A TOTAL SYNTHESIS OF (+)-GEODIAMOLIDES A AND B, THE NOVEL CYCLODEPSIPEPTIDES[1,‡]

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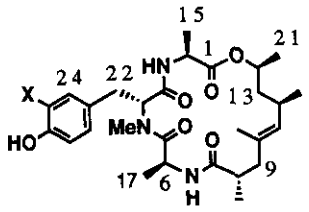
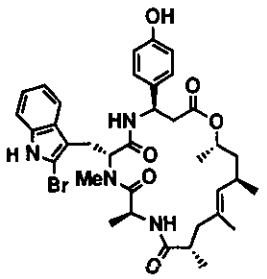
Abstract —— Diastereo-controlled total synthesis of (+)-geodiamolides A (1) and B (2) has been accomplished via a prior synthesis of the tetrapropionate-derived fragment **7** and of the halogenated N-methyltyrosyltripeptide **6**, the latter involving direct halogenation of the tripeptide **5**, and subsequent coupling of both fragments followed by the trichlorobenzoyl chloride-mediated macrolactonization, respectively.

The isolation and structural elucidation of two novel cyclodepsipeptides, (+)-geodiamolides A (1) and B (2) from the marine sponge Geodia sp., have recently been reported by Chan and co-workers.[2] Geodiamolides A and B, like the closely related cyclodepsipeptide jaspamide (3),[3] are active against the fungus Candida albicans. These cyclodepsipeptides **1** and **2** are composed of the same polypropionate fragment of twelve carbons and a tripeptide which contains the unique amino acid. The pharmacological activity coupled with their unique structural features has prompted us to initiate our effort directed toward the total synthesis of these cyclodepsipeptides. We wish to report here a full account of the experiments for the diastereo-controlled total synthesis of (+)-geodiamolides A (1)[4] and B (2).[5]



1 Geodiamolide A X = I
2 Geodiamolide B X = Br

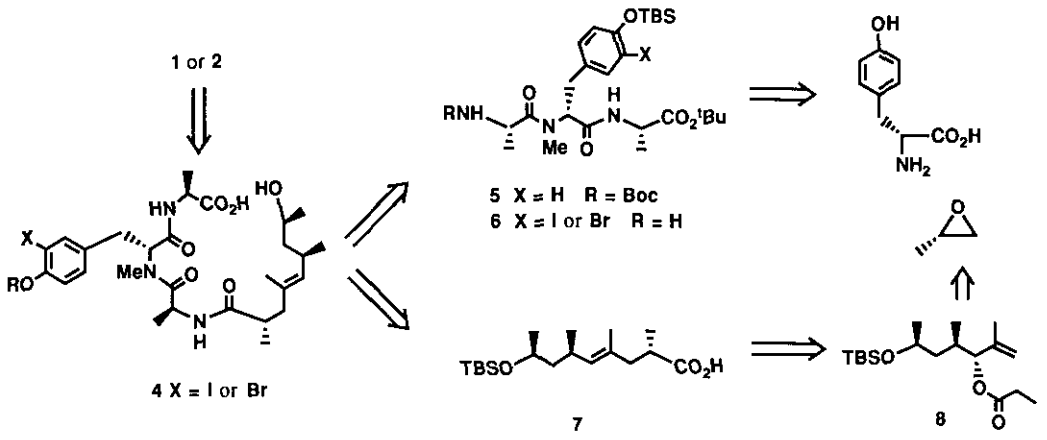


3 Jaspamide

‡This paper is dedicated to the memory of the late Professor Tetsuji Kametani.

Our strategy for elaboration of geodiamolides A (**1**) and B (**2**) centers around the coupling of the tripeptide (**6**) halogenated on D-tyrosine with the hydroxynonenoic acid **7** as shown in Scheme 1. To obtain both **1** and **2** with similar facility, we chose to try the direct halogenation of tripeptide **5**, which could be derived from the unnatural amino acid D-tyrosine. The construction of the hydroxynonenoic acid (**7**) would be achieved stereoselectively by means of 1,4-chirality transfer of **8** *via* the Ireland-Claisen rearrengement. The propionate (**8**) could be prepared from (S)-propylene oxide through the *syn*-2,4-dimethylbutyrolactone.

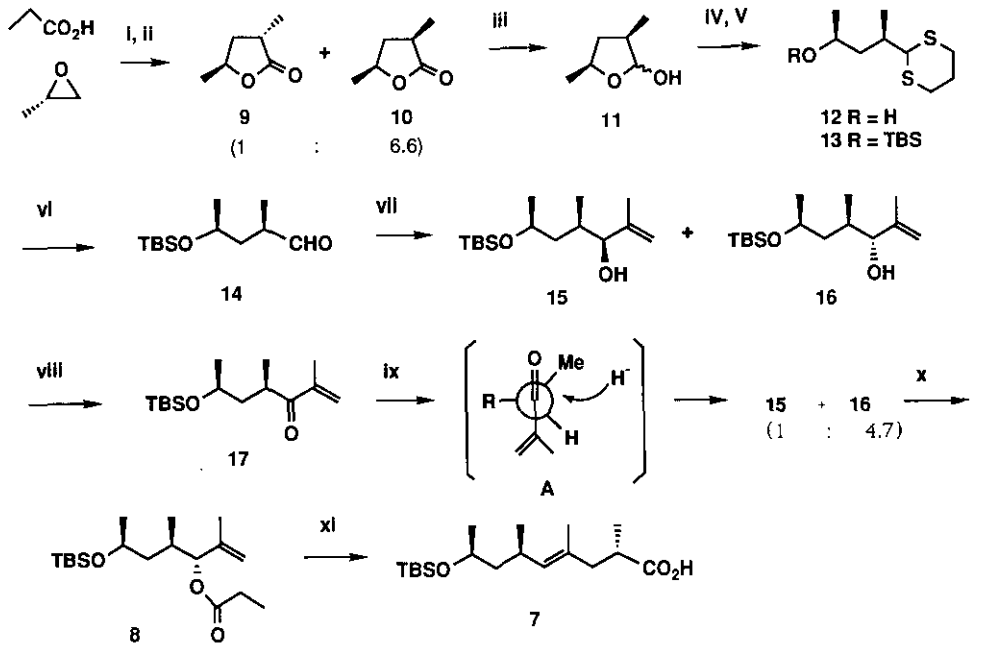
Scheme 1.



The first step in our route which controls the stereochemistry was the preparation of the lactone (**10**) from (S)-(-)-propylene oxide[6] (Scheme 2). The ring-opening of (S)-(-)-propylene oxide with the dianion of propionic acid gave the lactones **9** and **10** as a mixture of the 1:1 ratio in 62% combined yield. In order to obtain the lactone (**10**) in preference to the one of the α/γ-*anti* configuration, we tried the protonation of lithium enolate of these lactones under kinetic conditions.[7] Treatment of the mixture of lactones **9** and **10** with lithium diisopropylamide (LDA) in tetrahydrofuran at -78°C followed by protonation with a saturated NH_4Cl solution at -78°C resulted in preference of **10** over **9** (ca. 3:1). A higher *syn*/*anti* ratio (6.6:1) was obtained by using (1R)-(-)-10-camphorsulfonic acid as a proton source. Reduction of **10** with diisobutylaluminum hydride (DIBAL) in toluene at -78°C followed by treatment of the resulting lactol (**11**) with propanedithiol and boron trifluoride etherate afforded the 1,3-dithiane derivative (**12**), $[\alpha]_D^{27}$ + 19.7°(c 1.42, $CHCl_3$), in 58% yield. Silylation of **12** with t-butyldimethychlorosilane (TBSCl) in N,N-dimethylformamide (DMF) in the presence of

imidazole and subsequent oxidative hydrolysis of the resulting silyl ether (**13**) using N-chlorosuccinimide (NCS) and silver nitrate[8] in acetonitrile at -10°C afforded the aldehyde (**14**), $[\alpha]_D^{26}$ +23.2° (c 0.06, $CHCl_3$), in 38% yield. Reaction of the aldehyde (**14**) with isopropenylmagnesium bromide in tetrahydrofuran at -78° C gave the alcohols **15** and **16** as a 1:1 mixture in 95% yield. Although a number of reaction conditions [(i) addition of a copper bromide-dimethyl sulfide complex,[9] (ii) addition of magnesium bromide,[9] (iii) reaction with isopropenyl titanium tetraisopropoxide[10]] were examined, no stereoselectivity was obtained. Stereoselective introduction of the hydroxyl group was achieved using the following route. The ketone (**17**) prepared by the Swern oxidation of a mixture of the alcohols **15** and **16** was subjected to reduction with Red-Al in toluene at -78°C, which preferentially gave the alcohol (**16**), $[\alpha]_D^{27}$ +30.4° (c 0.90, $CHCl_3$), in 72% yield along with **15** (15% yield). This diastereoselectivity in favor of the alcohol **16** is consistent with the Cram-Felkin (non-chelate) open-chain model A of

Scheme 2.[a]



