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Total Synthesis

Templated Total Synthesis of Cu(I)-Methanobactin OB3b**

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Abstract: Methanobactin OB3b (Mbn-OB3b) is a unique natural product with stunning affinity for copper ions ($K_a \approx$ Cu(I) 10^{34}). Here, we report the first total synthesis of Cu(I)-bound methanobactin OB3b featuring as key transformations a cyclodehydration-thioacylation sequence, to generate the conjugated heterocyclic systems, and a copper-templated cyclization, to complete the caged structure of the very sensitive target compound.

Living organisms have developed specific strategies for regulating the transport and bioavailability of essential transition metals[1] while protecting themselves against their toxicity.[2] Relevant examples are methanotrophic bacteria, which depend on copper-dependent enzymes to oxidize methane, their vital energy source.[3] In case of a copper deficit, these bacteria secrete chalkophores, the methanobactins (Mbns), to sequestrate copper ions from the environment and to import them.[4]

Among the Mbns,[5] *Methylosinus trichosporium* OB3b methanobactin (Mbn-OB3b) (Scheme 1, apo-**1**) is probably the most well characterized. It has an enormous affinity for copper ($K_a \approx$ Cu(I) 10^{34}).[6] Its structure **1**, that was initially assigned by X-ray crystallography[7] and revised by NMR spectroscopy,[4c] features two unique ene-thiol groups conjugated with oxazolone rings as chelating ligands for Cu(I). The two chelating residues are embedded in an undecapeptide framework rigidified by a disulfide bond.

The biosynthetic machinery for the production of Cu-Mbn-OB3b (**1**) has been described.[8] Interestingly, the Mbns are ribosomally synthesized and post-translationally modified peptides (RiPPs), produced from the genetically encoded peptide **MbnA** (Scheme 1). The peculiar oxazolone-thioamides are oxidatively produced from two cysteine residues.[8c] The chalkophore apo-**1** seems to be completed by cleavage of the leader peptide, oxidative transamination of the *N*-terminal leucine,[8b] and disulfide bond formation. Mbn-OB3b has shown encouraging data in investigations for the treatment of Wilson's disease.[9] However, the reported acid sensitivity and temperature instability (37 °C) likely limit its usefulness in therapeutic applications. Understanding the structural features that govern copper selectivity would be important for the development of novel treatment options, and could likewise increase our understanding of copper transport in methanotrophic bacteria.

In order to gain access by synthesis, we traced back Cu-Mbn **1** to a protected open chain precursor **2** (Scheme 1) that was disconnected into four segments: Tripeptide **6**, tetrapeptide **4**, and oxazolone building blocks **3** and **5**. The latter were designed to carry phenolate leaving groups in the *β*-position, in order to enable an addition-elimination sequence (Scheme 2A) and to mask the thioamide group as a conjugated vinylthioether **7**. Tuning the reactivity of **7** by using different aryl groups (Ar) seemed important, to control stability and, possibly, 1,2 (**7**→**9**) vs. 1,4-addition (**7**→**8**, Scheme 2A).[10]

Compared to products of an Erlenmeyer-Plöchl synthesis[11] or its variants[12] (Scheme 2B), only limited data are available on azlactone thioenols.[13] *Z*-stereochemistry was expected, guided by H-bonding (**8**). For getting general access (Scheme 2C), hippuric acid **10** was cyclodehydrated[10e] to oxazolone **12**, which was subjected to soft enolization.[14] The bromomagnesium enolate such generated was then successfully thioacylated with pentafluorophenyl thionocarbonate **13** and DMAP.[15] For stabilizing the vinylthioether, the MOM group was found suitable. The stable vinylthioether **16** was obtained in 59 % yield as mixture of isomers ($E/Z = 1:1$). Preliminary experiments indicated that 1,4-additions were possible for substrate **16**.

