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Total Synthesis of (2*S*,3*R*,5*S*)-(-)-2,3-Dihydroxytetradecan-5-olide, A New Biologically Active δ-Lactone Produced by *Seiridium unicorne*

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Abstract: The first total synthesis of (2*S*,3*R*,5*S*)-(-)-2,3-dihydroxytetradecan-5-olide (**1**), a new biologically active δ-lactone produced by *Seiridium unicorne*, was accomplished from (*R*)-malic acid. In connection with the determination of the absolute configuration of **1**, (2*R*,3*S*,5*R*)-(+)-2,3-dihydroxytetradecan-5-olide (***ent*-1**) was also synthesized from D-glucose.

INTRODUCTION

In our series of studies on tree disease,[1] we have already communicated the isolation, structural determination, and total synthesis of (2*S*,3*R*,5*S*)-(-)-2,3-dihydroxytetradecan-5-olide (**1**) [Fig. 1], a new biologically active δ-lactone, produced by *Seiridium unicorne*.[2] This pathogen causes the resinous canker disease of *Chamaecyparis obtusa* Sieb. et Zucc (Hinoki), which occurs mainly in young trees.[3] In order to reveal the relationship between this tree disease and the abscisic activity of **1** against the leaves of *C. obtusa*,[1d] a sufficient amount of **1** is required by a synthetic approach. In connection with the determination of the absolute configuration of **1**, (2*R*,3*S*,5*R*)-(+)-2,3-dihydroxytetradecan-5-olide (***ent*-1**) was also synthesized from D-glucose prior to the synthesis of **1**, because the relative configuration of **1**, determined by using the ^{1}H-NMR experiments, is identical with that of D-glucose with respect to the C-2,3,5 stereogenic centers. In this paper, we describe in detail the total syntheses of **1** and ***ent*-1**.

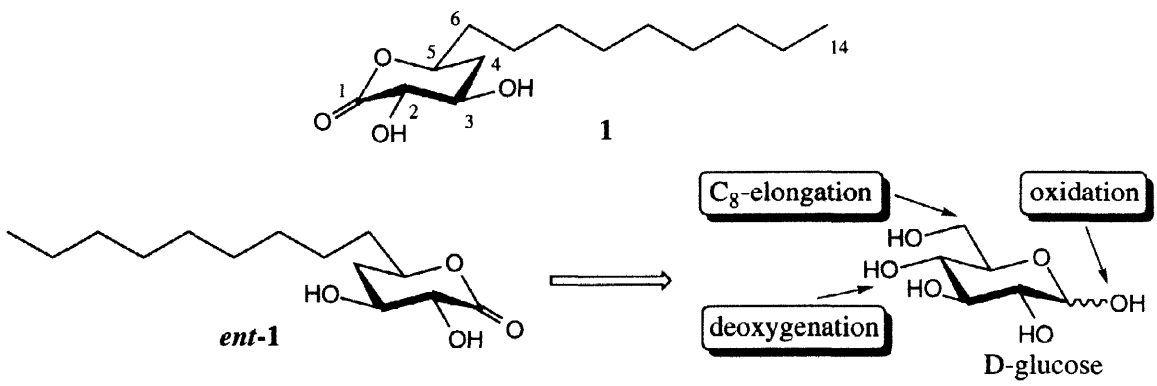

Fig. 1. Structures of a new biologically active δ-lactone (**1**) and its enantiomer (***ent*-1**)

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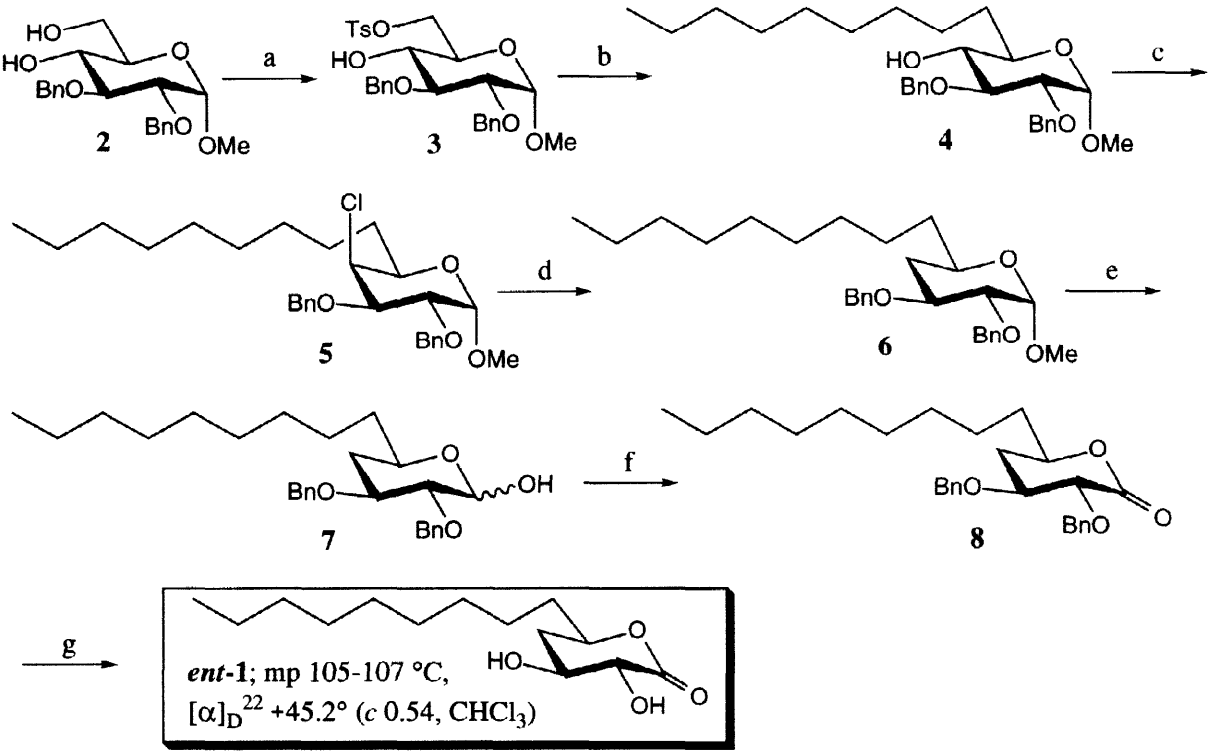
RESULTS AND DISCUSSION

