A Concise Stereoselective Total Synthesis of Synargentolide A from 3,4,6-Tri-*O*-acetyl-D-glucal

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Abstract: A short and highly stereoselective synthesis of the naturally occurring, α,β-unsaturated lactone synargentolide A is described from the chiral starting material 3,4,6-tri-*O*-acetyl-D-glucal. Key steps of the synthesis are lactol opening, Brown's asymmetric allylation, and a ring-closing metathesis (RCM) reaction.

Key words: 3,4,6-tri-*O*-acetyl-D-glucal, δ-lactones, synargentolide, Brown's allylation, RCM

(+)-Synargentolide A (**1**) (Figure 1) belongs to a family of polyacetate pyranone-containing natural products that have been found to exhibit a broad spectrum of biological activity. In 1998, Davies-Coleman and Rivett[2] isolated synargentolide A from *Syncolostemon argenteus* and the structure was proposed as **2** on the basis of spectroscopic analysis, Mosher's method, and acetonide formation. However, chemical synthesis of the proposed structure of **2** by the Marco group revealed that synthetic **2** was not identical to natural synargentolide A.[3] Recently, we reported that the correct structure of natural synargentolide A is structure **1** following total synthesis.[4] The synthesis used a cross-metathesis (CM) reaction as a key step. Based on our revised structure **1**, a report appeared.[5] Within our recently initiated program on the synthesis of natural lactones cryptopyramnoscatone B1 (**3**)[6a] and A1 (**4**)[6b] from the chiral pool compound 3,4,6-tri-*O*-acetyl-D-glucal (**5**), we have now devised a concise stereoselective total synthesis for synargentolide A.

The retrosynthetic concept is depicted in Scheme 1. It was envisaged that the target molecule **1** could be achieved from **8** by acrylation followed by RCM reaction, whereas **8** can be obtained from **7** by Brown's asymmetric allylation. Compound **7** in turn could be made from **6** by lactone opening. Lactone **6** is accessible from 3,4,6-tri-*O*-acetyl-D-glucal (**5**) by a successive sequence of reactions.

The synthesis of **1** began with commercially available tri-*O*-acetyl-D-glucal (**5**), deacetylation of which followed by selective silylation at the CH_2OH group, followed by MOM protection at C3 and C4, and then removal of the silyl protecting group afforded the alcohol **9** as reported.[6a] Tosylation of the primary hydroxy group in **9** (TsCl, Et_3N, CH_2Cl_2) furnished tosylate **10**, which on treatment with lithium aluminum hydride in tetrahydrofuran at reflux temperature provided the methyl compound **11** in 85% yield (Scheme 2). Subsequent pyridinium chlorochromate oxidation of the di-MOM ether **11** gave lactone **6** in 84% yield. The lactone **6** was reduced to a lactol using diisobutylaluminum hydride, which without purification was subjected to Wittig olefination using the stabilized two carbon ylide, ethyl (triphenylphosphoranylidene)acetate in refluxing benzene to furnish the required open chain α,β-unsaturated ester **12** with three requisite chiral centers at C4′, C5′, and C6′. Protection of the free hydroxy group as its MOM ether afforded tri-MOM ether **7**.

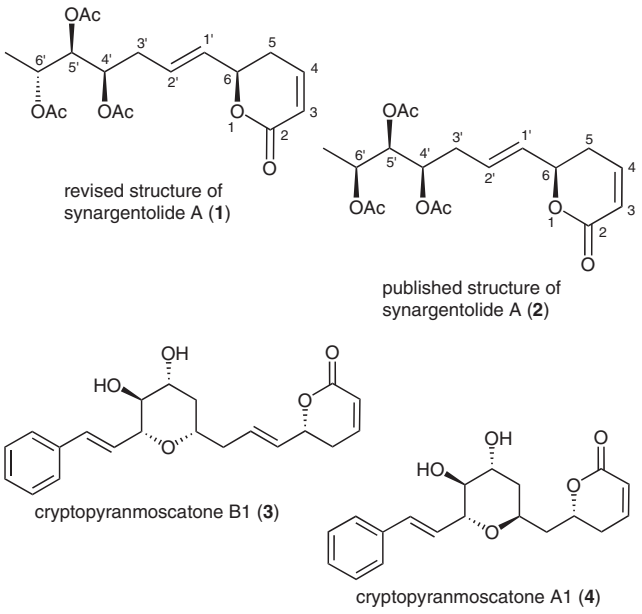
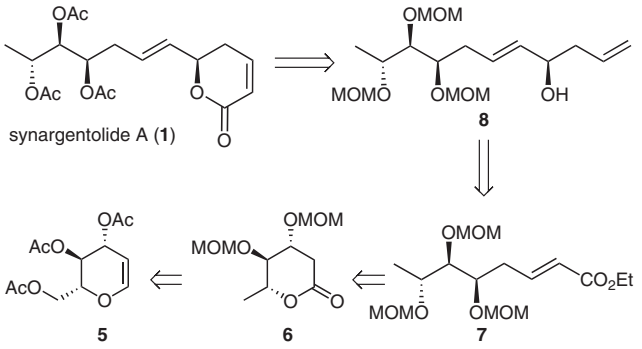


