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Asymmetric Synthesis of Pyrrolo[2,1-*a*]isoquinoline Derivatives by 1,3-Dipolar Cycloadditions of Stabilized Isoquinolinium *N*-Ylides with Sulfinyl Dipolarophiles

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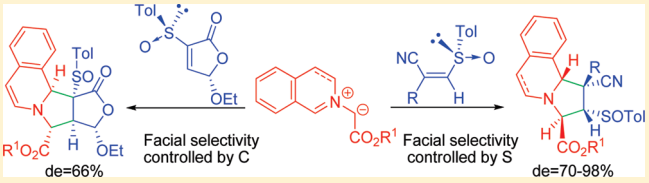
Supporting Information

ABSTRACT: Enantiomerically pure pyrrolo[2,1-*a*]isoquinoline derivatives are obtained by 1,3-dipolar reactions of isoquinolinium azomethine ylides with enantiopure 3-*p*-tolylsulfinylacrylonitriles, *tert*-butyl (2*E*)-4,4-diethoxy-2-*p*-tolylsulfinylbut-2-enoate, and 5-ethoxy-3-*p*-tolylsulfinylfuran-2(5*H*)-ones. Reactions evolve through the anti conformation of the ylide with complete regioselectivity. The facial selectivity is completely controlled by the configuration of the sulfinyl sulfur for acyclic dipolarophiles, whereas it is high (dr 83/17 or 89/11) but controlled by the C-5 configuration for sulfinylfuranones. Complete endo selectivity is observed with cyclic dipolarophiles and substituted acrylonitriles, but it is low with butenoate. The sulfinyl group also exerts a positive influence on the dipolarophilic reactivity toward these ylides.



INTRODUCTION

Pyrrolo[2,1-*a*]isoquinoline moieties[1] are present in alkaloid families, such as erythrina[2] and lamellarin,[3] and in more simple pyrrolo[2,1-*a*]isoquinoline derivatives,[4,5] all of them exhibiting diverse biological activities. Additionally, the importance of these heterocyclic systems is further enhanced by their utility as advanced intermediates for the synthesis of alkaloids.[1] Consequently, plenty of attention has been paid to the synthesis of these systems. Three main strategies have been developed for the asymmetric construction of polyhydro derivatives, the key steps of which employ *N*-acyliminium cyclization,[6] Mitsunobu reaction of optically pure 3-(tetrahydroisoquinolin-1-yl)propan-1-oles,[7] and asymmetric hydrogenation of prochiral iminium salts with a chiral Ru complex preformed from chiral amines.[8] However, the most straightforward way to obtain this moiety, which involves the [3 + 2] cycloadditions of stabilized isoquinolinium or 3,4-dihydroisoquinolinium ylides with proper chiral dipolarophiles (Scheme 1), has never been explored to our knowledge, despite the fact that asymmetric [3 + 2] cycloadditions are among the most efficient reactions for the construction of enantiopure five-membered heterocycles.[9]

Asymmetric cycloaddition of azomethine ylides derived from imino esters leading to pyrrolidines has been extensively studied.[9,10] In contrast, the use as the dipole of heteroaromatic *N*-ylides for preparing optically pure polycyclic products has been scarcely exploited. In this field we have reported some reactions of acyclic *N*-metalated azomethine ylides[11] and of thiazolium *N*-ylides[12] with activated vinyl sulfoxides,[13] which evidenced that the incorporation of the sulfinyl group to the dipolarophilic double bonds improves their reactivity as well as the endo/exo and π-facial selectivities of the cycloadditions.[14] These features prompted us to use activated acyclic (**3**−**6**)[15] and cyclic (**7**)[15b] vinyl sulfoxides (Figure 1) as dipolarophiles in the [3 + 2] cycloadditions with stabilized isoquinolinium ylides **1** and **2**.[16] The results obtained in this study are herein reported. The comparison of the results obtained in reactions of **7** with those from racemic furanone **8**,[17] which are also reported in this paper, allowed us to establish the role of the sulfinyl group at C-3 on the course of these reactions.

RESULTS AND DISCUSSION

The reaction of ylide **1**, generated in situ by treatment of **1**-**HBr** with base, with sufinylacrylonitrile **3** in acetonitrile, at room temperature using a 1:1.4:1.2 ratio of dipolarophile **3**:**1**-**HBr**:DBU, afforded a mixture of two adducts (Scheme 2). The major one (*endo*-**9**)[18] was isolated pure in 80% yield by filtration of the crude mixture. The minor adduct (*exo*-**9**)[18] was separated by flash column chromatography, but it could not be isolated as a pure compound, because it rapidly transformed into ethyl 1-cyanopyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**12**)[19,20] by elimination of sulfenic acid and further aromatization.

Ylide **1** reacted with substituted acrylonitriles **4** and **5** more slowly than with **3**, but with complete stereoselectivity, yielding only *endo*-**10** and *endo*-**11** adducts,[18] respectively (Scheme 2). The moderate yield of *endo*-**11** is due to its partial transformation into the corresponding 2,3-dehydroisoquinoline **13** (isolated in

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19% yield) on the silica gel during its purification by column chromatography.

The easy decomposition of the primary adducts **9**−**11** depicted in Scheme 2 could be ascribed to the presence of the enamine group. In order to avoid this problem, we studied the cycloaddition of dipole **2** (generated from **2-HBr**) to sulfinylacrylonitriles. As can be seen in Scheme 3, the reactions of **2** with **3** and **4** are completely stereoselective, yielding the endo adducts[18] (**14** and **15**, respectively). Reaction of **2** with **5** only yields compound **16**, resulting from the spontaneous desulfinylation of the corresponding undetected endo adduct, which must be less stable than *endo*-**11** (it is only partially desulfinylated), presumably due to steric reasons.

Next, we performed the reaction of *tert*-butyl (2*E*)-4,4-diethoxy-2-*p*-tolylsulfinylbut-2-enoate (**6**) with isoquinolinium **1-HBr** in acetonitrile at room temperature, using DBU as base. This reaction yielded a mixture of three products, two primary cycloadducts (*endo*- and *exo*-**17**)[18] and compound **18** in a ratio of 59:36:5 (Scheme 4).[21] Unfortunately, primary adducts **17** and acetal **18** are unstable in silica gel. Chromatographic separation of the mixture only provided the major *endo*-**17** as a pure compound, in 30% yield, along with a 51% of pyrroloisoquinoline **19**, derived from adducts **17** by elimination of sulfenic acid and subsequent aromatization and acetal hydrolysis. Compound **19** was also formed by hydrolysis of **18** during the chromatographic separation. Both the composition of the reaction mixture before chromatography and the isolated yields of *endo*-**17** and **19** (30 and 51%, respectively) are indicative that **19** results from the evolution of *endo*- and *exo*-**17**, which requires that the two primary adducts exhibit the same regiochemistry.

The 1,2,3,10b-tetrahydro- or 1,2,3,5,6,10b-hexahydropyrrolo-[2,1-*a*]isoquinoline framework of the primary adducts obtained from acyclic vinyl sulfoxides **3**−**6** was mainly determined by NMR (^{1}H-, ^{13}C- and NOESY experiments). Cycloadduct *exo*-**9** was chemically correlated with ethyl 1-cyanopyrrolo[2,1-*a*]-isoquinoline-3-carboxylate (**12**)[19] (Scheme 2). The NOE effects observed in compound **10** [H-5/H-3 (d) and H-10/H-10b (s)] and **15** (H-10 and singlet at 4.29 ppm of H-10b) support the regiochemistry indicated in Figure 2 and Schemes 2 and 3. Finally, the NOE effect observed in the NOESY experiment of *endo*-**17** between the singlet at 5.81 (H-10b) and H-10 (Scheme 4) and the ^{1}H chemical shift of the *tert*-butyl group of ester **17** allow assignment of the structure proposed for this compound.[22] The so-assigned regiochemistry agrees with the complete control of the regioselectivity reported by Tsuge et al.[16b,23] for cycloadditions of **1** with alkenes bearing one electron-withdrawing group.

