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SYNTHETIC STUDY ON CLUTIOLIDE BASED ON A REMOTE CHELATION CONTROLLED IRELAND-CLAISEN REARRANGEMENT†

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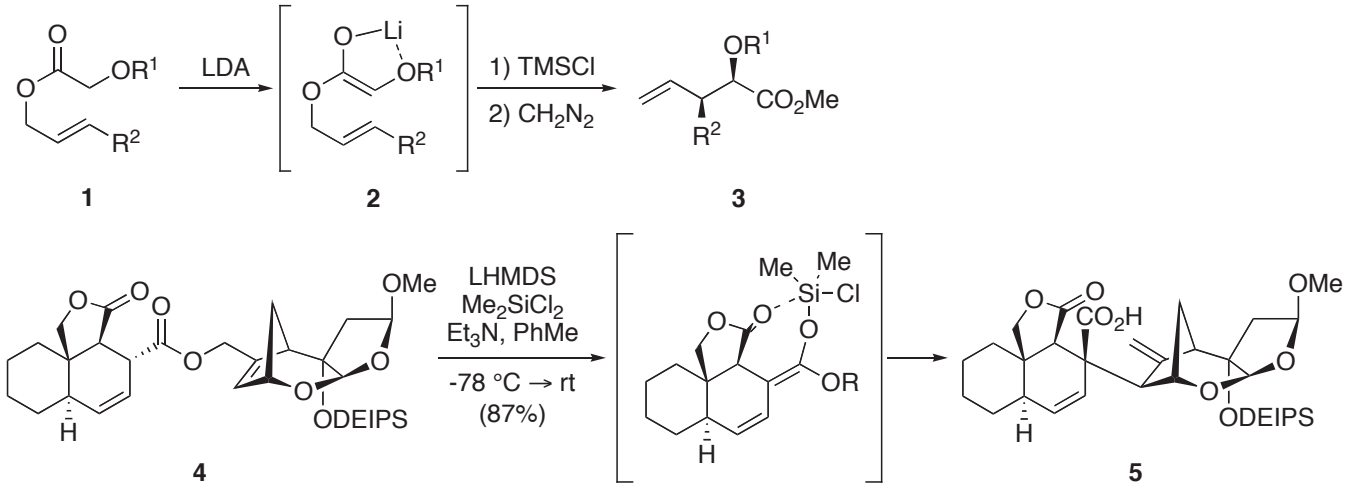
Abstract – A methodology feasible for the stereoselective synthesis of clutiolide, a secolabdane diterpene from *Clutia abyssinica,* was developed based on a remote chelation controlled Ireland-Claisen rearrangement.

INTRODUCTION

The Ireland-Claisen rearrangement often proceeds in high stereoselectivity in consequence of the reaction process via a chairlike transition state. In particular, Claisen rearrangement of protected allylic glycolates **1** affords the *syn*-products **3** in high stereoselectivity via a chelated lithium enolate **2** with *E*-geometry (Scheme 1).[1)] The chelated enolates derived from amino acid esters also undergo Claisen rearrangement in highly diastereoselective fashion.[2)]



Scheme 1. Chelation controlled Ireland-Claisen Rearrangement

†This paper is dedicated to the 80th birthday of Professor Emeritus Akira Suzuki on the occasion of his 80th birthday.

Previously, we reported that Ireland-Claisen rearrangement of **4** using LHMDS, Me_2SiCl_2, and Et_3N in toluene proceeded stereoselectively. To explain the observed high stereoselectivity, we proposed the reaction mechanism where the coordination of the silyl group to the lactone carbonyl at the γ-position controlled the geometry of the silyl ketene acetal and we referred this reaction as a remote chelation controlled Ireland-Claisen rearrangement.[3] To further demonstrate the synthetic utility of this methodology, we attempted to synthesize clutiolide (**6**).

The shrub *Clutia abyssinica* is distributed to the dry regions of Africa. Extracts of the aerial parts are popularly used to treat skin diseases and its root is used for the kidney cleansing as well as the extermination of roundworms. There are several characteristic secolabdane diterpenes isolated from the genus *Clutia*, namely clutiolide (**6**),[4a] dihydroclutiolide,[4a] isodihydroclutiolide,[4a] saudin,[4b] cluytene A[4c] and richardianidin-1 and 2[4d] *etc*. (Figure 1). This family of compounds has attracted much attention as a target for synthesis because of their intriguing molecular architectures and biological activities. For example, saudin was known to possess a significant hypoglycemic effect in nonalloxanized, rather than alloxanized fasting mice.[5,6] Clutiolide (**6**) were isolated from *Clutia abyssinica* by Euerby *et al*. in 1990 and structurally consists of a bicylic lactone and a δ-lactone attached to the furan moiety. Here we describe the study toward the synthesis of clutiolide (**6**) by taking advantage of our remote chelation controlled Ireland-Claisen rearrangement which we have previously developed.

