STUDIES ON THE NOVEL CYCLODEPSIPEPTIDES. A TOTAL SYNTHESIS OF (+)-JASPLAKINOLIDE (JASPAMIDE)[1]

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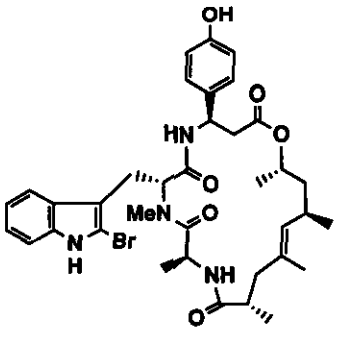
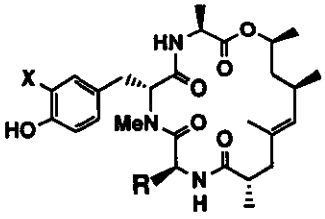
Abstract — Diastereocontrolled total synthesis of (+)-jasplakinolide (**1**) has been accomplished *via* coupling of the tetrapropionate-derived segment (**9**) with the tripeptide (**10**) followed by trichlorobenzoyl chloride-mediated macrolactonization.

(+)-Jasplakinolide (Jaspamide) (**1**)[3] and (+)-geodiamolides A (**2**) -F (**7**)[4] are biologically active cyclodepsipeptides isolated from marine sponges, and are composed of tripeptides linked to a common twelve-carbon segment. With their isolation and elucidation of their structures having been reported, synthetic work has appeared successively.[5] As one of the results reported, we exhibited a design for (+)-geodiamolides A (**2**) and B (**3**), consisting of the synthesis of the tetrapropionate-derived segment (**9**) and of the tripeptide containing a halogenated *N*-methyltyrosyl residue and subsequent coupling of them.[5e] We describe here the application of this methodology to a total synthesis of (+)-jasplakinolide (**1**)



Jasplakinolide (1)

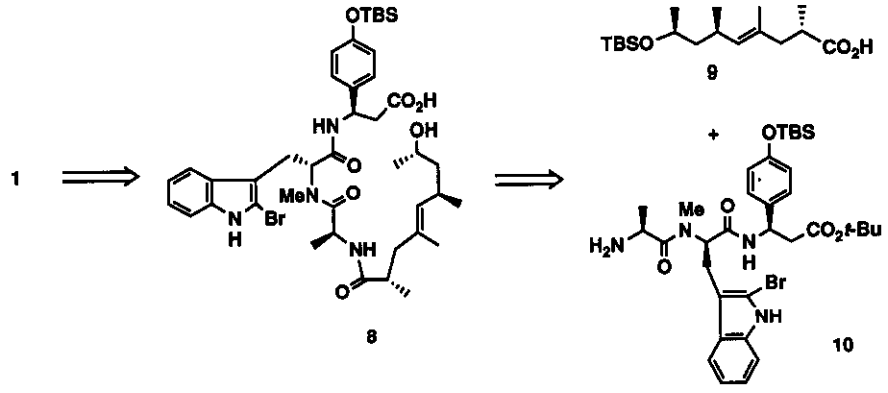


Geodiamolide

- **A R=Me, X = I (2)**
- **B R=Me, X = Br (3)**
- **C R=Me, X=Cl (4)**
- **D R=H , X=I (5)**
- **E R=H , X=Br (6)**
- **F R=H , X=Cl (7)**

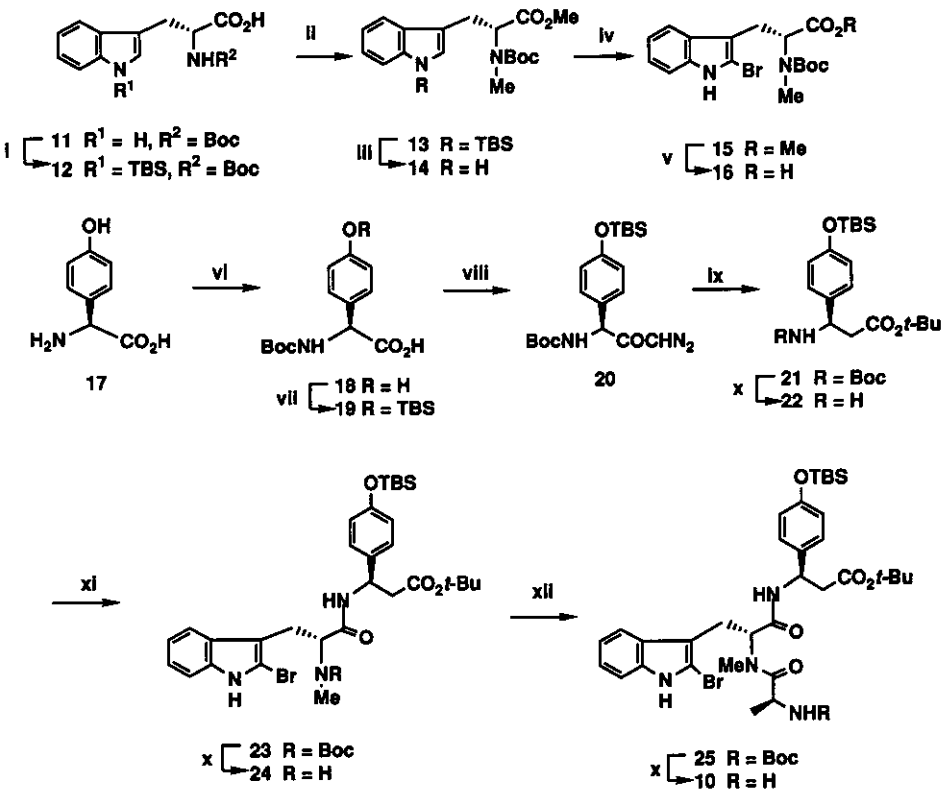
Our strategy is based on the cyclization of a seco acid (**8**) obtainable from coupling of a tripeptide (**10**) with the hydroxynonenoic acid (**9**), as shown in Scheme 1.

