Synthesis of (±)-Pseudodistomins A and B Acetates[1)]

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Pseudodistomins A and B, piperidine alkaloids isolated from the Okinawan tunicate *Pseudodistoma kanoko*, have been synthesized as their racemic acetates *via* a route involving Grignard coupling reaction to provide unambiguous proof of their structures.

Key words pseudodistomin A; pseudodistomin B; piperidine alkaloid; Grignard coupling; total synthesis

The structurally novel piperidine alkaloids pseudodistomins A and B are calmodulin antagonists which exhibit potent antineoplastic activity. They were isolated from the Okinawan tunicate *Pseudodistoma kanoko*, and their structures were initially proposed on the basis of UV, IR, ^{1}H- and ^{13}C-NMR and MS evidence.[2)] However, our work[3)] on total synthesis of the proposed structures of pseudodistomins A (3′*E*,5′*Z*-diene) and B (3′*E*,5′*E*-diene) indicated that the deduced structure of the alkenyl side-chain should be revised. Thus, Kobayashi's group and we jointly reinvestigated the structure of pseudodistomin B by both spectroscopic reanalysis and chemical degradation experiments and proposed that pseudodistomin B possesses a 6′*E*,8′*E*-tridecadiene structure in the side-chain. Recently Kobayashi's group[4)] revised the structure of pseudodistomin A to 6′*E*,8′*Z*-configuration based on chemical degradation and the combination of homonuclear Hartmann–Hahn spectroscopy (HOHAHA) and analysis of the coupling constants in the ^{1}H-NMR spectrum. Pseudodistomins and related compounds, including tetrahydropseudodistomin acetate **5**, have been chosen as targets for synthesis by several groups[5–7)] because of their unique bioactivities as well as their interesting structures.

We now report in detail the first synthesis of (±)-pseudodistomins A and B acetates, providing unambiguous confirmation of their structures.

Our synthetic strategy was divergent synthesis of three possible geometrical 6′,8′-dienyl isomers *via* a common intermediate **6** which had already been prepared *via* a route involving two photochemical reactions.[3)] Among the three isomers, two are expected to be identical with authentic pseudodistomins A and B acetates, respectively. We chose the coupling reaction[8)] of the tosylate **7** with Grignard reagents including the corresponding dienyl moiety for the construction of the tridecadienyl side-chains.

Treatment of the alcohol **6**[3)] with *p*-toluenesulfonyl chloride (*p*-TsCl) in the presence of Et_3N and dimethylaminopyridine (DMAP) gave the tosylate **7** in 70% yield. For the side-chain moiety of pseudodistomin B, (3*E*,5*E*)-1-bromo-3,5-decadiene (**8**) was prepared by the known method.[9)] The coupling reaction of the tosylate **7** with (3*E*,5*E*)-3,5-decadienylmagnesium bromide, prepared *in situ* from **8**, in the presence of Li_2CuCl_4 at −50 °C proceeded smoothly to give a mixture of the acetate **4** and the corresponding alcohol **9**, which was separated by medium-pressure liquid chromatography (MPLC) to afford **4** and **9** in 40% and 21% isolated yields, respectively. Acylation of the alcohol **9** with Ac_2O in pyridine gave the acetate **4**, which was identical with authentic pseudodistomin B acetate[2)] upon direct comparisons of their ^{1}H- and ^{13}C-NMR spectra. Thus, we have succeeded in the synthesis of (±)-pseudodistomin B acetate.

