Asymmetric cycloaddition of anthrone and maleimides catalyzed by C_2-chiral pyrrolidines

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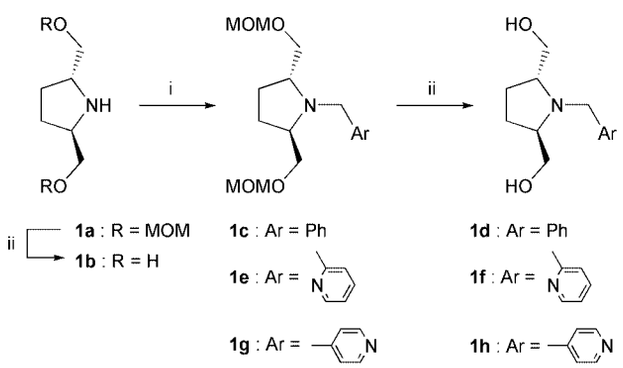
Catalytic asymmetric cycloaddition of anthrone † with *N*-alkyl- and *N*-arylmaleimides with various substituents in the aromatic ring was carried out in the presence of C_2-chiral pyrrolidines to afford chiral, non-racemic [4 + 2] adducts. Among them, good catalytic activity was observed with the pyrrolidines with a *N*-(4-pyridyl)methyl group **1h**, which was discussed from the viewpoint of conformational analysis. The best stereoselectivity of 87% ee was attained when the reaction of *N*-(2-*tert*-butylphenyl)maleimide **4j** and anthrone was promoted with **1h**.

The asymmetric Diels–Alder reaction has been studied extensively and recognized as an efficient method creating up to four chiral centres at one time. Almost all investigations focus on the use of stereogenic auxiliaries bound to one of the reactants[1] and on the use of chiral Lewis acids[2] either stoichiometric or catalytic amounts. On the other hand, only a few reports of base-catalyzed asymmetric [4 + 2] cycloaddition closely related to the Diels–Alder reaction have been published with anthrone[3] and 3-hydroxy-2-pyrone.[4] In these reports, natural cinchona alkaloids and proline derivatives were employed as catalysts, and though the ee's of the products were moderate the selectivity was improved by using a chiral auxiliary in the latter report. Recently, a different type of effective organocatalytic Diels–Alder reaction was reported with α,β-unsaturated aldehydes.[5] We have reported the asymmetric cycloaddition with moderate stereoselectivity catalyzed by C_2-chiral 2,5-bis(hydroxymethyl)pyrrolidine **1b** and high selectivity was attained with chiral *N*-substituted maleimides.[6] Now, we describe the catalytic asymmetric cycloaddition with up to 87% asymmetric yield with the devised base catalysts.



Scheme 1 *Reagents and conditions*: i, $ArCH_2Cl$, Pr^i_2EtN, THF, reflux, 9 h; ii, HCl, MeOH, 80 °C, 2 days.

Results and discussion

In the design of the catalyst structure, the solubility of catalyst was taken into account since the catalyst **1b**, which exhibited the best selectivity of 61% ee, has a problem of high solubility in water and its reuse is difficult. Because the hydroxy groups in **1b** were found to be indispensable for the asymmetric induction,[6] we started the catalyst modification by introducing substituents on the nitrogen atom in the pyrrolidine ring. First, we examined the *N*-benzyl derivative **1d**, which turned out to be practically inactive as a catalyst. On the basis that the cinchona alkaloids which exhibit high activity are aliphatic amines with aromatic rings containing a nitrogen atom, we prepared the chiral pyrrolidine derivatives with the 2-pyridylmethyl **1f** and 4-pyridylmethyl **1h** groups as well as other aromatic groups as catalyst candidates. Among them, the 4-pyridylmethyl derivative **1h** exhibited good catalytic activity for the [4 + 2] cycloaddition.

Starting from methoxymethyl (MOM) ether **1a**,[7] the *N*-benzyl derivative **1c**, the *N*-2-pyridylmethyl derivative **1e** and the 4-pyridylmethyl derivative **1g** were obtained by the reaction with the corresponding arylmethyl chlorides. Compounds **1c**, **1e** and **1g** were then deprotected with hydrochloric acid to afford

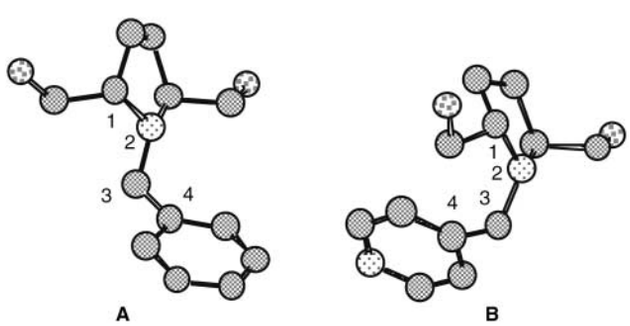


Fig. 1 The most stable conformation of **1d**, **1f** and **1h** calculated by PM3. **A**, benzyl derivative **1d** and 2-pyridylmethyl derivative **1f**; **B**, 4-pyridylmethyl derivative **1h**.

