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Total synthesis of luminmycin A, a cryptic natural product from *Photorhabdus luminescens*

Phil Servatius†, Tanja Stach†, and Uli Kazmaier*[a]

Keywords: Glidobactin / Isomerization / Luminmycin / Proteasome inhibitor / Syrbactin

Luminmycin A, a natural proteasome inhibitor transcripted by a silent gene cluster from *Photorhabdus luminescens*, belongs to the compound family of the syrbactins and is structurally closely related to the glidobactins. Key step for the synthesis of the 12-membered cyclopeptide ring is an intramolecular Horner-Wadsworth-Emmons reaction, while the double unsaturated fatty acid side chain can be obtained via phosphine-catalyzed isomerization of a corresponding acetylenic fatty acid ester.

Introduction

Proteasomes are ubiquitously found within the cytosol of all eukaryotes and archaes and are responsible for the degradation of damaged or excess proteins.[1] The target protein first undergoes ubiquitylation through the action of ubiquitin ligases, followed by a nucleophilic attack of a *N*-terminal threonine residue of the proteasome, resulting in cleavage of peptidic bonds.[2] Proteasomal degradation is an essential step during the cell cycle and is involved in regulation of gene expression and other cellular functions.[3] Thus, inhibition of this process has severe effects on cell viability since interrupted degradation of damaged proteins acts as a signal for apoptosis, and therefore, the proteasome presents an interesting target for the treatment of e.g. neurodegenerative diseases[4] or cancer.[5] Many proteasome inhibitors have been discovered in recent years.[6] Currently, three inhibitors are approved for clinical use for the treatment of multiple myeloma.[7] The peptide derived structures of bortezomib, ixazomib and carfilzomib (figure 1) possess electrophilic centers to interact with proteasome's threonine residue through nucleophilic addition. However, they show poor selectivity towards the proteasome since their electrophilic sites are prone to react with numerous endogenous compounds.[8]

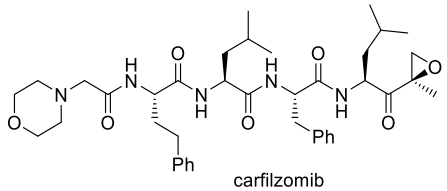

Figure 1: Approved proteasome inhibitor carfilzomib.

The compound class of syrbactins consists of more selective inhibitors.[9] Discovered independently, the natural product families of syringolin,[10] glidobactin[11] and cepafungin[12] have common structural features. A central 12-membered ring system with a crucial Michael acceptor is complemented by exocyclic amino acids and, in some cases, fatty acid residues. The Michael system is responsible for irreversible proteasome inhibition since the adduct formed by nucleophilic attack of threonine is stable under physiological conditions.[9b] Recently, Müller and co-workers were able to express silent megasynthetase gene clusters from *Photorhabdus luminescens* in heterologous hosts and elucidated the biochemical pathway of a new class of syrbactins, the luminmycins.[13] Luminmycin A was identified as one of the metabolites transcripted by the silent gene cluster and evinced structural similarity to the known proteasome inhibitor glidobactin A (figure 2).

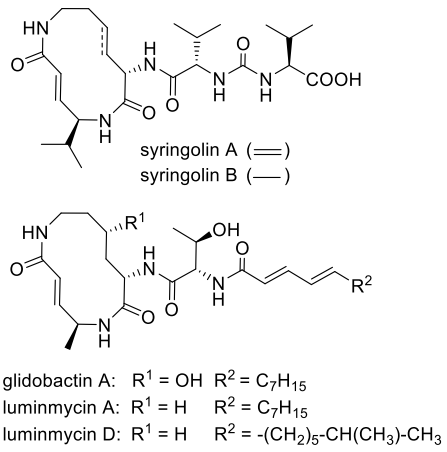

Figure 2: Natural occuring syrbactins.

Further luminmycins were detected in the culture broth and upon infection of crickets with *P. asymbiotica*.[14] While the linear structures of luminmycin B and C were speculated to be biosynthetic precursors, luminmycin D was identified as potential proteasome inhibitor. Luminmycin A and D differ only in the fatty acid moiety, as seen for glidobactin A-G.[11b, c] Both natural products possess striking biological activities against a series of human cancer cell lines, including colon carcinoma (HCT-116, 91.8 nM)[13b] and

