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# Total Synthesis and Configurational Assignment of Chondramide A

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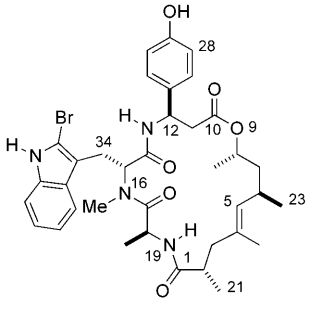
**Abstract:** The first total synthesis of the cyclodepsipeptide chondramide A (**2b**) is described. This depsipeptide is composed of four subunits, namely L-alanine, *N*-Me-D-tryptophan, 3-amino-2-methoxy-propionic acid (β-tyrosine derivative), and a 7-hydroxy-alkenoic acid. While the configuration of the stereogenic centers in the 7-hydroxy-alkenoic acid were known, the configuration of the tyrosine derivative required clarification and turned out to be (2*S*,3*R*) or (2L,3L), respectively. The synthesis of the 3-amino-2-methoxy-3-arylpropanoic ester **20b** relied on an asymmetric dihydroxylation yielding diol *ent*-**15a** followed by a regioselective Mitsunobu substitution leading to 3-azido-2-hydroxypropanoate **18b**. We could also show that the ester bond in the seco compound **26b** can be fashioned by a Mitsunobu esterification by using hydroxy ester (7*S*)-**7** and the tripeptide acid **25b**. This synthesis should allow for the preparation of various analogues.

**Keywords:** amino acids · asymmetric synthesis · cyclodepsipeptides · natural products · peptides

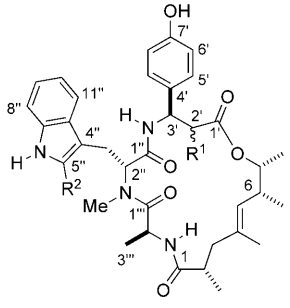
## Introduction

The actin system comprises a major part of the cytoskeleton of eukaryotic cells.[1] In nonmuscle cells there is a roughly equal proportion of polymeric F-actin and monomeric G-actin (globular). The polymerization of globular actin requires ATP. Among known natural products that disturb the actin system is cytochalasin, which blocks the polymerization 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 depolymerization of F-actin by binding between actin monomers.[4] 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 have gained clinical relevance as anticancer drugs.[5] Although not yet realized, small-molecule inhibitors of actin might have similar utility since cell division relies on actin turnover for cytokynesis and rapidly dividing cells should, therefore, be more susceptible to inhibition.

In addition to phalloidin, the jaspamide/chondramide family of cyclic depsipeptides[6] also stabilizes F-actin. Previous studies have shown that jasplakinolide binds competitively with phalloidin, which indicates that it interacts with a common binding site, despite being structurally dissimilar.[7] Jaspamide (Jasplakinolide, jas) (**1**; atom numbering follows the suggestions from the isolation papers) features a 19-membered macrocyclic ring. It was isolated from the marine sponge[8] *Jaspis splendens.* Related compounds were later




jasplakinolide (**1**)




| | $R^1$ | $R^2$ |
|---|---|---|
| chondramide A (**2**) | OMe | H |
| chondramide B (**3**) | OMe | Cl |
| chondramide C (**4**) | H | H |
| chondramide D (**5**) | H | Cl |

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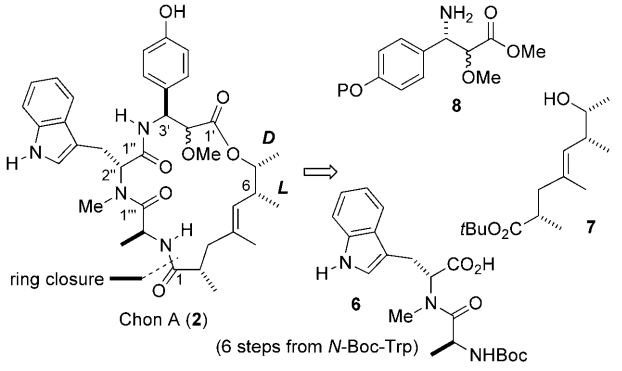
found in several other sponges.[9] While showing promising activity against cancer cell lines,[10] this activity is accompanied by significant toxicity. The major difference between the chondramides, which were isolated from the myxobacterium *Chondromyces crocatus*,[11] and jaspamide is a different polyketide moiety, resulting in an 18-membered ring in the chondramides. Quite recently the configurational assignment for chrondramide C (chon C) was achieved by independent total synthesis by the Waldmann[12] and Kalesse[13] groups. Not surprisingly, the 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[14] for the configuration of the ω-hydroxy acid required revision. We became interested in the synthesis of chondramide A (chon A), which is a closely related compound. Whereas the L-configuration for the amine-bearing stereocenters in the α-methoxy-β-tyrosine could be assumed, the configuration at the α-carbon atom (C2′) remained to be solved. In this paper we describe the syntheses of diastereomers of the methoxy-β-tyrosine subunit and their incorporation into the chrondramide scaffold leading to the total synthesis and configurational assignment of chon A.

## Results and Discussion

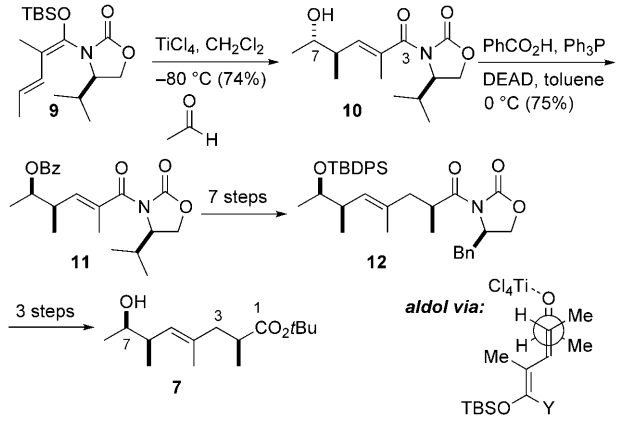
It was planned to close the macrocyclic ring by intramolecular amide formation (Scheme 1). The corresponding acyclic ester would originate from the known dipeptide acid **6**, a β-tyrosine isomer **8**, and the hydroxy ester **7**. The dipeptide acid **6** is available in six steps from *N*-Boc-D-tryptophan.[15]

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 alkylation to incorporate the last propionate unit (Scheme 2).[16] Overall this 12-step sequence allows for the preparation of ester **7** in gram amounts.

