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Stereoselective total synthesis of (−)-synrotolide diacetate from D-ribose☆

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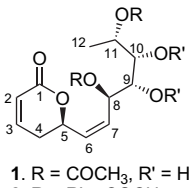
Abstract—Stereoselective total synthesis of synrotolide as its diacetate from D-ribose utilizing a diastereoselective Grignard reaction, preferential (*Z*)-Wittig olefination, asymmetric allylation, and ring closing metathesis as key steps is reported.

1. Introduction

Naturally occurring α,β-unsaturated lactones show varied pharmacological properties, while some exhibits antitumor activity, others posses interesting properties.[1] Notable among them contain a polyoxygenated chain connected with α,β-unsaturated lactone moiety having antimicrobial activity, antifungal activity, or cytotoxicity against human tumor cells.[2] (−)-Synrotolide **1**,[3] an α-pyrone-containing natural product was isolated from *Syncolostemon rotundifolius*, and shares structural similarities with (−)-spicigerolide.[2a] Continuing our interest in the synthesis of lactone skeleton-containing bioactive natural products,[4] herein we report the stereoselective total synthesis of synrotolide as its diacetate (**2**) from D-ribose through a chiron approach.



1. R = $COCH_3$, R' = H
2. R = R' = $COCH_3$

The reported strategy derives stereocenters at C(2), C(3), and C(4) from D-ribose translating as those of C(10), C(9), and C(8) of **2**, respectively. Additionally, chiral center at C(11) was generated by a diastereoselective Grignard reaction, and the one at C(5) by an asymmetric allylation reaction. Finally, the α-pyrone moiety was built from the corresponding bis-olefin by the Grubbs' catalyst assisted RCM protocol.

2. Results and discussion

Thus, the synthesis (Scheme 1) began following the literature procedure. The known[5] 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribofuranose **3**, obtained from D-ribose, on exposure to MeMgI in ether, resulted in a 9:1 separable diastereomeric mixture via a chelation controlled mode in favor of the desired diol **4** as the major product (76%).[6] Later, both the hydroxyl groups in **4** were protected as PMB ethers (PMBBr/NaH/THF/rt) to furnish **5** (74%). Compound **5**, on TBDMS deprotection (TBAF/THF/rt), afforded **6** (92%) with a free primary alcohol, which was oxidized to an aldehyde under Swern reaction conditions and subjected to a Wittig olefination reaction[7] [$(F_3CCH_2O)_2POCH_2COOMe$/KHMDS/18-crown-6/THF/−78 °C], to afford the corresponding α,β-unsaturated ester **7** in 88% yield predominantly as the (*Z*)-isomer, as characterized by ^1H and ^{13}C NMR spectroscopy. The coupling constant (J=9.05 Hz) and the chemical shift values (δ 6.18 and δ 6.00) of the olefinic protons confirmed the (*Z*)-geometry of the olefin.

With ester **7** in hand, our next task was the creation of an additional chiral center that corresponds to C(5) of the target compound. Thus, **7** was subjected to reduction with DIBAL–H in ether to afford the allylic alcohol **8** (95%), which was converted to the α,β-unsaturated aldehyde under Swern reaction conditions. This aldehyde, without further purification, on Keck asymmetric allylation[8] gave **9**, albeit in a low yield of ~25%. However, Maruoka allylation[9] afforded **9** in good yield (70%) as inseparable diastereomers (de 90%). Acryloylation of **9** (CH_2=CH–COCl/DIPEA/CH_2Cl_2/0–rt) gave separable bis-olefin **10** as the major

