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Synthesis of (±)-pterosin A via Suzuki–Miyaura cross-coupling reaction

Shao-Chien Hsu [a], Mogili Narsingam [a], Yi-Fang Lin [a], Feng-Lin Hsu [b], Biing-Jiun Uang [a,*]

[a] Department of Chemistry, National Tsing Hua University, Hsinchu 30013, Taiwan
[b] Graduate Institute of Pharmacognosy, School of Pharmacy, Taipei Medical University, Taipei 110, Taiwan

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ABSTRACT

A practical synthesis of (±)-pterosin A from commercially available 2-bromo-1,3-dimethyl-benzene **5** has been accomplished in 10% overall yield. The synthesis used Suzuki–Miyaura coupling reaction of C6-bromoindanone derivative **3** with potassium vinyltrifluoroborate **9**, which provided the corresponding vinylindanone **2** in >85% yield. The vinylindanone **2** could be further elaborated to pterosin A by reduction with LAH, selective protection of primary alcohol with TESCl, hydroboration–oxidation of vinyl group, protection of primary alcohol with TIPSCl, oxidation of the secondary alcohol, and desilylation with TBAF.

1. Introduction

Pterosin family are sesquiterpenoids that existed in bracken fern (*Pteridium aquilinum*).[1] Some pterosins have been shown to possess biological activity[2] including antibacterial[2,3] and cytotoxicity.[3] Although there had been some reports on the synthesis of pterosins,[4–6] the challenge of synthesizing pterosins usually was restricted by the continuous functional groups that somehow increased the complexity during the synthesis.[7] We need some substantial amount of pterosin A **1** (Fig. 1) and its derivatives for our biological studies. It needs a flexible methodology, that is, able to construct both the indanone core and the C6-side chain in an efficient manner.

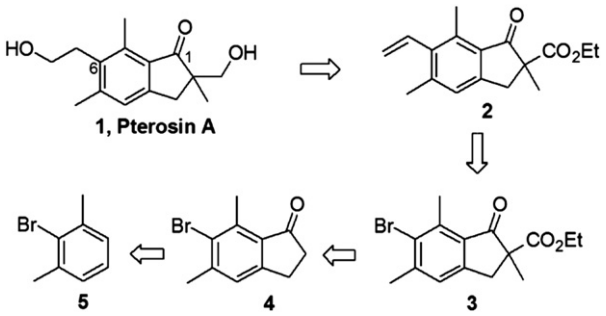

Fig. 1. Retrosynthesis of pterosin A.

The construction of indanone skeleton from benzene derivative using Friedel–Crafts/Nazarov cyclization methodology is documented.[8] Although this methodology has a drawback on the regioselectivity, it remains as a useful method for the synthesis of indanones from benzene derivatives.[5,9]

Taking the advantage of modern synthetic method using the Suzuki–Miyaura cross-coupling for the vinylation of aryl halides with potassium vinyltrifluoroborate,[10,11] we envisage that pterosin A might be synthesized by the following manner (Fig. 1): (1) prepare bromo-indanone **4** from **5** followed by ethoxycarbonylation and alkylation to furnish C2-quaternary center, (2) use Suzuki–Miyaura cross-coupling reaction to install a vinyl group at C6 of indanone **3** and it could be converted to the hydroxyethyl group to furnish the synthesis of pterosin A or elaborate to its derivatives.

2. Results and discussion

Our synthesis of pterosin A **1** was started from the reaction of 2-bromo-1,3-dimethylbenzene **5** with 3-chloro-propionyl chloride in the presence of $AlCl_3$. The reaction gave two isomeric products **6a** and **6b** as described in the literature.[5] The mixture of **6a** and **6b** was heated directly with concd H_2SO_4 at 90 °C to give the corresponding indanones **4** and **7** (vide infra) in 39% and 40% yield, respectively, (Scheme 1). However, it was found that the ^1H and ^{13}C NMR data of either **4** or **7** did not match with that were reported in the literature (Table 1).[5] Assignments of their structures by NOE experiments

* Corresponding author. E-mail address: bjuang@mx.nthu.edu.tw (B.-J. Uang).

