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Formal Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides to (*S*)-2-*p*-Tolylsulfinyl-2-cyclopentenone†

José Luis García Ruano,* Amelia Tito,* and M. Teresa Peromingo

Departamento de Química Orgánica, Universidad Autónoma, Cantoblanco, 28049 Madrid, Spain

joseluis.garcia.ruano@uam.es

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Azomethine ylides, derived from iminoesters **1** and DBU in the presence of silver salts, react with (*S*)-2-*p*-tolylsulfinyl-2-cyclopentenone **2** in a completely regio- and endoselective manner but with a low facial selectivity, affording a mixture of two cycloadducts **3** and **4**. When the ylides were prepared with LHMDS, only one diastereoisomer **3** was obtained in an almost quantitative yield. A nucleophilic addition/ring closure process easily accounts for the stereochemical results. Compounds **3** were transformed into optically pure 4-oxocyclopenta[*c*]dihydropyrroles and tetrahydropyrroles by elimination of the sulfinyl group.

1. Introduction

Asymmetric 1,3-dipolar cycloadditions offer a powerful and reliable synthetic methodology to access five-membered heterocyclic rings in a regio- and stereocontrolled fashion.[1] Most of the reported studies concern the use of acrylates as chiral dipolarophiles. Enantiomerically pure vinyl sulfoxides, widely used as dienophiles,[2] have been much less investigated as homochiral dipolarophiles.[2] Several years ago we initiated a research program to explore the scope and limitations of vinyl sulfoxides in asymmetric 1,3-dipolar cycloadditions. In this field, we have already reported the behavior of some sulfinyl ethylenes in reactions with diazoalkanes,[3] nitrile oxides,[4] and azomethine ylides.[5] All of these studies revealed the sulfinyl group as a good chiral auxiliary in 1,3-dipolar reactions, as well as the possibilities of the sulfinylated adducts as valuable synthetic intermediates.

α-Sulfinylcyclopentenone **2** has been widely used in asymmetric synthesis because of the structural interest of the resulting compounds. Thus, Posner,[6] Paquette,[7] and Tokoroyama[8] studied its Michael additions; Toru[9] explored its behavior in radical additions; and our group investigated its Diels−Alder reactions,[10,11] with excellent stereochemical results in most of the cases. However, its reactions with dipoles have not been previously studied. On the basis of these precedents, we decided to explore the behavior of compound **2** as a chiral dipolarophile. As dipoles we choose azomethine ylides,[12] intensively investigated by Grigg,[13] Kanemasa,[14] and other authors.[15] This election was based on the interest of obtaining adducts

† Dedicated to the memory of Prof. Jesús H. Rodríguez Ramos.

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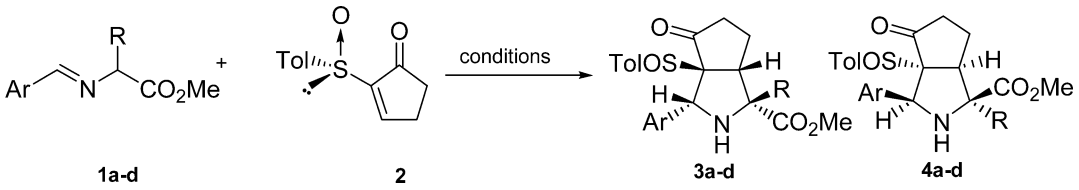
TABLE 1. Formal Asymmetric 1,3-Dipolar Cycloaddition of N-Metalated Azomethine Ylide Generated from Iminoesters 1a−d with 2



1a-d 2 3a-d 4a-d

	iminoester			conditions				product ratio[a] (*b*)	
entry		Ar	R	salt/base (equiv)	solvent	*T* (°C)	*t* (h)	**3**	**4**
1	**1a**	Ph	H	AgOAc/DBU (1.5/1.0)	MeCN	rt	0.20	52 (42)	48 (38)
2	**1a**	Ph	H	AgOAc/DBU (0.075/0.6)	MeCN	rt	0.25	50 (37)	50 (37)
3	**1b**	Ph	Me	AgOAc/DBU (0.075/0.6)	MeCN	rt	0.42	50 (12)	50 (12)
4	**1c**	2-Naph	H	AgOAc/DBU (0.075/0.6)	MeCN	0	1.50	58 (42)	42 (31)
5	**1d**	2-Naph	Me	AgOAc/DBU (0.075/0.6)	MeCN	rt	0.80	51 (34)	49 (33)
6	**1d**	2-Naph	Me	AgOAc/DBU (0.075/0.6)	MeCN	0	1.00	50 (22)	50 (22)
7	**1d**	2-Naph	Me	AgOAc/DBU (0.075/0.6)	THF	rt	0.25	57 (13)	43 (10)
8	**1d**	2-Naph	Me	AgOAc/DBU (0.075/0.6)	THF	0	1.00	50 (19)	50 (19)
9	**1d**	2-Naph	Me	DBU (1.0)	MeCN	0	0.75	52 (17)	48 (16)
10	**1c**	2-Naph	H	AgOAc/Et_3N (1.5/1.0)	MeCN	rt	1.20	55 (12)	45 (10)
11	**1c**	2-Naph	H	AgOAc/Et_3N (0.075/0.6)	MeCN	rt	1.20	52 (20)	48 (18)
12	**1d**	2-Naph	Me	LDA (1.1)	THF	−78	inst	90 (72)	10 (8)
13	**1d**	2-Naph	Me	LHMDS (1.1)	THF	−78	inst	>98 (91)	<2
14	**1d**	2-Naph	Me	NaHMDS (1.1)	THF	−78	inst	68 (48)	32 (23)
15	**1d**	2-Naph	Me	KHMDS (1.1)	THF	−78	inst	75 (54)	25 (18)
16	**1a**	Ph	H	LHMDS (1.1)	THF	−78	inst	>98 (89)	<2
17	**1b**	Ph	Me	LHMDS (1.1)	THF	−78	inst	>98 (91)	<2
18	**1c**	2-Naph	H	LHMDS (1.1)	THF	−78	inst	>98 (93)	<2

[a] Determined by ^1H NMR from the reaction crude. [b] Isolated yield (%).

containing the skeleton of 4-oxocyclopenta[*c*]pyrrolidine, which is present in compounds exhibiting interesting pharmacological properties as protease inhibitors[16] and analgesics,[17] as well as in some intermediates in the synthesis of kainic acid.[18] Moreover, to the best of our knowledge, the cyclopentenone ring has never been used as a dipolarophile in asymmetric 1,3-dipolar cycloadditions with azomethine ylides.[19] In this paper, we report the results obtained in the reactions of compound **2** with iminoesters under different conditions, as well as some chemical transformation of the resulting adducts involving the elimination of the sulfinyl group.

