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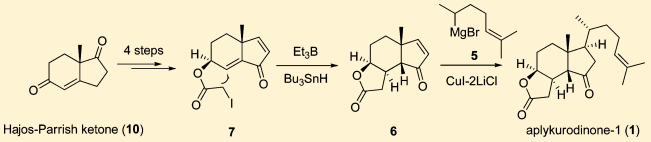
Protecting-Group-Free Total Synthesis of Aplykurodinone-1

Yu Tang,* Ji-tian Liu, Ping Chen, Ming-can Lv, Zhen-zhen Wang, and Yi-kun Huang

School of Pharmaceutical Science and Technology, Key Laboratory for Modern Drug Delivery & High-Efficiency, Collaborative Innovation Center of Chemical Science and Engineering, Tianjin University, Tianjin, 300072 P. R. China

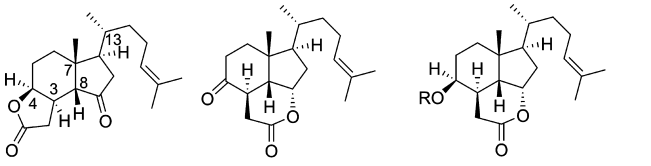
Supporting Information

ABSTRACT: A concise, stereoselective, and protecting-group-free total synthesis of aplykurodinone-1 from Hajos–Parrish ketone was described. The synthetic approach features a sequence of aerobic allylic oxidation and elimination of alcohol **9**. The key intermediate for this synthesis was formed by a stereoselective intramolecular radical cyclization.



The "degraded" steroid, aplykurodinone-1(**1**) was isolated from sea hare *Syphonota geographica* in 2005.[1] The structure of aplykurodinone-1 (**1**) allowed for concise assignment of the absolute configuration through spectroscopic methods, X-ray, and chemical correlation. Although the biological profile of aplykurodinone-1 remains unknown, various aplykurodines exhibit cytotoxic activity against a range of human cancer cell lines.[2] Aplykurodinone B (**2**) and 4-acetyl-aplykurodin B (**4**) exhibit high toxicity to the mosquito fish *Gambusia affinis* at 10 ppm.[3] Aplykurodinone-1 (**1**) and aplykurodinone B (**2**) comprise a *cis*-fused hydrindane moiety (C7–C8 configuration) and six contiguous stereogenic centers, one of which is an all-carbon quaternary center residing at stereocenter C13 and an unsaturated side chain connected to the tricyclic system (Scheme 1).

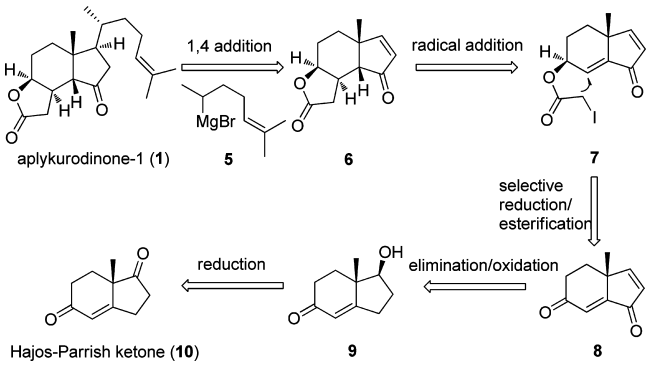
Scheme 1. Structure of Aplykudinones and Aplykurodins



To date, there have been two reports describing elegant synthetic efforts toward these natural products. In 2010, rac-**1** was accomplished by Zhang and Danishefsky, who employed a novel strategy featuring an anionically mediated Diels–Alder reaction to form the racemic hydrindane core.[4] De Paolis et al. reported the application of the Hajos–Parrish methodology, resulting in the concise formal enantioselective synthesis of **1**.[5] Recently, Yang and co-workers reported a unique SmI_2 mediated reductive cascade cyclization reaction constructing a cis-fused hydrindane moiety.[6] We pursued the synthesis of aplykurodinone-1 (**1**) by using a related similar Hajos–Parrish ketone strategy. With ketone **10** as starting material, the key intermediate **6** was synthesized in only five steps without using any protecting groups.[7,8]

A general design of our approach to aplykurodinone-1 (**1**) is shown in Scheme 2. The side chain **5** could be installed through

Scheme 2. Retrosynthetic Analysis of Aplykurodinone-1 (1)



1,4-conjugate addition of α,β-unsaturated ketone **6**.[6] The γ-lactone motif was formed by intramolecular radical cyclization of ester **7**.[9] A chemo- and diastereoselective reduction of diketone **8**, followed by esterification, would lead to ester **7**. Diketone **8** was synthesized through a sequence of aerobic allylic oxidation[10] and elimination of alcohol **9**, which could be readily accessible from chemo- and diastereoselective reduction of the Hajos–Parrish ketone **10**.

