Total Synthesis of Various Hormaomycin Analogues with Modified Amino Acid Residues

Dissertation

zur Erlangung des Doktorgrades

der Mathematisch-Naturwissenschaftlichen Fakultäten

der Georg-August-Universität zu Göttingen

vorgelegt von

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Göttingen 2008

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Tag der mündlichen Prüfung: 02.07.2008

Meinem Lehrer, Herrn Prof. Dr. A. de Meijere, danke ich herzlich für die interessante Themenstellung, die während dieser Arbeit erwiesene Unterstützung und die stete Diskussionsbereitschaft zu Fragen dieser Arbeit.

Dedicated to my family – with gratitude for understanding and patience

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ABBREVIATIONS

DCPM	dicyclopropylmethyl;
DIEA	*N*,*N*-diisopropylethylamine;
DMAP	4-dimethylaminopyridine;
EDC	*N*'-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride;
Fmoc	9-fluorenylmethyloxycarbonyl;
FmocOSu	*O*-(9-fluorenylmethyloxycarbonyl)-1-hydroxypyrrolidine-2,5-dione;
HATU	*O*-(7-azabenzotriazole-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate;
HOAt	7-aza-1-hydroxybenzotriazole;
MeZ	4-methylbenzyloxycarbonyl;
MeZOSu	*O*-(4-methylbenzyloxycarbonyl)-1-hydroxypyrrolidine-2,5-dione;
MOM	methoxymethyl;
Teoc	(2-trimethylsilylethyl)-oxycarbonyl;
TeocOSu	*O*-[(2-trimethylsilylethyl)-oxycarbonyl]-1-hydroxypyrrolidine-2,5-dione;
TMP	2,4,6-collidine;
Z	benzyloxycarbonyl;
ZOSu	*O*-benzyloxycarbonyl-1-hydroxypyrrolidine-2,5-dione.

INTRODUCTION

The exploration of microorganisms as sources of medicinally relevant compounds has a much shorter and less well-known history than the use of substances of plant or animal origin. Nevertheless, from the time of the discovery of the antibacterial effect of penicillin by A. Flemming in 1928[1] and the beginning of its widespread application and manufacturing during the Second World War, such substances, which are produced by bacteria and fungi, have been attracting an ever increasing attention of scientists. Among all the chemical entities, which are "manufactured" by these miniature "pharmaceutical factories", the so-called secondary metabolites occupy a special role. Secondary metabolites are those naturally produced substances, which do not play an apparent role in the internal economy of an organism that produces them. In microorganisms the ability to produce such compounds may have evolved because of certain selection advantages conferred upon them as a result of the interactions of the compounds with specific receptors in other organisms. Although almost 20 000 microbial metabolites and approximately 100 000 plant products have been described so far, secondary metabolites still appear to be an inexhaustible source of lead structures for new antimicrobials, antiviral, antitumor and immunosuppressive drugs as well as plant protecting agents. In addition, numerous secondary metabolites, such as Benzylpenicillin[2], Cephalosporin, Erythromycin, Strobilurin, etc. were lead structures that later became the basis for synthetic and semi-synthetic derivatives with improved pharmacological properties.[3] Some of these compounds play a key role not only in defense mechanisms of microorganisms, but may be used as signal substances for intercellular communication with a function similar to those of hormones and pheromones in higher organisms.[4] There are a lot of processes during the life cycle of a bacterium, which are regulated by such substances. For example, they regulate the metabolic capability and the quorum sensing[5] in Gram-negative pathogenic bacteria, the competence[6] and sporulation in *Bacillus*, the sporulation, multicellular differentiation and motility in *Myxococcus*, the antibiotic production, morphological differentiation and sporulation in *Streptomyces* and *Erwinia*, and gene transfer mechanisms in *Enterococcus*.[7,8,9] It appears to be very attractive to employ the knowledge about such compounds either in terms of controlling cellular proliferation or conversely to increase the production of a particular secondary metabolite. The latter possibility was first realized in the 1960s, when several metabolites of *Actinomycetes* were shown to control the production of antibiotics and the morphological differentiation (aerial mycelium formation) even in nanomolar concentrations. All these compounds were structurally very similar 2,3-disubstituted γ-butyrolactones, which nevertheless showed remarkably different spectra of action: a so-called A-factor (Khokhlov factor) stimulated the production of Streptomycin, so-called IM-type regulators stimulated the production of Staphylomycin and so-called VB-type regulators stimulated Virginiamycin production in different *Streptomyces* species.[10,11] There are also modified homoserine lactones, i.e. *N*-(β-ketocaproyl)-(*S*)-homoserine lactone (KHL) of *V. fischeri*, which can stimulate the Carbapenem antibiotic biosynthesis in *E. carovora*, and the B-factor of *A. mediterranei*, an adenosine derivative, which induces Rifamycin B synthesis in *Nocardia* species.[12]

The peptolide Hormaomycin **1** was isolated from *Streptomyces griseoflavus*, strain W-384, during the screening of intermolecular signal substances by Zäner et al. in 1989.[13,14] It was the first ever discovered such substance with a peptide structure, which induced the antibiotics production and aerial mycelium formation not only in the producing strain itself, but also in other *Streptomyces* species. Its e. g. the production of Hydroxystreptomycin in *S. flaveolus*, of Streptolin in *S. fridae*, of Tirandamycin in *S. griseoflavus*, strain 1306, and of Bafilomycin in *S. griseus*. A significant increase in the antibiotics production was observed already at a 0.05 µg/ L concentration of Hormaomycin. This compound also showed strong antibiotic activity against coryneform[15] bacteria (MIC = 0.0005 µg/mL for *Arthrobacter oxydans*).[16]

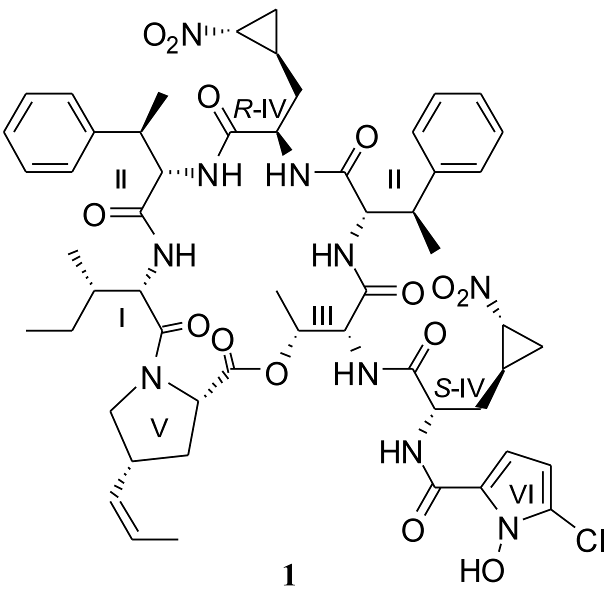

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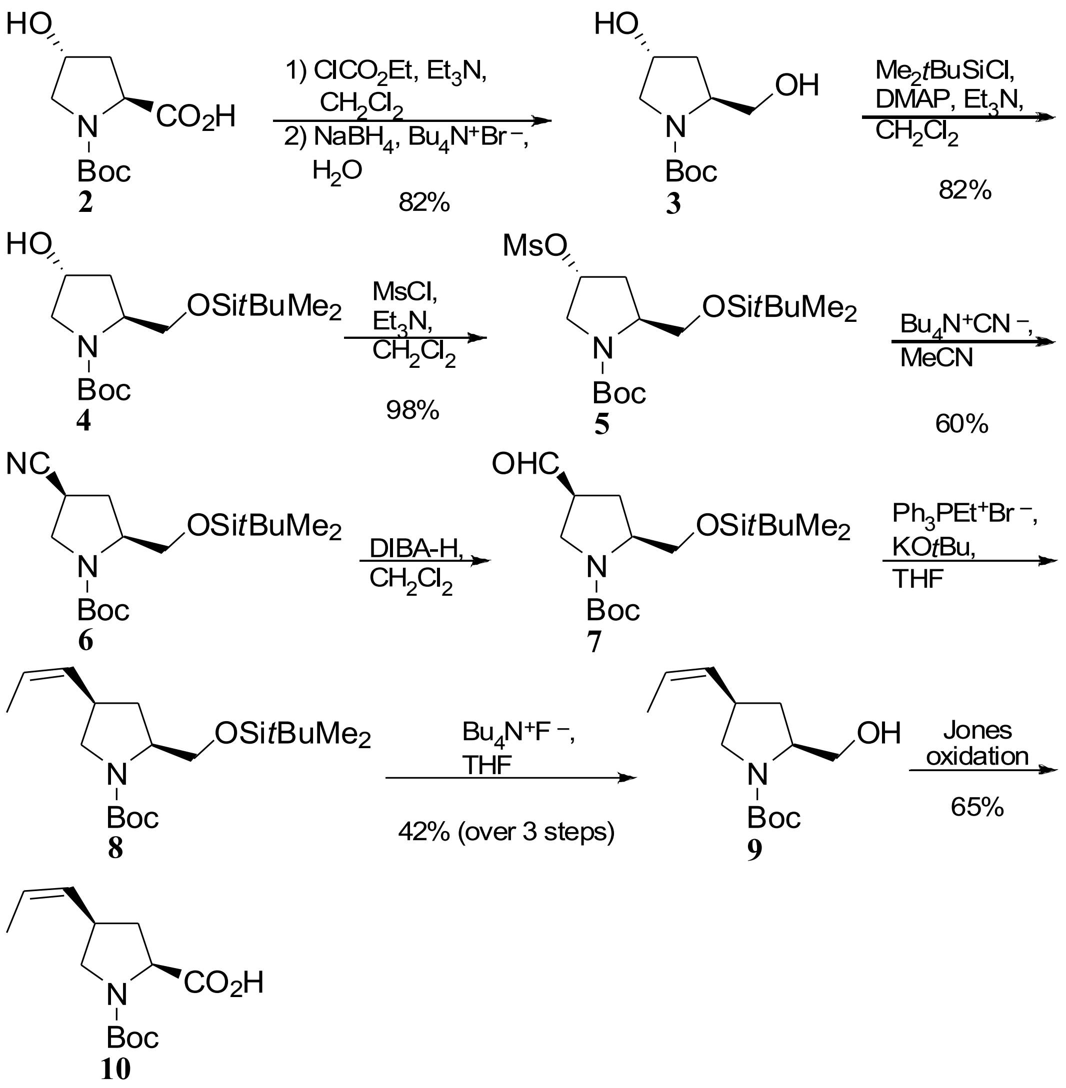
Figure 1. Structure and absolute configuration of Hormaomycin. I (*S*)-Ile; II (2*S*,3*R*)-(βMe)Phe; III (*R*)-a-Thr; IV (1'*R*,2'*R*)-(3-Ncp)Ala; V (2*S*,4*R*)-4-(*Z*)-(4-Pe)Pro; VI Chpca.

The constitution of this cyclic depsipeptide showed features unusual even for this structurally flexible class of compounds. Initial structural investigations performed by Zeeck et al.[14,16,17] disclosed that along with one residue of the proteinogenic (*S*)-isoleucine [Ile], Hormaomycin contains two units of 3-(2*S*,3*R*)-methylphenylalanine [(βMe)Phe, MeF], one of (2*R*)-*allo*-threonine [a-Thr] as well as two moieties of 3-(*trans*-2'-nitrocyclopropyl)alanine [(3-Ncp)Ala] and one of 4-(*Z*)-propenylproline [(4-Pe)Pro**]**. The side chain of **1** is terminated with a residue of 5-chloro-1-hydroxypyrrole-2-carboxylic acid [Chpca] (Figure 1). The latter three elements had never been found in any natural product before. A partial assignment of the absolute configuration of the (3-Ncp)Ala residues in **1** was later made by Zindel and de Meijere.[18,19] The retention times of the derivatized synthetically prepared enantiomerically pure mixtures of the diastereomers of 3-(*trans*-2'-nitrocyclopropyl)alanine were compared with the derivatized components in the total hydrolysate of natural Hormaomycin. These experiments unambiguously proved that both (3-Ncp)Ala residues in the cyclic depsipeptide **1** have the same (1'*R,*2'*R*) configuration in the 2-nitrosubstituted cyclopropyl moiety and the opposite configurations at the α-carbons. However, the assignment as to which diastereomer of the (3-Ncp)Ala residue is incorporated in the ring of **1** and which is attached in the side-chain, remained unsolved. To clarify the situation, feeding experiments with enantiomerically pure deuterium-labelled 3-(*trans*-2'-nitrocyclopropyl)alanine were carried out. (2*S*,1'*RS,*2'*RS*)-3,3-Dideuterio-3-(*trans*-2'-nitrocyclopropyl)alanine was first synthesized by Loscha[20] and the correspondingly deuterium-labelled Hormaomycin was indeed obtained after the appropriate feeding experiments, which were carried out by Alvermann.[21] ^{1}H-, ^{2}H-NMR and MS-ESI spectra of these labelled compounds unequivocally showed that the labelled amino acid had been incorporated twice. The possible explanation for this fact is that the (2*S*)-epimer initially administered, can later in the cell be epimerized by a specific enzyme, an epimerase, before the assembly of the peptide chain of Hormaomycin starts, or during this process, after the amino acid has been bound to the multienzyme complex. The relative and absolute configuration of the 4-(*Z*)-propenylproline moiety remained unclear, and no attempts to elucidate it had been made before Zlatopolski et al.[22] provided this amino acid in deuterium-labelled form for feeding experiments. This investigation disclosed the absolute configuration for the 4-(*Z*)-propenylproline moiety as well as for the (2*R*)- and the (2*S*)-3-(1'*R,*2'*R*)-(2'-nitrocyclopropyl)alanine residues.

While several synthetic accesses to D-*allo*-threonine and (2*S*,3*R*)-3-methylphenylalanine have been reported in the literature, the enantio- and diastereoselective synthesis of the previously unknown 3-(*trans*-2'-nitrocyclopropyl)alanine has mainly been investigated in our group. At first, (2*RS*,1'*S,*2'*S*)-, (2*RS*,1'*R,*2'*R*)- and (2*S*,1'*RS,*2'*RS*)-3-(*trans*-2'-nitrocyclopropyl)alanines were successfully prepared.[18,23] Unfortunately, a great number of steps and a relatively low overall yield strongly decreased the preparative value of this synthetic route. In fact, this procedure even did not enable one to obtain any enantiomerically pure diastereomer of 3-(*trans*-2'-nitrocyclopropyl)alanine. The improvement of the originally reported procedure was connected with the progress in the preparation of the enantiomerically pure (1'*R*,2'*R*)-(2'-nitrocyclopropyl)methanol which served as the key intermediate in this synthesis developed by Brandl and de Meijere et al.[24] Finally, all four possible diastereomers of 3-(*trans*-2'-nitrocyclopropyl)alanine were synthesized by Larionov and de Meijere, et al.[25] in enantiomerically pure form and in good to excellent yields. Significant progress was also achieved in the preparation of 4-(*Z*)-propenylproline. This compound was first prepared from 5-(2-dimethylaminopropyl)piperidone-2 in 1958, but only as a mixture of all four possible stereoisomers along with all possible stereoisomers of 4-allylproline.[26] The procedure more recently proposed by Melotto[27] allowed one to prepare 4-(*Z*)-propenylproline as an individual compound starting from *N*,*O*-diprotected pyroglutamic acid. The protocol, eventually developed by Zlatopolskiy, starts from natural (2*S*,4*R*)-4-hydroxyproline and leads to (2*S*,4*R*)-4-(*Z*)-propenylproline of good purity and, after 8 steps, with an overall yield of more than 10%.[28] Initially, *N*-Boc-protected[29] (2*S*,4*R*)-4-hydroxyproline **2** was converted to the corresponding prolinol **3** by sodium borohydride reduction of the mixed anhydride prepared with ethyl chloroformate. The primary hydroxy group of the resulting diol was selectively protected with $t\mathrm{BuMe_2SiCl}$,[30] and the secondary hydroxy group was converted to a methanesulfonyloxy group to be $\mathrm{S_N2}$-substituted with cyanide with inversion of the configuration. The resulting nitrile **6** was reduced to the corresponding aldehyde **7** with di-*n*-butylaluminum hydride and the (*Z*)-configured double bond was installed by a Wittig alkenation with triphenylethylphosphonium bromide. The hydroxy group in the aminoalcohol **8** was deprotected with tetrabutylammonium fluoride and the hydroxymethyl group in **9** was oxidized to the carboxylic acid functionality with Jones reagent to give the *N*-Boc-protected (2*S*,4*R*)-4-(*Z*)-propenylproline **10**.

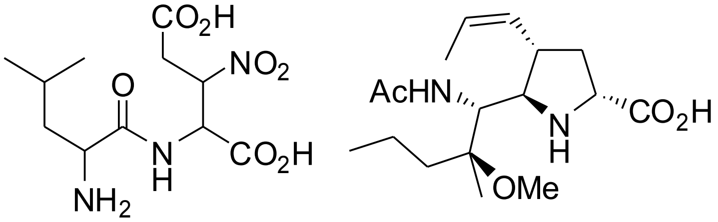


Scheme 1. Synthetic route to (2*S*,4*R*)-4-(*Z*)-propenylproline moiety.

Prior to the work of Zlatopolskiy,[28] no procedure for the synthesis of *N*-hydroxypyrrolecarboxylic acids or *N*-hydroxypyrrolecarboxamides had been reported in the literature. An attempted synthesis of 5-chloro-1-hydroxypyrrole-2-carboxylic acid by Ritzau turned out unsuccessful.[31]

Structure-activity relationships for Hormaomycin were investigated to some extent using analogues obtained by modification of the natural compound and also by precursor-induced biosynthesis employing certain synthetic amino acids. The cleavage of the lactone ring of Hormaomycin with potassium carbonate in methanol, which was carried out by Rössner,[16] produced only biologically inactive material. The same author performed a hydrogenation of the natural depsipeptide over a palladium on charcoal catalyst in methanol, which not only led to reduction of the double bond in the 4-(*Z*)-propenylproline moiety, but also an elimination of water and the reductive dehalogenation of the Chpca fragment as well as partial reduction of the nitro groups in both (3-Ncp)Ala residues. The resulting mixture of Hormaomycin-like substances did not show any antibiotic activity. Later, a fine tuning of the hydrogenation conditions of the native depsipeptide allowed Ritzau[31] to successfully prepare a Hormaomycin analogue containing a 4-propylproline instead of the original 4-(*Z*)-propenylproline moiety. This analogue did initiate the aerial mycelium formation in *Streptomyces* species even more pronouncedly than native Hormaomycin. It also showed antibiotic activity against coryneform bacteria, although its activity was noticeably lower than that of the unmodified depsipeptide. The same author prepared an analogue of Hormaomycin, which contained a bromine instead of a chlorine substituent in the Chpca fragment. This substitution caused only a little loss of the capability to induce the formation of the aerial mycelium, but a drastic decrease of the antibiotic activity. Feeding experiments with synthetic 2-(*trans*-2'-nitrocyclopropyl)glycine[32] and 3-(*trans*-2'-methoxycarbonylcyclopropyl)alanine[33] enabled Alvermann[21] to obtain both possible Hormaomycin analogues containing a 2-(*trans*-2'-nitrocyclopropyl)glycine residue instead of one (3-Ncp)Ala moiety and depsipeptides with both (3-Ncp)Ala fragments being substituted either by 2-(*trans*-2'-nitrocyclopropyl)glycine or by 3-(*trans*-2'-methoxycarbonylcyclopropyl)alanine moieties. All these analogues did not display any Hormaomycin-like activity.

As was already mentioned, Hormaomycin contains two moieties of 3-(*trans*-2'-nitrocyclopropyl)alanine. Aliphatic nitro compounds are very rare in nature, in fact, less than thirty such compounds have been isolated till now, and among them is the dipeptide nitropeptine **11** isolated from *S. xanthochromogenus*, which displayed noticeable antifungal activity.[34] One might therefore be tempted to suppose that the unique biological activity of Hormaomycin would be connected with its nitro group containing fragments. 3-(*trans*-2'-Nitrocyclopropyl)alanine itself (at least as a mixture of all possible isomers) was already tested and turned out to be inactive, but this inactivity might be due to the low capability of many amino acids to permeate across cell walls in the absence of a special transport mechanism because of their low lipophilicity. It was also known, that one of the new potent inhibitors of influenza neuraminidase, compound A-315675 **12,** contains a 4-(*Z*)-propenylproline fragment.[35] Therefore a more detailed study of the role of this fragment for the biological activity of Hormaomycin would be necessary.



11 **12**

Figure 2. Nitropeptine **11** and the natural product A-315675 **12**.

There is significant interest in the preparation of modified proteins containing unnatural amino acids, in particular, fluorinated amino acid analogues, and this is due, on the one hand, to the possibility of solving a number of fundamental problems related to the studies of protein structures as well as structure-property relationships, and, on the other hand, to the probable practical application of these proteins.[36,37,38] The replacement of amino acid residues in proteins by their analogues may give rise to proteins with new properties and, in particular, may favorably change the properties of well-known proteins toward their practical use. In particular, their lipophilicity, their substrate specificity, their stability, their pK_a values, their *in vivo* availability and improved permeation capability through certain body barriers, as well as their temperature optimum of action and folding kinetics can be modified.[39,40,41,42,43] Transport rates of peptides through membranes *in vivo* are known to be enhanced by increasing the lipophilicity. The site specific incorporation of highly lipophilic amino acids and amino acid analogues into biologically active peptides appears to be a major aim in modern peptide chemistry.

Fluorinated amino acids and derived peptides – both analogues of naturally occurring compounds and synthetic substances – claim an extraordinary interest in chemistry and biochemistry as well as in medicinal research because of their enormous variety of biological activities.[44,45] Thus the replacement of the phenylalanine residues in PvuII-endonuclease by 3-fluorophenylalanine leads to a twice as high specific activity compared to that of the native enzyme, while the introduction of 4-fluorophenylalanine reduces it fourfold.[46] An X-ray diffraction structure analysis of glutathione transferase M-1, in which Tyr residues were replaced by 3-fluorotyrosine has revealed multiple conformational changes in the structure of the modified enzyme, which changed its spectral and kinetic characteristics.[47]

Because of the high electron density, the trifluoromethyl group is capable to participate in hydrogen bonding[48] and may act also as a coordination site in metal complexes. Furthermore, the fluorine atoms can serve as powerful NMR labels for spectroscopic studies of metabolism and conformation.

The replacement of substantial amino acids in microbial proteins by synthetic analogues is a route to the preparation of compounds with potentially increased biological activity based on previously known microbial products.

The previously achieved progress in the synthesis of the Hormaomycin and its analogues as well as the investigation of the structure-activity relationships for these compounds which is briefly described above has lead to a list of desirable goals for the presented research:

- Synthesis of Hormaomycin and its all-peptide analogue to obtain enough material for *in vivo* biological tests.
- Synthesis of new Hormaomycin analogues, containing (2*R*)- and (2*S*)-3-(1'*S*,2'*R*)-(2'-fluoromethylcyclopropyl)alanine moieties instead of (2*R*)- and (2*S*)-3-(1'*R*,2'*R*)-(2'-nitrocyclopropyl)alanine.
- Synthesis of (2*R*)- and (2*S*)-3-(1'*S*,2'*R*)-(2'-fluoromethylcyclopropyl)alanines (mono-, di- and trifluoromethyl derivatives).
- Development of new improved protocols for the synthesis of (*R*)-*allo*-threonine and *β*-methylphenylalanine moieties.

MAIN PART

Once the absolute configuration of the native Hormaomycin had been established and the strategy of the synthesis and the route to Hormaomycin were developed by Zlatopolskiy,[49] the main aim of the present work was to synthesize 2'-fluoromethyl-substituted cyclopropylalanines and build the corresponding Hormaomycin analogues to test their biological activities to contribute to a wider knowledge of the structure-activity relations.

1. (Mono-, (Di- and (Trifluoromethyl)-substituted cyclopropylalanines

1.1. Development of a general protocol

Fluoromethyl-substituted cyclopropylalanines have never been described before. Like for the approach to 2'-nitrocyclopropylalanines,[25] the Belokon' method was chosen as a viable access route to all of the fluoromethyl-substituted cyclopropylalanines, employing the Ni(II)-complex of the Schiff base derived from glycine and (*S*)- or (*R*)-2-[(*N*-benzylprolyl)amino]benzophenone **13** as a reusable chiral auxiliary (Figure 3). In general, the configuration of the stereocenter, formed upon alkylation of C-2 of the glycine moiety, is the same as the configuration of the C-2 atom of the proline moiety; other stereocenters are neither generated nor involved in this transformation.

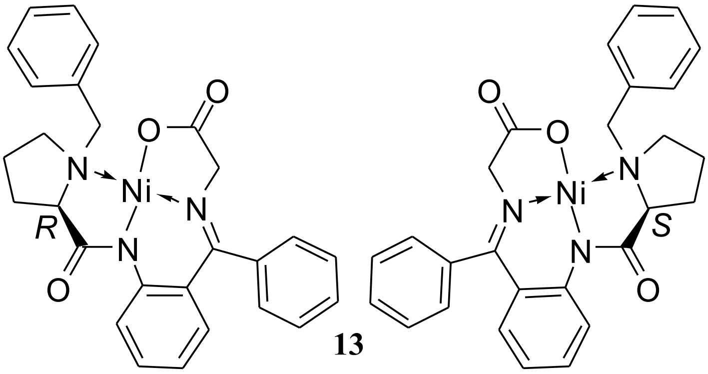


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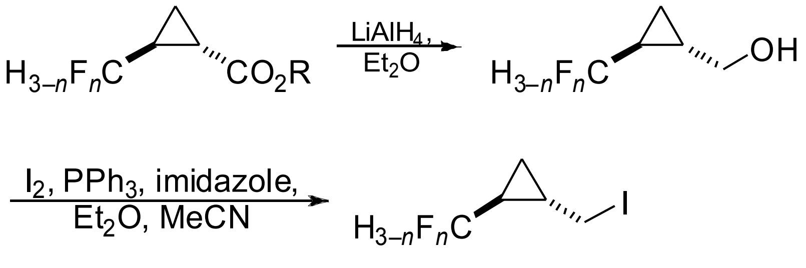
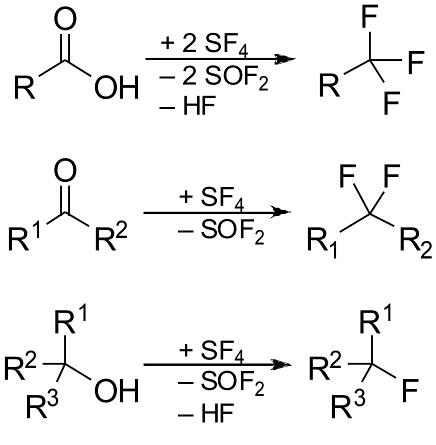
Figure 3. The Ni(II)-complexes of the Schiff base derived from glycine and (*R*)- or (*S*)-2-[(N-Benzylprolyl)amino]benzophenone [(*R*)- and (*S*)-Belokon' glycine complexes, (*R*)- and (*S*)-BGC].

2'-Fluoromethyl-substituted cyclopropylmethyl iodides were intended to be obtained by transformation of the corresponding alcohols, obtained by reduction of the corresponding carboxylates (Scheme 2). The fluoro-derivatives could be obtained from corresponding oxygenfunctionalised derivatives by treatment with different fluorinating reagents, e. g. with the pyridine-HF complex[50] for tertiary alcohols, with N,N-diethyl-α,α-difluoro-(*m-*methylbenzyl)amine[51] for sugars and with Xenon difluoride for aryl perfluoroalkyl sulfides.[52]



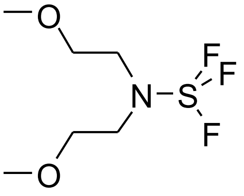
Scheme 2. Synthetic route to *trans*-fluoromethyl-substituted cyclopropylmethyl iodides.

Without taking into account the most exotic reagents (like XeF_2 or MoF_6[53]), almost all other fluorinating agents should be suitable to achieve the target. The most universal one is SF_4, as it successfully converts carboxylic acids to trifluoromethyl derivatives,[54] aldehydes and ketones to the corresponding difluorides[55] and alcohols to monofluorides (Scheme 3). However, SF_4 is problematic in handling because of its low boiling point (–40 °C)[56] and its extreme corrosireness to glass. With SF_4 it is necessary to use steel autoclaves (the usual reaction temperature is +130 °C, but +200 °C and even +270 °C[54] can be required for some compounds) for such transformations.



Scheme 3. Fluorinations with SF_4.

Other fluoro derivatives of sulfur (IV) which have been widely used in recent years for fluorinatuons of organic compounds are the dialkylaminosulfur trifluorides. They were first prepared in 1964[57] and first used as nucleophilic fluorination agents in 1973.[58] These substances are liquid under normal conditions and, as a rule, are able to bring about such transformations under much milder conditions. More recent publications brought forward bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo–Fluor®) **14** as a thermally stable and soft fluorinating agent, which ought to be applicable for virtually all of the above mentioned transformations.[59] Unfortunately, the neat reagent is not available in Germany, so a solution of **14** in THF (50% w/w) was used initially.



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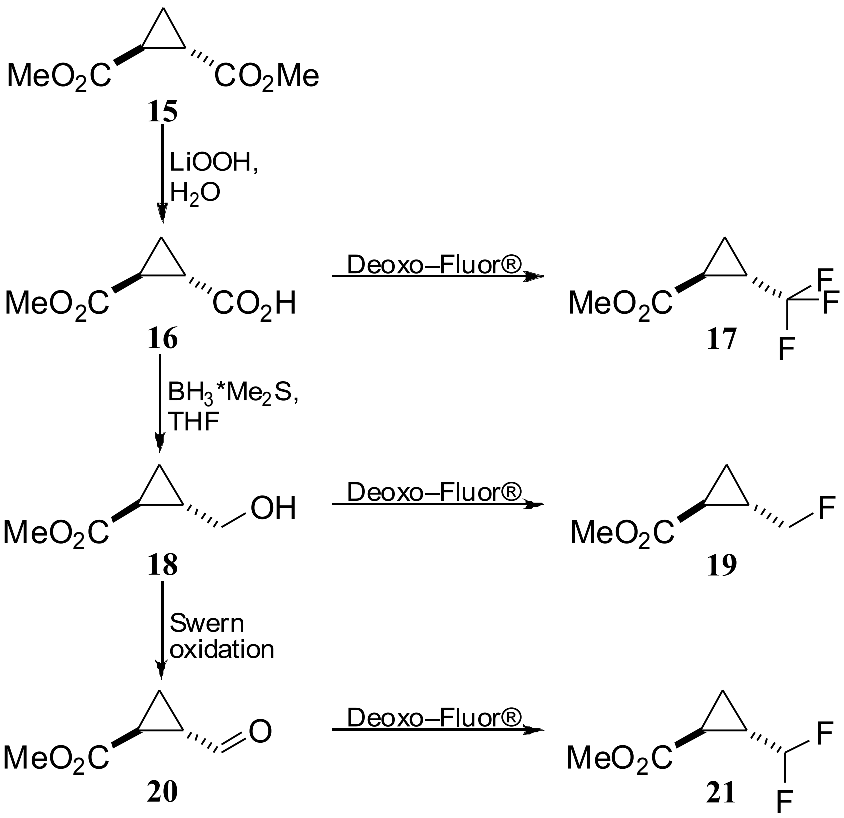
Deoxo-Fluor®.

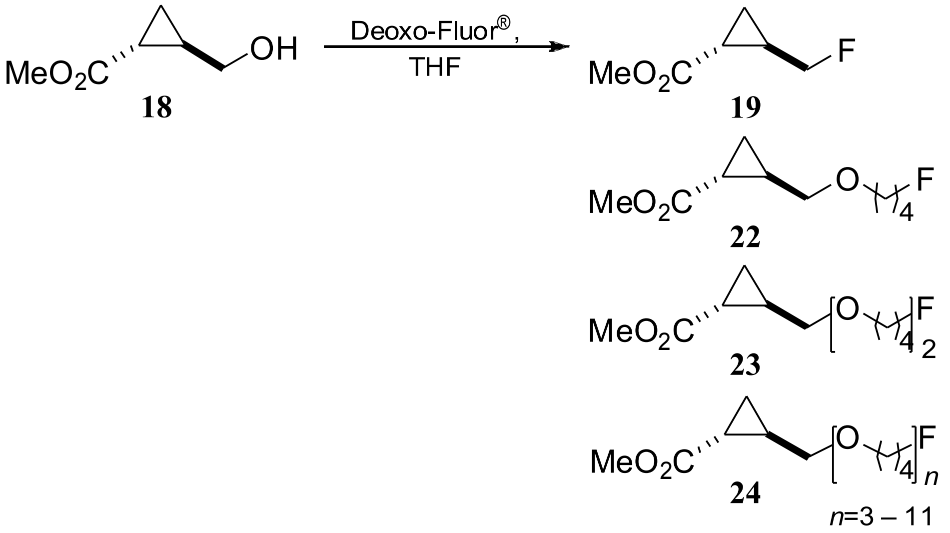
The synthetic route outlined in Scheme 4[60] was initially designed to access all three desired 2-fluoromethyl-substituted cyclopropanecarboxylates.



Scheme 4. Synthetic route to 2-fluoromethylcyclopropanecarboxylates.

1.2. Attempted syntheses according to the proposed synthetic route

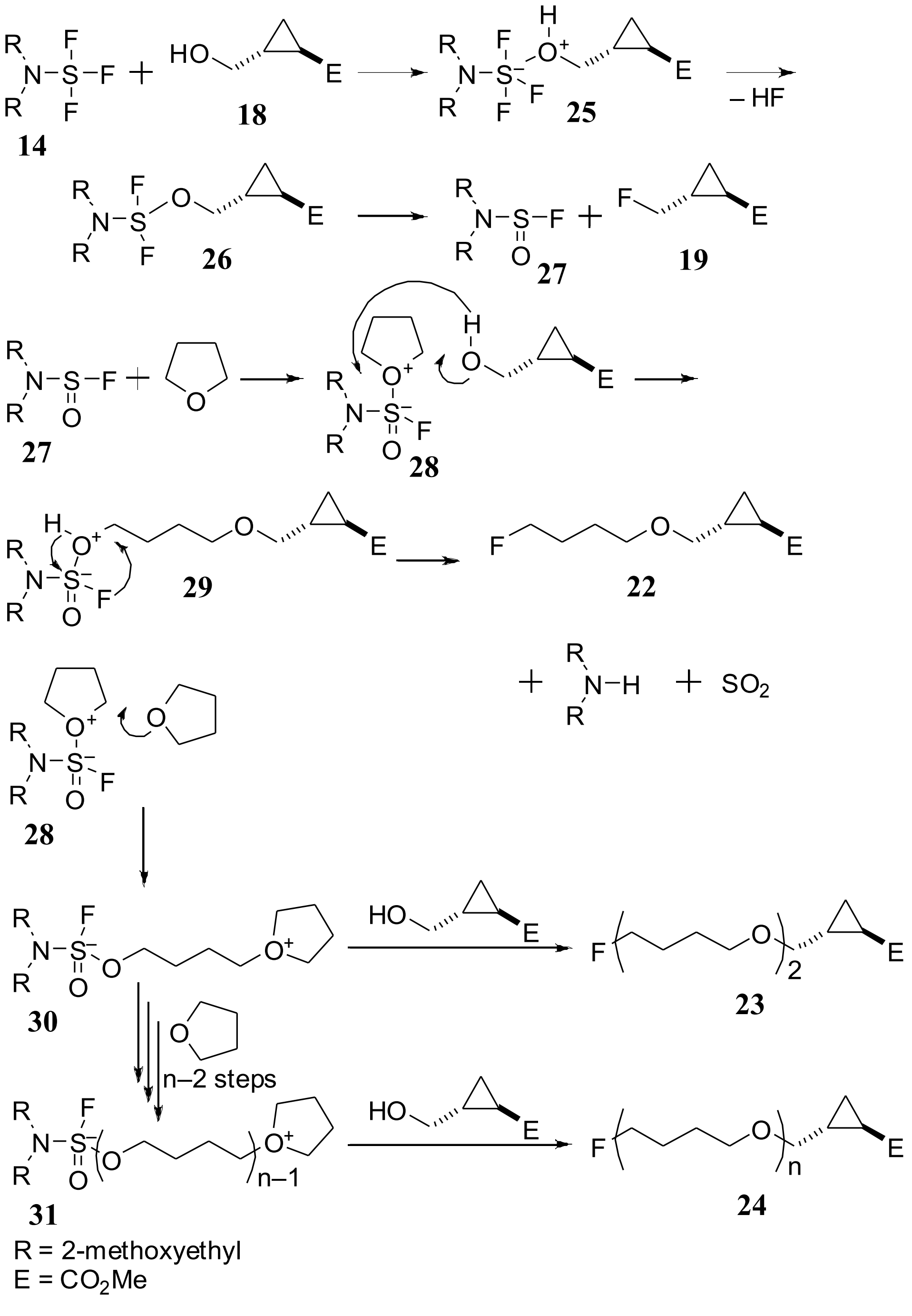
The very first attempt to access methyl *trans*-2-monofluoromethylcyclopropanecarboxylate **19** from the corresponding alcohol **18** gave unexpected results: the target monofluoromethyl-substituted ester was obtained in very low yield (only 14%), and a mixture of derivatives **24** was obtained (~31% using peak intensities in ESI-MS, main component with *n*=5) as well as compounds **22** (15%) and **23** (12%).



Scheme 5. The reaction of Deoxo-Fluor® in THF solution with methyl 2-hydroxymethyl-cyclopropanecarboxylate at ambient temperature.

The latter products are apparently formed by THF ring cleavage and a formal insertion of a 1,4-butanediol moiety into the C–OH bond before transformation to a C–F bond. The closest previously observed analogues of the observed reaction are the incorporation of THF into cycloadducts of tetracyanoethylene to dispiro[2.0.2.4]deca-7,9-diene,[61] and the reaction of alkyl chlorosulfinates with THF.[62]

The formation of products **22** – **24** can be rationalized assuming primary attack of the reagent **14** by the alcohol **18** molecule to form the HF molecule and the amidoester **26** which, in turn, produces target fluoride **19** and di-(2-methoxyethyl)-fluorosulfinamide **27**. The latter attaches on the oxygen of a tetrahydrofurane molecule to yield an oxonium ylide **28** which would first be attached either by a molecule of the hydroxymethylcyclopropanecarboxylate to yield the new ylide **29** or by another molecule of tetrahydrofurane to furnish **30**. Nucleofilic transfer of fluorine from sulfur to the vicinal carbon in **29** would yield **22**, and analogously **23** would come about from **30** after reaction with **18**. Further consecutive reactions of 30 with tetrahydrofuran and eventually with **18** and fluorine transfer would lead to the higher oligomeric products of type **24** (Scheme 6).

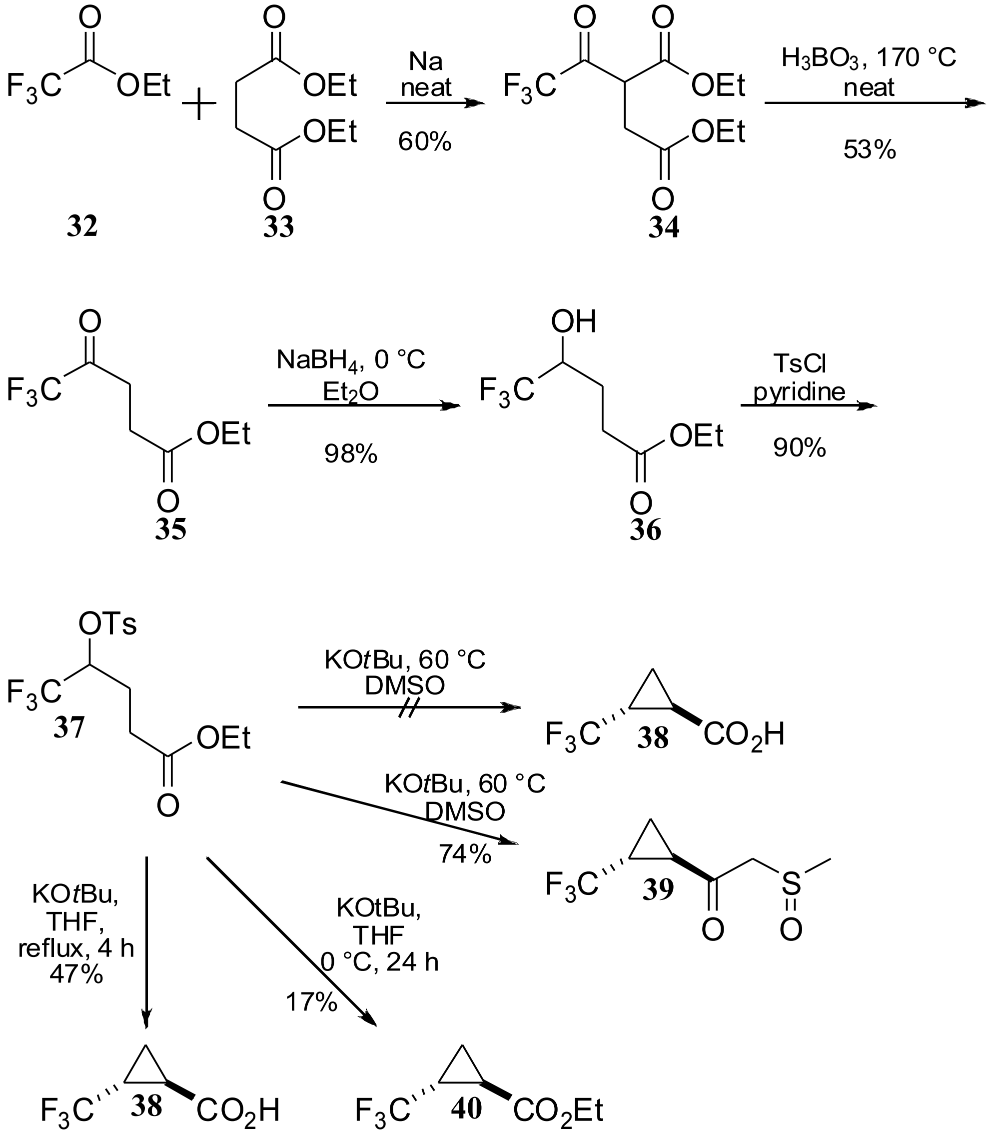


Scheme 6. Mechanistic rationalization of the oligoether formation upon reaction of 2-(hydroxymethyl)cyclopropanecarboxylate with Deoxo-Fluor® in tetrahydrofuran.

When the Deoxo-Fluor® reagent was employed as a solution in toluene (50% w/w), transformation of the alcohol **18** to the fluoride **19** occured smoothly (47% yield), and the carbaldehyde under the same conditions furnished the 2-(difluoromethyl)cyclopropanecarboxylate in 51% yield.

The attempted transformation of the carboxylic acid **16** to the trifluoromethyl derivative with this Deoxo-Fluor® solution was not successful. The acid was easily converted to the acyl fluoride, the latter, however, did not react any further with the fluorination reagent, not even at reflux.

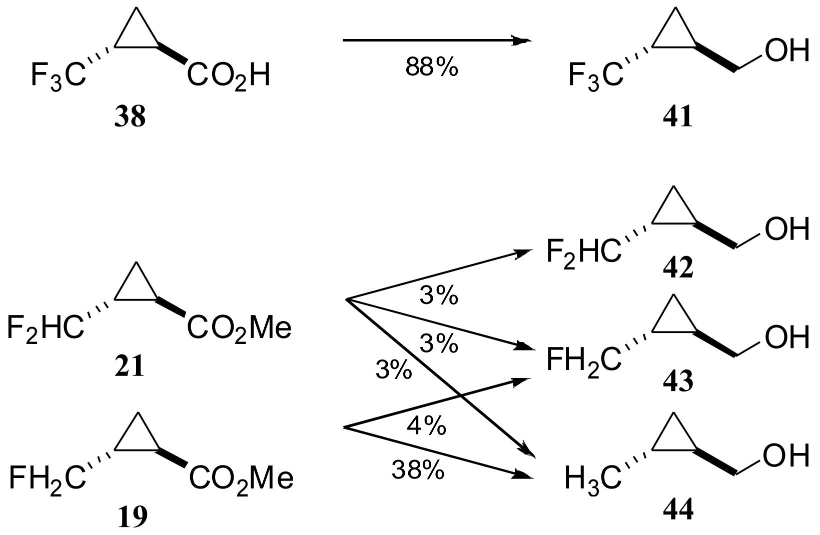
An alternative route to *trans*-2-(trifluoromethyl)cyclopropylmethanol is by way of the Claisen condensation product of diethyl succinate with ethyl trifluoroacetate[63] according to known procedure. However, the previously used conditions were modified for two of the four steps in order to achieve a better overall yield[64] (Scheme 7).



Scheme 7. Synthesis of *trans*-2-trifluoromethylcyclopropane carboxylic acid (yields are given after work-up).

Surprisingly, the reduction of the ketoester **35** to the hydroxyester **36** proceeded very slowly under the previously described conditions (H_2/PtO_2) – in several attempts (2 h, 24 h and 72 h) the yield of **36** was never better than 60%, and about 25% of the ketoester **35** was recovered. Yet, the reduction of **35** with crushed sodium borohydride in diethyl ether gave quantitative conversion and an excellent yield of **36**.

The final step, the attempted intramolecular 1,3-dehydrotosylation with potassium *tert*-butoxide in dimethylsulfoxide, also gave an unexpected result. The intermolecular condensation product **39** of the expected cyclopropanecarboxylate **40** with dimethylsulfoxide rather than **40** or the free acid **38**, was obtained in 74% yield. Among several other base/solvent combinations tested – NaOEt/EtOH, NaOMe/MeOH, KO*t*Bu/*t*BuOH, NaH/THF and KO*t*Bu/THF the last one gave the best yield (up to 45% at reflux) of the target acid **38**, as well as of the corresponding ethyl ester **40** (~17% at 0 °C); the latter was not obtained using any other solvent/base combinations.

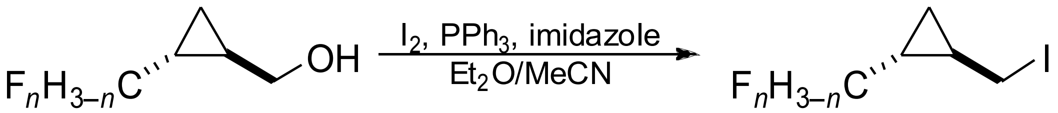


Scheme 8. Reductions of *trans*-2-fluoromethylcyclopropane carboxylic acid and esters with an excess of $LiAlH_4$ (2 equiv. $LiAlH_4$ in Et_2O, reflux).

The conversion of the carboxylic acid **38** and esters **21**, **19** to the corresponding cyclopropylmethyl alcohols was attempted according to the standard protocol by adding the substrate to a twofold excess of $LiAlH_4$ in diethyl ether under reflux. (2-Trifluoromethylcyclopropyl)methanol **41** thus was obtained in excellent yield (88%), but the difluoromethyl- **42** and especially monofluoromethylcyclopropylmethanol **43**, respectively, were obtained from the corresponding methyl cyclopropanecarboxylates **21** and **19**, respectively, in much poorer yield (3% and 4%, respectively). In the case of monofluoride the main product was trans-2-methyl-cyclopropylmethanol **44** (38%). In the case of the difluoride **21**, a mixture of the mono- **43** and difluoromethylcyclopropylmethanol **42** along with the non-fluorinated alcohol **44** was obtained in a ratio of approximately 1:1:1 (Scheme 8).

To avoid this overreduction, inverce addition of 1.1 equivalent of $LiAlH_4$ in diethyl ether solution (ca. 1 M) to the solution of the ester or the acid (in the case of the trifluoride) in diethyl ether (ca. 1 M) was practiced. This way, the desired alcohols were obtained in good yields (76%, 82% and 88% for **43**, **42** and **41** respectively).

The racemic *trans*-2-fluoromethylcyclopropylmethanols upon treatment with iodine/triphenylphosphine in the presence of imidasole were smoothly converted to corresponding iodides in very good yields (Scheme 9).

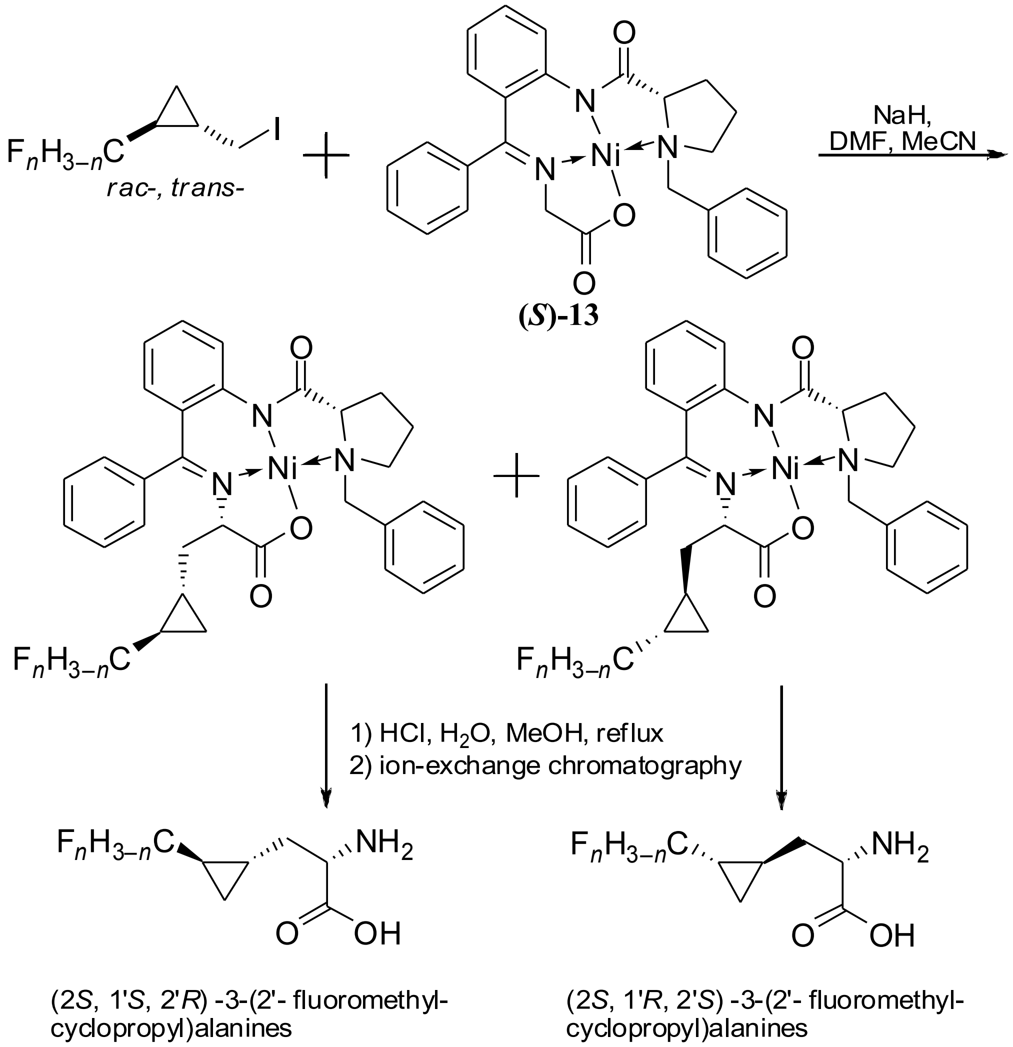


n 1 2 3
43 **42** **41**

n 1 2 3
45 **46** **47**
Yield (%): 91 88 90

Scheme 9. Synthesis of *trans*-2-(fluoromethyl)cyclopropylmethyl iodides from the corresponding cyclopropylmethanols.

Alkylation of the glycine equivalents derived from (*R*)- and (*S*)-2-[(*N*-benzylprolyl)amino]benzophenone [(*R*)- and (*S*)-BGC **13]** as reusable chiral auxiliaries with the racemic iodides **45** – **47**, employing the protocol of Larionov and de Meijere et al,[25] in each case led to a mixture of diastereomeric products, which could be separated by column chromatography. Unfortunately, the diastereomers could not be separated by fractional crystallization as was previously reported for the corresponding 3-(*trans*-2-nitrocyclopropyl)-alanine derivatives.[25] Absolute configuration of the Belokon' (2S,1'R,2'S)-3-(2'-trifluoromethylcyclopropy)lalanine complex was determined by a single crystal X-ray analysis.



Scheme 10. Synthesis of (2*S*)-3-(*trans*-2'-fluoromethylcyclopropyl)alanines by alkylation of the (S)-configured Belokon' glycine complex [(*S*)-BGC 13] with the racemic *trans*-2-fluoromethylcyclopropylmethyl iodides 45 – 47. For details see Table 1.

Table 1. Yields of products of reaction of corresponding racemic iodides with (*S*)- and (*R*)-BGC 13 (% BGC).

Iodide	Yield (% on BGC)			
	(*S*)-BGC		(*R*)-BGC	
	2*S*, 1'*S*, 2'*R*	2*S*, 1'*R*, 2'*S*	2*R*, 1'*S*, 2'*R*	2*R*, 1'*R*, 2'*S*
45	43.7	44.8	46.7	42.3
46	44.7	48.3	47.3	45.4
47	45.5	49.1	43.7	42.4

The separated target Ni complexes were decomposed by treatment with refluxing aqeous-methanolic HCl to give, after ion-exchange chromatography, the corresponding (2*S*,1'*S*,2'*R*)- [see Scheme 10, derived from (*S*)-BGC] and (2*R*,1'*S*,2'*R*)-3-(2'-fluoromethylcyclopropyl)alanines [derived from (*R*)-BGC] in good to excellent yields. The chiral auxiliary was recovered as the hydrochloride of 2-[(*N*-benzylprolyl)amino]benzophenone (~95%).

2. New and improved syntheses of some other non-proteinogenic amino acids

2.1. (R)-allo-Threonine

(*R*)-*allo*-threonine is commercially available, but extremely expensive (from 77.80 € for 250 mg from Alpha Aesar to 60.80 € for 25 mg from Fluka). Therefore a simple and inexpensive access to (*R*)-*allo*-threonine was desirable.

There are at least three principally different ways to approach this target amino acid:

1) Separation of the mixture of all four stereoisomers to provide individual substances or at least pairs of enantiomers, which should be resolved.
2) Preparation of mixture of two diastereomers and subsequent separation.
3) Enantioselective synthesis of the target stereoisomer from an achiral or from a chiral precursor.

One of the best ways to obtain the target amino acid in a diastereomerically pure state is by *in vitro* synthesis under enzyme catalysis.[65,66,67,68]

An enantioselective synthesis of (*R*)-*allo*-threonine from an achiral precursor employing the Sharpless asymmetric epoxidation[69] or an asymmetric aldol reaction under catalysis with a chiral gold complex[70] also should be possible.

The synthesis of (*R*)-*allo*-threonine from (*R*)-threonine as a chiral precursor was used by Zlatopolskiy.[71] Although (*R*)-threonine is less expensive (21 – 37 € for 5 g) than the target amino acid, the conversion requires five steps, and the overall yield is not better than 72%.

The separation of the mixture of all four stereoisomers, produced by a non–stereoselective synthesis, is well known, but tedious.[72,73,74,75]

The separation of diastereomers is much easier and does not require chiral phases for chromatography, one just has to determine an appropriate derivative and the proper conditions for satisfactory separation. In fact, the synthesis of threonine diastereomers by aldol-type condensation of acetaldehyde with the enolates of glycine equivalents is well described in the literature.[76, 77] The question is just to choose the route with the best enantiomeric/diastereomeric excess. The yield is not so important, because the starting materials are inexpensive and the chiral auxiliary or catalyst should be recycled. The Belokon' protocols are among the best to access enantiomerically pure non-proteogenic amino acids. Nickel(II) or copper(II) complexes of the Schiff bases derived from glycine and (*S*)- or (*R*)-2-*N*-(*N'*-benzylprolyl)aminobenzophenone (BPB),[78,79] aminoacetophenone (BPA)[80] or aminobenzaldehyd (BPH)[81] can be used as chiral nucleophilic glycine equivalents in reactions with alkyl halides or carbonyl compounds. The most versatile one is the nickel (II) aminobenzophenone derivative.

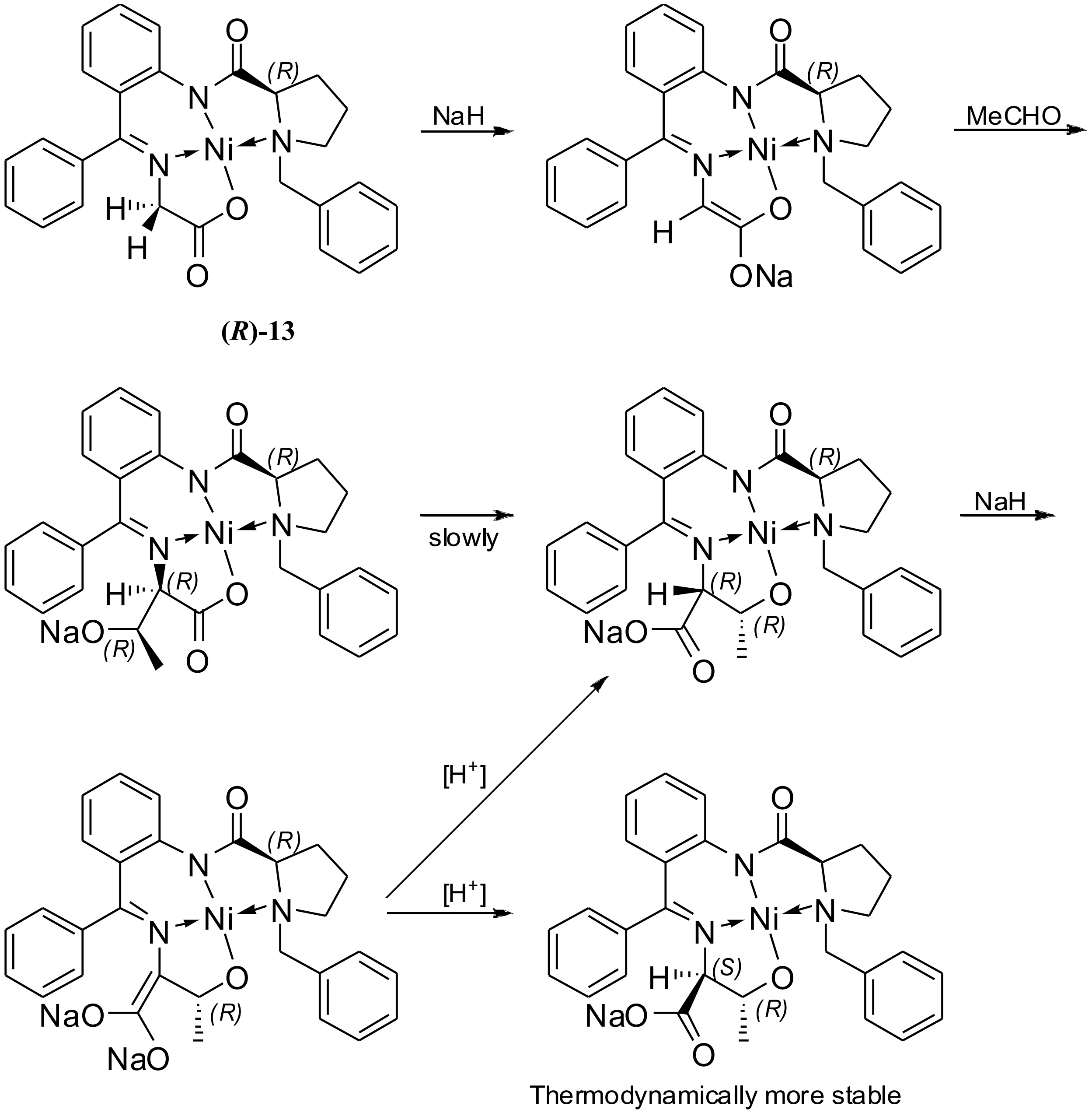
It is interesting that nickel(II) complexes of Schiff bases derived from 2-bromoglycine and (*S*)-BPB can be used as electrophilic glycine equivalents.[82]

Alkylations of the nickel(II) complexes of Schiff bases derived from glycine and (*S*)- or (*R*)-BPB **13** with alkyl halides virtually yields a single stereoisomer, in which the configuration of the newly formed stereogenic centerat C-2 of the amino acid moiety is the same as that in the proline moiety of the chiral auxiliary in the starting material.

In the reaction of enolate of this chiral glycine equivalent with aldehydes the situation is more complicated. The reaction of (*S*)-BGC with acetaldehyde under strongly basic conditions lead to (*R*)-threonine (inverse configuration relative to that of the proline moiety of (*S*)-BGC due to epimerization on C-2), but when a weaker base like triethylamine was employed, a mixture of (*R*)-threonine and (*S*)-*allo-t*hreonine[83] was obtained.

The hypothesis that the reaction of BGC with aldehydes under strongly basic conditions proceeds in two steps and is thermodimacally controlled was corroborated by experimental tests.[84] The initially formed main product in the aldol reaction of acetaldehyde with BGC had the same configuration at C-2 as the proline unit in BGC, but the product ratio changed in time from 95:5 after 30 s through 70:18 after 10 min to 5:95 after 24 h at ambient temperature. This epimerization comes along with possible rearrangement in the Ni complex. The newly formed hydroxide group of the product can coordinate the Ni atom liberating the carboxylate moiety and thus making the proton at C-2 accessible to base attack (Scheme 11). In order to obtain (*R*)-*allo-*threonine, it is necessary to carry out the aldol reaction of (*R*)-BGC with an excess of acetaldehyde under strongly basic conditions at low temperature and quench the reaction after a short time to avoid epimerisation.

This modified protocol indeed gave the (*R*)-*allo*-threonine in relatively poor yield (7.5% for Ni complex, 6% for amino acid), but with high enantiomeric purity in two steps. Bearing in mind that the starting materials are inexpensive and the chiral auxiliary is reusable (≥ 95% recovery), this protocol represents one of the best route to the extremely expensive (*R*)-*allo*-threonine.



Scheme 11. Mechanism of epimerisation of the threonine Belokon' complex.

It is also possible to obtain the (*R*)-*allo*-threonine starting from (*R*)-BGC and acetaldehyde under thermodynamic control (Et_3N as base, (*S*)-threonine : *(R)-allo*-threonine = 1:7), but it is necessary to leave the reaction mixture for two months for the reaction to go to completion.[85]

2.2. *β-Methylphenylalanines*

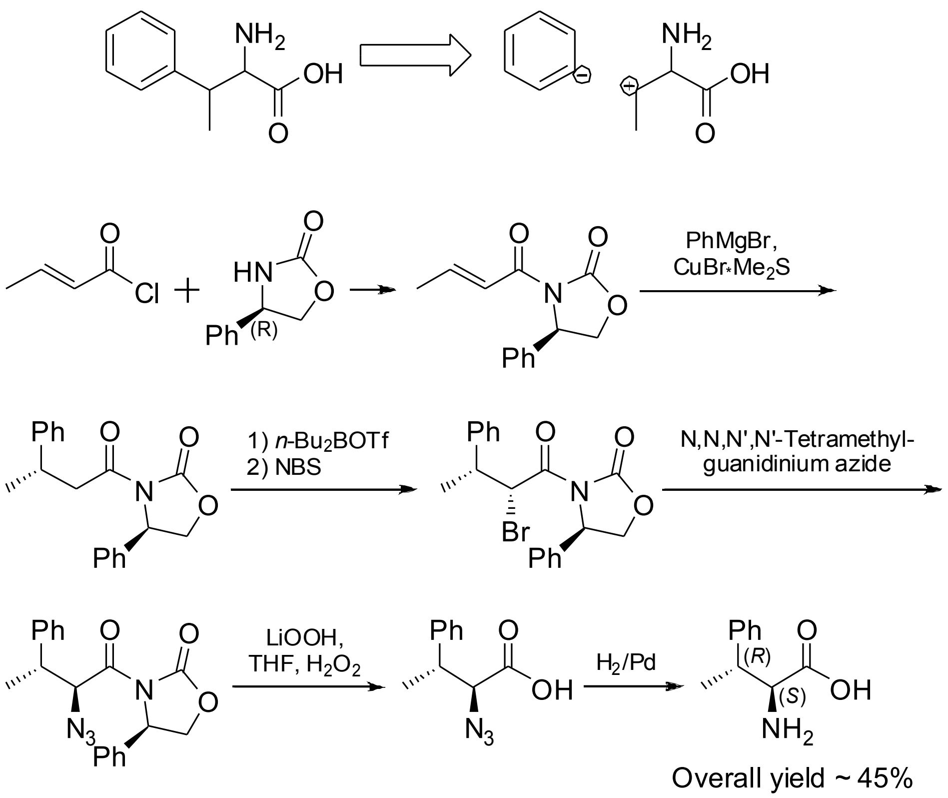
(2*S*,3*R*)-3-Methylphenylalanine (*L-β*–methylphenylalanine, (βMe)Phe, MeF) is a constituent of the peptidolactone Hormaomycin and is contained in the molecule twice. Thus it is required for the synthesis of Hormaomycin and the analogues envisaged here. In addition, a versatile protocol for the preparation of other β-alkylarylalanines would be desirable for incorporation in Hormaomycin analogues as well as in other peptides, as the incorporation of conformationally constrained α-amino acids into peptides is frequently used to study structure-activity relationships.[86, 87, 88] In this context, special attention should be paid to constrained analogues of phenylalanine such as these *β*–methylphenylalanines, since the naturally occurring phenylalanine unit is directly involved in a large number of molecular recognition processes.[89, 90]

In all cases, the three-dimensional arrangement of the phenylalanine residue is crucial in eliciting the desired response. The residue can be conformationally constrained by introducing an alkyl group at the β-position of an phenylalanine residue without significantly perturbing the backbone conformation. In particular, aromatic β-methyl-α-amino acids have been incorporated into peptides[89, 91, 92, 93] and confer on these systems a conformational side-chain rigidity that is very valuable for the study of both the specific topochemical arrays of the side chains and topochemical nature of the binding site.

The preparation of analogues of β-methylphenylalanine in enantiopure form is a challenging area in synthetic organic chemistry. Several strategies have been developed, and these include classical resolution,[94] enzymatic resolution in conjunction with HPLC,[91] or HPLC separation of derived peptides,[92] chiral preparative HPLC separation,[95] asymmetric synthesis from chiral precursors[96, 97] including the stereoselective alkylation of aromatic compounds with triflates of threonine stereoisomers,[98] the chiral auxiliary approach[99, 100, 101, 102] and enantioselective hydrogenation over a chiral catalyst.[103, 104]

All these approaches ought to be applicable to prepare unsubstituted β-methylphenylalanine. Separation protocols are suitable to approach any substituted amino acid, which can be synthesized. A stereoselective synthesis requires an optically active precursor, which, in turn, should be prepared or purchased; in many cases, these precursors are quite expensive or difficult to prepare. Chiral auxiliary approaches are better, and routes employing a chiral catalyst even better, although requires optically active auxiliaries or catalysts may have to be prepared.

To the best of our knowledge, synthetic way to *β*-methylphenylalanine using so-called "Evans amide" as chiral auxiliary is the most common approach to *β*-branched arylalanines and could be shown by Scheme 12:



Scheme 12. The classic "Evans" approach to (2*S*, 3*R*)-β-methylphenylalanine.

The crucial step in the "Evans" sequence is the Michael addition of the organometallic (usually – arylcuprate) reagent to the crotonoyl moiety attached to the chiral auxiliary. The respective arylcuprate can be produced from the corresponding arylmagnesium halide and CuBr × Me_2S complex. The organomagnesium reagent can be easily obtained from the corresponding aryl halide and metallic magnesium, or, in difficult situations, by the Knochel protocol with iPrMgCl × LiCl with subsequent transmetallation with CuCN × 2 LiCl,[105, 106] but in the case of oligohalogen-substituted arenes it could lead to mixtures of organometallic compounds and, in turn, mixtures of products.

The "Evans" route, with the employment of phenylmagnesium bromide has led to β-methylphenylalanine in eight steps (including the transmetallation) with an overall yield of approx. 45% (based on the crotonated chiral auxiliary)[107, 108].

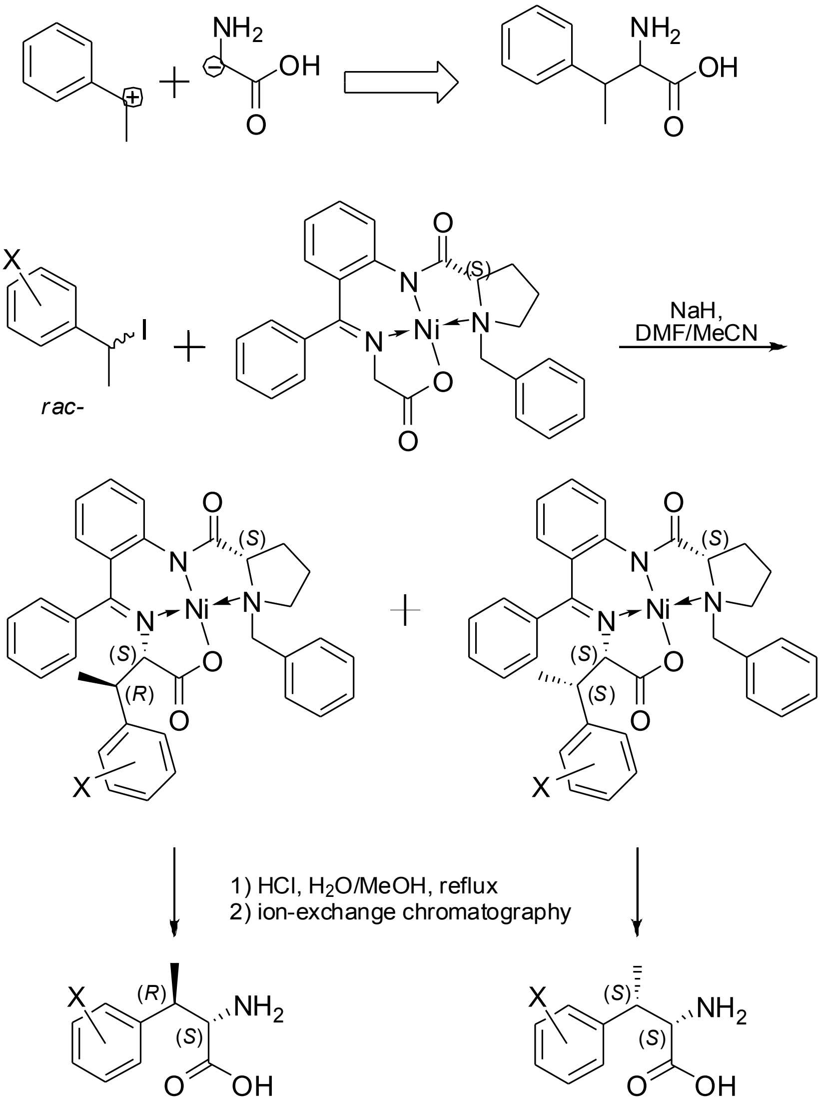
In view of the good performance of the Belokon' protocol for various eletrophilic reagents, it was straightforward to apply this approach to β-methylphenylalanines as well (Scheme 13).

Towards this, the (*S*)-configured Belokon' glycine complex (*S*)-BGC, **(*S*)-13** was alkylated with 1-phenylethyl iodide and various analogues with substituents in the aryl moiety, all in racemic form.

The diastereomeric Ni(II) complex products obtained in each case, could be separated by column chromatography, and the pure diastereomeres were decomposed with aqueous-methanolic HCl solution to furnish the target amino acids which were purified by ion-exchange chromatography. The obtained yields were very good (Table 2).

Table 2. Substituted β-methylphenylalanines by alkylation of the Belokon' glycine complex (*S*)-BGC with 1-arylethyl iodides (yields based on used (*S*)-BGC, d.e. ≥ 98%). See Scheme 13.

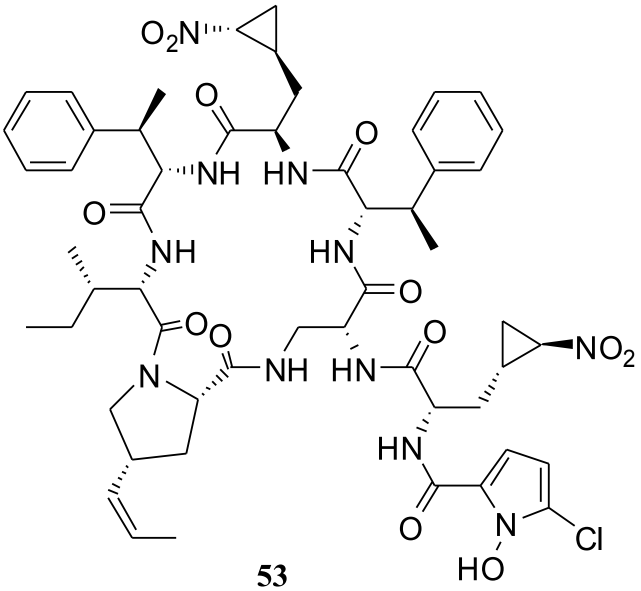
X	**Product**	**Yield (%)**	**Product**	**Yield (%)**
H	(2*S*, 3*S*)-**48**	35	(2*S*,3*R*)-**48**	38
o–Cl	(2*S*, 3*S*)-**49**	30	(2*S*,3*R*)-**49**	33
m–Cl	(2*S*, 3*S*)-**50**	34	(2*S*,3*R*)-**50**	35
p–Cl	(2*S*, 3*S*)-**51**	33	(2*S*,3*R*)-**51**	33
p–F	(2*S*, 3*S*)-**52**	37	(2*S*,3*R*)-**52**	36



Scheme 13. A new general route to (2*S*,3*R*)-*β*-methylarylalanines by alkylation of the Belokon' glycine complex (*S*)-BGC with 1-arylethyl iodides. For details see Table 2.

3. Hormaomycin and its all-peptide analogue

The total syntheses of Hormaomycin **1** itself and its all-peptide aza-analogue **53**, developed by B. Zlatopolskiy,[109, 110] were reproduced in order to provide large enough quantities (39 and 25 mg, respectively) for biological tests of their antimalarial activities[111].



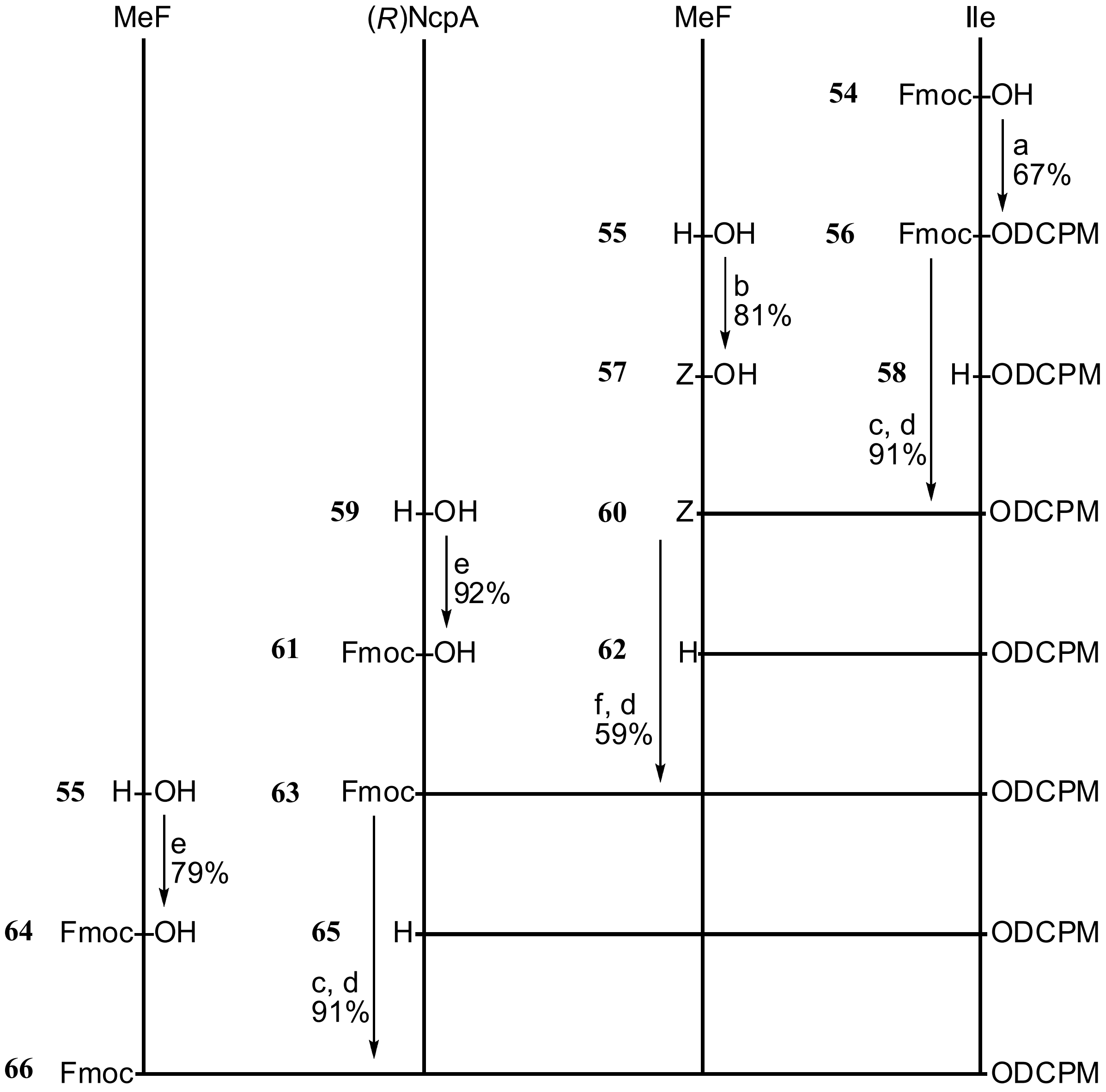
53

Figure 4. The all-peptide analogue of Hormaomycin, which showed the best antiparasitic activity *in vitro*.[111]

At first sight, the oligopeptide assembly leading to Hormaomycin does no appear to be a very complicated problem. “State of the art” peptide coupling methodology[112] allows one to prepare almost any peptides, that do not contain extremely sterically congested fragments such as α,α-dialkyl amino acids, *N*-alkyl amino acids or even more challenging *N*-aryl amino acids. With a proper choice of the coupling reagent, solvent and other experimental conditions, the oligopeptides are obtained in high yields and in high optical purities. As almost all amino acids, which comprise Hormaomycin itself and its anticipated analogues, are β-branched with the exception of 3-(2'-nitrocyclopropyl)alanine and the 3-(2'-fluoromethylcyclopropyl)alanines, HATU, as well as the combination of EDC and 7-aza-1-hydroxybenzotriazole (HOAt)[113] were used for each condensation step to ensure high yields. The most unusual fragment in Hormaomycin is the ester bond between the secondary (4-Pe)Pro moiety and the hydroxy group of *a*-Thr. Among several methods described in the literature for the creation of such bonds, the dialkylaminopyridine-promoted carbodiimide-mediated esterification was chosen.[114]

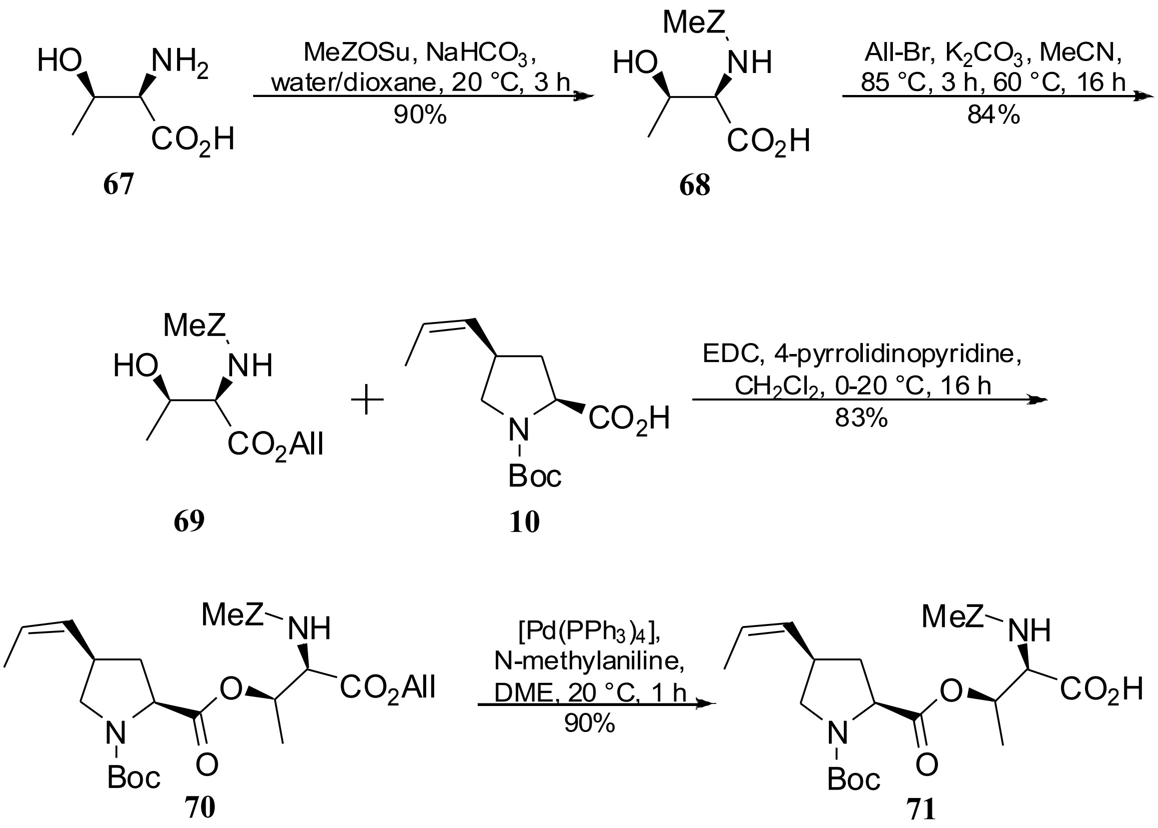
On the other hand, the reactivities of the double bond in the 4-(*Z*)-propenylproline residue and the nitrogroups in the nitrocyclopropylalanine moieties as well as, what is not so obvious, the ester bond between the propenylproline and (*R*)-*allo*-threonine residues make a proper choice of the protecting groups and also the conditions for their deprotection a real challenge. Thus, the presence of the double bond hampers the application of catalytic hydrogenolysis and HBr/AcOH reagent for the deprotection of peptides containing the propenylproline residue. The aliphatic nitrogroup in (3-Ncp)Ala is not compatible with reductive cleavage conditions, and the threonine ester bond is sensitive to alkaline and basic conditions.[115] Because of this base sensitivity the Fmoc strategy is unsuitable for the depsipeptide fragment, and other protecting groups had to be chosen for the ester moiety as well as for manipulations of intermediates that contain it.

