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TETRAHEDRON

Total Syntheses of Cepaciamides A and B, Novel Fungitoxic 3-Amino-2-piperidinone-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 amide-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 (2*S*)-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.

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

INTRODUCTION

Cepaciamides A (**1a**) and B (**2a**) were isolated from *Pseudomonas cepacia* D-202 as novel fungitoxic 3-amino-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**).

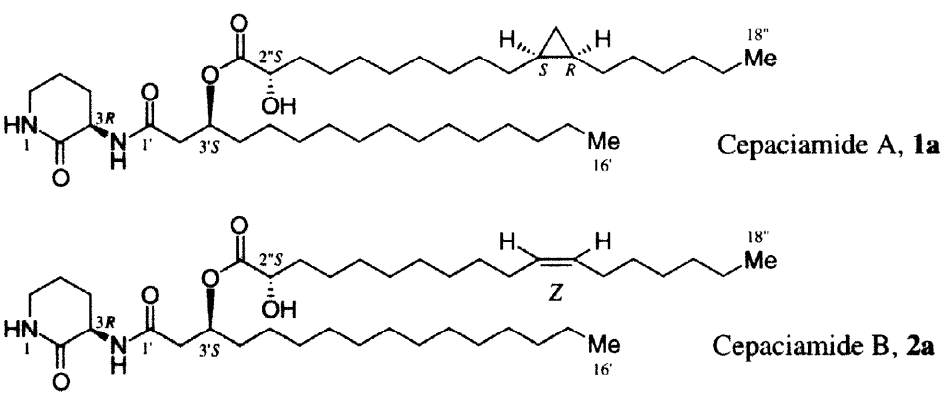

Fig. 1. Structures of cepaciamides A and B

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Cepaciamides A (**1a**) and B (**2a**) are constituted of (*R*)-3-amino-2-piperidinone (**1d**), amide-linked (*S*)-3-hydroxyhexadecanoic acid (**1e**), ester-linked (2*S*,11*S*,12*R*)-2-hydroxy-11,12-methyleneoctadecanoic acid (**1c**) for **1a** and (2*S*,11*Z*)-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 C_4-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 derivative[6] 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**.

