Tetrahedron 69 (2013) 1229–1233

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Enantioselective Diels–Alder reaction of anthrone and maleimide catalyzed by a simple chiral tertiary amine

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ARTICLE INFO

Article history:
Received 6 June 2012
Received in revised form 22 October 2012
Accepted 2 November 2012
Available online 16 November 2012

Keywords:
Diels–Alder reactions
Anthrones
Maleimide
Chiral tertiary amine

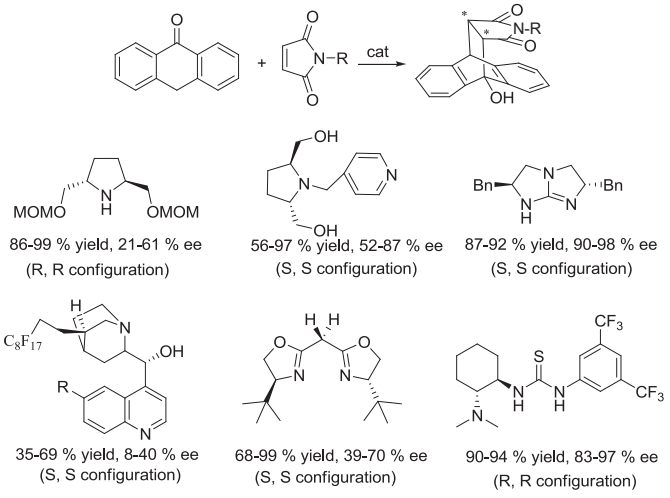
ABSTRACT

Simple chiral tertiary amines with a special imide skeleton were first successfully applied to catalyze the enantioselective D–A reaction of anthrone and maleimides in excellent yields (up to 96%) and enantioselectivities (up to 95% ee).

1. Introduction

The Diels–Alder reaction is one of the most straightforward and atom economical methods to construct chiral six-membered carbocyclic compounds in organic chemistry.[1] Among all the dienes, anthrone has been considered as one of the powerful diene component and can react with a variety of dienophiles.[2] Particularly, the cycloadditions of anthrone with *N*-substituted maleimide to construct anthrone derivatives, which are key intermediates for the preparations of some unsaturated lactams with antipsoriatic and antiproliferative biological activities, have been studied extensively.[3] Chiral bases, such as cinchona alkaloids,[4] pyrrolidine derivatives,[5] cyclic guanidines,[6] bisoxazolines,[7] and tertiary amine thioureas[8] have been used to promote those reactions in moderate to excellent enantioselectivities (Scheme 1). However either substrate scopes or enantioselectivities in this reaction were limited in most cases.

In the past years, chiral amines have been widely used as powerful promoters in asymmetric catalyses.[9] In particular, chiral 1,2-diphenylethane-1,2-diamine and cyclohexane-1,2-diamine are frequently used in asymmetric catalysis.[10] Imide protected tertiary amines with these chiral scaffolds, the key intermediates for the preparation of chiral catalysts, have drawn less attention as catalysts.[11] Recently, our group has successfully applied chiral monoimide protected cyclohexane-1,2-diamines to catalyze enantioselective double Michael reaction of *N*-Boc-3-nonsubstituted oxindoles with dienones in up to 98% yield and 89% ee.[12] Based on this backgrounds and our everlasting interests in development of new catalytic system for the enantioselective reaction of maleimide,[13] and the constructions of complex spiro- and bridged chiral moieties.[14] We wish to report our study on Diels–Alder



Scheme 1. Base-catalyzed Diels–Alder reaction of anthrones and maleimides.

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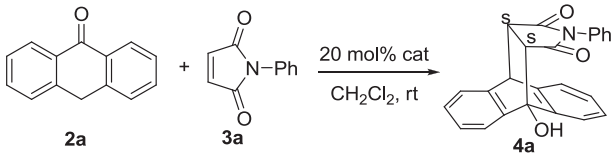
http://dx.doi.org/10.1016/j.tet.2012.11.011

reactions of anthrones and maleimides catalyzed by a simple chiral tertiary amine with a special and less reported imide skeleton.

2. Results and discussion

We first found that the reaction of anthrone **2a** and *N*-phenylmaleimide **3a** were performed smoothly with 20 mol % chiral tertiary amine **1a** in good yield and moderate enantioselectivity (90% yield, 55% ee; Table 1, entry 1). A series of chiral tertiary amine catalysts **1b**–**g** were then prepared via simple procedures (Fig. 1), and in an initial screening of catalytic activity, anthrone **2a** and *N*-phenylmaleimide **3a** were used as model reactants and the results were summarized in Table 1.

