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Conjugate Additions to Phenylglycinol-Derived Unsaturated δ-Lactams. Enantioselective Synthesis of Uleine Alkaloids

Mercedes Amat,*,† Maria Pérez,† Núria Llor,† Carmen Escolano,† F. Javier Luque,‡ Elies Molins,§ and Joan Bosch*,†

Laboratory of Organic Chemistry and Department of Physical Chemistry, Faculty of Pharmacy, University of Barcelona, 08028 Barcelona, Spain, and Institut de Ciència de Materials (CSIC), Campus UAB, 08193 Cerdanyola, Spain

amat@ub.edu; joanbosch@ub.edu

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The stereochemical outcome of the conjugate addition of a variety of stabilized nucleophiles (2-indoleacetic enolates and sulfur-stabilized anions) to the phenylglycinol-derived unsaturated lactams *trans*-**2**, *cis*-**2**, and its 8-ethyl-substituted analogue **10** is studied. The factors governing the *exo* or *endo* facial stereoselectivity are discussed. This methodology provides short synthetic routes to either *cis*- or *trans*-3,4-disubstituted enantiopure piperidines as well as efficient routes for the enantioselective construction of the tetracyclic ring system of uleine alkaloids, both in the normal and 20-epi series. The formal total synthesis of several alkaloids of this group is reported.

The alkaloids of the uleine group constitute a comparatively small group of indole alkaloids lacking the two-carbon link between the indole 3-position and the basic nitrogen atom, present in the greater part of monoterpenoid indole alkaloids.[1] These alkaloids are characterized by the presence of a tetracyclic 1,5-methanoazocino-[4,3-*b*]indole system bearing an ethyl substituent at the bridge carbon (Figure 1).

Biogenetically, the alkaloids of the uleine group are formed from stemmadenine, by fragmentation of the tryptamine bridge followed by isomerization of the resulting exocyclic iminium species to a more stable conjugated iminium cation and subsequent electrophilic cyclization on the indole 3-position[2] (Scheme 1). While the absolute configuration of the bridgehead C-15 position[3] results from their biogenetic origin from secologanin, there are alkaloids with each of the two possible configurations at C-20: H_{15} and H_{20} are *cis*, and consequently the ethyl substituent is equatorial with respect to the piperidine ring, in most of the alkaloids of this group, but *trans* in the 20-epi series.

Although the uleine alkaloids have received considerable synthetic attention,[1] their enantioselective synthesis has been little explored, and only one enantioselective total synthesis of alkaloids of this group has been reported so far.[4] A crucial problem associated with the synthesis of these alkaloids is the control of the absolute (and relative) configuration at C_{15} and C_{20}.

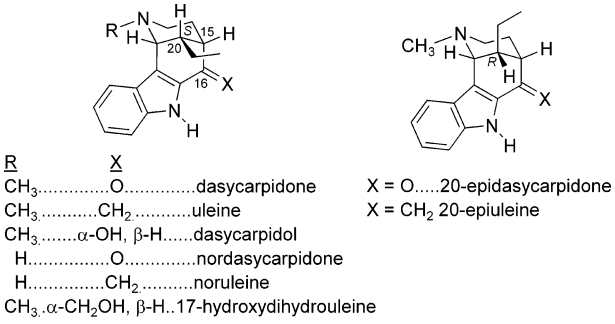
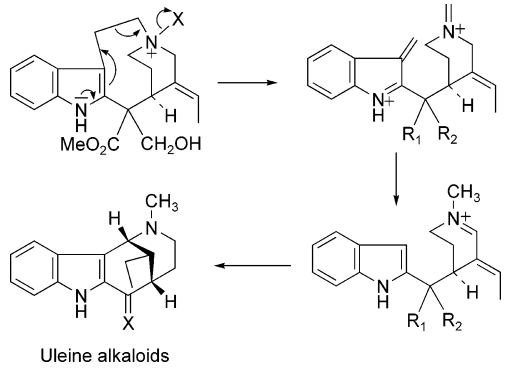


FIGURE 1. Uleine alkaloids.

SCHEME 1. Biosynthesis of Uleine Alkaloids



† Laboratory of Organic Chemistry.
‡ Laboratory of Physical Chemistry.
§ Institut de Ciència de Materials.

(1) (a) Joule, J. A. Indoles. The Monoterpenoid Indole Alkaloids; Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, 1983; Vol. 25, Part 4, Chapter 6. (b) Alvarez, M.; Joule, J. A. Monoterpenoid Indole Alkaloids; Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: Chichester, 1994; Suppl. to Vol. 25, Part 4, Chapter 6. (c) Alvarez, M.; Joule, J. A. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 2001; Vol. 57, Chapter 4.

(2) Atta-ur-Rahman; Basha, A. *Biosynthesis of Indole Alkaloids*; Clarendon Press: Oxford, 1983.

(3) The biogenetic numbering is used throughout this paper for all tetracyclic compounds. Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508.

(4) (a) Saito, M.; Kawamura, M.; Hiroya, K.; Ogasawara, K. *Chem. Commun.* **1997**, 765. (b) Tanaka, K.; Katsumura, S. *J. Am. Chem. Soc.* **2002**, *124*, 9660. (c) Jiricek, J.; Blechert, S. *J. Am. Chem. Soc.* **2004**, *126*, 3534.

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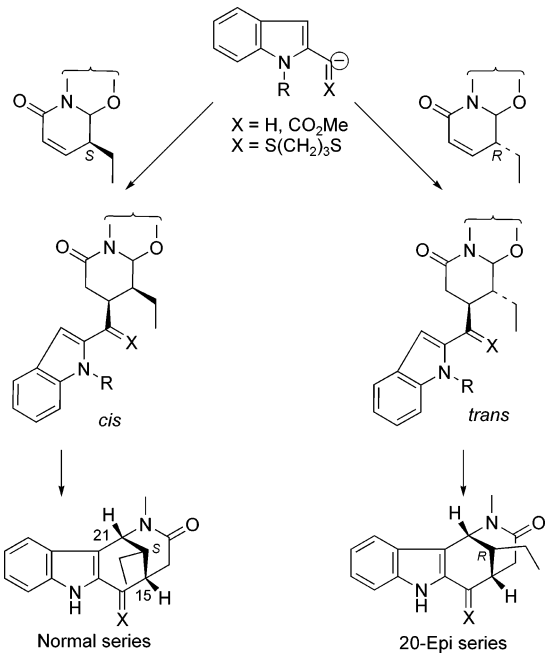
SCHEME 2. Synthetic Strategy



In the context of our studies on the enantioselective synthesis of piperidine-containing derivatives from phenylglycinol-derived bicyclic lactams,[5] we devised a general synthetic route to the uleine alkaloids, in which the key step would be the stereocontrolled conjugate addition of an indolylmethyl anion equivalent to an appropriate γ-ethyl α,β-unsaturated δ-lactam (bond formed $C_{15}-C_{16}$). A subsequent biomimetic cyclization on the indole 3-position of the masked acyl iminium ion present in the resulting enantiopure *cis* or *trans* 4,5-disubstituted 2-piperidone (bond formed C_7-C_{21}) would lead to the natural products, either in the normal or epi series, respectively (Scheme 2).[6] As a consequence of the bridgehead character of the stereocenters at C-15 and C-21, the absolute configuration of the stereogenic center generated at the piperidine 4-carbon (C-15) after the conjugate addition reaction would determine that of C-21 in the cyclization leading to the tetracyclic system of uleine alkaloids.

In recent work,[5a,7] we have demonstrated that the diastereomeric unsaturated lactams *cis*-**1** and *trans*-**1** undergo conjugate addition of organocuprates with opposite facial selectivity, a result that was rationalized by considering that the configuration of the C-8a stereocenter determines the conformation of the six-membered ring and that the attack of the nucleophile to these conformationally rigid lactams occurs under stereoelectronic control,[8] axial to the electrophilic carbon of the conjugate double bond (Figure 2). These conjugate additions constitute the key step of an enantiodivergent synthesis of both enantiomers of the antidepressant drug paroxetine (a *trans*-3,4-disubstituted piperidine).

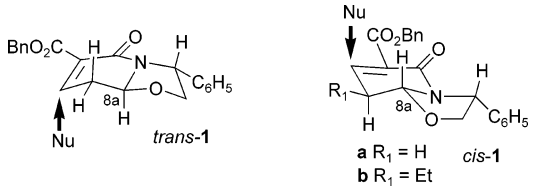


FIGURE 2. Stereoelectronic control.

Results and Discussion

Taking into account that α,β-unsaturated lactams are poor Michael acceptors[9] and that there are few examples of such conjugate additions to δ-lactams lacking an additional electron-withdrawing group on the nitrogen and/or in conjugation with the double bond,[10] to check the viability of the proposed conjugate addition−cyclization sequence, in our initial studies we examined the stereochemical outcome of the conjugate addition of 2-indoleacetate enolates to the model lactams *cis*-**2** and *trans*-**2**, which lack the ethyl substituent present in the natural products.

Reaction of lactam *trans*-**2** with the enolate of methyl 1-methyl-2-indoleacetate (**3a**) gave (64%) lactam ester **4a** as a mixture of epimers (3:2 ratio) at the isomerizable stereocenter α to the ester group, which could be separated by column chromatography (Scheme 3). The cyclization step was carried out in the presence of $TiCl_4$, using each epimer separately. The major isomer led to tetracycle (16*S*)-**5a** (44%), whereas the minor one led to the C-16 epimer (16*R*)-**5a** (50%),[11] thus indicating that the conjugate addition had taken place on the *exo* face of lactam *trans*-**2** with excellent facial selectivity.

The relative configuration of C-16 in these tetracycles was deduced from the $H_{15}-H_{16}$ *J* value and from the

(5) (a) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074. (b) Amat, M.; Cantó, M.; Llor, N.; Ponzo, V.; Pérez, M.; Bosch, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 335. (c) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919. (d) Amat, M.; Escolano, C.; Lozano, O.; Llor, N.; Bosch, J. *Org. Lett.* **2003**, *5*, 3139 and references therein. For reviews, see: (e) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1. (f) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843.

(6) For a preliminary communication of this part of the work, see: Amat, M.; Pérez, M.; Llor, N.; Martinelli, M.; Molins, E.; Bosch, J. *Chem. Commun.* **2004**, 1602.

(7) Amat, M.; Pérez, M.; Llor, N.; Lago, E.; Molins, E. *Org. Lett.* **2001**, *3*, 611.

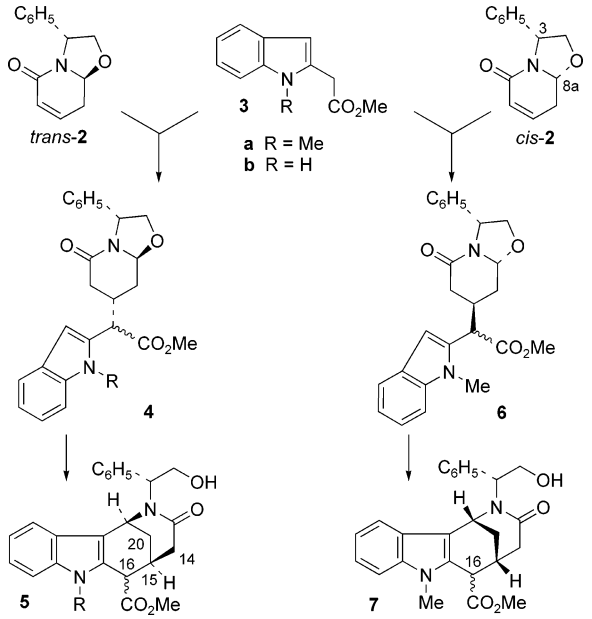
(8) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; p 221. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992; p 25.

(9) (a) Nagashima, H.; Ozaki, N.; Washiyama, M.; Itoh, K. *Tetrahedron Lett.* **1985**, *26*, 657. (b) Hagen, T. J. *Synlett* **1990**, 63.

(10) For the addition of organocuprates, see: (a) Overman, L. E.; Robichaud, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 300. (b) Herdeis, C.; Kaschinski, C.; Karla, R. *Tetrahedron: Asymmetry* **1996**, *7*, 867. (c) Muller, M.; Schoenfelder, A.; Didier, B.; Mann, A.; Wermuth, C.-G. *Chem. Commun.* **1999**, 683. (d) Deiters, A.; Martin, S. F. *Org. Lett.* **2002**, *4*, 3243. (e) Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, *124*, 14826. (f) Hanessian, S.; van Otterlo, W. A. L.; Nilsson, I.; Bauer, U. *Tetrahedron Lett.* **2002**, *43*, 1995. (g) Cossy, J.; Mirguet, O.; Gomez Pardo, D.; Desmurs, J.-R. *New J. Chem.* **2003**, *27*, 475. For the addition of stabilized anions, see: (h) Stork, G.; Schultz, A. G. *J. Am. Chem. Soc.* **1971**, *93*, 4074. (i) Herrmann, J. L.; Richman, J. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2599. (j) Kametani, T.; Surgenor, S. A.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 920. (k) Takano, S.; Sato, M.; Ogasawara, K. *Heterocycles* **1981**, *16*, 799. (l) Naito, T.; Miyata, O.; Ninomiya, I. *Heterocycles* **1987**, *26*, 1739. (m) Fujii, T.; Ohba, M.; Sakaguchi, J. *Chem. Pharm. Bull.* **1987**, *35*, 3628. (n) Forns, P.; Diez, A.; Rubiralta, M.; Solans, X.; Font-Bardia, M. *Tetrahedron* **1996**, *52*, 3563. (o) Etxarri, B.; González-Temprano, I.; Manteca, I.; Sotomayor, N.; Lete, E. *Synlett* **1999**, 1486. (p) Hanessian, S.; Gomtsyan, A.; Malek, N. *J. Org. Chem.* **2000**, *65*, 5623. (q) Hanessian, S.; Seid, M.; Nilsson, I. *Tetrahedron Lett.* **2002**, *43*, 1991.

(11) In both cases, minor amounts of the respective C-16 epimer were also formed as a consequence of the epimerization occurring at the ester α carbon during the cyclization step.

SCHEME 3. Tetracyclic Ring System of Uleine Alkaloids



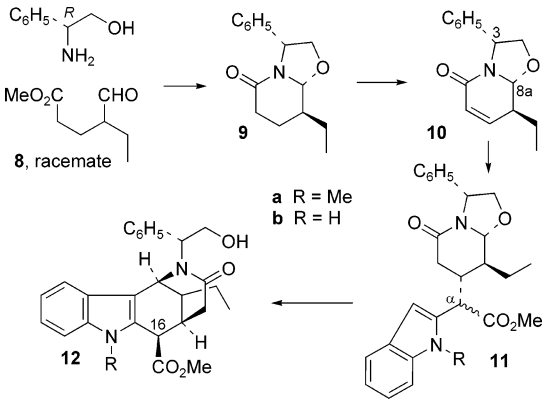
existence or absence of γ-gauche effects on C-14 and C-20 on the NMR spectra,[12] whereas the absolute configuration (C-15 is *S*) was inferred by comparing the NMR data of tetracycles **5a** with those of **12a**, whose absolute configuration was known from the X-ray analysis of its precursor (αR)-**11a** (see below).

The use of the enolate of indoleacetate **3b**, unsubstituted on the indole nitrogen, led to similar results. Conjugate addition to *trans*-**2** took place again with high *exo* facial stereoselectivity to give an epimeric mixture of lactam esters **4b** (3:2 ratio; 51%), which were separately cyclized to the respective tetracycles (16*S*)-**5b** and (16*R*)-**5b** in ~70% yield. In this series, epimerization at C-16 during cyclization occurred to a considerable extent (see the Experimental Section).

