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

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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.† These alkaloids are characterized by the presence of a tetracyclic 1,5-methanooxazino-[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‡ (Scheme 1). While the absolute configuration of the bridgehead C-15 position.§ results from their biogenetic origin from secologanin, there are alkaloids with the two possibilities for C-20: H15 and H20 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,† their enantioselective synthesis has been little explored, and only one enantioselective total synthesis of alkaloids of this group has been reported so far.¶ A crucial problem associated with the synthesis of these alkaloids is the control of the absolute (and relative) configuration at C15 and C20.

FIGURE 1. Uleine alkaloids.

SCHEME 1. Biosynthesis of Uleine Alkaloids

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In the course 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 stereocorelated conjugate addition of an indolylmethyl anion equivalent to an appropriate key step would be the stereocontrolled conjugate addition reaction would determine that of C-21 in 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-15 and C-21, the stereochemical outcome of the conjugate addition of 2-indolacacetate 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-indolacacetate (3a) gave (64\%) lactam ester 4a as a mixture of epimers (3:2 ratio) at the isomerizable stereocenter \(\alpha\) to the ester group, which could be separated by column chromatography (Scheme 3). The cyclization step was carried out in the presence of \(\text{TiCl}_4\), using each epimer separately. The major isomer led to tetracycle (16\%) 5a (44\%), whereas the minor one led to the C-16 epimer (16R)-5a (50\%), 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 \(\text{H}_{15}-\text{H}_{16}\) value and from the stereochemical outcome of the conjugate addition of \(\delta\)-lactams lacking an additional electron-withdrawing group on the nitrogen and/or in conjugation with the double bond,\(^6\) 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-indolacacetate enolates to the model lactams cis-2 and trans-2, which lack the ethyl substituent present in the natural products.

Results and Discussion

Taking into account that \(\alpha,\beta\)-unsaturated lactams are poor Michael acceptors\(^7\) and that there are few examples of such conjugate additions to \(\delta\)-lactams lacking an additional electron-withdrawing group on the nitrogen and/or in conjugation with the double bond,\(^8\) 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-indolacacetate enolates to the model lactams cis-2 and trans-2, which lack the ethyl substituent present in the natural products.

In recent work,\(^5,7\) 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 stereoelec-
Enantioselective Synthesis of Uleine Alkaloids

SCHEME 3. Tetracyclic Ring System of Uleine Alkaloids

![Diagram of the 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 (aR)-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 (16S)-5b and (16R)-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%) which were separately cyclized to the respective tetracycles (16S)-7 (from the major lactam ester) and (16R)-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 (16R)-7 with those of (16S)-5a, both of them with a trans \(\text{H}_{15}^1\text{H}_{15}^2\) relationship, made evident that these compounds were diastereomers and, consequently, that the absolute configuration of C-15 in (16R)-7 is \(\text{S}\). Similarly, (16S)-7 and (16R)-5a, both having a cis \(\text{H}_{15}^1\text{H}_{15}^2\) relationship, are also diastereomers, and therefore, the configuration at the piperidine 4-position in tetracycle (16S)-7 is also \(\text{R}\). 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.\(^{(14)}\)

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 adducts \(\text{R}^2\)-4,5-disubstituted 2-piperidone.\(^{(16)}\) The same stereoselectivity was observed from the conjugate addition of \(\text{R}^2\)-unsubstituted indoleacetate 3b, although \(\text{R}^2\)-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 \(\beta\)-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 (aS)-11a and (aR)-11a (3:7 ratio). Cyclization of the major isomer also took place in excellent yield (81%) to give tetracycle 12a. The absolute configuration of (aR)-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 (aS)-11b and (aR)-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.

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\(^{(13)}\) For the different reactivity of 3,8a-cis and trans related lactams in \(\alpha\)-amidoalkylation reactions, see: Amat, M.; Escolano, C.; Llor, N.; Huguet, M.; Perez, M.; Bosch, J. Tetrahedron: Asymmetry 2003, 14, 1879.