Our synthesis began with 2-methyl-1,3-cyclopentanedione **11** through the classical synthetic procedure to give the Hajos–Parrish ketone **10** with 99% ee value (Scheme 3).[11] Stereo- and regioselective reduction of ketone **10** using sodium borohydride in the presence of cerous chloride in methanol afforded alcohol **9** in high yield.[12] Next, we investigated the elimination procedure. Surprisingly, when the well-known Burgess reagent[13] was used in benzene with an oxygen atmosphere, the unexpected product **8** was obtained in one step (Table 1, entry 1). A similar result was reported by De Paolis et al. in

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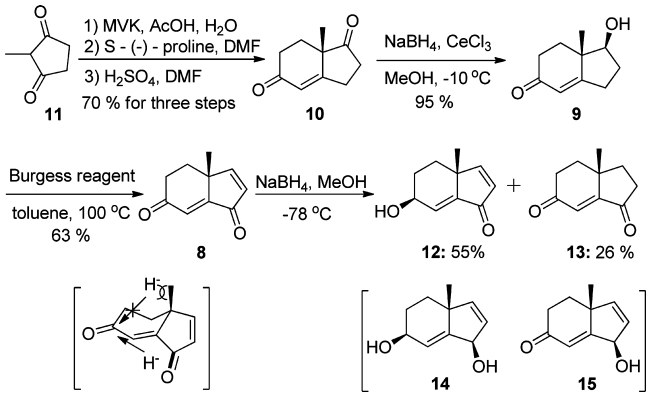
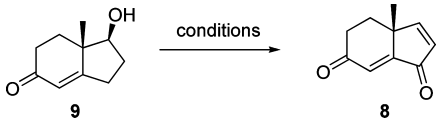
Scheme 3. Synthesis of Alcohol 12



2013.[5] Although the yield was a little low, the one-step aerobic oxidation/elimination strategy was demonstrated.

Table 1. Optimization Studies of the Reaction Conditions



entry	conditions[a]	8 (%)	9 (%)
1	Burgess reagent, benzene, reflux, 5 h	30	19
2	Burgess reagent, THF, reflux, 6 h	0	0
3	Burgess reagent, toluene, refux, 10 h	19	22
4	Burgess reagent, toluene, 100 °C, 30 h	63	25
5	Tf_2NH, dioxane, 100 °C, 6 h	48	9
6	*Con.* H_2SO_4, DMSO, 120 °C, 12 h	47	18
7	*Con.* H_2SO_4, DMSO, 150 °C, 6 h	40	5
8	*Con.* H_2SO_4, dioxane, 100 °C, 10 h	40	22
9[b]	*Con.* H_2SO_4, dioxane, 100 °C, 10 h	<1	99
10[c]	*Con.* H_2SO_4, dioxane, 100 °C, 10 h	35	24

[a]Reactions were carried out under an oxygen atmosphere. Burgess reagent (2 equiv), or acid (0.5 equiv). [b]Reactions were carried out under a nitrogen atmosphere. [c]Reactions were carried out under an air atmosphere.

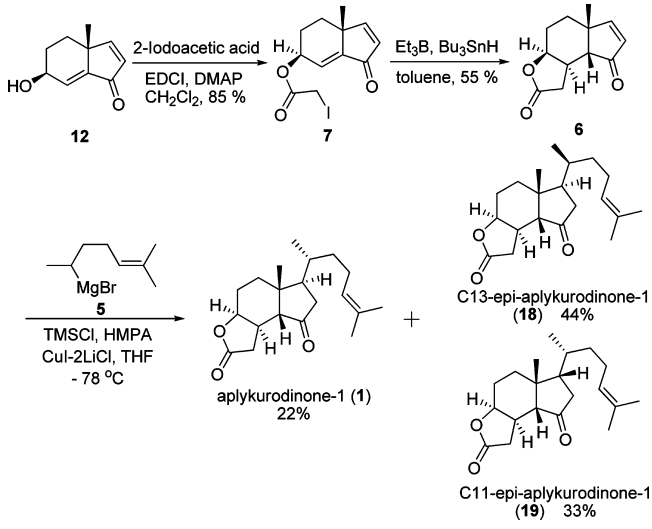
To improve the reaction efficiency, different catalysts and solvents were screened. Delightfully, Burgess reagent in toluene under an atmosphere of oxygen at 100 °C afforded diketone **8** in good yield (83% brsm, entry 4). Other solvents gave lower yields such as benzene. It even decomposed when THF was used as solvent (entry 2). Besides Burgess reagent, acids also played the same role in this transformation. Trifluoromethansulfonimide could give moderate yield in dioxane at 100 °C after 6 h (entry 5). Concentrated sulfuric acid was another effective catalyst for this reaction process, and a moderate yield was also obtained when DMSO or dioxane was used as solvent. The temperature also played an important role in the reaction. When the temperature increased from 100 °C to reflux in toluene, the yield decreased rapidly (Table 1, entries 3 and 4). A similar result was obtained when DMSO was used as solvent (Table 1, entries 6 and 7), which manifested that the starting material decomposed more rapidly at high temperature.