Figure 1 α,β-Unsaturated δ-lactones



Scheme 1 Retrosynthetic analysis for synargentolide A (**1**)

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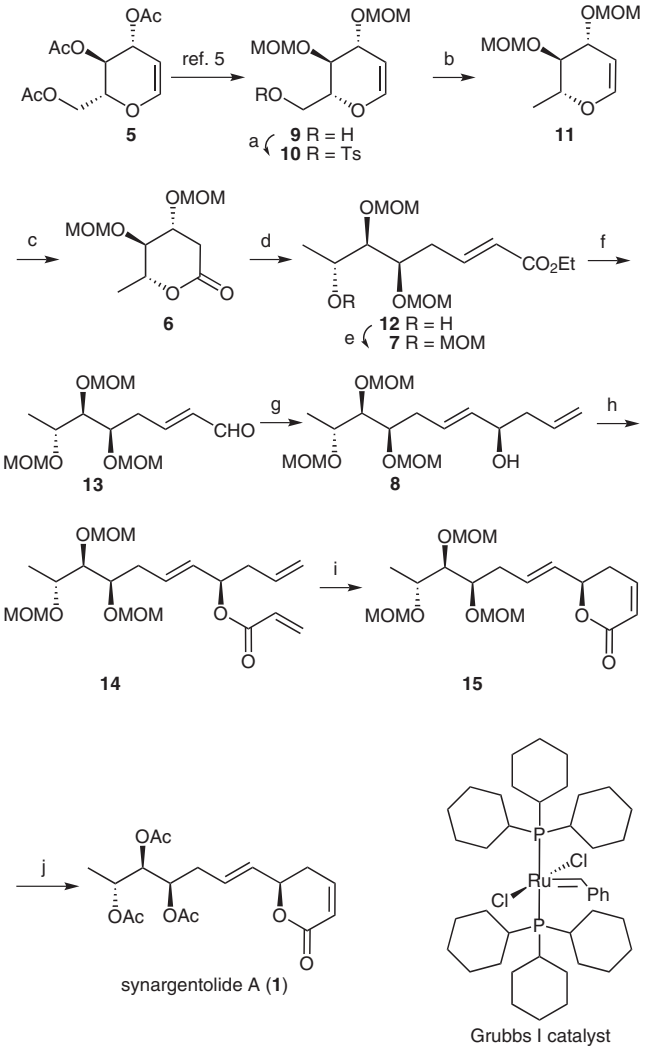
To establish a chiral center at C6, the diastereoselective allylation reaction was studied. In this context, the ester group in compound **7** was directly converted into the aldehyde by diisobutylaluminum hydride affording *E*-enal **13** in 75% yield followed by Brown's asymmetric allylation[7] using *B*-allyldiisocampheylborane to furnish the homoallylic alcohol **8** as a single diastereomer in 70% yield. Acylation of **8** with acryloyl chloride furnished acrylate **14**, which was then subjected to ring-closing metathesis in the presence of Grubbs' standard ruthenium catalyst [$PhCH{=}RuCl_2(PCy_3)_2$].[8]



