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Original article

Synthesis of the ABC skeleton of the aglycon of Echinoside A

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ABSTRACT

Echinoside A is a triterpene saponin isolated from the sea cucumber *Actinopyga echinites* (JAEGER), which displays potent antitumor activities *in vitro* and *in vivo*. Here, we report the synthesis of the ABC-fused ring skeleton of the aglycon of Echinoside A, with the enantiomerically pure (+)-Wieland–Miescher ketone being used as starting material and a Robinson annulation as the key reaction.

1. Introduction

Sea cucumber saponins are common secondary metabolites produced by holothurian species, which play an important role in the chemical defense of the slow-moving animals while show a wide spectrum of pharmacological activities. Echinoside A, a lanostane-type triterpene oligosaccharide, was isolated from the sea cucumber *Actinopyga echinites* (JAEGER) by Kitagawa *et al.* [1] (Fig. 1). This compound demonstrated potent activities *in vitro* and *in vivo* against a broad-spectrum of antitumor cells, especially it could directly kill P-gp-mediated multidrug-resistant tumor cells [2].

Echinoside A consists of a linear tetrasaccharide attached to a pentacyclic triterpene aglycon. The construction of the pentacyclic triterpene aglycon constitutes the most challenging part of the synthesis; in fact, the synthesis of Echinoside A has never been reported so far [3]. As shown in Scheme 1, we envisaged to construct the pentacyclic aglycon (**1**) by introduction of the double bond at the α position of the ketone in skeleton **2**, followed by reduction of the ketone. Compound **2** could be constructed via an intramolecular Aldol reaction from compound **3**, which would be synthesized through a Michael addition between the terminal alkyl iodide **5** and the ABC skeleton **4**. Herein, we report the synthesis of the key ABC skeleton intermediate (**4**).

2. Experimental

Commercial reagents were used without further purification unless specialized. Solvents were dried and redistilled prior to use in the usual way. Thin layer chromatography (TLC) was performed on precoated plates of Silica Gel HF254 (0.2 mm, Yantai, China). Flash column chromatography was performed on Silica Gel H (10–40 μ, Yantai, China). Optical rotations were determined with a Perkin–Elmer Model 241 MC polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 400 spectrometer with Me4Si as the internal standard. Chemical shifts were recorded in δ values and J values were given in Hz. Mass spectra were obtained on a HP5989A or a VG Quatro mass spectrometer.

Wieland–Miescher ketone **9**: A suspension of ketone **6** (25.0 g, 198.18 mmol) in water (60 mL) was treated with HOAc (0.6 mL), hydroquinone (225 mg, 2.043 mmol), and fresh distilled methyl vinyl ketone (32 mL, 387.10 mmol). Refluxed at 80 °C overnight, returned to the room temperature, NaCl (20.0 g) was added, then the mixture was diluted with EtOAc. The solution was washed with brine, dried with Na_2SO_4, and then concentrated to afford the crude product **8** (30.15 g, 78%).

In a standard glass vial with stirrer bar was added triketone **8** (6.14 g, 31.29 mmol) followed by the catalyst **10** (335 mg, 0.625 mmol) and benzoic acid (20 mg, 0.164 mmol). The resulting mixture darkened and was stirred for 7 days. The mixture was absorbed onto silica gel and purified by column chromatography (petroleum ether/EtOAc 3:1–1:1) to give the Wieland–Miescher ketone **9** (5.19 g, 93%, 90% *ee*) as a clear oil. Recrystallization from Et_2O gives a white crystalline solid (99.5% *ee*) [4]. ^{1}H NMR

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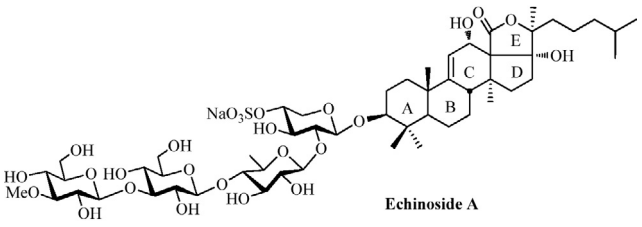


Fig. 1. The structure of Echinoside A.

(400 MHz, chloroform-*d*): δ 5.86 (d, 1H, J = 1.9 Hz), 2.80–2.68 (m, 2H), 2.57–2.43 (m, 4H), 2.22–2.09 (m, 3H), 1.72 (tdt, 1H, J = 13.3, 9.0, 4.4 Hz), 1.46 (s, 3H).

