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Total synthesis of (+)-synargentolide A

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ABSTRACT

The highly stereoselective total synthesis of polyacetate α,β-unsaturated δ-lactone natural product (+)-synargentolide A has been accomplished from inexpensive D-1,5-gluconolactone. Key reactions involved in the synthesis are hydroboration, Wittig olefination, Brown's asymmetric allylation, and a ring closing metathesis reaction.

1. Introduction

The polyacetate α,β-unsaturated δ-lactone ring containing natural products displays a wide range of biological activities.[1] Among them (+)-synargentolide A **1**,[2] hyptolide **2**,[3] spicigerolide **3**,[4] anamarine **4**,[5] and synrotolide **5**,[6] were isolated from *Syncolostemon* and *Hyptis* species (Fig. 1) and exhibit cytotoxicity against human tumor cells, as well as antifungal and antimicrobial activity.[7] Due to their biological activities, these molecules have become interesting synthetic targets for chemists.[1c,8] (+)-Synargentolide A can be isolated from the extracts of *Syncolostemon argenteus*; the structure was proposed to be **1b** by Davies–Coleman and Rivett[2] on the basis of extensive spectroscopic analysis, but has recently been revised to be **1a**.[9] To date, five total syntheses have been reported in the literature.[9,10]

As part of our ongoing research program on the total synthesis of biologically active lactone containing natural products,[11] we herein report an efficient stereoselective total synthesis of (+)-synargentolide A from the inexpensive and readily available starting material D-1,5-gluconolactone.

2. Results and discussion

Our retrosynthetic analysis revealed that the target molecule **1a** (Scheme 1) could be obtained via deprotection followed by acylation of **6**, which in turn can be prepared from **7** by acryloylation followed by ring-closing metathesis. Compound **7** is accessible from **8** via DIBAL-H reduction, oxidation, and Brown's asymmetric allylation. Compound **8** could be constructed by a sequence of reactions from olefin **9**, which in turn could be obtained from the chiral pool starting material D-1,5-gluconolactone.

Our synthesis started with D-1,5-gluconolactone, which was converted to diol **10** by known protocol.[12] Diol **10** was subjected to reductive elimination[13] with iodine-PPh_3-imidazole at reflux

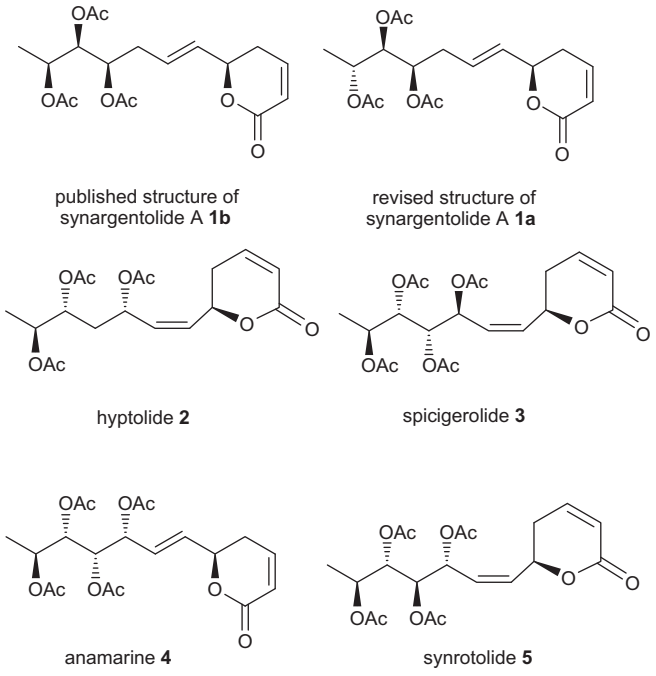

Figure 1. Polyacetate α,β-unsaturated δ-lactone natural products.

for 1 h to give olefin **9**. Compound **9** was subjected to hydroboration using 9-BBN[13c,14] to furnish the primary alcohol **11** in 78% yield. The primary hydroxy group of compound **11** was protected as the benzyl ether in the presence of NaH, BnBr, and *cat* TBAI in anhydrous THF to afford **12** in 95% yield. Selective deprotection of the terminal acetonide with PPTS in methanol furnished diol **13**. The primary alcohol was converted into the corresponding tosylate and treated with $LiAlH_4$ to give **14** in 85% yield over two steps. The secondary alcohol of compound **14** was protected as