Scheme 1



The route to the tryptophan-tyrosine portion of the tripeptide is similar to that by Grieco *et al.*[5a] Silylation of *N*-Boc-*D*-tryptophan (**11**) with *t*-butyldimethylsilyl chloride (TBSCl) followed by *N*-methylation of the resulting amino acid (**12**) afforded the completely protected ester (**13**) in 88% yield. Desilylation with tetra-butylammonium fluoride (TBAF) and subsequent bromination of **14** using *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide afforded the bromide (**15**), in 90% yield, which was hydrolyzed in 2*N* NaOH to give the acid (**16**). Synthesis of the β-tyrosine derivative was commenced with multi-protection of the commercially available *L*-4-hydroxyphenylglycine (**17**). Treatment of **17** with $(Boc)_2O$ in 0.5 *N*-NaOH/dioxane (1:1) followed by protection of the phenolic hydroxyl group in the carbamate (**18**) gave the silyl ether (**19**) in 46% yield. Treatment of **19** with ethyl chlorocarbonate and subsequently with diazomethane gave the diazoketone (**20**) in 69% yield. The Arndt-Eistert process was effected by treatment of **20** with silver benzoate in *t*-butanol in the presence of Et_3N to produce the ester (**21**) in 50 % yield. Selective removal of the *N*-*t*-Boc group in **21** with *t*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in CH_2Cl_2 followed by coupling of **22** with **16** using DCC in the presence of 1-hydroxybenzotriazole hydrate (HOBT) gave the dipeptide (**23**) in 75% yield. Removal of the *t*-butoxycarbonyl protecting group in **23** with TBSOTf in CH_2Cl_2 followed by coupling of **24** with *N*-Boc-L-alanine anhydride in CH_2Cl_2 in the presence of Et_3N gave the tripeptide (**25**), which was again treated with TBSOTf in the presence of 2,6-lutidine to give the desired peptide (**10**), $[\alpha]_D$ +47.3° (*c* 1.2, $CHCl_3$), in 60% yield.[6]

Scheme 2[a]

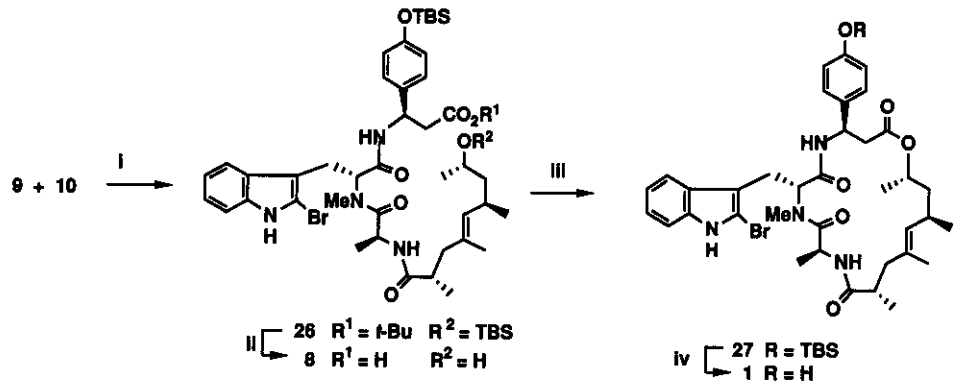


[a]Reagent and conditions: i, 3 x LDA, TBSCl; ii, NaH, MeI, DMF; iii, TBAF, THF; iv, NBS, benzoyl peroxide, CCl_4, reflux; v, 2N NaOH, THF; vi, $(Boc)_2O$, 0.5 N NaOH, dioxane; vii, TBSCl, imidazole, DMF; viii, $ClCO_2Et$, Et_3N and then CH_2N_2, *t*-BuOH, 80°C; ix, $AgOCOC_6H_5$, Et_3N, *t*-BuOH, 80 °C; x, TBSOTf, 2,6-lutidine, CH_2Cl_2; xi, 16, DCC, HOBT ; xii $(Boc\text{-}Ala)_2O$, Et_3N

Coupling of the tripeptide (**10**) with the polypropionate segment (**9**)[5e] was accomplished by treatment with 1.05 equiv. of DCC and 1.0 equiv. of HOBT in THF to give the corresponding amide (**26**) in 81% yield. Cleavage of the *t*-butyl ester in **26** and partial desilylation were effected simultaneously by treatment with trifluoroacetic acid (TFA) in dimethyl sulfide-ethanedithiol-CH_2Cl_2 (3:4:20, 0.3 ml) at 0°C to give the seco acid (**8**), $[\alpha]_D$ +0.6° (*c* 0.23, $CHCl_3$), in 50 % yield. The lactonization of **8** was effected by the Yamaguchi's procedure.[7] Treatment of **8** with 2,4,6-trichlorobenzoyl chloride in benzene in the presence of Et_3N followed by heating with 4-dimethylaminopyridine (DMAP) under reflux afforded the 19-membered compound (**27**) in 82 % yield. Desilylation of **27** with TBAF in THF furnished (+)-jasplakinolide (**1**), $[\alpha]_D$ +66.8° (*c* 0.8, CH_2Cl_2), in 93% yield. It was identical (^{1}H-nmr, ir, and ms) with the natural material, $[\alpha]_D$ +65.8° (*c* 1.535, CH_2Cl_2).[3]

In conclusion, diastereocontrolled total synthesis of (+)-jasplakinolide (**1**) was achieved *via* a procedure similar to that used for our total synthesis of (+)-geodiamolides A and B.

Scheme 3[a]



[a] Reagents and conditions: I, DCC, HOBT, THF; II, TFA, Me_2S - $HSCH_2CH_2SH$ - CH_2Cl_2 (3:4:20); III, 2,4,6-trichlorobenzoyl chloride, Et_3N, THF and then DMAP, C_6H_6, reflux; IV, TBAF, THF

EXPERIMENTAL

Optical rotation was measured with a JASCO DIP-140 polarimeter. Infrared spectra (ir) were recorded on a JASCO A-102 grating spectrophotometer and were calibrated with the 1601 cm^{-1} absorption of polystyrene. Nuclear magnetic resonance spectra (nmr) was taken on a JEOL JX-270 spectrometer in deuteriochloroform. Chemical shifts were reported in parts per milion (δ) downfield internal tetramethylsilane. Resonance patterns in ^1H-nmr are as s = singlet, d = doublet, t = triplet, q = quartet, m = mutiplet, and br = broad. Mass spectra (ms) at 70 eV were obtained on a JEOL JMS-D300 spectrometer combined with a JMA-1000 data processing system. Melting points were determined with a YANAGIMOTO micro melting point apparatus and are uncorrected. Elemental analyses were performed by analytical laboratory of this University. Column chromatography was carried out with silica gel (Merk, Silica gel 60). The phrase 'residue upon work-up' refers to the residue when the organic layer was separated, dried over $MgSO_4$, and evaporated under reduced pressure.