Total Synthesis of ent-1 from D-glucose

Three modifications, (1) C_8-elongation at the C-6 position, (2) deoxygenation at the C-4 position, and (3) oxidation at the C-1 position, are required for D-glucose and are achieved in that order.



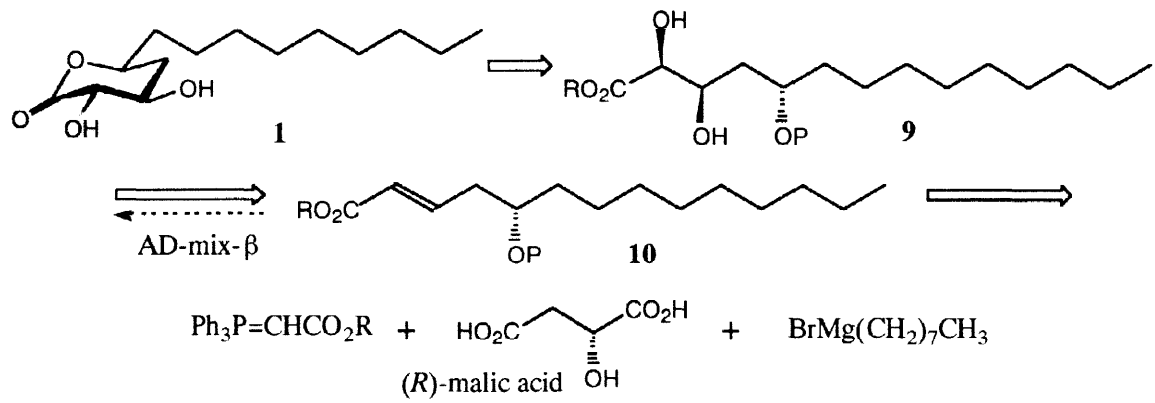
Scheme 1: (a) TsCl, pyridine / CH_2Cl_2, 95%; (b) $CH_3(CH_2)_7MgBr$, CuI / THF, 77%; (c) Ph_3P / CCl_4, 100%; (d) *n*-Bu_3SnH, AIBN / toluene, 92%; (e) 12 M H_2SO_4-dioxane (1:3), 93%; (f) PDC, MS 4A / CH_2Cl_2, 81%; (g) H_2, $Pd(OH)_2$ / EtOAc, 81%.

Known diol **2** obtained from D-glucose in 4 steps [(1) HCl/MeOH, (2) $PhCH(OMe)_2$, TsOH, (3) NaH, BnBr, (4) TsOH/MeOH][4] was selectively tosylated with tosyl chloride and pyridine to give tosylate **3** in 95% yield (Scheme 1). Elongation of **3** with a Grignard reagent [$CH_3(CH_2)_7MgBr$] in the presence of copper (I) iodide gave **4** in 77% yield.[5] Another C_8-elongation with the acetylide of 1-octyne for **3** or the corresponding bromide resulted in lower yields than that with the Grignard reagent. The secondary hydroxyl group of **4** was deoxygenated to give **6** *via* a two-step conversion: (1) chlorination of **4** with triphenylphosphine in refluxing carbon tetrachloride quantitatively, and (2) radical reduction of **5** with tributyltin hydride in 92% yield. The stereochemistry at the C-4 position of **5** was confirmed from the coupling constant of the H-4 (br. d, J = 2.6 Hz) in the ^{1}H-NMR spectrum. Acidic hydrolysis of **6** gave hemiacetal **7** as a 1:1 mixture of anomers in 93% yield (based on consumed **6**) and subsequent oxidation of **7** with pyridinium dichromate (PDC) gave δ-lactone **8** in 81% yield. Although bromine-oxidation in aqueous medium was also tried, PDC-oxidation gave a better yield. Two benzyl groups of **8** were deprotected by hydrogenolysis in the presence of $Pd(OH)_2$ in EtOAc to

give ***ent*-1** as a white powder in 81% yield. Although hydrogenolysis proceeded rapidly in MeOH, ring-opening was promoted to give methyl (2*R*,3*S*,5*R*)-trihydroxytetradecanoate in 34 % yield with ***ent*-1** in 38% yield. The spectral data (^{1}H-, ^{13}C-NMR, IR, MS) of ***ent*-1** were completely identical with those of natural **1**, except for the sign of the specific rotation.[2,6] From this result, the absolute structure of **1** was unambiguously determined as (2*S*,3*R*,5*S*)-(-)-2,3-dihydroxytetradecan-5-olide.