For the leucine-derived oxazolone **3**, TBS-protected acid **17**[16] and glycine benzyl ester hydrochloride were coupled to give amide **18** in 65 % yield (Scheme 3). Deprotection of the TBS group and oxidation of the resulting alcohol furnished an α-ketoamide, but oxazolone synthesis employing this ketone was unsuccessful. The cyclodehydratation and thioacylation of TBS-protected alcohol **18**, after its debenzyla-

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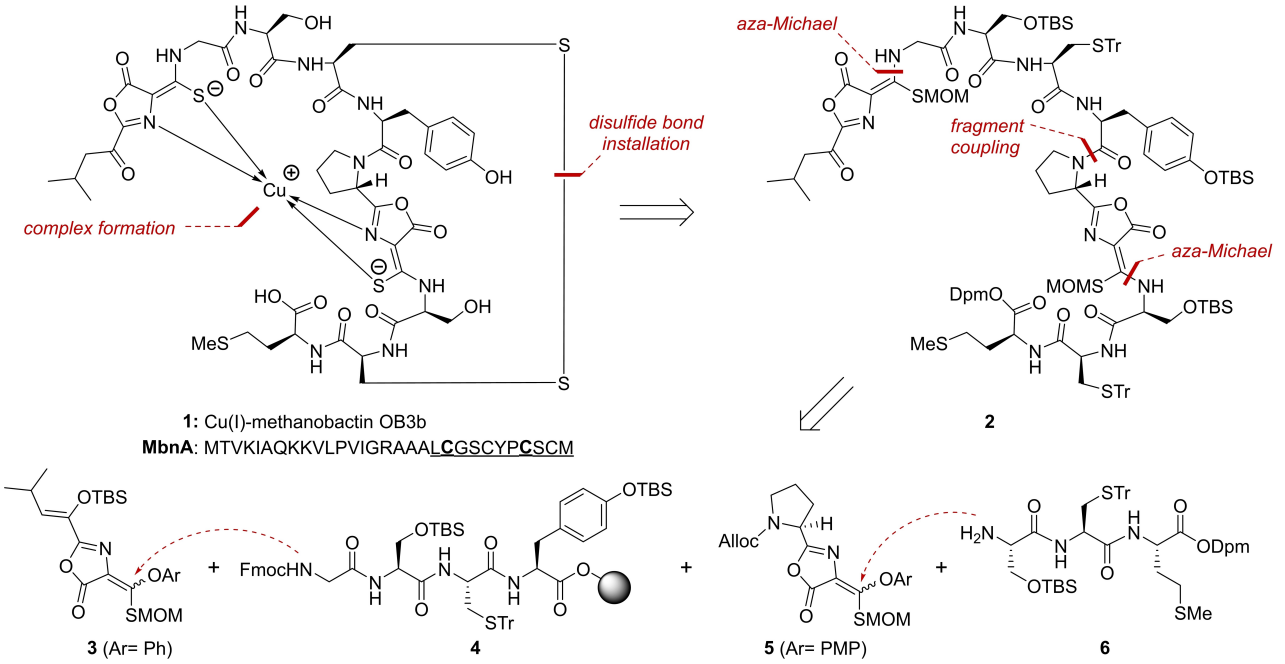
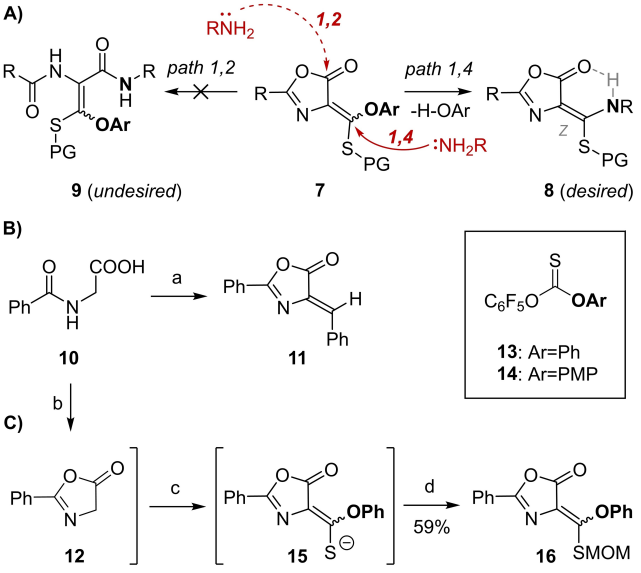
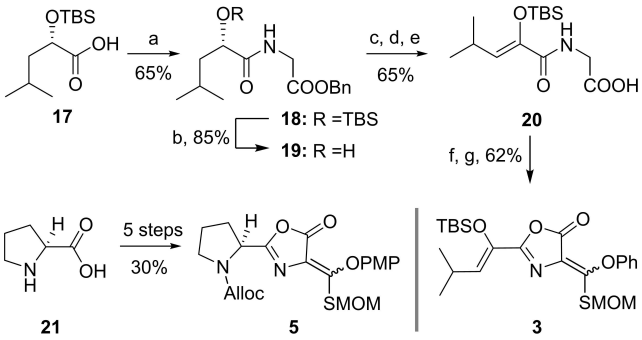


