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Preparation of Novel Unsymmetrical Bisindoles under Solvent-Free Conditions: Synthesis, Crystal Structures, and Mechanistic Aspects

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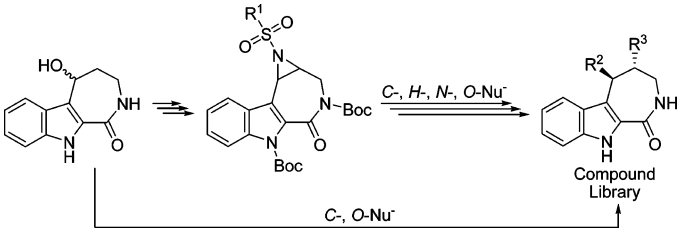

Indole aziridines and their hydroxyl derivatives have been used for the preparation of a small library of novel functionalized bisindoles. Diversification of these building blocks by solvent-free C−C-bond formation on solid support yielded annulated Hymenialdisine analogues under mild reaction conditions. Indoles as *C*-nucleophiles form potentially pharmacologically active bisindoles through an electrophilic aromatic substitution pathway in good to excellent yields. Further transformations of the indole aziridines with *H*-, *N*-, and *O*-nucleophiles demonstrate their versatility as key intermediates in diversity oriented synthesis. The hydroxyl precursor leads also to unsymmetrical bisindoles under similar reaction conditions. Important intermediates and final library compounds were confirmed by X-ray analysis. Theoretical studies on these systems show the possible cationic intermediate in the substitution pathway.

Introduction

Aziridines are versatile and highly valuable intermediates in organic synthesis.[1] In addition, natural products containing an aziridine moiety are known; some of them like Mitomycin A and B exhibit interesting biological activity.[2] Probably most importantly, aziridines serve as building blocks in drug research, such as in the development of neuramidase inhibitors[3] and calcium sensing receptor ligands,[4] and allow a straightforward preparation of diversified compound libraries. Thus, during the last decades significant attention has been paid to the racemic and stereoselective preparation of these nitrogen-containing three-membered-ring systems.[5] *N*-Arylsulfonylaziridines are especially important since they react smoothly with *C*-,[6] *O*-,[7] *S*-,[8] *N*-,[9] halogen-,[10] and hydrogen-nucleophiles[11] in the presence of Brønstedt bases, Brønstedt acids, or Lewis acids.[12]

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(1) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A., Ed.; Wiley-VCH: Weinheim, Germany, 2006.

(2) For an overview, see: Lowden, P. A. S. Aziridine Natural Products−Discovery, Biological Acitvity and Biosynthesis. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A., Ed.; Wiley-VCH: Weinheim, Germany, 2006; pp 399−442.

(3) (a) Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681−690. (b) Kim, C. U.; Lew, W.; Williams, M. A.; Wu, H.; Zhang, L.; Chen, X.; Escarpe, P. A.; Mendel, D. B.; Laver, W. G.; Stevens, R. C. *J. Med. Chem.* **1998**, *41*, 2451−2460.

(4) Kessler, A.; Faure, H.; Petrel, C.; Rognan, D.; Césario, M.; Ruat, M.; Dauban, P.; Dodd, R. H. *J. Med. Chem.* **2006**, *49*, 5119−5128.

(5) (a) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905−2920. (b) Tanner, D. *Angew. Chem., Int. Ed.* **1994**, *33*, 599−619. (c) Osborn, H. M. I.; Sweeney, J. *Tetrahedron*: *Asymmetry* **1997**, *8*, 1693−1715.

(6) For recent publications in this area see: (a) Beresford, K. J. M.; Church, N. J.; Young, D. W. *Org. Biomol. Chem.* **2006**, *4*, 2888−2897. (b) Pineschi, M.; Bertolini, F.; Crotti, P.; Macchia, F. *Org. Lett.* **2006**, *8*, 2627−2630. (c) Pattenden, L. C.; Wybrow, R. A. J.; Smith, S. A.; Harrity, J. P. A. *Org. Lett.* **2006**, *8*, 3089−3091. (d) Minakata, S.; Hotta, T.; Oderaotoshi, Y.; Komatsu, M. *J. Org. Chem.* **2006**, *71*, 7471−7472.

(7) For recent publications in this area see: (a) Sun, X.; Ye, S.; Wu, J. *Eur. J. Org. Chem.* **2006**, 4787−4790. (b) Das, B.; Reddy, V. S.; Tehseen, F. *Tetrahedron Lett.* **2006**, *47*, 6865−6868. (c) Xichun, F.; Guofu, Q.; Shucai, L.; Hanbing, T.; Lamei, W.; Xianming, H. *Tetrahedron*: *Asymmetry* **2006**, *17*, 1394−1401.

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In general, aziridines are prepared either via traditional cyclization reactions of 1,2-aminoalcohols, 1,2-aminohalides, or 1,2-azidoalcohols or via catalytic carbene- or nitrene-transfer methods to double bonds (C═N or C═C). Unfortunately, most catalytic aziridinations of olefins require a large excess of olefin, and need metal catalysts based on copper, rhodium, ruthenium, iron, cobalt, manganese, silver, or gold.[13] Also, electrochemical nitrene transfer methods were introduced.[14] Notably, these protocols were transferred to easily manageable protocols with phenyliodo(III) diacetate as an oxidant later on.[15] In addition, Sharpless and co-workers introduced the bromine-catalyzed aziridination procedure that does not necessarily require an excess of alkene.[16]

Kinase inhibitors are involved in fundamental regulatory cellular functions such as gene expression, cellular proliferation, differentiation, membrane transport, and apoptosis.[17] As one of the first kinase inhibitors, the bisindole Staurosporine (**1**) was found to be active in nanomolar concentration in the 1980s.[18] Besides, some other small molecules also act as kinase inhibitors as well.[19] Among them natural products like Hymenialdisine (HMD) (**2**) and its annulated derivatives **3** showed very promising kinase inhibiting properties[20] and prevent the production of cytokines (Figure 1).[21]

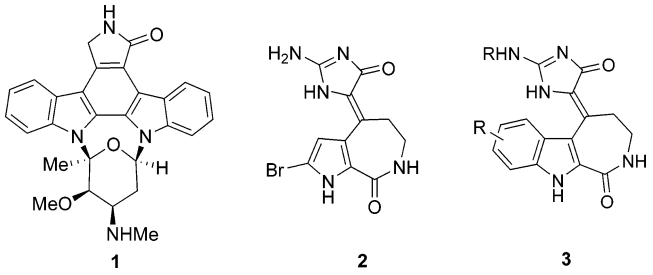


FIGURE 1. Structures of Staurosporine (**1**), Hymenialdisine (HMD) (**2**), and HMD analogues **3**.

On the basis of our experience with the application of catalytic reactions for the synthesis of new pharmacologically interesting compounds[22] and our background in catalytic oxidation methods,[23] we have been interested in the synthesis of potentially bioactive bisindoles as kinase inhibitors employing catalytic aziridination and epoxidation for diversity oriented synthesis[24] on complex organic natural product analogues. The prior work of Gray and co-workers[20c] showed that the kinase inhibiting activities of annulated HMDs (**3**) vary a great deal, if other heterocycles instead of imidazole are introduced. Therefore we focused on the introduction of different indoles onto the structure of annulated HMDs (**3**) to form new unsymmetrical bisindoles. Here, we report the detailed studies of a solvent-free, efficient, and easy to handle diversification strategy for annulated HMD-type bisindoles via C−C bond formation reaction on activated silica under mild reaction conditions, in which aziridines and hydroxyl compounds were used as the starting materials.

Results and Discussion

Several strategies for the synthesis of the pyrrolo[2,3-*c*]-azepine motif of HMD and the annulated derivatives have been published. The first total synthesis of HMD (**2**) was developed by Annoura.[25] Later Horne introduced another synthetic pathway[26] and Papeo developed a new total synthesis recently.[27]

(8) For recent publications in this area see: (a) Krishnaveni, N. S.; Surendra, K.; Rao, K. R. *Adv. Synth. Catal.* **2006**, *348*, 696−700. (b) Wu, J.; Sun, X.; Sun, W. *Org. Biomol. Chem.* **2006**, *4*, 4231−4235. (c) Kamal, A.; Reddy, D. R.; Rajendar *Tetrahedron Lett.* **2006**, *47*, 2261−2264. (d) Wu, J.; Sun, X.; Li, Y. *Eur. J. Org. Chem.* **2005**, 4271−4275.

(9) For recent publications in this area see: (a) Kessler, A.; Faure, H.; Petrel, C.; Rognan, D.; Césario, M.; Ruat, M.; Dauban, P.; Dodd, R. H. *J. Med. Chem.* **2006**, *49*, 5119−5128. (b) Markov, V. I.; Polyakov, E. V. *ARKIVOC* **2005**, *8*, 89−98. (c) Rinaudo, G.; Narizuka, S.; Askari, N.; Crousse, B.; Bonnet-Delpon, D. *Tetrahedron Lett.* **2006**, *47*, 2065−2068.

(10) For recent publications in this area see: (a) Ding, C.-H.; Dai, L.-X.; Hou, X.-L. *Synlett* **2004**, 2218−2220. (b) Ghorai, M. K.; Das, K.; Kumar, A.; Ghosh, K. *Tetrahedron Lett.* **2005**, *46*, 4103−4106. (c) Das, B.; Krishnaiah, M.; Venkateswarlu, K. *Tetrahedron Lett.* **2006**, *47*, 4457−4460. (d) Hanessian, S.; Del Valle, J. R.; Xue, Y.; Blomberg, N. *J. Am. Chem. Soc.* **2006**, *128*, 10491−10495.

(11) (a) Pak, C. S.; Kim, T. H.; Ha, S. J. *J. Org. Chem.* **1998**, *63*, 10006−10010. (b) Chandrasekhar, S.; Ahmed, M. *Tetrahedron Lett.* **1999**, *40*, 9325−9327. (c) Molander, G. A.; Stengel, P. J. *Tetrahedron* **1997**, *53*, 8887−8912.

(12) For reviews, see: (a) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701−2743. (b) Stamm, H. J. *Prakt. Chem.* **1999**, *341*, 319−331. (c) Pineschi, M. *Eur. J. Org. Chem.* **2006**, 4979−4988.

(13) (a) For an overview, see: Mö*β*ner, C.; Bolm, C. Catalyzed Asymmetric Aziridinations. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCW: Weinheim, Germany, 2004; Vol. 2, pp 389−402. (b) For recent developments with Au and Ag, see: Li, Z.; Ding, X.; He, C. *J. Org. Chem.* **2006**, *71*, 5876−5880. Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003**, *125*, 16202−16203.

(14) (a) Siu, T.; Yudin, A. K. *J. Am. Chem. Soc.* **2002**, *124*, 530−531. (b) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194−206.

(15) Krasnova, L. B.; Hili, R. M.; Chernoloz, O. V.; Yudin, A. K. *ARKIVOC* **2005**, *4*, 26−38.

(16) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844−6845.

(17) Bridges, A. J. *Chem. Rev.* **2001**, *101*, 2541−2572.

(18) Tamaoki, T.; Nomoto, H.; Takahashi, I.; Kato, Y.; Morimoto, M.; Tomita, F. *Biochem. Biophys. Res. Commun.* **1986**, *135*, 397−402.

(19) Huwe, A.; Mazitschek, R.; Giannis, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 2122−2138.

(20) (a) Cimino, G.; De Rosa, S.; De Stefano, S.; Mazzarella, L.; Puliti, R.; Sodano, G. *Tetrahedron Lett.* **1982**, *23*, 767−768. (b) Kitagawa, I.; Kobayashi, M.; Kitanaka, K.; Kido, M.; Kyoguku, Y. *Chem. Pharm. Bull.* **1983**, *31*, 2321−2328. (c) Wan, Y.; Hur, W.; Cho, C. Y.; Liu, Y.; Adrian, F. J.; Lozach, O.; Bach, S.; Mayer, T.; Fabbro, D.; Meijer, L.; Gray, N. S. *Chem. Biol.* **2004**, *11*, 247−259.

(21) Sharma, V.; Lansdell, T. A.; Jin, G.; Tepe, J. J. *J. Med. Chem.* **2004**, *47*, 3700−3703.