Compound **11**: 4 Å molecular sieves (2.5 g) and *p*-TsOH·H_2O (2.20 g, 11.566 mmol) were added to a solution of **9** (2.10 g, 11.783 mmol) in ethylene glycol (40 mL). After being stirred at room temperature for 30 min, the reaction mixture was poured slowly into a 2:1 mixture of ice-water/sat. aqueous $NaHCO_3$. The mixture was extracted with EtOAc four times, and the combined organic layers were washed with brine, dried over Na_2SO_4. Concentration and purification by silica gel column chromatography (petroleum ether/EtOAc = 6:1) afforded **11** (2.28 g, 87%) as a yellow oil [5]. ^{1}H NMR (400 MHz, chloroform-*d*): δ 5.82 (d, 1H, J = 1.9 Hz), 4.07–3.85 (m, 4H), 2.41 (ddd, 2H, J = 10.9, 4.8, 3.0 Hz), 2.35–2.24 (m, 2H), 1.96–1.85 (m, 1H), 1.85–1.59 (m, 5H), 1.36 (s, 3H).

Compound **12**: A solution of **11** (2.28 g, 10.257 mmol) in *n*-propanol (20 mL), was treated with PhSH (1.6 mL, 15.521 mmol), 37% HCHO (1.26 mL, 16.555 mmol), Et_3N (1.4 mL, 15.521 mmol), and HCOOK (1.044 g, 12.416 mmol) at 100 °C for 24 h. Then the mixture was diluted with CH_2Cl_2, and the solution was washed with saturated aqueous $NaHCO_3$ and brine, dried with Na_2SO_4. Concentration and purification by silica gel column chromatography (petroleum ether/EtOAc 8:1) afforded **12** (2.86 g, 81%) as yellow crystals [6]. ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.43–7.36 (m, 2H), 7.30–7.17 (m, 3H), 4.02–3.89 (m, 5H), 3.76 (d, 1H, J = 11.5 Hz), 2.66 (ddt, 1H, J = 15.5, 4.2, 2.0 Hz), 2.49 (dt, 1H, J = 16.0, 4.4 Hz), 2.37 (ddd, 1H, J = 16.0, 13.9, 4.9 Hz), 2.24 (td, 1H, J = 13.5, 4.9 Hz), 2.03 (td, 1H, J = 14.6, 5.6 Hz), 1.85 (td, 1H, J = 13.5, 4.5 Hz), 1.75 (ddt, 1H, J = 10.2, 4.5, 2.5 Hz), 1.70–1.62 (m, 2H), 1.57–1.50 (m, 1H), 1.32 (s, 3H).

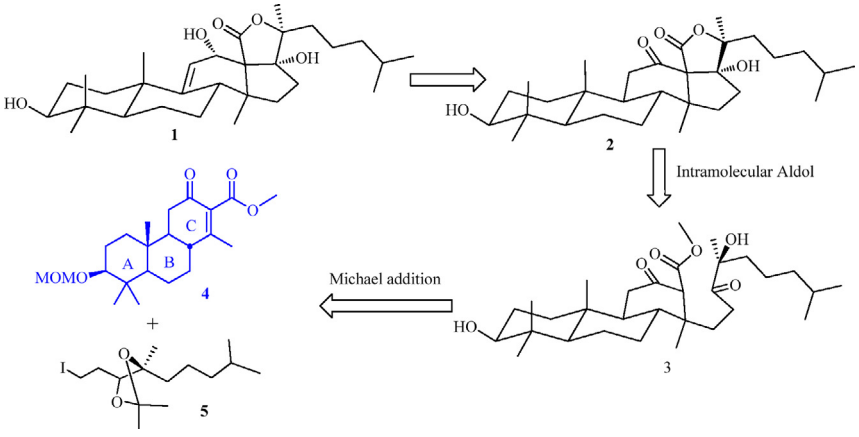
Compound **13**: A solution of **12** (6.30 g, 18.79 mmol) in THF/^{t}BuOH (100 mL/3.5 mL), was added to a stirred solution of 3 equiv. of lithium in liquid ammonia (500 mL) over a 20–30 min period. The solution was allowed to stir at −72 °C for another 45 min, whereupon 100 mL of THF was added followed by rapid addition of CH_3I (17.1 mL, 274.335 mmol). The mixture was allowed to stir for 30 min after which the ammonia was allowed to evaporate. The mixture was concentrated and the residue was diluted with CH_2Cl_2 and washed with water, brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 25:1) to afford **13** (2.86 g, 81%) as colorless oil [7]. ^{1}H NMR (500 MHz, chloroform-*d*): δ 3.98–3.83 (m, 4H), 2.62 (ddd, 1H, J = 15.1, 13.6, 6.3 Hz), 2.33 (ddd, 1H, J = 15.2, 5.3, 3.5 Hz), 1.99–1.90 (m, 1H), 1.89–1.83 (m, 1H), 1.77–1.64 (m, 3H), 1.55–1.43 (m, 4H), 1.24 (s, 3H), 1.08 (s, 3H), 1.04 (s, 3H).