2. Results and Discussion

We first studied the reactions of the α-sulfinylcyclopentenone **2**, prepared following previously reported methods,[9,20] with the N-metalated azomethine ylides generated from the corresponding iminoesters **1** under the standard conditions for 1,3-dipolar cycloadditions reported by Grigg (DBU or Et_3N in the presence of either a silver or lithium salt).[13] The results are indicated in Table 1.

The reaction of **1a** in acetonitrile with DBU (1.0 equiv) in the presence of AgOAc (1.5 equiv), at room temperature, afforded an almost equimolecular mixture of only two adducts, **3a** and **4a** (entry 1). Similar results were obtained by using the base and the silver salt in catalytic amounts[21] (entry 2). The latter conditions were then used in reactions of **2** with **1b**−**d** (entries 3−5). The structure of the dipole has scarce influence on the stereoselectivity, which is similar in all of the cases, but the reactivity is lower for **1b** and **1d** (R = Me). Both polymerization of the dipolarophile and hydrolysis of the dipoles contributed to lowering of the overall isolated yields when the temperature reaction was under 0 °C. [22]

We have studied the influence of the factors that were allowed to modify the stereoselectivity of the reactions of the ylides with 2-*p*-tolylsulfinyl acrylates,[5] but none of them improved our results.[23] Thus, the use of THF as a solvent (which provoked an inversion of the facial selectivity) decreases the reaction rate and therefore the yield (entries 7 and 8), but the stereoselectivity was scarcely modified. The same results were obtained when the reactions were conducted in the absence of the silver

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(22) At temperatures under 0 °C, polymerization of the dipolarophile is almost quantitative.

(23) We have also studied the influence of Lewis acids such as $EtAlCl_2$ or $ZnBr_2$ (which substantially modified the stereochemical results of the Diels−Alder reactions of compound **2**[10,11]), but we did not detect any changes in the composition of the reaction mixtures.

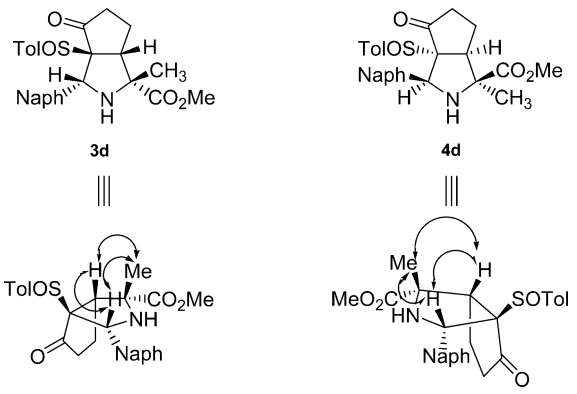

FIGURE 1. NOESY experiments for **3d** and **4d**.

salt (entry 9) or by using Et_3N instead of DBU as the base[24] (entries 10 and 11).

The relative stereochemistry of the substituents Ar and CO_2Me for the adducts **3** and **4** was established as cis on the basis of NOESY experiments (Figure 1). The absolute configuration of the four new stereocenters was unequivocally assigned by single-crystal X-ray analysis[25] in the case of compounds **3d** and **4d**.

On the basis of the configurational assignment of the cycloadducts **3** and **4**, we can conclude that all of the reactions are completely regio- and endoselective (with respect to the carbonyl group at the dipolarophile). By contrast, the π-facial selectivity is very poor in all of the conditions studied. The formation of diastereoisomers **3** and **4** can be explained by assuming the endo approach of the syn dipole to both faces of the dipolarophile, which adopts in each case a different conformation around the C−S bond in order to minimize their steric interactions with the dipole (Figure 2).

The higher stability of the syn configuration for dipoles, as a consequence of the association of the metal to both oxygen and nitrogen, is easily understandable. However, the strong interactions between the syn dipole and the methylene groups at the cyclopentenone ring (Figure 2) are not easily compatible with the complete endoselectivity observed in these cycloadditions. In other ways, the scarce influence of the different factors considered in this study (temperature, solvent, Lewis acids, etc.) on the stereochemical results is also difficult to rationalize in terms of a concerted cycloaddition.[26]

At this point, we decided to study the reactions of the iminoesters **1** and **2** in the presence of stronger bases. When **1d** was treated with LDA at −78 °C and then 2-*p*-tolylsulfinylcyclopentenone (**2**) was added (the standard reaction conditions for the Michael addition of the iminoester **1a** to 2-cyclohexenone),[27] we observed the immediate formation of a mixture of the same two compounds, **3d** and **4d**, but the stereoselectivity was substantially increased (80% de, entry 12, Table 1). This excellent result prompted us to optimize the reaction. The best conditions involved the use of LHMDS as the base, which yielded **3d** in an almost quantitative yield (entry 13). We have also studied the behavior of **1d** in the presence of NaHMDS and KHMDS (entries 14 and 15). In both cases, the reactions were more sluggish and slower, affording almost equimolecular mixtures of **3d** and **4d**. These results suggest that the essential role of the lithium cation is for achieving very high or complete stereoselectivity.[28] Finally, the iminoesters **1a**−**d** were treated with LHMDS and then with **2**, yielding only one diastereoisomer (**3a**−**d**) in isolated yields higher than 90% (entries 13 and 16−18).

All of these results can be explained by assuming that these reactions take place according to a nucleophilic addition/ring closure (NARC) process, in which the lithium acts as a tether between the reagent and the substrate (Figure 3). In the first step, the lithium of the dipole is associated with the sulfinyl oxygen at the electrophile. This species can evolve to the 1,4-addition product through two transition states, TS-**A** and TS-**B**, resulting from the approach of the nucleophile to each face of the sulfinylcyclopentenone (Figure 3). The strong steric interactions produced by the *p*-tolyl group to the approach of the nucleophile to the upper face of the cyclopentenone (TS-**B**) would explain that compounds **3a**−**d**, resulting from TS-**A**, were clearly favored. After the formation of the C−C bond, the stereochemistry of the ring closure (second step of the process) is imposed by the rigidity of the system (only the fusion cis is possible) and the stereochemistry of the C=N (*E* in all cases; Figure 3).

