SYNTHESIS OF (±)-TETRAHYDROPSEUDODISTOMIN, A HYDROGENATION PRODUCT OF ANTINEOPLASTIC ALKALOIDS, PSEUDODISTOMINS A AND B

Iwao Utsunomiya, Masashi Ogawa, and Mitsutaka Natsume*

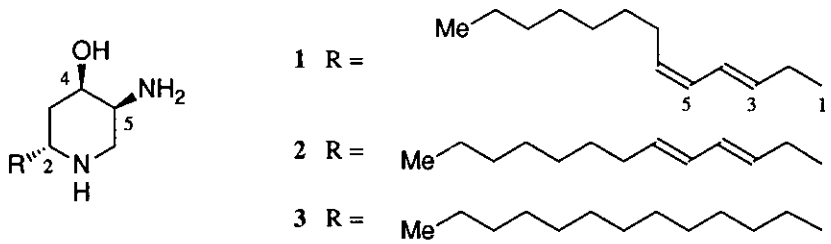
Research Foundation Itsuu Laboratory

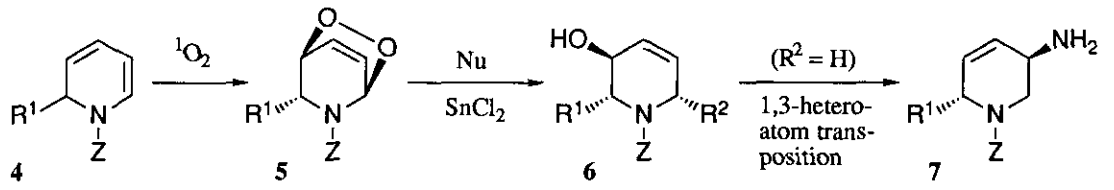
2-28-10 Tamagawa, Setagaya-ku, Tokyo 158, Japan

Abstract —— 2-Alkyl-1,2,3,6-tetrahydro-3-pyridinols (**6**, R^2 = H) with trans arrangement of the side chains were prepared by sodium cyanoborohydride reduction of the singlet oxygen adducts (**5**) of 1,2-dihydropyridine derivatives (**4**) in the presence of tin (II) chloride. Stereoselective synthesis of (±)-tetrahydropseudodistomin (**3**) was achieved starting from one of such reaction products (**10**) by way of **12** and **14**.

Potent antineoplastic piperidine alkaloids with calmodulin antagonistic activity, pseudodistomins A and B were isolated from the Okinawan tunicate Pseudodistoma kanoko, and their structures were shown to be [2R(3E, 5Z), 4R, 5S]- and [2R(3E, 5E), 4R, 5S]-5-amino-2-(3,5-tridecadienyl)-4-piperidinols (**1**) and (**2**).[1]

We have developed a novel type of carbon-carbon bond forming reaction using singlet oxygen adducts (**5**) of 1,2-dihydropyridine derivatives (**4**) to produce 2,6-dialkyl-1,2,3,6-tetrahydro-3-pyridinols (**6**) (Scheme 1).[2] Our intention of the synthesis of **1** and **2** was stimulated by the finding, reported in this paper, that the reduction of the above adducts (**5**) with sodium cyanoborohydride afforded 2-alkyl-1,2,3,6-tetrahydro-3-pyridinols (**6**, R^2 = H). With these compounds in hand, the stereocontrolled 1,3-transposition of the heteroatoms[3] would produce 2-





Scheme 1

alkyl-5-amino-1,2,5,6-tetrahydropyridine derivatives (**7**) with the amino group having the trans relationship to the C-2 substituent (R^1). The necessary hydroxy group at the C-4 position could be introduced by the hydroboration reaction on the double bond in **7**. According to this synthetic plan, we carried out a stereoselective synthesis of (±)-tetrahydropseudodistomin (**3**) as a model study.