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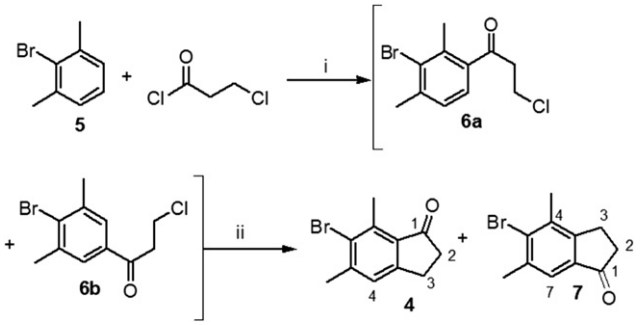
were unsuccessful. However, there is a weak correlation signal between C1–H7 on the HMBC spectrum of **7** and no such correlation signal for **4**. To further confirm the structure of our prepared products, X-ray crystallographic study was conducted and the structure of **4** is confirmed as shown in Fig. 2.



Scheme 1. Reagents and conditions: (i) $AlCl_3$, CH_2Cl_2, 0 °C to rt, 12 h; (ii) concd H_2SO_4, 90 °C, 1 h, 39% of **4**.

Table 1
NMR chemical shifts (ppm) of indanone **4** and **7** (all measured in $CDCl_3$)

Reported **4**[5]		**4**		**7**	
^{1}H NMR	^{13}C NMR	^{1}H NMR	^{13}C NMR	^{1}H NMR	^{13}C NMR
2.45 (s, 3H)	19.46	2.46 (s, 3H)	17.32	2.41 (s, 3H)	18.86
2.65 (s, 3H)	24.25	2.66 (t, 2H)	24.41	2.45 (s, 3H)	24.09
2.9 (t, 2H)	36.85	2.72 (s, 3H)	24.88	2.67 (t, 2H)	25.23
3.04 (t, 2H)	122.65	2.95 (t, 2H)	37.09	3.02 (t, 2H)	36.25
7.26 (s, 1H)	133.6	7.17 (s, 1H)	125.75	7.45 (s, 1H)	121.97
	136.7		127.88		134.97
	138.54		133.29		135.28
	152.83		138.72		136.06
	205		144.51		137.88
			154.38		152.24
			206.24		206.32

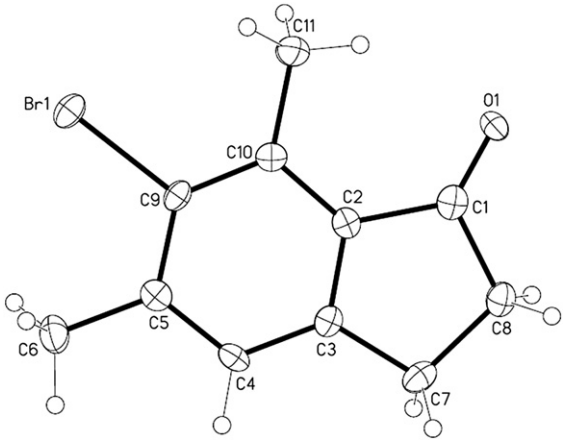
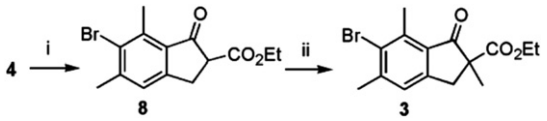


Fig. 2. X-ray single crystal analysis of indanone **4**.

Treatment of indanone **4** with sodium hydride and diethyl carbonate in refluxing toluene gave **8** in 88% yield. Subsequently, treatment of **8** with sodium hydride in THF and iodomethane afforded **3** in 86% yield (Scheme 2).



Scheme 2. Reagents and conditions: (i) NaH, diethyl carbonate, toluene, reflux, 88%; (ii) NaH, MeI, THF, 0 °C to rt, 86%.

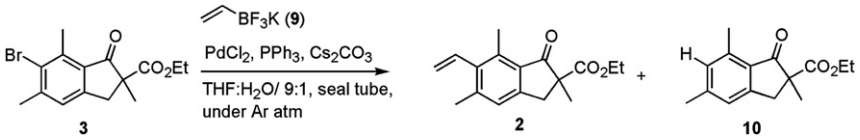
The direct hydroxyethylation using Grignard reagent with ethylene oxide is a straight forward way to construct C6 substitution.[6] It is difficult for us to receive ethylene oxide because this reagent is a controlled chemical in our case. Besides, it limits the further elaboration to other functional groups for the biological studies. The incorporation of a vinyl group at C6 may provide an alternative solution for the elaboration into hydroxyl group or other functional groups. The vinylation of aryl bromide has been shown that it could be achieved by using trivinylcyclotriboroxane,[12] vinylpolysiloxanes[13] or tributyl-vinyl-stannane in the palladium catalyzed coupling reaction.[14,15] However, the palladium catalyzed vinylation of 1,3-dimethyl-2-bromobenzene derivatives usually suffer from low yielding due to steric hindrance and the electron-rich nature that caused by the *ortho*,*ortho*′-disubstituted methyl groups.[11a] Recently, Molander's group had established an efficient Suzuki–Miyaura Cross-Coupling reactions of potassium vinyltrifluoroborate **9** with hindered aryl bromides, such as bromo mesitylene using RuPhos as a ligand.[10]

