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STEREOSELECTIVE SYNTHESIS OF A PIVOTAL CHIRAL INTERMEDIATE FOR NATURAL SALICYLIC MACROLIDES

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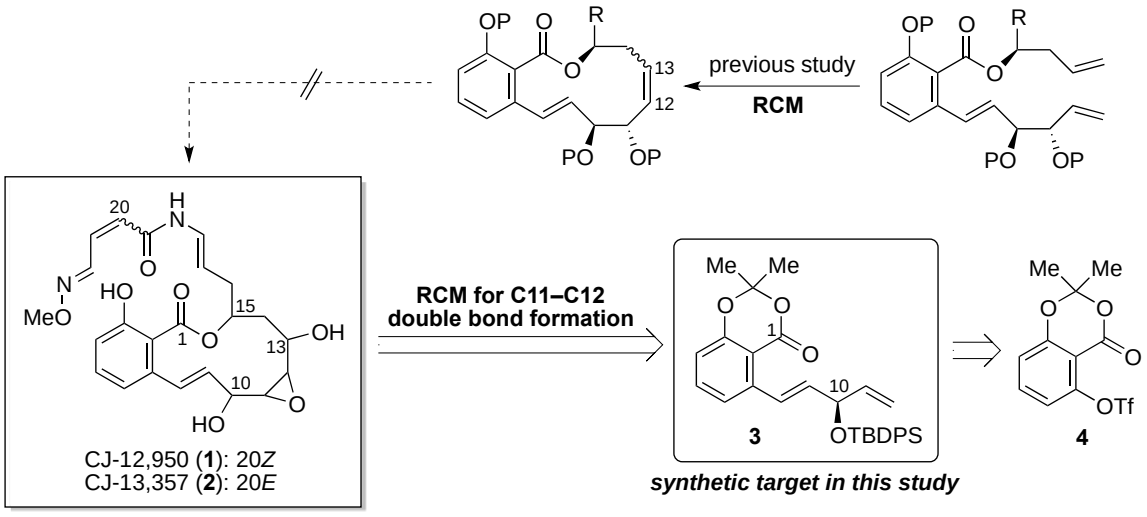
*This paper is dedicated to Professor Kiyoshi Tomioka on the occasion of his 70th birthday.

Abstract – As a part of our ongoing research projects on the synthesis of natural salicylic macrolides, the optically active protected salicylate bearing the chiral diene substituent was required as a pivotal synthetic intermediate. The synthesis of the compound was achieved with a high optical purity starting from D-mannitol through Heck coupling reaction and terminal methylenation as key C–C bond forming reactions.

INTRODUCTION

Salicylic macrolides with a 12-membered ring and an enamide side-chain have been found widely in nature, such as oximidines, salicylihalamides, and CJ-12,950, and have been reported to exhibit fascinating bioactivities.[1] Among them, CJ-12,950 and CJ-13,357 have been disclosed to be a promising new drug candidate for the treatment of hypercholesterolemia and hyperlipidemia.[2] The planar structures of these natural products were elucidated by means of COSY techniques and NOE experiments as shown in Scheme 1, but the stereostructures have not yet been analyzed,[2] and no total syntheses have been reported so far. In our research projects on the synthesis of salicylic macrolides, we previously reported a novel approach for construction of a 12-membered salicylate lactone skeleton utilizing ring-closing metathesis (RCM) as a key step leading to several potential precursors for salicylic macrolides including CJs (Scheme 1, previous study).[3] However, these attempts could not be linked to the success of the total synthesis of the natural products, due to low *E*/*Z* selectivity which should be precisely controlled for further stereoselective oxidation and difficulty of C11–C12 epoxide formation, and consequently, the other blueprints of synthetic strategy have been required. In this context, we set the protected salicylate compound **3** bearing the chiral diene substituent as a C1–C11 unit of the 12-membered macrolactone ring

