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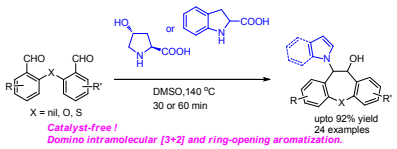

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A novel and efficient method for the direct synthesis of pyrrolyl or indolyl substituted 9,10-dihydrophenanthren-9-ol analogues

Qi Xia, Xinlei Zhao, Juan Zhang, Jiayi Wang* and Gonghua Song*

Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, Shanghai, 200237, P. R. China.

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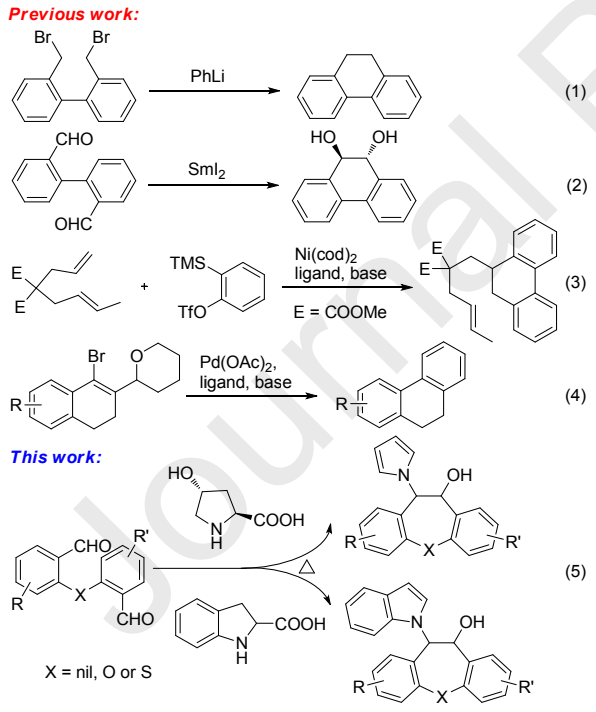
ABSTRACT

A novel domino intramolecular [3+2] cycloaddtion and ring-opening aromatization process has been successfully developed for the efficient direct synthesis of pyrrolyl or indolyl substituted 9,10-dihydrophenanthren-9-ol analogues. And 1-(phenanthren-9-yl)-1*H*-pyrroles can be easily obtained *via* dehydration of 10-(1*H*-pyrrol-1-yl)-9,10-dihydrophenanthren-9-ols. Furthermore, the MTT assay indicated that four compounds with indolyl substitutions showed obvious inhibitory activities against HepG2 cells, and compound *anti*-**4jb** displayed a lowest IC_{50} value of 9.99 μM.

* Corresponding author. Tel.: +86 21 64253140; fax: +86 21 6425 2603; e-mail:jiayi.wang@ecust.edu.cn, ghsong@ecust.edu.cn

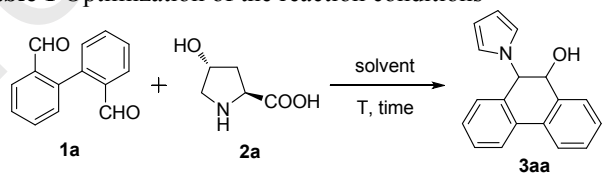
As an important class of polycyclic compounds, 9,10-dihydrophenanthrene derivatives, existing in many synthetic and natural products,[1] have shown various biological activities, such as antitumour,[2] antifungal,[3] antimicrobial,[4] antialgal,[5] antimalarial,[6] cytotoxic activities,[7] and so on. They are also useful building blocks in material science.[8] Therefore, the development of efficient methods for the synthesis of 9,10-dihydrophenanthrenes is of high interests. Hall and Turner[9] reported the synthesis of 9,10-dihydrophenanthrene through the reaction of 2,2'-di-(bromomethtl)diphenyl with lithium phenyl (eq 1). Suzuki[10] and Uemura[11] independently developed a SmI_2 catalyzed intramolecular pinacol coupling strategy to obtain the *trans*-9,10-dihydrophenanthrene-9,10-diol from 2,2'-dicarbonyl-1,1'-biphenyls.(eq 2). You and coworkers[12] modified the process into a one-pot cascade reaction. Sato and coworkers[13] reported a nickel-catalyzed [2+2+2] cycloaddition of arynes and alkenes (eq 3). Ray and coworkers[14] developed a palladium-assisted 6π electrocyclic reaction to obtain 9,10-dihydrophenanthrenes (eq 4). Although the reported methods are somehow effective to the construction of a 9,10-dihydrophenanthrene skeleton, they suffer from some drawbacks, such as the starting materials were not commercially available, transition metal catalysts were unavoidable in many cases, and limited substrate scopes. To the best of our knowledge, the direct synthesis of pyrrolyl or indolyl substituted 9,10-dihydrophenanthren-9-ols has not yet been reported. Thus, the development of a novel and efficient approach to the direct construction of pyrrolyl or indolyl substituted 9,10-dihydrophenanthren-9-ol analogues is highly desirable.



