Nucleophilic Addition of 1-Acetylindole Enolates to Pyridinium Salts. Stereoselective Formal Synthesis of (±)-Geissoschizine and (±)-Akagerine via 1,4-Dihydropyridines

M.-Lluïsa Bennasar,* Juan-Miguel Jiménez, Bernat Vidal, Bilal A. Sufi, and Joan Bosch

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona 08028, Spain

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Addition of the enolate derived from 1-acetylindole (**3**) to pyridinium salt **4b** followed by acid-induced cyclization of the resulting 1,4-dihydropyridine **5b** in the presence of lithium iodide gives tetracyclic 3,7-methano[1,4]diazonino[1,2-*a*]indole **6b**, which has subsequently been elaborated into the (*E*)-ethylidene derivative **7b**. From this compound is reported a stereocontrolled route to (±)-geissoschizine, involving closure of C ring by Pummerer reaction, methanolysis of the resulting pentacyclic lactam **12**, and desulfurization. A similar synthetic sequence starting from the enolate of **3** and 2-fluoropyridinium salt **15b** gives access to the pentacyclic dilactam **2**, which had previously been converted to (±)-akagerine through opening of the piperidone (D) ring.

The nucleophilic addition of indole-containing enolates to *N*-alkylpyridinium salts to give 1,4-dihydropyridines constitutes a general and versatile method for the synthesis of indole alkaloids.[1] Taking advantage of the high reactivity of both the dihydropyridine and indole rings, it is possible to build complex polycyclic structures, thus providing access to a variety of alkaloids belonging to different structural types. Starting from the enolates derived from 1-, 2-, and 3-indoleacetates, we have synthesized indole alkaloids of the C-mavacurine[2] and *Strychnos*[3] groups, as well as tetracyclic akuammiline-type substructures,[4] respectively. Similarly, starting from 2-acetylindole enolates, we have completed total syntheses of bridged (ervitsine) and fused 2-acylindole alkaloids of the ervatamine and silicine groups.[5]

In this paper, we report the extension of this methodology, using the enolate derived from 1-acetylindole as the nucleophilic partner. Successive formation of C-15/C-16 and C-2/C-3 (biogenetic numbering)[6] bonds, the former by nucleophilic attack of 1-acetylindole enolate to the γ-position of a pyridinium salt and the latter by acid-promoted cyclization of the resulting 1,4-dihydropyridine on the indole ring, affords tetracyclic 1-acylindole derivatives (**A**), from which we present short stereocontrolled synthetic routes to the alkaloids geissoschizine[7] and akagerine.[8]

Geissoschizine is a pivotal early intermediate in indole alkaloid biosynthesis that has received considerable attention from the synthetic standpoint,[9] although most of the reported syntheses suffer from some stereochemical problems, as they usually lead to C-3/C-15 trans derivatives and/or to the unnatural *Z* configuration (or *Z*/*E* mixtures) for the ethylidene double bond. Consequently, additional steps to promote epimerization at C-3 and/or *Z*−*E* isomerization are required. Akagerine, a tetracyclic indole alkaloid isolated in 1975 from *Strychnos usambarensis*[10] and later from several *Strychnos* species,[11] has a peculiar skeleton related to that of geissoschizine, but lacking the characteristic piperidine (D) ring and containing an additional link between N-1 and C-17; consequently, it incorporates a perhydroazepine ring fused to a tetrahydro-β-carboline unit. This alkaloid has attracted much less synthetic attention: only one total synthesis in the racemic series via dilactam **2** (Scheme 1)[12] and one enantioselective synthesis of (−)-akagerine[13] have been reported to date.

Results and Discussion

Scheme 1 outlines the unified strategy for the synthesis of (±)-geissoschizine and (±)-akagerine. It consists of

(1) For a review, see: Bosch, J.; Bennasar, M.-L. *Synlett* **1995**, 587.
(2) (a) Bennasar, M.-L.; Alvarez, M.; Lavilla, R.; Zulaica, E.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 1156. (b) Bennasar, M.-L.; Zulaica, E.; Jiménez, J.-M.; Bosch, J. *J. Org. Chem.* **1993**, *58*, 7756.
(3) (a) Alvarez, M.; Salas, M.; de Veciana, A.; Lavilla, R.; Bosch, J. *Tetrahedron Lett.* **1990**, *31*, 5089. (b) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299.
(4) (a) Bennasar, M.-L.; Zulaica, E.; Ramírez, A.; Bosch, J. *J. Org. Chem.* **1996**, *61*, 1239. (b) Bennasar, M.-L.; Zulaica, E.; Ramírez, A.; Bosch, J. *Tetrahedron* **1999**, *55*, 3117.
(5) (a) Bennasar, M.-L.; Vidal, B.; Bosch, J. *Chem. Commun.* **1996**, 2755. (b) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3597.
(6) Le Men, J.; Taylor, W. *Experientia* **1965**, *21*, 508.
(7) For a preliminary account of this part of the work, see: Bennasar, M.-L.; Jiménez, J.-M.; Sufi, B. A.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 9105.
(8) For a preliminary account of this part of the work, see: Bennasar, M.-L.; Vidal, B.; Sufi, B. A.; Bosch, J. *Chem. Commun.* **1998**, 2639.
(9) (a) Yamada, K.; Aoki, K.; Kato, T.; Uemura, D.; van Tamelen, E. E. *J. Chem. Soc., Chem. Commun.* **1974**, 908. (b) Hachmeister, B.; Thielke, D.; Winterfeldt, E. *Chem. Ber.* **1976**, *109*, 3825. (c) Benson, W.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 862. (d) Wenkert, E.; Vankar, Y. D.; Yadav, J. S. *J. Am. Chem. Soc.* **1980**, *102*, 7971. (e) Banks, B. J.; Calverley, M. J.; Edwards, P. D.; Harley-Mason, J. *Tetrahedron Lett.* **1981**, *22*, 1631. (f) Bohlmann, C.; Bohlmann, R.; Rivera, E. G.; Vogel, C.; Manandhar, M. D.; Winterfeldt, E. *Liebigs Ann. Chem.* **1985**, 1752. (g) Wenkert, E.; Guo, M.; Pestchanker, M. J.; Shi, Y.-J.; Vankar, Y. D. *J. Org. Chem.* **1989**, *54*, 1166. (h) Overman, L. E.; Robichaud, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 300. (i) Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161. (j) Lounasmaa, M.; Jokela, R.; Miettinen, J.; Halonen, M. *Heterocycles* **1992**, *34*, 1497. (k) Lounasmaa, M.; Jokela, R.; Anttila, U.; Hanhinen, P.; Laine, C. *Tetrahedron* **1996**, *52*, 6803. (l) Takayama, H.; Watanabe, F.; Kitajima, M.; Aimi, N. *Tetrahedron Lett.* **1997**, *38*, 5307. (m) Martin, S. F.; Chen, K. X.; Eary, C. T. *Org. Lett.* **1999**, *1*, 79. (n) See also: Birman, V. B.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 7219.
(10) Angenot, L.; Dideberg, O.; Dupont, L. *Tetrahedron Lett.* **1975**, 1357.
(11) Massiot, G.; Delaude, C. *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1988; Vol. 34, pp 211−329.
(12) Benson, W.; Winterfeldt, E. *Heterocycles* **1981**, *15*, 935.
(13) Danieli, B.; Lesma, G.; Mauro, M.; Palmisano G.; Passarella, D. *J. Org. Chem.* **1995**, *60*, 2506.

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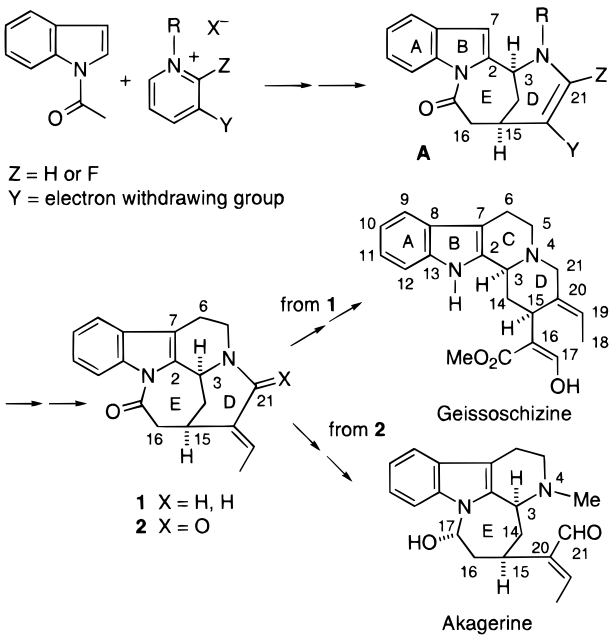
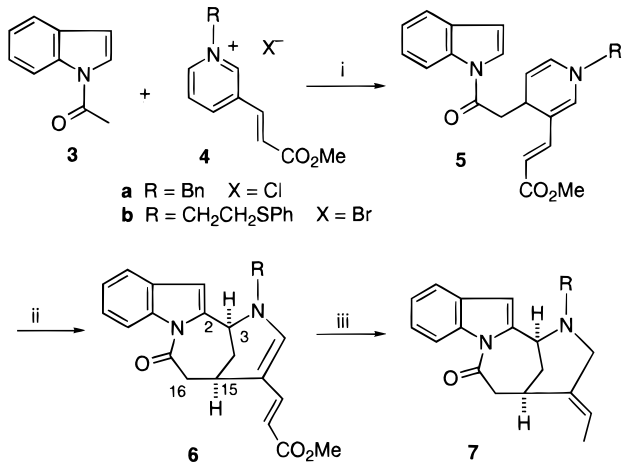
Scheme 1. Synthetic Strategy



three well-differentiated phases: (i) construction of the tetracyclic partially reduced 3,7-methano[1,4]diazonino-[1,2-*a*]indole system **A** (rings ABDE) using the above-mentioned nucleophilic addition−cyclization methodology; (ii) closure of the tryptamine bridge (C ring) by cyclization of the functionalized two-carbon N-4 substituent on the indole 3-position to give the apogeissoschizine-type[14,15] pentacyclic derivatives **1** or **2**; and (iii) opening of either the seven-membered lactam (E) ring or the piperidine (D) ring to give geissoschizine or akagerine, respectively. In the former case, we anticipated that the opening of E ring would easily occur to relieve the strain associated with the pentacyclic derivative **1** and that the bridgehead character of C-3 and C-15 in **1** would ensure the required C-3/C-15 cis relationship of geissoschizine. In the latter case, the opening of the piperidine ring has previously been effected from **2**,[12] taking advantage of the 2-piperidone moiety, so the preparation of this pentacyclic dilactam constitutes a formal total synthesis of akagerine. The oxo group at C-21 in **2** would be introduced either by oxidation of the piperidine ring of **1** (or a suitable tetracyclic precursor) or by substitution of a fluorine atom, which would be present in the starting pyridinium salt (Z = F), by a hydroxy group, taking advantage of the α-fluoro enamine moiety of **A**.

