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Total synthesis of (±)-Scrodentoid A

Shao-Dong Lv [a, b], Tian Tian [a], Liu-Qiang Zhang [b], Si-Yu Xu [a], Dong-Hai Zhao [a], Jun-Jie Wang [a], Jian-Guo Fu [a, **], Yi-Ming Li [b, ***], Chen-Guo Feng [a, c, *]

[a] The Research Center of Chiral Drugs, Innovation Research Institute of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, 201203, China
[b] School of Pharmacy, Shanghai University of Traditional Chinese Medicine, Shanghai, 201203, China
[c] Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs, Shanghai Jiao Tong University, Shanghai, 200240, China

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ABSTRACT

An efficient total synthesis of scrodentoid A was accomplished starting from a Hagemann's ester and a substituted (2-bromoethyl)benzene. Key reactions in this synthesis include *C*-alkylation of the Hagemann's ester, 6-*endo*-*Trig* cationic cyclization of an enone and Lewis acid promoted isomerization of a *cis*-fused ketone.

1. Introduction

Abiatane diterpenoids [1] are widely distributed natural products in the plant kingdom which exhibit a wide range of biological activities. Scrodentoid A (**1**) [2], the 19(4 → 3)-*abeo*-abietane diterpenoid, was firstly isolated by Li et al. in 2015 from the whole plant of *Scrophularia dentata*. [3] The absolute configuration of scrodentoid A was established by 2D NMR and X-ray crystallographic analysis. It significantly inhibited ConA-induced splenocyte proliferation and showed indiscernible cytotoxic activity against B16 or MCF-7 cells.

A number of synthetic studies of aromatic abietane diterpenoids have been reported since the first isolation in the late 1930s. [4] Most of the synthetic studies toward aromatic abietane diterpenoids have been focused on the synthesis of ferruginol (**2**) [5,6], and the polyene cyclization is the most used strategy. [7] The total synthesis of scrodentoid A (**1**) has not been reported yet. In this paper, we attempted to accomplish the first total synthesis of scrodentoid A (see Fig. 1).

As depicted in Scheme 1, scrodentoid A (**1**) may be synthesized from the key precursor **3** via several simple operations including benzylic oxidation, diastereoselective α-alkylation of ketone and Wittig reaction. The subsequent bond disconnection of **3** leads to enone **4,** which may go through an intramolecular cationic cyclization and be generated from Hagemann's ester **6** [8] and substituted (2-bromoethyl)benzene **5** via *C*-alkylation.

2. Results and discussion

The synthesis began with a four-step preparation of the (2-bromoethyl)benzene **5** (Scheme 2). The commercial reagent 2-isopropylphenol **7** was *O*-methylated with Me_2SO_4 to yield 2-isopropylanisole **8** in 85% yield. Bromination of electron-rich aromatic compound **8** with LiBr/$(NH_4)_2Ce(NO_3)_6$ selectively yielded 4-

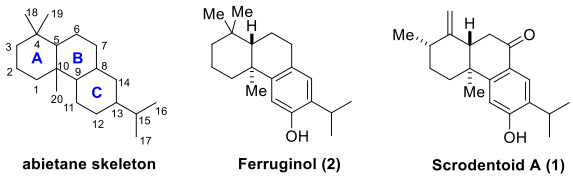

Fig. 1. Abirtane numbering system and scrodentoid A (**1**).

* Corresponding author. The Research Center of Chiral Drugs, Innovation Research Institute of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, 201203, China.
** Corresponding author.
*** Corresponding author.
E-mail address: fengcg@shutcm.edu.cn (C.-G. Feng).

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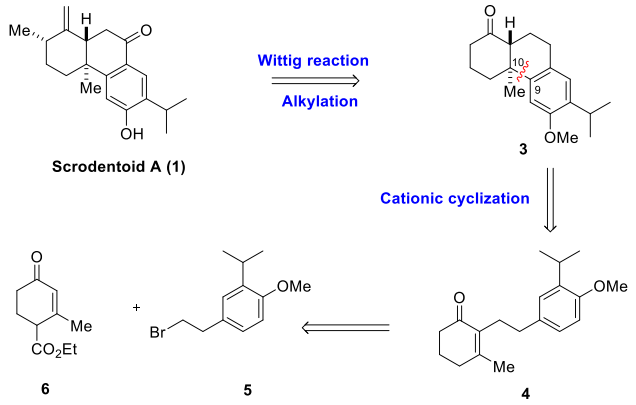
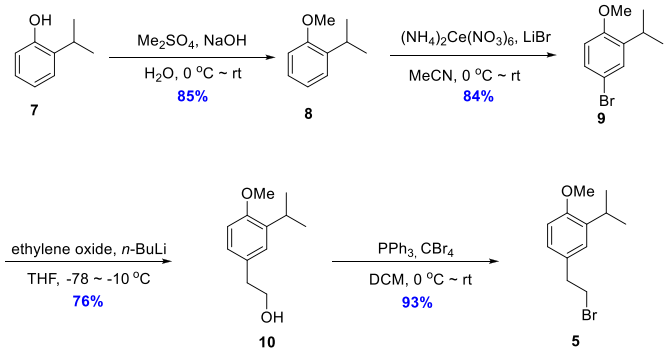


Scheme 1. Retrosynthesis for scrodentoid A (**1**).