Scheme 2 *Reagents and conditions:* (a) TsCl, Et_3N, DMAP (cat.), CH_2Cl_2, 0 °C–r.t., 0.5 h, 90%; (b) $LiAlH_4$, THF, reflux, 1 h, 85%; (c) PCC, silica gel, CH_2Cl_2, reflux, 8 h, 84%; (d) (i) DIBAL-H, CH_2Cl_2, 0 °C, 1 h; (ii) $Ph_3P{=}CHCOO_2Et$, benzene, reflux, 6 h, 89% (over 2 steps); (e) MOMCl, DIPEA, CH_2Cl_2, 0 °C–r.t., 8 h, 93%; (f) DIBAL-H, CH_2Cl_2, –78 °C, 0.5 h, 75%; (g) 1.0 M (+)-IPC_2B(allyl) in pentane, Et_2O, –100 °C, 3 h, 70%; (h) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C–r.t., 0.5 h, 86%; (i) Grubbs I catalyst (10 mol%), CH_2Cl_2, reflux, 5 h, 85%; (j) (i) 4 M HCl, MeCN–H_2O (4:1), 0 °C, 6 h; (ii) Ac_2O, py, CH_2Cl_2, 0 °C, 1 h, 79% (over 2 steps).

The expected conjugated δ-lactone **15** was formed in good yield. Finally, cleavage of all three MOM protecting groups of **15** followed by acetylation of the three liberated hydroxy functions was achieved in 79% overall yield to afford **1**, identical in its physical and spectral properties to the natural compound[2] and synthetic material.[4]

In summary, a concise total synthesis of the natural lactone synargentolide A (**1**) has been achieved in a highly stereoselective way using 3,4,6-tri-*O*-acetyl-D-glucal (**5**) as the chiral starting material.

Reactions were conducted under N_2 in anhyd solvents such as CH_2Cl_2, THF, and EtOAc. All reactions were monitored by TLC (silica-coated plates and visualizing under UV light). *n*-Hexane (bp 60–80 °C) was used. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous material. Air-sensitive reagents were transferred by syringe or double-ended needle. Evaporation of solvents was performed at reduced pressure on a Buchi rotary evaporator. ^1H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded on Varian FT-400 and Bruker UXNMR FT-300 (Avance) spectrometers; spectra are reported relative to TMS as an internal standard. Mass spectra were recorded E1 conditions at 70 eV on ES-MSD (Agilent technologies) spectrometers. Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. TLC was performed on Merck 60 F-254 silica gel plates. Optical rotations were measured with a Jasco DIP-370 Polarimeter.

[(2*R*,3*S*,4*R*)-3,4-Bis(methoxymethoxy)-3,4-dihydro-2*H*-pyran-2-yl]methyl 4-Methylbenzenesulfonate (10)

Et_3N (0.91 mL, 6.39 mmol), and DMAP (cat.) were added to a soln of **9** (1.0 g, 4.27 mmol) in anhyd CH_2Cl_2 (15 mL) at 0 °C. TsCl (977 mg, 5.12 mmol) was then added to the stirred soln. The resulting mixture was allowed to warm to r.t., stirred for 0.5 h, treated with 1 M aq HCl (3 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed sequentially with sat. $NaHCO_3$ (30 mL) and H_2O (20 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (silica gel, PE–EtOAc, 7:3) to give **10** (1.48 g, 90%) as a colorless syrup; R_f = 0.6 (PE–EtOAc, 7:3).

$[\alpha]_D^{25}$ +60.5 (*c* 0.9, $CHCl_3$).

IR (neat): 2949, 2826, 2360, 1447, 1177, 1034, 972, 815, 760 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.30 Hz, 2 H), 7.32 (d, *J* = 8.30 Hz, 2 H), 6.20 (dd, *J* = 6.04, 1.51 Hz, 1 H), 4.85–4.73 (m, 2 H), 4.69–4.61 (m, 3 H), 4.32–4.24 (m, 2 H), 4.18–4.10 (m, 1 H), 4.05–3.99 (m, 1 H), 3.78–3.72 (m, 1 H), 3.36 (s, 3 H), 3.33 (s, 3 H), 2.46 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.7, 143.5, 132.8, 129.7, 127.9, 100.0, 96.5, 95.2, 74.1, 71.8, 70.5, 67.6, 55.9, 55.4, 21.5.

MS (ESI): *m*/*z* = 411 $[M + Na]^+$.