To make use of tetracyclic substrates bearing different functionalized two-carbon N-4 substituents, we initially planned to prepare tetracycle **7a**, which incorporates an easily removable *N*-benzyl group (Scheme 2). Thus, reaction of the enolate derived from 1-acetylindole (**3**) with pyridinium salt **4a** gave 1,4-dihydropyridine **5a** in 22% yield. Acid-induced (TsOH, C_6H_6) cyclization in the presence of lithium iodide[16] gave tetracycle **6a** (50%), which was stereoselectively elaborated in 33% yield into

Scheme 2[a]



[a] Reagents and conditions: (i) LDA, THF, −30 °C, 1.5 h; (ii) TsOH−C_6H_6, LiI, THF, rt, 1.5 h; (iii) 2.5 N HCl, MeOH, reflux, 2 h, then $NaBH_4$, MeOH, 0 °C, 1 h.

the (*E*)-ethylidenepiperidine **7a** by the known[17] one-pot sequence consisting of treatment with refluxing aqueous HCl and subsequent sodium borohydride reduction. However, preliminary experimentation revealed that debenzylation of **7a** by hydrogenolysis [($Pd(OH)_2$, MeOH] took place with simultaneous hydrogenation of the ethylidene substituent. Therefore, we turned our attention to tetracycles **6b** and **7b**, which incorporate a 2-(phenylsulfanyl)ethyl group on the piperidine nitrogen able to induce closure of the C ring by electrophilic cyclization of a thionium ion generated by Pummerer rearrangement.[18] The nucleophilic addition−cyclization sequence from 1-acetylindole (**3**) was then extended to pyridinium bromide **4b**: in this way, tetracycle **6b** (a vinylogous urethane) was obtained (40%) through 1,4-dihydropyridine **5b** (20%) and then chemoselectively oxidized at the sulfur atom with *m*-CPBA to provide sulfoxide **8** as a mixture of stereoisomers (evident by NMR) in 89% yield (Scheme 3). Pummerer cyclization of these amino sulfoxides **8** was satisfactorily accomplished with trimethylsilyl triflate (TMSOTf) in the presence of diisopropylethylamine (DIPEA)[19] to give (60% yield) an epimeric mixture (NMR) of pentacyclic sulfides **9**, which were converted (80% yield) to pentacycle **10** by desulfurization with Ph_3SnH−AIBN in C_6H_6. Unfortunately, this pentacycle could not be converted into the desired lactam **1** since the application of the acid hydrolysis−decarboxylation−reduction sequence in order to transform the acrylate moiety into the (*E*)-ethylidene group resulted in decomposition, probably due to the opening of the seven-membered lactam ring.

For this reason, we decided to reverse the order of the steps in the above sequence and to elaborate the (*E*)-

(14) (a) This pentacyclic system is present in the alkaloid 2,7-dihydroxyapogeissoschizine: Quetin-Leclercq, J.; Dive, G.; Delaude, C.; Warin, R.; Bassleer, R.; Angenot, L. *Phytochemistry* **1994**, *35*, 533. For previous synthetic approaches, see: (b) Bennasar, M.-L.; Zulaica, E.; Sufi, B. A.; Bosch, J. *Tetrahedron* **1996**, *52*, 8601. (c) Birman, V. B.; Rawal, V. H. *J. Org. Chem*. **1998**, *63*, 9146.

(15) Dilactam **2** also constitutes an intermediate in an early synthesis of (±)-geissoschizine. See ref 9c.

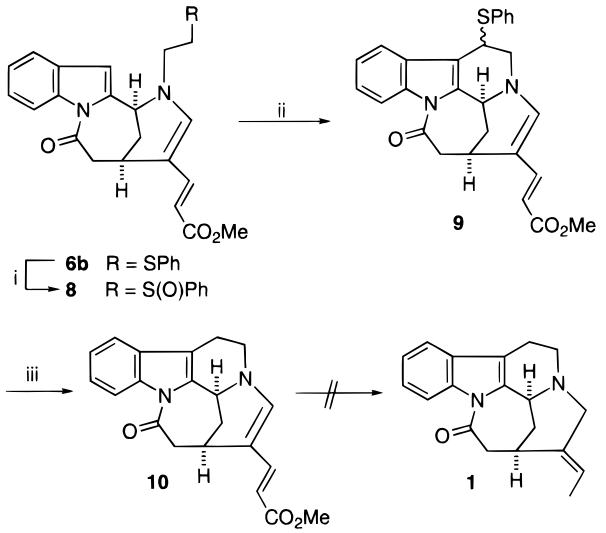
(16) For the use of this procedure to the synthesis of (*E*)-ethylidene-bearing indole alkaloids, see: Besselièvre, R.; Cosson, J.-P.; Das, B. C.; Husson, H.-P. *Tetrahedron Lett*. **1980**, *21*, 63. See also refs 2, 3a, 4a, 5b, and 9d,g.

(17) For a discussion on the effect of lithium iodide in the acid-induced cyclization of these kind of dihydropyridines, see: Bennasar, M.-L.; Jiménez, J.-M.; Sufi, B. A.; Bosch, J. *Tetrahedron Lett*. **1996**, *37*, 7653.

(18) (a) For a review, see: Padwa, A.; Gunn, D. E., Jr.; Osterhout, M. H. *Synthesis* **1997**, 1353. (b) For closure of the C ring of indolo-[2,3-*a*]quinolizidines by the Pummerer reaction, see: Amat, M.; Hadida, S.; Pshenichnyi, G.; Bosch, J. *J. Org. Chem*. **1997**, *62*, 3158.

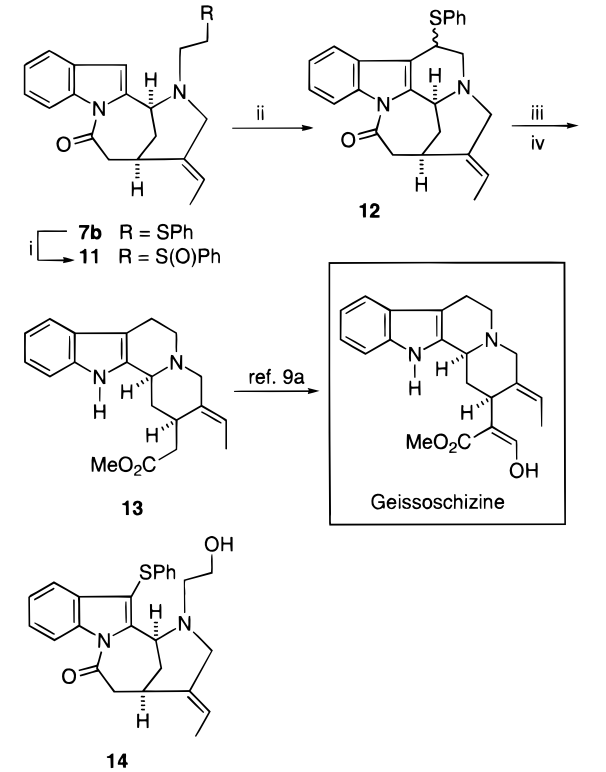
(19) Craig, D.; Daniels, K.; MacKenzie, A. R. *Tetrahedron* **1992**, *48*, 7803.

Scheme 3[a]



[a] Reagents and conditions: (i) *m*-CPBA, CH_2Cl_2, −78 °C, 30 min; (ii) TMSOTf, DIPEA, CH_2Cl_2, rt, 1.5 h; (iii) Ph_3SnH, AIBN, C_6H_6, reflux, 1 h.

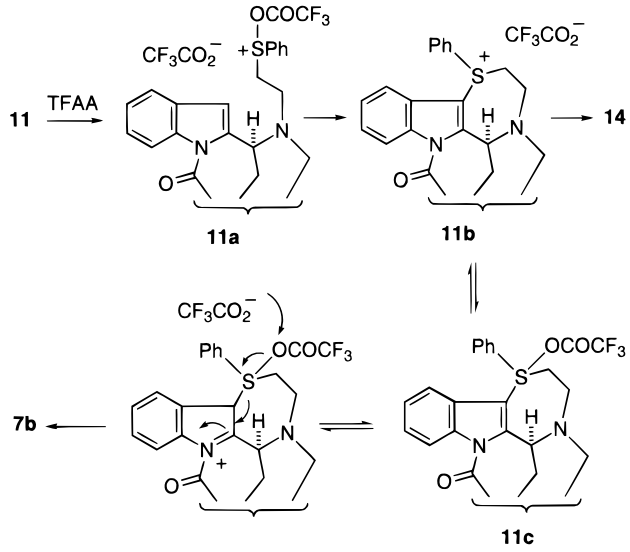
Scheme 4[a]



[a] Reagents and conditions: (i) TFA, CH_2Cl_2, 0 °C, 30 min, then *m*-CPBA, CH_2Cl_2, −78 °C, 30 min; (ii) TMSOTf, DIPEA, CH_2Cl_2, rt, 1.5 h; (iii) MeONa, 4:1 MeOH−THF, rt, 3 h; (iv) *n*-Bu_3SnH, AIBN, C_6H_6, reflux, 4 h.

ethylidene substituent from a less strained tetracyclic derivative, prior to the construction of the fifth ring. Accordingly, the (*E*)-ethylidenepiperidine **7b** was stereoselectively prepared (30%) in the usual way from tetracycle **6b** and then chemoselectively converted (80%) to sulfoxide **11** (mixture of stereoisomers at the sulfur atom) by sequential treatment with TFA (in order to protect the piperidine nitrogen) and *m*-CPBA (Scheme 4). Application of the above Pummerer reaction conditions (TMSOTf−DIPEA) to sulfoxide **11** worked equally well,