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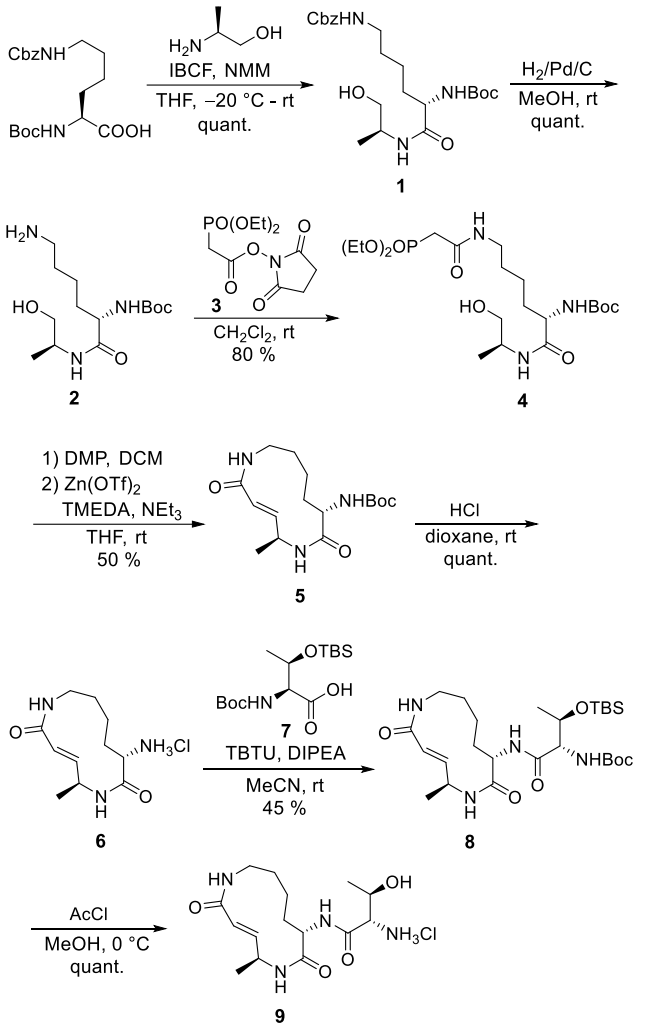
pancreatic cancer (18 nM).[14] Interestingly, no synthetic approach towards the luminmycins has been accomplished yet, although the comparable syringolins[5c, 15] and glidobactins[16] are well described in literature. Our longstanding interest in the synthesis of biologically active peptides and natural products[17] emphasized the development of a synthetic protocol towards this promising compound class. The key challenge is definitely the macrocyclization towards the 12-membered ring system, including a trans double bond. However, several methods to accomplish this goal have been developed, especially for the synthesis of the syringolins, and should in principle be applicable to the synthesis of luminmycin A.[5c,15] Most obvious is the ring closure via macrolactamization, an approach which was used by several groups, but in general gave only moderate yields.[5c,15b,16b] Kaiser et al. reported a ring closing metathesis to generate the β,γ-double bond of syringolin A,[5c] and Pirrung used an intramolecular Horner-Wadsworth-Emmons reaction, to generate the α,β-double bond of the unsaturated γ-amino acid.[15a,c,f] Ichikawa finally used an Ugi reaction to generate the stereogenic center of the unsaturated lysine in a highly stereoselective ring closing four componetn reaction.[15d,g,h] Construction of the dienic fatty acid moiety should be achieved through phosphine-catalyzed isomerization of the corresponding propargylic acid ester.[18]

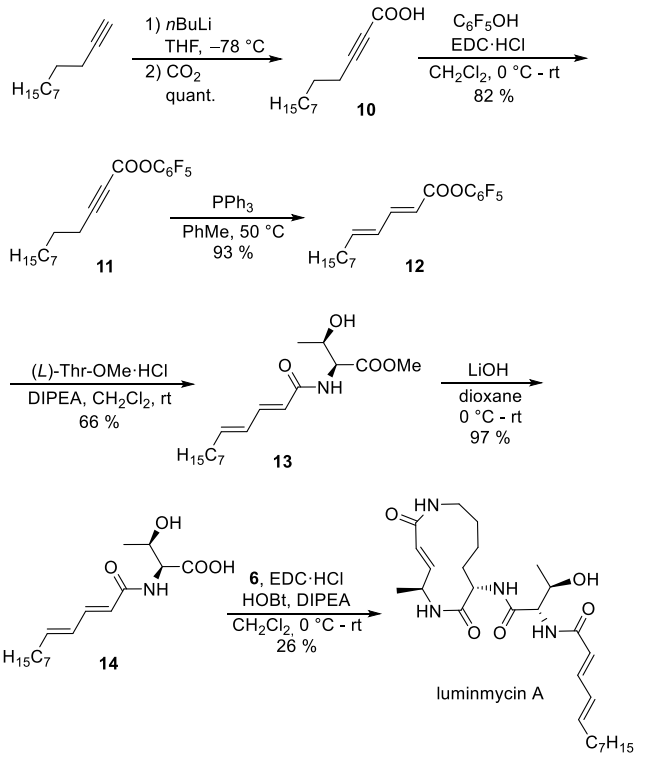
Results and Discussion

The initial step towards luminmycin A was the synthesis of a glidobamine-analogue macrocycle. Therefore, a similar approach as reported by Pirrung *et al.* for the synthesis of syringolin analogues was used.[15c] Coupling of *N*-protected lysine with L-alaninol afforded dipeptide **1** in quantitative yield (scheme 1). Hydrogenative cleavage of the Cbz-group and coupling of amine **2** with the *N*-hydroxysuccinimid (NHS) ester of phosphonoacetate (**3**) gave cyclization precursor **4** in good yield. Oxidation of the alcohol in **4** to the corresponding aldehyde with Dess-Martin periodinane[19] and olefination under HWE conditions using a protocol developed by Schauer and Helquist[20] afforded macrocycle **5** in 50 % yield after optimization. This was the most critical step throughout the synthesis. The yields varied and a by-product, resulting from aldol condensation, was detected frequently in the reaction mixture, but could never be isolated in pure form. In addition, varying amounts of separable cyclodimer were obtained. Boc-deprotection afforded the glidobamine-analogue **6** in quantitative yield. In order to attach the exocyclic threonine residue, fully protected threonine **7** had to be used in the coupling reaction, while complex mixtures were obtained if only *N*-protected Boc-Thr-OH was used instead. Global deprotection of both the Boc- and TBS-group in **8** was achieved in methanolic HCl solution and glidobactamine-analogue **9** was obtained in quantitative yield.

