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Total Synthesis and Configurational Assignment of Chondramide

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Introduction

The actin system comprises a major part of the cytoskeleton of eukaryotic cells.[1] In non muscle cells there is a roughly equal proportion of polymeric F-actin and monomeric G-actin (globular). The polymerisation of globular actin requires ATP. Among known natural products that disturb the actin system is cytochalasin which blocks the polymerisation of G-actin by binding to the end of the growing F-actin filaments.[2] On the other hand, the cyclic peptide phalloidin[3] prevents depolymerisation of F-actin by binding between actin monomers. Another key component of the cytoskeleton is the tubulin system. In this case the monomer tubulin forms a dynamic equilibrium with the polymer called microtubules. Compounds like taxol or the epothilones that disturb the tubulin system gained clinical relevance as anticancer drugs.[4]

Besides phalloidin, the jaspamide/chondramide family of cyclic depsipeptides[5] does also stabilize F-actin. In this regard, they are interesting lead compounds for drug design. For example, appropriate analogs thereof might be able to bind F-actin in a species dependent manner. Jaspamide (Jasplakinolide, jas) (1) features a 19-membered macrocyclic ring (Figure 1). It was isolated from the marine sponge[6] *Jaspis splendens*. Related compounds were later found in several other sponges.[7] While showing promising biological properties as an anti-actin agent, this activity is accompanied by significant toxicity. The major difference between the chondramides, which were isolated from the myxobacterium *Chondromyces crocatus*,[8] and jaspamide is a different polyketide moiety, resulting in an 18-membered ring. Quite recently the configurational assignment for chondramide C (chon C) was achieved independently by the Waldmann[9] and Kalesse[10] groups. Not surprisingly, the

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configurations of the three amino acids L-alanine, D-N-methyltryptophan, and L- β -tyrosine turned out to be the same as in jaspamide. However, the proposal[11] for the configuration of the ω -hydroxy acid required revision. We became interested in the synthesis of chondramide A (chon A) since preliminary results showed a higher therapeutic index against the parasite *toxoplasma gondii* as compared to chon B, chon C and jaspamide. While the L-configuration for the amine-bearing stereocenters in the α -methoxy- β -tyrosine could be assumed, the configuration at the α -carbon remained to be solved. In this paper we describe syntheses of diastereomers of the methoxytyrosine subunit and their incorporation into the chondramide scaffold leading to the total synthesis and configurational assignment of chondramide A.

Results and Discussion

It was planned to close the macrocyclic ring by intramolecular amide formation (Figure 2). The corresponding acyclic ester would originate from the known dipeptide acid **6**, a β -tyrosine isomer **8** and the hydroxy ester **7**. The dipeptide acid **6** is available in six steps from N-Boc-D-tryptophan.[12]

For the more challenging hydroxy ester **7** we recently reported a concise route that relies on a Kobayashi vinylogous aldol reaction with acetaldehyde, a Mitsunobu inversion at C7, and an asymmetric allylation to incorporate the last propionate unit (Scheme 1).[13] Overall this 12-step sequence allows for the preparation of ester **7** in gram amounts.

The *syn*-isomer (2D,3L) of 3-amino-2-methoxyester **8** is similar to the taxol side chain.[14] Accordingly, strategies that came to use in the synthesis of this side chain, a 3-phenylisoserine, or related compounds were considered.[15] For example, asymmetric nitroaldol reactions,[16] the Staudinger reaction leading to β -lactam intermediates,[17] the Sharpless asymmetric aminohydroxylation,[18] or asymmetric aldol reactions of glycolates to imines are known to produce these types of structures.[19] And finally, chemoselective substitution reactions on 2,3-dihydroxy-3-arylpropanoates would provide the *syn* diastereomer of **8**. [20] We opted for the latter due to its operational simplicity (Scheme 2). Thus, starting from 4-(triisopropylsilyloxy)benzaldehyde[21] (**13**) a Wittig reaction with (methoxycarbonylmethylene)triphenylphosphorane[22] provided cinnamate (*E*)-**14** in good yield. A subsequent asymmetric dihydroxylation[23] in presence of the ligand (DHQ)₂PHAL (ADMix- α), furnished an excellent yield of diol **15a**. As has been described by Sharpless et al. [20] the benzylic alcohol can be substituted by bromide through reaction of the diol with trimethyl orthoacetate, and treatment of the intermediate mixed orthoester with acetyl bromide. This way, a 67% yield of acetoxyl bromo ester **16a** could be secured after chromatographic separation of the wrong regioisomer. Substitution of the bromide on **16a** with sodium azide in DMSO at room temperature resulted in azide **17a** (70% yield). Proof of the regiochemistry came from a HMBC spectrum of **17a**. Thus, 3'-H [4.96 (d, *J* = 5.6 Hz, chon A numbering)] showed cross peaks to C-4' and C-5'. After saponification of the acetate, the 2-hydroxy group of **18a** was methylated using Meerwein's salt (Me₃OBf₄) [24] and proton sponge in dichloromethane. A final hydrogenation of azide **19a** in presence of Pd/C in methanol led to the desired *syn*-configured amino ester **20a**. The optical purity of **15a** and the propanoate derivatives derived from it could be estimated at the stage of the tripeptide ester **24a** to be $\gamma\gamma$ % by integration the corresponding 2'-H protons.