Scheme 5



rendering the pentacyclic sulfide **12** (mixture of C-6 stereoisomers) in 64% yield. In contrast, when the rearrangement was induced with TFA−TFAA in refluxing dichloromethane,[20] no cyclization was observed and a nearly equimolecular mixture of tetracyclic sulfides **7b** and **14** was unexpectedly obtained. Formation of sulfide **14** can be rationalized as depicted in Scheme 5, by considering the nucleophilic displacement of the acyloxy group by the indole ring in the initially formed (acyloxy)-sulfonium intermediate **11a** to give a pentacyclic sulfonium salt (**11b**), which undergoes a subsequent ring cleavage due to an external nucleophilic attack on the α-carbon.[21] On the other hand, reaction of sulfurane **11c** with TFA accounts for the formation of sulfide **7b**.[22]

As expected, the opening of the seven-membered lactam ring of pentacycle **12** occurred smoothly on treatment with methanolic sodium methoxide. A subsequent radical desulfurization using *n*-Bu_3SnH-AIBN gave methyl geissoschizoate **13** in 52% overall yield. Since **13** had previously been transformed into the alkaloid geissoschizine by formylation,[9a] the above synthesis constitutes a stereocontrolled formal synthesis of this alkaloid. It is worth mentioning that attempts to induce desulfurization before the opening of ring E resulted in failure. Thus, treatment of **12** with Raney nickel or nickel boride gave complex mixtures due to the lactam ring opening and/or reduction of the ethylidene group, whereas the use of radical conditions [*n*-Bu_3SnH (or Ph_3SnH)−AIBN in boiling benzene] caused concomitant isomerization of the exocyclic double bond.

(20) (a) Takano, S.; Iida, H.; Inomata, K.; Ogasawara, K. *Heterocycles* **1993**, *35*, 47. (b) Bonjoch, J.; Catena, J.-L.; Valls, N. *J. Org. Chem.* **1996**, *61*, 7106.

(21) For precedents of this abnormal Pummerer reaction, see: (a) Pyne, S. G.; Hajipour, A. R. *Tetrahedron* **1994**, *50*, 13501. (b) Amat, M.; Bennasar, M.-L.; Hadida, S.; Sufi, B. A.; Zulaica, E.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 5217.(c) Shinohara, T.; Takeda, A.; Toda, J.; Ueda, Y.; Kohno, M. Sano, T. *Chem. Pharm. Bull.* **1998**, *46*, 918. For related processes, see: (d) Kaneko, T. *J. Am. Chem. Soc.* **1985**, *107*, 5490. (e) Terauchi, H.; Tanitame, A.; Tada, K.; Nishikawa, Y. *Heterocycles* **1996**, *43*, 1719. (f) Arnone, A.; Bravo, P.; Capelli, S.; Fronza, G.; Meille, S. V.; Zanda, M.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1996**, *61*, 3375. (g) Volonterio, A.; Zanda, M.; Bravo, P.; Fronza, G.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1997**, *62*, 8031.

(22) For a similar reduction, see: (a) Cardwell, J.; Hewitt, B.; Ladlow, M.; Magnus, P. *J. Am. Chem. Soc.* **1988**, *110*, 2242. See also: (b) Kawasaki, T.; Suzuki, H.; Sakata, I.; Nakanishi, H.; Sakamoto, M. *Tetrahedron Lett.* **1997**, *38*, 3251.

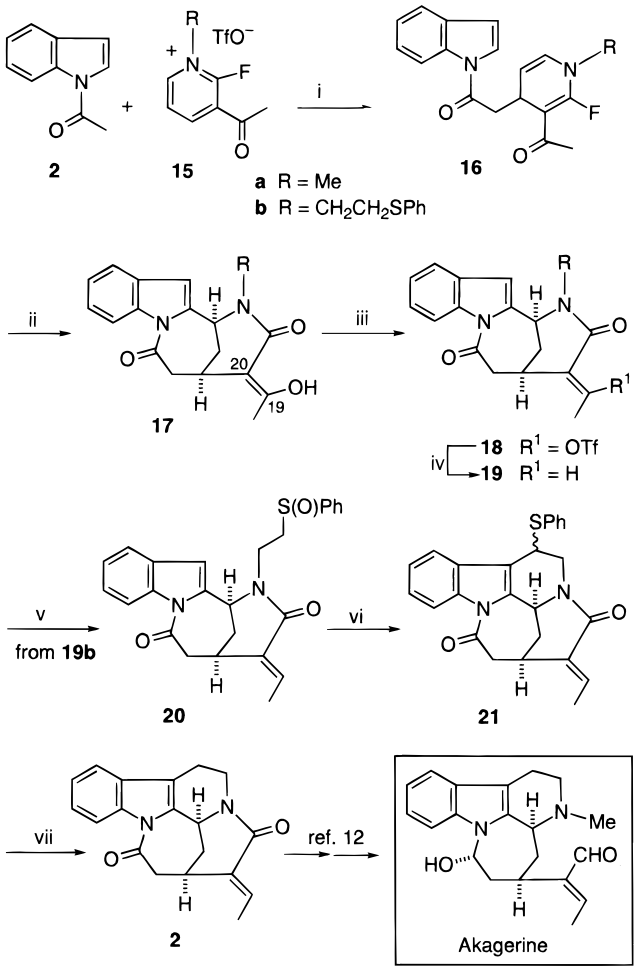
The access to the pentacyclic dilactam **2**, a known precursor of the indole alkaloid akagerine, required the chemoselective oxidation of C-21 in the above tetracyclic or pentacyclic intermediates. For this purpose, we chose the model tetracycle **7a** and pentacycle **12**. However, only complex mixtures were obtained when these compounds were exposed to oxidizing reagents such as benzeneseleninic anhydride (BSA)[23] or ruthenium oxide.[24] Because of this failure, we altered our initial synthetic plan to include a fluorine atom at the α-position of the starting pyridinium salt in the nucleophilic addition−cyclization sequence; in this manner, taking into account the easy hydrolysis of the C−F bond in 2-fluoropyridines,[25] we thought that we would be able to gain access to tetracyclic 3,7-methano[1,4]diazonino[1,2-*a*]indole systems embodying the required 2-piperidone moiety present in **2**.

We set out to explore the feasibility of this sequence using *N*-methylpyridinium salt **15a** as a model substrate (Scheme 6). Knowing that alkylation of 2-halopyridines with alkyl halides or tosylates is a difficult process,[26] we prepared this compound in good yield by alkylation of 3-acetyl-2-fluoropyridine[27] with methyl triflate. Exposure of pyridinium triflate **15a** to the enolate derived from 1-acetylindole (**3**) gave 1,4-dihydro-2-fluoropyridine **16a** in 25% yield. Its formation was evident in the ^{1}H NMR spectrum since the typical 1,4-dihydropyridine pattern was complicated by the ^{1}H−^{19}F coupling. As expected, treatment of a methanolic solution of 1,4-dihydropyridine **16a** with TsOH in the presence of lithium iodide brought about both cyclization upon the indole 2-position and concomitant cleavage of the C−F bond to give (50% yield) the tetracyclic lactam **17a**. Its spectroscopic data clearly showed that the acetyl group was in the enol form, presumably with a *Z* double bond configuration.

The next step in the synthesis was the stereoselective conversion of the acetyl group into the (*E*)-ethylidene substituent. This was initially planned through an elimination reaction, which would be effected upon the alcohol resulting from the chemoselective reduction of the enolized C-19 carbonyl group of **17a**. Thus, controlled $NaBH_4$ reduction of **17a** gave the corresponding alcohol (mixture of stereoisomers), which was treated with Martin Sulfurane to give the desired (*E*)-ethylidene derivative **19a** in moderate yield (30%). Less satisfactorily, a DBU-induced elimination of the mesylate derived from the above alcohol (19,20-dihydro-**17**) gave a 2:1 mixture of **19a** and the corresponding *Z* isomer in lower yield (21%).

With the aim of improving both the yield and the stereoselectivity of the above transformation, we decided to evaluate if the (*E*)-ethylidene substituent could be generated by Pd^0-catalyzed reduction of the (*Z*)-vinyl triflate **18a**,[28] which was satisfactorily prepared (90%) by treatment of enol **17a** with triflic anhydride in the presence of 1,8-bis(dimethylamino)naphthalene. To our delight, reduction of **18a** with *n*-Bu_3SnH in the presence of $Pd(Ph_3P)_4$ and LiCl stereoselectively gave **19a** in 76% overall yield from **17a**.

Scheme 6[a]



[a] Reagents and conditions: (i) LDA, THF, −30 °C, 1.5 h; (ii) TsOH−C_6H_6, LiI, MeOH, rt, 2 h; (iii) Tf_2O, 1,8-bis(dimethylamino)naphthalene, −40 to 0 °C (to −10 °C from **17b**), 1 h; (iv) *n*-Bu_3SnH, $Pd(PPh_3)_4$, LiCl, THF, reflux, 1 h; (v) *m*-CPBA, CH_2Cl_2, −78 °C, 30 min; (vi) TFAA, 2,6-di(*tert*-butyl)pyridine, CH_2Cl_2, rt, 30 min, then reflux, 1.5 h; (vii) *n*-Bu_3SnH, AIBN, C_6H_6, reflux, 1 h.

With a method in hand for the construction of the tetracyclic 4(*E*)-ethylidene-1,5-dioxo-3,7-methano[1,4]-diazonino[1,2-*a*]indole system, the development of an analogous synthetic sequence from 2-fluoro-1-[2-(phenylsulfanyl)ethyl]pyridinium triflate **15b** should allow the access to the target pentacyclic dilactam **2** after closure of the C ring by Pummerer cyclization. The required pyridinium salt **15b** was prepared by alkylation of 3-acetyl-2-fluoropyridine with 2-(phenylsulfanyl)ethyl triflate. As in the above *N*-methyl series, this salt was allowed to react with the enolate of 1-acetylindole (**3**) to give 1,4-dihydropyridine **16b** (23%), which was then cyclized to the tetracyclic enolic dilactam **17b** (58%). Subsequent Pd^0-catalyzed reduction of the corresponding triflate **18b** with *n*-Bu_3SnH stereoselectively afforded the (*E*)-ethylidene derivative **19b** in 42% overall yield from

(23) (a) Back, T. G. *J. Org. Chem*. **1981**, *46*, 1442. See also: (b) Danieli, B.; Lesma, G.; Palmisano, G.; Passarella, D.; Silavani, A. *Tetrahedron* **1994**, *50*, 6941.