The key step in the synthesis of Hormaomycin is the formation of the macrocycle. The greater facility, with which amide bonds can be formed, a consequence of the superior nucleophilicity of the amine over the hydroxy group, makes macrolactamization the preferred mode for ring closure. The amide bond between the (βMe)Phe and Ile residues appears to be least suitable for this cyclization because of the possibility of a *cyclo*-[Ile-(4-Pe)Pro] diketopiperazine formation (β-position to the ester bond) as well as significant epimerization and expected low yield, which are connected with the bulk of the side chains of these amino acids. To form the bond between a-Thr and (βMe)Phe as the last one is more preferable, because racemization would be suppressed by the urethane protection, and between the (βMe)Phe and (*R*)-(3-Ncp)Ala residues cyclization would proceed faster, since these residues have opposite configurations at their α-centers.[116] A ring closure forming the amide bond between Ile and (4-Pe)Pro should go along with a larger degree of epimerization, because proline is more basic than any primary amino acid, and that between (*R*)-(3-Ncp)Ala and (βMe)Phe is also less preferable, since the bulky side chain of the latter shields its amino group.

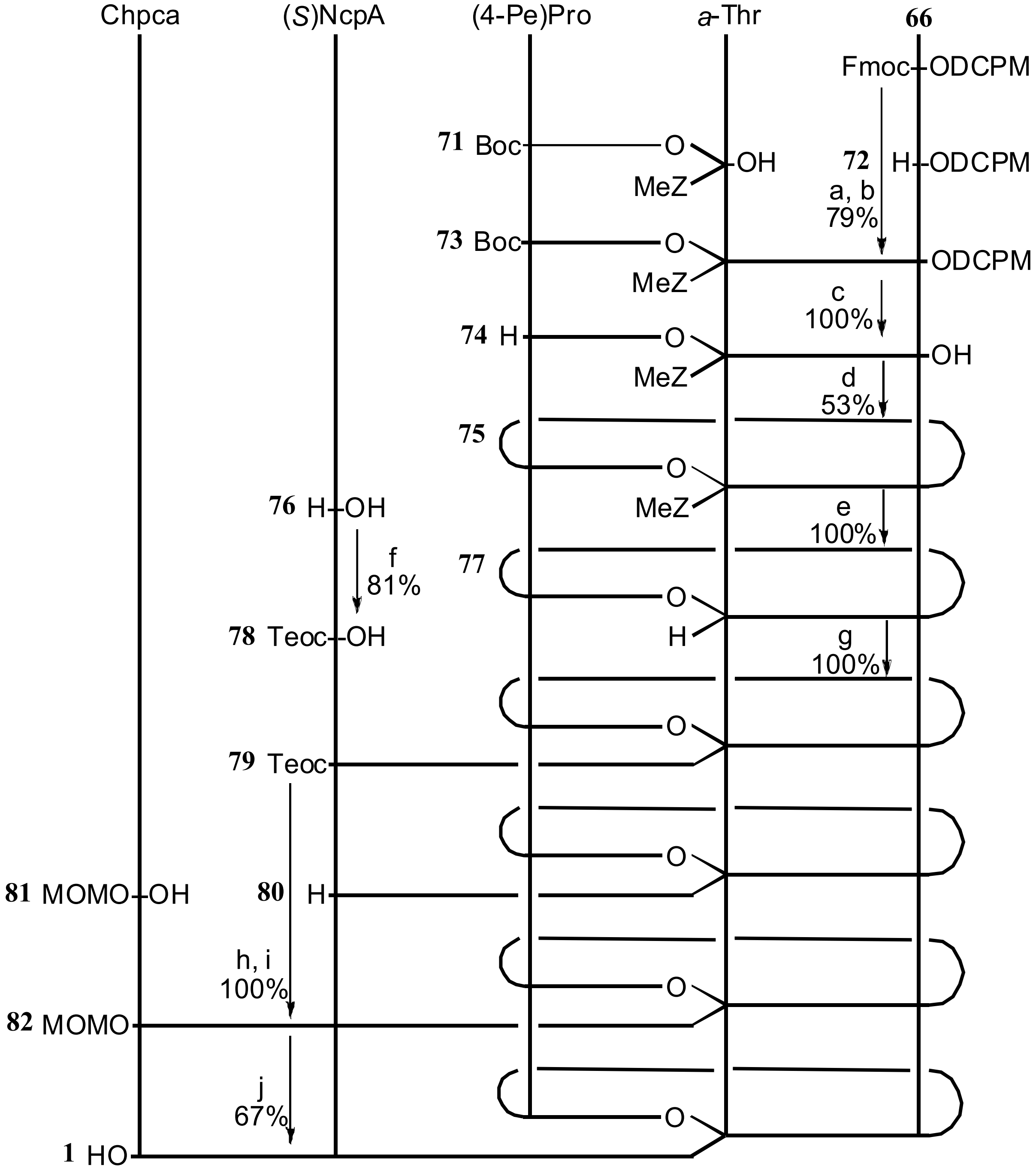


Scheme 14. Synthesis of tetrapeptide precursor **66** of Hormaomycin and its all-peptide analogue.

a) oxalyl chloride, pyridine/dicyclopropylmethanol, DMAP, CH_2Cl_2, 0→20 °C, 20 h; b) ZOSu, $NaHCO_3$, acetone/water, 2h; c) 50% Et_2NH/THF, 20 °C, 1 h; d) EDC, HOAt, DIEA, 2,4,6-collidine, CH_2Cl_2, 0→20 °C, 14 h; e) FmocOSu, $NaHCO_3$, acetone/water, 4 h; f) H_2, Pd/C, EtOAc, 20 °C, 40 min.



Scheme 15. Synthesis of diprotected ester acid **71**.

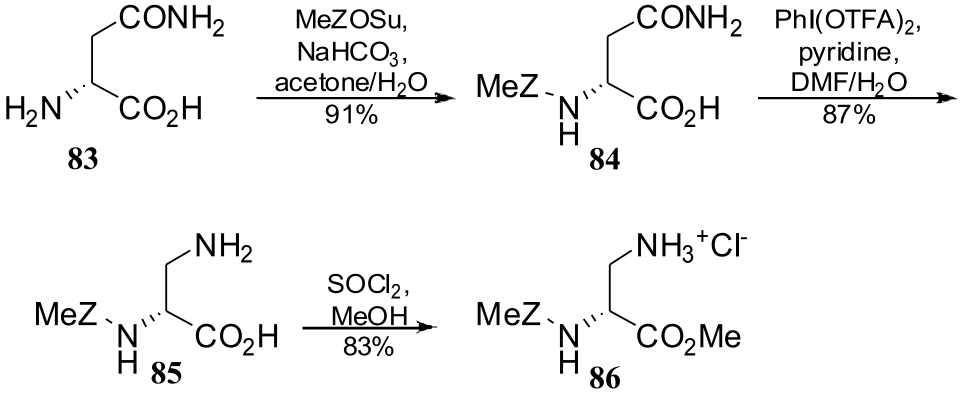


Scheme 16. Synthesis of Hormaomycin **1**.

a) 50% Et_2NH/THF, 20 °C, 1 h; b) HATU, HOAt, DIEA, TMP, CH_2Cl_2, 0→20 °C, 24 h; c) 2 M HCl in EtOAc, 20°C, 45 min; d) HATU, DIEA,TMP, CH_2Cl_2, 0→20 °C, 16 h; e) anisole, TFA, 20 °C, 2 h; f) TeocOSu, $NaHCO_3$, N,N-Dimethylaminopropylamine, water/acetone, 20 °C, 2 h; g) HATU, HOAt, DIEA, TMP, CH_2Cl_2, 20 °C, 6 h; h) TFA, 20 °C, 1 h; i) HATU, HOAt, DIEA, TMP, CH_2Cl_2, 20 °C, 4 h; j) $MgBr_2 \cdot Et_2O$, EtSH, CH_2Cl_2, 20 °C, 3.5 h.

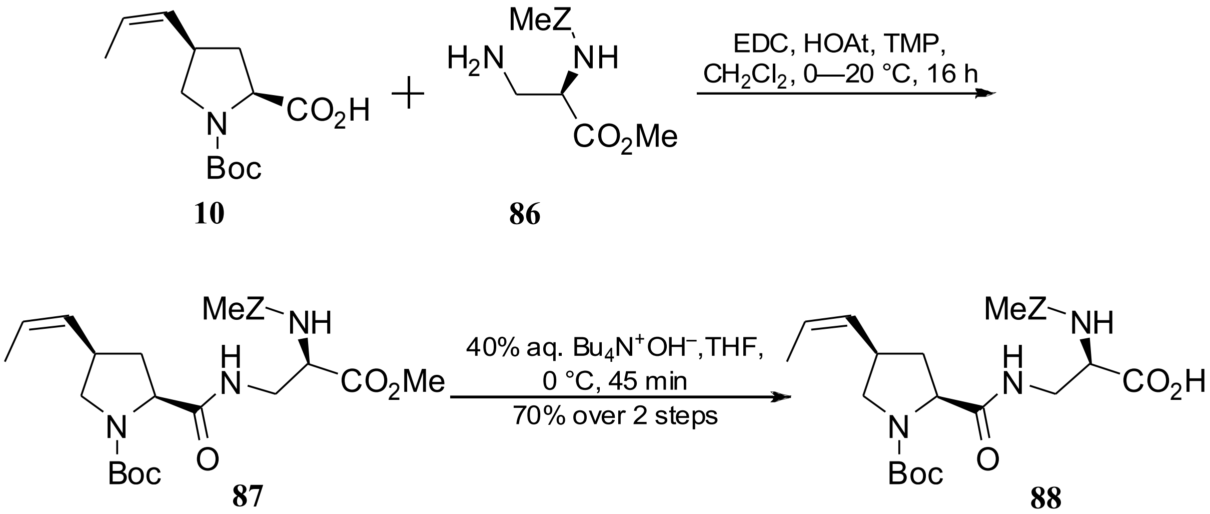
Having in mind to ring-close an acyclic precursor already containing the ester bond between the (4-Pe)Pro and the *a*-Thr residues, by forming the peptide bond between the Ile and (4-Pe)Pro moieties, the dicyclopropylmethyl ester of Ile **56** was condensed with *N*-Z-protected (βMe)Phe-OH **57**. After removal of the Z group from the *N*-terminus of the resulting dipeptide **60** by catalytic hydrogenation, the latter was coupled with *N*-Fmoc-protected-(2*R*,1'*R*,2'*R*)-(3-Ncp)Ala-OH **61** to yield the tripeptide **63**, which, in turn, after deprotection with Et_2NH/THF, was coupled with *N*-Fmoc-protected (βMe)Phe-OH **64** to give the *N,C*-protected tetrapeptide **66**.

In the case of Hormaomycin **1** itself, the 4-pyrrolidinopyridine-catalyzed condensation of the *N*-Boc-protected (4-Pe)Pro-OH **69** and *N*,*C*-protected a-Thr **118** gave the ester **70**, which, after palladium-promoted removal of the allyl group, was coupled with the tetrapeptide **66** using the HATU reagent in the presence of HOAt to give the hexadepsipeptide **73**.



Scheme 17. Synthesis of *N*-(4-methylbenzyloxycarbonyl-protected) methyl (2*R*)-2,3-diaminopropionate.

In the case of the all-peptide analogue **53,** the N_α-MeZ-protected 2,3-diaminopropionic acid ester **86** was obtained (Scheme 17) as the hydrochloride by esterification with methanol of the intermediate **85**, which in turn was prepared in 79% yield over two steps starting from (*R*)-asparagine **83** by initial acylation with MeZOSu and subsequent oxidation of the amide **84** with iodobenzene bis(trifluoroacetate) in close analogy to the published procedure.[117]

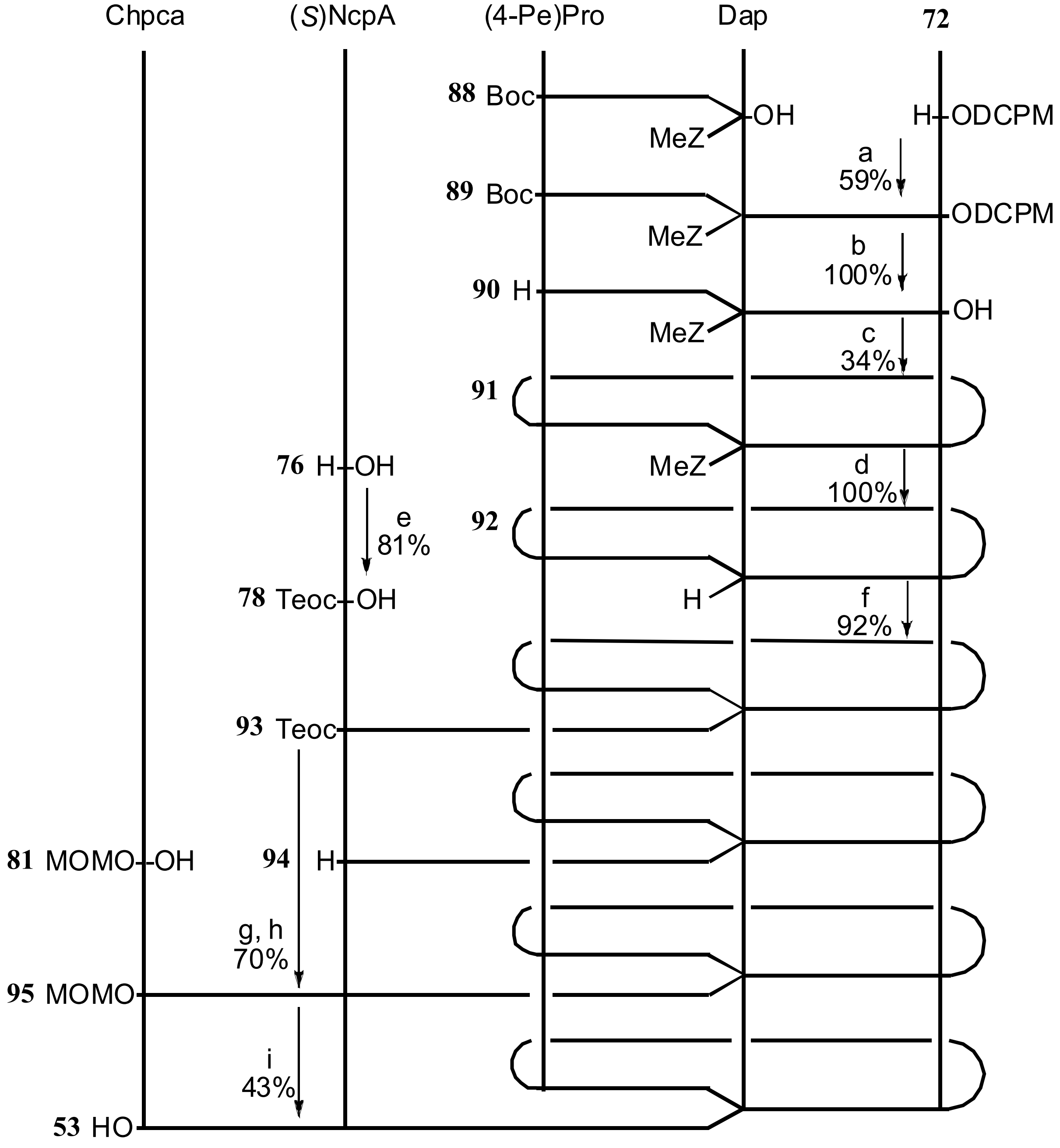


Scheme 18. Synthesis of diprotected dipeptide acid **88**.

The diamino ester **86** was coupled with the *N*-Boc-protected (2*S*,3*R*)-4-(*Z*)-propenylproline **10** using EDC and HOAt to give the intermediate dipeptide methyl ester **97**. Treatment of the latter with tetrabutylammonium hydroxide[118] gave the dipeptide acid **98** (70% yield over two steps), which was coupled with the O-dicyclopropylmethyl (DCPM) protected tetrapeptide **66** after deprotection of its terminal amino groups, to yield the branched hexapeptide **89** (59%).

These intermediates, the hexadepsipeptide **73** and the hexapeptide **89**, should not to be purified by column chromatography, because the DCPM protective group is labile towards silica gel.

The DCPM and Boc groups were removed from the termini of the hexadepsipeptide/ hexapeptide (the ESI-MS spectrum showed that the MeZ group stayed intact), and the cyclizing peptide condensation succeeded under high dilution conditions, using the HATU reagent. The cyclodepsipeptide **75** and cyclopeptide **91** were obtained in 53% and 34%, respectively, yield after HPLC purification.



Scheme 19. Synthesis of Hormaomycin all-peptide analogue **53**.

a) HATU, HOAt, DIEA, TMP, CH_2Cl_2, 0→20 °C, 24 h; b) 2 M HCl in EtOAc, 20°C, 45 min; c) HATU, DIEA, TMP, CH_2Cl_2, 0→20 °C, 16 h, d) anisole, TFA, 20 °C, 2 h; e) TeocOSu, $NaHCO_3$, N,N-Dimethylaminopropylamine, water/acetone, 20 °C, 2 h; f) HATU, HOAt, DIEA, TMP, CH_2Cl_2, 20 °C, 6 h; g) TFA, 20 °C, 1 h; h) HATU, HOAt, DIEA, TMP, CH_2Cl_2, 20 °C, 4 h; i) $MgBr_2 \cdot Et_2O$, EtSH, CH_2Cl_2, 20 °C, 3.5 h.

To complete the assembly of the target compounds, the *N*-MeZ-protected cyclic intermediates **75** and **91** were deprotected and first coupled with *N*-Teoc-protected

(2*S*,1'*R*,2'*R*)-(3-Ncp)Ala-OH **78**. After removal of the Teoc-group, the intermediates **80** and **94** in turn were coupled with the 1-OMOM-protected 5-chloro-1-hydroxypyrrole-2-carboxylic acid **81**. Finally, the MOM group was removed by treatment with $MgBr_2 \cdot Et_2O$ and EtSH in dichloromethane to give the target compounds **1** (Scheme 16) and **53** (Scheme 19) in 28% and in 13%, respectively, yield over 8 steps.

4. Hormaomycin analogues with fluoromethyl-substituted cyclopropylalanine residues

Once sufficient quantities of (2*S,*1'*S,*2'*R*)- and (2*R,*1'*S,*2'*R*)-3-(2'-fluoromethylcyclopropyl)alanine, *N*-Boc-protected (2*S,*4*R*)-4-(*Z*)-propenylproline, as well as the *O*-MOM protected 5-chloro-1-hydroxypyrrole-2-carboxylic acid, (*R*)-*allo*-threonine and (2*S*, 3*R*)-β-methylphenylalanine had been prepared, the assembly of the Hormaomycin analogues with 3-(2'-fluoromethylcyclopropyl)alanine residues could be initiated.

The same sequence that was developed by Zlatopolskiy for the synthesis of Hormaomycin and its aza–analogue, was successfully employed toward the synthesis of these new Hormaomycin analogues as well.

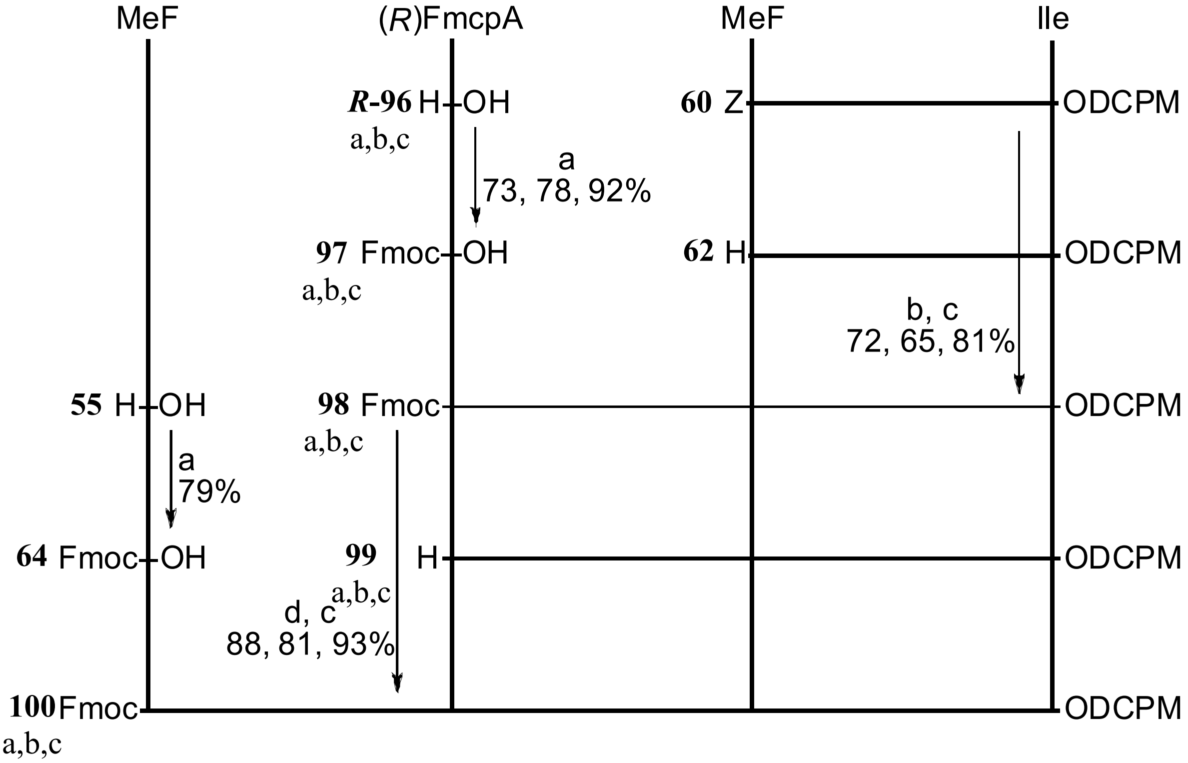
To prepare the Hormaomycin with fluoromethyl-substituted cyclopropylalanine moieties, the dicyclopropylmethyl ester of Ile **54**, was condensed with *N*-Z-protected (βMe)Phe-OH **55**. After removal of the Z group from the *N*-terminus of the resulting dipeptide **60** by catalytic hydrogenation, the latter was coupled with *N*-Fmoc-protected (2*R*,1'*R*,2'*R*)-(3-(mono-, di- or tri-)fluoromethylcyclopropyl)alanines **97 a-c** to yield tripeptides **98 a-c**, which, in turn, after deprotection with Et_2NH/THF, were coupled with *N*-Fmoc-protected (βMe)Phe-OH **64** to give *N,C*-protected tetrapeptides **100 a-c**.

The 4-pyrrolidinopyridine-catalyzed condensation of the *N*-Boc-protected (4-Pe)Pro-OH **10** and *N,C*-protected *a*-Thr **69** gave the ester **70**, which, after palladium-promoted removal of the allyl group, was coupled with the tetrapeptides using the HATU reagent in the presence of HOAt to give the corresponding hexadepsipeptides **101 a-c**.

The DCPM and Boc groups were removed from the termini of the hexadepsipeptides (the ESI-MS spectrum showed that the MeZ group stayed intact), and the cyclizing peptide condensation succeeded under high dilution conditions, using the HATU reagent. The cyclodepsipeptides **103 a-c** were obtained in 53, 60 and 54%, respectively, yield over 8 steps, after HPLC purification.

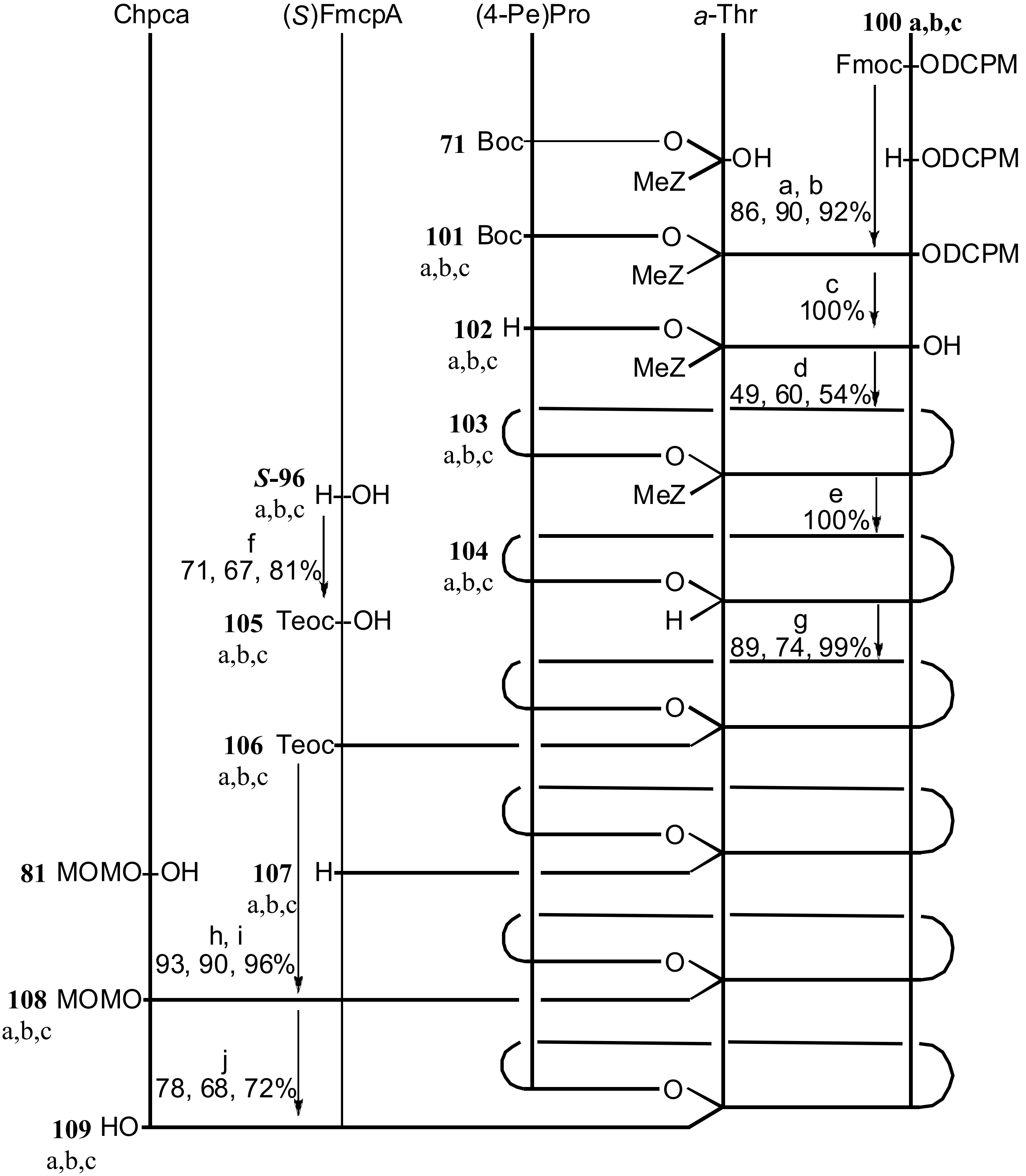
To complete the assembly of the corresponding Hormaomycin analogues, the *N*-MeZ-protected cyclic intermediates **103 a-c** were deprotected and first coupled with the corresponding *N*-Teoc-protected (2*S*,1'*R*,2'*R*)-(3-(mono-, di- or tri-)fluoromethylcyclopropyl)alanines **105 a-c**. After removal of the Teoc group, the intermediates **107 a-c** in turn were coupled with the 1-OMOM-protected 5-chloro-1-hydroxypyrrole-2-carboxylic acid **81**. Finally, the MOM group was removed by treatment with $MgBr_2 \cdot Et_2O$ and EtSH in dichloromethane to give after HPLC purification the target compounds **109 a-c** in 84, 82 and 72%, respectively (Scheme 20).

Because it was found, that MeZ-protected cyclohexadepsipeptide core of the native Hormaomycin has a significant antiparasitic activity, *N*-acetylated **110 c** and *N*-trifluoroacetylated **111 c** derivatives were prepared by coupling the deprotected cyclic intermediate **104 c** with acetic and trifluoroacetic acid.



Scheme 20. Synthesis of the tetrapeptide precursors of Hormaomycin analogues with a: monofluoromethyl-, b: difluoromethyl-, c: trifluoromethylcyclopropylalanine residues.

a) FmocOSu, $NaHCO_3$, acetone/water, 4 h; b) H_2, Pd/C, EtOAc, 20 °C, 40 min; c) EDC, HOAt, DIEA, 2,4,6-collidine, CH_2Cl_2, 0→20 °C, 14 h; d) 50% Et_2NH/THF, 20 °C, 1 h.



Scheme 21. Synthesis of of Hormaomycin analogues with a: monofluoromethyl-, b: difluoromethyl-, c: trifluoromethylcyclopropylalanine residues.

a) 50% Et_2NH/THF, 20 °C, 1 h; b) HATU, HOAt, DIEA, TMP, CH_2Cl_2, 0→20 °C, 24 h; c) 2M HCl in EtOAc, 20°C, 45 min; d) HATU, DIEA,TMP, CH_2Cl_2, 0→20 °C, 16 h; e) anisole, TFA, 20 °C, 2 h; f) TeocOSu, $NaHCO_3$, *N*,*N*-Dimethylaminopropylamine, water/acetone, 20 °C, 2 h; g) HATU, HOAt, DIEA, TMP, CH_2Cl_2, 20 °C, 6 h; h) TFA, 20 °C, 1 h; i) HATU, HOAt, DIEA, TMP, CH_2Cl_2, 20 °C, 4 h; j) $MgBr_2 \cdot Et_2O$, EtSH, CH_2Cl_2, 20 °C, 3.5 h.

5. Biological activity of Hormaomycin and analogues

Malaria (lat.: *mala aria* = bad air) is an infection caused by human-pathogenic *Protozoen*. The pathogens are transferred by the female *Anopheles* gnat, leading to a primary infection of the liver. In the following 'blood phase' of the illness erythrocytes are injured, in which the parasites are developing. During the release of the *Protozoen* from the infected erythrocytes, cell destruction is occurred, that lead to the characteristic fever. The *Plasmodium falciparum* causes the heaviest of the four observed disease pictures, called *Malaria tropica*. This pathogen causes the storage of specific proteins in the erythrocytes membranes, which lead to an adhering of infected blood cells at pre-venous capillaries. It causes thrombosis at the blood flow leading finally to death. Currently approx. 2.2 billion humans live in *Plasmodium*-endemic regions, approximately 500 million of them get sick with malaria annually. The estimated number of deaths caused by malaria is 1.5–3.0 million annually. Despite these, only five medicines of altogether 1300 developed since 1975 are used in malaria treating.

Anti-malaria active substances from plants:

- Quinine was the first chemically pure substance in the malaria therapy. The natural substance was first isolated in 1820 from the crust of the *Cinchona* tree resident in the Andes. Indians used the crust for the fever lowering, giving the first example of the often successful ethnomedical approach to the active substance search. On the basis of the structure of the Quinine synthetic analogues were developed.
- In the traditional Chinese medicine the Wormwood (*Artemisia annua*) has been used for more than 1500 years for the treatment of bleeding and against fever. The isolation of the active component, Artemisinin, was succeeded in 1972, but the substance, like many natural substances from plants, can be isolated only in very small yields, which causes high costs.

Anti-malaria active substances from microorganisms:

- Tetracyclines (like e.g. Doxycyclin) are antibacterial substances from microorganisms, that show a high activity against Gram-positive and negative organisms as well as against *Plasmodium*.
- Another antibacterially effective secondary metabolite with an activity against *Plasmodium* is Borrelidin.

— Among all secondary metabolites active against *Plasmodium falciparum* Gramicidin D holds an outstanding position with a subnanomolar activity and small toxicity. From the chemical point of view, it is the linear peptide, that is able to form ion channels in cell membranes.

There are some cyclic peptides, antiplasmoidale activities of which have been proved. Examples for this are Enniatine and Hormaomycin.

Resistance of *Plasmodium falciparum* against medicines is developing, like that observed for bacteria. In Africa most strains are Chloroquin-resistant, at the same time the effectiveness of Artemisinin in Asia slowly decreases.

So, it is necessary to provide new medicines for malaria treating and Hormaomycin is one of the best drug candidates.

Biological activity of Hormaomicyn and analogues was tested at the group of Dr. Marcel Kaiser (Parasite Chemotherapy group, Swiss Tropical Institute, Basel).

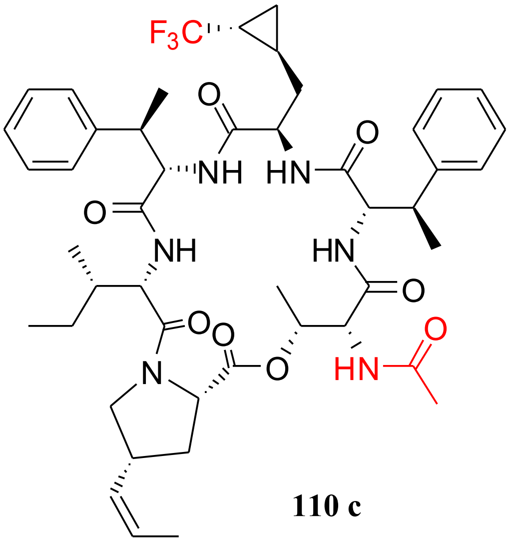
Activity table (IC-50[119] for substances and parasites, concentration in µg/ml):

Compound	*Leishmania donovani axen* strain MHOM-ET-67/L82	*Plasmodium falciparum* strain K1
Miltefosine	0.143	—
Chloroquine	—	0.089
103 c	2.125	0.042
110 c	1.730	0.151
109 c	0.205	0.183
111 c	2.370	0.265
Chloroquine/Artemisinin	—	0.045
53	4.8	0.023
91	--	0.061

Positions suggested for *in vivo* studies are marked yellow. Reference drugs are marked cyan.

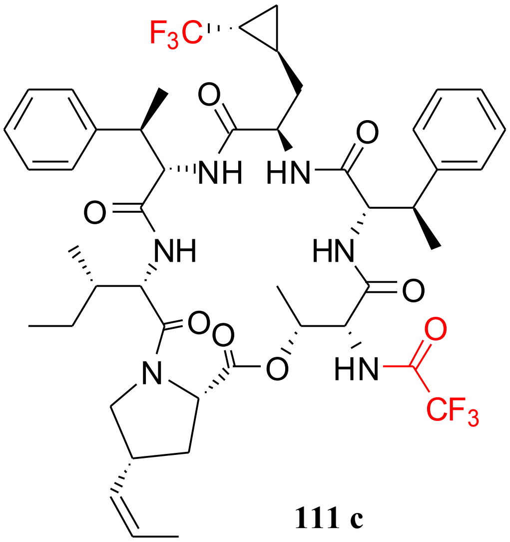
Compounds identification:

110 c: Acetylated cyclohexadepsipeptide with (2*R*,1'*R*,2'*R*)-3-(2'-Trifluoromethylcyclopropyl)alanine (*R*-tFmcpA).



110 c

111 c: Trifluoroacetylated cyclohexadepsipeptide with (2*R*,1'*R*,2'*R*)-3-(2'-Trifluoromethylcyclopropyl)alanine (*R*-tFmcpA).



111 c

EXPERIMENTAL PART

6. *General remarks*

^{1}H NMR: Bruker AM 250 (250 MHz), Varian Unity 300 (300 MHz), Inova 500 (500 MHz), Inova 600 (600 MHz). ^{1}H chemical shifts are reported in ppm relative to residual peaks of deuterated solvents: δ (ppm) = 2.49 for [D$_5$]DMSO, 4.65 for HOD in D_2O, 7.26 for $CHCl_3$, 1.73 and 3.55 for [D$_7$]THF, 3.35 for CHD_2OD. Higher–order NMR spectra were approximately interpreted as first-order spectra, if possible. For the characterization of the observed signal multiplicities the following abbreviations have been applied: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, as well as b = broad.

^{13}C NMR [additional DEPT (Distortionless Enhancement by Polarization Transfer) or APT (Attached Proton Test)]: Bruker AM 250 (62.9 MHz), AMX 300 (75.5 MHz) or Varian Unity 300 (75.5 MHz), Inova 500 (125.7 MHz), Inova 600 (125.7 MHz) instruments. ^{13}C chemical shifts are reported relative to peaks of deuterated solvents: δ (ppm) = 39.5 for [D$_6$]DMSO, 77.0 for $CDCl_3$, 25.5 and 3.55 for [D$_8$]THF, 3.35 for CD_3OD or to methanol in D_2O (δ = 49.5 ppm). The following abbreviations were applied: DEPT: + = primary or tertiary (positive signal in DEPT), – = secondary (negative signal in DEPT), Cquat = quaternary (no signal in DEPT); APT: + = primary or tertiary (positive signal in DEPT), – = secondary or quaternary (negative signal in APT).

IR measured as KBr pellets or thin films between KBr plates on a Bruker IFS 66 (FT-IR) spectrometer.

MS: EI-MS: Finnigan MAT 95, 70 eV, high resolution EI-MS spectra with perfluorkerosene as reference substance; DCI-MS: Finnigan MAT 95, 200 eV, reactant gas NH_3; ESI-MS: Finnigan LCQ. HPLC-MS: pump: Flux Instruments Rheos 4000; degasser: Flux Instruments ERC 3415α; detector: Linear UVIS-205; data system: Flux Instruments Janeiro; ESI: Finnigan LCQ, positive and negative ion mode; data system: Finnigan LCQ Xcalibur; column: Crom Superspher 100 RP-18 endcapped (4 µm, 2 x 100 mm); HPLC conditions: eluent A: H_2O (0.1% TFA), eluent B: MeCN (0.1% TFA). Analytical HPLC: instrument Instrumentelle Analytik Goebel GmbH, autosampler SA 360, pump 420, detector Celeno DAD UV, software Geminyx Version 1.91, column Nucleodur® C18 (250 mm × 3 mm, 5 µm, 100 Å), flow rate 0.5 ml/min. Preparative HPLC: instrument Jasco, pump Jasco PU–1587, detector Jasco UV–1575, Software Jasco-

BORWIN HSS–2000, column Nucleodur® C18 (250 mm × 20 mm, 5 µm, 100 Å), flow rate 18.0 ml/min.

Optical rotations: Perkin-Elmer 241 digital polarimeter, 1-dm cell; optical rotation values are given in 10^{-1} deg cm^2 g^{-1}; concentrations (c) are given in g/100 mL.

M.p.: Büchi 510 capillary melting point apparatus, uncorrected values.

TLC: Macherey-Nagel pre-coated sheets, 0.25 mm Sil G/UV254. The chromatograms were viewed under UV light and/or by treatment with phosphomolybdic acid (10% in ethanol), or ninhydrine (0.2% in ethanol), or I_2 vapor.

Column chromatography: Merck silica gel, grade 60, 230–400 mesh and Baker silica gel, 40–140 mesh.

Elemental analyses: Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Universität Göttingen.

Starting materials: Anhydrous solvents were prepared according to standard methods by distillation over drying agents and were stored under nitrogen. All other solvents were distilled before use.

All reactions were carried out with magnetic stirring and, when employing air- or moisture-sensitive materials, in flame-dried glassware under argon or nitrogen.

7. General synthetic protocols

7.1. Deprotection of N-Fmoc-protected peptides (GP 1)

The respective protected peptide (1 mmol) was taken up with acetonitrile or THF (2 mL), diethylamine (2 mL) was added, and the resulting mixture left at ambient temperature for 40 min. All volatiles were evaporated under reduced pressure, the residue was taken up with toluene (2 × 5 mL), which was evaporated under reduced pressure to remove the last traces of diethylamine. The obtained crude *N*-deprotected peptide was directly used in the next condensation step.

7.2. Peptide condensation step for the preparation of peptides using EDC/HOAt - mediated coupling (GP 2)

EDC (1.03 mmol) and HOAt (1.05 mmol) were added to a cooled (4 °C) solution of the respective *N*-protected amino acid (1 mmol) in anhydrous CH_2Cl_2 (3 mL). After 20 min, the solution of the appropriate crude *N*-deprotected peptide (0.97 mmol) and TMP (3 mmol) in anhydrous CH_2Cl_2 (1 mL) was added at the same temperature. The temperature was allowed to reach 20 °C and stirring was continued for 15 h. Then the reaction mixture was diluted with diethyl ether or ethyl acetate (30 mL) and washed with water (2 × 5 mL), 1 M $KHSO_4$ (3 × 5 mL), water (2 × 5 mL), 5% aqueous $NaHCO_3$ solution (3 × 5 mL), water (3 × 5 mL), brine (2 × 5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography or recrystallization.

7.3. Preparation of hexadepsipeptides and hexapeptides using HATU/HOAt mediated coupling (GP 3)

Deprotected according to GP 1 tetrapeptide (0.100 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL), ester acid / dipeptide acid (0.110 mmol), HATU (0.107 mmol) and HOAt (0.110 mmol) were added and the reaction mixture was cooled to 4 °C. DIEA (0.110 mmol) and TMP (0.300 mmol) were then added, the mixture was allowed to warm to 20 °C and stirring continued for an additional 15 h. The mixture was then taken up with Et_2O (40 mL) and after usual aqueous work-up (GP 2) the organic layer was concentrated to leave crude hexadepsipeptide / hexapeptide , which was purified by recrystallization and/or column chromatography.

7.4. Preparation of cyclohexadepsipeptides (GP 4)

The respective acyclic hexadepsipeptide (105 μmol) was deprotected by stirring with 2 M HCl solution in ethyl acetate (2 mL) at 20 °C for 1 h in dark place and followed concentration under reduced pressure to solid residue. The deprotected material was then dissolved in CH_2Cl_2 (1.0 L). The solution was cooled to 4 °C (internal temperature), HATU (122 μmol) and HOAt (104 μmol) were added, the mixture was stirred for 30 min, and then the solution of DIEA (305 μmol) in CH_2Cl_2 (50 mL, over a period of 30 min). The cooling bath was removed, and stirring was continued for an additional 2 h at ambient temperature. Then the reaction mixture was cooled again to 4 °C and second portions of HATU (122 μmol) and HOAt (104 μmol) were added, followed by a solution of DIEA (305 μmol) in CH_2Cl_2 (50 mL, over a period of 30 min). The temperature was allowed to reach 20 °C, and stirring was continued for 15 h. After this, the solvent was removed under reduced pressure, the residue was taken up with diethyl ether (50 mL), subjected to the usual aqueous work-up (see GP 2) and concentrated under reduced pressure, to give the crude product, which was finally purified by preparative HPLC.

7.5. Deprotection of N-MeZ protected cyclohexadepsipeptides (GP 5)

The respective *N*-MeZ protected cyclodepsipeptide (10 µmol) was treated with 10% anisole in TFA (1 mL) in the dark for 2 h. All volatiles were then removed under reduced pressure at 20 °C. The solid residue was taken up with toluene (2 × 10 mL), which was distilled off under reduced pressure to remove the last traces of anisole and TFA. The resulting crude deprotected depsipeptide was directly used for the appropriate coupling reaction.

7.6. Preparation of heptadepsipeptides and Hormaomycines using HATU/HOAt mediated coupling (GP 6)

Deprotected according to GP 5 depsidipeptide (0.100 mmol) was dissolved in anhydrous CH_2Cl_2 (4 mL), *N*-protected amino acid (0.320 mmol), HATU (0.300 mmol) and HOAt (0.300 mmol) were added and the reaction mixture was cooled to 4 °C. DIEA (0.102 mmol) and TMP (0.900 mmol) were then added as a solution in anhydrous CH_2Cl_2 (2 mL), the mixture was allowed to warm to 20 °C and stirring continued for an additional 15 h. The mixture was then taken up with EtOAc (100 mL) and after usual aqueous work-up (GP 2) the organic layer was concentrated to leave crude depsipeptide, which was purified by recrystallization and/or chromatography.

7.7. Removal of the MOM ether group using $MgBr_2{\bullet}Et_2O$ and EtSH (GP 7)

$MgBr_2{\bullet}Et_2O$ (1 mmol) and EtSH (0.5 mmol) were added to a vigorously stirred solution of the respective *O*-MOM protected derivative (0.1 mmol) in CH_2Cl_2 (15 mL), and stirring was continued for an additional 3.5 h (TLC control was impossible as the starting material and the product in all cases showed exactly the same R_f in all tested solvent systems). The mixture was then taken up with EtOAc (40 mL) and washed with 1 M $KHSO_4$ (3 × 10 mL), water (5 × 10 mL), brine (2 × 5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified first by crystallization and the crude product was finally purified with HPLC.

7.8. Reduction with $LiAlH_4$ (reverse addition) (GP 8)

A solution of $LiAlH_4$ in diethyl ether (1 M, 6 mL, 6 mmol) was added dropwise to the cooled (dry ice/acetone bath) solution of the respective carbonyl compound (20 mmol for ketones, 10 mmol for esters, 7,5 mmol for carboxylic acid) in diethyl ether (20 ml) and the mixture was stirred for an additional 30 min at –78 °C. The flask was immersed to ice/water bath, the mixture was stirred for an additional 2 hour and the saturated aqueous NH_4Cl solution was added dropwise under vigorous stirring (carefully – foam!) till H_2 gas evolution ceased. The mixture was stirred for an additional 15 min, filtered with suction through Celite® pad, filter cake was washed with diethyl ether (3 × 50 ml), combined filtrates concentrated under reduced pressure, giving the target alcohol.

7.9. Conversion alcohols to iodides (GP 9)

The respective racemic alcohol (12 mmol) was added to the solution of triphenylphosphine (5.5 g, 21 mmol) and imidazole (1.5 g, 22 mmol) in corresponding solvent mixture and the solution was cooled down to –5 °C (internal temperature, ice/salt bath). The solid iodine (6.0 g, 24 mmol) was added as one portion and the mixture was stirred for an additional 30 min at this temperature, bath was removed and the mixture was stirred at ambient temperature for 3 hour. The mixture was poured to pentane (200 ml) under vigorous stirring and the resulting mixture was washed with 20% (w/w) aqueous $Na_2S_2O_3 \times 5\ H_2O$ (100 mL), upper pentane layer was separated, water layer was extracted with pentane (2 × 50 mL) and discarded. Combined pentane solution (washing and extracts) was washed with 20% (w/w) aqueous $Na_2S_2O_3 \times 5\ H_2O$ (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude product as colorless liquid containing solid. This was purified with the column chromatography (silica gel, eluting with pentane), giving the pure corresponding target iodide.

7.10. Alkylation of the Ni(II)-complexes of Schiff bases, derived from glycine and (S)- or (R)-2-[(N-Benzylprolyl)amino]benzophenone (Belokon' glycine complexes; (S)- or (R)-BGC) (GP 10)

The respective Belokon' glycine complex (BGC) (2.00 g, 4.02 mmol) was suspended in DMF/MeCN mixture (2 + 4 mL) and degassed in two freeze-pump-thaw cycles (dry ice/acetone bath) under stirring, then NaH (60% in oil, 193 mg, 4.8 mmol) was added to the cold mixture and the system was thawed to 0°C under stirring till the color of the reaction mixture changed from orange to dark-brown. The mixture was frozen, the respective racemic iodide (4.22 mmol) was added with stirring, the bath was removed and the mixture was left to warm to 0 °C with stirring. When ice cover on flask started to thaw, the flask was immersed in an ice/water bath, and stirring was continued until all starting BGC had been consumed (TLC monitoring, chloroform/acetone 7:1, R_f=0.12). After ca. 1 h, 60% aqueous acetic acid (2 mL) was added dropwise. After an additional 10 min of stirring, the mixture was poured into vigorously stirred H_2O (100 mL). The resulting suspension was stirred for ca. 1 h, and the crude product (diastereomeric mixture) was filtered off, the filter cake was washed with H_2O (3 × 10 mL) and dried overnight over P_2O_5 under reduced pressure. The diastereomers were separated by column chromatography (silica gel, eluting with ethyl acetate).

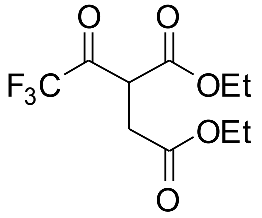
7.11. Decomposition of Belokon' amino acid complexes to obtain enantiomerically pure amino acids (GP 11)

6 M HCl (50 mL) was added to a refluxing solution of the respective Belokon' amino acid complex (1 mmol) in methanol (25 mL), the mixture was heated at reflux for an additional 10 min and concentrated under reduced pressure to leave behind a wet hydrochloride salt. The residue was treated with H_2O (100 mL), precipitated ligand (2-[(N-Benzylprolyl)amino]benzophenone) as a hydrochloride salt was filtered off, washed with H_2O (3 × 30 mL), dried and collected for recycling. The filtrate was combined with the washings, neutralized to pH = 6.0 with 5% aqueous ammonia and extracted with $CHCl_3$ (3 × 30 mL). The aqueous fraction was concentrated to ca. 10 mL and neutralized with 5% aqueous ammonia to pH = 6.5. The amino acid was separated from the nickel salts by elution of the neutralized concentrate through an H^+-form DOWEX ion-exchange resin column (ca. 150 g of resin) with 5–7% aqueous ammonia. The fraction of the eluate that showed red pigmentation on developing with ninhydrin, was collected. This was concentrated under reduced pressure at 40–45 °C. The crude amino acid was dissolved in minimal volume of hot water, the hot turbid solution was filtered and diluted with an equal volume of ethanol. The precipitate, formed after storing at –20 °C for 1 h, was filtered off, washed with cold ethanol (10 mL), and dried *in vacuo* at 40 °C to give the target amino acid.

8. (Fluoromethylcyclopropyl)alanines

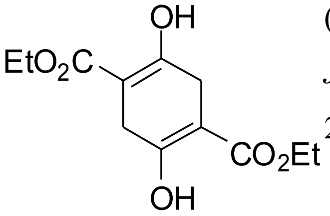
8.1. (Trifluoromethylcyclopropyl)alanines

*Racemic diethyl 2-trifluoroacetyl succinate (***34***):*[120] Ethyl trifluoroacetate **32** (31.0 g, 220 mmol) and diethyl succinate **33** (76.0 g, 440 mmol) were mixed in a 250-mL round-bottomed flask and sodium metal (thin plates, 5.0 g, 220 mmol) was added in one portion. The mixture was heated at reflux with vigorous stirring for 12 h, the reflux condenser was replaced by distillation head, and all volatiles were distilled out (ethanol at ambient pressure and excess of diethyl succinate at reduced pressure). After the mixture had cooled down to ambient temperature, the black tar residue was treated with 5 M aqueous H_2SO_4 (150 mL), the organic layer was separated, the water layer was extracted with diethyl ether (3 × 50 mL), the combined organic phases were washed with water (3 × 50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The viscous black residue was fractioned through a 15-cm Vigreux column *in vacuo*, giving 8.1 g of a predistillate (the product and starting diethyl succinate), 35.6 g main fraction (the target product) and 3.4 g of tail distillate (the target product

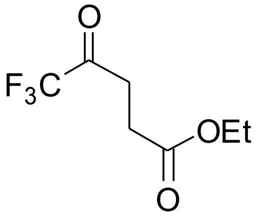


and the side product, diethyl 2,5-dioxo-cyclohexane-1,4-dicarboxylate). Yield 35.6 g, 131.7 mmol, 59.8%. 1H NMR (250 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.1 Hz, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H), 2.85 – 3.15 (m, 2 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 4.27 – 4.38 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.67, 13.89, 32.42, 48.45, 61.54, 62.66, 115.09 (q, *J* = 291.2 Hz), 166.03, 169.97, 186.81 (q, *J* = 36.9 Hz).

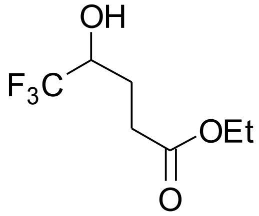
Diethyl 2,5-dihydroxycyclohexa-1.4-diene-1.4-dicarboxylate (side product of **34***)*: ^{1}H NMR (250 MHz, $CDCl_3$): 1.30 (t, *J* = 7.1 Hz, 6 H), 3.16 (s, 4 H), 4.23 (q, *J* = 7.1 Hz, 4 H), 12.2 (s, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 14.2 (+), 28.5 (–), 60.7 (–), 93.2 (Cquat), 168.4 (Cquat), 171.3 (Cquat).



*Ethyl 5,5,5-Trifluoro-4-oxovalerate (***35***)*[64]: Racemic diethyl 2-trifluoroacetosuccinate **34** (35.1 g, 130 mmol) was mixed with boric acid (8.1 g, 130 mmol) in a round-bottomed flask, equipped with a distillation head, and the mixture was stirred at 170 °C (bath temperature) overnight. The distilled ethanol was discarded, the residue was fractioned over a 15-cm Vigreux column *in vacuo*, giving the target ester as a colorless liquid (13,7 g, 69 mmol, 53 %). B. p. : 50–55 °C/10–11 mbar; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1,23 (t, *J* = 7.2 Hz, 3 H), 2.68 (t, *J* = 6.3 Hz, 2 H), 3.01 (t, *J* = 6.3 Hz, 2 H), 4.13 (q, *J* = 7.2 Hz, 2 H); ^{13}C NMR (250 MHz, $CDCl_3$): δ = 14.00, 26.90, 31.40, 61.10, 115.50 (q, *J* = 291.0 Hz), 171.20, 190.10 (q, *J* = 36.0 Hz).

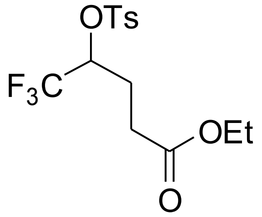


*Racemic ethyl 5,5,5-Trifluoro-4-oxivalerate (****36****)*[64]: To a solution of racemic ethyl 5,5,5-trifluoro-4-oxovalerate **35** (15,8 g, 79,7 mmol) in anhydrous diethyl ether (160 mL), cooled in an ice/salt bath, was added crushed sodium borohydride (1.51 g, 40.0 mmol) in one portion. The cold mixture was stirred for 10 min, the bath was removed, and the mixture was stirred for 4 h. 1 M aq. $KHSO_4$ (50 mL) was added slowly (carefully – foam!), the organic layer was separated, and the water layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure, giving the target hydroxyester (15.6 g, 77.9 mmol, 97.8%) as yellowish liquid. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1,25 (t, *J* = 7.1 Hz, 3 H), 1.80–2.12 (m, 2 H), 2.54 (t, *J* = 7.1 Hz, 2 H), 3.38–3.76 (bs, 1 H), 3.91–4.07 (m, 1 H), 4.14 (q, *J* = 7.1 Hz, 2 H);

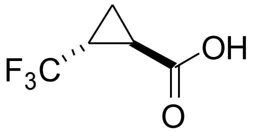


^{13}C NMR: δ = 9.03, 19.58, 24.57, 56.08, 64.59 (q, *J* = 31.2 Hz), 124.90 (q, *J* = 281.9 Hz), 173.83.

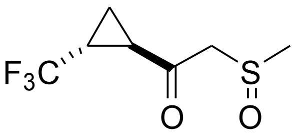
*Racemic ethyl 5,5,5-Trifluoro-4-tosyloxivalerate (***37***)*: To a solution of ethyl 5,5,5-trifluoro-4-hydroxyvalerate **36** (5.87 g, 29.3 mmol) in anhydrous pyridine (30 mL), cooled in ice/salt bath was added tosyl chloride (11.2 g, 58.6 mmol) as one portion, followed by DMAP (0.72 g, 5.9 mmol). The cold mixture was stirred for 10 min, the bath was removed, and the mixture was stirred at ambient temperature for 20 h. Water (5 mL) was added, the mixture was stirred for 30 min, poured into a vigorously stirred mixture of water (50 mL) and diethyl ether (100 mL) and stirred for an additional 10 min. The organic phase was separated, washed with aq. 6 M HCl (50 mL), water (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give target ester (9.3 g, 26.4 mmol, 90%) as light yellow viscous liquid. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1,27 (t, *J* = 7.14 Hz, 3 H), 1.93–2.08 (m, 1 H), 2.11–2.25 (m, 1 H), 2.44 (s, 3 H), 2.50 (t, *J* = 7.20 Hz, 2 H), 4.15 (q, *J* = 7.14 Hz, 2 H), 4.93–5.08 (m, 1 H), 7.34 (d, *J* = 8.25 Hz, 2 H), 7.78 (d, *J* = 8.32 Hz, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.07, 21.63, 23.65 (q, *J* = 1.7 Hz), 28.23, 60.82, 75.40 (q, *J* = 33.0 Hz), 127.90, 129.86, 130.78 (q, *J* = 243.5 Hz), 145.57, 156.52, 171.82.



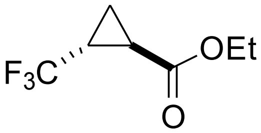
*Racemic trans-2-trifluoromethylcyclopropanecarboxylic acid (***38***)*: The solution of the ethyl 5,5,5-trifluoro-4-tosyloxivalerate **37** (6.4 g, 18 mmol) in anhydrous THF (10 mL) was added via syringe during 3 hour to vigorously stirred refluxing solution of potassium *tert*-butoxide (9.0 g, 80 mmol) in anhydrous THF (50 mL) under N_2-flow and the solution was refluxed for 4 h. The resulting mixture after cooling was diluted with water (100 mL) and organics were distilled out under reduced pressure. Alkaline water phase was washed with diethyl ether (3 × 30 mL), acidified with aqueous 6 M HCl to pH~1 and extracted with diethyl ether (5 × 50 mL). Combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure, giving crude product as black tar. Molecular distillation of this crude product gives target acid as colorless liquid (1.3 g, 8.4 mmol, 47%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25–1.48 (m, 2 H), 1.97–2.11 (m, 1 H), 2.12–2.29 (m, 1 H), 10.36 (bs, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 10.83 (–, q, *J* = 3.2 Hz), 16.56 (+, q, *J* = 2.6 Hz), 22.56 (+, q, *J* = 38.3 Hz), 124.50 (–, q, *J* = 271.2 Hz), 177.70.



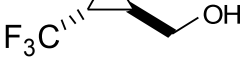
*Racemic 2-Methanesulfinyl-1-(trans-2-trifluoromethyl-cyclopropyl)-ethanone (***39***)*: Potassium *tert*-butoxide (4.9 g, 44 mmol) was dissolved in anhydrous DMSO (30 mL) under N_2-flow at ambient temperature and the solution was stirred for 1 hour. The solution of the ethyl 5,5,5-trifluoro-4-tosyloxyvalerate **37** (3.4 g, 10.0 mmol) in 5 ml of anhydrous DMSO was added dropwise and the resulting mixture was stirred for 24 hours at 50°C and 12 hours at 60°C (bath temperature). The mixture was diluted with water (50 mL) and washed with diethyl ether (5 × 20 mL), organic phases were discarded. The resulting alkaline solution was acidified with aqueous HCl (6 M) to pH~1 and extracted with diethyl ether (10 × 20 mL). Combined organic phases were washed with water (3 × 50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure, giving crude product as viscous dark oil containing solid. The molecular distillation of the crude product gives the yellow liquid, solidifying when stored at ambient temperature to waxy solid (6.6 g, 31 mmol, 70%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.30–1.42 (m, 2 H), 2.07 (s, 2 H), 2.08 (s, 3 H), 2.11–2.22 (m, 1 H), 2.65–2.75 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.85, 21.20, 23.17, 61.82, 126.09 (q, J=270.3 Hz), 155.62; MS-EI (77 eV): m/z (%) 214 (10, M$\rceil$+), 137 (14, M–$CH_2SOCH_3\rceil^{+}$), 109 (8, M–$COCH_2SOCH_3\rceil^{+}$), 89 (10, $C_4H_3F_2\rceil^{+}$), 77 (100, $CH_3SOCH_2\rceil^{+}$).



*Racemic ethyl trans-2-trifluoromethylcyclopropanecarboxylate (***40***)*: The solution of the ethyl 5,5,5-trifluoro-4-tosyloxivalerate (9.4 g, 26 mmol) in anhydrous THF (20 mL) was added via syringe during 1 hour to vigorously stirred solution of potassium *tert*-butoxide (14.9 g, 133 mmol) in anhydrous THF (100 mL) under N_2-flow and the solution was stirred for 24 hours. The resulting mixture was concentrated under reduced pressure at ambient temperature and diluted with water (100 mL). Alkaline water solution was extracted with diethyl ether (5 × 50 mL), combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure, giving crude product as black tar. Molecular distillation of this crude product gives target ester as colorless liquid (0.81 g, 4.4 mmol, 17%). Water phase work-up gives no other products, but tar. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.18–1.41 (m, 2 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.93–2.30 (m, 2 H), 4.08–4.29(q, J = 7.1 Hz, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 10.18 (–, q, J = 2.5 Hz), 13.93 (+), 16.71 (+, q, J = 2.9 Hz), 21.85 (+, q, J = 37.8 Hz), 61.27 (–), 124.78 (–, q, J = 266.7 Hz), 171.24 (–).

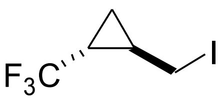


*Racemic (2-Trifluoromethyl-cyclopropyl) methanol(***41***):* Racemic *trans*-2-trifluoromethyl-cyclopropanecarboxylic acid (3.4 g, 18.6 mmol) was reduced with the

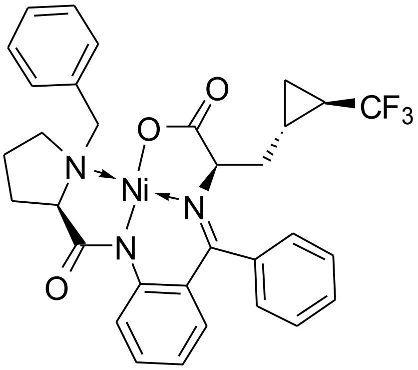


lithium aluminum hydride in diethyl ether (1.13 M, 8.3 mL, 9.4 mmol) according to GP 8, giving target alcohol as colorless liquid (2.3 g, 16.4 mmol, 88%). ^{1}H NMR (250 MHz, $CDCl_3$): 0.70–0.83 (m, 1 H), 0.94–1.06 (m, 1 H), 1.39–1.58 (m, 2 H), 1.95 (bd, *J* = 19.7 Hz, 1 H), 3.40–3.70 (m, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 6.28, 17.44, 17.86 (q, *J*=37.0 Hz), 63.68, 126.09 (q, *J*=270.3 Hz).

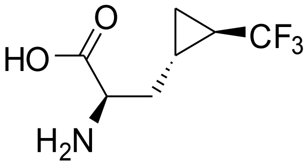
*Racemic trans-(2-Trifluoromethylcyclopropyl)methyl iodide (***47***)*: Racemic *trans*-(2-trifluoromethylcyclopropyl)methanol (1.7 g, 12 mmol) was iodinated according to GP 9 with triphenylphosphine (5.5 g, 21 mmol), imidazole (1.5 g, 22 mmol) and solid iodine (6.0 g, 24 mmol) in diethyl ether/acetonitrile mixture (36 + 24 ml), giving the target iodide as slightly yellowish liquid (2.7 g, 11 mmol, 90%). TLC: $R_f = 0.36$, pentane; ^{1}H NMR (250 MHz, $CDCl_3$): 0.75–0.87 (m, 1 H), 1.21–1.33 (m, 1 H), 1.41–1.57 (m, 1 H), 1.63–1.79 (m, 1 H), 3.03–3.21 (m, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 6.76, 13.51 (q, *J* = 3.0 Hz), 19.42 (q, *J* = 2.7 Hz), 25.06, 130.00 (q, *J* = 280.5 Hz)



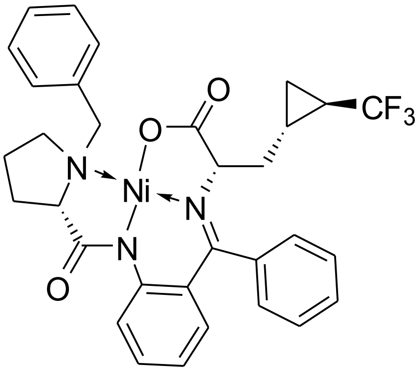
*(R)-Belokon' 3-(2-trifluoromethylcyclopropyl)alanine complex [(R)-B(tFmcpA)C, (2R,1'S,2'R)-***112***]*: (*R*)-BGC (3.17 g, 6.4 mmol) was alkylated with racemic *trans*-(2-trifluoromethylcyclopropyl)methyliodide **47** (1.67 g, 6.7 mmol) according to GP 10 using NaH (60% in oil, 305 mg, 7.6 mmol) in DMF/MeCN mixture (3 + 6 mL) during 4 hour, giving after chromatographycal separation (silica gel, eluted with EtOAc), (2*R*,1'*S*,2'*R*) component (1.73 g, 2.79 mmol, 43.7% on (*R*)-BGC, d.e.≥98%), (2*R*,1'*R*,2'*S*) component (1.68 g, 2.71 mmol, 42.4% on (*R*)-BGC, d.e.≥98%) and mixed fractions (0.17 g, 0.27 mmol, 4.3% on (*R*)-BGC) as well as products of the anion oxidation (0.12 g). For (2*R*,1'*S*,2'*R*) component ^{1}H NMR (250 MHz, $CDCl_3$): δ = –0.15– –0.09 (m, 1 H), 0.80–0.86 (m, 1 H), 0.90–0.98 (m, 1 H), 1.10–1.16 (m, 1 H), 1.76–1.84 (m, 1 H), 2.04–2.13 (m, 1 H), 2.13–2.21 (m, 1 H), 2.43–2.52 (m, 1 H), 2.57–2.71 (m, 2 H), 3.46 (dd, *J* = 5.6 Hz, 11.1 Hz, 1 H), 3.49–3.60 (m, 3 H), 3.92 (dd, *J* = 3.5 Hz, 9.1 Hz, 1 H), 4.42 (d, *J* = 12.7 Hz, 1 H), 6.56–6.65 (m, 2 H), 6.86 (d, *J* = 7.6 Hz, 1 H), 7.11 (ddd, *J* = 1.8 Hz, 6.8 Hz, 8.6 Hz, 1 H), 7.17 (t, *J* = 7.5 Hz, 1 H), 7.25–7.29 (m, 1 H), 7.33 (t, *J* = 7.7 Hz, 2 H), 7.41–



7.46 (m, 1 H), 7.47–7.54 (m, 2 H), 8.05 (d, $J = 7.1$ Hz, 2 H), 8.09 (d, $J = 8.7$ Hz, 1 H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=8.41, 11.74, 20.09 (q, $J = 36.9$ Hz,), 23.93, 30.70, 38.41, 57.24, 63.17, 69.52, 70.11, 120.70, 123.74, 125.93 (q, $J = 270.3$ Hz,), 126.23, 127.32, 127.35, 128.84, 128.89, 128.90, 129.05, 129.84, 131.48, 132.28, 133.12, 133.24, 133.69, 142.35, 170.75, 178.65, 180.45; MS-ESI: (positive) m/z (%) 1882 (100, 3M+Na$]^+$), 1263 (66, 2M+Na$]^+$), 810 (25, 2M+Na–$C_{13}H_{12}]^+$), 642 (15, M+Na$]^+$), 620 (3, M+H$]^+$), (negative) m/z (%) 618 (100, M–H$]^-$), 528 (40, M–$C_7H_7]^-$).



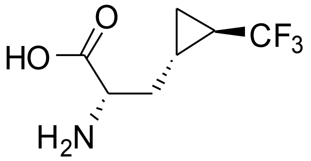
(2R,1'S,2'R)-3-(2-trifluoromethylcyclopropyl)alanine [(R)tFmcpA, ***R*-96 c**]: Compound (2*R*,1'*S*,2'*R*)-**112** (980 mg, 1.58 mmol) was decomposed and the amino acid was separated and purified according to GP 11 to give pure target amino acid **R-96 c** (275 mg, 1.39 mmol, 88%). $[\alpha]_D^{20}$ –20.0 (c = 0.2 in MeOH); ^{1}H NMR (250 MHz, CD_3OD): δ = 0.75–0.87 (m, 1 H), 0.94–1.07 (m, 1 H), 1.31–1.44 (m, 1 H), 1.47–1.67 (m, 2 H), 2.06–2.22 (m, 1 H), 3.54–3.63 (m, 1 H), 4.94 (bs, 3 H); ^{13}C NMR (62.9 MHz, CD_3OD): δ = 9.64, 13.10, 20.12 (q, $J = 36.9$ Hz), 34.88, 55.99, 127.80 (q, $J = 269.6$ Hz), 173.72; MS-EI (70 eV): m/z (%) 152 (100, M–$CO_2H]^+$), 74 (75, $C_2H_4NO_2]^+$)); MS-ESI: (positive) m/z (%) 198 (100, M+H$]^+$), (negative) m/z (%) 196 (60, M–H$]^-$).



(S)-Belokon' 3-(2-trifluoromethylcyclopropyl)alanine complex [(S)-B(tFmcpA)C, (2*S*,1'*S*,2'*R*)-**113**]: (*S*)-BGC (645 mg, 1.29 mmol) was alkylated with racemic (2-trifluoromethylcyclopropyl)methyl iodide **47** (340 mg, 1.36 mmol) according to GP 10 using NaH (60% in oil, 62 mg, 1.55 mmol) in DMF/MeCN mixture (1 + 2 mL) during 4 h, giving after chromatographycal separation (silica gel, eluted with EtOAc), (2*S*,1'*R*,2'*S*) component (393 mg, 634 µmol, 49.1% on (*S*)-BGC, d.e.≥98%), (2*S*,1'*S*,2'*R*) component (364 mg, 587 µmol, 45.5% on (*S*)-BGC, d.e.≥98%) and mixed fractions (33 mg, 53 µmol, 4.1% on (*S*)-BGC). For (2*S*,1'*S*,2'*R*) component ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.43–0.61 (m, 2 H), 1.00–1.13 (m, 1 H), 1.40–1.70 (m, 2 H), 1.99–2.26 (m, 3 H), 2.40–2.78 (m, 2 H), 3.33–3.65 (m, 4 H), 3.99 (dd, $J = 8.9$ Hz, 3.3 Hz, 1 H), 4.46 (d, $J = 12.6$ Hz, 1 H), 6.58–6.71 (m, 2 H), 6.84(d, $J = 7.5$ Hz, 1 H), 7.09–7.23 (m, 2 H), 7.29–7.40 (m, 3 H), 7.41–7.63 (m, 3 H), 8.04–8.12 (m, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.89 (q, $J = 1.3$ Hz), 30.67, 38.77, 57.24, 60.33, 63.21, 69.68, 70.14,

77.29, 120.74, 125.58 (q, $J = 237.9$ Hz), 126.24, 127.28, 128.35, 128.54, 128.86, 128.88, 128.89, 129.25, 129.90, 131.45, 131.93, 132.09, 132.24, 133.14, 133.34, 133.62, 142.27, 156.25, 156.27, 156.32, 170.47, 178.68, 180.43.

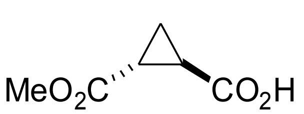
(2S,1'S,2'R)-3-(2-trifluoromethylcyclopropyl)alanine [(S)tFmcpA, ***S*-96 c**]: Compound



(2*S*,1'*S*,2'*R*)-**113** (210 mg, 339 µmol) was decomposed and the amino acid was separated and purified according to GP 11 to give pure target amino acid **c** (61 mg, 311 µmol, 92%).

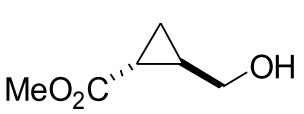
8.2. *(Difluoromethylcyclopropy)lalanines*

*Racemic monomethyl cyclopropane-trans-1,2-dicarboxylate (***16***)*[121]: The LiOH × H_2O (4.2 g,



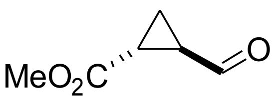
100 mmol) solution in methanol (100 mL) was added dropwise for 1 hour to vigorously stirred solution of racemic dimethyl cyclopropane-*trans*-1,2-dicarboxylate **15** (15.8 g, 100 mmol) in THF (400 mL) under N_2-flow and the resulting mixture was stirred for an additional 1 h. Solvents were evaporated under reduced pressure at ambient temperature, the residue was diluted with water (80 mL) and washed with diethyl ether. Organic phases were discarded, water phase was acidified with concentrated aqueous HCl (37%, 10 mL), saturated with solid NaCl and extracted with diethyl ether (3 × 50 mL). Combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure, giving clear oil, solidifying when dried *in vacuo* overnight (12.1 g, 84 mmol, 84%). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.42$–1.57 (m, 2 H), 2.11–2.27 (m, 2 H), 3.71 (s, 3 H), 9.76 (bs, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 15.87$, 22.07, 22.75, 52.31, 171.86, 178.13.

*Racemic methyl trans-2-hydroxymethylcyclopropanecarboxylate (***18***)*[122]: The borane – dimethyl

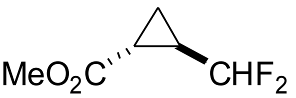


sulfide complex (10 M in Me_2S, 10.8 mL, 108 mmol) was added dropwise for 30 min to cold (ice/water bath) solution of the racemic monomethyl cyclopropane-*trans*-1,2-dicarboxylate **16** (12.9 g, 90 mmol) in THF (40 mL) and the resulting mixture was left to stir in melting bath overnight. The mixture was re-cooled (ice/water bath) and methanol (5 mL) was added dropwise under stirring. After H_2 gas evolution ceased, the mixture was diluted with methanol (100 mL) and concentrated under reduced pressure, this dilution-concentration procedure was repeated 3 times, giving crude product as clear oil (11.9 g), which was purified with chromatography (silica gel, eluted with Et_2O) to give pure hydroxyester **18** as colorless clear oil (11.1 g, 85 mmol, 95%). TLC: R_f=0.26 (Et_2O); ^{1}H NMR (250 MHz, $CDCl_3$): 1.06–1.29 (m, 2 H), 1.36–1.50 (m, 2 H), 1.99–2.25 (m, 2 H), 3.65 (s, 3 H), 4.58 (bs, 1 H); ^{13}C NMR (62.9 MHz, CDCl$_3$): 12.7, 18.1, 24.2, 51.8, 64.3, 174.5.

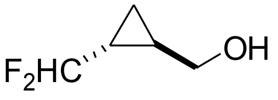
Racemic methyl trans-2-formylcyclopropanecarboxylate (**20**)[121]: To a vigorously stirred solution of oxalyl chloride (5.23 g, 3.5 mL, 41.2 mmol) in anhydrous CH$_2$Cl$_2$ (70 mL) cooled to –78 °C (dry ice/acetone bath) under nitrogen flow, was added a solution of anhydrous DMSO (6.89 g, 6.3 mL, 88.2 mmol) in anhydrous CH$_2$Cl$_2$ (3 mL) at such a rate that the temperature of the reaction mixture did not exceed –70 °C (about 40 min). After the mixture was stirred at –70 °C for an additional 30 min, a solution of the racemic methyl *trans*-2-hydroxymethylcyclopropanecarboxylate **18** (4.44 g, 34.1 mmol) was added dropwise under vigorous stirring keeping the temperature of the reaction mixture under –70 °C. The mixture was stirred at this temperature for an additional 1 h and anhydrous triethylamine (17.2 g, 24 mL, 170 mmol) was gradually added at –78 °C. After the addition was complete, the cooling bath was removed and the stirred mixture was allowed to reach room temperature. Then water (20 mL) was added and the mixture was acidified with aq. 12 M HCl (15 mL) at 0 °C (ice/salt bath). The organic layer was separated and the aqueous phase was extracted with diethyl ether (3 × 20 mL). Combined organic layers were washed with water (20 mL), brine (2 × 20 mL), dried over MgSO$_4$, filtered and concentrated under reduced pressure, giving the target aldehyde as colorless clear oil (4.19 g, 32.7 mmol, 96%). ^{1}H NMR (250 MHz, CDCl$_3$): 1.38-1.66 (m, 2H), 2.08-2.53 (m, 2H), 3.68 (s, 3H), 9.27 (d, 4.2 Hz); ^{13}C NMR (62.9 MHz, CDCl$_3$): 14.8, 21.9, 30.5, 52.2, 171.5, 198.1.



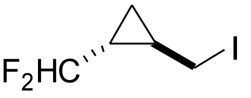
Racemic methyl trans-2-difluoromethylcyclopropanecarboxylate (**21**): The reaction was provided in PTFE flask. Deoxo-Fluor® **14** solution in toluene (50% w/w, 26.4 g, 59.7 mmol)was added under N$_2$-flow with stirring to the solution of racemic methyl *trans*-2-formyl-cyclopropanecarboxylate **20** (4.5 g, 35.1 mmol) in anhydrous CH$_2$Cl$_2$ (6 ml). Ethanol (0.1 mL) was added and the mixture was stirred for 48 hours at ambient temperature. Resulting solution was poured to vigorously stirred sat. aq. NaHCO$_3$ (150 mL), stirred till CO$_2$ gas evolution ceased, organic phase was separated, water phase was extracted with CH$_2$Cl$_2$ (3 × 50 mL), combined organic phases were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified with the column chromatography (silica gel, eluted with pentane/diethyl ether 4:1) to give pure target difluoroester **21** as colorless liquid (2.7 g, 18.0 mmol, 51%). ^{1}H NMR (250 MHz, CDCl$_3$): $\delta = 1.09–1.21$ (m, 1 H), 1.21–1.33 (m, 1 H), 1.82–2.00 (m, 2 H), 3.69 (s, 3 H), 5.76 (td, $J = 57.3$ Hz, 3.4 Hz, 1 H); ^{13}C NMR (62.9 MHz, CDCl$_3$): $\delta = 9.7$ (–, t, J=4.3 Hz), 15.5 (+, t,



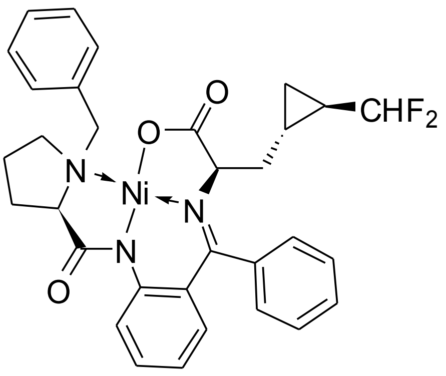
J=4.4 Hz), 22.8 (+, t, *J*=27.0 Hz), 51.9 (+), 114.6 (+, t, *J*=239.0 Hz), 172.5 (–); MS–EI (70eV): m/z (%) 150.1 (10%, $\mathrm{M}\rceil^{+}$), 149.1 (9%, $\mathrm{M{-}H}\rceil^{+}$), 119.1 (100%, $\mathrm{M{-}MeO}\rceil^{+}$), 99.1 (29%, $\mathrm{C_5H_4FO}\rceil^{+}$), 91.1 (30%, $\mathrm{M{-}CO_2Me}\rceil^{+}$), 59.0 (28%, $\mathrm{C_3H_4F}\rceil^{+}$), .



*Racemic trans-(2-difluoromethylcyclopropyl) methanol (***42***)*: Racemic methyl *trans*-2-difluoromethylcyclopropanecarboxylate **21** (2.52 g, 16.8 mmol) was reduced with the lithium aluminum hydride in diethyl ether (1.13 M, 7.4 mL, 8.4 mmol) according to GP 9. The crude product was purified with the column chromatography (silica gel, eluted with pentane/diethyl ether 1:1) to give the target difluoroalcohol **42** as colorless liquid (1.68 g, 13.8 mmol, 82%). TLC: R_f = 0.17 (pentane/ $\mathrm{Et_2O}$=4:1); ^{1}H NMR (600 MHz, $\mathrm{CDCl_3}$): δ = 0.58–0.63 (m, 1 H), 0.76–0.80 (m, 1 H), 1.15–1.24 (m, 1 H), 1.26–1.32 (m, 1 H), 2.57 (bs, 1 H), 3.40–3.53 (m, 2 H), 5.56 (td, *J* = 57.4 Hz, 4.5 Hz, 1 H); ^{13}C NMR (125.7 MHz, $\mathrm{CDCl_3}$): δ = 5.48 (–, t, *J*=4.5 Hz), 16.58 (+, t, *J*=4.0 Hz), 18.59 (+, t, *J*=27.1 Hz), 64.42 (–), 116.78 (+, t, *J*=237.5 Hz).



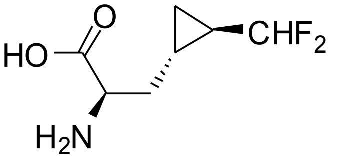
*Racemic trans-(2-difluoromethylcyclopropyl)methyl iodide (***46***)*: Racemic *trans*-(2-difluoromethylcyclopropyl) methanol **42** (1.68 g, 13.8 mmol) was iodinated according to GP 9 with triphenylphosphine (6.26 g, 23.9 mmol), imidazole (1.71 g, 25.1 mmol) and solid iodine (6.75 g, 26.5 mmol) in diethyl ether/acetonitrile mixture (41 + 27 ml), giving the target iodide as slightly yellowish liquid (2.81 g, 12.1 mmol, 88%). TLC: R_f = 0.17, pentane; ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$): δ = 0.63–0.74 (m, 1 H), 1.06–1.16 (m, 1 H), 1.16–1.33 (m, 1 H), 1.48–1.61 (m, 1 H), 3.04–3.17 (m, 2 H), 5.63 (td, *J* = 57.4 Hz, 3.9 Hz, 1 H); ^{13}C NMR (125.7 MHz, $\mathrm{CDCl_3}$): δ = 8.60 (–), 12.95 (–, t, *J* = 4.5 Hz), 18.85 (+, t, *J*=4.6 Hz), 25.73 (+, t, *J*=26.7 Hz), 115.70 (+, t, *J*=238.4 Hz); MS–EI (70 eV): m/z (%) 105,1 (100%, $\mathrm{M{-}I}\rceil^{+}$), 85.1 (20%, $\mathrm{C_5H_6F}\rceil^{+}$), 77.0 (30%, $\mathrm{C_4H_{10}F}\rceil^{+}$), 59.1 (95%, $\mathrm{C_3H_4F}\rceil^{+}$), 41.2 (31%, $\mathrm{C_3H_5}\rceil^{+}$).



