82] Moreover, subsequent studies showed the dependence of rearrangement from oxazoline-containing form to isooxazolidinone isomer on pH and temperature.[85,86] Both isomeric forms are physiological siderophores relevant for bacteria in processes of binding and cellular delivery of Fe(III).

Apart from acinetobactin, strains of human pathogenic *A. baumannii* may produce two other siderophores: baumannoferrin[87] (a hydroxamate siderophore) and fimsbactin.[88] Production of acinetobactin and baumannoferrin is highly conserved among clinical isolates while fimsbactin production appears to be less common. Fimsbactin is structurally related to acinetobactin because of the presence of the catechol and hydroxamate moieties together with an oxazoline ring; it possesses additionally oxazoline and 1,3- or 1,4-diaminopropane fragments.[88]

Preacinetobactin **86a** and prepseudomonine **86f** consist of three significant structural subunits, responsible for metal chelation, namely catechol/phenol oxazoline, hydroxamate and imidazole fragments. The proposed synthetic routes for the formation of these siderophores are based on two condensations of key heterocyclic motifs, *i.e.* aryloxazoline and imidazole part. The imidazole fragment **51a** was prepared in the same manner as described for anguibactin (Scheme 9). The synthesis of the second building block, aryloxazoline moiety, was initiated with preparation of *O*-protected benzoic acid **83a–b** precursors.[86,89] Crucial steps for the synthesis of phenol oxazoline moiety include amide formation *via* coupling of L-threonine methyl ester with protected acid **83a–b** using various coupling reagents (EDC/HOBt, TBTU) and Ishihara's dehydrative cyclization using Mo(VI) oxide catalyst[90] (49–70% total yield). Takeuchi *et al.* proposed a different route to aryloxazoline part applying methyl imidate of 2,3-dihydroxybenzoic acid and L-threonine derivative (15% total yield).[62]

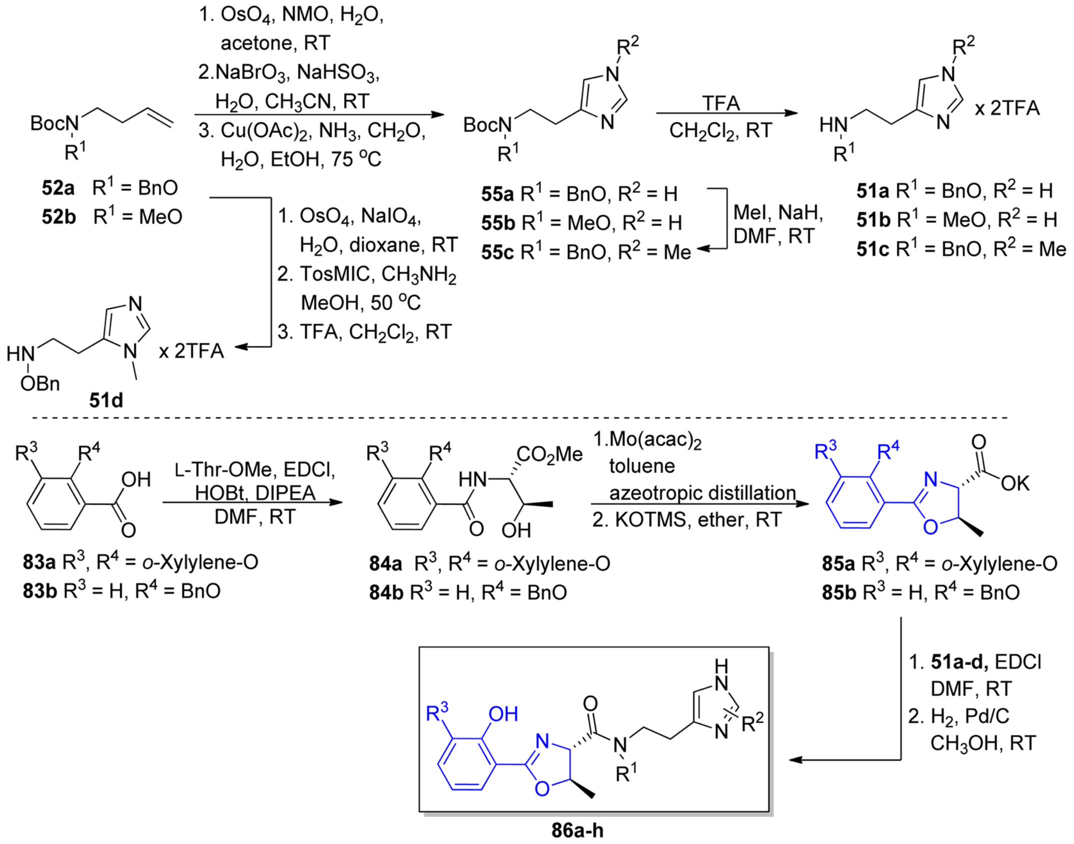
In order to identify the key structural motifs of preacinetobactin **86a** and prepseudomonine **86f** that influence their Fe(III) binding and cellular delivery, various analogs were synthesized.[86] Novel analogs were designed based on the modification of the iron-binding parts, *i.e.* aromatic, hydroxamate and imidazole fragments (Scheme 17). Proposed iron-binding mode for preacinetobactin revealed that catechol dihydroxyl and imidazole groups play crucial roles in iron binding. What is more interesting, phenolic oxazoline derivatives including prepseudomonine indicate that the 3′-hydroxyl group in the aromatic part is not crucial for metal binding. Further modification shows that *N*-methylation of the imidazole ring in both N^1 and N^3 positions did not decrease the iron-binding tendency and N^1 position is a promising drug conjugation site because modifications at this site did not interfere with the iron delivery function. Additionally, all hydroxamate bridge modifications abolished iron delivery in the cellular uptake machinery. Wencewicz *et al.*[91] prepared a rigid preacinetobactin analog *via* oxidation of oxazoline moiety to oxazole in order to block siderophore utilization in the pathogen growth process (Scheme 18). The strategy including rigid siderophore analogs preparation can be crucial in the synthesis of new antivirulence agents.

The stereoselective preparation of fimsbactins was proposed by Kim's group.[92,93] Their strategy for the synthesis was based on retrosynthetic analysis in which the framework construction was accomplished *via* amide bond formation in condensation reaction of two building blocks, aryloxazoline carboxylate and polyamine derivatives followed by catecholate part addition through ester formation (Fig. 13).

The preparation of the oxazoline carboxylates started from the coupling of *o*-xylyl-protected 3,4-dihydroxyl benzoic acid **83a**[90] with L-Ser-OMe, L-Thr-OMe or D-Thr-OMe in the presence of EDC and HOBt reagents. The obtained precursors **91**, **84a** and *ent*-**84a** were transformed into oxazoline forms *via* Ishihara's dehydrative cyclization catalyzed by a Mo(VI) oxide catalyst[94] followed by mild saponification using potassium trimethylsilanolate[95] which afforded the desired products **92**, **85a** and *ent*-**85a** in good yields (Scheme 19, part A). The synthesis of functionalized polyamine building blocks was accomplished by amide bond formation between putrescine[92] or *N*-monoacetyl-1,3-propanediamine[96] derivatives **93a–b** and *N*,*O*-protected L- or D-serine **94**, *ent*-**94** using EDCl, HOBt coupling reagents (Scheme 19, part B). After derivatization of functional groups and a subsequent global deprotection, fimsbactins **97**, **99** and derivatives *epi*-**97**, *dia*-**99**, *epi*-**99**, *ent*-**99** were obtained in 12–22% total yield (Scheme 20).

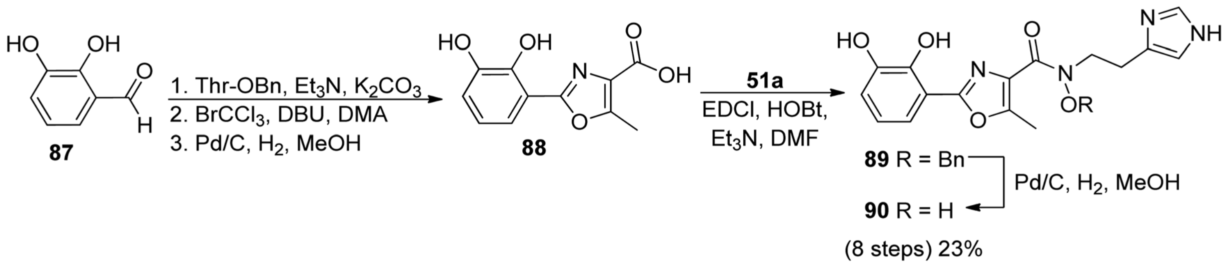
2.2.3 Polyamine based siderophores.

Three significant structural features of polyamine based aryloxazoline chelators are of importance: the type of polyamine backbone, chelator donor groups, and the symmetry. The oxazoline ligands

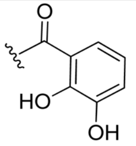


	R1	R2	R3	
86a	OH	H	OH	preacinteobactin (13 steps) 15%
86b	OMe	H	OH	
86c	H	H	OH	
86d	OH	N3-Me	OH	
86e	OH	N1-Me	OH	
86f	OH	H	H	prepseudomonine (10 steps) 14%
86g	OMe	H	H	
86h	H	H	H	

Scheme 17 The synthesis of preacinetobactin **86a** and analogs **86b–h**.[86]



Scheme 18 The synthesis of oxidized preacinetobactin.[91]

	R^1	R^2	R^3	R^4
A	H	H		A
B	CH_3	H		A
C	CH_3	CH_3		A
D	H	H		B
E	H	H		OH
F	H	H	H	A

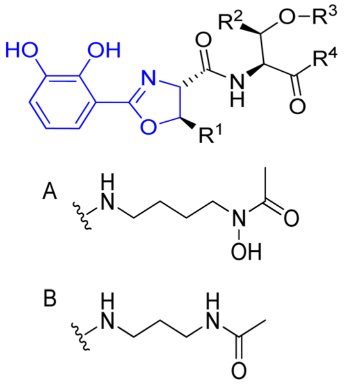
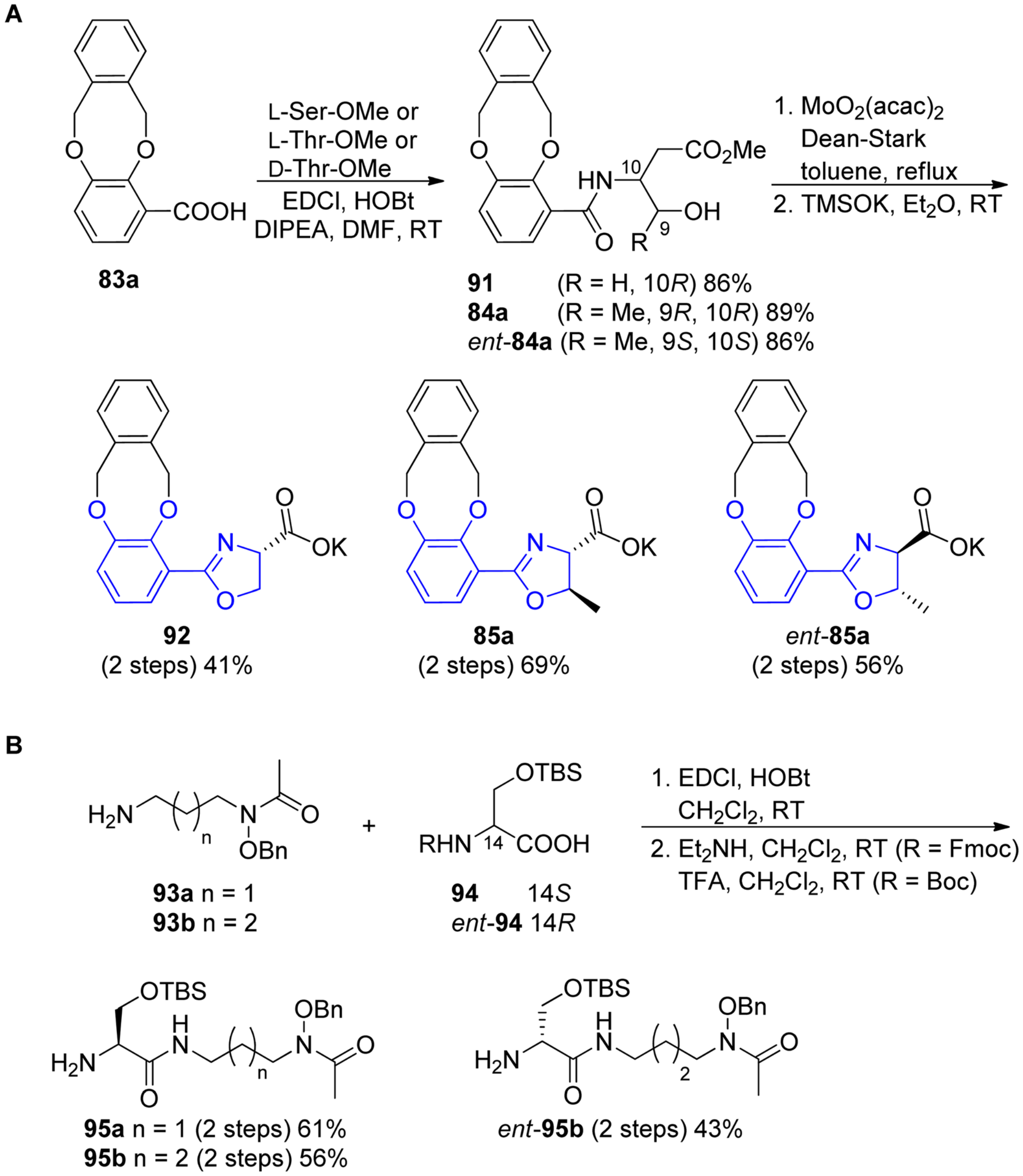


Fig. 13 Structures of fimsbactins A–F.