When sodium or potassium bases were used (these metals cannot act as a tether), the approaches of the syn dipole took place in a intermolecular manner. TS-**B′** would be the transition state resulting from the attack to the upper face (the steric interactions destabilizing TS-**B** do not exist), whereas TS-**A′**, which is identical to TS-**A** but without lithium (it has not been depicted in Figure 3), would be formed in the approach to the bottom face. Both new transition states exhibit similar stability, which justifies the observed low facial selectivity. A similar explanation can also account for the results obtained in the reactions conducted with DBU in the presence of silver salts. Seemingly, **2** does not react with azomethine ylides according to a concerted 1,3-dipolar cycloaddition. Instead, it reacts in a stepwise mechanism involving a NARC process.[29]

The adducts **3** and **4** were independently transformed into 4-oxocyclopenta[*c*]pyrrole derivatives by desulfiny-

(24) The reactions do not work by using highly hindered bases such as 2,2,6,6-tetramethylpiperidine.

(25) The authors have deposited atomic coordinates for **3d** and **4d** with the Cambridge Crystallographic Data Centre (Deposit Nos. 218777 and 218778, respectively). The coordinates can be obtained, upon request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

(26) To check that the obtained mixture (**3** + **4**) could be the result of thethermodynamic equilibration, because it had been observed in the reactions of **1** with sulfinyl acrylates under certain conditions (ref 5), we studied the behavior of both diastereoisomers after their chromatographic separation under the same conditions as those indicated in Table 1. All of the resulting trials were unfruitful because we recovered the unaltered starting materials. This suggests that the retro-1,3-dipolar reaction is not taking place under such conditions.

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(28) On the basis of the results obtained by Posner in the Michael addition of **2** with Grignard reagents and lithium enolates,[6] we have also studied the reaction of **1d** with **2** in the presence of $ZnBr_2$ by using LDA as a base. Under these conditions, we observed the completely stereoselective evolution into **3d** instead of the expected inversion of the facial selectivity.

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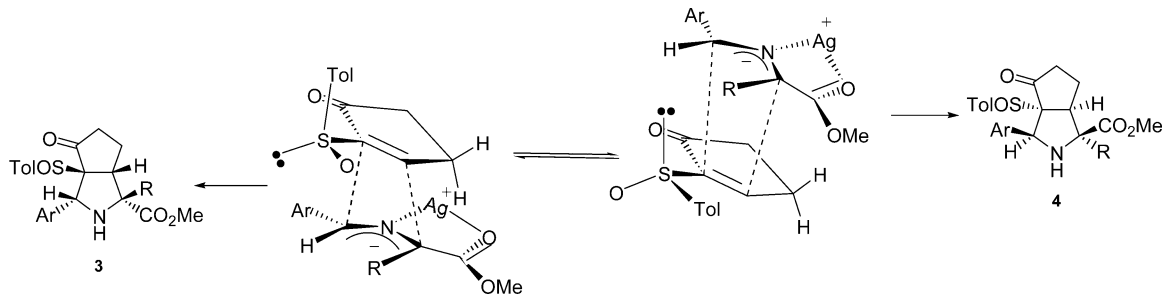

FIGURE 2. Favored endo approaches accounting for the formation of compounds **3** and **4**.

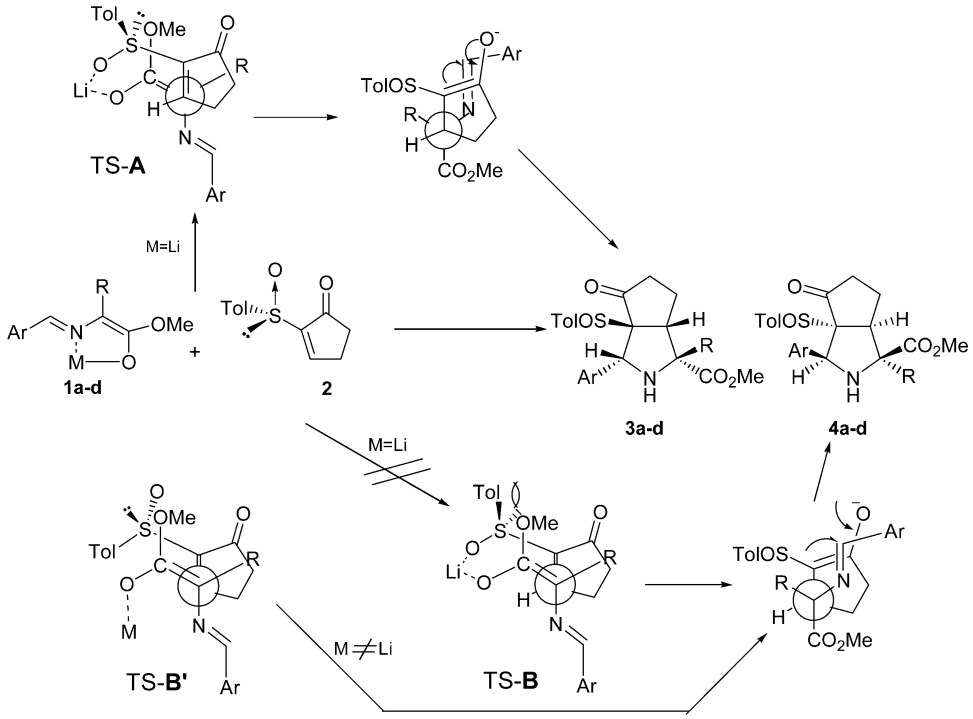

FIGURE 3. Stereochemical evolution of the substrates according to the NARC process.

lation. Thus, the hydrogenolysis of the C−S bond of compounds **3a**−**d** with Raney nickel at −20 °C afforded enantiomerically pure tetrahydropyrroles (−)-**5a**−**d**, whereas their enantiomers (+)-**5a**−**d** were exclusively obtained from **4a**−**d** (Scheme 1). Activated powdered zinc[30] simultaneously effected desulfinylation and hydrogenolysis of the benzylic C−N bond when R = Me or aromatization when R = H. Thus, compounds **3b**,**d** and **4b**,**d** evolved respectively into each enantiomer of the monocyclic α-aminoesters **6b**,**d**, whereas compounds **3a**,**c** and **4a**,**c** evolved into the corresponding aromatic rings **8a**,**c**. Finally, pyrolytic desulfinylation of **3b**,**d** and **4b,d** at refluxing toluene afforded respectively the enantiomers of 4-oxocyclopenta[*c*]dihydropyrrole **7** (Scheme 1), with an unusual bicyclic skeleton[31] potentially useful as a chiral synton. Under similar conditions, **3a** and **4a** were transformed into the same aromatic compound **8a**. Analogously, **3c** and **4c** (R = H, Ar = 2-Naph) were converted into **8c**. In all cases, the yields were very high, and the specific rotation results of the obtained enantiomers were identical but with the opposite sign, which supports their homochiral integrity.

