Review

A Comprehensive Achievement in the Total Synthesis of Antibacterial Furanomycin and Its Analogs

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A Comprehensive Achievement in the Total Synthesis of Antibacterial Furanomycin and Its Analogs

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Abstract: *L*-(+)-Furanomycin **1** is a miniature antibacterial natural product that contains an α-amino acid core. This non-proteinogenic α-amino acid was first isolated in 1967 by Katagiri and co-workers from the fermentation broth of *Streptomyces threomyceticus L-803* (ATCC 15795). It is a substrate of isoleucyl aminoacyl tRNA synthetase that replaces isoleucine in the protein translation process and exhibits antibacterial properties in vitro. It effectively acts as an antibacterial agent against *M. tuberculosis*, *E. coli*, *B. subtilis*, and some *Shigella* and *Salmonella* bacterial species at concentrations as low as the micromolar range. Consequently, synthetic chemists have garnered considerable interest from their specific structure-activity profile, distinctive chemical compositions, and distinct biological profile. This review comprehensively describes cutting-edge synthetic methodologies for synthesizing furanomycin and its analogs reported to date. Therefore, this review will offer an initial perspective on synthesizing furanomycin and its customized compounds.

Keywords: furanomycin; non-proteinogenic amino acids; antibiotics; natural products; total synthesis

1. Introduction

Amino acids are the essential building blocks of proteins, the most abundant biological macromolecules in all cell parts. [1–3] They are crucial in converting genetic information into essential biological products. These include enzymes, hormones, antibodies, muscle fibers, and other vital biological materials.[4–6] Besides the 20 proteinogenic amino acids, there are about 500 naturally occurring non-proteinogenic amino acids, many of which are building blocks for small bioactive peptide structures. The non-proteinogenic amino acids possess unique biological functional properties that are not found in the 20 standard amino acid building blocks. [7,8] The existence of natural peptides containing non-proteinogenic amino acids explicitly highlights the biological processes involved in their integration into peptides and their significant potential for use in protein engineering and medicinal chemistry.

The natural metabolites and peptides that contain non-proteinogenic amino acid residues highlight the process used to select and include these non-proteinogenic building blocks into nonribosomal peptides. Additionally, artificial amino acids have been created to be recognized by tRNAs and aminoacyl-tRNA synthetases, enabling their integration into proteins within living cells. This advancement holds potential for utilizing internally produced non-proteinogenic amino acids in protein engineering. [9,10] This compels researchers to synthesize alloproteins containing novel nonprotein amino acid residues, significantly expanding the potential for designing specific proteins with unique functions.

The infrequent and the most petite antibacterial natural product *L*-(+)-furanomycin **1** (Figure 1), with a molecular weight of 157 g/mol, was first reported by Katagiri and co-workers in 1967 (Figure

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1).[11] After that, in 2013, Banowetz *et al.* identified the ninhydrin-active compound *L*-furanomycin **1** being produced and released with selective antimicrobial properties by the plant root-associated γ–proteobacterium *Pseudomonas fluorescens SBW25*.[12] Very recently, Fariq *et al*. documented the production of furanomycin **1** from halophilic bacteria *Halomonas elongata* for the first time.[13] The absolute configuration of the isolated product has been conclusively established as $\alpha S,2R,5S$ by X-ray structural analysis of the *N*-acetyl derivative of **1** [14] and chemical methods. [15] The biological profile of (+)-*L*-furanomycin **1** exhibited antibacterial activity against numerous bacteria at low concentrations in the micromolar range (MIC 1 – 5 µg/mL).[11,16–18] Even though the chemical structure of (+)-*L*-furanomycin **1** differs from *L*-isoleucine **2** (Figure 1), it surprisingly preferred isoleucyl aminoacyl-tRNA synthetase.[17] In the protein translation processes, the conformation of enzyme-bound amino acids determines the affinity of an amino acid to aminoacyl-tRNA synthetase. These structural observations of compound **1** have been further supported by NMR studies that showed that the conformation of the enzyme-bound furanomycin is similar to the isoleucine.[17,19,20] Furthermore, standard amino acids featuring a methyl group, such as leucine (Leu) and valine (Val) substrates, are effectively recognized and differentiated from isoleucine by the enzymatic machinery. This essential function of the methyl group underscores the importance of understanding its influence on substrate recognition. It can be inferred that the C5-methyl group in compound **1** likely occupies the same binding pocket of the enzyme IleRS. While furanomycin **1** is recognized and activated by the enzyme IleRS in place of *L*-isoleucine **2**, its conformation does not precisely match that of isoleucine **2**. Thus, the research indicated that the larger side chain of furanomycin may interfere with the natural conformations and functions of essential proteins in cellular physiology. This alteration in protein structure accounts for its antibacterial effect in bacteria. In this scenario, although *L*-furanomycin **1** inhibits isoleucyl-tRNA formation in *E. coli*, other aminoacyl-tRNAs remain unaffected.[17,20,21]

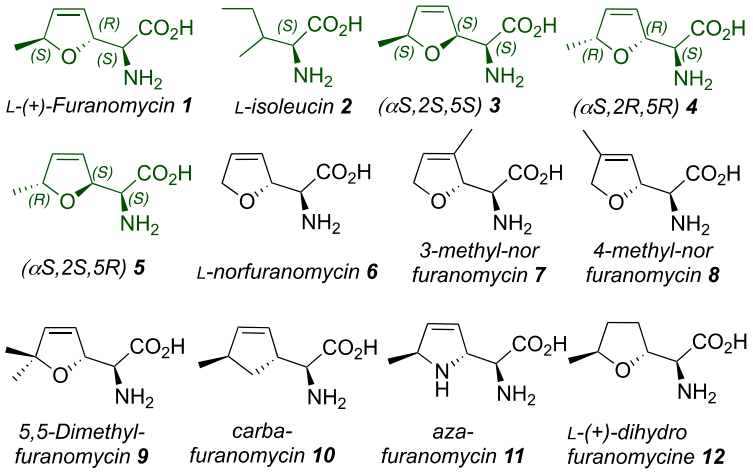

Figure 1. The chemical structure of furanomycin **1** and its isomers and analogs, **3-12** and *L*-isoleucine **2.**

The study aimed to understand the biological significance of compound **1** and its derivatives through structural analysis. As illustrated in Figure 1, the basic set of structures of furanomycin used to explore the SAR was expanded to include diastereomers of furanomycin **1** (**3**, **4**, and **5**), norfuranomycin **6,** 3-methyl-norfuranomycin **7**, 4-methyl-norfuranomycin **8,** furanomycin derivative **9,** which contains two methyl groups, carba-analogs **10,** aza-furanomycin **11**, and dihydrofuranomycin **12**. The structural prerequisites of isoleucyl aminoacyl-tRNA synthetase for furanomycin-like substrates were quite stringent. A very constricted SAR study was concluded, and all synthetic isomers and derivatives of the natural antibiotic **1** demonstrated different MICs against a panel of selected Gram-positive and Gram-negative wild-type pathogens, including *S. aureus* and *E. coli.* [21,22] Additionally, biological studies showed that changing the position of the methyl group in the central furan ring influenced the antibacterial properties of furanomycin **1**, including nor-

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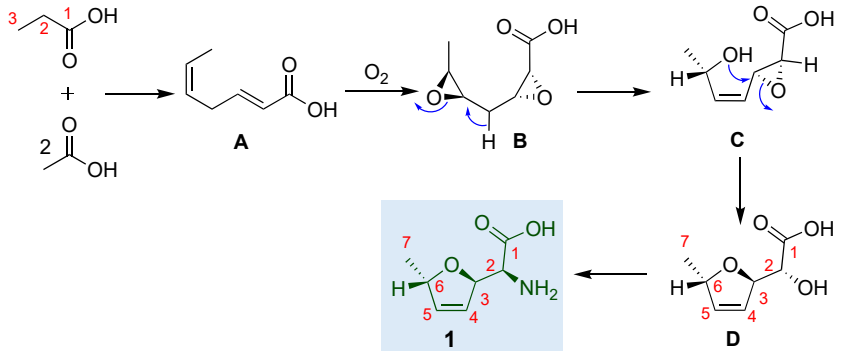
furanomycin **6**, 3-methyl-norfuranomycin **7**, and 4-methyl-norfuranomycin **8**, against certain Gram-negative bacteria. (Figure 1). In this context, many other *L*-(+)-furanomycin congeners have been chemically synthesized in enantiomerically pure or racemic forms and scrutinized biologically. For example, *L*-(+)-dihydrofuranomycin **12** exhibited borderline MIC (32-64 μg/mL) against *S. aureus*.

In contrast, the chiral carba-analogue **10** exhibited weak antibacterial activity (4 μg/mL) against an efflux pump-deficient *E. coli* and its antibacterial properties *in vitro* and *in vivo*. Likewise, *L*-(+)-furanomycin displays drug-like features, such as polarity, sufficient aqueous solubility, and moderate structural complexity, which render it an attractive synthetic target to medicinal chemists. To this end, several synthetic approaches targeting **1** have been developed, consisting of up to 20 steps. Some syntheses start from chiral substrates such as carbohydrates, amino acids, etc., whereas some approaches use achiral starting materials like furans, cyclopentadiene, etc. The approaches starting from amino acids are primarily attractive because they involve only six to seven steps, making them short and flexible enough to access furanomycin **1** and their analogs rapidly. Therefore, we briefly discuss in detail the synthetic studies of the synthesis of furanomycin **1** and its functionalized derivatives. The present review offers comprehensive information and motivation for developing new antibacterial targets. Investigating the intricate mechanisms of newly developed antibacterial agents would also be beneficial in identifying the best antibacterial candidates effectively.

2. Biosynthesis of Furanomycin:

Parry *et al.* proposed the biosynthetic pathway for furanomycin **1** (Scheme 1). [23,24] In biogenesis, the carbon skeleton of the inquisitive amino acid furanomycin **D** is formed via a polyketide pathway starting from one propionate and two acetate units. The carbon atom 6 in **D** could come from C-2 of propionate. During the oxidation at C-2, one of the propionate protons is lost from this site without forming a lactate intermediate. Later, the study strongly supported this observation by confirming that the 2-pro-*R* proton from the propionate unit. Since the configuration at C-6 of **D** is *S*, the introduction of the ether oxygen at C-2 of propionate occurs with an overall inversion of configuration. Overall, analogous to the polyether antibiotics, the substrate **A** could undergo epoxidation to form the epoxide intermediate **B,** the 5,6-epoxide ring could open, and the resulting hydroxyl group could attack the adjacent epoxide, producing the cyclic ether **D**. It can then easily be converted into furanomycin **1** (Scheme 1). [24] Labeling experiments with [1-^{13}C, $^{18}O_2$] acetate and $^{18}O_2$ gas proved that the ether oxygen originates from aerial oxygen, not acetate.