***N-tert*-Butoxycarbonyl-1-*tert*-butyldimethylsilyl-(*R*)-tryptophan (12)**

A stirred solution of diisopropylamine (4.10 ml, 29.28 mmol) in dry tetrahydrofuran (40 ml) at -78 °C under argon was treated with *n*-butyllithium (10 w/v % in hexane solution, 18.75 ml, 29.28 mmol). After 15 min, a solution of *N-tert*-Butoxycarbonyl-(*R*)-tryptophan (**11**) (2.97 g, 9.76 mmol) in dry tetrahydrofuran (10 ml) was added at -78 °C. To this mixture, a solution of *tert*-butyldimethylchlorosilane (TBSCl) (1.62 g, 10.73 mmol) in dry tetrahydrofuran (5 ml) was slowly added at -78 °C. The reaction mixture was then warmed up to -10 °C and quenched with saturated aqueous NH_4Cl and acidified with 10% HCl. The aqueous layer was extracted with ethyl acetate and the combined organic phases were washed with brine. The residue upon usual work-up was chromatograhed using methanol-CH_2Cl_2 (3:97) as an eluant to afford **12** (3.93 g, 96%) as a colorless solid, mp 61-63 °C (benzene-hexane). $[\alpha]_D^{27}$ -6.7° (*c* 1.025, $CHCl_3$). Ms m/z 418 (M^+). ^1H-Nmr ($CDCl_3$) δ 0.47 (6H, s, $SiMe_2$), 0.80 (9H, s, Si-*t*-Bu), 1.32 (9H, s, BocMe), 3.14 (1H, dd, J=6.5 and 12.8 Hz, βCH_2), 3.28 (1H, dd, J=6.0 and 12.8 Hz, βCH_2), 4.51-4.61 (1H, q, J=6.5 Hz, αCH), 4.91 (1H, br d, J=7 Hz, NH),

6.93 (1H, s, C_2-H), 6.99-7.09 (2H, m, C_5-H and C_6-H), 7.37-7.50 (2H, m, C_4-H and C_7-H). High resolution ms Calcd for $C_{22}H_{34}N_2O_4Si$: 418.2286. Found: 418.2293.

***N*-*tert*-Butoxycarbonyl-1-*tert*-butyldimethylsilyl-*N*-methyl-(*R*)-tryptophan methyl ester (13)**

To a solution of methyl iodide (3.14 ml, 46.94 mmol) and **12** (3.93 g, 9.39 mmol) in dry dimethylformamide (10 ml) was carefully added sodium hydride (60% oil dispersion, 0.901 g, 22.53 mmol) at 0 °C. After being stirred for 1 h at the same temperature, the reaction mixture was poured into water (50 ml). The aqueous layer was extracted with ethyl acetate (50 ml x 3). The combined organic phases were washed with water (30 ml x 3) and the residue upon work-up was chromatographed using benzene-CH_2Cl_2 (1:4) as an eluant to afford the title compound (**13**) (3.67 g, 88%) as a colorless oil. $[\alpha]_D^{25}$+48.2° (*c* 1.405, $CHCl_3$). Ms m/z 446 (M^+). ^{1}H-Nmr ($CDCl_3$) δ 0.60 and 0.61 (6H, s x 2, $SiMe_2$), 0.94 (9H, s, Si-*t*-Bu), 1.25 and 1.45 (9H, s x 2, BocMe), 2.73 and 2.79 (3H, s x 2, NMe), 3.13-3.31 and 3.40-3.51 (each 1H, m x 2, βCH_2) , 3.79 (3H, s, CO_2Me), 4.76-4.86 and 4.96-5.07 (1H, m x 2, αCH), 6.99 and 7.05 (1H, s x 2, C_2-H), 7.12-7.21 (2H, m, C_5-H and C_6-H), 7.47-7.54 (1H, m, C_4-H), 7.58-7.67 (1H, m, C_7-H). High resolution ms Calcd for $C_{24}H_{38}N_2O_4Si$: 446.2599. Found: 446.2644.

***N*-*tert*-Butoxycarbonyl-*N*-methyl-(*R*)-tryptophan methyl ester (14)**

To a solution of **13** (1.34 g, 3.00 mmol) in dry tetrahydrofuran (20 ml) was added a solution of tetra-*n*-butylammonium fluoride (TBAF) (1 M solution in dry tetrahydrofuran, 3.15 ml, 3.15 mmol) at 0 °C. After being kept for 30 min at the same temperature, the reaction mixture was washed with brine and the residue upon work-up was chromatographed using methanol-$CHCl_3$ (2 : 98 v/v) as an eluant to afford **14** (987 mg, 99%) as a colorless oil. $[\alpha]_D^{26}$+70.7° (*c* 0.93, $CHCl_3$). Ms m/z 332 (M^+). ^{1}H-Nmr ($CDCl_3$) δ 1.20 and 1.41 (9H, s x 2, BocMe), 2.74 and 2.78 (3H, s x 2, NMe), 3.10-3.27 and 3.40-3.47 (each 1H, m x 2, βCH_2), 3.72 and 3.77 (3H, s x 2, CO_2Me), 4.73-4.82 and 4.98-5.07 (1H, m x 2, αCH), 6.95 and 7.01 (1H, s x 2, C_2-H), 7.08-7.20 (2H, m, C_5-H and C_6-H), 7.34 (1H, d, J=7.88 Hz, C_4-H), 7.60 (1H, d, J=7.57 Hz, C_7-H), 8.41 and 8.49 (1H, s x 2, NH). Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.04; H, 7.20; N, 8.35.

