有机化学 DOI: 10.6023/cjoc202208014 研究论文
Chinese Journal of Organic Chemistry ARTICLE

Daphnezomines A 和 B 的四环核心骨架合成

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摘要 在虎皮楠生物碱家族中, daphnezomine A 型生物碱仅包含三位成员: daphnezomine A (**1**), daphnezomine B (**2**)以及 dapholdhamine B. 这些生物碱含有独特的氮杂金刚烷骨架, 9 个连续的手性立体中心, 因此呈现出巨大的合成挑战性. 报道了分子 **1** 和 **2** 的四环核心骨架的合成. 关键步骤包括一个黄氏酰胺活化增环反应和一个 Hutchins-Kabalka 还原重排反应.

关键词 全合成; 虎皮楠生物碱; daphnezomine A; daphnezomine B; 氮杂金刚烷; 黄氏酰胺活化增环反应; Hutchins-Kabalka 还原重排

Synthesis of Tetracyclic Core Structure of Daphnezomines A and B

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Abstract Among the tiniest *Daphniphyllum* alkaloid subfamilies, daphnezomine A-type alkaloids consist of only three known members, namely daphnezomine A (**1**), daphnezomine B (**2**) and dapholdhamine B. These alkaloids contain a unique aza-adamantane core along with nine contiguous stereogenic centers, thus presenting remarkable synthetic challenges. The synthesis of tetracyclic core structure of **1** and **2** was reported. The key steps in our approach include a Huang's amide-activation-annulation and a Hutchins-Kabalka reductive rearrangement.

Keywords total synthesis; *Daphniphyllum* alkaloids; daphnezomine A; daphnezomine B; aza-adamantane; Huang's amide-activation-annulation; Hutchins-Kabalka reductive rearrangement

1 Introduction

Since the isolation of daphnimacrine in 1909, more than 350 *Daphniphyllum* alkaloids have been isolated. They consist of a large family of structurally intriguing natural products with a wide range of bioactivity.[1] Owing to their promising pharmacological potential and complex architectures, *Daphniphyllum* alkaloids have attracted extensive activities from organic synthesis community over the past four decades.[2] Since Heathcock's seminal syntheses,[3] continuous efforts have resulted in elegant total syntheses by the groups of Carreira,[4] Li,[5] Smith,[6] Fukuyama/Yokoshima,[7] Dixon,[8] Zhai,[9] Qiu,[10] Gao,[11] Sarpong,[12] Li[13] and Lu[14]. Moreover, Hanessian and his co-workers

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Received August 13, 2022; revised September 2, 2022; published online October 10, 2022.
Project supported by the National Natural Science Foundation of China (No. 21971104), the Key Research Projects in Colleges and Universities of Education Department of Guangdong Province (No. 2021ZDZX2035), the Shenzhen Bay Laboratory (No. SZBL2019062801006), the Shenzhen Nobel Prize Scientists Laboratory Project (No. C17783101), the Guangdong Innovative Program (No. 2019BT02Y335), the Innovative Team of Universities in Guangdong Province (No. 2020KCXTD016), the Guangdong Provincial Key Laboratory of Catalysis (No. 2020B121201002) and the Shenzhen Science and Technology Innovation Committee (No. ZDSYS20190902093215877).
国家自然科学基金(No. 21971104)、广东省教育厅高校重点科研项目(No. 2021ZDZX2035)、深圳湾实验室(No. SZBL2019062801006)、深圳市诺贝尔奖科学家实验室(No. C17783101)、广东省本土创新团队项目(No. 2019BT02Y335)、广东省高校创新团队(No. 2020KCXTD016)、广东省催化化学重点实验室(No. 2020B121201002)、深圳市科技创新委员会(No. ZDSYS20190902093215877)资助项目.

have reported the total synthesis of a putative natural *Daphniphyllum* alkaloid.[11,15] Meanwhile, our group has also accomplished enantioselective total syntheses of calyciphylline A-type alkaloid himalensine A, daphnezomine A-type alkaloid dapholdhamine B, bukittinggine-type alkaloid caldaphnidine O and yuzurimine-type alkaloid caldaphnidine J.[2d,16]

2 Results and discussion

Amongst the tiniest *Daphniphyllum* alkaloid subfamilies, daphnezomine A-type alkaloids consist of only three known members, namely daphnezomine A (**1**),[17] daphnezomine B (**2**)[17] and dapholdhamine B (**3**)[18] (Figure 1). These alkaloids contain a unique aza-adamantane core along with nine contiguous stereocenters, thus signifying remarkable synthetic challenges. Fascinated by their complex caged structures, a program aiming to prepare these molecules in an efficient manner was initiated. Recently, our group has accomplished the first total synthesis of **3**.[16b] Soon after our report, Li and his co-workers reported efficient syntheses of **1** and **2**.[13] Herein, we would like to introduce our efforts toward the synthesis of **1** and **2**, which successfully fabricated the aza-tetracyclic core structure. The key transformations in our approach include Huang's amide-activation-annulation and Hutchins-Kabalka reductive rearrangement.