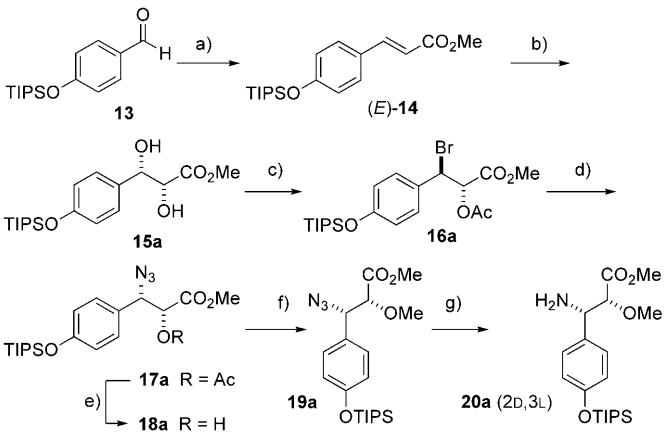
The *syn* isomer (2D,3L) of 3-amino-2-methoxyester **8** is similar to the taxol side chain.[17] Accordingly, strategies that came to use in the synthesis of this side chain, a 3-phenylisoserine, or related compounds were considered.[18] For example, asymmetric nitroaldol reactions,[19] the Staudinger reaction leading to β-lactam intermediates,[20] the Sharpless asymmetric aminohydroxylation,[21] or asymmetric aldol reactions of glycolates to imines are known to produce these types of structures.[22] And finally, chemoselective substitution reactions on 2,3-dihydroxy-3-arylpropanoates would provide the *syn* diastereomer of **8**.[23] We opted for the latter due to its operational simplicity (Scheme 3). Thus, by starting from 4-(triisopropylsilyloxy)benzaldehyde[24] (**13**) a Wittig reaction with (methoxycarbonylmethylene)triphenylphosphorane[25] provided cinnamate (*E*)-**14** in good yield. A subsequent asymmetric dihydroxylation[26] in the presence of the ligand $(DHQ)_2PHAL$ (AD-mix-α) and potassium osmate(VI) dihydrate, furnished an excellent yield of diol **15a**.




Scheme 1. Key fragments for the synthesis of chondramide A diastereomers. Boc = *tert*-butoxycarbonyl.




Scheme 2. Summary of the synthesis of hydroxy ester **7**. DEAD = diethylazodicarboxylate; TBDPS = *tert*-butyldiphenylsilyl; TBS = *tert*-butyldimethylsilyl.




Scheme 3. Synthesis of the (2D,3L)-diastereomer **20a** via the *anti*-acetoxy bromo ester **16a**. TIPS = triisopropylsilyl. a) $Ph_3PCHCO_2Me$, $CH_2Cl_2$, RT, 3 d, 88%; b) $(DHQ)_2PHAL$ = hydroquinine 1,4-phthalazinediyl diether, $K_2[OsO_2(OH)_4]$, *N*-methylmorpholine-*N*-oxide (NMO), *t*BuOH/$H_2O$, RT, 3 h, 92%; c) 1) $MeC(OMe)_3$, pyridinium *p*-toluenesulfonate (PPTS), $CH_2Cl_2$, RT, 90 min; 2) AcBr, $CH_2Cl_2$, RT, 90 min, 67%; d) NaN3, DMSO, RT, 4 h, 70%; e) NaOMe, MeOH, 0 °C, 30 min, 84%; f) $Me_3OBF_4$, proton sponge, $CH_2Cl_2$, RT, 24 h, 82%; g) Pd/C, $H_2$, MeOH, 20 h, 99%.

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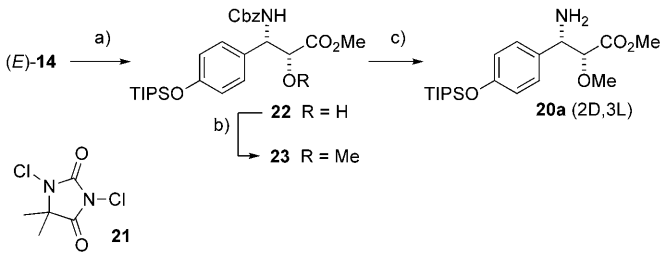
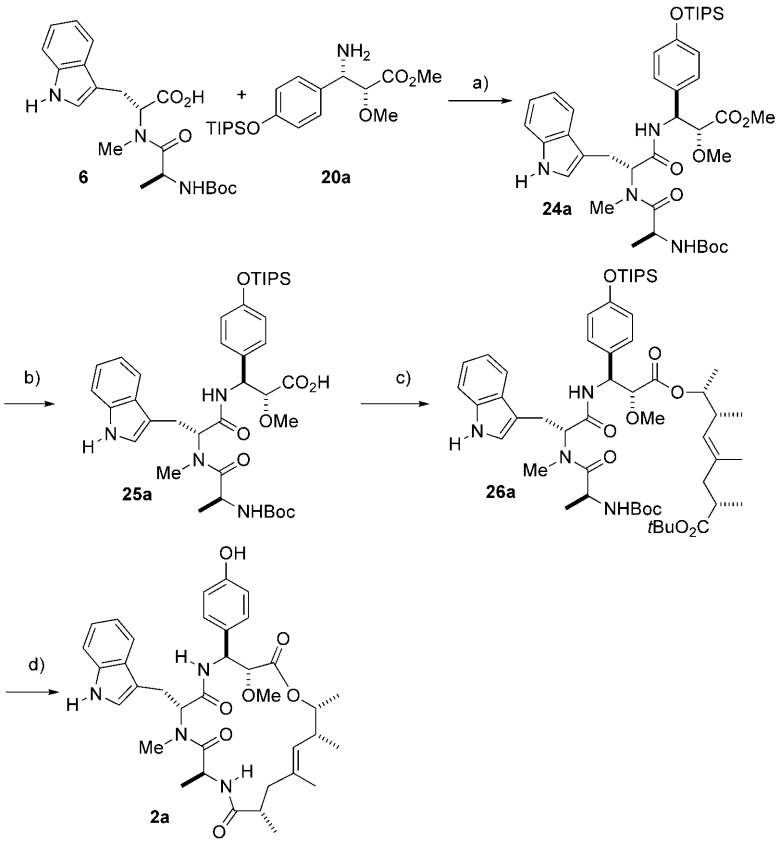
As has been described by Sharpless et al.[23] the benzylic alcohol can be substituted by bromide through the reaction of the diol with trimethyl orthoacetate, and treatment of the intermediate mixed orthoester with acetyl bromide. This way, a 67% yield of acetoxy bromo ester **16a** could be secured 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). After saponification of the acetate, the 2-hydroxy group of **18a** was methylated by using Meerwein's salt ($Me_3OBF_4$)[27] and proton sponge in dichloromethane. At this stage, proof of the regiochemistry of the bromination and, therefore, also the azide introduction came from a HMBC spectrum of **18a**. Thus, 3′-H ($\delta = 4.75$ ppm (d, $J =$ 3.3 Hz), chon A numbering) showed cross-peaks to C-4′ and C-5′. A final hydrogenation of azide **19a** in the presence of Pd/C in methanol led to the desired *syn*-configured amino ester **20a**. The enantiomeric excess (*ee*) value of **15a** and the propanoate derivatives derived from it could be estimated at the stage of the tripeptide ester **24a** to be 62% by integration of the corresponding 2′-H protons. This *ee* value could be confirmed by chiral HPLC (Eurocel 03).