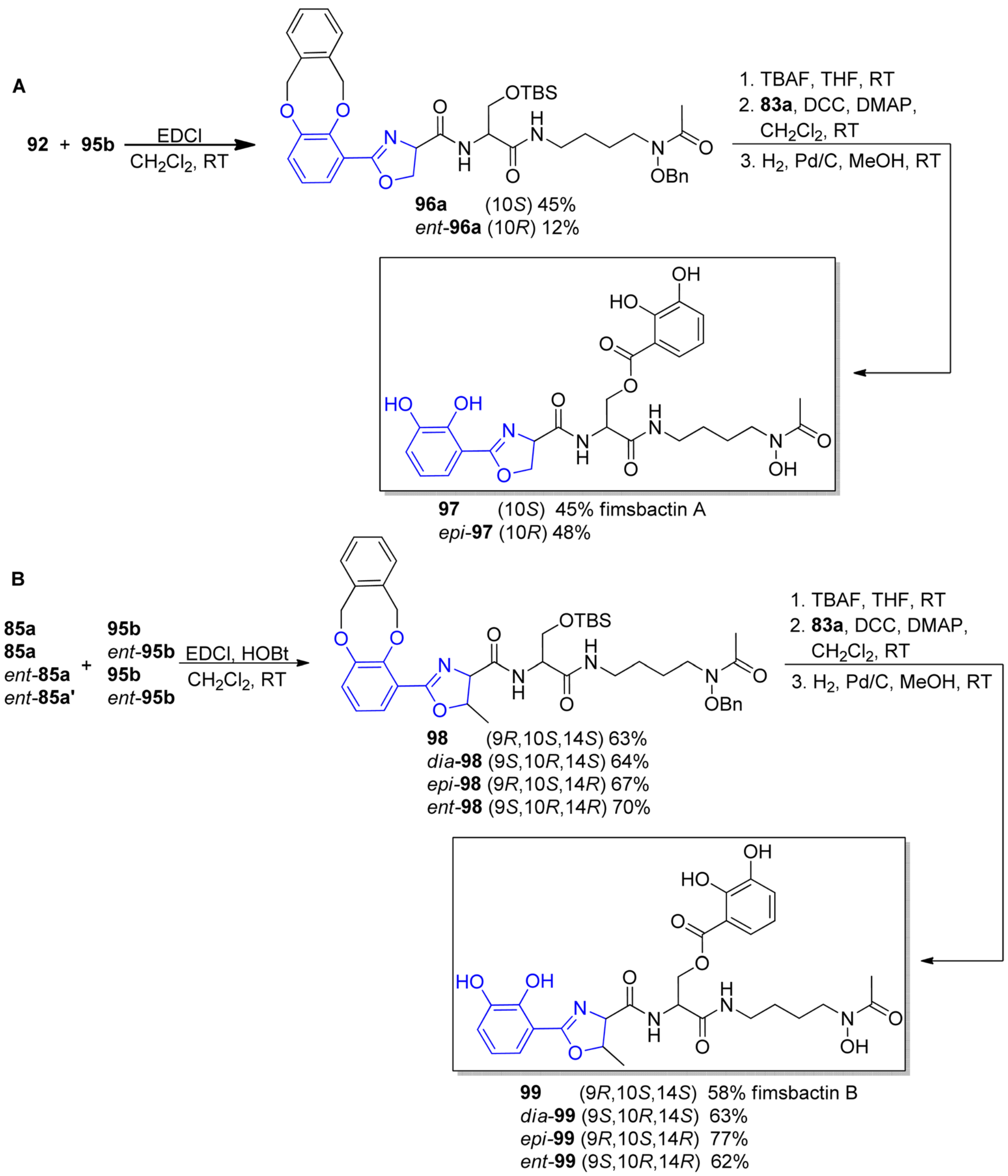
Scheme 19 Syntheses of the (A) aryloxazoline carboxylates **85a**, *ent*-**85a** and **92**; (B) polyamine **95a**, **95b** and *ent*-**95b** fragments.[92,93]

possessing the spermidine moiety are represented by compounds like parabactin, agrobactin, norspermidine based – fluvibactin, vibriobactin and vulnibactin, and 1,3-diaminopropane based – serratiochelin A.

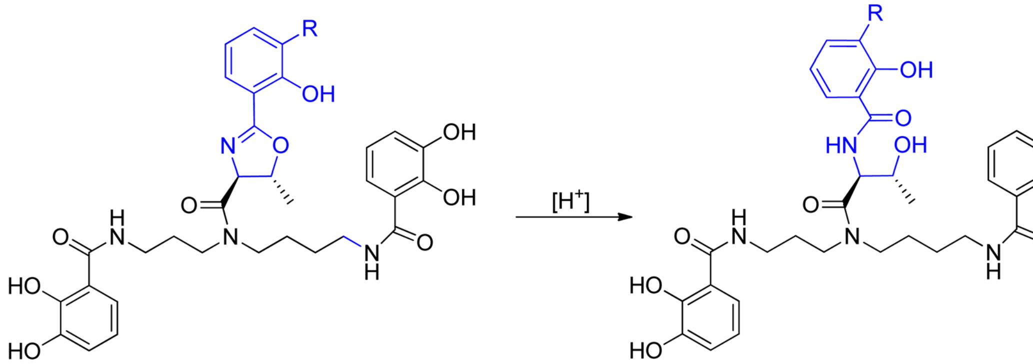
For the first time parabactin was isolated in 1975 by Tait from *Paracoccus denitrificans*.[97] In the first approach the structure of parabactin was not well defined, because of the unstable nature of oxazoline ring. Several years later, Neilands and coworkers[98,99] demonstrated that not an *N*-(2-hydroxybenzoyl)-L-threonyl fragment (parabactin A) but rather a (2-hydroxyphenyl)-4-carboxyl-5-methyl-2-oxazoline moiety is connected to the central nitrogen atom of the spermidine backbone in the original siderophore. Under the acidic conditions of Tait's isolation, the oxazoline ring was opened to the threonyl derivative (acid labile oxazoline ring). Moreover, Neilands' group showed that the hydrogen atoms of the oxazoline ring were *trans* to each other (Scheme 21).[99]

Agrobactin was isolated from iron-deficient cultures of *Agrobacterium tumefaciens*, the organism known to induce crown-gall in higher plants. *A. tumefaciens* not only produces a cancer-causing plasmid but is also interesting as a vector for incorporating foreign DNA into plants.[100] Exposure of agrobactin to acid opened the oxazoline ring giving agrobactin A, in which the UV spectra undergo a characteristic redshift, same like in the case of parabactin.[99]

Fluvibactin was isolated and purified from *Vibrio fluvialis* in 1993. It contains only one catechol-oxazoline unit and is structurally related to agrobactin from which it differs only in its



Scheme 20 Syntheses of fimsbactin A **97**, B **99** and their stereoisomers[92,93]



parabactin, R = H
agrobactin, R = OH

parabactin A, R = H
agrobactin A, R = OH

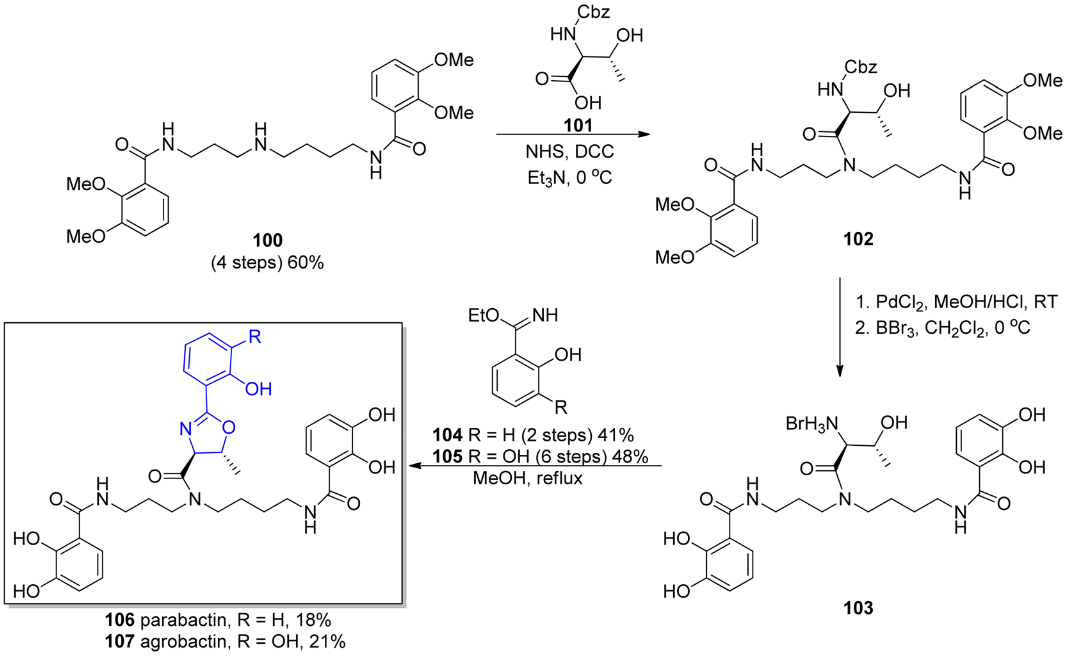
Scheme 21 The acid labile oxazoline ring.[98,99]

triamine-backbone.[101] A stereochemically modified version of fluvibactin efficiently removed iron without increasing microbial growth.[102]

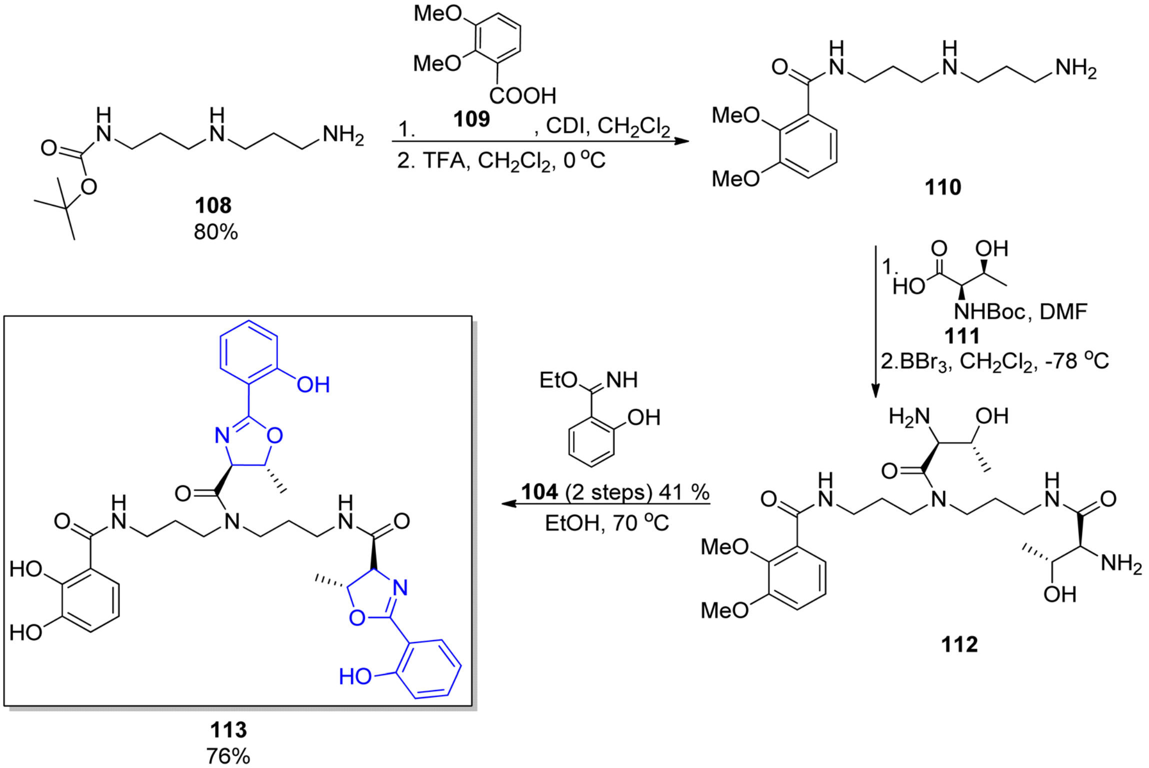
Vibriobactin (produced by *Vibrio cholerae*) is structurally highly similar to agrobactin with three minor alterations: (i) the polyamine backbone is norspermidine, (ii) it contains two L-threonines per molecule, forming two oxazoline rings, and (iii) it contains three DHB moieties as aryl caps. The discovery of the second oxazole ring in vibriobactin suggested some interesting possibilities in its metal-binding capacity.[103] Although *V. cholerae* can use heme directly as an iron source, it has been shown that vibriobactin is also an important virulence factor.[104]