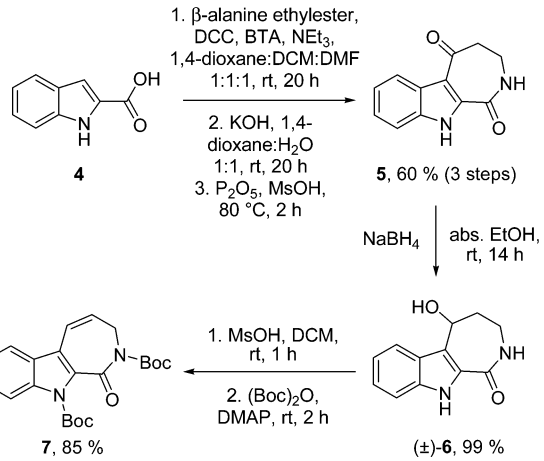
(22) (a) Kaiser, H. M.; Lo, W. F.; Riahi, A. M.; Spannenberg, A.; Beller, M.; Tse, M. K. *Org. Lett.* **2006**, *8*, 5761−5764. (b) Kumar, K.; Michalik, D.; Castro, I. G.; Tillack, A.; Zapf, A.; Arlt, M.; Heinrich, T.; Böttcher, H.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 746−757. (c) Michalik, D.; Kumar, K.; Zapf, A.; Tillack, A.; Arlt, M.; Heinrich, T.; Beller, M. *Tetrahedron Lett.* **2004**, *45*, 2057−2061. (d) Tewari, A.; Hein, M.; Zapf, A.; Beller, M. *Tetrahedron Lett.* **2004**, *45*, 7703−7707. (e) Khedkar, V.; Tillack, A.; Michalik, M.; Beller, M. *Tetrahedron* **2005**, *61*, 7622−7631. (f) Neumann, H.; Strübing, D.; Lalk, M.; Klaus, S.; Hübner, S.; Spannenberg, A.; Lindequist, U.; Beller, M. *Org. Biomol. Chem.* **2006**, *4*, 1365−1375. (g) Schwarz, N.; Tillack, A.; Alex, K.; Sayyed, I. A.; Jackstell, R.; Beller, M. *Tetrahedron Lett.* **2007**, *48*, 2897−2900.

(23) For recent publications in this area see: (a) Gelalcha, F. G.; Bitterlich, B.; Anilkumar, G.; Tse, M. K.; Beller, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7293−7296. (b) Bitterlich, B.; Anilkumar, G.; Gelalcha, F. G.; Spilker, B.; Grotevendt, A.; Jackstell, R.; Tse, M. K.; Beller, M. *Chem. Asian J.* **2007**, *2*, 521−529. (c) Anilkumar, G.; Bitterlich, B.; Gelalcha, F. G.; Tse, M. K.; Beller, M. *Chem. Commun.* **2007**, 289−291. (d) Tse, M. K.; Bhor, S.; Klawonn, M.; Anilkumar, G.; Jiao, H.; Döbler, C.; Spannenberg, A.; Mägerlein, W.; Hugl, H.; Beller, M. *Chem. Eur. J.* **2006**, *12*, 1855−1874. (e) Tse, M. K.; Bhor, S.; Klawonn, M.; Anilkumar, G.; Jiao, H.; Spannenberg, A.; Döbler, C.; Mägerlein, W.; Hugl, H.; Beller, M. *Chem. Eur. J.* **2006**, *12*, 1875−1888. (f) Tse, M. K.; Klawonn, M.; Bhor, S.; Döbler, C.; Anilkumar, G.; Hugl, H.; Mägerlein, W.; Beller, M. *Org. Lett.* **2005**, *7*, 987−990. (g) Tse, M. K.; Döbler, C.; Bhor, S.; Klawonn, M.; Mägerlein, W.; Hugl, H.; Beller, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5255−5260.

(24) (a) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46−58. (b) Schreiber, S. L. *Science* **2000**, *287*, 1964−1969. (c) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939−9953.

(25) Annoura, H.; Tatsuoka, T. *Tetrahedron Lett.* **1995**, *36*, 413−416.

SCHEME 1. Synthesis of Alcohol (±)-6 and Olefin 7

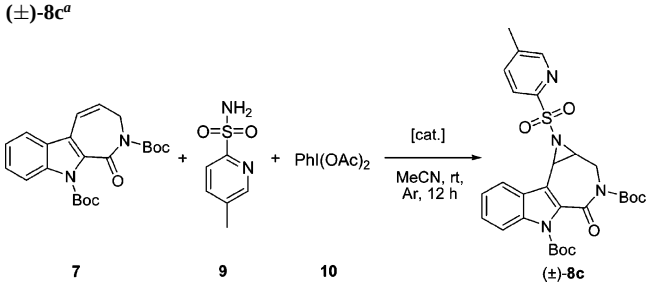


Annulated HMD derivatives (**3**) were usually prepared via the ketone **5** intermediate or the corresponding alcohol (±)-**6** and subsequent attachment of the imidazole heterocycle.[20c] Azepinoindole **5** is usually synthesized via intramolecular cyclization reactions with $MsOH/P_2O_5$.[28] In addition, protocols employing ring-closure metathesis[29] and polyphosphoric acid[30] were introduced.

Starting from indole-2-carboxylic acid (**4**) amide-bound formation with *β*-alanin ethyl ester in the presence of dicyclohexylcarbodiimine (DCC), triethylamine, and 4-hydroxybenzotriazole (BTA), subsequent ester cleavage and cyclization with phosphorus(V) oxide in methansulfonic acid yielded azepinoindole **5** (60%). Subsequent reduction of the keto-group with sodium borohydride in ethanol gave (±)-**6** in excellent yield (99%). The ease of isolation of (±)-**6** is strongly dependent on the purity of the azepino-indole **5**. Compound **5** has very low solubility in common organic solvents and can be purified by treatment with activated charcoal in hot acetone and subsequent recrystallization from a concentrated acetone solution. Olefin **7** was obtained by a one-pot elimination−protection procedure from (±)-**6** (Scheme 1).[20c] Introduction of two boc-protecting groups was crucial to provide a more stable and storable alkene from these acidic reaction conditions.

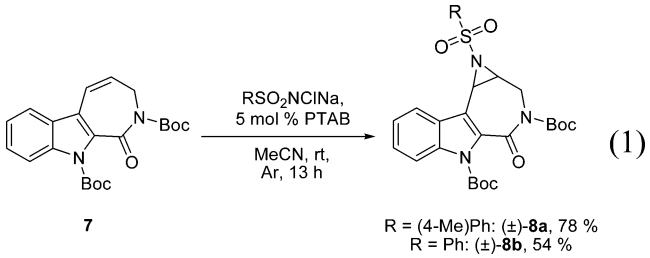
Next, we focused on the oxidation of olefin **7** to aziridines (±)-**8a**−**c**. As stated above, most catalytic aziridination methodologies generally require an excess of olefin. As a key building block for subsequent chemical diversification, it was crucial to introduce applicable and high-yielding aziridination methods. In this respect, we utilized the bromine-catalyzed aziridination protocol developed by Sharpless and co-workers,[16] because this method, in principle, does not require an excess of olefin. In contrast to conditions reported in the literature, we obtained our best results ((±)-**8a**: 78%) with an understoichiometric amount of the nitrogen source (chloramine-T) in the presence of only 5 mol % of phenyltrimethylammonium tribromide (PTAB) and 2 equiv of alkene **7** (eq 1).

TABLE 1. Copper-Catalyzed Aziridination of 7 to Aziridine (±)-8c[a]



entry	molar ratio of **7**:**9**:**10**	catalyst	conv [%]	yield[b] [%]
1	1:0.8:0.8	5 mol % of $Cu(OTf)_2$	45	27
2	1:0.8:0.8	5 mol % of $Fe(acac)_3$	23	0
3	1:0.8:0.8	5 mol % of $Cu(tfac)_2$	55	70
4	1:1.5:1.5	5 mol % of $Cu(tfac)_2$	50	62
5	1:0.8:0.8	10 mol % of $Cu(tfac)_2$	51	69

[a] Reaction conditions: olefin **7** (100 mg, 0.25 mmol), appropriate amounts of **9**, **10**, catalyst, 4 Å MS (500 mg), anhydrous CH_3CN (2 mL), Ar, 13 h. [b] Isolated yield based on recycled precursor **7**.



(1)

Employing these reaction conditions, we were able to reduce the degree of reaction side products such as the brominated olefin and the ring-opening product of the product aziridine with the amide salt.[31] Applying the same procedure to compound **7** with chloramine-B, aziridine (±)-**8b** was obtained in a reasonable (54%) yield.

Next, we planned to introduce a heterocyclic sulfonyl group to the aziridine motif. Once again the major drawback of most of the synthetic methods was the large excess of olefin required.[32] Optimization of the reaction conditions of the copper-catalyzed aziridination method introduced by Chang and co-workers[33] showed that a large excess of olefin **7** was not necessary to obtain the desired product (±)-**8c** in high yield (70%) (Table 1). The best result with respect to conversion and yield was obtained employing 5−10 mol % of copper(II) trifluoroacetylacetonate [$Cu(tfac)_2$] with a slight excess of olefin **7** (Table 1, entries 3 and 5). Unfortunately further attempts to introduce the 2-nitrobenezenesulfonyl group onto the aziridine via a gold-catalyzed procedure gave only a trace amount of the product.[13b]

We were delighted to be able to apply all of these methods for the preparation of aziridines (±)-**8a**−**c** in multigram-scale. With three different aziridines in hand, we looked for suitable conditions to affect the nucleophilic ring-opening reaction of

(26) (a) Xu, Y.-Z.; Yakushijin, K.; Horne, D. A. *J. Org. Chem.* **1997**, *62*, 456−464. (b) Sosa, A. C. B.; Yakushijin, K.; Horne, D. A. *J. Org. Chem.* **2000**, *65*, 610−611.

(27) Papeo, G.; Posteri, H.; Borghi, D.; Varasi, M. *Org. Lett.* **2005**, *7*, 5641−5644.

(28) Cho, H.; Matsuki, S. *Heterocycles* **1996**, *43*, 127−131.

(29) Chacun-Lefèvre, L.; Bénéteau, V.; Joseph, B.; Mérour, J.-Y. *Tetrahedron* **2002**, *58*, 10181−10188.

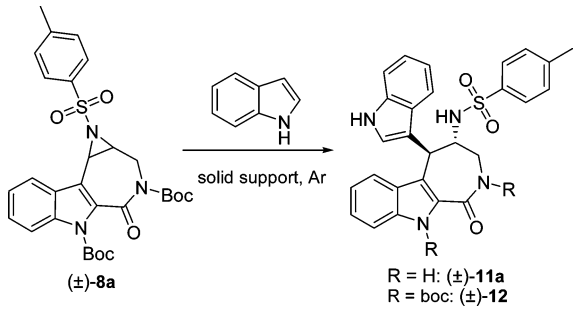
(30) Suzuki, H.; Shinpo, K.; Yamazaki, T.; Niwa, S.; Yokoyama, Y.; Murakami, Y. *Heterocycles* **1996**, *42*, 83−86.

(31) Stewart, I. C.; Lee, C. C.; Bergmann, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17616−17617.

(32) (a) Evans, D. A.; Bilodeau, M. T.; Faul, M. M.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328−5329. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744−6746. (c) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742−2753.

(33) Han, H.; Bae, I.; Yoo, E. J.; Lee, J.; Do, Y.; Chang, S. *Org. Lett.* **2004**, *6*, 4109−4112.

TABLE 2. Variation of Solid Support, Temperature, and Amount of *C*-Nucleophile in the Ring-Opening Reaction of Aziridine (±)-8a with Indole[a]



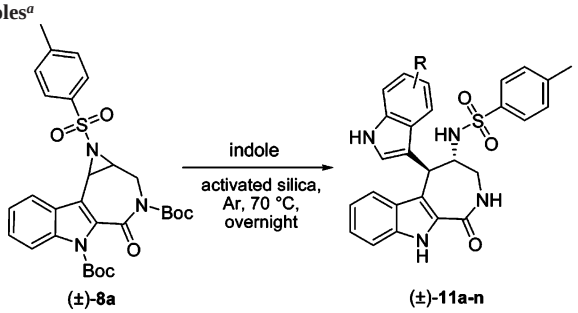
entry	solid support	temp [°C]	ratio of indole:(±)-**8a**	yield[b] [%]
1	activated silica	rt	10:1	0 (34)[c]
2	activated silica	40	10:1	75
3	activated silica	70	10:1	93
4	activated silica	70	3:1	81
5	activated silica	70	1:1	40
6	montmorillonite K-10	70	10:1	70
7	alumina (neutral)	70	10:1	21

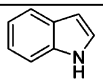
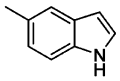
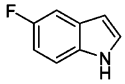
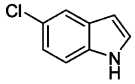
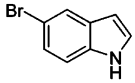
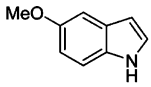
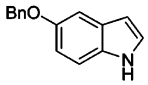
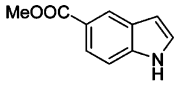
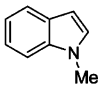
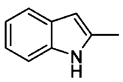
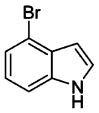
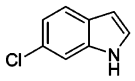
[a] Reaction conditions: aziridine (±)-**8a** (113 mg, 0.2 mmol), indole (234 mg, 2.00 mmol), 429 mg of solid support, Ar, 16 h. [b] Isolated yield of product (±)-**11a**. [c] Isolated yield of product (±)-**12**.

these aziridines. Therefore, key intermediate (±)-**8a** was allowed to react with indole as *C*-nucleophile in the presence of different acidic solid supports such as silica,[34,6d] alumina, and clay (Montmorillonite K-10).[35] Moreover, the reaction temperature and the ratio of indole to (±)-**8a** were varied (Table 2).

