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Straightforward Syntheses of Furanomycin Derivatives and their Biological Evaluation

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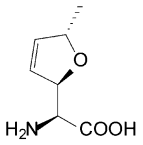
Abstract—Several types of furanomycin analogues were synthesized and investigated with respect to their antibacterial activity. Two different synthetic pathways were developed, based on aldol reactions/ring closing metathesis and an ester enolate Claisen rearrangement. Only the natural product and its desmethyl derivative showed antibacterial activity, pointing towards a narrow structure–activity relationship.

Introduction

In 1967, Katagiri et al. observed that metabolites of the fungus *Streptomyces threomyceticus* L-*803* inhibit the growing of Coliphage T2.[1] The active compound was isolated from the fermentation broth and was called furanomycin (**1**). Subsequent biological studies indicated that this unusual amino acid suppresses the growing of several types of micro-organisms such as *Echerichia coli*, *Bacillus subtilis* and several *Shigella*- and *Salmonella* strains. The absolute configuration was determined as α*S*,2*R*,5*S* via synthesis of furanomycin starting from glucose,[2] and by an X-ray structure of the *N*-acetyl derivative.[3]



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Labeling experiments indicated that furanomycin is formed via a polyketide pathway starting from two acetate and one propionate subunit.[4] The oxygen atom is introduced via epoxidation and the furane ring is formed by an intramolecular epoxide opening.[5]

The antibiotic activity of furanomycin results from an incorporation of this amino acid into bacterial proteines instead of isoleucine.[6] Therefore their biological activity is reduced in the presence of isoleucine.[1] Investigations in *E. coli* indicated that furanomycin hampers the formation of isoleucyl-*t*-RNA, while other aminoacyl-*t*-RNA are not affected.[7] Obviously isoleucyl-*t*-RNA synthetase accepts **1** as a substrate besides isoleucine, which explains the incorporation of **1** into peptides and proteins. This fact is quite surprising, because *t*-RNA-synthetases in general show a high substrate specificity. NMR studies reveal that the conformation of the enzyme bound furanomycin is very similar to the isoleucine analogue, although the structure of these two amino acids is different.[8] The δ-methyl group of the Ile plays a dominant role for substrate recognition and the differentiation between Ile, Leu and Val. Probably the 5-methyl group of **1** fits into the same binding pocket of the enzyme. The mechanism of action is highly interesting from a pharmaceutical point of view, and therefore several synthetic approaches towards this antibiotic were developed. Most syntheses are starting from carbohydrates,[9] other approaches are using tartaric acid,[10] serine,[11] or furanes,[12] giving rise to **1** in 8–20 steps.

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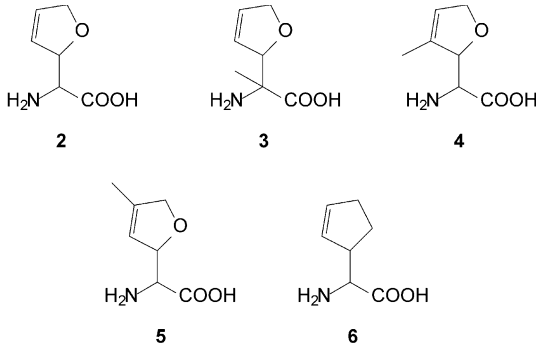
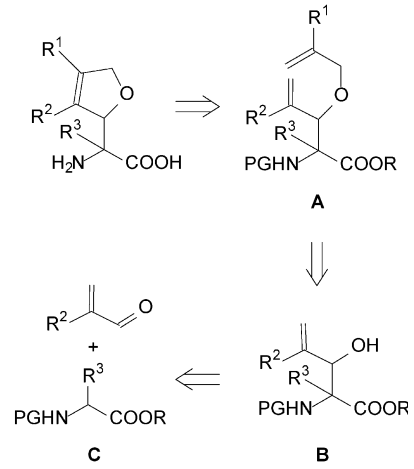
We were interested to see which structural parameters are definitely necessary for biological activity and which ones can be removed or modified. Therefore, our aim was to develop straightforward protocols towards derivatives without the 5-methyl group (norfuranomycin **2**) which is known to be also biologically active,[13] as well as the corresponding carba analogue (**6**) and hydrogenated products. Further derivatives should bear the methyl group at other positions (**3**–**5**), including the α position. As far as possible, we focused on a diastereoselective synthesis of the correct α,2 stereorelationship, without controlling the absolute configuration.



We decided to use the ring closing metathesis (RCM) for the construction of the dihydrofurane ring (Scheme 1). The required substrate **A** for the RCM should be accessible via *O*-allylation of β-hydroxyamino acid **B**, generated by aldol addition of a suitable protected amino acid derivative **C** (PG: protecting group) and an α,β-unsaturated aldehyde.

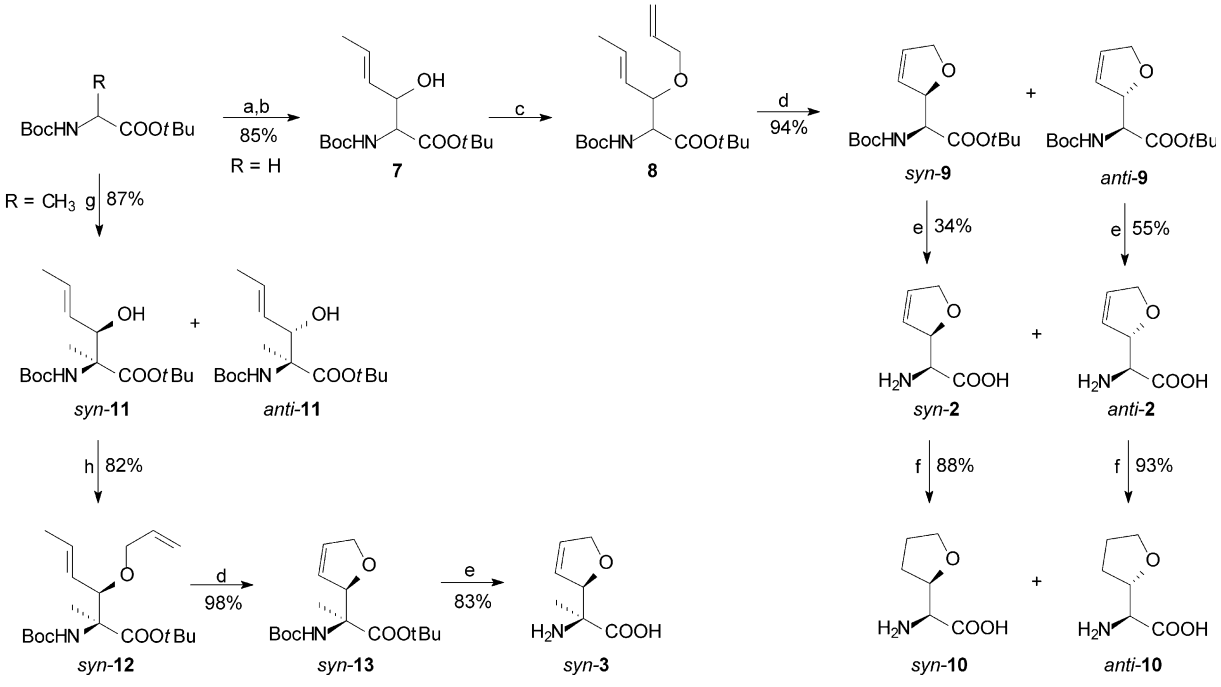


Scheme 1. Retrosynthetic analysis of furanomycin derivatives.