Inspired by these reports, we tried to conduct vinylation by Suzuki–Miyaura cross-coupling reaction in our synthesis. The *ortho*,*ortho*′-dimethyl groups could be an obstacle for the coupling reaction if we uses less expensive $PdCl_2$ as the catalyst. However, the electron-withdrawing benzoyl carbonyl group could be a benefit to this type of coupling reaction.[10,11] Initially, treatment of the bromoester **3** with potassium vinyltrifluoroborate **9** (1 equiv) in the presence of 2 mol % of $PdCl_2$, Cs_2CO_3 (3 equiv), and 6 mol % of PPh_3 afforded an almost equal amount of coupling product **2** and bromoester **3** as an inseparable mixture in 87% yield (Table 2, entry 1, Molander's typical reaction condition).[10b] When the amount of reagents and catalyst were doubled, the reaction gave a slightly improved yield of vinylated product **2**. However, some substantial amount of **3** remained in the mixture (Table 2, entry 2). To force the reaction toward completion and improve the yield of desired **2**, the catalyst loading was raised to 20 mol % for the coupling reaction and it afforded product **2** in 88% yield as a mixture with inseparable reduction product **10** (Table 2, entry 3). It was documented that the increase of palladium catalyst loading could cause the formation of reduction product.[11a] Through the optimization process, it was observed that the ratio of **2** and **10** could be slightly improved by decreasing the amount of Cs_2CO_3 (Table 2, entry 4). Decrease the amount of base and increase the reaction concentration of the reaction gave unsatisfactory results (Table 2, entries 5 and 6). There was no apparent improvement found whether the reaction temperature was lowered or raised (Table 2, entries 7 and 8). Attempt to speed up the catalytic cycle of coupling reaction by increasing the amount of PPh_3 and shorten the reaction time (Table 2, entry 9), but the reduction product **10** still can be found. Interestingly, when the reaction was prolonged, it was found that the reaction can go to completion with almost the same amount of reduction **10** was produced (Table 2, entry 10). The ratio of **2** and **10** could be further improved to 95:5 when the amount of potassium vinyltrifluoroborate **9** was decreased (Table 2, entries 11 and 12). However, the yield was decreased dramatically when the amount of **9** was decreased further (Table 2, entry 13).

It is crucial to use a proper amount of potassium vinyltrifluoroborate **9** in Suzuki–Miyaura reaction to suppress the reduction product. The reduction product **10** was eliminated by decreasing the amount of **9**.[11a] However, it is contrary to Wyatt's report that the reduction product was eliminated by increasing the amount of **9** (Table 2, entries 2, 10, and 11). These opposite findings may be due to the catalyst systems are different.[16] The result of entry 12 in Table 2 is compatible with Wyatt's result in terms of yield.[11a] This condition was selected for the preparation of vinylindanone **2**.

With the advanced intermediate **2** in hand, we continued our effort to construct 2′-hydroxyethyl group at C6 position. It is

Table 2
Optimization of the Suzuki–Miyaura reaction[17]



Entry[a]	**9** (equiv)	Cs_2CO_3 (equiv)	PPh_3 (mol %)	$PdCl_2$ (mol %)	Temp (°C)	THF:H_2O (9:1)/mL	Time (h)	Ratio[c] (**3**:**2**:**10**)	Yield (%)[d]
1	1	3	6	2	85	3	48	47:53:0	87
2	2	6	12	4	85	3	48	40:60:0	80
3	3	6	30	20	85	3	48	0:85:15	88
4	3	4	30	20	85	3	48	0:89:11	90
5	3	2	30	30	85	1	48	44:52:4	92
6	3	2	30	30	85	1	60	26:68:6	93
7	3	4	30	30	65	1	48	29:60:11	91
8	3	4	30	30	105[b]	1	48	0:86:14	93
9	3	4	60	30	85	1	24	13:77:10	93
10	3	4	60	30	85	1	48	0:91:9	91
11	2	4	30	20	85	3	48	0:93:7	90
12	1.5	4	30	20	85	3	48	0:95:5	90
13	1.2	4	30	20	85	3	48	22:72:6	92

