

## First total synthesis of (–)- and (+)-6-*O*-desmethylantofine†

Meng Wu, Ling Li, Bo Su, Zhihui Liu and Qingmin Wang\*

Received 18th June 2010, Accepted 12th August 2010

DOI: 10.1039/c0ob00287a

The first total synthesis of (–)-6-*O*-desmethylantofine (**A**) and its unnatural enantiomer (+)-6-*O*-desmethylantofine (**B**) is described. The synthetic route is efficient and practical with easily available glutamic acid dimethyl ester hydrochloride as the chiral material under mild conditions.

### Introduction

In 1965, Haznagy isolated a compound from *C. vincetoxicum* and named it C-1.<sup>1</sup> In 1969, Wiegrebe also isolated C-1 from *C. vincetoxicum* and confirmed its configuration as (–)-6-*O*-desmethylantofine (**A**)<sup>2</sup> (Fig. 1).

(–)-Antofine (**C**) (Fig. 1) is known for its extremely potent inhibition of cancer cell growth. Antofine has IC<sub>50</sub> values in the low nanomolar range, comparable to that of clinically employed cytotoxic drugs.<sup>3</sup> As an analogue of (–)-antofine (**C**), (–)-6-*O*-desmethylantofine (**A**) has attracted more and more attention in recent years. There were many reports about *in vitro* cytotoxic activity of (–)-6-*O*-desmethylantofine (**A**) against the KB cancer cell lines,<sup>3a,4</sup> with IC<sub>50</sub> values lower than that of (–)-antofine (**C**). Cytotoxicity significantly increased for **A** relative to **C**, indicating that the hydroxy group at C6 is of importance.

We have previously reported that (–)-antofine (**C**), isolated from *Cynanchum komarovii*, possessed excellent antiviral activity against tobacco mosaic virus (TMV).<sup>5</sup> (–)-6-*O*-Desmethylantofine (**A**) was also isolated from the same plant for the first time and was found to exhibit better *anti*-TMV activity than (–)-antofine (**C**).<sup>6</sup>

Up to now, (–)-6-*O*-desmethylantofine (**A**) can only be obtained by isolation. However, its natural abundance is very low (about

0.003% of the extraction of the plant mentioned above),<sup>6</sup> which restricts our research on the antiviral agent. Thus, an efficient and general approach to prepare 6-*O*-desmethylantofine would be very desirable. Due to the hydroxyl group at C6, the synthesis of 6-*O*-desmethylantofine is difficult. Only a few syntheses of (±)-6-*O*-desmethylantofine have been reported.<sup>4b,7</sup> However, optically pure (–)-6-*O*-desmethylantofine (**A**) or its unnatural enantiomer (+)-6-*O*-desmethylantofine (**B**) has not been reported. Herein, we report the first total synthesis of (–)-6-*O*-desmethylantofine (**A**) and its enantiomer **B**.

### Results and discussion

Our synthetic route is shown in Scheme 1. Perkin condensation of 3,4-dimethoxybenzaldehyde (**1**) and 4-hydroxyphenylacetic acid (**2**) could easily afford (*E*)-2-(4-acetoxyphenyl)-3-(3,4-dimethoxyphenyl)acrylic acid (**3**), which was converted to its corresponding ester **4** with methanol in the presence of concentrated sulfuric acid. Remarkably, acetyl deprotection and esterification of **3** was accomplished in one pot to afford **4**.

To the best of our knowledge, intramolecular oxidative coupling using oxidative coupling reagents such as thallium(III) trifluoroacetate (TTFA),<sup>8</sup> lead(IV) tetraacetate (Pb(OAc)<sub>4</sub>),<sup>9</sup> vanadium oxytrifluoride (VOF<sub>3</sub>),<sup>10</sup> iron(III) chloride (FeCl<sub>3</sub>)<sup>11</sup> and manganese(IV) dioxides (MnO<sub>2</sub>)<sup>12</sup> is the most convenient way to construct phenanthrene ring system. To test the coupling of ester **4**, we tried many oxidative coupling reagents such as VOF<sub>3</sub>, FeCl<sub>3</sub> and MnO<sub>2</sub>. The reaction using FeCl<sub>3</sub> gave the best yield (58%), whereas no oxidative coupling product **5** was

State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, Nankai University, Tianjin, 300071, People's Republic of China. E-mail: wang98h@263.net; Fax: +86-22-23499842

† Electronic supplementary information (ESI) available: <sup>1</sup>H, <sup>13</sup>C NMR and HRMS spectra for the compounds **1–7**, **8a–11a**, **A**. (To avoid repetition, the NMR and HRMS spectra for **8b–11b**, **B** are not given.) See DOI: 10.1039/c0ob00287a