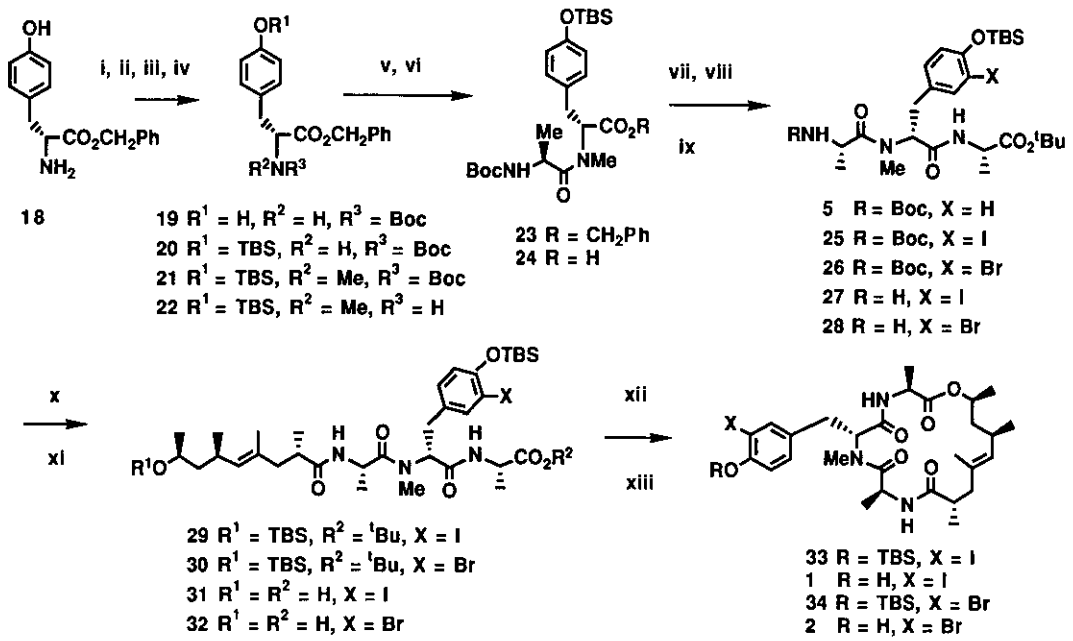
[a]Reagents and conditions: i, 2 equiv. LDA; ii, LDA and d-CSA; iii, DIBAL; iv, propane-1,3-dithiol, $BF_3{\cdot}OEt_2$; v, TBSCl, imidazole-DMF; vi, $AgNO_3$, NCS; vii, isopropenylmagnesium bromide, THF, -78°C; viii, Swern oxi.; ix, Red-Al; x, propionyl chloride, pyridine, DMAP; xi, LDA, THF, -78°C, then TBSCl-HMPA, -78°C ⟶ rt.

addition.[11] The alcohol (**16**) was then acylated with propionyl chloride and the resulting propionate (**8**) was subjected to the enolate Claisen rearrangement[12] to give the acyclic acid (**7**),[13] $[\alpha]_D^{26}$ -9.7°(c 1.30, $CHCl_3$), in 77% yield along with its epimer (6% yield). The stereochemistry of the major rearrangement product was assigned from the extensive precedent[14] of the Ireland-Claisen process.

Next we examined the construction of the tripeptides **27** and **28** as shown in Scheme 3. Silylation of N-Boc-D-tyrosine benzyl ester **19** which was readily obtained by treatment of D-tyrosine benzyl ester (**18**) with 2-Boc-thio-4,6-dimethylpyrimidine (Boc-SDP), with TBSCl followed by N-methylation provided the urethane **21** in 82% yield. Removal of the t-butoxycarbonyl protecting group of **21** with TFA in CH_2Cl_2 followed by coupling with N-Boc-L-alanine anhydride in CH_2Cl_2 in the presence of Et_3N gave the dipeptide **23**, $[\alpha]_D^{24}$ + 25.8°(c 1.75, MeOH), in 78% yield. Rductive cleavage of the benzyl ester in **23** and subsequent dicyclohexylcarbodiimide (DCC)-promoted coupling of the resulting acid **24** with L-alanine t-butyl ester in the presence of 1-hydroxybenzotriazole (HOBT) provided the linear tripeptide (**5**), $[\alpha]_D^{25}$ +8.0°(c 1.04, MeOH), in 72% yield. The treatment of **5** with iodine and $Hg(OAc)_2$ in acetic acid at 35°C afforded the monoiodide (**25**), $[\alpha]_D^{25}$ +31.5°(c 1.1, $CHCl_3$), in 78% yield as a sole product. The bromination of **5** was also effected by treatment with bromine in $CHCl_3$ at -5°C for 3 h to give the monobomide **26**, $[\alpha]_D^{26}$ +31.7°(c 0.5, $CHCl_3$), in 87% yield. The selective removal of the N-t-butoxycarbonyl group in **25** and **26** was effected by treatment with t-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in the presence of 2,6-lutidine followed by hydrolysis with a saturated NH_4Cl solution[15] to give **27** and **28** in 59% and 77% yield. Toward completion of the total synthesis of geodiamolides A and B, coupling of the tripeptides **27** and **28** with the polypropionate fragment **7** was accomplished with 1.05 equiv. of DCC and 1.0 equiv. of HOBT in THF to give the corresponding amides **29** and **30** in 79% and 68% yield, respectively. The simultaneous cleavage of the t-butyl ester in **29** and **30** and simultaneous partial desilylation were effected by treatment with TFA-ethanedithiol-CH_2Cl_2 (3:1:12) at 0°C to give the seco acids **31**, $[\alpha]_D^{26}$ +20.8°(c 0.47, $CHCl_3$), and **32**, $[\alpha]_D^{26}$ +38.6°(c 0.70, $CHCl_3$), in 59% and 38% yield, respectively. Although lactonization of **31** was examined by several procedures, only the Yamaguchi procedure was successful. Treatment of **31** with 2,4,6-trichlorobenzoyl chloride in benzene in the presence of triethylamine followed by

heating with 4-dimethylaminopyridine (DMAP) under reflux conditions[16] afforded the desired 18-membered compound (**33**) in 18% yield. Desilylation of **33** with n-Bu_4NF in THF furnished the synthetic (+)-geodiamolide A (**1**), $[\alpha]_D^{26}$ +55.1°(c 0.077, $CHCl_3$)[lit.[1] $[\alpha]_D^{25}$ +53°(c 0.04, $CHCl_3$)], in 79% yield, which was identical by direct comparison with an authentic sample of the natural material. Lactonization of **32** followed by desilylation by the same procedure as that described for **31** afforded (+)-geodiamolide B (**2**), $[\alpha]_D^{26}$ +107.9°(c 0.097, $CHCl_3$)[lit.[1] $[\alpha]_D^{22}$ +101°(c 0.04, $CHCl_3$)], in 85% yield, which was identical (270MHz ^{1}H-nmr, ir, and ms) in its spectral data with those of the natural material.

Scheme 3.[a]



[a]Reagents and conditions: i, Boc-SDP, Et_3N; ii, TBSCl, imidazole, DMF; iii, MeI, NaH, DMF; iv, TFA-CH_2Cl_2(1:1), 4 h, 0°C; v, Boc-*l*-alanine anhyderide, Et_3N; vi, H_2, 10% Pd/C, EtOH, 15h; vii, *l*-alanine *t*-butyl ester, HOBT, DCC, 0°C, 5 h; viii, I_2 and $Hg(OAc)_2$, AcOH or Br_2, $CHCl_3$, -5°C, 3 h; ix, TBSOTf, 2,6-lutidine and then sat. NH_4Cl solution; x, **7**, DCC, HOBT; xi, TFA-ethanedithiol, CH_2Cl_2, rt; xii, 2,4,6-trichlorobenzoyl chloride, Et_3N and then DMAP, benzene, reflux; xiii, n-Bu_4NF, THF, 0°C

In conclusion, diastereo-contorolled total synthesis of geodiamolides A and B was achieved with similar facility through the program involving the diastereoselective construction of the tetrapropionate-derived fragment from (S)-propylene oxide, the direct halogenation of the tripeptides, and the macrolactonization using the Yamaguchi procedure.

AKNOWLEDGMENT

We are grateful to Dr. Percy S. Manchand (Hoffmann-La Roche) and Professor Wilfred R. Chan (University of the West Indies) for kindly providing us with the spectral data of geodiamolide B and the authentic sample of geodiamolide A. We also acknowledge financial support from Pfizer Pharmaceuticals Inc.

EXPERIMENTAL

Optical rotation were 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 ^{1}H-nmr are as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, 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 micro 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.

Reaction of the Dianion of Propionic Acid with (S)-(-)-Propylene Oxide. A stirred solution of diisopropylamine (26 ml, 0.169 mol) in dry tetrahydrofuran (100 ml) at -78°C under argon was treated with n-butyllithium (1.6 M, 119 ml, 0.169 mol). After 15 min, propionic acid (6.3 ml, 84.4 mmol) was added. After 0.5 h, (S)-propylene oxide[6] (6.5 ml, 92.9 mmol) was added. After an additional 2 h at -78°C, the reaction mixture was then warmed to room temperature, stirred for 1 h, and then quenched with saturated NH_4Cl and extracted with ether. The combined organic phases were washed with brine and the residue upon work-up afforded an oil (10 g). To a solution of this residual oil in CH_2Cl_2 (80 ml) was added silica gel (50 g). The mixture was allowed to stand for 12 h at room temperature, and then silica gel was filtered off and the solvent was removed in vacuo. The residue was distilled to give a mixture of (2S,4S)-2,4-dimethylbutyrolactone **9** and (2R,4S)-2,4-dimethylbutyrolactone **10** (6.01g) in 62% combined yield as an oil, 60-62°C/7mm Hg.

