A NEW ENANTIOSPECIFIC APPROACH TO THE BISLACTONE STRUCTURE: FORMAL SYNTHESES OF (-)-AVENACIOLIDE AND (-)-ISOAVENACIOLIDE

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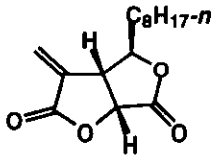
Abstract-A new synthetic methodology for the synthesis of the condensed bislactone structure was developed by using enantiospecific ring expansion of oxetane as a key step. This methodology was proven to be useful for the syntheses of natural products such as (-)-avenaciolide and (-)-isoavenaciolide.

(-)-Avenaciolide (**1**) and (-)-isoavenaciolide (**2**) are secondary metabolites isolated from *Aspergillus avenaceus*.[1] Due to their antifungal and antibacterial activities and unique bislactone structures, many enantioselective synthetic studies of **1** and **2** have been reported. Most of them have relied on optically



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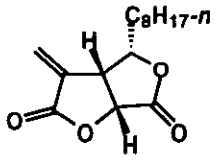

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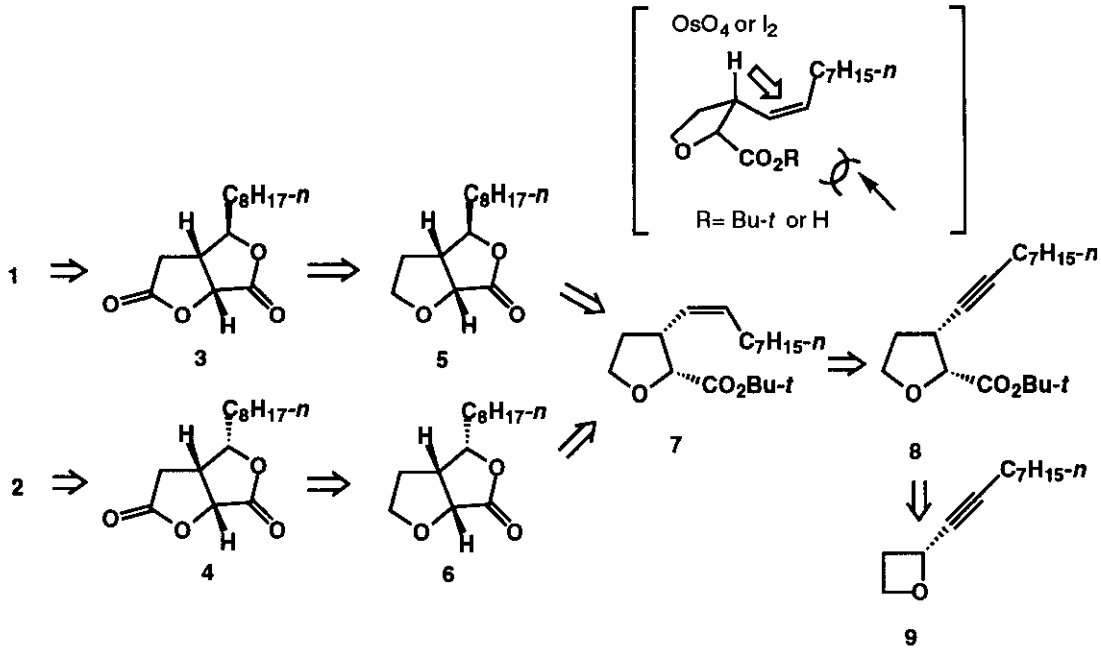
active natural products as the chiral sources,[2] but several studies have been carried out by using appropriate asymmetric reaction as a key step.[3] For the synthesis of these compounds, an efficient method to construct their bislactone structures bearing three consecutive asymmetric centers is indispensable. We have recently reported Cu-bipyrindine-catalyzed enantiospecific ring expansion of 2-alkynyloxetane to 3-alkynyltetrahydrofuran-2-carboxylate which can be readily converted into 3-(*Z*-alkenyl)tetrahydrofuran-2-carboxylate.[4a-c] On the other hand, it is well known that γ,δ-unsaturated acids or their ester derivatives bearing asymmetric centers at their α- and/or β-carbons can be converted into the corresponding γ-butyrolactones with high stereoselectivity.[5] Since tetrahydrofurans can be readily oxidized into the

This paper is dedicated to the memory of the late Professor Emeritus Shunichi Yamada.

corresponding γ-butyrolactones, the ring expansion product of 3-alkynyloxetane is a good starting material for the synthesis of natural products containing a bislactone structure. Thus, we examined the synthesis of **1** and **2** by using enantiospecific ring expansion as a key step.[6]

Synthetic Strategy

Our synthetic strategy is outlined in a retrosynthetic manner in Scheme 1. It has already been reported that racemic compounds (**5**) and (**6**) can be converted into racemic **1** and **2** in three steps, respectively.[7] Since compounds (**5**) and (**6**) are diastereomeric to each other only at the C-6 carbon, we planned to synthesize both compounds stereoselectively from the common intermediate, γ,δ-unsaturated ester (**7**). The *cis*-olefin moiety in **7** was considered to be conformationally fixed as described in Scheme 1, owing to allylic strain