Scheme 1. Chemical structure of Cu(I)-methanobactin OB3b (**1**) and retrosynthetic considerations. Alloc = allyloxycarbonyl; Ar = aryl; Dpm = diphenylmethyl; Fmoc = 9-fluorenylmethyloxycarbonyl; MOM = methoxymethyl; PMP = *p*-methoxyphenyl; TBS = *tert*-butyldimethylsilyl; Tr = triphenylmethyl.



Scheme 2. A) Reactivity of the general 5(4*H*)-oxazolone-thioamide scaffold **7** toward primary amine nucleophiles (RNH_2); B) Erlenmeyer-Plöchl synthesis; C) thioamide building block synthesis. The insert shows the general structure of the thioacylating reagents explored. Reagents and conditions: (a) Ac_2O, NaOAc, ΔT, PhCHO; (b) 2-chloro-4,6-dimethoxy-1,3,5-triazine (1.2 equiv), NMM (1.2 equiv), THF, 25 °C, 3 h; (c) **13** (1.4 equiv), $MgBr_2{\cdot}Et_2O$ (2.5 equiv), *i*-Pr_2NEt (3.0 equiv), DMAP (0.2 equiv), 1,4-dioxane, 25 °C, 1 h; (d) MOMCl (3.0 equiv), 25 °C, 1 h. DMAP = 4-(dimethylamino)pyridine; PG = protecting group.



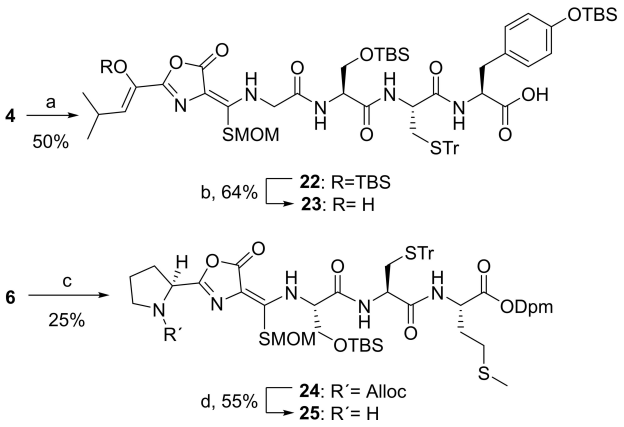
Scheme 3. Synthesis of amino-acid-derived azlactones **3** and **5**. Reagents and conditions: (a) NH_2-Gly-OBn·HCl (1.1 equiv), EDC·HCl (1.2 equiv), *i*-Pr_2NEt (3.3 equiv), CH_2Cl_2, 25 °C, 15 h; (b) 50% HF, CH_3CN, 6 h; (c) DMP (1.2 equiv), CH_2Cl_2, 0 °C→25 °C, 1 h; (d) TBSOTf (2.0 equiv), Et_3N (3.0 equiv), DMAP (0.2 equiv), THF, 0 °C→25 °C, 15 h; (e) 1,4-cyclohexadiene, 10% Pd/C, EtOH, 25 °C, 3 h; (f) 2-Chloro-4,6-dimethoxy-1,3,5-triazine (1.2 equiv), NMM (1.2 equiv), THF, 25 °C, 5 h; (g) **13** (1.4 equiv), $MgBr_2{\cdot}Et_2O$ (2.5 equiv), *i*-Pr_2NEt (3.0 equiv), DMAP (0.2 equiv), 1,4-dioxane, 25 °C, 1 h, then MOMCl (3.0 equiv), 25 °C, 1 h. Bn = benzyl; DMP = Dess Martin Periodinan; EDC = *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide; NMM = *N*-methylmorpholine; TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.