An alternative route to the (2D,3L)- β -tyrosine **20a** was based on an aminohydroxylation reaction[25,26,27] of cinnamate **14** using benzylcarbamate, 1,3-dichloro-5,5-dimethylhydantoin[28] and (DHQ)₂PHAL in a propanol/water mixture (Scheme 3). This produced the Cbz protected 2-hydroxy-3-amino acid ester **22**. Reductive cleavage of the Cbz protecting group (H₂, Pd/C, MeOH) gave as well β -tyrosine **20a**. In this case the etherification

was performed with MeI and Ag₂O in acetone. The optical purity of **20a** was estimated at the stage of the tripeptide ester **24a** to be 98% by integration the corresponding 2'-H protons.

Construction of the corresponding cyclodepsipeptide started with dipeptide acid **6** (Scheme 4). This acid was condensed with β -tyrosine derivative **20a** using TBTU in presence of additional hydroxybenzotriazole (HOBt) yielding tripeptide ester **24a**. The subsequent saponification of the ester group turned out to be crucial since cleavage of the TIPS ether or epimerization α to the carboxyl group had to be avoided. We therefore turned to the highly chemoselective trimethylstannol which produced tripeptide acid **25a** within 5 h at 80 °C.[29] The crude carboxylic acid could then be esterified with hydroxyester **7** under Yamaguchi conditions.[30] This way the Chon A precursor **26a** could be secured in 64% yield. The macrocyclization required cleavage of the N-Boc group and the *tert*-butylester. This was done with TFA in dichloromethane. It seemed that the N-Boc group cleaved quite easy, whereas the ester cleavage necessitated longer reaction times. After concentration of the reaction mixture, macrolactam formation on the residue was carried out in DMF (0.001 M) in presence of TBTU, HOBt and Hünig's base.[31,32] After work-up the crude cyclic depsipeptide was treated with TBAF in THF to cleave the phenolic triisopropylsilyl ether. Careful inspection of the NMR data showed that macrocycle **2a** did not correspond to natural chondramide A. The macrocycles show characteristic NMR signatures for the four methyl doublets. In **2a** (CD₃OD) they appear at δ = 0.81, 0.91, 0.92, 1.09 (2-CH₃).

Therefore, we surmised the (2L,3L)-3-amino-2-methoxy-tyrosine to be the isomer present in chondramide A. Based on the experience with the asymmetric dihydroxylation, we hoped to reach diastereomer **20b** from a Z-configured cinnamate. Accordingly, a Horner-Wittig reaction of aldehyde **13** with the Ando phosphonate[33] (NaH, THF) was performed resulting in a 27/73 *E/Z*-mixture of enoates **14** from which (*Z*)-**14** could be separated by flash chromatography (Scheme 5). Using (*Z*)-**14** a sequence of dihydroxylation [(DHQ)₂PHAL] as ligand, orthoester formation [(MeO)₃CMe], and reaction of the intermediate orthoester with acetyl bromide was expected to give acetoxy bromoester **16b**. The obtained material was converted in four steps to the presumed amino ester **20b**. This building block was then utilized for the synthesis of presumed cyclodepsipeptide **2b** (for details see supporting information). Again, the spectral data of the macrocycle **2b** (expected) did not match with those of chondramide A.

The conclusion from this rather unexpected finding was that either chondramide A contains a β -D-tyrosine derivative or that the substitution reaction on the benzylic position took a different course. The latter turned out to be the case. Thus, it seems that reaction of the presumed orthoester **A** with acetyl bromide led to isomerization of the cyclic oxonium ion **B** to the corresponding *trans* isomer **D** before reaction with the bromide (Scheme 6). Thus, instead of the *syn*-isomer, the corresponding *trans*-acetoxy bromo ester *ent*-**16a** was formed. Accordingly, this sequence led to 3-amino-tyrosine ester *ent*-**20a** and ultimately to chondramide A analogue **2c**.

The structure of *ent*-**20a** could be proven by performing an aminohydroxylation on enoate (*E*)-**14** with (DHQD)₂PHAL as ligand (Scheme 7). In fact, the two compounds showed identical NMR spectra and optical rotation. The optical purity of *ent*-**20a** from the aminohydroxylation amounted to 98% whereas the material from the dihydroxylation route (Scheme 5) turned out to be 36% according to analysis of the derived tripeptide.

Therefore access to the 2L,3L-diastereomer **20b** of 3-amino-2-methoxy tyrosine was sought from a diol precursor by substituting the benzylic hydroxyl function with an ammonia equivalent. Dihydroxylation of *E*-enoate **14** in presence of (DHQD)₂PHAL provided *ent*-**15** in excellent yield (Scheme 8). Initially we tried substitution of the 3-OH with diphenylphosphoryl azide and diethylazodicarboxylate (DEAD). However, under these

conditions no product was formed. On the other hand, the Mitsunobu reaction on ester diol *ent*-**15** with hydrazoic acid[34] (HN₃) in presence of DEAD/Ph₃P gave the desired azide **18b** (47% yield) together with the corresponding *syn*-isomer (8% yield).[35] The two isomers could be separated by chromatography at this stage. The pure *anti* 2-hydroxy-3-azido ester **18b** was carried on to the methylation step (Me₃OBf₄, proton sponge).[24] Hydrogenation of diastereomer **19b-anti** led to 3-amino-2-methoxy-tyrosine derivative **20b**. According to the integration of the 2'-H atoms in the ¹H NMR spectrum of **24b**, the ee of **20b** and its precursors is 72%.