Scheme 1. The biosynthetic pathway of furanomycin **1**.

3. Chemical Syntheses of *L*-(+)-Furanomycin and Its Analogues

Furanomycin **1** possesses a unique *trans*-2,5-substituted, five-membered unsaturated cyclic ring system with an *S*-configured amino acid side chain, setting them apart as crucial components in biological processes. Thus, the synthetic challenge is assembling *trans*-2,5-dihydrofuran ring and (*S*)-amino carboxylic acid units. Over the past few years, many approaches to synthesizing *L*-(+)-furanomycin have been developed. In this direction, At first, in 1975, Masamune and Ono reported

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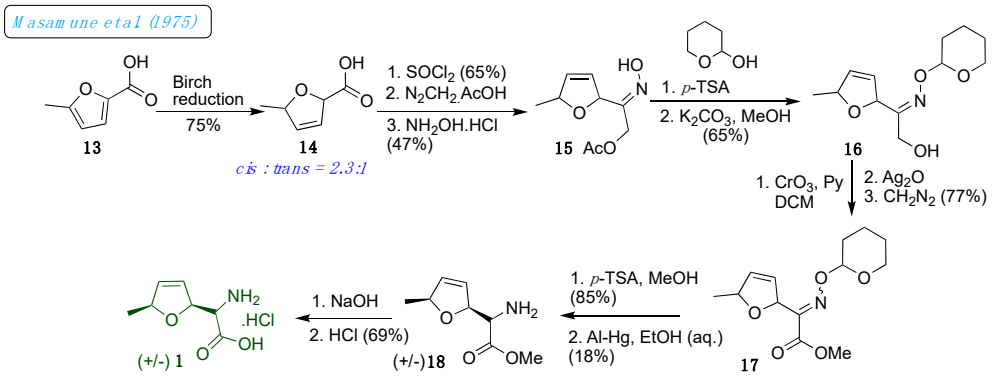
the total synthesis of the racemic (±)-furanomycin **1** (Scheme 2) in 16 steps, with an overall yield of <0.02%.[19]



Scheme 2. The synthesis of *dl*-furanomycin **1** from 5-methyl-2-furoic acid.

The 5-methyl-2-furoic acid **13** was utilized to access the *dl*-furanomycin **1.** The partial Birch reduction of **13** produced a crystalline mixture of diastereoisomeric 5-methyl-2,5-dihydrofuroic acids **14**, from which a *trans*-isomer was isolated in 23% yield as a minor isomer. The remaining acid mixture contained a major *cis*-isomer in 53% yield. The amino and acid groups in the structure were installed in the consecutive steps. Thus, acid **14** was converted into keto-acetates to oxime acetates **15** in a three-step reaction sequence. Next, the oxime protection introduced the acid group, followed by acetate deprotection, which produced alcohol **16**. Oxidation of **16** employing a modified Colline oxidation protocol followed by silver oxide treatment furnished acids; subsequently, acids were esterified with diazomethane to esters **17**. The oxime acetates **17** on a chemo-selective reduction of oximino-esters with aluminum amalgam in aqueous ethanol resulted in diastereoisomeric amino esters **18** in 18% yield. Diastereomeric amino esters **18** were converted into hydrochloride salts; the data obtained was identical to isolated furanomycin **1**.

Until 1979, the configurations at the asymmetric centers of (+)-furanomycin were not confirmed by X-ray studies or stereospecific synthesis. Based on a combination of spectroscopic and chemical degradation techniques, the first structural assignment of asymmetric centers of furanomycin **1** was established into (α*R*,2*R*,5*R*) configuration.[11] Due to structural ambiguity, Joullie *et al.* first developed the chirality transfer strategy to synthesize the furanomycin and its configurational isomers.[15] As shown in Scheme 3 (A), the synthesis proceeded with nine steps from the D-glucose. Thus, furanose derivative **19** was treated with excess sodium phenylselenide to afford diselenide **20**. Reductive removal of phenylseleno groups with the Raney nickel produced alcohol **21**. Tosylation of **21**, followed by base-catalyzed elimination, afforded 2,5-dihydrofuran **22**. The acid hydrolysis of **22** provided the aldehyde intermediate, which, upon being subjected to Ugi four-component reaction with (*R*)-(+)-*α*-methyl benzylamine, benzoic acid, and *tert*-butyl isocyanide afforded the diastereomeric adducts **23a** and **23b** (1:1). Debenzylation of **23a** and **23b** in acidic condition (95% formic acid) followed by hydrolysis with 6N HCl gave (*α*-1*R*,2*R*,5*S*)-furanomycin *ent*-**5** and 5*S*,2*R*-*α*–*S*-furanomycin **1**, respectively. In the synthetic study, the absolute and relative stereochemistry of **1** was accurately established for the first time.

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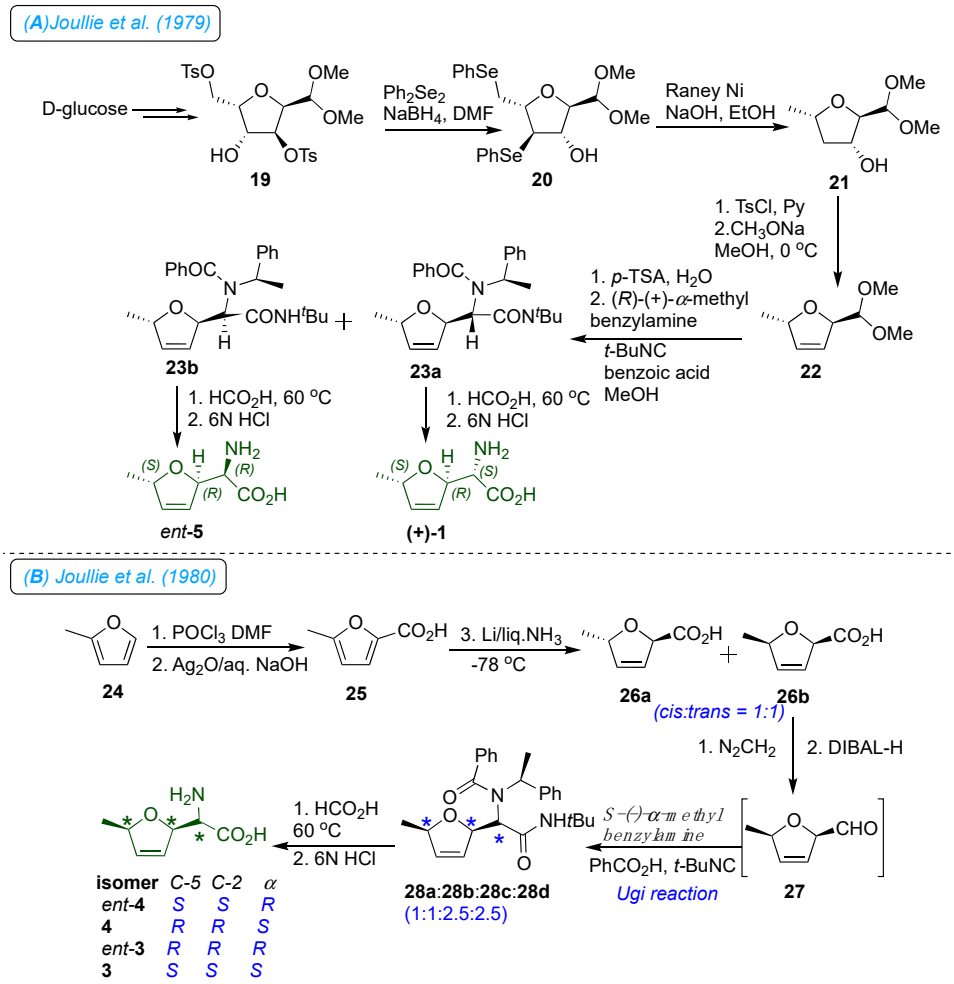

Scheme 3. (A) The synthesis of *L*-furoanomycin **1** from D-glucose, and (B) its **3**, *ent*-**3**, **4**, *ent*-4, *ent*-**5** from 2-methyl furan.

Later, as shown in Scheme 3 (B), the same group confirmed the configuration of naturally occurring antibiotic furanomycin as (*α*S,2*R*,5*S*) by synthesizing a series of four 2,5-*cis* stereoisomers of *α*-amino-2,5-dihydro-5-methylfuranacetic acid and two *trans* isomers from the D-glucose. [25] Five years later, they reported the synthesis of two new *trans*-isomers of furanomycin from D-glucosamine hydrochloride (Scheme 4). In this strategy, the compound **30** was efficiently prepared from D-glucosamine and stereo-selectively transformed into enantiomer (*α*–*R*,2*S*,5*R*)-furanomycin and its isomer with the opposite configuration at the amino acid functionality (*α*–*S*,2*S*,5*R*)-furanomycin **5** in good yields. [26]

1982, Parker *et al*. developed a synthetic strategy for furanomycin **1** and its diastereoisomer from D-ribose (Scheme 5).[27] A known sequence prepared the 1,3-diphenylimidazolidine derivative **33**.[28] It was further transformed into appropriately protected seven-carbon 3,6-anhydrous compounds by benzylating the primary alcohol **33**. Deprotection of the aldehyde followed Strecker-type side chain synthesis and subsequent acetylation of the resulting epimeric 2-hydroxyl groups provided **34a** and **34**, benzyl deprotection and mesylation followed by iodide replacement on **34a/b** afforded iodo derivatives **35a/b**. The catalytic hydrogenolysis of **35a/b** with Pd/C afforded a **36a/b.** The amine group was mounted on the ring's core structure following the deprotection of the 2-hydroxyl group and subsequent mesylation and azidation reactions. The 2,3-dihydrofurane ring in **37a/b** was created by methanolysis of the amide, removal of the isopropylidene to form a cyclic thiono-carbonate group, and then reductive decomposition of the cyclic thiono-carbonate group under Corey-Winter reaction conditions. This process also resulted in the reduction of azide and the formation of amine intermediates. Finally, hydrolysis of the amide gave *ent*-**3** and **4** diastereomers of antibiotic **1**.