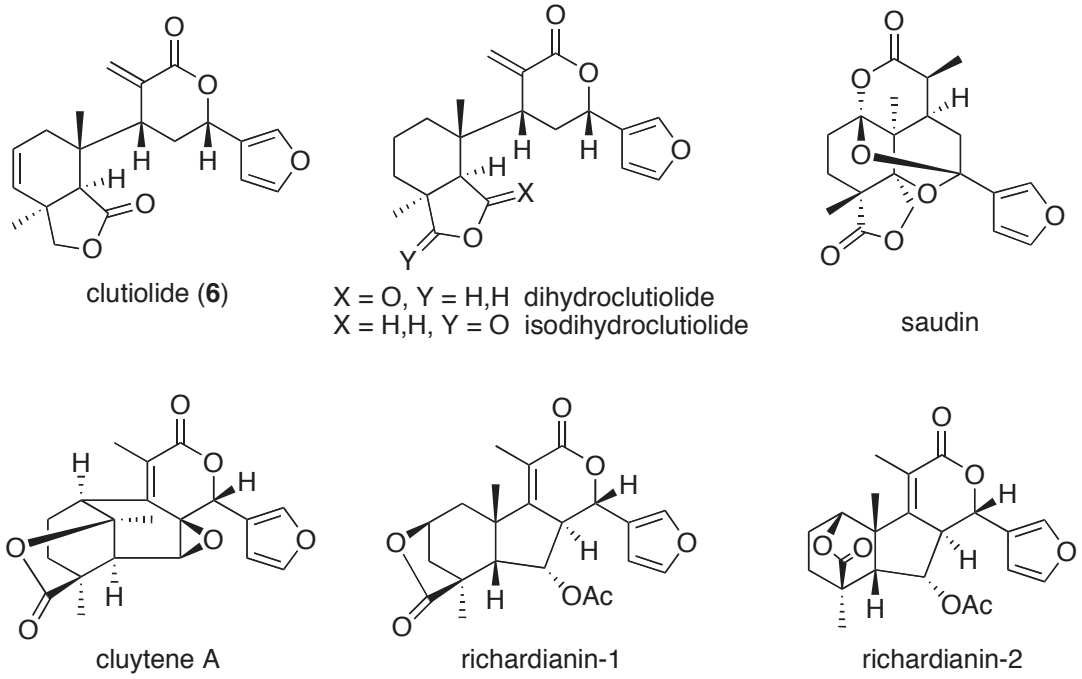
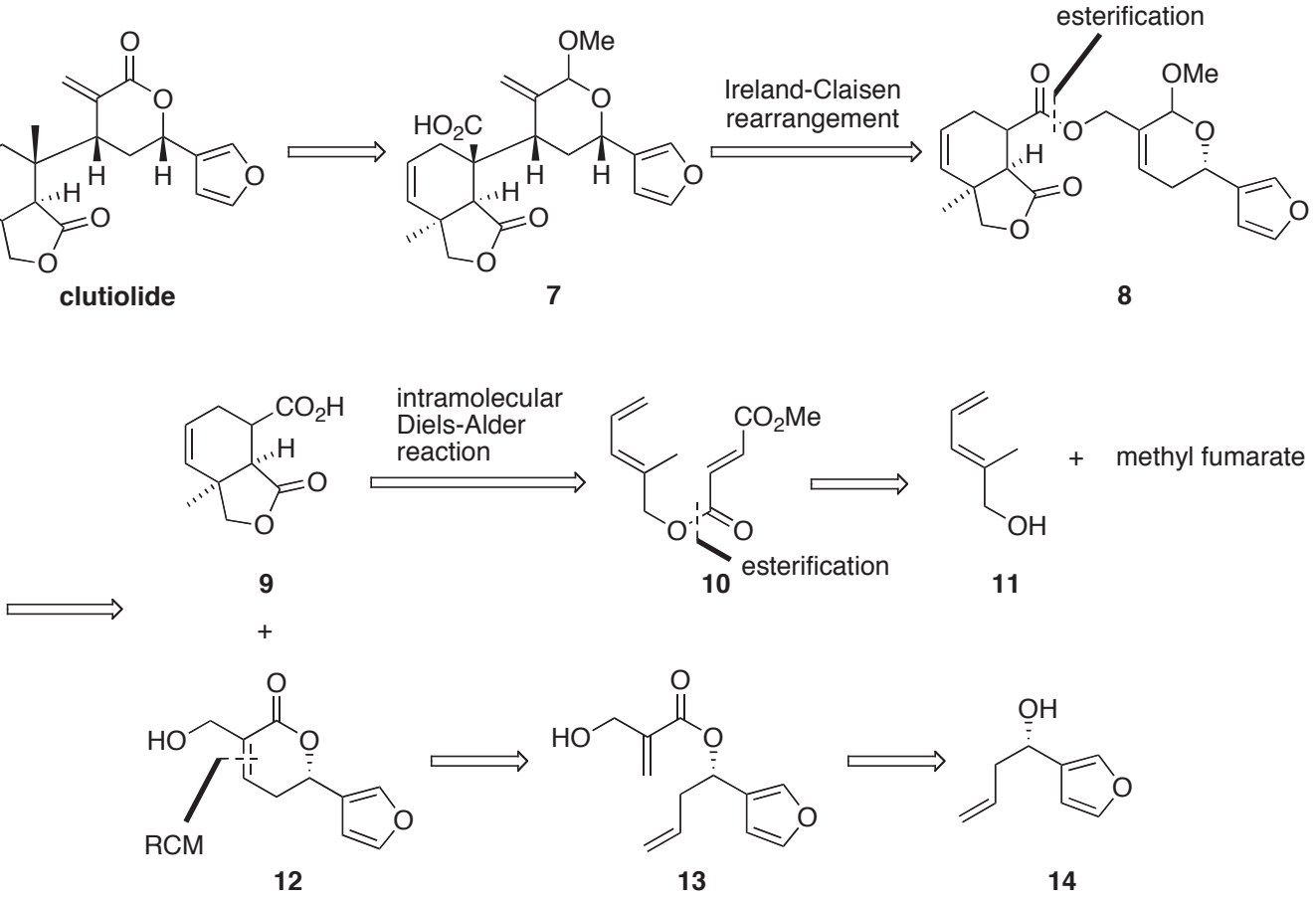


Figure 1. Secolabdan diterpenes derived from the genus *Clutia*

Our synthetic strategy leading to clutiolide (**6**) centers around the construction of the quaternary center by Ireland-Claisen rearrangement. Thus, the target molecule can be divided to the left-hand segment **9** and

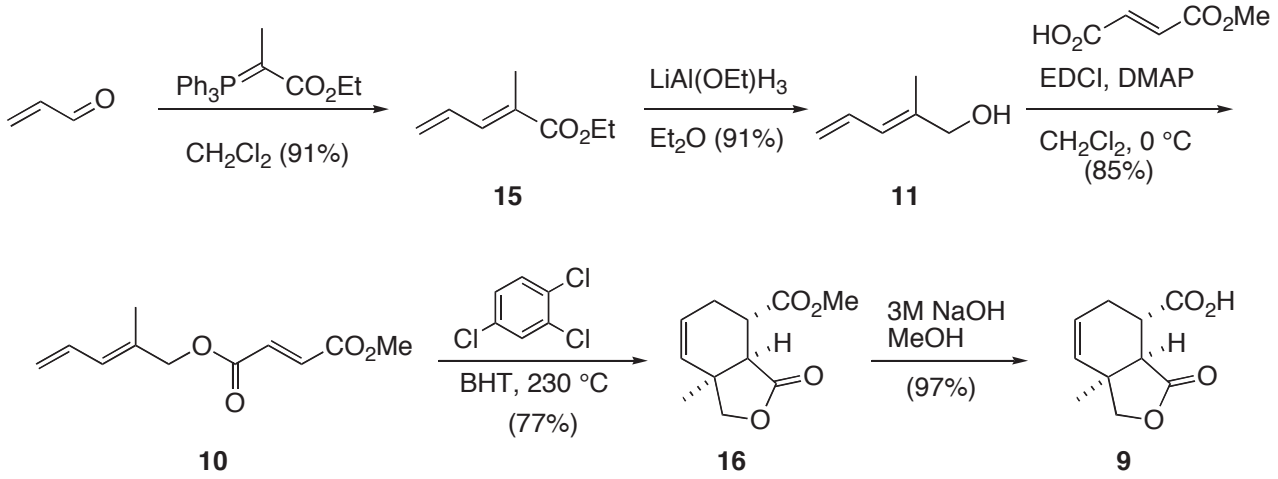
the right-hand segment **12** (Scheme 2). It is assumed that the bicyclic framework in **9** would be assembled by intramolecular Diels-Alder reaction of **10**, which is easily prepared by the esterification of **11** with methyl fumarate. On the other hand, the allylic alcohol **12** could be obtained by ring-closing metathesis of ester **13**, which is easily obtained from **14**.