As shown in Scheme 9 condensation of **20b** with dipeptide acid **6** and the hydroxy ester **7** (three steps) led via tripeptide ester **24b** to acyclic chondramide A precursor **26b** in good overall yield. Analysis of the ¹H NMR spectrum of **24b** indicated an ee of 99% for the dihydroxylation reaction (**14** to *ent*-**15a**). The proven sequence consisting of cleavage of the *tert*-butyl groups from the carbamate and ester function followed by macrolactam formation and fluoride-induced silyl ether cleavage gave a reasonable yield of cyclodepsipeptide **2b**. The spectral data of this synthetic compound proved to be identical to the ones from chondramide A. In **2b** (CD₃OD) the methyl doublets appear at δ = 0.83, 0.86, 0.92, 1.08 (2-CH₃). The optical rotation of synthetic **2b** was $[\alpha]_D^{20}$ = +7.9 (*c* 0.80, MeOH), the literature reports $[\alpha]_D^{20}$ = +2.1 (*c* 2.0, MeOH).[8] Furthermore, LC-MS studies at the HZI in Braunschweig confirmed this assignment.

Conclusion

In conclusion we developed a concise route to the cyclodepsipeptide chondramide A (**2b**). The synthesis established the configuration of the 3-amino-2-methoxy tyrosine to be (2*S*,3*R*) or (2*L*,3*L*). For the synthesis of the 3-amino-2-methoxy-3-arylpropanoic ester **20b**, the diol *ent*-**15** was converted to the corresponding 3-azido-2-hydroxypropanoate **18b** via a regioselective Mitsunobu reaction. Extension of the aminoester **20b** on the amino function with dipeptide acid **6** and the carboxyl function with the hydroxy ester **7** secured the open chain precursor **26b** of chondramide A. Macrolactam formation could be achieved with TBTU in DMF. This strategy should now allow for the preparation of chon A analogues having modifications in all four subunits.

Experimental Section

4-[(Triisopropylsilyl)oxy]benzaldehyde (**13**)

To a stirred solution of 4-hydroxybenzaldehyde (3.64 g, 29.8 mmol) in CH₂Cl₂ (60 mL) at 0 °C were added Et₃N (4.96 mL, 3.62 mmol) and DMAP (0.364 g, 2.98 mmol). The mixture was stirred for 10 min before TIPSCl (7.00 mL, 32.8 mmol) was added. The mixture was allowed to warm to room temperature. After stirring for 18 h, the reaction mixture was treated with water (20 mL) and the aqueous layer was extracted with CH₂Cl₂ (2 × 30 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 20:1) to afford aldehyde **13** (7.95 g, 96%) as a colorless oil. TLC (petroleum ether/EtOAc, 20:1): *R*_f = 0.33; ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 1.10 (d, *J* = 7.4 Hz, 18H, Si(CH(CH₃)₂)₃), 1.22–1.34 (m, 3H, Si(CH(CH₃)₂)₃), 6.97 (d, *J* = 8.4 Hz, 2H, H_{ar}), 7.77 (d, *J* = 8.7 Hz, 2H, H_{ar}), 9.87 (s, 1H, CHO); ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = 12.7 (Si(CH(CH₃)₂)₃), 17.8 (Si(CH(CH₃)₂)₃), 120.3 (C_{ar}), 130.2 (C_{ar}), 131.9 (C_{ar}), 161.9 (C_{ar}), 190.8 (CO).

Methyl (2*E*)-3-{4'-[(triisopropylsilyl)oxy]phenyl}acrylate ((*E*)-**14**)

To a stirred solution of aldehyde **13** (2.19 g, 7.87 mmol) in CH₂Cl₂ (30 mL) was added (carboethoxymethylene)triphenylphosphorane (3.16 g, 9.44 mmol) in one portion. After 3 d

the reaction mixture was concentrated in vacuo and the crude product was purified by flash chromatography (petroleum ether/EtOAc, 20:1) to give enoate ((*E*)-**14**) (2.32 g, 88%) as a colorless oil. TLC (petroleum ether/EtOAc, 20:1): $R_f = 0.33$; ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 1.09 (d, $J = 7.4$ Hz, 18H, $\text{Si}(\text{CH}(\text{CH}_3)_2)_3$), 1.17–1.35 (m, 3H, $\text{Si}(\text{CH}(\text{CH}_3)_2)_3$), 3.78 (s, 3H, OCH_3), 6.29 (d, $J = 16.0$ Hz, 1H, 2-H), 6.86 (d, $J = 8.7$ Hz, 2H, H_{ar}), 7.40 (d, $J = 8.7$ Hz, 2H, H_{ar}), 7.63 (d, $J = 16.0$ Hz, 1H, 3-H); ^{13}C NMR (100 MHz, CDCl_3): δ [ppm] = 12.6 ($\text{Si}(\text{CH}(\text{CH}_3)_2)_3$), 17.8 ($\text{Si}(\text{CH}(\text{CH}_3)_2)_3$), 51.5 (OCH_3), 115.2 (C-2), 120.3 (C_{ar}), 127.4 (C_{ar}), 129.7 (C_{ar}), 144.6 (C-3), 158.3 (C_{ar}), 167.8 (CO); HMRS (ESI): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{30}\text{O}_3\text{Si}$ 357.18564, found 357.18555.

