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CATALYTIC ASYMMETRIC SYNTHESIS OF BOTH ENANTIOMERS OF PYRROLIZIDINES 223H', 239K', 265H', AND 267H' FOUND IN MADAGASCAN FROGS (*MANTELLA*) AND THEIR AFFINITIES FOR NICOTINIC ACETYLCHOLINE RECEPTOR

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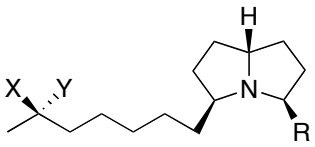
Abstract – The asymmetric synthesis of pyrrolizidines 223H', 239K', 265H', and 267H' has been achieved starting from 1,5-hexadiene *via* a common synthetic intermediate **5**. The affinity of both enanthiomers of **1**–**4** for nicotinic acetylcholine receptor was evaluated.

INTRODUCTION

A diverse array of biologically active, lipid-soluble alkaloids have been discovered in amphibian skin. During the past 30 years, over 800 alkaloids belonging to more than 20 structural classes have been detected.[1] Among them, a variety of 'izidines' (pyrrolizidines, indolizidines, and quinolizidines) have been reported. In 1993, four 3,5-disubstituted pyrrolizidines 223H' (**1**), 239K' (**2**), 265H' (**3**), and 267H' (**4**) were isolated from Madagascan frogs (*Mantella*).[2] It is known the relative structure of pyrrolizidine 223H' is identical to that of xenovenine found in an ant (*Solenopsis xenoveneum*).[3] It was recently reported that the absolute configuration of both alkaloids from frog and ant has the same absolute configuration, as shown in Chart 1.[1] However, the absolute configurations of the other three pyrrolizidnes remain unknown. The syntheses of chiral forms of xenovenine have been up to now reported several times,[4] whereas the syntheses of the other three have never been reported in either racemic or chiral forms. Among the

†This paper is dedicated to the memory of the late Dr. John W. Daly.

poison-dart frog alkaloids, 3,5-disubstituted, 5,8-disubstituted, and 5-substituted indolizidines[5] appear to represent an atypical and potent class of noncompetitive blockers for muscle-type and ganglionic nicotinic receptor-channels. However, the biological activity of homologues such as 3,5-disubstituted pyrrolizidines has not been investigated. Our current interest is in binding tests for the nicotinic acetylcholine receptor (nAChR) of these alkaloids, along with any detectable differences between the enantiomers. Accordingly, we developed a comprehensive synthetic program for preparing these alkaloids. In this paper we wish to report on the asymmetric synthesis of 3,5-disubstituted pyrrolizidines 223H' (**1**), 239K' (**2**), 265H' (**3**), and 267H' (**4**) from *trans*-2,5-disubstituted pyrrolidine as a common synthetic intermediate together with the synthesis of their enantiomers. In addition, their binding to the nicotinic acetylcholine receptor (nAChR) was examined.[6]



1 R = Me, X = Y = H **pyrrolizidine 223H'**
2 R = Me, X or Y = OH, Y or X = H **pyrrolizidine 239K'**
3 R = *n*-Pr, X-Y = O **pyrrolizidine 265H'**
4 R = *n*-Pr, X or Y = OH, Y or X = H **pyrrolizidine 267H'**

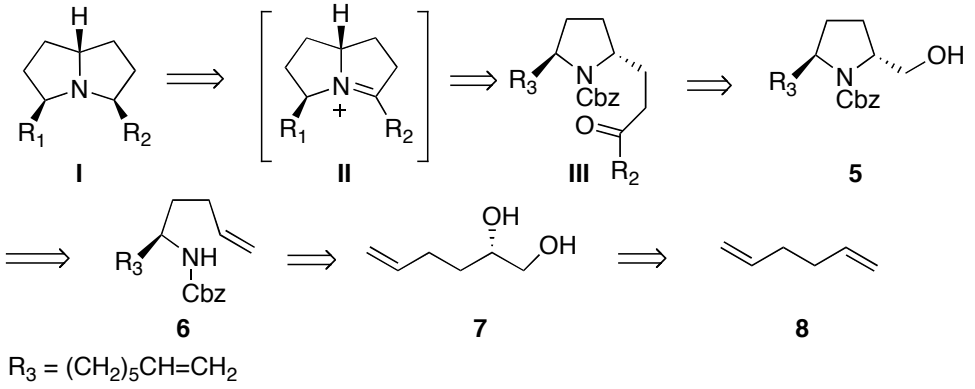
Chart 1

RESULTS AND DISCUSSION

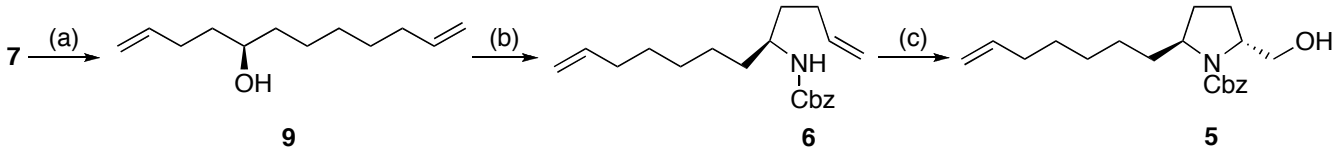
Our retrosynthetic analysis is shown in Scheme 1. The formation of 3,5-disubstituted pyrrolizidines could be stereoselectively accomplished by the reductive annulation of a ketopyrrolidines III *via* transient iminium ions II.[4d] The pyrrolidines could be constructed from the common intermediate, *trans*-2-hydroxymethyl-5-(6-heptenyl)pyrrolidine (**5**), prepared by the kinetically controlled intramolecular amidomercuration[4d] of a chiral 4-pentenylcarbamate **6**, which can be obtained from achiral 1,5-hexadiene (**8**) using the Sharpless asymmetric dihydroxylation (AD)[7] as a chiral source. The synthesis of the pyrrolidine was carried out as shown in Scheme 2.

The (*S*)-diol **7** (70% ee)[9] prepared by the $(DHQ)_2$-PYR[8] ligand-induced AD reaction of 1,5-hexadiene (**8**) was successively subjected to epoxidation,[10] and the regioselective cleavage of the resulting epoxide ring without further purification with 6-hexenylmagnesium bromide in conjunction with a cuprous iodide to give the alcohol **9** in 42% overall yield from **7**. The secondary alcohol **9** was converted *via* a four-step sequence (1. mesylation; 2. azidation; 3. reduction; 4. carbamation) into the desired *N*-benzyloxycarbonyl group (*N*-Cbz) **6** in 56% yield. The mercuric acetate-mediated cyclization of diene **6** followed by treatment with aqueous NaBr afforded the organomercurial, which was subjected to oxidative

demercuration[11] to provide the *trans* diastereomer **5** in 73% yield without the concomitant formation of the *cis* isomer and the azocine. This annulation proceeded stereoslectively and regioselectively.