[a] All reactions were conducted with 300 mg of **3**.
[b] THF was replaced by DME (1,2-dimethoxyethane).
[c] Ratios were determined by ^1H NMR of the isolated mixture.[17]
[d] Isolated yield of the mixture (**2**+**3**+**10**).

reasonable to control the regiochemistry on the hydration of vinyl group by using hydroboration/oxidation sequence (Scheme 3). However, treatment of **2** with borane etherate followed by H_2O_2/NaOH gave a complex mixture. There is no carbonyl signal in IR spectrum of the reaction product. To minimize the complexity, β-keto ester **2** was reduced to the corresponding diol by LAH then followed by a selective protection of the primary alcohol to provide **11** as a ~1:1 diastereomeric mixture. When **11** was treated with borane etherate followed by an oxidation using H_2O_2 and 2 N NaOH, an equal amount of the desired compound **12** and undesired regioisomer were detected. To improve the regioselectivity, 9-BBN was tested for the reaction. Unfortunately, no sign of reaction was observed. Finally, diol **12** was obtained as a diastereomeric mixture in 81% yield when dicyclohexylborane was used to react with **11** followed by oxidation with H_2O_2/2 N NaOH. Selective protection of the primary alcohol in **12** by using triisopropylsilyl chloride (TIPSCl) afforded **13** in 82% yield. The benzylic hydroxyl group of **13** was oxidized by using PDC to give keto compound **14**. Subsequently, both TIPS and TES groups of **14** were removed by using tetrabutylammonium fluoride (TBAF) in THF to give (±)-pterosin A **1** in 85% yield. Both ^1H and ^{13}C NMR spectra and other physical data of our synthetic compound **1** were in agreement with the known literature data.[6]

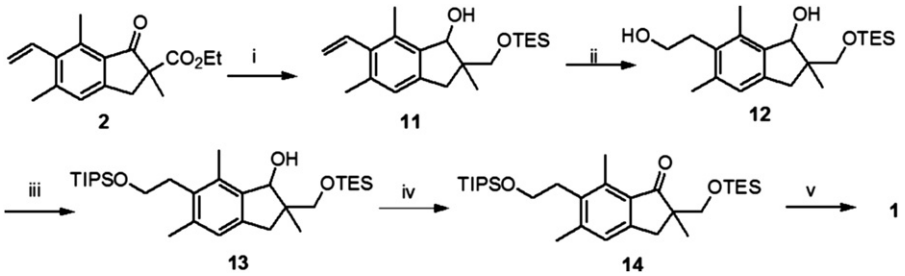
3. Conclusions

In summary, the vinylation of hindered aryl bromide by using potassium vinyltrifluoroborate **9** in the Suzuki–Miyaura cross-coupling reaction in the presence of $PdCl_2$ can be achieved in high yield. We have accomplished the synthesis of (±)-pterosin A in 9 steps and 10% overall yield. Although the overall yield of our synthetic pterosin A is lower than the reported synthesis,[6] vinylindanone **2** will be more versatile for the further elaboration to pterosin A derivatives for the biological and Structure–Activity Relationship studies.

4. Experimental section

4.1. General information

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a BRUKER AV-400 (400 MHz) or a Varian Mercury-400 (400 MHz). Data were reported in the following order; chemical shift as δ values referenced to $CDCl_3$ (7.24), integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiple), coupling constants in Hertz. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Mercury-400 (100 MHz). Chemical shifts are reported in δ values and referenced to $CDCl_3$ (77.00). High resolution mass spectra (HRMS) were recorded with Mass spectrometers in *m*/*z*, respectively, in NSC Instrumentation Center at NTHU. IR spectra were obtained on a Bomen MB 100FT spectrometer. Thin-layer chromatography was performed on silica gel G60 F254 (Merck) with short-wavelength UV light for visualization. Silica Gel 60 (particle size 63~200 um, purchased from Merck) was used for column chromatography.



Scheme 3. Reagents and conditions: (i) LAH, THF, −78 °C, 3 h then TESCl, Imidazole, CH_2Cl_2, 6 h, 2 steps 88%; (ii) Cy_2BH, 0 °C to rt, 12 h; then 2 N NaOH, H_2O_2, 0 °C, 4 h, 81%; (iii) TIPSCl, imidazole, 0 °C to rt, 3 h, 82%; (iv) PDC, CH_2Cl_2, 0 °C to rt, 4 h, 81%; (v) TBAF, THF, 0 °C to rt, 3 h, 85%.