Table 1
Catalyst screenings[a]



2a 3a 4a

Entry	Catalyst	Time (h)	Yield[b] (%)	ee (%)[c,d]
1	**1a**	6	91	55
2	**1b**	6	75	23
3	**1c**	30	85	11
4	**1d**	48	Nd	Nd
5	**1e**	20	83	47
6	**1f**	20	78	50
7	**1g**	6	81	35
8	**1h**	18	77	51

[a] Unless otherwise specified, all reactions were carried out using maleimide **3a** (0.24 mmol), anthrone **2a** (0.2 mmol), and catalyst (20 mol %) in CH_2Cl_2 (0.6 mL) at room temperature.
[b] Isolated yield.
[c] Enantiomeric excess was determined by HPLC using Chiralpak AD-H column.
[d] The absolute configuration of the product was determined as (*S*,*S*) by comparing with reported data.[6]

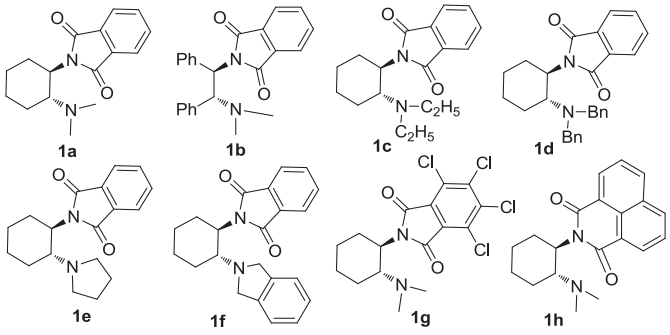
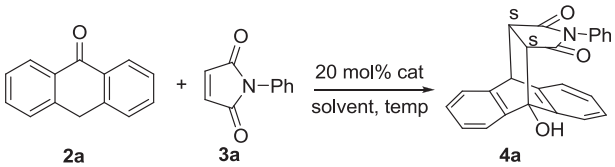


Fig. 1. Chiral tertiary amine catalysts studied.

All the cases afforded good yields (75–91% yields) and moderate enantioselectivities (11–55% ee) except catalyst **1d**. Chiral tertiary amine **1a** with (*R*,*R*)-1,2-cyclohexanediamine chiral scaffold afforded excellent yield and moderate enantioselectivity (91% yield, 55% ee; Table 1, entry 1). Catalyst **1b** with (1*R*,2*R*)-1,2-diphenyldiamine moiety gave a relatively lower yield and enantioselectivity (75% yield, 23% ee; Table 1, entry 2). The effects of the substituents on nitrogen atom of the catalyst were then examined. Catalysts **1c**–**f** gave negative effects on the enantioselectivities (Table 1, entries 3–6). No further improvements on yields and enantioselectivities were observed when catalysts **1g** and **1h** with bulkier substituents used (Table 1, entries 7 and 8). After a brief screening, catalyst **1a** was chosen for further optimizations.

The effects of the solvents and reaction temperature were also investigated and the results were listed in Table 2. All solvents gave moderate to good yields (50–91%), whereas the enantioselectivities varied strikingly (1–86% ee, Table 2, entries 1–9). When the reaction was carried out in chlorinated solvents, good yields and moderate to good enantioselectivities (89–91% yield, 55–86% ee, Table 2, entries 1–3) were observed. Aromatic hydrocarbon and ether solvents gave only moderate yields and moderate enantioselectivities (50–78% yield, 25–43% ee; Table 2, entries 4–7), and particularly, acetonitrile and DMF gave poor enantioselectivities (13% and 1% ee; Table 2, entries 8 and 9). 1,2-Dichloroethane, which gave the highest enantioselectivity with good conversion (86% ee, 90% yield; Table 2, entry 2), was chosen as the best suitable solvent for further screening of temperature. When the reaction temperature was decreased from room temperature to −10 °C, the enantioselectivities increased slightly (Table 2, entries 10–12). Further decreasing the temperature to −20 °C led to lower yield and enantioselectivity (83% yield, 84% ee, Table 2, entry 13). Through those screenings, the optimized reaction conditions were found to be reaction of 1.2 equiv **3a** with 1.0 equiv **2a** in the presence of 20 mol % of catalyst **1a** in 1,2-dichloroethane at −10 °C.