In addition, the mechanism of this oxidation/elimination process was studied. When the reaction was carried out in the absence of oxygen, nearly no diketone **8** or other products were obtained and the starting material was recovered (entry 9), indicating that the oxidation step was prior to the elimination step in this process. (Scheme 4)

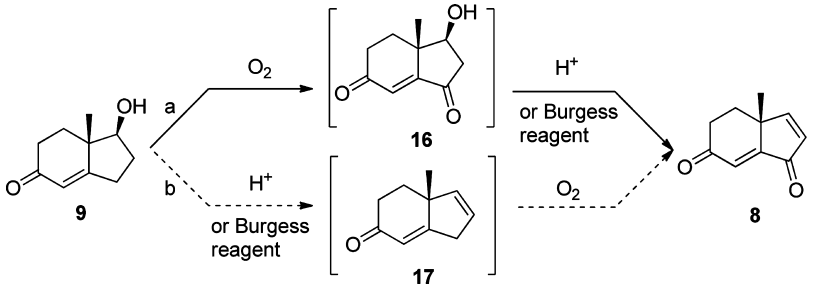
With diketone **8** in hand, we focused on the stereo- and regioselective reduction of the ketone. At first, L-selectride[14] was used as reductant. No reaction occurred with 1 equiv of the reductant. When an excess amount of L-selectride was added, undesired diol **14** was obtained. Tetramethylammonium triacetoxyborohydride[15] also gave a disappointing result. Finally, we found that, with sodium borohydride as reductant in methanol at −78 °C, alcohol **12** was obtained in moderate yield with good regio- and stereoselectivity. At the Luche conditions, an inseparable mixture of **12** and its regioisomer **15** (ca. 2:3) was obtained.

Condensation of alcohol **12** with 2-iodoacetic acid in the presence of EDCI and DMAP furnished iodide **7** in good yield (Scheme 5). With iodide **7** in hand, we next tried the AIBN-

Scheme 5. Total Synthesis of Aplykurodinone-1 (1)



Scheme 4. Possible Conversion Approach of 9 to 8



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catalyzed free radical ring-closing reaction.[16] However, no reaction happened when iodide **7** was submitted to AIBN and tributyltin hydride in anhydrous benzene at reflux. Only starting material was recycled even when the temperature was raised to 100 °C for a long reaction time (more than 48 h). Different solvents such as THF and toluene gave similar results. Finally, we found that triethyl boron promoted this free radical reaction smoothly. Treatment of iodide **7** with triethyl boron and tributyltin hydride in anhydrous toluene gave the key intermediate **6** in a reaction time of less than 5 min. Importantly, **6** was isolated as a single isomer in 55% yield with spectroscopic data in agreement with those reported.[4] With **6** in hand, the TMSCl-mediated 1,4-addition of the organocuprate derived from Grignard reagent **5** by applying the conditions described by Yang and co-workers[6] provided aplykurodinone-1 (**1**), as well as C13-*epi*-aplykurodinone-1 (**18**) and C11-*epi*-aplykurodinone-1 (**19**) in excellent yield.

In summary, we have developed here a concise and stereoselective route to total synthesis of aplykurodinone-1 with the protecting-group-free strategy. This synthetic approach features a sequence of aerobic allylic oxidation and elimination of alcohol **9**. The key intermediate **6** for this synthesis was formed by a stereoselective intramolecular radical cyclization. All the other chiral centers were controlled by the stereocenter at C7.

EXPERIMENTAL SECTION

(*S*)-7a-Methyl-2,3,7,7a-tetrahydro-1*H*-indene-1,5(6*H*)-dione (10). A 250 mL, three-neck, round-bottom flask equipped with a condenser and a magnetic stirring bar was charged with 2-methyl-1,3-cyclopentanedione (10 g, 89 mmol), 23 mL of deionized water, 0.3 mL of glacial acetic acid, and methyl vinyl ketone (12.5 mL, 153 mmol). The system was shielded from light with aluminum foil and placed under a slight positive pressure of nitrogen. The flask was placed in an oil bath, and the temperature was raised to 70 °C. After 4 h, the mixture was cooled, transferred to a separatory funnel, and extracted with ethyl acetate. The combined organic phase was washed with sat aq NaCl. The combined aqueous phase was extracted with ethyl acetate. The total ethyl acetate extract was collected and dried over $NaSO_4$. The solvent was concentrated to give the desired triketone as an orange oil (15.1 g, 83 mmol).

Another 250 mL flask equipped with a magnetic stirring bar and a nitrogen balloon was charged with *S*-(−)-proline (297 mg, 2.5 mmol) and 62 mL of DMF. The mixture was degassed four times at −60 °C by alternate evacuation and refilled with nitrogen. The system was shielded from light with aluminum foil, and the contents of the flask were stirred in a 15−16 °C bath for 1 h. To the resultant suspension was added the above residue (15.1 g, 83 mmol). A total of 20 mL of DMF was used to ensure complete transfer. The degassing procedure was repeated four times, and stirring at 15−16 °C was continued for 3 d as the mixture became yellow and then brown. A 25 mL flask equipped with a magnetic stirring bar, dropping funnel, and nitrogen inlet was charged with 10 mL of DMF. The contents of the flask were cooled to −20 °C, and 0.54 mL of concentrated sulfuric acid was added dropwise to maintain a temperature of −15 to −20 °C.

