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Enantioselective Total Synthesis of Doliculide, a Potent Cytotoxic Cyclodepsipeptide of Marine Origin and Structure-Cytotoxicity Relationships of Synthetic Doliculide Congeners

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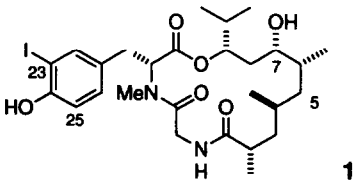
Abstract: The total synthesis of doliculide (**1**), a potent cytotoxic cyclodepsipeptide from the Japanese sea hare *Dolabella auricularia*, has been achieved. The key step of the synthesis is the construction of the stereogenic centers of a 15-carbon polyketide-derived dihydroxy acid moiety by a combination of the Evans aldol reaction and the Barton deoxygenation reaction. Furthermore, artificial congeners of doliculide were synthesized and the structure-cytotoxicity relationships were examined.

We have recently isolated doliculide (**1**) from the Japanese sea hare *Dolabella auricularia*[1] and have synthetically established its absolute stereostructure as depicted in **1**.[2] Doliculide (**1**) exhibits potent cytotoxicity against HeLa-S_3 cells with an IC_{50} of 0.005 μg/mL[3] and is structurally related to cyclodepsipeptides such as geodiamolides[4] and jaspamide (jasplakinolide).[5] Although this class of compounds have been the subject of synthetic investigations because of their biological activities and unique structural features,[6] their structure-activity relationships have not been explored. Herein we wish to report full details of the enantioselective total synthesis of **1** as well as investigation of the structure-cytotoxicity relationships of **1** and its artificial congeners.



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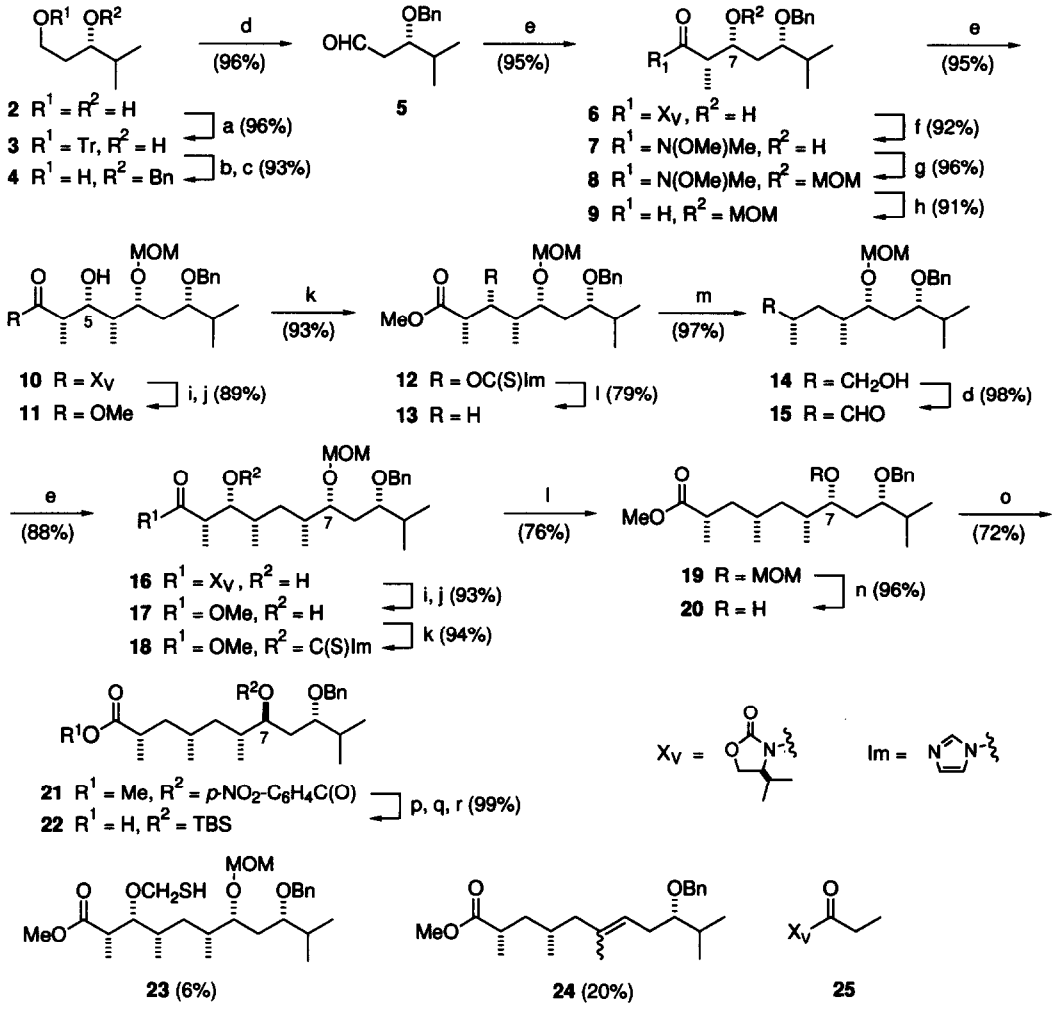
Synthetic Plan of Doliculide (1)

We have carried out a synthesis of doliculide (**1**) in order to confirm the deduced absolute stereostructure of **1**, to supply quantities of **1** enough for further biological investigations, and to synthesize artificial congeners of **1** for studying the structure-cytotoxicity relationships. Thus, we have devised (i) an enantioselective, practical, and flexible method for construction of the 1,3,5-*syn,syn*-trimethylalkane structure contained in the dihydroxy acid moiety of **1** and (ii) a synthetic route which enabled us to construct 16-membered dilactam-lactone ring efficiently.

Scheme 1



Reagents and Conditions: (a) TrCl, Et_3N, DMAP, CH_2Cl_2, rt; (b) BnBr, NaH, DMF, 0 °C → rt; (c) concd HCl, MeOH, THF, 30 °C; (d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C → 0 °C; (e) **25**, Bu_2BOTf, Et_3N, CH_2Cl_2, -78 °C → 0 °C; (f) Me(MeO)NH•HCl, Me_3Al, THF, -19 °C → -6 °C; (g) $MeOCH_2Cl$, *i*-Pr_2NEt, 0 °C → rt; (h) DIBAL, THF, -78 °C; (i) LiOH, H_2O_2, THF, H_2O, 0 °C; (j) CH_2N_2, ether, $CHCl_3$, rt; (k) Im_2CS, THF, reflux; (l) Bu_3SnH, toluene, reflux; (m) $LiAlH_4$, THF, 0 °C; (n) concd HCl, MeOH, 50 °C; (o) Ph_3P, *p*-$NO_2C_6H_4COOH$, $(EtOOCN)_2$, ether, rt; (p) NaOH, MeOH, H_2O, 45 °C; (q) TBSOTf, Et_3N, CH_2Cl_2, 0 °C; (r) K_2CO_3, MeOH, THF, H_2O, 40 °C.

Synthesis of Doliculide (1)

Synthesis of the dihydroxy acid derivative 22.

Starting from (*S*)-4-methyl-1,3-pentanediol (**2**),[7] aldehyde **5** was prepared by selective protection of the secondary hydroxyl group of **2** in three steps followed by oxidation (Scheme 1). An Evans aldol reaction[8] between aldehyde **5** and imide **25**[8] afforded aldol **6**. Conversion of aldol **6** into amide **7** and subsequent

protection of the C7 hydroxyl group of **7** provided methoxymethyl (MOM) ether **8**, which was reduced to give aldehyde **9**. The next task was construction of a 1,3,5-*syn,syn*-trimethylalkane structure, which was one of the crucial steps of the synthesis of doliculide (**1**). First, an Evans aldol reaction of **9** with **25** afforded aldol **10** with almost complete stereocontrol. All attempts to remove C5 hydroxyl group of **10** to construct a 1,3-*syn*-dimethylalkane structure failed.[9] Consequently, the chiral auxiliary of **10** was removed to give methyl ester **11** and a Barton deoxygenation reaction[10] of the derived thionoimidazolide **12** gave methyl ester **13** in satisfactory yield without any isolable byproduct. Methyl ester **13** was converted into aldehyde **15** in two steps, which was subjected to the sequence of reactions for the second C_3 homologation, i.e., the Evans aldol reaction, removal of the chiral auxiliary, and the Barton deoxygenation reaction, yielding methyl ester **19** in good overall yield. The only isolable byproduct in the deoxygenation step was the unstable mercaptomethyl ether **23**. Thus, we have efficiently constructed the 1,3,5-*syn,syn*-trimethylalkane structure contained in the dihydroxy acid moiety of **1**. The MOM protecting group of **19** was removed and the resultant C7 hydroxyl group of **20** was inverted by a Mitsunobu reaction.[11] In this step desired *p*-nitrobenzoate **21** was invariably accompanied by a mixture of olefins **24** as byproducts, and the best result was obtained when ether was used as solvent.[12] Hydrolysis of the ester groups of **21** gave a hydroxy acid. Without purification the hydroxy acid was silylated to give a disilylated compound, the silyl ester group of which was removed selectively to afford silyl ether **22** as the properly protected dihydroxy acid moiety of **1**.

Coupling of the components and construction of the 16-membered dilactam-lactone ring.

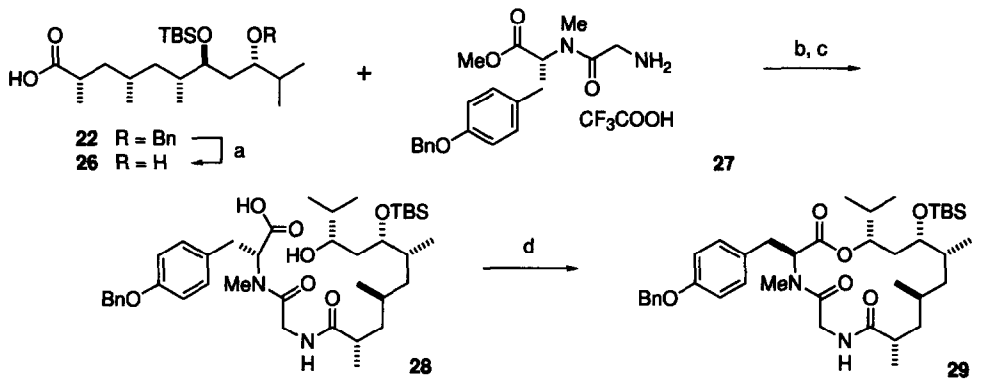
At first, we attempted to construct a 16-membered ring by means of a macrolactonization reaction. To examine the feasibility of this route, seco acid **28** was synthesized and subjected to the cyclization reaction under the conditions of Yamaguchi[13] (2,4,6-trichlorobenzoyl chloride, DMAP, triethylamine, benzene, rt) or Keck[14] (DCC, DMAP, camphorsulfonic acid, chloroform, reflux) (Scheme 2). Although the cyclization reaction proceeded smoothly, complete epimerization of the tyrosine moiety took place to afford **29** under both conditions. These results led us to examine a macrolactamization reaction as an alternative (Scheme 3).

N-Boc-3-iodo-*N*-methyl-*O*-TBS-D-tyrosine (D-**32**) was prepared from 3-iodo-*N*-methyl-D-tyrosine methyl ester (D-**30**)[15] in four steps.[16] Coupling of silyl ether **22** with glycine *tert*-butyl ester by diethyl phosphorocyanidate[17] (DEPC) and subsequent removal of the benzyl protecting group by hydrogenolysis produced amide **34**. Esterification of **34** with D-**32** by DCC/DMAP at -20 °C[18] gave protected seco acid **35** in high yield without epimerization of the tyrosine moiety.[19] Removal of the protecting groups of **35** by trifluoroacetic acid in dichloromethane afforded seco acid **36**. The macrolactamization of **36** was achieved satisfactorily with bis(2-oxo-3-oxazolidinyl)phosphinic chloride[20] (Bop-Cl) under high-dilution conditions to give doliculide silyl ether (**37**) in 74% yield along with the minor product, trifluoroacetate **38**,[21] which was easily converted to **37** by treatment with aqueous ammonia in methanol. Finally, the silyl protecting group of **37** was removed almost quantitatively to give doliculide (**1**), which was identical with natural **1** in all respects (mp, $[\alpha]_D$, UV, IR, ^1H and ^{13}C NMR, MS, TLC, and cytotoxicity).

Synthesis of Doliculide Congeners and Their Cytotoxicity

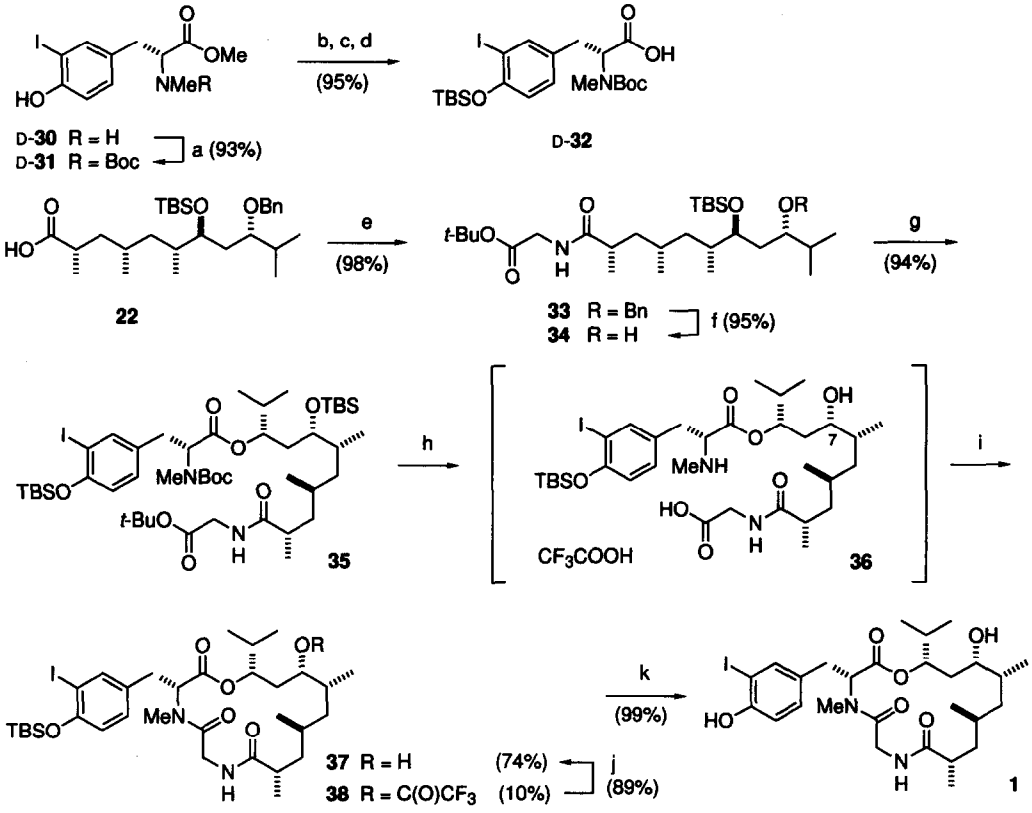
With completion of the enantioselective total synthesis of doliculide (**1**), we next investigated the structure-cytotoxicity relationships of **1** and its congeners.

Scheme 2



Reagents and Conditions: (a) H_2, 10% Pd/C, K_2CO_3, MeOH, rt; (b) DEPC, Et_3N, DMF, 0 °C; (c) LiOH, THF, H_2O, rt; (d) see text.

Scheme 3

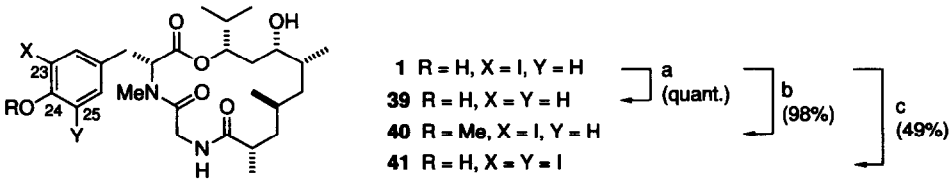


Reagents and Conditions: (a) $(Boc)_2O$, DMF, rt; (b) LiOH, THF, H_2O, rt; (c) TBSCl, imidazole, DMF, 50 °C; (d) K_2CO_3, H_2O, MeOH, THF, rt; (e) glycine *tert*-butyl ester hydrochloride, DEPC, Et_3N, DMF, 0 °C; (f) H_2, 20% $Pd(OH)_2/C$, dioxane, 40 °C; (g) D-**32**, DCC, DMAP, CH_2Cl_2, -20 °C; (h) CF_3COOH, CH_2Cl_2, rt; (i) Bop-Cl, Et_3N, CH_2Cl_2, 0 °C → 25 °C; (j) concd NH_3, MeOH, rt; (k) Bu_4NF, THF, 0 °C.

First, we examined the effects of the two hydroxyl groups, the iodine atom, and the 3-iodo-*N*-methyltyrosine moiety of doliculide (**1**) on the cytotoxicity. Deiododoliculide (**39**), doliculide methyl ether (**40**), and iododoliculide (**41**) were directly prepared from **1**, respectively (Scheme 4). Removal of the iodine atom at C23 of **1** by hydrogenolysis afforded **39**. Selective methylation of the C24 hydroxyl group of **1** gave **40**. Treatment of **1** with iodine/mercury(II) acetate afforded iododoliculide (**41**). This iodination reaction gave a complex mixture when an excess of mercury(II) acetate was employed. Deoxydoliculide (**46**) was synthesized starting from **37** by a sequence of reactions as follows (Scheme 5): (i) removal of the iodine atom of **37** by hydrogenolysis to give **42**; (ii) a Barton deoxygenation reaction of **42** by way of thionoimidazolide **43** to afford silyl ether **44**; (iii) iodination of **44** with iodine/mercury(II) trifluoroacetate[22] to yield deoxydoliculide silyl ether (**45**); and (iv) deprotection of the silyl protecting group of **45**. Epidoliculide (**49**) was synthesized from *N*-Boc-3-iodo-*N*-methyl-*O*-TBS-L-tyrosine (L-**32**) and amide **34** by following the sequence of reactions employed in the total synthesis of **1** (Scheme 6). Depsipeptide **51** was prepared from amide **34** by application of the same strategy as employed in the total synthesis of **1** (Scheme 7).

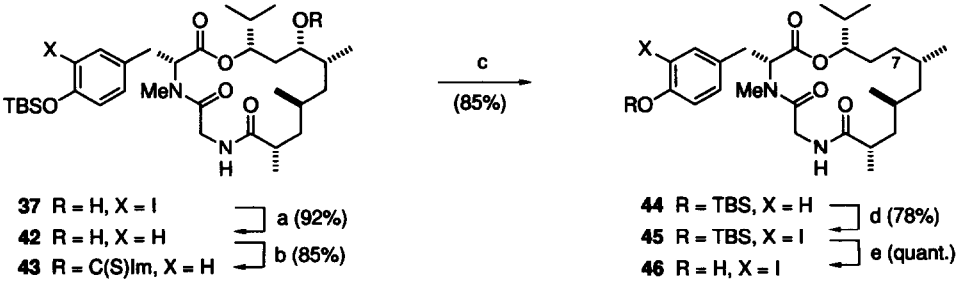
Second, we synthesized congeners possessing simpler structures than that of doliculide (**1**) to explore a minimum partial structure required for cytotoxicity. Depsipeptide **58** was synthesized from alcohol **55**, which was prepared from 1,9-nonanediol in five steps, by the sequeuce of reactions similar to those that were used in the last stage of the total synthesis of **1** (Scheme 8). Dipeptide **59** was prepared from 3-iodo-*N*-methyl-D-tyrosine methyl ester (D-**30**) (Scheme 9).[23]

Scheme 4



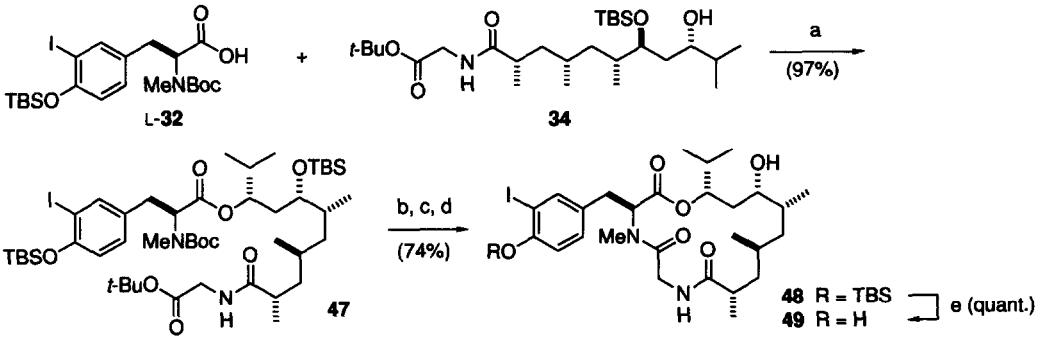
Reagents and Conditions: (a) H_2, 10% Pd/C, MeOH, rt; (b) MeI, Bu_4NI, K_2CO_3, DMF, rt; (c) I_2, $Hg(OAc)_2$, EtOH, rt.

