Hormaomycin Analogues by Precursor-Directed Biosynthesis – Synthesis of and Feeding Experiments with Amino Acids Related to the Unique 3-(*trans*-2′-Nitrocyclopropyl)alanine Constituent

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The deuterium-labeled racemic 3-(*trans*-2′-nitrocyclopropyl)-alanine (*rac*-[D_2]-**3**) and 3-(*trans*-2′-aminocyclopropyl)alanine (*rac*-[D_2]-**4**) as well as non-labeled *rac*-3-[*trans*-2-(hydroxycarbonyl)cyclopropyl]alanine (*rac*-**5a**) and *rac*-3-[*trans*-2-(methoxycarbonyl)cyclopropyl]alanine (*rac*-**5b**) were prepared in 43, 18, 88 and 49 % overall yield, respectively, along a general synthetic route applying alkylations of the lithium enolate of *tert*-butyl (diphenylmethylene)-aminoacetate (O′Donnel's glycine equivalent **11**) as a key step. Feeding experiments with these amino acids and *Streptomyces griseoflavus* (strain W 384) revealed that *rac*-[D_2]-**3**, *rac*-**5a** and *rac*-**5b** are incorporated to give hormaomycin **1b** and its analogue **23**, respectively, while *rac*-[D_2]-**4** is not. Feeding of *rac*-2-(*trans*-2′-nitrocyclopropyl)glycine (*rac*-**6**) unexpectedly gave the 5-nitronorvaline-containing hormaomycin analogues **25a–c**. This is rationalized as arising from a cyclopropyl to homoallyl anion rearrangement followed by enzymatic hydrogenation of the double bond. These experiments provided new insights into the substrate specificity of the enzyme which assembles hormaomycin.

Introduction

Among natural products containing a cyclopropyl moiety, the peptide lactone hormaomycin **1a** isolated from *Streptomyces griseoflavus* strain W 384 is the first antibiotic with 3-(*trans*-2′-nitrocyclopropyl)alanine [(3-Ncp)Ala] (**3**) as a constituent.[1] Compound **1a** exhibits a specific antibacterial activity, acts as a signal substance on streptomycetes,[1] and in addition showed some antimalaria activity.[1c] Intriguingly, the recently described belactosin A **2**, which exhibits a moderate antitumor activity,[2] contains 3-(*trans*-2′-aminocyclopropyl)alanine [(3-Acp)Ala] (**4**) as a key constituent. As part of our efforts to elucidate the biosynthesis of **1a** we first focused our interest on [(3-Ncp)Ala] **3** and proved the absolute configurations of both entities by enantioselective synthesis of authentic samples.[3] The next essential question to be addressed is whether **3** is completely biosynthesized before the assembly of **1a** by the assumed nonribosomal peptide synthetase (NRPS) (hormaomycin synthetase) and how specific this multienzyme complex would work if cyclopropyl amino acids related to **3** are fed to growing cultures of *Streptomyces griseoflavus* strain W 384.

In order to get deeper insights into the biosynthesis of **1a** and distinctive features of the NPRS we prepared the deuterium-labeled *rac*-[D_2]-**3**,[3] and (2′-aminocyclopropyl) alanine *rac*-[D_2]-**4**,[4] the known non-labeled *rac*-3-[*trans*-2′-(hydroxycarbonyl)cyclopropyl]alanine [*trans*-2-(2′-amino-2′-hydroxycarbonylethyl)cyclopropanecarboxylic acid], *trans*-2-amino-4,5-methanoadipic acid] [(3-Hcp)Ala] (*rac*-**5a**)[5] and *rac*-3-[*trans*-2′-(methoxycarbonyl)cyclopropyl]-alanine [(3-Mcp)Ala] (*rac*-**5b**) as well as *rac*-2-(*trans*-2′-nitrocyclopropyl)glycine [(2-Ncp)Gly] (*rac*-**6**)[3c] and *rac*-3-cyclopropylalanine [(3-Cp)Ala] (*rac*-**7**)[6] in the form of their hydrochlorides and tested their potential incorporation by feeding experiments with the hormaomycin **1a** producing strain.

Preparation of Cyclopropyl-Group Containing Amino Acids

rac-2-(*trans*-2′-Nitrocyclopropyl)glycine [(2-Ncp)Gly] (*rac*-**6**) was obtained according to the published procedure.[3c] Amino acids *rac*-[D_2]-**3** and *rac*-[D_2]-**4** were prepared from the same synthetic precursor – (*trans*-2′-nitrocyclopropyl)dideuteriomethanol (**9**) – applying the method which had also been used in the productive synthesis of all four stereoisomers of 3-(*trans*-2′-nitrocyclopropyl)alanine.[3a] To begin with, the known *tert*-butyl *trans*-2-nitro-

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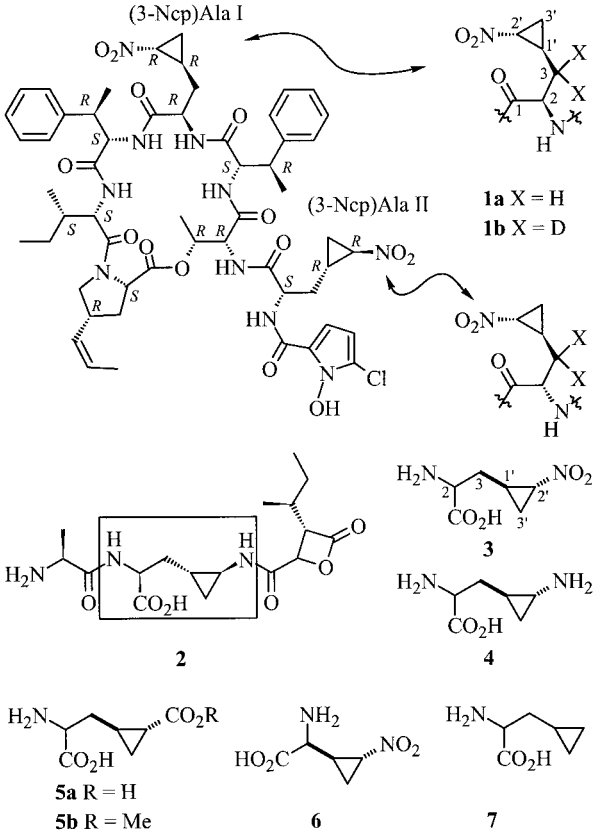
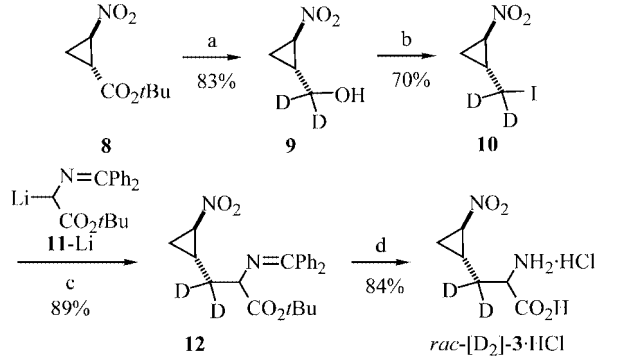


cyclopropylcarboxylate (**8**)[3a] was reduced with lithium aluminum deuteride to give *trans*-(2′-nitrocyclopropyl)-1,1-dideuteriomethanol (**9**) in 83 % isolated yield (Scheme 1). The alcohol **9** was converted into the iodide **10** by treatment with triphenylphosphane/iodine in the presence of imidazole.[7] After the alkylation with **10** of the lithium enolate (**11**-Li) of *tert*-butyl *N*-(diphenylmethylene)glycinate (**11**) (O'Donnel's glycine equivalent[8]) and subsequent one-pot removal of both protective groups from the product **12**, the racemic 3,3-dideuterio-3-(*trans*-2′-nitrocyclopropyl)alanine hydrochloride (*rac*-[D_2]-**3**·HCl) was obtained in 43 % yield over all four steps.



Scheme 1. Preparation of racemic 3,3-dideuterio-3-(*trans*-2′-nitrocyclopropyl)alanine hydrochloride (*rac*-[D_2]-**3**·HCl): a) $LiAlD_4$ (inverse addition of a solution in THF over 1 h), Et_2O, 20 °C, 2 h; b) Ph_3P, imidazole, I_2, Et_2O/MeCN, 0 °C, 2 h; c) THF, –78 °C → 20 °C, 56 h; d) 1 N aq. HCl, Et_2O, 20 °C, 2 d

After several unsuccessful attempts,[9] the 3,3-dideuterated amino acid dihydrochloride *rac*-[D_2]-**4**·2HCl was eventually obtained for feeding experiments starting from the deuterated (nitrocyclopropyl)methanol **9** in seven steps (Scheme 2). The nitro group in **9** was reduced to the amino group by catalytic hydrogenation over Pd/C[3c] to give the dideuterated (aminocyclopropyl)methanol **13** in quantitative yield. In a three-step sequence, using established methods,[10] the amino and the hydroxy groups in **13** were fully protected to give the [*N*,*N*-di(*tert*-butoxycarbonyl)amino] cyclopropylmethyl tetrahydropyranyl ether **16** in 65 % overall yield. The ether **16** was directly converted into the iodide **17** by treatment with iodine/1,2-bis(diphenylphosphanyl) ethane,[11] yet **17**, due to its limited stability, could be isolated in moderate yield only. After the coupling of **17** with the lithiated glycine equivalent **11**-Li and subsequent one-pot removal of all four protecting groups from the product **18**, the racemic 3,3-dideuterio-3-(*trans*-2′-aminocyclopropyl)alanine dihydrochloride (*rac*-[D_2]-**4**·2HCl) was isolated in very good yield (72 % over two steps) (Scheme 2).

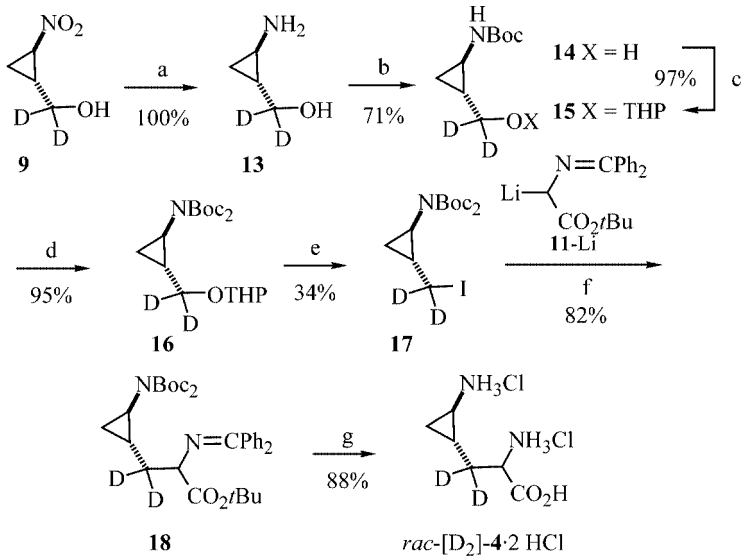
The last two amino acids in this series – *rac*-**5a** and *rac*-**5b** – were prepared in three simple steps each from the known methyl *trans*-[2′-(hydroxymethyl)cyclopropane]carboxylate (**19**)[12] following essentially the same synthetic routes as described above in overall yields of 88 and 49 %, respectively (Scheme 3).