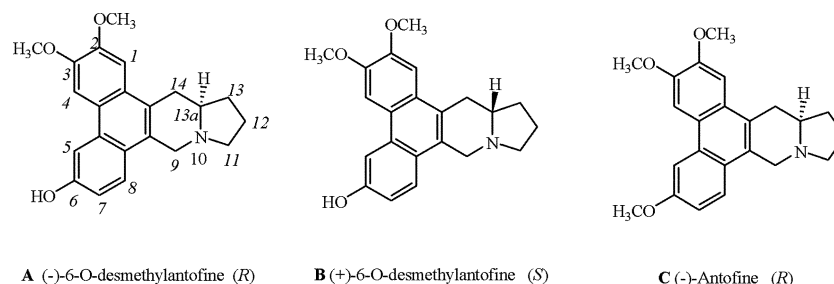
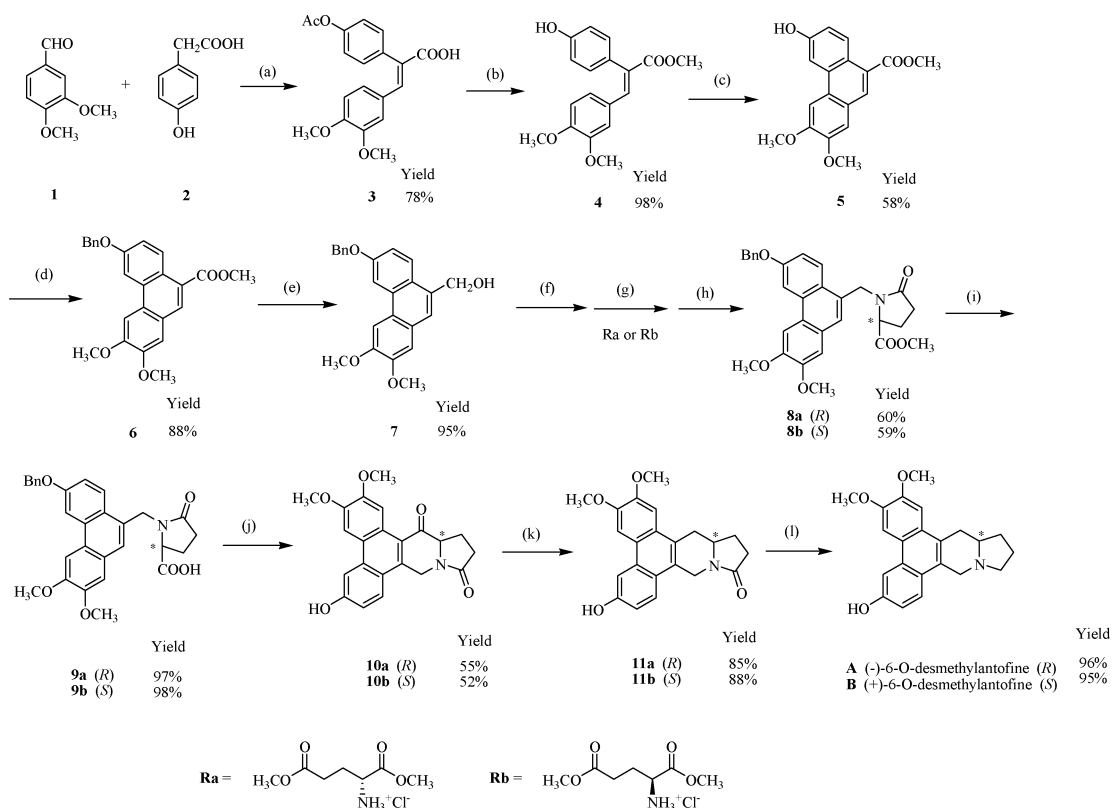


Fig. 1 Chemical structures of compounds **A**, **B** and **C**.



**Scheme 1** Synthesis of (-)-6-*O*-desmethylantofine (**A**) and (+)-6-*O*-desmethylantofine (**B**). Reagents and conditions: (a) Ac<sub>2</sub>O/Et<sub>3</sub>N; (b) CH<sub>3</sub>OH/concd. H<sub>2</sub>SO<sub>4</sub>; (c) FeCl<sub>3</sub>/CH<sub>2</sub>Cl<sub>2</sub>; (d) BnBr/K<sub>2</sub>CO<sub>3</sub>/CH<sub>3</sub>COCH<sub>3</sub>; (e) LiAlH<sub>4</sub>/THF; (f) PBr<sub>3</sub>/CH<sub>2</sub>Cl<sub>2</sub>; (g) Ra or Rb/K<sub>2</sub>CO<sub>3</sub>/DMF; (h) AcOH/MeOH; (i) KOH/MeOH/dioxane; (j) (COCl)<sub>2</sub>/CH<sub>2</sub>Cl<sub>2</sub>, SnCl<sub>4</sub>/CH<sub>2</sub>Cl<sub>2</sub> (k) NaBH<sub>4</sub>/EtOH, Et<sub>3</sub>SiH/CF<sub>3</sub>COOH/CH<sub>2</sub>Cl<sub>2</sub> (l) LiAlH<sub>4</sub>/THF.

found when using VOF<sub>3</sub> or MnO<sub>2</sub>. The coupling of ester **4** is much more complicated than that of polymethoxy substituted 2,3-diphenylacrylate.<sup>11b,12</sup> Then we protected the hydroxyl using a series of protecting groups such as acetyl, benzyl and methoxymethyl before coupling, but only to make the coupling reaction more complex.

Ester **5** was converted to its corresponding alcohol using lithium aluminium hydride, but the solubility of the corresponding alcohol was so poor that it was difficult to be purified, so it was impossible to be used in the following route. To improve the solubility in the following route, it is necessary to protect the hydroxy group. We introduced a benzyl group to compound **5** using benzyl bromide to afford **6**.

Ester **6** was easily converted to corresponding alcohol **7** by lithium aluminium hydride. **7** was treated with phosphorus tribromide and then reacted with D-glutamic acid dimethyl ester hydrochloride followed by cyclization in warm methanol and acetic acid to afford lactam ester **8a** successfully. The yield of the combined three steps from **7** to **8a** is high (60%). Ester **8a** was easily converted to the corresponding acid **9a** with potassium hydroxide.