4.2. Procedure for the preparation of pterosin A (1)

*4.2.1. 6-Bromo-5,7-dimethyl-1-indanone **4**.* To a stirred mixture of $AlCl_3$ (20.2 g, 151 mmol) and 3-chloro-propionyl chloride (16.5 g, 129 mmol) in CH_2Cl_2 (80 mL) was dropwise added 2-bromo-1,3-dimethylbenzene **2** (20.0 g, 108 mmol) in CH_2Cl_2 (40 mL) through an addition funnel over 40 min at 0 °C .The reaction mixture was warmed to room temperature and stirred for 12 h then quenched with ice (200 g) and 12 M HCl (50 mL). The mixture was stirred for 15 min then extracted with ethyl acetate (2×300 mL). The combined extract was successively washed with water (400 mL), brine (500 mL) dried (Na_2SO_4), and concentrated in vacuo. The residue was added concd H_2SO_4 (165 mL), and stirred at 90 °C for 1 h. After the reaction mixture was cooled to room temperature, it was quenched with the addition of ice (400 g). The reaction mixture was extracted with ethyl acetate (2×400 mL), and the combined extract was washed with water (500 mL), brine (500 mL), dried (anhydrous Na_2SO_4), and concentrated in vacuo. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate, 12:1, v/v) to give pure **4** (10.1 g, 39%) as solid and **7** (10.3 g, 40%). Compound **4**: mp: 81∼86 °C; ^{1}H NMR: δ 2.46 (s, 3H), 2.66 (t, J=6 Hz, 2H), 2.72 (s, 3H), 2.95 (t, J=6 Hz, 2H), 7.17 (s, 1H); ^{13}C NMR: δ 17.32, 24.41, 24.88, 37.09, 125.75, 127.88, 133.29, 138.72, 144.51, 154.38, 206.24; HRMS: calcd for $C_{11}H_{11}BrO$: 237.9993, found: 237.9993. IR (KBr) 3011, 1706, 1590, 1441; Compound **7**: ^{1}H NMR: δ 2.41 (s, 3H), 2.45 (S, 3H), 2.67 (t, J=6 Hz, 2H), 3.02 (t, J=6 Hz, 2H), 7.45 (s, 1H); ^{13}C NMR: δ 18.86, 24.09, 25.23, 36.25, 121.97, 134.97, 135.28, 136.06, 137.88, 152.24, 206.32 IR (KBr) 1689, 1598, 1435.

*4.2.2. 6-Bromo-5,7-dimethyl-1-oxo-indan-2-yl-carboxylic acid ethyl ester **8**.* A mixture containing sodium hydride (60% dispersion, 5.0 g, 125 mmol) and diethyl carbonate (30.5 mL, 251 mmol) in toluene (100 mL) was stirred mechanically with reflux. 1-Indanone **4** (10.0 g, 41.8 mmol) in toluene (50 mL) was added slowly to the above refluxing solution over a period of 3 h. The addition funnel was washed with toluene (20 mL) and the solution was added to the reaction mixture. The reaction mixture was refluxed for an additional 0.5 h then added slowly into a saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ethyl acetate (3×100 mL) and the combined ethyl acetate extracts were washed with brine, dried (anhydrous Na_2SO_4), and concentrated in vacuo. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate, 15:1, v/v) to give **8** (11.5 g, 88.4%) as solid. Mp: 108 °C ^{1}H NMR: δ 1.29 (t, J=7.2 Hz, 3H), 2,48 (s, 3H), 2.71 (s, 3H), 3.19 (dd, J=8.4, 17.2 Hz, 1H), 3.39 (dd, J=4.0, 17.2 Hz, 1H), 3.69 (dd, J=4.0, 8.4 Hz, 1H), 4.24 (m, 2H), 7.2 (s, 1H); ^{13}C NMR: δ 14.10, 17.52, 24.97, 28.92, 54.03, 61.56, 125.58, 128.34, 131.63, 139.59, 145.57, 152.87, 169.15, 198.89; HRMS: calcd for $C_{14}H_{15}BrO_3$: 310.0205, found: 310.0200. IR (KBr) 1738, 1709.

