Synthesis of Ilamycins/Rufomycins and Cyclomarins

Subjects: Biochemistry & Molecular Biology | Chemistry, Organic

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Ilamycins/rufomycins and cyclomarins are marine cycloheptapeptides containing unusual amino acids. Produced by Streptomyces sp., these compounds show potent activity against a range of mycobacteria, including multidrug-resistant strains of Mycobacterium tuberculosis. The cyclomarins are also very potent inhibitors of Plasmodium falciparum. Biosynthetically the cyclopeptides are obtained via a heptamodular nonribosomal peptide synthetase (NRPS) that directly incorporates some of the nonproteinogenic amino acids. A wide range of derivatives can be obtained by fermentation, while bioengineering also allows the mutasynthesis of derivatives, especially cyclomarins. Other derivatives are accessible by semisynthesis or total synthesis, reported for both natural product classes.

ilamycins rufomycins cyclomarins tuberculosis malaria cyclopeptides biosynthesis total synthesis natural products

1. Discovery of Anti-Tubercular Cycloheptapeptides

1.1. Discovery of the Ilamycins/Rufomycins

In 1962, two independent research groups investigated marine *Streptomycetes* from soil samples found on Japanese islands. Takita et al. observed that the culture filtrate of a new strain, *Streptomyces insulates* (A-165-Z1), later renamed *Streptomyces islandicus*, inhibited the growth of *Mycobacterium* 607 and *Mycobacterium phlei*. They isolated two antibiotics and named them ilamycin A and B (IlaA and IlaB)[1][2]. In addition, at this time Shibata et al. isolated two new antibiotics, rufomycin I and II (Ruf I and Ruf II), from the newly discovered *Streptomyces atratus* (46408), found to be especially active against acid-fast bacteria[3][4]. The compounds were also active against *Mycobacterium tuberculosis* and *Mycobacterium smegmatis* but almost inactive against most other bacteria, fungi, and yeasts. Subsequent research indicated that these two antibiotics possess very similar chemical structures [5][6][7][8][9][10].

The structures of ilamycins/rufomycins (**Figure 1**) are unusual, as these cyclic heptapeptides contain a series of atypical amino acids. Most prominent is the *N*-prenylated tryptophan ①, which can also be found in the epoxidized form [11][12]. At the *N*-terminus of the tryptophan, a γ,δ-unsaturated amino acid is incorporated ⑦ [13]. Common to all derivatives is a unique 3-nitrotyrosine ③, a building block not found in any other natural product. The greatest variability is observed in the leucine building block ⑤, which can be oxidized to different oxidation levels at a terminal methyl group. In its original description, ilamycin was proposed to contain an aldehyde functionality[10], but structural elucidation by NMR and X-ray crystallography showed that the aldehyde functionality undergoes cyclization with the nearby amide bond [14][15][16]. Very recently, a wide range of new ilamycins/rufomycins were described, differing mainly in the combination of different amino acid oxidation levels ⑤ and the *N*-prenyl substituent of ① (alkene, epoxide, diol)[14][15][16].

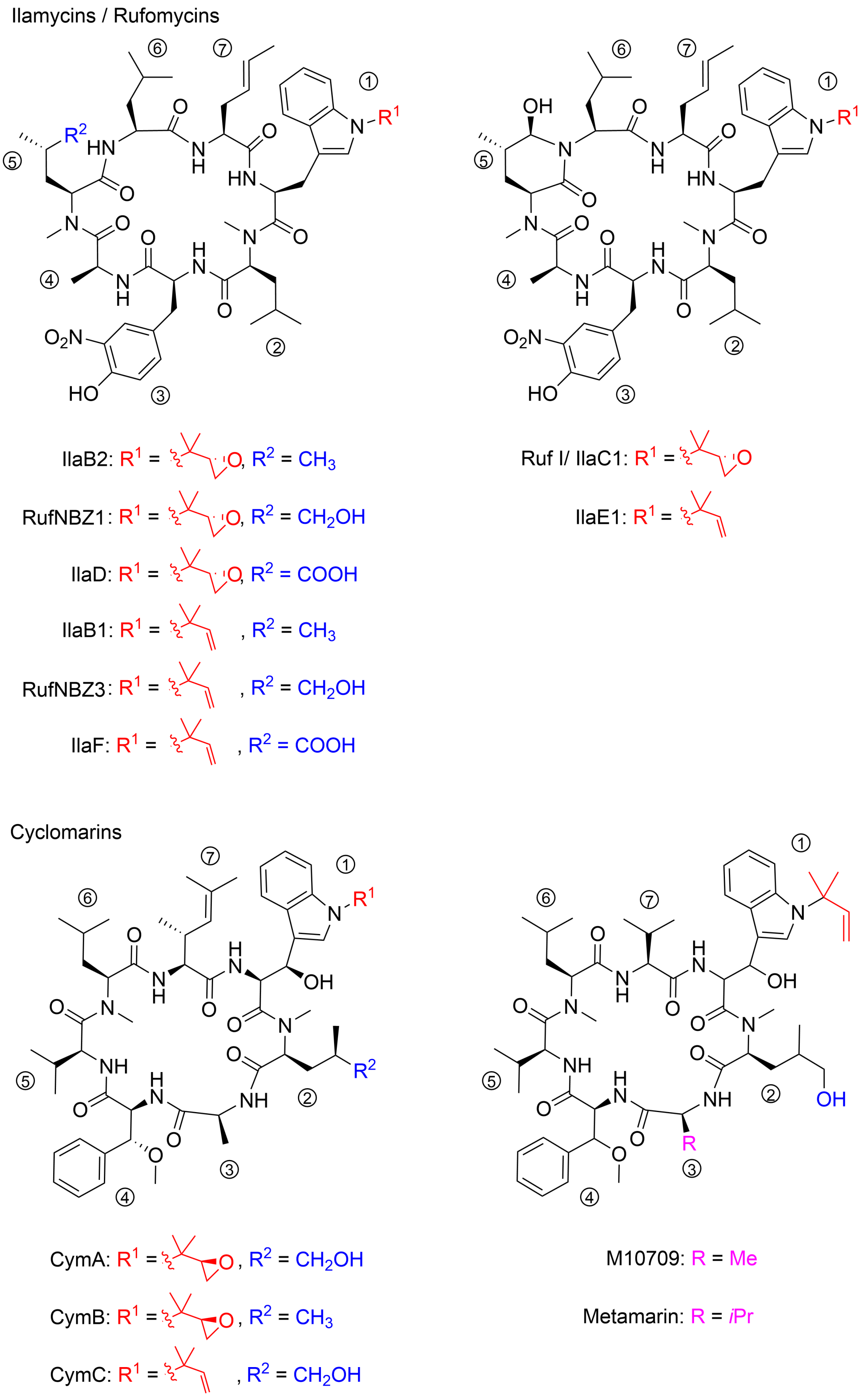


Figure 1. Selected ilamycins/rufomycins and cyclomarins.

1.2. Discovery of the Cyclomarins

In 1999, the research groups of Fenical and Clardy reported the isolation of three new anti-inflammatory cyclic peptides from extracts of a *Streptomyces* sp. collected in Mission Bay, California[17]. These secondary metabolites from the strain CNB-982, called cyclomarins (Cym) A−C, are structurally related to the rufomycins. Very similar amino acid building blocks are incorporated, although in a different sequence. As in the rufomycins, an *N*-prenylated tryptophan ① (CymC) is a notable building block that can also be epoxidized (CymA). However, in contrast to the rufomycins, in the cyclomarin series, the tryptophan units are β-hydroxylated. At the *N*-terminus of the tryptophan, a γ,δ-unsaturated amino acid is incorporated, not a linear one as found in the rufomycins, but one that is branched and dimethylated ⑦. One of the leucines is also oxidized at the δ position ②, at least in CymA and C, but at another position, as in the rufomycins. Most obvious is the replacement of the unique nitrotyrosine by another aromatic amino acid, *syn*-β-methoxyphenylalanine ④.