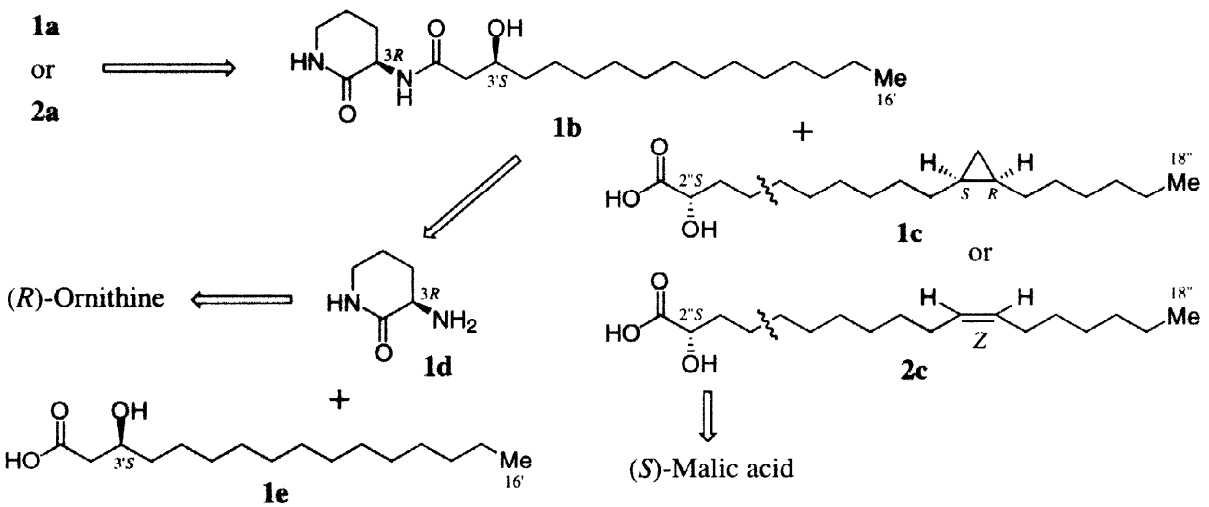


Fig. 2. Retrosynthetic analysis of cepaciamides

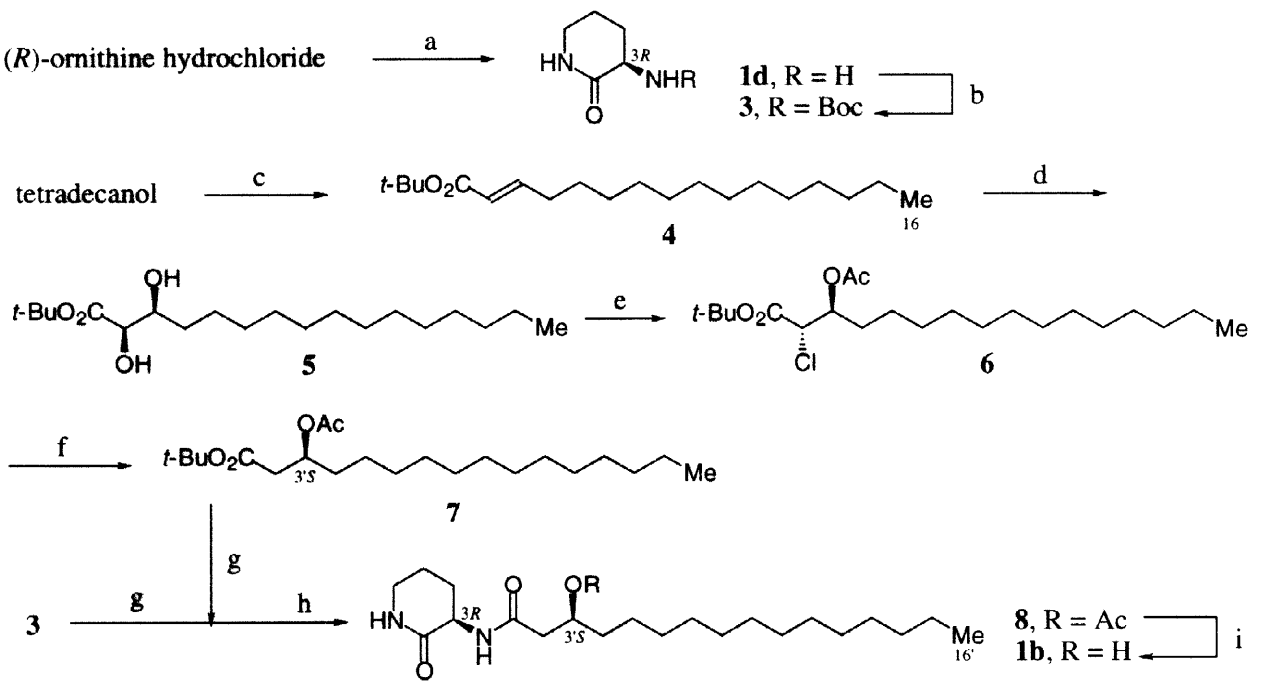
RESULTS AND DISCUSSIONS

Synthesis of the common amide-part

(*R*)-Ornithine hydrochloride was treated with hexamethyldisilazane in refluxing CH_3CN 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 Kusumoto[5] 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 ^{1}H-NMR signals of the corresponding (*R*)- and (*S*)-MTPA esters.[7] The absolute configuration of **5** was presumed to be (2*R*,3*S*)-configuration based on the usual enantiofacial selectivity of Sharpless AD[4] 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. Amide-formation 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-ethyl-carbodiimide hydrochloride (EDC·HCl),[9] 35%; diphenylphosphoryl azide (DPPA),[10] 31%; benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent),[11] 71%. Finally, diethyl-phosphoryl 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 (3*R*,3'*S*)-configuration in 99% yield. At this stage, the (3'*S*)-configuration of **1b** was confirmed by using the modified Mosher's method.[13] The spectral data (^{1}H-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**, (3*R*,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, (3*S*)-isomer of **1b** would be synthesized.