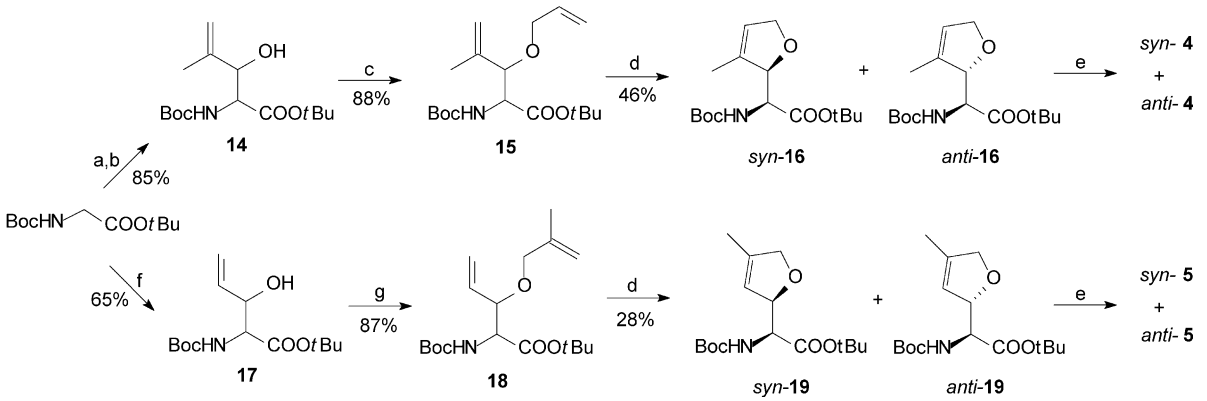
Results and Discussion

An overview over the synthetic steps carried out towards norfuranomycin and the α-methylated derivative is given in Scheme 2.

Boc-protected *t*-butylesters were chosen as starting materials for an easy simultaneous deprotection at the end of the synthesis. For the synthesis of norfuranomycin **2** the corresponding glycine ester was reacted in an aldol reaction with crotonaldehyde giving rise to **7** as a 1:1 diastereomeric mixture in 71% yield. The yield could be increased to 85% by using the titanium enolate, while the *anti* product was formed preferentially under these conditions (*syn*/*anti* 1:2). The subsequent



Scheme 2. Synthesis of **2**,**3** and the saturated derivatives **10**. Reagents and conditions: (a) 1. 2.5 equiv LDA, THF,−78 °C; 2. 1.5 equiv $TiCl(OiPr)_3$. (b) 3 equiv crotonaldehyde, THF,−78 °C, 3 h. (c) 1.5 equiv Allyl ethyl carbonate, 2.5 mol% $(allylPdCl)_2$, 11 mol% PPh_3, 50 °C, 3 d. (d) 2.5 mol% $(Cy_3P)_2Cl_2Ru$=CHPh, CH_2Cl_2, 40 °C, 16 h. (e) 4 M HCl/ dioxane, 16 h. (f) H_2, Pd/C, CH_3OH, 12 h. (g) 1. 2.5 equiv LDA, THF,−78 °C, 2. 3 equiv crotonal-dehyde, THF,−78 °C, 3 h. (h) 1.3 equiv KO*t*Bu, 2 equiv allyl bromide, DMF, 0 °C.



Scheme 3. Synthesis of **4** and **5.** Reagents and conditions: (a) 1. 2.5 equiv LDA, THF, −78 °C; 2. 1.5 equiv $TiCl(OiPr)_3$. (b) 3 equiv methacrolein, THF, −78 °C, 3 h. (c) 1.3 equiv KO*t*Bu, 2 equiv allyl bromide, DMF, 0 °C. (d) 2.5 mol% $(Cy_3P)_2Cl_2Ru=CHPh$, CH_2Cl_2, 40 °C, 3 d. (e) 4 M HCl/dioxane, 4 h. (f) 1. 2.5 equiv LDA, THF, −78 °C, 2. 3 equiv acrolein, THF, −78 °C, 3 h. (g) 1.3 equiv KO*t*Bu, 2 equiv methallyl bromide, DMF, 0 °C.

O-allylation was carried out under very mild conditions using a palladium catalyzed version.[14] Ring closing metathesis using Grubb's catalyst[15] provided **9** in excellent yield as a mixture of diastereomers, which could be easily separated by flash chromatography. Deprotection provided the diastereomerically pure norfuranomycins (**2**), while subsequent catalytic hydrogenation gave rise to the saturated derivatives *syn*- and *anti*-**10**. The *syn*-/*anti*-configuration was determined by comparison of the NMR data of **10** with those of natural norfuranomycin.

The α-methylated derivative **3** was obtained by the same protocol. The diastereomers could be separated on the aldol stage, and only the *syn* product **11** was converted further. In this case, the *syn*-configuration was determined by X-ray structure analysis (s. supplementary material). The palladium catalyzed allylation provided *syn*-**12** in 52% yield, while an allylation with allyl bromide in the presence of potassium *tert*-butylate resulted in a much higher yield. RCM and deprotection gave syn-**3** in high yield.

The 3- and 4-methylated derivatives **4** and **5** were prepared in analogy to **2** and **3** (Scheme 3). Aldol addition using 2-methacroleine provided **14** in high yield (*syn*/*anti* 1:1.4). Both allylation protocols were suitable for the conversion into **15**, while allylbromide (88% yield) was superior to the palladium catalyzed version (70% yield). In contrast to the unbranched furane rings, the RCM became problematic with the substituted derivatives. The yield of 46% could not be increased by prolonged reaction times (7 days) or higher temperatures (60 °C). The deprotection of **16** was also problematic. Under the acidic cleaving conditions decomposition was observed and we were not able to obtain analytically pure **4**. The crude product was nevertheless subjected to biological evaluation.

The situation with **5** was comparable. Our first attempt started from **7**, which was allylated with methallylbromide (86% yield). The yield in the subsequent RCM could not be increased to more than 6%. Therefore, we decided to use acroleine in the aldol step, although acroleine has a much higher tendency to polymerisation. This could explain the lower yield of **17** (*syn*/*anti* 1:1) in the first step. The *O*-allylation worked well, but the yield in the RCM was even lower as in the previous case. Interestingly, the cyclization products were formed as a *syn*/*anti* mixture of 2.5:1, while the aldol reaction provided a 1:1 mixture. Obviously, the *syn* stereoisomer gave a higher yield in the RCM. As usual the isomers could be separated at this stage. A comparable acid sensitivity was found also with these derivatives **19**, and the deprotected amino acids **5** had to be investigated as crude product.

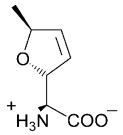
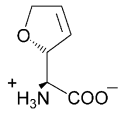
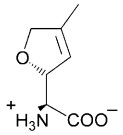
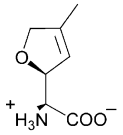
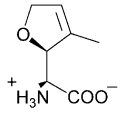
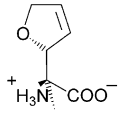
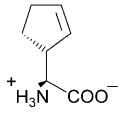
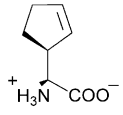
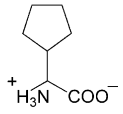
For the synthesis of cyclopentenylglycine (**6**), which is also known as an isoleucine-antagonist,[16] we chose another strategy. Cyclopentenylglycine was obtained by a modified version of the ester enolate Claisen rearrangement, developed in our laboratory[17] (Scheme 4).