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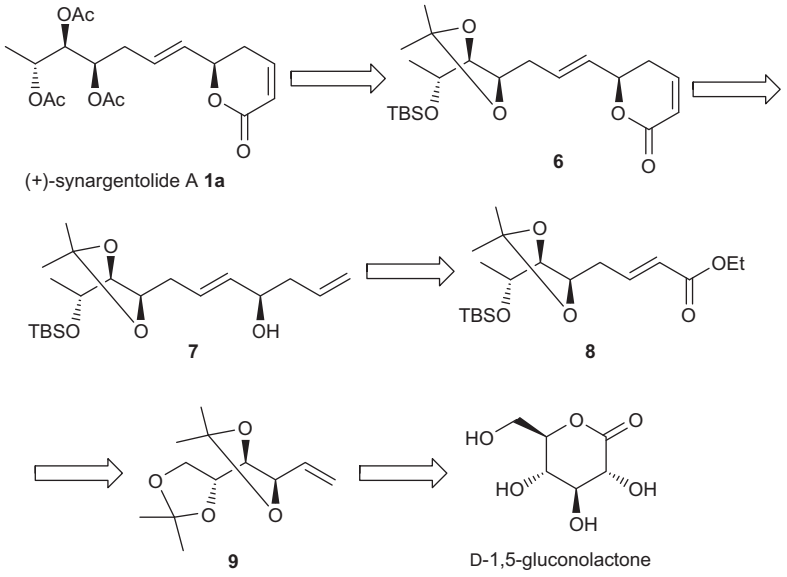
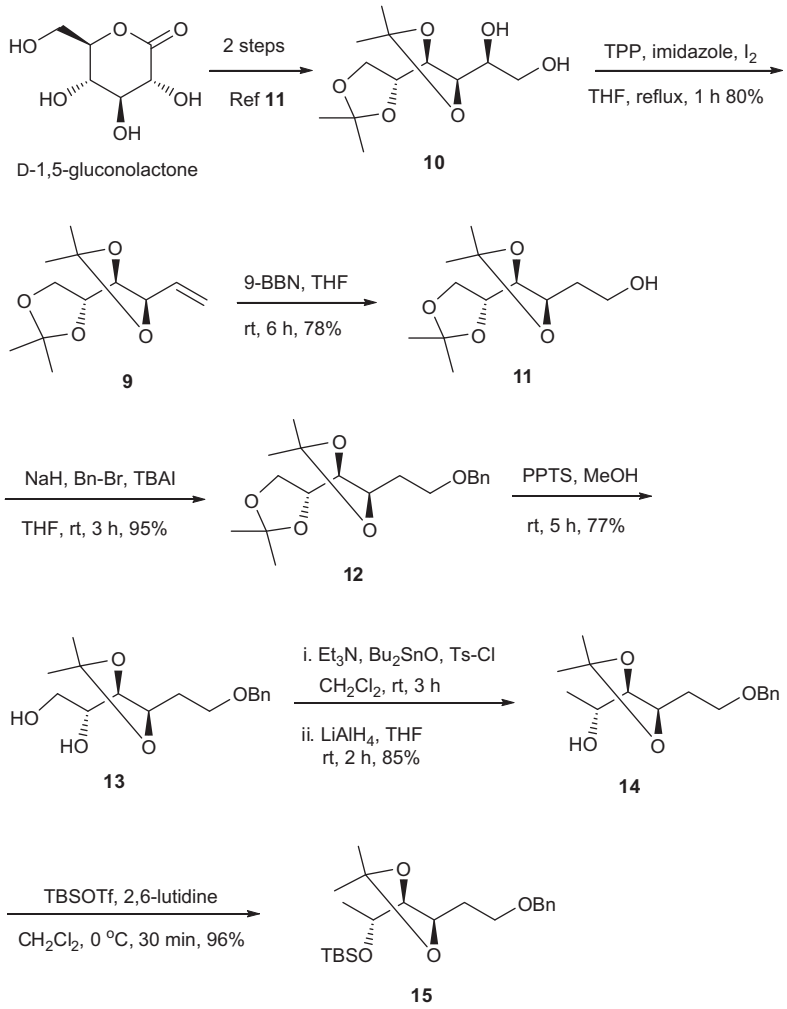


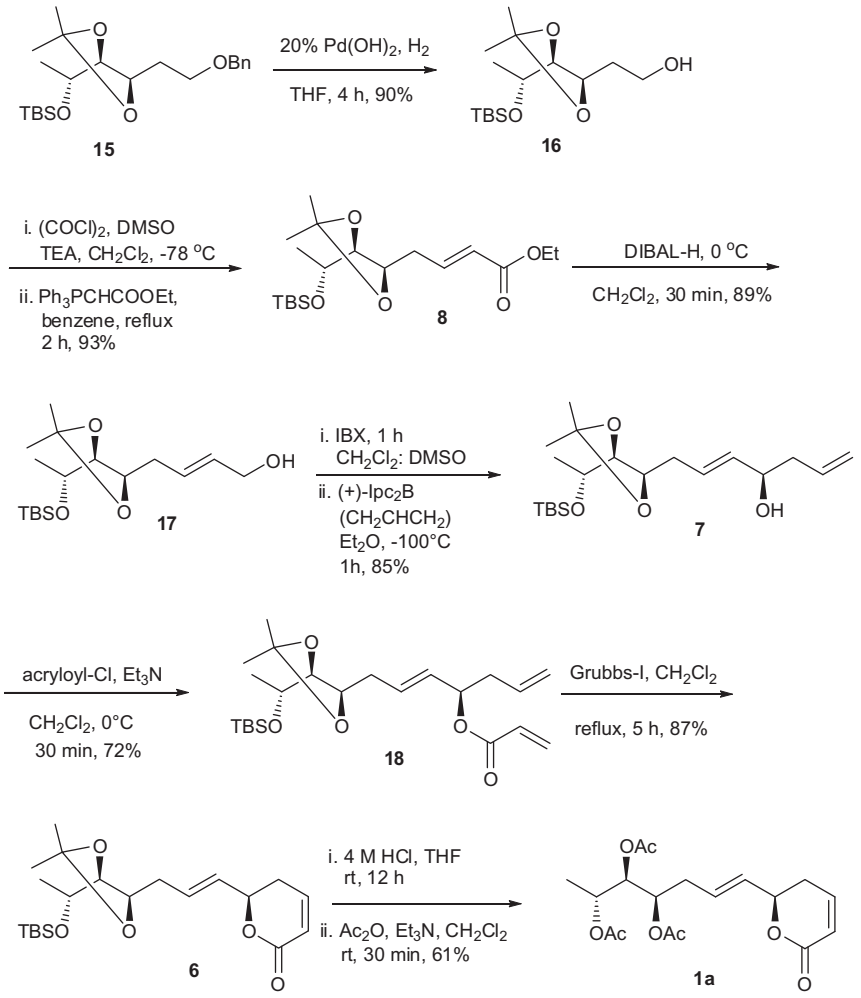
Scheme 1. Retrosynthetic analysis of (+)-synargentolide A.



