Organic & Biomolecular Chemistry

Dynamic Article Links

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 1411

www.rsc.org/obc

PAPER

Oxidative dearomatization/intramolecular Diels–Alder cycloaddition cascade for the syntheses of (±)-atisine and (±)-isoazitine†

Xiao-Yu Liu, Hang Cheng, Xiao-Huan Li, Qiao-Hong Chen,* Liang Xu and Feng-Peng Wang*

Received 9th October 2011, Accepted 8th November 2011
DOI: 10.1039/c1ob06704d

A convergent and efficient formal synthesis of (±)-atisine has been accomplished. The synthetic strategy is to efficiently construct the bicyclo[2.2.2]octane ring moiety by an oxidative dearomatization/intramolecular Diels–Alder cycloaddition cascade. The first total synthesis of another atisine-type C_{20}-diterpenoid alkaloid, (±)-isoazitine, has also been achieved employing the same strategy.

Introduction

Diterpenoid alkaloids, featuring polycyclic, highly bridged, and heavily substituted structures, constitute the largest and most complex group of terpenoid alkaloids.[1] The architectural features, physiological properties, and pharmacological activities of the diterpenoid alkaloids pose an alluring target for synthetic chemists and medicinal chemists.[2] Due to the structural diversity and complexity of the diterpenoid alkaloids, their synthesis could prompt the development of ingenious strategies and new methodology for complicated natural products.

The diterpenoid alkaloids can be divided into three broad categories: C_{20}-diterpenoid alkaloids, C_{19}-diterpenoid alkaloids, and C_{18}-diterpenoid alkaloids.[1] The atisine-type C_{20}-diterpenoid alkaloids, such as atisine (**1**)[3] and isoazitine (**2**)[4] (Fig. 1), possess a pentacyclic framework, characteristic of azabicyclo[3.3.1]nonane and bicyclo[2.2.2]octane moieties. The relative simplicity of atisine coupled with extensive structural data made it an ideal first synthetic target. It can be argued quite successfully that the total synthesis of the diterpenoid alkaloids can be traced back to the early 1960s when Nagata and co-workers reported the first total synthesis of atisine.[5a] So far, four different approaches[5] to Pelletier's synthetic intermediates (Fig. 1)[6] for atisine have been reported. The major advancement in the synthesis is to efficiently construct azabicyclo[3.3.1]nonane and bicyclo[2.2.2]octane ring systems.

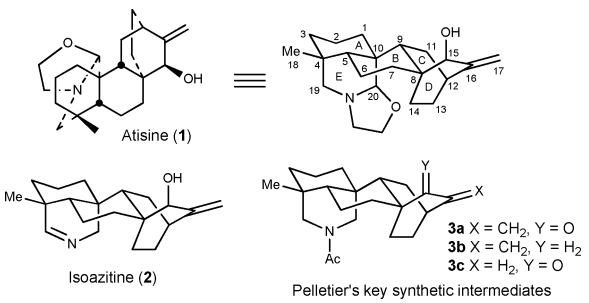


Fig. 1 Structures of atisine, isoazitine, and Pelletier's key synthetic intermediates.

Liao and co-workers have developed an efficient method to construct a bicyclo[2.2.2]octane ring system employing sequential oxidative dearomatization/intramolecular Diels–Alder (IMDA) cycloaddition.[7] This strategy has been elegantly applied to the formation of highly functionalized bicyclo[2.2.2]octane ring systems towards the total syntheses of natural products.[8] Consequently, we envisioned assembling the bicyclo[2.2.2]octane ring system of the key intermediate **3a** for diterpenoid alkaloids **1** and **2** by a cascade of oxidative dearomatization/IMDA cycloaddition.

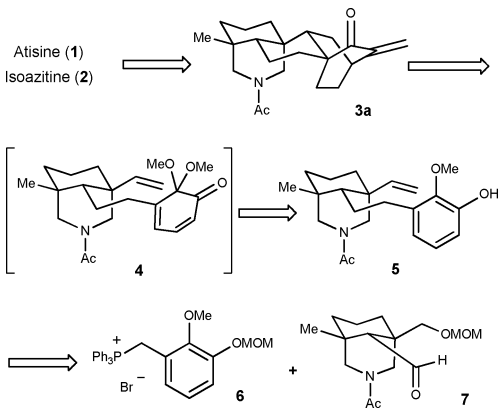
Results and discussion

Our retrosynthetic analysis of atisine (**1**) and isoazitine (**2**) is outlined in Scheme 1. The pentacyclic key intermediate **3a** for the targets was proposed to proceed from phenol precursor **5** *via* the masked *ortho*-benzoquinone ketal **4**[9] using the oxidative dearomatization/IMDA cycloaddition cascade. The precursor **5** could be readily generated by a Wittig reaction of aldehyde **7** with phosphonium salt **6**. The bicyclo[3.3.1]nonane ring system in aldehyde **7** may be accessed through the well-established double Mannich reaction.

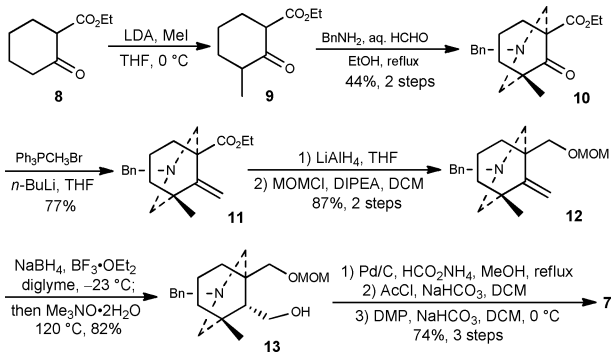
Aldehyde **7** was prepared as shown in Scheme 2. α-Methylation of commercially available ethyl 2-oxocyclohexanecarboxylate (**8**) using LDA as base provided product **9**,[10] which was subjected to double Mannich reaction with benzylamine and formaldehyde to afford azabicyclic compound **10** in 44% yield over 2 steps. Wittig methylenation of ketone **10** gave olefin **11** in 77% yield. Reduction of the ester group in **11** with $LiAlH_4$ followed by protection of the resulting alcohol provided the MOM ether **12** in 87% yield over two steps. According to the method reported by Fukumoto,[5d]

Department of Chemistry of Medicinal Natural Products, Sichuan University, No. 17, Duan 3, Renmin Nan Road, Chengdu, 610041. E-mail: qiaohongchen@yahoo.com.cn, wfp@scu.edu.cn; Fax: +86-28-85501368

† Electronic supplementary information (ESI) available: NMR spectra for two final products and all intermediates. CCDC reference number 834603. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06704d



Scheme 1 Retrosynthetic analysis for (±)-atisine and (±)-isoazitine.