In summary, the synthesis of the optically pure 4-oxocyclopenta[*c*]pyrrolidine derivatives can be achieved by reaction of **2** with N-metalated azomethine ylides, followed by desulfinylation with Raney nickel of the resulting adducts. The stereoselectivity depends on the reaction conditions becoming complete when LHMDS is used as the base. A NARC stepwise mechanism accounts for the observed stereoselectivity under the different conditions. Pyrolytic desulfinylation of the adducts affords 4-oxocyclopenta[*c*]dihydropyrroles when R = Me.

3. Experimental Section

General Methods. All moisture-sensitive reactions were performed in flame-dried glassware equipped with rubber septa under positive pressure of argon. THF and diethyl ether were distilled from sodium−benzophenone under argon and CH_2Cl_2 over P_2O_5. Lewis acids were commercially available and were used without further purification. $ZnBr_2$ was flame-dried in the reaction flask prior to use. Flash chromatography was carried out with silica gel Merck 60 (230−400 mesh, American Society for Testing and Materials). NMR spectra were determined in $CDCl_3$ solutions at 300 and 75 MHz for

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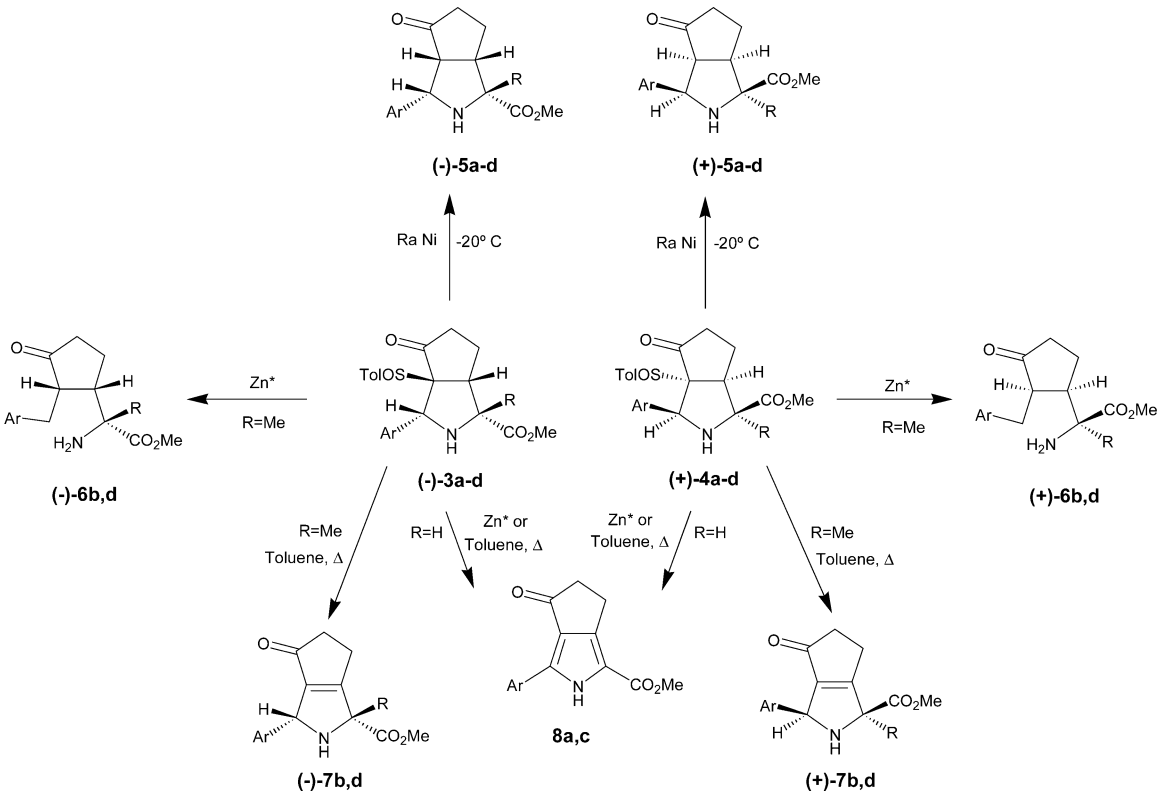
SCHEME 1



^{1}H and ^{13}C NMR, respectively; *J* values are given in hertz. Melting points were measured using a Gallenkamp apparatus in open capillary tubes and are uncorrected. The optical rotations were measured at room temperature (20−23 °C) using a Perkin-Elmer 241 MC polarimeter (concentration in g/100 mL). The compounds **1** and **2** were synthesized and purified according to the procedure described in refs 13 and 14 and refs 9 and 20, respectively.

Method A: Reactions with DBU. General Procedure. A solution of the corresponding iminoester **1** (1 equiv) in the appropriate solvent (5.5 mL/0.5 mmol) and AgOAc (amounts indicated in Table 1) was stirred for 10 min, and base (amounts indicated in Table 1) was added to the above solution. The reaction mixture was stirred for 10 min before addition of **2** (1 equiv) in the appropriate solvent (5.5 mL/0.5 mmol) at the temperature indicated in Table 1. When the reaction was completed (monitored by TLC ethyl acetate−hexane, 1:2), saturated aqueous ammonium chloride was added. The products were extracted with diethyl ether. The combined organic extracts were washed with brine. The organic layer was dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by flash column chromatography (ethyl acetate−hexane, 1:5) to give a mixture of cycloadducts **3** and **4**.