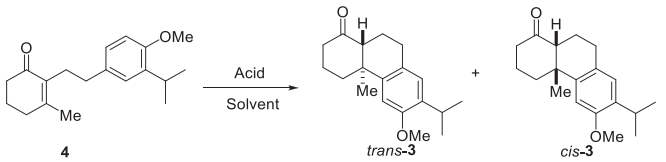


Scheme 2. Synthesis of substituted (2-bromoethyl)benzene **5**.

bromo-2-isopropylanisole **9** in 84% yield. [9] Addition of ethylene oxide to the lithium anion of **9** formed alcohol **10** in 76% yield, [10] which was followed by a bromination with PPh_3/CBr_4 to afford (2-bromoethyl)benzene **5** in 88% yield. [11] Next, *C*-alkylation of the Hagemann's ester **6** with (2-bromoethyl)benzene **5** in the presence of *t*-BuOK afforded **11** in 66% yield, [12] and the subsequent decarboxylation of **11** by treatment with aqueous KOH delivered enone **4** in 71% yield (Scheme 3).

In order to execute the planned intramolecular cationic cyclization, a number of acidic activation conditions were screened (Table 1). [13] This 6-*endo-Trig* cyclization is rather difficult, and the recovery of the starting material **4** was observed in most cases (entries 1–5), which may be attributed to the low reactivity of *β*-methyl substituted enone **4**. To our delight, the desired cyclization took place when it was treated by H_3PO_4 in xylene under 190 °C,

Table 1
Synthesis of **3** from enone **4** via 6-*endo-Trig* cyclization[a].



Entry	Acid	Solvent	*T* (°C)	Combined yield (%)[b]	*cis*/*trans*[c]
1	BF_3•Et_2O	DCM	rt ~ 100	N.R.	-
2	TMSOTf	toluene	rt ~ 160	N.R.	-
3	TBDPSCl	toluene	rt ~ 160	N.R.	-
4	TMSCl	toluene	rt ~ 160	N.R.	-
5	Ph_3B	toluene	rt ~ 160	N.R.	-
6	H_3PO_4	xylene	190	46	2.3/1
7	TBDMSOTf	toluene	160	65	2/1

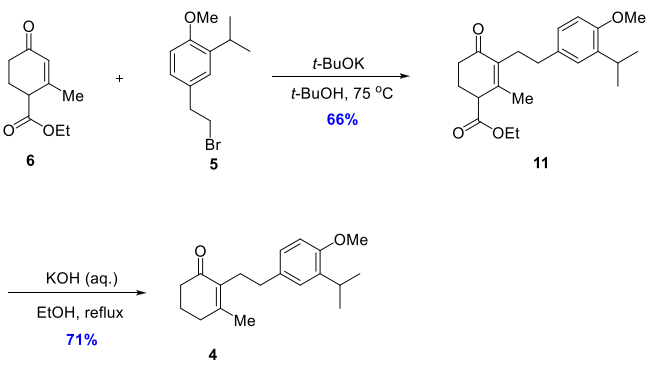
[a] Reaction conditions: enone **4** (1.0 equiv), acid (2.0 equiv), 8 h. N.R. = no reaction
[b] Isolated yield.
[c] Determined by ^1H NMR analysis.

with the undesired *cis*-decalin **3** as the major isomer (*cis*/*trans* = 2.3/1) (entry 6). [14] This result was improved by using TBDMSOTf (entry 7).

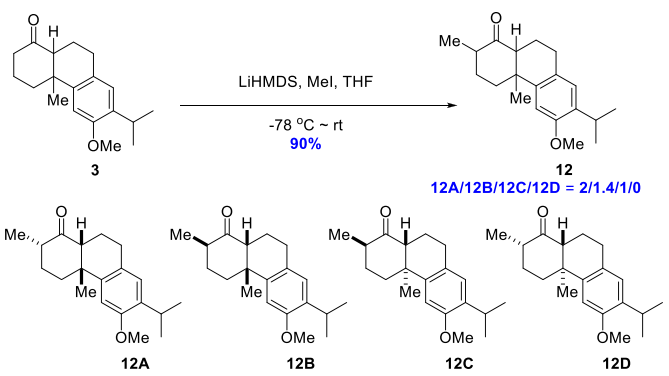
Methylation of the lithium anion of mixture **3** with MeI resulted in three diastereoisomers (**12A**/**12B**/**12C** = 2/1.4/1) in a combined yield of 90% (Scheme 4). [15] The stereochemistry of diastereoisomers were assingned by 2D NMR analysis. Unfortunately, the desired ketone **12D** was not observed. Therefore, several isomerization conditions were tested to generate ketone **12D** (Table 2). TMSOTf catalysis at room temperature proved to be the optimal reaction conditions, and the desired **12D** was generated in 37% isolated yield from an equilibration of diastereomers (**12A**/**12B**/**12D** = 0.5/1.5/1) (Table 2, entry 3).

