AN EXPEDITIOUS SYNTHESIS OF GEODIAMOLIDE A, AN 18-MEMBERED CYTOTOXIC DEPSIPEPTIDE FROM MARINE SPONGES[1,†]

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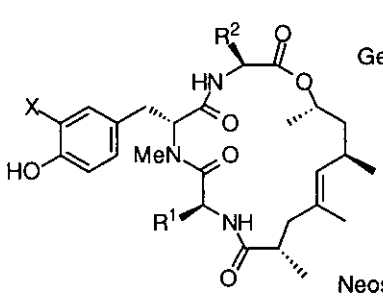
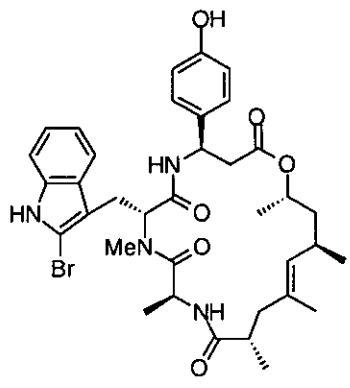
Abstract - Geodiamolide A (**1**) has been efficiently synthesized from the polypropionate and tripeptide units using the Evans asymmetric alkylation, the Mitsunobu esterification, and the macrolactamization with diphenyl phosphorazidate (DPPA) as key steps. Efficient esterification between the complex polyketide and tripeptide units was also realized under high pressure conditions.

The geodiamolides represent a novel class of secondary metabolites isolated from the various marine sponges *Geodia* sp.,[2a] *Pseudaxinyssa* sp.,[2b] *Hemiasterella minor*,[2c] and *Neosiphonia superstes*.[2d,2e] This unique class of compounds is represented by eight different related 18-membered depsipeptide structures which vary by the halogen substitution at the benzene ring and by the alanine, glycine, or valine residue at the peptide part, as shown in Figure 1. The molecular structures of geodiamolides are divided



		R^1	R^2	X
Geodiamolide	A :	Me	Me	I
	B :	Me	Me	Br
	C :	Me	Me	Cl
	D :	H	Me	I
	E :	H	Me	Br
	F :	H	Me	Cl
	TA .	Pr^i	Me	I
Neosiphoniamolide	.	H	Pr^i	I

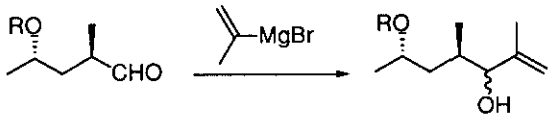


Jaspamide (Jasplakinolide)

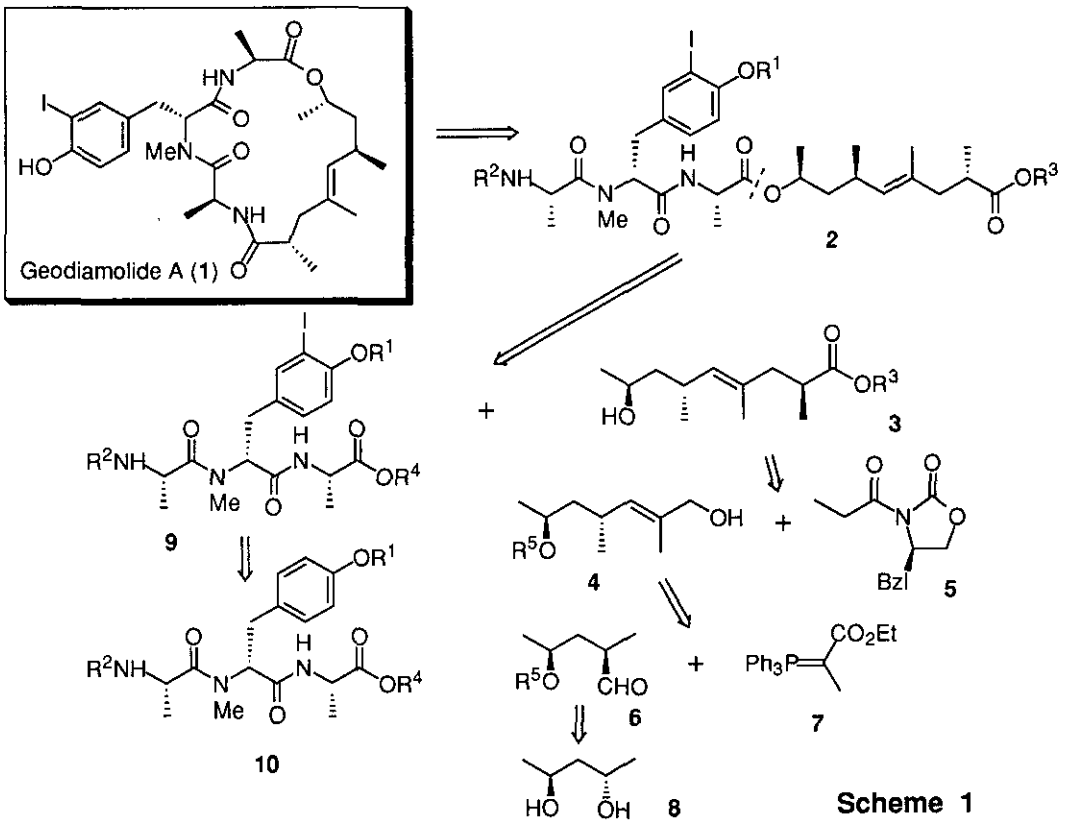
Figure 1

† Dedicated to the memory of the late Professor Shun-ichi Yamada.

into two gross parts: a polypropionate and a tripeptide. The former is also a constituent of jaspamide[3] (jasplakinolide),[4] which was isolated from the marine sponge *Jaspis* sp. Interesting cytotoxic and anti-fungal activities have been found in both geodiamolides and jaspamide. Interesting biological activities as well as unique structures of geodiamolides in addition to scarce availability in nature have stimulated many chemists to synthesize the unique depsipeptides.[1,5-10] Most of these syntheses adopted the Grignard reaction with low diastereoselectivity to construct the polypropionate part. Furthermore, they employed the macrolactonization using *N,N'*-dicyclohexylcarbodiimide (DCC) or the Yamaguchi method[11] for the final construction of the whole molecule but with lower efficiency (less than 25% yield).

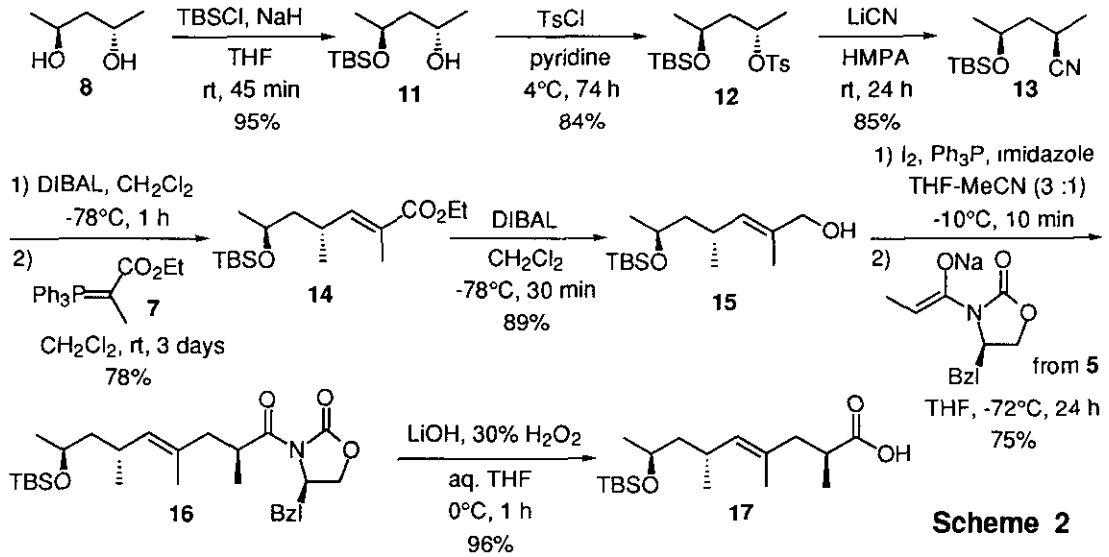


We have also succeeded in an expeditious synthesis of geodiamolide A and jaspamide.[1] The detail of the synthesis of geodiamolide A is described in this paper. This may promise the production of the biologically active unique depsipeptide on a large scale. The overall strategy for geodiamolide A (**1**) is shown in Scheme 1. The whole carbon skeleton (**2**) was perceived to be constructed from the polypropionate (**3**) and peptide (**9**) units. Macrolactamization of the linear precursor (**2**) was considered to be much superior to macrolactonization because the amino group is usually more nucleophilic than the



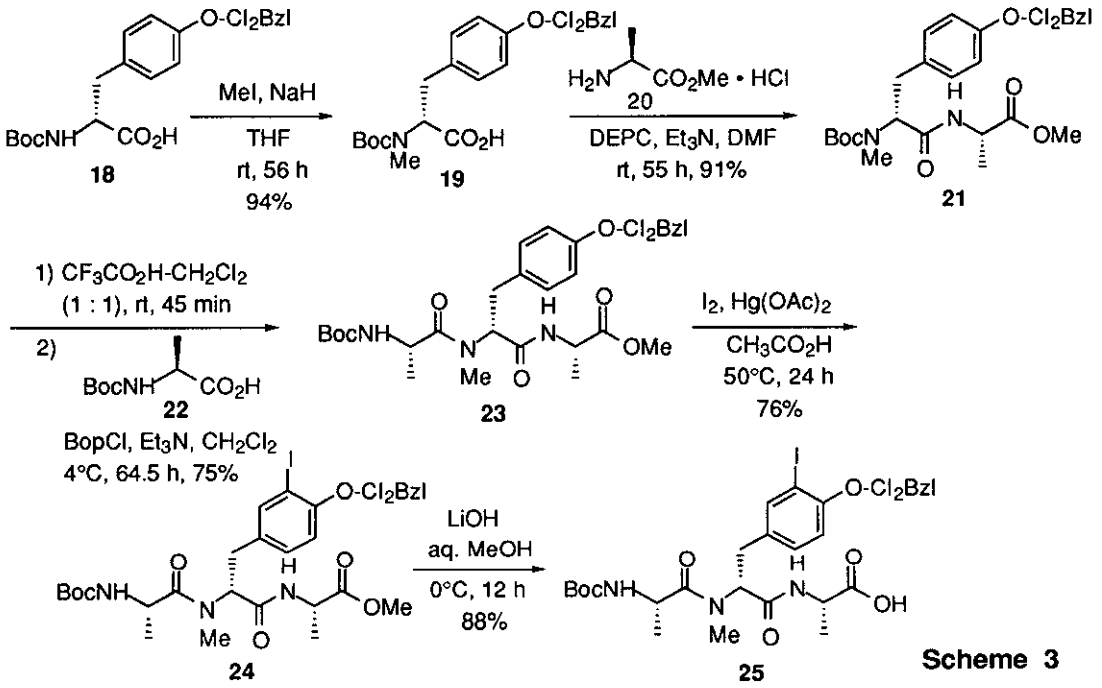
hydroxy group. The Evans asymmetric alkylation[12] of the oxazolidinone (**5**) with the trisubstituted olefin (**4**) was assumed a better strategy to construct the polypropionate unit (**3**). The construction of the trisubstituted olefin (**4**) was foreseen as resulting from the Wittig reaction of the phosphorane (**7**) with the aldehyde (**6**) prepared from the diol (**8**). Introduction of iodine to the tripeptide unit (**10**) was thought to produce the required tripeptide (**9**). According to this overall strategy, we launched the synthesis of geodiamolide A (**1**).

Commercially available (2*S*,4*S*)-2,4-pentanediol (**8**) was subjected to the monosilylation with *tert*-butyldimethylsilyl chloride (TBSCl), followed by tosylation of the resulting monoalcohol (**11**) with tosyl chloride (TsCl) to give the tosylate (**12**) (Scheme 2). The conversion of the tosylate (**12**) to the cyanide (**13**) sluggishly proceeded under the usual reaction conditions: potassium cyanide in dimethyl sulfoxide. However, use of lithium cyanide in hexamethylphosphortriamide (HMPA) afforded the cyanide (**13**) in good yield accompanied with inversion of configuration. The reduction of the cyanide followed by the Wittig reaction with the phosphorane (**7**) afforded the trisubstituted olefin ester (**14**), which was converted to the alcohol (**15**) with diisobutylaluminum hydride (DIBAL) in good yield. Although the attempted bromination of the alcohol (**15**) failed to give the bromide, the iodination with a mixture of iodine, triphenylphosphine, and imidazole quantitatively proceeded to give the photolabile iodide. The Evans asymmetric alkylation of the sodium enolate from the oxazolidinone (**5**) with the iodide afforded the alkylated product (**16**) with high diastereoselectivity (*E*:*Z*=96:4). Removal of the chiral auxiliary was easily achieved with lithium hydroxide-hydrogen peroxide to give the required polyketide (**17**) in an overall yield of 34% in 9 steps.