Scheme 5



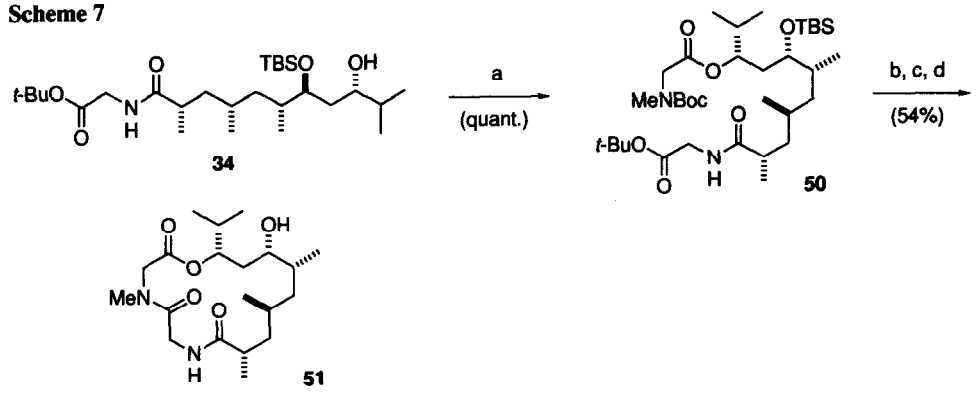
Reagents and Conditions: (a) H_2, 10% Pd/C, NaOAc, MeOH, rt; (b) Im_2CS, THF, reflux; (c) Bu_3SnH, toluene, reflux; (d) I_2, $Hg(O_2CCF_3)_2$, CH_2Cl_2, rt; (e) Bu_4NF, THF, 0 °C.

Scheme 6



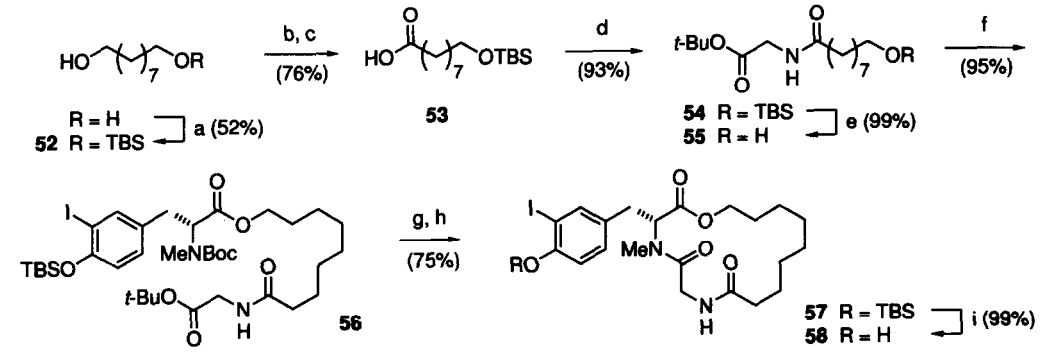
Reagents and Conditions: (a) DCC, DMAP, CH_2Cl_2, -20 °C; (b) CF_3COOH, CH_2Cl_2, rt; (c) Bop-Cl, Et_3N, CH_2Cl_2, 0 °C → 28 °C; (d) cocd NH_3, MeOH, rt; (e) Bu_4NF, THF, 0 °C.

Scheme 7



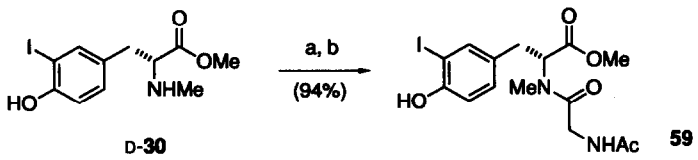
Reagents and Conditions: (a) *N*-Boc-*N*-methyl-glycine, DCC, DMAP, CH_2Cl_2, 0 °C; (b) CF_3COOH, CH_2Cl_2, rt; (c) Bop-Cl, Et_3N, CH_2Cl_2, 0 °C → 25 °C; (d) cocd NH_3, MeOH, rt.

Scheme 8



Reagents and Conditions: (a) TBSCl, NaH, THF, rt; (b) SO_3·Py, Et_3N, DMSO, rt; (c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *tert*-BuOH, H_2O, rt; (d) glycine *tert*-butyl ester hydrochloride, DEPC, Et_3N, DMF, 0 °C; (e) 47% aq. HF, MeCN, 0 °C; (f) D-**32**, DCC, DMAP, CH_2Cl_2, -20 °C; (g) CF_3COOH, CH_2Cl_2, rt; (h) Bop-Cl, Et_3N, CH_2Cl_2, 0 °C → 28 °C; (i) Bu_4NF, THF, 0 °C.

Scheme 9



D-30 59

Reagents and Conditions: (a) *N*-acetylglycine, DCC, HOBT, THF, 0 °C → rt; (b) K_2CO_3, MeOH, 0 °C.

The results of the evaluation of the cytotoxicity against HeLa-S_3 cells concerning congeners **39**, **40**, **41**, **46**, **49**, **51**, **58**, and **59** are summarized in Table 1. The weak cytotoxicity of deiododoliculide (**39**) (0.83 μg/mL) indicated that the C23 iodine atom of doliculide (**1**) is responsible for the potent cytotoxicity of **1** (0.013 μg/mL). Comparison of the cytotoxicity of **1** with those of doliculide methyl ether (**40**) (1.7 μg/mL) and iododoliculide (**41**) (5.7 μg/mL) suggested that the C24 phenolic hydroxyl group of **1** plays an important role to exhibit the remarkable cytotoxicity of **1**. Although the phenolic hydroxyl group is present in **41**, its cytotoxicity is very weak: this finding could be explained if one assume that the phenolic hydroxyl group of **41** would be unable to interact with a target molecule owing to the steric hindrance caused by the additional iodine atom at C25. The conformations of the 16-membered ring moiety of this series of compounds (**1**, **39**, **40**, **41**) are assumed to be nearly identical. The cytotoxicity of deoxydoliculide (**46**) (0.077 μg/mL) that is slightly weaker than that of **1** revealed that the C7 hydroxyl group of **1** is unimportant. Thus, the roles of the functional groups such as hydroxyl, phenolic hydroxyl, and iodo groups in **1** for cytotoxicity have been disclosed to a considerable extent.

It should be noted that epidoliculide (**49**) is approximately 400-fold less toxic than doliculide (**1**): this finding suggested that the conformation of the 16-membered dilactam-lactone ring may be important for cytotoxicity, because the conformation of **1** is largely different from that of **49**. The very weak cytotoxicity of depsipeptides **51** and **58**, and dipeptide **59** revealed that almost the whole structure including the stereochemistry of **1** is required for the strong cytotoxicity of **1**.

Table 1. *In Vitro* Cytotoxicity of Doliculide (**1**) and Congeners against HeLa-S_3 Cells

compound	**1**	**39**	**40**	**41**	**46**	**49**	**51**	**58**	**59**
IC_{50} (μg/mL)	0.013	0.83	1.7	5.7	0.077	5.0	> 10	> 10	> 10

Conclusion

We have achieved an efficient total synthesis of doliculide (**1**) and thus, the absolute stereostructure of doliculide has been confirmed to be **1**. The overall yield of the synthesis, based on the longest linear sequence, is 11%. A sequence of reactions for a practical C_3 homologation, i.e., the Evans aldol reaction, removal of the chiral auxiliary, and the subsequent Barton deoxygenation reaction was devised for the construction of the 1,3,5-*syn*,*syn*-trimethylalkane structure. This sequence of reactions for a C_3 homologation can be applicable to the synthesis of other natural products which contain 1,3-*syn*-dimethylalkane structure or its homologues.

We have synthesized artificial congeners of doliculide (**1**) and have investigated their structure-cytotoxicity relationships. The results are as follows: (i) the 3-iodo-*N*-methyltyrosine moiety as well as other moieties of **1** except for the aliphatic hydroxyl group are important elements for prominent cytotoxicity of **1**; (ii) the C23 iodine atom appears to contribute to cytotoxicity of **1** significantly; (iii) the C24 phenolic hydroxyl group seems to play an important role to exhibit remarkable cytotoxicity of **1**; and (iv) the C7 hydroxyl group is not essential for cytotoxicity of **1**. Further investigation is needed to explore the structure-cytotoxicity relationships in details.

Experimental

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofurane (THF) and diethyl ether were distilled from sodium/benzophenone prior to use. Toluene and hexane were distilled from sodium prior to use. Diisopropylethylamine, triethylamine, and dichloromethane were distilled from CaH_2. *N*,*N*-Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were distilled from CaH_2 under reduced pressure. All reactions involving organometallic reagents were conducted under a nitrogen atmosphere. Evaporation of solvents was carried out with a rotary evaporator under reduced pressure (ca. 20 Torr). Fuji silysia silica gel BW-820MH was employed for column chromatography. Merck precoated silica gel 60 F_{254} plates were used for thin-layer chromatography (TLC). Melting points are uncorrected. IR spectra were obtained with a JASCO IR-810 instrument in chloroform solutions. ^{1}H NMR spectra were recorded in deuteriochloroform on a JEOL JNM-C675 instrument (270 MHz), a JEOL EX-270 instrument (270 MHz), or a JEOL GX-500 instrument (500 MHz). Chemical shifts are reported in ppm from internal tetramethylsilane. *J* values are in hertz. ^{13}C NMR spectra were recorded in deuteriochloroform on a JEOL EX-270 instrument (67.8 MHz). Chemical shifts are reported in ppm from the central peak of deuteriochloroform (77.0 ppm). Mass spectra (EIMS/FABMS) were recorded on a JEOL JSM-LG2000 spectrometer. The matrix used in FABMS analysis was *m*-nitrobenzyl alcohol. NaI was added to the matrix in case of high-resolution mass spectroscopic analysis of compounds for which $(M + Na)^+$ is shown. Optical rotations were measured with a JASCO DIP-4 polarimeter.

The purity of all compounds submitted for high-resolution mass spectroscopic analysis was determined to be >90-95% by ^{1}H NMR analysis.

Trityl ether 3: To a solution of diol **2**[7] (625 mg, 5.3 mmol) in dichloromethane (10 mL) were added with stirring triphenylmethyl chloride (1.85 g, 6.6 mmol), triethylamine (1.2 mL, 8.6 mmol), and 4-dimethylaminopyridine (55.6 mg, 0.46 mmol). After 13 h, dichloromethane (40 mL) was added, and the solution was washed with water (2 × 10 mL), saturated aqueous NH_4Cl (3 × 10 mL), and brine (5 mL) successively, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography twice on silica gel [(50 g, benzene–hexane 2:1) and (16 g, benzene–hexane 1:1 → benzene)] to give trityl ether **3** (1.85 g, 96%) as colorless crystals. Recrystallization from ether–hexane gave colorless needles: mp 57–58 °C; $[\alpha]^{22}_D$ +24.4° (*c* 0.831, $CHCl_3$); IR ($CHCl_3$) 3500 (br), 3090, 3065, 1600, 1490, 1450, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, *J* = 6.9 Hz, 3 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 1.63 (dqq, *J* = 6.9, 6.9, 6.9 Hz, 1 H), 1.71 (m, 2 H), 2.83 (d, *J* = 2.6 Hz, 1 H), 3.24 (ddd, *J* = 5.6, 7.3, 9.2 Hz, 1 H), 3.40 (ddd, *J* = 4.9, 4.9, 9.2 Hz, 1 H), 3.50 (m, 1 H), 7.20–7.50 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 17.7 (q), 18.6 (q), 33.5 (t), 33.7 (d), 63.2 (t), 76.3 (d), 87.3 (s), 127.0 (d), 127.9 (d), 128.6 (d), 143.9 (s). Anal. Calcd for $C_{25}H_{28}O_2$: C, 83.30; H, 7.83. Found: C, 83.20; H, 7.68.

Alcohol 4: To a stirred solution of trityl ether **3** (1.00 g, 2.78 mmol) in DMF (2.8 mL) at 0 °C were added a 60% dispersion of sodium hydride in mineral oil (276.0 mg, 6.90 mmol) and benzyl bromide (0.86 mL, 7.2

mmol). After 5 min, the ice bath was removed and the solution was stirred for 2.5 h at room temperature. The reaction mixture was quenched by the slow addition of H_2O (4 mL), and extracted with benzene–hexane (1:1) (50 mL + 30 mL + 20 mL). The combined extracts were washed with brine (3 × 4 mL), dried (Na_2SO_4) , and concentrated. The residue was purified by column chromatography on silica gel (40 g, chloroform–hexane 1:4 → 2:3) to give a 7.7:1 mixture of a benzyl ether and dibenzyl ether (1.33 g).

To a solution of the crude benzyl ether (1.33 g) in methanol–THF (1:1, 6 mL) was added concentrated hydrochloric acid (0.3 mL). After 4 h at 30 °C, saturated aqueous $NaHCO_3$ (5 mL) was added dropwise and the mixture was extracted with ether (50 ml + 30 mL + 20 mL). The combined extracts were washed with brine (4 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, chloroform) to give alcohol **4** (534.8 mg, 93% from trityl ether **3**) as a colorless oil: $[\alpha]^{26}_D$ -49.7° (*c* 0.719, $CHCl_3$); IR ($CHCl_3$) 3470 (br), 1600, 1495, 1465, 1450, 1065, 1025, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (d, *J* = 6.9 Hz, 3 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 1.73 (ddd, *J* = 5.8, 5.8, 5.8 Hz, 2 H), 2.07 (dqq, *J* = 5.2, 6.9, 6.9 Hz, 1 H), 2.35 (br s, 1H), 3.45 (ddd, *J* = 5.2, 5.8, 5.8 Hz, 1 H), 3.76 (m, 2 H), 4.48 (d, *J* = 11.2 Hz, 1H), 4.62 (d, *J* = 11.2 Hz, 1 H), 7.25–7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 16.9 (q), 18.6 (q), 29.9 (d), 31.7 (t), 60.8 (t), 71.5 (t), 83.1 (d), 127.5 (d), 127.7 (d), 128.3 (d), 138.4 (s); MS (FAB) *m/z* (relative intensity) 209 [(M +H)$^+$, 23], 154 (100), 136 (62); HRMS (FAB) calcd for $C_{13}H_{21}O_2$ [(M + H)$^+$] 209.1542, found 209.1511.

Aldehyde 5: To a stirred solution of oxalyl chloride (0.21 mL, 2.4 mmol) in dichloromethane (4.0 mL) at -78 °C was added a solution of DMSO (0.34 mL, 4.8 mmol) in dichloromethane (0.5 mL + 0.5 mL rinse) dropwise. The resulting solution was stirred for 10 min at -78 °C and a solution of alcohol **4** (332.5 mg, 1.60 mmol) in dichloromethane (1.5 mL + 2 × 0.5 mL rinse) was added dropwise. The mixture was stirred for 20 min at -78 °C and triethylamine (1.1 mL, 7.9 mmol) was added, then the resulting mixture was warmed to 0 °C and stirred for 15 min. H_2O (3 mL) was added and the solution was stirred at 0 °C. After 30 min, the mixture was extracted with ether (30 mL + 2 × 10 mL). The combined extracts were washed with brine (2 × 3 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (20 g, acetone–hexane 1:10) to give aldehyde **5** (316.7 mg, 96%) as a colorless oil: $[\alpha]^{26}_D$ -34.7° (*c* 0.964, $CHCl_3$); IR ($CHCl_3$) 2730, 1720, 1600, 1495, 1460, 1450, 1385, 1085, 1065, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 2.03 (dqq, *J* = 5.3, 6.6, 6.6 Hz, 1 H), 2.49 (ddd, *J* = 1.5, 3.8, 16.3 Hz, 1 H), 2.63 (ddd, *J* = 2.6, 8.2, 16.3 Hz, 1 H), 3.79 (ddd, *J* = 3.8, 5.3, 8.2 Hz, 1 H), 4.51 (d, *J* = 11.9 Hz, 1 H), 4.58 (d, *J* = 11.9 Hz, 1 H), 7.23–7.37 (m, 5 H), 9.80 (dd, *J* = 1.5, 2.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.3 (q), 18.4 (q), 30.9 (d), 44.9 (t), 71.7 (t), 79.1 (d), 127.6 (d), 127.7 (d), 128.4 (d), 138.3 (s), 202.0 (d); MS (FAB) *m/z* (relative intensity) 207 [(M + H)$^+$, 89], 181 (50), 163 (100); HRMS (FAB) calcd for $C_{13}H_{19}O_2$ [(M + H)$^+$] 207.1385, found 207.1401.

Aldol 6: To a stirred solution of (*S*)-(+)-4-isopropyl-3-propionyl-2-oxazolidinone **25** (340.1 mg, 1.84 mmol) in dichloromethane (4.0 mL) at -78 °C were added di-*n*-butylboron triflate (Aldrich, 1.0 M solution in dichloromethane, 2.0 mL, 2.0 mmol) and triethylamine (0.33 mL, 2.4 mmol) successively. The reaction temperature was maintained at -78 °C for 30 min and at 0 °C for 50 min. The solution was recooled to -78 °C and a solution of aldehyde **5** (308.3 mg, 1.50 mmol) in dichloromethane (1.0 mL + 2 × 0.5 mL rinse) was added. The reaction temperature was held at -78 °C for 30 min and at 0 °C for 1 h. The reaction mixture was quenched by the addition of phosphate buffer (pH 7, 3.0 mL) at 0 °C , and treated with methanol (7.0 mL) and 30% aqueous H_2O_2 (1.5 mL) for 1 h at 0 °C. The organic solvents were removed in vacuo. To the residue H_2O (3 mL) was added, and the resultant solution was extracted with dichloromethane (25 mL + 15 mL + 10 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual

oil was purified by column chromatography on silica gel (75 g, acetone–hexane 1:5) to give aldol **6** (554.0 mg, 95%) as a colorless oil: $[\alpha]^{27}_D$ +19.1° (*c* 0.534, $CHCl_3$); IR ($CHCl_3$) 3480 (br), 1780, 1695, 1600, 1495, 1385, 1370, 1300, 1100, 1085, 1055 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3 H), 1.24 (d, *J* = 6.9 Hz, 3 H), 1.58 (ddd, *J* = 4.0, 4.0, 14.5 Hz, 1 H), 1.70 (ddd, *J* = 9.0, 9.0, 14.5 Hz, 1 H), 2.11 (dqq, *J* = 4.0, 6.9, 6.9 Hz, 1 H), 2.35 (dqq, *J* = 4.0, 6.9, 6.9 Hz, 1 H), 3.51 (ddd, *J* = 4.0, 4.0, 9.0 Hz, 1 H), 3.66 (d, *J* = 1.7 Hz, 1 H), 3.81 (dq, *J* = 4.0, 6.9 Hz, 1 H), 4.08 (dddd, *J* = 1.7, 4.0, 4.0, 9.0 Hz, 1 H), 4.18 (dd, *J* = 4.0, 9.2 Hz, 1 H), 4.23 (dd, *J* = 7.6, 9.2 Hz, 1 H), 4.42 (ddd, *J* = 4.0, 4.0, 7.6 Hz, 1 H), 4.44 (d, *J* = 11.4 Hz, 1 H), 4.62 (d, *J* = 11.4 Hz, 1 H), 7.20–7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 11.6 (q), 14.4(q), 16.4(q), 17.7(q), 18.0 (q), 28.1 (d), 29.3 (d), 33.1 (t), 42.4 (d), 58.1 (d), 63.0 (t), 70.8 (d), 70.8 (t), 83.2 (d), 127.3 (d), 127.5 (d), 128.1 (d), 138.2 (s), 153.4 (s), 176.0 (s); MS (FAB) *m/z* (relative intensity) 392 [(M + H)$^+$, 100], 374 (24), 284 (57), 266 (52), 130 (92), 109 (67); HRMS (FAB) calcd for $C_{22}H_{34}NO_5$ [(M + H)$^+$] 392.2437, found 392.2417.

Amide 7: To a stirred suspension of *N,O*-dimethylhydroxylamine hydrochloride (377.2 mg, 3.87 mmol) in THF (2.5 mL) at 0 °C was added trimethylaluminum (Aldrich, 2.0 M solution in toluene, 1.9 mL, 3.8 mmol) dropwise. The resulting homogeneous solution was stirred for 30 min at room temperature and recooled to -19 °C. A solution of aldol **6** (554.0 mg, 1.42 mmol) in THF (1 mL + 2 × 0.5 mL rinse) was added and the resultant mixture was stirred for 30 min at -19 °C and for 2 h at -6 °C. Dichloromethane (30 mL) and 0.5 M HCl (20 mL) were added at 0 °C, and the mixture was stirred for an additional 1 h, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 20 mL). The organic layer and the extracts were combined, washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (60 g, acetone–benzene 1:10) to give amide **7** (420.4 mg, 92%) as a colorless oil: $[\alpha]^{29}_D$ -15.3° (*c* 0.569, $CHCl_3$); IR ($CHCl_3$) 3470 (br), 1645, 1495, 1460, 1385, 1100, 1085, 1060, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (d, *J* = 6.9 Hz, 3 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 1.20 (d, *J* = 6.9 Hz, 3 H), 1.58 (ddd, *J* = 4.3, 4.3, 14.3 Hz, 1 H), 1.68 (ddd, *J* = 8.4, 8.4, 14.3 Hz, 1 H), 2.08 (dqq, *J* = 4.3, 6.9, 6.9 Hz, 1 H), 2.95 (m, 1 H), 3.18 (s, 3 H), 3.50 (ddd, *J* = 4.3, 4.3, 8.4 Hz, 1 H), 3.65 (s, 3 H), 3.98 (m, 1 H), 4.08 (d, *J* = 1.3 Hz, 1 H), 4.48 (d, *J* = 11.4 Hz, 1 H), 4.62 (d, *J* = 11.4 Hz, 1 H), 7.24–7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 12.0 (q), 16.8 (q), 18.0 (q), 29.5 (d), 31.8 (q), 33.4 (t), 40.0 (d), 61.3 (q), 70.9 (t), 71.4 (d), 83.4 (d), 127.4 (d), 127.5 (d), 128.2 (d), 138.2 (s), 176.9 (s); MS (FAB) *m/z* (relative intensity) 324 [(M + H)$^+$, 100], 263 (5), 216 (27), 198 (32); HRMS (FAB) calcd for $C_{18}H_{30}NO_4$ [(M + H)$^+$] 324.2175, found 324.2148.