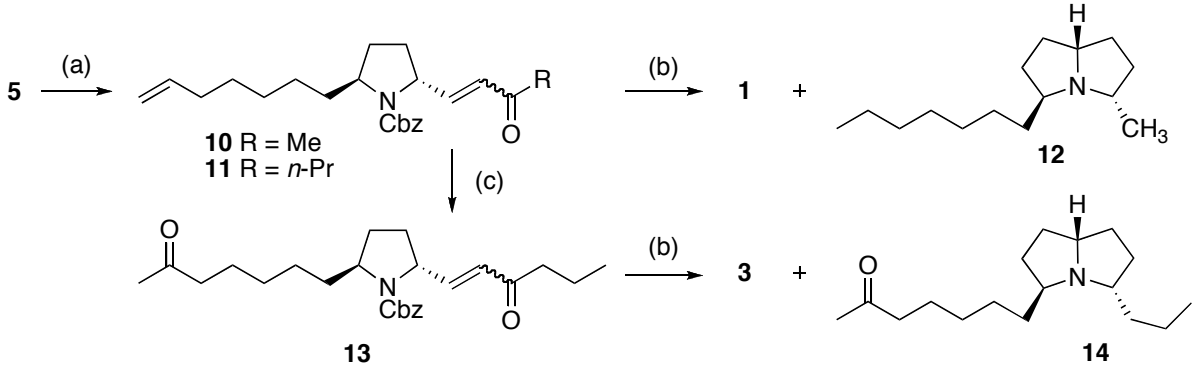


Scheme 1



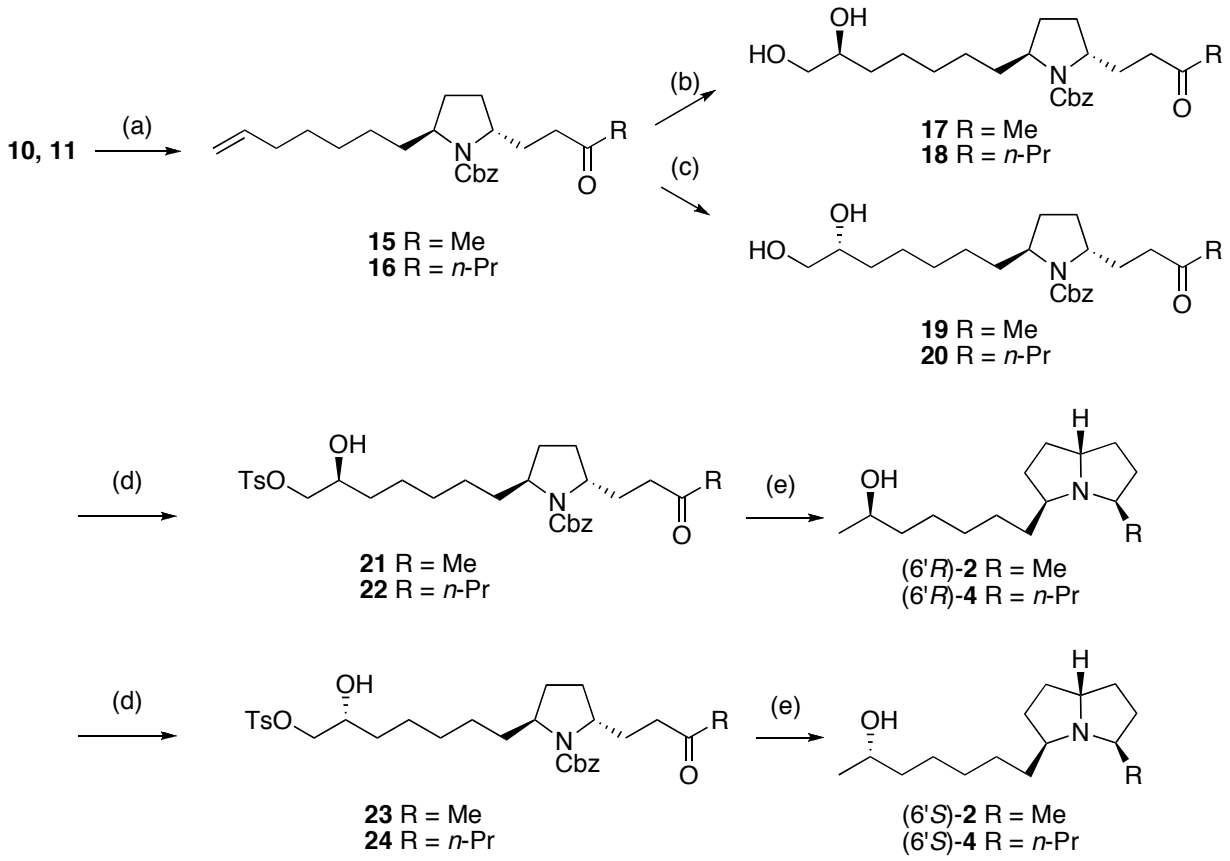
Scheme 2. (a) 1) $(MeO)_3CMe$/PPTS; 2) MeCOBr/cat. Et_3N; 3) K_2CO_3/MeOH/Et_2O; 4) 6-hexenylmagnesium bromide/CuI; (b) 1) MsCl/pyridine; 2) NaN_3; 3) $LiAlH_4$; 4) CbzCl/K_2CO_3; (c) 1) $Hg(OAc)_2$/THF; 2) NaBr; 3) $NaBH_4$/O_2/DMF

Having the common synthetic intermediate **5** in hand, we began with the elaboration of the ring appendage (hydroxymethyl). A Swern oxidation followed by the Horner–Emmons reaction using Masamune-Roush's conditions gave the α,β-unsaturated ketones **10** and **11** in 72 and 71% yields, respectively. A sequence of hydrogenolysis, the formation of immonium intermediate, and the reduction by the treatment of **10** with hydrogen in the presence of $Pd(OH)_2$ as a catalyst in methanol gave the desired (+)-pyrrolizidine 223H' (**1**) {$[\alpha]^{26}_D$ +10.2° ($CHCl_3$)}[12], lit.[4d]{$[\alpha]^{23}_D$ +10.9° ($CHCl_3$)}, in 54% yield along with its C-5 epimer **12** (10%). The spectral data for **1** were in agreement with previously reported data.[4d] The Wacker oxidation of the terminal olefin on **11** gave the diketone **13** in 73% yield. Exposure of the diketone to hydrogen under the above conditions proceeded regioselectively to give (+)-pyrrolizidines 265H' (**3**) {$[\alpha]^{27}_D$ +3.50° ($CHCl_3$)}, in 55% yield together with its C-5 epimer **14** (13%)}.



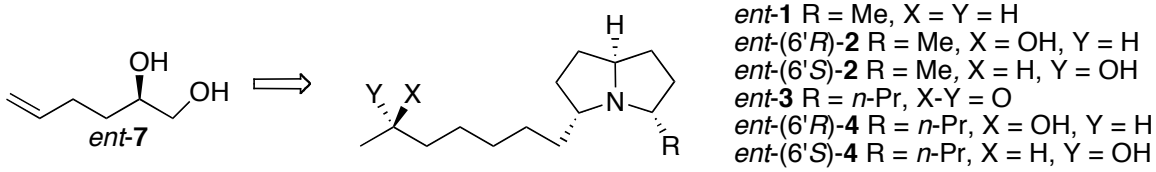
Scheme 3. (a) 1) $(COCl)_2$/DMSO/Et_3N; 2) $MeCOCH_2PO(OMe)_2$/iPr_2EtN/LiCl for **10**; *n*-$PrCOCH_2PO(OMe)_2$/iPr_2EtN/LiCl for **11**; (b) H_2/cat. $Pd(OH)_2$; (c) O_2/cat.$PdCl_2$/CuCl/DMF/H_2O

We then focused on the synthesis of pyrrolizidines 239K' and 267H'. The hydroxyl group of the C-3 appendage was installed *via* the AD reaction. Unfortunately, the AD reaction of **10** resulted in a mixture of diol and the tetraol. In advance of the AD, the conjugate olefin **10** was reduced with Red-Al, in the presence of CuBr[13], thus converting it to the monoolefin **15** in 74% yield. The $(DHQ)_2$-PYR[8] ligand-induced AD reaction of **15** afforded diol **17** in 84% yield. The selective monotosylation of primary hydroxyl group was accomplished in a two-step sequence (1. Bu_2SnO 2. *p*-TsCl) to give tosylate **21** in 58% yield. The formation of a pyrrolizidine ring was performed by exposing **21** to hydrogen in the presence of $Pd(OH)_2$ as a catalyst. The tosyloxy group of the resulting pyrrolizidine, without purification, was reduced with Super-Hydride®, to the desired pyrrolizidine 239K' (+)-(6'*R*-hydroxy)-**2**[14] in 58% yield[15] from **21**. Similarly, (+)-(6'*S*)-**2** was obtained from **15** *via* the $(DHQD)_2$-PYR[8] ligand-induced AD reaction of **15**[14] The two pyrrolizidines 267H' [(+)-(6'*S*)-and(+)-(6'*R*)-**4**][14] were next prepared from **16**, as shown in Scheme 4 by a similar procedure.[15]



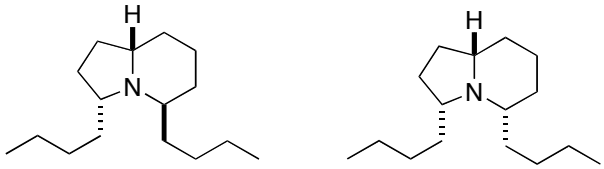
Scheme 4. (a) 1) Red-Al®/CuBr; (b) AD-mix-α [$(DHQD)_2$-PYR] ligand; (c) AD-mix-β ([$(DHQD)_2$-PYR] ligand; (d) 1) Bu_2SnO; 2) TsCl; (e) 1) H_2/cat. $Pd(OH)_2$; 2) Super-Hydride®

The analogous synthesis of six enantiomers of **1**, (6'*S*)-**2**, (6'*R*)-**2**, **3**, (6'*S*)-**4**, and (6'*R*)-**4** was performed starting from *ent*-**7** (80% ee) (Scheme 5).[6]



Scheme 5

With twelve chiral pyrrolizidines in hand, we turned our attention to examining their biological activity. The interaction of the prepared pyrrolizidines with the binding sites on carbamylcholine-activated nicotinic acetylcholine receptor (nAChR) channel complex from *Torpedo californica* electric organ was investigated using radiolabeled probe, [^{3}H]-thienyl-cyclohexylpiperidine ([^{3}H]-TCP). The K_i values for inhibition of [^{3}H]-TCP, compared to those for the 3,5-disubstituted indolizidines **25** and **26**,[5a] are shown in Table 1. Interestingly, the affinity of **1** was increased by one order compared with the corresponding indolizidines **25** and **26**. Since the introduction of a hydroxyl moiety in a side chain dramatically decreases the affinity, the structure–activity relationships suggest that hydrophobic interactions are important factors. As a result, the stereoconfiguration of the hydroxyl group had little effect on ion channel interactions. Surprisingly, no significant differences in affinities were observed between the two enantiomers.