Compound **14**: A solution of **13** (1.23 g, 4.86 mmol) in EtOH (15 mL) was treated with $NaBH_4$ (184 mg, 4.86 mmol) at −40 °C for 2 h. Diluted with Et_2O and washed with water and brine, the organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1) to afford **14** (1.10 g, 89%) as colorless crystal [7]. ^{1}H NMR (400 MHz, chloroform-*d*): δ 3.98–3.88 (m, 3H), 3.83 (dd, 1H, J = 7.5, 3.6 Hz), 3.30–3.20 (m, 1H), 1.74–1.24 (m, 12H), 1.05 (s, 3H), 0.99 (s, 3H), 0.80 (s, 3H).

Compound **15**: A solution of **14** (500 mg, 1.97 mmol) in EtOH/H_2O (18 mL/2 mL), was treated with PPTS (64 mg, 0.26 mmol) and refluxed for 2 h. The solvent was concentrated and diluted with CH_2Cl_2. The mixture was washed with water and brine, dried over Na_2SO_4, and concentrated, affording the crude product.

The crude product was dissolved in CH_2Cl_2 (10 mL), and was then treated with DIPEA (1.72 mL, 9.83 mmol), MOMCl (0.74 mL, 9.83 mmol) at room temperature for 2 h. Quenched with saturated NH_4Cl, diluted with CH_2Cl_2, and washed with water and brine, the resulting organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc 15:1) to afford **15** (490 mg, 98%) as colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*): δ 4.74 (d, 1H, J = 6.8 Hz), 4.60 (d, 1H, J = 6.8 Hz), 3.39 (s, 3H), 3.10–3.02 (m, 1H), 2.57 (td, 1H, J = 13.9, 7.0 Hz), 2.20 (dddd, 1H, J = 14.1, 5.0, 2.2, 1.3 Hz), 2.13–2.03 (m, 1H), 1.91–1.83 (m, 1H), 1.76 (dt, 1H, J = 6.7, 2.6 Hz), 1.74–1.68 (m, 1H), 1.68–1.53 (m, 4H), 1.16 (s, 3H), 1.13 (d, 1H, J = 3.3 Hz), 1.00 (s, 3H), 0.92 (s, 3H). ESI-MS (m/z): 277.1 $[M+Na]^+$. HRMS (m/z): $[M+H]^+$ calcd. for $C_{15}H_{27}O_3$ 255.1955, found 255.1952.

Compound **16**: A solution of **15** (1.5 g, 5.897 mmol) in dry toluene/THF (15 mL/5 mL), was treated with 60% NaH (472 mg, 11.8 mmol) at 0 °C for 30 min. HCOOEt (5 mL) was added and stirring continued at room temperature for 4 h. Quenched with saturated NH_4Cl, diluted with EtOAc and washed with water and brine, the resulting organic layer was dried over Na_2SO_4 and concentrated to afford a crude product.



Scheme 1. Retrosynthetic analysis of the aglycon **1**.

The crude product was dissolved in CH_2Cl_2 (10 mL) and then treated with MVK (2.0 mL, 23.56 mmol) and Et_3N (2.5 mL, 17.69 mmol). After stirring at room temperature for 4 h, the mixture was concentrated to afford a crude product.