Vulnibactin, which was isolated from culture supernatants of *Vibrio vulnificus* M-2799 grown in a low-iron medium, is possessing two salicylate caps that are tethered to the oxazoline ring.[105] Virulent *Vibrio vulnificus* is a halophilic estuarine bacterium that causes fatal septicemia and necrotizing wound infections in humans with high serum iron levels and vulnibactin enables it to acquire iron from highly iron saturated host proteins.[106] Vulnibactin is structurally related to vibriobactin, from which it differs only in its salicyloyl moieties on two oxazoline rings, while fluvibactin contains only one oxazoline ring consisting of L-threonine and 2,3-dihydroxybenzoic acid attached to the central nitrogen of norspermidine.[105]

Serratiochelin A was isolated from *Serratia* sp. V4 and discovered in *S. marcescens* in 1974.[107] Furthermore, in 2020 serratiochelin A was isolated from an iron-dependent co-culture of *Shewanella* sp. and the mechanism of its degradation to



Scheme 22 Synthesis of parabactin **106** and agrobactin **107** proposed by Bergeron and co-workers.[110,115]

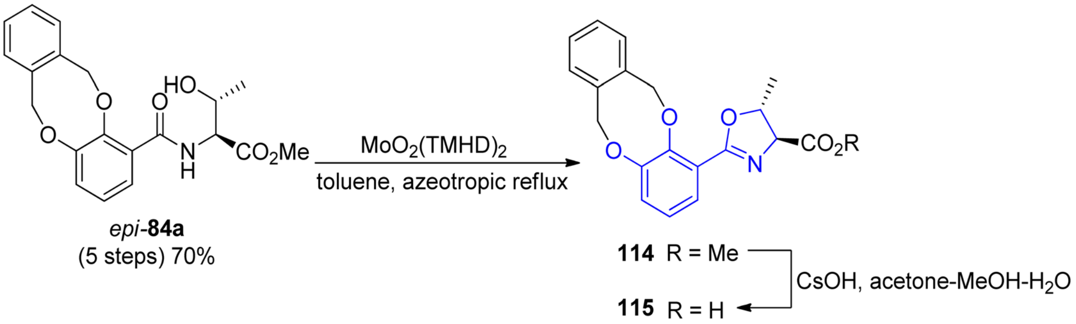


Scheme 23 The synthesis of vulnibactin **113**.[119]

serratiochelin C was proposed.[108] Serratiochelins are bis-catecholate siderophores that could be *tetra-* or hexadentate, moreover, serratiochelin A and B contain a propane-1,3-diamine backbone.[109]

So far total synthesis of six aryloxazoline iron chelators based on a polyamine backbone were described, namely the tris-amines parabactin, agrobactin, fluvibactin, vibriobactin and vulnibactin, and the diamine – serratiochelin A. The pioneering works in polyamine-based siderophores synthesis and explorations were performed by Bergeron's group. They proposed total syntheses of parabactin, agrobactin, fluvibactin, vibriobactin and vulnibactin. At the turn of years, this research field was supplemented by other scientists.

Based on performed research connected with structure exploration, in 1982 Bergeron's group synthesized parabactin **106** employing a stereospecific procedure under acid free conditions to preserve the oxazoline ring.[110] A proposed synthesis employed N^1,N^8-bis(2,3-dimethoxybenzoyl) spermidine **100** as a starting material, a unique reagent for the generation of spermidine phenolamides.[111] In the first step, *N*-Cbz-L-threonine **101** was condensed with N^1,N^8-bis(2,3-dimethoxybenzoyl)spermidine **100** in the presence of coupling reagents such as NHS and DCC under basic conditions. Afterwards, both carbobenzoxy and methyl protecting groups were removed from threonylamide **102**. In the last step, the most critical one, coupling of 2-hydroxybenzimido ethyl ester **104**, obtained before in a Pinner reaction[112] with the deprotected threonyl amide **103** was involved. As a result of this synthetic route, parabactin **106** was obtained in 18% total yield (Scheme 22).



Scheme 24 The dehydrative cyclization of *N*-(*o*,*m*-dialkoxybenzoyl)-L-threonine *epi*-**84a** *via* MoO_2 $(TMHD)_2$.[90]

Another synthetic route to parabactin **106** was proposed by Fujita in 1984.[113] The researchers decided to attach the catechol moieties in the final step of the synthesis ("inside-out" approach) in contrast to Bergeron's pathway.[110] The key intermediates for parabactin formation were dihydro-1,3-oxazole derivative (obtained in 7 steps, 40% total yield) and N^1,N^{10}-bis(benzyloxycarbonyl)-spermidine.[114] In the final step, condensation of both intermediates and deprotection of terminal amine groups of the spermidine backbone followed by incorporation of the catechol fragment led to parabactin **106** in 5% total yield.

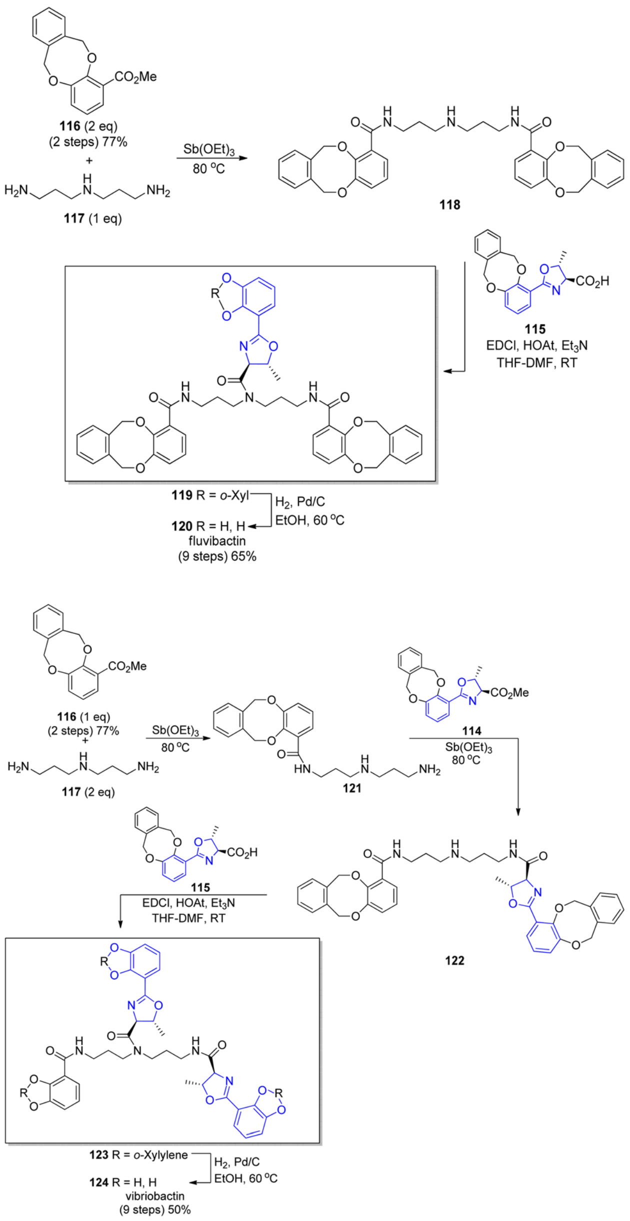
In the 1984 Bergeron's group obtained another spermidine-based aryloxazoline chelator, agrobactin **107**.[115] Due to the structural similarity to parabactin **106**, a previously developed methodology was applied,[110] with ethyl 2,3-dihydroxybenzimidate **105** (ref. 116) used in the stereospecific formation of the acid-sensitive *trans*-oxazoline ring subunit. The oxazoline-forming condensation between *N*-functionalized spermidine **100** and 2,3-dihydroxybenzimidate ester **105** afforded agrobactin **107** in 21% overall yield (Scheme 22).

The protocol for the synthesis of parabactin **106** (ref. 110) and agrobactin **107** (ref. 115) developed by Bergeron's group was utilized for further synthesis of vibriobactin **124**,[117] fluviabactin **120** (ref. 118) and vulnibactin **113** (ref. 119) (shown for the latter in Scheme 23). All these siderophores contain the symmetrical spermidine analog, *N*-(3-aminopropyl)-1,3-diaminopropane (norspermidine) scaffold. The selective activation of norspermidine **108**,[120] its *N*-acylation with 2,3-dimethoxybenzoic acid **107** and then with the activated L-threonine ester **111** was followed by threonyl fragment condensation with the ethyl imidate of mono- or dihydroxybenzoic acid **104** or **105**. The target siderophores vibriobactin, fluviabactin and vulnibactin **113** were formed in 29%, 23%, 25% total yields, respectively.

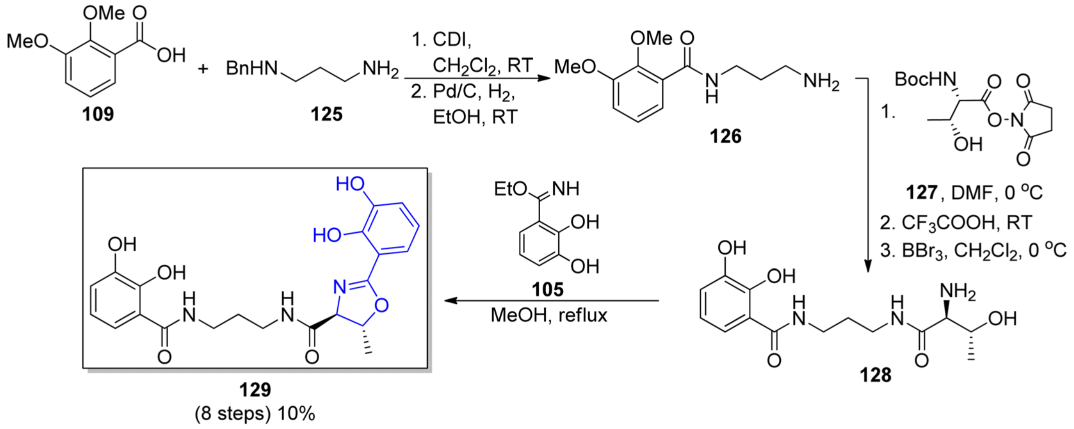
A new concept of norspermidine based synthesis of oxazoline-containing siderophores was proposed by Ishihara and co-workers.[90] The basis of this methodology lies in the oxazoline core construction at an early stage in total synthesis. Based on previously investigated approach for oxazoline and thiazoline rings formation *via* Mo(VI) oxides,[94,121] preparation of fluvibactin **120** and vibriobactin **124** was reported. In the synthesis, three building blocks were used: norspermidine **117**, 2,3-dialkoxybenzoate **116**, and 2-(*o*,*m*-dialkoxyphenol)oxazoline **115** prepared from *N*-(*o*,*m*-dialkoxybenzoyl)-L-threonine *epi*-**82a** *via* the Mo(VI) oxide catalyzed method. Dehydrative cyclization of *N*-(*o*,*m*-dialkoxybenzoyl)-L-threonine *epi*-**84a** was performed using $MoO_2(TMHD)_2$ (Scheme 24). Afterwards, a selective amide formation was conducted using Sb(III) alkoxide-catalyzed ester-amide transformation[122] of primary amine groups in norspermidine **117**. The amidation of the secondary amine group in products **118** and **122** was achieved using the respective carboxylic acid **115** and EDC, HOAt coupling reagents in the presence of base. In the course of this transformation fluvibactin **120** and vibriobactin **124** were obtained in overall yields of 65% and 50%, respectively (Scheme 25). This improved methodology eliminates the most inefficient step in the Bergeron methodology involving 2,3-dihydroxybenzimidate formation for oxazoline scaffold construction.