Similarly we synthesized two 6′,8′-dienes **3** and **17** for unambiguous structural confirmation of pseudodistomin A. According to the literature, (3*E*,5*Z*)-(**10**)[10)] and (3*Z*,5*E*)-2-(3,5-decadienyloxy)tetrahydro-2*H*-pyrans (**11**)[11)] were prepared stereoselectively and then converted to the corresponding alcohols **12** and **13** by treatment with *p*-toluenesulfonic acid (*p*-TsOH) in MeOH in 88% and 90% yields, respectively. Treatment of the alcohols **12** and **13** with PPh_3 and CBr_4 gave the bromides **14** and **15** in 92% and 93% yields, respectively. The configurations of the diene moieties in the bromides **14** and **15** were established from the ^{1}H-NMR spectral data. The coupling reaction of the tosylate **7** with (3*E*,5*Z*)-3,5-decadienylmagnesium bromide, prepared *in situ* from **14** in the presence of Li_2CuCl_4 gave a mixture of the acetate **3** (39%) and the corresponding alcohol **16** (27%). A similar coupling reaction of the tosylate **7** with (3*Z*,5*E*)-3,5-decadienylmagnesium bromide, prepared *in situ* from **15** gave a mixture of the acetate **17** (33%) and the alcohol **18** (18%). Acetylation of the alcohols **16** and **18** gave the acetates **3** and **17**, respectively. Direct comparisons of the ^{1}H- and ^{13}C-NMR spectra of each of the synthetic dienes **3** and **17** with those of authentic pseudodistomin A

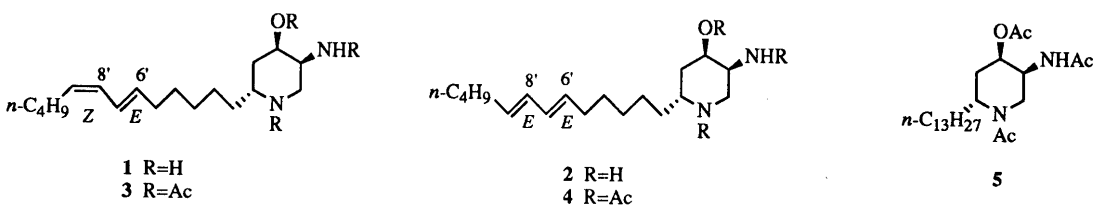

Chart 1

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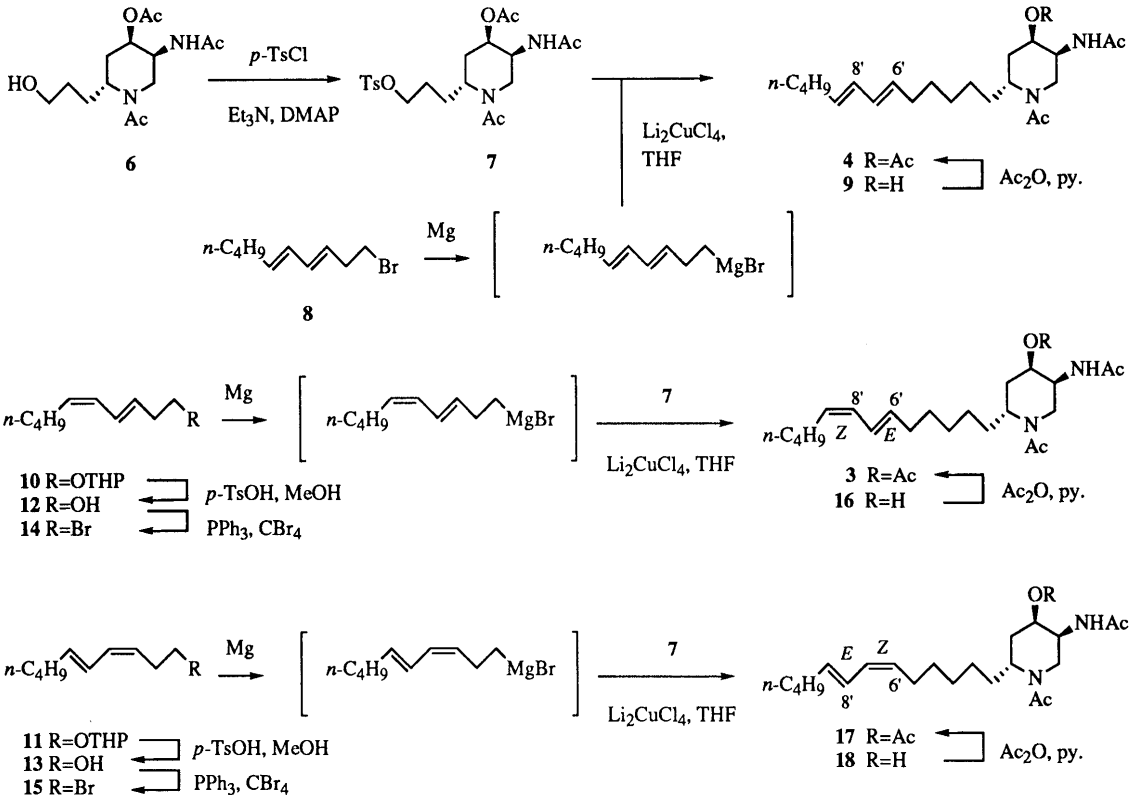