Table 2
Solvent screenings[a]



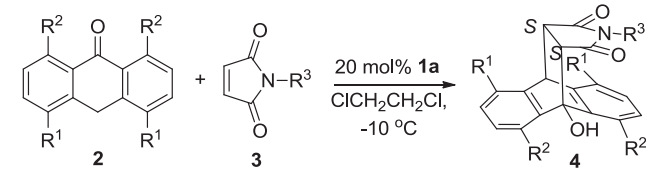
2a 3a 4a

Entry	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	ee (%)[c]
1	CH_2Cl_2	rt	6	91	55
2	$ClCH_2CH_2Cl$	rt	6	90	86
3	$CHCl_3$	rt	6	89	60
4	Toluene	rt	7	50	35
5	Xylene	rt	10	75	28
6	Et_2O	rt	10	60	25
7	THF	rt	10	78	43
8	Acetonitrile	rt	10	77	13
9	DMF	rt	10	58	1
10	$ClCH_2CH_2Cl$	10	6	91	90
11	$ClCH_2CH_2Cl$	0	12	92	90
12	$ClCH_2CH_2Cl$	−10	12	90	93
13	$ClCH_2CH_2Cl$	−20	18	83	84

[a] Unless otherwise specified, all reactions were carried out using maleimide **3a** (0.24 mmol), anthrone **2a** (0.2 mmol), and catalyst (20 mol %) in the solvent (0.6 mL) at room temperature.
[b] Isolated yield.
[c] Enantiomeric excess was determined by HPLC using Chiralpak AD-H column.

Under the optimized reaction condition, a range of *N*-substituted maleimides were broadened and the results were listed in Table 3. In general, all the *N*-substituted maleimides reacted smoothly and gave moderate to good yields and moderate to excellent enantioselectivities (70–97% yield, 40–93% ee; Table 3, entries 1–13). The positions of the substituents on the maleimides phenyl ring have some influences on the enantioselectivities. The *meta*-position substituted maleimides gave good yields and enantioselectivities (85% yield, 85% ee, Table 3, entry 2), whereas the *para*-position substituted, the enantioselectivity decreased sharply to only 40–76% ee (Table 3, entries 3–9). For less reactive *N*-alkyl maleimides, good yields and moderate enantioselectivities were obtained (70–95% yield, 43–70% ee; Table 3, entries 10–13). A series of substituted anthrones were also evaluated. Anthrones **2b** and **2c** gave good yields and moderate to good enantioselectivities

Table 3
Scope of substrates[a]



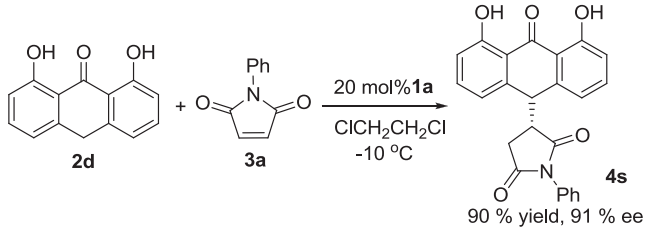
2a: R^1 = H, R^2 = H
2b: R^1 = H, R^2 = Cl
2c: R^1 = Cl, R^2 = H

Entry	2	R^3	Product	Yield[b] (%)	ee (%)[c]
1	**2a**	Ph	**4a**	90	93
2	**2a**	3-NO_2–C_6H_4	**4b**	85	85
3	**2a**	4-CH_3–C_6H_4	**4c**	91	51
4	**2a**	4-CH_3O–C_6H_4	**4d**	97	40
5	**2a**	4-OH–C_6H_4	**4e**	84	76
6	**2a**	4-NO_2–C_6H_4	**4f**	91	46
7	**2a**	4-Cl–C_6H_4	**4g**	95	46
8	**2a**	4-F–C_6H_4	**4h**	87	43
9	**2a**	4-Br–C_6H_4	**4i**	92	44
10	**2a**	Bn	**4j**	70	70
11	**2a**	CH_3	**4k**	95	47
12	**2a**	Cyclohexyl	**4l**	80	54
13	**2a**	Allyl	**4m**	85	43
14	**2b**	Ph	**4n**	85	95
15	**2b**	4-CH_3–C_6H_4	**4o**	87	73
16	**2b**	2-F–C_6H_4	**4p**	88	87
17	**2c**	Ph	**4q**	96	62
18	**2c**	4-CH_3–C_6H_4	**4r**	96	62

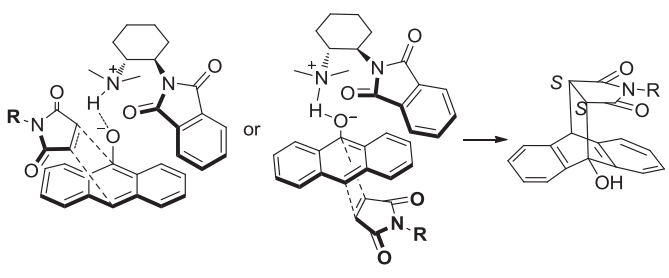
[a] Unless otherwise specified, all reactions were carried out using maleimide **3** (0.24 mmol), anthrone **2** (0.2 mmol), and catalyst **1a** (20 mol %) in $ClCH_2CH_2Cl$ (0.6 mL) at −10 °C.
[b] Isolated yield.
[c] Enantiomeric excess was determined by HPLC using Chiralpak AD-H column.