The most recent synthesis of fluvibactin **120** and vibriobactin **124** was described in 2013 by Raymond's group.[101] In their approach, 2-mercaptothiazoline was used to prepare a building block necessary to install the catechol-amide units in all siderophores. The 1,3-thiazolodine-2-thione functionality reacted with the primary amine group in norspermidine **117** in a very selective way. The central amine group in norspermidine **117** due to low reactivity[90] was functionalized using HATU as a coupling reagent followed by benzyloxycarbonyl-*N*-Cbz-L-threonine treatment. In the final step, a catechol-oxazoline building block obtained *via* Bergeron's methodology[110,115] was used leading to the desired siderophores in total yields of 20% (compound **120**) and 15% (compound **124**).

In the group of synthesized polyamine siderophores, equipped with aryloxazoline moiety serratiochelin A **129**



Scheme 25 Total synthesis of fluvibactin **120** and vibriobactin **124**.[90]



Scheme 26 The synthetic route for serratiochelin **129** synthesis.[107]

containing the 1,3-diaminopropane chain is also found. The synthetic route reported by Ehlert *et al.* for serratiochelin A **129** formation[107] was based on Bergeron's procedure described for agrobactin **105**.[115] In the initial stage, the catechol-amide fragment of **126** was formed through *N*-(3-aminopropyl)benzylamide[123] **125** coupling with 2,3-dimethoxybenzoic acid **109**. Subsequently, benzyl protection from the terminal amine group was removed, followed by *N*-(L-*N*-*t*-butoxycarbonylthreonyloxy) succinimide **127** incorporation. At the end all protecting groups were removed and the oxazoline core was formed using ethyl imidate of 2,3-dihydroxybenzoic acid **105** in total yield 10% (8 steps) (Scheme 26).

Many research groups have been interested in the synthesis of analogs of naturally occurring polyamine-based siderophores. The main goal for this trend is to investigate the relationship between structure and iron transporting ability.[124] Moreover, there is an increased interest in developing new antibiotic treatments by linking antibiotics to siderophore moieties (Trojan horse strategy). Many efforts were put into the structural modifications of spermidine-containing catechol-type siderophore, parabactin **106** and its natural analog agrobactin **107**.[124,125] All modifications of these siderophores had to be performed in such a way as to preserve the ability for iron binding and microbial growth under conditions of limited iron access. The aryloxazoline part directly linked to the central

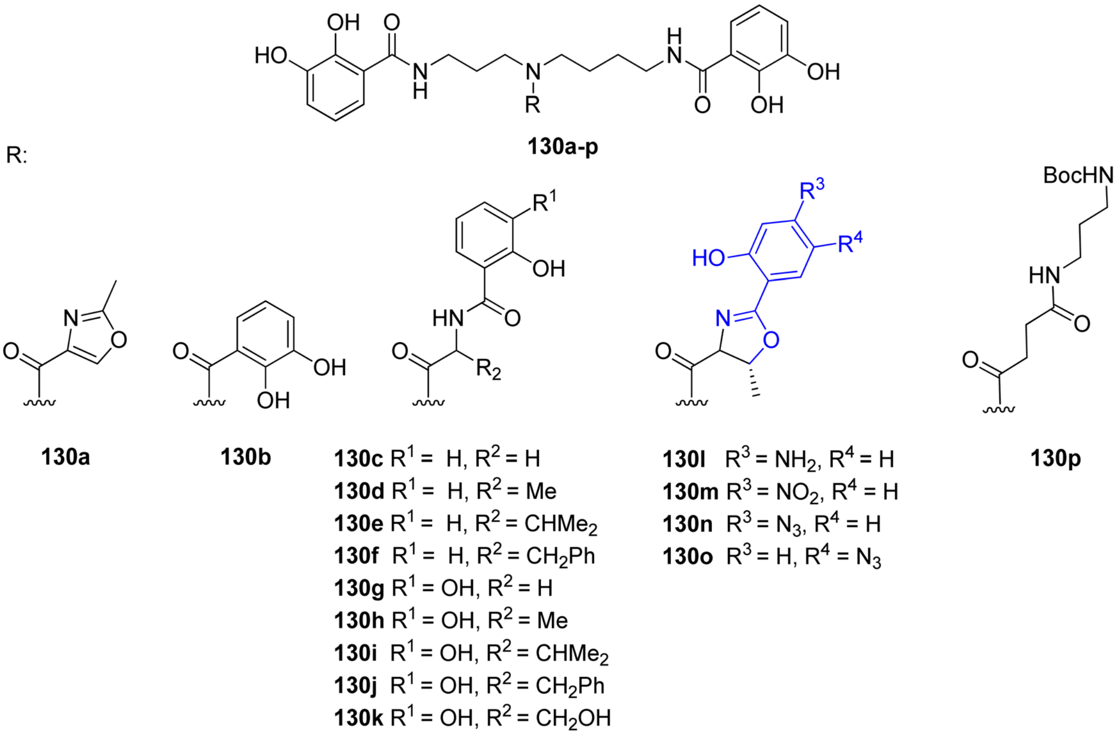


Fig. 14 Examples of parabactin analogs **130a–p**.[124,125]

amino group in the polyamine chain was mainly modified (Fig. 14). The performed research showed that the original structure of polyamine siderophore is still favoured as compared to analogs in coordination and iron transport system study.

In the previously cited work of Bergeron *et al.*[118] on the synthesis of L-fluvibactin **120**, the synthesis of unnatural enantiomer D-fluvibactin *ent*-**120** and L-homofluvibactin **145** were also presented (Scheme 27). This research revealed that modifications of the polyamine chain of the fluviabctin **120** (L-homofluvibactin **145**) do not affect bacterial growth and iron uptake machinery of *P. denitricans*. However, an invertion of the configuration of two carbon atoms in the oxazoline ring (D-fluvibactin, *ent*-**120**) inhibits microbial growth. D-Fluvibactin *ent*-**120** still functions as deferration agent with iron clearing efficiency similar to L-fluvibactin **120**, but due to the stereochemistry of the created ferric complex it cannot be utilized by the microorganisms.

2.2.4 Mycobactin-type siderophores. *Mycobacterium tuberculosis*, a species responsible for tuberculosis, serves as a source

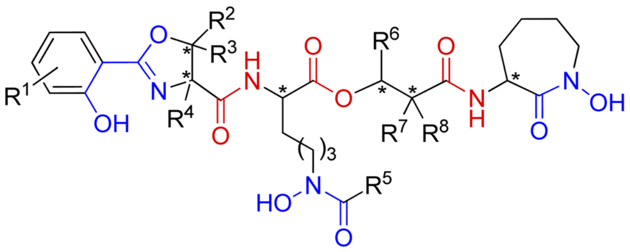
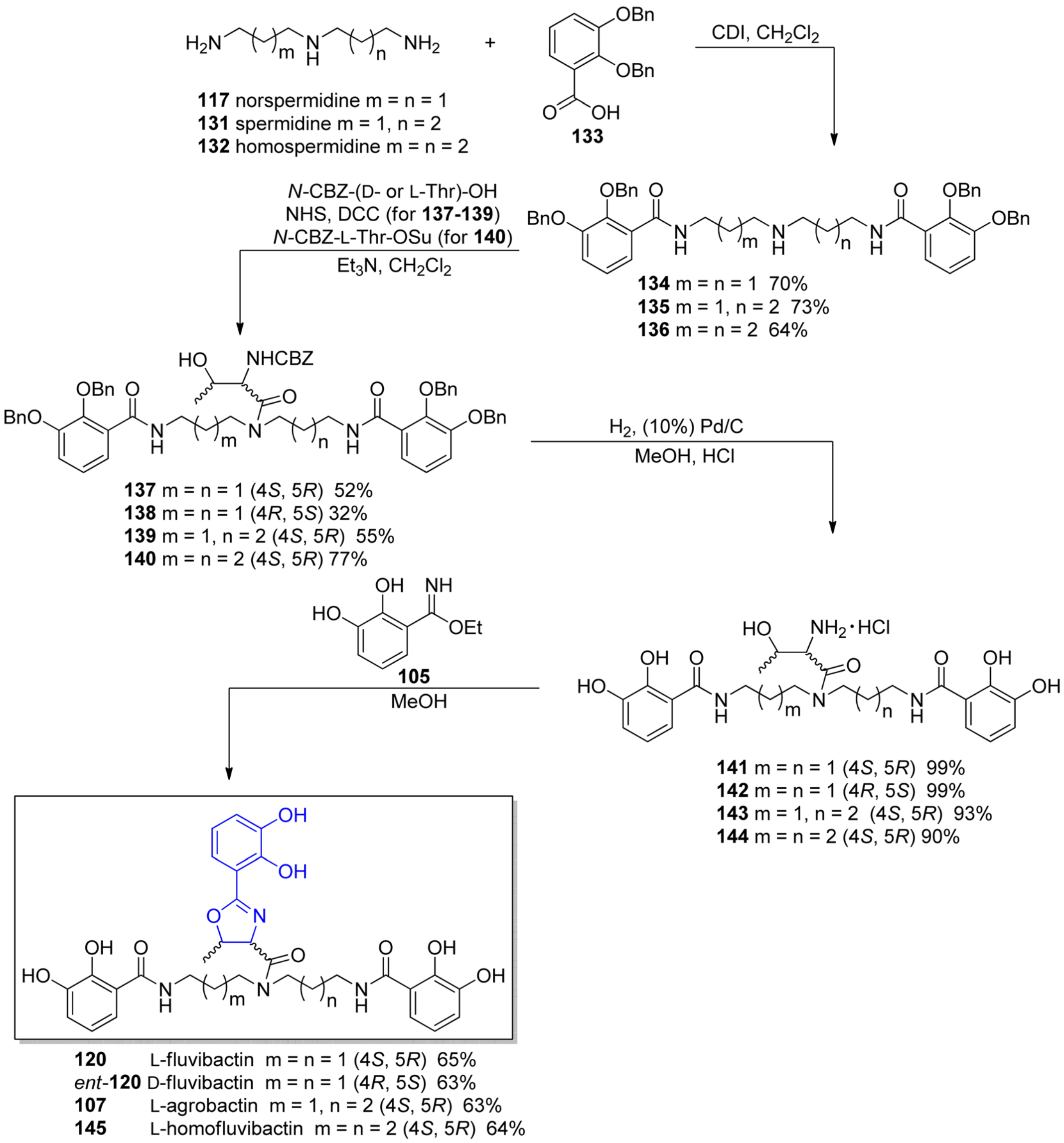


Fig. 15 A general structure of mycobactin type siderophores. Fragments engaged in iron coordination marked blue, amide and ester linkages shown in red. Possible chiral centres indicated by asterisks.



Scheme 27 Synthesis of L-fulvibactin **120** and its unnatural analogs.[118]

of various lipopeptidic siderophores called mycobactins.[126] Also strains of genus *Nocardia* produce similar lipid-soluble intracellular iron-binding compounds (nocobactins, formylobactins, brasilibactins, amamistatins and others).[127] Their common features include the presence of two amide and one ester connections, a seven-membered caprolactam ring at one end, and 2-aryloxazole or 2-aryloxazoline at the opposite end (Fig. 15).

