Dolabellin, a Cytotoxic Bisthiazole Metabolite from the Sea Hare *Dolabella auricularia*: Structural Determination and Synthesis†

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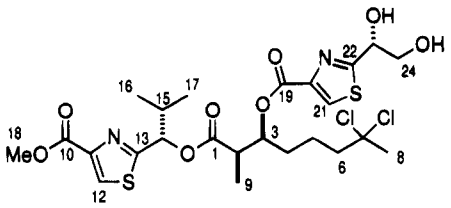
Dolabellin (**1**), a novel cytotoxic metabolite which consists of two thiazole hydroxy acids and a new dichlorinated β-hydroxy acid, was isolated from the Japanese sea hare *Dolabella auricularia*. The gross structure of **1** was elucidated on the basis of spectral data in conjunction with chemical degradations, which provided three methyl esters: methyl 2-(1-hydroxy-2-methylpropyl)thiazole-4-carboxylate (**2**), methyl 2-(1,2-dihydroxyethyl)thiazole-4-carboxylate (**3**), and methyl 7,7-dichloro-3-hydroxy-2-methyloctanoate (**4**). The absolute stereochemistry of **1** was determined by stereoselective syntheses of two degradation products **2** and **3** and two diastereomeric octanoates **7a**,**b** (the dechloro derivatives of degradation product **4**), and the enantioselective total synthesis of dolabellin itself. Dechlorodolabellin (**23**) was also synthesized.

The Indian Ocean sea hare *Dolabella auricularia* contains several bioactive peptides,[1] such as dolastatin 10,[2] in small amounts. Recently, we found that Japanese specimens of this animal contained new cytotoxic depsipeptides[3] and other unique metabolites.[4] Further examination of the bioactive constituents of the Japanese sea hare *D. auricularia* led to the isolation of a novel cytotoxic bisthiazole metabolite, dolabellin (**1**). We describe here the structural elucidation and synthesis of this compound.



dolabellin (**1**)

Results and Discussion

Isolation. The MeOH extract of the internal organs (20 kg) of the sea hare *D. auricularia* (33 kg, wet wt), collected in Mie Prefecture, Japan, was partitioned between EtOAc and water. The EtOAc-soluble material, which exhibited cytotoxicity against HeLa-S_3 cells with an IC_{50} of 1.2 μg/mL, was further partitioned between 9:1 MeOH/H_2O and hexane. The material obtained from the aqueous MeOH portion was subjected to bioassay-guided fractionation using silica gel (i. toluene/EtOAc and then EtOAc/MeOH, step gradient; ii. 2:1 hexane/acetone and then 9:1 acetone/MeOH) and ODS silica gel (7:3 MeOH/water to MeOH, linear gradient), successively, to afford an active fraction (IC_{50} = 0.37 μg/mL). The fraction was further separated repeatedly by a combination of reversed-phase HPLC and silica gel TLC (i. HPLC, 1:1 MeCN/water; ii. TLC, 2:1 $CHCl_3$/acetone; iii. HPLC, 65:35 MeOH/water) to afford dolabellin (**1**) as an oil in 7 × 10^{-6}% yield based on wet weight. Dolabellin (**1**) showed cytotoxicity against the same cells with an IC_{50} of 6.1 μg/mL.[5]

Gross Structure. Dolabellin (**1**) has a molecular formula of $C_{24}H_{32}Cl_2N_2O_8S_2$ as determined by HRFABMS [*m*/*z* 611.1039 (MH^-), Δ −1.6 mmu] and NMR data (Table 1). The presence of two chlorine atoms was supported by 5:4:1 isotope peaks at *m*/*z* 611/613/615 (MH^-) in the mass spectrum. The IR spectrum showed bands at 3450, 3130, and 1735 cm^{-1} that were assigned to hydroxyl, five-membered heteroaromatic, and ester groups, respectively. ^1H and ^{13}C NMR data are summarized in Table 1, in which multiplicities of ^{13}C NMR signals were determined by a DEPT experiment and all of the protonated carbons were assigned by ^1H–^{13}C COSY data (J_{CH} = 135 Hz). The comparison of two low-field signals (δ 8.12 and 8.13) in the ^1H NMR spectrum and eight sp^2-carbon resonances (δ 127.5, 128.2, 146.4, 146.9, 160.5, 161.7, 170.0, and 173.1) in the ^{13}C NMR spectrum with those for several thiazole-containing cyclic peptides[6] suggested the presence of two sets of 2-alkylthiazole-4-carboxylates (C10–C13 and C19–C22) in **1**. The remaining sp^2 carbon (C1: δ 172.3) of **1** was assigned to the carbonyl carbon of a saturated ester group. One quaternary carbon (C7: δ 90.2) and one methyl group (C8: δ_C 37.4 and δ_H 2.12) were assigned to a 1,1-dichloroethyl group, the presence of which was deduced by comparing NMR data with those of 2,2-dichlorononane.[7] Three partial structures, $-CH(CH_3)CH(OCOR)CH_2CH_2CH_2-$, $-CH(OCOR)CH(CH_3)_2$, and $-CH(OH)CH_2OH$, were de-

† Dedicated to Professor Koji Nakanishi on the occasion of his 70th birthday.

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(1) Pettit, G. R.; Kamano, Y.; Herald, C. L.; Fujii, Y.; Kizu, H.; Boyd, M. R.; Boettner, F. E.; Doubek, D. L.; Schmidt, J. M.; Chapuis, J.-C.; Michel, C. *Tetrahedron* **1993**, *49*, 9151–9170.

(2) Pettit, G. R.; Kamano, Y.; Herald, C. L.; Tuinman, A. A.; Boettner, F. E.; Kizu, H.; Schmidt, J. M.; Baczynskyj, L.; Tomer, K. B.; Bontems, R. J. *J. Am. Chem. Soc.* **1987**, 109, 6883–6885.

(3) (a) Sone, H.; Nemoto, T.; Ojika, M.; Yamada, K. *Tetrahedron Lett.* **1993**, *34*, 8445–8448. (b) Sone, H.; Nemoto, T.; Ishiwata, H.; Ojika, M.; Yamada, K. *Tetrahedron Lett.* **1993**, *34*, 8449–8452. (c) Ishiwata, H.; Nemoto, T.; Ojika, M.; Yamada, K. *J. Org. Chem.* **1994**, *59*, 4710–4711.

(4) Ojika, M.; Nemoto, T.; Yamada, K. *Tetrahedron Lett.* **1993**, *34*, 3461–3462.

(5) The cytotoxicity of **1** was weaker than that of the active fraction, from which **1** was isolated. This was attributable to the presence of doliculide, a potent cytotoxic substance with an IC_{50} of 0.001 μg/mL (ref 3c), in the active fraction.

(6) Typical chemical shifts for 2-alkylthiazole-4-carboxamides: δ_C 170 (C2), 149 (C4), 124 (C5), 161 (CO); δ_H 7.4–8.1 (H5). For a recent review, see: Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771–1791.

(7) NMR data for 2,2-dichlorononane: δ_C 90.6 (C2), 37.2 (C1); δ_H 2.05 (H1). Tordeux, M.; Boumizane, K.; Wakselman, C. *J. Org. Chem.* **1993**, *58*, 1939–1940.

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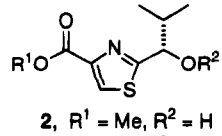
Table 1. NMR Data for Dolabellin (1) in $CDCl_3$

position	$^1H^a$	$^{13}C^b$	HMBC^c
1	–	172.3 s	H-2, 9, 14
2	2.99 dq (7.3, 7.3)	43.4 d	H-9
3	5.48 m	74.6 d	H-2, 9
4a	1.75 m	31.2 t	H-2
4b	1.89 m		
5	1.76 m	21.7 t	
6	2.22 m	49.1 t	H-8
7	–	90.2 s	H-8
8	2.12 s	37.4 q	
9	1.32 d (7.3)	12.6 q	H-2
10	–	161.7 s	H-12, 18
11	–	146.9 s	H-12
12	8.13 s	127.5 d	
13	–	170.0 s	H-12, 14, 15
14	5.98 d (5.9)	77.8 d	H-15, 16, 17
15	2.43 m	33.3 d	H-14, 16, 17
16	0.95 d (6.6)	17.2 q	H-14, 15, 17
17	0.94 d (6.6)	18.6 q	H-14, 15, 16
18	3.95 s	52.5 q	
19	–	160.5 s	H-21
20	–	146.4 s	H-21
21	8.12 s	128.2 d	
22	–	173.1 s	H-21, 23, 24
23	5.10 ddd (6.3, 5.0, 4.0)	72.1 d	
24a	4.03 ddd (11.6, 6.3, 5.0)	65.9 t	H-23
24b	4.08 ddd (11.6, 6.3, 4.0)		
23-OH	3.38 d (6.3)	–	
24-OH	2.39 t (6.3)	–	

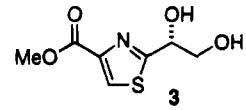
^{a} Recorded at 400 MHz. Coupling constants (Hz) are in parenthesis. ^{b} Recorded at 67.8 MHz. ^{c} Protons correlated to carbon resonances in ^{13}C column. Parameters were optimized for J_{CH} = 6 and 8 Hz.

rived from $^1H-^1H$ COSY data. The locations of two hydroxyl groups were determined from ^1H NMR measurement in the presence of deuterium oxide. The HMBC data summarized in Table 1 allowed us to connect the partial structures and functional groups described above. The ester linkage between C3 and C19, though not evidenced by the HMBC experiments, was obvious, since all other connectivities were established as described above. The gross structure of dolabellin is represented by **1**. Dolabellin (**1**) is structurally related to mirabimide E,[8] which contains a tetrachlorinated β-hydroxy fatty acid. Although several peptides containing thiazole amino acids are known,[6] dolabellin (**1**) is the first example of a natural product containing thiazole hydroxy acid.