In our previous work, we reported the synthesis of *N*-β-hydroxyethyl pyrroles and indoles from the reaction of aldehyde with *trans*-4-hydroxy-L-proline or indoline-2-carboxylic acid via a domino [3+2] cycloaddition and ring-opening aromatization process.[15] However, the transformation was not applicable to the aromatic aldehydes bearing an electron-donating or a weak electron-withdrawing group due to the low reactivity between aldehydes and azomethineylides in the intermolecular [3+2] cycloaddition. Fortunately, by replacing the two molecules of the aldehyde with a dialdehyde molecule participated in the intramolecular [3+2] cycloaddition, a novel methodology for the direct synthesis of pyrrolyl or indolyl substituted 9,10-dihydrophenanthren-9-ol analogues with wide substituent diversity was successfully accomplished and reported herein (eq 5).

At the outset, the assumption was tested by reaction of [1,1'-biphenyl]-2,2'-dicarbaldehyde **1a** with *trans*-4-hydroxy-L-proline **2a** in *N*,*N*-dimethylformamide (DMF) at 150 ℃. Gratifyingly, the expected product 10-(1*H*-pyrrol-1-yl)-9,10-dihydrophenanthren-9-ol **3aa** was obtained in 85% yield (Table 1, entry 1). Inspired by this result, we started to optimize the reaction conditions to improve the reaction efficiency. Among the solvents screened, dimethyl sulfoxide (DMSO) was found to be the most efficient solvent with a desired product yield of 91% (Table 1, entry 2). Xylenes was inferior and produced the product in 40% yield (Table 1, entry 3). Other solvents, such as toluene, 1,2-dichloroethane (DCE), acetonitrile, and ethanol, gave only trace of products (Table 1, entries 3-7). Furthermore, no desired product was detected in the solvent of 1,4-dioxane, tetrahedronfuran (THF) and water (Table 1, entries 8-10). By increasing the amount of **2a** (0.90 mmol), no considerable improvement was observed (Table 1, entry 11), whereas decreasing the amount of **2a** (0.60 mmol) lowered the yield obviously (Table 1, entry 12). In addition, by increasing or decreasing the reaction time did not show any further improvement in the product yield (Table 1, entries 13-14). Further investigation indicated that 140 ℃ was the optimal reaction temperature at which the product was obtained in a yield of 92% (Table 1, entries 15-17). Thus, the optimized condition was determined as follows: [1,1'-biphenyl]-2,2'-dicarbaldehyde **1a** (0.5 mmol), *trans*-4-hydroxy-L-proline **2a**

Table 1 Optimization of the reaction conditions[a]