Scheme 2. Retrosynthetic analysis of clutiolide

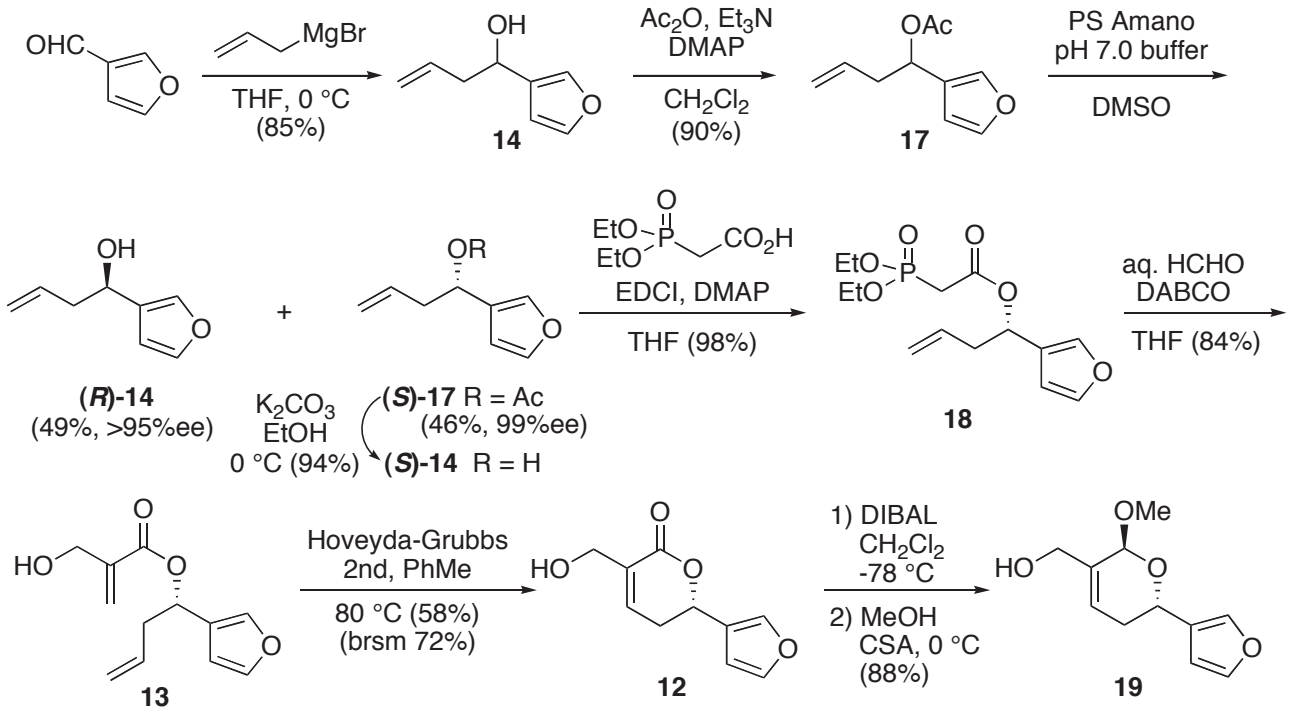
RESULTS AND DISCUSSION

Our synthesis of the left hand segment **9** commenced with Wittig reaction of acrolein with $Ph_3P{=}C(Me)CO_2Et$ to generate **15** in 91% yield (Scheme 3). Reduction of **15** with $LiAl(OEt)H_3$ gave allyl alcohol **11** in 91% yield,[7] which was esterified with mono-methyl fumarate to afford triene **10** in 85% yield. The intramolecular Diels-Alder reaction of **10** was performed under heating at 230 °C in 1,2,4-trichlorobenzene to afford the desired **16** in 77% yield as the sole product. Hydrolysis of **16** gave carboxylic acid **9** in 97% yield. Initially we attempted to separate the enantiomers by chromatography of the corresponding esters and amides derived from chiral alcohols and chiral amines. Optical resolution of **9** using a chiral resolving agents, such as quinidine and cinchonidine was also examined. However all attempts were fruitless. Therefore, we proceeded further using racemic compound **9**.



Scheme 3. Preparation of left segment **9**

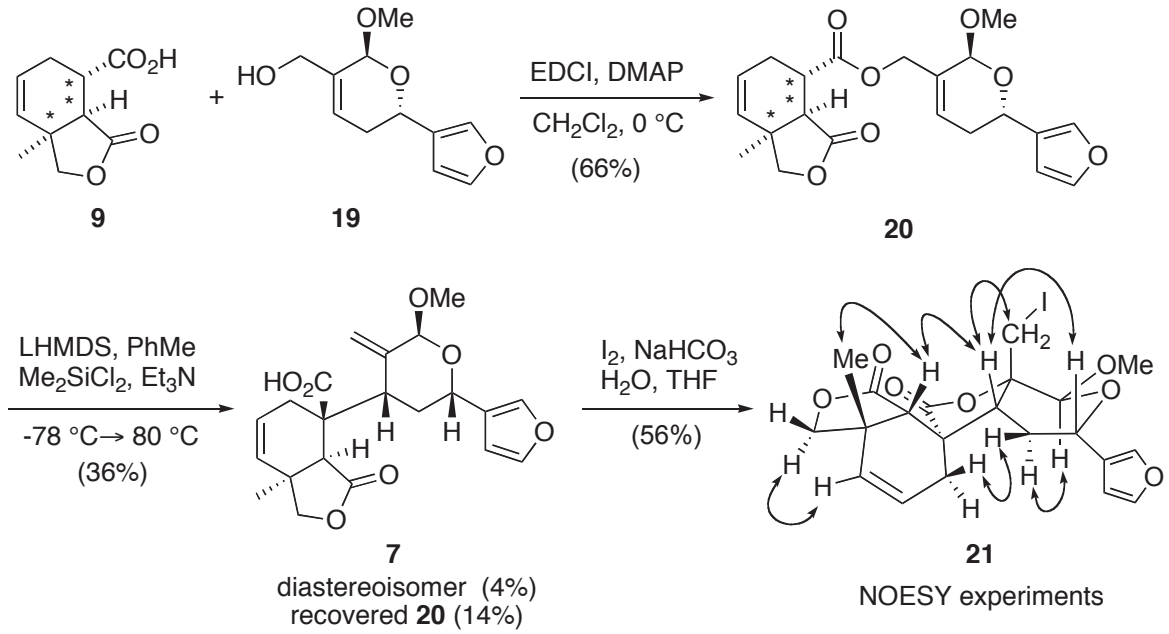
The right hand segment **12** was prepared from 3-furaldehyde as shown in Scheme 4. Allylation of 3-furaldehyde afforded **14**, which was then subjected to enzymatic kinetic resolution. Initially, we examined acetylation of **14** with vinyl acetate using various lipases; however, the results were unsatisfactory. Fortunately, it was found that lipase-catalyzed hydrolysis of acetate **17** furnished better results.[8] Thus, treatment of **17** with PS Amano in pH 7.0 buffer afforded (*R*)-**14** (99% ee) and (*S*)-**17** (87% ee) in 44% and 55% yields, respectively. The resulting (*S*)-**17** (87% ee) was again subjected to the second enzymatic hydrolysis. As a result, (*R*)-**14** (>95% ee) and (*S*)-**17** (99% ee) were obtained in 49% and 46% yields, respectively. Hydrolysis of **17**, followed by esterification gave phosphonate **18**,



Scheme 4. Preparation of right segment **19**

which was then converted to compound **13** by the reaction with formalin in the presence of DABCO. For the ring-closing metathesis of **13**, **13** was first treated with Grubbs 2nd generation catalyst in toluene (0.01 M). However, in this case, the corresponding dimer was obtained as a major product. After exploring various conditions, we were pleased to find that reaction of **13** with Hoveyda-Grubbs 2nd catalyst[9] at 80 °C in toluene furnished desired **12** in 58% yield, along with unreacted **13** (19%) and the dimer (6%). Reduction of **12** with DIBAL and subsequent acetalization gave methyl acetal **19** as a single isomer in good yield.