Feeding Experiments

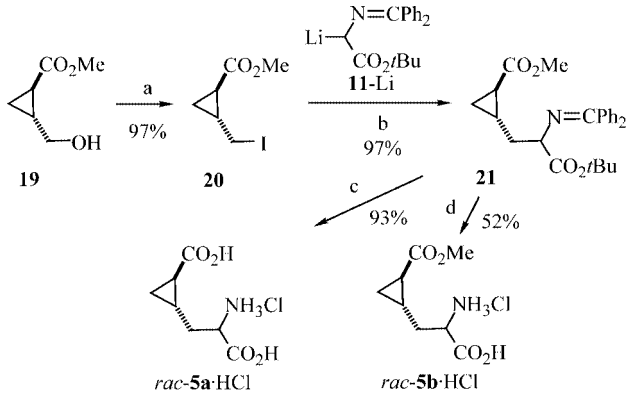
Previous feeding experiments with stable isotope-labeled lysines have already rigorously established that the 3-(*trans*-2′-nitrocyclopropyl)alanine units in hormaomycin **1a** originate from lysine.[13] However, these experiments could not answer the question, whether the unique amino acid is completely biosynthesized before the assembly of the peptide chain of hormaomycin **1a** or in a later phase of the biosynthesis. Upon feeding the deuterium-labeled amino acid *rac*-[D_2]-**3**·HCl, the labeled hormaomycin **1b** was obtained, as indicated by a ca. 90 % decrease of the intensities of the 3-H proton signals of both (3-Ncp)Ala fragments of hormaomycin in the ^{1}H-NMR spectrum as well as a significant decrease and broadening of the corresponding C-3 signals in its ^{13}C-NMR spectrum. Thus, 3-(*trans*-2′-nitrocyclopropyl)alanine is accepted by the hormaomycin synthetase and therefore should be established prior to the assembly of the peptide lactone. An incomplete (up to 10 %) suppression of the de novo biosynthesis of (3-Ncp)Ala cannot be excluded by the spectroscopic evidence.

However, free 3-(*trans*-2′-nitrocyclopropyl)alanine (**3**) could not be isolated from or even detected in traces in the culture broth upon interruption of the fermentation process before the hormaomycin production set in.[14]

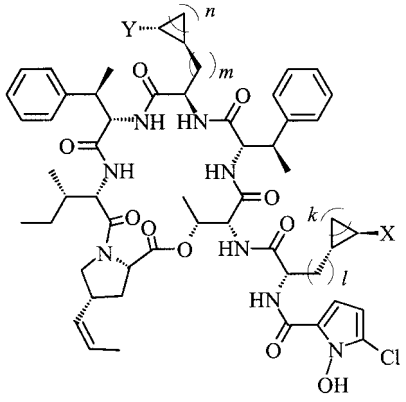
Since 3-(*trans*-2′-aminocyclopropyl)alanine (**4**) does exist in nature, at least as a constituent of belactosin A **2**,[2] it also had to be considered as a possible intermediate on the biosynthetic route to **3**. Therefore, feeding experiments with labeled *rac*-[D_2]-**4**·2HCl were performed. From these, hor-



Scheme 2. Preparation of racemic 3,3-dideuterio-3-(*trans*-2′-aminocyclopropyl)alanine dihydrochloride (*rac*-[D_2]-**4**·2 HCl): a) Pd/C, H_2 (2 bar), MeOH, 20 °C, 3 h; b) Boc_2O (di-*tert*-butyl pyrocarbonate), MeOH, 20 °C, 5 h; c) DHP (3,4-dihydro-2*H*-pyran), PPTS (pyridinium *p*-toluenesulfonate), CH_2Cl_2, 20 °C, 3 h; d) Boc_2O, DMAP (4-dimethylaminopyridine), MeCN, 20 °C, 48 h; e) I_2, dppe [1,2-bis(diphenylphosphanyl)ethane], CH_2Cl_2, 0 → 20 °C, 2 h; f) THF, –78 °C → 20 °C, 56 h; g) 1 N aq. HCl, Et_2O, 20 °C, 2 d



Scheme 3. Preparation of *rac*-3-[*trans*-2′-(hydroxycarbonyl)cyclopropyl]alanine (*rac*-**5a**·HCl) and *rac*-3-[*trans*-2′-(methoxycarbonyl) cyclopropyl]alanine (*rac*-**5b**·HCl): a) Ph_3P, imidazole, I_2, Et_2O/MeCN, 0 °C, 2 h; b) THF, –78 °C → 20 °C, 72 h; c) 1 N aq. HCl, Et_2O, 20 °C, 3 d; d) 1 N aq. HCl, Et_2O, 20 °C, 3.5 h



23 X = Y = CO_2Me, $k = l = m = n = 1$
24a X = Y = NO_2, $k = n = 1$, $l = m = 0$
24b X = Y = NO_2, $k = m = n = 1$, $l = 0$
24c X = Y = NO_2, $k = l = n = 1$, $m = 0$
25a X = Y = NO_2, $l = m = 1$, $k = n = 0$
25b X = Y = NO_2, $l = m = n = 1$, $k = 0$
25c X = Y = NO_2, $k = l = m = 1$, $n = 0$

Figure 1. Structures of the isolated new analogs **23**, **25** of hormaomycin **1a**

maomycin **1a** was isolated in the usual yield, but it was completely unlabeled, and no hormaomycin analogues were detected. Obviously H-(3-Acp)Ala-OH **4** is not a suitable substrate for the assumed hormaomycin synthetase, and it does not interfere with the normal hormaomycin biosynthesis.

Normally, a bacterial NRPS is not highly substrate selective, a fact which can be exploited to prepare natural peptide analogues by so-called precursor-directed biosynthesis.[15] In order to determine the tolerance limits of the H-(3-Ncp)Ala-OH recognition and building module of the hormaomycin synthetase, feeding experiments with 2′-hydroxycarbonyl- **5a** and 2′-methoxycarbonyl-substituted cyclopropylalanine **5b**, respectively, (2′-nitrocyclopropyl)-glycine (**6**) as well as the unsubstituted cyclopropylalanine (**7**) were performed.

Surprisingly, the feeding of both *rac*-**5a**·HCl and *rac*-**5b**·HCl yielded the same new hormaomycin analogue **23** with (3-Mcp)Ala instead of (3-Ncp)Ala units (Figure 1). In the feeding experiment with *rac*-**5b**·HCl the yield was higher (2.9 mg), and the structure could be confirmed by ESI-MS, ^{1}H- and ^{13}C-NMR spectra. The molecular ion at m/z = 1177 ([M + Na]$^+$) and the ESI-MS/MS indicated a twofold incorporation of the precursor. The ^{1}H-NMR spectrum of **23** (Figure 2) reveals two additional methoxy groups (δ_H = 3.60 and 3.62 ppm). Furthermore, significant changes compared to the spectrum of **1a** are visible in the range of –1.0

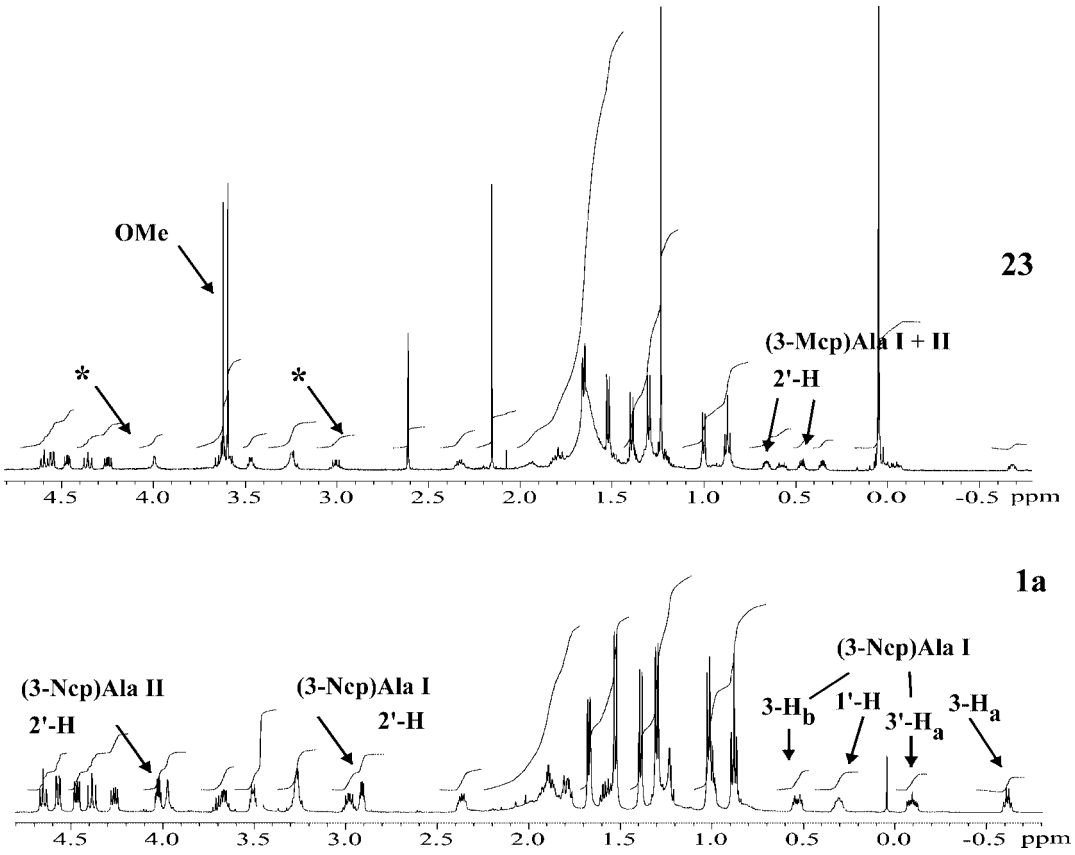


Figure 2. Comparison of the ^{1}H-NMR (500 MHz, $CDCl_3$) spectra of hormaomycin **1a** and its analogue **23**. Asterisks (*) mark the positions of the missing 2′-H signals of (3-Ncp)Ala in the spectrum of **23**

to 1.0 ppm. Especially the characteristic 2′-H proton signals of (3-Ncp)Ala I (δ_H = 2.94 ppm) and II (δ_H = 4.05 ppm) are missing in the spectrum of **23**.

With *rac*-**5a**·HCl being fed as a precursor, only 0.7 mg of a peptide-product mixture was isolated. The ESI-MS shows peaks for three molecular ions with *m*/*z* = 1177 ($[M_1 + Na]^+$), *m*/*z* = 1164 ($[M_2 + Na]^+$) and *m*/*z* = 1151 ($[M_3 + Na]^+$). The first one corresponds to **23**, the last to hormaomycin **1a**, and the third compound must be an analogue with only one (3-Mcp)Ala unit instead of (3-Ncp)Ala in the molecule.