Chart 2

acetate[2] established that the structure of pseudodistomin A acetate is not **17**, but **3**.

In conclusion, we have succeeded in the syntheses of (±)-pseudodistomins A and B acetates and thus provided unambiguous evidence for their structures.

Experimental

^{1}H-NMR spectra were measured using Varian XL-200 (200 MHz) and VXR-500 (500 MHz) instruments and ^{13}C-NMR spectra were measured with the VXR-500 (125 MHz) for solutions in $CDCl_3$ (tetramethylsilane was used as the internal reference). IR spectra were measured with Hitachi 270-30 and Perkin Elmer 1600 FTIR machines for solutions in $CHCl_3$. MS and high resolution MS (HR-MS) were taken with a Hitachi M-4100 instrument. HPLC was performed using a Waters Associates ALP/GPC 204 liquid chromatograph with a Develosil ODS-5 (10 × 250 mm) column and a UV detector set at 254 nm. Medium-pressure liquid chromatography (MPLC) was undertaken on a 530-4-10V apparatus (Yamazen) with Lobar größe B (310-25, Lichroprep Si60, Merck) as the column adsorbent. All melting points were determined with a Kofler-type hot-stage apparatus and are uncorrected. All reactions were carried out under nitrogen and the extracts from the reaction mixtures were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure.

(2α,4β,5β)-(±)-1-Acetyl-5-(acetylamino)-4-(acetyloxy)-2-[3-[(4-methylphenyl)sulfonyl]oxy]propylpiperidine (7) A solution of **6**[3] (90 mg, 0.3 mmol), *p*-TsCl (57 mg, 0.3 mmol), Et_3N (0.5 ml) and DMAP (5 mg) in CH_2Cl_2 (5 ml) was stirred at room temperature for 20 h and diluted with CH_2Cl_2. The mixture was washed with 10% HCl, and the organic layer was washed, dried and concentrated. The residue was purified by MPLC (MeOH–CH_2Cl_2, 5:95) to give **7** (95 mg, 70%) as colorless crystals, mp 154—155 °C (from Et_2O–MeOH). IR cm^{-1}: 1742 (OCO), 1678 (NHCO), 1632 (NCO), 1368, 1176 (OSO_2). ^{1}H-NMR (200 MHz) δ: 7.82 (2H, br d, J=8 Hz, ArH), 7.40 (2H, br d, J=8 Hz, ArH), 6.91 (1H, br d, J=7 Hz, NH), 5.10 (1H, m, 4-H), 4.89 (1H, m, 2-H), 4.48 (1H, br s, 5-H), 4.14—3.98 (2H, m, 3′-H_2), 3.86 (1H, br d, J=14.5 Hz, 6-Heq), 3.28 (1H, br d, J=14.5 Hz, 6-Hax), 2.50 (3H, s, $ArCH_3$), 2.12—2.00 (9H, br s, Ac × 3), 1.96—1.50 (6H, m, 3-H_2, 1′-H_2, 2′-H_2). *Anal.* Calcd for $C_{21}H_{30}N_2O_7S$: C, 55.49; H, 6.65; N, 6.16. Found: C, 55.24; H, 6.76; N, 5.99.