Methyl (2*S*,3*R*)-2,3-dihydroxy-3-{4'-[(triisopropylsilyl)oxy]phenyl}propanoate (*ent*-**15**)

To a stirred solution of enoate (*E*)-**14** (899 mg, 2.69 mmol) in *t*BuOH (2 mL) were added (DHQD)₂PHAL (10.0 mg, 0.013 mmol) and NMO [400 mg, 2.96 mmol, 60% in water (270 μL)]. The solution was cooled to 0 °C and $\text{K}_2\text{Os}_2(\text{OH})_4$ (2.00 mg, 0.005 mmol) was added. The reaction mixture was allowed to warm to room temperature and after stirring for 5 h, solid Na_2SO_3 (400 mg), water (2 mL) and EtOAc (5 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (2 $\times$ 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give diol (*ent*-**15**) (939 mg, 95%) as a colorless oil. TLC (petroleum ether/EtOAc, 2:1): $R_f = 0.25$; $[\alpha]^{20}_{\text{D}} = +1.0$ (*c* 1.00, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 1.08 (d, $J = 7.1$ Hz, 18H, $\text{Si}(\text{CH}(\text{CH}_3)_2)_3$), 1.15–1.32 (m, 3H, $\text{Si}(\text{CH}(\text{CH}_3)_2)_3$), 2.66 (d, $J = 6.4$ Hz, 1H, OH), 3.06 (d, $J = 6.1$ Hz, 1H, OH), 3.76 (s, 3H, OCH_3), 4.32 (dd, $J = 6.1$, 3.3 Hz, 1H, 2-H), 4.90 (dd, $J = 6.4$, 3.3 Hz, 1H, 3-H), 6.86 (d, $J = 8.7$ Hz, 2H, H_{ar}), 7.24 (d, $J = 7.9$ Hz, 2H, H_{ar}); ^{13}C NMR (100 MHz, CDCl_3): δ [ppm] = 12.6 ($\text{Si}(\text{CH}(\text{CH}_3)_2)_3$), 17.9 ($\text{Si}(\text{CH}(\text{CH}_3)_2)_3$), 52.7 (OCH_3), 74.4 (C-2), 74.8 (C-3), 119.8 (C_{ar}), 127.5 (C_{ar}), 132.2 (C_{ar}), 156.0 (C_{ar}), 173.3 (CO); HMRS (ESI): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{32}\text{O}_5\text{Si}$ 391.19112, found 391.190803.

Generation of a hydrazoic acid (HN_3) solution

To a stirred paste of NaN_3 (1.56 g, 24 mmol) and water (1.56 mL) was added toluene (8 mL). The mixture was cooled to 0 °C before concentrated sulfuric acid (0.581 mL, 12 mmol) was added dropwise. The organic layer was decanted and dried over Na_2SO_4 . To estimate the concentration, an aliquot (3 mL) of the hydrazoic acid solution in toluene was mixed with water (30 mL) and titrated with 0.3 N NaOH solution against phenolphthalein. Typically, concentrations of around 1.6 M were obtained.

Methyl (2*S*,3*S*)-3-azido-2-hydroxy-3-{4'-[(triisopropylsilyl)oxy]phenyl}propanoate (**18b**)

To a stirred solution of diol *ent*-**15** (800 mg, 2.17 mmol) in THF (5 mL) were added PPh_3 (683 mg, 2.61 mmol) and HN_3 (1.47 mL, 4.34 mmol, ~3M in toluene) at 0 °C, followed by dropwise addition of DEAD (1.29 mL, 2.82 mmol, 40% in toluene) within 4 h. The reaction mixture was allowed to warm to room temperature and after stirring for 14 h, saturated NaHCO_3 solution (4 mL) was added, followed by separation of the layers. The aqueous layer was extracted with EtOAc (2 $\times$ 15 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 9:1) provided azide **18b** (399 mg, 47%) as a colorless oil. The *syn*-diastereomer (66.0 mg, 8%, $R_f = 0.16$) was also obtained as a colorless oil. TLC (petroleum ether/EtOAc, 9:1): $R_f = 0.13$; $[\alpha]^{20}_{\text{D}} = +50.5$ (*c* 1.00, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): δ [ppm] = 1.08 (d, $J = 7.1$ Hz, 18H, $\text{Si}(\text{CH}(\text{CH}_3)_2)_3$), 1.17–1.30 (m, 3H, $\text{Si}(\text{CH}(\text{CH}_3)_2)_3$), 2.92 (s, 1H, OH), 3.68 (s, 3H, OCH_3), 4.49 (d, $J = 4.1$ Hz, 1H, 2-H), 4.80 (d, $J = 4.1$ Hz, 1H, 3-H), 6.86 (d, $J = 8.7$ Hz, 2H, H_{ar}), 7.18 (d, $J = 8.7$ Hz, 2H, H_{ar}); ^{13}C NMR (100 MHz, CDCl_3): δ [ppm] = 12.9 ($\text{Si}(\text{CH}(\text{CH}_3)_2)_3$), 18.2 ($\text{Si}(\text{CH}(\text{CH}_3)_2)_3$), 53.0 (OCH_3), 67.1 (C-3), 74.1 (C-2), 120.4 (C_{ar}), 126.9 (C_{ar}), 129.3 (C_{ar}), 157.0