diols **1d**, **1f** and **1h**, respectively (Scheme 1). The asymmetric cycloaddition of anthrone **3** with *N*-methylmaleimide **4a** and *N*-benzylmaleimide **4b** was carried out in chloroform at room temperature by using the 2-pyridylmethyl derivative **1f**, the 4-pyridylmethyl derivative **1h** and their MOM derivatives **1e** and **1g** (Table 1). As a reference, the reaction was also effected with the unsubstituted pyrrolidine **1b** and its MOM derivative **1a** as well as quinidine **2** which has been reported previously.[6] The reaction periods required for completion with **1h** with the 4-pyridylmethyl group were comparable with **1b** although they were longer than those with **2**. The reaction with the 2-pyridylmethyl counterpart **1f** was more sluggish. We also examined other pyrrolidine derivatives with 2-pyridyl, 4-pyridyl, benzimidazol-2-ylmethyl or 3,5-dimethylisoxazol-4-ylmethyl groups as well as the bis(pyrrolidine) derivative linked

† The IUPAC name for anthrone is 9,10-dihydroanthracen-9-one.

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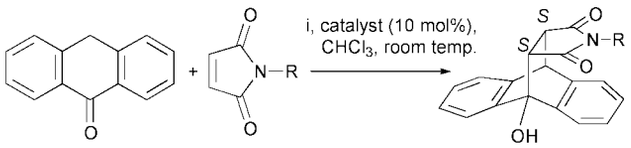
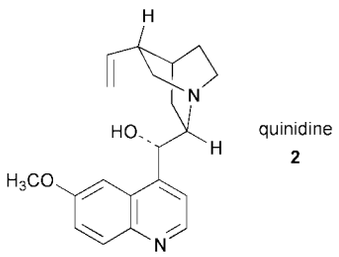
Table 1 Catalytic asymmetric cycloaddition of anthrone with *N*-benzylmaleimides



3 4a,b 5a,b

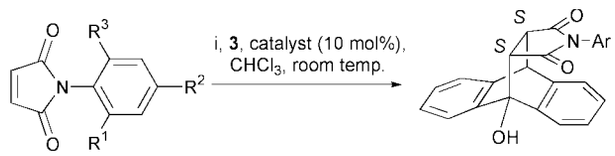


quinidine
2

R	Product	Catalyst	*t*/h	Yield (%)	Ee (%)[a]
Me	**5a**	**2**	0.25	99	35
		1b	2	88	59
		1h	2	99	74
Bn	**5b**	**2**	0.25	99	45
		1a	8	99	38
		1b	4	92	59
		1c	48	30	—
		1d	48	33	21
		1e	24	83	38
		1f	48	91	12
		1g	24	63	42
		1h	2	82	70

[a] By chiral HPLC analysis.

Table 2 Asymmetric cycloaddition of anthrone with phenylmaleimides



4c-j 5c-j

Product	R^1	R^2	R^3	Catalyst	*t*/h	Yield (%)	Ee (%)
5c	H	H	H	**2**	1	93	20
				1b	2	95	51
				1h	24	91	61
5d	H	CF_3	H	**2**	0.75	86	33
				1b	0.25	80	46
				1h	18	85	50
5e	H	F	H	**2**	0.25	89	30
				1b	1	93	55
				1h	18	88	57
5f	H	OMe	H	**2**	0.2	68	27
				1b	1	95	74
				1h	18	96	62
5g	Cl	H	Cl	**2**	4	80	38
				1b	2	72	59
				1h	24	55	63
5h	Br	Br	H	**2**	1.5	80	25
				1b	2	73	63
				1h	96	56	52
5i	Me	Me	H	**2**	10	75	11
				1b	5	53	50
				1h	72	50	47
5j	Bu^t	H	H	**2**	0.25	95	40
				1b	0.25	99	81
				1h	3	97	87

by a pyridine-2,5-diyl group, but their catalytic activity was poor.

The best activity among the pyrrolidine derivatives examined was found for **1h** and was rationalized by conformational analysis. We estimated the most stable conformation of **1d**, **1f** and **1h** by PM3 calculations starting from systematically created initial structures. In the most stable conformation **A** of **1d**,**f** and **B** of **1h**, the dihedral angles around C^1–N^2–C^3–C^4 are quite different and the aromatic groups orient in opposite directions (Fig. 1). An open space exists around the nitrogen atom in the pyrrolidine ring in **B**, which enables anthrone to approach it. In contrast, the nitrogen atom is shielded by the phenyl or 2-pyridyl group in **A**, which hinders the approach. In order to confirm the consideration that the nitrogen atom of the catalyst should be unhindered for good activity, we examined several achiral amines for the [4 + 2]cycloaddition. Secondary amines accelerated the reaction but tertiary amines, except 1-azabicyclo[2.2.2]octane, did not exhibit catalytic activity. This observation can be rationalized by the fact that the nitrogen atom of the bicyclic amine is naked, and suggests that the nitrogen atom of pyrrolidine **1h** is also naked.