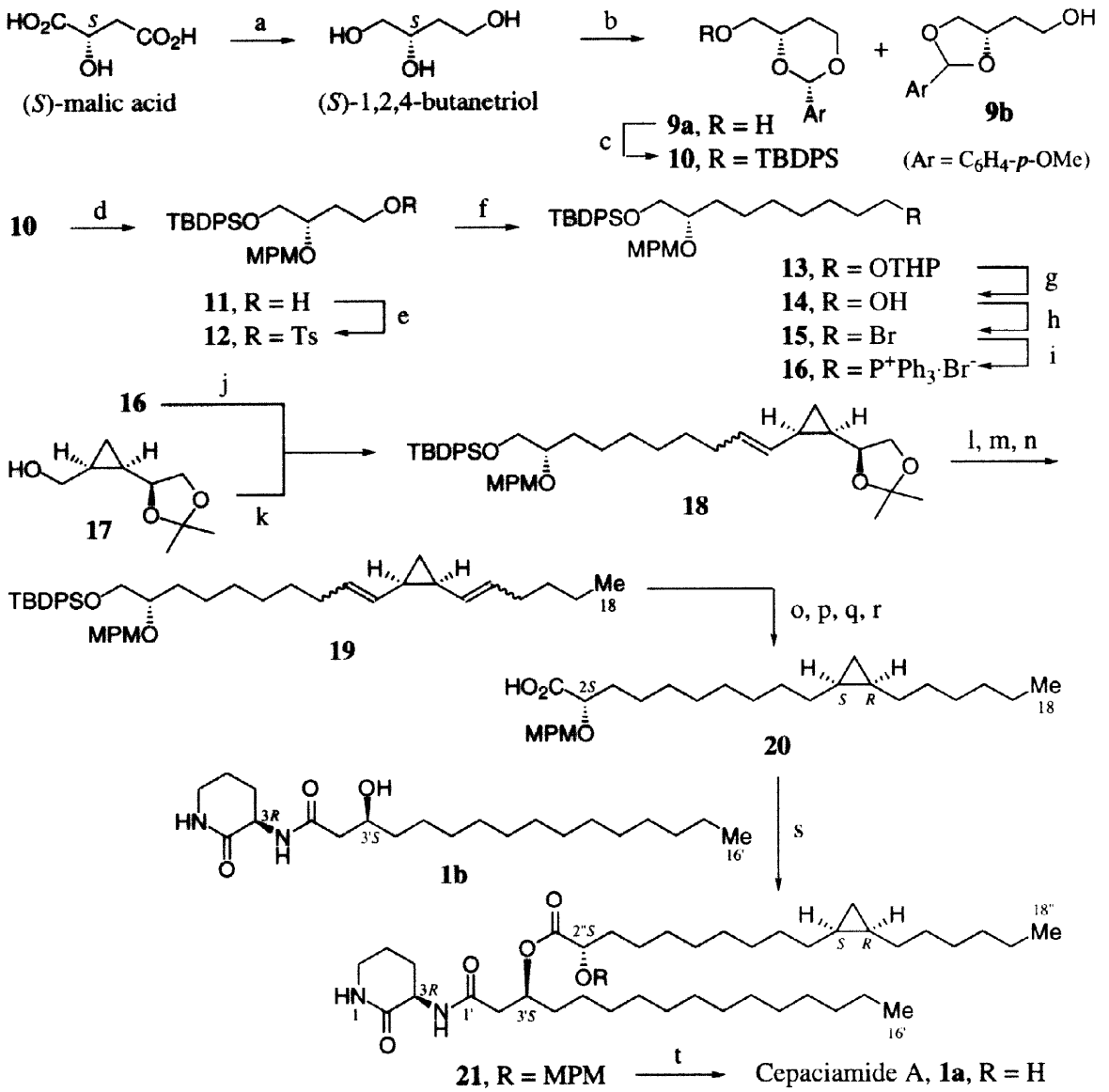


Scheme 1: (a) $(TMS)_2NH$ / CH_3CN; (b) $(Boc)_2O$ / $CHCl_3$, 82%, 2 steps; (c) Swern oxid., then Ph_3P=CHCOO*t*-Bu, 98%, 2 steps; (d) AD-mix-α, $MeSO_2NH_2$/ *t*-BuOH-H_2O, 83%, 98% *e.e.*; (e) $MeC(OMe)_3$, TMSCl / CH_2Cl_2, 64%; (f) *n*-Bu_3SnH, AIBN / PhH, 91%; (g) TFA / CH_2Cl_2, then evaporated to dryness; (h) DEPC, Et_3N / CH_2Cl_2, 96% from **3**; (i) K_2CO_3 / 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 (2*S*)-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 $BH_3 \cdot SMe_2$ and $B(OMe)_3$ in THF to give (*S*)-1,2,4-butanetriol[15] 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 ratio[16] 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 reduction[17] 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_5-elongation for **11** was designed by use of cross-coupling between tosylate **12** and the C_5-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_5-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 Wittig reaction. The Wittig 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 C_5-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) $BH_3{\cdot}SMe_2$, $B(OMe)_3$ / 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) CBr_4, Ph_3P / CH_2Cl_2, 88%, 3 steps; (i) Ph_3P / CH_3CN, quant.; (j) *n*-BuLi / THF; (k) Swern oxid. (82% as Wittig reaction); (l) PPTS / EtOH, 72%; (m) $NaIO_4$ / THF-H_2O; (n) Ph_3P^+-$(CH_2)_4CH_3{\cdot}Br^-$, *n*-BuLi / THF, 93%; (o) TBAF / THF, 99%; (p) $KO_2CN{=}NCO_2K$, AcOH / pyridine, 97%; (q) Swern oxid.; (r) $NaClO_2$, NaH_2PO_4, 2-methyl-2 butene / *t*-BuOH-H_2O, 98%, 2 steps; (s) DCC, DMAP / toluene, 80%; (t) CAN / CH_3CN-$CHCl_3$-H_2O, 80%.

