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CONSTRUCTION OF OPTICALLY ACTIVE SPIROKETAL BY DIRECT ALDOL REACTION

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Abstract – Novel preparation of symmetric spiroketal was developed by the use of direct aldol reaction of α-hydroxyacetophenone catalyzed by chiral dinuclear zinc catalyst. The spiroketal was obtained in excellent enantiomeric excess.

INTRODUCTION

Natural compounds often have cleverly designed skeletons to show biological activities. Spiroketal is one of the most important skeletons and is often contained in biologically active compounds.[1] Spiroketal is can be prepared by acid-catalyzed cyclization of keto diol.[1] Therefore, the preparation of a keto diol compound as an optically active form is important for the asymmetric synthesis of spiroketal. Didemnaketal (**1**), isolated from the ascidian of the genus *Didemnum*, contains a spiroketal moiety and has been recognized as a potent inhibitor of HIV-protease.[2] The spiroketal moiety of didemnaketal has a symmetric structural feature and there are two oxygenated functional groups on the carbon apart from the spiroketal moiety as shown in Figure 1. For the preparation of the spiroketal moiety of didemnaketal, we proposed a convenient and atom-economical strategy,[3] which enables construction of four chiral centers bearing a hydroxyl group at the same time by catalytic enantioselective direct aldol reaction of hydroxymethyl ketone.[4-6] Direct aldol reaction of a hydroxymethyl ketone to a keto dial could provide an optically active keto tetraol, which can be converted to spiroketal by acid-catalyzed cyclization (Scheme 1). We employed the chiral dinuclear zinc catalyst (**3**) for the direct aldol reaction developed by Trost *et al.* (Figure 2).[4,7] In this paper, our effort towards the development of a short constructive method of optically active spiroketals by the direct aldol reaction of hydroxymethyl ketones with achiral keto dial derivatives is reported.

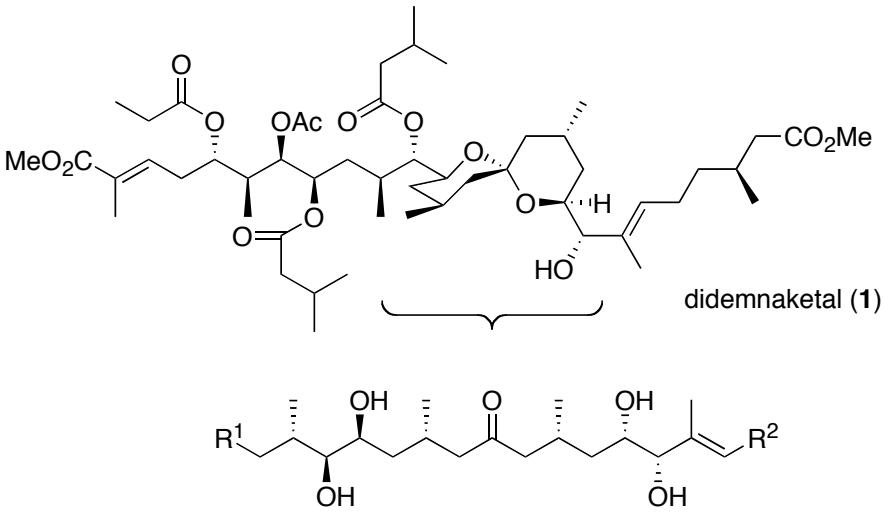
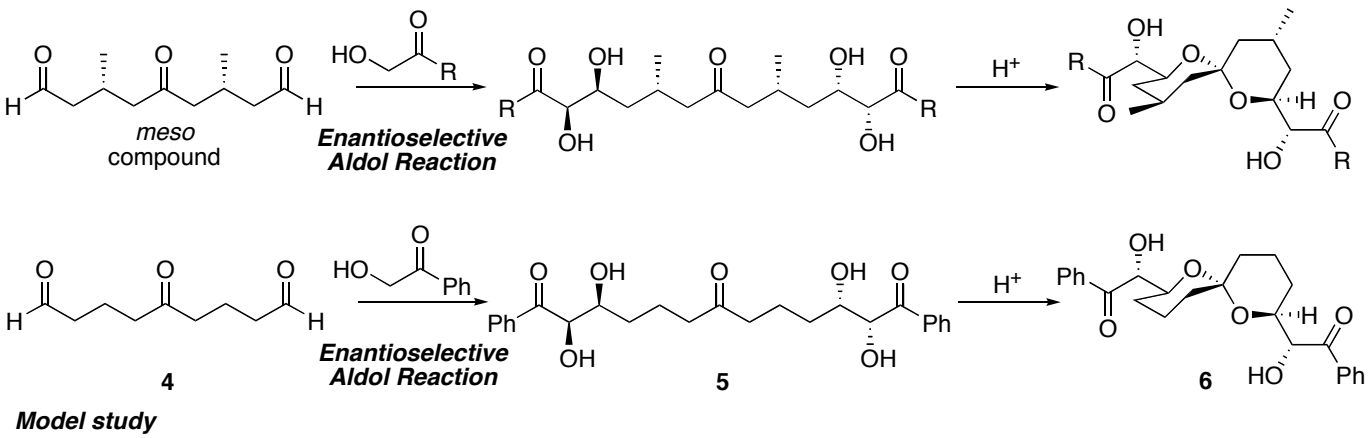