As to the MOM derivatives **1a**, **1e** and **1g**, the stereoselectivity was moderate and comparable with **2**. Diol **1f** with a 2-pyridylmethyl group exhibited poor stereoselection. On the other hand, the ee's (74 and 70%) of the products **5a** and **5b**, yielded with diol **1h** with a 4-pyridylmethyl group, were higher than those with **2** (35 and 45%) and **1b** (59%). Almost the same results were observed when the reaction was conducted in toluene and/or at lower temperature. The configuration of the products **5a** and **5b** was *S*,*S* throughout the entries in Table 1.

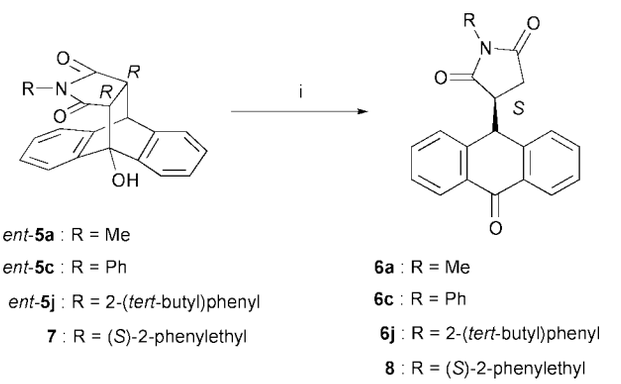
In order to attain improved stereoselectivity, we undertook the reaction between anthrone and various *N*-arylmaleimides **4c**–**j** catalyzed by **1b** and **1h** which exhibited good selectivity for the reaction with *N*-alkylmaleimides (Table 2). Various *N*-arylmaleimides having electron-attracting and electron-donating groups were prepared by heating the corresponding substituted anilines with maleic anhydride and zinc chloride.[8] Quinidine was also employed as a reference. It took longer for the reaction to complete with **1h**. The catalysts **1b** and **1h** always afforded higher ee's than **2**. The ee's of the *N*-phenyl adduct **5c** were rather poorer than those of the *N*-alkyl adducts (Table 1). The substituents on the aromatic ring, with the exception of 2-Bu^t group **4j**, did not affect the selectivity. The best asymmetric induction of 87% ee was attained when **1h** with an *N*-4-pyridylmethyl group was used in the reaction with **4j**. The configuration of **5j** was the same as the *N*-alkyl analogues **5a** and **5b**, and is described later. The ee of **5j** with **1b** with no *N*-substituent was also high, 81% ee. The high selectivity with **4j** with the 2-Bu^t group is partly ascribed to the conformation of **4j**. The aromatic ring stands perpendicular to the maleimide ring and one face of the latter is shielded with the Bu^t group.

For the determination of the absolute configuration, we employed the (−)-isomers *ent*-**5c** and *ent*-**5j** while the products of the present asymmetric synthesis were the (+)-isomers **5c** and **5j**. The adducts *ent*-**5a**[3] and **7**[6] were employed as the reference compounds whose *R*,*R*-configuration had been established. Compounds *ent*-**5a**, *ent*-**5c**, *ent*-**5j** and **7** were converted to ketones **6a**, **6c**, **6j** and **8**, respectively, by the action of triethylamine (Scheme 2). Their CD spectra showed the same pattern, a positive maximum at 243–249 nm and a negative maximum at 211–215 nm (Table 3), and the *R*,*R*-configuration was assigned to *ent*-**5c** and *ent*-**5j** based on this fact. Consequently, the *S*,*S*-configuration of **5c** (R = Ph) and **5j** (R = (2-Bu^t)Ph) from the present asymmetric cycloaddition was established. This conclusion was also supported by the observation in the chiral HPLC analysis that the major isomers of **5a**, **5c** and **5j** eluted faster (the retention times are given in the Experimental section). The *S*,*S*-configuration was also assigned to the other products based on the chiral HPLC analysis as well as the fact that they showed positive rotations.

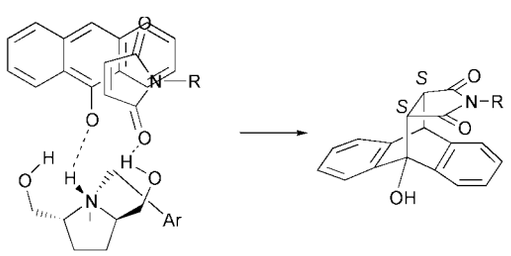
Table 3 CD spectra of the ketones derived from the cycloaddition products

Ketone	Ee (%)	[θ]/deg cm² dmol⁻¹ (λ/nm)[a]		
6a	52	+4700 (245)	0 (236)	−62000 (212)
8	[b]	+16000 (249)	0 (238)	−117000 (212)
6c	54	+5400 (243)	0 (235)	−7500 (215)
6j	71	+15000 (249)	0 (236)	−79000 (211)

[a] In MeOH. [b] 100% de.



Scheme 2 *Reagents and conditions*: i, Et_3N, MeOH, room temp., 1 day.



Scheme 3 Transition state model for the [4 + 2]cycloaddition.