Table 1

Formation of trans-2-Alkyl-1,2,3,6-terahydro-3-pyridinols (**6**, R^2 = H) by Sensitized Photooxygenation of **4**, Followed by Reduction with $NaBH_3CN$ in the Presence of $SnCl_2$

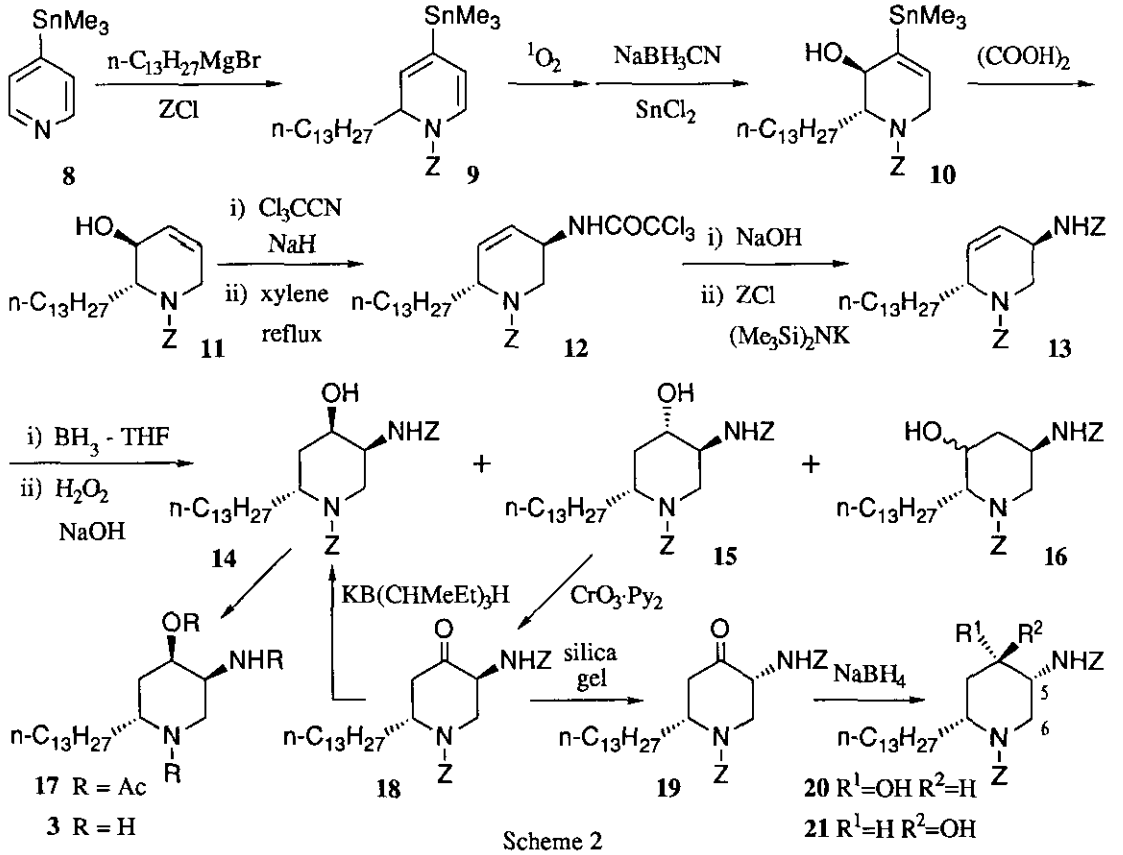
Entry	Starting Compound	R^1	Product	Yield %
1	**4a**	H	**6a**	64
2	**4b**	Me	**6b**	52
3	**4c**	n-Pr	**6c**	44
4	**4d**	vinyl	**6d**	53
5	**4e**	$n\text{-}C_{13}H_{27}$	**6e = 11**	42

1-Benzyloxycarbonyl-1,2-dihydropyridine (**4a**) and their 2-alkyl derivatives (**4b – 4e**) were subjected to the photooxygenation reaction using methylene blue as a sensitizer in purified dichloromethane, and the adducts (**5**) produced here were directly treated with sodium cyanoborohydride and an ethyl acetate suspension of tin (II) chloride (Table 1). As the singlet oxygen approaches to the dihydropyridine molecule from the opposite side of the 2-alkyl group,[2] the products obtained in 42 – 64% yields are trans-2-alkyl-1,2,3,6-tetrahydro-3-pyridinol derivatives (**6b – 6e**) in addition to the unsubstituted compound (**6a**).

