Pergamon

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Total Synthesis of Pseudodistomin C, a Sphingosine-Related Piperidine Alkaloid from Tunicate *Pseudodistoma kanoko*

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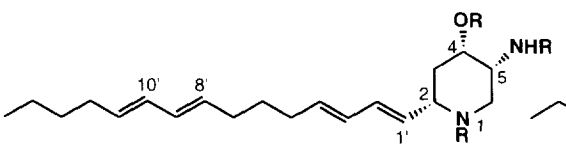
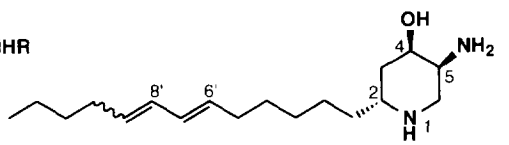
Abstract: Pseudodistomin C (**1**), a piperidine alkaloid isolated from the Okinawan tunicate *Pseudodistoma kanoko*, has been synthesized from D-serine to provide a further unambiguous evidence for the whole structure of **1** which possessed the opposite absolute configurations at the C-4 and C-5 chiral centers from those of pseudodistomins A (**2**) and B (**3**) obtained from the same tunicate.

During our continuing studies on search for bioactive substances from the Okinawan marine organisms,[1] we recently isolated a new cytotoxic piperidine alkaloid, pseudodistomin C (**1**),[2] from the tunicate *Pseudodistoma kanoko* and the structure of **1** was elucidated on the basis of spectral data and combination of the synthesis of both enantiomers of the ozonolysis product (**20**) and the chiral HPLC analysis. It was quite interesting and unexpected that pseudodistomin C (**1**) proved to possess opposite absolute configurations at the C-4 and C-5 chiral centers from those of pseudodistomin A (**2**) and B (**3**)[3] obtained from the same tunicate. Pseudodistomin A (**2**) and B (**3**) appear to be biogenetically associated with D-*erythro*-sphingosine derived from L-serine, whilst pseudodistomin C (**1**) has a structure related to L-*erythro*-sphingosine or D-serine.[4] Here we describe the first total synthesis of pseudodistomin C (**1**), the whole structure of which, consequently, has been unambiguously established.

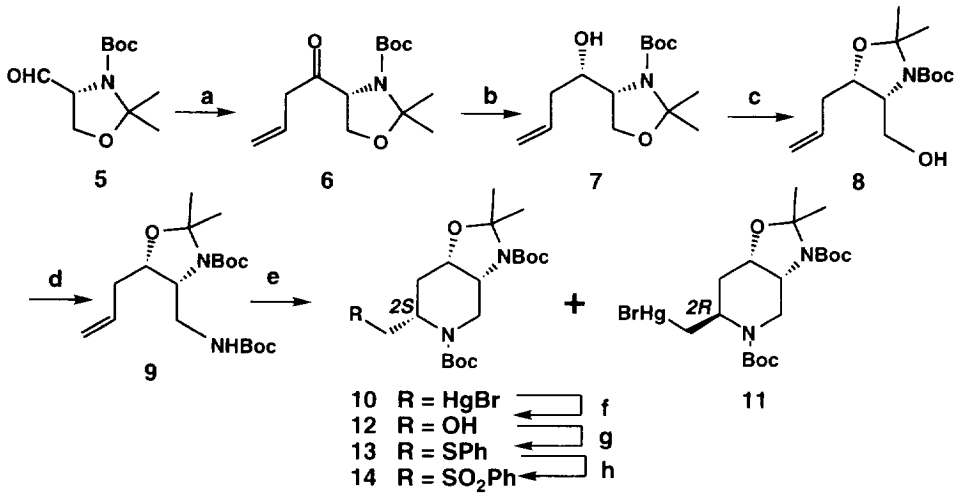


1 R=H **4** R=Ac



2 (6'*E*,8'*Z*) **3** (6'*E*,8'*E*)