Coupling of cyclopentenol with Boc-glycine gave rise to ester **20**,[18] which was subjected to a chelate Claisen rearrangement. Deprotonation with LDA occurs first at the acidic amide functionality, while a second equivalent base generates the ester enolate. Addition of zinc chloride results in the formation of a chelated enolate, which shows an increased stability towards decomposition. Therefore, the enolates can be warmed up to room temperature, conditions under which a Claisen rearrangement occurs, giving rise to protected cyclopentenyl glycine **21** in excellent yield. In principle, only the Boc-protecting groups had to be removed to obtain the target amino acid **6**. Unfortunately, in contrast to the furane derivatives, the diastereomers (*syn*/*anti* 8:2) could not be separated at this stage. Therefore, the isomeric mixture of **21** was converted into the corresponding iodolactones[19] *syn*- and *anti*-**22**, which could be separated via flash chromatography. Cleavage of the iodolactones with zinc in ethanol provided the diastereomerically pure cyclopentenyl glycine derivatives **21**, which were deprotected towards the required amino acids *syn*- and *anti*-**6**. The hydrogenated product **23** was directly obtained from **21**.

Biological tests

The growth inhibitory–activity of the furanomycin derivatives against several microorganisms was evaluated (Table 1). Furanomycin was used as a reference. The results obtained served to see general tendencies in

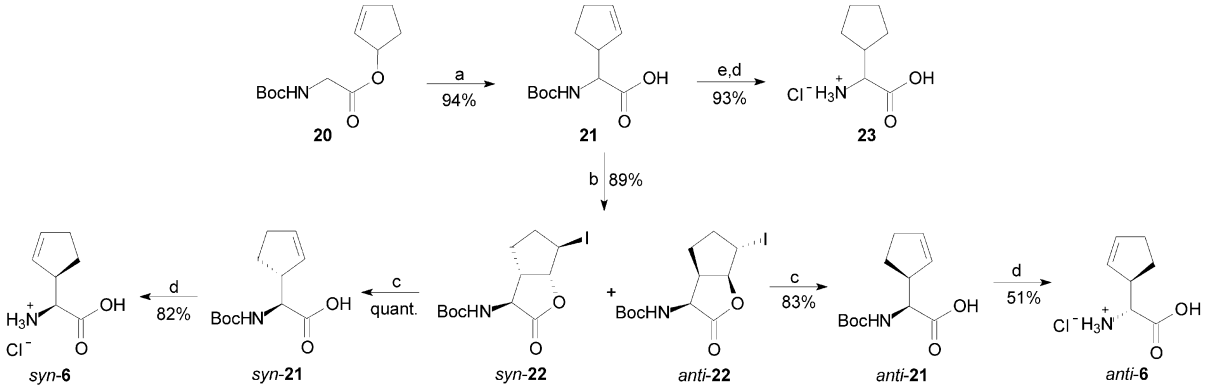
Table 1. Growth inhibition of furanomycin derivatives against eubacteria (MIC determination [μg/mL])

Derivative	Structure	*Staphylococcus aureus* 133	*Staphylococcus aureus* 44	*Proteus vulgaris* 1017	*Klebsiella pneumoniae* 8085	*Escherichia coli* N.	*Escherichia coli* A261
1		8	8	> 32	> 32	2	4
2		4	16	> 32	> 32	> 32	> 32
3		> 32	> 32	> 32	> 32	> 32	> 32
4		> 32	> 32	> 32	> 32	> 32	> 32
5		> 32	> 32	> 32	> 32	> 32	> 32
6		> 32	> 32	> 32	> 32	> 32	> 32
7		> 32	—		—	—	—
8		> 32	—		—	—	—
9		> 32	—	—	—	—	—

the structure–activity relationship. Removal of the methyl group (norfuranomycin) had no significant effect on the activity versus *S. aureus*, but versus *E. coli*. Obviously, this methyl group is not absolutely necessary for the biological activity. Variations of the position of the methyl group abolished activity. Replacing the oxygen in the dihydrofurane ring by carbon also resulted in inactive derivatives.

Experimental

All reactions were carried out in oven-dried glassware (100 °C) under argon. All solvents were dried before use. THF was distilled from sodium benzophenone, dichloromethane and diisopropylamine from calcium hydride. LDA solutions were prepared from freshly distilled diisopropylamine and commercially available *n*-butyllithium solution (15% in hexane) in THF at −20 °C directly before use. The starting materials and the products were purified by flash chromatography on silica gel (32–63 μm). Mixtures of ethyl acetate and hexane were used as eluents. TLC: commercially precoated Polygram© SIL-G/UV 254 plates (Macherey-Nagel). Visualization was accomplished with UV light, iodine, and potassium permanganate solution. ^{1}H and ^{13}C NMR: Bruker AC-300 spectrometer. Diastereomeric ratios were determined by NMR and analytical HPLC



Scheme 4. Synthesis of cyclopentenylglycine and derivatives. Reagents and conditions: (a) 1. 2.5 equiv LDA, 1.2 equiv $ZnCl_2$, THF, −78 °C → rt. (b) 1.5 equiv KI, 1.3 equiv I_2, 1.1 equiv $NaHCO_3$, Et_2O, H_2O, rt. (c) 1.3 equiv Zn, H_2O, HOAc, THF, rt. (d) 4 M HCl/dioxane, 5 h. (e) H_2, Pd/C, CH_3OH, 6 h.

using a Knauer Eurosphere column (250 × 4 mm, Si80, 5 μm, flow: 2 mL/min) and a Knauer UV detector.

General procedure for aldol reactions

In a typical experiment a solution of 25 mmol of LDA in 50 mL of anhydrous THF was added slowly at −78 °C under argon to a solution of 10 mmol of *N*-protected amino acid ester in 30 mL of THF. In general, a pale yellow solution was formed. After 10 min a solution of 30 mmol of the aldehyde in 45 mL of THF was added. After 3 h at −78 °C the reaction was quenched with 1N $KHSO_4$ solution . The mixture was diluted with diethyl ether and was allowed to warm to rt. H_2O was added and the layers were separated, the aqueous phase was extracted twice with diethyl ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, and the solvent was evaporated. The crude aldol product was purified by flash chromatography.

General procedure for palladium catalyzed *O*-allylations

Allyl (0.2 mmol) palladium chloride dimer was added to a solution of 1 mmol triphenylphosphine and 15 mmol of allyl methyl carbonate in 15 mL of THF. The clear yellow solution was stirred for 15 min at rt, before 10 mmol of the aldol product was added in 30 mL of THF. The mixture was warmed to rt overnight. The solvent was evaporated, and the crude product was purified by flash chromatography.

General procedure for *O*-allylations using allyl bromide

10 mmol of the aldol product and 20 mmol of the corresponding allyl bromide were dissolved in 30 mL DMF at 0 °C. Subsequently 13 mmol of potassium *t*-butylat were added and the yellow solution was warmed to rt overnight. H_2O was added and after separation of the layers the aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed twice with H_2O, dried over Na_2SO_4, and the solvent was evaporated. The crude product was purified by flash chromatography.

General procedure for ring closing metatheses (RCM)

Grubbs catalyst (0.2 mmol) was added to 10 mmol of the *O*-allylated product in 20 mL of dichloromethane. The dark purple solution was refluxed overnight. The solvent was evaporated, and the crude product was purified by flash chromatography.

