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First Total Synthesis of Pseudodistomin Tetrahydroacetate

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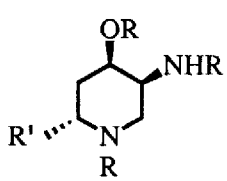
Keywords: total synthesis; pseudodistomin; reductive photocyclization; enamide; methylthio group; allyltributyltin; calmodulin antagonist

Abstract: *The first total synthesis of tetrahydroacetate of pseudodistomin, a novel antineoplastic piperidine alkaloid, was achieved via the route involving the reductive photocyclization of enamide and α-acylamino radical allylation.*

Pseudodistomins A and B (**1a, b**), potent antineoplastic piperidine alkaloids with calmodulin antagonistic activity, were isolated from the Okinawan tunicate *Pseudodistoma kanoko* as the first piperidine alkaloids from marine sources.[1] For the establishment of their structures which have been deduced from the spectral data, we have investigated the total synthesis of pseudodistomin A and B acetates (**1c, d**) and now succeeded in the first total synthesis of pseudodistomin tetrahydroacetate (**1f**) *via* the route involving the compound **1d**, proposed for pseudodistomin B acetate. Our synthesis has involved in two crucial photochemical reactions, reductive photocyclization of enamide[2] and α-acylamino photoallylation.[3]

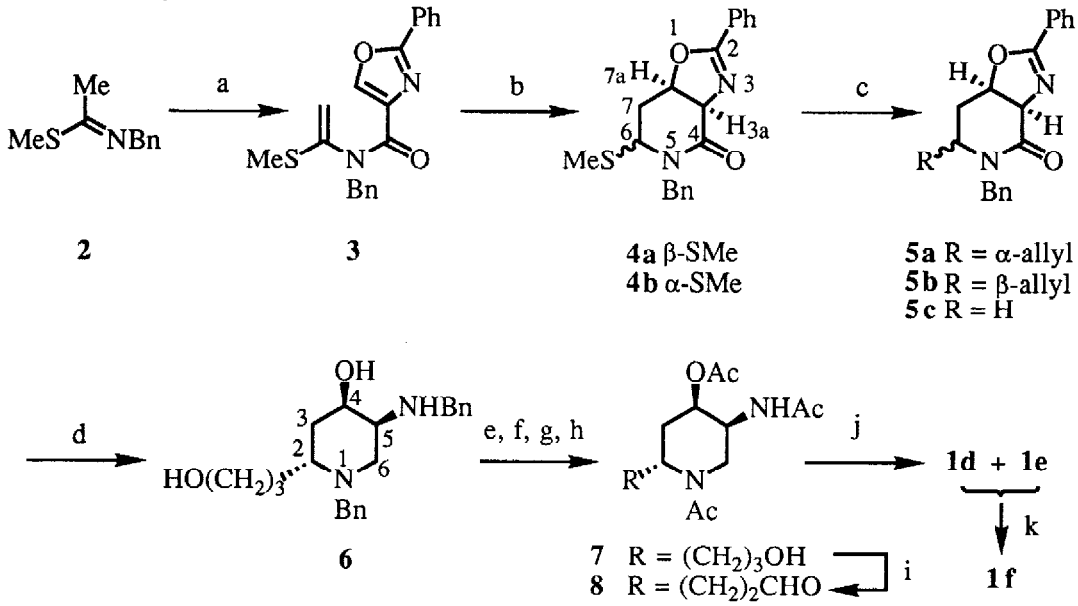


1a-f

1a R = H, R' = $(CH_2)_2$–3'–5'–$(CH_2)_6CH_3$
1b R = H, R' = $(CH_2)_2$–3'–5'–$(CH_2)_6CH_3$
1c R = Ac, R' = $(CH_2)_2$–3'–5'–$(CH_2)_6CH_3$
1d R = Ac, R' = $(CH_2)_2$–3'–5'–$(CH_2)_6CH_3$
1e R = Ac, R' = $(CH_2)_2$–3'–5'–$(CH_2)_6CH_3$
1f R = Ac, R' = $(CH_2)_{12}CH_3$