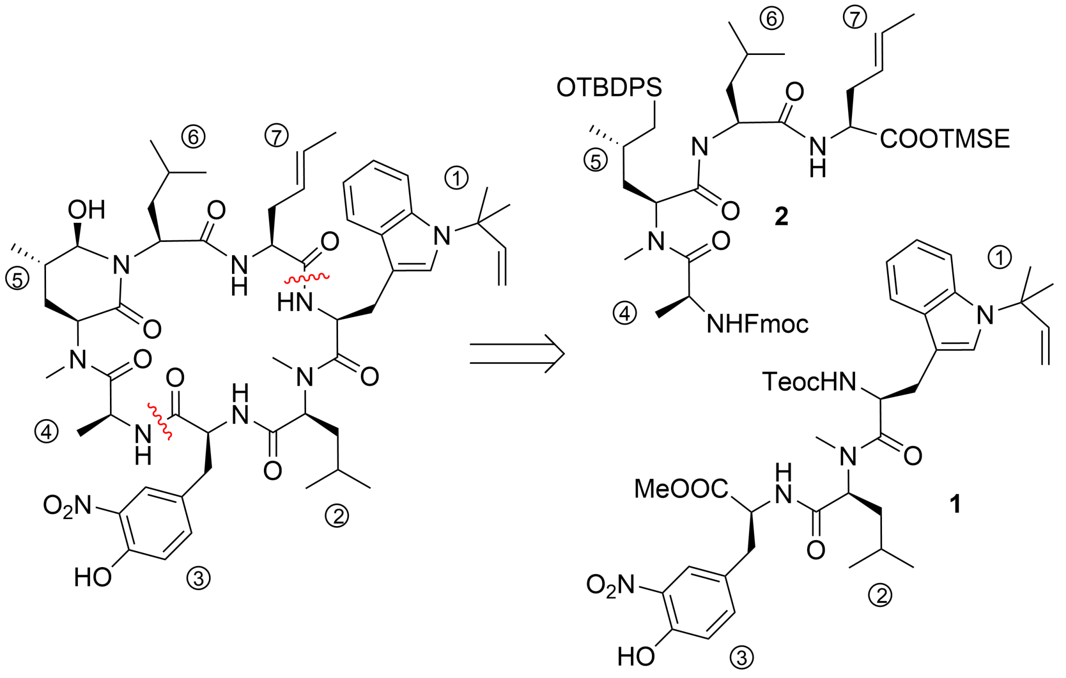
In 2010, the group of Mikami described the extraction of a new cyclomarin derivative M10709 from clinically isolated *Streptomyces* sp. IFM 10,709 [18]. Although not all stereogenic centers were determined properly, results revealed the compound was different from cyclomarin C only by the replacement of the unsaturated amino acid ⑦ by valine. The same structural motif was also found in a recently isolated metamarine in which a valine at position ③ replaced an alanine. The discovery of metamarine resulted from a larger soil metagenome project undertaken to discover rufomycin/cyclomarin-like antibiotics[19].

2. Total Syntheses of Marine Cycloheptapeptides

The interesting biological properties and unusual building blocks of marine cycloheptapeptides sparked the interest of synthetic chemists, and the syntheses of several different amino acids and fragments have been reported in a recent review [20]. Therefore, they will not be discussed in detail here, and the focus will be on the total syntheses of the natural products.

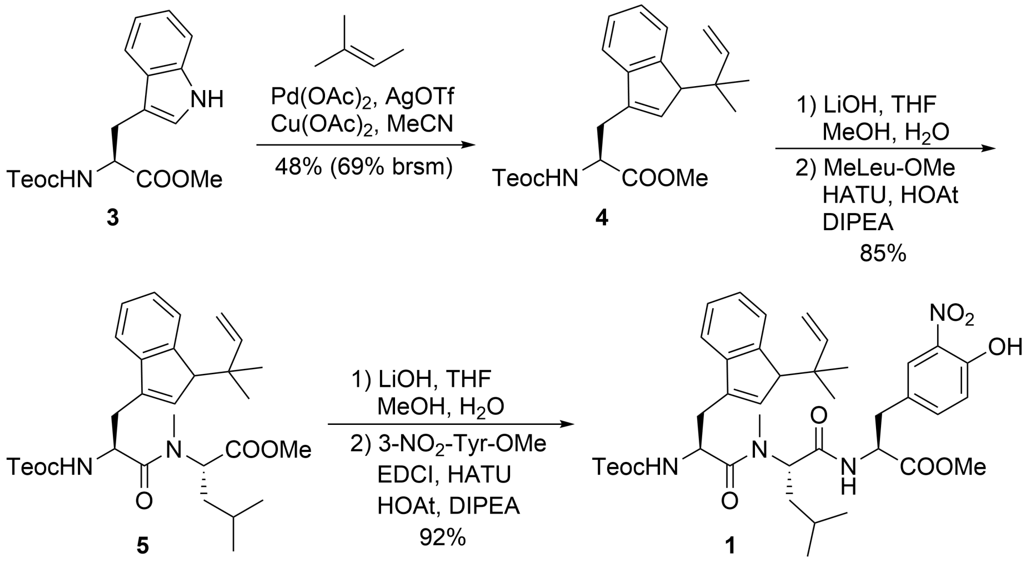
2.1. Total Synthesis of Ilamycins/Rufomycins

To date, only one synthetic route has been described for ilamycins E1 and F by Guo and Ye et al.[21] In their highly convergent strategy, the ilamycins were synthesized from two parts (**1** and **2**) that were linked between ① and ⑦ to the macrocyclic lactam (Scheme 1). The lower right tripeptide part **1** (①–③) was prepared in five steps from tryptophan, while the upper left tetrapeptide **2** (④–⑦) required 13 steps from glutamic acid. Final oxidation of the δ-hydroxyleucine ⑤ resulted in the described ilamycins.



Scheme 1. Retrosynthesis of ilamycins (Guo and Ye).

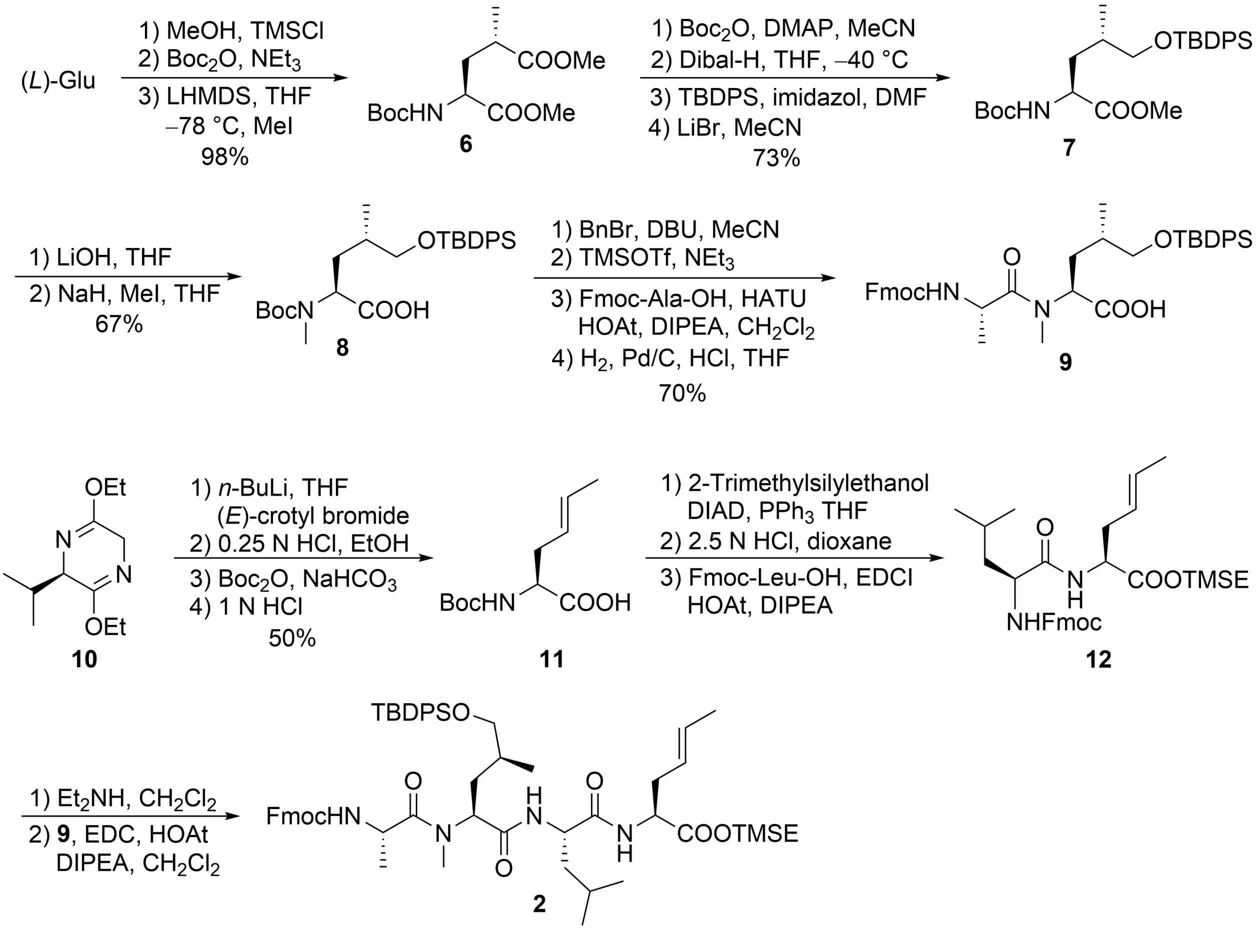
The synthesis of peptide fragment **1** was rather straightforward (Scheme 2). 2-(Trimethylsilyl)ethoxycarbonyl (Teoc)-protected tryptophan methylester **3** was subjected to a Pd-catalyzed *N*-*tert*-prenylation according to a protocol developed by Baran et al. [22]. Saponification of the ester moiety of **4** and peptide coupling with *N*-methylated Leu-OMe produced dipeptide **5**, which was further elongated to tripeptide **1**.



