Synthesis A. Kiefer, U. Kazmaier THIEME OPEN ACCESS Short Review

Syntheses of Cyclomarins – Interesting Marine Natural Products with Distinct Mode of Action towards Malaria and Tuberculosis

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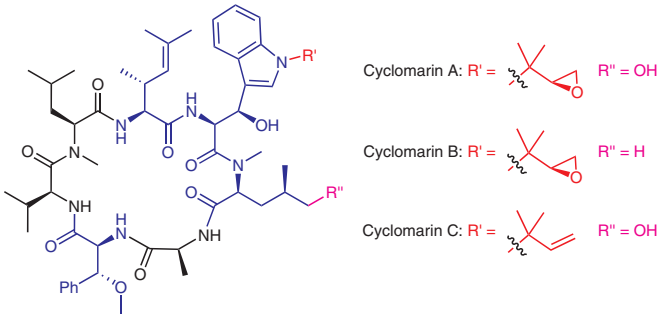

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Abstract The cyclomarins are cyclic heptapeptides from marine streptomycetes containing four rather unusual amino acids. Interestingly, the cyclomarins address two completely different targets: ClpC1, a subunit of the caseinolytic protease of *Mycobacterium tuberculosis* (MTB), as well as $PfAp_3Aase$ of *Plasmodium falciparum*. Therefore, the cyclomarins are interesting lead structures for the development of drugs targeting tuberculosis and malaria. As a result, several synthetic protocols towards the synthesis of these unusual building blocks as well as the natural products themselves have been developed, which will be discussed in this review.

Key words natural products, cyclopeptides, cyclomarins, total synthesis, malaria, tuberculosis

Alexander Kiefer (left) was born in Völklingen, Germany, in 1987. He received his B.Sc. in 2012 at Saarland University on natural product synthesis and his M.Sc. in 2014 on Pd-catalyzed allylic alkylations of chelated glycolates. After an internship at Bayer Pharma Healthcare in 2015, he is currently studying for his Ph.D. on the synthesis of biologically active natural product analogues in the research group of Prof. Dr. Uli Kazmaier at Saarland University. His interests involve medicinal chemistry and total synthesis and chemoenzymatic synthesis of natural products.

Uli Kazmaier (right), born in 1960, studied chemistry at the University of Stuttgart where he obtained his diploma (1985) and his Ph.D. (1989). Afterwards he joined as a postdoc the research groups of M. T. Reetz (Marburg) and B. M. Trost (Stanford). In 1992, he moved to Heidelberg starting his own scientific work as a habilitand at the Institute of Organic Chemistry. In 2000 he received a Novartis Chemistry Lectureship and an offer of a full professorship at the University Bayreuth. In 2001 he also obtained an offer of a full professorship at the University des Saarlandes, which he accepted. His current research interest extends to new organometallic reagents and reactions especially for amino acid and peptide synthesis. Besides the development of new synthetic protocols, the application of these new reactions towards the synthesis of natural products and other pharmaceutical relevant structures plays a central role.

1 Introduction

From the last century to the present, an uncountable number of peptidic secondary metabolites have been isolated from microorganisms such as bacteria or fungi.[1] Due to their diverse and unique structures, they exhibit a remarkable range of biological activities. This fact is not surprising since they are the highly optimized result of millions of years of evolutionary selection.[2] Thus, natural products play an important role in drug discovery, either as direct drug candidates or as lead structures.[3–7] Nevertheless, it should be mentioned, that the isolation from complex mixtures often cannot provide the desired natural product in amounts suitable for structure elucidation or complete biological evaluation. Therefore, innovative methods are required to produce the desired natural product by total synthesis. In addition, structural modifications provide important insights into the structure–activity relationship (SAR).[8]

An outstanding example is a small family of peptide natural products, the cyclomarins A–C (**1**–**3**), isolated in 1999 from the marine streptomycete strain CNB-982 (Figure 1).[9] The crude extract of a sample, collected from sediments at Mission Bay, showed moderate cytotoxicity against human colon cancer cells (HCT-116). Furthermore, the organism produced the novel cyclopeptides under saline culture conditions, whereas the main metabolite cyclomarin A (**1**) shows an IC_{50} value of 2.6 µM against various cancer cell lines. In addition to the anticancer properties, anti-inflammatory and antiviral activities were also observed.[10] Moreover, in 2011 Schmitt, Camacho, and co-workers from Novartis reported antibacterial activity against *Mycobacterium tuberculosis* (*Mtb*) in concentrations of 0.3 µM and 2.5 µM in culture broth medium and human-derived macrophages, respectively.[11] Interestingly, cyclomarin A (**1**) retains antitubercular activity against several resistant strains and also inhibits nonreplicating intracellular bacteria in macrophages with a mortality rate of 90% (after 5 d incubation) with a drug concentration of 2.5 µM. This fact suggested that a completely new molecular target structure might be involved.[12] Target profiling by chemical proteomics identified the ClpC1 subunit of the caseinolytic protease (Clp), where Schanda and co-workers, in 2018, determined the mode of action by NMR spectroscopic and crystallographic investigations.[13] In addition, cyclomarin A (**1**) shows an impressive antiparasitic activity against *Plasmodium falciparum* (*Pfalcp*), the pathogen of malaria.[14] By inhibition the growth of the blood stages of *Pfalcp*, cyclomarin A (**1**) binds a dimer of diadenosine triphosphate hydrolases (PfAp3Aase) and thereby prevents the formation of the enzyme-substrate complex.

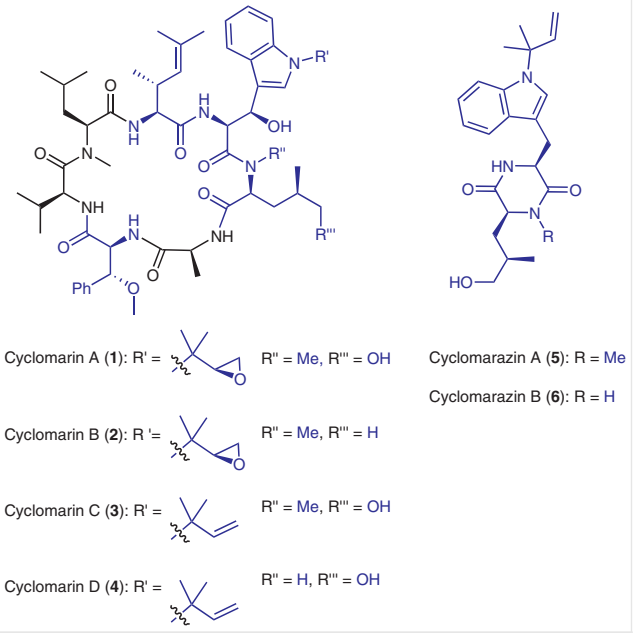


Figure 1 Chemical structures of cyclomarins and cyclomarazins

As already mentioned, cyclomarin B (**2**) and C (**3**) were also isolated in 1999, but in significantly smaller quantities. In the course of a broad screening for biologically active substances from the culture broth of the streptomycete strain BCC26924, cyclomarin C (**3**) was isolated in sufficient quantities and biologically evaluated.[15] Thus, cyclomarin C (**3**) shows antitubercular activity (MIC = 0.10 µg/mL, strain H37Ra) as well as antiplasmodial activity against multi-drug-resistant strain K1 with an IC_{50} value of 0.24 µg/mL. Furthermore the analogous cyclomarin D (**4**) (Figure 1), in principle *N*-desmethylcyclomarin C, was identified in the culture medium of a Palau-derived actinomycete species (*Salinospora arenicola* CNS-205).[16] In 2008, the structurally related metabolites cyclomarazins A (**5**) and B (**6**) (Figure 1) were also isolated.[16] It is thought that the cyclomarins and cyclomarazins have a common biosynthetic origin due to the similarity of two noncanonical amino acids. The biosynthesis of these compounds was investigated in detail by Moore and co-workers.[16–18]

Beside the three proteinogenic amino acids (L-Ala, L-Val, *N*-Me-L-Leu), the 21-membered cyclopeptides **1**–**4** differ by slight variation in the methylation and oxidation pattern of the noncanonical amino acids (blue), which were identified using 1D and 2D NMR techniques. Determination of the absolute stereochemistry was achieved by X-ray crystal structure of the diacetate derivative of cyclomarin A (**1**).[9] Some of the unusual amino acids, especially the β-methoxyphenylalanine moiety and derivatives thereof are not only incorporated in cyclomarins, they also can be found as key structural motifs in a variety of biologically active compounds, ranging from discokiolides[19] and callipeltins[20] to more complex cyclic depsipeptides, such as neamphamide A,[21] papuamides,[22] or mirabamides.[23] The β-hydroxytryptophan unit can be found in two variations, either with a *N′*-*tert*-prenyl residue or the oxidized *N′*-[(2*S*)-2,3-epoxy-1,1-dimethylpropyl] substituent, which is also a structural motif of another antitubercular class of natural products, the ilamycins.[24–26] Furthermore the δ-hydroxyleucine fragment is found in BZR-cotoxin II[27] and in leucinostatins,[28] whereas the 2-amino-3,5-dimethylhex-4-enoic acid is unique to cyclomarins.