The benzyl derivative was stable in strong base (KOH) and strong acid (HCl) from **8a** to **9a**. But interestingly, using SnCl<sub>4</sub> as Lewis acid, deprotection of benzyl group and intramolecular Friedel–Crafts acylation occurred in one pot to afford **10a** from **9a**.

**10a** was treated with sodium borohydride and then immediately converted to methylene using triethylsilane and trifluoroacetic acid

to give **11a**. At last, **11a** was reduced with lithium aluminium hydride to afford (-)-6-*O*-desmethylantofine (**A**). The overall yield is 9.68%. By the same procedure, we got (+)-6-*O*-desmethylantofine (**B**) using L-glutamic acid dimethyl ester hydrochloride in an overall yield of 9.32%. The enantiomeric excesses of **A** and **B** were determined. The *ee* values were 90% and 91% respectively.

## Conclusion

Optically pure (-)-6-*O*-desmethylantofine (**A**) and its enantiomer (+)-6-*O*-desmethylantofine (**B**) were first synthesized efficiently from cheap materials under mild conditions and their *ee* values is up to 90%. Intramolecular Friedel–Crafts acylation and deprotection of benzyl group of compounds **9a** and **9b** was successfully achieved in one pot using SnCl<sub>4</sub>. The chemistry described here provided a practical synthetic method of optically pure phenanthroindolizidine alkaloids for biochemical and pharmaceutical studies.

## Experimental

The melting points were determined with an X-4 binocular microscope melting-point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. <sup>1</sup>H NMR spectra were obtained by using Bruker AV 400 spectrometer. Chemical shifts (δ) were given in parts per million (ppm) and were measured downfield from internal tetramethylsilane. <sup>13</sup>C NMR spectra were recorded by using Bruker AV 400 (100 MHz) and CDCl<sub>3</sub> or DMSO-*d*<sub>6</sub> as a

solvent. Chemical shifts ( $\delta$ ) are reported in parts per million using the solvent peak. High-resolution mass spectra were obtained with an FT-ICR MS spectrometer (Ionspec, 7.0 T). The enantiomeric excesses of **A** and **B** were determined by HPLC with a Chiralcel AD-H column using Agilent 1100 instrument. Optical rotations were recorded with a Perkin-Elmer 341 MC polarimeter. All anhydrous solvents were dried and purified by standard techniques just before use.

**(E)-2-(4-Acetoxyphenyl)-3-(3,4-dimethoxyphenyl)acrylic acid (3).** A mixture of 4-hydroxyphenylacetic acid **2** (66.8 g, 0.44 mol), 3,4-dimethoxybenzaldehyde **1** (83.0 g, 0.44 mol), acetic anhydride (200 mL), and triethylamine (66.7 g, 0.66 mol) was heated at reflux for 9 h. The solution was cooled to room temperature, water (250 mL) was added, and the mixture was heated at reflux for 1 h. After being cooled to room temperature, the mixture was stirred in cold water for another 1 h. The precipitate was filtrated, washed with anhydrous ethanol to give **(E)-2-(4-Acetoxyphenyl)-3-(3,4-dimethoxyphenyl)acrylic acid 3** 117.4 g (78%), mp 244–247 °C;  $^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ ):  $\delta$  12.59 (br, 1 H, COOH), 7.72 (s, 1 H, C=CH), 7.23 (d,  $J = 7.6$  Hz, 2 H, Ar-H), 7.17 (d,  $J = 7.6$  Hz, 2 H, Ar-H), 6.87 (m, 2 H, Ar-H), 6.41 (s, 1 H, Ar-H), 3.72 (s, 3 H, OMe), 3.30 (s, 3 H, OMe), 2.22 (s, 3 H, COCH<sub>3</sub>);  $^{13}\text{C NMR}$  (100 MHz, DMSO)  $\delta$  169.2, 168.3, 149.8, 149.7, 147.8, 139.5, 134.3, 130.7, 129.6, 126.6, 125.2, 122.1, 111.9, 111.1, 55.3, 54.5, 20.8. HRMS (ESI): calcd. for C<sub>19</sub>H<sub>18</sub>O<sub>6</sub> [M - H]<sup>+</sup> 341.1031; found 341.1031.

**(E)-3-(3,4-Dimethoxyphenyl)-2-(4-hydroxyphenyl)acrylic acid methyl ester (4).** Compound **3** (40.4 g, 118.1 mmol) was added to dry methanol (600 mL). Concentrated sulfuric acid (24.1 g) was added, and the solution was stirred at reflux for 10 h. Most of the methanol was removed by rotary evaporation, and the residue was redissolved in dichloromethane and washed with saturated sodium hydrogen carbonate. The organic phase was dried over sodium sulfate, filtered, and evaporated to give 36.0 g (97%) of **4**. mp 127–128 °C;  $^1\text{H NMR}$  (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.76 (s, 1 H, C=CH), 7.10 (d,  $J = 8.4$  Hz, 2 H, Ar-H), 6.83–6.85 (m, 3 H, Ar-H), 6.73 (d,  $J = 8.4$  Hz, 1 H, Ar-H), 6.48 (d,  $J = 1.6$  Hz, 1 H, Ar-H), 3.84 (s, 3 H, OMe), 3.79 (s, 3 H, OMe), 3.46 (s, 3 H, OMe);  $^{13}\text{C NMR}$  (100 MHz, CDCl<sub>3</sub>)  $\delta$  169.2, 155.6, 149.9, 148.0, 140.6, 131.2, 129.5, 128.0, 127.5, 125.5, 115.9, 112.4, 110.4, 55.7, 55.1, 52.4. HRMS (ESI): calcd. for C<sub>18</sub>H<sub>18</sub>O<sub>5</sub> [M + Na]<sup>+</sup> 337.1046; found 337.1041