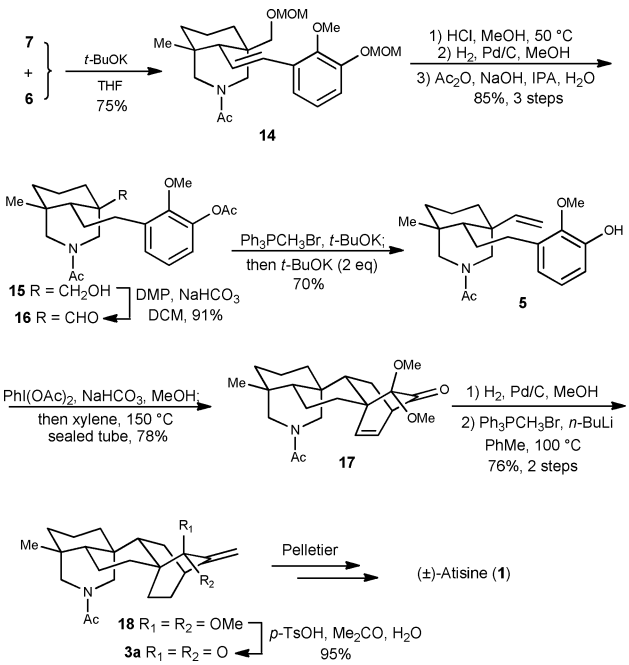


Scheme 2 Construction of A/E ring system.

stereoselective hydroboration of the terminal alkene in **12** was achieved by the addition of a solution of $NaBH_4$ in diglyme to the mixture of **12** and $BF_3{\cdot}OEt_2$ in diglyme at –23 °C. The resulting product was oxidized with trimethylamine *N*-oxide to give the desired isomer **13** in 82% yield, with trace amounts of the undesired diastereomer. Conversion of **13** to **7** was easily achieved in 74% overall yield by a three-step procedure including debenzylation, selective acylation of the amine and oxidation of the alcohol.

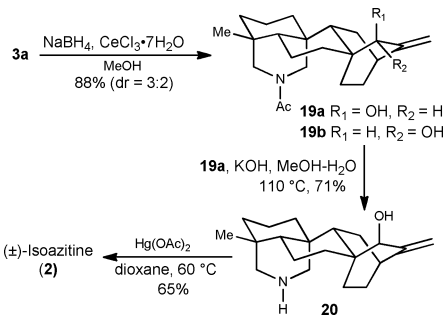
Having made azabicyclo[3.3.1]nonane **7**, it was treated with a Wittig reagent, generated *in situ* from (2-methoxy-3-methoxymethoxybenzyl)triphenyl-phosphonium bromide (**6**) and *t*-BuOK, to afford styrene **14** as E isomer in 75% yield. After removal of the MOM groups and hydrogenation of the alkene, the phenol was selectively protected as an acetate in the presence of a primary hydroxyl group, employing the method reported by Ray *et al.*[11] The double bond between C-9 and C-11 in the precursor **5** was introduced by oxidation of primary alcohol **15** to aldehyde **16** followed by a Wittig methylenation. The acetate in **16** was hydrolysed by the addition of two equivalents of *t*-BuOK to the reaction mixture after the Wittig reaction was completed.

At this point, we investigated the effect of solvents on the oxidative dearomatization/IMDA cascade, and found that methanol was detrimental to IMDA cycloaddition. Consequently, phenol **5** was oxidized with $PhI(OAc)_2$ in the presence of sodium bicarbonate using methanol as a solvent. After switching the solvent from methanol to xylene, the resulting masked *ortho*-quinone was subjected to thermal activation (150 °C) to provide pentacyclic compound **17** as a single isomer in 78% yield. Compound **17** was assigned as the intended *endo* product of the Diels–Alder reaction due to the critical correlation between H-14 and H-20 in its NOESY spectrum (see Electronic Supplementary Information for details†). This assignment was also confirmed by X-ray crystallographic analysis of its derivative **19b** described below. The remaining transformations from **17** to **3a** were straightforward and proceeded *via* ketal **18** in good yields (Scheme 3). The structure of **3a** was established by comparison of its IR data and melting point with those reported in the literature,[6] and by extensive NMR analyses. Based on the previous work by Pelletier and co-workers,[6] the present synthesis of the known compound **3a** constitutes a new formal total synthesis of (±)-atisine.



Scheme 3 Formal synthesis of (±)-atisine.

We also investigated the total synthesis of (±)-isoazitine (**2**) employing pentacyclic compound **3a** as an advanced intermediate. As illustrated in Scheme 4, Luche reduction ($NaBH_4$, $CeCl_3$)[12] of enone **3a** generated two separable isomers **19a** and **19b** (3 : 2) in 88% overall yield. The configuration of the hydroxyl group at C-15 of each isomer was confirmed by an X-ray crystallographic analysis of **19b** (Fig. 2).[13] Note that the configuration of this allylic hydroxyl group was always tentatively assigned in the literature based upon its polarity on alumina according to Pelletier's view.[14]



Scheme 4 Total synthesis of (±)-isoazitine.

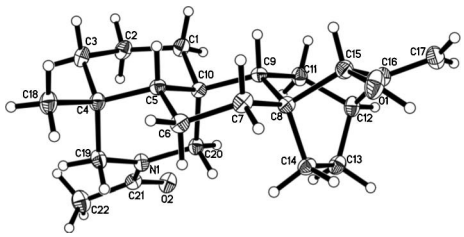


Fig. 2 X-ray crystallographic structure of compound **19b**.

Consequently, we have confirmed the configuration for the first time.

The acetamide in **19a** was hydrolysed with excess potassium hydroxide in methanol–water in a sealed tube. After extensive exploration, it was observed that the secondary amine in **20** can be selectively oxidized to imine in 65% yield employing $Hg(OAc)_2$ as oxidizing agent at 60 °C. Mercuric acetate oxidation of tertiary amines involves a four-center elimination from the *N*-mercurated complex.[15] Oxidation of compound **20** might be expected to undergo at one of the two α-methine positions (C-19 and C-20), since one of the hydrogens at both positions can be *trans* to an *N*-mercurated complex. The regioselectivity of the mercuric acetate oxidation at C-19 of **20** is probably because the proton at C-20 is more sterically hindered than the proton at C-19. This can be supported by the molecular model of compound **20**, from which we can observe that the ring B/C/D system in **20** confers much more steric hindrance to C-20 relative to C-19. Note when the reaction was carried out with 2 equivalents of $Hg(OAc)_2$ at 100 °C, the allylic alcohol in **20** was also oxidized to enone. Thus, the first total synthesis of (±)-isoazitine (**2**) was achieved. The spectroscopic data of synthetic **2** were identical in all aspects to those of the natural product.[16]

Conclusions

In summary, a new synthesis of the Pelletier's intermediate (**3a**) for the atisine-type alkaloids has been achieved in 19 steps. A distinctive feature of the synthesis is the application of an oxidative dearomatization/IMDA cycloaddition cascade to construct bicyclo[2.2.2]octane moiety. This synthetic strategy, in combination with the well-established construction of azabicyclo[3.3.1]nonane by a double Mannich reaction,[5d] enabled the synthetic route to be convergent and efficient. Furthermore, the first total synthesis of (±)-isoazitine (**2**) was achieved in 22 steps using the same strategy. The extension of this strategy to the synthesis of more complicated hetidine-type and hetisine-type diterpenoid alkaloids is currently under investigation in our laboratory.