Method B: Reactions with LHMDS. General Procedure. To a 1 M solution of LHMDS (0.25 mmol, 1.1 equiv) in THF (1.8 mL) at −78 °C was added a solution of the corresponding iminoester **1** (1.5 equiv) in THF (6.8 mL). The mixture was stirred at −78 °C for 30 min, and a solution of **2** (0.23 mmol, 1 equiv) in THF (6.8 mL) was added. After 5 min, the reaction was quenched at −78 °C with a saturated aqueous solution of NH_4Cl (12 mL) and extracted with ethyl acetate (2 × 10 mL). The organic extracts were washed with brine (7 mL) and dried ($MgSO_4$). The solvent was removed under vacuum and the crude purified by flash chromatography (ethyl acetate−hexane, 1:5) to give only cycloadduct **3**.

Methyl (−)-(1*R*,3*R*,3a*R*,6a*R*,*S*$_S$)-4-Oxo-3-phenyl-3a-*p*-tolylsulfinyloctahydrocyclopenta[*c*]pyrrole-1-carboxylate (3a): yellow oil; $[\alpha]_D$ −65.3 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3502, 1739, 1718 cm^{-1}; ^{1}H NMR δ 7.52−7.21 (m, 9H), 5.05 (s, 1H), 4.22 (d, 1H, *J* = 7.0), 3.85 (s, 3H), 3.49 (m, 1H), 2.51 (bs, 1H), 2.37 (s, 3H), 2.20−2.03 (m, 1H), 1.82−1.59 (m, 1H), 1.32−1.18 (m, 2H); ^{13}C NMR δ 210.1, 174.5, 142.1, 136.1, 136.0, 129.7, 128.4, 128.3, 127.6, 125.5, 83.8, 67.2, 63.8, 52.3, 41.5, 40.5, 22.5, 21.4; MS (electrospray+) *m*/*z* 398.2 (MH$^+$). Anal. Calcd for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.52; S, 8.07. Found: C, 66.31; H, 5.65; N, 3.68; S, 8.05.

Methyl (+)-(1*S*,3*S*,3a*S*,6a*S*,*S*$_S$)-4-Oxo-3-phenyl-3a-*p*-tolylsulfinyloctahydrocyclopenta[*c*]pyrrole-1-carboxylate (4a): yellow oil; $[\alpha]_D$ +161 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3428, 1758, 1739 cm^{-1}; ^{1}H NMR δ 7.61−7.21 (m, 9H), 4.95 (s, 1H), 4.15 (d, 1H, *J* = 7.0), 3.86 (s, 3H), 3.52 (m, 1H), 2.52 (bs, 1H), 2.39 (s, 3H), 2.0−2.01 (m, 1H), 1.80−1.59 (m, 1H), 0.97−0.86 (m, 2H); ^{13}C NMR δ 207.3, 171.5, 143.5, 137.2, 136.0, 129.3, 128.4, 128.1, 127.3, 125.5, 79.9, 67.5, 63.9, 52.0, 41.3, 40.5, 22.3, 21.4; MS (electrospray+) *m*/*z* 398.2 (MH$^+$). Anal. Calcd for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.52; S, 8.07. Found: C, 66.62; H, 5.98; N, 3.74; S, 8.39.

Methyl (−)-(1*R*,3*R*,3a*R*,6a*R*,*S*$_S$)-1-Methyl-4-oxo-3-phenyl-3a-*p*-tolylsulfinyloctahydrocyclopenta[*c*]pyrrole-1-carboxylate (3b): yellow oil; $[\alpha]_D$ −69.8 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3425, 1730, 1725 cm^{-1}; ^{1}H NMR δ 7.53−7.28 (m, 9H), 5.08 (s, 1H), 3.82 (s, 3H), 3.03 (dd, 1H, *J* = 9.4, *J* = 3.4), 2.41 (s, 3H), 2.31 (bs, 1H), 2.20−2.07 (m, 1H), 1.73 (s, 3H), 1.60−1.47 (m, 2H), 1.09−0.96 (m, 2H); ^{13}C NMR δ 211.3, 174.7, 142.3, 136.5, 136.4, 129.8, 128.4, 128.3, 127.6, 125.5, 85.5, 68.3, 64.9, 52.1, 48.6, 40.4, 25.2, 24.5, 21.3; MS (FAB) *m*/*z* 412.6 (MH$^+$). Anal. Calcd for $C_{23}H_{25}NO_4S$: C, 67.13; H, 6.12; N, 3.40; S, 7.79. Found: C, 67.35; H, 5.98; N, 3.52; S, 7.65.

Methyl (+)-(1*S*,3*S*,3a*S*,6a*S*,*S*$_S$)-1-Methyl-4-oxo-3-phenyl-3a-*p*-tolylsulfinyloctahydrocyclopenta[*c*]pyrrole-1-carboxylate (4b): yellow oil; $[\alpha]_D$ +167 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3385, 1745, 1730 cm^{-1}; ^{1}H NMR δ 7.60−7.21 (m, 9H), 4.97 (s, 1H), 3.77 (s, 3H), 2.85 (dd, 1H, *J* = 8.0, *J* = 8.0), 2.41 (bs, 1H), 2.39 (s, 3H), 2.08−1.87 (m, 1H), 1.63−1.49 (m, 2H), 1.42 (s, 3H), 0.87−0.80 (m, 1H); ^{13}C NMR δ 207.9, 173.9, 143.0, 137.2, 136.6, 129.8, 128.2, 128.0, 127.9, 126.6, 79.7, 68.0, 66.1, 52.2, 51.8, 40.8, 24.6, 24.3, 21.4; MS (FAB) *m*/*z* 412.6 (MH$^+$).

Anal. Calcd for $C_{23}H_{25}NO_4S$: C, 67.13; H, 6.12; N, 3.40; S, 7.79. Found: C, 67.45; H, 6.38; N, 3.68; S, 7.63.

Methyl (−)-(1*R*,3*R*,3a*R*,6a*R*,S_S)-3-(2-Naphthyl)-4-oxo-3a-*p*-tolylsulfinyloctahydrocyclopenta[*c*]pyrrole-1-carboxylate (3c): yellow needles (ethyl ether−hexane); mp 132−134 °C; $[\alpha]_D$ −85 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3484, 1735, 1729 cm^{-1}; ^1H NMR δ 7.99−7.25 (m, 11H), 5.18 (s, 1H), 4.25 (d, 1H, $J = 7.0$), 3.87 (s, 3H), 3.52 (m, 1H), 2.55 (bs, 1H), 2.38 (s, 3H), 2.20−2.05 (m, 1H), 1.80−1.63 (m, 1H), 1.40−1.25 (m, 2H); ^{13}C NMR δ 211.0, 171.2, 142.0, 136.0, 134.0, 133.4, 133.2, 129.8, 128.1, 127.9, 127.8, 126.5, 126.1, 126.0, 125.8, 125.7, 84.2, 67.5, 63.9, 52.0, 41.6, 40.4, 22.5, 21.4; MS (electrospray+) *m*/*z* 448.2 (MH^+). Anal. Calcd for $C_{26}H_{25}NO_4S$: C, 69.78; H, 5.63; N, 3.13; S, 7.16. Found: C, 69.62; H, 5.69; N, 3.38; S, 7.45.