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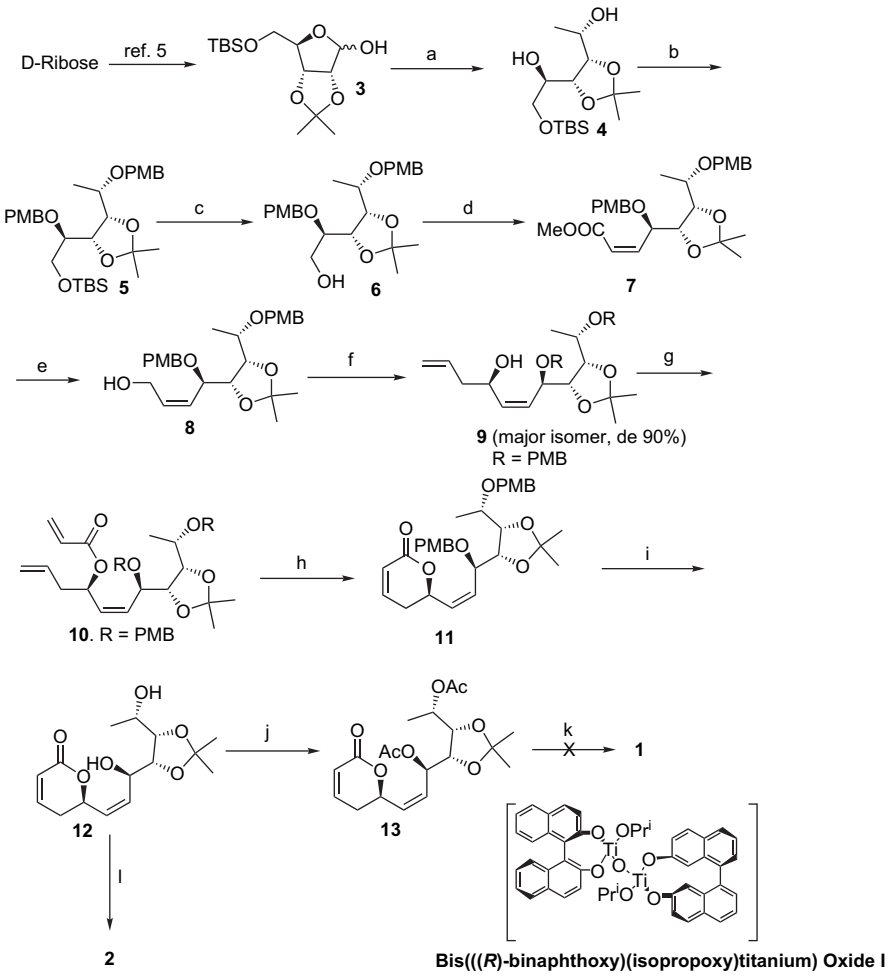

Scheme 1. Reagents and conditions: (a) MeMgI, ether, −78 °C, 6 h (76%); (b) PMBBr, NaH, THF, 0 °C–rt, 10 h (74%); (c) TBAF, THF, rt, 14 h (92%); (d) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h (90%); (ii) $(F_3CCH_2O)_2POCH_2COOMe$, KHMDS, 18-crown-6, THF, −78 °C,4 h (88%); (e) DIBAL–H, ether, 0 °C–rt, 6 h (95%); (f) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h (80%); (ii) **I**, allyltributyltin, CH_2Cl_2, 0 °C, 36 h (70%); (g) CH_2=CH–COCl, DIPEA, CH_2Cl_2, 0 °C–rt, 10 h (90%); (h) 10% PhCH=$RuCl_2(PCy_3)_2$, CH_2Cl_2, reflux, 8 h (85%); (i) $AlCl_3$, EtSH, CH_2Cl_2, rt, 0.5 h (70%); (j) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C–rt (90%); (k) $CuCl_2\cdot 2H_2O$, MeCN, rt, 5 h (88%); (l) (i) $CuCl_2\cdot 2H_2O$, MeCN, rt, 5 h; (ii) Ac_2O, pyridine, rt, 12 h (66% over two steps).