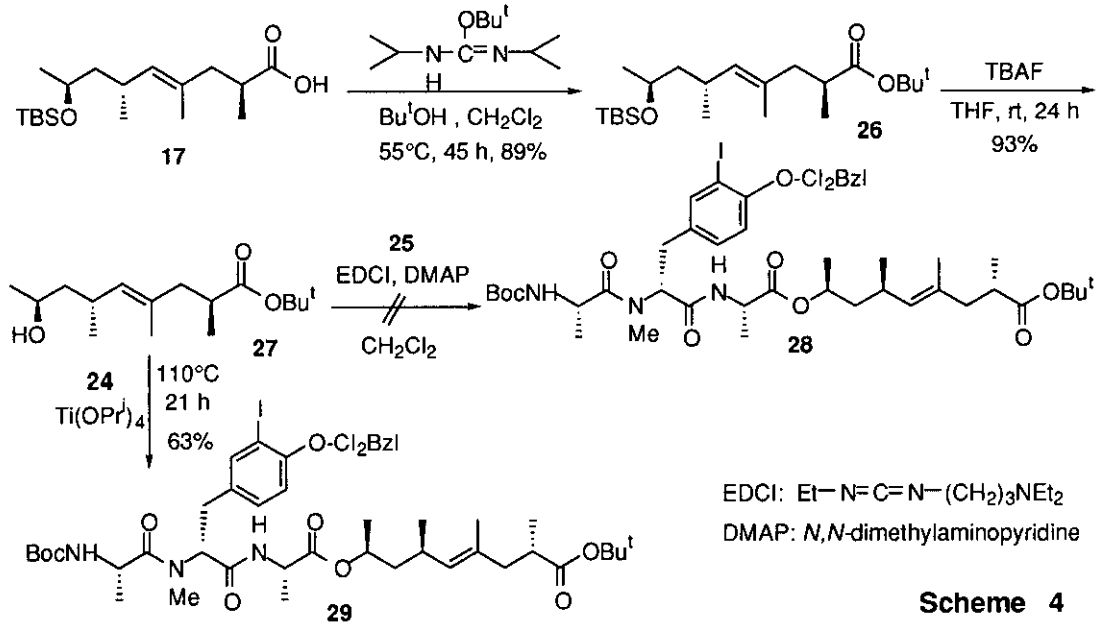
Scheme 2

The synthesis of the required tripeptide started from *N*-*tert*-butoxycarbonyl-O-2,6-dichlorobenzyl-(*R*)-tyrosine (Boc-(*R*)-Tyr(Cl_2Bzl)-OH, **18**), which was *N*-methylated according to the method of Benoiton,[13] as shown in Scheme 3. The *N*-methylated product (**19**) was coupled with (*S*)-alanine methyl ester hydrochloride (**20**) using diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$)[14] to give the dipeptide

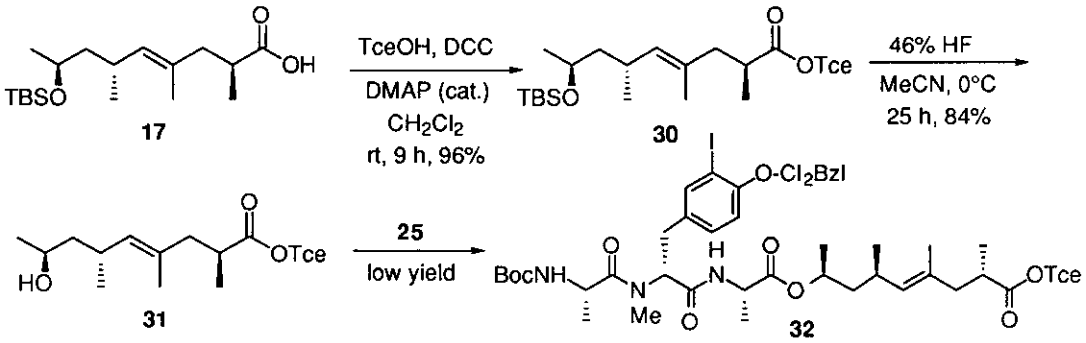


(**21**). After acidic removal of the Boc group, (*S*)-Boc-alanine (**22**) was coupled by use of bis-(2-oxo-3-oxazolidinyl)phosphinic chloride (BopCl)[15] to give the tripeptide (**23**). Iodination of the tripeptide with iodine-mercuric acetate afforded the iodinated tripeptide (**24**), which upon alkaline hydrolysis gave the tripeptide carboxylic acid (**25**).

The polyketide (**17**) was first converted to the *tert*-butyl ester (**26**) with *O-tert*-butyl-*N,N'*-diisopropylisourea,[16] and its TBS group was cleaved with tetrabutylammonium fluoride (TBAF) to give the alcohol (**27**) (Scheme 4). Coupling of the alcohol (**27**) with the tripeptide (**25**) did not proceed at all, and



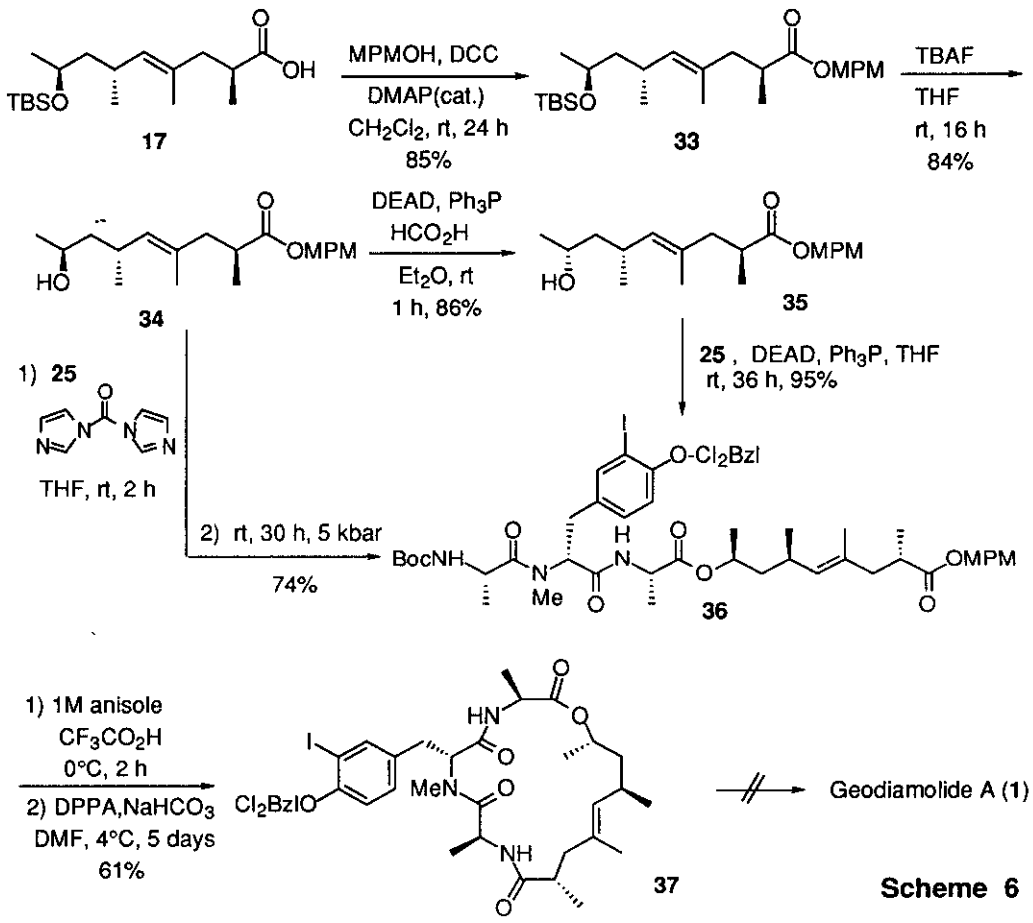
the alcohol (**27**) was recovered. The ester exchange method utilizing titanium isopropoxide[17] between the methyl ester (**24**) and (**27**), however, afforded the desired linear precursor (**29**) of geodiamolide A in 63% yield. Attempted removal of the *tert*-butyl ester function from **29** failed under various conditions, which led us to change the protective group at the carboxylic acid of the polyketide from the *tert*-butyl ester to the corresponding trichloroethyl (Tce) ester. Thus the carboxylic acid (**17**) was converted to the trichloroethyl ester (**30**), whose protective group at the hydroxyl function was deblocked with aq. hydrofluoric acid, as shown in Scheme 5. The resulting trichloroethyl ester (**31**) was subjected to the coupling with the tripeptide (**25**) or its derivatives under various conditions including the ester exchange method. However, all of the reactions so far tried failed to give the linear precursor (**32**) in good yield. We thought at this stage the use of the Mitsunobu reaction.[18] Although it gave multiproducts in the coupling of **25** with **31**, changing the trichloroethyl function with other protective groups which would not react with phosphine was considered to give a favorable result.



Scheme 5

The protective group we chose was the 4-methoxyphenylmethyl (MPM) group. Thus, the carboxylic acid (**17**) was converted to the *sec*-hydroxy MPM ester (**34**) *via* the corresponding TBS derivative (**33**), as shown in Scheme 6. The Mitsunobu reaction of **34** by use of formic acid smoothly afforded the MPM ester (**35**) which was inverted at the hydroxy function. The coupling of the alcohol (**35**) with the tripeptide (**25**) smoothly proceeded by use of triphenylphosphine and diethyl azodicarboxylate (DEAD) to give the linear precursor (**36**) in excellent yield. Furthermore, the imidazolide from the tripeptide (**25**) was found to be easily coupled with the alcohol (**34**) under a high pressure (5 kbar) to give **36**. This will be the first successful example of the esterification under a high pressure utilizing such a complicated functionalized substrate. Final task to synthesize geodiamolide A (**1**) was deblocking at the *N*- and *C*-terminals, cyclization, and deprotection of the tyrosine residue. Acidic treatment of **36**, followed by the cyclization with diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$)[14] afforded the 2,6-dichlorobenzyl derivative (**37**) of **1**. Unfortunately, however, final deprotection at the tyrosine residue did not smoothly proceed at all. Thus we had to change the protective group at the tyrosine residue from the 2,6-dichlorobenzyl to the more acid-labile TBS group.