General Procedure for Grignard Coupling Reaction of the Tosylate 7. (±)-Pseudodistomin B Acetate (4) and [2α(6*E*,8*E*),4β,5β]-(±)-1-Acetyl-5-(acetylamino)-2-(6,8-tridecadienyl)-4-piperidinol (9) A solution of Li_2CuCl_4 (0.005 M solution in tetrahydrofuran (THF), 0.05 ml, 2.5 × 10^{-7} mol) was added dropwise at −78 °C to a stirred solution of the tosylate **7** (42 mg, 0.093 mmol) in THF (2 ml). A solution of (3*E*,5*E*)-3,5-decadienylmagnesium bromide in THF (5 ml), prepared from (3*E*,5*E*)-1-bromo-3,5-decadiene[9] (200 mg, 0.92 mmol) and magnesium (32 mg, 1.36 mmol), was successively added to the above mixture at −78 °C and the mixture was stirred at −50 °C for 3 h. Then it was warmed to room temperature, the reaction was quenched with 10% H_2SO_4 (one drop) and H_2O, and the whole was extracted with EtOAc. The organic layer was washed, dried and concentrated. The residue was separated by MPLC (MeOH–AcOEt, 1:9) to give **4** (16 mg, 40%) and **9** (7.3 mg, 21%), each as a colorless oil. **4** was further purified with HPLC (MeOH–H_2O, 88:12, flow rate = 2.0 ml/min). IR cm^{-1}: 1740 (OCO), 1670 (NHCO), 1630 (NCO). ^{1}H-NMR (500 MHz) δ: 6.08 (4/5H, br d, J=8 Hz, NH), 6.01—5.94 (2H, m, 7′-H, 8′-H), 5.83 (1/5H, m, NH), 5.60—5.50 (2H, m, 6′-H, 9′-H), 5.15 (1H, m, 4-H), 4.91 (4/5H, m, 2-H), 4.61 (1/5H, br d, J=14.5 Hz, 6-Heq), 4.52 (1/5H, br s, 5-H), 4.36 (4/5H, br s, 5-H), 4.01 (1/5H, m, 2-H), 3.93 (4/5H, br d, J=14.5 Hz, 6-Heq), 3.29 (4/5H, br d, J=14.5 Hz, 6-Hax), 2.92 (1/5H, br d, J=14.5 Hz, 6-Hax), 2.20—2.00 (13H, m, 5′-H_2, 10′-H_2, Ac × 3), 1.79 (2H, m, 3-H_2), 1.62 and 1.52 (each 1H, m, 1′-H_2), 1.40—1.20 (10H, m, 2′—4′-H_2, 11′-H_2, 12′-H_2), 0.89 (3H, t, J=7 Hz, 12′-CH_3). ^{13}C-NMR δ: 170.7, 170.4 and 170.1 (each s, $\underline{C}OCH_3$), 132.6 and 132.0 (each d, 6′-C, 9′-C), 130.6 and 130.2 (each d, 7′-C, 8′-C), 66.9 (d, 4-C), 47.7 (d, 2-C), 47.1 (d, 5-C), 43.9 (t, 6-C), 32.4 and 32.3 (each t, 5′-C, 10′-C), 31.6 (t, 11′-C), 30.2, 29.2, 28.9 and 28.2 (each t, 3-C, 1′-C, 3′-C, 4′-C), 26.2 (t, 2′-C), 23.3, 21.7 and 21.0 (each q, $CO\underline{C}H_3$), 22.3 (t, 12′-C), 13.9 (q, 13′-C). HR-MS *m/z*: 420.2998 (M^+). Calcd for $C_{24}H_{40}N_2O_4$: 420.2986. The synthetic **4** was shown to be identical with authentic pseudodistomin B acetate[2] based on comparison of their spectra.