tion, was successful. However, low yield and unsatisfying regioselectivity of the successive aza-Michael addition (Scheme 2A) rendered this compound unusable. Interestingly, masking the ketoamide as an silyl enol ether was found more promising. Upon selective cleavage of the resulting benzyl ester, the surprisingly stable silyl-enol ether **20** was obtained in 65% yield. The acid **20** was then subjected to the cyclization-thioacylation sequence for providing the building block **3** in 62% yield. The proline-derived oxazolone was synthesized in a similar fashion, by converting L-proline (**21**) to the Alloc-protected[17] building

block **5** by using reagent **14** (5 steps, 30%, Supporting Information).

Tetrapeptide **4** was assembled on solid support starting from Fmoc protected amino acids *O*-TBS-(L)-tyrosine,[18] *S*-Tr-(L)-cysteine[19] and *O*-TBS-(L)-serine[20] in 70% yield (Supporting Information). Tripeptide **6** required neutral or mildly acid labile *C*-terminal protection. Here, the balance of stability and lability of a Dpm ester was key for success.[21] The *N*-terminal tripeptide **6** was synthesized in solution by using Alloc-protected amino acids in 45% yield (Supporting Information).

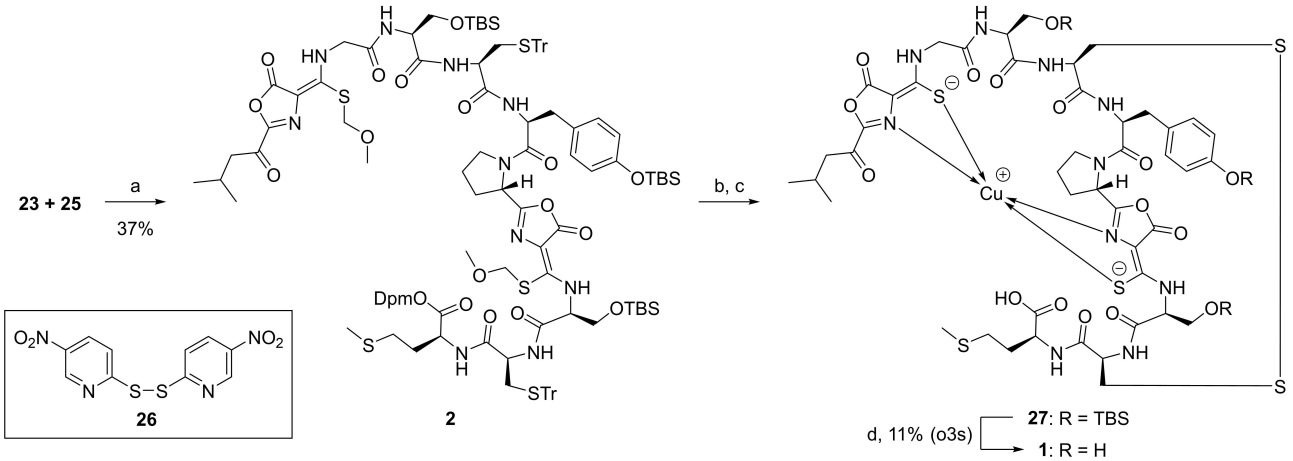
To achieve the assembly, solid-phase bound tetrapeptide **4** was Fmoc-deprotected, treated with Michael-acceptor **3**, and released from the support, to cleanly give the desired product **22** (50% yield, Scheme 4). In contrast, the azlactone **5** underwent a sluggish reaction with amine **6**, to obtain the 1,4-addition elimination product **24** (25% yield) together with the 1,2-addition product (Supporting Information). Apparently, the transformation benefits from an electron-withdrawing substituent at C2, which is absent in compound **5**. Still, the desired isomer **24** could be accessed on a gram scale.



