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Total Asymmetric Syntheses of (+)-Blastmycinone and Related γ-Lactones[1]

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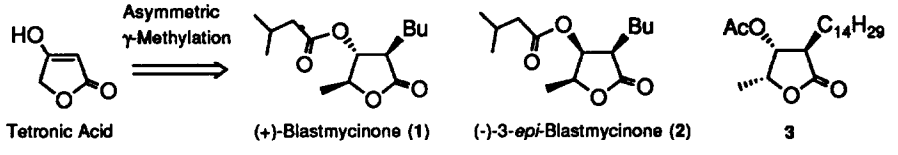
Abstract : *The freeze of the conformer was realized by the introduction of an alkyl substituent at α-position of tetronic acid using a readily available none C_2 chiral auxiliary (SMP or RMP), and conducted the desired asymmetric γ-methylation. Its application to expeditious total syntheses of (+)-blastmycinone (1) and (-)-3-epi-blastmycinone (2), and to the first total synthesis of (+)-(3R,4R,5R)-4-acetoxy-5-methyl-3-tetradecyltetrahydro-2(5H)-furanone (3) was described.*

INTRODUCTION

The fully functionalized γ-lactones which have three contiguous asymmetric centers on α, β, γ-positions are represented by (+)-blastmycinone (**1**) derived from antimycin A_3,[2] an antibiotic effective agent against fungi and yeasts, and (+)-(3*R*,4*R*,5*R*)-4-acetoxy-5-methyl-3-tetradecyltetrahydro-2(5*H*)-furanone (**3**)[3] isolated from Gorgonian coral *Plexaura flava* in Great Barrier Reef. Although several syntheses of (+)-blastmycinone (**1**) and (-)-3-*epi*-blastmycinone (**2**) have been published,[4-9] most of them are categorized by the asymmetric induction involving chiral pools. Only two methods have been reported as the asymmetric synthesis. One of them is the [2+2]cycloaddition reaction using menthyloxymethylketene by Fráter,[8] but the optical purity of the product was not so high (70 % ee), as well as being an unnatural (-)-blastmycinone. The other is an application of the Sharpless oxidation by Sato,[9] which required many steps (15 steps) to reach (+)-blastmycinone. There is no report on the asymmetric synthesis of **3**, but the synthesis of the enantiomer from (*S*)-lactic acid has been reported for the determination of the absolute stereochemistry.[10]

Chart 1



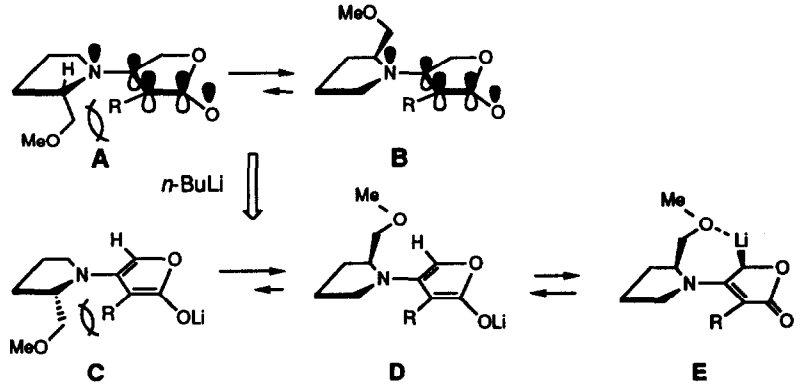
Tetronic Acid (+)-Blastmycinone (1) (-)-3-*epi*-Blastmycinone (2) 3

For the total syntheses of these natural γ-lactones we thought that asymmetric γ-methylation of tetronic acid could be reasonable strategy, because it has already a β-hydroxy-γ-lactone skeleton in itself. The asymmetric γ-methylation of tetronic acid derivatives are reported by Schlessinger[11] and Schmidt[12] independently. They used C_2 symmetric pyrrolidine derivatives {(+)-*trans*-2,5-dimethylpyrrolidine and (+)-*trans*-2,5-bis(methoxymethyl)pyrrolidine, respectively}. Though the high diastereoselectivity was performed

using these C_2 auxiliaries, major drawback of these methodologies from the synthetic point of view is the difficulty of their large scale preparation in an optically pure form.

As the chiral auxiliary on the methylation of tetronic acid derivative, we chose readily available (*S*)-2-methoxymethylpyrrolidine (SMP). In the case of the none C_2 chiral auxiliary the substrate enamine exists as an equilibrium condition between plausible two major conformers **A** and **B**, in which the lone pair electrons on the nitrogen in pyrrolidine ring was resonating with the *p*-orbitals of α,β-unsaturated γ-lactone. We expected that the bias on the two conformers **A** and **B** into the one conformer **B** could conduct the desired asymmetric γ-methylation, even if the none C_2 chiral auxiliary (SMP) is installed at β-position of tetronic acid, i.e. the introduction of the alkyl substituent at α-position may bias the equilibrium of the two conformers to the right, because the steric repulsion could operate between the introduced alkyl substituent and the methoxymethyl group of SMP, as shown in Fig. 1. Therefore, the preferential formation of the anion **D** or **E** can be possible whether the Schmidt's chelation[12] exists between the lithium salt generated on the γ-position of tetronic acid and the oxygen of the methoxymethyl group or not, because the rotation of the nitrogen - carbon (β-carbon on the tetronic acid) bond would be frozen at low temperature.

Fig. 1



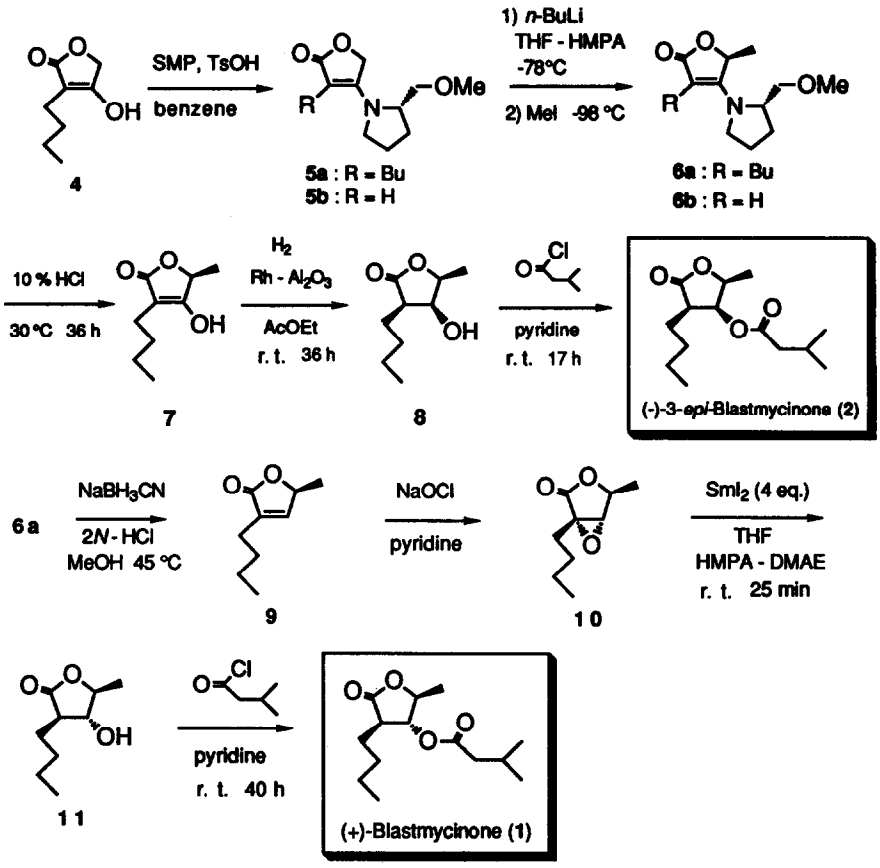
Here we describe the convenient asymmetric γ-methylation of tetronic acid according to the above hypothesis[13] and its application to the total syntheses of (+)-blastmycinone (**1**), (-)-3-*epi*-blastmycinone (**2**), and (+)-(3*R*,4*R*,5*R*)-4-acetoxy-5-methyl-3-tetradecyltetrahydro-2(5*H*)-furanone (**3**).

