JOC Article

Complete and Remarkable Reversal of Chemoselectivity in [4 + 2] Cycloadditions Involving Electron-Poor Indoles as Dienophiles. Diels−Alder versus Hetero-Diels−Alder Processes

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The reaction between indole-3-carboxaldehyde **1a** or indole-3-glyoxalate **1b** and 2,3-dimethylbutadiene under thermal activation leads exclusively to the Diels−Alder cycloadducts resulting from the participation of the indole 2,3-carbon−carbon double bond. The concomitant use of zinc chloride and high pressure (16 kbar) induces the primary cycloadduct to react further, and biscycloadducts **11** and **12** are now isolated in high yields, the result of two consecutive [4 + 2] processes on, first, the indole 2,3 C═C bond and, second, the 3-carbonyl unit. The possibility of using two different dienes in a tandem, sequential process is demonstrated by the preparation of tetracycle **13**. Interactions between the carbonyl dienophile and Danishefsky diene yield exclusively yet another type of product, namely the γ-dihydropyranones arising from the sequential [4 + 2] heterocycloaddition, hydrolysis of the silyl enol ether, and loss of methanol. Isolation of the Mukaiyama-type adduct **16** indicates that a stepwise mechanism may be involved, at least under zinc chloride catalysis. N,N-Disubstituted indole-3-glyoxamides undergo the expected, usual Diels−Alder process, with the 2,3 C═C bond acting as dienophile, and cycloadducts of the type **3** are obtained in high yields, regardless of the mode of activation. Remarkably, however, N-monosubstituted indole-3-glyoxamides react almost exclusively as heterodienophiles, the 3-carbonyl unit being now the preferred site of reactivity, and γ-dihydropyranones of the type **6** are isolated in yields ranging from 72 to 92%. Conformational analysis of the Diels−Alder adducts based on both ^{1}H NMR spectrometry and X-ray diffraction data indicates that the newly created cyclohexene and cyclohexanone rings adopt a *pseudo*boat conformation.

Introduction

The Diels−Alder (DA) reaction has proven to be a convenient way to assemble complex six-membered cycles due to its versatility as well as its high regio- and stereoselectivities.[1] The scope of this class of cycloaddition is very large and allows not only the synthesis of cyclohexene derivatives but also of a variety of heterocycles by swapping carbon atoms on the diene and/or the dienophile component with heteroatoms (O, N, S for instance; the so-called hetero-Diels−Alder (HDA) reaction).[2]

It has been known for a while that indoles can react as dienophiles in Diels−Alder cycloadditions to lead to nitrogenated polycycles useful in the synthesis of biologically active alkaloids.[3−5] Because of their high electron density, such systems have been mostly studied as

(1) See, for example: (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, UK, 1990 (b) Oppolzer, W. Combining C−C bonds. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 5, Chapter 4.1. (c) Fringuelli, F.; Taticchi, A. *The Diels−Alder Reaction*; John Wiley & Sons: Chichester, UK, 2002. (d) Nicolaou, K. C.; Snyder, S. C.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698.

(2) See, for example: (a) Boger, D. L.; Weinreb, S. N. In *Hetero Diels−Alder Methodology in Organic Synthesis*; Wasserman, H. H., Ed.; Academic Press: San Diego, CA, 1987; Vol. 47. (b) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1−120.

(3) (a) Takahashi, T.; Ishida, H.; Kohmoto, M. *Bull Chem. Soc. Jpn* **1976**, *49*, 1725−1726. (b) Raasch, M. S. *J. Org. Chem.* **1980**, *45*, 856−867. (c) Benson, S. C.; Palabrica, C. A.; Snyder, J. K. *J. Org. Chem.* **1987**, *52*, 4610−4614. (d) Bäckwall, J.-E.; Plobeck, N. A. *J. Org. Chem.* **1990**, *55*, 4528−4531. (e) Gieseler, A.; Steckhan, E.; Wiest, O.; Knoch, F. *J. Org. Chem.* **1991**, *56*, 1405−1411. (f) Markgraf, J. H.; Patterson, D. E. *J. Heterocycl. Chem.* **1996**, *33*, 109−111. (g) Haberl, U.; Steckhan, E.; Blechert, S.; Wiest, O. *Chem. Eur. J.* **1999**, *5*, 2859−2865. (h) Hsieh, M.-F.; Rao, P. D.; Liao, C. C. *Chem. Commun.* **1999**, 1441−1442. (i) Lee, L.; Snyder, J. K. *Adv. Cycloaddit.* **1999**, *6*, 119−171. (j) Benson, S. C.; Lee, L.; Yang, L.; Snyder, J. K. *Tetrahedron* **2000**, *56*, 1165−1180. (k) Bodwell, G. J.; Li, J. *Org. Lett.* **2002**, *4*, 127−130. (l) Bodwell, G. J.; Li, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3261−3262.

(4) (a) Wenkert, E.; Moeller, P. D. R.; Piettre, S. R. *J. Am. Chem. Soc.* **1988**, *110*, 7188−7194. (b) Kraus, G. A.; Raggon, J.; Thomas, P. J.; Bougie, D. *Tetrahedron Lett.* **1988**, *29*, 5605−5608. (c) Kraus, G. A.; Bougie, D. *J. Org. Chem.* **1989**, *55*, 2425−2428. (d) Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.* **1998**, *63*, 5304−5305. (e) Lynch, S. M.; Bur, S. K.; Padwa, A. *Org. Lett.* **2002**, *4*, 4643−4645. (f) Biolatto, B.; Kneeteman, M.; Paredes, E.; Mancini, P. *J. Org. Chem.* **2001**, *66*, 3906−3912. (g) Kishbaugh, T. L. S.; Gribble, G. W. *Tetrahedron Lett.* **2001**, *42*, 4783−4785.

(5) (a) Gieseler, A.; Steckhan, E.; Wiest, O. *Synlett*, **1990**, 275−277. (b) Gieseler, A.; Steckhan, E.; Wiest, O.; Knoch, F. *J. Org. Chem.* **1991**, *56*, 1405−1411. (c) Wiest, O.; Steckhan, E.; Grein, F. *J. Org. Chem.* **1992**, *57*, 4034−4037. (d) Wiest, O.; Steckhan, E. *Tetrahedron Lett.* **1993**, *40*, 6391−6394. (e) Haberl, U.; Steckhan, E.; Blechert, S.; Wiest, O. *Chem. Eur. J.* **1999**, *5*, 2859−2865. (f) Raasch, M. S. *J. Org. Chem.* **1980**, *45*, 867−870. (g) Markgraf, J. H.; Patterson, D. E. *J. Heterocycl. Chem.* **1996**, *33*, 109−111.

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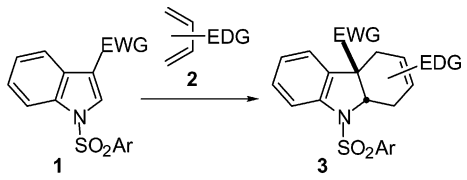
SCHEME 1



electron-rich dienophiles in the inverse-electron-demand version of the reaction.[3] Fewer examples of their use in normal-electron-demand Diels−Alder cycloadditions have been reported.[4] This latter behavior usually requires the presence of two electron-withdrawing substituents (EWG) on the N−C═C moiety of the indole nuclei.[6] Thus, for instance, the strong acceleration of the process resulting from placing both a sulfonyl group on the nitrogen atom and a carbonyl or nitro unit in position 3 of the dienophile component leads to the efficient formation of the desired cycloadducts **3** (Scheme 1).[4a] A carbon-centered electron-withdrawing group in position 3 of the dienophile usually impedes the rearomatization of the five-membered cycle whose structure now bears a quaternary center at the ring junction, a feature of many alkaloids (e.g., *Aspidosperma* and *Strychnos* alkaloids) (Figure 1). A drawback of the process is the very high temperatures needed to overcome the inherent inertness of the aromatic reactant.[4] This has kept the methodology from being applicable to sensitive substrates in the total synthesis of complex molecules. We recently developed a much milder thermal access to these derivatives by taking advantage of the positive effect of high pressure on the rate of Diels−Alder reactions.[7] In addition, combining high pressures and Lewis acid catalysis results in a biactivation of the process: under these conditions, the [4 + 2] cycloadditions occur at room temperature.

Classical electron-rich dienes have long been shown to also react with carbon-heteroatom double or triple bonds (typically C═O, C═S, C═N, or C≡N) to afford six-membered cycloadducts.[2] Dihydropyrans, for example, have been efficiently generated from aldehydes or ketones. Once again, activation by either Lewis acid catalysis or high pressure (or both) induces these reactions to occur under much milder conditions. The literature reports few examples of heterodienophiles competing with all-carbon dienophiles in [4 + 2] processes;[8] in these cases, the all-carbon dienophilic component was found to be deactivated. In the course of our studies on the dienophilicity of five-membered aromatic heterocycles, we observed complete and sometimes unexpected inversion of the chemoselectivity in reactions of indoles with electron-rich dienes. The 2,3-double bond reacted with some dienes in all-carbon Diels−Alder cycloadditions, whereas the carbonyl function of the electron-withdrawing group proved to be the most reactive site with other dienes, thereby getting involved in a cycloaddition process as a heterodienophile. In addition, cycloadducts of the

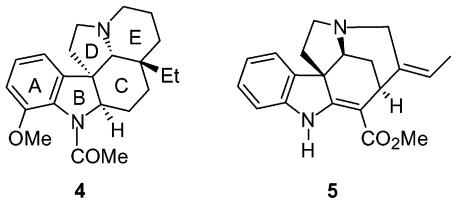
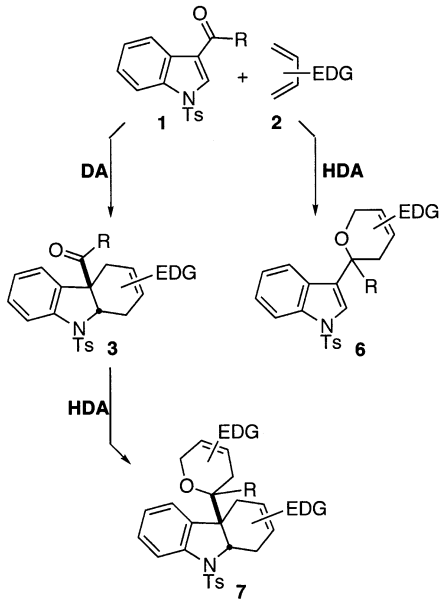
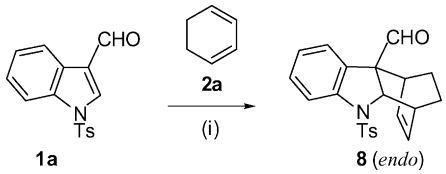


FIGURE 1. Structures of aspidospermine (**4**) and akuammicine (**5**).

SCHEME 2



SCHEME 3[a]



[a] Reagents and conditions: (i) $ZnCl_2$ (10 mol %), 16 kbar, 25 °C (62%).

type **3** sometime reacted further with the diene to generate bisadducts of type **7**. We report herein results regarding the chemoselectivity and show to what extent the reactivity of the aromatic dienophile can be modulated to favor either the classical process or the hetero-Diels−Alder reaction (Scheme 2).

Results and Discussion

We previously reported that the cycloaddition between indole **1a**, bearing a formyl group in position 3, and cyclohexadiene **2a** leads to diastereomeric products **8**, the result of a pericyclic process between the diene and the aromatic double bond (Scheme 3).[7] High pressure and Lewis acid catalysis increased both the yields and the endo/exo ratio from 80:20 to >98:2; not a trace of heterocycloadduct was detected in the crude reaction mixtures.

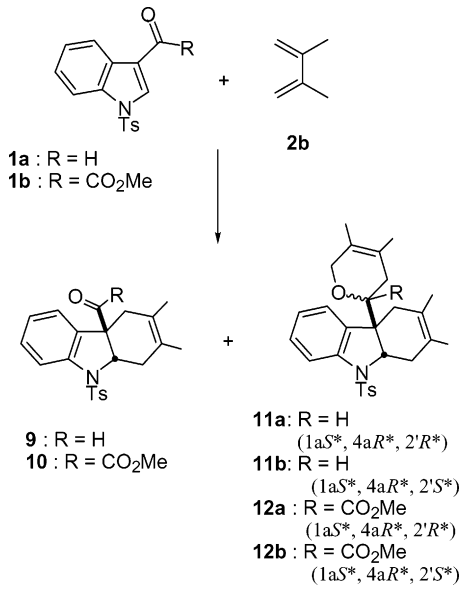
Indole-3-carboxaldehyde and -3-glyoxylate: The Case of 2,3-Dimethylbutadiene. (a) Indole-3-carbox-

(6) The presence of only one electron-withdrawing substituent on the indole nitrogen has been reported to be sufficient in the case of an intramolecular cycloaddition. See ref 4d,e.

(7) Chataigner, I.; Hess, E.; Toupet, L.; Piettre, S. R. *Org. Lett.* **2001**, *3*, 515−518.

(8) See, for example: (a) Keana, J. F. W.; Eckler, P. E. *J. Org. Chem.* **1976**, *41*, 2850−2854. (b) Sano, T.; Toda, J.; Kashiwaba, N.; Ohshima, T.; Tsuda, Y. *Chem. Pharm. Bull.* **1987**, *35*, 479−500.