Stereochemistry. On methanolysis using NaOMe in MeOH, dolabellin (**1**) provided three kinds of methyl ester: methyl 2-(1-hydroxy-2-methylpropyl)thiazole-4-carboxylate (**2**), methyl 2-(1,2-dihydroxyethyl)thiazole-4-carboxylate (**3**), and methyl 7,7-dichloro-3-hydroxy-2-methyloctanoate (**4**). The structures and absolute stereochemistries of these degradation products were determined as follows.



2, R^1 = Me, R^2 = H
5, R^1 = Et, R^2 = Ac



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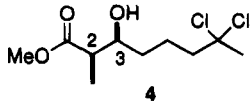

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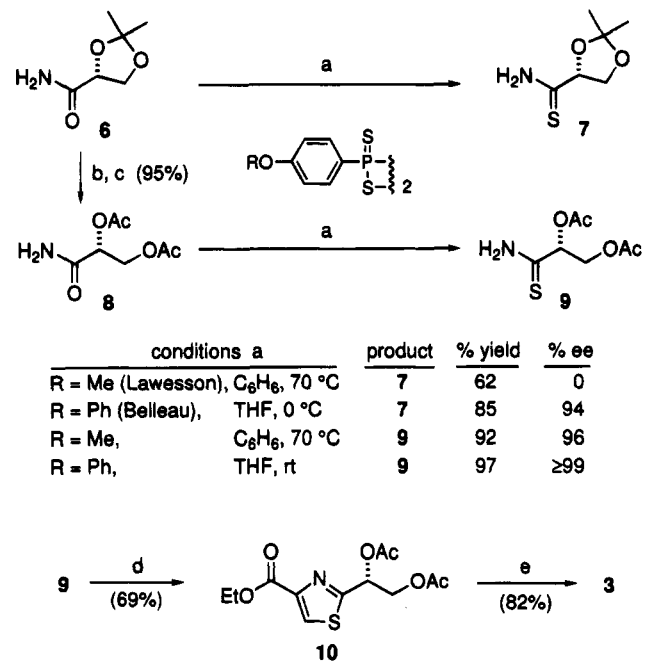
Methyl ester **2** was readily prepared by methanolysis of the known optically active thiazole derivative **5**, which

(8) Paik, S.; Carmeli, S.; Cullingham, J.; Moore, R. E.; Patterson, G. M. L.; Tius, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 8116–8125.

Scheme 1[a]

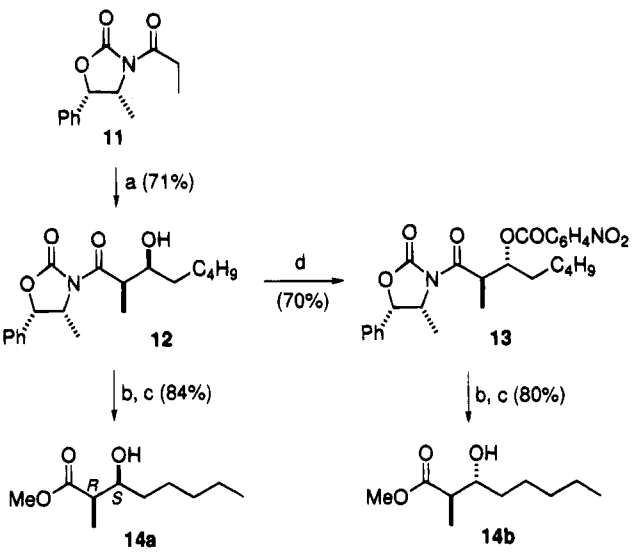


[a] (a) See above; (b) TFA, H_2O, THF, 0 °C and then rt; (c) Ac_2O, pyridine, 0 °C; (d) $BrCH_2COCOOEt$, acetone, −10 °C; $(CF_3CO)_2O$, pyridine, CH_2Cl_2, −20 °C and then 0 °C; (e) NaOMe, MeOH, rt.

was prepared by a modification[9] of the Hantzsch synthesis. This synthetic **2**, $[\alpha]^{28}_D$ −31.2° (*c* 0.61, $CHCl_3$), was identical to natural **2**, $[\alpha]^{26}_D$ −34° (*c* 0.12, $CHCl_3$), in all respects, revealing the *S* configuration at the stereocenter of **2**. The second methyl ester **3** was synthesized using the same strategy as for the preparation of **2**, and is summarized in Scheme 1. The known chiral amide **6**[10] was first converted to the corresponding thioamide **7** using the Lawesson reagent[11] at 70 °C. The reaction proceeded smoothly, but ^1H NMR measurement in the presence of a chiral shift reagent indicated that thioamide **7** was completely racemic. We next used a modified Lawesson reagent, 2,4-bis(4-phenoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Belleau reagent),[12] for the thionation of **6**. Owing to the high solubility of this reagent, the reaction could be conducted at 0 °C to give **7** with 94% ee. Further studies were made to prepare the optically pure thioamide that could be derived from amide **6**. Thus, amide **6** was converted to diacetate **8**, which was subjected to thionation. Chiral HPLC analysis revealed that thioamide **9** with 96% ee was obtained even at 70 °C by using the Lawesson reagent. Furthermore, thioamide **9** with the best optical purity (≥99% ee) was obtained in high (97%) yield using the Belleau reagent at ambient temperature (Scheme 1). The thiazole construction for **9** was accomplished by applying a modified Hantzsch synthetic procedure. Thus, treatment of **9** with ethyl bromopyruvate under the conditions reported by Schmidt and co-workers[9] afforded thiazole **10**. Chiral HPLC analysis of **10** indicated that partial racemization (86% ee) had occurred during the thiazole-forming reaction. Methanolysis of **10** followed by recrystallization

(9) Schmidt, U.; Gleich, P.; Griesser, H.; Utz, R. *Synthesis* **1986**, 992–998.
(10) Iwadare, K. *Bull. Chem. Soc. Jpn.* **1939**, 14, 131–134.
(11) Pedersen, B. S.; Scheibye, S.; Clausen, K.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 293–297.
(12) Lajoie, G.; Lépine, F.; Maziak, L.; Belleau, B. *Tetrahedron Lett.* **1983**, *24*, 3815–3818.

Scheme 2[a]



	$[\alpha]_D$	δ_{H3}	J_{H2-H3}
4	−10°	3.93	3.6
14a	−10°	3.89	3.6
14b	−4°	3.65	6.3

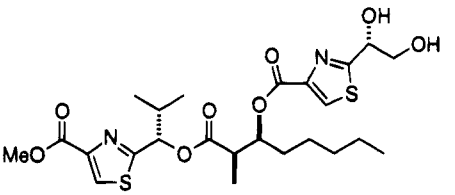
[a] (a) Hexanal, Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C and then 0 °C; (b) LiOH, H_2O_2, THF, H_2O, rt; (c) CH_2N_2, ether, rt; (d) p-$NO_2C_6H_4COOH$, $(EtOOCN{=})_2$, PPh_3, benzene, rt.

gave the desired methyl ester **3** with ≥99% ee (chiral HPLC analysis). Synthetic **3**, $[\alpha]^{25}_D$ +60.6° (*c* 0.051, MeOH), showed physical and spectral data identical to those for natural **3**, $[\alpha]^{25}_D$ +64° (*c* 0.02, MeOH), which establishes an *R* configuration at the stereocenter of **3**.

To determine the stereochemistry of the third degradation product **4**, we synthesized two diastereomers **14a** and **14b**, which are the dechloro derivatives of **4** (Scheme 2). The Evans aldol reaction[13] of hexanal with imide **11** gave *erythro*-adduct **12** with a diastereoselection of 98:2 (^{13}C NMR analysis),[14] which was readily converted to *erythro*-isomer **14a** by two steps. The *threo*-isomer **14b** was prepared from *p*-nitrobenzoate **13**, which in turn was obtained by the Mitsunobu reaction[15] of **12**. The ^1H NMR data (δ_{H3} and J_{H2-H3}) and specific rotations of the degradation product **4** and the synthetic material **14a** were quite similar (Scheme 2), which revealed that the stereochemistry of **4** was 2*R*,3*S*. On the basis of these results, we were able to determine the complete stereostructure of dolabellin, as shown in **1**.