Total Synthesis of 1 from (R)-malic acid

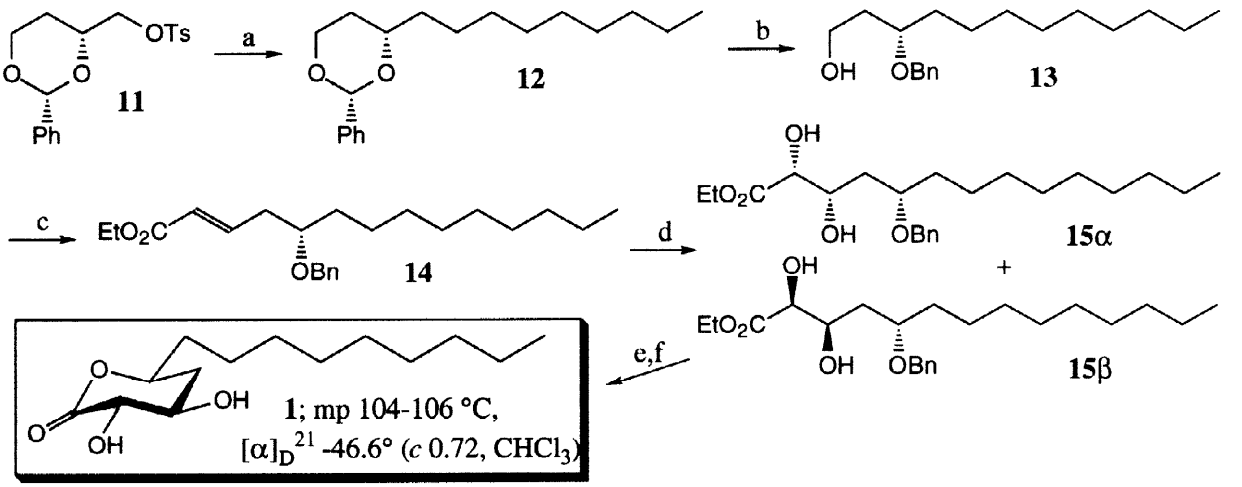
The total synthesis of natural form **1** would be accomplished by using L-glucose as the starting material; however, L-glucose is too expensive for practical use. Therefore, another route is required for the synthesis of a sufficient amount of **1**. The retrosynthesis of **1**, which involves asymmetric dihydroxylation (AD) as the key step, is shown in Scheme 2. Highly diastereoselective AD of a disubstituted olefin such as **10** would proceed to give a diol (**9**). In order to introduce the C-5 stereogenic center and C_8-carbon unit, (*R*)-malic acid, whose suitable derivative (**11**, Scheme 3) is known, was selected as the chiral starting material. In contrast to the synthesis of ***ent*-1** using a cyclic substrate, the final deprotection and subsequent lactonization of an acyclic substrate (**9**) would provide **1**.



Scheme 2: Retrosynthetic analysis of **1**

Known tosylate **11** obtained from (*R*)-malic acid in 3 steps [(1) BH_3·SMe, $B(OMe)_3$, (2) $PhCH(OMe)_2$, TsOH, (3) TsCl, pyridine][7] was elongated to give **12** in 97% yield with the same C_8-Grignard reagent as used in the synthesis of ***ent*-1** in the presence of copper (I) iodide (Scheme 3). Reductive cleavage of benzylidene acetal of **12** with diisobutylaluminum hydride[4b, 8] proceeded regioselectively at the sterically less-hindered primary site. Primary alcohol **13** was obtained in 99% yield as the sole product. Swern oxidation of **13** and subsequent Wittig reaction with (carbethoxymethylene)triphenylphosphorane in one-pot gave (*E*)-unsaturated ester **14** in 85% yield along with 10% of the (*Z*)-isomer. Both isomers could be readily separated by silica-gel column chromatography. Osmium oxidation of **14** without a chiral ligand was carried out to examine the intrinsic diastereofacial selectivity prior to Sharpless AD reaction.[9] The reaction of **14** with a catalytic amount of potassium osmate (VI) dihydrate and *N*-methylmorpholine *N*-oxide as a cooxidant in aqueous acetone gave an inseparable 1:1 mixture of diols **15α** (undesired) and **15β** (desired). Although the absolute configuration of **15α** and **15β** could not be determined at this stage, this result suggests that the reagent-control would be

possible for **14** under Sharpless AD conditions. In practice, the highly diastereoselective reaction with AD-mix-β proceeded to give a 1:21 mixture of **15**α and **15**β in 100% yield (91% *d.e.*). The ratio of **15**α and **15**β was determined from the integration of benzyl methylene-protons in the ^{1}H-NMR spectrum. The major product was revealed to be **15**β after the following conversion into **1**. The diastereofacial selectivity for **14** with AD-mix-β agreed with the usual prediction of the enantiofacial selectivity for *trans*-disubstituted olefins in AD. Hydrogenolysis of **15**β (91% *d.e.*) in the presence of $Pd(OH)_2$ in EtOH gave a mixture of the corresponding triols and **1** which was treated with acetic acid in refluxing benzene to promote lactonization. After the completion of lactonization, the reaction mixture was evaporated to dryness. The resulting powdery residue was reprecipitated from hexane/EtOAc to give **1** in 81% yield as a white powder, whose spectral data (^{1}H-, ^{13}C-NMR, IR, MS) were completely identical with those of natural **1**. The sign of the specific rotation of synthetic **1** was also similar to that of natural **1**.[2,6] The diastereomer derived from **15**α was completely removed by reprecipitation because the ^{1}H-NMR of **1** was observed as the single product.



Scheme 3: (a) $CH_3(CH_2)_7MgBr$, CuI / THF, 97%; (b) DIBAL-H / CH_2Cl_2, 99%; (c) Swern oxid. then $Ph_3P{=}CHCO_2Et$, 85%; (d) AD-mix-β, $MeSO_2NH_2$ / *t*-BuOH-H_2O (1:1), 100%, 91% *d.e.*; (e) H_2, $Pd(OH)_2$ / EtOH; (f) AcOH / benzene, 81%.