SCHEME 4



aldehyde. A similar result is obtained when the cycloaddition of **1a** is conducted under thermal conditions (195 °C) with 2,3-dimethylbutadiene (**2b**): the exclusive formation of compound **9** is observed, and the product is isolated in a good, 83% yield (Scheme 4; Table 1, entry 1). Not unexpectedly, the use of a Lewis acid allows for lower reaction temperatures and decreases the time needed to reach a similar conversion (entry 2). In this case, crude ^{1}H NMR spectrometry data indicate the presence of a structurally different product in minor amounts (13%) (see below). Compressing a mixture of indole **1a** and dimethylbutadiene (**2b**) (12 equiv) in the presence of a catalytic amount of zinc chloride (10 mol %) to 12 kbar for 48 h at room temperature induces a 67% conversion and the formation of the same cycloadduct **9**, together with a large amount of polymeric material (entry 3). Attempts to solve the problem arising from the polymerization process included decreasing the amount of diene. Thus, lowering it to 6 and then 4 equiv indeed resulted in much more workable crude mixtures, but at the expense of the conversion (entries 4 and 5). The problem is circumvented by increasing the pressure to 16 kbar: with 4 equiv of diene, the conversion increased to 69% in only 24 h and attained completion within 60 h. The ratio of the two different types of product evolves from an initial value of 40:60 to 5:95 (entries 6 and 7). Full optimization of the conditions is reached with 6 equiv of diene in 24 h (entry 8). 1D and 2D ^{1}H and ^{13}C NMR and mass spectrometry analyses indicate that the new compounds result from the interaction of the dienophile with 2 equiv of diene **2b** and allow the assignment to diastereomeric tetracyclic structures **11a** and **11b**. These compounds arise from a double cycloaddition process on (i) the 2,3-indole C=C and (ii) the carbonyl group. Using a large excess of diene generates a problem on a practical level. For instance, a 12 equiv excess leads in many cases to a discrepancy between the conversion rates and the isolated yields: these are often lower than expected on the basis of the crude NMR spectra. Indeed, the cycloadduct is trapped in a dense polymeric matrix resulting from the competing polymerization of the diene,[9] and extraction of the compound from the crude mixture using a Soxhlet apparatus does not lead to any improvement. This polymerization is favored by both pressure and Lewis acid catalysis and is difficult to control under these conditions. The amount of diene was further decreased in an attempt to maximize the formation of monoadduct **10**, at the expense of bisadducts **11**. Thus, the use of either 2 or 1 equiv of diene under otherwise identical conditions led to 50:50 and 100:0 mixtures of **9**/**11**, respectively, albeit in low conversion (entries 9 and 10). Despite its low practical utility, the later experiment unambiguously shows that the all-carbon Diels−Alder process is kinetically favored under these conditions and confirms the higher reactivity of the aromatic double bond over the formyl group. The assumed sequence of events was further verified by compressing to 12 kbar the primary cycloadduct **9** with diene **2b** (6 equiv) in the presence of 10 mol % of zinc chloride; this experiment furnished an identical 2:1 diastereomeric ratio of bisadducts **11a** and **11b**, isolated in 70% yield.[10]

These results prompted us to perform the heterocycloaddition on the monoadduct **9** with a different diene, i.e., *trans*-1-methoxy-3-trimethylsilyloxy-1,3-diene (**2c**, Danishefsky diene). Under the same conditions and after acidic hydrolysis of the enol ether function, the mixed bisadduct **13** was isolated in 37% yield, thus demonstrating the feasibility of a *sequential* tandem reaction (Scheme 5). As zinc chloride might react with this acid-sensitive diene in an undesired manner, a more gentle, lanthanide catalyst was used. A much better 76% yield was indeed obtained when the heterocycloaddition was carried out with 10 mol % of EuFOD.[11] As before, **13** was isolated as a 2:1 mixture of diastereomers, and crystallization of the major isomer in a mixture of heptanes and ethyl acetate afforded a material suitable for X-ray diffraction analysis (Figure 2). The observed relative configuration (1a*S**, 4a*R**,2′*R**) suggests a preferential approach from the more accessible *Re* face of the carbonyl function on the primary adduct, which implies a more favorable conformation placing the carbonyl group above the tolyl cycle (Figure 3). Such a conformation has been previously observed by X-ray crystallography analysis of an analogous primary cycloadduct (Figure 4).[6]

(b) Indole-3-glyoxylate. Ketoesters, in particular those derived from ketomalonates or glyoxylates, are known to behave as heterodienophiles in cycloadditions with enriched dienes.[2] This observation raises the question of the behavior of indole derivative **1b**, bearing a methyl ketoester functionality, in such reactions. The thermal cycloaddition between **1b** and dimethylbutadiene **2b** leads to the exclusive formation of monocycloadduct **10**, the result of the condensation of the diene on the

(9) The relative rates of both cycloaddition and polymerisation processes involved here can be unequally influenced by various factors among which the quality of the Lewis acid catalyst, or of the solvent, for example. The overall result can thus vary somewhat, depending on the experiment and lead to differences in reproducibility of yields and ratios. Nevertheless, the general trends observed in these experiments are reproducible.

(10) The use of pressure alone has the disadvantage of producing a large amount of polymers. Thus, while a complete conversion is observed and cycloadduct **10** is formed in an exclusive manner at 50 °C, the reaction is of little practical use (entry 11). Despite many efforts, these conditions could not been translated into good isolated yields.

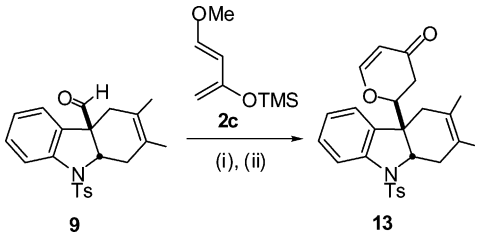
(11) EuFOD is europium tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate).

TABLE 1. Reactions between Indole Dienophiles and Dimethylbutadiene 2b. Formation of the Mono- vs Biscycloadducts

entry	indole	**2b** (equiv)	Lewis acid	*T* (°C)	time (h)	*P* (kbar)	convn (%)	ratio[a,b] **9**/**11** or **10**/**12**	yield[a,f] (%) of **9**/**11** or **10**/**12**
1	**1a**	**12**		**195**	**80**		**85**	**100:0**	**83:0**
2	**1a**	12	$ZnCl_2$	110	48		77	87:13	nd[d]
3	**1a**	12	$ZnCl_2$	25	48	12	67	97:3	nd[d]
4	**1a**	6	$ZnCl_2$	25	48	12	39	97:3	nd[d]
5	**1a**	4	$ZnCl_2$	25	48	12	25	100:0	nd[d]
6	**1a**	4	$ZnCl_2$	25	24	16	69	40:60	nd[d]
7	**1a**	4	$ZnCl_2$	25	60	16	100	5:95	nd[d]
8	**1a**	**6**	**$ZnCl_2$**	**25**	**24**	**16**	**100**	**2:98**	**0:90**[c]
9	**1a**	2	$ZnCl_2$	25	48	16	24	46:54	nd[d]
10	**1a**	1.1	$ZnCl_2$	25	24	16	11	100:0	nd[d]
11	**1a**	12		50	48	16	100	100:0	nd[e]
12	**1b**	**12**		**190**	**72**		**100**	**100:0**	**91:0**
13	**1b**	12	$ZnCl_2$	110	48		45	71:29	nd[d]
14	**1b**	4	$ZnCl_2$	25	72	12	100	30:70	31:69[c]
15	**1b**	**6**	**$ZnCl_2$**	**25**	**24**	**16**	**95**	**0:100**	**0:82**[c]
16	**1b**	12		50	48	16	100	100:0	nd[e]

[a] **9**/**11** for indole **1a**; **10**/**12** for indole **1b**. [b] Determined by NMR spectrometry on crude reaction mixtures. [c] Overall yield of the 2:1 diastereomeric mixture. [d] Not determined. [e] Extensive polymerization. [f] **11a**/**11b** for indole **1a**; **12a**/**12b** for indole **1b**.

SCHEME 5[a]



[a] Reagents and conditions: (i) EuFOD (10 mol %); (ii) TFA (76 % overall).

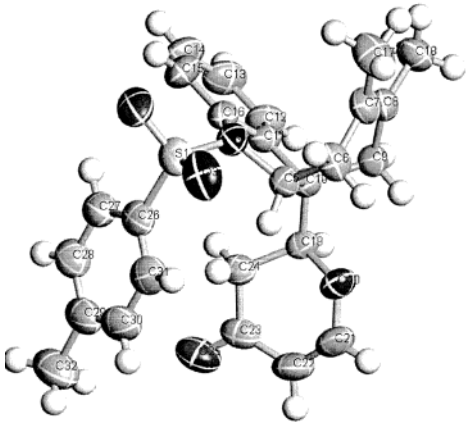


FIGURE 2. ORTEP drawing of bisadduct **13**.

aromatic double bond of the indole (Table 1, entry 12). Here again, the use of zinc chloride allows a decrease in both the temperature and the reaction time; however, while the conversion reaches only 45%, the formation of bisadducts **12a** and **12b** can already be observed (entry 13). As in the case of the 3-formyl indole derivative, combining high pressure and Lewis acid catalysis enhances the subsequent heterocycloaddition and furnishes the bisadducts **12** with a good 82% yield (entries 14 and 15).[12]

These experiments unambiguously demonstrate that a careful choice of the activation mode allows the selective formation of either monoadducts **9** and **10** (formed under thermal conditions) or bisadducts **11** and **12** (favored under high pressure and Lewis acid catalysis). The aromatic double bond proved the more reactive toward dimethylbutadiene in the cycloaddition process. In a second step, under hyperbaric conditions and in the presence of a Lewis acid catalyst, the carbonyl group reacted as dienophile in a second hetero-Diels–Alder step. The double cycloaddition can be performed either in a one-pot operation or stepwise, and this allows for the synthesis of mixed biscycloadducts arising from a sequential process involving two different dienes.

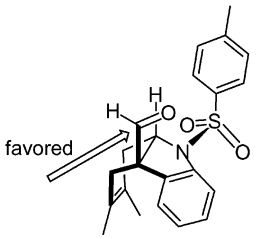


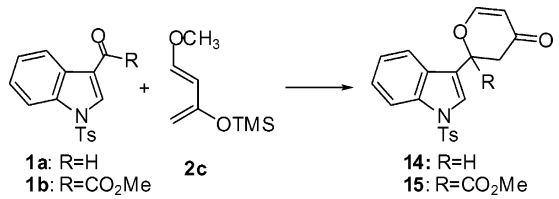
FIGURE 3. Facial selectivity in cycloaddition between **9** and **2c**.

Indole-3-carboxaldehyde and -3-glyoxylate: The Case of Danishefsky Diene. (a) Indole-3-carboxaldehyde. We previously reported that indole-3-carboxaldehyde derivative **1a** reacts with Danishefsky diene **2c** under thermal or hyperbaric activation to deliver normal Diels–Alder cycloadduct of the type **3**.[7] New data gathered since then (including 2D-NMR experiments) showed the misassignment of several nuclei, which led us to revise the structure of the product.[13] Regardless of the reaction conditions, hydrolysis of the initial adduct actually leads to the exclusive isolation of heterocycloadduct **14** (Scheme 6), the result of the interaction between the carboxaldehyde unit of **1a** and **2c**. The lack of an electron-withdrawing substituent on carbon 3 of product **14** keeps it from further reacting with the diene.

Under thermal activation (Table 2, entry 1), the enone **14** was isolated in a good 82% yield after triggering both

(12) The use of pressure alone parallels what had been obtained from indole **1a** (Table 1, entry 16).[9]

SCHEME 6[a]



[a] After TFA hydrolysis.

TABLE 2. Reactions between Indole 1a and Danishefsky Diene 2c

entry	**2c** (equiv)	reaction conditions	convn[a] (%)	yield of **14** (%)
1	12	170 °C, 24 h	100	82
2	12	$ZnCl_2$ cat. 110 °C, 24 h	80	56
3	12	12 kbar, 45 °C, 96 h	100	99
4	2	$ZnCl_2$ cat. 25 °C, 72 h	100	b
5	2	11 kbar, $ZnCl_2$ cat., 25 °C, 24 h	85[c]	70

[a] Determined by NMR spectrometry on crude reaction mixtures. [b] Isolation of **14**, **16** and **17** in a 53:31:16 ratio and in an overall 77% yield. [c] Presence of **14** and **17** in the crude mixture.

the hydrolysis of the silyl enol ether group and the loss of methanol upon acidic treatment. Zinc chloride catalysis also promoted the heterocycloaddition, but conversion and isolated yields were lower (entry 2), whereas high pressures had a more beneficial effect and led to a nearly quantitative formation of the dihydropyranone (entry 3). These observations are in line with the sensitivity of **2c** toward high temperatures and Lewis acids such as zinc chloride.

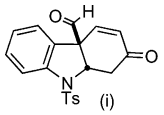
The mechanism of the hetero-Diels−Alder reaction has been studied in detail, and two different modes have been proposed, namely the traditional, concerted Diels−Alder-type cycloaddition or the stepwise condensation involving a Mukaiyama-type aldol reaction.[14] Both the Lewis acid catalyst and the solvent have been reported to have a dramatic influence on the mechanistic course: the Mukaiyama pathway has been observed with titanium- or boron-based catalysts, while the concerted Diels−Alder pathway has been proposed in reactions catalyzed by europium-, chromium-, and zinc-based Lewis acids in tetrahydrofuran. The zinc chloride catalyzed cycloaddition between indole **1a** and diene **2c** should thus proceed through the concerted mechanism. When the reaction was performed at room temperature rather than at 110 °C, a total consumption of the starting material occurred within 72 h (Table 2, entry 4). Chromatography of the crude mixture on triethylamine-pretreated silica allowed the isolation of compounds **14**, **16**, and **17** in a 53:31:16 ratio and an overall 77% yield (Figure 5). Quantitative conversion of both intermediates **16** and **17** to **14** can be separately achieved under acidic conditions (TFA in dichloromethane at room temperature). These observations suggest that, even when catalyzed by a zinc-based Lewis acid, this heterocycloaddition may go through a two-step mechanism via a Mukaiyama aldol reaction pathway, at least to some extent.[15] NMR analysis of crude mixtures from cycloadditions performed under high pressure and zinc chloride catalysis (entry 5) also revealed the presence of the same acyclic intermediate **17** together with **14** in a 36:64 ratio, whereas in the absence of Lewis acid, only the cyclized compounds **14** and **16** were observed (see entry 3).