We now present a tentative transition state model which affords the (*S*,*S*)-products (Scheme 3). The protonated pyrrolidine catalyst is considered to link with anthrone enolate through ionic interactions and hydrogen bonds.[3] It is noteworthy that high enantioselectivity is attained only when the catalysts have hydroxy groups and the reaction is effected in aprotic solvents (this report and reference 6). This fact indicates the importance of another hydrogen bond in the transition state. When the maleimide approaches from the upper-right direction, the transition state should be stabilized by the hydrogen bond between a carbonyl group of the maleimide and a hydroxy group of the catalyst. On the other hand, such stabilization cannot be expected when the maleimide attacks from the upper-left direction. Because the catalysts are of C_2-symmetry, the same stereochemical consideration can be applied to the approach from the lower side. Consequently, the (*S*,*S*)-products are afforded preferentially.

In conclusion, the asymmetric cycloaddition of anthrone with *N*-alkyl- and *N*-arylmaleimides was performed with high stereoselectivity by using C_2-chiral pyrrolidine **1h** with a *N*-4-pyridylmethyl group. The best ee of 87% was attained when maleimide **4j** with an *N*-(2-*tert*-butyl)phenyl group was employed. The configuration of the products was *S*,*S* throughout the present asymmetric synthesis with both *N*-alkyl- and *N*-arylmaleimides. The derivative of **4j** with a substituent on the maleimide ring is axially asymmetric and the optically active compound has been obtained by resolution and proved to be a useful chiral dienophile.[9] The present asymmetric synthesis can be applied to the kinetic resolution of analogous dienophiles and is currently under investigation. Recently, an analogue of the *N*-2-pyridylmethyl derivative **1e** was reported as a ligand of a rhodium complex for the enantioselective allylation of arylaldehydes.[10] The C_2-chiral pyrrolidines prepared herein are also considered to have potential as chiral ligands.

Experimental

All mps were measured on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with a JEOL-JNM-EX-270 (at 270 MHz for ^{1}H, 68 MHz for ^{13}C) and a JEOL A-500 (at 500 MHz for ^{1}H, 126 MHz for ^{13}C). *J* Values are given in Hz. IR spectra were recorded with a SHIMADZU FTIR-8600PC; absorbances are measured in cm^{-1}. Mass spectra were recorded with a JEOL JMS DX-300. The elemental analyses were performed by Kyoto University elemental analysis centre. Optical rotation was measured with a JASCO DIP-1000 (with a 10 cm cell) and are given in 10^{-1} deg cm^2 g^{-1}. CD spectra were measured with a JASCO J-720 (with a 0.1 cm cell). Chiral HPLC analyses were run with Sumipax OA-2000 (4 × 200 mm) on a JASCO 880-PU chromatographic system with an 875-UV detector (254 nm); eluent: hexane–CH_2ClCH_2Cl–EtOH = 450 : 50 : 2, 2.0 cm^3 min^{-1}. PM3 calculations were performed with Chem3D MOPAC (Cambridge Soft MOPAC version 4.0).

4-[(2*R*,5*R*)-2,5-Bis(methoxymethoxymethyl)pyrrolidinylmethyl]pyridine 1g—typical procedure for synthesis of the MOM derivatives 1c, 1e and 1g

To a solution of 4-pyridylmethyl chloride hydrochloride (213 mg, 1.3 mmol) in THF (5 cm^3), ethyldiisopropylamine (260 mg, 2.0 mmol) and (2*R*,5*R*)-2,5-bis(methoxymethoxymethyl)pyrrolidine[6] **1a** (220 mg, 1.0 mmol) were added. This mixture was refluxed for 9 h, and then CH_2Cl_2 (50 cm^3) and water (150 cm^3) were added. After the aqueous layer was made alkaline with 15% NaOH (20 cm^3), the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 cm^3). The organic layer and the extracts were combined and washed with saturated NaCl (100 cm^3) and dried over Na_2SO_4. After evaporation, the residue was purified with flash column chromatography (silica gel, 15% EtOAc in hexane) to give **1g** (92 mg, 32%); yellow oil; $[a]_D^{20}$ +31.9 (*c* 0.25, $CHCl_3$); δ_H ($CDCl_3$) 1.6–2.1 (m, 4H, CH_2CH_2), 3.2 (br s, 2H, 2 × C*H*), 3.32 (s, 6H, 2 × OCH_3), 3.95 (d, *J* 15.4, 1H, NCH*H*), 4.08 (d, *J* 15.4, 1H, NC*H*H), 4.56 (s, 4H, 2 × OCH_2), 7.2–7.3 (m, 2H, *pyridine ring*), 8.5–8.6 (m, 2H, *pyridine ring*); δ_C ($CDCl_3$) 27.3, 51.5, 55.2, 60.5, 69.5, 96.7, 123.1, 149.6, 150.4; IR (neat) 1216, 1151, 1111, 1045; HRMS (M^+) Calcd for $C_{16}H_{26}N_2O_4$: 310.1891; Found 310.1884.