Experimental

General procedures

All reactions were carried out under argon unless otherwise stated. All the chemicals were purchased from commercial sources and were used without further purification. THF, toluene, and xylene were distilled from sodium–benzophenone; dichloromethane was distilled from calcium hydride; methanol was distilled from Mg/I_2; diglyme was distilled from calcium hydride. Column chromatography was performed using 200–300 mesh silica gel. All new compounds gave satisfactory spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, HRMS). Melting points were determined on a Kofler block (uncorrected); IR spectra were recorded on a Nicolet 200 SXV spectrometer; HRMS spectra were obtained with a Bruker BioTOFQ mass spectrometer; NMR spectra were acquired on a Varian INOVA-400/54 spectrometer, with TMS as internal standard.

Ethyl 3-benzyl-5-methyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (10). To a solution of diisopropylamine (9.0 mL, 64.6 mmol) in anhydrous THF (125 mL) at 0 °C was added *n*-BuLi (25.8 mL, 64.6 mmol, 2.5 M solution in hexane), and the solution was stirred at 0 °C for 30 min. To this LDA solution was added dropwise a solution of 2-oxocyclohexanecarboxylate **8** (5.0 g, 29.4 mmol) in THF (25 mL), and the reaction was allowed to proceed with stirring at 0 °C for an additional 1 h. Methyl iodide (2.0 mL, 32.3 mmol) was added to the above reaction mixture, and the reaction was allowed to proceed at 0 °C for 30 min prior to being quenched by the addition of saturated NH_4Cl solution (50 mL) and water (50 mL). The subsequent mixture was extracted with diethyl ether (100 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to furnish a crude product (**9**), which was directly used for the next reaction without further purification. A mixture of **9**, benzylamine (4.8 mL, 44.1 mmol) and formaldehyde (7.1 mL, 88.1 mmol, 37% aqueous solution) in EtOH (120 mL) was heated under reflux for 48 h. After removal of the solvent under reduced pressure, the orange oil was suspended in water (150 mL), and the subsequent mixture was extracted with CH_2Cl_2 (80 mL × 3). The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give a residue, which was subjected to a flash column chromatography on silica gel, eluting with petroleum ether-EtOAc (100 : 1) to afford compound **10** (4.1 g, 44% over two steps) as a yellow oil. R_f 0.53 (petroleum ether–EtOAc 20 : 1); IR (film) 2927, 2858, 1735, 1456, 1261, 742, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.27 (m, 5H), 4.19 (q, J = 7.2 Hz, 2H), 3.49 (s, 2H), 3.20 (dd, J = 11.6, 2.4 Hz, 1H), 3.21–3.12 (m, 1H), 3.03–2.92 (m, 2H), 2.59–2.51 (m, 1H), 2.32 (dd, J = 11.2, 2.4 Hz, 1H), 2.25–2.20 (m, 1H), 2.11–2.06 (m, 1H), 1.86–1.77 (m, 1H), 1.61–1.55 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.1, 171.1, 138.3, 128.7, 128.4, 127.2, 66.8, 62.1, 62.1, 61.1, 58.8, 46.9, 42.0, 36.8, 20.9, 20.6, 14.1; HRESIMS m/z calcd for $C_{19}H_{25}NO_3Na$ $[M+Na]^+$: 338.1732, found 338.1727.

Ethyl 3-benzyl-5-methyl-9-methylene-3-azabicyclo[3.3.1]nonane-1-carboxylate (11). To a suspension of Ph_3PCH_3Br (11.9 g, 33.3 mmol) in anhydrous THF (150 mL) was slowly added *n*-BuLi (13.3 mL, 33.3 mmol, 2.5 M solution in hexane) at –20 °C, and the mixture was stirred for 30 min at 0 °C. A solution of **10** (7.0 g, 22.2 mmol) in anhydrous THF (50 mL) was added to the above Wittig reagent, and the reaction mixture was kept stirring for 2 h at room temperature prior to being quenched by the addition of saturated NH_4Cl solution (150 mL). The subsequent mixture was extracted with CH_2Cl_2 (100 mL × 3), the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, and the organic solvents were removed in vacuo. The crude residue was purified *via* chromatography eluting with petroleum ether–EtOAc (100 : 1) to afford alkene **11** (5.3 g)

as a colorless oil in 77% yield. R_f 0.60 (petroleum ether–EtOAc 30 : 1); IR (film) 3029, 2959, 2923, 1727, 1456, 1248, 1033, 893, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.25 (m, 5H), 4.76 (s, 1H), 4.56 (s, 1H), 4.23–4.15 (m, 2H), 3.41 (s, 1H), 3.40 (s, 1H), 3.13–3.04 (m, 1H), 3.03 (d, J = 11.2 Hz, 1H), 2.80 (d, J = 10.4 Hz, 1H), 2.65 (dd, J = 10.8, 2.0 Hz, 1H), 2.28–2.19 (m, 1H), 1.97 (d, J = 10.8 Hz, 1H), 1.96–1.93 (m, 1H), 1.83–1.78 (m, 1H), 1.60–1.46 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.6, 155.1, 139.1, 128.6, 128.3, 126.8, 102.5, 67.1, 63.0, 62.4, 60.5, 51.7, 41.0, 38.1, 35.7, 25.4, 21.3, 14.2; HRESI m/z calcd for $C_{20}H_{28}NO_2$ $[M+H]^+$: 314.2120, found 314.2116.

3-Benzyl-1-((methoxymethoxy)methyl)-5-methyl-9-methylene-3-azabicyclo[3.3.1]nonane (12). To a suspension of $LiAlH_4$ (114 mg, 3.0 mmol) in dry THF (8 mL) at 0 °C was slowly added a solution of **11** (785 mg, 2.5 mmol) in anhydrous THF (12 mL), and the mixture was stirred for 1 h at the same temperature. After sequential addition of H_2O (115 µL), 15% aqueous NaOH solution (115 µL), and H_2O (345 µL), the resulting mixture was filtered through Celite eluting with CH_2Cl_2. The filtrate was dried over anhydrous Na_2SO_4 and concentrated to give a residual oil, which was used directly for the next step.

To the primary alcohol, obtained from the above reaction, were sequentially added anhydrous CH_2Cl_2 (15 mL), DIPEA (1.75 mL, 10.0 mmol), and MOMCl (381 µL, 5.0 mmol) at 0 °C, and the reaction mixture was warmed to room temperature and stirred overnight. After being poured into water, the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified *via* flash chromatography, eluting with petroleum ether–EtOAc (100 : 1) to yield ether **12** as a colorless oil (679 mg, 87% over two steps). R_f 0.65 (petroleum ether–EtOAc 30 : 1); IR (film) 3028, 2923, 1458, 1372, 1150, 1109, 1038, 917, 893, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33–7.25 (m, 5H), 4.76 (s, 1H), 4.64 (s, 1H), 4.62 (s, 2H), 3.50–3.43 (m, 2H), 3.42, 3.30 (ABq, J = 13.2 Hz, 2H), 3.37 (s, 3H), 3.12–3.04 (m, 1H), 3.02 (d, J = 10.4 Hz, 1H), 2.77 (d, J = 10.0 Hz, 1H), 2.06 (d, J = 10.4 Hz, 1H), 2.00–1.95 (m, 1H), 1.88 (d, J = 10.4 Hz, 1H), 1.82–1.77 (m, 1H), 1.55–1.38 (m, 3H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.6, 139.4, 128.6, 128.2, 126.7, 100.2, 96.8, 74.3, 67.1, 63.4, 63.2, 55.2, 41.9, 41.5, 38.4, 36.6, 25.3, 21.4; HRESI m/z calcd for $C_{20}H_{30}NO_2$ $[M+H]^+$ 316.2277, found 316.2284.