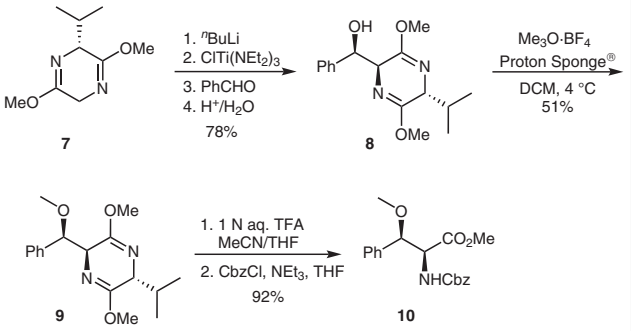
Soon after the isolation of the cyclopeptides, the first synthesis of the noncanonical amino acids of cyclomarin A (**1**) were reported by Yokokawa and co-workers.[29] Due to the highly complex heptapeptidic structure with 12 or 13 stereogenic centers and the four nonproteinogenic amino acid building blocks, it is hardly surprising, that already in 2004 a synthetically access to cyclomarin C (**3**) was achieved via a convergent strategy by Yao and co-workers.[30,31] Just over ten years later in 2016, Barbie and Kazmaier accomplished the synthesis of the natural products cyclomarin A (**1**), C (**3**), and D (**4**) and, as a simplified derivative, deoxycyclomarin C in a linear approach.[32–34]

In this review we will highlight the synthetic efforts towards these interesting natural products, beginning with the synthetic approaches towards the four noncanonical amino acids, and ending with the total synthesis of the natural products and derivatives, which will be discussed in detail.

2 Synthesis of the Building Blocks

2.1 (2*S*,3*R*)-β-Methoxyphenylalanine

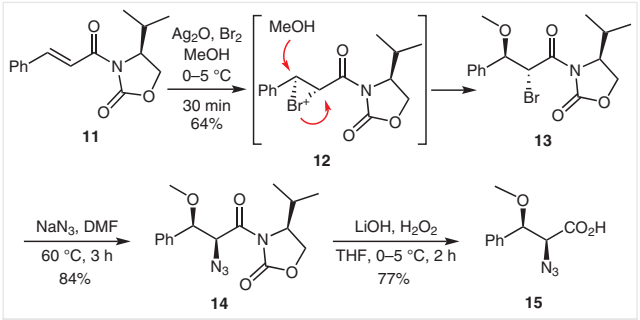
The first reported synthetic access by Yokokawa and co-workers[29] to β-methoxyphenylalanine was achieved by using Schöllkopf auxiliary **7** (Scheme 1).[35] Here, **7** was first deprotonated at low temperature with ^{n}BuLi. After $ClTi(NEt_2)_3$ mediated transmetalation and reaction with benzaldehyde, the secondary alcohol **8** was obtained in diastereomerically pure form in 78% yield.[36] Subsequent *O*-methylation using Meerwein salt and Proton sponge® gave methyl ether **9**.[37] Removal of the chiral auxiliary with aqueous TFA and final amine protection provided building block **10** in a high yield of 92%.[29]



Scheme 1 Synthesis of Cbz-protected (2*S*,3*R*)-β-methoxyphenylalanine using Schöllkopf auxiliary (Yokokawa)

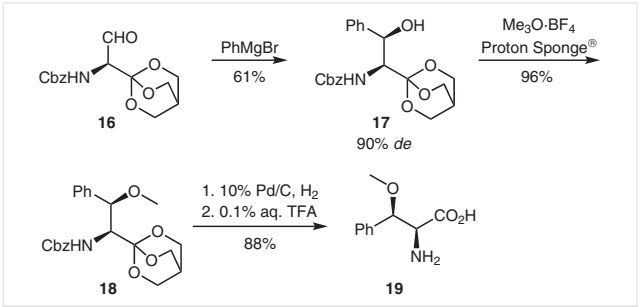
The synthesis route of Hajra and co-workers also used an auxiliary approach (Scheme 2).[38] The Evans auxiliary of cinnamic acid **11** was treated with bromine in a silver(I)-mediated halomethoxylation (via **12**) to give the desired methyl ether as a diastereomeric mixture, from which **13** was isolated in 64% yield. This was followed by an S_N2 reaction with sodium azide to provide *syn* product **14**;[39] the auxiliary was finally cleaved, giving acid **15**. To get the desired β-methoxyphenylalanine, the azide group just needs to be converted into an amino group.

Joullié and co-workers followed an entirely different approach based on a diastereoselective Grignard reaction towards the literature-known Lajoie's serine aldehyde **16**[40] (Scheme 3).[41] Via addition of phenylmagnesium bromide, the *syn* amino alcohol **17** was obtained in good diastereoselectivity, but unfortunately in moderate yield. Next, the



Scheme 2 Synthesis of (2*S*,3*R*)-2-azido-3-methoxy-3-phenylpropanoic acid via halomethoxylation (Hajra)

methyl ether **18** was generated also here by the use of Meerwein salt. Finally, the amino acid **19** was obtained by Cbz deprotection via hydrogenation and cleavage of the orthoester under aqueous acidic conditions.

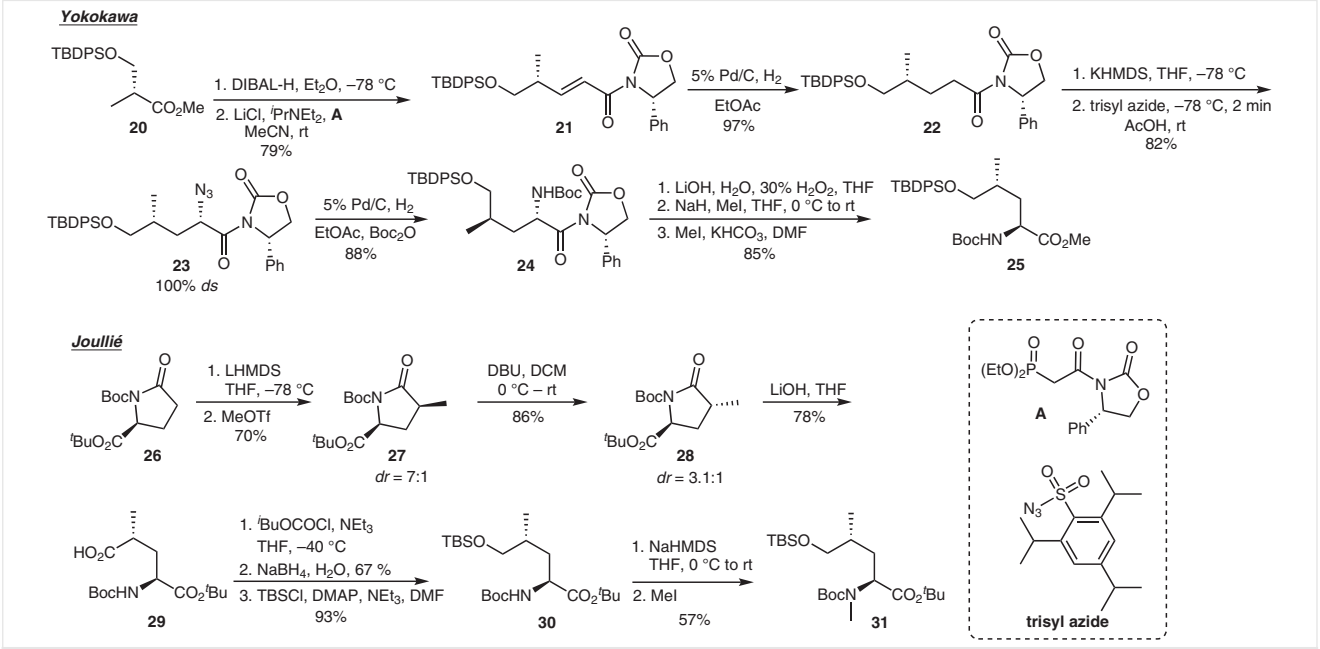


Scheme 3 Synthesis of (2*S*,3*R*)-β-methoxyphenylalanine via diastereoselective Grignard reaction as key step (Joullié)

2.2 (2*S*,4*R*)-γ-Hydroxyleucine

Yokokawa and co-workers also utilized an auxiliary-based approach for the synthesis of the δ-hydroxyleucine building block (Scheme 4).[29] For this purpose, the silyl-protected Roche ester **20** was reduced to the corresponding aldehyde using DIBAL-H. Subsequent Horner–Wadsworth–Emmons reaction with phosphonate **A** gave the α,β-unsaturated amide **21** in 79% yield over both steps.[42] After hydrogenation of the double bond in **21**, **22** was deprotonated using KHMDS at −78 °C; quenching the potassium enolate with 2,4,6-triisopropylphenylsulfonyl azide (trisyl azide) provided the diastereomerically pure azide **23**.[43,44] Subsequent hydrogenation of the azide group with palladium in the presence of Boc_2O afforded the protected amine **24** in good yield. Oxidative cleavage of the Evans auxiliary,[45] *N*-methylation, and esterification gave the desired product **25** in 85% yield over three steps.

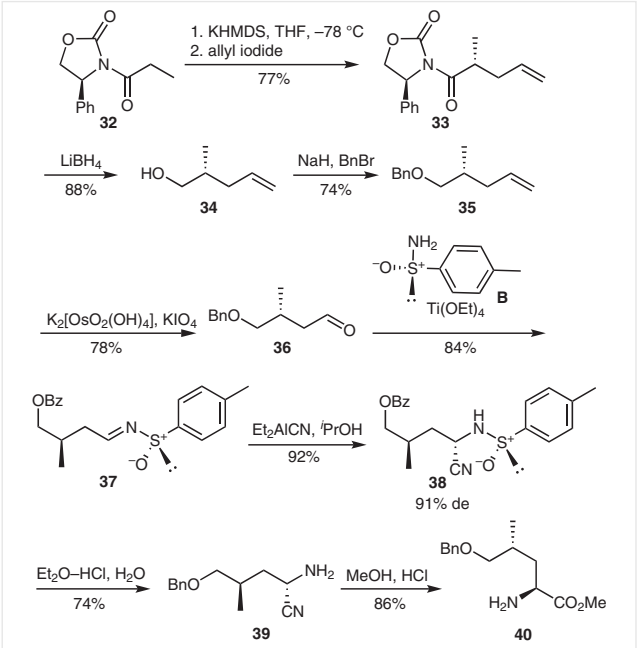
According to Joullié and co-workers the protected (*S*)-pyroglutamic acid **26** was used as starting material (Scheme 4).[46] α-Methylation of **26** gave **27** in a diastereomeric ratio of 7:1 in favor of the undesired diastereomer. However, to obtain the correct configuration in the product, the stereo-



Scheme 4 Comparison of two ex-chiral pool approaches for δ-hydroxyleucine (Yokokawa and Joullié)

genic center was inverted under basic conditions. The diastereomeric ratio of **28** was now 3.1:1 for the favored diastereomer. Acyclic building block **29** was obtained after hydrolysis with LiOH. To generate the desired alcohol, acid **29** was first activated as the mixed anhydride and then reduced with $NaBH_4$. Additional protection gave TBS ether **30**. For the final *N*-methylation, **30** was first deprotonated with excess NaHMDS and then treated with methyl iodide. The fully protected δ-hydroxyleucine **31** was thus obtained in 57% yield without epimerization.