Scheme 2. Synthesis of peptide fragment **1**.

For the larger fragment **2**, glutamic acid was converted into protected **8** (Scheme 3) according to a synthetic route developed during the synthesis of dysithiazolamide [23]. The glutamic acid was converted into the dimethyl ester and *N*-Boc protected before it was stereoselectively α-methylated at the sterically least-hindered ester moiety [24]

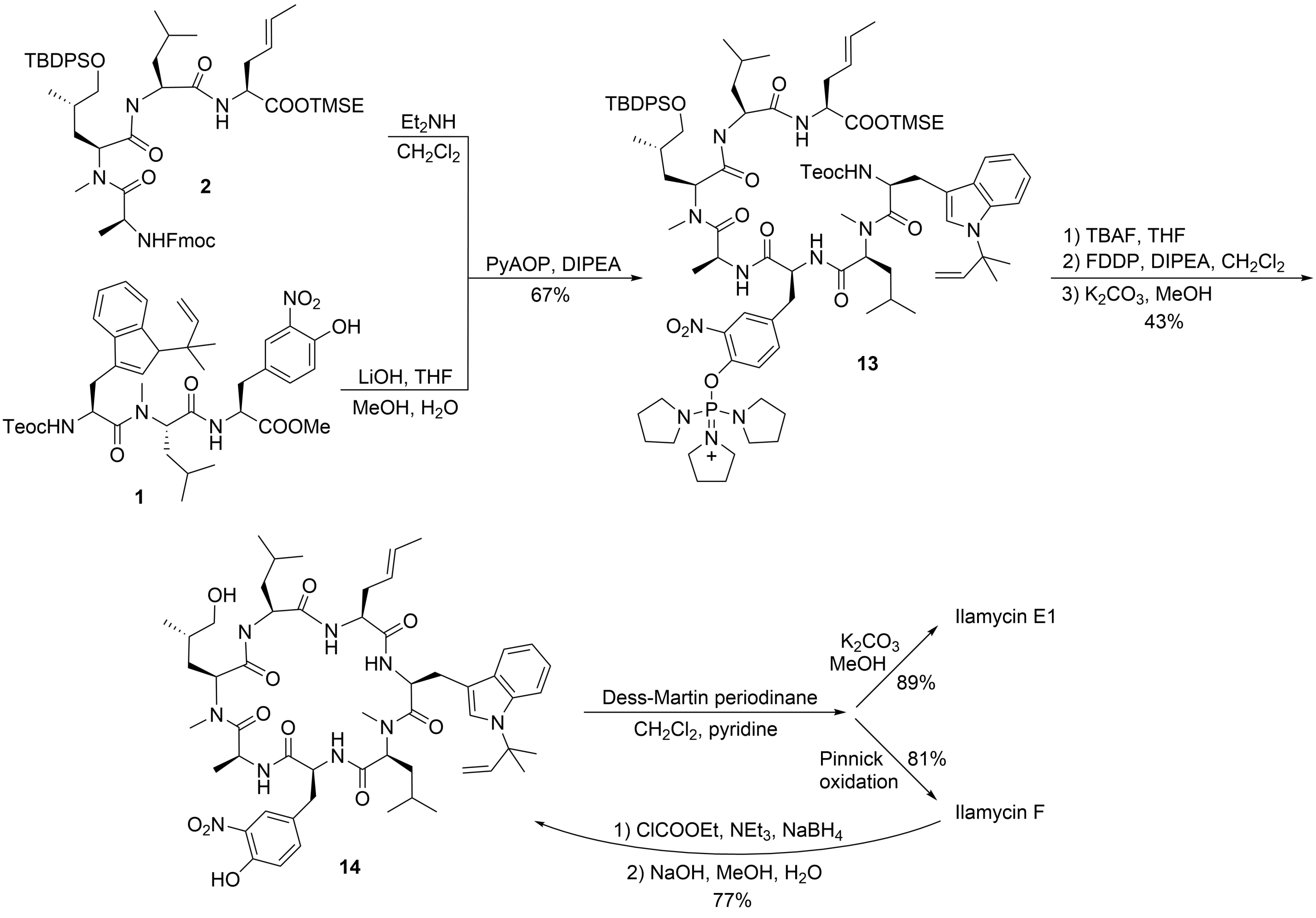
[25]. For the chemoselective reduction of the γ-ester **6**, a second *N*-Boc-protecting group was introduced, and the sterically least-hindered ester functionality was reduced with DIBAL-H. Silyl protection of the primary alcohol and subsequent mono-Boc deprotection yielded **7**. The methyl ester was saponified (to avoid α-methylation), and the Boc-amide was selectively *N*-methylated to **8** with NaH/MeI. The free carboxylic acid **8** was converted into the corresponding benzyl ester. TMSOTf/NEt$_3$ was used for selective cleavage of the *N*-Boc-protecting group without affecting the OTBDPS group. The free amine could be coupled with Fmoc-protected alanine, and the *C*-terminal benzyl ester was cleaved by catalytic hydrogenation to provide the free acid **9**.



Scheme 3. Synthesis of peptide fragment **2**.

Schöllkopf auxiliary **10**[26] was subjected to stereoselective crotylation to generate the *C*-terminal unsaturated amino acid of **2** (Scheme 3). Subsequent auxiliary cleavage provided *N*-Boc-protected amino acid **11**, which was converted into the corresponding TMSE ester. Boc-deprotection and peptide coupling produced dipeptide **12**. Subsequent Fmoc deprotection and coupling with **9** generated the linear tetrapeptide **2**.

With the two major building blocks produced, ilamycin synthesis could proceed to the final step (Scheme 4). Mild saponification of the methylester **1** and coupling with Fmoc-deprotected **2** using (2-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyAOP)[27] yielded **13** without significant epimerization. Global deprotection with TBAF resulted in the linear heptapeptide, which was subjected to macrolactamization. While many peptide coupling reagents have been investigated, the best results were obtained using pentafluorophenyl diphenylphosphinate (FDPP)1[28]. As a side product in addition to the expected cyclopeptide **14**, the diphenylphosphinylated ester was formed, which could directly be converted into **14** by treatment with K_2CO_3 in methanol, providing an overall yield of 43% of the desired **14**. Finally, only the primary OH-functionality needed to be oxidized. Depending on the oxidation protocol, both ilamycin E1 and F could be obtained. Ilamycin E1 was obtained as a single stereoisomer. Notably, ilamycin F is also available on a gram scale via fermentation, but the derivative E1, which is approximately 100-fold more potent, is not. Therefore, the authors developed a protocol to convert ilamycin F into intermediate **14** by reducing the mixed anhydride, permitting an interconversion of ilamycin F into ilamycin E1 [21].

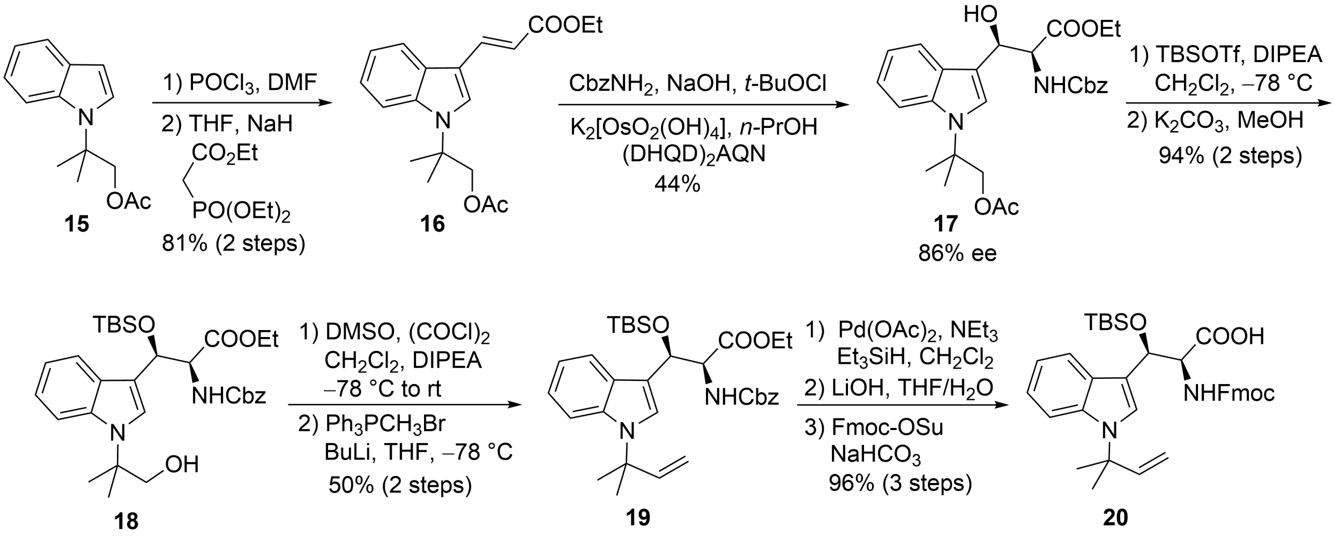


Scheme 4. Synthesis of ilamycinE1 and F.