2-Substituted indoles are known to be less reactive toward electron-rich dienes in classical Diels−Alder cycloadditions than their 3-substituted counterparts.[4a] When reacted with diene **2c**, the 2-formyl indole derivative **18** does indeed participate as a heterodienophile rather than all-carbon dienophile.[16] The faster zinc chloride catalyzed reaction leads to the sole compound **19** in 84% yield (Scheme 7).

(b) Indole-3-glyoxylate. The reactivity and chemoselectivity of ketoester-derived indole **1b** toward Danishefsky diene was next investigated and shown to be similar to that of **1a**: thus, exclusive heterodienophilicity is observed in the cycloadditions with **2c**. Carrying out this reaction under 12 kbar and at room temperature, with a 2-fold excess of diene, provides the corresponding dihydropyranone **15** in 60% isolated yield (Scheme 6). Worthy of note is the fact that these structures represent an entry into the synthesis of unnatural carbohydrates bearing an indolyl moiety in position 5 of the oxacycle.

Indole-3-glyoxamides and Danishefsky Diene. When indole **1c** and diene **2c** were heated to 180 °C for 48 h, a complete conversion was observed; acidic hydrolysis of the silyl enol ether afforded a 4:1 mixture of endo/exo cycloadduct **20a**/**20b**, isolated in fair yields (Scheme 8; Table 3, entry 1). No other product could be observed on the crude reaction material (NMR spectrometry), and the structure of the major diastereomer **20a**, which features a trans relationship between the ketoamide and the methoxy substituents, was further confirmed by X-ray analysis (Figure 4).[17] A completely reversed chemoselectivity (when compared to **1a** or **1b**) is thus observed as the aromatic 2,3-double bond proves to be the only reactive site in this case, and this all-carbon cycloaddition affords adducts **20** bearing a lateral chain (C−C−N) suitable for the construction of the D ring of the *Aspidosperma* alkaloids skeleton (Figure 1). The keto function of the electron-withdrawing group at position 3 was completely inert toward enriched dienes, and no hetero-Diels−Alder reactions took place under a variety

(13) Similarities in the chemical shifts and multiplicities of the aldehyde hydrogen in putative structure (i) with the C-2 hydrogen of compound **14**, on one hand, and C-2 hydrogen of structure (i) with H-2′ to the cyclic oxygen atom in the product, on the other hand, generated the misassignment. Inspection of the ORTEP drawing of analogous structure **20a** indicated the possibility for the aldehyde hydrogen in (i) to be in the shielding cone of the *p*-tolyl group.



(14) (a) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716−3717. (b) Danishefsky, S. J.; Larson, E.; Askin, D., Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246−1255.

(15) The solvent used in this heterocycloaddition (dichloromethane) may provide an explanation, as recently observed by Baldoli, C.; Maiorana, S.; Licandro, E.; Zinzalla, G.; Lanfranchi, M.; Tiripicchio, A. *Tetrahedron*: *Asymmetry* **2001**, *12*, 2159−2167.

(16) A recent publication reports on the reaction between an imine generated from **18** and Danishefsky diene **2c**. See: Kuethe, J. T.; Dormer, P. G.; Reamer, R. A.; Mathre, D. J.; Reider, P. J. *Tetrahedron Lett.* **2002**, *43*, 29−32.

(17) Endo addition can be defined as "that particular spatial arrangement of reactants in which the more bulky side of the diene is under the more bulky side of the dienophile", meaning the indole part in this case. See: Fringuelli, F.; Taticchi, A. in *Dienes in the Diels−Alder Reaction*; John Wiley and Sons Ltd: New York, 1990; pp 1−44.

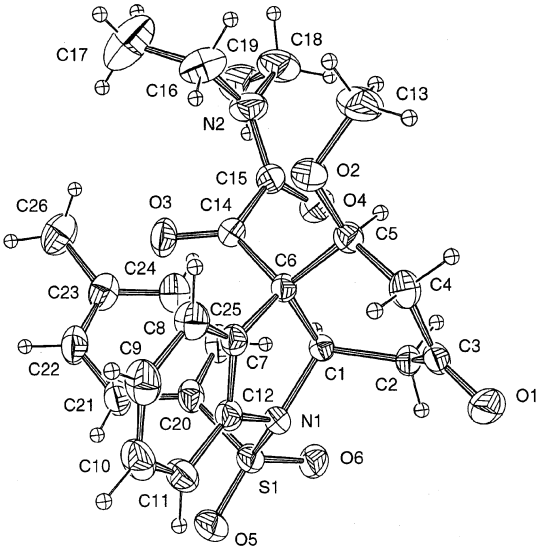
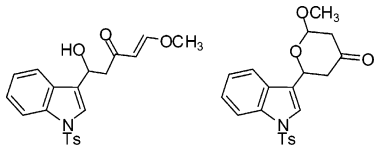


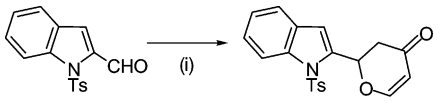
FIGURE 4. ORTEP diagram of adduct **20a** (endo).



16 **17**

FIGURE 5. Isolated intermediates from the HDA process.

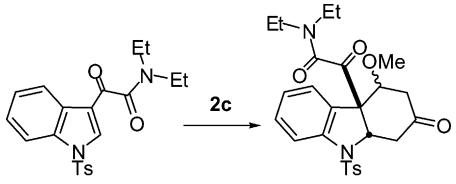
SCHEME 7[a]



18 **19**

[a] Reagents and conditions: (i) **2c**, $ZnCl_2$ (10 mol %), CH_2Cl_2, 25 °C (84%).

SCHEME 8



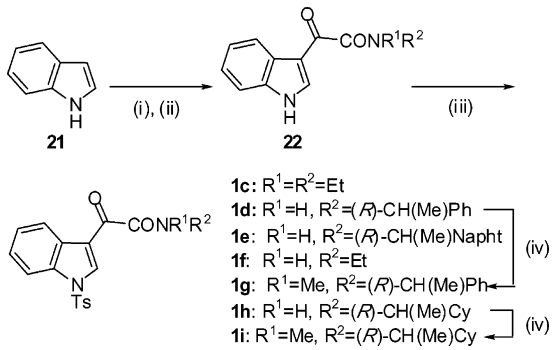
1c

20a: 1a*S**, 4*R**, 4a*R**
20b: 1a*S**, 4*S**, 4a*R**

of conditions. A 12 kbar compression at 45 °C led to a similar result (entry 2). Zinc chloride catalysis in refluxing toluene resulted in the decomposition of the diene and left the indole untouched (entry 3). Finally, the optimized conditions required the combination of high pressures and the mild europium Lewis acid catalysis (entry 4). The cycloaddition now took place at room temperature, leading quantitatively to a 4:1 endo/exo mixture of diastereomers, separated by chromatography on silica gel.

Attempts to develop diastereoselective versions of this reaction led us to apply the same sequence of reactions to chiral ketoamides **1d** and **1e**. Starting materials were

SCHEME 9[a]

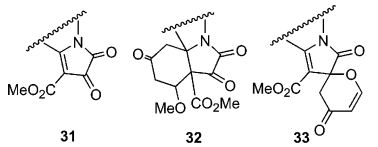


[a] Reagents and conditions: (i) $(COCl)_2$, Et_2O, 0 °C, 30 min; (ii) R_1R_2NH, Et_2O, 0−25 °C, overnight; (iii) TsCl, DIPEA, DMAP cat., CH_2Cl_2, 1 h; (iv) NaH, MeI, DMF, 0 °C.

easily prepared by sequential treatment of indole **21** with oxalyl chloride, quenching of the resulting acid chloride with the requisite chiral amine, and tosylation of the 3-acylindole (Scheme 9). While interaction of **1d** and **2c** gave rise to little reaction in refluxing toluene and in the presence of EuFOD (Table 3, entry 6), a strikingly different result was obtained when compressing a CH_2Cl_2 solution of the same substrates and catalyst to 12 kbar. Hydrolysis of the crude mixture yielded a material whose NMR data indicated complete consumption of the starting ketoamide and the formation of two structurally different compounds. In this case, the major transformation was found to be a hetero-Diels−Alder reaction involving the 3-keto group.[18] Thus, indole **1d** delivered cycloadduct **25**, isolated in 76% yield as a 2:1 diastereomeric mixture. A minor fraction was also collected and shown to contain bisadducts **29** (9%) (entry 7). Similarly, the naphthyl analogue **1e**, when placed under the same hyperbaric conditions, underwent total conversion and furnished heterocycloadducts **26** (86% isolated yield; a 2:1 mixture of diastereomers), along with some bisadducts **30** (entry 9). The site selectivity and yields were optimized in the absence of EuFOD, and 4-dihydropyrone **25**, now the exclusive product after hydrolysis, was isolated in excellent yields (entry 8). The constant 2:1 diastereomeric mixture observed in all these cases obviously reflects the limited induction power of the (*R*)-CH(Me)Ar unit in these processes.

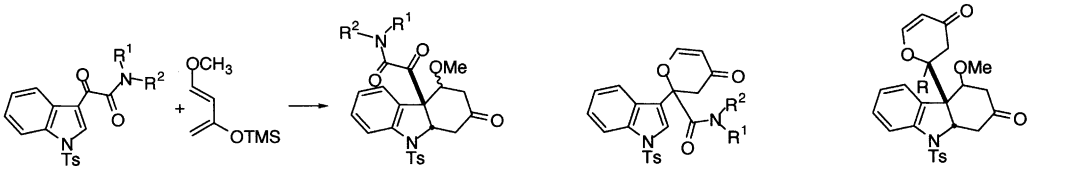
The remarkable reversal of chemoselectivity (compare entries 4 and 8, Table 3) led us to consider other substrates in an attempt to rationalize this behavior. Comparison of *N*,*N*-diethylketoamide **1c** and *N*-(methyl)-

(18) To the best of our knowledge, the only reported case of a ketoamide undergoing a [4 + 2] heterocycloaddition involves unsaturated 3-oxopyrrolidinone of the type **31** and Danishefsky diene **2c**, when either heated at 130 °C or compressed at 10 kbar. Compound **31** delivered either normal Diels−Alder cycloadducts **32** and heterocycloadducts **33** in variable amounts or exclusively the same cycloadducts **33**, depending on the conditions and the substituents. See: (a) Tsuda, Y.; Hosoi, S.; Katagiri, N.; Kaneko, C.; Sano, T. *Heterocycles* **1992**, *33*, 497−502. (b) Tsuda, Y.; Hosoi, S.; Katagiri, N.; Kaneko, C.; Sano, T. *Chem. Pharm. Bull.* **1993**, *41*, 2087−2095.



31 **32** **33**

TABLE 3. Reactions between Indole-3-glyoxamides 1c−i and Danishefsky Diene 2c

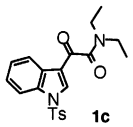
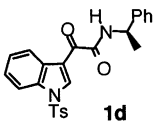
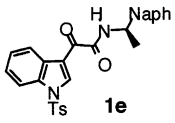
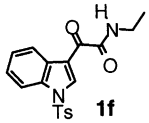
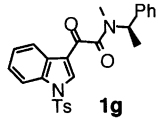
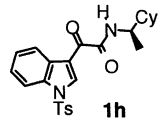
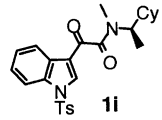


1c-i **2c**

type **3**
20: R^1=R^2=Et
23: R^1=Me, R^2=(R)-CH(Me)Ph
24: R^1=Me, R^2=(R)-CH(Me)Cy

type **6**
25: R^1=H, R^2=(R)-CH(Me)Ph
26: R^1=H, R^2=(R)-CH(Me)Naph
27: R^1=H, R^2=Et
28: R^1=H, R^2=(R)-CH(Me)Cy

type **7**
29: R=(R)-CONHCH(Me)Ph
30: R=(R)-CONHCH(Me)Naph

entry	starting indole	reaction conditions	conv. (%)[a]	cycloadduct ratio[a] type **3**	type **6**	type **7**	Yields (d.e.) (%)[b] type **3**	type **6**	type **7**
1	 **1c**	180°C, 48h	100	100	0	0	55 (60)	-	-
2		12 kbar, 45°C, 48h	100	100	0	0	60 (50)	-	-
3		$ZnCl_2$[c], 110°C, 24h	0[d]	-	-	-	-	-	-
4		**EuFOD[d], 12 kbar, 25°C, 38h**	**100**	**100**	**0**	**0**	**99 (60)**	**-**	**-**
5	 **1d**	180°C, 48h	100[d]	-	-	-	-	-	-
6		EuFOD[c], 110°C, 36h	0	-	-	-	-	-	-
7		EuFOD[c], 12 kbar, 25°C, 36h	100	0	90	10	-	76 (33)	8[h]
8		**12 kbar, 25°C, 36h**	**100**	**0**	**100**	**0**	**-**	**92 (33)**	**-**
9	 **1e**	EuFOD[c], 12 kbar, 25°C, 36h	100	0	91	9	-	86 (33)	7[h]
10	 **1f**	12 kbar, 25°C, 36h	15	0	100	0	-	-	-
11		**EuFOD[c], 12 kbar, 25°C, 36h**	**100**	**0**	**100**	**0**	**-**	**88**	**-**
12	 **1g**	EuFOD[c], 12 kbar, 25°C, 36h	55	-	-	-	-	-	-
13		**EuFOD[c], 16 kbar, 50°C, 36h**	**100**	**100**	**0**	**0**	**57[f,g]**	-	**-**
14	 **1h**	12 kbar, 25°C, 36h	80	0	100	0	-	-	-
15		**EuFOD[c], 12 kbar, 25°C, 36h**	**100**	**0**	**100**	**0**	**-**	**72 (33)**	**-**
16	 **1i**	**EuFOD[c], 16 kbar, 50°C, 36h**	**100**	**100**	**0**	**0**	**81[f]**	**-**	**-**

[a] Determined by NMR spectrometry on crude reaction mixtures. [b] Overall yield of the diastereomeric mixture. [c] 10 mol % catalysis. [d] Degradation of the reaction mixture. [e] 5 mol % catalysis. [f] Isolated as a mixture of four diastereomers. [g] A poor diastereoselectivity was observed in this case.[22] [h] Obtained as a mixture of eight diastereomers.

benzyl analogue **1d** indicates the N−H bond in the latter. To verify its implication, the secondary *N*-ethylketoamide **1f** was prepared and subjected to the action of diene **2c** under essentially the same conditions (entries 10 and 11). A complete consumption of the starting material resulted in the presence of EuFOD, and heterocycloadduct **27** was obtained in 88% yield. Here again, a complete reversal of chemoselectivity occurred as neither the normal Diels−Alder adduct (of the type **3**) nor the biscycloadduct (of the type **7**) could be observed in the crude mixture (^{1}H NMR spectrometry analysis). To further determine the involvement of the N−H bond in this process, the mono-N-substituted ketoamide **1d** was methylated (NaH, MeI) to afford indole **1g** (Scheme 9). When placed under the same conditions, a sluggish transformation occurred, leaving 45% of unconsumed starting material (entry 12).