Kinetic Protonation of the Enolate of the Butyrolactones 9 and 10. A stirred solution of diisopropylamine (4.43 ml, 31.6 mmol) in dry tetrahydrofuran(40 ml) at -78°C under argon was treated with n-butyllithium (1.6 M, 20.2 ml, 31.6 mmol). After 15 min, a solution of the mixture of lactones **9** and **10** (3g, 26.3 mmol) in dry tetrahydrofuran (10 ml) was added at -78°C. To this mixture, a solution of (1R)-(-)-10-camphorsulfonic acid (7.34g, 31.6 mmol) in dry tetrahydrofuran (50 ml) was slowly added at -90°C over 1 h and then warmed up to 0°C. The reaction mixture was quenched with saturated aqueous NH_4Cl and the organic layer was separated. The aqueous layer was extracted with ether and the combined organic phases were washed with brine. The residue upon work-up was distilled (60-62°C/7 mmHg) to give a mixture of **9** and **10** in 84% combined yield in a ratio of 1 : 6.6. These mixture was used for next step without separation. **10:** Ir_{max} 1720 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ 1.27 (3H, d, J = 7.08 Hz, C_2-Me), 1.42 (3H, d, J = 6.34Hz, C_4-Me), 1.43-1.56 (1H, m, C_3-H), 2.54 (1H, ddd, J = 5.37, 8.54 and 12.20 Hz, C_3-H), 2.62-2.74 (1H, m, C_2-H), and 4.43-4.55 (1H, m, C_4-H).

(3R,5S)-2-Hydroxy-3,5-dimethyltetrahydrofuran (11). To a stirred solution of the lactone (**10**) (3.5g, 30.7 mmol) in dry toluene (10 ml) was added diisobutylaluminum hydride (1 M, 33.8 ml, 33.8 mmol) at -78°C under argon. After 1 h, the reaction mixture was quenched with saturated NH_4Cl. The organic phase was washed with brine and the residure upon work-up gave a stereoisomeric mixture (**11**) (2.8g, 79%) as an oil. This lactol (**11**) was used for the next reaction without further purification.

2-[(1'R,3'S)-3'-Hydroxy-1'-methyl]butyl-1,3-dithiane (12). To a solution of the lactol (**11**) (2.77g, 23.9 mmol) containing the C-3 epimer and 1,3-propane dithiol (2.75 mmol, 26.3 mmol) in dry benzene (15 ml) at 0°C was added boron trifluoride etherate (2.94 ml, 23.9 mmol). After being stirred for 16 h at room temperature, the reaction mixture was diluted with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ether. The combined oganic phases were washed with brine and the residue upon work-up was chromatographed using CH_2Cl_2 as an eluant to afford, in the order of elution, the alcohol (**12**) (3.11g, 63%) as an oil and its epimer (0.47 g, 9.6%) as an oil. **12:** $[\alpha]_D^{27}$ +19.7° (c 1.42, $CHCl_3$). Ir_{max} 3400 cm^{-1}. Ms m/z 206 (M^+). ^{1}H-Nmr ($CDCl_3$) δ 1.12 (3H, d, J = 6.84 Hz, $C_{1'}$-Me), 1.22 (3H, d, J = 6.10 Hz, $C_{4'}$-Me), 1.45 (1H, ddd, J = 3.41, 9.52, and 13.92 Hz, $C_{2'}$-H), 1.74 (1H, ddd, J = 4.39, 9.52, and 13.92 Hz, $C_{2'}$-H), 1.80-1.92 (1H, m, $C_{1'}$-H), 2.05-2.22 (2H, m, $SCH_2CH_2CH_2S$), 2.89-2.97 (4H, m, $SCH_2CH_2CH_2S$), 3.83-3.95 (1H, m, $C_{3'}$-

H), 4.18 (1H, d, J = 3.90 Hz, C_2-H). High resolution ms Calcd for $C_9H_{18}OS_2$: 206.0798. Found: 206.0764. 2-[(1'S,3'S)-3'-Hydroxy-1'-methyl]butyl-1,3-dithiane: ^{1}H-Nmr ($CDCl_3$)δ 1.12 (3H, d, J = 6.84 Hz, $C_{1'}$-Me), 1.20 (3H, d, J = 6.10 Hz, $C_{4'}$-H), 1.43-1.56 (1H, m, $C_{2'}$-H), 1.70-1.80 (1H, m, $C_{2'}$-H), 1.77-1.92 (1H, m, $C_{1'}$-H), 2.04-2.16 (2H, m, $SCH_2C\underline{H}_2CH_2S$), 2.82-2.98 (4H, m, $SC\underline{H}_2CH_2C\underline{H}_2S$), 3.90-4.00 (1H, m, $C_{3'}$-H), 4.30 (1H, d, J = 3.85 Hz, C_2-H).

2-[(1'R,3'S)-3'-tert-Butyldimethylsiloxy-1'-methyl]butyl-1,3-dithiane (13). To a solution of tert-butyldimethylchlorosilane (5.21g, 34.6 mmol) and imidazole (4.91g, 72.1 mmol) in dry DMF (20 ml) was added a solution of **12** (5.95g, 28.8 mmol) in dry DMF (10 ml) at 0°C and the mixture was stirred for 4 h at room temperature. The reaction mixture was diluted with water (50 ml) and extracted with ethyl acetate (80 ml x 3). The organic phases were washed with water and the residue upon work-up was chromatographed using benzene as an eluant to afford **13** (9.15 g, 99%) as an oil. $[\alpha]_D^{25}$ +17.8°(c 0.87, $CHCl_3$). Ms m/z 320 (M^+). ^{1}H-Nmr ($CDCl_3$) δ 0.05 (3H, s, SiMe), 0.06 (3H, s, SiMe), 0.89 (9H, s, Si-t-Bu), 1.08 (3H, d, J = 6.83 Hz, $C_{1'}$-Me), 1.15 (3H, d, J = 6.10, $C_{4'}$-H), 1.33 (1H, ddd, J = 3.42, 9.77, and 13.43 Hz, $C_{2'}$-H), 1.73-1.80 (1H, m, $C_{2'}$-H), 1.79-1.92 (1H, m, $C_{1'}$-H), 2.05-2.17 (2H, m, $SCH_2C\underline{H}_2HH_2S$), 2.85-2.91 (4H, m, $SC\underline{H}_2CH_2C\underline{H}_2S$), 3.81-3.93 (1H, m, $C_{3'}$-H), 4.13 (1H, d, J = 3.66Hz, $C_{2'}$-H). Anal. Calcd for $C_{15}H_{32}OS_2Si$: C, 56.19; H, 10.06. Found: C, 56.17; H, 9.88.

(2R,4S)-4-tert-Butyldimethylsiloxy-2-methylpentanal (14). To a well-stirred solution of NCS (3.4 g, 25.5 mmol) and silver nitrate (4.32 g, 25.5 mmol) in aqueous 80% acetonitrile (20 ml) was added a solution of the dithiane **13** (4.8 g, 15 mmol) in acetonitrile (5 ml) at -10°C. The mixture was stirred for 10 min and treated successively at 1 min intervals with saturated aqueous sodium sulfite, saturated aqueous sodium carbonate, and brine. After the mixture was filtered through Celite, filter cake was washed thoroughly with hexane-CH_2Cl_2 (1:1 v/v) and then the organic phase of the filtrate was washed with brine. The residue upon work-up was chromatographed using CH_2Cl_2 as an eluant to afford the aldehyde **14** (1.3 g, 38%) as an oil. $[\alpha]_D^{25}$ +23.2°(c 0.06, $CHCl_3$). Ir_{max}(neat) 1720 cm^{-1}. Ms m/z 99 [M^+-131 (TBSO)]. ^{1}H-Nmr ($CDCl_3$)δ 0.05 (3H, s, SiMe), 0.07 (3H, s, SiMe), 0.88 (9H, s, Si-t-Bu), 1.08 (3H, d, J = 7.06 Hz, C_2-Me), 1.75 (3H, d, J = 6.11 Hz, C_5-H), 1.30 (1H, ddd, J = 3.67, 8.16, and 13.92 Hz, C_3-H), 1.93 (1H, ddd, 5.37, 8.55, and 14.16 Hz, C_3-H), 2.46-2.58 (1H, m, C_2-H), 3.84-3.97 (1H, m, C_4-H), 9.62 (1H, d, J = 1.61 Hz, CHO). High resolution ms Calcd for $C_{12}H_{26}O_2Si$: 230.1701.

Found: 230.1708.

Grignard Reaction of the Aldehyde 14. A solution of the aldehyde **14** (2.6g, 11.3 mmol) in dry tetrahydrofuran (30 ml) was cooled to -78°C and treated with isopropenylmagnesium bromide (1.03 M solution in dry tetrahydrofuran, 22ml). The mixture was stirred for 1.5 h at -78°C and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ether, and the combined organic phases were washed with brine. The residue upon work-up was chromatographed using hexane-benzene (20:80 v/v) as an eluant to afford, in the order of elution, (3R,4R,6S)-6-tert-butyldimethylsiloxy-3-hydroxy-2,4-dimethyl-1-heptene (**15**) (1.7g, 55.3%) as an oil and (3S,4R,6S)-6-tert-butyldimethylsiloxy-3-hydroxy-2,4-dimethyl-1-heptene (**16**) (1.22g, 39.7%) as an oil.