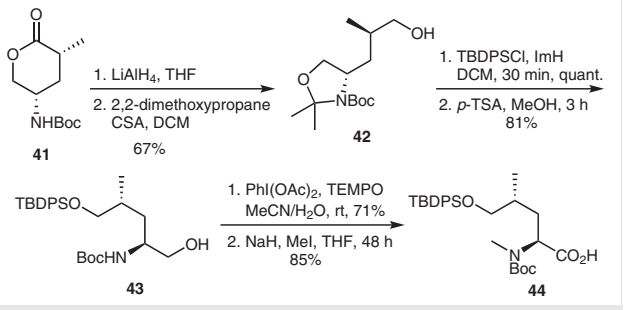
Besides the ex-chiral pool strategy, Joullié and co-workers developed a synthetic method based on an asymmetric Evans alkylation and an asymmetric Strecker reaction[47] as key steps (Scheme 5).[48] First, deprotonation of **32**, followed by the addition of allyl iodide gave oxazolidine **33** with a diastereomeric excess of >96%. Cleavage of the chiral Evans auxiliary under reductive conditions afforded alcohol **34**, which was subsequently protected as benzyl ether **35**. Next, the terminal double bond was oxidized in a one-pot sequence via dihydroxylation/periodate cleavage to obtain the corresponding aldehyde **36**. Subsequent condensation with an enantiopure (+)-(*S*)-*p*-toluenesufinamide **B** in the presence of $Ti(OEt)_4$ gave the desired chiral sulfinimine **37**. Carbonyl addition of Et_2AlCN provided amino nitrile **38** in 92% yield with a diastereomeric excess of 91%. Final cleavage of the sulfinyl auxiliary and hydrolysis of the nitrile group under acid conditions afforded the benzyl-protected methyl ester of (2*S*,4*R*)-δ-hydroxyleucine **40**.



Scheme 5 δ-Hydroxyleucine fragment via asymmetric Evans alkylation and an asymmetric Strecker reaction (Joullié)

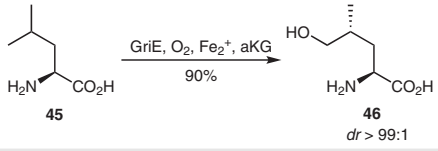
The synthesis of Chandrasekhar and co-workers in 2011 was achieved from amino lactone **41**, which was prepared according to the literature (Scheme 6).[49] Reductive ring opening of lactone **41** gave the amino alcohol, which subsequently protected as dimethyloxazolidine **42**. Next the primary alcohol function was silylated with TBDPSCl and imidazole. After removal of the oxazolidine under acidic con-

ditions, the resulting alcohol **43** was oxidized to the corresponding acid using (diacetoxyiodo)benzene and a catalytic amount of TEMPO in 71% yield. Final *N*-methylation afforded the building block **44**.[50]



Scheme 6 Synthesis of δ-hydroxyleucine from an amino lactone via a dimethyloxazolidine (Chandrasekhar)

In 2018, Zwick III and Renata reported the syntheses of δ-hydroxyleucine **46** via selective chemoenzymatic C–H functionalization (Scheme 7).[51] Thereby, they used an α-ketoglutarate-dependent dioxygenase (Fe/αKG) GriE as biocatalyst for the C5-hydroxylation of **45** to obtain the desired δ-hydroxyleucine **46** in 90% yield and perfect diastereoselectivity.



Scheme 7 Chemoenzymatic approach to δ-hydroxyleucine (Renata)

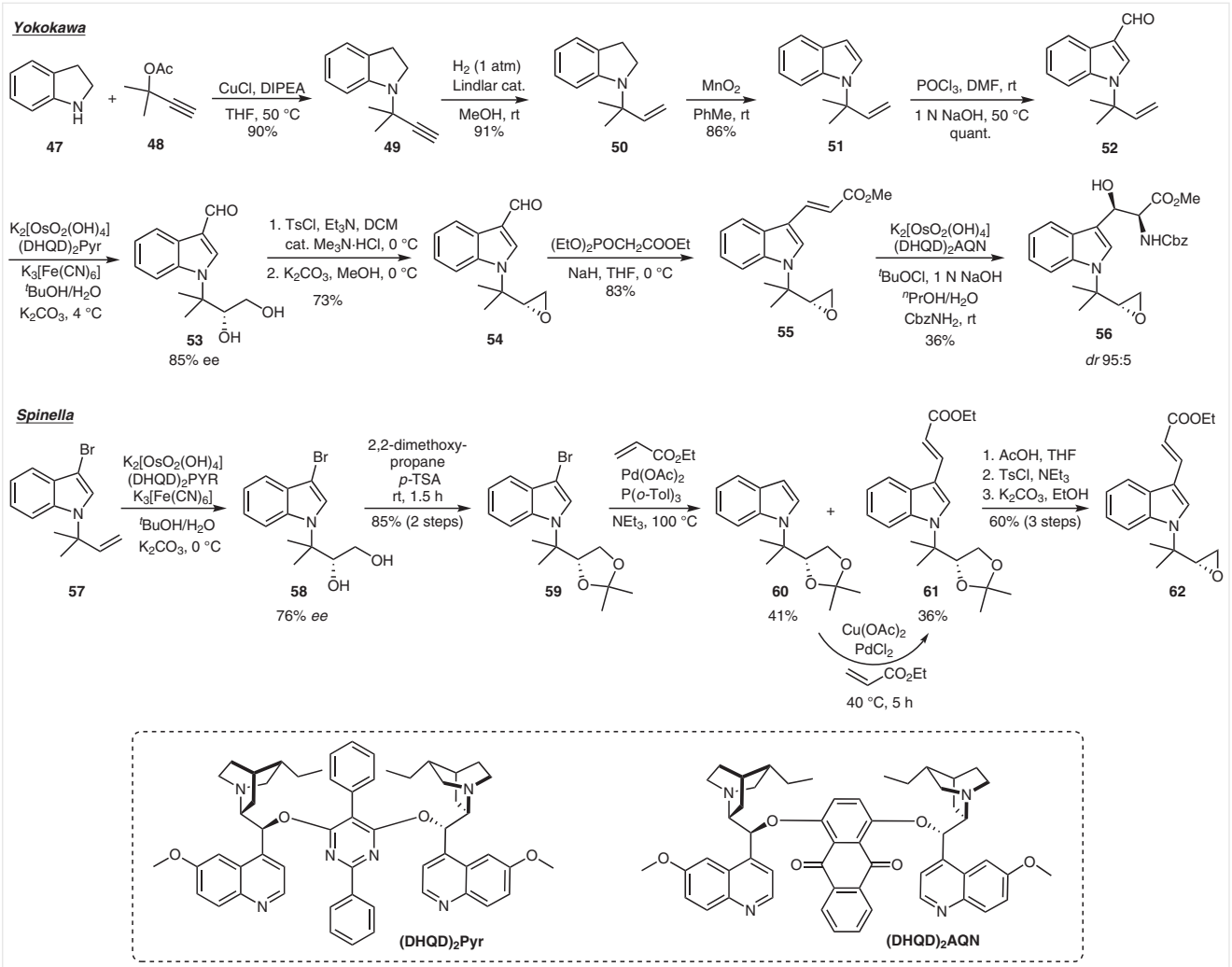
2.3 (2*S*,3*R*)-*N*′-[(2*R*)-2,3-Epoxy-1,1-dimethylpropyl]-3-hydroxytryptophan

For the third noncanonical amino acid unit Yokokawa and co-workers[29] used a literature-known protocol to gain access to *N*-propargylindoline 49 (Scheme 8).[45] Here, indoline (47) was reacted with 3-acetoxy-3-methylbut-1-yne (48) in a copper(I) chloride mediated substitution reaction to give *N*-propargylindoline 49 in excellent yield. Subsequent Lindlar hydrogenation afforded the *N*-*tert*-prenylated indoline 50, which was oxidized with MnO_2 to the *N*-*tert*-prenylated indole 51. In the subsequent Vilsmeier–Haack formylation, indole-3-carbaldehyde 52 was isolated quantitatively. Subsequently, the double bond in the *tert*-prenyl group was transformed into chiral diol 53 via Sharpless dihydroxylation;[45] using the cinchona alkaloid based ligand $(DHQD)_2Pyr$, the enantiomeric excess was 85%. Next, the primary alcohol function of 53 was tosylated and converted under basic conditions into the epoxide 54. Additional Horner–Wadsworth–Emmons reaction with triethyl phosphonoacetate provided the required *E*-configured olefin 55. Final Sharpless aminohydroxylation[45] released the desired β-hydroxytryptophan derivative **56** in moderate yield. In this reaction the regio- and diastereoselectivity were controlled by the cinchona alkaloid based ligand $(DHQD)_2AQN$, which gave product **56** with a diastereoselectivity of 95%.