Figure 1.



Scheme 1.

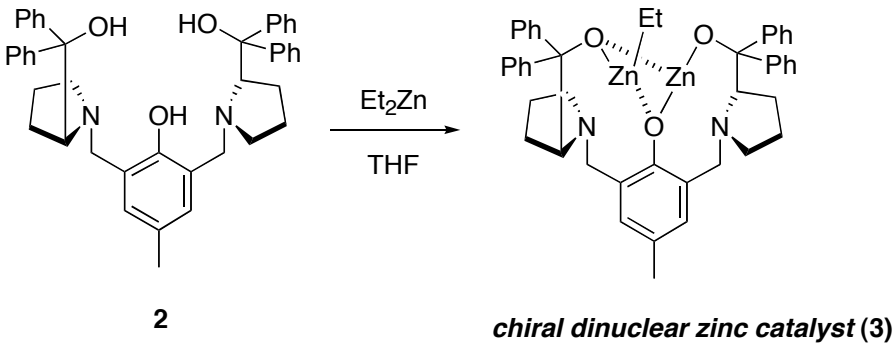
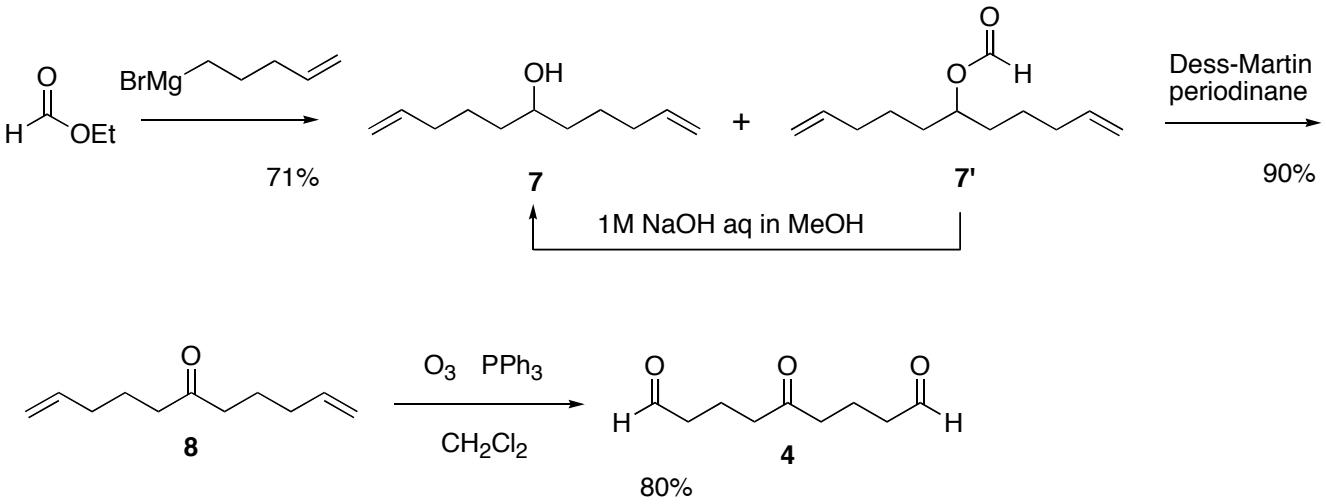


Figure 2.