Scheme 1. 1,3-Dipolar Approach to Enantiomerically Pure Polyhydropyrrolo[2,1-*a*]isoquinolines

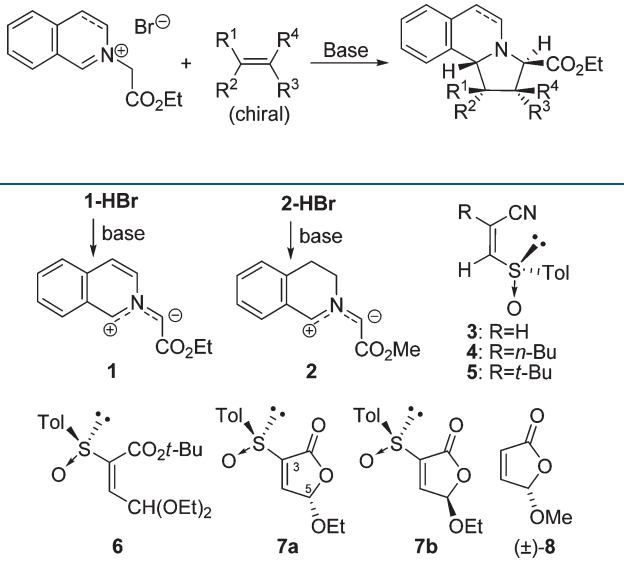
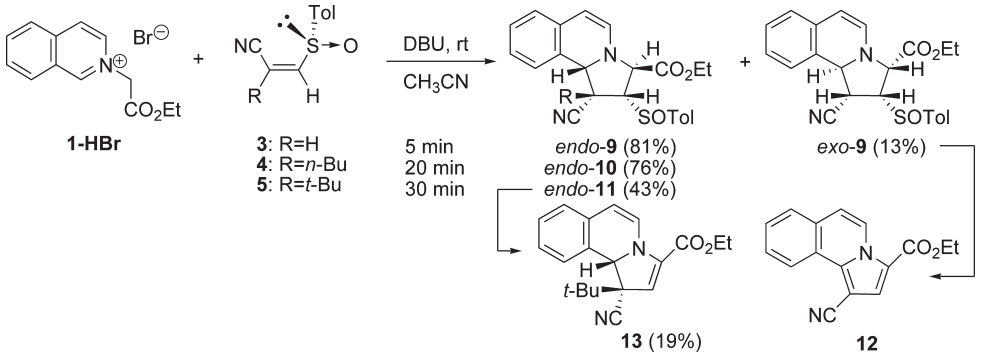
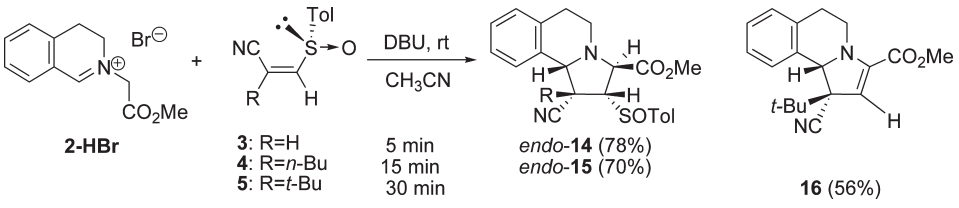


Figure 1. Dipoles and dipolarophiles used in this study.

Scheme 2. Reaction of Isoquinolinium Ylide 1 with (Z,R_S)-3-*p*-Tolylsulfinylacrylonitriles 3−5



Scheme 3. Reaction of Isoquinolinium Ylide 2 with (Z,R_S)-3-*p*-Tolylsulfinylacrylonitriles 3−5



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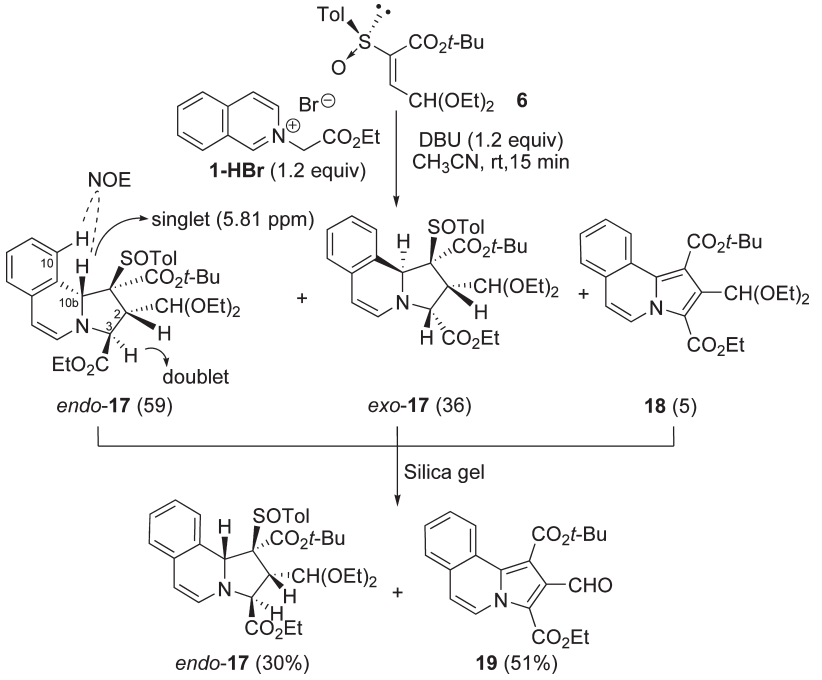
Scheme 4. Reaction of Isoquinolinium Ylide 1 with *tert*-Butyl (2*E*)-4,4-Diethoxy-2-*p*-tolylsulfinylbut-2-enoate (6)



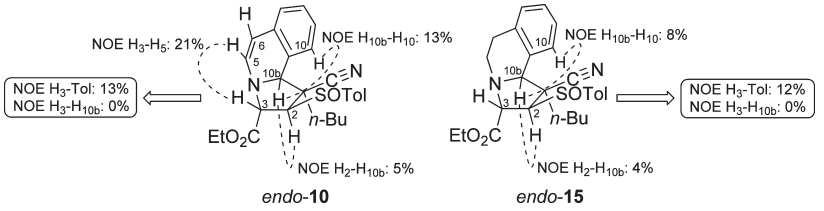


Figure 2. Significant NOE effects supporting the structure of adducts.

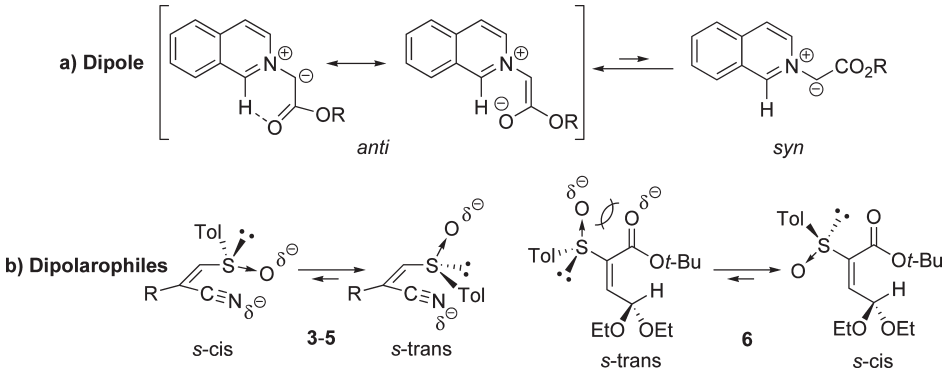


Figure 3. Favored conformations of dipole and dipolarophiles.

The configuration of the major or exclusive adduct obtained in these reactions was assigned by assuming that the stereochemistry of the dipolarophiles is maintained in the adducts and that they must be formed by attack of the *anti* conformation of the dipole,[24] stabilized by intramolecular hydrogen bonding (Figure 3a), to the less hindered face of the dipolarophiles (Figure 3b) in their most stable conformations from an electrostatic point of view (*s*-trans in **3**−**5** and *s*-cis in **6**). The absolute configuration of *endo*-**17**, determined by X-ray diffraction analysis,[25] confirms the above hypotheses.