An alternative route to the (2D,3L)-β-tyrosine **20a** was based on an aminohydroxylation reaction[28,29,30] of cinnamate (*E*)-**14** by using benzylcarbamate, 1,3-dichloro-5,5-dimethylhydantoin,[31] and $(DHQ)_2PHAL$ in a propanol/water mixture (Scheme 4). This produced the Cbz-protected 2-hydroxy-3-amino acid ester **22**. Reductive cleavage of the Cbz-protecting group ($H_2$, Pd/C, MeOH) gave β-tyrosine **20a** as well. In this case, the etherification was performed with MeI and $Ag_2O$ in acetone. The *ee* value of **20a** was estimated to be 90% by chiral HPLC (Eurocel 01).

Construction of the corresponding cyclodepsipeptide started with dipeptide acid **6** (Scheme 5). This acid was condensed with β-tyrosine derivative **20a** by using TBTU in the presence of additional 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 alpha 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.[32] The crude carboxylic acid could then be esterified with hydroxyester **7** under Yamaguchi conditions.[33] This way the chon A precursor **26a** could be secured in 64% yield. At this stage it was possible to remove the diastereomer resulting from the minor enantiomer of **20a** by chromatography. The macrocyclization required




Scheme 4. Synthesis of the (2D,3L)-3-amino-2-methoxy acid **20a** by an aminohydroxylation reaction. Cbz = carbobenzyloxy. a) $BnOC(O)NH_2$, NaOH, $(DHQ)_2PHAL$, **21**, $K_2[OsO_2(OH)_4]$, *n*PrOH/$H_2O$, 0 °C to RT, 22 h, 56%; b) $Ag_2O$, MeI, acetone, RT, 80%; c) Pd/C, $H_2$, MeOH, 24 h, 98%.




Scheme 5. Synthesis of diastereomer **2a**, which does not correspond to chondramide A, from the three building blocks **6**, **20a**, and **7**. a) diisoproylethylamine (DIEA), hydroxybenzotriazole (HOBt), 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), DMF, 0 °C, 2 h, 68%; b) $Me_3SnOH$, 1,2-dichloroethane (1,2-DCE); c) $Cl_3C_6H_2COCl$, $Et_3N$, 4-dimethylaminopyridine (DMAP), **7**, toluene, 0 °C to RT, 2 h, 64% (2 steps); d) 1) trifluoroacetic acid (TFA), $CH_2Cl_2$, 0 °C, 22 h; 2) HOBt, TBTU, DIEA, DMF, RT, 20 h; 3) tetrabutylammonium fluoride (TBAF), THF, 0 °C, 1 h, 29% (3 steps).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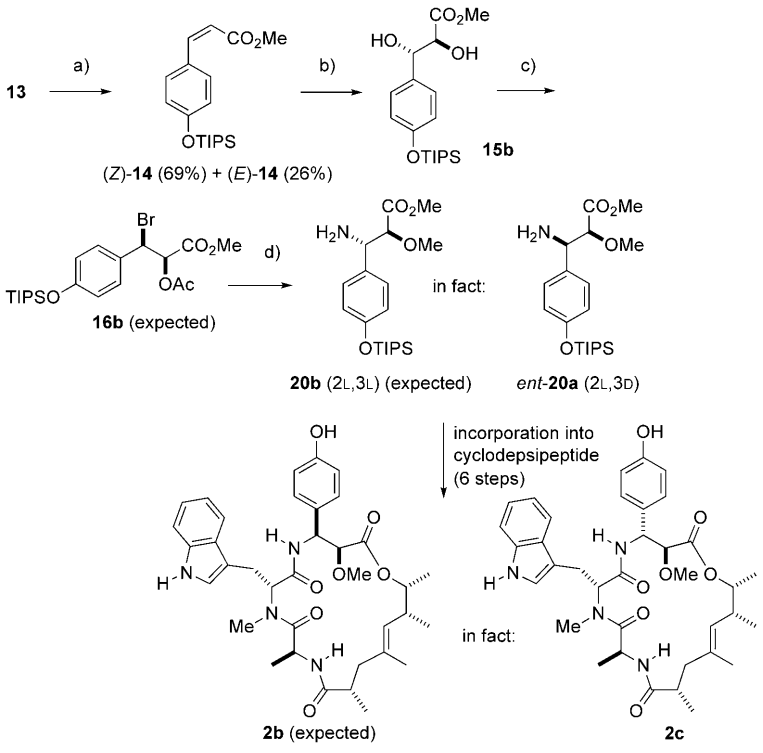
cleavage of the *N*-Boc group and the *tert*-butylester. This was done with TFA in dichloromethane. It seemed that the *N*-Boc group cleaved quite easy, whereas the ester cleavage necessitated longer reaction times. After concentration of the reaction mixture, macrolactam formation on the residue was carried out in DMF (0.001 M) in the presence of TBTU, HOBt, and Hünig's base.[34,35] After workup, the crude cyclic depsipeptide was treated with TBAF in THF to cleave the phenolic triisopropylsilyl ether. Careful inspection of the NMR spectroscopic data showed that macrocycle **2a** did not correspond to natural chondramide A. The macrocycles show characteristic NMR spectroscopic signatures for the four methyl doublets. In **2a** ($CD_3OD$) they appear at $\delta =$ 0.81, 0.91, 0.92, 1.09 ppm (2-$CH_3$).