Next, the double unsaturated fatty acid moiety had to be synthesized and attached to **9**. As outlined above, phosphine-catalyzed isomerization of the corresponding acetylenic acid ester should give rise to the desired diene.[18] Deprotonation of 1-undecyne and addition of CO_2 afforded unsaturated acid **10** in quantitative yield (scheme 2). To facilitate both, the isomerization and coupling with **9**, activation of **10** as Pfp-ester was performed.[18] The active ester **11** was isomerized using 5 mol% triphenylphosphine in toluene at 50 °C overnight. Unfortunately, all attempts to couple the activated dienic acid with **9** failed. This drawback called for another strategy to access the natural product. Consequently, active ester **12** was reacted with threonine methyl ester to give compound **13** in acceptable yield. Saponification of the methyl ester in **13** occurred readily and the carboxylic acid **14** was reacted with glidobamine-analogue **6**. Luminmycin A was obtained after column chromatography as a single diastereomer.



Scheme 1: Synthesis of glidobactamine-analogue **9**.



Scheme 2: Phosphine-catalyzed isomerization and total synthesis of luminmycin A.

Poor solubility of **6** and azlactone formation after activation of **14** limited the yield of this final coupling step. However, the azlactone could easily be separated by reversed phase column chromatography. The spectra of luminmycin A were in accordance to previously reported data and confirmed the elucidated structure of the natural product.[1]

Conclusions

A straightforward and short synthesis of the natural proteasome inhibitor luminmycin A was developed. The challenging macrocyclization was accomplished with acceptable yield after optimization. Phosphine-catalyzed isomerization of an activated acetylenic acid proceeded readily and gave the desired dienic fatty acid. However, coupling of this substrate with a glidobactamine analogue proved to be a non-trivial issue. This setback could be overcome by coupling of the fatty acid with threonine and following assembly into the natural scaffold. Further applications of this isomerization protocol are currently under investigation. Furthermore, the outlined synthesis of luminmycin A should provide access to luminmycin D as well as derivatives thereof through alteration of the fatty acids incorporated.

Experimental Section

General remarks: All air- or moisture-sensitive reactions were carried out in dried glassware (> 100 °C) under an atmosphere of nitrogen or argon. THF was distilled over Na/benzophenone prior to use. EtOAc and petroleum ether (PE) were distilled prior to use. Reactions were monitored by analytical TLC, which was performed on precoated silica gel on TLC PET-foils by *Sigma-Aldrich*. Visualization was accomplished with UV-light (254 nm), $KMnO_4$ solution or Ce(IV) solution. The products were purified by flash chromatography on silica gel columns (*Macherey-Nagel* 60, 0.063–0.2 mm) or by automated flash chromatography (*Grace Reveleris®*, *Teledyne Isco RediSep Rf* silica cartridges or *Kinesis* silica C-18 cartridges). Melting points were determined with a melting point apparatus *IA 9100* by *Electrothermal* and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a *Bruker AV II 400* [400 MHz (^1H), 100 MHz (^{13}C)] or a Bruker *AV 500* [500 MHz, (^1H), 125 MHz (^{13}C)] spectrometer in $CDCl_3$ unless otherwise specified. NMR spectra were evaluated using *NMR Processor* from *ACD*. Chemical shifts are reported in ppm relative to $Si(CH_3)_4$ and the solvent residual peak was used as the internal standard. Multiplicities are reported as br s (broad signal), s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). High resolution mass spectra were recorded with a *Finnigan MAT 95* spectrometer using the CI technique. Gas chromatography was performed on a *Shimadzu* (*GC-2010*, autoinjector *AOC-20i*, mass detector GCMS-QP2010, CI technique) with a *FS-Supreme-5ms* capillary column (25 m x 0.25 mm) and nitrogen as carrier gas. HPLC analyses were performed on a *Merck Hitachi D-7000* with a *Diode Array detector L-7455*. Optical rotations were measured with a *Perkin-Elmer* polarimeter (Model 341) in a thermostated (20 °C ± 1 °C) cuvette. The radiation source used was a sodium vapor lamp (λ = 589 nm). The concentrations are given in g/100 ml.

Benzyl *tert*-butyl ((*S*)-6-(((*S*)-1-hydroxypropan-2-yl)amino)-6-oxohexane-1,5-diyl)dicarbamate (1): To a solution of Boc-(L)-Lys(Cbz)-OH (1.90 g, 4.99 mmol) in dry THF (50 mL) were added *N*-methylmorpholine (0.61 mL, 561 mg, 5.55 mmol) and isobutyl chloroformate (0.72 mL, 754 mg, 5.52 mmol) dropwise at –20 °C. After stirring for 10 min at this temperature, a solution of (L)-alaninol (387 µL, 375 mg, 4.99 mmol) in dry THF (10 mL) was added dropwise, and the reaction was allowed to warm to room temperature overnight. For workup, the reaction was filtrated, and the residue was washed with diethyl ether and ethyl acetate. The filtrate was concentrated *in vacuo* and the residue was dissolved in ethyl acetate. HCl solution (1 M) was added and the layers were separated. The aqueous phase was extracted three times with ethyl acetate, and the combined organic phases were washed with sat. $NaHCO_3$ solution and dried over Na_2SO_4. The crude product **1** (2.18 g, 4.99 mmol, quant.) was obtained as a colourless oil and was used without further purification. R_f (**1**) = 0.07 (silica, CH_2Cl_2: MeOH 95:5). HPLC (Reprosil, *n*-hexane:*i*PrOH 70:30, 1 mL/min, 20 °C): t_R (**1**) = 16.4 min. $[\alpha]_D^{20}$ = –21.4 (c = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 6.9 Hz, 3 H), 1.39 (m, 2 H), 1.43 (s, 9 H), 1.51 (tt, *J* = 6.8, 6.8 Hz, 2 H), 1.63 (m, 1 H), 1.80 (m, 1 H), 3.17 (dt, *J* = 6.2, 6.2 Hz, 2 H), 3.45 (dd, *J* = 11.1, 5.8 Hz, 1 H), 3.66 (dd, *J* = 11.2, 3.5 Hz, 1 H), 3.94–4.08 (m, 2 H), 5.05 (m, 1 H), 5.09 (m, 2 H), 5.34 (br s, 1 H), 6.34 (d, *J* = 7.6 Hz, 1 H), 7.28–7.38 (m, 5 H) ppm. The signal of OH wasn't observed in the ^1H NMR spectrum. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.8, 22.4, 28.3, 29.5, 31.7, 40.2, 47.6, 54.7, 66.3, 66.7, 80.2, 128.0, 128.1, 128.5, 136.5, 156.0, 156.9, 172.3 ppm. HRMS (CI) calcd. for $C_{22}H_{36}N_3O^+$ $[M + H]^+$: 438.2599, found 438.2603.