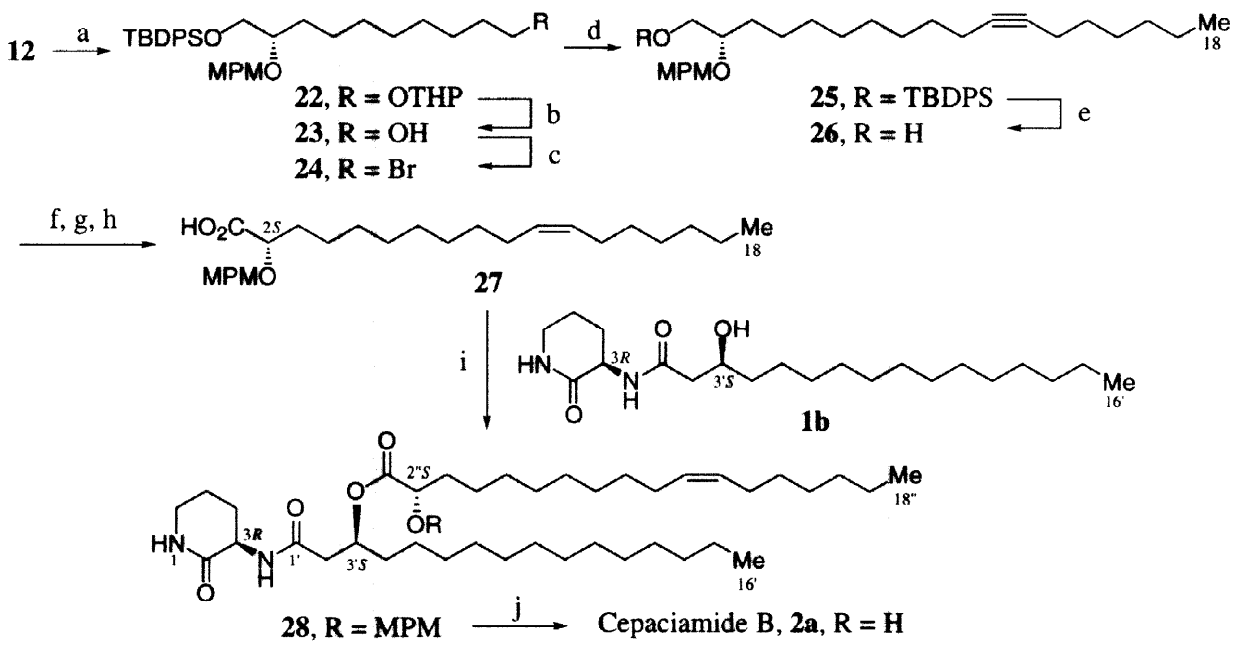
Thus, transacetalization of **18** with PPTS in ethanol gave the diol **18A** in 72% yield (97% based on the consumed **18**), which was treated with sodium metaperiodate in aqueous medium to give the required aldehyde **18B**. The Wittig reaction between pentyltriphenylphosphonium ylide and **18B** 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 ^{1}H-NMR spectrum. Deprotection of **19** with tetrabutylammonium fluoride (TBAF) in THF gave unsaturated primary alcohol **19A** in 99% yield. Diimide reduction[20] 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 DMAP[21] 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) $MgBr(CH_2)_6OTHP$, CuI / THF; (b) PPTS / EtOH; (c) CBr_4, Ph_3P / CH_2Cl_2; 79%, 3 steps; (d) *n*-BuLi, 1-octyne / THF-HMPA; (e) TBAF / THF, 86%, 2 steps; (f) H_2, Lindlar cat. / EtOAc, 100%; (g) Swern oxid.; (h) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene / *t*-BuOH-H_2O, 97%, 2 steps; (i) DCC, DMAP / toluene, 76%; (j) CAN / CH_3CN-$CHCl_3$-H_2O, 76%.

Lithium acetylide of 1-octyne (C_8-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 ℃) 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 ^{1}H-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 (2*S*)-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 (3*R*,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 lipids[23] 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. ^{1}H- and ^{13}C-NMR spectra were recorded with a JEOL JNM-EX-270 spectrometer (^{1}H: 270 MHz; ^{13}C: 67.8 MHz) and a Brucker AM-500 spectrometer (^{1}H: 500 MHz; ^{13}C: 125 MHz). In ^{1}H-NMR

spectra, chemical shifts are reported as δ (ppm) values relative to the residual proton (δ 7.26 ppm) of $CDCl_3$. In ^{13}C-NMR spectra, chemical shifts are reported as δ (ppm) values relative to δ 77.0 ppm of $CDCl_3$, and some aromatic and methylene ^{13}C-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 F_{254} 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 CH_3CN (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 $CHCl_3$ (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*)-from[3] and used for the next reaction. A solution of **1d** and di-*tert*-butyl dicarbonate (3.32 g, 15.2 mmol) in $CHCl_3$ (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 Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 50 g, $CHCl_3$:MeOH = 10:1) to give **3** (1.04 g, 82%, 2 steps) as a colorless oil: $[\alpha]_D^{24}$ -57.4° (*c* 1.07, $CHCl_3$); IR (film) 3295, 2976, 1693, 1669, 1494, 1392, 1365, 1332, 1248, 1167, 1074, 1047, 1025, 870, 753 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 1.44 (9H, 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); ^{13}C-NMR (67.8 MHz, $CDCl_3$) 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 $C_{10}H_{14}N_2O_3$ (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 ℃ under argon atmosphere. The stirring was continued for 60 min at the same temperature. After addition of triethylamine (100 ml, 717 mmol) at -78 ℃, 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 Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 500 g, hexane:Et_2O = 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, $CDCl_3$) 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, d, *J* = 15.2 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 H_2O (40 ml) at 4 ℃ was added **4** (2.46 g, 7.92 mmol) at once. The mixture was stirred vigorously for 4 h at 4 ℃. The reaction was quenched at 0 ℃ 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 Na_2SO_4, 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 ℃; $[\alpha]_D^{21}$ -4.60° (*c* 1.83, $CHCl_3$); IR (KBr) 3643, 3448, 2915, 2849, 1737, 1468, 1373, 1285, 1168, 1133, 1082, 850, 760, 724 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) 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); ^{13}C-NMR (67.8 MHz, $CDCl_3$) 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 $C_{20}H_{41}O_4$ (MH^+) *m/z* 345.3005, found 345.3005.