(85–96% yield, 62–95% ee; Table 3, entries 14–18). While 1,8-dihydroxy-9-anthrone **2d** afford only the Michael adducts in 90% yield and 91% ee, no Diels–Alder adduct was separated (Scheme 2).

On the basis of the above results and commonly accepted mechanism,[8] we proposed the plausible transition state model as shown in Scheme 3. The tertiary amine severed as a base to form anthrone enolate, which is bound to the protonated chiral amine. Thus the enolate would attack the maleimide from two possible directions, and thus lead to the corresponding product with (*S*,*S*)-configuration.



Scheme 2. The Michael reaction of 1,8-dihydroxy-9-anthrone **2d** with *N*-phenyl-maleimide.



Scheme 3. Plausible transition state models.

3. Conclusions

In summary, simple chiral tertiary amines with a special imide skeleton were first successfully applied to catalyze the enantioselective D–A reaction of anthrones and maleimide in excellent yields (up to 96%) and enantioselectivities (up to 95% ee). This protocol provided a potential and effective method for the construction of optically active unsaturated lactams.

4. Experimental

4.1. General

All reagent were obtained from commercial supplier without further purification. Commercial grade solvent was dried and purified by standard procedures as specified in Purification of Laboratory Chemicals, fourth Ed (Armarego, W. L. F.; Perrin, D. D. Butterworth Heinemann: 1997). NMR spectra were recorded with tetramethylsilane (TMS) as internal standard. ^1H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra at 75 MHz (Bruker Avance). Chemical shifts (δ) are reported in parts per million downfield from $CDCl_3$ (δ=7.26 ppm) for ^1H NMR and relative to the central $CDCl_3$ resonance (δ=77.0 ppm) for ^{13}C NMR spectroscopy. Flash column chromatography was carried out using silica gel eluting with ethyl acetate and petroleum ether. Reactions were monitored by TLC and visualized with ultraviolet light. Enantiomeric excess was determined by HPLC analysis on chiralpak AD-H. The absolute configurations of the known products were assigned by HPLC and optical rotation comparisons with the reported data,[6] and those of other adduct were deduced on the basis of those results.

4.2. Representative experimental procedure for D–A reaction

A mixture of maleimide **3** (0.24 mmol), anthrone **2** (0.2 mmol), and the catalyst (20 mol %) in 1,2-dichloroethane (0.6 mL) at −10 °C was stirred for 12 h (monitored by TLC). After evaporation under reduced pressure, the residue was purified through column chromatography on silica gel (petroleum ether/ethyl acetate=3/1) to yield pure products.

*4.2.1. (15S)-10-Hydroxy-13-phenyl-10,11-dihydro-9H-9,10-[3,4]epipyrroloanthracene-12,14(13H,15H)-dione (**4a**).* Known compound;[6] white solid; 90% yield; $[\alpha]_D^{20}$ +29.7 (*c* 0.7, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.75–7.40 (m, 3H), 7.32–7.22 (m, 8H), 6.50–6.47 (m, 2H), 4.84 (d, *J*=3.48 Hz, 1H), 3.49 (dd, *J*=3.54, 8.63 Hz, 1H), 3.27 (d, *J*=8.61 Hz, 1H) ppm; HRMS (ESI) for $C_{24}H_{17}NNaO_3$ ($[M+Na]^+$) calcd 390.1101, found 390.1107; enantiomeric excess: 93%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (major)=27.9 min, t_R (minor)=36.1 min.

*4.2.2. (15S)-10-Hydroxy-13-(3-nitrophenyl)-10,11-dihydro-9H-9,10-[3,4]epipyrroloanthracene-12,14(13H,15H)-dione (**4b**).* Known compound;[8c] white solid; 85% yield; $[\alpha]_D^{20}$ +6.0 (*c* 0.33, CH_2Cl_2); ^1H NMR (300 MHz, DMSO-d_6) δ 8.18 (d, *J*=1.3 Hz, 1H), 7.67–7.49 (m, 4H), 7.34–7.21 (m, 6H), 7.0 (s, 1H), 6.95 (m, 1H), 4.83 (d, *J*=3.29 Hz, 1H), 3.52 (dd, *J*=3.43, 8.40 Hz, 1H), 3.29 (d, *J*=8.43 Hz, 1H) ppm; HRMS (ESI) for $C_{24}H_{16}N_2NaO_5$ ($[M+Na]^+$) calcd 435.0951, found 435.0956; enantiomeric excess: 85%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (major)=61.7 min, t_R (minor)=65.4 min.