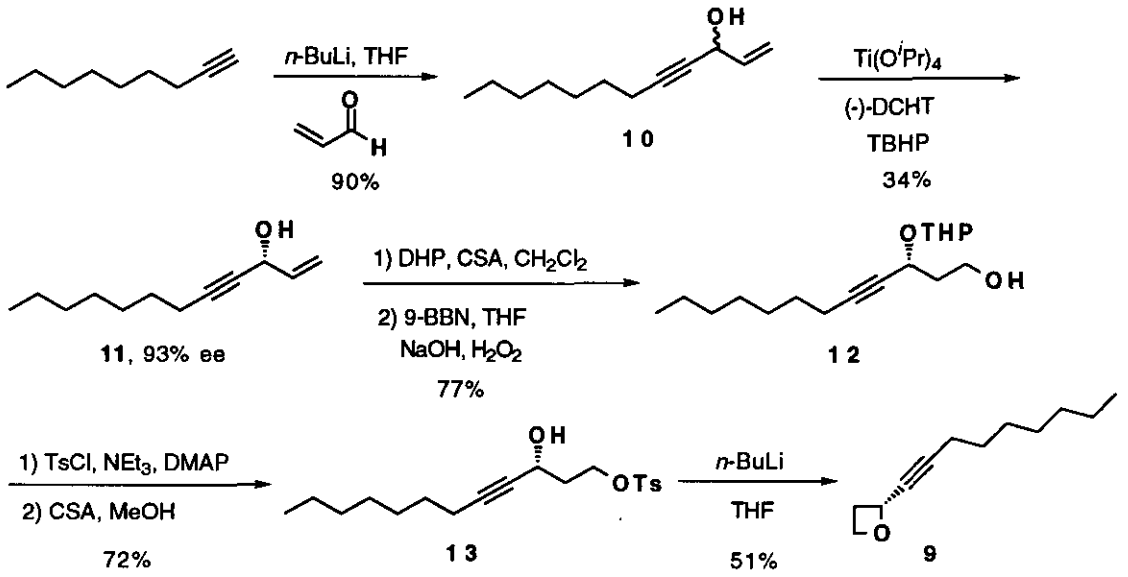
Scheme 1

and, therefore, the reagents should approach the olefin from the side distal to the ester or carboxylic acid group. Thus, stereoselective formation of **5** and **6** from **7** was considered to be possible by choosing proper reaction conditions for cyclization. For example, halolactonization of **7** and the subsequent dehalogenation were expected to give **5** and the combination of dihydroxylation, lactonization, and dehydroxylation was expected to give **6**. Compound (**7**) should be derived from **8** which is readily available in an enantiomerically enriched form by the ring expansion of (*R*)-2-(1-nonynyl)oxetane (**9**). Along these lines, we undertook the synthesis of compounds (**1**) and (**2**).

Synthesis of Optically Active Oxetane (9)

The requisite optically active (*R*)-**9** was prepared from (*R*)-**11** of 93% ee[8] which was obtained by titanium-mediated kinetic resolution of the corresponding racemic allylic alcohol (**10**),[9] by the sequence: i)

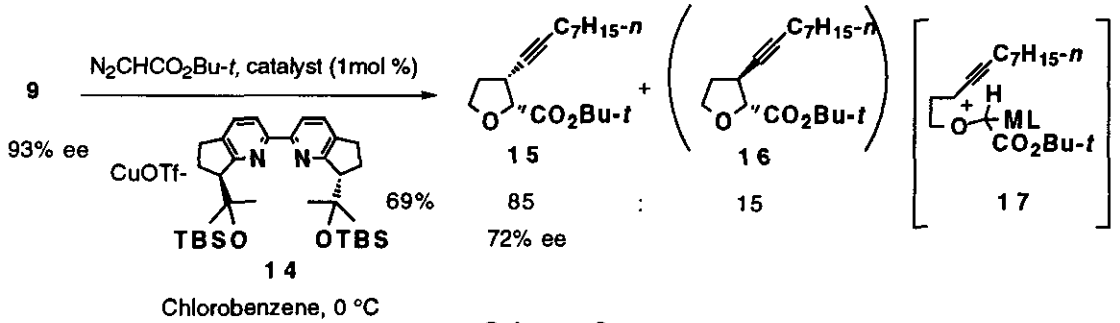
protection of the hydroxyl group, ii) hydroboration and oxidation, iii) tosylation of the resulting primary alcohol (**12**), iv) deprotection, v) treatment of the resulting secondary alcohol (**13**) with *n*-BuLi. (Scheme 2).