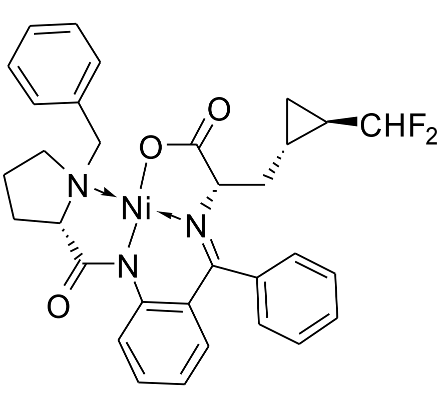
(R)-Belokon' 3-(2-difluoromethylcyclopropyl)alanine complex [(R)-B(dFmcpA)C, (2*R*,1'*S*,2'*R*)-**114***]*: (*R*)-BGC (2.00 g, 4.02 mmol) was alkylated with racemic *trans*-(2-difluoromethylcyclopropyl)methyl iodide **46** (980 mg, 4.22 mmol) according to GP 10 using NaH (60% in oil, 193 mg, 4.8 mmol) in DMF/ MeCN mixture (2 + 4 mL) during 1 h, giving (2*R*,1'*S*,2'*R*) component (1.14 g, 1.90 mmol, 47.3% on (*R*)-BGC, d.e.≥98%), (2*R*,1'*R*,2'*S*) component (1.10 g, 1.82 mmol, 45.4% on (*R*)-BGC, d.e.≥98%) and mixed fractions

(0.107 g, 0.18 mmol, 4.4% on (*R*)-BGC). For (2*R*,1'*S*,2'*R*) component $[\alpha]_D^{20}$ = –2830.0° (c=0.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ= –0.3 – –0.2 (m, 1 H), 0.6–0.7 (m, 1 H), 0.9–1.0 (m, 1 H), 1.0–1.1 (m, 1 H), 1.4–1.5 (m, 1 H), 2.0–2.1 (m, 1 H), 2.1–2.2 (m, 1 H), 2.4–2.5 (m, 1 H), 2.55–2.7 (m, 2 H), 3.4–3.5 (m, 1 H), 3.5–3.6 (m, 2 H), 3.55 (d, *J* = 12.7 Hz, 1 H), 3.90 (dd, *J* = 3.5 Hz, 9.6 Hz, 1 H), 4.43 (d, *J* = 12.7 Hz, 1 H), 5.51 (td, *J* = 57.4 Hz, 4.4 Hz, 1 H), 6.55–6.65 (m, 2 H), 6.87 (d, *J* = 7.2 Hz, 1 H), 7.07–7.12 (m, 1 H), 7.12–7.20 (m, 1 H), 7.22–7.28 (m, 1 H), 7.28–7.36 (m, 2 H), 7.38–7.44 (m, 1 H), 7.46–7.54 (m, 2 H), 8.00–8.50 (m, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=7.23 (–), 11.01 (+, t, *J* = 4.5Hz), 20.94 (+, t, *J* = 26.9 Hz), 23.95 (–), 30.66 (–), 39.07 (–), 57.21 (–), 63.10 (–), 69.84 (+), 70.08 (+), 116.73 (+, t, *J* = 238.0 Hz), 120.66 (+), 123.70 (+), 126.23 (–), 127.31 (+), 127.35 (+), 128.11 (+), 128.80 (+), 128.85 (+), 128.92 (+) 128.97 (+), 129.77 (+), 129.81 (+), 131.46 (+), 132.17 (+), 133.07 (+), 133.23 (–), 133.61 (–), 142.24 (–), 170.45 (–), 178.79 (–), 180.39 (–); MS-ESI: (positive) m/z (%) 624.2 (100%, M+Na]$^+$), 1225.0 (90%, 2M+Na]$^+$), 1827.4 (55%, 3M+Na]$^+$), 602.2 (16%, M+H]$^+$).

(2R,1'S,2'R)-3-(2-difluoromethylcyclopropyl)alanine (***R*-96 b**): (*2R,1'S,2'R*)-B(dFmcpA)C (730 mg, 1.21 mmol) was decomposed and the amino acid was separated and purified according to GP 11 to give pure target amino acid (210 mg, 1.17 mmol, 97%). $[\alpha]_D^{20}$ = +30.4° (c=0.5, H_2O); ^{1}H NMR (600 MHz, D_2O): δ = 1.21–1.30 (m, 1 H), 1.63–1.75 (m, 1 H), 1.98–2.08 (m, 1 H), 3.81 (t, *J* = 6.0 Hz, 1 H), 5.67 (td, *J* = 57.1 Hz, 4.8 Hz, 1 H); MS-ESI: (positive) m/z (%) 180 (100, M+H]$^+$), (negative) m/z (%) 357 (100, 2M–H]$^-$), 178 (55, M–H]$^-$).

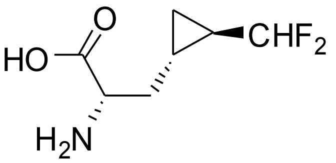


(S)-Belokon' 3-(2-difluoromethylcyclopropyl)alanine complex [(S)-B(dFmcpA)C, (2*S*,1'*S*,2'*R*)-**115**]: (*S*)-BGC (756 mg, 1.52 mmol) was alkylated with racemic *trans*-(2-difluoromethylcyclopropyl)methyl iodide **46** (370 mg, 1.60 mmol) according to GP 10 using NaH (60% in oil, 73 mg, 1.82 mmol) in DMF/ MeCN mixture (1 + 2 mL) during 1 hour, giving (2*S*,1'*R*,2'*S*) component (442 mg, 734 µmol, 48,3% on (*S*)-BGC, d.e.≥98%), (2*S*,1'*S*,2'*R*) component (409 mg, 679 µmol, 44.7% on (*S*)-BGC, d.e.≥98%) and mixed fractions (40 mg, 67 µmol, 4.4% on (*S*)-BGC). For (2*S*,1'*S*,2'*R*) component $[\alpha]_D^{20}$ = +2200° (c=0.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.25–0.37 (m, 1 H), 0.37–0.41 (m, 1 H), 0.85–0.95 (m, 1 H), 1.30–1.45 (m, 2 H), 2.00–2.10 (m, 1 H), 2.10–2.19 (m, 1 H), 2.19–2.23 (m, 1 H),



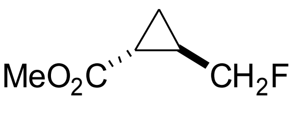
2.43–2.53 (m, 1 H), 2.60–2.70 (m, 1–H), 3.40–3.47 (m, 1–H), 3.47–3.6 (m, 2 H), 3.53 (d, J = 12.7 Hz, 1 H), 3.90–3.97 (m, 1 H), 4.41 (d, J = 12.7 Hz, 1 H), 5.41 (td, J = 57.2 Hz, 4.1 Hz, 1 H), 6.55–6.60 (m, 1 H), 6.60–6.65 (m, 1 H), 6.78–6.83 (m, 1 H), 7.08–7.12 (m, 1 H), 7.12–7.17 (m, 1 H), 7.25–7.38 (m, 3 H), 7.39–7.46 (m, 1 H), 7.46–7.57 (m, 2 H), 8.00–8.10 (m, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 8.38 (–, t, J = 4.2 Hz), 11.38 (+, dd, J=4 Hz, 5 Hz), 20.10 (+, dd, 26.1 Hz, 28.0 Hz), 23.85 (–), 30.67 (–), 39.18 (–), 57.19 (–), 63.16 (–), 69.96 (+), 70.15 (+), 116.44 (+, t, J=32.0 Hz), 120.66 (+), 123.66 (+), 126.25 (–), 127.33 (+), 127.44 (+), 128.13 (+), 128.81 (+), 128.85 (+), 129.04 (+), 129.12 (+), 129.83 (+), 131.29 (+), 131.45 (+), 132.15 (+), 133,11 (+), 133.28 (–), 133.62 (–), 142.29 (–), 170.33 (–), 178.76 (–), 180.36 (–); MS-ESI: (positive) m/z (%) 1828 (55%, 3M+Na]$^+$), 1225 (100%, 2M+Na]$^+$), 624 (70%, M+Na]$^+$), 602 (14%, M+H]$^+$), (negative) m/z (%) 600 (100%, M–H]$^-$).

(2S,1'S,2'R)-3-(2-difluoromethylcyclopropyl)alanine ***(S*-96 b*)***: (2*S*,1'*S*,2'*R*)-B(dFmcpA)C (180 mg, 299 µmol) was decomposed and the amino acid was separated and purified according to GP 11 to give pure target amino acid (50 mg, 278 µmol, 93%). $[\alpha]_D^{20}$ = –16.0° (c=0.3 in H_2O); ^{1}H NMR (600 MHz, D_2O):δ = 0.65–0.75 (m, 1 H), 0.90–1.00 (m, 1 H), 1.10–1.20 (m, 1 H), 1.30–1.41 (m, 1 H), 1.80–1.88 (m, 1 H), 2.01–2.08 (m, 1 H), 3.87 (dd, J = 6.6 Hz, 5.4 Hz, 1 H), 4.72 (bs, 3 H), 5.76 (td, J = 57.2 Hz, 4.8 Hz, 1 H); ^{13}C NMR (125.7 MHz, D_2O): δ = 6.93 (–, dd, J = 5.6 Hz, 3.3 Hz), 10.10 (+, dd, J = 5.9 Hz, 3.5 Hz), 19.92 (+, t, J = 27.1 Hz), 117.99 (+, t, J = 235.4 Hz), 174.20 (–); MS-ESI: (positive) m/z (%) 180.0 (100%, M+H]$^+$).



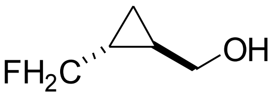
8.3. Monoluoromethylcyclopropylalanines

*Racemic methyl trans-2-monofluoromethylcyclopropanecarboxylate (***19***)*: The reaction was provided in PTFE flask. Deoxo-Fluor® solution in toluene (50% w/w, 24.3 g, 55.0 mmol) was added under N_2-flow with stirring to the solution of racemic methyl *trans*-2-hydroximethyl-cyclopropanecarboxylate **18** (6.5 g, 50.0 mmol) in anhydrous CH_2Cl_2 (5 ml) and the mixture was stirred overnight at ambient temperature. Resulting solution was poured to vigorously stirred sat. aq. $NaHCO_3$ (150 mL), stirred till CO_2 gas evolution ceased, organic phase was separated, water phase was extracted with CH_2Cl_2 (3 × 50 mL), combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified with the column chromatography (silica gel, eluted with pentane/diethyl ether 4:1) to give pure target

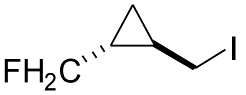


monofluoroester as colorless liquid (3.1 g, 23.6 mmol, 47%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80–0.98 (m, 1 H), 1.15–1.37 (m, 1 H), 1.60–1.72 (m, 1 H), 1.73–1.92 (m, 1 H), 3.67 (s, 3 H), 4.18 (ddd, *J* = 7.2 Hz, 9.8 Hz, 48.2 Hz, 1 H), 4.40 (ddd, *J* = 6.0 Hz, 9.8 Hz, 48.2 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.1 (–, d, *J* = 7.0 Hz), 18.0 (+, d, *J* = 5.8 Hz), 21.3 (+, d, *J* = 24.7 Hz), 51.8 (+), 84.7 (–, d, *J* = 168.7 Hz), 173.46 (–, d, *J* = 1.7 Hz); MS-EI (70 eV): m/z (%) 132.1 (25%, $M\rceil^{+}$), 131.1 (20%, $M–H\rceil^{+}$), 101.0 (100%, $M–MeO\rceil^{+}$), 71.0 (30%, $C_4H_4F\rceil^{+}$), 47.1 (80%, $C_2H_4F\rceil^{+}$).

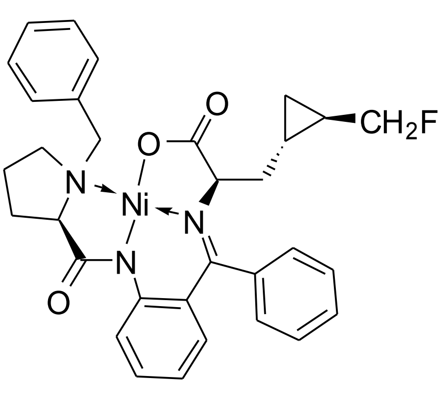
*Racemic trans-(2-monofluoromethylcyclopropyl) methanol (***43***)*: Racemic methyl *trans*-2-monofluoromethylcyclopropanecarboxylate **19** (2.2 g, 16.7 mmol) was reduced with the lithium aluminum hydride in diethyl ether (1.13 M, 7.4 mL, 8.4 mmol) according to GP 8. The crude product was purified with the column chromatography (silica gel, eluted with pentane/diethyl ether 1:1) to give the target monofluoroalcohol as colorless liquid (1.33 g, 12,8 mmol, 76%). ^{1}H NMR (600 MHz, $CDCl_3$): 0.47–0.55 (m, 2 H), 1.00–1.11 (m, 2 H), 2.64–2.74 (bs, 1 H), 3.33–3.49 (m, 2 H), 4.07–4.31 (m, 2 H); ^{13}C NMR (125.7 MHz, $CDCl_3$): 7.59 (–, d, *J* = 7.3 Hz), 16.49 (+, d, *J* = 25.1 Hz), 19.21 (+, d, *J* = 5.7 Hz), 65.31 (–, d, *J* = 1.3 Hz), 86.90 (–, d, *J* = 165.8 Hz).



*Racemic trans-(2-monofluoromethylcyclopropyl)methyl iodide (***45***)*: Racemic *trans*-(2-monofluoromethylcyclopropyl) methanol **43** (1.33 g, 12.8 mmol) was iodinated according to GP 9 with triphenylphosphine (5.81 g, 22.2 mmol), imidazole (1.58 g, 23.3 mmol) and solid iodine (6.25 g, 24.6 mmol) in diethyl ether/acetonitrile mixture (38 + 25 ml), giving the target iodide as light yellow liquid (2.50 g, 17.7 mmol, 91%). TLC: R_f = 0.11, pentane; ^{1}H NMR (300 MHz, $CDCl_3$): 0.59–0.68 (m, 1 H), 0.82–0.91 (m, 1 H), 1.11–1.25 (m, 1 H), 1.26–1.38 (m, 1 H), 3.13 (d, *J* = 7.6 Hz, 2 H), 4.22 (dd, *J* = 7.0 Hz, 48.4 Hz, 2 H); ^{13}C NMR (125.7 MHz, $CDCl_3$): 10.54 (–, d, *J* = 0.9 Hz) 15.40 (–, d, *J* = 7.0 Hz), 21.38 (+, d, *J* = 6.6 Hz), 24.06 (+, d, *J* = 25.2 Hz), 85.96 (–, d, *J* = 167.6 Hz); MS-EI (70 eV): m/z (%) 41.2 (100%, $C_3H_5\rceil^{+}$), 87.1 (38%, $M–I\rceil^{+}$), 67.1 (36%, $C_5H_7\rceil^{+}$).

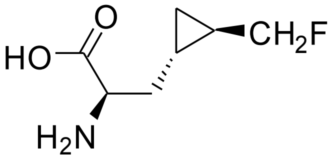


(R)-Belokon' 3-(2-monofluoromethylcyclopropyl)alanine complex [(R)-B(mFmcpA)C, (2*R*,1'*S*,2'*R*)-**116**]: (*R*)-BGC ***R*-13** (2.40 g, 4.8 mmol) was alkylated with racemic *trans*-(2-monofluoromethylcyclopropyl)methyl iodide **45** (1.07 g, 5.0 mmol) according to GP 10, using NaH (60% in oil, 230 mg, 5.7 mmol) in DMF/MeCN mixture (2.5 + 5 mL) during 3 h, giving after chromatographycal separation (silica gel, eluted with

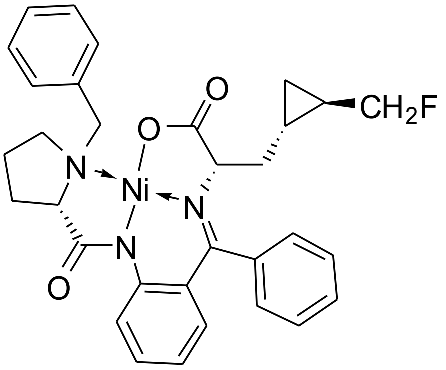


EtOAc) (2*R*,1'*S*,2'*R*) component (1.31 g, 2.24 mmol, 46.7% on (*R*)-BGC, d.e.≥98%), (2*R*,1'*R*,2'*S*) component (1.19 g, 2.03 mmol, 42.3% on (*R*)-BGC, d.e.≥98%) and mixed fractions (0.102 g, 0.17 mmol, 3.6% on (*R*) - BGC).

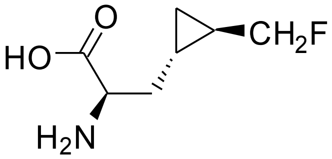
(2R,1'S,2'R)-3-(2-monofluoromethylcyclopropyl)alanine ***(R*-96 a*)***: (2*R*,1'*S*,2'*R*)-B(mFmcpA)C (1.11 g, 1.90 mmol) was decomposed and the amino acid was separated and purified according to GP 11 to give pure target amino acid (172 mg, 1.06 mmol, 96%).



(S)-Belokon' 3-(2'-monofluoromethylcyclopropyl)alanine complex [(S)-B(mFmcpA)C, (2*S*,1'*S*,2'*R*)-**117***]*: (*S*)-BGC ***S*-13** (2.40 g, 4.8 mmol) was alkylated with racemic *trans*-(2-monofluoromethyl-cyclopropyl)methyl iodide **45** (1.07 mg, 5.0 mmol) according to GP 10, using NaH (60% in oil, 230 mg, 5.7 mmol) in DMF/MeCN mixture (2.5 + 5 mL) during 3 h, giving after chromatographycal separation (silica gel, eluted with EtOAc) (2*S*,1'*R*,2'*S*) component (1.25 g, 2.15 mmol, 44.8% on (*S*)-BGC, d.e.≥98%), (2*S*,1'*S*,2'*R*) component (1.23 g, 2.10 mmol, 43.7% on (*S*)-BGC, d.e.≥98%) and mixed fractions (143 mg, 244 μmol, 5.1% on (*S*)-BGC).

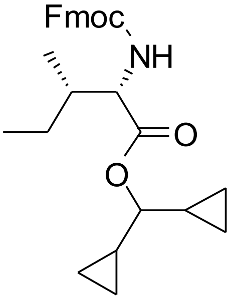


(2S,1'S,2'R)-3-(2-monofluoromethylcyclopropyl)alanine ***(S*-96 a*)***: (2*S*,1'*S*,2'*R*)-B(mFmcpA)C (1.20 g, 2.05 mmol) was decomposed and the amino acid was separated and purified according to GP 11 to give pure target amino acid (311 mg, 1.93 mmol, 94%).

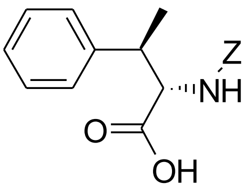


9. Hormaomycin and its all-peptide aza-analogue

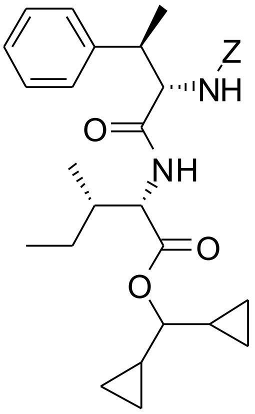
9.1. Hormaomycin



N-Fmoc Isoleucine dicyclopropylmethyl ester (Fmoc-Ile-ODCPM, **56***):*[109] To a stirred ice-cold solution of *N*-Fmoc protected isoleucine **54** (3.53 g, 10.0 mmol) in anhydrous CH_2Cl_2 (35 mL) oxalyl chloride (3.17 g, 25.0 mmol) and then DMF (15 drops) were added and stirring continued at the same temperature for 2 h. The mixture was then allowed to warm to 20 °C and stirred for an additional 1 h. Solvents were removed under reduced pressure at ambient temperature and the crude acylchloride was dried at 0.01 Torr for 2 h and used further without purification. The acylchloride was dissolved in anhydrous CH_2Cl_2 (35 mL) and the mixture of pyridine/dicyclopropylmethanol (1:1 v/v, 5.2 mL) was then added. After 40 min DMAP (0.02 g) was added to the mixture and stirring continued overnight under N_2-flow. The reaction mixture was then diluted with diethyl ether (150 mL), washed with aq. 1 M $KHSO_4$ (3 × 20 mL), water (2 × 20 mL), aq. 5% $NaHCO_3$ (3 × 20 mL), water (3 × 20 mL), brine (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane 1:10 (0.5% Et_3N), R_f = 0.24). The appropriate fractions were pooled, concentrated under reduced pressure, taken up with Et_2O/hexane 1:1 (100 mL), washed with water (3 × 20 mL), 3% aqueous $NaHCO_3$ (3 × 20 mL), water (3 × 20 mL), brine (2 × 10 mL), dried, filtered and concentrated under reduced pressure to give di-protected amino acid (3.0 g, 6.7 mmol, 67%) as a turbid oil. $[\alpha]_D^{20}$ –3.8 (c = 0.26, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ = 0.16–0.38 (m, 4 H), 0.38–0.51 (m, 2 H), 0.51–0.64 (m, 2 H), 0.94 (t, J = 7.5 Hz, 3 H), 0.96 (d, J = 7,5 Hz, 3 H), 1.02–1.16 (m, 2 H), 1.17–1.34 (m, 1 H), 1.39–1.47 (m, 1 H), 1.86–2.09 (m, 1 H), 3.90 (t, J = 8,8 Hz, 1 H), 4.20–4.27 (m, 1 H), 4.34–4.44 (m, 3 H), 5,36 (d, J = 9,8 Hz, 1 H), 5,16 (d, J = 6,0 Hz, 1 H), 7,23–7,46 (m, 4 H), 7,6 (d, J = 7,5 Hz, 2 H), 7,76 (d, J = 8,3 Hz, 2 H); ^{13}C NMR (62,9 MHz, $CDCl_3$): δ = 2.4, 2.6, 2.9 (–), 11.6 (+), 14.5, 15.3 (+), 14.6 (+), 24.9 (–), 38.1 (+), 47.1 (+), 58.3 (+), 66.8 (–), 83.4 (+), 119.8, 125.0, 126.9, 127.5 (+), 141.1 (C_{quat}), 143.7, 143.8 (C_{quat}), 156.0 (C_{quat}), 171.5, (C_{quat}).

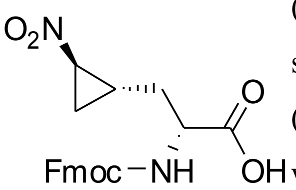


N-Z-(2S,3R)-β-Methylphenylalanine (Z-MeF, **57***):*[109] A solution of ZOSu (489 mg, 1.96 mmol) in acetone (6 mL) was added to a vigorously stirred solution of 3-(2*S*,3*R*)-methylphenylalanine **55** (359 mg, 2.00 mmol) and $NaHCO_3$ (505 mg, 6.00 mmol) in water (6 mL); stirring was continued for 2 h (if an emulsion formed, acetone and/or water were added to obtain a homogeneous solution).Acetone was then removed under reduced pressure, the residual fraction was diluted with water (25 mL) and washed with diethyl ether (3 × 10 mL). The organic fraction was back-extracted with aq. 5% $NaHCO_3$ (3 × 10 mL), the pH of the combined water fractions was adjusted to ~1 with aq. 1 M HCl and the resulting emulsion was extracted with diethyl ether (2 × 50 mL). The organic layer was washed with aq. 1 M $KHSO_4$ (2 × 10 mL), water (5 × 10 mL), brine (2 × 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was dissolved in diethyl ether (3 mL) and dicyclohexylamine (342 mg, 1.88 mmol) was added followed by hexane (20 mL) and the resulting precipitate was filtered and crystallized twice from EtOAc/hexane to give the dicyclohexylammonium salt of the target N-protected amino acid (800 mg, 1.62 mmol, 81%) as a white solid. To obtain an analytical sample, a small quantity of the dicyclohexylammonium salt dissolved in EtOAc and washed twice with aq. 1 M $KHSO_4$, three times with water, twice with brine to give, after prolonged drying at 0.02 Torr and 60 °C, the target N-protected amino acid. M.p. 77–79 °C; $[\alpha]_D^{20}$ 17.3 (c=0.76, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.31$, 1.36 (2 × d, $J = 7.0$ Hz, 3 H), 3.27–4.01 (m, 1 H), 4.43–4.68 (m, 1 H), 4.74–5.20 (m, 2 H), 5.30 (d, $J = 9.0$ Hz, 0.75 H), 6.25 (d, $J = 8.8$ Hz, 0.25 H), 7.03–7.35 (m, 10 H), 7.30–7.90 (bs, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 14.3$, 15.8 (+), 41.5, 41.8 (+), 59.1, 59.8 (+), 67.0, 67.4 (–), 127.0 (+), 127.5 (+), 127.6 (+), 127.9 (+), 128.0 (+), 128.3, 128.3 (+), 135.2, 135.9 (C_{quat}), 140.9, 141.4 (C_{quat}), 156.0, 157.1 (C_{quat}), 175.1, 175.4 (C_{quat}).



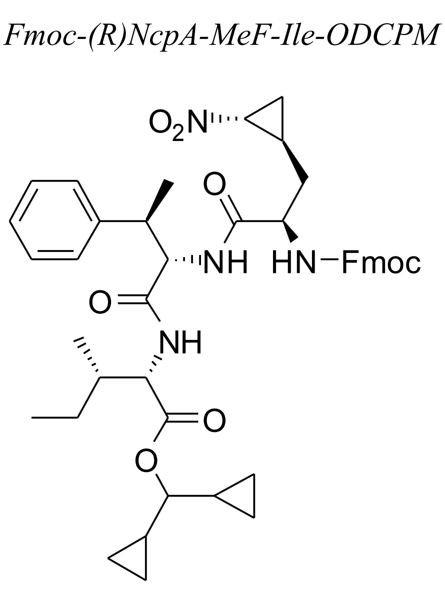
Z-MeF-Ile-ODCPM (**60**):[109] The di-protected isoleucine **56** (334 mg, 750 µmol) was *N*-deprotected according to GP 1 and the resulting amino ester was coupled with *N*-Z-protected β-methylphenylalanine **57** (223 mg, 710 µmol) employing EDC (140 mg, 730 µmol), HOAt (100 mg, 730 µmol) and TMP (260 mg, 2,13 mmol) in CH_2Cl_2 (5 mL) according to GP 2. After 6 h, the reaction mixture was subjected usual aqueous work-up and the resulting crude product was triturated with pentane and then purified by crystallization from hexanes to give target dipeptide (336 mg, 640 µmol, 91%) as a white solid. $R_f = 0.17$, EtOAc/hexanes 1:6 (0.5% Et_3N); m.p. 105–106 °C; $[\alpha]_D^{20}$ 9,0 (c = 0.31, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.23$–0.41 (m, 4 H), 0.41–0.53 (m, 2 H), 0.53–0.64 (m, 2 H), 0.81 (d, $J = 6.8$ Hz, 3 H), 0.89 (t, $J = 7.3$ Hz, 3 H), 0.95–1.21 (m, 3 H), 1.35 (d, $J = 7.3$ Hz, 3 H), 1.37–1.48 (m, 1 H), 1.71–1.90 (m, 1 H), 3.15–3.22 (m, 1 H), 3.90 (t, $J = 8.5$ Hz, 1 H), 4.26–4.42 (m, 2 H), 5.09 (s, 2 H), 5.42 (d, $J = 9.0$ Hz, 1 H), 6.06 (d, $J = 7.5$ Hz, 1 H), 7.15–7.30 (m, 6 H), 7.30–7.40 (m, 4 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 2.4$, 2.7 (–), 11.4 (+), 14.3, 14.5 (+), 14.8 (+), 16.7 (+), 24.9 (–), 37.9 (+), 42.2 (+), 56.1 (+), 60.1 (+), 66.5 (–), 82.9 (+), 126.5, 127.4, 127.5, 127.6, 128.0 (+), 128.1 (+), 136.2, 141.9 (C_{quat}), 156.1 (C_{quat}), 170.2, 170.5 (C_{quat}).

N-Fmoc-(2R,1'R,2'R)-3-(2'-Nitrocyclopropyl)alanine [(R)NcpA, ***61****]*:[109] A solution of FmocOSu



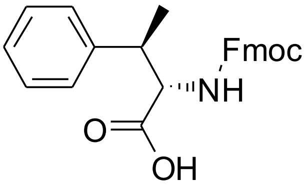
(0.416 g, 1.36 mmol) in acetone (7 mL) was added to a vigorously stirred solution of (2*R*,1'*R*,2'*R*)-3-(trans-2'-nitrocyclopropyl)alanine (2*R*,1'*R*,2'*R*)**-59** (0.2 g, 1.15 mmol) and $NaHCO_3$ (0.202 g, 2.40 mmol) in water (5 mL) (if precipitate formed acetone and/or water were added to obtain homogeneous solution) and stirring continued for an additional 3 h. Acetone was then removed under reduced pressure and pH of the residual water solution was adjusted to ~1 with aq. 1 M $KHSO_4$. The resulting emulsion was extracted with Et_2O (30 mL) and the ethereal layer was then back extracted with aq. 5% $NaHCO_3$ (5 × 10 mL). Combined aqueous fractions were washed with Et_2O (2 × 10 mL), acidified to pH~2 with aq. 1 M $KHSO_4$ and the resulting emulsion was extracted with Et_2O (4 × 10 mL). The organic phase was washed with aq. 1 M $KHSO_4$ (2 × 10 mL), water (3 × 10 mL), brine (2 × 5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was triturated with cold pentane and filtered. The resulting semisolid was dried at 0.02 Torr for prolonged time to give **61** (0.423 g, 93%) as a white foam. R_f = 0.08 EtOAc/hexanes 1:1; m.p. (softening) 50–57 °C; $[\alpha]_D^{20}$ 56.7 (c = 0.36, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ = 0.71–0.82 (m, 0.4 H), 1.11 (m, 0.6 H), 1.17–1.51 (m, 1 H), 1.75–2.13 (m, 2 H), 3.61–3.76 (m, 1 H), 3.76–3.89 (m, 1 H), 3.99–4.27 (m, 2 H), 4.27–4.56 (m, 2 H), 4.56–4.69 (m, 1 H), 4.71–4.87 (m, 1 H), 5.48 (d, *J* = 7.0 Hz, 0.6 H), 7.01–7.13 (m, 0.4 H), 7.23–7.42 (m, 5 H), 7.42–7.61 (m, 2 H), 7.75 (d, *J* = 7.5 Hz, 2 H); ^{13}C NMR (62.9 MHz, CDCl3): δ = 17.3, 17.6, 21.4, 22.0 (+), 32.8, 33.2, 46.8 (+), 53.0 (+), 59.0 (+), 66.7, 67.0, 119.8 (+), 124.2, 124.4 (+), 124.8 (+), 126.9, 127.6 (+), 141.1 (C_{quat}), 143.0, 143.3 (C_{quat}), 143.3, 143.5 (C_{quat}), 155.9, 156.8 (C_{quat}), 173.8, 174.6 (C_{quat}).

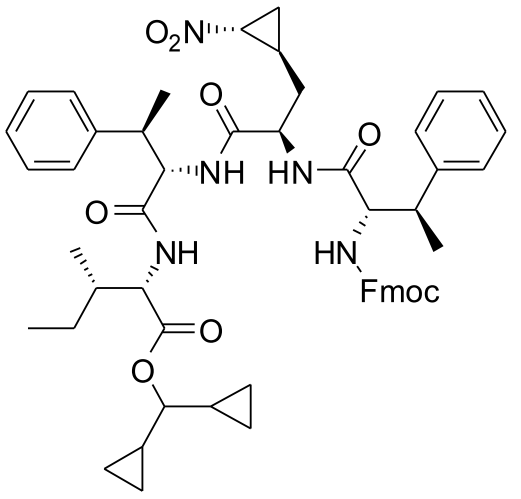
*Fmoc-(R)NcpA-MeF-Ile-ODCPM (****63****)*:[109] Dipeptide **60** (0.35 g, 0.67 mmol) was taken up with



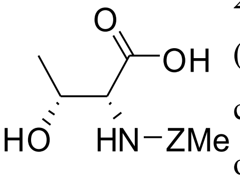
EtOAc (10 mL) and hydrogenated over 10% Pd/C (0.15 g) under ambient pressure of hydrogen for 2 h. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to give deprotected dipeptide **62**, which was directly used for the coupling with **61** (274 mg, 0.69 mmol), using EDC (137 mg, 0.72 mmol), HOAt (96 mg, 0.71 mmol) and TMP (0.25 mL, 2.02 mmol) according to GP 2 to give tripeptide **63** (405 mg, 79%) as a colorless solid after 2 recrystallizations from THF/hexanes 1:1. $R_f = 0.52$, EtOAc/hexanes 2:3; m.p 151–155 °C, $[\alpha]_D^{20}$ 3.8 (c = 0.26, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.20–0.38 (m, 4 H), 0.37–0.49 (m, 2 H), 0.49–0.62 (m, 2 H), 0.80 (d, J = 7.0 Hz, 3 H), 0.86 (t, J = 7.5 Hz, 3 H), 0.94–1.20 (m, 4 H), 1.33–1.49 (m, 1 H), 1.34 (d, J = 7.0 Hz, 3 H), 1.50–1.68 (m, 1 H), 1.71–1.85 (m, 2 H), 1.85–2.05 (m, 2 H), 3.15–3.29 (m, 1 H), 3.79 (t, J = 8.6 Hz, 1 H), 4.01–4.1 (m, 1 H), 4.16–4.29 (m, 1 H), 4.26–4.43 (m, 3 H), 4.49 (dd, J = 10.3 Hz, 7.0 Hz, 1 H), 4.57–4.65 (m, 1 H), 5.58 (d, J = 8.3 Hz, 1 H), 6.14 (d, J = 7.8 Hz, 1 H), 6.84 (d, J = 8.0 Hz, 1 H), 7.12–7.31 (m, 5 H), 7.33 (d, J = 7.8 Hz, 2 H), 7.36–7.45 (m, 2 H), 7.58 (d, J = 7.0 Hz, 2 H), 7.77 (d, J = 7.3 Hz, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 2.4, 2.7 (–), 11.4 (+), 14.1, 14.4 (+), 14.8 (+), 16.7 (+), 17.7 (–), 21.97 (+), 24.9 (–), 33.9 (–), 38.1 (+), 41.7 (+), 46.8 (+), 53.8 (+), 56.2 (+), 58.5 (+), 58.8 (+), 67.0 (–), 83.1 (+), 119.7, 124.8, 126.6, 127.3, 127.4, 128.2, 128.3, 140.96, 141.49 (C_{quat}), 141.5 (C_{quat}), 143.5, 143.6 (C_{quat}), 155.9 (C_{quat}), 169.8, 170.5, 171.0 (C_{quat}).

N-Fmoc-(2S,3R)-β-Methylphenylalanine (Fmoc-MeF, **64***)*: A solution of FmocOSu (810 mg, 2.40 mmol) in acetone (12 mL) was added to a vigorously stirred solution of 3-(2*S*,3*R*)-*β*-methylphenylalanine **55** (358 mg, 2.00 mmol) and $NaHCO_3$ (520 mg, 6.20 mmol) in water (8 mL); stirring was continued for 5 h (if an emulsion formed, acetone and/or water were added to obtain a homogeneous solution).Acetone was then removed under reduced pressure, the residual fraction was diluted with water (25 mL) and washed with diethyl ether (3 × 10 mL). The organic fraction was back-extracted with 5% aqueous $NaHCO_3$ (3 × 10 mL), the pH of the combined water fractions was adjusted to 1 with aq. 1 M $KHSO_4$ and the resulting emulsion was extracted with diethyl ether (3 × 30 mL). Combined organic layers were washed with aq. 1 M $KHSO_4$ (2 × 10 mL), water (5 × 10 mL), brine (2 × 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give, after prolonged drying at 0.02 Torr and 60 °C, the target *N*-protected amino acid **64** as colorless foam (636 mg, 1.58 mmol, 79%). M.p. 77–79 °C; $[\alpha]_D^{20}$ 17.3 (c=0.76, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.40 (d, J = 7.2 Hz, 3 H), 3.24–3.39 (m, 1 H), 4.13–4.24 (m, 1 H), 4.32 (dd, J = 10.1 Hz, 6.8 Hz, 2 H), 4.38–4.49 (m, 1 H), 4.64 (dd, J = 9.2 Hz, 5.6 Hz, 1 H), 5.30 (d, J = 9.2 Hz, 1 H), 7.10–7.36 (m, 6 H), 7.41 (t, J = 7.2 Hz, 2 H), 7.57 (d, J = 7.4 Hz, 1 H), 7.77 (d, J = 7.3 Hz, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.3, 15.8 (+), 41.5, 41.8 (+), 59.1, 59.8 (+), 67.0, 67.4 (–), 127.0 (+), 127.5 (+), 127.6 (+), 127.9 (+), 128.0 (+), 128.3, 128.3 (+), 135.2, 135.9 (C_{quat}), 140.9, 141.4 (C_{quat}), 156.0, 157.1 (C_{quat}), 175.1, 175.4 (C_{quat}).





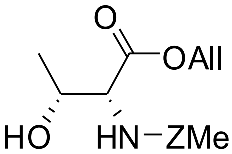
*Fmoc-MeF-(S)NcpA-MeF-Ile-ODCPM (***66***)*:[109] The tripeptide **63** (0.420 g, 0.549 mmol) was deprotected according to GP 1 and the resulting product **65** was then directly coupled with *N*-Fmoc-protected *β*-methylphenylalanine **64** (0.242 g, 0.603 mmol) according to GP 2 using EDC (0.114 g, 0.595 mmol), HOAt (0.080 g, 0.592 mmol) and TMP (0.200 g, 1.650 mmol) in CH_2Cl_2 (3 mL). After 1 h, a precipitate appeared in the reaction mixture and anhydrous DMF (2 mL) was added to obtain homogeneous solution. After 15 h the reaction mixture was concentrated under reduced pressure. The resulting solid was washed with water (100 mL), 5% aqueous $NaHCO_3$ (100 mL), water (100 mL), Et_2O (100 mL), pentane (50 mL), dried at 0.5 Torr and then crystallized twice from THF/hexanes to give **66** (0.430 g, 85%) as an off-white solid. R_f = 0.29, $CHCl_3$/MeOH 70:1; m.p 210–215 °C (decomp.), $[\alpha]_D^{20}$ –26.3 (c = 0.32, THF); ^{1}H NMR (250 MHz, [D8]THF): δ = 0.22–0.57 (m, 7 H), 0.67–0.90 (m, 2 H), 0.78–0.86 (m, 1 H), 0.81 (d, *J* = 6.5 Hz, 3 H), 0.83 (t, *J* = 7.3 Hz, 3 H), 0.92–1.19 (m, 4 H), 1.20 (d, *J* = 7.3 Hz, 3 H), 1.32 (d, *J* = 7.0 Hz, 3 H), 1.30–1.50 (m, 4 H), 3.07–3.16 (m, 1 H), 3.18–3.31 (m, 1 H), 3.81 (t, *J* = 8.5 Hz, 1 H), 3.89–4.01 (m, 1 H), 4.13–4.41 (m, 5 H), 4.41–4.51 (m, 1 H), 4.55–4.68 (m, 1 H), 6.97–7.40 (m, 16 H), 7.48 (d, *J* = 8.5 Hz, 1 H), 7.58 (d, *J* = 8.3 Hz, 1 H), 7.63–7.70 (m, 2 H), 7.77 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (62.9 MHz, [D8]THF): δ = 3.3, 3.5, 3.6, 3.7 (–,), 12.2 (+), 15.6, 15.9 (+), 16.1 (+), 17.7 (+), 18.7 (+), 18.9 (–), 23.2 (+), 26.2 (–), 35.0 (–), 39.1 (+), 42.8 (+), 44.1 (+), 48.5 (+), 52.8 (+), 57.4 (+), 59.3 (+), 60.2 (+), 62.1 (+), 67.8 (–,), 83.4 (+), 126.3, 126.4, 127.5, 127.7, 128.1, 128.6, 129.1, 129.1, 129.3, 129.4 (+), 142.5 (C_{quat}), 144.1 (C_{quat}), 144.4 (C_{quat}), 145.4, 145.6 (C_{quat}), 157.8 (C_{quat}), 171.1, 171.5, 171.9, 172.1 (C_{quat}).



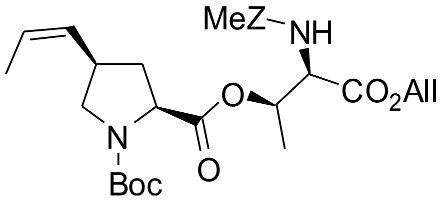
*MeZ-a-Thr-OH (***68***)*:[109] $NaHCO_3$ (0.180 g, 2.14 mmol) and then a solution of MeZOSu (0.608 g, 2.31 mmol) in dioxane (7 mL) were added to a vigorously stirred solution of (*R*)-*allo*-threonine **67** (0.25 g, 2.10 mmol) in water (7 mL) and stirring continued for 3 h (if precipitate formed dioxane and/or water were added to obtain homogeneous solution). The mixture was then concentrated under reduced pressure, diluted with water (40 mL) and washed with CH_2Cl_2 (4 × 10 mL). pH of the water fraction was adjusted to ~2 with solid $KHSO_4$ and the resulting emulsion was extracted with EtOAc (2 × 40 mL). The organic layer was washed with water (4 × 20 mL), brine (2 × 10 mL), dried and concentrated under reduced pressure. The residue was recrystallized from

Et$_2$O/hexanes and then from CH$_2$Cl$_2$/hexanes to give **68** (0.175 g, 39%) as a white solid. The mother liquor from the second crystallization was concentrated and recrystallized again from Et$_2$O/hexanes to give a second crop of **68** (0.23 g, 90% overall yield). $R_f = 0.13$ EtOAc/hexanes (2% AcOH), 3 runs; m.p. 78–80 °C; $[\alpha]_D^{20}$ 24.6 (c = 0.32, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$): $\delta = 1.27$ (d, $J = 6.5$ Hz, 3 H), 2.34 (s, 3 H), 3.70–4.40 (bs, 1 H), 4.05–4.27 (m, 1 H), 4.33–4.44 (m, 1 H), 5.07 (s, 2 H), 5.77 (d, $J = 7.5$ Hz, 1 H), 7.15 (d, $J = 8.0$ Hz, 2 H), 7.24 (d, $J = 8.0$ Hz, 2 H); ^{13}C NMR (62.9 MHz, CDCl3): $\delta = 18.7$ (+), 21.1 (+), 59.3 (+), 67.4 (–), 69.0 (+), 128.3, 129.2 (+), 132.7, 138.1 (C_{quat}), 156.9 (C_{quat}), 173.3 (C_{quat}).

*MeZ-a-Thr-OAll (***69***)*:[109] A suspension of dried K$_2$CO$_3$ (0.034 g, 0.247 mmol) in a solution of the *N*-protected acid **68** (0.12 g, 0.449 mmol) and allyl bromide (0.08 mL, 0.946 mmol) in anhydrous MeCN (4 mL) was vigorously stirred in a sealed tube at 85 °C for 2 h. The mixture was then allowed to cool to 60 °C and stirring continued for an additional 16 h. The reaction mixture was cooled to 20 °C, and Et$_2$O (50 mL) and water (20 mL) were then added. The organic layer was washed with water (4 × 10 mL), sat. aq. NaHCO$_3$ (2 × 10 mL), brine (2 × 5 mL), dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residual oil was triturated with Et$_2$O/pentane 1:2 to give a white solid. Then more pentane was added to complete precipitation and the precipitate was filtered off and dried under reduced pressure (0.116 g, 84%). $R_f = 0.16$ EtOAc/hexanes 1:3; m.p. 47–48 °C; $[\alpha]_D^{20}$ –20.4 (c = 0.30, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl3): $\delta = 1.20$ (d, $J = 6.5$ Hz, 3 H), 2.35 (s, 3 H), 2.74 (d, $J = 6.3$ Hz, 1 H), 4.09–4.26 (m, 1 H), 4.47 (dd, $J = 7.5$ Hz, 3.8 Hz, 1 H), 4.67 (d, $J = 5.3$ Hz, 2 H), 5.08 (s, 2 H), 5.20–5.41 (m, 2 H), 5.66 (d, $J = 7.3$ Hz, 1 H), 5.83–5.97 (m, 1 H), 7.17 (d, $J = 8.0$ Hz, 2 H), 7.26 (d, $J = 8.0$ Hz, 2 H); ^{13}C NMR (62.9 MHz, CDCl$_3$): $\delta = 18.7$ (+), 20.9 (+), 59.3 (+), 65.9 (–), 67.4 (–), 68.4 (+), 118.7 (–), 128.0, 128.9 (+), 132.8 (+), 132.8, 137.7 (C_{quat}), 156.4 (C_{quat}), 169.9 (C_{quat}).

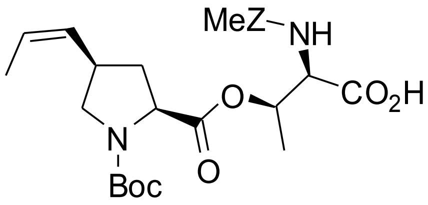


*Boc-(4-Pe)Pro-[MeZ-a-Thr]-OAll (***70***)*:[109] EDC (0.324 g, 1.69 mmol) was added to a cooled (4 °C) solution of the *N*-Boc-protected (2*S*,4*R*)-4-(*Z*)-propenylproline 118 **(**0.340 g, 1.33 mmol), the *N,C*-protected amino acid **69** (0.400 g, 1.30 mmol) and 4-pyrrolidinopyridine (0.250 g, 1.69 mmol) in anhydrous CH$_2$Cl$_2$ (3 mL). The temperature was allowed to reach 20 °C, and stirring was continued for 15 h. Then the reaction mixture was diluted with Et$_2$O (30 mL) and washed with aq. 1 M KHSO$_4$ (3 × 5 mL), water (2 × 5 mL), aq. 3% NaHCO$_3$ (3 × 5 mL), water (3 × 5 mL), brine (2 × 5 mL), dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by

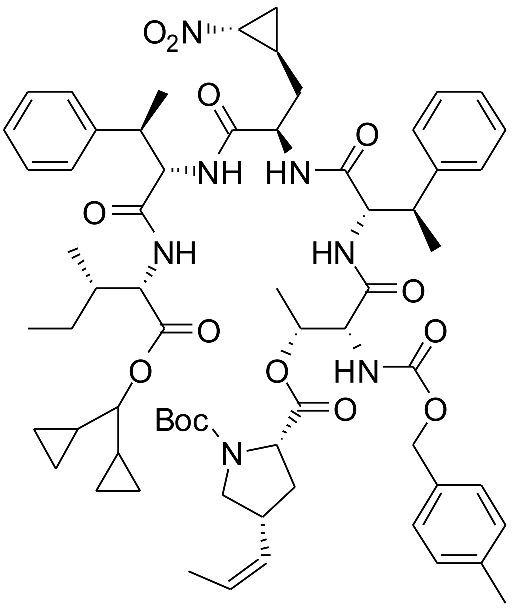


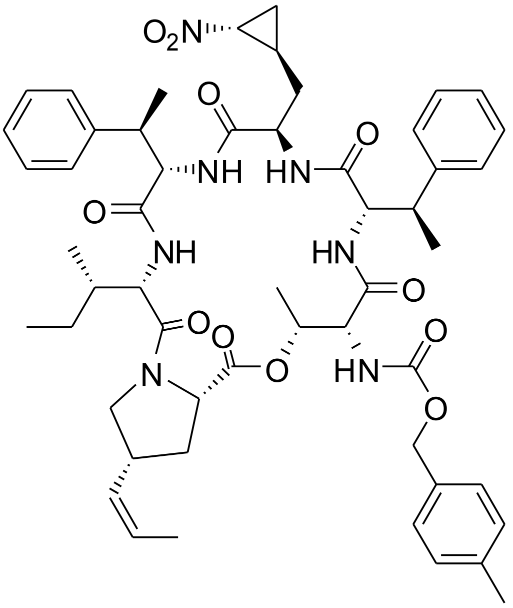
column chromatography (silica gel, eluted with EtOAc/hexane 1:6) to give **70** (0.588 g, 83%) as a turbid oil. R_f = 0.43 (EtOAc/hexane 1:3); $[\alpha]_\mathrm{D}^{20}$ –35.4 (c = 0.28, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.34 (d, J = 6.5 Hz, 3 H), 1.36 + 1.39 (2 × s, 9 H), 1.64 (dd, J = 1.5 Hz, 7.0 Hz, 3 H), 1.63–1.81 (m, 1 H), 2.21–2.46 (m, 1 H), 2.33 + 2.35 (2 × s, 3 H), 2.93–3.19 (m, 2 H), 3.51–3.67 + 3.69–3.83 (2 × m, 1 H), 4.10–4.27 (m, 1 H), 4.48–4.65 (m, 1 H), 4.68 (d, J = 5.2 Hz, 2 H), 4.97–5.13 (m, 2 H), 5.17–5.43 (m, 4 H), 5.54 (dq, J = 10.2 Hz, 7.0 Hz, 1 H), 5.80–6.01 (m, 1 H), 6.42 (d, J = 9.2 Hz, 1 H), 7.13 + 7.17 (2 × d, J = 7.9 Hz, 2 H), 7.23 + 7.25 (d, J = 7.9 Hz, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.8 (+), 15.8, 16.3 (+), 20.8 (+), 27.9 (+), 35.3, 36.1 (+), 35.8, 36.9 (–), 51.1, 51.3 (–), 57.0, 57.4 (+), 59.0, 59.1 (+), 65.5, 66.0 (–), 66.4, 67.0 (–), 70.8, 70.8 (+), 79.6, 79.7 (Cquat) 118.2, 118.9 (–), 126.3, 126.3 (+), 127.9 (+), 128.7, 128.8 (+), 129.0, 129.1 (+), 130.9, 131.2 (+), 132.7, 133.1 (Cquat), 137.2, 137.6 (Cquat), 153.0, 153.5 (Cquat), 155.4, 155.9 (Cquat), 168.4, 168.4 (Cquat), 171.6, 171.9 (Cquat).

*Boc-(4-Pe)Pro-[MeZ-a-Thr]-OH (***71***)*:[109] Pd[P(Ph)$_3$]$_4$ (0.034 g, 2.94 µmol) was added to a vigorously stirred solution of ester **70** (0.108 g, 0.198 mmol) and *N*-methyl aniline (0.08 mL, 0.738 mmol) in DME (3.5 mL) and the resulting suspension was stirred at ambient temperature for 2 h. The reaction mixture was then diluted with Et_2O (40 mL), washed with aq. 1 M $KHSO_4$ (3 × 10 mL), water (10 × 10 mL), brine (2 × 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was taken up with Et_2O/hexanes 1:2, filtered, concentrated and purified by column chromatography (silica gel, eluted with EtOAc/hexanes 1:2 + 1.5% AcOH, R_f = 0.34) to give **71** (0.121 g, 90%) as an yellow oil. $[\alpha]_\mathrm{D}^{20}$ –71.7 (c = 0.32, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.35 + 1.40 (2 × s, 9 H), 1.41 + 1.43 (2 × d, J = 5.7 Hz, 3 H), 1.63 + 1.65 (2 × dd, J = 1.5 Hz, 6.7 Hz, 3 H), 1.67–1.86 (m, 1 H), 2.24–2.49 (m, 1 H), 2.33 + 2.34 (2 × s, 3 H), 2.91–3.20 (m, 2 H), 3.40–4.30 (bs, 1 H), 3.61–3.73 (m, 1 H), 4.11–4.29 (m, 1 H), 4.51 (dd, J = 8.6 Hz, 3.5 Hz, 1 H), 5.05 (s, 2 H), 5.15–5.31 (m, 1 H), 5.31–5.44 (m, 1 H), 5.45–5.60 (m, 1 H), 5.63 + 6.46 (2 × d, J = 9.2 Hz, 1 H), 7.13 + 7.17 (2 × d, J = 7.9 Hz, 2 H), 7.21 + 7.22 (2 × d, J = 7.9 Hz, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.0 (+), 15.8, 16.3 (+), 21.0 (+), 28.1 (+), 35.5, 36.2 (+), 36.0, 37.0 (–), 51.3, 51.6 (–), 57.0, 57.5 (+), 59.1, 59.3 (+), 66.8, 67.0 (–), 71.2, 71.4 (+), 80.5, 80.6 (C_quat), 126.5, 126.5 (+), 128.1 (+), 128.1 (+), 128.9, 129.0 (+), 132.8, 133.0 (C_quat), 137.6, 137.9 (C_quat), 153.7, 154.2 (C_quat), 155.8, 156.4 (C_quat), 171.2, 171.7 (C_quat), 172.0, 172.2 (C_quat).

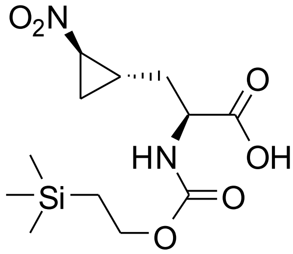


*Boc-(4-Pe)Pro-[MeZ-a-Thr]-MeF-(S)NcpA-MeF-Ile-ODCPM (***73***)*: Tetrapeptide **66** (180 mg, 0.21 mmol) was deprotected according to GP 1 in THF (2 mL), taken up with anhydrous CH$_2$Cl$_2$ (5 mL), ester acid **71** (0.114 g, 0.23 mmol), HATU (96 mg, 0.25 mmol) and HOAt (31 mg, 0.23 mmol) were added and the reaction mixture was cooled to 4 °C. After this, a solution of DIEA (29 mg, 0,22 mmol) and TMP (75 mg, 0.62 mmol) in CH$_2$Cl$_2$ (2 mL) were added at the same temperature within 5 min. The temperature was allowed to reach 20 °C, and stirring continued for an additional 15 h. After aqueous work-up according to GP 2 and two recrystallizations from EtOAc/hexanes 1:2, depsipeptide **73** (185 mg, 79%) was obtained as a colorless powder. R_f = 0.46 (EtOAc/hexanes 1:1); m.p. 125–127 °C, $[\alpha]_D^{20}$ –29.0 (c = 0.2, THF); ^{1}H NMR (600 MHz, CDCl$_3$): δ = 0.27–0.33 (m, 1 H), 0.33–0.44 (m, 3 H), 0.44–0.49 (m, 1 H), 0.49–0.57 (m, 2 H), 0.59–0.65 (m, 1 H), 0.75 (d, J = 6.8 Hz, 3 H), 0.89 (t, J = 7.3 Hz, 3 H), 0.95–1.11 (m, 4 H), 1.11–1.60 (m, 5 H), 1.24 (d, J = 7.5 Hz, 3 H), 1.27 (d, J = 7.5 Hz, 3 H), 1.36 (s, 9 H), 1.43 (d, J = 6.5 Hz, 3 H), 1.66 (dd, J = 6.9 Hz, 1.7 Hz, 3 H), 1.68–1.76 (m, 1 H), 1.80–1.90 (m, 1 H), 2.30 (s, 3 H), 2.35–2.42 (m, 1 H), 3.06–3.13 (m, 1 H), 3.13 (t, J = 10.5 Hz, 1 H), 3.18–3.31 (m, 2 H), 3.67 (dd, J = 10.2 Hz, 7.8 Hz, 1 H), 3.80–3.84 (m, 1 H), 4.02–4.07 (m, 1 H), 4.14 (dd, J = 10.7 Hz, 6.2 Hz, 1 H), 4.33 (dd, J = 8.9 Hz, 4.6 Hz, 1 H), 4.37 (dd, J = 9.5 Hz, 2.2 Hz, 1 H), 4.45 (dd, J = 9.9 Hz, 6.9 Hz 1 H), 4.57 (dt, J = 9.6 Hz, 5.1 Hz, 1 H), 4.62 (t, J = 10.3 Hz, 1 H), 4.96–5.06 (m, 2 H), 5.22–5.28 (m, 1 H), 5.46–5.51 (m, 1 H), 5.52–5.58 (m, 1 H), 6.54 (d, J = 8.2 Hz, 1 H), 6.89 (d, J = 8.9 Hz, 1 H), 6.99 (d, J = 9.6 Hz, 1 H), 7.06–7.12 (m, 2 H), 7.14–7.25 (m, 12 H) 7.49 (d, J = 9.8 Hz, 1 H), 7.86 (d, J = 5.9 Hz, 1 H); ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 2.48 (–), 2.82 (–), 2.90 (–), 3.01 (–), 11.59 (+), 13.20 (+), 14.16 (+), 14.64 (+), 15.57 (+), 17.77 (+), 18.41 (–), 18.86 (+), 19.43 (+), 21.11 (+), 21.77 (+), 25.23 (–), 26.85 (–), 28.23 (+), 31.46 (–), 31.53 (–), 36.28 (–), 36.32 (+), 37.30 (+), 40.45 (+), 42.00 (+), 50.62 (+), 52.08 (+), 56.43 (+), 59.30 (+), 59.49 (+), 61.01 (+), 61.62 (+), 61.99 (+), 66.89 (–), 70.53 (+), 80.93 (C$_{quat}$), 83.24 (+), 127.00 (+), 127.06 (+), 127.10 (+), 127.60 (+), 127.69 (+), 128.47 (+), 128.63 (+), 128.68 (+), 128.82 (+), 128.93 (+), 133.21 (C$_{quat}$), 137.83 (C$_{quat}$), 141.73 (C$_{quat}$), 141.90 (C$_{quat}$), 154.76 (C$_{quat}$), 155.75 (C$_{quat}$), 170.38 (C$_{quat}$), 170.43 (C$_{quat}$), 170.79 (C$_{quat}$), 171.37 (C$_{quat}$), 173.41 (C$_{quat}$), 174.06 (Cquat); MS-ESI: (positive), m/z (%) 1163 (100, M+Na]$^+$); (negative), m/z (%) 1138 (50, M–H]$^-$), 1175 (50, M+Cl]$^-$).

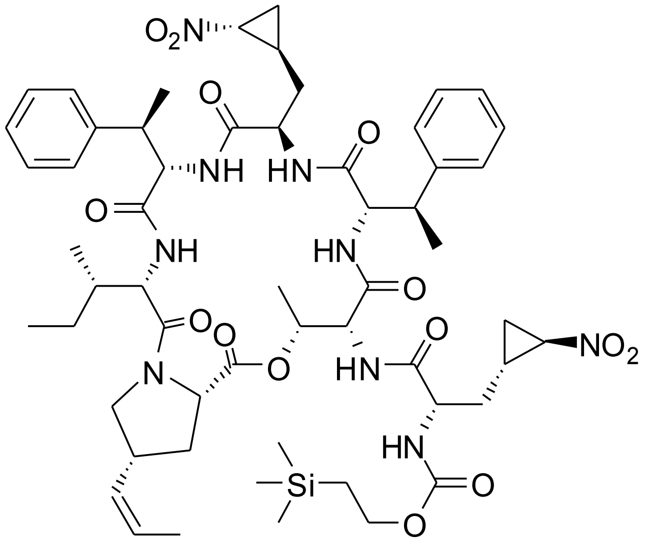




*N-MeZ protected cyclohexadepsipeptide (***75***)*: To the hexadepsipeptide **74** (0.188 g, 0.165 mmol) 2 M HCl in EtOAc (2 mL) was added, the reaction mixture was stirred for 45 min at ambient temperature in the dark place and then was concentrated under reduced pressure without any heating. The residue was triturated with dry Et_2O to give deprotected material **74** as a white solid [0.160 g; MS-ESI: positive mode, m/z (%) = 997 (100, M+H$]^+$), 1019 (5, M+Na$]^+$); negative mode, m/z (%) = 995 (50, M–H$]^-$)], which was taken up with anhydrous CH_2Cl_2 (1.5 L) and cyclized employing HATU (2 × 0.073 g, 2 × 0.192 mmol) and HOAt (2 × 0.022 g, 2 × 0.163 mmol) and solution of DIEA (2 × 0.062 g, 2 × 0.480 mmol) in CH_2Cl_2 (2 × 50 mL) according to GP 4 for 16 h. After this, the solvent was removed under reduced pressure, the residue was taken up with Et_2O (50 mL), and after usual aqueous work-up (GP 2), drying and filtration, the organic layer was concentrated under reduced pressure. The residue was purified first by column chromatography (acetone/hexanes 1:3, R_f = 0.17) and then by recrystallization (Et_2O/pentane) to give crude product (0.12 g), which was finally purified by preparative HPLC to give cyclodepsipeptide **75** (86 mg, 53% on 2 steps) as a white solid. Preparative HPLC: isocratic, 70% B, t_R = 19.3 min, purity > 98%; analytical HPLC: gradient 20% → 100% B for 20 min, then isocratic 100% B for 5 min t_R = 16.7 min, purity > 98%; $[\alpha]_D^{20}$ –15.5 (c = 0.20, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.61–0.67 (m, 1 H), 0.72 (d, J = 6.6 Hz, 3 H), 0.71–0.77 (m, 1 H), 0.79 (t, J = 7.2 Hz, 3 H), 1.04–1.12 (m, 1 H), 1.23 (d, J = 6.6 Hz, 3 H), 1.27–1.34 (m, 1 H), 1.37 (d, J = 6.6 Hz, 3 H), 1.37–1.43 (m, 1 H), 1.45–1.54 (m, 1 H), 1.54–1.57 (m, 1 H), 1.57 (d, J = 6.6 Hz, 3 H), 1.65 (dd, J = 6.6 Hz, 1.5 Hz, 3 H), 1.66–1.76 (m, 2 H), 2.20–2.25 (m, 1 H), 2.35 (s, 3 H), 3.01–3.07 (m, 1 H), 3.15–3.28 (m, 2 H), 3.54 (dq, J = 7.2 Hz, 6.6 Hz, 1 H), 3.71 (dd, J = 6.0 Hz, 5.4 Hz, 1 H), 3.74–3.77 (m, 1 H), 3.98 (dd, J = 10.5 Hz, 6.3 Hz, 1 H), 4.01–4.08 (m, 1 H), 4.46–4.54 (m, 2 H), 4.52–4.55 (m, 1 H), 4.67–4.70 (m, 1 H), 5.03 (d, J = 12.0 Hz, 1 H), 5.15 (d, J = 12.0 Hz, 1 H), 5.19–5.25 (m, 1 H), 5.39 (qd, J = 6.6 Hz, 1.8 Hz, 1 H), 5.56 (dq, J = 10.8 Hz, 6.6 Hz, 1 H), 5.96 (d, J = 5.3 Hz, 1 H), 6.20 (d, J = 7.4 Hz, 1 H), 6.28 (d, J = 9.7 Hz, 1 H), 6.49 (d, J = 9.4 Hz, 1 H), 7.11–7.37 (m, 14 H) 7.32 (d, J = 7.4 Hz, 1 H), 7.45 (d, J = 8.7 Hz, 1 H); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 10.3 (+), 13.3 (+), 14.6 (+), 17.3 (–), 17.7 (+), 18.4 (+), 21.2 (+), 21.3 (+), 24.7 (–), 32.0 (–), 35.4 (–), 36.6 (+), 39.4 (+), 44.5 (+), 52.5 (–), 53.3 (+), 54.6 (+), 58.6 (+), 59.0 (+), 59.4 (+), 60.1 (+), 60.7 (+), 67.2 (–), 72.6 (+), 127.1 (+), 127.2 (+), 127.5 (+), 127.6 (+), 128.3 (+), 128.6 (+), 128.8 (+), 129.2 (+), 127.8 (+), 128.0 (+), 133.2 (C_{quat}), 137.9 (C_{quat}), 140.9 (C_{quat}), 142.6 (C_{quat}), 156.3 (C_{quat}), 169.0 (C_{quat}), 170.3 (C_{quat}), 170.6 (C_{quat}), 171.1 (C_{quat}), 171.4 (C_{quat}), 173.1 (C_{quat}).

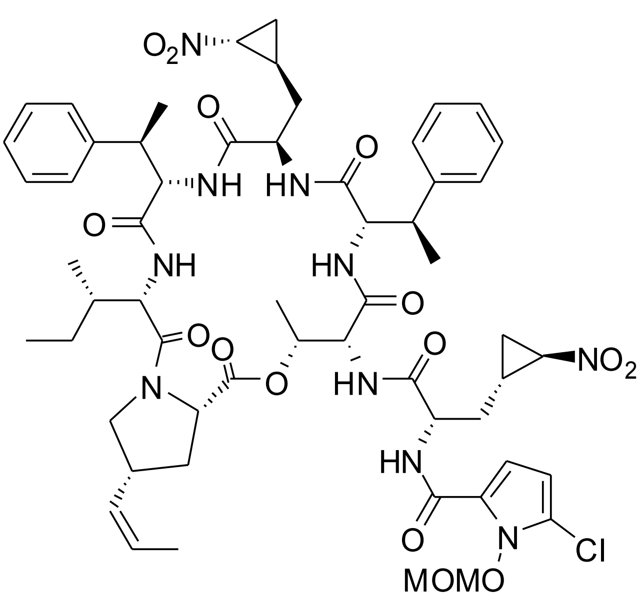


*N-Teoc-(2S,1'R,2'R)-3-(2'-Nitrocyclopropyl)alanine (***78***):*[109] A solution of TeocOSu (0.358 g, 1.38 mmol) in acetone (5 mL) was added to a vigorously stirred solution of (2*S*,1'*R*,2'*R*)-3-(2'-nitrocyclopropyl)alanine **76** (0.200 g, 1.15 mmol) and $NaHCO_3$ (0.202 g, 2.40 mmol) in water (7 mL) (if emulsion formed acetone and/or water were added to obtain homogeneous solution) and stirring continued for a further 2 h. *N*,*N*-dimethylaminopropylamine (0.055 mL, 0.44 mmol) was then added. After an additional 10 min acetone was removed under reduced pressure and pH of the residual water solution was adjusted to 2–3 with aq. 1 M $KHSO_4$. The resulting emulsion was extracted with Et_2O (50 mL) and the ethereal layer was washed with aq. 1 M $KHSO_4$ (2 × 10 mL), water (10 × 10 mL), brine (2 × 5 mL), dried, filtered and concentrated under reduced pressure. The residual oil (0.300 g) was dissolved in Et_2O (5 mL) and cyclohexylamine (0.094 g, 0.95 mmol) was added. The mixture was concentrated under reduced pressure and treated with boiling hexanes. The resulting precipitate was filtered off and washed with Et_2O/pentane 1:4 to give cyclohexylammonium salt of **78** (0.386 g, 81%) as a white solid. $R_f = 0.24$ EtOAc/hexanes 1:3 (2% AcOH); $[\alpha]_D^{20}$ 22.80 (c = 0.46, $CHCl_3$) for cyclohexylammonium salt; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.04 (s, 9 H), 1.00 (dd, *J* = 9.5 Hz, 7.3 Hz, 2 H), 1.09–1.18 (m, 1 H), 1.20–1.43 (m, 5 H), 1.50–1.70 (m, 2 H), 1.70–1.90 (m, 3 H), 1.90–2.19 (m, 4 H), 2.80–3.05 (m, 1 H) 3.95–4.23 (m, 4 H), 5.88 (d, *J* = 8.1 Hz, 1 H), 7.25–8.10 (bs, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = –1.9 (+), 17.3 (–), 17.3 (–), 22.0 (+), 33.1, 33.3 (–), 52.7, 53.2 (+), 59.0 (+), 63.7, 64.8 (–), 156.4, 157.4 (C_{quat}), 174.5, 174.8 (C_{quat}).

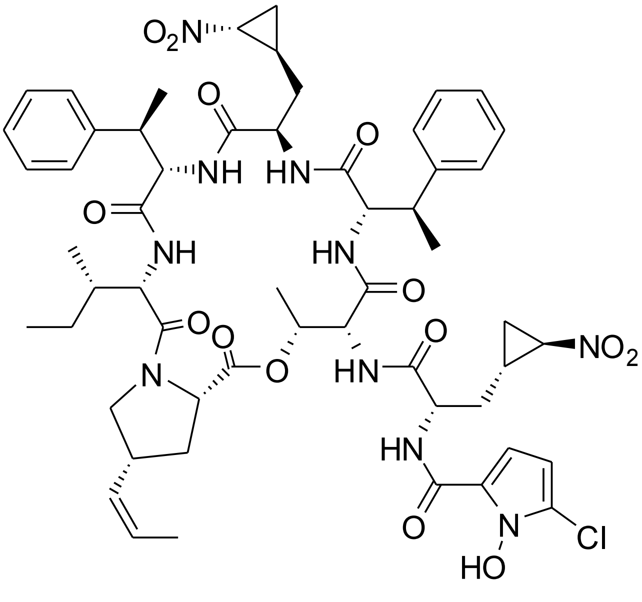


*N-Teoc protected heptadepsipeptide (***79***):*[109] An ethereal solution (50 mL) of the cyclohexylammonium salt of *N*-Teoc protected (2*S*,1'*R*,2'*R*)-3-(2'-nitrocyclopropyl)alanine **78** (8.1 mg, 19.41 µmol) was washed with aq. 1 M H_2SO_4 (3 × 5 mL), aq. 1 M $KHSO_4$ (2 × 5 mL), water (3 × 5 mL), brine (2 × 5 mL), dried, filtered and concentrated under reduced pressure. The resulting *N*-protected amino acid **78** was dried at 0.02 Torr for 2 h and then coupled with the depsipeptide **77** [obtained after deprotection of *N*-MeZ protected cyclodepsipeptide **75** (9.5 mg, 9.71 µmol) with 10% anisole in TFA (1.1 mL) for 2 h according to GP 5] using HATU (7.4 mg, 19.46 µmol), HOAt (2.6 mg, 19.24 µmol), DIEA (1.25 mg, 9.67 µmol) and TMP (7.04 mg, 58.10 µmol) in CH_2Cl_2 (0.7 mL) according to GP 6 for 15 h. The mixture was then diluted with EtOAc/Et_2O 1:1 (20 mL) to give after usual aqueous work-up (GP 2) the crude product **79** (8.0 mg, 73%, $R_f = 0.43$ acetone/hexanes 1:2) as a colorless glass which was used for the next step without any characterization.

*MOM-O-protected Hormaomycin (***82***)*:[109] Teoc group was cleaved from the compound **79** (8.0 mg, 7.08 µmol) with TFA (0.6 mL) for 1 h. The mixture was concentrated under reduced pressure at 20 °C and then taken up with toluene (3 × 15 mL) which was distilled off to remove the last traces of TFA. The resulting deprotected depsipeptide **80** was coupled with *O*-MOM protected acid **81** (2.9 mg, 14.10 µmol) using HATU (5.4 mg, 14.20 µmol), DIEA (0.92 mg, 7.12 µmol) and TMP (5.14 mg, 42.42 µmol) in CH_2Cl_2 (1 mL) according to GP 6 for 2.5 h. The mixture was then taken up with Et_2O (20 mL) and the crude product obtained after usual aqueous work-up (GP 2) was crystallized from CH_2Cl_2 / pentane to give *O*-MOM protected Hormaomycin **82** (8.0 mg, 96%, R_f = 0.36 acetone/hexanes 1:2) as a colorless glass which was used for the next step without any characterization.



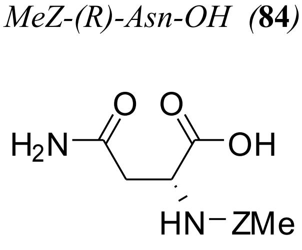
*Hormaomycin (***1***)*: *O*-MOM protected Hormaomycin **82** (8.0 mg, 6.82 µmol) was deprotected using $MgBr_2 \times Et_2O$ (52 mg, 201.36 µmol) and EtSH (0.10 mL, 1.9 mmol) in CH_2Cl_2 (10 mL) according to GP 7 for 3 h. The mixture was taken up with EtOAc and the crude product obtained after usual aqueous work-up was crystallized from CH_2Cl_2 / pentane to give 1 (5.5 mg, 72%, 50% on 5 steps from **75**) as a white solid, which was finally purified with preparative



HPLC. $R_f = 0.24$ acetone/hexanes 3:7; Preparative HPLC: isocratic, 62% B for 15 min, then gradient 62%→100% B for 1 min, then isocratic 100%B for 4 min, then gradient 100%→62% B for 1 min, then isocratic 62% B for 10 min, t_R = 5.7 min, purity > 98%; analytical HPLC: gradient 20% → 100% B for 20 min, then isocratic 100% B for 5 min t_R = 15.3 min, purity > 98%; $[\alpha]_D^{20}$ 20.0 (c = 0.1, MeOH); ^{1}H NMR (600 MHz, CDCl3): δ = –0.71 – –0.63 (m, 1 H), –0.20–0.10 (m, 1 H), 0.23–0.32 (m, 1 H), 0.49–0.56 (m, 1 H), 0.88 (t, *J* = 7.4 Hz, 3 H), 0.95–1.01 (m, 1 H), 1.02 (d, *J* = 6.9 Hz, 3 H), 1.04–1.14 (m, 1 H), 1.17–1.35 (m, 1 H), 1.30 (d, *J* = 7.0 Hz, 3 H), 1.39 (d, *J* = 7.3 Hz, 3 H), 1.47–1.54 (m, 1 H), 1.53 (d, *J* = 6.9 Hz, 3 H), 1.55–1.62 (m, 1 H), 1.67 (dd, *J* = 6.9 Hz, 1.6 Hz, 3 H), 1.75–1.84 (m, 2 H), 1.85–1.94 (m, 3 H), 2.30–2.40 (m, 1 H), 2.88–2.91 (m, 1 H), 2.96–3.02 (m, 1 H), 3.22–3.31 (m, 2 H), 3.43–3.50 (m, 1 H), 3.62–3.70 (m, 1 H), 3.93–4.00 (m, 1 H), 4.01–4.08 (m, 1 H), 4.26 (dd, *J* = 11.5 Hz, 6.0 Hz, 1 H), 4.38 (dd, *J* = 10.6 Hz, 10.6 Hz, 1 H), 4.46 (dd, *J* = 9.4 Hz, 4.5 Hz, 1 H), 4.57 (dd, *J* = 9.3 Hz, 2.3 Hz, 1 H), 4.66 (dd, *J* = 9.0 Hz, 9.0 Hz, 1 H), 5.08–5.14 (m, 1 H), 5.22–5.28 (m, 1 H), 5.40 (qd, *J* = 6.9 Hz, 2.4 Hz, 1 H), 5.58–5.65 (m, 1 H), 6.13 (d, *J* = 4.7 Hz, 1 H), 6.56 (d, *J* = 6.5 Hz, 1 H), 6.80 (d, *J* = 9.3 Hz, 1 H), 6.82 (d, *J* = 4.7 Hz, 1 H), 6.98–7.03 (m, 1 H), 7.09–7.18 (m, 5 H), 7.20–7.27 (m, 7 H), 8.05 (d, *J* = 9.1 Hz, 1 H), 9.06 (d, *J* = 9.3 Hz, 1 H); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 10.50 (+), 13.24 (+), 13.33 (+), 14.94 (+), 16.99 (+), 17.41 (–), 17.74 (+), 20.00 (+), 21.66 (+), 24.90 (–), 26.88 (–), 33.02 (–), 35.03 (–), 35.51 (–), 36.66 (–), 37.97 (+), 39.24 (+), 41.75 (+), 50.99 (+), 51.79 (+), 52.78 (–), 54.61 (+), 54.93 (+), 58.11 (+), 59.12 (+), 59.86 (+), 60.04 (+), 61.37 (+), 69.07 (+), 103.59 (+), 109.85 (+), 119.86 (C_{quat}), 121.55 (C_{quat}), 126.98 (+), 127.17 (+), 127.44 (+), 127.47 (+), 127.67 (+), 128.33 (+), 128.49 (+), 128.64 (+), 141.55 (C_{quat}), 142.11 (C_{quat}), 159.27 (C_{quat}), 168.54 (C_{quat}), 168.73 (C_{quat}), 169.75 (C_{quat}), 170.74 (C_{quat}), 171.26 (C_{quat}), 171.55 (C_{quat}), 172.86 (C_{quat}); MS-ESI: positive, m/z = 292 (100), 1151 (80, M+Na]$^+$); negative, m/z = 1127 (100, M–H]$^-$).

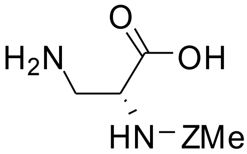
9.2. All-peptide aza-analogue of Hormaomycin

*MeZ-(R)-Asn-OH (***84***)*:[110] $NaHCO_3$ (0.520 g, 6.18 mmol) and then a solution of MeZOSu (0.775 g, 2.97 mmol) in acetone (7 mL) were added to a vigorously stirred solution of (*R*)-aspargine (0.442 g, 2.94 mmol) in water (10 mL), and stirring was continued for 3 h (if a precipitate formed, acetone and/or water was added to obtain a homogeneous solution). The mixture was then concentrated under reduced pressure, diluted with water (40 mL) and washed with CH_2Cl_2 (3 × 10 mL). The pH of the water fraction was adjusted to ~1 with solid $KHSO_4$, the

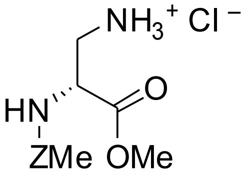


resulting precipitate was filtered off, washed with H_2O (5 × 20 mL), Et_2O (5 × 20 mL) and dried to give **84** (0.75 g, 2.67 mmol, 91%) as a colorless solid. M.p. 181–183 °C; $[\alpha]_D^{20} = 6.5$ (c = 1.00, DMF); ^1H NMR (500 MHz, [D6]acetone): $\delta = 2.30$ (s, 3 H), 2.50–3.55 (bs, 3 H), 2.65–2.85 (m, 2 H), 4.39–4.53 (m, 1 H), 5.03 (s, 2 H), 6.39–6.61 (bs, 1 H), 7.15 (d, $J = 8.0$ Hz, 2 H), 7.26 (d, $J = 8.0$ Hz, 2 H); ^{13}C NMR (125.7 MHz, [D6]DMSO): $\delta = 20.7$ (+), 36.7 (–), 50.5 (+), 65.3 (–), 127.8 (+), 128.8 (+), 133.8 (C_{quat}), 137.0 (C_{quat}), 155.7 (C_{quat}), 170.7 (C_{quat}), 173.0 (C_{quat}).

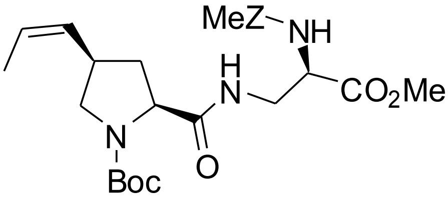
N_α-MeZ-2,3-diaminopropionic acid (MeZ-Dap-OH, **85***)*:[110] Iodobenzene bis(trifluoroacetate) (1.46 g, 3.40 mmol) and **84** were suspended by stirring in 50% (v/v) aqueous DMF (20 mL). After 15 min, pyridine (0.367 g, 4.64 mmol) was added, and the mixture was stirred for an additional 5 h. The emulsion formed was evaporated at 40–45 °C under reduced pressure. The residue was taken up with water (2 × 15 mL), which was evaporated under reduced pressure. The residual oil was taken up in water (50 mL) and washed with chloroform (3 × 10 mL). The aqueous layer was once more concentrated in vacuo, and the residue was dissolved in ethanol (20 mL). The pH value was adjusted to about 7 with pyridine, and the formed suspension was left at 4 °C for 12 h. The precipitate was filtered off and washed with ether (5 × 20 mL) to give, after drying, N_α-protected diamino acid **85** (0.51 g, 87%) as a colorless powder. $R_f = 0.32$ (MeCN/AcOH/H_2O 10:1:1); m.p. 210–216 °C (decomp.); $[\alpha]_D^{20}$ 38.1 (c=0.31, 0.1 N HCl); ^1H NMR (300 MHz, DCl in D_2O): $\delta = 2.28$ (s, 3 H), 3.28 (dd, $J = 12.6$ Hz, 9.6 Hz, 1 H), 3.49 (dd, $J = 12.6$ Hz, 4.5 Hz, 1 H), 4.44–4.55 (m, 1 H), 5.07 (s, 2 H), 7.22 (d, $J = 7.5$ Hz, 2 H), 7.28 (d, $J = 7.5$ Hz, 2 H).



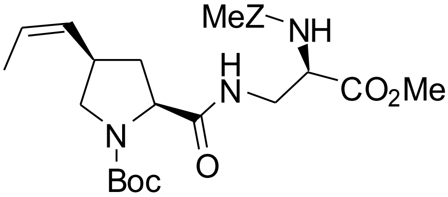
*MeZ-Dap-OMe hydrochloride (***86***)*:[110] To a solution of thionyl chloride (0.52 mL, 7.26 mmol) in anhydrous MeOH (10 mL) at –20 °C was added with stirring after 10 min the amino acid **85** (0.50 g, 1.98 mmol). The resulting thick suspension was stirred at 20 °C for 24 h to give a clear solution, which was then left at –20 °C for 16 h. Et_2O (40 mL) was added to complete the precipitation, and the solid was filtered off to give **86** (0.47 g, 78%) as long colorless needles. The mother liquor was concentrated, and the residue was recrystallized from MeOH/Et_2O to give a second crop of **86** (26 mg, 83% overall yield). M.p. 159–161 °C; $[\alpha]_D^{20} = 32.3$ (c=0.86, DMSO); ^1H NMR (250 MHz, [D6]DMSO): $\delta = 2.28$ (s, 3 H), 2.98–3.29 (m, 2 H), 3.66 (s, 3 H), 4.37–4.49 (m, 1 H), 5.08 (s, 2 H), 7.17 (d, $J = 7.9$ Hz, 2 H), 7.25 (d, $J = 7.9$ Hz, 2 H), 7.52 (d, $J = 8.3$ Hz, 1 H), 8.15–8.55 (bs, 3 H); ^{13}C NMR (62.9 MHz, [D6]DMSO): $\delta = 21.0$ (+), 39.2 (–), 52.0 (+), 52.8 (+), 66.0 (–), 128.2 (+), 129.1 (+), 133.8 (C_{quat}), 137.4 (C_{quat}), 156.3 (C_{quat}), 173.6 (C_{quat}).