Therefore, we surmised the (2L,3L)-3-amino-2-methoxy-propionic acid 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[36] (NaH, THF) was performed that resulted in a 73:27 *Z*/*E* mixture of enoates **14** from which (*Z*)-**14** could be separated by flash chromatography (Scheme 6). By using (*Z*)-**14**, a sequence of dihydroxylation (with $(DHQ)_2PHAL$ as the 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 the Supporting Information). In this sequence, the diastereomer resulting from the minor enantiomer of **20a** could be separated by chromatography at the stage of ester **26c**. 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 7). Thus, instead of the *syn* isomer, the corresponding *trans*-acetoxy bromo ester *ent*-**16a** was formed. Accordingly, this sequence led to 3-amino-2-methoxy-propionic 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 the ligand (Scheme 8). In fact, the two compounds showed identical NMR spectra and signs for the optical rotation. The measured values for *ent*-**20a** were $[\alpha]_D^{20} = -1.1$ ($c = 1.00$ in $CH_2Cl_2$, from enoate (*Z*)-**14** through dihydroxylation (cf. Scheme 6)) and −8.2 ($c = 1.00$ in $CH_2Cl_2$, prepared through aminohydroxylation from enoate (*E*)-**14** (cf. Scheme 8)), respectively. The enantiomeric excess of *ent*-**20a** from the aminohydroxylation amounted to 94%, whereas the material from the dihydroxylation route (Scheme 6) turned out to be 36% according to $^1H$ NMR spectroscopic analysis of the derived tripeptide.

Therefore, access to the 2L,3L-diastereomer **20b** of 3-amino-2-methoxy-propionic acid 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 9). Initially, we tried substitution of the 3-OH with diphenylphosphoryl azide and DEAD. However, under these conditions no product was formed. On the other hand, the




Scheme 6. Attempted synthesis of amino ester **20b** and its incorporation in the cyclodepsipeptide. The obtained product **2c** did not correspond to chondramide A. a) $(PhO)_2P(O)CH_2CO_2Me$, NaH, THF, −89°C to RT, 90 min; b) $(DHQ)_2PHAL$, $K_2[OsO_2(OH)_4]$, NMO, *t*BuOH/$H_2O$, RT, 20 h, 90%; c) 1) $MeC(OMe)_3$, PPTS, $CH_2Cl_2$, RT, 90 min; 2) AcBr, $CH_2Cl_2$, RT, 90 min, 65%; d) 1) $NaN_3$, DMSO, 67%; 2) NaOMe, MeOH, 78%; 3) $Me_3OBF_4$, $CH_2Cl_2$, 73%; 4) $H_2$, Pd/C, 98%.

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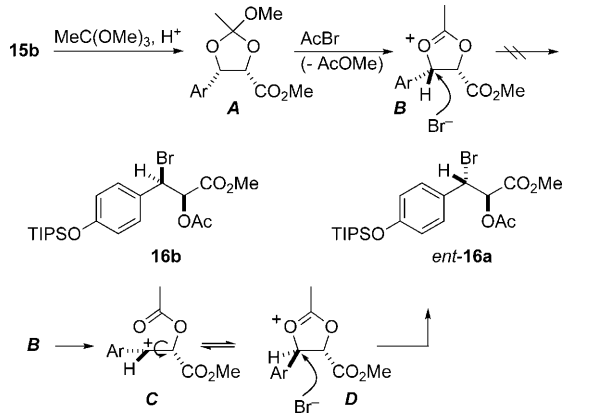
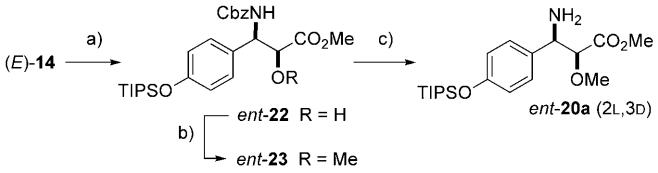
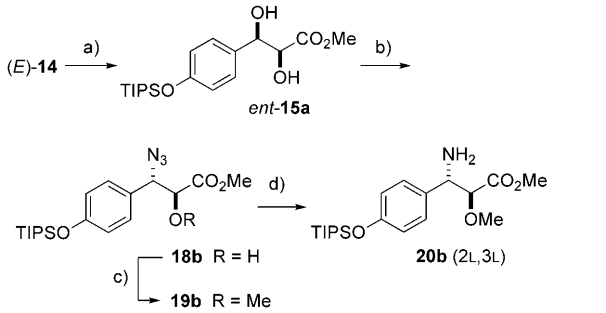



Scheme 7. Postulated formation of *ent*-**16a** from diol **15b** by isomerization of cyclic oxonium ion **B** to **D**.




Scheme 8. Independent synthesis of 3-amino-2-methoxy-propionic acid derivative *ent*-**20b** by aminhydroxylation. a) $BnOC(O)NH_2$, NaOH, $(DHQD)_2PHAL$, **21**, $K_2[OsO_2(OH)_4]$, *n*PrOH/$H_2O$, 0 °C to RT, 22 h, 52 %; b) $Ag_2O$, MeI, acetone, RT, 74 %; c) Pd/C, $H_2$, MeOH, 24 h, 91 %.




Scheme 9. Synthesis of the *anti*-diastereomer (2L,3L) **20b** by dihydroxylation and substitution of the benzylic hydroxyl group by azide. a) $(DHQD)_2PHAL$, $K_2[OsO_2(OH)_4]$, NMO, *t*BuOH/$H_2$, RT, 5 h, 95 %; b) $PPh_3$, $HN_3$, DEAD, THF, 0 °C to RT, 18 h, 47 %; c) $Me_3OBF_4$, proton sponge, $CH_2Cl_2$, 79 %; d) Pd/C, $H_2$, MeOH, 18 h, 98 %.