Synthesis. The stereochemistry of dolabellin (**1**) was unambiguously confirmed by total synthesis (Scheme 3). Ozonolysis of 6,6-dichloro-1-heptene[16] afforded 5,5-dichlorohexanal (**15**). Reaction of **15** with imide **11** under the conditions described in Scheme 3 afforded aldol adduct **16** with diastereoselection of 95:5 (^{13}C NMR analysis).[14] Removal of the chiral auxiliary of **16** followed by silylation and hydrolysis provided acid **17**, which was then coupled with methyl ester **2** under Keck conditions[17] to give diester **18**. After deprotection of the silyl group in **18**, the resulting alcohol **19** was coupled with acid **21** prepared from methyl ester **3** via acetonide **20**,[18] to afford dolabellin acetonide (**22**). Finally, removal of the acetonide group in **22** provided dolabellin (**1**), $[\alpha]^{24}_D$ −7.4° (*c* 0.38, $CHCl_3$), IC_{50} = 7.9 μg/mL (HeLa-S_3 cells), which was identical to natural **1**, $[\alpha]^{28}_D$ −7.3° (*c* 0.34, $CHCl_3$), IC_{50} = 6.1 μg/mL, in all respects (IR, ^1H and ^{13}C NMR, HPLC, specific rotation, and cytotoxicity).

The dechloro analogue **23** was also synthesized starting with the aldol adduct **12** instead of **16** by the same procedure as described in Scheme 3 (data for intermediates not shown). The dechloro analogue **23** was less cytotoxic against HeLa-S_3 cells (IC_{50} = 20 μg/mL) than dolabellin (**1**), suggesting that the aliphatic carbon chain of **1** may play a role in its cytotoxicity.



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Experimental Section

General. Melting points are uncorrected. NMR spectra were measured at 270 or 400 MHz for ^1H and 67.8 MHz for ^{13}C. *J* values are given in hertz. Both TLC analysis and preparative TLC were conducted on E. Merck precoated silica gel 60 F_{254} (0.25 mm layer thickness) unless otherwise noted. Fuji-Davison silica gel BW-820 MH was used for column chromatography. Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. Organic solvents for anhydrous reactions were distilled from the following drying agents: THF and ether (Na−benzophenone ketyl), benzene (Na), triethylamine and pyridine (calcium hydride), DMF (calcium hydride under reduced pressure), CH_2Cl_2 (P_2O_5), acetone (anhydrous K_2CO_3), and MeOH (Mg). All moisture-sensitive reactions were performed under an atmosphere of nitrogen.

Isolation of Dolabellin (1). *D. auricularia* (33 kg, wet wt) were collected by hand at a depth of 0−1 m off the coast of the Shima Peninsula, Mie Prefecture, Japan, in April 1993. The specimens, which were stored at −20 °C for several months, were divided into the internal organs and thick outer skin, and the former (20 kg) were extracted with MeOH (40 L). This methanolic extract was concentrated to ca. 2 L in vacuo and extracted with EtOAc (3 × 2 L). After concentration in vacuo, the EtOAc extract (91.4 g, IC_{50} against HeLa-S_3 cells = 1.2 μg/mL) was dissolved in 9:1 MeOH/water (1 L), and the solution was washed with hexane (2 × 1 L). Evaporation of the aqueous MeOH portion gave a dark brown oil (30.8 g), which was subjected to column chromatography over silica gel (590 g), eluting with 1:1 toluene/EtOAc, EtOAc, 95:5, 90:10, and 80:20 EtOAc/MeOH, and MeOH, successively. The fraction (2.68 g, IC_{50} = 0.91 μg/mL) eluted with EtOAc was chromatographed on silica gel (130 g) with 2:1 hexane/acetone and then 9:1 acetone/MeOH. The later fractions eluted with 2:1 hexane/acetone and the fractions eluted with 9:1 acetone/MeOH were combined (1.13 g, IC_{50} = 0.17 μg/mL) and applied to an ODS short column (Cosmosil 75C_{18}-OPN, 23 g), eluting with 4:1 MeOH/water and then MeOH. An early fraction (744 mg) eluted with 4:1 MeOH/water was subjected to MPLC [Develosil ODS 30/60 (70 g), linear gradient from 70:30 MeOH/water to MeOH, flow rate 5.0 mL/min]. The fraction eluted between 86:14 and 90:10 MeOH/water (91 mg, IC_{50} = 0.37 μg/

(13) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129. (b) Gage, J. R.; Evans D. A. *Org. Synth.* **1989**, *68*, 83−91.

(14) Optically pure aldol adduct was obtained after a single recrystallization.

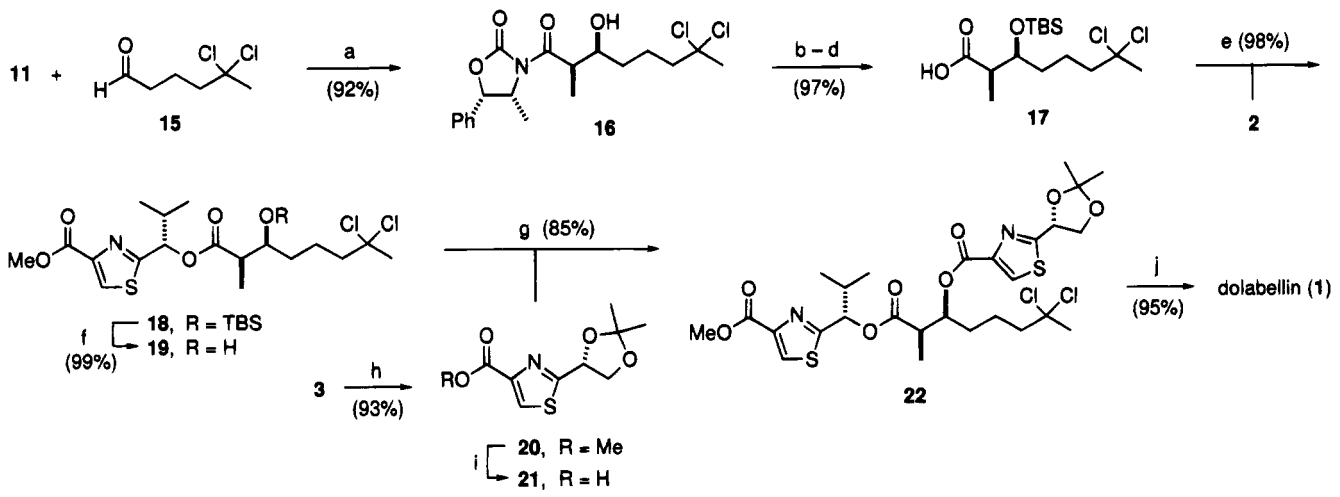
(15) (a) Mitsunobu, O. *Synthesis* **1981**, 1−28. (b) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017−3020.

(16) Lee, G. M.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 1281−1285, and references cited therein.

(17) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394−2395.

(18) Compound **20** has been reported previously: Iwakawa, M.; Kobayashi, Y.; Ikuta, S.; Yoshimura, J. *Chem. Lett.* **1982**, 1975−1978.

Scheme 3[a]



[a] (a) Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C and then 0 °C; (b) LiOH, H_2O_2, H_2O, THF, 0 °C; (c) TBSOTf, Et_3N, CH_2Cl_2, 0 °C; (d) K_2CO_3, H_2O, MeOH, THF, 40 °C; (e) **2**, DCC, DMAP, CSA, CH_2Cl_2, 0 °C and then rt; (f) HF, H_2O, CH_3CN, rt; (g) **21**, DCC, DMAP, CSA, CH_2Cl_2, 0 °C and then rt; (h) $(MeO)_2CMe_2$, CSA, acetone, rt; (i) NaOH, H_2O, MeOH, 0 °C and then rt; (j) TsOH, MeOH, rt.

mL) was separated by preparative HPLC [Develosil ODS-10/20 column (20 × 250 mm), 1:1 MeCN/water, flow rate 5.0 mL/min, detection at 215 nm, t_R = 44 min] to afford a yellow oil containing dolabellin (**1**) (5.9 mg). The crude oil was further purified by preparative TLC (2:1 $CHCl_3$/acetone) followed by preparative HPLC [Develosil ODS-HG-5 column (10 × 250 mm), 7:3 MeOH/water, flow rate 2.0 mL/min, detection at 254 nm, t_R = 27.5 min] to give pure **1** (2.7 mg) as a colorless oil: t_R = 17.7 min [Develosil ODS-HG-5 column (4.6 × 250 mm), 7:3 MeOH/water, flow rate 1.0 mL/min, detection at 254 nm]; R_f = 0.45 (2:1 $CHCl_3$/acetone); $[\alpha]^{28}_D$ −7.3° (*c* 0.34, $CHCl_3$); UV (MeOH) λ_{max} 204 (ϵ 29 400), 236 nm (14 600); IR ($CHCl_3$) 3450 (br), 3130, 3020, 2970, 2880, 1735, 1485, 1460, 1435, 1380, 1325, 1230, 1170, 1045, 1015, 985, 960, 930, 865 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; FABMS (relative intensity) *m/z* 633/635/637 (MNa^+, 4:4:1), 611/613/615 (MH^+, 55:41:12), 198 (100), 166 (97); HRFABMS calcd for $C_{24}H_{33}{}^{35}Cl_2N_2O_8S_2$ *m/z* 611.1055 (MH^+), found 611.1039.