**6-Hydroxy-2,3-dimethoxyphenanthrene-9-carboxylic acid methyl ester (5).** To a solution of **4** (10.10 g, 32.17 mmol) in dichloromethane (250 mL) was added anhydrous Iron(III) chloride (13.07 g, 80.41 mmol). The reaction solution was stirred at room temperature for 4.5 h, and then quenched with methanol (50 mL). Then H<sub>2</sub>O (200 mL) was added, and the mixture was stirred for an additional 0.5 h. The water phase was extracted with dichloromethane, the combined organic phase was dried over sodium sulfate and filtered. The solvent was removed by rotary evaporation, and the crude product was purified by column chromatography (petroleum ether/EtOAc, 3:1, v/v) to give 5.82 g (58%) of **5** as a white solid. mp 188–190 °C;  $^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ ):  $\delta$  9.91 (s, 1 H, Ar-OH), 8.66 (d,  $J = 9.2$  Hz, 1 H, Ar-H), 8.26 (s, 1 H, Ar-H), 8.03 (s, 1 H, Ar-H), 7.94 (s, 1 H, Ar-H), 7.59 (s, 1 H, Ar-H), 7.18 (d,  $J = 8.8$  Hz, 1

H, Ar-H), 4.04 (s, 3 H, OMe), 3.93 (s, 3 H, OMe), 3.92 (s, 3 H, OMe);  $^{13}\text{C NMR}$  (100 MHz, CDCl<sub>3</sub>)  $\delta$  168.3, 154.1, 150.9, 149.7, 131.9, 129.6, 128.6, 126.5, 125.5, 123.7, 123.2, 116.6, 109.1, 106.4, 103.1, 55.9, 52.1. HRMS (ESI): calcd. for C<sub>18</sub>H<sub>16</sub>O<sub>5</sub> [M + Na]<sup>+</sup> 335.0890; found 335.0889

**6-Benzyloxy-2,3-dimethoxyphenanthrene-9-carboxylic acid methyl ester (6).** To a solution of **5** (15.24 g, 48.85 mmol) in acetone (300 mL) was added benzyl bromide (10.02 g, 58.62 mmol), and potassium carbonate (10.11 g, 73.28 mmol). The reaction mixture was stirred for 10 h at reflux, then filtered. The filtrate was concentrated. The residue was purified by column chromatography (petroleum ether/EtOAc/CH<sub>2</sub>Cl<sub>2</sub>, 60:10:1, v/v/v) to give 17.28 g (88%) of **6** as a white solid. mp 156–157 °C;  $^1\text{H NMR}$  (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.94 (d,  $J = 9.2$  Hz, 1 H, Ar-H), 8.31 (s, 1 H, Ar-H), 7.97 (d,  $J = 2.8$  Hz, 1 H, Ar-H), 7.78 (s, 1 H, Ar-H), 7.54 (d,  $J = 7.2$  Hz, 2 H, Ar-H), 7.40–7.44 (m, 2 H, Ar-H), 7.34–7.37 (m, 2 H, Ar-H), 7.26 (s, 1 H, Ar-H), 5.30 (s, 2 H, benzyl-CH<sub>2</sub>), 4.10 (s, 3 H, OMe), 4.03 (s, 3 H, OMe), 4.01 (s, 3 H, OMe);  $^{13}\text{C NMR}$  (100 MHz, CDCl<sub>3</sub>)  $\delta$  168.1, 157.2, 150.9, 149.6, 136.9, 131.6, 129.6, 128.7, 128.4, 128.1, 127.6, 126.7, 125.5, 123.7, 123.3, 116.2, 109.2, 106.0, 103.1, 70.4, 56.0, 55.9, 52.1. HRMS (ESI): calcd. for C<sub>25</sub>H<sub>22</sub>O<sub>5</sub> [M + Na]<sup>+</sup> 425.1359; found 425.1352

**(6-Benzyloxy-2,3-dimethoxyphenanthren-9-yl)methanol (7).** To a mixture of lithium aluminium hydride (2.84 g, 74.78 mmol) in tetrahydrofuran (150 mL) at 0 °C was added dropwise a solution of **6** (10.02 g, 24.93 mmol) in tetrahydrofuran (150 mL). The solution was stirred at room temperature for 20 min, then heated at reflux for another 1.5 h. Then the solution was brought back to 0 °C, dichloromethane (200 mL) was added, followed by 2 N hydrochloric acid (70 mL). The solution was separated, the water phase was extracted with dichloromethane, the combined organic phase was dried over sodium sulfate and filtered. The solvent was removed by evaporation to give 9.12 g (97.9%) of **7** as a white solid. mp 184–186 °C;  $^1\text{H NMR}$  (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.10 (d,  $J = 8.8$  Hz, 1 H, Ar-H), 7.98 (d,  $J = 2.8$  Hz, 1 H, Ar-H), 7.78 (s, 1 H, Ar-H), 7.53–7.55 (m, 3 H, Ar-H), 7.40–7.44 (m, 2 H, Ar-H), 7.30–7.37 (m, 2 H, Ar-H), 7.19 (s, 1 H, Ar-H), 5.29 (s, 2 H, benzyl-CH<sub>2</sub>), 5.13 (d,  $J = 6.0$  Hz, 2 H, CH<sub>2</sub>), 4.08 (s, 3 H, OMe), 4.023 (s, 3 H, OMe), 1.75 (t,  $J = 6.0$  Hz, 1 H, OH);  $^{13}\text{C NMR}$  (100 MHz, DMSO- $d_6$ )  $\delta$  156.6, 149.3, 148.7, 137.2, 133.8, 131.0, 128.4, 127.9, 127.8, 126.7, 125.8, 123.8, 123.4, 121.8, 115.7, 108.5, 106.0, 104.0, 69.5, 61.6, 55.8, 55.4. HRMS (ESI): calcd. for C<sub>24</sub>H<sub>22</sub>O<sub>4</sub> [M + Na]<sup>+</sup> 397.1410; found 397.1402