RESULTS AND DISCUSSION

Butyl substituent on α-position of tetronic acid was easily introduced by the modified Ramage's method[14] to give α-butyltetronic acid (**4**) in 73 % yield. Required substrate **5a** for the asymmetric γ-methylation was obtained in 96 % yield by the condensation of α-butyltetronic acid (**4**) with SMP in benzene using a Dean-Stark condenser. The treatment of *n*-butyllithium (2.5 eq.) on **5a** (R = *n*-Bu) in THF and HMPA (10 eq.) at -78 °C for 1 h followed by the addition of methyl iodide (10 eq.) at - 98 °C afforded **6a** and its C-5 epimer (diastereomer ratio = 91 : 9)[15] in 91 % yield. On the other hand, the same reaction on **5b** (R = H) gave **6b** and its C-5 epimer (diastereomer ratio = 69 : 31)[15] in 97 % yield. The difference of diastereoselectivity in the methylation of **5a** and **5b** proved the substitution effect for the bias in the equilibrium of the enolate conformers

(C and D) in Fig. 1. For the determination of absolute configuration on the γ-position of **6a**, we tried the transformation of **6a** to the known (-)-3-*epi*-blastmycinone (**2**) as follows: hydrolysis of **6a** into tetronic acid derivative **7** with 10 % hydrochloric acid, followed by hydrogenation with 5 % rhodium-alumina under hydrogen pressure (5.5 kg/cm^2) gave (-)-3-*epi*-blastmycinolactol (**8**) {$[\alpha]_D^{25}$ -84.8° (0.66, MeOH), [Lit.[5a] $[\alpha]_D^{17}$ -96° (0.34, MeOH)]} in high yield. The NMR analysis using three equivalents of (*S*)-(-)-1,1'-bi-2-naphthol as a chiral shift reagent[16] showed **8** optically pure. (-)-3-*epi*-Blastmycinolactol (**8**) was converted into (-)-3-*epi*-blastmycinone (**2**) {$[\alpha]_D^{23}$ -79° (0.24, $CHCl_3$), lit., [5a] $[\alpha]_D^{18}$ -89° (0.90, $CHCl_3$)} by acylation with isovaleryl chloride as shown in Scheme 1. This result showed that the methylation occurred from the opposite side toward methoxymethyl group in the enolate conformer **D** or **E**.

Scheme 1. Expeditious Total Syntheses of (+)-Blastmycinone (**1**) and (-)-3-*epi*-Blastmycinone (**2**)

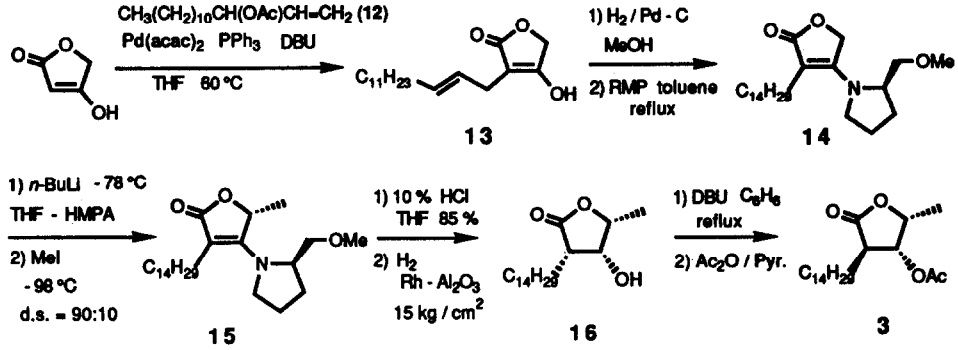


Now we had in hand lactol **8** with its full stereochemical information so we tried initially direct conversion of **8** into (+)-blastmycinone (**1**) with isovaleric acid on the Mitsunobu reaction[17] conditions. No reaction was observed on usual triphenylphosphine conditions probably due to steric hindrance around the hydroxy group,

and the reaction with trimethylphosphine gave the olefin **9** in 78 % yield because of the presence of an acidic α-hydrogen in the anti relationship to the hydroxy group. We tried therefore to get (-)-blastmycinolactol (**11**) from the olefin **9**, which was also available from **8** by the elimination with tosyl chloride and pyridine in 98 % yield. As more direct conversion, the reaction of enamine **6a** with sodium cyanoborohydride in 2*N*-HCl and MeOH at 45 °C gave the desired olefin **9** in 84 % yield, in which both the reduction of enamine and the elimination of SMP took place continuously. Epoxidation of **9** with sodium hypochlorite[7e] afforded α-epoxide **10** diastereoselectively (α : β = 16 : 1). The assignment of α-epoxide was determined by ^{1}H NMR, in which the proton on 4-position was observed as singlet, because the dihedral angle of 4-H to 5-H is almost 90°. The mixture of epoxides **10** was converted into (-)-blastmycinolactol (**11**) regioselectively with samarium(II) iodide-THF-HMPA in the presence of *N,N*-dimethylaminoethanol (Inanaga's method)[18] in 69 % yield. After the purification of **11** by the chromatography, acylation with isovaleryl chloride gave (+)-blastmycinone (**1**) in 80 % yield, whose spectroscopic data and optical rotation {[α]$_D^{25}$ +11.2° (0.85, $CHCl_3$), lit.,[5a] [α]$_D^{17}$ +10° (1.2, $CHCl_3$)} were identical with those reported.[5a]

We have established a method for the expeditious asymmetric total synthesis of (+)-blastmycinone (**1**) from α-butyltetronic acid (**4**) (6 steps) with high overall yield (22 %), compared with the literatures.[8,9]