***tert*-Butyl ((*S*)-6-amino-1-(((*S*)-1-hydroxypropan-2-yl)amino)-1-oxohexan-2-yl)carbamate (2):** A solution of **1** (875 mg, 2.00 mmol) in MeOH (10 mL) was treated with Pd on charcoal (88 mg, 10 w% Pd) and was hydrogenated overnight under atmospheric H_2-pressure. The reaction mixture was filtrated through a pad of celite, and the filtrate was concentrated *in vacuo*. Amine **2** (607 mg, 2.00 mmol, quant.) was obtained as a colorless resin. $[\alpha]_D^{20}$ = –12.3 (c = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (d, *J* = 6.8 Hz, 3 H), 1.40 (m, 2 H), 1.42 (s, 9 H), 1.48 (m, 2 H), 1.62 (m, 1 H), 1.78 (m, 1 H), 2.48–2.82 (br s, 3 H), 2.70 (t, *J* = 6.3 Hz, 2 H), 3.45 (dd, *J* = 11.2, 5.1 Hz, 1 H), 3.64 (dd, *J* = 11.0, 3.5 Hz, 1 H), 3.96–4.13 (m, 2 H), 5.39 (d, *J* = 5.3 Hz, 1 H), 6.58 (d, *J* = 6.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.9, 22.4, 28.3, 31.9, 32.3, 41.1, 47.5, 54.4, 65.6, 79.9, 155.7, 172.1 ppm. HRMS (CI) calcd. for $C_{14}H_{30}N_3O_4^+$ $[M + H]^+$: 304.2231, found 304.2250.

***tert*-Butyl ((*S*)-6-(2-(diethoxyphosphoryl)acetamido)-1-(((*S*)-1-hydroxypropan-2-yl)amino)-1-oxohexan-2-yl)carbamate (4):** To a solution of **2** (293 mg, 966 µmol) in CH_2Cl_2 (10 mL) was added a solution of 2,5-dioxopyrrolidin-1-yl 2-(diethoxyphosphoryl)acetate **3**[1] (318 mg, 1.08 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction was allowed to warm to room temperature overnight and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, CH_2Cl_2:MeOH 100:0, gradient 90:10) to obtain **4** (351 mg, 729 µmol, 75 %) as a colorless resin. R_f (**4**) = 0.22 (silica, CH_2Cl_2:MeOH 90:10).HPLC (Reprosil, *n*-hexane:iPrOH 70:30,1 mL/min,20 °C): t_R (**4**) = 19.4 min (> 99 %). $[\alpha]_D^{20}$ = –9.3 (c = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 6.9 Hz, 3 H), 1.32 (t, *J* = 7.1 Hz, 6 H), 1.39 (m, 2 H), 1.41 (s, 9 H), 1.52 (m, 2 H), 1.63 (m, 1 H), 1.77 (m, 1 H), 2.84 (d, *J* = 20.9 Hz, 2 H), 3.25 (dt, *J* = 5.9, 5.9 Hz, 2 H), 3.45 (dd, *J* = 11.1, 5.9 Hz, 1 H), 3.66 (dd, *J* = 11.2, 3.5 Hz, 1 H), 3.99–4.07 (m, 2 H), 4.12 (qd, *J* = 7.1, 3.0 Hz, 4 H), 5.46 (d, *J* = 7.7 Hz, 1 H), 6.69 (d, *J* = 7.6 Hz, 1 H), 7.01 (t, *J* = 5.5 Hz, 1 H) ppm. The signal of OH wasn't observed in the ^1H NMR spectrum. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3 (d, *J* = 5.9 Hz), 16.8, 22.4, 28.3, 28.6, 32.2, 35.1 (d, *J* = 131 Hz), 39.1, 47.5, 54.5, 62.8 (d, *J* = 6.6 Hz), 62.9 (d, *J* = 6.6 Hz), 65.9, 79.8, 155.7, 164.1, 172.1 ppm. HRMS (CI) calcd. for $C_{20}H_{41}N_3O_6P^+$ $[M + H]^+$: 482.2626, found 482.2650.