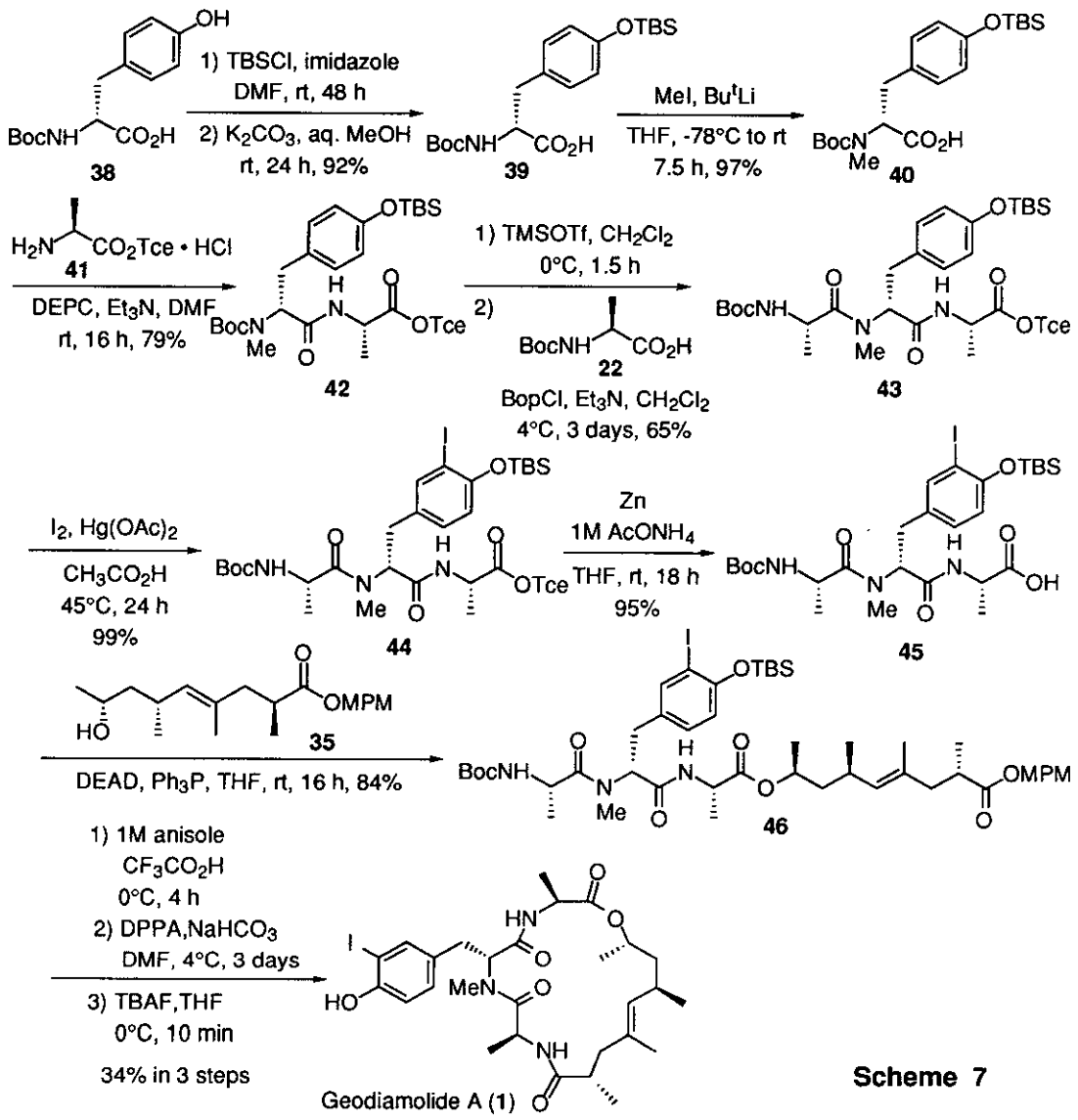
Boc-(*R*)-tyrosine (**38**) was first converted to the *O*-TBS tyrosine derivative (**39**), which was methylated



Scheme 6

with methyl iodide using *tert*-butyllithium,[6a] as shown in Scheme 7. The resulting *N*-methylated carboxylic acid (**40**) was coupled with (*S*)-alanine trichloroethyl ester hydrochloride (**41**) using DEPC to give the dipeptide (**42**). Selective deprotection of the Boc group from **42** with trimethylsilyl triflate (TMSOTf), followed by coupling with Boc-(*S*)-alanine (**22**) afforded the tripeptide (**43**), which was iodinated as above to give the iodide (**44**). Removal of the trichloroethyl function afforded the required tripeptide (**45**). Coupling of **45** with the polyketide (**35**) also smoothly proceeded under the Mitsunobu conditions to give the linear precursor (**46**). Treatment with trifluoroacetic acid-anisole followed by DPPA afforded the TBS derivative of **1**, whose TBS function was easily cleaved with TBAF to give geodiamolide A (**1**).

Thus, we succeeded in an expeditious synthesis of geodiamolide A in an overall yield of *ca.* 6% based on the starting diol (**8**) in 16 steps. The procedure developed here will offer a new synthetic strategy for complicated cyclic depsipeptides and can be used for the large scale synthesis of the biologically interesting molecule (**1**). Furthermore, the success of the esterification under a high pressure will stimulate the other application to the reactions under a high pressure.



Scheme 7

EXPERIMENTAL

General. Melting points are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-2 or SHIMADZU FTIR-8100 spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL PMX-60, FX-100, EX-270, or GSX-400 spectrometer in deuterio solvent using tetramethylsilane (TMS) or $CHCl_3$ as an internal standard. Mass spectra were obtained on a JEOL DX-300 spectrometer. Optical rotations were measured on a JASCO DIP-140 automatic polarimeter. Analytical thin layer chromatography was carried out using MERCK precoated silica gel (Art 5715). Column chromatography was carried out using silica gel BW-820MH or BW-200 (purchased from Fuji Davison Co.). Tetrahydrofuran (THF) was dried by

distillation from benzophenone ketyl. Diethyl ether (Et_2O) was dried by distillation from lithium aluminum hydride. Toluene and dichloromethane (CH_2Cl_2) were dried by distillation from calcium hydride. Other solvents were distilled and stored over molecular sieves (4A).

(2*S*, 4*S*)-4-*tert*-Butyldimethylsiloxy-2-pentanol (11)

To a solution of (2*S*,4*S*)-2,4-pentanediol (**8**) (1.050 g, 10.08 mmol) in THF (20 mL) was added NaH (60% oil suspension) (483 mg, 12.08 mmol) under an argon atmosphere. After being stirred at rt for 2 h, TBSCl (1.809 g, 12.03 mmol) was added and stirring was continued for 45 min. After dilution with Et_2O, the mixture was washed with 10% aqueous K_2CO_3, saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-820MH, 140 g, hexane : EtOAc = 10 : 1) to give **11** (2.091 g, 95%) as a colorless oil. $[\alpha]_D^{24}$ +38.2° (c = 1.2, $CHCl_3$); IR ν_{max}^{neat} cm^{-1}: 3400 (OH), 1460, 1250, 1116; ^1H NMR (400 MHz, $CHCl_3$ / $CDCl_3$) δ: 0.09, 0.10 (s x 2, 6H, $(CH_3)_2Si$), 0.91 (s, 9H, $(CH_3)_3C$), 1.17 (d, 3H, J = 6.2 Hz, CH_3-C(4)), 1.23 (d, 3H, J = 6.4 Hz, CH_3-C(2)), 1.46-1.69 (m, 2H, CH_2), 3.44 (brs, 1H, OH), 4.16-4.23 (m, 2H, CH x 2); *Anal.* Calcd for $C_{11}H_{26}O_2Si$: C, 60.49; H, 12.00. Found: C, 60.29; 11.97.

(2*S*, 4*S*)-4-*tert*-Butyldimethylsiloxy-2-pentyl 4-methylphenylsulfonate (12)

To a solution of **11** (2.189 g, 10.02 mmol) in pyridine (20 mL) was added TsCl (3.085 g, 16.18 mmol). After being stirred at 4℃ for 72 h, H_2O (2 mL) was then added and the mixture was stirred in an ice bath for 30 min. After dilution with Et_2O, the mixture was washed with 1M aqueous $KHSO_4$, saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-820MH, 100 g, hexane : EtOAc = 20 : 1) to give **12** (3.139 g, 84%) as a colorless oil. $[\alpha]_D^{24}$ +20.5° (c = 0.92, $CHCl_3$); IR ν_{max}^{neat} cm^{-1}: 2930, 1600, 1460, 1360, 1250, 1180; ^1H NMR (270 MHz, $CHCl_3$ / $CDCl_3$) δ: 0.04, 0.06 (s x 2, 6H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3C$), 1.09 (d, 3H, J = 5.9 Hz, CH_3-C(4)), 1.23 (d, 3H, J = 6.3 Hz, CH_3-C(2)), 1.53-1.80 (m, 2H, CH_2), 2.44 (s, 3H, CH_3-Ph), 3.84-3.91 (m, 1H, CH-OSi), 4.78-4.87 (m, 1H, CH-OSO_2), 7.32, 7.78 (ABq, 4H, J = 8.3 Hz, Ph); *Anal.* Calcd for $C_{18}H_{32}O_4SSi$: C, 50.03; H, 8.66. Found: C, 58.77; 8.82.

(2*S*, 4*S*)-4-*tert*-Butyldimethylsiloxy-2-methylpentanenitrile (13)

To a solution of **12** (2.365 g, 6.35 mmol) in HMPA (7 mL) was added LiCN (840 mg, 25.49 mmol) in an ice bath and the mixture was stirred at the same temperature for 30 min. After being stirred at rt for 24 h, the mixture was diluted with EtOAc, washed with H_2O, saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-820MH, 200 g, hexane : EtOAc = 20 : 1) to give **13** (1.227 g, 85%) as a colorless oil. $[\alpha]_D^{24}$ +10.0° (c = 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1}: 2950, 2375 (CN), 1460, 1370, 1250; ^1H NMR (400 MHz, $CHCl_3$ / $CDCl_3$) δ: 0.06, 0.07 (s x 2, 6H, $(CH_3)_2Si$), 0.89 (s, 9H, $(CH_3)_3C$), 1.19 (d, 3H, CH_3-C(2)), 1.31 (d, 3H, J = 6.9 Hz, CH_3-C(4)), 1.54-1.64, 1.84-1.91 (m x 2, 2H, CH_2), 2.72-2.79 (m, 1H, CH-CN), 3.90-3.97 (m, 1H, CH-OSi); *Anal.* Calcd for $C_{12}H_{25}NOSi$: C, 63.38; H, 11.08; N, 6.16. Found: C, 63.24; H, 11.04; N, 5.77.

Ethyl (2*E*, 4*R*, 6*S*)-6-*tert*-butyldimethylsiloxy-2,4-dimethyl-2-heptenoate (14)

To a stirred solution of **13** (1.313 g, 5.77 mmol) in CH_2Cl_2 (5 mL) cooled in a dry ice-acetone bath was added dropwise a 0.93 M solution of DIBAL in hexane (6.4 mL, 5.95 mmol) under an argon atmosphere. After being stirred at -78℃ for 1.5 h, the reaction mixture was quenched with 1 M aqueous $KHSO_4$, and warmed to rt. After dilution with Et_2O, the mixture was washed with H_2O, saturated brine, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude aldehyde. The phosphorane (**7**) (3.901 g, 10.76 mmol) was added to a solution of the crude aldehyde in CH_2Cl_2 (7 mL). After being stirred at rt for 3 days under an argon atmosphere, the reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 200 g, hexane : EtOAc = 20 : 1) to give **14** (1.418 g, 78%) as a colorless oil. $[\alpha]_D^{24}$ -15.8° (c = 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} : 2930, 1717 (C=O), 1256, 1134, 906; ^1H NMR (400 MHz, TMS / $CDCl_3$) δ: 0.05 (s, 6H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3C$), 1.10 (d, 3H, J = 6.6 Hz, CH_3-C(4)), 1.11 (d, 3H, J = 6.1 Hz, CH_3-C(7)), 1.29 (t, 3H, J = 7.1 Hz, CH_3-CH_2) 1.38-1.53 (m, 2H, CH_2-C(4)), 1.84 d, 3H, J = 0.2 Hz, CH_3-C=), 2.63-2.66 (m, 1H, CH=C), 3.76-3.79 (m, 1H, CH-OSi), 4.18 (q, 2H, J = 3.5 Hz, CH_3-CH_2), 6.56 (dd, 1H, J = 1.3, 8.6 Hz, CH=C); *Anal.* Calcd for $C_{17}H_{34}O_3Si$: C, 64.92; H, 10.90. Found: C, 64.57; 10.94.

(2*E*, 4*R*, 6*S*)-6-*tert*-Butyldimethylsiloxy-2,4-dimethyl-2-hepten-1-ol (15)

To a stirred solution of **14** (546 mg, 1.74 mmol) in CH_2Cl_2 (3 mL) cooled in a dry ice-acetone bath was added dropwise a 1.5 M solution of DIBAL in toluene (2.5 mL, 3.75 mmol) under an argon atmosphere. The mixture was stirred at -78℃ for 30 min. After being quenched with 1 M aqueous $KHSO_4$, the mixture was warmed to rt and diluted with Et_2O. The mixture was washed with H_2O, saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-820MH, 50 g, hexane : EtOAc = 10 : 1) to give **15** (421 mg, 89%) as a colorless oil. $[\alpha]_D^{24}$ -1.6° (c = 0.91, $CHCl_3$); IR ν_{max}^{neat} cm^{-1}: 3335 (OH), 2930, 1462, 1361, 1051, 835 ; ^1H NMR (400 MHz, TMS / $CDCl_3$) δ: 0.049, 0.051 (s x 2, 6H, $(CH_3)_2Si$), 0.89 (s, 9H, $(CH_3)_3C$), 0.93 (d, 3H, J = 6.8 Hz, CH_3-C(4)), 1.11 (d, 3H, J = 6.0 Hz, CH_3-C(6)), 1.19-1.33 (m, 2H, CH_2-C(4)), 1.67 (d, 3H, J = 1.5 Hz, CH_3-C=), 2.48-2.55 (m, 1H, CH=C), 3.73-3.81 (m, 1H, CH-OSi), 3.98 (s, 2H, CH_2-OH), 5.22 (dd, 1H, J = 1.3, 9.5 Hz, CH=C); *Anal.* Calcd for $C_{15}H_{32}O_2Si$: C, 66.12; H, 11.83. Found: C, 66.17; 11.67.