The endo approach of the anti-dipoles **1** or **2** to the less hindered face of the dipolarophiles **3**−**5** will be favored with respect to the exo approach due to the destabilizing interactions CO_2Et/SOTol and R/isoquinoline (Scheme 5). Consequently,

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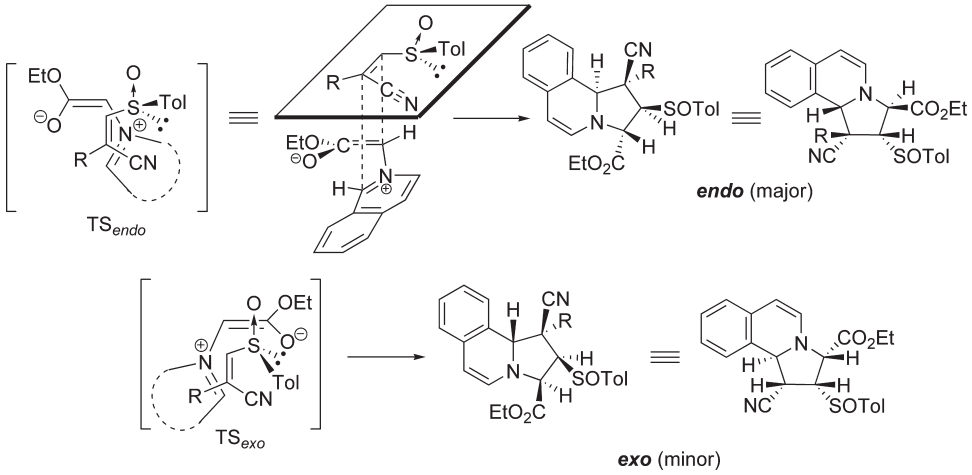
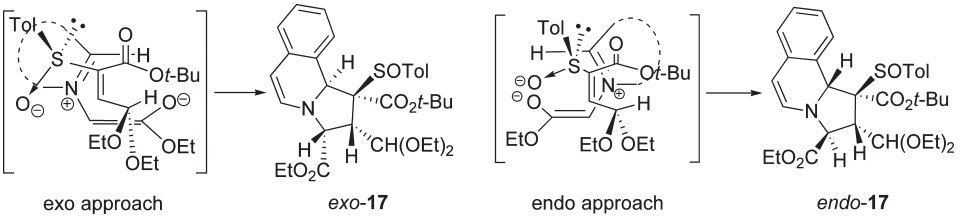
Scheme 5. Stereochemical Course of the Cycloaddition of Azomethine Ylide 1 to Vinyl Sulfoxides 3−5



Scheme 6. Stereochemical Course of the Cycloaddition of Azomethine Ylide 1 to Vinyl Sulfoxide 6

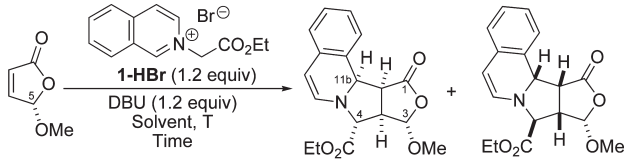


the endo adducts are obtained as the major **9** or exclusive (**10**, **11**, **14**, and **15**) ones. Additionally, in the endo approach there is an attractive interaction between the isoquinolinium ring and the cyano group.[26] The NOE effects H-2/H-10b and H-3/Tol (ortho protons) observed in adducts **10** and **15** (Figure 2) support the assignment of the proposed structures for the adducts.

The endo/exo selectivity of the reaction of **1** with **6** was lower than that observed with **3** (Scheme 2). This result can be justified by taking into account that the interactions destabilizing the exo approach [mainly $CO_2Et/CH(OEt)_2$] are partially balanced by the electrostatic interactions involving the sulfinyl oxygen (attractive in the exo approach and repulsive in the endo one, Scheme 6). The absolute configuration of the major adduct **17** shows that interaction destabilizing the exo approach [$CO_2Et/CH(OEt)_2$] is larger than the interaction existing in the endo approach (CO_2Et/SOTol).

The main conclusions deduced from the results obtained in the cycloadditions of isoquinolinium azomethine ylides **1** and **2** with acyclic sulfoxides **3**−**6** are (a) the reactions are completely regioselective, with the carbon bonded to the alkoxycarbonyl group of dipole generating a bond with the β-carbon of the dipolarophile. (b) The π-facial selectivity is complete and controlled by the configuration of the sulfinyl group. (c) The endo-selectivity is complete in reactions with **4** and **5**, very high with **3** (86:14 endo:exo), and moderate with **6** (62:38 endo:exo). It is dependent on the sulfinyl configuration and its interactions with the groups present at the dipoles. These results indicate that the sulfinyl group confers excellent properties to the double bonds for being used as dipolarophiles in asymmetric [3 + 2] cycloadditions with ylides **1** and **2**, opening a new straightforward route for the preparation of polyhydropyrrolo[2,1-*a*]isoquinolines in their optically pure form.

Table 1. Reactions of 5-Methoxyfuran-2(5*H*)-one [(±)-8] with Isoquinolinium Ylide 1



entry	solvent	reaction time (min)	temperature	*anti-endo*-**20**:*syn-endo*-**20** ratio
1	CH_3CN	5	rt	80:20
2	CH_2Cl_2	15	rt	65:35
3	toluene	90	rt	60:40
4	CH_3CN	30	−40 °C	80:20

At this point, we reasoned that adducts obtained from cyclic dipolarophiles would be less prone to desulfinylation than the previously obtained from acyclic dipolarophiles, which prompted us to study the reactions of sulfinylfuranones **7** and **8** (Figure 1) with ylide **1**. In order to evaluate the influence of the alkoxy group at C-5 at the furanone ring, we first studied the reaction of racemic 5-methoxyfuran-2(5*H*)-one [(±)-**8**] with **1**-**HBr**

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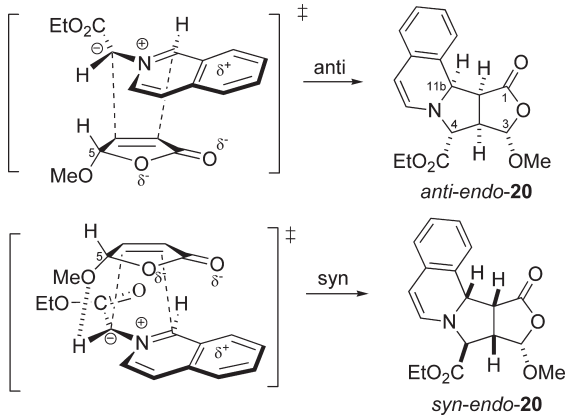
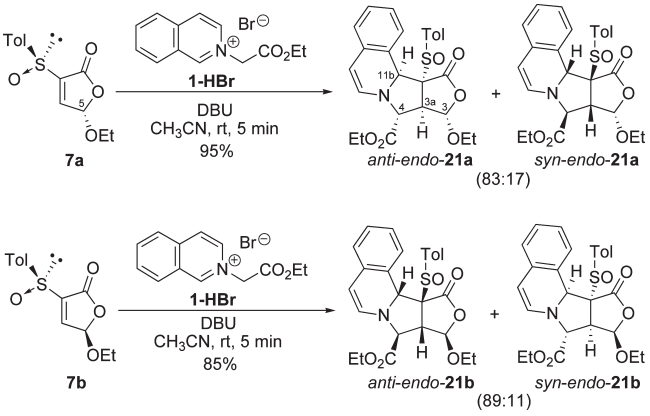
Scheme 7. Stereochemical Course of the Endo-Cycloaddition of Ylide 1 to 5-Methoxyfuranone (±)-8



Scheme 8. Cycloaddition of Isoquinolinium Ylide 1 to Sulfinylfuranones 7



(Table 1). This reaction afforded an 80:20 mixture of *anti-endo*-**20**[27] and *syn-endo*-**20** in acetonitrile at rt (entry 1, Table 1).[28] This composition was not altered at −40 °C, whereas stereoselectivity decreased in less polar solvents such as dichloromethane (entry 2) or toluene (entry 3), which also caused an increase in the reaction times.

From these results we can conclude that reaction of (±)-**8** with isoquinolinium ylide **1** is completely regioselective, with the generation of a bond between the negative extreme of the dipole and the β-carbon of the conjugated system, which suggests a significant contribution of the electrostatic interactions in the control of the favored approach. The endo selectivity is also complete (both adducts display H-4 and H-11b in a trans arrangement), which could be explained by the favorable electrostatic interactions of the oxygen of the furan ring with the positive nitrogen at the dipole and by the interaction of the carbonyl group with the aromatic ring of the dipole. Both factors favor the endo approaches (Scheme 7) but are absent in the exo ones. Finally, the moderate π-facial selectivity, which was lower in apolar solvents, suggests that steric interactions, clearly favoring the approach of the dipole to the opposite face to that occupied by the OMe group at C-5 at the furanone ring (anti approach), must be partially compensated by some kind of electrostatic interaction favoring the syn approach, which will reduce its importance in polar solvents, thus increasing the stereoselectivity (compare entry 1 with entries 2 and 3 of Table 1). Such interactions could be established between the hydrogen of the dipole and the oxygen of the OMe group at C-5 of dipolarophile (Scheme 7), as has been postulated in other cycloadditions.[14c]

Reactions of isoquinolinium bromide **1-HBr** with furanones **7a** and **7b** led to mixtures of syn and anti isomers as a result of the endo approach of the dipole to both faces of the double bond, the anti adducts (*anti-endo*-**21a** and *anti-endo*-**21b**)[27] being the major ones (Scheme 8). These were separated by flash column chromatography and then crystallized by precipitation in hexane−AcOEt (*anti-endo*-**21a**) or Et_2O (*anti-endo*-**21b**). Only one of the minor adducts (*syn-endo*-**21a**) could be isolated and properly characterized as a pure diastereoisomer.

