

TETRAHEDRON

Total Syntheses of Cepaciamides A and B, Novel Fungitoxic 3-Amino-2piperidinone-containing Lipids Produced by *Pseudomonas cepacia* D-202

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Abstract: Total syntheses of cepaciamides A and B were accomplished (R)-3-Amino-2-piperidinone was obtained via cyclization of (R)-ornithine. The common arnide-linked fatty acid was synthesized via Sharpless AD as the key step. Amide-formation was achieved with DEPC. In the preparation of two fatty acid segments, (S)-malic acid was used as the chiral source to introduce (25)-configuration. A known chiral cyclopropane derivative was introduced in the segment of cepaciamide A. The formation of (Z)-olefin in the segment of cepaciamide B was achieved by means of partial reduction of the acetylenic bond. Esterification between the fatty acid-segments and the amide-segment with DCC/DMAP and subsequent oxidative deprotection of the MPM group with CAN gave cepaciamides. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: cepaciamide; lipid; ornithine; cyclopropane; Pseudomonas cepacia.

INTRODUCTION

Cepaciamides A (1a) and B (2a) were isolated from *Pseudomonas cepacia* D-202 as novel fungitoxic 3amino-2-piperidinone-containing lipids against *Botrytis cinerea* and *Penicillium expansum*, which cause the storage rot of beet roots (Fig. 1).¹ The structural determination using synthetic methods and total syntheses of 1a and 1b have been preliminarily communicated.² In order to examine the structure-activity relationship of cepaciamides and their derivatives as biocontrol agents, stereochemically pure compounds must be supplied synthetically due to the difficulty in obtaining a sufficient amount of cepaciamides from *Pseudomonas cepacia* D-202 because of its low productivity. Furthermore, a large amount of various phospholipids, which occur in close proximity to the very near the cepaciamide fraction, interfere with isolation and purification. We describe here in detail the first total syntheses of cepaciamides A (1a) and B (2a).



Fig. 1. Structures of cepaciamides A and B

Cepaciamides A (1a) and B (2a) are constituted of (R)-3-amino-2-piperidinone (1d), amide-linked (S)-3-hydroxyhexadecanoic acid (1e), ester-linked (2S, 11S, 12R)-2-hydroxy-11, 12-methyleneoctadecanoic acid (1c) for 1a and (2S, 11Z)-2-hydroxy-11-octadecenoic acid (2c) for 2a.^{2a} Therefore, cepaciamides were retrosynthesized to four fragments (1d, 1e, 1c, 2c) or their suitably protected derivatives (Fig. 2). Amide-formation between 1d and 1e would provide 1b, and subsequent esterification between 1b and 1c or 2c would provide 1a or 2a, respectively. Cyclization of (R)-ornithine will provide 1d.³ The C-3' stereogenic center of 1e will be introduced *via* Sharpless asymmetric dihydroxylation (AD)⁴ according to the method reported by Oikawa and Kusumoto.⁵ The common C₄-unit, including the C-2 stereogenic center of 1c and 2c, can be retrosynthesized to (S)-malic acid. Carbon-chain elongation and incorporation of the known cyclopropane derivative⁶ would provide the segment corresponding to 1c. Carbon-chain elongation by alkylation of 1-octyne acetylide and partial reduction of the acetylenic bond would provide the segment corresponding to 2c.



Fig. 2. Retrosynthetic analysis of cepaciamides

RESULTS AND DISCUSSIONS

Synthesis of the common amide-part

(*R*)-Ornithine hydrochloride was treated with hexamethyldisilazane in refluxing CH₃CN by the known method to give the crude cyclized product, (*R*)-3-amino-2-piperidinone (1d),³ which could not be purified by recrystallization as described in the literature. Protection of the amino group of 1d with (Boc)₂O gave the stable Boc derivative 3 in 82% yield (2 steps), which could be purified by column chromatography (Scheme 1).

Among various approaches to the preparation of optically active 3-hydroxy-fatty acids, Oikawa and Kusumoto⁵ have reported an easy and practical method to give t-butyl (R)-3- and (S)-3-acetoxytetradecanoate via Sharpless AD.⁴ So we followed this method in order to obtain (S)-3-acetoxyhexadecanoate 7 as the segment for 1e. Swern oxidation of tetradecanol gave tetradecanal which was subjected to Wittig reaction in one-pot with (t-butoxycarbonylmethylene)triphenylphosphorane. t-Butyl (E)-2-hexadecenoate (4) was obtained in 98% yield without contamination of t-butyl (Z)-2-hexadecenoate after chromatographic purification.

Sharpless AD of 4 using AD-mix- α^4 gave the diol 5 in 83% yield, whose optical purity was determined to be 98% e.e. as judged by integration of the ¹H-NMR signals of the corresponding (R)- and (S)-MTPA esters.⁷ The absolute configuration of 5 was presumed to be (2R,3S)-configuration based on the usual enantiofacial selectivity of Sharpless AD⁴ and the result reported by Oikawa and Kusumoto.⁵ Regioselective chlorination of 5 was achieved with trimethyl orthoacetate and trimethylchlorosilane to give chloroacetate 6 in 64% yield with recovery (20%) of unreacted 5. Radical reduction of 6 with tributyltin hydride in the presence of a catalytic amount of α, α' -azobisisobutyronitrile in refluxing toluene gave the desired segment 7 in 91% yield. The Boc group of 3 and the t-butyl ester of 7 were independently deprotected with trifluoroacetic acid (TFA) in dichloromethane to give 1d as the TFA salt and (S)-3-acetoxyhexadecanoic acid, respectively. Amideformation between 1d and (S)-3-acetoxyhexadecanoic acid was examined with several condensation-reagents to give 8: for example, dicyclohexylcarbodiimide (DCC),⁸ 19%; 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC HCl),⁹ 35%; diphenylphosphoryl azide (DPPA),¹⁰ 31%; benzotriazol-1vloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent),¹¹ 71%. Finally, diethylphosphoryl cyanide $(DEPC)^{12}$ gave 8 in the best and reproducible yield, 96%. Deacetylation of 8 with potassium carbonate in methanol gave the desired amide 1b possessing (3R, 3'S)-configuration in 99% yield. At this stage, the $(3^{\circ}S)$ -configuration of 1b was confirmed by using the modified Mosher's method.¹³ The spectral data (¹H-NMR, IR, MS) of synthetic 1b were completely identical with those of 1b derived from 1a and 2a. Furthermore, the (3'R)-isomer of 1b, (3R,3'R)-3-(3'-hydroxyhexadecanoylamino)-2-piperidinone, was also synthesized according to the same route for 1b, except for the use of AD-mix- β .⁴ By using (S)ornithine, (3S)-isomer of 1b would be synthesized.



Scheme 1: (a) $(TMS)_2NH / CH_3CN$; (b) $(Boc)_2O / CHCl_3$, 82%, 2 steps; (c) Swern oxid., then $Ph_3P=CHCOOt+Bu$, 98%, 2 steps; (d) AD-mix- α , MeSO₂NH₂/ t-BuOH-H₂O, 83%, 98% e.e.; (e) MeC(OMe)₃, TMSCl / CH₂Cl₂, 64%; (f) n-Bu₃SnH, AIBN / PhH, 91%; (g) TFA / CH₂Cl₂, then evaporated to dryness; (h) DEPC, Et₃N / CH₂Cl₂, 96% from 3; (i) K₂CO₃ / MeOH, 99%.

Synthesis of cepaciamide A

Since the common amide-segment (1b) for cepaciamides has been prepared, the ester-linked carboxylic acid-segments 1c and 2c are required. While use of a non-protected segment 2c for the direct synthesis of 2a failed, use of a TBDPS-protected segment for esterification with DCC/DMAP gave an ester in moderate yield (65%).² However, subsequent desilylation with TBAF or HF-pyridine gave 2a in only 0-3% yield. From these preliminary results, we selected an MPM protective group which would be deprotected oxidatively on our substrates in a neutral medium. In the syntheses of ester-linked carboxylic acid-segments, (S)-malic acid was used as a chiral source to introduce (2S)-configuration because it is cheaper than optically active glycidol used in the structural determination of cepaciamides.^{2a} A suitable derivative of (S)-malic acid as the common precursor for carboxylic acid-segments would be readily prepared based on our previous work for the preparation of 3-benzyloxy-1-alkanol.¹⁴ (S)-Malic acid was reduced with BH₃·SMe₂ and B(OMe)₃ in THF to give (S)-1,2,4-butanetriol¹⁵ which was treated with *p*-methoxybenzaldehyde and pyridinium *p*-toluenesulfonate (PPTS) in refluxing benzene to give p-methoxybenzylidene acetals 9a (1,3-acetal, as a single diastereomer) and **9b** (1,2-acetal, as a mixture of two diastereomers) in *ca* 10:1 ratio¹⁶ and in 92% yield (Scheme 2). The ratio was increased up to ca 30:1 by column chromatography. Protection of 9a by t-butyldiphenylsilyl (TBDPS) group gave the silyl ether 10 which could be obtained as a single regioisomer after purification by column chromatography. DIBAL-H reduction¹⁷ of 10 in toluene gave primary alcohol 11 as the sole product because 10 was regioselectively reduced from the less-hindered site. Similar regioselective reduction with DIBAL-H proceeded for a benzylidene acetal in our previous study.¹⁴ The structure of 11 was confirmed from the ¹H-¹H-COSY spectrum of the corresponding acetate of 11. The C_{s} -elongation for 11 was designed by use of crosscoupling between tosylate 12 and the C5-Grignard reagent [(5-tetrahydropyranyloxypentyl)magnesium bromide] in the presence of copper (I) iodide.¹⁸ Thus, tosylation of 11 with p-toluenesulfonyl chloride and pyridine in dichloromethane gave 12 in 97% yield. Cross-coupling proceeded smoothly to give C_s -elongated derivative 13 which could not be purified because of the contamination with compounds derived from the Grignard reagent. Therefore, the crude 13 was treated with PPTS in ethanol to give primary alcohol 14 in 88% yield (2 steps) which could be purified by column chromatography.