These experiments clarify that cyclopropylalanines with other electron-withdrawing functional groups instead of the nitro group at C-2′ are accepted by the hormaomycin synthetase resulting in hormaomycin analogues. In the case of **5a** with a free hydroxycarbonyl group as a precursor, it is assumed that the acid residue is methylated by a strain characteristic methylase before or after the chain assembly. In contrast to the successful feeding with **5a/5b**, the administration of unsubstituted cyclopropylalanine (*rac*-**7**·HCl) led to complete inhibition of the hormaomycin production. Neither **1a** nor any analogue could be isolated.

The most unexpected result was obtained from the feeding experiment with *rac*-2-(*trans*-2′-nitrocyclopropyl)glycine (*rac*-**6**·HCl). In this case, three more hormaomycin analogues **25a**–**c** were isolated along with the native hormaomycin **1a**. The incorporation of one or two residues of (2-Ncp)Gly in the peptide lactone to yield its analogues **24a**, **24b** or **24c** (Figure 1) should cause a decrease of the molecular mass by 28, 14 and 14 units, respectively. However, according to their ESI-MS spectra, the molecular masses of these new compounds, surprisingly, were only 24, 12 and 12 units, respectively, lower than that of the natural product **1a**. This corresponds to the incorporation of one or two units of 5-nitronorvaline [(NO_2)Nva] instead of (2-Ncp)Gly moieties, respectively. In a rerun of the feeding experiment with *rac*-**6**·HCl under slightly modified conditions (5 L vessel instead of 1 L, addition of proline), the hormaomycin analogue **25a** was isolated again.

The ^{1}H-NMR spectrum of analogue **25a** was very similar to that measured for a hormaomycin analogue with two (NO_2)Nva instead of (3-Ncp)Ala residues, isolated from the respective feeding experiment with (*S*)-5-nitronorvaline (Figure 3).[16,17] The identity of these two substances was also supported by identical HPLC retention times.

A comparative ESI-MS/MS experiment showed that in the case of the analogues **25b** and **25c** the (NO_2)Nva residue had been incorporated in the side chain of hormaomycin or in the ring moiety, respectively. This was additionally confirmed by the coincidence of the HPLC retention time of **25b** with that of a synthetic hormaomycin analogue with a (NO_2)Nva residue in the side chain, and the retention time of **25c** with that of one compound isolated from feeding of H-(NO_2)Nva-OH.[16,17] This surprising behavior of

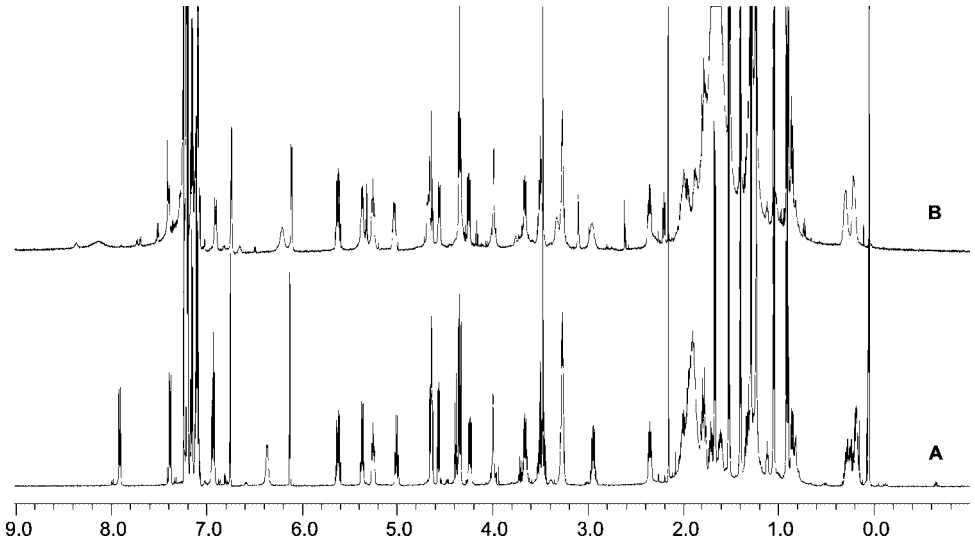
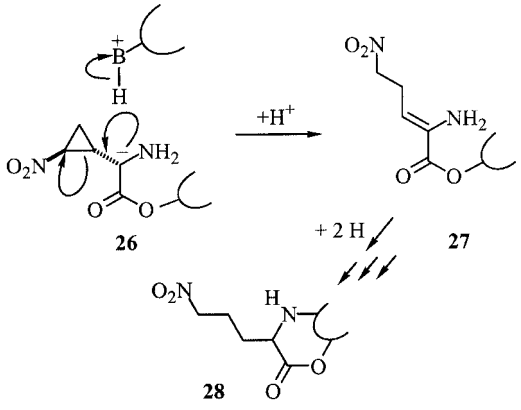


Figure 3. Comparison of ^{1}H NMR (600 MHz, $CDCl_3$) spectra of hormaomycin analog **25a** obtained from feeding experiments with (*S*)-5-nitronorvaline (trace A) and from feeding experiment with *rac*-2-(*trans*-2′-nitrocyclopropyl)glycine (*rac*-**6**·HCl) (trace B)

(2′-nitrocyclopropyl)glycine must have to do with the explicit susceptibility of its (2′-nitrocyclopropyl)methyl fragment to undergo a ring-opening rearrangement via a radical[18] or anion[19] intermediate (cf.[20]). It is most plausible that this transformation starts with a proton abstraction from C-2 as it is typical for the participation of a racemase,[21,22] which has already been proved in the biosynthesis of hormaomycin **1a** itself.[1e] In the case of (2-Ncp)Gly the enolate **26**, possibly bound to pyridoxal phosphate, is prone to undergo a cyclopropylcarbinyl to homoallyl rearrangement to give, after subsequent protonation, the corresponding nitroethylsubstituted α-aminoacrylic acid derivative **27** which, after enzymatic hydrogenation, would furnish the observed (NO_2)Nva residues in hormaomycin analogues **25a**–**c** (Scheme 4). Thus, rearrangement of (*trans*-2′-nitrocyclopropyl)glycine (**6**) before the assembly in the peptide is more likely.



Scheme 4. A plausible mechanism for the formation of 5-nitronorvaline [(NO_2)Nva) from (2′-nitrocyclopropyl)glycine **6** residues

Conclusions

According to the results of these feeding experiments with the known amino acids **3**, **4**, **5a**, **6** and **7** as well as with the new **5b** to *Streptomyces griseoflavus* (strain W-384) the following conclusions about some details of the hormaomycin synthetase responsible for the hormaomycin biosynthesis can be drawn:

1) 3-(*trans*-2′-Nitrocyclopropyl)alanine (**3**) is completely synthesized before the peptide chain of hormaomycin is assembled.

2) 3-(*trans*-2-Aminocyclopropyl)alanine (**4**) is neither an intermediate in the biosynthesis of 3-(*trans*-2-nitrocyclopropyl)alanine nor an acceptable substrate for the multienzyme complex, yet **4** does not interfere with the normal biosynthesis of hormaomycin.

3) The multienzyme complex tolerates some variation in the substrates to be accepted by the modules, which are normally loaded with **3**. An electron-withdrawing quality such as that of a methoxycarbonyl group at the C-2′ position appears to be essential.

4) The unexpected isolation of three hormaomycin analogues **25a**–**c** containing one or two (NO_2)Nva from a feeding experiment with *rac*-2-(*trans*-2′-nitrocyclopropyl)glycine (**6a**) indicates a cyclopropylcarbinyl to homoallyl anion rearrangement triggered by a racemase and subsequent enzymatic reduction of the intermediate.

In addition to these new insights into the biosynthesis of hormaomycin **1a**, especially the unique (3-Ncp)Ala units, previously unknown hormaomycin analogues have become available by precursor-directed biosynthesis.[16]

Experimental Section

General: ^{1}H- and ^{13}C-NMR spectra of amino acids and intermediates were recorded at 250 (^{1}H), and 62.9 MHz [^{13}C, additional DEPT (Distortionless Enhancement by Polarization Transfer)] with a Bruker AM 250 instrument. ^{1}H- and ^{13}C-NMR spectra of hormaomycin **1a** and analogues were recorded at 500 (^{1}H), and 125.7 MHz [^{13}C, additional APT (Attached Proton Test, down –, up +)] with a Varian Inova 500 (500 MHz), and at 600 (^{1}H)MHz with a Varian Inova 600 instrument in $CDCl_3$ soln., $CHCl_3$/$CDCl_3$

as internal reference (if not otherwise specified); δ in ppm, J in Hz. Whenever it was necessary and possible HMBC (Heteronuclear Multiple Bond Connectivity) and/or HMQC (Heteronuclear Multiple Quantum Coherence) spectra were also measured. The signals marked with an asterisk could not be unequivocally assigned. MS (EI): Finnigan MAT 95 spectrometer (70 eV). IR: Bruker IFS 66 (FT-IR) spectrophotometer, measured as KBr pellets, oils between KBr plates. HPLC: pump: Kontron P 420 system, detector: Kontron D 430, mixer: Kontron M 800, data system: Kontron data system 450-MT2, columns: Jasco Kromasil-100 C18 (analytical, 5 μm, 3 mm × 250 mm), Jasco Kromasil-100 (preparative, 5 μm, 8 mm × 250 mm). M.p.: Büchi 510 capillary melting point apparatus, values are uncorrected. TLC: Macherey–Nagel precoated sheets, 0.25 mm Sil G/UV_{254}. Column chromatography: Merck silica gel, grade 60, 230–400 mesh. Elemental analyses: Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Universität Göttingen. Starting materials: Anhydrous diethyl ether and THF were obtained by distillation from sodium benzophenone ketyl, MeOH from magnesium methoxide, MeCN and dichloromethane from P_4O_{10}. Racemic 2-(*trans*-2′-nitrocyclopropyl)glycine (*rac*-**6**)·HCl,[3c] *tert*-butyl 2-nitrocyclopropylcarboxylate (**8**),[3a,c] *tert*-butyl *N*-(diphenylmethylene)glycinate (**11**),[8a] methyl [*trans*-2′-(hydroxymethyl)cyclopropane]carboxylate **19**,[12,24] and a reference sample of **25b**[16] were prepared according to published procedures. The reference samples of **25a**,**c** were isolated from feeding experiments with (*S*)-5-nitronorvaline.[16] All other chemicals were used as commercially available (Merck, Acrõs, BASF, Bayer, Hoechst, Degussa AG, and Hüls AG). Organic extracts were dried with $MgSO_4$. Microbiology: Fermenters: Braun Biostat M (1 L), Braun Biostat B (5 L). The feedings experiments with *Streptomyces griseoflavus* (strain W 384) were carried out as described elsewhere.[1e,13,14]