\(^{(14)}\) 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 than 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 NH₃ 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 H₁₅⁻H₂₀ 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, 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

17, 18 in the addition of sulfur-stabilized anions to enones,19 there are few reports concerning the stereoselectivity of such conjugate addition reactions.19 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 piperidinone 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 29b 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

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TABLE 1. Conjugate Addition of Sulfur-Stabilized Nucleophiles*  

| entry | substrate | dithioacetal | product | R₁ | R₂ | R₃ | T (°C) (time (h)) | a/b ratio | yield (%) |
|-------|-----------|-------------|---------|----|----|----|------------------|-----------|-----------|
| 1     | trans-2   | 15          | 21      | H  | (CH₂)₃H- | H  | 0 (20)           | a         | 78        |
| 2     | trans-2   | 15          | 21      | H  | (CH₂)₃H- | H  | 0 (15)          | a         | 71        |
| 3     | trans-2   | 16          | 22      | C₆H₅ | (CH₂)₃H- | H  | 0 (20)          | >95.5     | 70        |
| 4     | trans-2   | 17          | 23      | CO₂Et | (CH₂)₃H- | H  | 0 (20)          | >95.5     | 72        |
| 5     | trans-2   | 18          | 24      | CO₂Et | (CH₂)₃H- | H  | 0 (5)           | a         | 68        |
| 6     | cis-2     | 15          | 25      | H  | (CH₂)₃H- | H  | 0 (20)          | a         | 68        |
| 7     | cis-2     | 16          | 26      | C₆H₅ | (CH₂)₃H- | H  | 0 (20)          | 25:75     | 80        |
| 8     | cis-2     | 16          | 26      | C₆H₅ | (CH₂)₃H- | H  | 25 (20)        | 22:78     | 81        |
| 9     | cis-2     | 16          | 26      | C₆H₅ | (CH₂)₃H- | H  | -78 (2)        | >95:5     | 74        |
| 10    | cis-2     | 16          | 26      | C₆H₅ | (CH₂)₃H- | H  | -78 (2)        | >95:5     | 75        |
| 11    | cis-2     | 17          | 27      | CO₂Et | (CH₂)₃H- | H  | 0 (20)          | 86:14     | 66        |
| 12    | cis-2     | 18          | 28      | CO₂Et | (CH₂)₃H- | H  | 0 (20)          | 86:14     | 70        |
| 13    | cis-2     | 15          | 29      | H  | (CH₂)₃H- | Et | 0 (20)          | >95:5     | 61        |
| 14    | cis-2     | 15          | 29      | H  | (CH₂)₃H- | Et | 25 (20)        | 43:57     | 54        |
| 15    | cis-2     | 19          | 30      | H  | C₆H₅ | Et | 0 (20)          | 60:40     | 61        |
| 16    | cis-2     | 19          | 30      | H  | C₆H₅ | Et | 25 (20)        | 16:84     | 66        |
| 17    | cis-2     | 16          | 31      | C₆H₅ | (CH₂)₃H- | Et | 0 (20)          | b         | 79        |
| 18    | cis-2     | 16          | 31      | C₆H₅ | (CH₂)₃H- | Et | -78 (20)      | b         | 90        |
| 19    | cis-2     | 16          | 31      | C₆H₅ | (CH₂)₃H- | Et | -78 (20)      | b         | 75        |
| 20    | cis-2     | 16          | 31      | C₆H₅ | (CH₂)₃H- | Et | 0 (20)          | <5:95     | 60        |
| 21    | cis-2     | 16          | 31      | C₆H₅ | (CH₂)₃H- | Et | 0 (4)         | <5:95     | 52        |
| 22    | cis-2     | 16          | 31      | C₆H₅ | (CH₂)₃H- | Et | -78 (0.5)     | 70:30     | 40        |
| 23    | cis-2     | 16          | 31      | C₆H₅ | (CH₂)₃H- | Et | -78 (2)       | 57:43     | 82        |
| 24    | cis-2     | 16          | 31      | C₆H₅ | (CH₂)₃H- | Et | -78 (2)       | 80:20     | 90        |

* See the general procedure in the Experimental Section.  
  a Determined by 1H NMR and/or after isolation by column chromatography.  
  b 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. 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 would 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. 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). 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.  