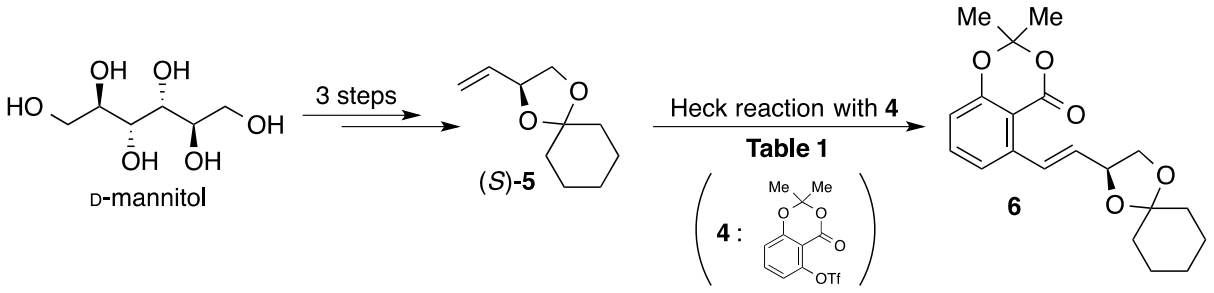
of CJs (Scheme 1), which would be a good precursor of RCM substrate for C11–C12 double bond formation followed by epoxidation. Because the absolute configuration of the stereogenic center (C10) is unknown, development of effective synthetic route accessible to both enantiomers of **3** is desirable for the purpose of future stereochemical elucidation. In this paper, we hope to present stereoselective synthesis of the pivotal intermediate **3** for the construction of salicylic macrolides through Heck coupling reaction of triflate **4** and terminal methylenation as key C–C bond forming reactions.



Scheme 1. Salicylic macrolide CJs and the potential synthetic precursor **3**

RESULTS AND DISCUSSION

The triflate **4** as a Heck substrate was prepared according to the reported procedure including acetonization of 2,6-dihydroxybenzoic acid followed by triflation.[4] It seemed that the most efficient and short-step transformation of the triflate **4** to the target molecule **3** as an optically active form would be asymmetric Heck reaction[5] of **4** with divinylcarbinol or its silyl ethers. Actually we devoted considerable efforts to achievement of this one-step transformation taking advantage of a wide range of chiral phosphine ligands and Pd catalysts. However, all of these attempts were disappointingly fruitless regarding to both enantioselectivity and chemical yield. Therefore, we turned the synthetic plan to late-stage construction of the terminal alkene, and the chiral block (*S*)-**5** was selected as a Heck coupling partner. This compound (*S*)-**5** could be easily synthesized from natural chiral pool, D-mannitol, through 3-step sequence of bis-ketalization with cyclohexanone, oxidative cleavage, and Wittig methylenation.[6] The corresponding *R*-enantiomer (*R*)-**5** has been reported to be prepared from L-ascorbic acid in 4 steps,[7] thus implying that both enantiomers of the target compound **3** would be accessible *via* the planned synthetic route. Heck coupling reaction of (*S*)-**5** with triflate **4** to obtain the coupling product **6** was thoroughly investigated, and the results are summarized in Scheme 2 and Table 1.



Scheme 2. Preparation of the chiral block (*S*)-**5** and Heck reaction with triflate **4**

Table 1. Optimization of Heck coupling reaction of **4** and (*S*)-**5**[a]