*4.2.3. (15S)-10-Hydroxy-13-(p-tolyl)-10,11-dihydro-9H-9,10-[3,4]epipyrroloanthracene-12,14(13H,15H)-dione (**4c**).* White solid; 80%

yield; $[\alpha]_D^{20}$ +9.5 (*c* 0.53, CH_2Cl_2); ^1H NMR (300 MHz, DMSO-d_6) δ 7.57–7.47 (m, 3H), 7.28–7.17 (m, 5H), 7.12 (d, *J*=8.06 Hz, 2H), 6.87 (s, 1H), 6.30 (d, *J*=8.06 Hz, 2H), 4.77 (d, *J*=3.17 Hz, 1H), 3.46 (dd, *J*=3.05, 8.32 Hz, 1H), 3.23 (d, *J*=8.43 Hz, 1H), 2.25 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 175.7, 142.2, 140.9, 139.0, 138.8, 136.6, 129.7, 128.1, 127.2, 127.1, 126.8, 126.7, 125.9, 124.6, 123.7, 121.0, 120.8, 77.2, 50.7, 47.6, 44.7, 21.1 ppm; HRMS (ESI) for $C_{25}H_{19}NNaO_3$ ($[M+Na]^+$) calcd 404.1257, found 404.1255; enantiomeric excess: 51%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (major)=29.7 min, t_R (minor)=35.8 min.

*4.2.4. (15S)-10-Hydroxy-13-(4-methoxyphenyl)-10,11-dihydro-9H-9,10-[3,4]epipyrroloanthracene-12,14(13H,15H)-dione (**4d**).* Known compound;[7] white solid; 97% yield; $[\alpha]_D^{20}$ +5.0 (*c* 0.48, CH_2Cl_2); ^1H NMR (300 MHz, DMSO-d_6) δ 7.57–7.47 (m, 3H), 7.27–7.16 (m, 5H), 6.92–6.86 (m, 3H), 6.31 (d, *J*=8.78 Hz, 2H), 4.77 (d, *J*=3.20 Hz, 1H), 3.71 (s, 3H), 3.44 (dd, *J*=3.27, 8.47 Hz, 1H), 3.22 (d, *J*=8.42 Hz, 1H) ppm; enantiomeric excess: 40%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (major)=36.6 min, t_R (minor)=43.6 min.

*4.2.5. (15S)-10-Hydroxy-13-(4-hydroxyphenyl)-10,11-dihydro-9H-9,10-[3,4]epipyrroloanthracene-12,14(13H,15H)-dione (**4e**).* White solid; 84% yield; $[\alpha]_D^{20}$ −10.4 (*c* 0.21, CH_2Cl_2); ^1H NMR (300 MHz, DMSO-d_6) δ 9.66 (s, 1H), 7.84–7.46 (m, 3H), 7.27–7.18 (m, 5H), 6.79 (d, *J*=8.73 Hz, 1H), 6.65 (d, *J*=8.76 Hz, 2H), 6.18 (d, *J*=8.55 Hz, 2H), 4.78 (d, *J*=3.27 Hz, 1H), 3.47 (dd, *J*=3.39, 8.46 Hz, 1H), 3.20 (d, *J*=8.46 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 174.2, 157.3, 144.7, 141.2, 139.7, 137.3, 127.7, 126.4, 126.3, 126.2, 126.0, 124.3, 123.6, 122.9, 121.1, 120.8, 115.2, 76.6, 50.5, 47.4, 43.7 ppm; enantiomeric excess: 76%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (minor)=22.7 min, t_R (major)=32.6 min.

*4.2.6. (15S)-10-Hydroxy-13-(4-nitrophenyl)-10,11-dihydro-9H-9,10-[3,4]epipyrroloanthracene-12,14(13H,15H)-dione (**4f**).* Known compound;[2h] white solid; 91% yield; $[\alpha]_D^{20}$ −11.5 (*c* 0.19, CH_2Cl_2); ^1H NMR (300 MHz, DMSO-d_6) δ 8.23 (d, *J*=8.79 Hz, 2H), 7.58–7.48 (m, 3H), 7.28–7.16 (m, 5H), 6.99 (s, 1H), 6.82 (d, *J*=8.79 Hz, 2H), 4.81 (d, *J*=3.24 Hz, 1H), 3.52 (dd, *J*=3.36, 8.43 Hz, 1H), 3.28 (d, *J*=8.46 Hz, 1H) ppm; HRMS (ESI) for $C_{24}H_{16}N_2NaO_5$ ($[M+Na]^+$) calcd 435.0951, found 435.0968; enantiomeric excess: 46%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (major)=55.2 min, t_R (minor)=60.6 min.