Increasing the pressure to 16 kbar led to a complete conversion and, this time, isolation of the normal Diels−Alder cycloadducts **23** (of the type **3**) in 57% yield (entry 13).

The striking difference of reactivity between the secondary and tertiary ketoamides, regardless of the reaction conditions, clearly reflects the influence of the second alkyl group. Thus, a secondary ketoamide (i.e., featuring an N−H bond) gives rise to heterocycloadducts of the type **6** in a largely predominant or exclusive manner (entries 7−11).[19] Installing a methyl group on the ketoamide nitrogen completely reverses the chemoselectivity, and the cycloadducts of type **3** are now the exclusive products (entries 1−4, 12, and 13).

The competitive (albeit slower) formation of bisadducts of the type **7** from dienophiles **1d** and **1e**, when catalyzed by EuFOD, indicates that different factors play a role in this reaction (entries 7 and 9).[20] The presence of an aryl moiety in the direct vicinity of the acyclic nitrogen may somewhat alter the site selectivity reversal due to the steric hindrance generated by the substituents on the amide nitrogen, and/or a possible π-stacking interaction (between the aryl substituent of the amide group and the indole ring). To evaluate the influence of these parameters, amides **1h** and **1i**, featuring the fully saturated analogue of the α-(methyl)benzyl substituent, were prepared in a similar way (Scheme 9). Compressing a mixture of indole **1h** and diene **2c** (6 equiv) led to an 80% conversion and the exclusive formation of dihydropyrane **29** (of the type **6**) (entry 14). Addition of EuFOD (10 mol %) increased the conversion and allowed the isolation of the product in 72% yield (entry 15). Again, a reversal of chemoselectivity is observed with *N*,*N*-dialkylamide **1i**: not a trace of heterocycloadducts (of the type **6** or **7**) was found to have formed and the normal Diels−Alder products **24** could be isolated in 81% yield (a mixture of four diastereomers) (entry 16). One of these adducts could be separated from the mixture by recrystallization from heptanes/dichloromethane. On the basis of previous data on both diastereomers of **20**, a relative assignment of the ^{1}H NMR spectrometry signal corresponding to an endo cycloadduct can confidently be made.[21]

To our knowledge, such a complete reversal of chemoselectivity has not been reported in the literature so far.

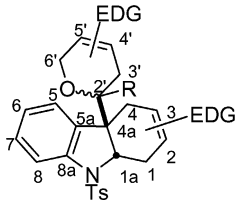


FIGURE 6. Numbering in type 7 bisadducts.

TABLE 4. Selected ^{1}H NMR Chemical Shifts and Coupling Constants of 20a, 20b, and 13

^{1}H	**20a** (endo) (ppm) (*J* (Hz))	**20b** (exo) (ppm) (*J* (Hz))	**13** (2′*R*) (ppm) (*J* (Hz))
1a	**5.20** (6.0; 6.4)	**5.41** (2.3; 5.6)	**4.06** (4.5; 4.9)
1	**2.85** (6.4; 16.4)	**3.01** (5.6; 17.0)	**2.30** (m)
	3.07 (6.0; 16.4)	**3.21** (2.3; 17.0)	**2.58** (4.9; 14.7)
3	**2.23** (8.3; 18.3)	**1.88** (2.3; 18.5)	
	2.48 (3.4; 18.3)	**2.56** (3.0; 18.5)	
4	**4.81** (3.4; 8.3)	**4.67** (2.3; 3.2)	**2.03** (14.9)
			2.51 (14.9)
2′			**4.06** (4.9; 4.9)
3′			**2.31** (4.9; 14.7)
			2.58 (4.9; 14.7)

Obviously, the dienophilic component seems to represent a borderline case, and small changes in the electronic and/or structural parameters induce the carbonyl group to become more reactive toward more polar dienes. The results compiled in Table 3 show that the energy difference between the two processes is most probably tenuous. Additional experiments will be needed to shed light on this phenomenon; work addressing this issue is in progress in these laboratories.

Conformational Analyses of the Cycloadducts. Three different molecules, namely **20a**, **20b**, and **13**, were chosen to analyze the conformations adopted by the molecules in solution. The various ^{1}H NMR spectrometry chemical shifts and coupling constants for hydrogens in positions 1a, 1, 3, 4, 2′, and 3′ (Figure 6) are compiled in Table 4.

In the endo diastereomer **20a**, the structure was solved by using X-ray diffraction on a monocrystal and features a concave boat-shape conformation for the cyclohexanone ring. Such a conformation arises from the presence of a five-membered cycle encompassing three sp^2 atoms.[23] The nearly identical coupling constant values between hydrogen 1a and both axial and equatorial hydrogens in position 1 (6.0 and 6.4 Hz) indicate similar dihedral angles between these atoms.[24] In the case of hydrogen 4, the observed ^3J values reflect a slight torsion of the C−C bonds of the pseudoboat. Indeed, the trans relationship between the methoxy and the ketoamide groups should yield dihedral angle values of 60 and 180° for hydrogens 3 with respect to hydrogen 4. The values of 3.4 and 8.3 Hz are indicative of smaller angles, in accordance with a decrease of the 1,4-steric interaction between H_{1ax} and H_4. Of particular note is the fact that the two carbonyl functions are in different planes, as shown by the ORTEP

(19) It should be noted that published NMR studies of the different conformations in secondary amides indicate a preference for the transoid conformation; see: Stewart, W. E.; Siddall, T. H. *Chem. Rev.* **1970**, *70*, 517−551. In the case of the secondary ketoamides discussed in this work, the probable intramolecular hydrogen bond is reflected by the presence of a single conformer, as indicated by ^{1}H and ^{13}C NMR spectrometries. For a secondary ketoamide featuring a transoid conformation for the amide group, two different hydrogen bonds may be invoked, depending on the conformation adopted by the dicarbonyl unit. Thus, a transoid conformation will allow hydrogen bonding with the oxygen atom of the keto group, while a cisoid conformation may achieve such a hydrogen bond with one of the sulfonyl oxygen atoms. Chelation with europium (for example) may thus involve either both the amide oxygen and the sulfonyl oxygen, or the oxygen atoms of both carbonyl groups, respectively. Clearly, the situation arising from the chelation of tertiary amides will be different. The presence of a hydrogen bond in secondary amides may result in a distortion of the -system, and a deconjugation between the electron withdrawing substituent and the 2,3-indole C=C bond, thus translating in a different chemoselectivity.

(20) Inasmuch as the heterocycloaddition suppresses the electron-withdrawing group on the indole ring, the normal [4 + 2] cycloaddition must occur prior to the hetero Diels−Alder reaction in the process leading to bisadducts of the type **7** (**29** and **30**).

(21) J_{H4-H3}= 3.4, 7.9 Hz.

(22) Analysis of the unseparable, purified mixture revealed the presence of two major compounds, whose relative stereochemistry could not be ascertained.

(23) Maddaluno, J.; Gaonac'h, O.; Marcual, A.; Toupet, L.; Giesner-Prettre, C. *J. Org. Chem.* **1996**, *61*, 5290−5306.

(24) Axial and equatorial nomenclature is used to differenciate geminal hydrogens (pseudo).

drawing of the molecule (Figure 4), thus suggesting an absence of conjugation between these groups; this may result from negative interactions between the oxygen atoms of the methoxy substituent on one hand and either one of the carbonyl functions on the other hand.

The exo counterpart **20b** of this molecule now possesses the methoxy group in axial position; the increased resultant steric hindrance with axial hydrogen 1 may induce a twisting of the boat-shape conformation to diminish these interactions. The observed ^3J values for H_{1a} are in accordance with such a situation. Thus, when compared to the endo isomer (vide supra), both coupling constants are smaller (2.3 and 5.6 Hz). The small ^3J values observed for hydrogen 4 confirm the twist and correspond to approximate dihedral angles of 40 and 70°.

A similar concave boat-shape conformation of the cycle resulting from the normal Diels−Alder reaction also exists in bisadduct **13**, as shown by the computer-generated graphic obtained from X-ray diffraction data (Figure 2). Here again, the ^3J values for hydrogen 1a are in accordance with the adoption of such a conformation in solution. The hydrogens in position 2′ and 3′ of the dihydropyranone ring display a typical ABX pattern.

Conclusion

The products arising from the reaction of electron-poor indoles with 1,3-dienes strongly depend on (i) the type of the electron-withdrawing substituent on position 3 of the indole, (ii) the diene involved in the cycloaddition process, and (iii) the method of activation. Thus, the thermal reaction between either indole-3-carboxaldehyde **1a** or indole-3-glyoxylate **1b** and 2,3-dimethylbuta-1,3-diene yields the expected Diels−Alder adducts **9** or **10**. Biactivation with zinc chloride and pressures up to 12 kbar furnish the same monocycloadducts **9** or **10**, along with minor amounts of bisadducts **11** or **12**. Forcing the conditions ($ZnCl_2$, 16 kbar) leads to the nearly exclusive formation of bisadducts **11** or **12** in high yields. The data unambiguously demonstrate that the preferred site of reactivity is the indole 2,3 carbon−carbon double bond and are in line with previous results obtained with other four-π-electron partners such as cyclohexadiene. The involvment of the 3-carbonyl unit as heterodienophile occurs efficiently only under forcing conditions.

The use of an electron-enriched diene such as Danishefsky's diene induces a reversal of the site selectivity, the γ-dihydropyranones being now the exclusive adducts formed in the process, regardless of the activation type. The study indicates that a two-step, Mukaiyama-type pathway may be followed under $ZnCl_2$ catalysis.

Indole-3-ketoamides **1c**−**i** constitute a unique set of dienophiles in the reaction with Danishefsky's diene. The results reported in this paper indicate that the site of reactivity is strongly dependent on both the number of substituent(s) on the acyclic nitrogen atom and their nature. Mono-N-substituted ketoamides undergo an heterocycloaddition reaction on the keto moiety in a nearly exclusive fashion, while a reversed site-selectivity occurs with the involvment of the indole 2,3-double bond as the only reacting entity in the case of N,N-disubstituted analogues (**1c**, **1g**, **1i**).

Experimental Section

Unless otherwise stated, ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in deuterated chloroform relative to $(CH_3)_4Si$ and $CDCl_3$, respectively. Chemical shifts are expressed in parts per million (ppm). Low-resolution and high-resolution mass spectra were recorded on Unicam ATI Automass and JEOL 500 spectrometers, respectively. IR spectra were recorded on Perkin-Elmer 16PC FT-IR spectrometers.

General Procedure for the Tosylation of Indole. A mixture of the indole derivative (1 equiv), DMAP (cat.), $(i\text{-Pr})_2$EtN (1.3−1.5 equiv), and TsCl (1.0−1.1 equiv) was stirred at room temperature for the requisite time. After quenching with 0.1 N HCl, the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel.

General Procedure for the *N*-Methylation of Indole-3-glyoxamide. To a suspension of NaH (60% in oil) (1.2 equiv) in dry DMF was added, at 0 °C, the indoleglyoxamide (1 equiv). The mixture was stirred for 15 min, and then MeI (1.5 equiv) was added dropwise. The resulting mixture was stirred until completion of the reaction (TLC monitored). The reaction was quenched with water and extracted with EtOAc. After concentration under reduced pressure, the residue was purified by flash chromatography on silica.

2-Oxo-*N*-(1-phenylethyl)-2-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]acetamide (1d). Prepared according to the general procedure using **22d** (292 mg, 1 mmol), DMAP (10 mg), $(i\text{-Pr})_2$EtN (226 μL, 1.3 mmol), and TsCl (190 mg, 1 mmol) in CH_2Cl_2 (3 mL). The reaction was stirred for 1 h and the product purified by flash chromatography (heptanes/EtOAc 4:1) to give **1d** as a white solid (439 mg, 98%, mp 169−170 °C): $[\alpha]^{20}_D$ = +57.3 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.54 (d, J = 7.1 Hz, 3H), 2.29 (s, 3H), 5.04−5.14 (m, 1H), 7.19−7.33 (m, 9H), 7.56 (d, J = 7.9 Hz, 1H), 7.81 (d, J = 8.3 Hz, 2H), 7.90−7.93 (m, 1H), 8.24−8.27 (m, 1H), 9.36 (s, 1H); ^{13}C NMR δ 21.5, 21.8, 49.1, 113.2, 115.9, 122.7, 125.0, 125.8, 126.0 (2C), 127.3 (2C), 127.6, 128.1, 128.8 (2C), 130.2 (2C), 134.1, 134.3, 138.5, 142.3, 145.9, 160.1, 181.7; IR (KBr) ν 3354, 1654, 1646, 1374, 1297, 1171 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 446 [$M^{+\bullet}$] (12), 298 (28), 155 (41), 91 (100). Anal. Calcd for $C_{25}H_{22}N_2O_4S$: C, 67.25; H, 4.97; N, 6.27; S, 7.18. Found: C, 67.29; H, 4.98; N, 6.28; S, 7.19.