Preparation of Cyclopropylalanine Derivatives

1,1-Dideuterio-(*trans*-2′-nitrocyclopropyl)methanol (9): To a stirred solution of the ester **8** (9.36 g, 50.0 mmol) in anhydrous diethyl ether (150 mL) was added $LiAlD_4$ (25.0 mmol, 30.1 mL of a 0.83 N solution in THF) under Ar at ambient temp. over a period of 1 h. Then the reaction mixture was stirred at the same temp. for an additional 2 h, cooled to 10 °C, and mixed with satd. Na_2SO_4 solution to quench the reaction. The organic phase was dried and concentrated under reduced pressure to give **9** (4.96 g, 83 %) as a colorless liquid. The alcohol **9** was used without further purification. ^{1}H NMR: δ = 1.26–1.34 (ddd, J = 10.3, 5.9, 7.2 Hz, 1 H, 3′-H), 1.72 (br. s, 1 H, OH), 1.81–1.89 (ddd, J = 5.9, 3.5 Hz, 1 H, 3′-H), 2.21–2.28 (m, 1 H, 1′-H), 4.26 (ddd,J = 10.3, 5.9, 3.5 Hz, 1 H, 2′-H) ppm. ^{13}C NMR: δ = 15.13 (–, C-3′), 26.99 (+, C-1′), 57.55 (+, C-2′), 59.2 (quint, J = 21.0 Hz, C-1) ppm.[25]

(*trans*-2-Aminocyclopropyl)-1,1-dideuteriomethanol (13):[26] To a solution of the alcohol **9** (2.38 g, 20.0 mmol) in MeOH (50 mL) was added under nitrogen 100 mg of palladium on charcoal (10 % Pd/C), and the resulting mixture was hydrogenated at ambient temp. in a Parr apparatus under a pressure of 2 bar of hydrogen for 3 h. Then the mixture was filtered through a pad of Celite (3 cm) and concentrated under reduced pressure to give the amino alcohol **13** (1.78 g, 100 %) as a colorless oil. ^{1}H NMR: δ = 0.36–0.43 (m, 1 H, 3′-H), 0.49–0.57 (m, 1 H, 3′-H), 1.01–1.03 (m, 1 H, 1′-H), 2.15–2.20 (m, 1 H, 2′-H), 2.87 (br. s, 3 H, NH_2, OH) ppm. ^{13}C NMR: δ = 11.8 (–, C-3′), 22.8 (+, C-1′), 29.4 (+, C-2′), 63.3 (quint, J = 21.0 Hz, C-1) ppm.

[*trans*-2-(*tert*-Butoxycarbonylamino)cyclopropyl]-1,1-dideuteriomethanol (14):[26b] To a solution of the crude amine **13** (1.78 g, 20.0 mmol) in anhydrous MeOH (100 mL) was added in one portion di-*tert*-butyl pyrocarbonate (Boc_2O) (8.73 g, 40.0 mmol), and the resulting solution was stirred at ambient temp. for 12 h, then concentrated under reduced pressure. The residue was taken up with diethyl ether (80 mL), the solution washed with H_2O (3 × 50 mL), dried and concentrated under reduced pressure. The product was purified by column chromatography (50 g of silica gel, 4 × 10 cm column, Et_2O, R_f = 0.37) to give the protected aminoalcohol **14** (2.69 g, 71 %) as a colorless oil. ^{1}H NMR: δ = 0.65–0.73 (m, 1 H, 3′-H), 0.75–0.81 (m, 1 H, 3′-H), 1.15–1.17 (m, 1 H, 1′-H), 1.43 [s, 9 H, $C(CH_3)_3$], 2.29–2.32 (m, 1 H, 2′-H), 2.98 (br. s, 1 H, OH), 4.91 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 10.9 (–, C-3′), 23.2 (+, C-1′), 28.3 (+, C-2′), 28.4 [+, $C(CH_3)_3$], 63.7 (quint, J = 21.0 Hz, C-1), 79.9 [C_{quat}, $C(CH_3)_3$], 157.1 (C_{quat}, NC=O) ppm.

***N*-(*tert*-Butoxycarbonyl)-2-(tetrahydropyran-2-yloxydideuteriomethyl)cyclopropylamine (15):** A solution of the protected aminoalcohol **14** (1.96 g, 10.4 mmol) and 3,4-dihydro-2*H*-pyran (DHP) (1.74 g, 1.88 mL, 20.8 mmol) in anhydrous CH_2Cl_2 (30 mL) was stirred with pyridine *p*-toluenesulfonate (PPTS) (261 mg, 1.04 mmol) at ambient temp. for 3 h. After this, the reaction mixture was diluted with Et_2O (50 mL), washed with a half-saturated aq. sodium chloride solution (50 mL), dried and concentrated under reduced pressure. Column chromatography of the residue (40 g of silica gel, 3 × 15 cm column, hexane/Et_2O, 1:1, R_f = 0.62) gave compound **15** (2.82 g, (97 %) as a colorless oil. ^{1}H NMR: δ = 0.70–0.75 (m, 2 H, 3-H), 1.42 [s, 9 H, $C(CH_3)_3$], 1.46–1.85 (m, 5 H, 2-H, 4′-H, 5′-H), 2.35–2.41 (m, 1 H, 1-H), 2.40–3.45 (m, 2 H, 3′-H), 3.74–3.81 (m, 2 H, 6- and 5′-H), 4.54–4.57 (m, 1 H, 2′-H), 4.87 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 13.9 (+, C-2), 19.3 (–, C-4′), 22.5 (–, C-3), 25.3 (–, C-5′), 28.2 [+, $C(CH_3)_3$], 30.4 (–, C-3′), 34.3 (+, C-1), 62.0 (–, C-6′), 68.0 (quint, J = 22.0 Hz, CD_2), 79.1 [C_{quat}, $C(CH_3)_3$], 98.3 (+, C-2′), 156.3 (C_{quat}, NC=O) ppm.

***N*-[Bis(*tert*-butoxycarbonyl)]-2-(tetrahydropyran-2-yloxydideuteriomethyl)cyclopropylamine (16):** To a vigorously stirred solution of the protected amino alcohol **15** (2.84 g, 10.4 mmol) in anhydrous MeCN (30 mL) was added under nitrogen 4-dimethylaminopyridine (DMAP) (257 mg, 2.1 mmol) and Boc_2O (2.40 g, 11.0 mmol) at ambient temp. After stirring for an additional for 2 h, the next portion of Boc_2O (1.31 g, 6.00 mmol) was added, the resulting solution was stirred at ambient temp. for 2 d, taken up with diethyl ether (80 mL), washed with H_2O (3 × 50 mL), dried and concentrated under reduced pressure. The product was purified by column chromatography (40 g of silica gel, 3 × 15 cm column, hexane/Et_2O, 3:1, R_f = 0.30) to give the protected aminoalcohol **16** (3.69 g, 95 %) as a colorless oil (as a 1.2:1 mixture of diastereomers **16a**,**b**). IR: $\tilde{\nu}$ = 2979 cm^{-1}, 2941, 1783, 1741, 1368, 1286, 1159, 1120, 1025, 912, 733. ^{1}H NMR (**16a**,**b**): δ = 0.82–0.89 (m, 2 H, 3-H), 0.99 (ddd, J = 6.3, 10.5, 11.2 Hz, 1 H, 2-H), 1.46, 1.48 [s, 9 H, $C(CH_3)_3$], 1.58–1.83 (m, 6 H, 3′-H, 4′-H, 5′-H), 2.48 (ddd, J = 3.2, 7.3, 11.2 Hz, 1 H, 1-H), 3.42–3.51 (m, 1 H, 6′-H), 3.80–3.87 (m, 1 H, 6′-H), 4.62 (t, J = 3.5 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (**16a**): δ = 14.7 (–, C-3), 19.4 (–, C-4′), 22.2 (+, C-2), 25.3 (–, C-5′), 27.9 [+, 2 $C(CH_3)_3$], 30.4 (–, C-3′), 32.2 (+, C-1), 62.05 (–, C-6′), 82.0 [C_{quat}, 2 $C(CH_3)_3$], 98.3 (+, C-2′), 152.8 (C_{quat}, 2 NC=O) ppm. ^{13}C NMR (**16b**): δ = 14.5 (–, C-3), 19.4 (–, C-4′), 22.1 (+, C-2), 25.3 (–, C-5′), 27.9 [+, 2 $C(CH_3)_3$], 30.4 (–, C-3′), 31.6 (+, C-1), 61.96 (–, C-6′), 82.0 [C_{quat}, 2 $C(CH_3)_3$], 98.1 (+, C-2′), 152.8 (C_{quat}, 2 NC=O) ppm. The quintet of the CD_2 group is of weak intensity. MS (CI): m/z (%) = 391 (5) [M + NH_4^+], 390 (35) [M + NH_4^+ – H], 378 (40) [M – CH_2O + NH_4^+ + NH_3], 288 (38), 204 (100), 192 (90).

Preparation of Iodides 10, 20. General Procedure (GP) 1: Iodine (5.07 g, 20 mmol) was added in small portions over a period of 30 min to an efficiently cooled (0 °C) solution of the respective al-

cohol (10.1 mmol), Ph_3P (4.71 g, 18 mmol) and imidazole (1.29 g, 18.9 mmol) in a mixture of anhydrous MeCN (20 mL) and Et_2O (30 mL) under argon. Stirring was continued at 0 °C for 2 h, then the reaction mixture was diluted with Et_2O (150 mL) and washed with a 20 % aq. solution of $Na_2S_2O_3$ (2 × 100 mL), brine (100 mL), dried and concentrated under reduced pressure. The residue was thoroughly extracted with hexane (100 mL) by vigorous stirring for 1 h in the dark, filtered and concentrated under reduced pressure. The residue was purified by column chromatography.