isomer in 90% yield. The newly created stereocenter was tentatively assigned as depicted in Scheme 1, based on literature precedence but was conclusively proved later. The RCM of **10** using Grubbs' catalyst[10] [10% PhCH=$RuCl_2(PCy_3)_2$/CH_2Cl_2/reflux/8 h] gave the α,β-unsaturated lactone **11** in 85% yield. With the complete skeleton in hand, wherein all the hydroxyl functionalities were present in their protected form, a stepwise release was planned. Initially, deprotection of PMB ethers was contemplated so that they in turn could be acetylated. Thus, Lewis acid[11] ($AlCl_3$/EtSH/CH_2Cl_2) mediated PMB deprotection of **11** gave **12** (70%), which on subsequent acetylation (Ac_2O/Et_3N/DMAP/CH_2Cl_2) afforded **13** (90%). Next, selective deprotection[12] of acetonide ($CuCl_2\cdot 2H_2O$/MeCN/rt/5 h) resulted in a product in 88% yield. However, ^1H NMR, physical data, and $[\alpha]_D^{25}$ values did not match with the reported values of the natural product. At this point in the synthesis, all our efforts to isolate **1** in homogeneous form did not bear fruit under different reaction conditions of acetonide deprotection, due to the parallel migration of allylic acetate. Hence it was decided to synthesize synrotolide as its diacetate derivative (**2**). Accordingly, **12** on acetonide deprotection ($CuCl_2\cdot 2H_2O$/MeCN/rt/5 h) and acetylation (Ac_2O/pyridine/rt/12 h), afforded **2**, mp 98–101 °C; $[\alpha]_D^{25}$ −10.60 (*c* 0.05, $CHCl_3$);{lit.[3] mp 102–103 °C; $[\alpha]_D^{25}$ −11.00 (*c* 0.09, $CHCl_3$)} in 66% yield over two steps. The physical and spectroscopic data of **2** were identical to the reported values of synrotolide diacetate. The synthesis of **2** also established the assigned stereochemistry of **9**. It is interesting to note that many bioactive natural products like spicigerolide[2a] and anamarine[13] are endowed with tetraacetates on their skeletons.

In conclusion, a stereoselective total synthesis of synrotolide diacetate was accomplished by a versatile strategy. A combination of diastereoselective Grignard reaction, preferential (*Z*)-Wittig olefination, asymmetric allylation, and ring closing metathesis was effectively utilized in accomplishing the synthesis.

3. Experimental

3.1. General methods

Solvents were dried over standard drying agents and freshly distilled prior to use. Chemicals were purchased and used

without further purification. All column chromatographic separations were performed using silica gel (Acme's, 60–120 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuo. ^1H NMR (200, 300, and 400 MHz) and ^{13}C NMR (50 and 75 MHz) spectra were measured with a Varian Gemini FT-200 MHz spectrometer, Bruker Avance 300 MHz, and Unity 400 MHz with tetramethylsilane as an internal standard for solutions in deuteriochloroform. *J* values are given in hertz. IR spectra were recorded on a Perkin–Elmer IR-683 spectrophotometer with NaCl optics. Optical rotations were measured with JASCO DIP 300 digital polarimeter at 25 °C. Mass spectra were recorded on CEC-21-11013 or Finnigan Mat 1210 double focusing mass spectrometer operating at a direct inlet system or LC/MSD Trap SL (Agilent Technologies).

3.2. (1*R*)-2-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-1-(4*R*,5*S*)-5-[(1*S*)-1-hydroxyethyl]-2,2-dimethyl-1,3-dioxolan-4-ylethan-1-ol (4)

To a solution of 2,3-*O*-isopropylidene-5-*O*-*tert*-butyldimethyl silyl-α-D-ribofuranose **3** (6.00 g, 19.70 mmol) in anhydrous ether (60.0 mL), MeMgI [prepared from Mg (1.44 g, 59.21 mmol) and MeI (3.69 mL, 59.21 mmol)] was added under an N_2 atmosphere at −78 °C and stirred for 6 h. After the completion of the reaction, it was quenched with saturated aq NH_4Cl (15 mL) and extracted with ethyl acetate (2×60 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated, and the residue was purified over silica gel (EtOAc/*n*-hexane, 1:19) to give a separable diastereomeric mixture (dr 9:1) of diol **4** (4.71 g, 76%) as the major product as a thick syrup. $[\alpha]_D^{25}$ +39.19 (*c* 0.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.95–3.75 (m, 4H), 3.68 (dt, 1H, *J*=3.0, 6.8, 9.8 Hz), 3.55 (dd, 1H, *J*=6.7, 9.8 Hz), 1.29 (s, 3H), 1.25 (s, 3H), 1.19 (d, 3H, *J*=6.0 MHz), 0.85 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 108.20, 82.00, 77.60, 70.00, 65.40, 64.60, 28.00, 26.00, 25.20, 20.20, 18.20, −5.50, −5.61; IR (thin film): 3417, 2931, 2859, 1251, 1220, 1116, 1066, 836, 778 cm^{-1}; FABMS: 321 $[M]^+$, 205 $[M-TBS]^+$. Anal. Calcd for $C_{15}H_{32}O_5Si$: C, 56.21; H, 10.06. Found: C, 56.19; H, 10.08%.