***tert*-Butyl ((5*S*,8*S*,*E*)-5-methyl-2,7-dioxo-1,6-diazacyclododec-3-en-8-yl)carbamate (5):**

Oxidation: Compound **4** (478 mg, 993 µmol) was dissolved in dry CH_2Cl_2 (5.0 mL) and treated carefully with Dess Martin periodinane (589 mg, 1.39 mmol) at room temperature. The reaction was stirred for 45 min and diluted with ethyl acetate (10 mL). A mixture of sat. $NaHCO_3$ and 2 % Na_2SO_3 (1:1) was added and the reaction was stirred for 5 min until the organic phase became clear. The layers were separated, and the aqueous phase was extracted two times with ethyl acetate. The combined organic phases were concentrated *in vacuo*, filtrated in order to remove the insoluble by-products and dried over Na_2SO_4. The crude aldehyde was used without further purification.

Macrolactamization: To a suspension of $Zn(OTf)_2$ (1.14 g, 3.14 mmol) in dry THF (500 mL) were added TMEDA (502 µL, 389 mg, 3.14mmol) and NEt_3 (547 µL, 397 mg, 4.17 mmol) at room temperature. The reaction mixture was stirred for 15 min at this temperature before a solution of the crude aldehyde (470 mg, 980 µmol) in dry THF (20 mL) was added dropwise over 14 h. The reaction was stirred for further two days and concentrated *in vacuo* to approximately 10 mL. Ethyl acetate (40 mL) was added and the organic phase was washed with water, $KHSO_4$ solution (1 M) and brine subsequently. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by reversed phase column chromatography (silica C-18, H_2O:MeCN gradient) to obtain macrocycle **5** (160 mg, 492 µmol, 50 %) as an off-white solid after lyophilisation, mp: 230 °C (decomposition). R_f (**5**) = 0.25 (silica, CH_2Cl_2:MeOH 90:10). HPLC (Reprosil, *n*-hexane: *i*PrOH 70:30, 1 mL/min, 20 °C): t_R (**5**) = 36.0 min (> 99 %). $[\alpha]_D^{20}$ = –35.2 (c = 0.5, MeOH). ^{1}H NMR (400 MHz, MeOH-d_4): δ = 1.12 (m, 1 H), 1.32 (d, *J* = 7.1 Hz, 3 H), 1.39–1.52 (m, 2 H), 1.44 (s, 9 H), 1.65 (m, 1 H), 1.80 (m, 1 H), 2.09 (m, 1 H), 3.11 (d, *J* = 15.5 Hz, 1 H), 3.49 (m, 1 H), 4.36 (m, 1 H), 4.56 (m, 1 H), 6.37 (d, *J* = 15.5 Hz, 1 H), 7.00 (dd, *J* = 15.4, 4.7 Hz, 1 H) ppm. The signals of NH weren't observed in the ^{1}H NMR spectrum. ^{13}C NMR (100 MHz, MeOH-d_4): δ = 18.8, 18.8, 28.8, 31.4, 31.6, 39.9, 47.7, 54.7, 80.8) 119.5, 149.6, 157.5, 169.9, 173.7 ppm. HRMS (CI) calcd. for $C_{16}H_{28}N_3O_4^+$ $[M + H]^+$: 326.2074, found 326.2075.

(5*S*,8*S*,*E*)-8-Amino-5-methyl-1,6-diazacyclododec-3-ene-2,7-dione hydrochloride (6): A solution of **5** (31.8 mg, 97.7 µmol) in dioxane (0.50 mL) was treated with HCl solution (0.50 mL, 2.00 mmol, 4 M in dioxane) at room temperature for 90 min. Afterwards, the reaction mixture was concentrated *in vacuo* and the crude product **6** (25.6 mg, 97.7 mmol, quant.) was obtained as an off-white solid after lyophilisation. ^{1}H NMR (400 MHz, MeOH-d_4): δ = 1.15 (m, 1 H), 1.36 (d, *J* = 7.1 Hz, 3 H), 1.43–1.55 (m, 2 H), 1.72 (m, 1 H), 1.94 (m, 1 H), 2.36 (m, 1 H), 3.18 (dt, *J* = 15.4, 3.4 Hz, 1 H), 3.59 (dd, *J* = 13.3, 13.3 Hz, 1 H), 4.19 (m, 1 H), 4.62 (dq, *J* = 6.3, 6.3 Hz, 1 H), 6.41 (d, *J* = 15.4 Hz, 1 H), 7.09 (dd, *J* = 15.5, 4.8 Hz, 1 H) ppm. The signals of NH weren't observed in the ^{1}H NMR spectrum. ^{13}C NMR (100 MHz, MeOH-d_4): δ = 18.1, 18.6, 29.8, 30.8, 39.9, 47.9, 53.9, 119.2, 150.4, 169.7, 169.9 ppm.