Incorporation of the chiral cyclopropane part was designed by use of Wittig reaction between the chiral phosphonium ylide derived from the alcohol 14 and the aldehyde 17A derived from the known cyclopropane derivative 17.⁶ According to the method reported by Morikawa *et al.*, 17 (*ca.* 100 *d. e.* purity)¹⁹ was prepared from (*R*)-2, 3-*O*-isopropylideneglyceraldehyde *via* diastereoselective cyclopropanation.⁶ Swern oxidation of 17 gave the aldehyde 17A quantitatively which was used for the Wittg reaction without purification. On the other hand, 14 was first converted into bromide 15 by treatment with carbontetrabromide and triphenylphosphine in dichloromethane. By treatment with triphenylphosphine in refluxing acetonitrile, bromide 15 was next converted into phosphonium salt 16 quantitatively which was also used for the Wittg reaction without purification. The chiral phosphonium ylide, which was generated from 16 with *n*-butyllithium in THF, was subjected to the Wittg reaction. The Wittg reaction gave olefin 18 as an inseparable mixture of geometric isomers (*E:Z = ca.* 1:5) in 82% yield. Since the olefinic bond of 18 will be reduced to a single bond at the appropriate stage, the inseparable mixture of 18 was used as such for the next reaction. Further elongation of the C₅-unit was also designed by use of Wittig reaction for the aldehyde derived from 18 *via* transacetalization and subsequent oxidative cleavage of a diol because it is convenient that the two olefinic bonds of the resulting diene will be reduced at the same time to provide a single product.



Scheme 2: (a) BH₃·SMe₂, B(OMe)₃ / THF, quant.; (b) *p*-methoxybenzaldehyde, PPTS / benzene, 92%; (c) TBDPSCl, imidazole / DMF, 100%; (d) DIBAL-H / toluene, 82 %; (e) TsCl, pyr. / CH_2Cl_2 , 97%; (f) MgBr(CH_2)₅OTHP, CuI / THF; (g) PPTS / EtOH; (h) CBr₄, Ph₃P / CH₂Cl₂, 88%, 3 steps; (i) Ph₃P / CH₃CN, quant; (j) *n*-BuLi / THF; (k) Swern oxid. (82% as Wittig reaction); (l) PPTS / EtOH, 72%; (m) NaIO₄ / THF-H₂O; (n) Ph₃P⁺-(CH₂)₄CH₃·Br⁻, *n*-BuLi / THF, 93%; (o) TBAF / THF, 99%; (p) KO₂CN=NCO₂K, AcOH / pyridine, 97%; (q) Swern oxid.; (r) NaClO₂, NaH₂PO₄, 2-methyl-2 butene / t-BuOH-H₂O, 98%, 2 steps; (s) DCC, DMAP / toluene, 80%; (t) CAN / CH₃CN-CHCl₃-H₂O, 80%.

Thus, transacetalization of 18 with PPTS in ethanol gave the diol 18A in 72% yield (97% based on the consumed 18), which was treated with sodium metaperiodate in aqueous medium to give the required aldehyde 18B. The Wittig reaction between pentyltriphenylphosphonium ylide and 18B gave C_{19} -diene 19 equipped with all the requisite carbons in 93% yield as an inseparable mixture of four geometric isomers. The ratio of the geometric isomers could not be determined in this case because of overlap of olefinic signals in the ¹H-NMR spectrum. Deprotection of 19 with tetrabutylammonium fluoride (TBAF) in THF gave unsaturated primary alcohol 19A in 99% yield. Diimide reduction²⁰ of 19A with potassium azodicarboxylate and acetic acid in pyridine gave saturated primary alcohol 19B in 97% yield. Catalytic hydrogenation of 19A did not give 19B

because the cyclopropane ring readily underwent reductive cleavage. Swern oxidation of **19B** to aldehyde **19C** and subsequent oxidation with sodium chlorite gave carboxylic acid **20** (98%, 2 steps) as the segment for **1a**.

Esterification between the acid-segment 20 and the amide-segment 1b possessing the secondary alcohol was carried out with DCC and DMAP²¹ to give the desired ester 21 in 80% yield. Final oxidative deprotection of the MPM group was first attempted with DDQ in $CH_2Cl_2-H_2O^{22}$ to give 1a in only 24% yield. This reaction took a relatively long time (20 h) in contrast to general cases of MPM-deprotection.²² Ceric (IV) ammonium nitrate (CAN) in $CH_3CN-CHCl_3-H_2O^{17b}$ was next used for depotection. In this case, the reaction was completed in 30 min to give 1a as a colorless oil in 80% yield. Since 1a partially solidifies or crystallizes out from its oil evaporated to dryness, attempts to recrystallize 1a from various solvent-systems were carried out. While recrystallization has been unsuccessful, an amorphous solid (mp 58-64 °C) has been obtained. The spectral data of synthetic 1a were identical with those of natural 1a.^{1b,2b} In this way, the first total synthesis of 1a was accomplished.

Synthesis of cepaciamide B

The acid-segment 27 for 2a was synthesized from the common intermediate, C_4 -tosylate 12. According to the same procedure as that for preparation of 15, except for using the C_6 -unit as the Grignard reagent, bromide 24 was obtained in 79% yield from 12 (Scheme 3).



Scheme 3: (a) MgBr(CH₂)₆OTHP, CuI / THF; (b) PPTS / EtOH; (c) CBr₄, Ph₃P / CH₂Cl₂; 79%, 3 steps; (d) *n*-BuLi, 1-octyne / THF-HMPA; (e) TBAF / THF, 86%, 2 steps; (f) H₂, Lindlar cat. / EtOAc, 100%; (g) Swern oxid.; (h) NaClO₂, NaH₂PO₄, 2-methyl-2-butene / *t*-BuOH-H₂O, 97%, 2 steps; (i) DCC, DMAP / toluene, 76%; (j) CAN / CH₃CN-CHCl₃-H₂O, 76%.

Lithium acetylide of 1-octyne (C_g -unit) was alkylated with 24 to give the C_{18} -alkyne 25 and 26 equipped with all the requisite carbons. At this stage, 26 was produced by a side reaction, that is, nucleophilic desilylation by the excess acetylide. Therefore, the mixture of 25 and 26 was treated with TBAF in THF to

give 26 in 86% yield from 24. Partial hydrogenation of 26 in the presence of Lindlar catalyst in ethyl acetate gave (Z)-olefin 26A quantitatively. Swern oxidation of 26A to aldehyde 26B and subsequent oxidation with sodium chlorite gave carboxylic acid 27 (97%, 2 steps) as the segment for 2a.

Esterification between the acid-segment 27 and the amide-segment 1b possessing the secondary alcohol was carried out to give the desired ester 28 in 76% yield under the same conditions as used in the synthesis of 1a. Final oxidative deprotection of the MPM group with CAN^{17b} gave 2a as an amorphous solid (mp 42-48 $^{\circ}$ C) in 76% yield. Although 2a as well as 1a partially solidifies or crystallizes out from its oil evaporated to dryness, 2a tends to not solidify or not crystallize readily. Although there are no spectral data of natural 2a alone, the ¹H-NMR spectrum of synthetic 2a corresponded to that of the mixture of 1a and 2a. Other spectral data substantiated the structural validity of 2a.^{2b} In this way, the first total synthesis of 2a was accomplished.

CONCLUSION

The first total syntheses of cepaciamides A (1a) and B (2a) were accomplished. Four segments were synthesized as follows. (R)-3-(t-Butoxycarbonyamino)-2-piperidinone (3) was obtained via cyclization of (R)-ornithine in 82% yield (2 steps). The common amide-linked fatty acid segment (7) was synthesized from tetradecanol in 59% overall yield (5 steps) via Sharpless AD as the key step. In the preparation of two fatty acid segments (20 for 1a and 27 for 2a), (S)-malic acid was used as the chiral source to introduce (2S)-configuration. The known chiral cyclopropane derivative, possessing the two required stereogenic centers, was incorporated in the segment for 1a via Wittig reaction. The overall yield of 20 was 45% in 18 steps from (S)-malic acid. The formation of (Z)-olefin in the segment for 2a was achieved by means of partial reduction of the acetylenic bond. The overall yield of 27 was 48% in 13 steps from (S)-malic acid. The assembly was achieved as follows. Amide-formation between deprotected 3 and 7 with DEPC and subsequent deacetylation gave the common amide segment (1b) possessing the secondary hydroxyl group in 96% yield (4 steps). Esterification between 20 and 1b with DCC/DMAP and subsequent oxidative deprotection of the MPM group with CAN gave cepaciamide A (1a) in 64% yield (2 steps). By the same two-step reaction, cepaciamide B (2a) was obtained from 27 and 1b in 58% yield. Therefore, the overall yields of both 1a and 2a are 13% in 31 steps for 1a and 26 steps for 2a.

These syntheses provided a sufficient amount of cepaciamides and will make it possible to examine the structure-activity relationship of cepaciamides and their derivatives as biocontrol agents. In practice, both cepaciamides could be synthesized in 100-mg scale and further upscaling is possible. As we have already synthesized (3R, 3'R)-3-(3'-hydroxyhexadecamido)-2-piperidinone,^{2a} the stereoisomers of cepaciamides would be synthesized by using (S)-ornithine and (R)-malic acid as starting materials. Furthermore, the synthesis of ornithine-containing lipids²³ would be possible because a successful result has been obtained in the preliminary study.^{2b} Although the amide-part **1b** has been reported to exhibit higher fungitoxic activity against *Botrytis cinerea* than **1a** in the case of using a limited amount of sample, ^{1b} more definitive results will be obtained and will be reported elsewhere.

EXPERIMENTAL

General Methods. ¹H- and ¹³C-NMR spectra were recorded with a JEOL JNM-EX-270 spectrometer (¹H: 270 MHz; ¹³C: 67.8 MHz) and a Brucker AM-500 spectrometer (¹H: 500 MHz; ¹³C: 125 MHz). In ¹H-NMR

spectra, chemical shifts are reported as δ (ppm) values relative to the residual proton (δ 7.26 ppm) of CDCl₃. In ¹³C-NMR spectra, chemical shifts are reported as δ (ppm) values relative to δ 77.0 ppm of CDCl₃, and some aromatic and methylene ¹³C-signals overlap. IR spectra were measured with a Perkin Elmer System 2000 FT-IR spectrometer. Mass spectra were recorded with a JEOL JMS-AX500 spectrometer or a JEOL JMS-SX102A spectrometer. Melting point values were obtained with a Yanaco micro-melting point apparatus MP-30 and are uncorrected. Specific rotation values were recordesd with a JASCO DIP-370 digital polarimeter. Column chromatography was carried out with Silica gel 60 (spherical, 70-140 mesh ASTM, KANTO CHEMICAL). Silica gel 60 F₂₅₄ precoated plates were used for analytical TLC (catalog no. 5715, Merck).