***trans*-1-(Dideuterioiodomethyl)-2-nitrocyclopropane (10):** Iodide **10** (6.59 g, 70 %) was obtained from the alcohol **9** (4.96 g, 41.6 mmol), PPh_3 (19.6 g, 74.7 mmol), imidazole (5.36 g, 78.7 mmol) and I_2 (21.1 g, 83.1 mmol) according to GP1 as a slightly yellow oil after column chromatography (100 g of silica gel, 4 × 20 cm column, hexane/Et_2O, 10:1, R_f = 0.33). IR: $\tilde{\nu}$ = 3098 cm^{-1}, 2961, 2897, 1547 (NO_2), 1435, 1369, 571 (C–I). ^1H NMR: δ = 1.21–1.29 (m, 1 H, 1-H), 2.05–2.13 (m, 1 H, 3-H), 2.41–2.49 (m, 1 H, 3-H), 4.15–4.20 (m, 1 H, 2-H) ppm. ^{13}C NMR: δ = 3.2 (quint, J = 22.2 Hz, C-1), 21.8 (–, C-3), 28.2 (+, C-1), 62.8 (+, C-2) ppm. MS (EI): *m*/*z* (%) = 229 (8) [M^+], 183 (18) [$M^+ - NO_2$], 102 (22) [$M^+ - I$], 86 (27) [$M^+ - CD_2I$], 56 (91) [$C_4D_2H_4$], 41 (100).[27]

Methyl *trans*-(2′-Iodomethylcyclopropane)carboxylate (20): Iodide **20** (7.67 g, 97 %) was obtained from the alcohol **19** (4.29 g, 33.0 mmol), PPh_3 (15.06 g, 57.4 mmol), imidazole (4.12 g, 60.5 mmol) and I_2 (16.21 g, 63.9 mmol) according to GP1 as a colorless oil after column chromatography (200 g of silica gel, 5 × 25 cm column, hexane/Et_2O, 4:1, R_f = 0.48). An analytical sample was additionally purified by bulb-to-bulb distillation at 0.002 Torr and at a bath temperature of 85–95 °C. IR: $\tilde{\nu}$ = 3061 cm^{-1}, 2674, 1732 (C=O), 1534, 1498, 1203, 1102, 943. ^1H NMR: δ = 0.89 (ddd, J = 5.0, 6.9, 10.8 Hz, 1 H, 3′-H), 1.41 (ddd, J = 5.0, 6.9, 9.1 Hz, 1 H, 3′-H), 1.57 (ddd, J = 5.0, 8.8, 10.8 Hz, 1 H, 1′-H), 1.79–1.91 (m, 1 H, 2′-H), 3.04 (dd, J = 7.1, 10.1 Hz, 1 H, CH_2I), 3.11 (dd, J = 4.2, 10.1 Hz, 1 H, CH_2I), 3.63 (s, 3 H, OMe) ppm. ^{13}C NMR: δ = 8.1 (–, CH_2I), 19.5 (–, C-3′), 25.2 (+, C-2′), 25.7 (+, C-1′), 51.8 (+, OMe), 173.0 (C_{quat}, C=O) ppm. MS (EI): *m*/*z* (%) = no mol peak, 181 (6), 139 (7), 127 (10) [I^+], 113 (100) [$M^+ - I$], 81 (18), 71 (35), 59 (30), 53 (20), 41 (18). $C_6H_9IO_2$ (240.0): calcd. C 30.02, H 3.78; found C 29.87, H 3.52.

Coupling of Iodides 10, 17, 20 with *tert*-Butyl *N*-(Diphenylmethylene)glycinate 11. General Procedure (GP) 2: To a stirred solution of the protected glycine **11** (40 mmol) in anhydrous THF (300 mL) was added dropwise *n*BuLi (40 mmol as a solution in hexane) at –78 °C over a period of 1 h under an atmosphere of argon. After stirring at this temp. for an additional 1 h, a solution of the respective iodide (40 mmol) in THF (50 mL) was added to the solution of the lithium enolate of **11** at the same temperature within 15 min. The mixture was stirred for 20 h at –78 °C, then allowed to warm to 20 °C over a period of 24 h and stirred at ambient temp. for an additional 12 h. After this, the mixture was poured into ice-cold water (100 mL), extracted with diethyl ether (3 × 60 mL), the combined organic layers were washed with H_2O (80 mL), brine (80 mL), dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel deactivated with triethylamine.

***tert*-Butyl 2-*N*-(Diphenylmethylene)-3,3-dideuterio-3-(*trans*-2′-nitrocyclopropyl)alanate (12):** Compound **12** (12.63 g, 97 %) was obtained from the iodide **10** (8.78 g, 38.3 mmol), *tert*-butyl *N*-(diphenylmethylene)glycinate (**11**) (10.58 g, 35.8 mmol) and *n*BuLi (35.8 mmol, 22.7 mL of a 1.58 N solution in hexane) according to GP2 as a colorless oil after column chromatography (100 g of silica gel, 4 × 20 cm column, hexane/Et_2O, 5:1, R_f = 0.20) as a 1.3:1 mixture of diastereomers **12a**,**b**. ^1H NMR (**12a**,**b**): δ = 0.98–1.11 (m, 1 H, 3′-H), 1.43 [s, 9 H, $C(CH_3)_3$], 1.68–1.85 (m, 1 H, 3′-H), 1.90–2.07 (m, 1 H, 1′-H), 3.95–4.05 (m, 1 H, 2-H), 4.05–4.16 (m, 1 H, 2′-H), 7.05–7.21 (m, 2 H, Ph-H), 7.25–7.56 (m, 6 H, Ph-H), 7.57–7.69 (m, 2 H, Ph-H) ppm. ^{13}C NMR (**12a**): δ = 17.7 (–, C-3′), 23.08 (+, C-1′), 28.0 [+, $C(CH_3)_3$], 34.0 (quint, J_{CD} = 25.0 Hz, C-3), 59.9 (+, C-2′), 65.08 (+, C-2), 81.6 [C_{quat}, $C(CH_3)_3$], 127.7, 128.0, 128.5, 128.7, 129.3, 130.5 (+, Ph-C), 136.33, 139.1 (C_{quat}, Ph-C), 170.24 (C_{quat}, C=N), 171.1 (C_{quat}, C=O) ppm. ^{13}C NMR (**12b**): δ = 18.7 (–, C-3′), 23.13 (+, C-1′), 28.0 [+, $C(CH_3)_3$], 34.0 (quint, J_{CD} = 25.0 Hz, C-3), 59.4 (+, C-2′), 65.06 (+, C-2), 81.56 [C_{quat}, $C(CH_3)_3$], 127.4, 128.07, 128.67, 128.73, 129.3, 130.5 (+, Ph-C), 136.27, 139.2 (C_{quat}, Ph-C), 170.16 (C_{quat}, C=N), 171.8 (C_{quat}, C=O) ppm. For spectroscopic and analytical data of the non-labeled compound see refs.[3b,d,e]

***tert*-Butyl 3-[*trans*-2′-(Di-*tert*-butoxycarbonylamino)cyclopropyl]-3,3-dideuterio-2-*N*-(diphenylmethylene)alanate (18):** To a solution of 1,2-bis(diphenylphosphanyl)ethane (dppe) (4.78 g, 12.0 mmol) in anhydrous CH_2Cl_2 (30 mL) was added a solution of iodine (3.05 g, 12.0 mmol) in CH_2Cl_2 (60 mL) at –10 °C over a period of 30 min under an atmosphere of argon. After stirring for an additional 30 min, a solution of the THP-protected alcohol **16** (3.74 g, 10.0 mmol) in CH_2Cl_2 (15 mL) was added dropwise at 0 °C, and the resulting mixture was warmed to ambient temp. over a period of 2 h. The reaction mixture was poured into hexane/Et_2O, (2:1) mixture (250 mL), the mixture filtered through a pad of Celite (2 cm) and concentrated under reduced pressure. The product was purified by flash column chromatography (100 g of silica gel, 6 × 7 cm column, hexane/Et_2O, 1:1) to give 1.36 g (34 %) of the rather unstable ***trans*-1-(di-*tert*-butoxycarbonylamino)-2-(dideuterioiodomethyl)cyclopropane** (**17**) which was immediately coupled with the glycinate **11**. **17:** ^1H NMR: δ = 0.76–0.89 (m, 2 H, 3-H), 0.91–1.00 (m, 1 H, 2-H), 1.44 [s, 18 H, 2 $C(CH_3)_3$], 2.46–2.50 (m, 1 H, 3-H) ppm. ^{13}C NMR: δ = 8.9 (quint, J = 22.2 Hz, CD_2), 13.4 (–, C-3), 19.3 (+, C-1), 25.2 [+, 2 $C(CH_3)_3$], 39.5 (+, C-1), 82.3 [C_{quat}, 2 $C(CH_3)_3$)], 152.3 (C_{quat}, 2 NC=O) ppm. Compound **18** (1.59 g, 82 %) was obtained from the iodide **17** (1.36 g, 3.4 mmol), *tert*-butyl *N*-(diphenylmethylene)glycinate (**11**) (1.0 g, 3.4 mmol) and *n*BuLi (3.4 mmol, 2.2 mL of a 1.56 N solution in hexane) according to GP2 as a yellow oil after column chromatography (50 g of silica gel, 3 × 15 cm column, hexane/Et_2O, 2:1, R_f = 0.40) as a 1.2:1 mixture of rotamers **18a**,**b**. ^1H NMR (**18a**,**b**): δ = 0.88–0.97 (m, 2 H, 3′-H), 1.20–1.23 (m, 1 H, 1′-H), 1.42, 1.45, 1.47 [s, 9 H, $C(CH_3)_3$], 2.32–2.36 (m, 1 H, 2′-H), 4.03 (m, 1 H, 2-H, **18b**), 4.12 (m, 1 H, 2-H, **18a**), 7.16–7.20 (m, 2 H, Ph-H), 7.30–7.45 (m, 6 H, Ph-H), 7.62–7.64 (m, 4 H, Ph-H) ppm. ^{13}C NMR (**18a**): δ = 16.7 (–, C-3′), 20.3 (+, C-1′), 28.0 [+, 2 $C(CH_3)_3$], 28.1 [+, $C(CH_3)_3$], 34.6 (+, C-2′), 65.8 (+, C-2), 81.0 [C_{quat}, $C(CH_3)_3$], 82.1 [C_{quat}, 2 $C(CH_3)_3$)], 128.0, 128.3, 128.6, 128.7, 130.19 (+, Ph-C), 136.6, 139.5 (C_{quat}, Ph-C), 152.9 (C_{quat}, 2 NC=O), 170.2 (C_{quat}, C=N*), 171.0 (C_{quat}, C=O*) ppm. ^{13}C NMR (**18b**): δ = 16.2 (–, C-3′), 20.3 (+, C-1′), 28.0 [+, 2 $C(CH_3)_3$], 28.1 [+, $C(CH_3)_3$], 33.7 (+, C-2′), 65.3 (+, C-2), 81.0 [C_{quat}, $C(CH_3)_3$], 82.1 [C_{quat}, 2 $C(CH_3)_3$], 128.0, 128.3, 128.6, 128.7, 130.12 (+, Ph-C), 136.7, 139.6 (C_{quat}, Ph-C), 153.0 (C_{quat}, 2 NC=O), 170.2 (C_{quat}, C=N), 171.0 (C_{quat}, C=O) ppm. The quintet of the CD_2 group is of weak intensity.[28]