3.3. 2-(*tert*-Butyl)-2-[(2*R*)-2-[(4-methoxybenzyl)oxy]-2-((4*R*,5*S*)-5-(1*S*)-1-[(4-methoxybenzyl)oxy]ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl]oxydimethylsilane (5)

To a suspension of diol **4** (1.58 g, 49.96 mmol) in anhydrous THF (10 mL), NaH (0.41 g, 17.28 mmol) in anhydrous THF (5 mL) was slowly added at 0 °C followed by addition of PMBBr (3.78 g, 17.28 mmol). The reaction mixture was stirred at room temperature for 10 h, quenched with saturated aq NH_4Cl, and extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with brine (1×10 mL), dried (Na_2SO_4), concentrated, and the residue was purified over silica gel (EtOAc/*n*-hexane, 1:32) to afford the PMB ether **5** (2.05 g, 74%) as colorless syrup. $[\alpha]_D^{25}$ +26.29 (*c* 1.02, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.02 (d, 4H, *J*=7.7 Hz), 6.65 (d, 4H, *J*=7.7 Hz), 4.51 (d, 1H, *J*=11.1 Hz), 4.29 (q, 2H, *J*=6.6, 11.0 Hz), 4.20 (q, 2H, *J*=6.6, 11.0 Hz), 4.09–4.01 (m, 2H), 3.85 (m, 1H), 3.68 (s, 6H), 3.65 (m, 2H), 1.35 (s, 3H), 1.24 (s, 3H), 1.15 (d, 3H, *J*=5.5 Hz), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.24, 130.85, 129.50, 113.60, 108.00, 79.00, 78.30, 76.18, 73.42, 71.56, 69.79, 64.17, 55.18, 26.78, 25.89, 25.67, 24.81, 18.38, 16.11, −5.41, −5.47; IR (neat): 2931, 1514, 1248, 1082, 835 cm^{-1}; FABMS: 578 $[M+NH_4]^+$. Anal. Calcd for $C_{31}H_{48}O_7Si$: C, 66.39; H, 8.63. Found: C, 66.42; H, 8.66%.

3.4. (2*R*)-2-[(4-Methoxybenzyl)oxy]-2-((4*R*,5*S*)-5-(1*S*)-1-[(4-methoxybenzyl)oxy]ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)ethan-1-ol (6)

A stirred solution of **5** (0.86 g, 1.54 mmol) in anhydrous THF (5 mL) was treated with TBAF (2.3 mL, 2.31 mmol, 1 M solution in THF) for 14 h at room temperature. The reaction mixture was extracted with ethyl acetate (2×25 mL) and the combined organic layers were washed with brine (1×10 mL), dried (Na_2SO_4), concentrated, and the residue was purified over silica gel (EtOAc/*n*-hexane, 1:45) to give **6** as light yellow syrup (0.63 g, 92%). $[\alpha]_D^{25}$ +57.25 (*c* 1.86, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.11 (d, 4H, *J*=8.5 Hz), 6.74 (d, 4H, *J*=8.5 Hz), 4.48−4.21 (m, 7H), 4.07 (t, 1H, *J*=6.7 Hz), 3.75 (s, 6H), 3.71 (m, 2H), 1.42 (s, 3H), 1.33 (s, 3H), 1.25 (d, 3H, *J*=5.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.40, 130.01, 129.83, 128.95, 113.33, 107.49, 79.07, 76.27, 72.6, 70.72, 69.41, 61.67, 54.80, 26.50, 26.29, 16.08; IR (neat): 3456, 1514, 1248, 1077, 1035, 821 cm^{-1}; LCMS: 464 $[M+NH_4]^+$. Anal. Calcd for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found: C, 67.22; H, 7.80%.