Actual synthesis was initiated from 4-trimethylstannylpyridine[4] (**8**) (Scheme 2). With this trimethylstannyl group at the C-4 position, alkylation of **8** proceeds only at the C-2 position.[5] Thus the Grignard reagent prepared from tridecyl bromide and the activated magnesium[6] was reacted with **8** in the presence of benzyloxycarbonyl chloride in tetrahydrofuran at -60 – -70°C to afford the 1,2-dihydropyridine derivative (**9**) in 84% conversion yield. This was submitted to the sensitized photooxygenation reaction in dichloromethane and the resulting mixture was treated successively with sodium cyanoborohydride and tin (II) chloride as shown above to give the piperidine derivative (**10**) in 66% yield. The trimethylstannyl substituent was removed by treating **10** with oxalic acid[5] in a mixture of tetrahydrofuran and water at 65°C to produce trans-1-benzyloxycarbonyl-2-tridecyl-1,2,3,6-

tetrahydro-3-pyridinol (**11**) in 98% yield.

The 1,3-transposition of the hydroxy group of **11** to the amino function in **12** with retention of the stereochemistry was carried out by treating **11** with trichloroacetonitrile in the presence of sodium hydride in tetrahydrofuran, followed by heating in xylene[3] to furnish the trichloroacetamide (**12**) in 76% yield. The amide function in **12** was changed to the readily cleavable carbamate group as in **13** by alkaline hydrolysis of **12** in aqueous dimethoxyethane, and subsequent treatment with potassium bis(trimethylsilyl)amide[7] in tetrahydrofuran, followed by addition of a tetrahydrofuran solution of benzyloxycarbonyl chloride. The carbamate compound (**13**) was produced in 88% yield. The next task, introduction of the hydroxy group was effected by the hydroboration of **13** in the usual manner, and three products (**14**), (**15**) and (**16**) were obtained in 7%, 74.5% and 11.5% yields, respectively. Among these, the product (**14**) was the requisite compound, since the triacetate (**17**) obtained from **14** (catalytic hydrogenation over 10% palladium-charcoal and acetylation with acetic anhydride in pyridine) was identified as triacetyltetrahydropseudodistomin by comparison of their ^{1}H and ^{13}C nmr spectra. The product (**15**) was the stereoisomer of **14**, because its oxidation with the Collins reagent[8] in dichloromethane,



Scheme 2

followed by reduction with potassium tri(sec-butyl)borohydride in tetrahydrofuran afforded **14** in 64% yield, accompanied by the recovery of **15** in 28% yield. Thus the major hydroboration product (**15**) was converted to the necessary material (**14**) in a good yield. The intermediary ketone derivative (**18**) was unstable and only purification over silica gel made **18** transformation into another ketone derivative (**19**) in 91% yield, calculated from **15**. Therefore the conversion from **15** to **14** had to be carried out without purification of the unstable ketone compound (**18**).

This unstability is readily understood by the fact that the compound (**18**) having the two axial substituents[9] tends to be epimerized into the compound (**19**) with the C-2 axial and C-5 equatorial substituents. Evidence for this stereochemical assignment was obtained from the ^{1}H nmr spectra of the sodium borohydride reduction products (**20**) and (**21**), where the coupling constant between the axial proton at the C-6 position and the C-5 proton is 12 Hz. The corresponding coupling constant in the nmr spectra of **14** and **15** is nealy 0 Hz. The third hydroboration product (**16**) was a regioisomer of **14** and **15** with the unknown stereochemistry of the hydroxy group.

Finally removal of the protecting group from **14** afforded tetrahydropseudodistomin (**3**) in 84% yield. Further study of the synthesis of pseudodistomins A (**1**) and B (**2**) is in progress.