***N*-*tert*-Butoxycarbonyl-*N*-methyl-2-bromo-(*R*)-tryptophan methyl ester (15)**

A mixture of **14** (1.16 g, 3.49 mmol), *N*-bromosuccinimide (652 mg, 3.66 mmol) and benzoyl peroxide (5 mg, 0.02 mmol) in dry CCl_4 (20 ml) was heated under reflux for 1 h and filtered through Celite. The filtrate was concentrated *in vacuo*. The residual oil was chromatographed using CH_2Cl_2 to afford the title compound (**15**) (1.31 g, 91%) as a colorless solid, mp 109-111 °C (ethyl acetate-ether-hexane). $[\alpha]_D^{26}$+86.3° (*c* 1.04, $CHCl_3$). Ms m/z 410 (M^+-1) and 412 (M^++1). ^{1}H-Nmr ($CDCl_3$) δ 1.23 and 1.36 (9H, s x 2, BocMe), 2.70 and 2.76 (3H, s x 2, NMe), 3.19 (1H, dd, J=10.50 and 14.65 Hz, βCH_2), 3.41 (1H, dd, J=4.15 and 14.90 Hz, βCH_2), 3.72 and 3.78 (3H, s x 2, CO_2Me), 4.68 (1H, dd, J=4.15 and 10.50 Hz, αCH), 7.07-7.17 (2H, m, C_5-H and C_6-H), 7.51 (1H, d, J=7.57 Hz, C_7-H), 8.40 and 8.58 (1H, br s x 2, NH). Anal. Calcd for $C_{18}H_{23}N_2O_4Br$: C, 52.56; H,5.64; N,6.81. Found: C,52.83; H,5.65; N,6.79.

***N*-*tert*-Butoxycarbonyl-*N*-methyl-2-bromo-(*R*)-tryptophan (16)**

To a solution of **15** (1.31 g, 3.19 mmol) in dry tetrahydrofuran (2.5 ml) was added 2N NaOH (2.39 ml, 4.78 mmol). After being stirred at room temperature for 3 h, the reaction mixture was neutralized with 5 % HCl and the aqueous layer was extracted with ethyl acetate (50 ml x 3). The combined organic phases were washed with

brine and the residue upon work up was chromatographed using methanol-CH_2Cl_2 (5:95) as an eluant to give **16** (767 mg, 61%) as a colorless solid, mp 80-83 °C ($CHCl_3$). $[\alpha]_D^{27}$+78.3° (*c* 0.71,$CHCl_3$). ^{1}H-Nmr ($CDCl_3$) δ 1.21 and 1.38 (9H, s x 2, BocMe), 2.67 and 2.78 (3H, s x 2, NMe), 3.19 (1H, dd, J=10.74 and 14.86 Hz, βCH_2), 3.41 (1H, dd, J=4.64 and 14.86 Hz, βCH_2), 4.57-4.64 and 4.74-4.82 (1H, m x 2, αCH), 7.07-7.18 (2H, m, C_5-H and C_6-H), 7.50-7.58 (1H, m, C_7-H), 8.21 and 8.31 (1H, br s x 2, NH). Anal. Calcd for $C_{17}H_{21}N_2O_4Br$: C, 51.40; H, 5.33; N, 7.05. Found: C, 51.40; H, 5.50; N, 7.05.

***N*-*tert*-Butoxycarbonyl-(*S*)-4-hydroxyphenylglycine (18)**

To a solution of (*S*)-4-hydroxyphenylglycine (**17**) (2.0 g, 11.96 mmol) in dioxane/H_2O (2:1, 72 ml) was added 1 N NaOH (24 ml, 0.024 mol) and dibutyl dicarbonate (2.87 g, 13.16 mmol). After being stirred at room temperature for 2 h, the reaction mixture was acidified (pH 2.3) with 5% $KHSO_4$ and the whole was extracted with ethyl acetate (50 ml x 3). The combined organic phases were washed with brine. The residue upon work-up was chromatographed using methanol-CH_2Cl_2 (3:97) as an eluant to afford **18** (2.19g, 60%) as a colorless solid, mp 91-94 °C (benzene). $[\alpha]_D^{27}$+127.2° (*c* 1.005, MeOH). Ms m/z 222 [M^+-45 (CO_2H)]. ^{1}H-Nmr ($CDCl_3$) δ 1.37 (9H, s, BocMe), 5.09 (1H, br s, αCH), 6.73 (2H, d, J=8.54 Hz, C_3-H and C_5-H), 7.15 (2H, d, J=8.54 Hz, C_2-H and C_6-H). High resolution ms Calcd for $C_{12}H_{16}NO_3$ [M^+-45 (CO_2H)]: 222.1129. Found: 222.1081.

***N*-*tert*-Butoxycarbonyl-*O*-*tert*-butyldimethylsilyl-(*S*)-4-hydroxyphenylglycine (19)**

To a solution of **18** (932.5 mg, 3.49 mmol) and imidazole (1.43 g, 20.96 mmol) in dry DMF (15 ml) was added TBSCl (631 mg, 4.2 mmol) at 0 °C. After being stirred at room temperature for 9 h, the reaction mixture was diluted with ethyl acetate (20 ml) and the whole was washed with water (50 ml x 3). The residue upon work-up was chromatograhed with $CHCl_3$ as an eluant to afford **19** (1.03 g, 77%) as a white crystal, mp 110-112 °C ($CHCl_3$). $[\alpha]_D^{26}$+93.1° (*c* 1.19, $CHCl_3$). Ms m/z 382 (M^++1). ^{1}H-Nmr ($CDCl_3$) δ 0.16 (6H, br s, $SiMe_2$), 0.96 (9H, br s, Si-*t*-Bu), 1.19 and 1.37 (9H, br s x 2, BocMe), 4.85-4.95 and 5.10-5.24 (1H, br x 2, αCH), 6.66 (2H, d, J=8.52 Hz, C_3-H and C_5-H), 7.20 (2H, d, J=8.52 Hz, C_2-H and C6-H). Anal. Calcd for $C_{19}H_{31}NO_5Si$: C, 59.82; H, 8.19; N, 3.67. Found: C, 59.83; H, 8.31; N, 3.62.