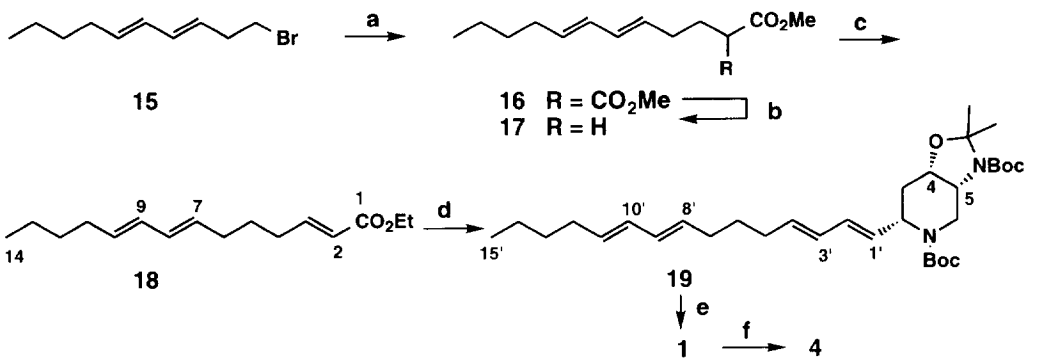
Our synthesis began with Garner's aldehyde (**5**)[5] derived from D-serine as summarized in Scheme 1. The Grignard reaction of allylmagnesium bromide with **5** afforded a 1:1 mixture of *erythro*- and *threo*-homoallyl alcohols. To obtain the *erythro*-alcohol (**7**)[6] practically, the diastereomeric mixture was oxidized with Dess-Martin periodinane[7] in DMF to give the ketone (**6**), which was reduced with $Zn(BH_4)_2$[8] to give *erythro*-alcohol (**7**) in 96% de (60% ee, vide infra). The *erythro*-alcohol (**7**) was transformed into the *t*-butyl carbamate (**9**) via isomeric alcohol (**8**) in 7 steps by our previous method[2]; the terminal amine was protected by the Boc group to simplify the deprotection. Amide mercuration of **9** with $Hg(OAc)_2$ in $CHCl_3$ afforded (2*S*)- and (2*R*)-piperidines (**10** and **11**) in a ratio of 1.5:1. The configuration of C-2 of **10** and **11** was clearly assigned by comparison of the ^1H NMR data with those of corresponding Cbz-derivatives.[2] The (2*S*)-



Scheme 1. (a) (1) CH_2=$CHCH_2MgBr$ (quant.) (2) Dess Martin periodinane, DMF (68 %); (b) $Zn(BH_4)_2$, benzene-Et_2O (quant.); (c) ref. 2, (4 steps, 56 %); (d) (1) Phthalimide, DIAD, PPh_3; (2) $H_2NNH_2 \cdot H_2O$, EtOH; (3) $(Boc)_2O$, 1N NaOH, dioxane (3 steps, 80 %); (e) (1) $Hg(OAc)_2$, $CHCl_3$; (2) NaBr, $NaHCO_3$ (2 steps, 84 %); (f) O_2, $NaBH_4$, DMF (90 %); (g) $(PhS)_2$, *n*-Bu_3P, pyridine (79 %); (h) Ph_2Se_2, 30% H_2O_2, CH_2Cl_2-Et_2O (73 %).

piperidine derivative (**10**) was oxidatively demercurated[9] to give alcohol (**12**), which was treated with diphenyl disulfide and tri-*n*-butylphosphine in pyridine followed by oxidation of the sulfide group of **13** with diphenyl diselenide and hydrogen peroxide[10] to furnish phenylsulfone (**14**).

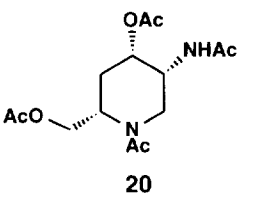
The side chain moiety of **1** was prepared as shown in Scheme 2, starting from known 1-bromo-3*E*, 5*E*-decadienoyl bromide (**15**).[11] Condensation of **15** and sodium dimethyl malonate afforded dimethyl ester (**16**), which was heated with sodium chloride in wet DMSO at 190 °C[12] to afford the corresponding ester (**17**). Reduction of the ester group of **17** with DIBAL in toluene and Wittig reaction provided ethyl tetradecatrienoate (**18**) with all *E*-configurations ($J_{2,3}$=15.8 Hz, $J_{7,8}$=16.4 Hz, and $J_{9,10}$=16.4 Hz). The ester (**18**) was reduced with DIBAL and the resulting alcohol was oxidized with pyridinium chlorochromate (PCC) to afford the corresponding aldehyde, which was subjected to Julia olefination[13] with the phenylsulfone (**14**). The sulfone (**14**) was treated with *n*-butyllithium in THF in the presence of HMPA at -78 °C to produce the orange sulfone anion,[14] which was allowed to react with the aldehyde obtained from **18**, and then quenched with benzoyl chloride to afford a diastereomeric mixture of β-benzoyloxy sulfones. Treatment of the crude mixture with sodium amalgam resulted in formation of the tetraene (**19**) possessing the backbone skeleton of pseudodistomin C (**1**). The ^{1}H NMR of **19** revealed that the last generated $\Delta^{1',2'}$-double bond was *E* ($J_{1',2'}$=14.0 Hz), and the HPLC analysis of the tetraene (**19**) using reversed-phase column showed a single peak predominantly, suggesting that the tetraene (**19**) possesses all *E*-configurations. Removal of the protective groups of **19** with 3N HCl afforded pseudodistomin C (**1**), whose ^{1}H NMR and EIMS spectra as well as R_f values on TLC were completely identical with those of natural specimen.[2] The synthetic pseudodistomin C (**1**) was acetylated with acetic anhydride in pyridine to furnish pseudodistomin C triacetate (**4**), which was also identified with the triacetate (**4**)[2] derived from natural specimen of **1** on the basis of ^{1}H