The mycobactins are now quite well-known siderophores since mycobactin P was first isolated from *Mycobacterium phlei* in 1949.[128] Due to the position of the hydrophobic alkyl tail (R_5 or R_6), mycobactins are classified into two types: P-type (after mycobactin P) or M-type (after mycobactin M), respectively.[129] Mycobactin J is one of the P-type mycobactins and is produced by *M. avium* ssp. *paratuberculosis* which is the causative agent of Johne's disease in cattle.[130]

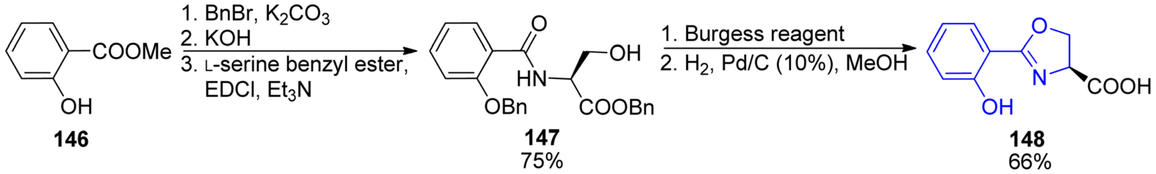
The carboxymycobactins are structurally related to the mycobactins except that their R_5 or R_6 alkyl side chain (Fig. 15) is shorter and terminates in a carboxylic acid, resulting in much greater hydrophilicity.[131] Pathogenic mycobacteria strains like *M. tuberculosis* and *M. bovis* express carboxymycobactins as the sole extracellular siderophores.[132,133]

Nocobactins NA1 and NA2 were isolated from *Nocardia asteroides* grown under conditions of iron deficiency. They are related in their structure to the mycobactins what was described by Ratledge and Snow in 1974.[134]

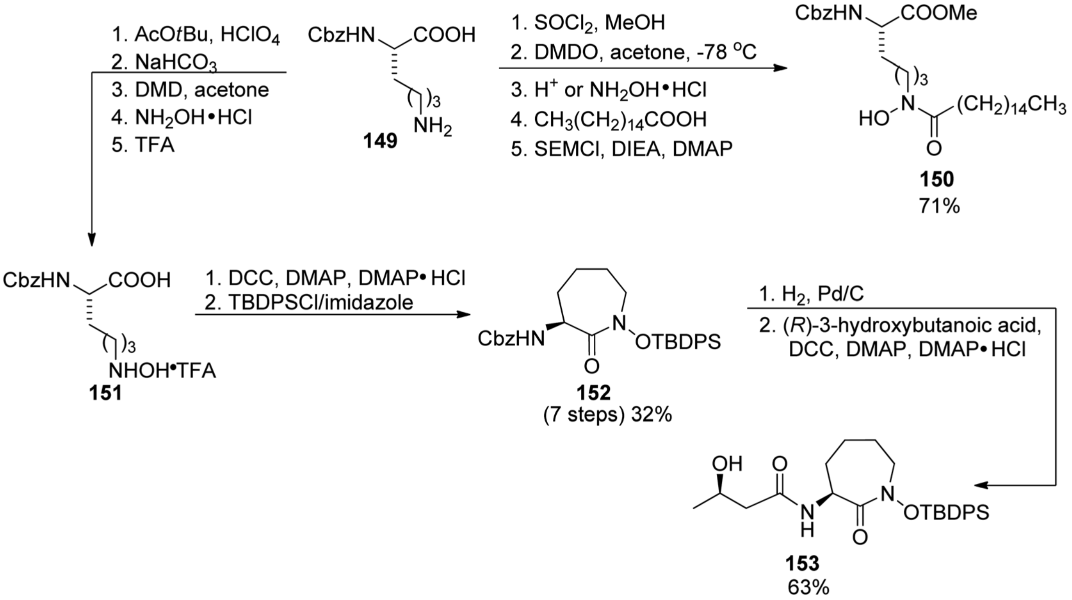
Amamistatin B (isolated from the actinomycete *Nocardia* – *Nocardia asteroides*[135]) is also structurally related to mycobactins siderophore as it contains lysine-derived *N*-formyl hydroxylamine. Amamistatin A has anti-proliferative, but not cell-killing, effects against several kinds of human tumor cell lines.[135] Amamistatin's anti-cancer activity is probably due to histone deacetylase enzymes inhibition mediated by the *N*-formyl hydroxylamine ligand.[136]

Brasilibactin A, a siderophore found in *Nocardia brasiliensis*[137] contains oxazoline moiety and a pentadecyl substituent. Brasilibactin A is a membrane-bound siderophore with structural similarity to the mycobactin class of siderophore in mycobacteria and possesses a nearly identical molecular nucleus, which includes a hydroxamic acid, an *N*-hydroxyformamide, and a 2-(2-hydroxyphenyl)-Δ^2-1,3-oxazoline.[138]

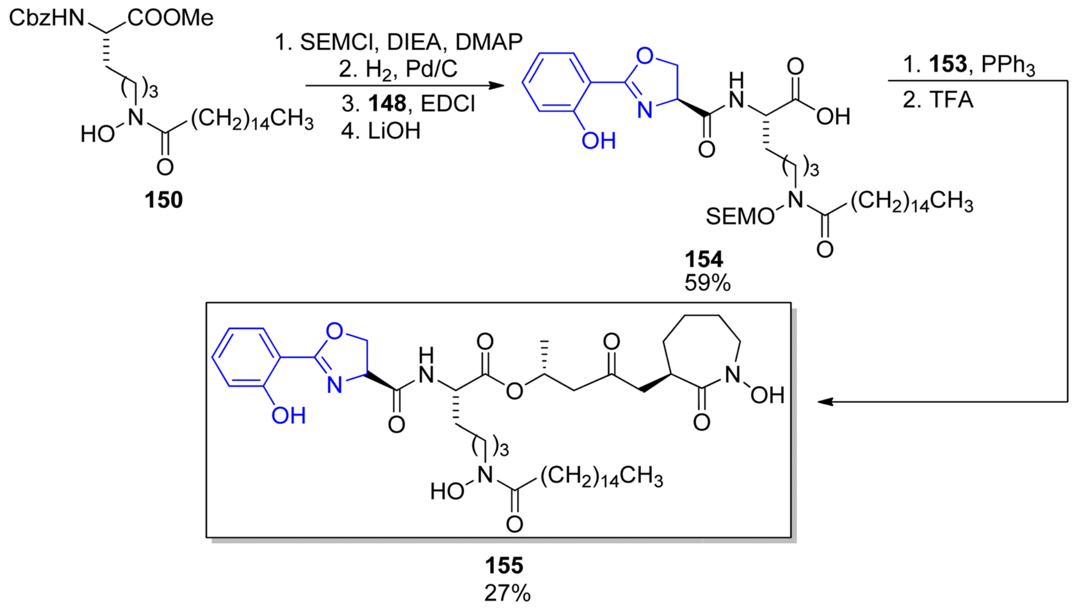
Nocardichelins A and B were isolated from the *Nocardia* sp. *Acta* 3026 and the structural characterization of the compounds was performed by mass spectrometry and NMR spectroscopy. The chemical structures of these siderophores are closely related to mycobactin siderophores. In contrast, comparison of nocardichelins A and B to brasilibactin A reveals that only the 4,5-dihydro-2-(2-hydroxyphenyl)-4-oxazolecarboxylic acid moiety is identical.[139]



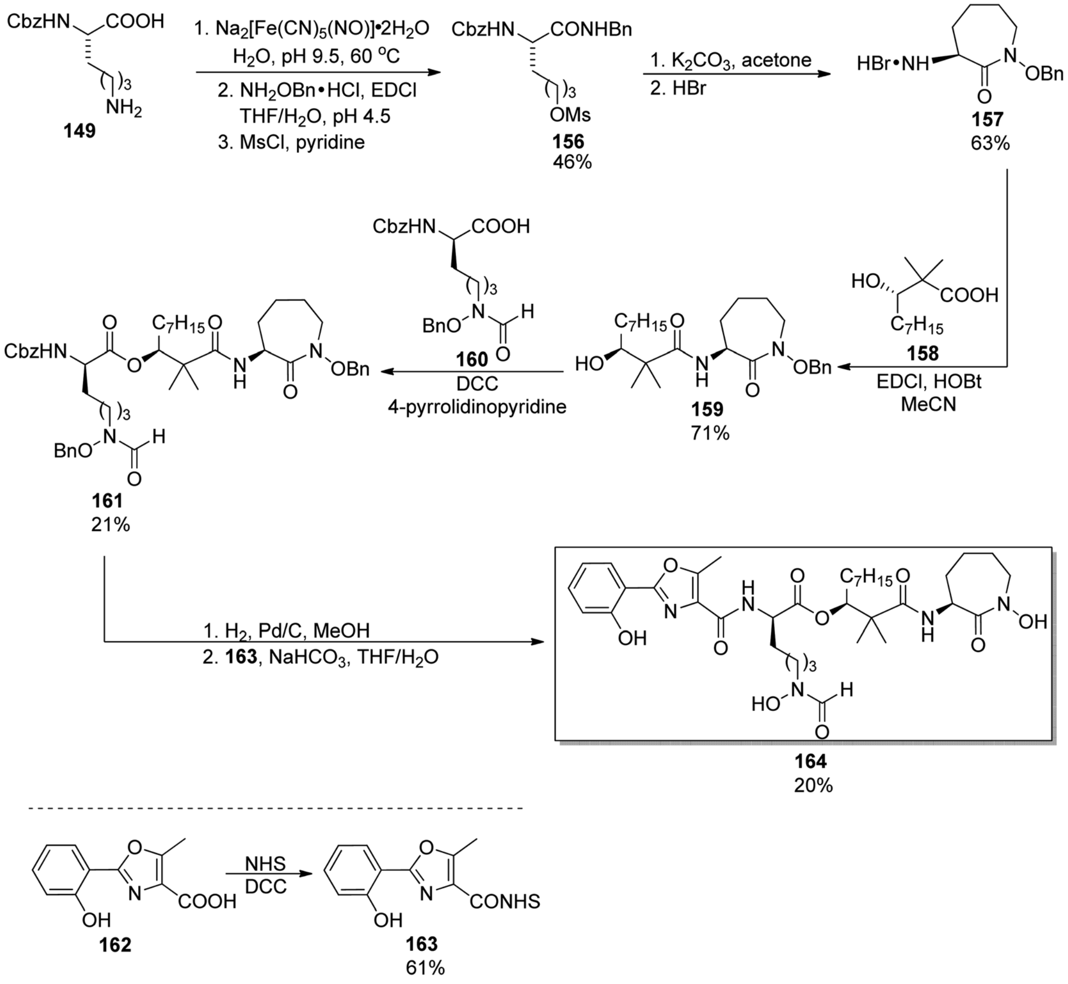
Scheme 28 Preparation of oxazoline derivative **148** as a part of synthesis of mycobactin S.[143]



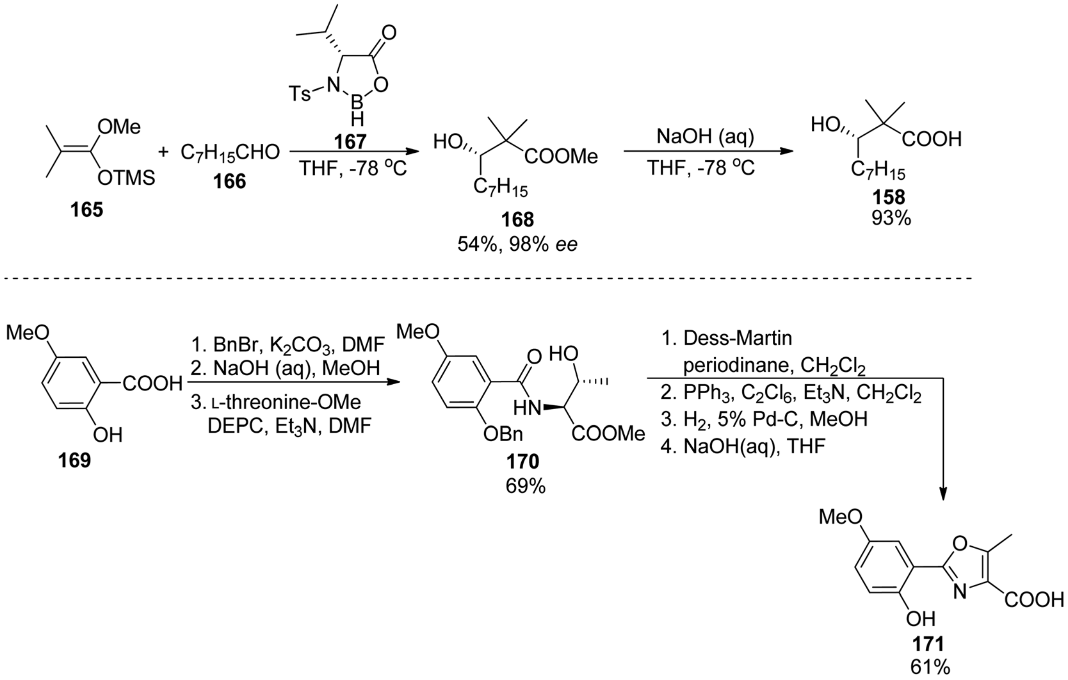
Scheme 29 The use of L-lysine for the preparation of two building blocks **150**, and cobactin T **153** in mycobactin S synthesis.[143]



Scheme 30 Assembling of mycobactic acid and its conversion to mycobactin S **155**.[143] Note that the configuration of a stereogenic centre bearing the methyl group was apparently wrong in the original paper.