(*S*)-*N*-*tert*-Butoxycarbonyl-4-*tert*-butyldimethylsiloxy-α-diazoacetylbenzylamine (20)

To a solution of the acid (**9**) (1.79 g, 4.69 mmol) and triethylamine (0.72 ml, 5.16 mmol) in dry ether (40 ml) was added ethyl chlorocarbonate (0.49 ml, 5.16 mmol) at 0°C. After being stirred for 1 h at the same temperature, a solution of diazomethane (6 mol equiv.) in ether was added. The mixture was then warmed up to room temperature and stirred for 7 h. The reaction mixture was washed with water and the organic phase was dried over $MgSO_4$. The residue upon work-up was chromatograhed with CH_2Cl_2 as an eluant to afford **20** (1.31 g, 69%) as an yellow oil. $[\alpha]_D^{25}$+152.2° (*c* 1.75, $CHCl_3$). Ms m/z 336 [M^+-69 ($COCN_2$)]. ^{1}H-Nmr ($CDCl_3$) δ 0.19 (6H, s, $SiMe_2$), 0.98 (9H, s, Si-*t*-Bu), 1.41 (9H, s, BocMe), 5.08-5.19 (1H, br, NH), 5.25 (2H, s, $COCH_2N_2$), 5.78-5.82 (1H, br s, αCH), 6.18 (2H, d, J=8.55 Hz, C_3-H and C_5-H), 6.81 (2H, d, J=8.55 Hz, C_2-H and C_6-H).

***N*-*tert*-Butoxycarbonyl-*O*-*tert*-butyldimethylsilyl-(*R*)-β-tyrosine *tert*-butyl ester (21)**

To a solution of **19** (1.31g, 3.23 mmol) in dry *tert*-butanol (10 ml) was rapidly added a solution of silver benzoate in triethylamine (10 w/w%, 1 ml) at 80° C. After being stirred for 3 min, the activated carbon (0.5 g) was added and the mixture was stirred for 1 min. The reaction mixture was filtered through Celite and the

filtrate was concentrated *in vacuo* The residual oil was chromatograhed with CH_2Cl_2 as an eluant to afford **21** (763.9 mg, 50%) as an oil. $[\alpha]_D^{26}$+19.5° (*c* 0.845, $CHCl_3$). Ms m/z 451 (M^+). ^{1}H-Nmr ($CDCl_3$) δ 0.17 (6H, s, $SiMe_2$), 0.97 (9H, s, Si-*t*-Bu), 1.33 (9H, s, BocMe), 1.42 (9H, s, CO_2*t*-Bu), 2.61-2.83 (2H, m, $^{\alpha}CH_2$), 4.93-5.07 (1H, br, $^{\beta}CH$), 6.79 (2H, d, J=8.54 Hz, C_3-H and C_5-H), 7.14 (2H, d, J=8.54 Hz, C_2-H and C_6-H). Anal. Calcd for $C_{24}H_{41}NO_5Si$: C, 63.82; H, 9.15; N, 3.10. Found: C, 63.72; H, 9.12; N, 3.15.

***O*-*tert*-Butyldimethylsilyl-(*R*)-β-tyrosine *tert*-butyl ester (22)**

To a solution of **21** (733.9 mg, 1.62 mmol) and 2,6-lutidine (0.303 ml, 2.60 mmol) in dry CH_2Cl_2 (1.5 ml) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (0.448 ml, 1.95 mmol) at 0 °C. The mixture was stirred for 3 h at the same temperature and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (5 ml x 3). The combined organic phases were washed with brine and the residue upon work-up was chromatographed using methanol-CH_2Cl_2 (5:95, v/v) as an eluant to afford **22** (340 mg, 60%) as a pale yellow oil. $[\alpha]_D^{25}$+13.1° (*c* 1.75, $CHCl_3$). Ms m/z 351 (M^+). ^{1}H-Nmr ($CDCl_3$) δ 0.18 (6H, s, $SiMe_2$), 0.99 (9H, s, Si-*t*-Bu), 1.41 (9H, s, CO_2*t*-Bu), 2.52-2.57 (2H, m, $^{\alpha}CH$), 4.31 (1H, t, J=6.96 Hz, $^{\beta}CH$), 6.79 (2H, d, J=8.54 Hz, C_3-H and C_5-H), 7.20 (2H, d, J=8.54 Hz, C_2-H and C_6-H). Anal. Calcd for $C_{19}H_{33}NO_3Si$: C, 64.91; H, .46; N, 3.98. Found: C, 64.69; H, 9.29; N, 4.08.

***N*-*tert*-Butoxycarbonyl-*N*-methyl-2-bromo-*(R)*-tryptophanyl-*O*-*tert*-butyldimethylsilyl-(*R*)-β-tyrosine *tert*-butyl ester (23)**

A solution of the dipeptide (**22**) (200 mg, 0.569 mmol) and **16** (226 mg, 0.569 mmol) in dry tetrahydrofuran (2 ml) was treated with 1-hydroxybenzotriazole hydrate (HOBT) (87.3 mg, 0.569 mmol) and dicyclohexyl-carbodiimide (DCC) (123 mg, 0.598 mmol) at -10 °C, and the mixture was stirred for 5 h at 0 °C. The resulting reaction mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was chromatographed using CH_2Cl_2 as an eluant to afford **23** (390 mg, 94%) as a solid, mp 59-60 °C (ethyl acetate-ether-hexane). Ms m/z 656 [M^+-1-73 (O*t*-Bu)] and 658 [M^++1-73 (O*t*-Bu)]. ^{1}H-Nmr ($CDCl_3$) δ 0.17 (6H, s, $SiMe_2$), 0.97 (9H, s, Si-*t*-Bu), 1.08 (9H, s, BocMe), 1.30 (9H, s, CO_2*t*-Bu), 2.81 and 2.89 (3H, s x 2, NMe), 4.96-5.08 (1H, br, Trp$^{\alpha}$CH), 5.25-5.42 (1H, br, β-Tyr$^{\beta}$CH), 6.80-6.83 (2H, m, β-TyrC_3-H and C_5-H), 6.90-7.20 (2H, m, TrpC_5-H and C_6-H), 7.50-7.63 (1H, br, TrpC_7-H), 8.13 and 8.19 (1H, br s x 2, TrpNH). Anal. Calcd for $C_{36}H_{52}N_3O_6BrSi$: C, 59.17; H, 7.17; N, 5.75. Found: C, 58.87; H, 7.14; N, 5.59.