4-[(2*R*,5*R*)-2,5-Bis(hydroxymethyl)pyrrolidinylmethyl]-pyridine 1h. To a solution of **1g** (91.2 mg, 0.29 mmol) in CH_3OH (10 cm^3), 12 M HCl (3 drops) was added. This solution was refluxed for 2 days and evaporated. The residue was dissolved in CH_3OH (5 cm^3), and the solution was passed through an ion-exchange resin, IRA-400 (OH^-). Evaporation gave **1h** (50 mg, 76%); yellow oil; $[a]_D^{20}$ +20.9 (*c* 0.14, CH_3OH); δ_H (CD_3OD) 1.7–2.0 (m, 4H, CH_2CH_2), 3.1–3.2 (m, 2H, 2 × C*H*), 3.4–3.6 (m, 6H, 2 × $CHCH_2$, 2 × O*H*), 4.0–4.1 (m, 4H, 2 × NCH_2), 7.4–7.5 (m, 2H, *pyridine ring*), 8.4–8.5 (m, 2H, *pyridine ring*); δ_C (CD_3OD) 28.5, 53.2, 64.5, 64.6, 125.8, 150.6, 154.0; IR (neat) 3197, 1219, 1055; HRMS (M^+) Calcd for $C_{12}H_{18}N_2O_2$: 222.1367; Found 222.1382.

1-Benzyl-[(2*R*,5*R*)-2,5-bis(hydroxymethyl)]pyrrolidine 1d. Yield 74% (from **1a**); yellow oil; $[a]_D^{20}$ +40.7 (*c* 0.65, CH_3OH); δ_H (CD_3OD) 1.7–2.1 (m, 4H, CH_2CH_2), 3.0–3.2 (m, 2H, 2 × C*H*), 3.3–3.4 (m, 2H, 2 × O*H*), 3.4–3.6 (m, 4H, 2 × $CHCH_2$), 3.92 (s, 2H, NCH_2), 7.2–7.4 (m, 5H, *Ph*); δ_C (CD_3OD) 28.4, 54.4, 64.2, 64.5, 128.6, 130.1, 130.3, 142.4; IR (neat) 3301, 1216,

1030, 700; HRMS (M^+) Calcd for $C_{13}H_{19}NO_2$: 221.1415; Found 221.1420.

General procedure for base-catalyzed asymmetric cycloaddition of anthrone and *N*-substituted maleimides

A mixture of anthrone **3** (19.4 mg, 0.1 mmol), *N*-substituted maleimide **4** (0.1 mmol), a catalyst (0.01 mmol) and $CHCl_3$ (1 cm^3) was stirred at room temperature during which the reaction conversion was assessed by TLC. After completion of the reaction, water (5 cm^3) and 3 M HCl (1 cm^3) were added. The mixture was extracted with CH_2Cl_2 (3 × 15 cm^3). The extracts were washed with saturated NaCl and dried over Na_2SO_4. After evaporation, the residue was purified with flash column chromatography (silica gel, 15% EtOAc in hexane).

4-Hydroxy-2-methyl-3a,4,9,9a-tetrahydro-4,9-[1′,2′]benzeno-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione 5a. 74% ee, colorless solid; mp 189–190 °C; $[a]_D^{20}$ +54.3 (*c* 0.6, $CHCl_3$); δ_H ($CDCl_3$) 2.49 (s, 3H, NC*H*$_3$), 3.10 (d, *J* 8.4, 1H, HOCC*H*), 3.30 (dd, *J* 3.5, 8.4, 1H, CHC*H*CH), 4.52 (s, 1H, O*H*), 4.72 (d, *J* 3.5, 1H, CHC*H*), 7.1–7.8 (m, 8H, *Ph*); δ_C ($CDCl_3$) 24.2, 44.5, 47.6, 50.7, 120.7, 120.8, 123.6, 124.4, 126.7, 126.8, 127.0, 127.2, 136.4, 138.9, 140.6, 142.4, 176.4, 177.8; Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59; Found C, 74.87: H, 4.83; N, 4.60%.

4-Hydroxy-2-benzyl-3a,4,9,9a-tetrahydro-4,9-[1′,2′]benzeno-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione 5b. 70% ee, colorless solid; mp 211–213 °C; $[a]_D^{20}$ +34.8 (*c* 0.7, $CHCl_3$); δ_H ($CDCl_3$) 3.11 (d, *J* 8.9, 1H, HOCC*H*), 3.31 (dd, *J* 3.5, 8.9, 1H, CHC*H*CH), 4.26 (s, NC*H*$_2$), 4.42 (s, 1H, O*H*), 4.70 (d, *J* 3.2, 1H, CHC*H*), 6.70 (d, *J* 5.9, 2H, *Ph*), 7.0–7.4 (m, 10H, *Ph*), 7.66 (d, *J* 7.3, 1H, *Ph*); δ_C ($CDCl_3$) 42.2, 44.4, 47.5, 50.6, 120.7, 123.6, 124.4, 127.2, 134.5, 136.4, 139.3, 140.6, 142.7, 176.0, 177.5; IR (Nujol) 3359, 1767, 1680; Anal. Calcd for $C_{25}H_{19}NO$: C, 78.72; H, 5.02; N, 3.67; Found C, 78.77; H, 4.99; N, 3.67%. HPLC (*S*,*S*)-isomer 19.6 min (major), (*R*,*R*)-isomer 21.5 min (minor).