The anti/syn and endo/exo character of compounds **20** and **21** was assigned from the values of the $J_{3,3a}$ and $J_{3a,4}$ coupling constants, respectively. Values smaller than 2.3 Hz are indicative of the antiperiplanar arrangement of the involved protons, which is associated with the anti and endo character of the adducts, whereas those larger than 6.9 Hz are characteristic of the synperiplanar arrangement, present in the syn and exo stereoisomer. The absolute configuration of adducts **21** was initially assigned as indicated in Scheme 8 on the assumption that the configurations at C-5 of the starting furanones **7a** and **7b** remained unaltered in the course of these reactions and that the anti-dipole was the only reactive species. These assignments were confirmed by X-ray diffraction analyses[29] of compounds *anti-endo*-**21a**, *syn-endo*-**21a**, and *anti-endo*-**21b**.

As we can see, all these cycloadditions evolve with a complete control of the regioselectivity and the endo selectivity, from the anti conformation of dipole **1**. This could be explained making use of the same reasons previously indicated for compound **8**, lacking of the sulfinyl group. The high but not complete facial selectivity observed in these reactions is also similar to that found from **8** (anti/syn ratio 80:20) with slightly better dr, mainly for **7b** (anti/syn ratio is 89:11). This fact suggests a moderate contribution of the sulfinyl group in the facial selectivity, which could be associated with the fact that steric effects of the sulfinyl group in the most stable conformation of **7b** (the tolyl and the ethoxy groups are positioned toward the same face of the double bond) reinforce the steric tendency imposed by the OMe group at C-5 at the furanone ring.[30]

In summary, we have demonstrated that the 1,3-dipolar reactions of isoquinolinium ylides with acyclic (**3**−**6**) and cyclic (**7a** and **7b**) sulfinyl ethylenes constitute a direct and efficient route to highly functionalized and enantiomerically pure 1,2,3,10b-tetrahydro- or 1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-3-carboxylates, a skeleton frequently found in compounds exhibiting valuable pharmacological activity.

EXPERIMENTAL SECTION

General Methods. Acetonitrile was dried over activated 4 Å molecular sieves. Silica gel 60 (230−400 mesh ASTM) and DC-Alufolien 60 F254 were used for flash column chromatography and analytical TLC, respectively. Melting points were determined in open capillary tubes and are uncorrected. NMR spectra were determined in $CDCl_3$ solutions, unless otherwise indicated, at 300 and 75 MHz for ^1H and ^{13}C NMR, respectively. Chemical shifts (δ) are reported in ppm and *J* values are given in hertz. The IR spectra frequencies are given in cm^{-1}. The optical rotations were measured at room temperature in the solvent and concentration (g/100 mL) indicated in each case. Isoquinolinium **1**-

HBr and **2-HBr** were synthesized according to the procedure described in ref 16a using ethanol as solvent.

Reaction of (Z)-3-*p*-Tolylsulfinylacrylonitriles 3−5 with Azomethine Ylides 1 and 2. General Procedure. To a stirred solution of sulfinylacrylonitrile (0.16 mmol) and the salt (0.22 mmol) in dry acetonitrile (4 mL), under argon and at room temperature, was added DBU (0.19 mmol). After the time indicated in each case, the solvent was evaporated in vacuo and the residue was dissolved in dichloromethane and it was washed with water. The aqueous layers were extracted with dichloromethane several times. The organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The purification method is indicated in each case.

Ethyl [(S)*R*]-1-Cyano-2-(*p*-tolylsulfinyl)-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (9). Compounds **9** were obtained as mixture of diastereoisomers *endo*- and *exo*-**9** following the general procedure from (*Z*)-3-[(*R*)-*p*-tolylsulfinyl]propenonitrile (**3**) and the isoquinolinium **1-HBr** after 5 min of reaction. The major adduct *endo*-**9** was separated by filtration of the crude mixture. The filtrate was evaporated and the residue was purified by flash column chromatography (AcOEt−hexane, 1:3). The combined yield is 93%.

[1*S*,2*R*,3*S*,10b*R*,(S)*R*]-*endo*-9. Yield: 81%, white solid. Mp ($CHCl_3$): 146−148 °C. $[\alpha]_D^{20}$: +402.0 (*c* 0.5, $CHCl_3$). IR (KBr): 2240, 1747, 1625, 1568, 1494, 1458, 1309, 1212, 1041 cm^{-1}. ^1H NMR δ: 7.72 and 7.31 (AA′BB′ system, 4 H), 7.21 (td, *J* = 7.5 and 1.3, 1 H), 7.08 (td, *J* = 7.5 and 1.3, 1 H), 7.01 (m, 1 H), 6.87 (m, 1 H), 6.26 (d, *J* = 7.6, 1 H), 5.39 (d, *J* = 7.6, 1 H), 5,13 (d, *J* = 4.9, 1 H), 4.83 (d, *J* = 5.5, 1 H), 4.14 (q, *J* = 7.2, 2 H), 3.92 (dd, *J* = 7.9 and 5.5, 1 H), 3.28 (dd, *J* = 7.9 and 4.9, 1 H), 2.44 (s, 3 H), 1.23 (t, *J* = 7.2, 3 H). ^{13}C NMR (DMSO-d_6) δ: 170.2 (CO), 141.6 (C), 139.6 (C), 134.9 (CH), 132.7 (C), 130.0 (CH), 128.8 (CH), 126.7 (CH), 125.9 (C), 125.6 (CH), 124.4 (CH), 124.3 (CH), 117.3 (CN), 98.4 (CH), 64.1 (CH), 62.6 (CH), 61.3 (CH_2), 59.5 (CH), 39.9 (CH), 21.1 (CH_3), 13.6 (CH_3). Anal. Calcd for $C_{23}H_{22}N_2O_3S$: C 67.96, H 5.46, N 6.89, S 7.89. Found: C 67.85, H 5.23, N 6.94, S 7.60.

[1*S*,2*R*,3*R*,10b*S*,(S)*R*]-*exo*-9. Yield: 12%. ^1H NMR δ: 7.69 and 7.36 (AA′BB′ system, 4 H), 7.15 (m, 2 H), 6.98 (m, 2 H), 6.06 (d, *J* = 7.5, 1 H), 5.31 (d, *J* = 7.5, 1 H), 5.26 (d, *J* = 3.8, 1 H), 4.05−3.73 (m, 5 H), 2.42 (s, 3 H), 1.05 (t, *J* = 7.2, 3 H).

Ethyl 1-Cyanopyrrolo[2,1-*a*]isoquinoline-3-carboxylate (12)[18]. Compound **12** was obtained by decomposition of adducts **9** upon standing in a refrigerator for 2 months. It was purified by flash column chromatography (AcOEt−hexane, 1:6). Yield: 80%. ^1H NMR δ: 9.32 (d, *J* = 7.5, 1 H), 8.95 (m, 1 H), 7.76 (s, 1 H), 7.64−7.80 (m, 3 H), 7.22 (d, *J* = 7.5, 1 H), 4.41 (q, *J* = 7.1, 2 H), 1.43 (t, *J* = 7.1, 3 H).