Entry	**2a** (mmol)	Solvent	T (°C)	Time (min)	Yield[b] (%)[dr][c]
1	0.75	DMF	150	30	85[87:13]
2	0.75	DMSO	150	30	91[87:13]
3	0.75	Xylenes	150	30	40[86:14]
4	0.75	Toluene	150	30	trace
5	0.75	DCE	150	30	trace
6	0.75	MeCN	150	30	trace
7	0.75	EtOH	150	30	trace
8	0.75	1,4-Dioxane	150	30	0
9	0.75	THF	150	30	0
10	0.75	H_2O	150	30	0
11	0.90	DMSO	150	30	90[87:13]
12	0.60	DMSO	150	30	78[87:13]
13	0.75	DMSO	150	20	88[87:13]
14	0.75	DMSO	150	40	84[87:13]
15	0.75	DMSO	160	30	87[87:13]
16	**0.75**	**DMSO**	**140**	**30**	**92[87:13]**
17	0.75	DMSO	130	30	72[87:13]

[a] Reaction conditions: [1,1'-biphenyl]-2,2'-dicarbaldehyde **1a** (0.5 mmol) and *trans*-4-hydroxy-L-proline in 1.5 mL solvent were stirred in a 10 mL-glass tube sealed with a cap in an oil bath at indicated temperature for 20-40 min.

[b] Isolated yields based on **1a**.

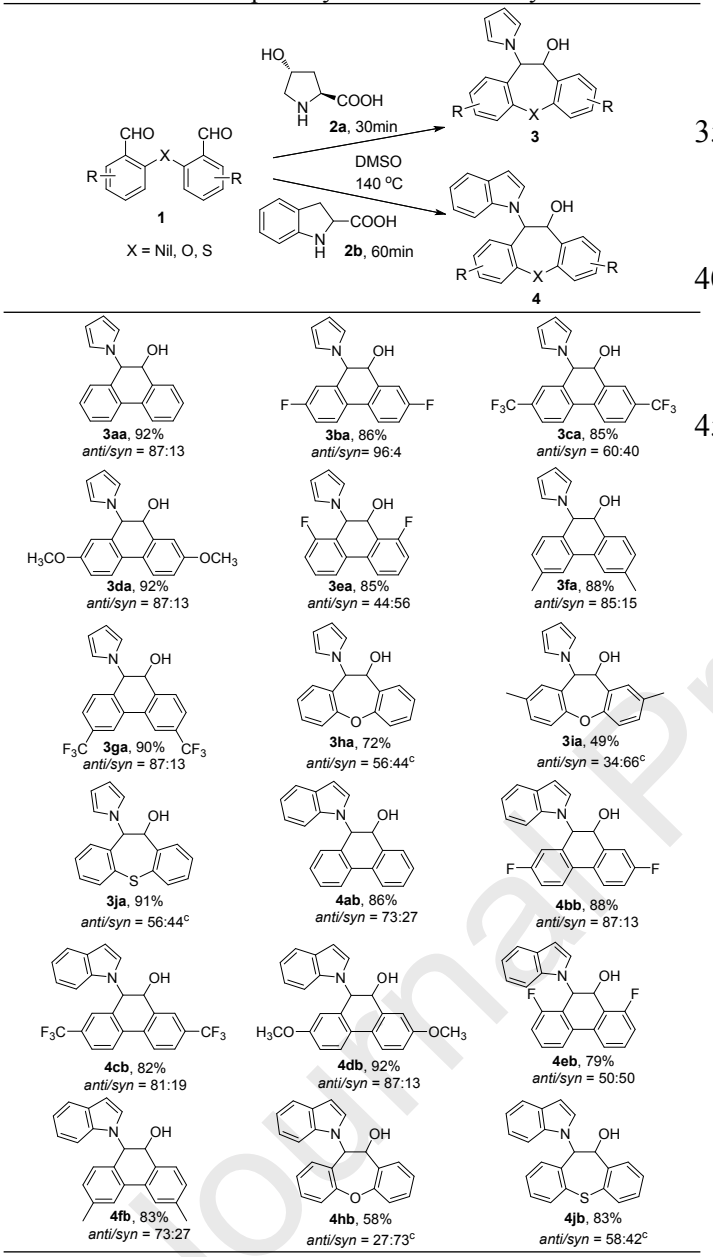
c Determined by ^{1}H-NMR.