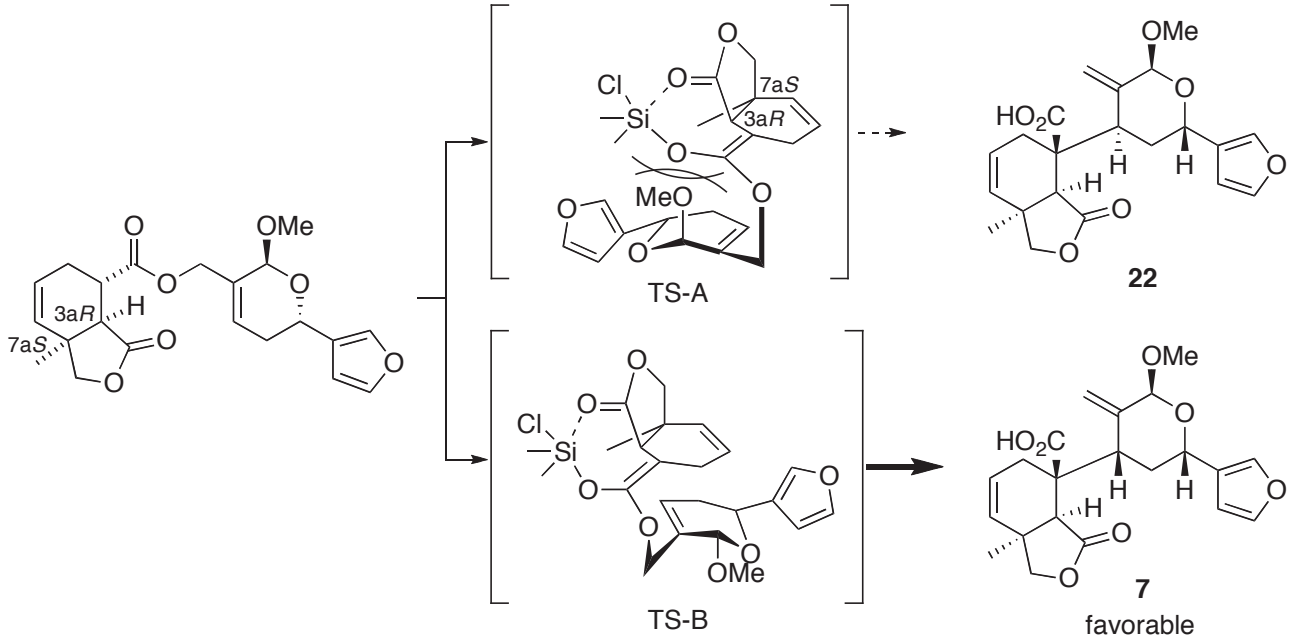
Esterification of racemic **9** with **19** under the conditions using EDCI and DMAP gave ester **20** in 66% yield as a diastereoisomeric mixture (Scheme 5). With **20** in hand, we then investigated the key Claisen rearrangement under various conditions.[10] When **20** was reacted with Me_2SiCl_2 in the presence of LHMDS and heated at 80 °C in toluene, the desired compound **7** and its unidentified diastereoisomer were obtained in 36% and 4% yields, respectively. This result suggested that, provided the pure (3a*R*,4*S*,7a*S*)-isomer is used, the desired **7** could be obtained selectively in ca. 70% yield. The stereochemistry of the major product was characterized by NOESY spectra of the corresponding iodolactonization product **21** derived from **7**. In contrast, the rearrangement under the conditions using KHMDS, TMSCl, and Et_3N turned out to be sluggish to afford a complex mixture including compound **7** (5%).

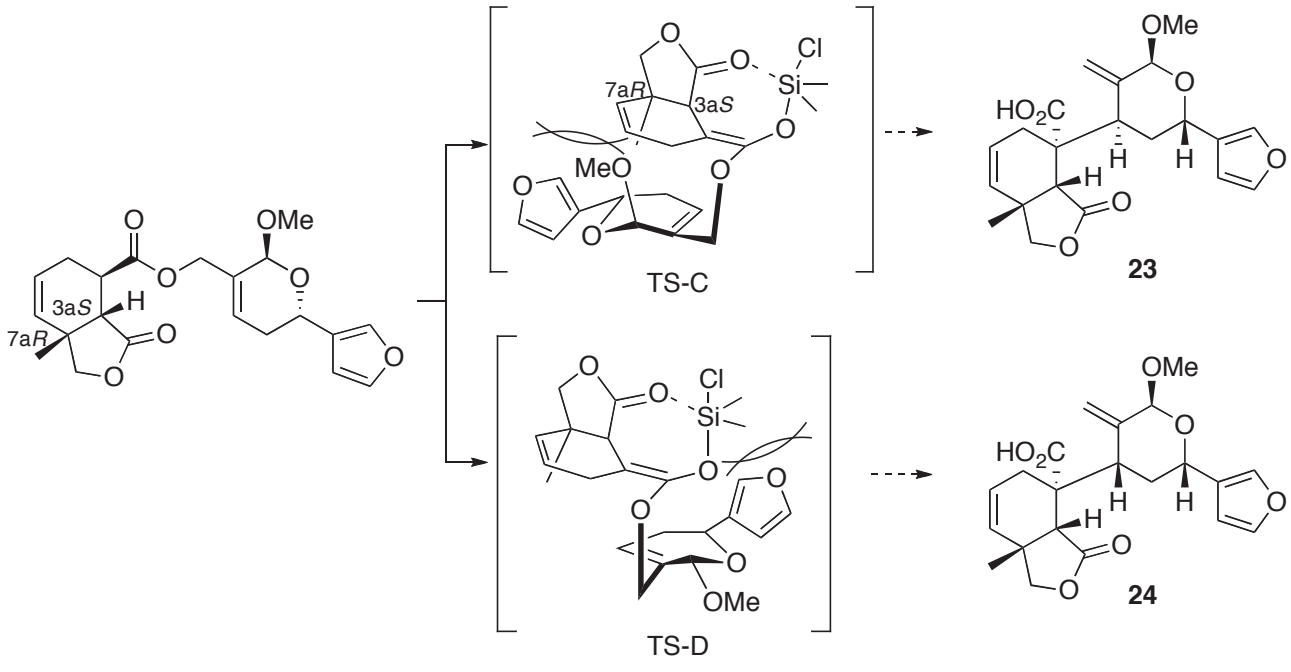


Scheme 5. Remote chelation controlled Ireland-Claisen rearrangement of **20**

The possible reaction courses of the Claisen rearrangement of **20** are shown in Scheme 6. Under the conditions employing LHMDS and Me_2SiCl_2, the coordination of the silyl group to the lactone carbonyl oxygen forces the silyl ketene acetal to take a Z-geometry. Regarding (3a*R*,7a*S*)-compound, there are two