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
pattern of these bicyclic lactams from GMIPP calculations is different since 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 a hypothetical methyl anion (a small nucletophile) or the anion derived from dithiolane 18 (a bulky nucletophile) 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-indoly)-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 nonionic character of the nucleophile, the equilibrium 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 stereo- selectivity 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 prepared6.7 by conjugate addition reactions of methyl organocuprates to lactams trans-1 and cis-1a,b followed by debenzylxocarbonylation. 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 cyclodehydration of diethyl 3-(2-oxoethyl)glutarate and (R)-phenylglycinol.5c Similarly, 33b was converted to lactam 42, which had previously been obtained by cyclodehydration 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 Boc₂O 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 benz[a]quinolinizidine alkaloids.23 Thus, treatment of 42 with borane brought about synthesis of both the chemoselective reduction of the lactam carboxyl group and the reductive opening of the oxazolidine ring affording 4-piperidinonacetate 45, whereas

**TABLE 2.** Electrostatic (\(E_{\text{ele}}\)), Polarization (\(E_{\text{pol}}\)), van der Waals (\(E_{\text{vdW}}\)) \(E_{\text{tot}}\) Energies Determined from GMIPP Calculations for the Attack of a Negatively Charged Classical Point Charge to the Two Faces of the Lactam Ring at C7

| lactam | face | \(E_{\text{ele}}\) | \(E_{\text{pol}}\) | \(E_{\text{vdW}}\) | \(E_{\text{tot}}\) |
|--------|------|-----------------|-----------------|-----------------|-----------------|
| cis-2  | 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

| lactam | face | \(\Delta E\) |
|--------|------|-------------|
| cis-2  | exo  | −2.7        |
|        | endo | −6.7        |
| 10     | exo  | +2.6        |
|        | endo | −4.6        |

\(a\) Values are in kcal/mol.

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2. Orozco, M.; Luque, F. J. In Molecular Electrostatic Potentials: Concepts and Applications; Murray, J. S., Sen, K., Eds.; Elsevier: Amsterdam, 1996; pp 181–218.
3. For reviews, see: (a) Fujii, T.; Ohba, M. Heterocycles 1988, 27, 1009. (b) Fujii, T.; Ohba, M. Heterocycles 1998, 47, 525.
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 NH3, followed by treatment of the resulting oxylactams with Et3SiH 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 TiCl4 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 TiCl4-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 benzyl C–N bond to give an intermediate 6-hydroxy-lactam, which, without further purification, was cyclized with TiCl4 to give the tetracyclic lactam, which, without further purification, was cyclized into the target tetracyclic alkaloids of the uleine group of nordasycarpidone, (52). Finally, conversion of the above synthesis also represents a formal synthesis of 17-hydroxydihydrouleine.

In conclusion, conjugate addition reactions of indole-acetic ester enolates and sulfur-stabilized nucleophiles to phenylglycinol-derived unsaturated δ-lactams allow the stereocorrelated formation of C–C bonds at the piperidine 4-position. Some factors governing the stereoselectivity of the process, namely the nature of the nucleophile, 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 stereoselective 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**

(3R,8aS)-5-Oxo-3-phenyl-2,3,6,7,8,8a-tetrahydro-5H-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 (3R,8aS)-5-oxo-3-phenyl-2,3,6,7,8,8a-tetrahydro-5H-oxazolo(3,2-a)pyridine (1.48 g, 95%) as a mixture of isomers: 1H NMR (300 MHz, selected resonances) δ 3.46 (masked s, 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), 5.45 (m, 2 H), 5.72 (t, J = 8.0 Hz, 1 H), 7.00 (d, J = 16.6 Hz, 1 H). 13C NMR (75.4 MHz, selected resonances) δ 12.4 (CH2), 27.1 (CH2), 58.9 (CH), 65.8 (CH), 72.9 (CH2), 88.3 (CH), 164.0 (C). Na2CO3 (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...
afford *trans*-2 (820 mg, 89%): IR (KBr) 1660, 1611 cm⁻¹; \(^1\)H NMR (300 MHz) δ 2.48 (dd, J = 17.4, 10.2, 2.2, 3 Hz, 1 H), 2.80 (dd, J = 17.4, 6.0, 0.7 Hz, 1 H), 2.81 (dd, J = 8.8, 7.0 Hz, 1 H), 4.49 (dd, J = 8.8, 7.0 Hz, 1 H), 5.25 (s, J = 7.0 Hz, 1 H, 5.42 (dd, J = 10.2, 6.0 Hz, 1 H), 5.50 (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), \(^1\)C NMR (75.4 MHz) δ 29.9 (CH₃), 57.9 (CH), 73.0 (CH₂), 86.7 (CH), 125.4 (CH₂), 125.9 (CH₂), 128.7 (CH), 127.5 (CH), 134.8 (CH), 139.2 (CH), 160.7 (C); mp 121–122 °C (Et₂O–hexane); \([\alpha]_{D}^{25} +50.5 (c 1.0, EtOH). Analyzed C₂₆H₂₉NO₄; C, 72.54; H, 6.09; N, 6.51. Found: C, 72.56; H, 6.08; N, 6.49.