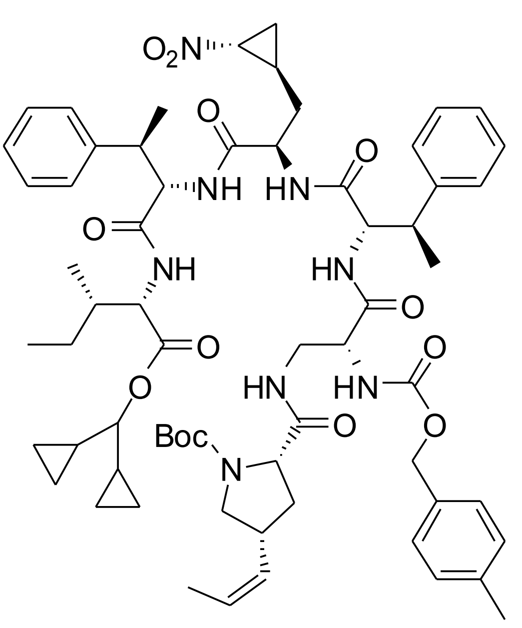
*Boc-(4-Pe)Pro-[MeZ-Dap]-OMe (**87**)*:[110] Compound **86** (0.127 g, 0.42 mmol) was coupled with the *N*-Boc protected (4-propenyl)proline **10** (0.11 g, 0.431 mmol) by treatment with EDC (85 mg, 0.44 mmol), HOAt (60 mg, 0.44 mmol) and TMP (0.314 g, 2.59 mmol) in CH$_2$Cl$_2$ (5 mL) according to GP 2 for 16 h. The crude product obtained after the usual aqueous workup (GP 2) was further purified by column chromatography (silica gel, eluted with acetone/hexane 2:5, R_f=0.13) to give an oily residue which was triturated with pentane to furnish the dipeptide ester **87** (0.14 g, 66%) as a colorless solid. The mother liquor was cooled to 4 °C, and the precipitate was filtered off to give a second crop of the **87** (10 mg, 71% overall yield). M.p. 160–162 °C; $[\alpha]_D^{20}$ –41.4 (c=0.35, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.40 (s, 9 H), 1.64 (dd, J = 6.9 Hz, 1.8 Hz, 3 H), 1.78–2.04 (m, 1 H), 2.11–2.57 (m, 1 H), 2.34 (s, 3 H), 2.97–3.15 (m, 1 H), 2.99 (dd, J = 9.3 Hz, 9.1 Hz, 1 H), 3.51–3.92 (m, 3 H), 3.75 (s, 3 H), 4.12 (dd, J = 8.2 Hz, 8.1 Hz, 1 H), 4.34–4.51 (m, 1 H), 5.02 (d, J = 12.3 Hz, 1 H), 5.08 (d, J = 12.3 Hz, 1 H), 5.17–5.30 (m, 1 H), 5.52 (dq, J = 10.5 Hz, 6.9 Hz, 1 H), 5.74–6.17 (bs, 1 H), 6.43–6.85 (bs, 1 H), 7.14 (d, J = 8.1 Hz, 2 H), 7.33 (d, J = 8.1 Hz, 2 H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 13.2 (+), 21.2 (+), 28.3 (+), 36.0 (+), 38.1 (–), 40.8 (–), 41.5 (–), 52.4 (–), 52.7 (+), 54.3 (+), 60.8 (+), 61.4 (+), 67.0 (–), 80.7 (C$_{quat}$), 126.5 (+), 128.3 (+), 129.1 (+), 129.4 (+), 133.2 (C$_{quat}$), 137.9 (C$_{quat}$), 154.4, 155.1 (C$_{quat}$), 156.3 (C$_{quat}$), 170.2, 171.0 (C$_{quat}$), 170.9, 173.0 (C$_{quat}$).



*Boc-(4-Pe)Pro-[MeZ-Dap]-OH (**88**)*:[110] A 40% aqueous solution of tetra-*n*-butylammonium hydroxide (0.20 g, 0.31 mmol) was added dropwise to an ice-cold solution of the dipeptide ester **87** (0.13 g, 0.26 mmol) in THF (2.0 mL) within 3 min, and stirring was continued at the same temperature for an additional 45 min (TLC monitoring to detect complete consuming of the starting material). A aq. 1 M H$_2$SO$_4$ (1 mL) was then added, and the mixture was diluted with Et$_2$O (50 mL). The organic layer was separated and washed with aq. 1 M KHSO$_4$ (2 × 10 mL), water (5 × 10 mL), brine (2 × 5 mL), dried over MgSO$_4$ and filtered. The filtrate was concentrated under reduced pressure to give the crude product which was finally purified by column chromatography (silica gel, eluted with acetone/hexane 4:7 +2% AcOH, R_f=0.36) to give dipeptide acid **88** (0.126 g, 99%) as an extremely viscous turbid oil. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.31 + 1.41 (2 × s, 9 H), 1.65 (d, J = 6.0 Hz, 3 H), 1.75–1.98 (m, 1 H), 2.33 (s, 3 H), 2.21–2.53 (m, 1 H), 2.93–3.21 (m, 2 H), 3.44–3.60 (m, 2 H), 3.60–4.03 (m, 1 H), 4.03–4.24 (m, 2 H), 4.30–4.39 + 4.41–4.54 (2 × bs,

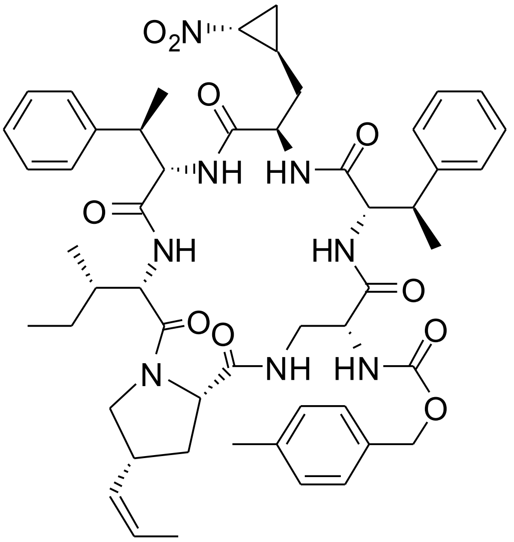


1 H), 5.04 (s, 2 H), 5.15–5.32 (m, 1 H), 5.55 (dq, *J* = 10.8 Hz, 7.0 Hz, 1 H), 6.25 (d, *J* = 6.5 Hz, 1 H), 7.12 (d, *J* = 7.5 Hz, 2 H), 7.22 (d, *J* = 7.5 Hz, 2 H), 7.42–7.65 (bs, 1 H).

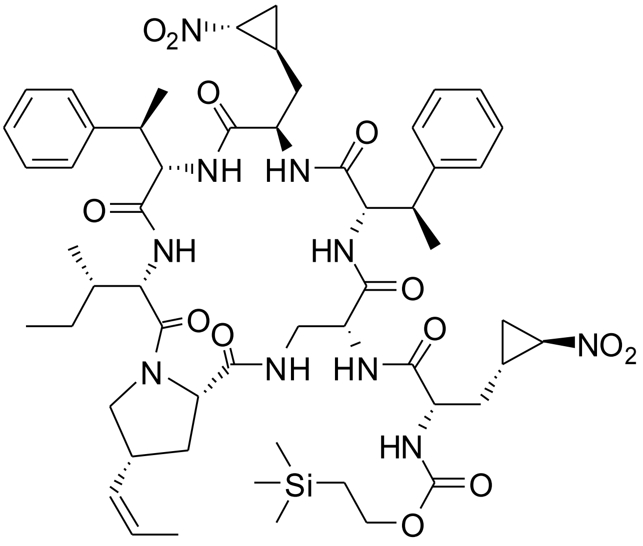


*Boc-(4-Pe)Pro-[MeZ-Dap]-MeF-(S)NcpA-MeF-Ile-ODCPM (**89**)*:[110] Tetrapeptide **66** (180 mg, 0.21 mmol) was deprotected according to GP 1 in THF (2 mL), taken up with anhydrous CH_2Cl_2 (5 mL), dipeptide acid **88** (0.114 g, 0.23 mmol), HATU (96 mg, 0.25 mmol) and HOAt (31 mg, 0.23 mmol) were added and the reaction mixture was cooled to 4 °C. After this, a solution of DIEA (29 mg, 0.22 mmol) and TMP (75 mg, 0.62 mmol) in CH_2Cl_2 (2 mL) were added at the same temperature within 5 min. The temperature was allowed to reach 20 °C, and stirring continued for an additional 15 h. After aqueous work-up according to GP 2 and two recrystallizations from EtOAc/hexanes 1:2, triprotected peptide **89** (185 mg, 79%) was obtained as a colorless powder. R_f = 0.46 (EtOAc/hexanes 1:1); m.p. 125–127 °C, $[\alpha]_D^{20}$ –29.0 (c = 0.2, THF); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.27–0.33 (m, 1 H), 0.33–0.44 (m, 3 H), 0.44–0.49 (m, 1 H), 0.49–0.57 (m, 2 H), 0.59–0.65 (m, 1 H), 0.75 (d, *J* = 6.8 Hz, 3 H), 0.89 (t, *J* = 7.3 Hz, 3 H), 0.95–1.11 (m, 4 H), 1.11–1.60 (m, 5 H), 1.24 (d, *J* = 7.5 Hz, 3 H), 1.27 (d, *J* = 7.5 Hz, 3 H), 1.36 (s, 9 H), 1.43 (d, *J* = 6.5 Hz, 3 H), 1.66 (dd, *J* = 6.9 Hz, 1.7 Hz, 3 H), 1.68–1.76 (m, 1 H), 1.80–1.90 (m, 1 H), 2.30 (s, 3 H), 2.35–2.42 (m, 1 H), 3.06–3.13 (m, 1 H), 3.13 (t, *J* = 10.5 Hz, 1 H), 3.18–3.31 (m, 2 H), 3.67 (dd, *J* = 10.2 Hz, 7.8 Hz, 1 H), 3.80–3.84 (m, 1 H), 4.02–4.07 (m, 1 H), 4.14 (dd, *J* = 10.7 Hz, 6.2 Hz, 1 H), 4.33 (dd, *J* = 8.9 Hz, 4.6 Hz, 1 H), 4.37 (dd, *J* = 9.5 Hz, 2.2 Hz, 1 H), 4.45 (dd, *J* = 9.9 Hz, 6.9 Hz 1 H), 4.57 (dt, *J* = 9.6 Hz, 5.1 Hz, 1 H), 4.62 (t, *J* = 10.3 Hz, 1 H), 4.96–5.06 (m, 2 H), 5.22–5.28 (m, 1 H), 5.46–5.51 (m, 1 H), 5.52–5.58 (m, 1 H), 6.54 (d, *J* = 8.2 Hz, 1 H), 6.89 (d, *J* = 8.9 Hz, 1 H), 6.99 (d, *J* = 9.6 Hz, 1 H), 7.06–7.12 (m, 2 H), 7.14–7.25 (m, 12 H) 7.49 (d, *J* = 9.8 Hz, 1 H), 7.86 (d, *J* = 5.9 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 2.48 (–), 2.82 (–), 2.90 (–), 3.01 (–), 11.59 (+), 13.20 (+), 14.16 (+), 14.64 (+), 15.57 (+), 17.77 (+), 18.41 (–), 18.86 (+), 19.43 (+), 21.11 (+), 21.77 (+), 25.23 (–), 26.85 (–), 28.23 (+), 31.46 (–), 31.53 (–), 36.28 (–), 36.32 (+), 37.30 (+), 40.45 (+), 42.00 (+), 50.62 (+), 52.08 (+), 56.43 (+), 59.30 (+), 59.49 (+), 61.01 (+), 61.62 (+), 61.99 (+), 66.89 (–), 70.53 (+), 80.93 (C_{quat}), 83.24 (+), 127.00 (+), 127.06 (+), 127.10 (+), 127.60 (+), 127.69 (+), 128.47 (+), 128.63 (+), 128.68 (+), 128.82 (+), 128.93 (+), 133.21 (C_{quat}), 137.83 (C_{quat}), 141.73 (C_{quat}), 141.90 (C_{quat}), 154.76 (C_{quat}), 155.75 (C_{quat}), 170.38 (C_{quat}), 170.43 (C_{quat}), 170.79 (C_{quat}), 171.37 (C_{quat}), 173.41 (C_{quat}), 174.06 (C_{quat}).

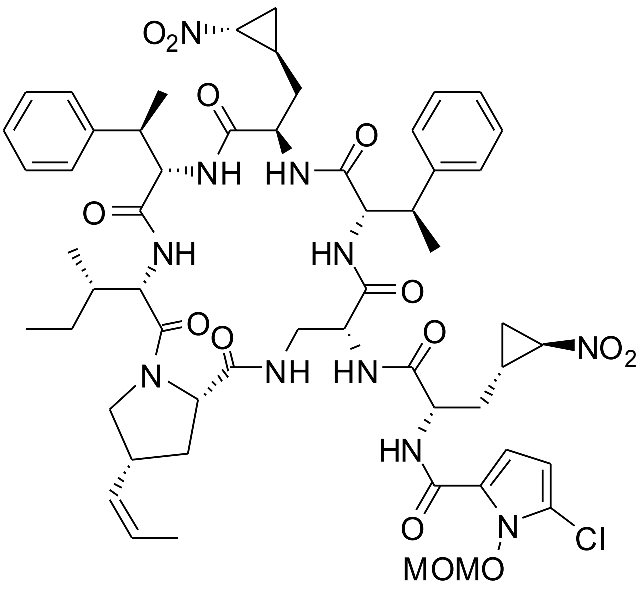
*N-MeZ protected cyclohexapeptide (***91***)*:[110] To the hexapeptide **89** (0.188 g, 0.165 mmol) 2 M HCl in EtOAc (2 mL) was added, the reaction mixture was stirred for 45 min at ambient temperature in the dark place and then was concentrated under reduced pressure without any heating. The residue was triturated with dry Et_2O to give deprotected material **90** as a white solid, which was taken up with anhydrous CH_2Cl_2 (1.5 L) and cyclized employing HATU (2 × 0.073 g, 2 × 0.192 mmol) and HOAt (2 × 0.022 g, 2 × 0.163 mmol) and solution of DIEA (2 × 0.062 g, 2 × 0.480 mmol) in CH_2Cl_2 (2 × 50 mL) according to GP 4 for 16 h. After this, the solvent was removed under reduced pressure, the residue was taken up with Et_2O (50 mL), and after usual aqueous work-up (GP 2), drying and filtration, the organic layer was concentrated under reduced pressure. The residue was purified first by column chromatography (silica gel, eluted with acetone/hexanes 2:3, R_f = 0.31) and then by recrystallization (Et_2O/pentane) to give crude product (0.12 g), which was finally purified by preparative HPLC to give cyclohexapeptide **91** (86 mg, 53% on 2 steps) as a white solid. Preparative HPLC: isocratic, 70% B for 30 min, t_R = 21.5 min, purity > 98%; analytical HPLC: isocratic, 62% B for, t_R = 22.9 min, purity > 98% $[\alpha]_D^{20}$ –15.5 (c = 0.20, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.61–0.67 (m, 1 H), 0.72 (d, J = 6.6 Hz, 3 H), 0.71–0.77 (m, 1 H), 0.79 (t, J = 7.2 Hz, 3 H), 1.04–1.12 (m, 1 H), 1.23 (d, J = 6.6 Hz, 3 H), 1.27–1.34 (m, 1 H), 1.37 (d, J = 6.6 Hz, 3 H), 1.37–1.43 (m, 1 H), 1.45–1.54 (m, 1 H), 1.54–1.57 (m, 1 H), 1.57 (d, J = 6.6 Hz, 3 H), 1.65 (dd, J = 6.6 Hz, 1.5 Hz, 3 H), 1.66–1.76 (m, 2 H), 2.20–2.25 (m, 1 H), 2.35 (s, 3 H), 3.01–3.07 (m, 1 H), 3.15–3.28 (m, 2 H), 3.54 (dq, J = 7.2 Hz, 6.6 Hz, 1 H), 3.71 (dd, J = 6.0 Hz, 5.4 Hz, 1 H), 3.74–3.77 (m, 1 H), 3.98 (dd, J = 10.5 Hz, 6.3 Hz, 1 H), 4.01–4.08 (m, 1 H), 4.46–4.54 (m, 2 H), 4.52–4.55 (m, 1 H), 4.67–4.70 (m, 1 H), 5.03 (d, J = 12.0 Hz, 1 H), 5.15 (d, J = 12.0 Hz, 1 H), 5.19–5.25 (m, 1 H), 5.39 (qd, J = 6.6 Hz, 1.8 Hz, 1 H), 5.56 (dq, J = 10.8 Hz, 6.6 Hz, 1 H), 5.96 (d, J = 5.3 Hz, 1 H), 6.20 (d, J = 7.4 Hz, 1 H), 6.28 (d, J = 9.7 Hz, 1 H), 6.49 (d, J = 9.4 Hz, 1 H), 7.11–7.37 (m, 14 H) 7.32 (d, J = 7.4 Hz, 1 H), 7.45 (d, J = 8.7 Hz, 1 H); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 10.3 (+), 13.3 (+), 14.6 (+), 17.3 (–), 17.7 (+), 18.4 (+), 21.2 (+), 21.3 (+), 24.7 (–), 32.0 (–), 35.4 (–), 36.6 (+), 39.4 (+), 44.5 (+), 52.5 (–),



53.3 (+), 54.6 (+), 58.6 (+), 59.0 (+), 59.4 (+), 60.1 (+), 60.7 (+), 67.2 (–), 72.6 (+), 127.1 (+), 127.2 (+), 127.5 (+), 127.6 (+), 128.3 (+), 128.6 (+), 128.8 (+), 129.2 (+), 127.8 (+), 128.0 (+), 133.2 (C_{quat}), 137.9 (C_{quat}), 140.9 (C_{quat}), 142.6 (C_{quat}), 156.3 (C_{quat}), 169.0 (C_{quat}), 170.3 (C_{quat}), 170.6 (C_{quat}), 171.1 (C_{quat}), 171.4 (C_{quat}), 173.1 (C_{quat}); MS-ESI: positive mode, m/z (%) = 1001 (100, M+Na]$^+$); negative mode, m/z (%) = 977 (100, M–H]$^-$).

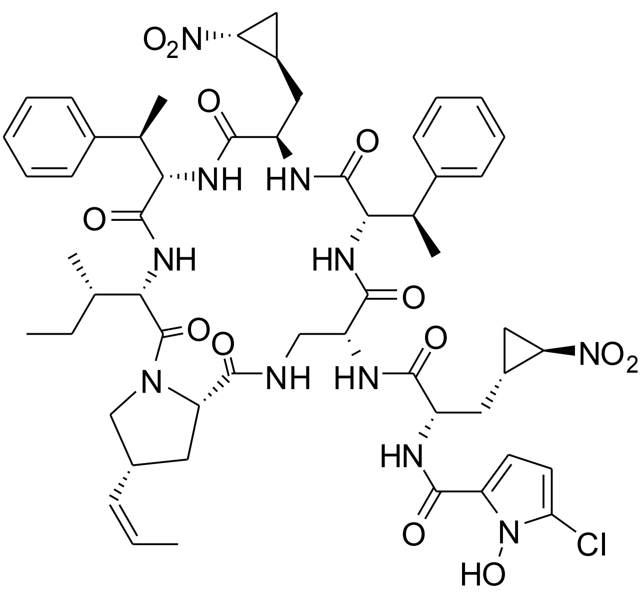


*N-Teoc protected heptapeptide (***93***):*[110] An ethereal solution (50 mL) of the cyclohexylammonium salt of *N*-Teoc protected (2*S*,1'*R*,2'*R*)-3-(2'-nitrocyclopropyl)alanine **78** (8.1 mg, 19.41 µmol) was washed with aq. 1 M H_2SO_4 (3 × 5 mL), aq. 1 M $KHSO_4$ (2 × 5 mL), water (3 × 5 mL), brine (2 × 5 mL), dried, filtered and concentrated under reduced pressure. The resulting *N*-protected amino acid **78** was dried at 0.02 Torr for 2 h and then coupled with the cyclohexapeptide **92** [obtained after deprotection of *N*-MeZ protected cyclohexapeptide **91** (9.5 mg, 9.71 µmol) with 10% anisole in TFA (1.1 mL) for 2 h according to GP 5] using HATU (7.4 mg, 19.46 µmol), HOAt (2.6 mg, 19.24 µmol), DIEA (1.25 mg, 9.67 µmol) and TMP (7.04 mg, 58.10 µmol) in CH_2Cl_2 (0.7 mL) according to GP 6 for 15 h. The mixture was then diluted with EtOAc/Et_2O 1:1 (20 mL) to give after usual aqueous work-up (GP 2) the crude product **79** (8.0 mg, 73%, R_f = 0.43 acetone/hexanes 1:2) as a colorless glass which was used for the next step without any characterization.



*MOM-O-protected Hormaomycin all-peptide analogue (***95***):*[110] Teoc group was cleaved from the compound **93** (8.0 mg, 7.08 µmol) with TFA (0.6 mL) for 1 h. The mixture was concentrated under reduced pressure at 20 °C and then taken up with toluene (3 × 15 mL) which was distilled off to remove the last traces of TFA. The resulting deprotected peptide **94** was coupled with *O*-MOM protected acid **81** (2.9

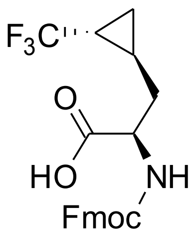
mg, 14.10 µmol) using HATU (5.4 mg, 14.20 µmol), DIEA (0.92 mg, 7.12 µmol) and TMP (5.14 mg, 42.42 µmol) in CH_2Cl_2 (1 mL) according to GP 6 for 2.5 h. The mixture was then taken up with Et_2O (20 mL) and the crude product obtained after usual aqueous work-up (GP 2) was crystallized from CH_2Cl_2 / pentane to give *O*-MOM protected all-peptide Hormaomycin analogue **95** (8.0 mg, 96%, R_f = 0.36 acetone/hexanes 1:2) as a colorless glass which was used for the next step without any characterization.



*Hormaomycin all-peptide analogue (***53***):*[110] *O*-MOM protected all-peptide Hormaomycin analogue **95** (8.0 mg, 6.82 µmol) was deprotected using $MgBr_2 \times Et_2O$ (52 mg, 201 µmol) and EtSH (0.10 mL, 1.9 mmol) in CH_2Cl_2 (10 mL) according to GP 7 for 3 h. The mixture was taken up with EtOAc and the crude product obtained after usual aqueous work-up (GP 2) was crystallized from CH_2Cl_2 / pentane to give **53** (5.5 mg, 72%, 50% on 5 steps from **91**) as a white solid, which was finally purified with preparative HPLC. R_f = 0.24 acetone/hexanes 3:7; preparative HPLC: isocratic, 75% B for 12 min, then gradient 62%→90% B for 1 min, then isocratic 90%B for 2 min, then gradient 90%→75% B for 1 min, then isocratic 75% B for 14 min, t_R = 10.4 min, purity > 98%; analytical HPLC: isocratic, 75% B t_R = 7.3 min $[\alpha]_D^{20}$ 61.0 (c = 0.1, MeOH); ^1H NMR (600 MHz, $CDCl_3$): δ = –0.60 – –0.54 (m, 1 H), –0.20–0.02 (m, 1 H), 0.25–0.31 (m, 1 H), 0.52 (ddd, *J* = 13.8 Hz, 4.8 Hz, 4.8 Hz, 1 H), 0.89 (t, *J* = 7.2 Hz, 3 H), 0.98–1.05 (m, 2 H), 1.07 (d, *J* = 7.2 Hz), 1.26–1.32 (m, 1 H) 1.30 (d, *J* = 7.2 Hz, 3 H), 1.40 (d, *J* = 7.2 Hz, 3 H), 1.54–1.60 (m, 1 H), 1.67 (d, *J* = 6.6 Hz, 3 H), 1.67–1.75 (m, 2 H), 1.84–1.93 (m, 3 H), 1.95–2.01 (m, 1 H), 2.20–2.27 (m, 1 H), 2.85–2.88 (m, 1 H), 3.04 (dq, *J* = 10.5 Hz, 7.2 Hz, 1 H), 3.18–3.30 (m, 2 H), 3.33 (d, *J* = 13.8 Hz, 1 H), 3.47–3.51 (m, 1 H), 3.68 (dq, *J* = 4.8 Hz, 7.2 Hz, 1 H), 3.93 (dd, *J* = 12.0 Hz, 5.4 Hz, 2 H), 3.94–3.98 (m, 1 H), 4.02–4.05 (m, 1 H), 4.11–4.23 (m, 1 H), 4.33 (dd, *J* = 10.5 Hz, 10.5 Hz, 1 H), 4.47 (dd, *J* = 9.6 Hz, 4.8 Hz, 1 H), 4.50 (dd, *J* = 9.0 Hz, 3.0 Hz, 1 H), 4.60–4.68 (m, 2 H), 5.14–5.20 (m, 1 H), 5.24–5.30 (m, 1 H), 5.61 (dq, *J* = 10.8 Hz, 6.6 Hz, 1 H), 6.15 (d, *J* = 4.8 Hz, 1 H), 6.46 (d, *J* = 6.6 Hz, 1 H), 6.78–6.83 (bs, 1 H), 6.83 (d, *J* = 4.8 Hz, 1 H), 7.02–7.06 (m, 2 H), 7.10–7.19 (m, 6 H), 7.20–7.24 (m, 5 H), 7.32 (d, *J* = 9.0 Hz, 1 H), 8.17 (d, *J* = 7.8 Hz, 1 H), 8.75 (d, $J = 8.4$ Hz, 1 H), 10.75–11.15 (bs, 1 H); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 10.3 (+), 13.2 (+), 13.3 (+), 14.8 (+), 16.9 (–), 17.1 (–), 17.5 (+), 20.0 (+), 21.6 (+), 25.1 (–), 32.9 (–), 35.0 (–), 35.7 (–), 36.3 (+), 37.8 (+), 38.0 (–), 39.1 (+), 41.6 (+), 50.9 (+), 51.8 (+), 52.0 (+), 53.0 (–), 54.5 (+), 58.0 (+), 59.2 (+), 60.0 (+), 60.3 (+), 63.5 (+), 103.6 (+), 109.8 (+),119.9 (C_{quat}), 121.6 (C_{quat}), 126.9 (+), 127.3 (+), 127.4 (+), 127.6 (+), 127.8 (+), 127.9 (+), 128.5 (+), 128.6 (+), 141.3 (C_{quat}), 142.1 (C_{quat}), 159.2 (C_{quat}), 168.4 (C_{quat}), 169.5 (C_{quat}), 170.3 (C_{quat}), 170.8 (C_{quat}), 171.7 (C_{quat}), 172.4 (C_{quat}), 172.5 (C_{quat}); MS (ESI): (positive) m/z (%): 1137 (100, $M+Na\rceil^{+}$), 1115 (32, $M+H\rceil^{+}$), (negative) m/z (%): 1113 (72, $M–H\rceil^{-}$).

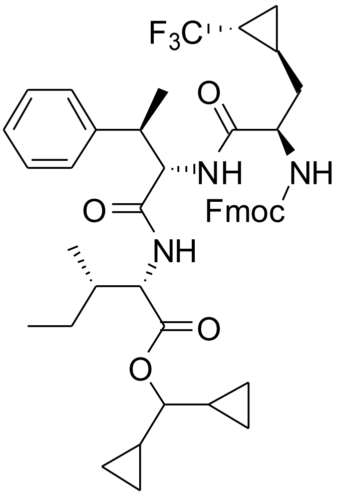
10. Hormaomycin analogues containing (fluoromethylcyclopropyl)alanine moieties

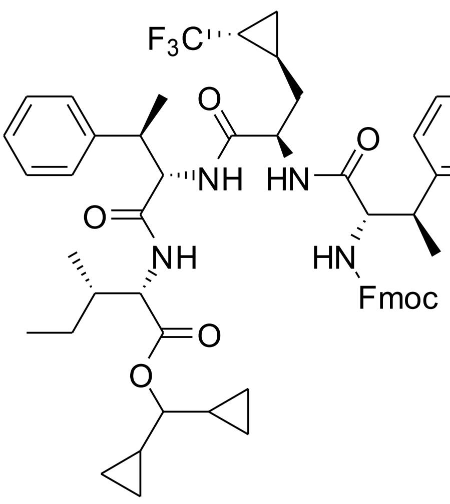
10.1. (Trifluoromethylcyclopropyl)alanyl-Hormaomycin



N-Fmoc-(2R,1'R,2'R)-3-(2'-Trifluoromethylcyclopropyl)alanine (Fmoc-(R)tFmcpA-OH, **97 c***)*: A solution of Fmoc-OSu (459 mg, 1.36 mmol) in acetone (7 mL) was added to a vigorously stirred solution of (2*R*,1'*R*,2'*R*)-3-(2'-trifluoromethylcyclopropyl)alanine ***R*-96 c** (225 mg, 1.14 mmol) and $NaHCO_3$ (0.202 g, 2.40 mmol) in water (5 mL) (if a precipitate formed, acetone and/or water was added to obtain a homogeneous solution) and stirring continued for an additional 3 h. Acetone was then removed under reduced pressure, and the pH of the residual water solution was adjusted to 1 with aq. 1 M $KHSO_4$. The resulting emulsion was extracted with diethyl ether (30 mL) and the ethereal layer was back-extracted with aq. 3% $NaHCO_3$ (5 × 10 mL). The combined aqueous fractions were washed with diethyl ether (2 × 10 mL), acidified to pH~2 with aq. 1 M $KHSO_4$, and the resulting emulsion was extracted with diethyl ether (4 × 10 mL). The organic phase was washed with aq. 1 M $KHSO_4$ (2 × 10 mL), water (3 × 10 mL), brine (2 × 5 mL), dried, filtered and concentrated under reduced pressure. The residue was triturated with cold pentane and filtered. The resulting extremely viscous oil was dried at 0.02 Torr for prolonged time to give the target protected amino acid **97 c** (390 mg, 0.930 mmol, 82%) as a colorless foam. R_f= 0.08 (EtOAc/hexane 1:1); m.p. (softening) 50–57 °C; $[\alpha]_D^{20}$ –56.7 (c=0.36, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): 0.38–0.44 + 0.57–0.64 + 0.79–0.86 (3 × m, 1 H), 0.91–0.97 + 1.00–1.09 (2 × m, 1 H), 1.14–1.22 + 1.26–1.34 (2 × m, 1 H), 1.35–1.53 + 1.85–1.88 (2 × m, 1 H), 1.80–1.85 (m, 1 H), 3.75–3.79 + 4.53–4.67 (2 × m, 1 H), 3.95–4.01 + 4.47–4.52 (2 × m, 1 H), 4.16–4.23 (m, 1 H), 4.36–4.47 (m, 1 H), 5.52 (d, *J* = 7.9 Hz, 0.7 H), 6.76 (d, *J* = 5.9 Hz, 0.3 H), 7.27–7.31 (m, 2 H), 7.35–7.41 (m, 2 H), 7.51 (t, J = 8.1 Hz, 0.6 H), 7.58 (t, J = 8.4 Hz, 1.4 H), 7.74 (d, *J* = 7.4 Hz, 2 H), 7.85–8.65 (bs, 1 H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 7.94 (–), 11.46 (+), 19.73 (+, q, *J* = 37.0 Hz), 34.65 (–), 47.10 (+), 53.48 + 53.82 (+), 67.14 + 67.87 (–), 120.00 (+), 124.97 (+), 125.96 (–, q, *J* = 272.4 Hz), 127.07 (+), 127.76 (+), 141.32 (C_{quat}), 143.51 (C_{quat}), 143.76 (C_{quat}), 155.79 + 156.71 (C_{quat}), 174.96 + 175.79 (C_{quat}); MS-ESI: (positive) m/z (%) 1302 (35, 3M-H+2Na]$^+$), 861 (100, 2M+Na]$^+$), 442 (M+Na]$^+$), (negative) m/z (%) 837 (100, 2M–H]$^-$), 418 (16, M–H]$^-$), 222 (14, M–FmOH–H]$^-$), 196 (15, FmOH]$^-$).

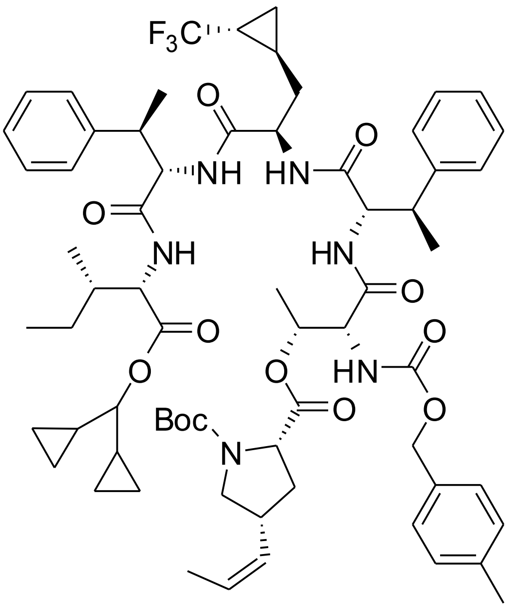
*Fmoc-(R)tFmcpA-MeF-Ile- ODCPM (***98** c*)*: Dipeptide **60** (434 mg, 834 µmol) was taken up with EtOAc (20 mL) and hydrogenated over 10% Pd/C (250 mg) under ambient pressure of hydrogen for 2 h. The reaction mixture was filtered through a pad of Celite® and concentrated under reduced pressure to give deprotected dipeptide **62**, which was directly used for the coupling with Fmoc-(*R*)tFmcpA-OH **97 c** (360 mg, 860 µmol), using EDC (172 mg, 896 µmol), HOAt (120 mg, 883 µmol) and TMP (310 µL, 2.5 mmol) according to GP 2. During reaction the white precipitate appeared. The mixture was diluted with diethyl ether (50 mL), stirred for 30 min and filtered, giving the crude product (1st crop, 473 mg after drying *in vacuo*). The filtrate was concentrated under reduced pressure at ambient temperature and diluted with diethyl ether (20 mL) giving the crude product (2nd crop, 130 mg after drying *in vacuo*). The residing filtrate was subjected usual aqueous work-up according to GP 2 to give the last portion of crude product (3rd crop, 100 mg after drying *in vacuo*). Combined crude product was re-crystallized from THF/hexane and the resulting off-white solid was dissolved in chloroform (50 mL) and subjected usual aqueous work-up according to GP 2 to give the pure tripeptide as white solid (535 mg, 679 µmol, 81%). R_f = 0.52; EtOAc/hexane 2:3; m.p. 151–155°C; $[\alpha]_D^{20}$ –3,8 (*c* =0.26, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.28–0.40 (m, 4 H), 0.43–0.53 (m, 2 H), 0.57–0.66 (m, 3 H), 0.88 (d, *J* = 6.7 Hz, 3 H), 0.90 (t, *J* = 7.4 Hz, 3 H), 0.94–1.00 (m, 1 H), 1.03–1.13 (m, 2 H), 1.13–1.22 (m, 2 H), 1.30–1.50 (m, 2 H), 1.41 (d, *J* = 6.8 Hz, 3 H), 1.58–1.70 (m, 1 H), 1.81–1.97 (m, 2 H), 3.28–3.38 (m, 1 H), 3.86 (t, *J* = 8.4 Hz, 1 H), 4.28 (t, *J* = 6.9 Hz, 1 H), 4.39–4.48 (m, 3 H), 4.48–4.57 (m, 1 H), 4.76 (t, *J* = 8.0 Hz, 1 H), 5.76 (d, *J* = 7.7 Hz, 1 H), 6.40 (d, *J* = 7.5 Hz, 1 H), 7.11 (d, *J* = 8.1 Hz, 1 H), 7.20–7.34 (m, 5 H), 7.35 (t, *J* = 7.4 Hz, 2 H), 7.46 (t, *J* = 7.4 Hz, 2 H), 7.60 (t, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 7.5 Hz, 2 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ = 2.57; 2.90, 8.18, 11.62,14.39, 14.66, 15.07, 15.07, 16.86, 19.70 (q, *J*=37.1 Hz), 25.14, 35.08, 38.13, 42.05, 47.07, 54.69,56.46, 58.79, 67.18, 83.44, 119.94, 124.99, 127.06, 127.55, 127.71, 128.54, 141.23, 141.28, 141.70, 143.57, 143.78, 155.95, 169.64, 170.55, 170.94.

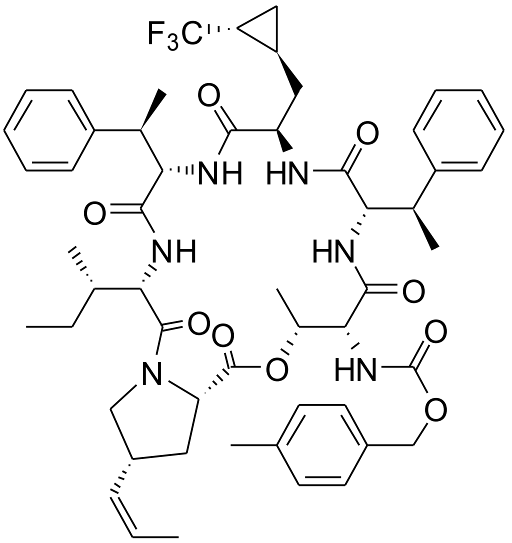




*Fmoc-MeF-(R)tFmcpA-MeF-Ile-ODCPM (***100 c***)*: The tripeptide **98 c** (394 mg, 500 µmol) was deprotected according to GP 1 and the resulting *C*-protected tripeptide **99 c** was then directly coupled with Fmoc-MeF-OH **64** (211 mg, 525 µmol) according to GP 2 using EDC (99 mg, 518 µmol), HOAt (70 mg, 512 µmol) and TMP (175 mg, 1440 µmol) in CH_2Cl_2 (3 mL). After 16 h the reaction mixture was diluted with chloroform (50 mL) and subjected usual aqueous work-up according to GP 2 to give the crude tetrapeptide, which was twice re-crystallized from THF/hexane, giving the pure target tetrapeptide as off-white solid (440 mg, 463 µmol, 93%). $R_f = 0.29$; $CHCl_3$/MeOH 70:1; m.p. 210–215 °C (decomp.); $[\alpha]_D^{20}$ –26,3 (c = 0.32, THF); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.22–0.36 (m, 4 H), 0.41 (t, J = 8.9 Hz, 3 H), 0.48–0.61 (m, 2 H), 0.62–0.71 (m, 1 H), 0.76 (d, J = 6.9 Hz, 3 H), 0.82 (t, J = 7.3 Hz, 3 H), 0.92–1.09 (m, 4 H), 1.09–1.18 (m, 1 H), 1.22–1.46 (m, 2 H), 1.26 (d, J = 6.9 Hz, 3 H), 1.39 (d, J = 6.6 Hz, 3 H), 1.71–1.89 (m, 1 H), 3.09–3.36 (m, 3 H), 3.81 (t, J = 8.4 Hz, 1 H), 4.15–4.33 (m, 3 H), 4.35–4.64 (m, 3 H), 4.62 (t, J = 8.3 Hz, 1 H), 5.95 (d, J = 7.1 Hz, 1 H), 6.40 (d, J = 7.4 Hz, 1 H), 7.08–7.45 (m, 16 H), 7.57 (t, J = 8.9 Hz, 2 H), 7.76 (d, J = 7.3 Hz, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 3.3 (–), 3.5 (–), 3.6 (–), 3.7 (–), 12.2 (+), 15.6 (+), 15.9 (+), 16.1 (+), 17.7 (+), 18.7 (+), 18.9 (–), 23.2 (+), 26.2 (–), 35.0 (–), 39.1 (+), 42.8 (+), 44.1 (+), 48.5 (+), 52.8 (+), 57.4 (+), 59.3 (+), 60.2 (+), 62.1 (+), 67.8 (–), 83.4 (+), 115,1 (+, q, J = 291.4 Hz), 126.4 (+), 127.5 (+), 127.7 (+), 128.1 (+), 128.6 (+), 129.1 (+), 129.1 (+), 129.3 (+), 129.4 (+), 142.5 (C_{quat}), 144.1 (C_{quat}), 144.4 (C_{quat}), 145.4 (C_{quat}), 145.6 (C_{quat}), 157.8 (C_{quat}), 171.1 (C_{quat}), 171.5 (C_{quat}), 171.9 (C_{quat}), 172.1 (C_{quat}).

Boc-(4-Pe)Pro-[MeZ-a-Thr]-MeF-(S)tFmcpA-MeF-Ile-ODCPM (**101 c**): The tetrapeptide **100 c** (332 mg, 350 µmol) was *N*-deprotected according to GP 1 with diethylamine (5 mL) and THF (5 mL), taken up with anhydrous CH_2Cl_2 (5 mL), the solution of the ester acid **71** (194 mg, 385 µmol), HATU (160 mg, 420 µmol) and HOAt (53 mg, 385µmol) in CH_2Cl_2 (3 mL) was added, and the reaction mixture was cooled to 4 °C. After this, a solution of DIEA (65 µL, 48 mg, 368 µmol) and TMP (140 µL, 127 mg, 1050 µmol) in CH_2Cl_2 (2 mL) was added at the same temperature within 5 min. The temperature was allowed to reach 20 °C, and stirring was continued for an additional 15 hours. After aqueous work-up according to GP 2 and two recrystallizations from EtOAc/hexane (1:2), the target hexadepsipeptide **101 c** (390 mg, 321 µmol, 92%) was obtained as a colorless solid. R_f = 0.46 (EtOAc/hexane 1:1); m.p. 125–127 °C; $[\alpha]_D^{20}$ –29.0 (c=0.2, THF); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.24–0.68 (m, 12 H), 0.75 (d, *J* = 6.9 Hz, 3 H), 0.88 (t, *J* = 7.1 Hz, 3 H), 0.98–1.17 (m, 5 H), 1.18–1.46 (m, 1 H), 1.24 (d, *J* = 6.6 Hz, 3 H), 1.27 (d, *J* = 6.7 Hz, 3 H), 1.36 (s, 9 H), 1.40 (d, *J* = 6.7 Hz, 3 H), 1.68 (d, *J* = 7.0 Hz, 3 H), 1.75–1.94 (m, 2 H), 2.29–2.46 (m, 1 H), 2.32 (s, 3 H), 3.07–3.33 (m, 4 H), 3.68 (t, *J* = 8.6 Hz, 1 H), 3.93 (t, *J* = 8.3 Hz, 1 H), 4.18–4.27 (m, 1 H), 4.32–4.54 (m, 4 H), 4.64 (t, *J* = 9.6 Hz, 1 H), 4.95–5.13 (m, 2 H), 5.20–5.34 (m, 1 H), 5.44–5.63 (m, 2 H), 6.60 (d, *J* = 7.7 Hz, 1 H), 6.70 (d, *J* = 8.8 Hz, 1 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 7.05–7.37 (m, 14 H), 7.45 (d, *J* = 10.1 Hz, 1 H), 7.76 (d, *J* = 8.1 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 2.48 (–), 2.82 (–), 2.90 (–), 3.01 (–), 11.59 (+), 13.20 (+), 14.16 (+), 14.64 (+), 15.57 (+), 17.77 (+), 18.41 (–), 18.86 (+), 19.43 (+), 21.11 (+), 21.77 (+), 25.23 (–), 26.85 (–), 28.23 (+), 31.46 (–), 31.53 (–), 36.28 (–), 36.32 (+), 37.30 (+), 40.45 (+), 42.00 (+), 50.62 (+), 52.08 (+), 56.43 (+), 59.30 (+), 59.49 (+), 61.01 (+), 61.62 (+), 61.99 (+), 66.89 (–), 70.53 (+), 80.93 (Cquat), 83.24 (+), 116,2 (+, q, *J* = 287.3 Hz), 127.00 (+), 127.06 (+), 127.10 (+), 127.60 (+), 127.69 (+), 128.47 (+), 128.63 (+), 128.68 (+), 128.82 (+), 128.93 (+), 133.21 (Cquat), 137.83 (Cquat), 141.73 (Cquat), 141.90 (Cquat), 154.76 (Cquat), 155.75 (Cquat), 170.38 (Cquat), 170.43 (Cquat), 170.79 (Cquat), 171.37 (Cquat), 173.41 (Cquat), 174.06 (Cquat).

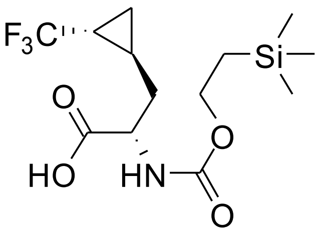




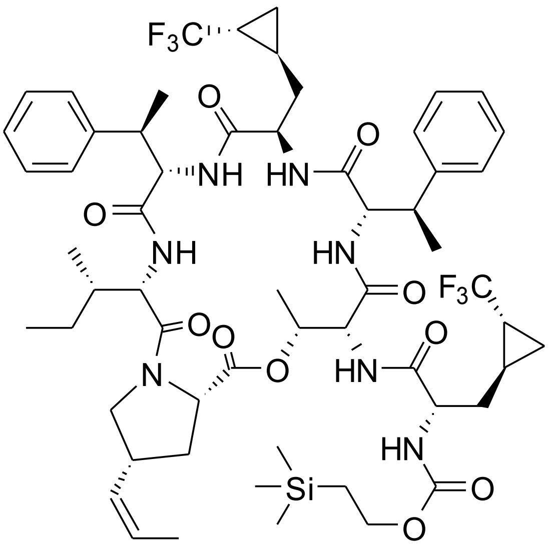
N-MeZ-protected cyclohexadepsipeptide **103 c** *(Cyclo-F$_3$6-MeZ)*: The hexadepsipeptide Boc-(4-Pe)Pro-[MeZ-a-Thr]-MeF-(*S*)tFmcpA-MeF-Ile-ODCPM (300 mg, 247 µmol) was ends-deprotected by treating with 2 M HCl solution in ethyl acetate (5 mL). The reaction mixture was stirred for 20 min in dark place (Al foil jacket) at ambient temperature and all volatiles were removed under reduced pressure *in vacuo* without any heating. The residue was triturated with anhydrous diethyl ether to give the hydrochloride of the deprotected material as a colorless solid (232 mg, 220 µmol, 89%). The ends-deprotected hexadepsipeptide, HATU (110 mg, 288 µmol) and HOAt (33 mg, 244 µmol) were dissolved in cold (4°C, internal temperature) anhydrous CH_2Cl_2 (2,5 L), and the solution of DIEA (120 µL, 93 mg, 720 µmol) in CH_2Cl_2 (100 mL) was added dropwise within 1 hour, the cooling bath was removed and the mixture was stirred for 2 hours at ambient temperature. Then the mixture was cooled again to 4°C (internal temperature), the second portions of HATU (110 mg, 288 µmol) and HOAt (33 mg, 244 µmol) were added, followed with dropwise addition of the solution of DIEA (120 µL, 93 mg, 720 µmol) in CH_2Cl_2 (100 mL) within 1 hour. The cooling bath was removed and the mixture was stirred for 18 hours at ambient temperature. The mixture was concentrated under reduced pressure, subjected to aqueous work-up according to GP 2 to give the crude protected cyclohexadepsipeptide (180 mg, 180 µmol, 73%) which was finally purified with the HPLC to give pure product (132 mg, 132 µmol, 54%). Preparative HPLC: isocratic, 82% B for 25 min, t_R = 15.4 min, purity > 98%; analytical HPLC: gradient 20% → 100% B for 20 min, then isocratic 100% B for 5 min t_R = 11.9 min, purity > 98%; $[\alpha]_D^{20}$ –15.5 (c = 0.20, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.61–0.67 (m, 1 H), 0.72 (d, *J* = 6.6 Hz, 3 H), 0.71–0.77 (m, 1 H), 0.79 (t, *J* = 7.2 Hz, 3 H), 1.04–1.12 (m, 1 H), 1.23 (d, *J* = 6.6 Hz, 3 H), 1.27–1.34 (m, 1 H), 1.37 (d, *J* = 6.6 Hz, 3 H), 1.37–1.43 (m, 1 H), 1.45–1.54 (m, 1 H), 1.54–1.57 (m, 1 H), 1.57 (d, *J* = 6.6 Hz, 3 H), 1.65 (dd, *J* = 6.6 Hz, 1.5 Hz, 3 H), 1.66–1.76 (m, 2 H), 2.20–2.25 (m, 1 H), 2.35 (s, 3 H), 3.01–3.07 (m, 1 H), 3.15–3.28 (m, 2 H), 3.54 (dq, *J* = 7.2 Hz, 6.6 Hz, 1 H), 3.71 (dd, *J* = 6.0 Hz, 5.4 Hz, 1 H), 3.74–3.77 (m, 1 H), 3.98 (dd, *J* = 10.5 Hz, 6.3 Hz, 1 H), 4.01–4.08 (m, 1 H), 4.46–4.54 (m, 2 H), 4.52–4.55 (m, 1 H), 4.67–4.70 (m, 1 H), 5.03 (d, *J* = 12.0 Hz, 1 H), 5.15 (d, *J* = 12.0 Hz, 1 H), 5.19–5.25 (m, 1 H), 5.39 (qd, *J* = 6.6 Hz, 1.8 Hz, 1 H), 5.56 (dq, *J* = 10.8 Hz, 6.6 Hz, 1 H), 5.96 (d, *J* = 5.3 Hz, 1 H), 6.20 (d, *J* = 7.4 Hz, 1 H), 6.28 (d, *J* = 9.7 Hz, 1 H), 6.49 (d, *J* = 9.4 Hz, 1 H), 7.11–7.37 (m, 14 H) 7.32 (d,

J = 7.4 Hz, 1 H), 7.45 (d, J = 8.7 Hz, 1 H); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 10.3 (+), 13.3 (+), 14.6 (+), 17.3 (–), 17.7 (+), 18.4 (+), 21.2 (+), 21.3 (+), 24.7 (–), 32.0 (–), 35.4 (–), 36.6 (+), 39.4 (+), 44.5 (+), 52.5 (–), 53.3 (+), 54.6 (+), 58.6 (+), 59.0 (+), 59.4 (+), 60.1 (+), 60.7 (+), 67.2 (–), 72.6 (+), 127.1 (+), 127.2 (+), 127.5 (+), 127.6 (+), 128.3 (+), 128.6 (+), 128.8 (+), 129.2 (+), 127.8 (+), 128.0 (+), 133.2 (C_{quat}), 137.9 (C_{quat}), 140.9 (C_{quat}), 142.6 (C_{quat}), 156.3 (C_{quat}), 169.0 (C_{quat}), 170.3 (C_{quat}), 170.6 (C_{quat}), 171.1 (C_{quat}), 171.4 (C_{quat}), 173.1 (C_{quat}).

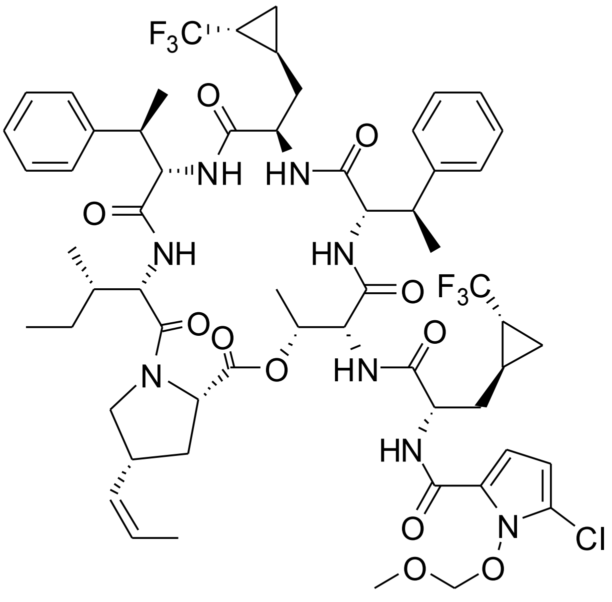
N-Teoc-(2S,1'S,2'R)-3-(2'-Trifluoromethylcyclopropyl)alanine (Teoc-(S)tFmcA-OH, **105 c***)*: A solution of TeocOSu (43 mg, 164 µmol) in acetone (1 mL) was added to a vigorously stirred solution of (2*S*,1'*S*,2'*R*)-3-(2'-trifluoromethylcyclopropyl)alanine ***S*-96 c** (27 mg, 137 µmol) and $NaHCO_3$ (24 mg, 286 µmol) in water (1 mL) (if an emulsion formed, acetone and/or water was added to obtain a homogeneous solution), and stirring was continued for another 2 h. *N,N*-dimethylaminopropylamine (8 µL, 6,4 mg, 52 µmol) was then added. After an additional 10 min acetone was removed under reduced pressure and the pH of the residual water solution was adjusted to 2–3 with aq. 1 M $KHSO_4$. The resulting emulsion was extracted with diethyl ether (50 mL), and the ethereal layer was washed with aq. 1 M $KHSO_4$ (2 × 10 mL), water (3 × 10 mL), brine (2 × 5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was dried overnight *in vacuo* to give glass-like product (38 mg, 111 µmol, 81%). R_f = 0.24 [EtOAc/hexane 1:3 (2% AcOH)]; $[\alpha]_D^{20}$ 22.80 (c = 0.46, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.04 (s, 9H), 1.00 (dd, J = 9.5 Hz, 7.3 Hz, 2 H), 1.11–1.18 (m, 1 H), 1.60–1.95 (m, 2 H), 1.98–2.19 (m, 2 H), 4.14–4.23 (m, 3 H), 4.33–4.59 (m, 1 H), 5.33–5.46 (m, 1 H), 7.08–7.25 (bs, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = –1.9 (+), 10.2 (–), 17.3 (–), 22.0 (+), 33.1 + 33.3 (–), 52.7 (+), 53.2 (+), 59.0 (+), 63.7 (+), 64.8 (–), 115.6 (q, J = 271.4 Hz), 157.4 (Cquat), 174.5 + 174.8 (Cquat).



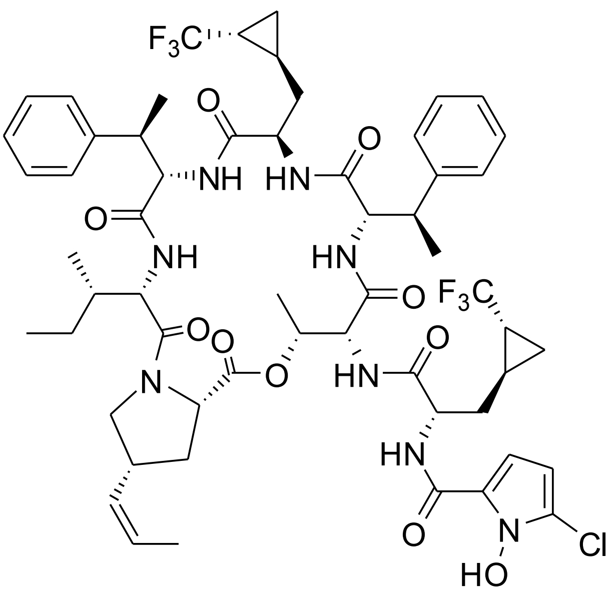
*Teoc-(S)tFmcpA-Cyclo-F$_3$6 (***106 c***)*: *N*-MeZ-protected cyclohexadepsipeptide **103 c** (25 mg, 25 µmol) was deprotected with 10% anisole in TFA (1.1 mL) in the dark at ambient temperature for 2 h, the residue was treated with toluene (5 mL), concentrated under reduced pressure and the residue was dried *in vacuo* at ambient temperature for 2 hours. The solution of Teoc-(S)tFmcpA-OH **105 c**, HATU (29 mg, 75 µmol) and HOAt (10 mg, 75 µmol) in CH_2Cl_2 (1.5 mL) was added at 4 °C, followed with DIEA (3 5 mg, 27 µmol) and TMP (27 mg, 225 µmol) solution in CH_2Cl_2 (1.5 mL) and the mixture was stirred at ambient temperature for 15 h. The reaction mixture was then diluted with diethyl ether (50 mL) and the crude product obtained after the usual aqueous work-up (GP 2) was purified by crystallization from CH_2Cl_2/pentane to give Teoc-(S)tFmcpA-Cyclo-F$_3$6 (**106 c**) (29 mg, 24,7 µmol, 99%) as a colorless solid ($R_f = 0.43$, acetone/hexane 1:2) which was used for the next step without any characterization.



MOM-O-protected Trifluoromethylcyclopropylalanyl Hormaomycin (MOM-O-F$_3$Horm, **108 c***)*: Teoc group was cleaved from the compound **106 c** (8.0 mg, 7.08 µmol) with TFA (0.6 mL) for 1 h. The mixture was concentrated under reduced pressure at 20 °C and then taken up with toluene (3 × 15 mL) which was distilled off to remove the last traces of TFA. The resulting deprotected depsipeptide **107 c** was coupled with *O*-MOM protected acid **81** (2.9 mg, 14.10 µmol) using HATU (5.4 mg, 14.20 µmol), DIEA (0.92 mg, 7.12 µmol) and TMP (5.14 mg, 42.42 µmol) in CH_2Cl_2 (1 mL) according to GP 6 for 2.5 h. The mixture was then taken up with Et_2O (20 mL) and the crude product obtained after usual aqueous work-up (GP 2) was crystallized from CH_2Cl_2 / pentane to give *O*-MOM protected



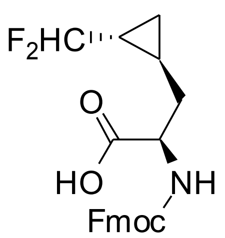
trifluoromethylcyclopropylalanyl Hormaomycin **108 c** (8.0 mg, 96%, $R_f = 0.36$ acetone/hexanes 1:2) as a colorless glass which was used for the next step without any characterization.



Trifluoromethylcyclopropylalanyl Hormaomycin (F$_3$Horm, **109 c***)*: *O*-MOM protected trifluoromethylcyclopropylalanyl Hormaomycin **108 c** (8.0 mg, 6.82 µmol) was deprotected using $MgBr_2 \times Et_2O$ (52 mg, 201 µmol) and EtSH (0.10 mL, 1.9 mmol) in CH_2Cl_2 (10 mL) according to GP 7 for 3 h. The mixture was taken up with EtOAc and the crude product obtained after usual aqueous work-up was crystallized from CH_2Cl_2 / pentane to give **109 c** as a white solid, which was finally purified with preparative HPLC. Yield 5.5 mg (72%, 55% over 5 steps from **103 c**). $R_f = 0.24$ acetone/hexanes 3:7; preparative HPLC: isocratic, 82% B for 30 min, $t_R = 16.8$ min, purity > 98%; analytical HPLC: gradient 20% → 100% B for 20 min, then isocratic 100% B for 5 min $t_R = 15.3$ min, purity > 98%; $[\alpha]_D^{20}$ 20.0 (c = 0.1, MeOH); ^1H NMR (600 MHz, $CDCl_3$): δ = –0.95 – –0.89 (m, 1 H), –0.41 – –0.33 (m, 1 H), –0.11 – 0.01 (m, 2 H), 0.05–0.09 (m, 1 H), 0.47–0.56 (m, 2 H), 0.86 (t, *J* = 7.1 Hz, 1 H), 0.89 (t, *J* = 7.4 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 1.03–1.09 (m, 2 H), 1.25–1.34 (m, 1 H), 1.30 (d, *J* = 7.1 Hz, 3 H), 1.52 (d, *J* = 6.9 Hz, 3 H), 1.66 (dd, *J* = 7.1 Hz, 1.7 Hz, 3 H), 1.79 (q, *J* = 11.7 Hz, 1 H), 1.84 (bs, 1 H), 1.87–1.95 (m, 1 H), 1.97–2.04 (m, 1 H), 2.31–2.37 (m, 1 H), 2.96–3.05 (m, 1 H), 3.03 (dq, *J* = 11.2 Hz, 6.8 Hz, 1 H), 3.06–3.20 (m, 2 H), 3.21–3.30 (m, 2 H), 3.45–3.53 (m, 1 H), 3.66 (dq, *J* = 7.1 Hz, 5.0 Hz, 1 H), 3.72–3.83 (m, 1 H), 3.89–4.02 (m, 2 H), 4.27 (dd, *J* = 10.6 Hz, 5.9 Hz, 1 H), 4.35 (t, *J* = 10.4 Hz, 1 H), 4.50 (dd, *J* = 9.3 Hz, 4.7 Hz, 1 H), 4.54 (dd, *J* = 9.2 Hz, 2.4 Hz, 1 H), 4.63 (t, *J* = 9.3 Hz, 1 H), 5.15 (td, *J* = 9.1 Hz, 6.2 Hz, 1 H), 5.25 (tt, *J* = 8.8 Hz, 1.8 Hz, 1 H), 5.35 (qd, *J* = 6.9 Hz, 2.3 Hz, 1 H), 5.61 (dq, *J* = 10.8 Hz, 6.9 Hz, 1 H), 5.95, 6.09 (2 × d, *J* = 4.5 Hz, *J* = 4.7 Hz, 1 H), 6.37, 6.79 (2 × d, *J* = 4.9 Hz, *J* = 4.7 Hz, 1 H), 6.43 (d, *J* = 7.7 Hz, 1 H), 6.88 (d, *J* = 9.8 Hz, 1 H), 7.07–7.32 (m, 12 H), 7.41 (d, *J* = 9.6 Hz, 1 H), 9.17 (d, *J* = 9.2 Hz, 1 H); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 8.69 (–, q, *J* = 6.2 Hz), 9.84(–, q, *J* = 4.7 Hz), 10.41 (+), 11.07 (+), 11.84 (+), 13.31, 13.60, 14.10, 14.80, 17.13 (–), 17.93 (+), 18.57(+, q, *J* = 38.5 Hz), 19.47(+, q, *J* = 36.9 Hz), 22.68 (+), 25.05 (+), 29.64 (–), 29.69 (–), 31.91 (–), 34.56 (–), 35.51 (–), 36.67 (–), 36.71 (+), 37.86 (+) 39.42 (+), 41.76, 42.11, 43.45, 44.57, 51.44 (+), 52.68 (+), 52.75 (–), 54.65 (+), 54.93 (+), 59.86 (+), 60.17 (+), 61.36 (+), 64.28, 66.56, 69.07 (+), 103.29 (+), 109.25 (+), 119.28, 121.63, 126.93 (+), 127.31 (+), 127.44 (+), 127.55 (+), 127.63 (+), 128.19 (+), 128.45 (+), 128.67 (+), 141.68 (Cquat), 141.97 (Cquat), 159.14 (Cquat), 168.72 (Cquat), 168.92 (Cquat), 170.07 (Cquat), 170.68 (Cquat), 171.21 (Cquat), 171.69 (Cquat), 172.65 (Cquat); HRMS: M+H]$^+$ calculated 1175.48021 measured 1175.47956; M+NH$_4$]$^+$ calculated 1192.50676 measured 1192.50686; M+Na]$^+$ calculated 1197.46216 measured 1197.46120.

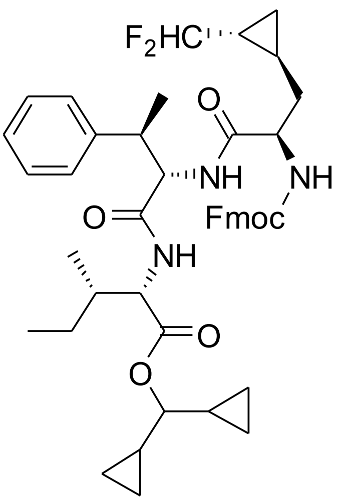
10.2. (Difluoromethylcyclopropyl)alanyl-Hormaomycin

N-Fmoc-(2R,1'R,2'R)-3-(2'-Difluoromethylcyclopropyl)alanine (Fmoc-(R)dFmcpA-OH, **97 b***)*: A solution of Fmoc-OSu (459 mg, 1.36 mmol) in acetone (7 mL) was added to a vigorously stirred solution of (2*R*,1'*R*,2'*R*)-3-(2'-difluoromethyl cyclopropyl) alanine ***R*-96 b** (225 mg, 1.14 mmol) and $NaHCO_3$ (0.202 g, 2.40 mmol) in water (5 mL) (if a precipitate formed, acetone and/or water was added to obtain a homogeneous solution) and stirring continued for an additional 3 h. Acetone was then removed under reduced pressure, and the pH of the residual water solution was adjusted to 1 with aq. 1 M $KHSO_4$. The resulting emulsion was extracted with diethyl ether (30 mL) and the ethereal layer was back-extracted with 3% aq. $NaHCO_3$ (5 × 10 mL, TLC control for the completeness of extraction was necessary). The combined aqueous fractions were washed with diethyl ether (2 × 10 mL), acidified to pH 2 with aq. 1 M $KHSO_4$, and the resulting emulsion was extracted with diethyl ether (4 × 10 mL). The organic phase was washed with aq. 1 M $KHSO_4$ (2 × 10 mL), water (3 × 10 mL), brine (2 × 5 mL), dried, filtered and concentrated under reduced pressure. The residue was triturated with cold pentane and filtered. The resulting extremely viscous oil was dried at 0.02 Torr for prolonged time to give the target protected amino acid **97 b** (390 mg, 0.930 mmol, 78%) as a colorless foam. $R_f = 0.08$ (EtOAc/hexane 1:1); m.p. (softening) 50–57 °C; $[\alpha]_D^{20}$ –56.7 (c = 0.36, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): 0.38–0.44 + 0.57–0.64 + 0.79–0.86 (3 × m, 1 H), 0.91–0.97 + 1.00–1.09 (2 × m, 1 H), 1.14–1.22 + 1.26–1.34 (2 × m, 1 H), 1.35–1.53 + 1.85–1.88 (2 × m, 1 H), 1.80–1.85 (m, 1 H), 3.75–3.79 + 4.53–4.67 (2 × m, 1 H), 3.95–4.01 + 4.47–4.52 (2 × m, 1 H), 4.16–4.23 (m, 1 H), 4.36–4.47 (m, 1 H), 5.52 (d, $J = 7.9$ Hz, 0.7 H), 6.76 (d, $J = 5.9$ Hz, 0.3 H), 7.27–7.31 (m, 2 H), 7.35–7.41 (m, 2 H), 7.51 (t, $J = 8.1$ Hz, 0.6 H), 7.58 (t, $J = 8.4$ Hz, 1.4 H), 7.74 (d, $J = 7.4$ Hz, 2 H), 7.85–8.65 (bs, 1 H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 7.94 (–), 11.46 (+), 19.73 (+, q, $J = 37.0$ Hz), 34.65 (–), 47.10 (+), 53.48 + 53.82 (+), 67.14 + 67.87 (–), 120.00 (+), 124.97 (+), 125.96 (–, q, $J = 272.4$ Hz), 127.07 (+), 127.76 (+), 141.32 (C_{quat}), 143.51 (C_{quat}), 143.76 (C_{quat}), 155.79 + 156.71 (C_{quat}), 174.96 + 175.79 (C_{quat}); MS-ESI: (positive)

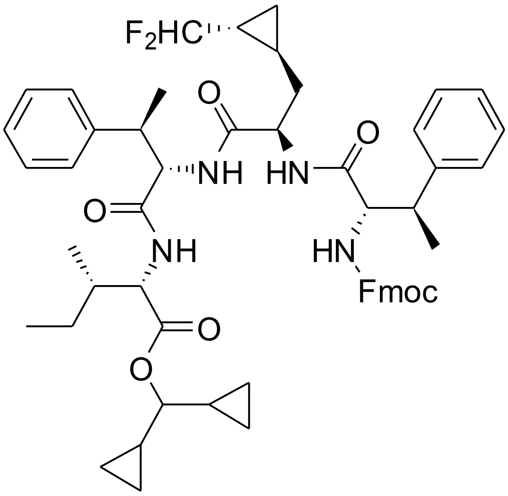


m/z (%): 1302 (35, 3M-H+2Na]$^+$), 861 (100, 2M+Na]$^+$), 442 (M+Na]$^+$), (negative) m/z (%): 837 (100, 2M–H]$^-$), 418 (16, M–H]$^-$), 222 (14, M–FmOH–H]$^-$), 196 (15, FmOH]$^-$).

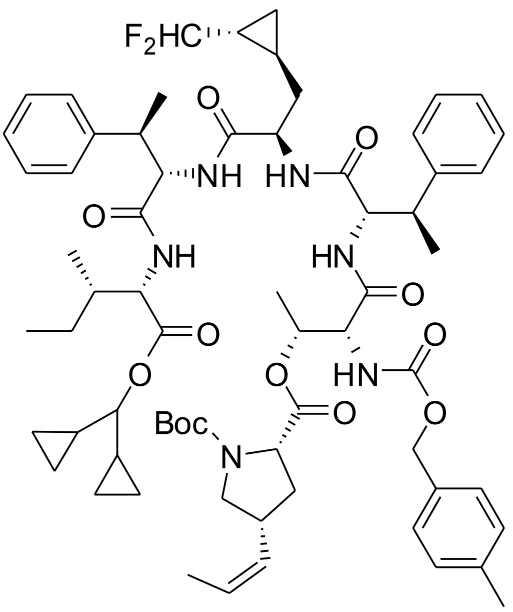
*Fmoc-(R)dFmcpA-MeF-Ile-ODCPM (***98** b*)*: Dipeptide **60** (434 mg, 834 μmol) was taken up with EtOAc (20 mL) and hydrogenated over 10% Pd/C (250 mg) under ambient pressure of hydrogen for 2 h. The reaction mixture was filtered through a pad of Celite® and concentrated under reduced pressure to give deprotected dipeptide **62**, which was directly used for the coupling with Fmoc-(*R*)dFmcpA-OH **97 b** (360 mg, 860 μmol), using EDC (172 mg, 896 μmol), HOAt (120 mg, 883 μmol) and TMP (310 μL, 2.5 mmol) according to GP 2. During reaction the white precipitate appeared. The mixture was diluted with diethyl ether (50 mL), stirred for 30 min and filtered, giving the crude product (1st crop, 173 mg after drying *in vacuo*). The filtrate was concentrated under reduced pressure at ambient temperature and diluted with diethyl ether (20 mL) and subjected usual aqueous work-up according to GP 2 to give the last portion of crude product (2nd crop, 112 mg after drying *in vacuo*). Combined crude product was re-crystallized from THF/hexane and the resulting off-white solid was dissolved in chloroform (50 mL) and subjected usual aqueous work-up according to GP 2 to give the pure tripeptide **98 b** as white solid (253 mg, 320 μmol, 65%). $R_f = 0.52$; EtOAc/hexane 2:3; m.p. 151–155 °C; $[\alpha]_D^{20}$ –3,8 (c = 0.26, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.28–0.40 (m, 4 H), 0.43–0.53 (m, 2 H), 0.57–0.66 (m, 3 H), 0.88 (d, J = 6.7 Hz, 3 H), 0.90 (t, J = 7.4 Hz, 3 H), 0.94–1.00 (m, 1 H), 1.03–1.13 (m, 2 H), 1.13–1.22 (m, 2 H), 1.30–1.50 (m, 2 H), 1.41 (d, J = 6.8 Hz, 3 H), 1.58–1.70 (m, 1 H), 1.81–1.97 (m, 2 H), 3.28–3.38 (m, 1 H), 3.86 (t, J = 8.4 Hz, 1 H), 4.28 (t, J = 6.9 Hz, 1 H), 4.39–4.48 (m, 3 H), 4.48–4.57 (m, 1 H), 4.76 (t, J = 8.0 Hz, 1 H), 5.76 (d, J = 7.7 Hz, 1 H), 6.40 (d, J = 7.5 Hz, 1 H), 7.11 (d, J = 8.1 Hz, 1 H), 7.20–7.34 (m, 5 H), 7.35 (t, J = 7.4 Hz, 2 H), 7.46 (t, J = 7.4 Hz, 2 H), 7.60 (t, J = 8.0 Hz, 2 H), 7.79 (d, J = 7.5 Hz, 2 H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 2.57, 2.90, 8.18, 11.62, 14.39, 14.66, 15.07, 15.07, 16.86, 19.70 (t, J = 37.1 Hz), 25.14, 35.08, 38.13, 42.05, 47.07, 54.69,56.46, 58.79, 67.18, 83.44, 119.94, 124.99, 127.06, 127.55, 127.71, 128.54, 141.23, 141.28, 141.70, 143.57, 143.78, 155.95, 169.64, 170.55, 170.94; HRMS: for M+H]$^+$ calculated 770.33752, found 770.39756.



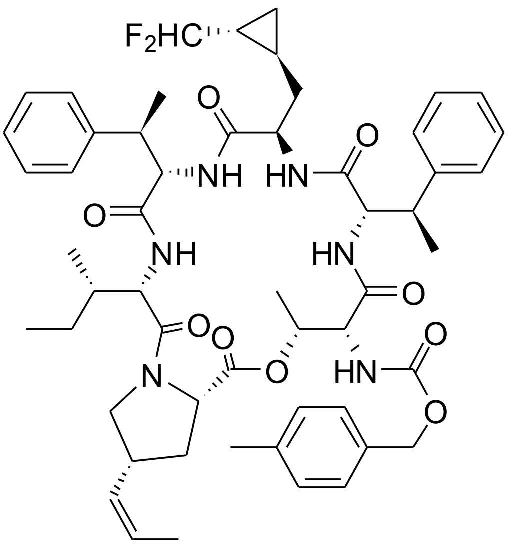
*Fmoc-MeF-(R)dFmcpA-MeF-Ile-ODCPM (***100 b***)*: The tripeptide **98 b** (394 mg, 500 µmol) was deprotected according to GP 1 and the resulting *C*-protected tripeptide **99 b** was then directly coupled with Fmoc-MeF-OH **64** (211 mg, 525 µmol) according to GP 2 using EDC (99 mg, 518 µmol), HOAt (70 mg, 512 µmol) and TMP (175 mg, 1440 µmol) in CH_2Cl_2 (3 mL). After 16 h the reaction mixture was diluted with chloroform (50 mL) and subjected usual aqueous work-up according to GP 2 to give the crude tetrapeptide, which was twice re-crystallized from THF/hexane, giving the pure target tetrapeptide **100 b** as off-white solid (440 mg, 463 µmol, 81%). R_f = 0.29; $CHCl_3$/MeOH 70:1; m.p. 210–215 °C (decomp.); $[\alpha]_D^{20}$ –16.0 (c=0.5 in THF); ^{1}H NMR (500 MHz, [D8]THF): δ = 0.23–0.32 (m, 4 H), 0.32–0.39 (m, 2 H), 0.40–0.55 (m, 4 H), 0.82 (d, *J* = 7.0 Hz, 3 H), 0.83 (d, *J* = 7.3 Hz, 3 H), 0.82–0.91 (m, 1 H), 0.94–1.05 (m, 3 H), 1.08–1.19 (m, 2 H), 1.22 (d, *J* = 7.1 Hz, 3 H), 1.32 (d, *J* = 7.0 Hz, 3 H), 1.36–1.47 (m, 2 H), 2.63 (bs, 1 H), 3.17 (dq, *J* = 9.2 Hz, 7.2 Hz, 1 H), 3.29 (dq, *J* = 7.2 Hz, 7.1 Hz, 1 H), 3.82 (t, *J* = 8.28, 1 H), 4.18–4.25 (m, 2 H), 4.25–4.31 (m, 1 H), 4.33–4.40 (m, 2 H), 4.41–4.48 (m, 1 H), 4.65–4.71 (m, 1 H), 5.40 (td, *J* = 57.5 Hz, 4.8 Hz, 1 H), 7.02–7.08 (m, 1 H), 7.09–7.29 (m, 12 H), 7.30–7.36 (m, 3 H), 7.49 (t, *J* = 9.3 Hz, 2 H), 7.63 (d, *J* = 7.5 Hz, 1 H), 7.67 (d, *J* = 7.7 Hz, 1 H), 7.76 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (125.7 MHz, [D8]THF): δ =2.76 (–), 2.98 (–), 3.04 (–), 3.21 (–), 7.67 (–), 11.68 (+), 11.99 (+, t, *J* = 4.2 Hz), 15.11 (+), 15.36 (+), 15.60 (+), 17.04 (+), 18.02 (+), 21.13 (+, t, *J* = 27.1 Hz), 25.80 (–), 36.03 (–), 38.53 (+), 42.03 (+), 43.33 (+), 48.06 (+), 53.44 (+), 56.91 (+), 58.78 (+), 61.62 (+), 67.28 (–), 82.82 (+), 118.34 (+, t, *J* = 236.9 Hz), 120.34 (+), 120.35 (+), 125.92 (+), 125.96 (+), 126.83 (+), 127.17 (+), 127.57 (+), 127.60 (+), 128.08 (+), 128.49 (+), 128.59 (+), 128.69 (+), 128.84 (+), 142.02 (–), 142.05 (–), 143.87 (–), 144.12 (–), 145.01 (–), 145.10 (–), 157.27 (–), 170.64 (–), 171.46 (–), 171.50 (–); HRMS: for $C_{55}H_{65}O_7N_4F_2$ ($[M+H]^+$) calculated: 931.48158; measured: 931.48094.



Boc-(4-Pe)Pro-[MeZ-a-Thr]-MeF-(S)dFmcpA-MeF-Ile-ODCPM (**101 b**): The tetrapeptide **100 b** (200 mg, 215 µmol) was *N*-deprotected according to GP 1 with diethylamine (5 mL) and THF (5 mL), taken up with anhydrous CH_2Cl_2 (5 mL), the solution of the ester acid **71** (119 mg, 235 µmol), HATU (98 mg, 256 µmol) and HOAt (32 mg, 235µmol) in CH_2Cl_2 (3 mL) was added, and the reaction mixture was cooled to 4 °C. After this, a solution of DIEA (30 mg, 225 µmol) and TMP (77 mg, 635 µmol) in CH_2Cl_2 (2 mL) was added at the same temperature within 5 min. The temperature was allowed to reach 20 °C, and stirring was continued for an additional 15 h. After aqueous work-up according to GP 2 and two recrystallizations from EtOAc/hexane (1:2), the crude hexadepsipeptide was finally purified with column chromatography (silica gel). All impurities were eluted out with EtOAc/hexane (1:1) and the substance was eluted out with methanol. After solvent evaporation under reduced pressure *C*-deprotected hexadepsipeptide **102 b** (236 mg, 198 µmol, 90%) was obtained as a colorless solid. R_f = 0.46 (THF); $[\alpha]_D^{20}$ –18.5 (c=0.2, THF); ^{1}H NMR (600 MHz, [D8]THF): δ = 0.23–0.30 (m, 1 H), 0.30–0.37 (m, 0.5 H), 0.37–0.43 (m, 0.5 H), 0.44–0.53 (m, 1 H), 0.79–1.02 (m, 2 H) 0.84 (d, *J* = 7.3 Hz, 3 H), 0.86 (*d, J* = 7.1 Hz, 3 H), 1.13 (d, *J* = 6.1 Hz, 2 H), 1.16 (d, *J* = 5.9 Hz, 2 H), 1.20 (t, *J* = 5.4 Hz, 2 H), 1.28 (t, *J* = 6.0 Hz, 2 H), 1.37 + 1.39 (2 s, 9 H), 1.42–1.53 (m, 2 H), 1.64 (t, *J* = 6.7 Hz, 2 H), 1.78–1.87 (m, 1 H), 2.26–2.33 (m, 1 H), 2.27 (s, 3 H), 2.91–3.60 (bs, 1 H), 2.93 (t, *J* = 10.3 Hz, 1 H), 2.99 (t, *J* = 10.2 Hz, 1 H), 3.05 (q, *J* = 8.6 Hz, 1 H), 3.16 (q, *J* = 8.7 Hz, 1 H), 3.17–3.28 (m, 2 H), 3.35–3.46 (m, 2 H), 3.64 (dd, *J* = 10.0 Hz, 7.5 Hz, 1 H), 4.07–4.35 (m, 3 H), 4.55–4.72 (m, 3 H), 4.91 (d, *J* = 12.3 Hz, 1 H), 5.04 (dd, *J* = 24.1 Hz, 12.2 Hz, 1 H), 5.19–5.36 (m, 3 H), 5.45–5.53 (m, 1 H), 6.90 (d, *J* = 8.1 Hz, 0.6 H), 6.97 (d, *J* = 8.7 Hz, 0.4 H), 7.03–7.29 (m, 14 H), 7.40 (d, *J* = 7.0 Hz, 0.5 H), 7.45 (d, *J* = 6.4 Hz, 0.5 H), 7.53–7.64 (m, 2 H), 7.93 (d, *J* = 5.4 Hz, 0.6 H), 7.97 (d, *J* = 6.1 Hz, 0.4 H); ^{13}C NMR (125.7 MHz, [D8]THF): δ = 7.79, 11.71, 11.96, 12.02, 12.99, 13.06, 15.78, 21.00, 21.01, 25.60, 25.89, 28.43, 28.49, 35.08, 35.38, 36.39, 36.64, 37.12, 37.67, 38.08, 41.30, 41.55, 42.38, 52.01, 52.45, 53.77, 53.88, 60.18, 67.74, 79.44, 80.04, 116.61, 118.49, 120.37, 126.39, 126.54, 126.76, 126.78, 127.09, 127.15, 128.37, 128.40, 128.57, 128.59, 128.77, 128.85, 129.43, 129.47, 130.69, 130.94, 134.93, 137.85, 143.87, 144.00, 153.38, 154.52, 156.96, 157.22, 169.91, 169.94, 170.87,

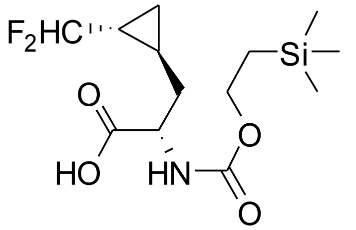


170.92, 171.35, 171.45, 171.93, 172.15, 172.41; MS-ESI: (positive) m/z (%) 1101.57 (100, M+H]$^+$).