(0.75 mmol), DMSO (1.5 mL) as solvent, and a 30-min reaction time at 140 ℃.

With the optimized conditions in hand, the generality of the reaction was evaluated by altering the diadldehydes and cyclic amino acids. At first, the symmetrical dialdehyde compounds were allowed to react with *trans*-4-hydroxy-L-proline **2a** or indoline-2-carboxylic acid **2b**. As shown in Table 2, the symmetrical [1,1'-biphenyl]-2,2'-dicarbaldehydes **1a-1g** afforded

the dihydrophenanthren-9-ols **3aa**-**3ga** and 10-(1*H*-indol-1-yl)-9,10-dihydrophenanthren-9-ols **4ab**-**4fb** in good to excellent yields of 79%-92% after the reaction. 2,2'-Oxydibenzaldehyde **1h** and 6,6'-oxybis(3-methylbenzaldehyde) **1i** generated pyrrol or indole substituted 10,11-dihydrodibenzo[b,f]oxepin-10-ols (**3ha**-**3ia** and **4hb**) in moderate yields. Furthermore, 2,2'-thiodibenzaldehyde **1j** was also applicable in this transformation and gave the corresponding 10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ols **3ja** and **4jb** in 91% and 83% yields, respectively. It should be noted that both electron-withdrawing (-F and -CF_3) and electron-donating groups (-Me, -OMe) on the phenyl ring werewell tolerated in this transformation. Except for products **3ea**, **3ia**, **4eb** and **4hb**, the *anti* diastereomers were obtained as the major products in most cases. And 2,7-difluoro-10-(1*H*-pyrrol-1-yl)-9,10-dihydrophenanthren-9-ol **4jb** was also obtained with high diastereoselectivity (*anti*/*syn* = 96:4).

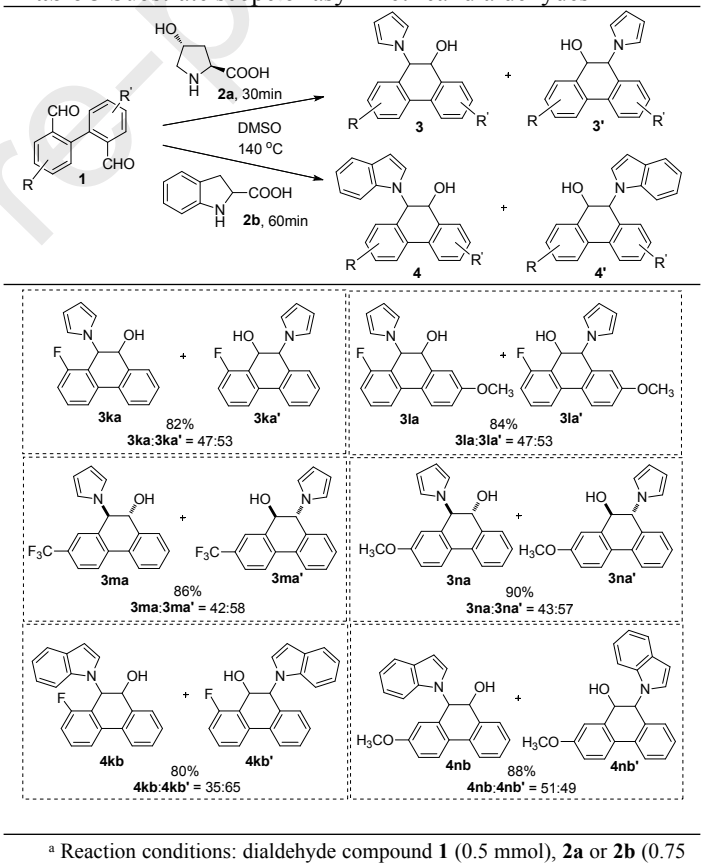
Table 2 Substrate scope of symmetrical dialdehydes [a,b]



[a] Reaction conditions: dialdehyde compound **1** (0.5 mmol), **2a** or **2b** (0.75 mmol) in 1.5 mL DMSO were stirred in a 10 mL-glass tube sealed with a cap in an oil bath at 140 ℃ for 30- or 60-min. [b] Isolated yields based on 1. Unless otherwise mentioned, the diastereomeric ratios were determined by ^{1}H NMR. [c] Diastereomeric ratios were calculated from the yields of the separated diastereomeric products.