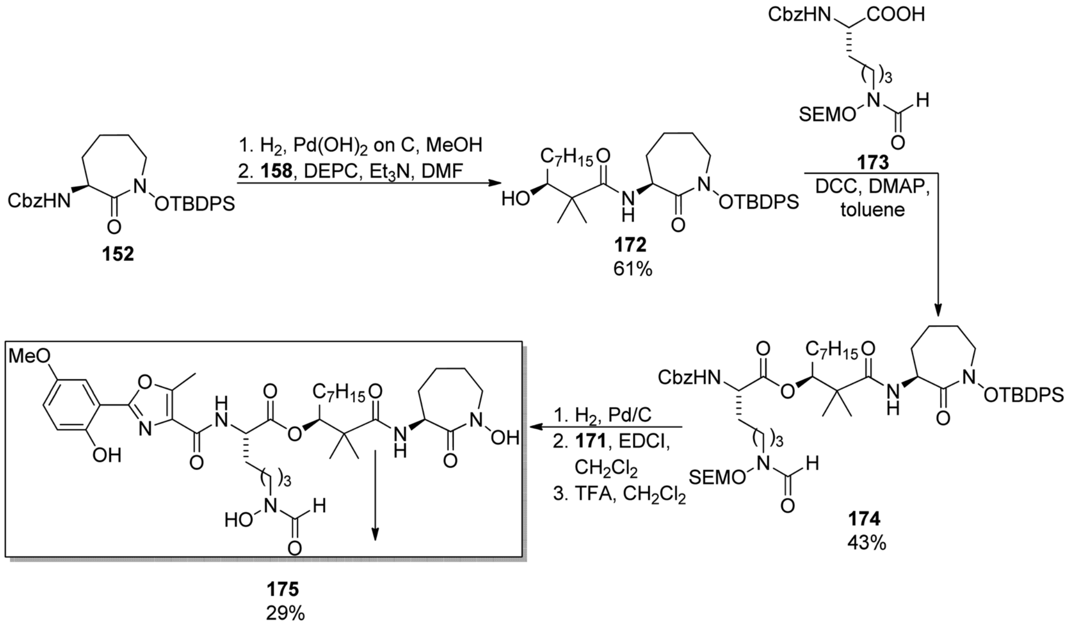
Scheme 31 Preparation of amamistatin B **164** by Miller and co-workers.[127]



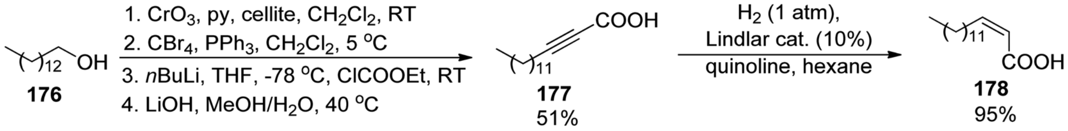
Scheme 32 Preparation of two components **158** and **171** of amamistatin A **175** by Yokokawa *et al.*[144]

Nocardimicins A, B, C, D, E and F members of the family of siderophores isolated from *Nocardia* sp. TP-A0674 (ref. 140) bear an undecyl chain and oxazole moiety. Nocardimicins are the first example of siderophores that have demonstrated inhibition activity to the muscarinic M3 receptor.[140] Nocardimicins G, H and I were isolated from *Nocardia nova* JCM 6044 and their chemical structures were determined by spectroscopic analysis using NMR and MS.[141]

First preparations of mycobactin type siderophores were described by Miller and coworkers.[142,143] They prepared mycobactin S2, an analog of mycobactin S with a long alkyl chain of the mycobactic acid residue replaced by a methyl group.[142] However, the modification resulted in lowered lipid solubility which was found essential for the siderophore activity in mycobacteria.[143] A total synthesis of mycobactin S was thus designed using a similar strategy: coupling of cobactin T and mycobactic acid derivative, *i.e.* two compounds formed in the



Scheme 33 Synthesis of amamistatin A **175**.[144]

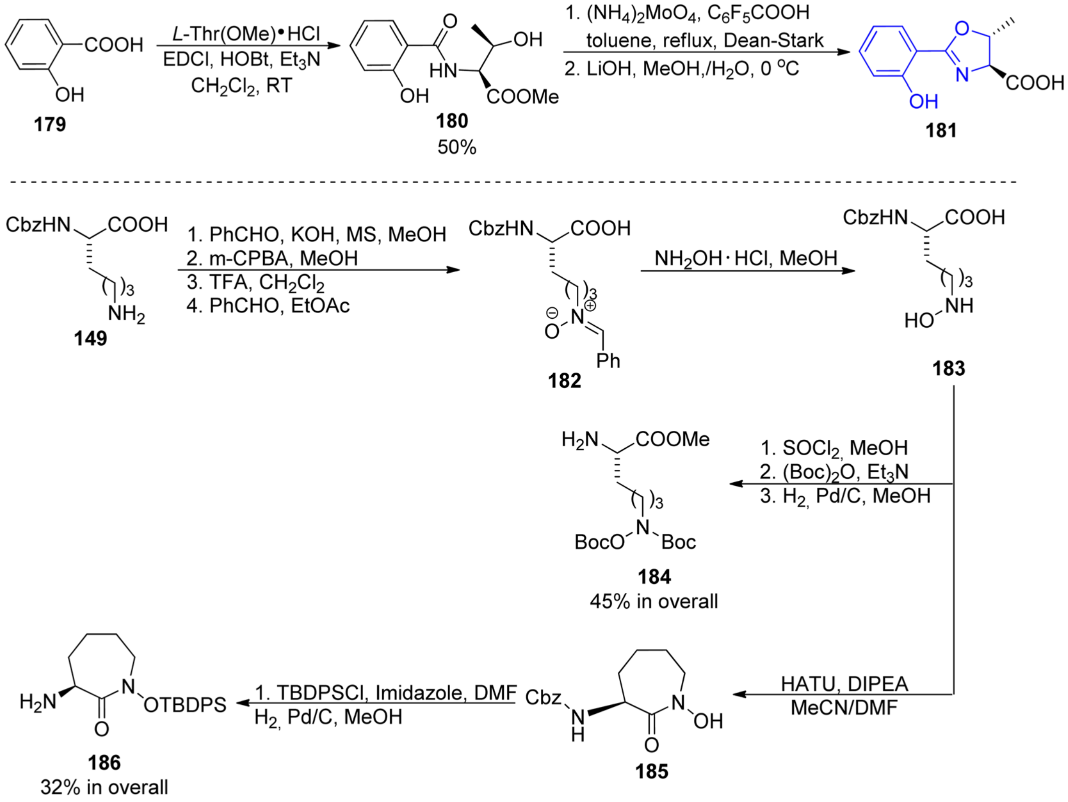


Scheme 34 Synthesis of unsaturated acid component **178** of mycobactin J **191**.[145]

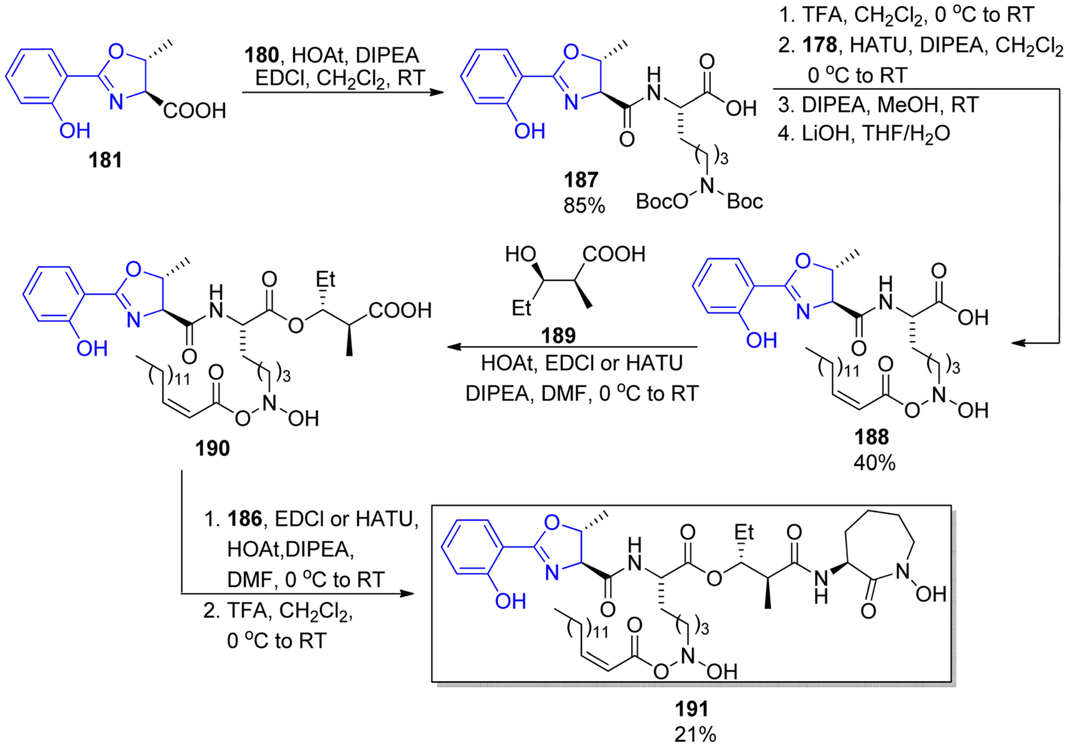
saponification process of mycobactins.[143] The first component was prepared from two building blocks, one **148** containing 2-aryloxazoline residue which was constructed from methyl salicylate **146** and L-serine benzyl ester, using Burgess' reagent to induce cyclization (Scheme 28). It was connected with L-lysine derivative **150** containing hydroxamic acid moiety and a pentadecane chain (Schemes 29 and 30). Cobactin T component was also based on the blocked L-lysine as a staring material, converted to the corresponding hydroxylamine **151** which underwent cyclization to yield a seven-membered ring (caprolactam derivative) with a preserved configuration of a stereogenic centre **152**. Coupling with (*R*)-3-hydroxybutanoic acid and deprotection gave cobactin T (**153**, Scheme 30). Its reaction with mycobactic acid followed by treatment with TFA afforded mycobactin S **155** (27% yield of the last stages). As it could be seen, L-amino acids and 3-hydroxybutanoic acid were used as sources of chirality.

Eleven years later, Miller's group accomplished the synthesis of amamistatin B, one of siderophores isolated form a strain of *Nocardia*.[127] Using methods previously developed in Miller's laboratory,[136] they prepared 2-aryl-oxazole and D-lysine-derived hydroxamic acid; a third component, (*S*)-3-hydroxy-2,2-dimethyldecanoic acid was also obtained following the procedure introduced by Yokokawa *et al.* (*vide infra*).[144] The last building block, a cyclic hydroxamic acid **157**, was synthesized by a modified route from Cbz-L-lysine **149** in 19% overall yield (Scheme 31); its configuration was preserved in the caprolactam derivative formed in the cyclization step. This component was then reacted with hydroxydecanoic acid **156**, and the product esterified using a linear hydroxamate **160**. Two enantiomers of the latter were used (one is shown in Scheme 31), which allowed preparation (after deprotection and reaction with oxazole part **163**) of amamistatin B **164** and its epimer. A similar protocol was applied in the synthesis of an analog lacking two hydroxyl groups, however, only the original siderophore was (moderately) active against *M. tuberculosis*.