Methoxymethyl ether 8: To a stirred solution of amide **7** (166.4 mg, 0.515 mmol) in *N,N*-diisopropylethylamine (0.75 mL, 4.3 mmol) at 0 °C was added chloromethyl methyl ether (0.25 mL, 3.3 mmol). After 2 h at room temperature, brine (2 mL) was added, and the mixture was extracted with ether (20 mL + 2 × 10 mL). The combined extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (20 g, acetone–hexane 1:7) to give methoxymethyl ether **8** (181.4 mg, 96%) as a colorless oil: $[\alpha]^{28}_D$ +9.4° (*c* 1.26, $CHCl_3$); IR ($CHCl_3$) 1650, 1495, 1460, 1380, 1140, 1090, 1065, 1030, 990, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92(d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 1.19 (d, *J* = 6.9 Hz, 3 H), 1.75 (ddd, *J* = 5.8, 5.8, 14.6 Hz, 1 H), 1.82 (ddd, *J* = 6.3, 6.3, 14.6 Hz, 1 H), 1.99 (dqq, *J* = 4.2, 6.6, 6.6 Hz, 1 H), 3.05–3.25 (m, 1 H), 3.16 (s, 3 H), 3.30–3.43 (m, 1 H), 3.36 (s, 3 H), 3.58 (s, 3 H), 3.95 (ddd, *J* = 5.8, 6.0, 6.3 Hz, 1 H), 4.50 (d, *J* = 11.5 Hz, 1 H), 4.56 (d, *J* = 11.5 Hz, 1 H), 4.62 (d, *J* = 6.8 Hz, 1 H), 4.67 (d, *J* = 6.8 Hz, 1 H), 7.22–7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 12.9(q), 17.3 (q), 18.1 (q), 30.1 (d), 32.1 (q), 34.1 (t), 40.1(d), 55.9 (q), 61.1 (q), 71.3 (t), 76.4 (d), 80.9 (d), 96.2 (t), 127.2 (d), 127.5 (d), 128.1 (d), 139.1 (s), 175.7 (s); MS (FAB) *m/z* (relative intensity) 368 [(M + H)$^+$, 30], 336 (100), 198 (78), 152 (62); HRMS (FAB) calcd for $C_{20}H_{34}NO_5$ [(M + H)$^+$] 368.2437, found 368.2439.

Aldehyde 9: To a stirred solution of methoxymethyl ether **8** (451.1 mg, 1.23 mmol) in THF (2.5 mL) at -78 °C was added diisobutylaluminum hydride (Aldrich, 1.0 M solution in hexane, 4.9 mL, 4.9 mmol) over 10 min. The solution was stirred for 10 min at -78 °C, quenched by the addition of ethyl acetate (1.5 mL), and warmed to room temperature. To the mixture 1 M HCl (7 mL) and ether (20 mL) were added. After being stirred for 1.5 h, the organic layer was separated. The aqueous layer was extracted with ether (2 × 20 mL). The organic layer and the extracts were combined, washed with brine (2 × 2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (45 g, acetone–hexane 1:15) to give aldehyde **9** (344.3 mg, 91%) as a colorless oil: $[\alpha]^{28}_D$ -8.6° (*c* 0.61, $CHCl_3$); IR ($CHCl_3$) 2820, 2720, 1725, 1495, 1145, 1100, 1070, 1035, 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (d, *J* = 6.9 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 1.04 (d, *J* = 6.9 Hz, 3 H), 1.65 (ddd, *J* = 3.6, 8.3, 14.5 Hz, 1 H), 1.85 (ddd, *J* = 5.3, 8.9, 14.5 Hz, 1 H), 2.07 (dqq, *J* = 4.6, 6.9, 6.9 Hz, 1 H), 2.27 (dq, *J* = 3.0, 6.9 Hz, 1 H), 3.20 (ddd, *J* = 3.6, 4.6, 8.9 Hz, 1 H), 3.28 (s, 3 H), 4.22 (ddd, *J* = 3.0, 5.3, 8.3 Hz, 1 H), 4.40 (d, *J* = 11.9 Hz, 1 H), 4.52 (d, *J* = 6.9 Hz, 1 H), 4.60 (d, *J* = 11.9 Hz, 1 H), 4.67 (d, *J* = 6.9 Hz, 1 H), 7.23–7.37 (m, 5 H), 9.57 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 6.8 (q), 16.9 (q), 18.2 (q), 29.6 (d), 31.6 (t), 49.0 (d), 55.5 (q), 70.8 (t), 74.1 (d), 79.8 (d), 95.7 (t), 127.6 (d), 127.9 (d), 128.3 (d), 138.5 (s), 203.9 (d); MS (FAB) *m/z* (relative intensity) 309 [(M + H)$^+$, 17], 277 (100), 139 (58); HRMS (FAB) calcd for $C_{18}H_{29}O_4$ [(M + H)$^+$] 309.2066, found 309.2079.

Aldol 10: To a stirred solution of (*S*)-(+)-4-isopropyl-3-propionyl-2-oxazolidinone **25** (120.3 mg, 0.650 mmol) in dichloromethane (1.5 mL) at -78 °C were added di-*n*-butylboron triflate (Aldrich, 1.0 M solution in dichloromethane, 0.72 mL, 0.72 mmol) and triethylamine (0.12 mL, 0.86 mmol) successively. The reaction temperature was maintained at -78 °C for 30 min and at 0 °C for 1 h. The solution was recooled to -78 °C and a solution of aldehyde **9** (132.6 mg, 0.431 mmol) in dichloromethane (0.5 mL + 2 × 0.5 mL rinse) was added. The reaction temperature was held at -78 °C for 30 min and at 0 °C for 1 h. The reaction mixture was quenched by the addition of phosphate buffer (pH 7, 1.5 mL) at 0 °C , and treated with methanol (3.5 mL) and 30% aqueous H_2O_2 (0.75 mL) for 1 h at 0 °C. The organic solvents were removed in vacuo, and the resultant solution was extracted with dichloromethane (20 mL + 2 × 10 mL). The combined extracts were washed with brine (4 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (36 g, acetone–hexane 1:7) to give aldol **10** (201.4 mg, 95%) as a colorless oil: $[\alpha]^{17}_D$ +9.0° (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) 3520 (br), 1780, 1695, 1605, 1495, 1465, 1385, 1300, 1145, 1100, 1060, 1030, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (d, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 0.93 (d, *J* = 6.9 Hz, 3 H), 0.99 (d, *J* = 6.9 Hz, 3 H), 1.28 (d, *J* = 6.9 Hz, 3 H), 1.59–1.92 (m, 3 H), 2.00 (dqq, *J* = 4.7, 6.9, 6.9 Hz, 1 H), 2.32 (dqq, *J* = 4.0, 6.9, 6.9 Hz, 1 H), 3.21 (m, 1 H), 3.30–3.42 (m, 1 H), 3.34 (s, 3 H), 3.90 (ddd, *J* = 2.3, 4.9, 8.6 Hz, 1 H), 4.00–4.10 (m, 2 H), 4.14–4.24 (m, 2 H), 4.38 (ddd, *J* = 4.0, 4.0, 7.3 Hz, 1 H), 4.44 (d, *J* = 11.2 Hz, 1 H), 4.52 (d, *J* = 11.2 Hz, 1 H), 4.62 (d, *J* = 6.4 Hz, 1 H), 4.68 (d, *J* = 6.4 Hz, 1 H), 7.22–7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 7.7 (q), 13.2 (q), 14.5 (q), 17.2 (q), 17.7 (q), 18.0 (q), 28.1 (d), 30.0 (d), 32.0 (t), 37.4 (d), 40.4 (d), 55.6 (q), 58.0 (d), 63.0 (t), 71.3 (t), 73.9 (d), 78.7 (d), 81.0 (d), 95.6 (t), 127.2 (d), 127.5 (d), 128.1 (d), 138.7 (s), 153.1 (s), 176.9 (s); MS (FAB) *m/z* (relative intensity) 494 [(M + H)$^+$, 3], 462 (58), 354 (60), 324 (29), 195 (61), 130 (100); HRMS (FAB) calcd for $C_{26}H_{40}NO_6$ [(M - OMe)$^+$] 462.2856, found 462.2854.

Methyl ester 11: To a stirred solution of aldol **10** (201.4 mg, 0.409 mmol) in H_2O–THF (1:4, 5.0 mL) at 0 °C were added 30% aqueous H_2O_2 (0.20 mL) and $LiOH·H_2O$ (51.2 mg, 1.22 mmol). After 1.5 h at 0 °C, powdered $Na_2S_2O_3·5H_2O$ (233.3 mg, 0.940 mmol) was added and the mixture was stirred for an additional 20 min, and then chloroform (20 mL) and brine (1.5 mL) were added. The mixture was acidified (pH 1) with concentrated hydrochloric acid and the organic layer was separated. The aqueous layer was extracted with

chloroform (2 × 10 mL). The organic layer and the extracts were combined, dried ($MgSO_4$), and concentrated. The residue was dissolved in chloroform (0.5 mL) and treated with ethereal diazomethane, and the resulting mixture was concentrated. The residual oil was purified by column chromatography on silica gel (20 g, acetone–hexane 1:7) to give methyl ester **11** (143.7 mg, 89%) as a colorless oil: $[\alpha]^{26}_D$ -48.6° (*c* 0.589, $CHCl_3$); IR ($CHCl_3$) 3500 (br), 1730, 1600, 1495, 1455, 1150, 1095, 1065, 1025, 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, *J* = 6.9 Hz, 3 H), 0.93 (d, *J* = 6.9 Hz, 3 H), 0.99 (d, *J* = 6.9 Hz, 3 H), 1.20 (d, *J* = 7.3 Hz, 3 H), 1.60-1.86 (m, 3 H), 2.02 (dqq, *J* = 4.6, 6.9, 6.9 Hz, 1 H), 2.74 (dq, *J* = 7.3, 7.3 Hz, 1 H), 3.17 (ddd, *J* = 3.3, 4.6, 9.2 Hz, 1 H), 3.21 (d, *J* = 2.3 Hz, 1 H), 3.36 (s, 3 H), 3.62 (s, 3 H), 3.89 (ddd, *J* = 2.3, 4.6, 9.2 Hz, 1 H), 3.93 (ddd, *J* = 2.3, 4.1, 7.3 Hz, 1 H), 4.37 (d, *J* = 11.2 Hz, 1 H), 4.54 (d, *J* = 11.2 Hz, 1 H), 4.59 (d, *J* = 6.6 Hz, 1 H), 4.70 (d, *J* = 6.6 Hz, 1 H), 7.23–7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 7.0 (q), 12.7 (q), 16.9 (q), 18.3 (q), 30.0 (d), 31.7 (t), 37.3 (d), 42.8 (d), 51.5 (q), 55.8 (q), 71.4 (t), 75.3 (d), 78.7 (d), 81.1 (d), 95.2 (t), 127.4 (d), 127.5 (d), 128.2 (d), 138.7 (s), 176.1 (s); MS (FAB) *m/z* (relative intensity) 397 [$(M + H)^+$, 12], 365 (100), 257 (20), 225 (21), 209 (22), 183 (22); HRMS (FAB) calcd for $C_{22}H_{37}O_6$ [$(M + H)^+$] 397.2590, found 397.2599.

Thionoimidazolide 12: To a stirred solution of methyl ester **11** (331.2 mg, 0.836 mmol) in THF (0.85 mL) was added 1,1'-thiocarbonyldiimidazole (743.0 mg, 4.17 mmol). The mixture was stirred for 10 h at 70 °C and concentrated. The residue was purified by column chromatography on silica gel (54 g, acetone–hexane 1:5) to give thionoimidazolide **12** (394.1 mg, 93%) as a colorless oil: $[\alpha]^{17}_D$ +6.9° (*c* 1.45, $CHCl_3$); IR ($CHCl_3$) 1735, 1605, 1495, 1465, 1385, 1325, 1285, 1095, 1030, 970, 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, *J* = 6.9 Hz, 3 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 1.00 (d, *J* = 6.9 Hz, 3 H), 1.11 (d, *J* = 6.9 Hz, 3 H), 1.69 (ddd, *J* = 4.3, 8.0, 14.5 Hz, 1 H), 1.86 (ddd, *J* = 6.0, 8.9, 14.5 Hz, 1 H), 2.07 (dqq, *J* = 4.3, 6.9, 6.9 Hz, 1 H), 2.22 (ddq, *J* = 2.4, 7.6, 6.9 Hz, 1 H), 3.09 (dq, *J* = 3.9, 6.9 Hz, 1 H), 3.25 (ddd, *J* = 4.3, 4.3, 8.9 Hz, 1 H), 3.41 (s, 3 H), 3.60 (s, 3 H), 3.79 (ddd, *J* = 2.4, 6.0, 8.0 Hz, 1 H), 4.40 (d, *J* = 11.5 Hz, 1 H), 4.57 (d, *J* = 11.5 Hz, 1 H), 4.59 (d, *J* = 7.1 Hz, 1 H), 4.67 (d, *J* = 7.1 Hz, 1 H), 6.22 (dd, *J* = 3.9, 7.6 Hz, 1 H), 7.03 (dd, *J* = 1.0, 1.7 Hz, 1 H), 7.23–7.39 (m, 5 H), 7.60 (dd, *J* = 1.0, 1.7 Hz, 1 H), 8.31 (dd, *J* = 1.0, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.7 (q), 10.7 (q), 17.0 (q), 18.0 (q), 29.3 (d), 31.1 (t), 37.3 (d), 40.6 (d), 51.8 (q), 56.1 (q), 70.5(t), 75.3(d), 80.5 (d), 84.8 (d), 95.4 (t), 117.8 (d), 127.3 (d), 127.4 (d), 128.2 (d), 130.6 (d), 136.7 (d), 138.5 (s), 173.4 (s), 183.9 (s); MS (FAB) *m/z* (relative intensity) 507 [$(M + H)^+$, 100], 227 (52), 163 (66), 113 (55); HRMS (FAB) calcd for $C_{26}H_{39}N_2O_6S$ [$(M + H)^+$] 507.2529, found 507.2544.

Methyl ester 13: To a stirred solution of thionoimidazolide **12** (165.5 mg, 0.327 mmol) in toluene (6.5 mL) was added tri-*n*-butyltin hydride (0.88 mL, 3.3 mmol). The solution was heated to reflux for 13 min. After cooling, the mixture was concentrated. The residual oil was purified by column chromatography on silica gel (56 g, ethyl acetate–hexane 1:10) to give methyl ester **13** (97.7 mg, 79%) as a colorless oil: $[\alpha]^{16}_D$ +15.1° (*c* 1.35, $CHCl_3$); IR ($CHCl_3$) 1730, 1605, 1495, 1460, 1150, 1090, 1065, 1035, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (d, *J* = 6.9 Hz, , 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 1.14 (d, *J* = 6.9 Hz, 3 H), 1.25 (ddd, *J* = 5.4, 9.4, 13.4 Hz, 1 H), 1.54–2.04 (m, 5 H), 2.57 (ddq, 5.4, 9.4, 6.9 Hz, 1 H), 3.27 (ddd, *J* = 4.3, 5.6, 6.9 Hz, 1 H), 3.35 (s, 3 H), 3.57 (ddd, *J* = 2.9, 6.6, 6.6 Hz, 1 H), 3.62 (s, 3 H), 4.50 (s, 2 H), 4.60 (d, *J* = 6.9 Hz, 1 H), 4.63 (d, *J* = 6.9 Hz, 1 H), 7.20–7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.2(q), 17.3 (q), 18.0 (q), 18.1 (q), 30.2 (d), 31.6 (t), 33.2 (d), 36.8 (t), 37.2 (d), 51.3 (q), 55.7 (q), 71.3 (t), 78.1 (d), 81.1(d), 95.5 (t), 127.3 (d), 127.5 (d), 128.2 (d), 139.0 (s), 177.1 (s); MS (FAB) *m/z* (relative intensity) 381 [$(M + H)^+$, 10], 349 (100), 241 (35), 227 (45), 211 (69), 179 (34); HRMS (FAB) calcd for $C_{22}H_{37}O_5$ [$(M + H)^+$] 381.2641, found 381.2614.

Alcohol 14: To a stirred solution of methyl ester **13** (48.5 mg, 0.128 mmol) in THF (1.3 mL) at 0 °C was added lithium aluminum hydride (Aldrich, 1.0 M solution in THF, 0.26 mL, 0.26 mmol) dropwise. After 10

min, the reaction mixture was quenched by the slow addition of methanol (0.1 mL) at 0 °C and warmed to room temperature. To the solution brine (0.1 mL), ether (10 mL), and $MgSO_4$ (1 g) were added successively. The resulting mixture was stirred for 1 h, filtered, and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, ethyl acetate–hexane 1:3) to give alcohol **14** (43.7 mg, 97%) as a colorless oil: $[\alpha]^{23}_D$ -19.1° (*c* 0.874, $CHCl_3$); IR ($CHCl_3$) 3460 (br), 1600, 1495, 1460, 1450, 1375, 1145, 1090, 1065, 1035, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87–1.03 (m, 1 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 1.54–1.87 (m, 5 H), 1.99 (dqq, *J* = 4.3, 6.9, 6.9 Hz, 1 H), 3.27 (ddd, *J* = 4.3, 5.0, 7.1 Hz, 1 H), 3.35–3.49 (m, 1 H), 3.37 (s, 3 H), 3.41 (br dd, *J* = 4.6, 4.6 Hz, 2 H), 3.59 (ddd, *J* = 2.8, 6.5, 6.5 Hz, 1 H), 4.47 (d, *J* = 11.7 Hz, 1 H), 4.54 (d, *J* = 11.7 Hz, 1 H), 4.61 (d, *J* = 6.8 Hz, 1 H), 4.65 (d, *J* = 6.8 Hz, 1 H), 7.23–7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 15.0 (q), 17.6 (q), 17.7 (q), 17.8 (q), 30.0 (d), 31.6 (t), 32.8 (d), 32.9 (d), 36.0 (t), 55.5 (q), 67.6 (t), 71.0 (t), 78.4 (d), 81.0 (d), 95.9 (t), 127.2 (d), 127.5 (d), 128.1 (d), 138.9 (s); MS (FAB) *m/z* (relative intensity) 375 [$(M + Na)^+$ 12], 321 (55), 291 (18), 213 (39), 183 (100); HRMS (FAB) calcd for $C_{21}H_{36}NaO_4$ [$(M + Na)^+$] 375.2512, found 375.2542.

Aldehyde 15: To a stirred solution of oxalyl chloride (0.050 mL, 0.57 mmol) in dichloromethane (1.0 mL) at -78 °C was added a solution of DMSO (0.080 mL, 1.1 mmol) in dichloromethane (0.5 mL + 0.5 mL rinse) dropwise. The resulting solution was stirred for 10 min at -78 °C and a solution of alcohol **14** (131.1 mg, 0.372 mmol) in dichloromethane (0.5 mL + 2 × 0.5 mL rinse) was added dropwise. The mixture was stirred for 10 min at -78 °C and triethylamine (0.26 mL, 1.9 mmol) was added, then the resulting mixture was warmed to 0 °C and stirred for 10 min. H_2O (2 mL) was added and the solution was stirred at 0 °C. After 30 min, the mixture was extracted with ether (20 mL + 2 × 10 mL). The combined extracts were washed with brine (2 × 3 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (13 g, ethyl acetate–hexane 1:7) to give aldehyde **15** (127.1 mg, 98%) as a colorless oil: $[\alpha]^{21}_D$ -14.3° (*c* 1.23, $CHCl_3$); IR ($CHCl_3$) 2820, 2710, 1720, 1605, 1495, 1460, 1145, 1090, 1065, 1035, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (d, *J* = 6.9 Hz, 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 1.04 (d, *J* = 6.9 Hz, 3 H), 1.18 (m, 1 H), 1.56–1.83 (m, 3 H), 1.91 (m, 1 H), 1.99 (dqq, *J* = 4.5, 6.9, 6.9 Hz, 1 H), 2.40 (m, 1 H), 3.25 (ddd, *J* = 4.5, 4.5, 7.2 Hz, 1 H), 3.34 (s, 3 H), 3.59 (ddd, *J* = 2.7, 6.5, 6.5 Hz, 1 H), 4.44 (d, *J* = 11.8 Hz, 1 H), 4.54 (d, *J* = 11.8 Hz, 1 H), 4.58 (d, *J* = 6.9 Hz, 1 H), 4.64 (d, *J* = 6.9 Hz, 1 H), 7.20–7.38 (m, 5 H), 9.50 (d, *J* = 2.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 14.2 (q), 17.5 (q), 17.6 (q), 29.8 (d), 31.3 (t), 32.7 (d), 33.6 (t), 43.8 (d), 55.6 (q), 71.0 (t), 77.7 (d), 80.7 (d), 95.5 (t), 127.2 (d), 127.5 (d), 128.1 (d), 138.9 (s), 204.9 (d); MS (FAB) *m/z* (relative intensity) 373 [$(M + Na)^+$, 4], 351 [$(M + H)^+$, 11], 349 (14), 335 (7), 319 (100), 289 (95); HRMS (FAB) calcd for $C_{21}H_{34}NaO_4$ [$(M + Na)^+$] 373.2355, found 373.2334.