Scheme 2. (a) Na, MeOH, $CH_2(CO_2CH_3)_2$ (74 %); (b) (1) NaCl, DMSO, H_2O, 190 °C (74 %); (c) (1) DIBAL, toluene; (2) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2 (2 steps, 68 %); (d) (1) DIBAL, CH_2Cl_2 (80 %); (2) PCC, CH_2Cl_2 (74 %); (3) *n*-BuLi, **14**, THF-HMPA; (4) NaHg, MeOH (13 % from **14**); (e) 3N HCl, EtOAc (34 %); (f) Ac_2O, pyridine (56 %).

NMR and EIMS spectra as well as TLC and HPLC examinations. The sign of the optical rotation of synthetic triacetate (**4**) ($[\alpha]_D$ +43° (*c* 1, $CHCl_3$)) was also the same as that of natural one ($[\alpha]_D$ +85° (*c* 0.98, $CHCl_3$)).[2]

Thus we found that our purpose of further structural confirmation of **1** by total synthesis was completed, although the absolute value of the optical rotation of synthetic triacetate (**4**) was smaller than that of natural specimen of **4**. The optical purity of the synthetic compound was examined by means of chiral HPLC analysis after conversion of the alcohol (**12**) into tetraacetate (**20**), which had been obtained by ozonolysis of **1**,[2] to reveal that the synthetic tetraacetate (**20**) obtained in this study was 60% ee. The optical purity of synthetic **4** was estimated to be parallel to this result. This result may be attributable to partial racemization during oxidation-reduction process to obtain the *erythro*-alcohol (**7**).[15]



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EXPERIMENTAL

***tert*-Butyl (4*R*,1'*S*)-2,2-Dimethyl-4-(1'-oxo-3'-butenyl)oxazolidine-3-carboxylate (6).** A suspension of Dess-Martin periodinane (6.49 g, 15.3 mmol) in DMF (50 mL) was added to a solution of 1:1 mixture of oxazolidine homoallyl alcohols[2] (3.77 g, 13.9 mmol) in 100 mL of DMF. The mixture was stirred for 4 h at rt, and quenched by addition of 500 mL of 1:1 mixture of 10 % NaS_2O_3-saturated $NaHCO_3$ solution, and the aqueous phase was extracted with ether (1000 mL x 3). The organic phase was washed with 500 mL of brine, dried over $MgSO_4$, and concentrated *in vacuo* to give yellow oil, which was purified by silica gel column chromatography (hexane/EtOAc, 85:15), to afford the ketone **6** (2.55 g, 68 %): colorless oil; $[\alpha]^{22}_D$ + 64° (*c* 1.0, $CHCl_3$); IR (neat) 1740, and 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 1.39 (6H, s), 1.48 (9H, s), 3.29 (2H, m), 3.93 (1H, m), 4.12 (1H, m), 4.35 (0.6H, dd, *J* = 2.7, 7.4 Hz), 4.48 (0.4H, m), 5.14 (1H, d, *J* = 17.2 Hz), 5.20 (1H, t, *J* = 9.4 Hz), and 5.91 (1H, ddt, *J* = 3.3, 9.4, 17.2 Hz); EIMS *m/z* 270 $(M+H)^+$, 254, 200, 196, and 57; HREIMS, found *m/z* 270.1696, calcd for $C_{14}H_{24}O_4N$ (M+H) 270.1705; Anal. Calcd for $C_{14}H_{23}O_4N$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.16; H, 8.56; N, 5.12.

***tert*-Butyl (4*R*,1'*S*)-2,2-Dimethyl-4-(1'-hydroxy-3'-butenyl)oxazolidine-3-carboxylate (7).** To a solution of the ketone **6** (6.8 g, 25.3 mmol) in benzene (50 mL) and ether (200 mL), 0.16 M of

$Zn(BH_4)_2$ in ether solution[8a] (157.6 mL) was added, and the mixture was stirred at rt for 15 min. After addition of saturated NH_4Cl aqueous solution (200 mL), the mixture was extracted with $CHCl_3$ (200 mL x 3) and washed with brine (200 mL x 3). The organic phase was dried over $MgSO_4$ and evaporated. The residue was subjected to silica gel column chromatography (hexane/EtOAc, 8:2) to give the alcohol **7**[6a] (6.8 g, quant., 96 % de): colorless oil; $[\alpha]^{23}_D$ -4.0° (*c* 1, C_6H_6). The HPLC analysis of the *erythro*-alcohol (**7**) and its *threo*-isomer (Develosil ODS HG-5, NOMURA Chemical; 10 x 250 mm; flow rate: 2.5 mL/min; RI detection; eluent: 55 % MeOH) showed peaks at t_R 48.8 and 50.4 min, respectively, in a ratio of 98:2.