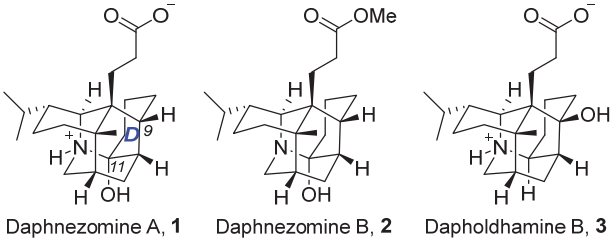
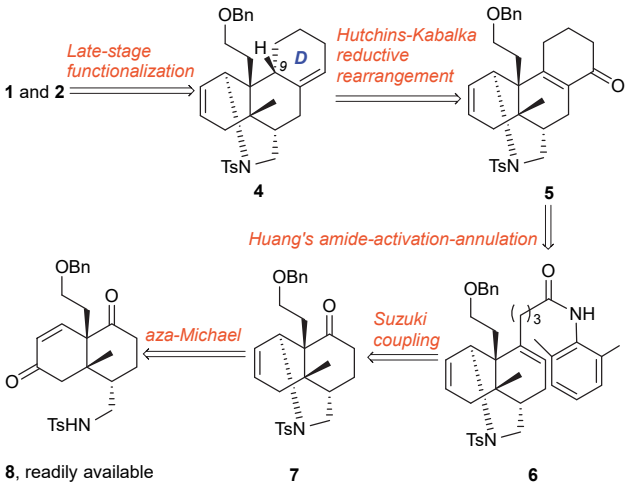


Figure 1 Daphnezomine A-type alkaloids

Despite our success in the synthesis of **3**, the subtle structural differences among **1**, **2** and **3** impelled us to explore different synthetic strategies. With the thoughts that the D-ring formation would be much more critical than the introduction of the isopropyl group, a new approach with a different late-stage strategy was designed. In a retrosynthetic perspective, we envisaged that the target molecules **1** and **2** could be synthesized via late-stage functionalizations from tetracycle **4** (Scheme 1).

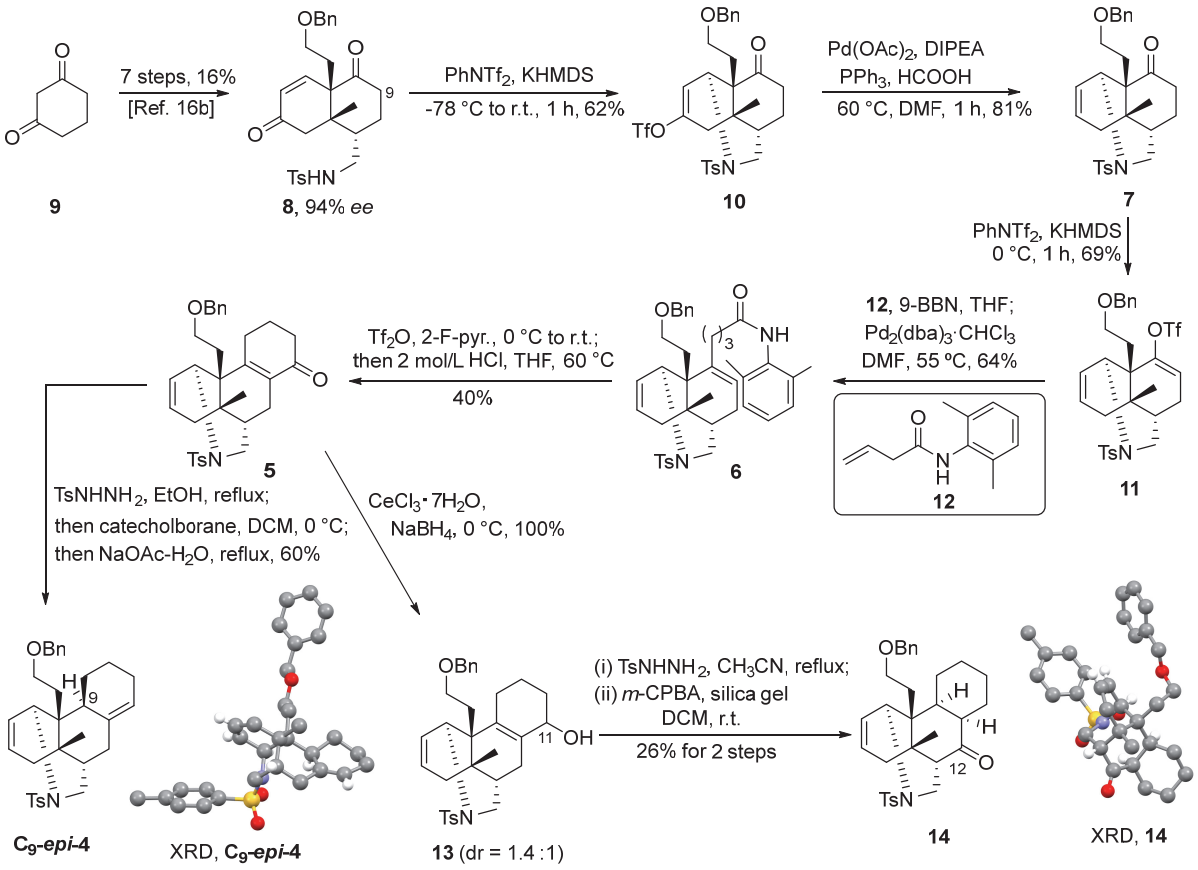
Specifically, a selective functionalization of the disubstituted alkene moiety in compound **4** would allow the installation of the desired isopropyl group, while a diastereoselective hydroboration of the trisubstituted alkene would introduce the ketone motif, which would be further converted to the carbinolamine functionality. In turn, we envision that a Hutchins-Kabalka reductive rearrangement of enone **5** would allow the construction of the trisubstituted alkene moiety in compound **4** as well as the desired stereocenter at C-9. Furthermore, the cyclohexenone motif in compound **5** could be fabricated from amide **6** via Huang's amide-activation-annulation. Last, amide **6** would be synthesized from tricycle ketone **7**, which could be further traced back to readily available chiral enone **8**.