2.2. Total Synthesis of Cyclomarins

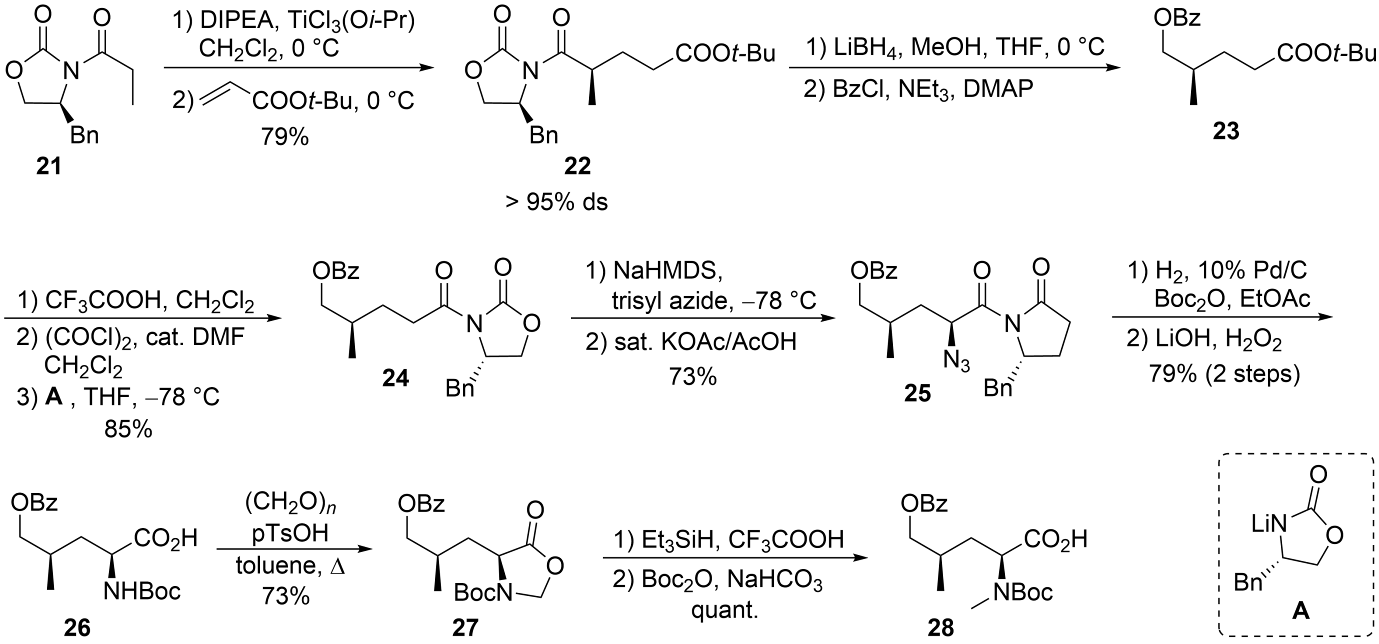
The amino acids present in the cyclomarins are slightly more complex than in the ilamycins, and various synthetic approaches have been undertaken to produce these building blocks and partial structures of cyclomarin [29]. These are covered in a recent review [20], and therefore only the routes applicable to the synthesis of cyclomarins and derivatives will be discussed here.

The first synthesis of cyclomarin C was reported in 2004 by Yao and coworkers [30]. The unusual *tert*-prenylated β-hydroxy-tryptophan ① was obtained from indole derivative **15** (Scheme 5). This compound is available from indole via *N*-alkylation with ethyl-α-bromo-propionate, subsequent α-methylation of the ester, LAH-reduction, and acetylation [31]. Formylation and a subsequent Horner–Wadsworth–Emmons reaction yielded α,β-unsaturated ester **16**, which could be subjected to a Sharpless aminohydroxylation [32]. Moderate yield and enantioselectivity of the desired β-hydroxytryptophan derivative **17** was obtained. Unfortunately, no comment was made concerning the regioselectivity of the reaction. Silylation of the β-hydroxy group and selective transesterification of the acetate gave rise to primary alcohol **18**, which could be oxidized to the aldehyde and methenylated via Wittig reaction. Finally, the Cbz-protecting group from **19** was removed selectively without affecting the generated double bond. Furthermore, the free amine was Fmoc-protected after saponification of the ester. The use of the Fmoc- or Alloc-protecting group is essential for the synthesis of cyclomarins because other protecting groups, such as Boc, cannot be removed later on without side reactions, such as the elimination of the β-hydroxy functionality[33].



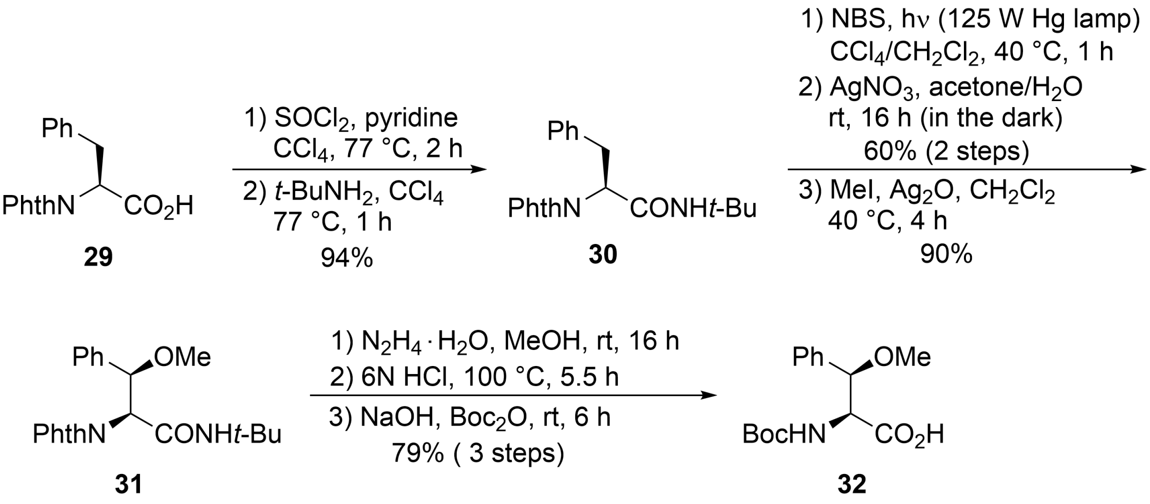
Scheme 5. Synthesis of protected tryptophan **20** (building block ①).

The synthesis of δ-hydroxyleucine building block ②, with the opposite configuration of the γ-methyl group than in amino acid ⑤ in the ilamycins, was obtained by classical asymmetric synthesis using chiral auxiliary chemistry (Scheme 6). According to Evans et al.[34], chiral oxazolidinone **21** was subjected as its titanium enolate in a Michael addition to *tert*-butyl acrylate to provide a good yield of **22** with high stereoselectivity. The imide was selectively reduced in the presence of the *tert*-butyl ester using $LiBH_4$, and the resulting primary alcohol was *O*-benzoylated to **23**. Acidic cleavage of the *tert*-butyl ester, activation of the carboxylic acid, and reapplication of the Evans auxiliary **A** provided oxazolidinone **24**. Deprotonation of **24** and stereoselective azidation produced azide **25**. Catalytic hydrogenation in the presence of Boc_2O resulted in the formation of the *N*-Boc-protected amino derivative, which was saponified to the corresponding amino acid **26**. The desired *N*-methyl group was introduced by conversion of **26** into the corresponding oxazolidinone **27**, which was reduced using triethylsilane in presence of trifluoroacetic acid. Subsequent cleavage of the Boc-protecting group required its reintroduction to **28**.