Aldol 16: To a stirred solution of (*S*)-(+)-4-isopropyl-3-propionyl-2-oxazolidinone **25** (97.4 mg, 0.526 mmol) in dichloromethane (1.2 mL) at -78 °C were added di-*n*-butylboron triflate (Aldrich, 1.0 M solution in dichloromethane, 0.58 mL, 0.58 mmol) and triethylamine (0.095 mL, 0.68 mmol) successively. The reaction temperature was maintained at -78 °C for 30 min and at 0 °C for 1 h. The solution was recooled to -78 °C and a solution of aldehyde **15** (122.8 mg, 0.351 mmol) in dichloromethane (0.5 mL + 2 × 0.5 mL rinse) was added. The reaction temperature was held at -78 °C for 30 min and at 0 °C for 1 h. The reaction mixture was quenched by the addition of phosphate buffer (pH 7, 1.0 mL) at 0 °C , and treated with methanol (2.5 mL) and 30% aqueous H_2O_2 (0.5 mL) for 3 h at 0 °C. The organic solvents were removed in vacuo, and the resulting solution was extracted with dichloromethane (20 mL + 2 × 10 mL). The combined extracts were washed with brine (3 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (31 g, ethyl acetate–hexane 1:4 → 1:2) to give aldol **16** (165.8 mg, 88%) as a colorless oil: $[\alpha]^{20}_D$ +40.1° (*c* 1.50, $CHCl_3$); IR ($CHCl_3$) 3490 (br), 1780, 1690, 1495, 1460, 1385, 1140,

1090, 1055, 1035, 990, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85–1.08 (m, 1 H), 0.87 (d, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 6.9 Hz, 6 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 1.27 (d, *J* = 6.9 Hz, 3 H), 1.58–1.94 (m, 5 H), 1.98 (dqq, *J* = 4.3, 6.9, 6.9 Hz, 1 H), 2.34 (dqq, *J* = 3.8, 6.9, 6.9 Hz, 1 H), 2.49 (d, *J* = 4.5 Hz, 1 H), 3.31 (ddd, *J* = 4.3, 5.4, 7.1 Hz, 1 H), 3.37 (s, 3 H), 3.57 (ddd, *J* = 3.0, 6.3, 6.3 Hz, 1 H), 3.72 (m, 1 H), 4.00 (dq, *J* = 6.9, 6.9 Hz, 1 H), 4.19 (dd, *J* = 3.8, 9.1 Hz, 1 H), 4.24 (dd, *J* = 7.6, 9.1 Hz, 1 H), 4.43 (ddd, *J* =3.8, 3.8, 7.6 Hz, 1 H), 4.51 (s, 2 H), 4.65 (s, 2 H), 7.21–7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.6 (q), 14.4 (q), 14.9 (q), 15.0 (q), 17.4 (q), 17.7 (q), 17.8 (q), 28.0 (d), 29.9 (d), 31.5 (t), 32.4 (d), 32.7 (d), 35.9 (t), 40.2 (d), 55.4 (q), 58.0 (d), 62.9 (t), 70.9 (t), 73.5 (d), 78.6 (d), 80.9 (d), 96.0 (t), 127.1 (d), 127.3 (d), 128.0 (d), 138.9 (s), 153.2 (s), 176.6 (s); MS (FAB) *m/z* (relative intensity) 558 [$(M + Na)^+$, 17], 504 (12), 396 (39), 366 (49), 130 (100); HRMS (FAB) calcd for $C_{30}H_{49}NNaO_7$ [$(M + Na)^+$] 558.3406, found 558.3398.

Methyl ester 17: To a stirred solution of aldol **16** (169.9 mg, 0.318 mmol) in H_2O–THF (1:4, 3.75 mL) at 0 °C were added 30% aqueous H_2O_2 (0.15 mL) and $LiOH·H_2O$ (39.8 mg, 0.949 mmol). After 1 h at 0 °C, powdered $Na_2S_2O_3·5H_2O$ (162.1 mg, 0.653 mmol) was added and the mixture was stirred for an additional 20 min, and then chloroform (25 mL) and brine (1 mL) were added. The mixture was acidified (pH 1) with concentrated hydrochloric acid and the organic layer was separated. The aqueous layer was extracted with chloroform (2 × 10 mL). The organic layer and the extracts were combined, dried ($MgSO_4$), and concentrated. The residue was dissolved in chloroform (0.5 mL) and treated with ethereal diazomethane, and the resulting mixture was concentrated. The residual oil was purified by column chromatography on silica gel (15 g, acetone–hexane 1:7 → 1:2) to give methyl ester **17** (129.7 mg, 93%) as a colorless oil: $[\alpha]^{19}_D$ -1.5° (*c* 1.30, $CHCl_3$); IR ($CHCl_3$) 3470 (br), 1730, 1495, 1460, 1150, 1095, 1060, 1035, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85–1.05 (m, 1 H), 0.87 (d, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 1.20 (d, *J* = 6.9 Hz, 3 H), 1.53–1.92 (m, 5 H), 1.98 (dqq, *J* = 4.3, 6.9, 6.9 Hz, 1 H), 2.25 (d, *J* = 5.0 Hz, 1 H), 2.65 (dq, *J* = 6.9, 6.9 Hz, 1 H), 3.30 (ddd, *J* = 4.3, 4.3, 7.1 Hz, 1 H), 3.36 (s, 3 H), 3.55 (ddd, *J* = 3.3, 6.2, 6.2 Hz, 1 H), 3.61 (m, 1 H), 3.66 (s, 3 H), 4.51 (s, 2 H), 4.63 (s, 2 H), 7.22–7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.4 (q), 14.3 (q), 15.0 (q), 17.5 (q), 17.7 (q), 30.0 (d), 31.3 (t), 32.4 (d), 32.9 (d), 35.9 (t), 42.8 (d), 51.4 (q), 55.4 (q), 71.0 (t), 74.0 (d), 78.9 (d), 81.1 (d), 96.0 (t), 127.2 (d), 127.4 (d), 128.1 (d), 138.9 (s), 176.0 (s); MS (FAB) *m/z* (relative intensity) 461 [(M + Na), 8], 439 [$(M + H)^+$, 4], 467 (68), 299 (47), 269 (100); HRMS (FAB) calcd for $C_{25}H_{42}NaO_6$ [$(M + Na)^+$] 461.2879, found 461.2876.

Thionoimidazolide 18: To a stirred solution of methyl ester **17** (94.9 mg, 0.217 mmol) in THF (0.25 mL) was added 1,1'-thiocarbonyldiimidazole (202.8 mg, 1.14 mmol). The mixture was stirred for 5 h at 70 °C and concentrated. The residue was purified by column chromatography on silica gel (15 g, acetone–hexane 1:7) to give thionoimidazolide **18** (111.1 mg, 94%) as a colorless oil: $[\alpha]^{20}_D$ -24.1° (*c* 1.11, $CHCl_3$); IR ($CHCl_3$) 1735, 1605,1495, 1460, 1380, 1325, 1280, 1095, 1060, 1035, 970, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (d, *J* = 6.9 Hz, 3 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 1.00 (d, *J* = 6.9 Hz, 3 H), 1.04–1.21 (m, 1 H), 1.23 (d, *J* = 7.2 Hz, 3 H), 1.51–1.83 (m, 3 H), 1.83–2.10 (m, 2 H), 2.03 (dqq, *J* = 4.0, 6.9, 6.9 Hz, 1 H), 3.06 (dq, *J* = 7.6, 7.2 Hz, 1 H), 3.27 (m, 1 H), 3.33 (s, 3 H), 3.56 (m, 1 H), 3.68 (s, 3 H), 4.44 (d, *J* = 11.6 Hz, 1 H), 4.53 (d, *J* = 11.6 Hz, 1 H), 4.57 (s, 2 H), 5.98 (dd, *J* = 3.5, 7.6 Hz, 1 H), 7.04 (s, 1 H), 7.20–7.35 (m, 5 H), 7.59 (s, 1 H), 8.31 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.4 (q), 14.1 (q), 15.0 (q), 17.4 (q), 17.6 (q), 29.8 (d), 32.0 (t), 32.4 (d), 33.0 (d), 36.6 (t), 41.9 (d), 51.9 (q), 55.6 (q), 71.0 (t), 77.6 (d), 81.0 (d), 85.6 (d), 95.6 (t), 117.8 (d), 127.1 (d), 127.2 (d), 128.0 (d), 130.8 (d), 136.6 (d), 138.9 (s), 173.3 (s), 184.3 (s); MS (FAB) *m/z* (relative intensity) 549 [$(M + H)^+$, 88], 269 (67), 109 (100); HRMS (FAB) calcd for $C_{29}H_{45}N_2O_6S$ [$(M + H)^+$] 549.2998, found 549.2983.

Methyl ester 19 and mercaptomethyl ether 23: To a stirred solution of thionoimidazolide **18** (146.4 mg, 0.267 mmol) in toluene (5.4 mL) was added tri-*n*-butyltin hydride (0.72 mL, 2.7 mmol). The solution was

heated to reflux for 10 min. After cooling, the mixture was concentrated. The residual oil was purified by column chromatography on silica gel (43 g, ethyl acetate–hexane 1:15) to give mercaptomethyl ether **23** (21.1 mg) and methyl ester **19** (92.7 mg). Further purification of crude **19** by column chromatography on silica gel (9.5 g, acetone–hexane 1:50) gave pure methyl ester **19** (85.8 mg, 76%) as a colorless oil: $[\alpha]^{20}_D$ +19.1° (*c* 0.858, $CHCl_3$); IR ($CHCl_3$) 1730, 1605, 1495, 1460, 1190, 1170, 1150, 1090, 1065, 1035, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (d, *J* = 6.9 Hz, 3 H), 0.85–1.15 (m, 2 H), 0.87 (d, *J* = 6.9 Hz, 3 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 1.12 (d, *J* = 6.9 Hz, 3 H), 1.32–1.56 (m, 2 H), 1.58–1.88 (m, 4 H), 1.99 (dqq, *J* = 4.2, 6.9, 6.9 Hz, 1 H), 2.57 (ddq, *J* = 4.7, 10.1, 6.9 Hz, 1 H), 3.28 (ddd, *J* = 4.2, 5.3, 7.3 Hz, 1 H), 3.35 (s, 3 H), 3.57 (ddd, *J* = 2.8, 6.5, 6.5 Hz, 1 H), 3.64 (s, 3 H), 4.48 (d, *J* = 11.5 Hz, 1 H), 4.53 (d, *J* = 11.5 Hz, 1 H), 4.60 (d, *J* = 6.8 Hz, 1 H), 4.64 (d, *J* = 6.8 Hz, 1 H), 7.20–7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.4(q), 17.5 (q), 17.9 (q), 18.3 (q), 20.4 (q), 28.2 (d), 30.0 (d), 31.8 (t), 32.5 (d), 37.3 (d), 40.5 (t), 41.0 (t), 51.3 (q), 55.6 (q), 71.0 (t), 78.4 (d), 81.0 (d), 95.8 (t), 127.2 (d), 127.5 (d), 128.1 (d), 139.0 (s), 177.2 (s); MS (FAB) *m/z* (relative intensity) 445 [$(M + Na)^+$, 4], 391 (68), 283 (58), 269 (48), 253 (100); HRMS (FAB) calcd for $C_{25}H_{42}NaO_5$ [$(M + Na)^+$] 445.2930, found 445.2915.

Further purification of crude **23** by column chromatography on silica gel (9 g, acetone–hexane 1:20) gave pure mercaptomethyl ether **23** (7.4 mg, 6%) as a colorless oil: $[\alpha]^{25}_D$ -3.6° (*c* 0.84, $CHCl_3$); IR ($CHCl_3$) 1730, 1605, 1500, 1460, 1150, 1090, 1065, 1035, 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85–1.15 (m, 2 H), 0.88 (d, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 1.21 (d, *J* = 6.9 Hz, 3 H), 1.56–1.92 (m, 4 H), 2.00 (dqq, *J* = 4.3, 6.9, 6.9 Hz, 1 H), 2.08 (t, *J* = 9.5 Hz, 1 H), 2.70 (dq, *J* = 6.9, 6.9 Hz, 1 H), 3.28 (ddd, *J* = 4.3, 4.3, 7.3 Hz, 1 H), 3.35 (s, 3 H), 3.55–3.72 (m, 2 H), 3.66 (s, 3 H), 4.47 (d, *J* = 11.6 Hz, 1 H), 4.53 (d, *J* = 11.6 Hz, 1 H), 4.62 (s, 2 H), 4.74 (d, *J* = 9.5 Hz, 2 H), 7.22–7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.7 (q), 14.9 (q), 15.4 (q), 17.6 (q), 17.9 (q), 29.9 (d), 31.9 (t), 32.9 (d), 33.9 (d), 37.1 (t), 42.4 (d), 51.7 (q), 55.7 (q), 68.3 (t), 71.0 (t), 77.9 (d), 81.1 (d), 82.0 (d), 95.9 (t), 127.3 (d), 127.5 (d), 128.2 (d), 139.0 (s), 175.7 (s); MS (FAB) *m/z* (relative intensity) 507 [$(M + Na)^+$, 3], 485 [$(M + H)^+$, 5], 453 (12), 407 (25), 329 (78), 299 (92), 269 (100); HRMS (FAB) calcd for $C_{26}H_{44}NaO_6S$ [$(M + Na)^+$] 507.2756, found 507.2761.

Alcohol 20: To a stirred solution of methyl ester **19** (82.6 mg, 0.196 mmol) in methanol (6.0 mL) was added concentrated hydrochloric acid (0.12 mL). The solution was stirred for 2 h at 50 °C. After cooling, the solution was concentrated to about 0.5 mL and saturated aqueous $NaHCO_3$ (2 mL) was added. The mixture was extracted with ether (20 mL + 2 × 10 mL). The combined organic extracts were washed with brine (1 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (25 g, ethyl acetate–hexane 1:10) to give alcohol **20** (70.9 mg, 96%) as a colorless oil: $[\alpha]^{19}_D$ -24.9° (*c* 1.14, $CHCl_3$); IR ($CHCl_3$) 3480 (br), 1730, 1495, 1460, 1195, 1170, 1090, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (d, *J* = 6.9 Hz, 3 H), 0.85–1.15 (m, 2 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 1.14 (d, *J* = 6.9 Hz, 3 H), 1.30–1.66 (m, 5 H), 1.77 (ddd, *J* = 4.0, 9.9, 13.5 Hz, 1 H), 2.14 (dqq, *J* = 4.0, 6.9, 6.9 Hz, 1 H), 2.58 (ddq, *J* = 5.0, 9.9, 6.9 Hz, 1 H), 3.48–3.57 (m, 2 H), 3.61–3.69 (m, 1 H), 3.64 (s, 3 H), 4.43 (d, *J* = 11.2 Hz, 1 H), 4.65 (d, *J* = 11.2 Hz, 1 H), 7.21–7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 15.9 (q), 18.1 (q), 18.5 (q), 20.6 (q), 28.1 (d), 29.1 (d), 32.4 (t), 35.7 (d), 37.3 (d), 40.6 (t), 40.7 (t), 51.2 (q), 70.9 (t), 74.9 (d), 85.2 (d), 127.6 (d), 127.7 (d), 128.3 (d), 137.9 (s), 177.2 (s); MS (FAB) *m/z* (relative intensity) 379 [$(M + H)^+$, 100], 271 (27), 253 (73); HRMS (FAB) calcd for $C_{23}H_{39}O_4$ [$(M + H)^+$] 379.2849, found 379.2841.

***p*-Nitrobenzoate 21 and olefins 24**(*E*:*Z* = 9:1): To a stirred solution of alcohol **20** (55.0 mg, 0.146 mmol) and triphenylphosphine (382.3 mg, 1.46 mmol) in ether (5.8 mL) was added *p*-nitrobenzoic acid (243.2 mg,

1.46 mmol). With vigorous stirring, diethyl azodicarboxylate (1.0 M solution in ether, 1.46 mL, 1.46 mmol) was added to the suspension over 10 min and resulting mixture was stirred for 17.5 h. The mixture was concentrated and the residue was purified by column chromatography on silica gel (96 g, ethyl acetate–hexane 1:20) to give olefins **24** (10.6 mg, 20%) and *p*-nitrobenzoate **21** (55.5 mg, 72%) as a colorless oil, respectively. **21**: $[\alpha]^{17}_D$ -59.6° (*c* 0.990 $CHCl_3$); IR ($CHCl_3$) 1725, 1610, 1530, 1500, 1465, 1350, 1280, 1120, 1105, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90–1.12 (m, 2 H), 0.92 (d, *J* = 6.6 Hz, 6 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 1.09 (d, *J* = 6.9 Hz, 3 H), 1.31 (ddd, *J* = 6.0, 7.9, 13.7 Hz, 1 H), 1.42–1.84 (m, 4 H), 1.97–2.16 (m, 2 H), 2.54 (ddq, *J* = 5.1, 9.6, 6.9 Hz, 1 H), 3.22 (ddd, *J* = 2.1, 4.5, 9.7 Hz, 1 H), 3.61 (s, 3 H), 4.37 (d, *J* = 11.1 Hz, 1 H), 4.52 (d, *J* = 11.1 Hz, 1 H), 5.40 (ddd, *J* = 1.9, 4.1, 10.1 Hz, 1 H), 7.17–7.37 (m, 5 H), 8.18 (d, *J* = 8.9 Hz, 2 H), 8.29 (d, *J* = 8.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.9 (q), 16.7 (q), 18.0 (q), 18.5 (q), 20.3 (q), 28.0 (d), 29.8 (t), 30.0 (d), 33.6 (d), 37.2 (d), 40.2 (t), 40.7 (t), 51.3 (q), 72.0 (t), 76.5 (d), 80.2 (d), 123.4 (d), 127.3 (d), 127.8 (d), 128.1 (d), 130.5 (d), 136.0 (s), 138.6 (s), 150.3 (s), 164.1 (s), 177.2 (s); MS (FAB) *m/z* (relative intensity) 528 [$(M + H)^+$, 14], 420 (7), 253 (33), 154 (100); HRMS (FAB) calcd for $C_{30}H_{42}NO_7$ [$(M + H)^+$] 528.2961, found 528.2993.

24(*E*:*Z* = 9:1): IR ($CHCl_3$) 1730, 1605, 1500, 1460, 1455, 1175, 1090, 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80–2.00 (m, 18 H), 1.57 (s, 3 H), 2.26 (m, 2 H), 2.50–2.64 (m, 1 H), 3.18 (ddd, *J* = 5.6, 5.6, 5.6 Hz, 0.9 H), 3.33 (dd, *J* = 6.6, 7.5 Hz, 0.1 H), 3.63 (s, 0.3 H), 3.66 (s, 2.7 H), 4.31 (d, *J* = 12.2 Hz, 0.1 H), 4.48 (d, *J* = 11.7 Hz, 0.9 H), 4.57 (d, *J* = 12.2 Hz, 0.1 H), 4.59 (d, *J* = 11.7 Hz, 0.9 H), 5.20 (m, 0.9 H), 5.31 (dd, *J* = 7.3, 8.6 Hz, 0.1 H), 7.20–7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ (major isomer) 15.9 (q), 18.0 (q), 18.1 (q), 18.7 (q), 19.4 (q), 28.7 (d), 29.3 (t), 31.0 (d), 37.3 (d), 41.2 (t), 48.1 (t), 51.4 (q), 71.8 (t), 84.4 (d), 122.8 (d), 127.3 (d), 127.6 (d), 128.2 (d), 134.7 (s), 139.2 (s), 177.4 (s); MS (FAB) *m/z* (relative intensity) 361 [$(M + H)^+$, 50], 253 (100); HRMS (FAB) calcd for $C_{23}H_{37}O_3$ [$(M + H)^+$] 361.2743, found 361.2774.

Silyl ether 22: To a stirred solution of *p*-nitrobenzoate **21** (50.0 mg, 0.0949 mmol) in methanol (3.8 mL) was added 20% (w/w) aqueous NaOH (0.76 mL). The solution was stirred for 2 h at 45 °C. After cooling, chloroform (30 mL) and brine (3 mL) were added. The mixture was acidified (pH 1) with concentrated hydrochloric acid and the organic layer was separated. The aqueous layer was extracted with chloroform (2 × 20 mL). The organic layer and the extracts were combined, dried ($MgSO_4$) and concentrated to give a mixture of a hydroxy acid and *p*-nitrobenzoic acid (52.0 mg).