***N*-Methyl-2-bromo-*(R)*-tryptophanyl-*O*-*tert*-butyldimethylsilyl-(*R*)-β-tyrosine *tert*-butyl ester (24)**

To a solution of **23** (110 mg, 0.151 mmol) and 2,6-lutidine (49.1 μl, 0.151 mol) in dry CH_2Cl_2 (1 ml) was added TBSOTf (72.7 μml, 0.316 mmol) at 0 °C. The mixture was stirred for 2 h at room temperature and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ethyl acetate (4 ml x 3) and the combined organic phases were washed with brine. The residue upon work-up was chromatographed using methanol-CH_2Cl_2 (5:95) as an eluant to afford **24** (77.6 mg, 82%) as a white solid, mp 51-52 °C (benzene). $[\alpha]_D^{26}$+41.9° (*c* 0.69, $CHCl_3$). ^{1}H-Nmr ($CDCl_3$) δ 0.16 (6H, s, $SiMe_2$), 0.96 (9H, s, Si-*t*-Bu), 1.33 (9H, s, CO_2*t*-Bu), 2.20 (3H, s, NMe), 2.53 (1H, dd, J=6.60 and 15.14 Hz, β-Tyr$^{\alpha}CH_2$), 2.73 (^{1}H, dd, J=6.60 and 15.14 Hz, β-Tyr$^{\alpha}CH_2$), 2.92 (1H, dd, J=9.27 and 14.40 Hz, Trp$^{\beta}CH_2$), 3.27 (1H, dd, J=4.15 and 14.40 Hz, Trp$^{\beta}CH_2$), 3.37 (1H, dd, J=4.15 and 9.27 Hz, Trp$^{\alpha}$CH), 5.30-5.38 (1H, m, β-Tyr$^{\beta}$CH), 6.74-6.77

(2H, m, β-TyrC3-H and C5-H), 7.07-7.19 (2H, m, TrpC5-H and C6-H), 7.10-7.13 (2H, m, β-TyrC2-H and C6-H), 7.26-7.65 (1H, m, TrpC7-H), 7.91 (1H, d, J=8.79 Hz, NH), 8.59 (1H, br s, TrpNH). Anal. Calcd for $C_{31}H_{44}N_3O_4BrSi$: C, 59.04; H, 7.03; N, 6.66. Found: C, 59.16; H, 7.18; N, 6.37.

***N*-*tert*-Butoxycarbonyl-*(S)*-alanyl-*N*-methyl-2-bromo-*(R)*-tryptophanyl-*O*-*tert*-butyldimethylsilyl-*(R)*-β-tyrosine *tert*-butyl ester (25)**

To a solution of the dipeptide (**24**) (70.0 mg, 0.111 mmol) and triethylamine (15.5 μl, 0.111 mmol) in dry CH_2Cl_2 (2 ml) was added *N*-Boc-*(S)*-alanine anhydride (42 mg, 0.117 mmol) at 0 °C. After being stirred for 5 h at room temperature, the reaction mixture was washed with water (2 ml) and the residue upon work-up was chromatographed using CH_2Cl_2 as an eluant to afford the tripeptide (**25**) (84.9 mg, 95 %) as a solid, mp 77-78 °C (ethyl acetate-benzene). $[\alpha]_D^{26}$+31.2° (*c* 0.185, $CHCl_3$). Ms m/z 801 (M^+-1) and 803 (M^++1). ^{1}H-Nmr ($CDCl_3$) δ *0.17 (6H, s, $SiMe_2$), 0.64 (3H, d, J=6.84 Hz, AlaMe), 0.97 (9H, s, Si-t-Bu),* 1.33 (9H, s, CO_2*t*-Bu), 1.37 (9H, s, BocMe), 2.65 (1H, dd, J=6.83 and 9.31 Hz, β-Tyr$^\alpha$$CH_2$), 2.80 (1H, dd, J=6.83 and 9.31 Hz, β-Tyr$^\alpha$$CH_2$), 2.97 (3H, s, NMe), 3.21(1H, dd, J=10.25 and 17.08 Hz, Trp$^\beta$$CH_2$), 3.38 (1H, dd, J=6.80 and 17.08 Hz), Trp$^\beta$$CH_2$), 4.22-4.33 (1H, m, Ala$^\alpha$CH), 5.13 (1H, d, J=6.84 Hz, NH), 5.30-5.38 (1H, m, β-Tyr$^\beta$CH), 5.64-5.70 (1H, m, Trp$^\alpha$CH), 6.72-6.75 (2H, m, β-TyrC3-H and C5-H), 6.92 (1H, d, J=8.30 Hz, NH), 7.03-7.14 (4H, m, TrpC5-H, TrpC6-H, β-TyrC2-H, and β-TyrC6-H), 7.02-7.23 (1H, m, TrpC4-H), 7.51-7.53 (1H, m, TrpC7-H), 8.34 (1H, s, TrpNH). Ir (KBr) 3318, 2978, 2931, 1730, 1689, 1654 cm^{-1}. Anal. Calcd for $C_{38}H_{57}N_4O_7BrSi$: C, 57.78; H, 7.27; N, 7.09. Found: C, 57.49; H, 7.40; N, 6.92.