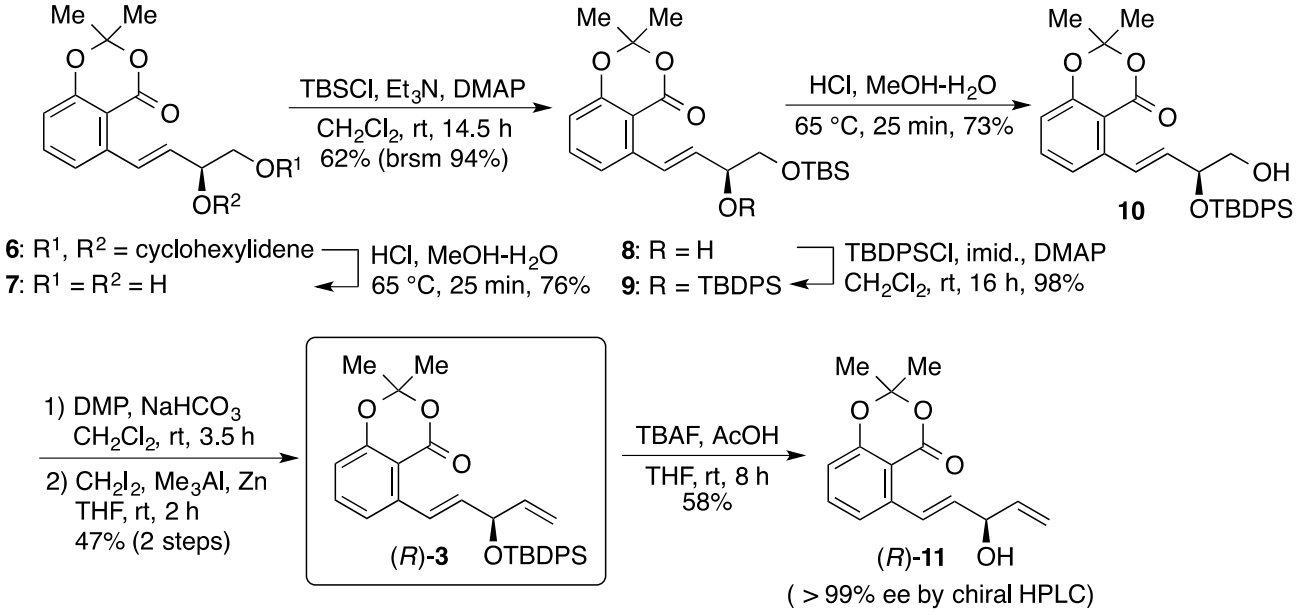
entry	catalyst with ligand (mol%)	solvent	base	temp.	time (h)	yield (%) of **6**
1	$Pd(OAc)_2$ (20), Ph_3P (40)	DMF	Et_3N	120 °C	24	0
2	$Pd(Ph_3P)_4$ (20)	DMF	Et_3N	120 °C	24	0
3	$Pd(Ph_3P)_2Cl_2$ (20)	DMF	Et_3N	120 °C	24	34
4	$Pd_2(dba)_3$ (10), dppe (20)	DMF	Et_3N	120 °C	24	22
5	$Pd_2(dba)_3$ (10), dppf (20)	DMF	Et_3N	120 °C	24	11
6	$PdCl_2$(dppe) (20)	DMF	Et_3N	120 °C	24	5
7	$PdCl_2$(dppf) (20)	DMF	Et_3N	120 °C	5	38
8	$PdCl_2$(dppf) (20)	toluene	Et_3N	reflux	24	0
9	$PdCl_2$(dppf) (20)	THF	Et_3N	reflux	17	34
10	$PdCl_2$(dppf) (20)	MeCN	Et_3N	reflux	24	28
11	$PdCl_2$(dppf) (20)	1,4-dioxane	Et_3N	reflux	12	50
12	$PdCl_2$(dppf) (20)	1,4-dioxane	DIPEA	reflux	24	42
13	$PdCl_2$(dppf) (20)	1,4-dioxane	K_2CO_3	reflux	19	56
14	$PdCl_2$(dppf) (20)	1,4-dioxane	Cs_2CO_3	reflux	24	68
15[b]	$PdCl_2$(dppf) (20)	1,4-dioxane	Cs_2CO_3	reflux	24	51
16[c]	**$PdCl_2$(dppf) (10)**	**1,4-dioxane**	**Cs_2CO_3**	**reflux**	**14**	**68**
17[c,d]	**$PdCl_2$(dppf) (10)**	**1,4-dioxane**	**Cs_2CO_3**	**reflux**	**36**	**60**

a) For all experiments, the reactions were carried out using 2 eq of triflate, 3 eq of base, and 3 eq of LiCl in 0.05 M substrate concentration. b) The amount of triflate was decreased to 1.2 eq. c) In these cases, the substrate concentration was 0.1 M. d) The large-scale experiment (4.3 g of the substrate used). The others were all 20 mg of the substrate used.