To a suspension of the crude hydroxy acid (52.0 mg) in dichloromethane (1.0 mL) at 0 °C were added triethylamine (0.10 mL, 0.72 mmol) and *tert*-butyldimethylsilyl triflate (0.11 mL, 0.48 mmol). After 15 min at 0 °C, K_2CO_3 (66.0 mg, 0.48 mmol), H_2O (1.5 mL), methanol (2 mL), and THF (1.5 mL) were added, and resultant mixture was stirred for 1 h at 40 °C. To the solution chloroform (30 mL) and brine (3 mL) were added. The mixture was acidified (pH 2) with 1 M HCl and the organic layer was separated. The aqueous layer was extracted with chloroform (2 × 20 mL). The organic layer and the extracts were combined, dried ($MgSO_4$), and concentrated. The residual oil was purified by column chromatography on silica gel (32 g, benzene → acetone–benzene 1:20) to give silyl ether **22** (44.8 mg, 99% from *p*-nitrobenzoate **21**) as a colorless oil: $[\alpha]^{21}_D$ -34.3° (*c* 0.829, $CHCl_3$); IR ($CHCl_3$) 2500–3300 (br), 1705, 1500, 1465, 1390, 1255, 1070, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 3 H), 0.03 (s, 3 H), 0.80–1.22 (m, 3 H), 0.83 (d, *J* = 6.6 Hz, 3 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.88 (s, 9 H), 0.90 (d, *J* = 6.6 Hz, 6 H), 1.07 (d, *J* = 6.9 Hz, 3 H), 1.34 (m, 2 H), 1.44–1.84 (m, 3 H), 2.06 (dqq, *J* = 4.0, 6.6, 6.6 Hz, 1 H), 2.49 (m, 1 H), 3.41 (m, 1 H), 3.82 (m, 1 H), 4.40 (d, *J* = 11.6 Hz, 1 H), 4.60 (d, *J* = 11.6 Hz, 1 H), 7.19–7.36 (m, 5 H), 10.78 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ -4.5 (q), -3.9 (q), 14.0 (q), 16.4 (q), 17.6 (q), 18.1 (s), 18.5 (q), 20.6 (q), 26.0 (q), 28.0 (d), 29.7 (d), 31.6 (t), 36.2 (d), 37.2 (d), 40.6 (t), 40.9 (t), 71.0 (t), 72.4 (d), 81.2 (d), 127.2 (d), 127.4 (d), 128.2 (d), 139.4 (s), 183.4 (s); MS (FAB) *m/z* (relative intensity) 501 [$(M + Na)^+$, 34], 479 [$(M + H)^+$, 43], 347 (46), 301 (39), 239 (98), 111 (100); HRMS (FAB) calcd for $C_{28}H_{51}O_4Si$ [$(M + H)^+$] 479.3557, found 479.3530.

Depsipeptide (29): A mixture of silyl ether **22** (2.4 mg, 0.0050 mmol), 10% Pd on carbon (3.3 mg), and anhydrous K_2CO_3 (0.6 mg, 0.004 mmol) in methanol (0.5 mL) was stirred under 1 atm of H_2 gas for 1 h. An acidic ion-exchange resin (Amberlite IRC-50, H^+ form, 48 mg) was added. The resulting mixture was stirred for 30 min and passed through an acidic ion-exchange resin column (Amberlite CG-50, H^+ form, 50 mg). The column was eluted with methanol (6 mL). The eluate was concentrated and chloroform (2 ml) was added. The mixture was filtered through a small plug of cotton and concentrated to give crude carboxylic acid **26** (2.2 mg) as a colorless oil.

To a stirred solution of *N*-Boc derivative of dipeptide **27**[24] (5.9 mg, 0.013 mmol) in dichloromethane (0.2 mL) was added trifluoroacetic acid (0.2 mL). After 10 min, the solution was concentrated and the residue was azeotropically dried with benzene (2 × 5 mL) to give crude dipeptide **27**.

To a stirred solution of crude carboxylic acid **26** (2.2 mg) and crude dipeptide **27** in DMF (0.15 mL) at 0 °C were added triethylamine (0.010 mL, 0.072 mmol) and DEPC (0.33 M solution in DMF, 0.055 mL, 0.018 mmol). After 50 min, brine (1 mL) was added and the mixture was extracted with ethyl acetate (30 mL). The extract was washed with brine (2 × 1 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, acetone–benzene 1:10) to give a methyl ester of seco acid **28** (3.5 mg, 96% from silyl ether **22**) as a colorless oil.

To a stirred solution of the methyl ester of seco acid **28** (3.5 mg, 0.0048 mmol) in H_2O–THF (1:2, 0.3 mL) was added $LiOH·H_2O$ (0.5 mg, 0.01 mmol). After 1 h, an acidic ion-exchange resin (Amberlite IRC-50, H^+ form, 61 mg) was added. The resulting mixture was stirred for 30 min and passed through an acidic ion-exchange resin column (Amberlite CG-50, H^+ form, 0.1 g). The column was eluted with methanol (10 mL). The eluate was concentrated, and the residue was azeotropically dried with benzene (2 × 5 mL) to give crude seco acid **28** (3.3 mg, 96%).

To a stirred solution of the crude seco acid **28** (3.3 mg) in chloroform (1.0 mL) were added 4-dimethylaminopyridine (2.9 mg, 0.024 mmol), camphorsulfonic acid (2.3 mg, 0.0099 mmol) and *N,N'*-dicyclohexylcarbodiimide (1.9 mg, 0.0092 mmol) successively. The resulting solution was stirred for 12 h at 60 °C. After cooling, acetic acid (0.002 mL) and methanol (0.1 mL) were added and the resulting mixture was stirred for 30 min and concentrated. The residue was purified by column chromatography on silica gel (2.5 g, acetone–benzene 1:20) and thin layer chromatography on silica gel (200 × 200 × 0.25 mm, acetone–benzene 1:7) successively to give depsipeptide **29** (1.4 mg, 42% from the methyl ester of seco acid **28**) as a colorless oil: ^{1}H NMR ($CDCl_3$) (rotamer ratio 3:2) δ -0.02 (s, 1.2 H), 0.01 (s, 1.2 H), 0.09 (s, 1.8 H), 0.16 (s, 1.8 H), 0.76–2.08 (m, 21 H), 0.88 (s, 3.6 H), 0.93 (s, 5.4 H), 1.10 (d, J = 6.9 Hz, 1.2 H), 1.14 (d, J = 6.6 Hz, 1.8 H), 2.25–2.48(m, 1 H), 2.65 (s, 1.8 H), 2.96 (dd, J = 8.9, 14.2 Hz, 0.4 H), 2.97 (s, 1.2 H), 3.19 (dd, J = 6.6, 14.2 Hz, 0.4 H), 3.26 (br d, J = 16.7 Hz, 0.4 H), 3.34 (d, J = 7.8 Hz, 1.2 H), 3.47 (dd, J = 2.3, 17.1 Hz, 0.6 H), 3.46–3.55 (m, 0.4 H), 3.71 (br d, J = 12.2 Hz, 0.6 H), 3.84 (t, J = 7.8 Hz, 0.6 H), 4.50 (dd, J = 7.1, 17.1 Hz, 0.6 H), 4.63 (dd, J = 6.6, 8.9 Hz, 0.4 H), 4.68 (dd, J = 6.4, 16.7 Hz, 0.4 H), 4.90 (m, 0.4 H), 5.03 (s, 2 H), 5.22 (dd, J = 4.5, 9.1 Hz, 0.6 H), 6.33 (br d, J = 7.1 Hz, 0.6 H), 6.43 (br d, J = 6.4 Hz, 0.4 H), 6.89 (d, J = 8.6 Hz, 1.2 H), 6.90 (d, J = 8.7 Hz, 0.8 H), 7.06 (d, J = 8.6 Hz, 1.2 H), 7.11 (d, J = 8.7 Hz, 0.8 H), 7.25–7.46 (m, 5 H); MS (EI) *m/z* (relative intensity) 637 [(M - Bu)$^+$, 100], 596 (5), 545 (9), 383 (18), 360 (48).

***N*-Boc-3-iodo-*N*-methyl-D-tyrosine methyl ester (D-31)**: To a stirred solution of 3-iodo-*N*-methyl-D-tyrosine methyl ester (D-**30**)[15] (211.0mg, 0.630 mmol) in DMF (3.0 mL) was added di-*tert*-butyl dicarbonate (165.0 mg, 0.756 mmol). After 2 h, the reaction mixture was concentrated. The residual oil was purified by column chromatography on silica gel (70 g, acetone–hexane 1:4) to give *N*-Boc-3-iodo-*N*-methyl-D-tyrosine methyl ester (D-**31**) (255.5 mg, 93%) as a colorless oil: $[\alpha]^{20}_D$ +63.1° (*c* 1.33, $CHCl_3$); IR ($CHCl_3$) 3500, 3280(br), 1745, 1685, 1605, 1490, 1440, 1395, 1370, 1330, 1250, 1170, 1145 cm^{-1}; ^{1}H NMR ($CDCl_3$) (rotamer ratio

3:2) δ 1.36 (s, 5.4 H), 1.41 (s, 3.6 H), 2.74 (s, 3 H), 2.90 (dd, *J* = 10.7, 14.4 Hz, 1 H), 3.19 (br d, *J* = 14.4 Hz, 1 H), 3.73 (s, 1.2 H), 3.76 (s, 1.8 H), 4.51 (dd, *J* = 4.3, 10.7 Hz, 0.6 H), 4.85 (dd, *J* = 5.4, 10.7 Hz, 0.4 H), 6.26 (br s, 0.4 H), 6.55 (br s, 0.6 H), 6.82 (d, *J* = 7.9 Hz, 0.4 H), 6.84 (d, *J* = 7.9 Hz, 0.6 H), 6.99 (d, *J* = 7.9 Hz, 0.6 H), 7.06 (d, *J* = 7.9 Hz, 0.4 H), 7.49 (s, 0.4 H), 7.51 (s, 0.6 H); ^{13}C NMR ($CDCl_3$) (major rotamer; ratio 3:2) δ 28.2 (q), 32.5 (q), 34.0 (t), 52.2 (q), 61.5 (d), 80.8 (s), 85.0 (s), 114.9 (d), 130.5 (d), 131.2 (s), 138.6 (d), 154.2 (s), 155.1 (s), 171.2 (s); MS (FAB) *m/z* (relative intensity) 436 [(M + H)$^+$, 24], 380 (47), 336 (96), 304 (42), 154 (100); HRMS (FAB) calcd for $C_{16}H_{23}INO_5$ [(M + H)$^+$] 436.0621, found 436.0641.

***N*-Boc-3-iodo-*N*-methyl-*O*-TBS-D-tyrosine (D-32):** To a stirred solution of *N*-Boc-3-iodo-*N*-methyl-D-tyrosine methyl ester (D-**31**) (323.6 mg, 0.744 mmol) in H_2O–THF (1:2.5, 4 mL) was added LiOH·H_2O (75.0 mg, 1.79 mmol). After 1 h, the mixture was passed through an acidic ion-exchange resin column (Amberlite CG-50, H^+ form, 1.8 g), and the column was eluted with methanol (30 mL). The eluate was concentrated, and azeotropically dried with ethanol (10 mL) and chloroform–benzene (1:1, 10 mL) successively to give a carboxylic acid (340 mg).

To the solution of the crude carboxylic acid (340 mg) in DMF (3 mL) were added imidazole (172.9 mg, 2.54 mmol) and *tert*-butyldimethylsilyl chloride (328.7 mg, 2.18 mmol). The mixture was stirred for 1 h at 50 °C and concentrated. The residue was dissolved in H_2O–methanol–THF (2:1:2) (5 mL) and K_2CO_3 (150.3 mg, 1.09 mmol) was added. After 30 min, 0.5 M HCl (15 mL) was added and the mixture was extracted with ethyl acetate (50 mL + 2 × 25 mL). The combined extracts were washed with brine (3 × 5 mL), dried ($MgSO_4$), and concentrated. The residual oil was purified by column chromatography on silica gel (23 g, chloroform → methanol–chloroform 1:10) to give *N*-Boc-3-iodo-*N*-methyl-*O*-TBS-D-tyrosine (D-**32**) [377.3 mg, 95% from *N*-Boc-3-iodo-*N*-methyl-D-tyrosine methyl ester (D-**31**)] as a colorless solid: $[\alpha]^{22}_D$ +49.4° (*c* 1.13, $CHCl_3$); IR ($CHCl_3$) 2500–3300 (br), 1720, 1690, 1600, 1490, 1395, 1370, 1290, 1255, 1165, 1150, 920, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) (rotamer ratio 1:1) δ 0.26 (s, 6 H), 1.05 (s, 9 H), 1.37 (s, 4.5 H), 1.42 (s, 4.5 H), 2.70 (s, 1.5 H), 2.77 (s, 1.5 H), 2.91 (dd, *J* = 10.8, 13.5 Hz, 0.5 H), 3.00 (dd, *J* = 10.8, 13.5 Hz, 0.5 H), 3.15–3.28 (m, 1 H), 4.62 (dd, *J* = 4.0, 10.8 Hz, 0.5 H), 4.79 (dd, *J* = 4.9, 10.8 Hz, 0.5 H), 6.74 (d, *J* = 8.3 Hz, 1 H), 6.99 (d, *J* = 8.3 Hz, 0.5 H), 7.07 (d, *J* = 8.3 Hz, 0.5 H), 7.59 (s, 0.5 H), 7.61 (s, 0.5 H), 10.65 (br s, 1 H); ^{13}C NMR ($CDCl_3$) (rotamer ratio 1:1) δ -4.1 (q), -4.1 (q), 18.3 (s), 25.8 (q), 28.1, 28.2 (rotamers, q), 32.3, 32.8 (rotamers, q), 33.3, 33.8 (rotamers, t), 60.2, 61.1 (rotamers, d), 80.6, 80.8 (rotamers, s), 90.2, 90.5 (rotamers, s), 118.2 (d), 129.7, 129.9 (rotamers, d), 131.6, 131.8 (rotamers, s), 139.6, 139.7 (rotamers, d), 153.9, 154.0 (rotamers, s), 155.0, 156.1 (rotamers, s), 176.0 (s); MS (FAB) *m/z* (relative intensity) 558 [(M + Na)$^+$, 31], 536 [(M + H)$^+$, 9], 480 (49), 478 (42), 44 (100); HRMS (FAB) calcd for $C_{21}H_{34}INNaO_5Si$ [(M + Na)$^+$] 558.1149, found 558.1150.

Amide 33: To a stirred solution of silyl ether **22** (42.2 mg, 0.0883 mmol) and glycine *tert*-bytul ester hydrochloride (Aldrich, 19.8 mg, 0.118 mmol) in DMF (0.45 mL) at 0 °C were added triethylamine (0.030 mL, 0.22 mmol) and DEPC (0.030 mL, 0.20 mmol). After 30 min, brine (2 mL) was added and the mixture was extracted with ether (20 mL + 2 × 10 mL). The combined extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (10 g, ethyl acetate–benzene 1:20) to give amide **33** (51.0 mg, 98%) as a colorless oil: $[\alpha]^{19}_D$ -26.4° (*c* 0.974, $CHCl_3$); IR ($CHCl_3$) 3430, 1735, 1670, 1510, 1370, 1250, 1155, 1070, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 3 H), 0.05 (s, 3 H), 0.80–1.30 (m, 3 H), 0.83 (d, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.89 (s, 9 H), 0.90 (d, *J* = 6.9 Hz, 6 H), 1.02 (d, *J* = 6.9 Hz, 3 H), 1.34 (m, 2 H), 1.40–1.70 (m, 2 H), 1.46 (s, 9 H), 1.76 (m, 1 H), 2.08 (dqq, *J* = 4.0, 6.9, 6.9 Hz, 1 H), 2.20 (ddq, *J* = 6.9, 6.9, 6.9 Hz, 1 H), 3.42 (m, 1 H), 3.80 (dd, *J* = 5.2, 18.2 Hz, 1 H), 3.80–3.90 (m, 1 H), 3.91 (dd, *J* = 5.2, 18.2 Hz, 1 H), 4.39 (d, *J* = 11.2 Hz, 1 H), 4,61 (d, *J* = 11.2 Hz, 1 H), 5.89 (br dd, *J* = 5.2, 5.2 Hz, 1 H), 7.22–7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ -4.6 (q), -3.9 (q),

14.1 (q), 16.3 (q), 18.0 (s), 18.5 (q), 18.5 (q), 20.8 (q), 25.9 (q), 28.0 (q), 28.3 (d), 29.6 (d), 31.6 (t), 36.1 (d), 39.0 (d), 40.3 (t), 41.5 (t), 41.8 (t), 71.1 (t), 72.1 (d), 81.4 (d), 81.8 (s), 127.3 (d), 127.5 (d), 128.2 (d), 139.3 (s), 169.1 (s), 176.6 (s); MS (FAB) *m/z* (relative intensity) 592 [(M + H)$^+$, 14], 460 (14), 404 (22), 296 (100); HRMS (FAB) calcd for $C_{34}H_{62}NO_5Si$ [(M + H)$^+$] 592.4398, found 592.4427.

Amide 34: A mixture of amide **33** (48.1 mg, 0.0814 mmol) and 20% $Pd(OH)_2$ on carbon (Aldrich, 16.4 mg) in 1,4-dioxane (2.0 mL) was stirred at 40 °C under 1 atm of H_2 gas for 1.5 h. The resulting solution was filtered through a membrane filter (pore size 0.50 μm) and concentrated. The residual oil was purified by column chromatography on silica gel (9 g, acetone–benzene 1:30) to give amide **34** (38.9 mg, 95%) as a colorless oil: $[\alpha]^{24}_D$ +0.4° (*c* 0.69, $CHCl_3$); IR ($CHCl_3$) 3430, 1735, 1670, 1510, 1465, 1370, 1250, 1160, 1065, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 3 H), 0.09 (s, 3 H), 0.81 (d, *J* = 6.6 Hz, 3 H), 0.85–1.07 (m, 2 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.90 (s, 9 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 0.93 (d, *J* = 6.9 Hz, 3 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 1.20–1.90 (m, 7 H), 1.47 (s, 9 H), 2.39 (ddq, *J* = 4.6, 9.9, 6.9 Hz, 1 H), 2.59 (br s, 1 H), 3.55 (m, 1 H), 3.82 (ddd, *J* = 2.0, 5.3, 7.3 Hz, 1 H), 3.88 (dd, *J* = 5.0, 18.5 Hz, 1 H), 3.97 (dd, *J* = 5.0, 18.5 Hz, 1 H), 6.08 (br dd, *J* = 5.0, 5.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ -4.6 (q), -4.4 (q), 14.5 (q), 17.7 (q), 18.0 (s), 18.4 (q), 19.1 (q), 20.5 (q), 25.8 (q), 28.0 (q), 28.1 (d), 34.2 (d), 34.8 (t), 35.5 (d), 39.1 (d), 41.5 (t), 41.8 (t), 41.8 (t), 73.1 (d), 73.3(d), 82.1 (s), 169.3 (s), 176.5 (s); MS (FAB) *m/z* (relative intensity) 502 [(M + H)$^+$, 43], 370 (13), 314 (65), 296 (100); HRMS (FAB) calcd for $C_{27}H_{56}NO_5Si$ [(M + H)$^+$] 502.3928, found 502.3955.

Protected seco acid 35: To a stirred solution of amide **34** (38.0 mg, 0.0758 mmol), *N*-Boc-3-iodo-*N*-methyl-*O*-TBS-D-tyrosine (D-**32**) (164.4 mg, 0.307 mmol), and 4-dimethylaminopyridine (11.0 mg, 0.0900 mmol) in dichloromethane (1.5 mL) at –20 °C was added *N*,*N*'-dicyclohexylcarbodiimide (70.9 mg, 0.344 mmol). After 2 h, the mixture was filtered through a small plug of cotton, and the solids were washed with benzene–hexane (1:1, 5 mL). The filtrate and washings were combined and concentrated. The residue was purified by column chromatography on silica gel (25 g, acetone–benzene 1:50) to give protected seco acid **35** (60.8 mg) and a mixture containing **35** (45.2 mg). The mixture was further purified twice by thin layer chromatography on silica gel [(200 × 200 × 1.0 mm, 2 plates, acetone–benzene 1:20) and (200 × 200 × 0.25 mm, 2 plates, ethyl acetate–benzene 1:10)] to give pure protected seco acid **35** (12.0 mg, total 72.8 mg, 94%) as a colorless solid: $[\alpha]^{24}_D$ +12.8° (*c* 1.17, $CHCl_3$); IR ($CHCl_3$) 3430, 3365, 1735, 1685, 1600, 1490, 1390, 1370, 1290, 1255, 1160, 1075, 920, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) (rotamer ratio 1:1) δ 0.03 (s, 6 H), 0.25 (s, 6 H), 0.80–1.30 (m, 15H), 0.89 (s, 9 H), 1.05 (s, 9 H), 1.15 (d, *J* = 6.9 Hz, 1.5 H), 1.16 (d, *J* = 6.6 Hz, 1.5 H), 1.33–1.55 (m, 3 H), 1.36 (s, 4.5 H), 1.40 (s, 4.5 H), 1.46 (s, 9 H), 1.62–1.81 (m, 2 H), 1.94 (m, 1 H), 2.38 (m, 1 H), 2.70 (s, 1.5 H), 2.78 (s, 1.5 H), 2.86 (dd, *J* = 10.9, 14.5 Hz, 0.5 H), 2.91 (dd, *J* = 10.9, 14.5 Hz, 0.5 H), 3.09–3.24 (m, 1 H), 3.50 (m, 1 H), 3.89 (d, *J* = 5.6 Hz, 1 H), 3.91 (d, *J* = 5.6 Hz, 1 H), 4.74–4.96 (m, 2 H), 6.06 (br dd, *J* = 5.6, 5.6 Hz, 0.5 H), 6.27 (br dd, *J* = 5.6, 5.6 Hz, 0.5 H), 6.72 (d, *J* = 8.2 Hz, 1 H), 7.00 (dd, *J* = 2.0, 8.2 Hz, 0.5 H), 7.06 (dd, *J* = 2.0, 8.2 Hz, 0.5 H), 7.60 (d, *J* = 2.0 Hz, 0.5 H), 7.62 (d, *J* = 2.0 Hz, 0.5 H); ^{13}C NMR ($CDCl_3$) (rotamer ratio 1:1) δ -4.8 (q), -4.2 (q), -4.2 (q), -4.1 (q), 13.7, 13.9 (rotamers, q), 17.4, 17.5 (rotamers, q), 17.5 (q), 17.9 (s), 18.2 (s), 18.9 (q), 21.0 (q), 25.7 (q), 25.8 (q), 27.9 (q), 28.2 (q), 28.2, 28.6 (rotamers, d), 31.2, 31.5 (rotamers, d), 31.8 (q), 31.9, 32.1 (rotamers, t), 33.4, 33.7 (rotamers, t), 36.0, 36.2 (rotamers, d), 38.6, 38.8 (rotamers, d), 40.2, 40.5 (rotamers, t), 40.8, 40.9 (rotamers, t), 41.8 (t), 59.4, 60.3 (rotamers, d), 72.1, 72.4 (rotamers, d), 77.4, 77.6 (rotamers, d), 79.8, 80.2 (rotamers, s), 81.7, 81.9 (rotamers, s), 90.2, 90.4 (rotamers, s), 118.0, 118.1 (rotamers, d), 129.7 (d), 131.8, 131.9 (rotamers, s), 139.4, 139.7 (rotamers, d), 153.7, 153.8 (rotamers, s), 154.9, 155.5 (rotamers, s), 169.0, 169.1 (rotamers, s), 170.6 (s), 176.3, 176.6 (rotamers, s); MS (FAB) *m/z* (relative intensity) 1041 [(M + Na)$^+$, 1], 1019 [(M + H)$^+$, 3], 919 (18), 863 (11), 805 (4), 731 (10), 296 (100); HRMS (FAB) calcd for $C_{48}H_{87}IN_2NaO_9Si_2$ [(M + Na)$^+$] 1041.4890, found 1041.4910.