3.5. Methyl-(*Z*,4*R*)-4-[(4-methoxybenzyl)oxy]-4-((4*R*,5*S*)-5-(1*S*)-1-[(4-methoxybenzyl)oxy]ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2-butenoate (7)

To a stirred solution of oxalyl chloride (0.37 mL, 3.36 mmol) in CH_2Cl_2 (5 mL) at −78 °C, DMSO (0.32 mL, 4.93 mmol) was added followed by compound **6** (1.00 g, 2.24 mmol) in CH_2Cl_2 (5 mL) and the contents were stirred for 1 h at −78 °C. Later, the reaction mixture was quenched with Et_3N (0.935 mL, 6.72 mmol) and diluted with CH_2Cl_2 (25 mL). The combined organic layers were washed with brine (1×15 mL), dried (Na_2SO_4), concentrated, and the residue was passed through a pad of silica gel to give the corresponding aldehyde (0.895 g, 90%), which was used as such for further reaction. To a stirred solution of $(F_3CCH_2O)_2POCH_2COOMe$ (0.56 mL, 2.66 mmol), 18-crown-6 (2.47 g, 9.36 mmol) in anhydrous THF (2 mL) at −78 °C followed by KHMDS (0.67 g, 2.93 mmol) was added and the reaction mixture was stirred for 30 min. To the reaction mixture, the aldehyde (0.80 g, 1.80 mmol) dissolved in THF (5 mL) was added. The reaction mixture was stirred for 4 h, quenched with saturated aq NH_4Cl, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated, and the residue was purified over silica gel (EtOAc/*n*-hexane, 1:9) to give the product **7** (0.79 g, 88%) as colorless syrup. $[\alpha]_D^{25}$ +58.57 (*c* 0.78, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.14 (d, 2H, *J*=8.3 Hz), 7.06 (d, 2H, *J*=8.3 Hz), 6.72 (dd, 4H, *J*=5.2, 8.3 Hz), 6.18 (dd, 1H, *J*=9.0, 12.0 Hz), 6.00 (d, 1H, *J*=11.3 Hz), 5.40 (dd, 1H, *J*=6.7, 9.0 Hz), 4.44 (d, 1H, *J*=11.3 Hz), 4.30 (q, 2H, *J*=8.3, 11.3 Hz), 4.22–4.08 (m, 3H), 3.77 (m, 1H), 3.75 (s, 6H), 3.72 (s, 3H), 1.39 (s, 3H), 1.29 (s, 3H), 1.26 (d, 3H,

J=6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.34, 158.86, 145.90, 129.58, 129.09, 123, 113.60, 131.00, 130.33, 108.02, 79.73, 78.17, 72.70, 71.68, 70.37, 69.68, 55.17, 51.33, 26.65, 25.04, 16.28; IR (neat): 1726, 1514, 1248, 1078, 1035, 822 cm^{-1}; LCMS: 518 $[M+NH_4]^+$. Anal. Calcd for $C_{28}H_{36}O_8$: C, 67.18; H, 7.25. Found: C, 67.15; H, 7.30%.

3.6. (*Z*,4*R*)-4-[(4-Methoxybenzyl)oxy]-4-((4*R*,5*S*)-5-(1*S*)-1-[(4-methoxybenzyl)oxy]ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2-buten-1-ol (8)

To a stirred solution of **7** (1.60 g, 3.20 mmol) in anhydrous ether (10 mL), DIBAL–H (5.68 mL, 8.00 mmol, 20% solution in toluene) was added dropwise at 0 °C and stirred for 6 h and diluted with methanol, sodium potassium tartrate, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated, and the residue was purified over silica gel (EtOAc/*n*-hexane, 1:3) to afford **8** (1.42 g, 95%) as thick syrup. $[\alpha]_D^{25}$ +24.30 (*c* 2.96, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.15 (d, 2H, J=8.4 Hz), 6.98 (d, 2H, J=8.4 Hz), 6.75 (dd, 4H, J=8.4, 12.9 Hz), 6.01 (td, 1H, J=6.8, 10.6 Hz), 5.55 (t, 1H, J=9.9 Hz), 4.47–4.30 (m, 4H), 4.24 (dd, 1H, J=4.5, 6.1 Hz), 4.14–4.03 (m, 3H), 3.96 (dd, 1H, J=6.8, 12.9 Hz), 3.76 (s, 3H), 3.759 (s, 3H), 3.719 (dd, 1H, J=4.5, 6.1 Hz), 2.35 (br s, 1H, OH), 1.44 (s, 3H), 1.32 (s, 3H), 1.16 (d, 3H, J=6.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.79, 158.51, 133.61, 130.20, 129.28, 128.67, 113.17, 107.48, 78.88, 76.39, 72.21, 71.40, 69.16, 68.93, 57.97, 54.68, 25.97, 24.31, 15.71; IR (neat): 3448, 1612, 1514, 1248, 1076, 1034, 821 cm^{-1}; LCMS: 495 $[M+Na]^+$. Anal. Calcd for $C_{27}H_{36}O_7$: C, 68.62; H, 7.68. Found: C, 68.65; H, 7.64%.