RESULTS AND DISCUSSION

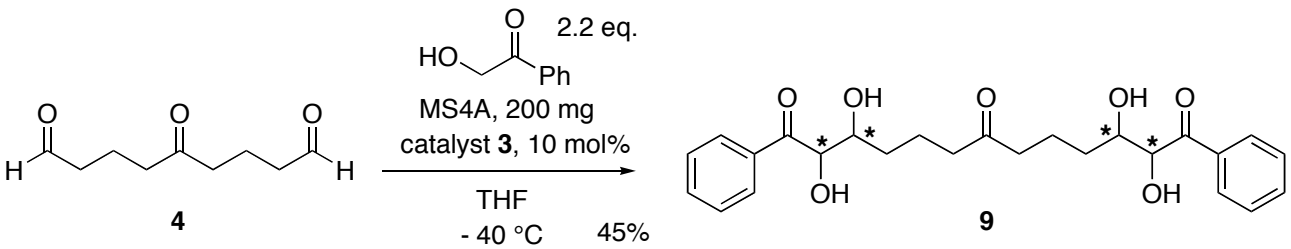
The model study for the construction of an optically active spiroketal is shown in Scheme 1. For the synthesis of the spiroketal moiety of didemnaketal, it is required to prepare the *meso*-keto dial. We

employed 5-oxo-1,9-nonanedial (**4**) prior to the reaction of *meso*-keto dial as an achiral keto dial for the examination of the direct aldol reaction. 5-Oxo-1,9-nonanedial (**4**) was prepared as shown in Scheme 2. Reaction of 5-pentenylmagnesium bromide with ethyl formate gave compound (**7**) along with formate (**7'**) which could be converted to **7** by alkaline hydrolysis. Oxidation of **7** with Dess-Martin periodinane (90%) and following ozonolysis of both of the terminal carbon-carbon double bonds of **8** gave the substrate (**4**) in 80% yield.



Scheme 2.

Enantioselective direct aldol reaction of compound (**4**) catalyzed by dinuclear zinc catalyst (**3**) was examined. 2-Hydroxyacetophenone (2.2 equivalent) was employed as a nucleophile. The ligand (**2**) was prepared from unnatural proline according to the reported procedure.[7] Trost et al. reported that the use of 2.5 mol% of catalyst achieved higher diastereo- and enantioselectivity along with a slight decrease of the yield than those with the use of 5 mol% of catalyst in the case of the reaction of 2-hydroxyacetophenone with 3-phenylpropionaldehyde.[4] In the case of our substrate (**4**), however, the reaction did not proceed at –20 °C in the presence of 2.5 mol% or 5 mol% of the catalyst. Under the presence of 10 mol% of catalyst (**3**), enantioselective aldol reaction of 2-hydroxyacetophenone to both aldehydes of **4** proceeded at –40 °C, and **9** was obtained in 45% yield as a diastereomeric mixture.



Scheme 3.

The diastereoselectivity (*syn* : *anti*) of the direct aldol reaction was determined by comparison of the spectral data. In the ^{1}H NMR spectral study of α,β-dihydroxy ketones, the proton chemical shift of the α position of the carbonyl group between both diastereomers showed significant difference as shown in Figure 3. The chemical shift of the α-proton of *syn* diastereomers and anti diastereomers of the representative α,β-dihydroxyketones showed 4.95-5.00 ppm and 5.22-5.24 ppm, respectively.[4] Two resonances at 4.97 and 5.20 ppm were observed in the ^{1}H NMR spectrum of the diastereomeric mixture of compound (**9**). Therefore, we determined that the resonance of 4.97 ppm was due to the *syn* diol and 5.20 was *anti* diol, and the diastereoselectivity of the direct aldol reaction was indicated as 2 : 1 (predominant stereochemistry of the dihydroxyl group was *syn*).

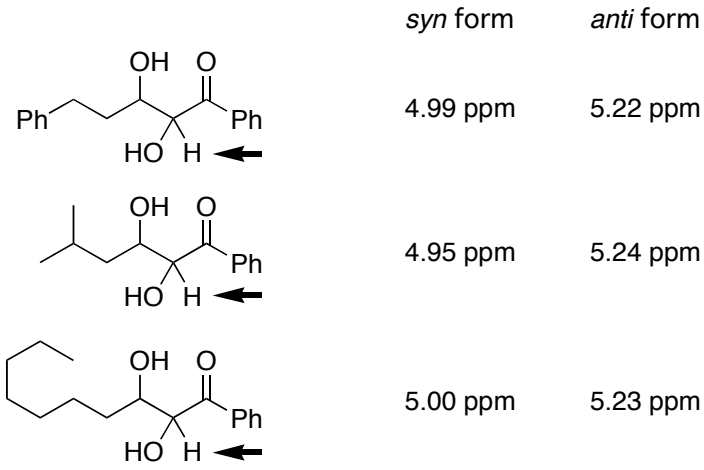
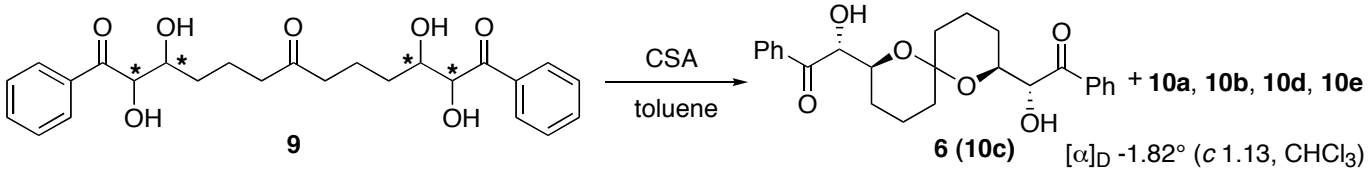