***(S)*-Alanyl-*N*-methyl-2-bromo-*(R)*-tryptophanyl-*O*-*tert*-butyldimethylsilyl-*(R)*-β-tyrosine *tert*-butyl ester (10)**

To a solution of **25** (41.4 mg, 0.052 mmol) and 2,6-lutidine (16.8 μl, 0.145 mmol) in dry CH_2Cl_2 (5 ml) was added TBSOTf (24.9 μl, 0.108 mmol) at 0 °C. After being stirred for 2 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and the aqueous layer was extracted with ethyl acetate (3 ml x 3). The combined organic phases were washed with brine and the residue upon work-up was chromatographed using methanol-CH_2Cl_2 (5:95 v/v) as an eluant to afford **10** (23.0 mg, 63%) as a solid, mp 49-50 °C (benzene). $[\alpha]_D^{25}$+47.3° (*c* 1.2, $CHCl_3$). Ms m/z 625 [M^+-2-73 (*t*-Bu)] and 627 [M^+-73 (*t*-Bu)]. ^{1}H-Nmr ($CDCl_3$) δ 0.17 (6H, s, $SiMe_2$), 0.69 (3H, d, J=6.83 Hz, AlaMe), 0.97 (9H, s, Si-*t*-Bu), 1.30 (9H, s, CO_2*t*-Bu), 2.59-2.76 (2H, m, β-Tyr$^\alpha$$CH_2$), 2.94 (3H, s, NMe), 3.18-3.38 (2H, m, Trp$^\beta$$CH_2$), 3.61-3.69 (1H, m, Ala$^\beta$CH), 5.30 (1H, dd, J=6.80 and 13.60 Hz, β-Tyr$^\beta$CH), 5.64 (1H, dd, J=5.87 and 10.76 Hz, Trp$^\alpha$CH), 6.73 (2H, d, J=8.54 Hz, β-TyrC3-H and C5-H), 7.05-7.14 (2H, m, TrpC5-H and C6-H), 7.06 (2H, d, J=8.55 Hz, β-TyrC2-H and C6-H), 7.19-7.23 (1H, m, TrpC7-H), 8.83 (1H, br s, TrpNH). Anal. Calcd for $C_{34}H_{49}N_4O_5BrSi$: C, 58.19; H, 7.04; N, 7.98. Found: C, 58.10; H, 7.24; N, 7.77.

***(2S,4E,6R,8S)*-8-*tert*-Butyldimethylsilyloxy-2,4,6-trimethyl-4-nonenoyl-*(S)*-alanyl-*N*-methyl-2-bromo-*(R)*-tryptophanyl-*O*-*tert*-butyldimethylsilyl-*(R)*-β-tyrosine *tert*-butyl ester (26)**

A solution of the tripeptide (**10**) (23 mg, 32.8 μmol), the carboxylic acid (**9**) (10.8 mg, 32.8 μmol), and HOBT (5.0 mg, 32.8 μmol) in dry tetrahydrofuran (0.6 ml) was treated with DCC (7.1 mg, 34.4 μmol) at -20 °C and the mixture was stirred for 6 h at 0 °C. The resulting reaction mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was chromatographed using methanol-$CHCl_3$ (2:98) as an eluant to

afford **26** (27.0 mg, 81%) as a solid, mp 68-69 °C (ethyl acetate-ether-hexane). $[\alpha]_D^{25}$+23.2° (*c* 0.97, $CHCl_3$). ^{1}H-Nmr ($CDCl_3$) δ 0.17 (6H, s, β-TyrSiMe_2), 0.33 (6H, s, C_8-OSiMe_2), 0.71 (3H, d, J=6.83 Hz, AlaMe), 0.87 (9H, s, C_8-OSi-*t*-Bu), 0.97 (9H, s, β-TyrOSi-*t*-Bu), 1.08 (3H, d, J=5.86 Hz, C_2-Me), 1.32 (9H, s, CO_2*t*-Bu), 1.54 (3H, s, C_4-Me), 1.89-2.00 (1H, m, C_3-H), 2.20-2.49 (3H, m, C_2-H, C_3-H and C_6-H), 2.68 (1H, dd, J=6.59 and 15.14 Hz, β-Tyr$^{\alpha}CH_2$), 2.83 (1H, dd, J=7.08 and 15.14 Hz, β-Tyr$^{\alpha}CH_2$), 3.01 (3H, s, NMe), 3.19 (1H, dd, J=10.50 and 15.13 Hz, Trp$^{\beta}CH_2$), 3.43 (1H, dd, J=5.61 and 10.50 Hz, Trp$^{\beta}CH_2$), 3.69-3.78 (1H, m, C_8-H), 4.46-4.55 (1H, m, Ala$^{\alpha}$CH), 4.94 (1H, d, J=9.52 Hz, C_5-H), 5.30-5.38 (1H, m, β-Tyr$^{\beta}$CH), 5.59-5.65 (1H, m, Trp$^{\alpha}$CH), 6.15 (1H, br d, J=6.10 Hz, AlaNH), 6.74 (2H, d, J=8.30 Hz, β-TyrC_3-H and C_5-H), 7.10-7.16 (2H, m, TrpC_5-H and C_6-H) , 7.13 (2H, d, J=8.30 Hz, β-TyrC_2-H and C_6-H), 7.51-7.54 (1H, m, TrpC_7-H), 8.04 (1H, s, TrpNH). Ir (KBr) 3270, 2954, 2830, 1735, 1655 cm^{-1}. Anal. Calcd for $C_{52}H_{83}N_4O_7BrSi$: C, 61.70; H, 8.26; N, 5.53. Found: C, 61.54; H, 8.13; N, 5.42.

(2*S*,4*E*,6*R*,8*S*)-8-Hydroxy-2,4,6-trimethyl-4-nonenoyl-*(S)*-alanyl-*N*-methyl-2-bromo-*(R)*-tryptophanyl-*O*-*tert*-butyldimethylsilyl-*(R)*-β-tyrosine (8)