(5'*S*)-5'-Benzyloxazolidinyl (2*S*, 4*E*, 6*R*, 8*S*)-8-*tert*-butyldimethylsiloxy-2,4,6-trimethyl-4-nonenamide (16)

To a stirred mixture of **15** (163 mg, 0.89 mmol), triphenylphosphine (234 mg, 0.89 mmol), and imidazole (64 mg, 0.94 mmol) in THF / MeCN (2.1 mL / 0.7 mL) in an ice-MeOH bath was added iodine (224 mg, 0.88 mmol) in one portion. The mixture was stirred at -10℃ for 10 min and quenched with saturated aqueous $Na_2S_2O_3$. After dilution with Et_2O, the mixture was washed with 1 M aqueous $KHSO_4$ and saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was rapidly purified by silica gel column chromatography (BW-200, 40 g, hexane : Et_2O = 10 : 1) under protection of light to give the crude iodide. A solution of a 1.0 M sodium hexamethyldisilazide in THF (1.25 mL, 1.25 mmol) was

added to a solution of the chiral oxazolidinone (**5**) (277 mg, 1,19 mmol) in THF (0.5 mL) cooled in a dry ice-acetone bath under an argon atmosphere. After being stirred at -78℃ for 1 h, the crude iodide in THF (0.5 mL x 2) was added dropwise to the reaction mixture. The mixture was stirred at -72℃ for 24 h, quenched with saturated aqueous NH_4Cl, and allowed to warm to rt. The mixture was extracted with CH_2Cl_2 (x 3). The organic extracts were washed with saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 50 g, hexane : EtOAc : benzene = 6 : 2 : 1) to give **16** (214 mg, 75%) as a pale yellow oil. $[\alpha]_D^{24}$ -35.2°(c = 0.94, $CHCl_3$); IR ν_{max}^{neat} cm^{-1}: 2930, 1782 (C=O), 1701 (C=O) 1350, 1209, 1051, 835; ^1H NMR (400 MHz, TMS / $CDCl_3$) δ: 0.04 (s, 6H, $(CH_3)_2Si$), (0.88 (s, $(CH_3)_3C$), 0.89 (d, J = 6.6 Hz, CH_3-C(6)), 12H), {1.10 (d, J = 6.0 Hz, CH_3-C(2)), 1.11 (d, J = 6.8 Hz, CH_3-C(8)), 6H}, 1.26-1.31, 1.41-1.48 (m x 2, 2H, CH_2-C(6)), 1.66 (d, 3H, J = 1.3 Hz, CH_3-C=), 1.99 (dd, 1H, J = 8.8, 13.7 Hz, C<u>H</u>$_2$-Ph), 2.36-2.47 (m, 2H, CH_2-C(3)), 2.61-2.67 (m, 1H, CH-C=), 3.28 (dd, 1H, J = 3.3, 13.4 Hz, C<u>H</u>$_2$-Ph), 3.74-3.79 (m, 1H, CH-C=O), 3.92-3.96 (m, 1H, CH- OSi), 4.12-4,21 (m, 2H, CH_2-O), 4.66-4.71 (m, 1H, N-CH), 5.01 (d, 1H, J = 9.3 Hz, CH=C), 7.26-7.34 (m, 5H, <u>Ph</u>); *Anal.* Calcd for $C_{28}H_{45}NO_4Si$: C, 68.95; H, 9.30; N, 2.87. Found: C, 68.88; H,9.21; N, 3.00.

(2*S*, 4*E*, 6*R*, 8*S*)-8-*tert*-Butyldimethylsiloxy-2,4,6-trimethyl-4-nonenoic acid (17)

To a solution of **16** (1.326 g, 2.72 mmol) in THF / H_2O (20 mL / 5 mL) was added dropwise 30% aq. H_2O_2 (2.4 mL) and LiOH (264 mg, 6.29 mmol) in one portion. The reaction mixture was stirred at 0℃ for 1 h and quenched with saturated 1 M aqueous Na_2SO_3 (25 mL). After dilution with Et_2O, the mixture was washed with saturated aqueous $NaHCO_3$, 1 M aqueous $KHSO_4$ and saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 140 g, hexane : Et_2O = 5 : 1) to give **17** (857 mg, 96%) as a colorless oil. $[\alpha]_D^{24.5}$ -9.2°(c = 1.1, $CHCl_3$) (lit.[5c] $[\alpha]_D^{26}$ -9.7° (c = 1.3, $CHCl_3$)), IR ν_{max}^{neat} cm^{-1}: 3200 (CO<u>OH</u>), 2959, 1713 (C=O), 1417, 1256, 1051, 835; ^1H NMR (400 MHz, TMS / $CDCl_3$) δ: 0.04 (s, 6H, $(CH_3)_2Si$), {0.88 (s, $(CH_3)_3C$), 0.91 (d, J = 6.8 Hz, CH_3-C(6)), 12H}, 1.10 (d, J = 6.1 Hz, CH_3-C(2)), 1.15 (d, J = 7.1 Hz, CH_3-C(8)), 6H}, 1.24-1.33, 1.40-1.47 (m x 2, 2H, CH_2-C(6)), 1.60 (d, 3H, J = 0.7 Hz, CH_3-C=), 2.00-2.06 (m, 1H, CH_2-C), 2.36-2.47 (m, 2H, CH_2-C=, CH-C=), 2.60-2.65 (m, 1H, CH-C=0), 3.73-3.78 (m, 1H, CH-OSi), 4.97 (d, 1H, J = 8.8 Hz, CH=C).

***N*-*tert*-Butoxycarbonyl-*O*-2,6-dichlorobenzyl-*N*-methyl-(*R*)-tyrosine (19)**

To a solution of *N*-*tert*-butoxycarbonyl-*O*-2',6'-dichlorobenzyl-(*R*)-tyrosine (**18**) (2.950 g, 6.70 mmol) in THF (18 mL) was carefully added NaH (60% oil suspension) (1.110 g, 27.75 mmol) and MeI (3.4 mL, 54.61 mmol) in an ice bath, and stirring was continued for 30 min. The reaction mixture was allowed to warm to rt and stirred for 56 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and washed with some portion of Et_2O. The aqueous layer was acidified to pH 4 with 1 M aqueous $KHSO_4$ and the mixture was extracted with EtOAc (x 3). The organic extracts were dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 100g, Et_2O only) to give **19** (2.866 g, 95%) as a white amorphous solid. Recrystallization from Et_2O gave

white crystals; mp 103-104℃; $[\alpha]_D^{24.5}$ -37.1° (c=1.0, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (COOH), 1680 (C=O), 1512, 1240, 1019, 763; ^1H NMR (400 MHz, TMS / $CDCl_3$) δ: 1.23, 1.29 (s x 2, 9H, $(CH_3)_3C$), 2.50, 2.51 (s x 2, 3H, N-CH_3), 2.87-2.96 (m, 1H, Tyr$^\beta CH_2$), 3.08-3.12 (m, 1H, Tyr$^\beta CH_2$), 4,56-4.58, 4.73-4.76 (m x 2, 1H, Tyr$^\alpha$CH), 5.18 (s, 2H, CH_2-Ph), 6.98 (d, 2H, J = 8.4 Hz, Tyr C_3-H, C_5-H), 7.15 (d, 2H, J = 8.3 Hz, Tyr C_2-H, C_6-H), 7.46 (dd, 2H, J = 8.4 Hz, Cl_2Ph C4-H), 7.55 (d, 2H, J = 8.3 Hz, Cl_2Ph C3-H, C5-H); *Anal.* Calcd for $C_{22}H_{25}Cl_2NO_5$: C, 57.72; H, 5.55; N, 3.08. Found: C, 58.13; H, 5.59; N, 2.98.

Boc-(*R*)-*N*-Me-Tyr(2,6-Cl_2Bzl)-(*S*)-Ala-OMe (21)

To a solution of **19** (849 mg, 1.87 mmol) and (*S*)-Ala-OMe•HCl (**20**) (310 mg, 2.22 mmol) in DMF (4 mL) was added DEPC (410 μL, 2.70 mmol) followed by Et_3N (680 μL, 4.87 mmol) in an ice bath, and the mixture was stirred for 2 h, and allowed to warm to rt and stirred for 55 h. After dilution with EtOAc, the mixture was washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 140g, hexane : EtOAc = 3 : 2) to give **21** (918 mg, y. 91%) as a white amorphous solid; mp 35-37℃; $[\alpha]_D^{24.5}$ +62.6° (c=0.93, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3324 (NH), 1746 (C=O), 1680 (C=O), 1512, 1240, 1163, 1019, 766 ; ^1H NMR (400 MHz, TMS / $CDCl_3$) δ: {1.23, 1.29 (s x 2, $(CH_3)_3C$), 1.32 (d, J = 0.7 Hz, Ala CH_3), 12H}, {2.77, 2.84 (s x 2, N-CH_3), 2.73-2.90 (m, Tyr$^\beta CH_2$), 4H}, 3.28-3.38 (m, 1H, Tyr$^\beta CH_2$), 3.73 (s, 3H, OCH_3), 4.54-4.61 (m, 1H, Ala$^\alpha$CH), 4.54-4.61 (m, 1H, Tyr$^\alpha$CH), 5.23 (s, 2H, CH_2-Ph), 6.94 (d, 2H, J = 8.3 Hz, Tyr C_3-H, C_5-H), 7.16 (d, 2H, J = 8.2 Hz, Tyr C_2-H, C_6-H), 7.24 (d, 1H, J = 7.5 Hz, Cl_2Ph C4-H), 7.55 (d, 2H, J = 7.7 Hz, Cl_2Ph C_3-H, C_5-H); *Anal.* Calcd for $C_{26}H_{29}Cl_2N_2O_6 \cdot 1/2H_2O$: C, 57.24; H, 5.54; N, 5.14. Found: C, 57.33; H, 5.95; N, 4.93.

Boc-(*S*)-Ala-(*R*)-*N*-Me-Tyr(2,6-Cl_2Bzl)-(*S*)-Ala-OMe (23)

To a solution of **21** (2.522 g, 5.03 mmol) in CH_2Cl_2 (5 mL) was added CF_3CO_2H (5 mL) in an ice bath. The reaction mixture was stirred at rt for 45 min, and concentrated. After dilution with EtOAc, the mixture was washed with saturated aqueous $NaHCO_3$ and saturated brine, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude *N*-terminal free peptide. BopCl (1.692 g, 6.45 mmol) and Et_3N (1.5 mL, 10.75 mmol) were added to a solution of the crude peptide and Boc-(*S*)-Ala-OH (**22**) (1.153 g, 6.09 mmol) in CH_2Cl_2 (4 mL) in an ice bath. The reaction mixture was stirred for at 4℃ 64.5 h. After dilution with EtOAc, the mixture was washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 200g, hexane : EtOAc = 3 : 2) to give **23** (2.162 g, 75%) as a white amorphous solid. Recrystallization from Et_2O gave white powders; mp 89℃; $[\alpha]_D^{27}$ +42.6° (c = 1.1, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3339 (NH), 1746 (C=O), 1655 (C=O), 1514, 1242, 1170, 756; ^1H NMR (400 MHz, TMS / $CDCl_3$) δ: 0.90 (d, 3H, J = 7.0 Hz, Ala CH_3), {1.40 (d, J = 4.6 Hz, Ala CH_3), 1.41 (s, $(CH_3)_3C$), 12H}, {2.88 (m, Tyr$^\beta CH_2$), 2.96 (s, N-CH_3), 4H}, 3.34-3.40 (m, 1H, Tyr$^\beta CH_2$), 3.73 (s, 3H, OCH_3), 4.38-4.43 (m, 1H, Ala$^\alpha$CH), 4.53-4.59 (m, 1H, Ala$^\alpha$CH), 5.57-5.61 (m, 1H, Tyr$^\alpha$CH), 5.14 (br d, 1H, J = 7.1 Hz, NH), 5.22, 5.30 (s x 2, 2H, CH_2-Ph), 6.70 (br d, 1H, J = 7.1 Hz, NH), 6.92 (d, 2H, J = 8.6

Hz, Tyr C3-H, C5-H), 7.13 (d, 2H, J = 8.6 Hz, Tyr C2-H, C6-H), 7.24 (d, 1H, J = 8.7 Hz, Cl_2Ph C4-H), 7.35 (d, 2H, J = 8.4 Hz, Cl_2Ph C3-H, C5-H); *Anal.* Calcd for $C_{29}H_{37}Cl_2N_3O_7 \cdot 1/4Et_2O$: C, 57.28; H, 6.33; N, 6.68. Found: C, 57.27; H, 6.00; N, 6.33.