tert-Butyl (2S,3S)-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, $CHCl_3$); IR (film) 2926, 2855, 1755, 1464, 1371, 1294, 1228, 1152, 1082, 850, 760, 724 cm^{-1}; ^1H-

NMR (270 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 6.6 Hz), 1.20-1.40 (22H, m), 1.47 (9H, s), 1.70 (2H, m), 2.06 (3H, s), 4.36 (1H, d, J = 5.9 Hz), 5.25 (1H, q, J = 5.9 Hz); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 14.0, 20.8, 22.6, 24.7, 27.7, 29.2, 29.27, 29.33, 29.4, 29.6, 30.0, 31.8, 59.3, 73.4, 83.1, 166.0, 169.7; EI-MS *m/z* 333 (for ^{37}Cl, M^+-*t*BuO, 8.0), 331 (for ^{35}Cl, M^+-*t*BuO, 22.9), 290 (7.9), 288 (19.4), 253 (34.8), 208 (11.2), 57 (100), 43 (92.9); HR-MS calcd. for $C_{18}H_{32}O_3{}^{35}Cl$ (M^+-*t*BuO) *m/z* 331.2040, found 331.2064.

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, $CHCl_3$); IR (film) 2926, 2855, 1745, 1458, 1369, 1294, 1239, 1157, 1082, 850, 760, 724 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) 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); ^{13}C-NMR (67.8 MHz, $CDCl_3$) 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^+-C_4H_7, 7.5), 297 (M^+-*t*BuO, 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 $C_{18}H_{35}O_4$ (M^+-C_4H_7) *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 Et_3N (0.15 ml, 1.08 mmol) were dissolved in CH_2Cl_2 (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 $CHCl_3$ (10 ml) and 1M HCl (10 ml). The aqueous layer was further extracted with $CHCl_3$ (10 ml x 3) and the combined organic layers were washed with brine (20 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 10 g, $CHCl_3$:acetone = 6:4) to give **8** (135 mg, 96%) as colorless crystals: mp 94-95 ℃; $[\alpha]_D^{22}$ -32.9° (*c* 0.28, $CHCl_3$); IR (KBr) 3357, 3306, 3197, 3073, 2920, 2851, 1733, 1685, 1652, 1543, 1498, 1455, 1417, 1368, 1249, 1168, 1026, 843, 721 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) 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); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 14.0, 20.9, 21.1, 22.6, 25.2, 27.0, 29.3, 29.4, 29.5, 29.6, 31.8, 34.0, 41.3, 41.5, 50.4, 71.4, 169.8, 170.4, 171.7; EI-MS *m/z* 410 (MH^+, 12.0), 410 (M^+, 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 $C_{23}H_{42}N_2O_4$ (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 $CHCl_3$ (20 ml) and aq. NH_4Cl (20 ml) and the aqueous layer was further extracted with $CHCl_3$ (10 ml x 3). The combined organic layers were washed with water (20 ml x 2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give **1b** (173 mg, 99%) as colorless crystals: mp 124-126 ℃; $[\alpha]_D^{22}$ -13.3°(*c* 1.05, $CHCl_3$); IR (KBr) 3334, 3273, 3234, 2919, 2851, 1683, 1651, 1574, 1492, 1471, 1423, 1345, 1213, 1106, 1055, 983, 720 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 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); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 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^+-H_2O, 17.2), 141 (15.0), 115 (100), 114 (39.7), 113 (42.0), 99 (39.6); HR-MS calcd. for $C_{21}H_{40}N_2O_3$ (M^+) *m/z* 368.3029, found 368.3004.

(2S,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 $NaHCO_3$ (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° (*c* 0.21, $CHCl_3$); IR (film) 3427, 2937, 2842, 1600, 1578, 1519, 1463, 1428, 1394, 1303, 1250, 1218, 1162, 1104, 1069, 1033, 912, 831, 779 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 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); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 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^+-OCH_3, 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.