Doliculide silyl ether (37) and trifluoroacetate 38: To a stirred solution of protected seco acid **35** (73.3 mg, 0.0720 mmol) in dichloromethane (1.0 mL) was added trifluoroacetic acid (1.0 mL). After 3 h, the solution was concentrated and azeotropically dried with benzene (20 mL) to give crude seco acid **36**.

To a stirred solution of the crude seco acid **36** in dichloromethane (70 mL) at 0 °C were added triethylamine (0.10 mL, 0.72 mmol) and Bop-Cl (95.5 mg, 0.375 mmol).The solution was slowly warmed to 25 °C over 6 h with stirring, and further stirred for 13 h at 25 °C. The mixture was washed with 0.1 M HCl (10 mL), brine (3 × 5 mL), saturated aqueous $NaHCO_3$ (10 mL), brine (5 mL), saturated aqueous NH_4Cl (5 mL), and brine (5 mL) successively. The organic layer was dried (Na_2SO_4) and concentrated. The residue was dissolved in chloroform (2 mL) and filtered through a small plug of cotton and the solids were washed with ether (20 mL). The filtrate and washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (17 g, acetone–hexane 1:6) to give doliculide silyl ether (**37**) (43.7 mg) and trifluoroacetate **38** (8.2 mg). Doliculide silyl ether (**37**) was further purified by thin layer chromatography on silica gel (200 × 200 × 1.0 mm, 2 plates, acetone–benzene 1:7) and column chromatography on silica gel (2 g, acetone–hexane 1:6) successively to give pure doliculide silyl ether (**37**) (39.1 mg, 74%) as a colorless solid: $[\alpha]^{23}_D$ -33.1° (*c* 0.580, $CHCl_3$); IR ($CHCl_3$) 3515, 3440, 1715, 1680 (sh), 1650, 1600, 1510, 1490, 1470, 1460, 1405, 1290, 1255,1035, 920, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.26(s, 6 H), 0.84 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 6 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 1.00–1.60 (m, 7 H), 1.05 (s, 9 H), 1.13 (d, *J* = 6.6 Hz, 3 H), 1.86 (m, 1 H), 2.03 (m, 1 H), 2.41 (ddq, *J* = 3.1, 12.0, 6.6 Hz, 1 H), 2.74 (br s, 1 H), 2.88 (dd, *J* = 12.4, 15.5 Hz, 1 H), 2.93 (s, 3 H), 3.28 (dd, *J* = 1.3, 16.8 Hz, 1 H), 3.42 (dd, *J* = 4.5, 15.5 Hz, 1 H), 3.58 (br d, *J* = 10.2 Hz, 1 H), 4.79 (dd, *J* = 8.9, 16.8 Hz, 1 H), 5.05 (ddd, *J* = 2.0, 5.0, 11.2 Hz, 1 H), 5.44 (dd, *J* = 4.5, 12.4 Hz, 1 H), 6.21 (br d, *J* = 8.9 Hz, 1 H), 6.73 (d, *J* = 8.4 Hz, 1 H), 7.03 (dd, *J* = 2.1, 8.4 Hz, 1 H), 7.59 (d, *J* = 2.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ -4.1 (q), -4.1 (q), 14.3 (q), 17.6 (q), 17.9 (q), 18.2 (q), 18.2 (s), 18.8 (q), 25.7 (q), 26.9 (d), 30.2 (t), 30.6 (q), 32.3 (d), 32.7(t), 34.2 (d), 39.1 (d), 39.7 (t), 42.9 (t), 44.9 (t), 58.0 (d), 65.5 (d), 77.2 (d), 90.6 (s), 118.3 (d), 128.7(d), 130.7 (s), 139.0 (d), 154.1 (s), 171.6 (s), 171.8 (s), 177.6 (s); MS (FAB) *m/z* (relative intensity) 731 [$(M + H)^+$, 55], 713 (25), 673 (36), 436 (73), 390 (56), 154 (100); HRMS (FAB) calcd for $C_{33}H_{56}IN_2O_6Si$ [$(M + H)^+$] 731.2952, found 731.2967.

Further purification of crude **38** by thin layer chromatography on silica gel (200 × 200 × 0.25 mm, acetone–chloroform 1:20) to give pure trifluoroacetate **38** (6.1 mg, 10%) as a colorless solid: $[\alpha]^{25}_D$ -23.8° (*c* 0.391, $CHCl_3$); IR ($CHCl_3$) 3435, 1785, 1730, 1680 (sh), 1655, 1600, 1510, 1490, 1470, 1465, 1290, 1255, 1165, 1040, 1000, 920, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.26 (s, 6 H), 0.88(d, *J* = 6.6 Hz, 3 H), 0.93(d, *J* = 6.9 Hz, 3 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 0.95–1.40 (m, 4 H), 1.05 (s, 9 H), 1.06 (d, *J* = 6.9 Hz, 3 H), 1.14 (d, *J* = 6.6 Hz, 3 H), 1.44–1.63 (m, 2 H), 1.80 (m, 1 H), 1.85 (m, 1 H), 2.18 (m, 1 H), 2.44 (ddq, *J* = 3.3, 12.2, 6.6 Hz, 1 H), 2.80 (dd, *J* = 12.4, 15.8 Hz, 1 H), 2.84 (s, 3 H), 3.23 (dd, *J* = 1.7, 16.9 Hz, 1 H), 3.45 (dd, *J* = 4.6, 15.8 Hz, 1 H), 4.79 (dd, *J* = 9.1, 16.9 Hz, 1 H), 4.90 (ddd, *J* = 2.1, 5.0, 11.5 Hz, 1 H), 5.12 (ddd, *J* = 2.4, 4.0, 12.3 Hz, 1 H), 5.59 (dd, *J* = 4.6, 12.4 Hz, 1 H), 6.19 (br d, *J* = 9.1 Hz, 1 H), 6.72 (d, *J* = 8.4 Hz, 1 H), 7.04 (dd, *J* = 2.1, 8.4 Hz, 1 H), 7.55 (d, *J* = 2.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ -4.1 (q), -4.0(q), 14.5 (q), 17.5 (q), 17.9 (q), 18.2 (q), 18.3 (s), 18.4 (q), 25.8 (q), 27.0 (t), 27.1 (d), 30.3 (q), 31.8 (d), 32.2 (d), 32.3 (t), 39.2 (d), 39.7 (t), 42.5 (t), 44.7 (t), 56.8 (d), 74.6 (d), 75.2 (d), 90.4 (s), 114.6 (q, J_{CF} = 286 Hz), 118.4 (d), 128.8 (d), 131.0 (s), 139.2 (d), 154.0 (s), 156.6 (q, $^2J_{CF}$ = 42.7 Hz), 170.0 (s), 171.1 (s), 177.6 (s); MS (FAB) *m/z* (relative intensity) 827 [$(M + H)^+$, 77], 769 (66), 713 (21), 493 (20), 436 (100), 390 (81); HRMS (FAB) calcd for $C_{35}H_{55}F_3IN_2O_7Si$ [$(M + H)^+$] 827.2776, found 827.2774.

Doliculide silyl ether (37) from trifluoroacetate 38: To a solution of trifluoroacetate **38** (12.7 mg, 0.0154 mmol) in methanol (0.5 mL) was added concentrated aqueous NH_3 (0.005 mL). After 1 h at room temperature, the solution was concentrated. The residue was purified by thin layer chromatography on silica

gel (200 × 200 × 0.25 mm , acetone–benzene 1:5) to give doliculide silyl ether (**37**) (10.0 mg, 89%) as a colorless solid.

Doliculide (1): To a stirred solution of doliculide silyl ether (**37**) (29.3 mg, 0.040 mmol) in THF (0.4 mL) at 0 °C was added tetra-*n*-butylammonium fluoride (Aldrich, 1.0 M solution in THF, 0.060 mL, 0.060 mmol). After 5 min, saturated aqueous NH_4Cl (2 mL) was added, and the mixture was extracted with ether (20 mL + 2 × 5 mL). The combined extracts were washed with brine (1 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, acetone–hexane 2:5) to give synthetic doliculide (**1**) (24.6 mg, 99%) as colorless crystals. Recrystallization from dichloromethane–hexane gave colorless needles: mp 173–174 °C; $[\alpha]^{24}_D$ -25.5 ° (*c* 0.656, MeOH); UV (MeOH) λ_{max} 207 (ε 25900), 227 (10500, sh), 284 nm (3000); IR ($CHCl_3$) 3500, 3420, 3200 (br), 1720, 1670, 1650, 1505, 1490, 1410, 1285, 1255, 1175, 1030, 995 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.84 (d, *J* = 7.0 Hz, 3 H), 0.95 (d, *J* = 7.0 Hz, 6 H), 0.96 (d, *J* = 7.0 Hz, 3 H), 1.00–1.11 (m, 3 H), 1.13 (d, *J* = 6.4 Hz, 3 H), 1.18 (m, 1 H), 1.33 (ddd, *J* = 2.4, 11.8, 13.9 Hz, 1 H), 1.44 (ddd, *J* = 1.9, 11.8, 13.9 Hz, 1 H), 1.52 (br dd, *J* = 11.8, 12.7 Hz, 1 H), 1.87 (m, 1 H), 2.03 (m, 1 H), 2.44 (ddq, *J* = 3.4, 11.8, 6.4 Hz, 1 H), 2.57 (br d, *J* = 4.0 Hz, 1 H), 2.88 (dd, *J* = 12.2, 15.4 Hz, 1 H), 2.96 (s, 3 H), 3.23 (dd, *J* = 1.8, 16.8 Hz, 1 H), 3.44 (dd, *J* = 4.3, 15.4 Hz, 1 H), 3.58 (br d, *J* = 11.8 Hz, 1 H), 4.80 (dd, *J* = 9.0, 16.8 Hz, 1 H), 5.06 (ddd, *J* = 1.8, 5.0, 11.8 Hz, 1 H), 5.50 (dd, *J* = 4.3, 12.2 Hz, 1 H), 6.31 (br d, *J* = 7.6 Hz, 1 H), 6.84 (br s, 1 H), 6.84 (d, *J* = 8.2 Hz, 1 H), 7.06 (dd, *J* = 2.1, 8.2 Hz, 1 H), 7.50 (d, *J* = 2.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.4 (q), 17.7 (q), 18.1 (q), 18.4 (q), 18.8 (q), 27.0 (d), 30.1 (t), 30.9 (q), 32.3 (d), 32.8 (t), 34.3 (d), 39.2 (d), 39.7 (t), 43.1 (t), 44.9 (t), 58.1 (d), 65.8 (d), 77.3 (d), 85.3 (s), 115.2 (d), 129.5 (d), 130.2 (s), 138.1 (d), 154.3 (s), 171.5 (s), 172.0 (d), 177.8 (s); MS (EI) *m/z* (relative intensity) 616 (M^+, 100), 598 (8), 573 (3), 545 (21), 420 (34), 383 (10), 322 (42), 309 (26), 296 (30), 276 (93). Anal. Calcd for $C_{27}H_{41}IN_2O_6$: C, 52.60; H, 6.70; N, 4.54. Found: C, 52.52; H, 6.62; N, 4.65.

Deiododoliculide (39): A mixture of doliculide (**1**) (2.5 mg, 0.0041 mmol) and 10% Pd on carbon (1.9 mg) in methanol (0.5 mL) was stirred under 1 atm of H_2 gas for 2 h. The resulting solution was filtered through a membrane filter (pore size 0.50 μm) and the filter was washed with methanol (3 mL). The filtrate and washings were combined and concentrated. The residual oil was purified by thin layer chromatography on silica gel (200 × 200 × 0.25 mm, acetone–chloroform 1:2) to give deiododoliculide (**39**) (2.0 mg, quantitative) as a colorless solid: $[\alpha]^{23}_D$ -34° (*c* 0.10, $CHCl_3$); IR ($CHCl_3$) 3100-3550, 3420, 1720, 1670 (sh), 1650, 1600, 1515, 1465, 1410, 1385, 1300, 1255, 1175, 1030, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (d, *J* = 6.6 Hz, 3 H), 0.96 (d, *J* = 5.9 Hz, 9 H), 0.98-1.15 (m, 3 H), 1.13 (d, *J* = 6.6 Hz, 3 H),1.24-1.60 (m, 4 H), 1.87 (m, 1 H), 2.03 (m, 1 H), 2.42 (ddq, *J* = 3.4, 12.0, 6.6 Hz, 1 H), 2.60 (br s, 1 H), 2.91 (dd, *J* = 12.6, 15.4 Hz, 1 H), 2.94 (s, 3 H), 3.20 (dd, *J* = 2.0, 16.8 Hz, 1 H), 3.48 (dd, *J* = 4.4, 15.4 Hz, 1 H), 3.58 (br d, *J* = 9.7 Hz, 1 H), 4.78 (dd, *J* = 8.9, 16.8 Hz, 1 H), 5.07 (ddd, *J* = 2.2, 5.2, 11.3 Hz, 1 H), 5.54 (dd, *J* = 4.4, 12.6 Hz, 1 H), 6.01 (br s, 1 H), 6.24 (br d, *J* = 8.9 Hz, 1 H), 6.74 (d, *J* = 8.4 Hz, 2 H), 7.05 (d, *J* = 8.4 Hz, 2 H); MS (FAB) *m/z* (relative intensity) 491 [$(M + H)^+$, 58], 473 (27), 455 (3), 235 (22), 196 (100); HRMS (FAB) calcd for $C_{27}H_{43}N_2O_6$ [$(M + H)^+$] 491.3121, found 491.3140.

Doliculide methyl ether (40): To a stirred solution of doliculide (**1**) (2.5 mg, 0.0041 mmol) in DMF (0.2 mL) were added methyl iodide (0.050 mL, 0.80 mmol), tetra-*n*-butylammonium iodide (2.7 mg, 0.0073 mmol), and anhydrous K_2CO_3 (5.7 mg, 0.041 mmol). After 30 min, saturated aqueous NH_4Cl (1 mL) was added, and the mixture was extracted with ether (25 mL). The organic layer was washed with brine (1 mL), dried (Na_2SO_4), and concentrated. The residue was purified by thin layer chromatography on silica gel (200 × 200 × 0.25 mm, acetone–chloroform 1:4) to give doliculide methyl ether (**40**) (2.5 mg, 98%) as a colorless solid: $[\alpha]^{24}_D$ -37° (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 3510, 3440, 1715, 1675 (sh), 1650, 1600, 1510, 1490, 1460,

1405, 1295, 1275, 1255, 1050, 1020, 995 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85(d, J = 6.6 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 6 H), 0.97 (d, J = 6.6 Hz, 3 H), 0.98-1.12 (m, 3 H), 1.13 (d, J = 6.6 Hz, 3 H), 1.23-1.54 (m, 4 H), 1.86 (m 1 H), 2.03 (m, 1 H), 2.41 (ddq, J = 3.2, 12.1, 6.6 Hz, 1 H), 2.62 (br s, 1 H), 2.89 (dd, J = 12.5, 15.5 Hz, 1 H), 2.93 (s, 3 H), 3.29 (dd, J = 1.7, 17.0 Hz, 1 H), 3.45 (dd, J = 4.4, 15.5 Hz, 1 H), 3.57 (br d, J = 9.2 Hz, 1 H), 3.86 (s, 3 H), 4.80 (dd, J = 8.9, 17.0 Hz, 1 H), 5.05 (ddd, J = 2.1, 5.3, 11.4 Hz, 1 H), 5.45 (dd, J = 4.4, 12.5 Hz, 1 H), 6.14 (br d, J = 8.9 Hz, 1 H), 6.74 (d, J = 8.4 Hz, 1 H), 7.14 (dd, J = 2.1, 8.4 Hz, 1 H), 7.61 (d, J = 2.1 Hz, 1 H); MS (FAB) *m/z* (relative intensity) 631 [(M + H)$^{+\cdot}$, 100], 613 (41), 491 (18), 393 (24), 336 (88); HRMS (FAB) calcd for $C_{28}H_{44}IN_2O_6$ [(M + H)$^+$] 631.2244, found 631.2261.

Iododoliculide (41): To a stirred solution of doliculide (**1**) (3.7 mg, 0.0060 mmol) in ethanol (0.1 mL) were added iodine (0.050 M solution in ethanol, 0.14 mL, 0.0070 mmol) and mercury(II) acetate (1.0 mg, 0.0031 mmol). After 20 min, saturated aqueous $Na_2S_2O_3$ (1 mL) was added, and the mixture was extracted with ethyl acetate (25 mL). The organic layer was washed with brine (1 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by thin layer chromatography on silica gel (200 × 200 × 0.25 mm, acetone–chloroform 1:5) to give iododoliculide (**41**) (2.2 mg, 49%) as a colorless solid: $[\alpha]^{30}_D$ -28° (*c* 0.13, $CHCl_3$); IR ($CHCl_3$) 3490, 3470 (br), 1720, 1680 (sh), 1655, 1510, 1460, 1410, 1320, 1295, 1260, 1155, 995 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (d, J = 6.9 Hz, 3 H), 0.95 (d, J = 6.9 Hz, 6 H), 0.97 (d, J = 5.9 Hz, 3 H), 1.00-1.23 (m, 3 H), 1.13 (d, J = 6.6 Hz, 3 H), 1.23-1.56 (m, 4 H), 1.86 (m, 1 H), 2.02 (m, 1 H), 2.41 (ddq, J = 3.2, 12.1, 6.6 Hz, 1 H), 2.52 (br s, 1 H), 2.85 (dd, J = 12.2, 15.5 Hz, 1 H), 2.95 (s, 3 H), 3.32 (dd, J = 2.0, 17.0 Hz, 1 H), 3.40 (dd, J = 4.6, 15.5 Hz, 1 H), 3.57 (br d, J = 11.2 Hz, 1 H), 4.81 (dd, J = 8.9, 17.0 Hz, 1 H), 5.05 (ddd, J = 2.2, 5.2, 11.5 Hz, 1 H), 5.39 (dd, J = 4.6, 12.2 Hz, 1 H), 5.70 (br s, 1 H), 6.15 (br d, J = 8.9 Hz, 1 H), 7.51 (s, 2 H); MS (FAB) *m/z* (relative intensity) 743 [(M + H)$^+$, 100], 725 (51), 505 (31), 448 (80); HRMS (FAB) calcd for $C_{27}H_{41}I_2N_2O_6$ [(M + H)$^+$] 743.1054, found 743.1065.

Deiododoliculide silyl ether (42): A mixture of doliculide silyl ether (**37**) (5.0 mg, 0.0068 mmol), sodium acetate (1.4 mg, 0.017 mmol), and 10% Pd on carbon (4.3 mg) in methanol (0.5 mL) was stirred under 1 atm of H_2 gas for 1.5 h. The resulting solution was filtered through a membrane filter (pore size 0.50 μm) and the filter was washed with methanol (3 mL). The filtrate and washings were combined and concentrated. The residual oil was purified by thin layer chromatography on silica gel (200 × 200 × 0.25 mm, acetone–chloroform 1:9) to give deiododoliculide silyl ether (**42**) (3.8 mg, 92%) as a colorless solid: $[\alpha]^{21}_D$ -26° (*c* 0.087, $CHCl_3$); IR ($CHCl_3$) 3510, 3430, 1715, 1670 (sh), 1650, 1610, 1510, 1470, 1465, 1410, 1255, 1170, 1030, 995, 910, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.18 (s, 6 H), 0.84 (d, J = 6.6 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 6 H), 0.97 (s, 9 H), 0.97 (d, J = 6.6 Hz, 3 H), 0.98-1.14 (m, 3 H), 1.12 (d, J = 6.6 Hz, 3 H), 1.16-1.60 (m, 4 H), 1.86 (m, 1 H), 2.30 (m, 1 H), 2.40 (ddq, J = 3.2, 12.1, 6.6 Hz, 1 H), 2.68 (br s, 1 H), 2.90 (s, 3 H), 2.92 (dd, J = 12.5, 15.5 Hz, 1 H), 3.24 (dd, J = 1.7, 17.0 Hz, 1 H), 3.46 (dd, J = 4.5, 15.5 Hz, 1 H), 3.58 (br d, J = 11.6 Hz, 1 H), 4.77 (dd, J = 8.9, 17.0 Hz, 1 H), 5.04 (ddd, J = 2.1, 5.1, 11.4 Hz, 1 H), 5.47 (dd, J = 4.5, 12.5 Hz, 1 H), 6.15 (br d, J = 8.9 Hz, 1 H), 6.76 (d, J = 8.6 Hz, 2 H), 7.04 (d, J = 8.6 Hz, 2 H); MS (FAB) *m/z* (relative intensity) 605 [(M + H)$^+$, 50], 587 (24), 547 (36), 310 (92), 264 (100); HRMS (FAB) calcd for $C_{33}H_{57}N_2O_6Si$ [(M + H)$^+$] 605.3985, found 605.3972.