Various combinations of a Pd source and a phosphine ligand were first surveyed in DMF at 120 °C (entries 1–7). While no coupling product was obtained when using $Pd(OAc)_2$–Ph_3P and $Pd(Ph_3P)_4$, (entries 1 and 2), $Pd(Ph_3P)_2Cl_2$ provided the desired product **6** in 34% yield (entry 3). The yields were decreased in the case of $Pd_2(dba)_3$ ($CHCl_3$ complex) and bidentate phosphine ligand dppe or dppf (entries 4 and 5). Although $PdCl_2$(dppe) ended in only poor yield (entry 6), the combination of $PdCl_2$(dppf) gave the product **6** in 38% yield within shortened reaction time 5 h (entry 7). Then solvent effects were examined using the same reagent combination as in entry 7 under reflux conditions (entries 8–11). Whereas less polar toluene solvent resulted in completely no reaction (entry 8), the coupling reaction proceeded in ethereal solvents (entries 9 and 11) and MeCN (entry 10), and 1,4-dioxane was found to

bring about the best 50% yield (entry 11). Further optimization was carried out with various types of base (entries 12–14), and the yield was improved with inorganic bases, and especially the yield reached to 68% in the presence of Cs_2CO_3 (entry 14). Here, we used 2 eq of triflate **4** to the olefin **5**, and this ratio was proved to be important for efficient coupling reaction because the yield was significantly dropped when using only 1.2 eq of triflate (entry 15). On the other hand, decreased amount of Pd catalyst (10 mol%) did not affect the yield when the higher substrate concentration was adopted (entry 16), thus getting to the optimal conditions for Heck reaction of **4** and (*S*)-**5**. In addition, this optimal condition was applicable for the large-scale preparation of **6**, as shown in entry 17, in which 4.3 g of (*S*)-**5** afforded 5.26 g of the product **6**.

With the coupling product **6** in hand, we forwarded the synthesis toward the target compound **3** including late-stage methylenation (Scheme 3). The first task was the protecting group manipulation of the vicinal diol to obtain the silylated primary alcohol **10**. Selective deprotection of the cyclohexylidene acetal of the compound **6** was expected to be somewhat difficult because of the existence of a similar propylidene acetal moiety. After exhaustive investigations of various acidic conditions including inorganic and organic acids, acidic resins, and various solvents, we at last found the best condition, HCl in MeOH–H_2O at 65 °C for 25 min, to get the desired diol **7** in 76% yield. Elevated temperature or prolonged reaction time gave rise to considerable overreaction at the propylidene acetal moiety. Introduction of a TBS group to the diol **7** proceeded predominantly onto the primary hydroxy group. However, competitive formation of bis-TBS ether was observed. Therefore, the reaction should be quenched before appearance of the bis-TBS ether on TLC to secure a practical 62% yield of the mono-TBS ether **8**, accompanied by 32%



Scheme 3. Completion of the synthesis of the target compound **3**

recovery of the diol **7** (brsm 94%). The secondary alcohol **8** was converted to the TBDPS ether **9** in 98% yield, and then subjected to the same controlled acidic condition as in the case of **6** to **7** for selective removal of the TBS group to furnish the silylated primary alcohol **10** in 73% yield. Oxidation of the alcohol **10** with Dess-Martin periodinane (DMP) in the presence of $NaHCO_3$ gave the corresponding aldehyde, which was used as a crude form without column chromatography because this aldehyde was prone to epimerize at the stereogenic center. The final methylenation of the aldehyde was achieved the most successfully under CH_2I_2–Me_3Al–Zn conditions[8] in 47% yield (2 steps), to accomplish the synthesis of the target compound (*R*)-**3**, which would be a pivotal intermediate for salicylic macrolide syntheses.