Scheme 1 Retrosynthetic analysis of **1** and **2**.

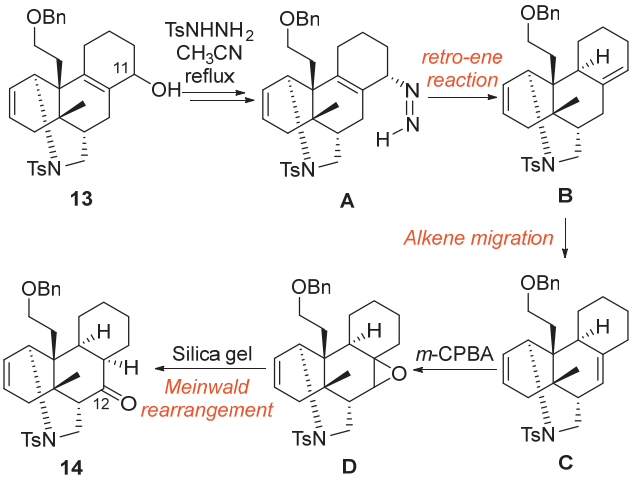
As shown in Scheme 2, we began our approach from chiral diketone **8**, which is readily available from 1,3-cyclohexandione (**9**) in seven steps.[16b] Subjecting diketone **8** to basic condition (KHMDS) triggered the desired aza-Michael addition. The so-afforded enol anion was then trapped with a triflating reagent ($PhNTf_2$) to give tricycle **10**. It is worth mentioning that only 1.0 equiv. of $PhNTf_2$ was used to avoid undesired enol triflation of the C-9 ketone. Subsequently, a palladium-mediated reduction of the enol triflate smoothly furnished the disubstituted alkene **7**. The C-9 ketone motif in intermediate **7** was then transformed to its corresponding enol triflate, as required in the next side chain installation. A Suzuki coupling reaction successfully introduced the amide-containing side chain to our core structure to give compound **6**. Next, Huang's amide-activation-annulation[19] was used to fabricate key cyclohexenone moiety in intermediate **5**. With this in mind, compound **6** was subjected to Tf_2O/2-F-Py condition, which triggered the amide activation process followed by the cyclization of the double bond on the nitrilium ion intermediate to afford corresponding *N*-arylcyclohexanimine. Without isolation, this *N*-arylcyclohexanimine moiety was then hydrolyzed under acidic conditions (2 mol/L HCl, THF, 60 °C) to produce cyclohexenone **5**.

At this juncture, it is required to set the C-9 stereocenter in a diastereoselective manner. Unfortunately, subjecting our enone substrate **5** to various Hutchins-Kabalka reductive rearrangement conditions[20] yielded **C$_9$-*epi*-4** as the sole product (Scheme 2). It is speculated that the reduction of the tosylhydrazone moiety occurred on the less sterically congested convex face, thus the following intramolecular hydride shift occurred on the *α*-face of our substrate. The stereochemistry of **C$_9$-*epi*-4** has been unambiguously assigned via single-crystal X-ray diffraction.[21] Alternatively, we noticed a unique method reported by Li *et al.*[22] that used allylic alcohol as substrate for Hutchins-Kabalka reductive rearrangement. With this in mind, enone **5** was first



Scheme 2 Synthesis of the tetracyclic core of **1** and **2**

subjected to reduction conditions ($NaBH_4$, $CeCl_3$•$7H_2O$) to quantitively produce allylic alcohol **13**, which was then subjected to Li's conditions ($TsNHNH_2$, acetonitrile, reflux) to yield a mixture of inseparable alkenes. To this end, this mixture was treated with *m*-CPBA/silica gel, with the hope to trigger a Meinwald rearrangement[23] to afford the corresponding C-11 ketone group. Surprisingly, compound **14** was isolated as the major product (26% for two steps). The structure of **14** was also unambiguously assigned via a single-crystal X-ray diffraction.[24] It is assumed that under Li's conditions, the so-afforded trisubstituted alkene might undergo a transannular migration and was then converted to C-12 ketone under Meinwald rearrangement conditions (Scheme 3).



Scheme 3 Plausible pathway for the formation of **14**.