Reaction of **12D** with $Mg/TiCl_4$ delivered olefin **13** in 53% yield, [16] which was followed by oxidation of **13** with CrO_3 in AcOH to provide compound **14** in 85% yield. [17] Finally, deprotection of methoxyl group occurred by treatment with EtSNa in DMF under 110 °C to afford (±)-scrodentoid A (**1**) in 85% yield (Scheme 5). [18]

In the meantime, an alternative synthetic route to the intermediate **12D** was also examined, where the Lewis acid promoted cyclization of 1,3-dithiolane **15** was the key step. The desired *trans*-decalin **16** as the major was furnished in the presence of TMSOTf via a highly diastereoselective 6-*endo-Trig* cyclization (*trans*/*cis* = 9/1) in 65% yield. [13] Deportection of the dithiolane **16** by PIFA (bis-trifluoroacetoxyiodobenzene) afforded the *trans*-**3**. Then methylation of the lithium anion of *trans*-**3** with MeI formed undesired **12C** exclusively, which may be explained by the steric effect of the

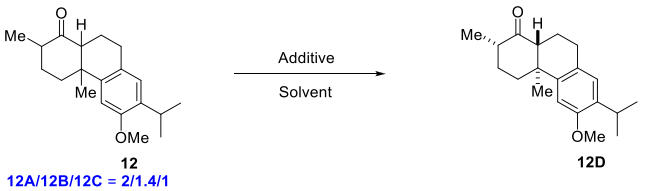


Scheme 3. Synthesis of enone **4**.



Scheme 4. Methylation of the mixture **3**.

Table 2
Synthesis of **12D** via isomerization[a] .

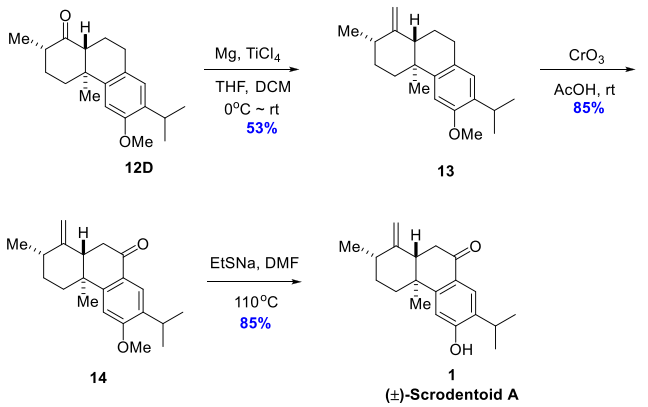


12
12A/12B/12C = 2/1.4/1

12D

Entry	Additive	Solvent	*T* (°C)	A/B/C/D[b]
1	BF_3•Et_2O	DCM	40	0.8/2.7/1/0
2	MeONa	MeOH	rt	2.5/3.8/1/1
3	TMSOTf	DCM	rt	0.5/1.5/0/1
4	TMSOTf	DCM	60	0.5/2.0/0/1

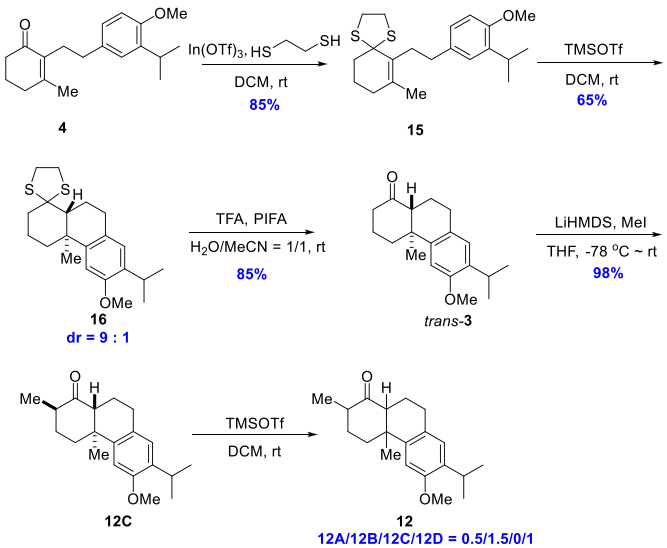
[a] Reaction conditions: **12** (1.0 equiv), additive (1.5 equiv).
[b] Determined by ^{1}H NMR analysis.



12D **13** **14** **1**
(±)-Scrodentoid A

Scheme 5. Synthesis of (±)-scrodentoid A.

methyl group. Isomerization of 12**C** in the presence of TMSOTf also gave the same diastereomer ratio (12A/12B/12D = 0.5/1.5/1) as starting from the above mixture of **12**, which showed that a thermodynamic equilibrium was established under the reaction conditions (Scheme 6).



4 **15**
16
dr = 9 : 1
trans-**3**
12C
12
12A/12B/12C/12D = 0.5/1.5/0/1

Scheme 6. A second synthetic route to the intermediate **12D**.

3. Conclusion

In conclusion, the total synthesis of (±)-scrodentoid A was achieved in 8 steps starting from **5** and the Hagemann's ester **6** with a total yield of 3.8%. *C*-alkylation of the Hagemann's ester, 6-*endo*-*Trig* cationic cyclization of an enone and Lewis acid promoted isomerization of a *cis*-fused ketone were key steps for this synthesis.

4. Experimental section

4.1. General

All non-aqueous reactions were run under a positive pressure of nitrogen. Anhydrous solvents were obtained using standard drying techniques. Commercial grade reagents were used without further purification. Flash chromatography was performed on 300–400 mesh silica gel with the indicated solvent systems. ^{1}H and ^{13}C NMR spectras were recorded on a Brüker Avance-600 HD spectrometer or Brüker Avance-400 HD spectrometer at ambient temperature. High-resolution mass spectras were determined on a Aglient 6545 Accurate-Mass Q-TOF spectrometer or JMS-HX 110 spectrometer.