For the purpose of determination of the optical purity of (*R*)-**3**, HPLC analyses were attempted using various chiral columns. However, the compound (*R*)-**3** was found to be difficult to separate the enantiomers by available chiral columns for HPLC, probably due to the low polar character of the compound (*R*)-**3**. Thus, the TBDPS ether (*R*)-**3** was transformed into the corresponding alcohol (*R*)-**11** by treatment with TBAF and AcOH, which was successfully determined to have high optical purity (> 99% ee) by employing CHIRALCEL OD-H as a chiral column. On the other hand, when the aldehyde purified by silica gel column chromatography after DMP oxidation was subjected to the methylenation, the optical purity of resultant (*R*)-**3** was determined as only 18% ee, indicating serious epimerization of the aldehyde occurred during the purification process on silica gel. In addition, as mentioned above, another target enantiomer (*S*)-**3** would be also available from (*R*)-**5** *via* the synthetic route established in this study.

In this paper, we developed efficient and stereoselective synthetic method toward the important intermediate **3** for salicylic macrolide syntheses, utilizing Heck coupling reaction and late-stage terminal methylenation as key C–C bond forming steps. Both enantiomers (*R*)-**3** and (*S*)-**3** can be synthesized by this method starting from (*S*)-**5** and (*R*)-**5**, which are prepared from natural chiral pool D-mannitol and L-ascorbic acid, respectively. Synthetic studies of natural salicylate macrolids including CJs using **3** as an important chiral block are now in progress in our laboratory, and will be reported with stereochemical elucidation in near future.

EXPERIMENTAL

Materials were obtained from commercial suppliers and used without further purification. Column chromatography was performed on Cica Silica Gel 60 N (spherical, neutral, 40–50 μm or 63–210 μm). Reactions and chromatographical fractions were monitored using precorted silica gel 60 F_{254} plates (Merck). NMR spectra were recorded on Varian GEMINI 300 spectrometer with $CHCl_3$ (7.26 ppm for ^1H) or $CDCl_3$ (77.0 ppm for ^{13}C) as an internal standard. Chemical shifts are expressed in δ (ppm) values, and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, dd = double-doublet, ddd =

double-double-doublet. IR spectra were measured on JASCO FT/IR-660. MS spectra were recorded on JEOL JMS-GCmateII or JEOL AX 505 spectrometer. The optical rotations were determined on a JASCO DIP-1000 instrument.

5-[3,4-*O*-Cyclohexylidenebut-1-ene-3,4-diol]-2,2-dimethylbenzo[1,3]dioxin-4-one (6) (entry 16 in Table 1): Under an Ar atmosphere, to a suspension of triflate **4** (78 mg, 0.24 mmol), LiCl (15 mg, 0.36 mmol), Cs_2CO_3 (117 mg, 0.36 mmol) and $PdCl_2$(dppf) (10 mg, 0.012 mmol) in 1,4-dioxane (0.5 mL), was added olefin **5** (20 mg, 0.12 mmol) in 1,4-dioxane (0.7 mL) and the reaction mixture was stirred for 14 h under reflux. The mixture was diluted with Et_2O and filtered through a celite pad. The solvent was removed under reduced pressure and the residue was purified by silica gel flash column chromatography (Hexane/EtOAc = 4:1) to provide the coupling product **6** (28 mg, 0.081 mmol, 68%) as an yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.76 (1H, d, *J* = 15.9 Hz), 7.45 (1H, dd, *J* = 9.1, 8.2 Hz), 7.28 (1H, d, *J* = 9.1 Hz), 6.88 (1H, d, *J* = 8.2 Hz), 6.15 (1H, dd, *J* = 15.9, 7.4 Hz), 4.80–4.73 (1H, m), 4.19 (1H, dd, *J* = 8.2, 6.2 Hz), 3.71 (1H, dd, *J* = 8.2, 7.4 Hz), 1.79–1.60 (16H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.9, 156.5, 140.5, 134.9, 131.3, 130.8, 121.4, 116.4, 110.7, 109.9, 105.1, 76.5, 68.9, 36.2, 35.3, 25.7, 25.4, 25.1, 23.9, 23.8; IR (neat): 2937, 1735 cm^{-1}; MS (EI): *m/z* 344 (M^+); HRMS (EI): Calcd for $C_{20}H_{24}O_5$ (M^+): 344.1624, found: 344.1605; $[\alpha]_D^{22}$ +26.6 (*c* 1.05, $CHCl_3$).