3 Conclusions

In summary, we have investigated the synthesis toward two highly challenging alkaloids daphnezomines A and B. Through key transformations including an *aza*-Michael addition and a Huang's amide-activation-annulation, we successfully fabricated the tetracyclic core of daphnezomines A and B. Inspirative stereochemical information was also observed in the late-stage rearrangements, such as Hutchins-Kabalka reductive rearrangement and Meinwald rearrangement. As our interests in caged natural products continues,[25] further efforts toward the total synthesis of these structurally fascinating alkaloids are currently underway in our laboratory and will be reported in due course.

4 Experimental section

Commercially available reagents were used without further purification and all solvents were of HPLC quality. Unless otherwise stated, reactions were carried out under an atmosphere of argon and heating was performed in an oil bath. Reactions were monitored by thin-layer chromatography (TLC; GF254) using plates supplied by Yantai

Chemicals (China). The plates were visualized under UV-light. Flash column chromatography was performed using silica gel (particle size, 0.040～0.063 mm) supplied by Yantai Chemicals (China). High resolution mass spectra (HRMS) were recorded on a Thermo Scientifific Q Exactive Hybrid Quadrupole Orbitrap mass spectrometer. Single crystal X-ray diffraction (SCXRD) data were collected by a Bruker D8 Venture X-ray single crystal diffractometer. Optical rotation data were collected on an Autopol automatic polarimeter (Rudolph Research Analytical) using HPLC grade $CHCl_3$. All new compounds were characterized by ^1H NMR, ^{13}C NMR. NMR data were acquired at 298 K using a 400 MHz Bruker AVANCE III HD spectrometer equipped with a Prodigy CryoProbe. For spectra recorded in $CDCl_3$, chemical shifts were reported relative to the signal for $CHCl_3$ (δ 7.26 for ^1H NMR and δ 77.0 for ^{13}C NMR). NMR data was analyzed using a MestReNova (v11.0.3-18688) by Mestrelab Research S. L. All NMR spectra for compounds **10**, **7**, **11**, **6**, **5**, **4**, **13** and **14** can be found in Supplementary Materials.

4.1 Synthesis of (1*S*,4a*S*,5*S*,8a*R*)-8a-(2-(benzyloxy)ethyl)-4a-methyl-8-oxo-10-tosyl-1,4,4a,5,6,7,8,8a-octahydro-1,5-(epiminomethano)naphthalen-3-yl trifluoromethanesulfonate (**10**)

To a solution of enone **8** (7.00 g, 14.14 mmol, 1.0 equiv.) and $PhNTf_2$ (5.05 g, 14.14 mmol, 1.0 equiv.) in dry THF (141 mL) under argon atmosphere, was added a solution of 0.5 mol/L KHMDS (28.3 mL, 14.14 mmol, 1.0 equiv.) in THF at −78 °C. After being stirred for 1 h at room temperature, the reaction mixture was cooled to 0 °C and quenched with saturated aqueous NH_4Cl (100 mL). THF was removed under reduced pressure and the residue was dissolved in EtOAc (100 mL) and H_2O (50 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (100 mL×3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE (petroleum ether), V∶V=1∶20 to 1∶8) to give compound **10**. White oil (6.24 g, 62%); $[\alpha]_D^{24}$ +119.0 (*c* 0.10, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.49 (d, J=8.0 Hz, 2H), 7.40～7.30 (m, 5H), 7.19 (d, J=8.0 Hz, 2H), 4.94 (d, J=6.8 Hz, 1H), 4.62 (d, J=6.8 Hz, 1H), 4.46 (dd, J=11.2, 13.2 Hz, 2H), 3.89～3.77 (m, 2H), 3.75 -3.65 (m, 1H), 3.31 (d, J=12.4 Hz, 1H), 3.16～3.02 (m, 1H), 2.49 (dd, J=8.4, 18.4 Hz, 1H), 2.39 (s, 3H), 2.26 (dd, J=2.0, 7.6 Hz, 1H), 2.20～2.10 (m, 1H), 2.07～1.90 (m, 3H), 1.68～1.62 (m, 1H), 1.47～1.37 (m, 1H), 1.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 212.1, 149.7, 144.1, 138.3, 135.6, 129.9, 128.4, 127.6, 127.5, 126.8, 118.1 (q, J=321.18 Hz), 112.6, 73.0, 68.0, 53.7, 53.0, 45.3, 40.38, 40.35, 39.2, 38.7, 29.0, 26.4, 23.8, 21.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −74.38; HRMS (ESI) calcd for $[C_{29}H_{33}F_3NO_7S_2$ $[M+H]^+$ 628.1645, found 628.1642.