*4.2.7. (15S)-13-(4-Chlorophenyl)-10-hydroxy-10,11-dihydro-9H-9,10-[3,4]epipyrroloanthracene-12,14(13H,15H)-dione (**4g**).* White solid; 95% yield; $[\alpha]_D^{20}$ +9.8 (*c* 0.57, CH_2Cl_2); ^1H NMR (300 MHz, DMSO-d_6) δ 7.57–7.50 (m, 3H), 7.47–7.41 (m, 2H), 7.28–7.16 (m, 5H), 6.92 (s, 1H), 6.47 (d, *J*=8.58 Hz, 2H), 4.78 (d, *J*=3.24 Hz, 1H), 3.47 (dd, *J*=3.38, 8.43 Hz, 1H), 3.24 (d, *J*=8.45 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 175.3, 142.1, 140.8, 138.6, 136.5, 134.8, 129.3, 129.2, 127.4, 127.3, 127.2, 126.9, 126.8, 124.6, 123.7, 121.0, 120.8, 77.2, 50.7, 47.6, 44.7 ppm; HRMS (ESI) for $C_{24}H_{16}ClNNaO_3$ ($[M+Na]^+$) calcd 424.0711, found 424.0723; enantiomeric excess: 46%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (major)=30.7 min, t_R (minor)=33.5 min.

*4.2.8. (15S)-13-(4-Fluorophenyl)-10-hydroxy-10,11-dihydro-9H-9,10-[3,4]epipyrroloanthracene-12,14(13H,15H)-dione (**4h**).* Known compound;[5b] white solid; 87% yield; $[\alpha]_D^{20}$ +8.0 (*c* 0.47, CH_2Cl_2); ^1H NMR (300 MHz, DMSO-d_6) δ 7.55–7.47 (m, 3H), 7.29–7.16 (m, 7H), 6.91 (s, 1H), 6.47–6.43 (m, 2H), 4.78 (d, *J*=3.33 Hz, 1H), 3.47 (dd, *J*=3.42, 8.45 Hz, 1H), 3.24 (d, *J*=8.43 Hz, 1H) ppm; enantiomeric excess: 43%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (major)=24.6 min, t_R (minor)=33.8 min.

*4.2.9. (15S)-13-(4-Bromophenyl)-10-hydroxy-10,11-dihydro-9H-9,10-[3,4]epipyrroloanthracene-12,14(13H,15H)-dione (**4i**).* Known compound;[7] white solid; 92% yield; $[\alpha]_D^{20}$ +11.3 (*c* 0.40, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J*=7.3 Hz, 1H), 7.56 (d, *J*=6.8 Hz, 1H), 7.44–7.40 (m, 3H), 7.34–7.23 (m, 5H), 6.40 (d, *J*=8.6 Hz, 2H), 4.83 (d, *J*=3.4 Hz, 1H), 4.52 (s, 1H), 3.49 (dd, *J*=8.6, 3.5 Hz, 1H), 3.27 (d, *J*=8.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 175.2, 142.1, 140.8, 138.6, 136.5, 132.3, 129.7, 127.7, 127.3, 127.2, 126.9, 126.9, 124.6, 123.7, 122.9, 121.0, 120.9, 77.2, 50.8, 47.6, 44.7 ppm; enantiomeric excess: 44%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (major)=17.6 min, t_R (minor)=21.3 min.

*4.2.10. (15S)-13-Benzyl-10-hydroxy-10,11-dihydro-9H-9,10-[3,4]epipyrroloanthracene-12,14(13H,15H)-dione (**4j**).* Known compound;[7] white solid; 70% yield; $[\alpha]_D^{20}$ +10.8 (*c* 0.47, CH_2Cl_2); ^1H NMR (300 MHz, DMSO-d_6) δ 7.51 (d, *J*=7.17 Hz, 1H), 7.44 (d, *J*=6.51 Hz, 2H), 7.24–7.04 (m, 8H), 6.85 (s, 1H), 6.23 (d, *J*=7.08 Hz, 2H), 4.73 (d, *J*=3.15 Hz, 1H), 4.24 (s, 2H), 3.41 (dd, *J*=3.33, 8.94 Hz, 1H), 3.19 (d, *J*=8.73 Hz, 1H) ppm; enantiomeric excess: 70%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (major)=16.8 min, t_R (minor)=18.8 min.

*4.2.11. (15S)-10-Hydroxy-13-methyl-10,11-dihydro-9H-9,10-[3,4]epipyrroloanthracene-12,14(13H,15H)-dione (**4k**).* Known compound;[4] white solid; 95% yield; $[\alpha]_D^{20}$ +23.4 (*c* 0.46, CH_2Cl_2); ^1H NMR (300 MHz, DMSO-d_6) δ 7.68 (d, *J*=7.32 Hz, 1H), 7.44–7.35 (m, 2H), 7.24–7.14 (m, 6H), 4.72 (d, *J*=3.45 Hz, 1H), 3.32 (dd, *J*=3.51, 8.53 Hz, 1H), 3.11 (d, *J*=8.52 Hz, 1H), 2.50 (s, 3H) ppm; HRMS (ESI) for $C_{19}H_{15}NNaO_3$ ($[M+Na]^+$) calcd 328.0944, found 390.0958; enantiomeric excess: 47%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (minor)=11.6 min, t_R (major)=14.6 min.