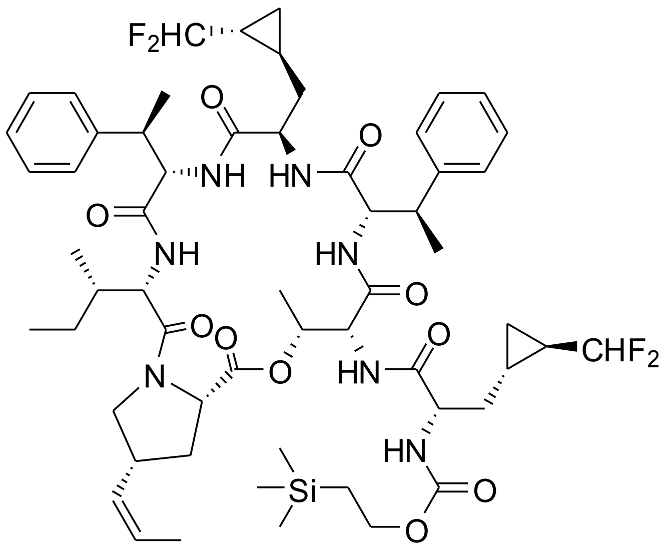


N-MeZ-protected cyclohexadepsipeptide **103 b** *(Cyclo-F$_2$6-MeZ)*: The hexadepsipeptide **101 b** (136 mg, 122 µmol) was ends-deprotected by treating with 2 M HCl solution in ethyl acetate (5 mL). The reaction mixture was stirred for 20 min in dark place (Al foil jacket) at ambient temperature and all volatiles were removed under reduced pressure *in vacuo* without any heating. The residue was triturated with anhydrous diethyl ether to give the hydrochloride of the deprotected material **102 b** as a colorless solid. HRMS for (M+H]$^+$): calculated 1001.51943, measured 1001.51859. The ends-deprotected hexadepsipeptide **102 b**, HATU (54 mg, 142 µmol) and HOAt (16 mg, 121 µmol) were dissolved in cold (4 °C, internal temperature) anhydrous CH_2Cl_2 (1,5 L), and the solution of DIEA (46 mg, 354 µmol) in CH_2Cl_2 (100 mL) was added dropwise within 1 h, the cooling bath was removed and the mixture was stirred for 2 h at ambient temperature. Then the mixture was cooled again to 4 °C (internal temperature), the second portions of HATU (54 mg, 142 µmol) and HOAt (16 mg, 121 µmol) were added, followed with dropwise addition of the solution of DIEA (46 mg, 354 µmol) in CH_2Cl_2 (100 mL) within 1 h. The cooling bath was removed and the mixture was stirred for 18 h at ambient temperature. The mixture was concentrated under reduced pressure, subjected to aqueous work-up according to GP 2 to give the crude protected cyclohexadepsipeptide (118 mg, 120 µmol, 98%) which was finally purified with the HPLC to give pure product **103 b** (72 mg, 73 µmol, 60%). Preparative HPLC: isocratic, 60% B for 8 min, then gradient 60%→100% B for 6 min, then isocratic 100% B for 11 min, t_R = 17.2 min, purity > 98%; analytical HPLC: isocratic 60% B for 10 min, then gradient 60% → 100% B for 20 min, then isocratic 100% B for 15 min t_R = 27.8 min, purity > 98%; $[\alpha]_D^{20}$ –20.0 (c = 0.15, THF); ^{1}H NMR (600 MHz, [D8]THF): δ = –0.05–0.02 (m, 1 H), 0.12–0.18 (m, 1 H), 0.27–0.34 (m, 1 H), 0.34–0.39 (m, 1 H), 0.74 (d, *J* = 6.6 Hz, 3 H), 0.79 (t, *J* = 7.5 Hz, 3 H), 1.10–1.24 (m, 2 H), 1.20 (d, *J* = 7.2, 3 H) 1.28 (d, *J* = 7.2 Hz, 3 H), 1.36–1.47 (m, 1 H), 1.49 (d, *J* = 6.9 Hz, 3 H), 1.60–1.70 (m, 1 H), 1.66 (dd, *J* = 1.7 Hz, 6.9 Hz, 3 H), 1.95–2.04 (m, 1 H), 2.12–2.18 (m, 1 H), 2.30 (s, 3 H), 2.88–2.96 (m, 1 H), 3.12–3.17 (m, 1 H), 3.22–3.31 (m, 1 H), 3.45–3.51 (m, 1 H), 3.70–3.76 (m, 1 H), 3.83–3.88 (m, 1 H), 4.17–4.23 (m, 1 H), 4.40–4.46 (m, 1 H), 4.52–4.70 (m, 4 H), 4.93–4.99 (m, 1 H), 4.99–5.02, 5.07–5.14 (2×m, 2 H), 5.27–5.33 (m, 1 H), 5.36–5.41 (m, 1 H), 5.51–5.58 (m, 1 H), 6.74–6.82 (m, 1 H), 7.07–7.22 (m, 9 H), 7.23–7.29 (m, 5 H), 7.30–7.40 (m, 1 H), 7.64 (d, *J* = 8.5 Hz, 1 H), 7.69 (d, *J* = 7.8 Hz, 1 H), 7.80–7.90, 8.18–8.22 (2×m, 1 H); ^{13}C NMR (125.7 MHz, [D8]THF): δ = 7.89 (–), 7.94 (–), 10.40 (+), 11.56, 11.61 (+), 13.15 (+), 13.20 (+), 15.32 (+), 18.45 (+), 18.60 (+), 21.07 (+), 20.45, 21.43 (+, t, *J* = 27.5 Hz), 30.42 (–), 31.12 (–), 34.85 (–), 35.95 (–), 36.07 (+), 37.29 (+), 39.19 (+), 46.26 (+), 52.52 (–), 54.81 (+), 55.01 (+), 58.88 (+), 60.25 (+), 60.66 (+), 61.70 (+), 73.01 (+), 118.17, 118.70 (+, t, *J* = 236.3 Hz), 126.81 (+), 126.90 (+), 126.96 (+), 127.55 (+), 128.07 (+), 128.47 (+), 128.50 (+), 128.59 (+), 128.65 (+), 128.72 (+), 128.94 (+), 129.46 (+), 129.71 (+), 130.70 (+), 135.35 (–), 137.67 (–), 143.81 (–), 144.84 (–), 156.58 (–), 168.96 (–), 170.94 (–), 171.04 (–), 171.35 (–), 172.90 (–), 172.90 (–); MS–ESI: positive – 1005.6 (100%, M+Na]$^{+}$); negative – 981.4 (100%, M–H]$^{-}$).

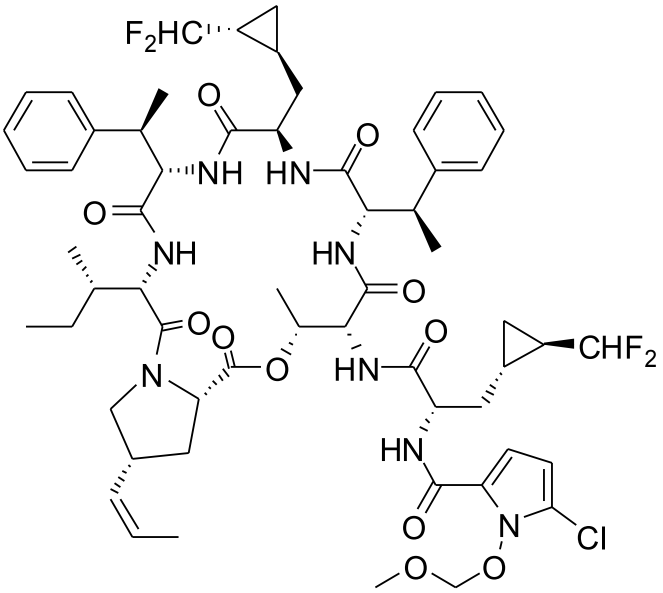
N-Teoc-(2S,1'S,2'R)-3-(2'-Difluoromethylcyclopropyl)alanine (Teoc-(S)dFmcpA-OH, **105 b***)*: A solution of TeocOSu (59 mg, 228 µmol) in acetone (1 mL) was added to a vigorously stirred solution of (2*S*,1'*S*,2'*R*)-3-(2'-difluoromethylcyclopropyl)alanine ***S*-96 b** (34 mg, 190 µmol) and $NaHCO_3$ (34 mg, 396 µmol) in water (1 mL) (if an emulsion formed, acetone and/or water was added to obtain a homogeneous solution), and stirring was continued for another 2 h. *N,N*-dimethylaminopropylamine (10 µL, 7.5 mg, 73 µmol) was then added. After an additional 10 min acetone was removed under reduced pressure and the pH of the residual water solution was adjusted to 2–3 with aq. 1 M $KHSO_4$. The resulting emulsion was extracted with diethyl ether (50 mL), and the ethereal layer was washed with aq. 1 M $KHSO_4$ (2 × 10 mL), water (3 × 10 mL), brine (2 × 5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was dried overnight *in vacuo* to give glass-like product **105 b** (41 mg, 127 µmol, 67%). R_f = 0.24 (EtOAc/hexane 1:3 +2% AcOH); $[\alpha]_D^{20}$ = 22.80 (c = 0.46, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, as cyclohexylammonium salt): δ = 0.01 (s, 9 H), 0.38–0.57 (m, 1 H), 0.65–0.80 (m, 1 H), 0.85–1.49 (m, 9 H), 1.50–1.85 (m, 5 H), 1.85–2.03 (m, 2 H), 2.72–3.00 (m, 1 H), 3.89–4.22 (m, 3 H), 5.50 (td, *J* = 57.6 Hz, 4.1 Hz, 1 H), 5.71 (d, *J* = 7.3 Hz, 1 H), 7.35 (bs, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$, as cyclohexylammonium salt): δ = –1.36, 7.24, 11.23, 17.39, 19.58 (t, *J* = 24.0 Hz), 24.04, 24.74, 30.67, 35.36, 50.21, 55.84, 62.78, 117.02 (t, *J* = 237.5 Hz), 156.25, 177.41.



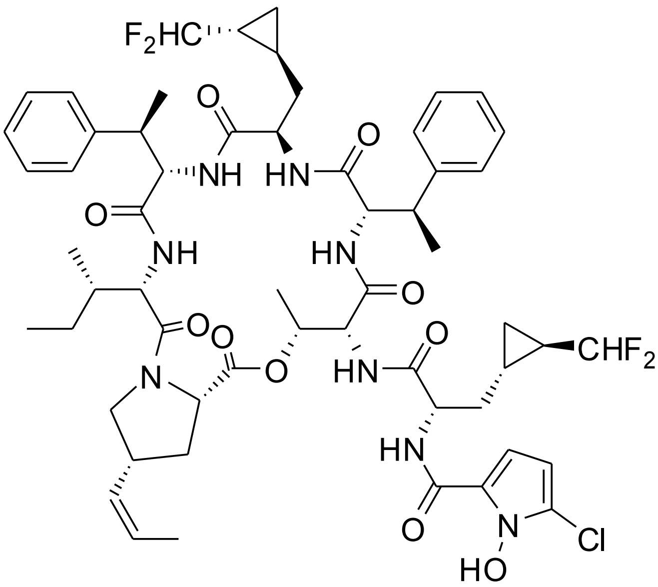
*Teoc-(S)dFmcpA-Cyclo-F$_2$6 (***106 b***)*: *N*-MeZ-protected cyclohexadepsipeptide **103 b** (62 mg, 63 µmol) was deprotected with 10% anisole in TFA (4 mL) in the dark at ambient temperature for 2 h, the residue was treated with toluene (5 mL), concentrated under reduced pressure and the residue was dried *in vacuo* at ambient temperature for 2 hours. The solution of Teoc-(*S*)dFmcpA-OH **105 b** (31 mg, 96 µmol), HATU (72 mg, 189 µmol) and HOAt (26 mg, 190 µmol) in CH_2Cl_2 (3 mL) was added at 4 °C, followed with DIEA (8.4 mg, 65 µmol) and TMP (69 mg, 568 µmol) solution in CH_2Cl_2 (5.5 mL) and the mixture was stirred at ambient temperature for 15 h. The reaction mixture was then diluted with diethyl ether (50 mL) and the crude product obtained after the usual aqueous work-up (GP 2) was purified by column chromatography (silica gel, eluted with EtOAc/hexane 1:1) to give Teoc-(*S*)dFmcpA-Cyclo-F$_2$6 (**106 b**) (53 mg, 46.5 µmol, 74%) as a colorless solid. $R_f = 0.34$, EtOAc/hexane 1:1; $[\alpha]_D^{20} = -7.0$ (c = 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.15– –0.02 (m, 2 H), 0.01–0.02 (m, 1 H), 0.05 (s, 9 H), 0.06–0.10 (m, 1 H), 0.28–0.42 (m, 2 H), 0.43–0.58 (m, 2 H), 0.78–0.88 (m, 2 H), 0.90 (t, *J* = 7.3 Hz, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 1.02 (t, *J* = 8.5Hz, 2 H), 1.07–1.20 (m, 3 H), 1.26 (d, *J* = 7.1 Hz, 3 H), 1.31 (d, *J* = 7.2 Hz, 3 H), 1.54 (d, *J* = 6.8 Hz, 3 H), 1.63 (d, *J* = 6.8 Hz, 3 H), 1.71 (dd, *J* = 11.8 Hz, 23.4 Hz, 1H), 1.86–1.95 (m, 1 H), 2.15–2.35 (m, 3 H), 3.11–3.27 (m, 1 H), 3.23 (t, *J* = 9.6 Hz, 1 H), 3.62–3.69 (m, 1 H), 3.71–3.82 (m, 1 H), 4.02–4.18 (m, 3 H), 4.20–4.30 (m, 1 H), 4.34–4.41 (m, 1 H), 4.48–4.57 (m, 1 H), 4.58–4.70 (m, 2 H), 4.74 (d, *J* = 8.9 Hz, 1 H), 5.17 (td, *J* = 60 Hz, 5.0 Hz, 1H), 5.19–5.25 (m, 1 H), 5.27–5.34 (m, 1 H), 5.47 (td, *J* = 55 Hz, 4.6 Hz, 1 H), 5.53–5.61 (d, *J* = 8.9 Hz, 1 H), 6.64 (d, *J* = 8.5 Hz, 1 H), 7.00–7.40 (m, 14H), 8.16 (s, 1 H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = –1.47 (+), 7.00 (–, t, *J* = 2.6 Hz), 7.44 (–, t, *J* = 4.2 Hz), 10.12 (+), 10.40 (+), 10.60 (+), 13.27 (+), 13.54 (+), 15.27 (+), 17.58 (–), 17.93 (+), 18.33 (+), 20.35 (+), 20.57 (+), 20.79 (+), 24.82 (–), 34.70 (–), 35.50 (–), 36.51 (+), 37.07 (+), 39.16 (+), 43.65 (+), 52.61 (–), 53.38 (+), 53.96 (+), 54.70 (+), 55.90 (+), 59.05 (+), 59.68 (+), 61.02 (+), 63.41 (–), 71.45 (+), 117.01 (+, t, *J* = 237.3 Hz), 117.24 (+, t, *J* = 237.7 Hz), 126.83 (+), 126.90 (+), 127.20 (+), 127.61 (+), 127.75 (+), 127.99 (+), 128.44 (+), 128.58 (+), 128.63 (+),141.79 (–), 156.34 (–), 168.38 (–), 170.09 (–), 170.75 (–), 171.17 (–), 171.27 (–),



171.90 (–); MS-ESI: (positive) m/z (%) 1163 (100, M+Na]$^{+}$), (negative) m/z (%) 1139 (100, M–H]$^{-}$).

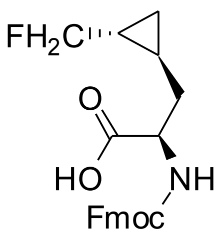


MOM-O-protected difluoromethylcyclopropylalanyl Hormaomycin (MOM-O-F_2Horm, **108 b***):* Teoc group was cleaved from the compound **106 b** (8.0 mg, 7.08 µmol) with TFA (0.6 mL) for 1 h. The mixture was concentrated under reduced pressure at 20 °C and then taken up with toluene (3 × 15 mL) which was distilled off to remove the last traces of TFA. The resulting deprotected depsipeptide **107 b** was coupled with *O*-MOM protected acid **81** (2.9 mg, 14.10 µmol) using HATU (5.4 mg, 14.20 µmol), DIEA (0.92 mg, 7.12 µmol) and TMP (5.14 mg, 42.42 µmol) in CH_2Cl_2 (1 mL) according to GP 6 for 2.5 h. The mixture was then taken up with Et_2O (20 mL) and the crude product obtained after usual aqueous work-up (GP 2) was crystallized from CH_2Cl_2 / pentane to give *O*-MOM protected difluoromethylcyclopropylalanyl Hormaomycin **108 b** (8.0 mg, 90%, R_f = 0.36 acetone/hexanes 1:2) as a colorless glass. ^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.47 – –0.37 (m, 2 H), 0.15–0.26 (m, 4 H), 0.45–0.55 (m, 2 H), 0.80–0.92 (m, 3 H), 0.87 (t, J = 7.3 Hz, 3 H),, 1.01 (d, J = 6.8 Hz, 3 H), 1.05–1.15 (m, 1 H), 1.20–1.28 (m, 2 H), 1.26 (d, J = 7.1 Hz, 3 H), 1.37 (d, J = 7.2 Hz, 3 H), 1.56 (d, J = 6.9 Hz, 3 H), 1.66 (d, J = 6.9Hz, 3 H), 1.70–1.82 (m, 3 H), 1.85–1.95 (m, 1 H), 2.31–2.38 (m, 1 H), 2.80–2.89 (m, 1 H), 3.20–3.30 (m, 2 H), 3.65–3.70 (m, 1 H), 3.73 (s, 3 H), 3.82–3.88 (m, 1 H), 3.91–3.99 (m, 1 H), 4.21–4.29 (m, 2 H), 4.62–4.73 (m, 3 H), 5.05 (td, J = 55.0 Hz, 5.0 Hz, 1 H), 5.08–5.14 (m, 1 H), 5.22–5.27 (m, 1 H), 5.30–5.37 (m, 1 H), 5.43–5.48 (m, 1 H), 5.52–5.59 (m, 2 H), 5.60–5.67 (m, 1 H), 6.12 (d, J = 4.7Hz, 1 H), 6.77–6.87 (m, 2 H), 7.02–7.10 (m, 3 H), 7.11–7.17 (m, 3 H), 7.20–7.28 (m, 3 H), 7.24–7.43 (m, 2 H), 7.55 (d, J = 9.5Hz, 1 H), 8.86 (d, J = 9.5Hz, 1 H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 6.82 (–, t, J = 3.4 Hz), 8.18 (–, t, J = 4.2 Hz), 10.01 (+, t, J = 4.4 Hz), 10.72 (+), 10.94 (+, t, J = 4.7 Hz), 13.31 (+), 13.50 (+), 14.09 (+), 15.07 (+), 17.45 (+), 18.55 (+), 19.69 (+, t, J = 26.9 Hz), 20.24 (+, t, J = 27.8 Hz), 24.94 (–), 26.90 (–), 29.68 (–), 35.51 (–), 36.00 (–), 36.72 (+), 37.07 (–), 38.62 (+), 39.54 (+), 43.14 (+), 50.96 (+), 52.65 (+), 52.72 (–), 54.70 (+), 54.90 (+), 59.26 (+), 59.41 (+), 59.97 (+), 61.44 (+), 70.11 (+), 104.24 (+), 106.05 (–), 111.15 (+), 116.70 (+, t, *J* = 237.5 Hz), 117.51 (+, t, *J* = 237.8 Hz), 119.36 (–), 121.83 (–), 126.72 (+), 126.96 (+), 127.31 (+), 127.51 (+), 127.53 (+), 128.25 (+), 128.37 (+), 128.64 (+), 142.14 (–), 142.54 (–), 158.11 (–), 168.84 (–), 169.99 (–), 170.17 (–), 170.92 (–), 171.32 (–), 171.43 (–), 171.90 (–); MS-ESI: (positive) m/z (%) 1205 (100, M+Na]$^+$), (negative) m/z (%) 1181 (100, M–H]$^–$).



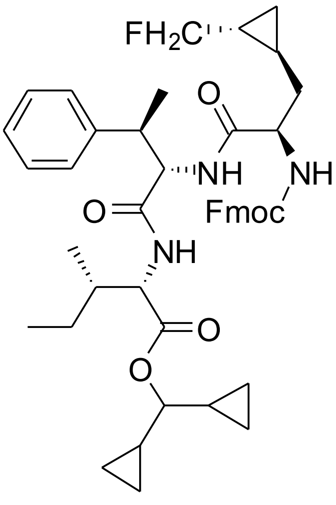
Difluoromethylcyclopropylalanyl Hormaomycin (F$_2$Horm, **109 b***)*: *O*-MOM protected difluoromethylcyclopropylalanyl Hormaomycin **108 b** (35 mg, 29.5 µmol) was deprotected using MgBr$_2$ × Et$_2$O (204 mg, 788 µmol) and EtSH (50 µL, 0.7 mmol) in CH$_2$Cl$_2$ (17 mL) according to GP 7 for 3 h. The mixture was taken up with EtOAc and the crude product obtained after usual aqueous work-up was crystallized from CH$_2$Cl$_2$ / pentane to give **109 b** (33 mg) as a white solid, which was finally purified with preparative HPLC. R$_f$ = 0.24 acetone/ hexanes 3:7; preparative HPLC: isocratic, 82% B for 25 min, t$_R$ = 15.4 min, purity > 98%; analytical HPLC: isocratic 60% B for 10 min, then gradient 60% → 100% B for 20 min, then isocratic 100% B for 15 min t$_R$ = 28.8 min, purity > 98%; [α]$_D^{20}$ 20.0 (c = 0.1, MeOH); ^{1}H NMR (250 Mhz, CDCl$_3$): δ = –0.62 – –0.50 (m, 2 H), –0.18 – –0.08 (m, 1 H), –0.07–0.01 (m, 1 H), 0.31–0.50 (m, 2 H), 0.86 (d, *J* = 6.3 Hz, 3 H), 0.92 (t, *J* = 7.3 Hz, 3 H), 1.03 (d, *J* = 6.5 Hz, 3 H), 1.11–1.19 (m, 2 H), 1.21–1.40 (m, 5 H), 1.47 (d, *J* = 7.1 Hz, 3 H), 1.54 (d, *J* = 6.8 Hz, 3 H), 1.69 (m, *J* = 6.7 Hz, 3 H), 1.78–1.85 (m, 2 H), 1.91–2.05 (m, 2 H), 2.34 (dd, *J* = 7.1 Hz, 7.4 Hz, 2 H), 2.95–3.17 (m, 1 H), 3.18–3.32 (m, 1 H), 3.33–3.59 (m, 3 H), 3.70 (dd, *J* = 4.7Hz, 6.7 Hz, 1 H), 3.91–4.47 (m, 3 H), 4.51–4.75 (m, 3 H), 5.02–5.18 (m, 1 H), 5.22–5.42 (m, 2 H), 5.56–5.73 (m, 1 H), 6.14 (d, *J* = 4.6 Hz, 1 H), 6.57–6.78 (m, 2 H), 6.82 (d, *J* = 4.7 Hz, 1 H), 6.98 (d, *J* = 9.8 Hz, 1 H), 7.10–7.37 (m, 10 H), 7.90 (d, *J* = 9.3 Hz, 1 H), 9.17 (d, *J* = 8.9 Hz, 1 H); ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 6.82 (–), 8.18 (–), 10.43 (+), 13.33 (+), 14.92 (+), 17.18 (+), 17.94 (+), 18.72 (+), 19.65 (+), 20.02 (+), 22.68 (+), 24.98 (+), 29.11 (+), 29.35 (–), 29.68 (–), 31.42 (–), 31.91 (–), 33.66 (–), 35.53 (+), 36.64 (–), 37.62 (+), 39.14 (+), 41.63 (+), 47.03 (+), 51.87 (+), 52.65 (–), 52.88 (+), 54.67 (+), 54.85 (+), 59.43 (+), 61.03 (+), 61.33 (+), 69.11 (+), 103.62 (+, t, *J* = 235.7 Hz), 109.46 (+, t, *J* = 237.3 Hz), 111.15 (+), 119.13 (–), 121.67 (–), 126.78 (+), 127.23 (+), 127.45 (+), 127.64 (+), 127.94 (+), 128.20 (+), 128.49 (+), 128.87 (+), 141.70 (–), 141.88 (–), 168.56 (–), 169.03 (–), 170.10 (–), 170.45 (–), 171.39 (–), 171.63 (–), 171.90 (–), 172.62 (–); MS-ESI: (positive) m/z (%) 1161 (100, M+Na]$^+$), (negative) m/z (%) 1137 (100, M–H]$^-$).

10.3. (Monofluoromethylcyclopropyl)alanyl-Hormaomycin

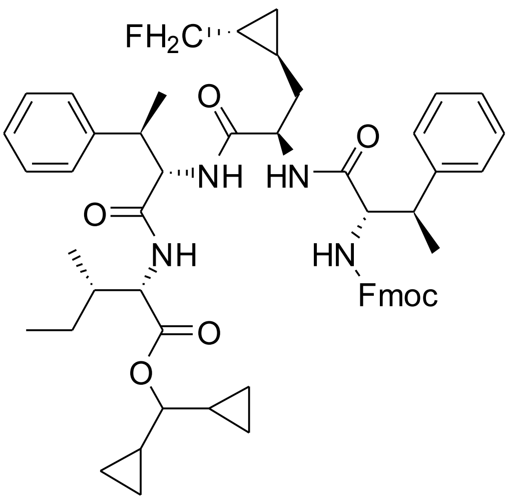


N-Fmoc-(2R,1'R,2'R)-3-(2'-Monofluoromethylcyclopropyl)alanine (Fmoc-(R)mFmcpA-OH, **97 a***)*: A solution of Fmoc-OSu (459 mg, 1.36 mmol) in acetone (7 mL) was added to a vigorously stirred solution of (2*R*,1'*R*,2'*R*)-3-(2'-monofluoromethyl cyclopropyl) alanine ***R*-96 a** (225 mg, 1.14 mmol) and NaHCO$_3$ (0.202 g, 2.40 mmol) in water (5 mL) (if a precipitate formed, acetone and/or water was added to obtain a homogeneous solution) and stirring continued for an additional 3 h. Acetone was then removed under reduced pressure, and the pH of the residual water solution was adjusted to 1 with aq. 1 M KHSO$_4$. The resulting emulsion was extracted with diethyl ether (30 mL) and the ethereal layer was back-extracted with aq. 3% NaHCO$_3$ (5 × 10 mL). The combined aqueous fractions were washed with diethyl ether (2 × 10 mL), acidified to pH 2 with aq. 1 M KHSO$_4$, and the resulting emulsion was extracted with diethyl ether (4 × 10 mL). The organic phase was washed with aq. 1 M KHSO$_4$ (2 × 10 mL), water (3 × 10 mL), brine (2 × 5 mL), dried, filtered and concentrated under reduced pressure. The residue was triturated with cold pentane and filtered. The resulting extremely viscous oil was dried at 0.02 Torr for prolonged time to give the target protected amino acid **97 a** (390 mg, 0.930 mmol, 73%) as a colorless foam. R_f=0.08 (EtOAc/hexane 1:1); m.p. (softening) 50–57 °C; $[\alpha]_D^{20}$ –56.7 (c=0.36, CHCl$_3$); ^{1}H NMR (600 MHz, CDCl$_3$): 0.38–0.44 + 0.57–0.64 + 0.79–0.86 (3 × m, 1 H), 0.91–0.97 + 1.00–1.09 (2 × m, 1 H), 1.14–1.22 + 1.26–1.34 (2 × m, 1 H), 1.35–1.53 + 1.85–1.88 (2 × m, 1 H), 1.80–1.85 (m, 1 H), 3.75–3.79 + 4.53–4.67 (2 × m, 1 H), 3.95–4.01 + 4.47–4.52 (2 × m, 1 H), 4.16–4.23 (m, 1 H), 4.36–4.47 (m, 1 H), 5.52 (d, *J* = 7.9 Hz, 0.7 H), 6.76 (d, *J* = 5.9 Hz, 0.3 H), 7.27–7.31 (m, 2 H), 7.35–7.41 (m, 2 H), 7.51 (t, J = 8.1 Hz, 0.6 H), 7.58 (t, J = 8.4 Hz, 1.4 H), 7.74 (d, *J* = 7.4 Hz, 2 H), 7.85–8.65 (bs, 1 H); ^{13}C NMR (125.7 MHz, CDCl$_3$): δ = 7.94 (–), 11.46 (+), 19.73 (+, d, *J* = 37.0 Hz), 34.65 (–), 47.10 (+), 53.48 + 53.82 (+), 67.14 + 67.87 (–), 120.00 (+), 124.97 (+), 125.96 (–, d, *J* = 272.4 Hz), 127.07 (+), 127.76 (+), 141.32 (C$_{quat}$), 143.51 (C$_{quat}$), 143.76 (C$_{quat}$), 155.79 + 156.71 (C$_{quat}$), 174.96 + 175.79 (C$_{quat}$); MS-ESI: (positive) m/z (%): 1302 (35, 3M-H+2Na]$^+$), 861 (100, 2M+Na]$^+$), 442 (M+Na]$^+$), (negative) m/z (%): 837 (100, 2M–H]$^-$), 418 (16, M–H]$^-$), 222 (14, M–FmOH–H]$^-$), 196 (15, FmOH]$^-$).

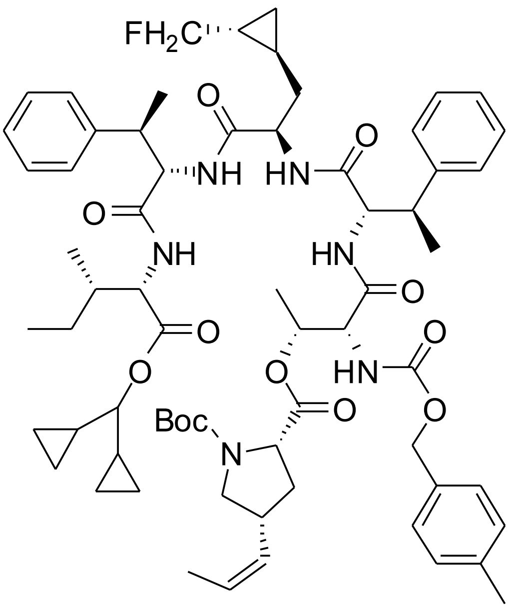
*Fmoc-(R)mFmcpA-MeF-Ile-ODCPM (***98 a***)*: Dipeptide **60** (434 mg, 834 µmol) was taken up with EtOAc (20 mL) and hydrogenated over 10% Pd/C (250 mg) under ambient pressure of hydrogen for 2 h. The reaction mixture was filtered through a pad of Celite® and concentrated under reduced pressure to give deprotected dipeptide **62**, which was directly used for the coupling with Fmoc-(*R*)mFmcpA-OH **97 a** (360 mg, 860 µmol), using EDC (172 mg, 896 µmol), HOAt (120 mg, 883 µmol) and TMP (310 µL, 2.5 mmol) according to GP 2. The mixture was diluted with chloroform (50 mL) and subjected usual aqueous work-up according to GP 2 to give the pure tripeptide **98 a** as white solid (535 mg, 679 µmol, 72%). $R_f = 0.52$; EtOAc/hexane 2:3; m.p. 151–155°C; $[\alpha]_D^{20}$ –3,8 (*c* =0.26, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$): δ = 0.28–0.40 (m, 4 H), 0.43–0.53 (m, 2 H), 0.57–0.66 (m, 3 H), 0.88 (d, *J* = 6.7 Hz, 3 H), 0.90 (t, *J* = 7.4 Hz, 3 H), 0.94–1.00 (m, 1 H), 1.03–1.13 (m, 2 H), 1.13–1.22 (m, 2 H), 1.30–1.50 (m, 2 H), 1.41 (d, *J* = 6.8 Hz, 3 H), 1.58–1.70 (m, 1 H), 1.81–1.97 (m, 2 H), 3.28–3.38 (m, 1 H), 3.86 (t, *J* = 8.4 Hz, 1 H), 4.28 (t, *J* = 6.9 Hz, 1 H), 4.39–4.48 (m, 3 H), 4.48–4.57 (m, 1 H), 4.76 (t, *J* = 8.0 Hz, 1 H), 5.76 (d, *J* = 7.7 Hz, 1 H), 6.40 (d, *J* = 7.5 Hz, 1 H), 7.11 (d, *J* = 8.1 Hz, 1 H), 7.20–7.34 (m, 5 H), 7.35 (t, *J* = 7.4 Hz, 2 H), 7.46 (t, *J* = 7.4 Hz, 2 H), 7.60 (t, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 7.5 Hz, 2 H); ^{13}C NMR (125.7 MHz, CDCl$_3$) δ = 2.57; 2.90, 8.18, 11.62,14.39, 14.66, 15.07, 15.07, 16.86, 19.70 (q, *J*=37.1 Hz), 25.14, 35.08, 38.13, 42.05, 47.07, 54.69,56.46, 58.79, 67.18, 83.44, 119.94, 124.99, 127.06, 127.55, 127.71, 128.54, 141.23, 141.28, 141.70, 143.57, 143.78, 155.95, 169.64, 170.55, 170.94.



*Fmoc-MeF-(R)mFmcpA-MeF-Ile-ODCPM (***100 a***)*: The tripeptide **98 a** (394 mg, 500 µmol) was deprotected according to GP 1 and the resulting *C*-protected tripeptide **99 a** was then directly coupled with Fmoc-MeF-OH **64** (211 mg, 525 µmol) according to GP 2 using EDC (99 mg, 518 µmol), HOAt (70 mg, 512 µmol) and TMP (175 mg, 1440 µmol) in CH$_2$Cl$_2$ (3 mL). After 16 h the reaction mixture was diluted with chloroform (50 mL) and subjected usual aqueous work-up according to GP 2 to give the crude

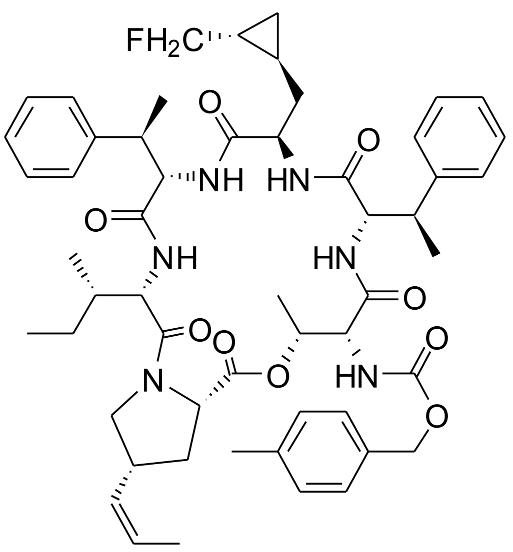


tetrapeptide, which was twice re-crystallized from THF/hexane, giving the pure target tetrapeptide **100 a** as off-white solid (440 mg, 463 µmol, 88%). R_f = 0.29; $CHCl_3$/MeOH 70:1; m.p. 210–215 °C (decomp.); $[\alpha]_D^{20}$ –26,3 (*c* = 0.32, THF); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.22–0.36 (m, 4 H), 0.41 (t, *J* = 8.9 Hz, 3 H), 0.48–0.61 (m, 2 H), 0.62–0.71 (m, 1 H), 0.76 (d, *J* = 6.9 Hz, 3 H), 0.82 (t, *J* = 7.3 Hz, 3 H), 0.92–1.09 (m, 4 H), 1.09–1.18 (m, 1 H), 1.22–1.46 (m, 2 H) 1.26 (d, *J* = 6.9 Hz, 3 H), 1.39 (d, *J* = 6.6 Hz, 3 H), 1.71–1.89 (m, 1 H), 3.09–3.36 (m, 3 H), 3.81 (t, *J* = 8.4 Hz, 1 H), 4.15–4.33 (m, 3 H), 4.35–4.64 (m, 3 H), 4.62 (t, *J* = 8.3 Hz, 1 H), 5.95 (d, *J* = 7.1 Hz, 1 H), 6.40 (d, *J* = 7.4 Hz, 1 H), 7.08–7.45 (m, 16 H), 7.57 (t, *J* = 8.9 Hz, 2 H), 7.76 (d, *J* = 7.3 Hz, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 3.3 (–), 3.5 (–), 3.6 (–), 3.7 (–), 12.2 (+), 15.6 (+), 15.9 (+), 16.1 (+), 17.7 (+), 18.7 (+), 18.9 (–), 23.2 (+), 26.2 (–), 35.0 (–), 39.1 (+), 42.8 (+), 44.1 (+), 48.5 (+), 52.8 (+), 57.4 (+), 59.3 (+), 60.2 (+), 62.1 (+), 67.8 (–), 83.4 (+), 115,1 (+, q, *J* = 291.4 Hz), 126.4 (+), 127.5 (+), 127.7 (+), 128.1 (+), 128.6 (+), 129.1 (+), 129.1 (+), 129.3 (+), 129.4 (+), 142.5 (C_{quat}), 144.1 (C_{quat}), 144.4 (C_{quat}), 145.4 (C_{quat}), 145.6 (C_{quat}), 157.8 (C_{quat}), 171.1 (C_{quat}), 171.5 (C_{quat}), 171.9 (C_{quat}), 172.1 (C_{quat}).

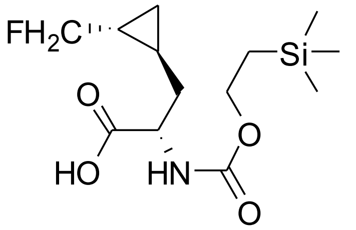


Boc-(4-Pe)Pro-[MeZ-a-Thr]-MeF-(S)mFmcpA-MeF-Ile-ODCPM (**101 a**): The tetrapeptide **100 a** (332 mg, 350 µmol) was *N*-deprotected according to GP 1, taken up with anhydrous CH_2Cl_2 (5 mL), the solution of the ester acid **71** (194 mg, 385 µmol), HATU (160 mg, 420 µmol) and HOAt (53 mg, 385µmol) in CH_2Cl_2 (3 mL) was added, and the reaction mixture was cooled to 4 °C. After this, a solution of DIEA (65 µL, 48 mg, 368 µmol) and TMP (140 µL, 127 mg, 1050 µmol) in CH_2Cl_2 (2 mL) was added at the same temperature within 5 min. The temperature was allowed to reach 20 °C, and stirring was continued for an additional 15 hours. After aqueous work-up according to GP 2 and two recrystallizations from EtOAc/hexane (1:2), the target hexadepsipeptide **101 a** (390 mg, 321 µmol, 86%) was obtained as a colorless solid. R_f=0.46 (EtOAc/hexane 1:1); m.p. 125–127 °C; $[\alpha]_D^{20}$ –29.0 (c=0.2, THF); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.24 – 0.68 (m, 12 H), 0.75 (d, *J* = 6.9 Hz, 3 H), 0.88 (t, *J* = 7.1 Hz, 3 H), 0.98 – 1.17 (m, 5 H), 1.18 – 1.46 (m, 1 H), 1.24 (d, *J* = 6.6 Hz, 3 H), 1.27 (d, *J* = 6.7 Hz, 3 H), 1.36 (s, 9 H), 1.40 (d, *J* = 6.7 Hz, 3 H), 1.68 (d, *J* = 7.0 Hz, 3 H), 1.75 – 1.94 (m, 2 H), 2.29 – 2.46 (m, 1 H), 2.32 (s, 3 H), 3.07 – 3.33 (m, 4 H), 3.68 (t, *J* = 8.6 Hz, 1 H), 3.93 (t, *J* = 8.3 Hz, 1 H), 4.18 – 4.27 (m, 1 H), 4.32 – 4.54 (m, 4 H), 4.64 (t, *J* = 9.6 Hz, 1 H), 4.95 – 5.13 (m, 2 H), 5.20 – 5.34 (m, 1 H), 5.44 – 5.63 (m, 2 H), 6.60 (d, *J* = 7.7 Hz, 1 H), 6.70 (d, *J* = 8.8 Hz, 1 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 7.05 – 7.37 (m, 14 H), 7.45 (d, *J* = 10.1 Hz, 1 H), 7.76 (d, *J* = 8.1 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 2.48 (–), 2.82 (–), 2.90 (–), 3.01 (–), 11.59 (+), 13.20 (+), 14.16 (+), 14.64 (+), 15.57 (+), 17.77 (+), 18.41 (–), 18.86 (+), 19.43 (+), 21.11 (+), 21.77 (+), 25.23 (–), 26.85 (–), 28.23 (+), 31.46 (–), 31.53 (–), 36.28 (–), 36.32 (+), 37.30 (+), 40.45 (+), 42.00 (+), 50.62 (+), 52.08 (+), 56.43 (+), 59.30 (+), 59.49 (+), 61.01 (+), 61.62 (+), 61.99 (+), 66.89 (–), 70.53 (+), 80.93 (C_{quat}), 83.24 (+), 116,2 (+, q, *J* = 287.3 Hz), 127.00 (+), 127.06 (+), 127.10 (+), 127.60 (+), 127.69 (+), 128.47 (+), 128.63 (+), 128.68 (+), 128.82 (+), 128.93 (+), 133.21 (C_{quat}), 137.83 (C_{quat}), 141.73 (C_{quat}), 141.90 (C_{quat}), 154.76 (C_{quat}), 155.75 (C_{quat}), 170.38 (C_{quat}), 170.43 (C_{quat}), 170.79 (C_{quat}), 171.37 (C_{quat}), 173.41 (C_{quat}), 174.06 (C_{quat}).

N-MeZ-protected cyclohexadepsipeptide **103 a** *(Cyclo-F$_1$6-MeZ)*: The hexadepsipeptide **101 a** (300 mg, 247 µmol) was ends-deprotected by treating with 2 M HCl solution in ethyl acetate (5 mL). The reaction mixture was stirred for 20 min in dark place (Al foil jacket) at ambient temperature and all volatiles were removed *in vacuo* without any heating. The residue was triturated with anhydrous diethyl ether to give the hydrochloride of the deprotected material **102 a** as a colorless solid (232 mg, 220 µmol, 89%). The ends-deprotected hexadepsipeptide **102 a**, HATU (110 mg, 288 µmol) and HOAt (33 mg, 244 µmol) were dissolved in cold (4 °C, internal temperature) anhydrous CH_2Cl_2 (2,5 L), and the solution of DIEA (120 µL, 93 mg, 720 µmol) in CH_2Cl_2 (100 mL) was added dropwise within 1 hour, the cooling bath was removed and the mixture was stirred for 2 hours at ambient temperature. Then the mixture was cooled again to 4 °C (internal temperature), the second portions of HATU (110 mg, 288 µmol) and HOAt (33 mg, 244 µmol) were added, followed with dropwise addition of the solution of DIEA (120 µL, 93 mg, 720 µmol) in CH_2Cl_2 (100 mL) within 1 hour. The cooling bath was removed and the mixture was stirred for 18 hours at ambient temperature. The mixture was concentrated under reduced pressure, subjected to aqueous work-up according to GP 2 to give the crude protected cyclohexadepsipeptide (180 mg, 180 µmol, 73%) which was finally purified with the HPLC to give pure product **103 a** (132 mg, 132 µmol, 49%).

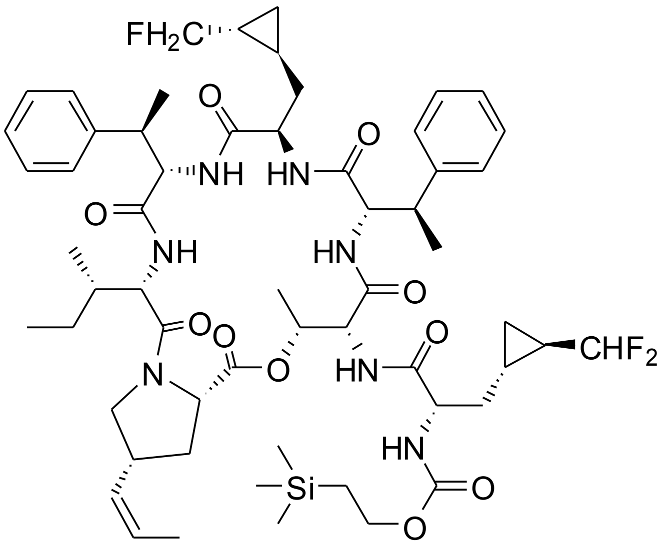


N-Teoc-(2S,1'S,2'R)-3-(2'-Monofluoromethylcyclopropyl)alanine (Teoc-(S)mFmcA-OH, **105 a***)*:



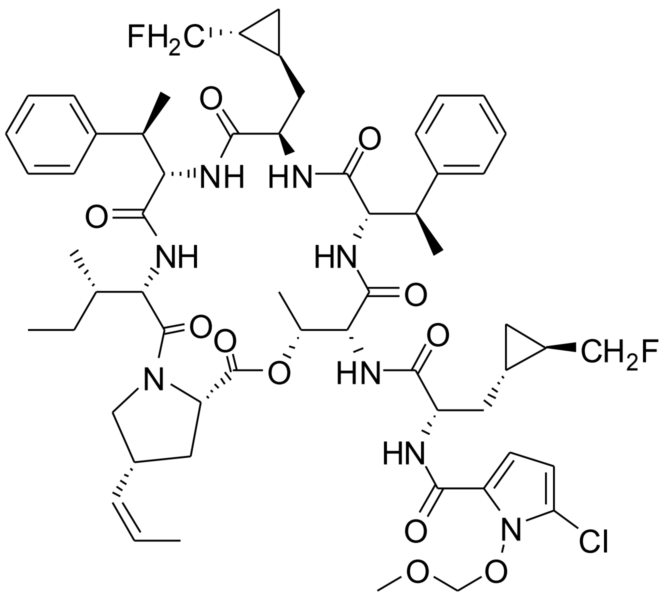
A solution of TeocOSu (43 mg, 164 µmol) in acetone (1 mL) was added to a vigorously stirred solution of (2*S*,1'*S*,2'*R*)-3-(2'-monofluoromethylcyclopropyl)alanine ***S*-96 a** (27 mg, 137 µmol) and $NaHCO_3$ (24 mg, 286 µmol) in water (1 mL) (if an emulsion formed, acetone and/or water was added to obtain a homogeneous solution), and stirring was continued for another 2 h. *N,N*-dimethylaminopropylamine (8 µL, 6,4 mg, 52 µmol) was then added. After an additional 10 min acetone was removed under reduced pressure and the pH of the residual water solution was adjusted to 2–3 with aq. 1 M $KHSO_4$. The resulting emulsion was extracted with diethyl ether (50 mL), and the ethereal layer was washed with aq. 1 M $KHSO_4$ (2 × 10 mL), water (3 × 10 mL), brine (2 × 5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was dried overnight *in vacuo* to give glass-like product **105 a** (38 mg, 111 µmol, 71%). R_f=0.24 [EtOAc/hexane 1:3 (2% AcOH)]; $[\alpha]_D^{20}$ = 22.80 (c = 0.46, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ = 0.04 (s, 9 H), 1.00 (dd, *J* = 9.5 Hz, 7.3 Hz, 2 H), 1.11–1.18 (m, 1 H), 1.60–1.95 (m, 2 H), 1.98–2.19 (m, 2 H), 4.14–4.23 (m, 3 H), 4.33–4.59 (m, 1 H), 5.33–5.46 (m, 1 H), 7.08–7.25 (bs, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = –1.9 (+), 10.2 (–), 17.3 (–), 22.0 (+), 33.1 + 33.3 (–), 52.7 (+), 53.2 (+), 59.0 (+), 63.7 (+), 64.8 (–), 115.6 (d, *J* = 271.4 Hz), 157.4 (C_{quat}), 174.5 + 174.8 (C_{quat}).

*Teoc-(S)mFmcpA-Cyclo-F_16 (***106 a***)*: *N*-MeZ-protected cyclohexadepsipeptide **103 a** (25 mg,

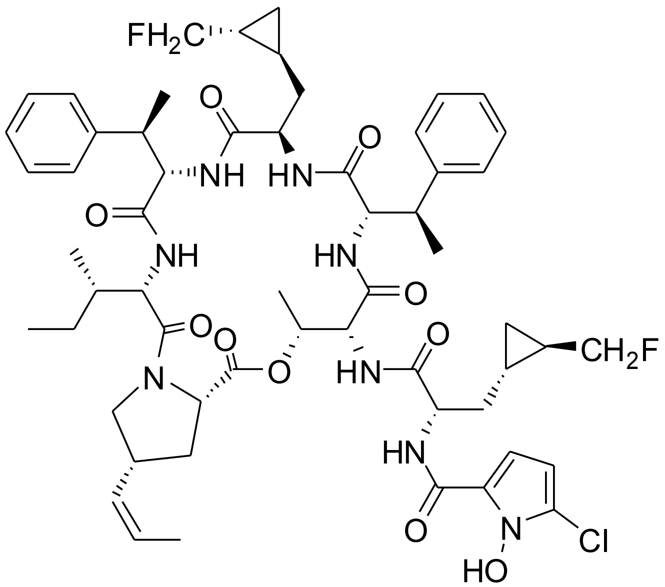


25 µmol) was deprotected with 10% anisole in TFA (1.1 mL) in the dark at ambient temperature for 2 h, the residue was treated with toluene (5 mL), concentrated under reduced pressure and the residue was dried *in vacuo* at ambient temperature for 2 hours. The solution of Teoc-(*S*)mFmcpA-OH **105 a**, HATU (29 mg, 75 µmol) and HOAt (10 mg, 75 µmol) in CH_2Cl_2 (1.5 mL) was added at 4 °C, followed with DIEA (3 5 mg, 27 µmol) and TMP (27 mg, 225 µmol) solution in CH_2Cl_2 (1.5 mL) and the mixture was stirred at ambient temperature for 15 h. The reaction mixture was then diluted with diethyl ether (50 mL) and the crude product obtained after the usual aqueous work-up (GP 2) was purified by

crystallization from CH_2Cl_2/pentane to give Teoc-(*S*)mFmcpA-Cyclo-F_26 (**106 a**) (29 mg, 24,7 µmol, 89%) as a colorless solid ($R_f = 0.43$, acetone/hexane 1:2) which was used for the next step without any characterization.



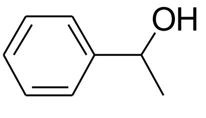
MOM-O-protected monofluoromethylcyclopropylalanyl Hormaomycin (MOM-O-F_1Horm, **108 a***)*: Teoc group was cleaved from the compound **106 a** (8.0 mg, 7.08 µmol) with TFA (0.6 mL) for 1 h. The mixture was concentrated under reduced pressure at 20 °C and then taken up with toluene (3 × 15 mL) which was distilled off to remove the last traces of TFA. The resulting deprotected depsipeptide **107 a** was coupled with *O*-MOM protected acid **81** (2.9 mg, 14.10 µmol) using HATU (5.4 mg, 14.20 µmol), DIEA (0.92 mg, 7.12 µmol) and TMP (5.14 mg, 42.42 µmol) in CH_2Cl_2 (1 mL) according to GP 6 for 2.5 h. The mixture was then taken up with Et_2O (20 mL) and the crude product obtained after usual aqueous work-up (GP 2) was crystallized from CH_2Cl_2 / pentane to give *O*-MOM protected monofluoromethylcyclopropylalanyl Hormaomycin **108 a** (8.0 mg, 93%, $R_f = 0.36$ acetone/hexanes 1:2) as a colorless glass which was used for the next step without any characterization.



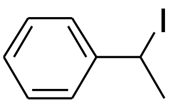
Monofluoromethylcyclopropylalanyl Hormaomycin (F_1Horm, **109 b***)*: *O*-MOM protected monofluoromethylcyclopropylalanyl Hormaomycin **108 a** (8.0 mg, 6.82 µmol) was deprotected using $MgBr_2 \times Et_2O$ (52 mg, 201.36 µmol) and EtSH (0.10 mL, 1.9 mmol) in CH_2Cl_2 (10 mL) according to GP 7 for 3 h. The mixture was taken up with EtOAc and the crude product obtained after usual aqueous work-up was crystallized from CH_2Cl_2 / pentane to give **109 a** (5.5 mg, 78%, 50% on 5 steps from **103 a**) as a white solid, which was finally purified with preparative HPLC. $R_f = 0.24$ acetone/hexanes 3:7; analytical HPLC: column B, isocratic, 65% MeCN in H_2O for 15 min, then gradient 65→99% MeCN in H_2O for 5 min, then isocratic, 99% MeCN, flow rate = 0.5 mL/min, $t_R = 14.54$ min, purity > 92%; preparative HPLC: isocratic, 62% MeCN in H_2O (+ 0.1% TFA) for 7 min, then gradient 65→99% MeCN in H_2O (+ 0.1% TFA) for 10 min, then isocratic, 62% MeCN in H_2O (+ 0.1% TFA), flow rate = 18 mL/min, $t_R = 12.54$ min; $[\alpha]_D^{20}$ 20.0 (c = 0.1, MeOH); ^{1}H NMR (600 MHz, CDCl3): δ = –0.71 – –0.63 (m, 1 H), –0.20–0.10 (m, 1 H), 0.23–0.32 (m, 1 H), 0.49–0.56 (m, 1 H), 0.88 (t, *J* = 7.4 Hz, 3 H), 0.95–1.01 (m, 1 H), 1.02 (d, *J* = 6.9 Hz, 3 H), 1.04–1.14 (m, 1 H), 1.17–1.35 (m, 1 H), 1.30 (d, *J* = 7.0 Hz, 3 H), 1.39 (d, *J* = 7.3 Hz, 3 H), 1.47–1.54 (m, 1 H), 1.53 (d, *J* = 6.9 Hz, 3 H), 1.55–1.62 (m, 1 H), 1.67 (dd, *J* = 6.9 Hz, 1.6 Hz, 3 H), 1.75–1.84 (m, 2 H), 1.85–1.94 (m, 3 H), 2.30–2.40 (m, 1 H), 2.88–2.91 (m, 1 H), 2.96–3.02 (m, 1 H), 3.22–3.31 (m, 2 H), 3.43–3.50 (m, 1 H), 3.62–3.70 (m, 1 H), 3.93–4.00 (m, 1 H), 4.03 (ddd, *J* = 6.8 Hz, 3.4 Hz, 3.4 Hz, 1 H), 4.26 (dd, *J* = 11.5 Hz, 6.0 Hz, 1 H), 4.38 (dd, *J* = 10.6 Hz, 10.6 Hz, 1 H), 4.46 (dd, *J* = 9.4 Hz, 4.5 Hz, 1 H), 4.57 (dd, *J* = 9.3 Hz, 2.3 Hz, 1 H), 4.66 (dd, *J* = 9.0, 9.0 Hz, 1 H), 5.08–5.14 (m, 1 H), 5.22–5.28 (m, 1 H), 5.40 (qd, *J* = 6.9 Hz, 2.4 Hz, 1 H), 5.58–5.65 (m, 1 H), 6.13 (d, *J* = 4.7 Hz, 1 H), 6.56 (d, *J* = 6.5 Hz, 1 H), 6.80 (d, *J* = 9.3 Hz, 1 H), 6.82 (d, *J* = 4.7 Hz, 1 H), 6.98–7.03 (m, 1 H), 7.09–7.18 (m, 5 H), 7.20–7.27 (m, 7 H), 8.05 (d, *J* = 9.1 Hz, 1 H), 9.06 (d, *J* = 9.3 Hz, 1 H); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 10.50 (+), 13.24 (+), 13.33 (+), 14.94 (+), 16.99 (+), 17.41 (–), 17.74 (+), 20.00 (+), 21.66 (+), 24.90 (–), 26.88 (–), 33.02 (–), 35.03 (–), 35.51 (–), 36.66 (–), 37.97 (+), 39.24 (+) 41.75 (+), 50.99 (+), 51.79 (+), 52.78 (–), 54.61 (+), 54.93 (+), 58.11 (+), 59.12 (+), 59.86 (+), 60.04 (+), 61.37 (+), 69.07 (+), 103.59 (+), 109.85 (+), 119.86 (C_{quat}), 121.55 (C_{quat}), 126.98 (+), 127.17 (+), 127.44 (+), 127.47 (+), 127.67 (+), 128.33 (+), 128.49 (+), 128.64 (+), 141.55 (C_{quat}), 142.11 (C_{quat}), 159.27 (C_{quat}), 168.54 (C_{quat}), 168.73 (C_{quat}), 169.75 (C_{quat}), 170.74 (C_{quat}), 171.26 (Cquat), 171.55 (C_{quat}), 172.86 (C_{quat}); MS-ESI: positive, m/z = 292 (100), 1151 (80, M+Na]$^+$); negative, m/z = 1127 (100, M–H]$^-$).

11. Other new non-proteinogenic amino acids

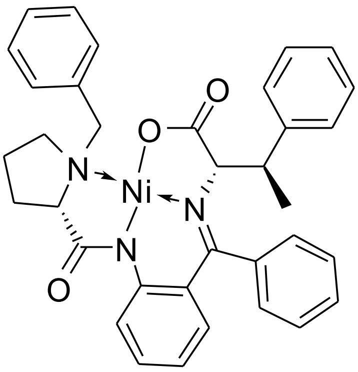
11.1. β-Methylphenylalanine



*Racemic 1-phenylethanol (***118***)*: Acetophenone (12.0 g, 100 mmol) was reduced with LiAlH$_4$ solution according to GP 8, giving the target racemic alcohol as colorless liquid (10.8 g, 88 mmol, 88%); ^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.49 (d, *J* = 6.5 Hz, 3 H), 2.20 (d, *J* = 3.1, 1 H), 4.82–4.92 (m, 1 H), 7.23–7.44 (m, 5 H); ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 25.12, 70.33, 125.35, 127.41, 128.45, 145.77.



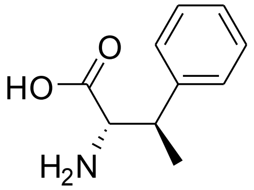
*Racemic 1-iod-1-phenylethane (***119***)*: Racemic 1-phenyl ethanol **118** (10.8 g, 88 mmol) was iodinated according to GP 9 using triphenylphosphine (40.0 g, 153 mmol), imidazole (10.9 g, 160 mmol) and iodine (43.1 g, 170 mmol) in diethyl ether/acetonitrile mixture (260 + 175 ml), giving the target iodide **119** as yellowish liquid (18.9 g, 81.7 mmol, 92,8%); ^{1}H NMR (250 MHz, CDCl$_3$): δ = 2.25 (d, *J* = 7.1 Hz, 3 H), 5.44 (q, *J* = 7.1, 1 H), 7.24–7.38 (m, 3 H), 7.44–7.55 (m, 2 H); ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 26.27, 28.99, 126.56, 127.95, 128.71, 145.32.



(S)-Belokon' (2S,3R)-β-methylphenylalanine complex [(S)-BFC, (2*S*,3*R*)-**120***]*: (*S*)-BGC (10.0 g, 20 mmol) was was alkylated with the racemic 1-iod-1-phenylethane **119** (4.9 g, 21 mmol) according to GP 10 using NaH (60% in oil, 1.0 g, 25 mmol) in DMF/MeCN mixture (10 + 20 mL), giving (2*S*,3*R*) component (3.78 g, 6.3 mmol, 63% on (*S*)-BGC), (2*S*,3*S*) component (3.13 g, 5.2 mmol, 52% on (*S*)-BGC) and mixed fractions (3.87 g, 6.4 mmol, 64% on (*S*)-BGC) as well as products of the anion oxidation (0.94 g); (2*S*,3*R*) component: ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1,13 (d, *J* = 7.34 Hz, 3 H), 1.34–1.51 (m, 2 H), 1.69–2.01 (m, 2 H), 2.22 (q, *J* = 7.90 Hz, 2 H), 2.71–2.95 (m, 2 H), 3.25 (t, *J* = 8.72 Hz, 1 H), 3.39 (d, *J* = 12.62 Hz, 1 H), 3.49 (d, *J* = 5.49 Hz, 3 H), 4.12 (d, *J* = 3.17 Hz, 1 H), 4.23 (d, *J* = 12.56 Hz, 1 H), 6.62–6.78 (m, 2 H), 6.99–7.07 (m, 1 H), 7.08–7.70 (m, 13 H), 7.98 (d, *J* = 8.28 Hz, 2 H), 8.26 (d, *J* = 8.56 Hz, 1 H); ^{13}C NMR (125.7 MHz, CDCl$_3$): δ = 18.27 (+), 22.92 (–), 30.67 (–), 44.84 (+), 50.56 (+, MeOH), 57.19 (–), 63.45 (–), 70.28 (+), 75.48 (+), 120.39 (+), 123.07 (+), 125.90 (–), 127.09 (+), 127.53 (+), 127.89 (+), 128.37 (+), 128.46 (+), 128.57 (+), 128.61 (+), 128.75 (+), 128.79 + 129.08 (+), 129.38 (+), 129.60 (+), 131.47 (+), 131.85 + 131.87 (+), 131.95 + 132.03 (+), 132.28 (+),

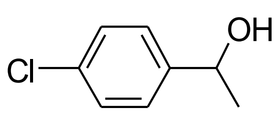
132.78 (–), 133.17 (–), 133.48 (+), 134.30 (–), 141.04 (–), 142.90 (–), 171.02 (–), 177.37 (–), 180.36 (–); $[\alpha]_D^{20}$=+2190.0° (c=0.2 in $CHCl_3$); MS-ESI (MeOH): 1827.6 (85%, 3M+Na]$^+$), 1225.1 (70%, 2M+Na]$^+$), 1205.0 (20%, 2M+H]$^+$), 624.3 (100%, M+Na]$^+$), 602.3 (48%, M+H]$^+$).

(2S,3R)-β-methylphenylalanine (MeF, **55***)*: (*S*)-BFC (3.78 g, 6.3 mmol) was decomposed and the amino acid was separated and purified according to GP 11 to give pure target amino acid (0.67 g, 3.7 mmol, 59%); ^{1}H NMR (300 MHz, D_2O): δ = 1.43 (d, *J* = 7.3 Hz, 3 H), 3.57 (qd, *J* = 7.3 Hz, 5.0 Hz, 1 H), 3.98 (d, *J* = 5.0 Hz, 1 H), 4.72 (bs, 3 H), 7.36–7.53 (m, 5 H); ^{13}C NMR (125.7 MHz, D_2O): δ = 13.81 (+), 39.46 (+), 60.75 (+), 127.81 (+), 127.86 (+), 129.17 (+), 140.38 (–), 173.24 (–); $[\alpha]_D^{20}$ –7.4 (c=0.5 in H_2O); MS-ESI (MeOH): (positive) m/z (%) 180 (100, M+H]$^+$), (negative) m/z (%) 178 (100, M–H]$^-$).

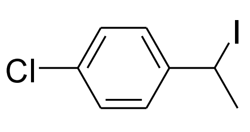


11.2. Substituted β-methylphenylalanines

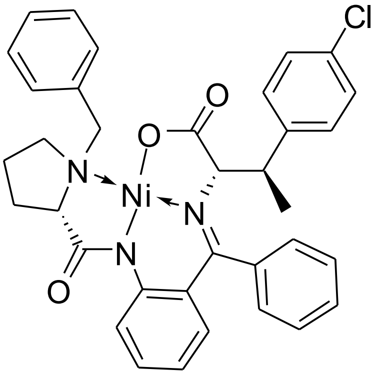
*Racemic 1-(p-chlorophenyl)ethanol (***121***)*: *p*-Chloroacetophenone (3.10 g, 20 mmol) was reduced with $LiAlH_4$ solution according to GP 8, giving the target racemic alcohol **121** as colorless liquid (3.07 g, 19.6 mmol, 98%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.42 (d, *J* = 6.5 Hz, 3 H), 2.65 (bs, 1 H), 5.36 (dq, *J* = 3.0 Hz, 6.5 Hz, 1 H), 7.20–7.35 (m, 4 H), ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 25.12, 69.50, 126.70, 128.43, 132.85, 144.14.



*Racemic 1-iod-1-(p-chlorophenyl)ethane (***122***)*: Racemic 1-(*p*-chlorophenyl)ethanol **121** (3.0 g, 19.2 mmol) was iodinated according to GP 9 using triphenylphosphine (6.7 g, 25.5 mmol), imidazole (2.0 g, 30 mmol) and iodine (9.4 g, 37.0 mmol) in toluene/acetonitrile mixture (100 + 20 ml). The mixture was heated to reflux for 30 min before work-up, diluted with *tert*-buthyl methyl ether (50 mL), washed with 10% w/w aqueous $NaHSO_3$ (3 × 50 mL), H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Crude iodide was purified with column chromatography (silica gel, eluted with pentane), giving the target iodide **122** as yellowish liquid (5.01 g, 18.8 mmol, 98%); TLC: pentane, R_f = 0.28; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.19 (d, *J* = 7.1 Hz, 3 H), 5.36 (q, *J* = 7.1 Hz, 1 H), 7.23–7.41 (m, 4H), ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.35, 28.81, 127.85, 128.82, 133.38, 143.88; MS-EI (70 eV): m/z (%) 141 (30, M(^{37}Cl)–I]$^+$), 139 (100, M(^{35}Cl)–I]$^+$), 103 (50, C_8H_7]$^+$), 77 (18, C_6H_5]$^+$).

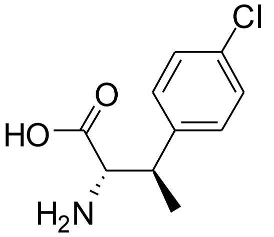


(S)-Belokon' (2S,3R)-beta-methyl(p-chlorophenyl)alanine complex [(S)-BpCFC (2*S*,3*R*)-**123***]*:



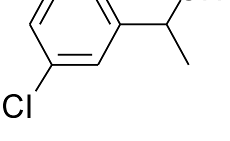
(*S*)-BGC (3.45 g, 6.9 mmol) was alkylated with the racemic 1-iod-1-(*p*-chlorophenyl)ethane **122** (1.95 g,7.3 mmol) according to GP 10 using NaH (60% in oil, 0.33 g, 8.3 mmol) in DMF/MeCN mixture (3.5 + 7.0 mL), giving after chromatogarphy (2*S*,3*R*) component (1.77 g, 2.8 mmol, 40.3% on (*S*)-BGC, d.e.≥98%), (2*S*,3*S*) component (1.83 g, 2.9 mmol, 41.6% on (*S*)-BGC, d.e.≥98%) and mixed fractions (0.67 g, 1.1 mmol, 15,2% on (*S*)-BGC) as well as products of the anion oxidation (0.11 g); (2*S*,3*R*) component: TLC: R_f = 0.17 (EtOAc); ^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.07 (d, 7.3 Hz), 1.45–1.65 (m, 1 H), 1.80–2.06 (m, 2 H), 2.14–2.36 (m, 3 H), 2.70–2.90 (m, 2 H), 3.29 (t, *J* = 8.6 Hz, 1 H), 3.40 (d, *J*=12.5 Hz, 1 H), 4.10 (d, *J*=3.1 Hz, 1 H), 4.24 (d, *J*=12.5 Hz, 1 H), 6.62–6.74 (m, 2 H), 7.00–7.06 (m, 1 H), 7.08–7.19 (m, 2 H), 7.22–7.37 (m, 5 H), 7.42–7.63 (m, 5 H), 7.94–8.03 (m, 2 H), 8.22–8.30 (m, 1 H); ^{13}C NMR (62.9 MHz, CDCl$_3$): 18.02, 22.69, 30.67, 44.18, 50.38, 57.40, 63.53, 70.18, 75.05, 106.97, 113.70, 120.39, 122.98, 125.66, 126.94, 127.64, 128.52, 128.76, 129.09, 129.62, 130.61, 131.32, 132.32, 133.12, 133.41, 133.51, 134.04, 139.37, 142.69, 171.12, 177.14, 180.32.

*(2S,3R)-β-methyl(p-chlorophenyl)alanine [(2S,3R)-***51***]*: (*S*)-BpCFC (2*S*,3*R*)-**122** (1.70 g,



2.7 mmol) was decomposed and the amino acid was separated and purified according to GP 11 to give pure target amino acid (512 mg, 2.4 mmol, 89%); ^{1}H NMR (300 MHz, D$_2$O): δ = 1.43 (d, *J* = 7.3 Hz, 3 H), 3.57 (qd, *J* = 7.3 Hz, 5.0 Hz, 1 H), 3.98 (d, *J* = 5.0 Hz, 1 H), 4.72 (bs, 3 H), 7.36–7.53 (m, 5 H); ^{13}C NMR (125.7 MHz, D$_2$O): δ = 13.81 (+), 39.46 (+), 60.75 (+), 127.81 (+), 127.86 (+), 129.17 (+), 140.38 (–), 173.24 (–); $[\alpha]_D^{20}$ –7.4 (c=0.5 in H$_2$O); MS-ESI (MeOH): positive 180.0 (100%), negative 178.2 (100%).

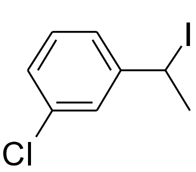
*Racemic 1-(m-chlorophenyl)ethanol (***124***)*: *m*-Chloroacetophenone (3.10 g, 20 mmol) was



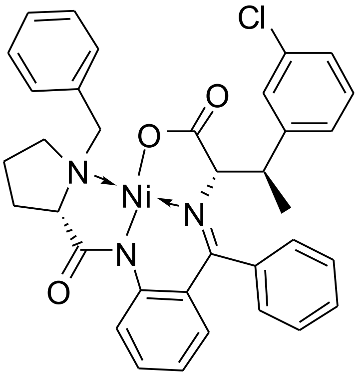
reduced with LiAlH$_4$ solution according to GP 8, giving the target racemic alcohol **124** as colorless liquid (3.09 g, 19.7 mmol, 98%); ^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.44 (d, *J* = 6.4 Hz, 3 H), 2.48 (bs, 1 H), 4.81 (dq, *J*=6.4 Hz, 3.3 Hz, 1 H), 7.16–7.30 (m, 3 H), 7.32–7.36 (m, 1 H); ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 25.12, 59.59, 123.48, 125.54, 127.41, 129.70, 134.22, 147.77; MS-EI (70 eV): m/z (%) 158 (10%, M(^{37}Cl)$]^{+}$), 156 (30%, M(^{35}Cl)$]^{+}$), 143 (25%, M(^{37}Cl)–

O+H$]^{+}$), 141 (100%, M(^{35}Cl)–O+H$]^{+}$, M(^{37}Cl)–OH$]^{+}$), 139.1 (45%, M(^{35}Cl)–OH$]^{+}$), 121.1 (15%, M–Cl$]^{+}$), 115.1 (13%, $C_6H_6{}^{37}Cl]^{+}$), 113.1 (40%, $C_6H_6{}^{35}Cl]^{+}$), 77.1 (75%, $C_6H_5]^{+}$).

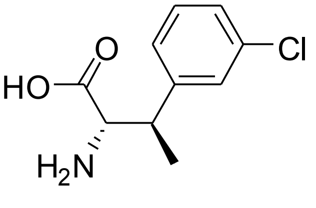
*Racemic 1-iod-1-(m-chlorophenyl)ethane (***125***)*: Racemic 1-(*m*-chlorophenyl)ethanol **124** (3.0 g, 19.2 mmol) was iodinated according to GP 9 using triphenylphosphine (6.7 g, 25.5 mmol), imidazole (2.0 g, 30 mmol) and iodine (9.4 g, 37.0 mmol) in toluene/acetonitrile mixture (100 + 20 ml). The mixture was heated to reflux for 30 min before work-up, diluted with *tert*-buthyl methyl ether (50 mL), washed with 10% w/w aqueous $NaHSO_3$ (3 × 50 mL), H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Crude iodide was purified with column chromatography (silica, eluted with pentane), giving the target iodide **125** as yellowish liquid (5.04 g, 18.9 mmol, 98%); TLC: $R_f = 0.28$, pentane; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.19 (d, *J* = 7.1 Hz, 3 H), 5.31 (q, *J* = 7.1 Hz, 1 H), 7.20–7.35 (m, 3 H), 7.41–7.44 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.72, 28,67, 124.80, 126.67, 128.01, 129.92, 134.28, 147.21.



(S)-Belokon' beta-methyl(m-chlorophenyl)alanine complex [(S)-BmCFC, (2*S*,3*R*)-**126***]*: (*S*)-BGC (3.45 g, 6.9 mmol) was alkylated with racemic 1-iod-1-(*m*-chlorophenyl)ethane (1.95 g,7.3 mmol) according to GP 10 using NaH (60% in oil, 0.33 g, 8.3 mmol) in DMF/MeCN mixture (3.5 + 7.0 mL), giving (2*S*,3*R*) component (1.83 g, 2.9 mmol, 41.6% on (*S*)-BGC, d.e.≥98%), (2*S*,3*S*) component (1.62 g, 2.5 mmol, 36.9% on (*S*)-BGC, d.e.≥98%) and mixed fractions (0.87 g, 1.4 mmol, 19.8% on (*S*)-BGC) as well as products of the anion oxidation (0.18 g). (2*S*,3*R*)-Component: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.11 (d, *J* = 7.3 Hz, 3 H), 1.43–1.64 (m, 1 H), 1.73–2.02 (m, 2 H), 2.27 (q, *J* = 7.6 Hz, 2 H), 2.75–2.94 (m, 2 H), 3.27 (t, *J* = 8.6 Hz, 1 H), 3.42 (d, *J* = 12.6 Hz, 1 H), 4.05–4.16 (m, 1 H), 4.25 (d, *J* = 12.6 Hz, 1 H), 6.62–6.74 (m, 2 H), 6.98–7.06 (m, 1 H), 7.08–7.19 (m, 2 H), 7.19–7.35 (m, 5 H), 7.37–7.46 (m, 3 H), 7.46–7.66 (m, 3 H), 7.93–8.00 (m, 2 H), 8.26–8.32 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 30.84, 44.62, 57.25, 63.45, 70.30, 75.18, 120.46, 123.17, 125.81, 127.86, 128.68, 128.91, 129.25, 131.52, 143.05, 143.34, 177.12, 180.39, 209,51.

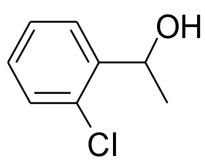


*(2S,3R)-β-methyl(p-chlorophenyl)alanine [(2S,3R)-***50***]*: (*S*)-BmCFC (2*S*,3*R*)-**126** (1.80 g, 2.8 mmol) was decomposed and the amino acid was separated and purified according to GP 11 to give pure target amino acid (573 mg, 2,7 mmol, 96%); ^{1}H NMR (300 MHz, D_2O): δ = 1.43 (d, *J* = 7.3 Hz, 3 H), 3.57 (qd, *J* = 7.3 Hz, 5.0 Hz, 1 H), 3.98 (d, *J* = 5.0 Hz, 1 H),

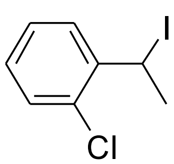


4.72 (bs, 3 H), 7.36–7.53 (m, 5 H); ^{13}C NMR (125.7 MHz, D_2O): $\delta = 13.81$ (+), 39.46 (+), 60.75 (+), 127.81 (+), 127.86 (+), 129.17 (+), 140.38 (–), 173.24 (–); $[\alpha]_D^{20}$ –7.4 (c=0.5 in H_2O); MS-ESI (MeOH): positive 180.0 (100%), negative 178.2 (100%).

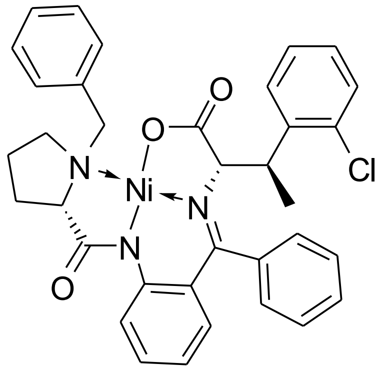
*Racemic 1-(o-chlorophenyl) ethanol (***127***)*: o-Chloroacetophenone (3.10 g, 20 mmol) was reduced with $LiAlH_4$ solution according to GP 8, giving the target racemic alcohol **127** as colorless liquid (2.98 g, 19.0 mmol, 95%); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.46$ (d, $J = 6.3$ Hz, 3 H), 2.50 (bs, 1 H), 5.26 (q, $J = 6.3$ Hz, 1 H), 7.12–7.34 (m, 3 H), 7.53–7.60 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 23.43$, 66.81, 126.33, 127.12, 128.29, 129.28, 131.48, 142.99; MS-EI (70 eV): m/z (%) 158.2 (4%, $M(^{37}Cl)^{\rceil+}$), 156.2 (12%, $M(^{35}Cl)^{\rceil+}$), 143.1 (18%, $M(^{37}Cl){-}O{+}H^{\rceil+}$), 141.1 (55%, $M(^{35}Cl){-}O{+}H^{\rceil+}$), 115.1 (10%, $C_6H_6{}^{37}Cl^{\rceil+}$), 113.1 (30%, $C_6H_6{}^{35}Cl^{\rceil+}$), 77.1 (100%, $C_6H_5{}^{\rceil+}$).



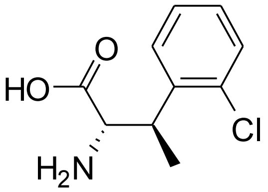
*Racemic 1-iod-1-(o-chlorophenyl) ethane (***128***)*: Racemic 1-(*o*-chlorophenyl)ethanol **127** (2.9 g, 18.5 mmol) was iodinated according to GP 7 using triphenylphosphine (6.7 g, 25.5 mmol), imidazole (2.0 g, 30.0 mmol) and iodine (9.4 g, 37.0 mmol) in toluene/acetonitrile mixture (100 + 20 ml). The mixture was heated to reflux for 30 min before work-up, diluted with *tert*-buthyl methyl ether (50 mL), washed with 10% w/w aqueous $NaHSO_3$ (3 × 50 mL), H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Crude iodide was purified with column chromatography (silica gel, eluted with pentane), giving the target iodide **128** as yellowish liquid (4.82 g, 18.1 mmol, 98%); TLC: pentane, $R_f = 0.28$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.25$ (d, $J = 7.1$ Hz, 3 H), 5.72 (q, $J = 7.1$ Hz, 1 H), 7.15–7.35 (m, 3 H), 7.60–7.67 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 20.54$, 27.75, 127.50, 127.57, 128.93, 129.89, 132.05, 142.11; MS-EI (70 eV): m/z (%) 141.1 (33%, $M(^{37}Cl){-}I^{\rceil+}$), 139.1 (100%, $M(^{35}Cl){-}I^{\rceil+}$), 103.1 (100%, $M{-}(H{+}Cl{+}I)^{\rceil+}$), 77.1 (75%, $C_6H_5{}^{\rceil+}$).



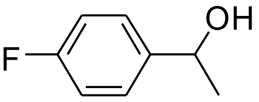
*(S)-Belokon' β-methyl(o-chlorophenyl)alanine complex [(S)-BoCFC, (2S,3R)-***129***]*: (*S*)-BGC (3.08 g, 6.2 mmol) was alkylated with racemic 1-iod-1-(*o*-chlorophenyl)ethane **128** (1.74 g, 6.5 mmol) according to GP 10 using NaH (60% in oil, 0.30 g, 7.4 mmol) in DMF/MeCN mixture (3.0 + 6.0 mL), giving (2*S*,3*R*) component [1.64 g, 2.6 mmol, 41.6% on (*S*)-BGC, d.e.≥98%], (2*S*,3*S*) component [1.49 g, 2.3 mmol, 37.7% on (*S*)-BGC, d.e.≥98%] and mixed fractions [0.76 g, 1.2 mmol, 19.2% on (*S*)-BGC] as well as products of the anion oxidation (0.12 g).



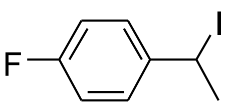
*(2S,3R)-β-Methyl(o-chlorophenyl)alanine [***(2S,3R)-49***]*: (S)-BoCFC (2S,3R)-**129** was decomposed and the amino acid was separated and purified according to GP 9 to give pure target amino acid (513 mg, 2,4 mmol, 96%).



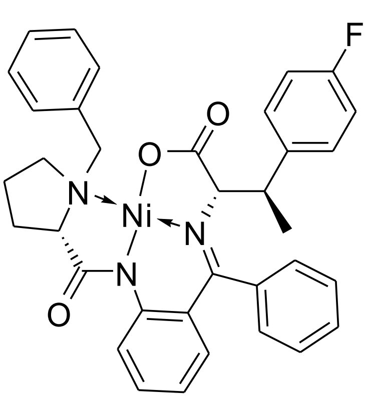
*Racemic 1-(p-fluorophenyl)ethanol (***130***)*: p-Fluoroacetophenone (2.76 g, 20.0 mmol) was reduced with LiAlH$_4$ solution according to GP 8, giving the target racemic alcohol **130** as colorless liquid (2.72 g, 19.4 mmol, 97%); TLC: $R_f = 0.27$, pentane; ^{1}H NMR (250 MHz, CDCl$_3$): $\delta = 1.45$ (d, $J = 6.5$ Hz, 3 H), 2.30 (bs, 1 H), 4.85 (q, $J = 6.5$ Hz, 1 H), 6.96–7.08 (m, 2 H), 7.25–7.37 (m, 2 H); ^{13}C NMR (62.9 MHz, CDCl$_3$): $\delta = 25.20$ (+), 69.65 (+), 115.16 (+, d, $J = 21.3$ Hz), 126.98 (+, d, $J = 8.1$ Hz), 141.45 (C$_{quat}$, d, $J = 3.1$ Hz), 162.00 (C$_{quat}$, d, $J = 245.1$ Hz); MS-EI (70 eV): m/z (%) 140.1 (22%, $\mathrm{M}\rceil^{+}$), 125.1 (100%, $\mathrm{C_8H_{10}F}\rceil^{+}$), 97.1 (60%, $\mathrm{C_6H_6F}\rceil^{+}$), 77.1 (20%, $\mathrm{C_6H_5}\rceil^{+}$), 43.2 (24%, $\mathrm{C_2H_3O}\rceil^{+}$).