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(26) (a) Dodd, R. H.; Poissonet, G.; Potier, P. *Heterocycles* **1989**, *29*, 365. (b) Dobbs, A. P.; Jones, K.; Veal, K. T. *Tetrahedron Lett*. **1997**, *38*, 5833. See also: (c) Vega, J. A.; Vaquero, J. J.; Alvarez-Builla, J.; Ezquerra, J.; Hamdouchi, C. *Tetrahedron* **1999**, *55*, 2317.

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(28) Ritter, K. *Synthesis* **1993**, 735.

17b. *m*-CPBA oxidation of sulfide **19b** gave sulfoxide **20** (90%, mixture of stereoisomers), which smoothly underwent Pummerer rearrangement at room temperature by treatment with TFAA in dichloromethane in the presence of 2,6-di(*tert*-butyl)pyridine.[22a] When the presumed acyloxy sulfide intermediate was refluxed in dichloromethane, the desired pentacyclic sulfide **21** (a single stereoisomer, undetermined configuration at C-6) was obtained in 71% yield. Finally, desulfurization of **21** with *n*-Bu_3SnH−AIBN gave the target pentacyclic dilactam **2** (72%). The ^1H NMR data of **2** are in agreement with those previously reported.[9c,12] Taking into account the previous work by Winterfeldt,[12] the synthesis of **2** represents a stereoselective formal total synthesis of (±)-akagerine.

In summary, the results here presented significantly expand the scope and potential of the methodology for indole alkaloid synthesis based on the reactivity of *N*-alkylpyridinium salts with indole-containing enolates. For the first time, 1-acetylindole enolates are used as nucleophilic partners in this methodology: the formation of three crucial C−C bonds (1, C-15/C-16; 2, C-2/C-3; 3, C-6/C-7) and subsequent opening of either the seven-membered lactam E ring or the 2-piperidone D ring give access to two structurally different tetracyclic alkaloids, geissoschizine and akagerine, respectively. On the other hand, for the first time a 2-fluoropyridinium salt is used as the electrophilic partner in the above methodology, to ultimately generate a 2-piperidone moiety.

Experimental Section

Melting points are uncorrected. Unless otherwise noted, NMR spectra were recorded in $CDCl_3$ solution at 300 (^1H) or 75 MHz (^{13}C). Only noteworthy IR absorptions (cm^{-1}) are listed. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck, 0.063−0.200 mm). Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04−0.06 mm). Drying of organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of the solvents was accomplished under reduced pressure with a rotatory evaporator. All nonaqueous reactions were performed under an argon atmosphere. Microanalyses and HRMS were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona. All compounds were synthesized in the racemic series.

Methyl 1-Benzyl-4-[2-(1-indolyl)-2-oxoethyl]-1,4-dihydropyridine-3(*E*)-acrylate (5a). LDA (10.7 mmol) was added to a solution of acetylindole **3**[29] (1 g, 6.29 mmol) in THF (75 mL) cooled at −78 °C, and the resulting solution was stirred at −78 °C for 30 min. Then, pyridinium chloride **4a**[2b] (1.8 g, 6.29 mmol) was added in portions, and the mixture was allowed to rise to −30 °C and stirred at this temperature for 1 h 30 min. The reaction mixture was partitioned between H_2O and Et_2O and extracted with Et_2O. Concentration of the organic extracts followed by flash chromatography (3:7 hexanes−Et_2O) gave dihydropyridine **5a**: 0.57 g (22%); IR (film) 1575, 1620, 1680, 1700; ^1H NMR 2.98 (dd, J = 14 and 10 Hz, 1H), 3.15 (dd, J = 14, 3 Hz, 1H), 3.68 (s, 3H), 4.15 (m, 1H), 4.34 (s, 2H), 5.06 (dd, J = 7.9, 5.2 Hz, 1H), 5.65 (d, J = 15.4 Hz, 1H), 5.91 (dd, J = 7.9, 1.5 Hz, 1H), 6.47 (d, J = 1 Hz, 1H), 6.60 (dd, J = 3.7, 0.7 Hz, 1H), 7.16 (m, 2H), 7.20−7.38 (m, 7H), 7.55 (dm, J = 7 Hz, 1H), 8.47 (d, J = 8 Hz, 1H); ^{13}C NMR 29.3 (CH), 42.5 (CH_2), 51.0 (CH_3), 57.2 (CH_2), 105.4 (CH), 107.3 (CH), 108.6 (C), 108.8 (CH), 116.5 (CH), 120.6 (CH), 123.5 (CH), 124.7 (CH), 124.8 (CH), 126.9 (CH), 127.8 (CH), 128.7 (CH), 128.9 (CH), 130.2 (C), 135.4 (C), 136.6 (C), 140.0 (CH), 145.3 (CH), 168.4 (C), 169.5 (C); HRMS calcd for $C_{26}H_{24}N_2O_3$ 412.1786, found 412.1785.

3-[(*E*)-2-(Methoxycarbonyl)vinyl]-1-[2-(phenylsulfanyl-)ethyl]pyridinium Bromide (4b). A mixture of methyl (*E*)-3-(3-pyridyl)acrylate (1.6 g, 9.6 mmol) and 2-(phenylsulfanyl)-ethyl bromide[30] (2.5 g, 11.5 mmol) was heated at 90−100 °C for 1 h. The reaction mixture was diluted with Et_2O, and the resulting precipitate was filtered to give pyridinium bromide **4b**: 3.1 g (86%); mp 124−125 °C (acetone−MeOH); ^1H NMR (DMSO-d_6) 3.71 (t, J = 6.4 Hz, 2H), 3.78 (s, 3H), 4.80 (t, J = 6.4 Hz, 2H), 7.02 (d, J = 16 Hz, 1H), 7.15−7.40 (m, 5H), 7.72 (d, J = 16 Hz, 1H), 8.14 (dd, J = 7.9 and 6 Hz, 1H), 8.86 (d, J = 7.9 Hz, 1H), 9.00 (d, J = 6 Hz, 1H), 9.44 (s, 1H). Anal. Calcd for $C_{17}H_{18}NO_2BrS$: C, 53.82; H, 4.79; N, 3.69; S, 8.44. Found: C, 53.56; H, 4.83; N, 3.72; S, 8.34.

Methyl 4-[2-(1-Indolyl)-2-oxoethyl]-1-[2-(phenylsulfanyl)ethyl]-1,4-dihydro-pyridine-3(*E*)-acrylate (5b). Operating as in the preparation of dihydropyridine **5a**, from acetylindole **3** (0.5 g, 3.14 mmol) and pyridinium bromide **4b** (1.2 g, 3.14 mmol) was obtained dihydropyridine **5b** after flash chromatography (Et_2O): 0.28 g (20%); mp 89−90 °C (hexanes−Et_2O); IR (film) 1576, 1607, 1664, 1700; ^1H NMR 2.99 (m, 3H), 3.10 (dd, J = 16, 3.2 Hz, 1H), 3.30 (t, J = 7 Hz, 2H), 3.68 (s, 3H), 4.05 (m, 1H), 5.01 (dd, J = 7.7, 5 Hz, 1H), 5.64 (d, J = 15.5 Hz, 1H), 5.78 (d, J = 7.7 Hz, 1H), 6.30 (s, 1H), 6.57 (d, J = 3.8 Hz, 1H), 7.20−7.35 (m, 9H), 7.53 (d, J = 7.7 Hz, 1H), 8.47 (d, J = 8.2 Hz, 1H); ^{13}C NMR 29.2 (CH), 34.0 (CH_2), 42.3 (CH_2), 51.0 (CH_3), 52.8 (CH_2), 105.4 (CH), 107.3 (CH), 108.4 (C), 108.7 (CH), 116.5 (CH), 120.6 (CH), 123.5 (CH), 124.8 (CH), 124.9 (CH), 126.7 (CH), 128.3 (CH), 129.1 (CH), 129.8 (CH), 130.2 (C), 134.3 (C), 135.4 (C), 139.5 (CH), 145.2 (CH), 168.4 (C), 169.5 (C). Anal. Calcd for $C_{27}H_{26}N_2O_3S$: C, 70.71; H, 5.71; N, 6.10; S, 6.99. Found: C, 70.67; H, 5.70; N, 6.11; S, 6.91.

Methyl 6-Benzyl-1-oxo-2,3,6,7-tetrahydro-1*H*-3,7-methano[1,4]diazonino[1,2-*a*]indole-4(*E*)-acrylate (6a). A solution of dihydropyridine **5a** (0.12 g, 0.29 mmol) and LiI (68 mg, 0.51 mmol) in THF (20 mL) cooled at −30 °C was treated with enough of a saturated C_6H_6 solution of dry TsOH to bring the pH to 3.5−4, and the reaction mixture was stirred at room temperature for 1 h 30 min. The mixture was poured into a saturated aqueous Na_2CO_3 solution and extracted with AcOEt. Concentration of the organic extracts gave a crude residue, which was chromatographed (98:2 $CHCl_3$−MeOH) to give **6a**: 60 mg (50%); IR (film) 1584, 1697; ^1H NMR 2.37 (m, 2H), 2.85 (dd, J = 13.9, 2.4 Hz, 1H), 3.03 (m, 1H), 3.49 (dd, J = 13.9, 6 Hz, 1H), 3.73 (s, 3H), 4.08 (s, 2H), 4.54 (br s, 1H), 5.52 (d, J = 15.3 Hz, 1H), 6.44 (s, 1H), 6.61 (s, 1H), 7.15−7.40 (m, 8H), 7.71 (d, J = 7.1 Hz, 1H), 8.19 (d, J = 8.2 Hz, 1H); ^{13}C NMR 25.5 (CH), 31.5 (CH_2), 45.5 (CH_2), 51.0 (CH_3), 52.4 (CH), 56.2 (CH_2), 104.5 (CH), 106.1 (C), 111.8 (CH), 115.8 (CH), 120.4 (CH), 123.4 (CH), 125.6 (CH), 127.0 (C), 127.4 (CH), 128.1 (CH), 128.9 (CH), 134.2 (C), 136.2 (C), 138.6 (C), 143.4 (CH), 145.7 (CH), 168.8 (C), 172.2 (C); HRMS calcd for $C_{26}H_{24}N_2O_3$ 412.1786, found 412.1786.