General procedure for deprotection

A 4 M HCl (5 mL) solution in dioxane was added to 1 mmol of the metathesis product at 0 °C. The mixture was stirred at this temperature until TLC showed complete removal of the protecting groups. The solvent was evaporated in vacuum and the crude product was dissolved in ethyl acetate. Ether was added to precipitate the amino acid as its hydrochloride. The precipitate was separated by centrifugation and dried in vacuum, before it was used for the biological studies.

Minimal inhibitory concentration (MIC) determination. MIC values were generated using a microdilution technique. A vitamin (thiamine, nicotinic acid, biotin) supplemented minimal medium containing 1% glucose and all amino acids except leucine and isoleucine was used. MIC was read as the lowest concentration of compound that completely inhibited bacterial growth.

***tert*-Butyl 2-(*tert*-butyloxycarbonyl)amino-3-hydroxyhexenoate (7).** Ester **7** was obtained by a slightly modified version of the general procedure for aldol reaction (5 mmol scale). 6 mmol of $ClTi(OiPr)_3$ were added to the lithium enolate, providing a dark red solution of the corresponding titanium enolate, which was reacted with crotonaldehyde. The aldol product was obtained after flash chromatography (hexanes/ethyl acetate, 85:15) as a colorless oil and a mixture of the diastereomers (*syn*/*anti* 1:2) in 85% yield (1.28 g, 4.2 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9H), 1.44 (s, 9H), 1.67 (d, 3H, *J* = 6.4 Hz), 2.35 (s, 1H), 4.17 (m, 1H), 4.36 (m, 0.3H, *syn*), 4.41 (m, 0.7H, *anti*), 5.19 (s, 1H), 5.46 (ddq, 1H, *J* = 15.4, 7.2, 1.5 Hz), 5.70 (dqd, 1H, *J* = 15.3, 6.6, 1.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.7 (q), 28.0, 28.1, 28.2, 28.5 (q), 58.5 (d, *syn*), 59.1 (d, *anti*), 73.1 (d,

anti), 74.0 (d, *syn*), 78.9 (s), 82.3 (s, *anti*), 82.7 (s, *syn*), 128.4, 128.8 (d), 128.9, 129.5 (d), 156.2 (s), 169.9 (s). Anal. calcd for $C_{15}H_{27}NO_5$ (301.38): C, 59.78; H, 9.03; N, 4.65. Found: C, 59.56; H, 8.91; N, 4.62.

***tert*-Butyl 2-(*tert*-butyloxycarbonyl)amino-3-allyloxy-hexenoate (8).** Allylation product **8** was obtained from **7** (2.5 g, 8.3 mmol) following the general procedure for palladium catalyzed allylations. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 98:2) giving rise to **8** as a colorless oil and a mixture of the diastereomers (*syn*/*anti* 1:2) in 55% yield (1.46 g, 4.3 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.41$ (s, 9H), 1.43 (s, 9H), 1.69 (dd, 3H, $J = 6.4$, 1.2 Hz), 3.72 (dd, 1H, $J = 12.9$, 5.9 Hz), 3.94 (ddt, 1H, $J = 12.9$, 5.9, 1.0 Hz), 4.13–4.21 (m, 2H), 5.13 (dd, 1H, $J = 10.3$, 1.6 Hz), 5.14 (d, 1H, $J = 15.4$ Hz), 5.20 (dd, 1H, $J = 17.2$, 1.6 Hz), 5.36 (d, 0.3H, $J = 7.8$ Hz, *syn*), 5.39 (d, 0.7H, $J = 7.8$ Hz, *anti*), 5.70 (dq, 1H,$J = 15.4$, 6.4 Hz), 5.79 (dddd, 1H, $J = 17.0$, 11.3, 11.1, 10.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.5$ (q), 27.8, 28.1 (q), 58.1 (d), 68.9 (d), 79.3 (d), 80.2 (s), 81.4 (s), 116.5 (d), 127.1 (d), 130.5 (d), 134.3 (d), 155.8 (s), 169.5 (s). Anal. calcd for $C_{18}H_{31}NO_5$ (341.45): C, 63.32; H, 9.15; N, 4.10. Found: C, 63.50; H, 9.09; N, 3.99.

***tert*-Butyl *N*-(*tert*-butyloxycarbonyl)-2-(2′,5′-dihydrofuranyl)-glycinate (9).** Cyclization product **9** was obtained from **8** (3.21 g, 9.4 mmol) following the general procedure for ring closing metatheses in 94% yield (2.63 g, 8.8 mmol). The diastereomers could be separated by flash chromatography (hexanes/ethyl acetate, 96:4). ***syn*-9**: colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.39$ (s, 9H), 1.46 (s, 9H), 4.32 (dd, 1H, $J = 9.2$, 2.2 Hz), 4.56 (m, 1H), 4.65 (m, 1H), 5.06 (d, 1H, $J = 9.2$ Hz), 5.22 (m, 1H), 5.73 (m, 1H), 5.93 (dd, 1H, $J = 6.2$, 1.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 27.6$, 27.8, 28.0 (q), 57.1 (d), 76.2 (t), 79.3 (s), 81.9 (s), 86.9 (d), 126.2 (d), 128.2 (d), 155.5 (s), 169.2, (s). Anal. calcd for $C_{15}H_{25}NO_5$ (299.37): C, 60.18; H, 8.42; N, 4.68. Found: C, 60.21; H, 8.28; N, 4.63.

***anti*-9.** Colorless solid, mp. 63 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.31$ (s, 18H), 4.38 (dd, 1H, $J = 9.2$, 3.3 Hz), 4.56–4.61 (m, 2H), 5.05 (m 1H), 5.18 (d, 1H, $J = 8.1$ Hz), 5.73 (d, 1H, $J = 4.4$ Hz), 6.00 (d, 1H, $J = 5.1$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 27.6$, 27.7, 28.1 (q), 57.3 (d), 75.8 (t), 79.5 (s), 81.8 (s), 86.5 (d), 125.4 (d), 128.8 (d), 155.2 (s), 168.8 (s). HRMS (FAB) calcd for $C_{15}H_{26}NO_5$ [$M^+ + H$] 300.1811, found 300.1828.

***syn*-Norfuranomycin hydrochloride (*syn*-2).** Deprotection of *syn*-**9** (300 mg, 1.0 mmol) according to the general procedure provided *syn*-**2** in 34% yield (62 mg, 0.34 mmol) as a colorless solid, mp 190–200 °C. ^{1}H NMR (300 MHz, CD_3OD): $\delta = 4.14$ (m, 1H), 4.59–4.77 (m, 2H), 5.33 (m, 1H), 5.88 (m, 1H), 6.22 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD): $\delta = 62.2$ (d), 77.4 (t), 85.3 (d), 125.9 (d), 132.8 (d). Anal. calcd for $C_6H_{10}NO_3Cl$ (179.60): C, 40.12; H, 5.61; N, 7.80. Found: C, 40.33; H, 5.38; N, 7.79.