Boc-(*S*)-Ala-(*R*)-*N*-Me-Tyr(3-I-*O*-2,6-Cl_2Bzl)-(*S*)-Ala-OMe (24)

To a solution of **23** (634 mg, 10.38 mmol) in AcOH (10 mL) was added I_2 (2.657 g, 10.47 mmol) and $Hg(OAc)_2$ (3.328 g, 1.04 mmol) at rt. The reaction mixture was stirred at 50℃ for 24 h and quenched with saturated aqueous $Na_2S_2O_3$. After dilution with EtOAc, the mixture was washed with saturated aqueous $NaHCO_3$, saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 100g, hexane : EtOAc = 1 : 1) to give **24** (580 mg, 76%) as a white amorphous solid; mp 62-64℃; $[\alpha]_D^{24.5}$ +26.4° (c=1.1, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3339 (NH), 2982, 1756 (C=O), 1640 (C=O), 1248, 1169, 756 ; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.98 (d, 3H, J = 6.9 Hz, Ala CH_3), {1.41 (s, $(CH_3)_3C$), 1.42 (d, J = 5.0 Hz, Ala CH_3), 12H}, 2.85 (dd, 1H, J = 10.7, 15.0 Hz, Tyr$^\beta CH_2$), 2.98 (s, 3H, N-CH_3), 3.36 (dd, 1H, J = 5.8, 15.3 Hz, Tyr$^\beta CH_2$), 3.73 (s, 3H, OCH_3), 4.38-4.43, 4.52-4.56 (m x 2, 2H, Ala$^\alpha$CH x 2), 5.24 (br d, 1H, J = 6.3 Hz, NH), 5.26 (s, 2H, $C\underline{H}_2$-Ph), 5.70 (dd, 1H, J = 5.9, 10.6 Hz, Tyr$^\alpha$CH), 6.78 (brd, 1H, J = 7.3 Hz, NH), 6.93 (d, 1H, J = 8.2 Hz, Tyr C5-H), 7.17 (dd, 1H, J = 2.0, 8.3 Hz, Tyr C6-H), 7.26 (d, 1H, J = 8.9 Hz, , Cl_2Ph C4-H), 7.36 (d, 2H, J = 8.9 Hz, Cl_2Ph C3-H, C5-H), 7.57 (d, 1H, J = 2.0 Hz, Tyr C2-H); FABMS (glycerin): m/z 736 (M+1).

Boc-(*S*)-Ala-(*R*)-*N*-Me-Tyr(3-I-*O*-2,6-Cl_2Bzl)-(*S*)-Ala-OH (25)

To a solution of **24** (367 mg, 0.50 mmol) in MeOH / H_2O (4 mL / 1 mL) was added in one portion LiOH (49 mg, 1.17 mmol). The reaction mixture was stirred at 0℃ for 12 h. The mixture was diluted with saturated aqueous $NaHCO_3$ and washed with some portion of Et_2O. The aqueous layer was acidified to pH 4 with 1 M aqueous $KHSO_4$ and the mixture was extracted with EtOAc (x 3). The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give **25** (318 mg, 88%) as white solids. Recrystallization from MeOH gave a white powder; mp 109-110℃; $[\alpha]_D^{24.5}$ +28.3°(c=1.1, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430 (C$\underline{O}$O$\underline{H}$, NH), 2984, 1670 (C=O), 1489, 1250, 1042 ; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.97 (d, 3H, J = 6.9 Hz, Ala CH_3), {1.41 (s, $(CH_3)_3C$), 1.45 (d, J = 7.7 Hz, Ala CH_3), 12H}, 2.87 (dd, 1H, J = 10.7, 15.2 Hz, Tyr$^\beta CH_2$), 2.96 (s, 3H, N-CH_3) 3.35 (dd, 1H, J = 4.6, 14.8 Hz, Tyr$^\beta CH_2$), 4.39-4.44, 4.54-4.59 (m x 2, 2H, Ala$^\alpha$CH x 2), 5.16 (br d, 1H, J = 4.6 Hz, NH), 5.16 (s, 2H, $C\underline{H}_2$-Ph), 5.57 (dd, 1H, J = 5.3, 10.5 Hz, Tyr$^\alpha$CH), 6.82 (br d, 1H, J = 7.3 Hz, NH), 6.93 (d, 1H, J = 8.9 Hz, Tyr C5-H), 7.17 (dd, 1H, J = 2.0, 8.9 Hz, Tyr C6-H), 7.17 (d, 1H, J = 8.9 Hz, Cl_2Ph C4-H), 7.36 (d, 2H, J = 8.9 Hz, Cl_2Ph C3-H, C5-H), 7.58 (d, 1H, J = 2.0 Hz, Tyr C2-H); FABMASS (glycerin) : m/z 722 (M+1).

***tert*-Butyl (2*S*, 4*E*, 6*R*, 8*S*)-8-*tert*-butyldimethylsiloxy-2,4,6-trimethyl-4-nonenoate (26)**

To a solution of **17** (102 mg, 0.305 mmol) in Bu^tOH / CH_2Cl_2 (0.9 mL / 0.3 mL) was added *O*-Bu^t-*N*,*N*'-diisopropylisourea (600 μL, 2.51 mmol). The reaction mixture was stirred at 55℃ for 45 h and

then quenched with saturated H_2O. The mixture was extracted with CH_2Cl_2 (x 3). The organic extracts were washed with saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 40 g, hexane : EtOAc = 10 : 1) to give **26** (104 mg, 89%) as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 2930, 1732 (C=O), 1367, 1151, 835; ^1H NMR (400 MHz, TMS / $CDCl_3$) δ: 0.04 (s, 6H, $(CH_3)_2Si$), {0.88 (s, $(CH_3)_3C$), 0.90 (d, J = 6.8 Hz, CH_3-$C_{(6)}$), 12H}, 1.04 (d, 3H, J = 6.8 Hz, CH_3-$C_{(2)}$), 1.09 (d, 3H, J = 6.1 Hz, CH_3-$C_{(8)}$), {1.40-1.46 (m, CH_2-$C_{(6)}$), 1.43 (s, $(CH_3)_3C$) ,11H}, 1.58 (d, 3H, J = 1.3 Hz, CH_3-C=), 1.92-1.98 (m, 1H, CH_2-C=), 2.31-2.50 (m, 3H, CH_2-C=, CH-C= , CH-C=0), 3.73-3.78 (m, 1H, CH-OSi), 4.95 (d, 1H, J = 8.6 Hz, CH=C).

tert-Butyl (2*S*, 4*E*, 6*R*, 8*S*)-8-hydroxy-2,4,6-trimethyl-4-nonenoate (27)

To a solution of **26** (481 mg, 1.23 mmol) in THF (3 mL) was added TBAF (979 mg, 3.10 mmol). The reaction mixture was stirred at rt for 24 h. After dilution with Et_2O, the mixture was washed with H_2O and saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 50 g, hexane : EtOAc = 8 : 1) to give **27** (307 mg, 93%) as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 3420 (OH), 2930, 1732 (C=O), 1458, 1257, 967; ^1H NMR (400 MHz, TMS / $CDCl_3$) δ: 0.94 (d, 3H, J = 6.6 Hz, CH_3-$C_{(6)}$) , 1.05 (d, 3H, J = 7.0 Hz, CH_3-$C_{(2)}$), 1.15 (d, 3H, J = 6.1 Hz, CH_3-$C_{(8)}$), {1.40 1.46 (m, CH_2-$C_{(6)}$), 1.43 (s, $(CH_3)_3C$), 11H}, 1.63 (d, 3H, J = 1.3 Hz, CH_3-C=), 1.94-2.00, 2.32-2.37 (m x 2, 2H, CH_2-C=), 2.46-2.55 (m, 2H, CH-C= , CH-C=0), 3.79-3.82 (m, 1H, CH-OSi), 5.02 (dd, 1H, J = 1.3, 9.7 Hz, CH=C); *Anal.* Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.90; H, 11.07.

tert-Butyl Boc-(*S*)-Ala-(*R*)-*N*-Me-Tyr(3-I-*O*-2,6-Cl_2Bzl)-(*S*)-Ala-8-oxy-(2*S*, 4*E*, 6*R*, 8*S*)-2,4,6-trimethyl-4-nonenoate (29)

To a mixture of **24** (34 mg, 0.046 mmol) and **27** (67 mg, 0.248 mmol) was added $Ti(O\text{-}Pr^i)_4$ (4 μL, 3.10 μmol). The reaction mixture was stirred at 110℃ for 21 h under reduced pressure by an aspirator (15-30 mmHg). After dilution with EtOAc, the mixture was washed with saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified on a TLC plate (Merck Art 5744 0.5 mm, hexane : EtOAc = 2 : 1) to give **29** (24 mg, 63%) as a colorless oil. ^1H NMR (270 MHz, TMS / $CDCl_3$) δ: 0.92 (d, 3H, J = 6.6 Hz, CH_3-$C_{(6)}$), 0.97 (d, 3H, J = 6.9 Hz, Ala CH_3), 1.06 (d, 3H, J = 6.6 Hz, CH_3-$C_{(2)}$), {1.22 (d, J = 6.3 Hz, CH_3-$C_{(8)}$), 1.36 (d, J = 6.6 Hz, Ala CH_3), 1.26-1.40 (m, CH_2-$C_{(6)}$), 8H}, 1.42, 1.43 (s x 2, $(CH_3)_3C$) x 2, 18H), 1.60 (d, 3H, J = 1.3 Hz, CH_3-C=), 1.93-2.05 (m, 1H, CH_2-C=), 2.30-2.53 (m, 3H, CH_2-C=, CH-C=, CH-C=0), 2.81-2.96 (m, 1H, Tyr$^\beta$$CH_2$), 2.99 (s, 3H, CH_3-N), 3.34-3.41 (m, 1H, Tyr$^\beta$$CH_2$), 4.36-4.54 (m, 2H, Ala$^\alpha$CH x 2), {4.89-4.94 (m, CH-O), 4.98 (d, J = 8.6 Hz, CH=C), 2H}, 5.18 (d, 1H, J = 6.6 Hz, NH), 5.27 (s, 2H, C<u>H</u>$_2$Ph), 5.54-5.58 (m, 1H, Tyr$^\alpha$CH), 6.76 (d, 1H, J = 6.9 Hz, NH), 6.94 (d, 1H, J = 8.6 Hz, Tyr C_5-H), 7.18 (dd, 1H. J = 1.7, 8.3 Hz, Tyr C_6-H), 7.25 (dd, 1H, J = 6.9, 8.9 Hz, Cl_2<u>Ph</u> C_4-H), {7.34 (d, J = 7.3 Hz), 7.35 (d, J = 8.6 Hz), 2H, Cl_2<u>Ph</u> C_3-H, C_5-H}, 7.58 (d, 1H, J = 1.7 Hz, Tyr C_2-H).

2,2,2-Trichloroethyl (2*S*, 4*E*, 6*R*, 8*S*)-8-*tert*-butyldimethylsiloxy-2,4,6-trimethyl-4-nonenoate (30)

To a solution of **17** (71 mg, 0.22 mmol) and TceOH (50 mL, 0.52 mmol) in CH_2Cl_2(0.5 mL) was added DCC (62 mg, 0.30 mmol) and DMAP (10 mg, 0.08 mmol) in an ice bath, and the mixture was stirred at the same temperature for 2 h and at rt for 9 h. After dilution with Et_2O, the mixture was successively washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 20 g, hexane : Et_2O = 10 : 1) to give **30** (107 mg, 96%) as a pale yellow oil. $[\alpha]_D^{24}$ -10.2° (c = 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1}: 2937, 1755 (C=O), 1458, 1102, 835; ^1H NMR (270 MHz, TMS / $CDCl_3$) δ: 0.04 (s, 6H, $(CH_3)_2Si$), {0.88 (s, $(CH_3)_3C$), 0.89 (d, J = 5.6 Hz, CH_3-C(6)), 12H}, 1.09 (d, 3H, J = 5.9 Hz, CH_3-C(2)), 1.17 (d, 3H, J = 6.6 Hz, CH_3-C(8)), 1.25-1.33 (m, 2H, CH_2-C(6)), 1.61 (d, 3H, J = 1.3 Hz, CH_3-C=), 1.90-2.11 (m, 2H, CH_2-C=), 2.41-2.45 (m, 1H, CH-C=), 2.72-2.78 (m, 1H, CH-C=0), 3.71-3.78 (m, 1H, CH-OSi), 4.71 (s, 2H, CH_2-Cl_3), 4.99 (d, 1H, J = 9.6 Hz, CH=C); *Anal.* Calcd for $C_{20}H_{37}O_2Cl_3Si$: C, 52.23; H, 8.11. Found: C, 52.39; H, 7.99.