EXPERIMENTAL

Melting points (mp) were taken on Yanagimoto micro-melting point apparatus and are not corrected. Mass spectra (ms) were measured on a Hitachi RMS-4 spectrometer. High resolution mass spectra (HRms) were determined on a JEOL JMS-DX-300 spectrometer. Ir spectra (ir) were recorded on a Hitachi 215 spectrophotometer. ^{1}H Nmr spectra were measured on a Varian EM 390 spectrometer (90 MHz) and a JEOL JMN-GX-400 spectrometer (400 MHz) in $CDCl_3$ with TMS as an internal reference unless otherwise specified. ^{13}C Nmr spectra were determined on a JEOL JMN-GX-400 spectrometer (100 MHz) in $CDCl_3$ and chemical shifts were given in ppm related to the resonance of $CDCl_3$ (77.0 ppm). Column chromatography was conducted on silica gel Fuji Davison BW 200 and preparative thin-layer chromatography (ptlc) was carried out on glass plates (20 × 20 cm) coated with Merck silica gel 60 PF_{254} (1 mm thick). Elemental analyses were kindly carried out by Shionogi Research Laboratories. Usual work-up refers to washing the organic layers with water or brine, drying on anhydrous sodium sulfate and evaporation of the solvents under reduced pressure.

Formation of (2α, 3β)-(±)-2-alkyl-1-benzyloxycarbonyl-1,2,3,6-tetrahydro-3-pyridinol [6 (R^2 = H)] — Typical example is shown at the preparation of **10** from **9**. **6a**: Colorless oil. Ms m/z: 233 (M^+). Ir ($CHCl_3$) cm^{-1}: 1689, 1652 (sh). ^{1}H Nmr (90 MHz) δ: 3.00 (1H, br s, OH), 3.43 (1H, dd, J=13, 5.5 Hz), 3.71 (1H, dd, J=13, 4.5 Hz), 3.86-3.99 (2H, m), 4.03-4.32 (1H, m), 5.11 (2H, s), 5.61-6.02 (2H, m), 7.30 (5H, s). **6b**: Colorless

prisms, mp 73.5-74°C (benzene-hexane). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.04; H, 6.95; N, 5.78. Ms m/z: 247 (M^+). Ir (KBr) cm^{-1}: 1685, 1655. ^1H Nmr (90 MHz) δ: 1.04 (3H, d, J=7.5 Hz), 2.51 (1H, d, J=9 Hz, OH), 3.55 (1H, d, J=19 Hz), 3.75-4.00 (1H, m), 4.35 (1H, d, J=19 Hz), 4.50 (1H, br q, J=7.5 Hz), 5.13 (2H, s), 5.69-6.05 (2H, m), 7.31 (5H, s). **6c**: Colorless syrup. Ms m/z: 275 (M^+). Ir (neat) cm^{-1}: 1692, 1657. ^1H Nmr (90 MHz) δ: 0.87 (3H, br s), 1.29 (4H, br s), 2.78 (1H, br s, OH), 3.46 (1H, br d, J=20 Hz), 3.74-4.05 (1H, m), 4.18-4.57 (1H, m), 4.37 (1H, br d, J=20 Hz), 5.13 (2H, s), 5.64-6.07 (2H, m), 7.31 (5H, s). **6d**: Colorless syrup. Ms m/z: 259 (M^+). Ir ($CHCl_3$) cm^{-1}: 1692, 1656. ^1H Nmr (90 MHz) δ: 3.07 (1H, br s, OH), 3.57 (1H, br d, J=19.5 Hz), 3.95-4.13 (1H, m), 4.30 (1H, br d, J=19.5 Hz), 5.10 (2H, s), 5.62 (1H, ddd, J=17.5, 9, 5.5 Hz), 5.65-6.05 (2H, m), 7.27 (5H, s). For the data of **6e**, see **11**.

1-Benzyloxycarbonyl-1,2-dihydro-2-tridecyl-4-trimethylstannylpyridine (9) — A solution of $C_{13}H_{27}Br$ (798 mg, 3.03 mmol) in THF (3 ml) was added dropwise to a suspension of the activated Mg[6] (77 mg, 3.21 mgatom) in THF (4 ml) with stirring under Ar atmosphere at room temperature. After 1 h, the mixture was cooled at -78°C and to this were added a solution of 4-trimethylstannylpyridine[4] (**8**) (268 mg, 1.11 mmol) in THF (7 ml) and then a solution of benzyloxycarbonyl chloride (367 mg, 2.15 mmol) in THF (3 ml). The reaction mixture was stirred at -70 – -60°C for 4h. Sat. $NaHCO_3$-H_2O was added, the whole was extracted with Et_2O, and the extract was worked up as usual. Column chromatography over silica gel (40 g) using hexane-CH_2Cl_2 (2:1) afforded 367 mg (59%, conversion yield: 84%) of **9** as colorless oil, together with the recovered **8** (80 mg, 30%). Ms m/z: 557, 558, 559, 560, 561, 563, 565 (M^+). Ir ($CHCl_3$) cm^{-1}: 1698. ^1H Nmr (90 MHz, 55°C) δ: 0.15 (9H, s), 0.86 (3H, dif t, J=6 Hz), 4.41-4.71 (1H, m), 5.04 (2H, s), 5.16 (1H, d, J=7.5 Hz), 5.55 (1H, d, J=6 Hz), 6.52 (1H, d, J=7.5 Hz), 7.03-7.28 (5H, m).