(2*R*,3*R*,4*R*)-3,4-Bis(methoxymethoxy)-2-methyl-3,4-dihydro-2*H*-pyran (11)

To a stirred suspension of $LiAlH_4$ (190 mg, 5.0 mmol) in anhyd THF (40 mL) at 0 °C was added dropwise a soln of **10** (1.3 g, 3.35 mmol) in anhyd THF (10 mL). The mixture was allowed to warm to reflux temperature and stirred for 1 h. It was then cooled to 0 °C, diluted with EtOAc (20 mL), and quenched by dropwise addition of sat. Na_2SO_4 soln (10 mL). The solid material was filtered through a Celite pad and washed thoroughly with hot EtOAc (3 × 30 mL). The combined organic layers were dried (anhyd Na_2SO_4). Removal of solvent under reduced pressure and purification by column chromatography (silica gel, PE–EtOAc, 7:3) afforded **11** (620 mg, 85%) as a colorless oil; R_f = 0.8 (PE–EtOAc, 7:3).

$[\alpha]_D^{25}$ +24.2 (*c* 0.95, $CHCl_3$).

IR (neat): 2937, 2892, 1218, 1106, 1035 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.29 (dd, *J* = 6.04, 1.32 Hz, 1 H), 4.87 (d, *J* = 6.61 Hz, 1 H), 4.78 (dd, *J* = 6.23, 2.83 Hz, 1 H), 4.70–4.64 (m, 3 H), 4.14–4.09 (m, 1 H), 4.01–3.90 (m, 1 H), 3.58–3.52 (m, 1 H), 3.39 (s, 3 H), 3.37 (s, 3 H), 1.36 (d, *J* = 6.61 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.3, 100.3, 96.8, 95.6, 77.1, 73.6, 73.5, 55.9, 55.4, 17.0.

MS (ESI): *m*/*z* = 241 $[M + Na]^+$.

(4*R*,5*R*,6*R*)-4,5-Bis(methoxymethoxy)-6-methyltetrahydro-2*H*-pyran-2-one (6)

To a soln of **11** (500 mg, 2.29 mmol) in CH_2Cl_2 (30 mL) was added a mixture of PCC (1.48 g, 6.88 mmol) and silica gel (2 g). The stirred suspension was refluxed for 8 h and then cooled and filtered through Celite. The Celite pad was washed several times with EtOAc, and the combined filtrates were concentrated. The crude product was purified by column chromatography (silica gel, PE–EtOAc, 7:3) to give **6** (450 mg, 84%) as a white solid; R_f = 0.2 (PE–EtOAc, 7:3); mp 56–58 °C.

$[\alpha]_D^{25}$ +95.0 (*c* 0.8, $CHCl_3$).

IR (neat): 2941, 2896, 1749, 1445, 1238, 1025 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.80 (d, *J* = 6.79 Hz, 1 H), 4.70–4.60 (m, 3 H), 4.21–4.10 (m, 1 H), 4.07–4.02 (m, 1 H), 3.59 (dd, *J* = 7.74, 2.45 Hz, 1 H), 3.38 (d, *J* = 7.93 Hz, 6 H), 2.80 (dd, *J* = 16.05, 4.34 Hz, 1 H), 2.68 (dd, *J* = 15.48, 4.15 Hz, 1 H), 1.48 (d, *J* = 6.42 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 96.1, 95.2, 78.3, 75.9, 73.5, 55.9, 55.6, 34.2, 18.8.

MS (ESI): *m*/*z* = 257 $[M + Na]^+$.

Ethyl (*E*,5*R*,6*R*,7*R*)-7-Hydroxy-5,6-bis(methoxymethoxy)oct-2-enoate (12)

A stirred soln of **6** (350 mg, 1.49 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C, then 1.6 M DIBAL-H in toluene (1.86 mL) was added slowly. After 1 h, the reaction was quenched with MeOH (1 mL) and aq potassium sodium tartrate (5 mL), and stirred at r.t. for 0.5 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL), dried (anhyd Na_2SO_4), filtered, and concentrated in vacuo to afford the crude lactol. This was used for the next step without further purification.