CONCLUSION

The total synthesis of ***ent*-1** was accomplished from the known derivative **2** of D-glucose in 41% overall yield in 7 steps and revealed the absolute structure of **1** as (2*S*,3*R*,5*S*)-(-)-2,3-dihydroxytetradecan-5-olide. The first total synthesis of **1** was also accomplished from the known derivative **11** of (*R*)-malic acid in 66% overall yield in 6 steps. Sharpless AD was effectively used for the introduction of the C-2 and C-3 stereogenic centers as we expected. This synthetic approach provided a sufficient amount of **1** for the biological study and made it possible to examine the influence of **1** on the resinous canker disease of *C.* obtusa. In practice, **1** was synthesized in one-gram scale and further upscaling is possible.

While synthetic **1** as well as natural **1** exhibited abscisic activity against the leaves of *C. obtusa*[1b] at the same concentrations with the evolution of typical Hinoki odor, ***ent*-1** exhibited no activity. The minimum

effective concentration (25 ppm) of **1** is higher than that of abscisterol A.[2b,2c] Other biological activities (growth inhibition, antifungal activity, etc.) of **1** and ***ent*-1** are now under examination 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). 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 measured 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).

Methyl 2,3-di-O-benzyl-6-O-tosyl-α-D-glucopyranoside (**3**). To a stirred solution of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **2** (1.73 g, 4.62 mmol) and pyridine (1.84 ml, 23.1 mmol) in CH_2Cl_2 (15 ml) was added *p*-toluenesulfonyl chloride (1.05 g, 5.54 mmol) at 4 ℃. After being stirred overnight at room temperature, the reaction mixture was diluted with CH_2Cl_2 (50 ml) and washed with 1M HCl (30 ml x 2). The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 80 g, hexane:EtOAc = 4:1) to give **3** (2.33 g, 95 %) as a colorless oil: $[\alpha]_D^{21}$ +15.6° (*c* 1.32, $CHCl_3$); IR (film) 3526, 3064, 3031, 2919, 1598, 1497, 1454, 1362, 1293, 1277, 1191, 1158, 1120, 1096, 1059, 978, 929, 815, 743, 698, 666 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.22 (1H, d, *J* = 2.6 Hz, OH), 2.43 (3H, s), 3.33 (3H, s), 3.37-3.48 (2H, m), 3.66-3.77 (2H, m), 4.22 (2H, d, *J* = 3.3 Hz), 4.55 (1H, d, *J* = 3.3 Hz), 4.63 (1H, d, *J* = 11.9 Hz), 4.68 (1H, d, *J* = 11.2 Hz), 4.75 (1H, d, *J* = 11.9 Hz), 4.99 (1H, d, *J* = 11.2 Hz), 7.29-7.40 (12H, m), 7.77 (2H, d, *J* = 17.9 Hz); ^{13}C-NMR ($CDCl_3$) δ 21.7, 55.3, 68.8, 68.9, 69.4, 73.2, 75.4, 79.4, 81.0, 98.1, 127.9, 128.0, 128.1, 128.5, 128.6, 129.8, 132.9, 137.8, 138.6, 144.8; EI-MS *m/z* 437 (M^+-91, 4.25), 155 (4.7), 91 (100); HR-EI-MS calcd. for $C_{21}H_{25}O_8S$ (M^+-91) *m/z* 437.1270, found 437.1265.

(2S,3R,4S,5S,6R)-3,4-Dibenzyloxy-5-hydroxy-2-methoxy-6-nonyl-tetrahydropyran (**4**). Magnesium turnings (1.0 g, 41.2 mmol) in dry THF (5.0 ml) were activated by a small piece of iodine with stirring and heating under argon atmosphere until the color of iodine disappeared. To initiate the generation of Grignard reagent, octyl bromide (neat, 0.5 ml, 2.96 mmol) was first added to the suspension of activated magnesium in THF and the mixture was heated until the reflux of THF occurred. Next, a solution of octyl bromide (6.62 ml, 38.3 mmol) in dry THF (35 ml) was added dropwise to the stirred mixture of magnesium and Grignard reagent in THF over 60 min with keeping the exothermeric reaction. The stirring was further continued for 30 min to give a Grignard reagent, octylmagnesium bromide. To the cooled solution of octylmagnesium bromide in THF at -25 ℃ was added copper (I) iodide (2.36 g, 12.4 mmol) and the mixture was stirred for 30 min at the same

temperature. A solution of **3** (2.18 g, 4.12 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 overnight. The reaction mixture was poured into aq. NH_4Cl (150 ml) and extracted with EtOAc (200 ml, 100 ml x 2). The combined extract was washed with brine (100 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 = 5:1) to give **4** (1.50 g, 77 %) as a colorless oil: $[\alpha]_D^{24}$ +19.0° (*c* 2.40, $CHCl_3$); IR (film) 3476, 3064, 3031, 2924, 2855, 1497, 1455, 1363, 1194, 1133, 1129, 1055, 753, 697 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.87 (3H, t, *J* = 7.3 Hz), 1.26 (12H, m), 1.30-1.60 (3H, m), 1.79 (1H, m), 2.14 (1H, br. s, OH), 3.22 (1H, t, *J* = 9.2 Hz), 3.37 (3H, s), 3.47 (1H, m), 3.50 (1H, dd, *J* = 9.2, 3.3 Hz), 3.73 (1H, t, *J* = 9.2 Hz), 4.58 (1H, d, *J* = 3.3 Hz), 4.66 (1H, d, *J* = 11.9 Hz), 4.69 (1H, d, *J* = 11.2 Hz), 4.76 (1H, d, *J* = 11.9 Hz), 5.03 (1H, d, *J* = 11.2 Hz), 7.29-7.40 (10H, m); ^{13}C-NMR ($CDCl_3$) δ 14.1, 22.7, 25.3, 29.3, 29.5, 29.7, 31.5, 31.9, 55.0, 70.5, 73.0, 73.7, 75.3, 80.0, 81.5, 97.8, 127.9, 128.0, 128.1, 128.5, 128.7, 138.0, 138.7; EI-MS *m/z* 493 (M^+-31, 0.34), 420 (M^+-50, 1.8), 379 (M^+-91, 7.3), 91 (100); HR-EI-MS calcd. for $C_{28}H_{36}O_3$ (M^+-50) *m/z* 420.2664, found 420.2675.