***anti*-Norfuranomycin hydrochloride (*anti*-2).** Deprotection of *anti*-**9** (256 mg, 0.8 mmol) according to the general procedure provided *anti*-**2** in 55% yield (85 mg, 0.47 mmol) as a colorless solid, mp 210–212 °C. ^{1}H NMR (300 MHz, CD_3OD): $\delta = 4.21$ (m, 1H), 4.58 (m, 1H), 4.68 (m, 1H), 5.29 (m, 1H), 5.70 (m, 1H), 6.21 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD): $\delta = 57.0$ (d), 77.4 (t), 84.9 (d), 123.8 (d), 133.0 (d), 168.7 (s). Anal. calcd for $C_6H_{10}NO_3Cl$ (179.60): C, 40.12; H, 5.61; N, 7.80. Found: C, 40.07; H, 5.42; N, 7.82.

***syn*-Dihydronorfuranomycin hydrochloride (*syn*-10).** Amino acid *syn*-**2** (30 mg, 0.17 mmol) was dissolved in 5 mL of methanol before Pd/C (10 mg) was added. The hydrogenation was carried out in a Parr apparatus at 40 psi H_2. After filtration of the catalyst and evaporation of the solvent *syn*-**10** was obtained as a colorless solid, mp 216 °C (decomp.). ^{1}H NMR (300 MHz, CD_3OD/D_2O): $\delta = 1.75$ (m, 1H), 1.85–1.91 (m, 3H), 3.73 (dd, 1H, $J = 14.5$, 7.7 Hz), 3.84 (dd, 1H, $J = 14.0$, 6.2 Hz), 3.92 (d, 1H, $J = 4.1$ Hz), 4.31 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD/D_2O): $\delta = 26.1$, 26.2 (t), 57.4 (d), 70.0 (t), 77.6 (d), 172.4 (s). HRMS (FAB) calcd for $C_6H_{12}NO_3$ [$M^+ + H$] 146.1115, found 146.1108.

***anti*-Dihydronorfuranomycin hydrochloride (*anti*-10).** Amino acid *anti*-**10** was obtained according to *syn*-**10** in 93% yield as a colorless solid, mp 226 °C. ^{1}H NMR (300 MHz, D_2O): $\delta = 1.74$–1.90 (m, 3H), 2.03 (m, 1H), 3.52 (d, 1H, $J = 6.0$ Hz) 3.73 (m, 2H), 4.15 (dt, 1H, $J = 6.9$ Hz). ^{13}C NMR (75 MHz, D_2O): $\delta = 26.1$, 29.3 (t), 58.6 (d), 69.5 (t), 78.1 (d), 173.2 (s). HRMS (FAB) calcd for $C_6H_{12}NO_3$ [$M^+ + H$] 146.1115, found 146.1098.

***tert*-Butyl 2-(*tert*-butyloxycarbonyl)amino-3-hydroxy-2-methyl-hexenoate (11).** Ester **11** was obtained from 30 mmol (7.36 g) Boc-Ala-O*t*Bu following the general procedure for aldol reaction as a 1:1 diasteromeric mixture in 87% yield (8.27 g, 26.2 mmol). The diastereomers could be separated by flash chromatography (hexanes/ethyl acetate, 9:1).

***syn*-11.** Colorless solid, mp 103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.37$ (s, 3H), 1.42, 1.44 (s, 18H), 1.69 (dd, 3H, $J = 6.6$, 1.4 Hz), 4.23 (d, 1H, $J = 7.4$ Hz), 5.07 (s, 1H), 5.45 (ddd, 1H, $J = 16.0$, 7.4, 1.6 Hz), 5.71 (dd, 1H, $J = 15.4$, 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.6$ (q), 20.4 (q), 27.7, 28.1 (q), 63.3 (s), 70.6 (d), 79.7 (s), 81.8 (s), 128.1 (d), 129.8 (d), 155.6 (s), 171.5 (s). Anal. calcd for $C_{16}H_{29}NO_5$ (315.41): C, 60.93; H, 9.27; N, 4.44. Found: C, 60.96; H, 9.31; N, 4.32.

***anti*-11.** Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.40$, 1.41, 1.43 (s, 18H), 1.51 (s, 3H), 1.66 (dd, 3H, $J = 6.5$, 0.6 Hz), 4.35 (d, 1H, $J = 6.7$ Hz), 4.89 (s, 1H), 5.37 (ddd, 1H, $J = 16.0$, 6.7, 1.5 Hz), 5.69 (ddd, 1H, $J = 16.3$, 6.5, 1.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.5$ (q), 20.8 (q), 27.6, 28.0, 28.1, 28.4 (q), 60.1 (s), 74.2 (d), 79.9 (s), 82.5 (s), 127.6 (d), 128.4, 128.6 (d), 155.8 (s), 172.1 (s). HRMS (FAB) calcd for $C_{16}H_{30}NO_5$ [$M^+ + H$] 316.2124, found 316.2145.

***tert*-Butyl *syn*-2-(*tert*-butyloxycarbonyl)amino-3-allyloxy-2-methyl-hexenoate (*syn*-12).** Allylation product *syn*-**12** was obtained from *syn*-**11** (2.86 g, 9.0 mmol) following the general procedure for *O*-allylations with allylbromide.

The crude product was purified by flash chromatography (hexanes/ethyl acetate, 98:2) giving rise to *syn*-**12** as a colorless oil in 82% yield (2.63 g, 7.4 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 18H), 1.43 (s, 3H), 1.72 (dd, 3H, *J* = 6.4, 1.5 Hz), 3.72 (dd, 1H, *J* = 12.8, 6.0 Hz), 3.83 (d, 1H, *J* = 8.8), 3.99 (m, 1H), 5.14 (m, 1H), 5.24 (m, 1H), 5.25–5.34 (m, 2H), 5.69 (dq, 1H, *J* = 15.2, 6.4 Hz), 5.82 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8 (q), 18.4 (q), 27.9, 28.4 (q), 63.2 (s), 69.0 (t), 79.2 (s), 81.1 (s), 84.3 (d), 116.8 (t), 125.7 (d), 133.1 (d), 134.5 (d), 155.5 (s), 171.5 (s). Anal. calcd for $C_{19}H_{33}NO_5$ (355.47): C, 64.20; H, 9.36; N, 3.94. Found: C, 64.17; H, 9.43; N, 3.91.

***tert*-Butyl *syn*-N-(*tert*-butyloxycarbonyl)-2-(2′,5′-dihydrofuranyl)-alaninate (*syn*-13).** Cyclization product *syn*-**13** was obtained from *syn*-**12** (2.33 g, 6.0 mmol) following the general procedure for ring closing metatheses in 98% yield (1.88 g, 6.0 mmol) after flash chromatography (hexanes/ethyl acetate, 95:5). Colorless solid, mp 60 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40, 1.44 (s, 18H), 1.43 (s, 3H), 4.64 (m, 2H), 5.03 (m, 1H), 5.17 (s, 1H), 5.76 (m, 1H), 6.00 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (q), 27.7, 27.9, 28.3 (q), 63.1 (s), 76.3 (t), 79.1 (s), 81.4 (s), 89.8 (d), 125.6 (s), 129.0 (s), 154.8 (s), 171.3 (s). Anal. calcd for $C_{16}H_{27}NO_5$ (313.39): C, 61.32; H, 8.68; N, 4.47. Found: C, 61.28; H, 8.52; N, 4.46.