(C_{ar}), 172.1 (CO); HMRS (ESI): [M+Na]⁺ calcd for C₁₉H₃₁N₃O₄Si 416.19760, found 416.197583.

Methyl (2S,3S)-3-azido-2-methoxy-3-{4'-[(triisopropylsilyl)oxy]phenyl}propanoate (19b)

To a stirred solution of alcohol **18b** (213 mg, 0.541 mmol) in CH₂Cl₂ (7 mL) was added Me₃OBf₄ (280 mg, 1.89 mmol) and proton sponge (580 mg, 2.71 mmol). After stirring for 20 h at room temperature in the dark, water (4 mL) was added and the mixture extracted with CH₂Cl₂ (2 × 10 mL). The combined organic extracts were washed with 1N HCl (5 mL), saturated NaHCO₃ solution (5 mL), and saturated NaCl solution (5 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to afford methyl ether **19b** (175 mg, 79%) as a colorless oil. TLC (petroleum ether/EtOAc, 9:1): *R*_f = 0.40; [α]²⁰_D = +36.6 (c 1.00, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 1.08 (d, *J* = 7.1 Hz, 18H, Si(CH(CH₃)₂)₃), 1.18–1.30 (m, 3H, Si(CH(CH₃)₂)₃), 3.34 (s, 3H, OCH₃), 3.71 (s, 3H, OCH₃), 3.95 (d, *J* = 6.6 Hz, 1H, 2-H) 4.68 (d, *J* = 6.9 Hz, 1H, 3-H), 6.86 (d, *J* = 8.7 Hz, 2H, H_{ar}), 7.22 (d, *J* = 8.4 Hz, 2H, H_{ar}); ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = 12.6 (Si(CH(CH₃)₂)₃), 17.8 (Si(CH(CH₃)₂)₃), 52.2 (OCH₃), 59.2 (OCH₃), 65.5 (C-3), 83.5 (C-2), 120.1 (C_{ar}), 127.5 (C_{ar}), 129.3 (C_{ar}), 156.5 (C_{ar}), 170.3 (CO); HMRS (ESI): [M+Na]⁺ calcd for C₂₀H₃₃N₃O₄Si 430.21325, found 430.21319.

Methyl (2S,3S)-3-amino-2-methoxy-3-{4'-[(triisopropylsilyl)oxy]phenyl}propanoate (20b)

To a stirred solution of azide **19b** (218 mg, 0.535 mmol) in MeOH (5 mL) was added a catalytic amount of Pd/C. After stirring for 18 h at room temperature the Pd/C was filtered off, and the filtrate concentrated in vacuo. The residue (98 mg, 98%) was used for the next step without further purification. TLC (petroleum ether/EtOAc, 3:7): *R*_f = 0.23; [α]²⁰_D = −6.2 (c 1.00, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 1.07 (d, *J* = 7.12 Hz, 18H, Si(CH(CH₃)₂)₃), 1.16–1.30 (m, 3H, Si(CH(CH₃)₂)₃), 2.20 (br s, 2H, NH₂), 3.37 (s, 3H, OCH₃), 3.59 (s, 3H, OCH₃), 4.00 (d, *J* = 5.3 Hz, 1H, 2-H), 4.26 (d, *J* = 5.3 Hz, 1H, 3-H), 6.83 (d, *J* = 8.4 Hz, 2H, H_{ar}), 7.17 (d, *J* = 8.4 Hz, 2H, H_{ar}); ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = 12.6 (Si(CH(CH₃)₂)₃), 17.8 (Si(CH(CH₃)₂)₃), 51.6 (OCH₃), 57.0 (C-3), 58.9 (OCH₃), 85.2 (C-2), 119.7 (C_{ar}), 128.0 (C_{ar}), 133.7 (C_{ar}), 155.5 (C_{ar}), 171.2 (CO); HMRS (ESI): [M+H]⁺ calcd for C₂₀H₃₅NO₄Si 382.24081, found 382.24086.