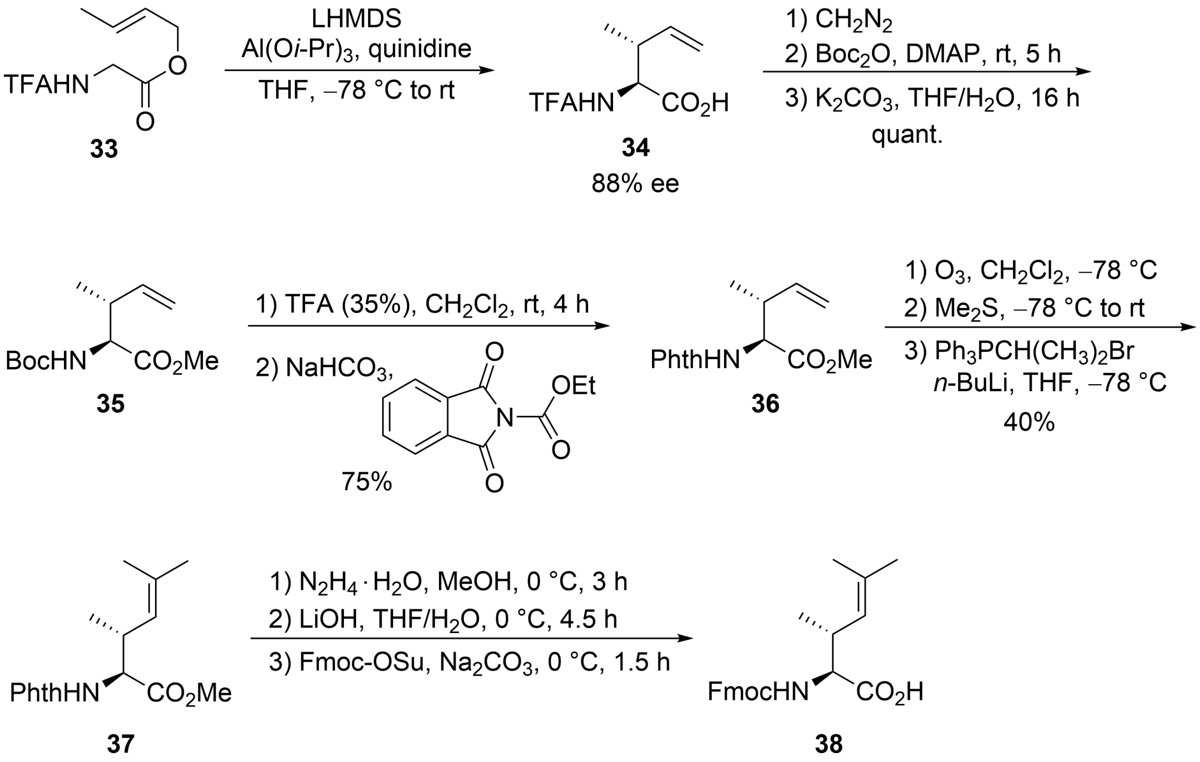
Scheme 6. Synthesis of protected hydroxyleucine **28** (building block ②).

The unusual β-methoxyphenylalanine ④ was obtained from *N*-phthaloyl-protected phenylalanine **29**, which was converted into the corresponding *tert*-butylamide **30** (Scheme 7). Oxygen functionality was introduced into the β-position by subjecting **30** to a Wohl–Ziegler bromination, providing a 1:1 diastereomeric mixture of the desired β-bromo derivative[35]. According to Easton et al., treatment of the diastereomeric mixture with $AgNO_3$ in aqueous acetone produced the desired (2*S*,3*R*)-β-hydroxyphenylalanine enantio- and diastereoselectively[36]. The stereochemical outcome can be explained by a preferred conformation of the benzylic carbenium ion in the substitution step. The best selectivities were obtained with the *tert*-butylamide. Subsequent *O*-methylation provided the methoxy derivative **31**, converted into the *N*-Boc-protected amino acid **32** under standard conditions.



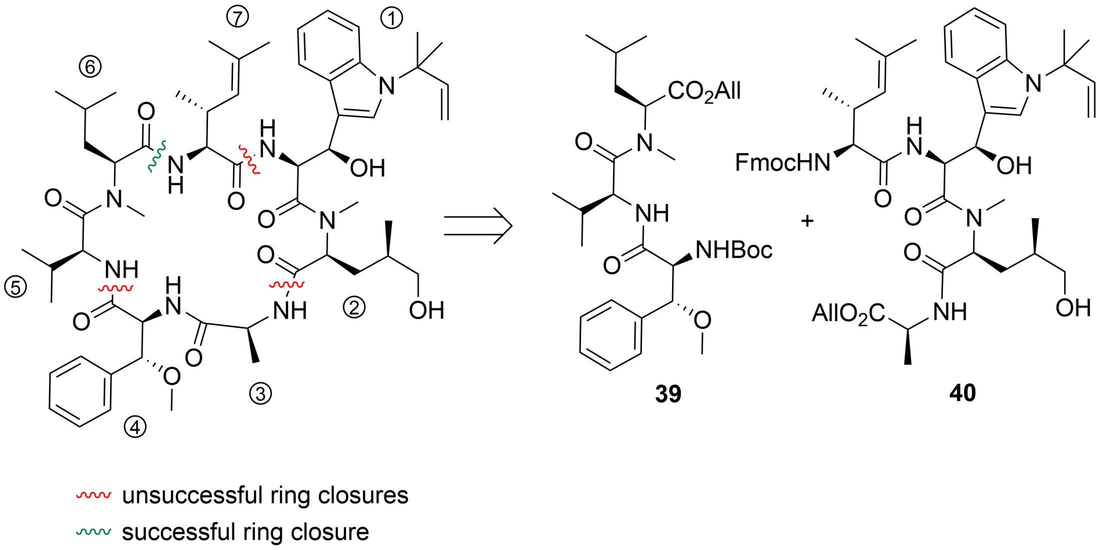
Scheme 7. Synthesis of protected β-methoxy phenylalanine **32** (building block ④).

Finally, the unsaturated amino acid ⑦ was obtained via an asymmetric chelate enolate Claisen rearrangement, developed by Kazmaier et al. (Scheme 8)[37][38]. Trifluoroacetyl (TFA)-protected glycine crotyl ester **33** was deprotonated and converted into a chelated aluminum ester enolate, which in the presence of quinidine underwent a [3,3]-sigmatropic rearrangement to unsaturated amino acid **34** with good yield and enantioselectivity. Epimerization of the α-stereogenic center was avoided by first converting **34** into the Boc-protected ester **35** and then, in a second step, into the corresponding phthaloyl-protected derivative **36**. A direct epimerization-free conversion (**34** to **36**) was not possible. Ozonolysis of the double bond and subsequent Wittig reaction produced protected amino acid **37**, finally converted into the Fmoc-protected acid **38**.



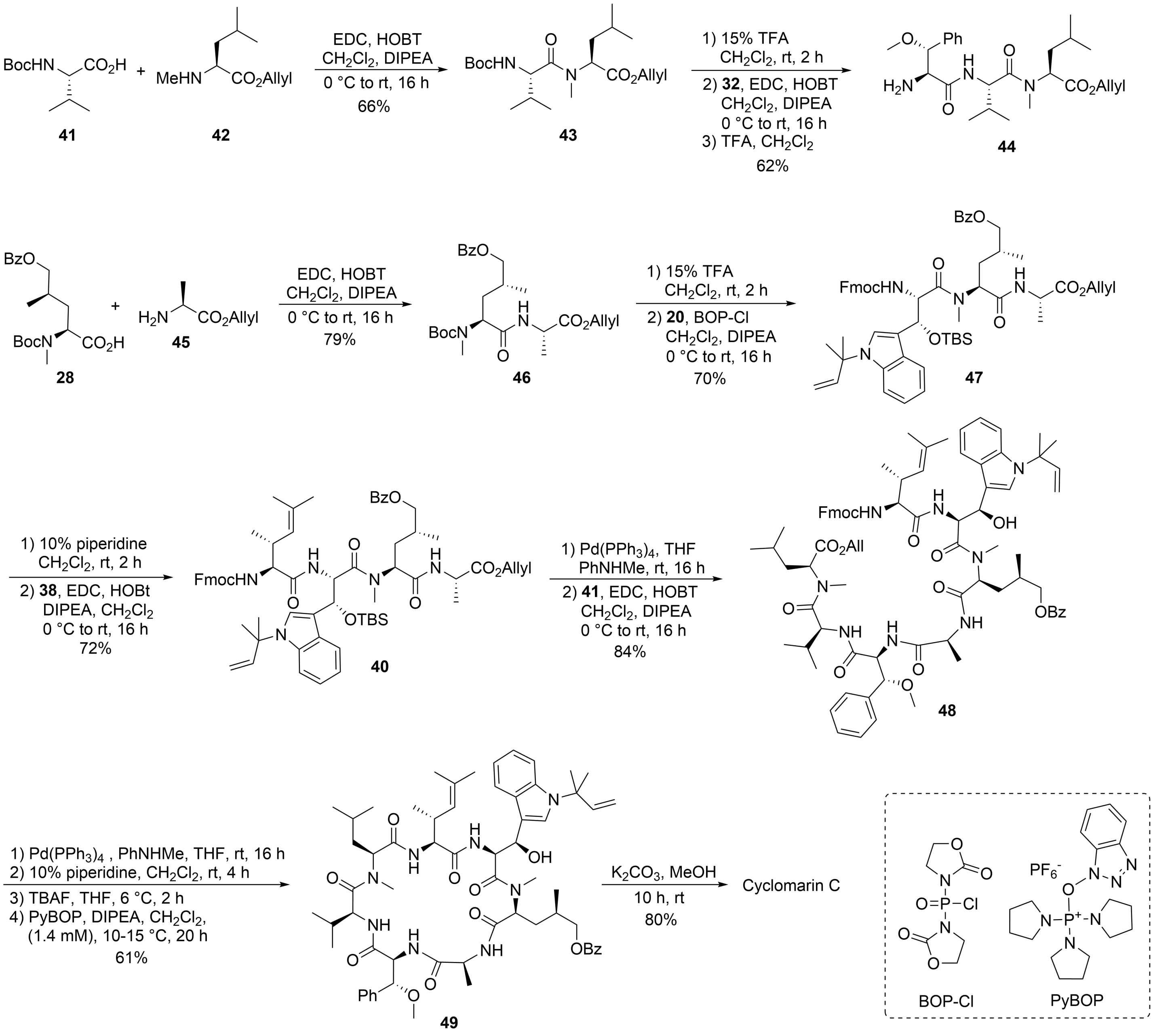
Scheme 8. Synthesis of protected dehydroamino acid **38** (building block ⑦).