The crude product was dissolved in $HOBu^t$ (25 mL) and then treated with $KOBu^t$ (990 mg, 8.85 mmol). After stirring at room temperature overnight, the mixture was quenched with water and concentrated. The residue was diluted with EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc 6:1) to afford **16** (1.52 g, 84%) as colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*): δ 5.78 (d, 1H, *J* = 1.5 Hz), 4.73 (d, 1H, *J* = 6.8 Hz), 4.59 (d, 1H, *J* = 6.8 Hz), 3.36 (s, 3H), 3.06 (dd, 1H, *J* = 11.5, 4.2 Hz), 2.52 (dddt, 1H, *J* = 14.2, 7.4, 5.3, 2.1 Hz), 2.35 (dt, 1H, *J* = 16.2, 4.9 Hz), 2.22 (ddd, 1H, *J* = 16.2, 12.7, 5.0 Hz), 2.10–1.97 (m, 2H), 1.92–1.84 (m, 1H), 1.76–1.43 (m, 6H), 1.25–1.15 (m, 1H), 1.10 (s, 3H), 1.04 (dd, 1H, *J* = 12.2, 2.8 Hz), 0.96 (s, 3H), 0.86 (s, 3H). ^{13}C NMR (101 MHz, chloroform-*d*): δ 201.23, 175.58, 119.84, 96.04, 84.34, 55.56, 52.45, 40.53, 39.30, 35.92, 35.02, 34.63, 34.19, 29.28, 28.11, 24.20, 21.33, 21.09, 16.49. ESI-MS (*m*/*z*): 329.4 $[M+Na]^+$; HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_{19}H_{30}O_3Na$ 329.2087, found 329.2091.

Compound **17**: A solution of **16** (38 mg, 0.12 mmol) in dimethoxyethane (2 mL) was treated with 60% NaH (10 mg, 0.25 mmol) and dimethyl carbonate (21 μL, 0.25 mmol). The mixture was refluxed under nitrogen for 2 h, and then quenched with saturated NH_4Cl and diluted with EtOAc. The mixture was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by preparative thin-layer chromatography (petroleum ether/EtOAc 4:1) to afford **17** (5 mg) as colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*): δ 6.83 (d, 1H, *J* = 8.1 Hz), 6.63 (d, 1H, *J* = 2.6 Hz), 6.50 (dd, 1H, *J* = 8.2, 2.6 Hz), 4.72 (d, 1H, *J* = 6.9), 4.60–4.56 (d, 1H, *J* = 6.9), 3.35 (s, 3H), 3.09 (dd, 1H, *J* = 11.7, 4.4 Hz), 2.81 (ddd, 1H, *J* = 16.7, 6.7, 1.8 Hz), 2.76–2.64 (m, 1H), 2.20–2.10 (m, 1H), 1.90–1.74 (m, 2H), 1.74–1.58 (m, 2H), 1.48–1.34 (m, 1H), 1.28–1.16 (m, 1H), 1.12 (s, 3H), 0.98 (s, 3H), 0.84 (s, 3H). ESI-MS (*m*/*z*): 327.4 $[M+Na]^+$.

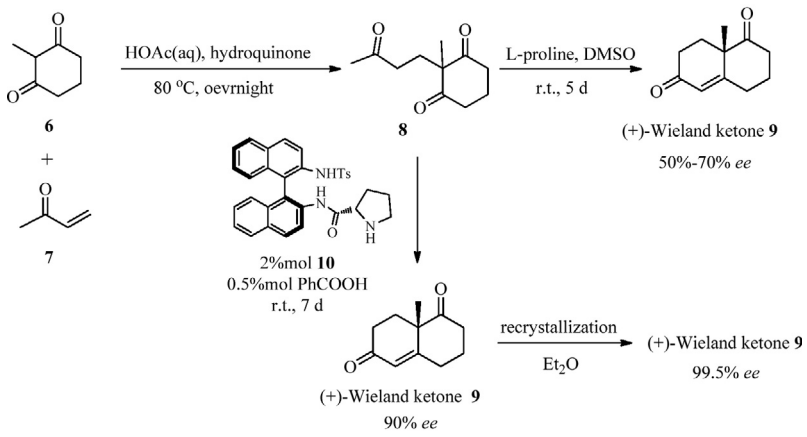
Compound **18**: A solution of **16** (60 mg, 0.196 mmol) in THF/EtOH (3 mL/0.03 mL) was added dropwise to a stirred liquid ammonia (10 mL) at −72 °C, and then lithium (60 mg) was added to the solution. The solution was allowed to stir for 4 h at −72 °C. Quenched with saturated NH_4Cl after which the ammonia was allowed to evaporate. The mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc 6:1) to afford **18** (1.52 g, 84%) as colorless oil. $[\alpha]_D^{25}$ 21.4 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, chloroform-*d*): δ 4.72 (dd, 1H, *J* = 6.8, 1.4 Hz), 4.59 (dd, 1H, *J* = 6.8, 1.5 Hz), 3.37 (s, 3H), 3.11–3.00 (m, 1H), 2.29 (dq, 3H, *J* = 11.6, 6.6, 5.1 Hz), 2.03 (t, 1H, *J* = 13.4 Hz), 1.99–1.92 (m, 1H), 1.88 (dt, 1H, *J* = 12.2, 3.6 Hz), 1.74 (m, 1H), 1.67–1.46 (m, 4H), 1.46–1.32 (m, 1H), 1.32–1.17 (m, 1H), 1.13–1.04 (m, 1H), 1.02–0.98 (m, 1H), 0.98–0.94 (m, 1H), 0.95 (s, 3H), 0.88 (s, 3H), 0.85 (d, 1H, *J* = 2.0 Hz), 0.82 (s, 3H). ^{13}C NMR (101 MHz, chloroform-*d*): δ 213.12, 96.01, 84.85, 55.77, 55.55, 54.25, 41.13, 40.95, 38.63, 36.81, 36.59, 35.31, 34.10, 34.01, 28.29, 24.09, 21.05, 16.53, 13.82. ESI-MS (*m*/*z*): 331.3 $[M+Na]^+$. HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_{19}H_{32}NaO_3$:331.2244, found 331.2244.