N-(*tert*-Butoxycarbonyl)-L-alanyl-*N*-((1S,2S)-2,3-dimethoxy-3-oxo-1-{4'-[(triisopropylsilyl)oxy]phenyl}propyl)-*N*-methyl-D-tryptophanamide (24b)

To a stirred solution of amine **20b** (151 mg, 0.388 mmol) and acid **6** (148 mg, 0.388 mmol) in DMF (7 mL) was added DIEA (197 μL, 1.16 mmol), HOBT (79.0 mg, 0.582 mmol) and TBTU (182 mg, 0.582 mmol) at 0 °C. After stirring for 2 h at 0 °C, water (4 mL) was added and the mixture extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with 1N HCl solution (5 mL), saturated NaHCO₃ solution (5 mL), water (5 mL) and saturated NaCl solution (5 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give tripeptide **24b** (212 mg, 73%) as a colorless foam. TLC (petroleum ether/EtOAc, 1:1): *R*_f = 0.29; [α]²⁰_D = +26.4 (c 1.00, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 0.90 (d, *J* = 6.4 Hz, 3H, Ala CH₃), 1.06 (d, *J* = 7.1 Hz, 18H, Si(CH(CH₃)₂)₃), 1.16–1.26 (m, 3H, Si(CH(CH₃)₂)₃), 1.40 (s, 9H, C(CH₃)₃), 2.94 (s, 3H, OCH₃), 3.26 (dd, *J* = 15.4, 5.2 Hz, 1H, CH₂), 3.33–3.39 (m, 1H, CH₂), 3.36 (s, 3H, NCH₃), 3.53 (s, 3H, OCH₃), 4.05 (d, *J* = 4.8 Hz, 1H, CHOCH₃), 4.47–4.55 (m, 1H, Ala CH), 5.37 (dd, *J* = 8.7, 5.1 Hz, 1H, β-Tyr CH), 5.44 (d, *J* = 7.4 Hz, 1H, Ala NH), 5.55 (dd, *J* = 9.7, 6.4 Hz, 1H, Trp CH), 6.75 (d, *J* = 8.7 Hz, 2H, β-Tyr H_{ar}), 6.91 (s, 1H, Trp H_{ar}), 7.04–7.11 (m, 4H, β-Tyr NH, β-Tyr H_{ar}, Trp H_{ar}), 7.14 (t, *J* = 7.5 Hz, 1H, Trp H_{ar}), 7.30 (d, *J* = 8.1 Hz, 1H, Trp H_{ar}), 7.58 (d, *J* = 7.6 Hz, 1H, Trp H_{ar}), 8.33 (br s, 1H, Trp NH); ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = 12.5 (Si(CH(CH₃)₂)₃), 17.8 (Si(CH(CH₃)₂)₃), 18.0 (Ala CH₃),

23.3 (CH₂), 28.3 (C(CH₃)₃), 30.7 (NCH₃), 46.7 (Ala CH), 51.7 (OCH₃)₃, 53.6 (β-Tyr CH), 56.7 (Trp CH), 59.1 (OCH₃), 79.5 (C(CH₃)₃), 82.4 (CHOCH₃), 110.6 (Trp C_{ar}), 111.1 (Trp C_{ar}), 118.4 (Trp C_{ar}), 119.4 (Trp C_{ar}), 119.8 (β-Tyr C_{ar}), 122.0 (Trp C_{ar}), 122.2 (Trp C_{ar}), 127.2 (Trp C_{ar}), 128.6 (β-Tyr C_{ar}), 129.1 (β-Tyr C_{ar}), 136.1 (Trp C_{ar}), 155.1 (CO), 155.7 (β-Tyr C_{ar}), 169.3 (CO), 170.2 (CO), 174.3 (CO); HMRS (ESI): [M+Na]⁺ calcd for C₄₀H₆₀N₄O₈Si 775.40726, found 775.406789.

***N*-(*tert*-Butoxycarbonyl)-L-alanyl-*N*-((1*S*,2*S*)-3-[[1'*R*,2'*R*,3'*E*,6'*S*]-7'-*tert*-butoxy-1',2',4',6'-tetramethyl-7'-oxo-3'-heptenyl]oxy]-2-methoxy-3-oxo-1-[4''-[(*triisopropylsilyl*)oxy]phenyl]propyl)-*N*-methyl-D-tryptophanamide (26b)**