***tert*-Butyl *N*-(Diphenylmethylene)-3-(*trans*-2′-methoxycarbonylcyclopropyl)alanate (21):** Compound **21** (12.63 g, 97 %) was obtained from the iodide **20** (7.67 g, 32.0 mmol), *tert*-butyl *N*-(diphenylmethylene)glycinate (**11**) (9.44 g, 32.0 mmol) and *n*BuLi (32.2 mmol, 19.5 mL of a 1.65 N solution in hexane) according to GP2 as a colorless oil after column chromatography (100 g of silica gel, 4 × 20 cm column, hexane/Et_2O, 5:2, R_f = 0.34) as a 1.2:1 mixture

of rotamers **21a**,**b**. IR(film): $\tilde{\nu}$ = 3082 cm^{-1}, 3058, 3004, 2977, 2950, 1729 (C=O), 1624, 1447, 1368, 1276, 1172. ^{1}H NMR (**21a**,**b**): δ = 0.65 (ddd, J = 5.0, 6.9, 10.8 Hz, 1 H, 3′-H, **21a**), 0.75 (ddd, J = 5.0, 6.9, 10.8 Hz, 1 H, 3′-H, **21b**), 1.06 (ddd, J = 5.0, 6.9, 9.1 Hz, 1 H, 3′-H, **21a**), 1.14 (ddd, J = 5.0, 6.9, 9.1 Hz, 1 H, 3′-H, **21b**), 1.15–1.18 (m, 1 H, 1 H, 1′-H), 1.27–1.32 (m, 1 H, 2′-H), 1.42 [s, 9 H, $C(CH_3)_3$], 1.85–2.10 (m, 2 H, 3-H), 3.47 (s, 3 H, CH_3, **21a**), 3.64 (s, 3 H, CH_3, **21b**), 4.04 (dd, J = 4.5, 9.0 Hz, 1 H, 2-H), 7.16–7.68 (m, 10 H, Ph-H) ppm. ^{13}C NMR (**21a**): δ = 14.7 (–, C-3′), 19.9 (+, C-1′), 20.7 (+, C-2′), 28.0 [+, $C(CH_3)_3$], 36.6 (–, C-3), 51.4 (+, CH_3), 65.1 (+, C-2), 81.1 [C_{quat}, $C(CH_3)_3$], 127.7, 127.9, 128.3, 128.4, 129.7, 130.0 (+, Ph-C), 132.1, 139.4 (C_{quat}, Ph-C), 170.80 (C_{quat}, C=N), 172.11 (C_{quat}, C=O), 174.4 (C_{quat}, C=O) ppm. ^{13}C NMR (**21b**): δ = 15.9 (–, C-3′), 19.7 (+, C-1′), 20.7 (+, C-2′), 28.0 [+, $C(CH_3)_3$], 36.9 (–, C-3), 51.5 (+, CH_3), 66.1 (+, C-2), 81.1 [C_{quat}, $C(CH_3)_3$], 127.8, 128.0, 128.5, 128.8, 129.6, 130.2 (+, Ph-C), 132.3, 139.5 (C_{quat}, Ph-C), 170.77 (C_{quat}, C=N), 172.08 (C_{quat}, C=O), 174.2 (C_{quat}, C=O) ppm.

Deprotection of Protected Amino Acids. General Procedure (GP) 3: The protected amino acids **12**, **18** or **21** (10 mmol) were taken up with diethyl ether (100 mL), 1 N HCl aq. solution (150 mL) was added, and the resulting mixture was vigorously stirred at ambient temperature for the indicated time. The aqueous phase was washed with Et_2O (2 × 80 mL) and the solvents evaporated in vacuo. The residue was washed with Et_2O (30 mL) and dried over P_2O_5 under reduced pressure to give the respective amino acid hydrochloride (dihydrochloride) in pure form.

***rac*-3,3-Dideuterio-3-(*trans*-2′-nitrocyclopropyl)alanine Hydrochloride *rac*-[D_2]-3·HCl:** Compound *rac*-[D_2]-**3**·HCl (5.91 g, 84 %) was obtained from **12** (14.01 g, 35.5 mmol) according to GP3 (2 d stirring) as a colorless powder, a 1:1 mixture of the diastereomers [D_2]-**3a**·HCl and [D_2]-**3b**·HCl, m.p. 179 °C (dec.). ^{1}H NMR (D_2O, [D_2]-**3a**,**b**·HCl): δ = 1.27–1.35 (m, 1 H, 3′-H), 1.87–1.94 (m, 1 H, 3′-H), 2.08–2.18 (m, 1 H, 1′-H), 4.14 (s, 1 H, 2-H, [D_2]-**3a**·HCl), 4.15 (s, 1 H, 2-H, [D_2]-**3b**·HCl), 4.34–4.39 (m, 1 H, 2′-H) ppm. ^{13}C NMR (D_2O, [D_2]-**3a**·HCl): δ = 18.09 (–, C-3′), 22.6 (+, C-1′), 30.2 (quint, J_{CD} = 21.0 Hz, C-3), 52.2 (+, C-2′), 58.3 (+, C-2), 171.5 (–, C=O) ppm. ^{13}C NMR (D_2O, [D_2]-**3b**·HCl): δ = 18.15 (–, C-3′), 21.9 (+, C-1′), 30.2 (quint, J_{CD} = 21.0 Hz, C-3), 52.2 (+, C-2′), 58.4 (+, C-2), 171.56 (–, C=O) ppm. MS (FAB): m/z (%) = 211 (100) [M – H^+], 177 (100) [M – Cl^+]. For spectroscopic and analytical data of the non-labeled compound see refs.[3a–d]

***rac*-3-(*trans*-2′-Aminocyclopropyl)-3,3-dideuterioalanine Dihydrochloride (*rac*-[D_2]-4·2 HCl):** Compound *rac*-[D_2]-**4**·2 HCl (542 mg, 88 %) was obtained from **18** (1.59 g, 2.81 mmol) according to GP3 (2 d stirring) as a colorless powder, a 1.1:1 mixture of the diastereomers [D_2]-**4a**·2HCl and [D_2]-**4b**·2HCl, m.p. 169 °C (dec.). ^{1}H NMR (D_2O, [D_2]-**4a**,**b**·2 HCl): δ = 0.65–0.71 (m, 1 H, 3′-H), 0.87–0.96 (m, 1 H, 3′-H), 1.14–1.21 (m, 1 H, 1′-H), 2.40–2.44 (m, 1 H, 2′-H), 3.97 (s, 1 H, 2-H, [D_2]-**4b**·2 HCl), 3.99 (s, 1 H, 2-H, [D_2]-**4a**·2 HCl) ppm. ^{13}C NMR (D_2O, [D_2]-**4a**·2 HCl): δ = 12.2 (–, C-3′), 15.0 (+, C-1′), 30.3 (+, C-2′), 32.5 (quint, J_{CD} = 20.1 Hz, C-3), 54.7 (+, C-2), 173.9 (–, C=O) ppm. ^{13}C NMR (D_2O, [D_2]-**4b**·2 HCl): δ = 12.4 (–, C-3′), 15.1 (+, C-1′), 30.3 (+, C-2′), 32.5 (quint, J_{CD} = 20.1 Hz, C-3), 54.7 (+, C-2), 173.9 (–, C=O) ppm. MS (CI): m/z (%) = 164 (75) [M – 2HCl + NH_4^+], 147 (100) [M – 2HCl + H^+].[29]

***rac*-3-[*trans*-2′-(Hydroxycarbonyl)cyclopropyl]alanine Hydrochloride (*rac*-5a·HCl):**[5] Compound **5a**·HCl (2.00 g, 93 %) was obtained from **21** (4.18 g, 10.26 mmol) according to GP3 (3 d stirring) as a colorless powder, m.p. 202–207 °C (dec.). ^{1}H NMR (D_2O): δ = 0.75–0.82 (m, 1 H, 3′-H), 0.99–1.10 (m, 1 H, 3′-H), 1.21–1.30 (m, 1 H, 1′-H), 1.31–1.45 (m, 1 H, 2′-H), 1.65–1.95 (m, 2 H, 3-H), 3.79–3.95 (m, 1 H, 2-H) ppm. ^{13}C NMR (D_2O): δ = 17.3 (–, C-3′), 20.4 (+, C-1′), 22.0 (+, C-2′), 35.2 (–, C-3), 55.7 (+, C-2), 175.0 (C_{quat}, C=O), 180.8 (C_{quat}, C=O) ppm.

***rac*-3-[*trans*-2′-(Methoxycarbonyl)cyclopropyl]alanine Hydrochloride (*rac*-5b·HCl):** Compound **5b**·HCl (1.47 g, 52 %) was obtained from **21** (5.18 g, 12.71 mmol) according to GP3 (3.5 h stirring) as a 1:1 mixture of the diastereomers **5ba**·HCl and **5bb**·HCl (colorless powder) after an additional treatment of the crude product (2.18 g) with 4 N HCl in EtOAc (50 mL) within 40 min, concentration of the resulting slurry and trituration of the residue with acetone/EtOAc, 1:1, m.p. 160–163 °C (dec.). R_f = 0.18 (MeCN/AcOH/H_2O = 10:1:1). IR(KBr): $\tilde{\nu}$ = 3450–2600 cm^{-1}, 1735 (C=O), 1709 (C=O), 1625, 1478, 1457, 1442, 1371, 1226, 1184. ^{1}H NMR (D_2O, **5ba**,**bb**·HCl): δ = 0.73–0.83 (m, 1 H, 3′-H), 0.98–1.12 (m, 1 H, 3′-H), 1.23–1.35 (m, 1 H, 1′-H), 1.35–1.51 (m, 1 H, 2′-H), 1.65–1.98 (m, 2 H, 3-H), 3.49 (s, 3 H, OMe), 3.92–4.02 (m, 1 H, 2-H) ppm. ^{13}C NMR (D_2O, **5ba**·HCl): δ = 16.9 (–, C-3′), 20.0 (+, C-1′), 22.0 (+, C-2′), 34.9 (–, C-3), 54.9 (+, OMe), 55.1 (+, C-2), 174.1 (C_{quat}, C=O), 179.2 (C_{quat}, C=O) ppm. ^{13}C NMR (D_2O, **5bb**·HCl): δ = 17.1 (–, C-3′), 20.4 (+, C-1′), 22.1 (+, C-2′), 35.2 (–, C-3), 54.9 (+, OMe), 55.2 (+, C-2), 174.2 (C_{quat}, C=O), 179.3 (C_{quat}, C=O) ppm. $C_8H_{14}ClNO_4$ (223.7): calcd. C 42.96, H 6.31, N 6.26; found C 42.74, H 6.36, N 6.02.

Feeding Experiment with *rac*-[D_2]-3·HCl: The *rac*-[D_2]-**3**·HCl (425 mg, 2.00 mmol) was fed to the growing culture using a 1-L fermenter to give the deuterated hormaomycin **1b** (16.7 mg). ^{1}H NMR: decreased: δ = –0.07 [0.15 H, 3-H_a, *(3-Ncp)Ala I*], 0.58 [0.14 H, 3-H_b, *(3-Ncp)Ala I*], 1.60 [0.10 H, 3-H_a, *(3-Ncp)Ala II*], 1.81 [0.15 H, 3-H_b, *(3-Ncp)Ala II*] ppm. ^{13}C NMR: decreased: δ = 33.0 [C-3, *(3-Ncp)Ala I*], 35.1 [C-3, *(3-Ncp)Ala II*] ppm.

Feeding Experiment with *rac*-[D_2]-4·2 HCl: The *rac*-[D_2]-**4**·2HCl (350 mg, 1.60 mmol) was fed to the growing culture using an 1-L fermenter to give unlabeled hormaomycin **1a** (8.1 mg).