4.2 Synthesis of (1*S*,4a*S*,5*S*,8a*R*)-8a-(2-(benzyloxy)ethyl)-4a-methyl-10-tosyl-1,4a,5,6,7,8a-hexahydro-1,5-(epiminomethano)naphthalen-8(4H)-one (**7**)

To a mixture of compound **10** (13.20 g, 21.05 mmol, 1.0 equiv.), $Pd(OAc)_2$ (474 mg, 2.11 mmol, 0.1 equiv.), PPh_3 (1106 mg, 4.21 mmol, 0.2 equiv.) and DIPEA (21.0 mL, 126.32 mmol, 6.0 equiv.) in dry DMF (211 mL) under argon atmosphere, was added HCOOH (3.20 mL, 84.21 mmol, 4.0 equiv.) at room temperature. After being stirred for 1 h at 60 °C, the reaction mixture was concentrated under reduced pressure. Then the reaction mixture was dissolved with EtOAc (100 mL) and brine (100 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (100 mL×4). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE, V∶V=1∶20 to 1∶8) to give compound **7**. White foam (8.17 g, 81%); m.p. 114～116 °C; $[\alpha]_D^{24}$ +158.0 (*c* 0.31, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.60 (d, J=8.4 Hz, 2H), 7.35～7.33 (m, 4H), 7.30～7.24 (m, 3H), 5.84 (td, J=3.6, 10.0 Hz, 1H), 5.14～5.07 (m, 1H), 4.50 (dd, J=11.6, 24.0 Hz, 2H), 4.31 (d, J=6.0 Hz, 1H), 3.93 (td, J=4.9, 8.9 Hz 1H), 3.65 (dd, J=2.0, 11.6 Hz, 1H), 3.55 (td, J=6.4, 8.8 Hz, 1H), 3.30 (td, J=2.8, 12.8 Hz, 1H), 3.00 (dt, J=10.4, 18.0 Hz, 1H), 2.49～2.43 (m, 1H), 2.42 (s, 3H), 2.19～2.08 (m, 1H), 2.06～2.03 (m, 1H), 2.00～1.97 (m, 1H), 1.87～1.79 (m, 1H), 1.64～1.57 (m, 1H), 1.56～1.51 (m, 1H), 1.50～1.41 (m, 1H), 0.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 213.7, 143.4, 138.5, 136.6, 131.9, 129.6, 128.3, 127.7, 127.4, 127.2, 119.2, 73.1, 68.2, 53.9, 52.7, 45.7, 40.8, 38.8, 38.6, 36.6, 29.5, 26.3, 24.3, 21.5; HRMS (ESI) calcd for $C_{28}H_{34}NO_4S$ $[M+H]^+$ 480.2203, found 480.2200.

4.3 Synthesis of (1*S*,4a*S*,5*S*,8a*R*)-8a-(2-(benzyloxy)ethyl)-4a-methyl-10-tosyl-1,4,4a,5,6,8a-hexahydro-1,5-(epiminomethano)naphthalen-8-yl trifluoromethanesulfonate (**11**)

To a solution of enone **7** (11.30 g, 23.60 mmol, 1.0 equiv.) and $PhNTf_2$ (16.85 g, 47.20 mmol, 2.0 equiv.) in dry THF (240 ml) under argon atmosphere, was added a solution of 1.0 mol/L KHMDS (31.0 mL, 30.70 mmol, 1.3 equiv.) in THF at 0 °C. After being stirred for 30 min at 0 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl (100 mL). THF was removed under reduced pressure and the residue was dissolved in EtOAc (100 mL) and H_2O (50 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (100 mL×3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE, V∶V=1∶4 to 3∶7) to give compound **11** (10.00 g, 69%). White foam, m.p. 86 ～ 88 °C; $[\alpha]_D^{24}$ +133.2 (*c* 1.05, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.64 (d, J=8.4 Hz, 2H), 7.38～7.32 (m, 4H),

7.31～7.23 (m, 3H), 5.95 (td, *J*=3.6, 10.0 Hz, 1H), 5.76 (dd, *J*=2.8, 4.8 Hz, 1H), 5.46～5.38 (m, 1H), 4.57～4.41 (m, 2H), 4.14 (d, *J*=6.0 Hz, 1H), 3.88～3.77 (m, 1H), 3.63～3.53 (m, 1H), 3.37～3.17 (m, 2H), 2.49～2.42 (m, 1H), 2.41 (s, 3H), 2.27～2.18 (m, 1H), 2.01～1.86 (m, 3H), 1.83～1.72 (m, 1H), 1.42～1.36 (m, 1H), 0.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 148.4, 143.1, 138.0, 137.3, 131.7, 129.3, 128.2, 127.7, 127.4, 126.8, 119.9, 118.5, 118.1 (q, *J*=321.18 Hz), 73.2, 67.3, 50.5, 45.4, 43.5, 38.7, 38.3, 35.7, 28.9, 28.5, 22.7, 21.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −74.48; HRMS (ESI) calcd for $C_{29}H_{33}F_3NO_6S_2$ $[M+H]^+$ 612.1696, found 612.1694.