Scheme 2

Enantiospecific Ring Expansion of Oxetane

With optically active oxetane (**9**) in hand, we next examined ring expansion of optically active oxetane (**9**) with Cu(I)OTf-chiral bipyrindine (**14**) complex in dichloromethane. As expected, the reaction proceeded with good stereoselectivity to give a mixture of 2,3-*cis*- (**15**, 73% ee) and 2,3-*trans*-tetrahydrofurans (**16**), which could be separated by silica gel chromatography, in a ratio of 87:13[4] but the yield of tetrahydrofurans (**15** and **16**) was low (26%). We also examined the reaction using the bipyrindine complex of Cu(I)OBu-*t* or Cu(I)(CF_3CO_2) [prepared by the reduction of Cu(II)(CF_3CO_2)$_2$-**14** complex with phenylhydrazine] but their catalytic activity was very poor. This suggested that the use of cationic copper complex is indispensable for oxygen-ylid formation. To increase the chemical yield, we next examined solvent effects. Reaction with Cu(I)OTf-**14** complex in fluorobenzene improved the chemical

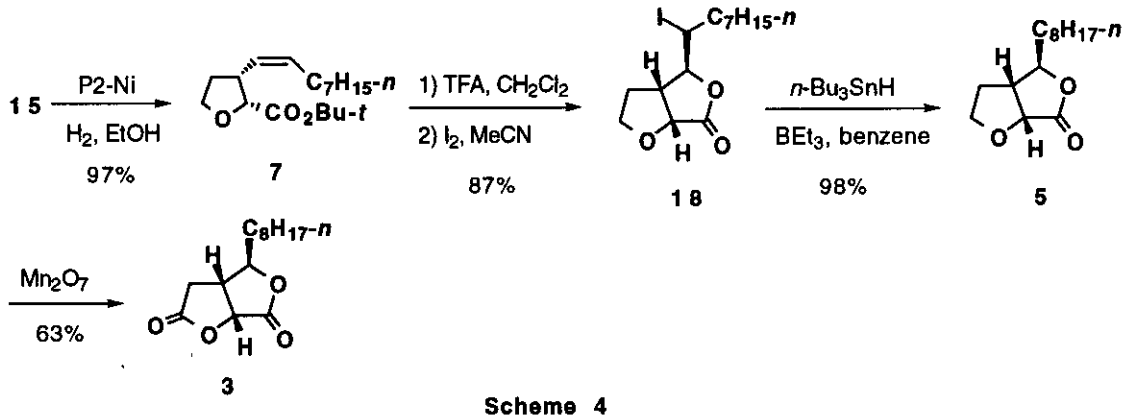


Scheme 3

yield to some extent (40%). Finally, chemical yield was improved to 69% with same level of stereoselectivity [**15** (72% ee):**16**= 85:15] when the reaction was conducted in chlorobenzene at 0 °C (Scheme 2). On the other hand, treatment of a dichloromethane solution of **9** with *t*-butyl diazoacetate in the presence of a catalytic amount of $Rh_2(OAc)_4$ gave a mixture of *cis*-**15**[10] and its *trans*-**16** in a good yield (76%) but the stereoselectivity was poor [**15** (26% ee):**16**= 55:45]. This suggested that the rhodium-catalyzed reaction largely proceeded through the cationic intermediate (**17**),[4a] which caused racemization. The obtained **15** (72% ee) was used for the next reaction without further improving its optical purity, since the bislactone compounds are often crystalline and their optical purity could be expected to be improved by recrystallization at an appropriate stage.

Syntheses of (-)-Avenaciolide and (-)-Isoavenaciolide

We first examined the synthesis of (-)-avenaciolide from optically active **15** (Scheme 4). Compound (**15**) was hydrogenated with P2-Ni catalyst[11] to afford *cis*-olefin (**7**). No *trans*-isomer was detected by ^1H NMR (270 MHz) analysis. Compound (**7**) was exposed to trifluoroacetic acid (TFA) and the resulting unsaturated carboxylic acid was subjected to iodolactonization to afford iodolactone (**18**) with high diastereoselectivity (38:1). Treatment of **18** with *n*-Bu_3SnH in the presence of a catalytic amount of