(2α, 3β)-(±)-1-Benzyloxycarbonyl-1,2,3,6-tetrahydro-2-tridecyl-4-trimethylstannyl-3-pyridinol (10) — Oxygen gas was bubbled into a cooled solution of **9** (769 mg, 1.37 mmol) and methylene blue (61 mg) in CH_2Cl_2 (200 ml) with stirring at -65°C for 30 min, while the mixture was irradiated externally by 500 W halogen lamp (JD 110V 500W-M5). After terminating the irradiation, $NaBH_3CN$ (136 mg, 2.16 mmol) and a suspension of $SnCl_2$ (391 mg, 2.06 mmol) in AcOEt (50 ml) were successively added at -50°C. The reaction mixture was further stirred at -50°C for 10 min and at 0°C for 4.5 h. Sat. $NaHCO_3$-H_2O was added, precipitate was removed by filtration and the CH_2Cl_2 layer was worked up as usual. The residue was purified by column chromatography over silica gel (45 g) with hexane-AcOEt (3:2) and recrystallization from hexane to afford 527 mg (66%) of **10** as colorless needles, mp 83-84.5°C. Anal. Calcd for $C_{29}H_{49}NO_3Sn$: C, 60.22; H, 8.54; N, 2.42. Found: C, 60.24; H, 8.43; N, 2.39. Ms m/z: 575, 576, 577, 578, 579, 581, 583 (M^+). Ir (KBr) cm^{-1}: 1680. ^1H Nmr (90 MHz, 55°C) δ: 0.17 (9H, s), 0.87 (3H, dif t, J=6 Hz), 3.52 (1H, ddd, J=19.5, 2, 2 Hz), 3.95 (1H, br d, J=9 Hz), 4.34 (1H, dd, J=19.5, 4 Hz), 5.11 (2H, s), 5.89 (1H, dd, J=4, 2 Hz), 7.14-7.39 (5H, m).

(2α, 3β)-(±)-1-Benzyloxycarbonyl-1,2,3,6-tetrahydro-2-tridecyl-3-pyridinol (11) — A solution of **10** (145

mg, 0.25 mmol) and $(COOH)_2$ (233 mg, 2.48 mmol) in THF (5 ml) and H_2O (1 ml) was warmed with stirring at 65°C for 5 h. After cooling at 0°C, the mixture was neutralized with sat. $NaHCO_3$-H_2O and extracted with CH_2Cl_2. Usual work-up and ptlc [hexane-AcOEt (1:1)] afforded 102 mg (98%) of **11** as colorless oil. Ms m/z: 346 ($C_{13}H_{27}CH{=}NH^+$-Z). Ir ($CHCl_3$) cm^{-1}: 1692. ^1H Nmr (90 MHz) δ: 0.87 (3H, dif t, J=6 Hz), 2.47 (1H, br s, OH), 3.47 (1H, br d, J=18 Hz), 3.71-4.07 (1H, m), 4.37 (1H, br d, J=18 Hz), 5.03 (1H, d, J=12 Hz), 5.20 (1H, d, J=12 Hz), 5.64-6.04 (2H, m), 7.17-7.42 (5H, m).