5-[But-1-ene-3,4-diol]-2,2-dimethylbenzo[1,3]dioxin-4-one (7): Under an Ar atmosphere, to a solution of acetal **6** (733 mg, 2.13 mmol) in MeOH (30 mL) was added 0.5 M aqueous HCl (4.2 mL) and the reaction mixture was stirred for 25 min at 65 °C. To the mixture was added saturated aqueous $NaHCO_3$ and the resulting mixture was washed with hexane. Then MeOH was removed under reduced pressure and the residual aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc) to provide the diol **7** (426 mg, 1.61 mmol, 76%) as an yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60 (1H, d, *J* = 15.9 Hz), 7.45 (1H, dd, *J* = 8.0, 8.0 Hz), 7.21 (1H, d, *J* = 8.0 Hz), 6.87 (1H, d, *J* = 8.0 Hz), 6.16 (1H, dd, *J* = 15.9, 6.0 Hz), 4.53–4.47 (1H, m), 3.80 (1H, dd, *J* = 11.3, 3.6 Hz), 3.65 (1H, dd, *J* = 11.3, 6.9 Hz), 1.71 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.5, 156.5, 141.2, 135.3, 132.8, 129.6, 121.8, 116.2, 110.6, 105.3, 72.9, 66.2, 25.6, 25.5; IR (neat): 3402, 2930, 1735 cm^{-1}; MS (EI): *m/z* 203 (M^+–$HOCHCH_2OH$); HRMS (EI): calcd for $C_{12}H_{11}O_3$ (M^+–$HOCHCH_2OH$): 203.0708, found: 203.0743; $[\alpha]_D^{23}$ +4.0 (*c* 1.17, $CHCl_3$).

5-[4-(*tert*-Butyldimethylsilyloxy)but-1-enyl]-2,2-dimethylbenzo[1,3]dioxin-4-one (8): Under an Ar atmosphere, to a solution of diol **7** (230 mg, 0.87 mmol) in CH_2Cl_2 (4.3 mL) was added TBSCl (158 mg, 1.05 mmol), Et_3N (0.4 mL, 2.61 mmol) and DMAP (11 mg, 0.087 mmol) at 0 °C. After stirring for 4.5 h at room temperature, TBSCl (105 mg, 0.70 mmol) was added to the reaction mixture and stirred for 13.5 h. To the mixture was added saturated aqueous $NaHCO_3$ and the residual aqueous layer was extracted

with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (Hexane/EtOAc = 7:3) to provide the TBS ether **8** (204.5 mg, 0.54 mmol, 62%) and recovered diol **7** (72.5 mg, 0.27 mmol, 32%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70 (1H, d, *J* = 15.4 Hz), 7.44 (1H, dd, *J* = 8.0, 8.0 Hz), 7.25 (1H, d, *J* = 8.0 Hz), 6.87 (1H, d, *J* = 8.0 Hz), 6.15 (1H, dd, *J* = 15.9, 6.3 Hz), 4.42 (1H, br s), 3.77 (1H, dd, *J* = 10.1, 3.8 Hz), 3.58 (1H, dd, *J* = 10.1, 7.7 Hz), 1.71 (6H, s), 0.92 (9H, s), 0.10 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.0, 156.6, 141.2, 135.0, 132.3, 129.9, 121.4, 116.3, 110.8, 105.2, 72.8, 67.0, 25.9, 25.8, 25.5, 18.4, –5.19, –5.24; IR (neat): 3474, 2931, 1735 cm^{-1}; MS (EI): *m/z* 321 (M^+–^{t}Bu); HRMS (EI): calcd for $C_{16}H_{21}O_5Si$ (M^+–^{t}Bu): 321.1158, found: 321.1148; $[\alpha]_D^{22}$ +12.2 (*c* 1.005, $CHCl_3$).