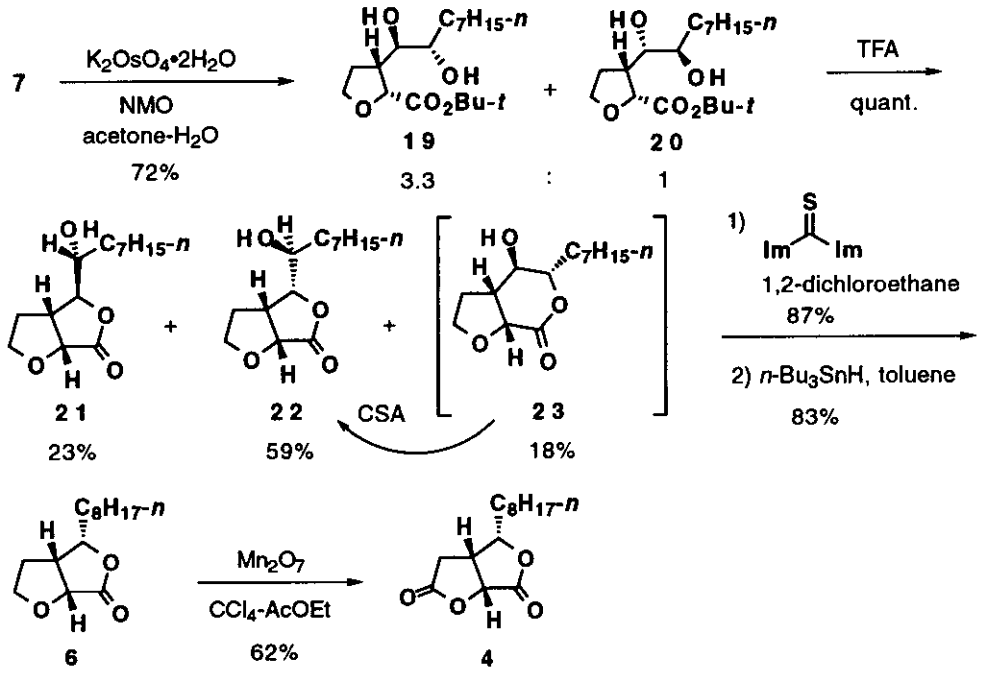


Scheme 4

BEt_3[12] gave lactone (**5**). At this stage, the enantiomeric excess of lactone (**5**) was improved to >90%[10] simply by recrystallization from hexane at 0 °C. Although the $RuCl_3$-aqueous $NaIO_4$ oxidation of lactone (**5**) has been reported, it proceeds slowly at room temperature. However, lactone (**5**) was found to be smoothly oxidized with Mn_2O_7[13] to bislactone (**3**). All the spectroscopic data of **3** are compatible with reported data,[2c] except for optical rotation.[14] **3**: $[\alpha]_D^{25}$ -1.5° (*c* 1.2, $CHCl_3$), [lit.,[3e] $[\alpha]_D^{27}$ -2.45° (*c* 1.96, $CHCl_3$); lit.,[3b] $[\alpha]_D^{27}$ -3.5° (*c* 1.2, $CHCl_3$); lit.,[2b] (enantiomer of **3**) $[\alpha]_D^{27}$ +6.17° (*c* 1.5, $CHCl_3$)].

Next we examined the synthesis of (-)-isoavenaciolide (**2**) (Scheme 5). Osmium-mediated dihydroxylation of **7** gave diastereomeric diol (**19**) and (**20**) in a ratio of 3.3:1. This mixture was then exposed to TFA to give a mixture of lactones (**21**, **22** and **23**) which were separated on silica gel chromatography. The six-membered lactone (**23**) could be converted into **22** by treatment with camphorsulfonic acid (CSA) in dichloromethane. Compound (**22**) was subjected to the Barton reaction[15] to give lactone (**6**). Compound

(**6**) was oxidized with Mn_2O_7[13] to **4**. The enantiomeric excess of bislactone (**4**) was improved to >90%[10] after recrystallization from hexane-ethyl acetate. All the spectroscopic data of **4** are compatible with reported data.[2c] The specific rotation of **4** was $[\alpha]_D^{26}$ -20.7° (*c* 1.2, $CHCl_3$) [lit.,[3b] $[\alpha]_D^{25}$ -21° (*c* 1.0, $CHCl_3$)].



Scheme 5

In conclusion, we were able to achieve formal total syntheses of (-)-avenaciolide and (-)-isoavenaciolide in a straightforward and enantioselective manner by ring expansion of oxetane as key steps. This result demonstrates the high utility of the enantiospecific ring expansion reaction in natural product synthesis.

EXPERIMENTAL

NMR spectra were recorded at 270 MHz on a JEOL EX-270 instrument. All signals were expressed as ppm down field from tetramethylsilane used as an internal standard (δ-value in $CDCl_3$). IR spectra were obtained with a SHIMADZU FTIR-8600 instrument. Optical rotation was measured with a JASCO DIP-360 automatic digital polarimeter. High-resolution mass spectra were recorded on a JEOL JMS-SX/SX 102A instrument. Column chromatography was conducted on Silica Gel BW-820MH, 70-200 mesh ASTM, available from FUJI SILYSIA CHEMICAL LTD. Solvents were dried and distilled shortly before use. Reactions were carried out under an atmosphere of nitrogen or argon if necessary.

dl-Dodec-1-en-4-yn-3-ol (10)

Butyllithium (58 mL, 1.6 mol/L in hexane) was added to a solution of 1-nonyne (14 mL, 85 mmol) in tetrahydrofuran (THF) (200 mL) at -78 °C. After stirring for 1 h at the temperature, acrolein (6.4 mL, 86

mmol) was added dropwise and the whole mixture was gradually raised to 0 °C. The mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The extract was dried over $MgSO_4$ and concentrated. Distillation of the residue (bp 106 °C/4 mmHg) gave alcohol (**10**) (13.7 g, 90%) as an oil.