Methyl (+)-(1*S*,3*S*,3a*S*,6a*S*,S_S)-3-(2-Naphthyl)-4-oxo-3a-*p*-tolylsulfinyloctahydrocyclopenta[*c*]pyrrole-1-carboxylate (4c): yellow needles (ethyl ether−hexane); mp 135−137 °C; $[\alpha]_D$ +164 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3418, 1741, 1735 cm^{-1}; ^1H NMR δ 7.91−7.18 (m, 11H), 4.96 (s, 1H), 4.12 (d, 1H, $J = 7.0$), 3.88 (s, 3H), 3.62 (m, 1H), 2.41 (s, 3H), 2.39 (bs, 1H), 2.20−2.00 (m, 1H), 1.80−1.60 (m, 1H), 0.98−0.81 (m, 2H); ^{13}C NMR δ 207.5, 170.2, 143.1, 137.1, 134.1, 133.4, 133.1, 129.8, 128.0, 127.7, 127.5, 126.3, 126.0, 125.9, 125.4, 125.3, 79.7, 67.1, 63.8, 51.8, 40.8, 40.0, 22.7, 21.4; MS (electrospray+) *m*/*z* 448.4 (MH^+). Anal. Calcd for $C_{26}H_{25}NO_4S$: C, 69.78; H, 5.63; N, 3.13; S, 7.16. Found: C, 69.71; H, 5.71; N, 3.31; S, 7.25.

Methyl (−)-(1*R*,3*R*,3a*R*,6a*R*,S_S)-1-Methyl-3-(2-naphthyl)-4-oxo-3a-*p*-tolylsulfinyloctahydrocyclopenta[*c*]pyrrole-1-carboxylate (3d): yellow needles (ethyl ether−hexane); mp 138−140 °C; $[\alpha]_D$ −94 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3415, 1732, 1728 cm^{-1}; ^1H NMR δ 7.95−7.25 (m, 11H), 5.21 (s, 1H), 3.82 (s, 3H), 3.01 (dd, 1H, $J = 3.9$, $J = 8.9$), 2.45 (bs, 1H), 2.37 (s, 3H), 2.21−2.01 (m, 1H), 1.73 (s, 3H), 1.70−1.58 (m, 1H), 1.20−0.98 (m, 2H); ^{13}C NMR δ 211.2, 174.8, 142.4, 136.5, 134.1, 133.4, 133.2, 129.8, 129.7, 128.1, 127.9, 127.8, 126.6, 126.1, 126.0, 125.9, 125.6, 85.6, 68.4, 65.0, 52.2, 48.8, 40.4, 25.3, 24.6, 21.4; MS (electrospray+) *m*/*z* 462.1 (MH^+). Anal. Calcd for $C_{27}H_{27}NO_4S$: C, 70.26; H, 5.90; N, 3.03; S, 6.95. Found: C, 70.51; H, 5.81; N, 3.25; S, 7.12.

Methyl (+)-(1*S*,3*S*,3a*S*,6a*S*,S_S)-1-Methyl-3-(2-naphthyl)-4-oxo-3a-*p*-tolylsulfinyloctahydrocyclopenta[*c*]pyrrole-1-carboxylate (4d): yellow needles (ethyl ether−hexane); mp 145−147 °C; $[\alpha]_D$ +168 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3428, 1731, 1729 cm^{-1}; ^1H NMR δ 7.90−7.23 (m, 11H), 5.14 (s, 1H), 3.82 (s, 3H), 2.99 (dd, 1H, $J = 8.2$, $J = 8.2$), 2.41 (s, 3H), 2.38 (bs, 1H), 2.15−2.05 (m, 1H), 1.73 (s, 3H), 1.62−1.52 (m, 1H), 0.98−0.83 (m, 2H); ^{13}C NMR δ 208.0, 174.1, 143.0, 136.6, 134.9, 133.2, 133.1, 129.9, 128.2, 128.1, 127.7, 126.8, 126.7, 126.3, 126.2, 125.9, 125.8, 82.3, 68.1, 66.0, 52.2, 40.9, 24.8, 24.5, 21.5; MS (electrospray+) *m*/*z* 462.1 (MH^+). Anal. Calcd for $C_{27}H_{27}NO_4S$: C, 70.26; H, 5.90; N, 3.03; S, 6.95. Found: C, 70.31; H, 5.93; N, 3.24; S, 7.02.

Desulfinylation. Method A: To a solution of the corresponding cycloadduct **3** or **4** in THF (2 mL/0.2 mmol) was added a suspension of activated Raney nickel in THF. The reaction was stirred at −20 °C for 30 min. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate−hexane, 1:2) to give **5**.

Methyl (−)-(1*R*,3*S*,3a*R*,6a*S*)-4-Oxo-3-phenyloctahydrocyclopenta[*c*]pyrrole-1-carboxylate (5a): yield 82%; yellow oil; $[\alpha]_D$ −55 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$) 3452, 1741, 1682 cm^{-1}; ^1H NMR δ 7.58−7.34 (m, 5H), 4.85 (d, 1H, $J = 9.0$), 3.94 (d, 1H, $J = 9.0$), 3.79 (s, 3H), 3.32−3.25 (m, 1H), 2.88−2.82 (m, 1H), 2.38−2.08 (m, 4H); ^{13}C NMR δ 206.3, 173.5, 133.0, 131.4, 125.4, 123.1, 64.0, 63.1, 52.6, 51.4, 41.2, 36.8, 25.1; MS (EI) *m*/*z* 259.2 (M^+). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.52; H, 6.81; N, 5.35.