Scheme 2. Total Synthesis of (3*R*,4*R*,5*R*)-4-Acetoxy-5-methyl-3-tetradecyl-tetrahydro-2-furanone (**3**)



(+)-(3*R*,4*R*,5*R*)-4-Acetoxy-5-methyl-3-tetradecyltetrahydro-2(5*H*)-furanone (**3**) is characteristic of having a long (C_{14}) alkyl chain on α-position of γ-lactone. In order to introduce this substituent we used a π-allylpalladium complex, because the conventional synthesis[14a] of this α-substituted tetronic acid was unsuccessful due to the insolubility of the lithium enolate of methyl palmitate in THF. Tetronic acid was converted into α-(2-tetrahydrodecenyl)tetronic acid (**13**) in 59 % under the π-allylpalladium complex reaction conditions.[19] Hydrogenation of the isolated double bond in **13** on 5 % palladium carbon under ambient hydrogen atmosphere afforded α-tetradecyltetronic acid quantitatively. Installation of a chiral auxiliary [(*R*)-2-methoxymethylpyrrolidine (RMP)] to the hydrogenated product under dehydrating conditions gave the enamine **14** in 75 % yield. In like manner as (+)-blastmycinone synthesis, the asymmetric γ-methylation proceeded with the diastereoselectivity (90 : 10) to give **15**, which was isolated on silica gel column chromatography in 79 % yield. Hydrolysis of the methylated enamine **15** with 10 % hydrochloric acid followed by hydrogenation (5

% rhodium-alumina, H_2 15 kg/cm^2) gave all cis γ-lactone **16** in high yield. Epimerization[20] of α-position with DBU and the subsequent acetylation afforded the desired product **3** in 41 % yield, accompanied with the acetate of **16** (30 % yield), which did not epimerized. The spectroscopic data and the optical rotation of **3** {$[\alpha]_D^{24}$ +36.0° (0.20, CH_2Cl_2), lit.,[3] $[\alpha]_D^{20}$ +36.1° (1.9, CH_2Cl_2)} were identical with those of the literature.[3]

CONCLUSION

We have demonstrated that the freeze of the conformer was realized by the introduction of an alkyl substituent at α-position of tetronic acid using a readily available none C_2 chiral auxiliary (SMP or RMP), and could conduct the desired asymmetric γ-methylation with good diastereoselectivity. This method proved to be practical by expeditious total syntheses of (+)-blastmycinone (**1**) and (-)-3-*epi*-blastmycinone (**2**), and by the first total synthesis of (+)-(3*R*,4*R*,5*R*)-4-acetoxy-5-methyl-3-tetradecyltetrahydro-2(5*H*)-furanone (**3**).

ACKNOWLEDGMENT

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EXPERIMENTAL SECTION

General: Melting points are taken with a micro hot-stage apparatus (Yanagimoto) and are uncorrected. Boiling points are determined on a micro distillation apparatus. The infrared (IR) spectra are recorded with a Shimadzu IR-410 diffraction grating infrared spectrophotometer and ^{1}H-NMR spectra are obtained with a JEOL JNM-GX-270, Varian XL-300, or JEOL JNM-GX-400 NMR spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) are determined on a JEOL JMS-01SG or Hitachi M-80 mass spectrometer. Wakogel C-200 (silica gel) (100-200 mesh, Wako) or neutral alumina gel (aluminum oxide 90 activated, Art. 1077, 70-230 mesh, Merck) were used for column chromatography except for the noted, and Kieselgel 60 F-254 plates (Merck) for thin layer chromatography (TLC) and preparative TLC (PTLC).

Material: Diisopropylamine was distilled from CaH_2 and THF was distilled from sodium benzophenone ketyl before use. *n*-BuLi (1.6 M hexane solution) and vinylmagnesium bromide (ca. 1M THF solution) were purchased from Wako Pure Chemical Industries, LTD and were titrated with *sec*-BuOH using *ortho*-phenanthroline as a indicator before use.

3-Butyl-4-hydroxy-2(5*H*)-furanone (4) To a solution of diisopropylamine (11.04 mL; 78.75 mmol) in THF (40 mL) was added *n*-BuLi (1.61 M in hexane; 46.7 mL; 75 mmol) at 0 °C and magnetically stirred for 0.5 h. A THF (40 mL) solution of methyl hexanoate (11.03 mL; 75 mmol) was added dropwise to the chilled (-78 °C) reaction mixture. After 30 min, a THF (40 mL) solution of 2,2-pentamethylene-1,3-dioxolan-4-one[14a] (4.69 g; 30 mmol) was added, then the reaction mixture was allowed to warm up gradually to room temperature under stirring for 18 h. THF was removed *in vacuo* from the reaction mixture, water was added to the residue, then washed with ether. The aqueous layer was acidified with *c*-HCl, concentrated *in vacuo* into half volume, and filtered to give 4 (2.89 g) as colorless crystals. The aqueous filtrate was extracted with ethyl acetate, dried ($MgSO_4$), and filtered to give another crop of 4 (0.89 g, totally 3.78 g, 73.1 %), mp 117-119 °C (water); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 3 H), 1.23 - 1.50 (m, 4 H), 2.17 (t, J = 7.5 Hz, 2 H), 4.63 (s, 2 H); IR ($CHCl_3$) 1730, 1660, 1640, 1100, 1050 cm^{-1}; MS m/z 157 (M^+, 2.5), 112 (33), 101 (100), 100 (32), 55 (34); Anal.Calcd for $C_9H_{12}O_3$: C, 61.52; H, 7.75. Found : C, 61.20; H, 7.56.

(*S*)-3-Butyl-4-[2-(methoxymethyl)-1-pyrrolidinyl]-2(5*H*)-furanone (5a) A solution of 3-butyl-4-hydroxy-2(5*H*)-furanone (4) (2.4 g; 15.4 mmol), (*S*)-2-methoxymethylpyrrolidine (1.67 mL; 16.9 mmol), and *p*-toluenesulfonyl acid monohydrate (293 mg; 1.54 mmol) in benzene (80 ml) was refluxed using a Dean-Stark condenser for 24 h. (*S*)-2-

Methoxymethylpyrrolidine (450 μL; 4.56 mmol; 0.3 eq.) was added because the starting material 4 was remained, and refluxed for another 24 h. After removal of the solvent, the resulting residue was chromatographed on alumina gel (ethyl acetate : hexane = 1 : 2) to give **5a** (3.74 g, 96 %) as a yellow oil, $[\alpha]_D^{20}$ -23.3° (1.47, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.91 (t, J = 6.9 Hz, 3 H), 1.23 - 1.50 (m, 4 H), 1.90 - 2.10 (m, 4 H), 2.16 - 2.42 (m, 2 H), 3.34 (s, 3 H), 3.20 - 3.50 (m, 3 H), 3.52 - 3.62 (m, 1 H), 3.82 - 3.95 (m, 1 H), 4.55 and 4.73 (ABq, J =14.5 Hz, each 1 H); IR ($CHCl_3$) 1725, 1610, 1430, 1110 cm^{-1}; MS m/z 253 (M^+,14), 208 (100), 166 (25); HRMS calcd for $C_{14}H_{23}O_3N$ (M^+) 253.1677, found 253.1700.