*4.2.3. 6-Bromo-2,5,7-trimethyl-1-oxo-indan-2-yl-carboxylic acid ethyl ester **3**.* To a stirred solution of compound **8** (5.00 g, 16.1 mmol) in dry THF (50 mL) was added sodium hydride (60% dispersion, 1.42 g, 35.4 mmol) in portions at 0 °C by a solid addition funnel. The reaction mixture was warmed to room temperature and stirred for another 1 h, then was added MeI (2.0 mL, 32.1 mmol) dropwise at 0 °C under argon atmosphere. The reaction mixture was warmed to room temperature again and stirred for 5 h, then was quenched with saturated aqueous NH_4Cl solution at 0 °C. The mixture was stirred for 15 min and extracted with ethyl acetate (3×100 mL). The combined extract was washed with water (100 mL), brine (100 mL), dried (anhydrous Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate, 15:1, v/v) to give **3** as solid (4.5 g, 86%). Mp=69 °C; ^{1}H NMR: δ 1.17 (t, J=7.2 Hz, 3H), 1.46 (s, 3H), 2.48 (s, 3H), 2.72 (s, 3H), 2.82 (d, J=17.2 Hz, 1H), 3.53 (d, J=17.2 Hz, 1H), 4.12 (dq, J=7.2, 2.0 Hz, 2H), 7.18 (s, 1H); ^{13}C NMR: δ 13.94, 17.57, 21.12, 24.97, 38.58, 56.59, 61.39, 125.59, 128.37, 131.12, 139.87, 145.43, 151.92, 171.88, 202.79; HRMS: calcd for $C_{15}H_{17}BrO_3$: 324.0361, found: 324.0355. IR (KBr) 1740, 1708, 1590, 1454.

*4.2.4. 2,5,7-Trimethyl-1-oxo-6-vinyl-indan-2-yl-carboxylic acid ethyl ester **2**.* A solution of potassium vinyltrifluoroborate, **9** (186 mg, 1.38 mmol), $PdCl_2$ (33 mg, 0.18 mmol), PPh_3 (73 mg, 0.27 mmol), Cs_2CO_3 (1.2 g, 3.7 mmol), and compound **3** (0.30 g, 0.92 mmol) in THF/H_2O (9:1) (3 mL) was heated at 85 °C with stirring under an argon atmosphere in a sealed tube for 48 h. After cooled to room temperature, the reaction mixture was diluted with H_2O (6 mL) and extracted with ethyl acetate (3×10 mL). The combined extract was dried (anhydrous Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (4% EtOAc in petroleum ether as eluent) to give an inseparable mixture of compounds **2** and **10** (0.23 g, 90% in total yield). Compound **2**: ^{1}H NMR: δ 1.21 (t, J=7.2 Hz, 3H), 1.46 (s, 3H), 2.33 (s, 3H), 2.59 (s, 3H), 2.83 (d, J=16.8 Hz, 1H), 3.58 (d, J=16.8 Hz, 1H), 4.15 (m, 2H), 5.22 (dd, J=18.0, 2.0 Hz, 1H), 5.61 (dd, J=11.2, 2.0 Hz, 1H), 6.61 (dd, J=11.2, 18.0 Hz, 1H), 7.11 (s, 1H); ^{13}C NMR: δ 13.94, 14.05, 21.21, 21.80, 38.84, 56.26, 61.21, 120.71, 124.92, 130.13, 133.80, 137.46, 138.49, 143.90, 151.93, 172.30, 203.8; HRMS: calcd for $C_{17}H_{20}O_3$: 272.1412, found: 272.1416; IR (KBr) 3083, 1736, 1705, 1439.