Next we investigated the stereochemical outcome of the conjugate addition−cyclization sequence from lactam *cis*-**2**. The conjugate addition of ester **3a** led again to an epimeric mixture of lactam esters **6** (3:2 ratio; 53% yield), which were separately cyclized to the respective tetracycles (16*S*)-**7** (from the major lactam ester) and (16*R*)-**7** without detectable epimerization at C-16. These cyclizations, involving a 3,8a-*cis* lactam, took place in lower yield and required harder conditions than the above cyclizations from the 3,8a-*trans* isomers.[13]

Comparison of the NMR spectroscopic data of tetracycle (16*R*)-**7** with those of (16*S*)-**5a**, both of them with a *trans* $H_{15}-H_{16}$ relationship, made evident that these compounds were diastereomers and, consequently, that the absolute configuration of C-15 in (16*R*)-**7** is *R*. Similarly, (16*S*)-**7** and (16*R*)-**5a**, both having a *cis* $H_{15}-H_{16}$ relationship, are also diastereomers, and therefore, the configuration at the piperidine 4-position in tetracycle (16*S*)-**7** is also *R*. This allowed us to conclude that the conjugate addition of **3a** to *cis*-**2** had also occurred on the *exo* face, which involves a facial stereoselectivity opposite to that observed when starting from *trans*-**2**. These results are in agreement with the stereochemical outcome of the conjugate addition of cyanocuprates to related lactams *cis*-**1** and *trans*-**1**[5a,7] and can be accounted for by considering that the process is kinetically controlled.[14]

SCHEME 4



Once it was demonstrated that the above approach can provide straightforward access to the tetracyclic ring system of uleine alkaloids with the natural configuration at the bridgehead carbons (e.g., **7**), we extended our studies using the unsaturated lactam **10**, which has the same *cis*-3,8a configuration as *cis*-**2** and incorporates the ethyl substituent with the required absolute configuration for the synthesis of alkaloids in the normal C-20 series. This lactam was prepared in 55% overall yield by cyclocondensation of (*R*)-phenylglycinol with racemic methyl 4-formylhexanoate (**8**), in a process involving a dynamic kinetic resolution,[15] followed by generation of the carbon−carbon double bond from the resulting lactam **9** via a β-keto sulfoxide (Scheme 4). The addition of the enolate ester **3a** to lactam **10** took place in excellent yield (83%) and complete facial selectivity to give the epimeric lactam esters (αS)-**11a** and (αR)-**11a** (3:7 ratio). Cyclization of the major isomer also took place in excellent yield (81%) to give tetracycle **12a**. The absolute configuration of (αR)-**11a** was unambiguously established by X-ray crystallography and indicated that the ethyl substituent had exerted a dramatic influence on the stereochemical course of the conjugate addition since it had occurred on the *endo* face of the carbon−carbon double bond to give an *all-trans* piperidine derivative, instead of the required *cis*-4,5-disubstituted 2-piperidone.[16]

The same stereoselectivity was observed from the enolate of the *N*-unsubstituted indoleacetate **3b**, although in this case the conjugate addition only took place in acceptable yield (40%) in the presence of CuCN to give a 7:3 epimeric mixture of lactam esters (αS)-**11b** and (αR)-**11b**. Both epimers were separately cyclized to give the same enantiopure tetracycle **12b**, thus indicating that epimerization at C-16 from the major isomer had occurred during cyclization.

(12) Bennasar, M.-L.; Alvarez, M.; Lavilla, R.; Zulaica, E.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 1156.

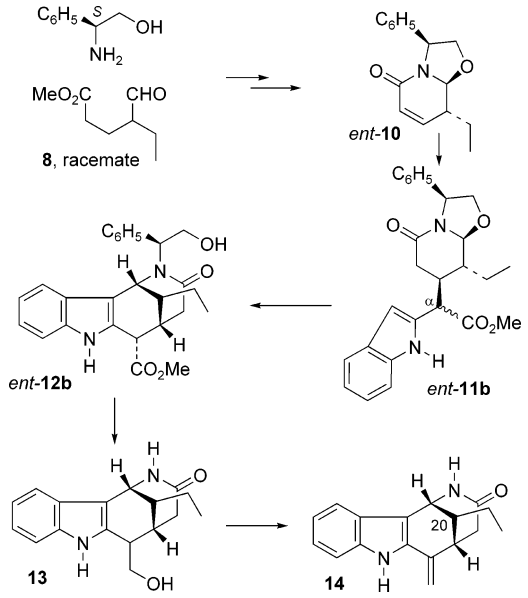
(13) For the different reactivity of 3,8a-*cis* and *trans* related lactams in α-amidoalkylation reactions, see: Amat, M.; Escolano, C.; Llor, N.; Huguet, M.; Pérez, M.; Bosch, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1679.

(14) Molecular mechanics (MM.; CVFF91 force field) calculations provide support to this conclusion because they indicated that the *exo* adducts **4a** and **6** are less stable that the corresponding C-7 epimers.

(15) For a recent review, see: Pellissier, H. *Tetrahedron* **2003**, *59*, 8291.

(16) According to MM calculations, the *endo* adducts **11a**, **24b**, **28b**, and **33b** were more stable than the respective *exo* epimers.

SCHEME 5. Enantioselective Total Synthesis of 20-Epiuleine Derivatives



Unfortunately, the absolute configuration at the piperidine 4-position in **11** and, consequently, at the bridgehead carbons in tetracycles **12** is the opposite of that present in uleine alkaloids. However, taking advantage of the fact that both enantiomers of phenylglycinol are commercially available, the trans stereoselectivity of the above conjugate additions can provide access to tetracyclic derivatives with the natural configuration in the 20-epi series. It is simply a matter of starting from the enantiomer of unsaturated lactam **10**, which was prepared from (*S*)-phenylglycinol as in the above *R*-series (Scheme 5).

As expected, conjugate addition of the enolate derived from **3b** to *ent*-**10**, followed by cyclization of the resulting epimeric mixture of lactam esters *ent*-**11b**, led to tetracycle *ent*-**12b**, which was chemoselectively reduced with Na/liq NH_3 to alcohols **13** (64%; epimeric mixture) and then converted (53%) to the nor-20-epiuleine derivative **14** via the corresponding mesylate.

The enantioselective access to the more widespread uleine alkaloids with a *cis* $H_{15}-H_{20}$ relationship (normal series) required the preparation of a *cis*-4,5-disubstituted 2-piperidone by stereocontrolled conjugate addition of an appropriate nucleophile to unsaturated lactam **10**, avoiding the undesired equilibration to the more stable *trans* isomers. Taking into account that metalated dithioacetals have been reported to undergo conjugated addition reactions to unsaturated amides and lactams in fair yields,[17,18] we decided to investigate the introduction of the required indolylmethyl substituent on the 4 position of the piperidine ring of lactam **10** by conjugate addition of a 2-(2-indolyl)-1,3-dithiane derivative. It should be mentioned that, although much effort has been devoted to identifying the factors governing the regioselectivity in the addition of sulfur-stabilized anions to enones,[19] there are few reports concerning the stereoselectivity of such conjugate addition reactions.[19e] For this reason, we became interested in studying the stereochemical outcome of the conjugate addition of a variety of dithioacetals to phenylglycinol-derived unsaturated lactams as a tool for the enantioselective generation of *cis* or *trans* 3,4-disubstituted piperidine derivatives. To explore the influence on the stereoselectivity of an alkyl substituent next to the electrophilic carbon of the double bond, in our study we used lactams *cis*-**2** and **10** as substrates, both with a *cis* 3,8a relative configuration. Moreover, to gain further insight into the factors governing the stereoselectivity of the reaction we also used lactam *trans*-**2**, the C-8a diastereomer of *cis*-**2**. The results are summarized in Table 1.[20]

The addition of 2-lithio-1,3-dithiane (**15**-Li) to the diastereomeric unsubstituted lactams *trans*-**2** and *cis*-**2** and the ethyl-substituted lactam **10** at low temperature (−78 °C), followed by stirring at 0 °C for 20 h in THF in the presence of HMPA, took place with excellent facial selectivity to give the corresponding *exo* adducts **21a**, **25a**, and **29a**, respectively (entries 1, 6, and 13). Similar results were observed in the addition of **15**-Li to *trans*-**2** in the absence of HMPA (entry 2). However, on raising the temperature to 25 °C lactam **10** afforded a nearly equimolecular mixture of isomers **29a** and **29b** (entry 14). On the other hand, conjugate addition of the lithium salt of bis(phenylthio)methane (**19**-Li) to lactam **10** at 0 °C took place with low *exo* stereoselectivity (entry 15), whereas at 25 °C the *endo* isomer **30b** was the major component of the reaction mixture (entry 16). The above results suggest that the addition of lithium salts **15**-Li and **19**-Li to **10** is reversible and that, under the same reaction conditions, **19**-Li affords a higher ratio of the thermodynamic *endo* isomer **b** (*trans* relative configuration of the substituents), presumably as a consequence of the higher steric hindrance in the corresponding adduct and the greater anion stability of **19**-Li as compared with **15**-Li.[21]

The reaction of 2-lithio-2-phenyl-1,3-dithiane (**16**-Li) with *trans*-**2** at 0 °C for 20 h again led to the corresponding *exo* isomer **16a** (entry 3), although with lower stereoselectivity than when using **15**-Li, whereas starting from *cis*-**2** an approximately 25:75 mixture of isomers, in which the *endo* derivative **26b** predominated, was obtained (entry 7). There was a similar result when the reaction of **16**-Li with *cis*-**2** was carried out at room temperature (entry 8). However, a reversal in the stereochemical outcome of the reaction was observed when the addition of **16**-Li to *cis*-**2** was performed under kinetic

(17) (a) Mpango, G. B.; Mahalanabis, K. K.; Mahdavi-Damghani, Z.; Snieckus, V. *Tetrahedron Lett.* **1980**, *21*, 4823. (b) Mpango, G. B.; Snieckus, V. *Tetrahedron Lett.* **1980**, *21*, 4827. See also ref 10i,n,o.

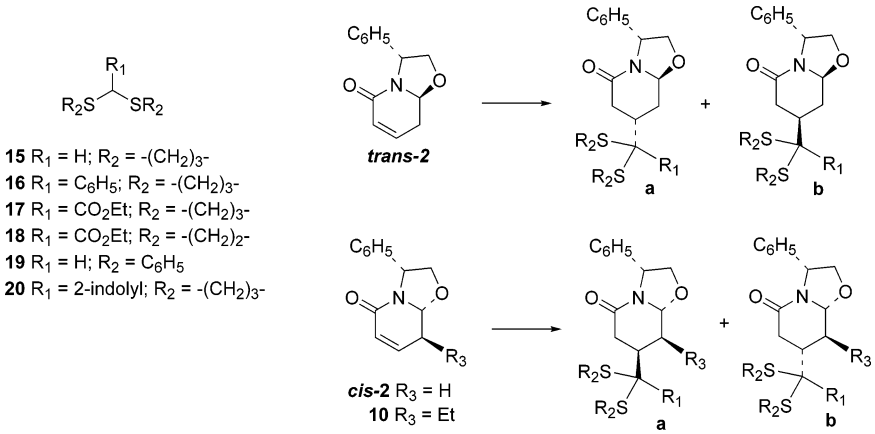
(18) For a recent review on 1,3-dithianes in natural product synthesis, see: Yus, M.; Nájera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147.

(19) (a) Ostrowski, P. C.; Kane, V. V. *Tetrahedron Lett.* **1977**, 3549. (b) Ager, D. J.; East, M. B. *J. Org. Chem.* **1986**, *51*, 3983. (c) Cohen, T.; Abraham, W. D.; Myers, M. *J. Am. Chem. Soc.* **1987**, *109*, 7923. (d) Page, P. C. B.; van Niel, M. B.; Prodger, J. C. *Tetrahedron* **1989**, *45*, 7643. (e) Sikorski, W. H.; Reich, H. J. *J. Am. Chem. Soc.* **2001**, *123*, 6527. (f) Juaristi, E.; Hernández-Rodríguez, M.; López-Ruiz, H.; Aviña, J.; Muñoz-Muñiz, O.; Hayakawa, M.; Seebach, D. *Helv. Chim. Acta* **2002**, *85*, 1999.

(20) For a preliminary account covering part of these results, see: Amat, M.; Pérez, M.; Llor, N.; Bosch, J. *Org. Lett.* **2002**, *4*, 2787.

(21) For pK_a values of dithioacetals **15**, **16**, and **19**, see: (a) Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Chem. Soc., Chem. Commun.* **1983**, 620. (b) Xie, L.; Bors, D. A.; Streitwieser, A. *J. Org. Chem.* **1992**, *57*, 4986. (c) Xie, L.; Streitwieser, A. *J. Org. Chem.* **1995**, *60*, 1339. (d) Alnajjar, M. S.; Zhang, X.-M.; Franz, J. A.; Bordwell, F. G. *J. Org. Chem.* **1995**, *60*, 4976.

TABLE 1. Conjugate Addition of Sulfur-Stabilized Nucleophiles[a]



entry	substrate	dithioacetal	product	R_1	R_2	R_3	*T* (°C) (time (h))	**a/b** ratio[b]	yield (%)
1	*trans*-**2**	**15**	**21**	H	$-(CH_2)_3-$	H	0 (20)	**a**	78
2	*trans*-**2**	**15**	**21**	H	$-(CH_2)_3-$	H	0 (15)[c]	**a**	71
3	*trans*-**2**	**16**	**22**	C_6H_5	$-(CH_2)_3-$	H	0 (20)	88:12	85
4	*trans*-**2**	**17**	**23**	CO_2Et	$-(CH_2)_3-$	H	0 (20)	>95:5	70
5	*trans*-**2**	**18**	**24**	CO_2Et	$-(CH_2)_2-$	H	0 (5)[c]	>95:5	72
6	*cis*-**2**	**15**	**25**	H	$-(CH_2)_3-$	H	0 (20)	*a*	68
7	*cis*-**2**	**16**	**26**	C_6H_5	$-(CH_2)_3-$	H	0 (20)	25:75	80
8	*cis*-**2**	**16**	**26**	C_6H_5	$-(CH_2)_3-$	H	25 (20)	22:78	81
9	*cis*-**2**	**16**	**26**	C_6H_5	$-(CH_2)_3-$	H	−78 (2)[c]	>95:5	74
10	*cis*-**2**	**16**	**26**	C_6H_5	$-(CH_2)_3-$	H	−78 (2)	>95:5	75
11	*cis*-**2**	**17**	**27**	CO_2Et	$-(CH_2)_3-$	H	0 (20)	86:14	66
12	*cis*-**2**	**18**	**28**	CO_2Et	$-(CH_2)_2-$	H	0 (20)	86:14	70
13	**10**	**15**	**29**	H	$-(CH_2)_3-$	Et	0 (20)	>95:5	61
14	**10**	**15**	**29**	H	$-(CH_2)_3-$	Et	25 (20)	43:57	54
15	**10**	**19**	**30**	H	C_6H_5	Et	0 (20)	60:40	61
16	**10**	**19**	**30**	H	C_6H_5	Et	25 (20)	16:84	66
17	**10**	**16**	**31**	C_6H_5	$-(CH_2)_3-$	Et	0 (20)	**b**	79
18	**10**	**16**	**31**	C_6H_5	$-(CH_2)_3-$	Et	−78 (20)	**b**	90
19	**10**	**16**	**31**	C_6H_5	$-(CH_2)_3-$	Et	−78 (20)[c]	**b**	75
20	**10**	**17**	**32**	CO_2Et	$-(CH_2)_3-$	Et	0 (20)	<5:95	60
21	**10**	**18**	**33**	CO_2Et	$-(CH_2)_2-$	Et	0 (4)[c]	<5:95	52
22	**10**	**20**	**34**	2-indolyl	$-(CH_2)_3-$	Et	0 (20)	34:66	70
23	**10**	**20**	**34**	2-indolyl	$-(CH_2)_3-$	Et	−78 (0.5)	70:30	40
24	**10**	**20**	**34**	2-indolyl	$-(CH_2)_3-$	Et	−78 (3)	57:43	82
25	**10**	**20**	**34**	2-indolyl	$-(CH_2)_3-$	Et	−78 (2)[c]	80:20	90

[a] See the general procedure in the Experimental Section. [b] Determined by ^1H NMR and/or after isolation by column chromatography. [c] In the absence of HMPA.

conditions, that is at low temperature (−78 °C) for a short reaction time (2 h) both in the absence and in the presence of HMPA (entries 9 and 10). Under these conditions, compound **26a**, resulting from an *exo* attack of the nucleophile, was stereoselectively formed. On the other hand, the addition of **16**−Li to lactam **10** stereoselectively afforded the thermodynamic *endo* isomer **31b** under a variety of conditions (entries 17−19). These results can be rationalized once again by considering the higher steric hindrance in the adducts resulting from **16**-Li and the higher stability of this anion as compared with **15**-Li.[21] In fact, when pure isomers **22a** and **26a** were stirred in the presence of 4 equiv of **16**-Li at 25 °C, a slow isomerization to the corresponding *endo* epimers **22b** and **26b** was observed, thus corroborating the reversibility of the reaction.