2,2,2-Trichloroethyl (2*S*, 4*E*, 6*R*, 8*S*)-8-hydroxy-2,4,6-trimethyl-4-nonenoate (31)

To a solution of **30** (1.619 g, 3.52 mmol) in MeCN (17 mL) was added dropwise 46% aqueous HF (850 μL) in an ice bath. The reaction mixture was stirred at 0℃ for 25 h and then, quenched with H_2O : CH_2Cl_2 (1 : 1). The mixture was extracted with CH_2Cl_2 (x 2). The organic extracts were dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 100 g, hexane : Et_2O = 7 : 3) to give **31** (1.017 g, 84%) as a colorless oil. $[\alpha]_D^{24}$ -19.2° (c = 0.90, $CHCl_3$); IR ν_{max}^{neat} cm^{-1}: 3326 (OH), 1626 (C=O), 1458, 1244; ^1H NMR (270 MHz, TMS / $CDCl_3$) δ: 0.94 (d, 3H, J = 6.6 Hz, CH_3-C(6)), 1.15 (d, 3H, J = 6.6 Hz, CH_3-C(2)), 1.18 (d, 3H, J = 6.9 Hz, CH_3-C(8)), 1.37-1.44 (m, 2H, CH_2-C(6)), 1.65 (s, 3H, CH_3-C=), 2.05-2.13 (m, 1H, CH_2-C=), 2.40-2.48 (m, 2H, CH_2-C=, CH-C=), 2.74-2.82 (m, 1H, CH-C=0), 3.75-3.82 (m, 1H, CH-O), 4.70 (s, 2H, CH_2-CCl_3), 5.05 (d, 1H, J = 9.2 Hz, CH=C); *Anal.* Calcd for $C_{14}H_{23}O_3Cl_3$: C, 48.64; H, 6.71. Found: C, 48.46; H, 6.66.

***p*-Methoxybenzyl (2*S*,4*E*,6*R*,8*S*)-8-*tert*-butyldimethylsiloxy-2,4,6-trimethyl-4-nonenoate (33)**

To a solution of **17** (3.109 g, 9.46 mmol) and *p*-anisalcohol (1.5 mL, 12.03 mmol) in CH_2Cl_2(20 mL) was added DCC (2.055 g, 9.96 mmol), DMAP (83 mg, 0.68 mmol) in an ice bath and stirring was continued at the same temperature for 1 h. The reaction mixture was stirred at rt for 24 h. The mixture was filtered through the pad of celite and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 200 g, hexane : EtOAc = 4 : 1) to give **33** (3.068g, 85%) as a colorless oil. $[\alpha]_D^{24}$ -10.0° (c = 0.85, $CHCl_3$) ; IR ν_{max}^{neat} cm^{-1}: 2957, 1734(C=O), 1516, 1250, 1049 ; ^1H NMR (270 MHz, TMS / $CDCl_3$) δ : 0.03 (s, 6H, $(CH_3)_2Si$), {0.87 (s, $(CH_3)_3C$), 0.87 (d, J = 1.3Hz, CH_3-C(6)), 12H}, 1.08 (d, 6H, J = 5.9Hz, CH_3-C(2), CH_3-C(8)), 1.24-1.44 (m, 2H, CH_2-C(6)), 1.56 (s, 3H, CH_3-C=), 1.99-2.04 (m,1H, CH_2-C=), 2.59-2.64 (m, 2H, CH_2-C=, CH-C=), 2.72-

2.78 (m, 1H, CH-C=0), 3.70-3.77 (m, 1H, CH-OSi), 3.81 (s, 3H, CH_3O), 4.71 (s, 2H, CH_2-Cl3), 4.94 (d, 1H, J = 9.6 Hz, CH=C), 5.02 (s, 2H, CH_2Ph), 7.01 (d, 2H, J = 8.6 Hz, CH_3OPh C_2-H, C_6-H), 7.23 (d, 2H, J = 10.2 Hz, CH_3OPh C_3-H, C_5-H) ; *Anal.* Calcd for $C_{26}H_{44}O_4Si$: C, 69.60; H, 9.88. Found : C, 69.62; H, 9.90.

p-Methoxybenzyl (2*S*, 4*E*, 6*R*, 8*S*)-8-hydroxy-2,4,6-trimethyl-4-nonenoate (34)

To a solution of **33** (3.504 g, 7.81 mmol) in THF (15 mL) was added TBAF (8.648 g, 27.41 mmol) in an ice bath. The reaction mixture was stirred at rt for 16 h. After dilution with Et_2O, the mixture was washed with H_2O and saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 200 g, hexane : acetone = 4 : 1) to give **34** (2.195 g, 84%) as a colorless oil. $[\alpha]_D^{24}$ -21.7° (c = 0.85, $CHCl_3$) ; IR $\nu_{max}^{neat}cm^{-1}$: 3400 (OH), 2963, 1732 (C=O), 1516, 1250, 1167, 1036, 828 ; ^1H NMR (270 MHz, TMS / $CDCl_3$) δ : 0.90 (d, 3H, J = 6.6 Hz, CH_3-$C_{(6)}$) , 1.10 (d, 3H, J = 6.9 Hz, CH_3-$C_{(2)}$), 1.14 (d, 3H, J = 5.9 Hz, CH_3-$C_{(8)}$), 1.36-1.42 (m, 2H, CH_2-$C_{(6)}$), 1.60 (d, 3H, J = 1.3 Hz, CH_3-C=), 1.97-2.09 (m, 1H, CH_2-C=), 2.38-2.58 (m, 2H, CH_2-C=, CH-C=), 2.60-2.78 (m, 1H, CH-C=0), {3.78-3.90 (m, CH-O), {3.81 (s, CH_3O) 4H}, 4.98 (d, 1H, J = 9.9 Hz, CH=C), 5.02 (s, C<u>H</u>2Ph) 3H}, 6.88, 7.26 (ABq, 4H, J = 9.1Hz, <u>Ph</u>) ; *Anal.* Calcd for $C_{20}H_{30}O_4$: C, 71.84; H, 9.04. Found : C, 72.25; H, 9.12.

p-Methoxybenzyl (2*S*, 4*E*, 6*R*, 8*R*)-8-hydroxy-2,4,6-trimethyl-4-nonenoate (35)

To a stirred solution of **34** (37 mg, 0.11 mmol) and DEAD (179 mg, 1.02 mmol) in Et_2O (4 mL) was carefully added Ph_3P (266 mg, 1.01 mmol) and HCO_2H (38 μL, 1.01 mmol) in an ice bath and stirring was continued at the same temperature for 10 min. The reaction mixture was stirred at rt for 1 h. The solvent was evaporated, and the residue was treated with MeOH and saturated aqueous $NaHCO_3$. The solvent was removed *in vacuo*. After dilution with Et_2O, the mixture was washed with H_2O and saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified on a TLC plate (Merck Art 5744, 0.5 mm, hexane : EtOAc = 1 : 1) to give **35** (32 mg, 86%) as a colorless oil. $[\alpha]_D^{24}$ -25.1° (c = 0.56, $CHCl_3$) ; IR $\nu_{max}^{neat}cm^{-1}$: 3400 (OH), 2961, 1732 (C=O), 1516, 1250, 1169, 1036, 828 ; ^1H NMR (270 MHz, TMS / $CDCl_3$) δ : 0.90 (d, 3H, J = 6.6 Hz, CH_3-$C_{(6)}$), 1.10 (d, 3H, J = 6.6 Hz, CH_3-$C_{(2)}$), 1.15 (d, 3H, J = 6.3 Hz, CH_3-$C_{(8)}$), 1.20-1.33 (m, 2H, CH_2-$C_{(6)}$), 1.61 (d, 3H, J = 1.0 Hz, CH_3-C=), 1.98-2.08 (m, 1H, CH_2-C=), 2.34-2.42 (m, 1H, CH_2-C=), 2.52-2.70 (m, 2H, CH-C=, CH-C=0), 3.63-3.72 (m, 1H, CH-O), 3.81 (s, 3H, CH_3O), {4.90 (d, J = 9.6 Hz, CH=C), 5.02 (ABq J = 8.9 Hz, C<u>H</u>2Ph) 3H}, 6.90, 7.28 (ABq, 4H, J = 8.9 Hz, <u>Ph</u>) ; *Anal.* Calcd for $C_{20}H_{30}O_4$: C, 71.84; H, 9.04. Found : C, 71.46; H, 8.95.

p-Methoxybenzyl Boc-(*S*)-Ala-(*R*)-*N*-Me-Tyr(3-I-*O*-2,6-Cl_2Bzl)-(*S*)-Ala-8-oxy-(2*S*,4*E*,-6*R*, 8*R*)-8-hydroxy-2,4,6-trimethyl-4-nonenoate (36)

(a) From 35. To a stirred solution of **25** (353 mg, 0.489 mmol) and **35** (109 mg, 0.326 mmol) in THF (4 mL) was carefully added DEAD (800 μL, 5.02 mmol) and Ph_3P (1.298 g, 4.95 mmol) in an ice bath and stirring was continued for 30 min. The reaction mixture was stirred at rt for 36 h. The solvent was

evaporated. After dilution with EtOAc, the mixture was washed with saturated aqueous $NaHCO_3$ and saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 84 g, hexane : acetone = 3 : 1) to give **36** (323 mg, 95%) as a pale yellow oil. IR ν_{max}^{neat} cm^{-1}: 3347 (NH), 2978, 1732 (C=O), 1682 (C=O), 1514, 1246, 1169, 1036, 828 ; ^1H NMR (270 MHz, TMS / $CDCl_3$) δ : 0.90 (d, 3H, J = 6.7 Hz, CH_3-$C_{(6)}$), 1.10 (d, 3H, J = 7.3 Hz, Ala CH_3), 1.04 (d, 3H, J = 6.2 Hz, CH_3-$C_{(2)}$), 1.21 (d, 3H, J = 6.1 Hz, CH_3-$C_{(8)}$), {1.40 (d, J = 8.6 Hz, Ala CH_3), 1.34-1.44 (m, CH_2-$C_{(6)}$), 1.40 (s, $(CH_3)_3C$) 13H}, {1.55-1.64 (m, CH_2-$C_{(6)}$) 1.61 (d, J = 1.2 Hz, CH_3-C=), 4H}, 2.02 (dd, 1H, J = 7.4, 14.4 Hz, CH_2-C=), 2.34-2.40 (m, 1H, CH_2-C=), 2.44-2.50 (m, 1H, CH-C=), 2.60-2.68 (m, 1H, CH-C=O), {2.82-2.90 (m, Tyr$^{\beta}CH_2$), 2.99, 3.30 (s x 2, CH_3-N) 4H}, 3.34-3.39 (m, 1H, Tyr$^{\beta}CH_2$), 3.81 (s, 3H, CH_3O), 4.44-4.47, 4.48-4.96 (m x 2, 2H, Ala$^{\alpha}$CH x 2), 4.87-4.96 (m, 1H, CH-O), 4.90 (d, 1H, J = 6.8 Hz, CH=C),5.01-5.06 (m, 3H, CH_2-$PhOCH_3$, NH), 5.21, 5.26 (s x 2, 2H, CH_2-Cl_2Ph), 5.54-5.60 (m, 1H, Tyr$^{\alpha}$CH), 6.76 (d, 1H, J = 7.3 Hz, NH), 6.88 (d, 1H, J = 8.5 Hz, Tyr C_5-H), 6.89 (d, 2H, J = 9.2 Hz, $PhOCH_3$ C_2-H, C_6-H), 7.12 (dd, 1H. J = 4.3, 8.6 Hz, Tyr C_6-H), 7.24 (d, 1H, J = 8.6 Hz, Cl_2Ph C_4-H), {7.33 (d, J = 9.2 Hz, $PhOCH_3$ C_3-H, C_5-H), 7.36 (d, J = 8.6 Hz, Cl_2Ph C_3-H, C_5-H), 4H}, 7.57 (d, 1H, J = 1.8 Hz Tyr C_2-H).