25 **26**

Chart 2

Table 1. Evalution of the Affinities of 1-4, 25 and 26 for the nAChR of *Torpedo californica*[16]

Compounds	**1**	(6'*S*)-**2**	(6'*R*)-**2**	**3**	(6'*S*)-**4**	(6'*R*)-**4**	**25**	**26**
*K*i, μM	0.067	8.33	5.83	0.33	3.13	3.13	0.42	0.37
Compounds	*ent*-**1**	*ent*-(6'*S*)-**2**	*ent*-(6'*R*)-**2**	*ent*-**3**	*ent*-(6'*S*)-**4**	*ent*-(6'*R*)-**4**		
*K*i, μM	0.050	3.33	8.33	0.83	2.29	2.92		

In summary, the total synthesis of both enantiomers of the six 3,5-disubstituted pyrrolizidines **1**-**4** has been asymmetrically achieved starting from a symmetrical 1,5-hexadiene. Their affinities for the nAChR channel of *T. californica* were evaluated for the first time.

EXPERIMENTAL

General. Melting points are uncorrected. NMR spectra were recorded at 300 MHz (^{1}H), 75 MHz (^{13}C) using $CDCl_3$. As an internal standard, tetramethylsilane was used for $CDCl_3$. Mass spectra were obtained by EI or FAB mode. Silica gel for chromatography was Fuji Silysia PSQ 100B. When the reagents sensitive to moisture were used, the reaction was performed under argon atmosphere.

(*R*)-5-Hydroxydodeca-1,11-diene [(*R*)-9].

To a solution of (*S*)-**7** (70% ee)[9] (4.374 g, 37.6 mmol) and PPTS (94.5 mg, 0.38 mmol) in CH_2Cl_2 (47.7 mL) was added trimethyl orthoacetate (6.22 mL, 48.88 mmol) at rt and the mixture was stirred at the same temperature for 15 min. After evaporation of the nixture, triethylamine (0.52 mL, 3.76 mmol) was added in a solution of the residue in CH_2Cl_2 (47.7 mL). To a solution was slowly added acetyl bromide (3.34 mL, 45.12 mmol) at 0 °C and then the mixture was stirred for 1 h. To the reacion mixture was added 1M HCl (52 mL). The mixture was extracted with CH_2Cl_2, dried over anhyd. Na_2SO_4, and evaporated. Pulverized NaOH (3.308 g, 82.72 mmol) was added a solution of MeOH (2.29 mL, 56.4 mmol) in Et_2O (92.1 mL) and the reaction was stirred for 2.5 h. The mixture was filtered over K_2CO_3 and washed with Et_2O. The filtrate and washings were distilled at an atmosphere to yield the crude epoxide. To a suspension of Mg (1.113 g, 45.9 mmol) in THF (18.7 mL) was added 1-bromohexene (7.343 g, 45.9 mmol) with heating. The prepared Grignard reagent was added to a suspension copper(I) iodide (5.83 g, 33.66 mmol) in THF (52.0 mL) at –78 °C and then the temperature was raised to –40 °C. To the mixture was added a solution of the crude epoxy in THF (6 mL) at the same temperature and the mixture was stirred for 3 h. The reaction was quenched with sat. aq. NH_4Cl and separated. The aqueous layer was extracted with Et_2O. The combined solutions were successively washed with sat. aq. NH_4Cl, water, and brine, dried over anhyd. Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane : EtOAc = 30 : 1) to give (*R*)-**9** (3.553g, 42%) as an oil; $[\alpha]^{27}_D$+0.86° (c 2.75, $CHCl_3$); IRν_{max}^{cm-1} (neat) 3354, 2930, 2856, 1640, 909; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.10-1.79 (10H, m), 1.96-2.25 (4H, m), 3.57-3.63 (1H, m), 4.91-5.08 (4H, m), 5.74-5.91 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.60, 28.97, 29.26, 30.18, 33.83, 36.55, 37.50, 71.45, 114.35, 114.77, 138.74, 139.11; Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.95; H, 12.31.

(*S*)-9; (71%); $[\alpha]^{28}_D$-0.93° (c 1.14, $CHCl_3$).

(*S*)-5-Benzyloxycarbonylaminodeca-1,11-diene [(*S*)-6].

To a solution of (*R*)-**9** (3.93 g, 18.61 mmol) and DMAP (340.7 mg, 2.79 mmol) in pyridine (31.4 mL) was dropwise added methanesulfonyl chloride (3.24 mL, 27.92 mmol) at 90 °C and the whole was stirred for 2 h. The mixture was raised to rt and was further stirred for 30 min. Then the reaction was diluted

with Et_2O and acidified with aq. $KHSO_3$ at 0 °C. The whole was separated and the aqueous layer was extracted with Et_2O. The combined solvents were successively washed with water and brine, dried over anhyd. Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane : EtOAc = 30 : 1) to give the mesylate (4.521 g, 93%) as an oil;

A suspension of the mesylate (4.46 g, 17.13 mmol) and NaN_3 (1.67 g, 25.7 mmol) in DMF (33.8 mL) was heated with stirring at 45 °C for 3 h. After addition of water at rt, the whole was extracted with Et_2O. The extract was dried over anhyd. Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane) to give the azide (2.486 g, 70%) as an oil; $[\alpha]^{26}_D$+13.21° (c 3.30, $CHCl_3$); IRν_{max}^{cm-1} (neat) 2933, 2857, 2097, 1641, 1458, 1342, 1256, 994, 912; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.28-1.65 (10H, m), 2.02-2.25 (4H, m), 3.27 (1H, qui, *J* = 6.59 Hz), 4.92-5.09 (4H, m), 5.73-5.87 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 26.07, 28.88, 29.02, 30.46, 33.80, 34.53, 62.48, 77.41, 114.50, 115.50, 137.62, 138.98; HRMS calcd for $C_{12}H_{21}N_3$ 207.1735, found 207.1743.

To a suspension of $LiAlH_4$ (1.591 g, 41.88 mmol) in THF (130.8 mL) was slowly dropwised a solution of the azide (2.894 g, 13.96 mL) in THF (20.0 mL) at 0 °C and the whole was stirred for 1 h. To the mixture were successively added water (1.6 mL), 2N NaOH (1.6 mL), and water (4.8 mL). The whole was filtered through Celite and washed with ether. To the combined solvents was added 2N NaOH (6.2 mL) and CbzCl (2.18 mL, 15.36 mmol) at 0 °C and the whole was stirred at rt for 2.5 h. The mixture was extracted with Et_2O. The extract was successively washed with 20% $KHSO_3$, sat. aq. $NaHCO_3$, and brine, dried over anhyd. Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane : EtOAc = 60 : 1) to give (3.787 g, 86%) (*S*)-**6** as an oil; $[\alpha]^{27}_D$-0.88° (c 1.99, $CHCl_3$); IRν_{max}^{cm-1} (neat) 3311, 3067, 3035, 2978, 2922, 2852, 1682, 1542, 1290, 1259, 916, 726, 696; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.20-1.66 (10H, m), 2.00-2.14 (4H, m), 3.62-3.66 (1H, m), 4.48-4.52 (1H, m), 4.91-5.04 (1H, m), 5.09 (2H, s), 5.73-5.85 (2H, m), 7.30-7.37 (5H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.21, 25.71, 28.84, 29.06, 30.21, 33.75, 34.71, 35.42, 50.99, 66.50, 114.35, 114.88, 127.90, 128.07, 128.52, 136.80, 138.16, 139.01, 156.18; HRMS calcd for $C_{20}H_{29}NO_2$ 315.2199, found 315.2171.

(*R*)-6; (61%); $[\alpha]^{26}_D$+1.24° (c 2.30, $CHCl_3$).

(2*R*,5*S*)-1-Benzyloxycarbonyl-2-hydroxymethyl-5-(6'-heptenyl)pyrrolidine (5).