(2S,3R,4R,5R,6R)-5-Chloro-3,4-dibenzyloxy-2-methoxy-6-nonyl-tetrahydropyran (**5**). A solution of **4** (1.45 g, 3.08 mmol) and triphenylphosphine (1.62 g, 6.16 mmol) in carbon tetrachloride (15 ml) was refluxed overnight. The reaction mixture was concentrated under reduced pressure and the resulting triphenylphosphine oxide was filtered off. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel 80 g, hexane:EtOAc = 8:1) to give **5** (1.51 g, 100 %) as a colorless oil: $[\alpha]_D^{22}$ +54.9° (*c* 1.18, $CHCl_3$); IR (film) 3089, 3064, 3031, 2926, 2855, 1607, 1587, 1497, 1455, 1355, 1194, 1110, 1049, 906, 756, 698 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.88 (3H, t, *J* = 7.3 Hz), 1.26 (12H, m), 1.30-1.60 (3H, m), 1.72 (1H, m), 3.37 (3H, s), 3.84 (1H, m), 3.90 (1H, dd, *J* = 9.9, 34.0 Hz), 4.03 (1H, dd, *J* = 9.9, 4.0 Hz), 4.24 (1H, br. d, *J* = 2.6 Hz), 4.61 (1H, d, *J* = 4.0 Hz), 4.67 (1H, d, *J* = 11.9 Hz), 4.73 (1H, d, *J* = 11.9 Hz), 4.76 (1H, d, *J* = 11.9 Hz), 4.87 (1H, d, *J* = 11.9 Hz), 7.27-7.43 (10H, m); ^{13}C-NMR ($CDCl_3$) δ 14.1, 22.6, 25.5, 29.2, 29.5, 31.8, 32.0, 55.3, 63.4, 68.6, 71.9, 73.9, 98.8, 127.7, 127.8, 128.1, 128.3, 128.4, 138.1, 138.4; EI-MS *m/z* 488 (M^+, 0.03, for ^{35}Cl), 458 (M^+-32, 0.3, for ^{37}Cl), 456 (M^+-32, 0.8, for ^{35}Cl), 399 (M^+-91, 2.4, for ^{37}Cl), 397 (M^+-91, 6.7, for ^{35}Cl), 91 (100); HR-EI-MS calcd. for $C_{28}H_{37}O_3{}^{35}Cl$ (M^+-32) *m/z* 456.2432, found 456.2433.

(2S,3R,4S,6R)-3,4-Dibenzyloxy-2-methoxy-6-nonyl-tetrahydropyran (**6**). A solution of **5** (1.50 g, 3.07 mmol), tributyltin hydride (0.99 ml, 3.68 mmol), and α,α'-azobisisobutyronitrile (25.2 mg, 0.15 mmol) in toluene (15 ml) was refluxed for 2 h under argon atmosphere. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel 100 g, hexane 100% then hexane:EtOAc = 8:1) to give **6** (1.28 g, 92 %) as a colorless oil: $[\alpha]_D^{22}$ +32.2° (*c* 1.28, $CHCl_3$); IR (film) 3089, 3064, 3031, 3007, 2926, 2855, 1606, 1587, 1497, 1455, 1357, 1191, 1111, 1050, 1029, 908, 734, 697 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.88 (3H, t, *J* = 6.6 Hz), 1.26 (12H, m), 1.30-1.60 (5H, m), 2.05 (1H, m), 3.36 (3H, s), 3.45 (1H, dd, *J* = 9.2, 3.3 Hz), 3.67 (1H, m), 3.90 (1H, m), 4.63 (1H, d, *J* = 4.0 Hz), 4.68 (1H, d, *J* = 11.9 Hz), 4.70 (1H, d, *J* = 11.9 Hz), 4.77 (1H, d, *J* = 11.9 Hz), 4.84 (1H, d, *J* = 11.9 Hz), 7.27-7.40 (10H, m); ^{13}C-NMR ($CDCl_3$) δ 14.1, 22.6, 25.7, 29.3, 29.5, 29.6, 31.8, 35.3, 37.5, 54.9, 67.2, 72.5, 73.2,

75.5, 80.7, 98.9, 127.7, 127.58, 127.64, 128.0, 128.3, 138.6, 139.0; EI-MS *m/z* 423 (M^+-31, 0.5), 422 (M^+-32, 0.3), 363 (M^+-91, 1.0), 331 (M^+-123, 2.4), 91 (100); HR-EI-MS calcd. for $C_{28}H_{39}O_3$ (M^+-31) *m/z* 423.2899, found 423.2914.