***N*-(1-Naphthalen-1-ylethyl)-2-oxo-2-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]acetamide (1e).** Prepared according to the general procedure using **22e** (342 mg, 1 mmol), DMAP (10 mg), $(i\text{-Pr})_2$EtN (226 μL, 1.3 mmol), and TsCl (200 mg, 1.05 mmol) in CH_2Cl_2 (4 mL). The reaction was stirred for 1 h and the product purified by flash chromatography (cyclohexane/EtOAc 17:3) to give **1e** as a white solid (479 mg, 97%, mp 71 °C): $[\alpha]^{20}_D$ = +14.3 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.77 (d, J = 6.8 Hz, 3H), 2.36 (s, 3H), 5.93−6.04 (m, 1H), 7.27 (d, J = 8.3 Hz, 2H), 7.33−7.62 (m, 7H), 7.71 (d, J = 8.3 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 8.3 Hz, 2H), 7.97−8.01 (m, 1H), 8.14 (d, J = 8.3 Hz, 1H), 8.29−8.33 (m, 1H), 9.47 (s, 1H); ^{13}C NMR δ 21.0, 21.5, 45.0, 113.1, 115.9, 122.5, 122.7, 122.8, 125.0, 125.2, 125.8 (2C), 126.6, 127.3 (2C), 128.1, 128.4, 128.9, 130.1 (2C), 130.7, 133.8, 134.1, 134.3, 137.6, 138.5, 145.9, 160.0, 181.6; IR (KBr) ν 3373, 1681, 1648, 1380, 1177 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 496 [$M^{+\bullet}$] (17), 298 (27), 170 (89), 155 (87), 144 (11), 91 (100). Anal. Calcd for $C_{29}H_{24}N_2O_4S$: C, 70.14; H, 4.87; N, 5.64; S, 6.46. Found: C, 70.25; H, 5.25; N, 5.77; S, 6.18.

***N*-Ethyl-2-oxo-2-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-acetamide (1f).** Prepared according to the general procedure using **22f** (223 mg, 0.5 mmol), DMAP (10 mg), $(i\text{-Pr})_2$EtN (0.70 mL, 4 mmol), and TsCl (0.61 g, 3.2 mmol) in CH_2Cl_2 (10 mL). The reaction was stirred for 1 h and the mixture purified by flash chromatography (cyclohexane/EtOAc 17:3) to give **1f** as a white solid (0.69 g, 62%, mp 54 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, J = 7.5 Hz, 3H), 2.30 (s, 3H), 3.33−3.43 (m, 2H), 7.21 (d, J = 8.3 Hz, 2H), 7.26−7.36 (m, 3H), 7.82 (d, J =

8.3 Hz, 2H), 7.90−7.94 (m, 1H), 8.25−8.28 (m, 1H), 9.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 21.5, 34.2, 113.1, 115.9, 122.7, 125.0, 125.8, 127.2 (2C), 128.1, 130.2 (2C), 134.1, 134.3, 138.4, 145.9, 161.0, 181.9; IR (KBr) ν 3385, 1684, 1654, 1381, 1291, 1178 cm^{-1}; MS (CI) *m*/*z* (relative intensity) 371 [M^+ + 1] (86), 217 (50), 144 (100). Anal. Calcd for $C_{19}H_{18}N_2O_4S$: C, 61.61; H, 4.90; N, 7.56; S, 8.65. Found: C, 61.64; H, 4.96; N, 7.51; S, 8.54.

***N*-Methyl-2-oxo-*N*-(1-phenylethyl)-2-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]acetamide (1g).** Prepared according to the general procedure using **1d** (223 mg, 0.5 mmol) and NaH (60% in oil) (24 mg, 0.6 mmol, MeI (47 μL, 0.75 mmol). The reaction was stirred for 75 min at 0 °C. The product was purified by flash chromatography (cyclohexane/EtOAc 4:1) to give **1f** as a white solid (151 mg, 66%, mp 140 °C): $[\alpha]^{20}_D$ = +34.5 (*c* 1, $CHCl_3$); (two rotamers) ^{1}H NMR δ 1.56 and 1.59 (d, *J* = 7.0 Hz, 3H), 2.30 (s, 3H), 2.62 and 2.74 (s, 3H), 5.04 and 6.04 (q, *J* = 7.0 Hz, 1H), 7.18−7.37 (m, 9H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.85−7.91 (m, 1H), 8.19−8.25 (m, 1H), 8.27 and 8.34 (s, 1H); ^{13}C NMR δ 15.1, 16.7, 21.3, 26.6, 29.4, 50.3, 55.2, 113.0, 117.4 and 117.7, 122.4 and 122.5, 124.9 and 124.9, 125.9 and 126.0, 126.8 and 126.8, 127.0 (2C), 127.6 and 127.7, 128.4 (2C), 128.5 (2C), 130.1 (2C), 133.8, 134.6 and 134.7, 135.2, 135.4, 138.3 and 138.9, 146.0 and 146.0, 166.0, 166.4, 186.2, 186.5; IR (KBr) ν 2929, 1655, 1633, 1385, 1172 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 460 [$M^{+\bullet}$] (15), 298 (7), 155 (34), 134 (44), 105 (62), 91 (100). Anal. Calcd for $C_{26}H_{24}N_2O_4S$: C, 67.81; H, 5.25; N, 6.08; S, 6.96. Found: C, 67.98; H, 5.22; N, 6.03; S, 6.82.

***N*-(1-Cyclohexylethyl)-2-oxo-2-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]acetamide (1h).** Prepared according to the general procedure using **22h** (1.20 g, 4 mmol), DMAP (20 mg), (*i*-Pr)$_2$EtN (1.05 mL, 6 mmol), and TsCl (0.84 g, 4.4 mmol) in CH_2Cl_2 (20 mL). The reaction was stirred for 2 h and the product purified by flash chromatography (cyclohexane/EtOAc 9:1) to give **1h** as a white solid (1.62 g, 90%, mp 51 °C): $[\alpha]^{20}_D$ = +6.3 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.00−1.80 (m, 11H), 1.20 (d, *J* = 6.8 Hz, 3H), 2.37 (s, 3H), 3.84−3.98 (m, 1H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.32−7.40 (m, 3H), 7.89 (d, *J* = 8.5 Hz, 2H), 7.97−8.00 (m, 1H), 8.31−8.35 (m, 1H), 9.45 (s, 1H); ^{13}C NMR δ 17.4, 21.3, 25.8 (2C), 26.1, 28.8, 28.9, 42.7, 49.6, 113.0, 115.8, 122.5, 124.8, 125.6, 127.0 (2C), 128.0, 129.9 (2C), 133.9, 134.2, 138.2, 145.7, 160.3, 181.9; IR (KBr) ν 3366, 1684, 1648, 1595, 1382 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 452 [$M^{+\bullet}$] (5), 298 (37), 155 (55), 115 (12), 91 (100). Anal. Calcd for $C_{25}H_{28}N_2O_4S$: C, 66.35; H, 6.24; N, 6.19; S, 7.08. Found: C, 66.38; H, 6.17; N, 5.99; S, 6.78.

***N*-(1-Cyclohexyl-ethyl)-*N*-methyl-2-oxo-2-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-acetamide (1i):** Prepared according to the general procedure using **1h** (223 mg, 0.5 mmol), NaH (60% in oil) (24 mg, 0.6 mmol), MeI (47 μL, 0.75 mmol). The reaction was stirred for 2 h at 0 °C. The product was purified by flash chromatography (cyclohexane/EtOAc 17:3) to give **1i** as a white solid (80 mg, 34%, mp 61−63%): $[\alpha]^{20}_D$ = +29.3 (c 1, $CHCl_3$); (two rotamers) ^{1}H NMR (200 MHz) δ 0.64−1.81 (m, 11H), 1.23 and 1.25 (d, *J* = 6.8 Hz, 3H), 2.37 (s, 3H), 2.82 and 2.94 (s, 3H), 3.26−3.42 and 4.40−4.53 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.36−7.43 (m, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.93−7.98 (m, 1H), 8.27−8.35 (m, 2H); ^{13}C NMR (50 MHz) δ 15.2 and 16.2, 21.2, 25.5 (2C), 25.6 and 25.6, 25.8, 29.0, 29.4 and 29.5, 29.6 and 29.9, 39.4 and 39.9, 52.8 and 58.6, 112.9, 117.3 and 117.6, 122.3 and 122.4, 124.7, 125.8 and 126.7, 126.9 (2C), 129.9 (2C), 133.7 and 134.5, 135.2 and 135.2, 145.9, 166.2 and 166.6, 186.4 and 186.6; IR (KBr) ν 2926, 1653, 1636, 1383, 1173 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 466 [$M^{+\bullet}$] (7), 383 (7), 298 (66), 155 (50), 140 (46), 111 (29), 91 (100). Anal. Calcd for $C_{26}H_{30}N_2O_4S$: C, 66.93; H, 6.48; N, 6.00; S, 6.87. Found: C, 66.99; H, 6.12; N, 5.97; S, 6.56.

General Procedure for the High-Pressure Reactions. Noncatalyzed Reactions. To a solution of the requisite indole, in dry dichloromethane at room temperature under argon, were added hydroquinone (10 mg) and the diene. The resultant mixture was transferred into a high-pressure vessel and compressed at the desired pressure and the desired temperature. After the decompression, the solvent and excess diene were evaporated under reduced pressure. Chromatography of the residue on silica led to the isolation of the cycloadduct(s).

Catalyzed Reactions under High Pressure. To a stirred solution of the requisite indole derivative **1** in dry dichloromethane was added the Lewis acid at room temperature. The mixture was stirred for 15 min. Hydroquinone and distilled diene **2** were then added, and the resultant mixture was transferred into a high-pressure vessel and compressed at the desired pressure and temperature. After decompression, the mixture was evaporated under reduced pressure. Chromatography of the residue on silica led to the isolation of the cycloadduct(s).

The ketones resulting from the hydrolysis of the silyl enol ether in the case of cycloadducts derived from Danishefsky diene were obtained in the following manner. After reaction, removal of the excess diene was achieved by bulb-to-bulb distillation under reduced pressure (50 °C/0.1bar). The residue (0.3 mmol scale) was then stirred overnight in methanol (2 mL) in the presence of silica (100 mg). Filtration and purification as above delivered the desired products.

General Procedure for Thermal Cycloadditions. A vessel containing the requisite indole and diene in dry degassed toluene was sealed and then heated in a sand bath at the desired temperature. After cooling, the solvents and excess diene were removed under reduced pressure and the residue chromatographed.

General Procedure for the Hydrolysis of Hetero-Diels−Alder Cycloadducts. After the reaction, the excess diene was removed by bulb-to-bulb distillation under reduced pressure (60 °C/0.2 mmHg). A solution of trifluoroacetic acid (2%) in CH_2Cl_2 was added to the residue at 0 °C, and the solution was stirred for 15−30 min.[25] An aqueous saturated solution of $NaHCO_3$ was added, and the reaction mixture was extracted three times with CH_2Cl_2. After concentration of the organic phases under reduced pressure, the residue was purified by flash chromatography on silica.

2,3-Dimethyl-9-(toluene-4-sulfonyl)-1,4,9,9a-tetrahydrocarbazole-4a-carbaldehyde (9). Purification of the residue by flash chromatography (heptanes/EtOAc 9:1): mp = 112 °C; ^{1}H NMR δ 1.51 (s, 3H), 1.66 (s, 3H), 2.15 (d, *J* = 14.5 Hz, 1H), 2.26 (s, 3H), 2.37−2.50 (m, 1H), 2.45 (d, *J* = 14.5 Hz, 1H), 2.53 (dd, *J* = 5.6, 14.7 Hz, 1H), 4.49 (dd, *J* = 5.6, 7.2 Hz, 1H), 6.93 (dd, *J* = 1.5, 7.5 Hz, 1H), 6.99 (dd, *J* = 7.2, 7.5 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 2H), 7.21 (ddd, *J* = 1.5 Hz, 7.2, 8.3 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.3 Hz, 1H), 9.02 (s, 1H); ^{13}C NMR δ 19.0, 19.0, 21.4, 35.0, 37.1, 61.3, 62.4, 116.1, 124.1, 124.7, 126.0, 127.1 (2C), 127.4, 129.4, 129.4 (2C), 131.0, 133.7, 142.5, 144.1, 196.3; MS (EI) *m*/*z* 381 (53), 352 (93), 299 (100), 196 (54), 155 (71), 91 (75); IR (NaCl) 2875, 1736, 1606, 1357, 1173; exact mass *m*/*z* calcd for $C_{22}H_{23}NO_3S$ 381.1399, found 381.1395.

[2,3-Dimethyl-9-(toluene-4-sulfonyl)-1,4,9,9a-tetrahydrocarbazol-4a-yl]oxoacetic Acid Methyl Ester (10). Purification of the residue by flash chromatography (heptanes/EtOAc 9:1): ^{1}H NMR δ 1.44 (s, 3H), 1.64 (s, 3H), 2.27 (s, 3H), 2.28−2.68 (m, 2H), 2.38 (d, *J* = 14.7 Hz, 1H), 2.62 (d, *J* = 14.7 Hz, 1H), 3.56 (s, 3H), 4.81 (dd∼t, *J* = 5.5 Hz, 1H), 6.95 (dd−t, *J* = 7.5 Hz, 1H), 7.03−7.22 (m, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.50−7.58 (m, 1H); ^{13}C NMR δ 19.1, 19.2, 21.5, 37.2, 37.9, 52.4, 61.0, 64.4, 115.8, 124.3, 125.0, 125.7, 127.3 (2C), 127.8, 129.4 (3C), 130.8, 134.3, 142.9, 144.0, 162.6, 193.7; MS (EI) *m*/*z* 439 (23), 352 (100), 298 (38), 196 (41); IR (NaCl) 2924, 1736, 1597, 1477, 1459, 1356, 1168; exact mass *m*/*z* calcd for $C_{24}H_{25}NO_5S$ 439.1454, found 439.1448.