(B) From 34 under high pressure conditions. To a stirred solution of **25** (420 mg, 0.58 mmol) in THF (2 mL) was added carbonyldiimidazole (84 mg, 0.58 mmol) in an ice bath and stirring was continued for 15 min. After the reaction mixture was stirred at rt for 2 h, **34** (137 mg, 0.41 mmol) in THF (1 mL) was added, and the mixture was stirred at rt for 30 h under a high pressure (5 kbar). After dilution with EtOAc, the mixture was successively washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$ and saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 50 g, hexane : EtOAc = 3 : 2) to give **36** (315 mg, 74%) as a colorless oil. This sample is identical with the sample obtained by the Mitsunobu method by TLC and ^1H-NMR spectroscopy.

O-Cl_2Bzl-Geodiamolide A (37)

To a solution of **36** (38 mg, 0.036 mmol) in anisole (160 mL, 0.15 mmol) was added dropwise CF_3CO_2H (1.5 mL) in an ice bath, and the mixture was stirred at the same temperature for 2 h. The solvent was evaporated. The residue was triturated with hexane and decanted to give the linear precursor as a crude material. DPPA (42 μL, 0.19 mmol) in DMF (5 mL) and then $NaHCO_3$ (48 mg, 0.57 mmol) were added to a solution of the crude product in DMF (30 mL) in an ice bath and the mixture was stirred at 4℃ for 5 days. After dilution with EtOAc, the mixture was washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$ and saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 10 g, benzene : acetone = 4 : 1) to give **37** (18 mg, 61%) as a white solid. ^1H NMR (270 MHz, $CDCl_3$) δ : 0.87 (d, 3H, J = 6.6 Hz, CH_3-$C_{(6)}$), 1.07 (d, 3H, J = 6.9 Hz, Ala CH_3), 1.15 (d, 3H, J = 6.9 Hz, CH_3-$C_{(2)}$), {1.24 (d, J = 5.3 Hz, CH_3-$C_{(8)}$), 1.20-1.44 (m, CH_2-$C_{(6)}$), 1.35 (d, J = 7.3 Hz, Ala CH_3), 8H}, 1.50 (s, 3H CH_3-C=), 1.99-2.23 (m, 2H, CH_2-C=), 2.25-2.47 (m, 1H, CH-C=), 2.60-2.68 (m, 1H, CH-C=O), {2.95-3.07 (m, Tyr$^{\beta}CH_2$), 2.98 (s, CH_3-N),

4H}, 3.11-3.23 (m, 1H, Tyr$^{\beta}$CH$_2$), 4.38-4.56, 4.64-4.79 (m x 2, 2H, Ala$^{\alpha}$CH x 2), 4.82-4.94 (m, 1H, CH-O), 4.93 (d, 1H, J = 9.2 Hz, CH=C), {5.18-5.25 (m, Tyr$^{\alpha}$CH), 5.27 (s, CH$_2$-Cl$_2$Ph), 3H}, 6.49 (d, 1H, J = 6.3 Hz, NH), 6.60 (d, 1H, J = 8.3 Hz, NH), 6.94 (d, 1H, J = 8.6 Hz, Tyr C$_5$-H), 7.20 (dd, 1H, J = 2.0, 8.3 Hz, Tyr C$_6$-H), 7.20-7.24 (m, 1H, Cl$_2$Ph C$_4$-H), 7.35 (d, 2H, J = 7.3 Hz, Cl$_2$Bzl C$_3$-H, C$_5$-H), 7.60 (d, 1H, J = 2.0 Hz, Tyr C$_2$-H) ; FABMS (glycerin, m-nitrobenzylalcohol) m /z 800 (M+1).

***N-tert*-Butoxycarbonyl-*O-tert*-butyldimethylsiloxy-(*R*)-tyrosine (39)**

A mixture of *N-tert*-butoxycarbonyl-(*R*)-tyrosine (**38**) (4.976 g, 17.69 mmol), TBSCl (8.232 g, 54.61 mmol), and imidazole (12.179 g, 178.88 mmol) in DMF (17 mL) was stirred at rt for 48 h. The reaction mixture was diluted with EtOAc, washed with 1M KHSO$_4$, saturated aqueous NaHCO$_3$, and saturated brine, dried over Na$_2$SO$_4$, and concentrated *in vacuo*. K$_2$CO$_3$ (3.668 g, 26.64 mmol) in H$_2$O (50 mL) was added to a solution of the crude disilylate in THF (100 mL) and MeOH (50 mL). The mixture was stirred at rt for 24 h. After evaporation, the residue was diluted with Et$_2$O and washed with aqueous saturated NaHCO$_3$. The aqueous layer was acidified to pH 4 with 1M aqueous KHSO$_4$ and the mixture was extracted with EtOAc (x3). The organic extracts were washed with saturated brine, and dried over Na$_2$SO$_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 100g, Et$_2$O : hexane = 1 : 1) to give **39** (6.417 g, 92%) as a colorless amorphous solid. $[\alpha]_D^{25}$ -30.4° (c=1.5, CHCl$_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320 (COOH, NH), 2950, 1684 (C=O), 1653 (C=O), 1472, 1417, 1258 ; ^{1}H NMR (270 MHz, CHCl$_3$ / CDCl$_3$) δ: 0.18 (s, 6H, (CH$_3$)$_2$Si), 0.97 (s, 9H, (CH$_3$)$_3$C), 1.42 (s, 9H, (CH$_3$)$_3$C), 2.89-3.20 (m, 2H, Tyr$^{\beta}$CH$_2$), 4,56-4.58(m, 1H, Tyr$^{\alpha}$CH), 4.89 (br d, 1H, J = 6.9 Hz, NH), 6.78 (d, 2H, J = 8.6 Hz, Tyr C$_3$-H, C$_5$-H), 7.04 (d, 2H, J = 8.3 Hz, Tyr C$_2$-H, C$_6$-H); *Anal.* Calcd for C$_{20}$H$_{33}$NO$_5$Si: C, 60.73; H, 58.41; N, 3.54. Found: C, 60.42; H, 8.19; N, 3.58.

***N-tert*-Butoxycarbonyl-*O-tert*-butyldimethylsiloxy-*N*-methyl-(*R*)-tyrosine (40)**

To a solution of **39** (709 mg, 1.79 mmol) in THF (5.5 mL) was carefully added 1.7M Bu^{t}Li in pentane (2.3 mL, 3.91 mmol) in a dry ice acetone bath, and the mixture was stirred for 30 min. MeI (3.4 mL, 54.61 mmol) was added to the mixture in an ice bath, and stirring was continued for 10 min. After the mixture was allowed to warm to rt and stirred for 7.5 h, it was quenched with aqueous saturated NaHCO$_3$, diluted with EtOAc, and washed with 1M KHSO$_4$, and saturated brine. The mixture was dried over Na$_2$SO$_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-820MH, 80 g, hexane : acetone = 3 : 1) to give **40** (708 mg, 97%) as a colorless amorphous solid. $[\alpha]_D^{25}$ +57.7° (c=1.1, CHCl$_3$) (lit.,[6a] $[\alpha]_D$ +47.3° (c = 0.81, CHCl$_3$)); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (COOH, NH), 2861, 1732 (C=O), 1611 (C=O), 1512, 1260, 1028; ^{1}H NMR (270 MHz, CHCl$_3$ / CDCl$_3$) δ: 0.17 (s, 6H, (CH$_3$)$_2$Si), 0.97 (s, 9H, (CH$_3$)$_3$C), 1.36, 1.42 (s x 2, 9H, (CH$_3$)$_3$C), 2.63, 2.72 (s x 2, 3H, N-CH$_3$), 2.63-3.26 (m, 2H, Tyr$^{\beta}$CH$_2$), 4.56-4.63 (m, 1H, Tyr$^{\alpha}$CH), 6.76 (d, 2H, J = 8.3 Hz, Tyr C$_3$-H, C$_5$-H), 7.05 (d, 2H, J = 7.6 Hz, Tyr C$_2$-H, C$_6$-H); *Anal.* Calcd for C$_{21}$H$_{35}$NO$_5$Si: C, 61.58; H, 8.61; N, 3.42. Found: C, 61.64; H, 8.42; N, 3.20.

Boc-(*S*)-Ala-OTce

To a solution of Boc-(*S*)-Ala-OH (**22**) (3.690 g, 19.50 mmol) in CH_2Cl_2 (40 mL) was added TceOH (2.0 mL, 20.80 mmol), DCC (5.166 g, 25.04 mmol), and DMAP (214 mg, 1.75 mmol) in an ice bath, and the mixture was stirred with ice cooling for 1 h, and then at rt for 18 h. The mixture was filtered through the pad of celite and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-200, 200 g, hexane : EtOAc = 4 : 1) to give Boc-(*S*)-Ala-OTce (6.075 g, 97%) as a white solid; mp 58-59℃, $[\alpha]_D^{25}$ -21.8° (c = 1.0, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3347 (NH), 2982, 1717 (C=O), 1684 (C=O), 1217, 1159, 1061; ^1H NMR (270 MHz, $CHCl_3$ / $CDCl_3$) δ: 1.45 (s, 9H, $(CH_3)_3C$), 1.48 (d, 3H, J = 7.3 Hz, $AlaCH_3$), 4.43-4.48 (m, 1H, AlaβCH), 4.79 (ABq, 2H, J = 11.9 Hz, CH_2CCl_3), 4,98 (br, 1H, NH); *Anal.* Calcd for $C_{10}H_{16}NO_4Cl_3$: C, 37.46; H, 5.03; N, 4.37. Found: C, 37.36; H, 5.01; N, 4.19.

H-(*S*)-Ala-OTce·HCl (41)

To a solution of Boc-(*S*)-Ala-OTce (5.062 g, 15.79 mmol) was added 4N HCl-dioxane (50 mL) in an ice bath. After 10 min stirring in an ice bath, the mixture was allowed to warm to rt and stirred for 2 h. The solvent was evaporated to give **41** (3.690 g, 91%) as a white solid. The salt was used in the next step without further purification; mp 167-169℃; IR ν_{max}^{nujor} cm^{-1}: 3300-2500 (NH_4), 2924, 1784 (C=O), 1458, 1377, 1188, 1073, 806; ^1H NMR (270 MHz, $CHCl_3$ / CD_3OD + $CDCl_3$) δ: 1:58 (d, 3H, J = 7.3 Hz, CH_3), 4.08 (q, 1H, J = 7.3 Hz, CH), 4.78 (ABq, 2H, J = 11.9 Hz, CH_2).

Boc-(*R*)-N-Me-Tyr(TBS)-(*S*)-Ala-OTce (42)

To a stirred solution of **40** (343 mg, 0.84 mmol) and **41** (255 mg, 0.99 mmol) in DMF (2 mL) was added DEPC (150 μL, 0.99 mmol) followed by Et_3N (310 μL, 2.22 mmol) in an ice bath, and stirring was continued for 30 min. The reaction mixture was allowed to warm to rt and was stirred for 16 h. After dilution with EtOAc, the mixture was washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 70g, hexane : EtOAc = 2 : 1) to give **42** (401 mg, y. 79%) as a white solid. Recrystallization from hexane gave a white powder; mp 90-92℃; $[\alpha]_D^{25}$ +44.8° (c=0.86, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3328 (NH), 2957, 1771 (C=O), 1698 (C=O), 1684 (C=O), 1509, 1259, 1148, 918; ^1H NMR (270 MHz, $CHCl_3$ / $CDCl_3$) δ: 0.16, 0.17 (s x 2, 6H, $(CH_3)_2Si$), 0.95, 0.96 (s x 2, 9H, $(CH_3)_3C$), 1.31, 1.39 (s x 2, 9H, $(CH_3)_3C$), 1.45 (d, 3H, J = 7.3 Hz, Ala CH_3), 2.74, 2.82 (s x 2, 3H, N-CH_3), 2.79-2.87 (m, 1H, Tyr$^{\beta}CH_2$), 3.25 (dd, 1H, J = 5.6, 13.9 Hz, Tyr$^{\beta}CH_2$), {4.60-4.74 (m, Ala$^{\alpha}$CH), 4.76 (br, Tyr$^{\alpha}$CH), 4.78 (ABq, J = 11.9 Hz, CH_2Cl_3) 4H}, {6.74 (d, J = 7.6 Hz, Tyr C3-H, C5-H), 6.74 (br, NH) 3H}, 7.06 (d, 2H, J = 7.3 Hz, Tyr C2-H, C6-H); *Anal.* Calcd for $C_{26}H_{41}N_2O_6Cl_3Si$: C, 51.02; H, 6.75; N, 4.58 Found: C, 50.84; H, 6.66; N, 4.58.