possible transition states, TS-A and TS-B. However, in TS-A taking a boat conformation, there can be the significant steric repulsion between the methoxy group and the silyl substituent, whereas such an interaction would not be observed in TS-B. On the other hand, as for transition states from (3a*S*, 7a*R*)-compound, both TS-C and TS-D would have experienced severe steric repulsion between the furyl group and the 7a*R*-methyl group and between the furyl group and the silyl substituent, respectively. Consequently, TS-B would be the most favorable transition state which leads to the desired **7**.





Scheme 6. Possible transition states for Ireland-Claisen rearrangement of **20**

CONCLUSION

We succeeded in the stereoselective synthesis of compound **7**, a promising precursor for the synthesis of clutiolide (**6**), utilizing a remote chelation controlled Ireland-Claisen rearrangement we have previously developed. The synthesis of clutiolide is now ongoing in our laboratory.

EXPERIMENTAL

Where appropriate, reactions were performed in flame-dried glassware under argon atmosphere. All extracts were dried over $MgSO_4$ and concentrated by rotary evaporation below 30 °C at 25 Torr unless otherwise noted. Commercial reagents and solvents were used as supplied with following exceptions. *N*,*N*-Dimethyformamide (DMF), dichloromethane (CH_2Cl_2), triethylamine, benzene and toluene (PhMe) were distilled from CaH_2. Methanol (MeOH) was distilled from sodium. Thin-layer chromatography (TLC) was performed using glass-packed silica gel plates (0.2 or 0.5 mm thickness). Column chromatography was performed using silica gel (particle size 100-210 mm (regular), 40-50 mm (flash)). Optical rotations were recorded on a digital polarimeter at ambient temperature, JEOL DIP-370 or P-2200. Infrared spectra were measured on a Fourier transform infrared spectrometer, JEOL FT/IR-230. ^{1}H NMR (400 and 500 MHz) and ^{13}C NMR (100 and 75 MHz) spectra were measured using $CDCl_3$ as solvent, and chemical shifts are reported as δ values in ppm based on internal $CHCl_3$ (7.26 ppm, ^{1}H; 77.0 ppm, ^{13}C). HRMS spectra were taken in EI or FAB mode.

(*E*)-Ethyl 2-methylpenta-2,4-dienoate (15): To a stirred solution of acrolein (6.2 g, 0.11 mol) in CH_2Cl_2 (150 mL) was added (carbethoxyethylidene)triphenylphosphorane (40 g, 0.11 mol), and the reaction mixture was refluxed for 4 h. The mixture was allowed to cool to room temperature and diluted with pentane (100 mL). The resulting solid was filtered off, and the filtrate was concentrated in vauo. Addition of pentane and filtration were repeated three times to give compound **15** (14.1 g, 0.101 mol, 91%) as pale yellow oil: FT-IR (neat) ν 2977, 1714, 1575, 1448, 1245, 1099, 912 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.16 (d, *J* = 9.9 Hz, 1H), 6.66 (ddd, *J* = 9.9, 10.2, 16.5 Hz, 1H), 5.56 (d, *J* = 16.5 Hz, 1H), 5.44 (d, *J* = 10.2 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 1.95 (s, 3H), 1.31 (t, *J* = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.3, 138.2, 132.2, 128.1, 124.3, 60.6, 14.2, 12.6; HRMS (EI) calcd for $C_8H_{12}O_2$: 140.0837, found: 140.0812.

(*E*)-2-Methylpenta-2,4-dien-1-ol (11): To an ice-cooled suspension of $LiAlH_4$ (0.83 g, 21.9 mmol) in Et_2O (66 mL) was added EtOH (1.27 mL, 22.5 mmol), and the mixture was stirred for 15 min. To this suspension was added dropwise a solution of compound **15** (4.0 g, 28.6 mmol) in Et_2O (5.0 mL) over 5 min. After stirring for 2.5 h, the reaction was quenched by addition of H_2O (4 mL), 3 M aqueous NaOH (4 mL), and H_2O (12 mL) in that order. The resulting solid was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (SiO_2 150 g, hexane/EtOAc = 5/1 to

2/1) to afford compound **11** (2.56 g, 26.1 mmol, 91%) as a colorless oil: FT-IR (neat) ν 3332, 2917, 1654, 1600, 1428, 1214, 1141, 1066, 997, 900 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.63-6.54 (m, 1H), 6.08 (d, *J* = 10.8 Hz, 1H), 5.21 (d, *J* = 16.5 Hz, 1H), 5.11 (d, *J* = 9.9 Hz, 1H), 4.13 (s, 2H), 1.79 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 137.7, 132.5, 125.3, 117.0, 68.1, 14.0.

Methyl (*E*)-2-methylpenta-2,4-dienyl fumarate (10): To an ice-cooled solution of **11** (3.0 g, 30.6 mmol) in CH_2Cl_2 (100 mL) were added EDCI (7.0 g, 36.7 mmol), mono-methyl fumarate (4.78 g, 36.7 mmol), and DMAP (373 mg, 3.06 mmol). After stirring at rt for 2 h, the reaction mixture was diluted with sat. aq. $NaHCO_3$ (100 mL) and extracted with EtOAc (100 mL x 3). Combined organic layer was dried, concentrated, and chromatographed (SiO_2 120 g, hexane/EtOAc = 5/1) to give compound **10** (5.47 g, 26.0 mmol, 85%) as colorless oil: FT-IR (neat) ν 2952, 1727, 1650, 1438, 1376, 1301, 1159, 987, 910, 775 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.89 (s, 2H), 6.64-6.52 (m, 1H), 6.11 (d, *J* = 10.5 Hz, 1H), 5.27 (d, *J* = 16.8 Hz, 1H), 5.19 (d, *J* = 10.2 Hz, 1H), 4.66 (s, 2H), 3.82 (s, 3H), 1.86 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.3, 164.6, 133.5, 133.4, 131.9, 129.0, 128.0, 118.5, 70.2, 52.3, 14.3; HRMS (EI) calcd for $C_{11}H_{14}O_4$: 210.0892, found: 210.0869.