Mitsunobu reaction on ester diol *ent*-**15** with hydrazoic acid[37] ($HN_3$) in presence of DEAD/$Ph_3P$ gave the desired azide **18b** (47 % yield) together with the corresponding *syn* isomer (8 % yield).[38] 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 ($Me_3OBF_4$, proton sponge).[27] Hydrogenation of diastereomer *anti*-**19b** led to 3-amino-2-methoxy-propionic acid derivative **20b**. According to the integration of the 2′-H atoms in the $^1$H NMR spectrum of **24b**, the *ee* of **20b** and its precursors is 72 %. This value was confirmed by chiral HPLC (Eurocel 03).

As shown in Scheme 10 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 $^1$H NMR spectrum of **24b** indicated an *ee* of 72 % for the dihydroxylation reaction (**14** to *ent*-**15a**). The *ee* values of **15a** and its derivatives depend very much on the used oxidant. Thus, instead of using NMO[23] (72 % *ee*), $K_3[Fe(CN)_6]$ led to an *ee* of 99 %. 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**. If β-tyrosine derivative **20b** with an *ee* of 72 % (NMO as oxidant) was used for the synthesis of **2b** the minor diastereomer could be separated by chromatography on the final stage. The spectral data of this synthetic compound proved to be identical to the ones from chondramide A. In **2b** ($CD_3OD$), the methyl doublets appear at $\delta = 0.80$, 0.86, 0.92, 1.08 ppm (2-$CH_3$). The optical rotation of synthetic **2b** was $[\alpha]_D^{20} = +7.9$ ($c = 0.80$ in MeOH), the literature reports $[\alpha]_D^{20} = +2.1$ ($c = 2.0$ in MeOH).[11] Furthermore, LCMS studies at the HZI in Braunschweig confirmed this assignment. In the context of this synthesis, we also explored a more direct access to the depsipeptide **26b** (Scheme 10). Since the 7-epimer of hydroxy ester **7**, compound (7*S*)-**7** is more easily available by the vinylogous aldol approach relative to **7** we investigated the esterification under Mitsunobu conditions.[39] In fact, reaction of acid **25b** with alcohol (7*S*)-**7** in presence of $Ph_3P$ and DEAD gave rise to ester **26b** in reasonable yield.

## Conclusion

We have developed a concise route to the cyclodepsipeptide chondramide A (**2b**). The synthesis established the configuration of the 3-amino-2-methoxypropanoic acid to be (2*S*,3*R*) or (2L,3L). 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** by 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 with modifications in all four subunits.

## Experimental Section

### Determination of the *ee* values for the products of aminohydroxylation and dihydroxylation reactions

*Materials and methods*: The derivatized cellulose-based silica chiral stationary phases (CSP) Eurocel 01 and Eurocel 03 had a particle size of

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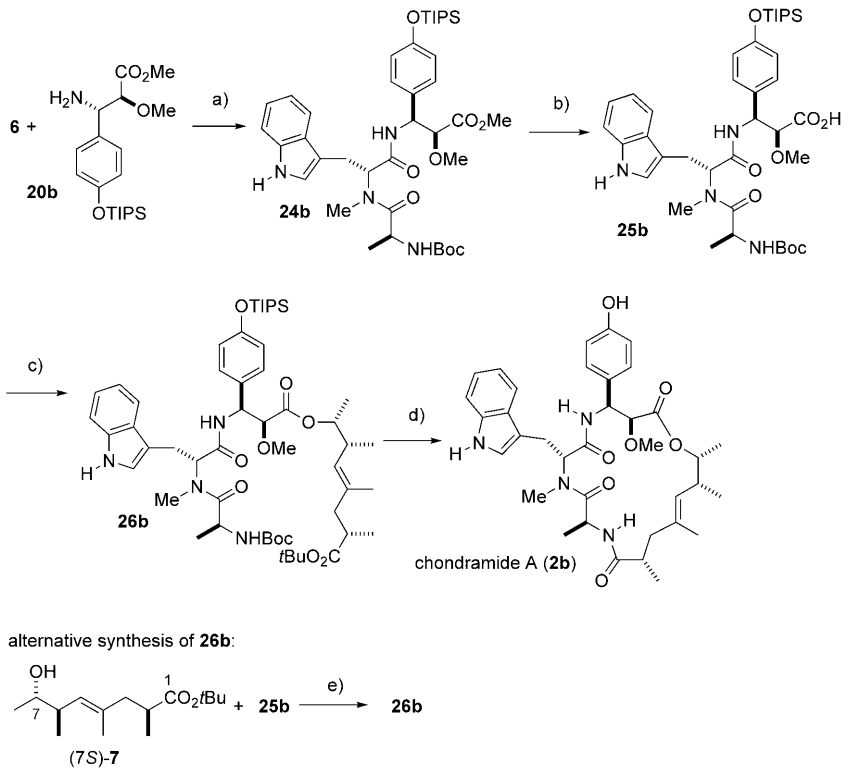


Scheme 10. Synthesis of chondramide A (**2b**). a) DIEA, HOBt, TBTU, DMF, 0 °C, 2 h, 73 %; b) $Me_3SnOH$, 1,2-DCE, 80 °C, 5 h; c) $Cl_3C_6H_2COCl$, $Et_3N$, DMAP, **7**, toluene, 0 °C to RT, 2 h, 69 % (2 steps); d) 1) TFA, $CH_2Cl_2$, 0 °C, 22 h; 2) HOBt, TBTU, DIEA, DMF, RT, 20 h; 3) TBAF, THF, 0 °C, 1 h, 24 % (3 steps); e) $PPh_3$, DEAD, THF, 0 °C to RT, 5 h, 63 % (from **24b**).

5 μm and a pore diameter of 1000 Å with an approximate surface area of 25 $m^2 g^{-1}$ donated by Knauer GmbH, Berlin (Germany). The chiral selector of Eurocel 01 is the 3,5-dimethyl phenyl carbamate group and 4-methyl benzoate for the Eurocel 03 stationary phase. The HPLC separations of **15a**, *ent*-**15a**, **22**, and *ent*-**22** on the Eurocel columns were carried out with a Knauer Smartline System equipped with a Smartline Manager 5000 with degasser and LPG unit, a pump 1000, PDA detector 2800, and a Smartline column oven. The samples were introduced by use of an autosampler 3950. The chromatograms obtained were analyzed with the help of ChromGate software.