4.2. Typical procedure for the synthesis of scrodentoid A (**1**) [19]

4.2.1. 1-isopropyl-2-methoxybenzene (**8**)

To a solution of 2-isopropylphenol **7** (27.24 g, 200 mmol) in H_2O (100 mL) was added 23% aq. solution of sodium hydroxide (24.00 g, 600 mmol) in H_2O (80 mL) dropwise at 0 °C and the mixture was stirred at room temperature for 1 h. Dimethylsulfate (50.44 g, 400 mmol) was added slowly for 10 min, and the mixture was stirred for 24 h at 120 °C and then allowed to cool to room temperature. A solution of dilute hydrochloric acid was added until the pH reached 7 and the mixture was extracted with ethyl acetate for three times. The combine organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subject to column chromatography on silica gel (PE) to give **8** (25.50 g) as colorless oil in 85% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.16 (td, *J* = 7.5, 1.4 Hz, 1H), 6.92 (td, *J* = 7.5, 1.2 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 3.82 (s, 3H), 3.32 (hept, *J* = 7.0 Hz, 1H), 1.21 (d, *J* = 7.0 Hz, 6H); EI-MS (*m*/*z*): 150 (M^+).

4.2.2. 4-bromo-2-isopropyl-1-methoxybenzene (**9**)

LiBr (28.71 g, 330 mmol) and $(NH_4)_2Ce(NO_3)_6$ (180.84 g, 330 mmol) were added to an oven-dried flask under N_2 and then acetonitrile (300 mL) was added at 0 °C. The mixture was stirred at 0 °C for 1 h. The flask was flushed with N_2 and a solution of **8** (45.00 g, 300 mmol) in acetonitrile (80 mL) was added slowly and the reaction was stirred at room temperature for 12 h. The solvent was removed under reduce pressure. The residual was diluted with water and extracted with ethyl acetate for three times. The combine organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subject to column chromatography on silica gel (PE) to afford **9** (57.50 g) in 84% yield as colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, *J* = 2.5 Hz, 1H), 7.24 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 1H), 3.80 (s, 3H), 3.27 (hept, *J* = 6.9 Hz, 1H), 1.18 (d, *J* = 6.9 Hz, 6H); EI-MS (*m*/*z*): 228 (M^+).

4.2.3. 2-(3-isopropyl-4-methoxyphenyl)ethan-1-ol (**10**)

To a solution of **9** (52.70 g, 230 mmol) in THF (150 mL) was added *n*-butyllithium (1.6 M in hexanes, 287.5 ml, 460 mmol) dropwise at −78 °C and the mixture was stirred at the temperature for 2 h on oven-dried flask under N_2. Ethylene oxide (23 mL,

460 mmol) in THF (80 mL) was added dropwise about 1 h and the solution was stirred for 1 h. Raising the temperature slowly, the mixture was allowed to stir at −10 °C for 2 h. The mixture was then quenched with saturated aq. solution of NH_4Cl (140 mL) at 0 °C. Then it was extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (PE/EA = 5/1) to give **10** (33.90 g) as colorless oil in 76% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05 (d, J = 2.2 Hz, 1H), 7.01 (dd, J = 8.2, 2.2 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 3.82 (t, J = 6.6 Hz, 2H), 3.81 (s, 3H), 3.30 (hept, J = 6.9 Hz, 1H), 2.80 (t, J = 6.6 Hz, 2H), 1.59 (s, 1H), 1.20 (d, J = 6.9 Hz, 6H); EI-MS (m/z): 194 (M^+).

4.2.4. 4-(2-bromoethyl)-2-isopropyl-1-methoxybenzene (**5**)

A solution of CBr_4 (44.92 g, 135.3 mmol) and **10** (23.86 g, 123 mmol) in DCM (114 mL) was added to an oven-dried flask at 0 °C for 20 min and then PPh_3 (35.44 g, 135.3 mmol) in DCM (40 mL) was added slowly for 10 min. Then the mixture was stirred at room temperature for overnight. The solvent was removed under reduce pressure. The residual was diluted with water and extracted with ethyl acetate for three times. The combine organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subject to column chromatography on silica gel (PE) to afford **5** (29.50 g) as light yellow oil in 93% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.03 (d, J = 2.2 Hz, 1H), 7.00 (dd, J = 8.2, 2.2 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 3.81 (s, 3H), 3.53 (t, J = 7.8 Hz, 2H), 3.30 (hept, J = 6.9 Hz, 1H), 3.10 (t, J = 7.8 Hz, 2H), 1.20 (d, J = 6.9 Hz, 6H); EI-MS (m/z): 256 (M^+).

4.2.5. ethyl 2-methyl-4-oxocyclohex-2-ene-1-carboxylate (**6**)

t-BuOK (2.80 g, 25 mmol) and paraformaldehyde (7.50 g, 250 mmol) were added to a 1L oven-dried three-necked round bottom flask equip with thermometer and condenser under N_2 and then *t*-BuOH (250 mL) was added at room temperature. Ethyl acetoacetate (63.2 ml, 500 mmol) was added to the mixture at 0 °C for 1 h and then *t*-BuOK (7.00 g, 62.5 mmol) was added. The solution was allowed to reflux for 24 h. A solution of dilute hydrochloric acid was added until the pH reached 7 at 0 °C. The residual was diluted with water and extracted with ethyl acetate for three times. The combine organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subject to reduced pressure distillation to give **6** (31.40 g) as colorless oil in 69% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (s, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.27 (t, J = 4.9 Hz, 1H), 2.62−2.50 (m, 1H), 2.39−2.31 (m, 2H), 2.26−2.17 (m, 1H), 2.03 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H); EI-MS (m/z): 182 (M^+).