(3-Benzyl-1-((methoxymethoxy)methyl)-5-methyl-3-azabicyclo-[3.3.1]nonan-9-yl)methanol (13). To a stirred mixture of olefin **12** (1.5 g, 4.8 mmol) and $BF_3{\cdot}OEt_2$ (2.4 mL, 19.0 mmol) in anhydrous diglyme (35 mL) was slowly added a solution of $NaBH_4$ (540 mg, 14.3 mmol) in diglyme (35 mL) at –23 °C under argon, and the mixture was stirred for 13 h at the same temperature. The mixture was allowed to warm to room temperature prior to the addition of $Me_3NO{\cdot}2H_2O$ (3.7 g, 33.3 mmol). The subsequent reaction mixture was heated at 120 °C for 7 h before being cooled down to 0 °C. After the addition of 10% ammonium hydroxide (50 mL), the mixture was extracted with diethyl ether (60 mL × 3). The organic layers were washed with brine, dried, and concentrated to give a residue, which was subjected to flash chromatography column (petroleum ether–EtOAc = 10 : 1 to 5 : 1) to deliver alcohol **13** (1.3 g, 82%) as a colorless oil. R_f 0.33 (petroleum ether–EtOAc 5 : 1); IR (film) 3426, 2924, 2855, 1459, 1217, 1106, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.23 (m, 5H), 5.15 (br.s, 1H, exchangeable with D_2O), 4.59, 4.58 (AB, J = 6.4 Hz, 2H), 3.80 (dd, J = 11.6, 5.2 Hz, 1H), 3.68 (br.d, J = 10.0 Hz, 1H), 3.47–3.39 (m, 2H), 3.25–3.45 (m, 2H), 3.32 (s, 3H), 2.49–2.41 (m, 1H), 2.34–2.19 (m, 4H), 1.65–1.49 (m, 4H), 1.37–1.30 (m, 2H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.0, 128.9, 128.4, 127.1, 96.8, 74.8, 62.8, 60.6, 58.2, 55.8, 55.5, 50.5, 41.9, 38.1, 36.6, 34.2, 27.8, 20.1; HRESI m/z calcd for $C_{20}H_{32}NO_3$ $[M+H]^+$ 334.2382, found 334.2384.

3-Acetyl-1-((methoxymethoxy)methyl)-5-methyl-3-azabicyclo [3.3.1]nonane-9-carbaldehyde (7). To a solution of **13** (3.5 g, 10.5 mmol) in anhydrous MeOH (70 mL) were added Pd–C (3.0 g) and anhydrous ammonium formate (3.2 g, 50.7 mmol), and the mixture was refluxed for 10 min. After being cooled down to room temperature and filtered through Celite, the filtrate was concentrated to give a crude product. To a stirred solution of above crude amine in CH_2Cl_2 (50 mL) were added saturated $NaHCO_3$ (50 mL) and acetyl chloride (3.85 mL, 51.0 mmol), and the subsequent mixture was stirred overnight at room temperature. After being basified with ammonium hydroxide (25% v/v), the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated to give a residue, which was directly employed in the next step.

To a solution of the residue in dry CH_2Cl_2 (150 mL) was added $NaHCO_3$ (5.0 g, 59.5 mmol) and Dess–Martin periodinane (5.2 g, 12.3 mmol) and the mixture was stirred for 1 h at 0 °C prior to being quenched by the addition of saturated $Na_2S_2O_3$. The mixture was extracted with CH_2Cl_2 (100 mL × 2). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (petroleum ether–EtOAc = 1 : 2) of the crude residue afforded aldehyde **7** (2.2 g, 74% over three steps) as a colorless oil. R_f 0.20 (petroleum ether–EtOAc 1 : 1); IR (film) 3406, 2954, 2921, 1716, 1622, 1457, 1151, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, some signals exist as a pair due to the presence of rotamers) δ 10.02 (d, J = 3.2 Hz, 1H), 4.55/4.54, 4.53/4.52 (AB, J = 6.8 Hz, 2H), 4.38 (d, J = 14.0 Hz, 1H), 3.76/3.44 (dd, J = 13.2, 2.4 Hz, 1H), 3.22/2.87 (dd, J = 14.0, 2.4 Hz, 1H), 3.58–3.48 (m, 1H), 3.36–3.26 (m, 1H), 3.32/3.31 (s, 3H), 2.23 (dd, J = 11.2, 4.8 Hz, 1H), 2.13 (s, 3H), 1.92–1.84 (m, 1H), 1.73–1.63 (m, 3H), 1.60–1.39 (m, 3H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, signals for the rotamers are included) δ 204.4, 204.3, 169.7, 96.7, 96.6, 73.7, 60.1, 60.0, 55.6, 55.5, 53.2, 50.2, 49.5, 44.4, 40.8, 40.5, 38.7, 38.2, 35.2, 34.9, 34.1, 33.5, 26.0, 25.9, 22.4, 19.8; HRESI m/z calcd for $C_{15}H_{26}NO_4$ $[M+H]^+$ 284.1862, found 284.1860.

1-(9-(2-Methoxy-3-(methoxymethoxy)styryl)-1-((methoxy-methoxy)methyl)-5-methyl-3-azabicyclo[3.3.1]nonan-3-yl) ethanone (14). To a stirred suspension of **6** (10.6 g, 20.3 mmol) in anhydrous THF (40 mL) was slowly added a solution of *t*-BuOK (2.3 g, 20.3 mmol) in anhydrous THF (40 mL) under argon at 0 °C, and the mixture was stirred at the same temperature for 30 min. A solution of **7** (2.3 g, 8.13 mmol) in THF (40 mL) was added dropwise to the above Wittig reagent, and the reaction mixture was stirred at 35 °C for 9 h prior to being quenched with aqueous NH_4Cl (40 mL). The resulting mixture was extracted with CH_2Cl_2 (80 mL × 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to furnish a residue, which was subjected to column chromatography on

silica gel, using petroleum ether–acetone (6 : 1) as eluent, to afford styrene **14** (2.70 g, 75%) as a white solid. m.p. 128–129 °C; R_f 0.46 (petroleum ether–acetone 3 : 1); IR (film) 2955, 2924, 1643, 1468, 1262, 1152, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, some signals are described as a pair due to the presence of amide rotamers) δ 7.08–6.96 (m, 3H), 6.76/6.73 (d, J = 16.0 Hz, 1H), 6.32/6.29 (d, J = 16.0 Hz, 1H), 5.22 (s, 2H), 4.54, 4.52/4.51 (AB, J = 6.4 Hz, 2H), 4.38/4.26 (d, J = 13.6 Hz, 1H), 3.80 (s, 3H), 3.66/3.40 (d, J = 13.2 Hz, 1H), 3.51 (s, 3H), 3.30/3.27 (s, 3H), 3.25–3.20 (m, 2H), 3.19 (d, J = 13.2 Hz, 1H), 2.76 (br.d, J = 14.0 Hz, 1H), 2.19/2.16 (s, 1H), 2.13/2.12 (s, 3H), 2.10–2.04 (m, 1H), 1.87–1.74 (m, 3H), 1.60–1.54 (m, 2H), 0.83/0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, all signals for the amide rotamers are listed) δ 169.8, 150.6, 131.6, 128.4, 128.3, 127.6, 124.2, 119.8, 115.4, 115.3, 96.8, 96.7, 95.1, 75.1, 74.6, 61.0, 56.2, 55.2, 53.0, 52.8, 52.2, 49.3, 47.9, 44.3, 40.7, 40.5, 38.2, 37.6, 35.2, 34.9, 34.1, 33.4, 27.1, 22.5, 20.2; HRESI m/z calcd for $C_{25}H_{37}NO_6Na$ $[M+Na]^+$ 470.2519, found 470.2514.