The results demonstrate that a high molar ratio of indole at a moderate temperature of 70 °C (Table 2, entry 3) gave the desired bisindole (±)-**11a** in excellent yield (93%). In principle, only a slight excess of indole is consumed and it can be recycled. Since indole sublimes during the reaction, 10 equiv of indole is used to ensure efficient conversion of the aziridine to our product. All arylations proceeded with excellent regioselectivity at the benzylic position of (±)-**8a** and at the 3-position of the attached indole. The best conditions were then tested with other solid supports such as clay (Montmorillonite K-10) (Table 2, entry 6) and alumina (Table 2, entry 7). These solid supports exhibit significant disadvantages such as side product formation or lower yields. For example, employing clay as the solid support we observed both possible ring-opening products of the aziridine by ^{1}H NMR. In the case of neutral alumina the desired product (±)-**11a** was formed in lower yield. The ^{1}H NMR spectrum of the reaction mixture indicated also that deprotection of both boc-groups under the employed reaction conditions on clay or alumina was not complete. In contrast, the protecting boc-groups could be easily removed under the reaction conditions on activated silica. The isolation of the *N*,*N*-di-boc-protected ring-opening product (±)-**12** in low yields at room temperature (Table 2, entry 1) provides direct evidence that the ring-opening reaction proceeds significantly faster than the deprotection of the boc-protecting groups under mild conditions. Moreover, the deprotection of the nitrogen atoms does not seem to be required for the activation of the indole for the ring-opening reaction. In a few attempts (Table 2, entries 1, 2, and 7), the ring-opening products with only one protecting group were also observed (^{1}H NMR) on the lactam moiety.

TABLE 3. Ring-Opening Reactions of (±)-8a with Various Indoles[a]

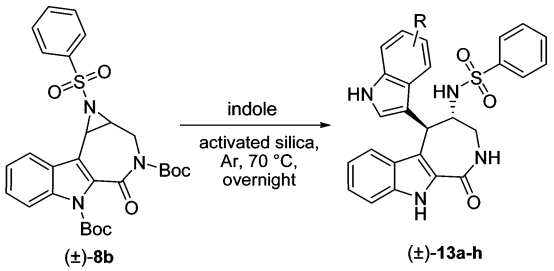


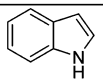
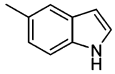
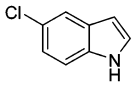
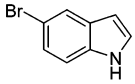
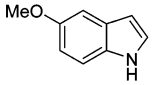
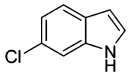
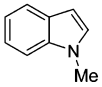
entry	substrate	product	yield[b] [%]
1		(±)-**11a**	93
2		(±)-**11b**	81
3		(±)-**11c**	99
4		(±)-**11d**	57
5		(±)-**11e**	84
6		(±)-**11f**	93
7		(±)-**11g**	72
8		(±)-**11h**	67
9		(±)-**11i**	86
10		(±)-**11k**	96
11		(±)-**11l**	70
12		(±)-**11m**	85
13		(±)-**11n**	76

[a] Reaction conditions: aziridine (±)-**8a** (113 mg, 0.20 mmol), indole derivative (2.00 mmol), activated silica (0.040−0.063 mm, 429 mg), 70 °C, Ar, overnight. [b] Isolated yield.

(34) Hudlicky, T.; Rinner, U.; Finn, K. J.; Ghiviriga, I. *J. Org. Chem.* **2005**, *70*, 3490−3499.
(35) Nadir, U. K.; Singh, A. *Tetrahedron Lett.* **2005**, *46*, 2083−2086.

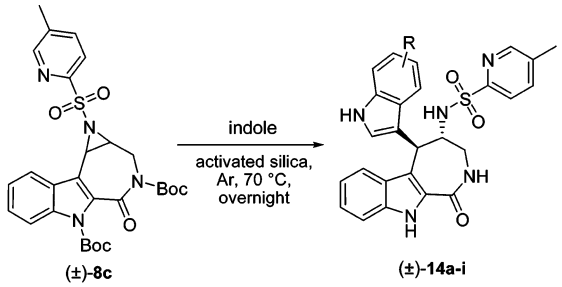
TABLE 4. Ring-Opening Reactions of (±)-8b with Various Indoles[a]

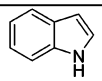
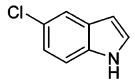
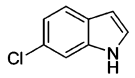
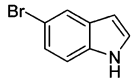
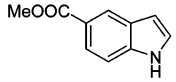
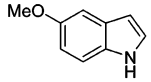
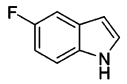
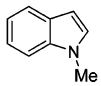


entry	substrate	product	yield[b] [%]
1		(±)-**13a**	66
2		(±)-**13b**	58
3		(±)-**13c**	41
4		(±)-**13d**	83
5		(±)-**13e**	59
6		(±)-**13f**	61
7		(±)-**13g**	39
8		(±)-**13h**	36

[a] Reaction conditions: aziridine (±)-**8b** (111 mg, 0.20 mmol), indole derivative (2.00 mmol), activated silica (0.040−0.063 mm, 429 mg), 70 °C, Ar, overnight. [b] Isolated yield.

TABLE 5. Ring-Opening Reactions of (±)-8c with Various Indoles[a]



entry	substrate	product	yield[b] [%]
1		(±)-**14a**	92
2		(±)-**14b**	72
3		(±)-**14c**	89
4		(±)-**14d**	60
5		(±)-**14e**	66
6		(±)-**14f**	47
7		(±)-**14g**	68
8		(±)-**14h**	62
9		(±)-**14i**	82

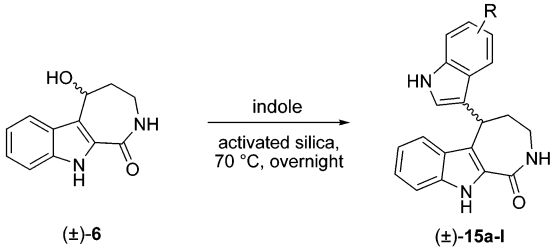
[a] Reaction conditions: aziridine (±)-**8b** (114 mg, 0.20 mmol), indole derivative (2.00 mmol), activated silica (0.040−0.063 mm, 429 mg), 70 °C, Ar, overnight. [b] Isolated yield.

Next, we adopted the optimized protocol to the preparation of unsymmetrical bisindoles starting from aziridines (±)-**8a**−**c**. All reactions ran overnight at 70 °C and yielded the trans-ring-opening product (see the crystal structure of (±)-**11f**) in good to excellent yields (Table 3).

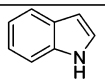
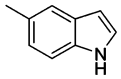
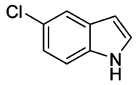
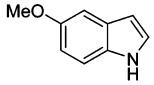
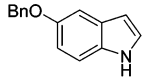
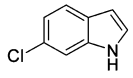
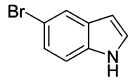
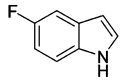
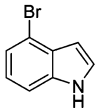
Functional groups on the indole ring such as halides and alkoxy and ester groups were tolerated under these mild reaction conditions. However, under similar conditions the ring-opening product with 5-nitro-indole was only obtained in poor (<20%) yields. Using 5,6-dimethylindole we obtained an inseparable 70:30 mixture of two different regioisomers likely caused by the electron-rich aromatic system of the substrate. The reaction of (±)-**8a** with indole (Table 3, entry 1) also can be performed on gram-scale and provided the desired product in excellent yield (95%). Employing the precursors (±)-**8b** and (±)-**8c** under the same reaction conditions, compounds (±)-**13a**−**h** (36−83%) and (±)-**14a**−**i** (47−92%) were obtained in moderate to good yield.

To determine the structural influence of the aryl-sulfonamide side chain in biological screenings, we also decided to prepare the analogues (±)-**15a**−***l***. For this purpose we tested the hydroxyl-precursor (±)-**6** under similar reaction conditions. Fortunately the desired bisindoles (±)-**15a**−***l*** were obtained in moderate to good yields (Table 6). Direct benzylations with alcoholic precursors were of significant interest for the preparation of diarylmethanes.[36] Usually Lewis acid catalyst in homogeneous solution is required for this reaction.[37] To the best of our knowledge this is the first direct benzylation of indoles

TABLE 6. Formation of Bisindoles (±)-15a−l from Alcohol (±)-6[a]



(±)-6 (±)-15a-l

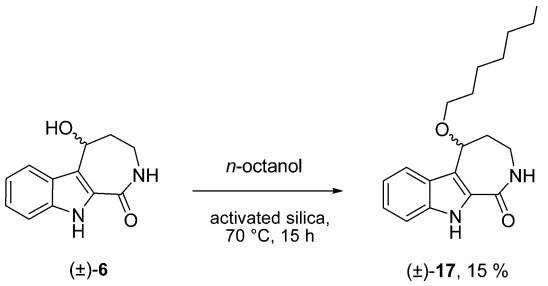
entry	substrate	product	yield[b] [%]
1		(±)-**15a**	91
2		(±)-**15b**	52
3		(±)-**15c**	64
4		(±)-**15d**	53
5		(±)-**15e**	56
6		(±)-**15f**	38
7		(±)-**15g**	58
8		(±)-**15h**	44
9		(±)-**15i**	62
10		(±)-**15k**	56
11		(±)-**15l**	51

[a] Reaction conditions: alcohol (±)-**6** (100 mg, 0.462 mmol), indole derivative (4.62 mmol), activated silica (0.040−0.063 mm, 800 mg), 70 °C, overnight. [b] Isolated yield.

with an alcohol precursor on solid support.[22a] The reaction of alcohol (±)-**6** with *C*-nucleophiles on silica enables a convenient access to this class of compounds. Compared with the method employing olefin **7a** and other heterocyclic *C*-nucleophiles under strong acidic conditions (MsOH as solvent), our method is more managable.[20c]

To demonstrate the versatility of the aziridines for further diversification reactions, we examined aziridine (±)-**8a** in ring-opening reactions with *H*-, *O*-, and *N*-nucleophiles. First (±)-**16a** was prepared by reductive ring-opening reaction with ammonium formate in the presence of palladium on charcoal.[38] After deprotection with TFA, (±)-**16b** was obtained in excellent yield (73%, over two steps). This product can give direct comparison information for the structural influence of the indole group in products (±)-**11a**−**n**. Direct deprotection of crude (±)-**16a** with TFA in CH_2Cl_2 gave (±)-**16b** in similar yield (68%) (Scheme 2).[39] It should be noted that this two-step aziridination−hydrogenation sequence offers a straightforward approach to novel sulfonylated tryptamine derivatives, which may be of interest in various pharmaceutical applications.

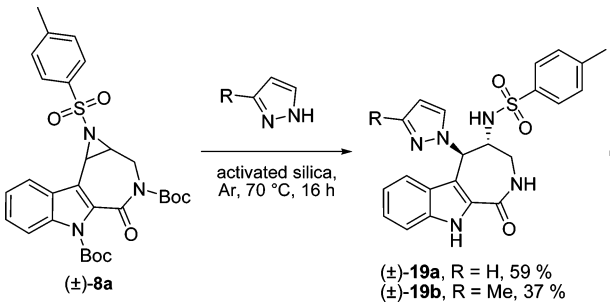
Next, we turned our interests to other nucleophiles such as alcohols or amines. Initial experiments designed to react aziridine (±)-**8a** with *n*-octanol similar to the indole-ring-opening reactions on silica led only to the decomposition of the starting material. However, the reaction of alcohol (±)-**6** with *n*-octanol proceeded overnight with low conversion of (±)-**6** on silica. After 15 h the desired substitution product (±)-**17** was isolated in 15% yield (eq 2). Further we tried to convert alcohol (±)-**6** on silica with tosylamide and various amines. Unfortunately these reactions failed to produce any conversion.