Compound **19**: To a mixture of 60% NaH (28 mg, 0.93 mmol) and 30% KH (15 mg, 0.11 mmol) in dry THF (0.5 mL) was added **18** (48 mg, 0.16 mmol) in dry THF (2 mL) and dimethyl carbonate (33 μL, 0.40 mmol) at 0 °C. The temperature was raised to 70 °C and the mixture refluxed for 4 h. After cooling down to 0 °C, the mixture was acidized with 50% HOAc, and diluted with EtOAc. The mixture was washed with water, aq. $NaHCO_3$, and brine, respectively. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc 15:1) to afford **19** (38 mg, 67%) as colorless oil. $[\alpha]_D^{25}$ 23.0 (*c* 0.70, $CHCl_3$); ^{1}H NMR (400 MHz, chloroform-*d*): δ 12.05 (s, 1H), 4.73 (t, 1H, *J* = 5.1 Hz), 4.60 (dd, 1H, *J* = 6.9, 2.6 Hz), 3.73 (s, 3H), 3.38 (s, 3H), 3.09 (dd, 1H, *J* = 11.7, 4.2 Hz), 2.39 (dd, 1H, *J* = 15.7, 5.2 Hz), 2.25–2.05 (m, 2H), 1.99–1.88 (m, 1H), 1.80–1.49 (m, 6H), 1.38 (ddd, 2H, *J* = 16.4, 9.5, 3.5 Hz), 1.04 (td, 2H, *J* = 12.6, 5.2 Hz), 0.97 (s, 3H), 0.91–0.88 (m, 1H), 0.86 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (101 MHz, chloroform-*d*): δ 172.61, 171.77, 96.50, 95.99, 84.97, 55.57, 54.45, 51.37, 50.02, 38.62, 37.18, 36.14, 34.56, 31.87, 30.90, 28.59, 28.35, 24.05, 21.00, 16.66, 13.80. ESI-MS (*m*/*z*): 389.4 $[M+Na]^+$. HRMS (*m*/*z*): $[M+Na]^+$ calcd. for $C_{21}H_{34}NaO_5$ 389.2298, found 389.2300.