Kinetic Resolution of *dl*-10

To a suspension of allylic alcohol (**10**) (13.0 g, 72 mmol) and activated MS 3Å (3.9 g) in CH_2Cl_2 (290 mL) was added (-)-dicyclohexyl tartrate (3.4 g, 11 mmol) and titanium tetraisopropoxide (2.2 mL, 7.5 mmol) at -20 °C. After being stirred for 30 min, *tert*-butyl hydroperoxide (18.5 mL, 6.0 mol/L in isooctane) was added at the temperature. The mixture was left in refrigerator (-20 °C) for 3 days. The mixture was poured on pre-cooled (0 °C) $FeSO_4 \cdot 7H_20$ (25 g) and citric acid (8.5 g) in water (77 mL). After vigorous stirring for 1 h, the mixture was extracted with CH_2Cl_2, and the extract was dried over $MgSO_4$, and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 19:1~9:1) gave optically active **11**, (5.3 g, 41%) as an oil. Enantiomeric excess of **11** was determined to be 77% ee by HPLC analysis (Daicel Chiralcel OF; 0.46 cm x 25 cm, hexane/*i*-PrOH=9:1) after *p*-nitrobenzoylation. Accordingly, **11** (5.3 g, 77% ee) was again subjected to kinetic resolution under the same reaction conditions to give **11** of 93% ee (4.4 g). **11** (93% ee); $[\alpha]_D^{26}$ -27.1° (*c* 2.46, $CHCl_3$). ^1H NMR: δ 5.97 (ddd, *J*= 5.3, 9.9 and 16.8 Hz, 1H), 5.45 (dt, *J*= 1.3 and 16.8 Hz, 1H), 5.20 (dt, *J*= 1.3 and 9.9 Hz, 1H), 4.91-4.83 (m, 1H), 2.24 (dt, *J*= 2.0 and 6.9 Hz, 2H), 1.83 (d, *J*= 6.3 Hz, 1H), 1.56-1.27 (m, 10H), 0.89 (t, *J*= 6.9 Hz, 3H). IR (KBr): 3422, 2957, 2858, 2220, 1647, 1468, 1402, 1261, 1146, 1113, 1015, 986, 926, 723 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.71; H, 10.94.

(3*R*)-3-(2-Tetrahydropyranyloxy)dodec-4-yn-1-ol (12)

To a solution of alcohol (**11**, 4.4 g, 24.4 mmol) and *dl*-camphorsulfonic acid (112 mg, 0.48 mmol) in dichloromethane (48 mL) was added dihydropyran (2.3 mL, 26 mmol) at rt. After being stirred for 30 min, triethylamine (1 mL) was added and the mixture was concentrated under reduced pressure. Silica gel chromatography of the residue (hexane-ethyl acetate = 8:2) gave the corresponding tetrahydropyranyl (THP) ether (6.0 g, 87%) as an oil. $[\alpha]_D^{26}$ +33.5° (*c* 4.63, $CHCl_3$). IR (KBr): 3445, 2934, 2858, 2220, 1651, 1468, 1202, 1117, 1015, 928, 907, 870, 818, 723 cm^{-1}. Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.21; H, 10.54.

To a solution of the above THP ether (5.4 g, 21 mmol) in THF (30 mL) was added 9-BBN (61 mL, 0.5 mol/L in THF) at 0 °C, and the mixture was allowed to gradually warm to rt. After being stirred for 4 h, the mixture was quenched with a small amount of water. To this mixture were added 3*N* aqueous NaOH (20 mL) and 35% H_2O_2 (20 mL). After vigorous stirring for 6 h, the mixture was diluted with water and extracted with ethyl acetate. The extract was dried over anhydrous $MgSO_4$ and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 8:2) gave alcohol (**12**) (5.1 g, 88%) as an oil. **12**; $[\alpha]_D^{26}$ +79.9° (*c* 2.56, $CHCl_3$). IR (KBr): 3445, 2932, 2858, 2239, 1638, 1468, 1202, 1132, 1020, 995, 905, 870, 816, 723 cm^{-1}. HRFABMS m/z Calcd for $C_{17}H_{31}O_3$ (M^++H): 283.2273. Found 283.2275.

(3*R*)-3-Hydroxy-1-(*p*-toluenesulfonyloxy)dodec-4-yn (13)

p-Toluenesulfonyl chloride (3.8 g, 20 mmol) was added to a solution of 4-(*N,N*-dimethylamino)pyridine (20 mg, 0.16 mmol), triethylamine (3.0 mL, 22 mmol), and alcohol (**12**) (5.1 g, 18 mmol) in dichloromethane (36 mL). After being stirred for 30 min, the mixture was directly subjected to silica gel chromatography (hexane-ethyl acetate = 9:1~8:2) to give the corresponding tosylate (6.3 g, 80%) as an oil. $[\alpha]_D^{26}$ +37.4° (*c* 1.74, $CHCl_3$). IR (KBr): 3447, 2932, 2858, 2239, 1742, 1599, 1466, 1364, 1177, 1020, 972, 920, 816, 665, 556 cm^{-1}. HRFABMS m/z Calcd for $C_{24}H_{37}O_5S$ (M^++H): 437.2362. Found 437.2363.

To a solution of the above tosylate (6.3 g, 15 mmol) in MeOH (145 mL) was added *dl*-camphorsulfonic acid (33.7 mg, 1.5 mmol). After being stirred for 3 h, the mixture was quenched with triethylamine (1 mL) and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 9:1) gave alcohol (**13**) (4.6 g, 90%) as an oil. **13**; $[\alpha]_D^{26}$ +3.8° (*c* 1.03, $CHCl_3$). ^1H NMR: δ 7.80 (d, *J*= 8.3 Hz, 2H), 7.34 (d, *J*= 8.3 Hz, 2H), 4.47 (tt, *J*= 2.0 and 6.6 Hz, 1H), 4.25 (dt, *J*= 6.6 and 9.9 Hz, 1H), 4.17 (dt, *J*= 6.6 and 9.9 Hz, 1H), 2.45 (s, 3H), 2.14 (dt, *J*= 2.0 and 7.3 Hz, 2H), 2.00 (dt, *J*= 6.6 and 6.6 Hz, 2H), 1.51-1.21 (m, 10H), 0.88 (t, *J*= 6.6 Hz, 3H). IR (KBr): 3528, 2930, 2858, 1744, 1599, 1466, 1864, 1177, 1097, 999, 970, 918, 816, 779, 665, 556 cm^{-1}. Anal. Calcd for $C_{19}H_{28}O_4S$: C, 64.74; H, 8.01. Found: C, 64.69; H, 7.91.