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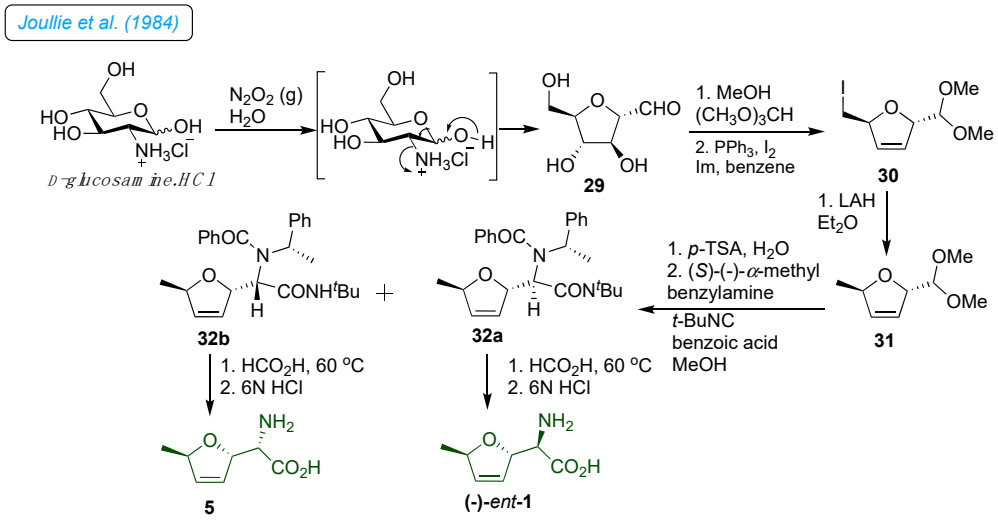
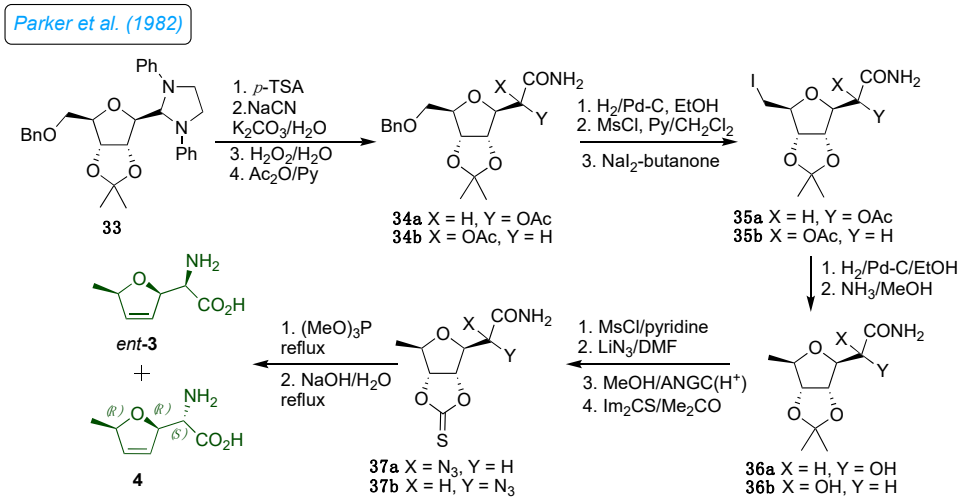


Scheme 4. The furoanomycin (-)-**1** synthesis and its isomer **5** from D-glucosamine.



Scheme 5. The synthesis of *ent*-**3** and **4** from D-ribose.

As shown in Scheme 6, Kang *et al.* reported a highly enantioselective total synthesis of (+)-furanomycin **1** utilizing the mercury cation-mediated stereoselective cyclizations of γ-hydroxy alkene **40** as a critical step.[29] The sequential mercury-promoted cyclization postulated the required *trans*-2,5-disubstituted tetrahydrofuran and the (*S*)-amino acid side unit from homoallylic compounds **40**. The silyl ether **38** was prepared from dimethyl *L*-tartrate by a known literature method and followed by PPh_3 mediated iodination, which afforded iodide **39**, transformed into an essential diene diol **40** via substitution of the vinyl group followed by hydrolysis of acetonide. The formation of *trans*- and *cis*-2,5-disubstituted tetrahydrofurans **41a/b** was achieved with $Hg(OCOCF_3)_2$ and K_2CO_3 followed by triethyl borane/$LiBH_4$ mediated demercuration. The tetrahydrofurans **41a/b** transformed to the corresponding trichloroacetimidate separated as **42a** and **42b**. The $Hg(OCOCF_3)_2$ mediated intramolecular amination produced the desired mercuric bromide in 95% yield, sequentially converted to the dihydro-1,3-oxazine **43** via demercuration followed by protection. The bicyclic compound **43** was transformed into dihydrofurane intermediate **44** by acid-catalyzed hydrolysis and iodination reactions. Elimination in **44** established an endocyclic double bond, and Zn promoted reductive *N-O* bond cleavage that smoothly afforded compound **45**. Oxidation of primary hydroxyl group in Swern-oxidation condition, successive Pinnick oxidation of the aldehyde to acid, and removal of Cbz group provided unmasked **1** (Scheme 6).

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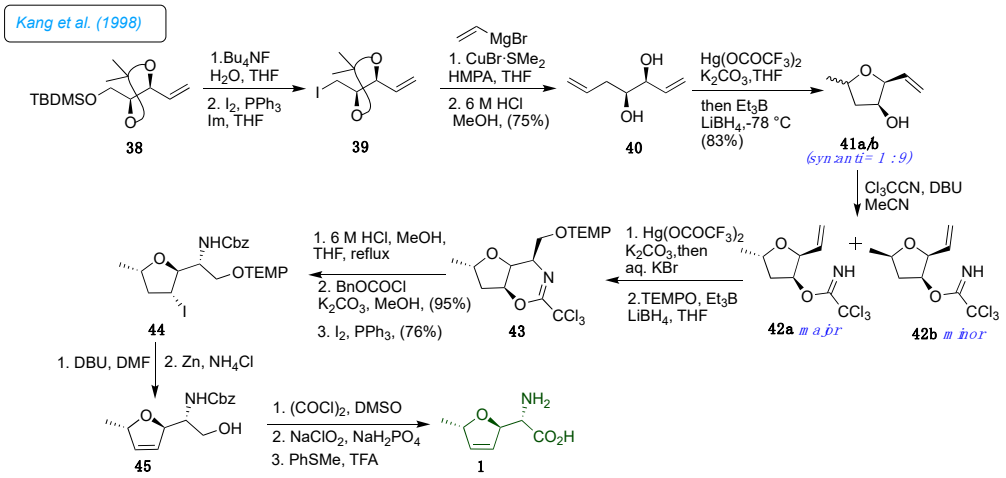
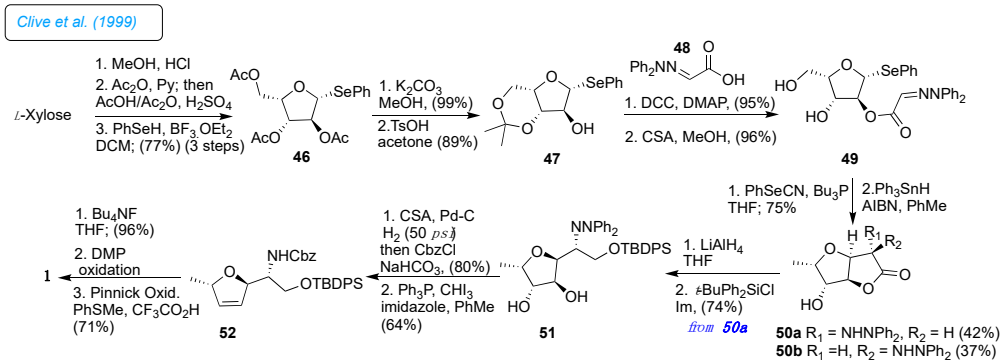


Scheme 6. The enantioselective synthesis of furanomycin **1** from *L*-tartaric acid.

In 1999, Clive and a co-worker developed the chiral pool strategy for synthesizing **1**, which involved radical cyclization as a key step.[30] The synthesis started from L-xylose, which was converted into its methyl glycoside **46** via a three-step sequence with an overall yield of 77% without isolation of the intermediates (Scheme 7). Compound **46** is used for mild hydrolysis, followed by acetonide protection provided by ketal **47**. Next, DCC-mediated coupling **47** with (2,2-diphenylhydrazono)acetic acid **48** gave the hydrazone ester **49** in 95% yield. The critical one-step radical cyclization and deoxygenation of the C5-OH group of **49** were accomplished with AIBN and Ph_3SnH reagent, which provided the isomeric mixture of chromatographically separable hydrazino lactones **50a** (43%) and **50b** (37%) epimeric at C2.



Scheme 7. The synthesis of furanomycin **1** from *L*-xylose.

Further, compound **50a** was converted into compound **51** by reducing the ester and protecting the primary hydroxyl group. The dihydrofuran ring **52** was created by removing the remaining two hydroxyl groups with PPh_3 and CHI_3. Extensive *bis*-dehydration was also noted in the corresponding furan system. Under optimum conditions, **51** was obtained in 64% yield. Finally, desilyation and the oxidation of the primary hydroxyl group to acid were achieved. In the oxidation steps to avoid the epimerization at the C2 position, the Dess-Martin conditions were used instead of the Swern oxidation, and treatment with TFA in the presence of PhSMe observed free amino group and liberated furanomycin **1** of 98% purity.