***tert*-Butyl (4*R*,5*S*)-2,2-Dimethyl-4-[(*tert*-Butoxycarbonyl)amino]methyl-5-(2'-propenyl)-oxazolidine-3-carboxylate (9).** The *erythro*-alcohol (**7**) was transformed into the isomeric alcohol (**8**) by the same procedures as previously described.[2] To a solution of the alcohol **8** (1.0 g, 3.8 mmol) in THF (12 mL) was added phthalimide (724.1 mg, 4.57 mmol), diisopropyl azodicarboxylate (DIAD, 1.08 g, 5.33 mmol), and triphenylphosphine (1.3 g, 4.57 mmol), and the mixture was stirred at rt for 20 h. After evaporation of the solvent, the residue was purified by silica gel column chromatography (hexane/EtOAc, 3:1) to give the phthalimide (1.6 g), which was then treated with hydrazine monohydrate (0.8 mL) in EtOH (16 mL) and stirred at rt for 15 h. After addition of 2 N NaOH (30 mL) and extraction with EtOAc (50 mL x 3), the organic phase was evaporated under reduced pressure. The residue was dissolved in dioxane (17 mL), and 1N NaOH (9 mL) and di-*t*-butyl dicarbonate ($(Boc)_2O$, 1.08 g, 4.95 mmol) in dioxane (3.3 mL) were added to this solution. After stirring at rt for 1 h, the reaction mixture was concentrated to half volume and partitioned between saturated NH_4Cl and EtOAc (50 mL x 3). The organic layer was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc, 4:1) to give the *t*-butyl carbamate **9** (1.1 g, 80 % from **8**): colorless oil; $[\alpha]^{23}_D$ -11° (*c* 1.0, $CHCl_3$); IR (neat) 3350 and 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 1.43 (6H, s), 1.50 (18H, s), 2.32 (0.7H, m), 2.41 (1.4H, br m), 3.12-3.32 (1H, br m), 3.34-3.42 (0.3H, m), 3.45-3.60 (1H, br m), 3.80-3.96 (0.7H, br m), 4.02-4.16 (1H, br m), 4.96 (0.5H, br s), 5.12 (2H, dd, *J* = 11.4, 16.0 Hz), 5.48 (0.5H, br s), and 5.80 (1H, m); EIMS *m/z* 371 (M^++H), 370 (M^+), 355, and 57; HREIMS, found *m/z* 370.2430, calcd for $C_{19}H_{34}O_5N_2$ (M^+) 370.2468.

***tert*-Butyl (3a*R*,6*S*,7a*S*)-6-[(Bromomercurio)methyl]-3-*tert*-butoxycarbonyl)-2,2-dimethylperhydrooxazolo[4,5-*c*]pyridine-5-carboxylate (10) and *tert*-Butyl (3a*R*,6*R*,7a*S*)-6-[(Bromomercurio)methyl]-3-*tert*-butoxycarbonyl)-2,2-dimethylperhydrooxazolo[4,5-*c*]pyridine-5-carboxylate (11).** To a solution of compound **9** (3.35 g, 9.06 mmol) in $CHCl_3$ (150 mL), mercuric acetate (3.75 g, 11.78 mmol) was added, and the mixture was stirred at rt for 18 h, at 40 °C for 24 h, and at 50 °C for 15 h. After addition of saturated $NaHCO_3$ aqueous solution (130 mL), the mixture was stirred for 20 min. Then, saturated NaBr solution (130 mL) was added and the mixture was stirred for 3 h at rt. Extraction with $CHCl_3$ (200 mL x 3) followed by evaporation of the solvent afforded a residue, which was purified by silica gel column chromatography (hexane/EtOAc, 4:1) to give the piperidine derivative **10** (2.99 g, 51%) together with 2-epimer **11** (1.92 g, 33 %). **10**: amorphous powder; $[\alpha]^{27}_D$ -4.6° (*c* 1.0, $CHCl_3$); IR (neat) 1690 and 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 1.49 (24H, s), 1.90 (1H, br d, *J* = 14.4 Hz), 2.15 (1.5H, m), 2.37 (0.3H, br m), 2.50 (0.5H, br s), 2.81 (1H, br s), 3.30 (0.3H, br m), 3.43-3.56 (0.7H, br m), 3.76-3.95 (1H, br m), 4.20 (1H, br dd), 4.31 (0.7H, br s), and 4.46 (0.7H, br m); EIMS *m/z* 652 (M^+), 635 (M^+-CH_3), 579, 479, 257, 199, 155, 112, and 57; HREIMS, found *m/z* 652.1232, calcd for $C_{19}H_{33}O_5N_2{}^{81}Br^{202}Hg$ (M^+) 652.1257. **11**: amorphous powder; $[\alpha]^{23}_D$ -49° (*c* 1.0, $CHCl_3$); IR (neat) 1680 and 1360 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 1.44 (6H, s), 1.51 (18H, s), 1.87 (2H, m), 2.21 (2H, m), 2.89