**(R)-1-((6-Benzyloxy-2,3-dimethoxyphenanthren-9-yl)methyl)-5-oxo-pyrrolidine-2-carboxylic acid methyl ester (8a).** Compound **7** (9.30 g, 24.87 mmol) was dissolved in dry dichloromethane (500 mL) and cooled to 0 °C. A solution of phosphorus tribromide (3.5 mL, 37 mmol) in dichloromethane (20 mL) was added dropwise. The solution was then stirred at room temperature overnight, then poured over ice water, the water phase was extracted with dichloromethane (40 mL  $\times$  2). The combined organic phase was dried over sodium sulfate, filtered and evaporated to give a white solid. The solid was then dissolved in *N,N*-dimethylformamide (300 mL). *D*-Glutamic acid dimethyl ester hydrochloride (7.89 g, 37.31 mmol) was added and allowed to

stir for 20 min. Potassium carbonate (5.15 g, 37.31 mmol) was added, and the mixture was allowed to stir at room temperature for 12 h. The solution was then distilled under reduced pressure to remove *N,N*-dimethylformamide. To the residue was added dichloromethane and water. The water phase was extracted with dichloromethane. The combined organic phase was dried over sodium sulfate, filtered and rotary evaporated. The crude product was dissolved in methanol (200 mL) and acetic acid glacial (120 mL) and stirred for 8 h at 45–50 °C. The solution was rotary evaporated, and the crude product was purified by column chromatography (petroleum ether/EtOAc, 2:1 then 1:1, v/v) to give 7.49 g (60%) of **8a** as a white solid. mp 182–183 °C;  $[\alpha]_D^{20}$  –56.0 (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.03 (d, *J* = 8.8 Hz, 1 H, Ar–H), 7.97 (d, *J* = 2.4 Hz, 1 H, Ar–H), 7.78 (s, 1 H, Ar–H), 7.52–7.54 (m, 2 H, Ar–H), 7.40–7.44 (m, 2 H, Ar–H), 7.34–7.37 (m, 2 H, Ar–H), 7.31 (dd, *J* = 2.4, 8.8 Hz, 1H, Ar–H), 7.16 (s, 1 H, Ar–H), 5.50 (d, *J* = 14.4 Hz, 1 H, N–CH<sub>2</sub>), 5.28 (s, 2 H, benzyl-CH<sub>2</sub>), 4.40 (d, *J* = 14.4 Hz, 1 H, N–CH<sub>2</sub>), 4.09 (s, 3 H, OMe), 4.03 (s, 3 H, OMe), 3.84 (dd, *J* = 2.8, 9.2 Hz, 1 H, N–CH), 3.58 (s, 3 H, OMe), 2.55–2.64 (m, 1 H, N–CH–CH<sub>2</sub>), 2.04–2.48 (m, 1 H, NCO–CH<sub>2</sub>), 2.08–2.18 (m, 1 H, N–CH–CH<sub>2</sub>), 1.95–2.02 (m, 1 H, NCO–CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 174.6, 172.3, 157.4, 149.6, 149.4, 137.0, 131.7, 128.7, 128.1, 127.7, 127.6, 126.6, 126.2, 126.2, 124.6, 124.4, 115.8, 108.2, 106.4, 103.3, 70.4, 58.6, 56.0, 55.9, 52.2, 44.4, 29.8, 22.8. HRMS (ESI): calcd. for C<sub>30</sub>H<sub>29</sub>NO<sub>6</sub> [M + Na]<sup>+</sup> 522.1887; found 522.1883