A similar synthetic approach was used earlier by Yokokawa, Shioiri, and co-workers who prepared amamistatin A, which differs only by the presence of a methoxy substituent from B form.[144] In the paper describing the synthesis, a stereoselective



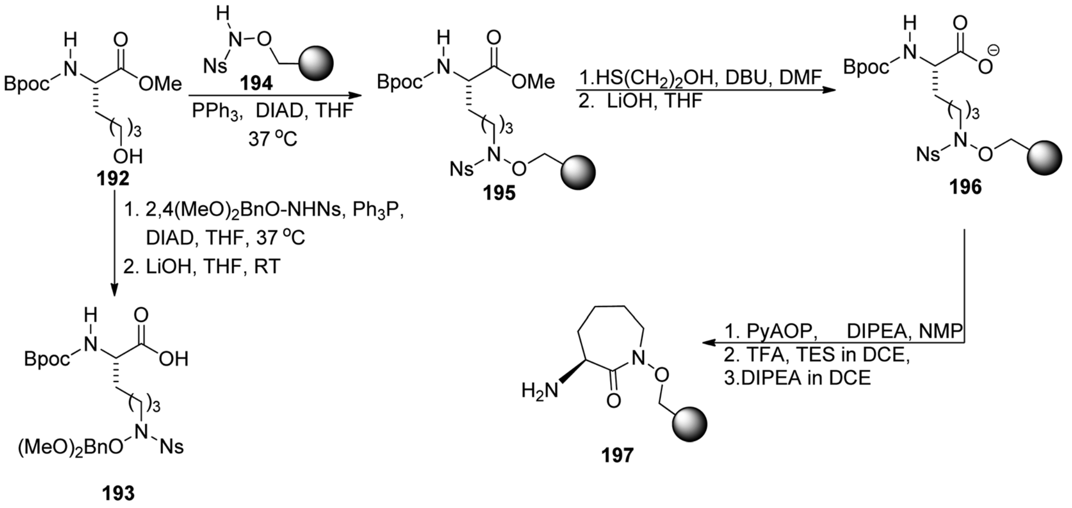
Scheme 35 Synthesis of three synthons **181**, **184** and **186** of mycobactin J **191**.[145]



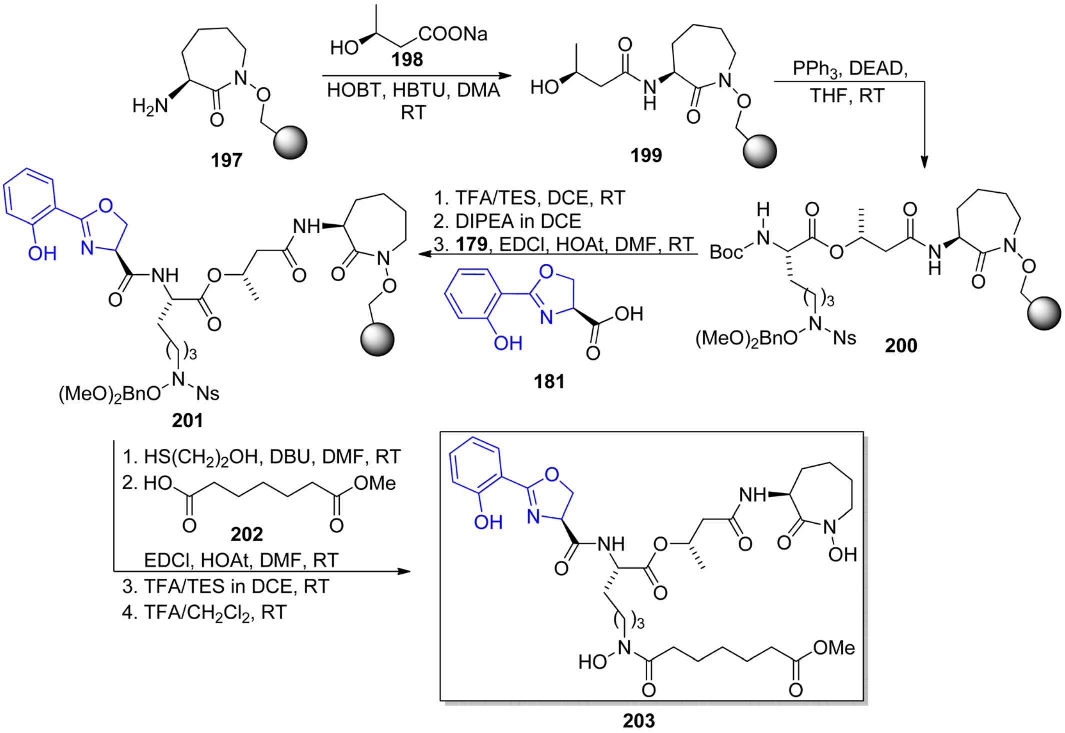
Scheme 36 Assembling of four components into mycobactin J **191**.[145]

preparation of (*S*)-3-hydroxy-2,2-dimethyldecanoic acid **158** was presented utilizing aldol reaction of octanal **166** and methyl trimethylsilyl dimethylketene acetal **165** in the presence of stoichiometric amounts of a chiral oxazaborolidinone **167** obtained from D-valine; hydrolysis of the resulting ester **168** afforded the desired acid **158** in 50% overall yield (Scheme 32). The oxazole component **171** was prepared starting from 5-methoxysalicylic acid **169**, and ring closure of **170** was achieved through a Wipf's variant of Robinson–Gabriel synthesis (oxidation with Dess–Martin reagent followed by dehydration of the intermediate ketoamides, Scheme 32). Amamistatin A **175** was constructed by a stepwise addition of subsequent building blocks to the caprolactam derivative **152** (Scheme 33; this compound **152** and a linear hydroxamate **173** were prepared by previously described methods[143]), and the overall yield of the seven steps was *ca.* 7.5% (part of the unreacted intermediates, however, could be recovered).

Among other compounds from the mycobactin family, a total synthesis of J form **191** was described by Kapur and co-workers in 2018.[145] The specific component of this compound,

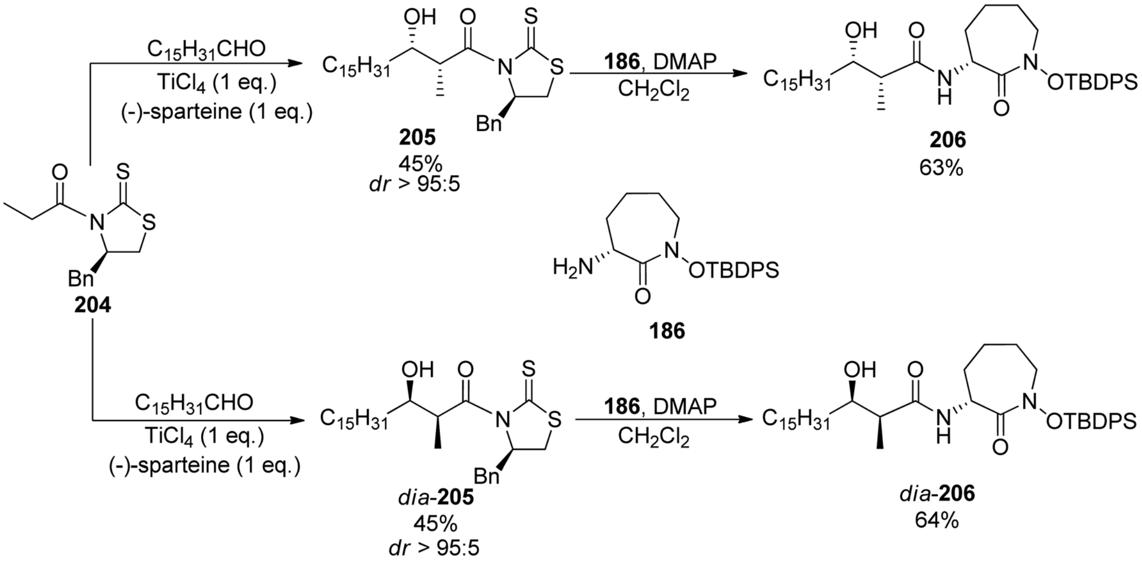


Scheme 37 Synthesis of synthons used for preparation of carboxymycobactin T.[146]

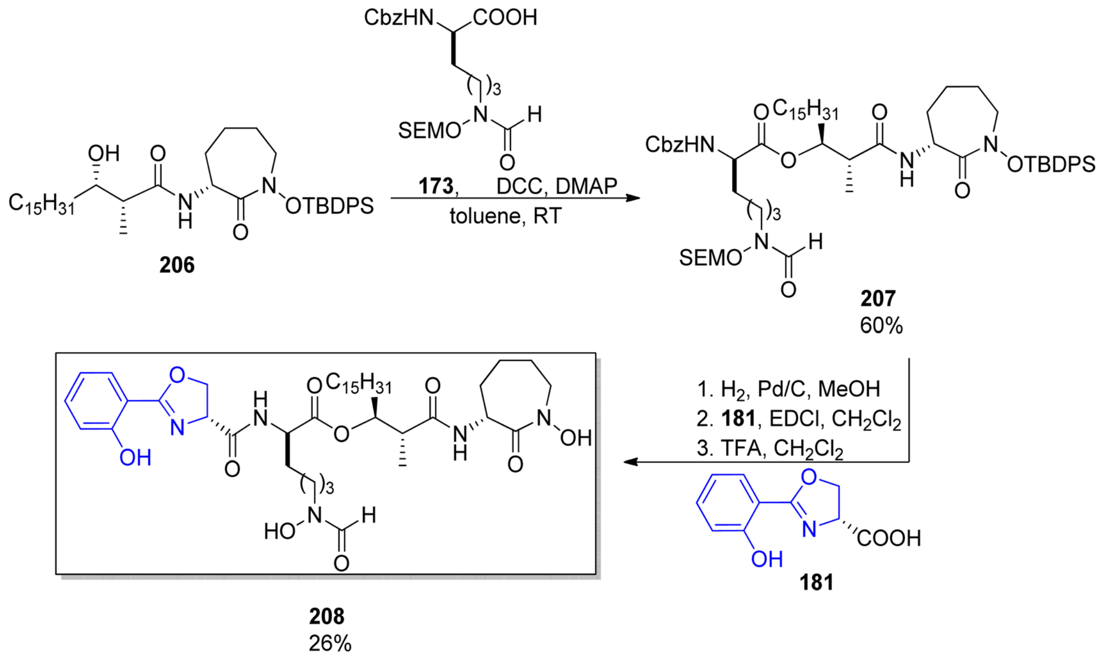


Scheme 38 Solid-phase synthesis of carboxymycobactin T **203**.[146]

a long-chain carboxylic acid **178** with a double C═C bond with (*Z*) configuration, was prepared in 48% overall yield *via* oxidation of 1-tetradecanol **176** to tetradecanal, its Corey–Fuchs conversion to alkyne, its esterification with chloroformate, and hydrolysis (Scheme 34). Thus obtained acid **177** with a carbon–carbon triple bond was stereospecifically hydrogenated over Lindlar catalyst to give (*Z*)-pentadec-2-enoic acid **178**. It was attached to a mycobactic acid fragment which in turn was constructed from salicylic acid **179**, L-threonine methyl ester, and a fragment derived from Cbz-L-lysine **184**; oxazoline **181** formation was achieved by molybdate-mediated cyclization with a retention of configuration (Schemes 35 and 36). The second synthon also required L-lysine which was converted to a cyclic amide using HATU; coupling with (2*S*,3*R*)-3-hydroxy-2-methylpentanoic acid **189** (a source of two stereogenic centres in the final molecule) resulted in the cobactin fragment **190**. However, in contrast to Miller's preparations,[142,143] the attempts of esterification to yield mycobactin J were unsuccessful.



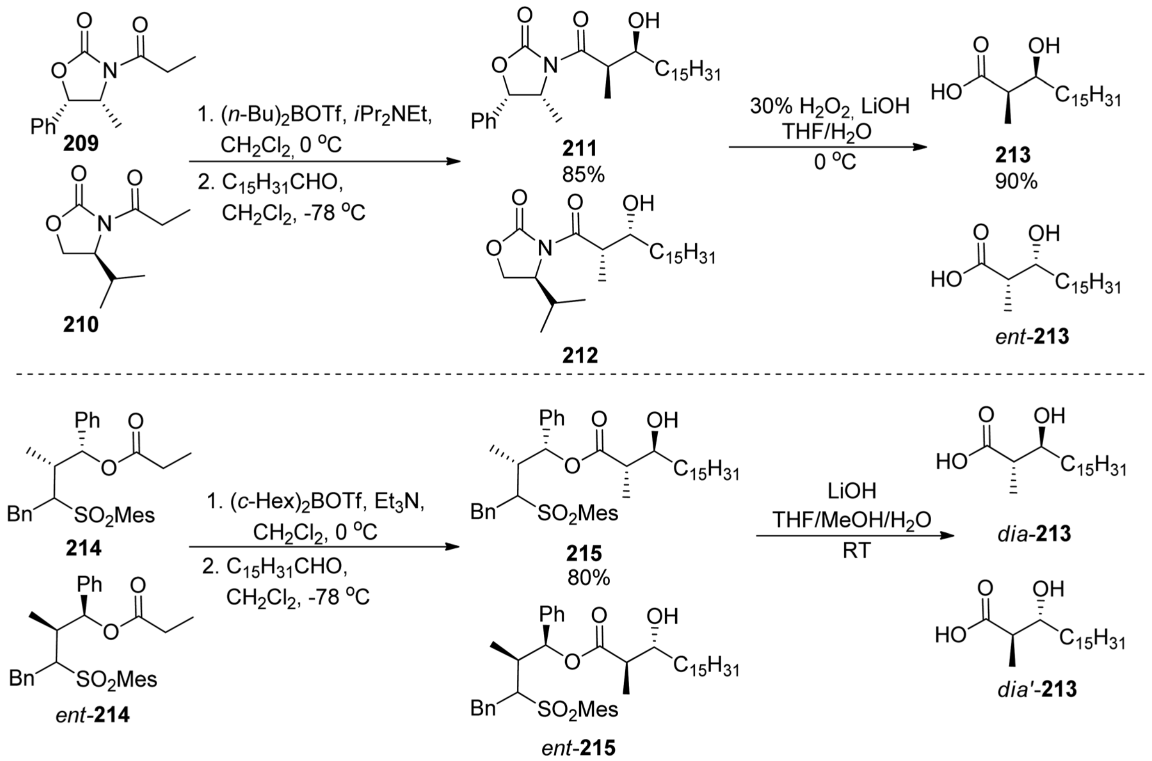
Scheme 39 Preparation of two diastereomers of hydroxyacid-caparolactam part of brasilibactin A **208**.[147]



Scheme 40 Synthesis of brasilibactin **208** by Mitchell and Show.[147]

Instead, a chiral pentanoic acid derivative **189** was first connected to mycobactic acid **188,** and a cyclic hydroxamic acid **186** was added in a subsequent step yielding the desired final product **191** (21% yield over three steps).