The flask containing the brown residue in DMF was placed in an oil bath and heated to 95 °C. When the temperature reached 70−75 °C, a 6.2 mL aliquot of the concentrated sulfuric acid in DMF solution was added in one portion. The reaction mixture was heated to 95 °C for 3 h. After 1 h, an additional 2.5 mL aliquot of concentrated sulfuric acid in DMF solution was added.

After cooling to room temperature, the solvent was removed on a rotary evaporator to give a brown oil. The material was diluted with 100 mL of ethyl acetate, and the solution was washed with 2 N sulfuric acid solution, sat aq $NaHCO_3$, and sat aq NaCl. Each aqueous phase was extracted with ethyl acetate. The combined ethyl acetate solution was dried over Na_2SO_4 and concentrated to give a brown oil. The residue was purified by silica gel flash column chromatography (gradient eluent: 30−50% EtOAc in petroleum) to give 12.6 g of a light yellow solid. The material was dissolved in 40 mL of ethyl acetate at reflux. Then, 6 mL of petroleum was added and refluxed. The mixture was cooled down and filtrated to give Hajos−Parrish ketone **10** (10 g, 61 mmol) as a white solid. The total yield for the three steps was 70%. 99.2% ee;[11] mp: 60−62 °C; R_f = 0.45 (40% EtOAc in petroleum); $[\alpha]_D^{25}$ = 230 [*c* 0.1 $CHCl_3$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.86 (td, 1H, *J* = 13.6, 5.6 Hz), 2.10 (ddd, 1H, *J* = 13.6, 5.2, 2.4 Hz), 2.40−2.58 (m, 3H), 2.73−2.85 (m, 2H), 2.93−3.03 (m, 1H), 5.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 20.5, 26.8, 29.2, 32.9, 35.8, 48.7, 123.8, 169.8, 198.1, 216.5; mass spectrum (ESI): *m*/*e* (% relative intensity) 165.1 (100) $(M + H)^+$; HRMS (ESI): *m*/*e* calcd for $C_{10}H_{12}O_2Na^+$ $(M + Na)^+$: 187.0735, found 187.0728; HPLC (AD-H column, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min), t_R 15.8 min (major), 16.7 min (minor).

(1*S*,7a*S*)-1-Hydroxy-7a-methyl-2,3,7,7a-tetrahydro-1*H*-inden-5(6*H*)-one (9). To a 250 mL flask equipped with a magnetic stirring bar was added Hajos−Parrish ketone **10** (2.0 g, 12.2 mmol) and 50 mL of methanol. The flask was placed at −10 °C for 10 min. Then, sodium borohydride (116 mg, 3.0 mmol) was added in 6 portions and the mixture was stirred at −15 °C for 6 h. After the reaction was complete, the mixture was quenched with 1 N HCl and was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (gradient eluent: 40−50% EtOAc in hexanes) to give alcohol **9** (1.95 g, 11.7 mmol) in 95% yield as a white solid. mp: 48−52 °C; R_f = 0.23 (40% EtOAc in petroleum); $[\alpha]_D^{25}$ = 80 [*c* 0.1 $CHCl_3$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.74−1.89 (m, 2H), 2.05−2.18 (m, 2H), 2.37−2.58 (m, 3H), 2.68−2.76 (m, 1H), 3.85 (dd, 1H, *J* = 10.4, 8.0 Hz), 4.52 (brs, 1H), 5.80(s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$), δ 15.1, 26.5, 28.9, 33.3, 34.1, 45.3, 80.3, 123.1, 176.3, 198.8; mass spectrum (ESI): *m*/*e* (% relative intensity) 167.0 (100) $(M + H)^+$; HRMS (ESI): *m*/*e* calcd for $C_{10}H_{14}O_2Na^+$ $(M + Na)^+$: 189.0891, found 189.0887.

(*R*)-3a-Methyl-4,5-dihydro-1*H*-indene-1,6(3a*H*)-dione (8). To a solution of alcohol **9** (22 mg, 0.13 mmol) in 2 mL of toluene was added Burgess reagent (57 mg, 0.26 mmol). The mixture was stirred under an oxygen atmosphere at 100 °C for 30 h. After the solution was cooled down to room temperature, sat aq NaCl was added. The aqueous phase was extracted with ethyl acetate. The combined organic layers were collected, dried over Na_2SO_4, and concentrated under reduced pressure. Then, the residue was purified by silica gel flash column chromatography (gradient eluent: 30−40% EtOAc in hexanes) to give diketone **8** (14 mg, 0.086 mmol l) in 66% yield as a yellow solid (5 mg of alcohol **9** was recycled). mp: 70−74 °C; R_f = 0.52 (40% EtOAc in petroleum); $[\alpha]_D^{25}$ = 170 [*c* 0.1 $CHCl_3$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 3H), 2.04 (td, 1H, *J* = 13.2, 5.2 Hz), 2.14 (ddd, 1H, *J* = 13.6, 5.6, 1.8 Hz), 2.60 (dd, 1H, *J* = 18.4, 5.4 Hz), 2.79 (ddd, 1H, *J* = 18.8, 13.2, 5.4 Hz), 6.27 (s, 1H), 6.33 (d, 1H, *J* = 6.0 Hz), 7.60 (d, 1H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 23.6, 32.3, 34.8, 43.1, 121.5, 133.2, 159.1, 166.5, 195.7, 199.2; mass spectrum (ESI): *m*/*e* (% relative intensity) 163.0 (100) $(M + H)^+$; HRMS (ESI): *m*/*e* calcd for $C_{10}H_{10}O_2Na^+$ $(M + Na)^+$: 185.0578, found 185.0577.