Compound **20**: A solution of **19** (47 mg, 0.13 mmol) in dry CH_2Cl_2 (2 mL) was treated with pyridine (50 μL) and PhSeCl (50 mg, 0.256 mmol) at 0 °C. The mixture was then stirred at room temperature overnight. Diluted with CH_2Cl_2 and washed with 1 mol/L HCl and water. The organic layer was added 30% H_2O_2 (1.5 mL), stirred at room temperature for 10 min until the yellow solution turned to colorless. The organic layer was washed with aq. $NaHCO_3$ and brine, respectively, and was then dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 6:1) to afford **20** (34 mg, 73%) as colorless oil. $[\alpha]_D^{25}$ 16.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, chloroform-*d*): δ 7.40 (d, 1H, *J* = 1.8 Hz), 4.73 (d, 1H, *J* = 6.8 Hz), 4.59 (d, 1H, *J* = 6.8 Hz), 3.78 (s, 3H), 3.37 (s, 3H), 3.07 (dd, 1H, *J* = 11.7, 4.3 Hz), 2.50 (dd, 1H, *J* = 15.8, 3.3 Hz), 2.44 (tdd, 1H, *J* = 10.6, 4.1, 1.8 Hz), 2.17 (dd, 1H, *J* = 15.7, 14.3 Hz), 2.09 (dd, 1H, *J* = 13.0, 3.5 Hz), 1.84–1.72 (m, 2H), 1.64 (dt, 1H, *J* = 13.0, 3.5 Hz), 1.60–1.40 (m, 3H), 1.30–1.21 (m, 1H), 1.02 (dd, 1H, *J* = 13.3, 3.9 Hz), 0.96 (s, 3H), 0.90 (s, 3H), 0.88 (d, 1H, *J* = 2.5 Hz), 0.82 (s, 3H). ^{13}C NMR (126 MHz, chloroform-*d*): δ 195.54, 165.07, 161.25, 131.26, 96.04, 84.61, 55.58, 53.97, 52.90, 52.21, 38.79, 38.65, 37.15, 36.21, 36.05, 32.14, 28.06, 24.04, 21.42, 16.35, 14.27. ESI-MS (*m*/*z*): 387.3 $[M+Na]^+$; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{21}H_{33}O_5$: 365.2323, found 365.2326.

Compound **21**: To a solution of **20** (30 mg, 0.082 mmol) in dry THF (1 mL) was added a freshly prepared solution of Me_2CuLi (0.38 mL, 0.09 mmol) in THF. After being stirred at −78 °C for 1 h, the mixture was quenched with saturated NH_4Cl. The resulting mixture was diluted with EtOAc and washed with water and brine, respectively. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc 5:1) to afford **21** (28 mg, 89%) as yellow oil. $[\alpha]_D^{25}$ 14.0 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, chloroform-*d*): δ 12.13 (s, 0.13H), 4.73 (d, 1H, *J* = 6.7 Hz), 4.60 (d, 1H, *J* = 6.8 Hz), 3.75 (s, 3H), 3.38 (s, 3H), 3.08 (ddd, 2H, *J* = 11.6, 4.9, 2.5 Hz), 2.42 (dd, 1H, *J* = 13.2, 3.6 Hz), 2.16 (dq, 1H, *J* = 13.2, 3.9 Hz), 2.13–2.03 (m, 1H), 1.75 (dt, 1H, *J* = 11.6, 4.0 Hz), 1.69 (ddd, 2H, *J* = 10.8, 4.6, 2.3 Hz), 1.61–1.47 (m, 3H), 1.43–1.29 (m, 2H), 1.27–1.15 (m, 2H), 1.11–1.04 (m, 1H), 0.99 (d, 3H, *J* = 6.4 Hz), 0.97 (s, 3H), 0.95–0.90 (m, 1H), 0.88 (s, 3H), 0.83 (s, 3H). HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{22}H_{37}O_5$ 381.2636, found 381.2638.

Compound **4**: A solution of **21** (822 mg, 2.160 mmol) in dry CH_2Cl_2 (20 mL) was treated with pyridine (0.5 mL) and PhSeCl (827 mg, 4.320 mmol) at 0 °C. After stirring at room temperature overnight, the mixture was diluted with CH_2Cl_2 and washed with 1 mol/L HCl and water. The organic layer was added 30% H_2O_2 (2.0 mL), stirred at room temperature for 10 min until the yellow solution turned to colorless. The mixture was washed with aq. $NaHCO_3$ and brine, respectively, and was then dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc 6:1–4:1) to afford **4** (406 mg, 49%) as white solid together with **20** (335 mg, 41%). **4**: $[\alpha]_D^{25}$ 7.56 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, chloroform-*d*): δ 4.74 (d, 1H, *J* = 6.8 Hz), 4.60 (d, 1H, *J* = 6.8 Hz), 3.81 (s, 3H), 3.38 (s, 3H),



Scheme 2. Preparation of (+)-Wieland–Miescher ketone **9**.