4-[(*S*)-2-(Methoxymethyl)-1-pyrrolidinyl]-2(5*H*)-furanone (5b) The benzene solution (40 mL) of tetronic acid (1.48 g; 14.73 mmol), (*S*)-2-methoxymethylpyrrolidine (1.48 g; 14.73 mmol), and *p*-toluenesulfonic acid monohydrate (280 mg; 1.47 mmol) was refluxed using a Dean-Stark condenser for 24 h. After removal of the solvent, the silica gel chromatography ($CHCl_3$: MeOH = 10 : 1) of the residue afforded **5a** (2.2 g, 75 %) as colorless crystals, mp 71-71.5 °C (AcOEt-hexane); $[\alpha]_D^{25}$ -119.2° (1.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.85 - 2.10 (m, 4 H), 3.20 - 3.45 (m, 4 H), 3.34 (s, 3 H), 3.72 - 3.80 (m, 1 H), 4.55 - 5.15 (br m, 3 H); IR ($CHCl_3$) 1725, 1605, 1430, 1345, 1155, 1115, 1060 cm^{-1}; MS m/z 197 (M^+, 13), 153 (9), 152 (100), 70 (4); Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found : C, 60.92; H, 7.73; N, 7.10.

(*S*)-3-Butyl-4-[(*S*)-2-(methoxymethyl)-1-pyrrolidinyl]-5-methyl-2(5*H*)-furanone (6a) To a solution of (*S*)-3-butyl-4-[2-(methoxymethyl)-1-pyrrolidinyl]-2(5*H*)-furanone (**5a**) (1.10 g; 4.34 mmol) in THF (70 mL) and hexamethylphosphoramide (HMPA) (7.55 mL; 43.42 mmol) was added dropwise *n*-BuLi (1.64 M in hexane; 6.62 mL; 10.86 mmol) at -78 °C and stirred for 1 h. The resulting mixture was cooled to -98 °C (liquid nitrogen-MeOH) then methyl iodide (2.7 mL; 43.42 mmol) was added. After 2 h, saturated ammonium chloride (20 mL) was added to the reaction mixture. The resulting mixture was extracted with ether (3 x 100 ml), the ethereal layer was washed with water (3 x 50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The diastereomer ratio (91 : 9) was determined by the integration of the C-5 methine protons (δ 4.88 and 4.80) on ^1H NMR (300 MHz) of the crude product. Purification by a medium pressure silica gel column chromatography [Kieselgel 60 PF_{254} (Merck), AcOEt : hexane = 1 : 2] gave **6a** (894 mg, 77 %) and C-5 epimer of **6a** (70 mg, 6 %), and their mixture (86 mg, 8 %). **6a**: a yellow oil; HPLC (^tR 6.35 min, Column Lichrosorb si-60, 4.0 ϕ x 25 cm) (AcOEt : hexane = 1 : 1, 1.0 mL/min); $[\alpha]_D^{20}$ + 75.7° (1.09, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 6.7 Hz, 3 H), 1.25 - 1.50 (m, 4 H), 1.42 (d, J = 6.3 Hz, 3 H), 1.90 - 2.21 (m, 5 H), 2.34 - 2.45 (m, 1 H), 3.33 (s, 3 H), 3.22 - 3.43 (m, 3 H), 3.54 - 3.62 (m, 1 H), 4.00 - 4.08 (m, 1 H), 4.88 (q, J = 6.3 Hz, 1 H); IR ($CHCl_3$) 1720, 1610, 1420, 1130, 1100 cm^{-1}; MS m/z 267 (M^+, 12), 223 (14), 222 (100), 180 (11); HRMS calcd for $C_{15}H_{25}O_3N$ (M^+) 267.1832, found 267.1818. C-5 epimer of **6a** (minor diastereomer): HPLC (^tR 8.04 min, Column Lichrosorb si-60, 4.0 ϕ x 25 cm) (AcOEt : hexane = 1 : 1, 1.0 mL/min); ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 7.1 Hz, 3 H), 1.25 - 1.50 (m, 4 H), 1.50 (d, J = 6.3 Hz, 3 H), 1.90 - 2.19 (m, 5 H), 2.35 - 2.47 (m, 1 H), 3.14-3.20 (m, 1 H), 3.34 (s, 3 H), 3.30 - 3.51 (m, 3 H), 3.39 - 4.00 (m, 1 H), 4.80 (q, J = 6.3 Hz, 1 H).

4-[(*S*)-2-(Methoxymethyl)-1-pyrrolidinyl]-5-methyl-2(5*H*)-furanone (6b) To a solution of 4-[2-(methoxymethyl)-1-pyrrolidinyl]-2(5*H*)-furanone (**5b**) (48 mg, 0.24 mmol) in THF (5 mL) and HMPA (418 μL, 2.4 mmol) was added dropwise *n*-BuLi (1.65 M in hexane; 173 μL; 0.29 mmol) at -78 °C and stirred for 1 h. Methyl iodide (150 μL, 2.4 mmol) was added to the reaction mixture and stirred for additional 2.5 h. The crude product obtained by the same work-up described above was purified by silica gel PTLC (ethyl acetate) to give a mixture of **6b** and its C-5 epimer (50 mg, 97 %, diastereomer ratio = 69 : 31), ^1H NMR (300 MHz, $CDCl_3$) δ 1.51 (d, J = 6.4 Hz, 3 H, major diastereomer) [1.55 (d, J = 6.4 Hz, minor diastereomer)], 1.70 - 2.15 (m, 4 H), 3.20 - 3.50 (m, 4 H), 3.34 (s, 3 H), [3.72 (m), 4.05 (m)] (total 1 H), [4.50 (br s), 4.57 (s), 4.61 (br s)] (total 1 H), [4.95 (br q, J = 6.4 Hz), 5.25 (br)] (total 1H); IR ($CHCl_3$) 1730, 1610, 1420, 1330, 1180, 1120 1090 cm^{-1}; MS m/z 211 (M^+, 8), 180 (5), 167 (10), 166 (100), 139 (3), 94 (3), 70 (4); HRMS calcd for $C_{11}H_{17}NO_3$ (M^+) 211.1208, found 211.1234.