In addition to this synthesis, a further partial synthesis was developed by Spinella and co-workers, that gave access to substrates for Sharpless aminohydroxylations. They used a transition-metal-catalyzed cross-coupling reaction as the key step (Scheme 8).[52] The synthesis started with bromide **57**. Sharpless dihydroxylation of bromide **57** gave diol **58** with 76% ee, which was converted into acetal **59** in an overall yield of 85% over two steps. Building block **59** was then reacted in a Heck coupling with ethyl acrylate to give α,β-unsaturated ester **61**. However, very high amounts of catalyst were required and the desired product **61** was still only obtained in 36% yield. Furthermore, large amounts of the reduced indole **60** were formed as a side product. Alternative approaches using the analogous iodoindole or an acrylic stannane in the Stille coupling were also not successful. Thus, an alternative oxidative coupling of the nonhalogenated indole **60** with acrylic ester was investigated.[52] After optimization of reaction conditions, the desired building block **61** was finally obtained in a very good yield of 86%. After cleavage of the acetal, the epoxide **62** was synthesized according to the protocol of Yokokawa and co-workers.[29]

Joullié and co-workers also reported a synthesis for this building block (Scheme 9).[53] In analogy to their synthesis of β-methoxyphenylalanine, the hydroxytryptophan moiety was prepared by Grignard addition of an arylmagnesium compound to the Lajoie serine aldehyde **16**. The required *tert*-prenylindole **51** was synthesized according to Yokokawa and co-workers.[29] *tert*-Prenylindole **51** was converted by NBS-mediated bromination into **57**, which was treated with magnesium turnings to give the corresponding organomagnesium species; subsequent addition of this nucleophile to the aldehyde **16** gave the secondary alcohol **63** in moderate yield, but in a good diastereoselectivity of 85%.

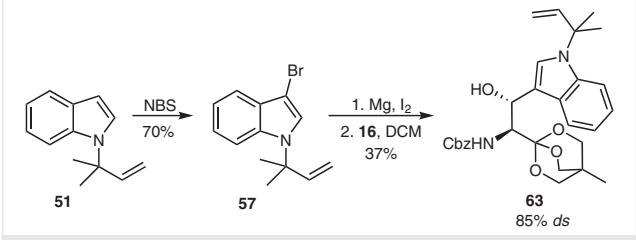
Furthermore, long reaction times and high temperatures were required to gain the desired organometallic species; therefore the use of iodoindole building block **64** was appropriated (Scheme 10). In analogy to the first proposed synthesis of this building block, the epoxide moiety was prepared by Sharpless dihydroxylation, followed by tosylation and subsequently elimination. It was found that the dihydroxylation of **64** provided **65** with 91% ee, while the formation of the epoxide **66** proceeded in comparable yields to the first synthesis. Next, halogen–metal exchange using ^{n}BuLi at low temperature and subsequent transmetalation with magnesium bromide gave the corresponding organomagnesium compound **67**, which reacted with aldehyde **16** to give secondary alcohol **68**. Despite the good diastereoselectivity, the yield was quite low. An additional disadvantage in the synthesis route is the fact that two equivalents of **67** need to be used with the aldehyde **16**. The secondary alcohol **68** was subsequently protected as TBS ether **69**. Af-



Scheme 8 Two synthetic routes to the β-hydroxytryptophan moiety (Yokokawa and Spinella)

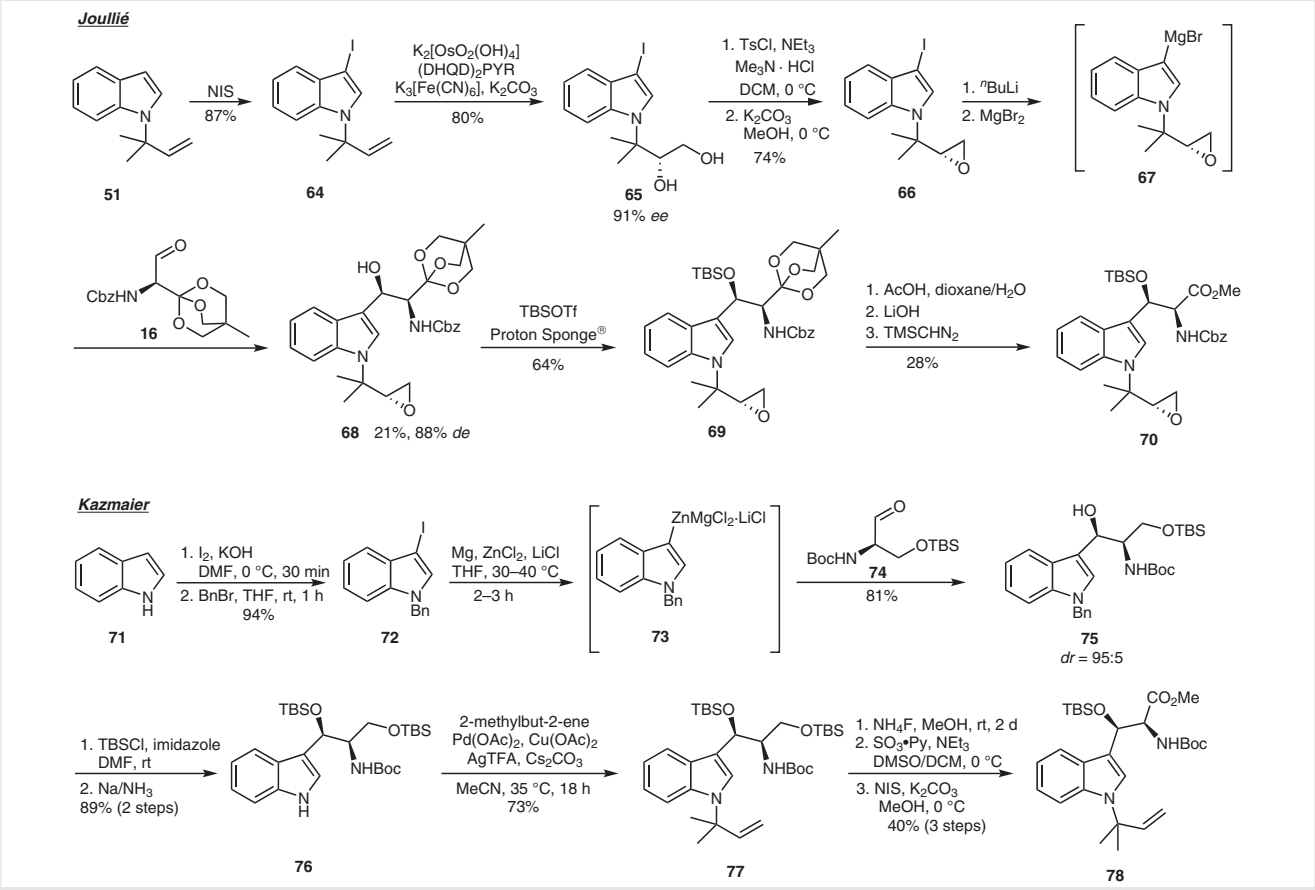
ter cleaving the orthoester under acetic acid conditions and saponification with lithium hydroxide, the acid was converted into its methyl ester **70**.

A similar strategy for the synthesis of *N′-tert*-prenyltryptophan **78** was chosen by Barbie and Kazmaier (Scheme 10).[54] Here, a simple one-pot protocol without an additional purification step gave iodoindole **72** in 94% yield.



Scheme 9 Grignard addition of *N-tert*-prenylindol-3-ylmagnesium bromide to the Lajoie serin aldehyde (Joullié)

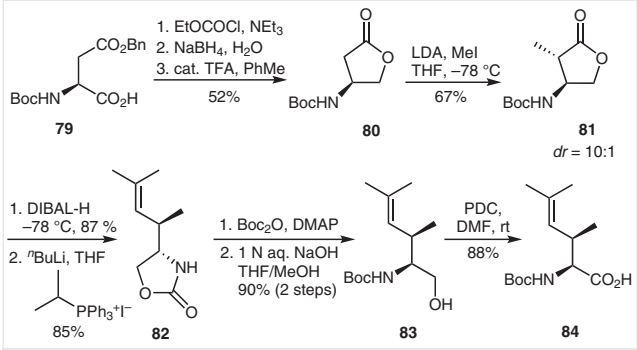
To improve the selectivity of the chelate-controlled carbonyl addition towards aldehyde **74**, a protocol described by Knochel and co-workers was used.[55] The corresponding zinc reagent **73**, formed via transmetalation of the in situ formed Grignard reagent from **72** in the presence of LiCl, reacted with **74** to give the desired alcohol **75** in high yield and excellent diastereoselectivity. While the introduction of an orthogonal protecting group, e.g. MOM or TBDPS, failed, a second TBS group was chosen. Benzyl cleavage under reductive conditions provided the fully protected derivative **76** in 89% over two steps. With **76** in hand, the chemoselective reverse *N′*-prenylation was achieved by using a protocol by Baran and co-workers to obtain **77**.[56] Selective deprotection of the primary OH function with ammonium fluoride and subsequent two-step oxidation sequence of Parikh–Doering reaction[57] and NIS-mediated oxidation[58] gave the fully protected *N′-tert*-prenylated tryptophan **78**.



Scheme 10 Optimized route for the fully protected β-hydroxytryptophan (Joullié and Kazmaier)

2.4 (2*S*,3*R*)-2-Amino-3,5-dimethylhex-4-enoic Acid

Because of its unique structure, so far there is just one published fragment synthesis of the aminohexenoic acid **84** by Yokokawa and co-workers in 2002 (Scheme 11).[29] Here, the synthetic sequence started with the commercially available aspartic acid derivative **79**. This was converted into the corresponding alcohol after activation as a mixed anhydride and then reduced with $NaBH_4$; subsequent acid-catalyzed intramolecular transesterification generated lactone **80** in 52% yield. Next, the lithium enolate of **80** was reacted with methyl iodide at low temperatures to give **81** with a diastereomeric ratio of 10:1 for the favored diastereomer.[59] DIBAL-H reduction of **81** to the corresponding lactol and subsequent Wittig reaction gave the oxazolidinone **82** in good yield. In the next step, oxazolidinone **82** was Boc-protected and converted into the primary alcohol **83** by hydrolysis. Final pyridinium dichromate (PDC) mediated oxidation[60] gave the desired Boc-protected aminohexenoic acid **84** in 88% yield.