(*R*)-2-(1-Nonynyl)oxetane (9)

Butyllithium (7.3 mL, 1.6 mol/L in hexane) was added to a solution of tosylate(**13**)(4.2 g, 12 mmol) in THF (60 mL) at 0 °C and gradually raised to 50 °C. After being stirred for 3 h at the same temperature, the mixture was cooled to rt, quenched with water (100 mL), and extracted with ethyl acetate. The extract was dried over anhydrous $MgSO_4$ and concentrated. Kugelrohr distillation (160 °C, 2 mmHg) gave oxetane (**9**) (1.1 g, 51%) as an oil. This product (**9**) was immediately used for the next reaction because it decomposed slowly on standing. **9**; $[\alpha]_D^{26}$ +33.3° (*c* 1.51, $CHCl_3$). ^1H NMR: δ 5.37-5.30 (m, 1H), 4.68-4.56 (m, 2H), 2.96-2.68 (m, 2H), 2.27 (dt, *J*= 1.7 and 6.9 Hz, 2H), 1.59-1.28 (m, 10H), 0.88 (t, *J*= 6.9 Hz, 3H). IR (KBr): 2932, 2237, 2214, 1674, 1468, 1342, 1259, 1165, 1119, 1059, 964, 910, 723 cm^{-1}.

***tert*-Butyl (2*R*,3*R*)-3-(1-nonynyl)tetrahydrofuran-2-carboxylate (15)**

To a suspension of $CuOTf{\cdot}0.5C_6H_6$ (1.1 mg, 4.4 μmol) in chlorobenzene (0.8 mL) was added a solution of chiral bipyrindine (**14**) (2.8 mg, 4.8 μmol) in chlorobenzene (0.2 mL). After 30 min, the mixture was filtered through a packed adsorbent cotton under argon and to the filtrate was added oxetane (**9**) (45 mg, 0.25 mmol). To the solution was added dropwise a solution of *tert*-butyl diazoacetate (100 μL, 0.38 mmol) in chlorobenzene (0.4 mL) over a period of 30 min at 0 °C. The mixture was raised to rt and concentrated. Silica gel chromatography of the residue (hexane-*i*-Pr_2O = 19:1~9:1) gave **15** (44 mg, 59%) as an oil. The enantiomeric excess of **15** was determined to be 73% ee by ^1H NMR analysis using a chiral shift reagent [Eu(hfc)3]. **15**; $[\alpha]_D^{26}$ -1.6° (*c* 0.41, $CHCl_3$). ^1H NMR: δ 4.42 (d, *J*= 7.9 Hz, 1H), 4.18 (dt, *J*= 5.0, 7.9 and 7.9 Hz, 1H), 3.56 (dt, *J*= 7.9 and 7.9 Hz, 1H), 2.94 (dtt, *J*= 2.3, 7.9 and 7.9 Hz,

1H), 2.19-2.08 (m, 1H), 2.07 (dt, *J*= 2.3 and 6.9 Hz, 2H), 1.44 (s, 9H), 1.44-1.21 (m, 10H), 0.88 (t, *J*= 6.9 Hz, 3H). IR (KBr): 3450, 2932, 2858, 2360, 1742, 1458, 1367, 1308, 1250, 1221, 1161, 1099, 988, 920, 845 cm^{-1}. Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.13; H, 10.17.

***tert*-Butyl (2*R*,3*R*)-3-[(*Z*)-1-nonenyl]tetrahydrofuran-2-carboxylate (7)**

To a mixture of ethanol (1.5 mL) and 2*N* aqueous NaOH (80 μL) was added $NaBH_4$ (62.5 mg, 1.7 mmol) at rt. After being stirred for 10 min, the mixture was filtered through a pad of celite. A portion (213 μL) of the filtrate was added dropwise to a suspension of $Ni(OAc)_2{\cdot}4H_2O$ (42.3 mg, 0.17 mmol) in ethanol (4 mL) with vigorous stirring under hydrogen. To this mixture were added ethylenediamine (34 μL, 0.51 mmol) and **15** (200 mg, 0.68 mmol) in ethanol (1.8 mL). After being stirred for 3 h, the mixture was diluted with water and extracted with ethyl acetate. The extract was dried over anhydrous $MgSO_4$ and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 9:1) gave **7** (201 mg, 97%) as an oil. **7**; $[\alpha]_D^{26}$ -73° (*c* 0.91, $CHCl_3$). ^1H NMR: δ 5.51 (dt, *J*= 7.3 and 10.9 Hz, 1H), 5.26 (dd, *J*= 10.9 and 10.9 Hz, 1H), 4.33 (d, *J*= 7.6 Hz, 1H), 4.23 (dt, *J*= 4.6 and 7.9 Hz, 1H), 3.92 (dt, *J*= 7.9 and 7.9 Hz, 1H), 3.39 (dddd, *J*= 7.6, 7.9, 10.9 and 15.8 Hz, 1H), 2.19-2.07 (m, 3H), 1.90 (ddt, *J*= 7.9, 7.9 and 12.2 Hz, 1H), 1.46 (s, 9H), 1.41-1.22 (m, 10H), 0.96 (t, *J*= 6.9 Hz, 3H). IR (KBr): 3466, 2930, 2856, 2365, 1740, 1458, 1367, 1310, 1250, 1159, 1101, 988, 920, 847, 723 cm^{-1}. Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 72.90; H, 10.77.