***tert*-Butyl ((2*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-1-(((5*S*,8*S*,*E*)-5-methyl-2,7-dioxo-1,6-diazacyclododec-3-en-8-yl)amino)-1-oxobutan-2-yl)carbamate (8):** To a solution of *N*-(*tert*-butoxycarbonyl)-*O*-(*tert*-butyldimethylsilyl)-(*L*)-threonine (37.0 mg, 111 µmol) and **6** (25.6 mmol, 97.7 µmol) in dry CH_2Cl_2 (1.0 mL) and dry MeOH (0.25 mL) were added HOBt (16.5 mg, 122 µmol), EDC·HCl (21.8 mg, 114 µmol) and DIPEA (18.8 µL, 13.9 mg, 108 µmol) subsequently at 0 °C. The reaction was allowed to warm to room temperature overnight and was then diluted with CH_2Cl_2. HCl solution (1 M) was added and the layers were separated. The aqueous phase was extracted three times with CH_2Cl_2, and the combined organic layers were washed with sat. $NaHCO_3$ solution and dried over Na_2SO_4. Purification by column chromatography (silica, CH_2Cl_2:MeOH 100:0, gradient 95:5) afforded compound **8** (23.6 mg, 43.6 µmol, 45 %) as an off-white solid after lyophilisation. R_f (**8**) = 0.02 (silica, CH_2Cl_2:MeOH 95:5). HPLC (Reprosil, *n*-hexane:*i*PrOH 70:30, 1 mL/min, 20 °C): t_R (**8**) = 23.0 min (> 99 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.08 (s, 3 H), 0.86 (s, 9 H), 1.12 (d, *J* = 6.2 Hz, 3 H), 1.22–1.40 (m, 3 H), 1.30 (d, *J* = 7.0 Hz, 3 H), 1.46 (s, 9 H), 1.66 (m, 1 H), 1.92 (m, 1 H), 2.04 (m, 1 H), 3.12 (m, 1 H), 3.42 (m, 1 H), 4.09 (d, *J* = 7.7 Hz, 1 H), 4.46 (qd, *J* = 5.5, 5.5 Hz, 1 H), 4.68 (m, 1 H), 4.86 (m, 1 H), 5.25 (d, *J* = 8.2 Hz, 1 H), 6.07 (t, *J* = 7.1 Hz, 1 H), 6.34 (d, *J* = 15.4 Hz, 1 H), 7.07 (dd, *J* = 15.3, 4.6 Hz, 1 H), 7.22 (d, *J* = 7.0 Hz, 1 H), 7.68 (d, *J* = 6.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.0, –4.5, 17.7, 17.9, 18.7, 19.8, 25.7, 28.3, 30.3, 31.0, 39.1, 46.0, 52.6, 59.9, 68.2, 80.4, 117.9, 147.9, 156.0, 167.5, 170.0, 170.3 ppm. HRMS (CI) calcd. for $C_{26}H_{48}N_4O_6Si^+$ $[M + H]^+$: 540.3338, found 540.3359.

(2*S*,3*R*)-2-Amino-3-hydroxy-*N*-((5*S*,8*S*,*E*)-5-methyl-2,7-dioxo-1,6-diazacyclododec-3-en-8-yl)butanamide hydrochloride (9): To a solution of **8** (22.2 mg, 41.1 µmol) in MeOH (1.0 mL) was added acetyl chloride (28.4 µL, 31.2 mg, 397 µmol) at 0 °C. The reaction was stirred for 3.5 h at this temperature and was then concentrated *in vacuo*. The crude hydrochloride **9** (14.9 mg, 41.1 µmol, quant.) was obtained as an off-white solid after lyophilization, mp 125 °C (decomposition). R_f (**9**) = 0.03 (silica, CH_2Cl_2: MeOH 90:10). $[\alpha]_D^{20}$ = –21.4 (c = 0.5, MeOH). ^{1}H NMR (400 MHz, MeOH-d_4): δ = 1.15 (m, 1 H), 1.31 (d, *J* = 6.4 Hz, 3 H), 1.34 (d, *J* = 7.1 Hz, 3 H), 1.44 – 1.60 (m, 2 H), 1.70 (m, 1 H), 1.87 (m, 1 H), 2.21 (m, 1 H), 3.19 (d, *J* = 15.5 Hz, 1 H), 3.58 (dd, *J* = 13.2, 13.2 Hz, 1 H), 3.81 (d, *J* = 6.5 Hz, 1 H), 4.01 (ddq, *J* = 6.4, 6.4, 6.4 Hz, 1 H), 4.57 (dq, *J* = 6.1, 6.1 Hz, 1 H), 4.68 (m, 1 H), 6.44 (d, *J* = 15.5 Hz, 1 H), 7.11 (dd, *J* = 15.5, 4.8 Hz, 1 H) ppm. The signals of OH and NH weren't observed in the ^{1}H NMR spectrum. ^{13}C NMR (100 MHz, MeOH-d_4): δ = 19.0, 20.2, 30.9, 31.0, 40.3, 47.8, 54.2, 60.1, 67.7, 118.8, 151.2, 168.3, 172.7 ppm. The signal of one carbonyl group was not observed in the ^{13}C NMR spectrum. HRMS (CI) calcd. for $C_{15}H_{27}N_4O_4^+$ $[M + H]^+$: 327.2027, found 327.2032.

Pentafluorophenyl dodec-2-ynoate (11): A solution of 1-undecyne (767 mg, 5.04 mmol) in dry THF (25 mL) was cooled to –78 °C before *n*-BuLi (2.0 mL, 5.0 mmol, 2.5 M in hexane) was added dropwise. The reaction was stirred for 10 min before gaseous CO_2 was bubbled through the solution for 5 min. Afterwards, the reaction was allowed to warm to room temperature quickly. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in diethyl ether. HCl solution (1 M) was added, and the layers were separated. The aqueous phase was extracted three times with diethyl ether, the combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude acid (981 mg, 5.00 mmol) was dissolved in dry CH_2Cl_2 (20 mL) before pentafluorophenol (1.06 g, 5.76 mmol) and EDC·HCl (1.06 g, 5.53 mmol) were added subsequently at 0 °C. The reaction was stirred for 2 h at this temperature and concentrated *in vacuo*. Purification by column chromatography (silica, petroleum ether) afforded **11** (1.48 g, 4.08 mmol, 82 %) as a colorless oil. R_f (**11**) = 0.66 (silica, petroleum ether:ethyl acetate 90:10). GC/MS (Supreme DB5, column flow 1.25 mL/min, injector 250 °C; 60 °C (2 min), 200 °C (5 °C/min), 220 °C (20 °C/min), 5 min): t_R (**11**) = 28.76 min (> 99 %, m/z 363). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.8 Hz, 3 H), 1.22–1.37 (m, 10 H), 1.44 (m, 2 H), 1.65 (tt, *J* = 7.4, 7.4 Hz, 2 H), 2.44 (t, *J* = 7.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 18.9, 22.6, 27.2, 28.8, 29.0, 29.2, 29.3, 31.8, 70.7, 95.9, 148.8 ppm. The four aromatic signals weren't observed in the ^{13}C NMR spectrum. HRMS (CI) calcd. for $C_{18}H_{20}F_5O_2^+$ $[M + H]^+$: 363.1378, found 363.1398.