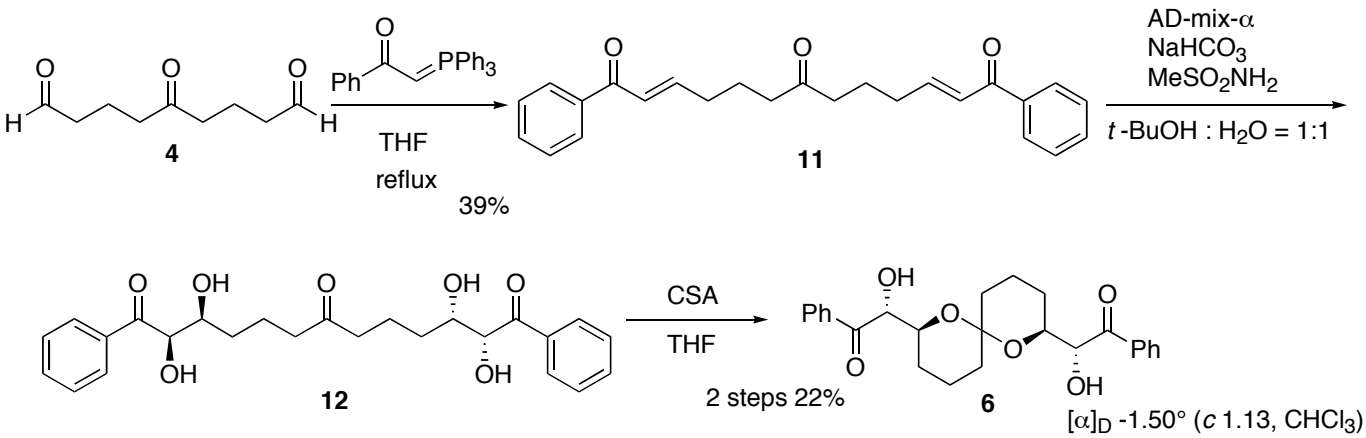
Figure 3. The chemical shifts of the α-proton of α,β-dihydroxy ketones reported by Trost *et al.*[4]

The formation of spiroketal from keto tetraol (**9**) was performed under an acid-catalyzed condition (Scheme 4). Camphorsulfonic acid (10 mol%)-catalyzed cyclization in toluene proceeded to give spiroketals as a diastereomeric mixture in 64% yield and five diastereomers (**10a**-**10e**) (1 : 1 : 2 : 1.2 : 1, as an elution order) could be isolated by HPLC separation. ^{1}H NMR spectra indicated that two spiroketals (**10b**) and (**10c** (**6**)) have symmetric structures. Enantiomeric excess of compound (**10c** (**6**)) was 96% ee, which was determined by chiral HPLC analysis (chiralcel OD-H).



Scheme 4.

As mentioned above, five isomers of spiroketal were isolated. For determination of the absolute stereochemistry, the desired spiroketal (**6**) was synthesized by an alternative route through asymmetric dihydroxylation.[8] The substrate (**11**) was prepared by Wittig reaction of 2-(triphenylphosphoranylidene)acetophenone with compound (**4**) as shown in Scheme 5. Enantioselective dihydroxylation of both carbon-carbon double bonds of **11** was performed by the use of AD-mix-α.[9] The reaction proceeded to give tetraol derivative (**12**) which was converted to spiroketal (**6**) by the treatment with (+)-(*S*)-camphor-10-sulfonic acid in THF (2 steps 22% yield, 96% ee). NMR spectra and $[\alpha]_D$ value of **6** were identical with those of **10c** prepared by the direct aldol reaction.



Scheme 5.