5-[4-(*tert*-Butyldimethylsilyloxy)-3-(*tert*-butyldiphenylsilyloxy)but-1-enyl]-2,2-dimethylbenzo[1,3]dioxin-4-one (9): To a solution of alcohol **8** (724 mg, 1.92 mmol) in CH_2Cl_2 (10 mL) was added TBDPSCl (0.75 mL, 2.87 mmol), imidazole (326 mg, 4.79 mmol) and DMAP (23 mg, 0.192 mmol) at 0 °C. The reaction mixture was stirred for 16 h at room temperature and diluted with saturated aqueous $NaHCO_3$, then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (Hexane/EtOAc = 9:1) to provide the TBDPS ether **9** (1.16 g, 1.88 mmol, 98%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.84–7.78 (4H, m), 7.59 (1H, d, *J* = 15.9 Hz), 7.49–7.39 (7H, m) 7.11 (1H, d, *J* = 7.7 Hz), 6.90 (1H, d, *J* = 8.0 Hz), 6.25 (1H, dd, *J* = 15.9, 6.6 Hz), 4.55–4.49 (1H, m), 3.72–3.58 (2H, m), 1.77 (6H, s), 1.18 (9H, s), 0.90 (9H, s) 0.02 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.7, 156.5, 141.7, 135.9, 135.8, 134.8, 134.7, 134.1, 133.9, 129.4, 129.3, 128.6, 127.4, 127.3, 121.4, 115.8, 110.8, 105.0, 74.7, 67.6, 72.1, 26.0, 25.8, 25.6, 19.4, 18.4, –5.26, –5.31; IR (neat): 2930, 1740 cm^{-1}; MS (EI): *m/z* 559 (M^+–^{t}Bu); HRMS (EI): calcd for $C_{32}H_{39}O_5Si_2$ (M^+–^{t}Bu): 559.2336, found: 559.2294; $[\alpha]_D^{21}$ +58.2 (*c* 1.02, $CHCl_3$).

5-[3-(*tert*-Butyldiphenylsilyloxy)-4-hydroxybut-1-enyl]-2,2-dimethylbenzo[1,3]dioxin-4-one (10): To a solution of TBS ether **9** (500 mg, 0.81 mmol) in MeOH (20 mL) was added 0.5 M aqueous HCl (3.0 mL) and the reaction mixture was stirred for 20 min at 65 °C. To the mixture was added saturated aqueous $NaHCO_3$ and the residual aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (Hexane/EtOAc = 7:3) to provide the alcohol **10** (297 mg, 0.59 mmol, 73%) as an yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72–7.69 (4H, m), 7.43–7.36 (8H, m), 6.91 (1H, d, *J* = 8.0 Hz), 6.84 (1H, d, *J* = 8.2 Hz), 6.03 (1H, dd, *J* = 15.9, 7.1 Hz), 4.52–4.47 (1H, m), 3.61–3.59 (2H, m) 1.58 (6H, s), 1.11 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.8, 156.3, 141.1, 135.7, 135.5, 135.3, 134.9, 133.3, 133.1, 129.9, 129.6, 129.4, 127.5, 127.3, 121.5, 116.1, 110.5, 105.0, 74.8, 66.6,

27.0, 25.8, 25.2, 19.2; IR (neat): 3430, 1638 cm^{-1}; MS (EI): *m/z* 445 (M^+–^{t}Bu); HRMS (EI): calcd for $C_{26}H_{25}O_5Si$ (M^+–^{t}Bu): 445.1471, found: 445.1482; $[\alpha]_D^{20}$ +108.8 (*c* 1.525, $CHCl_3$).

5-[3-(*tert*-Butyldiphenylsilyloxy)penta-1,4-dienyl]-2,2-dimethylbenzo[1,3]dioxin-4-one (3): To a solution of alcohol **10** (31.6 mg, 0.063 mmol) in CH_2Cl_2 (0.5 mL) was added DMP (54 mg, 0.126 mmol) and $NaHCO_3$ (31 mg, 0.378 mmol). The reaction mixture was stirred for 3.5 h at room temperature and diluted with saturated aqueous $NaHCO_3$, then extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude mixture of aldehyde. This compound was used for the next reaction without further purification.