Ethyl [1*S*,2*R*,3*S*,10b*S*,(S)*R*]-1-Butyl-1-cyano-2-(*p*-tolylsulfinyl)-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (*endo*-10). Compound *endo*-**10** was obtained as the sole compound following the general procedure from (*Z*)-2-*n*-butyl-3-[(*R*)-*p*-tolylsulfinyl]propenonitrile (**4**) and the isoquinolinium **1-HBr** after 20 min of reaction. It was purified by filtration of the solid formed upon addition of Et_2O to the reaction mixture. Yield: 76%, white solid. Mp (Et_2O−hexane): 122−123 °C. $[\alpha]_D^{20}$: +555.4 (*c* 0.5, $CHCl_3$). IR (KBr): 2233, 1742, 1630, 1568, 1493, 1458, 1084, 1044 cm^{-1}. ^1H NMR δ: 7.57 and 7.32 (AA′BB′ system, 4 H), 7.24 (td, *J* = 7.4 and 0.9, 1 H), 7.07 (m, 2 H), 6.97 (d, *J* = 7.4, 1 H), 6.20 (d, *J* = 7.6, 1 H), 5.45 (d, *J* = 7.6, 1 H), 4.95 (d, *J* = 3.8, 1 H), 4.51 (s, 1 H), 3.95 (q, *J* = 7.1, 2 H), 3.45 (d, *J* = 3.8, 1 H), 2.39 (s, 3 H), 1.92 (m, 1 H), 1.60 (m, 2 H), 1.32 (m, 3 H), 1.06 (t, *J* = 7.1, 3 H), 0.89 (t, *J* = 7.1, 3 H). ^{13}C NMR δ: 170.2 (CO), 142.4 (C), 139.5 (C), 135.2 (CH), 132.8 (C), 130.1 (CH), 129.4 (CH), 126.6 (CH), 125.5 (CH), 125.3 (CH), 124.9 (C), 124.4 (CH), 118.3 (CN), 102.0 (CH), 70.2 (CH), 69.6 (CH), 62.7 (CH), 62.0 (CH_2), 52.8 (C), 36.4 (CH_2), 27.9 (CH_2), 22.6 (CH_2), 21.4 (CH_3), 13.8 (CH_3), 13.7 (CH_3). Anal. Calcd for $C_{27}H_{30}N_2O_3S$: C 70.10, H 6.54, N 6.06, S 6.93. Found: C 69.94, H 6.55, N 6.00, S 7.06.

Ethyl [1*S*,2*R*,3*S*,10b*R*,(S)*R*]-1-*tert*-Butyl-1-cyano-2-(*p*-tolylsulfinyl)-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (11-*endo*). Compound *endo*-**11** was obtained as the sole compound following the general procedure from (*Z*)-2-*tert*-butyl-3-[(*R*)-*p*-tolylsulfinyl]propenonitrile (**5**) and the isoquinolinium **1-HBr** after 30 min of reaction. It was purified by flash column chromatography (AcOEt−hexane, 1:3).Yield: 43%, white solid. Mp (Et_2O−hexane): 116−117 °C. $[\alpha]_D^{20}$: +613.8 (*c* 0.5, $CHCl_3$). IR (KBr): 2229, 1736, 1630, 1567, 1491, 1081, 1051 cm^{-1}. ^1H NMR δ: 7.57 and 7.34 (AA′BB′ system, 4 H), 7.23 (m, 2 H), 7.08 (m, 2 H), 6.25 (d, *J* = 7.6, 1 H), 5.56 (d, *J* = 7.6, 1 H), 5.01 (d, *J* = 3.1, 1 H), 4.81 (s, 1 H), 3.96 (dq, *J* = 7.1 and 2.0, 2 H), 3.58 (d, *J* = 3.1, 1 H), 2.42 (s, 3 H), 1.21 (s, 9 H), 1.02 (t, *J* = 7.1, 3 H). ^{13}C NMR δ: 170.3 (CO), 142.2 (C), 139.9 (C), 136.1 (CH), 134.1 (C), 130.1 (CH), 129.4 (CH), 125.4 (C), 125.2 (CH), 124.7 (CH), 124.0 (CH), 118.5 (CN), 103.6 (CH), 69.7 (CH), 65.7 (CH), 61.9 (CH_2), 60.9 (CH), 59.8 (C), 36.5 (C), 27.7 (CH_3), 21.4 (CH_3), 13.8 (CH_3). Anal. Calcd for $C_{27}H_{30}N_2O_3S$: C 70.10, H 6.54, N 6.06, S 6.93. Found: C 69.96, H 6.41, N 5.98, S 7.06.

Ethyl (1*R*,10b*S*)-1-*tert*-Butyl-1-cyano-1,10b-dihydropyrrolo-[2,1-*a*]isoquinoline-3-carboxylate (13). Although this compound was not detected in the ^1H NMR spectrum of the crude reaction mixture, it was obtained after the flash column chromatography by decomposition of adduct *endo*-**11** on the silica gel. Yield: 19%. IR (film): 2216, 1701, 1421, 1222, 1088 cm^{-1}. ^1H NMR δ: 7.58 (m, 1 H), 7.44 (d, *J* = 7.7, 1 H), 7.20 (m, 2 H), 7.05 (dd, *J* = 7.3 and 2.0, 1 H), 5.75 (d, *J* = 7.7, 1 H), 5.75 (s, 1 H), 4.88 (s, 1 H), 4.30 (dq, *J* = 6.9 and 3.6, 2 H), 1.35 (t, *J* = 6.9, 3 H), 1.21 (s, 9 H). ^{13}C NMR δ: 160.1, 136.5, 133.6, 127.95, 127.90, 126.6, 125.2, 125.0, 123.9, 118.8, 110.1, 104.6, 63.5, 61.6, 57.0, 36.9, 27.5, 14.1.

Methyl [1*S*,2*R*,3*S*,10b*R*,(S)*R*]-1-Cyano-2-(*p*-tolylsulfinyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (*endo*-14). Compound *endo*-**14** was obtained as the sole compound following the general procedure from (*Z*)-3-[(*R*)-*p*-tolylsulfinyl]propenonitrile (**3**) and **2-HBr** after 5 min of reaction. It was purified by filtration of the solid formed upon addition of CH_3CN−Et_2O (1:1) to the reaction mixture. The filtrate was evaporated and purified by flash column chromatography (AcOEt−hexane, 1:10). Yield: 78%, white solid. Mp (Et_2O): 155−156 °C. $[\alpha]_D^{20}$: +153.6 (*c* 0.5, $CHCl_3$). IR (KBr): 2243, 1725, 1596, 1494, 1084, 1046 cm^{-1}. ^1H NMR δ: 7.73 and 7.37 (AA′BB′ system, 4 H), 7.20 (m, 3 H), 6.95 (m, 1 H), 4.54 (d, *J* = 5.0, 1 H), 4.52 (d, *J* = 5.2, 1 H), 3.98 (dd, *J* = 8.1 and 5.2, 1 H), 3.67 (s, 3 H), 3.40 (dd, *J* = 8.1 and 5.0, 1 H), 3.37 (m, 1 H), 2.99 (m, 3 H), 2.44 (s, 3 H). ^{13}C NMR δ: 171.5 (CO), 142.9 (C), 139.4 (C), 135.0 (C), 131.3 (C), 130.3 (CH), 129.2 (CH), 127.7 (CH), 126.4 (CH), 126.0 (CH), 125.0 (CH), 116.5 (CN), 67.5 (CH), 64.4 (CH), 63.3 (CH), 52.4 (CH_3), 45.6 (CH_2), 37.0 (CH), 29.3 (CH_2), 21.5 (CH_3). Anal. Calcd for $C_{22}H_{22}N_2O_3S$: C 66.98, H 5.62, N 7.10, S 8.13. Found: C 66.64, H 5.44, N 7.03, S 8.09.

Methyl [1*S*,2*R*,3*S*,10b*S*,(S)*R*]-1-*n*-Butyl-1-cyano-2-(*p*-tolylsulfinyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (*endo*-15). Compound *endo*-**15** was obtained as the sole compound following the general procedure from (*Z*)-2-*n*-butyl-3-[(*R*)-*p*-tolylsulfinyl]propenonitrile (**4**) and **2-HBr** after 20 min of reaction. It was purified by flash column chromatography (AcOEt−hexane, 1:3). Yield: 70%, white solid. Mp: 106−107 °C. $[\alpha]_D^{20}$: +146.0 (*c* 0.5, $CHCl_3$). IR (KBr): 2233, 1752, 1493, 1427, 1083, 1050 cm^{-1}. ^1H NMR δ: 7.61 and 7.34 (AA′BB′ system, 4 H), 7.21 (m, 3 H), 7.12 (m, 1 H), 4.49 (d, *J* = 3.9, 1 H), 4.29 (s, 1 H), 3.64 (d, *J* = 3.9, 1 H), 3.54 (s, 3 H), 3.51 (m, 1 H), 3.00 (m, 3 H), 2.42 (s, 3 H), 2.08 (m, 1 H), 1.86 (m, 1 H), 1.62 (m, 1 H), 1.34 (m, 3 H), 0.92 (t, *J* = 7.1, 3 H). ^{13}C NMR δ: 172.0 (CO), 142.4 (C), 139.6 (C), 135.4 (C), 130.9 (C), 130.0 (CH), 129.4 (CH), 127.9 (CH), 126.2 (CH), 126.0 (CH) 124.7 (CH), 119.2 (CN), 73.7 (CH), 69.2 (CH), 62.7 (CH), 52.4 (CH_3), 51.4 (C), 46.3 (CH_2), 37.9 (CH_2), 29.1 (CH_2), 27.8 (CH_2), 22.7 (CH_2), 21.4 (CH_3),

13.8 (CH_3). Anal. Calcd for $C_{26}H_{30}N_2O_3S$: C 69.30, H 6.71, N 6.22, S 7.12. Found: C 69.35, H 6.59, N 6.28, S 7.26.