*Racemic 1-iod-1-(p-fluorophenyl)ethane (***131***)*: Racemic 1-(*p*-fluorophenyl)ethanol **130** (2.5 g, 17.8 mmol) was iodinated according to GP 9 using triphenylphosphine (8.1 g, 30.7 mmol), imidazole (2.2 g, 32.6 mmol) and iodine (9.0 g, 35.6 mmol) in diethyl ether/acetonitrile mixture (50 + 35 ml), giving the target iodide **131** as yellowish liquid (4.31 g, 17.2 mmol, 96,8%); TLC: $R_f = 0.37$ pentane; ^{1}H NMR (250 MHz, CDCl$_3$): $\delta = 2.20$ (d, $J = 7.1$, 3 H), 5.40 (q, $J = 7.1$ Hz, 1 H), 6.92–7.06 (m, 2 H), 7.36–7.48 (m, 2 H); ^{13}C NMR (62.9 MHz, CDCl$_3$): $\delta = 24.85$ (+), 29.13 (+), 115.54 (+, d, $J = 21.6$ Hz), 128.20 (+, d, $J = 8.3$ Hz), 141.24 (C$_{quat}$), 161.86 (C$_{quat}$, d, $J = 247.2$ Hz).

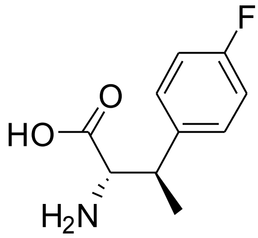


*(S)-Belokon' β-methyl(p-fluorophenyl)alanine complex [(S)-BpFFC, (2S,3R)-***132***]*: (*S*)-BGC (2.84 g, 5.7 mmol) was alkylated with racemic 1-iod-1-(*p*-fluorophenyl)ethane **131** (1.50 g, 6.0 mmol) according to GP 10 using NaH (60% in oil, 0.28 g, 6.8 mmol) in DMF/MeCN mixture (3.0 + 6.0 mL), giving (2*S*,3*R*) component [1.53 g, 2.5 mmol, 43.2% on (*S*)-BGC, d.e.≥98%], (2*S*,3*S*) component [1.63 g, 2.6 mmol, 46.1% on (*S*)-BGC, d.e.≥98%] and mixed fractions [0.33 g, 0.52 mmol, 9.2% on (*S*)-BGC] as well as products of the anion oxidation (0.13 g) after chromatography (silica gel, eluted with ethyl acetate). ^{1}H NMR (250 MHz, CDCl$_3$): $\delta = 1.85$–2.02 (m, 1 H), 2.03–2.21 (m, 1 H), 2.06 (d, $J = 7.1$ Hz, 3 H) 2.50–2.75 (m, 1 H), 2.80–2.98 (m, 1 H), 3.31–3.52 (m, 4 H), 3.59 (d,



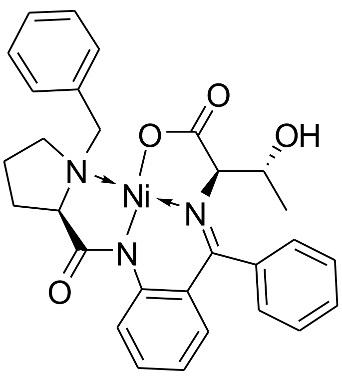
J = 12.7 Hz, 1 H), 4.09 (d, *J* = 5.0 Hz, 1 H), 4.39 (d, *J* = 2.6 Hz, 1 H), 6.50–6.71 (m, 5 H), 6.75 (t, *J* = 8.6 Hz, 2 H), 7.01–7.17 (m, 2 H), 7.22–7.34 (m, 4 H), 7.47–7.58 (m, 2 H), 8.04 (d, *J* = 7.3 Hz, 2 H), 8.20 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.12, 23.27, 30.71, 43.94, 46.16, 56.71, 63.19, 70.39, 75.66, 114.83 (d, *J* = 21.0 Hz), 120.63, 123.13, 126.31, 127.46, 128.20, 128.75, 128.88, 128.94, 129.09 (d, *J* = 7.9 Hz), 129.58, 131.43, 133.04, 133.52, 133.75, 134.48 (d, *J* = 269.7 Hz), 142.39, 170.75, 176.73, 180.14.

*(2S,3R)-β-Methyl-(p-fluorophenyl)alanine [***(2S,3R)-52***]*: (S)-BpFFC (2S,3R)-**132** was decomposed and the amino acid was separated and purified according to GP 11 to give pure target amino acid (433 mg, 2,2 mmol, 94%).



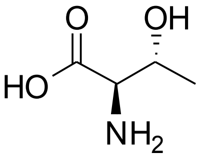
11.3. (R)-allo-Threonine

(R)-Belokon' (R)-allo-Threonine complex [(R)-BTC, **133***]*: (*R*)-BGC (21.4 g, 43.0 mmol) was suspended in DMF/MeCN mixture (20 + 40 mL) and degassed with two freeze-pump-thaw cycles (dry ice/acetone bath) under stirring, then NaH (60% in oil, 2.0 g, 50 mmol) was added to cold mixture and the system was thawed to 0 °C under stirring till H_2 gas evolution ceased. The♣ mixture was frozen, acetaldehyde (2.0 g, 45 mmol) was added under stirring and system was left to warm to 0 °C on air under stirring. When ice cover on flask started to thaw, 60% aqueous acetic acid (4.5 mL) was added. After additional 10 min stirring the mixture was concentrated under reduced pressure (bath temp ~50 °C) and liquid residue was poured into a vigorously stirred mixture of H_2O (0.5 L) and $CHCl_3$ (100 mL). Organic layer was separated and washed with H_2O (2 × 100 mL), combined water phases were extracted with $CHCl_3$ (3 × 50 mL), combined organic phases were concentrated under reduced pressure to ~20 ml and left overnight at ambient temperature to crystallize. Crystals were filtered out, washed with cold $CHCl_3$ (~10 ml) and recrystallized from $CHCl_3$, giving orange crystals, uniform by TLC (1.76 g, 3.2 mmol, 7.5%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.5 Hz, 3 H), 1.94–2.12 (m, 3 H), 2.25–2.59 (m, 2 H), 2.67–2.84 (m, 1 H), 3.38–3.61 (m, 1 H), 3.45 (dd, *J* = 11.1 Hz, 5.8 Hz, 1 H), 3.55 (d, 12.6 Hz, 1 H), 3.75–3.97 (m, 3 H), 4.42 (d, *J* = 12.6 Hz, 1 H), 6.65 (d, *J* = 3.87 Hz, 2 H), 6.95 (m, 1 H), 7.09–7.23 (m, 2 H), 7.35 (t, *J* = 7.52 Hz, 2 H), 7.41–



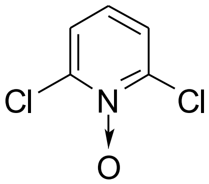
7.56 (m, 3 H), 8.06 (d, $J = 7.02$ Hz, 2 H), 8.14 (d, $J = 8.61$ Hz, 1 H); ^{1}H NMR (250 MHz, [D6]DMSO): $\delta = 0.88$ (d, $J = 6.3$ Hz, 3 H), 1.81–2.18 (m, 2 H), 2.29–2.40 (m, 2 H), 3.45–3.58 (m, 3 H), 3.61–3.87 (m, 2 H), 4.04 (d, $J = 12.2$ Hz, 1 H), 6.12 (d, $J = 5.1$ Hz, 1 H), 6.54 (d, $J = 7.8$ Hz, 1 H), 6.64 (t, $J = 7.1$ Hz, 1 H), 7.02–7.19 (m, 3 H), 7.30–7.62 (m, 6 H), 7.99 (d, $J = 8.6$ Hz, 1 H), 8.35 (d, $J = 7.4$ Hz, 2 H), hydroxyl sygnal is masked with H_2O absorption; ^{13}C NMR (62.9 MHz, [D6]DMSO): $\delta = 20.19$, 22.61, 30.24, 57.43, 62.38, 69.27, 69.71, 75.82, 119.78, 123.20, 126.05, 127.24, 127.75, 128.20, 128.31, 128.46, 128.86, 128.96, 129.38, 130.96, 131.45, 131.55, 132.48, 134.01, 134.76, 142.61, 169.08, 174.67, 180.18.

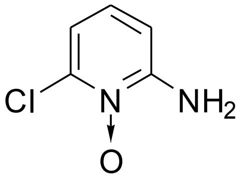
(2R,3R)-2-Amino-3-hydroxybutyric acid [(R)-allo-Threonine, **67***]*: (R)-Belokon' (*R*)-*allo*-Threonine complex **133** (1.76 g, 3.2 mmol) was decomposed and the amino acid was separated according to GP 11 to give the target amino acid (351 mg, 2.9 mmol, 92%).



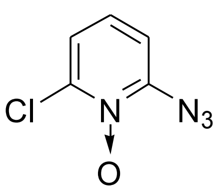
11.4. 1-Hydroxy-5-chloropyrrole-2-carboxylic acid

*2,6-Dichloropyridine-1-oxide (***134***)*:[123] 2,6-dichloropyridine (11.10 g; 75.5 mmol) was dissolved in trifluoroacetic acid (88 mL) at ambient temperature under stirring and aqueous H_2O_2 (30% in H_2O, 16 mL) was added dropwise during 10 min. and the mixture was carefully heated to reflux. Additional portions of H_2O_2 (2 mL each) were added twice after 1 h and 2 h. The mixture was refluxed for 3 h under stirring, then the heating bath was removed and after short (~15 min) air-cooling the reflux condenser was changed to distillation head. The solvent mixture was distilled out under reduced pressure (bath temperature ≤ 50 °C) and liquid dark red-brown residue was poured to ice/water mixture (200 mL) under stirring. Solid K_2CO_3 was added portionswise to vigorously stirring mixture (carefully–foam!) till CO_2 gas evolution ceased, then solid NaCl (about 60g) was added to saturation. The precipitate formed was filtered off, wet precipitate was dissolved in CH_2Cl_2 (50 mL) and last drops of water phase were separated in separation funnel. Combined water phases were extracted with CH_2Cl_2 (5 × 50 ml). Extracts and the solution of precipitate were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure at ambient temperature till first crystals appeared. The solution was homogenized with CH_2Cl_2 (~1 mL) and diluted with hexane (150 mL). The precipitate formed was filtered off, washed on filter with pentane (2 × 50 mL) and dried *in vacuo* overnight, giving target product **134** (9.11 g, 55.5 mmol, 73.5%) as white solid. Starting 2,6-dichloropyridine (2.09 g, 14.1 mmol, 18.7%) was recovered from filtrate; TLC: $R_f = 0.12$ EtOAc:hexane 1:1.

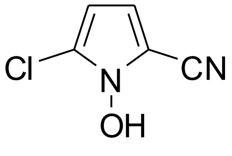




*2-Amino-6-chloropyridine-1-oxide(***135***):*[28] 2,6-dichloropyridine-1-oxide **134** (4.50 g; 27.4 mmol) was placed to thick-wall ampoule (250 mL), covered with 75 mL of methanolic ammonia solution (25% w/w, obtained by anhydrous gaseous ammonia condensation in absolute methanol), sealed and heated at 105 °C (bath temperature) under stirring. After 24 h the mixture was cooled in ice/ water bath, the ampoule was open and solvents were removed at the reduced pressure. The dark-brown crystalline residue was treated with methanol/chloroform mixture (1:4, 10 mL), NH_4Cl precipitate was filtered out, washed with chloroform (3 × 5 mL) and discarded, the filtrate was concentrated under reduced pressure and residing oil was purified with column chromatography (methanol/chloroform mixture, 1:10), giving target product **135** as off-white solid (2.32 g, 16.0 mmol, 58.6%); TLC: MeOH:$CHCl_3$=1:10, R_f=0.3; m.p.=133-134 °C.

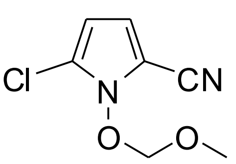


*2-Azido-6-chloropyridine-1-oxide (***136***):*[28] 2-amino-6-chloropyridine-1-oxide **135** (4.33 g, 30.0 mmol) was dissolved in 10% aqueous HCl (96 mL) at +5 °C (inner temperature, during the reaction time reagents addition rates were selected not to overheat the reaction mixture higher than +5 °C) under vigorous stirring, the mixture was stirred for additional 15 min and aq. $NaNO_2$ (2.5 M, 13 mL, 32.5 mmol) was added dropwise. The mixture was stirred for 15 min and aq. NaN_3 (2.5 M, 13 ml, 32.5 mmol) was added dropwise, cooling bath was removed and the mixture was left to stir and warm to ambient temperature. The reaction mixture was extracted with CH_2Cl_2 (8 × 50 mL), combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to ~100 mL, diluted with hexane (300 mL) and concentrated under reduced pressure to ~50 mL. The precipitate was filtered off, washed with hexane (3 × 10 mL) and dried *in vacuo*, giving target product **136** as a pale-yellow crystalline solid (4.42g, 25.9 mmol, 86.4%); m.p. 82–83 °C (decomp.); ^1H NMR (250 MHz, $CDCl_3$): δ = 6.85 (dd, J = 8.3 Hz, 1.8 Hz, 1 H), 7.12 (dd, J = 8.3 Hz, 1 H), 7.25 (dd, J = 8.3 Hz, 1.8 Hz, 1 H).

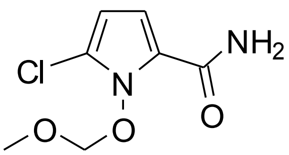


*5-Chloro-1-hydroxy-1H-pyrrole-2-carbonitrile (***137***):* 2-Azido-6-chloropyridine-1-oxide **136** (3.91 g; 22.9 mmol) was dissolved in toluene (150 mL), the system was degassed, filled with N_2 and the solution was refluxed and stirred under N_2 flow for 30 min. The reaction mixture was filtered through silica gel (50 mL) to remove tar products; the silica gel on filter was washed with toluene (200 mL), filtrates were combined and the toluene was removed under reduced pressure. Light-brown crystal residue was dissolved in minimum chloroform volume and filtered through silica gel (50 mL). Traces of starting material and side products were washed out with chloroform (TLC control), the product

was eluted with ethyl acetate/hexane mixture (1:3). Eluate concentration under reduced pressure gives target product **137** as off-white crystals (2.47 g, 17.3 mmol, 76%) uniform by TLC; m.p. 100–101 °C; ^{1}H NMR (250 MHz, CDCl$_3$): $\delta = 6.03$ (d, $J = 5.0$ Hz, 1 H), 6.66 (d, $J = 5.0$ Hz, 1 H),
8.94 (s, 1 H).

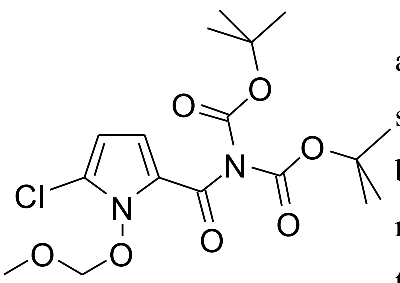


5-Chloro-1-methoxymethoxy-1H-pyrrole-2-carbonitrile *(***138***)*:[28] 5-Chloro-1-hydroxy-1H-pyrrole-2-carbonitrile **137** (1.0g, 7.0mmol), and TEBAC (110 mg, 0.5 mmol) were dissolved in CH$_2$Cl$_2$ (15 mL) and aqueous NaOH solution (24% w/w, 2.2 mL) was added dropwise under vigorous stirring at ambient temperature. Chloro-methoxy-methane (MOM-Cl, 1.6g, 14 mmol) was added as one portion and stirring was continued for 30 min. The mixture was diluted with CH$_2$Cl$_2$ (20ml) and organic layer was separated. Water layer was diluted with H$_2$O (10 mL) and extracted with CH$_2$Cl$_2$ (3 × 10mL). Combined organic layers were concentrated under reduced pressure giving 1.29g crude product, which was purified with the column chromatography (silica gel, eluted with EtOAc:hexane 1:7), giving the target product **138** as colorless liquid (1.15 g, 6.3 mmol, 88.0%); ^{1}H NMR (250 MHz, CDCl$_3$): $\delta = 3.73$ (s, 3 H), 5.17 (s, 2 H), 6.05 (d, $J = 4.8$ Hz, 1 H), 6.64 (d, $J = 4.8$ Hz, 1 H).



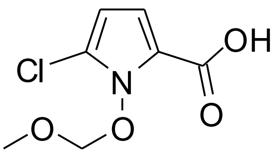
5-Chloro-1-methoxymethoxy-1H-pyrrole-2-carboxamide *(***139***)*:[28] 5-Chloro-1-methoxymethoxy-1H-pyrrole-2-carbonitrile **138** (3.53g, 18.9 mmol), and tetrabutylammonium hydrosulfate (1.35 g, 3.9 mmol) were dissolved in CH$_2$Cl$_2$ (40 mL) in 250-ml round-bottomed flask under vigorous stirring, the solution of 2.0 g NaOH in 8.0 mL H$_2$O was added, followed with aqueous H$_2$O$_2$ solution (30%, 14 mL; carefully–foam!). The mixture was vigorously stirred for 30 min, organic layer was separated, water layer was washed with CH$_2$Cl$_2$ (10 mL), saturated with solid NaCl and extracted with CH$_2$Cl$_2$ (2 × 20mL). Combined organic layers were concentrated under reduced pressure. The residue (4.88g) was purified with column chromatography (silica gel, eluted with EtOAc: hexane 1:1), giving the target product as light-yellow extremely viscose oil (3.65 g). The crystalline product was obtained after dissolving the product in diethyl ether (10 mL) and precipitation with hexane (100 mL). The crystalline precipitate was filtered out, rinsed with pentane (3 × 10 mL) and dried *in vacuo*, giving the target product **139** as white solid (3.18 g, 15.5 mmol, 82.2%); m.p.: 60–61 °C.

*Di-tert-butyl [5-Chloro-1-(methoxymethoxy)pyrrol-2-yl]carbonylimidodicarbamate (***140***):*[28]



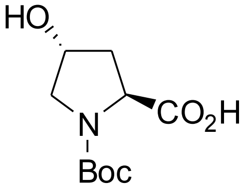
The solution of 4-pyrrolidino pyridine (0.22 g, 1.5 mmol) in anhydrous acetonitrile (20 mL) was added dropwise to vigorously stirred solution of 5-chloro-1-methoxymethoxy-1H-pyrrole-2-carboxamide **139** (3.45 g, 16.9 mmol) and di-*tert*-butyl pyrocarbonate (22.1 g, 101.2 mmol) in anhydrous acetonitrile (65 mL) and the stirring was continued for 1.5 hour. Solvents were evaporated under reduced pressure, oily yellowish residue was purified with column chromatography (silica gel, eluted with ethyl acetate/hexane 1:8), giving the target product **140** as colorless oil, solidified while drying *in vacuo* overnight to white solid (5.46 g, 13.5 mmol, 79.8%); m.p.: 62–69 °C.

*5-Chloro-1-methoxymethoxy-1H-pyrrole-2-carboxylic acid (***81***):*[28] Di-tert-butyl [5-Chloro-1-(methoxymethoxy)pyrrol-2-yl]carbonylimidodicarbamate **140** (5.42 g, 13.4 mmol) was dissolved in dioxane (65 mL) under stirring at 55 °C (bath temperature) and aq. 1 M NaOH (18 mL) was added as one portion. The mixture was stirred overnight, and then all volatiles were removed under reduced pressure. Paste-like residue was dissolved in H_2O (150 mL) and the solution was washed with CH_2Cl_2 (3 × 50 mL). Water layer was separated, acidified with aq. 1M $KHSO_4$ to pH~2 and extracted with CH_2Cl_2 (3 × 50 mL). Combined organic layers were concentrated under reduced pressure, giving 2.08g crude product as pink solid, which was purified with flash-chromatography (silica gel, eluted with diethyl ether) to give target product **81** as colorless solid (2.05 g, 10.0 mmol, 74.6%); m.p.: 123–124 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 3.68$ (s, 3 H), 5.25 (s, 2 H), 6.06 (d, $J = 5.0$ Hz, 1 H), 6.95 (d, $J = 5.0$ Hz, 1 H), 11.75 (bs, 1 H).



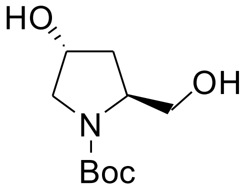
11.5. (2S,4R)-N-Boc-4-(Z)-Propenylproline

*(2S,4R)-N-Boc-4-Hydroxyproline (***2***):*[124] (2*S*,4*R*)-4-Hydroxyproline (32.8 g, 250 mmol) was dissolved in H_2O (170 mL) with stirring, THF (340 mL) and the solution of NaOH (11.0 g, 275 mmol) in H_2O (100 mL) were successively added with vigorous stirring, followed with di-*tert*-butyl dicarbonate (82.6 g, 367 mmol) and the mixture was left to stir overnight. The mixture was acidified with aq. 1M $KHSO_4$ to pH~2, organic layer was separated, aqueous layer was extracted with ethyl acetate (3 × 100 mL), combined extracts were washed

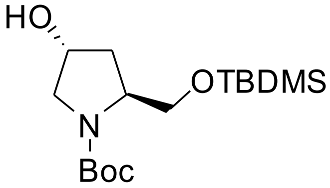


with brine (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude *N*-protected amino acid as colorless sypup. The syrup was dissolved in EtOAc (300 mL) and back-extracted with aq. 10% NaOH (3 × 100 mL). Organic layer was discarded, combined aqueous phases were acidified with aq. 1M $KHSO_4$ to pH~2 and extracted with diethyl ether (3 × 100 mL). Combined extracts were washed with aq. 1M $KHSO_4$ (3 × 100 mL) and brine (2 × 100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure giving target *N*-protected amino acid **2** as glass-like solid (50.2 g, 217 mmol, 87%); TLC: $R_f = 0.18$ (ethyl acetate/ hexane 1:1 + 5% acetic acid).

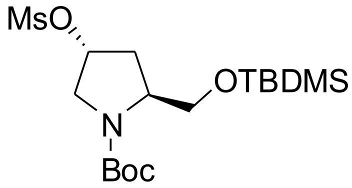
*(2S,4R)-N-Boc-4-Hydroxyprolinol (***3***):*[28] To a solution of (2*S*,4*R*)-*N*-Boc-4-Hydroxyproline **2** (50.2 g, 217 mmol) and triethylamine (33.6 mL, 239 mmol) in CH_2Cl_2 (600 mL) was added at –30 °C ethyl chloroformate (21.9 mL, 229 mmol), and the mixture was stirred for 40 min. To this mixture tetrabutylammonium bromide (7.44 g, 23.1 mmol) was added and then carefully, by small portions a suspension of $NaBH_4$ (35.0 g, 925 mmol) in ice-cold water (44 mL). The reaction mixture was allowed to warm to –10 °C and stirred for 1 h. The temperature of the mixture was further increased to 0 °C, and stirring was continued at this temperature for 1 h. The pH value of the aqueous layer was then carefully adjusted to 5–6 with 50% acetic acid, the mixture was stirred till H_2 gas evolution ceased and filtered through Celite® pad. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The aqueous layer was discarded, and the combined organic fractions were dried over $MgSO_4$, filtered, concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, eluted with EtOAc/hexane 2:1, $R_f = 0.13$) to give the target diol **3** (21.44 g, 98.7 mmol, 45%) as a colorless syrup. $[\alpha]_D^{20}$ –58.8 (c = 1.0, EtOH); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.47 (s, 9 H), 1.57–1.80 (m, 1 H), 1.89–1.98 (bs, 1 H), 1.98–2.11 (m, 1 H), 3.35–3.63 (m, 3 H), 3.70 (t, *J* = 9.4 Hz, 1 H), 4.04–4.25 (m, 1 H), 4.29–4.45 (m, 1 H), 4.95–5.09 (bs, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.3 (+), 37.3 (–), 54.9 + 55.6 (–), 57.7 + 58.6 (+), 63.8 + 66.4 (–), 68.8 (+), 80.4 (C_{quat}), 155.0 + 156.9 (C_{quat}).



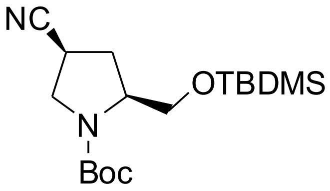
*(2S,4R)-N-Boc-O-TBDMS-4-Hydroxyprolinol (***4***):*[125] (2*S*,4*R*)-*N*-Boc-4-Hydroxyprolinol **3** (3.28 g, 15 mmol) was dissolved under N_2-flow in ice-cold vigorously stirred mixture of triethyl amine (2.5 mL, 1.8 g, 18 mmol) and CH_2Cl_2 (100 mL), DMAP (0.1 g) was added, followed with TBDMS-Cl toluene solution (55.2% w/w, 4.55 g, 16 mmol) and the mixture was left to stir at ambient temperature overnight. The mixture was diluted with diethyl



ether (300 mL) to form precipitate, which was filtered out; filter cake was washed with diethyl ether (3 × 20 mL) and discarded. Combined filtrates were concentrated under reduced pressure to give oily residue, which was purified with the column chromatography (silica gel, eluted with ethyl acetate/hexane 1:3) to give target product **4** as colorless oil (2.2 g, 6.6 mmol, 44%).

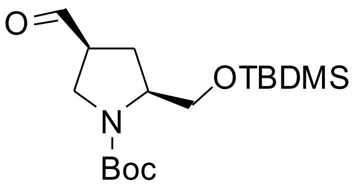


*(2S,4R)-N-Boc-O-TBDMS-4-Mesyloxyprolinol (***5***):*[28] To a solution of (2*S*,4*R*)-*N*-Boc-*O*-TBDMS-4-Hydroxyprolinol **4** (2.26 g, 6.8 mmol) and triethylamine (1.4 mL, 10.2 mmol) in CH_2Cl_2 (6 mL) at –78 °C was added mesyl chloride (0.7 mL, 1.05 g, 9.2 mmol) within 5 min. The mixture was allowed to warm to 0 °C and stirred for an additional 3 h, before aq. sat. $NaHCO_3$ (5 mL) was added. The reaction mixture was extracted with diethyl ether (3 × 20 mL), combined extracts were washed with H_2O (3 × 20 mL), aq. 1M $KHSO_4$ (3 × 20 mL), H_2O (3 × 20 mL), brine (2 × 20 mL) and dried over $MgSO_4$. Concentration under reduced pressure gave the target product **5** (2.53 g, 6.2 mmol, 94%) as a light yellow oil. R_f = 0.53 (EtOAc/hexane, 2:5); $[\alpha]_D^{20}$ –38.5 (c = 0.55, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = –0.01 (s, 6 H), 0.85 (s, 9 H), 1.44 (s, 9 H), 2.30–2.49 (m, 2 H), 3.02 (s, 3 H), 3.44–3.63 (m, 2 H), 3.63–4.15 (m, 3 H), 5.25–5.33 (m, 1 H); ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 353 K): δ = –5.7 (+), 17.8 (C_{quat}), 25.6 (+), 28.3 (+), 34.8 (–), 38.4 (+), 52.4 (–), 57.0 (+), 63.4 (–), 78.9 (+), 79.6 (C_{quat}), 153.6 (C_{quat}).

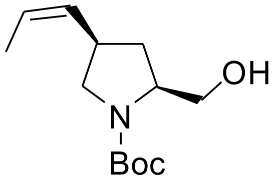


*(2S,4S)-N-Boc-O-TBDMS-4-Cyanoprolinol (***6***):*[28] A sealed round-bottomed flask, containing a solution of the mesyl ester **5** (2.53 g, 6.2 mmol) and tetrabutylammonium cyanide (3.44 g, 12.8 mmol) in anhydrous MeCN (3 mL) was immersed to an oil-bath which was preheated to 65–68 °C. The mixture was stirred for 6 h, diluted with ethyl acetate/hexane mixture (1:4, 25 mL), washed with water (5 × 5 mL) and brine (2 × 5 mL), dried over $MgSO_4$ and filtered through a pad of silica gel (1 cm). The solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, eluted with EtOAc/hexane 1:3, R_f = 0.50) to give target nitrile **6** (1.31 g, 62%) as a yellowish oil which solidified to a colorless solid upon seeding. M.p. 55–58 °C; $[\alpha]_D^{20}$ –25.9 (c = 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 358 K): δ = 0.10 (s, 6 H), 0.94 (s, 9 H), 1.48 (s, 9 H), 2.29–2.46 (m, 2 H), 2.90–3.01 (m, 1 H), 3.42 (dd, *J* = 8.2 Hz, 10.6 Hz, 1 H), 3.74 (dd, *J* = 3.0 Hz, 9.8 Hz, 1 H), 3.79–3.95 (m, 2 H), 3.96 (dd, *J* = 8.2 Hz, 10.6 Hz, 1 H); ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 358 K): δ = –5.6 (+), 17.9 (C_{quat}), 25.7 (+), 26.3 (+), 28.2 (+), 31.9 (–), 49.8 (–), 57.8 (+), 62.9 (–), 80.0 (C_{quat}), 119.8 (C_{quat}), 153.2 (C_{quat}).

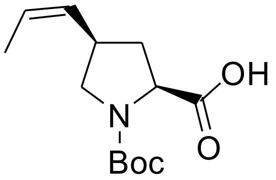
*(2S,4S)-N-Boc-O-TBDMS-4-Formylprolinol (**7**)*:[28] A 1 M solution of DIBAH in hexane (36.3 mL, 36.3 mmol) was added dropwise at –30 °C over 10 min to a stirred solution of the (2*S*,4*S*)-*N*-Boc-*O*-TBDMS-4-cyanoprolinol **6** (9.15 g, 26.9 mmol) in anhydrous CH_2Cl_2 (90 mL). The reaction mixture was stirred at –30 to –20 °C for 2 h, then methanol (2.5 mL) was added dropwise at 0 °C within 3 min, and stirring was continued at the same temperature for 15 min. A saturated aqueous NH_4Cl solution (8.5 mL) was added, and the mixture was allowed to warm to 20 °C. After 45 min, the reaction mixture was diluted with diethyl ether (80 mL), saturated aqueous potassium sodium tartrate (14 mL) was added and vigorous stirring was continued for an additional 1 h. The phases were separated, and the organic fraction was washed twice with a solution of citric acid (5.14 g, 26.72 mmol) in water (120 mL), with water (5 × 50 mL), brine (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was taken up with hexane (30 mL), filtered through a pad of Celite® and concentrated under reduced pressure to give the target aldehyde **7** (8.76 g, 95% crude) as a colorless oil, which was used for the next step without further purification. R_f = 0.37 (EtOAc/hexane, 1:4); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.03 (s, 6 H), 0.86 (s, 9 H), 1.43 (s, 9 H), 1.78–2.20 (m, 1 H), 2.22–2.41 (m, 1 H), 2.78–3.12 (m, 1 H), 3.45–4.02 (m, 5 H), 9.63 (s, 1 H).



*(2S,4R)-N-Boc-4-(Z)-Propenylprolinol (**9**)*:[28] A freshly prepared solution of *t*BuOK (10.0 g, 89.3 mmol) in THF (100 mL) was added to a suspension of ethyltriphenylphosponium bromide (40.0 g, 107.6 mmol) in THF (50 mL) at 0 °C. The cooling bath was removed, and stirring continued for an additional 2 h. The mixture was cooled to –78°C (dry ice/acetone bath), and a solution of (2*S*,4*S*)-*N*-Boc-*O*-TBDMS-4-formylprolinol **7** (8.8 g, 25.5 mmol) in THF (30 mL) was added dropwise within 2 h. Stirring was continued at the same temperature for an additional 24 h, and then the mixture was allowed to warm to 20 °C for 24 h. After 48 h, the reaction flask was immersed into an ice/water bath, and aq. sat. Na_2SO_4 (50 mL) was added. Organic layer was separated, water layer was washed with THF (2 × 50 mL), combined organic phases were concentrated under reduced pressure, yellow oily residue was taken up with CH_2Cl_2/ diethyl ether mixture (1:4, 200 mL), precipitate was filtered out through the pad of silica gel (5 cm) and filter cake was washed with CH_2Cl_2/diethyl ether mixture (1:4, 100 mL), filtrate was concentrated under reduced pressure, the residue was dissolved in diethyl ether (20 mL), the solution was filtered, concentrated under reduced pressure, the residue was dissolved in diethyl ether /hexane mixture (1:1, 20 mL), the solution was filtered, concentrated under reduced pressure, the residue was dissolved in hexane (20 mL), the solution was filtered, concentrated



under reduced pressure, the residue was dissolved in pentane (20 mL), the solution was filtered, concentrated, and the residue was finally purified by column chromatography (silica gel, eluted with EtOAc/ hexane 1:8, $R_f = 0.51$) to give pure (2*S*,4*R*)-*N*-Boc-*O*-TBDMS-4-(*Z*)-propenylprolinol **8** (5.3 g), which was dissolved in THF (10 mL) and deprotected by treating with the tetra-*n*-butylammonium fluoride trihydrate (6.25 g, 19.8 mmol) with stirring at ambient temperature. After 2 h, the mixture was diluted with diethyl ether (100 mL), washed with water (5 × 20 mL), brine (2 × 20 mL), dried over $MgSO_4$, concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, eluted with EtOAc/hexane 2:5, $R_f = 0.32$) to give target unsaturated alcohol **9** (1.70 g, 7.0 mmol, 28% over 2 steps from aldehyde) as a colorless oil which solidified into a colorless solid upon seeding. M.p. 41–43 °C; $[\alpha]_D^{20}$ –47.9 (c = 0.97, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ = 1.16–1.27 (m, 1 H), 1.46 (s, 9 H), 1.65 (dd, *J* = 6.9 Hz, 0.8 Hz, 3 H), 2.06–2.19 (m, 1 H), 2.83–2.96 (m, 1 H), 2.85–3.10 (m, 1 H), 3.52–3.77 (m, 3 H), 3.96(dd, *J* = 14.9 Hz, 7.6 Hz, 1 H), 5.11–2.24 (m, 1 H), 5.30 (dd, *J* = 8.9 Hz, 1.8 Hz, 1 H), 5.52 (dq, *J* = 9.8 Hz, 6.9 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.2 (+), 28.4 (+), 35.2 (+), 35.8 (–), 52.7 (–), 61.1 (+), 67.6 (–), 80.4 (C_{quat}), 126.3 (+), 129.8 (+), 156.8 (C_{quat}).



*(2S,4R)-N-Boc-4-(Z)-Propenylproline (***10***):*[28] A 2.67 M solution of Jones reagent[126] (30.5 mL, 81.4 mmol) was added to a solution of unsaturated alcohol **9** (1.96 g, 8.14 mmol) in freshly distilled acetone (670 mL) at 4 °C (inner temperature) within 1 h, and the mixture was stirred at the same temperature for an additional 4 h. Isopropyl alcohol (10 mL) was then added dropwise within 10 min, and the mixture was allowed to warm to 20 °C. Organic solution was decanted out of inorganic solid, latter was washed with diethyl ether (100 ml) and combined organics was concentrated under reduced pressure at ambient temperature to ca. 20 mL. Inorganic solid precipitate was dissolved in water (100 mL) and extracted with diethyl ether (2 × 50 mL). Extracts were combined with the organic concentrate, washed with water (2 × 50 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure, giving the crude product (2.15 g) as colorless oil. This was dissolved in diethyl ether (100 mL) and extracted with saturated aqueous $NaHCO_3$ solution (5 × 40 mL). The combined aqueous fractions were washed with diethyl ether (2 × 50 mL), the pH of the aqueous fractions was carefully adjusted to 2.5–3 with solid $KHSO_4$, the formed emulsion was extracted with diethyl ether (2 × 100 mL) and the organic fraction was washed with aq. 1 M $KHSO_4$ (3 × 50 mL), water (3 × 50 mL), brine (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was finally purified by column chromatography (silica gel, eluted with EtOAc/hexane 1:3 + 2%

AcOH, $R_f = 0.27$) to give the target unsaturated amino acid **10** (1.44 g, 69%) as a colorless solid. M.p. 84–85 °C; $[\alpha]_D^{20}$ –84.4 (c = 0.86, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.42, 1.48 (2 s, 9 H), 1.66 (d, J = 6.8 Hz, 3 H), 1.72–1.84, 1.93–2.12 (m, 1 H), 2.27–2.54 (m, 1 H), 2.87–3.24 (m, 2 H), 3.64–3.86 (m, 1 H), 4.25 + 4.35 (2 × dd, J = 8.3 Hz, 8.3 Hz, 1 H), 5.26 (ddq, J = 9.6 Hz, 8.5 Hz, 1.8 Hz, 1 H), 5.52 (dq, J = 8.5 Hz, 6.8 Hz, 1 H), 10.30–11.40 (bs, 1 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.1 (+), 28.1 + 28.3 (+), 35.7 + 36.1 (+), 36.2 + 37.3 (–), 51.4 + 51.9 (–), 58.9 + 59.1 (+), 80.6 (C_{quat}), 126.6 + 126.9 (+), 129.0 + 129.2 (+), 153.6 +154.8 (C_{quat}), 177.3 + 178.4 (C_{quat}).

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SUMMARY

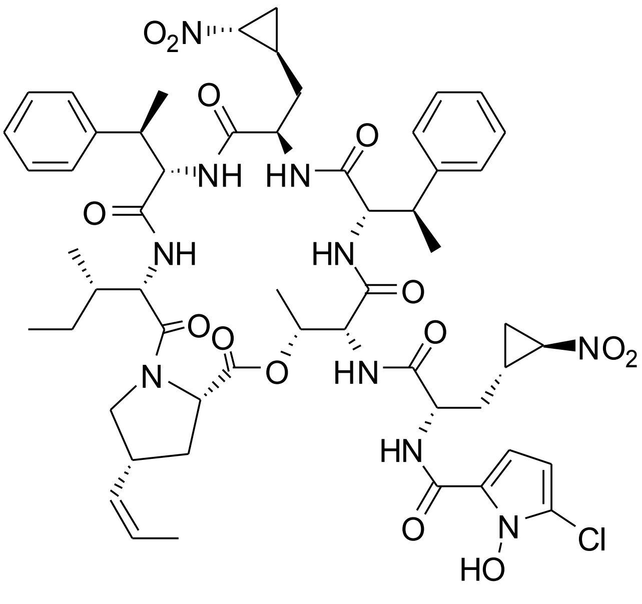
Hormaomycin **1** and its all-peptide aza-analogue **53** were synthesized in quantities of 39 and 34 mg respectively, using the protocol developed by B. Zlatopolskiy, to have enough material for *in vitro* and *in vivo* biological tests.

(*R*)-*allo*-Threonine **67** was prepared on a multigram scale employing a modified Belokon' protocol providing kinetically controlled conditions for an aldol reaction between the glycine complex enolate and acetaldehyde.

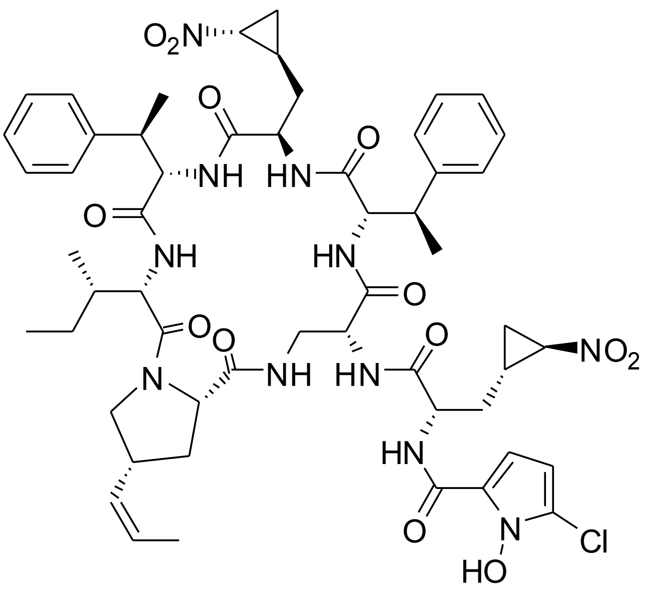
A new synthesis of *β*-methyl(haloaryl)alanines **48 – 52** was developed on the basis of the Belokon' protocol using commercially available haloacetophenones as starting materials for the preparation of 1-(haloaryl)ethyl iodides to alkylate the (*S*)-configured Belokon' glycine complex (*S*)-BGC **13**. *β*-Methylphenylalanine **(2*S*,3*R*)-48** was prepared on a multigram scale according to this protocol.

(2*R*)- and (2*S*)-3-(1'*S*,2'*R*)-(2'-Fluoromethylcyclopropyl)alanines [mono- (***R*-96 a** and ***S*-96 a**), di- (***R*-96 b** and ***S*-96 b**) and trifluoromethyl (***R*-96 c** and ***S*-96 c**) derivatives] were prepared employing the protocol developed by O. Larionov for the preparation of 3-(2-*trans*-nitrocyclopropyl)alanines.[25]

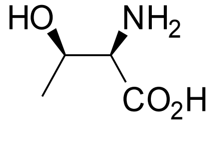
New Hormaomycin analogues **109 a-c**, containing (2*R*)- and (2*S*)-3-(1'*S*,2'*R*)-(2'-fluoromethylcyclopropyl)alanine moieties instead of (2*R*)- and (2*S*)-3-(1'*R*,2'*R*)-(2'-nitrocyclopropyl)alanine were synthesized, and their *in vitro* antimalarial activities were tested. The activities turned out to be comparable to the one for native Hormaomycin and in the case of the MeZ-protected cyclic peptidolactone core with (2*R*)-3-(1'*S*,2'*R*)-(2'-trifluoromethylcyclopropyl)alanine **103 c** twice better than that of the reference drug Chloroquine against the malaria parasite *Plasmodium falciparum* strain K1.



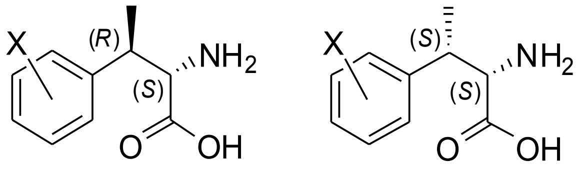
Hormaomycin **1**



Hormaomycin all-peptide aza-analogue **53**



(R)-allo-Threonine **67**



β-Methylphenylalanines

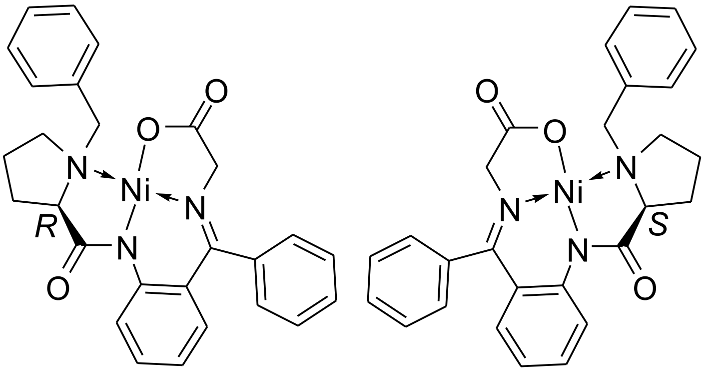
48 X = H

49 X = *o*-Cl

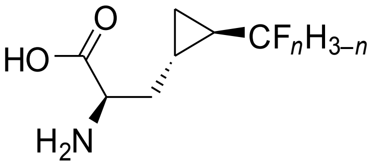
50 X = *m*-Cl

51 X = *p*-Cl

52 X = *p*-F



Belokon' glycine complexes **R-13** *and* **S-13**

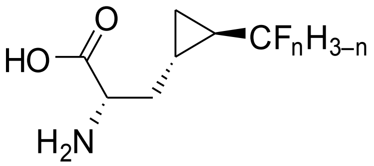


***R*-96 a** $n = 1$

***R*-96 b** $n = 2$

***R*-96 c** $n = 3$

(2R,1'S,2'R)-3-(fluoromethylcyclopropyl)alanines

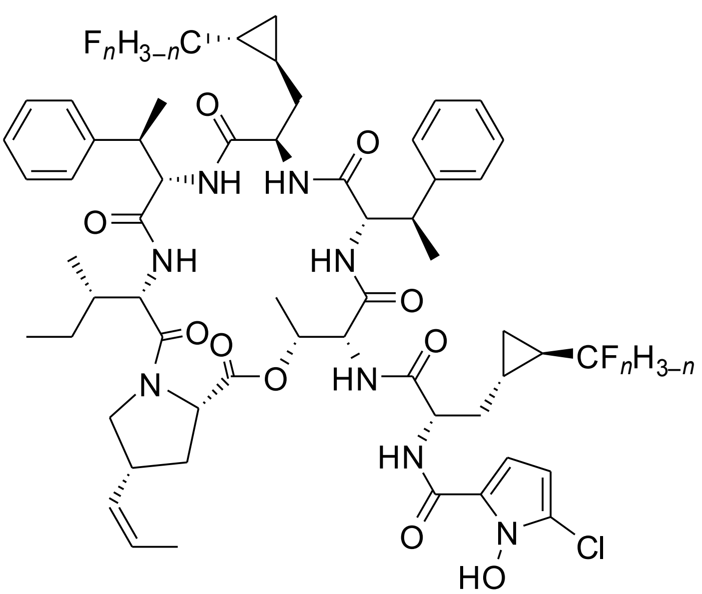


***S*-96 a** ($n = 1$)

***S*-96 b** ($n = 2$)

***S*-96 c** ($n = 3$)

(2S,1'S,2'R)-3-(fluoromethylcyclopropyl)alanines



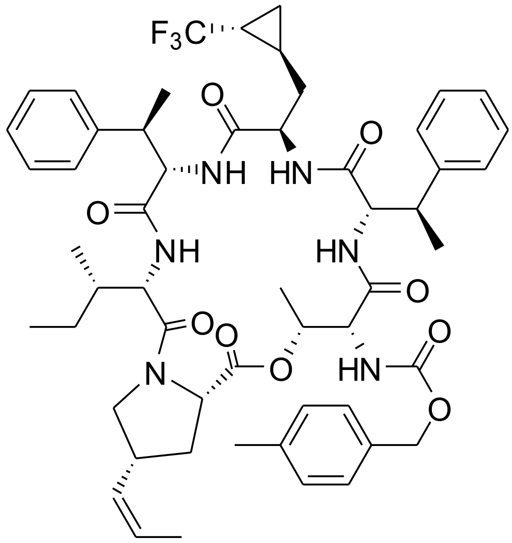
(Fluoromethylcyclopropyl)alanyl

Hormaomycin analogues

109 a (*n* = 1)

109 b (*n* = 2)

109 c (*n* = 3)



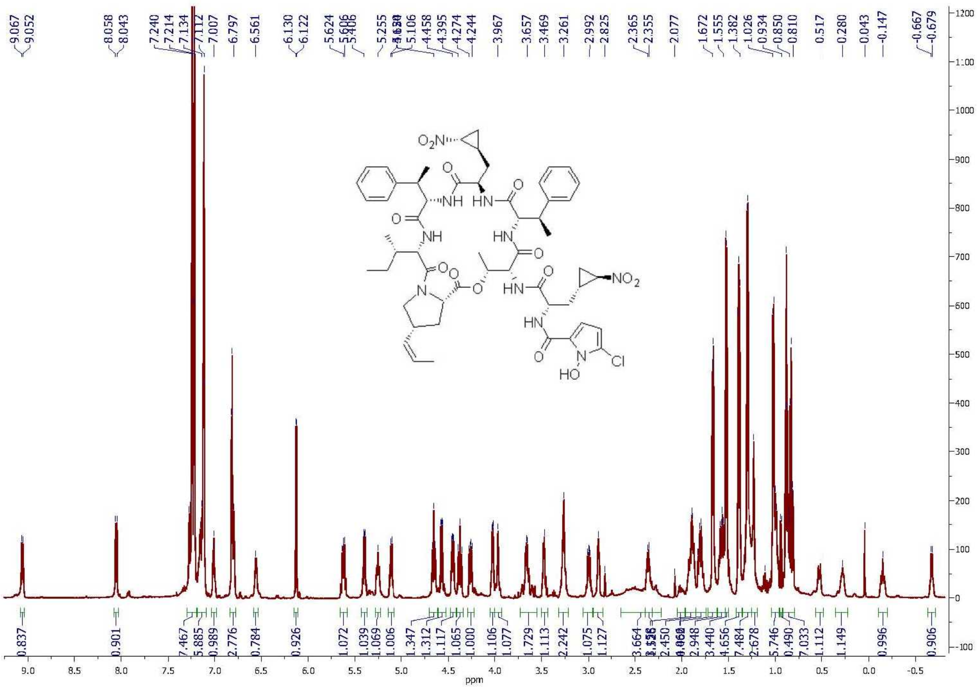
MeZ-protected cyclohexadepsipeptide

103 c

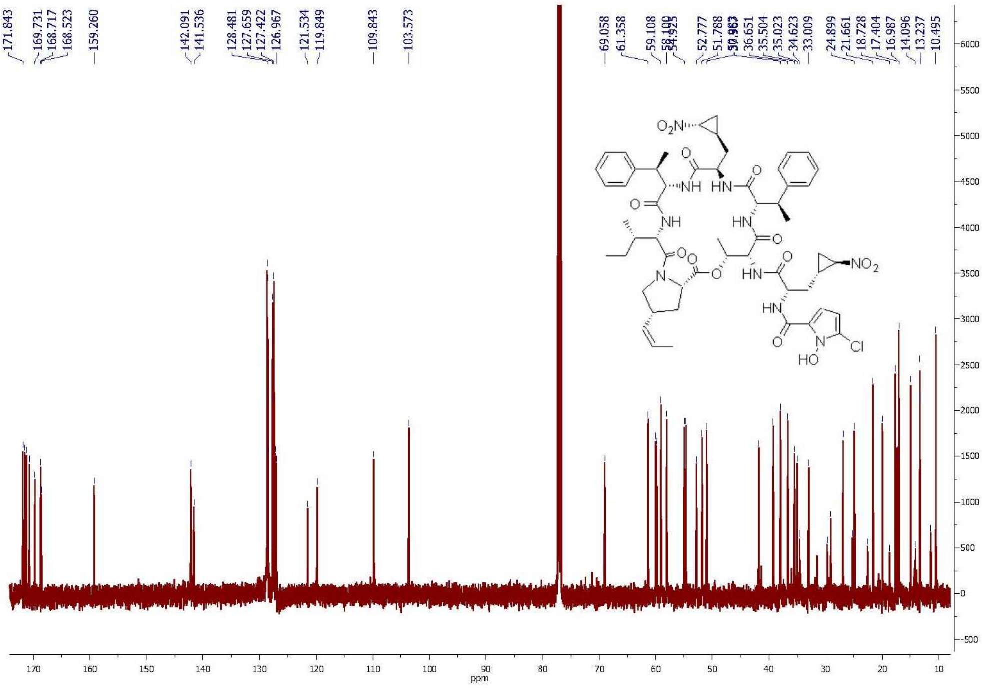
SPECTRAL DATA

1. NMR

Hormaomycin **1**

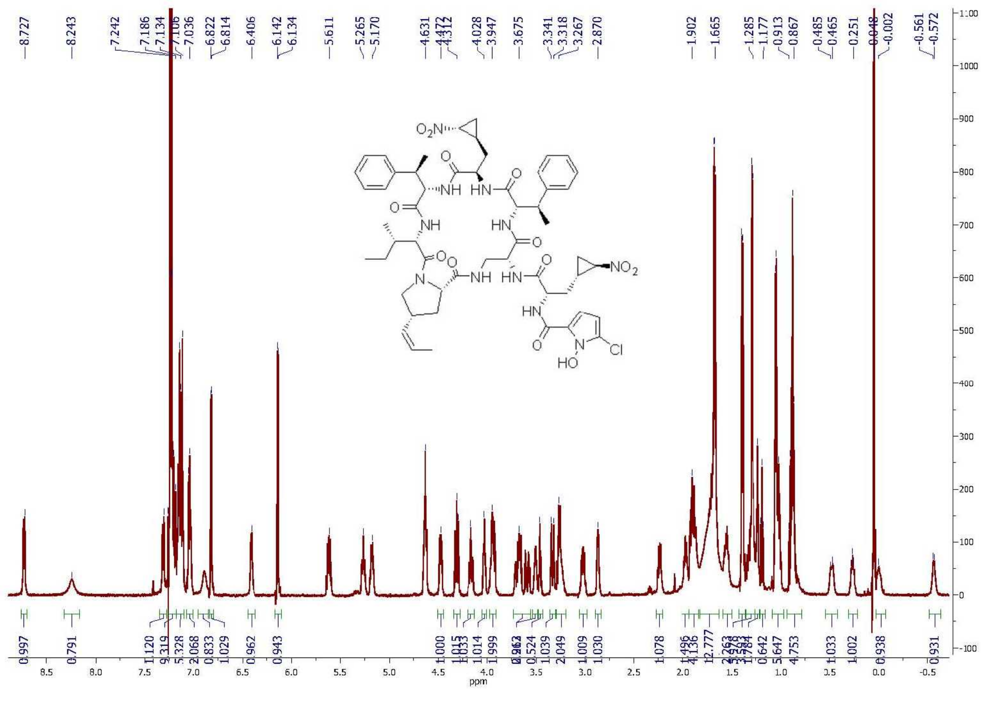


^{1}H NMR (600 MHz, CDCl$_3$)

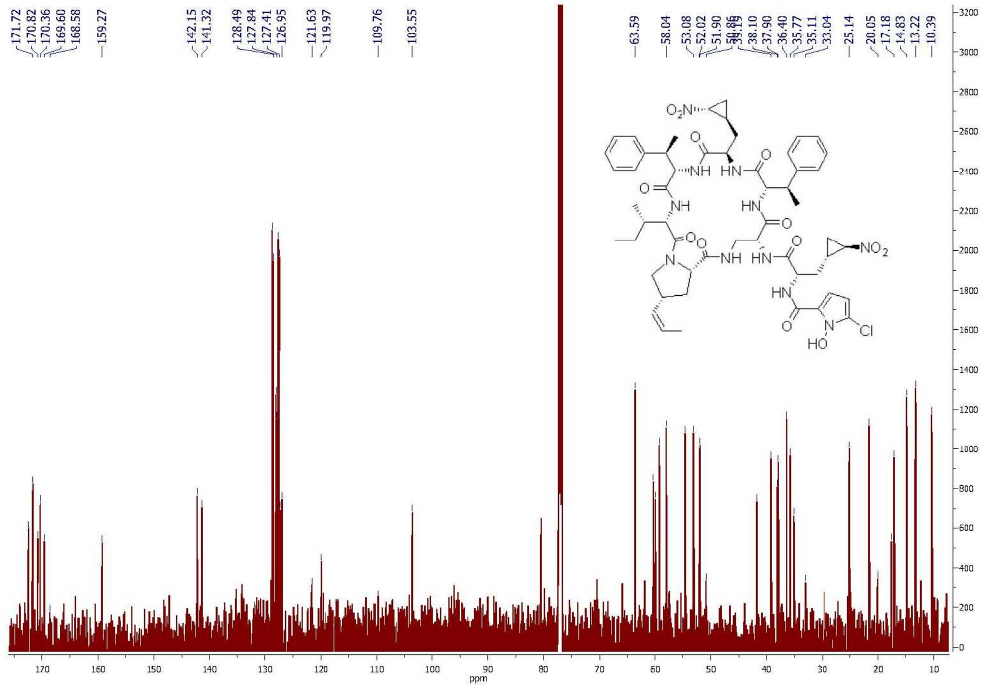


^{13}C NMR (150.8 MHz, CDCl$_3$)

Hormaomycin all-peptide aza-analogue **53**

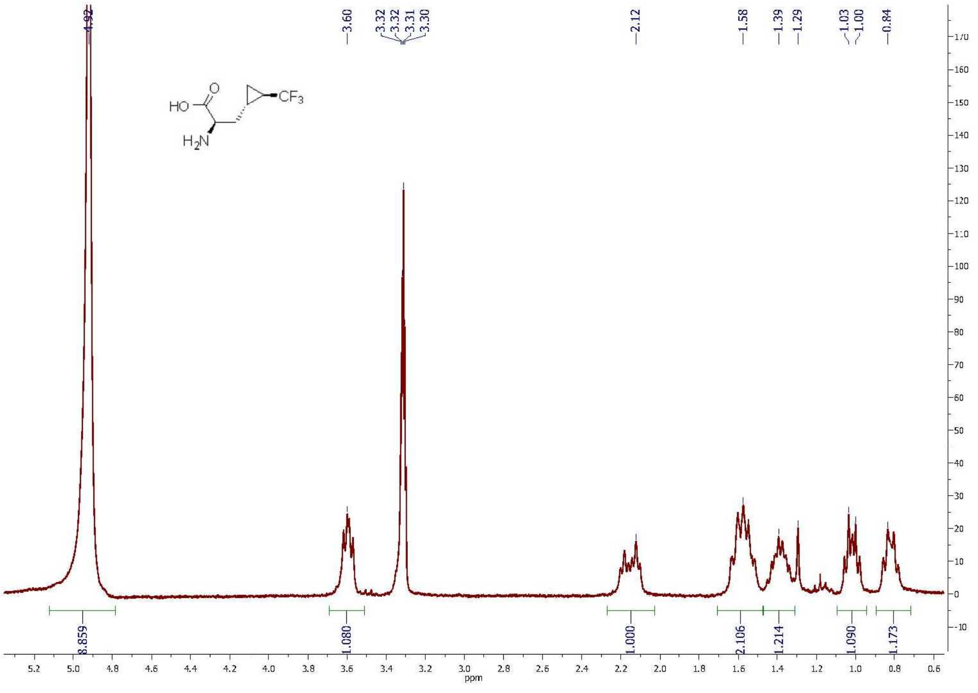


^{1}H NMR (600 MHz, $CDCl_3$)

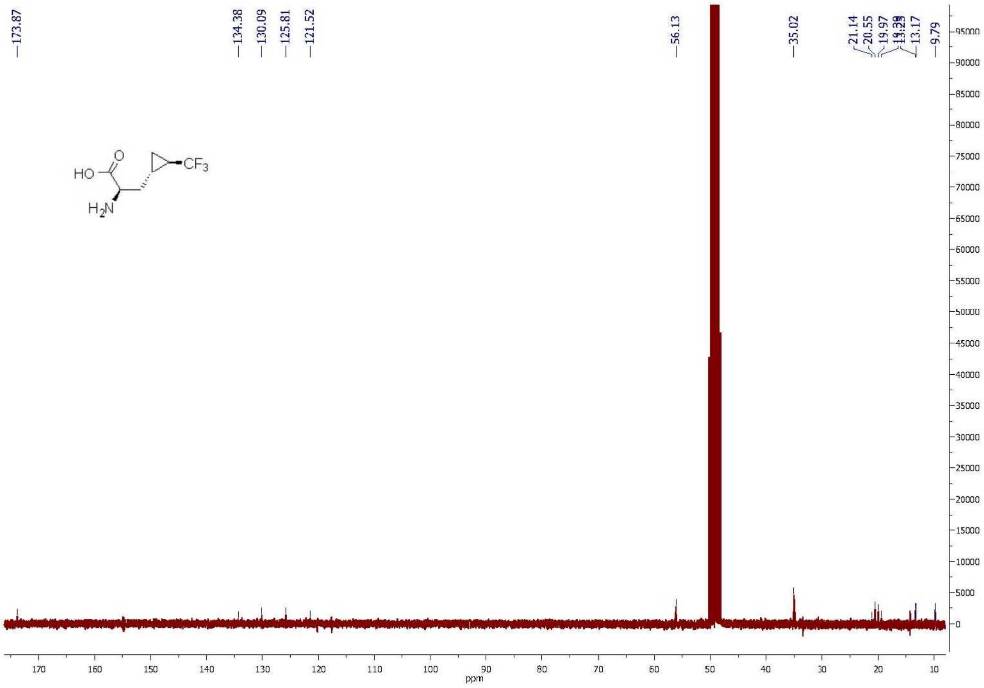


^{13}C NMR (150.8 MHz, $CDCl_3$)

(2*R*,1'*S*,2'*R*)-3-(2'-trifluoromethylcyclopropyl)alanine

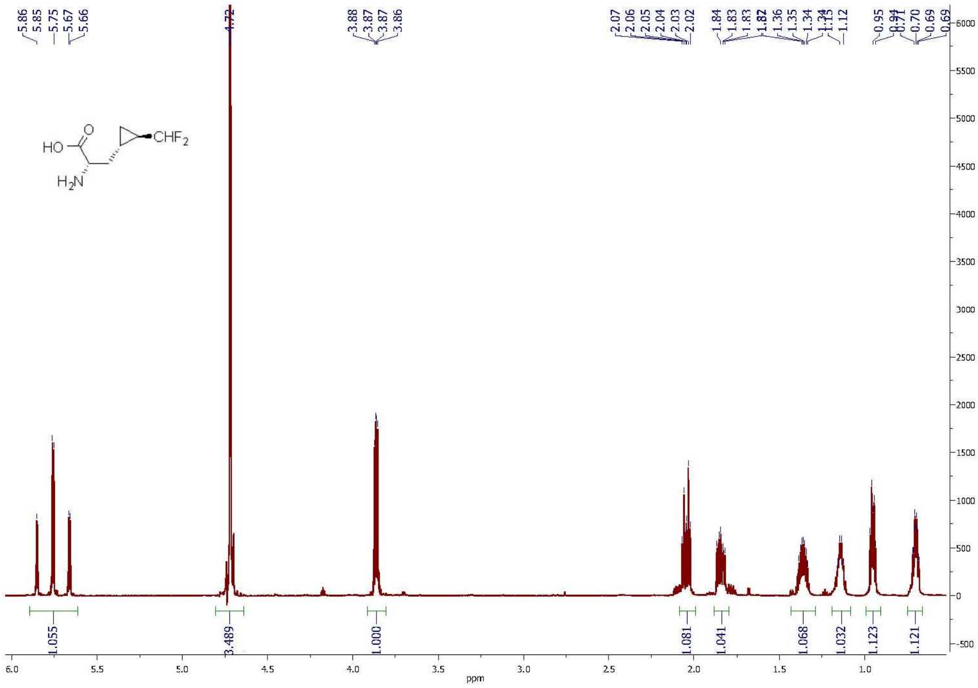


^{1}H NMR (600 MHz, CD_3OD)

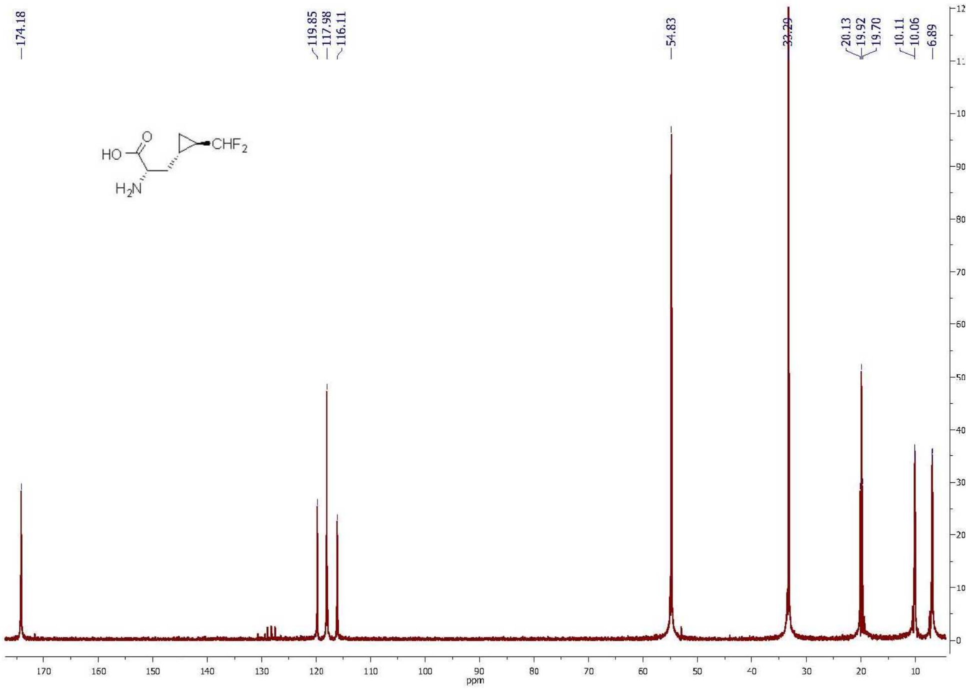


^{13}C NMR (125.7 MHz, CD_3OD)

(2*S*,1'*S*,2'*R*)-3-(2'-difluoromethylcyclopropyl)alanine

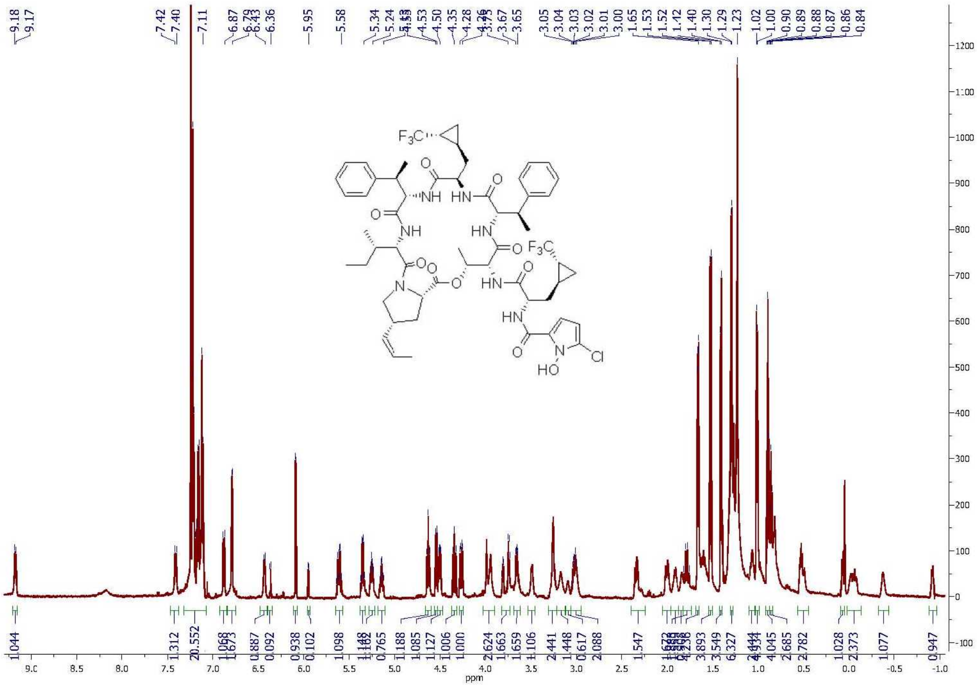


^{1}H NMR (600 MHz, D_2O)

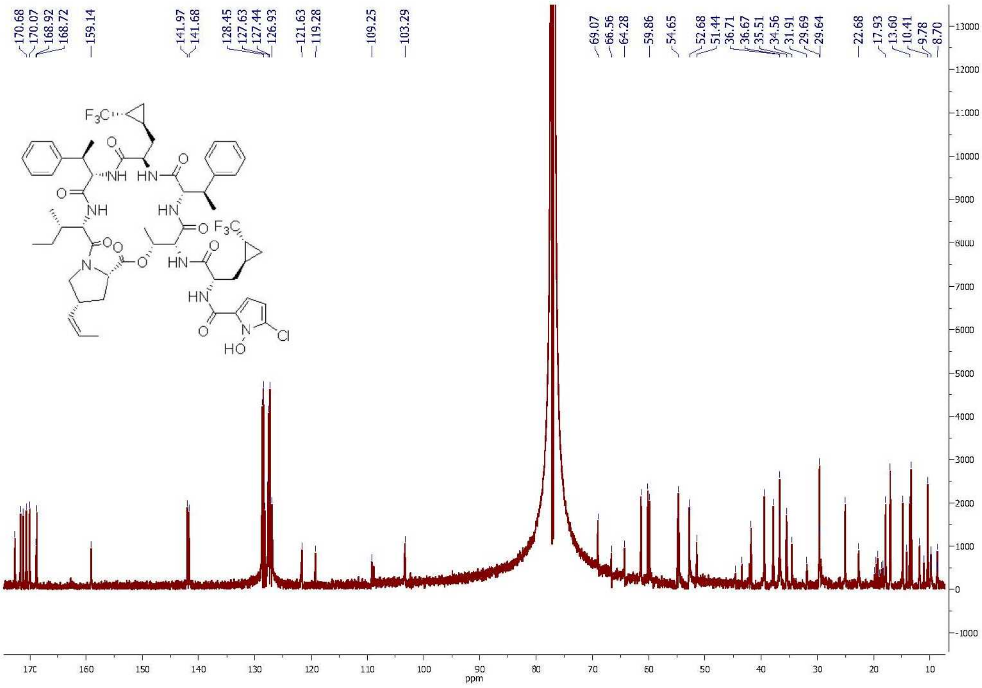


^{13}C NMR (125.7 MHz, D_2O)

(Trifluoromethylcyclopropyl)alanyl Hormaomycin



^{1}H NMR (600 MHz, $CDCl_3$)



^{13}C NMR (125.7 MHz, $CDCl_3$)

2. X-Ray

Belokon' (2S,1'S,2'R)–3–(2'–trifluoromethylcycloprpopyl)alanine complex

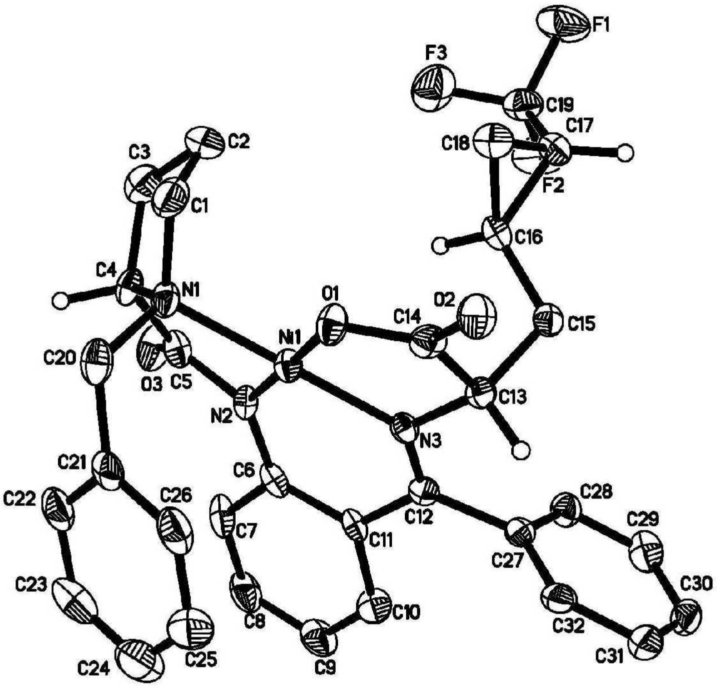


Table 1. Crystal data and structure refinement for dk25.

Identification code	dk25	
Empirical formula	$C_{32}H_{30}F_3N_3NiO_3$	
Formula weight	620.30	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	$P\,4_3\,2_1\,2$	
Unit cell dimensions	a = 9.9745(2) Å	α = 90°.
	b = 9.9745(2) Å	β = 90°.
	c = 57.255(2) Å	γ = 90°.
Volume	5696.4(2) $Å^3$	
Z	8	
Density (calculated)	1.447 Mg/m^3	
Absorption coefficient	0.740 mm^{-1}	
F(000)	2576	
Crystal size	0.52 × 0.14 × 0.10 mm^3	
Theta range for data collection	2.49 to 25.49°.	
Index ranges	–11<=h<=11, –12<=k<=11, –68<=l<=69	
Reflections collected	35391	
Independent reflections	5151 [R(int) = 0.0644]	
Completeness to theta = 25.49°	98.3 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9297 and 0.6996	
Refinement method	Full–matrix least–squares on F^2	
Data / restraints / parameters	5151 / 0 / 379	
Goodness–of–fit on F^2	1.144	
Final R indices [I>2sigma(I)]	R_1 = 0.0480, wR_2 = 0.0945	
R indices (all data)	R_1 = 0.0571, wR_2 = 0.0968	
Absolute structure parameter	0.03(2)	
Largest diff. peak and hole	0.466 and –0.706 e.$Å^{-3}$	

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters ($Å^2$ × 10^3) for dk25. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
Ni(1)	650(1)	5721(1)	9554(1)	18(1)
O(1)	1058(3)	6987(3)	9783(1)	23(1)
O(2)	1591(3)	9151(3)	9834(1)	27(1)
O(3)	–1249(3)	2638(3)	9289(1)	35(1)
N(1)	93(3)	4427(3)	9789(1)	22(1)
N(2)	250(3)	4424(3)	9332(1)	20(1)
N(3)	1218(3)	6989(3)	9339(1)	17(1)
C(1)	–754(5)	4990(4)	9980(1)	35(1)
C(2)	–2129(5)	5080(5)	9871(1)	40(1)
C(3)	–2244(4)	3720(5)	9748(1)	32(1)
C(4)	–794(4)	3408(4)	9670(1)	23(1)
C(5)	–621(4)	3446(4)	9410(1)	25(1)
C(6)	872(4)	4348(4)	9114(1)	22(1)
C(7)	886(5)	3121(4)	8984(1)	29(1)
C(8)	1604(5)	3014(4)	8779(1)	34(1)
C(9)	2324(5)	4076(5)	8691(1)	35(1)
C(10)	2283(4)	5285(4)	8807(1)	26(1)
C(11)	1550(4)	5446(4)	9017(1)	20(1)
C(12)	1543(4)	6797(4)	9124(1)	18(1)
C(13)	1267(4)	8361(4)	9443(1)	21(1)
C(14)	1327(4)	8193(4)	9709(1)	22(1)
C(15)	22(4)	9203(4)	9377(1)	20(1)
C(16)	–1261(4)	8621(4)	9468(1)	21(1)
C(17)	–2486(4)	9515(4)	9476(1)	25(1)
C(18)	–1814(4)	9061(4)	9700(1)	26(1)
C(19)	–3768(4)	8888(5)	9408(1)	30(1)
C(20)	1351(4)	3822(4)	9893(1)	27(1)
C(21)	2408(4)	3540(4)	9709(1)	25(1)
C(22)	2419(4)	2358(4)	9583(1)	33(1)
C(23)	3324(5)	2169(5)	9403(1)	43(1)
C(24)	4265(6)	3142(6)	9352(1)	53(1)
C(25)	4304(5)	4315(6)	9483(1)	49(1)
C(26)	3367(4)	4514(5)	9661(1)	34(1)
C(27)	1940(4)	7937(4)	8962(1)	19(1)
C(28)	1088(4)	8283(4)	8779(1)	25(1)
C(29)	1483(5)	9227(5)	8616(1)	31(1)
C(30)	2731(5)	9841(4)	8638(1)	33(1)
C(31)	3571(4)	9531(4)	8822(1)	31(1)
C(32)	3168(4)	8568(4)	8986(1)	24(1)
F(1)	–4847(3)	9639(3)	9465(1)	47(1)
F(2)	–3841(3)	8699(3)	9176(1)	47(1)
F(3)	–3995(3)	7678(3)	9506(1)	46(1)

Table 3. Selected bond lengths [Å] and angles [°] for dk25.

Ni(1)–N(3)	1.855(3)	C(4)–C(5)	1.496(5)	C(19)–F(2)	1.345(4)
Ni(1)–N(2)	1.860(3)	C(6)–C(11)	1.403(5)	C(19)–F(3)	1.348(5)
Ni(1)–O(1)	1.864(3)	C(6)–C(7)	1.431(5)	C(19)–F(1)	1.351(5)
Ni(1)–N(1)	1.942(3)	C(7)–C(8)	1.379(6)	C(20)–C(21)	1.517(6)
O(1)–C(14)	1.303(5)	C(8)–C(9)	1.377(7)	C(21)–C(22)	1.382(6)
O(2)–C(14)	1.220(5)	C(9)–C(10)	1.378(6)	C(21)–C(26)	1.391(6)
O(3)–C(5)	1.237(5)	C(10)–C(11)	1.415(5)	C(22)–C(23)	1.381(6)
N(1)–C(1)	1.495(5)	C(11)–C(12)	1.480(5)	C(23)–C(24)	1.382(8)
N(1)–C(4)	1.510(5)	C(12)–C(27)	1.517(5)	C(24)–C(25)	1.389(8)
N(1)–C(20)	1.515(5)	C(13)–C(14)	1.532(5)	C(25)–C(26)	1.398(7)
N(2)–C(5)	1.382(5)	C(13)–C(15)	1.547(5)	C(27)–C(32)	1.384(6)
N(2)–C(6)	1.396(4)	C(15)–C(16)	1.499(5)	C(27)–C(28)	1.392(5)
N(3)–C(12)	1.290(4)	C(16)–C(18)	1.506(5)	C(28)–C(29)	1.384(6)
N(3)–C(13)	1.494(5)	C(16)–C(17)	1.513(5)	C(29)–C(30)	1.393(6)
C(1)–C(2)	1.509(7)	C(17)–C(19)	1.477(6)	C(30)–C(31)	1.381(6)
C(2)–C(3)	1.534(6)	C(17)–C(18)	1.516(5)	C(31)–C(32)	1.402(6)
C(3)–C(4)	1.545(6)				

N(3)–Ni(1)–N(2)	94.78(13)	N(3)–C(12)–C(27)	122.4(3)
N(3)–Ni(1)–O(1)	86.47(12)	C(11)–C(12)–C(27)	115.4(3)
N(2)–Ni(1)–O(1)	178.60(12)	N(3)–C(13)–C(14)	107.4(3)
N(3)–Ni(1)–N(1)	177.93(14)	N(3)–C(13)–C(15)	111.8(3)
N(2)–Ni(1)–N(1)	87.14(13)	C(14)–C(13)–C(15)	109.7(3)
O(1)–Ni(1)–N(1)	91.60(12)	O(2)–C(14)–O(1)	125.3(4)
C(14)–O(1)–Ni(1)	116.2(2)	O(2)–C(14)–C(13)	120.2(4)
C(1)–N(1)–C(4)	104.6(3)	O(1)–C(14)–C(13)	114.6(3)
C(1)–N(1)–C(20)	109.2(3)	C(16)–C(15)–C(13)	112.9(3)
C(4)–N(1)–C(20)	113.3(3)	C(15)–C(16)–C(18)	120.5(3)
C(1)–N(1)–Ni(1)	114.8(2)	C(15)–C(16)–C(17)	118.2(3)
C(4)–N(1)–Ni(1)	107.7(2)	C(18)–C(16)–C(17)	60.3(3)
C(20)–N(1)–Ni(1)	107.5(2)	C(19)–C(17)–C(16)	116.2(4)
C(5)–N(2)–C(6)	122.2(3)	C(19)–C(17)–C(18)	118.7(4)
C(5)–N(2)–Ni(1)	113.7(2)	C(16)–C(17)–C(18)	59.6(3)
C(6)–N(2)–Ni(1)	123.8(3)	C(16)–C(18)–C(17)	60.1(2)
C(12)–N(3)–C(13)	120.7(3)	F(2)–C(19)–F(3)	106.0(4)
C(12)–N(3)–Ni(1)	127.7(3)	F(2)–C(19)–F(1)	105.8(3)
C(13)–N(3)–Ni(1)	111.6(2)	F(3)–C(19)–F(1)	105.2(3)
N(1)–C(1)–C(2)	103.5(3)	F(2)–C(19)–C(17)	111.5(3)
C(1)–C(2)–C(3)	101.9(4)	F(3)–C(19)–C(17)	114.5(3)
C(2)–C(3)–C(4)	104.0(3)	F(1)–C(19)–C(17)	113.0(4)
C(5)–C(4)–N(1)	111.2(3)	N(1)–C(20)–C(21)	112.1(3)
C(5)–C(4)–C(3)	112.9(3)	C(22)–C(21)–C(26)	119.2(4)
N(1)–C(4)–C(3)	106.4(3)	C(22)–C(21)–C(20)	121.8(4)
O(3)–C(5)–N(2)	126.5(3)	C(26)–C(21)–C(20)	119.0(4)
O(3)–C(5)–C(4)	119.0(4)	C(23)–C(22)–C(21)	120.7(5)
N(2)–C(5)–C(4)	114.5(3)	C(22)–C(23)–C(24)	120.4(5)
N(2)–C(6)–C(11)	121.7(3)	C(23)–C(24)–C(25)	119.7(5)
N(2)–C(6)–C(7)	121.0(4)	C(24)–C(25)–C(26)	119.7(5)

C(11)–C(6)–C(7)	117.3(3)	C(21)–C(26)–C(25)	120.2(5)
C(8)–C(7)–C(6)	120.8(4)	C(32)–C(27)–C(28)	120.1(4)
C(9)–C(8)–C(7)	121.7(4)	C(32)–C(27)–C(12)	120.8(3)
C(8)–C(9)–C(10)	118.7(4)	C(28)–C(27)–C(12)	119.0(3)
C(9)–C(10)–C(11)	121.6(4)	C(29)–C(28)–C(27)	120.2(4)
C(6)–C(11)–C(10)	119.8(4)	C(28)–C(29)–C(30)	119.5(4)
C(6)–C(11)–C(12)	123.0(3)	C(31)–C(30)–C(29)	120.9(4)
C(10)–C(11)–C(12)	117.2(3)	C(30)–C(31)–C(32)	119.4(4)
N(3)–C(12)–C(11)	122.1(3)	C(27)–C(32)–C(31)	119.9(4)

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for dk25. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\, h^2 a^{*2}U^{11} + \ldots + 2\, h\, k\, a^*\, b^*\, U^{12}\,]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Ni(1)	23(1)	16(1)	17(1)	0(1)	–2(1)	0(1)
O(1)	32(2)	17(1)	21(1)	1(1)	–2(1)	–5(1)
O(2)	31(2)	21(2)	30(2)	–4(1)	–3(1)	–6(1)
O(3)	51(2)	26(2)	27(2)	–1(1)	–8(1)	–15(2)
N(1)	29(2)	19(2)	17(2)	3(1)	0(1)	1(2)
N(2)	24(2)	15(2)	21(2)	4(1)	–3(1)	–1(2)
N(3)	17(2)	16(2)	17(2)	0(1)	–3(1)	2(1)
C(1)	50(3)	23(2)	31(2)	0(2)	14(2)	–3(2)
C(2)	40(3)	31(3)	48(3)	3(2)	20(2)	11(2)
C(3)	28(3)	37(3)	30(2)	6(2)	–2(2)	–4(2)
C(4)	26(2)	17(2)	25(2)	5(2)	–1(2)	–8(2)
C(5)	29(2)	20(2)	26(2)	3(2)	–6(2)	4(2)
C(6)	25(2)	16(2)	24(2)	–3(2)	–8(2)	6(2)
C(7)	49(3)	15(2)	24(2)	2(2)	–6(2)	3(2)
C(8)	51(3)	21(2)	30(2)	–5(2)	1(2)	10(2)
C(9)	47(3)	33(3)	24(2)	–5(2)	6(2)	14(2)
C(10)	35(3)	29(3)	15(2)	–2(2)	1(2)	2(2)
C(11)	23(2)	15(2)	22(2)	1(2)	–4(2)	6(2)
C(12)	11(2)	22(2)	21(2)	2(2)	–5(2)	0(2)
C(13)	22(2)	16(2)	24(2)	–1(2)	4(2)	–1(2)
C(14)	17(2)	24(2)	26(2)	–2(2)	0(2)	–3(2)
C(15)	27(2)	17(2)	16(2)	–2(2)	1(2)	1(2)
C(16)	23(2)	16(2)	24(2)	–2(2)	–3(2)	4(2)
C(17)	23(2)	22(2)	30(2)	0(2)	2(2)	5(2)
C(18)	23(2)	33(3)	22(2)	–2(2)	–2(2)	2(2)
C(19)	27(2)	40(3)	24(2)	2(2)	2(2)	6(2)
C(20)	33(3)	24(2)	23(2)	5(2)	–10(2)	–3(2)
C(21)	22(2)	28(2)	24(2)	7(2)	–10(2)	6(2)
C(22)	28(3)	27(3)	43(2)	9(2)	–10(2)	7(2)
C(23)	39(3)	41(3)	50(3)	–6(2)	–9(2)	20(3)
C(24)	46(3)	59(4)	54(3)	8(3)	10(3)	23(3)
C(25)	29(3)	45(3)	74(4)	14(3)	8(3)	2(3)
C(26)	31(3)	26(3)	44(3)	6(2)	–11(2)	5(2)
C(27)	21(2)	16(2)	18(2)	–5(2)	2(2)	0(2)

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(28)	28(2)	24(2)	23(2)	4(2)	–1(2)	2(2)
C(29)	46(3)	28(2)	20(2)	0(2)	–1(2)	4(2)
C(30)	45(3)	21(2)	31(2)	2(2)	17(2)	1(2)
C(31)	30(2)	24(2)	40(2)	–1(2)	10(2)	–2(2)
C(32)	21(2)	24(2)	28(2)	–3(2)	5(2)	2(2)
F(1)	27(1)	67(2)	46(2)	0(1)	0(1)	19(1)
F(2)	30(2)	80(2)	31(1)	–11(1)	–6(1)	–4(1)
F(3)	31(2)	48(2)	59(2)	10(1)	–3(1)	–10(1)

Table 5. Hydrogen coordinates (× 10^4) and isotropic displacement parameters ($Å^2 \times 10^3$) for dk25.