Scheme 2. Synthesis of the compound **15**.

the TBS ether with TBSOTf and 2,6-lutidine in CH_2Cl_2 to furnish **15** in 96% yield (Scheme 2).

The cleavage of benzyl ether in **15** using $Pd(OH)_2$ afforded the primary alcohol **16**. Oxidation of **16** under Swern conditions gave



Scheme 3. Synthesis of (+)-synargentolide A **1a**.

the corresponding aldehyde, which was subjected to C_2-Wittig olefination to yield α,β-unsaturated ester **8** in 93% yield. Reduction of the ester **8** to allylic alcohol **17** was achieved with DIBAL-H. The allylic alcohol **17** was oxidized with IBX to furnish an α,β-unsaturated aldehyde, which was allylated with (+)-Ipc_2B(allyl) (Brown's asymmetric allylation)[15] to furnish the required homoallylic alcohol **7** as a single diastereomer.[16] Acryloylation of **7** with acryloyl chloride, Et_3N in anhydrous CH_2Cl_2 furnished acrylate **18**, which was subjected to ring closing metathesis (RCM) with Grubbs' first generation catalyst[17] to furnish lactone **6** in 87% yield. Finally, the cleavage of the protecting groups in lactone **6** with 4 M HCl in THF gave trihydroxy lactone, which was acylated in the presence of Ac_2O, Et_3N, and *cat* DMAP to afford (+)-synargentolide A in 61% yield (Scheme 3). The spectroscopic data and specific rotation of our synthetic compound **1a** $[\alpha]_D^{25} = +53.8$ (*c* 0.8, $CHCl_3$), were in agreement with the data previously reported; Lit.[2] $[\alpha]_D$ = +40 (*c* 1.1, $CHCl_3$); Lit. [9b] $[\alpha]_D$ = +66.4 (*c* 1.0, $CHCl_3$).

3. Conclusions

In conclusion, we have demonstrated an efficient and straightforward strategy for the total synthesis of (+)-synargentolide A, in a highly stereoselective manner starting from inexpensive and readily available D-1,5-gluconolactone. The synthesis involves hydroboration, C_2-Wittig olefination, Brown's asymmetric allylation, and ring closing metathesis as key reactions.

4. Experimental section

4.1. General

All reagents were of reagent grade and used without further purification unless specified otherwise. Solvents for the reactions were distilled prior to use: THF, toluene, and diethyl ether were distilled from Na and benzophenone ketyl and CH_2Cl_2 from CaH_2. All air- and moisture-sensitive reactions were conducted under a nitrogen atmosphere in flame-dried or oven-dried glassware with magnetic stirring. The ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ as the solvent on a 300 MHz spectrometer at ambient temperature. The coupling constants *J* are given in Hz. The chemical shifts are reported in ppm on a scale downfield from TMS as the internal standard and signal patterns are indicated as follows: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, td = triplet of double, q = quartet, m = multiplet, br = broad. FTIR spectra were recorded on KBr pellets $CHCl_3$/neat (as mentioned) and reported in wave number (cm^{-1}). Optical rotations were measured on a digital polarimeter using a 1 mL cell with a 1 dm path length. For low (MS) and high (HRMS) resolutions, *m*/*z* ratios are reported as values in atomic mass units. Mass analysis was performed in ESI mode. Column chromatography was carried out using silica gel (60–120 mesh or 100–200 mesh) packed in glass columns. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use.

4.1.1. (4*S*,4^1*R*,5*R*)-2,2,2^1,2^1-Tetramethyl-5-vinyl-4,4^1-bi(1,3-dioxolan) 9

To a stirred solution of diol **10** (10 g, 38.16 mmol) in dry THF (150 ml) were added triphenylphosphine (30.0 g, 114.50 mmol) and imidazole (15.6 g, 229.00 mmol) followed by iodine (29.0 g, 114.50 mmol) at 0 °C. The reaction mixture was refluxed for 1 h, cooled to room temperature, then decanted into saturated aqueous $Na_2S_2O_3$ (100 ml) and extracted with ethyl acetate (2 × 30 mL). The combined organic phase was washed with saturated aqueous $Na_2S_2O_3$ (1 × 50 mL), saturated aqueous $NaHCO_3$ (1 × 40 mL), and with brine (1 × 30 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was subjected to flash column chromatography (silica gel, 5% EtOAc/hexane as an eluent) to afford olefin **9** (6.96 g, 80%) as a colorless oil R_f = 0.5 (silica gel, 10% EtOAc/hexane). $[\alpha]_D^{25} = -5.75$ (*c* 3.0, $CHCl_3$). IR (neat) ν_{max}: 2932, 1379, 1253, 1051, 962, 841 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 (s, 3H), 1.37 (s, 3H), 1.38 (s, 6H), 3.60 (t, *J* = 7.55 Hz, 1H), 3.83–3.94 (m, 1H), 3.99–4.11 (m, 2H), 4.26–4.35 (m, 1H), 5.16 (d, *J* = 10.5 Hz, 1H), 5.38 (d, *J* = 17.1 Hz, 1H), 5.81–5.96 (m, 1H) ppm ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.8, 117.1, 109.6, 109.3, 81.0, 80.4, 76.6, 66.9, 26.9, 26.8, 26.6, 25.2 ppm. ESI-MS: *m*/*z*: 251 (M+Na).$^+$