Methyl (1*R*,10b*S*)-1-*tert*-Butyl-1-cyano-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (16). Compound **16** was obtained as the sole compound following the general procedure from (*Z*)-2-*tert*-butyl-3-[(*R*)-*p*-tolylsulfinyl]propenonitrile (**5**) and **2-HBr** after 30 min of reaction. It was purified by flash column chromatography (AcOEt−hexane, 1:60). Yield: 56%, white solid. Mp (AcOEt−hexane): 122−123 °C. $[\alpha]_D^{20}$: +128.6 (*c* 0.5, $CHCl_3$). IR (film): 2222, 1710, 1486, 1455, 1250, 1093 cm^{-1}. ^1H NMR δ: 7.25 (m, 3 H), 7.07 (m, 1 H), 5.77 (s, 1 H), 5.06 (s, 1 H), 4.32 (m, 1 H), 3.83 (s, 3 H), 2.98 (m, 1 H), 2.85 (m, 1 H), 2.48 (m, 1 H) 1.21 (s, 9 H). ^{13}C NMR δ: 161.7 (CO), 142.7 (C), 136.8 (C), 134.0 (C), 128.9 (CH), 128.5 (CH), 127.2 (CH), 126.4 (CH), 118.6 (CN), 113.5 (CH), 66.1 (CH), 62.3 (C), 52.1 (CH_3), 43.8 (CH_2), 38.6 (C), 27.9 (CH_2), 25.4 (CH_3). Anal. Calcd for $C_{19}H_{22}N_2O_2$: C 73.52, H 7.14, N 9.03. Found: C 73.35, H 7.11, N 9.04.

Reaction of Dipolarophiles 6−8 with Azomethine Ylides 1. General Procedure. To a stirred solution of 1.13 mmol of dipolarophile and 400 mg (1.35 mmol) of isoquinolinium **1-HBr** in dry acetonitrile (40 mL), under argon atmosphere and at room temperature, was added DBU (1.35 mmol). After the time indicated in each case, the solvent was evaporated in vacuo and the residue was dissolved in dichloromethane and washed with water. The aqueous layers were extracted with dichloromethane several times. The organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The products were isolated by column chromatography with the eluent indicated in each case.

1-*tert*-Butyl 3-Ethyl 2-(diethoxymethyl)-1-*p*-tolylsulfinyl-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]isoquinoline-1,3-dicarboxylate (17). Compound **17** was obtained as a mixture of diastereoisomers from *tert*-butyl 4,4-diethoxy-2-*p*-tolylsulfinylbut-2-enoate (**6**) and isoquinolinium bromide **1-HBr** following the general procedure after 15 min of reaction. The ^1H NMR analyses of the crude reaction mixture shows the signals corresponding to primary adducts *endo*- and *exo*-**17** along with those of compound **18** in a 59:36:5 ratio. The products were isolated by flash column chromatography (AcOEt−hexane, 1:5).

[1*R*,2*R*,3*R*,10b*S*,(S)*S*]-*endo*-17. Compound *endo*-**17** was obtained as the major cycloadduct. Yield: 30%, yellow pale solid. Mp (AcOEt-hexane): 135−136 °C (dec). $[\alpha]_D^{20}$: −125.7 (*c* 0.35, $CHCl_3$). IR (KBr): 1732, 1698, 1626, 1463, 1366, 1254, 1037 cm^{-1}. ^1H NMR δ: 7.78 and 7.24 (AA′BB′ system, 4 H), 7.50 (d, *J* = 7.3 and 1.6, 1 H), 7.11 (m, 2 H), 6.88 (dd, *J* = 7.3 and 2.5, 1 H), 6.11 (d, *J* = 7.3, 1 H), 5.81 (s, 1 H), 5.13 (d, *J* = 7.3, 1 H), 4.68 (d, *J* = 8.5, 1 H), 4.34−4.24 (m, 3 H), 3.73 (dq, *J* = 9.1 and 7.1, 1 H), 3.45 (dd, *J* = 8.5 and 4.2, 1 H), 3.27−3.14 (m, 2 H), 2.95 (dq, *J* = 9.1 and 7.1, 1 H), 2.39 (s, 3 H), 1.35 (t, *J* = 7.1, 3 H), 1.14 (t, *J* = 7.1, 3 H), 1.04 (s, 9 H), 0.54 (t, *J* = 7.1, 3 H).^{13}C NMR δ: 170.9 (CO), 167.5 (CO), 141.4 (C), 138.1 (C), 134.1 (CH), 134.0 (C), 128.9 (CH), 128.5 (CH), 127.9 (CH) 127.7 (CH), 125.4 (C), 125.0 (CH), 124.3 (CH), 99.9 (CH) 96.5 (CH), 83.7 (C), 82.5 (C), 68.1 (CH), 65.8 (CH), 62.4 (CH_2), 61.6 (CH_2), 56.5 (CH_2), 42.8 (CH), 27.4 (CH_3), 21.3 (CH_3), 15.1 (CH_3), 14.3 (CH_3), 14.2 (CH_3). MS (ESI+): *m*/*z* (%) 606 [M + Na^+] (43), 584 [M + H^+] (38), 510 (100), 444 (58). HRMS-ESI: *m*/*z* [M + H^+] calcd for $C_{32}H_{42}NO_7S$ 584.2676, found 584.2672.

[1*R*,2*R*,3*S*,10b*R*,(S)*S*]-*exo*-17. Compound *exo*-**17** was obtained as the minor cycloadduct. It could not be isolated diastereoisomerically pure. The chemical shifts were measured from the ^1H NMR spectrum of a mixture *endo*- and *exo*-**17** in a ratio 70:30. It was indicated that only the signals that are not overlapped are those of other compounds. ^1H NMR δ: 7.73 and 7.32 (AA′BB′ system, 4 H), 6.77 (d, *J* = 7.5, 2 H), 6.49 (d, *J* = 7.5, 1 H), 5.99 (d, *J* = 7.5, 1 H), 5.20 (d, *J* = 5.4, 1 H), 5.09 (d, *J* = 7.0, 1 H), 5.07 (s, 1 H), 4.11 (dd, *J* = 7.0 and 5.4, 1 H), 2.41 (s, 3 H), 1.11 (s, 9 H).

1-*tert*-Butyl 3-Ethyl 2-(diethoxymethyl)pyrrolo[2,1-*a*]isoquinoline-1,3-dicarboxylate (18). Compound **18** was obtained nearly pure after several flash column chromatographies of different mixtures of cycloadducts **17**. Yield: indeterminate, pale yellow solid. Mp: 129−131 °C. IR (KBr): 1713, 1689, 1413, 1377, 1247, 1213, 1067 cm^{-1}. ^1H NMR δ: 9.24 (d, *J* = 7.7, 1 H), 8.35 (m, 1 H), 7.65 (m, 1 H), 7.49 (m, 2 H), 7.00 (d, *J* = 7.7, 1 H), 6.16 (s, 1 H), 4.44 (q, *J* = 7.1, 2 H), 3.74 (dq, *J* = 9.3 and 7.1, 1 H), 3.60 (dq, *J* = 9.3 and 7.1, 1 H), 1.69 (s, 9 H), 1.44 (t, *J* = 7.1, 3 H), 1.25 (t, *J* = 7.1, 6 H). ^{13}C NMR δ: 167.3 (CO), 161.5 (CO), 131.8 (C), 130.6 (C), 128.7 (C), 127.8 (CH), 127.6 (CH), 126.9 (CH), 124.5 (C), 124.4 (CH), 124.0 (CH), 113.6 (CH), 113.3 (C), 112.5 (C), 98.8 (CH), 81.7 (C), 63.4 (CH_2), 60.5 (CH_2), 28.1 (CH_3), 15.2 (CH_3), 14.3 (CH_3). MS (ESI+): *m*/*z* (%) 464 [M + Na^+] (42), 396 (12), 340 (30), 294 (100). HRMS-ESI: *m*/*z* [M + Na^+] calcd for $C_{25}H_{31}NO_6Na$ 464.2043, found 464.2040.