Methyl (+)-(1*S*,3*R*,3a*S*,6a*R*)-4-Oxo-3-phenyloctahydrocyclopenta[*c*]pyrrole-1-carboxylate (5a): yield 84%; yellow oil; $[\alpha]_D$ +59 (*c* 1.8, $CHCl_3$).

Methyl (−)-(1*R*,3*S*,3a*R*,6a*S*)-1-Methyl-4-oxo-3-phenyloctahydrocyclopenta[*c*]pyrrole-1-carboxylate (5b): yield 86%; yellow oil; $[\alpha]_D$ −58 (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) 3441, 1752, 1694 cm^{-1}; ^1H NMR δ 7.59−7.31 (m, 5H), 4.89 (d, 1H, $J = 10.0$), 3.81 (s, 3H), 3.24−3.17 (dd, 1H, $J = 10.0$, $J = 8.0$), 2.94−2.87 (dd, 1H $J = 15.0$, $J = 8.0$), 2.41 (bs, 1H), 2.18−2.00 (m, 3H), 1.87−1.78 (m, 1H); ^{13}C NMR δ 211.0, 175.1, 135.4, 134.1, 127.4, 125.5, 63.8, 60.4, 53.1, 50.0, 41.4, 34.3, 23.4; MS (EI) *m*/*z* 273.4 (M^+). HRMS (EI) $C_{16}H_{19}NO_3$ required 273.1365, found 273.1369.

Methyl (+)-(1*S*,3*R*,3a*S*,6a*R*)-1-Methyl-4-oxo-3-phenyloctahydrocyclopenta[*c*]pyrrole-1-carboxylate (5b): yield 83%; yellow oil; $[\alpha]_D$ +61 (*c* 1.7, $CHCl_3$).

Methyl (−)-(1*R*,3*S*,3a*R*,6a*S*)-3-(2-Naphthyl)-4-oxooctahydrocyclopenta[*c*]pyrrole-1-carboxylate (5c): yield 85%; yellow needles (ethyl ether−hexane); mp 105−107 °C; $[\alpha]_D$ −61 (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) 3448, 1753, 1694 cm^{-1}; ^1H NMR δ 7.82−7.34 (m, 7H), 4.88 (d, 1H, $J = 9.0$), 3.97 (d, 1H, $J = 2.0$), 3.81 (s, 3H), 3.34−3.27 (m, 1H), 2.91−2.85 (m, 1H), 2.41−2.10 (m, 4H); ^{13}C NMR δ 218.4, 174.2, 135.4, 135.2, 133.4, 128.6, 128.4, 128.2, 126.5, 126.3, 126.2, 125.9, 67.2, 66.4, 55.6, 53.0, 44.9, 39.9, 28.8; MS (EI) *m*/*z* 309.6 (M^+). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.66; H, 6.37; N, 4.45.

Methyl (+)-(1*S*,3*R*,3a*S*,6a*R*)-3-(2-Naphthyl)-4-oxooctahydrocyclopenta[*c*]pyrrole-1-carboxylate (5c): yield 83%; yellow needles (ethyl ether−hexane); mp 108−111 °C; $[\alpha]_D$ +65 (*c* 2.0, $CHCl_3$).

Methyl (−)-(1*R*,3*S*,3a*R*,6a*S*)-1-Methyl-3-(2-naphthyl)-4-oxooctahydrocyclopenta[*c*]pyrrole-1-carboxylate (5d): yield 86%; yellow needles (ethyl ether−hexane); mp 111−113 °C; $[\alpha]_D$ −64 (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) 3441, 1736, 1684 cm^{-1}; ^1H NMR δ 7.86−7.34 (m, 7H), 4.91 (d, 1H, $J = 9.0$), 3.84 (s, 3H), 3.21−3.15 (dd, 1H, $J = 10.3$, $J = 8.0$), 2.98−2.90 (dd, 1H, $J = 15.0$, $J = 8.0$), 2.20−2.02 (m, 3H), 1.92−1.82 (m, 1H); ^{13}C NMR δ 217.2, 174.7, 136.7, 133.3, 133.1, 127.9, 127.7, 127.6, 125.9, 125.8, 125.7, 125.4, 69.3, 62.5, 55.9, 52.1, 50.2, 39.2 (2C), 25.0; MS (EI) *m*/*z* 323.6 (M^+). HRMS (EI) $C_{20}H_{21}NO_3$ required 323.1521, found 323.1523.

Methyl (+)-(1*S*,3*R*,3a*S*,6a*R*)-1-Methyl-3-(2-naphthyl)-4-oxooctahydrocyclopenta[*c*]pyrrole-1-carboxylate (5d): yield 88%; yellow needles (ethyl ether−hexane); mp 112−110 °C; $[\alpha]_D$ +67 (*c* 2.0, $CHCl_3$).

Method B: To a solution of the corresponding cycloadduct **3** or **4** (1 equiv) in THF (7 mL/0.5 mmol) was added activated powdered Zn (2 g/0.5 mmol) and saturated aqueous ammonium chloride (7 mL/0.5 mmol). The mixture was stirred vigorously at room temperature under argon for 30 min and diluted with a 1:1 mixture of ethyl acetate and hexane (100 mL/0.5 mmol). The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (3 × 20 mL/0.5 mmol), dried (Na_2SO_4), and evaporated. The crude mixture was purified by flash chromatography (ethyl acetate−hexane, 1:2) to give the compound **6**. In these reaction conditions, compounds **3a**,**c** and **4a**,**c** evolved into the corresponding aromatic rings, **8a**,**c**, respectively.

Methyl (−)-(2*R*)-2-Amino-2-[(1*S*,2*S*)-2-benzyl-3-oxocyclopentyl]propanoate (6b): yield 84%; yellow oil; $[\alpha]_D$ −57 (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) 3438, 1737, 1699 cm^{-1}; ^1H NMR δ 7.52−7.28 (m, 5H), 3.64 (s, 3H), 3.20−3.04 (m, 2H), 2.75−2.69 (m, 1H), 2.47−2.40 (m, 1H), 2.38−2.29 (m, 1H), 2.05−1.93 (m, 1H), 1.85−1.59 (m, 5H), 1.20 (s, 3H); ^{13}C NMR δ 221.1, 176.2, 136.8, 130.9, 128.2, 127.6, 61.2, 60.0, 50.8, 46.8, 37.7, 37.0, 25.0, 22.3; MS (EI) *m*/*z* 275.4 (M^+). HRMS (EI) $C_{16}H_{21}NO_3$ required 275.1521, found 275.1525.