**(R)-1-((6-Benzyloxy-2,3-dimethoxyphenanthren-9-yl)methyl)-5-oxo-pyrrolidine-2-carboxylic acid (9a).** Compound **8a** (2.18 g, 4.37 mmol) was stirred in a solution of dioxane (50 mL), methanol (40 mL) and 2 mol L<sup>-1</sup> aqueous potassium hydroxide (30 mL) for 2 h. The mixture was rotary evaporated to remove dioxane and methanol, and the resulting mixture was cooled to 0 °C and acidified with 2 mol L<sup>-1</sup> hydrochloric acid until pH = 1–2, then washed with water and dried to give 2.08 g (98%) of **9a** as a white solid. mp 276–278 °C;  $[\alpha]_D^{20}$  –67.6 (*c* 0.5, DMF); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.21 (d, *J* = 2.4 Hz, 1 H, Ar–H), 8.02 (s, 1 H, Ar–H), 7.96 (d, *J* = 9.2 Hz, 1 H, Ar–H), 7.57–7.59 (m, 2 H, Ar–H), 7.40–7.45 (m, 4 H, Ar–H), 7.33–7.37 (m, 1 H, Ar–H), 7.30 (dd, *J* = 2.4, 9.2 Hz, 1H, Ar–H), 5.38 (d, *J* = 14.8 Hz, 1 H, N–CH<sub>2</sub>), 5.37 (s, 2 H, benzyl-CH<sub>2</sub>), 4.23 (d, *J* = 15.2 Hz, 1 H, N–CH<sub>2</sub>), 4.02 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 3.75 (dd, *J* = 2.8, 9.2 Hz, 1 H, N–CH), 2.33–2.43 (m, 2 H, N–CH–CH<sub>2</sub>, NCO–CH<sub>2</sub>), 2.13–2.23 (m, 1 H, NCO–CH<sub>2</sub>), 1.90–1.96 (m, 1 H, N–CH–CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 174.1, 173.1, 156.9, 149.4, 149.2, 137.1, 131.3, 128.4, 128.0, 127.9, 127.5, 126.3, 125.5, 124.8, 123.9, 123.7, 116.0, 108.5, 106.2, 104.0, 69.5, 58.0, 55.8, 55.4, 43.3, 29.2, 22.4. HRMS (ESI): calcd. for C<sub>29</sub>H<sub>27</sub>NO<sub>6</sub> [M – H]<sup>+</sup> 484.1766; found 484.1765

**(R)-6-Hydroxy-2,3-dimethoxyphenanthro[9,10-*b*]-11,14-indolizidinedione(10a).** To a solution of **9a** (1.44 g, 2.97 mmol) in dry dichloromethane (100 mL) was added oxalyl chloride (0.49 g, 3.86 mmol) and *N,N*-dimethylformamide (0.1 mL). The mixture was stirred for 4.5 h at room temperature. Tin(IV) chloride (0.69 mL, 5.94 mmol) was added slowly under nitrogen at 0 °C, and then the mixture was stirred overnight at 35 °C under nitrogen. The solution was cooled to room temperature, and 2 mol L<sup>-1</sup> hydrochloric acid (70 mL) was added. The organic phase was

rotary evaporated, and the crude product was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>–EtOAc, 3:1, v/v) to give 0.62 g (55%) of **10a** as a light-yellow solid. mp 260–261 °C;  $[\alpha]_D^{20}$  –94.4 (*c* 0.5, DMF); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 10.41 (s, 1 H, Ar–OH), 8.99 (s, 1 H, Ar–H), 8.14 (d, *J* = 8.8 Hz, 1 H, Ar–H), 8.02 (d, *J* = 2.0 Hz, 1 H, Ar–H), 7.95 (s, 1 H, Ar–H), 7.23 (dd, *J* = 2.0, 8.8 Hz, 1 H, Ar–H), 5.55 (d, *J* = 18.4 Hz, 1 H, 9-H), 4.78 (d, *J* = 18.0 Hz, 1 H, 9-H), 4.54–4.57 (m, 1 H, 13a-H), 4.02 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 2.30–2.44 (m, 4 H, 12-H, 13-H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 196.1, 172.8, 159.2, 149.6, 148.4, 139.6, 133.9, 127.3, 123.7, 123.3, 120.3, 119.8, 117.5, 107.4, 106.7, 103.5, 60.5, 55.3, 55.1, 39.9, 29.4, 20.4. HRMS (ESI): calcd. for C<sub>22</sub>H<sub>19</sub>NO<sub>5</sub> [M + Na]<sup>+</sup> 400.1155; found 400.1152

**(R)-6-Hydroxy-2,3-dimethoxyphenanthro[9,10-*b*]-11-quinolizidinone(11a).** A mixture of **10a** (0.41 g, 1.09 mmol), sodium borohydride (0.12 g, 3.26 mmol) and ethanol (50 mL) was stirred for 40 min at room temperature. The mixture was cooled to 0 °C, and then 2 mol L<sup>-1</sup> hydrochloric acid (10 mL) was added slowly. Dichloromethane (100 mL) and water (50 mL) was added to the solution, then the water phase was extracted with dichloromethane (30 mL). The combined organic phase was dried over sodium sulfate, filtered, and rotary evaporated, and the product was dissolved in dry dichloromethane (50 mL), and then triethylsilane (0.63 g, 5.44 mmol) and trifluoroacetic acid (1.24 g, 20.88 mmol) was added. The mixture was stirred for 3.5 h at 33–36 °C. The solution was cooled to room temperature, and dichloromethane (50 mL) and water (50 mL) was added. The water phase was extracted with dichloromethane (20 mL × 3). The combined organic phase was rotary evaporated, and the crude product was purified by column chromatography (petroleum ether/EtOAc, 1:3, v/v and then CH<sub>2</sub>Cl<sub>2</sub>–EtOAc, 1:8, v/v) to give 0.34 g (85%) of **11a** as a light-yellow solid. mp 221 °C dec;  $[\alpha]_D^{20}$  –85.6 (*c* 1, DMF); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.76 (s, 1 H, Ar–H), 7.74 (s, 1 H, Ar–H), 7.55 (d, *J* = 8.8 Hz, 1 H, Ar–H), 7.10 (d, *J* = 8.4 Hz, 1 H, Ar–H), 7.04 (s, 1 H, Ar–H), 6.94 (s, 1 H, OH), 5.30 (d, *J* = 17.2 Hz, 1 H, 9-H), 4.47 (d, *J* = 17.2 Hz, 1 H, 9-H), 4.06 (s, 3 H, OMe), 4.01 (s, 3 H, OMe), 3.93–3.94 (m, 1H, 13a-H), 3.30–3.34 (m, 1H, 14-H), 2.53–2.78 (m, 4H, 14-H, 12-H, 13-H), 2.00–2.09 (m, 1H, 13-H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 173.1, 155.6, 149.0, 148.2, 130.0, 125.7, 124.0, 123.4, 123.2, 122.8, 121.6, 116.5, 106.5, 104.1, 103.9, 55.4, 55.3, 52.3, 40.1, 32.1, 29.4, 24.4. HRMS (ESI): calcd. for C<sub>22</sub>H<sub>21</sub>NO<sub>4</sub> [M + H]<sup>+</sup> 364.1543; found 364.1540