(2S,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 TBDPSCl (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 Na_2SO_4, 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**: $[\alpha]_D^{20}$ -0.81° (*c* 0.61, $CHCl_3$); IR (film) 3071, 2937, 2842, 1617, 1518, 1458, 1428, 1363, 1303, 1250, 1218, 1162, 1112, 1069, 1033, 912, 825, 741 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 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), 7.36-7.50 (8H, m), 7.65-7.77 (4H, m); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 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^+-*t*Bu, 49.2), 121 (100); HR-MS calcd. for $C_{24}H_{25}O_4Si$ (M^+-*t*Bu) *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 $MgSO_4$ 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, $CHCl_3$); 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}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 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); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 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^+-*t*Bu, 100), 121 (51.8), 57 (16.7); HR-MS calcd. for $C_{28}H_{36}O_4Si$ (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 CH_2Cl_2 (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. $NaHCO_3$ (30 ml), and brine (30 ml). The organic layer was dried over anhydrous Na_2SO_4, 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: $[\alpha]_D^{24}$ -22.7° (*c* 1.06, $CHCl_3$); 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}; ^{1}H-NMR (270 MHz, $CDCl_3$) 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); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 19.2, 21.6, 26.8, 31.4, 55.2, 65.6, 67.5, 72.0, 75.3, 113.7, 127.7, 127.9, 129.3, 129.7, 129.8, 130.4, 133.1, 133.2, 133.3, 135.6, 144.6, 159.1; EI-MS *m/z* 561 (M^+-*t*Bu, 0.12), 490 (0.24), 433 (5.95), 431 (3.44), 353 (38.1), 273 (4.13), 199 (16.3), 121 (100), 91 (6.11); HR-MS calcd. for $C_{31}H_{33}O_6SiS$ (M^+-*t*Bu) *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 ℃ 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 ℃. 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. NH_4Cl (200 ml) and extracted with EtOAc (200 ml, 100 ml x 2). The combined extracts weres washed with brine (100 ml), dried over anhydrous Na_2SO_4, 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: $[\alpha]_D^{21}$ -15.2°(*c* 1.28, $CHCl_3$); 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}; ^{1}H-NMR (270 MHz, $CDCl_3$) 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), 7.33-7.48 (6H, m), 7.64-7.75 (4H, m); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 19.2, 25.3, 25.6, 26.8, 29.3, 29.6, 31.6, 32.8, 55.3, 63.0, 66.3, 71.7, 79.3, 113.6, 127.6, 129.3, 129.6, 130.4, 133.6, 135.6, 159.2; FD-MS *m/z* 535 (MH^+, 61.8), 534 (M^+, 100), 533 (M^+-H, 97.6), 477 (M^+-*t*Bu, 29.3), 390 (13.7), 279 (27.8), 208 (61.8), 121 (84.5), 57 (16.8); HR-MS calcd. for $C_{33}H_{46}O_4Si$ (M^+) *m/z* 534.3164, found 534.3134.