(*R*)-3-(tert-Butoxycarbonylamino)-2-piperidinone (3). A mixture of (*R*)-ornithine hydrochloride (1.00 g, 5.93 mmol) and hexamethyldisilazane (12.5 ml, 59.2 mmol) in dry CH₃CN (25 ml) was refluxed for 2 days. After addition of MeOH (50 ml), the reaction mixture was concentrated under reduced pressure. The residue was dissolved in CHCl₃ (30 ml) and the resulting precipitate was filtered through a Celite pad. The filtrate was concentrated under reduced pressure to give crude (*R*)-3-amino-2-piperidinone (1d) as a brownish oil, which could not be crystallized as described in the preparation of (*S*)-from³ and used for the next reaction. A solution of 1d and di-*tert*-butyl dicarbonate (3.32 g, 15.2 mmol) in CHCl₃ (30 ml) was stirred for 4 h at room temperature. The reaction mixture was washed with water (30 ml) and brine (30 ml), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 50 g, CHCl₃): MeOH = 10:1) to give 3 (1.04 g, 82%, 2 steps) as a colorless oil: $[\alpha]_{p}^{-2} - 57.4^{\circ}$ (c 1.07, CHCl₃); IR (film) 3295, 2976, 1693, 1669, 1494, 1392, 1365, 1332, 1248, 1167, 1074, 1047, 1025, 870, CHCl₃); IR (film) 3295, 2976, 1693, 160, 1494, s), 1.58 (1H, m), 1.90 (2H, m), 2.47 (1H, m), 3.31 (2H, m), 4.02 (1H, m), 5.43 (1H, br. s, NH), 6.06 (1H, br. s, NH); ¹³C-NMR (67.8 MHz, CDCl₃) δ 21.0, 27.8, 28.3 (x 3), 41.6, 51.4, 79.5, 155.8, 171.9; FD-MS *m/z* 215 (MH^{*}, 100), 214 (M^{*}, 84.4); HR-MS calcd. for C₁₀H₁₄N_{2O₃} (M⁺) *m/z* 214.1318, found 214.1308.

tert-Butyl (E)-2-hexadecenoate (4). To a stirred solution of oxalyl chloride (20.0 ml, 229 mmol) and dimethyl sulfoxide (21.0 ml, 296 mmol) in dry CH_2Cl_2 (1000 ml) was added dropwise tetradecanol (25.0 g, 117 mmol) in dry CH_2Cl_2 (200 ml) at -78 °C under argon atmosphere. The stirring was continued for 60 min at the same temperature. After addition of triethylamine (100 ml, 717 mmol) at -78 °C, the reaction mixture was allowed to warm to room temperature with stirring to give crude tetradecanal, which was used for the next reaction in one-pot. (*tert*-Butoxycarbonylmethylene)triphenylphosphorane (69.1 g, 184 mmol) was added to the resulting mixture containing tetradecanal at room temperature. After being stirred vigorously for 40 h, the reaction mixture was washed with water (500 ml x 2) and brine (500 ml), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 500 g, hexane:Et, Q = 50:1) to give 4 (35.5 g, 98%) as a colorless oil: IR (film) 3071, 3295, 2926, 2855, 1717, 1654, 1457, 1392, 1367, 1290, 1257, 1156, 1127, 981, 854 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) δ 0.86 (3H, t, J = 6.6 Hz), 1.17-1.35 (20H, m), 1.41 (2H, m), 1.45 (9H, s), 2.13 (2H, q, J = 7.3 Hz), 5.70 (1H, dt, J = 15.2, 7.3 Hz); EI-MS m/z 310 (M⁺, 0.6), 255 (100), 237 (17.0), 57 (29.2), 56 (12.5); HR-MS calcd. for $C_{20}H_{38}O_2$ (M⁺) m/z 310.2882, found 310.2905.

tert-Butyl (2R, 3S)-2, 3-dihydroxyhexadecanoate (5). To a stirred suspension of AD-mix- α (11.1 g) and methanesulfonamide (753 mg, 7.92 mmol) in tert-BuOH (40 ml) and H₂O (40 ml) at 4 °C was added 4 (2.46 g, 7.92 mmol) at once. The mixture was stirred vigorously for 4 h at 4 °C. The reaction was quenched at 0 °C by addition of sodium sulfite (12.0 g) and then warmed to room temperature and stirred for 60 min. After being concentrated to remove most of tert-BuOH, the reaction mixture was extracted with EtOAc (50 ml x 3). The combined organic layers were washed with 2 M KOH (50 ml), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 100 g, hexane:EtOAc = 7:3) to give 5 (2.25 g, 83%) as colorless crystals: mp 51.5-52.0 °C; $[\alpha]_D^{-1}$ -4.60° (c 1.83, CHCl₃); IR (KBr) 3643, 3448, 2915, 2849, 1737, 1468, 1373, 1285, 1168, 1133, 1082, 850, 760, 724 cm⁻¹; 'H-NMR (270 MHz, CDCl₃) δ 0.88 (3H, t, J = 6.6 Hz), 1.20-1.41 (22H, m), 1.45-1.63 (2H, m), 1.51 (9H, s), 1.82 (1H, d, J = 9.6 Hz, OH), 3.06 (1H, d, J = 5.0 Hz, OH), 3.82 (1H, m), 3.96 (1H, dd, J = 5.0, 2.3 Hz); ¹³C-NMR (67.8 MHz, CDCl₃) δ 14.1, 22.7, 25.8, 28.0, 29.3, 29.5, 29.6, 31.9, 33.9, 72.7, 73.2, 83.0, 172.9; FD-MS m/z 345 (MH⁺, 100), 344 (M⁺, 6.8), 288 (40.3), 269 (4.7), 244 (14.4), 243 (74.0), 57 (84.5); HR-MS calcd. for C₂₀H₄₁O₄ (MH⁺) m/z 345.3005, found 345.3005.

tert-Butyl (25, 35)-3-acetoxy-2-chlorohexadecanoate (6). A solution of 5 (2.13 g, 6.19 mmol), trimethyl orthoacetate (1.18 ml, 9.29 mmol), and chlorotrimethylsilane (1.18 ml, 9.29 mmol) in CH_2Cl_2 (45 ml) was stirred for 3 days at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 100 g, hexane:EtOAc = 13:1) to give 6 (1.60 g, 64%, 80% based on consumed 5) as a colorless oil and unreacted 5 (0.43 g, 20%). Data for 6: $[\alpha]_D^{20}$ -0.71° (c 5.93, CHCl₃); IR (film) 2926, 2855, 1755, 1464, 1371, 1294, 1228, 1152, 1082, 850, 760, 724 cm⁻¹; ¹H-

tert-Butyl (S)-3-acetoxyhexadecanoate (7). A solution of 6 (1.48 g, 3.66 mmol), tributyltin hydride (1.48 ml, 5.49 mmol), and α, α' -azobisisobutyronitrile (30.0 mg, 0.183 mmol) in benzene (18 ml) was refluxed for 4 h. Sodium fluoride (15 g) was added to the cooled and stirred reaction mixture and the vigorous stirring was continued overnight. The insoluble materials were filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 100 g, hexane:EtOAc = 12:1) to give 7 (1.24 g, 91%) as a colorless oil: $[\alpha]_{D}^{20}$ -2.02° (c 1.82, CHCl₃); IR (film) 2926, 2855, 1745, 1458, 1369, 1294, 1239, 1157, 1082, 850, 760, 724 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) δ 0.87 (3H, t, J = 6.9 Hz), 1.16-1.40 (22H, m), 1.42 (9H, s), 1.56 (2H, m), 2.02 (3H, s), 2.43 (1H, dd, J = 15.2, 6.4 Hz), 2.49 (1H, dd, J = 15.2, 6.9 Hz), 5.18 (1H, quint, J = 6.6 Hz); ¹³C-NMR (67.8 MHz, CDCl₃) δ 14.1, 21.1, 22.6, 25.1, 28.0, 29.3, 29.36, 29.44, 29.49, 29.6, 31.9, 34.0, 40.6, 70.8, 80.7, 169.7, 170.3; EI-MS m/z 315 (M^{*}-C₄H₇, 7.5), 297 (M^{*}-fBuO, 5.9), 255 (33.3), 254 (21.4), 237 (50.6), 236 (16.3), 57 (100), 56 (33.5), 55 (23.9), 43 (92.9); HR-MS calcd. for C₁₈H₃, O₄ (M^{*}-C₄H₇) m/z 315.2536, found 315.2554.

(3R, 3'S)-3-(3'-Acetoxyhexadecanoylamino)-2-piperidinone (8). A solution of 3 (73.0 mg, 341 µmol) in TFA (1.0 ml) was stirred for 30 min at room temperature and then concentrated to dryness to give 1d as the TFA salt. A solution of 7 (163 mg, 440 µmol) in TFA (1.0 ml) was stirred for 30 min at room temperature and then evaporated to dryness to give (S)-3-acetoxyhexadecanoic acid. The amine and acid components thus obtained and Et₃N (0.15 ml, 1.08 mmol) were dissolved in CH₂Cl₂ (3.0 ml) and DEPC (100 µl, 660 µmol) was added to this solution. After being stirred for 5 h at the same temperature, the mixture was partitioned between CHCl₃ (10 ml) and 1MHCl (10 ml). The aqueous layer was further extracted with CHCl₄ (10 ml x 3) and the combined organic layers were washed with brine (20 ml), dried over anhydrous Na₂SQ₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 10 g, CHCl₃:acetone = 6:4) to give 8 (135 mg, 96%) as colorless crystals: mp 94-95 °C; $[\alpha]_{p}^{22}$ -32.9° (c 0.28, CHCl₃); IR (KBr) 3357, 3306, 3197, 3073, 2920, 2851, 1733, 1685, 1652, 1543, 1498, 1455, 1417, 1368, 1249, 1168, 1026, 843, 721 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) δ 0.87 (3H, t, J = 6.6 Hz), 1.14-1.37 (22H, m), 1.48 (1H, m), 1.61 (2H, m), 1.92 (2H, m), 2.05 (3H, s), 2.42-2.62 (3H, m), 3.33 (2H, m), 4.27 (1H, dt, J = 11.5, 5.6 Hz), 5.17 (1H, quint, J = 6.3 Hz), 6.04 (1H, br. s), 6.65 (1H, br. d, J = 5.6 Hz); ¹³C-NMR (67.8 MHz, CDCl₃) δ 14.0 (MH⁺, 12.0), 410 (Mf⁺, 32.8), 367 (12.6), 351 (46.6), 350 (70.3), 141 (43.9), 115 (100), 114 (41.7), 113 (79.0), 98 (16.9), 43 (31.9); HR-MS calcd. for C₂₃H₄₂N₂O₄ (M⁺) m/z 410.3144, found 410.3127.