CONCLUSION

A model study for the construction of the optically active spiroketal moiety of didemnaketal and a development of a simple and atom-economical preparative method was examined. The optical purity of spiroketal (**6**) prepared by the direct aldol reaction was excellent (96% ee).

EXPERIMENTAL

All reactions were carried out under an argon atmosphere. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AV-300 and the chemical shifts are given in ppm using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for ^{1}H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR as an internal standard, respectively. IR spectra were taken with a Perkin-Elmer PARAGON 1000 FT-IR and only noteworthy absorption was listed. Mass spectra were measured on a Micromass LCT.

6-Hydroxy-1,10-undecadiene (7):[10] To a solution of 4-pentenylmagnesium bromide, prepared from 5-bromopentene (7.9 mL, 67.1 mmol) with magnesium (1.96 g, 80.5 mmol), in THF (35 mL) was added ethyl formate (3.2 mL, 40.3 mmol) at 0 °C and the resulting mixture was stirred at ambient temperature for 15 h. Saturated aqueous ammonium chloride was added to the reaction mixture and the mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. Methanol (35 mL) and 1M NaOH (3.5 mL, 3.5 mmol) were added to the residue and the mixture was stirred at ambient temperature for 15 h. The mixture was concentrated under vacuum and water was added to the residue. The mixture was extracted with ether and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography (hexane : AcOEt = 5 : 1) to afford **7** as a colorless oil (4.8 g, 28.8 mmol) in 71% yield. IR (neat) νcm^{-1}; 3351, 3077, 2933, 1641, 994, 990. ^{1}H NMR (300 MHz, $CDCl_3$) δ; 5.81 (ddt, J = 16.9, 10.3, 6.6 Hz, 2H), 5.00 (d, J = 16.9 Hz, 2H), 4.95 (d, J = 10.3 Hz, 2H), 3.61 (brs, 1H), 2.14-2.04 (m, 4H), 1.60-1.38 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 138.7, 114.6, 71.7, 36.9, 33.7, 24.9.

1,10-Undecadien-6-one (8): Dess-Martin periodinane (12.4 g, 29.2 mmol) was added to a solution of **7** (4.84 g, 28.8 mmol) in CH_2Cl_2 (100 mL) at ambient temperature and the mixture was stirred at the same temperature for 1 h. 10% Aqueous sodium thiosulfate was added to the reaction mixture and the mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography (hexane : AcOEt = 15 : 1) to afford **8** as a colorless oil (4.3 g, 26 mmol) in 90% yield. IR (neat) νcm^{-1}; 3077, 2936, 1715, 1640, 995, 912. ^{1}H NMR (300 MHz, $CDCl_3$) δ; 5.75 (ddt, J = 17.1, 10.3, 6.7 Hz, 2H), 4.99 (d, J = 17.1 Hz, 2H), 4.95 (d, J = 10.3 Hz, 2H), 2.39 (t, J = 7.4 Hz, 4H), 2.04 (q, J = 7.4 Hz, 4H), 1.66 (quint, J = 7.4 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 210.8, 138.0, 115.1, 41.9, 33.1, 22.8. HRESIMS calcd for $C_{11}H_{19}O$: 167.1436 $(M+H)^+$, found: 167.1409.

5-Oxononanedial (4): Ozone gas was introduced to a solution of **8** (1.0 g, 6.0 mmol) in CH_2Cl_2 (20 mL) at –78 °C for 4 h (reaction was monitored by TLC). After the reaction completed, a solution of triphenylphosphine (4.7 g, 18 mmol) in CH_2Cl_2 (25 mL) was added to the reaction mixture at –78 °C and the mixture was stirred at ambient temperature for 15 h. The solvent was removed under vacuum and the residue was purified by column chromatography (AcOEt) to afford **4** as a colorless oil (819 mg, 4.8 mmol) in 80% yield. IR (neat) νcm^{-1}; 2934, 1716. ^{1}H NMR (300 MHz, $CDCl_3$) δ; 9.74 (t, J = 1.3 Hz, 2H), 2.47 (td, J = 7.0, 1.3 Hz, 4H), 2.45 (t, J = 7.0 Hz, 4H), 1.87 (quint, J = 7.0 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 209.2, 201.8, 42.9, 41.3, 15.9. HRESIMS calcd for $C_9H_{15}O_3$: 171.1021 $(M+H)^+$, found: 171.1036.