*4.2.12. (15S)-13-Cyclohexyl-10-hydroxy-10,11-dihydro-9H-9,10-[3,4]epipyrroloanthracene-12,14(13H,15H)-dione (**4l**).* Known compound;[7] white solid; 80% yield; $[\alpha]_D^{20}$ +1.5 (*c* 0.34, CH_2Cl_2); ^1H NMR (300 MHz, DMSO-d_6) δ 7.51 (d, *J*=7.04 Hz, 1H), 7.44 (d, *J*=6.77 Hz, 2H), 7.23–7.09 (m, 5H), 6.69 (s, 1H), 4.66 (d, *J*=3.21 Hz, 1H), 3.24 (dd, *J*=3.41, 8.42 Hz, 1H), 3.02 (d, *J*=8.45 Hz, 1H), 1.60–1.45 (m, 6H), 1.03–0.96 (m, 3H), 0.76–0.65 (m, 2H) ppm. HRMS (ESI) for $C_{24}H_{23}NNaO_3$ ($[M+Na]^+$) calcd 396.1570, found 396.1580; enantiomeric excess: 54%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (major)=9.8 min, t_R (minor)=11.9 min.

*4.2.13. (15S)-13-Allyl-10-hydroxy-10,11-dihydro-9H-9,10-[3,4]epipyrroloanthracene-12,14(13H,15H)-dione (**4m**).* White solid; 85% yield; $[\alpha]_D^{20}$ +15.8 (*c* 0.40, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J*=7.3 Hz, 1H), 7.50 (d, *J*=7.3 Hz, 1H), 7.37 (d, *J*=7.1 Hz, 1H), 7.24–7.14 (m, 5H), 4.92–4.79 (m, 2H), 4.74 (d, *J*=3.4 Hz, 1H), 4.61 (s, 1H), 4.56 (d, *J*=1.3 Hz, 1H), 4.49 (s, 1H), 3.70 (d, *J*=5.3 Hz, 2H) ppm; ^{13}C NMR (75Mz, $CDCl_3$) 177.3, 175.9, 142.5, 140.8, 139.0, 136.5, 129.5, 127.1, 127.0, 126.7, 126.6, 124.5, 123.6, 120.9, 120.6, 118.0, 77.0, 50.5, 47.4, 44.4, 40.6 ppm; HRMS (ESI) for $C_{21}H_{17}NNaO_3$ ($[M+Na]^+$) calcd 354.1101, found 354.1099; enantiomeric excess: 43%, determined by HPLC (Chiralpak OD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (minor)=10.1 min, t_R (major)=14.5 min.

*4.2.14. (9R,10S,15S)-4,5-Dichloro-10-hydroxy-13-phenyl-10,11-dihydro-9H-9,10-[3,4]epipyrroloanthracene-12,14(13H,15H)-dione (**4n**).* Known compound;[7] white solid; 85% yield; $[\alpha]_D^{20}$ +12.5 (*c* 0.43, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.65–7.45 (m, 2H), 7.33–7.24 (m, 7H), 6.59–6.56 (m, 2H), 5.93 (d, *J*=3.62 Hz, 1H), 4.66 (s, 1H), 3.51

(dd, J=3.65, 8.73 Hz, 1H), 3.26 (d, J=8.73 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 174.2, 144.5, 143.1, 135.5, 133.9, 131.0, 130.7, 130.1, 129.2, 129.0, 128.3, 128.2, 128.1, 127.6, 126.1, 119.9, 119.6, 76.5, 49.8, 46.1, 37.6 ppm; enantiomeric excess: 95%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (major)=25.8 min, t_R (minor)=46.0 min.

*4.2.15. (9R,10S,15S)-4,5-Dichloro-10-hydroxy-13-(p-tolyl)-10,11-dihydro-9H-9,10-[3,4]epipyrroloanthracene-12,14(13H,15H)-dione (**4o**).* Known compound;[6] white solid; 87% yield; $[\alpha]_D^{20}$ −40.2 (c 0.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65–7.62 (m, 2H), 7.47–7.23 (m, 4H), 7.13–7.11 (m, 2H), 6.45 (d, J=8.27 Hz, 2H), 5.93 (d, J=3.63 Hz, 1H), 4.67 (s, 1H), 3.50 (dd, J=3.65, 8.72 Hz, 1H), 3.24 (d, J=8.72 Hz, 1H), 2.31 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 174.3, 144.6, 143.2, 139.2, 135.6, 134.0, 131.0, 130.1, 129.8, 128.2, 128.1, 128.1, 127.6, 125.8, 119.9, 119.6, 77.4, 49.8, 46.2, 37.7, 21.1 ppm; enantiomeric excess: 73%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (major)=24.7 min, t_R (minor)=42.2 min.