(±)-6 (±)-17, 15 % (2)

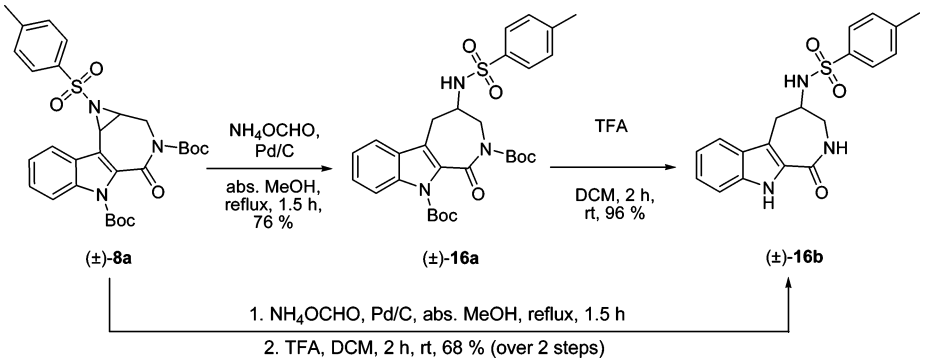
Next, aziridine (±)-**8a** was successfully converted with MeOH as an *O*-nucleophile by reaction with ceric ammonium nitrate (CAN) (Scheme 3).[40] Hence, (±)-**18a** was synthesized from (±)-**8a** in MeOH with 10 mol % of CAN at room temperature for 9 h in excellent yield (99%) based on recycled aziridine (±)-**8a** (52%). Further, the catalyst loading up to 40 mol % gave full conversion of (±)-**8a** (TLC) and the subsequent deprotection of (±)-**18a** on silica at 70 °C yielded (±)-**18b** in good yield (74%).

In addition, we also explored the ring-opening reaction of aziridine (±)-**8a** in the presence of pyrazoles on activated silica. To our delight, reactions employing our standard reaction conditions (Table 2) yielded compounds (±)-**19a** and (±)-**19b** in moderate yields (37% and 59%, eq 3).

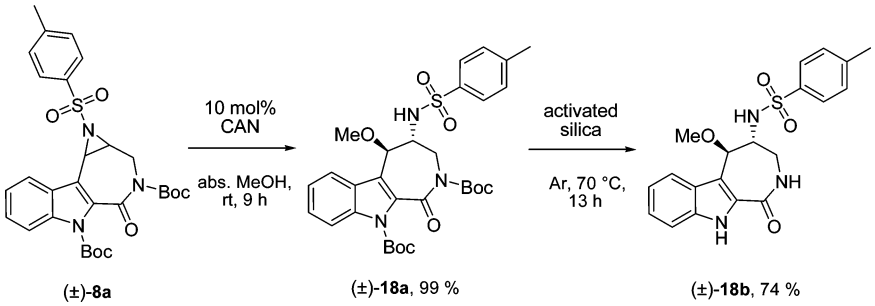


(±)-8a (±)-19a, R = H, 59 %
(±)-19b, R = Me, 37 % (3)

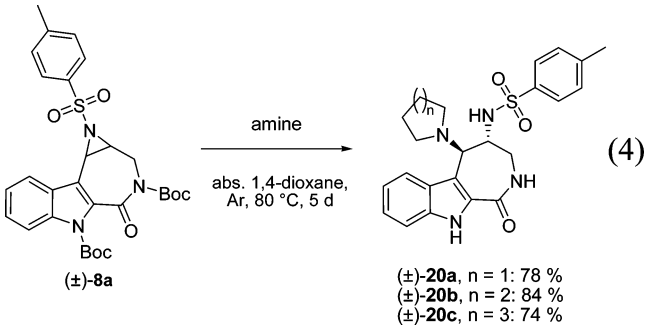
SCHEME 2. Formation of Protected Sulfonamides (±)-16a from (±)-8a and Subsequent Deprotection to (±)-16b



SCHEME 3. Synthesis of (±)-18a and Subsequent Deprotection to (±)-18b



Aziridine (±)-**8a** could be opened smoothly with more volatile secondary amines.[41] To our surprise, (±)-**8a** underwent the direct amination reaction smoothly at 80 °C in homogeneous solution without any catalyst or further activating reagent (e.g., organic base, etc.) to give also the in situ deprotected compounds (±)-**20a**−**c** (eq 4). Depending on the solubility of the products during the recrystallization step, we obtained good to very good yields (74−84).



(4)

X-ray Crystallographic Studies. Single crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of methanol, ethyl acetate, diethyl ether, or dichlormethane solutions. The molecular structures of **7**, (±)-**8a**, (±)-**8b**, (±)-**8c**, (±)-**11f**, and (±)-**15d** confirmed our assignments (see the Supporting Information). Among them, the crystal structure of bisindole (±)-**11f** has been reported by us previously.[22a] The C═C double bond in olefin **7** exhibits a length of 1.323(2) Å. Possibly with respect to the nonplanarity of the seven-membered ring, the olefinic C═C bond puckered from the plane of the indole moiety [torsion angle: 156.0(2)°]. The molecular structures of aziridines (±)-**8a**−**c** showed that the angles between the three-atom-ring plane of the aziridines and the indole plane are almost in the same range for all aziridines [(±)-**8a**: 57.7-(2)°; (±)-**8b**: 60.3(1)°; (±)-**8c**: 61.4(1)°]. Also, the bond lengths of the aziridine moieties of (±)-**8a**−**c** showed the structural similarities of these compounds: (a) C−C: (±)-**8a** 1.471(4) Å, (±)-**8b** 1.473(2) Å, (±)-**8c** 1.472(2) Å; (b) N−C: (±)-**8a** 1.502(4) Å, (±)-**8b** 1.501(2) Å, (±)-**8c** 1.512(2) Å; (b) C−N: (±)-**8a** 1.490(4) Å, (±)-**8b** 1.488(2) Å, (±)-**8c** 1.493(2) Å. The X-ray analysis of bisindole (±)-**11f** gives direct evidence for the trans configuration of the ring-opening product. The comparison of bisindole (±)-**11f** and its analogue (±)-**15d** without the tosyl-amide side chain showed significant differences in the angle between the two planes of the indole ring systems [(±)-**11f**: 83.37(6)°; (±)-**15d**: 73.87(5)°] in the crystal structures. However, in both cases the planes of the indole systems are clearly out of the same plane from each other.

Mechanistic Aspects. Inspired by the previous reports about the concept of an aza-fulvenium ion as the intermediate in the reaction mechanism,[26a] we became interested in the process of the charge-stabilization of the cationic intermediate during the bisindole formation from alcohol (±)-**6** and aziridines (±)-**8a**−**c**. It is well-known that the elimination of benzylic OH-groups proceeds smoothly to afford olefins in the presence of acids. Thus a carbocationic intermediate is formed in situ and subsequent elimination of proton yields the corresponding olefin.

(36) (a) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913−3917. (b) Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 238−242.

(37) (a) Brandt, S. D.; Freemanb, S.; McGagha, P.; Abdul-Halima, N.; Alder, J. F. *J. Pharm. Biomed. Anal.* **2004**, *36*, 675−691. (b) Magesh, C. J.; Nagarajan, R.; Karthik, M.; Perumal, P. T. *Appl. Catal. A* **2004**, *266*, 1−10. (c) El Gihani, M. T.; Heaney, H.; Shuhaibar, K. F. *Synlett* **1996**, 871−872. (d) Crookes, D. L.; Parry, K. P.; Smith, G. F., *Pol. J. Chem.* **1979**, *53*, 73−78.

(38) Sayyed, I. A. Ph.D. Thesis, University of Pune, India, 2003.

(39) Davis, F. A.; Wu, Y.; Yan, H.; McCoull, W.; Prasad, K. R. *J. Org. Chem.* **2003**, *68*, 2410−2419.

(40) Chandrasekhar, S.; Narsihmulu, Ch; Sultana, S. S. *Tetrahedron Lett.* **2002**, *43*, 7361−7363.

(41) Mao, J.; Wan, B.; Wang, R.; Wu, F.; Lu, S. *J. Org. Chem.* **2004**, *69*, 9123−9127.

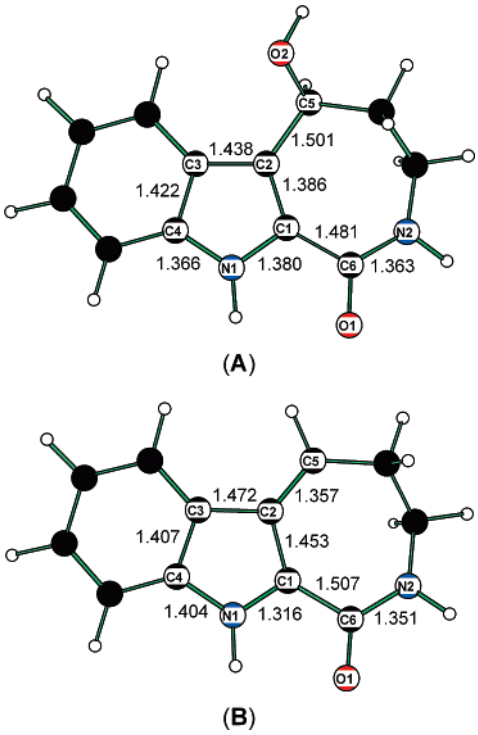
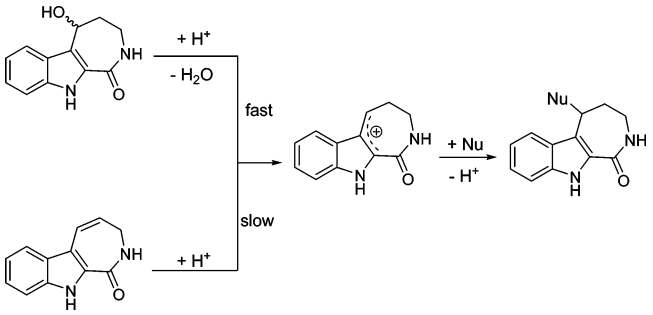


FIGURE 2. Calculated molecular structures of alcohol (±)-**6** (**A**) and the cationic intermediate (**B**).

During initial ^{1}H NMR experiments of alcohol (±)-**6** with MsOH in CD_2Cl_2, only olefin **7a** was observed immediately after addition of a catalytic amount of MsOH to alcohol (±)-**6**. Further, the boc-protected olefin **7** did not react with indole on silica to form the desired product (±)-**15a**. Here, only olefin **7a** was observed on TLC. In fact, olefin **7** can be deprotected on activated silica at 70 °C overnight to yield the *N*,*N*-deprotected olefin **7a** in 98% yield. Attempts to produce bisindole from **7a** on silica or in MsOH with indole were performed. However, no reaction was observed on silica and no well-defined product could be isolated from the MsOH-reaction system. This indicates that the generation of the active cationic intermediate from **7a** is significantly slower than that from the hydroxyl precursor (±)-**6**.

To understand the structure of the cationic intermediate (**B**), we have carried out B3LYP/6-311G(d) density functional theory calculations along with the alcohol (**A**) by using the Spartan 04 program package.[42] As shown in Figure 2, the five-membered ring in **A** has a pyrrole moiety and the exocyclic C2−C5 bond length is 1.501 Å. In the cationic intermediate (**B**), however, the C2−C5 and C1−N1 bond lengths become shorter (1.357 and 1.316 Å, respectively) and the C1−C2 bond length becomes longer (1.453 Å). This change is due to the delocalization effect with the formation of the butadiene moiety of N1−C1−C2−C5. In addition to the changes of the bond lengths, it is also interesting to compare the Mulliken charges between **A** and **B**. Therefore it seems to be clear that the positive charge from a theoretical perspective point of view has to be delocalized over C1, C2, and C5 (the computed Mulliken charges—for **A**: N1 = −0.701; C1 = 0.156; C2 = −0.021; C5 = −0.030; for **B**: N1 = −0.632; C1 = 0.242; C2 = −0.018; C5 = −0.094). This stands in contrast to the known literature and established azafulvenium ion.[26a]

SCHEME 4. Proposed Mechanism for the Synthesis of Unsymmetrical Bisindoles from Alcohol (±)-6



On the basis of the DFT calculations and our observations of the reactions of alcohol (±)-**6** with indoles on silica, we believe the reaction proceeds through the attack of the indole to the LUMO of the cationic diene species, which is stabilized by delocalization of the positive charge on the N1−C1−C2−C5 moiety (Scheme 4). It is also possible for the same charge stabilization mechanism to proceed during the ring-opening and subsequent aromatic substitution reactions of aziridines (±)-**8a**−**c** with indoles.