(2α, 5β)-(±)-1-Benzyloxycarbonyl-1,2,3,6-tetrahydro-5-trichloroacetamino-2-tridecylpyridine (12) — To a stirred solution of **11** (123 mg, 0.30 mmol) in THF (3 ml) was added 50% NaH in mineral oil (16 mg, 0.33 mmol) at room temperature under Ar atmosphere, and the mixture was refluxed for 5 min and then cooled at 0°C. A solution of Cl_3CCN (56 mg, 0.39 mmol) in THF (1 ml) was added dropwise to this mixture, and the whole was stirred at room temperature for 1 h. After xylene (5 ml) was added and most of THF was distilled off, the reaction mixture was refluxed at 160-170°C for 3 h. Sat. $NaHCO_3$-H_2O was added, the whole was extracted with CH_2Cl_2 and worked up as usual. Ptlc [hexane-AcOEt (7:1)] afforded 126 mg (76%) of **12** as colorless syrup. Ms m/z: 558, 560, 562 (M^+). Ir ($CHCl_3$) cm^{-1}: 1710, 1692, 1654. ^1H Nmr (90 MHz) δ: 0.86 (3H, dif t, J=6 Hz), 3.17 (1H, dd, J=15, 3 Hz), 4.32 (1H, br d, J=15 Hz), 5.03 (1H, d, J=12 Hz), 5.17 (1H, d, J=12 Hz), 5.70-6.17 (2H, m), 7.17-7.42 (5H, m).

(2α, 5β)-(±)-1-Benzyloxycarbonyl-5-benzyloxycarbonylamino-1,2,3,6-tetrahydro-2-tridecylpyridine (13) — A solution of **12** (124 mg, 0.22 mmol) in 10% NaOH-H_2O (1 ml) and DME (1.5 ml) was stirred at room temperature for 14 h. Sat. NaCl-H_2O was added, the mixture was extracted with 10% MeOH in CH_2Cl_2, and usual work-up gave a colorless residue, which was dried over P_2O_5 under reduced pressure. To a cooled solution (–70°C) of this in THF (4 ml) was added $(Me_3Si)_2NK$ (77 mg, 0.39 mmol) with stirring, and after 5 min, ZCl (70 mg, 0.39 mmol) dissolved in THF (0.3 ml) was added at –70°C. The reaction mixture was further stirred at the same temperature for 1 h, quenched with sat. $NaHCO_3$-H_2O, and the whole was extracted with CH_2Cl_2. Usual work-up and ptlc [hexane-AcOEt (6:1)] afforded 107 mg (88%) of **13** as colorless syrup. Ms m/z: 548 (M^+). Ir ($CHCl_3$) cm^{-1}: 1708, 1690. ^1H Nmr (90 MHz) δ: 0.87 (3H, dif t, J=6 Hz), 3.08 (1H, dd, J=14, 3 Hz), 4.31 (1H, d, J=14 Hz), 4.80-5.20 (NH and 4H, m), 5.62-5.97 (2H, m), 7.13-7.42 (10H, m).

Hydroboration of 13 — To a solution of **13** (251 mg, 0.46 mmol) in THF (6 ml) was added 1M BH_3-THF solution (0.95 ml, 0.95 mmol) at 0°C under Ar atmosphere, and the mixture was stirred at the same temperature for 30 min. To this was added successively H_2O (0.2 ml), 10% NaOH-H_2O (1 ml) and 30% H_2O_2-H_2O (0.8 ml) at 0°C, and the mixture was further stirred at room temperature for 1 h. Sat. NH_4Cl-H_2O was added, the whole was extracted with CH_2Cl_2 and worked up as usual. Ptlc (1% MeOH in CH_2Cl_2) gave 29 mg (11.5 %) of **16** and a mixture of **14** and **15**. The latter was purified by ptlc [hexane-AcOEt (2:1)] to afford 17 mg (7%) of **14** and 188 mg (74.5%) of **15**. **(2α, 4β, 5β)-(±)-1-Benzyloxycarbonyl-5-benzyloxycarbonylamino-2-tridecyl-4-**