Standaert *et al.* reported concise and efficient synthesis of *L*-(+)-furanomycin **1** in seven total steps starting from the (*R*)-Garner aldehyde **53** (Scheme 8).[31] The first step in the synthesis was the stereoselective addition of acetylide **54** to the (*R*)-Garner aldehyde **53** to afford a 9:1 mixture of diastereomers **55**, which was stereoselectively reduced with LAH to give allenic alcohol **56**. This transformation proceeded via trans-hydrometallation followed by *anti*-elimination of the alkoxide to allenic alcohol. This approach showed the usefulness of constructing a dihydrofuran ring system directly propargyl alcohols, simplifying the synthetic problem with a stereoselective addition of

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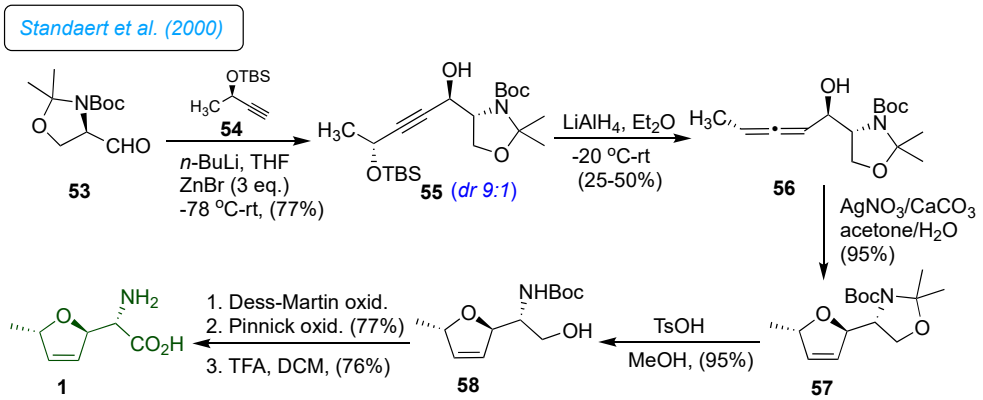
acetylene to *L*-serine. Next, the *trans*-2,5 dihydrofuran ring **57** was formed by Ag-assisted cyclization of the allenicalcohol **56** in the dark, affording the dihydrofuran **57** in 97% yield. Base catalyzed selective deprotection of the *O*, *N*-acetonide in **57** afforded furanomycinol **58**. The sequential oxidation using the Dess-Martin reagent followed by $NaClO_2$, as a procedure reported by Clive for oxidation of *N*-Cbz furanomycinol [30] and further TFA-mediated deprotection of the amino group yielded the desired (+)-furanomycin **1** in 76% yield.



Scheme 8. The synthesis of *L*-(+)-furanomycin **1** from Garner aldehyde.

Jäger *et al.* presented a novel stereoselective 1,3-dipolar cycloaddition of nitrile oxides to furan for the synthesis of *L*-(+)-furanomycin **1**, its C5-epimer analog **4** and 5,5-dimethyl analog furanomycin **9** based on previous work (Scheme 9A).[32] The new synthesis method has some unique features compared to previous ones. It can determine the relative arrangement of the three stereocenters in intermediate tetrahydrofuran-3,4-diols. It used a chiral glycine equivalent called glyceronitrile oxide as a starting material, providing a direct route to four of the eight stereoisomers of **1**. Different nucleophiles (such as Grignard reagents) can produce structural analogs **1** from the main epoxide **61**. As outlined in Scheme 9A, diisopropylidene mannitol was transformed to known hydroxamic acid chloride **59** in three steps.[33] The 1,3-dipolar cycloaddition of **59** with 2-methylfuran **24 in** TEA gave a mixture of the diastereomeric furoisoxazolines **60a/b** (*dr* 60:40). The major dihydrofuran **60a** exposed to epoxidation with DMDO afforded stable epoxide **61** with high selectivity (*dr* >95:5). The *endo*-stereoselective hydride transfer with sodium cyanoborohydride on **61**, as well as regioselective epoxide opening with MeMgBr, led to alcohols **62a** and **62b**, respectively. Subsequently, the hydroboration-oxidation reaction of the compound **60a** led to high *exo*-selectivity of the alcohol **62c**, which is C5-epimer of **62a**. The 3,4 dihydrofuran ring **63a-c** was effortlessly obtained from isoxazolines **62a-c** by successive LAH reduction followed by a twofold mesylation and demesylation procedure. Finally, in **63a-c** on acetonide hydrolysis, subsequent diol cleavage to an aldehyde, and further oxidation to an acid using Pinnick oxidation conditions provided **64a-c**. Cleavage of the carbamate in **64a-c** provided **1**, 5,5-dimethyl analog **9** and 5-epimer **4** (Scheme 9A).

The same group in 2005 reported the synthesis of *L*-carba-furanomycin **10.** As shown in Scheme 9B, the 1,3-dipolar cycloaddition of cyclopentadiene **65** and the chiral nitrile oxide **59** gave a mixture of **66a/b** in 80% yield (*dr* 56:44).[34] Worthy of note, the compound cyclopentadiene **65** serves as the cyclopentene core of carba-furanomycin **10**, and the chiral cyclopentaisoxazoline **67** contains three stereogenic centers that provide stereogenic carba-furanomycin **10**. Thus, the mix of **66a/b** was treated with dilute TFA in aqueous methanol to provide diols, which were benzylated to give **67a/b** in 78% yield. The stereoselective reduction of the cyclopentaisoxazoline **67a** was followed by amino alcohol protection to the amino group with Boc_2O in dioxane and water (3:1), providing the significant product cyclopentenol **68**. The acetylation was trailed by introducing the methyl group and subsequent debenzylation (Na, liq.NH_3) to give diol **69**. The intermediate aldehyde was prepared by cleavage of diol **29** with $Pb(OAc)_4$, which was directly oxidized to the carboxylic acid in Pinnick oxidation, followed by esterification with diazomethane providing methyl ester **70**. Finally, the NH-Boc deprotection in **70** with 90% TFA and hydrolysis of ester gave *L*-carba-furanomycin **10**.

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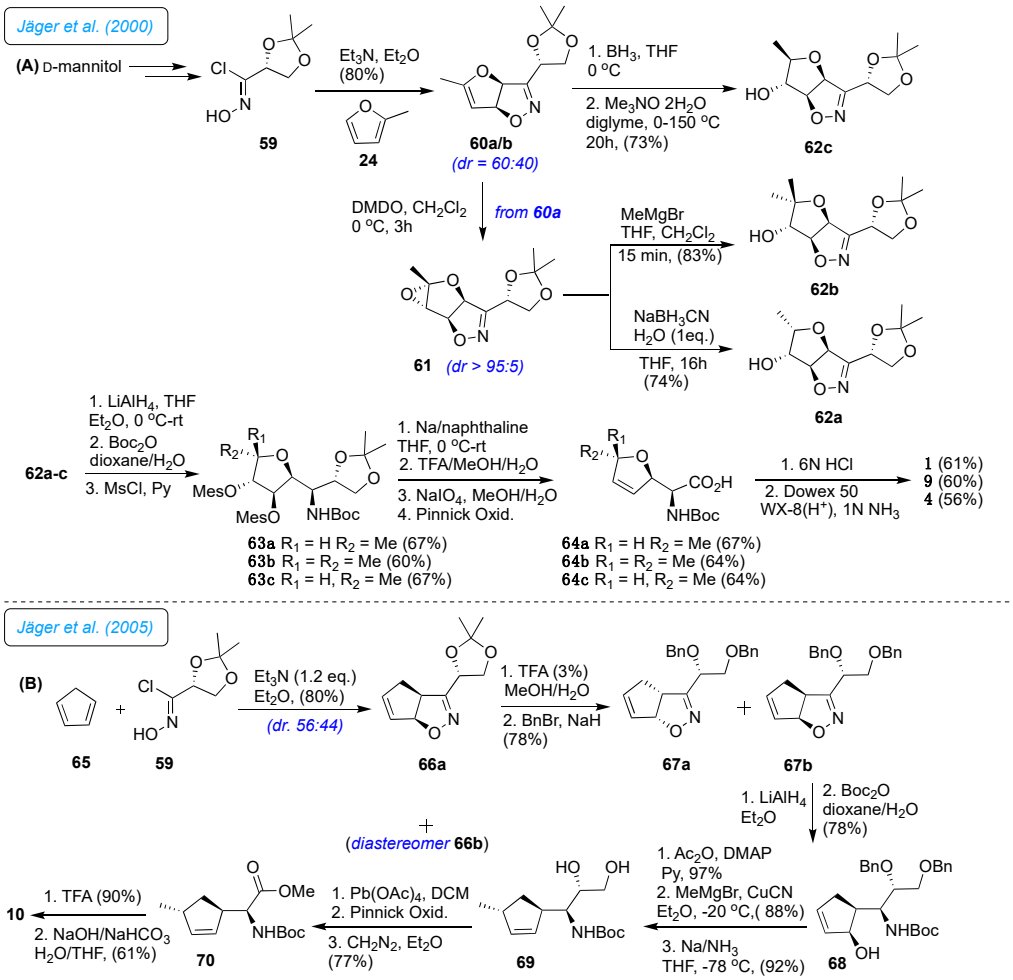

Scheme 9. (A) The synthesis of L-furanomycin **1** and its analogs **6**, **7** from 2-methyl furan and D-mannitol; (B) A synthesis of compound **6** from cyclopentadiene and D-mannitol.

Kazmaier *et al.* developed straightforward protocols for the 3- and 4-methylated derivatives, corresponding to hydrogenated analogs of furanomycin (Scheme 10) and carba-furanomycin (Scheme 11). [22] They wanted to determine the structural parameters required for biological activity and identify those that can be altered or removed. Their goal was to create simple procedures for producing derivatives without the 5-methyl group (norfuranomycin **6**), also found to be biologically active. Thus, the glycine esters **71a/b** were used to synthesize norfuranomycin **6** and its α-methylated derivative **78**. Primarily, the synthesis of norfuranomycin **6** started with a titanium-assisted aldol reaction of crotonaldehyde with glycine ester **71a, which** resulted in a preferentially *anti*-product **72a/b** (*syn*/*anti* 1:2) in good yields (Scheme 10). The palladium-catalyzed *O*-allylation followed by Grubbs cyclization on **72a/b** yielded a separable mixture of diastereomers *syn*-**73a** and *anti*-**73b**. After removing the Boc groups, they could obtain diastereomerically pure norfuranomycin **6** and *anti*-**74**. Consequently, independent catalytic hydrogenation of **73a/b** provided the saturated derivatives *syn*-**75a** and *anti*-**75b**. On the other hand, the synthesis of α-methylated derivatives *syn*-**78** was achieved following the same synthetic protocol from **71b**.