4.2.6. ethyl 3-(3-isopropyl-4-methoxyphenethyl)-2-methyl-4-oxocyclohex-2-ene-1-carboxylate (**11**)

t-BuOK (7.39 g, 66 mmol) were added to a oven-dried round bottom flask equip with condenser under N_2 and then *t*-BuOH (220 mL) was added at room temperature. **6** (12.00 g, 66 mmol) was added and stirred for 1 h. Then **5** (15.40 g, 60 mmol) was added at room temperature and the mixture was stirred at 75 °C for 18 h. The residual was diluted with water and extracted with ethyl acetate for three times. The combine organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subject to column chromatography on silica gel (PE/EA = 5/1) to give **11** (14.18 g) as yellow oil in 66% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (d, J = 2.1 Hz, 1H), 6.96 (dd, J = 8.2, 2.1 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.29 (d, J = 6.9 Hz, 1H), 3.24 (t, J = 4.9 Hz, 1H), 2.65−2.53 (m, 5H), 2.38 (dt, J = 16.9, 5.2 Hz, 1H), 2.29−2.24 (m, 1H), 2.21−2.15 (m, 1H), 1.80 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.20 (d, J = 6.9 Hz, 6H); LRMS (ESI): 359 (M + H)$^+$; HRMS (ESI): calcd for $C_{12}H_{31}O_4$ (M + H)$^+$: 359.2217, found: 359.2228.

4.2.7. 2-(3-isopropyl-4-methoxyphenethyl)-3-methylcyclohex-2-en-1-one (**4**)

To a solution of **11** (15.04 g, 42 mmol) in EtOH (84 mL) was added KOH (13.17 g, 253.2 mmol) and H_2O (13 mL) with condenser under N_2 at room temperature. The mixture was allowed to reflux for 30 h. A solution of dilute hydrochloric acid was added until the pH reached 6 at 0 °C. The residual was diluted with water and extracted with ethyl acetate for three times. The combine organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subject to column chromatography on silica gel (PE/EA = 5/1) to give **4** (8.52 g) as a yellow solid in 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99−6.94 (m, 2H), 6.75 (d, J = 8.3 Hz, 1H), 3.80 (s, 3H), 3.29 (hept, J = 6.9 Hz, 1H), 2.55 (br s, 4H), 2.40 (t, J = 6.1 Hz, 2H), 2.28 (t, J = 6.1 Hz, 2H), 1.97−1.89 (m, 2H), 1.69 (s, 3H), 1.19 (d, J = 6.9 Hz, 6H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 156.2, 154.9, 136.6, 134.7, 134.1, 126.4, 126.4, 111.3, 55.5, 38.0, 34.4, 32.9, 27.8, 26.6, 22.8, 22.8, 22.3, 21.1; LRMS (ESI): 287 (M + H)$^+$; HRMS (ESI): calcd for $C_{19}H_{27}O_2$ (M + H)$^+$: 287.2006, found: 287.2012 .

4.2.8. 7-isopropyl-6-methoxy-4a-methyl-3,4,4a,9,10,10a-hexahydrophenanthren-1(2H)-one (**3**)

To a solution of **4** (572 mg, 2 mmol) in toluene (10 mL) under N_2 was added TBDMSOTf (0.92 ml, 4 mmol) in a 35 ml of sealed tube at room temperature. Then the mixture was stirred at 160 °C for 8 h. The mixture was quenched with a saturated aq. solution of $NaHCO_3$ (10 mL) at 0 °C. It was extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (PE/EA = 15/1) to give **3** (372 mg) as brown oily mixture in 65% yield. Data for *trans*-**3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.74 (s, 1H), 3.81 (s, 3H), 3.24 (dt, J = 13.8, 6.9 Hz, 1H), 2.88−2.69 (m, 2H), 2.60 (d, J = 12.4 Hz, 1H), 2.49−2.35 (m, 3H), 2.20−2.11 (m, 1H), 2.08−1.98 (m, 2H), 1.92−1.72 (m, 2H), 1.19 (d, J = 6.9 Hz, 3H), 1.18 (d, J = 6.9 Hz, 3H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 155.2, 143.4, 135.1, 127.0, 126.6, 107.0, 55.6, 55.5, 42.6, 40.9, 37.2, 28.2, 26.5, 23.6, 22.8, 22.7, 22.6, 17.7; LRMS (ESI): 287 (M + H)$^+$; HRMS (ESI): calcd for $C_{19}H_{27}O_2$ (M + H)$^+$: 287.2006, found: 287.2011. Data for *cis*-**3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.69 (s, 1H), 3.79 (s, 3H), 3.22 (dt, J = 13.8, 6.9 Hz, 1H), 2.88−2.69 (m, 2H), 2.60 (dd, J = 12.4, 2.5 Hz, 1H), 2.49−2.35 (m, 3H), 2.20−2.11 (m, 1H), 2.08−1.98 (m, 2H), 1.92−1.72 (m, 2H), 1.35 (s, 3H), 1.19 (d, J = 6.9, 3H), 1.18 (d, J = 6.9, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4, 155.3, 141.2, 135.1, 127.0, 126.7, 107.5, 57.3, 55.5, 40.6, 38.9, 36.5, 29.7, 29.1, 27.9, 22.8, 22.8, 22.6, 21.7; LRMS (ESI): 287 (M + H)$^+$; HRMS (ESI): calcd for $C_{19}H_{27}O_2$ (M + H)$^+$: 287.2006, found: 287.2011.