Scheme 4. Synthesis of *C*- and N-terminus. Reagent and conditions: (a) 1. 20% piperidine in DMF (2×10 min), 25 °C; 2. **3** (1.0 equiv), CH_2Cl_2, 25 °C, 7 h; 3. 30% HFIP in CH_2Cl_2 (2×30 min), 25 °C; (b) 0.5% TFA in CH_2Cl_2, 25 °C, 1 h; (c) **5** (1.0 equiv), CH_2Cl_2, 25 °C, 5 days; (d) $[Pd(PPh_3)_4]$ (0.2 equiv), *N*,*N*′-DMBA (3.0 equiv), CH_2Cl_2, 25 °C, 3 min. DMF = *N*,*N*′-dimethylformamide; *N*,*N*′-DMBA = 1,3-dimethylbarbituric acid; HFIP = hexafluoroisopropanol; TFA = trifluoroacetic acid.

After selective removal of the silyl-enol ether **22** under carefully controlled conditions (0.5% TFA in CH_2Cl_2), the carboxyl group of resulting acid **23** was activated with PyAOP (Scheme 5). In parallel, the *N*-terminal Alloc group of peptide **24** was rapidly cleaved.[17] The resulting labile amine **25** was immediately combined with activated acid **23**, to successfully obtain the linear peptide **2** as a single isomer in 37% yield (Scheme 5).

With precursor **2** accessible, Tr- and Dpm-groups were successfully deprotected by rapid treatment with 5% TFA in HFIP and triethylsilane (TES). HFIP as the solvent shortened the reaction time[22] and left the oxazolone rings intact. Unfortunately, the free peptide thiol such obtained was too labile (base, oxidation) or too unreactive (neutral) to effect disulfide bond formation. These results suggested that pre-organizing the peptide chain might be necessary. It was then found that treatment of peptide **2** with Cu(I) salts mildly deprotected the MOM groups, directly forming a stable Cu(I)-cryptate. Its exposure to reagent **26** smoothly installed the disulfide bond. The resultant Cu(I)-complex **27** was then briefly exposed to a buffered solution of hydrogen fluoride pyridine complex with strict timing control, in order to effect deprotection an minimal decomposition (Scheme 5). Finally, preparative HPLC purification at controlled pH allowed the successful isolation of pure Cu(I)-Mbn-OB3b (**1**, Supporting Information). Several instabilities and decomposition pathways were observed en route (Supporting Information) and were difficult to be entirely suppressed. The mass balance of the final steps particularly suffered when rigorous purification was pursued.



Scheme 5. Completion of Cu-Mbn-OB3b synthesis. Reagent and conditions: (a) **23** (1.2 equiv), PyAOP (1.2 equiv), HOAt (0.12 equiv), 2,6-lutidine (2.4 equiv), CH_2Cl_2, 25 °C, 30 min then **25** (1.0 equiv), CH_2Cl_2, 25 °C, 45 min; (b) 5% TFA, HFIP/Et_3SiH (95:5), 25 °C, 5 min; (c) CuI (3.5 equiv), 3% 2,6-lutidine, CH_2Cl_2/CH_3CN/EtOH (5:5:2), 25 °C, 10 min, then **26** (0.65 equiv), 25 °C, 1 h; (d) 70% HF-Py/2,6-lutidine (1:1), HFIP/Et_3SiH (2.8:1), 25 °C, 6 min. HOAt = 1-hydroxy-7-azabenzotriazole; PyAOP = (7-azabenzotriazol-1-yloxy)trispyrrolidinophosphonium hexafluorophosphate.