Preparation of dinuclear zinc catalyst (3). To a solution of ligand (**2**) (31.9 mg, 0.05 mmol) in THF (0.5 mL) was added to a solution of diethylzinc (1 M in hexane, 0.1 mL, 0.1 mmol) at ambient

temperature and the mixture was stirred at the same temperature for 30 min to obtain the catalyst (**3**) as 0.1M solution in THF.

1,13-Diphenyl-2,3,11,12-tetrahydroxytrideca-1,7,13-trione (9): A solution of catalyst (**3**) in THF (0.1 M in THF, 0.29 mL, 0.029 mmol) was added to the mixture of 2-hydroxyacetophenone (88.1 mg, 0.65 mmol), **4** (50 mg, 0.29 mmol), and dried powdered MS 4A (200 mg) in THF (1 mL) at –40 °C and the mixture was stirred at the same temperature for 15 h. Saturated aqueous ammonium chloride was added to the mixture and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography (hexane : AcOEt = 2 : 1) to afford **9** as a colorless oil (diastereomeric mixture, 57 mg, 0.13 mmol) in 44% yield. IR (neat) νcm^{-1}; 3436, 2947, 1701, 1685, 1676, 1598, 1560, 1542, 1449, 1272, 1074. ^1H NMR (300 MHz, $CDCl_3$) δ; 7.98-7.85 (m, 4H), 7.66-7.59 (m, 2H), 7.56-7.47 (m, 4H), 5.23-5.18 (m, 0.7H), 5.00-4.94 (m, 1.3H), 3.96-3.76 (m, 6H), 2.51-2.17 (m, 4H), 1.97-1.00 (m, 8H). HRESIMS calcd for $C_{25}H_{28}O_6Na$: 447.1737 $(M-H_2O+Na)^+$, found: 447.1791.

2,8-Bis(1-hydroxy-2-oxo-2-phenylethyl)-1,7-dioxaspiro[5.5]undecane (10): To a solution of **9** (10 mg, 0.022 mmol) in toluene (3 mL) was added (+)-(*S*)-camphor-10-sulfonic acid (0.56 mg, 0.0022 mmol) and the mixture was stirred at ambient temperature for 30 min. The mixture was concentrated under vacuum and the residue was purified by column chromatography (hexane : AcOEt = 2 : 1) to afford compound (**10**) as a white solid (diastereomeric mixture, 6.2 mg, 0.014 mmol) in 64% yield. The diasteremeric mixture was purified again by HPLC (hexane : isopropanol = 10 : 1) to afford five isomers. **10-a** (1.0 mg): Colorless crystals. mp 168-172°C (ether). IR (KBr) νcm^{-1}; 3469, 2946, 1686, 1560, 1542, 1458, 1285, 1109. ^1H NMR (300 MHz, $CDCl_3$) δ; 7.90 (d, J = 7.4 Hz, 2H), 7.87 (d, J = 7.4 Hz, 2H), 7.75 (t, J = 7.4 Hz, 1H), 7.66 (t, J = 7.4 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 4.88 (dd, J = 7.2, 2.7 Hz, 1H), 4.56 (dd, J = 9.2, 8.3 Hz, 1H), 3.75 (d, J = 7.2 Hz, 1H), 3.54 (dt, J = 11.7, 2.7 Hz, 1H), 2.58 (d, J = 9.2 Hz, 1H), 2.23 (ddd, J = 11.3, 8.3, 2.4 Hz, 1H), 1.66-1.42 (m, 4H), 1.32-1.03 (m, 5H), 0.91-0.82 (m, 2H), 0.51-0.41 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 201.9, 199.7, 136.0, 134.5, 133.7, 133.6, 129.3, 128.9, 128.4, 128.2, 96.5, 75.4, 74.5, 72.6, 70.8, 34.2, 29.7, 28.3, 25.3, 17.8, 17.0. HRESIMS calcd for $C_{25}H_{28}O_6Na$: 447.1784 $(M+Na)^+$, found: 447.1785. Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.75; H, 6.60. **10-b** (1.0 mg): Colorless crystals. mp 155-158 °C (ether). IR (KBr) νcm^{-1}; 3470, 2916, 1677, 1598, 1560, 1542, 1426, 1271, 1102. ^1H NMR (300 MHz, $CDCl_3$) δ; 7.73 (dt, J = 7.4, 1.3 Hz, 4H), 7.61 (tt, J = 7.4, 1.3 Hz, 2H), 7.47 (t, J = 7.4 Hz, 4H), 4.92 (dd, J = 7.5, 6.4 Hz, 2H), 3.54 (d, J = 7.5 Hz, 2H), 3.26 (ddd, J = 10.8, 6.4, 2.3 Hz, 2H), 1.44-1.34 (m, 4H), 1.32-1.16 (m, 6H), 0.91-0.78 (m, 2H) ^{13}C NMR (75 MHz, $CDCl_3$) δ; 201.7, 135.3, 133.8, 128.8, 128.6, 97.0, 74.9, 72.4, 34.7, 26.0, 17.4. HRESIMS calcd for $C_{25}H_{28}O_6Na$: 447.1784 $(M+Na)^+$, found: 447.1800. Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.84; H, 6.51. **10-c (6)** (2.0 mg): Colorless crystals. mp 152-156 °C (ether).