Feeding Experiment with*rac*-5a·HCl: The *rac*-**5a**·HCl (1.10 g, 5.25 mmol) was fed to the growing culture using a 5-L fermenter to give after additional purification (by preparative HPLC: gradient 80 % MeCN in H_2O → 85 % MeCN in H_2O within 51 min, flow rate 3.5 mL/min), a mixture of **1a** and **23** (0.4 mg).

Feeding Experiment with*rac*-5b·HCl: The *rac*-**5b**·HCl (1.20 g, 5.37 mmol) was fed to the growing culture using a 5-L fermenter to give the hormaomycin analogue **23** (2.9 mg). ^{1}H NMR: δ = –0.78to –0.65 [m, J = 6.7, 6.7, 6.7 Hz, 1 H, 3′-H_a, *(3-Mcp)Ala I*], –0.12 to –0.04 [m, 1 H, 3-H_a, *(3-Mcp)Ala I*], 0.34 [ddd, J = 7.5, 3.5, 3.5 Hz, 1 H, 1′-H, *(3-Mcp)Ala I*], 0.45* [ddd, J = 8.5, 4.5, 4.5 Hz, 1 H, 2′-H, *(3-Mcp)Ala*], 0.53–0.63 [m, 1 H, 3-H_b, *(3-Mcp)Ala I*], 0.61–0.69* [m, 1 H, 2′-H, *(3-Mcp)Ala*], 0.85 (t, J = 7.0 Hz, 3 H, 5-H, *Ile*), 0.91–1.11 [m, J = 7.0, 1 H, 3′-H_b, *(3-Mcp)Ala I*], 1.00 [q, J = 7.0, 1 H, 3′-H_a, *(3-Mcp)Ala II*], 1.05 (d, J = 7.0 Hz, 3 H, 1′-H, *Ile*), 1.27–1.35 (m, 1 H, 4-H_a, *Ile*), 1.30 [d, J = 7.0 Hz, 3 H, 4-H, *(β-Me)Phe II*], 1.40 [d, J = 7.0 Hz, 3 H, 4-H, *(β-Me)Phe I*], 1.48–1.56 (m, 1 H, 4-H_b, *Ile*), 1.52 (d, J = 7.0 Hz, 3 H, 4-H, *a-Thr*), 1.60–1.69 [m, 1 H, 3-H_a, *(3-Mcp)Ala II*], 1.66 [dd, J = 7.0, 1.5 Hz, 3 H, 3′-H, *(4-Pe)Pro*], 1.60–2.06 [m, 5 H, 3-H_b, 1′-H, 3′-H_b, *(3-Mcp)Ala II*, 3-H, *Ile*, 3-H_a, *(4-Pe)Pro*], 2.31–2.39 [m, 1 H, 3-H_b, *(4-Pe)Pro*], 3.00 [dq, J = 10.5, 7.0 Hz, 1 H, 3-H, *(β-Me)Phe II*], 3.19–3.32 [m, 2 H, 4-H, 5-H_a, *(4-Pe)Pro*], 3.43–3.50 [m, 1 H, 2-H, *(3-Mcp)Ala I*], 3.53–3.65* [m, 1 H, 3-H, *(β-Me)Phe I*], 3.60 [s, 3 H, OMe, *(3-Mcp)Ala II*], 3.62 [s, 3 H, OMe, *(3-Mcp)Ala I*], 3.95–4.02 [m, 1 H, 5-H_b, *(4-Pe)Pro*], 4.28 [dd, J = 11.5, 6.0 Hz, 1 H, 2-H, *(4-Pe)Pro*], 4.35 [dd, J = 10.5, 10.5 Hz, 1 H, 2-H, *(β-Me)Phe II*], 4.46 [dd, J = 10.0, 5.0 Hz, 1 H, 2-H, *(β-Me)Phe I*], 4.55 (dd, J = 9.5, 2.5 Hz, 1 H, 2-H, *a-Thr*), 4.60 (dd, J = 9.0,

9.0 Hz, 1 H, 2-H, *Ile*), 5.06–5.14 [m, 1 H, 2-H, *(3-Mcp)Ala II*], 5.23–5.28 [m, 1 H, 1′-H, *(4-Pe)Pro*], 5.38 (dq, J = 2.5, 7.0 Hz, 1 H, 3-H, *a-Thr*), 5.60 [dq, J = 10.5, 7.0 Hz, 1 H, 2′-H, *(4-Pe)Pro*], 6.08 (d, J = 4.5 Hz, 1 H, 4-H, *Chpca*), 6.68 (d, J = 8.0 Hz, 1 H, NH), 6.75 (d, J = 5.0 Hz, 1 H, NH), 6.76 (d, J = 4.5 Hz, 1 H, 3-H, *Chpca*), 6.98 (d, J = 10.5 Hz, 1 H, NH), 7.00–7.04 (m, 1 H, Ar-H), 7.10–7.17 (m, 4 H, Ar-H), 7.15–7.19 (m, 1 H, Ar-H), 7.21–7.25 (m, 4 H, Ar-H), 7.25–7.35 (br., 1 H, NH), 7.90 (d, J = 9.0 Hz, 1 H, NH), 9.05 (d, J = 9.5 Hz, 1 H, NH) ppm; the OH signal in the *Chpca* moiety was not observed. ^{13}C NMR: δ = 10.3 (+, C-5, *Ile*), 13.3 [+, C-3′, *(4-Pe)Pro*], 14.2 [–, C-3′, *(3-Mcp)Ala I*], 14.3 [+, C-4, *(β-Me)Phe I*], 14.5 [–, C-3′, *(3-Mcp)Ala II*], 14.9 (+, C-1′, *Ile*), 16.9 (+, C-4, *a-Thr*), 17.2 [+, C-2′, *(3-Mcp)Ala I*], 17.8 [+, C-4, *(β-Me)Phe II*], 18.4 [+, C-2′, *(3-Mcp)Ala II*], 18.8 [+, C-1′, *(3-Mcp)Ala I*], 19.8 [+, C-1′, *(3-Mcp)Ala II*], 25.0 (–, C-4, *Ile*), 35.2 [–, C-3, *(3-Mcp)Ala I*], 35.5 [–, C-3, *(4-Pe)Pro*], 36.7 [+, C-4, *(4-Pe)Pro*], 37.0 [–, C-3, *(3-Mcp)Ala II*], 37.5 (+, C-3, *Ile*), 39.9 [+, C-3, *(β-Me)Phe I*], 42.0 [+, C-3, *(β-Me)Phe II*], 51.6 [+, C-2, *(3-Mcp)Ala II*], 51.7 [+, C-2, OMe, *(3-Mcp)Ala I*], 52.6 [–, C-5, *(4-Pe)Pro*], 52.7 [+, OMe, *(3-Mcp)Ala II*], 54.5 (+, C-2, *Ile*), 55.0 (+, C-2, *a-Thr*), 59.9 [+, C-2, *(β-Me)Phe II*], 60.1 [+, C-2, *(β-Me)Phe I*], 61.3 [+, C-2, *(4-Pe)Pro*], 69.3 (+, C-3, *a-Thr*), 103.4 (+, C-4, *Chpca*), 109.4 (+, C-3, *Chpca*), 119.2 (C_{quat}, C-2, *Chpca*), 121.5 (C_{quat}, C-5, *Chpca*), 127.09, 127.12, 127.4, 127.73, 128.5, 128.6 (+, Ar-C), 127.68 [+, C-1′, *(4-Pe)Pro*], 128.1 [+, C-2′, *(4-Pe)Pro*], 141.8, 141.9 (C_{quat}, Ar-C), 159.2 (C_{quat}, C-1, *Chpca*), 168.9, 169.1, 170.1, 170.4, 171.3, 171.6, 172.5 (C_{quat}, C-1) ppm. MS (ESI, positive): m/z = 1177 (100) [M + Na$^+$]. ESI-MS/MS: 1177 (positive ion): 1161, 1141, 1034, 1087, 1060; 1160: 1016, 923, 877, 811, 792, 764; 923: 810, 764; 810: 649, 631; 649: 480, 462, 434.

Feeding Experiment with *rac*-6·HCl (without addition of proline): The *rac*-**6**·HCl (350 mg, 1.78 mmol) was fed to the growing culture using a 1-L fermenter to give after additional purification (by preparative HPLC: 55 % MeCN in H_2O 10 min, then gradient 55 % MeCN in H_2O → 100 % MeCN within 10 min, flow rate 2.5 mL/min) the pure **25a** (0.5 mg), the mixture of **25a** and **25b** (0.8 mg) (fraction A), and the mixture of **25c** and hormaomycin **1a** (0.6 mg) (fraction B).

25a: MS (ESI): positive, m/z = 1149 (48) [M – H$^+$ + 2Na$^+$], 1128 (100) [M + Na$^+$]. ESI-MS/MS: 1127 (positive ion): 1110, 1091, 1010, 984; 1010: 963, 935, 873, 885, 827; 873: 760, 714; 760: 599; 599: 552, 506, 466, 455, 437, 409, 391. ^{1}H NMR: see Figure 3 and ref.[15]

Fraction A: MS (ESI): positive, m/z = 1139 (100) [M_1 + Na$^+$], 1127 (100) [M_2 + Na$^+$]. ESI-MS/MS: 1139 (positive ion): 1103, 1022, 996; 1022: 965, 885, 867, 839; 885: 772, 726; 772: 715, 697, 611; 611: 593, 577, 554, 455, 437, 409.

Fraction B: MS (ESI): positive, m/z = 1139 (100) [M_1 + Na$^+$], 1151 (100) [M_2 + Na$^+$]. ESI-MS/MS: 1139 (positive ion): 1103, 1022, 996; 1022: 965, 885, 867, 839; 885: 772, 726; 772: 725, 644, 611; 611: 564, 484, 449, 421.

HPLC experiments: column: Nucleosil-C_{18}, 100 Å, 5 μm, 250 × 3 mm, 65 % MeCN in H_2O (0.1 % TFA), flow rate 0.5 mL/min. Fraction A: **25a/25b**: 1:1; **25a**: t_R = 13.74 min; **25b**: t_R = 14.44 min. Mixed sample with synthetic **25b**: peak with t_R = 14.44 min increased. **25a**: t_R = 13.72 min; mixed probe with **25a** isolated from the feeding experiment with H-(*S*)-NO_2Nva-OH: One peak. Fraction B: **25c/1a**: 1:1; **25c**: t_R = 16.18 min; **25a**: t_R = 13.74 min; **1a**: t_R = 17.22 min. Mixed probe with **25c** isolated from the feeding experiment with H-(*S*)-NO_2Nva-OH: one peak.

Feeding Experiment with *rac*-6·HCl (with addition of proline): The mixture of *rac*-**6**·HCl (1.10 g, 5.60 mmol) and proline (760 mg, 6.6 mmol) was fed to the growing culture using a 5-L fermenter to give after additional purification (by preparative HPLC: 80 % MeOH in H_2O, flow rate 2.5 mL/min) **25a** (1.1 mg).