(3a*R*,6*S*)-6-Hydroxy-3a-methyl-3a,4,5,6-tetrahydro-1*H*-inden-1-one (12) and (*R*)-3a-Methyl-3,3a,4,5-tetrahydro-1*H*-indene-1,6(2*H*)-dione (13). To a 50 mL flask equipped with a magnetic stirring bar was added diketone **8** (200 mg, 1.23 mmol) and 10 mL of methanol. The flask was placed at −78 °C for half an hour. Sodium borohydride (12 mg, 0.31 mmol) was added to the flask in four portions; then the mixture was stirred at −78 °C for 3 h. An additional amount of sodium borohydride (4 mg, 0.1 mmol) was added, and the stirring was continued for another 3 h before the reaction was complete. A 2 mL aliquot of the sat aq NH_4Cl solution was added to quench the reaction. The contents of the flask were warmed to room temperature. After methanol was removed on a rotary evaporator, sat aq NaCl was added. The aqueous phase was extracted with ethyl acetate three times. The combined organic layers were collected, dried over Na_2SO_4, and concentrated under reduced

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pressure. The residue was purified by silica gel flash column chromatography (gradient eluent: 20−40% EtOAc in hexanes) to give allylic alcohol **12** (105 mg, 0.64 mmol) in 52% yield as a light yellow oil and diketone **13** (55 mg, 0.34 mmol) in 28% yield as a yellow solid.

(3a*R*,6*S*)-6-Hydroxy-3a-methyl-3a,4,5,6-tetrahydro-1*H*-inden-1-one (12). R_f = 0.37 (40% EtOAc in petroleum); $[\alpha]_D^{25}$ = 40 [*c* 0.2 $CHCl_3$]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.63(td, 1H, *J* = 13.8, 3.2 Hz), 1.84(dt, 1H, *J* = 12.6, 3.6 Hz), 1.91−1.99(m, 1H), 2.20−2.26 (m, 1H), 4.45 (td, 1H, *J* = 8.4, 3.6 Hz), 6.16 (d, 1H, *J* = 6.0 Hz), 6.35 (d, 1H, *J* = 3.6 Hz), 7.46 (d, 1H, *J* = 6.0 Hz); ^{13}C NMR(150 MHz, $CDCl_3$), δ 25.7, 28.7, 32.2, 43.1, 67.6, 129.3, 132.0, 146.3, 167.3, 197.2; mass spectrum (ESI): *m*/*e* (% relative intensity) 165.1 (100) $(M + H)^+$; HRMS (ESI): *m*/*e* calcd for $C_{10}H_{13}O_2^+$ $(M + H)^+$: 165.0916, found 165.0901.

(*R*)-3a-Methyl-3,3a,4,5-tetrahydro-1*H*-indene-1,6(2*H*)-dione (13). mp: 90−94 °C; R_f = 0.69 (40% EtOAc in petroleum); $[\alpha]_D^{25}$ = 540 [*c* 0.1 $CHCl_3$]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.75−1.81 (m, 1H), 2.03 (td, 1H, *J* = 13.8, 4.8 Hz), 2.14 (dd, 1H, *J* = 12.6, 9.0 Hz), 2.21(ddd, 1H, *J* = 13.2, 5.4, 1.8 Hz), 2.47−2.53 (m, 2H), 2.58−2.69 (m, 2H), 6.26 (s, 1H); ^{13}C NMR(150 MHz, $CDCl_3$), δ 22.9, 34.1, 35.3, 36.2, 37.1, 39.7, 122.6, 161.0, 199.9, 207.0; mass spectrum (ESI): *m*/*e* (% relative intensity) 165.1 (100) $(M + H)^+$; HRMS (ESI): *m*/*e* calcd for $C_{10}H_{12}O_2Na^+$ $(M + Na)^+$: 187.0735, found 187.0731.