Atom	x	y	z	U(eq)
H(1A)	–430	5886	10029	42
H(1B)	–760	4389	10118	42
H(2A)	–2184	5831	9759	48
H(2B)	–2834	5189	9992	48
H(3A)	–2852	3778	9611	38
H(3B)	–2582	3023	9856	38
H(4A)	–546	2494	9727	27
H(7A)	394	2371	9040	35
H(8A)	1603	2186	8697	41
H(9A)	2838	3978	8552	41
H(10A)	2759	6029	8745	32
H(13A)	2095	8831	9389	25
H(15A)	131	10122	9439	24
H(15B)	–31	9268	9204	24
H(16A)	–1433	7664	9425	25
H(17A)	–2354	10473	9430	30
H(18A)	–1297	9735	9790	31
H(18B)	–2283	8384	9796	31
H(20A)	1118	2976	9974	32
H(20B)	1723	4447	10011	32
H(22A)	1797	1669	9620	39
H(23A)	3300	1364	9315	52
H(24A)	4884	3009	9228	63
H(25A)	4962	4978	9451	59
H(26A)	3386	5319	9750	41
H(28A)	233	7871	8767	30
H(29A)	908	9453	8490	37
H(30A)	3007	10482	8525	39
H(31A)	4413	9966	8837	38
H(32A)	3738	8349	9113	29

Belokon' (2S,1'R,2'S)–3–(2'–difluoromethylcycloprpopyl)alanine complex

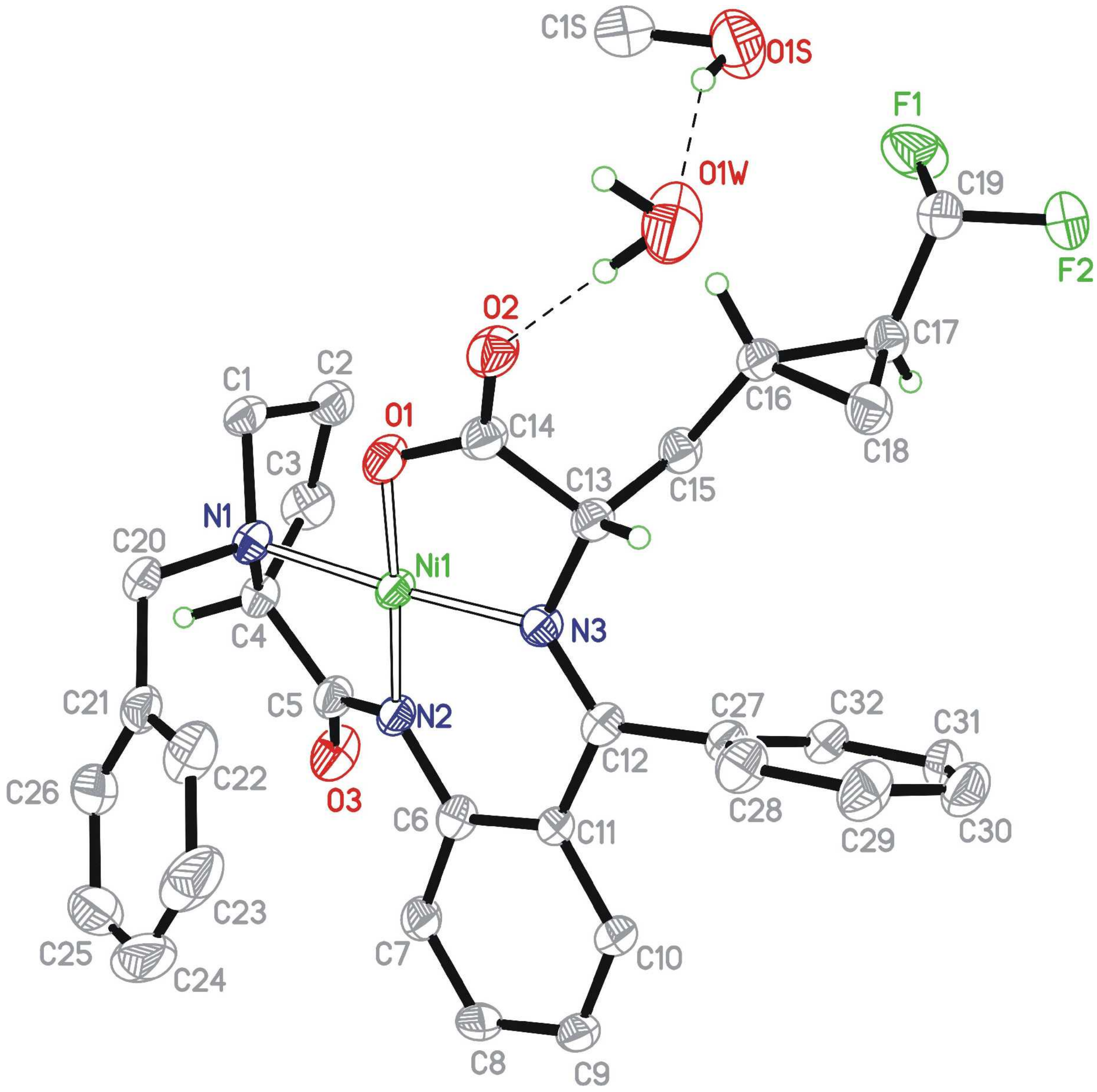


Table 1. Crystal data and structure refinement for DK33.

Identification code	dk33
Empirical formula	$C_{32}H_{31}F_2N_3NiO_3 \times CH_3OH \times H_2O$
Formula weight	651.36
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 2_1

Unit cell dimensions	a = 9.2565(6) Å	α = 90°.
	b = 11.8858(6) Å	β = 90.67(3)°.
	c = 14.020(1) Å	γ = 90°.
Volume	1542.4(5) Å^3	
Z	2	
Density (calculated)	1.403 Mg/m^3	
Absorption coefficient	0.687 mm^{-1}	
F(000)	682	
Crystal size	0.33 × 0.22 × 0.08 mm^3	
Theta range for data collection	1.45 to 29.50°.	
Index ranges	–12<=h<=12, –16<=k<=16, –19<=l<=19	
Reflections collected	16960	
Independent reflections	8238 [R(int) = 0.0657]	
Completeness to theta = 29.50°	99.6 %	
Absorption correction	Numerical	
Max. and min. transmission	0.9101 and 0.7030	
Refinement method	Full–matrix least–squares on F^2	
Data / restraints / parameters	8238 / 1 / 532	
Goodness–of–fit on F^2	1.009	
Final R indices [I>2sigma(I)]	R_1 = 0.0487, wR_2 = 0.1122	
R indices (all data)	R_1 = 0.0542, wR_2 = 0.1203	
Absolute structure parameter	0.008(11)	
Largest diff. peak and hole	0.733 and –0.498 e.Å^{-3}	

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for DK33. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
Ni(1)	6637(1)	6446(1)	6486(1)	22(1)
O(1)	6124(3)	4947(2)	6282(2)	30(1)
O(2)	6366(3)	3228(2)	6888(2)	33(1)
O(3)	6212(3)	9717(2)	6378(2)	37(1)
F(1)	3635(2)	3038(2)	10665(2)	52(1)
F(2)	5499(3)	2441(2)	11481(1)	45(1)
N(1)	5336(3)	6946(2)	5473(2)	23(1)
N(2)	7204(3)	7937(2)	6611(2)	23(1)
N(3)	7775(3)	5924(2)	7494(2)	22(1)

Atom	x	y	z	U(eq)
C(1)	3886(3)	6393(3)	5495(2)	27(1)
C(2)	3156(4)	6952(3)	6339(2)	34(1)
C(3)	3586(4)	8180(3)	6219(2)	37(1)
C(4)	5026(3)	8166(2)	5674(2)	26(1)
C(5)	6227(3)	8684(2)	6253(2)	26(1)
C(6)	8506(3)	8276(2)	7030(2)	24(1)
C(7)	9127(4)	9322(2)	6794(2)	29(1)
C(8)	10420(4)	9675(2)	7193(2)	30(1)
C(9)	11153(3)	9014(3)	7854(2)	27(1)
C(10)	10608(4)	7967(3)	8075(2)	26(1)
C(11)	9284(3)	7582(2)	7674(2)	22(1)
C(12)	8817(3)	6436(3)	7944(2)	22(1)
C(13)	7327(3)	4784(2)	7793(2)	25(1)
C(14)	6564(4)	4254(2)	6932(2)	27(1)
C(15)	6288(3)	4840(2)	8651(2)	25(1)
C(16)	6127(3)	3697(2)	9111(2)	25(1)
C(17)	5959(3)	3622(2)	10178(2)	27(1)
C(18)	7360(4)	3275(3)	9732(2)	29(1)
C(19)	5052(4)	2705(3)	10571(2)	33(1)
C(20)	5991(3)	6763(2)	4511(2)	24(1)
C(21)	7481(3)	7251(3)	4425(2)	29(1)
C(22)	8695(4)	6612(4)	4676(2)	41(1)
C(23)	10067(4)	7065(5)	4615(3)	61(1)
C(24)	10253(6)	8161(7)	4305(3)	81(2)
C(25)	9038(6)	8823(4)	4048(3)	63(1)
C(26)	7681(5)	8347(3)	4101(2)	39(1)
C(27)	9624(3)	5890(2)	8759(2)	24(1)
C(28)	10658(4)	5072(3)	8583(2)	30(1)
C(29)	11461(4)	4622(3)	9341(3)	37(1)
C(30)	11249(4)	4989(3)	10260(2)	36(1)
C(31)	10219(4)	5811(3)	10439(2)	31(1)
C(32)	9412(3)	6263(2)	9690(2)	27(1)
O(1W)	6817(4)	1184(2)	7878(2)	55(1)
O(1S)	4185(5)	1132(2)	8736(2)	62(1)
C(1S)	3302(6)	1648(4)	8054(3)	62(1)

Table 3. Selected bond lengths [Å] and angles [°] for DK33.

Ni(1)–N(2)	1.856(2)	C(2)–C(3)	1.523(5)	C(17)–C(19)	1.486(4)
Ni(1)–N(3)	1.859(2)	C(3)–C(4)	1.545(5)	C(17)–C(18)	1.504(5)
Ni(1)–O(1)	1.865(2)	C(4)–C(5)	1.501(4)	C(20)–C(21)	1.503(4)
Ni(1)–N(1)	1.944(2)	C(6)–C(7)	1.410(4)	C(21)–C(26)	1.392(5)
O(1)–C(14)	1.290(4)	C(6)–C(11)	1.414(4)	C(21)–C(22)	1.398(5)
O(2)–C(14)	1.235(4)	C(7)–C(8)	1.381(4)	C(22)–C(23)	1.383(6)
O(3)–C(5)	1.240(4)	C(8)–C(9)	1.386(4)	C(23)–C(24)	1.385(9)
F(1)–C(19)	1.378(4)	C(9)–C(10)	1.379(4)	C(24)–C(25)	1.415(9)

F(2)–C(19)	1.372(3)	C(10)–C(11)	1.418(4)	C(25)–C(26)	1.380(6)
N(1)–C(1)	1.495(4)	C(11)–C(12)	1.480(4)	C(27)–C(28)	1.389(4)
N(1)–C(20)	1.501(4)	C(12)–C(27)	1.504(4)	C(27)–C(32)	1.395(4)
N(1)–C(4)	1.506(4)	C(13)–C(14)	1.527(4)	C(28)–C(29)	1.396(4)
N(2)–C(5)	1.359(4)	C(13)–C(15)	1.551(4)	C(29)–C(30)	1.376(5)
N(2)–C(6)	1.395(4)	C(15)–C(16)	1.512(4)	C(30)–C(31)	1.390(5)
N(3)–C(12)	1.299(3)	C(16)–C(17)	1.509(4)	C(31)–C(32)	1.390(4)
N(3)–C(13)	1.478(3)	C(16)–C(18)	1.513(4)	O(1S)–C(1S)	1.393(5)
C(1)–C(2)	1.523(4)				

N(2)–Ni(1)–N(3)	95.16(10)	N(3)–C(12)–C(11)	121.6(2)
N(2)–Ni(1)–O(1)	176.25(10)	N(3)–C(12)–C(27)	121.8(3)
N(3)–Ni(1)–O(1)	86.47(9)	C(11)–C(12)–C(27)	116.6(2)
N(2)–Ni(1)–N(1)	87.09(10)	N(3)–C(13)–C(14)	106.4(2)
N(3)–Ni(1)–N(1)	176.16(11)	N(3)–C(13)–C(15)	111.1(2)
O(1)–Ni(1)–N(1)	91.47(9)	C(14)–C(13)–C(15)	110.2(2)
C(14)–O(1)–Ni(1)	115.05(19)	O(2)–C(14)–O(1)	123.3(3)
C(1)–N(1)–C(20)	109.0(2)	O(2)–C(14)–C(13)	120.9(3)
C(1)–N(1)–C(4)	104.3(2)	O(1)–C(14)–C(13)	115.7(2)
C(20)–N(1)–C(4)	112.8(2)	C(16)–C(15)–C(13)	110.9(2)
C(1)–N(1)–Ni(1)	113.54(18)	C(17)–C(16)–C(18)	59.7(2)
C(20)–N(1)–Ni(1)	111.02(18)	C(17)–C(16)–C(15)	119.2(2)
C(4)–N(1)–Ni(1)	105.99(17)	C(18)–C(16)–C(15)	117.8(3)
C(5)–N(2)–C(6)	122.3(2)	C(19)–C(17)–C(18)	116.5(3)
C(5)–N(2)–Ni(1)	113.8(2)	C(19)–C(17)–C(16)	118.4(3)
C(6)–N(2)–Ni(1)	123.94(19)	C(18)–C(17)–C(16)	60.3(2)
C(12)–N(3)–C(13)	120.0(2)	C(17)–C(18)–C(16)	60.03(19)
C(12)–N(3)–Ni(1)	128.6(2)	F(2)–C(19)–F(1)	104.7(3)
C(13)–N(3)–Ni(1)	111.29(18)	F(2)–C(19)–C(17)	110.3(3)
N(1)–C(1)–C(2)	103.3(2)	F(1)–C(19)–C(17)	111.6(3)
C(1)–C(2)–C(3)	102.3(3)	N(1)–C(20)–C(21)	113.4(2)
C(2)–C(3)–C(4)	105.8(3)	C(26)–C(21)–C(22)	118.8(3)
C(5)–C(4)–N(1)	110.8(2)	C(26)–C(21)–C(20)	120.9(3)
C(5)–C(4)–C(3)	111.4(2)	C(22)–C(21)–C(20)	120.4(3)
N(1)–C(4)–C(3)	105.7(2)	C(23)–C(22)–C(21)	120.5(4)
O(3)–C(5)–N(2)	127.1(3)	C(22)–C(23)–C(24)	120.3(5)
O(3)–C(5)–C(4)	118.2(3)	C(23)–C(24)–C(25)	120.0(4)
N(2)–C(5)–C(4)	114.6(2)	C(26)–C(25)–C(24)	118.7(5)
N(2)–C(6)–C(7)	120.6(2)	C(25)–C(26)–C(21)	121.7(4)
N(2)–C(6)–C(11)	122.1(2)	C(28)–C(27)–C(32)	119.6(3)
C(7)–C(6)–C(11)	117.3(3)	C(28)–C(27)–C(12)	120.3(3)
C(8)–C(7)–C(6)	121.8(3)	C(32)–C(27)–C(12)	119.9(3)
C(7)–C(8)–C(9)	120.9(3)	C(27)–C(28)–C(29)	119.7(3)
C(10)–C(9)–C(8)	119.0(3)	C(30)–C(29)–C(28)	120.7(3)
C(9)–C(10)–C(11)	121.2(3)	C(29)–C(30)–C(31)	119.8(3)
C(6)–C(11)–C(10)	119.8(3)	C(30)–C(31)–C(32)	120.0(3)
C(6)–C(11)–C(12)	123.5(2)	C(31)–C(32)–C(27)	120.2(3)
C(10)–C(11)–C(12)	116.7(2)		

Table 4. Hydrogen bonds for DK33 [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
O(1S)–H(1OS)...O(1W)	1.04(4)	1.79(4)	2.731(6)	148(3)
O(1W)–H(1OW)...O(2)	0.95(7)	1.88(7)	2.827(3)	171(7)
O(1W)–H(2OW)...O(3)#1	0.91(8)	1.88(8)	2.784(4)	169(7)

Symmetry transformations used to generate equivalent atoms:

#1 x,y–1,z

Table 5. Anisotropic displacement parameters (Å^2 × 10^3) for DK33. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\, h^2 a^{*2}U^{11} + ... + 2\, h\, k\, a^*\, b^*\, U^{12}\,]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Ni(1)	23(1)	20(1)	22(1)	1(1)	–6(1)	–2(1)
O(1)	37(1)	24(1)	27(1)	0(1)	–11(1)	–2(1)
O(2)	43(1)	22(1)	32(1)	–2(1)	–8(1)	–4(1)
O(3)	45(1)	24(1)	41(1)	–2(1)	–14(1)	8(1)
F(1)	28(1)	59(1)	71(2)	23(1)	4(1)	–2(1)
F(2)	52(1)	51(1)	32(1)	15(1)	–9(1)	–10(1)
N(1)	22(1)	23(1)	23(1)	–2(1)	–5(1)	3(1)
N(2)	26(1)	22(1)	22(1)	1(1)	–6(1)	–2(1)
N(3)	24(1)	18(1)	24(1)	1(1)	–3(1)	0(1)
C(1)	20(1)	35(1)	27(1)	–2(1)	–4(1)	–5(2)
C(2)	29(2)	45(2)	29(1)	–3(1)	0(1)	–5(2)
C(3)	32(2)	39(2)	41(2)	–8(1)	2(1)	2(2)
C(4)	26(2)	27(1)	24(1)	–1(1)	–4(1)	1(1)
C(5)	30(2)	23(1)	24(1)	2(1)	–7(1)	–1(1)
C(6)	24(1)	23(1)	24(1)	–1(1)	–2(1)	4(1)
C(7)	34(2)	25(1)	26(1)	7(1)	–6(1)	–5(1)
C(8)	32(2)	28(1)	30(1)	0(1)	0(1)	–13(1)
C(9)	24(1)	34(1)	24(1)	–4(1)	0(1)	–8(1)
C(10)	25(2)	27(1)	25(1)	–1(1)	–4(1)	–5(1)
C(11)	23(1)	23(1)	19(1)	0(1)	–2(1)	–4(1)
C(12)	22(1)	22(1)	23(1)	–4(1)	–3(1)	3(1)
C(13)	27(2)	20(1)	27(1)	3(1)	–7(1)	–2(1)
C(14)	28(2)	24(1)	30(1)	0(1)	–5(1)	–3(1)
C(15)	26(2)	23(1)	26(1)	2(1)	–3(1)	2(1)
C(16)	26(2)	23(1)	26(1)	2(1)	–5(1)	–3(1)
C(17)	28(2)	25(1)	27(1)	3(1)	–5(1)	1(1)
C(18)	27(2)	30(1)	31(1)	7(1)	–4(1)	4(1)
C(19)	32(2)	33(2)	33(2)	7(1)	–7(1)	–4(1)
C(20)	23(1)	28(1)	21(1)	–2(1)	–5(1)	0(1)

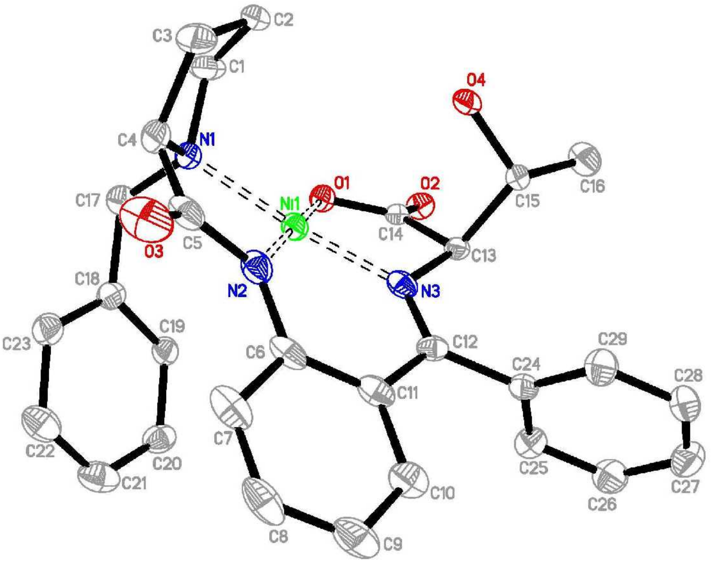
Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(21)	27(2)	39(2)	21(1)	–6(1)	0(1)	–1(1)
C(22)	29(2)	59(3)	33(2)	–12(2)	–2(1)	9(2)
C(23)	25(2)	115(4)	44(2)	–28(2)	–1(2)	1(2)
C(24)	41(3)	157(6)	44(2)	–32(3)	16(2)	–48(4)
C(25)	71(3)	83(3)	35(2)	–12(2)	13(2)	–46(3)
C(26)	45(2)	44(2)	28(2)	–4(1)	3(1)	–11(2)
C(27)	22(1)	25(1)	26(1)	3(1)	–5(1)	–2(1)
C(28)	27(2)	32(2)	33(2)	–2(1)	–3(1)	6(1)
C(29)	32(2)	35(2)	43(2)	3(1)	–11(1)	9(1)
C(30)	34(2)	36(2)	39(2)	7(1)	–16(1)	–2(1)
C(31)	35(2)	35(2)	22(1)	4(1)	–8(1)	–4(1)
C(32)	24(1)	31(2)	26(1)	0(1)	–6(1)	–3(1)
O(1W)	89(2)	32(1)	43(1)	–2(1)	–20(2)	6(1)
O(1S)	102(3)	50(2)	36(1)	8(1)	–7(2)	–22(2)
C(1S)	73(3)	68(3)	45(2)	9(2)	–12(2)	–40(3)

Table 6. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters (Å$^2 \times 10^3$) for DK33.

Atom	x	y	z	U(eq)
H(1S)	2334	1757	8315	75
H(2S)	3238	1171	7485	75
H(3S)	3712	2380	7882	75
H(101)	3390(40)	6510(30)	4920(20)	23(7)
H(102)	4100(50)	5470(30)	5500(30)	39(11)
H(201)	3540(40)	6630(30)	6940(20)	30(9)
H(202)	2050(50)	6820(30)	6260(30)	43(11)
H(301)	2800(50)	8590(30)	5870(30)	35(10)
H(302)	3730(40)	8560(30)	6840(20)	17(7)
H(4)	4940(40)	8560(20)	5060(20)	17(7)
H(7)	8770(40)	9700(30)	6390(20)	18(8)
H(8)	10870(40)	10430(30)	6960(20)	23(8)
H(9)	12170(50)	9280(30)	8140(30)	36(10)
H(10)	11130(30)	7540(20)	8496(19)	4(6)
H(13)	8100(40)	4270(30)	7980(20)	18(7)
H(151)	5360(40)	5130(30)	8470(20)	25(9)
H(152)	6730(30)	5390(30)	9090(20)	14(7)
H(16)	5480(40)	3200(30)	8770(20)	23(8)
H(17)	5950(40)	4260(30)	10520(20)	25(8)
H(181)	8190(50)	3740(30)	9790(30)	37(10)
H(182)	7630(40)	2350(30)	9760(30)	31(9)
H(19)	4910(50)	2070(30)	10190(30)	34(10)
H(20A)	5270(40)	7110(30)	4050(20)	26(8)
H(20B)	6080(50)	5990(30)	4360(30)	41(11)
H(22)	8530(50)	5900(40)	4850(30)	43(12)

Atom	x	y	z	U(eq)
H(23)	10960(50)	6320(40)	4850(30)	60(13)
H(24)	11300(60)	8520(50)	4280(40)	77(16)
H(25)	9180(7)	9650(5)	3830(4)	80(17)
H(26)	6880(40)	8820(30)	3900(20)	23(9)
H(28)	10740(40)	4840(30)	7910(30)	30(10)
H(29)	12180(40)	4070(30)	9200(30)	31(9)
H(30)	11920(50)	4710(30)	10790(30)	39(11)
H(31)	10010(40)	5960(20)	11070(20)	16(7)
H(32)	8610(40)	6830(30)	9810(30)	31(9)
H(1OW)	6740(90)	1840(60)	7500(50)	108(16)
H(2OW)	6620(80)	780(60)	7340(50)	108(16)
H(1OS)	5040(40)	890(30)	8310(30)	28(9)

(R)-Belokon' (R)-allo-Threonine complex [(R)-BTC, ***133****]*



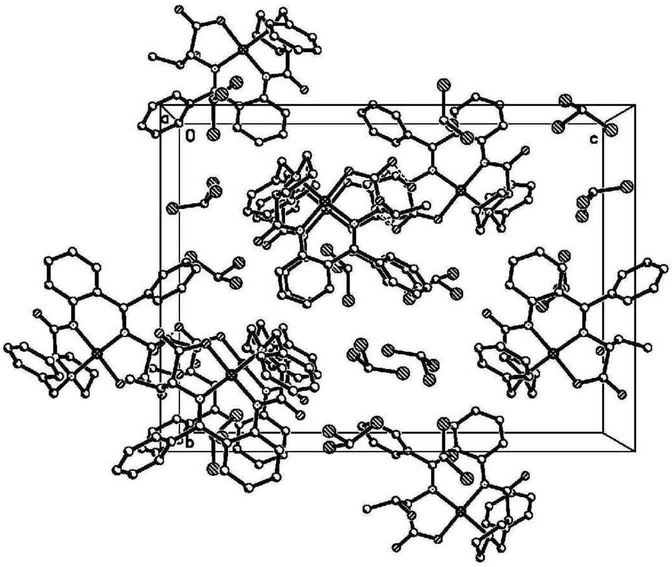


Table 1. Crystal data and structure refinement for dk14.

Identification code	dk14	
Empirical formula	$C_{29}H_{29}N_3NiO_4 \times 3CHCl_3$	
Formula weight	900.37	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 10.3057(3) Å	α = 90°.
	b = 16.3778(5) Å	β = 90°.
	c = 22.3882(7) Å	γ = 90°.
Volume	3778.8(2) $Å^3$	
Z	4	
Density (calculated)	1.583 Mg/m^3	
Absorption coefficient	1.191 mm^{-1}	
F(000)	1832	
Crystal size	0.46 × 0.04 × 0.02 mm^3	
Theta range for data collection	1.54 to 27.50°.	
Index ranges	–13<=h<=13, –21<=k<=21, –29<=l<=29	
Reflections collected	39822	
Independent reflections	8679 [R(int) = 0.0734]	
Completeness to theta = 27.50°	100.0 %	
Absorption correction	Multi–scan	
Max. and min. transmission	0.9766 and 0.6104	
Refinement method	Full–matrix least–squares on F^2	
Data / restraints / parameters	8679 / 0 / 442	
Goodness–of–fit on F^2	1.056	
Final R indices [I>2sigma(I)]	R_1 = 0.0523, wR_2 = 0.1207	
R indices (all data)	R_1 = 0.0763, wR_2 = 0.1319	
Absolute structure parameter	–0.01(2)	
Largest diff. peak and hole	0.943 and –0.977 e.$Å^{-3}$	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for dk14. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
Ni(1)	1621(1)	7738(1)	1538(1)	18(1)
O(1)	1901(3)	6843(2)	1026(1)	20(1)
O(2)	2393(3)	6539(2)	84(1)	21(1)
O(3)	384(4)	8930(3)	2948(2)	44(1)
O(4)	–288(3)	7772(2)	382(1)	23(1)
N(1)	906(4)	7036(2)	2154(2)	24(1)
N(2)	1504(4)	8592(2)	2075(2)	23(1)
N(3)	2163(3)	8384(2)	907(2)	19(1)
C(1)	–103(5)	6470(4)	1913(2)	36(1)
C(2)	–1229(5)	7041(4)	1784(2)	39(1)
C(3)	–1254(5)	7569(4)	2344(2)	38(1)
C(4)	175(5)	7590(3)	2559(2)	29(1)
C(5)	705(4)	8448(3)	2551(2)	27(1)
C(6)	2226(4)	9319(3)	2030(2)	23(1)
C(7)	2512(5)	9803(3)	2537(2)	31(1)
C(8)	3249(5)	10506(3)	2491(2)	32(1)
C(9)	3713(5)	10775(3)	1944(2)	34(1)
C(10)	3449(5)	10311(3)	1446(2)	28(1)
C(11)	2725(4)	9589(3)	1476(2)	23(1)
C(12)	2582(4)	9127(3)	913(2)	18(1)
C(13)	2014(4)	7946(2)	333(2)	16(1)
C(14)	2107(4)	7037(3)	475(2)	18(1)
C(15)	708(4)	8148(3)	40(2)	19(1)
C(16)	668(5)	7890(3)	–609(2)	28(1)
C(17)	1948(4)	6563(3)	2472(2)	25(1)
C(18)	3116(4)	7075(3)	2621(2)	20(1)
C(19)	4111(4)	7139(3)	2199(2)	22(1)
C(20)	5197(4)	7616(3)	2317(2)	25(1)
C(21)	5293(5)	8037(3)	2853(2)	32(1)
C(22)	4322(5)	7973(3)	3268(2)	30(1)
C(23)	3227(4)	7486(3)	3154(2)	25(1)
C(24)	2990(4)	9539(3)	347(2)	20(1)
C(25)	4193(5)	9347(3)	99(2)	23(1)
C(26)	4582(5)	9712(3)	–427(2)	30(1)
C(27)	3791(5)	10279(3)	–705(2)	37(1)
C(28)	2598(5)	10470(3)	–452(2)	36(1)
C(29)	2207(5)	10109(3)	72(2)	30(1)
C(1S)	–2507(5)	9689(3)	1036(3)	37(1)
Cl(1)	–3508(2)	9117(1)	1511(1)	53(1)
Cl(2)	–878(2)	9638(1)	1264(1)	52(1)
Cl(3)	–3050(1)	10702(1)	1021(1)	45(1)
C(2S)	3213(5)	4962(3)	1011(2)	32(1)
Cl(4)	1987(1)	4515(1)	1453(1)	31(1)
Cl(5)	4603(1)	5146(1)	1447(1)	43(1)
Cl(6)	3602(2)	4345(1)	401(1)	53(1)
C(3S)	856(7)	2611(4)	613(3)	56(2)

Atom	x	y	z	U(eq)
Cl(7)	2278(3)	2266(2)	926(1)	97(1)
Cl(8)	–368(3)	1910(2)	776(1)	126(1)
Cl(9)	948(4)	2770(2)	–127(1)	158(2)

Table 3. Selected bond lengths [Å] and angles [°] for dk14.

Ni(1)–N(2)	1.848(4)	C(4)–C(5)	1.508(7)	C(21)–C(22)	1.370(7)
Ni(1)–N(3)	1.853(4)	C(6)–C(7)	1.414(6)	C(22)–C(23)	1.405(7)
Ni(1)–O(1)	1.883(3)	C(6)–C(11)	1.415(7)	C(24)–C(29)	1.378(6)
Ni(1)–N(1)	1.940(4)	C(7)–C(8)	1.384(7)	C(24)–C(25)	1.395(6)
O(1)–C(14)	1.291(5)	C(8)–C(9)	1.386(8)	C(25)–C(26)	1.380(6)
O(2)–C(14)	1.231(5)	C(9)–C(10)	1.377(6)	C(26)–C(27)	1.384(7)
O(3)–C(5)	1.235(6)	C(10)–C(11)	1.399(6)	C(27)–C(28)	1.390(8)
O(4)–C(15)	1.421(5)	C(11)–C(12)	1.478(6)	C(28)–C(29)	1.374(7)
N(1)–C(4)	1.487(6)	C(12)–C(24)	1.496(6)	C(1S)–Cl(3)	1.750(5)
N(1)–C(1)	1.495(6)	C(13)–C(14)	1.526(6)	C(1S)–Cl(1)	1.754(6)
N(1)–C(17)	1.503(6)	C(13)–C(15)	1.533(6)	C(1S)–Cl(2)	1.757(6)
N(2)–C(5)	1.367(6)	C(15)–C(16)	1.513(6)	C(2S)–Cl(6)	1.746(5)
N(2)–C(6)	1.407(6)	C(17)–C(18)	1.506(6)	C(2S)–Cl(5)	1.759(5)
N(3)–C(12)	1.290(6)	C(18)–C(23)	1.375(6)	C(2S)–Cl(4)	1.764(5)
N(3)–C(13)	1.480(5)	C(18)–C(19)	1.397(6)	C(3S)–Cl(9)	1.680(8)
C(1)–C(2)	1.519(8)	C(19)–C(20)	1.391(6)	C(3S)–Cl(7)	1.720(7)
C(2)–C(3)	1.522(8)	C(20)–C(21)	1.388(7)	C(3S)–Cl(8)	1.744(7)
C(3)–C(4)	1.550(7)				

N(2)–Ni(1)–N(3)	94.71(16)	N(3)–C(12)–C(11)	121.6(4)
N(2)–Ni(1)–O(1)	174.34(15)	N(3)–C(12)–C(24)	120.8(4)
N(3)–Ni(1)–O(1)	86.21(14)	C(11)–C(12)–C(24)	117.6(4)
N(2)–Ni(1)–N(1)	87.83(17)	N(3)–C(13)–C(14)	106.6(3)
N(3)–Ni(1)–N(1)	174.48(16)	N(3)–C(13)–C(15)	111.0(3)
O(1)–Ni(1)–N(1)	91.75(15)	C(14)–C(13)–C(15)	110.8(3)
C(14)–O(1)–Ni(1)	114.6(3)	O(2)–C(14)–O(1)	123.7(4)
C(15)–O(4)–H(4O)	109.5	O(2)–C(14)–C(13)	120.9(4)
C(4)–N(1)–C(1)	104.3(4)	O(1)–C(14)–C(13)	115.4(4)
C(4)–N(1)–C(17)	112.9(3)	O(4)–C(15)–C(16)	112.1(4)
C(1)–N(1)–C(17)	110.3(4)	O(4)–C(15)–C(13)	108.0(3)
C(4)–N(1)–Ni(1)	105.3(3)	C(16)–C(15)–C(13)	112.0(4)
C(1)–N(1)–Ni(1)	112.0(3)	C(18)–C(17)–N(1)	112.9(4)
C(17)–N(1)–Ni(1)	111.7(3)	C(23)–C(18)–C(19)	119.3(4)
C(5)–N(2)–C(6)	121.3(4)	C(23)–C(18)–C(17)	122.1(4)
C(5)–N(2)–Ni(1)	114.5(3)	C(19)–C(18)–C(17)	118.6(4)
C(6)–N(2)–Ni(1)	124.1(3)	C(20)–C(19)–C(18)	120.3(4)
C(12)–N(3)–C(13)	120.0(4)	C(21)–C(20)–C(19)	120.0(4)
C(12)–N(3)–Ni(1)	129.2(3)	C(22)–C(21)–C(20)	119.8(5)
C(13)–N(3)–Ni(1)	110.7(3)	C(21)–C(22)–C(23)	120.5(4)
N(1)–C(1)–C(2)	102.6(5)	C(18)–C(23)–C(22)	120.1(4)
C(1)–C(2)–C(3)	101.9(4)	C(29)–C(24)–C(25)	119.7(4)

C(2)–C(3)–C(4)	104.7(4)	C(29)–C(24)–C(12)	121.3(4)
N(1)–C(4)–C(5)	112.1(4)	C(25)–C(24)–C(12)	119.0(4)
N(1)–C(4)–C(3)	106.1(4)	C(26)–C(25)–C(24)	120.0(5)
C(5)–C(4)–C(3)	111.2(4)	C(25)–C(26)–C(27)	120.3(5)
O(3)–C(5)–N(2)	127.8(5)	C(26)–C(27)–C(28)	119.2(5)
O(3)–C(5)–C(4)	119.3(4)	C(29)–C(28)–C(27)	120.8(5)
N(2)–C(5)–C(4)	112.9(4)	C(28)–C(29)–C(24)	120.0(5)
N(2)–C(6)–C(7)	121.8(4)	Cl(3)–C(1S)–Cl(1)	109.3(3)
N(2)–C(6)–C(11)	121.2(4)	Cl(3)–C(1S)–Cl(2)	110.9(3)
C(7)–C(6)–C(11)	116.9(4)	Cl(1)–C(1S)–Cl(2)	111.1(3)
C(8)–C(7)–C(6)	121.4(5)	Cl(6)–C(2S)–Cl(5)	110.3(3)
C(7)–C(8)–C(9)	121.4(4)	Cl(6)–C(2S)–Cl(4)	111.2(3)
C(10)–C(9)–C(8)	118.1(5)	Cl(5)–C(2S)–Cl(4)	110.1(3)
C(9)–C(10)–C(11)	122.2(5)	Cl(9)–C(3S)–Cl(7)	113.9(5)
C(10)–C(11)–C(6)	120.0(4)	Cl(9)–C(3S)–Cl(8)	110.5(4)
C(10)–C(11)–C(12)	116.5(4)	Cl(7)–C(3S)–Cl(8)	108.3(4)
C(6)–C(11)–C(12)	123.5(4)		

Table 4. Anisotropic displacement parameters (Å^2 × 10^3) for dk14. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Ni(1)	16(1)	25(1)	14(1)	–1(1)	1(1)	0(1)
O(1)	19(2)	25(2)	16(1)	1(1)	1(1)	–1(1)
O(2)	22(2)	19(2)	21(2)	–3(1)	2(1)	–1(1)
O(3)	28(2)	72(3)	32(2)	–27(2)	9(2)	3(2)
O(4)	14(1)	33(2)	21(1)	4(1)	–2(1)	–1(1)
N(1)	17(2)	40(2)	15(2)	4(2)	0(2)	–6(2)
N(2)	19(2)	32(2)	18(2)	–1(2)	–1(2)	4(2)
N(3)	14(2)	24(2)	20(2)	–4(2)	–1(2)	3(2)
C(1)	20(2)	60(4)	28(3)	–2(2)	–1(2)	–16(2)
C(2)	18(2)	75(4)	25(2)	17(3)	–7(2)	–16(2)
C(3)	15(2)	57(4)	44(3)	14(3)	0(2)	0(2)
C(4)	22(2)	46(3)	18(2)	4(2)	3(2)	–3(2)
C(5)	17(2)	43(3)	20(2)	–8(2)	–2(2)	5(2)
C(6)	16(2)	30(2)	23(2)	–11(2)	–6(2)	7(2)
C(7)	28(3)	37(3)	27(3)	–11(2)	–8(2)	11(2)
C(8)	39(3)	29(2)	29(2)	–13(2)	–15(2)	13(2)
C(9)	36(3)	26(2)	38(3)	–12(2)	–14(2)	4(2)
C(10)	27(2)	23(2)	32(2)	–4(2)	–5(2)	3(2)
C(11)	17(2)	25(2)	25(2)	–8(2)	–4(2)	4(2)
C(12)	12(2)	19(2)	24(2)	–1(2)	0(2)	1(2)
C(13)	15(2)	19(2)	15(2)	–1(2)	0(2)	–3(2)
C(14)	14(2)	22(2)	17(2)	2(2)	–1(2)	–5(2)
C(15)	16(2)	22(2)	19(2)	5(2)	–2(2)	–2(2)
C(16)	25(2)	37(3)	22(2)	–3(2)	1(2)	4(2)
C(17)	22(2)	30(2)	23(2)	1(2)	0(2)	–2(2)
C(18)	16(2)	20(2)	25(2)	6(2)	–2(2)	2(2)

Atom	U11	U22	U33	U23	U13	U12
C(19)	17(2)	30(2)	19(2)	4(2)	0(2)	1(2)
C(20)	18(2)	24(2)	32(2)	4(2)	1(2)	1(2)
C(21)	22(2)	30(3)	44(3)	–2(2)	–7(2)	0(2)
C(22)	31(3)	27(3)	32(3)	–8(2)	–6(2)	2(2)
C(23)	21(2)	31(2)	23(2)	3(2)	2(2)	1(2)
C(24)	21(2)	18(2)	19(2)	–1(2)	–4(2)	–4(2)
C(25)	26(2)	21(2)	23(2)	–2(2)	2(2)	–1(2)
C(26)	26(3)	39(3)	25(2)	–2(2)	4(2)	–1(2)
C(27)	42(3)	42(3)	28(3)	8(2)	0(2)	–14(2)
C(28)	31(3)	35(3)	41(3)	16(2)	–13(2)	–2(2)
C(29)	31(3)	25(2)	33(3)	5(2)	–4(2)	1(2)
C(1S)	41(3)	30(3)	40(3)	–7(2)	–2(3)	4(2)
Cl(1)	52(1)	45(1)	64(1)	21(1)	2(1)	–5(1)
Cl(2)	33(1)	62(1)	62(1)	4(1)	0(1)	12(1)
Cl(3)	41(1)	27(1)	67(1)	8(1)	7(1)	3(1)
C(2S)	29(3)	24(2)	43(3)	7(2)	–8(2)	1(2)
Cl(4)	27(1)	31(1)	33(1)	6(1)	1(1)	1(1)
Cl(5)	29(1)	35(1)	65(1)	–5(1)	–10(1)	–4(1)
Cl(6)	56(1)	66(1)	37(1)	–10(1)	13(1)	–11(1)
C(3S)	50(4)	39(3)	80(5)	8(3)	–1(4)	–8(3)
Cl(7)	103(2)	75(1)	112(2)	–16(1)	–50(2)	35(1)
Cl(8)	132(2)	161(3)	85(2)	–77(2)	71(2)	–107(2)
Cl(9)	175(3)	186(3)	114(2)	104(2)	–52(2)	–100(3)

Table 5. Hydrogen coordinates (× 10^4) and isotropic displacement parameters ($Å^2 \times 10^3$) for dk14.

Atom	x	y	z	U(eq)
H(4O)	–1015	7901	241	27
H(1A)	–347	6050	2211	43
H(1B)	201	6196	1544	43
H(2A)	–2052	6736	1734	47
H(2B)	–1067	7373	1422	47
H(3A)	–1824	7325	2652	46
H(3B)	–1568	8125	2251	46
H(4A)	220	7372	2976	34
H(7A)	2191	9641	2917	37
H(8A)	3440	10811	2841	39
H(9A)	4201	11266	1914	40
H(10A)	3769	10487	1069	33
H(13A)	2736	8103	58	19
H(15A)	580	8753	58	23
H(16A)	–178	8032	–780	42
H(16B)	801	7299	–637	42
H(16C)	1355	8173	–830	42
H(17A)	1585	6333	2845	30

Atom	x	y	z	U(eq)
H(17B)	2222	6101	2216	30
H(19A)	4044	6855	1831	26
H(20A)	5873	7654	2030	30
H(21A)	6029	8369	2932	38
H(22A)	4390	8259	3636	36
H(23A)	2561	7441	3446	30
H(25A)	4745	8964	292	28
H(26A)	5396	9574	–598	36
H(27A)	4060	10535	–1065	45
H(28A)	2047	10854	–643	43
H(29A)	1396	10252	245	36
H(1SA)	–2575	9459	623	44
H(2SA)	2886	5497	858	38
H(3SA)	627	3141	808	67

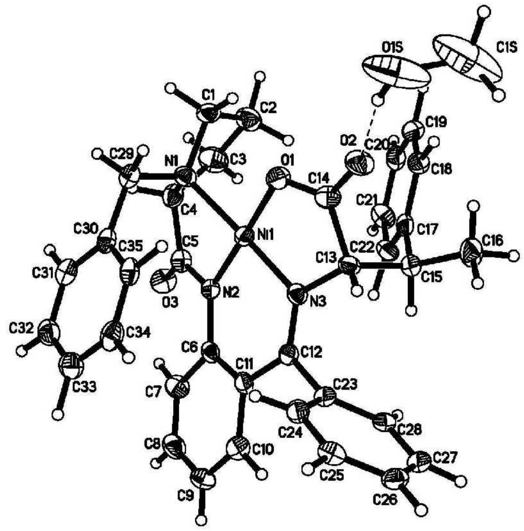
Table 6. Hydrogen bonds for dk14 [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
O(4)–H(4O)...O(2)#1	0.84	2.02	2.842(4)	167.4

Symmetry transformations used to generate equivalent atoms:

#1 x–1/2,–y+3/2,–z

Belokon' (2S,3S)–β–methylphenylalanine complex



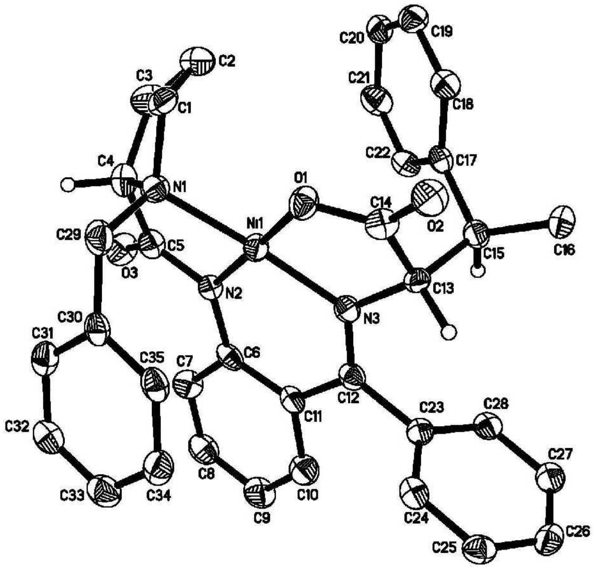


Table 1. Crystal data and structure refinement for dk24.

Identification code	dk24	
Empirical formula	$C_{35}H_{33}N_3NiO_3 \times CH_3OH$	
Formula weight	634.40	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P\ 2_1\ 2_1\ 2_1$	
Unit cell dimensions	a = 8.5832(5) Å	α = 90°.
	b = 15.6673(9) Å	β = 90°.
	c = 23.0536(14) Å	γ = 90°.
Volume	3100.1(3) $Å^3$	
Z	4	
Density (calculated)	1.359 Mg/m^3	
Absorption coefficient	0.670 mm^{-1}	
F(000)	1336	
Crystal size	0.44 × 0.05 × 0.03 mm^3	
Theta range for data collection	1.57 to 27.50°.	
Index ranges	–11<=h<=11, –20<=k<=20, –29<=l<=29	
Reflections collected	30404	
Independent reflections	7118 [R(int) = 0.1278]	
Completeness to theta = 27.50°	100.0 %	
Absorption correction	None	
Max. and min. transmission	0.9802 and 0.7569	
Refinement method	Full–matrix least–squares on F^2	
Data / restraints / parameters	7118 / 0 / 530	
Goodness–of–fit on F^2	0.880	
Final R indices [I>2sigma(I)]	R_1 = 0.0412, wR_2 = 0.0691	
R indices (all data)	R_1 = 0.0805, wR_2 = 0.0785	
Absolute structure parameter	–0.003(13)	
Largest diff. peak and hole	0.432 and –0.449 e.$Å^{-3}$	

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for dk24. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
Ni(1)	2054(1)	9205(1)	8575(1)	20(1)
O(1)	988(3)	8645(2)	7982(1)	26(1)
O(2)	–724(3)	8848(2)	7268(1)	31(1)
O(3)	5523(3)	9569(2)	9650(1)	32(1)
N(1)	3170(3)	8165(2)	8772(1)	23(1)
N(2)	3123(3)	9736(2)	9178(1)	20(1)
N(3)	791(3)	10126(2)	8417(1)	20(1)
C(1)	3683(4)	7635(2)	8268(2)	28(1)
C(2)	4977(5)	8140(3)	8009(2)	34(1)
C(3)	5862(4)	8458(3)	8549(2)	40(1)
C(4)	4656(4)	8460(2)	9041(2)	27(1)
C(5)	4469(4)	9320(2)	9327(1)	25(1)
C(6)	2561(4)	10441(2)	9496(1)	22(1)
C(7)	3320(4)	10734(2)	10007(1)	28(1)
C(8)	2701(5)	11377(2)	10333(2)	31(1)
C(9)	1339(5)	11774(3)	10182(2)	34(1)
C(10)	600(4)	11522(2)	9682(2)	30(1)
C(11)	1206(4)	10870(2)	9321(1)	23(1)
C(12)	352(3)	10717(2)	8779(1)	21(1)
C(13)	–2(4)	10052(2)	7849(1)	21(1)
C(14)	58(4)	9111(2)	7679(1)	25(1)
C(15)	811(4)	10641(2)	7391(1)	23(1)
C(16)	–223(4)	10760(3)	6856(2)	34(1)
C(17)	2459(4)	10362(2)	7250(1)	22(1)
C(18)	2775(4)	9750(2)	6827(1)	25(1)
C(19)	4306(4)	9511(2)	6703(2)	27(1)
C(20)	5523(4)	9877(2)	6990(2)	28(1)
C(21)	5231(4)	10488(3)	7409(2)	32(1)
C(22)	3717(4)	10736(3)	7538(1)	26(1)
C(23)	–1059(4)	11243(2)	8656(1)	21(1)
C(24)	–2483(4)	10956(2)	8866(1)	25(1)
C(25)	–3839(4)	11411(2)	8761(1)	27(1)
C(26)	–3779(4)	12155(2)	8434(2)	27(1)
C(27)	–2367(4)	12443(2)	8228(2)	27(1)
C(28)	–1009(4)	11995(2)	8338(1)	23(1)
C(29)	2144(5)	7639(2)	9163(2)	29(1)
C(30)	1379(4)	8146(2)	9640(2)	24(1)
C(31)	2088(5)	8289(2)	10171(1)	28(1)
C(32)	1397(4)	8795(2)	10586(2)	30(1)
C(33)	–35(4)	9173(3)	10477(2)	32(1)
C(34)	–790(4)	9025(2)	9954(2)	30(1)
C(35)	–74(4)	8512(2)	9538(2)	26(1)
O(1S)	–2649(3)	7889(2)	6589(2)	87(1)
C(1S)	–2335(6)	8264(5)	6031(3)	125(3)

Table 3. Selected bond lengths [Å] and angles [°] for dk24.

Ni(1)–N(3)	1.841(3)	C(4)–C(5)	1.508(5)	C(20)–C(21)	1.383(5)
Ni(1)–N(2)	1.861(3)	C(6)–C(11)	1.402(4)	C(21)–C(22)	1.388(5)
Ni(1)–O(1)	1.865(2)	C(6)–C(7)	1.423(4)	C(23)–C(28)	1.389(4)
Ni(1)–N(1)	1.944(3)	C(7)–C(8)	1.364(5)	C(23)–C(24)	1.390(4)
O(1)–C(14)	1.287(4)	C(8)–C(9)	1.370(5)	C(24)–C(25)	1.386(4)
O(2)–C(14)	1.232(4)	C(9)–C(10)	1.373(5)	C(25)–C(26)	1.390(5)
O(3)–C(5)	1.235(4)	C(10)–C(11)	1.416(5)	C(26)–C(27)	1.377(5)
N(1)–C(4)	1.492(4)	C(11)–C(12)	1.469(4)	C(27)–C(28)	1.384(5)
N(1)–C(1)	1.495(4)	C(12)–C(23)	1.492(4)	C(29)–C(30)	1.507(5)
N(1)–C(29)	1.507(4)	C(13)–C(14)	1.525(5)	C(30)–C(31)	1.384(5)
N(2)–C(5)	1.370(4)	C(13)–C(15)	1.566(5)	C(30)–C(35)	1.393(5)
N(2)–C(6)	1.411(4)	C(15)–C(17)	1.516(4)	C(31)–C(32)	1.378(5)
N(3)–C(12)	1.302(4)	C(15)–C(16)	1.531(5)	C(32)–C(33)	1.387(5)
N(3)–C(13)	1.481(4)	C(17)–C(18)	1.395(4)	C(33)–C(34)	1.389(5)
C(1)–C(2)	1.489(5)	C(17)–C(22)	1.395(4)	C(34)–C(35)	1.394(5)
C(2)–C(3)	1.543(6)	C(18)–C(19)	1.396(5)	O(1S)–C(1S)	1.439(7)
C(3)–C(4)	1.535(5)	C(19)–C(20)	1.362(5)		

N(3)–Ni(1)–N(2)	95.05(12)	N(3)–C(12)–C(11)	121.1(3)
N(3)–Ni(1)–O(1)	86.25(11)	N(3)–C(12)–C(23)	120.4(3)
N(2)–Ni(1)–O(1)	178.45(11)	C(11)–C(12)–C(23)	118.5(3)
N(3)–Ni(1)–N(1)	173.33(12)	N(3)–C(13)–C(14)	106.7(3)
N(2)–Ni(1)–N(1)	87.57(11)	N(3)–C(13)–C(15)	110.2(3)
O(1)–Ni(1)–N(1)	91.06(11)	C(14)–C(13)–C(15)	112.4(3)
C(14)–O(1)–Ni(1)	115.8(2)	O(2)–C(14)–O(1)	124.4(3)
C(4)–N(1)–C(1)	104.1(3)	O(2)–C(14)–C(13)	120.1(3)
C(4)–N(1)–C(29)	114.8(3)	O(1)–C(14)–C(13)	115.4(3)
C(1)–N(1)–C(29)	109.5(3)	C(17)–C(15)–C(16)	113.8(3)
C(4)–N(1)–Ni(1)	105.0(2)	C(17)–C(15)–C(13)	113.0(3)
C(1)–N(1)–Ni(1)	115.5(2)	C(16)–C(15)–C(13)	110.9(3)
C(29)–N(1)–Ni(1)	108.1(2)	C(18)–C(17)–C(22)	118.0(3)
C(5)–N(2)–C(6)	122.0(3)	C(18)–C(17)–C(15)	122.0(3)
C(5)–N(2)–Ni(1)	113.0(2)	C(22)–C(17)–C(15)	120.0(3)
C(6)–N(2)–Ni(1)	124.7(2)	C(17)–C(18)–C(19)	120.7(3)
C(12)–N(3)–C(13)	119.3(3)	C(20)–C(19)–C(18)	120.7(3)
C(12)–N(3)–Ni(1)	127.0(2)	C(19)–C(20)–C(21)	119.4(3)
C(13)–N(3)–Ni(1)	112.6(2)	C(20)–C(21)–C(22)	120.9(4)
C(2)–C(1)–N(1)	103.6(3)	C(21)–C(22)–C(17)	120.4(3)
C(1)–C(2)–C(3)	102.4(3)	C(28)–C(23)–C(24)	119.0(3)
C(4)–C(3)–C(2)	105.4(3)	C(28)–C(23)–C(12)	122.9(3)
N(1)–C(4)–C(5)	111.6(3)	C(24)–C(23)–C(12)	118.0(3)
N(1)–C(4)–C(3)	105.6(3)	C(25)–C(24)–C(23)	120.8(3)
C(5)–C(4)–C(3)	113.3(3)	C(24)–C(25)–C(26)	119.7(3)
O(3)–C(5)–N(2)	128.2(3)	C(27)–C(26)–C(25)	119.6(3)
O(3)–C(5)–C(4)	117.9(3)	C(26)–C(27)–C(28)	120.8(3)
N(2)–C(5)–C(4)	113.9(3)	C(27)–C(28)–C(23)	120.0(3)

C(11)–C(6)–N(2)	120.6(3)	C(30)–C(29)–N(1)	113.8(3)
C(11)–C(6)–C(7)	117.6(3)	C(31)–C(30)–C(35)	118.4(3)
N(2)–C(6)–C(7)	121.7(3)	C(31)–C(30)–C(29)	122.6(3)
C(8)–C(7)–C(6)	121.0(3)	C(35)–C(30)–C(29)	118.9(3)
C(7)–C(8)–C(9)	121.9(4)	C(32)–C(31)–C(30)	121.3(4)
C(8)–C(9)–C(10)	118.5(4)	C(31)–C(32)–C(33)	120.0(4)
C(9)–C(10)–C(11)	122.1(4)	C(32)–C(33)–C(34)	120.0(4)
C(6)–C(11)–C(10)	118.8(3)	C(33)–C(34)–C(35)	119.2(3)
C(6)–C(11)–C(12)	125.5(3)	C(30)–C(35)–C(34)	121.0(3)
C(10)–C(11)–C(12)	115.7(3)		

Table 4. Anisotropic displacement parameters (Å^2 × 10^3) for dk24. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\, h^2 a^{*2}U^{11} + ... + 2\, h\, k\, a^*\, b^*\, U^{12} \,]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Ni(1)	24(1)	18(1)	20(1)	0(1)	–3(1)	1(1)
O(1)	27(1)	23(1)	27(1)	–2(1)	–7(1)	2(1)
O(2)	32(1)	33(1)	29(2)	–8(1)	–8(1)	–1(1)
O(3)	26(1)	33(1)	37(2)	–2(1)	–7(1)	0(1)
N(1)	23(2)	25(1)	20(2)	–3(1)	–3(1)	3(1)
N(2)	21(2)	20(1)	19(1)	1(1)	0(1)	1(1)
N(3)	21(1)	21(2)	18(2)	–1(1)	–2(1)	–2(1)
C(1)	33(2)	25(2)	26(2)	–5(2)	–3(2)	12(2)
C(2)	34(2)	39(2)	29(2)	–4(2)	4(2)	8(2)
C(3)	33(2)	45(2)	42(2)	–7(2)	6(2)	0(2)
C(4)	29(2)	26(2)	26(2)	3(2)	–5(2)	–1(2)
C(5)	25(2)	27(2)	24(2)	2(2)	–1(1)	–2(2)
C(6)	28(2)	20(2)	17(2)	1(1)	3(1)	–8(1)
C(7)	27(2)	31(2)	28(2)	–3(2)	–1(1)	–3(2)
C(8)	36(2)	34(2)	22(2)	–4(2)	–3(2)	–6(2)
C(9)	50(3)	29(2)	23(2)	–8(2)	–1(2)	2(2)
C(10)	36(2)	26(2)	28(2)	0(2)	1(2)	0(2)
C(11)	30(2)	23(2)	16(2)	2(2)	0(1)	–2(2)
C(12)	26(2)	18(2)	20(2)	2(2)	3(1)	–2(2)
C(13)	21(2)	24(2)	18(2)	–4(1)	–2(1)	7(2)
C(14)	22(2)	24(2)	28(2)	–4(2)	0(1)	–2(2)
C(15)	28(2)	22(2)	19(2)	1(2)	–1(1)	1(2)
C(16)	30(2)	44(2)	27(2)	6(2)	–3(2)	14(2)
C(17)	25(2)	22(2)	18(2)	5(1)	2(1)	–1(1)
C(18)	28(2)	23(2)	23(2)	0(1)	0(2)	–2(2)
C(19)	32(2)	21(2)	27(2)	0(2)	3(2)	2(2)
C(20)	27(2)	32(2)	25(2)	7(2)	4(2)	4(2)
C(21)	31(2)	38(2)	26(2)	–3(2)	–1(2)	–4(2)
C(22)	31(2)	30(2)	19(2)	–4(2)	0(1)	1(2)
C(23)	26(2)	17(2)	20(2)	–2(1)	–1(1)	1(1)
C(24)	32(2)	20(2)	21(2)	0(1)	–2(1)	–3(2)
C(25)	28(2)	29(2)	24(2)	–6(2)	2(2)	0(2)

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(26)	30(2)	24(2)	26(2)	–8(2)	–7(2)	8(2)
C(27)	37(2)	19(2)	24(2)	–3(2)	–1(2)	4(2)
C(28)	31(2)	18(2)	21(2)	–5(1)	1(2)	1(2)
C(29)	39(2)	21(2)	26(2)	4(1)	–1(2)	0(2)
C(30)	26(2)	21(2)	24(2)	7(1)	0(2)	–4(2)
C(31)	26(2)	25(2)	31(2)	8(1)	–2(2)	–1(2)
C(32)	34(2)	30(2)	25(2)	3(2)	1(2)	–6(2)
C(33)	34(2)	31(2)	31(2)	3(2)	8(2)	–5(2)
C(34)	23(2)	29(2)	36(2)	11(2)	2(2)	–2(2)
C(35)	26(2)	26(2)	25(2)	9(2)	1(2)	–5(2)
O(1S)	40(2)	114(3)	107(3)	–78(3)	1(2)	–3(2)
C(1S)	68(4)	219(8)	88(5)	–93(5)	–24(3)	49(5)

Table 5. Hydrogen coordinates (× 10^4) and isotropic displacement parameters (Å^2 × 10^3) for dk24.

Atom	x	y	z	U(eq)
H(1OS)	–2088	8124	6841	104
H(1S)	–1229	8415	6006	150
H(2S)	–2970	8779	5983	150
H(3S)	–2592	7853	5725	150
H(1A)	2800(40)	7562(19)	7978(13)	20(8)
H(1B)	4130(40)	7080(20)	8455(15)	32(9)
H(2A)	5730(50)	7770(30)	7699(17)	56(12)
H(2B)	4560(40)	8670(20)	7786(15)	34(10)
H(3A)	6930(40)	8070(20)	8677(15)	52(11)
H(3B)	6360(40)	8940(20)	8469(16)	38(12)
H(4)	4900(40)	8070(30)	9346(17)	48(12)
H(7)	4370(40)	10450(20)	10095(13)	25(9)
H(8)	3310(40)	11550(20)	10627(14)	24(9)
H(9)	920(40)	12210(20)	10396(15)	28(10)
H(10)	–380(30)	11841(19)	9577(12)	14(8)
H(13)	–1240(40)	10206(19)	7887(13)	21(8)
H(15)	1010(30)	11220(20)	7618(13)	20(9)
H(161)	–430(40)	10200(30)	6623(16)	49(12)
H(162)	280(40)	11200(20)	6548(16)	42(11)
H(163)	–1230(30)	10991(18)	6955(11)	9(7)
H(18)	1920(30)	9494(17)	6604(12)	16(8)
H(19)	4420(30)	9070(20)	6402(14)	24(8)
H(20)	6610(40)	9770(20)	6916(14)	29(10)
H(21)	6150(40)	10730(30)	7590(16)	57(12)
H(22)	3480(30)	11154(19)	7886(13)	16(8)
H(24)	–2450(30)	10482(19)	9103(13)	17(8)
H(25)	–4830(40)	11220(20)	8952(15)	38(11)
H(26)	–4820(30)	12457(18)	8357(11)	9(7)

Atom	x	y	z	U(eq)
H(27)	–2460(40)	12950(20)	8013(14)	29(10)
H(28)	–10(40)	12220(20)	8236(15)	34(11)
H(291)	2830(40)	7190(20)	9332(14)	34(10)
H(292)	1190(40)	7360(20)	8881(15)	48(11)
H(31)	3080(50)	8000(30)	10253(17)	67(14)
H(32)	1950(40)	8878(19)	10950(14)	32(9)
H(33)	–710(40)	9550(20)	10782(15)	32(10)
H(34)	–1890(40)	9240(20)	9864(14)	48(10)
H(35)	–680(40)	8380(20)	9135(15)	31(10)

Table 6. Hydrogen bonds for dk24 [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
O(1S)–H(1OS)...O(2)	0.84	1.90	2.727(4)	166.1

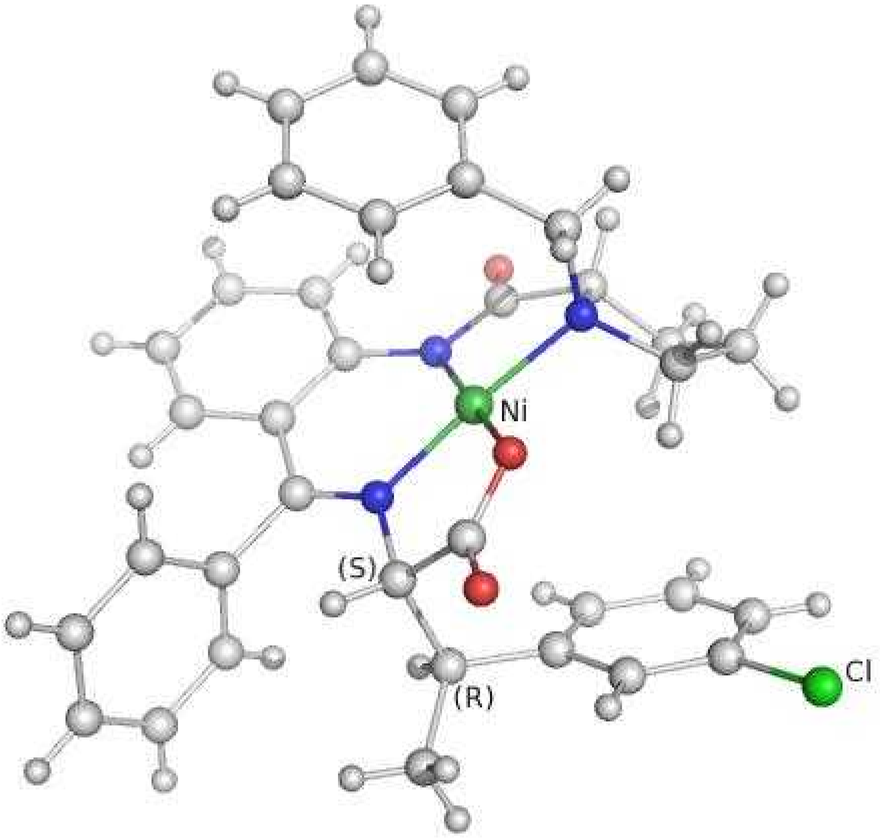


Table 1. Crystal data and structure refinement for sw005.

Identification code	sw005	
Empirical formula	$C_{35}H_{32}ClN_3NiO_3$	
Formula weight	636.80	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	orthorhombic	
Space group	P 2_1 2_1 2_1	
Unit cell dimensions	a = 8.0379(16) Å	α = 90°.
	b = 15.338(3) Å	β = 90°.
	c = 24.070(5) Å	γ = 90°.
Volume	2967.4(10) $Å^3$	
Z	4	

Density (calculated)	1.425 Mg/m^3
Absorption coefficient	2.103 mm^{-1}
F(000)	1328
Crystal size	0.40 × 0.25 × 0.03 mm^3
Theta range for data collection	3.42 to 61.04°.
Index ranges	–8<=h<=8, –13<=k<=17, –26<=l<=27
Reflections collected	21464
Independent reflections	4364 [R(int) = 0.0350]
Completeness to theta = 61.04°	96.9 %
Max. and min. transmission	0.9396 and 0.4868
Refinement method	Full–matrix least–squares on F^2
Data / restraints / parameters	4364 / 0 / 389
Goodness–of–fit on F^2	1.040
Final R indices [I>2sigma(I)]	R_1 = 0.0215, wR_2 = 0.0515
R indices (all data)	R_1 = 0.0230, wR_2 = 0.0525
Absolute structure parameter	–0.008(12)
Largest diff. peak and hole	0.135 and –0.204 e.Å^{-3}

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for sw005. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	10555(3)	10303(1)	2012(1)	27(1)
C(2)	11820(3)	10222(1)	2401(1)	37(1)
C(3)	11444(3)	10002(1)	2947(1)	40(1)
C(4)	9809(3)	9884(1)	3104(1)	35(1)
C(5)	8540(3)	9973(1)	2721(1)	28(1)
C(6)	8910(2)	10166(1)	2170(1)	21(1)
C(7)	7555(2)	10205(1)	1743(1)	21(1)
N(8)	7104(2)	9491(1)	1492(1)	18(1)
C(9)	6799(3)	11047(1)	1615(1)	22(1)
C(10)	7575(3)	11794(1)	1834(1)	29(1)
C(11)	7010(3)	12621(1)	1731(1)	34(1)
C(12)	5570(3)	12719(1)	1416(1)	33(1)
C(13)	4747(3)	12009(1)	1204(1)	29(1)

	x	y	z	U(eq)
C(14)	5344(3)	11151(1)	1282(1)	22(1)
N(15)	4598(2)	10432(1)	1015(1)	20(1)
C(16)	3098(2)	10501(1)	752(1)	21(1)
O(17)	2038(2)	11077(1)	801(1)	28(1)
C(18)	2705(2)	9740(1)	376(1)	21(1)
C(19)	1383(2)	9135(1)	614(1)	25(1)
C(20)	1661(2)	8304(1)	281(1)	25(1)
C(21)	3542(2)	8232(1)	268(1)	22(1)
N(22)	4190(2)	9169(1)	281(1)	18(1)
C(23)	5042(2)	9375(1)	–261(1)	21(1)
C(24)	5769(3)	10280(1)	–267(1)	23(1)
C(25)	4908(3)	10992(1)	–484(1)	28(1)
C(26)	5606(3)	11826(1)	–450(1)	37(1)
C(27)	7119(3)	11953(2)	–191(1)	39(1)
C(28)	7997(3)	11250(1)	14(1)	35(1)
C(29)	7323(3)	10421(1)	–30(1)	26(1)
O(30)	6896(2)	8369(1)	720(1)	20(1)
C(31)	7904(2)	8102(1)	1104(1)	19(1)
O(32)	8789(2)	7453(1)	1075(1)	22(1)
C(33)	7893(2)	8649(1)	1633(1)	19(1)
C(34)	6928(2)	8161(1)	2108(1)	21(1)
C(35)	8142(3)	7582(1)	2436(1)	26(1)
C(36)	5420(3)	7673(1)	1894(1)	21(1)
C(37)	3845(2)	8048(1)	1913(1)	27(1)
C(38)	2473(3)	7605(2)	1712(1)	34(1)
C(39)	2621(3)	6789(2)	1481(1)	32(1)
C(40)	4193(3)	6420(1)	1459(1)	27(1)
Cl(41)	4435(1)	5391(1)	1153(1)	39(1)
C(42)	5580(3)	6838(1)	1666(1)	23(1)
Ni(43)	5684(1)	9377(1)	894(1)	18(1)

Table 3. Bond lengths [Å] and angles [°] for sw005.

C(1)–C(2)	1.387(3)	N(15)–Ni(43)	1.8617(15)	C(28)–C(29)	1.388(3)
C(1)–C(6)	1.392(3)	C(16)–O(17)	1.233(2)	C(28)–H(28)	0.9500
C(1)–H(1)	0.9500	C(16)–C(18)	1.509(3)	C(29)–H(29)	0.9500
C(2)–C(3)	1.390(4)	C(18)–N(22)	1.498(2)	O(30)–C(31)	1.296(2)
C(2)–H(2)	0.9500	C(18)–C(19)	1.523(3)	O(30)–Ni(43)	1.8749(13)
C(3)–C(4)	1.380(4)	C(18)–H(18)	1.0000	C(31)–O(32)	1.225(2)
C(3)–H(3)	0.9500	C(19)–C(20)	1.522(3)	C(31)–C(33)	1.525(3)
C(4)–C(5)	1.383(3)	C(19)–H(19A)	0.9900	C(33)–C(34)	1.571(3)
C(4)–H(4)	0.9500	C(19)–H(19B)	0.9900	C(33)–H(33)	1.0000
C(5)–C(6)	1.390(3)	C(20)–C(21)	1.517(3)	C(34)–C(36)	1.514(3)
C(5)–H(5)	0.9500	C(20)–H(20A)	0.9900	C(34)–C(35)	1.538(3)
C(6)–C(7)	1.499(3)	C(20)–H(20B)	0.9900	C(34)–H(34)	1.0000
C(7)–N(8)	1.302(2)	C(21)–N(22)	1.529(2)	C(35)–H(35A)	0.9800

C(7)–C(9)	1.460(3)	C(21)–H(21A)	0.9900	C(35)–H(35B)	0.9800
N(8)–C(33)	1.479(2)	C(21)–H(21B)	0.9900	C(35)–H(35C)	0.9800
N(8)–Ni(43)	1.8441(15)	N(22)–C(23)	1.506(2)	C(36)–C(37)	1.391(3)
C(9)–C(10)	1.406(3)	N(22)–Ni(43)	1.9298(16)	C(36)–C(42)	1.399(3)
C(9)–C(14)	1.427(3)	C(23)–C(24)	1.507(3)	C(37)–C(38)	1.382(3)
C(10)–C(11)	1.370(3)	C(23)–H(23A)	0.9900	C(37)–H(37)	0.9500
C(10)–H(10)	0.9500	C(23)–H(23B)	0.9900	C(38)–C(39)	1.375(3)
C(11)–C(12)	1.392(3)	C(24)–C(29)	1.391(3)	C(38)–H(38)	0.9500
C(11)–H(11)	0.9500	C(24)–C(25)	1.393(3)	C(39)–C(40)	1.385(3)
C(12)–C(13)	1.373(3)	C(25)–C(26)	1.400(3)	C(39)–H(39)	0.9500
C(12)–H(12)	0.9500	C(25)–H(25)	0.9500	C(40)–C(42)	1.379(3)
C(13)–C(14)	1.414(3)	C(26)–C(27)	1.380(3)	C(40)–Cl(41)	1.753(2)
C(13)–H(13)	0.9500	C(26)–H(26)	0.9500	C(42)–H(42)	0.9500
C(14)–N(15)	1.409(2)	C(27)–C(28)	1.380(3)		
N(15)–C(16)	1.367(2)	C(27)–H(27)	0.9500		

C(2)–C(1)–C(6)	119.9(2)	C(23)–N(22)–C(21)	109.53(14)
C(2)–C(1)–H(1)	120.1	C(18)–N(22)–Ni(43)	106.36(11)
C(6)–C(1)–H(1)	120.1	C(23)–N(22)–Ni(43)	110.17(11)
C(1)–C(2)–C(3)	120.0(2)	C(21)–N(22)–Ni(43)	112.49(11)
C(1)–C(2)–H(2)	120.0	N(22)–C(23)–C(24)	112.18(14)
C(3)–C(2)–H(2)	120.0	N(22)–C(23)–H(23A)	109.2
C(4)–C(3)–C(2)	119.9(2)	C(24)–C(23)–H(23A)	109.2
C(4)–C(3)–H(3)	120.0	N(22)–C(23)–H(23B)	109.2
C(2)–C(3)–H(3)	120.0	C(24)–C(23)–H(23B)	109.2
C(3)–C(4)–C(5)	120.4(2)	H(23A)–C(23)–H(23B)	107.9
C(3)–C(4)–H(4)	119.8	C(29)–C(24)–C(25)	118.62(18)
C(5)–C(4)–H(4)	119.8	C(29)–C(24)–C(23)	119.11(17)
C(4)–C(5)–C(6)	120.0(2)	C(25)–C(24)–C(23)	122.22(18)
C(4)–C(5)–H(5)	120.0	C(24)–C(25)–C(26)	119.7(2)
C(6)–C(5)–H(5)	120.0	C(24)–C(25)–H(25)	120.2
C(5)–C(6)–C(1)	119.73(19)	C(26)–C(25)–H(25)	120.2
C(5)–C(6)–C(7)	120.50(18)	C(27)–C(26)–C(25)	120.6(2)
C(1)–C(6)–C(7)	119.76(17)	C(27)–C(26)–H(26)	119.7
N(8)–C(7)–C(9)	122.03(17)	C(25)–C(26)–H(26)	119.7
N(8)–C(7)–C(6)	119.17(16)	C(28)–C(27)–C(26)	120.2(2)
C(9)–C(7)–C(6)	118.79(16)	C(28)–C(27)–H(27)	119.9
C(7)–N(8)–C(33)	120.52(15)	C(26)–C(27)–H(27)	119.9
C(7)–N(8)–Ni(43)	127.87(13)	C(27)–C(28)–C(29)	119.3(2)
C(33)–N(8)–Ni(43)	111.25(11)	C(27)–C(28)–H(28)	120.4
C(10)–C(9)–C(14)	118.91(17)	C(29)–C(28)–H(28)	120.4
C(10)–C(9)–C(7)	117.19(17)	C(28)–C(29)–C(24)	121.6(2)
C(14)–C(9)–C(7)	123.90(16)	C(28)–C(29)–H(29)	119.2
C(11)–C(10)–C(9)	122.6(2)	C(24)–C(29)–H(29)	119.2
C(11)–C(10)–H(10)	118.7	C(31)–O(30)–Ni(43)	115.20(11)
C(9)–C(10)–H(10)	118.7	O(32)–C(31)–O(30)	125.45(17)
C(10)–C(11)–C(12)	118.34(19)	O(32)–C(31)–C(33)	119.77(16)
C(10)–C(11)–H(11)	120.8	O(30)–C(31)–C(33)	114.75(16)
C(12)–C(11)–H(11)	120.8	N(8)–C(33)–C(31)	106.87(14)
C(13)–C(12)–C(11)	121.16(19)	N(8)–C(33)–C(34)	111.82(15)

C(13)–C(12)–H(12)	119.4	C(31)–C(33)–C(34)	110.39(15)
C(11)–C(12)–H(12)	119.4	N(8)–C(33)–H(33)	109.2
C(12)–C(13)–C(14)	121.7(2)	C(31)–C(33)–H(33)	109.2
C(12)–C(13)–H(13)	119.1	C(34)–C(33)–H(33)	109.2
C(14)–C(13)–H(13)	119.1	C(36)–C(34)–C(35)	113.43(16)
N(15)–C(14)–C(13)	121.57(17)	C(36)–C(34)–C(33)	112.53(15)
N(15)–C(14)–C(9)	121.17(16)	C(35)–C(34)–C(33)	109.60(16)
C(13)–C(14)–C(9)	117.15(17)	C(36)–C(34)–H(34)	107.0
C(16)–N(15)–C(14)	121.79(15)	C(35)–C(34)–H(34)	107.0
C(16)–N(15)–Ni(43)	114.06(12)	C(33)–C(34)–H(34)	107.0
C(14)–N(15)–Ni(43)	123.48(13)	C(34)–C(35)–H(35A)	109.5
O(17)–C(16)–N(15)	128.29(17)	C(34)–C(35)–H(35B)	109.5
O(17)–C(16)–C(18)	117.87(17)	H(35A)–C(35)–H(35B)	109.5
N(15)–C(16)–C(18)	113.77(16)	C(34)–C(35)–H(35C)	109.5
N(22)–C(18)–C(16)	112.17(15)	H(35A)–C(35)–H(35C)	109.5
N(22)–C(18)–C(19)	104.95(14)	H(35B)–C(35)–H(35C)	109.5
C(16)–C(18)–C(19)	113.10(16)	C(37)–C(36)–C(42)	118.31(18)
N(22)–C(18)–H(18)	108.8	C(37)–C(36)–C(34)	120.88(17)
C(16)–C(18)–H(18)	108.8	C(42)–C(36)–C(34)	120.80(17)
C(19)–C(18)–H(18)	108.8	C(38)–C(37)–C(36)	120.8(2)
C(20)–C(19)–C(18)	102.15(16)	C(38)–C(37)–H(37)	119.6
C(20)–C(19)–H(19A)	111.3	C(36)–C(37)–H(37)	119.6
C(18)–C(19)–H(19A)	111.3	C(39)–C(38)–C(37)	121.3(2)
C(20)–C(19)–H(19B)	111.3	C(39)–C(38)–H(38)	119.4
C(18)–C(19)–H(19B)	111.3	C(37)–C(38)–H(38)	119.4
H(19A)–C(19)–H(19B)	109.2	C(38)–C(39)–C(40)	117.8(2)
C(21)–C(20)–C(19)	102.59(16)	C(38)–C(39)–H(39)	121.1
C(21)–C(20)–H(20A)	111.2	C(40)–C(39)–H(39)	121.1
C(19)–C(20)–H(20A)	111.2	C(42)–C(40)–C(39)	122.29(19)
C(21)–C(20)–H(20B)	111.2	C(42)–C(40)–Cl(41)	118.69(17)
C(19)–C(20)–H(20B)	111.2	C(39)–C(40)–Cl(41)	119.02(16)
H(20A)–C(20)–H(20B)	109.2	C(40)–C(42)–C(36)	119.51(19)
C(20)–C(21)–N(22)	105.74(15)	C(40)–C(42)–H(42)	120.2
C(20)–C(21)–H(21A)	110.6	C(36)–C(42)–H(42)	120.2
N(22)–C(21)–H(21A)	110.6	N(8)–Ni(43)–N(15)	94.91(7)
C(20)–C(21)–H(21B)	110.6	N(8)–Ni(43)–O(30)	86.07(6)
N(22)–C(21)–H(21B)	110.6	N(15)–Ni(43)–O(30)	174.53(6)
H(21A)–C(21)–H(21B)	108.7	N(8)–Ni(43)–N(22)	175.85(6)
C(18)–N(22)–C(23)	111.90(14)	N(15)–Ni(43)–N(22)	88.38(6)
C(18)–N(22)–C(21)	106.33(14)	O(30)–Ni(43)–N(22)	90.89(6)

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$)for sw005. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	30(1)	18(1)	32(1)	–6(1)	–2(1)	–2(1)
C(2)	31(1)	22(1)	58(2)	–14(1)	–11(1)	1(1)
C(3)	55(2)	20(1)	46(2)	–8(1)	–29(1)	7(1)
C(4)	57(2)	22(1)	26(1)	–2(1)	–13(1)	2(1)
C(5)	38(1)	20(1)	25(1)	–3(1)	–4(1)	1(1)
C(6)	29(1)	12(1)	22(1)	–4(1)	–3(1)	0(1)
C(7)	23(1)	19(1)	20(1)	1(1)	3(1)	–1(1)
N(8)	21(1)	13(1)	21(1)	0(1)	2(1)	1(1)
C(9)	31(1)	16(1)	18(1)	0(1)	–1(1)	0(1)
C(10)	40(1)	20(1)	26(1)	–2(1)	–8(1)	–1(1)
C(11)	49(2)	16(1)	36(1)	–3(1)	–9(1)	–4(1)
C(12)	49(1)	17(1)	34(1)	–1(1)	–5(1)	7(1)
C(13)	38(1)	19(1)	29(1)	–1(1)	–6(1)	4(1)
C(14)	31(1)	16(1)	18(1)	0(1)	0(1)	2(1)
N(15)	24(1)	16(1)	20(1)	0(1)	0(1)	0(1)
C(16)	22(1)	18(1)	23(1)	5(1)	3(1)	0(1)
O(17)	25(1)	20(1)	39(1)	0(1)	1(1)	6(1)
C(18)	22(1)	20(1)	22(1)	2(1)	–2(1)	5(1)
C(19)	20(1)	24(1)	32(1)	0(1)	0(1)	0(1)
C(20)	21(1)	23(1)	31(1)	0(1)	–2(1)	–2(1)
C(21)	23(1)	16(1)	26(1)	–3(1)	–2(1)	–3(1)
N(22)	18(1)	15(1)	22(1)	1(1)	2(1)	–1(1)
C(23)	24(1)	22(1)	18(1)	–1(1)	1(1)	1(1)
C(24)	27(1)	23(1)	18(1)	0(1)	7(1)	1(1)
C(25)	36(1)	28(1)	21(1)	3(1)	8(1)	6(1)
C(26)	60(2)	20(1)	31(1)	5(1)	16(1)	8(1)
C(27)	56(2)	27(1)	34(1)	–3(1)	15(1)	–12(1)
C(28)	39(1)	34(1)	33(1)	–3(1)	9(1)	–14(1)
C(29)	29(1)	26(1)	24(1)	1(1)	6(1)	–5(1)
O(30)	21(1)	17(1)	22(1)	–2(1)	–2(1)	0(1)
C(31)	18(1)	17(1)	22(1)	1(1)	1(1)	–5(1)
O(32)	19(1)	18(1)	28(1)	–2(1)	1(1)	4(1)
C(33)	17(1)	15(1)	25(1)	0(1)	–4(1)	1(1)
C(34)	25(1)	17(1)	21(1)	0(1)	0(1)	2(1)
C(35)	27(1)	22(1)	27(1)	4(1)	–6(1)	–2(1)
C(36)	22(1)	21(1)	21(1)	7(1)	3(1)	1(1)
C(37)	26(1)	25(1)	30(1)	10(1)	3(1)	3(1)
C(38)	20(1)	42(1)	41(1)	22(1)	2(1)	2(1)
C(39)	24(1)	38(1)	33(1)	17(1)	–5(1)	–8(1)
C(40)	30(1)	27(1)	24(1)	6(1)	1(1)	–9(1)
Cl(41)	43(1)	36(1)	40(1)	–8(1)	–2(1)	–17(1)
C(42)	23(1)	23(1)	24(1)	5(1)	0(1)	–1(1)
Ni(43)	20(1)	15(1)	20(1)	–1(1)	–2(1)	1(1)

Table 5. Hydrogen coordinates (× 10^4) and isotropic displacement parameters ($Å^2 \times 10^3$) for sw005.

	x	y	z	U(eq)
H(1)	10811	10451	1638	32
H(2)	12943	10318	2294	44
H(3)	12312	9932	3211	48
H(4)	9554	9742	3479	42
H(5)	7416	9903	2833	33
H(10)	8530	11722	2062	34
H(11)	7585	13115	1872	40
H(12)	5151	13288	1347	40
H(13)	3749	12097	1000	35
H(18)	2310	9968	10	26
H(19A)	1555	9035	1016	30
H(19B)	251	9371	553	30
H(20A)	1155	7794	468	30
H(20B)	1196	8355	–98	30
H(21A)	3913	7931	–74	26
H(21B)	3952	7902	594	26
H(23A)	4230	9318	–568	26
H(23B)	5941	8945	–326	26
H(25)	3852	10911	–654	34
H(26)	5034	12309	–607	44
H(27)	7557	12525	–155	46
H(28)	9052	11334	184	42
H(29)	7937	9936	106	31
H(33)	9065	8755	1755	23
H(34)	6511	8616	2370	26
H(35A)	7531	7265	2725	38
H(35B)	8996	7947	2610	38
H(35C)	8671	7165	2184	38
H(37)	3711	8614	2066	32
H(38)	1407	7871	1733	41
H(39)	1677	6488	1341	38
H(42)	6636	6560	1654	28

Table 6. Torsion angles [°] for sw005.