*4.2.5. 2,5,7-Trimethyl-2-triethylsilanyloxymethyl-6-vinyl-indan-1-ol **11**.* To a stirred dry THF (10 mL) solution containing compound **2** (1.3 g, 4.7 mmol) was added lithium aluminum hydride (0.212 g, 5.73 mmol) at −78 °C under argon atmosphere. The reaction mixture was stirred for 3 h then warmed to 0 °C and quenched with ethyl acetate at 0 °C. The mixture was washed with 2 M potassium sodium tartrate solution (20 mL) and extracted with ethyl acetate (3×20 mL). The combined extract was washed with brine (20 mL), dried (anhydrous Na_2SO_4), and concentrated in vacuo. The crude residue was directly used for next step without purification. To a stirred solution containing above crude product (0.85 g, 3.66 mmol) in dry CH_2Cl_2 (20 mL) was added imidazole (0.50 g, 7.3 mmol) and TESCl (0.60 mL, 3.6 mmol) sequentially at 0 °C under argon atmosphere. The mixture was stirred at same temperature for 6 h, then was diluted with H_2O (20 mL) followed by extraction with CH_2Cl_2 (3×10 mL). The combined extract was washed with brine (25 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (10% EtOAc in petroleum ether as eluent) to give **11** (0.85 g, 88%) as a syrup. ^{1}H NMR: δ 0.52 (q, J=8.4 Hz, 6H), 0.94 (t, J=8.4 Hz, 9H), 1.18 (s, 3H), 2.27 (s, 3H), 2.35 (s, 3H), 2.57−2.68 (m, 2H), 3.34−3.42 (m, 2H), 4.98 (d, J=6.4 Hz, 1H), 5.19 (d, J=17.6 Hz, 1H), 5.51 (d, J=11.2 Hz, 1H), 6.64 (dd, J=11.2, 17.6 Hz, 1H), 6.85 (s, 1H); ^{13}C NMR: δ 4.32 (3C), 6.72 (3C), 16.26, 18.04, 21.16, 40.37, 48.50, 69.55, 79.13, 119.28, 123.97, 133.62, 135.27, 136.18, 136.65, 140.15, 140.87; HRMS: calcd for $C_{21}H_{34}O_2Si$: 346.2328, found: 346.2332. IR (KBr) 3325, 3082, 1607, 1457.

*4.2.6. 6-(2′-Hydroxy-ethyl)-2,5,7-trimethyl-2-triethylsilanyloxy-methyl-indan-1-ol **12**.* To a stirred dry THF (25 mL) solution containing **11** (0.85 g, 2.4 mmol) was added $(Cy)_2BH$ (0.87 g, 4.9 mmol) slowly at 0 °C under argon atmosphere. The mixture was warmed to room temperature and stirred for 12 h then was added 2 N NaOH (6 mL) and H_2O_2 (3 mL) at 0 °C. After stirred for 4 h the reaction mixture was extracted with ethyl acetate (3×20 mL). The extract was washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (10% EtOAc in petroleum ether as eluent) to give **12** (0.72 g, 81%) as a gummy syrup. ^{1}H NMR: δ 0.52 (q, J=8.4 Hz, 6H), 0.94 (t, J=8.4 Hz, 9H), 1.15 (s, 3H), 2.29 (s, 3H), 2.37 (s, 3H), 2.56, 2.63 (ABq, J_{AB}=16.4 Hz, 2H), 2.9 (t, J=7.2 Hz, 2H), 3,33, 3.38 (ABq, J_{AB}=9.2 Hz, 2H), 3.66 (t,

J=7.2 Hz, 2H), 4.91 (s, 1H), 6.82 (s, 1H); ^{13}C NMR: δ 4.29 (3C), 6.70 (3C), 15.18, 18.05, 20.49, 32.53, 40.35, 48.38, 61.65, 69.56, 79.13, 124.4, 133.1, 134.8, 137.2, 140.4, 140.5; HRMS: calcd for $C_{21}H_{36}O_3Si$: 364.2434, found: 364.2427. IR (KBr) 3297, 1238, 1092, 1015, 741.

4.2.7. 2,5,7-Trimethyl-2-triethylsilanyloxymethyl-6-(2-triisopro-pylsilyloxy-ethyl)-indan-1-ol ***13****.* To a stirred solution of **12** (0.70 g, 1.9 mmol) in dry CH_2Cl_2 (5 mL) was added imidazole (262 mg, 3.84 mmol) and TIPSCl (0.45 mL, 2.11 mmol) sequentially at 0 °C under argon atmosphere. The reaction mixture was warmed to room temperature and stirred for 3 h, then was diluted with H_2O (10 mL) followed by extraction with CH_2Cl_2 (3×10 mL). The combined organic layer was washed with brine (10 mL), dried (anhydrous Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (4% EtOAc in petroleum ether as eluent) to give **13** (0.82 g, 82%). ^{1}H NMR: δ 0.52 (q, J=8.4 Hz, 6H), 0.94 (t, J=8.4 Hz, 9H), 0.98–1.07 (m, 21H), 1.1 (s, 3H), 1.53 (d, J=4.8 Hz, 1H), 2.34 (s, 3H), 2.39 (s, 3H), 2,57, 2.64 (ABq, J_{AB}=16 Hz, 2H), 2.93 (t, J=7.6 Hz, 2H), 3,34, 3.39 (ABq, J_{AB}=9.6 Hz, 2H), 3.71 (t, J=7.2 Hz, 2H), 4.91 (d, J=4.8 Hz 1H), 6.81 (s, 1H); ^{13}C NMR: δ 4.34 (3C), 6.74 (3C), 11.96 (3C), 15.17, 17.97 (6C), 18.09, 20.52, 33.11, 40.33, 48.448, 62.30, 69.61, 79.32, 124.332, 133.75, 134.79, 137.30, 140.19, 140.44; HRMS: calcd for $C_{30}H_{56}O_3Si_2$: 520.3768, found: 520.3763. IR (KBr) 3322, 1608, 1462, 1238, 1098, 1013.