15: $[\alpha]_D^{27}$ +30.0 (c 0.87, $CHCl_3$). Ms m/z 273 (M^++1). ^{1}H-Nmr ($CDCl_3$) δ 0.05 (3H, s, SiMe), 0.06 (3H, s, SiMe), 0.87 (3H, d, J = 6.11 Hz, C_4-Me), 0.88 (9H, s, Si-t-Bu), 1.14 (3H, d, J = 5.86 Hz, C_7-H), 1.12-1.22 (1H, m, C_5-H), 1.47 (1H, ddd, J = 3.42, 9.52, and 13.18 Hz, C_5-H), 1.55 (1H, br s, C_3-OH), 1.70 (3H, s, C_2-Me), 1.91-1.97 (1H, m, C_4-H), 3.83 (1H, d, J = 6.11 Hz, C_3-H), 3.84-3.95 (1H, m, C_6-H), 4.91 (2H, d, J = 12.94 Hz, C_1-H). Anal. Calcd for $C_{15}H_{32}O_2Si$: C, 66.11; H, 11.84. Found: C, 66.12; H, 11.78.

16: $[\alpha]_D^{27}$ +30.4°(c 0.90, $CHCl_3$). Ms m/z 273 (M^++1). ^{1}H-Nmr ($CDCl_3$) δ 0.08 (6H, s, $SiMe_2$), 0.87 (3H, d, J = 6.59Hz, C_4-Me), 0.89 (9H, s, Si-t-Bu), 1.10-1.12 (1H, m, C_5-H), 1.15 (3H, d, J = 6.10 Hz, C_7-H), 1.64-1.77 (1H, m, C_5-H), 1.69 (3H, S, C_2-Me), 1.77-1.87 (1H, m, C_4-H), 2.30 (1H, br s, C_3-OH), 3.75 (1H, d, J = 7.87 Hz, C_3-H), 3.83-3.94 (1H, m, C_6-H), 4.89 (2H, d, J = 12.20 Hz, C_1-H). Anal. Calcd for $C_{15}H_{37}O_2Si$: C, 66.11; H, 11.84. Found C, 66.25; H, 11.91.

(4R,6S)-6-tert-Butyldimethylsiloxy-2,4-dimethyl-1-hepten-3-one (17). To a stirred solution of oxalyl chloride (48.6 x 10^{-3} ml, 0.557 mmol) in dry CH_2Cl_2 (5 ml) was added dropwise a solution of dimethyl sulfoxide (DMSO) (79.1 x 10^{-3} ml, 1.11 mmol) in dry CH_2Cl_2 (1 ml) at -78°C. To this reaction mixture was added a solution of alcohols **15** and **16** (138.0 mg, 0.506 mmol) in dry CH_2Cl_2 (1 ml) and stirring was continued for 40 min. Triethylamine (0.155 ml, 1.11 mmol) was then added and the mixture was stirred for 30 min at the same temperature. The reaction mixture was warmed to 0°C and stirred for 1 h at the same temperature. The reaction mixture was diluted with water and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine and the residue upon work up was chromatgraphed using hexane-benzene (1:4 v/v) as an eluant to give the ketone 17

(123.7 mg, 90%) as an oil. $[\alpha]_D^{26}$ -5.8°(c 0.46, $CHCl_3$). Ir_{max} 1680 cm^{-1}. Ms m/z 213 [M^+-57 (t-Bu)]. ^{1}H-Nmr($CDCl_3$) δ 0.08 (6H, s, $SiMe_2$), 0.90 (9H, s, Si-t-Bu), 1.07 (3H, d, J = 6.83 Hz, C_4-Me), 1.12 (3H, d, J = 5.86 Hz, C_7-H), 1.25-1.35 (1H, m, C_5-H), 1.74-1.84 (1H, m, C_5-H), 1.87 (3H, s, C_2-Me), 3.37-3.50 (1H, m, C_4-H), 3.81-3.92 (1H, m, C_6-H), 5.77 (1H, s, C_1-H), 6.02 (1H, s, C_1-H). Anal. Calcd for $C_{15}H_{30}O_2Si$: C, 66.61; H, 11.18. Found: C, 66.48; H, 11.33.

Reduction of 17 with Red-Al. A solution of the ketone **17** (70 mg, 0.259 mmol) in dry toluene (5 ml) was cooled to -78°C and treated with sodium bis(2-methoxyethoxy)aluminum hydride (0.187 ml, 70% w/v toluene solution). After being stirred for 1 h, the mixture was quenched with saturated aqueous NH_4Cl. The reaction mixture was filtered through Celite and the filtrate was diluted with benzene (10 ml). The organic phase was washed with brine and the residue upon work-up was chromatographed using hexane-benzene (1:4 v/v) as an eluant to afford, in the order of elution, the alcohols (**15**) (53.7 mg, 79.2%) as an oil and (**16**) (11.4 mg, 16.9%) as an oil.

(3R,4R,6S)-6-tert-Butyldimethylsiloxy-2,4-dimethyl-3-propanoyloxy-1-heptene (8). To a solution of the alcohol (**16**) (452.4 mg, 1.66 mmol) in dry CH_2Cl_2 (5 ml) was added pyridine (0.269 ml, 3.32 mmol) at 0°C, followed by propionyl chloride (0.216 ml, 2.49 mmol) and a catalytic amount of DMAP. After being stirred for 0.5 h, the reaction mixture was washed with brine and the residue upon work-up was chromatographed using hexane-benzene (1:1 v/v) as an eluant to afford the propionate **8** (540 mg, 99%) as an oil. $[\alpha]_D^{26}$ +19.6°(c 1.12, $CHCl_3$). Ir_{max} 1740 cm^{-1}. Ms m/z 313 [M^+-15(Me)]. ^{1}H-Nmr ($CDCl_3$) δ 0.05 (3H, s, SiMe), 0.06 (3H, s, SiMe), 0.86 (3H, d, J = 6.59 Hz, C_4-Me), 0.88 (9H, s, Si-t-Bu), 0.99-1.09 (1H, m, C_5-H), 1.13 (3H, d, J = 6.10 Hz, C_7-H), 1.16 (3H, t, J = 7.57 Hz, $MeCH_2CO$), 1.52-1.61 (1H, m, C_5-H), 1.70 (3H, s, C_2-Me), 1.92-2.12 (1H, m, C_4-H), 2.36 (2H, q, J = 7.57 Hz, $MeCH_2CO$), 3.81-3.92 (1H, m, C_6-H), 4.89 (2H, d, J = 5.86 Hz, C_1-H), 5.00 (1H, d, J = 6.59 Hz, C_3-H). Anal. Calcd for $C_{18}H_{36}O_3Si$: C, 65.80; H, 11.04. Found. C, 65.67; H, 10.84.

Ireland-Claisen Rearrangement of 8. A stirred solution of diisopropylamine (69.1×10^{-3} ml, 0.493 mmol) in dry tetrahydrofuran (2 ml) at -78°C under argon was treated with n-butyllithium (1.6 M, 0.316 ml). After 15 min, to this solution was added a solution of the propionate **8** (134.9 mg, 0.411 mmol) in dry tetrahydrofuran (1 ml). After the reaction mixture was stirred for 4 min, a solution of tert-butyldimethylchlorosilane (74.6 mg, 0.493 mmol) in dry

tetrahydrofuran (0.5 ml) was added and then hexamethylphosphoric triamide (78.6 x 10^{-3} ml, 0.452 mmol) was added. The reaction mixture was then warmed to room temperature, stirred for 8 h. After cooling at 0°C, the reaction mixture was quenched with saturated aqueous NH_4Cl and the solution was diluted with excess 5% HCl, extracted with ether. The ether extracts were washed with brine and the residue upon work-up was chromatographed using benzene-CH_2Cl_2 (1:4 v/v) as an eluant to afford (2S,4E,6R,8S)-tert-butyldimethylsiloxy-4-nonenoic acid (**7**) (103 mg, 77%) as an oil and its epimer (7.8 mg, 5.8%) as an oil. $[\alpha]_D^{26}$ -9.7°(c 1.30, $CHCl_3$). Ir $_{max}$ 1710 cm^{-1}. Ms m/z 328 [M^+-15(Me)]. ^{1}H-Nmr ($CDCl_3$)δ 0.04 (6H, s, $SiMe_2$), 0.88 (9H, s, Si-t-Bu), 0.89 (3H, d, J = 4.88 Hz, C_6-Me), 1.09 (3H, d, J = 4.64 Hz, C_2-Me), 1.12 (3H, d, J = 5.37 Hz, C_9-H), 1.24-1.34 (1H, m, C_7-H), 1.38-1.48 (1H, m, C_7-H), 1.59 and 1.60 (3H, s x 2, C_4-Me), 2.03 (1H, dd, J = 8.30 and 13.43 Hz, C_3-H), 2.39 (1H, dd, J = 6.84 and 13.43 Hz, C_3-H), 2.37-2.48 (1H, m, C_6-H), 2.55-2.68 (1H, m, C_2-H), 3.69-3.81 (1H, m, C_8-H), 4.97 (1H, d, J = 9.52 Hz, olefine proton). Anal. Calcd for $C_{18}H_{36}O_3Si$: C, 65.80; H, 11.04. Found: C, 66.08; H, 11.18.