Conclusion

In summary, a practical and easy to handle protocol for the synthesis of unsymmetrical bisindoles was developed. The arylation reactions proceed in a highly regio- and stereoselctive manner at the benzylic position of the azepino[3,4-*b*]indol-1(10*H*)-one moiety and at the 3-position of the attached indole on a solid support. The solvent-free synthetic protocol is easily manageable and yields the desired bisindoles from the aziridines or alcohols. In addition, boc-protecting groups can be removed in situ smoothly. The versatility of these aziridines was demonstrated with *H*-, *O*-, and *N*-nucleophiles in a diversity oriented synthesis to build up a small compound library. X-ray analysis confirmed the molecular structures of important key intermediates and library compounds. Specifically, the molecular structure of (±)-**11f** gives direct evidence for the trans-ring-opening reaction. In addition, DFT calculations indicate that the mechanism might proceed via a charge stabilized azabutadiene motif, which reacts further exclusively at the benzylic position to rebuild the aromatic ring system.

Experimental Section

5-Hydroxy-2,3,4,5-tetrahydroazepino[3,4-*b*]indol-1(10*H*)-one ((±)-6). Ketone **5** (3.31 g, 15.5 mmol) was suspended in degassed absolute ethanol (250 mL) under argon.[43] Then freshly ground $NaBH_4$ (2.92 g, 77.3 mmol) was added and the reaction mixture was stirred at ambient temperature overnight (~14 h). The mixture was filtered over celite and washed with acetone. After removal of the solvent under reduced pressure, purification by column chromatography (silica gel 70−230 mesh, CH_2Cl_2 to CH_2Cl_2:MeOH 100:7 as a gradient eluent) yielded an off-white solid (3.30 g, 99%). R_f 0.40 (CH_2Cl_2:MeOH:NEt_3 100:10:1). Mp 167−169 °C (ethyl acetate). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.29 (1H, br s), 8.15 (1H, dd, J = 6.0, 3.2 Hz), 7.78 (1H, d, J = 7.9 Hz), 7.41 (1H, d, J = 8.1 Hz), 7.19 (1H, ddd, J = 8.1, 7.0, 1.1

(42) *SPARTAN'04*: Copyright 1991−2005 by Wavefunction Inc.; www.wavefun.com.

(43) For the synthesis of the precursors, please see the Supporting Information.

Hz), 7.04 (1H, ddd, J = 8.1, 7.0, 1.0 Hz), 5.23 (1H, d, J = 6.6 Hz), 5.18−5.10 (1H, m), 3.59−3.45 (1H, m), 3.22−3.08 (1H, m), 2.22−2.10 (1H, m), 2.07−1.93 (1H, m). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 163.7, 135.8, 127.7, 126.8, 123.9, 121.5, 119.5, 119.1, 112.1, 63.5, 36.5, 35.5. IR (KBr) ν (cm^{-1}) 3520 m, 3281 s, 3211 sh, 3051 m, 2952 m, 2917 m, 2861 sh, 1647 s, 1550 s, 1478 s, 1456 m, 1412 m, 1362 m, 1334 s, 1297 m, 1239 w, 1185 w, 1160 w, 1144 w, 1063 w, 1047 m, 1003 m, 958 m, 924 w, 881 m, 792 m, 740 s, 680 m, 606 w, 539 w, 465 w, 435 w. MS (EI) *m*/*z* (rel. intensity) 217 (13), 216 (72), 200 (13), 199 (36), 198 (100), 197 (50), 189 (13), 186 (11), 172 (10), 171 (25), 170 (37), 169 (50), 168 (13), 159 (35), 158 (17), 155 (14), 154 (15), 149 (14), 145 (16), 144 (30), 143 (29), 142 (12), 141 (11), 140 (15), 130 (12), 129 (12), 128 (10), 117 (13), 116 (17), 114 (11), 89 (17), 83 (11), 78 (13), 77 (18), 71 (14), 69 (12), 63 (19), 57 (22), 55 (16), 44 (46), 43 (14), 41 (17). HRMS (ESI) calcd for $C_{12}H_{12}N_2O_2Na$ (M + Na$^+$) 239.0791, found 239.0803. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.59; H, 5.33; N, 12.90.

(*Z*)-Di-*tert*-butyl 1-Oxoazepino[3,4-*b*]indole-2,10(1*H*,3*H*)-dicarboxylate (7). To a solution of alcohol (±)-**6** (3.30 g, 15.3 mmol) in CH_2Cl_2 (500 mL) was added methanesulfonic acid (0.730 g, 7.63 mmol) dropwise. The solution was stirred at room temperature for ∼40 min. After the full conversion of (±)-**6** as indicated by TLC analysis, 4-dimethylaminopyridine (4.47 g, 36.6 mmol) and di-*tert*-butyl dicarbonate (6.97 g, 30.5 mmol) were added. The reaction was monitored by TLC (CH_2Cl_2:MeOH:NEt_3 100:10:1) and portions of di-*tert*-butyl dicarbonate (3 × 2.30 g, 3 × 10.2 mmol) were added further to complete the reaction. The solvent was removed in vacuo and the residual brown reaction mixture was purified via column chromatography (silica gel 70−230 mesh, *n*-hexane:ethyl acetate 6:1, packed with 1% NEt_3) to yield a white solid (5.19 g, 85%). Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of a solution of diethyl ether at room temperature. R_f 0.23 (*n*-hexane:ethyl acetate 6:1). Mp 127−128 °C (Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.11 (1H, d, J = 8.5 Hz), 7.67 (1H, d, J = 7.9 Hz), 7.48 (1H, ddd, J = 8.4, 7.2, 1.3 Hz), 7.31 (1H, ddd, J = 8.1, 7.2, 0.9 Hz), 7.19 (1H, d, J = 9.6 Hz), 6.57 (1H, dt, J = 9.7, 6.5 Hz), 4.29 (2H, br s), 1.64 (9H, s), 1.55 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.3, 151.4, 149.5, 138.3, 132.1, 131.2, 128.0, 125.9, 125.5, 123.8, 123.4, 120.4, 114.8, 84.8, 83.5, 43.6, 28.2, 27.9. IR (KBr) ν (cm^{-1}) 3438 w, 3053 w, 2983 m, 2940 w, 1764 s, 1730 s, 1691 sh, 1670 w, 1532 w, 1448 m, 1418 m, 1373 s, 1339 s, 1326 s, 1278 m, 1264 m, 1229 s, 1141 s, 1118 s, 1027 m, 1016 m, 1011 m, 976 m, 951 w, 895 w, 862 m, 834 m, 805 m, 780 m, 767 m, 747 s, 695 w, 674 w, 607 w, 588 w, 511 w, 470 w, 442 w. MS (EI) *m*/*z* (rel. intensity) 398 (2), 242 (7), 199 (11), 198 (100), 197 (33), 170 (6), 169 (20), 157 (6), 56 (7), 44 (21), 41 (13). HRMS (ESI+) calcd for $C_{22}H_{26}N_2O_5Na$ (M + Na$^+$) 421.1734, found 421.1735.

(*Z*)-2,3-Dihydroazepino[3,4-*b*]indol-1(10*H*)-one (7a). Olefin **7** (600 mg, 1.51 mmol) was dissolved in CH_2Cl_2 and activated silica (1.0 g, 0.040−0.063 mm) was added. After removal of the solvent the mixture was heated at 70 °C for 16 h. Purification by column chromatography (silica gel 70−230 mesh, *n*-hexane:ethyl acetate 1:1 to ethyl acetate as the gradient eluent) yielded a white solid (293 mg, yield: 98%). R_f 0.44 (ethyl acetate). Mp 198 °C (*n*-hexane: ethyl acetate). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.86 (1H, br s), 7.91 (1H, unresolved dd), 7.76 (1H, d, J = 8.1 Hz), 7.45 (1H, unresolved ddd), 7.28 (1H, ddd, J = 8.1, 7.0, 1.1 Hz), 7.15 (1H, d, J = 10.0 Hz), 7.12 (1H, ddd, J = 7.9, 7.0, 0.9 Hz), 6.04 (1H, dt, J = 9.9, 6.5 Hz), 3.53 (2H, unresolved dd). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 163.9, 136.1, 130.6, 125.3, 125.2, 124.5, 124.0, 120.0, 119.9, 116.0, 112.3, 38.4. IR (KBr) ν (cm^{-1}) 3209 s, 3060 sh, 2984 sh, 2924 sh, 1911 w, 1627 s, 1574 sh, 1525 s, 1500 m, 1478 s, 1438 m, 1419 m, 1394 m, 1333 s, 1301 m, 1271 m, 1246 w, 1233 w, 1156 m, 1114 w, 1071 w, 1021 w, 1007 w, 932 w, 904 m, 854 w, 810 m, 775 m, 758 s, 675 m, 620 w, 596 m, 586 w, 564 w, 515 m, 436 m, 423 m. MS (EI) *m*/*z* (rel. intensity) 199 (20), 198 (100), 170 (20), 169 (77), 168 (12), 155 (16), 154 (16), 140 (11), 115 (24), 86 (30), 84 (50), 83 (13), 71(12), 70 (11), 69 (14), 63 (11), 57 (21), 55 (18), 51 (18), 49 (62), 43 (19), 41 (18). HRMS (EI) calcd for $C_{12}H_{10}N_2O$ (M$^+$) 198.0788, found 198.0782.

Aziridiniation of (*Z*)-Di-*tert*-butyl 1-Oxoazepino[3,4-*b*]indole-2,10(1*H*,3*H*)-dicarboxylate (7) with Chloramine-T, Synthesis of (±)-8a. Olefin **7** (3.10 g, 7.78 mmol) was dissolved under argon in anhydrous acetonitrile (200 mL), then $PhNMe_3Br_3$ (146 mg, 0.390 mmol) and chloramine-T × $3H_2O$ (1.10 g, 3.89 mmol) were added. The mixture was stirred for 13 h and was quenched with saturated Na_2SO_3(aq) (200 mL). After extraction with ethyl acetate (3 × 200 mL), the combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude orange solid product was purified by column chromatography (silica gel 70−230 mesh, *n*-hexane to *n*-hexane:ethyl acetate 5:1 as the gradient eluent) to yield a white solid product (1.74 g, 78%) and a pure fraction of starting material **7** (1.19 g, 38%). The product was recrystallized from ethyl acetate:*n*-heptane (1:4) at 4 °C. Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of a solution of ethyl acetate at room temperature. Mp 169−170 °C (ethyl acetate). R_f 0.24 (*n*-hexane: ethyl acetate 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.03 (1H, d, J = 8.5 Hz), 7.89 (2H, d, J = 8.3 Hz), 7.44−7.34 (3H, m), 7.17−6.95 (2H, m), 4.60 (1H, br s), 3.92 (1H, d, J = 6.9 Hz), 3.81−3.72 (1H, m), 3.60 (1H, br s), 2.49 (3H, s), 1.59 (9H, s), 1.56 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.9, 151.8, 148.9, 145.4, 137.9, 134.6, 130.3, 130.1, 128.5, 127.8, 126.9, 123.7, 120.2, 117.1, 114.8, 85.3, 84.5, 35.6, 28.2, 27.7, 21.9. ^{1}H NMR (300 MHz, 323 K, $CDCl_3$) δ (ppm) 8.04 (1H, ddd, J = 8.6, 1.0, 0.7 Hz), 7.89 (2H, unresolved ddd), 7.37 (1H, ddd, J = 8.5, 6.7, 1.8 Hz), 7.21−7.12 (2H, m), 4.60−4.47 (1H, m), 3.95 (1H, d, J = 6.8 Hz), 3.76 (1H, ddd, J = 9.0, 7.0, 4.5 Hz), 3.72−3.58 (1H, m), 2.48 (3H, s), 1.59 (9H, s), 1.57 (9H, s). ^{13}C NMR (75 MHz, 323 K, $CDCl_3$) δ (ppm) 159.8, 152.1, 149.0, 145.3, 138.1, 135.2, 130.5, 130.1, 128.5, 127.8, 127.1, 123.7, 120.4, 117.2, 114.8, 85.3, 84.5, 45.7 (br s), 41.9 (br s), 35.8, 28.3, 27.8, 21.8. IR (KBr) ν (cm^{-1}) 3428 w, 2977 w, 2934 w, 1745 s, 1723 s, 1701 s, 1596 w, 1556 w, 1477 w, 1447 m, 1396 m, 1369 s, 1323 s, 1289 s, 1260 m, 1225 m, 1207 m, 1160 s, 1124 m, 1111 m, 1091 m, 1018 w, 999 w, 974 w, 951 w, 876 w, 864 w, 829 w, 811 w, 768 w, 741 m, 706 w, 679 m, 659 w, 590 w, 567 m, 548 m, 509 w. MS (EI) *m*/*z* (rel. intensity) 567 (3), 511 (2), 367 (4), 356 (7), 300 (21), 256 (24), 212 (53), 181 (26), 155 (11), 131 (31), 91 (18), 59 (56), 57 (47), 56 (100), 55 (36), 53 (12), 51 (13), 49 (13). HRMS (ESI) calcd for $C_{29}H_{33}N_3O_7SNa$ (M + Na$^+$) 590.1931, found 590.1937. HPLC (column: Reprosil 100 Chiral-NR 8 μm, solvent: *n*-hexane:ethanol 97:7, flow = 0.8 mL/min) t_R = 63.37, 70.22 min. Anal. Calcd for $C_{29}H_{33}N_3O_7S$: C, 61.36; H, 5.86; N, 7.40; S, 5.65. Found: C, 61.16; H, 5.57; N, 7.16; S, 5.68.