(3R,4S,6R)-3,4-Dibenzyloxy-2-hydroxy-6-nonyl-tetrahydropyran (**7**). A solution of **6** (1.27 g, 2.79 mmol) in 1,4-dioxane (18 ml) and 12 M H_2SO_4 (6 ml) was refluxed for 8 h. The reaction mixture was partitioned between EtOAc (50 ml) and water (50 ml). The organic layer was washed with water (50ml x 2) and sat. aq. $NaHCO_3$ (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 = 5:1) to give starting material **6** (0.21 g, 17%) and product **7** (1:1 anomeric mixture, 0.96 g, 78%; 93% based on consumed **6**) as a colorless oil: IR (film) 3396, 3089, 3064, 3031, 2925, 2855, 1607, 1497, 1455, 1362, 1208, 1103, 1029, 910, 842, 735, 697 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.88 (3H, t, *J* = 6.6 Hz), 1.26 (12H, m), 1.30-1.70 (5H, m), 2.08 (1H, m), 2.80 (0.5H, d, *J* = 2.5 Hz, OH for α-anomer), 2.96 (0.5H, d, *J* = 5.3 Hz, OH for β-anomer), 3.24 (0.5H, t, *J* = 8.3 Hz), 3.37 (0.5H, m), 3.47 (0.5H, dd, *J* = 9.2, 3.3 Hz), 3.59 (0.5H, m), 3.90 (0.5H, m), 3.94 (0.5H, m), 4.61 (0.5H, dd, *J* = 7.3, 5.3 Hz, for β-anomer), 4.68-4.94 (4H, m, benzyl methylene x 2), 5.23 (0.5H, br. t, *J* = 2.5 Hz, for α-anomer), 7.25-7.41 (10H, m); EI-MS *m/z* 422 (M^+-18, 0.2), 349 (M^+-91, 1.1), 91 (100); HR-EI-MS calcd. for $C_{21}H_{33}O_4$ (M^+-91) *m/z* 349.2378, found 349.2394.

(2R,3S,5R)-2,3-Dibenzyloxytetradecan-5-olide (**8**). To a stirred mixture of **7** (960 mg, 2.18 mmol) and molecular sieves 4A (activated powder, 2.0 g) in CH_2Cl_2 (15 ml) was added PDC (1.64 g, 4.36 mmol) at 0 ℃. After being stirred for 3 h at room temperature, the reaction mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel 50 g, hexane:EtOAc = 10:1) to give **8** (777 mg, 81 %) as a colorless oil: $[\alpha]_D^{23}$ +64.2° (*c* 1.65, $CHCl_3$); IR (film) 3089, 3065, 3032, 2926, 2855, 1747, 1606, 1587, 1497, 1455, 1393, 1361, 1216, 1117, 1029, 911, 861, 830, 736, 698 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.88 (3H, t, *J* = 7.0 Hz), 1.26 (12H, m), 1.35-1.76 (5H, m), 2.26 (1H, ddd, *J* = 13.9, 5.3, 2.6 Hz), 3.88 (1H, ddd, *J* = 11.2, 6.6, 5.3 Hz), 4.03 (1H, d, *J* = 6.6 Hz), 4.32 (1H, m), 4.59 (1H, d, *J* = 11.9 Hz), 4.67 (1H, d, *J* = 11.9 Hz), 4.72 (1H, d, *J* = 11.2 Hz), 5.04 (1H, d, *J* = 11.2 Hz), 7.27-7.43 (10H, m); ^{13}C-NMR ($CDCl_3$) δ 14.1, 22.6, 24.8, 29.26, 29.29, 29.4, 29.5, 31.8, 34.8, 35.5, 72.0, 74.1, 75.7, 76.4, 79.5, 127.6, 127.8, 128.0, 128.4, 137.3, 137.8, 170.6; EI-MS *m/z* 438 (M^+, 0.1), 347 (M^+-91, 2.1), 107 (9.3), 91 (100); HR-EI-MS calcd. for $C_{21}H_{31}O_4$ (M^+-91) *m/z* 347.2222, found 347.2229.

(2R,3S,5R)-(+)-2,3-Dihydroxytetradecan-5-olide (***ent*-1**). A mixture of **8** (653 mg, 1.49 mmol) and $Pd(OH)_2$ (200 mg) in EtOAc (15 ml) was vigorously stirred overnight at room temperature under hydrogen atmosphere. The catalyst was filtered through a Celite pad and the filtrate was concentrated under reduced pressure to give a powdery residue. Reprecipitation from EtOAc/hexane gave ***ent*-1** (314 mg, 81%) as a white powder: mp 105-107 ℃; $[\alpha]_D^{22}$ +45.2° (*c* 0.54, $CHCl_3$); IR (KBr) 3422, 2921, 2852, 1720, 1467, 1387, 1342, 1245, 1223, 1189, 1096, 1050, 1033, 995, 954, 928, 870, 821, 772, 688, 646, 594, 532 cm^{-1}; ^{1}H- and ^{13}C-NMR spectra of ***ent*-1** were completely identical with those of natural **1**;[2] EI-MS *m/z* 259 (MH^+, 1.0), 258 (M^+, 0.5), 240 (M^+-18, 0.5), 222 (M^+-36, 0.8), 60 (100); HR-EI-MS calcd. for $C_{14}H_{27}O_4$ (MH^+) *m/z* 259.1910,

found 259.1929.

(2R,4S)-4-Nonyl-2-phenyl-1,3-dioxane (**12**). According to the method described in the synthesis of **4**, a solution of octylmagnesium bromide in dry THF (35 ml) was prepared from magnesium turnings (840 mg, 34.6 mmol), iodine, and octyl bromide (5.98 ml, 34.6 mmol). To this solution was successively added copper (I) iodide (1.98 g, 10.4 mmol) and (2*R*,4*R*)-2-phenyl-4-(tosyloxy)methyl-1,3-dioxane **11** (3.01 g, 8.64 mmol) in dry THF (15 ml) at -25 ℃ under argon atmosphere. The temperature was gradually allowed to warm to room temperature with stirring over 2 h. The reaction mixture was poured into aq. NH_4Cl (150 ml) and extracted with EtOAc (200 ml, 100 ml x 2). The combined extract was washed with brine (100 ml) dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 200 g, hexane:EtOAc = 10:1) to give **12** (2.44 g, 97 %) as a colorless oil: $[\alpha]_D^{21}$ -21.4° (*c* 1.07, $CHCl_3$); IR (film) 3067, 3036, 2925, 2854, 1496, 1465, 1455, 1399, 1363, 1312, 1240, 1215, 1174, 1141, 1114, 1082, 1057, 1028, 982, 912, 841, 749, 722, 697 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.90 (3H, t, *J* = 6.6 Hz), 1.29 (12H, m), 1.38-1.90 (6H, m), 3.81 (1H, m), 3.96 (1H, dt, *J* = 2.6, 12.5 Hz), 4.27 (1H, ddd, *J* = 12.5, 5.3, 1.3 Hz), 5.52 (1H, s), 7.29-7.40 (3H, m), 7.48-7.53 (2H, m); ^{13}C-NMR ($CDCl_3$) δ 14.1, 22.7, 25.0, 29.3, 29.6, 31.4, 31.9, 36.0, 67.1, 77.3, 101.1, 126.0, 128.2, 128.6, 138.9; EI-MS *m/z* 291 (MH^+, 16.9), 290 (M^+, 90.0), 289 (M^+-H, 100), 213 (M^+-77, 6.8); HR-EI-MS calcd. for $C_{19}H_{30}O_2$ (M^+) *m/z* 290.2246, found 290.2228.