We also examined the stereoselectivity in the conjugate addition of sulfur-stabilized enolates **17**-Li and **18**-Li, which whould allow the introduction of an acetate chain at the 4 position of the piperidine ring after desulfurization. The addition of the masked glyoxylate anions **17**-Li and **18**-Li to the diastereomeric lactams *trans*-**2** and *cis*-**2** at 0 °C for 20 h predominantly afforded the kinetic *exo* isomers **23a**, **24a** (entries 4 and 5) and **27a**, **28a** (entries 11 and 12), respectively.[16] Again the *exo* stereoselectivity was higher from the unsaturated lactam *trans*-**2** than from *cis*-**2**. In sharp contrast, under the same conditions, the conjugate addition of the highly stabilized enolates **17**-Li and **18**-Li to lactam **10** occurred with almost complete *endo* facial selectivity, affording the *endo* isomers **32b** and **33b** (entries 20 and 21).[16] The above results evidenced that, as already observed when using indoleacetic ester enolates, under the same reaction conditions the *endo*/*exo* ratio using sulfur-stabilized nucleophiles is much higher from the 8-ethyl-substituted lactam **10** than from the deethyl analogue *cis*-**2**. In contrast, the related lactams *cis*-**1a** and *cis*-**1b**, the latter bearing an ethyl substituent at C-8 (see Figure 2), undergo conjugate addition of cuprates with the same *exo* selectivity.[5a,7]

To better understand why the conjugate addition of stabilized nucleophiles to the 8-ethyl-substituted lactam **10** and its deethyl analogue *cis*-**2** takes place with different facial selectivity we first examined the reactivity

TABLE 2. Electrostatic (E_{ele}), Polarization (E_{pol}), van der Waals (E_{vW}), and Total Interaction (E_{tot}) Energy Determined from GMIPp Calculations for the Attack of a Negatively Charged Classical Point Charge to the Two Faces of the Lactam Ring at C7[a]

lactam	face	E_{ele}	E_{pol}	E_{vW}	E_{tot}
cis-**2**[b]	*exo*	−4.9	−12.2	+2.5	−14.5
	endo	+1.0	−11.6	+2.3	−8.3
10	*exo*	−5.2	−11.7	+1.1	−15.9
	endo	+1.7	−11.3	+0.8	−8.9

[a] Values are in kcal/mol. [b] Data taken from ref 5a.

TABLE 3. Energy Changes for the Formation of the Enolate Adduct[a]

lactam	face	ΔE
cis-**2**	*exo*	−2.7
	endo	−6.7
10	*exo*	+2.6
	endo	−4.6

[a] Values are in kcal/mol.

pattern of these bicyclic lactams from GMIPp calculations[22] (see the Computational Methods). To this end, we determined the GMIPp interaction energy profile for the approach of a negatively charged classical point particle along the line perpendicular to the six-membered ring passing through carbon 7. As noted in Table 2, the two faces of the lactam ring have different susceptibility to the attack of a nucleophilic reagent. Thus, the *exo* attack is found to be energetically more favorable than the *endo* attack by 6−7 kcal/mol. Moreover, the results in Table 2 also show that such a preference clearly stems from the electrostatic term, and that replacement of the hydrogen atom by an ethyl group has negligible influence on the intrinsic reactivity of lactams *cis*-**2** and **10**.

Table 3 shows the reaction energies corresponding to the formation of the enolate adducts obtained by nucleophilic attack of either a hypothetical methyl anion (a small nucleophile) or the anion derived from dithiolane **18** (a bulky nucleophile) on the two faces of the unsaturated C-7 carbon of *cis*-**2** and **10**. For the attack of the methyl anion, the adducts are highly favored (by around 82 kcal/mol) compared to the separate reactants, and the energy difference between the enolates formed upon addition on the *exo* or *endo* faces is less than 1.5 kcal/mol. However, the energetic stabilization of the enolate adducts is drastically reduced in the case of the bulky anion derived from dithiolane **18**. In fact, the addition of this anion on the *exo* face of the substituted lactam **10** is even predicted to be energetically disfavored. More importantly, the relative energy of the two enolates is clearly different, the adduct formed upon attack on the *endo* face being energetically preferred by 4 (cis-**2**) and 6 (**10**) kcal/mol.

Consequently, it can be concluded that even though the intrinsic reactivity of lactams *cis*-**2** and **10** favors a nucleophilic attack on the *exo* face owing to a better electrostatic interaction, the steric hindrance associated with the enolate resulting from the approach of a bulky anion to the *exo* face tends to reverse such a reactivity preference.

Finally, with our synthetic purpose in mind, we undertook the conjugate addition of the dilithium salt of 2-(2-indolyl)-1,3-dithiane (**20**) to lactam **10**. When the reaction was carried out in THF−HMPA at 0 °C for 20 h, a 34:66 mixture of *exo* and *endo* isomers, **34a** and **34b**, respectively, was obtained in good chemical yield (70%) (entry 22). Probably as a consequence of the dianionic character of the nucleophile, the equilibration between the desired kinetic *exo* addition product to the thermodynamic *endo* adduct (a *trans* 4,5-disubstituted 2-piperidone) was slower in this case than in the above experiments with **16**−Li. As could be expected, the *exo* stereoselectivity leading to the desired *cis* isomer **34a** was improved (*exo*/*endo* 7:3), although the chemical yield was only moderate (40%), when the reaction was carried out at lower temperature (−78 °C) for a short time (30 min) in order to minimize the equilibration process (entry 23). Longer reaction times (3 h) under the same conditions resulted in a higher chemical yield but a lower stereoselectivity (entry 24). However, to our delight, in the absence of HMPA the reaction took place at −78 °C in an extraordinarily high yield (90%) and good stereoselectivity from the synthetic standpoint (*exo*/*endo* ratio 4:1; entry 25). After column chromatography the required enantiopure piperidone *cis*-**34a** was isolated in 72% yield.

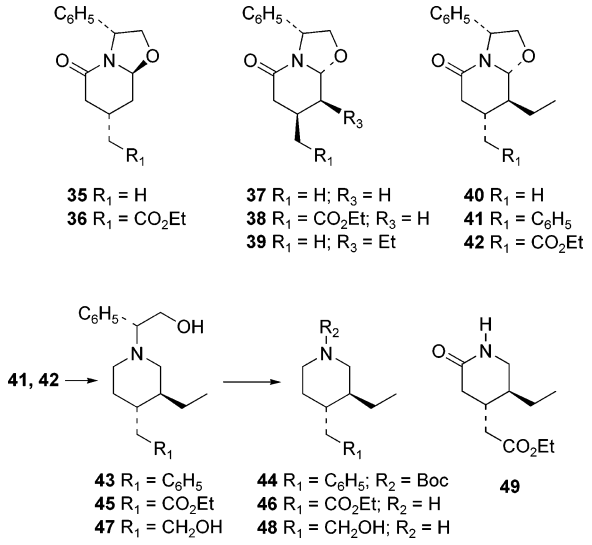
The stereochemical identity of some adducts obtained in the above conjugate addition reactions was established by desulfurization with nickel boride and comparison of the specific rotation and spectroscopic data of the resulting compounds with those of related lactams of known configuration previously prepared in our laboratory. Thus, desulfurization of **21a**, **25a**, and **29a/30a** afforded **35**, **37**, and **39**, respectively, which had previously been prepared[5a,7] by conjugate addition reactions of methyl organocuprates to lactams *trans*-**1** and *cis*-**1a,b** followed by debenzyloxycarbonylation. On the other hand, desulfurization of **29b** and **30b** gave **40**, the C-7 epimer of **39**. Treatment of compounds **24a** and **28a** with nickel boride afforded **36** and **38**, respectively, which are C-7 diastereomers of bicyclic lactams obtained by cyclocondensation of diethyl 3-(2-oxoethyl)glutarate and (*R*)-phenylglycinol.[5b] Similarly, **33b** was converted to lactam **42**, which had previously been obtained by cyclocondensation of a racemic aldehyde diester and (*R*)-phenylglycinol.[5b] Finally, the configuration of **26a**, **26b**, and **31b** was unambiguously established by X-ray crystallography.

The synthetic usefulness of the above chiral substituted lactams is illustrated by their conversion to enantiopure *trans*-3,4-disubstituted piperidines (Scheme 6). Thus, desulfurization of **31b** followed by lactam reduction with simultaneous reductive ring opening of the oxazolidine present in **41** afforded piperidine **43**, whose debenzylation in the presence of $(Boc)_2O$ gave the *trans*-4-benzyl-3-ethylpiperidine derivative **44**. On the other hand, lactam **42** was converted to valuable intermediates for the synthesis of indolo[2,3-*a*]- and benzo[*a*]quinolizidine alkaloids.[23] Thus, treatment of **42** with borane brought about both the chemoselective reduction of the lactam carbonyl group and the reductive opening of the oxazolidine ring affording 4-piperidineacetate **45**, whereas

(22) (a) Luque, F. J.; Orozco, M. *J. Comput. Chem.* **1998**, *19*, 866. (b) Orozco, M.; Luque, F. J. In *Molecular Electrostatic Potentials: Concepts and Applications*; Murray, J. S., Sen, K., Eds.; Elsevier: Amsterdam, 1996; pp 181−218.

(23) For reviews, see: (a) Fujii, T.; Ohba, M. *Heterocycles* **1988**, *27*, 1009. (b) Fujii, T.; Ohba, M. *Heterocycles* **1998**, *47*, 525.

SCHEME 6. Synthesis of Enantiopure *trans*-3,4-Disubstituted Piperidines

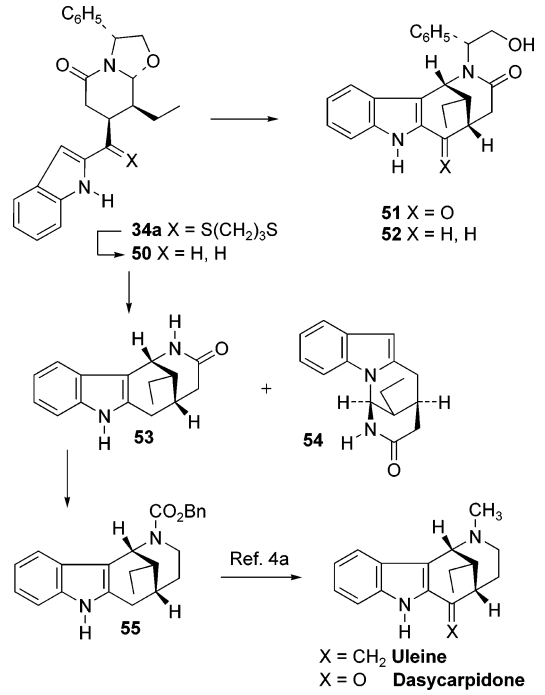


reduction of **42** with alane caused the additional reduction of the ester group yielding 4-piperidineethanol **47**. Debenzylation of **45** and **47** by catalytic hydrogenation gave *trans*-3-ethyl-4-piperidineacetate **46** and *trans*-3-ethyl-4-piperidineethanol **48**, respectively. Alternatively, hydrogenolysis of the C−N bond of **42** with Ca in liquid NH_3, followed by treatment of the resulting oxylactams with Et_3SiH in THF afforded lactam **49**.

Finally, conversion of the *cis*-substituted lactam **34a** into the target tetracyclic alkaloids of the uleine group required, as the key steps, the closure of the carbocyclic ring and the removal of the chiral inductor. Treatment of **34a** with $TiCl_4$ under several reaction conditions afforded in poor yields (∼20%) tetracyclic keto lactam **51** resulting from both deprotection of the dithioacetal function and intramolecular amidoalkylation (Scheme 7). A similar $TiCl_4$-promoted cyclization of **50**, prepared by desulfurization of **34a**, gave tetracycle **52**, again in low yield (∼20%). For this reason we decided to first remove the chiral inductor. This was accomplished by treatment of **34a** with sodium in liquid ammonia, which brought about the reductive desulfurization and cleavage of the benzylic C−N bond to give an intermediate 6-hydroxylactam, which, without further purification, was cyclized with $TiCl_4$ to give the tetracyclic lactam **53** in 35% overall yield. Minor amounts (6%) of the regioisomer **54**, resulting from cyclization on the indole nitrogen, were also formed.[24] Finally, borane reduction of the lactam carbonyl group of **53** followed by treatment of the resulting secondary amine with benzyl chloroformate gave (40% overall yield) carbamate **55**, which had previously been converted[4a] into the alkaloids (+)-dasycarpidone and (+)-uleine. Taking into account previous correlations,[25] the above synthesis also represents a formal synthesis of nordasycarpidone, (−)-dasycarpidol, and (−)-17-hydroxydihydrouleine.

In conclusion, conjugate addition reactions of indoleacetic ester enolates and sulfur-stabilized nucleophiles

SCHEME 7. Enantioselective Formal Synthesis of Uleine Alkaloids



to phenylglycinol-derived unsaturated δ-lactams allow the stereocontrolled formation of C−C bonds at the piperidine 4-position. Some factors governing the stereoselectivity of the process, namely the nature of the nuclophile, the configuration of the stereocenter at the angular position (C-8a), and the presence or absence of a γ-substituent, have been identified. By choosing the appropriate indole-containing nucleophile, the above methodology opens short synthetic routes for the enantioselective construction of the bridged tetracyclic system of uleine alkaloids either in the normal or 20-epi series. The availability of both enantiomers of phenylglycinol allows the preparation, in each particular case, of 4-substituted derivatives in both enantiomeric series.

Experimental Section

(3*R*,8a*S*)-5-Oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridine (*trans*-2). Methyl phenylsulfinate (1.29 g, 8.29 mmol) and KH (1.0 g, 20 wt % dispersion in mineral oil, 25 mmol) were added to a solution of (3*R*,8a*S*)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine[5a] (950 mg, 4.37 mmol) in THF (15 mL). The suspension was heated at reflux for 1.5 h and concentrated. The resulting residue was taken up in 0.5 M aqueous H_3PO_4 and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was washed with hexane and chromatographed ($CHCl_3$) to give **(3*R*,8a*S*)-5-oxo-3-phenyl-6-(phenylsulfinyl)-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine** (1.48 g, 95%) as a mixture of isomers: ^{1}H NMR (300 MHz, selected resonances) δ 3.46 (masked s, 1 H), 3.48 (dd, J = 10.6, 7.6 Hz, 1 H), 3.71 (t, J = 8.5 Hz, 1 H), 3.84 (t, J = 8.5 Hz, 1 H), 4.54 (m, 2 H), 5.04 (m, 2 H), 5.27 (t, J = 8.0 Hz, 1 H), 5.33 (t, J = 8.0 Hz, 1 H); ^{13}C NMR (75.4 MHz, selected resonances) δ 12.4 (CH_2), 27.1 (CH_2), 58.9 (CH), 65.8 (CH), 72.9 (CH_2), 88.3 (CH), 164.0 (C). Na_2CO_3 (2.69 g, 25.3 mmol) was added to a solution of the β-keto sulfoxide (1.53 g, 4.5 mmol) in toluene (54 mL), and the mixture was heated at reflux for 7 h, filtered through Celite, and concentrated. The resulting oil was chromatographed (7:3 EtOAc−hexane) to

(24) For a related cyclization, see ref 10n.
(25) (a) Joule, J. A.; Ohashi, M.; Gilbert, B.; Djerasi, C. *Tetrahedron* **1965**, *21*, 1717. (b) Gràcia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 3939.

afford *trans*-**2** (820 mg, 89%): IR (KBr) 1660, 1611 cm^{-1}; ^1H NMR (300 MHz) δ 2.48 (dddd, J = 17.4, 10.2, 3.2, 2.3 Hz, 1 H), 2.80 (dddd, J = 17.4, 6.0, 6.0, 0.7 Hz, 1 H), 3.86 (dd, J = 8.8, 7.0 Hz, 1 H), 4.49 (dd, J = 8.8, 7.0 Hz, 1 H), 5.25 (t, J = 7.0 Hz, 1 H), 5.42 (dd, J = 10.2, 6.0 Hz, 1 H), 5.99 (ddd, J = 9.9, 3.2, 0.7 Hz, 1 H), 6.48 (ddd, J = 9.9, 6.0, 2.3 Hz, 1 H), 7.22−7.40 (m, 5 H); ^{13}C NMR (75.4 MHz) δ 29.9 (CH_2), 57.9 (CH), 73.0 (CH_2), 86.7 (CH), 125.4 (CH), 125.9 (CH), 128.7 (CH), 127.5 (CH), 134.8 (CH), 139.2 (C), 160.7 (C); mp 121−122 °C (Et_2O−hexane); $[\alpha]^{22}_D$ +50.5 (*c* 1.0, EtOH). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.56; H, 6.08; N, 6.57.