Methyl (3a*R,4*S**,7a*S**)-1,3,3a,4,5,7a-hexahydro-7a-methyl-3-oxoisobenzofuran-4-carboxylate (16):** A mixture of **10** (2.7 g, 12.8 mmol) and BHT (0.28 g, 1.28 mmol) in 1,2,4-trichlorobenzene (642 mL) was degassed, and stirred at 230 °C for 39 h. The reaction mixture was concentrated and chromatographed (SiO_2 150 g, hexane/EtOAc = 5/1) to afford compound **16** (2.08 g, 9.9 mmol, 77%) as a yellow oil: FT-IR (neat) ν 2921, 2854, 1774, 1444, 1369, 1261, 1205, 1024, 740 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.85-5.80 (m, 1H), 5.47 (dt, *J* = 7.5, 0.9 Hz, 1H), 4.04 (d, *J* = 6.6 Hz, 1H), 3.97 (d, *J* = 6.6 Hz, 1H), 3.73 (s, 3H), 3.25-3.22 (m, 1H), 3.12 (d, *J* = 1.6 Hz, 1H), 2.59-2.52(m, 1H), 2.22 -2.15 (m, 1H), 1.17 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 177.1, 173.9, 129.8, 128.2, 77.4, 51.9, 46.1, 39.1, 35.0, 23.2, 21.4; HRMS (EI) calcd for $C_{11}H_{14}O_4$: 210.0892, found: 210.0861.

(3a*R,4*S**,7a*S**)-1,3,3a,4,5,7a-hexahydro-7a-methyl-3-oxoisobenzofuran-4-carboxylic acid (9):** To a stirred solution of compound **16** (1.7 g, 8.10 mmol) in MeOH (17 mL) was added 3 M aq. NaOH (17.0 mL), and the mixture was stirred for 10 h. After the mixture was washed with Et_2O (20 mL x 3), the aqueous layer was adjusted to pH 2 by addition of HCl and extracted with Et_2O (20 mL x 3). Organic extracts were washed with brine (3 mL), dried, and concentrated to afford a carboxylic acid **(9)**, which was subjected to next reaction without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.90-5.82 (m, 1H), 5.51-5.49 (m, 1H), 4.05 (d, *J* = 9.0 Hz, 1H), 3.99 (d, *J* = 9.0 Hz, 1H), 3.32-3.28 (m, 1H), 3.18-3.16 (m, 1H), 2.56 (dd, *J* = 5.1, 17.0 Hz, 1H), 2.23-2.17 (m, 1H), 1.23 (s, 3H).

1-(Furan-3-yl)but-3-en-1-ol (14): To a stirred solution of 3-furaldehyde (1.00 g, 10.4 mmol) in THF (34.7 mL) at -78 °C was added allylmagnesium chloride (1.38 M solution in THF, 18.9 mL, 26.0 mmol), and the mixture was stirred for 2 h. The reaction mixture was diluted with sat. aq. NH_4Cl (30 mL),

extracted with EtOAc (30 mL x 3), dried, and concentrated. The residue was purified by chromatography (SiO_2 40 g, hexane/EtOAc = 10/1) to give compound **14** (1.2 g, 8.81 mmol, 85%). FT-IR (neat) ν 3407, 2924, 1641, 1502, 1430, 1301, 1161, 1028, 920, 868, 798 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40 (s, 2H), 6.41 (s, 1H), 5.89-5.75 (m, 1H), 5.21-5.15 (m, 2H), 4.72 (t, *J* = 6.0 Hz, 2H), 2.59-2.44 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.2, 139.0, 134.1, 128.4, 118.4, 108.5, 66.0, 42.3; HRMS (EI) calcd for $C_8H_9O_2$: 137.0603, found: 137.0573.

1-(Furan-3-yl)but-3-enyl acetate (17): To a stirred solution of **14** (9.27 g, 57.0 mmol) in CH_2Cl_2 (66 mL) were added Et_3N (33 mL, 230 mmol), Ac_2O (10.2 mL, 108 mmol) and DMAP (0.69 g, 5.6 mmol). After stirring at 15 h, the mixture was washed with 2 M HCl (50 mL), sat. aq. $NaHCO_3$ (50 mL), and brine (50 mL). Organic extracts were dried, concentrated, and chromatographed (SiO_2 300 g, hexane/EtOAc = 30:1) to give **17** (9.27 g, 51.4 mmol, 90%) as an yellow oil: FT-IR (neat) ν 1739, 1504, 1373, 1240, 1162, 1025, 931, 875, 800 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.37 (s, 1H) 6.39 (s, 1H), 5.83 (t, *J* = 6.9 Hz, 1H), 5.79- 5.65 (m, 1H), 5.14 -5.05 (m, 2H) 2.68 -2.51 (m, 2H) 2.04 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.2, 143.1, 140.1, 133.1, 124.4, 118.0, 108.9, 67.6, 39.1, 21.1; HRMS (EI) calcd for $C_{10}H_{12}O_3$: 180.0786, found: 180.0780.

(*S*)-1-(Furan-3-yl)but-3-enyl acetate ((*S*)-17) and (*R*)-1-(Furan-3-yl)but-3-en-1-ol ((*R*)-14): To a stirred solution of **17** (30 g, 165 mmol) in DMSO (81 mL) and Na-K phosphate buffer (pH 7.0, 822 mL) was added lipase PS Amano (1.85 g), and the mixture was stirred at rt for 43 h. The reaction mixture was extracted with Et_2O (1.0 L x 3), washed with sat. $NaHCO_3$ (1.0 L) and brine (1.0 L), dried, and concentrated. The residue was purified by chromatography (SiO_2 800 g, hexane/EtOAc = 30/1 to 5/1) to give **(*S*)-17** (16.4 g, 91 mmol, 55 %) and **(*R*)-14** (10 g, 72.5 mmol, 44 %). The resulting (*S*)-**17** was treated with PS Amano analogously. Totally **(*R*)-14** (11.1 g, 80.4 mmol, 49%, >95%ee) and **(*S*)-17** (13.6 g, 75.5 mmol, 46%, 99%ee) were obtained. **(*S*)-17**; $[\alpha]_D^{24}$ -60.6 (*c* 0.97, $CHCl_3$): **(*R*)-14**; $[\alpha]_D^{24}$ +31.6 (*c* 1.09, $CHCl_3$).

(*S*)-1-(Furan-3-yl)but-3-en-1-ol ((*S*)-14). To an ice-cooled solution of **(*S*)-17** (3.08 g, 16.6 mmol) in EtOH (55 mL) was added K_2CO_3 (4.58 g, 33.2 mmol) and the mixture was stirred at 0 °C for 10 h. The reaction mixture was diluted with sat. NH_4Cl (50 mL), extracted with EtOAc (55 mL x 3), dried, and concentrated to give (*S*)-**14** (2.17 g, 15.7 mmol, 94%): **(*S*)-14**; $[\alpha]_D^{24}$ -28.0 (*c* 1.43, $CHCl_3$).