3-(2-(3-Acetyl-1-(hydroxymethyl)-5-methyl-3-azabicyclo [3.3.1]-nonan-9-yl)ethyl)-2-methoxyphenyl acetate (15). The mixture of styrene **14** (2.70 g, 6.04 mmol) and concentrated HCl (15 mL) in MeOH (70 mL) was heated at 50 °C for 30 min. After addition of 25% ammonium hydroxide (25 mL) at 0 °C, the organic solvent was removed under reduced pressure, and the residue was extracted with CH_2Cl_2 (80 mL × 3). The organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated to give a white amorphous powder. To a solution of the crude product obtained above in MeOH (120 mL) was added Pd–C (500 mg), and the reaction was allowed to proceed with stirring in the presence of hydrogen atmosphere at room temperature for 2 h. After removal of insoluble material by filtration through Celite, the filtrate was concentrated to generate a residue. Isopropyl alcohol (85 mL) was added to this residue, and then a solution of NaOH (762 mg, 19.0 mmol) in H_2O (5 mL) and Ac_2O (1.80 mL, 19.0 mmol) were added to the mixture. The reaction was kept to proceed with stirring at room temperature for 3 h before removing organic solvent. The residue was dissolved in water and basified with 25% ammonium hydroxide, and the resulting mixture was extracted with CH_2Cl_2 (60 mL × 3). The combined organic extracts were washed with brine, dried with anhydrous Na_2SO_4, and concentrated to yield a residue, which was chromatographed over silica gel eluting with petroleum ether–acetone (2 : 1) to afford acetate **15** (2.04 g, 85% over three steps) as a white amorphous powder. R_f 0.35 (petroleum ether–acetone 3 : 2); IR (film) 3392, 2956, 2923, 2853, 1766, 1620, 1463, 1374, 1198, 1011 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, some signals exist as a pair due to the presence of amide rotamers) δ 7.05–7.02 (m, 2H), 6.94–6.91 (m, 1H), 4.10 (t, J = 13.2 Hz, 1H), 3.86/3.52 (d, J = 10.8 Hz, 1H), 3.80 (s, 3H), 3.37–3.32 (m, 1H), 3.29–3.23 (m, 1H), 3.07/2.98 (dd, J = 13.2, 2.0 Hz, 1H), 2.76–2.63 (m, 2H), 2.59/2.46 (d, J = 13.6 Hz, 1H), 2.35 (s, 3H), 2.07/2.05 (s, 3H), 1.87–1.72 (m, 3H), 1.69–1.49 (m, 5H), 1.38–1.30 (m, 1H), 0.91/0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, all signals for the amide rotamers are listed) δ 169.7, 169.6, 169.2, 149.8, 143.7, 136.8, 136.6, 128.2, 128.0, 124.2, 121.6, 121.4, 68.3, 67.9, 61.1, 52.4, 48.4, 47.3, 45.3, 44.6, 43.5, 41.0, 40.8, 39.2, 38.5, 35.1, 34.9, 34.5, 33.8, 32.4, 32.2, 25.9, 25.4, 25.2, 22.4, 20.8, 20.3, 20.2; HRESI m/z calcd for $C_{23}H_{34}NO_5$ $[M+H]^+$ 404.2437, found 404.2446.

3-(2-(3-Acetyl-1-formyl-5-methyl-3-azabicyclo[3.3.1]nonan-9-yl)ethyl)-2-methoxyphenyl acetate (16). To a stirred solution of **15** (2.04 g, 5.06 mmol) in CH_2Cl_2 (100 mL) were added $NaHCO_3$ (4.5 g, 53.5 mmol) and Dess–Martin periodinane (3.4 g, 8.02 mmol) at 0 °C. After being stirred for 2 h at room temperature, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted with CH_2Cl_2 (60 mL × 2). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give a residue, which was chromatographed on silica gel (petroleum ether–acetone = 4 : 1) to afford **16** (1.85 g, 91%) as an off-white foam. R_f 0.50 (petroleum ether–acetone 3 : 2); IR (film) 3424, 2957, 2924, 2854, 1766, 1717, 1639, 1465, 1265, 1196, 1008 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, some signals appear as pairs due to the presence of amide rotamers) δ 9.23/9.10 (s, 1H), 7.05–6.91 (m, 3H), 4.47/4.18 (d, J = 14.0 Hz, 1H), 3.76 (s, 3H), 3.60/3.09 (d, J = 13.6 Hz, 1H), 3.35/3.31 (d, J = 12.8 Hz, 1H), 2.92/2.62 (d, J = 14.0 Hz, 1H), 2.72–2.56 (m, 2H), 2.33 (s, 3H), 2.08 (s, 3H), 1.83–1.67 (m, 3H), 1.65–1.57 (m, 3H), 1.52–1.44 (m, 1H), 1.35–1.18 (m, 2H), 0.97/0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, all signals for the amide rotamers are listed) δ 203.7, 203.5, 170.0, 169.0, 149.8, 143.7, 135.9, 135.8, 127.8, 124.1, 121.8, 61.1, 52.2, 50.8, 50.0, 47.1, 45.8, 44.0, 43.4, 40.9, 40.4, 40.2, 33.8, 33.0, 32.1, 32.0, 31.6, 31.5, 28.3, 28.0, 25.5, 25.4, 22.4, 20.9, 19.5, 19.4; HRESI m/z calcd for $C_{23}H_{32}NO_5$ $[M+H]^+$ 402.2280, found 402.2283.