(3*R*,8a*R*)-5-Oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridine (*cis*-2). Operating as described above, from (3*R*,8a*R*)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo-[3,2-*a*]pyridine[5a] (300 mg, 1.4 mmol), THF (10 mL), methyl phenylsulfinate (437 mg, 2.8 mmol), and KH (840 mg, 20 wt % dispersion in mineral oil, 21 mmol) was obtained **(3*R*,8a*R*)-5-oxo-3-phenyl-6-(phenylsulfinyl)-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine** (487 mg, 97%) as a mixture of isomers: IR (film) 1661 cm^{-1}; ^1H NMR (300 MHz, selected resonances for two isomers) δ 3.29 (dd, J = 6.6, 0.9 Hz, 1 H), 3.35 (dd, J = 10.5, 7.8 Hz, 1 H), 4.05 (2dd, J = 9.0, 2.1 Hz, 2 H), 4.18 (2dd, J = 9.0, 6.9 Hz, 2 H), 4.88 (td, J = 9.9, 3.0 Hz, 2 H), 5.00 (d, J = 6.9 Hz, 2 H, H-3); ^{13}C NMR (75.4 MHz, selected resonances) δ 12.8 (CH_2), 16.9 (CH_2), 26.5 (CH_2), 27.2 (CH_2), 59.2 (CH), 59.5 (CH), 65.3 (CH), 65.4 (CH), 73.7 (CH_2), 73.8 (CH_2), 88.1 (CH), 88.8 (CH), 162.0 (C), 162.2 (C). From the β-keto sulfoxide (487 mg, 136 mmol), toluene (15 mL), and Na_2CO_3 (804 mg) was obtained *cis*-**2** (260 mg, 89%) after flash chromatography (2:1 EtOAc−$CHCl_3$): IR (film) 1670, 1606 cm^{-1}; ^1H NMR (300 MHz) δ 2.60 (dddd, J = 17.2, 11.7, 3.3, 2.1 Hz, 1 H), 2.82 (dddd, J = 17.1, 6.6, 4.5, 0.9 Hz, 1 H), 4.10 (dd, J = 9.0, 1.5 Hz, 1 H), 4.20 (dd, J = 9.0, 6.9 Hz, 1 H), 5.03 (dd, J = 6.9, 1.5 Hz, 1 H), 5.11 (dd, J = 11.7, 4.5 Hz, 1 H), 5.94 (ddd, J = 9.9, 3.0, 0.9 Hz, 1 H), 6.52 (dd, J = 9.9, 2.1 Hz, 1 H), 7.10−7.35 (m, 5 H); ^{13}C NMR (75.4 MHz) δ 29.9 (CH_2), 57.3 (CH), 74.0 (CH_2), 86.8 (CH), 126.1 (CH), 126.2 (CH), 128.3 (CH), 127.3 (CH), 135.9 (CH), 140.7 (C), 161.1 (C); mp 45−50 °C; $[\alpha]^{22}_D$ +5.2 (*c* 1.0, $CHCl_3$).

Methyl (3*R*,7*S*,8a*S*)-α-(1-Methyl-2-indolyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine-7-acetate (4a). LDA was prepared by addition of diisopropylamine (0.31 mL, 2.22 mmol) to a cooled (−78 °C) solution of *n*-BuLi (1.3 mL of a 1.6 M solution in hexanes, 2.08 mmol) in THF (4 mL). The mixture was stirred at −78 °C for 5 min and at 0 °C for 5 min, and cooled at −78 °C. Then, a solution of ester **3a**[12] (422 mg, 2.08 mmol) in THF (30 mL) was added dropwise, and the mixture was stirred at −78 °C for 30 min. A solution of *trans*-**2** (300 mg, 1.39 mmol) in THF (5 mL) was added via cannula, and the mixture was stirred at 0 °C for 4 h, poured into saturated aqueous $NaHCO_3$, and extracted with EtOAc. The combined organic extracts were dried and concentrated to give an oil. Flash chromatography (Et_2O) afforded 230 mg of (α*S*)-**4a** and 140 mg of (α*R*)-**4a** (overall yield 64%). (α*S*)-**4a** (lower R_f): IR (NaCl) 1737, 1663 cm^{-1}; ^1H NMR (300 MHz) δ 1.97 (dt, J = 14.0, 5.0 Hz, 1 H, H-8), 2.06 (ddd, J = 14.0, 7.5, 5.2 Hz, 1 H, H-8), 2.43 (dd, J = 17.0, 7.0 Hz, 1 H, H-6), 2.72 (ddd, J = 17.0, 5.0, 0.8 Hz, 1 H, H-6), 3.07 (m, 1 H, H-7), 3.67 (s, 3 H, CH_3N), 3.72 (dd, J = 8.5, 7.0 Hz, 1 H, H-2), 3.77 (s, 3 H, CH_3O), 3.82 (d, J = 11.0 Hz, 1 H, C*H*CO_2Me), 4.45 (t_{ap}, J = 8.5 Hz, 1 H, H-2), 4.83 (t_{ap}, J = 5.3 Hz, 1 H, H-8a), 5.41 (t_{ap}, J = 7.5 Hz, 1 H, H-3), 6.52 (s, 1H, H-3 ind), 7.12 (tm, J = 7.8 Hz, 1 H, H-5 ind), 7.23 (tm, J = 7.5 Hz, 1 H, H-6 ind), 7.24−7.42 (m, 6 H, ArH), 7.57 (dm, J = 7.8 Hz, 1 H, H-4 ind); ^{13}C NMR (75.4 MHz) δ 30.0 (CH_3N), 30.0 (C-8); 31.3 (C-7), 37.0 (C-6), 47.2 (*C*HCO_2Me), 52.6 (CH_3O), 58.0 (C-3), 71.7 (C-2), 85.7 (C-8a), 101.5 (C-3 ind), 109.3 (C-7 ind), 119.9 (C-4 ind), 120.6 (C-5 ind), 121.9 (C-6 ind), 125.8, 128.9 (C-*o*, *m*), 126.0 (C-3a ind), 127.7 (C-*p*), 134.2 (C-2 ind), 137.5 (C-*i*), 139.6 (C-7a ind), 168.7 (NCO), 171.2 (COO); mp 65−69 °C (Et_2O); $[\alpha]^{22}_D$ +53.8 (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.26; N, 6.69. Found: C, 71.49; H, 6.63; N, 6.29. (α*R*)-**4a** (higher R_f): IR (film) 1734, 1661 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.12 (ddd, J = 14.0, 6.0, 4.5 Hz, 1 H), 2.23 (dd, J = 17.3, 6.0 Hz, 1 H), 2.31 (m, 1 H), 2.48 (dd, J = 17.3, 5.2 Hz, 1 H), 2.98 (m, 1 H), 3.69 (s, 3 H), 3.72 (s, 3 H), 3.80 (dd, J = 8.7, 7.5 Hz, 1 H), 3.87 (d, J = 11.0 Hz, 1 H), 4.52 (t_{ap}, J = 8.3 Hz, 1H), 5.14 (t_{ap}, J = 5.5 Hz, 1 H), 5.37 (t_{ap}, J = 8.0 Hz, 1 H), 6.52 (s, 1 H), 7.10 (ddd, J = 7.8, 7.0, 1.2 Hz, 1 H), 7.20 (tm, J = 7.0 Hz, 1 H), 7.25−7.40 (m, 6 H), 7.56 (dm, J = 7.8 Hz, 1 H); ^{13}C NMR (75.4 MHz) δ 29.8 (CH_3), 31.0 (CH_2), 32.7 (CH), 35.4 (CH_2), 46.6 (CH), 52.7 (CH_3), 58.1 (CH), 72.0 (CH_2), 86.0 (CH), 101.0 (CH), 109.3 (CH), 119.9 (CH), 120.5 (CH), 121.9 (CH), 125.9 (CH), 128.9 (CH), 125.9 (C), 127.7 (CH), 134.6 (CH), 137.4 (C), 139.7 (C), 168.5 (C), 171.3 (C); mp 240−245 °C (Et_2O); $[\alpha]^{22}_D$ −123.6 (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{25}H_{26}N_2O_4 \cdot 1H_2O$: C, 68.79; H, 6.46; N, 6.41. Found: C, 68.70; H, 6.18; N, 6.40.

(1*S*,5*S*,6*S*)-2-[(1*R*)-2-Hydroxy-1-phenylethyl]-6-(methoxycarbonyl)-7-methyl-3-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole [(16*S*)-5a]. $TiCl_4$ (90 μL, 0.82 mmol) was added to a cooled (0 °C) solution of (α*S*)-**4a** (230 mg, 0.55 mmol) in CH_2Cl_2 (2 mL), and the resulting mixture was stirred for 2 h, poured into saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (EtOAc) to give (16*S*)-**5a** (100 mg, 44%) and trace amounts of (16*R*)-**5a** and starting material. (16*S*)-**5a**: IR (KBr) 1731, 1621 cm^{-1}; ^1H NMR (300 MHz) δ 2.12 (dt, J = 13.2, 3.3 Hz, 1 H), 2.28 (dm, J = 13.2 Hz, 1 H), 2.46 (d, J = 18.0 Hz, 1 H), 3.09 (dm, J = 10.0 Hz, 1 H), 3.17 (dd, J = 18.0, 9.1 Hz, 1 H), 3.62 (s, 3 H), 3.72 (s, 3 H), 3.81 (d, J = 1.4 Hz, 1 H), 3.86 (ddd, J = 14.5, 4.3, 2.6 Hz, 1 H), 4.05 (ddd, J = 14.5, 9.4, 6.3 Hz, 1 H), 4.63 (br t, J = 2.7 Hz, 1 H), 4.86 (dd, J = 9.4, 4.3 Hz, 1 H), 4.92 (dd, J = 6.3, 2.6 Hz, 1 H), 7.10−7.50 (m, 9 H); ^{13}C NMR (75.4 MHz) δ 29.1 (CH_2), 29.6 (CH), 30.2 (CH_3), 39.2 (CH_2), 46.9 (CH), 51.2 (CH), 52.6 (CH_3), 64.6 (CH_2), 70.3 (CH), 109.5 (CH), 112.6 (C), 118.3 (CH), 120.1 (CH), 122.1 (CH), 124.6 (C), 127.4 (CH), 127.7 (CH), 128.7 (CH), 130.3 (C), 137.5 (C), 137.6 (C), 170.9 (C), 171.5 (C); mp 205−208 °C (Et_2O−CH_2Cl_2); $[\alpha]^{22}_D$ −6.1 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.26; N, 6.69. Found: C, 71.66; H, 6.27; N, 6.62.

(1*S*,5*S*,6*R*)-2-[(1*R*)-2-Hydroxy-1-phenylethyl]-6-(methoxycarbonyl)-7-methyl-3-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole [(16*R*)-5a]. Operating as described above, starting from (α*R*)-**4a** (50 mg, 0.12 mmol) in CH_2Cl_2 (4 mL) and $TiCl_4$, (20 μL, 0.18 mmol) at rt for 5 h, pure (16*R*)-**5a** (25 mg, 50%), trace amounts of (16*S*)-**5a**, and starting material (10 mg) were obtained after flash chromatography (EtOAc). (16*R*)-**5a**: IR (film) 1733, 1620 cm^{-1}; ^1H NMR (300 MHz) δ 2.00 (m, 1 H), 2.30 (dt, J = 13.2, 3.3 Hz, 1 H), 2.54 (d, J = 19.0 Hz, 1 H), 2.87 (dd, J = 19.0, 8.2 Hz, 1 H), 3.15 (m, 1 H), 3.57 (s, 3 H), 3.85 (s, 3 H), 3.90 (ddd, J = 13.5, 4.7, 2.9 Hz, 1 H), 4.03 (ddd, J = 13.5, 9.3, 6.4 Hz, 1 H), 4.18 (d, J = 6.0 Hz, 1 H), 4.58 (m, 1 H), 4.78 (m, 1 H), 4.85 (dd, J = 6.1, 2.4 Hz, 1 H), 7.10−7.50 (m, 9 H); ^{13}C NMR (75.4 MHz) δ 29.6 (CH), 30.5 (CH_3), 32.8 (CH_2), 35.5 (CH_2), 46.2 (CH), 50.8 (CH), 52.6 (CH_3), 64.7 (CH_2), 70.1 (CH), 109.5 (CH), 112.4 (C), 117.9 (CH), 120.3 (CH), 122.2 (CH), 124.5 (C), 125.5 (CH), 127.7 (CH), 128.8 (CH), 131.3 (C), 137.7 (C), 138.0 (C), 170.2 (C), 172.0 (C).

Methyl (3*R*,7*S*,8a*S*)-α-(2-Indolyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine-7-acetate (4b). LDA (3.72 mL of a 1.5 M solution in cyclohexane, 5.58 mmol) was added to a solution of ester **3b**[26] (520 mg, 2.75 mmol) in THF (48 mL) at −78 °C. After 1 h, a solution of *trans*-**2** (400 mg, 1.86 mmol) in THF (5 mL) was added via cannula, and the mixture was stirred at −78 °C for 5 h. The resulting mixture was poured into saturated aqueous $NaHCO_3$ and

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extracted with EtOAc. The combined organic extracts were dried and concentrated to give an oil. Flash chromatography (Et_2O) afforded (α*S*)-**4b** and (α*R*)-**4b** (380 mg, overall yield 51%, 63:37 ratio). (α*S*)-**4b** (lower R_f): IR (film) 3300, 1734, 1646 cm^{-1}; ^1H NMR (300 MHz) δ 1.90 (m, 2 H), 2.34 (dd, *J* = 17.0, 7.0 Hz, 1 H), 2.64 (dd, *J* = 17.0, 5.0 Hz, 1 H), 2.83 (m, 1 H), 3.73 (dd, *J* = 8.7, 7.5 Hz, 1 H), 3.74 (s, 3 H), 3.80 (d, *J* = 10.5 Hz, 1 H), 4.44 (t_{ap}, *J* = 8.5 Hz, 1 H), 4.97 (t_{ap}, *J* = 5.2 Hz, 1 H), 5.38 (t_{ap}, *J* = 7.8 Hz, 1 H), 6.44 (d, *J* = 2.0 Hz, 1 H), 7.11 (tm, *J* = 7.5 Hz, 1 H), 7.19 (tm, *J* = 7.2 Hz, 1 H), 7.22−7.41 (m, 6 H), 7.56 (d, *J* = 7.7 Hz, 1 H), 8.75 (br s, 1 H); ^{13}C NMR (75.4 MHz) δ 29.6 (CH_2), 32.7 (CH), 36.5 (CH_2), 48.9 (CH), 52.6 (CH_3), 58.0 (CH), 71.7 (CH_2), 85.7 (CH), 102.7 (CH), 111.1 (CH), 119.9 (CH), 120.2 (CH), 122.1 (CH), 125.7 (CH), 128.8 (CH), 127.6 (CH), 127.6 (C), 131.8 (CH), 136.4 (C), 139.4 (C), 168.6 (C), 172.4 (C); $[\alpha]^{22}_D$ +12.2 (*c* 0.5, EtOH); HMRS calcd for $C_{24}H_{24}N_2O_4$ 404.1736, found 404.1734. (α*R*)-**4b** (higher R_f): IR (film) 3300, 1734, 1647 cm^{-1}; ^1H NMR (300 MHz) δ 2.09 (dt, *J* = 14.2, 5.0 Hz, 1 H), 2.19 (ddd, *J* = 14.2, 7.7, 5.5 Hz, 1 H), 2.23 (dd, *J* = 17.0, 7.5 Hz, 1 H), 2.40 (dd, *J* = 17.0, 5.0 Hz, 1 H), 2.76 (m, 1 H), 3.77 (s, 3 H), 3.77 (masked, 1 H), 3.80 (d, *J* = 10.2 Hz, 1 H), 4.48 (t_{ap}, *J* = 8.5 Hz, 1 H), 5.07 (t_{ap}, *J* = 5.2 Hz, 1 H), 5.37 (t_{ap}, *J* = 8.0 Hz, 1 H), 6.40 (d, *J* = 2.0 Hz, 1 H), 7.09 (tm, *J* = 7.5 Hz, 1 H), 7.17 (tm, *J* = 7.3 Hz, 1 H), 7.20−7.39 (m, 6 H), 7.54 (d, *J* = 7.7 Hz, 1 H), 8.70 (br s, 1 H); ^{13}C NMR (75.4 MHz) δ 31.0 (CH_2), 33.0 (CH), 35.1 (CH_2), 48.9 (CH), 52.6 (CH_3), 58.1 (CH), 71.8 (CH_2), 85.8 (CH), 103.1 (CH), 111.0 (CH), 120.0 (CH), 120.3 (CH), 122.2 (CH), 125.8 (CH), 128.8 (CH), 127.5 (C), 127.6 (CH), 131.7 (CH), 136.4 (C), 139.5 (C), 168.7 (C), 172.4 (C); mp 168−171 °C (Et_2O−acetone−hexane); $[\alpha]^{22}_D$ −45.1 (*c* 0.2, EtOH). Anal. Calcd for $C_{24}H_{24}N_2O_4 \cdot {}^1/_2H_2O$: C, 69.71; H, 6.09; N, 6.77. Found: C, 69.73; H, 5.90; N, 6.80.