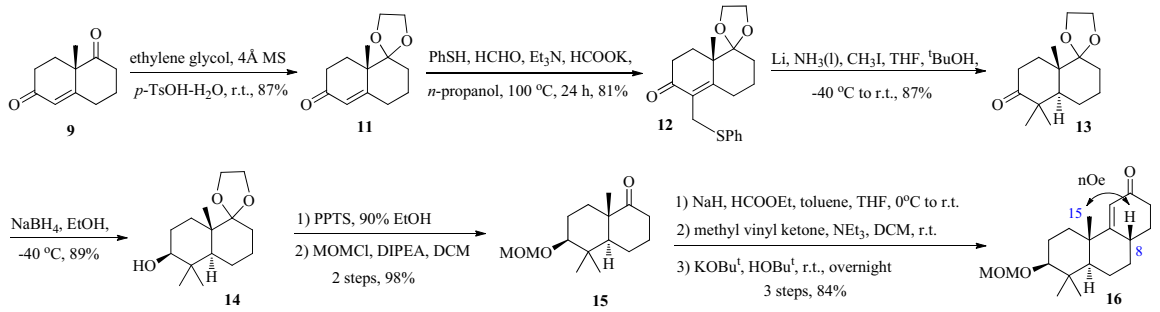
3.09 (dd, 1H, J = 11.6, 4.3 Hz), 2.47 (dd, 1H, J = 15.8, 3.3 Hz), 2.39–2.23 (m, 2H), 2.14 (dd, 1H, J = 15.8, 14.4 Hz), 1.91 (s, 3H), 1.79 (dt, 2H, J = 13.1, 3.8 Hz), 1.70–1.42 (m, 5H), 1.15 (dd, 1H, J = 12.8, 4.3 Hz), 1.02 (dd, 1H, J = 13.3, 3.8 Hz), 0.97 (s, 3H), 0.90 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (101 MHz, chloroform-d): δ 195.99, 167.69, 162.39, 133.01, 96.04, 84.58, 77.24, 55.61, 53.90, 52.25, 51.92, 39.96, 38.57, 37.33, 36.27, 30.09, 28.04, 24.13, 21.38, 19.31, 16.35, 14.34. ESI-MS (m/z): 401.3 $[M+Na]^+$. HRMS (m/z): $[M+H]^+$ calcd. for $C_{22}H_{35}O_5$: 379.2479, found: 379.2480.

3. Results and discussion

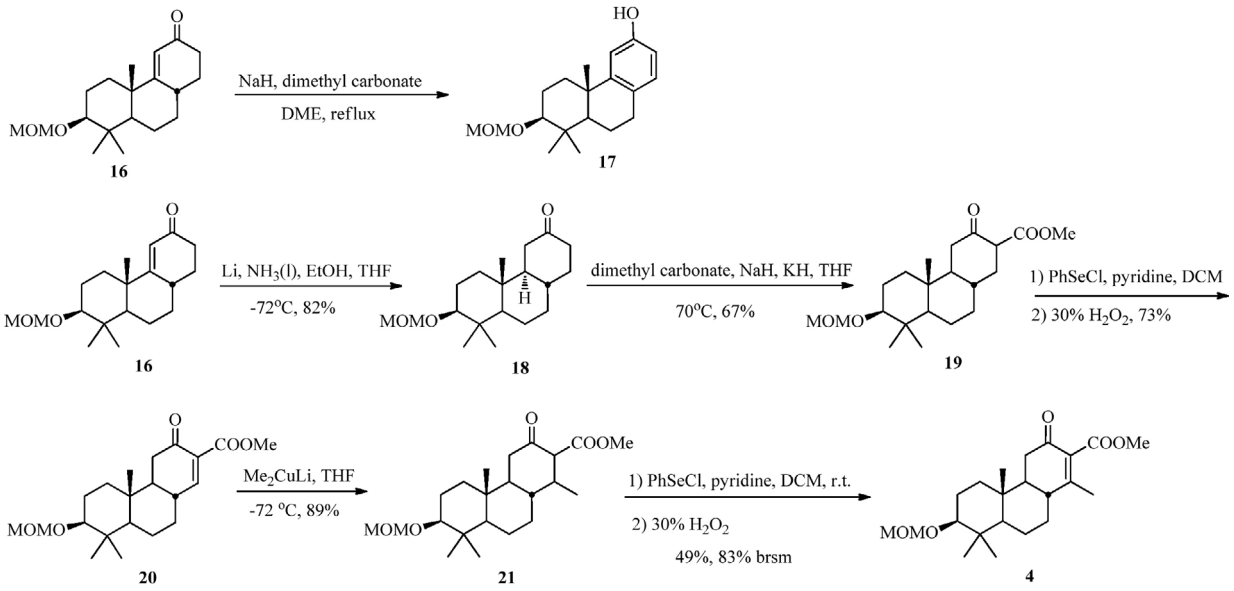
Our synthesis started with the preparation of (+)-Wieland–Miescher ketone (**9**) through a Robinson annulation reaction (Scheme 2). The Michael addition between 2-methyl-1,3-cyclohexanedione **6** and methyl vinyl ketone (MVK) **7** provided the triketone **8**. Then, the L-proline-promoted aldolization of triketone **8** yielded the Wieland–Miescher ketone **9**, albeit in poor enantioselectivity (50–70% *ee*) [8]. Following the procedure reported by Bonjoch [9], treatment of triketone **8** with *N*-tosyl-(*S*)-binam-prolinamide (catalyst **10**) through a solvent-free Robinson annulation procedure afforded **9** in high enantioselectivity (90% *ee*). In addition, the (+)-Wieland–Miescher ketone **9** could be enantiomerically enriched by recrystallization from Et_2O (99.5% *ee*).