Next, the scope of asymmetrical dialdehydes was also investigated (Table 3). In order to verify the regioselectivity of the reaction, we began with the reaction of 3-fluoro-[1,1'-Biphenyl]-2,2'-dicarboxaldehyde **1k** with *trans*-4-hydroxy-L-proline **2a**. As anticipated, two regioisomers **3ka** and **3ka'** were obtained by column chromatography with a ratio of 47:53. The structure of 1-fluoro-10-(1*H*-pyrrol-1-yl)-9,10-dihydrophenanthren-9-ol **3ka** was proved by the presence of the doublet peak at δ 54.6 ppm in the ^{13}C NMR spectrum, while two doublet peaks at δ 72.0 and 64.1 ppm identified the structure of **3ka'**. Similar results were also obtained for the reaction of dialdehyde **1l** with *trans*-4-hydroxy-L-proline **2a**, and dialdehyde **1k** with indoline-2-carboxylic acid **2b**. Interestingly, for the [1,1'-biphenyl]-2,2'-dicarbaldehydes bearing only one substituent at the C4-position, the reactions with *trans*-4-hydroxy-L-proline **2a** could diastereoselectively afford the *anti* diastereomers (**3ma and 3ma', 3na and 3na'**) in good yields of 86%-90%. The structures of **3ma** and **3na** were further confirmed by X-ray diffraction analysis (Fig. 1).[17] However, the reaction between dialdehyde **1n** and indoline-2-carboxylic acid **2b** lead to an inseparable diastereomeric mixture of **4nb** and **4nb'** in a total yield of 88%.[18]

Table 3 Substrate scope of asymmetrical dialdehydes [a,b]



[a] Reaction conditions: dialdehyde compound **1** (0.5 mmol), **2a** or **2b** (0.75 mmol) in 1.5 mL DMSO were stirred in a 10 mL-glass tube sealed with a cap in an oil bath at 140 ℃ for 30- or 60-min. [b] Isolated yields based on **1**. The ratios of **3**:**3'** and 4:4'were determined by ^{1}H NMR.

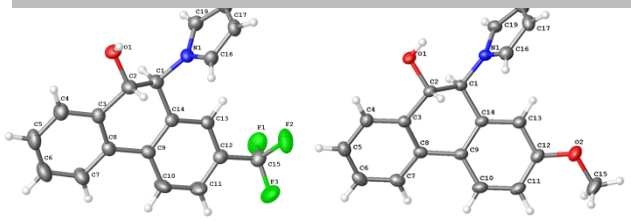
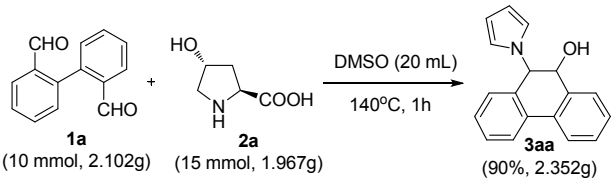