Methanolysis of Dolabellin (1). To a stirred solution of **1** (4.9 mg, 0.008 mmol) in 1.0 mL of MeOH at 0 °C was added a 0.1 M solution of NaOMe in MeOH (0.02 mL). The mixture was stirred at ambient temperature for 20 h. After addition of an acidic ion-exchange resin (Amberlite IRC-50, 200 mg), the mixture was stirred for 1 min and then poured on a pad of the same resin (200 mg). The resin was washed with MeOH (20 mL) several times. The filtrate and washings were combined and evaporated to give an oil, which was subjected to preparative TLC (5:2 benzene/acetone) to afford **2** (0.9 mg, 50%) and **3** (0.9 mg, 50%) as solids, and **4** (1.0 mg), which contained a trace amount of impurities, as an oil. Crude **4** was further purified by preparative TLC (3:2 hexane/EtOAc) to give pure **4** (1.0 mg, 50%) as a colorless oil.

Methyl (*S*)-2-(1-Hydroxy-2-methylpropyl)thiazole-4-carboxylate (2): colorless needles; mp 50−51 °C (hexane); R_f = 0.56 (5:2 benzene/acetone); $[\alpha]^{26}_D$ −34° (*c* 0.12, $CHCl_3$); UV (MeOH) λ_{max} 205 (ϵ 13 300), 237 nm (7300); IR ($CHCl_3$) 3600, 3400 (br), 3120, 1730, 1245, 1225 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.93 (d, J = 6.6 Hz, 3 H), 1.03 (d, J = 6.9 Hz, 3 H), 2.27 (dqq, J = 4.6, 6.9, 6.6 Hz, 1 H), 2.60 (br s, 1 H; OH), 3.95 (s, 3 H), 4.89 (d, J = 4.6 Hz, 1 H), 8.17 (s, 1 H); EIMS *m/z* (relative intensity) 215 (M^+, 7), 184 (8), 173 (76), 172 (78), 157 (19), 140 (100), 113 (53), 84 (22); HREIMS calcd for $C_9H_{13}NO_3S$ *m/z* 215.0616 (M^+), found 215.0601.

Methyl (*R*)-2-(1,2-Dihydroxyethyl)thiazole-4-carboxylate (3): colorless needles; mp 198−199 °C (benzene/MeOH); R_f = 0.13 (5:2 benzene/acetone); $[\alpha]^{25}_D$ +64° (*c* 0.02, MeOH); UV (MeOH) λ_{max} 206 (ϵ 12 000), 236 nm (7400); IR (KBr) 3280, 3230, 3120, 1720, 1705, 1505, 1110, 1055 cm^{-1}; ^1H NMR (270 MHz, methanol-d_4) δ 3.74 (dd, J = 11.6, 5.9 Hz, 1 H), 3.90 (s, 3 H), 3.92 (dd, J = 11.6, 3.6 Hz, 1 H), 4.95 (dd, J = 5.9, 3.6 Hz, 1 H), 8.33 (s, 1 H); FABMS (addition of NaI) *m/z* (relative intensity) 226 (MNa^+, 100); HRFABMS calcd for $C_7H_9NO_4SNa$ *m/z* 226.0150 (MNa^+), found 226.0126.

Methyl (2*R*,3*S*)-7,7-Dichloro-3-hydroxy-2-methyloctanoate (4): colorless oil; R_f = 0.78 (5:2 benzene/acetone) and 0.60 (3:2 hexane/EtOAc); $[\alpha]^{27}_D$ −10° (*c* 0.17, $CHCl_3$); IR ($CHCl_3$) 3550 (br), 1720, 1460, 1435, 1170 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.20 (d, J = 7.3 Hz, 3 H), 1.40−2.00 (m, 4 H), 2.15 (s, 3 H), 2.24 (m, 2 H), 2.55 (br s, 1 H; OH), 2.56 (dq, J = 3.6, 7.3 Hz, 1 H), 3.72 (s, 3 H), 3.93 (m, 1 H, changes to ddd, J = 7.9, 3.9, 3.6 Hz upon addition of D_2O); FABMS (addition of NaI) *m/z* (relative intensity) 279/281/283 (MNa^+, 35:25:10), 243/245 (49:19), 173 (100); HRFABMS calcd for $C_{10}H_{18}{}^{35}Cl_2O_3Na$ *m/z* 279.0531 (MNa^+), found 279.0520.

Synthesis of 2. The starting material, ethyl (*S*)-2-(1-acetoxy-2-methylpropyl)thiazole-4-carboxylate (**5**), was synthesized in optically pure form by the method of Schmidt and co-workers:[9] mp 51.5−52.5 °C (hexane) (lit.[9] mp 52−53 °C); $[\alpha]^{24}_D$ −43.6° (*c* 0.677, $CHCl_3$) (lit.[9] $[\alpha]^{20}_D$ −38.6° (*c* 1.09, $CHCl_3$)).

To a stirred solution of thiazole **5** (280 mg, 1.03 mmol) in MeOH (7.0 mL) at ambient temperature was added a 1.0 M solution of NaOMe in MeOH (0.30 mL). After being stirred at ambient temperature for 1.5 h, the reaction mixture was poured into well-stirred saturated aqueous NH_4Cl (20 mL). The mixture was extracted with EtOAc (3 × 30 mL), and the combined organic layers were washed with saturated aqueous NaCl (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography (3:2 hexane/EtOAc) to give methyl ester **2** (220 mg, 99%) as crystals: colorless needles; mp 49.5−50.5 °C (hexane); $[\alpha]^{28}_D$ −31.2° (*c* 0.61, $CHCl_3$); IR, ^1H NMR, and MS spectra were identical to those of **2** derived from **1**; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 16.1 (q), 18.6 (q), 34.6 (d), 52.1 (q), 75.9 (d), 127.3 (d), 145.7 (s), 161.7 (s), 176.9 (s). Anal. Calcd for $C_9H_{13}NO_3S$: C, 50.22; H, 6.09; N, 6.50. Found: C, 50.28; H, 6.01; N, 6.45.

(*R*)-2,2-Dimethyl-1,3-dioxolane-4-thiocarboxamide (7). Method A using the Lawesson reagent: to a stirred solution of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxamide (**6**)[10] (146 mg, 1.01 mmol) in benzene (4.0 mL) was added the Lawesson reagent[11] (247 mg, 0.611 mg), and the mixture was stirred at 70 °C for 1.3 h. After cooling, the reaction mixture was poured into a mixture of saturated aqueous $NaHCO_3$ (5 mL) and ice (5 g), and the aqueous mixture was then extracted with ether (4 × 13 mL). The combined organic layers were washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated to give an oil, which was purified by column chromatography with 7:2 hexane/acetone providing thioamide **7** (100 mg, 62% yield, 0% ee) as crystals: colorless plates; mp 95−96 °C (hexane/benzene); $[\alpha]^{27}_D$ 0° (*c* 0.69, $CHCl_3$). The enantiomeric excess

of **7** was determined by ^{1}H NMR measurement in $CDCl_3$ in the presence of 0.3 mol equiv of tris[3-[(heptafluoropropyl)-hydroxymethylene]-(+)-camphorato]europium(III): the oxymethine signals due to the *R*-enantiomer (δ 4.79) and the *S*-enantiomer (δ 4.86) were observed separately.

Method B using the Belleau reagent: using the procedure described for method A, amide **6** (20.4 mg, 0.141 mmol) was subjected to thionation with the Belleau reagent[12] (44 mg, 0.083 mmol) in THF (1.2 mL) at 0 °C for 1.5 h to afford thioamide **7** (19.3 mg, 85% yield, 94% ee) as crystals: colorless plates; mp 76–77 °C (hexane/CH_2Cl_2); R_f = 0.68 (2:1 hexane/acetone); $[\alpha]^{27}_D$ +71.2° (*c* 0.82, $CHCl_3$); IR ($CHCl_3$) 3480, 3355, 3160, 1585, 1410, 1385, 1065 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.44 (s, 3 H), 1.49 (s, 3 H), 4.10 (dd, *J* = 8.9, 6.3 Hz, 1 H), 4.47 (dd, *J* = 8.9, 7.6 Hz, 1 H), 4.86 (dd, *J* = 7.6, 6.3 Hz, 1 H), 7.30–8.20 (br, 2 H).

(*R*)-2,3-Diacetoxypropanamide (8). To a stirred solution of amide **6** (201 mg, 1.39 mmol) in 4:1 THF/water (6.25 mL) at 0 °C was added TFA (0.25 mL, 3.3 mmol). The solution was gradually warmed to ambient temperature over 12 h with stirring. After additional stirring for 60 h, TFA (0.25 mL, 3.3 mmol) was added and the solution was stirred for 4 h at ambient temperature. The reaction mixture was concentrated to give diol (184 mg) as colorless crystals, which was used without further purification. To a stirred solution of the above diol (184 mg) in pyridine (2.0 mL) at 0 °C was added acetic anhydride (2.0 mL). After being stirred at 0 °C for 1.5 h, the reaction mixture was concentrated. The residual solid was purified by column chromatography (3:2 hexane/acetone) to give diacetate **8** (250 mg, 95%) as crystals: colorless needles; mp 90–91 °C (benzene/MeOH); R_f = 0.75 (3:1 $CHCl_3$/MeOH); $[\alpha]^{29}_D$ +1.6° (*c* 1.22, $CHCl_3$); IR ($CHCl_3$) 3530, 3495, 3400, 1745, 1700, 1575, 1230 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.07 (s, 3 H), 2.18 (s, 3 H), 4.40 (dd, *J* = 12.2, 5.0 Hz, 1 H), 4.81 (dd, *J* = 12.2, 3.0 Hz, 1 H), 5.41 (dd, *J* = 5.0, 3.0 Hz, 1 H), 5.68 (br s, 1H), 6.16 (br s, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.6 (q), 20.7 (q), 62.9 (t), 71.5 (d), 169.4 (s), 169.8 (s), 170.6 (s); CIMS *m/z* (relative intensity) 190 (MH^+, 32), 173 (7), 158 (5), 148 (100), 145 (6), 130 (68). Anal. Calcd for $C_7H_{11}NO_5$: C, 44.45; H, 5.86; N, 7.40. Found: C, 44.66; H, 5.57; N, 7.29.