(3a*R*,6*S*)-3a-Methyl-1-oxo-3a,4,5,6-tetrahydro-1*H*-inden-6-yl 2-Iodoacetate (7). To a solution of allylic alcohol **12** (50 mg, 0.3 mmol) in 15 mL of dichloromethane was added EDCI (115 mg, 0.6 mmol) and DMAP (4 mg, 0.03 mmol). The flask was placed at −15 °C for half an hour. Then, 2-iodoacetic acid (112 mg, 0.6 mmol) was added in one portion. The mixture was stirred at −15 °C for 3 h before the reaction was complete. After the mixture was warmed up to room temperature, sat aq NaCl was added. The aqueous phase was extracted with dichloromethane three times. The combined organic layers were collected, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (gradient eluent: 10−20% EtOAc in hexanes) to give iodide **7** (85 mg, 0.25 mmol) in 85% yield as a light yellow oil. The light yellow oil was then recrystallized with 40% ethyl acetate in petroleum to give iodide **7** (60 mg, 0.18 mmol) in 60% yield as a white solid. mp: 94−96 °C; R_f = 0.75 (40% EtOAc in petroleum); $[\alpha]_D^{25}$ = −80 [*c* 0.1 $CHCl_3$]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.70 (td, 1H, *J* = 13.8, 3.6 Hz), 1.90 (dt, 1H, *J* = 13.2, 3.6 Hz), 1.99−2.06 (m, 1H), 2.28−2.33 (m, 1H), 3.72 (d, 2H, *J* = 2.4 Hz), 5.53 (td, 1H, *J* = 8.4, 2.4 Hz), 6.19 (d, 1H, *J* = 6.0 Hz), 6.30 (d, 1H, *J* = 4.2 Hz), 7.46 (d, 1H, *J* = 6.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$), δ −5.7, 24.6, 25.2, 32.1, 42.7, 70.9, 123.8, 132.3, 148.9, 166.6, 168.5, 195.9; mass spectrum (ESI): *m*/*e* (% relative intensity) 333.0 (100) $(M + H)^+$; HRMS (ESI): *m*/*e* calcd for $C_{12}H_{13}IO_3Na^+$ $(M + Na)^+$: 354.9807, found 354.9808.

(3a*S*,5a*R*,8a*R*,8b*R*)-5a-Methyl-3a,4,5,5a-tetrahydro-1*H*-indeno[5,4-*b*]furan-2,8(8a*H*,8b*H*)-dione (6). Iodide **7** (100 mg, 0.3 mmol) was added to a predried flask equipped with a magnetic stirring bar, and the system was placed under a slight positive pressure of nitrogen. A 40 mL portion of anhydrous toluene was added, followed with triethylborane (0.3 mL, 1 M in hexane). Then, a solution of tributyltin hydride (0.8 mL, 3.0 mmol) in 5 mL of anhydrous toluene was added dropwise to the mixture at room temperature. Once the addition was over, anhydrous air was injected to the flask immediately. The mixture was allowed to stir at room temperature for 5 min before the reaction was complete. The solvent was removed under reduced pressure. The residue was purified by silica gel flash column chromatography (gradient eluent: 10−40% EtOAc in hexanes) three times to give lactone **6** (34 mg, 0.17 mmol) in 55% yield as a white solid. mp: 92−94 °C; R_f = 0.35 (40% EtOAc in petroleum); $[\alpha]_D^{25}$ = 70 [*c* 0.1 $CHCl_3$]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.36−1.42 (m, 1H), 1.53 (ddd, 1H, *J* = 14.4, 6.0, 2.8 Hz), 1.63−1.68 (m, 1H), 1.76−1.81 (m, 1H), 2.10 (d, 1H, *J* = 3.6 Hz), 2.58 (dd, 1H, *J* = 18.6, 8.4 Hz), 2.83 (dd, 1H, *J* = 18.6, 10.8 Hz), 3.28−3.34 (m, 1H), 4.68−4.72 (m, 1H), 6.18 (d, 1H, *J* = 5.4 Hz), 7.31 (d, 1H, *J* = 5.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$), δ 24.3, 27.7, 28.0, 31.9, 33.8, 43.9, 52.9, 77.1, 131.1, 170.9, 176.1, 209.0; mass spectrum (ESI): *m*/*e* (% relative intensity) 207.0 (100) $(M + H)^+$; HRMS (ESI): *m*/*e* calcd for $C_{12}H_{15}O_3$ $(M + H)^+$: 207.1021, found 207.1014.

Aplykurodinone-1(1), C13-*epi*-Aplykurodinone-1 (18), and C11-*epi*-Aplykurodinone-1 (19). To a 50 mL flask was added CuI (230 mg, 1.2 mmol), LiCl (102 mg, 2.4 mmol), and 5 mL of THF. The mixture was stirred at room temperature for 5 min until the solution became clean. Then, the flask was placed at −78 °C for 20 min before the Grignard reagent **5** (9.2 mL, 0.13 mmol) was added. After 10 min, HMPA (0.2 mL, 1.2 mmol) was added, and the mixture was stirred for another 5 min. To another flask was added lactone **6** (25 mg, 0.12 mmol) and 5 mL of dry THF, which cooled to −78 °C when TMSCl (0.15 mL, 1.2 mmol) was added to this solution. Then, the solution of lactone **6** and TMSCl was cannulated to the previous cuprate reagent at −78 °C. The reaction was stirred at −78 °C for 6 h before being quenched with sat NH_4Cl and warmed to room temperature. The aqueous phase was extracted with ethyl acetate three times. The combined organic layers were collected, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (gradient eluent: 10−20% EtOAc in hexanes) and a reduction−oxidation sequence to give the C11-*epi*-aplykurodinone-1 (**19**) as a white solid (12.6 mg, 33%) and a pair of aplykurodinone-1 (**1**) and C13-*epi*-aplykurodinone-1 (**18**) as white solids (25.2 mg combined, NMR ratio **1**:**18** = 1:2).