piperidinol (14): Colorless syrup. Ms m/z: 458 (M^+–$PhCH_2O$·–H·). Ir ($CHCl_3$) cm^{-1}: 1690. ^1H Nmr (90 MHz) δ: 0.87 (3H, dif t, J=6 Hz), 3.00 (1H, br d, J=15 Hz), 3.30 (1H, br s, OH), 4.07 (1H, br d, J=15 Hz), 4.99 (2H, s), 5.04 (2H, s), 5.28 (1H, br d, J=6 Hz, NH), 7.13-7.40 (10H, m). **(2α, 4α, 5β)-(±)-1-Benzyloxycarbonyl-5-benzyloxycarbonylamino-2-tridecyl-4-piperidinol (15)**: Colorless syrup. Ms m/z: 458 (M^+–$PhCH_2O$·–H·). Ir ($CHCl_3$) cm^{-1}: 1690. ^1H Nmr (90 MHz) δ: 0.87 (3H, dif t, J=6 Hz), 3.43 (1H, br d, J=15 Hz), 5.00 (2H, s), 5.01 (1H, d, J=13 Hz), 5.15 (1H, d, J=13 Hz), 5.36 (1H, br d, J=6 Hz, NH), 7.13-7.52 (10H, m). **(2α, 3ξ, 5β)-(±)-1-Benzyloxycarbonyl-5-benzyloxycarbonylamino-2-tridecyl-3-piperidinol (16)**: Colorless syrup. Ms m/z: 458 (M^+–$PhCH_2O$·–H·). Ir ($CHCl_3$) cm^{-1}: 1690. ^1H Nmr (90 MHz) δ: 0.86 (3H, dif t, J=6 Hz), 2.59 (1H, br s, OH), 2.88 (1H, br d, J=15 Hz), 4.06 (1H, br d, J=15 Hz), 4.97 (2H, s), 5.03 (2H, s), 7.12-7.41 (10H, m).

(±)-Triacetyltetrahydropseudodistomin (17) — A solution of **14** (9 mg, 0.016 mmol) in 95% EtOH (15 ml) was catalytically hydrogenated over 10% Pd-C (5 mg) at atmospheric pressure for 3 h. The catalyst was removed by filtration and the filtrate was evaporated in vacuo to give a syrup, which was dissolved in pyridine (0.5 ml) and stirred with Ac_2O (0.3 ml) at room temperature for 14 h. Sat. $NaHCO_3$-H_2O was added, the mixture was extracted with CH_2Cl_2, the extract was successively washed with sat. $CuSO_4$-H_2O, H_2O, sat. $NaHCO_3$-H_2O and H_2O, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. Purification of the residue by ptlc (3% MeOH in CH_2Cl_2) afforded 4 mg (60%) of **17** as colorless oil. HRms Calcd for $C_{24}H_{44}N_2O_4$: 424.3301. Found: 424.3296. Ms m/z: 424 (M^+), 365, 322, 306, 305, 263, 262, 181. Ir ($CHCl_3$) cm^{-1}: 3340, 1740, 1675, 1635, 1374, 1248, 1042. ^1H Nmr (400 MHz) δ: (major conformer) 0.88 (3H, t, J=7 Hz), 1.25 (24H, br s), 1.73-1.81 (2H, m), 2.03 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 3.30 (1H, d, J=14 Hz), 3.96 (1H, d, J=14 Hz), 4.34 (1H, br s), 4.93 (1H, br d, J=5 Hz), 5.06-5.22 (1H, m), 5.87 (1H, d, J=7.5 Hz, NH); (minor conformer) 2.92 (1H, d, J=14 Hz), 4.00 (1H, br s), 4.51 (1H, br s), 4.62 (1H, d, J=14 Hz), 5.64 (1H, d, J=7.5 Hz, NH). ^{13}C Nmr δ: 14.0, 21.0, 21.7, 22.6, 23.1, 26.2, 28.2, 29.2, 29.4, 29.4, 29.5, 30.0, 31.8, 43.7, 46.8, 47.5, 66.8, 170.0, 170.1, 170.6. These ^1H and ^{13}C nmr spectral data are identical with those in the literature.[1]