$[\alpha]_D^{25}$ -1.82° (*c* 1.13, $CHCl_3$, 96% ee). IR (KBr) νcm^{-1}; 3424, 2957, 1686, 1664, 1598, 1560, 1542, 1458, 1269, 1123. ^{1}H NMR (300 MHz, $CDCl_3$) *δ*; 7.86 (dt, *J* = 7.4, 1.3 Hz, 4H), 7.61 (tt, *J* = 7.4, 1.3 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 4H), 4.74 (dd, *J* = 7.6, 3.5 Hz, 2H), 3.42 (d, *J* = 7.6 Hz, 2H), 3.40 (dt, *J* = 10.4, 3.5 Hz, 2H), 1.70-1.52 (m, 2H), 1.49-1.20 (m, 8H), 1.09 (td, *J* = 13.2, 4.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*; 200.2, 135.1, 133.8, 128.7, 128.5, 96.6, 75.0 70.9, 34.6, 25.6, 17.8. HRESIMS calcd for $C_{25}H_{28}O_6Na$: 447.1784 $(M+Na)^+$, found: 447.1806. Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.55; H, 6.59. **10-d** (1.2 mg): White crystals. mp 130-131 °C (hexane-AcOEt). IR (KBr) νcm^{-1}; 3468, 2953, 1685, 1676, 1599, 1578, 1560, 1449, 1274, 1114. ^{1}H NMR (300 MHz, $CDCl_3$) *δ*; 7.93 (dt, *J* = 7.4, 1.3 Hz, 2H), 7.77 (d, *J* = 7.4, 1.3 Hz, 2H), 7.65 (tt, *J* = 7.4 , 1.3 Hz, 1H), 7.62-7.45 (m, 3H), 7.40 (t, *J* = 7.4 Hz, 2H), 4.86 (dd, *J* = 7.4, 3.2 Hz, 1H), 4.72 (dd, *J* = 7.7, 6.5 Hz, 1H), 3.77 (dt, *J* = 10.4, 3.2 Hz, 1H), 3.58 (d, *J* = 7.4 Hz, 1H), 3.41 (ddd, *J* = 11.1, 6.5, 2.3 Hz, 1H), 3.12 (d, *J* = 7.7 Hz, 1H), 1.82-1.55 (m, 4H), 1.42-1.19 (m, 6H), 1.01-0.82 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*; 201.9, 200.6, 135.3, 133.9, 133.5, 128.9, 128.8, 128.5, 128.4, 98.3, 77.2, 75.5, 74.8, 71.1, 34.1, 29.5, 25.7, 25.5, 17.9, 17.2. HRESIMS calcd for $C_{25}H_{28}O_6Na$: 447.1784 $(M+Na)^+$, found: 447.1812. Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.66; H, 6.68. **10-e** (1.0 mg): White crystals. mp 143-146 °C (hexane-AcOEt). IR (KBr) νcm^{-1}; 3468, 2947, 1685, 1598, 1560, 1542, 1449, 1274, 1131. ^{1}H NMR (300 MHz, $CDCl_3$) *δ*; 8.0 (dt, *J* = 6.8, 1.5 Hz, 2H), 7.79-7.67 (m, 3H), 7.48 (tt, *J* = 6.8, 1.5 Hz, 1H), 7.42 (dt, *J* = 6.8, 1.5 Hz, 2H), 7.32-7.24 (m, 2H), 5.15 (dd, *J* = 6.1, 3.2 Hz, 1H), 4.93 (dd, *J* = 7.1, 2.8 Hz, 1H), 4.09 (dt, *J* = 12.0, 2.8 Hz, 1H), 3.93 (d, *J* = 7.1 Hz, 1H), 3.88(dt, *J* = 11.5, 2.8 Hz, 1H), 3.66 (d, *J* = 6.1 Hz, 1H), 1.96-1.68 (m, 3H), 1.65-1.20 (m, 5H), 1.01-0.88 (m, 2H), 0.76-0.68 (m, 1H), 0.13- -0.05 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*; 200.1, 198.7, 134.4, 134.2, 133.6, 129.1, 128.8, 128.7, 128.0, 98.7, 76.3, 75.4, 74.1, 71.5, 35.0, 27.3, 25.5, 22.7, 19.3, 16.2. HRESIMS calcd for $C_{25}H_{28}O_6Na$: 447.1784 $(M+Na)^+$, found: 447.1814. Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.87; H, 6.43.