1: R_f = 0.36 (20% EtOAc in petroleum); $[\alpha]_D^{25}$ = 10 [*c* 0.1 $CHCl_3$]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.00 (d, 3H, *J* = 6.6 Hz), 1.03 (s, 3H), 1.07−1.13 (m, 1H), 1.36−1.49 (m, 2H), 1.60 (s, 3H), 1.61−1.65 (m, 2H), 1.68 (s, 3H), 1.72−1.76 (m, 2H), 1.84−1.94 (m, 2H), 2.02−2.14 (m, 3H), 2.43−2.54 (m, 2H), 2.58 (dd, 1H, *J* = 8.4, 18.0 Hz), 2.89 (dd, 1H, *J* = 1.8, 18.0 Hz), 4.63 (q, 1H, *J* = 7.2 Hz), 5.06 (t, 1H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.7, 18.7, 21.4, 24.3, 24.8, 25.7, 31.6, 32.8, 33.4, 34.4, 35.7, 41.3, 41.7, 48.2, 57.1, 78.5, 124.2, 131.6, 176.2, 217.9; mass spectrum (ESI): *m*/*e* (% relative intensity) 319.3 (100) $(M + H)^+$; HRMS (ESI): *m*/*e* calcd for $C_{20}H_{30}O_3$ $(M + Na)^+$: 341.2093, found 341.2096.

18: R_f = 0.36 (20% EtOAc in petroleum); $[\alpha]_D^{25}$ = 10 [*c* 0.1 $CHCl_3$]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (d, 3H, *J* = 6.6 Hz), 1.07 (s, 3H), 1.14−1.20 (m, 1H), 1.40−1.44 (m, 1H), 1.148−1.53 (m, 1H), 1.61 (s, 3H), 1.67−1.72 (m, 5H), 1.80 (d, 1H, *J* = 10.2 Hz), 1.89−2.10 (m, 5H), 2.13 (dd, 1H, *J* = 10.2, 19.2 Hz), 2.41 (dd, 1H, *J* = 10.2, 19.2 Hz), 2.54−2.60 (m, 2H), 2.82−2.90 (m, 1H), 4.58 (q, 1H, *J* = 7.2 Hz), 5.08 (t, 1H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.7, 17.8, 21.8, 24.3, 25.4, 25.7, 31.5, 32.9, 33.3, 33.4, 36.2, 40.3, 41.2, 47.6, 56.5, 78.3, 124.1, 131.9, 176.2, 218.1; mass spectrum (ESI): *m*/*e* (% relative intensity) 319.1 (100) $(M + H)^+$; HRMS (ESI): *m*/*e* calcd for $C_{20}H_{30}O_3$ $(M + Na)^+$: 341.2093, found 341.2090.

19: R_f = 0.39 (20% EtOAc in petroleum); $[\alpha]_D^{25}$ = −30 [*c* 0.1 $CHCl_3$]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (d, 3H, *J* = 6.6 Hz), 1.08−1.19 (m, 2H), 1.26−1.34 (m, 1H), 1.39 (s, 3H), 1.52−1.58 (m, 2H), 1.60 (s, 3H), 1.69 (s, 3H), 1.76−1.85 (m, 1H), 1.90−1.95 (m, 1H), 1.97−2.06 (m, 3H), 2.09 (dd, 1H, *J* = 12.6, 19.8 Hz), 2.19 (brs, 1H), 2.35 (dd, 1H, *J* = 9.0, 19.8 Hz), 2.48−2.68 (m, 2H), 3.29 (dt, 1H, *J* = 7.8, 16.8 Hz), 4.30 (dt, 1H, *J* = 6.6, 14.4 Hz), 5.09 (t, 1H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.6, 17.8, 24.3, 25.30, 25.39, 25.4, 25.7, 30.3, 31.9, 32.3, 36.7, 38.1, 41.5, 49.2, 58.2, 77.3, 124.0, 131.9, 175.8, 216.1; mass spectrum (ESI): *m*/*e* (% relative intensity) 319.3 (100) $(M + H)^+$; HRMS (ESI): *m*/*e* calcd for $C_{20}H_{30}O_3$ $(M + Na)^+$: 341.2093, found 341.2099

Reduction of Aplykurodinone-1 (1) and C13-*epi*-Aplykurodinone-1 (18) to 1a and 18a.[17] To a solution of the mixture of **1** and **18** (26 mg, 0.08 mmol) in 5 mL of methanol was added $NaBH_4$ (5 mg, 0.12 mmol) in two portions at 0 °C. The mixture was stirred at 0 °C for 30 min before the reaction was complete. The reaction was quenched by carefully adding water and the temperature was raised to room temperature. After removal of the solvent, the rest aqueous phase was extracted with ethyl acetate five times. The combined organic layers were collected, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (gradient eluent: 10−20% EtOAc in hexanes)

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to give **1a** (6 mg, 23%) as a light yellow oil and **18a** (12 mg, 46%) as a light yellow oil.