4.1.2. 2-(4*S*,4^1*R*,5*R*)-2,2,2^1,2^1-Tetramethyl-4,4^1-bi(1,3-dioxolan)-5-yl)ethanol 11

At first, 9-BBN (54 mL, 26.97 mmol, 0.5 M in THF) was added dropwise to a well stirred solution of olefin **9** (4.1 g, 17.98 mmol) in anhydrous THF (35 mL) at 0 °C and the reaction mixture was stirred for 6 h at room temperature. Then the reaction mixture was quenched with 3 M NaOH (10 mL) at 0 °C, followed by the dropwise addition of 30% H_2O_2 (15 mL) and the resulting solution was stirred for 4 h at room temperature. The organic phase was separated and the aqueous layer extracted with ethyl acetate (3 × 20 mL). The combined organic phase was washed with brine (1 × 30 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was subjected to flash column chromatography (silica gel, 20% EtOAc/hexane) to obtain primary alcohol **11** (3.45 g, 78%). R_f = 0.4 (silica gel, 40% EtOAc/hexane). $[\alpha]_D^{25} = +15.5$ (*c* 0.8, $CHCl_3$). IR (neat) ν_{max}: 3446, 2988, 1380, 1215, 1068, 847 cm^{-1}.^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 3H), 1.35 (s, 3H), 1.38 (s, 6H), 1.76–1.90 (m, 1H), 1.95–2.07 (m, 1H), 3.56 (t, *J* = 8.1 Hz, 1H), 3.75–3.82 (m, 2H), 3.86–4.17 (m, 4H) ppm.^{13}C NMR ($CDCl_3$, 75 MHz): δ 109.7, 109.1, 81.1, 79.8, 77.1, 67.8, 60.7, 35.9, 27.1, 26.8, 26.5, 25.1 ppm ESI-MS: *m*/*z*: 247 (M+H).$^+$

4.1.3. (4*S*,4^1*R*,5*R*)-5-(2-(Benzyloxy)ethyl)-2,2,2^1,2^1-tetramethyl-4,4^1-bi(1,3-dioxolane) 12

Primary alcohol **11** (3.3 g, 13.41 mmol) in dry THF (25 mL) was added to a stirred solution of 60% NaH (0.8 g, 20.12 mmol) in anhydrous THF (10 mL) at 0 °C and stirred for 15 min. Then benzyl bromide (1.6 mL, 13.41 mmol) and a catalytic amount of TBAI were added at 0 °C and the reaction mixture was allowed to stir at room temperature for 3 h. After completion of the reaction, the reaction mixture was quenched with cold water (10 mL). The organic phase was separated and the aqueous layer extracted with ethyl acetate (1 × 15 mL). The combined organic phase was washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4, the organic solvent was evaporated, and the crude product was purified by silica gel column chromatography (silica gel, 5% EtOAc/hexane) to give compound **12** (4.28 g, 95%). R_f = 0.4 (silica gel, 10% EtOAc/hexane). $[\alpha]_D^{25} = +17.6$ (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}: 2987, 1371, 1216, 1061, 848, 737 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.33 (s, 3H), 1.35 (s, 3H), 1.38 (s, 3H), 1.40 (s, 3H), 1.78–1.92 (m, 1H), 2.07–2.21 (m, 1H), 3.52–3.71 (m, 3H), 3.95 (dd, *J* = 7.5, 5.2 Hz, 1H), 3.98–4.08 (m, 2H), 4.12 (dd, *J* = 7.5, 6.0 Hz, 1H), 4.53 (s, 2H), 7.27–7.38 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.4, 128.3, 127.6, 127.4, 109.5, 108.9, 81.2, 77.5, 76.9, 72.9, 67.6, 67.2, 33.8, 27.2, 26.9, 26.6, 25.2 ppm. ESI-MS: *m*/*z*: 359 (M+Na)$^+$ HRMS (ESI-MS): Anal. calcd for $C_{19}H_{28}O_5Na$ (M+Na)$^+$ 359.1829, found 359.1833.

4.1.4. (*R*)-1-((4*R*,5*R*)-5-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol 13

To a stirred solution of **12** (4.1 g, 12.20 mmol) in MeOH (45 mL) was added PPTS (0.76 g, 3.05 mmol) at 0 °C, stirred for 5 h at room temperature; then the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL) at 0 °C. The methanol was evaporated under reduced pressure, and the crude compound was extracted with ethyl acetate (3 × 30 mL). The combined organic phase was washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4, the solvent was evaporated, and the crude product was purified by silica gel column chromatography (silica gel, 50% EtOAc/hexane as an eluent) to obtain the desired product **13** (2.78 g, 77%). R_f = 0.5 (silica gel, EtOAc). $[\alpha]_D^{25} = +8.7$ (*c* 2.8, $CHCl_3$). IR (neat) ν_{max}: 3418, 2932, 1371, 1219, 1079, 772 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.38 (br s, 6H), 1.68 (br s, 1H), 1.87–2.15 (m, 2H), 3.59–3.80 (m, 6H), 4.11 (td, *J* = 7.0, 4.3 Hz, 1H), 4.53 (s, 2H), 7.29–7.40 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.7, 128.4, 127.8, 127.7, 108.6, 80.7, 77.0, 73.1, 72.7, 67.1, 64.0, 33.7, 27.1, 26.8 ppm. ESI-MS: *m*/*z*: 319 (M+Na)$^+$ HRMS (ESI-MS): Anal. calcd for $C_{16}H_{24}O_5Na$ (M+Na)$^+$ 319.1516, found 319.1520.