Aziridiniation of (*Z*)-Di-*tert*-butyl 1-Oxoazepino[3,4-*b*]indole-2,10(1*H*,3*H*)-dicarboxylate (7) with Chloramine-B, Synthesis of (±)-8b. Olefin **7** (1.51 g, 3.78 mmol) was dissolved under argon in anhydrous acetonitrile (200 mL), then $PhNMe_3Br_3$ (71 mg, 0.189 mmol) and chloramine-B × 3 H_2O (405 mg, 1.89 mmol) were added. The mixture was stirred for 13 h and was quenched with saturated Na_2SO_3(aq) (200 mL). After extraction with ethyl acetate (3 × 200 mL), the combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude orange product was purified by column chromatography (silica gel 70−230 mesh, *n*-hexane to *n*-hexane:ethyl acetate (8:1) as the gradient eluent) to yield a white solid product and the starting material (0.81 g). The product was recrystallized from CH_2Cl_2:*n*-hexane to yield a white solid product (0.57 g, 54%). Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of a solution of ethyl acetate at room temperature. R_f 0.24 (*n*-hexane:ethyl acetate 6:1). Mp 203 °C (CH_2Cl_2:ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.05−7.99 (3H, m), 7.71 (1H, unresolved dd), 7.59 (2H, unresolved dd), 7.40 (1H, unresolved ddd), 7.13 (1H, unresolved dd), 7.06 (1H, s), 4.60 (1H, s), 3.96

(1H, d, J = 6.6 Hz), 3.85−3.74 (1H, m), 3.61 (1H, s), 1.59 (9H, s), 1.56 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.8, 151.8, 148.9, 137.9, 137.7, 134.2, 130.3, 129.5, 128.4, 127.8, 126.9, 123.8, 120.1, 116.9, 114.8, 85.3, 84.5, 35.8, 28.2, 27.8. ^{1}H NMR (400 MHz, 323 K, $CDCl_3$) δ (ppm) 8.03 (3H, m), 7.69 (1H, unresolved dddd), 7.57 (1H, unresolved dddd), 7.40 (1H, ddd, J = 8.4, 6.7, 1.7 Hz), 7.21−7.12 (2H, m), 4.54 (1H, d, J = 12.5 Hz), 3.90 (1H, d, J = 6.8 Hz), 3.83−3.76 (1H, m), 3.74−3.57 (1H, m), 1.59 (9H, s), 1.57 (9H, s). ^{13}C NMR (100 MHz, 323 K, $CDCl_3$) δ (ppm) 159.8, 152.1, 149.0, 138.3, 138.1, 134.1, 130.5, 129.5, 128.4, 127.8, 127.1, 123.8, 120.3, 117.0, 114.9, 85.3, 84.5, 45.6, 42.0, 36.0, 28.3, 27.8. IR (KBr) ν (cm^{-1}) 3423 w, 3119 w, 3070 w, 2981 m, 2932 w, 1751 s, 1720 s, 1696 s, 1607 w, 1556 w, 1474 sh, 1448 m, 1428 sh, 1395 m, 1369 s, 1338 s, 1322 s, 1290 s, 1261 s, 1222 s, 1208 s, 1170 s, 1150 s, 1125 m, 1091 s, 1020 m, 1002 m, 976 m, 954 m, 895 w, 879 m, 857 m, 811 m, 773 m, 754 m, 744 s, 726 m, 692 w, 670 w, 639 w, 594 m, 555 m, 504 w, 486 w, 442 w. MS (EI) m/z (rel. intensity) 553 (1), 353 (18), 356 (36), 213 (81), 212 (100), 199 (10), 198 (75), 197 (25), 185 (63), 184 (60), 183 (60), 169 (31), 168 (13), 167 (17), 157 (16), 156 (26), 155 (43), 142 (11), 130 (13), 129 (22), 128 (25), 127 (15), 126 (10), 101 (14), 78 (42), 77 (63), 64 (11), 57 (68), 56 (87), 55 (43), 53 (11), 51 (29), 50 (18), 44 (69), 41 (85), 40 (16), 39 (76). HRMS (EI) calcd for $C_{28}H_{31}N_3O_7S$ (M^+) 553.1877, found 553.1877. Anal. Calcd for $C_{28}H_{31}N_3O_7S$: C, 60.74; H, 5.64; N, 7.59; S, 5.79. Found: C, 60.53; H, 5.93; N, 7.56; S, 6.02.

Copper-Catalyzed Aziridiniation of (*Z*)-Di-*tert*-butyl 1-Oxoazepino[3,4-*b*]indole-2,10(1*H*,3*H*)-dicarboxylate, Synthesis of (±)-8c.[33] Olefin **7** (4.00 g, 10.0 mmol), $PhI(OAc)_2$ (2.58 g, 8 mmol), 5-methylpyridine-2-sulfonamide (1.38 g, 8.00 mmol), copper(II) trifluoroacetylacetonate [$Cu(tfac)_2$] (148 mg, 0.40 mmol), and activated 4 Å molecular sieve (20 g) were suspended under argon in anhydrous acetonitrile (80 mL). The mixture was stirred for 13 h. It was then diluted with ethyl acetate (400 mL) and washed with water (400 mL). The aqueous layer was further extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude solid product was purified by column chromatography (silica gel 70−230 mesh, *n*-hexane to *n*-hexane:ethyl acetate 4:1 as the gradient eluent) to yield a white solid product (2.44 g, 76%) and a pure fraction of starting material **7** (1.74 g, 43%). The product was recrystallized from diethyl ether:*n*-hexane. Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of a solution of CH_2Cl_2 at ambient temperature. R_f 0.06 (*n*-hexane:ethyl acetate 4:1). Mp 149−150 °C (Et_2O:*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.57 (1H, s), 8.01 (1H, d, J = 8.5 Hz), 7.99 (1H, d, J = 8.0 Hz), 7.71 (1H, dd, J = 8.0, 1.7 Hz), 7.67 (1H, d, J = 8.0 Hz), 7.39−7.44 (1H, m), 7.22−7.27 (1H, m), 4.60 (1H, br s), 4.21 (1H, d, J = 7.0 Hz), 3.93 (1H, ddd, J = 8.9, 7.0, 4.7 Hz), 3.63 (1H, br s), 2.44 (3H, s), 1.57 (9H, s), 1.53 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$, 323 K) δ (ppm) 159.7, 153.4, 151.8, 150.8, 148.8, 138.5, 138.2, 138.0, 130.4, 127.7, 127.0, 123.6, 122.8, 120.7 117.2, 114.6, 85.1, 84.2, 45.4, 42.2, 35.8, 28.1, 27.7, 18.5. IR (KBr) ν (cm^{-1}) 3443 s, 2981 s, 2934 m, 1770 sh, 1749 s, 1721 s, 1635 w, 1558 w, 1447 s, 1394 m, 1370 s, 1315 s, 1292 sh, 1259 s, 1227 s, 1156 s, 1104 s, 1083 s, 1024 m, 1000 m, 975 m, 952 m, 850 m, 832 m, 810 w, 767 m, 751 m, 744 m, 693 m, 679 w, 659 w, 638 w, 589 w, 569 m, 562 m, 549 m, 524 w, 495 w, 469 w, 425 w. HRMS (ESI) calcd for $C_{28}H_{33}N_4O_7S^+$ ($M + H^+$) m/z 569.2064, found 569.2072 and calcd for $C_{28}H_{32}N_4O_7SNa$ ($M+Na^+$) m/z 591.1884, found 591.1897. Anal. Calcd for $C_{28}H_{32}N_4O_7S$: C, 59.14; H, 5.67; N, 9.85; S, 5.64. Found: C, 58.93; H, 5.46; N, 9.54; S, 5.80.

General Procedure for the Ring-Opening Reaction of Aziridines with Indoles (General Procedure A). Aziridine (±)-**8a**−**c** (0.2 mmol) and an indole derivative (2 mmol) were dissolved in an appropriate solvent (e.g., CH_2Cl_2, acetone or ethyl acetate) and activated silica (429 mg, 0.040−0.063 mm) was added. The solvent was removed under reduced pressure and the solid mixture was heated under argon at 70 °C overnight (~12−16 h). Purification by column chromatography (silica gel 70−230 mesh, CH_2Cl_2 to CH_2Cl_2:MeOH 10:1 as the gradient eluent) yielded the crude product. It was then washed or recrystallized as described below and in the Supporting Information.

***N*-(5-(1*H*-Indol-3-yl)-1-oxo-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indol-4-yl)tosylamide ((±)-11a).** A crude product was obtained following general procedure A. It was dissolved in CH_2Cl_2; *n*-hexane was added dropwise until some precipitate was formed. Then the solution was cooled to 4 °C and finally filtered to yield a white solid product (90 mg, 93%). R_f 0.12 (CH_2Cl_2:MeOH 20:1). Mp 145−146 °C (CH_2Cl_2:*n*-hexane, dec). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.34 (1H, br s), 10.73 (1H, br s), 8.06−7.96 (2H, m), 7.61 (2H, d, J = 8.1 Hz), 7.38 (1H, d, J = 8.1 Hz), 7.27−7.20 (3H, m), 7.08 (1H, unresolved ddd), 7.04−6.96 (1H, m), 6.92 (1H, d, J = 8.1 Hz), 6.80−6.71 (3H, m), 4.69 (1H, d, J = 4.3 Hz), 3.64−3.56 (1H, m), 3.51−3.47 (1H, m), 3.19−3.06 (1H, m), 2.37 (3H, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 164.0, 142.4, 137.6, 136.3, 136.2, 129.4, 127.5, 126.6, 125.1, 124.7, 123.7, 120.9, 120.6, 118.7, 118.4, 117.5, 117.4, 116.8, 115.4, 112.1, 111.7, 54.6, 41.6, 25.0, 21.1. IR (KBr) ν (cm^{-1}) 3361 s, 3057 m, 2923 m, 2863 m, 1926 w, 1644 s, 1547 m, 1481 s, 1455 s, 1338 s, 1291 m, 1244 w, 1222 w, 1185 w, 1158 s, 1088 s, 1006 w, 989 w, 943 w, 883 w, 814 m, 744 s, 661 m, 578 m, 552 m, 531 m, 428 w. MS (CI) m/z (rel. intensity) 485 (12), 484 (39), 329 (35), 314 (19), 313 (100), 312 (21), 301 (15), 300 (82), 272 (19), 271 (29), 270 (11), 243 (24), 242 (15), 216 (12), 212 (20), 185 (20), 145 (86), 91 (15). HRMS (ESI) calcd for $C_{27}H_{25}N_4O_3S$ ($M + H^+$) 485.1642, found 485.1639.