To a solution of (*S*)-**6** (3.226 g, 10.23 mmol) in THF (186 mL) was added mercuric acetate (3.419 g, 10.74 mmol) and then the reaction mixture was stirred for 18 h at rt. Sat. aq. $NaHCO_3$ (878.5 mg, 10.23 mmol) was added to the mixture with ice cooling. After 30 min of stirring, sat. aq. KBr (5.127 g, 40.92 mmol) was added to the mixture. After 2 h of stirring, the THF layer was separated. The aquous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried. After evaporation,

the resulting residue was purified by silica gel column chromatography (*n*-hexane : EtOAc = 15 : 1) to give the organomercurial (5.307 g, 87%) as an oil;

Oxygen (O_2) was bubbled into a suspension of $NaBH_4$ (466 mg, 12.28 mmol) in DMF (125 m) for 1 h, and to this was dropwise added a solution of organomercurial (5.219 g, 8.77 mmol) in DMF (363 mL) over 3 h with continuous introduction of O_2. The bubbling of O_2 into the mixture was continued for 1 h, and Et_2O was added. The reaction mixture was filtered through Celite, and the filtrate was evaporated. The residue was purified by silica gel column chromatography (*n*-hexane : EtOAc = 5 : 1) to give **5** (2.445 g, 84%) as an oil; $[\alpha]^{26}_{D}$+31.49° (c 2.75, $CHCl_3$); IRν_{max}^{cm-1} (neat) 3440, 2926, 2855, 1682, 1498, 1415, 1355, 1197, 1112, 1050, 909, 772, 732, 697; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.21-2.13 (14H, m), 3.80-4.00 (1H, m), 4.01-4.11 (1H, m), 4.91-5.09 (2H, m), 5.11-5.37 (2H, m), 5.70-5.84 (1H, m), 7.28-7.40 (5H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 26.42, 26.70, 26.85, 28.33, 28.91, 29.02, 32.78, 32.89, 33.69, 33.84, 59.17, 60.51, 67.35, 114.49, 128.16, 128.24, 128.34, 128.68, 139.10, 156.81; HRMS calcd for $C_{20}H_{29}NO_3$ 331.2148, found 331.2121.

ent-**5**; (63%); $[\alpha]^{26}_{D}$-38.61° (c 1.03, $CHCl_3$).

(2*R*,5*S*)-1-Benzyloxycarbonyl-2-(3'-oxo-1'-butenyl)-5-(6'-heptenyl)pyrrolidine (10).

To a solution of oxalyl chloride (482.5 μL, 5.56 mmol) in CH_2Cl_2 (7.0 mL) was dropwise added DMSO (783.8 μL, 11.12 mmol) at –78 °C, and the mixture was stirred for 10 min. To the whole was added a solution of **5** (922 mg, 2.78 mmol) in CH_2Cl_2 (7.0 mL) at the same temperature, and the mixture was stirred for 30 min. Then triethylamine (2.31 mL, 16.68 mmol) was dropwise added to the mixture and the whole was raised to –30 °C. After raising to rt, the mixture was stirred for 10 min and quenched with water. Then the whole was diluted with Et_2O and separated. The aqueous layer was extracted with Et_2O. The combined organic layers were dried and evaporated to yield the aldehyde. Without further purification, dimethyl (2-oxopropyl)phosphonate (245.9 mL, 1.78 mmol) and *N*,*N*-diisopropylethylamine (310.7 mL, 1.78 mmol) was successively added to a suspension of LiCl (75.5 mg, 1.78 mmol) in MeCN (12 mL) at 0 °C. To the whole was added a solution of the aldehyde in MeCN (9 mL) and the mixture was stirred at rt for 20 h. The whole was quenched with sat. aq. NH_4Cl at 0 °C, diluted with Et_2O, and separated. The aqueous layer was extracted with ether and the combined layers were dried over anhyd. Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane : EtOAc = 10 : 1) to give **10** (394 mg, 72%) as an oil; $[\alpha]^{26}_{D}$+59.60° (c 2.15, $CHCl_3$); IRν_{max}^{cm-1} (neat) 2927, 2856, 1698, 1630, 1456, 1405, 1351, 1255, 1187, 1104, 698; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.23-2.24 (14H, m), 2.10, 2.24 (6 : 5 ratio 3H, s), 3.85-3.92 (1H, m), 4.45-4.58 (1H, m), 4.91-5.16 (4H, m), 5.75-5.81 (1H, m), 5.91, 6.03 (6 : 5 ratio 1H, d, *J* = 15.9 Hz), 6.58, 6.67 (6 : 5 ratio 1H, dd, *J* = 15.9, 6.0 Hz), 7.36-7.28 (5H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 26.53, 26.59, 26.67, 27.51, 27.62, 27.67, 28.47,

28.85, 28.96, 29.00, 29.14, 29.49, 32.75, 32.87, 33.80, 33.83, 34.00, 58.11, 58.17, 58.26, 58.76, 66.84, 67.06, 114.40, 114.46, 128.16, 128.19, 128.28, 128.36, 128.56, 128.60, 129.44, 129.57, 136.69, 136.72, 139.04, 139.15, 146.45, 146.88, 154.20, 154.41, 198.21, 198.56; HRMS calcd for $C_{23}H_{31}NO_3$ 369.2304, found 369.2304.

ent-**10**; (70%); $[\alpha]^{26}_D$-72.24° (c 2.59, $CHCl_3$).

(2*R*,5*S*)-1-Benzyloxycarbonyl-2-(3'-oxo-1'-hexenyl)-5- (6'-heptenyl)pyrrolidine (11).

By the analogous procedure described for **10**, Swern oxidation of **5** (922 mg, 2.78 mmol) with oxalyl chloride (482.5 μL, 5.56 mmol), DMSO (783.8 μL, 11.12 mmol), and triethylamine (2.31 mL, 16.68 mmol) gave the aldehyde, which was converted with LiCl (141.6 mg, 3.34 mmol), dimethyl(2-oxopentyl)phosphonate (539.4 μL, 3.34 mmol), DIEPA (581.8 μL, 3.34 mmol) into **11** (785 mg, 71%) as a solid; mp 69-70 °C; $[\alpha]^{26}_D$+59.90° (c 1.94 $CHCl_3$); IRν_{max}^{cm-1} (KBr) 2927, 2858, 1698, 1630, 1466, 1418, 1376, 1349, 1193, 1110, 771, 755, 702; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.86-0.94 (3H, m), 1.23-2.24 (16H, m), 2.32, 2.51 (5 : 4 ratio 2H, t, *J* = 7.14 Hz), 3.84-3.92 (1H, m), 4.45-4.56 (1H, m), 4.91-5.19 (4H, m), 5.73-5.85 (1H, m), 5.92, 6.04 (5 : 4 ratio 1H, d, *J* = 15.94 Hz), 6.62, 6.68 (5 : 4 ratio 1H, dd, *J* = 6.04, 15.94 Hz), 7.28-7.36 (5H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.89, 13.93, 17.56, 26.54, 26.62, 27.64, 28.50, 28.87, 28.97, 29.02, 29.09, 29.15, 29.44, 32.87, 33.80, 33.84, 34.03, 42.65, 42.86, 58.15, 58.25, 58.32, 58.76, 66.81, 66.99, 114.40, 114.46, 128.10, 128.15, 128.18, 128.31, 128.52, 128.59, 128.81, 136.70, 136.80, 139.04, 139.16, 145.04, 145.61, 154.26, 154.38, 200.31, 200.59; HRMS calcd for $C_{25}H_{35}NO_3$ 397.2617, found 397.2613.

ent-**11**; (72%); $[\alpha]^{26}_D$-65.25° (c 2.48, $CHCl_3$).

(3*R*,5*S*,8*S*)-5-Heptyl-3-methylpyrrolizidine (1) and (3*S*,5*S*,8*S*)-5-Heptyl-3-methylpyrrolizidine (12).

A suspension of **10** (200 mg, 0.54 mmol), $Pd(OH)_2$ (35 mg) in MeOH (6 mL) was stirred under hydrogen atmosphere for 20 h. The reaction mixture was filtered through Celite and washed with CH_2Cl_2. The combined organic solvents were evaporated. The residue was purified by basic alumina column chromatography (*n*-hexane : Et_2O = 7 : 1) to give **1** (65 mg, 54%) and **12** (12 mg, 10%) as oils; **1**; $[\alpha]^{26}_D$+10.02° (c 0.71, $CHCl_3$); IRν_{max}^{cm-1} (neat) 2955, 2925, 2855, 1461, 1371, 1353, 1130, 1103, 745, 723; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, t, *J* = 7.10 Hz), 1.09 (3H, d, *J* = 6.04 Hz), 1.26-1.99 (20H, m), 2.57-2.62 (1H, m), 2.71-2.78 (1H, m), 3.59 (1H, qui, *J* = 6.59 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.28, 22.08, 22.84, 27.45, 29.53, 30.06, 31.89, 32.05, 32.28, 32.61, 34.62, 37.29, 61.83, 65.11, 66.81; HRMS calcd for $C_{15}H_{29}N$ 223.2300, found 223.2315. **12**; $[\alpha]^{28}_D$+21.73° (c 0.75, $CHCl_3$); IRν_{max}^{cm-1} (neat) 2926; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, t, *J* = 6.59 Hz), 1.18 (3H, d, *J* = 7.14 Hz), 1.26-2.10 (20H, m), 2.86-2.91 (1H, m), 3.19-3.27 (1H, m), 3.55-3.61 (1H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.31,

17.32, 22.87, 27.44, 29.58, 30.11, 31.08, 32.07, 32.77, 33.45, 38.64, 57.76, 57.93, 66.27; HRMS calcd for $C_{15}H_{29}N$ 223.2300, found 223.2271.

ent-**1**; (59%); $[\alpha]^{26}_{D}$-10.93° (c 1.45, $CHCl_3$). *ent*-**12**; (16%); $[\alpha]^{29}_{D}$-28.07° (c 1.02, $CHCl_3$).