Feeding Experiments with Cyclopropylalanine *rac*-7·HCl: This experiment was repeated three times. Different quantities of *rac*-**7**·HCl (400 mg, 2.42 mmol; 800 mg, 4.83 mmol; 1.60 g, 9.66 mmol) were fed to the growing culture using a 1-L fermenter. Neither hormaomycin **1a** nor any analogue was isolated in any of these experiments.

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[1] Isolation and properties: a) N. Andres, H. Wolf, H. Zähner, E. Rössner, A. Zeeck, W. A. König, V. Sinnwell, *Helv. Chim. Acta* **1989**, *72*, 426–437; b) E. Rössner, A. Zeeck, W. A. König, *Angew. Chem.* **1990**, *102*, 84–85; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 64–65; c) K. Otoguro, H. Ui, A. Ishiyama, N. Arai, M. Kobayashi, Y. Takahashi, R. Masuma, K. Shiomi, H. Yamada, S. Omura, *J. Antibiotics* **2003**, *56*, 322–324. For the total synthesis see: d) B. D. Zlatopolskiy, A. de Meijere, *Chem. Eur. J.* **2004**, *10*, 4718–4727. Final structure elucidation: e) B. Zlatopolskiy, K. Loscha, P. Alvermann, S. I. Kozhushkov, S. V. Nikolaev, A. Zeeck, A. de Meijere, *Chem. Eur. J.* **2004**, *10*, 4708–4717. The formula of **1a** as presented here and in these previous publications do depict the correct configuration in the (*S*)-isoleucine (Ile) moiety. The formulas in our recently published "Corrigendum" (see *Chem. Eur. J.* **2004**, *10*, 5568) were indeed erroneous in this respect.

[2] Isolation and properties: a) A. Asai, A. Hasegawa, K. Ochiai, Y. Yamashita, T. Mizukami, *J. Antibiotics* **2000**, *53*, 81–83; b) H. Yamaguchi, A. Asai, T. Mizukami, Y. Yamashita, S. Akinaga, S.-i. Ikeda, Y. Kanda, *Eur. Patent 1,166,781 A1* **2000**; *Chem. Abstr.* **2000**, *133*, 751; c) A. Asai, T. Tsujita, S. V. Sharma, Y. Yamashita, S. Akinaga, M. Funakoshi, H. Kobayashi, T. Mizukami, M.-s. Asahi-machi, *Biochem. Pharmacol.* **2004**, *67*, 227–234. Total synthesis of belactosin A: d) O. V. Larionov, A. de Meijere, *Org. Lett.* **2004**, *6*, 2153–2156; e) A. Armstrong, J. N. Scutt, *Chem. Commun.* **2004**, 510–511.

[3] Preparations of the non-labeled enantiomerically pure 3-(*trans*-2′-nitrocyclopropyl)alanines (**3**): a) O. V. Larionov, T. F. Savelieva, K. A. Kochetkov, N. S. Ikonnokov, S. I. Kozhushkov, D. S. Yufit, J. A. K. Howard, V. N. Khrustalev, Yu. N. Belokon, A. de Meijere, *Eur. J. Org. Chem.* **2003**, 869–877. For the synthesis of enantiomerically pure mixtures of epimers of **3** see also: b) J. Zindel, A. Zeeck, W. A. König, A. de Meijere, *Tetrahedron Lett.* **1993**, *34*, 1917–1920; c) J. Zindel, A. de Meijere, *Synthesis* **1994**, 190–194; d) J. Zindel, A. de Meijere, *J. Org. Chem.* **1995**, *60*, 2968–2973; e) J. Zindel, *Dissertation*, University of Göttingen, **1993**.

[4] Preliminary communication: a) M. Brandl, S. I. Kozhushkov, K. Loscha, O. V. Kokoreva, D. S. Yufit, J. A. K. Howard, A. de Meijere, *Synlett* **2000**, 1741–1744. This strategy was recently applied for the preparation of enantiomerically pure **4**, which in turn was used in the total synthesis of **2** (see ref. [2e]); b) A. Armstrong, J. N. Scutt, *Org. Lett.* **2003**, *5*, 2331–2334. For an alternative approach to **4** see also: c) O. V. Larionov, S. I. Kozhushkov, M. Brandl, A. de Meijere, *Mendeleev Commun.* **2003**, 199–200.

[5] The amino acid **5** has previously been prepared in four steps starting from 2-amino-4-pentenoic acid with an overall yield of

only 44 %. It has been shown to be a selective partial agonist of the *N*-methyl-D-aspartate (NMDA) receptor site: R. Pellicciari, B. Natalini, M. Marinozzi, B. M. Sadeghpour, A. A. Cordi, T. H. Lanthorn, W. F. Hood, J. B. Monahan, *Farmaco* **1991**, *46*, 1243–1264.

[6] a) C. Hamon, B. J. Rawlings, *Synth. Commun.* **1996**, *26*, 1109–1116, and references cited therein. This compound was prepared by alkylation of the lithiated O'Donnel's glycine equivalent **11** with iodomethylcyclopropane followed by acid-catalyzed deprotection, see also: b) E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415; c) D. Tzalis, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 3685–3688.

[7] E. J. Corey, S. G. Pyne, W. Su, *Tetrahedron Lett.* **1983**, *24*, 4883–4886.

[8] a) M. J. O'Donnell, R. L. Polt, *J. Org. Chem.* **1982**, *47*, 2663–2666; b) for recent reviews see: M. J. O'Donnell, *Aldrichimica Acta* **2001**, *34*, 3–15, and ref.[3] cited therein.

[9] Several of the conceivable approaches to **4** such as the Curtius degradation of protected 3-(*trans*-2-hydroxycarbonylcyclopropyl)alanine as well as substitution of the 3-[*trans*-2-(*tert*-butoxycarbonyl)aminocyclopropyl]methanol tosylate with the nucleophilic O'Donnell glycine equivalent **11** were tested without any success. The starting materials for these attempted transformations were prepared from dimethyl *trans*-1,2-cyclopropanedicarboxylate according to published procedures. Cf. a) R. Csuk, Y. v. Scholz, *Tetrahedron* **1995**, *51*, 7193–7206; b) R. Csuk, Y. v. Scholz, *Tetrahedron* **1994**, *50*, 10431–10442.

[10] a) M. Coblentz, J. Royer, J. Dreux, *Bull. Soc. Chim. Fr.* **1963**, 1279–1280; b) N. Miyashita, A. Yoshikoshi, P. A. Greico, *J. Org. Chem.* **1977**, *42*, 3772–3774; c) G. Kokotos, J. M. Padron, T. Martin, W. A. Gibbons, V. S. Martin, *J. Org. Chem.* **1998**, *63*, 3741–3744; d) G. Bold, H. Steiner, L. Moesch, B. Walliser, *Helv. Chim. Acta* **1990**, *73*, 405–410.

[11] a) S. P. Schmidt, D. W. Brooks, *Tetrahedron Lett.* **1987**, *28*, 767–768; b) A. Martinez-Grau, D. P. Curran, *Tetrahedron* **1997**, *53*, 5679–5698; c) D. P. Curran, J. Xu, E. Lazzarini, *J. Chem. Soc. Perkin Trans. 1 Chem. Soc. Perkin Trans. 1* **1995**, 3049–3060; d) M. Lautens, S. Kumanovic, *J. Am. Chem. Soc.* **1995**, *117*, 1954–1964.

[12] J. E. Baldwin, G. E. C. Chang, *Tetrahedron* **1982**, *38*, 825–835.

[13] M. Brandl, S. I. Kozhushkov, B. Zlatopolskiy, P. Alvermann, B. Geers, A. Zeeck, A. de Meijere, *Eur. J. Org. Chem.* **2005**, 123–135.

[14] For experimental details see: P. Alvermann, *Dissertation*, University of Göttingen, **2001**.

[15] H. von Döhren, U. Keller, J. Vater, R. Zocher, *Chem. Rev.* **1997**, *97*, 2675–2705.

[16] B. Zlatopolskiy, M. Radzom, A. Zeeck, A. de Meijere, *Eur. J. Org. Chem.*, manuscript submitted.

[17] Different samples of hormaomycin **1a** and hormaomycin analogues often have noticeable differences in their ^{1}H-NMR spectra. Moreover, at least for one hormaomycin analogue, 1H-NMR spectra measured with the same spectrometer, in the same solvent, at the same temperature, and from the same sample showed distinct differences. See ref.[1d] for a deeper discussion.

[18] a) A. L. J. Beckwith, K. U. Ingold, in: *Rearrangements in Ground and Excited States*, vol. 1 (Ed.: P. de Mayo), Academic Press, New York, **1980**, pp. 161–310; b) J. C. Walton, in *Methods of Organic Chemistry (Houben-Weyl)*, vol. E17c (Ed.: A. de Meijere), Thieme, Stuttgart, **1997**, pp. 2438–2525.

[19] a) D. Wendisch, in: *Methoden der Organischen Chemie (Houben-Weyl)*, vol. 4/3 (Ed.: E. Müller), Thieme, Stuttgart, **1971**, pp. 399–405; c) G. Boche, H. M. Walborsky, *Cyclopropane-Derived Reactive Intermediates* (Eds.: S. Patai, Z. Rappoport), Wiley, Chichester, **1990**, and references therein.

[20] a) M.-t. Lai, L.-d. Liu, H.-w. Liu, *J. Am. Chem. Soc.* **1991**, *113*, 7388–7397; b) M.-t. Lai, H.-w. Liu, *J. Am. Chem. Soc.* **1992**, *114*, 3160–3162.

[21] M. A. Marahiel, T. Stachelhaus, H. D. Mootz, *Chem. Rev.* **1997**, *97*, 2651–2673.

[22] In the radical homoallylic rearrangement of hypoglycine A the arising intermediate inactivates general Acyl-CoA Dehydrogenase, see ref.[20]

[23] U. M. Reinscheid, B. D. Zlatopolskiy, A. Zeeck, C. Griesinger, A. de Meijere, *Chem. Eur. J.*, in press.

[24] For the synthesis of the starting di- and monomethyl esters of *trans*-cyclopropane-1,2-dicarboxylic acid, the protocol of Csuk et al. (ref.[9b]) was used. See also: K. M. Edvinsson, M. Hersloef, P. Holm, N. Kann, D. J. Keeling, J. P. Mattsson, B. Norden, V. Shcherbukhin, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 503–508.

[25] a) For spectroscopic and analytical data of the non-deuterated compound see refs.[3d,4]; b) for another method of preparation of a non-deuterated compound see also: L. Dechoux, E. Doris, *Tetrahedron Lett.* **1994**, *35*, 2017–2020.

[26] a) For spectroscopic and analytical data of the non-deuterated compound see refs.[3e,9a]; b) for another method of preparation of the non-deuterated compound see refs.[9a,9b]

[27] For spectroscopic and analytical data of the non-deuterated compound see ref.[3a]

[28] For spectroscopic and analytical data of the non-deuterated compound see Supporting Information in ref.[4b]

[29] For spectroscopic and analytical data of the non-deuterated compound see ref.[4c] and Supporting Information in ref.[4b]

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