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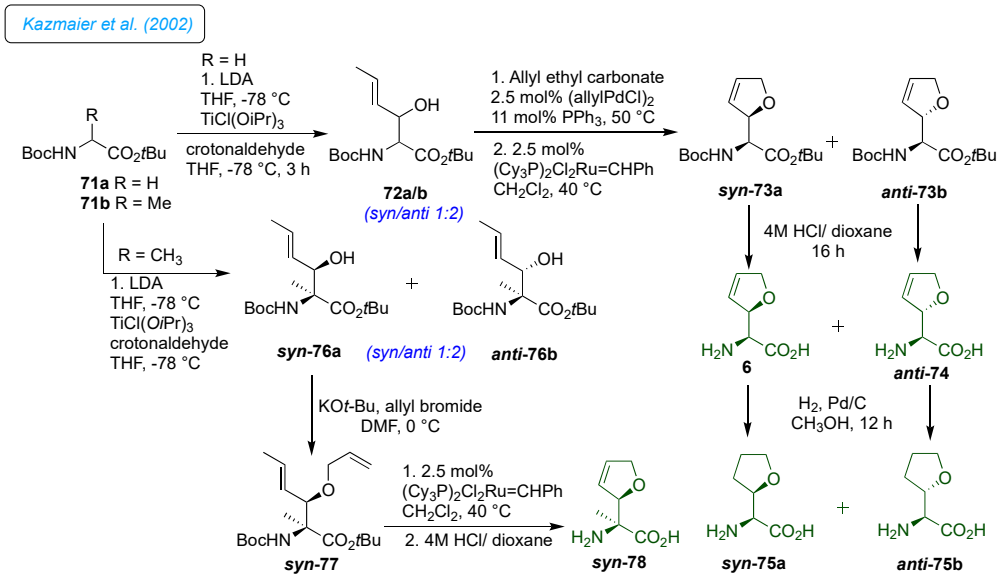
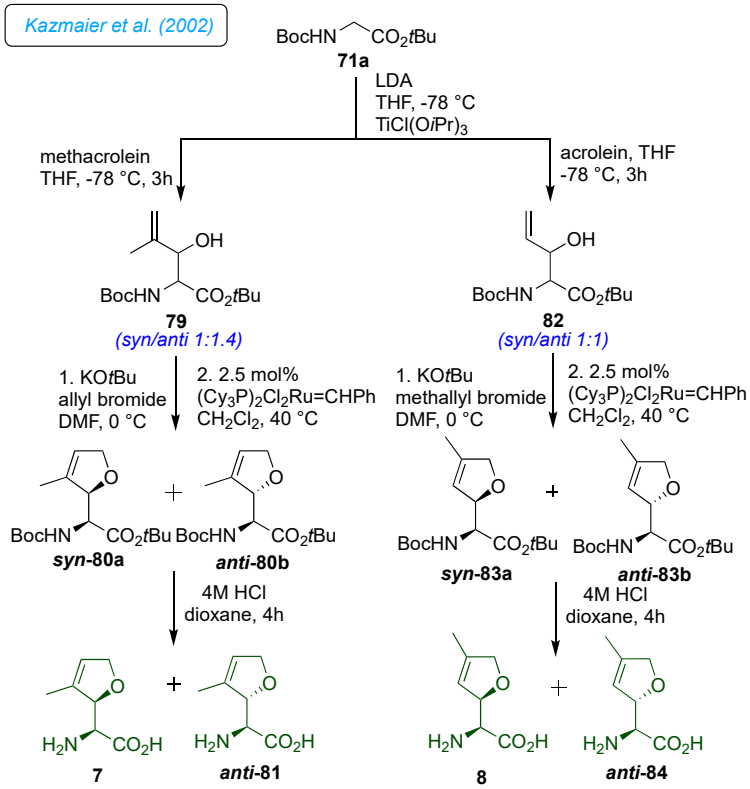


Scheme 10. The synthesis of norfuranomycin **6** and its analogs from glycine ester.



Scheme 11. The synthesis of 3-methyl-norfuranomycin **7** and 4-methyl-norfuranomycin **8** from glycine ester.

The 3-methylated derivatives **7** and *anti*-**81** and 4-methylated derivatives **8** and *anti*-**84** were synthesized from methacrolein and acrolein by a similar protocol described in Scheme 10 (Scheme 11).

For synthesizing *syn*-**89a** and *anti*-**89b**, the precursor ester **85** was obtained by coupling cyclopentenol with Boc-glycine (Scheme 12). [35] The protected cyclopentenyl glycine diastereomers (*syn*/*anti* 8:2) **86a/b** were obtained through a base-promoted Claisen rearrangement of ester **85** with zinc chloride and iodolactonation of a diastereomeric mixture of **86** provided separable *syn*-**87a** and *anti*-**87b** in good yields. Further, cleavage of iodolactones and subsequent deprotection afforded the desired diastereomerically pure cyclopentenyl glycine *syn*-**89a** and *anti*-**89b**. In addition, fully

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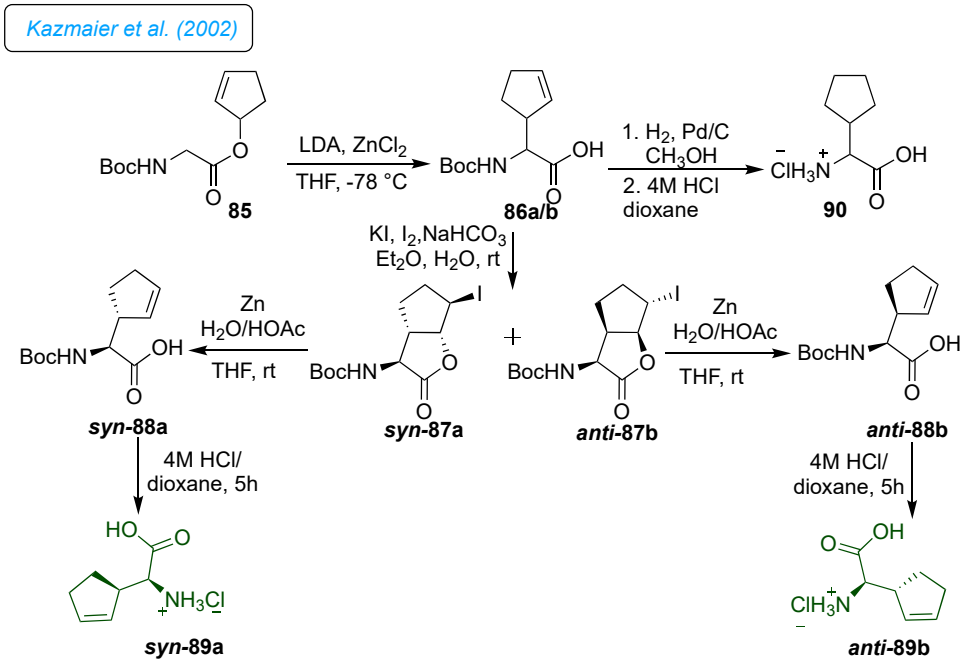
saturated cyclopentane glycine derivative **90** was directly obtained from **86** after hydrogenation and deprotection.



Scheme 12. The synthesis of carba-norfuranomycin **89a/b** from cyclopentenol with glycine ester.

In 2007, Krause and co-workers developed a strategy to prepare novel furanomycin analogs **96** and **100** employing the gold-catalyzed cycloisomerization of *α*-of hydroxyallenes **94a/b** as the foremost step (Scheme 13 A and B).[36] Notably, the present gold-catalyzed strategy is more efficient for cyclizing highly functionalized substrates than the traditional approach, where stoichiometric amounts of silver salts are used. As shown in Scheme 13, the reactive hydroxy allenes **94a/b** were favorably synthesized by the copper-mediated S_N2, substituting propargyl oxiranes **93**, obtained from Garner's aldehyde (*S*)-**91** via conjugated enynes **92a/b** Wittig olefination with the propargyl phosphonium salts. Further, Au(III)-catalyzed cycloisomerization of the *α*-hydroxyallene **94a/b** retained the formation of the 2,5-dihydrofuran by **95** in good yield. Here, the sterically challenging allene reacted sluggishly and gave the dihydrofuran a lower yield, accompanied by several side products. The low reactivity of alkene **92** led to the utilization of the electron-rich alkyne (Scheme 13B) for the epoxidation reaction, producing oxirane **97** (1:1 mixture of diastereomers) with a 79% yield. Later, a stereoselective hydroxyl allene scaffold **98** was generated and subjected to a cycloisomerization reaction with 1 mol% of $AuCl_3$, which ended with 89% of bicyclic dihydrofuran **99** with concomitant acetal cleavage. Next, the oxidation of the primary hydroxyl in the Pinnick oxidation condition gave a better carboxylic acid yield (35% over 2 steps). Finally, acidic cleavage of the Boc group **99** afforded the bicyclic furanomycin derivative **100** as a 1:1 mixture of diastereomers.

Later, in 2013, the same group expanded the gold-catalyzed cycloisomerization of *α*-hydroxyallene strategy towards the first synthesis of the azafuranomycin analogs (*αS*, 2*R*)-(2,5-dihydro-1*H*-pyrrol-2-yl)glycine **106a/b** in 13 linear steps with an overall yield of 2.4% starting from the Cbz-protected(*R*)-Garner aldehyde **101** (Scheme 14). [37] The vital step, gold-catalyzed cycloisomerization of *α*-amino allenes **104a/b** to dihydropyrroles **105a/b,** gave a good yield. As described in Scheme 13, dihydropyrroles **105a/b** were converted into respective aza-furanomycin **106a/b** with a higher yield.