N-Boc-D-tyrosine Benzyl Ester (19). To a solution of **18** (2.62 g, 9.66 mmol) and triethylamine (2.02 ml, 14.49 mmol) in water (10 ml) was added a solution of Boc-SDP (2.55 g, 10.62 mmol) in dioxane (10 ml) at room temperature. After being stirred for 24 h, the reaction mixture was acidified with 10% HCl at 0°C and then extracted with ethyl acetate (80 ml x 3). The combined organic phases were washed with 5% HCl (30 ml x 2) and the residue upon work-up was recrystallized from ether-hexane to afford **19** (3.27g, 91.2%), mp 125-126°C. $[\alpha]_D^{26}$ +0.7°(c 1.18, $CHCl_3$). Ms m/z 371(M^+). ^{1}H-Nmr ($CDCl_3$)δ 1.41 (9H, s, Boc Me), 2.92-3.05 (2H, m, Tyr$^\beta$$CH_2$), 4.52-4.60 (1H, m, Tyr$^\alpha$CH), 5.02 (1H, d, J = 8.40 Hz, NH), 5.06-5.20 (2H, m, CO_2CH_2Ph), 6.66 (2H, d, J = 8.40 Hz, Tyr C_3-H and C_5-H), 6.86 (2H, d, J = 8.54 Hz, Tyr C_2-H and C_6-H), 7.31-7.36 (5H, m, CO_2CH_2Ph). Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 68.14; H, 6.83; N, 3.99.

O-tert-Butyldimethylsilyl-N-Boc-D-tyrosine Benzyl Ester (20). To a solution of tert-butyldimethylchlorosilane (3.02g, 27.0 mmol) and imidazole (2.85 g, 41.8 mmol) in dry DMF (30 ml) was added a solution of **19** (6.75 g, 18.2 mmol) in dry DMF (20 ml) at 0°C. The resulting solution was stirred for 7 h at room temperature. The reaction mixture was diluted with ethyl acetate (100 ml) and the solution was washed with water (2 x 100 ml). The residue upon work-up was chromatographed using benzene as an eluant to afford **20** (8.29 g, 93.3 %) as a colorless oil.

$[\alpha]_D^{24}$ +6.1°(c 0.98, MeOH). ^{1}H-Nmr ($CDCl_3$)δ 0.17 (6H, s, $SiMe_2$), 0.97 (9H, s, Si-t-Bu), 1.41 (9H, s, Boc Me), 3.00 (2H, br s, Tyr$^{\beta}CH_2$), 4.51-4.63 (1H, m, Tyr$^{\alpha}CH$), 5.13 (2H, dd, J = 12.45 and 18.31 Hz, CO_2CH_2Ph), 6.70 (2H, d, J = 8.30 Hz, Tyr C_3-H and C_5-H)), 6.89 (2H, d, J = 8.30 Hz, Tyr C_2-H and C_6-H). 7.28-7.37 (5H, m, CO_2CH_2Ph). Anal. Calcd for $C_{27}H_{39}O_5NSi$: C, 66.7; H, 8.09; N, 2.88. Found: C, 66.95; H, 7.97; N, 2.92.

O-tert-Butyldimethylsilyl-N-Boc-N-methyl-D-tyrosine Benzyl Ester (21). To a solution of methyl iodide (0.081 ml, 1.3 mmol) and **19** (211mg, 0.435 mmol) in dry DMF (2 ml) was carefully added sodium hydride (60 % oil dispersion, 19.1 mg, 0.48 mmol) at 0°C. The reaction mixture was allowed to warm to room temperature and was stirred for 3 h. The reaction mixture was poured into water (5 ml) and extracted with ethyl acetate (3 x 30 ml). The combined organic phases were washed with water (3 x 10 ml) and the residue upon work-up was chromatographed using benzene as an eluant to afford the title compound (**21**) (177.8 mg, 82 %) as an oil. $[\alpha]_D^{24}$ +48.5°(c 1.34, MeOH). Ms m/z 499 (M^+). ^{1}H-Nmr ($CDCl_3$)δ 0.17 (6H, s, $SiMe_2$), 0.97 (9H, s, Si-t-Bu), 1.33 and 1.37 (9H, s x 2, Boc Me), 2.66 and 2.77 (3H, s x 2, NMe), 2.97-3.04 (1H, m, Tyr$^{\beta}CH_2$), 3.17-3.32 (1H, m, Tyr$^{\beta}CH_2$), 4.47-4.57 and 4.82-4.92 (1H, m x 2, Tyr$^{\alpha}CH$), 5.18 (2H, s, CO_2CH_2Ph), 6.75 (2H, d, J = 8.06 Hz, Tyr C_3-H and C_5-H), 7.01 (2H, d, J = 8.30 Hz, Tyr C_2-H and C_6-H), 7.34 (5H, s, CO_2CH_2Ph). Anal. Calcd for $C_{28}H_{41}NO_5Si$: C, 67.30; H, 8.27; N, 2.80. Found: C, 67.49; H, 8.13; N, 2.90.

O-tert-Butyldimethylsilyl-N-methyl-D-tyrosine Benzyl Ester (22). To a solution of **21** (6.26g, 12.55 mmol) in dry CH_2Cl_2 (6 ml) was added TFA (6 ml) at 0°C and the reaction mixture was stirred for 4 h. The volatiles were removed in vacuo at 0°C. The resulting residue was chromatographed using CH_2Cl_2 as an eluant to afford the title compound **22** (4.25 g, 84.9 %) as a colorless oil. $[\alpha]_D^{24}$ -2.2°(c 1.41, MeOH). Ms m/z 399 (M^+). ^{1}H-Nmr ($CDCl_3$) δ 0.17 (6H, s, $SiMe_2$), 0.97 (9H, s, Si-t-Bu), 2.35 (3H, s, NMe), 2.87-2.90 (2H, m, Tyr$^{\beta}CH_2$), 3.44 (1H, t, J = 6.84 Hz, Tyr$^{\alpha}CH$), 5.08 (2H, dd, J = 12.21 and 15.14 Hz, CO_2CH_2Ph), 6.71 (2H, d, J = 8.30 Hz, Tyr C_3-H and C_5-H), 6.97 (2H, J = 8.30 Hz, Tyr C_2-H and C_6-H), 7.22-7.34 (5H, m, CO_2CH_2Ph). Anal. Calcd for $C_{23}H_{33}NO_3Si$: C, 69.13; H, 8.32; N, 3.51. Found. C, 69.22; H, 8.23; N, 3.57.

Boc-Ala-N-Me-D-Tyr(O-TBS)-OBzl (23). To a solution of **22** (3.29 g, 8.25 mmol) and triethylamine (1.15 ml, 8.25 mmol) in dry CH_2Cl_2 (30 ml) was added N-Boc-L-alanine anhydride (2.97 g, 8.25 mmol) at room temperature. After being stirred for 10 h,

the reaction mixture was washed with H_2O (5 ml) and the residue upon work-up was chromatographed using ethyl acetate-hexane (4:96 v/v) as an eluant to afford **23** (4.30 g, 91%) as an oil. $[\alpha]_D^{24}$ +25.8°(c 1.75, MeOH). Ms m/z 497 [M^+-73(O-t-Bu)]. ^{1}H-Nmr ($CDCl_3$) δ 0.14 (6H, s, $SiMe_2$), 0.85 (3H, d, J = 6.83 Hz, Ala Me), 0.95 (9H, s, Si-t-Bu), 1.42 (9H, s, Boc Me), 2.81 (3H, s, NMe), 2.96 (1H, dd, J = 11.72 and 15.21 Hz, Tyr$^{\beta}CH_2$), 3.33 (1H, dd, J = 4.97, 14.64 Hz, Tyr$^{\beta}CH_2$), 4.42-4.52 (1H, m, Ala $^{\alpha}$CH), 5.17 (2H, dd, J = 12.23 and 16.63 Hz, CO_2CH_2Ph), 5.26-5.34 (1H, m, Tyr $^{\alpha}$CH), 5.41 (1H, d, J = 8.38 Hz, NH), 6.72 (2H, d, J = 8.54 Hz, Tyr C_3-H and C_5-H), 7.00 (2H, d, J = 8.30 Hz, Tyr C_2-H and C_6-H), 7.34 (5H, s, CO_2CH_2Ph). Anal. Calcd for $C_{31}H_{46}N_2O_6Si$: C, 65.23; H, 8.12; N, 4.91. Found. C, 65.02; H, 7.97; N, 4.84.