3.7. (5*Z*,7*R*)-7-[(4-Methoxybenzyl)oxy]-7-((4*R*,5*S*)-5-(1*S*)-1-[(4-methoxybenzyl)oxy]ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)-1,5-heptadien-4-ol (9)

To a stirred solution of oxalyl chloride (0.44 mL, 4.00 mmol) in CH_2Cl_2 at –78 °C, DMSO (0.38 mL, 5.33 mmol) was added followed by compound **8** (1.26 g, 2.67 mmol) in CH_2Cl_2 and the reaction mixture was stirred for 1 h at −78 °C, quenched with Et_3N (1.11 mL, 8.0 mmol), and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give the corresponding aldehyde (1.00 g, 80%), which was used directly for further reaction.

To a stirred solution of $TiCl_4$ (0.03 mL, 0.25 mmol) in CH_2Cl_2 was added dried $Ti(O^iPr)_4$ (0.22 mL, 0.74 mmol) at 0 °C under N_2. The solution was allowed to warm to room temperature. After 1 h, (*R*)-binaphthol (0.28 g, 0.99 mmol) was added at room temperature and the solution was stirred for 3 h. The mixture was cooled to 0 °C, and treated with silver(I) oxide (0.11 g, 0.49 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature, and stirred there for 5 h under exclusion of direct light to furnish chiral bisTi(IV) oxide (*R*,*R*)-**I** was treated with compound **8** (1.16 g, 2.46 mol) and allyltributyltin (0.85 mL, 2.71 mol) at −15 °C. The whole mixture was warmed to 0 °C and allowed to stir for 36 h. The reaction mixture was quenched with saturated $NaHCO_3$, and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried (Na_2SO_4), concentrated, and the residue was purified over silica gel (EtOAc/*n*-hexane, 1:3.5) to give the allylated product **9** (0.88 g, 70%) as light yellow syrup. $[\alpha]_D^{25}$ +12.86 (*c* 0.003, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.09 (dd, 2H, J=3.7, 8.3 Hz), 7.03 (d, 2H, J=8.3 Hz), 6.76–6.72 (m, 4H), 5.85–5.46 (m, 3H), 5.14–5.08 (m, 2H), 4.40 (dd, 2H, J=6.0, 11.3 Hz), 4.23–4.05 (m, 5H), 3.90 (dq, 1H, J=2.2, 6.0 Hz), 3.76 (s, 3H), 3.75 (s, 3H), 3.70 (dd, 1H, J=2.2, 6.7 Hz), 2.29 (dd, 2H, J=6.0, 12.0 Hz), 1.41 (s, 3H), 1.31 (s, 3H), 1.21 (d, 3H, J=6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.10, 137.24, 134.11, 130.37, 128.02, 127.32, 118.18, 113.73, 108.88, 79.61, 78.99, 72.39, 71.51, 69.26, 55.20, 41.90, 26.79, 25.01, 16.60; IR (neat): 3445, 2930, 1609, 1513, 1250, 1073, 1034, 822 cm^{-1}; FABMS: 530 $[M+NH_4]^+$. Anal. Calcd for $C_{30}H_{40}O_7$: C, 70.29; H, 7.86. Found: C, 70.26; H, 7.82%.