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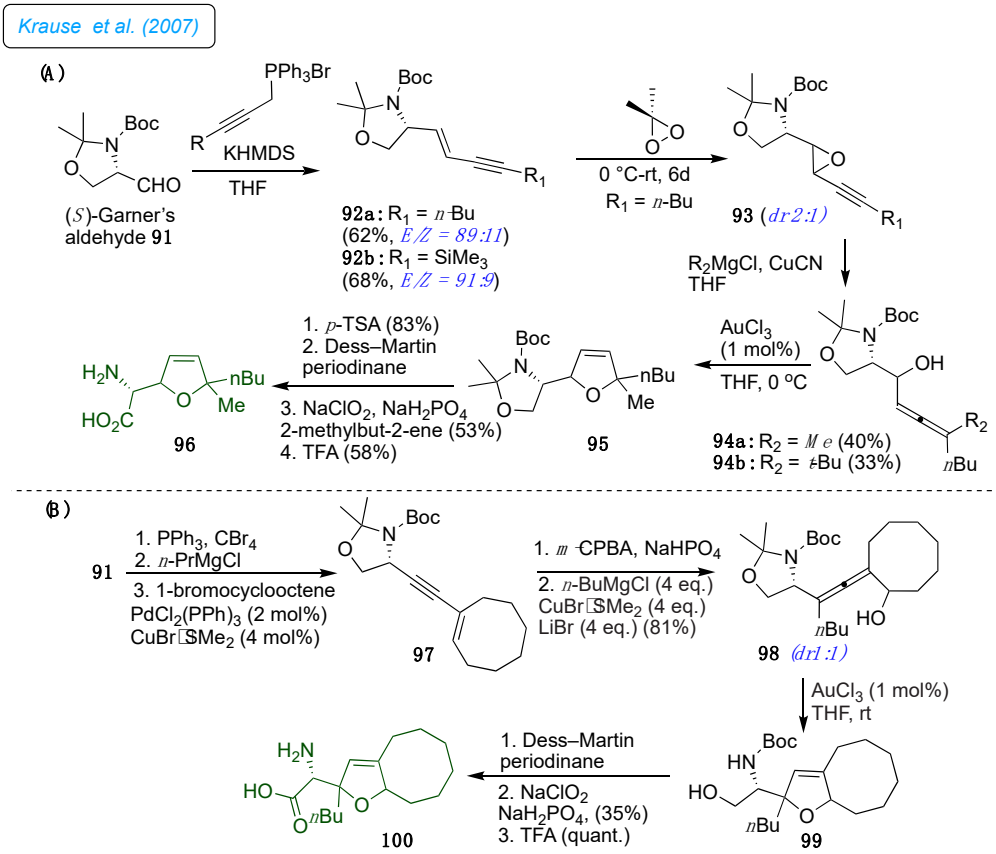
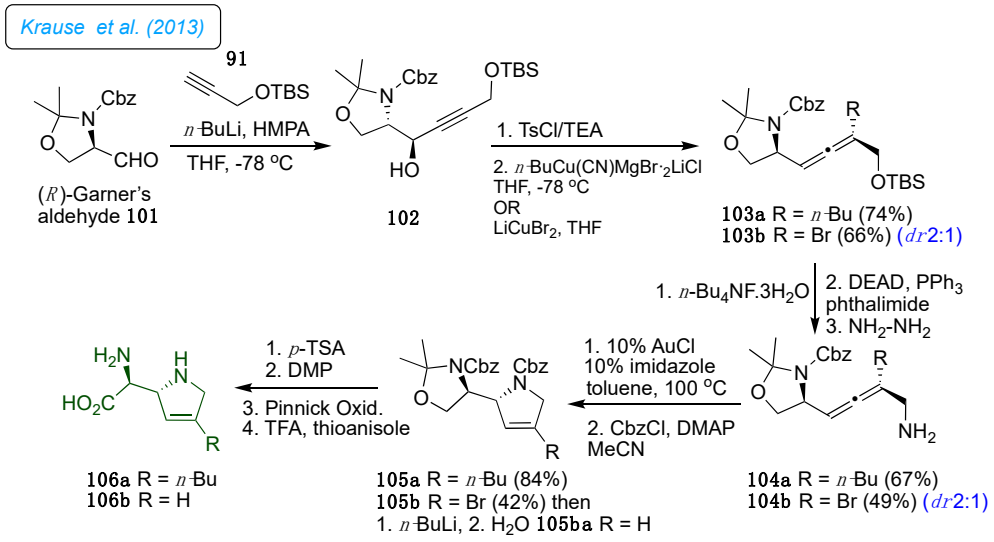


Scheme 13. Synthesis of furanomycin **96** and **100** analogs from *S*-Garnaldehyde **91**.



Scheme 14. Synthesis of aza-furanomycin **106a** and **106b** analogs from *R*-Garnaldehyde.

Chattopadhyay *et al.* have demonstrated the synthesis of optically pure nor-furanomycin from Garner's aldehyde **53** (Scheme 15).[38] Thus, the alcohols **107a** and **107b** obtained by Grignard reaction from Garner's aldehyde **53** yielded the diastereomers in a 3:7 ratio, unfavorable for the natural furanomycin 1. The treatment of allyl bromide with *syn*- and *anti*-diastereomers provided a corresponding separable mixture of allyl ethers. Distinctly, the critical ring-closing metathesis reaction of related allyl ethers worked well, resulting in the dihydrofuran derivatives **108a** and **108b,** respectively, in good yields. The oxazolidine unit in both isomers was removed to *N*-Boc-protected amino alcohols. Jones' oxidation of alcohols was carried out under biphasic conditions, which was afforded *N*-Boc-protected norfuranomycin derivatives **109a** and **109b**. This methodology further

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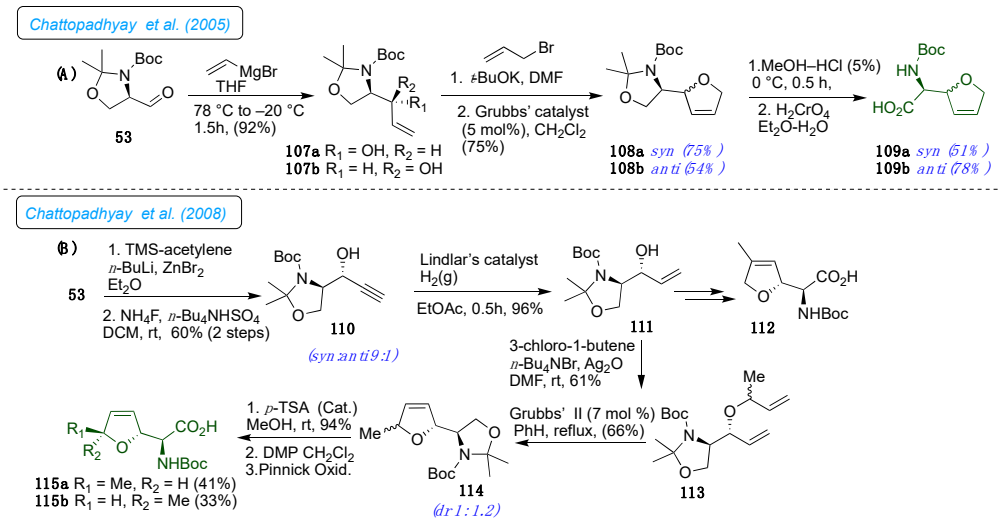
extended for the synthesis of dihydro furanylglycine, furanyl glycine, furanyl alanine, and homo-furanyl alanine derivatives from enantiomerically pure aldehydes derived from the natural amino acids such as serine, aspartic acid, and glutamic acid.



Scheme 15. The synthesis of NHBoc-protected furanomycine **115a/b** and norfuroanomycin **109a/b** from *R*-Garner's aldehyde.

On a similar line, in 2008, the same group demonstrated the synthesis of N-protected derivatives of *L*-(+)-furanomycin **1** and its 5′-*epi*-furanomycin **4** and 4-methyl norfuranomycin **112** from D-serine as a chiral pool through a critical ring-closing metathesis (RCM).[39] The linear concise eight-step synthesis of the *N*-Boc L-(+)-furanomycin **115a** was achieved in an overall yield of 9% from Garner's aldehyde **53**. The simple and short methodology was developed from a common intermediate for the syntheses of the *N*-protected derivatives of 5′-*epi*-furanomycin **115b** and 4-methyl norfuranomycin **112** (Scheme 15). Adding lithium trimethylsilyl acetylide to Garner's aldehyde **53** made the **110** a separable mixture in *syn: anti* 9:1. After deprotection of *syn*-propargyl alcohol **110** and partial hydrogenation of the acetylene group afforded a common intermediate, allyl alcohol **111**. Ensuing alkylating of the **111** with 3-chloro-1-butene with Ag_2O afforded a mixture of dienes **113** in moderate yield. Then, employing RCM protocol on mixture **113** delivered the desired oxazolidine rings as an inseparable diastereomeric mixture (1:1.2) **114**. Further, deprotection and oxidation of corresponding alcohols to acids afforded **115a** and **115b** in a combined 74% yields. The HPLC separation provided the *N*-Boc derivative of *L*-(+)-furanomycin **115a** as a major isomer, reflecting that the diastereoselectivity in the RCM reaction favored the *trans*-isomer. Correspondingly, allyl alcohol **111** was also utilized to synthesize the *N*-Boc derivative of 4-methyl norfuranomycin **112**—alkylation with methallyl bromide, followed by RCM, sequential deprotection, and oxidation procedures.

Vedejs *et al.* developed the palladium-catalyzed coupling of an aziridinylzinc chloride intermediate with alkenyl and aryl halides with the retention of aziridine stereochemistry (Scheme 16).[40] The synthesis of protected 5,5-dimethyl furanomycin **122** was achieved to demonstrate the protocol's potential. The stannylated aziridine **116** and iodoacrylate **117** afforded coupled product **118** under standard conditions of the Negeshi coupling. The Grignard addition on **118** afforded the tertiary alcohol **119**, followed by acid-catalyzed aziridine cleavage, providing dihydrofuran **120**. The deprotection of the trityl group, subsequent protection of amine as Boc derivative, and benzyl deprotection under Na/NH_3 reduction furnished primary alcohol **121**. The primary alcohol **121** was treated with Dess-Martin periodinane, followed by Pinnick oxidation, which produced protected 5,5-dimethyl furanomycin **122**.

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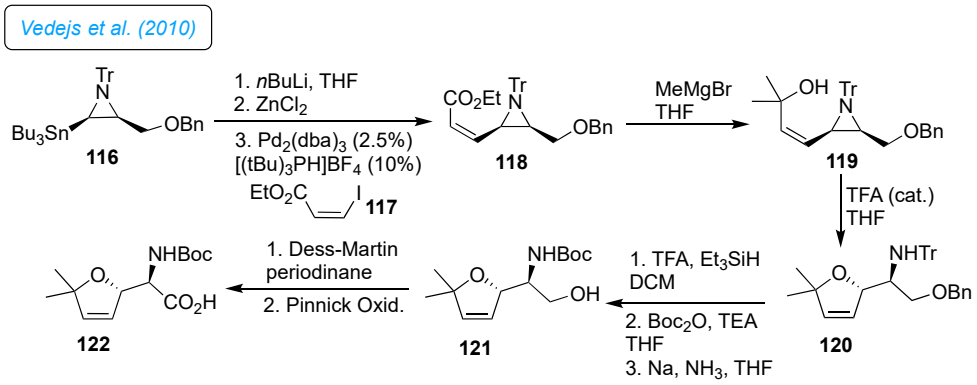
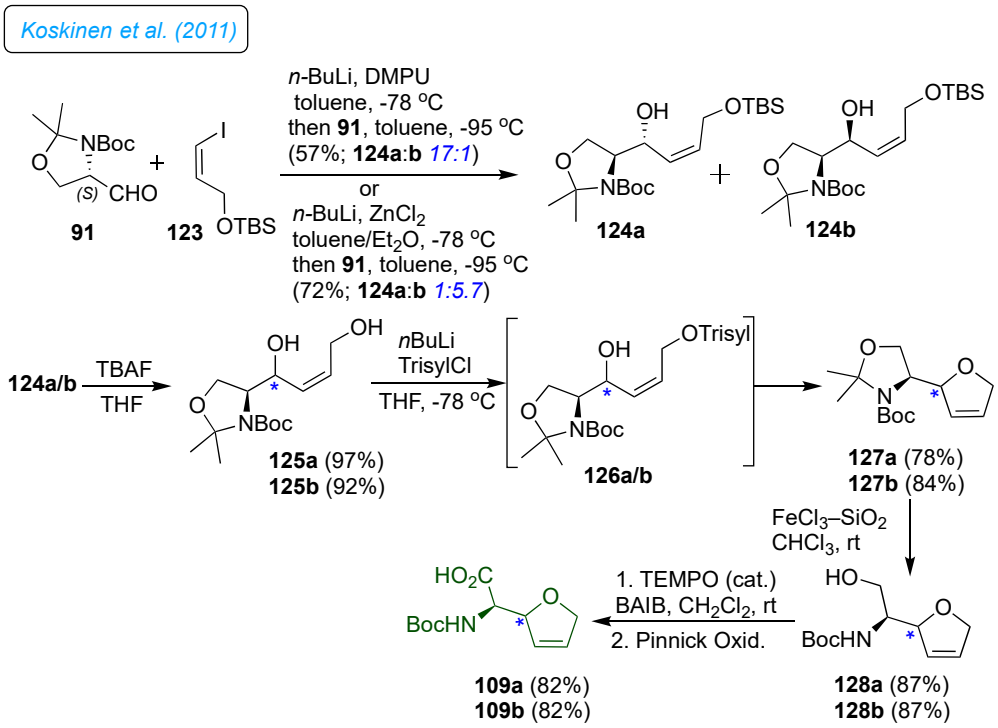


Scheme 16. The synthesis of analogue of furoanomycin **122** from chiral aziridine **116**.