Pentafluorophenyl (2*E*,4*E*)-dodeca-2,4-dienoate (12): Pentafluorophenylester **11** (374 mg, 1.032 mmol) was dissolved in toluene (5.0 mL), treated with triphenylphosphine (14.9 mg, 56.8 µmol) and heated to 50 °C overnight (16 h). The reaction mixture was concentrated *in vacuo*, and the crude product was purified by column chromatography (silica, petroleum ether:ethyl acetate 98:2). The isomerized compound **12** (308 mg, 850 µmol, 82 %) was obtained as a colourless oil. R_f (**12**) = 0.38 (silica, petroleum ether:ethyl acetate 98:2). GC/MS (Supreme DB5, column flow 1.25 mL/min, injector 250 °C; 60 °C (2 min), 200 °C (5 °C/min), 220 °C (20 °C/min), 5 min): t_R (**12**) = 30.73 min (> 99 %, m/z 363). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.8 Hz, 3 H), 1.22–1.36 (m, 8 H), 1.45 (m, 2 H), 2.23 (dt, *J* = 6.7, 6.7 Hz, 2 H), 5.99 (d, *J* = 15.3 Hz, 1 H), 6.24–6.35 (m, 2 H, 8-H), 7.52 (dd, *J* = 15.3, 10.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.6, 28.5, 29.1, 29.1, 31.8, 33.2, 115.0, 128.0, 148.6, 149.9, 162.8 ppm. The four aromatic signals weren't observed in the ^{13}C NMR spectrum. HRMS (CI) calcd. for $C_{18}H_{20}F_5O_2^+$ $[M + H]^+$: 363.1378, found 363.1395.

Methyl ((2*E*,4*E*)-dodeca-2,4-dienoyl)-(L)-threoninate (13): To a solution of pentafluorophenylester **12** (145 mg, 400 µmol) in dry CH_2Cl_2 (4.0 mL) was added DIPEA (143 µL, 106 mg, 820 µmol) at room temperature. Afterwards, HCl·H-(*L*)-Thr-OMe (74.0 mg, 436

µmol) was added and the reaction was stirred for 3 days. For workup, the reaction was concentrated *in vacuo*. The residue was redissolved in diethyl ether and HCl solution (1 M) was added. The layers were separated, and the aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed with sat. $NaHCO_3$ solution and dried over Na_2SO_4. The crude prouct was purified by column chromatography (silica, petroleum ether:ethyl acetate 70:30) to obtain **13** (82.3 mg, 264 µmol, 66 %) as an off-white solid, mp 113 °C. R_f (**13**) = 0.17 (silica, petroleum ether:ethyl acetate 50:50). HPLC (Reprosil, *n*-hexane:*i*PrOH 80:20, 1 mL/min, 20 °C): t_R (**13**) = 18.7 min (> 99 %). $[\alpha]_D^{20}$ = –3.7 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H), 1.22 (d, *J* = 6.4 Hz, 3 H), 1.17–1.34 (m, 8 H), 1.41 (tt, *J* = 6.8, 6.8 Hz, 2 H), 2.15 (dt, *J* = 7.1, 6.7 Hz, 2 H), 2.30 (br s, 1 H), 3.77 (s, 3 H), 4.36 (qd, *J* = 6.4, 2.5 Hz, 1 H), 4.70 (dd, *J* = 8.9, 2.5 Hz, 1 H), 5.87 (d, *J* = 15.0 Hz, 1 H), 6.06–6.18 (m, 2 H), 6.35 (d, *J* = 8.8 Hz, 1 H), 7.23 (dd, *J* = 15.0, 9.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 19.9, 22.6, 28.7, 29.1, 31.8, 33.0, 52.6, 57.2, 68.2, 120.7, 128.1, 142.6, 144.2, 166.8, 171.7 ppm. HRMS (CI) calcd. for $C_{17}H_{29}NO_4^+$ $[M + H]^+$: 311.2097, found 311.2085.