***syn* -α-Methyl-norfuranomycin hydrochloride (*syn*-3).** Deprotection of *syn*-**13** (940 mg, 3.0 mmol) according to the general procedure provided *syn*-**3** in 83% yield (480 mg, 2.5 mmol) as a colorless solid, mp 175 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 1.50 (s, 3H), 4.64 (dddd, 1H, *J* = 13.6, 4.4, 2.6, 1.5 Hz), 4.81 (dddd, 1H, *J* = 13.6, 6.2, 2.6, 1.8 Hz), 5.20 (dddd, 1H, *J* = 8.5, 4.4, 2.2, 1.5 Hz), 5.96 (dtd, 1H, *J* = 6.6, 2.6, 1.5 Hz), 6.32 (ddd, 1H, *J* = 6.2, 3.4, 1.5 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ = 18.1 (q), 63.7 (s), 77.5 (t), 89.1 (d), 123.8 (d), 133.6 (d), 172.1 (s). HRMS (FAB) calcd for $C_7H_{12}NO_3$ [M^+ + H] 158.0817, found 158.0811.

***tert*-Butyl 2-(*tert*-butyloxycarbonyl)amino-3-hydroxy-4-methyl-hexenoate (14).** Ester **14** was obtained by a slightly modified version of the general procedure for aldol reactions, starting from Boc-Gly-OtBu (2.32 g, 10.0 mmol). $ClTi(OiPr)_3$ (2.74 g, 10.5 mmol) was added to the lithium enolate, followed by methacrolein (0.5mL, 6.0 mmol) after 10 min. **14** was obtained after flash chromatography (hexanes/ethyl acetate, 85:15) as a colorless oil and a mixture of diastereomers (*syn*/*anti* 1:1.4) in 85% yield (1.54 g, 5.1 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39, 1.45 (s, 18H), 1.74 (s, 1.2H *syn*), 1.76 (s, 1.8H *anti*), 2.45 (s, 1H), 4.35 (m, 1H), 4.40 (m, 1H), 4.93 (s, 1H), 5.02 (s, 1H), 5.15 (s, 0.6H, *anti*), 5.41 (s, 0.4H, *syn*). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 18.7 (q), 27.7, 27.8, 28.0, 28.02 (q), 56.3, 57.2 (d), 75.2, 76.2 (d), 79.5, 80.0 (s), 82.1, 82.7 (s), 111.9 (t), 143.3, 143.6 (s), 155.8 (s), 169.1, 170.0 (s). Anal. calcd for $C_{15}H_{27}NO_5$ (301.38): C, 59.78; H, 9.03; N, 4.65. Found: C, 59.44; H, 9.02; N, 4.78.

***tert*-Butyl 2-(*tert*-butyloxycarbonyl)amino-3-allyloxy-4-methyl-hexenoate (15).** Allylation product **15** was obtained from **14** (4.37 g, 14.0 mmol) following the general procedure for *O*-allylations with allylbromide. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 95:5) giving rise to **15** as a colorless oil in 88% yield (4.34 g, 12.7 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38, 1.39, 1.42, 1.44 (s, 18H), 1.72 (s, 3H), 3.72 (dd, 1H, *J* = 12.5, 6.2 Hz), 3.82 (d, 0.5H, *J* = 7.0 Hz, *anti*), 4.00 (dd, 1H, *J* = 12.9, 5.1 Hz), 4.11 (d, 0.5H, *J* = 2.6 Hz, *syn*), 4.31 (dd, 1H, *J* = 9.5, 3.3 Hz), 4.95–5.05 (m, 3H), 5.11 (dd, 1H, *J* = 10.3, 1.8 Hz), 5.20 (dt, 1H, *J* = 17.0, 1.8 Hz), 5.80 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 18.9 (q), 27.9, 28.0, 28.2 (q), 55.62, 55.65 (d), 70.0, 70.3 (t), 79.3, 79.6 (s), 81.7 (s), 81.9, 83.4 (d), 113.6 (t), 114.9, 117.0 (t), 134.2 (d), 140.7 (s), 155.8 (s), 169.7 (s). Anal. calcd for $C_{18}H_{31}NO_5$ (341.45): C, 63.32; H, 9.15; N, 4.10. Found: C, 63.16; H, 9.15; N, 4.12.

***tert*-Butyl *N*-(*tert*-butyloxycarbonyl)-2-(2′,5′-dihydro-3-methylfuranyl)-glycinate (16).** Cyclization product **16** was obtained from **15** (1.70 g, 5.0 mmol) following the general procedure for ring closing metatheses in 46% yield (669 mg, 2.1.mmol). The diastereomers could be separated by flash chromatography (hexane/ethyl acetate, 98:2).

***syn*-16.** Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39, 1.42, 1.43, 1.45 (s, 18H), 1.72 (s, 3H), 3.68 (m, 1H), 3.92 (m, 1H), 4.38 (m, 1H), 4.93 (m, 1H), 5.29 (d, 1H, *J* = 7.7 Hz), 5.51 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.2 (q), 27.7, 27.8, 28.0, 28.1 (q), 55.4 (d), 75.6 (t), 79.5 (s), 79.3 (s), 89.1 (s), 129.3 (d), 140.8 (s), 155.0 (s), 168.4 (s). Anal. calcd for $C_{16}H_{27}NO_5$ (313.39): C, 61.32; H, 8.68; N, 4.48. Found: C, 61.42; H, 8.50; N, 4.33.

***anti*-16.** Colorless solid, mp 117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38, 1.41, 1.42, 1.43 (s, 18H), 1.71 (s, 3H), 3.75 (m, 1H), 4.08 (m, 1H), 4.30 (d, 1H, *J* = 9.4 Hz), 4.97 (m, 1H), 5.07 (d, 1H, *J* = 9.6 Hz), 5.61 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8 (q), 27.7, 27.8, 28.0 (q), 56.4 (d), 79.2 (s), 81.5 (s), 83.6 (d), 75.4 (t), 128.5 (d), 140.4 (s), 155.5 (s), 169.5, (s). Anal. calcd for $C_{16}H_{27}NO_5$ (313.39): C, 61.32; H, 8.68; N, 4.48. Found: C, 61.17; H, 8.75; N, 4.39.

***syn* 3-Methyl-norfuranomycin hydrochloride (*syn*-4).** Deprotection of *syn*-**16** (125 mg, 0.40 mmol) according to the general procedure provided *syn*-**4** in 45% yield (28 mg, 0.18 mmol) as a brownish solid. ^{1}H NMR (300 MHz, CD_3OD): δ = 1.75 (s, 3H), 4.12 (m, 1H), 4.54–4.71 (m, 2H), 5.29 (m, 1H), 5.88 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD): δ = 17.4 (q), 62.6 (d), 77.4 (t), 85.3 (d), 125.9 (d), 139.5 (s). HRMS (FAB) calcd for $C_7H_{12}NO_3$ [M^+ + H] 158.0817, found 158.0831.

***anti* 3-Methyl-norfuranomycin hydrochloride (*anti*-4).** Deprotection of *anti*-**16** (125 mg, 0.40 mmol) according to the general procedure provided *anti*-**4** in 52% yield (33 mg, 0.21 mmol) as a brownish solid. ^{1}H NMR (300 MHz, CD_3OD): δ = 1.74 (s, 3H), 4.08 (m, 1H), 4.58–4.75 (m, 2H), 5.18 (m, 1H), 5.93 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD): δ = 18.5 (q), 63.3 (d), 77.6 (t), 81.6 (d), 124.9 (d), 139.1 (s). HRMS (FAB) calcd for $C_7H_{12}NO_3$ [M^+ + H] 158.0817, found 158.0803.