9: ^{1}H-NMR (200 MHz) δ: 6.52 (1/2H, br d, J=8 Hz, NH), 6.32 (1/2H, br d, J=8 Hz, NH), 6.01—5.94 (2H, m, 7′-H, 8′-H), 5.60—5.50 (2H, m, 6′-H, 9′-H), 4.90 (1/2H, m, 2-H), 4.65 (1/2H, br d, J=14.5 Hz, 6-Heq), 4.40 (1H, m, 4-H), 4.30 (1H, br s, 5-H), 4.18 (1/2H, m, 2-H), 3.93 (1/2H, br d, J=14.5 Hz, 6-Heq), 3.28 (1/2H, br d, J=14.5 Hz, 6-Hax), 2.91

(1/2H, br d, J=14.5 Hz, 6-Hax), 2.20—2.00 (10H, m, 5′-H_2, 10′-H_2, Ac×2), 1.79 (2H, m, 3-H_2), 1.62 and 1.52 (each 1H, m, 1′-H_2), 1.40—1.20 (10H, m, 2′—4′-H_2, 11′-H_2, 12′-H_2), 0.90 (3H, t, J=7 Hz, 12′-CH_3). **9** was acetylated (Ac_2O–pyridine) to give **4**, which was identical with the sample obtained above based on comparison of their spectra.

(3*E*,5*Z*)-3,5-Decadien-1-ol (12) A solution of (3*E*,5*Z*)-2-(3,5-decadienyloxy)tetrahydro-2*H*-pyran (**10**)[10] (1.04 g, 4.37 mmol) and *p*-TsOH (47 mg) in MeOH (5 ml) was stirred at room temperature for 10 h. Na_2CO_3 (70 mg) was added to this solution and the solvent was evaporated. H_2O was added to the residue and the whole was extracted with Et_2O. The extract was washed with brine, dried and concentrated. The residue was purified by MPLC (AcOEt–hexane, 15:85) to give **12** (588 mg, 88%) as a colorless oil (bp 165 °C/5 mmHg). IR cm^{-1}: 3600—3400 (OH). ^{1}H-NMR (200 MHz) δ: 6.49 (1H, br dd, J=15, 11 Hz, 4-H), 6.02 (1H, br t, J=11 Hz, 5-H), 5.67 (1H, dt, J=15, 7 Hz, 3-H), 5.41 (1H, dt, J=11, 7 Hz, 6-H), 3.72 (2H, br s, 1-H_2), 2.42 (2H, q, J=7 Hz, 2-H_2), 2.22 (2H, br q, J=6 Hz, 7-H_2), 1.48—1.24 (4H, m, 8-H_2, 9-H_2), 0.92 (3H, t, J=7 Hz, 9-CH_3). HR-MS *m/z*: 154.1352 (M^+). Calcd for $C_{10}H_{18}O$: 154.1355.

(3*E*,5*Z*)-1-Bromo-3,5-decadiene (14) PPh_3 (1.65 g, 6.3 mmol) and CBr_4 (1.82 g, 5.5 mmol) were added to a stirred solution of **12** (588 mg, 3.8 mmol) in MeCN (5 ml), and the mixture was stirred at room temperature for 1 h. The solvent was evaporated and the residue was purified by MPLC (hexane) to give **14** (762 mg, 92%) as a pale yellow oil (bp 150 °C/5 mmHg). ^{1}H-NMR (200 MHz) δ: 6.24 (1H, br dd, J=15, 11 Hz, 4-H), 5.99 (1H, br t, J=11 Hz, 5-H), 5.64 (1H, dt, J=15, 7 Hz, 3-H), 5.43 (1H, dt, J=11, 7 Hz, 6-H), 3.40 (2H, t, J=7 Hz, 1-H_2), 2.87 (2H, br q, J=7 Hz, 2-H_2), 2.18 (2H, br q, J=7 Hz, 7-H_2), 1.45—1.25 (4H, m, 8-H_2, 9-H_2), 0.90 (3H, t, J=7 Hz, 9-CH_3). HR-MS *m/z*: 218.0498 (M^+). Calcd for $C_{10}H_{17}{}^{81}Br$: 218.0494. *m/z*: 216.0514 (M^+). Calcd for $C_{10}H_{17}{}^{79}Br$: 216.0514.