1-*tert*-Butyl 3-Ethyl 2-formylpyrrolo[2,1-*a*]isoquinoline-1,3-dicarboxylate (19). Although this compound was not detected in the ^1H NMR spectrum of the crude reaction mixture, it was obtained after the flash column chromatography by decomposition of adducts **17** on the silica gel. Yield: 51%, yellow solid. Mp: 175−176 °C. IR (KBr): 1713, 1693, 1673, 1413, 1377, 1249, 1219, 1160, 1106, 1065 cm^{-1}. ^1H NMR δ: 10.67 (s, 1 H), 9.26 (d, *J* = 7.6, 1 H), 8.46 (m, 1 H), 7.69 (m, 1 H), 7.58 (m, 2 H), 7.15 (d, *J* = 7.6, 1 H), 4.49 (q, *J* = 7.1, 2 H), 1.70 (s, 9 H), 1.45 (t, *J* = 7.1, 3 H). ^{13}C NMR δ: 188.4 (CHO), 165.8 (CO), 160.6 (CO), 131.0 (C), 130.2 (C), 129.6 (C), 128.7 (CH), 128.3 (CH), 127.6 (C), 127.3 (CH), 124.6 (C), 124.5 (CH), 124.0 (CH), 116.0 (CH), 112.7 (C), 82.7 (C), 61.5 (CH_2), 27.9 (CH_3), 14.3 (CH_3). MS (ESI+): *m*/*z* (%) 368 [M + H^+] (30), 312 (45), 294 (100), 59 (68). HRMS-ESI: *m*/*z* [M + H^+] calcd for $C_{21}H_{22}NO_5$ 368.1492, found 368.1500.

Ethyl (±)-3-Methoxy-1-oxo-3a,4,11b,11c-tetrahydro-1*H*,3*H*-furo[3′,4′:3,4]pyrrolo[2,1-*a*]isoquinoline-4-carboxylate (*endo*-20). A mixture of diastereoisomers *anti-endo*-**20** and *syn-endo*-**20** in 77:23 ratio was obtained from 5-methoxyfuran-2(5*H*)-one (**8**) and the isoquinolinium **1-HBr** after 5 min. They were purified by flash column chromatography (AcOEt−hexane, 2:5). The combined yield is 80%.

(±)-(3*R*,3a*S*,4*S*,11b*R*,11c*R*)-*anti-endo*-20. Compound *anti-endo*-**20** was obtained as the major product. Yield: 63%, red oil. IR (film): 1782, 1734, 1626, 1567, 1458, 1115 cm^{-1}. ^1H NMR δ: 7.15 (m, 3 H), 6.94 (m, 1 H), 6.04 (d, *J* = 7.6, 1 H), 5.31 (d, *J* = 1.1, 1 H), 5.31 (d, *J* = 7.6, 1 H), 5.16 (d, *J* = 6.8, 1 H), 4.25 (d, *J* = 2.2, 1 H), 4.24 (q, *J* = 7.1, 2 H), 3.49 (s, 3 H), 3.41 (dd, *J* = 8.2 and 6.8, 1 H), 3.24 (ddd, *J* = 8.2, 2.2 and 1.1, 1 H), 1.32 (t, *J* = 7.1, 3 H). ^{13}C NMR δ: 173.4 (CO), 170.1 (CO), 133.5 (CH), 131.8 (C), 128.1 (CH) 127.0 (CH), 125.6 (C), 125.4 (CH), 124.3 (CH), 107.1 (CH), 101.2 (CH), 69.4 (CH), 62.9 (CH), 61.8 (CH_2), 56.4 (CH_3), 48.0 (CH), 47.7 (CH), 14.0 (CH_3). MS (ESI+): *m*/*z* (%) 352 [M + Na^+] (33), 330 [M + H^+] (100). HRMS-ESI: *m*/*z* [M + H^+] calcd for $C_{18}H_{20}NO_5$ 330.1335, found 330.1339.

(±)-(3*R*,3a*R*,4*R*,11b*S*,11c*S*)-*syn-endo*-20. Compound *syn-endo*-**20** was obtained as the minor product. Yield: 16%, red oil. IR (film): 1778, 1736, 1626, 1568, 1494, 1146 cm^{-1}. ^1H NMR δ: 7.19 (m, 1 H), 7.12 (m, 2 H), 6.96 (d, *J* = 7.3, 1 H), 6.01 (d, *J* = 7.6, 1 H), 5.49 (d, *J* = 6.9, 1 H), 5.29 (d, *J* = 7.6, 1 H), 5.01 (d, *J* = 7.2, 1 H), 4.92 (d, *J* = 1.6, 1 H), 4.22 (q, *J* = 7.1, 2 H), 3.60 (s, 3 H), 3.56 (ddd, *J* = 9.1, 6.9 and 1.6, 1 H), 3.29 (dd, *J* = 9.1 and 7.2, 1 H), 1.31 (t, *J* = 7.1, 3 H). ^{13}C NMR δ: 172.4 (CO), 171.2 (CO), 135.1 (CH), 132.1 (C), 128.2 (CH), 126.9 (CH), 125.9 (C), 125.2 (CH), 124.4 (CH), 102.4 (CH), 100.6 (CH), 65.7 (CH), 63.5 (CH), 61.7 (CH_2), 58.2 (CH_3), 50.8 (CH), 44.0 (CH), 14.1 (CH_3). MS (ESI+): *m*/*z* (%) 352 [M + Na^+] (28), 330 [M + H^+] (100). HRMS-ESI: *m*/*z* [M + H^+] calcd for $C_{18}H_{20}NO_5$ 330.1335, found 330.1333.

Ethyl [3*S*,(S)*S*]-3-Ethoxy-11c-*p*-tolylsulfinyl-1-oxo-3a,4,11b,-11c-tetrahydro-1*H*,3*H*-furo[3′,4′:3,4]pyrrolo[2,1-*a*]isoquinoline-4-carboxylate (*endo*-21a). A mixture of diastereoisomers *anti-endo*-**21a** and *syn-endo*-**21a** in 83:17 ratio was obtained from [5*S*,(S)*S*]-5-ethoxy-3-*p*-tolylsulfinylfuran-2(5*H*)-one (**7a**) and the isoquinolinium

1-HBr after 5 min. They were purified by flash column chromatography (acetone−hexane, 1:4). The combined yield is 95%.

[3*S*,3a*R*,4*R*,11b*S*,11c*R*,(S)*S*]-*anti-endo*-21a. Compound *anti-endo*-**21a** was obtained as the major product. Yield: 79%, white solid. Mp (hexane−AcOEt): 134−135 °C (dec). $[\alpha]_D^{20}$: +304.0 (*c* 0.5, $CHCl_3$). IR (KBr): 1772, 1741, 1630, 1150, 1082, 1051 cm^{-1}. ^1H NMR δ: 7.70 and 7.34 (AA′BB′ system, 4 H), 7.41 (m, 1 H), 7.19 (m, 2 H), 6.95 (m, 1 H), 6.01 (d, *J* = 7.5, 1 H), 5.42 (d, *J* = 7.5, 1 H), 5.29 (s, 1 H), 5.23 (d, *J* = 2.6, 1 H), 4.31 (s, 1 H), 4.10 (m, 2 H), 3.64 (m, 1 H), 3.49 (m, 1 H), 3.35 (d, *J* = 2.6, 1 H), 2.42 (s, 3 H), 1.31 (t, *J* = 7.1, 3 H), 1.10 (t, *J* = 7.1, 3 H). ^{13}C NMR δ: 168.4 (CO), 167.6 (CO), 143.0 (C), 136.0 (C), 133.2 (CH), 131.4 (C), 129.8 (CH), 128.8 (CH), 128.7 (CH), 126.8 (CH), 125.9 (CH), 124.6 (CH), 124.0 (C), 105.4 (CH), 103.0 (CH), 78.1 (C), 70.4 (CH), 66.4 (CH), 65.6 (CH_2), 62.0 (CH_2), 51.2 (CH), 21.4 (CH_3), 14.6 (CH_3), 14.0 (CH_3). Anal. Calcd for $C_{26}H_{27}NO_6S$: C 64.85, H 5.65, N 2.91, S 6.66. Found: C 64.74, H 5.69, N 2.95, S 6.82.