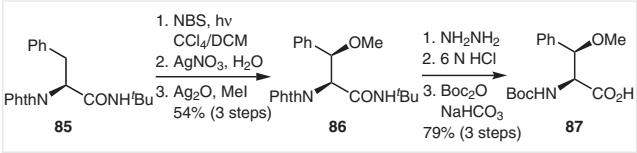


Scheme 11 Fragment synthesis of Boc-protected aminohexenoic acid (Yokokawa)

3 Total Synthesis of Cyclomarin C by Yao and Co-workers

Yao and co-workers[30,31] started their synthesis of the β-methoxyphenylalanine derivative with *tert*-butylamide **85** derived from phthaloyl-protected L-phenylalanine. To obtain the oxygen function in the β-position, **85** was first brominated in the benzyl position via Wohl–Ziegler reaction

(dr 1:1) (Scheme 12).[61] Subsequent silver(I)-mediated nucleophilic substitution with water yielded the *syn* diastereomer preferentially. After removal of the undesired stereoisomer, *O*-methylation with silver(I) oxide and methyl iodide provided methyl ether **86**. The phthaloyl group was then removed with hydrazine. Hydrolysis of the amide and final Boc protection gave β-methoxyphenylalanine **87** in a good yield of 79% over three steps.

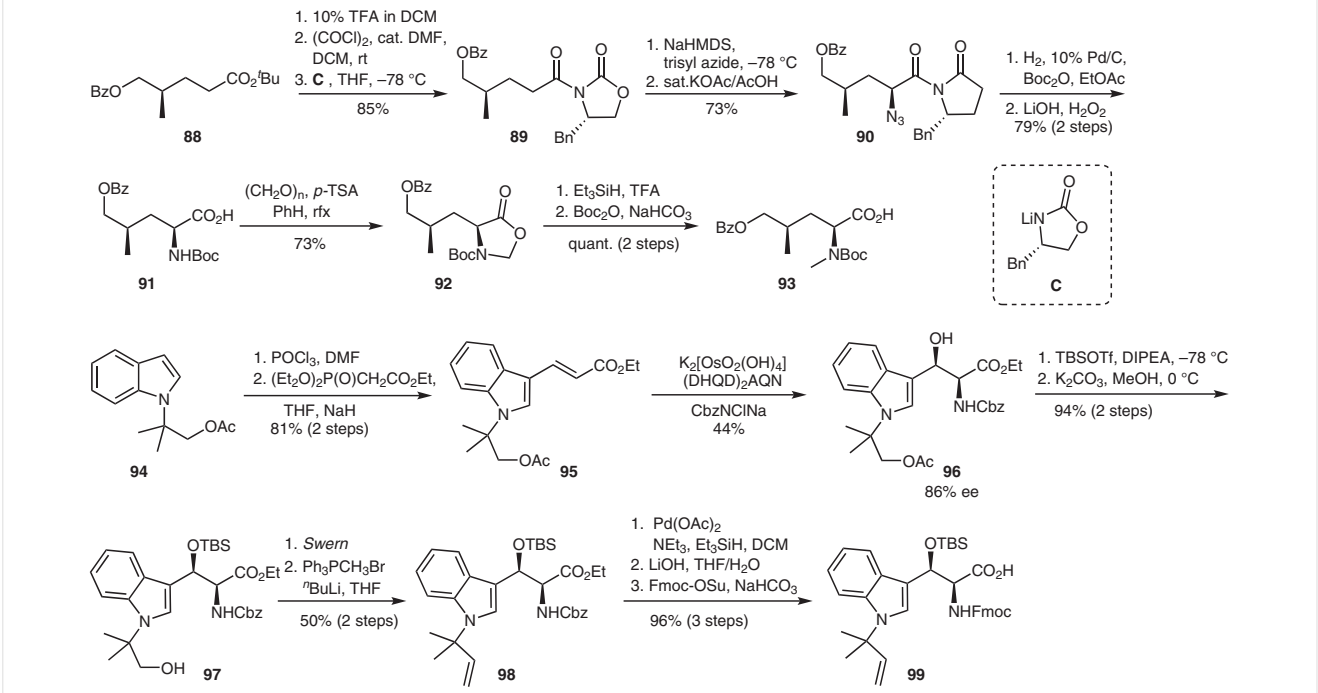


Scheme 12 Synthesis of β-methoxyphenylalanine

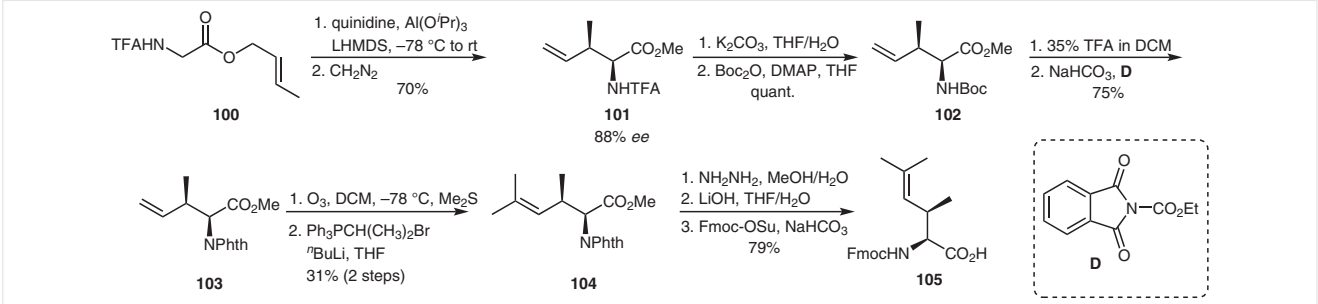
The route for the preparation of the δ-hydroxyleucine unit is also based on classical auxiliary chemistry, starting from **88**, which was initially prepared by a reported procedure[62] (Scheme 13). After acidic hydrolysis of the *tert*-butyl ester and activation by oxalyl chloride, the generated acid chloride was reacted with lithiated Evans auxiliary **C** to give oxazolidinone **89**. Diastereoselective azidation with trisyl azide after enolization of **89** provided azide **90**. This was then protected in situ by catalytic hydrogenation with palladium in the presence of Boc_2O; subsequent oxidative cleavage of the auxiliary released the carboxylic acid **91** in 79% yield over two steps. The introduction of the *N*-methyl group was carried out in a two-step sequence. First, acid **91** was converted into the hemiaminal **92** using paraformaldehyde. Ring opening by ionic hydrogenation[60] with triethylsilane and TFA and subsequent Boc protection provided the desired building block **93** in quantitative yield.

Also in their synthetic route towards the *N′-tert*-prenylated tryptophan building block **99**, the asymmetric Sharpless aminohydroxylation was used as key step (Scheme 13). First, the α,β-unsaturated ester **95** was generated in two steps by formylation of indole derivative **94** followed by Horner–Wadsworth–Emmons reaction in 81% yield. Subsequent reaction with CbzNClNa in the presence of catalytic amounts $K_2[OsO_2(OH)_4]$ and $(DHQD)_2AQN$ gave the 3-hydroxytryptophan derivative **96** in moderate yield and 86% ee, however the regioselectivity was not reported. Silyl protection of the secondary alcohol and saponification of the acetyl group provided the primary alcohol **97**. Subsequent Swern oxidation[60] and methylene-Wittig reaction[60] gave the *tert*-prenylated derivative **98** in 50% yield for both steps. Via final protection group transformations gave building block **99** for the peptide coupling.

To obtain the last non-proteinogenic amino acid **105**, Kazmaier's asymmetric chelate enolate-Claisen rearrangement with quinidine as chiral alkaloid ligand was used (Scheme 14).[63] Deprotonation of the ester **100** and transmetalation to the chelated aluminum species yielded amino acid derivative **101** via a [3,3]-sigmatropic rearrangement with high ee. Subsequent protecting group manipulations were necessary to suppress partial racemization of the α-stereogenic center. Ozonolysis of the terminal double bond



Scheme 13 Evans diastereoselective azidation and Sharpless aminohydroxylation as key steps for the δ-hydroxyleucine unit and *N′-tert*-prenylated tryptophan



Scheme 14 Synthesis of protected aminohexenoic acid via asymmetric ester enolate Claisen rearrangement

in **103** followed by Wittig reaction provided the desired derivative **104** in only 31% yield.[64] Final protecting group interconversions delivered Fmoc-amino acid **105**.

3.1 Macrocyclization Studies and Completion of Total Synthesis

With all noncanonical amino acid building blocks in hand, several strategies for the construction of the linear heptapeptide scaffold and the macrolactamization of cyclomarin C were examined (Figure 2)[31] in which four different sites for cyclization were investigated with the goal to minimize the number of linear steps. Because of its acid lability, the β-hydroxytryptophan moiety should be installed as late as possible.