4.2.9. 7-isopropyl-6-methoxy-2,4a-dimethyl-3,4,4a,9,10,10a-hexahydrophenanthren-1(2H)-one (**12**)

To a solution of LiHMDS (1M in THF, 7.15 ml, 7.15 mmol) at −78 °C under N_2 was added a solution of **3** (1.86 g, 6.5 mmol) in THF (7 mL) .The mixture was stirred for 1 h at −78 °C and then MeI was added. The solution was stirred at room temperature for 5 h. The mixture was then quenched with a saturated aq. solution of NH_4Cl (10 mL) at 0 °C. Then it was extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (PE/EA = 15/1) to give **12A** (800 mg, 41%), **12B** (560 mg, 28.7%), **12C** (400 mg, 20.3%) as a yellow solid. Data for **12A**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.71 (s, 1H), 3.82 (s, 3H), 3.25 (hept, J = 7.1 Hz, 1H), 3.09 (m, 1H), 2.65 (dd, J = 17.1, 6.8 Hz, 1H), 2.59 (dt, J = 14.2, 3.2 Hz, 1H),

2.46–2.43 (m, 1H), 2.41–2.35 (m, 2H), 2.04–1.87 (m, 3H), 1.44 (s, 3H), 1.32 (dd, $J = 13.0$, 2.8 Hz, 1H), 1.23 (d, $J = 7.1$ Hz, 3H), 1.22 (d, $J = 7.1$ Hz, 3H), 0.98 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 212.2, 155.0, 138.3, 134.9, 128.4, 127.1, 106.2, 55.4, 54.1, 44.8, 42.3, 37.6, 34.1, 30.3, 26.4, 25.0, 22.7, 22.5, 18.4, 14.6; LRMS (ESI): 301 $(M + H)^+$; HRMS (ESI): calcd for $C_{20}H_{29}O_2$ $(M + H)^+$: 301.2162, found: 301.2159. Data for **12B**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.69 (s, 1H), 3.80 (s, 3H), 3.23 (hept, $J = 6.9$ Hz, 1H), 2.79–2.75 (m, 2H), 2.55 (m, 1H), 2.44 (dd, $J = 12.5$, 1.3 Hz, 1H), 2.16 (td, $J = 13.8$, 4.2 Hz, 1H), 2.08–1.93 (m, 2H), 1.85–1.77 (m, 2H), 1.60 (qd, $J = 13.3$, 3.8 Hz, 1H), 1.29 (s, 3H), 1.20 (t, $J = 6.9$ Hz, 3H), 1.19 (t, $J = 6.9$ Hz, 3H), 1.06 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 216.4, 155.3, 142.5, 134.9, 126.4, 126.2, 107.8, 58.6, 55.4, 40.8, 40.7, 36.3, 31.0, 29.3, 26.8, 26.4, 24.9, 22.7, 22.6, 14.5; LRMS (ESI): 301 $(M + H)^+$; HRMS (ESI): calcd for $C_{20}H_{29}O_2$ $(M + H)^+$: 301.2162, found: 301.2157. Data for **12C**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.75 (s, 1H), 3.81 (s, 3H), 3.24 (hept, $J = 6.9$ Hz, 1H), 2.87–2.73 (m, 3H), 2.62–2.56 (m, 1H), 2.27–2.19 (m, 2H), 2.16–2.08 (m, 1H), 2.02–1.95 (m, 1H), 1.85–1.72 (m, 2H), 1.23 (d, $J = 7.4$ Hz, 3H), 1.20 (d, $J = 6.9$ Hz, 3H), 1.19 (d, $J = 6.9$, Hz, 3H), 1.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 216.4, 155.1, 143.6, 135.0, 126.9, 126.4, 106.9, 55.5, 50.5, 43.5, 42.5, 32.7, 28.6, 28.1, 26.4, 23.7, 22.8, 22.6, 18.3, 17.5; LRMS (ESI): 301 $(M + H)^+$; HRMS (ESI): calcd for $C_{20}H_{29}O_2$ $(M + H)^+$: 301.2162, found: 301.2151.