[3*S*,3a*S*,4*S*,11b*R*,11c*S*,(S)*S*]-*syn-endo*-21a. Compound *syn-endo*-**21a** was obtained as the minor product. Yield: 16%, white solid. Mp (hexane−AcOEt): 159−161 °C (dec). $[\alpha]_D^{20}$: −418.8 (*c* 0.25, $CHCl_3$). IR (KBr): 1764, 1729, 1631, 1493, 1083, 1057 cm^{-1}. ^1H NMR δ: 7.46 (m, 3 H), 7.45−7.19 (m, 4 H), 7.01 (m, 1 H), 5.93 (d, *J* = 7.6, 1 H), 5.37 (d, *J* = 7.6, 1 H), 5.28 (s, 1 H), 4.94 (d, *J* = 1.2, 1 H), 4.40 (d, *J* = 7.3, 1 H), 4.31 (m, 2 H), 3.69 (m, 2 H), 3.44 (m, 1 H), 2.39 (s, 3 H), 1.36 (t, *J* = 7.2, 3 H), 1.17 (t, *J* = 7.1, 3 H). ^{13}C NMR δ: 170.1 (CO), 168.0 (CO), 143.0 (C), 135.8 (C), 135.7 (CH), 132.1 (C), 130.2 (CH), 129.1 (CH), 127.4 (CH), 125.8 (CH), 124.8 (CH), 124.7 (CH), 102.0 (CH), 100.9 (CH), 82.7 (C), 66.8 (CH), 66.7 (CH_2), 65.5 (CH), 62.1 (CH_2), 44.8 (CH), 21.5 (CH_3), 14.9 (CH_3), 14.3 (CH_3). Anal. Calcd for $C_{26}H_{27}NO_6S$: C 64.85, H 5.65, N 2.91, S 6.66. Found: C 64.68, H 5.55, N 2.87, S 7.10.

Ethyl [3*R*,(S)*S*]-3-Ethoxy-11c-*p*-tolylsulfinyl-1-oxo-3a,4,11b,11c-tetrahydro-1*H*,3*H*-furo[3′,4′:3,4]pyrrolo[2,1-*a*]isoquinoline-4-carboxylate (*endo*-21b). A mixture of diastereoisomers *anti-endo*-**21b** and *syn-endo*-**21b** in 89:11 ratio was obtained from [5*R*,(S)*S*]-5-ethoxy-3-*p*-tolylsulfinylfuran-2(5*H*)-one (**7b**) and the isoquinolinium **1-HBr** after 5 min. They were purified by flash column chromatography (AcOEt−hexane, 1:2). The combined yield is 85%.

[3*R*,3a*S*,4*S*,11b*R*,11c*S*,(S)*S*]-*anti-endo*-21b. Compound *anti-endo*-**21b** was obtained as the major product. Yield: 76%, white solid. Mp: 147−148 °C (dec). $[\alpha]_D^{20}$: −410.4 (*c* 0.5, $CHCl_3$). IR (KBr): 1751, 1628, 1494, 1080, 1053 cm^{-1}. ^1H NMR δ: 7.52 (m, 1H), 7.46 and 7.27 (AA′BB′ system, 4 H), 7.29 (m, 2 H), 7.03 (m, 1 H), 5.99 (d, *J* = 7.5, 1 H), 5.44 (s, 1 H), 5.43 (d, *J* = 7.5, 1 H), 5.19 (d, *J* = 2.1, 1 H), 4.36 (m, 3 H), 3.41 (m, 1 H), 3.28 (q, *J* = 7.0, 2 H), 2.38 (s, 3 H), 1.41 (t, *J* = 7.1, 3 H), 0.83 (t, *J* = 7.0, 3 H). ^{13}C NMR δ: 168.6 (CO), 168.3 (CO), 142.4 (C), 135.5 (C), 134.0 (CH), 131.4 (C), 129.7 (CH), 129.1 (CH), 127.7 (CH), 126.2 (CH), 125.5 (CH), 124.9 (CH), 124.4 (C), 106.5 (CH), 103.3 (CH), 82.2 (C), 72.2 (CH), 65.3 (CH), 65.1 (CH_2), 62.3 (CH_2), 48.9 (CH), 21.3 (CH_3), 14.4 (CH_3), 14.3 (CH_3). Anal. Calcd for $C_{26}H_{27}NO_6S$: C 64.85, H 5.65, N 2.91, S 6.66. Found: C 64.95, H 5.53, N 2.90, S 7.15.

[3*R*,3a*R*,4*R*,11b*S*,11c*R*,(S)*S*]-*syn-endo*-21b. Compound *syn-endo*-**21b** was obtained as the minor product. Yield: 9%, yellow solid. Mp: 108−110 °C (dec). $[\alpha]_D^{20}$: +90.07 (*c* 0.675, $CHCl_3$). IR (film): 1770, 1749, 1631, 1596, 1493, 1146, 1082, 1049 cm^{-1}. ^1H NMR δ: 7.69 (AA′BB′ system, 2 H), 7.41 (m, 3 H), 7.24 (m, 2 H), 6.99 (m, 1 H), 5.91 (d, *J* = 7.6, 1 H), 5.37 (d, *J* = 7.1, 1 H), 5.35 (d, *J* = 7.6, 1 H), 4.89 (s, 1 H), 4.85 (d, *J* = 1.3, 1 H), 3.89 (m, 1 H), 3.80 (m, 2 H), 3.67 (m, 1 H), 3.59 (dd, *J* = 7.1 and 1.3, 1 H), 2.45 (s, 3 H), 1.26 (t, *J* = 7.1, 3 H), 1.17 (t, *J* = 7.1, 3 H). ^{13}C NMR δ: 169.7 (CO), 168.5 (CO), 143.5 (C), 135.6 (C), 134.7 (CH), 132.1 (C), 130.1 (CH), 128.9 (CH), 127.7 (CH), 126.3 (CH), 125.4 (CH), 124.8 (CH), 124.2 (C), 101.3 (CH), 100.8 (CH), 81.4 (C), 66.8 (CH_2), 66.4 (CH), 65.0 (CH), 61.6 (CH_2), 45.8 (CH), 21.4 (CH_3), 14.9 (CH_3), 13.9 (CH_3). MS (FAB+): *m*/*z* (%) 482 [M + H^+] (65), 342 (100). HRMS-FAB: *m*/*z* [M + H^+] calcd for $C_{26}H_{28}NO_6S$ 482.1637, found 482.1644.

■ ASSOCIATED CONTENT

Supporting Information. NMR spectra of all new compounds and X-ray ORTEP and crystallographic data for compounds *endo*-**17**, *anti-endo*-**21a**, *syn-endo*-**21a**, and *anti-endo*-**21b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The endo or exo terms indicate, respectively, the cis or trans arrangement of the CN (or CO_2t-Bu) group with respect to the dihydropyridine (for **1-HBr**) or tetrahydropyridine (for **2-HBr**) moieties at the pyrrolidine ring formed in the reactions from azomethine ylide. They are related to the endo and exo addition modes of dipole, using as a reference the nitrile group at the dipolarophile.

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(20) Compound **12** is also obtained from *endo*-**9** upon standing for several weeks in the refrigerator.

(21) Dipolarophile **6** did not react with stabilized thiazolium *N*-ylide.

(22) When the ester group is located at C-2, the δ value is 1.39−1.50 ppm, whereas when it is positioned at C-1 and adopts a trans arrangement with respect to H-10b, the δ value is 1.08−1.12 ppm.

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(24) Therefore, the adducts with H-3 and H-10b in a trans arrangement were formed predominantly.

(25) CCDC809008 contains the supplementary crystallographic data for *endo*-**17**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223.

(26) Attractive interaction between the electron-withdrawing substituent at the dipolarophile and the heteroaromatic ring of the ylide has been proposed by other authors; see ref 16a.

(27) The syn or anti character of these adducts is indicative of the cis or trans relationship between H-3 and H-3a, respectively. It is related to the face of the dipolarophile where the dipole approaches, taking as a reference the spatial arrangement of the alkoxy group (for this nomenclature, see: (a) Keller, E.; de Lange, B.; Rispens, M. T.; Feringa, B. L. *Tetrahedron* **1993**, *49*, 8899. (b) Trost, B. M.; Crawley, M. L. *Chem.—Eur. J.* **2004**, *10*, 2237). Thus, syn-adducts result from the approach of dipole to the face where the OEt group is positioned, whereas the anti-adducts are obtained by approach to the opposite face. The endo or exo terms indicate, respectively, the cis or trans arrangement adopted by furanone and dihydropyridine moieties at the pyrrolidine ring formed in the reactions from azomethine ylide. They are related to the endo and exo addition modes of dipole, using as a reference the carbonyl group at the furanone ring..

(28) It is noteworthy that compound **8** did not react with thiazolium ylide (see ref 12).

(29) CCDC809009, CCDC809010, and CCDC809011 contain the supplementary crystallographic data for *anti-endo*-**21a**, *anti-endo*-**21b**, and *syn-endo*-**21a**, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge

Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223.

(30) The reactions of ylide **1** with sulfinylfuranones **7** were assayed in different solvents. Unfortunately, the reaction mixtures obtained in less polar solvent than acetonitrile (toluene or dichloromethane) were complex and any certain conclusion can be inferred.