First Yao and co-workers investigated a sequence based on a retrosynthetic peptide bond cleavage between the β-hydroxytryptophan and the aminohexenoic acid unit (route A). This resulted in linear precursor **106**, which was synthesized in a [3+3+1] peptide fragment strategy. While the coupling of the individual peptide fragments proceeded without mayor problems, the *C*-terminal saponification of the methyl ester in **106** and subsequent cyclization under various conditions, unfortunately provided the desired product in trace amounts only. So, in alternative linear pre-

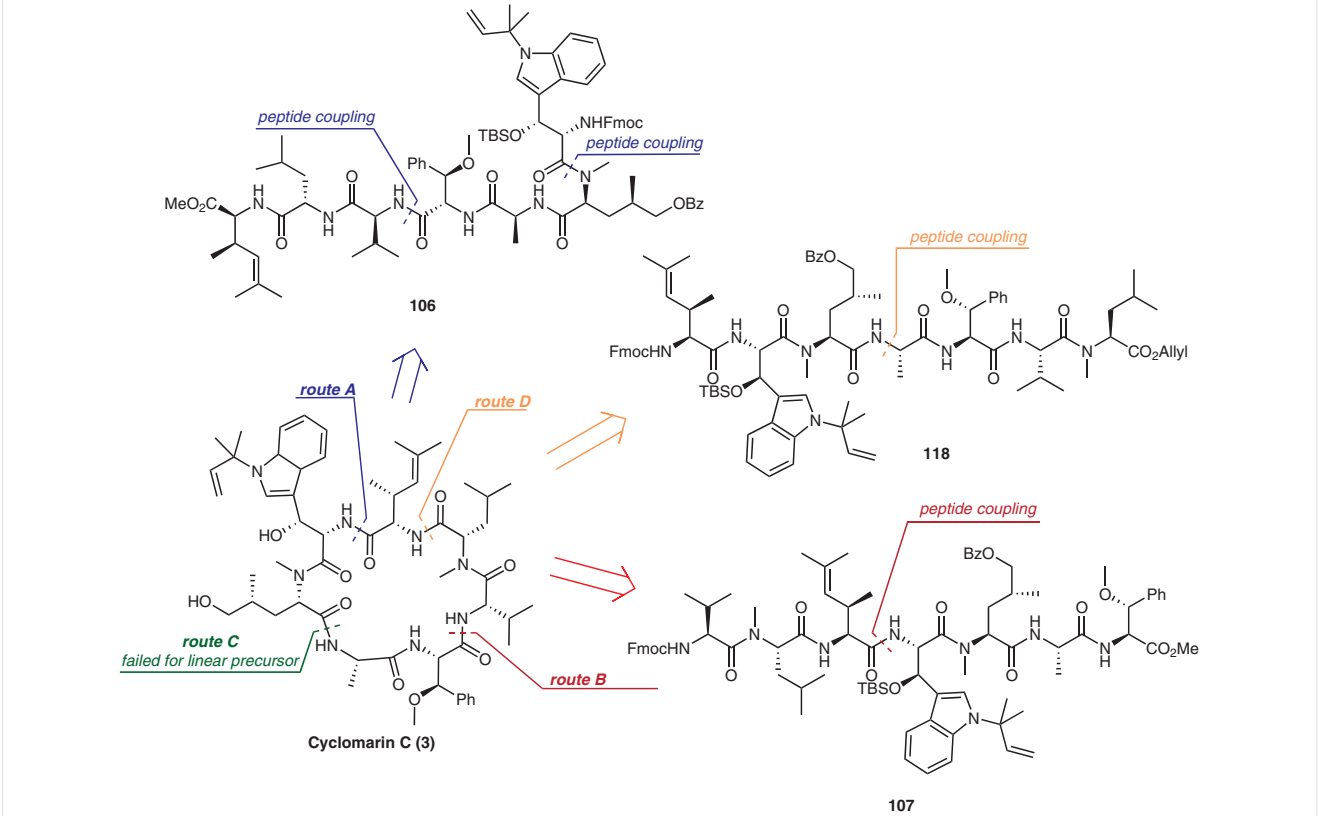
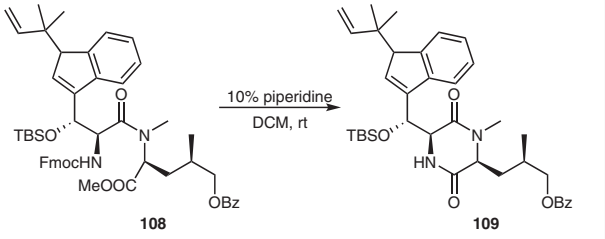


Figure 2 Outline of tested macrocyclization sites and their corresponding linear precursors



Scheme 15 Spontaneous cyclization during Fmoc deprotection to give a diketopiperazine

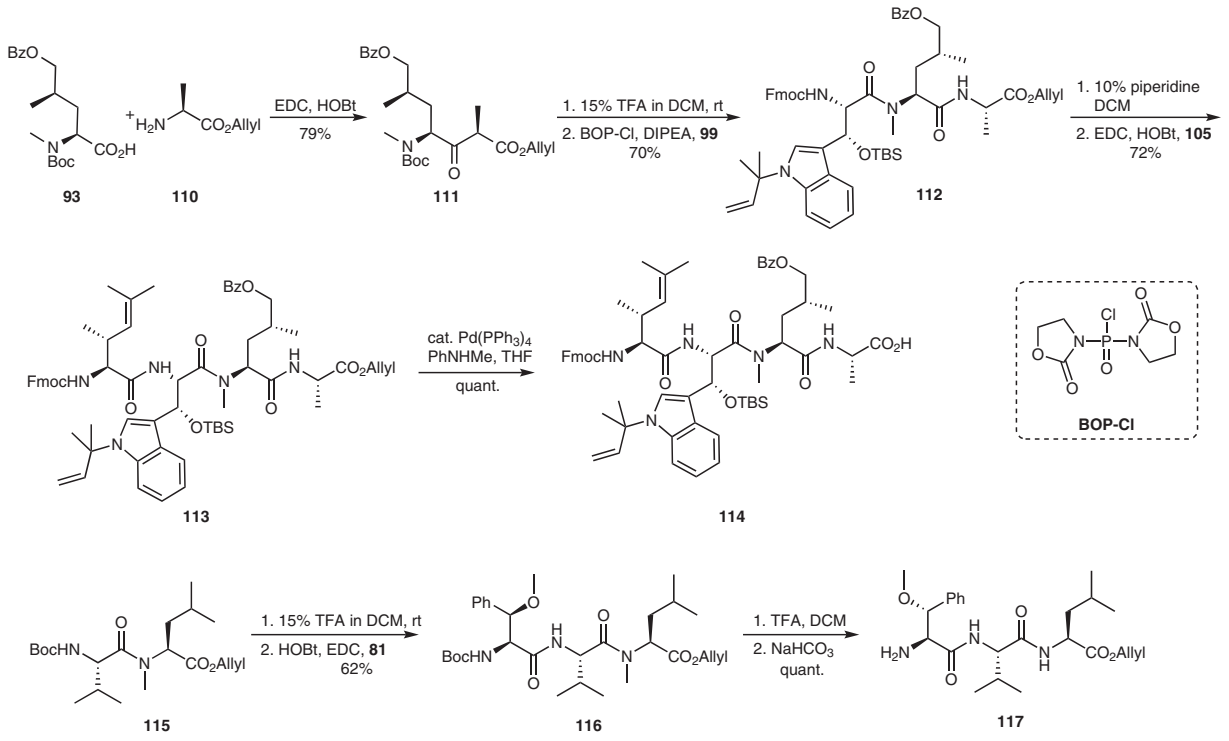
cursors, the rather labile β-hydroxytryptophan moiety was placed in the middle region of the peptide for macrocyclization.

The second possible site for macrocyclization was the peptide bond between the L-valine and β-methoxyphenylalanine unit (route B). To construct the precursor **107**, a [4+3]-fragment strategy was pursued this time; the linear heptapeptide was obtained in 60% yield. Here, the cleavage of the methyl ester again caused problems, so that the saponification after *N*-terminal deprotection gave only 41% yield. Following attempts for macrocyclization again failed. Similar to route A, the final step resulted in complex mixtures under a variety of conditions. These indicated that the two sterically demanding residues of β-methoxyphenylalanine and *N*-Me-valine are not suitable for cyclization.

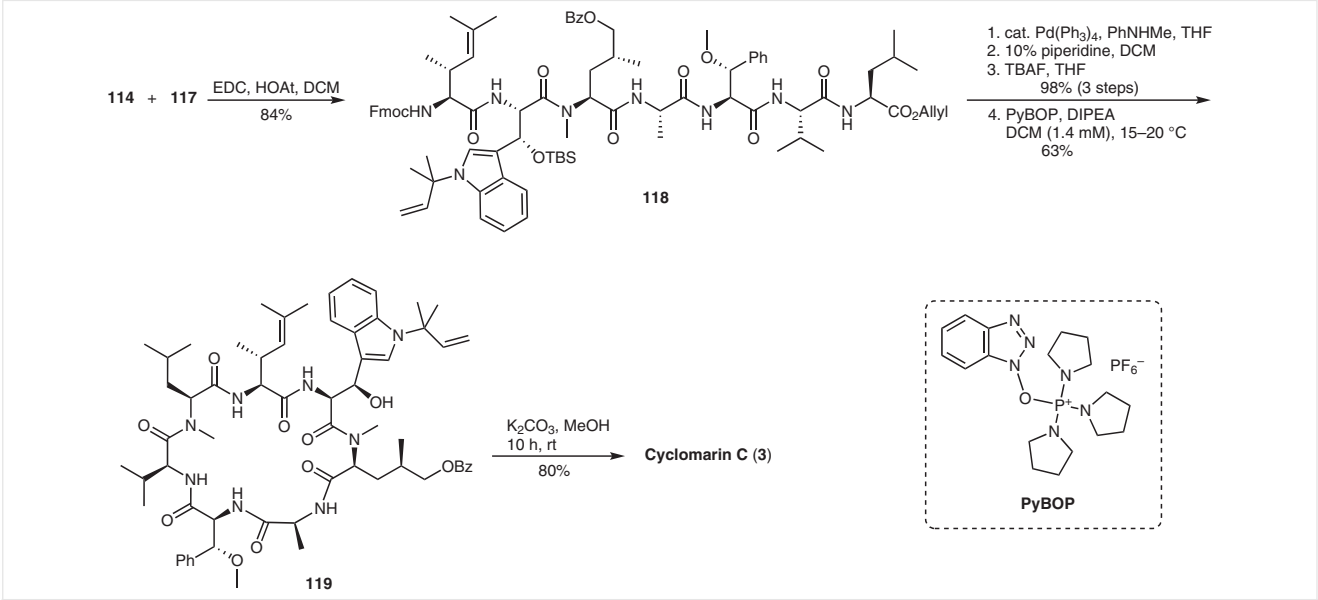
In a third attempt, the ring closure was planned between the L-alanine and the δ-hydroxyleucine moiety (route C). However, this route failed already at a very early stage, the *N*-terminal deprotection; under the basic conditions a spontaneous cyclization to give diketopiperazine **109** took place (Scheme 15).