Conversion of 15 into 14 — A solution of **15** (25 mg, 0.044 mmol) in CH_2Cl_2 (15 ml) was added to a solution of Collins reagent[8] (213 mg, 0.83 mmol) in CH_2Cl_2 (15 ml) with stirring at 0°C. After 30 min, 5% NaOH-H_2O was added at 0°C and the mixture was extracted with CH_2Cl_2. Usual work-up afforded the unstable ketone derivative **18** (26 mg). ^1H Nmr (90 MHz) δ: 0.89 (3H, dif t, J=6 Hz), 2.38 (1H, dd, J=15, 4.5 Hz), 2.86 (1H, dd, J=15, 6 Hz), 5.06 (1H, d, J=13.5 Hz), 5.07 (2H, s), 5.20 (1H, d, J=13.5 Hz), 7.21-7.47 (10H, m). To a solution of **18** in THF (5 ml) was added 0.5 M potassium tri(sec-butyl)borohydride (K-selectride) in THF (0.20 ml, 0.1 mmol) at -70°C. After stirring at the same temperature for 15 min, the reaction mixture was quenched with sat. NH_4Cl-H_2O, extracted with CH_2Cl_2 and worked up as usual. Ptlc [hexane-AcOEt (2:1)] afforded 16 mg (64%) of **14** and 7 mg (28%) of the recovery of **15**.

(2α, 5α)-(±)-1-Benzyloxycarbonyl-5-benzyloxycarbonylamino-2-tridecyl-4-piperidinone (19) — Oxida-

tion of **15** (11 mg, 0.019 mmol) in CH_2Cl_2 (6 ml) with Collins reagent (103 mg, 0.40 mmol) in CH_2Cl_2 (10 ml) was carried out as above, and the crude compound (**18**) (11 mg) formed here was purified by ptlc [hexane-AcOEt (3:1)] to give 10 mg (91%) of the epimerized compound (**19**). Ms m/z: 429 ($M^+-Z\cdot$). Ir ($CHCl_3$) cm^{-1}: 1708. ^1H Nmr (90 MHz) δ: 0.87 (3H, dif t, J=6 Hz), 2.39 (1H, d, J=13 Hz), 5.11 (2H, s), 5.20 (2H, s), 5.70 (1H, br s, NH), 7.22-7.50 (10H, m).

Sodium Borohydride Reduction of 19 — A solution of **19** (171 mg, 0.30 mmol) in MeOH (5 ml) was stirred with $NaBH_4$ (31 mg, 0.82 mmol) at 0°C for 15 min. Sat. NH_4Cl-H_2O was added, the mixture was extracted with 10% MeOH containing CH_2Cl_2 and worked up as usual. Separation by ptlc [hexane-AcOEt (2:1)] afforded 117 mg (68%) of **20** and 47 mg (27%) of **21**. **(2α, 4α, 5α)-(±)-1-Benzyloxycarbonyl-5-benzyloxycarbonylamino-2-tridecyl-4-piperidinol (20)**: Colorless syrup. Ms m/z: 431($M^+-Z\cdot$). Ir ($CHCl_3$) cm^{-1}: 1710, 1692. ^1H Nmr (90 MHz) δ: 0.87 (3H, dif t, J=6 Hz), 2.97 (1H, s, OH), 2.97 (1H, dd, J=12, 12 Hz), 5.04 (2H, s), 5.09 (2H, s), 5.50 (1H, d, J=8.5 Hz, NH), 7.15-7.40 (10H, m). **(2α, 4β, 5α)-(±)-1-Benzyloxycarbonyl-5-benzyloxycarbonylamino-2-tridecyl-4-piperidinol (21)**: Colorless syrup. Ms m/z: 431 ($M^+-Z\cdot$). Ir ($CHCl_3$) cm^{-1}: 1693. ^1H Nmr (90 MHz) δ: 0.87 (3H, dif t, J=6 Hz), 2.63 (1H, dd, J=12, 12 Hz), 3.17 (1H, br s, OH), 5.03 (2H, s), 5.07 (2H, s), 7.13-7.43 (10H, m).

(±)-Tetrahydropseudodistomin (3) — A solution of **14** (83 mg, 0.15 mmol) in 95% EtOH (16 ml) was catalytically hydrogenated over 10% Pd-C (41 mg) at atmospheric pressure for 2 h. The catalyst was removed by filtration and the filtrate was evaporated in vacuo to afford 37 mg (84%) of **3** as colorless amorphous solid. HRms Calcd for $C_{18}H_{38}N_2O$: 298.2984. Found: 298.2996. Ir (KBr) cm^{-1}: 3400. ^1H Nmr [90 MHz, $CDCl_3$-CD_3OD (2:1)] δ: 0.87 (3H, dif t, J=6 Hz), 1.95 (1H, br d, J=15 Hz), 2.68-3.09 (4H, m), 3.92 (1H, br s).

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