1a: R_f = 0.45 (40% EtOAc in petroleum); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.92 (d, 3H, J = 6.6 Hz), 1.10 (s, 3H), 1.35−1.47 (m, 4H), 1.54−1.65 (m, 8H), 1.69 (s, 3H), 1.85−1.91 (m, 1H), 1.95−2.10 (m, 3H), 2.21−2.27 (m, 1H), 2.33−2.37 (m, 1H), 2.50 (dd, 1H, J = 2.4, 18.0 Hz), 2.72 (dd, 1H, J = 9.0, 18.0 Hz), 3.76−3.80 (m, 1H), 4.68 (q, 1H, J = 7.2 Hz), 5.08 (t, 1H, J = 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.7, 18.8, 22.7, 24.5, 24.8, 25.7, 32.6, 33.8, 34.1, 36.0, 36.3, 39.8, 42.4, 52.1, 56.7, 76.4, 79.7, 124.6, 131.4, 176.9; mass spectrum (ESI): m/e (% relative intensity) 343.9 (100) $(M + Na)^+$; HRMS (ESI): m/e calcd for $C_{20}H_{32}O_3$ $(M + Na)^+$: 343.2249, found 343.2247.

18a: R_f = 0.40 (40% EtOAc in petroleum); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (d, 3H, J = 6.6 Hz), 1.09 (s, 3H), 1.30−1.39 (m, 3H), 1.43−1.50 (m, 3H), 1.55−1.64 (m, 6H), 1.68 (s, 3H), 1.86−1.93 (m, 1H), 1.96−2.08 (m, 3H), 2.21−2.25 (m, 1H), 2.26−2.34 (m, 1H), 2.52 (dd, 1H, J = 2.4, 18.0 Hz), 2.71 (dd, 1H, J = 9.0, 18.0 Hz), 3.76−3.80 (m, 1H), 4.67 (q, 1H, J = 7.2 Hz), 5.07 (t, 1H, J = 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.7, 18.5, 23.2, 24.5, 25.4, 25.7, 32.3, 32.8, 34.1, 36.3, 36.4, 38.7, 42.2, 51.4, 56.3, 76.5, 79.7, 124.5, 131.5, 177.1; mass spectrum (ESI): m/e (% relative intensity) 343.7 (100) $(M + Na)^+$; HRMS (ESI): m/e calcd for $C_{20}H_{32}O_3$ $(M + Na)^+$: 343.2249, found 343.2248.

Oxidation of 1a and 18a to Aplykurodinone-1 (1) and C13-*epi*-Aplykurodinone-1 (18).[18] To a solution of compound **1a** (5 mg, 0.016 mmol) in 5 mL of dichloromethane was added DMP (13 mg, 0.03 mmol), and the solution was stirred at room temperature for 2 h before the reaction was complete. The reaction was quenched with sat aq $NaHCO_3$ solution and extracted with dichloromethane. The combined organic layers were collected, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (gradient eluent: 10−20% EtOAc in hexanes) to give aplykurodinone-1 (**1**) (2.8 mg, 0.009 mmol) in 47% yield as a white solid. The C13-*epi*-aplykurodinone-1 (**18**) (6.9 mg, 0.022 mmo) was obtained in the same manner in 58% yield as a white solid.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of compounds and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yutang@tju.edu.cn (Y.T.).

Notes

The authors declare no competing financial interest.

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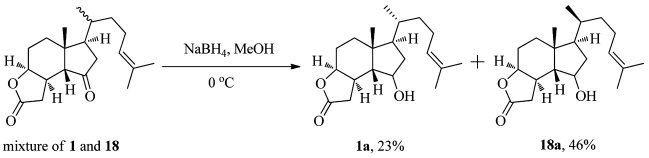
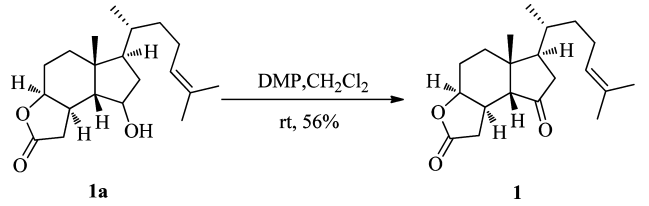
(17) Aplykurodinone-1 (**1**) and C13-*epi*-aplykurodinone-1 (**18**) could be separated through a reduction−oxidation sequence (easily separated after reduction). Both the NMR data of aplykurodinone-1 (**1**) and C13-*epi*-aplykurodinone-1 (**18**) matched the samples synthesized respectively by Danishefsky[4] and Yang[6]. (Please refer to the comparison of the spectra at the end of the Supporting Information.)



(18) Oxidation of **1a** and **18a** to aplykurodinone-1 (**1**) and C13-*epi*-aplykurodinone-1 (**18**).



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