Methyl 1-Oxo-6-[2-(phenylsulfanyl)ethyl]-2,3,6,7-tetrahydro-1*H*-3,7-methano[1,4]diazonino[1,2-*a*]indole-4(*E*)-acrylate (6b). Operating as above, from dihydropyridine **5b** (0.25 g, 0.54 mmol), tetracycle **6b** was obtained after flash chromtography (4:6 hexanes−Et_2O): 0.1 g (40%); mp 210 °C (Et_2O); IR (film) 1580, 1690; ^1H NMR 2.25 (dm, J = 13.5 Hz, 1H), 2.35 (dt, J = 13.5, 1.7 Hz, 1H), 2.90 (m, 5H), 3.27 (m, 1H), 3.46 (m, 1H), 3.74 (s, 3H), 4.62 (dt, J = 4.9, 1.4 Hz, 1H), 5.50 (d, J = 15.2 Hz, 1H), 6.30 (s, 1H), 6.40 (s, 1H), 7.20−7.45 (m, 8H), 7.45 (d, J = 7.6 Hz, 1H), 8.15 (d, J = 8.2 Hz, 1H); ^{13}C NMR 25.5 (CH), 31.3 (CH_2), 33.1 (CH_2), 45.5 (CH_2), 51.2 (CH_3), 51.4 (CH_2), 53.9 (CH), 104.6 (CH), 106.5 (C), 111.4 (CH), 115.7 (CH), 120.4 (CH), 123.5 (CH), 125.6 (CH), 127.0 (CH), 127.6 (C), 129.2 (CH), 130.4 (CH), 134.5, (C), 134.9 (C), 138.5 (C), 142.5 (CH), 145.5 (CH), 168.8 (C), 172.0 (C). Anal. Calcd for $C_{27}H_{26}N_2O_3S \cdot {}^1/_4H_2O$: C, 70.03; H, 5.77; N, 6.05; S, 6.92. Found: C, 69.90; H, 5.64; N, 6.06; S, 6.71.

6-Benzyl-4(*E*)-ethylidene-1-oxo-2,3,4,5,6,7-hexahydro-1*H*-3,7-methano[1,4]diazonino[1,2-*a*]indole (7a). A suspension of tetracycle **6a** (148 mg, 0.36 mmol) in MeOH (8.5

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mL) and 2.5 N aqueous HCl (17 mL) was refluxed for 2 h and then concentrated. The residue was dissolved in MeOH (20 mL), treated with $NaBH_4$ (0.1 g, excess) at 0 °C, and stirred at this temperature for 1 h. The solvent was evaporated, and the residue was partitioned between H_2O and Et_2O and extracted with Et_2O. The organic extracts were dried and concentrated, and the residue was chromatographed (flash, Et_2O) to give **7a**: 42 mg (33%); IR (film) 1693; ^{1}H NMR 1.68 (d, J = 6.8 Hz, 3H), 2.18 (dt, J = 13.5, 2.2 Hz, 1H), 2.41 (m, 1H), 3.06 (m, 4H), 3.24 (masked, 1H), 3.22 and 3.36 (2d, J = 13.9 Hz, 2H), 4.26 (dd, J = 5.2, 2.2 Hz, 1H), 5.39 (q, J = 6.8 Hz, 1H), 6.31 (s, 1H), 7.20−7.30 (m, 7H), 7.53 (d, J = 7 Hz, 1H), 8.29 (d, J = 8 Hz, 1H); ^{13}C NMR 12.3 (CH_3), 29.4 (CH), 34.8 (CH_2), 47.2 (CH_2), 54.0 (CH_2), 56.0 (CH), 58.8 (CH_2), 112.0 (CH), 115.9 (CH), 120.0 (CH), 120.4 (CH), 123.3 (CH), 124.6 (CH), 126.9 (CH), 128.0 (C), 128.3 (CH), 128.6 (CH), 135.0 (C), 135.3 (C), 137.9 (C), 138.5 (C), 174.2 (C); HRMS calcd for $C_{24}H_{24}N_2O$ 356.1888, found 356.1886.

4(*E*)-Ethylidene-1-oxo-6-[2-(phenylsulfanyl)ethyl]-2,3,4,5,6,7-hexahydro-1*H*-3,7-methano[1,4]diazonino[1,2-*a*]indole (7b). Operating as above, from tetracycle **6b** (0.5 g, 1.1 mmol) was obtained the ethylidene derivative **7b** after flash chromatography: 132 mg (30%); mp 142 °C (hexanes−AcOEt); ^{1}H NMR 1.67 (dd, J = 6.9, 1.1 Hz, 3H), 2.18 (dt, J = 13.4, 2.2 Hz, 1H), 2.30 (m, 2H), 2.55 (m, 1H), 3.05 (m, 6H), 3.22 (br s, 1H), 4.25 (dd, J = 5.4, 2.4 Hz, 1H), 5.48 (q, J = 6.9 Hz, 1H), 6.30 (s, 1H), 7.20−7.35 (m, 7H), 7.47 (dm, J = 7.2 Hz, 1H), 8.25 (dd, J = 8.2, 0.8 Hz, 1H); ^{13}C NMR 12.3 (CH_3), 29.2 (CH), 31.7 (CH_2), 34.6 (CH_2), 47.0 (CH_2), 53.6 (CH_2), 54.0 (CH_2), 56.2 (CH), 111.8 (CH), 115.8 (CH), 120.1 (CH), 120.8 (CH), 123.3 (CH), 124.7 (CH), 125.9 (CH), 128.2 (C), 128.8 (CH), 129.3 (CH), 134.6 (C), 135.2 (C), 136.3 (C), 137.8 (C), 174.0 (C). Anal. Calcd for $C_{25}H_{26}N_2OS$: C, 74.59; H, 6.51; N, 6.96; S, 7.96. Found: C, 74.35; H, 6.60; N, 6.70; S, 7.60.

Methyl 13-Oxo-7-(phenylsulfanyl)-1,2,5,6,7,12a-hexahydro-2,12-ethanoindolo[2,3-*a*]quinolizine-3(*E*)-acrylate (9). *m*-CPBA (22 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) was slowly added to a solution of sulfide **6b** (50 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) at −78 °C, and the resulting mixture was stirred at −78 °C for 30 min. The reaction was quenched with solid K_2CO_3 (excess), and the stirring was continued at −78 °C for 10 min. The resulting mixture was diluted with CH_2Cl_2 and washed with H_2O. The organic solution was concentrated, and the residue was chromatographed (flash, AcOEt) to give sulfoxide **8** as a 1:1 mixture of stereoisomers: 46 mg (89%).

A solution of the above sulfoxides **8** (30 mg, 0.063 mmol) in dry CH_2Cl_2 (5 mL) containing diisopropylethylamine (0.045 mL, 0.25 mmol) at 0 °C was treated with trimethylsilyl triflate (0.045 mL, 0.25 mmol), and the mixture was stirred at room temperature for 1.5 h. The mixture was poured into 10% aqueous Na_2CO_3 and extracted with CH_2Cl_2. After concentration of the extracts and flash chromatography (6:4 hexanes−AcOEt) of the residue, pentacycle **9** was obtained as a 3:1 mixture of stereoisomers: 17 mg (60%); IR (KBr) 1583, 1703; ^{1}H NMR (major isomer) 2.25 (dm, J = 14.3 Hz, 1H), 2.48 (dd, J = 14.3, 3.6 Hz, 1H), 2.81 (br d, J = 17 Hz, 1H), 2.84 (m, 1H), 3.30 (dd, J = 17, 10 Hz, 1H), 3.69 (s, 3H), 3.82 (d, J = 14.8 Hz, 1H), 4.03 (dd, J = 14.8, 5.5 Hz, 1 H), 4.51 (br s, 1H), 4.62 (dd, J = 5.5, 1.8 Hz, 1H), 5.28 (d, J = 15.4 Hz, 1H), 6.58 (s, 1H), 7.10 (d, J = 15.4 Hz, 1H), 7.33 (m, 5H), 7.43 (m, 2H), 7.81 (dm, J = 7 Hz, 1H), 7.93 (dm, J = 8 Hz, 1H); ^{13}C NMR 23.2 (CH), 27.2 (CH_2), 41.8 (CH), 46.6 (CH_2), 51.5 (CH_3), 52.7 (CH), 57.2 (CH_2), 107.5 (CH), 113.0 (C), 114.5 (CH), 117.4 (C), 119.7 (CH), 123.6 (CH), 125.3 (CH), 127.8 (CH), 127.9 (C), 129.5 (CH), 131.9 (CH), 134.5 (C), 136.2 (C), 136.7 (C), 145.5 (CH), 146.3 (CH), 168.2 (C), 172.9 (C). Anal. Calcd for $C_{27}H_{24}N_2O_3S$: C, 71.03; H, 5.30; N, 6.14. Found: C, 69.92; H, 5.31; N, 5.86.