C(6)–C(1)–C(2)–C(3)	0.3(3)	C(29)–C(24)–C(25)–C(26)	–1.0(3)
C(1)–C(2)–C(3)–C(4)	–1.6(3)	C(23)–C(24)–C(25)–C(26)	176.43(17)
C(2)–C(3)–C(4)–C(5)	0.9(3)	C(24)–C(25)–C(26)–C(27)	–1.7(3)
C(3)–C(4)–C(5)–C(6)	1.2(3)	C(25)–C(26)–C(27)–C(28)	3.1(3)
C(4)–C(5)–C(6)–C(1)	–2.6(3)	C(26)–C(27)–C(28)–C(29)	–1.7(3)
C(4)–C(5)–C(6)–C(7)	175.87(18)	C(27)–C(28)–C(29)–C(24)	–1.1(3)
C(2)–C(1)–C(6)–C(5)	1.8(3)	C(25)–C(24)–C(29)–C(28)	2.4(3)
C(2)–C(1)–C(6)–C(7)	–176.63(17)	C(23)–C(24)–C(29)–C(28)	–175.07(18)
C(5)–C(6)–C(7)–N(8)	–86.7(2)	Ni(43)–O(30)–C(31)–O(32)	179.03(14)
C(1)–C(6)–C(7)–N(8)	91.7(2)	Ni(43)–O(30)–C(31)–C(33)	1.12(19)
C(5)–C(6)–C(7)–C(9)	94.2(2)	C(7)–N(8)–C(33)–C(31)	–148.24(16)
C(1)–C(6)–C(7)–C(9)	–87.4(2)	Ni(43)–N(8)–C(33)–C(31)	25.46(17)
C(9)–C(7)–N(8)–C(33)	–179.76(17)	C(7)–N(8)–C(33)–C(34)	90.9(2)
C(6)–C(7)–N(8)–C(33)	1.1(2)	Ni(43)–N(8)–C(33)–C(34)	–95.44(15)
C(9)–C(7)–N(8)–Ni(43)	7.7(3)	O(32)–C(31)–C(33)–N(8)	164.80(16)
C(6)–C(7)–N(8)–Ni(43)	–171.41(13)	O(30)–C(31)–C(33)–N(8)	–17.2(2)
N(8)–C(7)–C(9)–C(10)	–168.78(18)	O(32)–C(31)–C(33)–C(34)	–73.4(2)
C(6)–C(7)–C(9)–C(10)	10.3(3)	O(30)–C(31)–C(33)–C(34)	104.65(18)
N(8)–C(7)–C(9)–C(14)	10.7(3)	N(8)–C(33)–C(34)–C(36)	81.08(19)
C(6)–C(7)–C(9)–C(14)	–170.22(17)	C(31)–C(33)–C(34)–C(36)	–37.8(2)
C(14)–C(9)–C(10)–C(11)	–1.3(3)	N(8)–C(33)–C(34)–C(35)	–151.71(16)
C(7)–C(9)–C(10)–C(11)	178.2(2)	C(31)–C(33)–C(34)–C(35)	89.45(18)
C(9)–C(10)–C(11)–C(12)	2.6(3)	C(35)–C(34)–C(36)–C(37)	139.08(18)
C(10)–C(11)–C(12)–C(13)	–1.1(3)	C(33)–C(34)–C(36)–C(37)	–95.8(2)
C(11)–C(12)–C(13)–C(14)	–1.8(3)	C(35)–C(34)–C(36)–C(42)	–41.7(2)
C(12)–C(13)–C(14)–N(15)	–173.16(19)	C(33)–C(34)–C(36)–C(42)	83.5(2)
C(12)–C(13)–C(14)–C(9)	3.1(3)	C(42)–C(36)–C(37)–C(38)	0.0(3)
C(10)–C(9)–C(14)–N(15)	174.72(17)	C(34)–C(36)–C(37)–C(38)	179.25(18)
C(7)–C(9)–C(14)–N(15)	–4.7(3)	C(36)–C(37)–C(38)–C(39)	–0.8(3)
C(10)–C(9)–C(14)–C(13)	–1.6(3)	C(37)–C(38)–C(39)–C(40)	0.4(3)
C(7)–C(9)–C(14)–C(13)	178.96(18)	C(38)–C(39)–C(40)–C(42)	0.9(3)
C(13)–C(14)–N(15)–C(16)	–12.0(3)	C(38)–C(39)–C(40)–Cl(41)	–178.58(15)
C(9)–C(14)–N(15)–C(16)	171.86(16)	C(39)–C(40)–C(42)–C(36)	–1.7(3)
C(13)–C(14)–N(15)–Ni(43)	158.05(15)	Cl(41)–C(40)–C(42)–C(36)	177.77(14)
C(9)–C(14)–N(15)–Ni(43)	–18.1(2)	C(37)–C(36)–C(42)–C(40)	1.2(3)
C(14)–N(15)–C(16)–O(17)	–17.3(3)	C(34)–C(36)–C(42)–C(40)	–178.03(17)
Ni(43)–N(15)–C(16)–O(17)	171.77(15)	C(7)–N(8)–Ni(43)–N(15)	–22.72(16)
C(14)–N(15)–C(16)–C(18)	165.75(16)	C(33)–N(8)–Ni(43)–N(15)	164.15(12)
Ni(43)–N(15)–C(16)–C(18)	–5.17(19)	C(7)–N(8)–Ni(43)–O(30)	151.88(16)
O(17)–C(16)–C(18)–N(22)	170.58(15)	C(33)–N(8)–Ni(43)–O(30)	–21.24(12)
N(15)–C(16)–C(18)–N(22)	–12.1(2)	C(7)–N(8)–Ni(43)–N(22)	–165.1(9)
O(17)–C(16)–C(18)–C(19)	–71.0(2)	C(33)–N(8)–Ni(43)–N(22)	21.7(10)
N(15)–C(16)–C(18)–C(19)	106.34(18)	C(16)–N(15)–Ni(43)–N(8)	–162.12(12)
N(22)–C(18)–C(19)–C(20)	–38.25(18)	C(14)–N(15)–Ni(43)–N(8)	27.13(14)
C(16)–C(18)–C(19)–C(20)	–160.83(16)	C(16)–N(15)–Ni(43)–O(30)	97.8(7)
C(18)–C(19)–C(20)–C(21)	42.26(19)	C(14)–N(15)–Ni(43)–O(30)	–73.0(7)
C(19)–C(20)–C(21)–N(22)	–30.77(19)	C(16)–N(15)–Ni(43)–N(22)	15.35(12)
C(16)–C(18)–N(22)–C(23)	–98.07(17)	C(14)–N(15)–Ni(43)–N(22)	–155.40(14)

C(19)–C(18)–N(22)–C(23)	138.74(15)
C(16)–C(18)–N(22)–C(21)	142.37(15)
C(19)–C(18)–N(22)–C(21)	19.19(18)
C(16)–C(18)–N(22)–Ni(43)	22.28(16)
C(19)–C(18)–N(22)–Ni(43)	–100.90(13)
C(20)–C(21)–N(22)–C(18)	7.30(19)
C(20)–C(21)–N(22)–C(23)	–113.78(17)
C(20)–C(21)–N(22)–Ni(43)	123.34(14)
C(18)–N(22)–C(23)–C(24)	64.54(19)
C(21)–N(22)–C(23)–C(24)	–177.81(15)
Ni(43)–N(22)–C(23)–C(24)	–53.56(17)
N(22)–C(23)–C(24)–C(29)	83.0(2)
N(22)–C(23)–C(24)–C(25)	–94.5(2)
C(31)–O(30)–Ni(43)–N(8)	11.66(12)
C(31)–O(30)–Ni(43)–N(15)	112.2(6)
C(31)–O(30)–Ni(43)–N(22)	–165.51(12)
C(18)–N(22)–Ni(43)–N(8)	122.0(9)
C(23)–N(22)–Ni(43)–N(8)	–116.6(9)
C(21)–N(22)–Ni(43)–N(8)	5.9(10)
C(18)–N(22)–Ni(43)–N(15)	–20.61(11)
C(23)–N(22)–Ni(43)–N(15)	100.86(12)
C(21)–N(22)–Ni(43)–N(15)	–136.63(12)
C(18)–N(22)–Ni(43)–O(30)	164.81(11)
C(23)–N(22)–Ni(43)–O(30)	–73.72(12)
C(21)–N(22)–Ni(43)–O(30)	48.80(12)

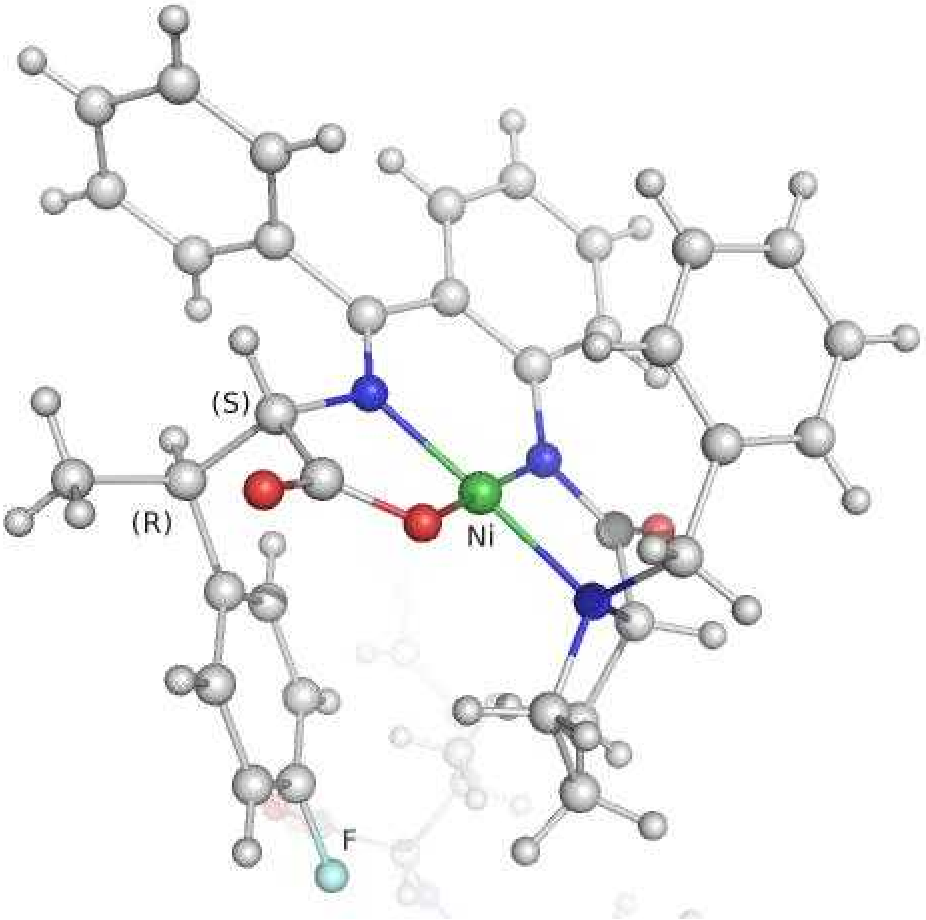


Table 1. Crystal data and structure refinement for sw007.

Identification code	sw007_1	
Empirical formula	$C_{35}H_{32}FN_3NiO_3$	
Formula weight	620.35	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	orthorhombic	
Space group	$P\ 2_1\ 2_1\ 2_1$	
Unit cell dimensions	a = 11.146(2) Å	α = 90°.
	b = 19.625(4) Å	β= 90°.
	c = 26.276(5) Å	γ = 90°.
Volume	5748(2) Å^3	
Z	8	

Density (calculated)	1.434 Mg/m^3
Absorption coefficient	1.372 mm^{-1}
F(000)	2592
Crystal size	0.25 × 0.15 × 0.10 mm^3
Theta range for data collection	2.81 to 60.02°.
Index ranges	–11<=h<=12, –20<=k<=14, –29<=l<=26
Reflections collected	40395
Independent reflections	7958 [R(int) = 0.0404]
Completeness to theta = 60.02°	95.4 %
Max. and min. transmission	0.8750 and 0.7255
Refinement method	Full–matrix least–squares on F^2
Data / restraints / parameters	7958 / 0 / 777
Goodness–of–fit on F^2	1.024
Final R indices [I>2sigma(I)]	R_1 = 0.0253, wR_2 = 0.0615
R indices (all data)	R_1 = 0.0275, wR_2 = 0.0628
Absolute structure parameter	–0.032(14)
Largest diff. peak and hole	0.371 and –0.244 e.Å^{-3}

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for sw007. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Ni(01)	8667(1)	909(1)	9527(1)	24(1)
Ni(02)	2579(1)	7972(1)	8358(1)	26(1)
O(003)	2613(2)	5999(1)	8385(1)	34(1)
O(004)	2427(2)	9973(1)	8393(1)	32(1)
F(005)	2685(1)	7881(1)	10638(1)	44(1)
O(006)	8806(1)	85(1)	9178(1)	27(1)
N(007)	8671(2)	1707(1)	9909(1)	24(1)
N(008)	10048(2)	1254(1)	9169(1)	25(1)
F(009)	7167(1)	2101(1)	7733(1)	50(1)
O(010)	7830(1)	–889(1)	9017(1)	31(1)
C(011)	2819(2)	6611(1)	8394(1)	28(1)
O(012)	9513(1)	2802(1)	9872(1)	31(1)
C(013)	4499(2)	7733(1)	9504(1)	30(1)

	x	y	z	U(eq)
O(014)	2013(1)	7085(1)	8442(1)	30(1)
C(015)	6853(2)	704(1)	10273(1)	23(1)
C(016)	4801(2)	6788(1)	8868(1)	29(1)
N(017)	7345(2)	528(1)	9842(1)	24(1)
C(018)	2310(2)	9351(1)	8416(1)	27(1)
C(019)	4643(2)	479(1)	10409(1)	26(1)
C(020)	1337(2)	9059(1)	8752(1)	32(1)
C(021)	10064(2)	2007(1)	9242(1)	27(1)
C(022)	3733(2)	57(1)	10574(1)	30(1)
C(023)	8168(2)	1761(1)	10401(1)	25(1)
C(024)	3939(2)	9025(1)	7856(1)	26(1)
C(025)	4900(2)	8566(1)	7757(1)	25(1)
C(026)	6146(2)	681(1)	8805(1)	25(1)
C(027)	2812(2)	6991(1)	10044(1)	33(1)
C(028)	5836(2)	286(1)	10483(1)	24(1)
C(029)	11224(2)	992(1)	9956(1)	25(1)
C(030)	4104(2)	6871(1)	8358(1)	27(1)
C(031)	5843(2)	9398(1)	7196(1)	34(1)
C(032)	7249(2)	1827(1)	11406(1)	30(1)
C(033)	3985(2)	–552(1)	10818(1)	32(1)
C(034)	3175(2)	7623(1)	10200(1)	33(1)
N(035)	3017(2)	8857(1)	8197(1)	26(1)
C(036)	4872(2)	9826(1)	7269(1)	33(1)
C(037)	8098(2)	2289(1)	11238(1)	31(1)
C(038)	9991(2)	1125(1)	8594(1)	29(1)
C(039)	6582(2)	478(1)	8332(1)	30(1)
C(040)	4952(2)	7868(1)	7951(1)	26(1)
C(041)	6093(2)	–312(1)	10744(1)	27(1)
N(042)	1087(2)	8334(1)	8618(1)	33(1)
C(043)	6046(2)	7437(1)	7852(1)	27(1)
C(044)	8548(2)	2258(1)	10750(1)	30(1)
C(045)	6035(2)	6970(1)	7451(1)	28(1)
C(046)	5841(2)	8770(1)	7434(1)	31(1)
C(047)	6927(2)	951(2)	7966(1)	35(1)
C(048)	4006(2)	8005(1)	9944(1)	33(1)
C(049)	7306(2)	1275(1)	10573(1)	24(1)
C(050)	9391(2)	2215(1)	9716(1)	26(1)
C(051)	10558(2)	567(1)	10279(1)	28(1)
C(052)	3942(2)	9648(1)	7591(1)	31(1)
C(053)	5163(3)	6049(1)	8948(1)	39(1)
C(054)	155(2)	8712(2)	7786(1)	36(1)
C(055)	9525(2)	2290(1)	8748(1)	30(1)
C(056)	11226(2)	1196(1)	11009(1)	34(1)
C(057)	6366(2)	1856(1)	8540(1)	35(1)
C(058)	764(3)	7986(2)	9120(1)	52(1)
C(059)	6863(2)	1331(1)	11074(1)	28(1)
C(060)	11147(2)	919(1)	9386(1)	29(1)
C(061)	7899(2)	–326(1)	9221(1)	26(1)
C(062)	11921(2)	1499(1)	10175(1)	30(1)

	x	y	z	U(eq)
C(063)	–523(2)	9303(2)	7759(1)	46(1)
N(064)	4048(2)	7591(1)	8191(1)	25(1)
C(065)	5785(2)	175(1)	9211(1)	26(1)
C(066)	4174(2)	7092(1)	9329(1)	26(1)
C(067)	11931(2)	1595(1)	10697(1)	32(1)
C(068)	3316(2)	6727(1)	9604(1)	32(1)
C(069)	6037(2)	1374(1)	8902(1)	33(1)
C(070)	905(2)	8541(2)	7382(1)	37(1)
C(071)	10073(2)	1823(1)	8350(1)	32(1)
C(072)	6871(2)	–53(1)	9545(1)	25(1)
C(073)	314(3)	9560(2)	6943(1)	53(1)
C(074)	6825(2)	1624(2)	8087(1)	37(1)
C(075)	10547(2)	672(1)	10800(1)	30(1)
C(076)	5171(2)	–733(1)	10911(1)	30(1)
C(077)	7915(2)	6503(1)	7725(1)	35(1)
C(078)	7035(2)	7449(1)	8175(1)	31(1)
C(079)	989(2)	8968(2)	6967(1)	47(1)
C(080)	876(3)	8514(2)	9525(1)	60(1)
C(081)	–451(3)	9725(2)	7337(1)	54(1)
C(082)	7948(2)	6977(2)	8117(1)	37(1)
C(083)	5109(2)	–446(1)	9007(1)	34(1)
C(084)	6959(2)	6511(1)	7386(1)	33(1)
C(085)	1702(3)	9029(1)	9316(1)	41(1)
C(086)	68(2)	8257(1)	8250(1)	42(1)

Table 3. Bond lengths [Å] and angles [°] for sw007.

Ni(01)–N(017)	1.8484(18)	C(026)–C(065)	1.511(3)	C(055)–H(05G)	0.9900
Ni(01)–N(007)	1.8618(19)	C(027)–C(034)	1.369(4)	C(056)–C(067)	1.379(3)
Ni(01)–O(006)	1.8651(16)	C(027)–C(068)	1.386(3)	C(056)–C(075)	1.389(3)
Ni(01)–N(008)	1.9273(19)	C(027)–H(02D)	0.9500	C(056)–H(05H)	0.9500
Ni(02)–N(035)	1.853(2)	C(028)–C(041)	1.388(3)	C(057)–C(074)	1.373(4)
Ni(02)–N(064)	1.853(2)	C(029)–C(062)	1.387(3)	C(057)–C(069)	1.392(3)
Ni(02)–O(014)	1.8640(17)	C(029)–C(051)	1.403(3)	C(057)–H(05I)	0.9500
Ni(02)–N(042)	1.934(2)	C(029)–C(060)	1.507(3)	C(058)–C(080)	1.492(4)
O(003)–C(011)	1.224(3)	C(030)–N(064)	1.480(3)	C(058)–H(05J)	0.9900
O(004)–C(018)	1.230(3)	C(030)–H(03A)	1.0000	C(058)–H(05K)	0.9900
F(005)–C(034)	1.372(3)	C(031)–C(046)	1.381(3)	C(059)–H(05L)	0.9500

O(006)–C(061)	1.298(3)	C(031)–C(036)	1.384(4)	C(060)–H(06A)	0.9900
N(007)–C(050)	1.376(3)	C(031)–H(03B)	0.9500	C(060)–H(06B)	0.9900
N(007)–C(023)	1.412(3)	C(032)–C(059)	1.376(3)	C(061)–C(072)	1.524(3)
N(008)–C(021)	1.490(3)	C(032)–C(037)	1.382(3)	C(062)–C(067)	1.385(3)
N(008)–C(060)	1.504(3)	C(032)–H(03C)	0.9500	C(062)–H(06C)	0.9500
N(008)–C(038)	1.533(3)	C(033)–C(076)	1.391(3)	C(063)–C(081)	1.387(4)
F(009)–C(074)	1.373(3)	C(033)–H(03D)	0.9500	C(063)–H(06D)	0.9500
O(010)–C(061)	1.230(3)	C(034)–C(048)	1.368(4)	C(065)–C(083)	1.530(3)
C(011)–O(014)	1.299(3)	C(036)–C(052)	1.383(3)	C(065)–C(072)	1.560(3)
C(011)–C(030)	1.524(3)	C(036)–H(03E)	0.9500	C(065)–H(06E)	1.0000
O(012)–C(050)	1.231(3)	C(037)–C(044)	1.379(3)	C(066)–C(068)	1.396(3)
C(013)–C(048)	1.388(3)	C(037)–H(03F)	0.9500	C(067)–H(06F)	0.9500
C(013)–C(066)	1.387(3)	C(038)–C(071)	1.516(3)	C(068)–H(06G)	0.9500
C(013)–H(01A)	0.9500	C(038)–H(03G)	0.9900	C(069)–H(06H)	0.9500
C(015)–N(017)	1.304(3)	C(038)–H(03H)	0.9900	C(070)–C(079)	1.377(4)
C(015)–C(049)	1.460(3)	C(039)–C(047)	1.392(3)	C(070)–H(07A)	0.9500
C(015)–C(028)	1.504(3)	C(039)–H(03I)	0.9500	C(071)–H(07B)	0.9900
C(016)–C(053)	1.520(3)	C(040)–N(064)	1.306(3)	C(071)–H(07C)	0.9900
C(016)–C(066)	1.521(3)	C(040)–C(043)	1.506(3)	C(072)–H(07D)	1.0000
C(016)–C(030)	1.558(3)	C(041)–C(076)	1.390(3)	C(073)–C(081)	1.378(4)
C(016)–H(016)	1.0000	C(041)–H(04A)	0.9500	C(073)–C(079)	1.385(4)
N(017)–C(072)	1.480(3)	N(042)–C(086)	1.500(3)	C(073)–H(07E)	0.9500
C(018)–N(035)	1.376(3)	N(042)–C(058)	1.527(3)	C(075)–H(07F)	0.9500
C(018)–C(020)	1.510(3)	C(043)–C(078)	1.392(3)	C(076)–H(07G)	0.9500
C(019)–C(022)	1.380(3)	C(043)–C(045)	1.396(3)	C(077)–C(084)	1.387(4)
C(019)–C(028)	1.397(3)	C(044)–H(04B)	0.9500	C(077)–C(082)	1.388(4)
C(019)–H(01C)	0.9500	C(045)–C(084)	1.379(3)	C(077)–H(07H)	0.9500
C(020)–N(042)	1.491(3)	C(045)–H(04C)	0.9500	C(078)–C(082)	1.384(4)
C(020)–C(085)	1.539(3)	C(046)–H(04D)	0.9500	C(078)–H(07I)	0.9500

C(020)–H(02A)	1.0000	C(047)–C(074)	1.362(4)	C(079)–H(07J)	0.9500
C(021)–C(050)	1.510(3)	C(047)–H(04E)	0.9500	C(080)–C(085)	1.474(4)
C(021)–C(055)	1.535(3)	C(048)–H(04F)	0.9500	C(080)–H(08A)	0.9900
C(021)–H(02B)	1.0000	C(049)–C(059)	1.409(3)	C(080)–H(08B)	0.9900
C(022)–C(033)	1.384(3)	C(051)–C(075)	1.385(3)	C(081)–H(08C)	0.9500
C(022)–H(02C)	0.9500	C(051)–H(05A)	0.9500	C(082)–H(08D)	0.9500
C(023)–C(044)	1.404(3)	C(052)–H(05B)	0.9500	C(083)–H(08E)	0.9800
C(023)–C(049)	1.427(3)	C(053)–H(05C)	0.9800	C(083)–H(08F)	0.9800
C(024)–N(035)	1.403(3)	C(053)–H(05D)	0.9800	C(083)–H(08G)	0.9800
C(024)–C(052)	1.408(3)	C(053)–H(05E)	0.9800	C(084)–H(08H)	0.9500
C(024)–C(025)	1.423(3)	C(054)–C(063)	1.387(4)	C(085)–H(08I)	0.9900
C(025)–C(046)	1.409(3)	C(054)–C(070)	1.394(4)	C(085)–H(08J)	0.9900
C(025)–C(040)	1.464(3)	C(054)–C(086)	1.513(4)	C(086)–H(08K)	0.9900
C(026)–C(069)	1.388(3)	C(055)–C(071)	1.519(3)	C(086)–H(08L)	0.9900
C(026)–C(039)	1.393(3)	C(055)–H(05F)	0.9900		

N(017)–Ni(01)–N(007)	95.73(8)	C(048)–C(034)–F(005)	118.7(2)	O(010)–C(061)–C(072)	120.9(2)
N(017)–Ni(01)–O(006)	86.36(8)	C(027)–C(034)–F(005)	117.9(2)	O(006)–C(061)–C(072)	114.6(2)
N(007)–Ni(01)–O(006)	174.24(8)	C(018)–N(035)–C(024)	121.5(2)	C(067)–C(062)–C(029)	120.8(2)
N(017)–Ni(01)–N(008)	176.23(8)	C(018)–N(035)–Ni(02)	114.40(15)	C(067)–C(062)–H(06C)	119.6
N(007)–Ni(01)–N(008)	88.03(8)	C(024)–N(035)–Ni(02)	124.01(16)	C(029)–C(062)–H(06C)	119.6
O(006)–Ni(01)–N(008)	89.91(7)	C(031)–C(036)–C(052)	121.1(2)	C(054)–C(063)–C(081)	120.6(3)
N(035)–Ni(02)–N(064)	95.23(9)	C(031)–C(036)–H(03E)	119.4	C(054)–C(063)–H(06D)	119.7
N(035)–Ni(02)–O(014)	172.41(7)	C(052)–C(036)–H(03E)	119.4	C(081)–C(063)–H(06D)	119.7
N(064)–Ni(02)–O(014)	87.16(8)	C(044)–C(037)–C(032)	121.1(2)	C(040)–N(064)–C(030)	120.4(2)
N(035)–Ni(02)–N(042)	87.88(8)	C(044)–C(037)–H(03F)	119.4	C(040)–N(064)–Ni(02)	128.90(17)
N(064)–Ni(02)–N(042)	172.78(8)	C(032)–C(037)–H(03F)	119.4	C(030)–N(064)–Ni(02)	110.66(14)
O(014)–Ni(02)–N(042)	90.60(8)	C(071)–C(038)–N(008)	105.37(19)	C(026)–C(065)–C(083)	114.08(18)
C(061)–O(006)–Ni(01)	115.52(14)	C(071)–C(038)–H(03G)	110.7	C(026)–C(065)–C(072)	112.26(18)
C(050)–N(007)–C(023)	121.07(19)	N(008)–C(038)–H(03G)	110.7	C(083)–C(065)–C(072)	110.5(2)
C(050)–N(007)–Ni(01)	114.28(14)	C(071)–C(038)–H(03H)	110.7	C(026)–C(065)–H(06E)	106.5
C(023)–N(007)–Ni(01)	123.70(16)	N(008)–C(038)–H(03H)	110.7	C(083)–C(065)–H(06E)	106.5
C(021)–N(008)–C(060)	112.03(18)	H(03G)–C(038)–H(03H)	108.8	C(072)–C(065)–H(06E)	106.5
C(021)–N(008)–C(038)	106.97(17)	C(047)–C(039)–C(026)	121.4(2)	C(013)–C(066)–C(068)	118.2(2)
C(060)–N(008)–C(038)	109.60(17)	C(047)–C(039)–H(03I)	119.3	C(013)–C(066)–C(016)	119.9(2)
C(021)–N(008)–Ni(01)	107.17(13)	C(026)–C(039)–H(03I)	119.3	C(068)–C(066)–C(016)	121.7(2)
C(060)–N(008)–Ni(01)	108.11(13)	N(064)–C(040)–C(025)	121.8(2)	C(056)–C(067)–C(062)	120.4(2)
C(038)–N(008)–Ni(01)	113.00(14)	N(064)–C(040)–C(043)	118.4(2)	C(056)–C(067)–H(06F)	119.8
O(003)–C(011)–O(014)	125.1(2)	C(025)–C(040)–C(043)	119.8(2)	C(062)–C(067)–H(06F)	119.8
O(003)–C(011)–C(030)	120.3(2)	C(028)–C(041)–C(076)	120.4(2)	C(027)–C(068)–C(066)	121.2(2)
O(014)–C(011)–C(030)	114.6(2)	C(028)–C(041)–H(04A)	119.8	C(027)–C(068)–H(06G)	119.4

C(048)–C(013)–C(066)	121.4(2)
C(048)–C(013)–H(01A)	119.3
C(066)–C(013)–H(01A)	119.3
C(011)–O(014)–Ni(02)	115.01(15)
N(017)–C(015)–C(049)	121.8(2)
N(017)–C(015)–C(028)	119.4(2)
C(049)–C(015)–C(028)	118.74(18)
C(053)–C(016)–C(066)	112.68(19)
C(053)–C(016)–C(030)	110.61(19)
C(066)–C(016)–C(030)	114.53(19)
C(053)–C(016)–H(016)	106.1
C(066)–C(016)–H(016)	106.1
C(030)–C(016)–H(016)	106.1
C(015)–N(017)–C(072)	120.85(19)
C(015)–N(017)–Ni(01)	128.11(16)
C(072)–N(017)–Ni(01)	111.02(13)
O(004)–C(018)–N(035)	128.1(2)
O(004)–C(018)–C(020)	118.8(2)
N(035)–C(018)–C(020)	112.9(2)
C(022)–C(019)–C(028)	119.5(2)
C(022)–C(019)–H(01C)	120.2
C(028)–C(019)–H(01C)	120.2
N(042)–C(020)–C(018)	110.96(18)
N(042)–C(020)–C(085)	103.89(19)
C(018)–C(020)–C(085)	112.8(2)
N(042)–C(020)–H(02A)	109.7
C(018)–C(020)–H(02A)	109.7
C(085)–C(020)–H(02A)	109.7
N(008)–C(021)–C(050)	111.64(19)
N(008)–C(021)–C(055)	104.18(18)
C(050)–C(021)–C(055)	113.91(19)
N(008)–C(021)–H(02B)	109.0
C(050)–C(021)–H(02B)	109.0
C(055)–C(021)–H(02B)	109.0
C(019)–C(022)–C(033)	121.0(2)
C(019)–C(022)–H(02C)	119.5
C(033)–C(022)–H(02C)	119.5
C(044)–C(023)–N(007)	121.9(2)
C(044)–C(023)–C(049)	117.36(19)
N(007)–C(023)–C(049)	120.59(19)
N(035)–C(024)–C(052)	121.5(2)
N(035)–C(024)–C(025)	121.2(2)
C(052)–C(024)–C(025)	117.3(2)
C(046)–C(025)–C(024)	119.3(2)
C(046)–C(025)–C(040)	116.6(2)
C(024)–C(025)–C(040)	124.0(2)
C(069)–C(026)–C(039)	118.4(2)
C(069)–C(026)–C(065)	119.4(2)
C(039)–C(026)–C(065)	122.2(2)
C(034)–C(027)–C(068)	117.9(2)
C(034)–C(027)–H(02D)	121.0
C(068)–C(027)–H(02D)	121.0
C(041)–C(028)–C(019)	119.6(2)
C(041)–C(028)–C(015)	119.13(19)
C(019)–C(028)–C(015)	121.2(2)
C(076)–C(041)–H(04A)	119.8
C(020)–N(042)–C(086)	113.0(2)
C(020)–N(042)–C(058)	105.55(19)
C(086)–N(042)–C(058)	109.4(2)
C(020)–N(042)–Ni(02)	105.87(14)
C(086)–N(042)–Ni(02)	112.67(15)
C(058)–N(042)–Ni(02)	110.10(17)
C(078)–C(043)–C(045)	118.5(2)
C(078)–C(043)–C(040)	121.7(2)
C(045)–C(043)–C(040)	119.5(2)
C(037)–C(044)–C(023)	121.9(2)
C(037)–C(044)–H(04B)	119.1
C(023)–C(044)–H(04B)	119.1
C(084)–C(045)–C(043)	121.0(2)
C(084)–C(045)–H(04C)	119.5
C(043)–C(045)–H(04C)	119.5
C(031)–C(046)–C(025)	121.9(2)
C(031)–C(046)–H(04D)	119.1
C(025)–C(046)–H(04D)	119.1
C(074)–C(047)–C(039)	117.6(2)
C(074)–C(047)–H(04E)	121.2
C(039)–C(047)–H(04E)	121.2
C(034)–C(048)–C(013)	117.8(2)
C(034)–C(048)–H(04F)	121.1
C(013)–C(048)–H(04F)	121.1
C(059)–C(049)–C(023)	118.8(2)
C(059)–C(049)–C(015)	116.3(2)
C(023)–C(049)–C(015)	124.97(18)
O(012)–C(050)–N(007)	128.2(2)
O(012)–C(050)–C(021)	118.3(2)
N(007)–C(050)–C(021)	113.5(2)
C(075)–C(051)–C(029)	120.9(2)
C(075)–C(051)–H(05A)	119.5
C(029)–C(051)–H(05A)	119.5
C(036)–C(052)–C(024)	121.6(2)
C(036)–C(052)–H(05B)	119.2
C(024)–C(052)–H(05B)	119.2
C(016)–C(053)–H(05C)	109.5
C(016)–C(053)–H(05D)	109.5
H(05C)–C(053)–H(05D)	109.5
C(016)–C(053)–H(05E)	109.5
H(05C)–C(053)–H(05E)	109.5
H(05D)–C(053)–H(05E)	109.5
C(063)–C(054)–C(070)	119.2(3)
C(063)–C(054)–C(086)	120.0(2)
C(070)–C(054)–C(086)	120.8(2)
C(071)–C(055)–C(021)	101.93(18)
C(071)–C(055)–H(05F)	111.4
C(021)–C(055)–H(05F)	111.4
C(071)–C(055)–H(05G)	111.4
C(021)–C(055)–H(05G)	111.4
H(05F)–C(055)–H(05G)	109.2
C(067)–C(056)–C(075)	119.7(2)
C(067)–C(056)–H(05H)	120.1
C(075)–C(056)–H(05H)	120.1
C(066)–C(068)–H(06G)	119.4
C(026)–C(069)–C(057)	121.2(2)
C(026)–C(069)–H(06H)	119.4
C(057)–C(069)–H(06H)	119.4
C(079)–C(070)–C(054)	119.9(3)
C(079)–C(070)–H(07A)	120.0
C(054)–C(070)–H(07A)	120.0
C(038)–C(071)–C(055)	103.28(18)
C(038)–C(071)–H(07B)	111.1
C(055)–C(071)–H(07B)	111.1
C(038)–C(071)–H(07C)	111.1
C(055)–C(071)–H(07C)	111.1
H(07B)–C(071)–H(07C)	109.1
N(017)–C(072)–C(061)	107.32(18)
N(017)–C(072)–C(065)	110.66(18)
C(061)–C(072)–C(065)	111.72(17)
N(017)–C(072)–H(07D)	109.0
C(061)–C(072)–H(07D)	109.0
C(065)–C(072)–H(07D)	109.0
C(081)–C(073)–C(079)	119.9(3)
C(081)–C(073)–H(07E)	120.0
C(079)–C(073)–H(07E)	120.0
C(047)–C(074)–C(057)	123.6(2)
C(047)–C(074)–F(009)	118.7(2)
C(057)–C(074)–F(009)	117.6(3)
C(051)–C(075)–C(056)	119.7(2)
C(051)–C(075)–H(07F)	120.1
C(056)–C(075)–H(07F)	120.1
C(033)–C(076)–C(041)	119.7(2)
C(033)–C(076)–H(07G)	120.1
C(041)–C(076)–H(07G)	120.1
C(084)–C(077)–C(082)	119.2(2)
C(084)–C(077)–H(07H)	120.4
C(082)–C(077)–H(07H)	120.4
C(082)–C(078)–C(043)	120.2(2)
C(082)–C(078)–H(07I)	119.9
C(043)–C(078)–H(07I)	119.9
C(070)–C(079)–C(073)	120.6(3)
C(070)–C(079)–H(07J)	119.7
C(073)–C(079)–H(07J)	119.7
C(085)–C(080)–C(058)	105.2(2)
C(085)–C(080)–H(08A)	110.7
C(058)–C(080)–H(08A)	110.7
C(085)–C(080)–H(08B)	110.7
C(058)–C(080)–H(08B)	110.7
H(08A)–C(080)–H(08B)	108.8
C(073)–C(081)–C(063)	119.7(3)
C(073)–C(081)–H(08C)	120.1
C(063)–C(081)–H(08C)	120.1
C(078)–C(082)–C(077)	120.7(2)
C(078)–C(082)–H(08D)	119.6
C(077)–C(082)–H(08D)	119.6
C(065)–C(083)–H(08E)	109.5
C(065)–C(083)–H(08F)	109.5
H(08E)–C(083)–H(08F)	109.5

C(062)–C(029)–C(051)	118.2(2)
C(062)–C(029)–C(060)	120.9(2)
C(051)–C(029)–C(060)	120.9(2)
N(064)–C(030)–C(011)	107.36(19)
N(064)–C(030)–C(016)	112.04(18)
C(011)–C(030)–C(016)	112.32(18)
N(064)–C(030)–H(03A)	108.3
C(011)–C(030)–H(03A)	108.3
C(016)–C(030)–H(03A)	108.3
C(046)–C(031)–C(036)	118.6(2)
C(046)–C(031)–H(03B)	120.7
C(036)–C(031)–H(03B)	120.7
C(059)–C(032)–C(037)	118.4(2)
C(059)–C(032)–H(03C)	120.8
C(037)–C(032)–H(03C)	120.8
C(022)–C(033)–C(076)	119.7(2)
C(022)–C(033)–H(03D)	120.2
C(076)–C(033)–H(03D)	120.2
C(048)–C(034)–C(027)	123.4(2)
C(074)–C(057)–C(069)	117.7(3)
C(074)–C(057)–H(05I)	121.1
C(069)–C(057)–H(05I)	121.1
C(080)–C(058)–N(042)	106.6(2)
C(080)–C(058)–H(05J)	110.4
N(042)–C(058)–H(05J)	110.4
C(080)–C(058)–H(05K)	110.4
N(042)–C(058)–H(05K)	110.4
H(05J)–C(058)–H(05K)	108.6
C(032)–C(059)–C(049)	122.4(2)
C(032)–C(059)–H(05L)	118.8
C(049)–C(059)–H(05L)	118.8
N(008)–C(060)–C(029)	112.42(18)
N(008)–C(060)–H(06A)	109.1
C(029)–C(060)–H(06A)	109.1
N(008)–C(060)–H(06B)	109.1
C(029)–C(060)–H(06B)	109.1
H(06A)–C(060)–H(06B)	107.9
O(010)–C(061)–O(006)	124.6(2)
C(065)–C(083)–H(08G)	109.5
H(08E)–C(083)–H(08G)	109.5
H(08F)–C(083)–H(08G)	109.5
C(045)–C(084)–C(077)	120.2(2)
C(045)–C(084)–H(08H)	119.9
C(077)–C(084)–H(08H)	119.9
C(080)–C(085)–C(020)	102.7(2)
C(080)–C(085)–H(08I)	111.2
C(020)–C(085)–H(08I)	111.2
C(080)–C(085)–H(08J)	111.2
C(020)–C(085)–H(08J)	111.2
H(08I)–C(085)–H(08J)	109.1
N(042)–C(086)–C(054)	114.3(2)
N(042)–C(086)–H(08K)	108.7
C(054)–C(086)–H(08K)	108.7
N(042)–C(086)–H(08L)	108.7
C(054)–C(086)–H(08L)	108.7
H(08K)–C(086)–H(08L)	107.6

Table 4. Anisotropic displacement parameters ($\text{Å}^2 \times 10^3$)for sw007. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Ni(01)	23(1)	26(1)	25(1)	−1(1)	2(1)	0(1)
Ni(02)	30(1)	25(1)	24(1)	0(1)	3(1)	−2(1)
O(003)	44(1)	23(1)	36(1)	−1(1)	7(1)	−7(1)
O(004)	35(1)	27(1)	36(1)	0(1)	0(1)	2(1)
F(005)	56(1)	45(1)	30(1)	−6(1)	14(1)	3(1)
O(006)	26(1)	26(1)	29(1)	−1(1)	3(1)	0(1)
N(007)	22(1)	26(1)	25(1)	0(1)	0(1)	1(1)
N(008)	27(1)	23(1)	25(1)	0(1)	−1(1)	3(1)
F(009)	54(1)	52(1)	44(1)	24(1)	−12(1)	−14(1)
O(010)	37(1)	26(1)	29(1)	−2(1)	−1(1)	0(1)
C(011)	38(1)	27(2)	20(1)	−2(1)	4(1)	−4(1)
O(012)	31(1)	23(1)	38(1)	−3(1)	2(1)	1(1)
C(013)	33(1)	31(2)	26(1)	5(1)	1(1)	−1(1)
O(014)	32(1)	29(1)	30(1)	−2(1)	4(1)	−3(1)
C(015)	21(1)	25(2)	23(1)	3(1)	−3(1)	3(1)
C(016)	33(1)	27(2)	27(1)	2(1)	0(1)	2(1)
N(017)	24(1)	25(1)	21(1)	1(1)	−3(1)	3(1)
C(018)	30(1)	25(2)	25(1)	1(1)	−5(1)	1(1)
C(019)	27(1)	28(2)	25(1)	3(1)	1(1)	3(1)
C(020)	40(1)	26(2)	30(1)	1(1)	6(1)	4(1)
C(021)	22(1)	26(2)	33(1)	0(1)	2(1)	2(1)
C(022)	21(1)	35(2)	33(1)	−1(1)	−1(1)	3(1)
C(023)	22(1)	27(2)	25(1)	−2(1)	−4(1)	7(1)
C(024)	33(1)	27(2)	19(1)	−2(1)	−2(1)	−7(1)

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(025)	31(1)	22(2)	22(1)	–1(1)	2(1)	–2(1)
C(026)	22(1)	27(2)	27(1)	–1(1)	–4(1)	1(1)
C(027)	37(1)	34(2)	27(1)	4(1)	4(1)	0(1)
C(028)	25(1)	28(2)	20(1)	–1(1)	2(1)	–1(1)
C(029)	21(1)	23(2)	32(1)	0(1)	–2(1)	5(1)
C(030)	34(1)	22(2)	25(1)	0(1)	6(1)	1(1)
C(031)	41(1)	33(2)	28(1)	2(1)	5(1)	–9(1)
C(032)	32(1)	35(2)	22(1)	–1(1)	–2(1)	6(1)
C(033)	32(1)	30(2)	33(1)	–3(1)	6(1)	–5(1)
C(034)	38(1)	39(2)	23(1)	0(1)	3(1)	10(1)
N(035)	31(1)	26(1)	22(1)	0(1)	0(1)	–1(1)
C(036)	46(2)	26(2)	27(1)	4(1)	–1(1)	–5(1)
C(037)	34(1)	31(2)	27(1)	–8(1)	–6(1)	4(1)
C(038)	30(1)	34(2)	24(1)	–1(1)	3(1)	–2(1)
C(039)	34(1)	28(2)	29(1)	2(1)	–4(1)	1(1)
C(040)	32(1)	29(2)	19(1)	–1(1)	–2(1)	–3(1)
C(041)	26(1)	31(2)	24(1)	–1(1)	2(1)	6(1)
N(042)	39(1)	27(1)	33(1)	1(1)	10(1)	–4(1)
C(043)	29(1)	27(2)	24(1)	4(1)	4(1)	–3(1)
C(044)	26(1)	31(2)	32(1)	–1(1)	–3(1)	3(1)
C(045)	28(1)	31(2)	26(1)	4(1)	2(1)	–2(1)
C(046)	35(1)	30(2)	26(1)	1(1)	2(1)	–4(1)
C(047)	33(1)	45(2)	26(1)	4(1)	–2(1)	2(1)
C(048)	41(1)	29(2)	30(1)	–3(1)	–1(1)	1(1)
C(049)	21(1)	27(1)	24(1)	1(1)	0(1)	3(1)
C(050)	22(1)	24(2)	33(1)	3(1)	–4(1)	2(1)
C(051)	25(1)	21(2)	38(1)	1(1)	–4(1)	1(1)
C(052)	41(2)	27(2)	23(1)	1(1)	–1(1)	0(1)
C(053)	53(2)	31(2)	33(1)	1(1)	3(1)	8(1)
C(054)	24(1)	39(2)	45(1)	–4(1)	–6(1)	–1(1)
C(055)	29(1)	28(2)	33(1)	6(1)	1(1)	1(1)
C(056)	32(1)	35(2)	34(1)	–2(1)	–2(1)	2(1)
C(057)	41(1)	26(2)	38(1)	4(1)	–17(1)	–3(1)
C(058)	70(2)	40(2)	47(2)	10(1)	34(1)	9(2)
C(059)	27(1)	32(2)	25(1)	1(1)	–1(1)	3(1)
C(060)	26(1)	27(2)	34(1)	3(1)	1(1)	5(1)
C(061)	27(1)	31(2)	22(1)	3(1)	–4(1)	2(1)
C(062)	25(1)	28(2)	36(1)	4(1)	1(1)	3(1)
C(063)	37(2)	54(2)	48(2)	–6(1)	–3(1)	11(2)
N(064)	34(1)	22(1)	20(1)	–2(1)	1(1)	–4(1)
C(065)	23(1)	32(2)	25(1)	–2(1)	–2(1)	0(1)
C(066)	30(1)	26(2)	23(1)	4(1)	–3(1)	2(1)
C(067)	29(1)	29(2)	39(1)	–6(1)	–2(1)	–3(1)
C(068)	39(1)	29(2)	27(1)	1(1)	1(1)	–4(1)
C(069)	31(1)	37(2)	30(1)	–2(1)	–9(1)	3(1)
C(070)	32(1)	42(2)	38(1)	–11(1)	–5(1)	3(1)
C(071)	30(1)	35(2)	31(1)	4(1)	4(1)	1(1)
C(072)	28(1)	24(1)	23(1)	–1(1)	0(1)	–2(1)
C(073)	54(2)	63(2)	43(2)	9(2)	–18(1)	–3(2)

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(074)	32(1)	41(2)	37(1)	16(1)	–9(1)	–8(1)
C(075)	28(1)	27(2)	35(1)	7(1)	2(1)	2(1)
C(076)	36(1)	25(2)	30(1)	4(1)	5(1)	2(1)
C(077)	33(1)	31(2)	42(1)	11(1)	10(1)	2(1)
C(078)	31(1)	32(2)	30(1)	4(1)	1(1)	–5(1)
C(079)	40(2)	68(2)	32(1)	–8(1)	–6(1)	–1(2)
C(080)	58(2)	80(3)	41(2)	19(2)	–8(1)	–12(2)
C(081)	56(2)	53(2)	53(2)	–2(2)	–14(2)	17(2)
C(082)	31(1)	41(2)	38(1)	10(1)	–2(1)	–5(1)
C(083)	33(1)	34(2)	34(1)	4(1)	–6(1)	–9(1)
C(084)	37(1)	30(2)	32(1)	2(1)	9(1)	–2(1)
C(085)	68(2)	31(2)	24(1)	3(1)	6(1)	9(2)
C(086)	28(1)	39(2)	57(2)	–1(1)	10(1)	–5(1)

Table 5. Hydrogen coordinates (× 10^4) and isotropic displacement parameters (Å^2 × 10^3) for sw007.

	x	y	z	U(eq)
H(01A)	5072	7991	9318	36
H(016)	5566	7049	8826	35
H(01C)	4458	898	10245	31
H(02A)	588	9335	8714	38
H(02B)	10915	2163	9271	32
H(02C)	2921	185	10519	36
H(02D)	2232	6740	10232	39
H(03A)	4531	6603	8089	32
H(03B)	6498	9533	6988	40
H(03C)	6938	1852	11742	36
H(03D)	3350	–844	10922	38
H(03E)	4844	10250	7095	40
H(03F)	8376	2633	11463	37
H(03G)	10668	833	8483	35
H(03H)	9229	898	8501	35
H(03I)	6645	5	8258	36
H(04A)	6904	–433	10810	33
H(04B)	9132	2582	10646	35
H(04C)	5382	6970	7218	34
H(04D)	6492	8468	7377	37
H(04E)	7224	811	7644	42
H(04F)	4239	8442	10064	40
H(05A)	10110	201	10138	33
H(05B)	3289	9954	7634	37
H(05C)	5557	6001	9279	58
H(05D)	5719	5910	8678	58
H(05E)	4447	5759	8938	58
H(05F)	8639	2258	8749	36
H(05G)	9764	2770	8692	36
H(05H)	11204	1278	11365	40

	x	y	z	U(eq)
H(05I)	6277	2330	8604	42
H(05J)	–67	7808	9106	63
H(05K)	1317	7602	9187	63
H(05L)	6277	1013	11187	34
H(06A)	11870	1123	9230	35
H(06B)	11137	428	9298	35
H(06C)	12398	1784	9964	35
H(06D)	–1043	9420	8032	56
H(06E)	5219	419	9443	32
H(06F)	12426	1938	10842	39
H(06G)	3073	6290	9487	38
H(06H)	5732	1521	9221	39
H(07A)	1358	8131	7391	45
H(07B)	9612	1840	8028	39
H(07C)	10918	1949	8280	39
H(07D)	6601	–418	9785	30
H(07E)	379	9852	6656	64
H(07F)	10076	387	11014	36
H(07G)	5350	–1143	11087	36
H(07H)	8539	6177	7688	42
H(07I)	7084	7782	8436	37
H(07J)	1513	8855	6695	56
H(08A)	85	8719	9602	71
H(08B)	1206	8312	9841	71
H(08C)	–926	10126	7319	65
H(08D)	8604	6977	8347	44
H(08E)	4427	–294	8801	51
H(08F)	4819	–721	9293	51
H(08G)	5650	–721	8796	51
H(08H)	6941	6199	7110	40
H(08I)	2549	8886	9355	49
H(08J)	1588	9476	9484	49
H(08K)	–692	8358	8430	50
H(08L)	34	7776	8136	50

Table 6. Torsion angles [°] for sw007.

N(017)–Ni(01)–O(006)–C(061)	11.08(15)
N(007)–Ni(01)–O(006)–C(061)	122.6(7)
N(008)–Ni(01)–O(006)–C(061)	–168.31(15)
N(017)–Ni(01)–N(007)–C(050)	–166.44(15)
O(006)–Ni(01)–N(007)–C(050)	82.5(8)
N(008)–Ni(01)–N(007)–C(050)	13.31(15)
N(017)–Ni(01)–N(007)–C(023)	24.62(17)
O(006)–Ni(01)–N(007)–C(023)	–86.5(8)
N(008)–Ni(01)–N(007)–C(023)	–155.63(17)
N(017)–Ni(01)–N(008)–C(021)	155.7(12)
C(024)–C(025)–C(046)–C(031)	–1.9(3)
C(040)–C(025)–C(046)–C(031)	175.0(2)
C(026)–C(039)–C(047)–C(074)	0.1(3)
C(027)–C(034)–C(048)–C(013)	0.2(4)
F(005)–C(034)–C(048)–C(013)	179.5(2)
C(066)–C(013)–C(048)–C(034)	–0.7(3)
C(044)–C(023)–C(049)–C(059)	1.6(3)
N(007)–C(023)–C(049)–C(059)	177.35(19)
C(044)–C(023)–C(049)–C(015)	–176.8(2)
N(007)–C(023)–C(049)–C(015)	–1.1(3)

N(007)–Ni(01)–N(008)–C(021)	–20.47(13)
O(006)–Ni(01)–N(008)–C(021)	164.91(13)
N(017)–Ni(01)–N(008)–C(060)	–83.4(12)
N(007)–Ni(01)–N(008)–C(060)	100.47(15)
O(006)–Ni(01)–N(008)–C(060)	–74.15(14)
N(017)–Ni(01)–N(008)–C(038)	38.1(13)
N(007)–Ni(01)–N(008)–C(038)	–138.05(16)
O(006)–Ni(01)–N(008)–C(038)	47.33(16)
O(003)–C(011)–O(014)–Ni(02)	–172.36(17)
C(030)–C(011)–O(014)–Ni(02)	8.8(2)
N(035)–Ni(02)–O(014)–C(011)	113.2(6)
N(064)–Ni(02)–O(014)–C(011)	4.65(14)
N(042)–Ni(02)–O(014)–C(011)	–168.48(14)
C(049)–C(015)–N(017)–C(072)	179.95(19)
C(028)–C(015)–N(017)–C(072)	3.4(3)
C(049)–C(015)–N(017)–Ni(01)	1.7(3)
C(028)–C(015)–N(017)–Ni(01)	–174.86(15)
N(007)–Ni(01)–N(017)–C(015)	–16.2(2)
O(006)–Ni(01)–N(017)–C(015)	158.43(19)
N(008)–Ni(01)–N(017)–C(015)	167.7(11)
N(007)–Ni(01)–N(017)–C(072)	165.40(14)
O(006)–Ni(01)–N(017)–C(072)	–19.99(14)
N(008)–Ni(01)–N(017)–C(072)	–10.7(13)
O(004)–C(018)–C(020)–N(042)	163.1(2)
N(035)–C(018)–C(020)–N(042)	–21.1(3)
O(004)–C(018)–C(020)–C(085)	–80.8(3)
N(035)–C(018)–C(020)–C(085)	95.0(2)
C(060)–N(008)–C(021)–C(050)	–94.8(2)
C(038)–N(008)–C(021)–C(050)	145.12(18)
Ni(01)–N(008)–C(021)–C(050)	23.7(2)
C(060)–N(008)–C(021)–C(055)	141.87(17)
C(038)–N(008)–C(021)–C(055)	21.8(2)
Ni(01)–N(008)–C(021)–C(055)	–99.70(16)
C(028)–C(019)–C(022)–C(033)	0.8(3)
C(050)–N(007)–C(023)–C(044)	–12.3(3)
Ni(01)–N(007)–C(023)–C(044)	155.89(17)
C(050)–N(007)–C(023)–C(049)	172.2(2)
Ni(01)–N(007)–C(023)–C(049)	–19.6(3)
N(035)–C(024)–C(025)–C(046)	–176.5(2)
C(052)–C(024)–C(025)–C(046)	4.6(3)
N(035)–C(024)–C(025)–C(040)	6.8(3)
C(052)–C(024)–C(025)–C(040)	–172.1(2)
C(022)–C(019)–C(028)–C(041)	–3.1(3)
C(022)–C(019)–C(028)–C(015)	175.2(2)
N(017)–C(015)–C(028)–C(041)	80.9(3)
C(049)–C(015)–C(028)–C(041)	–95.7(3)
N(017)–C(015)–C(028)–C(019)	–97.4(3)
C(049)–C(015)–C(028)–C(019)	86.0(3)
O(003)–C(011)–C(030)–N(064)	159.75(18)
O(014)–C(011)–C(030)–N(064)	–21.4(2)
O(003)–C(011)–C(030)–C(016)	–76.6(3)
N(017)–C(015)–C(049)–C(059)	–167.7(2)
C(028)–C(015)–C(049)–C(059)	8.9(3)
N(017)–C(015)–C(049)–C(023)	10.8(3)
C(028)–C(015)–C(049)–C(023)	–172.6(2)
C(023)–N(007)–C(050)–O(012)	–15.1(3)
Ni(01)–N(007)–C(050)–O(012)	175.60(18)
C(023)–N(007)–C(050)–C(021)	167.21(18)
Ni(01)–N(007)–C(050)–C(021)	–2.0(2)
N(008)–C(021)–C(050)–O(012)	167.16(19)
C(055)–C(021)–C(050)–O(012)	–75.2(3)
N(008)–C(021)–C(050)–N(007)	–14.9(3)
C(055)–C(021)–C(050)–N(007)	102.7(2)
C(062)–C(029)–C(051)–C(075)	3.4(3)
C(060)–C(029)–C(051)–C(075)	–174.3(2)
C(031)–C(036)–C(052)–C(024)	–0.3(4)
N(035)–C(024)–C(052)–C(036)	177.6(2)
C(025)–C(024)–C(052)–C(036)	–3.5(3)
N(008)–C(021)–C(055)–C(071)	–39.4(2)
C(050)–C(021)–C(055)–C(071)	–161.3(2)
C(020)–N(042)–C(058)–C(080)	–1.8(3)
C(086)–N(042)–C(058)–C(080)	–123.6(3)
Ni(02)–N(042)–C(058)–C(080)	112.1(2)
C(037)–C(032)–C(059)–C(049)	0.3(4)
C(023)–C(049)–C(059)–C(032)	–1.3(3)
C(015)–C(049)–C(059)–C(032)	177.3(2)
C(021)–N(008)–C(060)–C(029)	64.6(2)
C(038)–N(008)–C(060)–C(029)	–176.8(2)
Ni(01)–N(008)–C(060)–C(029)	–53.3(2)
C(062)–C(029)–C(060)–N(008)	–97.6(3)
C(051)–C(029)–C(060)–N(008)	80.1(3)
Ni(01)–O(006)–C(061)–O(010)	179.72(17)
Ni(01)–O(006)–C(061)–C(072)	0.9(2)
C(051)–C(029)–C(062)–C(067)	–2.0(3)
C(060)–C(029)–C(062)–C(067)	175.8(2)
C(070)–C(054)–C(063)–C(081)	–0.7(4)
C(086)–C(054)–C(063)–C(081)	179.9(3)
C(025)–C(040)–N(064)–C(030)	176.55(18)
C(043)–C(040)–N(064)–C(030)	–0.3(3)
C(025)–C(040)–N(064)–Ni(02)	–1.6(3)
C(043)–C(040)–N(064)–Ni(02)	–178.44(14)
C(011)–C(030)–N(064)–C(040)	–154.51(18)
C(016)–C(030)–N(064)–C(040)	81.7(2)
C(011)–C(030)–N(064)–Ni(02)	23.95(19)
C(016)–C(030)–N(064)–Ni(02)	–99.82(18)
N(035)–Ni(02)–N(064)–C(040)	–11.33(19)
O(014)–Ni(02)–N(064)–C(040)	161.44(19)
N(042)–Ni(02)–N(064)–C(040)	–126.5(7)
N(035)–Ni(02)–N(064)–C(030)	170.38(14)
O(014)–Ni(02)–N(064)–C(030)	–16.85(14)
N(042)–Ni(02)–N(064)–C(030)	55.2(8)
C(069)–C(026)–C(065)–C(083)	139.1(2)

O(014)–C(011)–C(030)–C(016)	102.2(2)
C(053)–C(016)–C(030)–N(064)	–163.25(19)
C(066)–C(016)–C(030)–N(064)	68.1(3)
C(053)–C(016)–C(030)–C(011)	75.8(3)
C(066)–C(016)–C(030)–C(011)	–52.8(3)
C(019)–C(022)–C(033)–C(076)	1.7(3)
C(068)–C(027)–C(034)–C(048)	–0.1(4)
C(068)–C(027)–C(034)–F(005)	–179.4(2)
O(004)–C(018)–N(035)–C(024)	–7.2(3)
C(020)–C(018)–N(035)–C(024)	177.40(18)
O(004)–C(018)–N(035)–Ni(02)	176.56(18)
C(020)–C(018)–N(035)–Ni(02)	1.2(2)
C(052)–C(024)–N(035)–C(018)	–21.7(3)
C(025)–C(024)–N(035)–C(018)	159.4(2)
C(052)–C(024)–N(035)–Ni(02)	154.10(17)
C(025)–C(024)–N(035)–Ni(02)	–24.8(3)
N(064)–Ni(02)–N(035)–C(018)	–159.97(15)
O(014)–Ni(02)–N(035)–C(018)	92.0(6)
N(042)–Ni(02)–N(035)–C(018)	13.50(15)
N(064)–Ni(02)–N(035)–C(024)	23.93(17)
O(014)–Ni(02)–N(035)–C(024)	–84.1(6)
N(042)–Ni(02)–N(035)–C(024)	–162.60(17)
C(046)–C(031)–C(036)–C(052)	3.1(4)
C(059)–C(032)–C(037)–C(044)	0.3(4)
C(021)–N(008)–C(038)–C(071)	4.2(2)
C(060)–N(008)–C(038)–C(071)	–117.5(2)
Ni(01)–N(008)–C(038)–C(071)	121.91(16)
C(069)–C(026)–C(039)–C(047)	1.4(3)
C(065)–C(026)–C(039)–C(047)	–179.0(2)
C(046)–C(025)–C(040)–N(064)	–169.8(2)
C(024)–C(025)–C(040)–N(064)	7.0(3)
C(046)–C(025)–C(040)–C(043)	7.0(3)
C(024)–C(025)–C(040)–C(043)	–176.2(2)
C(019)–C(028)–C(041)–C(076)	3.0(3)
C(015)–C(028)–C(041)–C(076)	–175.4(2)
C(018)–C(020)–N(042)–C(086)	–94.4(2)
C(085)–C(020)–N(042)–C(086)	144.1(2)
C(018)–C(020)–N(042)–C(058)	146.1(2)
C(085)–C(020)–N(042)–C(058)	24.6(2)
C(018)–C(020)–N(042)–Ni(02)	29.4(2)
C(085)–C(020)–N(042)–Ni(02)	–92.11(18)
N(035)–Ni(02)–N(042)–C(020)	–23.84(14)
N(064)–Ni(02)–N(042)–C(020)	91.8(7)
O(014)–Ni(02)–N(042)–C(020)	163.60(13)
N(035)–Ni(02)–N(042)–C(086)	100.09(17)
N(064)–Ni(02)–N(042)–C(086)	–144.3(7)
O(014)–Ni(02)–N(042)–C(086)	–72.47(17)
N(035)–Ni(02)–N(042)–C(058)	–137.47(18)
N(064)–Ni(02)–N(042)–C(058)	–21.8(8)
O(014)–Ni(02)–N(042)–C(058)	49.97(18)
N(064)–C(040)–C(043)–C(078)	–95.6(3)
C(039)–C(026)–C(065)–C(083)	–40.6(3)
C(069)–C(026)–C(065)–C(072)	–94.2(2)
C(039)–C(026)–C(065)–C(072)	86.1(3)
C(048)–C(013)–C(066)–C(068)	1.0(3)
C(048)–C(013)–C(066)–C(016)	–175.4(2)
C(053)–C(016)–C(066)–C(013)	134.2(2)
C(030)–C(016)–C(066)–C(013)	–98.2(3)
C(053)–C(016)–C(066)–C(068)	–42.1(3)
C(030)–C(016)–C(066)–C(068)	85.5(3)
C(075)–C(056)–C(067)–C(062)	3.2(4)
C(029)–C(062)–C(067)–C(056)	–1.3(4)
C(034)–C(027)–C(068)–C(066)	0.5(4)
C(013)–C(066)–C(068)–C(027)	–0.9(3)
C(016)–C(066)–C(068)–C(027)	175.4(2)
C(039)–C(026)–C(069)–C(057)	–0.8(3)
C(065)–C(026)–C(069)–C(057)	179.6(2)
C(074)–C(057)–C(069)–C(026)	–1.2(4)
C(063)–C(054)–C(070)–C(079)	1.7(4)
C(086)–C(054)–C(070)–C(079)	–178.8(2)
N(008)–C(038)–C(071)–C(055)	–28.7(2)
C(021)–C(055)–C(071)–C(038)	41.8(2)
C(015)–N(017)–C(072)–C(061)	–154.60(19)
Ni(01)–N(017)–C(072)–C(061)	23.9(2)
C(015)–N(017)–C(072)–C(065)	83.3(2)
Ni(01)–N(017)–C(072)–C(065)	–98.19(17)
O(010)–C(061)–C(072)–N(017)	165.01(19)
O(006)–C(061)–C(072)–N(017)	–16.2(2)
O(010)–C(061)–C(072)–C(065)	–73.5(3)
O(006)–C(061)–C(072)–C(065)	105.3(2)
C(026)–C(065)–C(072)–N(017)	65.2(2)
C(083)–C(065)–C(072)–N(017)	–166.16(18)
C(026)–C(065)–C(072)–C(061)	–54.3(3)
C(083)–C(065)–C(072)–C(061)	74.3(2)
C(039)–C(047)–C(074)–C(057)	–2.2(4)
C(039)–C(047)–C(074)–F(009)	179.6(2)
C(069)–C(057)–C(074)–C(047)	2.8(4)
C(069)–C(057)–C(074)–F(009)	–179.0(2)
C(029)–C(051)–C(075)–C(056)	–1.6(4)
C(067)–C(056)–C(075)–C(051)	–1.7(4)
C(022)–C(033)–C(076)–C(041)	–1.9(3)
C(028)–C(041)–C(076)–C(033)	–0.5(3)
C(045)–C(043)–C(078)–C(082)	–4.1(3)
C(040)–C(043)–C(078)–C(082)	170.4(2)
C(054)–C(070)–C(079)–C(073)	–1.3(4)
C(081)–C(073)–C(079)–C(070)	–0.2(4)
N(042)–C(058)–C(080)–C(085)	–23.0(3)
C(079)–C(073)–C(081)–C(063)	1.3(4)
C(054)–C(063)–C(081)–C(073)	–0.8(4)
C(043)–C(078)–C(082)–C(077)	2.5(4)
C(084)–C(077)–C(082)–C(078)	0.6(4)
C(043)–C(045)–C(084)–C(077)	0.4(3)

C(025)–C(040)–C(043)–C(078)	87.5(3)	C(082)–C(077)–C(084)–C(045)	–2.1(4)
N(064)–C(040)–C(043)–C(045)	78.9(3)	C(058)–C(080)–C(085)–C(020)	37.9(3)
C(025)–C(040)–C(043)–C(045)	–98.0(3)	N(042)–C(020)–C(085)–C(080)	–38.9(3)
C(032)–C(037)–C(044)–C(023)	0.1(4)	C(018)–C(020)–C(085)–C(080)	–159.2(2)
N(007)–C(023)–C(044)–C(037)	–176.8(2)	C(020)–N(042)–C(086)–C(054)	49.5(3)
C(049)–C(023)–C(044)–C(037)	–1.1(3)	C(058)–N(042)–C(086)–C(054)	166.8(2)
C(078)–C(043)–C(045)–C(084)	2.7(3)	Ni(02)–N(042)–C(086)–C(054)	–70.4(3)
C(040)–C(043)–C(045)–C(084)	–172.0(2)	C(063)–C(054)–C(086)–N(042)	–101.4(3)
C(036)–C(031)–C(046)–C(025)	–2.0(3)	C(070)–C(054)–C(086)–N(042)	79.1(3)

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1. V. Raev, N. Vasilieva, S. Kruglov, A. Kurinov **Migration of Radionuclides from Chernobyl's losses by vertical soil profile of meadows.** *Theses of reports of the third All-Union conference on agricultural radiology.* Obninsk, **1990**, Vol. IV, 16.

2. S. Kruglov, R. Alexakhin, V. Raev, N. Sanzharova, S. Fesenko, V. Anisimov, S. Spiridonov, V. Osipov **Radionuclides Migration in Natural and Semi-natural ecosystems. In: The behaviour of radionuclide in natural and semi-natural environments.** *Report for the Period 1 October 1991 - 30 November 1992. CEC coordinated ECP-5 Project. Contract Number COSU-CT-91-0005. Doc. ENEA-DISP/ARA-MET* **1992**, 6, 49–108.

3. S. Kruglov, V. Raev **Parameters of cerium, cesium, ruthenium and strontium radionuclide migration in the basic soil types of 30-km Chernobyl NPP zone.** *Radiobiological congress. Kiev 20-25 sept. 1993. Theses of reports. Part II.* Puschino **1993,** 528–529.

4. V. V. Razin, N. V. Ulin, V. A. Raev, N. Yu. Zadonskaya, D. S. Zuev **Synthesis and dehydrbromination of nitrile and methyl ester of 3-bromomethyl- and 3-methoxymethyl-3-bromocyclobutanecarboxylic acids.** *Russian J. Org. Chem.*, **2003**, *39, 1*, 40–48; *Zh. Org. Khim. (russ.),* **2003**, *39, 1*, 51–59.

5. V. A. Raev, E. M. Kharicheva **Microwave irradiation using for synthesis of pyrazolines and cyclopropanes from aliphatic diazo compounds.** *Theses of report of the fourth youth conference on Organic Chemistry,* St.Petersburg, **2004**, 128

6. D. Kuznetsov, V. Raev, G. Kuranov, O. Arapov, R. Kostikov, **Microwave Activation in Organic Synthesis (Review)**, *Russian J. Org. Chem.*, **2005**, *41*, *12*, 1719–1749; *Zh. Org. Khim. (russ.),* **2005**, *41, 12*, 1757–1787.

LEBENSLAUF

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Ich wurde am 21. September 1965 als erster von zwei Söhnen des Schlossers Alexander Raev und seiner Ehefrau, der Hausfrau Valentina Raeva geb. Kiseleva, in Murmansk (UdSSR) geboren.

Von September 1972 bis Juni 1982 besuchte ich die Grund- und Mittelschule No. 45 in Murmansk, an der ich im Juni 1982 das Abitur ablegte. Während der Schulzeit nahm ich im Jahre 1981 an der Physikalischen Regional-Schülerolympiade (3. Platz) und im Jahre 1982 an der Chemischen Regional-Schülerolympiade (2. Platz) teil.

Im Herbstsemester 1982 begann ich das Studium der Chemie an der Chemischen Fakultät der Staatlichen Universität Leningrad, UdSSR. Meine Freizeit verbrachte ich als freiwilliger wissenschaftlicher Mitarbeiter in der Gruppe von Prof. Dr. V. I. Ivanskij.

Im Herbstsemester 1982 begann ich das Studium der Organischen Chemie unter der wissenschaftlichen Anleitung von Dr. V. V. Razin und zum Juni 1987 fertigte ich meine Diplomarbeit zu dem Thema „Zum Problem der Synthese des Bicyclo[1.1.1]pentans“ an. Am 22. Juni 1987 bestand ich meine Diplomprüfung vor der Staatlichen Prüfungskommission, wobei mir die Qualifizierung des Diplom-Chemikers zuerkannt wurde.

Nach dem Universitätsstudium war ich als Diplom-Ingenieur in Chemie in dem Allunions-Forschungs-Institut für Landwirtschaftliche Radiologie in Obninsk, Kaluga Gebiet, UdSSR, tätig. Im April und im August 1988, im Juni 1989 und im Juli 1990 habe ich je zweiwöchige Dienstreisen in das Gebiet des Chernobyl-Kernunfalls als offizieller Reise-Ingenieur durchgeführt.

Im Mai 1993 habe ich einen zusätzlichen Kurs zur Ausbildung in ökonomischen Fragen und von Juni 1993 bis Oktober 1995 arbeitete ich als Manager in der Bescheinigung von medizinischen Präparaten in der Firma „Jablochko SO“ in St. Peterburg, Russland.

Im Oktober 1995 habe ich ein gemeinsames Finanzprojekt mit der Bank „Inkombank“ durchgeführt und von Oktober 1995 bis April 1997 arbeitete ich als Vorstandsvorsitzender der Firma „Investitionsfond „Slavutych“ in Simferopol, Krim, Ukraine.

Im Mai 1997 wurde dieses Projekt Teil eines anderen Projektes bei der Firma „Geschäftsbank „Kreditprombank“, und von Mai 1997 bis März 2002 arbeitete ich als Hauptwirtschaftswissenschaftler an der Aktienabteilung der Firma „Geschäftsbank „Kreditprombank“ in Kiew, Ukraine.

Ab Juli 2002 setzte ich das Studium der Chemie an der Chemischen Fakultät der Staatlichen Universität Sankt-Petersburg, Russland, unter der wissenschaftlichen Anleitung von Prof. Dr. R. R. Kostikov fort und zum Juni 2004 fertigte ich meine Magisterarbeit zu dem Thema „Einfluss von Mikrowellenbestrahlung des Ethyldiazoacetats, Reaktionsweisen mit und ohne Stickstoff-Abspaltung“ an.

Am 22. Juni 2004 bestand ich meine Magisterprüfung vor der Staatlichen Prüfungskommission, wobei mir die Qualifizierung eines Magisters im Fachgebiet Chemie zuerkannt wurde.

Seit Januar 2005 arbeite ich an meiner Dissertation unter der wissenschaftlichen Anleitung von Prof. Dr. Armin de Meijere im Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen.

Meine Sprachkenntnisse sind: Englisch – gut, Deutsch – Grundkenntnisse.

ACKNOLEDGEMENT

I would like to thank Professor Dr. A. de Meijere for giving me an opportunity to work in his excellent group, for his help and support during the period of the work on my PhD thesis. I am grateful also for opening me new perspectives in my life and carrier.

I am extremely grateful to Prof. Dr. Rafael Kostikov, who helped me to come back to chemistry after a too long period of “business”.

My thanks are also due to Dr. V. Belov for his valuable support at the beginning and help in and outside the laboratory. I would like to thank Dr. S. Kozhushkov for his advice, support, and scientific and non-scientific discussions.

I am also very grateful to my nice colleagues for the wonderful working atmosphere: Alessandra Zanobini, Alexander Lygin, Andrey Savchenko, Daniel Frank, Farina Brackmann, Hans-Wolf Sünemann, Heiko Schill, Irina Martynova, Karsten Rauch, Ligang Zhao, Marco Marradi, Oleg Larionov, Sergey Kozhushkov, Shamil Nizamov, Stefan Beußhausen, Vadim Korotkov and Viktar Bahutski.

I am indebted to Prof. Dr. A. de Meijere and Deutsche Forschungsgemeinschaft (SFB 416 project) for the financial support of my research.

I am very thankful to Prof. Dr. A. Zeck for co-refereeing this thesis.

I am very grateful to Mr. Machinek and his entire group for the fast and precise NMR measurements and discussions of NMR problems; to Dr. H. Frauendorf – for MS and LC-MS measurements; to Mr. F. Hambloch – for the elemental analysis; to Mrs. Pfeil – for the measurements of optical rotatory power; to Stefan and Heiko – for their help with computers; Alessandra, Hans and Heiko – for their help with the NMR instrument, Heiko – for his help with GC chromatograph, Vadim – for his help with FT-IR instrument.

I am very thankful to Dr. Dmitrii Yufit (Durham University, UK) and Mr. Christian Grosse for determining of the X-ray structures of my compounds.

I appreciate the assistance and help of Mrs. Gabriele Keil-Knepel in most of the organizational issues.

I am very grateful to Alexander Lygin and Vadim Korotkov for their careful proofreading of this manuscript.

I am very grateful to Farina Brackmann for the corrections of my German in important documents.

I am grateful to Andrey Savchenko for mushrooms.

Thank you all!