(25) In the case of the cycloadducts **26** and **29**, it was necessary to use a solution of 10% of TFA in CH_2Cl_2 during 18 h at room temperature.

4a-(4,5-Dimethyl-3,6-dihydro-2*H*-pyran-2-yl)-2,3-dimethyl-9-(toluene-4-sulfonyl)-4,4a,9,9a-tetrahydro-1*H*-carbazole (11a). Purification of the residue by flash chromatography (heptanes/EtOAc 9:1) (major diastereomer): ^{1}H NMR δ 0.70−0.95 (m, 1H), 1.20 (s, 3H), 1.34 (s, 3H), 1.36 (s, 3H), 1.64 (s, 3H), 1.20−1.30 (m, 1H), 1.92 (d, J = 14.3 Hz, 1H), 2.26 (s, 3H), 2.15−2.30 (m, 1H), 2.55 (d, J = 14.7 Hz, 1H), 2.63 (dd, J = 4.1, 14.7 Hz, 1H), 2.92 (dd, J = 3.4, 10.9 Hz, 1H), 3.50−3.70 (m, 2H), 4.21 (dd∼t, J = 4.1 Hz, 1H), 6.83−7.15 (m, 5H), 7.56−7.65 (m, 3H); ^{13}C NMR δ 13.6, 18.1, 19.2, 19.4, 21.5, 30.8, 37.6, 38.6, 53.7, 65.2, 70.4, 79.3, 114.7, 123.2, 123.5, 124.0, 124.1, 126.0, 127.0, 127.4 (2C), 128.0, 129.4 (2C), 135.1, 136.0, 143.0, 143.7. **11b** (minor diastereomer): ^{1}H NMR δ 0.70−0.95 (m, 1H), 1.19 (s, 3H), 1.24 (s, 3H), 1.34 (s, 3H), 1.42 (s, 3H), 1.30−1.40 (m, 1H), 2.11 (d, J = 14.3 Hz, 1H), 2.26 (s, 3H), 2.15−2.75 (m, 4H), 3.50−3.70 (m, 2H), 3.98 (dd∼t, J = 5.3 Hz, 1H), 6.83−7.15 (m, 5H), 7.56−7.65 (m, 3H); ^{13}C NMR δ 13.6, 18.3, 19.2, 19.3, 21.5, 30.4, 36.5, 37.7, 53.9, 66.0, 70.2, 78.5, 114.7, 123.1, 123.6, 124.0, 125.1, 126.0, 127.0, 127.4 (2C), 128.0, 129.4 (2C), 135.2, 135.5, 143.0, 143.7; MS (EI) *m*/*z* 463 (30), 352 (100), 299 (10), 271 (8), 196 (45); IR (NaCl) 2922, 1597, 1478, 1458, 1357, 1169, 1091; exact mass *m*/*z* calcd for $C_{28}H_{33}NO_3S$ 463.2181, found 463.2186.

2-[2,3-Dimethyl-9-(toluene-4-sulfonyl)-1,4,9,9a-tetrahydrocarbazol-4a-yl]-4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-carboxylic Acid Methyl Ester (12a). Purification of the residue by flash chromatography (heptanes/EtOAc 9:1) (major diastereomer): ^{1}H NMR δ 0.70−0.92 (m, 1H), 1.02 (s, 3H), 1.10−1.40 (m, 2H), 1.28 (s, 3H), 1.29 (s, 3H), 1.54−1.74 (m, 1H), 1.62 (s, 3H), 2.05 (dd, J = 3.6, 14.7 Hz, 1H), 2.28 (s, 3H), 2.66 (dd, J = 3.6, 14.7 Hz, 1H), 3.60 (s, 3H), 3.70−3.90 (m, 1H), 4.00−4.20 (m, 1H), 4.60 (dd−t, J = 3.6 Hz, 1H), 6.85 (ddd−dt, J = 0.8, 7.5 Hz, 1H), 6.98−7.30 (m, 2H), 7.17 (d, J = 7.9 Hz, 2H), 7.50−7.70 (m, 3H); ^{13}C NMR δ 13.5, 18.5, 19.0, 19.3, 21.5, 33.1, 36.7, 37.2, 51.9, 56.7, 64.0, 66.8, 81.7, 113.6, 121.1, 123.1, 123.2, 126.4, 126.8, 127.1, 127.5 (2C), 128.3, 129.7 (2C), 134.6, 135.6, 143.2, 143.9, 172.4. **12b** (minor diastereomer): ^{1}H NMR δ 0.80−1.40 (m, 8H), 1.21 (s, 3H), 1.50−1.70 (m, 1H), 1.58 (s, 3H), 1.87 (d, J = 14.3 Hz, 1H), 2.10−2.25 (m, 1H), 2.28 (s, 3H), 2.47−2.60 (m, 1H), 3.40−3.55 (m, 1H), 3.58 (s, 3H), 3.70−3.90 (m, 1H), 4.80 (dd−t, J = 3.8 Hz, 1H), 6.80−6.90 (m, 1H), 6.98−7.30 (m, 4H), 7.50−7.70 (m, 3H); ^{13}C NMR δ 13.5, 18.4, 19.2, 19.7, 21.5, 32.7, 37.1, 37.5, 51.7, 56.7, 65.3, 66.9, 82.5, 113.8, 122.1, 122.7, 122.8, 125.5, 126.3, 126.5, 127.5, 127.5 (2C), 129.4 (2C), 133.5, 135.7, 143.5, 144.0, 172.5; MS (EI) *m*/*z* 521 (8), 352 (100), 298 (5), 196 (31), 170 (23); IR (NaCl) 2921, 1734, 1596, 1476, 1458, 1354, 1266, 1167, 1092; exact mass *m*/*z* calcd for $C_{30}H_{33}NO_5S$ 521.2236, found 521.2224.

2-[2,3-Dimethyl-9-(toluene-4-sulfonyl)-1,4,9,9a-tetrahydrocarbazol-4a-yl]-2,3-dihydropyran-4-one (13). Purification of the residue by flash chromatography (heptanes/EtOAc 3:1) (minor diastereomer): ^{1}H NMR δ 1.00−2.62 (m, 9H), 1.44 (s, 3H), 2.28 (s, 3H), 3.32 (dd, J = 2.6, 15.3 Hz, 1H), 4.03−4.07 (m, 1H), 5.15−5.19 (m, 1H), 6.83 (d, J = 8.7 Hz, 1H), 6.81−7.25 (m, 5H), 7.54 (d, J = 8.3 Hz, 2H), 7.83 (d, J = 8.7 Hz, 1H); ^{13}C NMR δ 19.2, 19.3, 21.5, 35.5, 36.1, 37.4, 52.9, 64.8, 82.8, 106.6, 115.3, 124.6, 126.2, 126.7, 126.9 (2C), 129.0, 129.8, 130.9 (2C), 133.3, 134.4, 142.9, 144.8, 163.0, 192.1. (Major diastereomer): ^{1}H NMR δ 1.23 (d, J = 15.4 Hz, 1H), 1.41 (s, 3H), 1.46 (ddd, J = 1.5, 3.0, 15.4 Hz, 1H), 1.65 (s, 3H), 2.03 (d, J = 14.9 Hz, 1H), 2.23 (s, 3H), 2.31 (d, J = 13.6 Hz, 1H), 2.51 (d, J = 14.9 Hz, 1H), 2.58 (dd, J = 4.9, 14.7 Hz, 1H), 3.55 (dd, J = 2.6, 15.4 Hz, 1H), 4.06 (dd (≈t), J = 4.7, 4.7 Hz, 1H), 5.14 (dd, J = 1.1, 5.8 Hz, 1H), 6.86−6.97 (m, 2H), 7.01 (d, J = 5.8 Hz, 1H), 7.10 (d, J = 8.1 Hz, 2H), 7.15 (dd, J = 1.9, 8.3 Hz, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 19.3, 19.4, 21.5, 36.8, 37.4, 37.5, 53.2, 64.6, 83.3, 106.8, 115.7, 124.4 (2C), 126.6, 126.8, 127.2 (2C), 129.1, 129.9 (2C), 134.0, 134.4, 142.9, 145.0, 162.9, 191.7; IR (KBr) ν 2926, 1669, 1589, 1359, 1169 cm^{-1}, MS (EI) *m*/*z* (relative intensity) 449 [M$^{+\bullet}$] (80), 352 (62), 297 (16), 196 (79), 142 (38), 115 (39), 91 (100). Anal. Calcd for $C_{26}H_{27}NO_4S$: C, 69.46; H, 6.05; N, 3.12; S, 7.13. Found: C, 69.37; H, 5.92; N, 3.44; S, 6.98.

2-[1-(Toluene-4-sulfonyl)-1*H*-indol-3-yl]-2,3-dihydropyran-4-one (14). Purification of the residue by flash chromatography (heptanes/EtOAc 7:3): ^{1}H NMR δ 2.28 (s, 3H), 2.76 (dd, J = 3.8, 16.8 Hz, 1H), 2.99 (dd, J = 12.8, 16.8 Hz, 1H), 5.47 (d, J = 6.0 Hz, 1H), 5.64 (dd, J = 3.8, 12.8 Hz, 1H), 7.18 (d, J = 8.3 Hz, 2H), 7.21 (dd∼t, J = 7.9 Hz, 1H), 7.30 (dd, J = 7.9, 8.7 Hz, 1H), 7.38 (d, J = 6.0 Hz, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.54 (s, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.94 (d, J = 8.7 Hz, 1H); ^{13}C NMR δ 21.6, 41.4, 74.6, 107.5, 113.8, 119.3, 120.0, 123.5, 124.0, 125.3, 126.9 (2C), 128.2, 130.0 (2C), 134.9, 135.2, 145.3, 162.8, 191.5; MS (EI) *m*/*z* 367 (72), 297 (100), 212 (22), 184 (28), 142 (96), 115 (54), 91 (48); IR (NaCl, cm^{-1}) 2950, 1681, 1661, 1601, 1192, 1157; exact mass *m*/*z* calcd for $C_{20}H_{17}NO_4S$ 367.0879, found 367.0866.

4-Oxo-2-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-3,4-dihydro-2*H*-pyran-2-carboxylic Acid Methyl Ester (15). Purification of the residue by flash chromatography (heptanes/EtOAc 2:1): ^{1}H NMR δ 2.28 (s, 3H), 3.16 (d, J = 16.6 Hz, 1H), 3.36 (d, J = 16.6 Hz, 1H), 3.66 (s, 3H), 5.39 (d, J = 6.0 Hz, 1H), 7.18 (d, J = 8.7 Hz, 2H), 7.20−7.30 (m, 2H), 7.31 (d, J = 6.0 Hz, 1H), 7.60 (s, 1H), 7.70 (d, J = 8.7 Hz, 2H), 7.68−7.75 (m, 1H), 7.89 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 21.6, 43.2, 53.6, 82.9, 108.0, 113.6, 118.0, 121.4, 123.7, 125.1, 125.3, 127.0 (2C), 127.1, 130.0 (2C), 134.7, 135.2, 145.4, 160.6, 169.0, 189.1; MS (EI) *m*/*z* 425 (68), 366 (100), 355 (59), 296 (73), 200 (36), 155 (25), 91 (40); IR (NaCl, cm^{-1}) 2970, 1752, 1680, 1597, 1447, 1374, 1273, 1190; exact mass (EI) *m*/*z* calcd for $C_{22}H_{19}NO_6S$ 425.0933, found 425.0930.

5-Hydroxy-1-methoxy-5-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]pent-1-en-3-one (16): ^{1}H NMR δ 2.28 (s, 3H), 2.90−3.00 (m, 2H), 3.64 (s, 3H), 3.83 (d, J = 3.0 Hz, 1H), 5.36 (m, 1H), 5.52 (d, J = 12.8 Hz, 1H), 7.14 (d, J = 8.3 Hz, 2H), 7.10−7.20 (m, 1H), 7.24 (dd∼t, J = 7.2 Hz, 1H), 7.48 (s, 1H), 7.50−7.58 (m, 1H), 7.57 (d, J = 12.8 Hz, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.90 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 22.0, 47.3, 58.2, 64.5, 106.2, 114.1, 120.6, 123.2, 123.6, 124.6, 125.2, 127.3 (2C), 129.1, 130.3 (2C), 135.6, 135.8, 145.4, 164.3, 199.6; MS (CI isobutane) *m*/*z* 400 (M + H$^+$), 300; IR (NaCl) 3400, 3000, 1731, 1681, 1596, 1461, 1376, 1183.

2-Methoxy-6-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]tetrahydropyran-4-one (17) (major isomer): ^{1}H NMR δ 2.27 (s, 3H), 2.44−2.80 (m, 3H), 2.56 (dd, J = 8.7, 15.1 Hz, 1H), 3.50 (s, 3H), 4.76 (dd, J = 3.0, 8.7 Hz, 1H), 4.88 (dd, J = 4.1, 9.8 Hz, 1H), 7.17 (d, J = 8.3 Hz, 2H), 7.15−7.20 (m, 1H), 7.28 (dd−t, J = 7.8 Hz, 1H), 7.51 (s, 1H), 7.50−7.58 (m, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.93 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 21.5, 46.2, 47.7, 56.7, 67.2, 101.3, 113.7, 120.0, 121.5, 123.1, 123.3, 125.1, 126.9 (2C), 128.4, 129.9 (2C), 135.0, 135.3, 145.1, 204.4. (Minor isomer): ^{1}H NMR δ 2.27 (s, 3H), 2.44−2.80 (m, 4H), 3.38 (s, 3H), 5.18 (d, J = 3.4 Hz, 1H), 5.28 (dd, J = 4.7, 9.8 Hz, 1H), 7.17 (d, J = 8.3 Hz, 2H), 7.15−7.20 (m, 1H), 7.28 (dd−t, J = 7.8 Hz, 1H), 7.51 (s, 1H), 7.50−7.58 (m, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.93 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 21.5, 46.6, 47.2, 55.4, 64.5, 99.8, 113.8, 120.0, 121.8, 122.8, 123.3, 125.1, 126.9 (2C), 128.3, 129.9 (2C), 135.0, 135.3, 145.1, 203.6; MS (EI) *m*/*z* 399 (38), 367 (37), 297 (12), 212 (38), 184 (100); exact mass (CI isobutane) *m*/*z* calcd for $C_{21}H_{21}NO_5S$ 399.1141, found 399.1130.