Scheme 17. The synthesis of NH-Boc-protected norfuroanomycin **109a/b** from *S*-Garnaldehyde **91**.

Koskinen *et al.* utilized Garner's aldehyde as a chiral precursor for synthesizing Boc-protected *epi*-norfuranomycin **109a** and **109b** isomers.[41] The alcohols **124a** and **124b** were prepared by coupling **91** with vinyl iodide **123** (Scheme 18). Deprotection of the TBS ethers separately with tetrabutylammonium fluoride in THF provided the diols **125a** and **125b**. Then, In the critical step, both diols were subjected independently to the cyclization reaction through the in-situ formation of sulfonate **126a/b,** which led to the 2,5-dihydrofuran **127a and 127b,** respectively. In the next step, the *N, O*-acetal was removed with $FeCl_3$ adsorbed on silica in $CHCl_3$ to provide primary alcohols **128a** and **128b** in excellent yields. Finally, oxidation of amino alcohols with TEMPO/BAIB and further oxidation to acids gave target molecules **109a** and **109b**.

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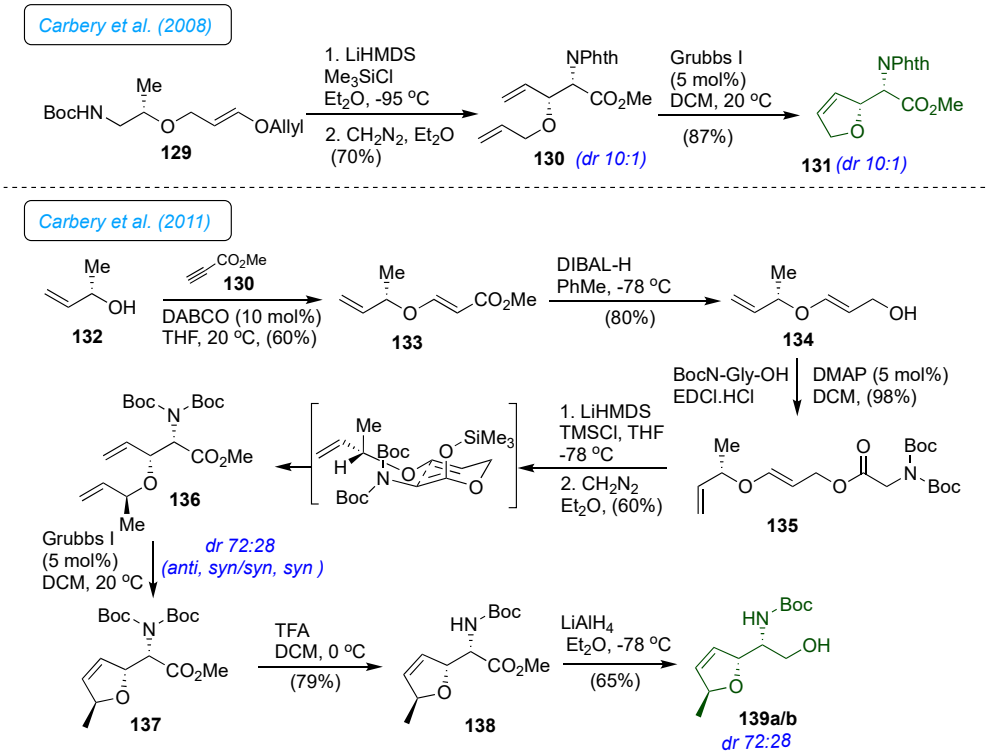

Scheme 18. The synthesis of intermediate of furanomycin **139a/b** from (*S*)-but-3-en-2-ol.

Carbery *et al.* utilized the Ireland-Claisen [3,3]-sigmatropic rearrangement of an allylic glycinate **135** bearing a remote chiral enol ether to synthesize natural antibiotic **1** (Scheme 19).[42] The synthesis started from the *oxy*-Michael reaction of chiral allylic alcohol **132** with methyl propiolate **130** catalyzed by DABCO to provide vinylogous carbonate **133**. DIBAL-H mediated reduction of the ester and consequent rapid EDCl mediated coupling of **134** with di-Boc-glycine afforded appropriate allylic glycinate **135**. The Ireland-Claisen [3,3]-sigmatropic rearrangement of an allylic glycinate **135** bearing a remote chiral enol ether afforded *syn*-β-alkoxy α-amino ester **136** as two inseparable diastereomers in a ratio of *anti, syn*/*syn, syn* = 72:28. Subsequent ring-closing metathesis reaction of **136** with Grubbs Ist catalyst gave the cyclic olefin **137**. NOE experiments confirmed the formation of dihydrofuran **137** in a stereo-controlled manner. The mono-Boc deprotection of **137** was achieved with TFA to afford **138**. The diastereomeric mixture of **139a/b** was achieved through LAH-mediated reduction of ester **138**. The formal total synthesis of furanomycin **1** has been reported.

Ha *et al.* utilized chiral aziridine to synthesize *L*-(+)-furanomycin **1** and its analogs (**Scheme 20**).[43] The synthesis started from the stereoselective Pd-catalyzed etherification of 3-hydroxyalkyl aziridine **140,** which provided a diastereomeric mixture of **141a/b** (*dr* 39:61). The RCM on **141a/b** and chromatography separation gave **142**. The identification of the configuration of two diastereomers was confirmed by NOE experiments of corresponding 5′-methyldihydrofuran fused oxazolidin-2-one **143** as a major product. The α-methylbenzyl group of the oxazolidine-2-one **143** was removed by treatment with Na and liq.NH_3. Subsequent hydrolysis of the oxazolidine-2-one, followed by Boc-protection, gave *N*-Boc-amino alcohol. Further, alcohol oxidation provided **144,** and *N*-Boc deprotection provided furanomycin **1**. For the synthesis of norfuranomycin **6**, the allylic alcohol **140** was protected as allyl ether **145**. Following the similar reaction sequences described for the synthesis of furanomycin **1**, the synthesis of *N*-Boc-protected norfuranomycin **109a** was accomplished.

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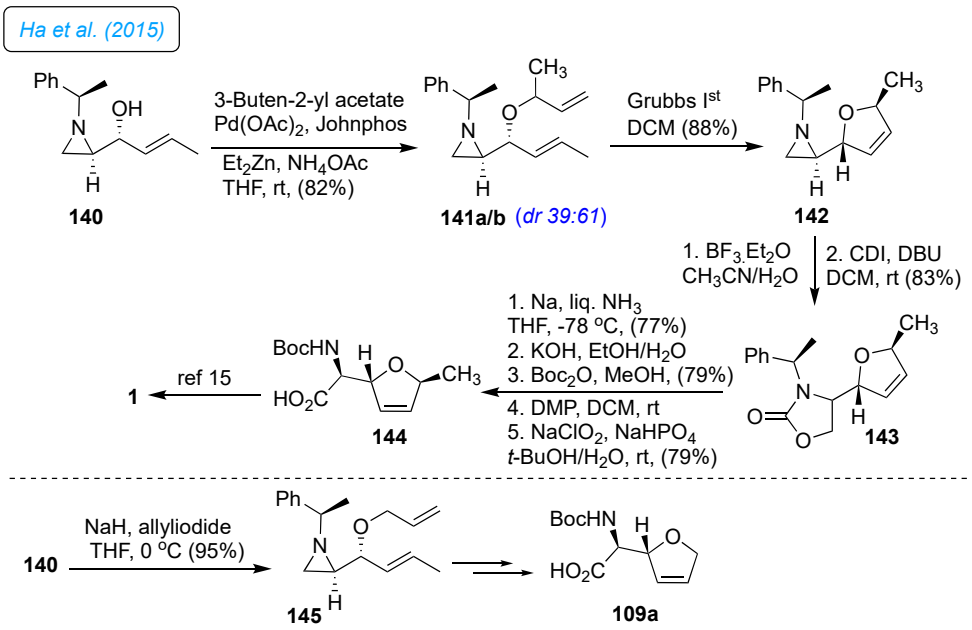
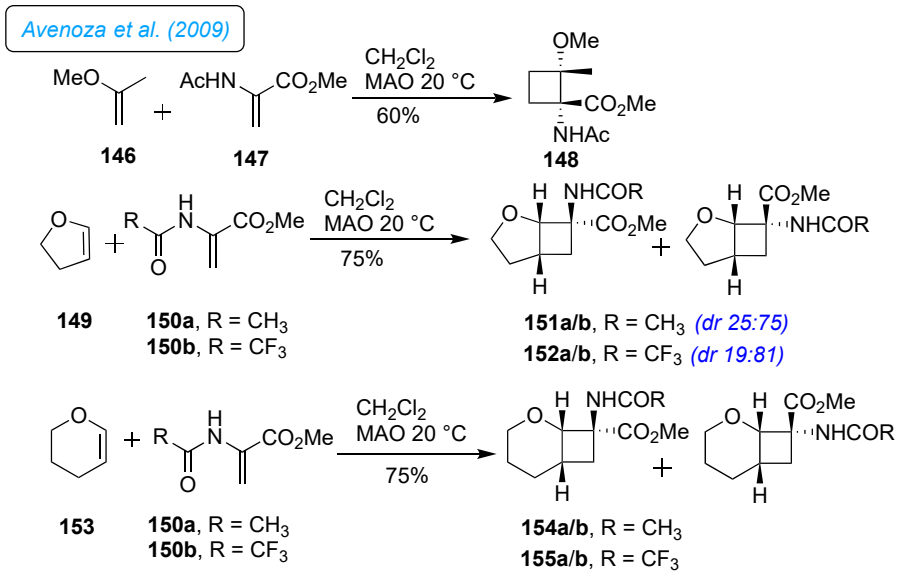


Scheme 19. The synthesis of analogue of furoanomycin **122** from chiral aziridine **116**.