3.8. (*Z*,4*R*)-1-Allyl-4-[(4-methoxybenzyl)oxy]-4-((4*R*,5*S*)-5-(1*S*)-1-[(4-methoxybenzyl)oxy]ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2-butenyl acrylate (10)

To a stirred solution of **9** (0.40 g, 0.78 mmol) and *N*-ethyldiisopropylamine (0.14 mL, 1.56 mmol) in CH_2Cl_2 (5 mL), acryloyl chloride (0.07 mL, 1.09 mmol) was added dropwise at 0 °C and stirred at room temperature for 10 h. The reaction mixture was treated with water (1×15 mL) and extracted into CH_2Cl_2 (2×15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/*n*-hexane, 1:9) to afford the acrylate **10** (0.39 g, 90%) as thick yellow syrup. $[\alpha]_D^{25}$ +16.13 (*c* 1.38, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.05 (dd, 4H, J=8.5, 16.4 Hz), 6.74 (dd, 4H, J=3.1, 8.5 Hz), 6.409 (dd, 1H, J=1.5, 17.1 Hz), 6.09 (dd, 1H, J=10.1, 17.1 Hz), 5.84–5.643 (m, 3H), 5.50–5.31 (m, 2H), 5.13–5.04 (m, 2H), 4.39 (dd, 2H, J=3.9, 10.9 Hz), 4.25–4.00 (m, 4H), 3.89 (dt, 1H, J=4.6, 7.8 Hz), 3.76 (s, 3H), 3.757 (s, 3H), 3.71–3.65 (m, 1H), 2.41 (m, 2H), 1.41 (s, 3H), 1.30 (s, 3H), 1.18 (d, 3H, J=5.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.76, 158.66, 132.85, 132.36, 132.10, 131.81, 130.35, 130.14, 129.86, 128.17, 117.88, 117.23, 113.16, 107.28, 79.1, 78.98, 77.55, 72.55, 69.58, 69.38, 69.20, 68.78, 54.53, 38.30, 26.26, 24.40, 15.47; IR (neat): 2930, 1722, 1513, 1248, 1190, 1037, 817 cm^{-1}; LCMS: 584 $[M+NH_4]^+$. Anal. Calcd for $C_{33}H_{42}O_8$: C, 69.94; H, 7.47. Found: C, 69.91; H, 7.44%.

3.9. (6*R*)-6-[(*Z*,3*R*)-3-[(4-Methoxybenzyl)oxy]-3-((4*R*,5*S*)-5-(1*S*)-1-[(4-methoxybenzyl)oxy]ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)-1-propenyl]-5,6-dihydro-2*H*-2-pyranone (11)

A solution of **10** (0.41 g, 0.72 mmol) and first generation Grubbs' catalyst (0.059 g, 0.07 mmol) in anhydrous CH_2Cl_2 (15 mL) was stirred at reflux for 8 h. After the completion of the reaction, solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel, EtOAc/*n*-hexane, 1:4) to afford **11** (0.33 g, 85%) as thick syrup. $[\alpha]_D^{25}$ +11.66 (*c* 0.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12–7.02 (m, 4H), 6.82–6.72 (m, 5H), 6.00 (d, 1H, J=9.8 Hz), 5.78 (m, 1H), 5.58 (ddd, 1H, J=5.2, 6.7, 6.0 Hz), 4.88 (q, 1H, J=6.7 Hz), 4.46–4.38 (m,

2H), 4.21–4.15 (m, 3H), 4.07–3.93 (m, 2H), 3.76 (s, 6H), 3.70 (t, 1H, J=6.7 Hz), 2.36 (m, 2H), 1.40 (s, 3H), 1.30 (s, 3H), 1.21 (d, 3H, J=5.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.00, 159.00, 144.00, 131.00, 130.80, 129.00, 127.60, 121.20, 113.60, 108.00, 79.50, 77.00, 72.00, 69.60, 69.00, 55.00, 29.00, 26.50, 24.50, 16.40; IR (thin film): 3380, 2926, 2856, 1722, 1514, 1379, 1247, 1033, 817 cm^{-1}; ESIMS: 556 $[M+NH_4]^+$. Anal. Calcd for $C_{31}H_{38}O_8$: C, 69.13; H, 7.11. Found: C, 69.10; H, 7.07%.