((2*E*,4*E*)-Dodeca-2,4-dienoyl)-L-threonine (14): A solution of **13** (60.7 mg, 195 µmol) in dioxane (2.0 mL) was cooled to 0 °C and treated with a LiOH solution (244 µL, 244 µmol, 1.0 M in H_2O). The cooling bath was removed, and the reaction was stirred at room temperature for 2 h. Afterwards, the reaction mixture was concentrated *in vacuo*, and the residue was redissolved in diethyl ether. HCl solution (1 M) was added, and the layers were separated. The aqueous phase was extracted three times with diethyl ether, and the combined organic layers were dried over Na_2SO_4. The crude product **14** (56.3 mg, 189 µmol, 97 %) was used without further purification after lyophilisation. mp 97 °C. R_f (**14**) = 0.03 (silica, petroleum ether:ethyl acetate 50:50). $[\alpha]_D^{20}$ = –23.2 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H), 1.21 (d, *J* = 6.4 Hz, 3 H), 1.17–1.34 (m, 9 H), 1.40 (m, 2 H, 6-H), 2.14 (dt, *J* = 6.6, 6.6 Hz, 2 H), 4.47 (qd, *J* = 6.3, 1.9 Hz, 1 H), 4.63 (dd, *J* = 8.3, 2.0 Hz, 1 H), 5.92 (d, *J* = 15.0 Hz, 1 H), 6.06–6.18 (m, 2 H), 6.71 (br s, 1 H), 6.98 (d, *J* = 8.3 Hz, 1 H), 7.23 (dd, *J* = 15.1, 9.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 19.2, 22.6, 28.8, 29.1, 29.2, 31.8, 33.1, 57.7, 67.6, 120.3, 128.1, 143.3, 144.9, 168.2, 173.5 ppm. HRMS (CI) calcd. for $C_{16}H_{28}NO_4^+$ $[M + H]^+$: 298.2013, found 298.2025.

Luminmycin A: To a solution of **6** (25.6 mg, 97.7 mmol) and **14** (32.0 mg, 108 µmol) in dry CH_2Cl_2 (1.0 mL) were added HOBt (16.7 mg, 109 µmol), EDC·HCl (22.5 mg, 117 µmol) and DIPEA (18 µL, 13.3 mg, 103 µmol) subsequently at 0 °C. The reaction was allowed to warm to room temperature within 4.5 h. The reaction was diluted with CH_2Cl_2 and HCl solution (1 M) was added. The layers were separated, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with sat. $NaHCO_3$ solution and dried over Na_2SO_4. The crude product was purified by reversed phase column chromatography (silica C-18, H_2O:MeCN 90:10, gradient 10:90) to afford luminmycin A (12.8 mg, 25.4 µmol, 26 %) as an off-white solid after lyophilisation, mp 195 °C (decomposition). In addition, a separable by-product (10.2 mg, 39.0 µmol, 36 %) was obtained, which appeared to be an azlactone formed by the threonine residue after activation. R_f (**luminmycin A**) = 0.13 (silica, CH_2Cl_2:MeOH 90:10). HPLC (Reprosil, *n*-hexane:*i*PrOH 50:50, 1 mL/min, 20 °C): t_R (**luminmycin A**) = 21.2 min. $[\alpha]_D^{20}$ = –15.4 (c = 0.36, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.86 (t, *J* = 7.1 Hz, 3 H), 0.93 (m, 1 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 1.20 (d, *J* = 6.9 Hz, 3 H), 1.18–1.29 (m, 10 H), 1.38 (m, 2 H), 1.44 (m, 1 H), 1.68 (m, 1 H), 2.05 (m, 1 H), 2.13 (dt, *J* = 7.3, 6.9 Hz, 2 H), 2.95 (m, 1 H), 3.27 (m, 1 H), 3.99 (m, 1 H), 4.32 (dd, *J* = 8.5, 4.1 Hz, 1 H), 4.40 (m, 1 H), 4.51 (m, 1 H), 4.93 (d, *J* = 5.0 Hz, 1 H), 6.09 (dt, *J* = 14.6, 7.2 Hz, 1 H), 6.17 (d, *J* = 15.5 Hz, 1 H), 6.18 (dd, *J* = 15.5, 10.7 Hz, 1 H), 6.23 (d, *J* = 15.5 Hz, 1 H), 6.78 (dd, *J* = 15.3, 4.6 Hz, 1 H), 7.00 (dd, *J* = 15.1, 10.7 Hz, 1 H), 7.35 (t, *J* = 6.3 Hz, 1 H), 7.63 (d, *J* = 7.3 Hz, 1 H), 8.01 (d, *J* = 8.5 Hz, 1 H), 8.46 (d, *J* = 7.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.9, 17.1, 18.3, 19.6, 22.0, 28.3, 28.5, 28.5, 29.6, 30.1, 31.2, 32.2, 37.9, 45.6, 51.5, 58.0, 66.5, 118.4, 122.9, 128.5, 139.8, 142.1, 146.7, 165.5, 165.8, 169.4, 170.5 ppm. HRMS (CI) calcd. for $C_{25}H_{41}N_4O_4^+$ $[M – C_2H_4O + H]^+$: 461.3122, found 461.3132.

Supporting Information (see footnote on the first page of this article): Copies of NMR spectra of all compounds.

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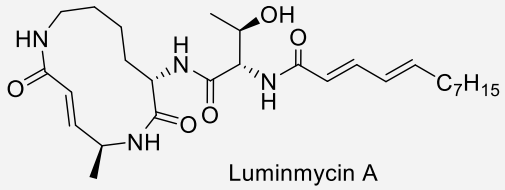
Natural Product Synthesis



Luminmycin A

Phil Servatius, Tanja Stach and Uli Kazmaier Page No. – Page No.

Total synthesis of luminmycin A, a cryptic natural product from *Photorhabdus luminescens*

Luminmycin A, a natural proteasome inhibitor has been synthesized for the first time. Key steps are an intramolecular Horner-Wadsworth-Emmons reaction and a PPh_3-catalyzed isomerization of a acetylenic fatty acid ester, giving access to the double unsaturated fatty acid side chain.

Keywords: Glidobactin / Isomerization / Luminmycin / Proteasome inhibitor / Syrbactin