(*R*)-2,3-Diacetoxypropanethioamide (9). Method C using the Lawesson reagent: using the procedure described for the preparation of thioamide **7** (method A), diacetate **8** (19.1 mg, 0.101 mmol) was subjected to thionation with the Lawesson reagent (26.5 mg, 0.066 mmol) in benzene (1.6 mL). Crude product was purified by column chromatography (4:3 hexane/EtOAc), to provide thioamide **9** (19.1 mg, 92% yield, 96% ee) as crystals. The optical purity of **9** was determined by chiral HPLC analysis using a CHIRALCEL OD column (4.6 × 250 mm) (9:1 hexane/2-propanol, flow rate 1.0 mL/min, detection at 254 nm). The racemic compound (±)-**9** prepared from (±)-**7** (method A) showed two peaks: t_R = 33.3 min (*R*-enantiomer) and 37.2 min (*S*-enantiomer).

Method D using the Belleau reagent: using the procedure described for the preparation of thioamide **7** (method B), diacetate **8** (190 mg, 1.00 mmol) was subjected to thionation with the Belleau reagent (316 mg, 0.598 mmol) in THF (10 mL) at 0 °C for 45 min and then at ambient temperature for 2.3 h to afford **9** (201 mg, 97% yield, ≥99% ee): colorless needles; mp 78–78.5 °C (benzene/MeOH); $[\alpha]^{29}_D$ +51.2° (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 3490, 3440, 3375, 1745, 1595, 1230 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.07 (s, 3 H), 2.19 (s, 3 H), 4.51 (dd, *J* = 12.2, 4.9 Hz, 1 H), 4.68 (dd, *J* = 12.2, 3.0 Hz, 1 H), 5.76 (dd, *J* = 4.9, 3.0 Hz, 1 H), 7.51 (br s, 2 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.6 (q), 20.8 (q), 64.8 (t), 76.8 (d), 169.3 (s), 170.7 (s), 200.1 (s); EIMS *m/z* (relative intensity) 205 (M^+, 65), 145 (71), 141 (4), 120 (17), 103 (100). Anal. Calcd for $C_7H_{11}NO_4S$: C, 40.97; H, 5.40; N, 6.82. Found: C, 41.00; H, 5.13; N, 6.73.

Ethyl (*R*)-2-(1,2-Diacetoxyethyl)thiazole-4-carboxylate (10). To a stirred solution of thioamide **9** (158 mg, 0.770 mmol) in acetone (1.2 mL) at −10 °C was added ethyl bromopyruvate (0.12 mL, 0.80 mmol), and stirring was continued for 80 min. The reaction mixture was then poured into a well-stirred mixture of $CHCl_3$ (4 mL) and saturated aqueous $KHCO_3$ (4 mL). The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 2 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was immediately dissolved in CH_2Cl_2 (1.0 mL). The solution was cooled to −20 °C, and pyridine (0.14 mL, 1.7 mmol) and trifluoroacetic anhydride (0.12 mL, 0.85 mmol) were added with stirring. The temperature of the solution was allowed to rise to 0 °C over a 3-h period. The mixture was then poured into a well-stirred mixture of $CHCl_3$ (4 mL) and saturated aqueous $KHCO_3$ (4 mL). The organic phase was separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 4 mL). The combined organic layers were washed with 1 M $KHSO_4$ (4 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography (3:1 hexane/EtOAc) to give thiazole **10** (160 mg, 69% yield) as a colorless oil. The optical purity of **10** was determined to be 86% ee by chiral HPLC analysis under the conditions used for **9**: t_R = 27.0 min for **10** and 19.0 min for *ent*-**10**. **10**: R_f = 0.59 (1:1 hexane/acetone); $[\alpha]^{29}_D$ +44.6° (*c* 0.89, $CHCl_3$); IR ($CHCl_3$) 3130, 1750, 1370, 1230 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.40 (t, *J* = 7.3 Hz, 3 H), 2.05 (s, 3 H), 2.17 (s, 3 H), 4.43 (q, *J* = 7.3 Hz, 2 H), 4.49 (dd, *J* = 12.2, 6.3 Hz, 1 H), 4.72 (dd, *J* = 12.2, 3.3 Hz, 1 H), 6.35 (dd, *J* = 6.3, 3.3 Hz, 1 H), 8.18 (s, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.1 (q), 20.4 (q), 20.5 (q), 61.3 (t), 64.1 (t), 70.5 (d), 127.9 (d), 147.2 (s), 160.8 (s), 166.3 (s), 169.1 (s), 170.0 (s); EIMS *m/z* (relative intensity) 301 (M^+, 2), 256 (11), 229 (9), 216 (10), 199 (100), 187 (48); HREIMS calcd for $C_{10}H_{10}NO_5S$ *m/z* 256.0279 (M-EtO)$^+$, found 256.0284.

Synthesis of 3. To a stirred solution of thiazole **10** (89.0 mg, 0.296 mmol) in MeOH (15 mL) at 0 °C was added a 1.0 M solution of NaOMe in MeOH (0.24 mL). After being stirred at ambient temperature for 1 h, an acidic ion-exchange resin (Amberlite IRC-50, H^+ form, 2 g) was added to the reaction mixture and the mixture was stirred for 3 min. The mixture was poured on a pad of the same resin (2 g). The resin was washed with MeOH several times, and the filtrate and washings were combined and concentrated to give crude crystals of methyl ester **3**. Recrystallization from benzene/MeOH gave optically pure **3** (39.6 mg, 66%). The optical purity of synthetic **3** was determined to be ≥99% ee by chiral HPLC analysis using a CHIRALCEL OD column (4.6 × 250 mm) (4:1 hexane/2-propanol, flow rate 1.0 mL/min, detection at 254 nm): t_R = 21.9 min for **3** and 16.9 min for *ent*-**3**. **3**: colorless needles; mp 199–200 °C; $[\alpha]^{25}_D$ +60.6° (*c* 0.051, MeOH); IR, ^{1}H NMR, and MS spectra were identical to those of methyl ester **3** derived from dolabellin (**1**); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 51.9 (q), 65.8 (t), 72.1 (d), 128.9 (d), 145.5 (s), 161.4 (s), 175.7 (s). Anal. Calcd for $C_7H_9NO_4S$: C, 41.37; H, 4.46; N, 6.89. Found: C, 41.72; H, 4.24; N, 6.73.

(4*R*,5*S*)-3-[(2*R*,3*S*)-3-Hydroxy-2-methyloctanoyl]-4-methyl-5-phenyl-2-oxazolidinone (12). To a stirred solution of (4*R*,5*S*)-4-methyl-5-phenyl-3-propionyl-2-oxazolidinone (**11**)[13] (126 mg, 0.542 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C were added dibutylboron triflate (1.0 M solution in CH_2Cl_2, 0.60 mL) and triethylamine (0.11 mL, 0.79 mmol), successively. After 30 min, the solution was cooled to −78 °C and hexanal (0.075 mL, 0.62 mmol) was added. The reaction mixture was kept at −78 °C for 1.5 h and then at 0 °C for 30 min and diluted with 0.5 M phosphate buffer (pH 7, 1.2 mL) and MeOH (2.4 mL) at 0 °C. To the mixture cooled to −10 °C was added a mixture of 30% aqueous H_2O_2 (1.2 mL) and MeOH (3 mL) dropwise. The mixture was stirred at 0 °C for 1 h and diluted with saturated aqueous $Na_2S_2O_5$ (2 mL). The mixture was concentrated, and the resulting aqueous solution was extracted with ether (4 × 6 mL). The combined organic extracts were washed with 5% aqueous $NaHCO_3$ (5 mL) and saturated aqueous NaCl (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography (7:1 then 6:1 hexane/EtOAc) to give aldol **12** (129 mg, 71%) as crystals. The diastereoselectivity of the product was shown to be 98:2 by ^{13}C NMR analysis. Single recrystallization from hexane gave optically pure **12**: colorless needles; mp 90.5–91.5 °C; R_f = 0.40 (3:1 hexane/EtOAc); $[\alpha]^{19}_D$ +29.4° (*c* 0.602, $CHCl_3$); IR ($CHCl_3$) 3540 (br), 1780, 1685, 1460, 1365, 1345, 1235, 1195 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.90 (m, 6 H), 1.23 (d, *J* = 6.9 Hz, 3 H), 1.28–1.60 (m, 8 H), 2.87 (br s, 1H; OH), 3.78 (dq, *J* = 2.6, 6.9 Hz, 1 H), 3.97 (m, 1 H, changes to ddd, *J* =

8.4, 4.3, 2.6 Hz upon addition of D_2O), 4.79 (dq, J = 7.3, 6.9 Hz, 1 H), 5.67 (d, J = 7.3 Hz, 1 H), 7.27–7.48 (m, 5 H); EIMS m/z (relative intensity) 333 (M^+, 1), 315 (6), 262 (100), 178 (7), 134 (9), 118 (20). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.17; H, 8.03; N, 4.15.