Methyl 13-Oxo-1,2,5,6,7,12a-hexahydro-2,12-ethanoindolo[2,3-*a*]quinolizine-3(*E*)-acrylate (10). A solution of sulfide **9** (160 mg, 0.35 mmol), Ph_3SnH (0.24 g, 0.70 mmol), and AIBN (5 mg) in C_6H_6 (12 mL) was refluxed for 1 h. The mixture was concentrated, and the residue was chromatographed (hexanes−AcOEt, increasing polarity) to give pentacycle **10**: 97 mg (80%); mp 206 °C (acetone−Et_2O); IR (KBr) 1583, 1690; ^{1}H NMR 2.33 (dm, J = 14.3 Hz, 1H), 2.47 (dd, J = 14.3, 3.3 Hz, 1H), 2.82 (m, 2H), 2.98 (d, J = 17.6 Hz, 1H), 3.03 (m, 1H), 3.23 (dd, J = 17.6, 8.8 Hz, 1H), 3.58 (m, 1H), 3.66 (s, 3H), 3.80 (m, 1H), 4.54 (br s, 1H), 5.32 (d, J = 15.7 Hz, 1H), 6.41 (s, 1H), 7.09 (d, J = 15.7 Hz, 1H), 7.30 (m, 3H), 8.07 (dm, J = 7 Hz, 1H); ^{13}C NMR 20.9 (CH_2), 23.7 (CH), 27.5 (CH_2), 45.4 (CH_2), 49.8 (CH_2), 51.0 (CH_3), 52.3 (CH), 107.2 (CH), 113.3 (C), 115.0 (CH), 117.4 (CH), 117.6 (C), 123.6 (CH), 124.9 (CH), 128.8 (C), 135.4 (C), 136.4 (C), 146.0 (CH), 146.9 (CH), 168.2 (C), 172.5 (C). Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.45; H, 5.80; N, 8.01.

Pummerer Rearrangement of Sulfoxides 11. TFA (0.022 mL, 0.25 mmol) was slowly added to a solution of sulfide **7b** (90 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) at 0 °C, and the resulting solution was stirred at 0 °C for 30 min. *m*-CPBA (45 mg, 0.25 mmol) in CH_2Cl_2 (1 mL) was slowly added at −78 °C, and the stirring was continued for 15 min. The reaction was quenched with solid K_2CO_3 (excess), and the mixture was stirred at −78 °C for 10 min, diluted with CH_2Cl_2, and washed with H_2O. The organic solution was concentrated, and the residue was chromatographed (flash, 98:2 AcOEt−DEA) to give sulfoxide **11** as a 1:1 mixture of stereoisomers: 74 mg (80%).

Method A. TFA (0.030 mL, 0.38 mmol) and TFAA (0.053 mL, 0.38 mmol) were added at room temperature to a solution of sulfoxides **11** (40 mg, 0.096 mmol) in CH_2Cl_2 (4 mL). After being refluxed for 5 h, the mixture was cooled, poured into 10% aqueous Na_2CO_3, and extracted with CH_2Cl_2. The organic extracts were dried and concentrated, and the residue was chromatographed (flash, hexanes−AcOEt and ACOEt). The initial elution gave sulfide **7b**: 10 mg (26%). Further elution gave **4(*E*)-ethylidene-6-(2-hydroxyethyl)-1-oxo-8-(phenylsulfanyl)-2,3,4,5,6,7-hexahydro-1*H*-3,7-methano[1,4]diazonino[1,2-*a*]indole (14):** 11 mg (28%); IR (film) 1690; ^{1}H NMR 1.71 (dd, J = 6.8, 1.3 Hz, 3H), 2.12 (m, 2H), 2.43 and 2.64 (2m, 2H), 3.06 (m, 4H, 16-H), 3.28 (br s, 1H), 3.42 and 3.51 (2m, 2H), 5.01 (dd, J = 5.5, 2.1 Hz, 1H), 5.51 (q, J = 6.8 Hz, 1H), 7.05−7.40 (m, 7H), 7.50 (dm, J = 7.7 Hz, 1H), 8.24 (dm, J = 8.3 Hz, 1H); ^{13}C NMR 12.3 (CH_3), 29.7 (CH), 34.5 (CH_2), 47.2 (CH_2), 53.3 (CH), 53.4 (CH_2), 55.3 (CH_2), 57.8 (CH_2), 115.6 (CH), 120.0 (CH), 121.3 (CH), 123.9 (CH), 125.4 (CH), 125.8 (CH), 126.1 (CH), 128.8 (C), 128.9 (CH), 129.3 (C), 134.2 (C), 136.8 (C), 136.9 (C), 140.0 (C), 174.2 (C).

Method B. Sulfoxides **11** (100 mg, 0.24 mmol) in dry CH_2Cl_2 (10 mL) containing diisopropylethylamine (0,17 mL, 0.96 mmol) at 0 °C were treated with trimethylsilyl triflate (0,17 mL, 0.96 mmol), and the mixture was stirred at room temperature for 1.5 h. The mixture was poured into 10% aqueous Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give **3(*E*)-ethylidene-13-oxo-7-(phenylsulfanyl)-2,12-ethanoindolo[2,3-*a*]quinolizidine** (**12**, 62 mg, 64%, 3:1 epimeric mixture). Flash chromatography (AcOEt) allowed the isolation of major epimer: IR (KBr) 1720; ^{1}H NMR (300 MHz, biogenetic numbering, assignments aided by ^{1}H−^{1}H COSY and HMQC) 1.60 (dd, J = 6.8, 2 Hz, 3H, 18-H), 2.11 (dt, J = 14.3, 4.2 Hz, 1H, 14-H), 2.39 (dd, J = 14.5, 4.4 Hz, 1H, 16-H), 2.53 (dt, J = 14.3, 2.7 Hz, 1H, 14-H), 3.07 (dd, J = 14.5, 11.6 Hz, 1H, 16-H), 3.10 (d, J = 13.2 Hz, 1H, 21-H), 3.39 (m, 1H, 15-H), 3.50 (d, J = 15.0 Hz, 1H, 5-H), 4.03 (br d, J = 13.2 Hz, 1H, 21-H), 4.25 (br s, 1H, 3-H), 4.55 (dd, J = 6.5, 2.2 Hz, 1H, 6-H), 5.40 (q, J = 6.8 Hz, 1H, 19-H), 7.25−7.40 (m, 5H, Ar), 7.50 (m, 2H, Ar), 7.81 (dm, J = 7.1 Hz, 1H, 9-H), 7.93 (dm, J = 7.9 Hz, 1H, 12-H); ^{13}C NMR 12.5 (C-18), 25.9 (C-15), 30.5 (C-14), 39.8 (C-6), 45.4 (C-16), 51.9 (C-21), 53.6 (C-3), 58.0 (C-5), 114.2 (C-12), 117.9 (C-7), 120.0 (C-9), 120.9 (C-19), 123.3 (C-10), 124.9 (C-11), 127.0 (Ph), 128.5 (C-8), 129.3, 131.1 (Ph), 136.0, 136.2, 136.2 (Ph, C-2, C-20), 137.4 (C-13), 174.1 (CO).

Methyl (2*RS*, 12b*SR*)-3(*E*)-Ethylideneindolo[2,3-*a*]quinolizidine-2-acetate [Methyl Geissoschizoate (13)].[9h] MeONa (5.3 mg, 0.097 mmol) was added to a solution of pentacycle **12** (26 mg, 0.065 mmol) in MeOH (2 mL) and THF (0.5 mL), and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was poured into aqueous NH_4Cl and extracted with AcOEt. The organic extracts were dried and concentrated. The residue was dis-

solved in C_6H_6 (4 mL), and the resulting solution was treated with *n*-Bu_3SnH (32 mL, 0.12 mmol) and AIBN (2 mg) at reflux temperature for 4 h. The mixture was concentrated, and the residue was chromatographed (hexanes−AcOEt, increasing polarity) to give **13**: 11 mg (52%); ^{1}H NMR (300 MHz) 1.65 (dd, *J* = 6.8, 1.5 Hz, 3H), 2.17 (m, 3H), 2.31 (dt, *J* = 14.2, 3.5 Hz, 1H), 2.64 (m, 1H), 2.94 (d, *J* = 12.4 Hz, 1H), 2.98−3.20 (m, 3H), 3.27 (ddd, *J* = 13, 6.1, 1.3 Hz, 1H), 3.55 (br d, *J* = 12.4 Hz, 1H), 3.69 (s, 3H), 4.27 (br s, 1H), 5.47 (q, *J* = 6.8 Hz, 1H), 7.12 (m, 2H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 8.57 (br s, 1H); ^{13}C NMR 12.6 (CH_3), 17.9 (CH_2), 30.5 (CH_2), 31.1 (CH), 37.2 (CH_2), 51.4 (CH_2), 51.8 (CH_3), 52.7 (CH), 53.2 (CH_2), 107.6 (C), 111.1 (CH), 118.0 (CH), 119.4 (CH), 120.5 (CH), 121.4 (CH), 127.9 (C), 133.9 (C), 135.9 (C), 136.1 (C), 174.0 (C).

3-Acetyl-2-fluoro-1-methylpyridinium Trifluoromethanesulfonate (15a). Methyl trifluoromethanesulfonate (2.4 mL, 21.7 mmol) was added to 3-acetyl-2-fluoropyridine[27] (2 g, 14.4 mmol). The resulting mixture was diluted with anhydrous CH_2Cl_2 (2 mL) and stirred at room temperature for 15 min. The precipitate was filtered and washed with anhydrous Et_2O to give pyridinium triflate **15a** (3.92 g, 90%), which was immediately used in the next step without further purification.

3-Acetyl-2-fluoro-4-[2-(1-indolyl)-2-oxoethyl]-1-methyl-1,4-dihydropyridine (16a). Operating as in the preparation of 1,4-dihydropyridines **5**, from acetylindole **2** (0.5 g, 3.14 mmol) and pyridinium triflate **15a** (0.95 g, 3.14 mmol) was obtained 1,4-dihydropyridine **16a** (245 mg, 25%) after flash chromatography (95:3:2 Et_2O−acetone−DEA): mp 138 °C (Et_2O−hexanes); IR (KBr) 1690; ^{1}H NMR 2.37 (d, *J* = 7 Hz, 3H), 2.71 (dd, *J* = 13.5, 10 Hz, 1H), 3.06 (d, *J* = 2.5 Hz, 3H), 3.28 (dd, *J* = 13.5, 3.2 Hz, 1H), 4.16 (m, 1H), 5.09 (m, 1H), 5.80 (dd, *J* = 7.6, 5.1 Hz, 1H), 6.63 (d, *J* = 3.8 Hz, 1H), 7.28 (m, 2H), 7.55 (dm, *J* = 7 Hz, 1H), 7.94 (d, *J* = 3.8 Hz, 1H), 8.48 (d, *J* = 8 Hz, 1H); ^{13}C NMR 30.5 (CH_3), 33.7 (CH), 34.3 (CH_3), 44.4 (CH_2), 91.8 (C), 108.3 (CH), 108.9 (CH), 116.6 (CH), 120.6 (CH), 123.5 (CH), 124.7 (CH), 126.1 (CH), 128.5 (CH), 130.5 (C), 135.5 (C), 160.4 (C, *J* = 266.8 Hz), 169.5 (C), 193.3 (C). Anal. Calcd for $C_{18}H_{17}N_2O_2F$: C, 69.22; H, 5.48; N, 8.97. Found: C, 69.20; H, 5.44; N, 8.98.