**(–)-6-O-desmethylantofine (A).** A mixture of **11a** (0.18 g, 0.50 mmol), lithium aluminium hydride (0.04 g, 1.00 mmol) and tetrahydrofuran (25 mL) was heated at reflux under nitrogen for 0.5 h. The solution was cooled to 0 °C, at which point EtOAc (10 mL) was added dropwise, followed by water (20 mL). Then dichloromethane (100 mL) and methanol (50 mL) was added, then the water phase was extracted with dichloromethane (20 mL × 3). The combined organic phase was dried over sodium sulfate, filtered and evaporated, then the product was placed under vacuum in the dark for 2 h to give 0.16 g (94%) of **A** as a white solid. mp: 217–218 °C (lit.<sup>2</sup> 226–228 °C);  $[\alpha]_D^{20}$  –51.2 (*c* 0.25, MeOH) (lit.<sup>4</sup>  $[\alpha]_D^{20}$  –54.5 (*c* 0.88, MeOH)); 90% *ee* [flow rate 1.0 mL min<sup>-1</sup>, n-hexane/2-propanol 85:15 and 0.1% triethylamine, 254 nm, *t*<sub>R</sub> (major) = 22.75 min, *t*<sub>R</sub> (minor) = 25.14 min]. <sup>1</sup>H NMR (400 MHz,

DMSO-*d*<sub>6</sub>):  $\delta$  9.69 (s, 1 H, OH), 7.95 (s, 1 H, Ar-H), 7.92 (s, 1 H, Ar-H), 7.73 (d,  $J$  = 8.8 Hz, 1 H, Ar-H), 7.31 (s, 1 H, Ar-H), 7.09 (d,  $J$  = 9.2 Hz, 1 H, Ar-H), 4.55 (d,  $J$  = 15.2 Hz, 1 H, 9-H), 3.99 (s, 3 H, OMe), 3.94 (s, 3 H, OMe), 3.53 (d,  $J$  = 14.8 Hz, 1 H, 9-H), 3.30–3.35 (m, 2 H, 13a-H, 11-H), 2.72–2.78 (m, 1 H, 11-H), 2.32–2.38 (m, 2 H, 14-H), 2.12–2.18 (m, 1 H, 13-H), 1.82–1.90 (m, 2 H, 12-H), 1.59–1.69 (m, 1 H, 13-H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  155.3, 149.0, 148.0, 129.9, 126.3, 126.1, 124.4, 124.0, 122.6, 122.2, 116.2, 106.4, 104.0, 103.9, 59.8, 55.4, 55.3, 54.4, 53.2, 32.9, 30.8, 21.1. HRMS (ESI): calcd. for C<sub>22</sub>H<sub>23</sub>NO<sub>3</sub> [M + H]<sup>+</sup> 350.1751; found 350.1753

**(S)-1-((6-Benzyloxy-2,3-dimethoxyphenanthren-9-yl)methyl)-5-oxo-pyrrolidine-2-carboxylic acid methyl ester (8b)**. With the L-Glutamic acid dimethyl ester hydrochloride as a material, a procedure analogous to the preparation of **8a** was used, **7** (8.52 g, 22.78 mmol) give **8b** (6.70 g, 59%) as a white solid: mp 182–183 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> 52.4 (*c* 1, CH<sub>2</sub>Cl<sub>2</sub>); other data are the same as those for **8**.

**(S)-1-((6-Benzyloxy-2,3-dimethoxyphenanthren-9-yl)methyl)-5-oxo-pyrrolidine-2-carboxylic acid (9b)**. A procedure analogous to the preparation of **9a** was used, **8b** (3.06 g, 6.12 mmol) gave **9b** (2.91 g, 98%) as a white solid: mp 277–279 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> 40.8 (*c* 0.5, DMF); other data are the same as those for **9**.

**(S)-6-Hydroxy-2,3-dimethoxyphenanthro[9,10-*b*]-11,14-indolizidinedione(10b)**. A procedure analogous to the preparation of **10a** was used, **9b** (2.00 g, 4.12 mmol) gave **10b** (0.80 g, 52%) as a light-yellow solid. mp 253–255 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> 63.4 (*c* 1, DMF); other data are the same as those for **10a**.

**(S)-6-Hydroxy-2,3-dimethoxyphenanthro[9,10-*b*]-11-quinolizidinone(11b)**. A procedure analogous to the preparation of **11a** was used, **10b** (0.52 g, 1.38 mmol) gave **11b** (0.44 g, 88%) as a light-yellow solid. mp 230 °C dec; [ $\alpha$ ]<sub>D</sub><sup>20</sup> 56.2 (*c* 1, DMF); other data are the same as those for **11a**.

**(+)-6-O-desmethylantofine (B)**. A procedure analogous to the preparation of **A** was used, **11a** (0.20 g, 0.55 mmol) gave **12a** (0.18 g, 95%) as a white solid. mp: 219–220 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> 66.4 (*c* 0.25, Methanol); 91% *ee* [flow rate 1.0 mL min<sup>-1</sup>, n-hexane/2-propanol 85:15 and 0.1% triethylamine, 254 nm, *t*<sub>R</sub> (major) = 25.02 min, *t*<sub>R</sub> (minor) = 22.80 min]. other data are the same as those for **B**.

## Acknowledgements

We are grateful to the National Key Project for Basic Research (2010CB126100) and the National Natural Science Foundation of China (20872072, 30890143) for generous financial support for our programs

## Notes and references

- (a) A. Haznagy, K. Szendrei and L. Toth, *Pharmazie*, 1965, **20**(9), 541–548; (b) A. Haznagy, L. Toth and K. Szendrei, *Pharmazie*, 1965, **20**, 649–651; (c) L. Ferenczy, J. Zsolt, A. Haznagy, L. Toth and A. Szendrei, *Acta Microbiol. Acad. Sci. Hung.*, 1965, **66**(12), 337–344.
- W. Wiegrebe, L. Faber, H. Brockman and K. U. Bidzikiewicz, *Justus Liebigs Ann. Chem.*, 1969, **721**, 154–162.
- (a) D. Staerk, A. K. Lykkeberg, J. Christensen, B. A. Budnik, F. Abe and J. W. Jaroszewski, *J. Nat. Prod.*, 2002, **65**, 1299–1302; (b) S. K. Lee, K.-A. Nam and Y.-H. Heo, *Planta Med.*, 2003, **69**, 21–25.
- (a) A. Toribio, A. Bonfils, E. Delannay, E. Prost, D. Harakat, E. Henon, B. Richard, M. Litaudon, J.-M. Nuzillard and J.-H. Renault, *Org. Lett.*, 2006, **8**(17), 3825–3828; (b) Y. Fu, S. K. Lee, H. Y. Min, T. Lee, J. W. Lee, M. S. Chengd and S. H. Kim, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 97–100.
- (a) T. Y. An, R. Q. Huang, Z. Yang, D. K. Zhang, G. R. Li, Y. C. Yao and J. Gao, *Phytochemistry*, 2001, **58**, 1267–1269; (b) Y. C. Yao, T. Y. An, J. Gao, Z. Yang, X. S. Yu, Z. Jin, G. R. Li, R. Q. Huang, C. X. Zhu and F. J. Wen, *Chin. J. Org. Chem.*, 2001, **21**, 1024–1028; (c) G. R. Li, T. Y. An, Z. Yang, R. Q. Huang, Z. G. Li, Y. C. Yao, X. S. Yu, and J. Gao, CN 132164 2A, 2001 [Chem. Abstr. 137: 76069].
- (a) Q. M. Wang, K. L. Wang, Z. Q. Huang, Y. X. Liu, H. Li, T. S. Hu, Z. Jin, Z. J. Fan, R. Q. Huang CN 101189968, 2008 [Chem. Abstr. 149: 97630]; (b) Z. Q. Huang, Y. X. Liu, Z. J. Fan, Q. M. Wang, G. R. Li, Y. C. Yao, X. S. Yu and R. Q. Huang, *Fine Chemical Intermediates (Ch.)*, 2007, **37**, 20–24.
- (a) W. Wiegrebe, L. Faber and H. Budzikiewicz, *Justus Liebigs Ann. Chem.*, 1970, **733**, 125–140; (b) D. S. Bhakuni and P. K. Gupta, *Indian J. Chem.*, 1982, **21B**(5), 393–395.
- (a) E. C. Taylor, J. G. Andrade, G. J. H. Rall and A. Mckillop, *J. Am. Chem. Soc.*, 1980, **102**, 6513–6519; (b) A. Mckillop, A. G. Turrell, D. W. Young and E. C. Taylor, *J. Am. Chem. Soc.*, 1980, **102**, 6504–6512; (c) G. Bringmann, R. Walter and R. Weirich, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 977–991.
- K. S. Feldman and S. M. Ensel, *J. Am. Chem. Soc.*, 1994, **116**, 3357–3366.
- (a) B. Halton, A. I. Maidment, D. L. Officer and J. M. Warner, *Aust. J. Chem.*, 1984, **37**, 2119–2128; (b) D. A. Evans, C. J. Dinsmore, D. A. Evrard and K. M. DeVries, *J. Am. Chem. Soc.*, 1993, **115**, 6426–6427; (c) A. Furstner and J. W. J. Kennedy, *Chem.-Eur. J.*, 2006, **12**, 7398–7410.
- (a) K. L. Wang, M. Y. Lü, A. Yu, X. Q. Zhu and Q. M. Wang, *J. Org. Chem.*, 2009, **74**, 935–938; (b) K. L. Wang, M. Y. Lü, Q. M. Wang and R. Q. Huang, *Tetrahedron*, 2008, **64**, 7504–7510.
- K. L. Wang, Y. N. Hu, Z. Li, M. Wu, Z. H. Liu, B. Su, A. Yu, Y. Liu and Q. M. Wang, *Synthesis*, 2009, **7**, 1083–1090.