(0.7H, dd, J = 3.0, 15.0 Hz), 2.95 (0.4H, dd, J = 3.0, 15.0 Hz), 3.80 (0.3H, dd, J = 9.1, 3.0 Hz), 3.91 (0.7H, dd, J = 9.1, 3.0 Hz), and 4.35 (3H, m); EIMS *m/z* 650 (M^+), 635 (M^+-CH_3), 579, 479, 257, 199, 155, 112, and 57; HREIMS, found *m/z* 650.1314, calcd for $C_{19}H_{33}O_5N_2{}^{79}Br^{202}Hg$ (M^+) 650.1277.

***tert*-Butyl (3a*R*,6*S*,7a*S*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-6-(hydroxymethyl)-perhydrooxazolo[4,5-*c*]pyridine-5-carboxylate (12).** Oxygen (O_2) was bubbled into a suspension of $NaBH_4$ (64.8 mg, 0.87 mmol) in DMF (40 mL) at rt for 1 h, and to this was dropwise added a solution of **10** (871 mg, 1.34 mmol) in DMF (45 mL) over 2 h with continuous introduction of O_2. The bubbling of O_2 into the mixture was further continued for 1 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure to give a residue, which was chromatographed (silica gel, hexane/EtOAc, 2:1) to give **12** (507 mg, 90 %): colorless needles; mp 104 °C; $[\alpha]^{24}_D$ -7.3° (*c* 1.0, $CHCl_3$); IR (KBr) 3440 and 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 1.57 (6H, s), 1.64 (18H, s), 1.96 (1H, br m), 2.04 (1H, br m), 2.88 (1H, br m), 3.48-3.73 (2H, br m), 3.80 (1H, br m), 3.92 (1H, br m), and 4.19-4.46 (2H, br m); EIMS *m/z* 386 (M^+), 371 (M^+-CH_3), 355 (M^+-CH_2OH), 255 (M^+-CH_2OH-Boc), 199 (M^+-CH_2OH-Boc-C_4H_9), 155, 112, and 57; HREIMS, found *m/z* 371.2157, calcd for $C_{18}H_{31}O_6N_2$ (M-CH_3) 371.2182.

***tert*-Butyl (3a*R*,6*S*,7a*S*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-6-(phenylthiomethyl)-perhydrooxazolo[4,5-*c*]pyridine-5-carboxylate (13).** To a solution of the alcohol **12** (486 mg, 1.16 mmol) and diphenyl disulfide (421 mg, 1.93 mmol) in pyridine (1 mL), tri-*n*-butylphosphine (480 µl, 1.93 mmol) was added dropwise at rt. After stirring for 4.5 h at rt, the reaction mixture was diluted with 20 mL of ether and washed with 20 mL of 10 % $NaHCO_3$ and 10 mL of brine. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed (silica gel, hexane/ EtOAc, 85:15) to give **13** (439 mg, 79 %): colorless needles; mp 109 °C; $[\alpha]^{25}_D$ +9.5° (*c* 1, $CHCl_3$); IR (neat) 1700 and 1400 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 1.44 (24H, s), 2.00 (1H, br m), 2.10-2.41 (1H, br m), 2.64 (1H, br m), 3.12-3.51 (2H, br m), 3.72-3.93 (1H, br m), 4.20 (2H, br s), 4.23-4.50 (1H, br m), and 7.28-7.60 (5H, br m); EIMS *m/z* 478 (M^+), 405 (M^+-C_4H_9O), 355, 294, 255 (M^+-CH_2SPh-Boc), 199, and 57; HREIMS, found *m/z* 478.2503, calcd for $C_{25}H_{38}O_5N_2S$ (M^+) 478.2501.

***tert*-Butyl (3a*R*,6*S*,7a*S*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-6-(phenylsulfonyl-methyl)perhydrooxazolo[4,5-*c*]pyridine-5-carboxylate (14).** To a solution of phenyl sulfide **13** (439 mg, 0.92 mmol) and diphenyl diselenide (287 mg, 0.92 mmol) in 15 % CH_2Cl_2-ether (3 mL), a solution of 30 % hydrogen peroxide (621 mL) in 15 % CH_2Cl_2-ether (2 mL) was added dropwise at 0 °C. After stirring for 1h at 0 °C and at rt for 6 h, saturated $NaHCO_3$ solution (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (100 mL x 3). The organic phase was washed with brine and dried ($MgSO_4$) and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc, 7:3) to afford sulfone **14** (344 mg, 73 %): colorless plates (from MeOH); mp 68 °C; $[\alpha]^{25}_D$ -0.6° (*c* 1, $CHCl_3$); IR (neat) 1710, 1400, and 1320 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 1.43 (24H, s), 2.00 (2H, br m), 2.22-2.61 (0.5H, br m), 3.33-3.62 (2H, br m), 3.65-3.90 (1H, br m), 4.10 (2.5H, m), 4.78 (1H, br m), 7.53 (2H, t, J = 7.3 Hz), 7.61 (1H, dd, J = 7.3, 13.4 Hz), and 7.89 (2H, br d, J = 7.3 Hz); EIMS *m/z* 510 (M^+), 495 (M^+-CH_3), 454, 439, 398, 339, 295, 252, 199, and 57; HREIMS, found *m/z* 510.2431, calcd for $C_{25}H_{38}O_7N_2S$ (M^+) 510.2400.