***tert*-Butyl 2-(*tert*-butyloxycarbonyl)amino-3-hydroxypentenoate (17).** Ester **17** was obtained from 30 mmol (6.94 g) Boc-Gly-OtBu following the general procedure for aldol reaction as a 1:1 diasteromeric mixture in 65% yield (5.58 g, 19.4 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.41$, 1.43, 1.45 (s, 18H), 2.48 (s, 1H), 4.24 (m, 0.5H, *syn*), 4.41 (m, 0.5H, *anti*), 4.53 (m, 1H), 5.21 (dd, 2H, $J = 10.5$, 1.3 Hz), 5.21 (m, 1H), 5.33 (dd, 1H, $J = 17.2$, 1.4 Hz), 5.77 (ddd, 0.5H, $J = 16.2$, 11.0, 5.3 Hz, *anti*), 5.88 (ddd, 0.5H, $J = 17.2$, 10.5, 5.3 Hz, *syn*). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.0$, 28.8 (q), 58.2 (d, *syn*), 59.0 (d, *anti*), 73.1 (d, *syn*), 74.1 (d, *anti*), 80.5 (s, *syn*), 81.0 (s, *anti*), 82.6 (s, *syn*), 82.9 (s, *anti*), 116.6 (t, *syn*), 117.0 (t, *anti*), 135.5 (d, *anti*), 136.5 (d, *syn*), 156.1 (s), 168.8 (s, *anti*), 169.8 (s, *syn*). Anal. calcd for $C_{14}H_{25}NO_5$ (287.36): C, 58.52; H, 8.77; N, 4.87. Found: C, 58.46; H, 8.76; N, 4.85.

***tert*-Butyl 2-(*tert*-butyloxycarbonyl)amino-3-methallyloxypentenoate (18).** Allylation product **18** was obtained from **17** (1.00 g, 3.5 mmol) following the general procedure for *O*-allylations with allylbromide. Methallylbromide (940 mg, 7.0 mmol) was used as the allylation reagent. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 98:2) giving rise to **18** as a colorless oil in 87% yield (2.97 g, 8.7 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = .41$, 1.44 (s, 18H), 1.67 (s, 1.5H, *syn*), 1.68 (s, 1.5H, *anti*), 3.65 (d, 0.5H, $J = 12.5$ Hz), 3.78 (d, 0.5H, $J = 12.9$ Hz), 3.88 (d, 0.5H, $J = 12.1$ Hz), 3.90 (d, 0.5H, $J = 12.1$ Hz), 4.03 (m, 0.5H, *anti*), 4.20–4.25 (m, 1H, *syn*), 4.32 (dd, 0.5H, $J = 8.8$, 4.5 Hz, *anti*), 4.77–4.91 (m, 2H), 5.18 (m, 1H), 5.26–5.33 (m, 2H), 5.74 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.3$, 19.4 (q), 27.8, 28.1 (q), 57.2, 57.8 (d), 72.3, 72.5 (t), 79.3, 80.3 (s), 79.8 (d), 81.6, 81.8 (s), 111.87, 111.93 (t), 118.8 (t), 134.2, 134.3 (d), 141.5 (s), 155.7 (s), 168.9, 169.3 (s). Anal. calcd for $C_{18}H_{31}NO_5$ (341.45): C, 63.32; H, 9.15; N, 4.10. Found: C, 63.24; H, 9.19; N, 4.03.

***tert*-Butyl *N*-(*tert*-butyloxycarbonyl)-2-(2′,5′-dihydro-4-methylfuranyl)-glycinate (19).** Cyclization product **19** was obtained from **18** (2.97 g, 8.7 mmol) following the general procedure for ring closing metatheses in 28% yield (759 mg, 2.4 mmol). The diastereomers could be separated by flash chromatography (hexanes/ethyl acetate, 96:6).

***syn*-19.** Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.45$ (s, 18H), 1.72 (s, 3H), 4.25 (dd, 1H, $J = 9.2$, 1.8 Hz), 4.41 (m, 2H), 5.07 (d, 1H, $J = 9.6$ Hz), 5.17 (m, 1H), 5.35 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.9$ (q), 27.6, 27.7, 27.8, 27.9, 28.0, 29.4 (q), 57.3 (d), 78.7 (t), 79.2 (s), 81.8 (s), 87.5 (d), 120.2 (d), 138.0 (s), 155.5 (s), 169.4 (s). Anal. calcd for $C_{16}H_{27}NO_5$ (313.39): C, 61.32; H, 8.68; N, 4.48. Found: C, 61.22; H, 8.54; N, 4.45.

***anti*-19.** Colorless wax. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (s, 18H), 1.75 (s, 3H), 4.32 (dd, 1H, $J = 9.2$, 3.3 Hz), 4.44 (s, 2H), 5.06 (m, 1H), 5.21 (d, 1H, $J = 8.1$ Hz), 5.32 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 12.0$ (q), 27.6, 27.7, 27.8, 28.0, 28.1, 29.4 (q), 57.6 (d), 78.3 (t), 79.5 (s), 81.4 (s), 87.0 (d), 119.4 (d), 138.9 (s), 156.0 (s), 169.0 (s). Anal. calcd for $C_{16}H_{27}NO_5$ (313.39): C, 61.32; H, 8.68; N, 4.48. Found: C, 61.52; H, 8.72; N, 4.35.

***syn*-4-Methyl-norfuranomycin hydrochloride (*syn*-5).** Deprotection of *syn*-**18** (125 mg, 0.40 mmol) according to the general procedure provided *syn*-**5** in 37% yield (24 mg, 0.15 mmol) as a dark yellow solid. ^{1}H NMR (300 MHz, CD_3OD): $\delta = 1.73$ (s, 3H), 4.15 (m, 1H), 4.51 (m, 2H), 5.26 (m, 1H), 5.42 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD): $\delta = 12.4$ (q), 58.6 (d), 77.7 (t), 85.9 (d), 130.3 (d), 139.4 (s). HRMS (FAB) calcd for $C_7H_{12}NO_3$ [$M^+ + H$] 158.0817, found 158.0831.

***anti*-4-Methyl-norfuranomycin hydrochloride (*anti*-5).** Deprotection of *anti*-**18** (125 mg, 0.40 mmol) according to the general procedure provided *anti*-**8** in 52% yield (33 mg, 0.21 mmol) as a brown solid. ^{1}H NMR (300 MHz, CD_3OD): $\delta = 1.72$ (s, 3H), 4.19 (m, 1H), 4.42–4.56 (m, 2H), 5.39 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD): $\delta = 12.6$ (q), 58.9 (d), 77.5 (t), 85.6 (d), 129.9 (d), 139.1 (s). HRMS (FAB) calcd for $C_7H_{12}NO_3$ [$M^+ + H$] 158.0817, found 158.0805.

***N*-(*tert*-Butyloxycarbonyl)-2-(cyclopent-2-enyl)glycine (21).** A freshly prepared LDA (25 mmol) solution in 5 mL THF was added to a stirred mixture of allylic ester **20**[18] (2.41 g, 10 mmol) and zinc chloride (1.64 g, 11 mmol) in 40 mL dry THF at −78 °C. The mixture was allowed to warm up to room temperature overnight. The resulting clear solution was diluted with ether and hydrolyzed with 1 N hydrochloric acid. After separation of the aqueous layer the rearrangement product was extracted twice with 1 N sodium hydroxide solution. Acidification of the aqueous layer with $KHSO_4$ and re-extraction with ether gave the desired *n*-protected amino acid 21 in excellent yield (2.27 g, 9.4 mmol, 94%) as a pale yellow wax. The diastereomers were separated via the iodolactones 22. Therefore the iodolactones *syn*- and *anti*-22 (367 mg, 1 mmol) were dissolved in a mixture of 5 mL THF, H_2O and HOAc (0.1 mL each) at 0 °C. Zinc powder (111 mg, 1.7 mmol) was added and the mixture was allowed to warm up to rt. After stirring for 1 h the mixture was filtered through a plug of Celite. The solution was washed twice with 0.1 N NaOH, the aqueous solution was acidified with 1 N HCl and the amino acids were extracted with EtOAc.