Acylation of the thioimidate **2**[2] with 2-phenyloxazole-4-carbonyl chloride[4] in the presence of triethylamine gave the (methylthio)enamide **3** which was then subjected to reductive photocyclization[2] in the presence of sodium borohydride in acetonitrile-methanol (9:1) to give the lactams **4a**[5] and **4b**[5] in 59 and 7 % yields respectively from the thioimidate **2**. Irradiation[3] of the (methylthio)lactam **4a** with high-pressure mercury lamp (Pyrex filter)

in the presence of allyltributyltin in toluene-acetonitrile (7:3) for 3 days gave the desired α-allyllactam **5a**[5] in 40% yield with the formation of small amount of β-allyl- **5b**[5] (21%) and hydrogenated lactams **5c**[5] (15%). Treatment of the allyllactam **5a** with borane-THF complex followed by hydrogen peroxide-sodium hydroxide resulted in the conversions (64% yield) of three functional groups, that is, oxidation of allyl group to the propanol, reduction of lactam carbonyl group to the amine, and opening reaction[6] of oxazoline moiety to the aminoalcohol **6**[5]. Selective protection of the primary hydroxyl group of the diol **6** with silyl group, debenzylation by hydrogenolysis in the presence of Pearlman's catalyst, acetylation, and desilylation gave the triacetyl alcohol **7** in four steps in overall 50% yield. Oxidation of the alcohol **7** with pyridinium chlorochromate in the presence of sodium acetate gave the unstable aldehyde **8** which was successively condensed with *E*-2-decenylphosphorane[7] under the Wittig condition to give a mixture of two dienes **1d, e** in 46% yield from **7**. The mixture was directly subjected to catalytic hydrogenation in the presence of 10% palladium on carbon to afford a single product **1f** in quantitative yield. The saturated product **1f** is found to be identical with pseudodistomin tetrahydroacetate by comparisons of IR, ^{1}H- and ^{13}C-NMR spectra with those of the authentic sample, provided by Professor J. Kobayashi, Hokkaido University, Japan.



(a) 2-phenyloxazole-4-carbonyl chloride, Et_3N; (b) hv/$NaBH_4$ in MeCN-MeOH; (c) hv/  $SnBu_3$ in toluene-MeCN; (d) i) BH_3•THF ii) H_2O_2, NaOH; (e) TBDMSCl/imidazole; (f) H_2/$Pd(OH)_2$-C; (g) Ac_2O-Py; (h) AcOH-THF-H_2O; (i) PCC-NaOAc; (j) C_7H_{15}  $CH_2P^+Ph_3$•Br^-, NaH, THF; (k) H_2/10% Pd-C

Thus, we have now succeeded in the first total synthesis of pseudodistomin tetrahydroacetate (**1f**) which has provided the concrete evidence for the deduced structures of pseudodistomins A and B (**1a, b**) except the position and geometry of the diene in the alkenyl side chain.

Careful separation of a mixture of two dienes **1d, e**, prepared by the above mentioned Wittig reaction, by medium-pressure column chromatography and reversed-phase HPLC (ODS) provided almost equal amount of each pure diene **1d**[8] and **1e**.[9] Among them, the diene **1d** would be expected to be pseudodistomin B acetate based on our synthetic reaction sequence including the Wittig reaction. However, direct comparisons of ^{1}H- and ^{13}C-NMR spectra of synthetic diene **1d** with those of the authentic pseudodistomin B acetate have shown that their spectra are not superimposable but very closely resembled, particularly signals due to the diene moiety in the alkenyl side chain. This fact has suggested that the deduced structure[1] on the alkenyl part of pseudodistomin B acetate should be revised.

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5. **4a**: mp 166-167°C; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 5.23 (1H, br dd, *J*=10 and 4 Hz, 7a-H),5.15 (1H, d, *J*=10 Hz, 3a-H), 4.45 (1H, m, 6-H), 2.67 (1H, dt, *J*=12 and 1 Hz, 7-Heq), 2.16 (1H, br dt, *J*=12 and 4 Hz, 7-Hax), 2.12 (3H, s, SMe). **4b**: oil; ^{1}H-NMR ($CDCl_3$, 200MHz) δ 5.44 (1H, td, *J*=10 and 6 Hz, 7a-H), 4.97 (1H, d, *J*=10 Hz, 3a-H), 4.34 (1H, t, *J*=3.5 Hz, 6-H), 2.60 (1H, ddd, *J*=13.5, 6, and 3.5 Hz, 7-Heq), 2.14 (3H, s, SMe), 1.93 (1H, ddd, *J*=13.5, 10, and 3.5 Hz, 7-Hax). **5a**: oil; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 5.71 (1H, dddd, *J*=18, 10, 8, and 6 Hz, 2'-H), 5.28 (1H, td, *J*=10 and 6 Hz, 7a-H), 5.03 (1H, d, *J*=10 Hz, 3a-H), 3.42 (1H, m, 6-H), 2.36 (1H, ddd, *J*=13.5, 6, and 4 Hz, 7-Heq), 1.76 (1H, ddd, *J*=13.5, 10, and 4.5 Hz, 7-Hax). **5b**: mp 186-187°C; NMR ($CDCl_3$, 500 MHz) δ 5.67 (1H, dddd, *J*=18, 10, 8, and 6 Hz, 2'-H), 5.17 (1H, br dd, *J*=9.5 and 5 Hz, 7a-H), 5.06 (1H, d, *J*=10.5 Hz, 3a-H), 3.38 (1H, m, 6-H), 2.45 (1H, dt, *J*=15.5 and 2.5 Hz, 7-Heq), 1.88 (1H, dt, *J*=15.5 and 5 Hz, 7-Hax). **5c:** oil; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 5.19 (1H, br dt, *J*=10 and 4 Hz, 7a-H), 4.98 (1H, d, *J*=10 Hz, 3a-H), 3.36 (1H, ddd, *J*=13.5, 11, and 3.5 Hz, 6-Hax), 3.09 (1H, dtd, *J*=13.5, 4, and 1 Hz, 6-Heq), 2.14 (1H, dq,