(S)-3-Benzyloxy-1-dodecanol (**13**). To a solution of **12** (2.30 g, 7.92 mmol) in dry CH_2Cl_2 (25 ml) was added dropwise DIBAL-H (24.8 ml, 23.8 mmol, 0.96 M solution in hexane) at -78 ℃ under argon atmosphere. The mixture was gradually allowed to warm to room temperature and the stirring was continued overnight. To the reaction mixture cooled to 0 ℃ was successively added sat. aq. Rochelle salt (3.0 ml) and EtOAc (30 ml). After being stirred for 1 h at room temperature, the mixture was filtered through a Celite pad. The filtrate was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give **13** (2.29 g, 99 %) as a colorless oil: $[\alpha]_D^{22}$ +35.9° (*c* 1.17, $CHCl_3$); IR (film) 3387, 3089, 3065, 3032, 2926, 2855, 1606, 1497, 1466, 1455, 1378, 1350, 1207, 1093, 1066, 1028, 908, 734, 697 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.89 (3H, t, *J* = 6.6 Hz), 1.27 (14H, m), 1.46-1.89 (4H, m), 2.45 (1H, t, *J* = 5.3 Hz), 3.58-3.87 (3H, m), 4.48 (1H, d, *J* = 11.2 Hz), 4.60 (1H, d, *J* = 11.2 Hz), 7.27-7.40 (5H, m); ^{13}C-NMR ($CDCl_3$) δ 14.1, 22.6, 25.1, 29.3, 29.5, 29.6, 29.8, 31.9, 33.4, 35.8, 60.8, 70.9, 78.6, 127.6, 127.8, 128.4, 138.4; EI-MS *m/z* 293 (MH^+, 0.8), 292 (M^+, 3.8), 274 (M^+-18, 5.6), 201 (M^+-91, 0.4), 107 (29.1), 91 (100); HR-EI-MS calcd. for $C_{19}H_{32}O_2$ (M^+) *m/z* 292.2403, found 292.2377.

Ethyl (2E,5S)-5-benzyloxy-2-tetradecenoate (**14**). To a stirred solution of oxalyl chloride (0.78 ml, 8.97 mmol) in CH_2Cl_2 (30 ml) was added dropwise dimethyl sulfoxide (0.85 ml, 12.0 mmol) at -78 ℃ under argon atmosphere. After 5 min, to this solution was added dropwise a solution of **13** (1.75 g, 5.98 mmol) in dry CH_2Cl_2 (10 ml) at -78 ℃. The mixture was stirred for 30 min at the same temperature. After the addition of triethylamine (4.16 ml, 29.9 mmol), the temperature was gradually allowed to warm to room temperature to give a crude aldehyde which was used for the next Wittig reaction in one-pot. To the mixture containing a crude aldehyde was added (ethoxycarbonylmethylene)triphenylphosphorane (4.17 g, 12.0 mmol) at room

temperature and the mixture was stirred overnight. Hexane (60 ml) was added to the reaction mixture and the resulting insoluble materials were filtered off. The filtrate was diluted with EtOAc (100 ml), washed with 1M HCl (50 ml) and 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 = 15:1) to give **14** (1.84 g, 85 %) as a colorless oil: $[\alpha]_D^{21}$ -8.92° (*c* 1.46, $CHCl_3$); IR (film) 3089, 3065, 3031, 2927, 2855, 1722, 1656, 1606, 1587, 1497, 1465, 1455, 1392, 1368, 1350, 1319, 1267, 1176, 1095, 1069, 1047, 1029, 981, 908, 864, 809, 735, 697 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.89 (3H, t, *J* = 6.9 Hz), 1.26 (12H, m), 1.29 (3H, t, *J* = 7.3 Hz), 1.35-1.62 (4H, m), 2.45 (2H, br. t, *J* = 6.0 Hz), 3.51 (1H, quint, *J* = 6.0 Hz), 4.19 (2H, q, *J* = 7.3 Hz), 4.51 (1H, d, *J* = 11.9 Hz), 4.54 (1H, d, *J* = 11.9 Hz), 5.88 (1H, br. d, *J* = 15.5 Hz), 6.99 (1H, dt, *J* = 15.5, 6.0 Hz), 7.27-7.40 (5H, m); ^{13}C-NMR ($CDCl_3$) δ 14.1, 14.3, 22.6, 25.3, 29.3, 29.5, 29.56, 29.62, 31.9, 34.0, 36.8, 60.2, 71.1, 77.8, 123.4, 127.5, 127.7, 128.3, 138.5, 145.5, 166.4; EI-MS *m/z* 361 (MH^+, 0.2), 360 (M^+, 0.8), 315 (M^+-45, 0.2), 91 (100); HR-EI-MS calcd. for $C_{23}H_{36}O_3$ (M^+) *m/z* 360.2665, found 360.2673.