(3R, 3'S)-3-(3'-Hydroxyhexadecanoylamino)-2-piperidinone (1b). A mixture of 8 (195 mg, 475 µmol) and potassium carbonate (194 mg, 1.40 mmol) in MeOH (10 ml) was stirred for 22 h at room temperature. The reaction mixture was partitioned between CHCl₃ (20 ml) and aq. NH₄Cl (20 ml) and the aqueous layer was further extracted with CHCl₃ (10 ml x 3). The combined organic layers were washed with water (20 ml x 2), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give 1b (173 mg, 99%) as colorless crystals: mp 124-126 °C; $[\alpha]_{D}^{22}$ -13.3° (*c* 1.05, CHCl₃); IR (KBr) 3334, 3273, 3234, 2919, 2851, 1683, 1651, 1574, 1492, 1471, 1423, 1345, 1213, 1106, 1055, 983, 720 cm⁻¹; ¹H-NMR (270 MHz, CDCl₄) & 0.87 (3H, t, *J* = 6.3 Hz), 1.14-1.73 (25H, m), 1.94 (2H, m), 2.27 (1H, dd, *J* = 15.0, 8.9 Hz), 2.42 (1H, dd, *J* = 15.0, 2.6 Hz), 2.51 (1H, m), 3.35 (2H, m), 3.87 (1H, br. s, OH), 3.97 (1H, m), 4.25 (1H, dt, *J* = 11.8, 5.3 Hz), ⁵.99 (1H, br. s), 6.67 (1H, br. d, *J* = 5.3 Hz); ¹³C-NMR (67.8 MHz, CDCl₄) & 14.1, 21.2, 22.6, 25.5, 27.1, 29.3, 29.5, 29.7, 31.9, 36.8, 41.8, 42.8, 50.7, 68.7, 171.6, 173.0; EI-MS m/z 369 (MH⁺, 5.1), 368 (M⁺, 18.7), 351 (M⁺-OH, 5.0), 350 (M⁺+₁₂O, 17.2), 141 (15.0), 115 (100), 114 (39.7), 113 (42.0), 99 (39.6); HR-MS calcd. for C₂₁H₄₀N_{2O3} (M⁺) m/z 368.3029, found 368.3004.

(25, 4S)-4-Hydroxymethyl-2-(p-methoxyphenyl)-1, 3-dioxane (9a). A mixture of (S)-1, 2, 4-butanetriol (12.7 g, 120 mmol), p-methoxybezaldehyde (21.9 ml, 180 mmol), and PPTS (302 mg, 1.2 mmol) in benzene (250 ml) was refluxed for 5 h with removing the resulting water by the Dean-Stark trap. After addition of NaHCO₃ (500 mg, 5.95 mmol), the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 300 g, hexane:EtOAc = 1:1) to give a mixture of 9a and 9b (24.7 g, 92%, 9a:9b = ca 10:1) as a colorless oil. Rechromatography gave a more purified fraction (9a:9b = ca 30:1) which was used for the next reaction. Data for 9a: $[\alpha]_D^{20} + 19.0^\circ$ (c 0.21, CHCl₃); IR (film) 3427, 2937, 2842, 1600, 1578, 1519, 1463, 1428, 1394, 1303, 1250, 1218, 1162, 1104, 1069, 1033, 912, 831, 779 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) & 1.44 (1H, br. d, J = 12.5 Hz), 1.91 (1H, dq, J = 12.5, 5.3 Hz),

2.15 (1H, br. s, OH), 3.58-3.74 (2H, m), 3.80 (3H, s), 3.90-4.05 (2H, m), 4.28 (1H, dd J = 12.5, 5.3 Hz), 5.50 (1H, s), 6.89 (2H, d, J = 8.6 Hz), 7.42 (2H, d, J = 8.6 Hz); ¹³C-NMR (67.8 MHz, CDCl₃) & 26.8, 55.3, 65.7, 66.6, 77.2, 101.2, 113.6, 127.4, 132.0, 160.0; EI-MS *m*/z 225 (MH⁺, 8.1), 224 (M⁺, 43.3), 223 (M⁺-H, 43.4), 193 (M⁺-OCH₃, 49.0), 135 (100), 121 (29.7); HR-MS calcd. for $C_{12}H_{16}O_4$ (M⁺) *m*/z 224.1048, found 224.1064.

(25, 4S)-4-(tert-Butyldiphenylsilyloxy)methyl-2-(p-methoxyphenyl)-1, 3-dioxane (10). A solution of 9a (9a:9b = ca 30:1, 16.0 g, 71.3 mmol), imidazole (7.69 g, 113 mmol), and TBDPSCI (20.0 ml, 78.4 mmol) in DMF (160 ml) was stirred for 5 h at room temperature. The reaction mixture was partitioned between water (500 ml) and EtOAc (300 ml) and the aqueous layer was further extracted with EtOAc (200 ml x 2). The combined organic layers were washed with water (200 ml x 2) and brine (200 ml), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 400 g, hexane:EtOAc = 6:1) to give 10 (33.0 g, 100%) as a colorless oil. The regioisomer derived from 9b was completely removed by rechromatography (flash) to give 10 as a single regioisomer. Data for 10: $[\alpha]_{p}^{20}$ - 0.81° (c 0.61, CHCl₃); IR (film) 3071, 2937, 2842, 1617, 1518, 1458, 1428, 1363, 1303, 1250, 1218, 1162, 1112, 1069, 1033, 912, 825, 741 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) & 1.07 (9H, s), 1.64 (1H, br. d, J = 12.5 Hz), 1.86 (1H, dq, J = 12.5, 5.0 Hz), 3.68 (1H, dd, J = 10.5, 5.6 Hz), 3.80 (3H, s), 3.85 (1H, dd, J = 10.5, 5.3 Hz), 3.94-4.10 (2H, m), 4.28 (1H, dd, J = 12.5, 5.3 Hz), 5.47 (1H, s), 6.88 (2H, d, J = 8.6 Hz), 7.36 (8H, m), 7.65-7.77 (4H, m); ¹³C-NMR (67.8 MHz, CDCl₃) & 19.3, 26.8, 28.1, 55.6, 66.8, 66.9, 77.2, 101.0, 113.5, 127.4, 127.6, 129.6, 132.0, 133.5, 135.6, 159.8; EI-MS *m/z* 461 (M⁺-H, 0.2), 405 (M⁺-tBu, 49.2), 121 (100); HR-MS calcd. for C₂₄H₂₅O₄Si (M⁺-tBu) *m/z* 405.1522, found 405.1542.

(S)-4-(tert-Butyldiphenylsilyloxy)-3-(p-methoxybenzyloxy)-1-butanol (11). To a stirred solution of 10 (7.5 g, 16.2 mmol) in dry toluene (80 ml) at -78 °C under argon atmosphere was added dropwise DIBAL-H (0.95 M solution in hexane, 51.3 ml, 48.7 mmol) over 1 h. The mixture was allowed to warm to room temperature and then stirred overnight. The reaction was quenched by addition of sat. aq. Rochelle salt (20 ml) and the reaction mixture was stirred vigorously for 2 h. The reaction mixture was dried over anhydrous MgSO₄ and filtered through a Celite pad. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel 200 g, hexane:EtOAc = 3:1) to give 11 (6.17 g, 82%) as a colorless oil: $[\alpha]_D^{21}$ -35.9° (c 0.61, CHCl₃); IR (film) 3446, 3071, 2937, 2929, 2842, 1612, 1588, 1515, 1472, 1428, 1392, 1362, 1303, 1249, 1174, 1112, 1069, 1034, 912, 823, 741, 703 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) & 1.08 (9H, s), 1.81 (2H, m), 2.40 (1H, br. s, OH), 3.63-3.83 (5H, m), 3.80 (3H, s), 4.42 (1H, d, J = 11.4 Hz), 4.61 (1H, d, J = 11.4 Hz), 6.86 (2H, d, J = 8.6 Hz), 7.22 (2H, d, J = 8.6 Hz), 7.35-7.50 (6H, m), 7.65-7.77 (4H, m); ¹³C-NMR (67.8 MHz, CDCl₃) & 19.2, 26.8, 34.1, 55.3, 60.5, 65.9, 71.8, 78.5, 113.8, 127.7, 129.5, 129.8, 130.4, 133.3, 135.6, 159.2; FD-MS m/z 465 (MH⁺, 69.5), 464 (M⁺, 76.0), 463 (40.7), 407 (M⁺-dBu, 100), 121 (51.8), 57 (16.7); HR-MS calcd. for C₂₈H₃₆O₄Si (M⁺) m/z 464.2383, found 464.2351.

(S)-4-(tert-Butyldiphenylsilyloxy)-3-(p-methoxybenzyloxy)-1-butyl p-toluenesulfonate (12). To a stirred solution of 11 (2.71 g, 5.83 mmol) and pyridine (1.41 ml, 17.5 mmol) in CH₂Cl₂ (25 ml) was added p-toluenesulfonyl chloride (1.66 g, 8.75 mmol) at 4 °C. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (100 ml), washed successively with 1 M HCl (30 ml x 2), sat. aq. NaHCO₃ (30 ml), and brine (30 ml). The organic layer was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 150 g, hexane:EtOAc = 5:1) to give 12 (3.51 g, 97%) as a colorless oil: $[\alpha]_p^{24}$ -22.7° (c 1.06, CHCl₃); IR (film) 3071, 3049, 2937, 2999, 2957, 2932, 2858, 1613, 1599, 1588, 1514, 1471, 1428, 1391, 1361, 1304, 1249, 1189, 1177, 1112, 1036, 999, 958, 926, 823, 769, 742, 704 cm⁻¹; 'H-NMR (270 MHz, CDCl₃) δ 1.05 (9H, s), 1.82 (1H, m), 1.98 (1H, m), 2.42 (3H, s), 3.43-3.75 (3H, m), 3.81 (3H, s), 4.06-4.25 (2H, m), 4.24 (1H, d, J = 11.2 Hz), 4.51 (1H, d, J = 11.2 Hz), 6.83 (2H, d, J = 8.6 Hz), 7.12 (2H, d, J = 8.6 Hz), 7.31 (2H, d, J = 7.9 Hz), 7.32-7.50 (6H, m), 7.60-7.74 (4H, m), 7.78 (2H, d, J = 7.9 Hz); ¹³C-NMR (67.8 MHz, CDCl₃) δ 1.02, δ 1.02, δ 1.02, δ 1.02, δ 1.02, δ 1.03, 121 (100), 91 (6.11); HR-MS calcd. for C₃₁H₃₃O₆SiS (M^{*}-rBu) m/z 561.1767, found 561.1833.