*Dihydroxyester **15a***: Column: Eurocel 03, 5 μm, 250×4.6 mm, isocratic, hexane/2-propanol (98.3:1.7 v/v), 1 mL $min^{-1}$, 20 °C, UV: 210 nm; dihydroxylation carried out with NMO as the oxidant, 62 % *ee*; $t_r$ (minor) 33.0, $t_r$ (major) 39.9 min; dihydroxyester *ent*-**15a**: dihydroxylation carried out with NMO as the oxidant, 72 % *ee*; dihydroxylation carried out with $K_3[Fe(CN)_6]$ as the oxidant, 99 % *ee*.

*Carbamate **22***: Column: Eurocel 01, 5 μm, 250×4.6 mm, isocratic, methanol/water (95:5 v/v), 1 mL $min^{-1}$, 20 °C, UV: 220 nm, 90 % *ee*; $t_r$ (minor) 6.2, $t_r$ (major) 7.3 min; carbamate *ent*-**22**: 94 % *ee*.

**Aldehyde 13**: $Et_3N$ (4.96 mL, 3.62 mmol) and DMAP (0.364 g, 2.98 mmol) were added to a stirred solution of 4-hydroxybenzaldehyde (3.64 g, 29.8 mmol) in $CH_2Cl_2$ (60 mL) at 0 °C. 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 $CH_2Cl_2$ (2×30 mL). The combined organic layers were dried over $Na_2SO_4$, 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; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=1.10 (d, $J$=7.4 Hz, 18H; $Si(CH(CH_3)_2)_3$), 1.22–1.34 (m, 3H; $Si(CH(CH_3)_2)_3$), 6.97 (d, $J$=8.4 Hz, 2H; $H_{ar}$), 7.77 (d, $J$=8.7 Hz, 2H; $H_{ar}$), 9.87 ppm (s, 1H; CHO); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=12.7 ($Si(CH(CH_3)_2)_3$), 17.8 ($Si(CH(CH_3)_2)_3$), 120.3 ($C_{ar}$), 130.2 ($C_{ar}$), 131.9 ($C_{ar}$), 161.9 ($C_{ar}$), 190.8 ppm (CO).

**Compound (*E*)-14**: (Carbomethoxymethylene)triphenylphosphorane (3.16 g, 9.44 mmol) was added in one portion to a stirred solution of aldehyde **13** (2.19 g, 7.87 mmol) in $CH_2Cl_2$ (30 mL). 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; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=1.09 (d, $J$=7.4 Hz, 18H; $Si(CH(CH_3)_2)_3$), 1.17–1.35 (m, 3H; $Si(CH(CH_3)_2)_3$), 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 ppm (d, $J$=16.0 Hz, 1H; 3-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=12.6 ($Si(CH(CH_3)_2)_3$), 17.8 ($Si(CH(CH_3)_2)_3$), 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 ppm (CO); HMRS (ESI): $m/z$: calcd for $C_{19}H_{30}O_3Si$: 357.18564 $[M+Na]^+$; found: 357.18555.

**Compound *ent*-15**: *By using NMO as the oxidant*: $(DHQD)_2PHAL$ (10.0 mg, 0.013 mmol) and NMO (400 mg, 2.96 mmol, 60 % in water (270 μL)) were added to a stirred solution of enoate (*E*)-**14** (899 mg, 2.69 mmol) in *t*BuOH (2 mL). The solution was cooled to 0 °C and $K_2[Os_2O_2(OH)_4]$ (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 (2×10 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. $[\alpha]_D^{20}$=+1.0 ($c$=1.00 in $CH_2Cl_2$).

*By using $K_3[Fe(CN)_6]$ as the oxidant*: $K_2[Os_2O_2(OH)_4]$ (4.00 mg, 0.012 mmol) and methanesulfonamide (0.274 g, 2.89 mmol) were added to a stirred mixture of $K_3[Fe(CN)_6]$ (2.85 g, 8.66 mmol), $(DHQD)_2PHAL$ (23 mg, 0.029 mmol), and $K_2CO_3$ (1.20 g, 8.66 mmol) in *t*BuOH/$H_2O$ 1:1 (28 mL). The mixture was stirred for 15 min and then enoate (*E*)-**14** (0.965 g, 2.89 mmol) in *t*BuOH (2 mL) was added in one portion. The reaction mixture was cooled to 0 °C, slowly allowed to warm to room temperature and stirred for 20 h. Then solid $Na_2SO_3$ (5.00 g) and EtOAc (20 mL) were added and the aqueous layer was extracted with EtOAc (2×20 mL). The combined organic layers were washed with 1 N NaOH solution (30 mL), 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**) (0.885 g, 83 %) as a colorless oil. $[\alpha]_D^{20}$=+1.8 ($c$=1.00 in $CH_2Cl_2$); TLC (petroleum ether/EtOAc 2:1): $R_f$=0.25; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=1.08 (d, $J$=7.1 Hz, 18H; $Si(CH(CH_3)_2)_3$), 1.15–1.32 (m, 3H; $Si(CH(CH_3)_2)_3$), 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 ppm (d, $J$=7.9 Hz, 2H; $H_{ar}$); $^{13}$C NMR (100 MHz,

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$CDCl_3$): $\delta = 12.6$ ($Si(CH(CH_3)_2)_3$), 17.9 ($Si(CH(CH_3)_2)_3$), 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 ppm (CO); HMRS (ESI): *m/z*: calcd for $C_{19}H_{32}O_5Si$: 391.19112 $[M+Na]^+$; found: 391.190803.

**Generation of a hydrazoic acid ($HN_3$) solution**: Toluene (8 mL) was added to a stirred paste of $NaN_3$ (1.56 g, 24 mmol) and water (1.56 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 hydazoic 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.

**Compound 18b**: $PPh_3$ (683 mg, 2.61 mmol) and $HN_3$ (2.7 mL, 4.34 mmol, ~1.6 M in toluene) were added to a stirred solution of diol *ent*-**15** (800 mg, 2.17 mmol) in THF (5 mL) 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× 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): $R_f = 0.13$; $[\alpha]_D^{20} = +50.5$ ($c = 1.00$ in $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 1.08$ (d, $J = 7.1$ Hz, 18H; $Si(CH(CH_3)_2)_3$), 1.17–1.30 (m, 3H; $Si(CH(CH_3)_2)_3$), 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 ppm (d, $J = 8.7$ Hz, 2H; $H_{ar}$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 12.9$ ($Si(CH(CH_3)_2)_3$), 18.2 ($Si(CH(CH_3)_2)_3$), 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 ppm (CO); HMRS (ESI): *m/z*: calcd for $C_{19}H_{31}N_3O_4Si$: 416.19760 $[M+Na]^+$; found: 416.197583.