(1*R*,2*R*,5*R*)-2-Octyl-3,6-dioxabicyclo[3.3.0]octan-4-one (5)

To a solution of ester (**7**)(50 mg, 0.17 mmol) in dichloromethane (0.17 mL) was added trifluoroacetic acid (0.17 mL) at rt. After being stirred for 20 min, the mixture was concentrated under vacuum and diluted with acetonitrile (1.7 mL). To this solution was added iodine (129 mg, 0.51 mmol) at 0 °C and the mixture was left in refrigerator (0 °C) for 20 h. The mixture was decolorized with aqueous $Na_2S_2O_3$ (3 mL) and extracted with ethyl acetate. The extract was dried over anhydrous $MgSO_4$ and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 8:2) gave the corresponding iodolactone (**18**) (54 mg, 87%) as an oil.

Tributyltinhydride (36 μL, 0.14 mmol) and triethylborane (12 μL, 1.0 mol/L in THF) was added to a solution of the above iodolactone (**7**)(45 mg, 0.12 mmol) in benzene (0.25 mL) at rt. After being stirred for 1 h, the mixture was quenched with saturated aqueous solution of KF (0.2 mL). After vigorous stirring for 2 h, the mixture was filtered through a short pad of celite and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 9:1~7:3) gave lactone (**5**) (29 mg, 98%) as an oil. Recrystallization from hexane at 0 °C gave optically pure **5** of >90% ee. **5**; $[\alpha]_D^{18}$ +14.4° (*c* 1.07, $CHCl_3$). mp 47-48 °C. ^1H NMR: δ 4.63 (d, *J*= 7.9 Hz, 1H), 4.25 (dt, *J*= 3.6 and 6.6 Hz, 1H), 4.03 (ddd, *J*= 4.0, 7.6 and 8.9 Hz, 1H), 3.81 (ddd, *J*= 6.6, 8.9 and 8.9 Hz, 1H), 2.81 (ddt, *J*= 3.6, 4.6 and 8.9 Hz, 1H), 2.24 (dddd, *J*= 7.6, 8.9, 8.9 and 12.9 Hz, 1H), 1.91 (dddd, *J*= 4.0, 6.6, 8.9 and 12.9 Hz, 1H), 1.72-1.27 (m, 14H), 0.88 (t, *J*= 6.9 Hz, 3H). IR (KBr): 2920, 2856, 1757, 1472, 1360, 1199, 1086, 995, 957, 937, 901, 189, 719, 629, 536 cm^{-1}. HRFABMS m/z Calcd for $C_{14}H_{24}O_3$ (M^++H): 241.1804. Found 241.1797.

(1*R*,2*R*,5*R*)-2-Octyl-3,6-dioxabicyclo[3.3.0]octane-4,7-dione (3)

To a solution of lactone (**5**)(21.0 mg, 0.087 mmol) in CCl_4 (0.9 mL) and ethyl acetate (0.9 mL) was added Mn_2O_7[13] (0.6 mL, 0.74 mol/L in CCl_4) in portion at 0 °C. The mixture was gradually warmed to rt, filtered through a short pad of celite, and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 9:1~7:3) gave bislactone (**3**) (14.0 mg, 63%) as an oil. **3**; $[\alpha]_D^{25}$ -1.5° (*c* 1.20, $CHCl_3$). ^1H NMR: δ 5.01 (d, *J*= 7.6 Hz, 1H), 4.35 (dt, *J*= 5.3 and 7.6 Hz, 1H), 3.10-3.00 (m, 2H), 2.94 (dd, *J*= 9.2 and 17.8 Hz, 1H), 2.56 (dd, *J*= 3.6 and 17.8 Hz, 1H), 1.80-1.20 (m, 14H), 0.89 (t, *J*= 6.9 Hz, 3H). IR (KBr): 2926, 2856, 1782, 1458, 1246, 1219, 1150, 1076, 1009, 974, 928, 858, 721, 706 cm^{-1}. HRFABMS m/z Calcd for $C_{14}H_{22}O_4$ (M^++H): 255.1596. Found 255.1595.