The (+)-Wieland–Miescher ketone **9** was selectively protected as ketal **11**, which was subsequently subjected to Kirk–Petrow conditions (Scheme 3) [10]. Indeed, ketal **11** was treated with PhSH, HCHO, Et_3N and HCOOK in *n*-propanol at 100 °C for 24 h to furnish the thiol **12** in 81% yield. Reductive alkylation of the enone under Birch conditions provided the 4,4-dimethyl-trans-decalone derivative **13** (87%), which was reduced into the corresponding alcohol **14** by $NaBH_4$ (89%) [11]. Deacetalization followed by protection of the hydroxyl group of **14** with MOMCl afforded the protected ketone **15** in 98% over two steps. Then, the annulation of **15** in order to give the tricyclic enone **16** was achieved under the standard conditions exemplified in Spencer's work [12]. More precisely, the annulation was accomplished by formylation of the ketone **15**, followed by a Robinson annulation employing MVK **7**, with concomitant removal of the formyl group under basic conditions. Enone **16** was finally isolated in 84% yield over three steps. The stereochemistry of the C8-H was determined by NOE analysis which exhibits a strong correlation with the C15-H. Other attempts employing 3-penten-2-one and 4-methyl-3-penten-2-one instead of MVK failed to construct the corresponding triketone intermediate *via* the Robinson annulation.

With the annulation product **16** in hand, we focused our efforts on the installation of the methoxycarbonyl group at the C-13 position (Scheme 4). Treatment of **16** with lithium diisopropylamide (LDA) in −78 °C, followed by addition of methyl chloroformate led to no product, whereas treatment of **16** with NaH and dimethyl carbonate in dimethoxyethane afforded the aromatization product **17**. Consequently, we decided to reduce the C9–C11 double bond at an earlier stage. At first, hydrogenation of **16** was adopted in the presence of catalytic Pd/C, but the desired saturated ketone was isolated in a mixture of the two C9-isomers. Gratifyingly, reduction under Birch conditions yielded the saturated ketone **18** as a single isomer (82%) [13]. Carbomethoxylation was then achieved by heating at 70 °C a mixture of **18** and dimethyl carbonate in the presence of NaH and KH in THF. Subsequent phenylselenation and dehydroselenation of **19** provided the desired α,β-unsaturated ketone **20** in 73% yield [14]. Methylation of **20** with Me_2CuLi in THF afforded ketone **21** in 89% yield, which was subjected to a similar phenylselenation/dehydroselenation protocol, thus providing the desired key intermediate **4** in 49% yield (83% yield based on recovered starting materials).



Scheme 3. Construction of the ABC ring framework.



Scheme 4. Synthesis of the key ABC skeleton intermediate **4**.

4. Conclusion

In conclusion, we have achieved the synthesis of the key ABC-fused ring skeleton of the aglycon of Echinoside A (*i.e.*, **4**). The synthesis starts from the (+)-Wieland–Miescher ketone and requires 16 steps and in 13% overall yield with Robinson annulation as a key reaction. The availability of this advanced intermediate would facilitate the synthesis of Echinoside A and the related saponins from sea cucumbers.

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