Boc-Ala-N-Me-D-Tyr(O-TBS) (24). To a suspension of 10 % Pd-C (200 mg) in dry ethanol (15 ml) was added **23** (1.54 g, 2.70 mmol) and the mixture was stirred under hydrogen atmosphere for 15 h, filtered through Celite, and concentrated in vacuo. The residual oil was chromatographed using methanol-CH_2Cl_2 (1:99 v/v) to afford the title compound **24** (1.12 g, 86.4 %) as a colorless solid, mp 67-68°C. $[\alpha]_D^{25}$ +14.0°(c 1.04, MeOH). ^{1}H-Nmr ($CDCl_3$) δ 0.15 (6H, s, $SiMe_2$), 0.89 (3H, d, J = 6.84 Hz, Ala Me), 0.96 (9H, s, Si-t-Bu), 1.42 (9H, s, Boc Me), 2.86 (3H, s, NMe), 2.93-3.04 (1H, m, Tyr$^{\beta}CH_2$), 3.31-3.41 (1H, m, Tyr$^{\beta}CH_2$), 4.45-4.55 (1H, m, Ala$^{\alpha}$CH), 5.21-5.29 (1H, m, Tyr$^{\alpha}$CH), 5.55 (1H, d, J = 7.89 Hz, NH), 6.74 (2H, d, J = 8.30 Hz, Tyr C_3-H and C_5-H), 7.03 (2H, d, J = 8.30 Hz, Tyr C_2-H and C_6-H). Anal. Calcd for $C_{24}H_{40}N_2O_6Si$: C, 59.97; H, 8.39; N, 5.83. Found: C, 60.1; H, 8.39; N, 5.84.

Boc-Ala-N-Me-D-Tyr(O-TBS)-Ala-O-tert-Bu (5). To a solution of Ala-O-tert-Bu hydrochloride (397 mg, 2.18 mmol) and N-methylmorpholine (0.24 ml, 2.18 mmol) in dry CH_2Cl_2 (15 ml) was added **24** (1.05 g, 2.18 mmol) at -5°C and the resulting mixture was treated with DCC (451 mg, 2.18 mmol) and HOBT (100 mg, 0.655 mol) at -5°C. The reaction mixture was stirred for 5 h at 0°C. The precipitate was removed off by filtration and the filtrate was concentrated in vacuo. The residue was column chromatographed using CH_2Cl_2-benzene (20:80 v/v) as an eluant to afford **5** (1.10 g, 82.8 %) as a colorless solid, mp 52-53°C. $[\alpha]_D^{25}$ +8.0°(c 1.035, MeOH). Ms m/z 534 [M^+-73(O-t-Bu)]. ^{1}H-Nmr ($CDCl_3$) δ 0.13 (6H, s, $SiMe_2$), 0.88 (3H, d, J = 6.84 Hz, Ala Me), 0.95 (9H, s, Si-t-Bu), 1.35 (3H, d, J = 7.04 Hz, Ala Me), 1.41 (9H, s, Boc Me), 1.45 (9H, s, O-t-Bu), 2.84-2.94 (1H, m, Tyr $^{\beta}CH_2$), 2.94 (3H, s, NMe), 3.27-3.38 (1H, m, Tyr$^{\beta}CH_2$), 4.36-4.49 (2H, m, Ala$^{\alpha}$CH), 5.25 (1H, d, J = 6.75 Hz, NH), 5.48-5.57 (1H, m, Tyr$^{\alpha}$CH), 6.71 (2H, d, J = 8.30 Hz, Tyr C_3-H and C_5-H), 7.03 (2H, d, J = 8.54 Hz, Tyr C_2-H and C_6-H). Anal. Calcd for

$C_{31}H_{51}N_3O_7SI$: C, 61.25; H, 8.79; N, 6.91. Found: C, 61.34. H, 8.88; N, 7.08.

Boc-Ala-N-Me-D-Tyr(O-TBS-3-I)-Ala-O-tert-Bu (25). To a solution of **5** (600mg, 0.987 mmol) and iodine (300.6 mg, 1.184 mmol) in AcOH (7ml) was added $(AcO)_2Hg$ (377.5 mg, 1.184 mmol) at 35°C. After being stirred for 2.5 h at the same temperature, the solvent was removed under reduced pressure and the resulting residue was chromatographed using benzene-CH_2Cl_2 (1:4 v/v) as an eluant to give **25** as a solid, mp 53-54°C. $[\alpha]_D^{25}$ +31.5°(c 1.1, $CHCl_3$). Ms m/z 660 [M^+-73(O-t-Bu)]. ^{1}H-Nmr ($CDCl_3$) δ 0.23 (6H, s, $SiMe_2$), 0.97 (3H, d, J = 6.83 Hz, Ala Me), 1.04 (9H, s, Si-t-Bu), 1.36 (3H, d, J = 7.33 Hz, Ala Me), 1.42 (9H, s, Boc Me), 1.46 (9H, s, O-t-Bu), 2.84 (1H, dd, J = 10.98 and 15.13 Hz, Tyr$^\beta$$CH_2$), 2.96 (3H, s, NMe), 3.32 (1H, dd, J = 5.85 and 15.13 Hz, Tyr$^\beta$$CH_2$), 4.40-4.48 (2H, m, Ala$^\alpha$CH), 5.23 (1H, d, J = 7.08 Hz, NH), 5.51 (1H, dd, J = 5.74 and 10.87 Hz, Tyr$^\alpha$CH), 6.71 (1H, d, J = 8.30 Hz, NH), 6.71 (1H, d, J = 8.30 Hz, Tyr C_5-H), 7.03 (1H, dd, J = 2.20 and 8.30 Hz, Tyr C_6-H), 7.55 (1H, d, J = 2.19 Hz, Tyr C_2-H). Anal. Calcd for $C_{31}H_{52}N_3O_7ISi$: C, 50.74; H, 7.14; N, 5.73. Found: C, 50.74; H, 6.97; N, 5.65.

Boc-Ala-N-Me-D-Tyr(3-Br-O-TBS)-Ala-O-tert-Bu (26). To a solution of **5** (101.9 mg, 0.168 mmol) in $CHCl_3$ (2 ml) was added bromine (8.64×10^{-3} ml, 0.168 mmol) at -5°C and the mixture was stirred at the same temperature for 3 h. The reaction mixture was washed with saturated $NaHCO_3$ and brine, and the residue upon work-up was chromatographed using benzene-CH_2Cl_2 (1:4 v/v) as an eluant to afford **26** (100 mg, 87%) as a solid, mp 57-58°C. $[\alpha]_D^{26}$ +31.7° (c 0.5, $CHCl_3$). Ms m/z 612[M^+-1-73(O-t-Bu)] and 614 [M^++1-73(O-t-Bu)]. ^{1}H-Nmr ($CDCl_3$) δ 0.20 (6H, s, $SiMe_2$), 0.96 (3H, d, J = 6.84 Hz, Ala Me), 1.02 (9H, s, Si-t-Bu), 1.36 (3H, d, J = 7.33 Hz, Ala Me), 1.41 (9H, s, Boc Me), 1.45 (9H, s, O-t-Bu), 2.85 (1H, dd, J = 10.74 and 15.13 Hz, Tyr$^\beta$$CH_2$), 2.96 (3H, s, NMe), 3.33 (1H, dd, J = 5.37 and 15.13 Hz, Tyr$^\beta$$CH_2$), 4.40-4.45 (2H, m, Ala$^\alpha$CH), 5.23 (1H, d, J = 6.83 Hz, NH), 5.52 (1H, dd, J = 5.86 and 11.19 Hz, Tyr$^\alpha$CH), 6.76 (1H, d, J = 8.30 Hz, NH), 6.76 (1H, d, J = 8.30 Hz, Tyr C_5-H), 6.99 (1H, dd, J = 2.44 and 8.30 Hz, Tyr C_6-H), 7.31 (1H, d, J = 1.95 Hz, Tyr C_2-H). Anal. Calcd for $C_{31}H_{52}N_3O_7BrSi$: C, 54.22; H, 7.63; N, 6.12. Found: C, 54.03; H, 7.61; N, 6.31.

Ala-N-Me-D-Tyr(O-TBS-3-I)-Ala-O-tert-Bu (27). To a solution of **25** (512 mg, 0.698 mmol) and 2,6-lutidine (0.285 ml, 2.09 mmol) in dry CH_2Cl_2 (7 ml) was added TBSOTf (0.337 ml, 1.47 mmol) at room temperature. The mixture was stirred for 2.5 h at the same temperature and quenched with saturated aqueous NH_4Cl and extracted with ether. The combined organic phases were washed with brine and the residue upon

work-up was chromatographed using methanol-$CHCl_3$ (5:95 v/v) as an eluant to afford **27** (327.5 mg, 80%) as a solid, mp 51-52°C. $[\alpha]_D^{25}$ +57.1°(c 0.82, $CHCl_3$). Ms m/z 634 (M^++1). ^{1}H-Nmr ($CDCl_3$)δ 0.23 (6H, s, $SiMe_2$), 0.95 (3H, d, J = 6.59 Hz, Ala Me), 1.04 (9H, s, Si-t-Bu), 1.33 (3H, d, J = 7.08 Hz, Ala Me), 1.44 (9H, s, O-t-Bu), 2.82-2.87 (1H, m, Tyr$^\beta CH_2$), 2.89 (3H, s, NMe), 3.22 (1H, dd, J = 6.34 and 14.79 Hz, Tyr$^\beta CH_2$), 3.76 (1H, q, J = 6.84 Hz, Ala$^\alpha$CH), 4.36-4.47 (1H, m, Ala$^\alpha$CH), 5.44 (1H, dd, J = 6.60 and 10.01 Hz, Tyr$^\alpha$CH), 6.58 (1H, d, J = 7.81 Hz, NH), 6.71 (1H, d, J = 8.30 Hz, Tyr C_5-H), 7.03 (1H, dd, J = 2.20, and 8.30 Hz, Tyr C_6-H), 7.56 (1H, d, J = 2.20 Hz, Tyr C_2-H). Anal. Calcd for $C_{26}H_{44}N_3O_5ISi$: C, 49.28; H, 7.00; N, 6.63. Found: C, 49.00; H, 6.85; N, 6.47.