4-Acetyl-6-methyl-1,5-dioxo-2,3,4,5,6,7-hexahydro-1*H*-3,7-methano[1,4]diazonino[1,2-*a*]indole (17a). A solution of dihydropyridine **16a** (0.38 g, 1.21 mmol) and LiI (0.27 g, 2 mmol) in MeOH (20 mL) cooled at −40 °C was treated with enough of a saturated C_6H_6 solution of anhydrous TsOH to bring the pH to 2−3, and the mixture was stirred at room temperature for 2 h. The solvent was evaporated, and the residue was directly purified by flash chromatography (95:5 Et_2O−DEA) to give tetracycle **17a**: 188 mg (50%); mp 161 °C (Et_2O); IR (KBr) 1596, 1627, 1698; ^{1}H NMR 2.10 (s, 3H), 2.40 (dt, *J* = 13.5, 2.2 Hz, 1H), 2.54 (m, 1H), 2.83 (s, 3H), 3.02 (dd, *J* = 13.3, 2.5 Hz, 1H), 3.21 (ddd, *J* = 13.3, 6.5, 1.6 Hz, 1H), 3.25 (m, 1H), 4.71 (dm, *J* = 4.8 Hz, 1H), 6.63 (s, 1H), 7.22−7.36 (m, 2H), 7.51 (dm, *J* = 7.7 Hz, 1H), 8.17 (d, *J* = 8 Hz, 1H), 15.21 (s, 1H); ^{13}C NMR 18.4 (CH_3), 29.4 (CH), 32.1 (CH_3), 32.4 (CH_2), 47.7 (CH_2), 57.5 (CH), 96.7 (C), 112.6 (CH), 115.5 (CH), 120.5 (CH), 123.6 (CH), 125.8 (CH), 127.7 (C), 134.7 (C), 138.5 (C), 168.9 (C), 171.7 (C), 172.1 (C). Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.56; H, 5.86; N, 9.03.

4(*E*)-Ethylidene-6-methyl-1,5-dioxo-2,3,4,5,6,7-hexahydro-1*H*-3,7-methano[1,4]diazonino[1,2-*a*]indole (19a). Method A. $NaBH_4$ (12.2 mg, 0.32 mmol) was added to a cooled (0 °C) solution of tetracycle **17** (50 mg, 0.16 mmol) in 5:2:1 EtOH−MeOH−H_2O (4 mL), and the resulting mixture was stirred at 0 °C for 4 h. The solvents were removed, and the residue was partitioned between H_2O and AcOEt and extracted with AcOEt. Evaporation of the organic extracts gave a crude alcohol (mixture of stereoisomers). A solution of Martin Sulfurane (320 mg, 0.48 mmol) in CH_2Cl_2 (1.5 mL) was slowly added to a solution of the above alcohol in CH_2Cl_2 (2 mL) cooled at −78 °C, and the mixture was allowed to rise to room temperature with stirring. The mixture was poured into a saturated aqueous Na_2CO_3 solution and extracted with CH_2Cl_2. Evaporation of the organic extracts followed by flash chromatography gave **19a**: 14 mg (30%); IR (film) 1608, 1660, 1698; ^{1}H NMR 1.90 (d, *J* = 7.3 Hz, 3H), 2.39 (dt, *J* = 13.4, 2.4 Hz, 1H), 2.58 (dt, *J* = 13.4, 5 Hz, 1H), 2.92 (s, 3H), 3.05 (dd, *J* = 13.8, 4.2 Hz, 1H), 3.16 (dd, *J* = 13.8, 6.8 Hz, 1H), 3.49 (m, 1H), 4.75 (dd, *J* = 5, 1.4 Hz, 1H), 6.64 (s, 1H), 7.14 (q, *J* = 7.3 Hz, 1H), 7.28 (m, 2H), 7.52 (d, *J* = 7 Hz, 1H), 8.20 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR 13.8 (CH_3), 28.9 (CH), 32.1 (CH_2), 32.2 (CH_3), 46.0 (CH_2), 57.1 (CH), 112.9 (CH), 115.6 (CH), 120.5 (CH), 123.7 (CH), 125.7 (CH), 127.8 (C), 130.0 (C), 135.1 (C), 136.3 (CH), 138.3 (C), 163.0 (C), 171.0 (C); HRMS calcd for $C_{18}H_{18}N_2O_2$ 294.1368, found 294.1369. When the above alcohol was converted into the corresponding mesylate by treatment with mesyl chloride (0.039 mL, 0.45 mmol) and Et_3N (0.08 mL, 0.56 mmol) at 0 °C for 1.5 h and then treated with DBU (0.14 mL, 0.96 mmol) in 1:1 DMSO−toluene (4 mL) at 40 °C for 3 h, a 2:1 mixture of **19a** and the corresponding *Z* isomer was obtained: 10 mg (21%). *Z* isomer: IR (film) 1615, 1659, 1699; ^{1}H NMR 2.22 (d, *J* = 7.2 Hz, 3H), 2.36 (dm, *J* = 13.5 Hz, 1H), 2.50 (dm, *J* = 13.5 Hz, 1H), 2.96 (s, 3H), 3.10 (m, 3H), 4.76 (d, *J* = 6.2 Hz, 1H), 6.13 (q, *J* = 7.2 Hz, 1H), 6.64 (s, 1H), 7.28 (m, 2H), 7.52 (dd, *J* = 7, 1 Hz, 1H), 8.24 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR 15.9 (CH_3), 32.0 (CH_2), 32.3 (CH_3), 36.5 (CH), 46.7 (CH_2), 56.4 (CH), 112.8 (CH), 115.7 (CH), 120.5 (CH), 123.7 (CH), 125.7 (CH), 127.9 (C), 130.5 (C), 135.6 (C), 137.8 (C), 138.9 (CH), 163.7 (C), 171.0 (C); HRMS calcd for $C_{18}H_{18}N_2O_2$ 294.1368, found 294.1360.

Method B. Tf_2O (0.035 mL, 0.21 mmol) was slowly added to a stirred solution of tetracycle **17a** (60 mg, 0.19 mmol) and 1,8-bis(dimethylamino)naphthalene (46 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) at −40 °C. The mixture was allowed to rise to 0 °C in a period of 1 h. The solvent was evaporated, and the resulting residue was directly purified by flash chromatography (hexane−AcOEt, increasing polarity) to give triflate **18a**: 77 mg (90%); ^{1}H NMR (300 MHz) 2.22 (s, 3H), 2.45 (dm, *J* = 14.1 Hz, 1H), 2.62 (ddd, *J* = 14.1, 6.1, 2.8 Hz, 1H), 3.01 (s, 3H), 3.11 (m, 2H), 3.43 (m, 1H), 4.84 (d, *J* = 6.1 Hz, 1H), 6.69 (s, 1H), 7.25−7.36 (m, 2H), 7.52 (d, *J* = 7.5 Hz, 1H), 8.25 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR 18.7 (CH_3), 31.6 (CH), 31.9 (CH_2), 33.5 (CH_3), 44.0 (CH_2), 56.4 (CH), 114.4 (CH), 116.4 (CH), 121.3 (CH), 124.6 (CH), 126.6 (CH), 128.4 (C), 135.1 (C), 138.3 (C), 149.4 (C), 160.3 (C), 169.9 (C). LiCl (22 mg, 0.5 mmol) and $Pd(PPh_3)_4$ (4 mg, 0.003 mmol) were added to a solution of triflate **18a** (77 mg, 0.17 mmol) in THF (2 mL) at room temperature. *n*-Bu_3SnH (99 mg, 0.091 mL, 0.33 mmol) was slowly added, and the resulting mixture was refluxed for 1 h. Additional LiCl (22 mg, 0.5 mmol) and $Pd(PPh_3)_4$ (4 mg, 0.003 mmol) were added, and the mixture was refluxed for an additional period of 2 h. The mixture was concentrated, and the residue was purified by flash chromatography (hexanes−AcOEt, increasing polarity) to give **19a**: 44 mg (85%).

3-Acetyl-2-fluoro-1-[(2-phenylsulfanyl)ethyl] Trifluoromethanesulfonate (15b). Tf_2O (0.67 g, 0.4 mL, 2,4 mmol) was added to a solution of 2-(phenylsulfanyl)ethanol (0.30 g, 0.27 mL, 2 mmol) and triethylamine (0.26 g, 0.37 mL, 2.4 mmol) in anhydrous CH_2Cl_2 (1 mL) at 0 °C, and the mixture was stirred at 0 °C for 2 h. The solvent was removed to give crude 2-(phenylsulfanyl)ethyl trifluoromethanesulfonate (moisture sensitive). A mixture of the above triflate and 3-acetyl-2-fluoropyridine[27] (0.14 g, 1 mmol) was stirred at room temperature for 12 h. The resulting oil was washed with anhydrous Et_2O to give pyridinium triflate **15b** (0.35 g, 90%), which was immediately used in the next step without further purification.