1-(9-(3-Hydroxy-2-methoxyphenethyl)-1-methyl-5-vinyl-3-aza-bicyclo[3.3.1]nonan-3-yl)ethanone (5). To a suspension of Ph_3PCH_3Br (3.8 g, 10.6 mmol) in dry THF (30 mL) was slowly added a solution of t-BuOK (1.2 g, 10.6 mmol) in THF (30 mL) at 0 °C, and the mixture was stirred at 0 °C for 30 min. To this mixture was slowly added a solution of aldehyde **16** (1.7 g, 4.24 mmol) in THF (30 mL), and the subsequent reaction mixture was warmed up to room temperature and stirred for an additional 3 h prior to the addition of another portion of t-BuOK (950 mg, 8.48 mmol). The reaction was allowed to proceed with stirring for 2 h at 35 °C prior to being quenched by addition of saturated NH_4Cl solution. After extracting the resulting mixture with CH_2Cl_2 (50 mL × 3), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give a residue. The residue was purified by column chromatography on silica gel with petroleum ether–acetone (5 : 1) as eluent to furnish phenol **5** (1.06 g, 70%) as a white solid. m.p. 137–139 °C; R_f 0.42 (petroleum ether–acetone 3 : 2); IR (film) 3197, 2957, 2925, 2854, 1618, 1586, 1468, 1276, 1008, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, some signals exist as pairs due to the presence of amide rotamers) δ 6.94 (t, J = 8.0 Hz, 1H), 6.82 (dd, J = 8.0, 1.6 Hz, 1H), 6.67 (dd, J = 8.0, 1.6 Hz, 1H), 5.92/5.90 (br.s, 1H), 5.69/5.64 (t, J = 7.2 Hz, 1H), 5.10–4.90 (m, 2H), 4.43/4.20 (d, J = 14.0 Hz, 1H), 3.79 (s, 3H), 3.52/3.32 (d, J = 13.2 Hz, 1H), 3.23/3.10 (dd, J = 13.2, 2.0 Hz, 1H), 2.74/2.61 (d, J = 14.0 Hz, 1H), 2.70–2.54 (m, 2H), 2.11/2.10 (s, 3H), 1.86–1.41 (m, 8H), 1.27–1.22 (m, 1H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, all signals for the amide rotamers are listed) δ 169.7, 149.1, 145.2, 135.4, 128.6, 128.4, 124.8, 121.4, 113.7, 112.4, 112.1, 61.9, 52.2, 49.1, 46.9, 49.0, 43.9, 41.0, 40.8, 40.7, 40.2, 38.9, 38.9, 34.4, 33.7, 32.5, 32.4, 27.3, 27.2, 25.8, 22.4, 20.5; HRESI m/z calcd for $C_{22}H_{32}NO_3$ $[M+H]^+$ 358.2382, found 358.2374.

14-Acetyl-11,11-dimethoxy-8-methyl-3,4,4a,5,6,7,8,8a,9,10-decahydro-3,10a-ethano-4b,8-(methanoiminomethano) phenanthren-12-one (17). To a stirred mixture of PIDA (102 mg, 0.317 mmol) and $NaHCO_3$ (44 mg, 0.523 mmol) in MeOH (16 mL) was added a solution of **5** (75 mg, 0.210 mmol) in MeOH (16 mL) at 0 °C, and the mixture was stirred at the same temperature for 30 min. After addition of xylene (150 mL) to the resulting mixture, methanol was cautiously removed under reduced pressure at room temperature. The resulting solution was heated at 150 °C in a sealed tube for 4 h. The solvent was then evaporated off, and the residue was chromatographed over silica gel with petroleum ether–EtOAc (1 : 1) to afford pentacyclic compound **17** (63 mg) as a white solid in 78% yield. m.p. 172–174 °C; R_f 0.38 (petroleum ether–EtOAc 1 : 2); IR (film) 2955, 2923, 2851, 1729, 1636, 1461, 1376, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, some signals exist as pairs due to the presence of amide rotamers) δ 6.25–6.11 (m, 2H), 4.15/4.02 (d, J = 14.0 Hz, 1H), 3.46/3.45 (s, 3H), 3.33/3.32 (s, 3H), 3.28 (d, J = 13.2 Hz, 1H), 3.25–3.07 (m, 2H), 2.70/2.59 (d, J = 14.0 Hz, 1H), 2.18–1.97 (m, 3H), 2.05/2.03 (s, 3H), 1.83–1.71 (m, 4H), 1.70–1.59 (m, 2H), 1.52–1.42 (m, 4H), 1.18–1.14 (m, 1H), 0.88/0.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, all signals for the amide rotamers are listed) δ 203.6, 203.3, 169.4, 140.2, 139.5, 126.2, 125.7, 95.8, 55.6, 55.5, 52.5, 52.4, 49.4, 49.3, 48.5, 48.4, 48.3, 47.3, 44.2, 43.8, 43.1, 41.0, 40.7, 39.2, 37.6, 36.9, 33.1, 32.4, 25.9, 25.8, 25.6, 25.4, 22.5, 22.4, 20.9, 17.7; HRESI m/z calcd for $C_{23}H_{34}NO_4$ $[M+H]^+$ 388.2488, found 388.2481.

1-(1,1-Dimethoxy-8-methyl-2-methylenedodecahydro-3,10a-ethano-4b,8-(methanoiminomethano)phenanthren-14-yl) ethanone (18). To a solution of **17** (50 mg, 0.129 mmol) in MeOH (5 mL) was added Pd–C (5 mg), and the reaction mixture was stirred under an atmosphere of hydrogen at room temperature for 2 h. The mixture was filtered through Celite rinsing with EtOAc. The solvent was removed under reduced pressure to afford a white solid.

n-BuLi (0.23 mL, 0.57 mmol, 2.5 M solution in hexane) was added dropwise to a stirred suspension of Ph_3PCH_3Br (243 mg, 0.68 mmol) in anhydrous toluene (4 mL) at 0 °C under argon, and the reaction mixture was stirred for 30 min. A solution of the white solid obtained above in anhydrous toluene (4 mL) was slowly added to the reaction mixture at 0 °C, and the reaction was allowed to proceed with heating at 100 °C for 8 h prior to being cooled to 0 °C. The reaction was then quenched by addition of saturated NH_4Cl solution (5 mL), and the resulting mixture was extracted with CH_2Cl_2 (5 mL× 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give a residue, which was purified by flash chromatography on silica gel (petroleum ether–acetone = 12 : 1) to afford **18** (38 mg, 76% over two steps) as a white powder. R_f 0.68 (petroleum ether–acetone 3 : 1); IR (film) 2924, 2853, 1647, 1460, 1377, 1116 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, some signals exist as pairs due to the presence of amide rotamers) δ 5.20/5.18 (s, 1H), 5.11/5.08 (s, 1H), 4.43/4.15 (d, J = 13.2 Hz, 1H), 3.56/3.31 (s, 1H), 3.35/3.34 (s, 3H), 3.29/3.28 (s, 3H), 3.12 (d, J = 12.8 Hz, 1H), 3.07/2.63 (d, J = 13.6 Hz, 1H), 2.38–2.36 (m, 1H), 2.11/2.08 (s, 3H), 1.94–1.86 (m, 2H), 1.81–1.38 (m, 14H), 1.37–1.17 (m, 1H), 1.11–1.06 (m, 1H), 0.86/0.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, all signals for the amide rotamers are listed) δ 169.5, 169.4, 149.7, 149.3, 112.6, 112.2, 102.3, 102.1, 52.6, 51.8, 51.3, 51.2, 49.1, 47.4, 46.8, 44.3, 44.2, 42.3, 42.1, 41.9, 41.1, 40.8, 40.1, 39.9, 37.7, 37.4, 37.1, 33.2, 32.4, 29.6, 29.5, 28.0, 27.4, 26.7, 26.4, 25.9, 23.9, 22.5, 21.0, 17.7; HRESI m/z calcd for $C_{24}H_{38}NO_3$ $[M+H]^+$ 388.2852, found 388.2844.