4.2.10. (2S,4aS*,10aR*)-7-isopropyl-6-methoxy-2,4a-dimethyl-3,4,4a,9,10,10a-hexahydrophenanthren-1(2H)-one (**12D**)*

To a solution of the mixture of **12** (900 mg, 3 mmol) in DCM (6 mL) was added TMSOTf (0.81 ml, 4.5 mmol) at room temperature. After being stirred for 18 h, the mixture was quenched with a saturated aq. solution of $NaHCO_3$ (10 mL) at 0 °C. Then it was extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (PE/EA = 150/1) to give **12D** (333 mg) as a yellow solid in 37% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.73 (s, 1H), 3.81 (s, 3H), 3.31–3.18 (m, 1H), 2.88–2.69 (m, 2H), 2.63–2.58 (m, 1H), 2.52–2.43 (m, 1H), 2.36 (ddd, $J = 13.3$, 4.3, 2.5 Hz, 1H), 2.24–2.16 (m, 1H), 2.03–1.93 (m, 2H), 1.88–1.63 (m, 2H), 1.20 (d, $J = 3.4$ Hz, 3H), 1.18 (d, $J = 3.4$ Hz, 3H), 1.06 (d, $J = 6.4$ Hz, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.6, 155.1, 143.6, 135.0, 126.9, 126.5, 106.9, 55.5, 55.2, 44.4, 43.1, 37.4, 32.0, 28.2, 26.4, 23.6, 22.8, 22.6, 17.9, 14.4; LRMS (ESI): 301 $(M + H)^+$; HRMS (ESI): calcd for $C_{20}H_{29}O_2$ $(M + H)^+$: 301.2162, found: 301.2157.

4.2.11. (2S,4aS*,10aS*)-7-isopropyl-6-methoxy-2,4a-dimethyl-1-methylene-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (**13**)*

To a suspension of Mg (77 mg, 3.2 mmol), $TiCl_4$ (88 μL, 0.8 mmol) and DCM (1.6 mL) was added a solution of **12D** (120 mg, 0.4 mmol) in DCM (1.2 mL) and THF (0.8 mL) at 0 °C. After being stirred for 1 h at 0 °C, the resulting green-black mixture was stirred for overnight at room temperature. The reaction mixture was cooled to 0 °C. Saturated potassium carbonate solution (5 mL) was added and the mixture was diluted with ether (5 mL). The organic layer was separated, dried, evaporated and purified by chromatography on silica gel (PE) to **13** (63 mg) as colorless oil in 53% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.76 (s, 1H), 4.82 (d, $J = 1.4$ Hz, 1H), 4.67 (d, $J = 1.4$ Hz, 1H), 3.80 (s, 3H), 3.23 (hept, $J = 6.9$ Hz, 1H), 2.86–2.81 (m, 2H), 2.25–2.17 (m, 2H), 2.12–2.03 (m, 1H), 1.86–1.75 (m, 3H), 1.67 (td, $J = 13.1$, 4.3 Hz, 1H), 1.38 (qd, $J = 13.1$, 4.1 Hz, 1H), 1.20 (d, $J = 4.9$ Hz, 3H), 1.19 (d, $J = 4.9$ Hz, 3H), 1.10 (d, $J = 6.5$ Hz, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 154.7, 145.2, 134.4, 126.7, 126.5, 107.6, 103.8, 55.5, 48.7, 39.7, 38.7, 38.3, 32.9, 29.6, 26.5, 22.9, 22.8, 22.7, 22.0, 18.2; LRMS (ESI): 299 $(M + H)^+$; HRMS (ESI): calcd for $C_{21}H_{31}O$ $(M + H)^+$: 299.2369, found: 299.2378.

4.2.12. (2S,4aS*,10aS*)-7-isopropyl-6-methoxy-2,4a-dimethyl-1-methylene-2,3,4,4a,10,10a-hexahydrophenanthren-9(1H)-one (**14**)*

To a solution of CrO_3 (30 mg) in acetic acid (0.8 mL) under N_2 was added a solution of **13** (60 mg, 0.2 mmol) in acetic acid (1.5 mL) at room temperature. The mixture was stirred at room temperature for 6 h. The residual was diluted with water and extracted with ether for three times. The combine organic layers were sequentially washed with saturated aq. solution of $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (PE/EA = 25/1) to give **14** (54 mg) as a white solid in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 6.81 (s, 1H), 4.92 (d, $J = 1.6$ Hz, 1H), 4.71 (d, $J = 1.6$ Hz, 1H), 3.90 (s, 3H), 3.26 (hept, $J = 6.9$ Hz, 1H), 2.79–2.58 (m, 3H), 2.35–2.29 (m, 1H), 2.15–2.03 (m, 1H), 1.93–1.74 (m, 2H), 1.42 (qd, $J = 13.1$, 3.9 Hz, 1H), 1.23 (d, $J = 5.8$ Hz, 3H), 1.21 (d, $J = 5.8$ Hz, 3H), 1.13 (d, $J = 6.5$ Hz, 3H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 161.6, 154.0, 152.0, 135.6, 125.7, 124.0, 105.6, 105.4, 55.4, 47.5, 39.8, 38.1, 38.0, 37.8, 32.5, 26.6, 22.5, 22.4, 21.1, 18.3; LRMS (ESI): 299 $(M + H)^+$; HRMS (ESI): calcd for $C_{21}H_{29}O_2$ $(M + H)^+$: 313.2162, found: 313.2161.