4.1.5. (*R*)-1-((4*R*,5*R*)-5-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol 14

To a stirred solution of diol **13** (2.55 g, 8.61 mmol) and dibutyltin oxide (0.43 g, 1.72 mmol) in anhydrous DCM (35 mL), was added Et_3N (1.8 mL, 12.91 mmol) dropwise at 0 °C, then the reaction mixture was allowed to warm to room temperature. After 15 min, the reaction mixture was cooled to 0 °C and then *p*-toluenesulfonylchloride (1.64 g, 8.61 mmol) was added portionwise and stirred for 3 h at room temperature. After complete consumption of the starting material, the reaction mixture was quenched with water (15 mL), and extracted with CH_2Cl_2 (2 × 15 mL). The organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting monotosylated compound was directly used for the next step without further purification.

The monotosylate compound in THF (40 mL) was added dropwise to a well stirred suspension of LAH (0.56 g, 14.66 mmol) in anhydrous THF (10 mL) at 0 °C. The reaction mixture was allowed to stir for 2 h at room temperature and the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (10 mL) at 0 °C. Next ethyl acetate (50 mL) and water (20 mL) were added, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic phase was washed with brine (1 × 25 mL), dried over anhydrous Na_2SO_4 and concentrated at reduced pressure and the residue was purified by silica gel column chromatography (silica gel, 12% EtOAc/hexane as an eluent) to yield compound **14** (2.05 g, 85% over two steps). R_f = 0.4 (silica gel, 20% EtOAc/hexane). $[\alpha]_D^{25} = +20.5$ (*c* 0.8, $CHCl_3$). IR (neat) ν_{max}: 3442, 2985, 1370, 1240, 1089, 877, 738 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.19 (d, *J* = 6.8 Hz, 3H), 1.35 (s, 6H), 1.78–2.05 (m, 2H), 2.26 (br s, 1H), 3.51- 3.71 (m, 3H), 3.76–3.88 (m, 1H), 4.05 (td, *J* = 8.3, 3.7 Hz, 1H), 4.50 (s, 2H), 7.27–7.35 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.1, 128.3, 127.7, 127.6, 108.3, 84.2, 75.0, 73.0, 67.5, 67.3, 34.5, 27.2, 27.0, 18.9 ppm ESI-MS: *m*/*z*: 303 (M+Na)$^+$ HRMS (ESI-MS): Anal. calcd for $C_{16}H_{24}O_4Na$ (M+Na)$^+$ 303.1566, found 303.1576.

4.1.6. ((*R*)-1-((4*S*,5*R*)-5-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethoxy)(*tert*-butyl)dimethylsilane 15

To a solution of alcohol **14** (2.0 g, 7.14 mmol) in anhydrous CH_2Cl_2 (20 mL), 2,6-lutidine (1.25 mL, 10.71 mmol) was added and the reaction mixture was stirred at 0 °C under a nitrogen atmosphere. After 5 min, TBSOTf (2.0 mL, 8.56 mmol) was added dropwise and stirred at the same temperature for 30 min. After complete consumption of the starting material, the reaction mixture was quenched with water (8 mL), and extracted with CH_2Cl_2 (1×15 mL). The organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (3% EtOAc/hexane as an eluent) to yield the TBS protected compound **15** (2.70 g, 96%). R_f = 0.6 (10% EtOAc/hexane). $[\alpha]_D^{25} = +11.7$ (*c* 1.5, $CHCl_3$). IR (neat) ν_{max}: 2932, 1370, 1254, 1097, 835, 775 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.21 (d, *J* = 6.0 Hz, 3H), 1.36, (s, 3H), 1.38 (s, 3H), 1.78–1.88 (m, 1H), 2.02–2.12 (m, 1H), 3.50 (t, *J* = 7.0 Hz, 1H), 3.56–3.70 (m, 2H), 3.76–3.83 (m, 1H), 3.99–4.07 (m, 1H), 4.52 (s, 2H), 7.27–7.36 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.6, 128.2, 127.5, 127.3, 108.5, 84.9, 76.4, 72.9, 70.0, 67.5, 35.1, 27.3, 27.2, 25.8, 25.6, 21.2, −4.3, −4.5 ppm. ESI-MS: *m*/*z*: 417 $(M+Na)^+$; HRMS (ESI-MS): Anal. calcd for $C_{22}H_{38}O_4NaSi$ $(M+Na)^+$ 417.2431, found 417.2443.