To circumvent additional disappointment in route D, the linear heptapeptide precursor was cyclized between the aminohexenoic acid and the *N*-Me-leucine moiety, using a [4+3]-coupling strategy for the synthesis of linear precursor **118**. To prevent strong basic conditions for *C*-terminal deprotection, the methyl ester function was replaced by a terminal allyl ester. Thus, the synthesis of the desired peptide sequence started with the construction of tetrapeptide **114**.

δ-Hydroxyleucine **93** was coupled under standard conditions with allyl L-alaninate (**110**) to dipeptide **111** (Scheme 16). After *N*-terminal deprotection with TFA in dichloromethane, building block **99** was attached to give tripeptide **112** using a Bop-Cl/DIPEA protocol.[65] Fmoc-cleavage with 10% piperidine in dichloromethane and additional EDC/HOBt mediated coupling[64] with aminohexenoic acid building block **105** afforded tetrapeptide **113** in 72% yield. Final allyl ester cleavage under Pd catalysis[64] led quantitatively to acid **114**. The tripeptide **117** was also synthesized via standard peptide couplings.



Scheme 16 Synthesis of the desired tetrapeptide and tripeptide segments



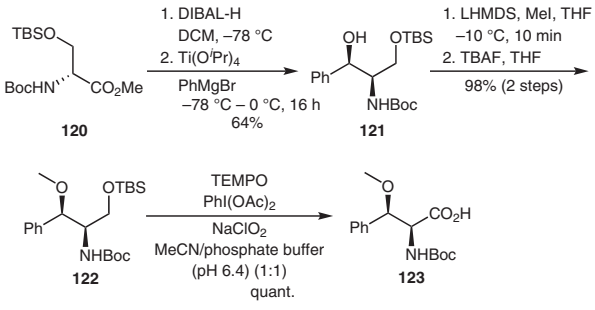
Scheme 17 Coupling between tetrapeptide and tripeptide segments and final the macrocyclization steps to cyclomarin C

For the [3+4] fragment coupling, removal of the *N*-Boc-protecting group of **116** with 15% TFA afforded the second precursor **117**. The fragment coupling of **114** and **117** was performed using EDC/HOAt to give **118** in excellent yield (Scheme 17); with HOBt significantly lower yields were achieved. The protecting groups were subsequently removed and macrolactamization under high dilution conditions using PyBOP/DIPEA provided protected cyclomarin C (**119**) in 63%.[66] Finally, treatment of **129** with K_2CO_3 in methanol at room temperature afforded the natural product cyclomarin C (**3**) in 80% yield after preparative HPLC.

4 Total Synthesis of Cyclomarin A and C by Barbie and Kazmaier

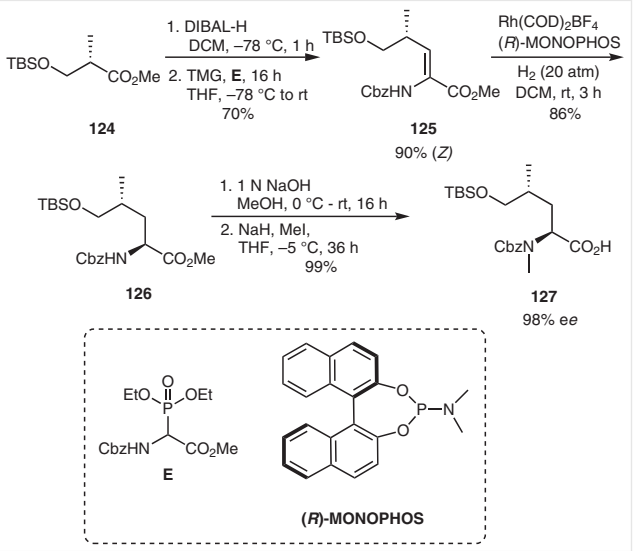
In accordance with Yao and co-workers,[30,31] Barbie and Kazmaier[32,33] chose the same macrolactamization site for the synthesis of the cyclomarins A and C, but used a linear strategy for the generation of the required heptapeptides.[32,33] The tryptophan building blocks need to be incorporated as late as possible in the synthesis from a common pentapeptide precursor.

The synthesis of the β-methoxyphenylalanine building block **123** should be facilitated by chelate-controlled arylmetal addition to a protected (*R*)-serinaldehyde (Scheme 18), which was obtained from ester **120** by reduction with one equivalent of DIBAL-H. In the subsequent reaction with a phenyl titanium species, generated from PhMgBr and Ti(O*i*-Pr)$_4$, the desired product **121** was obtained as a single diastereomer.[67] Subsequent *O*-methylation and cleavage of the silyl ether with TBAF provided the primary alcohol **122** in nearly quantitative yield. Final oxidation with $NaClO_2$ in the presence of catalytic amounts of TEMPO and (diacetoxyiodo)benzene led quantitatively to the required amino acid **123**.



Scheme 18 Chelate-controlled Grignard addition towards (*R*)-serinaldehyde

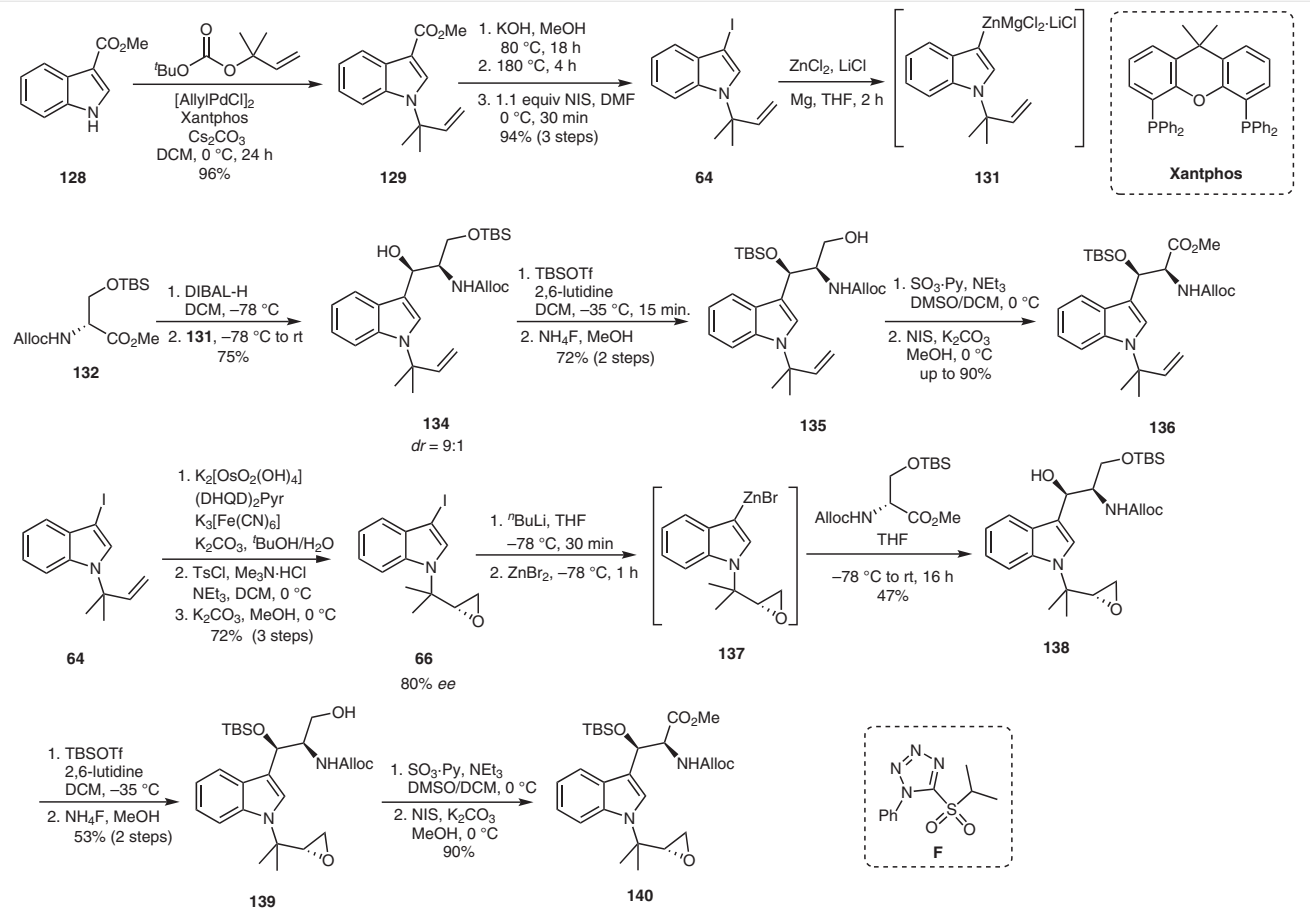
For the synthesis of the δ-hydroxyleucine **127**, the silyl-protected Roche ester **124** was used as the starting material, which was reduced to the corresponding aldehyde via DIBAL-H and then reacted with phosphonoglycine ester **E** to give the protected α,β-unsaturated amino acid **125** (Scheme 19).[68,69] By using the chiral phosphoramidite ligand (*R*)-MONOPHOS, the dehydroamino acid **125** was stereoselectively hydrogenated, providing the desired amino acid ester **126** in good yield and high enantioselectivity.[70,71] Saponification and subsequent *N*-methylation gave the amino acid building block **127** almost quantitatively.