***N*-(5-(1*H*-Indol-3-yl)-1-oxo-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indol-4-yl)benzenesulfonamide ((±)-13a).** A crude product was obtained following general procedure A. It was recrystallized from CH_2Cl_2 to yield a white solid product (61 mg, 66%). R_f 0.37 (CH_2Cl_2:MeOH 10:1) mp 189 °C (CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.33 (1H, br s), 10.73 (1H, d, J = 2.2 Hz), 8.10 (1H, d, J = 5.9 Hz), 7.98 (1H, dd, J = 6.3, 3.2 Hz), 7.80−7.74 (2H, m), 7.60 (1H, unresolved dddd), 7.52−7.42 (2H, m), 7.39 (1H, d, J = 8.3 Hz), 7.25 (1H, d, J = 8.1 Hz), 7.09 (1H, unresolved ddd), 7.04−6.97 (1H, m), 6.91 (1H, d, J = 8.1 Hz), 6.83−6.78 (2H, m), 6.75 (1H, unresolved ddd), 6.62 (1H, d, J = 2.2 Hz), 4.71 (1H, d, J = 4.2 Hz), 3.65 (1H, dd, J = 10.8, 6.1 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 164.0, 140.7, 136.3, 126.2, 132.3, 129.0, 127.6, 127.5, 126.5, 125.1, 124.7, 123.7, 121.0, 120.6, 118.7, 118.5, 117.4, 117.0, 115.3, 112.1, 111.7, 54.9, 54.4, 41.3. IR (KBr) ν (cm^{-1}) 3411 s, 3313 s, 3063 m, 2874 m, 1640 s, 1550 m, 1480 s, 1454 m, 1419 m, 1338 s, 1294 sh, 1265 sh, 1245 m, 1220 m, 1161 s, 1088 s, 1011 w, 989 w, 950 m, 879 w, 812 w, 739 s, 688 s, 585 s, 528 m, 488 m, 451 m, 426 m. MS (EI) m/z (rel. intensity) 470 (22), 329 (23), 314 (11), 313 (49), 312 (13), 301 (11), 300 (51), 272 (14), 271 (24), 270 (11), 243 (28), 242 (17), 216 (18), 212 (17), 207 (13), 185 (19), 145 (91), 77 (22), 69 (12), 45 (11), 44 (100), 43 (21), 41 (10). HRMS (EI) calcd for $C_{26}H_{22}N_4O_3S$ (M^+) 470.1407, found 470.1407.

***N*-(5-(1*H*-Indol-3-yl)-1-oxo-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indol-4-yl)-5-methylpyridine-2-sulfonamide ((±)-14a).** A crude product was obtained following general procedure A. It was washed with diethyl ether and finally filtered to yield a white solid product (89 mg, 92%). R_f 0.17 (CH_2Cl_2:MeOH 100:5). mp >300 °C (Et_2O). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.28 (1H, s), 10.67 (1H, d, J = 2.0 Hz), 8.25 (1H, br s), 8.02−8.06 (2H, m), 7.61 (2H, m), 7.34 (1H, d, J = 8.2 Hz), 7.22 (1H, d, J = 8.1 Hz), 7.17 (1H, d, J = 7.9 Hz), 6.96−7.08 (3H, m), 6.81−6.85 (1H, m), 6.71−6.76 (2H, m), 4.82 (1H, d, J = 5.3 Hz), 4.03 (1H, dd, J = 12.9, 6.6 Hz), 3.49 (1H, dd, J = 14.0, 3.9 Hz), 3.17−3.26 (1H, m), 2.30 (3H, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 164.3, 155.3, 149.9, 138.1, 136.8, 136.5, 136.4, 127.7, 127.5, 125.4, 124.8, 123.8, 121.0, 120.9, 120.8, 118.8, 118.5, 118.1, 116.9, 115.8, 112.2, 111.8, 55.8, 42.9, 40.1, 18.2. IR (KBr) ν (cm^{-1}) 3411 s, 3359 s, 3191 sh, 3083 sh, 2871 m, 1930 w, 1648 s, 1556 m 1485 s, 1456 s, 1340 s,

1307 s, 1247 w, 1223 m, 1202 w, 1163 s, 1131 w, 1109 m, 1094 s, 1051 w, 1028 w, 1003 m, 993 m, 960 m, 881 w, 835 w, 807 w, 747 s, 663 s, 636 m, 612 m, 575 m, 554 s, 530 m, 501 w, 427 w. HRMS (CI) calcd for $C_{26}H_{22}N_5O_3S$ (M^-) 484.1449, found 484.1437.

General Procedure for the Reaction of 5-Hydroxy-2,3,4,5-tetrahydroazepino[3,4-*b*]indol-1(10*H*)-one ((±)-6) with Indoles (General Procedure B). Alcohol (±)-**6** (100 mg, 0.462 mmol) and an indole derivative (4.62 mmol) were dissolved in the heat with an appropriate solvent (acetone or dichloromethane and ethyl acetate) and activated silica (800 mg, 0.040−0.063 mm) was added. The solvent was removed under reduced pressure and the mixture was heated to 70 °C overnight (∼12−16 h). Purification by column chromatography (silica gel 70−230 mesh, CH_2Cl_2 to CH_2Cl_2:MeOH 20:1 as the gradient eluent) yielded the crude product. It was then washed or recrystallized as described below and in the Supporting Information.

5-(1*H*-Indol-3-yl)-2,3,4,5-tetrahydroazepino[3,4-*b*]indol-1(10*H*)-one ((±)-15a). A crude product was obtained following general procedure B. After recrystallization from hot MeOH a white solid (133 mg, yield: 91%) was obtained at 4 °C. R_f 0.23 (CH_2Cl_2:MeOH 20:1). Mp 271 °C (MeOH, dec). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.24 (1H, br s), 10.76 (1H, d, J = 1.9 Hz), 8.11 (1H, dd, J = 5.7, 4.0 Hz), 7.52 (1H, d, J = 7.7 Hz), 7.38 (1H, d, J = 8.1 Hz), 7.32 (1H, d, J = 8.1 Hz), 7.12−7.01 (3H, m), 6.94 (1H, unresolved ddd), 6.79−6.70 (2H, m), 4.95 (1H, dd, J = 5.3, 5.1 Hz), 3.36−3.25 (1H, m), 3.22−3.08 (1H, m), 2.34−2.23 (2H, m). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 164.1, 136.4, 136.0, 127.8, 127.4, 125.8, 123.8, 123.6, 121.0, 120.9, 119.3, 119.0, 118.6, 118.3, 118.3, 112.1, 111.6, 37.7, 34.8, 33.4. IR (KBr) ν (cm^{-1}) 3351 s, 3306 s, 3055 m, 2951 m, 2930 m, 2865 m, 1895 w, 1780 w, 1623 s, 1575 m, 1542 s, 1482 s, 1455 m, 1447 m, 1420 m, 1402 m, 1369 m, 1335 s, 1310 m, 1293 m, 1246 m, 1223 m, 1190 w, 1158 m, 1112 w, 1095 m, 1054 m, 1039 w, 1010 m, 991 w, 973 w, 946 w, 913 w, 880 w, 819 w, 776 m, 765 sh, 752 s, 745 s, 713 m, 678 m, 653 m, 631 w, 605 m, 585 m, 528 w, 505 m, 473 w, 446 w, 424 w, 408 w. MS (EI) *m*/*z* (rel. intensity) 316 (21), 315 (100), 298 (39), 297 (12), 286 (22), 285 (30), 272 (15), 271 (20), 269 (13), 258 (23), 257 (35), 256 (15), 243 (12), 198 (45), 128 (10), 44 (13). HRMS (EI) calcd for $C_{20}H_{17}N_3O$ (M^+) 315.1366, found 315.1366.

Di-*tert*-butyl 4-(4-Methylphenylsulfonamido)-1-oxo-4,5-dihydroazepino[3,4-*b*]indole-2,10(1*H*, 3*H*)-dicarboxylate ((±)-16a). Aziridine (±)-**8a** (200 mg, 0.352 mmol) and ammonium formate (33 mg, 0.528 mmol) were dissolved in absolute MeOH (10 mL). After addition of Pd/C (10 mg, 5%(w/w)) the reaction was heated to reflux for 1.5 h. After cooling to room temperature the reaction mixture was filtered and the solvent was removed in vacuo. Purification by column chromatography (silica gel 70−230 mesh, *n*-hexane:ethyl acetate 6:1) yielded an off-white solid (155 mg, 76%). R_f 0.58 (*n*-hexane:ethyl acetate 1:1). mp 71 °C (ethyl acetate:*n*-hexane). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.97 (1H, d, J = 8.6 Hz), 7.84 (1H, d, J = 7.1 Hz), 7.73 (1H, d, J = 8.3 Hz), 7.51 (1H, unresolved ddd), 7.50−7.44 (3H, m), 7.33 (1H, unresolved ddd), 4.00−3.84 (2H, m), 3.54 (1H, dd, J = 14.7, 8.3 Hz), 2.99 (1H, dd, J = 15.7, 3.2 Hz), 2.88 (1H, dd, J = 15.7, 6.6 Hz), 2.44 (3H, s), 1.53 (9H, s), 1.45 (9H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 161.1, 150.6, 148.5, 143.0, 138.4, 137.4, 130.2, 129.8, 127.8, 127.4, 126.5, 123.3, 123.1, 120.8, 114.0, 84.4, 82.6, 52.3, 47.8, 27.5, 27.2, 26.0, 21.0. IR (KBr) ν (cm^{-1}) 3439 m, 3267 sh, 2978 m, 2927 m, 2856 sh, 1742 s, 1599 w, 1553 w, 1450 m, 1415 m, 1395 m, 1370 s, 1326 m, 1236 m, 1158 s, 1122 sh, 1092 m, 1064 m, 1022 w, 992 m, 956 w, 893 w, 852 w, 816 w, 764 m, 750 m, 707 w, 664 m, 590 w, 552 w, 524 w. MS (EI) *m*/*z* (rel. intensity) 569 (1), 383 (9), 369 (7)339 (12), 275 (6), 199 (14), 198 (100), 197 (19), 185 (33), 184 (18), 91 (8), 56 (42), 55 (14). HRMS (ESI) calcd for $C_{29}H_{35}N_3NaO_7S$ ($M + Na^+$) 592.2088, found 592.2091.

4-Methyl-*N*-(1-oxo-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indol-4-yl)benzenesulfonamide ((±)-16b). Compound (±)-**16a** (90 mg, 0.158 mmol) was dissolved in 7:1 CH_2Cl_2:TFA and the mixture was stirred for 2 h at room temperature. Then saturated $NaHCO_3$-(aq) (30 mL) was added slowly and the mixture was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were dried over $MgSO_4$. After filtration the solvent was removed under reduced pressure to yield a green oil. Purification by column chromatography (silica gel 70−230 mesh, ethyl acetate) yielded a white solid (56 mg, 96%). R_f 0.46 (*n*-hexane:ethyl acetate 1:1). Mp 206 °C (ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.27 (1H, s), 8.00 (1H, d, J = 6.2 Hz), 7.97 (1H, unresolved dd), 7.76 (2H, d, J = 8.3 Hz), 7.43−7.32 (4H, m), 7.19 (1H, ddd, J = 8.2, 7.0, 1.0 Hz), 7.00 (1H, unresolved ddd), 3.58−3.46 (1H, m), 3.32−3.27 (2H, m), 3.00 (1H, dd, J = 17.1, 5.4 Hz), 2.91 (1H, dd, J = 16.9, 8.7 Hz), 2.38 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 163.9, 142.7, 138.2, 136.0, 129.7, 127.1, 126.9, 126.5, 124.1, 119.5, 119.2, 112.8, 112.1, 51.9, 46.7, 31.4, 21.0. IR (KBr) ν (cm^{-1}) 3297 s, 3247 s, 3061 sh, 2918 m, 1615 s, 1550 m, 1478 s, 1452 s, 1414 m, 1325 s, 1284 s, 1269 m, 1228 w, 1185 w, 1154 s, 1117 w, 1092 m, 1061 w, 1005 w, 957 w, 916 w, 889 m, 943 w, 832 w, 812 m, 787 w, 761 m, 741 m, 662 m, 590 w, 570 w, 550 m, 522 m, 431 w. MS (EI) *m*/*z* (rel. intensity) 369 (11), 199 (29), 198 (100), 185 (31), 169 (17), 167 (13), 158 (11), 157 (12), 155 (10), 130 (19), 129 (19), 128 (13), 91 (19), 44 (11). HRMS (EI) calcd for $C_{19}H_{20}N_3O_3S$ ($M + H^+$) 370.1220, found 370.1228.