(2*R*,5*S*)-Benzyloxycarbonyl-2-(3'-oxo-1'-hexenyl)-5-(6'-oxoheptyl)pyrrolidine (13).

A suspension of $PdCl_2$ (11.2 mg, 0.063 mmol) and CuCl (68.7 mg, 0.69 mmol) in a mixture of water and DMF (500 μL, 1 : 7) was stirred under oxygen for 1 h. To the whole was added a solution of **11** in a mixture of water and DMF (182 μL, 1 : 7) and then under oxygen the reaction mixture was heated with stirring at 40 °C overnight. 3N HCl (1 mL) was added to the whole and the aqueous layer was extracted with Et_2O. The extract was dried over anhyd. Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane : EtOAc = 3 : 1) to give **13** (189 mg, 73%) as a solid; mp 63-64 °C; $[\alpha]^{27}_{D}$+57.96° (c 1.67, $CHCl_3$); IRν_{max}^{cm-1} (KBr) 2937, 2858, 1698, 1631, 1467, 1420, 1350, 1323, 1192, 1110, 970, 771, 760, 704; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.84-0.92 (3H, m), 1.20-1.28 (4H, m), 1.45-1.71 (8H, m), 1.85-1.95 (2H, m), 2.09, 2.11 (unknown ratio 3H, s), 2.27-2.36 (2H, m), 2.40, 2.48 (5 : 4 ratio 2H, t, *J* = 7.14 Hz), 3.81-3.90 (1H, m), 4.45, 4.51 (5 : 4 ratio 1H, t, *J* = 7.14 Hz), 4.93, 5.05 (1H, d, 5 : 4 ratio 1H, d, *J* = 12.64 Hz), 5.13, 5.17 (5 : 4 ratio 1H, d, *J* = 4.40 Hz), 5.89, 6.02 (5 : 4 ratio 1H, d, *J* = 15.93 Hz), 6.59, 6.65 (unknow ratio 1H, dd, *J* = 6.04, 15.93 Hz), 7.25-7.34 (5H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.92, 13.97, 17.57, 23.77, 23.90, 26.59, 26.68, 27.68, 28.52, 29.09, 29.21, 29.46, 30.08, 32.81, 33.96, 42.89, 42.96, 43.74, 43.83, 58.06, 58.19, 58.35, 58.69, 66.87, 67.05, 128.15, 128.18, 128.24, 128.34, 128.45, 128.57, 128.62, 128.84, 136.70, 136.83, 145.01, 145.58, 154.29, 154.38, 200.35, 200.64, 209.17, 209.40; Anal. Calcd for $C_{25}H_{35}NO_4$: C, 72.61; H, 8.53; N, 3.39. Found: C, 72.71; H, 8.58; N, 3.16.

ent-**13**; (70%); $[\alpha]^{26}_{D}$-65.15° (c 0.91, $CHCl_3$).

(3*R*,5*S*,8*S*)-5-(6'-Oxoheptyl)-3-propylpyrrolizidine (3) and (3*S*,5*S*,8*S*)-5-(6'-Oxoheptyl)-3-propylpyrrolizidine (14).

A suspension of **13** (187mg, 0.45 mmol), $Pd(OH)_2$ (18 mg) in MeOH (11 mL) was stirred under hydrogen atmosphere for 20 h. The reaction mixture was filtered through Celite and washed with CH_2Cl_2. The combined organic solvents was evaporated. The residue was purified by basic alumina column chromatography (*n*-hexane : Et_2O = 7 : 1) to give **3** (66 mg, 55%) and **14** (15 mg, 13%) as oils; **3**; $[\alpha]^{27}_{D}$+3.50° (c 0.96, $CHCl_3$); IRν_{max}^{cm-1} (neat) 2929, 2859, 1717; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.59 Hz), 1.15-1.56 (16H, m), 1.84-1.95 (4H, m), 2.10 (3H, s), 2.39 (2H, t, *J* = 7.69 Hz), 2.56-2.58 (2H, br s), 3.51 (1H, t, *J* = 6.04 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.61, 20.53, 24.10, 27.16, 29.68, 30.04, 31.87, 31.89, 37.04, 39.51, 43.98, 64.69, 66.70, 66.79, 209.61; HRMS calcd for $C_{17}H_{31}NO$ 265.2406, found 265.2377. **14**; $[\alpha]^{25}_{D}$+7.98° (c 0.81 $CHCl_3$); IRν_{max}^{cm-1} (neat) 2931, 2862, 1717; ^{1}H-NMR

(300 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 6.59 Hz), 1.17-1.86 (16H, m), 1.89-2.01 (4H, m), 2.13 (3H, s), 2.42 (2H, t, *J* = 7.69 Hz), 2.83-2.82 (1H, br s), 2.98-3.10 (1H, br s), 3.51-3.59 (1H, br s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.63, 21.63, 24.07, 27.11, 29.62, 30.03, 30.25, 30.98, 31.79, 32.17, 33.81, 38.64, 43.94, 57.73, 63.88, 65.94, 209.58; HRMS calcd for $C_{17}H_{31}NO$265.2406, found 265.2390.

ent-**3**; (55%); $[\alpha]^{26}_{D}$-4.0° (c 0.60, $CHCl_3$). *ent*-**14**; (11%); $[\alpha]^{25}_{D}$-12.69° (c 0.98, $CHCl_3$).

(2*R*,5*S*)-1-Benzyloxycarbonyl-2-(3'-oxobutyl)-5-(6'-heptenyl)pyrrolidine (15).

To a suspension of CuBr (1.05 g, 7.29 mmol) in THF (14.6 mL) was added Red-Al (2.04 mL, 7.29 mmol) at 0 °C and then the whole was stirred 30 min. After cooling to –78 °C, 2-butanol (2.69 mL, 29.28 mmol) was added to the reaction mixture. After being stirred for 5 min, a solution of **10** (541 mg, 1.46 mmol) in THF (4.9 mL) was dropwise added to the mixture. The whole was stirred for 10 min, raised to –20 °C, and stirred for 12 h. The reaction was quenched with water and sat. aq. NH_4Cl and extracted with Et_2O. The extract was washed with water and sat. NH_4Cl, dried over anhyd. Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane : EtOAc = 10 : 1) to give **15** (402 mg, 74%) as an oil; $[\alpha]^{29}_{D}$+42.02° (c 2.29, $CHCl_3$); IRν_{max}^{cm-1} (neat) 2926, 2856, 1697, 1640, 1454, 1406, 1356, 1102, 698; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.20-1.35 (6H, m), 1.56-1.66 (4H, m), 1.81-2.14 (6H, m), 1.99, 2.14 (1 : 1.1 ratio 3H, s), 2.27-2.42 (2H, m), 3.74-3.79 (2H, m), 4.94 (2H, t-like, *J* = 10.44, 18.13 Hz), 5.05, 5.17 (each 1H, ABq, *J* = 12.09 Hz), 5.72-5.83 (1H, m), 7.27-7.35 (5H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 26.67, 26.88, 27.23, 27.58, 27.86, 28.02, 28.52, 28.97, 29.09, 29.26, 29.76, 29.93, 32.63, 33.89, 34.03, 41.13, 41.23, 41.31, 57.53, 57.93, 58.44, 58.50, 66.67, 114.27, 114.32, 127.92, 127.96, 128.18, 128.46, 128.51, 136.92, 138.98, 139.09, 154.11, 154.46, 208.06, 208.50; HRMS calcd for $C_{23}H_{33}NO_3$ (M^+) 371.2460, found 371.2456.

ent-**15**; (75%); $[\alpha]^{27}_{D}$-47.31° (c 2.21, $CHCl_3$).

(2*R*,5*S*)-1-Benzyloxycarbonyl-2-(3'-oxohexyl)-5-(6'-heptenyl)pyrrolidine (16).