Thionoimidazolide 43: To a stirred solution of deiododoliculide silyl ether (**42**) (6.0 mg, 0.0099 mmol) in THF (0.2 mL) was added 1,1'-thiocarbonyldiimidazole (22.8 mg, 0.128 mmol). The mixture was stirred for 5 h at 70 °C and concentrated. The residue was purified by thin layer chromatography on silica gel (200 × 200 × 0.25 mm, acetone–hexane 1:4) to give thionoimidazolide **43** (6.0 mg, 85%) as a colorless solid: $[\alpha]^{25}_D$ -27° (*c* 0.32, $CHCl_3$); IR ($CHCl_3$) 3430, 1735, 1655, 1610, 1510, 1470, 1460, 1410, 1385, 1350, 1335, 1285, 1255, 1170, 1105, 1100, 990, 975, 910, 840, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.17 (s, 6 H), 0.89 (d, J = 6.6 Hz, 3 H),

0.94 (d, J = 6.9 Hz, 3 H), 0.95 (d, J = 6.3 Hz, 3 H), 0.96 (s, 9 H), 0.98-1.35 (m, 4 H), 1.14 (d, J = 4.6 Hz, 3 H), 1.14 (d, J = 6.6 Hz, 3 H), 1.49-1.70 (m, 2 H), 1.82-1.98 (m, 2 H), 2.37-2.55 (m, 2 H), 2.79 (dd, J = 12.2, 15.7 Hz, 1 H), 2.82 (s, 3 H), 3.15 (dd, J = 1.5, 16.7 Hz, 1 H), 3.44 (dd, J = 4.8, 15.7 Hz, 1 H), 4.80 (dd, J = 9.4, 16.7 Hz,1 H), 4.87 (ddd, J = 2.2, 5.1, 11.7 Hz, 1 H), 5.66 (m, 1 H), 5.70 (dd, J = 4.8, 12.2 Hz, 1 H), 6.19 (br d, J = 9.4 Hz, 1 H), 6.73 (d, J = 8.6 Hz, 2 H), 7.00 (d, J = 8.6 Hz, 2 H), 7.04 (br s, 1H), 7.62 (br s, 1 H), 8.33 (br s, 1 H); MS (FAB) *m/z* (relative intensity) 715 [(M+ H)$^+$, 17], 657 (3), 587 (64), 529 (34), 367 (17), 310 (100); HRMS (FAB) calcd for $C_{37}H_{59}N_4O_6SSi$ [(M + H)$^+$] 715.3924, found 715.3907.

Silyl ether 44: To a stirred solution of thionoimidazolide **43** (5.4 mg, 0.0076 mmol) in toluene (0.4 mL) was added tri-*n*-butyltin hydride (0.040 mL, 0.15 mmol). The solution was heated to reflux for 5 min. After cooling, the mixture was concentrated. The residue was purified by thin layer chromatography on silica gel (200 × 200 × 0.25 mm, acetone–hexane 1:3) to give silyl ether **44** (3.8 mg, 85%) as a colorless solid: $[\alpha]^{23}_D$ -5.2° (*c* 0.21, $CHCl_3$); IR ($CHCl_3$) 3420, 1725, 1675 (sh), 1650, 1610, 1510, 1475, 1465, 1410, 1260, 1175, 1000, 915, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 6 H), 0.83 (d, J = 6.9 Hz, 3 H), 0.87-1.42 (m, 8 H), 0.90 (d, J = 6.6 Hz, 6 H), 0.92 (d, J = 5.9 Hz, 3 H), 0.96 (s, 9H), 1.12 (d, J = 6.6 Hz, 3 H), 1.50 (m, 1 H), 1.64 (m, 1H), 1.84 (dqq J = 6.6, 6.6, 6.6 Hz, 1 H), 2.39 (ddq, J = 3.4, 12.1, 6.6 Hz, 1 H), 2.85 (s, 3 H), 2.89 (dd, J = 12.5, 15.5 Hz, 1 H), 3.24 (dd, J = 1.5, 17.0 Hz, 1 H), 3.52 (dd, J = 4.6, 15.5 Hz, 1 H), 4.72 (dd, J = 8.1, 17.0 Hz, 1 H), 4.75 (m, 1 H), 5.63 (dd, J = 4.6, 12.5 Hz, 1 H), 6.28 (br d, J = 8.1 Hz, 1 H), 6.74 (d, J = 8.4 Hz, 2 H), 7.03 (d, J = 8.4 Hz, 2 H); MS (FAB) *m/z* (relative intensity) 589 [(M + H)$^+$, 77], 573 (8), 531 (57), 367 (8), 310 (100); HRMS (FAB) calcd for $C_{33}H_{57}N_2O_5Si$ [(M + H)$^+$] 589.4037, found 589.4059.

Deoxydoliculide silyl ether (45): To a stirred solution of silyl ether **44** (3.9 mg, 0.0066 mmol) in dichloromethane (0.1 mL) were added iodine (0.050 M solution in dichloromethane, 0.40 mL, 0.020 mmol) and mercury(II) trifluoroacetate (0.050 M solution in dichloromethane, 0.40 mL, 0.020 mmol). After 45 min, saturated aqueous $Na_2S_2O_3$ (2 mL) was added, and the mixture was extracted with ether (25 mL). The organic layer was washed with brine (1 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by thin layer chromatography on silica gel (200 × 200 × 0.25 mm, acetone–chloroform 1:20) to give deoxydoliculide silyl ether (**45**) (3.7 mg, 78%) as a colorless solid: $[\alpha]^{24}_D$ -16° (*c* 0.23, $CHCl_3$); IR ($CHCl_3$) 3420, 1730, 1680 (sh), 1660, 1600, 1510, 1490, 1475, 1465, 1410, 1290, 1255, 1040, 920, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.26 (s, 6 H), 0.83 (d, J = 6.6 Hz, 3 H), 0.90 (d, J = 6.9 Hz, 6 H), 0.90-1.41 (m, 8 H), 0.92 (d, J = 6.1 Hz, 3 H), 1.04 (s, 9 H), 1.13 (d, J = 6.6 Hz, 3 H), 1.41-1.73 (m, 2 H), 1.84 (dqq, J = 6.9, 6.9, 6.9 Hz, 1 H), 2.40 (ddq, J = 3.3, 12.2, 6.6 Hz, 1 H), 2.84 (dd, J = 12.1, 15.5 Hz, 1 H), 2.87 (s, 3 H), 3.31 (dd, J = 1.7, 17.1 Hz, 1 H), 3.47 (dd, J = 4.6, 15.5 Hz, 1 H), 4.74 (dd, J = 8.1, 17.1 Hz, 1 H), 4.71-4.80 (m, 1 H), 5.58 (dd, J = 4.6, 12.1 Hz, 1 H), 6.28 (br d, J = 8.1 Hz, 1 H), 6.72 (d, J = 8.3 Hz, 1 H), 7.02 (dd, J = 2.3, 8.3 Hz, 1 H), 7.57 (d, J = 2.3 Hz, 1 H); MS (FAB) *m/z* (relative intensity) 715 [(M + H)$^+$, 100], 699 (7), 657 (71), 436 (99); HRMS (FAB) calcd for $C_{33}H_{56}IN_2O_5Si$ [(M + H)$^+$] 715.3004, found 715.2999.

Deoxydoliculide (46): To a stirred solution of deoxydoliculide silyl ether (**45**) (5.9 mg, 0.0083 mmol) in THF (0.3 mL) at 0 °C was added tetra-*n*-butylammonium fluoride (Aldrich, 1.0 M solution in THF, 0.015 mL, 0.015 mmol). After 5 min, saturated aqueous NH_4Cl (1 mL) was added, and the mixture was extracted with ether (25 mL). The organic layer was washed with brine (1 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by thin layer chromatography on silica gel (200 × 200 × 0.25 mm, acetone–chloroform 1:5) to give deoxydoliculide (**46**) (5.0 mg, quantitative) as a colorless solid: $[\alpha]^{23}_D$ -15° (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) 3420, 3200 (br), 1730, 1655, 1605, 1510, 1490, 1465, 1415, 1290, 1260, 1180, 1130, 1080, 1040, 1000 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (d, J = 6.9 Hz, 3 H), 0.90-1.45 (m, 8 H), 0.90 (d, J = 6.6 Hz, 6 H), 0.91 (d, J = 5.9 Hz, 3 H), 1.13 (d, J = 6.6 Hz, 3 H), 1.52 (m, 1 H), 1.66 (m, 1 H), 1.85 (dqq, J = 6.6, 6.6,

6.6 Hz, 1 H), 2.43 (ddq, J = 3.3, 12.2, 6.6 Hz, 1 H), 2.85 (dd, J = 12.2, 15.5 Hz, 1 H), 2.90 (s, 3 H), 3.27 (dd, J = 1.8, 16.9 Hz, 1 H), 3.49 (dd, J = 4.5, 15.5 Hz, 1 H), 4.76 (dd, J = 8.2, 16.9 Hz, 1 H), 4.71-4.78 (m, 1 H), 5.61 (dd, J = 4.5, 12.2 Hz, 1 H), 6.09 (br s, 1 H), 6.35 (br d, J = 8.2 Hz, 1 H), 6.86 (d, J = 8.3 Hz, 1 H), 7.07 (dd, J = 2.0, 8.3 Hz, 1 H), 7.48 (d, J = 2.0 Hz, 1 H); MS (FAB) *m/z* (relative intensity) 601 [(M + H)$^+$, 100], 583 (3), 322 (44); HRMS (FAB) calcd for $C_{27}H_{42}IN_2O_5$ [(M + H)$^+$] 601.2139, found 601.2138.

3-Iodo-*N*-methyl-L-tyrosine methyl ester (L-30): The title compound was prepared from 3-iodo-L-tyrosine (Aldrich) according to the literature method:[15,25] $[\alpha]^{31}_D$ +26.4° (*c* 0.935, MeOH); HRMS (FAB) calcd for $C_{11}H_{15}INO_3$ [(M + H)$^+$] 336.0097, found 336.0126.

***N*-Boc-3-iodo-*N*-methyl-L-tyrosine methyl ester (L-31):** $[\alpha]^{20}_D$ -60.6° (*c* 1.04, $CHCl_3$); HRMS (FAB) calcd for $C_{16}H_{23}INO_5$ [(M + H)$^+$] 436.0621, found 436.0627.

***N*-Boc-3-iodo-*N*-methyl-*O*-TBS-L-tyrosine (L-32):** $[\alpha]^{30}_D$ -46.9° (*c* 1.08, $CHCl_3$); HRMS (FAB) calcd for $C_{21}H_{33}INNa_2O_5Si$ [(M - H + 2Na)$^+$] 580.0969, found 580.0967.

Protected seco acid 47: To a stirred solution of amide **34** (10.4 mg, 0.0208 mmol), *N*-Boc-3-iodo-*N*-methyl-*O*-TBS-L-tyrosine (L-**32**) (43.7 mg, 0.0817 mmol), and 4-dimethylaminopyridine (3.2 mg, 0.026 mmol) in dichloromethane (0.5 mL) at -20 °C was added *N*,*N*'-dicyclohexylcarbodiimide (21.0 mg, 0.102 mmol). After 2 h, the mixture was filtered through a small plug of cotton, and the solids were washed with benzene–hexane (1:1, 5 mL). The filtrate and washings were combined and concentrated. The residue was purified by thin layer chromatography on silica gel (200 × 200 × 0.25 mm, 2 plates, ethyl acetate–benzene 1:10) to give protected seco acid **47** (20.4 mg, 97%) as a colorless solid: $[\alpha]^{27}_D$ -25.1° (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 3430, 3370, 1735, 1685, 1600, 1510, 1490, 1475, 1465, 1395, 1370, 1335, 1290, 1260, 1160, 1085, 1040, 920, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) (rotamer ratio 5:4) δ 0.05 (s, 6 H), 0.25 (s, 6 H), 0.77-0.98 (m, 12 H), 0.89 (s, 9 H), 1.00-1.60 (m, 5 H), 1.05 (s, 9 H), 1.16 (d, J = 6.6 Hz, 3 H), 1.36 (s, 5 H), 1.39 (s, 4 H), 1.45 (s, 9 H), 1.62-1.81 (m, 3 H), 1.90 (m, 1 H), 2.41 (m, 1 H), 2.74 (s, 1.33 H), 2.76 (s, 1.67 H), 2.77-2.94 (m, 1 H), 3.19 (dd, J = 5.1, 14.7 Hz, 1 H), 3.47-3.60 (m, 1 H), 3.87 (dd, J = 5.1, 18.1 Hz, 1 H), 3.94 (dd, J = 5.1, 18.1 Hz, 1 H), 4.85-4.96 (m, 2 H), 6.26 (br t, J = 5.1 Hz, 0.44 H), 6.33 (br t, J = 5.1 Hz, 0.56 H), 6.72 (d, J = 8.6 Hz, 1 H), 6.99 (br d, J = 8.6 Hz, 0.56 H), 7.06 (br d, J = 8.6 Hz, 0.44 H), 7.57-7.62 (m, 1 H); MS (FAB) *m/z* (relative intensity) 1019 [(M + H)$^+$, 5], 961 (2), 919 (31), 863 (15), 787 (5), 731 (11), 436 (30), 296 (100); HRMS (FAB) calcd for $C_{48}H_{88}IN_2O_9Si_2$ [(M + H)$^+$] 1019.5070, found 1019.5050.

Epidoliculide silyl ether (48): To a stirred solution of protected seco acid **47** (10.8 mg, 0.0106 mmol) in dichloromethane (0.5 mL) was added trifluoroacetic acid (0.5 mL). After 3 h, the solution was concentrated and azeotropically dried with benzene (10 mL) to give a crude seco acid.

To a stirred solution of the crude seco acid in dichloromethane (10 mL) at 0 °C were added triethylamine (0.015 mL, 0.11 mmol) and Bop-Cl (15.6 mg, 0.0613 mmol). The solution was slowly warmed to 15 °C over 12 h with stirring and further stirred for 1 h at 28 °C. Dichloromethane (20 mL) was added and the resulting mixture was washed with 0.1 M HCl (2 mL), brine (2 × 2 mL), saturated aqueous $NaHCO_3$ (2 mL), and brine (3 × 2 mL) successively. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (1 g, acetone–benzene 1:15) to give a mixture of epidoliculide silyl ether (**48**) and its trifluoroacetate as an oil (8.1 mg).

The mixture (8.1 mg) was dissolved in concentrated aqueous NH_3-MeOH (1:100, 0.4 mL). After 1.5 h, the mixture was concentrated and the residual oil was purified by thin layer chromatography on silica gel (200 × 200 × 0.25 mm, acetone–benzene 1:7) to give epidoliculide silyl ether (**48**) (5.7 mg, 74%) as a colorless solid:

$[\alpha]^{28}_D$ -130° (*c* 0.17, $CHCl_3$); IR ($CHCl_3$) 3510, 3450, 1720, 1680 (sh), 1660, 1600, 1510, 1490, 1415, 1310, 1285, 1260, 1180, 1040, 1030, 920, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.26 (s, 6 H), 0.85 (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.98-1.55 (m, 7 H), 1.01 (d, *J* = 7.0 Hz, 3 H), 1.05 (s, 9 H), 1.14 (d, *J* = 6.6 Hz, 3 H), 1.80 (m, 1 H), 2.08 (m, 1 H), 2.42 (ddq, *J* = 3.2, 12.1, 6.6 Hz, 1 H), 2.70 (s, 3 H), 3.23 (dd, *J* = 5.0, 14.0 Hz, 1 H), 3.30 (dd, *J* = 1.1, 17.2 Hz, 1 H), 3.31 (dd, *J* = 9.9, 14.0 Hz, 1 H), 3.53 (dd, *J* = 5.0, 9.9 Hz, 1 H), 3.61-3.76 (m, 2 H), 4.76 (dd, *J* = 8.9, 17.2 Hz, 1 H), 4.86 (ddd, *J* = 1.4, 5.1, 9.7 Hz, 1 H), 6.07 (br d, *J* = 8.9 Hz, 1 H), 6.75 (d, *J* = 8.3 Hz, 1 H), 6.98 (dd, *J* = 2.0, 8.3 Hz, 1 H), 7.54 (d, *J* = 2.0 Hz, 1 H); MS (FAB) *m/z* (relative intensity) 731[(M + H)$^+$, 93], 713 (51), 673 (64), 493 (19), 436 (100); HRMS (FAB) calcd for $C_{33}H_{56}IN_2O_6Si$ [(M + H)$^+$] 731.2952, found 731.2969.

Epidoliculide (49): To a stirred solution of epidoliculide silyl ether (**48**) (4.5 mg, 0.0062 mmol) in THF (0.4 mL) at 0 °C was added tetra-*n*-butylammonium fluoride (Aldrich, 1.0 M solution in THF, 0.010 mL, 0.010 mmol). After 5 min, saturated aqueous NH_4Cl (2 mL) was added, and the mixture was extracted with ether (25 mL). The organic layer was washed with brine (1 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by thin layer chromatography on silica gel (200 × 200 × 0.25 mm, acetone–chloroform 1:3) to give epidoliculide (**49**) (3.8 mg, quantitative) as a colorless solid. Recrystallization from dichloromethane–hexane gave colorless needles: mp 162–164 °C; $[\alpha]^{29}_D$ -130° (*c* 0.16, $CHCl_3$); IR ($CHCl_3$) 3100-3550, 3500, 3450, 1720, 1680 (sh), 1660, 1605, 1510, 1490, 1465, 1415, 1350, 1310, 1285, 1185, 1175, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.98-1.55 (m, 7 H), 1.01 (d, *J* = 6.3 Hz, 3 H), 1.14 (d, *J* = 6.6 Hz, 3 H), 1.80 (m, 1 H), 2.08 (m, 1 H), 2.43 (ddq, *J* = 3.2, 11.8, 6.6 Hz, 1 H), 2.72 (s, 3 H), 3.25 (dd, *J* = 5.7, 14.2 Hz, 1 H), 3.31 (dd, *J* = 1.7, 17.4 Hz, 1 H), 3.32 (dd, *J* = 9.4, 14.2 Hz, 1 H), 3.54 (dd, *J* = 5.7, 9.4 Hz, 1 H), 3.64-3.76 (m, 2 H), 4.77 (dd, *J* = 9.1, 17.4 Hz, 1 H), 4.86 (ddd, *J* = 1.8, 5.4, 11.4 Hz, 1 H), 5.51 (br s, 1 H), 6.09 (br d, *J* = 9.1 Hz, 1 H), 6.92 (d, *J* = 8.3 Hz, 1 H), 7.02 (dd, *J* = 2.0, 8.3 Hz, 1 H), 7.46 (d, *J* = 2.0 Hz, 1 H); MS (FAB) *m/z* (relative intensity) 617[(M + H)$^+$, 100], 599 (53), 573 (20); Anal. Calcd for $C_{27}H_{41}IN_2O_6$: C, 52.60; H, 6.70; N, 4.54. Found: C, 52.65; H, 6.47; N, 4.36.

Protected seco acid 50: To a stirred solution of amide **34** (7.4 mg, 0.015 mmol), *N*-Boc-*N*-methyl-glycine (13.3 mg, 0.0704 mmol),[26] and 4-dimethylaminopyridine (2.0 mg, 0.016 mmol) in dichloromethane (0.3 mL) at 0 °C was added *N,N'*-dicyclohexylcarbodiimide (12.1 mg, 0.0586 mmol). After 1.5 h, the mixture was filtered through a small plug of cotton, and the solids were washed with benzene–hexane (1:1, 3 mL). The filtrate and washings were combined and concentrated. The residue was purified by column chromatography on silica gel (5 g, acetone–benzene 1:25) to give protected seco acid **50** (10.0 mg, quantitative) as a colorless oil: $[\alpha]^{22}_D$ -8.0° (*c* 0.60, $CHCl_3$); IR ($CHCl_3$) 3430, 1740, 1690, 1510, 1475, 1460, 1395, 1370, 1250, 1160, 1070, 835 cm^{-1}; ^1H NMR ($CDCl_3$) (rotamer ratio 11:9) δ 0.03 (s, 3.30 H), 0.05 (s, 2.70 H), 0.81-0.94 (m, 12 H), 0.89 (s, 9 H), 1.03-1.24 (m, 2 H), 1.16 (d, *J* = 6.6 Hz, 3 H), 1.42-1.53 (m, 3 H), 1.43 (s, 4.95 H), 1.46 (s, 4.05 H), 1.47 (s, 9 H), 1.62-1.80 (m, 3 H), 1.91 (m, 1 H), 2.40 (m, 1 H), 2.92 (s, 1.35 H), 2.93 (s, 1.65 H), 3.54 (m, 1 H), 3.89-3.99 (m, 4 H), 4.92 (m, 1 H), 6.07 (br t, *J* = 4.5 Hz, 0.55 H), 6.21 (br t, *J* = 4.5 Hz, 0.45 H); MS (FAB) *m/z* (relative intensity) 695 [(M + Na)$^+$, 4], 673 [(M + H)$^+$, 9], 615 (1), 573 (61), 517 (27), 385 (26), 296 (100); HRMS (FAB) calcd for $C_{35}H_{68}N_2O_8SiNa$ [(M + Na)$^+$] 695.4643, found 695.4659.