[1*S*,5*S*,6*S*(and 6*R*)]-2-[(1*R*)-2-Hydroxy-1-phenylethyl]-6-(methoxycarbonyl)-3-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole [(16*S*)-5b and (16*R*)-5b]. $TiCl_4$ (90 μL, 0.82 mmol) was added to a cooled (0 °C) solution of (α*S*)-**4b** (100 mg, 0.25 mmol) in CH_2Cl_2 (3 mL), and the mixture was stirred at rt for 5 h, poured into saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (EtOAc) to give (16*S*)-**5b** and (16*R*)-**5b** (60 mg, 60%, 58:42 ratio). Similarly, starting from (α*R*)-**4b** (125 mg, 0.31 mmol), CH_2Cl_2 (4 mL), and $TiCl_4$ (50 μL, 0.46 mmol), tetracycles (16*S*)-**5b** and (16*R*)-**5b** (88 mg, 70%, 13:87 ratio) were obtained after flash chromatography (EtOAc). (16*S*)-**5b** (lower R_f): IR (film) 1734, 1617 cm^{-1}; ^1H NMR (300 MHz) δ 2.17 (dt, *J* = 13.2, 3.4 Hz, 1 H), 2.28 (dm, *J* = 13.2 Hz, 1 H), 2.46 (d, *J* = 16.5 Hz, 1 H), 3.13 (m, 1 H), 3.13 (m, 1 H), 3.73 (s, 3 H), 3.78 (br s, 1 H), 3.85 (dm, *J* = 12.4 Hz, 1 H), 4.04 (ddd, *J* = 12.4, 9.4, 6.2 Hz, 1 H), 4.57 (t_{ap}, *J* = 3.0 Hz, 1 H), 4.86 (dd, *J* = 6.2, 2.5 Hz, 1 H), 4.90 (m, 1 H), 7.10−7.50 (m, 9 H), 8.50 (br s, 1 H); ^{13}C NMR (75.4 MHz) δ 28.1 (CH), 29.7 (CH_2), 39.2 (CH_2), 47.0 (CH), 51.0 (CH), 52.6 (CH_3), 64.7 (CH_2), 70.4 (CH), 111.4 (CH), 113.9 (C), 118.1 (CH), 120.6 (CH), 122.7 (CH), 125.1 (C), 127.4 (CH), 128.8 (CH), 127.7 (CH), 128.2 (C), 136.2 (C), 137.6 (C), 170.8 (C), 171.0 (C); $[\alpha]^{22}_D$ −2.0 (*c* 0.55, EtOH); MS-EI *m/z* 404 (M^+, 10), 268 (10), 245 (34), 225 (70), 193 (100), 161 (75), 148 (33); HMRS calcd for $C_{24}H_{24}N_2O_4$ 404.1736, found 404.1739. (16*R*)-**5b** (higher R_f): IR (film) 1733, 1620 (NCO) cm^{-1}; ^1H NMR (300 MHz) δ 2.05 (dm, *J* = 13.0 Hz, 1 H), 2.27 (ddd, *J* = 13.0, 4.5, 3.0 Hz, 1 H), 2.40 (d, *J* = 19.0 Hz, 1 H), 3.00 (dd, *J* = 19.0, 9.0 Hz, 1 H), 3.20 (m, 1 H), 3.87 (s, 3 H), 3.91 (dm, *J* = 14.0 Hz, 1 H), 4.05 (d, *J* = 4.3 Hz, 1 H), 4.11 (ddd, *J* = 14.0, 9.3, 6.6 Hz, 1 H), 4.59 (t_{ap}, *J* = 2.7 Hz, 1 H), 4.81 (dd, *J* = 9.3, 4.4 Hz, 1 H), 4.93 (dd, *J* = 6.6, 2.5 Hz, 1 H), 7.10−7.45 (m, 9 H), 9.00 (br s, 1 H); ^{13}C NMR (75.4 MHz) δ 28.3 (CH), 32.8 (CH_2), 35.6 (CH_2), 46.8 (CH), 50.9 (CH), 52.7 (CH_3), 64.6 (CH_2), 70.2 (CH), 111.5 (CH), 112.5 (C), 118.1 (CH), 120.4 (CH), 122.4 (CH), 125.0 (C), 127.5 (CH), 128.8 (CH), 127.8 (CH), 129.0 (C), 136.3 (C), 137.7 (C), 171.4 (C), 171.5 (C); mp 202−206 °C (Et_2O−hexane); MS-EI *m/z* 404 (M^+, 5), 373 (3), 284 (30), 268 (5), 245 (87), 225 (25), 193 (35); HMRS calcd for $C_{24}H_{24}N_2O_4$ 404.1736, found 404.1735.

Methyl (3*R*,7*R*,8a*R*)-α-(1-Methyl-2-indolyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine-7-acetate (6). Operating as described for the preparation of **4a**, from *n*-BuLi (2.2 mL of a 1.6 M solution in hexanes, 3.5 mmol), diisopropylamine (495 μL, 3.5 mmol), **3a** (708 mg, 3.5 mmol), and *cis*-**2** (500 mg, 2.32 mmol), epimers (α*S*)-**6** and (α*R*)-**6** (520 mg, 53%, 63:37 ratio) were obtained after flash chromatography (2:1 EtOAc−hexane). (α*S*)-**6** (higher R_f): IR (film) 1736, 1662 cm^{-1}; ^1H NMR (300 MHz) δ 2.09 (dd, *J* = 17.0, 7.2 Hz, 1 H), 2.24 (ddd, *J* = 14.0, 9.3, 7.2 Hz, 1 H), 2.37 (ddd, *J* = 17.0, 6.0 Hz, 1 H), 2.40 (m, 1 H), 3.00 (m, 1 H), 3.72 (s, 3 H), 3.73 (s, 3 H), 3.85 (d, *J* = 11.0 Hz, 1 H), 4.10 (dd, *J* = 9.0, 0.9 Hz, 1 H), 4.24 (dd, *J* = 9.0, 6.0 Hz, 1 H), 4.94 (dd, *J* = 6.0, 0.9 Hz, 1 H), 5.11 (dd, *J* = 9.3, 4.5 Hz, 1 H), 6.50 (s, 1 H), 7.09 (tm, *J* = 7.8 Hz, 1 H), 7.15−7.38 (m, 7 H), 7.56 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR (75.4 MHz) δ 29.9 (CH_3), 31.7 (CH_2), 32.9 (CH), 35.4 (CH_2), 47.7 (CH), 52.6 (CH_3), 58.4 (CH), 74.3 (CH_2), 86.0 (CH), 101.1 (CH), 109.3 (CH), 119.9 (CH), 120.5 (CH), 121.9 (CH), 126.3 (CH), 128.6 (CH), 127.4 (C), 127.7 (CH), 134.8 (C), 137.4 (C), 140.9 (C), 166.5 (C), 171.3 (C); mp 132−140 °C; $[\alpha]^{22}_D$ −10.5 (*c* 1.0, $CHCl_3$); MS-EI *m/z* 418 (M^+, 13), 325 (57), 136 (45), 108 (76); HMRS calcd for $C_{25}H_{26}N_2O_4$ 418.1892, found 418.1891. (α*R*)-**6** (lower R_f): IR (NaCl) 1736, 1666 cm^{-1}; ^1H NMR (300 MHz) δ 2.03 (ddd, *J* = 14.0, 9.0, 7.5 Hz, 1 H), 2.21 (dt, *J* = 14.0, 4.5 Hz, 1 H), 2.28 (dd, *J* = 17.0, 7.0 Hz, 1 H); 2.61 (dd, *J* = 17.0, 5.7 Hz, 1 H), 3.14 (m, 1 H), 3.66 (s, 3 H), 3.79 (s, 3 H), 3.85 (d, *J* = 10.8 Hz, 1 H), 4.03 (dd, *J* = 9.3, 0.9 Hz, 1 H), 4.15 (dd, *J* = 9.3, 6.6 Hz, 1 H), 4.88 (dd, *J* = 9.0, 4.5 Hz, 1 H), 4.94 (d, *J* = 6.6 Hz, 1 H), 6.52 (s, 1 H), 7.14 (tm, *J* = 7.8 Hz, 1 H), 7.20−7.38 (m, 7 H), 7.60 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR (75.4 MHz) δ 30.0 (CH_3), 30.9 (CH_2), 31.6 (CH), 36.3 (CH_2), 48.0 (CH), 52.6 (CH_3), 58.5 (CH), 74.2 (CH_2), 85.9 (CH), 101.5 (CH), 109.3 (CH), 119.9 (CH), 120.5 (CH), 121.9 (CH), 126.3 (CH), 128.6 (CH), 127.5 (C), 127.7 (CH), 134.4 (C), 137.5 (C), 140.9 (C), 166.5 (C), 171.3 (C); $[\alpha]^{22}_D$ −18.8 (*c* 1.0, $CHCl_3$); MS-EI *m/z* 418 (M^+, 96), 325 (17), 287 (100), 203 (76); HMRS calcd for $C_{25}H_{26}N_2O_4$ 418.1892, found 418.1891.

(1*R*,5*R*,6*S*)-2-[(1*R*)-2-Hydroxy-1-phenylethyl]-6-(methoxycarbonyl)-7-methyl-3-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole [(16*S*)-7]. $TiCl_4$ (35 μL, 0.32 mmol) was added to a solution of (α*S*)-**6** (135 mg, 0.32 mmol) in CH_2Cl_2 (2 mL) at rt, and the resulting mixture was heated at reflux for 2 h. $TiCl_4$ (35 μL, 0.32 mmol) was added twice after 2 and 6 h, and the mixture was heated at reflux for an additional 18 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (4:1 EtOAc−hexane to EtOAc) to give (16*S*)-**7** (34 mg, 25%): IR (film) 3350, 1735, 1620 cm^{-1}; ^1H NMR (300 MHz) δ 1.90 (dm, *J* = 13.0 Hz, 1 H), 2.24 (dt, *J* = 13.0, 3.3 Hz, 1 H), 2.52 (d, *J* = 19.0 Hz, 1 H), 2.85 (dd, *J* = 19.0, 8.1 Hz, 1 H), 3.13 (m, 1 H), 3.54 (s, 3 H), 3.83 (s, 3 H), 4.14 (d, *J* = 6.3 Hz, 1 H), 4.18−4.25 (m, 2 H), 4.54 (dd, *J* = 3.6, 2.6 Hz, 1 H), 5.67 (t, *J* = 7.0 Hz, 1 H), 7.10−7.50 (m, 9 H); ^{13}C NMR (75.4 MHz) δ 29.3 (CH), 30.4 (CH_3), 33.6 (CH_2), 34.9 (CH_2), 46.2 (CH), 47.4 (CH), 52.6 (CH_3), 62.3 (CH), 63.1 (CH_2), 109.3 (CH), 113.0 (C), 118.0 (CH), 119.8 (CH), 122.0 (CH), 124.4 (C), 127.5 (CH), 127.6 (CH), 128.6 (CH), 131.6 (C), 136.6 (C), 137.3 (C), 170.8 (C), 172.3 (C); mp 118 °C (Et_2O−CH_2Cl_2); $[\alpha]^{22}_D$ +40.5 (*c* 1.0, $CHCl_3$).

(1*R*,5*R*,6*R*)-2-[(1*R*)-2-Hydroxy-1-phenylethyl]-6-(methoxycarbonyl)-7-methyl-3-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole [(16*R*)-7]. $TiCl_4$ (125 μL, 0.12 mmol) was added to a solution of (α*R*)-**6** (190 mg, 0.45 mmol) in CH_2Cl_2 (10 mL), and the resulting mixture was heated at reflux 17 h. $TiCl_4$ (50 μL, 0.45 mmol) was added, and the mixture was heated at reflux for an additional 4 h, poured into saturated solution $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (4:1 EtOAc−

hexane, 4.9:0.1 EtOAc−EtOH) to afford (16*R*)-**7** (38 mg, 20%): IR (film) 3375, 1733, 1624 cm^{-1}; ^{1}H NMR (300 MHz) δ 2.00 (dt, J = 13.0, 3.0 Hz, 1 H), 2.20 (dm, J = 13.0 Hz, 1 H), 2.47 (d, J = 18.6 Hz, 1 H), 3.05 (dm, J = 9.6 Hz, 1 H), 3.16 (dd, J = 18.6, 9.3 Hz, 1 H), 3.38 (br s, 1 H), 3.58 (s, 3 H), 3.68 (s, 3 H), 3.80 (d, J = 1.2 Hz, 1 H), 4.25 (m, 2 H), 4.52 (t, J = 2.4 Hz, 1 H), 5.57 (t, J = 6.3 Hz, 1 H), 7.00−7.40 (m, 9 H); ^{13}C NMR (75.4 MHz) δ 29.6 (CH), 29.8 (CH_2), 30.1 (CH_3), 38.5 (CH_2), 47.2 (CH), 47.5 (CH), 52.5 (CH_3), 63.3 (CH), 63.7 (CH_2), 109.2 (CH), 112.5 (C), 118.3 (CH), 119.6 (CH), 121.9 (CH), 124.5 (C), 127.6 (CH), 127.7 (CH), 128.6 (CH), 130.6 (C), 136.4 (C), 137.3 (C), 171.5 (C), 171.5 (C); $[\alpha]^{22}_D$ +35.6 (*c* 1.0, $CHCl_3$).

(3*R*,8*S*,8a*R*)-8-Ethyl-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridine (10). Operating as described for the preparation of *trans*-**2**, starting from **9**[27] (500 mg, 2.04 mmol), THF (20 mL), methyl phenylsulfinate (636 mg, 4.08 mmol) and KH (400 mg, 20 wt % dispersion in mineral oil, 10 mmol), **(3*R*,8*S*,8a*R*)-8-ethyl-5-oxo-3-phenyl-6-(phenylsulfinyl)-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine** (715 mg, 95%) was obtained as a mixture of isomers. Major isomer: IR (film) 1658 cm^{-1}; ^{1}H NMR (300 MHz, selected resonances) δ 0.93 (t, J = 7.2 Hz, 3 H), 3.37 (dd, J = 10.5, 7.8 Hz, 1 H), 4.08 (dd, J = 9.0, 1.2 Hz, 1 H), 4.17 (dd, J = 9.0, 6.9 Hz, 1 H), 4.58 (d, J = 8.7, 1 H), 4.99 (d, J = 6.9 Hz, 1 H); ^{13}C NMR (75.4 MHz) δ 10.7 (CH_3), 18.3 (CH_2), 23.9 (CH_2), 39.8 (CH), 59.6 (CH), 65.7 (CH), 73.6 (CH_2), 91.4 (CH), 140.6 (C), 141.2 (C), 161.7 (C). A solution of the β-keto sulfoxide (600 mg, 1.62 mmol) in toluene (15 mL) was heated in the presence of $NaCO_3$ (1.0 g, 9.0 mmol) to give **10** (335 mg, 85%) after flash chromatography (7:3 EtOAc−hexane): IR (film) 1670 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.10 (t, J = 7.8 Hz, 3 H), 1.59 (m, 1 H), 1.85 (m, 1 H), 2.67 (m, 1 H), 4.11 (dd, J = 9.0, 1.5 Hz, 1 H), 4.19 (dd, J = 9.0, 6.6 Hz, 1 H), 4.81 (d, J = 10.8 Hz, 1 H), 5.04 (dd, J = 6.6, 1.5 Hz, 1 H), 5.93 (dd, J = 9.9, 3.0 Hz, 1 H), 6.39 (dd, J = 9.9, 1.8 Hz, 1 H), 7.10−7.35 (m, 5 H); ^{13}C NMR (75.4 MHz) δ 10.8 (CH_3), 23.1 (CH_2), 42.4 (CH), 57.5 (CH), 74.1 (CH_2), 91.0 (CH), 125.5 (CH), 126.3 (CH), 128.4 (CH), 127.4 (CH), 140.8 (C), 141.3 (CH), 161.1 (C); $[\alpha]^{22}_D$ +116.1 (*c* 1.0, $CHCl_3$).