Methyl (+)-(2*S*)-2-Amino-2-[(1*R*,2*R*)-2-benzyl-3-oxocyclopentyl]propanoate (6b): yield 82%; yellow oil; $[\alpha]_D$ +59 (*c* 1.8, $CHCl_3$).

Methyl (−)-(2*R*)-2-Amino-2-[(1*S*,2*S*)-2-(2-naphthylmethyl)-3-oxocyclopentyl]propanoate (6d): yield 85%; yellow oil; $[\alpha]_D$ −68 (*c* 2, $CHCl_3$); IR ($CHCl_3$) 3441, 1736, 1705 cm^{-1}; ^1H NMR δ 7.83−7.27 (m, 7H), 3.64 (s, 3H), 3.23−3.01 (m, 2H),

2.77−2.68 (m, 1H), 2.46−2.38 (m, 1H), 2.31−2.27 (m, 1H), 2.09−1.88 (m, 1H), 1.85−1.56 (m, 5H), 1.20 (s, 3H); ^{13}C NMR δ 220.7, 175.2, 136.4, 133.5, 132.2, 129.8, 128.5, 128.1, 127.9, 127.6, 126.0, 125.5, 61.8, 61.0, 50.4, 46.3, 37.4, 36.5, 25.5, 22.4; MS (EI) *m*/*z* 325.5 (M^+). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.69; H, 7.23; N, 4.35.

Methyl (+)-(2*S*)-2-Amino-2-[(1*R*,2*R*)-2-(2-naphthylmethyl)-3-oxocyclopentyl]propanoate (6d): yield 81%; yellow oil; $[\alpha]_D$ +71 (*c* 1.8, $CHCl_3$).

Method C: A solution of **3b**,**d** or **4b**,**d** in toluene (2 mL/0.2 mmol) was refluxed for 2.5 h. The solvent was evaporated under vacuum, and the residue was purified by column chromatography (ethyl acetate−hexane, 1:3). Under these reaction conditions, compounds **3a**,**c** and **4a**,**c** evolve into the corresponding aromatic rings, **8a**,**c**, respectively.

Methyl (−)-(1*S*,3*S*)-1-Methyl-3-phenyl-4-oxo-1,2,3,4,5,6-hexahydrocyclopenta[*c*]pyrrole-1-carboxylate (7b): yield 92%; yellow oil; $[\alpha]_D$ −52 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3458, 1737, 1712 cm^{-1}; ^{1}H NMR δ 7.54−7.31 (m, 5H), 4.64 (s, 1H), 3.71 (s, 3H), 2.64−2.57 (m, 2H), 2.12−1.84 (m, 2H), 1.35 (s, 3H); ^{13}C NMR δ 205.1, 173.0, 146.1, 137.5, 134.6, 128.9, 128.3, 125.9, 77.2, 56.0, 55.3, 44.5, 25.6, 23.4; MS (EI) *m*/*z* 271.9 (M^+). HRMS (EI) $C_{16}H_{17}NO_3$ required 271.1208, found 271.1210.

Methyl (+)-(1*R*,3*R*)-1-Methyl-3-phenyl-4-oxo-1,2,3,4,5,6-hexahydrocyclopenta[*c*]pyrrole-1-carboxylate (7b): yield 93%; yellow oil; $[\alpha]_D$ +57 (*c* 1.1, $CHCl_3$).

Methyl (−)-(1*S*,3*S*)-1-Methyl-3-(2-naphthyl)-4-oxo-1,2,-3,4,5,6-hexahydrocyclopenta[*c*]pyrrole-1-carboxylate (7d): yield 96%; yellow oil; $[\alpha]_D$ −59 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) 3440, 1741, 1735 cm^{-1}; ^{1}H NMR δ 7.68−7.23 (m, 7H), 4.68 (s, 1H), 3.73 (s, 3H), 2.69−2.51 (m, 2H), 2.18−1.81 (m, 2H), 1.31 (s, 3H); ^{13}C NMR δ 209.4, 179.6, 148.5, 135.8, 133.4, 133.1, 132.8, 127.8, 127.3, 127.0, 126.8, 125.9, 125.4, 125.1, 72.3, 59.2, 54.2, 42.9, 26.1, 23.8; MS (EI) *m*/*z* 321.7 (M^+). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.92; H, 6.12; N, 3.47.

Methyl (+)-(1*R*,3*R*)-1-Methyl-3-(2-naphthyl)-4-oxo-1,2,-3,4,5,6-hexahydrocyclopenta[*c*]pyrrole-1-carboxylate (7d): yield 92%; yellow oil; $[\alpha]_D$ +63 (*c* 1.2, $CHCl_3$).

Methyl 4-Oxo-3-phenyl-2,4,5,6-tetrahydrocyclopenta-[*c*]pyrrole-1-carboxylate (8a): yield 95%; yellow needles (ethyl ether−hexane); mp 125−127 °C; IR ($CHCl_3$) 3452, 1734, 1705 cm^{-1}; ^{1}H NMR δ 7.51−7.24 (m, 5H), 3.81 (s, 3H), 2.82−2.71 (m, 2H), 2.58−2.49 (m, 2H); ^{13}C NMR δ 212.1, 160.6, 137.5, 131.5, 131.1, 125.4, 125.3, 124.9, 124.7, 124.2, 123.5, 119.3, 51.8, 43.6, 16.8; MS (EI) *m*/*z* 255.9 (M^+). Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.35; H, 5.12; N, 5.58.

Methyl 3-(2-Naphthyl)-4-oxo-2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole-1-carboxylate (8c): yield 96%; yellow needles (ethyl ether−hexane); mp 129−130 °C; IR ($CHCl_3$) 3449, 1744, 1712 cm^{-1}; ^{1}H NMR δ 7.81−7.27 (m, 7H), 3.80 (s, 3H), 2.85−2.76 (m, 2H), 2.61−2.52 (m, 2H); ^{13}C NMR δ 210.1, 165.1, 137.9, 136.7, 136.1, 132.7, 129.2, 129.1, 126.5, 126.1, 125.8, 125.4, 125.0, 123.9, 123.2, 117.0, 52.3, 43.1, 15.4; MS (EI) *m*/*z* 305.6 (M^+). HRMS (EI) $C_{19}H_{15}NO_3$ required 305.1052, found 305.1049.

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