Boc-(*S*)-Ala-(*R*)-*N*-Me-Tyr(TBS)-(*S*)-Ala-OTce (43)

To a solution of **42** (207 mg, 0.34 mmol) in CH_2Cl_2 (0.5 mL) was added TMSOTf (100 mL, 0.52 mmol) in an ice bath. The reaction mixture was stirred at 0℃ for 1.5 h and quenched with saturated $NaHCO_3$. After dilution with EtOAc, the mixture was washed with saturated aqueous $NaHCO_3$ and saturated brine,

dried over Na_2SO_4, and concentrated *in vacuo* to give the crude peptide. BopCl (121 mg, 0.49 mmol) and Et_3N (0.06 mL, 0.43 mmol) were added to a solution of the crude peptide and **22** (83 mg, 0.44 mmol) in CH_2Cl_2 (0.5 mL) in an ice bath. The reaction mixture was stirred at 4℃ for 3 days. After dilution with EtOAc, the mixture was washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 30g, hexane : Et_2O = 1 : 1) to give **43** (148 mg, 65%) as a colorless amorphous solid. $[\alpha]_D^{25}$ +35.4° (c = 0.30, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3432 (NH), 2992, 1792 (C=O), 1699 (C=O), 1684 (C=O), 1653 (C=O), 1510, 1254, 1165, 908 ; ^1H NMR (270 MHz, $CHCl_3$ / $CDCl_3$) δ: 0.14 (s, 6H, $(CH_3)_2Si$), 0.88 (d, 3H, J = 6.9 Hz, Ala CH_3), 0.95 (s, 9H, $(CH_3)_3C$), 1.40 (s, 9H, $(CH_3)_3C$), 1.51 (d, 3H, J = 7.4 Hz, Ala CH_3), 2.82-2.88 (m, 1H, Tyr$^\beta$$CH_2$), 2.95 (s, 3H, N-$CH_3$), 3.32-3.49 (m, 1H, Tyr$^\beta$$CH_2$), 4.36-4.38 (m, 1H, Ala$^\alpha$CH), 4.64-4.70 (m, 1H, Ala$^\alpha$CH), 5.11 (d, 1H, J = 5.9 Hz, NH), 5.58-5.77 (m, 1H, Tyr$^\alpha$CH), 6.71 (d, 2H, J = 8.6 Hz, Tyr C_3-H, C_5-H), 6.84 (d, 1H, J = 6.9 Hz, NH), 7.02 (d, 2H, J = 8.3 Hz, Tyr C_2-H, C_6-H); *Anal.* Calcd for $C_{29}H_{46}N_3O_7Cl_3Si \cdot H_2O$: C, 49.67; H, 6.90; N, 5.99. Found: C, 49.34; H, 6.41; N, 5.54.

Boc-(*S*)-Ala-(*R*)-*N*-Me-Tyr(3-I-OTBS)-(*S*)-Ala-OTce (44)

To a solution of **43** (58 mg, 0.085 mmol) in AcOH (3 mL) was added I_2 (254 mg, 1.00 mmol) and $Hg(OAc)_2$ (314 mg, 0.99 mmol) at rt. The reaction mixture was stirred at 45℃ for 24 h and quenched with saturated aqueous $Na_2S_2O_3$. After dilution with EtOAc, the mixture was washed with saturated aqueous $NaHCO_3$, saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 10 g, Hexane : EtOAc = 2 : 1) to give **44** (68 mg, 99%) as a pale yellow amorphous solid. $[\alpha]_D^{25}$ +41.7°(c=0.27, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440 (NH), 2952, 1792 (C=O), 1698 (C=O), 1670 (C=O), 1653 (C=O), 1458, 1377, 1048; ^1H NMR (270 MHz, $CHCl_3$ / $CDCl_3$) δ: 0.22 (s, 6H, $(CH_3)_2Si$), 0.97 (d, 3H, J = 6.9 Hz, Ala CH_3), 1.03 (s, 9H, $(CH_3)_3C$), 1.40 (s, 9H, $(CH_3)_3C$), 1.45 (d, 3H, J = 7.6 Hz, Ala CH_3), 2.82 (dd, 1H, J = 11.2, 15.2 Hz, Tyr$^\beta$$CH_2$), 2.97 (s, 3H, N-$CH_3$), 3.34 (dd, 1H, J = 5.6, 15.2 Hz, Tyr$^\beta$$CH_2$), 4.35-4.40, 4.61-4.68 (m x 2, 2H, Ala$^\alpha$CH x 2), 4.71 (ABq, 2H, J = 11.9 Hz, CH_2CCl_3), 5.10 (br d, 1H, J = 6.3 Hz, NH), 5.59 (dd, 1H, J = 5.6, 11.2 Hz, Tyr$^\alpha$CH), 6.70 (d, 1H, J = 8.6 Hz, Tyr C_5-H), 6.90 (d, 1H, J = 8.6 Hz, NH), 7.03 (dd, 1H, J = 2.0, 8.3 Hz, Tyr C_6-H), 7.53 (d, 1H, J = 2.3 Hz, Tyr C_2-H); *Anal.* Calcd for $C_{29}H_{45}N_3O_7Cl_3ISi$: C, 43.05; H, 5.61; N, 5.19. Found: C, 43.32; H, 5.61; N, 5.00.

Boc-(*S*)-Ala-(*R*)-*N*-Me-Tyr(3-I-OTBS)-(*S*)-Ala-OH (45)

To a solution of **44** (68 mg, 0.084 mmol) in THF (1 mL) and 1N aqueous $AcONH_4$ (0.5 mL) was added in one portion Zn (120 mg). The reaction mixture was stirred at rt for 18 h. The mixture was filtered through the pad of celite and concentrated *in vacuo*. The residue was diluted with EtOAc, and washed with 1M $KHSO_4$ and saturated brine, dried over Na_2SO_4, and concentrated *in vacuo* to give **45** (54 mg, 95%) as a white solid. Recrystallization from Et_2O-hexane gave white crystals; mp 108-109℃; $[\alpha]_D^{25}$ +31.3° (c=0.40, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (COOH, NH), 2954, 1792 (C=O), 1684 (C=O), 1652 (C=O), 1635 (C=O), 1456, 1339, 1107 ; ^1H NMR (270 MHz, $CDCl_3$) δ: 0.23 (s, 6H, $(CH_3)_2Si$),

0.96 (d, 3H, J = 6.6 Hz, Ala CH_3), 1.08 (s, 9H, $(CH_3)_3C$), 1.40 (s, 9H, $(CH_3)_3C$), 1.44 (d, 3H, J = 7.3 Hz, Ala CH_3), 2.85 (dd, 1H, J = 11.4, 14.7 Hz, Tyr$^{\beta}CH_2$), 2.96 (s, 3H, N-CH_3) 3.32 (dd, 1H, J = 5.3, 14.8 Hz, Tyr$^{\beta}CH_2$), 4.41-4.51, 4.53-4.61 (m x 2, 2H, Ala$^{\alpha}$CH x 2), 5.24 (br d, 1H, J = 6.6 Hz, NH), 5.56 (dd, 1H, J = 5.4, 10.7 Hz, Tyr$^{\alpha}$CH), 6.71 (d, 1H, J = 8.3 Hz, Tyr C_5-H), 6.82 (brd, 1H, J = 7.3 Hz, NH) 7.03 (dd, 1H, J = 2.0, 8.9 Hz, Tyr C_6-H), 7.54 (d, 1H, J = 1.7 Hz, Tyr C_2-H); *Anal.* Calcd for $C_{27}H_{44}N_3O_7ISi \cdot H_2O$: C, 46.62; H, 6.67; N, 6.04. Found: C, 46.44; H, 6.52; N, 6.02.

_p_-Methoxybenzyl Boc-(*S*)-Ala-(*R*)-*N*-Me-Tyr(3-I-*O*-TBS)-(*S*)-Ala-8-oxy-(2*S*, 4*E*, 6*R*, 8*S*)-2,4,6-trimethyl-4-nonenoate (46)

To a stirred solution of **45** (54 mg, 0.080 mmol) and **35** (23 mg, 0.069 mmol) in THF (0.5 mL) was carefully added DEAD (100 μL, 0.63 mmol) and Ph_3P (156 mg, 0.59 mmol) in an ice bath, and stirring was continued for 30 min. The reaction mixture was stirred at rt for 16 h, and the solvent was evaporated. After dilution with EtOAc, the mixture was washed with saturated aqueous $NaHCO_3$ and saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (BW-200, 84 g, benzene : acetone = 12 : 1) to give **46** (58 mg, 84%) as a colorless amorphous solid. $[\alpha]_D^{25}$ +17.5° (c = 0.19, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3354 (NH), 2994, 1771 (C=O), 1732 (C=O), 1680 (C=O), 1516, 1370, 1254, 1170, 1099, 756; ^{1}H NMR (270 MHz, $CHCl_3$ / $CDCl_3$) δ: 0.22 (s, 6H, $(CH_3)_2Si$), 0.88 (d, 3H, J = 5.6 Hz, CH_3-$C_{(6)}$), 0.96 (d, 3H, J = 6.9 Hz, Ala CH_3), 1.03 (s, 9H, $(CH_3)C$), 1.10 (d, 3H, J = 6.9 Hz, CH_3-$C_{(2)}$), 1.20 (d, 3H, J = 5.9 Hz, CH_3-$C_{(8)}$), {1.33 (d, J = 7.3 Hz, Ala CH_3), 1.24-1.39 (m, CH_2-$C_{(6)}$) 5H}, 1.40 (s, 9H, $(CH_3)_3C$), 1.57 (s, 3H, CH_3-C=), 1.97-2.05 (m, 1H, CH_2-C=), 2.32-2.47 (m, 2H, CH_2-C=, CH-C=), 2.59-2.65 (m, 1H, CH-C=0), 2.82 (dd, 1H, J = 11.2, 15.2 Hz, Tyr$^{\beta}CH_2$), 2.95 (s, 3H, CH_3-N), 3.32 (dd, 1H, J = 5.0, 11.2 Hz, Tyr$^{\beta}CH_2$), 3.81 (s, 3H, CH_3O), 4.32-4.56 (m, 2H, Ala$^{\alpha}$CH x 2), 4.86-4.93 (m, 1H, CH-O), 4.95 (d, 1H, J = 8.9 Hz, CH=C), 5.01 (d, 2H, J = 3.3 Hz, $C\underline{H}_2$-PhOCH_3), 5.17 (d, 1H, J = 6.6 Hz, NH), 5.52 (dd, 1H, J = 5.0, 10.2 Hz, Tyr$^{\alpha}$CH), 6.70 (d, 1H, J = 8.2 Hz, Tyr C_5-H), 6.72 (br, 1H, NH), 6.88 (d, 2H, J = 8.6 Hz, $\underline{Ph}OCH_3$ C_2-H, C_6-H), 7.02 (d, 1H, J = 8.3 Hz, Tyr C_6-H), 7.27 (d, 1H, J = 7.9 Hz, $\underline{Ph}OCH_3$ C_3-H, C_5-H), 7.53 (s, 1H, Tyr C_2-H).

Geodiamolide A (1)

To a solution of **46** (18 mg, 0.018 mmol) in anisole (45 mL, 0.41 mmol) was added dropwise CF_3CO_2H (0.4 mL) in an ice bath, and the mixture was stirred at the same temperature for 4 h and concentrated. The residue was triturated with hexane and decanted to give the linear precursor as a crude material. DPPA (7.5 μL, 0.035 mmol) in DMF (0.75 mL), and then $NaHCO_3$ (10 mg, 0.12 mmol) were added to a solution of the crude product in DMF (2 mL) in an ice bath, and the mixture was stirred at 4℃ for 3 days. After dilution with EtOAc, the mixture was washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$ and saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. TBAF (20 mg, 0.076 mmol) was added to a solution of the crude geodiamolide A derivative in THF (1 mL) in an ice bath. The reaction mixture was stirred at 0℃ for 10 min. After dilution with EtOAc, the mixture was washed with H_2O and saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by

silica gel column chromatography (BW-200, 5 g, $CHCl_3$: MeOH = 98 : 2) to give **1** (4 mg, 34%) as a white solid. $[\alpha]_D^{25}$ +51.6° (c = 0.17, $CHCl_3$) (lit.,[2a] $[\alpha]_D^{26}$ +53° (c = 0.04, $CHCl_3$). The IR ($CHCl_3$) and ^{1}H-NMR ($CDCl_3$) spectra of this sample were identical with those of authentic geodiamolide A. FABMS (glycerin) m / z : 642 (M + 1).

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