(3*Z*,5*E*)-3,5-Decadien-1-ol (13) According to the procedure described for the preparation of **12**, (3*Z*,5*E*)-2-(3,5-decadienyloxy)tetrahydro-2*H*-pyran (**11**)[11] (2.87 g, 12.1 mmol)) was treated with *p*-TsOH (122 mg) in MeOH (10 ml) to give **13** (1.67 g, 90%) as a colorless oil (bp 165 °C/5 mmHg). IR cm^{-1}: 3600—3400 (OH). ^{1}H-NMR (500 MHz) δ: 6.32 (1H, br dd, J=15, 11 Hz, 5-H), 6.12 (1H, br t, J=11 Hz, 4-H), 5.72 (1H, dt, J=15, 7 Hz, 6-H), 5.30 (1H, dt, J=11, 7 Hz, 3-H), 3.68 (2H, t, J=7 Hz, 1-H_2), 2.46 (2H, br q, J=7 Hz, 2-H_2), 2.11 (2H, br q, J=7 Hz, 7-H_2), 1.41—1.28 (4H, m, 8-H_2, 9-H_2), 0.90 (3H, t, J=7 Hz, 9-CH_3). HR-MS *m/z*: 154.1345 (M^+). Calcd for $C_{10}H_{18}O$: 154.1355.

(3*Z*,5*E*)-1-Bromo-3,5-decadiene (15) According to the procedure described for the preparation of **14**, **13** (1.67 g, 10.9 mmol) was treated with PPh_3 (4.6 g, 17.9 mmol) and CBr_4 (5.42 g, 16.4 mmol) in MeCN (5 ml) to give **15** (2.20 g, 93%) as a pale yellow oil (bp 150 °C/5 mmHg). ^{1}H-NMR (200 MHz) δ: 6.18 (1H, br dd, J=15, 11 Hz, 5-H), 6.08 (1H, br t, J=11 Hz, 4-H), 5.76 (1H, dt, J=15, 7 Hz, 6-H), 5.39 (1H, dt, J=11, 7 Hz, 3-H), 3.40 (2H, t, J=7 Hz, 1-H_2), 2.74 (2H, br q, J=7 Hz, 2-H_2), 2.12 (2H, br q, J=7 Hz, 7-H_2), 1.48—1.20 (4H, m, 8-H_2, 9-H_2), 0.90 (3H, t, J=7 Hz, 9-CH_3). HR-MS *m/z*: 218.0502 (M^+). Calcd for $C_{10}H_{17}{}^{81}Br$: 218.0494. *m/z*: 216.0526 (M^+). Calcd for $C_{10}H_{17}{}^{79}Br$: 216.0514.

Pseudodistomin A Acetate (3) and [2α(6*E*,8*Z*),4β,5β]-(±)-1-Acetyl-5-(acetylamino)-2-(6,8-tridecadienyl)-4-piperidinol (16) According to the general procedure, a mixture of **7** (42 mg, 0.093 mmol) and Li_2CuCl_4 (0.005 M solution in THF, 0.05 ml, 2.5×10^{-7} mol) was treated with (3*E*,5*Z*)-3,5-decadienylmagnesium bromide in THF (5 ml), prepared from **14** (210 mg, 0.97 mmol) and magnesium (35 mg, 1.46 mmol), to give **3** (15 mg, 39%) and **16** (9.3 mg, 27%), each as a colorless oil.