(S)-9-(tert-butyldiphenylsilyloxy)-8-(p-methoxybenzyloxy)-1-nonyl bromide (**15**). To a stirred solution of **14** (1.90 g, 3.55 mmol) in CH_2Cl_2 (20 ml) was added triphenylphosphine (1.41 g, 4.26 mmol) and carbon tetrabromide (1.12 g, 4.26 mmol) at 4 ℃. 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, $CHCl_3$); 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}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 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* = 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), 7.33-7.48 (6H, m), 7.64-7.75 (4H, m); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 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 ^{81}Br, MH^+, 4.51), 598 (for ^{81}Br, M^+, 9.18), 597 (for ^{79}Br, MH^+, 15.1), 596 (for ^{79}Br, M^+, 7.50), 541 (for ^{81}Br, M^+-*t*Bu, 39.0), 539 (for ^{79}Br, M^+-*t*Bu, 31.3), 121 (100), 57 (10.3); HR-MS calcd. for $C_{33}H_{45}O_3Si^{79}Br$ (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 CH_3CN (10 ml) was refluxed for 3 days under argon atmosphere. After evaporation of CH_3CN under reduced pressure, the residue was dried up *in vacuo* at 60 ℃ for 5 h to give **16** (3.10 g, 100%) as a yellow oil: ^{1}H-NMR (270 MHz, $CDCl_3$) 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, $C_{51}H_{60}O_3SiP^+$, 60.3), 262 (34.4), 121 (100), 57 (16.7); HR-MS calced for $C_{51}H_{60}O_3SiP$ (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 CH_2Cl_2 (5.0 ml) was added dropwise (1*R*,2*S*,4*S'*)-1-(2',2'-dimethyl-1',3'-dioxolane-4'-yl)-2-(hydroxymethyl)cyclopropane **17** (345 mg, 2.00 mmol) in dry CH_2Cl_2 (3.0 ml) at -78 ℃ 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 ℃, the reaction mixture was allowed to warm to room temperature with stirring. The reaction mixture was diluted with CH_2Cl_2 (20 ml) and washed with water (20 ml) and brine (20 ml). The organic layer was dried over anhydrous Na_2SO_4, 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 ℃ under argon atmosphere. The mixture was stirred for 20 min at room temperature and cooled again to -78 ℃. 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. NH_4Cl (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 Na_2SO_4, 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}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 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, 8.7 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), 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* 670 (M^+, 0.03), 613 (M^+-*t*Bu, 0.46), 612 (1.03), 537 (1.89), 417 (1.26), 333 (1.74), 199 (21.0), 121 (100), 57 (1.38); HR-MS calcd. for $C_{42}H_{58}O_5Si$ (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) was stirred for 2 days at 50 ℃. The reaction mixture was concentrated under reduced pressure and the residue was purified 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}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 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 *Z*-isomer), 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); EI-MS *m/z* 612 (M^+-H_2O, 0.04), 537 (0.33), 417 (0.32), 333 (0.83), 199 (7.72), 121 (100), 57 (0.76); HR-MS calcd. for $C_{39}H_{52}O_4Si$ (M^+-H_2O) *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 H_2O (4.0 ml) at 4 ℃. After being stirred for 1 h at room temperature, the reaction mixture was partitioned between water (20 ml) and $CHCl_3$ (20 ml). The aqueous layer was further extracted with $CHCl_3$ (10 ml x 3). The combined organic layers were washed with brine (30 ml), dried over anhydrous Na_2SO_4, 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 ℃ under argon atmosphere. The mixture was stirred for 30 min at room temperature and cooled to -78 ℃. 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. NH_4Cl (20 ml) and water (20 ml). The reaction mixture was extracted with $CHCl_3$ (20 ml x 3) and the combined extracts were washed with brine (50 ml), dried over anhydrous Na_2SO_4, 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}; ^{1}H-NMR (270 MHz, $CDCl_3$) 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^+-*t*Bu, 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. NH_4Cl (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 Na_2SO_4, 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}; ^{1}H-NMR (270 MHz, $CDCl_3$) 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^+-CH_3O, 0.14), 293 (7.88), 199 (0.46), 121 (100); HR-MS calcd. for $C_{27}H_{42}O_3$ (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. $NaHCO_3$ (50 ml), and brine (50 ml). The organic layer was dried over anhydrous Na_2SO_4, 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°(*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}; ^{1}H-NMR (270 MHz, $CDCl_3$) 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), 4.56 (1H, d, J = 11.2 Hz), 6.89 (2H, d, J = 8.6 Hz), 7.28 (2H, d, J = 8.6 Hz); ^{13}C-NMR (67.8 MHz, $CDCl_3$) 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 *m/z* 419 (MH^+, 1.81), 418 (M^+, 6.11), 387 (M^+-CH_3O, 0.27), 199 (0.60), 121 (100); HR-MS calcd. for $C_{27}H_{46}O_3$ (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 CH_2Cl_2 (5.0 ml) was added dropwise **19B** (442 mg, 1.06 mmol) in dry CH_2Cl_2 (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 CH_2Cl_2 (20 ml) and washed with water (20 ml) and brine (20 ml). The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude aldehyde (**19C**) which was used for the next oxidation without further purification. To a stirred mixture of **19C**, 2-methyl-2-butene (0.4 ml), and $NaH_2PO_4 \cdot 2H_2O$ (165 mg, 1.06 mmol) in *t*-BuOH (4.0 ml) and H_2O (1.4 ml) was added $NaClO_2$ (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 $CHCl_3$ (10 ml x 3). The combined extracts were washed with brine (10 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 20 g, $CHCl_3$:MeOH = 20:1) to give **20** (449 mg, 98%) as a colorless oil: $[\alpha]_D^{22}$ -25.7°(*c* 1.10, $CHCl_3$); 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}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ -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), the chemical shift of the carboxyl proton could not be assigned due to broadening.; ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 10.9, 14.1, 15.7, 22.7, 24.9, 28.7, 29.2, 29.3, 29.4, 29.6, 30.2, 31.9, 32.4, 55.3, 72.3, 77.3, 113.9, 129.0, 129.8, 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 $C_{27}H_{44}O_4$ (M^+) *m/z* 432.3240, found 432.3212.