The compound (**26**) (19.3 mg, 19.1 μmol) was dissolved in the solution of 1,2-ethanedithiol-dimethyl sulfide-CH_2Cl_2 (3:4:20 v/v, 0.3 ml). Trifluoroacetic acid (0.14 ml, 1.91 mmol) was added to this solution at 0 °C. After being stirred for 4 h, the reaction mixture was concentrated at 0 °C *in vacuo*. The residue was chromatographed using methanol-$CHCl_3$ (5:95 v/v) as an eluant to afford **8** (8 mg, 50%) as a solid, mp 91-92 °C (ethyl acetate). $[\alpha]_D$25 +0.60° (*c* 0.23, $CHCl_3$). ^{1}H-Nmr ($CDCl_3$) δ 0.18 (6H, s, SiMe_2), 0.58 (3H, d, J=6.84 Hz, AlaMe), 0.88 (3H, d, J=6.59 Hz, C_6-Me), 0.98 (9H, s, Si-*t*-Bu), 1.08 (3H, d, J=6.83 Hz, C_9-Me), 1.12 (3H, d, J=6.10 Hz, C_2-Me), 1.38-1.43 (2H, m, C_7-H), 1.56 (3H, s, C_4-Me), 2.23-2.32 (1H, m, C_3-H), 2.36-2.48 (1H, m, C_2-H), 2.62-2.82 (2H, m, β-Tyr$^{\alpha}CH_2$), 3.02 (3H, s, NMe), 3.10-3.18 and 3.27-3.36 (each 1H, m x 2, Trp$^{\beta}CH_2$), 3.64-3.78 (1H, m, C_8-H), 4.50-4.52 (1H, m, Ala$^{\alpha}$CH), 4.88 (1H, d, J=9.42 Hz, C_5-H), 5.34-5.43 (1H, m, β-Tyr$^{\beta}$CH), 5.58-5.63 (^{1}H, m, Trp$^{\alpha}$CH), 6.31 (1H, d, J=6.75 Hz, AlaNH), 6.77 (2H, d, J=8.54 Hz, β-TyrC_3-H and C5-H), 7.06-7.19 (2H, m, TrpC_5-H and C_6-H), 7.16 (2H, d, J=8.54 Hz, β-TyrC_2-H and C_6-H), 7.47-7.54 (2H, m, β-TyrNH and TrpC_7-H), 8.18 (1H, s, TrpNH). Anal. Calcd for $C_{42}H_{61}N_4O_7BrSi$: C, 59.91; H, 7.30; N, 6.66. Found: C, 59.89; H, 7.60; N, 6.55.

(2*S*,4*E*,6*R*,8*S*)-8-Hydroxy-2,4,6-trimethyl-4-nonenoyl-*(S)*-alanyl-*N*-methyl-2-bromo-*(R)*-tryptophanyl-*O*-*tert*-butyldimethylsilyl-*(R)*-β-tyrosine ρ-lactone (27)

To solution of the seco acid (**8**) (3.0 mg, 3.56 μmol) and triethylamine (0.546 μl, 3.92 μmol) in dry tetrahydrofuran (0.5 ml) was added 2,4,6-trichlorobenzoyl chloride (0.57 μl, 3.56 μmol) at room temperature and the mixture was stirred for 2.5 h. The resulting precipitate was filtered off and the filtrate was diluted with dry benzene (80 ml). This benzene solution was slowly added to a refluxing solution of dimethylaminopyridine (2.61 mg, 21.4 μmol) in benzene (30 ml) over a period of 8 h. The reaction mixture was washed with a saturated aqueous NH_4Cl. The residue upon work-up was chromatographed using $CHCl_3$ as eluant to afford the monomeric lactone (**27**) (2.3 mg, 82% yield) as an oil. $[\alpha]_D^{25}$+60.8° (*c* 1.15, $CHCl_3$). Ms m/z 823 (M^+) and 825 (M^++2). ^{1}H-Nmr ($CDCl_3$) δ 0.18 (6H, s, SiMe_2), 0.72 (3H, d, J=6.60 Hz, AlaMe), 0.81 (3H, d, J=6.59 Hz, C_6-Me), 0.97 (9H, s, Si-*t*-Bu), 1.04 (3H, d, J=6.35 Hz, C_9-Me), 1.10 (3H, d, J=6.59 Hz, C_2-Me), 1.56 (3H, s, C_4-Me), 1.85 (1H, d, J=15.14 Hz, C_3-H), 2.18-2.29 (1H, m, C_6-H), 2.33-2.52 (2H, m,

C_2-H and C_3-H), 2.57-2.72 (2H, m, β-Ala$^{\alpha}CH_2$), 2.96 (3H, s, NMe), 3.19-3.39 (2H,m, Trp$^{\beta}CH_2$), 4.55-4.65 (1H, m, C_8-H), 4.66-4.74 (2H, m, C_5-H and Ala$^{\alpha}$CH), 5.27-5.33 (1H, m, β-Tyr$^{\beta}$CH), 5.83 (1H, dd, J=6.34 and 10.26 Hz, Trp$^{\alpha}$CH), 6.60 (1H, d, J=6.59 Hz, AlaNH), 6.74 (2H, d, J=8.54 Hz, β-TyrC_3-H and C_5-H), 7.04 (2H, d, J=8.54 Hz, β-TyrC_2-H and C_6-H), 7.07-7.18 (2H, m, TrpC_5-H and C_6-H), 7.48 (1H, d, J=9.03 Hz, β-TyrNH), 7.54-7.57 (1H, m, TrpC_7-H), 8.11 (1H, d, J=15.14 Hz, C_3-H). Anal. Calcd for $C_{42}H_{59}N_4O_6BrSi$: C, 61.22; H, 7.22; N, 6.80. Found: C, 61.50; H, 7.52; N, 6.50.

Jasplakinolide (1)

To a solution of the pre-jasplakinolide (**27**) (2.0 mg, 2.43 μmol) in dry tetrahydrofuran (0.5 ml) was added a solution of TBAF (0.06 M tetrahydrofuran solution, 40.5 μl, 2.43 μmol) at 0 °C. After being kept for 10 min at the same temperature, the reaction mixture was washed with brine, and the residue upon work-up was chromatographed using $CHCl_3$ as an eluant to afford jasplakinolide (**1**) (1.6 mg, 93%). The ir ($CHCl_3$) and ^{1}H-nmr ($CDCl_3$) spectra of this sample were identical with those of authentic jasplakinolide.[3] $[\alpha]_D^{26}$+66.8° (*c* 0.8, CH_2Cl_2). (lit.,[3] $[\alpha]_D^{26}$+65.8° (*c* 1.535, CH_2Cl_2)). Ms m/z 708 (M^+-1) and 710 (M^++1). High resolution ms Calcd for $C_{36}H_{45}N_4O_6Br$: 708.2520 (M^+-1) and 710.2501 (M^++1). Found: 708.2532 (M^+-1) and 710.2459 (M^++1).

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