(4*R*,5*S*)-3-[(2*R*,3*R*)-3-[(4-Nitrobenzoyl)oxy]-2-methyloctanoyl]-4-methyl-5-phenyl-2-oxazolidinone (13). To a stirred solution of aldol **12** (41.3 mg, 0.124 mmol), triphenylphosphine (222 mg, 0.846 mmol), and *p*-nitrobenzoic acid (138 mg, 0.826 mmol) in benzene (3.3 mL) was added a solution of diethyl azodicarboxylate (0.13 mL, 0.85 mmol) in benzene (0.67 mL) at ambient temperature. After being stirred for 9 h at ambient temperature, the reaction mixture was concentrated. The residual oil was purified by column chromatography (step gradient from 15:1 to 8:1 hexane/acetone) to give *p*-nitrobenzoate **13** (41.8 mg, 70%) as a colorless oil: R_f = 0.31 (6:1 hexane/acetone); $[\alpha]^{19}_D$ −18.6° (*c* 1.29, $CHCl_3$); IR ($CHCl_3$) 1780, 1725, 1700, 1605, 1530, 1345, 1275 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.85 (d, J = 6.6 Hz, 3 H), 0.88 (m, 3 H), 1.29 (d, J = 6.9 Hz, 3 H), 1.32–1.64 (m, 6 H), 1.66–1.94 (m, 2 H), 4.28 (dq, J = 8.3, 6.9 Hz, 1 H), 4.66 (dq, J = 7.3, 6.6 Hz, 1 H), 5.43 (d, J = 7.3 Hz, 1 H), 5.52 (ddd, J = 8.3, 7.6, 3.3 Hz, 1 H), 7.22–7.44 (m, 5 H), 8.20–8.33 (m, 4 H); EIMS m/z (relative intensity) 482 (M^+, 10), 382 (5), 315 (67), 244 (44), 182 (19), 150 (100), 134 (76), 118 (22), 104 (21); HREIMS calcd for $C_{26}H_{30}N_2O_7$ m/z 482.2053, found 482.2059.

Methyl (2*R*,3*S*)-3-Hydroxy-2-methyloctanoate (14a). To a stirred solution of aldol **12** (26 mg, 0.078 mmol) in 4:1 THF/water (4 mL) at 0 °C were added 30% aqueous H_2O_2 (0.035 mL, 0.31 mmol) and aqueous LiOH (5 M solution, 0.025 mL, 0.13 mmol), and the mixture was stirred for 2 h at 0 °C. Aqueous $Na_2S_2O_3$ (0.75 M solution, 0.25 mL, 0.19 mmol) was added and the mixture was washed with CH_2Cl_2 (4 × 1 mL). The aqueous layer was acidified (ca. pH 1) with 6 M HCl and extracted with CH_2Cl_2 (4 × 1 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated. The residue was dissolved in ether (1.5 mL) and treated with a solution of diazomethane in ether at ambient temperature. The reaction mixture was evaporated and the residual oil was purified by column chromatography (2:1 hexane/ether) to give methyl ester **14a** (12.3 mg, 84%) as a colorless oil: R_f = 0.58 (3:1 hexane/EtOAc); $[\alpha]^{22}_D$ −10° (*c* 0.40, $CHCl_3$); IR ($CHCl_3$) 3550 (br), 1720, 1460, 1440, 1175 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.89 (t, J = 6.6 Hz, 3 H), 1.18 (d, J = 7.3 Hz, 3 H), 1.20–1.54 (m, 8 H), 2.46 (br s, 1 H; OH), 2.55 (dq, J = 3.6, 7.3 Hz, 1 H), 3.71 (s, 3 H), 3.89 (m, 1 H, changes to ddd, J = 7.9, 3.9, 3.6 Hz upon addition of D_2O); FABMS (addition of NaI) m/z (relative intensity) 211 (MNa^+, 61), 173 (100); HRFABMS calcd for $C_{10}H_{20}O_3Na$ m/z 211.1310 (MNa^+), found 211.1299.

Methyl (2*R*,3*R*)-3-Hydroxy-2-methyloctanoate (14b). Using a procedure similar to that described for the preparation of **14a**, *p*-nitrobenzoate **13** (21.7 mg, 0.045 mmol) was hydrolyzed with 30% aqueous H_2O_2 (0.02 mL, 0.2 mmol) and aqueous LiOH (5 M solution, 0.03 mL, 0.15 mmol) at 0 °C for 3 h and then at ambient temperature for 18 h. After methylation with diazomethane, the crude product was purified by column chromatography (7:1 and then 5:1 hexane/EtOAc) to give methyl ester **14b** (6.8 mg, 80%) as a colorless oil: R_f = 0.38 (3:1 hexane/EtOAc); $[\alpha]^{22}_D$ −4° (*c* 0.12, $CHCl_3$); IR ($CHCl_3$) 3520 (br), 1720, 1460, 1440, 1175 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.89 (m, 3 H), 1.21 (d, J = 6.9 Hz, 3 H), 1.24–1.54 (m, 8 H), 2.50 (br s, 1 H; OH), 2.54 (dq, J = 6.3, 6.9 Hz, 1 H), 3.65 (m, 1 H, changes to ddd, J = 7.9, 6.3, 3.4 Hz upon addition of D_2O), 3.71 (s, 3 H); FABMS (addition of NaI) m/z (relative intensity) 211 (MNa^+, 40), 173 (100); HRFABMS calcd for $C_{10}H_{20}O_3Na$ m/z 211.1310 (MNa^+), found 211.1330.

5,5-Dichlorohexanal (15). The starting material, 6,6-dichloro-1-heptene[16] was prepared using the procedure of Normant and co-workers:[19] ^1H NMR ($CDCl_3$) δ 1.78 (m, 2 H), 2.07–2.26 (m, 4 H), 2.15 (s, 3 H), 4.95–5.12 (m, 2 H), 5.81 (dddd, J = 16.8, 10.2, 6.6, 6.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.9 (t), 32.9 (t), 37.4 (q), 49.2 (t), 90.7 (s), 115.4 (t), 137.8 (d).

(19) Villieras, J.; Perriot, P.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1979**, 765–768.

A stream of ozone gas was passed through a solution of 6,6-dichloro-1-heptene (1.84 g, 11.1 mmol) in CH_2Cl_2 (30 mL) at −78 °C until a persistent blue color was observed in the solution. The solution was then flushed with nitrogen, and acetic acid (12 mL) and zinc powder (3.5 g, 54 mmol) were added. The mixture was stirred at 0 °C for 1 h and then filtered. Water (20 mL) was added to the filtrate and the mixture was extracted with ether (2 × 100 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (3 × 20 mL) and saturated aqueous NaCl (20 mL), dried ($MgSO_4$), and concentrated. Bulb-to-bulb distillation (bp 100 °C, ca. 3 Torr) afforded aldehyde **15** (1.24 g, 66%) as a colorless liquid: R_f = 0.43 (5:1 hexane/EtOAc); IR ($CHCl_3$) 2830, 2730, 1730 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.04 (m, 2 H), 2.17 (s, 3 H), 2.40 (m, 2 H), 2.55 (dt, J = 1.3, 6.9 Hz, 2 H), 9.80 (t, J = 1.3 Hz, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 18.3 (t), 37.3 (q), 42.8 (t), 48.7 (t), 90.0 (s), 201.3 (d); EIMS m/z (relative intensity) 132 [$(M - HCl)^+$, 5], 115 (30), 97 (100); HREIMS calcd for $C_6H_9{}^{35}ClO$ m/z 132.0342 $(M - HCl)^+$, found 132.0364.

(4*R*,5*S*)-3-[(2*R*,3*S*)-7,7-Dichloro-3-hydroxy-2-methyloctanoyl]-4-methyl-5-phenyl-2-oxazolidinone (16). To a stirred solution of oxazolidinone **11**[13] (353 mg, 1.52 mmol) in CH_2Cl_2 (3.5 mL) at −78 °C were added dibutylboron triflate (1.0 M solution in CH_2Cl_2, 1.70 mL) and triethylamine (0.30 mL, 2.2 mmol), successively. The temperature of the mixture was maintained at −78 °C for 30 min and then at 0 °C for 1 h. The mixture was again cooled to −78 °C, and a solution of freshly distilled aldehyde **15** (171 mg, 1.02 mmol) in CH_2Cl_2 (1.5 mL + 2 × 1.0 mL rinse) was added. The reaction temperature was kept at −78 °C for 30 min and then at 0 °C for 1.5 h. The mixture was diluted with 0.5 M phosphate buffer (pH 7, 3.8 mL) at 0 °C. MeOH (11.4 mL) and 30% aqueous H_2O_2 (1.9 mL) were added, and the mixture was stirred for 1 h at 0 °C. The mixture was concentrated, and the resulting aqueous solution was extracted with CH_2Cl_2 (60 mL + 2 × 30 mL). The combined extracts were washed with saturated aqueous NaCl (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography (5:1 hexane/EtOAc) to give aldol **16** (377 mg, 92%) as crystals. The diastereoselectivity of the product was shown to be 95:5 by ^{13}C NMR analysis. Single recrystallization from hexane/CH_2Cl_2 gave optically pure **16**: colorless needles; mp 139–140 °C; R_f = 0.38 (3:1 hexane/EtOAc); $[\alpha]^{24}_D$ +13.2° (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 3550 (br), 1780, 1690, 1460, 1370, 1345, 1235, 1200 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 3 H), 1.25 (d, J = 6.9 Hz, 3 H), 1.4–2.0 (m, 4 H), 2.16 (s, 3 H), 2.26 (m, 2 H), 2.93 (d, J = 3.4 Hz, 1 H; OH), 3.79 (dq, J = 2.6, 6.9 Hz, 1 H), 4.05 (m, 1 H, changes to ddd, J = 8.9, 4.2, 2.6 Hz upon addition of D_2O), 4.81 (dq, J = 7.3, 6.6 Hz, 1 H), 5.69 (d, J = 7.3 Hz, 1 H), 7.28–7.49 (m, 5 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 10.5 (q), 14.2 (q), 22.3 (t), 33.1 (t), 37.1 (q), 42.4 (d), 49.4 (t), 54.6 (d), 71.2 (d), 78.8 (d), 90.6 (s), 125.5 (d, 2 C), 128.6 (d), 128.7 (d, 2 C), 133.0 (s), 152.5 (s), 176.7 (s); FABMS m/z (relative intensity) 402/404/406 (MH^+, 100:67:15), 384 (40), 366 (5). Anal. Calcd for $C_{19}H_{25}Cl_2NO_4$: C, 56.72; H, 6.26; N, 3.48. Found: C, 56.78; H, 6.42; N, 3.39.