To a soln of the above lactol in benzene (10 mL) was added $Ph_3P{=}CHCO_2Et$ (572 mg, 1.64 mmol) and the mixture was stirred at reflux for 6 h. After completion of the reaction (TLC monitoring), benzene was removed under reduced pressure, the residue was dissolved in Et_2O, and petroleum ether was added. The triphenylphosphine oxide that crystallized out was filtered off and the filtrate was concentrated to dryness. The crude product was purified by column chromatography (silica gel, PE–EtOAc, 7:3) to afford the pure α,β-unsaturated ester **12** (406 mg, 89%) as a colorless oil; R_f = 0.3 (PE–EtOAc, 7:3).

$[\alpha]_D^{25}$ +6.8 (*c* 0.95, $CHCl_3$).

IR (neat): 3488, 2937, 2826, 1719, 1653, 1447, 1269, 1177, 1024 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00–6.88 (m, 1 H), 5.89 (dt, *J* = 15.67, 1.32 Hz, 1 H), 4.73–4.59 (m, 4 H), 4.17 (q, *J* = 7.17 Hz, 2 H), 3.90–3.78 (m, 2 H), 3.48–3.46 (m, 1 H), 3.42 (s, 3 H), 3.39 (s, 3 H), 3.28–3.22 (br m, OH), 2.63–2.51 (m, 1 H), 2.50–2.38 (m, 1 H), 1.30 (t, *J* = 7.17 Hz, 3 H), 1.20 (d, *J* = 6.23 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 144.4, 123.8, 98.2, 96.9, 84.5, 77.1, 66.6, 60.1, 56.0 (d, 2 C), 33.9, 18.9, 14.1.

MS (ESI): *m*/*z* = 329 $[M + Na]^+$.

Ethyl (*E*,5*R*,6*R*,7*R*)-5,6,7-Tris(methoxymethoxy)oct-2-enoate (7)

To a cooled (0 °C) soln of **12** (300 mg, 0.98 mmol) in CH_2Cl_2 (10 mL) were added sequentially DIPEA (0.48 mL, 2.94 mmol) and MOMCl (0.11 mL, 1.45 mmol) and the mixture was stirred at r.t. for 8 h. The solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, PE–EtOAc, 7:3) to afford **7** (318 mg, 93%) as a colorless liquid; R_f = 0.5 (PE–EtOAc, 7:3).

$[\alpha]_D^{25}$ +8.3 (*c* 0.9, $CHCl_3$).

IR (neat): 2937, 2825, 2360, 1719, 1655, 1446, 1269, 1029 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06–6.94 (m, 1 H), 5.93 (dt, *J* = 15.86, 1.51 Hz, 1 H), 4.81–4.63 (m, 6 H), 4.19 (q, *J* = 7.55 Hz, 2 H), 3.91–3.78 (m, 2 H), 3.61 (t, *J* = 4.53 Hz, 1 H), 3.43 (s, 3 H), 3.39 (s, 3 H), 3.37 (s, 3 H), 2.67–2.55 (m, 1 H), 2.52–2.40 (m, 1 H), 1.29 (t, *J* = 7.55 Hz, 3 H), 1.25 (d, *J* = 6.79 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 144.7, 123.7, 97.6, 96.9, 95.0, 80.9, 76.6, 72.8, 60.1, 55.9, 55.8, 55.3, 34.6, 15.9, 14.1.

MS (ESI): *m*/*z* = 373 $[M + Na]^+$.

(*E*,5*R*,6*R*,7*R*)-5,6,7-Tris(methoxymethoxy)oct-2-enal (13)

DIBAL-H (0.35 mL, 0.57 mmol) was added to a stirred soln of ester **7** (200 mg, 0.57 mmol) in CH_2Cl_2 (5 mL) at –78 °C and the mixture was allowed to stir at this temperature for 0.5 h (TLC monitoring). The reaction was quenched with aq MeOH at 0 °C. Then sat. sodium potassium tartrate soln was added, and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (2 × 2 mL) and H_2O (2 × 2 mL), dried (anhyd Na_2SO_4), and concentrated under vacuum. The crude aldehyde was purified by column chromatography (silica gel, PE–EtOAc, 7:3) to afford **13** (131 mg, 75%) as a colorless liquid; R_f = 0.4 (PE–EtOAc, 7:3).

$[\alpha]_D^{25}$ +4.3 (*c* 1.15, $CHCl_3$).