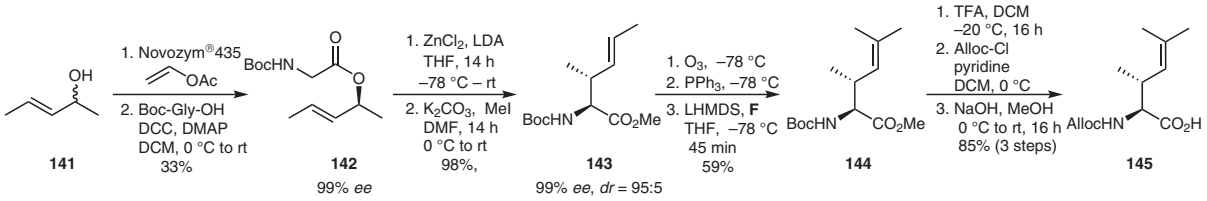
Scheme 19 Asymmetric hydrogenation of an α,β-unsaturated amino acid as the key step in the synthesis of δ-hydroxyleucine

A new synthetic strategy was chosen for the tryptophans because of the acid lability of the β-hydroxy group (Scheme 20). According to a method of Stanley and coworkers, which allows a regioselectively prenylation of electron-deficient indoles, indole-3-carboxylic acid ester **128** was nearly quantitatively *N′-tert*-prenylated.[72] Subsequently, the methyl ester **129** was saponified and after acidification the free acid was decarboxylated;[73] iodination with *N*-iodosuccinimide (NIS) provided the common precursor **64** in 94% yield over three steps.

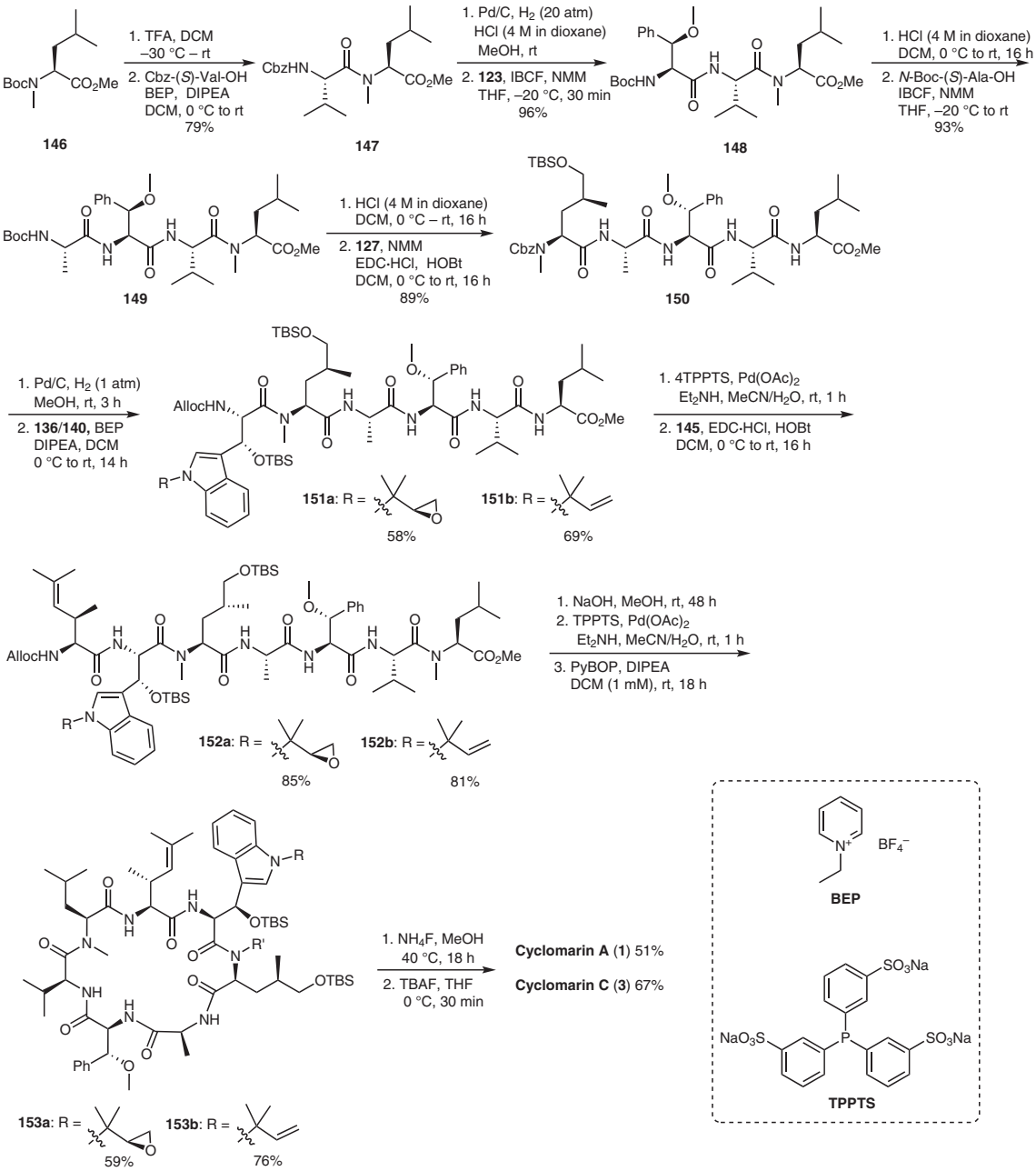
The organozinc species **131** was generated from iodoindole **64** using a literature-known protocol,[55] which was then added to the previously prepared protected D-serine aldehyde at low temperature. Thus, amino alcohol **134** was obtained in good yield and satisfactory diastereomeric ratio. After silyl protection of the secondary alcohol **134**, the primary OH function were selectively deprotected with ammonium fluoride to give **135**. Alcohol **135** was finally transformed into methyl ester **136** in a two-step sequence of Parikh–Doering reaction[57] and NIS-mediated oxidation.[58]



Scheme 20 An approach for the fully protected *N*′-substituted β-hydroxytrytophans



Scheme 21 Synthesis of protected aminohexenoic acid via asymmetric ester enolate Claisen rearrangement



Scheme 22 Peptide coupling steps towards the linear precursors and completion of the natural product synthesis via macrolactamization

In order to obtain the epoxidized β-hydroxytryptophan **140**, building block **64** was converted by a sequence of Sharpless dihydroxylation followed by tosylation and elimination into epoxide **66** with acceptable selectivity (Scheme 20). Subsequently, the epoxyindole **66** was lithiated with ^{n}BuLi at –78 °C and transmetalated with $ZnBr_2$.[74] Then, zinc reagent **137** was reacted with the aldehyde from **132**, whereby the desired product **138** was formed in moderate yield, but with perfect stereoselectivity. The completion of building block **140** was analogous to **136**.

Starting material for the last building block, the γ,δ-unsaturated amino acid **145**, was the racemic allyl alcohol **141**, which was subjected to a enzymatic kinetic resolution[75] and reacted with Boc-protected glycine (Scheme 21). Ester enolate Claisen rearrangement of the enantiomerically enriched ester **142** gave the desired amino acid ester **143** with perfect chirality transfer and very high diastereoselectivity.[76,77] Ozonolysis of the double bond led to the corresponding aldehyde, which was then transformed into ester **144** in a Julia–Kocienski olefination with sulfone **F**.[78] Thereby, a partial epimerization of the β-stereogenic center could not be suppressed completely. Following protecting group manipulation and final saponification gave acid **145** in good yield of 85% for three steps.

4.1 Peptide Coupling and Macrolactamization

With all the building blocks in hand, the successive assembly of the linear heptapeptides **152a** and **152b** began with the formation of the dipeptide **147** (Scheme 22) using 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP) as the coupling reagent.[79,80] Hydrogenolytic cleavage of the Cbz protecting group required a hydrogen pressure of 20 atm and two equivalents of HCl were added to avoid formation of the diketopiperazine. The activated acid **123** was thus coupled with the HCl salt of the dipeptide in 96% yield to give the tripeptide **148**.[81] Standard peptide couplings were used to build up pentapeptide **150**. For the incorporation of the sensitive β-hydroxytryptophan building blocks **136** and **140** a BEP protocol was used. Both hexapeptides were obtained in satisfactory yield of 58% (**151a**) and 69% (**151b**). The Alloc protecting group was removed via palladium-catalysis and subsequent EDC/HOBt mediated coupling afforded the desired heptapeptides **152a** and **152b**. Saponification of the methyl esters followed by N-terminal deprotection under Pd catalysis[82] gave the free linear heptapeptides, which cyclized according to the method described by Yao and co-workers.[30,31] Under these conditions, the O-silylated cyclopeptides **153a** and **153b** were obtained in good yield. Final two-stage deprotection with ammonium fluoride and TBAF provided cyclomarin A (**1**) in 51% and cyclomarin C (**3**) in 67% yield.

5 Conclusion

In summary, suitable protocols for all noncanonical amino acids were established by a couple of research groups, especially by Yokokawa and Joullié. Macrolactamization studies of Yao and co-workers identified the best position site for macrocyclization. So, the first synthesis of cyclomarin C (**3**) was thus achieved by a convergent strategy under high dilution conditions. Barbie and Kazmaier achieved the first total synthesis of cyclomarin A (**1**) in a linear straightforward route. In addition, this synthesis afforded by slight modifications also the natural product cyclomarin C (**3**) and simplified derivatives thereof for SAR studies, which are currently under investigation.

Acknowledgment

We thank Dr. Philipp Barbie for his enthusiasm and outstanding contribution

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