Methyl (3*R*,7*R*,8*S*,8a*R*)-8-Ethyl-α-(1-methyl-2-indolyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]-pyridine-7-acetate (11a). A solution of **3a** (499 mg, 2.46 mmol) in THF (7 mL) was added dropwise to a cooled solution (−78 °C) of LDA (1.64 mL of a 1.5 M solution in cyclohexane, 2.46 mmol) in THF (6 mL). After the mixture was stirred at −78 °C for 1 h, HMPA (432 μL, 2.46 mmol) and a solution of **10** (300 mg, 1.23 mmol) in THF (4 mL) were added via cannula at −78 °C. The mixture was stirred at 0 °C for 3 h and at rt for 18 h, poured into saturated aqueous NH_4Cl, and extracted with EtOAc. The combined organic extracts were washed with water, dried, and concentrated to give an oil. Flash chromatography (8:2 EtOAc−hexane) afforded (α*S*)-**11a** and (α*R*)-**11a** (458 mg, 83%, 3:7 ratio). (α*S*)-**11a** (lower R_f): IR (film) 1736, 1661 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.94 (t, J = 7.5 Hz, 3 H), 1.62 (m, 1 H), 1.70 (m, 1 H), 1.76 (m, 1 H), 2.44 (dd, J = 17.1, 7.0 Hz, 1 H), 2.60 (dd, J = 17.1, 4.2 Hz, 1 H), 2.59 (m, 1 H), 3.55 (s, 3 H), 3.57 (s, 3 H), 3.76 (d, J = 8.7 Hz, 1 H), 4.18 (m, 2 H), 4.70 (d, J = 8.0 Hz, 1 H), 4.98 (t, J = 4.0 Hz, 1 H), 6.46 (s, 1 H), 7.10 (tm, J = 7.8 Hz, 1 H), 7.21 (tm, J = 8.1 Hz, 1 H), 7.28−7.44 (m, 6 H), 7.56 (dm, J = 7.8 Hz, 1 H); ^{13}C NMR (75.4 MHz) δ 10.3 (CH_3), 25.1 (CH_2), 29.8 (CH_3), 35.0 (CH_2), 37.6 (CH), 42.8 (CH), 46.5 (CH), 52.3 (CH_3), 57.6 (CH), 73.9 (CH_2), 91.0 (CH), 101.6 (CH), 109.1 (CH), 119.7 (CH), 120.4 (CH), 121.6 (CH), 126.8 (CH), 128.6 (CH), 127.3 (C), 127.6 (CH), 134.7 (C), 137.3 (C), 140.9 (C), 167.1 (C), 171.2 (C); mp 149−152 °C (EtOAc−hexane); $[\alpha]^{22}_D$ −70.0 (*c* 1.0, EtOH). Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.35; H, 6.77; N, 6.12. (α*R*)-**11a** (higher R_f): IR (KBr) 1751, 1676 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.11 (t, J = 7.2, 3 H), 1.71 (m, 1 H), 1.80 (m, 1 H), 1.82 (m, 1 H), 2.00 (dd, J = 16.0, 2.5 Hz, 1 H), 2.11 (dd, J = 16.0, 4.5 Hz, 1 H), 2.64 (dm, J = 12.0 Hz, 1 H), 2.90 (s, 3 H), 3.51 (d, J = 12.0 Hz, 1 H), 3.68 (s, 3 H), 4.20 (dd, J = 9.3, 6.3 Hz, 1 H), 4.25 (dd, J = 9.3, 1.5 Hz, 1 H), 4.65 (d, J = 6.3 Hz, 1 H), 4.93 (dd, J = 6.3, 1.5 Hz, 1 H), 6.40 (s, 1 H), 7.00 (ddd, J = 8.0, 6.0, 2.0 Hz, 1 H), 7.11 (ddd, J = 8.0, 8.0, 1.0 Hz, 1 H), 7.33 (d, J = 7.2 Hz, 1 H), 7.40−7.54 (m, 5 H), 7.47 (dt, J = 8.0, 1.0 Hz, 1 H); ^{13}C NMR (75.4 MHz) δ 11.2 (CH_3), 27.0 (CH_2), 28.7 (CH_3), 33.2 (CH_2), 40.9 (CH), 45.1 (CH), 47.3 (CH), 52.3 (CH_3), 57.3 (CH), 73.9 (CH_2), 91.5 (CH), 99.6 (CH), 109.5 (CH), 119.3 (CH), 120.0 (CH), 121.2 (CH), 127.4 (C), 127.6 (CH), 128.6 (CH), 127.7 (CH), 135.3 (C), 136.9 (C), 141.0 (C), 167.1 (C), 171.8 (C); mp 166−169 °C (Et_2O); $[\alpha]^{22}_D$ −49.0 (*c* 1.0, EtOH). Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.74; H, 6.83; N, 6.28.

(1*S*,5*R*,6*R*,12*S*)-12-Ethyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-6-(methoxycarbonyl)-7-methyl-3-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (12a). $TiCl_4$ (120 μL, 1.08 mmol) was added to a solution of (α*R*)-**11a** (160 mg, 0.36 mmol) in CH_2Cl_2 (8 mL), and the resulting mixture was heated at reflux for 5 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (8:2 EtOAc−hexane) to give **12a** (140 mg, 81%): IR (KBr) 3375, 1736, 1628 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.61 (t, J = 7.5 Hz, 3 H, CH_3), 1.39 (m, 2 H, CH_2), 1.80 (m, 1 H, H-12), 2.40 (d, J = 19.0 Hz, 1 H, H-4), 2.76 (dd, J = 19.0, 8.7 Hz, 1 H, H-4), 2.86 (m, 1 H, H-5), 3.57 (s, 3 H, CH_3N), 3.85 (s, 3 H, CH_3O), 3.91 (dd, J = 12.5, 2.7 Hz, 1 H, H-2′), 4.00 (dd, J = 12.5, 5.4 Hz, 1 H, H-2′), 4.15 (d, J = 6.0 Hz, 1 H, H-6), 4.42 (m, 1 H, H-1), 4.69 (dd, J = 5.4, 2.7 Hz, 1 H, H-1′), 4.90 (br s, 1 H, OH), 7.10−7.52 (m, 8 H, ArH), 7.65 (dm, J = 7.8 Hz, 1 H, H-11); ^{13}C NMR (75.4 MHz) δ 11.1 (CH_3), 23.7 (CH_2), 30.5 (CH_3N), 32.0 (C-4), 33.5 (C-5), 42.8 (C-12), 47.3 (C-6), 52.5 (CH_3O), 53.8 (C-1), 64.7 (C-2′), 70.6 (C-1′), 109.5 (C-8), 114.3 (C-11b), 117.7 (C-11), 120.0 (C-10), 121.9 (C-9), 124.5 (C-11a), 127.7 (C-*p*), 128.2, 128.3 (C-*o*, *m*), 131.3 (C-6a), 137.3 (C-7a), 137.8 (C-*i*), 169.9 (NCO), 171.8 (COO); mp 115−117 °C; $[\alpha]^{22}_D$ −10.5 (*c* 1.0, EtOH). Anal. Calcd for $C_{27}H_{30}N_2O_4 \cdot 1CH_2Cl_2$: C, 68.23; H, 6.44; N, 5.80. Found: C, 68.23; H, 6.51; N, 5.71.

Methyl (3*R*,7*R*,8*S*,8a*R*)-8-Ethyl-α-(2-indolyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine-7-acetate (11b). A solution of **3b** (1.55 g, 8.22 mmol) in THF (25 mL) was added to a cooled (−78 °C) solution of LDA (10.9 mL of 1.5 M solution in cyclohexane, 16.4 mmol) in THF (20 mL). After the mixture was stirred at −78 °C for 1 h, HMPA (1.44 mL, 8.2 mmol) and CuCN (734 mg, 8.22 mmol) were added. Then, a solution of **10** (1.0 g, 4.11 mmol) in THF (5 mL) was added via cannula at −78 °C. The mixture was stirred at −78 °C for 30 min, at 0 °C for 1 h, and at rt for 15 h. The resulting mixture was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried, and concentrated to give an oil. Flash chromatography (6:4 EtOAc−hexane to EtOAc) afforded (α*S*)-**11b** and (α*R*)-**11b** (706 mg, 40%, 7:3 ratio), **10** (325 mg), and **5-ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-1*H*-2-pyridone** (**56**; 140 mg). (α*S*)-**11b** (lower R_f): IR (KBr) 3268, 1733, 1665 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.79 (t, J = 7.5 Hz, 3 H, CH_3), 1.50 (m, 2 H, CH_2), 1.90 (m, 1 H, H-8), 2.41 (m, 2 H, H-6), 2.45 (m, 1 H, H-7), 3.58 (s, 3 H, CH_3O), 3.65 (d, J = 9.0 Hz, 1 H, C*H*CO_2Me), 4.16 (m, 2 H, H-2), 4.65 (d, J = 8.4 Hz, 1 H, H-8a), 4.98 (m, 1 H, H-3), 6.37 (s, 1 H, H-3 ind), 7.09 (t, J = 7.8 Hz, 1 H, H-5 ind), 7.17 (t, J = 7.8 Hz, 1 H, H-6 ind), 7.33−7.43 (m, 6 H, ArH), 7.57 (d, J = 7.8 Hz, 1 H, H-4 ind), 8.70 (br s, 1 H, NH); ^{13}C NMR (75.4 MHz) δ 10.1 (CH_3), 24.7 (CH_2), 35.1 (C-6), 39.6 (C-7), 42.6 (C-8), 48.6 (*C*HCO_2Me), 52.4 (CH_3O), 57.8 (C-3), 74.1 (C-2), 91.1 (C-8a), 102.8 (C-3 ind), 111.0 (C-7 ind), 120.0 (C-4 ind), 120.2 (C-5 ind), 122.1 (C-6 ind), 126.8, 128.6 (C-*o*, *m*), 127.8 (C-*p*), 128.6 (C-3a ind), 132.6 (C-2 ind), 136.2 (C-*i*), 140.9 (C-7a ind), 166.6 (NCO), 172.8 (COO); $[\alpha]^{22}_D$ −123.6 (*c* 0.55, EtOH). Anal.

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Calcd for $C_{26}H_{28}N_2O_4 \cdot {}^1/_2H_2O$: C, 70.73; H, 6.62; N, 6.34. Found: C, 71.05; H, 7.02; N, 6.05. (α*R*)-**11b** (higher R_f): IR (film) 3298, 1732, 1664 cm^{-1}; ^1H NMR (500 MHz) δ 1.09 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.77 (m, 2 H, CH_2), 1.82 (m, 1 H, H-8), 2.13 (dd, *J* = 16.0, 4.2 Hz, 1 H, H-6), 2.24 (dd, *J* = 16.0, 5.7 Hz, 1 H, H-6), 2.47 (m, 1 H, H-7), 3.65 (d, *J* = 10.0 Hz, 1 H, C*H*CO_2Me), 3.76 (s, 3 H, CH_3O), 4.14 (dd, *J* = 9.0, 1.0 Hz, 1 H, H-2), 4.21 (dd, *J* = 9.0, 6.6 Hz, 1 H, H-2), 4.70 (d, *J* = 7.2 Hz, 1 H, H-8a), 4.94 (d, *J* = 6.6, 1.0 Hz, 1 H, H-3), 6.27 (d, *J* = 1.2 Hz, 1 H, H-3 ind), 7.04 (td, *J* = 7.2, 1.2 Hz, 1 H, H-5 ind), 7.11 (tm, *J* = 7.2 Hz, 1 H, H-6 ind), 7.24−7.33 (m, 6 H, ArH), 7.48 (d, *J* = 8.1 Hz, 1 H, H-4 ind), 8.62 (br s, 1 H, NH); ^{13}C NMR (75.4 MHz) δ 10.7 (CH_3), 25.3 (CH_2), 33.8 (C-6), 40.1 (C-7), 44.2 (C-8), 49.0 (*C*HCO_2Me), 52.5 (CH_3O), 58.0 (C-3), 74.2 (C-2), 91.3 (C-8a), 102.6 (C-3 ind), 111.1 (C-7 ind), 119.7 (C-4 ind), 120.2 (C-5 ind), 121.9 (C-6 ind), 126.7, 128.6 (C-*o*, *m*), 127.8 (C-*p*), 128.4 (C-3a ind), 132.0 (C-2 ind), 136.1 (C-*i*), 140.6 (C-7a ind), 167.1 (NCO), 172.5 (COO); $[\alpha]^{22}_D$ −348.5 (*c* 0.2, EtOH); MS-EI *m/z* 432 (M^+, 21), 244 (100), 149 (25), 124 (33). HMRS calcd for $C_{26}H_{28}N_2O_4$ 432.2049, found 432.2040. **56**: IR (film) 3330, 1668 cm^{-1}; ^1H NMR (300 MHz) δ 1.08 (t, *J* = 7.5 Hz, 3 H), 2.31 (q, *J* = 7.5 Hz, 2 H), 4.13 (m, 1 H), 4.30 (dd, *J* = 11.4, 4.8 Hz, 1 H), 6.29 (dd, *J* = 7.2, 4.8 Hz, 1 H), 6.53 (d, *J* = 9.3 Hz, 1 H), 7.04 (dm, *J* = 1.8 Hz, 1 H), 7.22 (dd, *J* = 9.3, 2.7 Hz, 1 H), 7.26−7.39 (m, 5 H); ^{13}C NMR (75.4 MHz) δ 14.7 (CH_3), 24.9 (CH_2), 60.0 (CH), 63.2 (CH_2), 120.1 (CH), 121.8 (C), 127.8 (CH), 128.8 (CH), 128.1 (CH), 132.0 (CH), 136.8 (C), 140.7 (CH), 162.8 (C). Anal. Calcd for $C_{15}H_{17}NO_2 \cdot {}^1/_2H_2O$: C, 71.79; H, 7.38; N, 5.40. Found: C, 71.62; H, 7.21; N, 5.59.

(1*S*,5*R*,6*R*,12*S*)-12-Ethyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-6-(methoxycarbonyl)-3-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (12b). Operating as described for the preparation of **12a**, starting from (α*S*)-**11b** (650 mg, 1.5 mmol) in CH_2Cl_2 (30 mL) and $TiCl_4$ (500 μL, 4.5 mmol), tetracycle **12b** (225 mg, 35%) was obtained after flash chromatography (7:3 EtOAc−hexane). Similarly, treatment of (α*R*)-**11b** (550 mg, 1.27 mmol) in CH_2Cl_2 (26 mL) with $TiCl_4$ (420 μL, 3.81 mmol) gave **12b** (228 mg, 51%) after flash chromatography (7:3 EtOAc−hexane). **12b**: IR (KBr) 3254, 3409, 1736, 1620 cm^{-1}; ^1H NMR (500 MHz) δ 0.58 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.27 (m, 1 H, CH_2), 1.35 (m, 1 H, CH_2), 1.82 (m, 1 H, H-12), 2.27 (d, *J* = 19.0 Hz, 1 H, H-4), 2.83 (dd, *J* = 19.0, 8.7 Hz, 1 H, H-4), 2.86 (m, 1 H, H-5), 3.84 (s, 3 H, CH_3O), 3.84 (m, 1 H, H-2′), 3.86 (m, 1 H, H-2′), 4.01 (d, *J* = 4.5 Hz, 1 H, H-6), 4.43 (m, 1 H, H-1), 4.67 (dd, *J* = 6.0, 2.5 Hz, 1 H, H-1′), 4.85 (br s, 1 H, OH), 7.19−7.39 (m, 7 H, ArH), 7.47 (dd, *J* = 8.0, 1.0 Hz, 1 H, H-8), 7.60 (dd, *J* = 8.5, 2.0 Hz, 1 H, H-11), 9.02 (br s, 1 H, NH); ^{13}C NMR (75.4 MHz) δ 11.2 (CH_3), 24.1 (CH_2), 32.8 (C-5), 33.1 (C-4), 42.9 (C-12), 47.8 (C-6), 52.6 (CH_3O), 54.6 (C-1), 64.9 (C-2′), 71.4 (C-1′), 111.6 (C-8), 114.4 (C-11b), 117.9 (C-11), 120.3 (C-10), 122.3 (C-9), 124.8 (C-11a), 127.8 (C-*p*), 128.4, 128.4 (C-*o*, *m*), 129.1 (C-6a), 136.5 (C-7a), 137.8 (C-*i*), 171.0 (NCO), 171.2 (COO); mp 176−180 °C (Et_2O); $[\alpha]^{22}_D$ −8.8 (*c* 0.5, EtOH). Anal. Calcd for $C_{26}H_{28}N_2O_4 \cdot {}^1/_4H_2O$: C, 71.46; H, 6.57; N, 6.41. Found: C, 71.20; H, 6.39; N, 6.26.