By the analogous procedure described for **15**, the reduction of **11** (969 mg, 2.44 mmol) using CuBr (1.74 g, 12.2 mmol), Red-Al (3.40 mL, 12.2 mmol), 2-butanol (4.47 mL, 43.92 mmol) gave **16** (737 mg, 76%) as an oil; $[\alpha]^{26}_{D}$+39.12° (c 1.85, $CHCl_3$); IRν_{max}^{cm-1} (neat) 2927, 2858, 1695, 1457, 1407, 1355, 1109, 699; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.84-0.92 (3H, m), 1.21-1.36 (8H, m), 1.46-1.75 (6H, m), 1.89-2.12 (6H, m), 2.23-2.49 (4H, m), 3.74-3.80 (2H, m), 4.94 (2H, t-like, *J* = 10.44, 17.58 Hz), 5.06, 5.17 (each 1H, ABq, *J* = 12.09 Hz), 5.72-5.84 (1H, m), 7.27-7.35 (5H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.01, 17.48, 26.67, 26.89, 27.21, 27.50, 27.86, 28.03, 28.55, 28.97, 29.09 29.26, 32.64, 33.81, 33.89, 34.03, 40.22, 40.38, 44.59, 44.66, 57.21, 57.70, 57.90, 58.49, 66.65, 114.27, 114.32, 127.80, 127.90, 127.96, 128.12, 128.45, 136.95, 138.98, 139.09, 154.13, 154.43, 210.26, 210.61; HRMS calcd for $C_{25}H_{37}NO_3$ (M^+) 399.2773, found 399.2764.

ent-**16**; (73%); $[\alpha]^{26}_{D}$-46.33° (c 1.14, $CHCl_3$).

(2*R*,5*S*,6'*S*)-1-Benzyloxycarbonyl-2-(3'-oxobutyl)-5-(6',7'-dihydroxyheptyl)pyrrolidine (17).

A solution of **15** (371 mg, 1.0 mmol) in *t*-BuOH (2 mL) was added to a mixture of commercially available AD-mix-α [used $(DHQ)_2$-PYR as ligand] (1.41 g), *t*-BuOH (3 mL), and H_2O (5 mL) at 0 °C. After the reaction mixture was stirred for 24 h at the same temperature, sodium sulfite (2.058 g) was added to the mixture. The mixture was stirred for 30 min, filtered through a Celite pad, and washed with EtOAc (50 mL) three times. The organic layer was separated, dried over anhyd. Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane : EtOAc = 2 : 3) to give **17** (330 mg, 81%) as an oil; $[\alpha]^{26}_{D}$+36.90° (c 2.20, $CHCl_3$); IRν_{max}^{cm-1} (neat) 3428, 2932, 1694, 1498, 1411, 1356, 1199, 1163, 1106, 772, 751, 699; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.22-1.41 (8H, m), 1.53-1.70 (4H, m), 1.85-2.21 (7H, m), 2.00, 2.15 (1 : 1 ratio 3H, s), 2.30 (2H, t, *J* = 7.69 Hz), 2.37-2.54 (2H, m), 3.40-3.46 (1H, m), 3.61-3.80 (4H, m), 5.06, 5.16 (each 1H, ABq, *J* = 12.09 Hz), 7.23-7.36 (5H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.22, 25.69, 26.36, 26.45, 26.73, 26.92, 27.24, 27.53, 27.88, 28.00, 28.47, 29.02, 29.65, 29.79, 29.88, 29.97, 32.13, 32.33, 33.16, 33.25, 34.03, 41.13, 41.29, 57.11, 57.58, 57.91, 58.26, 66.71, 66.87, 66.96, 72.09, 72.30, 77.40, 127.95, 128.07, 128.18, 128.48, 128.54, 136.77, 136.92, 154.20, 154.51, 208.17, 208.67; HRMS calcd for $C_{23}H_{35}NO_5$ (M^+) 405.2515, found 405.2519 .

ent-**17**; (84%); $[\alpha]^{25}_{D}$-44.60° (c 2.35, $CHCl_3$).

(2*R*,5*S*,6'*S*)-1-Benzyloxycarbonyl-2-(3'-oxohexyl)-5-(6',7'-dihydroxyheptyl)pyrrolidine (18).

By the analogous procedure described for **17**, the dihydroxylation of **16** (349 mg, 0.88 mmol) with AD-mix-α (DHQ_2PYR (1.293 g) in *t*-BuOH (4.8 mL), and H_2O (4.8 mL) gave **18** (261 mg, 70%) as an oil; $[\alpha]^{26}_{D}$+37.62° (c 1.32, $CHCl_3$). IRν_{max}^{cm-1} (neat) 3420, 2931, 2857, 1694, 1455, 1411, 1357, 1308, 1163, 1105, 772, 752, 699; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.19-1.39 (8H, m), 1.47-1.62 (4H, m), 1.82-2.12 (4H, m), 1.94, 2.21 (1 : 1 ratio 3H, s), 2.24-2.66 (4H, m), 3.34-3.39 (1H, m), 3.58-3.76 (4H, m), 5.03, 5.13 (each 1H, ABq, *J* = 12.09 Hz), 7.23-7.32 (5H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.51, 25.60, 25.68, 26.38, 26.47, 26.62, 26.71, 26.89, 27.23, 27.53, 27.88, 27.99, 28.46, 29.47, 29.65, 29.79, 29.97, 32.31, 33.18, 33.25, 34.01, 41.13, 41.29, 57.11, 57.58, 57.90, 58.37, 58.41, 66.71, 66.85, 66.96, 72.09, 72.31, 72.39, 127.96, 128.07, 128.18, 128.48, 128.56, 136.78, 136.90, 154.22, 154.51, 208.18, 208.68; HRMS calcd for $C_{23}H_{35}NO_5$ (M^+) 405.2515, found 405.2517.

ent-**18**; (92%); $[\alpha]^{26}_{D}$-40.09° (c 1.31, $CHCl_3$).

(2*R*,5*S*,6'*R*)-1-Benzyloxycarbonyl-2-(3'-oxobutyl)-5-(6',7'-dihydroxyheptyl)pyrrolidine (19).

By the analogous procedure described for **17**, the dihydroxylation of **15** (375 mg, 1.01 mmol) with AD-mix-β ($DHQD_2$PYR (1.424 g) in *t*-BuOH (5.1 mL), and H_2O (5.1 mL) gave **19** (357 mg, 87%) as an oil; $[\alpha]^{26}_{D}$+34.99° (c 2.16, $CHCl_3$); IRν_{max}^{cm-1} (neat) 3365, 2932, 2856, 1691, 1466, 1412, 1355, 1331,

1310, 1213, 1106, 771, 699, 603; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.81-0.90 (3H, m), 1.09-1.43 (10H, m), 1.46-1.63 (6H, m), 1.86-2.07 (4H, m), 2.20-2.44 (4H, m), 2.88-3.14 (2H, m), 3.33-3.42 (1H, brs, m), 3.56-3.77 (4H, m), 5.03, 5.14 (each 1H, ABq, *J* = 12.64 Hz), 7.23-7.33 (5H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.95, 17.44, 25.31, 25.41, 25.51, 25.68, 26.39, 26.68, 26.86, 27.03, 27.17, 27.30, 27.39, 27.50, 27.83, 27.94, 28.44, 29.15, 29.49, 29.65, 32.19, 32.33, 33.13, 33.19, 34.01, 40.14, 40.28, 44.56, 44.65, 57.21, 57.29, 57.67, 57.87, 58.26, 58.34, 58.38, 66.67, 66.77, 66.88, 72.12, 72.27, 72.33, 76.87, 77.40, 127.89, 127.96, 128.04, 128.16, 128.19, 128.24, 128.28, 128.42, 128.46, 136.72, 136.84, 154.20, 154.45. 210.32, 210.78; HRMS calcd for $C_{25}H_{39}NO_5$ (M^+) 433.2828, found 433.2808.

ent-**19**; (81%); $[\alpha]^{26}_D$-42.37° (c 1.49, $CHCl_3$).

(2*R*,5*S*,6'*R*)-1-Benzyloxycarbonyl-2-(3'-oxohexyl)-5-(6',7'-dihydroxyheptyl)pyrrolidine (20).

By the analogous procedure described for **17**, the dihydroxylation of **16** (396 mg, 0.99 mmol) with AD-mix-β (DHQD$_2$PYR (1.467 g) in *t*-BuOH (5.5 mL), and H_2O (5.5 mL) gave **20** (353 mg, 82%) as an oil; $[\alpha]^{27}_D$+34.55° (c 1.22, $CHCl_3$); IRν_{max}^{cm-1} (neat) 3362, 2931, 2856, 1691, 1466, 1412, 1356, 1331, 1310, 1212, 1106, 771, 746, 604: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.83-0.92 (3H, m), 1.06-1.48 (10H, m), 1.51-1.81 (6H, m), 1.88-2.20 (4H, m), 2.25-2.51 (4H, m), 3.36-3.45 (1H, m), 3.61-3.79 (4H, m), 5.06, 5.16 (each 1H, ABq, *J* = 12.09 Hz), 7.27-7.40 (5H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.92, 13.95, 17.44, 25.53, 25.68, 26.45, 26.68, 26.82, 27.14, 27.23, 27.36, 27.41, 27.80, 27.92, 28.43, 29.47, 29.64, 29.72, 32.30, 33.18, 33.28, 34.00, 40.14, 40.28, 44.56, 44.65, 57.21, 57.65, 57.85, 58.37, 66.65, 66.76, 66.87, 72.25, 72.33, 127.89, 127.96, 128.02, 128.42, 128.45, 136.70, 136.81, 154.19, 154.43, 210.34, 210.78; HRMS calcd for $C_{25}H_{39}NO_5$ (M^+) 433.2828, found 433.2827.

ent-**20**; (76%); $[\alpha]^{26}_D$-43.54° (c 0.52, $CHCl_3$).