Ala-N-Me-D-Tyr(3-Br-O-TBS)-Ala-O-tert-Bu (28). As described for **27**, the tripeptide (**26**) (60 mg) was transformed to **28** (39.4 mg, 77%), mp 53-54°C. $[\alpha]_D^{26}$ +60.0°(c 1.02, $CHCl_3$). Ms m/z 586 (M^+) and 588 (M^++2). ^{1}H-Nmr ($CDCl_3$)δ 0.21 (6H, s, $SiMe_2$), 0.95 (3H, d, J = 6.83 Hz, Ala Me), 1.02 (9H, s, Si-t-Bu), 1.34 (3H, d, J = 7.32 Hz, Ala Me), 1.45 (9H, s, O-t-Bu), 2.83-2.98 (1H, m, Tyr$^\beta CH_2$), 2.90 (3H, s, NMe), 3.24 (1H, dd, J = 6.10 and 14.89 Hz, Tyr$^\beta CH_2$), 3.77 (1H, q, J = 6.83 Hz, Ala$^\alpha$CH), 4.37-4.48 (1H, m, Ala$^\alpha$CH), 5.47 (1H, dd, J = 6.34 and 10.25 Hz, Tyr$^\alpha$CH), 6.64 (1H, d, J = 7.82 Hz, NH), 6.77 (1H, d, J = 8.30 Hz, Tyr C_5-H), 7.00 (1H, dd, J = 2.20 and 8.30 Hz, Tyr C_6-H), 7.33 (1H, d, J = 2.19 Hz, Tyr C_2-H). High resolution ms Calcd for $C_{26}H_{44}N_3O_5BrSi$: 585.2231 (M^+-1) and 587.2212 (M^++1). Found: 585.2387 (M^+-1) and 587.2150 (M^++1).

(2S,4E,6R,8S)-8-tert-Butyldimethylsiloxy-2,4,6-trimethyl-4-nonenoyl-Ala-N-Me-D-Tyr(O-TBS-3-I)-Ala-O-tert-Bu (29). A solution of the tripeptide **27** (88.1 mg, 0.139 mmol) and the carboxylic acid **7** (45.7 mg, 0.139 mmol) in dry tetrahydrofuran (2 ml) was treated with HOBT (21.3 mg, 0.139 mmol) and DCC (30.1 mg, 0.146 mmol) at -5°C, and the resulting reaction mixture was stirred for 5 h at 0°C. The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was chromatographed using CH_2Cl_2-benzene (1:1 v/v) as an eluent to afford **29** (104.2 mg, 80%) as a solid, mp 39-40°C. $[\alpha]_D^{25}$ +15.7°(c 1.04, $CHCl_3$). ^{1}H-Nmr ($CDCl_3$)δ 0.03 (6H, s, C_8-$OSiMe_2$), 0.23 (6H, s, Tyr-$SiMe_2$), 0.88 (9H, s, C_8-OSi-t-Bu), 1.04 (9H, s, Tyr-OSi-t-Bu), 1.09 (3H, d, J = 5.86 Hz, C_9-H), 1.37 (3H, d, J = 7.22 Hz, Ala Me), 1.45 (9H, s, O-t-Bu), 1.56 (3H, s, C_4-Me), 1.97 (1H, dd, J = 8.78 and 12.99 Hz, C_3-H), 2.26-2.51 (1H, m, C_3-H), 2.26-2.51 (1H, m, C_2-H), 2.26-2.51 (1H, m, C_6-H), 2.84 (1H, dd, J = 10.99 and 15.13 Hz, Tyr$^\beta CH_2$), 2.98 (3H, s, NMe), 3.33 (1H, dd, J = 5.06 and 14.77 Hz, Tyr$^\beta CH_2$), 3.68-3.81 (1H,

m, C_8-H), 4.35-4.46 (1H, m, Ala$^{\alpha}$CH), 4.60-4.70 (1H, m, Ala$^{\alpha}$CH), 4.95 (1H, d, J = 9.28 Hz, C_5-H), 5.47 (1H, dd, J = 5.71 and 10.31 Hz, Tyr$^{\alpha}$CH), 6.30 (1H, d, J = 4.95 Hz, NH), 6.71 (1H, d, J = 8.30 Hz, Tyr C_5-H), 6.78 (1H, d, J = 7.18 Hz, NH), 7.03 (1H, dd, J = 1.98 and 8.30 Hz, Tyr C_6-H), 7.54 (1H, d, J = 2.04, Tyr C_2-H). Anal. Calcd for $C_{44}H_{78}N_3O_7ISi_2$: C, 55.97; H, 8.33; N, 4.45. Found C, 56.27; H, 8.34; N, 4.30.

(2S,4E,6R,8S)-8-tert-Butyldimethylsiloxy-2,4,6-trimethyl-4-nonenoyl-Ala-N-Me-D-Tyr(3-Br-O-TBS)-Ala-O-tert-Bu (30). As described for **29**, The compound **30** (128.2 mg, 68%) was obtained by the condensation of the tripeptide **28** (123.5 mg, 0.211 mmol) with the carboxylic acid **7** (69.2 mg, 0.211 mmol). $[\alpha]_D^{26}$ +17.6°(c 0.85, $CHCl_3$). Ms m/z 838 [M^+-1-57(t-Bu)] and 840 [M^++1-57(t-Bu)]. ^{1}H-Nmr ($CDCl_3$) δ0.04 (6H, s, C_8-OSiMe_2), 0.20 (6H, s, Tyr-SiMe_2), 0.88 (9H, s, C_8-OSi-t-Bu), 1.02 (9H, s, Tyr-OSi-t-Bu), 1.09 (3H, d, J = 6.11 Hz, C_9-H), 1.37 (3H, d, J = 7.33 Hz, Ala Me), 1.45 (9H, s, O-t-Bu), 1.56 (3H, s, C_4-Me), 1.91-2.01 (1H, m, C_3-H), 2.27-2.37 (1H, m, C_3-H), 2.30-2.40 (1H, m, C_2-H), 2.34-2.47 (1H, m, C_6-H), 2.86 (1H, dd, J = 10.97 and 15.53 Hz, Tyr$^{\beta}$$CH_2$), 2.98 (3H, s, NMe), 3.35 (1H, dd, J = 5.57 and 15.53 Hz, Tyr$^{\beta}$$CH_2$), 3.68-3.80 (1H, m, C_8-H), 4.35-4.45 (1H, m, Ala$^{\alpha}$CH), 4.60-4.70 (1H, m, Ala$^{\alpha}$CH), 4.96 (1H, d, J = 9.28 Hz, C_5-H), 5.48 (1H, dd, J = 5.53 and 10.67 Hz, Tyr$^{\alpha}$CH), 6.27 (1H, d, J = 5.91 Hz, NH), 6.76 (1H, d, J = 8.30 Hz, Tyr C_5-H), 7.00 (1H, dd, J = 2.20 and 8.30 Hz, Tyr C_6-H), 7.31 (1H, d, J = 2.20 Hz, Tyr C_2-H). Anal. Calcd for $C_{44}H_{78}N_3O_7BrSi_2$: C, 58.90; H, 8.76; N, 4.68. Found: C, 59.10; H, 8.75; N, 4.56.

(2S,4E,6R,8S)-8-Hydroxy-2,4,6-trimethyl-4-nonenoyl-Ala-N-Me-D-Tyr(O-TBS-3-I)-Ala (31). To a solution of **29** (129 mg, 0.137 mmol) in dry CH_2Cl_2 (2.5 ml) was added ethanedithiol (0.343 ml, 4.09 mmol) at 0°C and stirring was continued for 0.5 h at the same temperature. Trifluoroacetic acid (1.06 ml, 13.7 mmol) was then added at the same temperature and the mixture was stirred for 4 h at 0°C. The solvent was evaporated off and the residual oil was chromatographed using methanol-$CHCl_3$ (3:97 v/v) as eluant to afford **31** (62.9 mg, 60%) as a solid which was recrystalized from ether, mp 79-81°C. $[\alpha]_D^{26}$ +20.8°(c 0.47, $CHCl_3$). Ms m/z 773 (M^+). ^{1}H-Nmr ($CDCl_3$) δ 0.24 (6H, s, SiMe_2), 0.89 (3H, d, J = 6.84 Hz, C_6-Me), 1.00 (3H, d, J = 6.84 Hz, Ala Me), 1.04 (9H, s, Si-t-Bu), 1.11 (6H, d x 2, J = 6.35 Hz, C_2-Me and C_9-H), 1.42 (3H, d, J = 7.32 Hz, Ala Me), 1.57 (3H, s, C_4-Me), 2.01 (1H, dd, J = 8.92 and 18.08 Hz, C_3-H), 2.27 (1H, dd, J = 8.33 and 15.28 Hz, C_3-H), 2.36-2.53 (2H, m, C_2-H and C_6-H), 2.83 (1H, dd, J = 10.19 and 14.55 Hz, Tyr

$^{\beta}CH_2$), 2.94 (3H, s, NMe), 3.28 (1H, dd, J = 5.86 and 14.48 Hz, Tyr$^{\beta}CH_2$), 3.64-3.77 (1H, m, C_8-H), 4.53-4.67 (1H, m, Ala$^{\alpha}$CH), 4.75-4.86 (1H, m, Ala$^{\alpha}$CH), 4.95 (1H, d, J = 9.43 Hz, C_5-H), 5.45 (1H, dd, J = 6.12 and 9.93 Hz, Tyr$^{\alpha}$CH), 6.72 (1H, d, J = 8.30 Hz, NH), 6.72 (1H, d, J = 8.30 Hz, Tyr C_5-H), 7.04 (1H, dd, J = 1.96 and 8.30 Hz, Tyr C_6-H), 7.17 (1H, d, J = 7.98 Hz, NH), 7.56 (1H, d, J = 1.96 Hz, Tyr C_2-H). High resolution ms Calcd for $C_{34}H_{56}N_3O_7ISi$: 773.2931, Found: 773.2909.