(*S*)-1-(Furan-3-yl)but-3-enyl diethylphosphonoacetate (18): To an ice-cooled solution of (*S*)-**14** (3.0 g, 32.6 mmol) in THF (60 mL) were added DMAP (265 mg, 2.17 mmol), EDCI (6.25 g, 32.6 mmol), and diethyl phosphonoacetate (5.2 mL, 32.6 mmol) . After stirring at rt for 3.5 h, DMAP (100 mg, 0.82 mmol) and EDCI (2.0 g, 10.4 mmol) were added and stirring was continued at rt for additional 2 h. The mixture was diluted with sat. aq. $NaHCO_3$ (100 mL), extracted with EtOAc (100 mL x 3), and washed with brine (100 mL). Organic extracts were dried, concentrated, and chromatographed (SiO_2 600 g, hexane/EtOAc =

1/1) to give compound **18** (12.6 g, 39.8 mmol, 95%) as colorless oil: $[\alpha]_D^{24}$ -37.5 (*c* 0.995, $CHCl_3$); FT-IR (neat) ν 3466, 3126, 3078, 2982, 1733, 1504, 1394, 1259, 1162, 1113, 1021, 957, 875, 602 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.38 (s, 1H), 6.43 (s, 1H), 5.87 (t, *J* = 6.8 Hz, 1H), 5.77 (ddt, *J* = 7.1, 10.0, 17.4 Hz, 1H), 5.12 (d, *J* = 17.6 Hz, 1H), 5.09 (d, *J* = 11.2 Hz, 1H), 4.13 (dq, *J* = 7.5, 15.0 Hz, 4H), 2.96 (d, *J* = 20.5 Hz, 2H), 2.71-2.56 (m, 2H), 1.34-1.28 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.0, 143.1, 140.5, 132.8, 123.9, 118.2, 108.8, 69.1, 62.5, 38.9, 35.0, 33.7, 16.2; HRMS (EI) calcd for $C_{14}H_{21}O_6P$: 316.1076, found 316.1075.

(*S*)-1-(Furan-3-yl)but-3-enyl 2-(hydroxymethyl)acrylate (13): To an ice-cooled solution of **18** (6.70 g, 21.2 mmol) in THF (106 mL) were added formalin (35% aqueous solution, 106 mL, 1.30 mol) and DABCO (3.56 mL, 31.8 mmol). After stirring at rt for 18 h, the mixture was diluted with sat. $NaHCO_3$ (200 mL), and extracted with EtOAc (200 mL x 3). Combined extracts were dried, concentrated, and chromatographed (SiO_2 250 g, hexane/EtOAc = 3/1 to 2/1) to give compound **13** (3.97 g, 17.9 mmol, 84%) as colorless oil: $[\alpha]_D^{24}$ -38.3 (*c* 1.09, $CHCl_3$); FT-IR (neat) ν 3442, 1712, 1643, 1504, 1263, 1157, 1022, 874, 796, 601 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.39 (s, 1H), 6.41 (s, 1H), 6.27 (s, 1H), 5.93 (t, *J* = 6.8 Hz, 1H), 5.83 (s, 1H), 5.75 (ddt, *J* = 9.8, 17.0, 4.4 Hz, 1H), 5.13 (d, *J* = 17.0 Hz, 1H), 5.10 (d, *J* = 9.8 Hz, 1H), 4.32 (s, 2H), 2.73-2.59 (m, 2H), 2.44 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.4, 143.2, 140.3, 139.4, 132.9, 125.9, 124.2, 118.4, 108.8, 68.3, 62.4, 39.1; HRMS (EI) calcd for $C_{12}H_{14}O_4$: 222.0892, found 222.0890.

(*S*)-6-(Furan-3-yl)-5,6-dihydro-3-(hydroxymethyl)pyran-2-one (12): To a stirred solution of compound **13** (1.50 g, 6.75 mmol) in degassed toluene (135 mL) was added 2nd generation Hoveyda-Grubbs catalyst (60 mg, 0.101 mmol). After 10 h and 15 h, the catalysts (30 mg, 0.050 mmol) were added respectively and the mixture was stirred at 80 °C for additional 18 h. The reaction mixture was concentrated, and chromatographed (SiO_2 45 g, hexane/EtOAc = 2:1 to 1:1) to give compound **12** (752 mg, 3.88 mmol, 58%) as colorless oil, unreacted **13** (283 mg, 0.189 mmol, 19%), and dimer (93 mg, 0.22 mmol, 6%): **12;** $[\alpha]_D^{24}$ -68.0 (*c* 1.18, $CHCl_3$); FT-IR (neat) ν 3407, 1697, 1503, 1379, 1220, 1126, 1019, 873, 792, 599, 493 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.42 (s, 1H), 6.93 (s, 1H), 6.46 (s, 1H), 5.43 (dd, *J* = 4.9, 10.7 Hz, 1H), 4.33 (s, 2H), 3.40 (s, 1H), 2.75-2.60 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 164.8, 143.7, 140.0, 139.6, 131.7, 123.5, 108.5, 72.5, 61.1, 30.0.

((2*S*,6*S*)-6-(Furan-3-yl)-5,6-dihydro-2-methoxy-2*H*-pyran-3-yl)methanol (19): To a stirred solution of **12** (53 mg, 0.273 mmol) in CH_2Cl_2 (2 mL) at -78 °C was added DIBAL (1.02 M in hexane, 0.53 mL, 0.546 mmol) and the mixture was stirred for 2 h. The reaction was quenched by addition of potassium sodium tartrate (20% aqueous solution, 2 mL). After stirring for 12 h, the mixture was extracted with EtOAc (100 mL x 3), washed by brine (20 mL), dried, and concentrated to afford a crude hemiacetal. To an ice-cooled solution of crude hemiacetal in methanol (2 mL) was added CSA (6.3 mg, 0.0273 mmol).

After stirring at 0 °C for 16 h, the reaction mixture was diluted with sat. aq. $NaHCO_3$ (2 mL), and extracted with EtOAc (5 mL x 3). Organic extracts were washed with brine (2 mL), dried, concentrated, and chromatographed (SiO_2 2 g, hexane/EtOAc = 1:1) to give compound **19** (50 mg, 0.238 mmol, 87%) as colorless oil: $[\alpha]_D^{24}$ -24.5 (*c* 1.00, $CHCl_3$); FT-IR (neat) ν 3411, 2898, 1503, 1394, 1156, 1024, 956, 875, 777, 601 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.41 (s, 1H), 6.44 (s, 1H), 6.01 (d, *J* = 5.4 Hz, 1H), 5.00 (s, 1H), 4.85 (dd, *J* = 3.4, 11.2 Hz, 1H), 4.14 (d, *J* = 12.7 Hz, 1H), 4.09 (d, *J* = 12.2 Hz, 1H), 3.49 (s, 3H), 2.58 (s, 1H), 2.42-2.33 (m, 1H), 2.28-2.21 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.2, 139.3, 135.8, 126.0, 125.1, 108.8, 97.3, 63.6, 61.6, 55.2, 30.7; HRMS (EI) calcd for $C_{11}H_{14}O_4$: 210.0892, found 210.0864.