Methyl 2-Methoxycarbonyl-5*E*,7*E*-dodecadienoate (16). To absolute MeOH (9.5 mL), sodium (309 mg, 16.1 mmol) was added gradually in small pieces, and to this solution dimethyl malonate (2.45 mL, 16.1 mmol) was added over a period of about 20 min. Then the mixture was heated under reflux for 5 min. To the mixture, 1-bromo-3*E*,5*E*-decadiene[11] **15** (3.64 g, 13.4 mmol) was added quickly, and the

mixture was stirred for 3.5 days at 38 °C. After addition of saturated NH_4Cl solution (20 mL), the mixture was extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (cyclohexane/hexane, 98:2) to give methyl 2-methoxycarbonyl-5*E*,7*E*-dodecadienoate **16** (2.67 g, 74 %): colorless oil; IR (neat) 1740 and 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.85 (3H, t, J = 7.1 Hz), 1.30 (4H, m), 2.00 (2H, m), 2.08 (4H, m), 3.38 (1H, t, J = 7.2 Hz), 3.72 (6H, s), 5.48 (1H, ddd, J = 6.7, 7.2, 15.7 Hz), 5.59 (1H, ddd, J = 6.7, 7.2, 15.7 Hz), and 5.98 (2H, dd, J = 10.5, 15.7 Hz); EIMS *m/z* 268 (M^+), 237, 219, 205, 150, 136, and 55; HREIMS, found *m/z* 268.1662, calcd for $C_{15}H_{24}O_4$ (M^+) 268.1675.

Methyl 5*E*,7*E*-Dodecadienoate (17). To a solution of methyl ester **16** (2.63 g, 9.80 mmol) in DMSO (12 mL) was added sodium chloride (904 mg, 14.7 mmol) and water (0.35 mL, 19.6 mmol), and the mixture was heated at 190 °C for 4 h. After cooling, the mixture was diluted by water (24 mL) and extracted by ether (36 mL x 3). To the organic layer, a solution of CH_2N_2 (in excess) in ether (25 mL) was added at 0 °C to convert the partially-produced acid into the methyl ester. After stirring for 30 min, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 95:5) to yield the methyl ester **17** (1.52 g, 74 %): colorless oil; IR (neat) 1720 and 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.89 (3H, t, J = 7.0 Hz), 1.32 (6H, m), 1.96 (4H, m), 2.05 (2H, m), 3.71 (3H, s), 5.49 (1H, ddd, J = 6.8, 7.0, 15.6 Hz), 5.58 (1H, ddd, J = 6.8, 7.0, 15.6 Hz), and 6.00 (2H, dt, J = 10.5, 15.6 Hz); EIMS *m/z* 210 (M^+), 209 (M^+-H), 195 (M^+-CH_3), 153, 137, 129, 111, and 57; HREIMS, found *m/z* 210.1648, calcd for $C_{13}H_{22}O_2$ (M^+) 210.1619; Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.11; H, 10.40.

Ethyl 2*E*,7*E*,9*E*-Tetradecatrienoate (18). To a cooled (-78 °C) solution of the methyl ester **17** (799 mg, 3.81 mmol) in dry toluene (8.4 mL), 1.0 M DIBAL solution in toluene (6.5 mL) was added with stirring. After stirring for 1.5 h, cooled MeOH (0.3 mL) was dropwise added and stirring was continued for 20 min at -65 °C. After addition of ether (18 mL) and saturated Rochelle solution (saturated potassium sodium tartrate aqueous solution, 3.5 mL), the mixture was stirred for 30 min. The mixture was extracted with ether (25 mL x 2), and the organic phases were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to afford crude aldehyde. To a solution of the crude aldehyde in dry CH_2Cl_2 (34 mL) was added ethyl (triphenylphosphoranylidene)acetate (1.99 g, 5.72 mmol) and the mixture was stirred at rt for 14 h. The solvent was removed by evaporation and the residue was subjected to silica gel column chromatography (hexane/EtOAc, 95:5) to give the ethyl ester **18** (648 mg, 68 %): colorless oil; IR (neat) 1730, 1660, 1320, and 1280 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.89 (3H, t, J = 7.1 Hz), 1.29 (3H, t, J = 7.1 Hz), 1.33 (4H, m), 1.55 (2H, m), 2.07 (4H, m), 2.20 (2H, dt, J = 7.0, 8.4 Hz), 4.19 (2H, q, J = 7.1 Hz), 5.51 (1H, dt, J = 6.9, 16.4 Hz), 5.59 (1H, dt, J = 7.0, 16.4 Hz), 5.81 (1H, d, J = 15.8 Hz), 6.01 (1H, dd J = 11.8, 16.4 Hz), 6.02 (1H, dd, J = 11.8, 16.4 Hz), and 6.95 (1H, dt, J = 7.0, 15.8 Hz); EIMS *m/z* 250 (M^+), 221 (M^+-Et), 204 (M^+-EtOH), 177 (M^+-CO_2Et), 114, 107, 81, 67, and 55; HREIMS, found *m/z* 250.1958, calcd for $C_{16}H_{26}O_2$ (M^+) 250.1933.

***tert*-Butyl (3a*R*,6*S*,7a*S*)-3-*tert*-Butoxycarbonyl-2,2-dimethyl-6-(1*E*,3*E*,8*E*,10*E*-pentadecatetraenyl)perhydrooxazolo[4,5-*c*]pyridine-5-carboxylate (19).** To a solution of the ethyl ester **18** (290 mg, 1.16 mmol) in CH_2Cl_2 (3 mL) was dropwise added 0.93 M DIBAL solution in hexane (3.5 mL) and stirred for 15 min at -78 °C. After addition of cooled MeOH (0.1 mL), the mixture was warmed to rt. To this mixture, ether (7.5 mL) and Rochelle solution (1.5 mL) were added and the mixture was further stirred for 1 h. The mixture was extracted with ether (20 mL x 3), and the residue was subjected to silica gel column

chromatography (hexane/EtOAc, 95:5) to give the alcohol (267.7 mg, 80 %). Part of this alcohol (58 mg, 0.28 mmol) was dissolved in CH_2Cl_2 (1.7 mL), and PCC (114.2 mg, 0.53 mmol) in CH_2Cl_2 (8 mL) was added to this solution. After stirring for 1h at rt, the reaction mixture was poured on a Florisil column and eluted with ether (300 mL), and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column (hexane/EtOAc, 95:5) to give aldehyde (43 mg, 74 %). This oxidation reaction was repeated to obtain the aldehyde (178 mg). A solution of 1.6 M *n*-butyllithium in hexane (0.54 mL, 0.86 mmol) was added to solution of sulfone **14** (367 mg, 0.72 mmol) in THF (1.8 mL) containing HMPA (0.6 mL) at -78 °C. After 10 min at -78 °C a solution of the aldehyde (178 mg, 0.86 mmol) in THF (1.1 mL) was added over 4 min. After stirring for 1.5 h, benzoyl chloride (0.18 mL, 1.44 mmol) was added in one portion. The reaction mixture was allowed to warm to rt over 1 h, and then 3-(*N*,*N*-dimethyl-amino)propyl-1-amine (1.4 mL) was added in one portion. The reaction mixture was diluted with H_2O (14 mL), and extracted with ether (31 mL x 3). The organic phase was washed with saturated NH_4Cl (45 mL), 5 % aqueous $NaHCO_3$ (45 mL), and brine (45 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was subjected to silica gel column (hexane/EtOAc, 9:1) to afford diastereomeric mixture of the β-benzoyloxy sulfone, which was subsequently treated with 5 % sodium amalgam (529 mg, 1.4 mmol) in THF (2.4 mL) and dry MeOH (0.7 mL) at -20 °C for 3.5 h. Then, 159 mg of 5 % sodium amalgam was added again at -20 °C, and after 7.5 h the reaction mixture was poured into H_2O (15 mL), and extracted with ether (45 mL x 3). The organic phase was washed with brine (15 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was subjected to silica gel column (hexane/EtOAc, 9:1) to give the tetraene **19** (48 mg, 13 % yield from **14**). The HPLC analysis (Develosil ODS-5; 10 x 250 mm; flow rate: 2.0 mL/min; UV detection at 230 nm; eluent: 90 % MeOH) showed only a peak at t_R 8.0 min predominantly. **19**: colorless oil ; $[\alpha]^{25}_D$ -33° (*c* 1, $CHCl_3$); IR (neat) 1690 and 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 0.89 (3H, t, *J* = 7.1 Hz), 1.34 (4H, m), 1.42 (6H, s), 1.48 (18H, s), 1.49 (4H, m), 1.60 (2H, br s), 2.06 (6H, m), 2.17 (1H, m), 2.66-2.85 (0.5H, br m), 2.95 (0.5H, m), 3.80 (0.7H, br d, *J* = 7.0 Hz), 3.93 (0.35H, br d, *J* = 7.0 Hz), 4.19 (1H, br m), 4.53 (0.7H, br m), 4.85 (0.3H, br s), 5.39 (0.3H, m), 5.51 (1H, dd, *J* = 6.9, 14.0 Hz), 5.57 (1H, dd, *J* = 7.0, 14.0 Hz), 5.64 (1H, br m), 5.75 (0.7H, br d, *J* = 14.0 Hz), 5.97 (2H, dd, *J* = 11.4, 14.0 Hz), and 6.00 (2H, dd, *J* = 10.1, 14.0 Hz); ^{13}C NMR ($CDCl_3$) δ_C 13.9 (C-15'), 22.2 (C-14'), 28.4 (Boc), 28.6 (Boc), 28.9 (acetonide-CH_3), 31.6, 32.0, 32.1 (C-5', 7', and 12'), 45.3, 48.0, 53.5, 57.0, 60.0, 69.0, 69.7, 70.8, 76.2, 79.8, 80.4, 94.0, 129.8, 129.9, 130.0, 130.3, 130.8, 131.7, 132.6, and 134.2; EIMS *m/z* 559 (M^++H), 501 (M^+-C_4H_{10}), 459 (M^+-Boc+H), 402 (M^+-C_4H_9-Boc+H), 359, 344, 327, 255, 199, 173, 141, 98, and 57; HREIMS, found *m/z* 501.3318, calcd for $C_{29}H_{45}O_5N_2$ (M^+-C_4H_{10}) 501.3328.