After the desired building blocks were created, the synthesis of cyclomarin C and especially the best position for macrocyclization was investigated (Scheme 9)[30][39]. An attempt to align the synthesis to the biosynthetic pathway and to cyclize the linear heptapeptide precursor between the unusual tryptophan ① and the unsaturated amino acid ⑦ failed. Although obtaining the linear peptide in a [3+3+1] peptide fragment coupling strategy was straightforward, the final deprotection and ring closure yielded only trace amounts of the desired product. The same was true for attempts to cyclize the linear heptapeptide between the methoxyphenylalanine ④ and valine ⑤. The trial to cyclize between the sterically less demanding hydroxyleucine ② and alanine ③ failed early in the synthesis stage. All attempts to prolong the ①,② dipeptide at the *N*-terminus failed. Under the basic conditions for Fmoc-deprotection, spontaneous cyclization to the corresponding diketopiperazine occurred, comparable to the previously discussed biosynthetic side reaction, which resulted in the formation of the cyclomarazines. The ultimately successful route was the cyclization between the unsaturated amino acid ⑦ and the *C*-terminal *N*-methylleucine ⑥. The linear heptapeptide was obtained via a [4+3]-coupling strategy. An allyl ester was used as the *C*-terminal protecting group to avoid the basic reaction conditions required for the saponification of the *C*-terminal ester, which caused problems in previous cyclization attempts.



Scheme 9. Cyclization attempts for cyclomarin C[39].

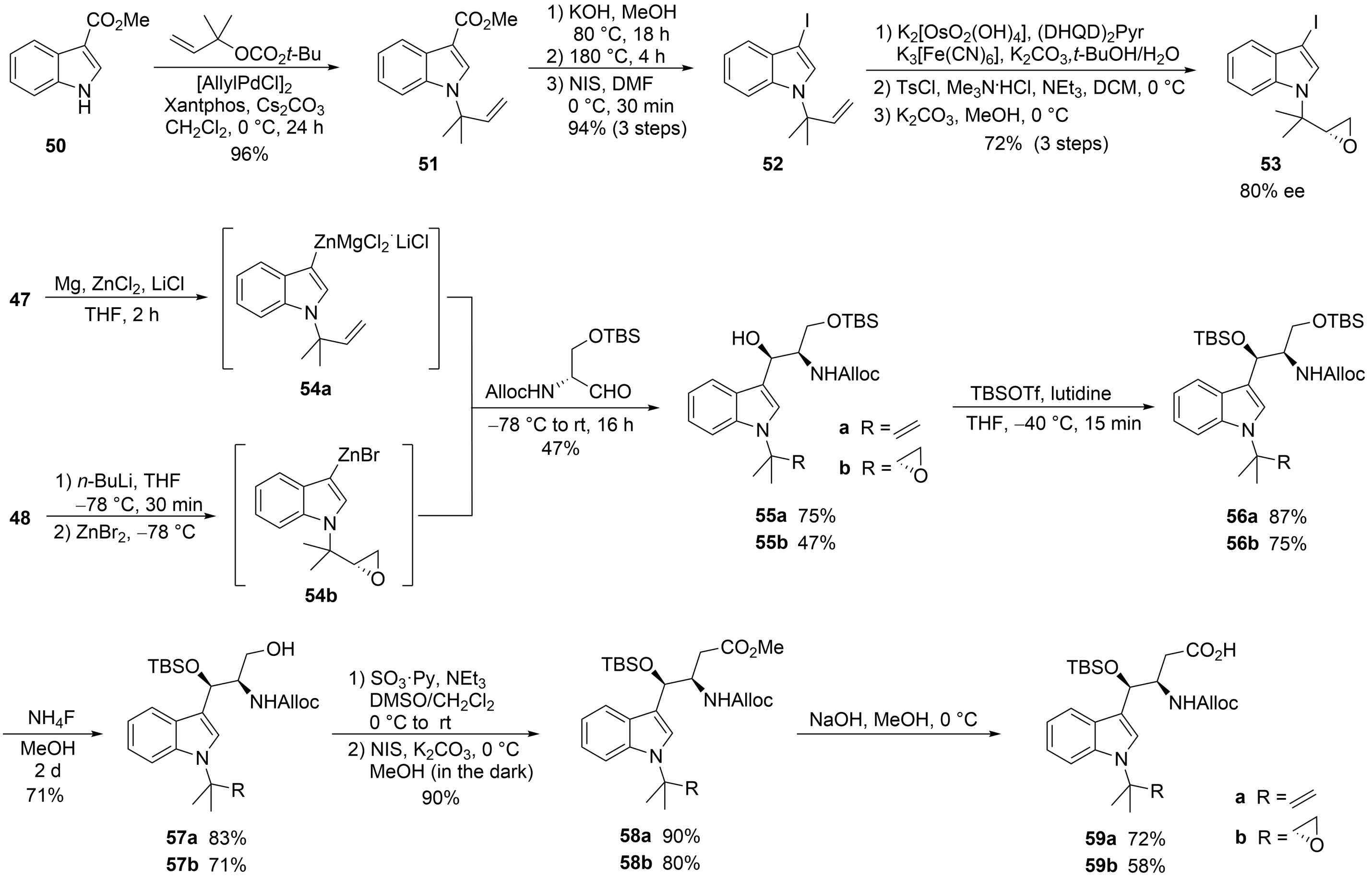
The desired tri- and tetrapeptide **39** and **40** were synthesized using classical peptide coupling reactions and a combination of Boc- and Fmoc-protecting groups (Scheme 10). Because of the acid lability of β-hydroxytryptophan, Fmoc had to be used after incorporating this building block into the growing peptide chain. The synthesis of the peptide fragments was straightforward. An adequate yield of the tripeptide **39** was obtained from *N*-Boc-valine **41** and *N*-methylleucine allyl ester **42**. Boc-cleavage and coupling with methoxyphenylalanine **32** produced **39**, which was also *N*-deprotected to tripeptide **44**.



Scheme 10. Synthesis of cyclomarin C.

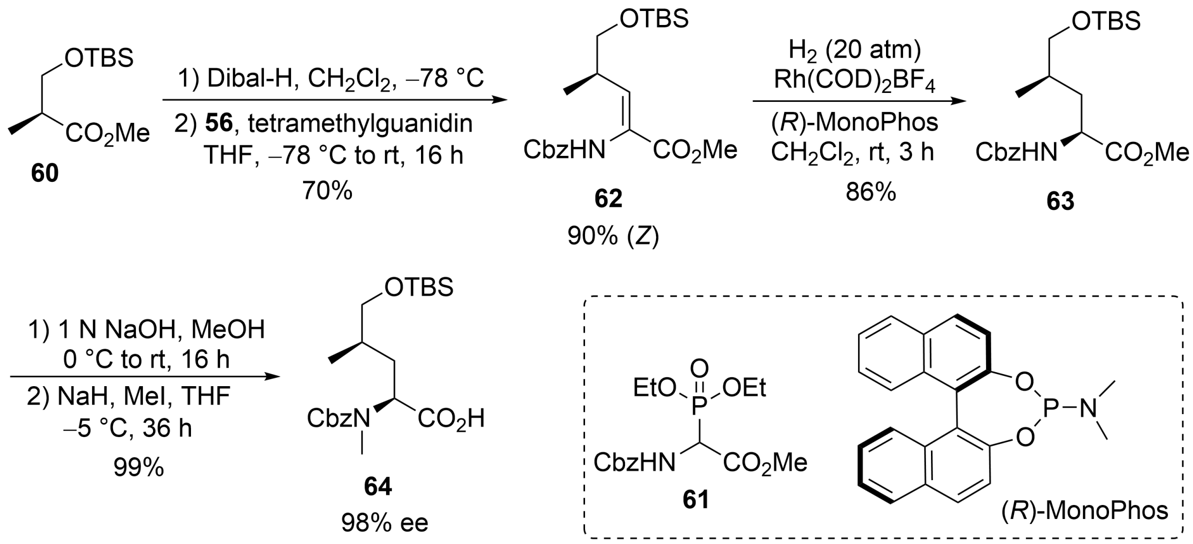
The synthesis of the tetrapeptide started with the coupling of protected δ-hydroxyleucine **28** with alanine allyl ester **45**. After *N*-deprotection, the Fmoc-protected tryptophan **20** was coupled using Bop-Cl/DIPEA[40]. Careful removal of the Fmoc-protecting group from **47** and EDC/HOBT-coupling with the unsaturated building block **38** provided tetrapeptide **40**. Finally, the *C*-terminal allyl ester was cleaved under mild Pd-catalyzed conditions, and the two peptide fragments were ready for the fragment coupling. An excellent yield of **48** was obtained using EDC/HOAt, which proved more suitable than HOBT. Subsequent deprotection of the *C*- and the *N*-terminus and removal of the OTBS-protecting group from the hydroxytryptophan provided the linear peptide precursor, which could be cyclized to **49** using PyBOP[41] under high dilution conditions and providing good yields. Finally, the benzoyl group had to be removed from the hydroxyleucine and cyclomarin C was purified via preparative HPLC.