**Compound 19b**: $Me_3OBF_4$ (280 mg, 1.89 mmol) and proton sponge (580 mg, 2.71 mmol) were added to a stirred solution of alcohol **18b** (213 mg, 0.541 mmol) in $CH_2Cl_2$ (7 mL). After stirring for 20 h at room temperature in the dark, water (4 mL) was added and the mixture extracted with $CH_2Cl_2$ (2×10 mL). The combined organic extracts were washed with 1 N HCl (5 mL), saturated $NaHCO_3$ solution (5 mL), and saturated NaCl solution (5 mL). The extracts were then dried over $Na_2SO_4$, 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): $R_f = 0.40$; $[\alpha]_D^{20} = +36.6$ ($c = 1.00$ in $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 1.08$ (d, $J = 7.1$ Hz, 18H; $Si(CH(CH_3)_2)_3$), 1.18–1.30 (m, 3H; $Si(CH(CH_3)_2)_3$), 3.34 (s, 3H; $OCH_3$), 3.71 (s, 3H; $OCH_3$), 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 ppm (d, $J = 8.4$ Hz, 2H; $H_{ar}$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 12.6$ ($Si(CH(CH_3)_2)_3$), 17.8 ($Si(CH(CH_3)_2)_3$), 52.2 ($OCH_3$), 59.2 ($OCH_3$), 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 ppm (CO); HMRS (ESI): *m/z*: calcd for $C_{20}H_{33}N_3O_4Si$: 430.21325 $[M+Na]^+$; found: 430.21319.

**Compound 20b**: A catalytic amount of Pd/C was added to a stirred solution of azide **19b** (218 mg, 0.535 mmol) in MeOH (5 mL). 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): $R_f = 0.23$; $[\alpha]_D^{20} = -6.2$ ($c = 1.00$ in $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 1.07$ (d, $J = 7.12$ Hz, 18H; $Si(CH(CH_3)_2)_3$), 1.16–1.30 (m, 3H; $Si(CH(CH_3)_2)_3$), 2.20 (br s, 2H; $NH_2$), 3.37 (s, 3H; $OCH_3$), 3.59 (s, 3H; $OCH_3$), 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 ppm (d, $J = 8.4$ Hz, 2H; $H_{ar}$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 12.6$ ($Si(CH(CH_3)_2)_3$), 17.8 ($Si(CH(CH_3)_2)_3$), 51.6 ($OCH_3$), 57.0 (C-3), 58.9 ($OCH_3$), 85.2 (C-2), 119.7 ($C_{ar}$), 128.0 ($C_{ar}$), 133.7 ($C_{ar}$), 155.5 ($C_{ar}$), 171.2 ppm (CO); HMRS (ESI): *m/z*: calcd for $C_{20}H_{35}NO_4Si$: 382.24081 $[M+H]^+$; found: 382.24086.

**Compound 24b**: DIEA (197 μL, 1.16 mmol), HOBt (79.0 mg, 0.582 mmol), and TBTU (182 mg, 0.582 mmol) were added to a stirred solution of amine **20b** (151 mg, 0.388 mmol) and acid **6** (148 mg, 0.388 mmol) in DMF (7 mL) 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 1 N HCl solution (5 mL), saturated $NaHCO_3$ solution (5 mL), water (5 mL), and saturated NaCl solution (5 mL), dried over $Na_2SO_4$, 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): $R_f = 0.29$; $[\alpha]_D^{20} = +26.4$ ($c = 1.00$ in $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 0.90$ (d, $J = 6.4$ Hz, 3H; Ala $CH_3$), 1.06 (d, $J = 7.1$ Hz, 18H; $Si(CH(CH_3)_2)_3$), 1.16–1.26 (m, 3H; $Si(CH(CH_3)_2)_3$), 1.40 (s, 9H; $C(CH_3)_3$), 2.94 (s, 3H; $NCH_3$), 3.26 (dd, $J = 15.4$, 5.2 Hz, 1H; $CH_2$), 3.33–3.39 (m, 1H; $CH_2$), 3.36 (s, 3H; $OCH_3$), 3.53 (s, 3H; $OCH_3$), 4.05 (d, $J = 4.8$ Hz, 1H; $CHOCH_3$), 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 ppm (br s, 1H; Trp NH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 12.5$ ($Si(CH(CH_3)_2)_3$), 17.8 ($Si(CH(CH_3)_2)_3$), 18.0 (Ala $CH_3$), 23.3 ($CH_2$), 28.3 ($C(CH_3)_3$), 30.7 ($NCH_3$), 46.7 (Ala CH), 51.7 ($OCH_3$), 53.6 (β-Tyr CH), 56.7 (Trp CH), 59.1 ($OCH_3$), 79.5 ($C(CH_3)_3$), 82.4 ($CHOCH_3$), 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 ppm (CO); HMRS (ESI): *m/z*: calcd for $C_{40}H_{60}N_4O_8Si$: 775.40726 $[M+Na]^+$; found: 775.406789.

**Compound 26b**: *By Yamaguchi esterification*: $Me_3SnOH$ (105 mg, 0.580 mmol) was added to a stirred solution of tripeptide fragment **24b** (87.0 mg, 0.116 mmol) in 1,2-dichloroethane (2 mL). After stirring for 5 h at 80 °C, TLC showed complete conversion and the reaction mixture was diluted with $KHSO_4$ (5 % in water, 4 mL). The aqueous layer was extracted with EtOAc (2×5 mL) and the combined organic layers were dried over $Na_2SO_4$, 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. $Et_3N$ (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 $NaHCO_3$ solution (3 mL) was added and the aqueous layer was extracted with EtOAc (2×5 mL). The combined organic layers were dried over $Na_2SO_4$, 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.