(S)-9-(tert-Butyldiphenylsilyloxy)-8-(p-methoxybenzyloxy)-1-nonanol (14). Magnesium turnings (729 mg, 30.0 mmol) in dry THF (3.0 ml) were activated by a small piece of iodine with stirring and heating under argon atmosphere until the color of iodine disappeared. To initiate generation of the Grignard reagent, 5-(tetrahydropyranyloxy)-1-pentyl bromide (0.53 g, 2.11 mmol) was first added to the suspension of activated magnesium in THF and the mixture was heated to reflux. Next, a solution of 5-(tetrahydropyranyloxy)-1-pentyl bromide (7.00 g, 27.9 mmol) in dry THF (27 ml) was added dropwise to the stirred mixture over 60

min with keeping the exothermeric reaction. The stirring was further continued for 30 min to give a Grignard reagent, 5-(tetrahydropyranyloxy)-1-pentylmagnesium bromide. To the cooled Grignard reagent (20 ml, transferred to another flask with a syringe) at -25 $^{\circ}$ was added copper (I) iodide (1.16 g, 6.08 mmol) and the mixture was stirred for 30 min at the same temperature under argon atmosphere. A solution of 12 (2.50 g, 4.04 mmol) in dry THF (10 ml) was added dropwise to the Grignard reagent-mixture at -25 $^{\circ}$. The temperature was gradually allowed to warm to room temperature and the stirring was continued for 4 h. The reaction mixture was poured into aq. NH₄Cl (200 ml) and extracted with EtOAc (200 ml, 100 ml x 2). The combined extracts weres washed with brine (100 ml), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was separated by column chromatography (silica gel 150 g, hexane:EtOAc = 10:1) to give a crude 13 (2.82 g), containing impurities derived from the Grignard reagent. The crude 13 was used for the next reaction. A solution of 13 (2.82 g) and PPTS (50 mg, 0.20 mmol) in EtOH (40 ml) was stirred for 3 days at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel 100 g, hexane:EtOAc = 3:1) to give 14 (1.90 g, 88%, 2 steps) as a colorless oil: $[\alpha]_{0}^{21}$ -15.2° (c 1.28, CHCl₃); IR (film) 3374, 3072, 3049, 3000, 2932, 2958, 1614, 1588, 1514, 1464, 1428, 1391, 1361, 1302, 1248, 1174, 1112, 1069, 1038, 938, 824, 742, 703 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) δ 1.07 (9H, s), 1.17-1.43 (8H, m), 1.44-1.63 (5H, m), 3.46 (1H, m), 3.58-3.69 (3H, m), 3.73 (1H, dd, J = 10.6, 5.9 Hz), 3.80 (3H, s), 4.43 (1H, d, J = 11.6 Hz), 4.60 (1H, d, J = 11.6 Hz), 6.85 (2H, d, J = 8.6 Hz), 7.23 (2H, d, J = 8.6 Hz), 7.23 (2H, d, J = 8.6 Hz), 7.33-7.48 (6H, m), 7.64-7.75 (4H, m); ¹³C-NMR (67.8 MHz, CDCl₃) δ 19.2, 25.3, 25.6, 26.8, 29.3, 29.6, 31.6, 32.8, 55.3, 63.0, 66.

(S)-9-(tert-butyldiphenylsilyloxy)-8-(p-methoxybenzyloxy)-1-nonyl bromide (15). To a stirred solution of 14 (1.90 g, 3.55 mmol) in CH₂Cl₂ (20 ml) was added triphenylphosphine (1.41 g, 4.26 mmol) and carbon tetrabromide (1.12 g, 4.26 mmol) at 4 °C. After being stirred for 30 min at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 50 g, hexane:EtOAc = 20:1) to give 15 (2.12 g, 100%) as a colorless oil: $[\alpha]_D^{21}$ -8.77° (c 1.00, CHCl₃); IR (film) 3071, 3049, 2999, 2931, 2958, 1614, 1588, 1514, 1464, 1428, 1390, 1361, 1302, 1248, 1173, 1112, 1069, 1038, 938, 824, 742, 703 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) & 1.07 (9H, s), 1.17-1.60 (10H, m), 1.84 (2H, quint, *J* = 6.6 Hz), 3.40 (2H, t, *J* = 6.6 Hz), 3.46 (1H, m), 3.62 (1H, dd, *J* = 11.2 Hz), 6.85 (2H, d, *J* = 8.6 Hz), 7.23 (2H, d, *J* = 8.6 Hz), 7.33-7.48 (6H, m), 7.64-7.75 (4H, m); ¹³C-NMR (67.8 MHz, CDCl₃) & 19.2, 25.2, 26.8, 28.1, 28.7, 29.4, 31.6, 32.8, 34.0, 55.3, 66.3, 71.8, 79.3, 113.7, 127.6, 129.3, 129.6, 131.2, 133.6, 135.6, 159.0; FD-MS *m/z* 599 (for ⁸¹Br, MH⁺, 4.51), 598 (for ⁸¹Br, M⁺, 9.18), 597 (for ⁷⁹Br, MH⁺, 15.1), 596 (for ⁷⁹Br, M⁺, 7.50), 541 (for ⁸¹Br, M⁺, 49.0), 539 (for ⁷⁹Br, M⁺, 7Bu, 31.3), 121 (100), 57 (10.3); HR-MS calcd. for C₃₃H₄₅O₃Si⁷⁹Br (M⁺) *m/z* 596.2322, found 596.2300.

(S)-9-(tert-Butyldiphenylsilyloxy)-8-(p-methoxybenzyloxy)-1-nonyltriphenylphosphonium bromide (16). A solution of 15 (2.12 g, 3.55 mmol) and triphenylphosphine (931 mg, 3.55 mmol) in dry CH₃CN (10 ml) was refluxed for 3 days under argon atmosphere. After evaporation of CH₃CN under reduced pressure, the residue was dried up in vacuo at 60 °C for 5 h to give 16 (3.10 g, 100%) as a yellow oil: ¹H-NMR (270 MHz, CDCl₃) δ 1.03 (9H, s), 1.08-1.85 (12H, m), 3.41 (1H, m), 3.58 (1H, dd, J = 10.6, 4.6 Hz), 3.69 (1H, dd, J = 10.6, 5.9 Hz), 3.77 (3H, s), 3.67-3.85 (2H, m), 4.39 (1H, d, J = 11.2 Hz), 4.57 (1H, d, J = 11.2 Hz), 6.81 (2H, d, J = 8.6 Hz), 7.20 (2H, d, J = 8.6 Hz), 7.29-7.43 (6H, m), 7.59-7.90 (19H, m); FAB-MS m/z 779 (for cation-part, C₅₁H₆₀O₃SiP⁺, 60.3), 262 (34.4), 121 (100), 57 (16.7); HR-MS calced for C₅₁H₆₀O₃SiP (cation-part, corresponds to M⁺-Br) m/z 779.4049, found 779.4054. This phosphonium salt was used for the next Wittig reaction without further purification.

(1R,2R,4S',9''S)-1-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)-2-[10''-(tert-butyldiphenylsilyloxy)-9"-(p-methoxybenzyloxy)decen-1"-yl]cyclopropane (18). To a stirred solution of oxalyl chloride (266 µl, 3.04 mmol) and dimethyl sulfoxide (290 µl, 4.08 mmol) in dry CH₂Cl₂ (5.0 ml) was added dropwise (1R,2S,4S')-1-(2',2'-dimethyl-1',3'-dioxolane-4'-yl)-2-(hydroxymethyl)cyclopropane 17 (345 mg, 2.00 mmol) in dry CH₂Cl₂ (3.0 ml) at -78 °C under argon atmosphere. The stirring was continued for 20 min at the same temperature. After addition of triethylamine (1.42 ml, 10.2 mmol) at -78 °C, the reaction mixture was allowed to warm to room temperature with stirring. The reaction mixture was diluted with CH₂Cl₂ (20 ml) and washed with water (20 ml) and brine (20 ml). The organic layer was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give a crude aldehyde (17A) which was used for the next Wittig reaction without further purification. To a stirred solution of phosphonium salt 16 (3.10 g, 3.55 mmol) in dry THF (10 ml) was added dropwise *n*-BuLi (1.53 M solution in hexane, 2.32 ml, 3.55 mmol) at -78 °C. To this ylide solution was

added dropwise a solution of aldehyde 17A in dry THF (4.0 ml). The reaction was gradually allowed to warm to room temperature over 1 h and was quenched by addition of sat. aq. NH₄Cl (20 ml) and water (20 ml). The reaction mixture was extracted with EtOAc (20 ml x 3) and the combined extracts were washed with brine (50 ml), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 100 g, hexane:EtOAc = 10:1) to give 18 (1.10 g, 82%) as a colorless oil: IR (film) 3071, 3048, 2986, 2932, 2957, 1614, 1588, 1514, 1464, 1428, 1379, 1370, 1348, 1302, 1248, 1216, 1172, 1113, 1064, 1039, 1009, 962, 939, 848, 824, 756, 742, 703 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) & 0.61 (1H, m), 1.07 (9H, s), 1.00-1.18 (3H, m), 1.19-1.80 (10H, m), 1.36 (3H, s), 1.45 (3H, s), 1.92-2.20 (2H, m), 3.47 (1H, m), 3.57-3.70 (3H, m), 3.74 (1H, dd, J = 10.6, 5.3 Hz), 3.80 (3H, s), 4.05 (1H, dd, J = 7.3, 4.6 Hz), 4.44 (1H, d, J = 11.2 Hz), 4.60 (1H, d, J = 11.2 Hz), 5.01 (0.83H, t, J = 11.2 Hz, for Z-isomer), 5.12 (0.17H, dd, J = 15.2, 7.3 Hz, for *E*-isomer), 5.43 (0.83H, dt, J = 11.2, 7.3 Hz, for Z-isomer), 5.56 (0.17H, dt, J = 15.2, 7.3 Hz, for *E*-isomer), 5.43 (0.83H, dt, J = 11.2, 5.57 (1.89), 5.77 (1.89), 417 (1.26), 333 (1.74), 199 (21.0), 121 (100), 57 (1.38); HR-MS calcd. for C₄₂H₅₈O₅Si (M⁺) m/z 670.4053, found 670.4033.