Depsipeptide 51: To a stirred solution of protected seco acid **50** (13.3 mg, 0.0198 mmol) in dichloromethane (0.3 mL) was added trifluoroacetic acid (0.3 mL). After 3 h, the solution was concentrated and azeotropically dried with benzene (20 mL) to give a crude seco acid.

To a stirred solution of the crude seco acid in dichloromethane (20 mL) at 0 °C were added triethylamine (0.050 mL, 0.36 mmol) and Bop-Cl (20.1 mg, 0.0790 mmol). The solution was slowly warmed to 25 °C over 6 h with stirring, and further stirred for 6 h at 25 °C. The mixture was washed with 0.1 M HCl (5 mL), brine

(3 mL), saturated aqueous $NaHCO_3$ (5 mL), H_2O (3 mL), and brine (3 mL) successively. The organic layer was dried (Na_2SO_4) and concentrated to give a mixture of depsipeptide **51** and its trifluoroacetate as an oil (20.7 mg).

The mixture (20.7 mg) was dissolved in concentrated aqueous NH_3-MeOH (1:100, 1 mL). After 2 h, the mixture was concentrated and the residual oil was purified by thin layer chromatography on silica gel (200 × 200 × 0.25 mm, acetone–benzene 1:2) and thin layer chromatography on silica gel (200 × 200 × 0.25 mm, acetone–chloroform 1:1) successively to give depsipeptide **51** (4.1 mg, 54%) as a colorless solid: $[\alpha]^{24}_D$ -13° (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) 3520, 3440, 1720, 1660, 1510, 1490, 1465, 1415, 1305, 1260, 1135, 1030, 990, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (d, *J* = 6.9 Hz, 3 H), 0.93 (d, *J* = 6.9 Hz, 6 H), 0.96-1.57 (m, 7 H), 0.99 (d, *J* = 5.9 Hz, 3 H), 1.14 (d, *J* = 6.6 Hz, 3 H), 1.82 (m, 1 H), 2.06 (m, 1 H), 2.43 (ddq, *J* = 3.4, 12.1, 6.6 Hz, 1 H), 3.05 (br s, 1 H), 3.16 (s, 3 H), 3.42 (dd, *J* = 1.7, 16.9 Hz, 1 H), 3.44 (d, *J* = 17.2 Hz, 1 H), 3.59 (br d, *J* = 10.9 Hz, 1 H), 4.64 (d, *J* = 17.2 Hz, 1 H), 4.87 (dd, *J* = 9.1, 16.9 Hz, 1 H), 5.01 (ddd, *J* = 2.0, 5.3,11.6 Hz, 1 H), 6.10 (br d, *J* = 9.1 Hz, 1 H); MS (FAB) *m/z* (relative intensity) 385 [(M + H)$^+$, 100], 367 (46); HRMS (FAB) calcd for $C_{20}H_{37}N_2O_5$ [(M + H)$^+$] 385.2702, found 385.2715.

Silyl ether 52: A 60% dispersion of sodium hydride in mineral oil (114.9 mg, 2.87 mmol) was washed with hexane (2.0 ml) and suspended in THF (5.5 mL). To this suspension 1,9-nonanediol (Tokyo kasei, 458.5 mg, 2.86 mmol) was added with stirring. After 45 min, *tert*-butyldimethylsilyl chloride (431.9 mg, 2.87 mmol) was added and the resulting mixture was vigorously stirred for 1.5 h. The reaction mixture was poured into ether (50 mL). The organic layer was washed with 10% aqueous K_2CO_3 (15 mL) and brine (15 mL), dried (Na_2SO_4) , and concentrated. The residue was purified by column chromatography on silica gel (40 g, ethyl acetate-hexane 1:10 → 1:5 → 2:1) to give silyl ether **52** (411.0 mg, 52%) as a colorless oil: IR ($CHCl_3$) 3620, 1255, 1095, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 1.24-1.42 (m, 10 H), 1.42-1.62 (m, 5 H), 3.59 (t, *J* = 6.6 Hz, 2 H), 3.62 (t, *J* = 6.6 Hz, 2 H); MS (FAB) *m/z* (relative intensity) 275 [(M + H)$^+$, 100], 259 (4), 217 (24), 133 (25), 115 (24); HRMS (FAB) calcd for $C_{15}H_{35}O_2Si$ [(M + H)$^+$] 275.2407, found 275.2398.

Carboxylic acid 53: To a stirred solution of silyl ether **52** (42.3 mg, 0.154 mmol) in DMSO (0.8 mL) were added triethylamine (0.20 mL, 1.4 mmol) and sulfur trioxide pyridine complex (82.0 mg, 0.515 mmol). After 2 h, sulfur trioxide pyridine complex (111.7 mg, 0.702 mmol) was added and the solution was stirred for 14 h. The reaction mixture was poured into H_2O (4 mL) and the mixture was extracted with ether (50 mL + 2 × 25 mL). The extracts were combined and washed with saturated aqueous NH_4Cl (2 × 5 mL), saturated aqueous $NaHCO_3$ (5 mL), and brine (5 mL) successively, dried (Na_2SO_4), and concentrated to give a crude aldehyde (42.7 mg).

To a stirred solution of the crude aldehyde (42.7 mg) in *tert*-butyl alcohol (3.2 mL) were added 2-methyl-2-butene (0.75 mL, 7.1 mmol) and a solution of $NaClO_2$ (80% purity, 174.3 mg, 1.54 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (168.5 mg, 1.08 mmol) in H_2O (1.4 mL). After 10 min, the mixture was concentrated and H_2O (3 mL) was added. The mixture was acidified (pH 3) with 0.5 M HCl and extracted with ether (3 × 15 mL). The extracts were combined, washed with cold H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (5 g, ethyl acetate–hexane 1:8) to give carboxylic acid **53** (34.0 mg, 76%) as a colorless oil: IR ($CHCl_3$) 2500-3350, 1710, 1255, 1090, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 1.24-1.42 (m, 8 H), 1.50 (m, 2 H), 1.63 (m. 2 H), 2.34 (t, *J* = 7.4 Hz, 2 H), 3,59 (t, *J* = 6.6 Hz, 2 H); MS (FAB) *m/z* (relative intensity) 289 [(M + H)$^+$, 78], 271 (19), 255 (20), 231 (62), 213 (100), 133 (20), 115 (24); HRMS (FAB) calcd for $C_{15}H_{33}O_3Si$ [(M + H)$^+$] 289.2199, found 289.2186.

Amide 54: To a stirred solution of carboxylic acid **53** (17.3 mg, 0.0601 mmol) and glycine *tert*-butyl ester hydrochloride (Aldrich, 14.2 mg, 0.0841 mmol) in DMF (0.40 mL) at 0 °C were added triethylamine (0.020 mL, 0.14 mmol) and DEPC (0.020 mL, 0.13 mmol). After 40 min, brine (2 mL) was added and the mixture was extracted with ether (20 mL + 2 × 10 mL). The combined extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, ethyl acetate–benzene 1:20 → 1:15) to give amide **54** (22.3 mg, 93%) as a colorless oil: IR ($CHCl_3$) 3430, 1735, 1670, 1510, 1370, 1250, 1155, 1090, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.22-1.40 (m, 8 H), 1.42-1.56 (m, 2 H), 1.47 (s, 9 H), 1.63 (m, 2 H), 2.21 (t, J = 7.6 Hz, 2 H), 3.58 (t, J = 6.6 Hz, 2 H), 3.93 (d, J = 5.0 Hz, 2 H), 5.94 (br t, J = 5.0 Hz, 1 H); MS (FAB) *m/z* (relative intensity) 402 [$(M + H)^+$, 20], 346 (100), 330 (7), 288 (30), 214 (26); HRMS (FAB) calcd for $C_{21}H_{44}NO_4Si$ [$(M + H)^+$] 402.3040, found 402,3049.

Alcohol 55: To a stirred solution of amide **54** (17.1 mg, 0.0426 mmol) in acetonitrile (0.30 mL) at 0 °C was added 47% hydrofluoric acid (0.050 mL, 1.6 mmol). After 20 min, the reaction mixture was poured into ice-saturated aqueous $NaHCO_3$ (1:1, 2 mL) and the mixture was extracted with ether (3 × 10 mL). The extracts were combined, washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, ethyl acetate–hexane 1:1 → 3:1) to give alcohol **55** (12.1 mg, 99%) as a colorless oil: IR ($CHCl_3$) 3250-3600, 3430, 1735, 1670, 1515, 1370, 1155, 1050, 1040, 1020, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25-1.43 (m, 8 H), 1.48 (s, 9 H), 1.56 (m, 2 H), 1.64 (m, 2 H), 1.75 (br s, 1 H), 2.23 (t, J = 7.6 Hz, 2 H), 3.63 (t, J = 6.6 Hz, 2 H), 3.94 (d, J = 5.0 Hz, 2 H), 5.97 (br s, 1 H); MS (FAB) *m/z* (relative intensity) 288 [$(M + H)^+$, 30], 232 (100), 214 (10); HRMS (FAB) calcd for $C_{15}H_{30}NO_4$ [$(M + H)^+$] 288.2175, found 288.2186.

Protected seco acid 56: To a stirred solution of alcohol **55** (11.0 mg, 0.0383 mmol), *N*-Boc-3-iodo-*N*-methyl-*O*-TBS-D-tyrosine (D-**32**) (84.1 mg, 0.157 mmol), and 4-dimethylaminopyridine (5.6 mg, 0.046 mmol) in dichloromethane (0.8 mL) at -20 °C was added *N,N'*-dicyclohexylcarbodiimide (35.5 mg, 0.172 mmol). After 40 min, the mixture was filtered through a small plug of cotton, and the solids were washed with benzene–hexane (1:1, 3 mL). The filtrate and washings were combined and concentrated. The residue was purified by column chromatography on silica gel (2 g, benzene → acetone–benzene 1:20 → 1:10), column chromatography on silica gel (4 g, benzene → acetone–benzene 1:20), and thin layer chromatography on silica gel (200 × 200 × 1.0 mm, 2 plates, acetone–benzene 1:5) successively to give protected seco acid **56** (29.2 mg, 95%) as a colorless oil: $[\alpha]^{28}_D$ +28.8° (*c* 0.310, $CHCl_3$); IR ($CHCl_3$) 3430, 1735, 1685, 1600, 1510, 1485, 1390, 1370, 1330, 1285, 1255, 1160, 1040, 920, 840 cm^{-1}; ^1H NMR (CDCl3) (rotamer ratio 4:3) δ 0.24 (s, 6 H), 1.04 (s, 9 H), 1.26-1.38 (m, 8 H), 1.36 (s, 5.14 H), 1.39 (s, 3.86 H), 1.46 (s, 9 H), 1.52-1.70 (m, 4 H), 2.21 (t, J = 7.6 Hz, 2 H), 2.69 (s, 1.29 H), 2.73 (s, 1.71 H), 2.86 (br t, J = 10.8 Hz, 0.43 H), 2.91 (br t, J = 10.7 Hz, 0.57 H), 3.10-3.24 (m, 1 H), 3.92 (d, J = 5.0 Hz, 2 H), 4.11 (br t, J = 6.6 Hz, 2 H), 4.56 (br dd, J = 4.5, 10.7 Hz, 0.57 H), 4.78 (br dd, J = 5.1, 10.8 Hz, 0.43 H), 5.96 (br s, 1 H), 6.72 (d, J = 8.3 Hz, 1 H), 6.97 (br d, J = 8.3 Hz, 0.57 H), 7.04 (br d, J = 8.3 Hz, 0.43 H), 7.58 (br s, 1 H); MS (FAB) *m/z* (relative intensity) 805 [$(M + H)^+$, 6], 749 (5), 705 (24), 649 (100), 560 (15), 434 (14), 390 (52), 347 (20), 301 (23); HRMS (FAB) calcd for $C_{36}H_{62}IN_2O_8Si$ [$(M + H)^+$] 805.3320, found 805.3329.

Silyl ether 57: To a stirred solution of protected seco acid **56** (22.7 mg, 0.0282 mmol) in dichloromethane (0.5 mL) was added trifluoroacetic acid (0.5 mL). After 1.5 h, the solution was concentrated and azeotropically dried with benzene (10 mL) to give a crude seco acid.

To a stirred solution of the crude seco acid in dichloromethane (28 mL) at 0 °C were added triethylamine (0.040 mL, 0.29 mmol) and Bop-Cl (35.9 mg, 0.141 mmol). The solution was slowly warmed to 28 °C over

15 h with stirring. The mixture was washed with 10% aqueous citric acid (3 mL), H_2O (3 mL), saturated aqueous $NaHCO_3$ (3 mL), H_2O (3 mL), and brine (3 mL) successively. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (3 g, acetone–benzene 1:10) and thin layer chromatography on silica gel (200 × 200 × 0.25 mm, 2 plates, acetone–hexane 2:5) successively to give silyl ether **57** (13.3 mg, 75%) as a colorless oil: $[\alpha]^{27}_D$ +80.0° (*c* 0.664, $CHCl_3$); IR ($CHCl_3$) 3410, 1735, 1670 (sh), 1650, 1600, 1485, 1415, 1285, 1255, 1175, 1040, 920, 840 cm^{-1}; ^1H NMR ($CDCl_3$) (major rotamer; ratio 10:1) δ 0.25 (s, 6 H), 1.04 (s, 9 H), 1.10-1.42 (m, 8 H), 1.47-1.74 (m, 4 H), 2.24 (dt, *J* = 13.2, 5.9 Hz, 1 H), 2.32 (dt, *J* = 13.2, 5.9 Hz, 1 H), 2.72 (s, 3 H), 3.12 (dd, *J* = 10.7, 14.4 Hz, 1 H), 3.28 (dd, *J* = 5.1, 14.4 Hz, 1 H), 3.89 (dt, *J* = 11.0, 5.6 Hz, 1 H), 3.90 (dd, *J* = 3.6, 17.5 Hz, 1 H), 4.12 (dd, *J* = 4.9, 17.5 Hz, 1 H), 4.14 (dd, *J* = 5.1, 10.7 Hz, 1 H), 4.40 (dt, *J* = 11.0, 5.4 Hz, 1 H), 6.60 (br s, 1 H), 6.73 (d, *J* = 8.2 Hz, 1 H), 6.98 (dd, *J* = 2.3, 8.2 Hz, 1 H), 7.55 (d, *J* = 2.3 Hz, 1 H); MS (FAB) *m/z* (relative intensity) 631 [$(M + H)^+$, 100], 573 (47), 390 (70), 347 (23); HRMS (FAB) calcd for $C_{27}H_{44}IN_2O_5Si$ [$(M + H)^+$] 631.2064, found 631.2043.

Depsipeptide 58: To a stirred solution of silyl ether **57** (11.0 mg, 0.0175 mmol) in THF (0.2 mL) at 0 °C was added tetra-*n*-butylammonium fluoride (Aldrich, 1.0 M solution in THF, 0.025 mL, 0.025 mmol). After 5 min, saturated aqueous NH_4Cl (2 mL) was added, and the mixture was extracted with ether (20 + 2 × 10 mL). The extracts were combined, washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by thin layer chromatography on silica gel (200 × 200 × 0.25 mm, 2 plates, acetone–hexane 1:1) to give depsipeptide **58** (8.9 mg, 99%) as a colorless solid. Recrystallization from dichloromethane–hexane gave colorless needles: mp 177–178 °C; $[\alpha]^{27}_D$ +89.0° (*c* 0.444, $CHCl_3$); IR ($CHCl_3$) 2800-3500, 3400, 1740, 1650, 1600, 1575, 1505, 1490, 1415, 1330, 1285, 1175, 1110, 1070, 1030, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) (major rotamer; ratio 10:1) δ 1.14-1.42 (m, 8 H), 1.48-1.76 (m, 4 H), 2.26 (dt, *J* = 13.7, 6.4 Hz, 1 H), 2.33 (dt, *J* = 13.7, 6.4 Hz, 1 H), 2.75 (s, 3 H), 3.11 (dd, *J* = 10.6, 14.5 Hz, 1 H), 3.30 (dd, *J* = 4.9, 14.5 Hz, 1 H), 3.91 (dt, *J* = 11.0, 4.9 Hz, 1 H), 3.95 (dd, *J* = 3.6, 17.4 Hz, 1 H), 4.08 (dd, *J* = 4.6, 17.4 Hz, 1 H), 4.22 (dd, *J* = 4.9, 10.6 Hz, 1 H), 4.38 (dt, *J* = 11.0, 5.4 Hz, 1 H), 6.02 (br s, 1 H), 6.62 (br s, 1 H), 6.90 (d, *J* = 8.3 Hz, 1 H), 7.03 (d, *J* = 2.0, 8.3 Hz, 1 H), 7.47 (d, *J* = 2.0 Hz, 1 H); MS (FAB) *m/z* (relative intensity) 517 [$(M + H)^+$, 100], 276 (34). Anal. Calcd for $C_{21}H_{29}IN_2O_5$: C, 48.85; H, 5.66; N, 5.43. Found: C, 49.21; H, 5.39; N, 5.30.

Dipeptide 59: To a stirred solution of 3-iodo-*N*-metyl-D-tyrosine methyl ester (D-**30**)[15] (16.1 mg, 0.0481 mmol), *N*-acetylglycine (Nacalai, 11.6 mg, 0.0991 mmol), and 1-hydroxybenzotriazole (13.8 mg, 0.102 mmol) in THF (0.5 mL) at 0 °C was added *N,N'*-dicyclohexylcarbodiimide (21.2 mg, 0.103 mmol). After 30 min, the ice bath was removed and the mixture was stirred at room temperature for 1.5 h. The mixture was filtered through a small plug of cotton, and the solids were washed with benzene (3 mL). The filtrate and washings were combined and concentrated. The residue was dissolved in ethyl acetate (30 mL) and resulting solution was washed with H_2O (2 mL), saturated aqueous $NaHCO_3$ (2 mL), saturated aqueous NH_4Cl (2 mL), and brine (2 mL) successively. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (2.5 g, acetone–chloroform 1:3 → 1:1) to give a mixture of dipeptide **59** and an *N,O*-diacylated compound as an oil (22.7 mg).

To a stirred solution of the mixture (22.7 mg) in methanol (0.5 mL) at 0 °C was added anhydrous K_2CO_3 (3.3 mg, 0.024 mmol). After 30 min, saturated aqueous NH_4Cl (2 mL) was added, and the mixture was extracted with ethyl acetate (30 mL). The organic layer was washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by thin layer chromatography on silica gel (200 × 200 × 0.25 mm, 2 plates, methanol-chloroform 1:10) to give dipeptide **59** (19.6 mg, 94%) as a colorless solid: $[\alpha]^{30}_D$ +40.8° (*c* 0.745, $CHCl_3$); IR ($CHCl_3$) 2900-3500, 3410, 1745, 1650, 1605, 1575, 1505, 1490, 1440, 1415, 1370, 1355, 1330, 1290, 1250, 1180, 1105, 1040, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) (rotamer ratio 4:1) δ 2.01 (s, 0.6 H),

2.03 (s, 2.4 H), 2.83 (s, 2.4 H), 2.82-2.89 (m, 0.2 H), 2.93 (dd, J = 10.6, 14.7 H, 0.8 H), 2.93 (s, 0.6 H), 3.21-3.33 (m, 0.2 H), 3.28 (dd, J = 5.5, 14.7 Hz, 0.8 H), 3.52 (dd, J = 3.5, 17.0 Hz, 0.2 H), 3.75 (s, 2.4 H), 3.77 (s, 0.6 H), 3.91 (dd, J = 4.0, 17.7 Hz, 0.8 H), 3.98-4.12 (m, 0.2 H), 4.05 (dd, J = 4.1, 17.7 Hz, 0.8 H), 4.43 (dd, J = 4.6, 10.2 Hz, 0.2 H), 5.14 (dd, J = 5.5, 10.6 Hz, 0.8 H), 6.20-7.20 (br s, 1 H), 6.51 (m, 1 H), 6.84 (d, J = 8.3 Hz, 0.2 H), 6.87 (d, J = 8.3 Hz, 0.8 H), 7.02 (dd, J = 2.0, 8.3 Hz, 1 H), 7.46 (d, J = 2.0 Hz, 0.2 H), 7.47 (d, J = 2.0 H, 0.8 H); MS (FAB) *m/z* (relative intensity) 435 [$(M + H)^+$, 100], 336 (51); HRMS (FAB) calcd for $C_{15}H_{20}IN_2O_5$ [$(M + H)^+$] 435.0417, found 435.0424.

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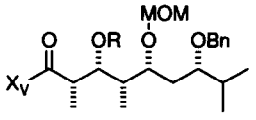

60 R = $(CO)_2OMe$
61 R = $(CO)_2OH$

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21. Trifluoroacetylation of the C7 hydroxyl group appeared to occur under the deprotection conditions.
22. In this case, mercury(II) trifluoroacetate was far more effective for iodination than mercury(II) acetate.
23. Although condensation of D-**30** with *N*-acetylglycine gave a mixture of desired **59** and an *N,O*-diacylated compound, selective methanolysis of the aryl ester group readily converted the *N,O*-diacylated compound to **59**.
24. *N*-Boc derivative of dipeptide **27** was prepared as follows: *N*-methyl-D-tyrosine methyl ester was coupled with *N*-Boc-glycine by bis(2-oxo-3-oxazolidinyl)phosphinic chloride[20] (Bop-Cl) to give a dipeptide, the phenolic hydroxyl group of which was protected as a benzyl ether to give *N*-Boc derivative of dipeptide **27**.
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