3: IR cm^{-1}: 1740 (OCO), 1680 (NHCO), 1635 (NCO). ^{1}H-NMR (500 MHz) δ: 6.29 (1H, br dd, J=15, 11 Hz, 7′-H), 5.93 (1H, t, J=11 Hz, 8′-H), 5.78 (1H, br d, J=6 Hz, NH), 5.63 (1H, dt, J=15, 7.5 Hz, 6′-H), 5.30 (1H, br dt, J=11, 7.5 Hz, 9′-H), 5.15 (1H, br dt, J=12, 6.5 Hz, 4-H), 4.93 (1H, m, 2-H), 4.61 (1/5H, br d, J=14.5 Hz, 6-Heq), 4.50 (1/5H, br s, 5-H), 4.33 (4/5H, br s, 5-H), 3.96 (4/5H, br d, J=14.5 Hz, 6-Heq), 3.28 (4/5H, br d, J=14.5 Hz, 6-Hax), 2.92 (1/5H, br d, J=14.5 Hz, 6-Hax), 2.16 (2H, m, 10′-H_2), 2.07 (2H, m, 5′-H_2), 2.05, 2.04 and 2.03 (each 3H, s, Ac×3), 1.80—1.50 (4H, m, 3-H_2, 1′-H_2), 1.40—1.26 (10H, m, 2′—4′-H_2, 11′-H_2, 12′-H_2), 0.90 (3H, t, J=7 Hz, 12′-CH_3). ^{13}C-NMR δ: 170.6, 170.4 and 170.0 (each s, $\underline{C}OCH_3$), 134.3 and 130.3 (each d, 6′-C, 7′-C), 128.6 and 125.9 (each d, 8′-C, 9′-C), 66.9 (d, 4-C), 47.6 (d, 2-C), 47.2 (d, 5-C), 43.7 (t, 6-C), 32.8 (t, 5′-C), 31.9 (t, 11′-C), 30.2, 29.2, 29.0 and 28.4 (each t, 3-C, 1′-C, 3′-C, 4′-C), 27.4 (t, 10′-C), 26.2 (t, 2′-C), 23.4, 21.8 and 21.0 (each q, $CO\underline{C}H_3$), 22.3 (t, 12′-C), 14.0 (q, 13′-C). HR-MS *m/z*: 420.2990 (M^+). Calcd for $C_{24}H_{40}N_2O_4$: 420.2986. The synthetic **3** was shown to be identical with authentic pseudodistomin A acetate[2] based on comparison of their spectra.

16: ^{1}H-NMR (200 MHz) δ: 6.29 (1H, br dd, J=15, 11 Hz, 7′-H), 5.93 (1H, t, J=11 Hz, 8′-H), 5.63 (1H, dt, J=15, 7.5 Hz, 6′-H), 5.30 (1H, br dt, J=11, 7.5 Hz, 9′-H), 4.89 (1/2H, m, 2-H), 4.64 (1/2H, br d, J=14.5 Hz, 6-Heq), 4.40 (1H, m, 4-H), 4.29 (1H, br s, 5-H), 4.15 (1/2H, m, 2-H), 3.93 (1/2H, br d, J=14.5 Hz, 6-Heq), 3.26 (1/2H, br d, J=14.5 Hz, 6-Hax), 2.90 (1/2H, br d, J=14.5 Hz, 6-Hax), 2.16—2.00 (10H, m, 5′-H_2, 10′-H_2, Ac×2), 1.80—1.50 (4H, m, 3-H_2, 1′-H_2), 1.40—1.26 (10H, m, 2′—4′-H_2, 11′-H_2, 12′-H_2), 0.90 (3H, t, J=7 Hz, 12′-CH_3). **16** was acetylated (Ac_2O–pyridine) to give **3**, which was identical with the sample obtained above by spectral comparisons.

[2α(6*Z*,8*E*),4β,5β]-(±)-1-Acetyl-5-(acetylamino)-4-(acetyloxy)-2-(6,8-tridecadienyl)piperidine (17) and [2α(6*Z*,8*E*),4β,5β]-(±)-1-Acetyl-5-(acetylamino)-2-(6,8-tridecadienyl)-4-piperidinol (18) According to the general procedure, a mixture of **7** (39 mg, 0.086 mmol) and Li_2CuCl_4 (0.005 M solution in THF, 0.05 ml, 2.5×10^{-7} mol) was treated with (3*Z*,5*E*)-3,5-decadienylmagnesium bromide in THF (5 ml), prepared from **15** (180 mg, 0.83 mmol) and magnesium (30 mg, 1.25 mmol), to give **17** (12 mg, 33%) and **18** (5.8 mg, 18%), each as a colorless oil.