*By Mitsunobu esterification*: $Me_3SnOH$ (30.0 mg, 0.165 mmol) was added to a stirred solution of tripeptide fragment **24b** (25.0 mg, 0.033 mmol) in 1,2-dichloroethane (1 mL). After stirring for 5 h at 80 °C, TLC showed complete conversion and the reaction mixture was diluted with $KHSO_4$ (5 % in water, 2 mL). The aqueous layer was extracted with EtOAc (2× 3 mL) and the combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to afford the crude acid **25b** as a colorless foam. This crude product and alcohol (7*S*)-**7** (13.0 mg, 0.050 mmol) were dissolved in THF (2 mL) and $Ph_3P$ (26.0 mg, 0.099 mmol) was added at 0 °C. This was followed by the dropwise addition of DEAD (0.045 mL, 0.099 mmol, 40 % in toluene). The cooling bath was removed and the mixture stirred for 4 h at room temperature. The reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give ester **26b** (20 mg, 63 % over two steps) as a colorless foam. TLC (petroleum ether/EtOAc 2:1): $R_f = 0.19$; $[\alpha]_D^{20} = +11.3$ ($c = 1.00$ in $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 0.81$ (d, $J = 7.1$ Hz, 3H; 2′-$CH_3$), 0.82 (d, $J = 6.4$ Hz, 3H; 1′-$CH_3$), 0.91 (d, $J = 6.6$ Hz, 3H; Ala $CH_3$), 1.01 (d, $J = 6.9$ Hz, 3H; 6′-$CH_3$), 1.05 (d, $J = 7.1$ Hz, 18H; $Si(CH(CH_3)_2)_3$), 1.14–1.27 (m, 3H; $Si(CH(CH_3)_2)_3$), 1.40 (s, 9H; $C(CH_3)_3$), 1.41 (s, 9H; $C(CH_3)_3$), 1.57 (s, 3H; 4′-$CH_3$), 1.93 (dd, $J = 13.7$, 7.6 Hz, 1H; $CH_2$), 2.34 (dd, $J = 13.6$, 6.7 Hz, 1H; $CH_2$), 2.40–2.49 (m, 2H; 6′-H, 2′-H), 2.95 (s, 3H; $NCH_3$), 3.24 (dd, $J = 15.5$, 9.9 Hz, 1H; Trp $CH_2$), 3.31–3.39 (m, 1H; Trp $CH_2$), 3.40 (s, 3H; $OCH_3$), 4.05 (d, $J = 4.3$ Hz, 1H; $CHOCH_3$), 4.48–4.59 (m, 2H; Ala CH, 1′-H), 4.86 (d, $J =$

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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 ppm (br s, 1H; Trp NH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=12.6 (Si($CH$($CH_3$)$_2$)$_3$), 16.4 (4′-$CH_3$), 16.6 (6′-$CH_3$), 17.2 (1′-$CH_3$), 17.6 (2′-$CH_3$), 17.9 (Si(CH($CH_3$)$_2$)$_3$), 18.2 (Ala $CH_3$), 23.4 (Trp $CH_2$), 28.1 (C($CH_3$)$_3$), 28.3 (C($CH_3$)$_3$), 30.8 ($NCH_3$), 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 ($OCH_3$), 75.9 (C-1′), 79.5 ($C$($CH_3$)$_3$), 79.9 ($C$($CH_3$)$_3$), 81.9 ($CHOCH_3$), 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 ppm (CO); HMRS (ESI): $m/z$: calcd for $C_{54}H_{84}N_4O_{10}Si$: 999.58489 $[M+Na]^+$; found: 999.584938.

**Chondramide A (2b)**: TFA (33.0 μL, 0.45 mmol) was added to a stirred solution of compound **26b** (44.0 mg, 0.045 mmol) in $CH_2Cl_2$ (1 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and after stirring for 22 h, 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 (45 mL) and DIEA (30.0 μL, 0.180 mmol), HOBt (21.0 mg, 0.158 mmol), and TBTU (49.0 mg, 0.158 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 (3×20 mL) and the combined organic layers were washed with 5% aqueous $KHSO_4$ solution (20 mL), water (20 mL), saturated $NaHCO_3$ solution (20 mL), water (2×20 mL), and saturated NaCl solution (20 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The crude product was dissolved in THF (0.5 mL) and TBAF·3$H_2O$ (28.0 mg, 0.090 mmol) was added at 0 °C. After stirring for 1 h, the solvent was removed in vacuo followed by flash chromatography (petroleum ether/ethyl acetate 1:1; then petroleum ether/acetone 3:2) of the residue to give depsipeptide **2b** (9.00 mg, 31% over three steps) as a colorless foam. TLC (petroleum ether/acetone 3:2): $R_f$=0.13; $[\alpha]_D^{20}$=+7.9 ($c$=0.80 in MeOH); $^1$H NMR (400 MHz, MeOD): $\delta$=0.80 (d, $J$=7.1 Hz, 3H; Ala $CH_3$), 0.86 (d, $J$=6.1 Hz, 3H; 7-$CH_3$), 0.91 (d, $J$=6.6 Hz, 3H; 6-$CH_3$), 1.08 (d, $J$=6.8 Hz, 3H; 2-$CH_3$), 1.68 (s, 3H; 4-$CH_3$), 2.03 (dd, $J$=13.0, 2.6 Hz, 1H; $CH_2$), 2.23 (dd, $J$=12.6, 12.6 Hz, 1H; $CH_2$), 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 $CH_2$), 3.08 (s, 3H; $NCH_3$), 3.14 (s, 3H; $OCH_3$), 3.85 (d, $J$=10.1 Hz, 1H; $CHOCH_3$), 4.47–4.56 (m, 1H; 7-H), 4.73–4.81 (m, 1H; Ala CH), 4.81–4.87 (m, 1H; 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 ppm (d, $J$=7.8 Hz, 1H; Trp $H_{ar}$); $^{13}$C NMR (100 MHz, MeOD): $\delta$=16.0 (4-$CH_3$), 17.9 (6-$CH_3$), 18.4 (Ala $CH_3$), 18.9 (7-$CH_3$), 19.1 (2-$CH_3$), 26.4 (Trp $CH_2$), 30.9 ($NCH_3$), 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 ($OCH_3$), 79.2 (C-7), 83.4 ($CHOCH_3$), 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 ppm (CO); HMRS (ESI): $m/z$: calcd for $C_{36}H_{46}N_4O_7$: 669.32587 $[M+Na]^+$; found: 669.326358.

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