To a stirred solution of tripeptide fragment **24b** (87.0 mg, 0.116 mmol) in 1,2-dichloroethane (2 mL) was added Me₃SnOH (105 mg, 0.580 mmol). After stirring for 5 h at 80 °C, TLC showed complete conversion and the reaction mixture was diluted with KHSO₄ (5% in water, 4 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo to afford the crude acid **25b** as a colorless foam. This crude product was dissolved in toluene (2.5 mL) and cooled to 0 °C. Et₃N (48.0 μL, 0.348 mmol) and 2,4,6-trichlorobenzoyl chloride (20.0 μL, 0.128) were added. After 30 min, hydroxy ester **7** (33.0 mg, 0.128 mmol) in toluene (0.2 mL) and DMAP (57.0 mg, 0.464 mmol) were added and the yellow reaction mixture was stirred for 1 h at 0 °C, allowed to warm to room temperature and stirred again for 1 h. Then, saturated NaHCO₃ solution (3 mL) was added and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 2:1) provided ester **26b** (78.0 mg, 69% over two steps) as a colorless foam. TLC (petroleum ether/EtOAc, 2:1): *R*_f = 0.19; [α]_D²⁰ = +11.3 (*c* 1.00, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 0.81 (d, *J* = 7.1 Hz, 3H, 2'-CH₃), 0.82 (d, *J* = 6.4 Hz, 3H, 1'-CH₃), 0.91 (d, *J* = 6.6 Hz, 3H, Ala CH₃), 1.01 (d, *J* = 6.9 Hz, 3H, 6'-CH₃), 1.05 (d, *J* = 7.1 Hz, 18H, Si(CH(CH₃)₂)₃), 1.14–1.27 (m, 3H, Si(CH(CH₃)₂)₃), 1.40 (s, 9H, C(CH₃)₃), 1.41 (s, 9H, C(CH₃)₃), 1.57 (s, 3H, 4'-CH₃), 1.93 (dd, *J* = 13.7, 7.6 Hz, 1H, CH₂), 2.34 (dd, *J* = 13.6, 6.7 Hz, 1H, CH₂), 2.40–2.49 (m, 2H, 6'-H, 2'-H), 2.95 (s, 3H, NCH₃), 3.24 (dd, *J* = 15.5, 9.9 Hz, 1H, Trp CH₂), 3.31–3.39 (m, 1H, Trp CH₂), 3.40 (s, 3H, OCH₃), 4.05 (d, *J* = 4.3 Hz, 1H, CHOCH₃), 4.48–4.59 (m, 2H, Ala CH, 1'-H), 4.86 (d, *J* = 9.4 Hz, 1H, 3'-H), 5.36 (dd, *J* = 8.7, 4.3 Hz, 1H, β-Tyr CH), 5.44 (d, *J* = 7.4 Hz, 1H, Ala NH), 5.52 (dd, *J* = 9.4, 6.6 Hz, 1H, Trp CH), 6.73 (d, *J* = 8.7 Hz, 2H, β-Tyr H_{ar}), 6.90 (s, 1H, Trp H_{ar}), 7.04 (d, *J* = 8.9 Hz, 1H, β-Tyr NH), 7.07–7.12 (m, 1H, Trp H_{ar}), 7.13–7.18 (m, 1H, Trp H_{ar}), 7.14 (d, *J* = 7.9 Hz, 2H, β-Tyr H_{ar}), 7.30 (d, *J* = 7.9 Hz, 1H, Trp H_{ar}), 7.58 (d, *J* = 7.6 Hz, 1H, Trp H_{ar}), 8.15 (br s, 1H, Trp NH); ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = 12.6 (Si(CH(CH₃)₂)₃), 16.4 (4'-CH₃), 16.6 (6'-CH₃), 17.2 (1'-CH₃), 17.6 (2'-CH₃), 17.9 (Si(CH(CH₃)₂)₃), 18.2 (Ala CH₃), 23.4 (Trp CH₂), 28.1 (C(CH₃)₃), 28.3 (C(CH₃)₃), 30.8 (NCH₃), 37.6 (C-2'), 38.6 (C-6'), 43.4 (C-5'), 46.7 (Ala CH), 53.6 (β-Tyr CH), 56.7 (Trp CH), 59.2 (OCH₃), 75.9 (C-1'), 79.5 (C(CH₃)₃), 79.9 (C(CH₃)₃), 81.9 (CHOCH₃), 110.9 (Trp C_{ar}), 111.1 (Trp C_{ar}), 118.6 (Trp C_{ar}), 119.5 (Trp C_{ar}), 119.6 (β-Tyr C_{ar}), 122.1 (Trp C_{ar}), 127.3 (Trp C_{ar}), 128.0 (C-3'), 129.1 (β-Tyr C_{ar}), 129.2 (Trp C_{ar}), 133.7 (C-4'), 136.1 (Trp C_{ar}), 155.1 (CO), 155.8 (β-Tyr C_{ar}), 169.2 (CO), 169.3 (CO), 174.2 (CO), 175.8 (CO); HMRS (ESI): [M + Na]⁺ calcd for C₅₄H₈₄N₄O₁₀Si 999.58489, found 999.584938.

Chondramide A (2b)

To a stirred solution of compound **26b** (40.0 mg, 0.041 mmol) in CH₂Cl₂ (1 mL) was added TFA (61.0 μL, 0.820 mmol) at 0 °C. After stirring for 22 h at 0 °C, the solvent was removed in vacuo. For azeotropic removal of TFA the residue was taken up in toluene (3 × 0.5 mL) and concentrated in vacuo each time. The crude product was dissolved in DMF (40 mL) and DIEA (56.0 μL, 0.328 mmol), HOBT (39.0 mg, 0.287 mmol) and TBTU (90.0 mg, 0.287 mmol) were added. The solution was stirred at room temperature for 20 h and then diluted with water (20

mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 × 20mL) and the combined organic layers were washed with 5% aqueous KHSO₄ solution (20 mL), water (20 mL), saturated NaHCO₃ solution (20 mL), water (2×20 mL) and saturated NaCl solution (20 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was dissolved in THF (0.5 mL) and TBAF·3H₂O (26.0 mg, 0.082 mmol) was added at 0 °C. After stirring for 1 h, the solvent was removed in vacuo followed by flash chromatography (petroleum ether/acetone, 3:2) of the residue to give depsipeptide **2b** (8.00 mg, 24% over three steps) as a colorless foam. TLC (petroleum ether/acetone, 3:2): R_f = 0.13; [α]_D²⁰ = +7.9 (c 0.80, MeOH); ¹H NMR (400 MHz, MeOD): δ [ppm] = 0.80 (d, *J* = 7.1 Hz, 3H, Ala CH₃), 0.86 (d, *J* = 6.1 Hz, 3H, 7-CH₃), 0.91 (d, *J* = 6.6 Hz, 3H, 6-CH₃), 1.08 (d, *J* = 6.8 Hz, 3H, 2-CH₃), 1.68 (s, 3H, 4-CH₃), 2.03 (dd, *J* = 13.0, 2.6 Hz, 1H, CH₂), 2.23 (dd, *J* = 12.6, 12.6 Hz, 1H, CH₂), 2.45–2.57 (m, 1H, 6-H), 2.59–2.72 (m, 1H, 2-H), 3.02 (d, *J* = 8.1 Hz, 2H, Trp CH₂), 3.08 (s, 3H, NCH₃), 3.14 (s, 3H, OCH₃), 3.85 (d, *J* = 10.1 Hz, 1H, CHOCH₃), 4.47–4.56 (m, 1H, 7-H), 4.73–4.81 (m, 1H, Ala CH), 4.81–4.87 (5-H), 5.03 (d, *J* = 9.9 Hz, 1H, β-Tyr CH), 5.52 (dd, *J* = 8.1, 8.1 Hz, 1H, Trp CH), 6.67 (d, *J* = 8.6 Hz, 2H, β-Tyr H_{ar}), 6.83 (s, 1H, Trp H_{ar}), 6.95–7.02 (m, 1H, Trp H_{ar}), 6.99 (d, *J* = 8.6 Hz, 2H, β-Tyr H_{ar}), 7.02–7.09 (m, 1H, Trp H_{ar}), 7.26 (d, *J* = 8.1 Hz, 1H, Trp H_{ar}), 7.57 (d, *J* = 7.8 Hz, 1H, Trp H_{ar}); ¹³C NMR (100 MHz, MeOD): δ [ppm] = 16.0 (4-CH₃), 17.9 (6-CH₃), 18.4 (Ala CH₃), 18.9 (7-CH₃), 19.1 (2-CH₃), 26.4 (Trp CH₂), 30.9 (NCH₃), 38.7 (C-6), 40.2 (C-2), 45.9 (Ala CH), 46.0 (C-3), 55.7 (β-Tyr CH), 56.9 (Trp CH), 58.3 (OCH₃), 79.2 (C-7), 83.4 (CHOCH₃), 110.1 (Trp C_{ar}), 112.2 (Trp C_{ar}), 116.1 (β-Tyr C_{ar}), 119.4 (Trp C_{ar}), 119.6 (Trp C_{ar}), 122.3 (Trp C_{ar}), 124.4 (Trp C_{ar}), 128.5 (Trp C_{ar}), 129.1 (C-5), 129.5 (β-Tyr C_{ar}), 131.3 (β-Tyr C_{ar}), 134.7 (C-4), 137.9 (Trp C_{ar}), 157.9 (β-Tyr C_{ar}), 171.3 (CO), 173.5 (CO), 174.9 (CO), 176.9 (CO); HMRS (ESI): [M+Na]⁺ calcd for C₃₆H₄₆N₄O₇ 669.32587, found 669.326358.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Structures of jasplakinolide and the chondramides. The atom numbering follows the suggestions from the isolation papers.

Figure 2.
Key fragments for the synthesis of chondramide A diastereomers.

Scheme 1.
Summary of the synthesis of hydroxy ester **7**.

Scheme 2.
Synthesis of the (2D,3L)-diastereomer **20a** via the *anti*-acetoxy bromo ester **16a**.

Scheme 3.

Synthesis of the (2D,3L)-3-amino-2-methoxy acid **20a** via an aminohydroxylation reaction.

Scheme 4.

Synthesis of diastereomer **2a** which does not correspond to chondramide A from the three building blocks **6**, **20a**, and **7**.

Scheme 5.

Attempted synthesis of amino ester **20b** and its incorporation in the cyclodepsipeptide. The obtained product **2c** did not correspond to chondramide A.

Scheme 6.

Postulated formation of *ent*-**16a** from diol **15b** via isomerization of cyclic oxonium ion **B** to **D**.

Scheme 7.

Independent synthesis of 3-amino-2-methoxy-tyrosine derivative *ent-20b* by aminhydroxylation.

Scheme 8.

Synthesis of the anti-diastereomer (2L,3L) **20b** via dihydroxylation and substitution of the benzylic hydroxyl group by azide.

Scheme 9.
Synthesis of chondramide A (**2b**).

Table Caption**Table 1**

Head 1 ^[a]	Head 2	Head 3 ^[b]	Head 4 ^[c]	Head 5
column 1	column 2	column 3	column 4	column 5
column 1	column 2	column 3	column 4	column 5

^[a]Table Footnote.

^[b]...