4-Hydroxy-2-phenyl-3a,4,9,9a-tetrahydro-4,9-[1′,2′]benzeno-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione 5c. 61% ee; colorless solid; mp 208–209 °C; $[a]_D^{20}$ +37.0 (*c* 0.5 in $CHCl_3$); δ_H ($CDCl_3$) 3.25 (d, *J* 8.6, 1H, HOCHC*H*), 3.46 (dd, *J* 3.5, 8.6, 1H, CHC*H*CH), 4.56 (s, 1H, O*H*), 4.83 (d, *J* 3.2, 1H, CHC*H*), 6.4–6.5 (m, 2H, *Ph*), 7.2–7.3 (m, 8H, *Ph*), 7.40 (d, *J* 7.3, 1H, *Ph*), 7.55 (d, *J* 7.7, 1H, *Ph*), 7.73 (d, *J* 7.3, 1H, *Ph*); δ_C ($CDCl_3$) 44.8, 47.7, 50.8, 120.9, 121.1, 123.8, 124.7, 126.3, 126.8, 126.9, 127.2, 127.3, 129.0, 129.1, 130.8, 136.6, 138.8, 140.9, 142.3, 175.6, 177.1; IR (Nujol) 3420, 1773, 1700; HRMS (M^+) Calcd for $C_{24}H_{17}NO_3$: 367.1207; Found 367.1197; HPLC (*S*,*S*)-isomer 30.5 min (major), (*R*,*R*)-isomer 33.6 min (minor).

4-Hydroxy-2-(4-trifluoromethylphenyl)-3a,4,9,9a-tetrahydro-4,9-[1′,2′]benzeno-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione 5d. 50% ee; colorless solid; mp 219–220 °C; $[a]_D^{20}$ +20.0 (*c* 0.5, $CHCl_3$); δ_H ($CDCl_3$) 3.30 (d, *J* 8.9, 1H, HOCHC*H*), 3.51 (dd, *J* 3.5, 8.6, 1H, CHC*H*CH), 4.47 (s, 1H, O*H*), 4.84 (d, *J* 3.5, 1H, CHC*H*), 6.67 (d, *J* 8.4, 2H, *Ph*), 7.2–7.3 (m, 5H, *Ph*), 7.42 (d, *J* 7.0, 1H, *Ph*), 7.57 (d, *J* 8.4, 3H, *Ph*), 7.74 (d, *J* 7.3, 1H, *Ph*); δ_C ($CDCl_3$) 44.8, 47.7, 50.9, 120.9, 121.1, 123.8, 124.7, 126.1, 126.2, 126.3, 126.6, 126.7, 126.9, 127.3, 127.4, 134.0, 136.6, 138.7, 140.8, 142.1, 145.1, 176.6; IR (Nujol) 3505, 1780, 1706, 1323; HRMS (M^+) Calcd for $C_{25}H_{16}F_3NO_3$: 435.1081; Found 435.1064; HPLC (*S*,*S*)-isomer 18.6 min (major), (*R*,*R*)-isomer 20.3 min (minor).

4-Hydroxy-2-(4-fluorophenyl)-3a,4,9,9a-tetrahydro-4,9-[1′,2′]-benzeno-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione 5e. 57% ee; colorless solid; mp 191–192 °C; $[a]_D^{20}$ +28.4 (*c* 0.5, $CHCl_3$); δ_H ($CDCl_3$) 3.25 (d, *J* 8.6, 1H, HOCHC*H*), 3.47 (dd, *J* 3.5, 8.6, 1H, CHC*H*CH), 4.52 (s, 1H, O*H*), 4.82 (d, *J* 3.5, 1H, CHC*H*), 6.43–6.48 (m, 2H, *Ph*), 6.98 (t, *J* 8.5, 2H, *Ph*), 7.2–7.3 (m, 4H, *Ph*), 7.40 (d, *J* 6.2, 2H, *Ph*), 7.55 (d, *J* 7.6, 1H, *Ph*), 7.73 (d, *J* 7.3, 1H, *Ph*); δ_C ($CDCl_3$) 44.8, 47.6, 50.8, 116.0, 116.4, 120.9, 121.1, 123.8, 124.7, 126.7, 126.9, 127.0, 127.2, 127.3, 128.1, 128.2, 136.6, 138.7, 140.9, 142.1, 160.6, 164.2, 175.5, 177.0; IR (Nujol) 3400, 1774, 1703; HRMS (M^+) Calcd for $C_{24}H_{16}FNO_3$: 385.1113; Found 385.1102; HPLC (*S*,*S*)-isomer 28.3 min (major), (*R*,*R*)-isomer 31.2 min (minor).

4-Hydroxy-2-(4-methoxyphenyl)-3a,4,9,9a-tetrahydro-4,9-[1′,2′]benzeno-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione 5f. 74% ee; colorless solid; mp 206–207 °C; $[a]_D^{20}$ +29.0 (*c* 0.5, $CHCl_3$); δ_H ($CDCl_3$) 3.24 (d, *J* 8.3, 1H, HOCHC*H*), 3.47 (dd, *J* 3.5, 8.6, 1H, CHC*H*CH), 3.75 (s, 3H, OC*H*$_3$), 4.55 (s, 1H, O*H*), 4.82 (d, *J* 3.8, 1H, CHC*H*), 6.38 (d, *J* 8.4, 2H, *Ph*), 6.80 (d, *J* 8.9, 2H, *Ph*), 7.2–7.3 (m, 5H, *Ph*), 7.40 (d, *J* 7.0, 1H, *Ph*), 7.55 (d, *J* 7.0, 1H, *Ph*), 7.73 (d, *J* 7.6, 1H, *Ph*); δ_C ($CDCl_3$) 44.8, 47.6, 50.7, 55.4, 114.5, 120.9, 121.1, 123.4, 123.7, 124.7, 126.8, 126.9, 127.2, 127.3, 127.5, 136.6, 138.8, 141.0, 142.3; IR (Nujol) 3380, 1695; HRMS (M^+) Calcd for $C_{25}H_{19}NO_4$: 397.1313; Found 397.1307; HPLC (*S*,*S*)-isomer 58.6 min (major), (*R*,*R*)-isomer 67.2 min (minor).

4-Hydroxy-2-(2,6-dichlorophenyl)-3a,4,9,9a-tetrahydro-4,9-[1′,2′]benzeno-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione 5g. 63% ee; colorless solid; mp 229–231 °C; $[a]_D^{20}$ +20.6 (*c* 0.5, $CHCl_3$); δ_H ($CDCl_3$) 3.42 (d, *J* 9.5, 1H, HOCHC*H*), 3.60 (dd, *J* 3.2, 9.2, 1H, CHC*H*CH), 4.39 (s, 1H, O*H*), 4.86 (d, *J* 3.2, 1H, CHC*H*), 7.2–7.4 (m, 9H, *Ph*), 7.59 (d, *J* 7.3, 1H, *Ph*), 7.69 (d, *J* 7.3, 1H, *Ph*); δ_C ($CDCl_3$) 44.3, 47.7, 50.7, 120.6, 121.6, 123.6, 125.3, 126.7, 126.8, 127.5, 127.6, 128.2, 128.4, 131.2, 133.6, 134.5, 137.0, 141.3, 142.9, 173.7, 175.4; IR (Nujol) 3420, 1773, 1700; HRMS (M^+) Calcd for $C_{24}H_{15}Cl_2NO_3$: 435.0428; Found 435.0435; HPLC (*S*,*S*)-isomer 22.5 min (major), (*R*,*R*)-isomer 27.2 min (minor).

4-Hydroxy-2-(2,4-dibromophenyl)-3a,4,9,9a-tetrahydro-4,9-[1′,2′]benzeno-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione 5h. 63% ee; colorless solid; mp 206–207 °C; $[a]_D^{20}$ +21.0 (*c* 0.5, $CHCl_3$); δ_H ($CDCl_3$) 3.34 (d, *J* 8.1, 1H, HOCHC*H*), 3.55 (dd, *J* 3.2, 8.8, 1H, CHC*H*CH), 4.36 and 4.47 (s, 1H, O*H*), 4.82 (d, *J* 3.2, 1H, CHC*H*), 7.2–7.5 (m, 11H, *Ph*); δ_C ($CDCl_3$) 44.7, 48.0, 51.1, 121.0, 121.2, 122.7, 123.8, 124.2, 124.8, 127.0, 127.2, 127.3, 129.8, 130.6, 131.1, 131.8, 135.7, 136.8, 138.5, 141.1, 142.0, 174.3, 175.9; IR (Nujol) 3440, 1770, 1700; HRMS (M^+) Calcd for $C_{24}H_{15}Br_2NO_3$: 526.9379; Found 526.9419; HPLC (*S*,*S*)-isomer 18.2 min (major), (*R*,*R*)-isomer 23.6 min (minor).

4-Hydroxy-2-(2,6-dimethyl)-3a,4,9,9a-tetrahydro-4,9-[1′,2′]-benzeno-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione 5i. 50% ee; colorless solid; mp 211–213 °C; $[a]_D^{20}$ +20.6 (*c* 0.5, $CHCl_3$); δ_H ($CDCl_3$) 0.94 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 3.37 (d, *J* 3.2, 9.2, 1H, HOCHC*H*), 3.55 (dd, *J* 3.2, 9.2, 1H, CHC*H*CH), 4.50 (s, 1H, O*H*), 4.86 (d, *J* 3.5, 1H, CHC*H*), 6.9–7.3 (m, 6H, *Ph*), 7.3–7.4 (m, 3H, *Ph*), 7.59 (d, *J* 7.3, 1H, *Ph*), 7.69 (d, *J* 7.3, 1H, *Ph*); δ_C ($CDCl_3$) 16.1, 17.7, 17.9, 44.3, 47.6, 50.6, 54.3, 120.6, 121.6, 123.6, 125.1, 126.6, 126.7, 126.8, 127.5, 127.6, 127.9, 128.2, 128.4, 128.5, 129.5, 132.2, 133.7, 134.3, 134.7, 136.2, 137.2, 138.5, 139.8, 141.5, 143.0, 175.2, 176.8; IR (Nujol) 3420, 1770, 1700; HRMS (M^+) Calcd for $C_{26}H_{21}NO_3$: 395.152; Found 395.1517; HPLC (*S*,*S*)-isomer 19.3 min (major), (*R*,*R*)-isomer 23.5 min (minor).