14-Acetyl-8-methyl-2-methylenedecahydro-3,10a-ethano-4b,8-(methanoiminomethano)phenanthren-1(5*H*)-one (3a). A solution of *p*-TsOH (17 mg, 0.099 mmol) in acetone (0.6 mL) was added to a stirred mixture of **18** (25 mg, 0.065 mmol) in acetone (2.4 mL) and H_2O (0.3 mL). The reaction was allowed to proceed with stirring at room temperature for 30 min prior to being quenched with aqueous $NaHCO_3$ (1 mL). The mixture was extracted with CH_2Cl_2 (5 mL × 3). The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give a residue, which was subjected to flash chromatography, eluting with petroleum ether–acetone (6 : 1), to give **3a** (21 mg) as a white solid in 95% yield. m.p. 150–153 °C; R_f 0.50 (petroleum ether–acetone 3 : 1); IR (film) 2926, 2869, 1709, 1643, 1460, 1279 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, some signals exist as pairs due to the presence of amide rotamers) δ 5.97/5.94 (s, 1H), 5.25/5.23 (s, 1H), 4.52/4.15 (d, J = 13.6 Hz, 1H), 3.66/3.32 (d, J = 12.8 Hz, 1H), 3.60/3.15 (dd, J = 12.8, 2.0 Hz, 1H), 3.10/2.66 (d, J = 13.6 Hz, 1H), 2.81–2.77 (m, 1H), 2.18–2.12 (m, 1H), 2.11/2.08 (s, 3H), 1.95–1.58 (m, 10H), 1.53–1.23 (m, 6H), 1.02–0.98 (m, 1H), 0.87/0.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, all signals for the amide rotamers are listed) δ 203.2, 202.6, 169.6, 146.5, 145.9, 118.0, 117.6, 52.5, 49.1, 49.0, 47.4, 46.6, 44.5, 43.4, 43.2, 41.7, 40.9, 40.6, 39.7, 39.6, 38.6, 37.9, 35.7, 33.2, 32.5, 28.8, 28.6, 27.9, 27.5, 26.2, 25.9, 25.8, 25.0, 24.9, 22.5, 20.8, 17.2, 17.1; HRESI m/z calcd for $C_{22}H_{32}NO_2$ $[M+H]^+$ 342.2433, found 342.2426.

1-Hydroxy-8-methyl-2-methylenedodecahydro-3,10a-ethano-4b,8-(methanoiminomethano)phenanthren-14-yl)ethanone (19). To a solution of **3a** (60 mg, 0.176 mmol) in MeOH (5 mL) was added $CeCl_3 \cdot 7H_2O$ (462 mg, 1.24 mmol) and $NaBH_4$ (47 mg, 1.24 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. After quenching the reaction by addition of aqueous NH_4Cl (2 mL) and aqueous $NaHCO_3$ (2 mL), the mixture was extracted with CH_2Cl_2 (8 mL × 3). The extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give a residue, which was purified *via* chromatography over silica gel, eluting with petroleum ether–EtOAc (1 : 1), to afford a pair of epimers **19a** (30 mg) and **19b** (23 mg) in 88% overall yield.

19a: white solid; m.p. 170–172 °C; R_f 0.43 (petroleum ether–EtOAc 1 : 2); IR (film) 3392, 2924, 2853, 1622, 1461, 1377, 1063, 895 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, some signals exist as pairs due to the presence of amide rotamers) δ 5.12/5.09 (s, 1H), 5.07/5.04 (s, 1H), 4.45/4.14 (d, J = 14.0 Hz, 1H), 3.62 (br.s, 1H), 3.58/3.31 (d, J = 12.8 Hz, 1H), 3.57/3.14 (dd, J = 12.8, 2.0 Hz, 1H), 3.07/2.66 (d, J = 13.6 Hz, 1H), 2.37–2.34 (m, 1H), 2.12/2.09 (s, 3H), 2.04–1.87 (m, 2H), 1.80–1.72 (m, 2H), 1.68–1.54 (m, 6H), 1.51–1.31 (m, 5H), 1.28–1.17 (m, 2H), 1.13–1.03 (m, 1H), 0.87/0.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, all signals for the amide rotamers are listed) δ 169.5, 156.5, 155.8, 110.3, 109.7, 76.8, 76.6, 52.6, 49.2, 47.5, 47.0, 42.1, 41.1, 40.8, 39.9, 39.8, 39.2, 38.9, 37.4, 37.3, 36.7, 36.1, 33.2, 32.5, 31.3, 31.2, 28.3, 28.0, 27.4, 26.4, 25.9, 26.0, 22.5, 20.9, 17.5; HRESI m/z calcd for $C_{22}H_{34}NO_2$ $[M+H]^+$ 344.2590, found 344.2589.

19b: white needles were crystallized from EtOAc; m.p. 172–173 °C; R_f 0.37 (petroleum ether–EtOAc 1 : 2); IR (film) 3461,

2928, 2867, 1624, 1443, 1278, 1048, 894 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, some signals exist as pairs due to the presence of amide rotamers) δ 5.11/5.08 (s, 1H), 5.05/5.02 (s, 1H), 4.48/4.16 (d, J = 13.6 Hz, 1H), 3.63 (br.s, 1H), 3.62/3.32 (d, J = 13.2 Hz, 1H), 3.61/3.15 (dd, J = 13.2, 2.0 Hz, 1H), 3.11/2.66 (d, J = 13.6 Hz, 1H), 2.36–2.33 (m, 1H), 2.12/2.09 (s, 3H), 1.95 (dt, J = 12.8, 5.6 Hz, 1H), 1.80–1.55 (m, 9H), 1.52–1.33 (m, 5H), 1.21–1.08 (m, 2H), 1.07–1.01 (m, 1H), 0.88/0.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, all signals for the amide rotamers are listed) δ 169.5, 156.3, 155.6, 109.6, 109.2, 79.8, 79.6, 52.6, 49.7, 47.4, 46.6, 47.2, 47.0, 41.8, 41.1, 40.8, 39.9, 39.8, 37.7, 37.0, 35.7, 35.6, 33.8, 33.6, 33.3, 32.5, 27.5, 27.4, 27.0, 26.0, 22.5, 20.9, 20.7, 20.6, 17.6, 17.5; HRESI m/z calcd for $C_{22}H_{34}NO_2$ $[M+H]^+$ 344.2590, found 344.2582.

8-Methyl-2-methylenedodecahydro-3,10a-ethano-4b,8-(methanoiminomethano)phenanthren-1-ol (20). A mixture of **19a** (20 mg, 0.058 mmol) and KOH (170 mg, 3.03 mmol) in MeOH (2 mL) and H_2O (0.3 mL) was heated at 110 °C in a sealed tube for 48 h. After removing the solvent, the residue was partitioned in water (5 mL) and CH_2Cl_2 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL × 2), and the combined organic extracts were washed with water and brine, and dried over Na_2SO_4. The solvents were evaporated off, and the residue was chromatographed on silica gel eluting with petroleum ether–acetone (3 : 2) to give **20** (resin, 12 mg, 71%). R_f 0.22 (petroleum ether–acetone 3 : 2); IR (film) 3387, 2925, 2855, 1661, 1461, 1377, 1077, 895 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.08 (s, 1H), 5.02 (s, 1H), 3.59 (s, 1H), 3.28 (dd, J = 12.8, 2.4 Hz, 1H), 2.96 (d, J = 13.2 Hz, 1H), 2.83 (dd, J = 13.2, 2.4 Hz, 1H), 2.62 (d, J = 13.2 Hz, 1H), 2.31 (br.s, 1H), 2.21–1.92 (m, 4H), 1.75–1.52 (m, 7H), 1.48–1.36 (m, 3H), 1.23–1.14 (m, 2H), 1.07–1.01 (m, 1H), 0.93–0.85 (m, 1H), 0.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.7, 126.4, 76.9, 52.6, 50.0, 46.1, 40.8, 39.8, 39.7, 37.4, 36.6, 36.3, 32.6, 31.5, 28.0, 27.5, 26.5, 26.2, 23.5, 17.5; HRESI m/z calcd for $C_{20}H_{32}NO$ $[M+H]^+$: 302.2484, found 302.2493.