(2S, 3R, 4R, 13S)-14-(tert-Butyldiphenylsilyloxy)-13-(p-methoxybenzyloxy)-3,4-methylene-5-tetradecen-1, 2-diol (18A). A solution of 18 (1.08 g, 1.61 mmol) and PPTS (20.3 mg, 80.5 µmol) in EtOH (16 ml) wasstirred for 2 days at 50 °C. The reaction mixture was concentrated under reduced pressure and the residue waspurified by column chromatography (silica gel 40 g, hexane:EtOAc = 1:1) to give 18A (729 mg, 72%; 97%based on consumed 18) as a colorless oil and unreacted 18 (282 mg, 26%). Data for 18A: IR (film) 3388,3071, 3048, 2999, 2931, 2957, 1613, 1588, 1514, 1464, 1428, 1390, 1361, 1302, 1248, 1173, 1113, 1064, $1038, 961, 911, 824, 756, 740, 703 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) <math>\delta$ 0.52 (1H, m), 1.07 (9H, s), 0.93-1.15 (3H, m), 1.18-1.80 (10H, m), 1.92-2.26 (4H, m), 3.32 (1H, m), 3.49 (2H, m), 3.58-3.77 (3H, m), 3.80 (3H, s), 4.44 (1H, d, J = 11.2 Hz), 4.61 (1H, d, J = 11.2 Hz), 4.99 (0.87H, t, J = 11.2 Hz, for Zisomer), 5.12 (0.13H, dd, J = 15.2, 8.7 Hz, for E-isomer), 5.45 (0.87H, dt, J = 11.2, 7.3 Hz, for Z-isomer), 5.57 (0.13H, dt, J = 15.2, 7.3 Hz, for E-isomer), 6.85 (2H, d, J = 8.6 Hz), 7.24 (2H, d, J = 8.6 Hz), 7.33-7.47 (6H, m), 7.63-7.76 (4H, m); El-MS m/z 612 (M⁺H₂O, 0.04), 537 (0.33), 417 (0.32), 333 (0.83), 199 (7.72), 121 (100), 57 (0.76); HR-MS calcd. for C₃₉H₃₂O₄Si (M⁺-H₂O) m/z 612.3635, found 612.3654.

(2S, 11R, 12S)-1-(tert-Butyldiphenylsilyloxy)-2-(p-methoxybenzyloxy)-11, 12-methylene-9, 13-octadiene (19). To a stirred solution of diol 18A (767 mg, 1.22 mmol) in THF (8.0 ml) was added a solution of sodium periodate (390 mg, 1.82 mmol) in H₂O (4.0 ml) at 4 °C. After being stirred for 1 h at room temperature, the reaction mixture was partitioned between water (20 ml) and CHCl₃ (20 ml). The aqueous layer was further extracted with CHCl₃ (10 ml x 3). The combined organic layers were washed with brine (30 ml), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give a crude aldehyde (18B) which was used for the next Wittig reaction without further purification. To a solution of pentyltriphenylphosphonium bromide (1.51 g, 3.66 mmol) in dry THF (8.0 ml) was added dropwise n-BuLi (1.53 M solution in hexane, 2.39 ml, 3.66 mmol) at 0 °C under argon atmosphere. The mixture was stirred for 30 min at room temperature and cooled to -78 °C. To this ylide solution was added dropwise a solution of aldehyde 18B in dry THF (3.0 ml). The reaction was gradually allowed to warm to room temperature over 30 min and quenched by addition of sat. aq. NH₄Cl (20 ml) and water (20 ml). The reaction mixture was extracted with CHCl₃ (20 ml x 3) and the combined extracts were washed with brine (50 ml), dried over anhydrous Na2SO4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 50 g, hexane:EtOAc = 20:1) to give 19 (743 mg, 93%) as a colorless oil: IR (film) 3071, 3048, 3012, 2999, 2930, 2857, 1613, 1588, 1514, 1464, 1442, 1428, 1390, 1378, 1361, 1348, 1302, 1248, 1172, 1113, 1064, 1039, 1008, 999, 957, 891, 824, 758, 741, 703 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) δ 0.45 (1H, m), 0.88 (3H, m), 1.07 (9H, s), 1.10-1.87 (17H, m), 1.93-2.23 (4H, m), 3.47 (1H, m), 3.63 (1H, dd, J = 10.6, 4.6 Hz), 3.74 (1H, dd, J = 10.6, 5.9 Hz), 3.80 (3H, s), 4.44 (1H, d, J = 11.2 Hz), 4.60 (1H, d, J = 11.2 Hz), 4.98-5.24 (2H, m), 5.36-5.62 (2H, m), 6.85 (2H, d, J = 8.6 Hz), 7.24 (2H, d, J = 8.6 Hz), 7.33-7.47 (6H, m), 7.63-7.76 (4H, m); EI-MS m/z 652 (M⁺, 0.27), 595 (M⁺-tBu, 0.52), 517 (0.51), 453 (1.11), 333 (1.16), 199 (9.67), 121 (100), 57 (1.15); HR-MS calcd. for $C_{43}H_{60}O_3Si (M^*) m/z$ 652.4312, found 652.4309.

(2S, 11R, 12S)-2-(p-Methoxybenzyloxy)-11, 12-methylene-9, 13-octadecadien-1-ol (19A). A solution of 19 (740 mg, 1.13 mmol) and TBAF (1.0 M solution of THF, 1.70 ml, 1.70 mmol) in THF (1.70 ml) was stirred overnight at room temperature. After addition of aq. NH₄Cl (20 ml), the reaction mixture was extracted with EtOAc (10 ml x3). The combined extracts were washed with water (30 ml) and brine (30 ml), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 30 g, hexane:EtOAc = 3:1) to give 19A (462 mg, 99%) as a colorless oil: IR (film) 3426, 3068, 3011, 2929, 2856, 1613, 1587, 1514, 1465, 1442, 1421, 1377, 1347, 1303, 1249, 1173, 1111, 1074, 1038, 958, 822, 770, 725, 707 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) δ 0.44 (1H, m), 0.90 (3H, m), 1.03-

1.71 (15H, m), 1.73-2.03 (3H, m), 2.06-2.24 (4H, m), 3.49 (2H, m), 3.68 (1H, m), 3.80 (3H, s), 4.46 (1H, d, J = 11.2 Hz), 4.56 (1H, d, J = 11.2 Hz), 4.98-5.23 (2H, m), 5.36-5.62 (2H, m), 6.89 (2H, d, J = 8.6 Hz), 7.27 (2H, d, J = 8.6 Hz); EI-MS m/z 415 (MH⁺, 0.22), 414 (M⁺, 0.67), 383 (M⁺-CH₃O, 0.14), 293 (7.88), 199 (0.46), 121 (100); HR-MS calcd. for C₂₇H₄₂O₃ (M⁺) m/z 414.3134, found 414.3106.

(2S, 11S, 12R)-2-(p-Methoxybenzyloxy)-11, 12-methyleneoctadecan-1-ol (19B). To a stirred mixture of 19A (460 mg, 1.11 mmol) and potassium azodicarboxylate (6.47 g, 33.3 mmol) in pyridine (20 ml) was added dropwise acetic acid (3.81 ml, 66.6 mmol) at room temperature. After being stirred for 2 days, the reaction mixture was diluted with EtOAc (50 ml), washed successively with 1 M HCl (50 ml x 3), sat. aq. NaHCO₃ (50 ml), and brine (50 ml). The organic layer was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 20 g, hexane:EtOAc = 3:1) to give 19B (453 mg, 97%) as a colorless oil: $[\alpha]_{D}^{22} + 11.6^{\circ}(c \ 1.12, CHCl_3)$; IR (film) 3427, 3058, 2990, 2925, 2854, 1614, 1587, 1514, 1465, 1397, 1348, 1303, 1249, 1173, 1077, 1039, 822, 755, 723 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) δ -0.33 (1H, dd, J = 8.9, 4.9 Hz), 0.51-0.72 (3H, m), 0.89 (3H, t, J = 6.6 Hz), 1.03-1.70 (26H, m), 1.93 (1H, br. s, OH), 3.49 (2H, m), 3.66 (1H, m), 3.80 (3H, s), 4.46 (1H, d, J = 11.2 Hz), 6.58 (2H, d, J = 8.6 Hz), 7.28 (2H, d, J = 8.6 Hz); ¹³C-NMR (67.8 MHz, CDCl₃) δ 10.9, 14.1, 15.8, 22.7, 25.4, 28.7, 29.3, 29.5, 29.6, 29.8, 30.2, 30.8, 31.9, 55.3, 64.3, 71.2, 79.5, 113.9, 129.4, 130.6, 159.3; EI-MS mlz 419 (MH⁺, 1.81), 418 (M⁺, 6.11), 387 (M⁺-CH₃O, 0.27), 199 (0.60), 121 (100); HR-MS calcd. for C₂₇H₄₆O₃ (M⁺) m/z 418.3446, found 418.3448.