IR (neat): 2939, 2826, 2362, 1692, 1447, 1150, 1031 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.52 (d, *J* = 7.74 Hz, 1 H), 6.93–6.81 (m, 1 H), 6.19 (dt, *J* = 15.86, 1.32 Hz, 1 H), 4.80–4.57 (m, 6 H), 3.90–3.75 (m, 2 H), 3.60 (t, *J* = 4.53 Hz, 1 H), 3.40 (s, 3 H), 3.36 (s, 3 H), 3.34 (s, 3 H), 2.79–2.67 (m, 1 H), 2.62–2.48 (m, 1 H), 1.22 (d, *J* = 6.42 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.7, 154.3, 134.9, 97.7, 97.2, 95.1, 81.0, 76.8, 72.9, 56.0 (d, 2 C), 55.5, 35.3, 16.1.

MS (ESI): *m*/*z* = 329 $[M + Na]^+$.

(4*R*,5*E*,8*R*,9*R*,10*R*)-8,9,10-Tris(methoxymethoxy)undeca-1,5-dien-4-ol (8)

A soln of 1.0 M (+)-IPC_2B(allyl) in pentane (0.21 mL, 0.47 mmol) in Et_2O (2 mL) was cooled to –100 °C and a soln of aldehyde **13** (100 mg, 0.32 mmol) in Et_2O (10 mL) was added slowly. The mixture was stirred at –100 °C for 3 h and then warmed to 0 °C. The reaction was quenched by the dropwise addition of aq 30% H_2O_2 (0.2 mL) and 1 M NaOH (0.3 mL). The mixture was diluted with EtOAc (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 4 mL), dried ($MgSO_4$), filtered, and concentrated. The crude mixture was further purified by column chromatography (silica gel, PE–EtOAc, 7:3) to give homoallyl alcohol **8** (79 mg, 70%) as a clear liquid; R_f = 0.3 (PE–EtOAc, 7:3).

$[\alpha]_D^{25}$ –10.4 (*c* 1.15, $CHCl_3$).

IR (neat): 3456, 2932, 2825, 2337, 1444, 1218, 1103, 1032 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.88–5.46 (m, 3 H), 5.17–5.02 (m, 2 H), 4.77–4.53 (m, 6 H), 4.14–4.01 (m, 1 H), 3.88–3.76 (m, 1 H), 3.74–3.53 (m, 2 H), 3.37 (s, 9 H), 2.57–2.02 (m, 4 H), 1.16 (d, *J* = 6.04 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.9, 134.4, 126.7, 117.5, 97.5, 96.7, 94.6, 79.5, 77.6, 72.3, 72.1, 55.8 (d, 2 C), 55.4, 41.6, 34.6, 15.4.

MS (ESI): *m*/*z* = 371 [M + Na]$^+$.

(1*R*,2*E*,5*R*,6*R*,7*R*)-1-Allyl-5,6,7-tris(methoxymethoxy)oct-2-enyl Acrylate (14)

Acryloyl chloride (0.02 mL, 0.24 mmol) was added dropwise under N_2 to a soln of **8** (70 mg, 0.20 mmol) and Et_3N (0.06 mL, 0.42 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at 0 °C for 0.5 h. After completion, the mixture was poured into brine (2 mL) and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were washed with 1 M aq HCl, dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (silica gel, PE–EtOAc, 7:3) to afford the corresponding acrylic ester **14** (68 mg, 86%) as a colorless oil; R_f = 0.8 (PE–EtOAc, 7:3).

$[\alpha]_D^{25}$ –5.5 (*c* 1.0, $CHCl_3$).

IR (neat): 2934, 2824, 2361, 1724, 1620, 1406, 1268, 1192, 1033 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.37 (d, *J* = 17.18 Hz, 1 H), 6.14–6.01 (m, 1 H), 5.83–5.68 (m, 2 H), 5.54 (dd, *J* = 15.67, 6.98 Hz, 1 H), 5.33 (q, *J* = 6.61 Hz, 1 H), 5.13–5.02 (m, 2 H), 4.75–4.54 (m, 7 H), 3.87–3.75 (m, 1 H), 3.68–3.55 (m, 2 H), 3.39 (s, 3 H), 3.34 (d, *J* = 4.15 Hz, 6 H), 2.50–2.16 (m, 4 H), 1.19 (d, *J* = 6.42 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3, 133.1, 130.5, 130.0, 129.8, 128.7, 117.9, 97.7, 96.9, 95.1, 80.7, 77.4, 73.7, 73.1, 55.9 (d, 2 C), 55.4, 38.9, 34.7, 16.1.