(*S*)-3-Butyl-4-hydroxy-5-methyl-2(5*H*)-furanone (7) (*S*)-3-Butyl-4-[(*S*)-2-(methoxymethyl)-1-pyrrolidinyl]-5-methyl-2(5*H*)-furanone (**6a**) (200 mg; 0.75 mmol) was stirred with 10 % hydrochloric acid (10 mL) in THF (25 mL) at 30 °C for 48 h. The reaction mixture was extracted with ethyl acetate and the extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue on silica gel (AcOEt : hexane = 2 : 1) gave **7** (113 mg, 89 %) as colorless crystals, mp 58-59 °C (AcOEt-hexane); $[\alpha]_D^{20}$ +17.3° (1.04, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3 H), 1.24 - 1.58 (m, 4 H), 1.50 (d, J = 6.6 Hz, 3 H), 2.21 (t, J = 7.3 Hz, 2 H), 4.84 (q, J = 6.6 Hz,1 H), 10.5 (br, 1H); IR ($CHCl_3$) 3600 - 2200, 1735, 1660, 1080 cm^{-1}; MS m/z 170 (M^+, 6), 128 (42), 115 (100), 114 (48), 98 (68), 69 (42), 55 (77); HRMS calcd for $C_9H_{14}O_3$ (M^+) 170.0942, found 170.0951.

(3*R*,4*S*,5*S*)-3-Butyl-4-hydroxy-5-methyltetrahydro-2-furanone [(-)-3-*epi*-Blastmycinolactol] (8) (*S*)-3-Butyl-4-hydroxy-5-methyl-2(5*H*)-furanone (**7**) (100 mg; 0.59 mmol) was hydrogenated on 5 % Rh - Al_2O_3 (246 mg, Rh 12.3 mg,

20 mol%) in AcOEt (5 mL) under hydrogen pressure (5.5 Kg/cm^2) using an autoclave for 24 h. The reaction mixture was filtered through celite and concentrated *in vacuo*. The residue was purified on silica gel (PTLC) (AcOEt : hexane = 1 : 1) to give **8** (95 mg, 94 %) as colorless crystals, mp 101 - 102 °C (AcOEt-hexane); $[\alpha]_D^{25}$ -84.8° (0.66, MeOH) [Lit.[5a] mp 99.5-100 °C; $[\alpha]_D^{17}$ -96° (0.34, MeOH)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (br t, J = 7.2 Hz, 3 H), 1.44 (d, J = 6.6 Hz, 3 H), 1.30 - 1.50 (m, 4 H), 1.58 - 1.72 (m, 1 H), 1.82 (br d, J = 5.0 Hz, 1 H, OH), 1.80 - 1.90 (m, 1 H), 2.58 (dt, J = 9.9, 5.0 Hz, 1 H), 4.32 (dt, J = 5.0, 3.3 Hz, 1 H), 4.45 (dq, J = 6.6, 3.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 13.63, 13.82, 22.51, 22.51, 22.93, 29.66, 47.54, 71.03, 79.23, 178.25; IR ($CHCl_3$) 3400 (br), 1770, 1190 cm^{-1}; MS m/z 173 (M^++1, 0.8), 172 (M^+,1.2), 116 (100), 100 (52), 99 (54), 85 (41), 82 (46), 57 (78); Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found : C, 62.36; H, 9.00.

(3*R*,4*S*,5*S*)-3-Butyl-4-isovaleryloxy-5-methyltetrahydrofuran-2-one [3-*epi*-Blastmycinone] (2) To a solution of (3*R*,4*S*,5*S*)-3-butyl-4-hydroxy-5-methyltetrahydro-2-furanone (**8**) (20 mg; 0.118 mmol) and 4-dimethylaminopyridine (DMAP) (3 mg; 0.024 mmol) in pyridine (1 mL) was added isovaleryl chloride (43 μL; 0.35 mmol) and the mixture was stirred for 17 h. After condensation of the reaction mixture, purification of the residue on silica gel (PTLC) (AcOEt : hexane = 1 : 2) gave 3-*epi*-blastmycinone (**2**) (14 mg; 50 %) as colorless crystals, mp 45-46 °C (AcOEt-hexane); $[\alpha]_D^{25}$ -79.2° (0.24, $CHCl_3$) [lit.,[5a] $[\alpha]_D^{18}$ -89° (0.90, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 6.9 Hz, 3 H), 0.98 (d, J = 6.6 Hz, 6 H), 1.28 (d, J = 6.5 Hz, 3 H), 1.26 - 1.41 (m, 5 H), 1.77 - 1.89 (m, 1 H), 2.10 - 2.25 (m, 1 H), 2.27 (d, J = 6.6 Hz, 2 H), 2.71 (dt, J = 9.9, 5.1 Hz, 1 H), 4.57 (dq, J = 6.5, 3.3 Hz, 1 H), 5.62 (dd, J = 5.3, 3.4 Hz, 1 H); IR ($CHCl_3$) 1775, 1740, 1515, 1420, cm^{-1}; MS (FAB) 257 (M^++1, 87), 183 (83), 93 (90), 57 (100).

(*S*)-3-Butyl-5-methyl-2(5*H*)-furanone (9) (Method A) To a solution of (*S*)-3-butyl-4-[(*S*)-2-(methoxymethyl)-1-pyrrolidinyl]-5-methyl-2(5*H*)-furanone (**6a**) (50 mg, 0.187 mmol) in MeOH (3 mL) was added sodium cyanoborohydride (118 mg, 10 eq.) and 2 *N* hydrochloric acid (1 drop) to adjust pH 3.8 by a indicator (bromocresol green), then stirred for 5 d at 45 °C. During the reaction time, sodium cyanoborohydride (118 mg, 10 eq.) was added nine times and pH 3.8 was kept by adding dropwise 2 *N* hydrochloric acid. The reaction mixture was neutralized with sodium hydrogen carbonate, then extracted with ethyl acetate. The extract was washed with 10 % hydrochloric acid, with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue on silica gel (PTLC, hexane : ethyl acetate = 2 : 1) to give **9** (17 mg, 60 %) as a colorless oil. The washed acidic water was alkalized with sodium hydrogen carbonate, and reextracted with ethyl acetate. The residue obtained from the same work-up was subjected to the same procedure to give another crop of **9** (7 mg, 24 %). The combined yield was 84 %.

(Method B) To a solution of (3*R*,4*S*,5*S*)-3-butyl-4-hydroxy-5-methyltetrahydro-2-furanone (**8**) (20 mg; 0.11 mmol) in THF (2 mL) were added trimethylphosphine (1M solution in THF, 151 μL, 0.15 mmol), and diethyl azodicarboxylate (24 μL, 0.15 mmol) at 0 °C and stirred for 1 h. Isovaleric acid (15 μL, 0.14 mmol) was added to the reaction mixture then stirred for 4 h at 0 °C and for 2 d at 40 °C. After removal of the solvent, the residue was purified by silica gel PTLC (hexane: ether = 2 : 1) to give **9** (14 mg, 78 %).