4.2.13. (2S,4aS*,10aS*)-6-hydroxy-7-isopropyl-2,4a-dimethyl-1-methylene-2,3,4,4a,10,10a-hexahydrophenanthren-9(1H)-one (**scrodentoid A**, **1**)*

A solution of **14** (63 mg, 0.2 mmol) and NaSEt (185 mg, 2.2 mmol) in DMF (3 mL) was stirred at 110 °C for 4 h. The mixture was diluted with water and extracted with ethyl acetate for three times. The combine organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (PE/EA = 5/1) to give **scrodentoid A** (**1**) (51 mg) as a white solid in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 6.84 (s, 1H), 4.91 (s, 1H), 4.68 (s, 1H), 3.27–3.15 (m, 1H), 2.77–2.61 (m, 3H), 2.20 (dt, $J = 12.9$, 3.4 Hz, 1H), 2.11–1.98 (m, 1H), 1.87–1.81 (m, 1H), 1.72 (td, $J = 13.3$, 4.3 Hz, 1H), 1.41–1.34 (m, 1H), 1.28 (d, $J = 6.8$ Hz, 3H), 1.27 (d, $J = 6.8$ Hz, 3H), 1.11 (d, $J = 6.5$ Hz, 3H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 159.1, 154.3, 151.9, 133.4, 126.7, 124.0, 111.2, 105.5, 47.4, 39.4, 38.0, 37.9, 37.6, 32.5, 26.8, 22.4, 22.3, 21.1, 18.3; LRMS (ESI): 321 $(M + Na)^+$; HRMS (ESI): calcd for $C_{20}H_{26}O_2Na$ $(M + Na)^+$: 321.1825, found: 321.1819.

*4.2.14. 6-(3-isopropyl-4-methoxyphenethyl)-7-meth yl-1,4-dithiaspiro [4.5]dec-6-ene (**15**)*

To a solution of **5** (1.14 g, 4 mmol) in DCM (20 mL) was added 1,2-ethanedithiol (1.0 mL, 12 mmol) and indium (III) trifluoromethanesulfonate (899 mg, 1.6 mmol) successively at room temperature. After being stirred for 24 h, the mixture was quenched with H_2O (10 mL). Then it was extracted with dichloromethane for three times. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel (PE/EA = 20/1) to give **15** as colorless oil (1.23 g, 85%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.10 (d, $J = 8.5$ Hz, 1H), 7.04 (dd, $J = 8.3$ Hz, 2.0 Hz, 1H), 6.77 (d, $J = 8.3$ Hz, 1H), 3.80 (s, 3H), 3.36–3.28 (m, 5H), 2.84–2.80 (m, 2H), 2.53–2.49 (m, 2H), 2.24–2.21 (m, 2H), 1.99 (t, $J = 6.2$ Hz, 2H), 1.82–1.78 (m, 2H), 1.74 (s, 3H),1.21 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 154.9, 136.8, 135.3, 134.3, 130.9, 126.0, 125.8, 110.3, 72.1, 55.5, 44.4, 40.2, 36.2, 33.8, 31.7, 26.8, 22.8, 22.5, 20.9; EI-MS (*m*/*z*, %): 362 (M^+, 6.2), 301 (100), 163 (82.5); HRMS (EI): *m*/*z* calcd for $C_{21}H_{30}OS_2$: 362.1738, found: 362.1743.

4.2.15. (4aS,10aR*)-7-isopropyl-6-methoxy-4a-methyl-3,4,4a,9,10,10a-hexahydro-2H-spiro[phenanthrene-1,2'-[1,3]dithiolane] (**16**)*

To a solution of **15** (73 mg, 0.2 mmol) in DCM (10 mL) was added

TMSOTf (54 μL, 0.3 mmol) at room temperature. After being stirred for 24 h, the mixture was quenched with H_2O (5 ml). Then it was extracted with dichloromethane for three times. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel (PE/EA = 20/1) to give **16** as colorless oil (47 mg, 65%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.86 (s, 1H), 6.70 (s, 1H), 3.78 (s, 3H), 3.36–3.31 (m, 1H), 3.30–3.19 (m, 3H), 3.15–3.09 (m, 1H), 2.92–2.79 (m, 2H), 2.36–2.22 (m, 2H), 2.25 (d, J = 12.5 Hz, 1H), 2.08 (d, J = 11.8 Hz, 1H), 1.98–1.84 (m, 3H), 1.73 (d, J = 12.8 Hz, 1H), 1.49 (d, J = 12.8 Hz, 1H), 1.18 (s, 3H),1.21–1.16 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.0, 146.0, 134.5, 126.8, 126.6, 106.5, 72.9, 55.5, 51.4, 46.7, 40.6, 39.6, 38.4, 37.9, 29.6, 26.4, 24.8, 22.8, 22.6, 21.9, 21.6; EI-MS (m/z, %): 362 (M^+, 100), 347 (21.0), 131 (43.1); HRMS (EI): m/z calcd for $C_{21}H_{30}OS_2$: 362.1738, found: 362.1732.

4.2.16. (4aS,10aR*)-7-isopropyl-6-methoxy-4a-methyl-3,4,4a,9,10,10a-hexahydrophenanthren-1(2H)-one (trans-**3**)*

To a solution of **16** (47 mg, 0.13 mmol) in a mixture of acetonitrile (0.65 mL) and water (0.65 mL) was added trifluoroacetic acid (97 μL, 1.3 mmol) and PIFA (168 mg, 0.39 mmol) successively at room temperature. After being stirred for 3 h, the mixture was quenched with H_2O (5 mL). Then it was extracted with DCM for three times. The combined organic extracts were washed with brine, dried over sodium sulfate and filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel (PE/EA = 15/1) to give *trans*-**3** as colorless oil (32 mg, 85%).

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Appendix A. Supplementary data

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