1,13-Diphenyl-2,11-tridecadiene-1,7,13-trione (11): To a solution of **4** (200 mg, 1.17 mmol) in THF (5 mL) was added 2-(triphenylphosphoranylidene)acetophenone (983.5 mg, 2.6 mmol) and the mixture was stirred under reflux for 15 h. The mixture was concentrated under vacuum and the residue was purified by column chromatography (hexane : AcOEt = 3 : 1) to afford **11** (173 mg, 0.46 mmol) in 39% yield. Colorless crystals. mp 60-62 °C (ether). IR (KBr) νcm^{-1}; 2931, 1709, 1666, 1617, 1578, 1560, 1542, 1448, 979. ^{1}H NMR (300 MHz, $CDCl_3$) *δ*; 7.92 (d, *J* = 7.2 Hz, 4H), 7.56 (t, *J* = 7.2 Hz, 2H), 7.46 (t, *J* = 7.2 Hz, 4H), 7.01 (dt, *J* = 15.4, 7.2 Hz, 2H), 6.89 (d, *J* = 15.4 Hz, 2H), 2.48 (t, *J* = 7.2 Hz, 4H), 2.33 (q, *J* = 7.2 Hz, 4H), 1.83 (quint, *J* = 7.2 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*; 209.5, 190.6, 148.4, 137.8, 132.7, 128.52, 128.50, 126.4, 41.8, 32.0, 22.0. HRESIMS calcd for $C_{25}H_{27}O_3$: 375.1960 $(M+H)^+$, found: 375.1953. Anal. Calcd for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found: C, 80.26; H, 6.99.

(1'*R*,1''*R*,2*S*,8*S*)-2,8-Bis(1-hydroxy-2-oxo-2-phenylethyl)-1,7-dioxaspiro[5.5]undecane (6): A solution of **11** (60 mg, 0.14 mmol) in *t*-butanol (0.34 mL) was added to the suspension of AD-mix-α (410 mg), methanesulfonamide (27.2 mg, 0.28 mmol), and $NaHCO_3$ (62.5 mg, 0.74 mmol) in *t*-butanol (0.68 mL) and the mixture was stirred at ambient temperature for 15 h. AD-mix-α (205 mg) was added to the mixture and the mixture was stirred at the same temperature for further 7 h. Saturated $NaHCO_3$ solution (5 mL) was added to the mixture and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum to afford **12**, which was used for the next step without further purification. To a solution of **12** in THF (5 mL) was added a catalytic amount of (+)-(*S*)-camphor-10-sulfonic acid and the mixture was stirred at ambient temperature for 1 h and at 50 °C for 30 min. The mixture was concentrated under vacuum and the residue was purified by column chromatography (hexane : AcOEt = 1 : 1) to afford **6** (13 mg, 0.03 mmol) in 22% yield. Colorless crystals. mp 140-143 °C (ether). $[\alpha]_D^{25}$ –1.50° (*c* 1.13, $CHCl_3$). IR (KBr) νcm^{-1}; 3424, 2957, 1686, 1664, 1598, 1560, 1542, 1458, 1269, 1123. ^{1}H NMR (300 MHz, $CDCl_3$) δ; 7.86 (dt, *J* = 7.4, 1.3 Hz, 4H), 7.61 (tt, *J* = 7.4, 1.3 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 4H), 4.74 (dd, *J* = 7.6, 3.5 Hz, 2H), 3.42 (d, *J* = 7.6 Hz, 2H), 3.40 (dt, *J* = 10.4, 3.5 Hz, 2H), 1.70-1.52 (m, 2H), 1.49-1.20 (m, 8H), 1.09 (td, *J* = 13.2, 4.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 200.2, 135.1, 133.8, 128.7, 128.5, 96.6, 75.0 70.9, 34.6, 25.6, 17.8. HRESIMS calcd for $C_{25}H_{28}O_6Na$: 447.1784 $(M+ Na)^+$, found: 447.1743. Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.82; H, 6.44.

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