(Method C) A mixture of (3*R*,4*S*,5*S*)-3-butyl-4-hydroxy-5-methyltetrahydro-2-furanone (**8**) (734 mg; 4.31 mmol), *p*-toluenesulfonyl chloride (2.47 g; 12.94 mmol; 3 eq.), and DMAP (105 mg; 0.862 mmol; 0.2 eq.) in pyridine (16 mL) was stirred for 12 h at room temperature and for 3 d at 40 °C. After condensation of the reaction mixture *in vacuo*, the residue was chromatographed on silica gel column (hexane : AcOEt = 5 : 1) to give **9** (655 mg, 98%) as a colorless oil. **9** : $[\alpha]_D^{22}$ +79.2° (1.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 3 H), 1.41 (d, J = 6.8 Hz, 3 H), 1.31 - 1.43 (m, 2 H), 1.49 - 1.59 (m, 2 H), 2.27 (tt, J = 7.7, 1.7 Hz, 2 H), 4.99 (qq, J = 6.8, 1.7 Hz, 1 H), 6.99 (q, J = 1.7 Hz, 1 H); IR ($CHCl_3$) 1750, 1320, 1120, 1090, 1030, 860 cm^{-1}; MS m/z 154 (M^+, 43), 112 (100), 111 (63), 67 (40), 55 (56), 43 (36); HRMS calcd for $C_9H_{14}O_2$ (M^+) 154.0922, found 154.0975.

(3*S*,4*S*,5*S*)-3-Butyl-3,4-epoxy-5-methyltetrahydrofuran-2-one (10) To a solution of (*S*)-3-butyl-5-methyl-2(5*H*)-furanone (**9**) (40 mg; 0.26 mmol) in pyridine (2.6 mL) was added sodium hypochlorite (5% chlorine; 1.5 mL) at 0 °C and stirred for 1 h then for additional 1 h at room temperature. To the reaction mixture was added 1 *N* sodium hydrogen carbonate (2 mL) . The resulting mixture was extracted with dichloromethane. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the starting material (16 mg, 40 %). The aqueous layer was acidified with 10 % hydrochloric acid then extracted with ethyl acetate. The extract was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (AcOEt : hexane = 1 : 5) to give **10** (17 mg, conversion yield 64 %) as a colorless oil. The diastereomer ratio [(3*S*,4*S*,5*S*) to (3*R*,4*R*,5*S*)] was 16 : 1 by ^{1}H NMR analysis. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (br t, J = 6.8 Hz, 3 H), 1.39 (d, J = 6.8 Hz, 3 H), 1.30 - 1.50 (m, 4 H), 1.80 - 1.90 (m, 1 H), 2.06 - 2.16 (m, 1 H), 3.80 (s, 1H, major isomer) [3.90 (d, J = 1.5 Hz, minor isomer)], 4.60 (q, J = 6.8 Hz, 1H, major isomer) [4.56 (dq, J = 1.5, 6.8 Hz, minor isomer)]; IR ($CHCl_3$) 1780, 1160, 1120, 1060

cm^{-1}; MS m/z 171 (M^++1, 0.5), 170 (M^+, 1.0), 85 (53), 69 (100), 57 (85), 41 (41); HRMS calcd for $C_9H_{14}O_3$ 170.0942, found 170.0951.

(3*R*,4*R*,5*S*)-3-Butyl-4-hydroxy-5-methyltetrahydro-2-furanone [(-)-Blastmycinolactol] (11) To a solution of (3*S*,4*S*,5*S*)-3-butyl-3,4-epoxy-5-methyltetrahydrofuran-2-one (10) (123 mg; 0.72 mmol) in THF (2.5 mL) were added sequentially HMPA (628 mL), *N*,*N*-dimethylaminoethanol (290 mL; 2.89 mmol) and SmI_2 (0.1 M; 29 mL; 2.89 mmol) at room temperature under nitrogen atmosphere, and the mixture was stirred for 25 min. The reaction mixture was poured into ether, washed with saturated sodium hydrogen carbonate, and with water. The ethereal extract was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue on silica gel column chromatography (AcOEt : hexane = 1: 3) gave 11 (56 mg, 69 %) as colorless crystals, mp 49.5-51.0 °C (ether-petroleum ether), [Lit.[5a] mp 49.5-50.5 °C (ether : petroleum ether)]; $[\alpha]_D^{25}$ -19.8° (1.250, MeOH) [Lit.[5a] $[\alpha]_D^{18}$ -18° (1.09, MeOH)]; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.2 Hz, 3 H), 1.46 (d, *J* = 6.4 Hz, 3 H), 1.30 - 1.70 (m, 5 H), 1.80 - 1.95 (m, 1 H), 2.10 (br s, 1 H, OH), 2.55 (ddd, *J* = 8.6, 7.5, 5.8 Hz, 1H), 4.20 (quintet, *J* = 6.4 Hz, 1H); IR ($CHCl_3$) 3400 (br), 1700, 1180, 1060 cm^{-1}; MS m/z 173 (M^++1, 3), 172 (M^+, 0.5), 116 (65), 100 (46), 99 (51), 84 (50), 71 (34), 57 (100); MS (FAB) 185 (M^++Na), 173 (M^++1).

(3*R*,4*R*,5*S*)-3-Butyl-4-isovaleryloxy-5-methyltetrahydro-2-furanone [(+)-Blastmycinone] (1) To a solution of (3*R*,4*R*,5*S*)-3-butyl-4-hydroxy-5-methyltetrahydro-2-furanone (11) (50 mg; 0.29 mmol) in pyridine (2.5 mL) was added isovaleryl chloride (106 μL; 0.87 mmol) and the mixture was stirred for 40 h under nitrogen atmosphere. After concentration of the reaction mixture in vacuo the residue was purified on silica gel column chromatography (AcOEt : hexane = 1 : 6) to give (+)-blastmycinone (1) (68 mg; 80 %) as a colorless oil, $[\alpha]_D^{25}$ +11.2 (0.85, $CHCl_3$), [Lit.[5a] $[\alpha]_D^{17}$ +10 (1.20, $CHCl_3$)]; ^1H NMR (300MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.1 Hz, 3 H), 0.97 (d, *J* = 6.5 Hz, 6 H), 1.25 - 1.47 (m, 4 H), 1.47 (d, *J* = 6.6 Hz, 3 H), 1.66 - 1.70 (m, 1 H), 1.80 - 1.95 (m, 1 H), 2.11 (nonet, *J* = 6.5 Hz, 1 H), 2.23 (d, *J* = 7.0 Hz, 2 H), 2.69 (dt, *J* = 8.3, 5.6 Hz, 1 H), 4.37 (dq, *J* = 6.6, 4.7 Hz, 1 H), 4.95 (dd, *J* = 5.6, 4.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.71, 19.39, 22.27, 22.32, 25.66, 28.88, 28.99, 43.07, 46.38, 78.36, 79.35, 172.38, 175.86 ; IR ($CHCl_3$) 1755, 1735 cm^{-1}; MS m/z 257 (M^++1, 3.5), 200 (10), 155 (9), 99 (76), 85 (100), 57 (46); MS (FAB) 257 (M^++1), 155, 85, 57.