To a suspension of zinc (167 mg, 2.55 mmol) in THF (0.4 mL) at 0 °C was added trimethylaluminium (1.08 M in hexanes, 0.16 mL, 0.17 mmol) and diiodomethane (0.07 mL, 0.851 mmol). After the reaction mixture was stirred for 10 min at room temperature, a solution of the aldehyde in THF (0.5 mL) was added at 0 °C and stirred for 2 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$, filtered through a celite pad and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (Hexane/EtOAc = 9:1) to provide the diene **3** (14.9 mg, 0.0299 mmol, 47% in 2 steps) as an yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.73–7.68 (4H, m), 7.44–7.30 (8H, m), 7.06 (1H, d, *J* = 8.0 Hz), 6.83 (1H, d, *J* = 8.0 Hz), 6.05 (1H, dd, *J* = 15.9, 6.6 Hz), 5.89 (1H, ddd, *J* = 17.3, 10.4, 6.4 Hz), 5.18 (1H, d, *J* = 17.3 Hz), 5.04 (1H, d, *J* = 10.4 Hz), 4.88–4.84 (1H, m), 1.69 (6H, s), 1.11 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.9, 156.6, 141.5, 139.4, 136.0, 135.9, 135.5, 134.9, 133.9, 133.9, 129.5, 129.4, 127.9, 127.4, 121.5, 116.0, 114.5, 110.8, 105.1, 75.2, 27.0, 25.7, 25.5, 19.3; IR (neat): 2932, 1738 cm^{-1}; MS (EI): *m/z* 498 (M^+); HRMS calcd for $C_{31}H_{34}O_4Si$ (M^+): 498.2226, found: 498.2206; $[\alpha]_D^{17}$ +62.9 (*c* 0.42, $CHCl_3$).

5-(3-Hydroxypenta-1,4-dienyl)-2,2-dimethylbenzo[1,3]dioxin-4-one (11): TBDPS ether **10** (17.6 mg, 0.0353 mmol) was charged in test tube. TBAF (1.0 M in THF, 0.1 mL, 0.10 mmol) and AcOH (6 μL, 0.10 mmol) were added into the test tube. After reaction mixture was stirred for 4 h at room temperature, TBAF (1.0 M in THF, 0.07 mL, 0.07 mmol) and AcOH (3 μL, 0.05 mmol) was added into the test tube. The mixture was stirred for 4 h, diluted with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel flash column chromatography (Hexane/EtOAc = 7:3) to provide the alcohol **11** (5.3 mg, 0.0204 mmol, 58%) as an yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.66 (1H, d, *J* = 15.9 Hz), 7.45 (1H, dd, *J* = 8.0, 8.0 Hz), 7.25 (1H, d, *J* = 8.0 Hz), 6.88 (1H, d, *J* = 8.0 Hz), 6.20 (1H, dd, *J* = 15.9, 6.3 Hz), 6.00 (1H, ddd, *J* = 17.3, 10.4, 6.0 Hz), 5.37 (1H, d, *J* = 17.3 Hz), 5.21 (1H, d, *J* = 10.4 Hz), 4.92–4.87 (1H, m), 1.71 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.2, 156.7, 141.1, 135.1, 134.4, 129.3, 129.0, 121.5, 116.4, 115.6, 110.9, 105.3, 73.7, 25.7; IR (neat): 3444, 1735 cm^{-1}; MS (EI): *m/z* 203 (M^+–

HOCHCH=CH_2); HRMS calcd for $C_{12}H_{11}O_3$ (M^+–HOCHCH=CH_2): 203.0708, found: 203.0736; $[\alpha]_D^{24}$ – 12.3 (*c* 0.82, $CHCl_3$).

The optical purities of the alcohol **11** were determined as > 99% ee by chiral HPLC analyses using CHIRALCEL OD-H (eluent: hexane/^{i}PrOH = 9:1, flow rate: 1 mL/min, temperature: 25 °C, retention time: 13.5 min (*R*-isomer) and 15.6 min (*S*-isomer)).

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