The second synthesis of cyclomarin C and the first for cyclomarin A were reported in 2016 by Barbie and Kazmaier[42]. Both natural products differ only in the oxidation state of the prenylated β-hydroxytryptophan unit ①, which is epoxidized in cyclomarin A. Therefore, a synthetic protocol was developed which gave access to both tryptophan derivatives (Scheme 11). The synthesis started with a relatively new method for regioselective *tert*-prenylation of electron-demanding indoles[43]. Using indole ester **50**, a palladium-catalyzed protocol delivered the required product **51** in almost quantitative yield. At 0 °C, no competitive *n*-prenylation was observed. In the next step, the activating ester functionality needed to be replaced by iodine. Saponification of the ester and heating the neat acid to 180 °C resulted in a clean decarboxylation to the *N*-prenylated indole, which could be iodinated in almost quantitative yield. Iodide **52** was used as a key building block for the synthesis of cyclomarin C, and after epoxidation, cyclomarin A. According to Yokohama et al.[44], **52** was subjected to a Sharpless dihydroxylation, which unfortunately demonstrated only moderate stereoselectivity. The best results were obtained with $(DHQD)_2Pyr$ as chiral ligand, but the ee did not exceed 80 %[45]. Subsequent tosylation of the primary OH-group and treatment with a base provided a good yield of the desired epoxide **53**. The iodides **52** and **53** were next converted into organometallic reagents and reacted with a protected serinal. While the corresponding Grignard reagents provided only moderate yields and selectivities, zinc reagents were found to be superior. According to Knochel et al.[46][47], **52** was presumably converted into the indole–zinc–magnesium complex **54a**, which was reacted with freshly prepared protected serinal to give the desired *syn*-configured **55a** as a single diastereomer. In the case of the epoxyindole **53**, a slightly different protocol was used. To avoid side reactions during the metalation step, **53** was lithiated at −78 °C with *n*-BuLi and transmetallated with $ZnBr_2$[46][47]. The zinc reagent **54b** was directly reacted with the aldehyde to create **55b**. According to NMR and HPLC, only two diastereomers (ratio 9:1) could be detected following the Sharpless dihydroxylation step. Obviously, the carbonyl addition also here was highly stereoselective. Next, the secondary OH-functionality was TBS-protected under the assumption that a primary OTBS-group could be removed selectively[48]. Notably, only a combination of TBSOTf and lutidine gave the desired product **56a** in high yield, while all other methods failed and resulted in the decomposition of **55a**. Interestingly, no complete conversion was obtained for **55b**, but the silyl ether **56b** was obtained as a single stereoisomer. Obviously, the undesirable diastereomer did not undergo silylation. Next, the primary silyl protecting group was removed using NH_4F in MeOH[49]. The free alcohols **57** had to be oxidized to the desired carboxylic acids **59**, which were found to be highly sensitive and not very stable. By far, the best results were obtained using a two-step protocol beginning with a Parikh–Doering oxidation[50]. The also very labile aldehydes were directly oxidized to the corresponding methyl esters **58** with *N*-iodosuccinimide in MeOH[51]. These are stable, can be stored under standard refrigeration, and should be saponified to the free acids **59** on demand.



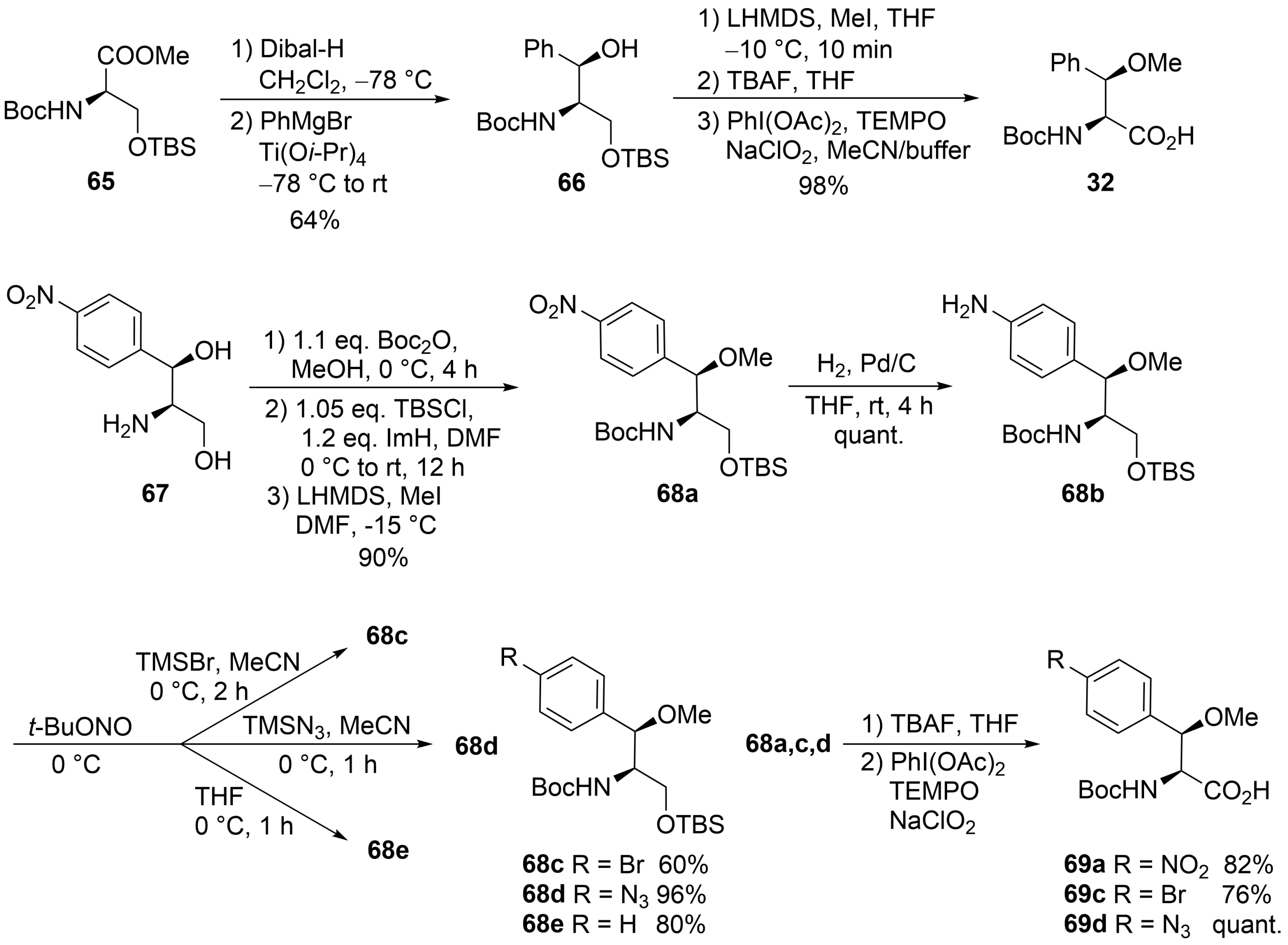
Scheme 11. Synthesis of tryptophan derivative **59** (building block ①).

A straightforward protocol was developed for the protected δ-hydroxyleucine ② , starting with the commercially available (*S*)-Roche ester, which was *O*-silylated to **60** (Scheme 12). Subsequent Dibal-H reduction provided the corresponding aldehyde, which was subjected to a Horner–Wadsworth–Emmons reaction using Schmidt's phosphonoglycinate **61**. The unsaturated amino acid **62** obtained was subjected to asymmetric hydrogenation[53] using (*R*)-MonoPhos as a chiral ligand[54][55]. Subsequent saponification of **63** and *N*-methylation yielded the desired building block **64**.



Scheme 12. Synthesis of δ-hydroxyleucine derivative 59 (building block ②).