3-Acetoxy-1-tetradecene (12) To a solution of vinylmagnesium bromide (0.69 M in THF, 85 mL, 58.4 mmol) in THF (60 mL) was added a solution of dodecyl aldehyde (10 mL, 53.1 mmol) in THF (50 mL) at 0 °C over 3 h. After being quenched with saturated ammonium chloride solution (40 mL), the reaction mixture was condensed, extracted with dichloromethane, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. To this residue were added acetic anhydride (71 mL), pyridine (46.5 mL), and 4-dimethylaminopyridine (649 mg, 5.31 mmol) at 0 °C and the mixture was stirred at room temperature for 18 h. Condensation of the reaction mixture *in vacuo* and silica gel column chromatography (AcOEt : hexane = 1 : 25) afforded 12 (9.86 g, 73 %), which was purified by the Kügelrohr distillation for an analytical sample, a colorless oil; bp 120-130 °C / 0.2 mmHg (bath temp.); ^1H NMR (300MHz, $CDCl_3$) δ 0.88 (br t, *J* = 6.7 Hz, 3 H), 1.20 - 1.37 (m, 18 H), 1.52 - 1.70 (m, 2 H), 2.06 (s, 3 H), 5.13 - 5.26 (m, 3 H), 5.77 (ddd, *J* = 17.4, 10.5, 6.4 Hz, 1 H); IR ($CHCl_3$) 1730, 1225 cm^{-1}; MS m/z 255 (M^++1, 0.04), 254 (M^+, 0.15), 183 (37), 99 (68), 97 (33), 83 (35), 43 (100); HRMS calcd for $C_{16}H_{30}O_2$ (M^++1) 254.2243, found 254.2229; Anal Calcd for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89 . Found: C, 75.55; H, 11.87 .

4-Hydroxy-3-[(*E*)-2-tetradecenyl]-2(5*H*)-furanone (13) The mixed solution of tetronic acid (5.31 g; 53 mmol), 3-acetoxy-1-tetradecene (12) (2.69 g; 10.6 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (7.94 mL; 53 mmol), $Pd(acac)_2$ (180 mg; 0.53 mmol), and PPh_3 (556 mg; 2.12 mmol) in THF (100 mL) was refluxed for 2 d under nitrogen atmosphere. After condensation of the reaction mixture, the residue was acidified with 10 % hydrochloric acid and saturated with NaCl , then extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the resulting residue on silica gel chromatography (AcOEt : hexane = 2 : 1) gave 13 (1.84 g, 59 %) as colorless crystals, mp 95-97 °C (AcOEt-hexane); ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (br t, *J* = 6.9 Hz, 3 H), 1.20 - 1.40 (m, 18 H), 2.07 (br q, *J* = 6.8 Hz, 2 H), 2.97 (br d, *J* = 6.8 Hz, 2 H), 4.58 (br s, 2 H), 5.59 (br dt, *J* = 15.4, 6.8, 1 H), 5.80 (br dt, *J* = 15.4, 5.8 Hz, 1 H); IR ($CHCl_3$) 1750, 1680,1100, 1050 cm^{-1}; MS m/z 294 (M^+,10), 194 (44), 101 (100); HRMS calcd for $C_{18}H_{30}O_3$ (M^+) 294.2193, found 294.2208.

(*R*)-4-[2-(Methoxymethyl)-1-pyrrolidinyl]-3-tetradecyl-2(5*H*)-furanone (14) A mixture of 4-hydroxy-3-[(*E*)-2-tetradecenyl]-2(5*H*)-furanone (13) (925 mg, 3.14 mmol) and 5 % Pd-C (1.34 g) in methanol (100 mL) was stirred under hydrogen atmosphere (1 atm) for 24 h. The reaction mixture was filtered on hyflosuper-cell and concentrated *in vacuo*. Purification of the resulting residue on silica gel column chromatography ($CHCl_3$: MeOH = 7 : 1) afforded 4-hydroxy-3-tetradecyl-2(5*H*)-furanone (930 mg, 100 %) as colorless crystals, mp 94-97 °C ($CHCl_3$-MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (br t, *J* = 6.8

Hz, 3 H), 1.15 - 1.35 (m, 22 H), 1.40 - 1.53 (m, 2 H), 2.18 (br t, J = 7.7 Hz, 2 H), 4.63 (br s, 2 H), 7.2 - 7.4 (br s, 1 H, OH); IR ($CHCl_3$) 3600-2300 (br), 1740, 1670, 1410, 1050 cm^{-1}; MS m/z 296 (M^+, 3), 235 (14),137 (26), 114 (100), 101 (66); HRMS calcd for $C_{18}H_{32}O_3$ (M^+) 296.2349, found 296.2323. A mixture of 4-hydroxy-3-tetradecyl-2(5*H*)-furanone (500 mg, 1.68 mmol), (*R*)-2-methoxymethylpyrrolidine (0.38 mmol, 3.04 mmol, 1.8 eq.), and *p*-toluenesulfonic acid monohydrate (3.2 mg, 0.17 mmol, 0.01 eq.) in toluene (40 mL) was refluxed for 2 d under nitrogen atmosphere using a Dean-Stark condenser. The reaction mixture was evaporated under reduced pressure, then the residue was chromatographed on alumina gel (AcOEt : hexane = 1 : 3) to give **14** (497 mg, 75 %) as a yellow oil, $[\alpha]_D^{22}$ +19.8° (0.43, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (br t, J = 6.8 Hz, 3 H), 1.20 - 1.38 (m, 22 H), 1.38 - 1.50 (m, 2 H), 1.90 - 2.06 (m, 4 H), 2.24 (t of ABd, J = 15.2, 7.6 Hz, 1 H), 2.34 (t of ABd, J = 15.2, 8.2 Hz, 1 H), 3.22 - 3.46 (m, 3 H), 3.34 (s, 3 H), 3.54 - 3.62 (m, 1 H), 3.85 - 3.93 (m, 1 H), 4.55 (ABd, J = 14.7 Hz, 1 H), 4.72 (ABd, J = 14.7 Hz,1 H); IR ($CHCl_3$) 1730, 1620, 1615, 1460, 1430, 1350, 1120 cm^{-1}; MS m/z 393 (M^+, 6), 348 (100), 210 (14), 166 (18), 70 (6); HRMS calcd for $C_{24}H_{43}NO_3$ (M^+) 393.3241, found 393.3263.