4.4 Synthesis of 4-((1*S*,4a*S*,5*S*,8a*R*)-8a-(2-(benzyloxy)ethyl)-4a-methyl-10-tosyl-1,4,4a,5,6,8a-hexahydro-1,5-(epiminomethano)naphthalen-8-yl)-*N*-(2,6-dimethylphenyl)butanamide (**6**)

A solution of compound **12** (434 mg, 2.30 mmol, 1.5 equiv.) and 9-BBN (12.2 mL, 6.12 mmol, 0.5 mol/L in THF, 4.0 equiv.) was stirred at room temperature for 16 h. An aqueous solution of K_3PO_4 (3.1 mL, 1.95 g, 9.18 mmol, 3.0 mol/L, 6.0 equiv.) was degassed under argon atmosphere, added slowly and the resulting biphasic mixture was stirred vigorously for 3 h. A solution of enol triflate **11** (935 mg, 1.53 mmol, 1.0 equiv.) in DMF (30 mL) was added and the mixture was purged from traces of hydrogen gas (vacuum was applied until the mixture started to boil and then the flask was refilled with argon). $AsPh_3$ (187 mg, 0.61 mmol, 0.4 equiv.) and $Pd_2(dba)_3$•$CHCl_3$ (158 mg, 0.153 mmol, 0.1 equiv.) were added and the resulting mixture was warmed to 55 °C. The resulting mixture was stirred at this temperature for 12 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (100 mL) and poured into water (50 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (50 mL×3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE, *V*∶*V*=1∶4) to give compound **6** (638 mg, 64%). White foam, m.p. 160～162 °C; $[\alpha]_D^{24}$ +106.5 (*c* 0.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 (s, 1H), 7.51 (d, *J*=8.0 Hz, 2H), 7.36～7.25 (m, 5H), 7.22 (d, *J*=8.0 Hz, 2H), 7.06 (s, 2H), 5.84 (dt, *J*=3.6, 10.0 Hz, 1H), 5.67 (s, 1H), 5.15 (dd, *J*=6.4, 10.0 Hz, 1H), 4.47 (dd, *J*=12.0, 16.4 Hz, 2H), 3.96 (d, *J*=6.4 Hz, 1H), 3.74～3.64 (m, 1H), 3.54～3.44 (m, 1H), 3.37 (dd, *J*=2.0, 12.0 Hz, 1H), 3.05 (dd, *J*=3.2, 12.0 Hz, 1H), 2.70～2.59 (m, 1H), 2.47～2.40 (m, 1H), 2.39 (s, 3H), 2.36～2.28 (m, 1H), 2.24 (s, 6H), 2.22～2.14 (m, 1H), 2.14～2.07 (m, 1H), 2.05～1.97 (m, 1H), 1.97～1.90 (m, 2H), 1.90～1.66 (m, 4H), 1.38～1.31 (m, 1H), 0.93 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.2, 143.0, 138.1, 137.2, 135.5, 134.9, 134.5, 132.5, 129.4, 128.38, 128.38, 128.0, 127.64, 127.64, 126.9, 126.8, 125.7, 119.9, 73.0, 68.0, 52.5, 46.0, 43.9, 40.1, 39.6, 36.7, 34.3, 32.1, 31.6, 30.7, 24.6, 23.8, 21.5, 18.5; HRMS (ESI) calcd for $C_{40}H_{47}N_2O_4S$ $[M+H]^+$ 653.3408, found 653.3405.

4.5 Synthesis of (4*S*,4a*S*,10*S*,10a*S*)-4a-(2-(benzyloxy)ethyl)-10a-methyl-12-tosyl-4,4a,5,6,7,9,10,10a-octahydro-4,10-(epiminomethano)phenanthren-8(1*H*)-one (**5**)

To a cooled (0 °C) solution of compound **6** (681 mg, 1.04 mmol, 1.0 equiv.) and 2-fluoropyridine (0.162 mL, 1.88 mmol, 1.8 equiv.) in dry DCM (20 mL) under argon atmosphere was added Tf_2O (0.228 mL 1.36 mmol, 1.3 equiv.). After being stirred for 15 mins at 0 °C, the solution was warmed to room temperature and stirred for 1 h. DCM was removed under reduced pressure and the residue was dissolved in THF (20 mL) and 2 mol/L HCl (10 mL). The resulting mixture was warmed to 60 °C and stirred for 13 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (20 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (20 mL×3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE, *V*∶*V*=1∶8 to 1∶4 to 1∶2) to give compound **5** (220 mg, 40%). Pale-yellow oil, m.p. 126～128 °C; $[\alpha]_D^{24}$ +122.3 (*c* 0.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54 (d, *J*=8.0 Hz, 2H), 7.39～7.26 (m, 5H), 7.22 (d, *J*=8.0 Hz, 2H), 5.93 (dt, *J*=3.2, 9.6 Hz ,1H), 5.23 (dd, *J*=6.4, 9.8 Hz, 1H), 4.47 (q, *J*=12.0 Hz, 2H), 4.04 (d, *J*=6.0 Hz, 1H), 3.69～3.60 (m, 1H), 3.47 (td, *J*=4.8, 9.2 Hz, 1H), 3.32 (dd, *J*=2.0, 12.0 Hz, 1H), 3.17～3.08 (m, 1H), 2.54～2.44 (m, 1H), 2.39 (s, 3H), 2.37～2.25 (m, 3H), 2.25～2.20 (m, 1H), 2.20～2.14 (m, 1H), 2.00～1.85 (m, 4H), 1.79～1.64 (m, 2H), 1.50～1.44 (m, 1H), 0.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 198.8, 155.7, 143.0, 137.9, 137.6, 134.9, 132.5, 129.5, 128.4, 127.72, 127.68, 126.7, 119.9, 73.0, 68.1, 52.5, 45.8, 45.6, 39.6, 39.5, 37.4, 34.0, 31.8, 28.0, 26.3, 24.6, 22.4, 21.5; HRMS (ESI) calcd for $C_{32}H_{38}NO_4S$ $[M+H]^+$ 532.2516, found 532.2516.