(2S,4E,6R,8S)-8-Hydroxy-2,4,6-trimethyl-4-nonenoyl-Ala-N-Me-D-Tyr(3-Br-O-TBS)-Ala (32). As described for the seco acid (**31**), the compound **30** (72.5 mg) was transformed to **32** (22.5 mg, 38%), mp 69-70°C (ether). $[\alpha]_D^{26}$ +38.6°(c 0.695, $CHCl_3$). Ms m/z 725 (M^+-1) and 727 (M^++1). ^{1}H-Nmr ($CDCl_3$) δ 0.20 (6H, s, $SiMe_2$), 0.88 (3H, d, J = 6.69 Hz, C_6-Me), 1.02 (9H, s, Si-t-Bu), 1.10 (6H, d, J = 6.32 Hz, C_2-Me and C_9-H), 1.42 (3H, d, J = 7.33 Hz, Ala Me), 1.57 (3H, s, C_4-Me), 2.00 (1H, dd, J = 5.94 and 14.77 Hz, C_3-H), 2.27 (1H, dd, J = 8.49 and 11.72 Hz, C_3-H), 2.36-2.52 (2H, m, C_2-H and C_6-H), 2.84 (1H, dd, J = 10.17 and 16.84 Hz, Tyr$^{\beta}CH_2$), 2.92 (3H, s, NMe), 3.28 (1H, dd, J = 6.28 and 14.94 Hz, Tyr$^{\beta}CH_2$), 3.67-3.75 (1H, m, C_8-H), 4.51-4.63 (1H, m, Ala$^{\alpha}$CH), 4.75-4.85 (1H, m, Ala$^{\alpha}$CH), 4.95 (1H, d, J = 9.53 Hz, C_5-H), 5.45 (1H, dd, J = 6.14 and 9.98 Hz, Tyr$^{\alpha}$CH), 6.66 (1H, d, J = 6.96 Hz, NH), 6.77 (1H, d, J = 8.34 Hz, Tyr C_5-H), 7.00 (1H, dd, J = 2.20 and 8.34 Hz, Tyr C_6-H), 7.13 (1H, d, J = 8.06 Hz, NH), 7.32 (1H, d, J = 2.20 Hz, Tyr C_2-H). High resolution ms Calcd for $C_{34}H_{56}N_3O_7BrSi$: 725.3068 (M^+-1) and 727.3048 (M^++1). Found: 725.3110 (M^+-1) and 727.3018 (M^++1).

Geodiamolide A (O-TBS) (33). To a solution of **31** (19.3 mg, 24.9 x 10^{-3} mmol) and triethylamine (3.82 x 10^{-3} ml, 27.4 x 10^{-3} mmol) in dry terahydrofuran (1 ml) was added 2,4,6-trichlorobenzoyl chloride (3.99 x 10^{-3} ml, 24.9 x 10^{-3} mmol) 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 (100 ml). This benzene solution was slowly added to a refluxing solution of DMAP (18.3 mg, 0.15 mmol) in benzene (100 ml) over a period of 10 h. The reaction mixture was washed with a saturated aqueous citric acid solution, water, saturated aqueous $NaHCO_3$, and water, and the residue upon work-up was chromatographed using $CHCl_3$ as an eluant to afford the monomeric lactone (**33**) (3.4 mg, 18 %) as an oil. $[\alpha]_D^{25}$ +56.0°(c 0.17, $CHCl_3$). Ms m/z 755 (M^+). ^{1}H-Nmr ($CDCl_3$) δ 0.24 (6H, s, $SiMe_2$), 0.88 (3H, d, J = 6.60 Hz, C_{20}-H), 1.06 (9H, s, Si-t-Bu), 1.15 (3H, d, J = 6.59 Hz, C_{18}-H), 1.26 (3H, d, J = 6.11 Hz, C_{21}-H), 1.36 (3H, d, J = 7.08 Hz, C_{17}-H), 1.51 (3H, s, C_{19}-H), 2.06-2.18 (1H, m, C_{12}-H), 2.00-2.22 (2H, m, C_9-H), 2.27-2.37 (1H, m, C_8-

H), 2.89-2.97 (1H, m, C_{22}-H), 2.97 (3H, s, C_{16}-H), 3.14 (1H, dd, J = 7.30 and 14.87 Hz, C_{22}-H), 4.44-4.55 (1H, m, C_6-H), 4.68-4.78 (1H, m, C_2-H), 4.87-4.94 (1H, m, C_{14}-H), 4.94 (1H, d, J = 9.77 Hz, C_{11}-H), 5.21 (1H, dd, J = 7.60 and 9.31 Hz, C_4-H), 6.48 (1H, d, J = 6.60 Hz, NH), 6.55 (1H, d, J = 7.81 Hz, NH), 6.73 (1H, d, J = 8.30 Hz, C_{27}-H), 7.03 (1H, dd, J = 2.20 and 8.30 Hz, C_{28}-H), 7.58 (1H, d, J = 2.20 Hz, C_{24}-H). High resolution ms Calcd for $C_{34}H_{54}N_3O_6ISi$: 755.2825. Found: 755.2799.

Geodiamolide B (O-TBS) (34). As described for pre-geodiamolide (**33**), the seco-acid **32** (6.1 mg) was transformed to the pre-geodiamolide B (**34**) (1.4 mg, 23.5 %). $[\alpha]_D^{27}$ +23.6°(c 0.35, $CHCl_3$). Ms m/z 692 [M^++1-15(Me)] and 708 [M^+-1-15(Me)]. ^{1}H-Nmr ($CDCl_3$)δ 0.21 (6H, s, $SiMe_2$), 0.88 (3H, d, J = 6.59 Hz, C_{20}-H), 1.02 (9H, s, Si-t-Bu), 1.05 (3H, d, J =6.83 Hz, C_{15}-H), 1.15 (3H, d, J = 6.60 Hz, C_{18}-H), 1.25 (3H, d, J = 4.87 Hz, C_{21}-H), 1.36 (3H, d, J = 7.08 Hz, C_{17}-H), 1.51 (3H, s, C_{19}-H), 2.01-2.19 (1H, m, C_{12}-H), 2.06-2.18 (2H, m, C_9-H), 2.27-2.36 (1H, m, C_8-H), 2.90-2.99 (1H, m, C_{22}-H), 2.97 (3H, s, C_{16}-H), 3.15 (1H, dd, J = 6.75 and 14.63 Hz, C_{22}-H), 4.47-4.52 (1H, m, C_6-H), 4.70-4.75 (1H, m, C_2-H), 4.86-4.96 (1H, m, C_{14}-H), 4.94 (1H, d, J = 9.18 Hz, C_{11}-H), 5.22 (1H, dd, J = 6.93 and 9.00 Hz, C_4-H), 6.48 (1H, d, J = 6.86 Hz, NH), 6.59 (1H, d, J = 7.74 Hz, NH), 6.78 (1H, d, J = 8.30 Hz, C_{27}-H), 7.00 (1H, dd, J = 2.19 and 8.30 Hz, C_{28}-H), 7.34 (1H, d, J = 2.19 Hz, C_{24}-H). High resolution ms Calcd for $C_{34}H_{54}N_3O_6BrSi$: 707.2963 (M^+-1) and 709.2943 (M^++1). Found: 707.2965 (M^+-1) and 709.2949 (M^++1).

Geodiamolide A. (1) To a solution of the pre-geodiamolide A (**33**) (3 mg, 3.97 x 10^{-3} mmol) in dry tetrahydrofuran (0.6 ml) was added a solution of n-tetrabutylammonium fluoride (0.1 ml, 39.7 x 10^{-3} M solution in dry tetrahydrofuran, 3.97 x 10^{-3} mmol) 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 methanol-$CHCl_3$ (2 : 98 v/v) as an eluant to afford Geodiamolide A (**1**) (2mg, 79 %). $[\alpha]_D^{26}$ +55.1°(c 0.077, $CHCl_3$). The ir ($CHCl_3$), ^{1}H-nmr ($CDCl_3$) spectra, and rf value of this sample were identical with those of authentic geodiamolide A.

Geodiamolide B (2). As described for geodiamolide A, the pre-geodiamolide B (**34**) (1.4 mg) was transformed to geodiamolide B (**2**) (1mg, 85%). $[\alpha]_D^{26}$ +107.9°(c 0.097, $CHCl_3$). The ir ($CHCl_3$) and ^{1}H-nmr ($CDCl_3$) spectra of this sample were identical with those of authentic geodiamolide B.

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