3.10. (6*R*)-6-((*Z*,3*R*)-3-Hydroxy-3-(4*R*,5*S*)-5-[(1*S*)-1-hydroxyethyl]-2,2-dimethyl-1,3-dioxolan-4-yl-1-propenyl)-5,6-dihydro-2*H*-2-pyranone (12)

To a stirred solution of **11** (0.22 g, 0.41 mmol) in anhydrous CH_2Cl_2 (8 mL) was added EtSH (0.12 mL, 1.63 mmol) followed by $AlCl_3$ (0.03 g, 0.24 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 30 min and then quenched with saturated aq $NaHCO_3$ solution. The organic layers were extracted with ethyl acetate, washed with brine, and dried (Na_2SO_4). After evaporation of the solvent, the crude residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:3) to afford **12** (0.085 g, 70%) as syrup. $[\alpha]_D^{25}$ +28.83 (*c* 0.95, $CHCl_3$); ^{1}H NMR (300 MHz): δ 6.85 (ddd, 1H, J=9.8, 6.0, 3.7 Hz), 6.00 (br d, 1H, J=9.8 Hz), 5.69 (dd, 1H, J=7.5, 2.6 Hz), 5.33 (m, 1H), 4.56 (ddd, 1H, J=12.0, 8.3, 2.0 Hz), 4.08 (q, 1H, J=14.3, 6.7 Hz), 4.04–3.87 (m, 3H), 2.44 (m, 2H), 1.46 (s, 3H), 1.35 (s, 3H), 1.26 (d, 3H, J=6.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 162.82, 142.02, 132.76, 128.06, 122.13, 106.34, 82.00, 65.02, 64.20, 60.96, 30.80, 26.11, 25.37, 16.82; IR (thin film): 3426, 3390, 2889, 1721, 1369, 1219, 1038, 828, 775 cm^{-1}; FABMS: 321 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.33; H, 7.38%.

3.11. (1*R*,2*R*,3*Z*)-2-(Acetyloxy)-1-[(1*S*,2*S*)-1,2-di(acetyloxy)propyl]-4-[(2*R*)-6-oxo-3,6-dihydro-2*H*-2-pyranyl]-3-butenyl acetate (2)

To a solution of **12** (0.08 g, 0.27 mmol) in MeCN (2 mL) was added $CuCl_2\cdot 2H_2O$ (0.14 g, 0.80 mmol) at 0 °C. After 5 h, the reaction was quenched by adding saturated aq $NaHCO_3$ solution at the same temperature, filtered through Celite, and washed with ethyl acetate. The combined organic layers were dried (Na_2SO_4), concentrated, and chromatographed over silica gel to give the corresponding tetrol (0.06 g, 88%). The tetrol (0.06 g, 0.23 mmol) was dissolved in pyridine, Ac_2O (0.09 mL, 0.93 mmol) was added at 0 °C, and stirred for 12 h. Then the reaction mixture was quenched with aq $CuSO_4$ and extracted with ethyl acetate (2×10 mL), and the organic phase was washed with brine and dried (Na_2SO_4). After evaporation of the solvent, the crude residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:5.6) to afford the desired product **2** (0.065 g, 66% for overall two steps). Mp 98–101 °C; $[\alpha]_D^{25}$ −10.60 (*c* 0.05, $CHCl_3$); ^{1}H NMR (300 MHz): δ 6.89 (ddd, 1H, J=9.8, 5.8, 3.2 Hz), 6.06 (br d, 1H, J=9.8 Hz), 5.86–5.82 (m, 2H), 5.44 (ddd, 1H, J=7.2, 3.8, 1.7 Hz), 5.29 (dd, 1H, J=7.9, 3.5 Hz), 5.23 (ddd, 1H, J=7.9, 3.4, 1.2 Hz), 5.04 (dd, 1H, J=6.8 Hz), 4.96 (m, 1H), 2.41 (m, 2H), 2.12 (s, 6H), 2.06 (s, 3H), 2.02 (s, 3H), 1.25 (d, 3H, J=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.20, 170.10, 169.69, 169.64, 162.70, 144.50, 132.50, 126.00, 121.40, 76.72, 71.90, 70.80, 68.50, 29.20, 21.10, 21.00, 20.80, 14.50; IR (KBr): 3432, 2924, 1739, 1714, 1633, 1383, 1259, 1022, 960 cm^{-1}; EIMS: 426 $[M]^+$, 196, 178, 153, 136. Anal. Calcd for $C_{20}H_{26}O_{10}$: C, 56.33; H 6.15. Found: C, 56.30; H, 6.11%.

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