(*R*)-4-[(*R*)-2-(Methoxymethyl)-1-pyrrolidinyl]-5-methyl-3-tetradecyl-2(5*H*)-furanone (15) To a solution of (*R*)-4-[2-(methoxymethyl)-1-pyrrolidinyl]-3-tetradecyl-2(5*H*)-furanone (**14**) (352 mg; 0.894 mmol) and HMPA (1.56 mL; 8.94 mmol) in THF (18 mL) was added *n*-BuLi (1.62 M hexane solution; 1.38 mL; 2.24 mmol) at -78 °C and stirred for 1 h. The resulting mixture was chilled to -98 °C (MeOH - liquid nitrogen), and methyl iodide (557 μL; 8.94 mmol) was added to the reaction mixture. After one hour, a saturated ammonium chloride solution was added, then the reaction mixture was allowed to warm to the room temperature and extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The diastereomer ratio (90 : 10) was determined by the integration of the C-5 methine protons (δ 4.87 and 4.79) on ^1H NMR (300 MHz) of the crude product. Purification of the resulting residue on alumina gel chromatography (AcOEt : hexane = 1 : 1) gave **15** (288 mg, 79 %) as a yellow oil. The diastereomeric purity of this product was ascertained to be 100 % by HPLC analysis. $[\alpha]_D^{20}$ -45.6° (0.67, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (br t, J = 6.8 Hz, 3 H), 1.20 - 1.40 (m, 24 H), 1.42 (d, J = 6.5 Hz, 3 H), 1.85 - 2.06 (m, 4 H), 2.08 - 2.20 (m, 1 H), 2.34 - 2.44 (m, 1 H), 3.20 - 3.40 (m, 3 H), 3.33 (s, 3 H), 3.52 - 3.62 (m, 1 H), 3.98 - 4.06 (m, 1 H), 4.87 (q, J = 6.5 Hz, 1 H); IR ($CHCl_3$) 1725, 1620, 1615, 1455, 1425, 1125, 1110 cm^{-1}; MS m/z 407 (M^+, 8), 364 (26), 363 (100), 224 (11), 180 (10); HRMS calcd for $C_{25}H_{45}NO_3$ 407.3397 found 407.3409 .

(3*S*,4*R*,5*R*)-4-Hydroxy-3-tetradecyl-5-methyltetrahydro-2-one (16) A mixture of (*R*)-4-[(*R*)-2-(methoxymethyl)-1-pyrrolidinyl]-5-methyl-3-tetradecyl-2(5*H*)-furanone (**15**) (234 mg, 0.574 mmol), 10 % hydrochloric acid (7.4 mL), and THF (1.5 mL) was stirred at 40 °C for 5 d. The reaction mixture was diluted with ethyl acetate (200 ml) and washed with brine to pH 4 of the aqueous layer, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the resulting residue on silica gel column chromatography ($CHCl_3$: MeOH = 9 : 1) gave (*R*)-4-hydroxy-5-methyl-3-tetradecyl-2(5*H*)-furanone (151 mg, 85 %) as colorless crystals, mp 70-73 °C ($CHCl_3$-MeOH); $[\alpha]_D^{25}$ -4.10° (0.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (br t, J = 6.8 Hz, 3 H), 1.15 - 1.40 (m, 22 H), 1.49 (d, J = 6.8 Hz, 3 H), 1.40 - 1.55 (m, 2 H), 2.18 (br t, J = 7.6 Hz, 2 H), 4.81 (q, J = 6.8 Hz, 1 H); IR ($CHCl_3$) 3600 - 2400 (br), 1735, 1600, 1470, 1450, 1400, 1070 cm^{-1}; MS m/z 310 (M^+, 18), 194 (16), 151 (20), 138 (38), 128 (87), 115 (100), 110 (30), 98 (36), 84 (23), 57 (18); HRMS calcd for $C_{19}H_{34}O_3$ (M^+) 310.2507, found 310.2513.
(*R*)-4-Hydroxy-5-methyl-3-tetradecyl-2(5*H*)-furanone (24 mg; 0.077 mmol) was hydrogenated on 5 % Rh-Al_2O_3 (80 mg) (10 mL) in AcOEt (10 mL) under hydrogen pressure (15 Kg/cm^2) using an autoclave at 45 °C for 4 d. The reaction mixture was filtered on celite and concentrated *in vacuo*. The residue was purified on silica gel (PTLC) (AcOEt : hexane = 1 : 2) to give **16** (20 mg, 83 %) as colorless crystals, mp 86-88 °C (AcOEt-hexane); $[\alpha]_D^{25}$ +37.2° (0.80, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (br t, J = 7.2 Hz, 3 H), 1.20 - 1.40 (m, 24 H), 1.44 (d, J = 6.5 Hz, 3 H), 1.68 - 1.72 (m, 1 H), 1.76 - 1.90 (m, 1 H), 2.58 (dt, J = 10.1, 4.7 Hz, 1 H), 4.32 (dd, J = 4.7, 3.0 Hz, 1 H), 4.45 (dq, J = 6.5, 3.0 Hz, 1 H); IR ($CHCl_3$) 3400 (br), 1770, 1180, 1120 cm^{-1}; MS m/z 312 (M^+, 1.2), 129 (53), 116 (100), 99 (22), 57 (21); HRMS calcd for $C_{19}H_{36}O_3$ (M^+) 312.2263, found 312.2265.

(3*R*,4*R*,5*R*)-4-Acetoxy-5-methyl-3-tetradecyltetrahydro-2-furanone (3) A mixture of (3*S*,4*R*,5*R*)-4-hydroxy-3-tetradecyl-5-methyltetrahydro-2-one (**16**) (52 mg; 0.166 mmol) and DBU (300 μL; 2.13 mmol; 12.8 eq.) in benzene (20 mL) was refluxed for 20 h. The reaction mixture was poured into 1 % hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with saturated sodium hydrogen carbonate, with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was dissolved in pyridine (2.6 ml) and acetic anhydride (324 μl, 3.35 mmol), and DMAP (9.7 mg; 0.08 mmol) were added and the mixture was stirred for 3 h. The reaction mixture was poured into ice-water, extracted with ethyl acetate. The extract was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the resulting residue on preparative TLC (AcOEt : hexane = 1 : 4) gave **3** (23.8 mg, 41 %, R_f = 0.48) accompanied by unepimerized (3*S*,4*R*,5*R*)-4-acetoxy-5-methyl-3-tetradecyl-tetrahydro-2-furanone (17.7 mg, 30 %, R_f = 0.40). **3**: colorless crystals; $[\alpha]_D^{24}$ +36.0° (0.20, CH_2Cl_2) [Lit.[3] $[\alpha]_D^{20}$ +36.1° (1.9, CH_2Cl_2)]; ^1H NMR

(300 MHz, $CDCl_3$) δ 0.88 (br t, J = 6.8 Hz, 3 H), 1.20 - 1.30 (m, 22 H), 1.34 (d, J = 6.5 Hz, 3 H), 1.40 - 1.53 (m, 2 H), 1.53 - 1.82 (m, 2 H), 2.12 (s, 3 H), 2.60 (m, 1 H), 4.76 (dq, J = 6.5, 4.8 Hz, 1 H), 5.17 (dd, J = 4.8, 2.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 20.71, 22.69, 27.00, 28.51, 29.26, 29.29, 29.35, 29.51, 29.59, 29.63, 29.66, 31.91, 47.09, 75.51, 76.70, 170.12, 176.62.

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