(3a*R,7a*S**)-((2*S*,6*S*)-6-(Furan-3-yl)-5,6-dihydro-2-methoxy-2*H*-pyran-3-yl)methyl 1,3,3a,4,5,7a-hexahydro-7a-methyl-3-oxoisobenzofuran-4-carboxylate (20):** To an ice-cooled solution of compound **9** (1.36 g, 6.92 mmol) and compound **19** (1.45 g, 6.92 mmol) in CH_2Cl_2 (35 mL) were added EDCI (2.0 g, 10.4 mmol) and DMAP (83.8 mg, 0.69 mmol). After stirring at rt for 2.5 h, EDCI (0.40 g, 2.1 mmol) and DMAP (83.8 mg, 0.69 mmol) were added, and stirring was continued for 11.5 h. To the mixture was added sat. aq. $NaHCO_3$ (50 mL), extracted with EtOAc (50 mL x 3). Organic extracts were washed with brine (50 mL), dried, concentrated, and chromatographed (SiO_2 75 g, hexane/EtOAc = 3:1) to give compound **20** (1.77 g, 4.557 mmol, 66%) as colorless oil and recovered compound **19** (180 mg, 0.853 mmol, 12%): **20**; FT-IR (neat) ν 2899, 1773, 1735, 1254, 1190, 1097, 1050, 961, 876 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.42 (s, 1H), 6.44 (s, 1H), 6.09 (t, *J* = 5.4 Hz, 1H), 5.86-5.81 (m, 1H), 5.48 (d, *J* = 8.8 Hz, 1H), 4.95 (s, 1H), 4.86 (dd, *J* = 3.7, 11.0 Hz, 1H), 4.73-4.69 (m, 1H), 4.60 (d, *J* = 12.2 Hz, 1H), 4.03 (d, *J* = 8.8 Hz, 1H), 3.98 (d, *J* = 8.8 Hz, 1H), 3.46 (s, 3H), 3.28-3.24 (m, 1H), 3.12 (t, *J* = 3.4 Hz, 1H), 2.86 (dd, *J* = 5.2, 18.3 Hz, 1H), 2.43-2.36 (m, 1H), 2.30-2.17 (m, 2H), 1.18 (d, *J* = 5.4 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 177.1, 172.6, 143.3, 139.3, 131.8, 129.9, 128.2, 126.8, 125.9, 108.8, 96.3, 65.0, 61.2, 55.5, 52.0, 46.2, 39.2, 36.3, 30.9, 23.3, 22.1; HRMS (EI) calcd for $C_{21}H_{24}O_7$: 388.1523, found 388.1530.

(3a*S*,4*S*,7a*S*)-4-((2*S*,4*S*,6*S*)-6-(Furan-3-yl)-tetrahydro-2-methoxy-3-methylene-2*H*-pyran-4-yl)-1,3,-3a,4,5,7a-hexahydro-7a-methyl-3-oxoisobenzofuran-4-carboxylic acid (7): To a stirred solution of **20** (85 mg, 0.215 mmol) in PhMe (2 mL) at -78 °C was added a solution of LHMDS (1.0 M in hexane, 0.64 mL, 0.64 mmol) and the mixture was stirred for 30 min. A mixture of dichlorodimethylsilane (1.0 mL, 8.24 mmol) and Et_3N (1.0 mL, 7.17 mmol) was centrifuged at 3000 rpm for 5 min and the supernatant (0.3 mL), regarding to include dichlorodimethylsilane (1.24 mmol) and Et_3N (1.08 mmol), was added to the reaction mixture. After stirring at –78 °C for 1 h, the mixture was allowed to warm gradually to 80 °C and stirring was continued at 80 °C for an additional 10 h. The mixture was diluted with sat. aq. NH_4Cl (2 mL), extracted with EtOAc (10 mL x 3), washed with brine, dried, and concentrated. The residue was

purified by chromatography (SiO_2 10 g, hexane-EtOAc, 3/1 to 1/1) afforded compound **7** (31 mg, 80 μmol, 36%) as colorless oil and diastereoisomer (3 mg, 8 μmol, 4%) and **20** (12 mg, 0.031 mmol, 14%); **7**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 2H), 6.36 (s, 1H), 5.86-5.82 (m, 1H), 5.61 (s, 1H), 5.56 (s, 1H), 5.43 (d, *J* = 10.2 Hz, 1H), 5.19 (s, 1H), 4.73 (dd, *J* = 3.7, 11.5, 1H), 4.34 (dd, *J* = 6.8, 9.2 Hz, 1H), 3.96 (d, *J* = 8.8 Hz, 1H), 3.90 (d, *J* = 8.8 Hz, 1H), 3.37 (s, 3H), 3.28 (s, 1H), 2.86 (dd, *J* = 6.8, 18.2 Hz, 1H), 2.12-1.99 (m, 3H), 1.14 (s, 3H); HRMS (EI) calcd for $C_{21}H_{24}O_7$: 388.1523, found 388.1530.

Iodolactonization of 7: To an ice-cooled solution of **7** (14 mg, 0.036 mmol) in THF (0.5 mL) were added iodine (27 mg, 0.108 mmol) and sat. aq. $NaHCO_3$ (0.5 mL), and a mixture was stirred for 2 h. The reaction mixture was diluted with sat. aq. $Na_2S_2O_3$ (1 mL), and stirring was continued for 30 min. The mixture was extracted with Et_2O (5 mL x 3), washed with brine (1 mL), dried, and concentrated. The residue was purified by flash chromatography (SiO_2 1g, hexane/EtOAc = 3/1) to afford compound **41** (10 mg, 0.0195 mmol, 56%) as colorless oil. $[\alpha]_D^{24}$ +14.0 (*c* 0.8, $CHCl_3$); FT-IR (neat) ν 3149, 2927, 2251, 1766, 1208, 1149, 1027, 735, 602 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 2H), 6.39 (s, 1H), 5.78-5.73 (m, 1H), 5.59 (dt, *J* = 1.3, 10.2 Hz, 1H), 4.95 (dd, *J* = 4.2, 10.2 Hz, 1H) 4.84 (s, 1H), 4.06 (d, *J* = 8.8 Hz, 1H), 4.00 (d, *J* = 8.8 Hz, 1H), 3.83 (d, *J* = 11.2 Hz, 1H), 3.53-3.48 (m, 5H), 3.27 (s, 1H), 2.37-2.31 (m, 1H), 2.24 (dt, *J* = 2.6, 17.8 Hz, 1H), 2.11 (dd, *J* = 5.4, 17.6 Hz, 1H), 2.05-1.93 (m, 1H), 1.36 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.3, 175.9, 143.6, 138.9, 130.2 , 126.8, 125.1 108.2, 100.0, 80.7, 77.2, 65.2, 56.8, 50.8, 44.5, 42.6, 28.7, 28.2, 21.4, 11.5, HRMS (EI) calcd for $C_{21}H_{23}IO_7$: 514.0488, found 514.0507.

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