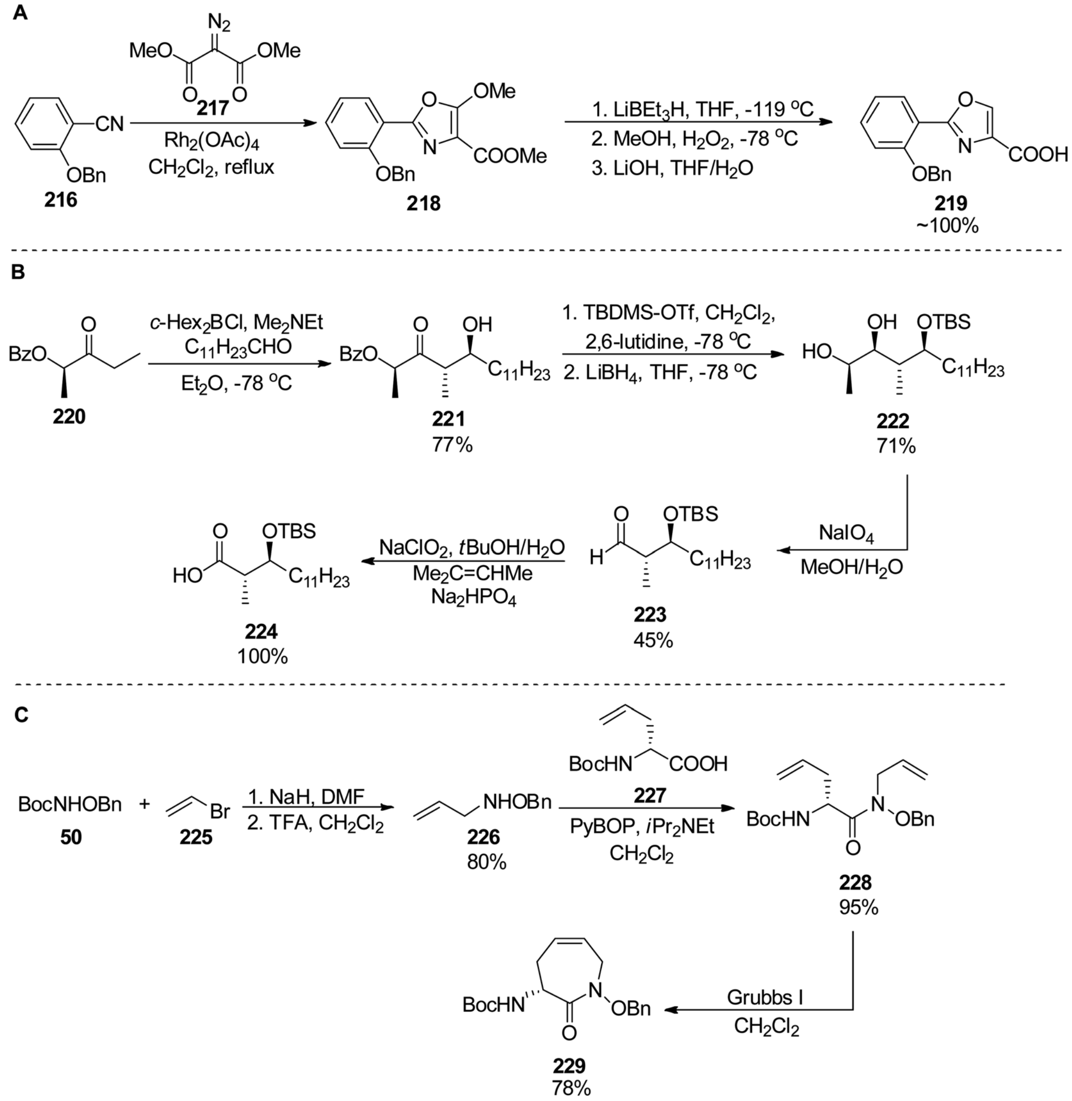
Carboxymycobactin T **203** and its three analogs were prepared by Slomczynska and co-workers using a solid-phase approach.[146] L-Norleucine **192** derivative was reacted with nosyl-activated hydroxylamine bound to Wang resin **194;** PyAOP-induced cyclization afforded an immobilized



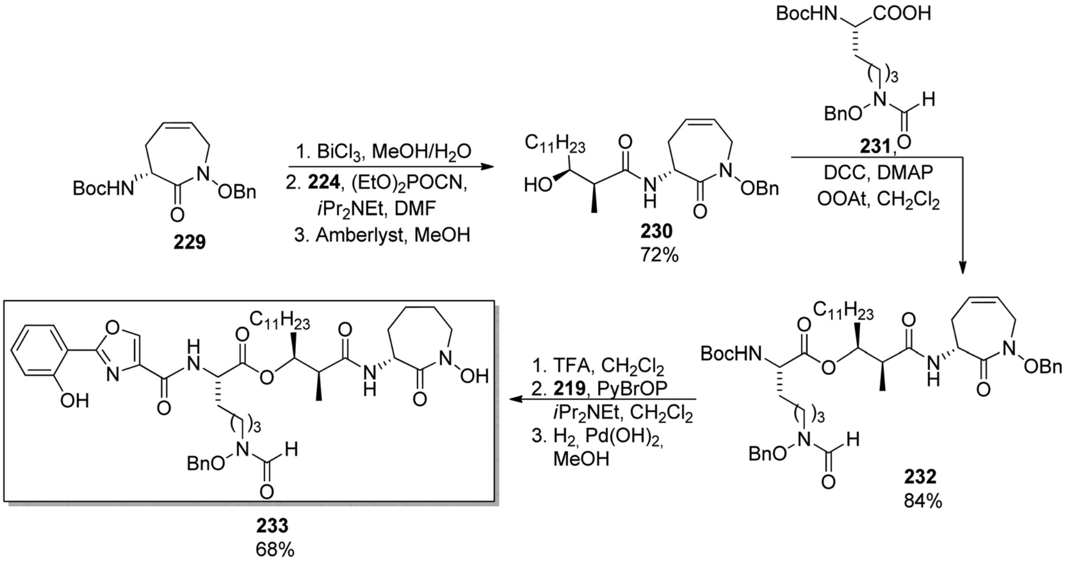
Scheme 41 Preparation of four diastereomers of hydroxyacid part of brasilibactin A by Ying and Hong.[138]

caprolactam derivative **197** (Scheme 37) to which subsequent fragments were connected (Scheme 38): (*S*)-3-hydroxybutyric acid **198**, another L-norleucine-derived component **200**, and 2-(2-hydroxyphenyl)oxazoline-4-carboxylic acid **181** which preparation was described by Miller's group.[143] To the obtained skeleton, a monomethyl ester of heptane-1,7-dioic acid **202** was attached as a side chain and the carboxymycobactin T **203** was removed from the resin. Its epimer with the opposite configuration of carbon atom bearing methyl group was prepared by the same route with (*R*)-3-hydroxybutyric acid *ent*-**198** as one of components; in case of two analogs bearing amide instead of ester linkage, separation of diastereomeric mixture appeared necessary due to unexpected epimerization.

In 2007, two research groups reported on a synthesis of brasilibactin A. In a paper of Mitchell and Shaw, preparation of two diastereomers differing in the configuration of the β-hydroxyacid component allowed the assignment of absolute configuration of the naturally occurring form.[147] This fragment was prepared using the titanium-mediated aldol reaction of chiral thiazolidinethione auxiliary **204** with hexadecanal which led to *syn* products **205** and *dia*-**205** with the absolute configuration dependent on the amount of (−)-sparteine added (45% yield and diasteromeric ratio >95 : 5 were noted in both cases, Scheme 39). Coupling with caprolactam-based amine **186** released the auxiliary and resulted in the respective diastereomeric products **206** and *dia*-**206**. Their subsequent reactions with the known building blocks derived from D-lysine **173** and, finally, oxazoline fragment **181** prepared from D-serine followed the previously reported procedures and led to brasilibactin A **208** (found to be a 17*R*,18*S* isomer; Scheme 40) and its (17*S*,18*R*)-analog. Independently, Ying and Hong prepared four diastereomers differing by configurations of these two stereocentres.[138] The four hydroxyacid components **213**, *ent*-**213**, *dia*-**213** and *dia′*-**213** were prepared by diastereoselective aldol reactions from *N*-propanoyloxazilidinones (*syn* isomers) and *O*-propanoylnorephedrines (*anti* selectivity, Scheme 41). The



Scheme 42 Preparation of three components **219**, **224** and **229** of nocoardimicin B.[148]



Scheme 43 Synthesis of nocardimicin B **233**.[148]

overall synthetic strategy was similar to the one of Mitchell and Shaw, and the stereochemical assignment of natural brasilibactin A **208** was identical.

Banks and Moody prepared nocardimicin B **233** from four usual components, though they modified the synthesis of particular building blocks.[148] The 2-aryloxazole part **219** was obtained by rhodium-catalyzed reaction of 2-benzoyloxybenzonitrile **216** with dimethyl diazomalonate **217**; removal of the methoxy group and hydrolysis gave the 2-aryloxazole-4-carboxylic acid **219** in *ca.* 67% yield (Scheme 42). The linear hydroxamic acid component **231** was prepared by a previously established method, while for the β-hydroxycarboxylic acid, an *anti*-selective aldol reaction was applied between a lactate-derived (*R*)-ketone and dodecanal under Patterson conditions.[149] Standard four-step manipulation provided the desired hydroxyacid **224** in 25% overall yield. The cyclic hydroxamic acid **229** was prepared using ring-closing metathesis (RCM) as a key step. *O*-Benzyl-*N*-Boc-hydroxylamine **50** was converted into *N*-allyl derivative **226** which in turn reacted with (*R*)-Boc-allylglycine **227** to give the respective amide **228**. RCM employing Grubbs' catalyst yielded a seven-membered caprolactam derivative with a double bond **229** (59% yield from hydroxylamine derivative, Scheme 42). Starting from this building block **229**, all fragments were connected subsequently, and the final step involved a hydrogenative deprotection, but also reduction of the C=C bond, and yielded the expected siderophore **233** (Scheme 43).

Concluding this part, sidorophores containing an oxazole or oxazoline ring exhibit a significant similarity of four main chiral synthons which can be appropriately assembled. Part of these fragments inherit chirality of the starting amino acid residues, however, others are prepared in stereoselective reactions (for example, 3-hydroxycarboxylic acid in aldol reaction). Though a total synthesis of all known members of the family has not been accomplished yet (as exemplified by other mycobactins, nocobactin, and formobactin), the general procedure for their preparation should not differ much from their analogs obtained in the laboratories.

3 Conclusions

In this comprehensive review we presented the total synthesis of naturally occurring siderophores bearing arylthiazoline and aryloxazoline subunits. During the years a development of synthetic strategies has been observed to find the optimal approach for synthons used for many siderophores. The progress of characterization techniques allowed to determine configurations of all stereogenic centres and to correctly describe all stereoisomers. The yield of the total synthesis and enantiomeric purity of prepared compounds have been greatly improved which is important from the application point of view. Amounts of siderophores required in biomedical studies are typically in the range of hundred milligrams, two orders of magnitude more than typically isolated from natural sources.

Conflicts of interest

There are no conflicts to declare.

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