4.1.7. 2-((4*R*,5*S*)-5-((*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol 16

At first, 20% $Pd(OH)_2$ was added to a solution of **15** (2.6 g, 6.60 mmol) in anhydrous THF (25 mL) and stirred for 4 h under a hydrogen atmosphere. After complete consumption of the starting material, the reaction mixture was filtered through a pad of Celite The filtrate was concentrated under reduced pressure and the residue was purified on silica gel using (12% EtOAc-hexane as an eluent) to afford the primary alcohol **16** (1.80 g, 90%) as a colorless liquid. R_f = 0.3 (20% EtOAc/hexane). $[\alpha]_D^{25} = -5.8$ (*c* 1.1, $CHCl_3$). IR (neat) ν_{max}: 3450, 2935, 1374, 1252, 1082, 834, 775 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 1.22 (d, *J* = 6.0 Hz, 3H), 1.35, (s, 3H), 1.38 (s, 3H), 1.70–1.85 (m, 1H), 1.91–2.04 (m, 1H), 3.47 (t, *J* = 6.8 Hz, 1H), 3.69–3.82 (m, 3H), 4.03 (td, *J* = 9.0, 3.0 Hz, 1H) ppm ^{13}C NMR ($CDCl_3$, 75 MHz): δ 108.8, 84.8, 79.3, 70.4, 61.2, 36.8, 27.3, 27.1, 25.8, 21.4, 17.9, −4.3, −4.5 ppm ESI-MS: *m*/*z*: 327$(M+Na)^+$ HRMS (ESI-MS): Anal. calcd for $C_{15}H_{32}O_4NaSi$ $(M+Na)^+$ 327.1962, found 327.1968.

4.1.8. (*E*)-Ethyl 4-((4*R*,5*S*)-5-((*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enolate 8

At first, DMSO (1.5 mL, 21.05 mmol) was added slowly to the well stirred solution of oxalyl chloride (0.91 mL, 10.52 mmol) in anhydrous CH_2Cl_2 (5 mL) at −78 °C. After stirring for 20 min at −78 °C, alcohol **16** (1.6 g, 5.26 mmol) in anhydrous CH_2Cl_2 (15 mL) was added to the above solution. After stirring for 1 h, Et_3N (4.4 mL, 31.56 mmol) was introduced *via* a syringe. Next, the reaction mixture was stirred for 30 min at −78 °C, and then for 20 min at −50 °C followed by the addition of water (15 mL). The organic phase was separated and the aqueous layer was washed with CH_2Cl_2 (2×10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the aldehyde as a pale yellow syrup, which was used for the next step without further purification.

This crude aldehyde was treated with the stabilized C2-Wittig ylide (3.2 g, 9.40 mmol) in dry benzene at reflux for 2 h. After completion of the reaction (TLC analysis), benzene was removed under vacuum, and the crude ester was subjected to column chromatography using silica gel (4% EtOAc/hexane as an eluent) to afford α,β-unsaturated ester **8** as a colorless liquid. (1.82 g, 93% over two steps). R_f = 0.7 (silica gel, 10% EtOAc/hexane). $[\alpha]_D^{25} = +22.6$ (*c* 2.3, $CHCl_3$). IR (neat) ν_{max}: 2933, 1723, 1656, 1371, 1256, 1171, 1078, 834, 776 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.22 (d, *J* = 5.9 Hz, 3H), 1.29 (t, *J* = 6.9 Hz, 3H), 1.36, (s, 3H), 1.39 (s, 3H), 2.38–2.47 (m, 1H), 2.63–2.71 (m, 1H), 3.46 (t, *J* = 6.9 Hz, 1H), 3.74–3.81 (m, 1H), 4.03 (td, *J* = 7.9, 2.9 Hz, 1H), 4.19 (q, *J* = 6.9 Hz, 2H), 5.90 (d, *J* = 15.8 Hz, 1H), 7.01 (dt, *J* = 15.8, 6.9 Hz, 1H), ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.3, 144.7, 123.4, 108.9, 84.2, 78.0, 70.5, 60.1, 37.1, 27.2, 27.1, 25.7, 21.5, 17.9, 14.2, −4.3, −4.5 ppm. ESI-MS: *m*/*z*: 395 $(M+Na)^+$ HRMS (ESI-MS): Anal. calcd for $C_{19}H_{36}O_5NaSi$ $(M+Na)^+$ 395.2224, found 395.2236.

4.1.9. (*E*)-4-((4*R*,5*S*)-5-((*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-en-1-ol 17

To a stirred solution of compound **8** (1.5 g, 4.03 mmol) in dry CH_2Cl_2 (20 mL) was added DIBAL-H (8.87 mL, 8.87 mmol, 1.0 M solution in toluene) at −78 °C for 10 min. Next, the reaction mixture was stirred for 30 min at 0 °C. After completion of the reaction, the reaction mixture was quenched with a saturated sodium potassium tartrate solution (10 mL) and was stirred vigorously at room temperature for an additional 1 h after which the contents were extracted into CH_2Cl_2 (2×15 mL). The combined organic layers were washed with brine solution (20 mL), dried over anhydrous Na_2SO_4, and the solvent removed under reduced pressure to afford the crude aldehyde. The crude product was subjected to flash column chromatography on silica gel (12% EtOAc/hexane as an eluent) to give allylic alcohol **17** (1.18 g, 89%) as a clear liquid. R_f = 0.3 (20% EtOAc/hexane). $[\alpha]_D^{25} = +8.9$ (*c* 2.7, $CHCl_3$). IR (neat) ν_{max}: 3429, 2932, 1373, 1256, 1101, 1073, 972, 834, 776 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.22 (d, *J* = 5.6 Hz, 3H), 1.36, (s, 3H), 1.39 (s, 3H), 2.25–2.34 (m, 1H), 2.49–2.55 (m, 1H), 3.45 (t, *J* = 7.2 Hz, 1H), 3.75–3.82 (m, 1H), 3.97 (td, *J* = 7.2, 3.2 Hz, 1H), 4.12 (br s, 2H), 5.70–5.83 (m 2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 131.5, 128.6, 108.6, 84.2, 79.0, 70.4, 63.6, 37.3, 27.3, 27.2, 25.8, 21.3, 17.9, −4.2, −4.5 ppm ESI-MS: *m*/*z*: 353 $(M+Na)^+$ HRMS (ESI-MS): Anal. calcd for $C_{17}H_{34}O_4NaSi$ $(M+Na)^+$ 353.2118, found 353.2119.