***syn*-21.** 241 mg (1.0 mmol, 100%) colorless solid, mp 104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.36$ (s, 9H), 1.58 (m, 1H), 1.90 (m, 1H), 2.29 (m, 2H), 3.12 (m, 1H), 4.22 (d, 1H, $J = 5.1$ Hz), 5.58 (m, 1H), 5.77 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD): $\delta = 24.5$ (d), 27.9 (q), 31.7 (d), 48.2 (s), 55.8 (d), 79.6 (s), 130.3 (d), 132.9 (d), 155.6 (s), 173.9 (s).

***anti*-21.** Two hundred mg (0. 83 mmol, 83%) pale yellow solid, mp 125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (s, 9H), 1.70 (m, 1H), 2.09 (m, 1H), 2.34 (m, 2H), 3.31 (m, 1H), 4.32 (dd, 1H, $J = 8.8$, 4.5 Hz), 4.82 (d, 1H, $J = 8.5$ Hz), 5.53 (dd, 1H, $J = 5.1$, 1.5 Hz), 5.96 (dd, 1H, $J = 5.5$, 2.2 Hz). ^{13}C NMR (75 MHz, CD_3OD): $\delta = 26.0$ (d), 28.0 (q), 32.2 (d), 47.2 (s), 56.0 (d), 80.0 (s), 127.9 (d), 135.5 (d), 155.9 (s), 176.5 (s). HRMS (FAB)

calcd for $C_{12}H_{20}NO_4$ [$M^+ + H$] 242.1392, found 242.1401.

Iodolactones (22). A solution of KI (200 mg, 1.2 mmol), I_2 (250 mg, 1.0 mmol) and $NaHCO_3$ (70 mg, 0.85 mmol) were dissolved in 2mL water. Amino acid **21** (190 mg, 0.8 mmol) was added in 2 mL of ether. After stirring overnight, the mixture was diluted with water and ether (15 mL each) and the layers were separated. The organic layer was washed with NaS_2O_3 solution and the solvent was removed in vacuum. The diastereomers could be separated by flash chromatography (hexanes/ethyl acetate, 9:1) giving a overall yield of 89% (250 mg, 0.7 mmol).

***syn*-22.** Pale yellow solid, mp 159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.44$ (s, 9H), 1.85 (d, 1H, $J = 15.4$ Hz), 2.26 (m, 2H), 2.46 (m, 1H), 2.98 (m, 1H), 3.77 (m, 1H), 4.40 (m, 1H), 5.19 (m, 1H), 5.33 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD): $\delta = 27.9$ (d), 28.2 (q), 31.5 (t), 35.0 (t), 44.5 (d), 57.8 (d), 81.0 (s), 91.6 (d), 155.3 (s), 174.8 (s). Anal. calcd for $C_{12}H_{18}NO_4I$ (367.18): C, 39.25; H, 4.94; N, 3.81; I 34.56. Found: C, 39.52; H, 5.13; N, 3.82; I 34.83.

***anti*-22.** Colorless solid, mp 140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.44$ (s, 9H), 1.77 (m, 1H), 2.02–2.20 (sh, 3H), 3.56 (m, 1H), 4.46 (m, 1H), 4.56 (m, 1H), 5.06 (m, 1H), 5.14 (m, 1H).^{13}C NMR (75 MHz, CD_3OD): $\delta = 22.7$ (t), 28.0 (q), 28.3 (d), 34.5 (t), 41.4 (d), 53.2 (d), 80.5 (s), 89.7 (d), 155.0 (s), 174.2 (s). Anal. calcd for $C_{12}H_{18}NO_4I$ (367.18): C, 39.25; H, 4.94; N, 3.81. Found: C, 39.32; H, 5.04; N, 3.80.

***syn*-Cyclopentenylglycine hydrochloride (*syn*-6).** Deprotection of *syn*-**21** (190 mg, 0.80 mmol) according to the general procedure provided *syn*-**6** in 82% yield (115 mg, 0.65 mmol) as a colorless solid, mp. 180 °C (decomp.). ^{1}H NMR (300 MHz, CD_3OD): $\delta = 1.78$ (m, 1H), 2.11 (m, 1H), 2.43 (m, 2H), 3.40 (m, 1H), 4.08 (d, 1H, $J = 4.8$ Hz), 5.71 (ddd, 1H, $J = 9.9$, 2.2, 1.5 Hz), 6.02 (ddd, 1H, $J = 10.3$, 2.6, 2.2 Hz). ^{13}C NMR (75 MHz, CD_3OD): $\delta = 25.3$ (t), 32.9 (t), 56.9 (d), 75.7 (d), 129.2 (t), 136.8 (t), 171.1 (s). Anal. calcd for $C_7H_{12}NO_2Cl$ (177.63): C, 47.33; H, 6.81; N, 7.89. Found: C, 47.21; H, 6.78; N, 7.92.

***anti*-Cyclopentenylglycine hydrochloride (*anti*-6).** Deprotection of *anti*-**21** (190 mg, 0.80 mmol) according to the general procedure provided *anti*-**6** in 51% yield (71 mg, 0.40 mmol) as a colorless solid, mp. 180 °C (decomp.). ^{1}H NMR (300 MHz, CD_3OD): $\delta = 1.79$ (m, 1H), 2.36 (m, 1H), 2.42 (m, 2H), 3.37 (m, 1H), 3.98 (d, 1H, $J = 4.8$ Hz), 5.63 (ddd, 1H, $J = 9.9$, 2.2, 1.5 Hz), 5.82 (ddd, 1H, $J = 10.7$, 3.3, 2.2 Hz). ^{13}C NMR (75 MHz, CD_3OD): $\delta = 26.8$ (t), 32.9 (t), 57.1 (d), 75.7 (d), 128.5 (t), 136.7 (t), 171.1 (s). Anal. calcd for $C_7H_{12}NO_2Cl$ (177.63): C, 47.33; H, 6.81; N, 7.89. Found: C, 47.29; H, 6.85; N, 7.87.

Cyclopentylglycine hydrochloride (23). Amino acid **23** was obtained from **21** (280 mg, 1.1 mmol) via hydrogenation and subsequent deprotection as a colorless solid (185 mg, 1.03 mmol, 93%), mp 200 °C (decomp).^{1}H NMR (300 MHz, CD_3OD): $\delta = 1.50$ (m, 2H), 1.67 (m, 4H), 1.90 (m, 2H), 2.32 (m, 1H), 3.85 (dd, 1H, $J = 7.4$, 2.9 Hz). ^{13}C NMR (75 MHz, CD_3OD): $\delta = 25.8$, 26.0 (t), 29.90, 29.92 (t), 43.3 (d), 57.6 (d), 171.6 (s). Anal. calcd for $C_7H_{14}NO_2Cl$ (179.65): C, 46.80; H, 7.85; N, 7.80. Found: C, 46.86; H, 7.86; N, 7.77.

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