Scheme 20. The synthesis of cyclobutane α-amino acid derivative analogs of furanomycin from acylaminoacrylates and cyclic vinyl ethers.

Furanomycin **1** is an important amino acid antibiotic that has led to the synthesis of numerous analogs; on the same line, cyclobutane α-amino acids are crucial targets in organic synthesis. In this context, Avenoza *et al*. established a Michael-Dieckmann process and a stereoselective Michael-aldol methodology for synthesizing cyclobutane amino acid analogs. [44,45] The same strategy was extended for the synthesis of 2-oxabicyclo[3.2.0]heptane as distinctive conformationally restricted dihydronorfuranomycin analogs via stereoselective Michael-aldol process with 2,3-dihydrofuran and 2-acylaminoacrylates derivatives (Scheme 20). [46] The protocol was primarily examined with [2+2] cycloaddition reaction of the 2-methoxy-propene **146** as a donor alkene and methyl 2-acetamidoacrylate **147** as an acceptor alkene in the presence of Lewis acid methyl aluminoxane (MAO) in methylene chloride at 20 °C which led to a substituted single isomer of cyclobutane **148** in 60% yield. The bulky aluminum-derived Lewis acid MAO obtained this exclusive selectivity in the cycloaddition reaction. In support, the 2D NMR experiments determined the stereochemistry of the newly generated structure **148**. To extend the scope of the reactivity of alkenes with different cyclic

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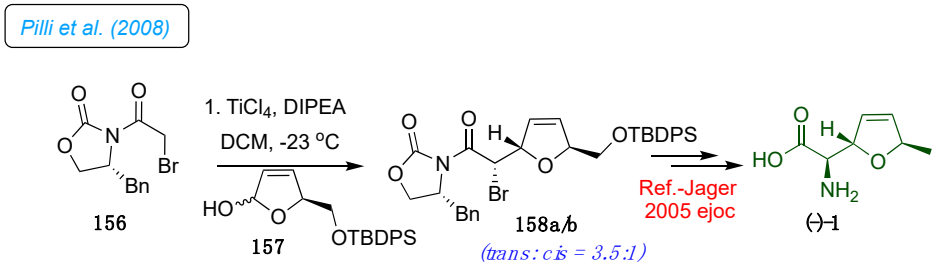
vinyl ether, 2,3-dihydrofuran **149** and 3,4-dihydro-2*H*-pyran **153** were elaborated under the optimized reaction conditions. Therefore, the methyl 2-acetamidoacrylate **150a** reacted with 2,3-dihydrofuran **149** and 3,4-dihydro-2*H*-pyran **153,** resulting in a diastereomeric mixture of 2-oxabicyclo[3.2.0]heptanes core **151a/b** (*dr* 25:75) and 2-oxabicyclo-[4.2.0]octane core **154b** as a significant isomer. The same reaction applied to alkene acceptor trifluoroacetamidoacrylate **150b** with 2,3-dihydrofuran **153** using MAO enhanced the selectivity and afforded **152a/b** (*dr* 19:81) in 75% yield.

Meanwhile, the addition of **153** made **155b** a significant product. Conformational studies of cyclobutane dihydronorfuranomycin analogs **151a** and **152b** were conducted to understand the interesting dynamic properties in the solution. Both compounds were found to have relatively rigid conformations.

Pilli et al. developed the stereoselective addition of chiral titanium enolates to 5-substituted five-membered oxocarbenium ions, as outlined in Scheme 21.[47] The methodology application was elaborated to synthesize key intermediate **158** in a diastereoselective manner from γ-lactols **157** derived from (*S*)-glutamic acid. After desilylation of **158a/b** with aqueous HF/CH_3CN and $LiBH_4$ reduction, it allowed the efficient preparation of the corresponding *trans*-2,5-disubstituted tetrahydrofuran diols with the recovery of the chiral auxiliary. The bromo derivative *trans*-**158a** is a critical intermediate for the preparation of (-)-furanomycin **1**, the enantiomeric form of the isoleucine antagonist (+)-furanomycin **1** (Scheme 21). Therefore, employing the protocol developed by Jager *et al.* could synthesize both isomers of **1**.[18]



Scheme 21. The synthesis of (-)-furoanomycin **1** from chiral auxiliary **158a/b.**

Bartoli and co-workers reported a new method for synthesizing the (*R*)-Garner-type aldehyde **161** and adding a vinyl organocerium compound to provide intermediate *syn*-**162a** for (+)-furanomycin synthesis.[48] Thus, the hydroxyl group of L-serine was protected with silyl ether (Scheme 22). Reduction of the ester to the corresponding amino alcohol and *N*-Boc protection of this amino alcohol afforded the desired intermediate **160** in high yield. The cyclohexylidine protection of amino alcohol **160** and cleavage of the silyl ether moiety, followed by Parikh–Doering oxidation of primary alcohol to optically pure stable aldehyde **161**. A vinyl cerium reagent was diastereoselectively added to aldehyde **161** to get the carbon framework in a mixture of **162a/b** (*dr* 82:18). Selective deprotection of cyclic ketal of **163a/b** served the valuable building blocks **163a/b** in the syntheses of naturally occurring and pharmacologically exciting compounds. [16,49]

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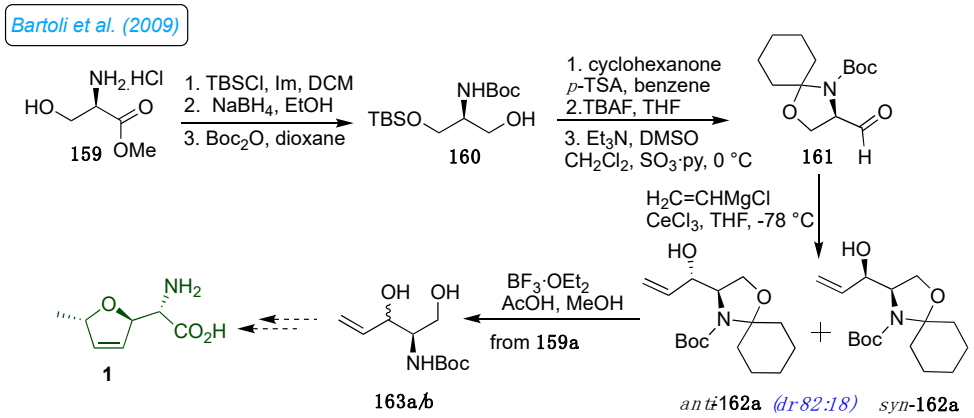

Scheme 22. The synthesis of essential precursor **161** for the synthesis of furanomycin.

5. Conclusions and Outlooks:

Medicinal chemistry employs powerful tools such as total synthesis, semi-synthesis, and de novo synthesis to iteratively optimize natural products and create patentable drug molecules with enhanced pharmacokinetic, physicochemical, and toxicological properties. Medicinal chemistry programs can uncover pathways to future therapies like reverse genetics by carefully selecting natural antibiotic lead structures and valid targets. In silico modeling of the binding of these privileged structures to their targets enables the conception of less complex molecules with improved properties, which can serve as scaffolds for medicinal and combinatorial chemistry. Medicinal and combinatorial organic chemists have devised numerous effective methods to produce innumerable novel and diverse molecules for human health care. The chiral pool, primarily α-amino acids, remains crucial for targeting molecules in chiral synthesis. The efforts outlined in this review on synthesizing natural products should further fortify and accelerate translational research using chiral building blocks, offering new biomedical breakthroughs and disease treatments.

The present review outlines synthetic studies on the antibacterial natural product furanomycin **1** and its analogs. Furanomycin **1** prevents the formation of isoleucyl–tRNA in *E. coli* while sparing other aminoacyl–tRNAs. Aminoacyl–tRNA synthetases are vital in all organisms and are being explored as new targets in bacterial protein synthesis. Combined drug-like features of furanomycin **1,** such as polarity, sufficient solubility, and moderate structural complexity, make it attractive to medicinal chemists, in addition to its antibacterial activity in vitro and in vivo. Several synthetic approaches towards **1** have been developed, some of which consist of up to 20 steps. Many syntheses have started from chiral templates such as D-glucose, D-ribose, D-glucosamine, L-xylose, D-mannitol, and dimethyl-L-tartrate. Other approaches have used amino acids like serine, glycine, or furanes as starting points. Approaches starting from amino acids were captivating; with six to seven steps, they were short and flexible enough to access isomers and close congeners to evaluate the SAR rapidly. First, it was necessary to learn which structural parts in furanomycin were essential for activity and which parts could be removed or modified. Since norfuranomycin had been reported to exhibit antibacterial activity (MIC) against some Gram-negative bacteria, straightforward protocols toward derivatives of **1** were envisaged. To gain rapid insight into SARs, control of diastereoselectivity was considered more important than controlling the absolute configuration. A ring-closing metathesis was used to construct the dihydrofuran ring. Only L-(+)-dihydrofuranomycin **6** showed borderline MIC (32-64 mg/mL) against *S. aureus,* and the chiral carbon-analog **10** exhibited weak antibacterial activity (4 mg/mL) against an efflux-pump-deficient *E. coli.*

In summary, the chemical synthesis of both natural and non-natural versions of furanomycin could offer valuable lead compounds for studying protein translation processes and modification. Creating modified non-proteinogenic amino acids could provide new insights into protein function, expand the genetic code in organisms, and produce diverse peptide libraries for drug discovery.[50,51] This review will provide an initial perspective on synthesizing furanomycin and its modified compounds.

Author Contributions: Author Contributions: "Conceptualization, R.R; visualization, R.R.; writing—original draft preparation, R.R., and R.M.; writing—review and editing, R.R. and R.M.; supervision, R.R. and R.M.; All authors have read and agreed to the published version of the manuscript."

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Conflicts of Interest: The authors declare no conflicts of interest.

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