5-(Octyloxy)-2,3,4,5-tetrahydroazepino[3,4-*b*]indol-1(10*H*)-one ((±)-17). Alcohol (±)-**6** (100 mg, 0.462 mmol) and *n*-octanol (602 mg, 4.62 mmol) were dissolved in acetone and activated silica (800 mg, 0.040−0.063 mm) was added. The solvent was removed under reduced pressure and the mixture was heated to 70 °C for 15 h. Purification by column chromatography (silica gel 70−230 mesh, ethyl acetate) yielded 23 mg (15%) of a colorless solid. R_f 0.31 (ethyl acetate). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.38 (1H, br s), 8.18 (1H, dd, J = 6.2, 3.0 Hz), 7.63 (1H, d, J = 8.1 Hz), 7.42 (1H, d, J = 8.3 Hz), 7.20 (1H, ddd, J = 8.3, 7.0, 1.1 Hz), 7.04 (1H, ddd, J = 7.9, 7.0, 0.9 Hz), 4.88 (1H, unresolved dd), 3.68−3.50 (2H, m), 3.49−3.37 (1H, m), 3.22−3.09 (1H, m), 2.46−2.32 (1H, m), 1.98−1.84 (1H, m), 1.57−1.43 (2H, m), 1.39−1.14 (10H, m), 0.84 (3H, t, J = 6.9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 163.4, 135.7, 127.7, 127.6, 123.9, 120.8, 119.4, 117.1, 112.2, 71.7, 67.4, 35.5, 31.2, 30.8, 29.8, 28.8, 28.7, 25.9, 22.1, 14.0. HRMS (ESI) calcd for $C_{20}H_{28}N_2NaO_2$ ($M + Na^+$) 351.2043, found 351.2046.

Di-*tert*-butyl 5-Methoxy-4-(4-methylphenylsulfonamido)-1-oxo-4,5-dihydroazepino[3,4-*b*]indole-2,10(1*H*,3*H*)-dicarboxylate ((±)-18a). Aziridine (±)-**8a** (284 mg, 0.50 mmol) was suspended in absolute MeOH (5 mL) and ceric ammonium nitrate (CAN) (27 mg, 0.05 mmol) was added. The reaction was stirred at room temperature for 9 h until no further changes were observed by TLC. The solvent was removed in vacuo. Purification by column chromatography (silica gel 70−230 mesh, *n*-hexane:ethyl acetate 3:1) yielded the starting material (150 mg) and a white solid product (141 mg, 47%, 99% based on recycled starting material). R_f 0.21 (*n*-hexane:ethyl acetate 3:1). Mp 79−80 °C (*n*-hexane:ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.00 (1H, d, J = 8.6 Hz), 7.82 (1H, d, J = 8.3 Hz), 7.73 (2H, d, J = 8.1 Hz), 7.60 (1H, d, J = 7.8 Hz), 7.55 (1H, ddd, J = 8.4, 7.2, 1.2 Hz), 7.47 (2H, d, J = 7.8 Hz), 7.39 (1H, unresolved ddd), 4.70 (1H, br s), 4.07−3.96 (1H, m), 3.83 (1H, dd, J = 14.9, 5.6 Hz), 3.43 (1H, dd, J = 14.8, 10.4 Hz), 2.99 (3H, s), 2.44 (3H, s), 1.54 (9H, s), 1.38 (9H, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 160.4, 150.1, 148.4, 143.2, 138.3, 136.7, 130.7, 130.0, 127.8, 127.7, 126.5, 123.8, 122.4, 120.1, 114.1, 85.0, 82.2, 76.1, 56.5, 55.0, 46.7, 27.5, 27.2, 21.0. IR (KBr) ν (cm^{-1}) 3438 m, 3278 m, 2981 m, 2933 m, 2821 w, 1753 s, 1679 w, 1665 w, 1649 w, 1599, 1548 w, 1477 sh, 1449 s, 1416 m, 1394 sh, 1372 s, 1350 s, 1325 s, 1288 s, 1261 m, 1228 m, 1213 m, 1160 s, 1093 s, 1078 sh, 1043 w, 1025 m, 994 s, 958 w, 892 m, 862 m, 833 m, 815 w, 785 m, 772 m, 753 m, 707 w, 664 m, 596 w, 553 s, 538 sh, 472 w. MS (EI) *m*/*z* (rel. intensity) 599 (1), 499 (4), 399 (13), 339 (11), 338 (15), 288 (33), 274 (17), 244 (29), 228 (11),

215 (15), 214 (13), 213 (26), 212 (100), 198 (12), 187 (14), 186 (28), 185 (92), 184 (31), 183 (19), 169 (12), 156 (17), 155 (20), 130 (24), 129 (16), 128 (14), 92 (13), 91 (36), 60 (15), 57 (12), 56 (51), 55 (14), 44 (72), 41 (79). HRMS (EI) calcd for $C_{30}H_{37}N_3O_8S$ (M^+) 599.2296, found 599.2296.

***N*-(5-Methoxy-1-oxo-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indol-4-yl)-4-methylbenzenesulfonamide ((±)-18b).** Sulfonamide (±)-**18a** (128 mg, 0.213 mmol) was dissolved in CH_2Cl_2 and activated silica (600 mg, 0.040−0.063 mm) was added. The solvent was removed in vacuo and the residue was heated to 70 °C for 13 h. Purification by column chromatography (silica gel 70−230 mesh, *n*-hexane:ethyl acetate 1:2) yielded a white solid (63 mg, 74%). R_f 0.31 (*n*-hexane:ethyl acetate). Mp 170 °C (*n*-hexane:ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.54 (1H, br s), 8.01−7.92 (2H, m), 7.77 (2H, unresolved ddd), 7.46−7.37 (4H, m), 7.21 (1H, ddd, J = 8.3, 6.9, 1.0 Hz), 7.04 (1H, ddd, J = 8.3, 6.9, 1.0 Hz), 4.42 (1H, d, J = 3.9 Hz), 3.76−3.69 (1H, m), 3.46−3.38 (1H, m), 3.19−3.10 (1H, m), 3.06 (3H, s), 2.40 (3H, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 163.4, 142.7, 138.5, 135.8, 129.6, 128.0, 127.9, 126.6, 124.0, 120.2, 119.7, 112.8, 112.3, 76.5, 55.3, 51.6, 40.9, 21.0. IR (KBr) ν (cm^{-1}) 3349 s, 3284 m, 3199 m, 2927 m, 2823 sh, 1733 w, 1651 s, 1597 w, 1578 w, 1549 m, 1480 s, 1445 m, 1341 s, 1291 m, 1248 w, 1211 w, 1185 sh, 1158 s, 1116 m, 1091 s, 1020 m, 996 m, 960 m, 884 m, 839 w, 815 m, 781 w, 740 m, 663 m, 615 w, 538 m, 430 w. HRMS (EI) calcd for $C_{20}H_{21}N_3NaO_4S$ ($M + Na^+$) 422.1145, found 422.1145.

2,3,4,5-Tetrahydro-5-(1*H*-pyrazol-1-yl)-4-(tosylamino)azepino-[3,4-*b*]indol-1(10*H*)-one ((±)-19a). Aziridine (±)-**8a** (113 mg, 0.2 mmol) and 1*H*-pyrazole (136 mg, 2.0 mmol) were dissolved in an CH_2Cl_2 and activated silica (429 mg, 0.040−0.063 mm) was added. The solvent was removed under reduced pressure and the solid mixture was heated under argon at 70 °C for 16 h. Purification by column chromatography (silica gel 70−230 mesh, CH_2Cl_2 to CH_2Cl_2:MeOH 50:1 as the gradient eluent) yielded the crude product. This was dissolved in CH_2Cl_2 and *n*-hexane was added dropwise. After cooling to 4 °C a white solid (51 mg, 59%) was collected by filtration. R_f 0.34 (CH_2Cl_2:MeOH 10:1). Mp 206 °C (CH_2Cl_2:*n*-hexane). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.67 (1H, s), 8.23 (1H, d, J = 5.1 Hz), 8.20 (1H, d, J = 3.9 Hz), 7.53 (2H, unresolved ddd), 7.46 (1H, d, J = 2.2 Hz), 7.41 (1H, unresolved ddd), 7.31−7.26 (3H, m), 7.18−7.12 (1H, m), 6.89−6.84 (2H, m), 6.05 (1H, unresolved dd), 5.79 (1H, d, J = 6.1 Hz), 3.96 (1H, unresolved ddd), 3.31−3.26 (1H, m), 2.37 (3H, s) ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 163.2, 142.5, 139.0, 138.0, 135.9, 129.7, 129.6, 128.3, 126.9, 126.3, 124.1, 119.8, 119.4, 112.4, 110.4, 105.0, 61.6, 56.4, 42.4, 21.0. IR (KBr) ν (cm^{-1}) 3321 w, 3060 m, 2921 m, 1645 s, 1599 m, 1580 w, 1554 m, 1479 s, 1454 m, 1397 m, 1338 s, 1288 s, 1248 w, 1221 w, 1185 m, 1160 s, 1091 s, 1046 m, 1020 w, 1007 w, 992 w, 944 w, 882 w, 837 w, 814 m, 747 s, 705 m, 662 m, 579 m, 552 m, 534 m, 433 w. MS (EI) *m*/*z* (rel. intensity) 435 (4), 265 (12), 264 (71), 222 (13), 213 (23), 212 (100), 198 (19), 197 (19), 196 (12), 185 (74), 184 (23), 183 (11), 169 (18), 156 (16), 155 (19), 97 (10), 91 (30), 83 (12), 71 (15), 68 (33), 57 (24), 55 (17). HRMS (EI) calcd for $C_{22}H_{21}N_5O_3S$ (M^+) 435.1360, found 435.1360.

General Procedure for Ring-Opening Reactions of Aziridines with Secondary Amines (Procedure C). Aziridine (±)-**8a** (142 mg, 0.25 mmol) was dissolved in absolute 1,4-dioxane (5 mL) under argon in a Schlenk tube with a Teflon screwed stopper. After addition of the appropriate amine (1.25 mmol) the sealed reaction vessel was heated to 80 °C for 5 d. Then it was cooled to room temperature and the solvent was removed in vacuo. Purification by column chromatography (silicagel 70−230 mesh, CH_2Cl_2 to CH_2Cl_2:MeOH 30:1 as a gradient eluent) yielded an oily, pale-yellow product. This was washed or recrystallized from hot diethyl ether as described below and in the Supporting Information.

4-Methyl-*N*-(1-oxo-5-(pyrrolidin-1-yl)-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indol-4-yl)benzenesulfonamide ((±)-20a). A crude product was obtained following general procedure C. Recrystallization from boiling diethyl ether yielded a white solid (86 mg, 78%). R_f 0.37 (CH_2Cl_2:MeOH 10:1). Mp 185 °C (Et_2O). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.49 (1H, br s), 7.89−7.76 (2H, m), 7.72 (2H, d, J = 8.3 Hz), 7.44−7.33 (4H, m), 7.18 (1H, unresolved ddd), 7.01 (1H, unresolved ddd), 3.94 (1H, d, J = 3.4 Hz), 3.81−3.69 (1H, m), 3.52−3.40 (1H, m), 3.11−2.97 (1H, m), 2.40 (3H, s), 2.38−2.26 (2H, m), 2.16−2.01 (2H, m), 1.54−1.35 (4H, br s). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 164.1, 142.5, 138.9, 135.7, 129.5, 128.6, 128.5, 126.6, 123.5, 120.5, 119.1, 113.1, 112.1, 61.0, 54.0, 50.0, 42.8, 22.8, 21.0. IR (KBr) ν (cm^{-1}) 3337 s, 3204 s, 3061 sh, 2964 m, 2873 m, 2803 m, 1918 w, 1739 w, 1645 s, 1577 w, 1547 s, 1484 s, 1444 s, 1337 s, 1305 m, 1289 m, 1246 m, 1214 m, 1186 w, 1156 s, 1092 s, 1042 w, 1007 w, 991 m, 948 m, 877 w, 835 w, 814 m, 776 m, 741 s, 660 s, 579 m, 550 s, 536 s, 436 m. MS (EI) *m*/*z* (rel. intensity) 438 (5), 367 (44), 283 (13), 213 (60), 212 (100), 199 (10), 198 (72), 197 (17), 185 (67), 169 (12), 167 (14), 156 (19), 155 (24), 129 (11), 128 (16), 92 (12), 91 (29), 71 (51), 70 (68). HRMS (EI) calcd for $C_{23}H_{26}N_4O_3S$ (M^+) 438.1720, found 438.1721.

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Supporting Information Available: All experimental procedures, characterization of all other compounds, molecular structures, and crystallographic data of **7**, (±)-**8a**−**c,** (±)-**11f**, and (±)-**15d** and atom coordinates of calculated (±)-**6** (**A**) and cationic intermediate (**B**). This material is available free of charge via the Internet at http://pubs.acs.org.

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