The NMR data of synthetic **1** compared favourably to reported data (Supporting Information).[4c] High resolution mass (HR-MS) and diamagnetic NMR analysis confirmed the presence of a Cu(I) ion (Supporting Information), supported by the characteristic isotopic pattern of copper.[23] Interestingly, HR-MS analysis of Cu-Mbn-OB3b (**1**) in acidic medium showed an additional signal of the apo-ligand ion[7] (Supporting Information), indicating the acid lability that complicated its isolation. UV/Vis spectra displayed the distinctive absorbance pattern of natural Cu-Mbn-OB3b (**1**) in the 350–390 nm region (Supporting Information).[7b,24] Cyclic voltammetry (Figure 1 and Supporting Information) confirmed the copper oxidation state. In the anodic direction, a quasi-reversible Cu(I)/Cu(II) redox couple centred at +60 mV (vs. ferrocenium/ferrocene, Fc^+/Fc) was observed, indicating the oxidation state of copper as +1. Lastly, the unit cell parameters of synthetic Cu(I)-Mbn-OB3b (**1**) obtained by X-ray diffraction of microcrystals confirmed the chemical structure and identity (Supporting Information).[24]

In conclusion, the total synthesis of Cu(I)-Methanobactin OB3b (**1**) was accomplished by 1) novel construction of the unprecedented azlactone-thioamide rings in a masked form, 2) assembly of the Mbn-peptide sequence by means of 1,4-addition-elimination and fragment condensation, 3) copper templated cyclization, and 4) a controlled final deprotection optimized to afford pure material. We specifically note that many other assembly variants failed in our hands, that masking the thioamide sulfur atoms was key, and that many advanced intermediates showed pronounced sensitivity. Preorganization by chelation - and not by the disulfide bond - seems to shape and stabilize the peptide scaffold. While Mbn may be biosynthesized and transported in its apo-form,[8a] additional stabilization *in cellulo* of this chemically labile entity must be suspected. Interestingly, we have found that the two azlactone rings display distinct chemical stability and reactivity. This observation warrants further investigation, because, the methanobactins found in nature have a variable *N*-terminal heterocycle, whereas the *C*-terminal oxazolone stays invariant.[4a] Considering that Mbn is a superb ligand for copper ions,[24] chemical modifications of the ligand itself might be ultimately involved in effecting Cu-uptake and -release, either directly, or by conformational reprogramming.[25] The successful development of synthetic methodology for the Cu-Mbn-OB3b structure (**1**) will enable further studies along this line.

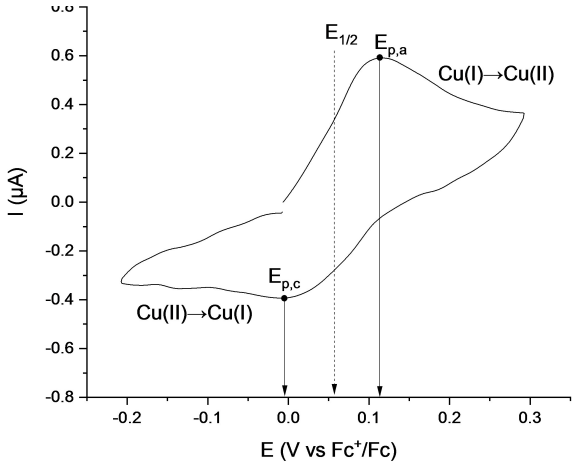


Figure 1. Cyclic voltammogram of synthetic Cu(I)-Mbn-OB3b (**1**) in CH_3CN/H_2O (9/1) plus 0.4 M $TBAPF_6$ (scan rate 50 mVs^{-1}). The solid arrows indicate the cathodic ($E_{p,c}$) and anodic ($E_{p,a}$) peak potentials, the dotted arrow the average ($E_{1/2}$) of the peak potentials. $TBAPF_6$ = tetrabutylammonium hexafluorophosphate.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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