4.6 Synthesis of (4*S*,4a*R*,4b*S*,10*S*,10a*S*)-4a-(2-(benzyloxy)ethyl)-10a-methyl-12-tosyl-1,4,4a,4b,5,6,7,9,10,10a-decahy-dro-4,10-(epiminomethano)phenanthrene (**C$_9$-epi-4**)

To a solution of **5** (21 mg, 0.0395 mmol, 1.0 equiv.) in dry EtOH (3 mL) was added *p*-$TsNHNH_2$ (8.1 mg, 0.0435 mmol, 1.1 equiv.). The reaction mixture was stirred and heated under reflux for 4 h. The solvent was removed and the reaction flask was recharged with argon followed by adding of dry DCM (3 mL). The solution was cooled to 0 °C as catecholborane (7.1 mg, 0.0593 mmol, 1.5 equiv.) was injected into the flask. The reaction mixture was stirred at 0 °C for 3 h, after which $NaOAc$•$3H_2O$ (16 mg, 0.1185 mmol, 3.0 equiv.) was added into the solution at 0 °C. The mixture was allowed to warm to room temperature over 30 min, heated under reflux for 12 h, cooled down to room temperature, filtered, washed with DCM and concentrated under reducer pressure. At last, the residue was purified by column chromatography (eluent: EtOAc/

PE, V∶V=1∶4) to give **C9-*epi*-4** (12 mg, 60%). White solid, m.p. 120～122 ℃; $[\alpha]_D^{24}$ +12.0 (*c* 0.10, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.63 (d, J=8.4 Hz, 2H), 7.38～7.27 (m, 5H), 7.23 (d, J=8.0 Hz, 2H), 5.83 (td, J=3.4, 9.8 Hz, 1H), 5.28 (s, 1H), 5.09～5.02 (m, 1H), 4.54～4.44 (m, 2H), 3.81 (d, J=6.0 Hz, 1H), 3.65～3.56 (m, 1H), 3.46～3.38 (m, 1H), 3.24～3.09 (m, 2H), 2.72～2.62 (m, 1H), 2.50～2.42 (m, 1H), 2.41 (s, 3H), 2.33～2.24 (m, 1H), 2.03～1.85 (m, 4H), 1.79～1.74 (m, 1H), 1.74～1.69 (m, 1H), 1.68～1.61 (m, 1H), 1.60 (s, 2H), 1.50～1.40 (m, 2H), 0.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.0, 138.3, 138.0, 137.2, 132.7, 129.4, 128.4, 127.6, 127.6, 127.3, 121.1, 120.2, 73.2, 68.3, 57.5, 47.1, 42.0, 40.69, 40.65, 40.1, 35.9, 35.3, 29.7, 29.5, 25.2, 23.5, 22.9, 21.5; HRMS (ESI) calcd for $C_{32}H_{40}NO_3S$ $[M+H]^+$ 518.2723, found 518.2723.

4.7 Synthesis of (4*S*,4a*S*,10*S*,10a*S*)-4a-(2-(benzyloxy)ethyl)-10a-methyl-12-tosyl-1,4,4a,5,6,7,8,9,10,10a-decahydro-4,10-(epiminomethano)phenanthren-8-ol (**13**)

To a solution of **5** (380 mg, 0.72 mmol, 1.0 equiv.) and $CeCl_3 \cdot 7H_2O$ (400 mg, 1.07 mmol, 1.5 equiv.) in MeOH (7 mL) under 0 °C was added $NaBH_4$ (27 mg, 0.72 mmol, 1.0 equiv.). Then the solution was stirred at 0 °C in 30 min and quenched with saturated aqueous NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (20 mL×3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reducer pressure. At last, the residue was purified by column chromatography (eluent: EtOAc/PE, V∶V=1∶4) to give isomers **13a** and **13b**.

For **13a**: 222 mg, 58%. White foam, m.p. 125～127 ℃; $[\alpha]_D^{24}$ +116.0 (*c* 0.10, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.55 (d, J=8.4 Hz, 2H), 7.38～7.26 (m, 5H), 7.23 (d, J=8.0 Hz, 2H), 5.98 (dt, J=3.2, 9.6 Hz, 1H), 5.52～5.40 (m, 1 H), 4.47 (dd, J=12.0, 20.8 Hz, 2H), 4.13 (d, J=6.4 Hz, 1H), 3.90～3.81 (m, 1H), 3.69 (dt, J=6.0, 9.2 Hz, 1H), 3.51 (dt, J=4.8, 9.2 Hz, 1H), 3.27 (d, J=13.2 Hz, 1H), 3.07 (d, J=9.2 Hz, 2H), 2.47 (d, J=18.0 Hz, 1H), 2.39 (s, 3H), 2.35～2.21 (m, 2H), 2.11～2.02 (m, 1H), 1.98～1.83 (m, 4H), 1.82～1.67 (m, 2H), 1.64～1.59 (m, 1H), 1.57～1.47 (m, 1H), 1.36～1.29 (m, 1H), 0.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 142.7, 138.3, 138.2, 133.8, 133.1, 132.7, 129.6, 128.4, 127.7, 127.6, 126.4, 120.5, 73.0, 68.7, 67.4, 52.3, 45.1, 44.2, 40.1, 39.7, 34.2, 31.9, 31.4, 31.3, 25.9, 24.8, 21.5, 17.7; HRMS (ESI) calcd for $C_{32}H_{39}NNaO_4S$ $[M+Na]^+$ 556.2492, found 556.2491.