(2*R*,5*S*,6'*S*)-1-Benzyloxycarbonyl-2-(3'-oxobutyl)-5-
(6'-hydroxy-7'-*p*-toluenesulfonyloxy)heptyl-pyrrolidine (21).

A solution of **17** (319 mg, 0.79 mmol) and di-*n*-butyltin oxide (237 mg, 0.95 mmol) in toluene-THF (10 : 1) (28.4 mL) was refluxed with Dean-Stark apparatus for 6 h. The solvent was reduced to one of third amount under vacuo. To the rest were added triethylamine (2.71 mL, 0.04 mmol) and *p*-toluenesulfonyl chloride (177 mg, 0.95 mmol) and the whole was stirred at rt for 12 h. The reaction was quenched with brine, filtered through Celite, and washed with EtOAc. The combined organic solvents were dried over anhyd. Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane : EtOAc = 5 : 1) to give **21** (390 mg, 88%) as an oil; $[\alpha]^{27}_D$+24.97° (c 1.87, $CHCl_3$); IRν_{max}^{cm-1} (neat) 3446, 2937, 2858, 1694, 1497, 1454, 1410, 1357, 1189, 1176, 1098, 970, 816, 772, 699, 666; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.13-1.40 (8H, m), 1.52-1.60 (4H, m), 1.82-2.14 (7H, m), 1.96, 2.10 (1 : 1.1 ratio 3H, s), 2.26 (2H, t, *J* = 7.69 Hz), 2.39 (3H, s), 3.72-3.87 (3H, m), 3.93-3.96 (1H, m), 5.01, 5.12

(each 1H, ABq, *J* = 12.09 Hz), 7.24-7.31 (5H, m), 7.75 (2H, d, *J* = 7.14 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.73, 24.97, 25.19, 26.32, 26.50, 26.77, 27.07, 27.36, 27.74, 27.85, 28.32, 28.99, 29.29, 29.64, 29.79, 32.17, 32.71, 33.84, 40.95, 41.10, 56.96, 57.43, 57.71, 58.14, 66.55, 66.62, 69.01, 69.17, 73.94, 127.63, 127.83, 128.02, 128.12, 128.16, 128.33, 128.37, 129.83, 132.62, 136.69, 136.75, 144.87, 153.99, 154.29, 208.05, 208.46.

ent-**21**; (58%); $[\alpha]^{27}_{D}$-29.50° (c 1.53, $CHCl_3$).

(2*R*,5*S*,6'*S*)-1-Benzyloxycarbonyl-2-(3'-oxohexyl)-5-(6'-hydroxy-7'-*p*-toluenesulfonyloxyheptyl)-pyrrolidine (22).

By the analogous procedure described for **21**, the monotsylation of **18** (239 mg, 0.56 mmol) with di-*n*-butyltin oxide (178 mg, 0.67 mmol), triethylamine (2.30 mL, 0.028 mmol), and *p*-toluenesulfonyl chloride (133 mg, 0.67 mmol) in toluene-THF (21.3 mL) gave **22** (291 mg, 90%) as an oil; $[\alpha]^{27}_{D}$+20.49° (c 1.45, $CHCl_3$); IRν_{max}^{cm-1} (neat) 3445, 2935, 1694, 1598, 1497, 1455, 1410, 1357, 1189, 1176, 1098, 971, 815, 754, 699, 667; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.80-0.88 (3H, m), 1.13-1.44 (10H, m), 1.47-1.60 (6H, m), 1.82-2.09 (4H, m), 2.19-2.42 (7H, m), 2.39 (3H, s), 3.72-3.88 (4H, m), 3.92-3.96 (1H, m), 5.01, 5.12 (each 1H, ABq, *J* = 12.64 Hz), 7.22-7.31 (7H, m), 7.75 (2H, d, *J* = 8.24 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.86, 17.33, 21.72, 24.95, 25.18, 26.30, 26.36, 26.48, 26.77, 27.04, 27.29, 27.73, 27.85, 28.35, 28.97, 29.29, 32.17, 32.71, 33.84, 40.04, 40.17, 44.44, 44.50, 57.11, 57.56, 57.70, 58.11, 66.52, 66.59, 69.01, 69.17, 73.92, 77.40, 127.61, 127.71, 127.83, 127.95, 128.12, 128.34, 129.70, 129.72, 129.81, 132.62, 136.72, 136.77, 144.82, 144.85, 154.01, 154.26, 210.20, 210.55.

ent-**22**; (93%); $[\alpha]^{27}_{D}$-28.75° (c 1.70, $CHCl_3$).

(2*R*,5*S*,6'*R*)-1-Benzyloxycarbonyl-2-(3'-oxobutyl)-5-(6'-hydroxy-7'-*p*-toluenesulfonyloxyheptyl)-pyrrolidine (23).

By the analogous procedure described for **21**, the monotosylation of **19** (351 mg, 0.87 mmol) with di-*n*-butyltin oxide (259 mg, 1.04 mmol), triethylamine (3.20 mL, 0.044 mmol), and *p*-toluenesulfonyl chloride (209 mg, 1.04 mmol) in toluene-THF (33.5 mL) gave **23** (438 mg, 90%) as an oil; $[\alpha]^{27}_{D}$+31.25° (c 1.33, $CHCl_3$); 3447, 2937, 2858, 1696, 1498, 1458, 1410, 1357, 1188, 1176, 1098, 970, 816, 699, 668; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.11-1.40 (8H, m), 1.52-1.63 (4H, m), 1.82-2.14 (7H, m), 1.99, 2.14 (1.2 : 1 ratio 3H, s), 2.29 (2H, t, *J* = 7.69 Hz), 2.44 (3H, s), 3.74-3.90 (3H, m), 3.97-4.01 (1H, m), 5.04, 5.15 (each 1H, ABq, *J* = 12.64 Hz), 7.32-7.35 (5H, m), 7.77 (2H, d, *J* = 8.24 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.85, 25.28, 26.47, 26.51, 26.59, 26.83, 27.15, 27.45, 27.82, 27.92, 28.40, 28.99, 29.37, 29.75, 29.91, 32.37, 32.74, 33.92, 41.07, 41.22, 57.03, 57.50, 57.79, 58.20, 58.25, 58.32, 66.64, 66.71, 69.37, 69.40, 74.04, 127.75, 127.81, 127.93, 128.12, 128.22, 128.27, 128.42, 128.48, 129.77, 129.81, 129.94, 132.64, 136.78, 136.84, 144.98, 145.02, 154.10, 154.38, 208.15, 208.58.

ent-**23**; (95%); $[\alpha]^{27}_{D}$-34.92° (c 2.39, $CHCl_3$).

(2*R*,5*S*,6'*R*)-1-Benzyloxycarbonyl-2-(3'-oxohexyl)-5-(6'-hydroxy-7'-*p*-toluenesulfonyloxy)heptyl-pyrrolidine (24).

By the analogous procedure described for **21**, the monotosylation of **20** (351 mg, 0.87 mmol) with di-*n*-butyltin oxide (259 mg, 1.04 mmol), triethylamine (3.20 mL, 0.044 mmol), and *p*-toluenesulfonyl chloride (209 mg, 1.04 mmol) in toluene-THF (33.5 mL) gave **23** (438 mg, 90%) as an oil; $[\alpha]^{27}_{D}$+27.57° (*c* 1.03, $CHCl_3$); IRν_{max}^{cm-1} (neat) 3446, 2935, 1694, 1598, 1497, 1456, 1410, 1357, 1176, 1098, 970, 816, 754, 699, 666; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.81-0.90 (3H, m), 1.15-1.44 (10H, m), 1.46-1.62 (6H, m), 1.79-2.09 (4H, m), 2.21-2.55 (7H, m), 2.42 (3H, s), 3.74-3.89 (4H, m), 3.94-3.99 (1H, m), 5.03, 5.14 (each 1H, ABq, *J* = 12.64 Hz), 7.25-7.33 (7H, m), 7.77 (2H, d, *J* = 8.24 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.95, 17.41, 21.82, 25.25, 26.45, 26.56, 26.83, 27.12, 27.36, 27.80, 27.92, 28.41, 29.35, 32.37, 32.74, 33.90, 33.96, 40.13, 40.20, 40.28, 44.53, 44.60, 57.17, 57.64, 57.75, 58.29, 66.61, 66.65, 69.11, 69.32, 74.01, 77.38, 77.41, 77.55, 127.78, 127.90, 128.02, 128.40, 128.43, 129.78, 129.91, 130.04, 132.64, 136.84, 144.93, 144.98, 154.10, 154.34, 210.29, 210.64.

ent-**24**; (92%); $[\alpha]^{26}_{D}$-32.82° (c 3.21, $CHCl_3$).