J=14.5 and 4 Hz, 7-Heq), 1.98 (1H, ddt, J=14.5, 11, and 4 Hz, 7-Hax). **6**: oil; ^{1}H-NMR ($CDCl_3$-D_2O, 500 MHz) δ 3.92 (1H, br s, 4-H), 3.67 (2H, m, 3'-H), 2.83 (1H, m, 2-H), 2.75 1H, br dt, J=9 and 3.5 Hz, 5-H), 2.48 (1H, dd, J=11.5 and 4 Hz, 6-Heq), 2.25 (1H, br dd, J=11.5 and 9 Hz, 6-Hax).

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8. **1d**: oil; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.04-5.94 (m, 4'- and 5'-H), 5.84 (br d, J=5 Hz, NHAc), *5.63 (m, NHAc), 5.60 and 5.52 (each br dt, J=14 and 7 Hz, 3'- and 6'-H), 5.14 (m, 4-H), *5.12 (m, 4-H), 4.97 (br s, 2-H), *4.63 (br d, J=14.5 Hz, 6-Heq), *4.51 (br s, 5-H), 4.36 (br s, 5-H), *4.03 (br s, 2-H), 3.96 (br d, J=14.5 Hz, 6-Heq), 3.29 (br d, J=14.5 Hz, 6-Hax), *2.93 (br d, J=14.5 Hz, 6-Hax), 2.16-1.96 (m, 2'-H_2, 7'-H_2, and Ac × 3), 1.82-1.59 (m, 3- and 1'-H_2), 1.36-1.23 (m, 8'~12'-H_2), 0.88 (t, J=7 Hz, 13'-H_3). As in the case of authentic pseudodistomin A and B acetates,[1] several protons were observed in 4:1 ratio, indicating the presence of two slowly interconverting conformations due to the amide rotation of *N*-acetates, and the asterisks show the signals of the minor conformer. ^{1}H-^{1}H COSY spectrum has unambiguously established the position of the diene as follows: Signals at δ 4.97 (2-H) has correlated with only signals at δ 1.82-1.59 which are assignable to 1'-H_2 and 3-H_2. Both signals at δ 5.60 and 5.52 (3'-H and 6'-H) have orrelated with signals at δ 2.16-1.96 which are assignable to allylic methylenes, 2'-H_2 and 7'-H_2. Cross peaks between signals at δ 1.82-1.59 (1'-H_2) and at δ 2.16-1.96 (2'-H_2) have established the presence of two methylene moieties between the 2-position in iperidine ring and 3'-position in the diene part. ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 170.6s, 170.5s, 170.0s, 133.5d, 131.3d, 130.0d, 129.9d, 66.8d, 47.3d, 47.0d, 43.7t, 32.6t, 31.8t, 29.9t, 29.3t, 29.3t, 29.2t, 29.1t, 28.5t, 23.3q, 22.6t, 21.7q, 21.0q, 14.1q.
9. **1e**: oil; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.36-6.14, 5.99-5.86, 5.74-5.56, and 5.42-5.18 (each m, 3'~6'-H), 5.86 (m, NHAc), *5.63 (m, NHAc), 5.15 (m, 4-H), *5.12 (m, 4-H), 4.98 (br s, 2-H), *4.64 (br d, J=15 Hz, 6-Heq), *4.51 (br s, 5-H), 4.34 (br s, 5-H), *4.03 (br s, 2-H), 3.97 (br d, J=15 Hz, 6-Heq), 3.30 (br d, J=15 Hz, 6-Hax), *2.94 (br d, J=15 Hz, 6-Hax), 2.20-1.96 (m, 2'-H_2, 7'-H_2, and Ac × 3), 1.90-1.50 (m, 3- and 1'- H_2), 1.41-1.20 (m, 8'~12'-H_2), 0.88 (t, J=7 Hz, 13'-H_3). As in the case of **1d**, several protons were observed in 4:1 ratio, indicating the presence of two slowly interconverting conformations due to the amide rotation of *N*-acetates[1] and the asterisks show the signals of the minor conformer.

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