4.1.10. (*R*,*E*)-7-((4*R*,5*S*)-5-((*R*)-1-(*tert*-Butyldimethylsilyloxy)-ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)hepta-1,5-dien-4-ol 7

Allylic alcohol **17** (0.43 g, 1.30 mmol) in dry DCM (10 mL) was added dropwise to a well stirred solution of IBX (0.55 g, 1.95 mmol) in anhydrous DMSO (8 mL) at 0 °C, after which the reaction mixture was allowed to stir for 1 h at room temperature. After completion of the reaction (TLC analysis), the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo to obtain the crude residue, which was subjected to flash column chromatography using 3% EtOAc/hexane as eluent to furnish the aldehyde, which was used for the next reaction.

A solution of (+)-IPC_2B(allyl) (1.27 mL, 1.27 mmol, 1.0 M solution in pentane) in anhydrous Et_2O (5 mL) was cooled to −100 °C after which a solution of the aldehyde (0.38 g, 1.15 mmol) in dry diethyl ether (10 mL) was added slowly under an N_2 atmosphere. The mixture was stirred at −100 °C for 1 h and then warmed to 0 °C. The reaction mass was quenched by the dropwise addition of 30% H_2O_2 (2 mL) and 1 M NaOH (2 mL). The mixture was diluted with ethyl acetate (10 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with brine (1×15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude reaction mixture was purified by silica gel column chromatography (10% EtOAc/hexane as an elu-

ent) to give homoallyl alcohol **7** (0.41 g, 85% over two steps) as a colorless liquid. R_f = 0.5 (20% EtOAc/hexane). $[\alpha]_D^{25} = +15.8$ (*c* 1.6, $CHCl_3$). IR (neat) ν_{max}: 3445, 2955, 1374, 1254, 1075, 973, 834, 776 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.22 (d, *J* = 6.0 Hz, 3H), 1.36, (s, 3H), 1.39 (s, 3H), 1.69 (br s, 1H), 2.23–2.38 (m, 3H), 2.48–2.57 (m, 1H), 3.47 (t, *J* = 6.8 Hz, 1H), 3.71–3.84 (m, 1H), 3.95 (td, *J* = 7.5, 3.0 Hz, 1H), 4.17 (q, *J* = 6.8 Hz, 1H), 5.11 (s, 1H), 5.15 (d, *J* = 6.8 Hz, 1H), 5.58 (dd, *J* = 15.8, 6.8 Hz, 1H), 5.70–5.91 (m 2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 134.7, 134.3, 127.6, 117.9, 108.6, 84.1, 79.1, 71.6, 70.5, 41.8, 37.2, 27.3, 27.2, 25.8, 21.4, 17.9, −4.2, −4.5 ppm ESI-MS: *m*/*z*: 393 $(M+Na)^+$ HRMS (ESI-MS): Anal. calcd for $C_{20}H_{38}O_4NaSi$ $(M+Na)^+$ 393.2431, found 393.2449.

4.1.11. (*R*,*E*)-7-((4*R*,5*S*)-5-((*R*)-1-(*tert*-Butyldimethylsilyloxy)-ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)hepta-1,5-dien-4-yl acrylate 18

Acryloyl chloride (0.11 mL, 1.33 mmol) was added dropwise under N_2 atmosphere to a solution of homoallyl alcohol **7** (0.33 g, 0.89 mmol) and Et_3N (0.25 mL, 1.78 mmol) in CH_2Cl_2 (8 mL). The mixture was stirred at 0 °C for 30 min. After completion of the reaction (TLC analysis), the reaction mixture was poured into cold water (5 ml), and extracted with CH_2Cl_2 (2 × 5 mL). The organic phase was washed with brine (1 × 8 mL), dried over anhydrous Na_2SO_4, and the organic solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (3% EtOAc/hexane as an eluent) to afford acrylate **18** (0.27 g, 72%) as a colorless oil. R_f = 0.5 (5% EtOAc/hexane). $[\alpha]_D^{25} = +18.7$ (*c* 2.0, $CHCl_3$). IR (neat) ν_{max}: 1726, 1257, 1189, 1075, 971, 834, 774 cm^{-1}.^1H NMR ($CDCl_3$, 300 MHz): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.21 (d, *J* = 6.0 Hz, 3H), 1.36, (s, 3H), 1.38 (s, 3H), 2.23–2.63 (m. 4H), 3.46 (t, *J* = 6.9 Hz, 1H), 3.70–3.88 (m, 1H), 3.90–4.22 (m, 1H), 5.02–5.19 (m, 2H), 5.39 (q, *J* = 6.4 Hz, 1H), 5.54 (dd, *J* = 15.4, 6.8 Hz, 1H), 5.65–5.96 (m, 3H), 6.11 (dd, *J* = 17.1, 10.4 Hz, 1H), 6.40 (d, *J* = 17.1 Hz, 1H) ppm ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.3, 133.2, 130.4, 130.1, 130.0, 128.8, 117.8, 108.6, 83.9, 78.8, 73.7, 70.4, 38.9, 37.0, 27.3, 27.2, 25.8, 21.4, 17.9, −4.2, −4.5 ppm ESI-MS: *m*/*z*: 447 $(M+Na)^+$ HRMS (ESI-MS): Anal. calcd for $C_{23}H_{40}O_5NaSi$ $(M+Na)^+$ 447.2537, found 447.2545.