(2S, 11S, 12R)-2-(p-Methoxybenzyloxy)-11, 12-methyleneoctadecanoic acid (20). To a stirred solution of oxalyl chloride (139 µl, 1.59 mmol) and dimethyl sulfoxide (151 µl, 2.12 mmol) in dry CH₂Cl₂ (5.0 ml) was added dropwise **19B** (442 mg, 1.06 mmol) in dry CH₂Cl₂ (3.0 ml) at -78 °C under argon atmosphere. The stirring was continued for 20 min at the same temperature. After addition of triethylamine (738 µl, 5.30 mmol) at -78 °C, the reaction mixture was allowed to warm to room temperature with stirring. The reaction mixture was diluted with CH₂Cl₂ (20 ml) and washed with water (20 ml) and brine (20 ml). The organic layer was dried over anhydrous Na₃SO₄, and concentrated under reduced pressure to give a crude aldehyde (**19**C) which was used for the next oxidation without further purification. To a stirred mixture of **19**C, 2-methyl-2-butene (0.4 ml), and NaH₂PO₄·2H₂O (165 mg, 1.06 mmol) in *t*-BuOH (4.0 ml) and H₂O (1.4 ml) was added NaClO₂ (451 mg, 4.24 mmol as 85% purity) at room temperature. After being stirred for 1 h, the reaction mixture was acidified with 1 M HCl (10 ml) and extracted with CHCl₃ (10 ml x 3). The combined extracts were washed with brine (10 ml), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 20 g, CHCl₃:MeOH = 20:1) to give **20** (449 mg, 98%) as a colorless oil: [α]_p²² -25.7° (c 1.10, CHCl₃); IR (film) 3450-2500, 3059, 2989, 2925, 2855, 1717, 1614, 1587, 1515, 1465, 1442, 1397, 1377, 1303, 1250, 1174, 1110, 1038, 932, 847, 822, 759, 723 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) & -0.33 (1H, dd, J = 8.9, 4.9 Hz), 0.51-0.73 (3H, m), 0.89 (3H, t, J = 6.9 Hz), 1.03-1.60 (24H, m), 1.78 (2H, m), 3.81 (3H, s), 3.97 (1H, t, J = 5.9 Hz), 4.44 (1H, d, J = 11.2 Hz), 4.62 (1H, d, J = 11.2 Hz), 6.89 (2H, d, J = 8.6 Hz), 7.28 (2H, d, J = 8.6 Hz), 1.29.8, 159.6, 176.3; EI-MS m/z 433 (MH⁺, 0.83), 432 (M⁺, 3.33), 431 (M⁺-H, 1.53), 415 (M⁺-OH, 0.43), 121 (100); HR-MS calcd. for C

Cepaciamide A p-methoxybenzyl ether, (3R, 3'S, 2'S, 11'S, 12'R)-3-(3'-[2''-(p-methoxybenzyloxy)-11",12"-methyleneoctadecanoyloxy Jhexadecanoylamino] -2-piperidinone (21). To a stirred suspension of acidcomponent 20 (200 mg, 462 µmol) and alcohol-component 1b (114 mg, 308 µmol) in dry toluene (3.0 ml) was added DCC (95.5 mg, 462 µmol) and DMAP (5.64 mg, 46.2 µmol) at room temperature. The stirring was continued overnight. After addition of MeOH (0.5 ml) and DCC (50 mg), the reaction mixture was further stirred for 2 h, diluted with EtOAc (5 ml) and hexane (5 ml), and filtered through a Celite pad. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel 10 g, gradient elution, hexane:EtOAc = 1:1, 1:3, 1:5, 100% EtOAc) to give 21 (193 mg, 80%) as a colorless oil: [α]_p²² -43.4° (c 1.03, CHCl₃); IR (film) 3292, 3060, 2924, 2854, 1732, 1667, 1614, 1586, 1540, 1514, 1494, 1466, 1378, 1360, 1332, 1303, 1249, 1207, 1174, 1108, 1039, 890, 822, 757, 722 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) δ -0.34 (1H, dd, J = 8.6, 5.3 Hz), 0.50-0.72 (3H, m), 0.87 (3H, t, J = 6.6 Hz), 0.88 (3H, t, J= 6.6 Hz), 1.00-1.53 (46H, m), 1.55-1.82 (5H, m), 1.88 (2H, m), 2.40-2.60 (3H, m), 3.30 (2H, m), 3.79 (3H, s), 3.86 (1H, t, J = 6.6 Hz), 4.23 (1H, dt, J = 11.9, 5.9 Hz), 4.30 (1H, d, J = 11.2 Hz), 4.61 (1H, d, J= 11.2 Hz), 5.31 (1H, quint, J = 6.3 Hz), 6.00 (1H, br. s, NH), 6.60 (1H, br. d, J = 5.9 Hz, NH), 6.85 (2H, d, J = 8.6 Hz), 7.25 (2H, d, J = 8.6 Hz); ¹³C-NMR (67.8 MHz, CDCl₃) δ 10.9, 14.1, 15.7, 20.9, 22.6, 25.2, 25.4, 27.1, 28.7, 29.3, 29.5, 29.6, 29.7, 30.1, 30.2, 31.88, 31.92, 33.0, 34.0, 41.1, 41.6, 50.6, 55.2, 71.7, 71.8, 77.9, 113.7, 129.6, 129.8, 159.3, 164.6, 171.4, 172.4; FD-MS m/z 783 (MH⁺, 85.5), 782 (M⁺, 36.7), 646 (100), 431 (2.50), 368 (24.0), 351 (15.0), 141 (4.71), 121 (62.4), 98 (7.28); HR-MS calcd. for $C_{48}H_{82}N_2O_6$ (M⁺) *m/z* 782.6173, found 782.6138.

Cepaciamide A, (3R, 3'S, 2'S, 11'S, 12'R) -3 - [3' - (2''-hydroxy -11'', 12''-methyleneoctadecanoyloxy)hexadecanoylamino]-2-piperidinone (1a). To a stirred mixture of 21 (189 mg, 241 µmol) in CH₃CN (3.0 ml),CHCl₃ (1.0 ml) and H₂O (0.3 ml) was added CAN (264 mg, 482 µmol) at room temperature. After beingstirred for 30 min, the reaction mixture was partitioned between water (20 ml) and CHCl₃ (20 ml). The aqueouslayer was further extracted with CHCl₃ (10 ml x 2) and the combined organic layers were dried over anhydrousNa₂SO₄, and concentrated under reduced pressure. The residue was purified by preparative TLC(CHCl₃:MeOH = 20:1, double development) to give 1a (128 mg, 80%) as a colorless amorphous solid (mp 58-64 °C). Other spectral data have been reported.^{2b}

(S)-10-(tert-Butyldiphenylsilyloxy)-9-(p-methoxybenzyloxy)-1-decanol (23). According to the same method as described in the synthesis of 14, a Grignard reagent, 6-(tetrahydropyranyloxy)-1-hexylmagnesium bromide in THF (30 ml) was prepared from magnesium turnings (729 mg, 30.0 mmol) and 6-(tetrahydropyranyloxy)-1-hexyl bromide (7.95 g, 30.0 mmol). To the cooled Grignard reagent (4.0 ml, transferred to another flask with a syringe) at -25 °C was added copper (I) iodide (229 mg, 1.20 mmol) and the mixture was stirred for 30 min at the same temperature under argon atmosphere. A solution of 12 (620 mg, 1.00 mmol) in dry THF (5 ml) was added dropwise to the Grignard reagent-mixture at -25 °C. The temperature was gradually allowed to warm to room temperature and the stirring was continued for 4 h. The reaction mixture was poured into aq. NH₄Cl (50 ml) and extracted with EtOAc (50 ml, 20 ml x 2). The combined extracts were washed with brine (50 ml), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was separated by column chromatography (silica gel 50 g, hexane:EtOAc = 10:1) to give a crude 22 (699 mg), containing impurities derived from the Grignard reagent. The crude 22 was used for the next reaction. A solution of 22 (699 mg) and PPTS (12.6 mg, 0.05 mmol) in EtOH (10 ml) was stirred for 3 days at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was colorless oil: $(\alpha_{1p}^{-1}-17.8^{\circ}$ (c 1.81, CHCl₃); IR (film) 3391, 3071, 3049, 3000, 2931, 2957, 1613, 1588, 1514, 1463, 1428, 1391, 1361, 1303, 1248, 1173, 1112, 1069, 1038, 938, 824, 741, 703 cm¹; ¹H-NMR (270 MHz, CDCl₃) δ 1.06 (9H, s), 1.17-1.43 (10H, m), 1.44-1.63 (5H, m), 3.46 (1H, m), 3.58-3.69 (3H, m), 3.73 (1H, dd, J = 10.6, 5.3 Hz), 3.80 (3H, s), 4.43 (1H, d, J = 11.6 Hz), 4.60 (1H, d, J = 11.6 Hz), 6.85 (2H, d, J = 8.6 Hz), 7.23 (2H, d, J = 8.6 Hz), 7.33-7.48 (6H, m), 7.64-7.75 (4H, m); ¹³C-NMR (67.8 MHz, CDCl₃) δ 19.2, 25.3, 25.7, 26.8, 29.3, 29.5, 29.6, 31

(S)-10-(tert-butyldiphenylsilyloxy)-9-(p-methoxybenzyloxy)-1-decyl bromide (24). According to the same method as described in the synthesis of 15, treatment of 23 (334 mg, 609 µmol) with triphenylphosphine (240 mg, 914 µmol) and carbon tetrabromide (303 mg, 914 µmol) in CH,CL (3.0 ml) gave 24 (362 mg, 97%) as a colorless oil: $[\alpha]_D^{21}$ -8.36° (c 1.00, CHCl₃); IR (film) 3072, 3049, 3000, 2931, 2957, 1614, 1588, 1515, 1464, 1428, 1391, 1361, 1302, 1248, 1173, 1113, 1069, 1038, 1009, 938, 823, 741, 703 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) & 1.07 (9H, s), 1.16-1.60 (12H, m), 1.85 (2H, quint., J = 6.6 Hz), 3.41 (2H, t, J = 6.6 Hz), 3.46 (1H, m), 3.62 (1H, dd, J = 10.6, 5.3 Hz), 3.73 (1H, dd, J = 10.6, 5.9 Hz), 3.80 (3H, s), 4.43 (1H, d, J = 11.2 Hz), 4.60 (1H, d, J = 11.2 Hz), 6.85 (2H, d, J = 8.6 Hz), 7.23 (2H, d, J = 8.6 Hz), 7.36 (3H, s), 4.43 (1H, dm), 7.64-7.75 (4H, m); ¹³C-NMR (67.8 MHz, CDCl₃) & 19.2, 25.2, 26.8, 28.1, 28.7, 29.4, 31.6, 32.8, 34.0, 55.3, 66.3, 71.8, 79.3, 113.7, 127.6, 129.3, 129.6, 131.2, 133.6, 135.6, 159.0; FD-MS m/z 613 (for ⁸¹Br, MH⁺, 44.7), 612 (for ⁸¹Br, M⁺·1Bu, 46.9), 121 (66.6), 57 (9.01); HR-MS calcd. for $C_{34}H_{47}O_3$ SiBr (M⁺) m/z 596.2322, found 596.2300.