(2*R*,3*S*)-3-(*tert*-Butyldimethylsiloxy)-7,7-dichloro-2-methyloctanoic Acid (17). To a stirred solution of aldol **16** (235 mg, 0.585 mmol) in 4:1 THF/water (10 mL) at 0 °C were added 30% aqueous H_2O_2 (0.27 mL, 2.6 mmol) and $LiOH{\cdot}H_2O$ (73.6 mg, 1.76 mmol). The mixture was stirred for 1 h at 0 °C. Powdered $Na_2S_2O_3{\cdot}5H_2O$ (290 mg, 1.17 mmol) was then added, and the mixture was stirred for an additional 20 min. After adding CH_2Cl_2 (40 mL) and saturated aqueous NaCl (10 mL), the mixture was acidified (ca. pH 2) with 10% aqueous citric acid, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The organic layer and extracts were combined, dried ($MgSO_4$), and concentrated. The residue was dissolved in CH_2Cl_2 (3.0 mL) and cooled to 0 °C. Triethylamine (0.82 mL, 5.9 mmol) and *tert*-butyldimethylsilyl triflate (0.67 mL, 2.9 mmol) were added with stirring, and the mixture continued to be stirred for 3 h at 0 °C. Then, K_2CO_3 (808 mg, 5.85 mmol), water (7 mL), MeOH (15 mL), and THF (14 mL) were added, and the mixture was stirred for 2 h at 40 °C. To the solution were added $CHCl_3$

(80 mL) and saturated aqueous NaCl (10 mL) were added to the solution, and the mixture was acidified (ca. pH 2) with 10% aqueous citric acid. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (2 × 50 mL). The organic layer and extracts were combined, dried ($MgSO_4$), and concentrated. The residual oil was purified by column chromatography (5:1 hexane/EtOAc) to give acid **17** (203 mg, 97%) as a colorless oil: $R_f = 0.58$ (2:1 hexane/acetone); $[\alpha]^{27}_D$ −18.6° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3100 (br), 1760, 1710, 1380, 1360, 1260 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.11 (s, 3 H), 0.14 (s, 3 H), 0.91 (s, 9 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 1.48−1.88 (m, 4 H), 2.15 (s, 3 H), 2.19 (m, 2 H), 2.65 (dq, *J* = 4.6, 6.9 Hz, 1 H), 3.99 (ddd, *J* = 6.8, 5.0, 4.6 Hz, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −4.7 (q), −4.3 (q), 11.0 (q, 3 C), 18.0 (s), 21.7 (t), 25.8 (q), 34.1 (t), 37.4 (q), 44.6 (d), 49.8 (t), 73.0 (d), 90.4 (s), 181.0 (s); FABMS *m/z* (relative intensity) 357/359/361 (MH^+, 100: 75:16), 339 (46), 321 (25); HRFABMS calcd for $C_{15}H_{31}{}^{35}Cl_2O_3Si$ *m/z* 357.1419 $(MH)^+$, found 357.1429.

Methyl 2-[(*S*)-1-[[(2*R*,3*S*)-3-(*tert*-Butyldimethylsiloxy)-7,7-dichloro-2-methyloctanoyl]oxy]-2-methylpropyl]thiazole-4-carboxylate (18). To a stirred solution of methyl ester **2** (35.3 mg, 0.164 mmol), acid **17** (47.6 mg, 0.134 mmol), DMAP (6.4 mg, 0.052 mmol), and 10-camphorsulfonic acid (6.3 mg, 0.027 mmol) in CH_2Cl_2 (0.60 mL) at 0 °C was added DCC (32.4 mg, 0.157 mmol). The mixture was stirred at 0 °C for 2 h and then at ambient temperature for 4.5 h. The mixture was diluted with 1:1 hexane/EtOAc (3 mL) and filtered through a small plug of cotton. The solid was washed with 1:1 hexane/EtOAc (3 mL). The filtrate and washings were combined and diluted with 1:1 hexane/EtOAc (24 mL). The solution was washed in succession with 10% aqueous citric acid (3 mL), water (3 mL), saturated aqueous $NaHCO_3$ (3 mL), water (3 mL), and saturated aqueous NaCl (3 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography (6:1 hexane/EtOAc) to give ester **18** (72.2 mg, 98% yield) as a colorless oil; $R_f = 0.60$ (2:1 hexane/acetone); $[\alpha]^{28}_D$ −31.7° (*c* 0.774, $CHCl_3$); IR ($CHCl_3$) 3130, 1740, 1460, 1245, 1220 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (s, 3 H), 0.08 (s, 3 H), 0.88 (s, 9 H), 0.97 (d, *J* = 6.6 Hz, 6 H), 1.22 (d, *J* = 6.9 Hz, 3 H), 1.50−1.86 (m, 4 H), 2.14 (s, 3 H), 2.16 (m, 2 H), 2.44 (dqq, *J* = 5.3, 6.9, 6.6 Hz, 1 H), 2.74 (dq, *J* = 6.6, 6.9 Hz, 1 H), 3.95 (s, 3 H), 3.97 (m, 1 H), 6.01 (d, *J* = 5.3 Hz, 1 H), 8.14 (s, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −4.5 (q), −4.3 (q), 13.3 (q), 17.1 (q), 18.0 (s), 18.6 (q), 20.9 (t), 25.7 (q), 33.3 (d), 34.1 (t), 37.3 (q, 3 C), 45.0 (d), 49.8 (t), 52.3 (q), 72.9 (d), 77.1 (d), 90.4 (s), 127.2 (d), 146.8 (s), 161.6 (s), 170.5 (s), 173.5 (s); FABMS *m/z* (relative intensity) 554/556/558 (MH^+, 10:9:2), 518 (2); HRFABMS calcd for $C_{24}H_{42}{}^{35}Cl_2NO_5SSi$ *m/z* 554.1930 $(MH)^+$, found 554.1955.

Methyl 2-[(*S*)-1-[[(2*R*,3*S*)-7,7-Dichloro-3-hydroxy-2-methyloctanoyl]oxy]-2-methylpropyl]thiazole-4-carboxylate (19). To a stirred solution of ester **18** (67.6 mg, 0.122 mmol) in acetonitrile (2.7 mL) at ambient temperature was added 47% hydrofluoric acid (0.30 mL, 8.1 mmol). After being stirred at ambient temperature for 20 h, the reaction mixture was poured into a mixture of ice (15 g) and saturated aqueous $NaHCO_3$ (15 mL), and the resulting mixture was extracted with ether (30 mL, 2 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography (4:1 hexane/acetone) to give alcohol **19** (53.3 mg, 99%) as a colorless oil; $R_f = 0.19$ (4:1 hexane/acetone); $[\alpha]^{27}_D$ −33.9° (*c* 1.16, $CHCl_3$); IR ($CHCl_3$) 3450 (br), 3130, 1730, 1245, 1230 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.97 (d, *J* = 6.9 Hz, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H), 1.27 (d, *J* = 7.3 Hz, 3 H), 1.40−2.02 (m, 4 H), 2.16 (s, 3 H), 2.24 (m, 2 H), 2.43 (dqq, *J* = 5.3, 6.9, 6.9 Hz, 1 H), 2.66 (dq, *J* = 3.6, 7.3 Hz, 1 H), 3.80 (d, *J* = 4.6 Hz, 1 H; OH), 3.95 (s, 3 H), 4.01 (m, 1 H, changes to ddd, *J* = 8.9, 5.0, 3.6 Hz upon addition of D_2O), 6.10 (d, *J* = 5.3 Hz, 1 H), 8.16 (s, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 10.4 (q), 16.8 (q), 18.7 (q), 22.4 (t), 33.2 (t), 33.4 (d), 37.2 (q), 45.0 (d), 49.4 (t), 52.3 (q), 71.4 (d), 77.2 (d), 90.5 (s), 127.4 (d), 146.6 (s), 161.5 (s), 170.1 (s), 174.5 (s); FABMS *m/z* (relative intensity) 440/442/444 (MH^+, 45:26:8), 404 (5); HRFABMS calcd for $C_{18}H_{28}{}^{35}Cl_2NO_5S$ *m/z* 440.1065 $(MH)^+$, found 440.1035.