8-Methyl-2-methylene-1,2,3,4,4a,5,6,7,8,8a,9,10-dodecahydro-3,10a-ethano-4b,8-(methanoazenometheno)phenanthren-1-ol ((±)-isoazitine, 2). To a stirred solution of **20** (7.8 mg, 0.026 mmol) in dioxane (0.6 mL) was added $Hg(OAc)_2$ (10.0 mg, 0.031 mmol), and the reaction mixture was heated at 60 °C for 2 h. After addition of water (2 mL) and CH_2Cl_2 (2 mL), the mixture was basified with 25% ammonium hydroxide. The aqueous phase was extracted with CH_2Cl_2 (3 mL × 2), and the organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give a residue, which was subjected to flash chromatography on silica gel, eluting with petroleum ether–EtOAc (2 : 1), to afford (±)-isoazitine (**2**) (5.0 mg) as an oil in 65% yield. R_f 0.42 (petroleum ether–EtOAc 1 : 1); IR (film) 3301, 2925, 2854, 1661, 1461, 1376, 1077, 1020, 895 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44 (br.s, 1H), 5.11 (br.s, 1H), 5.05 (br.s, 1H), 3.93 (br.d, J = 19.2 Hz, 1H), 3.62 (s, 1H), 3.43 (dd, J = 19.2, 2.8 Hz, 1H), 2.34 (br.s, 1H), 2.17–2.11 (m, 1H), 1.74–1.49 (m, 9H), 1.39–1.34 (m, 1H), 1.29–1.20 (m, 2H), 1.16–1.11 (m, 1H), 1.07 (s, 3H), 1.04–0.90 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0, 156.6, 109.7, 77.0, 55.7, 47.6, 41.5, 38.9, 38.4, 37.6, 37.5, 36.4, 36.2, 31.1, 28.5, 27.1, 26.3, 23.8, 20.3, 19.7; HRESI m/z calcd for $C_{20}H_{30}NO$ $[M+H]^+$ 300.2327, found 300.2330.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (No. 30873147) for financial support of this research. We thank Dr Jesús G. Díaz (Universidad de La Laguna, Spain) for offering the original NMR spectra of natural isoazitine and Dr Jun-Biao Chang (Zhengzhou University, China) for assisting with X-ray analysis.

Notes and references

1 For recent reviews, see: (*a*) F. P. Wang, Q. H. Chen and X. Y. Liu, *Nat. Prod. Rep.*, 2010, **27**, 529–570; (*b*) F. P. Wang and X. T. Liang, in *The Alkaloids: Chemistry and Biology*, ed. G. A. Cordell, Elsevier Science, New York, 2002, vol. 59, pp. 1–280; (*c*) F. P. Wang, Q. H. Chen and X. T. Liang, in *The Alkaloids: Chemistry and Biology*, ed. G. A. Cordell, Elsevier Science, New York, 2009, vol. 67, pp. 1–78; (*d*) F. P. Wang and Q. H. Chen, in *The Alkaloids: Chemistry and Biology*, ed. G. A. Cordell, Elsevier Science, New York, 2010, vol. 69, pp. 1–577.
2 E. C. Cherney and P. S. Baran, *Isr. J. Chem.*, 2011, **51**, 391–405.
3 (*a*) S. W. Pelletier and W. A. Jacobs, *J. Am. Chem. Soc.*, 1954, **76**, 4496–4497; (*b*) S. W. Pelletier, R. Aneja and K. W. Gopinath, *Phytochemistry*, 1968, **7**, 625–635.
4 J. G. Díaz, J. G. Ruiz and G. de la Fuente, *J. Nat. Prod.*, 2000, **63**, 1136–1139.
5 (*a*) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi and Y. Hayase, *J. Am. Chem. Soc.*, 1963, **85**, 2342–2343; (*b*) S. Masamune, *J. Am. Chem. Soc.*, 1964, **86**, 291–292; (*c*) R. W. Guthrie, Z. Valenta and K. Wiesner, *Tetrahedron Lett.*, 1966, **7**, 4645–4654; (*d*) M. Ihara, M. Suzuki, K. Fukumoto, T. Kametani and C. Kabuto, *J. Am. Chem. Soc.*, 1988, **110**, 1963–1964.
6 (*a*) S. W. Pelletier and W. A. Jacobs, *J. Am. Chem. Soc.*, 1956, **78**, 4144–4145; (*b*) S. W. Pelletier and P. C. Parthasarathy, *Tetrahedron Lett.*, 1963, **4**, 205–208.
7 Y. K. Chen, R. K. Peddinti and C. C. Liao, *Chem. Commun.*, 2001, 1340–1341.
8 For a recent review, see: (*a*) S. P. Roche and J. A. Porco Jr., *Angew. Chem., Int. Ed.*, 2011, **50**, 4068–4093. For the applications in the total synthesis of natural products, see: (*b*) H. Y. Shiao, H. P. Hsieh and C. C. Liao, *Org. Lett.*, 2008, **10**, 449–452; (*c*) K. C. Nicolaou, Q. Y. Toh and D. Y.-K. Chen, *J. Am. Chem. Soc.*, 2008, **130**, 11292–11293; (*d*) Z. Gu and A. Zakarian, *Org. Lett.*, 2011, **13**, 1080–1082; (*e*) G. Mehta and P. Maity, *Tetrahedron Lett.*, 2011, **51**, 1753–1756; (*f*) T. Suzuki, A. Sasaki, N. Egashira and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2011, **50**, 9177–9179.
9 For a review, see: D. Magdziak, S. J. Meek and T. R. R. Pettus, *Chem. Rev.*, 2004, **104**, 1383–1430.
10 S. N. Huckin and L. Weiler, *J. Am. Chem. Soc.*, 1974, **96**, 1082–1087.
11 V. Srivastava, A. Tandon and S. Ray, *Synth. Commun.*, 1992, **22**, 2703–2710.
12 J. L. Luche, *J. Am. Chem. Soc.*, 1978, **100**, 2226–2227.
13 The crystallographic data of compound **19b** can be found in the electronic supplementary information. Deposition Number is CCDC 834603.
14 S. W. Pelletier, *Tetrahedron*, 1961, **14**, 76–112.
15 N. J. Leonard and D. E. Morrow, *J. Am. Chem. Soc.*, 1958, **80**, 371–375.
16 See Electronic Supplementary Information (ESI) for a comparison of the ^1H and ^{13}C NMR spectra of natural isoazitine and synthetic isoazitine.