(3*R*,5*S*,6'*R*,8*S*)-5-(6'-Hydroxyheptyl)-3-methylpyrrolizidine [(6'*R*)-2].

A suspension of **21** (162 mg, 0.29 mmol), $Pd(OH)_2$ (16.2 mg) in MeOH (9.1 mL) was stirred under hydrogen atmosphere for 12 h. The reaction mixture was filtered through Celite and washed with CH_2Cl_2. The combined organic solvents were evaporated. To a solution of the residue in THF (1.4 mL)was dropwise added 1.0 M Super-Hydride® in THF (1.16 mL) and the whole was stirred at rt for 5 h. The reaction mixture was quenched with ice and basified with 2N NaOH. The mixture was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over anhyd. Na_2SO_4, and evaporated. The residue was purified by basic alumina column chromatography (ether) to give (6*R*)-**2** (34 mg, 50%) as an oil; $[\alpha]^{26}_{D}$+11.37° (c 1.00, $CHCl_3$); IRν_{max}^{cm-1} (neat) 3385, 2927, 2857, 1458, 1374, 1128; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.09 (3H, d, *J* = 6.04 Hz), 1.17 (3H, d, *J* = 6.04 Hz), 1.21-1.62 (14H, m), 1.85-2.03 (4H, m), 2.61 (1H, qui-like, *J* = 7.14 Hz), 2.75 (1H, six-like, *J* = 6.04 Hz), 3.58 (1H, qui, *J* = 6.59 Hz), 3.78 (1H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.88, 23.75, 26.01, 27.45, 30.11, 31.89, 32.27, 32.63, 34.65, 36.91, 39.55, 62.06, 65.26, 66.91, 68.28; HRMS calcd for $C_{15}H_{29}NO$ (M^+) 239.2249, found 239.2233.

ent-(6'*R*)-**2**; (57%); $[\alpha]^{26}_{D}$-11.45° (c 0.26, $CHCl_3$).

(3*R*,5*S*,6'*R*,8*S*)-5-(6'-Hydroxyheptyl)-3-propylpyrrolizidine [(6'*R*)-4].

By the analogous procedure described for (6'*R*)-**2**, the annulation of **22** (291 mg, 0.50 mmol) with hydrogen in the presence of cat. $Pd(OH)_2$ (29.1 mg) in MeOH (16.4 mL) gave the pyrrolizidine, which

was converted with 1.0 M Super-Hydride® (1.5 mL, 1.5 mmol) in THF to (6*R*)-**4** (79 mg, 59%) as an oil; $[\alpha]^{28}_{D}$+7.29° (c 0.63, $CHCl_3$); IRν_{max}^{cm-1} (neat) 3384, 2955, 2927, 2857, 1459, 1374, 1107, 945; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, t-like, *J* = 6.59, 7.14 Hz), 1.18 (3H, d, *J* = 6.04 Hz), 1.21-1.65 (16H, m), 1.67-1.70 (2H, brs, m), 1.87-2.00 (4H, m), 2.59-2.66 (2H, brs, s), 3.55 (1H, qui-like, *J* = 6.04 Hz), 3.75-3.82 (1H, brs, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.72, 20.63, 23.77, 26.06, 27.39, 30.19, 31.98, 37.23, 39.61, 64.74, 66.73, 66.90, 68.35; HRMS calcd for $C_{17}H_{33}NO$ (M^+) 267.2562, found 267.2538.

ent-(6'*R*)-**4**; (44%); $[\alpha]^{26}_{D}$-7.14° (c 0.96, $CHCl_3$).

(3*R*,5*S*,6'*S*,8*S*)-5-(6'-Hydroxyheptyl)-3-methylpyrrolizidine [(6'*S*)-2].

By the analogous procedure described for (6*R*)-**2**, the annulation of **23** (380 mg, 0.68 mmol) with hydrogen in the presence of cat. $Pd(OH)_2$ (38 mg) in MeOH (21.4 mL) gave the pyrrolizidine, which was converted with 1.0 M Super-Hydride® (2.04 mL, 2.04 mmol) in THF to (6*S*)-**2** (95 mg, 58%) as an oil; $[\alpha]^{26}_{D}$+4.61° (c 0.95, $CHCl_3$); IRν_{max}^{cm-1} (neat) 3354, 2927, 2857, 1458, 1374, 1120; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.08 (3H, d, *J* = 6.59 Hz), 1.16 (3H, d, *J* = 6.04 Hz), 1.24-1.58 (14H, m), 1.87-2.00 (4H, m), 2.58 (1H, qui-like, *J* = 6.04 Hz), 2.75 (1H, six-like, *J* = 7.14 Hz), 3.58 (1H, qui, *J* = 6.59 Hz), 3.77 (1H, six-like, *J* = 6.04 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 22.20, 23.77, 26.04, 27.48, 30.16, 31.98, 32.36, 32.67, 34.69, 37.27, 39.58, 61.89, 65.14, 66.77, 68.35; Anal. Calcd for $C_{15}H_{29}NO$: C, 75.26; H, 12.21; N, 5.85. Found: C, 75.23; H, 12.37; N, 5.57.

ent-(6'*S*)-**2**; (58%); $[\alpha]^{26}_{D}$-4.47° (c 0.77, $CHCl_3$).

(3*R*,5*S*,6'*S*,8*S*)-5-(6'-Hydroxyheptyl)-3-propylpyrrolizidine [(6'*S*)-4].

By the analogous procedure described for (6*R*)-**2**, the annulation of **24** (352 mg, 0.60 mmol) with hydrogen in the presence of cat. $Pd(OH)_2$ (35.2 mg) in MeOH (19.8 mL) gave the pyrrolizidine, which was converted with 1.0 M Super-Hydride® (1.80 mL, 1.80 mmol) in THF to (6*S*)-**4** (87 mg, 54%) as an oil; $[\alpha]^{26}_{D}$+0.90° (c 1.72, $CHCl_3$); IRν_{max}^{cm-1} (neat) 3355, 2955, 2927, 2857, 1459, 1371, 1106, 944; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.92 (3H, t-like, *J* = 6.59, 7.14 Hz), 1.18 (3H, d, *J* = 6.04 Hz), 1.21-1.73 (16H, m), 1.75-1.84 (2H, brs), 1.87-2.05 (4H, m), 2.60-2.67 (2H, brs), 3.55 (1H, qui-like, *J* = 6.04 Hz), 3.76-3.83 (1H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.60, 20.53, 23.65, 25.95, 27.30, 30.07, 31.86, 31.90, 37.09, 39.48, 64.69, 66.70, 66.87, 68.33; HRMS calcd for $C_{17}H_{33}NO$ (M^+) 267.2562, found 267.2535.

ent-(6'*S*)-**4**; (61%); $[\alpha]^{27}_{D}$-1.28° (c 0.54, $CHCl_3$).

Assay protocol[17]

Membranes enriched in nAChR are harvested from homogenates of *Torpedo califurnica* electric organs by differential centrifugation as described in the literature. Binding of [^{3}H]-TCP (sp. act 57.6 Ci/mmole) to carbamylcoline-activated nAChR is used as a functional binding assay as described by Kats et al. [^{3}H]-TCP is available from the National Institute of Drug Abuse.

Binding assay

Test compounds **1**-**4** and *ent*-**1**-**4** were dissolved in DMSO to make 100 mM stocks. A second stock of 1 mM in buffer (50 mM Tris HCl, pH=7.4) is prepared by diluting 10 μL DMSO stock into 1 mL buffer. Stocks of 100 times the desired test concentrations were prepared by further dilutions with buffer. 25 μg of *Torpedo* membranes were added to the final volume of 250 μL of buffer containing [^{3}H]-TCP, 100 μM carbamylcoline, and the test drug **1**-**4** and *ent*-**1**-**4** at varied concentrations. Nonspecific binding is determined in presence of 5 mM amantadiene HCl. Bound [^{3}H]-TCP is separated by vacuum filtration over GF/B filters presoaked in 0.05% polyethyleneimine. Incubation time was 30 s at 23 °C. Radioactivity retained on the filters, after washing with 5 mL ice cold buffer, was quantitated by liquid scintillation. All tests were performed in triplicate and data reported as % of control. Six concentrations were selected for each test compound covering a range 1000 times the lowest effective concentration. The percent inhibition of carbamylcholine stimulated [^{3}H]-TCP binding was plotted vs concentration. Each compound was tested twice and means +SEM from 6 values at each concentration were used to generate the concentration-response function. The IC_{50} values determined graphically from the log concentration-response curves were then used to obtain the inhibitory equilibrium constant (Ki) using the Cheng-Prusoff equation (Ki=IC_{50}/l+[D]/K_D). The results are shown in Table l.

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