(1*R*,5*S*,12*R*)-12-Ethyl-6-(hydroxymethyl)-3-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (13). Into a three-necked, 100 mL round-bottomed flask equipped with a coldfinger condenser charged with dry ice−acetone were condensed 30 mL of NH_3 at −78 °C. The temperature was raised to −33 °C, and sodium metal was added in small portions until the blue color persisted. After the mixture was stirred at −33 °C for 5 min, a solution of *ent*-**12b** (250 mg, 0.58 mmol) in THF (3 mL) was added, and the mixture was stirred at −33 °C for 3 h. The reaction was quenched by addition of solid NH_4Cl until the blue color disappeared, and the mixture was stirred at rt for 4 h. The resulting residue was digested at rt with CH_2Cl_2, and the resulting suspension was filtered and concentrated. Flash chromatography (EtOAc) afforded (16*S*)-**13** and (16*R*)-**13** (105 mg, 64%, 2:1 ratio). (16*S*)-**13**: IR (film) 3286, 2960, 2930, 1650 cm^{-1}; ^1H NMR (400 MHz) δ 1.04 (t, *J* = 7.2 Hz, 3 H), 1.56 (dt, *J* = 14.0, 7.2 Hz, 1 H), 1.67 (dt, *J* = 14.0, 7.2 Hz, 1 H), 1.96 (t, *J* = 7.2 Hz, 1 H), 2.06 (d, *J* = 18.0 Hz, 1 H), 2.39 (d, *J* = 8.4 Hz, 1 H), 2.45 (dd, *J* = 18.0, 8.4 Hz, 1 H), 3.23 (dt, *J* = 9.2, 4.8 Hz, 1 H), 3.83 (m, 2 H), 4.45 (t, *J* = 3.0 Hz, 1 H), 6.73 (d, *J* = 4.4 Hz, 1 H), 7.06−7.10 (m, 2 H), 7.24 (dd, *J* = 6.8, 2.4 Hz, 1 H), 7.48 (dd, *J* = 6.8, 2.4 Hz, 1 H), 8.97 (s, 1 H); ^{13}C NMR (100.6 MHz) δ 11.6 (CH_3), 23.7 (CH_2), 29.0 (CH_2), 33.5 (CH), 42.3 (CH), 42.4 (CH), 46.1 (CH), 64.8 (CH_2), 111.2 (CH), 114.6 (C), 117.0 (CH), 119.7 (CH), 121.6 (CH), 124.8 (C), 135.1 (C), 136.0 (C), 173.2 (C); $[\alpha]^{22}_D$ −152.4 (*c* 1.1, EtOH); MS-EI *m/z* 284 (M^+, 47), 253 (41), 208 (41), 195 (100), 180 (50); HMRS calcd for $C_{17}H_{20}N_2O_2$ 284.1525, found 284.1521. (16*R*)-**13**: ^1H NMR (300 MHz, selected resonances) δ 1.01 (t, *J* = 7.5 Hz, 3 H), 2.08 (d, *J* = 18.3 Hz, 1 H), 2.75 (dd, *J* = 18.3, 8.7 Hz, 1 H), 2.79 (t, *J* = 6.9 Hz, 1 H), 3.77 (m, 2 H), 4.39 (d, *J* = 0.9 Hz, 1 H), 9.23 (br s, 1 H); ^{13}C NMR (75.4 MHz) δ 11.5 (CH_3), 23.5 (CH_2), 32.2 (CH), 35.6 (CH_2), 37.5 (CH), 45.3 (CH), 46.0 (CH), 64.4 (CH_2), 111.0 (CH), 115.0 (C), 116.9 (CH), 119.3 (CH), 121.4 (CH), 124.7 (C), 134.9 (C), 136.2 (C), 173.8 (C). When the reaction time was 5 min instead of 3 h, **13** (50%) and **(1*R*,5*S*,6*S*,12*R*)-12-ethyl-6-(hydroxymethyl)-2-[(1*S*)-2-hydroxy-1-phenylethyl]-3-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole** (**57**, 15%) were obtained after flash chromatography (EtOAc to 95:5 EtOAc−EtOH). **57**: IR (film) 3305, 2932, 1613 cm^{-1}; ^1H NMR (400 MHz) δ 0.76 (t, *J* = 7.6 Hz, 3 H, CH_3), 1.33 (m, 2 H, CH_2), 1.83 (t, *J* = 7.6 Hz, 1 H, H-12), 2.28 (d, *J* = 19.2 Hz, 1 H, H-4), 2.39 (dd, *J* = 8.4, 5.2 Hz, 1 H, H-5), 2.63 (dd, *J* = 19.2, 8.8 Hz, 1 H, H-4), 3.22 (dt, *J* = 8.8, 5.2 Hz, 1 H, H-6), 3.88 (m, 3 H, C*H*$_2$OH, H-2′), 4.00 (dd, *J* = 9.2, 6.0 Hz, 1 H, H-2′), 4.42 (d, *J* = 0.8 Hz, 1 H, H-1), 4.72 (dd, *J* = 6.0, 2.8 Hz, 1 H, H-1′), 5.00 (d, *J* = 6.0 Hz, 1 H, OH), 7.11−7.40 (m, 7 H, ArH), 7.49 (dd, *J* = 6.8, 1.6 Hz, 1 H, H-8), 7.60 (dd, *J* = 6.8, 2.0 Hz, 1 H, H-11), 9.07 (s, 1 H, NH); ^{13}C NMR (75.4 MHz) δ 11.2 (CH_3), 23.9 (CH_2), 30.7 (C-4), 32.9 (C-5), 42.4 (C-6), 43.5 (C-12), 55.3 (C-1), 64.7 (CH_2OH), 64.9 (C-2′), 71.2 (C-1′), 111.4 (C-8), 112.7 (C-11b), 117.6 (C-11), 120.1 (C-10), 121.7 (C-9), 124.8 (C-11a), 127.8 (C-*p*), 128.3, 128.5 (C-*o*, *m*); 136.0 (C-6a), 136.2 (C-7a), 137.7 (C-*i*), 171.5 (NCO); $[\alpha]^{22}_D$ −6.1 (*c* 0.56, EtOH); MS-EI *m/z* 404 (M^+, 30), 373 (35), 284 (30), 268 (63), 196 (100), 168 (86); HMRS calcd for $C_{25}H_{28}N_2O_3$ 404.2100, found 404.2099.

(1*R*,5*S*,12*R*)-12-Ethyl-6-methylene-3-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (14). Mesyl chloride (43 μL, 0.55 mmol) and Et_3N (91 μL, 0.66 mmol) were added to a cooled (0 °C) solution of **13** (107 mg, 0.37 mmol) in CH_2Cl_2 (18 mL). The mixture was stirred at 0 °C for 2 h, diluted with CH_2Cl_2, dried, and concentrated to give the mesylate derivative (150 mg), which was used without further purification in the next step. DBU (60 μL, 0.4 mmol) was added to a solution of the mesylate (150 mg) in THF (2 mL), and the mixture was heated at reflux for 24 h. Additional DBU (60 μL, 0.4 mmol) was added, and the mixture was heated at reflux for 24 h. The mixture was concentrated, and the residue was taken up in EtOAc and washed with cool aqueous H_2SO_4. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried and concentrated to give an oil. Flash chromatography (95:5 EtOAc−EtOH) gave **14** (53.1 mg, 53%): ^1H NMR (400 MHz) δ 1.07 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.64 (m, 1 H, CH_2), 1.72 (m, 1 H, CH_2), 2.12 (t, *J* = 7.2 Hz, 1 H, H-12), 2.27 (d, *J* = 18.8 Hz, 1 H, H-4), 2.86 (dd, *J* = 18.8, 8.0 Hz, 1 H, H-4), 2.98 (d, *J* = 8.0 Hz, 1 H, H-5), 4.52 (m, 1 H, H-1), 5.01 (s, 1 H, CH_2=), 5.15 (s, 1 H, CH_2=), 6.58 (br s, 1 H, NH), 7.10 (td, *J* = 8.0, 0.8 Hz, 1 H, H-10), 7.19 (td, *J* = 8.0, 1.2 Hz, 1 H, H-9), 7.29 (d, *J* = 8.4 Hz, 1 H, H-8), 7.49 (d, *J* = 7.6 Hz, 1 H, H-11), 8.23 (s, 1 H, NH); ^{13}C NMR (100.6 MHz) δ 11.5 (CH_3), 23.5 (CH_2), 36.1 (C-4), 39.3 (C-5), 42.0 (C-12), 46.5 (C-1), 105.3 (CH_2=), 111.2 (C-8), 118.1 (C-11), 119.5 (C-11b), 120.2 (C-10), 123.6 (C-9), 125.2 (C-11a), 131.5 (C-6a), 136.7 (C-7a), 141.7 (C-6), 172.5 (NCO); $[\alpha]^{22}_D$ +87.1 (*c* 0.4, EtOH).

General Procedure for Conjugate Addition Reactions. *n*-BuLi (1.6 M solution in hexanes) or LDA (1.5 M solution in cyclohexane, 1.5−5 mmol) and HMPA (0−2 mmol) were added

to a cooled solution (−78 °C) of the dithioacetal (**15**−**19**; 1.5−5 mmol) in THF. After the mixture was stirred at −78 °C for 1 h, a solution of the unsaturated lactam *trans*-**2**, *cis*-**2,** or **10** (1 mmol) in THF was added via cannula, and the mixture was stirred at the temperature for the reaction time indicated in Table 1. The resulting mixture was poured into saturated NH_4Cl and extracted with EtOAc. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed to afford **21**−**33** (see the Supporting Information for details).

[3*R*,7*S*(and 7*R*),8*S*,8a*R*]-8-Ethyl-7-[2-(2-indolyl)-1,3-dithian-2-yl]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (34a and 34b). *n*-BuLi (15.4 mL of a 1.6 M solution in cyclohexane, 22.6 mmol) was added to a cooled solution (−78 °C) of 2-(2-indolyl)-1,3-dithiane[28] (**20**; 2.9 g, 12.3 mmol) in THF (40 mL). The mixture was stirred at −30 °C for 2 h and added to a cooled solution (−78 °C) of **10** (600 mg, 2.46 mmol) in THF (10 mL). The resulting mixture was stirred at 0 °C for 20 h, poured into saturated aqueous NH_4Cl, and extracted with EtOAc. The combined organic extracts were dried and concentrated to give and oil. Flash chromatography (2:8 to 7:3 EtOAc−hexane) afforded **34a** (843 mg, 72%) and **34b** (207 mg, 18%). **34a**: IR (film) 3280, 1650 cm^{-1}; ^1H NMR (300 MHz) δ 0.87 (t, J = 7.2 Hz, 3 H, CH_3), 1.26 (m, 1 H, CH_2), 1.58 (m, 1 H, CH_2), 1.86 [m, 2 H, CH_2-($CH_2S)_2$], 2.03 (m, 1 H, H-8), 2.64 (m, 3 H, H-6, CH_2S), 2.79 (m, 1 H, H-7), 2.88 (masked, 2 H, CH_2S), 2.90 (dd, J = 15.6, 6.0 Hz, 1 H, H-6), 3.95 (dd, J = 9.0, 1.5 Hz, 1 H, H-2), 4.13 (dd, J = 9.0, 7.2 Hz, 1 H, H-2), 4.80 (dd, J = 7.2, 1.5 Hz, 1 H, H-3), 4.85 (d, J = 6.6 Hz, 1 H, H-8a), 6.84 (dd, J = 2.4, 1.2 Hz, 1 H, H-3 ind), 7.13 (td, J = 7.2, 1.2 Hz, 1 H, H-5 ind), 7.19−7.27 (m, 7 H, ArH), 7.38 (dd, J = 8.1, 1.2 Hz, 1 H, H-7 ind), 7.59 (d, J = 7.2 Hz, 1 H, H-4 ind), 8.57 (br s, 1 H, NH); ^{13}C NMR (75.4 MHz) δ 12.5 (CH_3), 21.0 (CH_2), 24.2 [$CH_2(CH_2S)_2$], 27.9, 28.5 (CH_2S), 35.3 (C-6), 44.8 (C-8), 46.9 (C-7), 57.5 (CS_2), 58.5 (C-3), 74.0 (C-2), 91.0 (C-8a), 106.4 (C-3 ind), 111.1 (C-7 ind), 120.0 (C-4 ind), 120.6 (C-5 ind), 122.4 (C-6 ind), 126.3, 128.4 (C-*o*, *m*), 127.1 (C-*p*), 128.4 (C-3a ind), 136.0 (C-2 ind), 136.9 (C-*i*), 141.3 (C-7a ind), 167.5 (NCO); $[\alpha]^{22}_D$ +17.1 (*c* 0.5, MeOH). Anal. Calcd for $C_{27}H_{33}N_2S_2O_2 \cdot {}^1/_2H_2O$: C, 66.50; H, 6.41; N, 5.74. Found: C, 66.63; H, 6.38; N, 5.87. **34b**: ^1H NMR (300 MHz) δ 0.88 (t, J = 7.5 Hz, 3 H, CH_3), 1.19 (m, 1 H, CH_2), 1.40 (m, 1 H, CH_2), 1.78 [m, 2 H, CH_2($CH_2S)_2$], 2.23 (m, 2 H, H-6, H-7), 2.53 (m, 5 H, CH_2S, H-8), 2.87 (d, J = 15.3 Hz, 1 H, H-6), 4.16 (dd, J = 9.3, 2.1 Hz, 1 H, H-2), 4.21 (dd, J = 9.3, 5.7 Hz, 1 H, H-2), 4.67 (d, J = 9.0 Hz, 1 H, H-8a), 4.96 (dd, J = 5.7, 2.1 Hz, 1 H, H-3), 6.81 (dd, J = 2.1, 0.9 Hz, 1 H, H-3 ind), 7.09 (td, J = 7.2, 1.2 Hz, 1 H, H-5 ind), 7.16 (td, J = 7.2, 1.5 Hz, 1 H, H-6 ind), 7.22−7.32 (m, 6 H, ArH), 7.50 (dd, J = 7.8, 0.9 Hz, 1 H, H-7 ind), 7.57 (d, J = 7.5 Hz, 1 H, H-4 ind), 8.71 (br s, 1 H, NH); ^{13}C NMR (75.4 MHz) δ 10.3 (CH_3), 24.1 [CH_2-($CH_2S)_2$], 26.5 (CH_2), 27.5, 27.6 (CH_2S), 34.3 (C-6), 41.6 (C-8), 48.2 (C-7), 58.1 (C-3), 60.9 (CS_2), 74.4 (C-2), 90.7 (C-8a), 105.5 (C-3 ind), 111.1 (C-7 ind), 119.7 (C-4 ind), 120.3 (C-5 ind), 121.9 (C-6 ind), 127.4 (C-*p*), 127.4, 127.9 (C-*o*, *m*), 128.5 (C-3a ind), 135.9 (C-2 ind), 137.5 (C-*i*), 140.0 (C-7a ind), 167.5 (NCO); $[\alpha]^{22}_D$ +99.3 (*c* 0.5, MeOH). Anal. Calcd for $C_{27}H_{33}N_2S_2O_2$: C, 67.71; H, 6.32; N, 5.85. Found: C, 67.71; H, 6.62; N, 5.62.