(1*R*,2*R*,5*R*,9*S*)-2-(1-Hydroxy)-3,6-dioxabicyclo[3.3.0]octan-4-one (22)

To a solution of olefin (**7**)(137 mg, 0.46 mmol) in water (1.8 mL) and acetone (1.8 mL) were added 4-methylmorpholine *N*-oxide (108 mg, 0.92 mmol) and potassium osmate dihydrate (8.5 mg, 0.023 mmol) at rt. After being stirred for 3 h, the mixture was diluted with water, extracted with ethyl acetate, dried over $MgSO_4$, and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 7:3) to give a diastereomeric mixture of diols (**19**) and (**20**) (**19**: **20**= 3.3:1) (110 mg, 72%) as an oil, which was used for the following reaction without separation.

Trifluoroacetic acid was added to the above diastereomeric mixture of diols (**19**) and (**20**) (110 mg, 0.33 mmol) at rt. After being stirred for 1 h, the mixture was concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 7:3~6:4~1:1) gave lactone (**22**) (50 mg, 59%) as an oil. The six membered lactone (**23**) could be converted into lactone (**22**) (**22**: **23**=1.5:1) by treated with CSA (0.1 eq.) in dichloromethane at rt for 6 h. **22**; $[\alpha]_D^{26}$ -40° (*c* 0.91, $CHCl_3$). ^1H NMR: δ 4.77 (d, *J*= 7.9 Hz, 1H), 4.30 (dd, *J*= 5.6 and 7.9 Hz, 1H), 3.95 (dd, *J*= 5.9 and 7.9 Hz, 2H), 3.82 (ddd, *J*= 3.0 7.9 and 7.9 Hz, 1H), 3.22 (ddt, 5.6, 7.9 and 7.9 Hz, 1H), 2.26-2.06 (m, 2H), 2.00-1.20 (m, 12H), 0.89 (t, *J*= 6.9 Hz, 3H). IR (KBr): 3450, 2955, 2928, 2856, 1773, 1647, 1458, 1207, 1086, 1009, 974, 766, 723 cm^{-1}. HRFABMS m/z Calcd for $C_{14}H_{22}O_4$ (M^++H): 257.1753. Found 257.1754.

(1*R*,2*S*,5*R*)-2-Octyl-3,6-dioxabicyclo[3.3.0]octan-4-one (6)

Thiocarbonyldiimidazole (120 mg, 1.34 mmol) was added to a solution of alcohol (**22**) (78 mg, 0.30 mmol) in dichloroethane (1.6 mL) at rt and gradually raised to 70 °C. After being stirred for 12 h at the temperature, the mixture was cooled and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 7:3) gave the corresponding thiocarbonylimidazolide (97 mg, 87%) as an oil.

To a refluxing solution of *n*-BuSnH (110 μL, 0.41 mmol) in toluene (17 mL) was added dropwise a solution of the above thiocarbonylimidazolide (97 mg, 4.2 mmol) in toluene (4.2 mL) over a period of 30 min. The mixture was concentrated and subjected to silica gel chromatography (hexane-ethyl acetate = 1:1) to give lactone (**6**) (53 mg, 83%) as an oil. **6**; $[\alpha]_D^{18}$ -40° (*c* 0.43, $CHCl_3$). ^1H NMR: δ 4.76 (d, *J*= 8.3 Hz, 1H), 4.53 (dt, *J*= 5.6 and 8.3 Hz, 1H), 4.00-3.88 (m, 2H), 3.10 (ddt, *J*= 5.6, 8.3 and 8.3 Hz, 1H), 2.02-1.93 (m, 2H), 1.89-1.27 (m, 14H), 0.89 (t, *J*= 6.9 Hz, 3H). IR (KBr): 2928, 2856, 1782, 1466,

1348, 1200, 1088, 972, 806, 750, 723 cm^{-1}. HRFABMS m/z Calcd for $C_{14}H_{25}O_3$ (M^++H): 241.1804. Found 241.1804.

(1*R*,2*S*,5*R*)-2-Octyl-3,6-dioxabicyclo[3.3.0]octane-4,7-dione (4)

To a solution of lactone(**6**)(52 mg, 0.22 mmol) in CCl_4 (2.2 mL) and ethyl acetate (2.2 mL) was added Mn_2O_7[13] (1.5 mL, 0.74 mol/L in CCl_4) dropwise at 0 °C. The mixture was gradually raised to rt, filtered through a short pad of celite, and concentrated. Silica gel chromatography of the residue (hexane-ethyl acetate = 7:3) gave bislactone (**4**) (34 mg, 62%) as colorless crystals. Recrystallization from hexane-ethyl acetate gave optically pure **4** of >90% ee. **4**; $[\alpha]_D^{26}$ -20.7° (*c* 1.2, $CHCl_3$). mp 110-111 °C. ^{1}H NMR: δ 5.17 (d, *J*= 8.3 Hz, 1H), 4.62 (dt, *J*= 5.6 and 8.6 Hz, 1H), 3.48 (ddd, *J*= 5.6, 9.6 and 17.8 Hz, 1H), 2.64 (d, *J*= 9.6 Hz, 2H), 1.87-1.28 (m, 14H), 0.89 (t, *J*= 6.9 Hz, 3H). IR (KBr): 2922, 1776, 1717, 1468, 1294, 1217, 1163, 1063, 943, 914, 872, 804, 725, 646, 555 cm^{-1}. HRFABMS m/z Calcd for $C_{14}H_{23}O_4$ (M^++H): 255.1596. Found 255.1597.

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