Methyl (*R*)-2-[4-(2,2-Dimethyl-1,3-dioxolanyl)]thiazole-4-carboxylate (20). To a stirred suspension of methyl ester **3** (44.1 mg, 0.202 mmol) in acetone (2.0 mL) at ambient temperature were added 2,2-dimethoxypropane (1.0 mL, 8.2 mmol) and 10-camphorsulfonic acid (4.5 mg, 0.019 mmol). The mixture was stirred at ambient temperature for 6 h, diluted with saturated aqueous $NaHCO_3$ (2 mL), and extracted with ether (4 × 4 mL). The combined extracts were washed with saturated aqueous NaCl (2 mL), dried (Na_2SO_4), and concentrated. The residual solid was purified by column chromatography (2.5:1 and then 2:1 hexane/EtOAc) twice to give acetonide **20**[18] (45.8 mg, 93%) as crystals: colorless needles; mp 80−80.5 °C (hexane) (lit.[18] mp 78.5−79 °C); $R_f = 0.53$ (2:1 hexane/acetone); $[\alpha]^{27}_D$ +55.5° (*c* 0.45, CH_2Cl_2) (lit.[18] $[\alpha]_D$ +55.6° (CH_2Cl_2)); IR ($CHCl_3$) 3130, 1730, 1245, 1225 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.47 (s, 3 H), 1.60 (s, 3 H), 3.96 (s, 3 H), 4.09 (dd, *J* = 8.6, 5.0 Hz, 1 H), 4.47 (dd, *J* = 8.6, 6.6 Hz, 1 H), 5.42 (qd, *J* = 6.6, 5.0 Hz, 1 H), 8.16 (s, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 24.9 (q), 26.3 (q), 52.3 (q), 70.2 (t), 75.2 (d), 111.1 (s), 127.6 (d), 146.9 (s), 161.6 (s), 173.5 (s); CIMS *m/z* (relative intensity) 244 (MH^+, 23), 228 (85), 212 (11), 186 (100), 154 (72). Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.39; N, 5.76. Found: C, 49.58; H, 5.34; N, 5.62.

Dolabellin Acetonide (22). To a stirred solution of acetonide **20** (28.7 mg, 0.118 mmol) in MeOH (1.0 mL) was added 2 M NaOH (0.15 mL) at 0 °C. After being stirred at 0 °C for 2 h and then at ambient temperature for 2.5 h, the solution was again cooled to 0 °C and acidified (ca. pH 3) with 5% aqueous $KHSO_4$. The aqueous mixture was extracted with EtOAc (6 mL, 3 × 4 mL). The combined organic layers were washed with saturated aqueous NaCl (2 mL), dried (Na_2SO_4), and concentrated to give crude acid **21** (26.7 mg) as a solid, which was used without purification.

Using the procedure described for the preparation of ester **18**, alcohol **19** (36.5 mg, 0.083 mmol) and the above crude acid **21** (26.7 mg, 0.118 mmol) were coupled in the presence of DCC (30.2 mg, 0.146 mmol), DMAP (5.9 mg, 0.048 mmol), and 10-camphorsulfonic acid (5.8 mg, 0.025 mmol). The crude product was purified by column chromatography (12:1 benzene/acetone) twice followed by preparative TLC (200 × 100 mm, 1 mm layer thickness, 2 plates, 1:1 benzene/ether) to give ester **22** (46.0 mg, 85%) as crystals: colorless needles; mp 112−114 °C (hexane/CH_2Cl_2); $R_f = 0.50$ (2:1 benzene/ether); $[\alpha]^{24}_D$ +3.6° (*c* 0.87, $CHCl_3$); IR ($CHCl_3$) 3130, 1735, 1245, 1230 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.9 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 1.31 (d, *J* = 7.3 Hz, 3 H), 1.47 (s, 3 H), 1.59 (s, 3 H), 1.66−1.94 (m, 4 H), 2.12 (s, 3 H), 2.22 (m, 2 H), 2.44 (dqq, *J* = 5.6, 6.9, 6.6 Hz, 1 H), 3.00 (dq, *J* = 6.9, 7.3 Hz, 1 H), 3.95 (s, 3 H), 4.10 (dd, *J* = 8.9, 5.0 Hz, 1 H), 4.46 (dd, *J* = 8.9, 6.6 Hz, 1 H), 5.41 (dd, *J* = 6.6, 5.0 Hz, 1 H), 5.46 (m, 1 H), 5.99 (d, *J* = 5.6 Hz, 1 H), 8.14 (s, 1 H), 8.15 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 12.5 (q), 16.9 (q), 18.3 (q), 21.4 (t), 24.8 (q), 26.2 (q), 31.0(t), 33.0 (d), 37.1 (q), 43.2 (d), 48.8 (t), 52.1 (q), 70.0 (t), 74.3 (d), 75.0 (d), 77.4 (d), 90.0 (s), 110.9 (s), 127.2 (d), 127.6 (d), 146.5 (s), 146.6 (s), 160.2 (s), 161.3 (s), 169.7 (s), 171.9 (s), 173.4 (s); FABMS *m/z* (relative intensity) 651/653/655 (MH^+, 50:40:11), 615 (4). Anal. Calcd for $C_{27}H_{36}Cl_2N_2O_8S_2$: C, 49.77; H, 5.57; N, 4.30. Found: C, 50.10; H, 5.80; N, 4.33.

Dolabellin (1). To a stirred solution of ester **22** (42.1 mg, 0.064 mmol) in MeOH (2.0 mL) at ambient temperature was added *p*-toluenesulfonic acid monohydrate (2.2 mg, 0.012 mmol). After being stirred at ambient temperature for 20 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (1 mL). The aqueous mixture was extracted with EtOAc (10 mL, 3 × 5 mL). The combined organic layers were washed with water (3 mL) and saturated aqueous NaCl (3 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography (5:1 hexane/acetone) to give dolabellin (**1**, 37.4 mg, 95%) as a colorless oil. This compound showed a single peak in HPLC analysis (for the HPLC conditions, see the section for the isolation of **1**) and was identical to natural **1** by HPLC coinjection. Synthetic **1**: $[\alpha]^{24}_D$ −7.4° (*c* 0.38, $CHCl_3$); IR, ^1H and ^{13}C NMR, and FABMS spectra were identical to those of **1**.

Dechlorodolabellin (23). Using the procedure for the synthesis of dolabellin (**1**), dechlorodolabellin (**23**) was synthesized from aldol **12** as a colorless oil in seven steps and in 32% overall yield: $R_f = 0.28$ (2:1 hexane/acetone); $[\alpha]^{22}_D$ −3.7° (*c* 0.27, $CHCl_3$); IR ($CHCl_3$) 3430 (br), 3130, 1735, 1230, 1100 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.86 (m, 3 H), 0.94 (d, J = 6.9 Hz, 3 H), 0.95 (d, J = 6.9 Hz, 3 H), 1.29 (d, J = 6.9 Hz, 3 H), 1.20−1.40 (m, 4 H), 1.60−1.90 (m, 2 H), 2.43 (dqq, J = 5.6, 6.9, 6.9 Hz, 1 H), 2.68 (br s, 1 H; OH), 2.95 (dq, J = 5.6, 6.9 Hz, 1 H), 3.65 (br s, 1 H; OH), 3.94 (s, 3 H), 4.01 (m, 1 H, changes to dd, J = 11.6, 5.3 Hz upon addition of D_2O), 4.08 (m, 1 H, changes to dd, J = 11.6, 4.0 Hz upon addition of D_2O), 5.10 (m, 1 H, changes to dd, J = 5.3, 4.0 Hz upon addition of D_2O), 5.45 (ddd, J = 8.3, 5.6, 5.3 Hz, 1 H), 5.97 (d, J = 5.6 Hz, 1 H), 8.10 (s, 1 H), 8.13 (s, 1 H); ^{13}C NNR (67.8 MHz, $CDCl_3$) δ 12.2 (q), 14.0 (q), 17.2 (q), 18.6 (q), 22.4 (t), 25.1 (t), 31.5 (t), 31.9 (t), 33.3 (d), 43.4 (d), 52.5 (q), 65.9 (t), 72.0 (d), 75.2 (d), 77.7 (d), 127.5 (d), 127.9 (d), 146.6 (s), 146.8 (s), 160.5 (s), 161.8 (s), 170.2 (s), 172.5 (s), 173.0 (s); FABMS m/z (relative intensity) 565 (MNa^+, 22), 543 (MH^+, 76), 198 (100), 166 (73); HRFABMS calcd for $C_{24}H_{35}N_2O_8S_2$ m/z 543.1835 (MH^+), found 543.1868.

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Supporting Information Available: ^1H and ^{13}C NMR spectra and HPLC traces of natural and synthetic **1**; ^1H NMR spectra of **4**, **13**, **14a**, and **14b**; ^{13}C NMR spectra of **10**, **15**, **17**−**19**, and **23** (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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