MS (ESI): *m*/*z* = 425 [M + Na]$^+$.

(6*R*)-6-[(*E*,4*R*,5*R*,6*R*)-4,5,6-Tris(methoxymethoxy)hept-1-enyl]-5,6-dihydro-2*H*-pyran-2-one (15)

A soln of Grubbs I catalyst (10 mg, 0.01 mmol, 10 mol%) in CH_2Cl_2 (20 mL) was added dropwise to a soln of **14** (50 mg, 0.12 mmol) in CH_2Cl_2 (30 mL) at r.t., and stirring was continued for 5 h under reflux conditions. The solvent was evaporated and the crude product was purified by column chromatography (silica gel, PE–EtOAc, 6:4) to give lactone **15** (39 mg, 85%) as a colorless oil; R_f = 0.3 (PE–EtOAc, 6:4).

$[\alpha]_D^{25}$ –12.1 (*c* 0.9, $CHCl_3$).

IR (neat): 2930, 2825, 2337, 1722, 1383, 1217, 1102, 1031 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.86–6.80 (m, 1 H), 6.02 (d, *J* = 9.92 Hz, 1 H), 5.94–5.85 (m, 1 H), 5.69 (dd, *J* = 15.87, 6.94 Hz, 1 H), 4.91–4.84 (m, 1 H), 4.78–4.56 (m, 6 H), 3.86–3.77 (m, 1 H), 3.69–3.58 (m, 2 H), 3.39 (s, 3 H), 3.37 (s, 3 H), 3.35 (s, 3 H), 2.53–2.23 (m, 4 H), 1.20 (d, *J* = 6.94 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9, 144.5, 130.7, 129.7, 121.6, 97.7, 97.0, 95.1, 80.7, 80.4, 77.8, 73.0, 55.9 (d, 2 C), 55.5, 34.6, 29.6, 16.1.

MS (ESI): *m*/*z* = 397 [M + Na]$^+$.

(1*R*,2*R*,4*E*)-2-Acetoxy-1-[(1*R*)-1-acetoxyethyl]-5-[(2*R*)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]pent-4-enyl Acetate [Synargentolide A (1)]

To a stirred soln of **15** (25 mg, 0.067 mmol) in MeCN–H_2O (4:1, 5 mL) was added 4 M HCl (2 mL) at 0 °C and the mixture was stirred at this temperature for 6 h. The mixture was quenched with solid $NaHCO_3$ (20 mg) and filtered, the solvent was removed under reduced pressure and the crude triol was used for further reactions.

Pyridine (0.03 mL, 0.37 mmol) and Ac_2O (0.02 mL, 0.20 mmol) were added sequentially to a stirred soln of the above triol in anhyd CH_2Cl_2 (3 mL) at 0 °C. The mixture was stirred for 1 h and then diluted with CH_2Cl_2 (10 mL). The organic layer was washed sequentially with 5% aq $NaHCO_3$ (2 × 3 mL) and brine (2 × 3 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, PE–EtOAc, 6:4) to give **1** (18 mg, 79% over 2 steps) as a colorless oil; R_f = 0.5 (PE–EtOAc, 6:4).

$[\alpha]_D^{25}$ +35 (*c* 1.0, $CHCl_3$).

IR (neat): 1739, 1371, 1225, 1024, 980 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.87–6.79 (m, 1 H), 6.01 (dt, *J* = 9.82, 1.70 Hz, 1 H), 5.77–5.58 (m, 2 H), 5.19–5.10 (m, 1 H), 5.07–5.01 (m, 1 H), 4.99–4.90 (m, 1 H), 4.89–4.80 (m, 1 H), 2.44–2.37 (m, 2 H), 2.31–2.23 (m, 2 H), 2.15 (s, 3 H), 2.05 (s, 3 H), 2.01 (s, 3 H), 1.17 (d, *J* = 6.23 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 171.0, 169.9, 163.8, 144.5, 130.8, 128.3, 121.5, 77.5, 73.7, 69.5, 67.3, 33.9, 29.6, 21.0, 20.9, 20.7, 16.0.

MS (ESI): *m*/*z* = 391 [M + Na]$^+$.

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