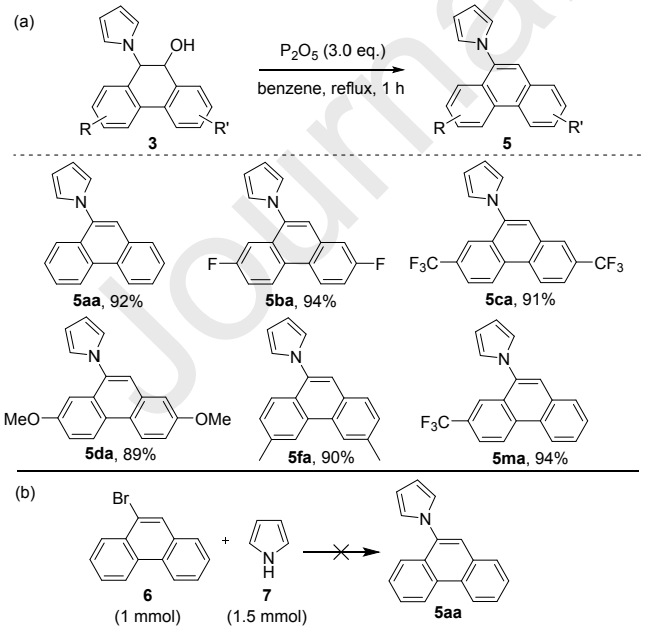
Figure 1. Crystal structures of **3ma** and **3na**.



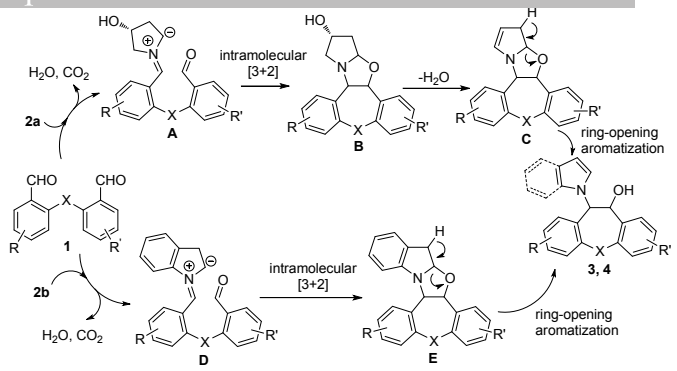
Scheme 1. Gram-scale synthesis of **3aa**.

In order to prove the practicality of the method, we carried out a gram-scale experiment under optimized conditions (Scheme 1). The product **3aa** was obtained in 90% yield with the reaction of 10 mmol of **1a** and 15 mmol of **2a**. Next, six 1-(phenanthren-9-yl)-1*H*-pyrroles (**5aa**-**5da**, **5fa** and **5ma**) were obained in 89-94% yields through the dehydration of 10-(1*H*-pyrrol-1-yl)-9,10-dihydrophenanthren-9-ols with P_2O_5 in benzene (Scheme 2, (a)). We also attempted to synthesize 1-(phenanthren-9-yl)-1*H*-pyrrole **5aa** from the reaction of 9-bromophenanthrene **6** and pyrrole **7**. However, no desired product was detected under various Ullmann reaction conditions (Scheme 2, (b))[19].

Based on the literatures[16b,20] and our previous work,[15] a plausible reaction mechanism was proposed in Scheme 3. The reaction of one aldehyde group from the dialdehyde compound with *trans*-4-hydroxy-L-proline **2a** or indoline-2-carboxylic acid **2b** produces an azomethineylide intermediate **A** or **D**, which undergoes intramolecular [3+2] cycloaddition with another aldehyde group and gave the bicyclic 1,3-oxazolidine **B** or **E**. Dehydration of **B** forms intermediate **C**. The final product **3** or **4** was accomplished through the ring-opening aromatization of corresponding intermediate **C** or **E**, respectively.



Scheme 2. Synthesis of 1-(phenanthren-9-yl)-1*H*-pyrroles.



Scheme 3. Proposed mechanism.

Table 4 IC_{50} values of compounds on the viability of HepG2 cells.