3-Acetyl-2-fluoro-4-[2-(1-indolyl)-2-oxoethyl]-1-[2-(phenylsulfanyl)ethyl]-1,4-dihydropyridine (16b). Operating as in the preparation of 1,4-dihydropyridines **5** and **16a**, from acetylindole **2** (0.14 g, 0.89 mmol) and pyridinium triflate **15b** (0.35 g, 0.89 mmol) was obtained 1,4-dihydropyridine **16b** (90 mg, 23%) after flash chromatography (hexanes−Et_2O, increasing polarity); IR (KBr) 1582, 1681, 1698; ^{1}H NMR 2.36 (d, *J* = 7.1 Hz, 3H), 2.77 (dd, *J* = 13.9, 9.8 Hz, 1H), 3.08 (m, 2H), 3.22 (dd, *J* = 13.9, 3.1 Hz, 1H), 3.43 and 3.61 (2m, 2H), 4.11 (m, 1H), 5.11 (m, 1H), 5.76 (dd, *J* = 7.6, 4.9 Hz, 1H), 6.63 (d, *J* = 3.8 Hz, 1H), 7.20−7.40 (m, 7H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.86 (d, *J* = 3.8 Hz, 1H), 8.48 (d, *J* = 8 Hz, 1H); ^{13}C NMR 30.7

(CH_3), 33.0 (CH), 33.3 (CH_2), 43.9 (CH_2), 46.8 (CH_2), 92.3 (C), 108.9 (CH), 108.9 (CH), 116.6 (CH), 120.6 (CH), 123.6 (CH), 124.8 (CH), 126.0 (CH), 127.0 (CH), 127.4 (CH), 129.2 (CH), 130.0 (CH), 130.5 (C), 134.0 (C), 135.5 (C), 159.9 (C, J = 266.8 Hz), 169.5 (C), 193.4 (C); HRMS calcd for $C_{25}H_{23}N_2O_2FS$ 434.1464, found 434.1468. Anal. Calcd for $C_{25}H_{23}N_2O_2FS$: C, 69.10; H, 5.34; N, 6.45; S, 7.38. Found: C, 68.83; H, 5.50; N, 6.33; S, 7.41.

4-Acetyl-1,5-dioxo-6-[(2-phenylsulfanyl)ethyl]-2,3,4,5,6,7-hexahydro-1*H*-3,7-methano[1,4]diazonino[1,2-*a*]indole (17b). Dihydropyridine **16b** (0.1 g, 0.23 mmol) in dry MeOH (12 mL) was allowed to react with a saturated C_6H_6 solution of anhydrous TsOH and LiI (52 mg, 0.39 mmol) and worked up as described for the preparation of tetracycle **17a**. After flash chromatography (hexanes−AcOEt, increasing polarity), tetracycle **17b** was obtained: 58 mg (58%); IR (film) 1594, 1626, 1701; ^{1}H NMR 2.09 (s, 3H), 2.32 (dm, J = 14 Hz, 1H), 2.44 (m, 1H), 2.81 (m, 1H), 2.96 (br d, J = 12.8 Hz, 1H), 3.15 (m, 4H), 3.60 (m, 1H), 4.80 (d, J = 5.1 Hz, 1H), 6.16 (s, 1H), 7.26−7.33 (m, 7H), 7.42 (d, J = 7.6 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H); ^{13}C NMR 18.4 (CH_3), 29.3 (CH), 30.7 (CH_2), 32.3 (CH_2), 44.4 (CH_2), 47.7 (CH_2), 56.9 (CH), 96.7 (C), 112.5 (CH), 115.5 (CH), 120.6 (CH), 123.7 (CH), 125.8 (CH), 126.3 (CH), 129.2 (CH), 129.2 (CH), 129.3 (C), 135.0 (C), 135.2 (C), 138.4 (C), 168.9 (C), 171.7 (C), 172.7 (C); HRMS calcd for C_{25}-$H24N_2O_3S$ 432.1507, found 432.1505.

4(*E*)-Ethylidene-1,5-dioxo-6-[2-(phenylsulfanyl)ethyl]-2,3,4,5,6,7-hexahydro-1*H*-3,7-methano[1,4]diazonino[1,2-*a*]indole (19b). To a solution of tetracycle **17b** (60 mg, 0.13 mmol) and 1,8-bis(dimethylamino)naphthalene (38 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) cooled at −40 °C was added a solution of Tf_2O (0.030 mL, 0.18 mmol) in CH_2Cl_2 (120 mL) in four portions, at 15 min intervals. The temperature of the mixture was allowed to rise to −10 °C over a period of 1 h. The reaction mixture was concentrated, and the residue was directly purified by flash chromatography (hexanes−AcOEt, increasing polarity) to give the vinyl triflate **18b** (32 mg, 50%), along with recovered starting material (20 mg). LiCl (22 mg, 0.5 mmol) and $Pd(PPh_3)_4$ (8 mg, 0.007 mmol) were added to a solution of the above triflate (3 × 32 mg, 0.17 mmol) in THF (4 mL) at room temperature. n-Bu_3SnH (99 mg, 0.091 mL, 0.33 mmol) was slowly added, and the resulting mixture was refluxed for 1 h. The solvent was removed, and the resulting residue was purified by flash chromatography (hexanes−AcOEt, increeasing polarity) to give the (*E*)-ethylidene derivative **19b**: 60 mg (85%); IR (film) 1614, 1661, 1699; ^{1}H NMR 1.91 (d, J = 7.3 Hz, 3H), 2.33 (br d, J = 13.6 Hz, 1H), 2.50 (dm, J = 13.6 Hz, 1H), 2.87 (m, 1H), 3.01 (dd, J = 13.8, 3.9 Hz, 1H), 3.22 (m, 3H), 3.44 (m, 1H), 3.68 (m, 1H), 4.86 (d, J = 5.5 Hz, 1H), 6.17 (s, 1H), 7.17 (q, J = 7.3 Hz, 1H), 7.24−7.35 (m, 7H), 7.42 (d, J = 7.7 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H); ^{13}C NMR 13.8 (CH_3), 28.8 (CH), 30.3 (CH_2), 32.0 (CH_2), 45.4 (CH_2), 46.1 (CH_2), 56.6 (CH), 112.7 (CH), 115.6 (CH), 120.5 (CH), 123.7 (CH), 125.8 (CH), 126.2 (CH), 127.7 (C), 129.1 (CH), 129.1 (CH), 129.8 (C), 135.3 (C), 135.4 (C), 136.9 (CH), 138.3 (C), 162.9 (C), 171.0 (C); HRMS calcd for $C_{25}H_{24}N_2O_2S$ 416.1558, found 416.1563.

3(*E*)-Ethylidene-4,13-dioxo-7-(phenylsulfanyl)-2,12-ethanoindolo[2,3-*a*]quinolizidine (21). Sulfide **19b** (25 mg, 0.06 mmol) was allowed to react with *m*-CPBA (13.4 mg, 0.06 mmol) in dry CH_2Cl_2 (4 mL) as described for the preparation of sulfoxide **8**. After workup and flash chromatography (95:5 AcOEt−DEA), sulfoxide **20** was obtained as a 1:1 mixture of stereoisomers: 24 mg (90%).

TFAA (49 mg, 0.033 mL, 0.23 mmol) was slowly added to a solution of sulfoxides **20** (23 mg, 0.058 mmol) and 2,6-di(*tert*-butyl)pyridine (44 mg, 0.052 mL, 0.23 mmol) in dry CH_2Cl_2 (2 mL) cooled at 0 °C. After being stirred at room temperature for 30 min, the mixture was refluxed for 1 h 30 min. The solvent was evaporated, and the residue was chromatographed (1:1 hexanes−AcOEt) to give pentacycle **21**: 17 mg (71%); ^{1}H NMR (300 MHz) 1.77 (d, J = 7.4 Hz, 3H), 2.37 (dd, J = 14.6, 5.3 Hz, 1H), 2.39 (dt, J = 14.5, 4.3 Hz, 1H), 2.62 (dt, J = 14.5, 2.7 Hz, 1H), 3.20 (dd, J = 14.6, 10.7 Hz, 1H), 3.55 (br, 1H), 3.60 (dd, J = 14.1, 6.2 Hz, 1H), 4.62 (dm, J = 6.2 Hz, 1H), 4.68 (br s, 1H), 5.07 (dd, J = 14.1, 2.1 Hz, 1H), 7.09 (q, J = 7.4 Hz, 1H), 7.26−7.35 (m, 5H), 7.64 (m, 2H), 7.90 (m, 2H); ^{13}C NMR 14.0 (CH_3), 26.8 (CH_2), 27.2 (CH), 43.5 (CH), 46.7 (CH_2), 49.5 (CH_2), 51.8 (CH), 114.6 (CH), 120.3 (C), 120.4 (CH), 123.9 (CH), 125.6 (CH), 127.9 (CH), 128.8 (C), 129.1 (CH), 133.0 (C), 133.5 (CH), 136.9 (C), 137.3 (C), 137.8 (C), 137.8 (CH), 164.6 (CO), 172.8 (CO).

3(*E*)-Ethylidene-4,13-dioxo-2,12-ethanoindolo[2,3-*a*]-quinolizidine (2).[9c,12] AIBN (catalytic amount) and n-Bu_3SnH (0.020 mL, 0.072 mmol) were added to a solution of pentacycle **21** (15 mg, 0.036 mmol) in dry C_6H_6 (0.8 mL) at room temperature. The reaction vessel was then placed in a preheated (100 °C) oil bath, and the mixture was refluxed for 1 h. Evaporation of the solvent followed by flash chromatography of the residue gave pentacyclic dilactam **2**: 8 mg (72%); ^{1}H NMR 1.77 (d, J = 7.3 Hz, 3H), 2.51 (dt, J = 14.4, 5.1 Hz, 1H), 2.60 (dt, J = 14.4, 2.6 Hz, 1H), 2.67 (ddd, J = 16.1, 3.9, 0.9 Hz, 1H), 2.77 (m, 1H), 3.24 (m, 1H), 3.29 (dd, J = 16.1, 9.5 Hz, 1H), 3.44 (m, 1H), 3.49 (br, 1H), 4.67 (m, 1H), 4.73 (m, 1H), 7.05 (qd, J = 7.3, 1.3 Hz, 1H), 7.25−7.34 (m, 2H), 7.40 (dm, J = 7.5 Hz, 1H), 8.04 (dm, J = 8 Hz, 1H); ^{13}C NMR 14.3 (CH_3), 20.0 (CH_2), 27.3 (CH_2), 27.6 (CH), 42.4 (CH_2), 47.0 (CH_2), 51.9 (CH), 115.2 (CH), 117.8 (CH), 120.1 (C), 123.9 (CH), 125.2 (CH), 129.3 (C), 132.6 (C), 135.8 (C), 136.8 (C), 138.1 (CH), 166.1 (C), 172.1 (C); HRMS calcd for $C_{19}H_{18}N_2O_2$ 306.1368, found 306.1375.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **2**, **5a**, **6a**, **7a**, **12**−**14**, **17b**, **19a**,**b**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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