Pseudodistomin C (1). To a solution of the tetraene **19** (21.0 mg, 37.6 μmol) in EtOAc (0.5 mL) was added 3 N HCl (0.5 mL). After stirring at rt for 6 h, saturated $NaHCO_3$ aqueous solution (5 mL) was added and the mixture was extracted with EtOAc (10 mL x 3). The organic phase was washed with brine (15 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH, 1:1) to yield **1** (4.1 mg, 34 %), which was identical with the natural product (**1**)[2] by comparison of TLC, ^1H NMR, and EIMS data. **1**: colorless oil; $[\alpha]^{24}_D$ -24° (*c* 0.7, MeOH); HREIMS, found *m/z* 318.2666, calcd for $C_{20}H_{34}ON_2$ (M^+) 318.2671.

Pseudodistomin C Triacetate (4). Synthetic pseudodistomin C (**1**, 4.1 mg, 12.8 μmol) was treated with Ac_2O (0.5 mL) and pyridine (1 mL) at rt for 1.5 h. After evaporation of solvent *in vacuo*, the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH, 9:1) to afford pseudodistomin C

triacetate (**4**, 3.2 mg, 56 %): colorless oil; $[\alpha]^{23}_{D}$ +43° (*c* 0.5, $CHCl_3$), which was also identified with the triacetate (**4**) of natural specimen on the basis of comparisons of TLC, HPLC, ^{1}H NMR, EIMS and optical rotation (natural **4**[2]:$[\alpha]^{22}_{D}$ +85° (*c* 0.98, $CHCl_3$)). The HPLC analysis of synthetic **4** (Develosil ODS-5; 10 x 250 mm; flow rate: 2.0 mL/min; UV detection at 230 nm; eluent: 85 % MeOH) showed a peak at t_R 26.8 min, which was identical with that of natural **4**.[2]

Conversion of 12 to 20 and Chiral HPLC Analysis. To a solution of the alcohol **12** (30 mg, 70 μmol) in CH_2Cl_2 (0.5 mL), TFA (15 μL) was added. The mixture was stirred for 20 h at rt, and the solvents were removed by evaporation under reduced pressure. The residue was treated with pyridine (1 mL) and Ac_2O (0.5 mL) for 2 h at rt After evaporation *in vacuo*, the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH, 95:5) followed by reversed-phase HPLC (YMC-Pak AM323, 10 x 250 mm; flow rate: 2.0 mL/min ; UV detection at 215 nm; eluent: 35 % MeOH) to give tetraacetate (**20**, 2.1 mg, 10 % yield, t_R 10.8 min), which was subjected to chiral HPLC analysis (CHIRALPAK AD, Daicel Chemical Ind.; 4.6 x 250 mm; flow rate: 0.5 mL/min; UV detection at 215 nm; eluent: hexane/2-propanol, 8:2) to show peaks at t_R 16.5 and 15.0 min corresponding to **20** and its enantiomer, respectively, in a ratio of 80:20.

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References and Notes

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15. In our previous study,[2] chiral HPLC had showed that no crucial racemization occurred since the *erythro*-alcohol (**7**) and its *threo*-isomer were separated after conversion into monopivaloyl esters by 4-times repeated silica gel chromatographies.

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