Compd.	IC_{50} (μM)	Compd.	IC_{50} (μM)
3aa	>50	**4eb**	>50
3ba	>50	*anti*-**4eb**	>50
3ca	>50	syn-**4hb**	>50[a]
3da	>50	*anti*-**4hb**	>50
3ha	>50	*anti*-**4jb**	9.99
3ja	>50	**5aa**	>50
4ab	43.97	**5ba**	>50
anti-**4ab**	35.94	**5ca**	>50
4cb	>50	**5da**	>50
anti-**4cb**	22.45	**5ma**	>50
4db	>50	doxorubicin	5.75
anti-**4db**	>50		

With the synthesized pyrrolyl or indolyl substituted 9,10-dihydrophenanthren-9-ol analogues and 1-(phenanthren-9-yl)-1*H*-pyrroles in hand, we further evaluated their cytotoxicity on human hepatocellular carcinoma cells (HepG2) with the MTT assay. Among the tested compounds, four compounds showed obvious inhibitory activities, and the IC_{50} values on the viability of HepG2 cells after 24 h incubation in the presence of the tested compounds were shown in Table 4. Interestingly, all the four active compounds contained the indoly-substitution, and the *anti* diastereomers showed lower IC_{50} values than those of their diastereomeric mixtures (*anti*-**4ab**, 35.94 μM *vs* **4ab**, 43.97 μM; *anti*-**4cb**, 22.45 μM *vs* **4cb**, >50 μM). Compound *anti*-**4jb** exhibited the highest activity aginst HepG2 cells with an IC_{50} value of 9.99 μM, while the IC_{50} value of the positive control doxorubicin was 5.75 μM. The results indicate that the indoly substituted 10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ols might serve as potential lead compounds for anticancer drug discovery.

In conclusion, a domino catalyst-free intramolecular [3+2] cycloaddition and ring-opening aromatization process between dialdehyde compounds and *trans*-4-hydroxy-L-proline or indoline-2-carboxylic acid has been successfully developed for the efficient direct synthesis of pyrrolyl or indolyl substituted 9,10-dihydrophenanthren-9-ols, 10,11-dihydrodibenzo[*b*,*f*]oxepin-10-ols and 10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ols. Both electron-withdrawing and electron-donating groups on the phenyl ring are well tolerated in this transformation. And the reaction can be smoothly enlarged to gram-scale. Besides, 1-(phenanthren-9-yl)-1*H*-pyrroles can be easily obtained via the dehydration of 10-(1*H*-pyrrol-1-yl)-9,10-dihydrophenanthren-9-ols. Furthermore, the indolyl-substituted *anti* diastereomers showed potential better activity against HepG2 cells than diastereomeric mixtures in the cytotoxic activity test, and the compound *anti*-**4jb** displayed the lowest IC_{50} value of 9.99 μM. Further studies both on the application of the synthetic method and on the bioactivity of synthesized compounds are ongoing in our laboratory.

Ack

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Supplementary Material

Supplementary data (experimental procedures, characterization data of products, and copies of ^{1}H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at http://....

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17. CCDC 1539494 (**3ma**) and 1539495 (**3na**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
18. Table S1-S5 contains the detailed analysis of NMR spectra of **3ka**-**3na**, **4kb** and **4nb**. Please see Supplementary Material for details.
19. For examples of Ullmann reaction between aryl bromide and pyrrole, see: (a) R.M. Adhikari, D.C. Beckers, J. Org. Chem. 74 (2009) 3341. (b) X. Li, D. Yang, Y. Jiang, H. Fu, Green Chem. 12 (2010) 1097. (c) J. Richardson, J.C. Ruble, E.A. Love, S. Berritt, J. Org. Chem. 82 (2017) 3741. (d) Z.C. Cao, X.L. Li, Q.Y. Luo, H. Fang, Z.J. Shi, Org. Lett. 20 (2018) 1995.
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Highlights

- ✓ A domino intramolecular [3+2] cycloaddition and ring-opening aromatization process.
- ✓ Direct synthesis of pyrrolyl or indolyl substituted 9,10-dihydrophenanthren-9-ol analogues
- ✓ Compound *anti*-**4jb** displayed a lowest IC_{50} value of 9.99 μM (24 h) against HepG2 cells.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: