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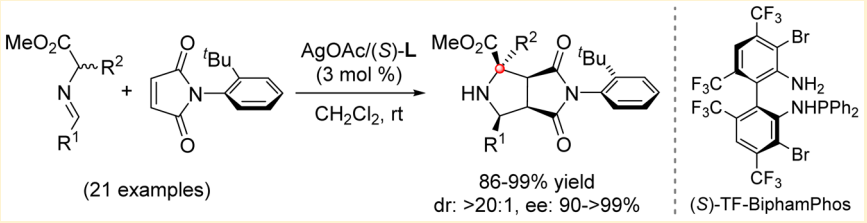
Silver(I)-Catalyzed Atroposelective Desymmetrization of *N*-Arylmaleimide via 1,3-Dipolar Cycloaddition of Azomethine Ylides: Access to Octahydropyrrolo[3,4-*c*]pyrrole Derivatives

Hua-Chao Liu,[†] Hai-Yan Tao,[‡] Hengjiang Cong,[†] and Chun-Jiang Wang*[,†]

[†]College of Chemistry, Molecular Sciences, Wuhan University, Wuhan, China, 430072

[‡]State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin, China, 300071

Supporting Information

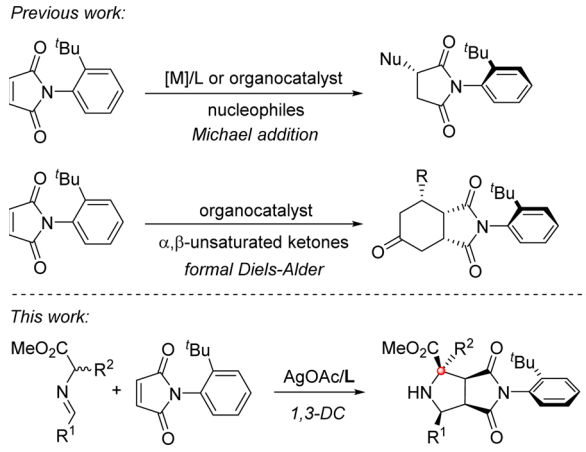


ABSTRACT: A highly efficient Ag(I)-catalyzed atroposelective desymmetrization of *N*-(2-*t*-butylphenyl)maleimide via 1,3-dipolar cycloaddition of in situ generated azomethine ylides has been established successfully, affording a facile access to a series of biologically important and enantioenriched octahydropyrrolo[3,4-*c*]pyrrole derivatives in generally high yields (up to 99%) with excellent levels of diastereo-/enantioselectivities (up to 99% ee, >20:1 dr). Subsequent transformations led to fascinating 2*H*-pyrrole and polysubstituted pyrrole compounds without loss of stereoselectivity. The absolute configuration of the generated chiral axis has been unambiguously identified as (*M*) through single-crystal X-ray diffraction analysis. Furthermore, on the basis of the comprehensive experimental results and the absolute configuration of one of the cycloadducts, the origin of the stereoselectivity was proposed to be attributed to the steric congestion imposed by the bulky PPh_2 group of the chiral ligand and the *tert*-butyl group of *N*-(2-*t*-butylphenyl)maleimide. The possible hydrogen bond interaction between the NH_2 group of the chiral ligand and one of the carbonyl groups of *N*-(2-*t*-butylphenyl)maleimide is considered to facilitate stabilizing the transition state.

INTRODUCTION

Catalytic enantioselective desymmetrization of prochiral or meso molecules[1,2] has attracted much attention as a direct and efficient tool for the synthesis of enantioenriched compounds possessing one or more stereogenic elements. Because of important biological activities and popular employments in chiral ligands and catalysts,[3] the enantioselective construction of atropisomeric compounds through desymmetrization strategy exhibits an ever-growing interest in organic synthesis. However, compared with extensively investigated biaryl axially chiral compounds with a C−C chiral axis,[4] the synthesis of other optically pure atropisomeric compounds, especially C−N axially chiral compounds, is also particularly appealing and more challenging. Since the pioneering works of Curran et al.,[5] who first reported the construction of C−N axially chiral *ortho*-*t*-butylanilides as stable atropisomers, considerable efforts have been devoted to the catalytic asymmetric synthesis of highly functionalized C−N axially chiral compounds.[6] Later on, Duan et al. reported elegant methodologies for the desymmetric construction of enantiomerically enriched atropisomeric succinimides by employing *N*-(2-*t*-butylphenyl)maleimides as the prochiral Michael acceptors and formal Diels−Alder dienophiles (Scheme 1).[7] In contrast to those well-established desymmetrization strategies for the synthesis of succinimides containing both atom and axial chirality, the asymmetric

Scheme 1. Catalytic Asymmetric Desymmetrization Employing Prochiral *N*-(2-*t*-Butylphenyl)maleimide



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construction of octahydropyrrolo[3,4-*c*]pyrrole scaffolds frequently found in numerous bioactive pharmaceutical ingredients (Figure 1)[8−11] received less attention, and an expedient desymmetric approach to the highly functionalized octahydropyrrolo[3,4-*c*]pyrrole derivatives still remains elusive to date.

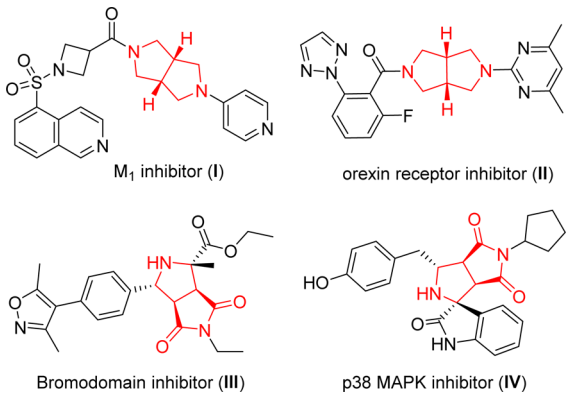


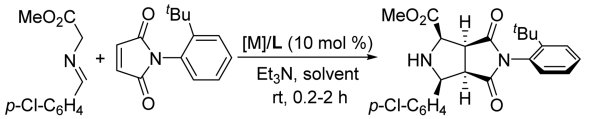
Figure 1. Typical examples of bioactive pharmaceuticals containing octa-hydropyrrolo[3,4-*c*]pyrrole motif.

Recently, we developed enantioselective desymmetrization of prochiral spiro cyclohexadienone lactones and cyclopentenediones[12] via 1,3-dipolar cycloaddition of azomethine ylides[13,14] with the help of Ag(I)/TF-BiphamPhos complex, leading to high densely functionalized bicyclic pyrrolidines and spirolactone-pyrrolidine compounds in enantiopure forms. Merging our previous works[15] and the construction of octahydropyrrolo-[3,4-*c*]pyrrole frameworks without axial chirality,[16] we envisaged that Ag(I)/TF-BiphamPhos complex could be employed as an effective catalyst for atroposelective desymmetrization of prochiral *N*-(2-*t*-butylphenyl)maleimides with azomethine ylides, affording octahydropyrrolo[3,4-*c*]pyrrole derivatives decorated with four adjacent stereogenic centers and one N−C chiral axis through 1,3-dipolar cycloaddition reaction. In this article, we report an efficient silver(I)-catalyzed atroposelective desymmetrization 1,3-dipolar cycloaddition reaction of azomethine ylide with prochiral *N*-(2-*t*-butylphenyl)maleimide to afford enantiomerically enriched octahydropyrrolo[3,4-*c*]pyrrole derivatives bearing four adjacent stereocenters and one N−C chiral axis.

RESULTS AND DISCUSSION

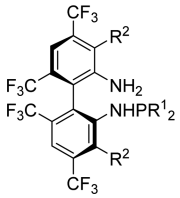
Initially, the readily available imino ester **1a** and prochiral *N*-(2-*t*-butylphenyl)maleimide **2a** were selected as the model substrates to identify the optimal reaction conditions with Ag(I)/chiral TF-BiphamPhos complex as the catalyst and Et_3N as the base at room temperature. To our delight, the transformation proceeded efficiently and reached completion within 0.2 h, affording the desired cycloadduct **3aa** in high yield with excellent diastereoselectivity (dr > 20:1) and high enantioselectivity (89% enantiomeric excess, ee). Switching the metal precursor from AgOAc to $CuBF_4$ gave rise to a dramatic reduction of enantioselectivity, albeit remaining reactive (Table 1, entries 1 and 2). To improve the enantioselectivity, we then tested a series of available chiral TF-BiphamPhos ligands from our lab (entries 3−6). Gratifyingly, TF-BiphamPhos (*S*)-**L5** exhibited the most outstanding chiral induction, giving octahydropyrrolo [3,4-*c*]pyrrole **3aa** in quantitative yield with exclusive diastereoselectivity (>20:1 dr) and excellent enantioselectivity (95% ee, entry 6). Furthermore,

Table 1. Screening Studies of the Catalytic Asymmetric Desymmetrization of Prochiral *N*-(2-*t*-Bbutylphenyl)maleimide 2a[a]



entry	L	[M]	solvent	yield (%)[b]	ee (%)[c]
1	(*S*)-**L1**	$CuBF_4$	CH_2Cl_2	90	32
2	(*S*)-**L1**	AgOAc	CH_2Cl_2	94	89
3	(*S*)-**L2**	AgOAc	CH_2Cl_2	86	39
4	(*S*)-**L3**	AgOAc	CH_2Cl_2	90	44
5	(*S*)-**L4**	AgOAc	CH_2Cl_2	85	36
6	(*S*)-**L5**	AgOAc	CH_2Cl_2	99	95
7[d]	(*S*)-**L5**	AgOAc	CH_2Cl_2	99	98
8[d,e]	(*S*)-**L5**	AgOAc	MeOH	88	91
9[d,f]	(*S*)-**L5**	AgOAc	MeCN	95	92
10[d]	(*S*)-**L5**	AgOAc	PhMe	95	96
11[d]	(*S*)-**L5**	AgOAc	THF	90	97
12[d]	(*S*)-**L5**	AgOAc	EtOAc	89	97
13[d,g]	(*S*)-**L5**	AgOAc	CH_2Cl_2	99	98

[a]All reactions were carried out with 0.30 mmol of **2** (1.0 equiv) and 0.36 mmol of **1a** (1.2 equiv) in 2 mL of solvent in 2 h unless specified. $CuBF_4$ = $Cu(CH_3CN)_4BF_4$. [b]Isolated yield. [c]>20:1 dr was determined by crude ^{1}HNMR, and ee was determined by HPLC analysis. [d]Without Et_3N. [e]In 5 h. [f]In 3 h. [g]3 mol % AgOAc and 4 mol % (*S*)-**L5** were used.



L1: R^1 = Ph, R^2 = H
L2: R^1 = 3,5-bis(methyl)phenyl, R^2 = H
L3: R^1 = 3,5-bis(trifluoromethyl)phenyl, R^2 = H
L4: R^1 = Cy, R^2 = H
L5: R^1 = Ph, R^2 = Br

improved enantioselectivity (98% ee) was obtained without adding Et_3N as the extra base, and similar results could be also observed in many examples of employing moderately basic charged ligand acetate as Brønsted base (entry 7).[16,17] Subsequently, no better results could be obtained by varying the solvents for this transformation (entries 8−12), and a little lower enantioselectivity was observed with MeOH and MeCN as the solvent probably because of the disfavored competitive hydrogen-bonding activation between the dipolarophile **2a** or chiral ligand TF-BiphamPhos and the polar solvent (vide infra). Finally, a 3 mol % catalyst loading was employed without significant influence on the reaction outcome, which was identified as the optimal reaction conditions, delivering the cycloadduct in quantitative yield and 98% ee (entry 13).

With the optimized reaction conditions in hand, we first explored the scope of a series of imino esters derived from glycinate, and the results are shown in Table 2. Various examined non-α-substituted imino esters (**1a**−**1i**) containing electronically divergent substituents on the phenyl ring (Table 2, entries 1−9) reacted smoothly with *N*-(2-*t*-butylphenyl)-maleimide, giving the corresponding products (**3aa**−**3ai**) in excellent yields (98−99%) and enantioselectivity (96−99% ee). Additionally, imino esters (**1j**−**1k**) bearing a heteroaromatic or fused ring (entries 10−11) were also well tolerated, resulting in the desired cycloadducts (**3ja**−**3ka**) in quantitative yield and in enantiopure forms (98−99% ee). Furthermore, when cinnamyl

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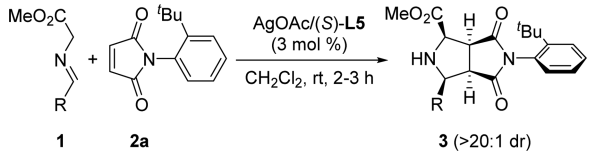
Table 2. Substrate Scope of Azomethine Ylides Derived from Glycinate for Ag-Catalyzed Desymmetrization of *N*-(2-*t*-Butylphenyl)maleimide 2a[a]



1 2a 3 (>20:1 dr)

entry	R	1	3	yield (%)[b]	ee (%)[c]
1	*p*-Cl-C_6H_4	**1a**	**3aa**	99	98
2	*m*-Cl-C_6H_4	**1b**	**3ba**	99	98
3	*p*-Br-C_6H_4	**1c**	**3ca**	99	97
4	*m*-Br-C_6H_4	**1d**	**3da**	99	98
5	*o*-F-C_6H_4	**1e**	**3ea**	98	96
6	*p*-MeO-C_6H_4	**1f**	**3fa**	99	99
7	*m*-MeO-C_6H_4	**1g**	**3ga**	99	98
8	*p*-Me-C_6H_4	**1h**	**3ha**	99	99
9	Ph	**1i**	**3ia**	99	99
10	2-thienyl	**1j**	**3ja**	99	>99
11	2-naphthyl	**1k**	**3ka**	99	98
12	cinnamyl	**1l**	**3la**	99	90
13[d]	*n*-Bu	**1m**	**3ma**	86	92

[a]All reactions were carried out with 0.30 mmol of **2a** (1.0 equiv) and 0.36 mmol of **1** (1.2 equiv) in 2 mL of CH_2Cl_2 at rt. [b]Isolated yield. [c]>20:1 dr was determined by crude ^{1}H NMR and ee value was determined by HPLC analysis. [d]In 6 h.

aldehyde derived imino ester (**1l**) was employed as the precursor of azomethine ylide, the annulation process could also proceed successfully, delivering the corresponding octahydropyrrolo[3,4-*c*]pyrrole derivative (**3la**) in high yield and with 90% ee (entry 12). Remarkably, the challenging imino ester (**1m**) derived from aliphatic aldehydes could also be employed in this transformation as a suitable reaction partner, affording the corresponding cycloadduct (**3ma**) with the satisfactory enantioselectivity (entry 13). The absolute configuration of the cycloadduct **3aa** has been unambiguously identified as (*M*,1*R*,3*S*,3a*R*,6a*S*) by single-crystal X-ray diffraction analysis (Figure 2).[18]

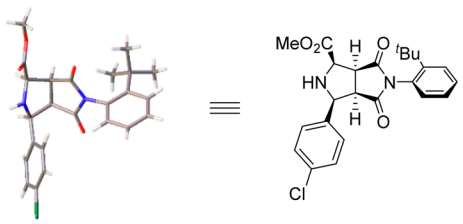
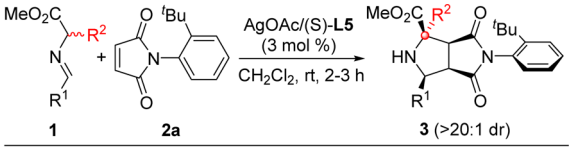


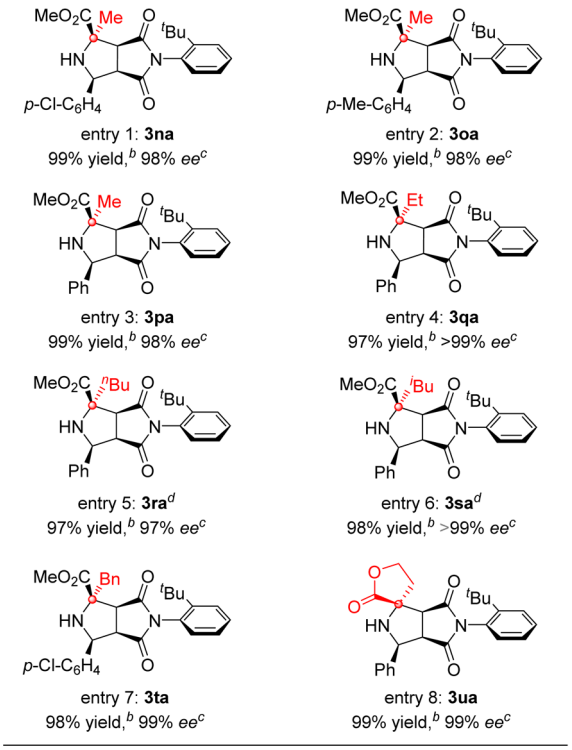
Figure 2. X-ray crystal structure of (*M*,1*R*,3*S*,3a*R*,6a*S*)-**3aa**.

Encouraged by the excellent asymmetric induction with glycinate-derived imino esters, we next evaluated the scope of various more sterically hindered imino esters derived from α-substituted-α-amino acids (as highlighted in Table 3). To our delight, alanine-derived imino esters (**3n**−**3p**) have proven to be excellent substrates regardless of electronic properties (electron-deficient, -rich, and -neutral) of aromatic substitutes, giving access to the corresponding endo-products (**3na**−**3pa**) on par with the results observed in the model reaction (entries 1−3). Excellent yield and stereochemistry could be also obtained even for the substrates (**3q**−**3t**) with larger steric

Table 3. Substrate Scope of Azomethine Ylides Derived from α-Substituted-α-Amino Acids for Ag-Catalyzed Desymmetrization of *N*-(2-*t*-Butylphenyl)maleimide 2a[a]



1 2a 3 (>20:1 dr)



[a]All reactions were carried out with 0.30 mmol of **2a** (1.0 equiv) and 0.36 mmol of **1** (1.2 equiv) in 2 mLof CH_2Cl_2 at rt. [b]Isolated yield. [c]>20:1 dr was determined by crude ^{1}H NMR, and ee value was determined by HPLC analysis. [d]In 5 h.

hindrance (entries 4−7). Meanwhile, the methodology for the *rac*-homoserine derived cyclic imino ester (**3u**) also performed well providing the desired highly functionalized adduct (**3ua**) in quantitative yield with up to 99% ee, in which an additional spiro quaternary stereogenic centers was formed among the four adjacent stereocenters (entry 8).

To further explore this synthetic potential, several transformations of the cycloadduct **3aa** were conducted in toluene with DDQ as oxidant. Partial and complete oxidation readily occurred leading to fascinating 2*H*-pyrrole **4aa** and polysubstituted pyrrole compound[19] **5aa**, respectively, when mixing the reaction system with or without silica gel.[15b] No erosion of enantioselectivity was observed in the above oxidation processes (Scheme 2).

On the basis of the absolute configuration of the cycloadduct **3aa** and our previous work,[20] a plausible transition state accounting for the origin of the stereoselectivity was proposed as illustrated in Scheme 3. Under standard condition, imino esters are coordinated to the silver center of the catalytically active species consisting of Ag(I)/(*S*)-TF-BiphamPhos complex, promoting the in situ formation of azomethine ylide in a tetradentate manner. Subsequently, the prochiral *N*-(2-*t*-butylphenyl)maleimide is exclusively forced to approach from

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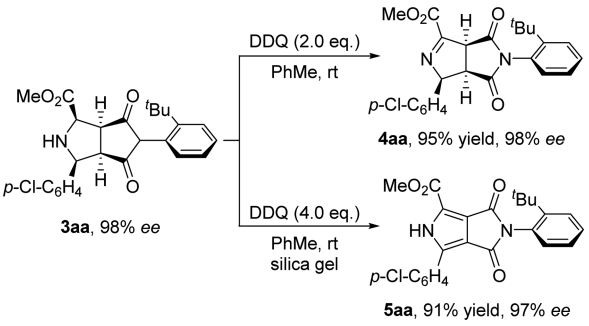
Scheme 2. Elaboration of the Cycloadduct 3aa



the Si face (C═N) of the azomethine ylide in which the *tert*-butyl group was far away from the metal center because of the steric congestion imposed by the bulky PPh_2 group of the chiral ligand and the *tert*-butyl group of *N*-(2-*t*-butylphenyl)-maleimide, which leads to the observed four adjacent stereogenic centers and one N−C chiral axis in this desymmetrization process. In addition, the transition state is considered to be further stabilized by the possible hydrogen bond interaction between the NH_2 group of the chiral ligand and one of the carbonyl groups of *N*-(2-*t*-butylphenyl)-maleimide.

CONCLUSION

In conclusion, we have developed a Ag(I)-catalyzed atroposelective desymmetrization of prochiral *N*-(2-*t*-butylphenyl)-maleimide through azomethine ylide-involved 1,3-dipolar cycloaddition reaction, affording enantioenriched octahydropyrrolo[3,4-*c*]pyrrole derivatives possessing four adjacent stereocenters and one N−C axis. This novel desymmetrization process works well with a broad substrate scope to afford the corresponding annulation products with great yields (up to 99%) and excellent stereoselectivity control (up to 99% ee, > 20:1 dr). Notably, the versatile conversion of annulation product leads to fascinating 2*H*-pyrrole and polysubstituted pyrrole compounds, both of which are structurally important nitrogen-containing heterocycles and which can provide a potential and valuable building block serving as a precursor for drug discovery.

EXPERIMENTAL SECTION

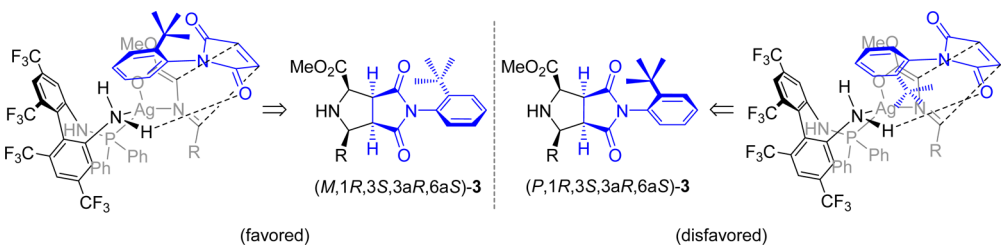
General Information. All commercial materials were used without further purification unless otherwise noted. All reactions were carried out under a nitrogen atmosphere. All reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel 60 F254. Products were purified by flash chromatography on silica gel 60 (300−400 mesh). ^{1}H NMR spectra were recorded on 300 and 400 MHz spectrometer in $CDCl_3$. Chemical shifts are reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The data are reported as (s = single, d = double, t = triple, q = quartet, m = multiple or unresolved, br = broad single, coupling constants in Hz, integration). ^{13}C NMR spectra were recorded on 75 and 100 MHz spectrometer in $CDCl_3$ or DMSO-d_6. Chemical shifts are reported in ppm with the internal $CDCl_3$ and DMSO signal at 77.0 and 39.5 ppm as a standard, respectively. High-resolution MS spectra were recorded with an LTQ FT Ultra mass spectrometer, equipped with a DART (Direct Analysis in Real Time) ion source. Specific optical rotation $[\alpha]_D^T$ was measured on a polarimeter with a cell of 1 dm path length at 20 °C. Enantiomeric ratios were determined by HPLC, using a chiralpak AS-H, AD-H, and ID-H column with hexane and *i*-PrOH as solvents. *N*-(2-*t*-Butylphenyl)maleimide substrate **2** was prepared according to the literature procedure.[21] Chiral ligands **L1**-**L5** were prepared according our previous procedure.[15a]

General Procedure for Asymmetric Desymmetrization of *N*-(2-*t*-Butylphenyl) maleimide with Azomethine Ylide Catalyzed by AgOAc/(*S*)-TF-BiphamPhos. Under argon atmosphere, (*S*)-TF-BiphamPhos **L5** (9.6 mg, 0.012 mmol) and AgOAc (1.5 mg, 0.009 mmol) were dissolved in 2.0 mL CH_2Cl_2 and were stirred at room temperature for about 30 min. Then, the imino ester **1** (0.40 mmol) and *N*-(2-*t*-butylphenyl)maleimide **2** (0.30 mmol) were added sequentially. Once the starting material was consumed (monitored by TLC), the organic solvent was removed and the residue was purified by column chromatography using mixtures of petroleum ether/ethyl acetate (4/1 → 2/1 → 1/1) to give the product, which was then directly analyzed by HPLC to determine the enantiomeric excess.

*(M,1R,3S,3aR,6aS)-Methyl 5-(2-(tert-Butyl)phenyl)-3-(4-chlorophenyl)-4,6-dioxo octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**3aa**).* Prepared according to the general procedure starting from imine ester **1a** and *N*-(2-*t*-butylphenyl)maleimide; yield: 131 mg, 99%; white solid; mp 180−182 °C; $[\alpha]_D^{20}$ = −129.5 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.52−7.40 (m, 3H), 7.40−7.23 (m, 4H), 6.91−6.83 (m, 1H), 4.57 (d, *J* = 7.8 Hz, 1H), 4.16 (d, *J* = 6.0 Hz, 1H), 3.85 (s, 3H), 3.77−3.68 (m, 1H), 3.62−3.53 (m, 1H), 2.50 (br s, 1H), 1.22 (s, 9H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 176.9, 175.3, 170.2, 147.7, 137.6, 131.6, 131.1, 130.7, 129.4, 129.1, 128.5, 127.7, 127.3, 62.4, 61.3, 51.5, 48.7, 47.6, 35.2, 31.3. HRMS calcd for $C_{24}H_{25}ClN_2O_4$ + H^+: 441.1576; found: 441.1571. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (Chiralpak AS-H, *i*-propanol/hexane = 50/50, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.33 and 11.05 min.

(M,1R,3S,3aR,6aS)-Methyl 5-(2-(tert-Butyl)phenyl)-3-(3-chlorophenyl)-4,6-dioxo- octahydropyrrolo[3,4-c]pyrrole-1-

Scheme 3. Proposed Transition State Leading to (M,1R,3S,3aR,6aS)-3



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*carboxylate (**3ba**)*. Prepared according to the general procedure starting from imine ester **1b** and *N*-(2-*t*-butylphenyl)maleimide; yield: 131 mg, 99%; white solid; mp 170−172 °C; $[\alpha]_D^{20}$ = −98.0 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.55−7.51 (m, 1H), 7.49 (dd, J_1 = 1.2 Hz, J_2 = 1.2 Hz, 1H), 7.38−7.30 (m, 2H), 7.30−7.21 (m, 3H), 6.88 (dd, J_1 = 1.2 Hz, J_2 = 1.2 Hz, 1H), 4.60−4.55 (m, 1H), 4.18−4.14 (m, 1H), 3.86 (s, 3H), 3.72 (t, *J* = 7.6 Hz, 1H), 3.58 (t, *J* = 8.4 Hz, 1H), 2.51 (br s, 1H), 1.22 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.9, 175.3, 170.3, 147.7, 141.3, 132.6, 130.9, 130.7, 129.7, 129.5, 128.6, 127.2, 127.0, 126.2, 62.4, 61.3, 51.5, 48.8, 47.6, 35.2, 31.3. HRMS calcd for $C_{24}H_{25}ClN_2O_4$ + H^+: 441.1576; found: 441.1571. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (Chiralpak AS-H, *i*-propanol/hexane = 50/50, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.10 and 11.89 min.

*(M,1R,3S,3aR,6aS)-Methyl 3-(4-Bromophenyl)-5-(2-(tert-butyl)phenyl)-4,6-dioxo- octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**3ca**)*. Prepared according to the general procedure starting from imine ester **1c** and *N*-(2-*t*-butylphenyl)maleimide; yield: 144 mg, 99%; white solid; mp 181−183 °C; $[\alpha]_D^{20}$ = −126.50 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.51−7.44 (m, 3H), 7.39−7.31 (m, 3H), 7.29−7.24 (m, 1H), 6.86 (dd, J_1 = 1.2 Hz, J_2 = 1.2 Hz, 1H), 4.55 (d, *J* = 8.0 Hz, 1H), 4.16 (d, *J* = 7.2 Hz, 1H), 3.85 (s, 3H), 3.75−3.70 (m, 1H), 3.58−3.54 (m, 1H), 2.49 (br s, 1H), 1.22 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.9, 175.4, 170.3, 147.7, 138.1, 131.1, 130.7, 129.5, 128.5, 127.3, 120.2, 62.5, 61.4, 51.5, 48.7, 47.6, 35.2, 31.3. HRMS calcd for $C_{24}H_{25}BrN_2O_4$ + H^+: 485.1070; found: 485.1069. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak AS-H, *i*-propanol/hexane = 50/50, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.18 and 10.70 min.

*(M,1R,3S,3aR,6aS)-Methyl 3-(3-Bromophenyl)-5-(2-(tert-butyl)phenyl)-4,6-dioxo- octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**3da**)*. Prepared according to the general procedure starting from imine ester **1d** and *N*-(2-*t*-butylphenyl)maleimide; yield: 144 mg, 99%; white solid; mp 156−158 °C; $[\alpha]_D^{20}$ = −96.0 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.71−7.67 (m, 1H), 7.49 (dd, J_1 = 1.2 Hz, J_2 = 1.2 Hz, 1H), 7.43−7.37 (m, 2H), 7.37−7.26 (m, 2H), 7.24−7.18 (m, 1H), 6.89 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 4.59−4.54 (m, 1H), 4.17−4.13 (m, 1H), 3.86 (s, 3H), 3.74−3.69 (m, 1H), 3.60−3.54 (m, 1H), 2.50 (br s, 1H), 1.22 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.9, 175.3, 170.3, 147.8, 141.6, 130.9, 130.7, 130.0, 130.0, 129.8, 129.5, 128.6, 127.2, 126.6, 121.3, 62.3, 61.2, 51.5, 48.8, 47.6, 35.2, 31.3. HRMS calcd for $C_{24}H_{25}BrN_2O_4$ + H^+: 485.1070; found: 485.1068. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (Chiralpak AS-H, *i*-propanol/hexane = 50/50, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.39 and 13.30 min.

*(M,1R,3S,3aR,6aS)-Methyl 5-(2-(tert-Butyl)phenyl)-3-(2-fluorophenyl)-4,6-dioxoo- ctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**3ea**)*. Prepared according to the general procedure starting from imine ester **1e** and *N*-(2-*t*-butylphenyl)maleimide; yield: 125 mg, 98%; white solid; mp 174−176 °C; $[\alpha]_D^{20}$ = −106.0 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.62−7.55 (m, 1H), 7.47 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 7.34−7.20 (m, 3H), 7.18−7.11 (m, 1H), 7.10−7.02 (m, 1H), 6.80 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 4.78 (d, *J* = 6.4 Hz, 1H), 4.19 (d, *J* = 6.0 Hz, 1H), 3.86 (s, 3H), 3.79−3.70 (m, 2H), 2.55 (br s, 1H), 1.22 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.0, 175.2, 170.3, 160.2 (d, *J* = 242.7 Hz), 147.7, 131.0, 130.7, 129.4, 128.9 (d, *J* = 8.1 Hz), 128.5, 127.7 (d, *J* = 4.2 Hz), 127.2, 125.8 (d, *J* = 13.6 Hz), 124.1 (d, *J* = 2.5 Hz), 114.4 (d, *J* = 20.7 Hz), 61.2, 56.9, 51.5, 47.8, 47.4, 35.2, 31.3. HRMS calcd for $C_{24}H_{25}FN_2O_4$ + H^+: 425.1871; found: 425.1865. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (Chiralpak AS-H, *i*-propanol/hexane = 50/50, flow rate 1.0 mL/min, λ = 220 nm); t_r = 5.49 and 9.86 min.

*(M,1R,3S,3aR,6aS)-Methyl 5-(2-(tert-Butyl)phenyl)-3-(4-methoxyphenyl)-4,6-dio- xooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**3fa**)*. Prepared according to the general procedure starting from imine ester **1f** and *N*-(2-*t*-butylphenyl)-maleimide; yield: 130 mg, 99%; white solid; mp 179−181 °C; $[\alpha]^{20}{}_D$ = −126.0 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.49 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 7.42−7.37 (m, 2H), 7.36−7.30 (m, 1H), 7.29−7.23 (m, 1H), 6.92−6.85 (m, 3H), 4.56 (d, *J* = 8.4 Hz, 1H), 4.15 (d, *J* = 7.2 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.73−3.69 (m, 1H), 3.56−3.50 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.1, 175.4, 170.4, 158.5, 147.7, 131.1, 130.8, 130.3, 129.4, 128.5, 128.4, 127.3, 113.1, 62.9, 61.4, 54.9, 51.5, 48.8, 47.7, 35.3, 31.3. HRMS calcd for $C_{25}H_{28}N_2O_5$ + H^+: 437.2071; found: 437.2067. The product was analyzed by HPLC to determine the enantiomeric excess: 99% ee (Chiralpak AS-H, *i*-propanol/hexane = 50/50, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.69 and 13.68 min.

*(M,1R,3S,3aR,6aS)-Methyl 5-(2-(tert-Butyl)phenyl)-3-(3-methoxyphenyl)-4,6-dio- xooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**3ga**)*. Prepared according to the general procedure starting from imine ester **1g** and *N*-(2-*t*-butylphenyl)maleimide; yield: 130 mg, 99%; white solid; mp 150−152 °C; $[\alpha]_D^{20}$ = −109.0 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.48 (dd, J_1 = 1.2 Hz, J_2 = 1.2 Hz, 1H), 7.36−7.21 (m, 3H), 7.10−7.02 (m, 2H), 6.91 (dd, J_1 = 1.2 Hz, J_2 = 1.2 Hz, 1H), 6.80 (dd, J_1 = 2.4 Hz, J_2 = 2.4 Hz, 1H), 4.56 (d, *J* = 8.4 Hz, 1H), 4.15 (d, *J* = 6.8 Hz, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.74−3.68 (m, 1H), 3.60−3.53 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.0, 175.2, 170.4, 158.9, 147.8, 140.1, 131.0, 130.8, 129.5, 128.8, 128.6, 127.2, 119.8, 112.9, 112.6, 109.5, 63.3, 61.4, 54.9, 51.5, 48.9, 47.7, 35.3, 31.3. HRMS calcd for $C_{25}H_{28}N_2O_5$ + H^+: 437.2071; found: 437.2069. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (Chiralpak AS-H, *i*-propanol/hexane = 50/50, flow rate 1.0 mL/min, λ = 220 nm); t_r = 7.36 and 12.33 min.

*(M,1R,3S,3aR,6aS)-Methyl 5-(2-(tert-Butyl)phenyl)-4,6-dioxo-3-(p-tolyl)octahydr- opyrrolo[3,4-c]pyrrole-1-carboxylate (**3ha**)*. Prepared according to the general procedure starting from imine ester **1h** and *N*-(2-*t*-butylphenyl)-maleimide; yield: 125 mg, 99%; white solid; mp 176−178 °C; $[\alpha]_D^{20}$ = −114.0 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.48 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 7.39−7.33 (m, 2H), 7.33−7.29 (m, 1H), 7.29−7.23 (m, 1H), 7.18−7.12 (m, 2H), 6.90 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 4.57 (d, *J* = 8.4 Hz, 1H), 4.15 (d, *J* = 7.2 Hz, 1H), 3.85 (s, 3H), 3.74−3.68 (m, 1H), 3.58−3.52 (m, 1H), 2.30 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.0, 175.3, 170.4, 147.7, 136.2, 135.4, 131.1, 130.8, 129.4, 128.5, 128.4, 127.2, 63.2, 61.4, 51.4, 48.9, 47.8, 35.3, 31.3, 20.8. HRMS calcd for $C_{25}H_{28}N_2O_4$ + H^+: 421.2122; found: 421.2118. The product was analyzed by HPLC to determine the enantiomeric excess: 99% ee (Chiralpak AS-H, *i*-propanol/hexane = 50/50, flow rate 1.0 mL/min, λ = 220 nm); t_r = 5.73 and 10.37 min.

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*(M,1R,3S,3aR,6aS)-Methyl 5-(2-(tert-Butyl)phenyl)-4,6-dioxo-3-phenyloctahydro- pyrrolo[3,4-c]pyrrole-1-carboxylate (**3ia**).* Prepared according to the general procedure starting from imine ester **1i** and *N*-(2-*t*-butylphenyl)maleimide; yield: 121 mg, 99%; white solid; mp 178−180 °C; $[\alpha]_D^{20}$ = −112.0 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.51−7.45 (m, 3H), 7.40−7.22 (m, 5H), 6.90 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 4.59 (d, J = 8.4 Hz, 1H), 4.16 (d, J = 6.8 Hz, 1H), 3.85 (s, 3H), 3.75−3.69 (m, 1H), 3.61−3.54 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.0, 175.3, 170.4, 147.7, 138.4, 131.1, 130.8, 129.4, 128.5, 127.8, 127.3, 127.2, 63.4, 61.4, 51.5, 48.8, 47.7, 35.2, 31.3. HRMS calcd for $C_{24}H_{26}N_2O_4$ + H^+: 407.1965; found: 407.1960. The product was analyzed by HPLC to determine the enantiomeric excess: 99% ee (Chiralpak AS-H, *i*-propanol/hexane = 50/50, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.12 and 9.99 min.

*(M,1R,3S,3aR,6aS)-Methyl 5-(2-(tert-Butyl)phenyl)-4,6-dioxo-3-(thiophen-2-yl)oc- tahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**3ja**).* Prepared according to the general procedure starting from imine ester **1j** and *N*-(2-*t*-butylphenyl)maleimide; yield: 123 mg, 99%; white solid; mp 200−202 °C; $[\alpha]_D^{20}$ = −74.0 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.49 (dd, J_1 = 1.2 Hz, J_2 = 1.2 Hz, 1H), 7.37−7.32 (m, 1H), 7.30−7.23 (m, 2H), 7.18−7.13 (m, 1H), 7.05−6.96 (m, 2H), 4.89 (d, J = 8.4 Hz, 1H), 4.12 (d, J = 6.8 Hz, 1H), 3.84 (s, 3H), 3.74−3.68 (m, 1H), 3.58−3.51 (m, 1H), 2.72 (br s, 1H), 1.23 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.0, 174.8, 170.0, 147.7, 142.5, 131.1, 130.7, 129.4, 128.5, 127.1, 126.6, 124.9, 124.6, 61.1, 59.1, 51.4, 48.9, 47.6, 35.2, 31.3. HRMS calcd for $C_{22}H_{24}N_2O_4S$ + H^+: 413.1530; found: 413.1524. The product was analyzed by HPLC to determine the enantiomeric excess: >99% ee (Chiralpak AS-H, *i*-propanol/hexane = 50/50, flow rate 1.0 mL/min, λ = 220 nm); t_r = 7.14 and 13.41 min.

*(M,1R,3S,3aR,6aS)-Methyl 5-(2-(tert-Butyl)phenyl)-3-(naphthalen-2-yl)-4,6-dioxo- octahydropyrrolo[3,4-c]-pyrrole-1-carboxylate (**3ka**).* Prepared according to the general procedure starting from imine ester **1k** and *N*-(2-*t*-butylphenyl)maleimide; yield: 136 mg, 99%; white solid; mp 188−190 °C; $[\alpha]_D^{20}$ = −137.5 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 8.03−7.95 (m, 1H), 7.87−7.80 (m, 2H), 7.80−7.74 (m, 1H), 7.58−7.50 (m, 1H), 7.49−7.38 (m, 3H), 7.32−7.10 (m, 2H), 6.92 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 4.74 (d, J = 8.4 Hz, 1H), 4.19 (d, J = 6.8 Hz, 1H), 3.88 (s, 3H), 3.78−3.72 (m, 1H), 3.70−3.63 (m, 1H), 1.20 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.1, 175.4, 170.4, 147.7, 136.5, 132.9, 132.6, 131.1, 130.7, 129.4, 128.5, 127.7, 127.5, 127.2, 127.1, 126.4, 126.0, 125.6, 125.1, 63.3, 61.5, 51.5, 49.0, 47.8, 35.2, 31.3. HRMS calcd for $C_{28}H_{28}N_2O_4$ + H^+: 457.2122; found: 457.2120. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (Chiralpak AS-H, *i*-propanol/hexane = 50/50, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.73 and 15.91 min.

*(M,1R,3R,3aR,6aS)-Methyl 5-(2-(tert-Butyl)phenyl)-4,6-dioxo-3-((E)-styryl)octah- ydropyrrolo[3,4-c]pyrrole-1-carboxylate (**3la**).* Prepared according to the general procedure starting from imine ester **1l** and *N*-(2-*t*-butylphenyl)maleimide; yield: 128 mg, 99%; white solid; mp 93−95 °C; $[\alpha]_D^{20}$ = −88.0 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.54 (dd, J_1 = 1.2 Hz, J_2 = 1.2 Hz, 1H), 7.49−7.30 (m, 4H), 7.28−7.20 (m, 3H), 6.90 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 6.80−6.70 (m, 1H), 6.45 (dd, J_1 = 7.2 Hz, J_2 = 7.2 Hz, 1H), 4.18−4.08 (m, 2H), 3.83 (s, 3H), 3.76−3.69 (m, 1H), 3.55−3.49 (m, 1H), 1.28 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.2, 175.4, 170.1, 147.6, 136.2, 132.5, 131.0, 130.0, 129.8, 128.6, 128.4, 127.8, 127.6, 126.6, 125.4, 62.7, 62.4, 52.4, 49.3, 48.5, 35.5, 31.5. HRMS calcd for $C_{26}H_{28}N_2O_4$ + H^+: 433.2122; found: 433.2121. The product was analyzed by HPLC to determine the enantiomeric excess: 90% ee (Chiralpak AD-H, *i*-propanol/hexane = 50/50, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.30 and 8.48 min.

*(M,1R,3R,3aR,6aS)-Methyl 3-Butyl-5-(2-(tert-butyl)phenyl)-4,6-dioxooctahydrop- yrrolo[3,4-c]pyrrole-1-carboxylate (**3ma**).* Prepared according to the general procedure starting from imine ester **1m** and *N*-(2-*t*-butylphenyl)maleimide; yield: 100 mg, 86%; colorless viscous oil; $[\alpha]_D^{20}$ = +47.5 (*c* 1.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.55 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 7.41−7.34 (m, 1H), 7.30−7.24 (m, 1H), 6.85 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 4.03 (d, J = 7.6 Hz, 1H), 3.80 (s, 3H), 3.70−3.64 (m, 1H), 3.39−3.28 (m, 2H), 2.05−1.94 (m, 1H), 1.67−1.58 (m, 1H), 1.56−1.47 (m, 2H), 1.41−1.33 (m, 2H), 1.28 (s, 9H), 0.91 (t, J = 7.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.4, 175.8, 170.4, 147.7, 130.9, 129.9, 129.8, 128.8, 127.5, 62.7, 62.1, 52.4, 49.5, 48.5, 35.6, 31.5, 30.8, 29.9, 22.6, 13.8. HRMS calcd for $C_{22}H_{30}N_2O_4$ + H^+: 387.2287; found: 387.2271. The product was analyzed by HPLC to determine the enantiomeric excess: 92% ee (Chiralpak AS-H, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 220 nm); t_r = 4.89 and 6.44 min.

*(M,1R,3S,3aR,6aS)-Methyl 5-(2-(tert-Butyl)phenyl)-3-(4-chlorophenyl)-1-methyl- 4,6-dioxooctahydropyrrolo[3,4-c]-pyrrole-1-carboxylate (**3na**).* Prepared according to the general procedure starting from imine ester **1n** and *N*-(2-*t*-butylphenyl)maleimide; yield: 135 mg, 99%; white solid; mp 166−168 °C; $[\alpha]_D^{20}$ = −111.0 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.49 (dd, J_1 = 1.2 Hz, J_2 = 1.2 Hz, 1H), 7.45−7.38 (m, 2H), 7.36−7.28 (m, 3H), 7.28−7.21 (m, 1H), 6.78 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 4.90−4.81 (m, 1H), 3.84 (s, 3H), 3.71−3.64 (m, 1H), 3.46−3.41 (m, 1H), 2.52 (br s, 1H), 1.68 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.9, 174.6, 172.6, 147.6, 135.3, 133.8, 130.6, 129.8, 129.6, 128.9, 128.5, 128.4, 127.4, 67.3, 61.3, 55.2, 52.7, 49.8, 35.6, 31.5, 23.8. HRMS calcd for $C_{25}H_{27}ClN_2O_4$ + H^+: 455.1732; found: 455.1725. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (Chiralpak AS-H, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 220 nm); t_r = 7.49 and 11.32 min.

*(M,1R,3S,3aR,6aS)-Methyl 5-(2-(tert-Butyl)phenyl)-1-methyl-4,6-dioxo-3-(p-tolyl)- octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**3oa**).* Prepared according to the general procedure starting from imine ester **1o** and *N*-(2-*t*-butylphenyl)maleimide; yield: 129 mg, 99%; white solid; mp 136−138 °C; $[\alpha]_D^{20}$ = −109.0 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.47 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 7.37−7.28 (m, 3H), 7.26−7.20 (m, 1H), 7.18−7.13 (m, 2H), 6.83 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 4.84 (d, J = 8.4 Hz, 1H), 3.85 (s, 3H), 3.67 (dd, J_1 = 8.0 Hz, J_2 = 8.8 Hz, 1H), 3.43 (d, J = 8.0 Hz, 1H), 2.30 (s, 3H), 1.68 (s, 3H), 1.20 (s, 9H).; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.1, 174.8, 172.8, 147.6, 137.8, 133.4, 130.7, 129.7, 129.6, 129.1, 128.8, 127.4, 126.8, 67.4, 62.1, 55.7, 52.7, 50.7, 35.6, 31.5, 23.8, 21.1. HRMS calcd for $C_{26}H_{30}N_2O_4$ + H^+: 435.2278; found: 435.2273. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (Chiralpak AS-H, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.76 and 9.94 min.

(M,1R,3S,3aR,6aS)-Methyl 5-(2-(tert-Butyl)phenyl)-1-methyl-4,6-dioxo-3-phenyl- octahydropyrrolo[3,4-c]pyrrole-1-car-

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*boxylate (**3pa**)*. Prepared according to the general procedure starting from imine ester **1p** and *N*-(2-*t*-butylphenyl)-maleimide; yield: 125 mg, 99%; white solid; mp 163−165 °C; $[\alpha]_D^{20}$ = −100.0 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.51−7.43 (m, 3H), 7.41−7.26 (m, 4H), 7.26−7.20 (m, 1H), 6.82 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 4.87 (d, *J* = 8.8 Hz, 1H), 3.85 (s, 3H), 3.70 (dd, J_1 = 8.0 Hz, J_2 = 8.8 Hz, 1H), 3.44 (d, *J* = 8.0 Hz, 1H), 1.68 (s, 3H), 1.20 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.0, 174.6, 172.7, 147.6, 136.5, 130.7, 129.7, 129.6, 128.8, 128.3, 128.2, 127.3, 127.0, 67.4, 62.1, 55.6, 52.6, 50.1, 35.6, 31.5, 23.8. HRMS calcd for $C_{25}H_{28}N_2O_4$ + H^+: 421.2122; found: 421.2117. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (Chiralpak AS-H, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 220 nm); t_r = 7.29 and 10.34 min.

*(M,1R,3S,3aR,6aS)-Methyl 5-(2-(tert-Butyl)phenyl)-3-(4-chlorophenyl)-1-ethyl-4,6 -d-ioxooctahydropyrrolo[3,4-c]-pyrrole-1-carboxylate (**3qa**)*. Prepared according to the general procedure starting from imine ester **1q** and *N*-(2-*t*-butylphenyl)maleimide; yield: 126 mg, 97%; white solid; mp 183−185 °C; $[\alpha]_D^{20}$ = −92.5 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.53−7.44 (m, 3H), 7.40−7.33 (m, 2H), 7.33−7.26 (m, 2H), 7.25−7.18 (m, 1H), 6.80 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 4.72 (dd, J_1 = 5.2 Hz, J_2 = 8.4 Hz, 1H), 3.85 (s, 3H), 3.65 (dd, J_1 = 8.0 Hz, J_2 = 8.8 Hz, 1H), 3.42 (d, *J* = 7.6 Hz, 1H), 2.77 (br s, 1H), 2.25−2.14 (m, 1H), 1.98−1.86 (m, 1H), 1.20 (s, 9H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.0, 174.6, 171.8, 147.5, 136.8, 130.6, 129.7, 129.5, 128.7, 128.2, 128.2, 127.2, 127.0, 71.1, 61.2, 55.1, 52.4, 49.8, 35.5, 31.5, 27.6, 7.8. HRMS calcd for $C_{26}H_{30}N_2O_4$ + H^+: 435.2278; found: 435.2278. The product was analyzed by HPLC to determine the enantiomeric excess: >99% ee (Chiralpak AD-H, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.78 and 20.67 min.

*(M,1R,3S,3aR,6aS)-Methyl 1-Butyl-5-(2-(tert-butyl)phenyl)-3-(4-chlorophenyl)-4, 6-dioxooctahydropyrrolo[3,4-c]-pyrrole-1-carboxylate (**3ra**)*. Prepared according to the general procedure starting from imine ester **1r** and *N*-(2-*t*-butylphenyl)maleimide; yield: 135 mg, 97%; white solid; mp 162−164 °C; $[\alpha]_D^{20}$ = −87.0 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.54−7.44 (m, 3H), 7.40−7.33 (m, 2H), 7.33−7.26 (m, 2H), 7.25−7.18 (m, 1H), 6.79 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 4.73 (dd, J_1 = 6.4 Hz, J_2 = 8.8 Hz, 1H), 3.84 (s, 3H), 3.64 (dd, J_1 = 7.6 Hz, J_2 = 9.2 Hz, 1H), 3.40 (d, *J* = 7.6 Hz, 1H), 2.75 (br s, 1H), 2.23−2.08 (m, 1H), 1.93−1.82 (m, 1H), 1.48−1.26 (m, 4H), 1.20 (s, 9H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.0, 174.6, 172.0, 147.5, 136.8, 130.7, 129.7, 129.5, 128.7, 128.2, 128.2, 127.2, 127.0, 70.6, 61.3, 55.3, 52.4, 49.8, 35.5, 34.5, 31.5, 25.7, 22.4, 13.8. HRMS calcd for $C_{28}H_{34}N_2O_4$ + H^+: 463.2591; found: 463.2590. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak ID-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 19.27 and 34.34 min.

*(M,1R,3S,3aR,6aS)-Methyl 5-(2-(tert-Butyl)phenyl)-3-(4-chlorophenyl)-1-isobutyl- 4,6-dioxooctahydropyrrolo[3,4-c]-pyrrole-1-carboxylate (**3sa**)*. Prepared according to the general procedure starting from imine ester **1s** and *N*-(2-*t*-butylphenyl)maleimide; yield: 136 mg, 98%; white solid; mp 194−196 °C; $[\alpha]_D^{20}$ = −85.5 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.52−7.43 (m, 3H), 7.40−7.33 (m, 2H), 7.33−7.26 (m, 2H), 7.25−7.19 (m, 1H), 6.79 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 4.71 (dd, J_1 = 7.2 Hz, J_2 = 8.8 Hz, 1H), 3.84 (s, 3H), 3.65 (dd, J_1 = 8.0 Hz, J_2 = 8.8 Hz, 1H), 3.36 (d, *J* = 7.6 Hz, 1H), 2.81 (d, *J* = 6.8 Hz, 1H), 2.20−2.09 (m, 1H), 1.85 (dd, J_1 = 4.8 Hz, J_2 = 14.0 Hz, 1H), 1.80−1.68 (m, 1H), 1.20 (s, 9H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.8, 174.6, 172.6, 147.5, 136.6, 130.7, 129.64, 129.58, 128.8, 128.3, 128.2, 127.3, 126.9, 70.2, 61.8, 56.1, 52.3, 50.1, 42.9, 35.6, 31.5, 24.4, 24.2, 22.0. HRMS calcd for $C_{28}H_{34}N_2O_4$ + H^+: 463.2591; found: 463.2591. The product was analyzed by HPLC to determine the enantiomeric excess: >99% ee (Chiralpak ID-H, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 220 nm); t_r = 8.54 and 29.88 min.

*(M,1R,3S,3aR,6aS)-Methyl 1-Benzyl-5-(2-(tert-butyl)-phenyl)-3-(4-chlorophenyl)- 4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**3ta**)*. Prepared according to the general procedure starting from imine ester **1t** and *N*-(2-*t*-butylphenyl)maleimide; yield: 156 mg, 98%; white solid; mp 204−206 °C; $[\alpha]_D^{20}$ = −27.5 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.55−7.44 (m, 3H), 7.40−7.26 (m, 5H), 7.26−7.18 (m, 2H), 7.17−7.07 (m, 2H), 6.71 (dd, J_1 = 1.2 Hz, J_2 = 1.2 Hz, 1H), 4.93 (dd, J_1 = 4.0 Hz, J_2 = 4.0 Hz, 1H), 3.84 (s, 3H), 3.76−3.67 (m, 1H), 3.63−3.51 (m, 2H), 3.12 (d, *J* = 13.6 Hz, 1H), 2.42 (br s, 1H), 1.23 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.6, 174.4, 171.0, 147.5, 135.7, 134.7, 134.0, 130.6, 129.7, 129.6, 129.4, 128.9, 128.8, 128.6, 128.5, 127.5, 127.4, 71.0, 60.3, 54.0, 52.3, 48.8, 40.1, 35.6, 31.6. HRMS calcd for $C_{31}H_{31}ClN_2O_4$ + H^+: 531.2045; found: 531.2035. The product was analyzed by HPLC to determine the enantiomeric excess: 99% ee (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 11.92 and 22.89 min.

*(M,3R,3′S,3a′R,6a′S)-5′-(2-(tert-Butyl)phenyl)-3′-phenyl-hexahydro-2H,4′H-spiro- [furan-3,1′-pyrrolo[3,4-c]pyrrole]-2,4′,6′(5′H)-trione (**3ua**)*. Prepared according to the general procedure starting from imine ester **1u** and *N*-(2-*t*-butylphenyl)maleimide; yield: 124 mg, 99%; white solid; mp 190−192 °C; $[\alpha]_D^{20}$ = −42.5 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.47 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 7.46−7.40 (m, 2H), 7.39−7.33 (m, 2H), 7.33−7.27 (m, 2H), 7.26−7.22 (m, 1H), 7.03 (dd, J_1 = 1.6 Hz, J_2 = 1.6 Hz, 1H), 4.78−4.68 (m, 1H), 4.63−4.54 (m, 1H), 4.54−4.44 (m, 1H), 3.74 (t, *J* = 7.6 Hz, 1H), 3.50 (d, *J* = 7.6 Hz, 1H), 2.65−2.58 (m, 1H), 2.42−2.30 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.5, 175.4, 175.3, 147.6, 138.4, 131.1, 130.6, 129.4, 128.6, 127.6, 127.4, 127.2, 66.9, 64.2, 62.9, 52.2, 49.2, 36.2, 35.3, 31.3. HRMS calcd for $C_{25}H_{26}N_2O_4$ + H^+: 419.1965; found: 419.1962. The product was analyzed by HPLC to determine the enantiomeric excess: 99% ee (Chiralpak AD-H, *i*-propanol/hexane = 50/50, flow rate 1.0 mL/min, λ = 220 nm); t_r = 4.60 and 6.01 min.

*Procedure for the Synthesis of (M,3S,3aR,6aS)-Methyl 5-(2-(tert-butyl)phenyl)-3- (4-chlorophenyl)-4,6-dioxo-3,3a,4,5,6,6a-hexahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**4aa**)*. To a solution of **3aa** (132.3 mg, 0.30 mmol, 98% ee) in 3 mL toluene was added DDQ (136.2 mg, 0.60 mmol); the mixture was stirred for 24 h at room temperature. Then, a saturated solution of $NaHCO_3$ and CH_2Cl_2 (30 mL) was added sequentially, the organic phases was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were washed with water and were evaporated, and the residue was purified by column chromatography to give **4aa** in 95% yield (125 mg) as a white solid; mp 133−135 °C; $[\alpha]_D^{20}$ = −170.0 (*c* 0.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 400

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MHz) δ 8.20−8.14 (m, 2H), 7.54 (dd, J_1 = 1.2, J_2 = 1.2 Hz, 1H), 7.45−7.38 (m, 2H), 7.37−7.31 (m, 1H), 7.26−7.18 (m, 1H), 6.95 (dd, J_1 = 1.2, J_2 = 1.2 Hz, 1H), 5.39 (d, J = 10.0 Hz, 1H), 4.73 (d, J = 9.6 Hz, 1H), 4.08−3.98 (m, 1H), 3.77 (s, 3H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 175.5, 172.5, 172.4, 169.9, 168.3, 147.7, 138.2, 131.2, 130.4, 129.9, 129.8, 129.6, 128.6, 127.5, 75.8, 57.0, 52.9, 47.0, 35.6, 31.6. HRMS calcd for $C_{24}H_{23}ClN_2O_4$ + H^+: 439.1419; found: 439.1418. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (Chiralpak AD-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 19.69 and 37.78 min.

*Procedure for the Synthesis of (M)-Methyl 5-(2-(tert-Butyl)phenyl)-3-(4-chloroph- enyl)-4,6-dioxo-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5aa**).* To a solution of **3aa** (132.3 mg, 0.30 mmol, 98% ee) in 3 mL toluene was added DDQ (272.4 mg, 1.20 mmol) and a small amount of silica gel; the mixture was stirred for 36 h at room temperature. Then, a saturated solution of $NaHCO_3$ and CH_2Cl_2 (30 mL) was added, the organic phases was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were evaporated, and the residue was purified by column chromatography to give **5aa** in 91% yield (119 mg) as a pink solid; mp 177−179 °C; $[\alpha]_D^{20}$ = +6.0 (*c* 0.30, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 10.34 (br s, 1H), 8.18−8.08 (m, 2H), 7.66−7.58 (m, 1H), 7.53−7.36 (m, 3H), 7.35−7.26 (m, 1H), 7.02 (d, J = 7.5 Hz, 1H), 4.00 (s, 3H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 164.4, 162.8, 160.1, 149.2, 136.2, 134.0, 131.5, 130.3, 129.6, 129.3, 128.5, 128.2, 127.1, 126.1, 125.0, 118.8, 53.0, 35.6, 31.7. HRMS calcd for $C_{24}H_{21}ClN_2O_4$ + H^+: 437.1263; found: 437.1261. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak AD-H, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 220 nm); t_r = 5.65 and 10.44 min.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00396.

^{1}H and ^{13}C NMR spectra of all compounds, HPLC chromatograms (compounds **3aa**−**3ua**, **4aa**, **5aa**) (PDF)

crystallographic data for compound **3aa** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: cjwang@whu.edu.cn.

Notes

The authors declare no competing financial interest.

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