2-[1-(Toluene-4-sulfonyl)-1*H*-indol-2-yl]-2,3-dihydropyran-4-one (19). Purification of the residue by flash chromatography (heptanes/EtOAc 7:3): ^{1}H NMR δ 2.25 (s, 3H), 2.89 (dd, J = 6.4, 17.0 Hz, 1H), 2.97 (dd, J = 9.4, 17.0 Hz, 1H), 5.46 (d, J = 6.0 Hz, 1H), 6.25 (dd, J = 6.4, 9.4 Hz, 1H), 6.74 (s, 1H), 7.12 (d, J = 8.1 Hz, 2H), 7.18 (m, 1H), 7.24 (d, J = 6.0 Hz, 1H), 7.29 (m, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.62 (d, J = 8.1 Hz, 2H), 8.08 (d, J = 8.7 Hz, 1H); ^{13}C NMR δ 21.5, 41.4, 73.4, 107.6, 111.7, 114.9, 212.5, 124.0, 125.8, 126.5 (2C), 128.4, 129.7 (2C), 135.5, 136.4, 137.3, 145.1, 162.1, 191.4; MS (EI) *m*/*z* 367 (54), 233 (34), 232 (29), 212 (39), 184 (32), 142

(44), 91 (100); IR (NaCl) 2359, 1676, 1594, 1369, 1149; exact mass (EI) *m*/*z* calcd for $C_{20}H_{17}NO_4S$ 367.0879, found 367.0862.

***N*,*N*-Diethyl-2-[4-methoxy-2-oxo-9-(toluene-4-sulfonyl)-1,2,3,4,9,9a-hexahydrocarbazol-4a-yl]-2-oxoacetamide (20).** Purification of the residue by flash chromatography (heptanes/EtOAc 2:1) **20a** (major diastereomer): ^{1}H NMR δ 0.69 (t, J = 7.2 Hz, 3H), 1.04 (t, J = 7.2 Hz, 3H), 2.14−2.60 (m, 2H), 2.23 (dd, J = 8.3, 18.3 Hz, 1H), 2.28 (s, 3H), 2.48 (dd, J = 3.4, 18.3 Hz, 1H), 2.57−3.48 (m, 2H), 2.85 (dd, J = 6.4, 16.4 Hz, 1H), 3.07 (dd, J = 6.0, 16.4 Hz, 1H), 3.19 (s, 3H), 4.81 (dd, J = 3.4, 8.3 Hz, 1H), 5.20 (dd, J = 6.0, 6.4 Hz, 1H), 6.97 (m, 1H), 7.12 (d, J = 7.9 Hz, 2H), 7.16−7.30 (m, 2H), 7.53−7.64 (m, 3H); ^{13}C NMR δ 11.4, 12.3, 20.5, 38.0, 38.6, 40.5, 43.6, 56.3, 60.4, 63.7, 76.0, 114.7, 123.6, 125.9, 126.5, 126.9 (2C), 128.6 (2C), 129.1, 133.1, 141.5, 143.3, 164.3, 196.5, 204.7; MS (EI) *m*/*z* 399 (3), 344 (7), 284 (16), 242 (29), 184 (37), 156 (28), 138 (19), 100 (100). Anal. Calcd for $C_{26}H_{30}N_2O_6S$: C, 62.63; H, 6.06; N, 5.62; S, 6.43. Found: C, 62.58; H, 6.21; N, 5.41; S, 6.44. **20b** (minor diastereomer): ^{1}H NMR δ 0.61 (t, J = 7.2 Hz, 3H), 1.05 (t, J = 7.2 Hz, 3H), 1.88 (dd, J = 2.3, 18.5 Hz, 1H), 2.05−2.42 (m, 2H), 2.28 (s, 3H), 2.56 (dd, J = 3.0, 18.5, 1H), 3.01 (dd, J = 5.6, 17.0 Hz, 1H), 3.08−3.43 (m, 2H), 3.21 (dd, J = 2.3, 17.0 Hz, 1H), 3.25 (s, 3H), 4.67 (dd, J = 2.3, 3.0 Hz, 1H), 5.41 (dd, J = 2.3, 5.6 Hz, 1H), 6.95 (m, 1H), 7.11 (d, J = 7.9 Hz, 2H), 7.43 (m, 1H), 7.59 (m, 1H), 7.66 (d, J = 7.9 Hz, 2H), 7.68 (m, 1H); ^{13}C NMR δ 11.3, 12.3, 20.6, 36.4, 38.1, 40.4, 43.2, 55.7, 60.4, 62.9, 79.4, 115.1, 123.6, 125.2, 126.5, 126.9 (2C), 128.6 (2C), 129.6, 132.8, 141.1, 143.3, 164.1, 193.9, 205.6; MS (DCI, *iso*butane) *m*/*z* 499 (39), 345 (100), 157 (56); exact mass (DCI, isobutane) *m*/*z* calcd for $C_{26}H_{30}N_2O_6S$ 499.1903, found 499.1907.

General Procedure for the Synthesis of the Indole-3-glyoxamide. To a stirred and cooled solution of indole in dry ether under argon was added oxalyl chloride (1.1−1.25 equiv) dropwise. After 30−60 min at 0 °C, the reaction mixture was evaporated under reduced pressure, and dry ether (5−10 mL) was added to the residue and evaporated twice in order to remove the excess oxalyl chloride. Then, to a cooled solution of the crude product in dry ether (10−20 mL) was added the amine (2.0 equiv), and the mixture was stirred overnight at room temperature under argon. A saturated aqueous solution of $NaHCO_3$ was added, and the solution was extracted with CH_2Cl_2. After drying over $MgSO_4$, the solvent was evaporated under vacuum.

2-(1*H*-Indol-3-yl)-2-oxo-*N*-(1-phenylethyl)acetamide (22d). Purification by flash chromatography (heptanes/EtOAc 2:1) (83%, mp 213 °C).[26]

2-(1*H*-Indol-3-yl)-*N*-(1-naphthalen-1-ylethyl)-2-oxoacetamide (22e). Purification by flash chromatography and elution with heptanes/EtOAc (7:3 first, then 1:1) (69%, mp 189 °C).[27]

***N*-Ethyl-2-(1*H*-indol-3-yl)-2-oxoacetamide (22f).** Oxalyl chloride (0.52 mL, 6 mmol) was added dropwise to a solution of indole **21** (588 mg, 5 mmol) in dry ether (10 mL) at 0 °C. The mixture was stirred for 30 min and evaporated under reduced pressure; the residue was washed twice with ether (2 × 10 mL). To a slurry of the crude product in ether (10 mL) were sequentially added $EtNH_2$·HCl (652 mg, 8 mmol) and (i-Pr)$_2$EtN (1.40 mL, 8 mmol) at 0 °C. Stirring was continued overnight at room temperature. The resultant mixture was poured into water (10 mL) and extracted three times with dichloromethane (3 × 10 mL). The combined organic phases were dried and evaporated to give a crude product, isolated as a yellow solid (1023 mg, 95%), and used without purification in the next step.[28]

***N*-(1-Cyclohexylethyl)-2-(1*H*-indol-3-yl)-2-oxoacetamide (22h).** Prepared according to the general procedure using indole (588 mg, 5 mmol), oxalyl chloride (515 μL, 6 mmol), and 1(*R*)-cyclohexylethylamine (1490 μL, 10 mmol). The reaction mixture was stirred overnight at rt. After concentration of the crude mixture, the residue was dissolved in hot EtOAc and filtered through silica to give **22h** as a pale yellow solid (1298 mg, 87%, mp 192 °C): $[\alpha]^{25}_D = -21.0$ (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 0.99−1.77 (m, 11H), 1.20 (d, J = 6.8 Hz, 3H), 3.84−3.97 (m, 1H), 7.28−7.47 (m, 4H), 8.43 (d, j = 7.2 Hz, 1H), 9.10 (d, J = 3.0 Hz, 1H), 9.26 (bs, 1H); ^{13}C NMR δ 17.8, 26.1 (2C), 26.3, 28.9, 29.2, 43.1, 49.7, 111.6, 113.4, 122.4, 123.4, 124.1, 126.7, 135.7, 138.3, 161.7, 181.0; IR (KBr) ν 3333, 3273, 1654, 1602, 1232 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 299 [M$^{+\bullet}$] (2), 144 (100), 116 (9), 89 (9). Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.18; H, 7.44; N, 9.13; S, 6.78.

2-[4-Methoxy-2-oxo-9-(toluene-4-sulfonyl)-1,2,3,4,9,9a-hexahydrocarbazol-4a-yl]-*N*-methyl-2-oxo-*N*-(1-phenylethyl)acetamide (23).[29] Purification of the residue by flash chromatography (cyclohexane/EtOAc 7:3) (two diastereomers, 1:1): ^{1}H NMR δ 1.25 and 1.40 (d, J = 7.0 Hz, 3H), 2.04 and 2.20 (s, 3H), 2.31−2.45 (m, 1H), 2.36 (s, 3H), 2.54 and 2.69 (dd, J = 3.4, 18.3 Hz and 4.9, 18.1 Hz, 1H), 3.00−3.33 and 5.74 (m and q, J = 7.0 Hz, 3H), 3.25 and 3.29 (s, 3H), 4.94 and 5.26 (dd, J = 3.4, 7.5 Hz and 2.3, 4.9 Hz, 1H), 5.27−5.35 (m, 1H), 6.07 (d, J = 7.1 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 6.95−7.35 (m, 7H), 7.37−7.51 (m, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.69 and 7.82 (d, J = 7.9 Hz, 1H); ^{13}C NMR δ 14.9 and 15.8, 21.3 and 21.4, 26.9 and 27.9, 39.4 and 39.6, 44.4 and 44.8, 50.2 and 55.5, 57.4 and 57.9, 60.0 and 60.9, 64.9 and 66.3, 77.9, 115.8 and 116.0, 124.3 and 124.6, 126.4 and 126.6, 127.1, 127.2 and 127.3, 127.5 and 127.7, 127.6, 127.8 and 127.9, 128.2, 128.6, 129.6, 130.0 and 130.2, 134.1, 137.2 and 138.3, 142.6 and 143.8, 144.4, 165.3 and 165.9, 197.7 and 198.1, 205.5 and 205.8; IR (KBr) ν 3395, 1724, 1636, 1597, 1165 cm^{-1}; MS (CI) *m*/*z* (relative intensity) 561 [MH$^+$] (91), 405 (100), 357 (51), 185 (45), 157 (52), 105 (82). Anal. Calcd for $C_{31}H_{32}N_2O_6S$: C, 66.41; H, 5.75; N, 5.00; S, 5.72. Found: C, 66.35; H, 5.71; N, 5.11; S, 5.66.

***N*-(1-Cyclohexylethyl)-2-[4-methoxy-2-oxo-9-(toluene-4-sulfonyl)-1,2,3,4,9,9a-hexahydrocarbazol-4a-yl]-*N*-methyl-2-oxoacetamide (24).** Purification of the residue by flash chromatography (cyclohexane/EtOAc 4:1) (major diastereomer): ^{1}H NMR δ 0.78−1.72 (m, 11H), 0.99 (d, J = 6.8 Hz, 3H), 1.88 (s, 3H), 2.30−2.38 (m, 1H), 2.32 (s, 3H), 2.49−2.57 (m, 1H), 3.01 (dd, J = 6.4, 16.2 Hz, 1H), 3.11 (dd, J = 6.4, 16.2 Hz, 1H), 3.26 (s, 3H), 4.14−4.24 (m, 1H), 4.88 (dd, J = 3.4, 7.9 Hz, 1H), 5.33 (dd ≈ t, J = 6.4, 6.4 Hz, 1H), 7.05 (dd ≈ t, J = 7.5, 7.5 Hz, 1H), 7.17 (d, J = 8.3 Hz, 2H), 7.20−7.36 (m, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.69 (m ≈ d, 2H); ^{13}C NMR δ 15.1, 21.4, 25.7, 25.8, 26.0, 27.6, 29.2, 29.7, 39.5, 39.8, 44.5, 52.7, 57.3, 61.0, 64.8, 76.5, 115.9, 124.4, 126.9, 127.5, 127.6 (2C), 129.5 (2C), 130.1, 134.0, 142.5, 144.3, 166.2, 197.8, 205.7; IR (NaCl) ν 2925, 1718, 1630, 1597, 1356, 1168 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 566 [M$^{+\bullet}$] (3), 411 (50), 298 (38), 284 (45), 220 (48), 184 (52), 155 (50), 111 (55), 91 (100); HRMS calcd for $C_{31}H_{38}N_2O_6S$ (M$^{+\bullet}$) 566.2451, found 566.2445.

4-Oxo-2-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-3,4-dihydro-2*H*-pyran-2-carboxylic Acid (1-Phenylethyl)amide (25). Purification of the residue by flash chromatography (heptanes/EtOAc 1:1) (major diastereomer): ^{1}H NMR δ 1.46 (d, J = 6.8 Hz, 3H), 2.25 (s, 3H), 3.17 (d, J = 17.0 Hz, 1H), 3.25 (d, J = 17.0 Hz, 1H), 5.00−5.10 (m, 1H), 5.40 (d, J = 6.0 Hz, 1H), 6.68 (d, J = 7.9 Hz, 1H), 7.01−7.25 (m, 10H), 7.39 (d, J = 7.9 Hz, 1H), 7.53 (s, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.86 (d, J = 8.7 Hz, 1H); ^{13}C NMR δ 21.2, 21.5, 43.1, 49.1, 84.0, 108.5, 113.6, 118.3, 120.9, 123.5, 125.2, 125.8, 126.0 (2C), 126.8 (2C), 127.0, 127.5, 128.6 (2C), 129.9 (2C), 134.5, 135.2, 141.9, 145.3, 158.7, 167.5, 189.7; IR (KBr) ν 3413, 1732, 1670, 1372, 1175 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 514 [M$^{+\bullet}$] (7), 393 (17), 366 (90), 296 (12), 212 (57), 155 (29), 91 (100); HRMS calcd

(26) Primafiore, G.; Da Settimo, F.; Taliani, S.; Morini, A. M.; Novellino, E.; Greco, G.; Lovecchia, A.; Besnard, F.; Trincavelli, L.; Costoc, B.; Martini, C. *J. Med. Chem.* **2001**, *44*, 2286−2297.