Cepaciamide A p-methoxybenzyl ether, (3R,3'S,2"S,11"S,12"R)-3-{3'-[2"-(p-methoxybenzyloxy)-11",12"-methyleneoctadecanoyloxy]hexadecanoylamino}-2-piperidinone (**21**). To a stirred suspension of acid-component **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: $[\alpha]_D^{22}$ -43.4°(*c* 1.03, $CHCl_3$); 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}; ^{1}H-NMR (270 MHz, $CDCl_3$) 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); ^{13}C-NMR (67.8 MHz, $CDCl_3$) 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 CH_3CN (3.0 ml), $CHCl_3$ (1.0 ml) and H_2O (0.3 ml) was added CAN (264 mg, 482 μmol) at room temperature. After being stirred for 30 min, the reaction mixture was partitioned between water (20 ml) and $CHCl_3$ (20 ml). The aqueous layer was further extracted with $CHCl_3$ (10 ml x 2) and the combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by preparative TLC ($CHCl_3$: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. NH_4Cl (50 ml) and extracted with EtOAc (50 ml, 20 ml x 2). The combined extracts were washed with brine (50 ml), dried over anhydrous Na_2SO_4, 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 purified by column chromatography (silica gel 40 g, hexane:EtOAc = 3:1) to give **23** (442 mg, 81%, 2 steps) as a colorless oil: $[\alpha]_D^{21}$ -17.8° (*c* 1.81, $CHCl_3$); 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 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) 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); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 19.2, 25.3, 25.7, 26.8, 29.3, 29.5, 29.6, 31.6, 32.8, 55.3, 63.0, 66.4, 71.7, 79.4, 113.7, 127.6, 129.3, 129.6, 131.2, 133.6, 135.6, 159.0; FD-MS *m/z* 549 (MH^+, 60.4), 548 (M^+, 100), 547 (M^+-H, 76.9), 491 (M^+-*t*Bu, 8.86), 390 (17.5), 279 (34.9), 121 (29.5), 57 (4.69); HR-MS calcd. for $C_{34}H_{48}O_4Si$ (M^+) *m/z* 548.3322, found 548.3296.

(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_2Cl_2 (3.0 ml) gave **24** (362 mg, 97%) as a colorless oil: $[\alpha]_D^{21}$ -8.36° (*c* 1.00, $CHCl_3$); 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}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 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), 7.33-7.48 (6H, m), 7.64-7.75 (4H, m); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 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 ^{81}Br, MH^+, 44.7), 612 (for ^{81}Br, M^+, 100), 611 (for ^{79}Br, MH^+, 60.1), 610 (for ^{79}Br, M^+, 97.7), 555 (for ^{81}Br, M^+-*t*Bu, 51.1), 553 (for ^{79}Br, M^+-*t*Bu, 46.9), 121 (66.6), 57 (9.01); HR-MS calcd. for $C_{34}H_{47}O_3SiBr$ (M^+) *m/z* 596.2322, found 596.2300.

(S)-2-(p-Methoxybenzyloxy)-11-octadecyn-1-ol (**26**). To a solution of 1-octyne (174 μl, 1.18 mmol) in dry THF (2.0 ml) and dry HMPA (514 μl, 2.96 mmol) at -78 °C under argon atmosphere was added dropwise *n*-BuLi (1.61 M solution in hexane, 733 μl, 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 μmol) 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. NH_4Cl (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 Na_2SO_4, and concentrated under reduced pressure. The residue containing (*S*)-1-(*tert*-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. NH_4Cl (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 Na_2SO_4, 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: $[\alpha]_D^{21}$ +8.42°(*c* 0.95, $CHCl_3$); IR (film) 3434, 2930, 2957, 1614, 1587, 1515, 1464, 1428, 1391, 1361, 1302, 1249, 1173, 1113, 1069, 1038, 1009, 822, 741, 703 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) 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); ^{13}C-NMR (67.8 MHz, $CDCl_3$) 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 (MH^+, 29.3), 402 (M^+, 100), 292 (0.04), 121 (1.06); HR-MS calcd. for $C_{26}H_{42}O_3$ (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° (*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}; ^{1}H-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); ^{13}C-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^+-CH_3O, 2.37), 137 (15.3), 121 (100); HR-MS calcd. for $C_{26}H_{44}O_3$ (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), $NaH_2PO_4 \cdot 2H_2O$ (184 mg, 1.18 mmol), and $NaClO_2$ (503 mg, 4.72 mmol as 85% purity) at room temperature to give **27** (480 mg, 97%) as a colorless oil: $[\alpha]_D^{22}$ -25.6°(*c* 1.11, $CHCl_3$); 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}; ^{1}H-NMR (270 MHz, $CDCl_3$) 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), 4.63 (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.; ^{13}C-NMR (67.8 MHz, $CDCl_3$) 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 $C_{26}H_{42}O_4$ (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: $[\alpha]_D^{23}$ -45.5° (*c* 1.60, $CHCl_3$); 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}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 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, d, *J* = 11.2 Hz), 4.61 (1H, d, *J* = 11.2 Hz), 5.23-5.41 (3H, m), 5.82 (1H, br. s, NH), 6.54 (1H, br. d, *J* = 5.9 Hz, NH), 6.86 (2H, d, *J* = 8.6 Hz), 7.26 (2H, d, *J* = 8.6 Hz); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 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 $C_{47}H_{80}N_2O_6$ (M^+) *m/z* 768.6016, found 768.6004.

Cepaciamide B, (3R,3'S,2"S,11'Z)-3-[3'-(2"-hydroxy-11"-octadecenoyloxy)hexadecanoylamino]-2-piperidinone (**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]

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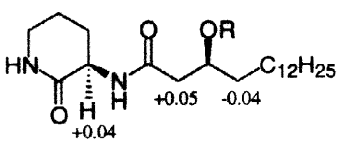

R = (*S*)- or (*R*)-MTPA

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