17: IR cm^{-1}: 1740 (OCO), 1680 (NHCO), 1635 (NCO). ^{1}H-NMR (500 MHz) δ: 6.27 (1H, br dd, J=15, 11 Hz, 8′-H), 5.94 (1H, br t, J=11 Hz, 7′-H), 5.76 (1H, br d, J=6 Hz, NH), 5.66 (1H, dt, J=15, 7.5 Hz, 9′-H), 5.26 (1H, br dt, J=11, 7.5 Hz, 6′-H), 5.15 (1H, br dt, J=12, 6.5 Hz, 4-H), 4.93 (1H, m, 2-H), 4.61 (1/5H, br d, J=14.5 Hz, 6-Heq), 4.51 (1/5H, br s, 5-H), 4.33 (4/5H, br s, 5-H), 3.96 (4/5H, br d, J=14.5 Hz, 6-Heq), 3.28 (4/5H, br d, J=14.5 Hz, 6-Hax), 2.92 (1/5H, br d, J=14.5 Hz, 6-Hax), 2.16 (2H, m, 5′-H_2), 2.10 (2H, m, 10′-H_2), 2.05, 2.04 and 2.03 (each 3H, s, Ac×3), 1.80—1.50 (4H, m, 3-H_2, 1′-H_2), 1.40—1.27 (10H, m, 2′—4′-H_2, 11′-H_2, 12′-H_2), 0.90 (3H, t, J=7 Hz, 12′-CH_3). ^{13}C-NMR δ: 170.6, 170.4 and 170.0 (each s, $\underline{C}OCH_3$), 134.9 and 129.7 (each d, 8′-C, 9′-C), 128.9 and 125.6 (each d, 6′-C, 7′-C), 66.9 (d, 4-C), 47.6 (d, 2-C), 47.2 (d, 5-C), 43.7 (t, 6-C), 32.6 (t, 5′-C), 31.6 (t, 11′-C), 30.2, 29.6, 29.0 and 28.4 (each t, 3-C, 1′-C, 3′-C, 4′-C), 27.6 (t, 10′-C), 26.2 (t, 2′-C), 23.4, 21.8 and 21.0 (each q, $CO\underline{C}H_3$), 22.3 (t, 12′-C), 14.0 (q, 13′-C). HR-MS *m/z*: 420.2982 (M^+). Calcd for $C_{24}H_{40}N_2O_4$: 420.2986.

18: ^{1}H-NMR (200 MHz) δ: 6.27 (1H, br dd, J=15, 10.5 Hz, 8′-H), 5.94 (1H, br t, J=10.5 Hz, 7′-H), 5.66 (1H, dt, J=15, 7.5 Hz, 9′-H), 5.26 (1H, br dt, J=10.5, 7.5 Hz, 6′-H), 4.90 (1/2H, m, 2-H), 4.65 (1/2H, br d, J=14.5 Hz, 6-Heq), 4.40 (1H, m, 4-H), 4.29 (1H, br s, 5-H), 4.15 (1/2H, m, 2-H), 3.98 (1/2H, br d, J=14.5 Hz, 6-Heq), 3.26 (1/2H, br d, J=14.5 Hz, 6-Hax), 2.91 (1/2H, br d, J=14.5 Hz, 6-Hax), 2.16—2.00 (10H, m, 5′-H_2, 10′-H_2, Ac×2), 1.80—1.50 (4H, m, 3-H_2, 1′-H_2), 1.40—1.27 (10H, m, 2′—4′-H_2, 11′-H_2, 12′-H_2), 0.90 (3H, t, J=7 Hz, 12′-CH_3). **18** was acetylated (Ac_2O–pyridine) to give **17**, which was identical with the sample obtained above based on comparison of their spectra.

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