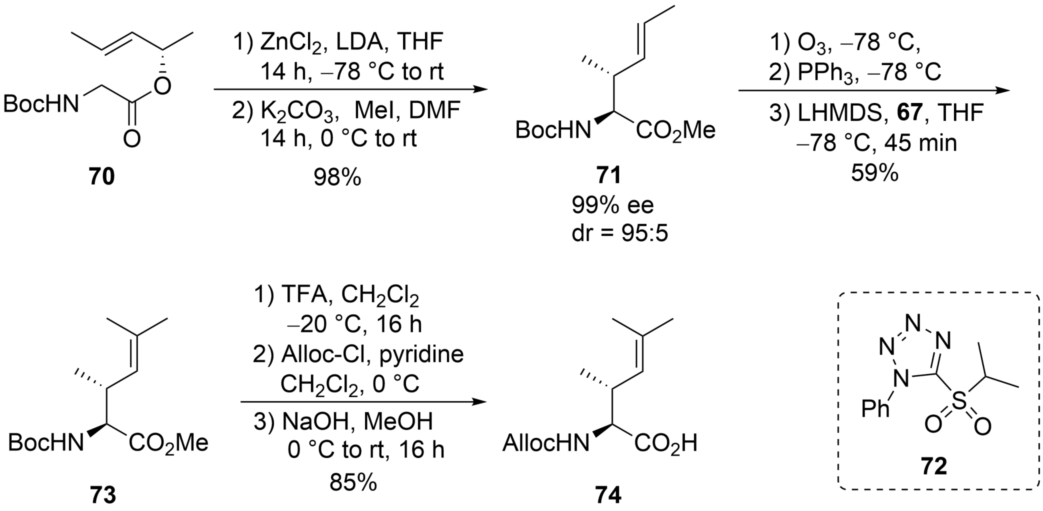
The third unusual amino acid, β-methoxyphenylalanine ④, could be obtained similarly to the tryptophan building block ① (Scheme 13). Protected (*R*)-serine **65** was reduced to the corresponding aldehyde, which was subjected to a chelate-controlled aryl-metal addition. The addition of phenylmagnesium bromide provided an acceptable yield but only moderate diastereoselectivity (7:3). In contrast, in the presence of titanium salts, the desired coupling product **66** could be obtained as a single diastereomer in enantiomerically pure form. Further standard transformations yielded building block **32**.



Scheme 13. Synthesis of β-methoxyphenylalanine derivatives (building block ④).

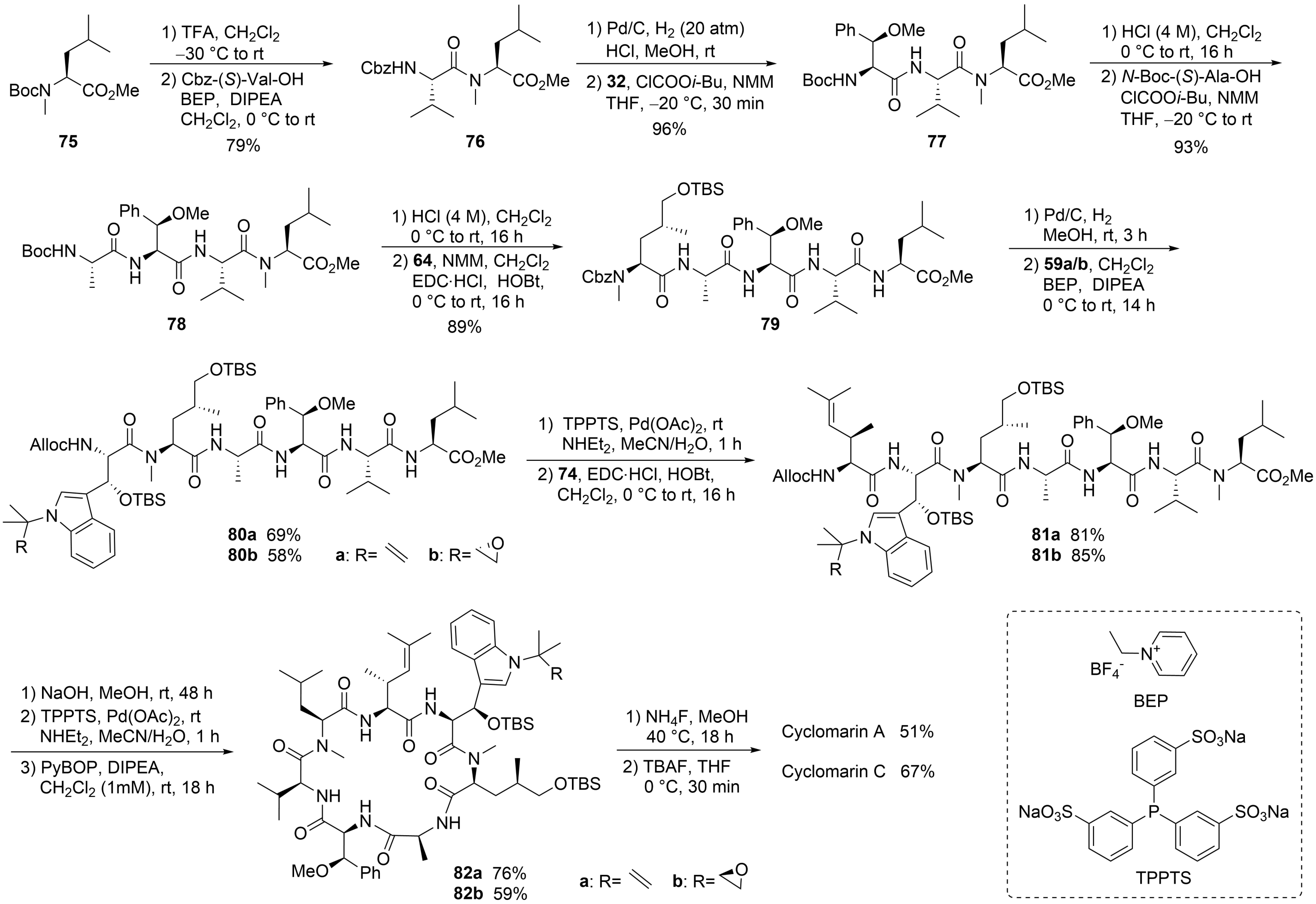
An alternative protocol, which also permitted the synthesis of substituted building blocks, was developed starting from commercially available chloramphenicol base **67** (Scheme 13)[56]. Thus, the amino diol was first converted stepwise into the protected derivative **68a**. The nitro functionality could easily be reduced to the corresponding aniline derivative **68b**, an ideal candidate for further structural variations via diazonium chemistry. Depending on the reaction conditions and additives used, several new derivatives **68c-e** could be obtained, which could be oxidized to the corresponding amino acids **69a-d**, while deamination of **68b** provided the unsubstituted building block **32**.

For the synthesis of the fourth, the unsaturated amino acid ⑦, also a chelate enolate Claisen rearrangement, was used starting with chiral ester **70** (Scheme 14)[57][58][59]. Rearrangement of the corresponding zinc enolate proceeded with complete chirality transfer and high stereoselectivity, and ester **71** was obtained after *O*-methylation. Ozonolysis provided the desired aldehyde, which was subjected to a Wittig reaction. However, only tiny amounts of the desired product could be obtained, even with a large excess of the Wittig reagents, which also caused the chiral aldehyde’s epimerization. Better results were obtained with a modified Julia–Kocienski reagent **72**, normally used for (*E*)-selective olefination[60]. Under these conditions, the desired unsaturated building block **73** could be obtained almost epimerization-free. Saponification and change in the *N*-protecting group provided amino acid **74**.



Scheme 14. Synthesis of unsaturated amino acid **69** (building block ⑦).

With all required building blocks synthesized, the linear synthesis of cyclomarins A and C started with protected *N*-methylleucine **75** (⑥) to cyclize the linear heptapeptide at the same position as achieved by Yao et al. (Scheme 15) [30][39]. The linear strategy was chosen to avoid epimerizations during fragment couplings, and three of the unusual building blocks were incorporated at the end of the synthesis, also allowing for modification of these building blocks and to obtain derivatives for structure-activity relationship (SAR) studies.



Scheme 15. Syntheses of cyclomarin A and C.

The hydrogenolysis of the Cbz-protecting group in dipeptide **76** was not a trivial task. The reaction required an H_2 pressure of 20 bar to proceed, and two equivalents of HCl had to be added to avoid diketopiperazine formation. The hydrochloride salt was directly coupled with the activated amino acid **32** in the presence of excess base. The next steps were standard peptide couplings. BEP[61][62] was used to incorporate the sensitive tryptophan building blocks **59**. The Alloc protecting group was removed, Pd-catalyzed, and the linear heptapeptide was cyclized using Yao's protocol[30][39]. Finally, a two-step protocol was needed to remove the two OTBS protecting groups separately, providing good yields of cyclomarins A and C. Notably, cyclomarin D (desmethylcyclomarin C), missing only the *N*-methyl group of the δ-hydroxyleucin, was also obtained by this protocol[63].

References

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