4-Hydroxy-2-(2-*tert*-butylphenyl)-3a,4,9,9a-tetrahydro-4,9-[1′,2′]benzeno-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione 5j. 87% ee; colorless solid; mp 192–193 °C; $[a]_D^{20}$ +34.8 (*c* 0.5, $CHCl_3$); δ_H ($CDCl_3$) 1.21 (s, 9H, 3 × CC*H*$_3$), 3.30 (d, *J* 8.9, 1H, HOCHC*H*), 3.52 (dd, *J* 3.5, 8.6, 1H, CHC*H*CH), 4.66 (s, 1H, O*H*),

4.84 (d, *J* 3.5, 1H, CHC*H*), 6.97 (t, *J* 6.8, 1H, *Ph*), 7.2–7.5 (m, 9H, *Ph*), 7.58 (d, *J* 7.0, 1H, *Ph*), 7.72 (d, *J* 6.8, 1H, *Ph*); δ_C ($CDCl_3$) 31.6, 35.5, 44.6, 48.0, 51.0, 121.0, 121.4, 123.9, 125.0, 126.9, 127.0, 127.3, 127.4, 128.4, 129.6, 129.8, 130.1, 137.2, 139.0, 141.5, 142.5, 147.7, 176.8, 178.6; IR (Nujol) 3480, 1770, 1700; HRMS (M^+) Calcd for $C_{28}H_{25}NO_3$: 423.1833; Found 423.1861; HPLC (*S*,*S*)-isomer 12.1 min (major), (*R*,*R*)-isomer 14.4 min (minor).

(10*S*)-10-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)anthracen-9(10*H*)-one (*S*)-6c—typical procedure for conversion of adduct 5 to ketone 6

To a solution of *ent*-**5c** (75 mg, 0.18 mmol) in CH_3OH (4 cm^3), triethylamine (2 drops) was added, and the mixture was stirred at room temperature for 1 day. After evaporation, the residue was purified with flash column chromatography (silica gel, 15% EtOAc in hexane) to give **6c** (26 mg, 35% yield); colorless solid; $[\alpha]_D^{20}$ −140.2 (*c* 1.0, CH_3OH); δ_H ($CDCl_3$) 2.07 (dd, *J* 5.1, 19.4, 1H, CHCH_2), 2.41 (dd, *J* 9.5, 19.4, 1H, CHCH_2), 3.5–3.7 (m, 1H, CH_2C*H*), 5.26 (d, *J* 3.24, 1H, Ph-C*H*), 7.0–7.2 (m, 2H, *Ph*), 7.4–7.7 (m, 9H, *Ph*), 8.1–8.2 (m, 2H, *Ph*); δ_C ($CDCl_3$) 29.3, 29.8, 42.0, 49.9, 126.2, 127.8, 128.0, 128.1, 128.1, 128.6, 128.7, 128.8, 129.1, 131.4, 132.4, 133.2, 133.5, 133.7, 138.1, 142.2, 173.8, 176.8, 183.6; HRFABMS $(M + H)^+$ Calcd for $C_{24}H_{18}NO_3$: 368.1285; Found 368.1258.

(10*S*)-10-[2,5-Dioxo-1-(2-*tert*-butylphenyl)pyrrolidin-3-yl]-anthracen-9(10*H*)-one (*S*)-6j. 35% yield; yellow oil; $[\alpha]_D^{20}$ −69.3 (*c* 1.0, CH_3OH); δ_H ($CDCl_3$) 1.27 (s, 9H, 3 × CCH_3), 2.09 (dd, *J* 5.4, 18.8, 1H, CHCH_2), 2.42 (dd, *J* 9.5, 18.6, 1H, CHCH_2), 3.6–3.7 (m, 1H, CH_2C*H*), 5.31 (d, *J* 3.0, 1H, Ph-C*H*), 6.3–6.4 (m, 2H, *Ph*), 7.2–7.3 (m, 2H, *Ph*), 7.4–7.5 (m, 2H, *Ph*), 7.5–7.7 (m, 4H, *Ph*), 8.3–8.4 (m, 2H, *Ph*); δ_C ($CDCl_3$) 29.4, 31.6, 31.7, 35.7, 41.5, 50.3, 121.0, 127.3, 127.8, 127.9, 128.1, 128.4, 128.7, 128.9, 129.8, 130.2, 132.4, 133.2, 133.6, 133.7, 138.4, 142.3, 147.8, 174.9, 178.0, 183.6; IR (neat) 1184, 1251, 1661, 1668, 1713; HRFABMS $(M + H)^+$ Calcd for $C_{28}H_{26}NO_3$: 424.1914; Found 424.1937.

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