General Procedure for Desulfurization Reactions. $NiCl_2 \cdot 6H_2O$ (7−10 mmol) was added to a cooled solution (0 °C) of the dithioacetal (1 mmol) in 1:3 THF−MeOH (ca. 50 mL). When the dissolution was complete, $NaBH_4$ (21−30 mmol) was added portionwise, and the mixture was stirred at 0−25 °C for 1−8 h and filtered through Celite. The filtrate was concentrated and partitioned between saturated aqueous NaCl and CH_2Cl_2. The combined organic extracts were dried and concentrated to give the desired product **35**−**42** (see the Supporting Information for details).

(3*R*,7*S*,8*S*,8a*R*)-8-Ethyl-7-(2-indolylmethyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (50). Following the above general procedure, from dithioacetal **34a** (150 mg, 0.31 mmol) in 1:3 THF−MeOH (10 mL), $NiCl_2 \cdot 6H_2O$ (745 mg, 3.1 mmol), and $NaBH_4$ (356 mg, 9.4 mmol) at 0 °C for 2 h was obtained compound **50** (70 mg, 60%) after flash chromatography (3:7 EtOAc−hexane): IR (film) 1640 cm^{-1};^1H NMR (300 MHz) δ 1.10 (t, J = 7.5 Hz, 3 H, CH_3), 1.57 (m, 1 H, CH_2), 1.94 (m, 2 H, CH_2, H-8), 2.26 (dd, J = 18.3, 5.5 Hz, 1 H, H-6), 2.30−2.50 (m, 3 H, H-6, H-7, CH_2-In), 2.96 (d, J = 12.3 Hz, 1 H, CH_2In), 4.00 (dd, J = 9.0, 1.0 Hz, 1 H, H-2), 4.12 (dd, J = 9.0, 7.0 Hz, 1 H, H-2), 4.64 (d, J = 9.3 Hz, 1 H, H-8a), 4.90 (br d, J = 6.0 Hz, 1 H, H-3), 6.22 (d, J = 2.1 Hz, 1 H, H-3 ind), 7.06 (m, 3 H, ArH), 7.25 (m, 5 H, ArH), 7.49 (m, 1 H, ArH), 8.62 (br s, 1 H, NH); ^{13}C NMR (75.4 MHz) δ 11.4 (CH_3), 21.1 (CH_2), 27.1 (CH_2In), 34.1 (C-7), 37.0 (C-6), 43.8 (C-8), 59.4 (C-3), 73.8 (C-2), 90.0 (C-8a), 100.4 (C-3 ind), 110.6 (C-7 ind), 119.5 (CH), 119.6 (C-4 ind), 121.0 (CH), 126.2 (CH), 127.5 (CH), 128.5 (CH), 128.6 (C-3a ind), 135.9 (C-2 ind), 137.0 (C-*i*), 141.3 (C-7a ind), 167.0 (NCO); $[\alpha]^{22}_D$ +13.8 (*c* 0.55, MeOH). Anal. Calcd for $C_{24}H_{26}N_2O_2 \cdot {}^1/_2H_2O$: C, 70.58; H, 6.53; N, 6.72. Found: C, 70.66; H, 6.59; N, 6.67.

(1*R*,5*S*,12*S*)-12-Ethyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-3,6-dioxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (51). $TiCl_4$ (70 μL, 0.62 mmol) was added to a solution of dithioacetal **34a** (100 mg, 0.2 mmol) in CH_2Cl_2 (5 mL), and the resulting mixture was heated at reflux 6 h, poured into saturated solution $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (EtOAc) to afford tetracycle **51** (16 mg, 20%) and starting material (22 mg). **51**: IR (film) 1652, 1640 cm^{-1}; ^1H NMR (400 MHz) δ 0.64 (t, J = 7.2 Hz, 3 H, CH_3), 1.06 (m, 1 H, CH_2), 1.25 (m, 1 H, CH_2), 2.40 (m, 1 H, H-12), 2.85 (d, J = 19.0 Hz, 1 H, H-4), 2.99 (dm, J = 8.5 Hz, 1 H, H-5), 3.15 (dd, J = 18.8, 8.6 Hz, 1 H, H-4), 4.10 (m, 1 H, H-2′), 4.24 (dd, J = 10.5, 4.2 Hz, 1 H, H-2′), 4.49 (m, 1 H, H-1), 5.86 (dd, J = 8.0, 4.2 Hz, 1 H, H-1′), 7.13−7.32 (m, 8 H, ArH), 7.51 (dd, J = 11.2, 1.2 Hz, 1 H, ArH), 9.20 (br s, 1 H, NH); ^{13}C NMR (100.6 MHz) δ 11.5 (CH_3), 23.9 (CH_2), 36.1 (C-4), 45.9 (C-5), 48.3 (C-12), 49.6 (C-1), 61.5 (C-1′), 63.2 (C-2′), 113.1 (C-8), 120.6 (CH), 121.5 (CH), 124.8 (C-11b), 127.0 (C-11a), 127.4 (CH), 127.7 (CH), 128.0 (CH), 128.9 (CH), 129.1 (C-6a), 136.2 (C-7a), 138.0 (C-*i*), 170.6 (NCO), 191.4 (CO). Anal. Calcd for $C_{24}H_{24}N_2O_3 \cdot H_2O$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.72; H, 6.20; N, 6.58.

(1*R*,5*S*,12*S*)-12-Ethyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-3-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (52). Operating as described above, from $TiCl_4$ (75 μL, 0.68 mmol) and **50** (85 mg, 0.23 mmol) in CH_2Cl_2 (7 mL) for 7 h were obtained tetracycle **52** (15 mg, 17%) and starting material (10 mg) after flash chromatography (EtOAc). **52**: IR (film) 1670 cm^{-1}; ^1H NMR (400 MHz) δ 0.63 (t, J = 7.2 Hz, 3 H, CH_3), 0.98 (m, 1 H, CH_2), 1.12 (m, 1 H, CH_2), 2.02 (m, 1 H, H-12), 2.48 (d, J = 19.0 Hz, 1 H, H-4), 2.55 (m, 1 H, H-5), 2.62 (d, J = 17.2 Hz, 1 H, H-6), 2.97 (dd, J = 17.2, 5.6 Hz, 1 H, H-6), 3.08 (dd, J = 19.0, 8.4 Hz, 1 H, H-4), 4.18−4.30 (m, 3 H, H-2′, H-1), 5.74 (dd, J = 8.0, 5.6 Hz, 1 H, H-1′), 7.00−7.40 (m, 9 H, ArH), 8.10 (br s, 1 H, NH); ^{13}C NMR (100.6 MHz) δ 11.7 (CH_3), 22.6 (CH_2), 28.2 (C-6), 29.0 (C-5), 40.6 (C-4), 43.4 (C-12), 49.8 (C-1), 62.0 (C-1′), 63.5 (C-2′), 110.8 (C-8), 117.5 (CH), 119.7 (CH), 121.6 (CH), 126.4 (C), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.7 (C), 132.5 (C), 136.1 (C-7a), 136.6 (C-*i*), 173.0 (NCO); MS-EI *m/z* 374 (M^+, 4), 343 (7), 238 (16), 195 (96), 180 (100); HMRS calcd for $C_{24}H_{26}N_2O_2$ 374.1994, found 374.1986.

(1*R*,5*S*,12*S*)-12-Ethyl-3-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (53). Operating as described for the preparation of **13**, from liquid NH_3 (30 mL), sodium, and **34a** (300 mg, 0.62 mmol) in THF (8 mL) at −33 °C for 25 min was obtained an intermediate 6-hydroxylactam (200 mg, 94%) as an oil, which was used without further purification in the next reaction. $TiCl_4$ (103 μL, 0.94 mmol) was added to a cooled (0 °C) solution of the oil in CH_2Cl_2 (150 mL), and the

(28) Rubiralta, M.; Casamitjana, N.; Grierson, D. S.; Husson, H.-P. *Tetrahedron* **1988**, *44*, 443.

mixture was stirred at rt for 1 h, poured into saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (99:1 CH_2Cl_2−MeOH) to give tetracycles **53** (55 mg, 35%) and **54** (10 mg, 6%). **53**: IR (film) 3256, 1650 cm^{-1}; ^1H NMR (400 MHz) δ 0.96 (t, J = 7.5 Hz, 3 H, CH_3), 1.36 (m, 2 H, CH_2), 2.24 (m, 1 H, H-12), 2.25 (d, J = 18.4 Hz, 1 H, H-4), 2.52 (dd, J = 17.2, 1.2 Hz, 1 H, H-6), 2.56 (m, 1 H, H-5), 2.86 (dd, J = 18.4, 8.4 Hz, 1 H, H-4), 3.06 (dd, J = 17.2, 6.0 Hz, 1 H, H-6), 4.43 (m, 1 H, H-1), 6.79 (br s, 1 H, NH), 7.07−7.15 (m, 2 H, H-9, H-10), 7.28 (d, J = 6.0 Hz, 1 H, H-8), 7.45 (d, J = 7.6 Hz, 1 H, H-11), 7.85 (br s, 1 H, NH); ^{13}C NMR (100.6 MHz) δ 12.1 (CH_3), 22.8 (CH_2), 27.5 (C-6), 29.2 (C-5), 39.7 (C-4), 41.4 (C-12), 46.6 (C-1), 110.7 (C-8), 112.3 (C-11b), 117.0 (C-9), 119.7 (C-11), 121.5 (C-10), 126.2 (C-11a), 130.9 (C-6a), 136.0 (C-7a), 173.5 (NCO); $[\alpha]^{22}_D$ −82.2 (*c* 0.3, $CHCl_3$); MS-EI *m/z* 254 (M^+, 75), 195 (76), 180 (100), 168 (51); HMRS calcd for $C_{16}H_{18}N_2O$ 254.1419, found 254.1457. **54**: IR (film) 1667 cm^{-1}; ^1H NMR (400 MHz) δ 1.05 (t, J = 7.5 Hz, 3 H, CH_3), 1.57 (m, 2 H, CH_2), 2.35 (m, 1 H, H-12), 2.44 (d, J = 18.4 Hz, 1 H, H-4), 2.58 (m, 1 H, H-5), 2.84 (dd, J = 18.4, 7.2 Hz, 1 H, H-4), 2.90 (d, J = 17.6 Hz, 1 H, H-6), 3.31 (dd, J = 17.6, 6.4 Hz, 1 H, H-6), 5.52 (br s, 1 H, H-1), 6.28 (br s, 1 H, H-7), 6.63 (br s, 1H, NH), 7.09−7.18 (m, 2 H, H-8, H-9), 7.27 (d, J = 8.4 Hz, 1 H, H-11), 7.51 (d, J = 7.6 Hz, 1 H, H-10); ^{13}C NMR (75.4 MHz) δ 11.6 (CH_3), 22.2 (CH_2), 26.5 (C-6), 27.2 (C-5), 39.1 (C-4), 39.9 (C-12), 60.2 (C-1), 101.5 (C-7), 108.3 (C-11), 119.8 (C-10), 120.2 (C-8), 120.6 (C-9), 129.2 (C-6a), 131.2 (C-11a), 135.5 (C-7a), 171.9 (NCO); $[\alpha]^{22}_D$ −105.8 (*c* 2.0, $CHCl_3$); MS-EI *m/z* 254 (M^+, 27), 183 (100), 154 (24), 130 (30); HMRS calcd for $C_{16}H_{18}N_2O$ 254.1419, found 254.1416.

(1*R*,5*S*,12*S*)-*N*-(Benzyloxycarbonyl)-12-ethyl-3-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (55). BH_3·Me_2S (100 μL of a 5 M solution in Et_2O, 0.49 mmol) was added to a cooled solution (0 °C) of **53** (120 mg, 0.47 mmol) in toluene (2.5 mL), and the mixture was heated at reflux for 6 h. Then, the mixture was cooled, 10% aqueous $CaCO_3$ (2 mL) was added, and stirring was continued for 20 min. The layers were separated, and the organic layer was dried and concentrated to give 110 mg (97%) of the tetracyclic amine. To a solution of this amine (110 mg, 0.46 mmol) in CH_2Cl_2 (7 mL) were added $CaCO_3$ (164 mg) and benzyloxycarbonyl chloride (236 μL of a 50% solution in toluene, 0.7 mmol). The mixture was stirred at rt for 90 min, poured into water, and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give and oil, which was chromatographed (4:6 Et_2O−hexane) to afford **55** (72 mg, 41%): $[\alpha]^{22}_D$ +89.0 (*c* 0.33, $CHCl_3$) (lit.[4a] $[\alpha]^{22}_D$ +89.4 (*c* 0.4, $CHCl_3$)).

Computational Methods

The generalized molecular interaction potential with polarization (GMIPp)[22] was used to investigate the reactivity pattern of unsaturated lactams *cis*-**2** and **10**. The GMIPp functional computes the interaction energy between the molecule, which is treated at the quantum mechanical (QM) level, and a classical probe. Such an interaction energy is expressed as the addition of three terms (see eq 1): (i) the electrostatic contribution between the QM charge distribution of the isolated molecule and the classical particle; (ii) a polarization contribution determined from perturbation theory; and (iii) a classical dispersion-repulsion term. In eq 1, R_A and R_B stand for the positions of the nuclei (Z_A) in the molecule and of the atoms in the classical probe, $C_{\mu i}$ denotes the coefficient of atomic orbitals in the molecular orbital−linear combination of atomic orbitals, $P_{\mu\nu}$ is the first-order density matrix, ϕ is the set of atomic orbitals, ξ denotes the energy of molecular orbitals, and ϵ and R^* are the van der Waals parameters. The QM molecule was described at the Hartree−Fock (HF) level using the 6-31G(d) basis,[29] and the van der Waals parameters were taken from an in-house quantum mechanical−molecular mechanical parametrization.[30] The classical particle was defined by a nonpolarizable point charge of −1 units of electron and van der Waals parameters of a carbon atom. The parameters ϵ_{AB} and R^*_{AB} were computed from the atomic parameters using the relationships $\epsilon_{AB} = (\epsilon_A\epsilon_B)^{1/2}$ and $R^*_{AB} = R^*_A + R^*_B$. GMIPp calculations were performed on the most stable conformation of the lactams. To this end, a preliminary exploration was performed at the molecular mechanical level using the CVFF91[31] force field implemented in the Insight-II[32] program, and the geometry of the selected conformers was subsequently optimized at the HF/6-31G(d) level. GMIPp calculations were performed using MOPETE program.[33]

$$\mathrm{GMIPp} = \sum_A \frac{Z_A}{|R_B - R_A|} - \sum_i^{occ}\sum_\mu\sum_\nu P_{\mu\nu}\left\langle \phi_\mu \left| \frac{1}{|R_B - r|} \right| \phi_\nu \right\rangle + \sum_i^{occ}\sum_j^{vir} \frac{1}{\xi_i - \xi_j}\left\{ \sum_\mu\sum_\nu c_{\mu i}c_{\nu j}\left\langle \phi_\mu \left| \frac{1}{|R_B - r|} \right| \phi_\nu \right\rangle \right\}^2 + \sum_A \epsilon_{AB}\left[\left(\frac{R^*_{AB}}{|R_B - R_A|} \right)^{12} - 2\left(\frac{R^*_{AB}}{|R_B - R_A|} \right)^{6} \right] \quad (1)$$

The energetics of the conjugate addition of the anion derived from **18** to the lactams was examined from B3LYP[34] calculations using the 6-31G(d) basis set. For the sake of completeness, calculations were also performed for the addition of methyl anion to the lactams. The geometry of the reactants and the enolate adducts formed from the conjugate addition reaction were fully optimized, and in all cases the minimum energy nature of the optimized geometries was confirmed from the inspection of the harmonic vibrational frequencies. Calculations were performed using Gaussian-98.[35]

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Supporting Information Available: X-ray crystallographic data for compounds α*R*-**11a**, **26a**, **26b**, and **31b** (CIF), complete details of computational methods, and general experimental procedures and experimental details and characterization data for compounds *ent*-**9**−*ent*-**12**, **21**−**33**, and **35**−**49**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.
(30) Alhambra, C.; Luque, F. J.; Orozco, M. *J. Phys. Chem.* **1995**, *99*, 3084.
(31) Maple, J. R.; Dinur, U.; Hagler, A. T. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 5350.
(32) Insight-II (version 97.0), Molecular Simulations, San Diego, 1997.
(33) Mopete. Luque, F. J.; Alhambra, C.; Orozco, M. University of Barcelona, 2001.
(34) (a) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(35) Gaussian 98. Rev. A.7. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W. Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1998.