(S)-2-(p-Methoxybenzyloxy)-11-octadecyn-1-ol (26). To a solution of 1-octyne (174 μ l, 1.18 mmol) in dry THF (2.0 ml) and dry HMPA (514 μ l, 2.96 mmol) at -78 °C under argon atmosphere was added dropwise n-BuLi (1.61 M solution in hexane, 733 μ l, 1.18 mmol) and the mixture was stirred for 30 min at the same temperature. To this acetylide solution was added a solution of 24 (362 mg, 592 μ mol) in dry THF (2.0 ml) at -78 °C. The reaction was gradually allowed to warm to room temperature. After being stirred for 3 h, the reaction mixture was partitioned between sat. aq. NH₄Cl (10 ml) and EtOAc (10 ml). The aqueous layer was further extracted with EtOAc (10 ml x 2) and the combined organic layers were washed with water (20 ml) and brine (20 ml), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue containing (S)-1-(tent-butyldiphenylsilyloxy)-2-(p-methoxybenzyloxy)-11-octadecyne (25) and 26 was used for the next reaction without separation. A solution of the mixture of 25 and 26 in THF (2.0 ml) was treated with TBAF (1.0 M solution in THF, 1.20 ml, 1.20 mmol) for 5 h at room temperature. After addition of aq. NH₄Cl (10 ml), the reaction mixture was extracted with EtOAc (10 ml x 3). The combined extract was washed with water (10 ml) and brine (10 ml), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 10 g, hexane:EtOAc = 3:1) to give **26** (205 mg, 86%, 2 steps) as a colorless oil: $[\alpha]_{2}^{21}$ +8.42° (c 0.95, CHCl₃); IR (film) 3434, 2930, 2957, 1614, 1587, 1515, 1464, 1428, 1391, 1361, 1302, 1249, 1173, 1113, 1069, 1038, 1009, 822, 741, 703 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) δ 0.89 (3H, t, J = 6.9 Hz), 1.20-1.69 (22H, m), 1.89 (1H, br. s, OH), 2.14 (4H, t, J = 6.9 Hz), 3.49 (2H, m), 3.67 (1H, m), 3.81 (3H, s), 4.46 (1H, d, J = 11.2 Hz), 4.56 (1H, d, J = 11.2 Hz), 6.89 (2H, d, J = 8.6 Hz), 7.27 (2H, d, J = 8.6 Hz); ¹³C-NMR (67.8 MHz, CDCl₃) δ 14.4, 18.8, 22.6, 25.4, 28.5, 28.8, 29.1, 29.5, 29.8, 30.8, 31.4, 55.3, 64.3, 71.2, 77.2, 79.5, 113.9, 129.4, 130.6, 159.3; FD-MS m/z 403 (4M⁺, 29.3), 402 (M⁺, 100), 292 (0.04), 121 (1.06); HR-MS calcd. for C₂₆H₄₂O₃ (M⁺) m/z 402.3134, found 402.3147.

(2S, 11Z)-2-(p-Methoxybenzyloxy)-11-octadecen-1-ol (26A). A mixture of 26 (245 mg, 609 µmol) and Lindlar catalyst (50 mg) in EtOAc (6.0 ml) was stirred overnight under hydrogen atmosphere at ordinary temperature and pressure. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give 26A (246 mg, 100%) as a colorless oil: $[\alpha]_D^{22} + 10.3^{\circ} (c \ 1.30, CHCl_3)$; IR (film) 3425, 3003, 2926, 2955, 1614, 1587, 1514, 1465, 1428, 1400, 1378, 1348, 1303, 1249, 1173, 1111, 1080, 1039, 1009, 822, 756, 723 cm⁻¹; ¹H-NMR (270 MHz, CDCl_3) δ 0.89 (3H, t, J = 7.3 Hz), 1.17-1.69 (22H, m), 1.89-2.12 (5H, m), 3.50 (2H, m), 3.68 (1H, m), 3.80 (3H, s), 4.46 (1H, d, J = 11.2 Hz), 4.56 (1H, d, J = 11.2 Hz), 5.35 (2H, m), 6.89 (2H, d, J = 8.6 Hz), 7.27 (2H, d, J = 8.6 Hz); ¹³C-NMR (67.8 MHz, CDCl_3) δ 14.1, 22.6, 25.4, 29.0, 29.3, 29.47, 29.51, 29.7, 29.8, 30.8, 31.8, 55.2, 64.3, 71.2, 79.4, 113.9, 129.4, 129.8, 129.9, 130.6, 159.3; EI-MS m/z 405 (MH⁺, 1.80), 404 (M⁺, 6.05), 373 (M⁺-CH₃O, 2.37), 137 (15.3), 121 (100); HR-MS calcd. for C₂₆H₄₄O₃ (M⁺) m/z 404.3290, found 404.3302.

(2S, 11Z)-2-(p-Methoxybenzyloxy)-11-octadecenoic acid (27). According to the same method as described in the synthesis of **20**, **26A** (476 mg, 1.76 mmol) was treated with oxalyl chloride (154 µl, 1.76 mmol), dimethyl sulfoxide (167 µl, 2.35 mmol), and triethylamine (822 µl, 5.90 mmol) to give a crude aldehyde (**26B**) which was used for the next oxidation without further purification. Aldehyde **26B** was treated with 2-methyl-2-butene (0.5 ml), NaH₂PO₄:2H₂O (184 mg, 1.18 mmol), and NaClO₂ (503 mg, 4.72 mmol as 85% purity) at room temperature to give **27** (480 mg, 97%) as a colorless oil: $[a]_{p}^{22}$ -25.6° (*c* 1.11, CHCl₃); IR (film) 3450-2500, 3003, 2926, 2955, 1720, 1613, 1587, 1514, 1465, 1442, 1404, 1377, 1348, 1303, 1250, 1174, 1112, 1038, 968, 847, 822, 758, 724 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) δ 0.88 (3H, t, *J* = 7.3 Hz), 1.17-1.60 (20H, m), 1.78 (2H, m), 1.90-2.10 (4H, m), 3.80 (3H, s), 3.96 (1H, t, *J* = 5.9 Hz), 4.42 (1H, d, *J* = 11.2 Hz), 5.35 (2H, m), 6.88 (2H, d, *J* = 8.6 Hz), 7.28 (2H, d, *J* = 8.6 Hz), the chemical shift of the carboxyl proton could not be assigned due to broadening: ¹⁻³C-NMR (67.8 MHz, CDCl₃) δ 14.1, 22.6, 25.0, 27.2, 29.0, 29.20, 29.24, 29.38, 29.44, 29.7, 31.8, 32.5, 55.3, 72.2, 77.2, 113.9, 129.1, 129.8, 129.9, 130.3, 159.6, 176.9; EI-MS *m/z* 419 (MH⁺, 0.63), 418 (M⁺, 1.92), 296 (2.40), 245 (4.04), 199 (2.40), 152 (6.61), 137 (45.7), 121 (100); HR-MS calcd. for C₂₆H₄₂O₄ (M⁺) *m/z* 418.3063, found 418.3041.

Cepaciamide B p-methoxybenzyl ether, (3R, 3'S, 2'S, 11'Z)-3- $\{3'-[2''-(p-methoxybenzyloxy)-11''-octadecenoyloxy]hexadecanoylamino}$ -2-piperidinone (28). According to the same method as described in the synthesis of 21, esterification between acid-component 27 (227 mg, 542 µmol) and alcohol-component 1b (100 mg, 271 µmol) with DCC (112 mg, 542 µmol) and DMAP (6.62 mg, 54.2 µmol) gave 28 (159 mg, 76%) as a colorless oil: $[\alpha]_p^{-23}$ -45.5° (c 1.60, CHCl₃); IR (film) 3292, 3068, 3005, 2923, 2854, 1732, 1668, 1614, 1586, 1539, 1514, 1494, 1466, 1378, 1360, 1332, 1303, 1249, 1208, 1180, 1174, 1110, 1038, 891, 822, 758, 724 cm⁻¹; ¹H-NMR (270 MHz, CDCl₃) & 0.87 (6H, t, J = 6.6 Hz), 1.00-1.78 (47H, m), 1.80-2.09 (6H, m), 2.42-2.61 (3H, m), 3.30 (2H, m), 3.79 (3H, s), 3.86 (1H, t, J = 5.9 Hz), 4.23 (1H, dt, J = 11.9, 5.9 Hz), 4.30 (1H, dt, J = 11.2 Hz), 4.61 (1H, dt, J = 11.2 Hz), 5.23-5.41 (3H, m), 5.82 (1H, br. s, NH), 6.54 (1H, br. dt, J = 5.9 Hz, NH), 6.86 (2H, dt, J = 8.6 Hz), 7.26 (2H, dt, J = 8.6 Hz); ¹³C-NMR (67.8 MHz, CDCl₃) & 14.1, 20.9, 22.6, 22.7, 25.2, 25.4, 27.0, 27.2, 29.0, 29.29, 29.34, 29.47, 29.53, 29.7, 29.8, 31.8, 31.9, 33.0, 33.9, 34.0, 41.1, 41.7, 50.7, 55.2, 71.7, 71.8, 77.9, 113.7, 129.6, 129.8, 129.9, 159.3, 169.7, 171.3, 172.4; FD-MS m/z 769 (MH⁺, 100), 768 (M⁺, 66.9), 632 (75.2), 618 (21.9), 385 (27.0), 338 (16.6), 351 (11.3), 141 (4.21), 121 (56.9); HR-MS calcd. for C₄H₈₀N₂O₆ (M⁺ m/z 768.6016, found 768.6004.

Cepaciamide B, (3R, 3'S, 2'S, 11'Z)-3-[3'-(2"-hydroxy-11"-octadecenoyloxy)hexadecanoylamino]-2piperidinone (2a). According to the same method as described in the synthesis of 1a, deprotection of 28 (159 mg, 207 µmol) with CAN (227 mg, 414 µmol) gave 2a (102 mg, 76%) as a colorless amorphous solid (mp 42-48 °C). Other spectral data have been reported.^{2b} Acknowledgment: We are grateful to Mr. K. Watanabe and Dr. E. Fukushi in our faculty for measuring the MS spectra.

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HN
$$HN$$
 HN $HO H$ H

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