4.1.12. (*R*)-6-((*E*)-3-((4*R*,5*S*)-5-((*R*)-1-(*tert*-Butyldimethyl silyl-oxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-1-enyl)-5,6-dihydro-2*H*-pyran-2-one 6

A solution of Grubbs' first-generation catalyst G-I (0.029 g, 0.035 mmol, 10 mol%) in CH_2Cl_2 (20 ml) was added drop wise to a solution of **18** (0.15 g, 0.35 mmol) in CH_2Cl_2 (30 mL) at rt. The solution was then degassed with argon for 10 min and stirring was continued for 5 h at reflux. The solvent was evaporated under reduced pressure and the crude product purified by silica gel column chromatography (20% EtOAc/hexane as an eluent) to give lactone **6** (0. 122 g, 87%) as a clear liquid. R_f = 0.3 (40% EtOAc/hexane). $[\alpha]_D^{25} = +31.8$ (*c* 1.5, $CHCl_3$). IR (neat) ν_{max}: 2931, 1729, 1377, 1249, 1075, 833, 776 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.22 (d, *J* = 6.0 Hz, 3H), 1.36 (s, 3H), 1.39 (s, 3H), 2.28–2.64 (m. 4H), 3.46 (t, *J* = 7.1 Hz, 1H), 3.71–3.85 (m, 1H), 3.96 (td, *J* = 7.5, 3.2 Hz, 1H), 4.91 (q, *J* = 7.1 Hz, 1H), 5.69 (dd, *J* = 15.4, 6.6 Hz, 1H), 5.86–6.00 (m, 1H), 6.05 (d *J* = 9.6 Hz, 1H), 6.88 (dt, *J* = 9.6, 4.3 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.0, 144.5, 131.0, 129.2, 121.5, 108.6, 83.9, 78.7, 78.0, 70.5, 36.9, 29.6, 27.3, 27.1, 25.8, 21.4, 17.9, −4.2, −4.5 ppm ESI-MS: *m*/*z*: 419 $(M+Na)^+$ HRMS (ESI-MS): Anal. calcd for $C_{21}H_{36}O_5NaSi$ $(M+Na)^+$ 419.2224, found 419.2234.

4.1.13. (2*R*,3*R*,4*R*,*E*)-7-((*R*)-6-Oxo-3,6-dihydro-2H-pyran-2-yl)heap-6-ene-2,3,4-triacetate [(+)-synargentolide A] 1a

To a well stirred solution of compound **6** (0.1 g, 0.25 mmol) in THF (8 mL) was added 4 M HCl (1.0 mL) solution at 0 °C then the reaction mixture was warmed to room temperature and stirred for 12 h. The reaction mixture was quenched with solid $NaHCO_3$ and filtered. The filtrate was removed under reduced pressure to give the crude trihydroxy lactone, which was used for the next step without further purification.

To a pre-cooled (0 °C) solution of trihydroxy lactone (0.045 g, 0.18 mmol) in anhydrous CH_2Cl_2 (5 mL) was added triethylamine (0.15 mL, 1.11 mmol), Ac_2O (0.08 mL, 0.93 mmol), followed by DMAP (2 mg) under a nitrogen atmosphere. The reaction mixture was then allowed to stir for 30 min at room temperature. After completion of the reaction (TLC analysis) it was poured into cold water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The organic phase was washed with brine (1 × 8 mL), and dried over anhydrous Na_2SO_4. The organic solvent was then removed under reduced pressure. The crude product was purified by column chromatography on silica gel (15% EtOAc/hexane as the eluent) to give synargentolide **1a** (0.056 g, 61% over two steps) as a colorless oil. R_f = 0.5 (40% EtOAc/hexane). $[\alpha]_D^{25} = +52$ (*c* 0.8, $CHCl_3$). IR (neat) ν_{max}: 2924, 1736, 1373, 1219, 1055, 1021 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.19 (d, *J* = 5.9 Hz, 3H), 2.02 (s, 3H), 2.06 (s, 3H), 2.15 (s, 3H), 2.27–2.34 (m, 2H), 2.39–2.45 (m, 2H), 4.84–4.90 (m, 1H), 4.95–5.02 (m, 1H), 5.09 (dd, *J* = 6.9, 2.9 Hz, 1H), 5.20 (td, *J* = 7.9, 2.9 Hz, 1H), 5.66 (dd, *J* = 15.8, 5.9 Hz, 1H), 5.69–5.78 (m, 1H), 6.04 (d, *J* = 9.9 Hz, 1H), 6.86 (dt, *J* = 9.9, 3.9 Hz, 1H) ppm ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.2, 170.1, 170.0, 163.7, 144.5, 130.9, 128.4, 121.5, 77.5, 73.6, 69.5, 67.2, 33.9, 29.5, 21.0, 20.8, 20.7, 16.2 ppm ESI-MS: *m*/*z*: 391 $(M+Na)^+$ HRMS (ESI-MS): Anal. calcd for $C_{18}H_{24}O_8Na$ $(M+Na)^+$ 391.1363, found 391.1375.

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