For **13b**: 159 mg, 42%. White foam, m.p. 155～157 ℃; $[\alpha]_D^{24}$ +130.0 (*c* 0.10, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.56 (d, J=8.4 Hz, 2H), 7.38～7.26 (m, 5H), 7.23 (d, J=8.0 Hz, 2H), 5.90 (dt, J=3.2, 9.6 Hz, 1H), 5.30～5.20 (m, 1H), 4.46 (dd, J=12.0, 18.0 Hz, 2H), 4.15～4.06 (m, 1H), 3.96 (d, J=6.4 Hz, 1H), 3.68 (dt, J=5.6, 9.2 Hz, 1H), 3.49 (dt, J=4.8, 9.6 Hz, 1H), 3.32 (d, J=12.4 Hz, 1H), 3.12 (d, J=12.4 Hz, 1H), 2.83～2.70 (m, 1H), 2.40 (s, 3H), 2.26～2.16 (m, 1H), 2.01～1.97 (m, 1H), 1.95～1.82 (m, 3H), 1.77 (s, 1H), 1.72～1.63 (m, 2H), 1.63～1.57 (m, 2H), 1.57～1.50 (m, 1H), 1.43～1.34 (m, 2H), 0.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 142.6, 138.4, 138.3, 134.1, 132.4, 132.3, 129.5, 128.4, 127.7, 127.6, 126.6, 120.6, 73.0, 70.9, 68.5, 52.1, 45.7, 43.9, 40.2, 39.8, 34.3, 32.8, 32.0, 31.8, 25.5, 24.5, 21.5, 19.6; HRMS (ESI) calcd for $C_{32}H_{39}NNaO_4S$ $[M+Na]^+$ 556.2492, found 556.2491.

4.8 Synthesis of (4*S*,4a*R*,4b*S*,8a*R*,10*S*,10a*S*)-4a-(2-(benzyloxy)ethyl)-10a-methyl-12-tosyl-4,4a,4b,5,6,7,8,8a,10,10a-decahydro-4,10-(epiminomethano)phenanthren-9(1*H*)-one (**14**)

To a solution of **13a** (or **13b**) (543 mg, 1.02 mmol, 1.0 equiv.) in dry CH_3CN (20 mL) was added *p*-$TsNHNH_2$ (1.89 g, 10.19 mmol, 10.0 equiv.). The reaction mixture was stirred and heated at reflux for 2 h. The solvent was removed and the residue was dissolved in DCM (30 mL). *m*-CPBA (415 mg, 85%, 2.04 mmol, 2.0 equiv.) and silica gel (1086 mg, 200% weight) were added and stirred at room temperature for about 10 h. The mixture was filtered, washed with DCM (30 mL×3) and concentrated under reducer pressure. At last, the residue was purified by column chromatography (eluent: EtOAc/PE, V∶V=1∶4) to give **14** (141 mg, 26%). White solid, m.p. 104～106 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, J=8.4 Hz, 2H), 7.42～7.34 (m, 4H), 7.34～7.29 (m, 1H), 7.26 (s, 1H), 7.24 (s, 1H), 5.77 (td, J=3.6, 10.0 Hz, 1H), 5.24～5.15 (m, 1H), 4.52 (dd, J=11.6, 22.8, 2H), 4.37 (d, J=6.0 Hz, 1H), 3.63～3.57 (m, 1H), 3.57～3.46 (m, 2H), 3.40 (dd, J=2.0, 12.6 Hz, 1H), 3.14 (dd, J=3.6, 12.8 Hz, 1H), 2.41 (s, 3H), 2.39～2.33 (m, 1H), 2.05～2.01 (m, 1H), 1.93～1.84 (m, 1H), 1.72～1.64 (m, 4H), 1.52～1.41 (m, 1H), 1.38～1.12 (m, 6H), 0.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 212.3, 143.6, 138.1, 136.7, 130.3, 129.7, 128.4, 127.7 (2C), 127.1, 121.2, 73.4, 65.9, 58.0, 57.2, 47.4, 43.9, 42.1, 39.8, 39.6, 38.2, 28.9, 27.7, 25.9, 25.4, 23.6, 21.9, 21.5; HRMS (ESI) calcd for $C_{32}H_{39}NNaO_4S$ $[M+Na]^+$ 556.2492, found 556.2492.

Supporting Information Experimental characterization data and copies of X-ray, ^1H NMR, ^{13}C NMR and ^{19}F NMR. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

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