Ethyl (2S,3R,5S)-5-benzyloxy-2,3-dihydroxytetradecanoate (**15β**). A solution of **14** (361 mg, 1.0 mmol) in *t*-BuOH (1.0 ml) was added to a stirred mixture of AD-mix-β (1.4 g) and methanesulfonamide (95 mg, 1.0 mmol) in *t*-BuOH (4.0 ml) and H_2O (5.0 ml) at 4 ℃. The mixture was stirred overnight at the same temperature. After addition of Na_2SO_3 (1.5 g) at 4 ℃, the reaction mixture was stirred for 30 min at r.t. and partitioned between EtOAc (30 ml) and H_2O (30 ml). The aqueous layer was further extracted with EtOAc (10 ml x 2). The combined organic layer was washed with 2M KOH (10 ml x 2) and brine (20 ml), 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 an inseparable mixture of **15β** and **15α** (395 mg, 100 %, 91% *d.e.*) as a colorless oil. A large scale-reaction using **14** (1.87 g, 5.19 mmol) also gave an inseparable mixture of **15β** and **15α** (1.85 g, 90 %, 91% *d.e.*).

Data for **15β** (**15α**:**15β** = 1:21, 91% *d.e.*): $[\alpha]_D^{21}$ +27.3° (*c* 1.27, $CHCl_3$); IR (film) 3467, 3090, 3065, 3031, 2926, 2855, 1738, 1497, 1466, 1455, 1369, 1254, 1210, 1095, 1028, 945, 866, 848, 820, 735, 698 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.89 (3H, t, *J* = 6.6 Hz), 1.27 (14H, m), 1.31 (3H, t, *J* = 7.3 Hz), 1.47-1.78 (3H, m), 1.99 (1H, ddd, *J* = 15.0, 9.9, 3.3 Hz), 2.80 (1H, d, *J* = 5.9 Hz, OH), 3.13 (1H, br. d, *J* = 6.6 Hz, OH), 3.74 (1H, m), 4.02 (1H, dd, *J* = 6.6, 2.0 Hz), 4.24 (1H, m), 4.28 (2H, q, *J* = 7.3 Hz), 4.52 (1H, d, *J* = 11.2 Hz), 4.58 (1H, d, *J* = 11.2 Hz), 7.27-7.40 (5H, m); ^{13}C-NMR ($CDCl_3$) δ 14.09, 14.14, 22.6, 25.3, 29.3, 29.5, 29.6, 29.7, 31.9, 33.6, 37.0, 61.9, 69.5, 71.4, 74.0, 76.7, 127.7, 127.9, 128.4, 138.4, 173.2; EI-MS *m/z* 395 (MH^+, 0.4), 394 (M^+, 0.3), 376 (M^+-18, 0.1), 321 (M^+-73, 0.1), 303 (M^+-91, 0.2), 291 (M^+-103, 0.7), 91 (100); HR-EI-MS calcd. for $C_{23}H_{39}O_5$ (MH^+) *m/z* 395.2797, found 395.2807.

Osmium oxidation of ***14*** *without a chiral ligand.* A mixture of **14** (100 mg, 0.28 mmol), *N*-methylmorphorine *N*-oxide (97.5 mg, 0.83 mmol), and $K_2OsO_4 \cdot 2H_2O$ (1 mg) in acetone (3.0 ml) and H_2O (1.0 ml) was stirred overnight at room temperature. The reaction mixture was partitioned between EtOAc (10 ml) and H_2O (10 ml). The organic layer was washed with 1M HCl (10 ml) and brine (10 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a 1:1 mixture of **15α** and **15β** (100 mg, 92%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) for a 1:1 mixture of **15α** and **15β**: δ 0.89 (3H, t, *J* = 6.6 Hz), 1.27

(14H, m), 1.31 (3H, t, J = 7.3 Hz), 1.47-1.78 (3H, m), 1.99 (1H, m), 3.10 (2H, br. s, OH x 2), 3.73 (1H, m), 4.02 (1H, s), 4.15 (0.5H, m, for **15α**), 4.24 (0.5H, m, for **15β**), 4.28 (2H, q, J = 7.3 Hz), 4.44 (1H, d, J = 11.2 Hz, for **15α**), 4.52 (1H, d, J = 11.2 Hz, for **15β**), 4.58 (1H, d, J = 11.2 Hz, for **15β**), 4.63 (1H, d, J = 11.2 Hz, for **15α**), 7.27-7.40 (5H, m).

(2S,3R,5S)-(-)-2,3-Dihydroxytetradecan-5-olide (**1**). A mixture of **15β** (1.84 g, 4.66 mmol, 91% *d.e.*) and $Pd(OH)_2$ (100 mg) in EtOH (30 ml) was vigorously stirred for 3 h at room temperature under hydrogen atmosphere. The catalyst was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was dissolved in benzene (50 ml) and acetic acid (0.5 ml). The solution was refluxed for 4 h and concentrated to give a powdery residue. Reprecipitation from EtOAc/hexane (1:3) gave **1** (1.09 g, 81%) as a white powder: mp 104-106 ℃; $[\alpha]_D^{21}$ -46.6° (*c* 0.72, $CHCl_3$); IR (KBr) 3422, 2921, 2852, 1720, 1467, 1387, 1342, 1245, 1223, 1189, 1096, 1050, 1033, 995, 954, 928, 870, 821, 772, 688, 646, 594, 532 cm^{-1}; ^1H- and ^{13}C-NMR spectra of **1** were completely identical with those of natural **1**;[2] EI-MS *m/z* 259 (MH^+, 0.8), 258 (M^+, 0.6), 240 (M^+-18, 0.4), 222 (M^+-36, 0.6), 60 (100); HR-EI-MS calcd. for $C_{14}H_{26}O_4$ (M^+) *m/z* 258.1832, found 258.1851.

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