4.2.8. 2,5,7-Trimethyl-2-triethylsilanyloxymethyl-6-(2-triisopro-pylsilyloxy-ethyl)-indan-1-one ***14****.* To a stirred solution of compound **13** (0.80 g, 1.5 mmol) in dry CH_2Cl_2 (5 mL) was added pyridinium dichromate (1.15 g, 3.07 mmol) at 0 °C under argon atmosphere. The reaction mixture was warmed to room temperature and stirred for 4 h, then was concentrated in vacuo. The residue was purified by silica gel column chromatography (3% EtOAc in petroleum ether as eluent) to give **14** (0.64 g, 81%) as a colorless syrup. ^{1}H NMR: δ 0.48 (q, J=8.4 Hz, 6H), 0.83 (t, J=8.4 Hz, 9H), 0.98–1.07 (m, 21H), 1.08 (s, 3H), 2.41 (s, 3H), 2.6–2.65 (m, 4H), 2.96 (t, J=7.6 Hz, 2H), 3.34 (d, J=17.2, 1H), 3.48 (d, J=9.6 Hz, 1H), 3.69–3.72 (m, 3H), 7.05 (s, 1H); ^{13}C NMR: δ 4.26 (3C), 6.56 (3C), 11.91 (3C), 13.66, 17.90 (6C), 20.63, 21.35, 32.21, 36.72, 51.64, 62.20, 68.07, 125.44, 132.14, 135.01, 137.71, 144.24, 152.43, 210.58; HRMS: calcd for $C_{30}H_{54}O_3Si_2$: 518.3611, found: 518.3602. IR (KBr) 3388, 1703, 1601, 1462, 1013.

4.2.9. 6-(2-Hydroxy-ethyl)-2-hydroxymethyl-2,5,7-trimethyl-indan-1-one ***1****.* To a stirred solution of **14** (0.64 g, 1.2 mmol) in dry THF (5 mL) was added tetra-*n*-butylammonium fluoride (0.65 g, 2.4 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at room temperature for 3 h then added H_2O (10 mL) followed by extraction with ethyl acetate (3×20 mL). The combined organic layer was washed with brine (10 mL), dried (anhydrous Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (20% EtOAc in petroleum ether as eluent) to give **1** (0.26 g, 85%). ^{1}H NMR: δ 1.19 (s, 3H), 2.4 (s, 3H), 2.62 (s, 3H), 2.72 (d, J=16.8 Hz, 1H), 2.97 (t, J=7.2 Hz, 2H), 3.06 (d, J=17.2 Hz, 1H), 3.57 (d, J=10.8 Hz, 1H), 3.7 (t, J=7.2 Hz, 2H), 3.76 (d, J=10.8 Hz, 1H), 7.08 (s, 1H); ^{13}C NMR: δ 13.72, 20.95, 21.29, 31.71, 36.67, 50.77, 61.29, 67.84, 125.80, 131.55, 135.01, 138.10, 144.98, 152.38, 212.00; HRMS: calcd for $C_{15}H_{20}O_3$: 248.1412, found: 248.1408. IR (KBr) 3387, 1686, 1599, 1042.

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Supplementary data

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre (deposition number: CCDC 885874). Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.01.055.

References and notes

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16. Although $PdCl_2(dppf)\cdot CH_2Cl_2$ system allows the reaction can be done without using seal tube,[11a] the $PdCl_2$ system was chosen because of its lower cost.
17. Product ratios were determined from the ^{1}H NMR spectra by peaks integration of aryl hydrogens at chemical shifts δ 7.18 (s, 1H, starting materials 3) 7.11 (s, 1H, vinylindanone 2), 7.05 (s, 1H) and 6.94 (s, 1H, reduction product **10**) of the partially purified reaction mixture.