(27) Kawate, T.; Yamonaka, M.; Nagawa, M. *Heterocycles* **1999**, *50*, 1033−1039.

(28) (a) Brimblecombe, R. W.; Downing, D. F.; Green, D. M.; Hunt, R. R. *Brit. J. Pharmacol.* **1964**, *23*, 43−54. (b) Alemany, A.; Fernandy Alvarey, E.; Nieto Lopez, O.; Rubio Herraey, M. E. *Bull. Soc. Chim. Fr.* **1974**, *12*, 2883−2888.

for $C_{29}H_{26}N_2O_5S$ [$M^{+\bullet}$] 514.1563, found 514.1558. (Minor diastereomer): ^{1}H NMR δ 1.35 (d, J = 6.8 Hz, 3H), 2.26 (s, 3H), 3.12 (d, J = 17.0 Hz, 1H), 3.20 (d, J = 17.0 Hz, 1H), 4.98−5.08 (m, 1H), 5.34 (d, J = 6.4 Hz, 1H), 6.74 (d, J = 7.9 Hz, 1H), 7.12−7.29 (m, 10H), 7.59 (s, 1H), 7.59−7.61 (m, 1H), 7.66 (d, J = 8.3 Hz, 2H), 7.89 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 21.2, 21.5, 43.2, 49.1, 84.1, 108.6, 113.8, 118.4, 120.9, 123.7, 125.3, 125.9, 126.0 (2C), 126.9 (2C), 127.2, 127.7, 128.8 (2C), 130.0 (2C), 134.6, 135.4, 142.1, 145.3, 158.6, 167.4, 189.5; IR (KBr) ν 3413, 1732, 1670, 1372, 1175 cm^{-1}; MS (EI) m/z (relative intensity) 514 [$M^{+\bullet}$] (3), 393 (9), 366 (50), 296 (6), 212 (35), 155 (24), 91 (100); HRMS calcd for $C_{29}H_{26}N_2O_5S$ [$M^{+\bullet}$] 514.1563, found 514.1553.

4-Oxo-2-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-3,4-dihydro-2*H*-pyran-2-carboxylic Acid (1-Naphthalen-1-ylethyl)amide (26). Purification of the residue by flash chromatography (cyclohexane/EtOAc 2:1) (major diastereomer): ^{1}H NMR δ 1.71 (d, J = 6.8 Hz, 3H), 2.31 (s, 3H), 3.24 (d, J = 17.0 Hz, 1H), 3.37 (d, J = 17.0 Hz, 1H), 5.45 (d, J = 6.0 Hz, 1H), 5.83−5.92 (m, 1H), 6.73 (d, J = 8.3 Hz, 1H), 6.94−7.05 (m, 2H), 7.14 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 6.0 Hz, 1H), 7.23−7.29 (m, 1H), 7.32−7.43 (m, 4H), 7.59 (s, 1H), 7.61 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.3 Hz, 1H), 7.76−7.82 (m, 2H), 7.90 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 20.0, 21.6, 43.3, 45.1, 81.2, 108.7, 113.6, 118.3, 121.1, 122.6, 122.9, 123.5, 124.9, 125.1, 125.8, 126.0, 126.6, 126.8 (2C), 127.0, 128.6, 128.7, 129.9 (2C), 130.9, 133.7, 134.6, 135.2, 136.7, 145.2, 158.5, 167.2, 189.5. (Minor diastereomer): ^{1}H NMR δ 1.61 (d, J = 6.8 Hz, 3H), 2.35 (s, 3H), 3.20 (d, J = 16.6 Hz, 1H), 3.27 (d, J = 16.6 Hz, 1H), 5.34 (d, J = 6.2 Hz, 1H), 5.86−5.96 (m, 1H), 6.72 (d, J = 8.3 Hz, 1H), 7.01 (d, J = 6.2 Hz, 1H), 7.22−7.37 (m, 4H), 7.43−7.56 (m, 4H), 7.66 (s, 1H), 7.67 (d, J = 6.8 Hz, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.84 (d, J = 7.5 Hz, 1H), 7.87−7.91 (m, 1H), 7.98 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 19.9, 21.6, 43.4, 45.0, 84.1, 108.6, 113.9, 118.5, 120.8, 122.7, 123.2, 123.6, 125.1, 125.3, 125.7, 126.1, 126.8, 127.0 (2C), 127.2, 128.8, 128.9, 130.0 (2C), 131.0, 133.9, 134.7, 135.4, 137.0, 145.3, 158.5, 167.2, 189.4; IR (NaCl) ν 3367, 2922, 1675, 1598, 1174 cm^{-1}; MS (EI) m/z (relative intensity) 564 [$M^{+\bullet}$] (5), 393 (37), 366 (33), 296 (27), 210 (28), 155 (95), 140 (50), 129 (42), 91 (100); HRMS calcd for $C_{33}H_{28}N_2O_5S$ ($M^{+\bullet}$) 564.1719, found 564.1704.

4-Oxo-2-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-3,4-dihydro-2*H*-pyran-2-carboxylic Acid Ethylamide (27). Purification of the residue by flash chromatography (cyclohexane/EtOAc 9:11): ^{1}H NMR δ 1.05 (t, J = 7.2 Hz, 3H), 2.26 (s, 3H), 3.15−3.33 (m, 4H), 5.37 (d, J = 6.2 Hz, 1H), 6.9 (bs, 1H), 7.16 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 6.2 Hz, 1H), 7.15−7.30 (m, 2H), 7.63 (s, 1H), 7.63−7.66 (m, 1H), 7.69 (d, J = 8.7 Hz, 2H), 7.90 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 14.4, 21.3, 34.6, 43.2, 83.9, 108.2, 113.5, 118.6, 120.9, 123.5, 125.1, 125.6, 126.7 (2C), 127.1, 129.9 (2C), 134.3, 135.1, 145.3, 158.9, 168.0, 189.7; IR (KBr) ν 3350, 1683, 1602, 1271, 1173 cm^{-1}; MS (EI) m/z (relative intensity) 438 [$M^{+\bullet}$] (17), 366 (100), 296 (78), 212 (28), 155 (26), 91 (34); HRMS calcd for $C_{23}H_{22}N_2O_5S$ ($M^{+\bullet}$) 438.1249, found 438.1248.

4-Oxo-2-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-3,4-dihydro-2*H*-pyran-2-carboxylic Acid (1-Cyclohexylethyl)amide (28). Purification of the residue by flash chromatography (cyclohexane/EtOAc 7:3) (major diastereomer): ^{1}H NMR δ 0.68−1.70 (m, 11H), 1.09 (d, J = 6.8 Hz, 3H), 2.33 (s, 3H), 3.21 (d, J = 16.8 Hz, 1H), 3.32 (d, J = 16.8 Hz, 1H), 3.77−3.90 (m, 1H), 5.44 (d, J = 6.0 Hz, 1H), 6.32 (d, J = 8.7 Hz, 1H), 7.19−7.35 (m, 2H), 7.22 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 6.0 Hz, 1H), 7.63−7.67 (m, 1H), 7.66 (s, 1H), 7.73 (d, J = 8.1 Hz, 2H), 7.95 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 17.6, 21.4, 25.7 (2C), 26.0, 28.5, 28.8, 42.7, 43.2, 49.8, 84.2, 108.5, 113.7, 118.7, 120.9, 123.5, 125.2, 125.7, 126.8 (2C), 127.0, 129.9 (2C), 134.5, 135.2, 145.2, 158.6, 167.3, 189.7; IR (KBr) ν 3422, 1684, 1604, 1265, 1176 cm^{-1}; MS (EI) m/z (relative intensity) 520 [$M^{+\bullet}$] (11), 366 (95), 296 (58), 212 (100), 155 (40), 91 (85); HRMS calcd for $C_{29}H_{32}N_2O_5S$ [$M^{+\bullet}$] 520.2032, found 520.2015. (Minor diastereomer): ^{1}H NMR δ 0.82−1.75 (m, 11H), 1.01 (d, J = 6.8 Hz, 3H), 2.34 (s, 3H), 3.20 (d, J = 17.0 Hz, 1H), 3.33 (d, J = 17.0 Hz, 1H), 3.77−3.90 (m, 1H), 5.47 (d, J = 6.2 Hz, 1H), 6.30 (d, J = 9.0 Hz, 1H), 7.20−7.35 (m, 2H), 7.23 (d, J = 7.9 Hz, 2H), 7.28 (d, J = 6.2 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.64 (s, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.96 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 17.8, 21.5, 26.0 (2C), 26.2, 28.8, 29.1, 42.9, 43.4, 49.9, 84.3, 108.6, 113.8, 118.7, 120.9, 123.6, 125.3, 125.7, 126.9 (2C), 127.2, 130.0 (2C), 134.6, 135.3, 145.3, 158.8, 167.4, 189.6; IR (KBr) ν 3420, 1684, 1375, 1265, 1176 cm^{-1}; MS (EI) m/z (relative intensity) 520 [$M^{+\bullet}$] (15), 452 (12), 366 (23), 312 (15), 212 (20), 158 (100), 91 (29); HRMS calcd for $C_{29}H_{32}N_2O_5S$ [$M^{+\bullet}$] 520.2032, found 520.2040.

2-[4-Methoxy-2-oxo-9-(toluene-4-sulfonyl)-1,2,3,4,9,9a-hexahydrocarbazol-4a-yl]-4-oxo-3,4-dihydro-2*H*-pyran-2-carboxylic Acid (1-Phenylethyl)amide (29).[29] Purification of the residue by flash chromatography (cyclohexane/EtOAc 3:2) (two diastereomers, 1:1): ^{1}H NMR δ 1.53 (d, J = 6.8 Hz, 3H), 2.29 and 2.33 (s, 3H), 2.30−2.54 (m, 3H), 2.78 (ddd, J = 1.7, 5.3, 15.1 Hz, 1H), 2.93−3.03 (m, 2H), 3.27 and 3.35 (s, 3H), 4.01−4.16 (m, 2H), 5.06−5.17 (m, 1H), 5.47 (d, J = 6.4 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 7.08−7.32 (m, 9H), 7.46 (d, J = 7.9 Hz, 1H), 7.60 (bs, 1H), 7.69 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 8.7 Hz, 1H); ^{13}C NMR δ 21.2, 21.5, 30.0, 43.0, 43.2, 44.3, 49.0, 56.4, 56.7, 58.1, 74.9, 76.8, 84.1, 108.6, 113.7, 118.4, 120.9, 123.5, 125.2, 125.8, 126.0 (2C), 126.9 (2C), 127.1, 127.5, 128.6 (2C), 129.9 (2C), 134.6, 135.3, 141.9, 145.2, 158.5, 167.3, 189.5, 206.1, 207.7; IR (NaCl) ν 3364, 2929, 1715, 1681, 1600, 1172 cm^{-1}; MS (EI) m/z (relative intensity) 514 [$M^{+\bullet} - C_5H_8O_2$] (8), 393 (19), 366 (95), 212 (43), 155 (22), 91 (100). Anal. Calcd for $C_{34}H_{34}N_2O_7S$: C, 66.43; H, 5.58; N, 4.56; S, 5.22. Found: C, 66.37; H, 5.94; N, 4.55; S, 5.26.

2-[4-Methoxy-2-oxo-9-(toluene-4-sulfonyl)-1,2,3,4,9,9a-hexahydrocarbazol-4a-yl]-4-oxo-3,4-dihydro-2*H*-pyran-2-carboxylic Acid (1-Naphthylethyl)amide (30).[29] Purification of the residue by flash chromatography (cyclohexane/EtOAc 2:1) (two diastereomers): ^{1}H NMR δ 1.71 (d, J = 6.8 Hz, 3H), 2.29 and 2.33 (s, 3H), 2.30−2.54 (m, 3H), 2.78 (ddd, J = 1.5, 5.1, 14.9 Hz, 1H), 2.95−3.03 (m, 2H), 3.27 and 3.35 (s, 3H), 4.01−4.14 (m, 2H), 5.45 (d, J = 6.0 Hz, 1H), 5.79−5.97 (m, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.94−7.63 (m, 7H), 7.14 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 6.0 Hz, 1H), 7.61 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.7 Hz, 1H), 7.76−7.82 (m, 2H), 7.90 (d, J = 8.7 Hz, 1H); ^{13}C NMR δ 20.0, 21.5, 30.0, 43.1, 43.4, 44.4, 45.1, 56.4, 56.8, 58.2, 75.0, 76.9, 84.2, 108.7, 113.6, 118.3, 121.1, 122.6, 122.9, 123.5, 124.9, 125.1, 125.8, 126.0, 126.6, 126.8 (2C), 127.0, 127.5, 128.6, 128.7, 129.9 (2C), 130.9, 133.7, 134.6, 135.2, 136.8, 145.2, 158.5, 167.2, 189.4, 206.2, 207.7; IR (NaCl) ν 3368, 2925, 1719, 1690, 1598, 1175 cm^{-1}.

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Supporting Information Available: ^{1}H NMR spectra of compounds **9**, **12**, **16**, **20a**, **22d**, **23,** and **26** and ^{13}C NMR spectra of compounds **1d**, **9**, **10**, **12**, **14**, **16**, **17**, **19**, **26,** and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) This compound was isolated as a 1:1 mixture of diastereomers; hence, no assignment of the ^{13}C NMR signals is reported.