*4.2.16. (9R,10S,15S)-4,5-Dichloro-13-(2-fluorophenyl)-10-hydroxy-10,11-dihydro-9H-9,10-[3,4]epipyrroloanthracene-12,14(13H,15H)-dione (**4p**).* Known compound;[6] white solid; 88% yield; $[\alpha]_D^{20}$ −39.5 (c 0.44, CH_2Cl_2); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.20 (m, 1H), 7.83 (s, 1H), 7.74–7.31 (m, 8H), 7.00 (d, J=8.79 Hz, 1H), 5.60 (d, J=3.57 Hz, 1H), 3.68 (dd, J=3.36, 8.49 Hz, 1H), 3.46 (d, J=8.50 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 172.0, 145.5, 142.3, 134.5, 132.9, 129.8, 129.1, 128.2, 127.6, 127.0, 126.7, 126.4, 126.0, 123.4, 119.4, 118.9, 118.2, 115.3, 115.0, 76.0, 49.0, 45.8, 39.7 ppm; enantiomeric excess: 87%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (major)=18.0 min, t_R (minor)=31.5 min.

*4.2.17. (9S,10R,15S)-1,8-Dichloro-10-hydroxy-13-phenyl-10,11-dihydro-9H-9,10-[3,4]epipyrroloanthracene-12,14(13H,15H)-dione (**4q**).* Known compound;[6] white solid; 96% yield; $[\alpha]_D^{20}$ +88.4 (c 0.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (m, 2H), 7.33–7.24 (m, 7H), 6.59–6.56 (m, 2H), 5.93 (d, J=3.64 Hz, 1H), 4.66 (s, 1H), 3.51 (dd, J=3.65, 8.73 Hz, 1H), 3.25 (d, J=8.72 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 174.1, 144.5, 143.2, 135.6, 133.9, 131.0, 130.7, 130.1, 129.1, 129.0, 128.3, 128.1, 128.0, 127.6, 126.1, 119.9, 119.6, 77.4, 49.9, 46.1, 37.6 ppm; enantiomeric excess: 62%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (major)=25.3 min, t_R (minor)=44.5 min.

*4.2.18. (9S,10R,15S)-1,8-Dichloro-10-hydroxy-13-(p-tolyl)-10,11-dihydro-9H-9,10-[3,4]epipyrroloanthracene-12,14(13H,15H)-dione (**4r**).* Known compound;[6] white solid; 96% yield; $[\alpha]_D^{20}$ −45.5 (c 0.4, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.62 (m, 2H), 7.47–7.21 (m, 4H), 7.12 (d, J=8.08 Hz, 2H), 6.45 (d, J=8.23 Hz, 2H), 5.93 (d, J=3.58 Hz, 1H), 4.67 (s, 1H), 3.50 (dd, J=3.64, 8.70 Hz, 1H), 3.24 (d, J=8.70 Hz, 1H), 2.31 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 174.3, 144.5, 143.1, 139.2, 135.5, 133.9, 131.0, 130.0, 129.8, 128.2, 128.1, 127.5, 125.8, 119.9, 119.6, 77.4, 49.8, 46.1, 37.6, 21.1 ppm; enantiomeric excess: 62%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (major)=25.1 min, t_R (minor)=43.0 min.

*4.2.19. (R)-3-(4,5-Dihydroxy-10-oxo-9,10-dihydroanthracen-9-yl)-1-phenylpyrrolidine-2,5-dione (**4s**).* Known compound;[6] white solid; 90% yield; $[\alpha]_D^{20}$ +38.7 (c 0.62, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.2 (s, 1H), 12.1 (s, 1H), 7.58–7.40 (m, 5H), 7.09–6.93 (m, 6H), 5.18 (d, J=2.88 Hz, 1H), 3.52–3.49 (m, 1H), 2.52 (dd, J=9.42, 18.62 Hz, 1H), 2.21 (dd, J=5.01, 18.59 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.2, 176.4, 173.9, 163.3, 163.0, 143.8, 139.6, 137.2, 136.7, 131.4, 129.2, 128.9, 126.3, 119.0, 118.6, 118.0, 117.0, 116.4, 115.7, 51.0, 42.2, 29.5 ppm; enantiomeric excess: 91%, determined by HPLC (Chiralpak AD-H column, hexane/2-propanol=80/20, 1.0 mL/min, 230 nm), t_R (major)=26.9 min, t_R (minor)=32.6 min.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.11.011. These data include MOL files and InChIKeys of the most important compounds described in this article.

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