(3S,8aR)-5-Oxo-3-phenyl-2,3,8a-tetrahydro-5H-oxazo-
lo[3,2-\(\alpha\)]pyridine (cis-2). Operating as described above, from (3S,8aR)-5-oxo-3-phenyl-2,3,6,7,8a-hexahydro-5H-oxazo-
lo[3,2-\(\alpha\)]pyridine (300 mg, 1.4 mmol), THF (10 mL), methyl p-toluenesulfonate (437 mg, 2.8 mmol), and KH (840 mg, 20 wt % dispersion in mineral oil, 21 mmol) was obtained (3S,8aR)-5-oxo-3-phenyl-6-(phenylsulfinyl)-2,3,6,7,8a-hexahydro-5H-oxazo-
lo[3,2-\(\alpha\)]pyridine (348 mg, 97%) as a mixture of isomers: IR (film) 1661 cm⁻¹; \(^1\)H NMR (300 MHz, selected resonances for two isomers) δ 3.29 (dd, J = 6.6, 0.9 Hz, 1 H), 3.39 (dd, J = 7.8, 1.0 Hz, 1 H), 4.18 (2dd, J = 9.0, 2.1 Hz, 1 H), 4.30 (d, 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); \(^1\)C NMR (75.4 MHz, selected resonances) δ 12.8 (CH₂), 16.9 (CH₂), 26.5 (CH₂), 27.2 (CH₂), 59.2 (CH), 59.5 (CH₃), 65.3 (CH₃), 73.7 (CH₂), 73.8 (CH₂), 88.1 (CH), 88.8 (CH), 162.0 (C), 162.2 (C). From the \(\beta\)-keto sulfonate (487 mg, 136 mmol), toluene (15 mL), and Na₂CO₃ (804 mg) was obtained cis-(200 mg, 89%) after flash chromatography (21 EtOAc–CHCl₃). IR (film) 1670, 1606 cm⁻¹; \(^1\)H NMR (300 MHz) δ 2.60 (ddd, J = 17.2, 11.7, 3.3, 2.1 Hz, 1 H), 2.82 (ddd, 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), \(^1\)C NMR (75.4 MHz) δ 29.9 (CH₂), 57.3 (CH), 74.0 (CH₂), 86.8 (CH₂), 126.1 (CH), 126.2 (CH₂), 128.3 (CH), 128.7 (CH), 135.9 (CH), 161.1 (C); mp 45–50 °C; \([\alpha]_{D}^{25} +52.5 (c 1.0, CHCl₃).

Methyl (3R,7S,8aS)-\(\alpha\)-(1-Methyl-2-indolyl)-5-oxo-3-phen-
yl-2,3,6,7,8a-hexahydro-5H-oxazolo[3,2-\(\alpha\)]pyridine-7-
acetate (4a). LDA was prepared by addition of disobutyl-
amine (0.31 mL, 2.22 mmol) to a cooled (−78 °C) solution of \(\alpha\)-BuLi (1.3 mL of a 1.6 M solution in hexanes) 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 (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 NaHCO₃, and extracted with EtOAc. The combined organic extracts were dried and concentrated to give the oil. Flash chromatography (Et₂O) afforded 230 mg of (aR)-4a and 140 mg of (aR)-4a (overall yield 64%).

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Enantioselective Synthesis of Uleine Alkaloids

Methyl (3R,7R,8aR)-1-(Methyl-2-indolyl)-5-oxo-2,3,5,6,7,8a-hexahydropyrano[4,3-c]pyridine-7-acetic acid (6a).

A mixture of (15S,5S,6S,6R)-1-(1-Methyl-2-indolyl)-5-oxo-3-phenylmethanoazocino[4,3-b]indole (16S)-5b (16R)-5b, TiCl4 (90 µL, 0.82 mmol) was added to a cooled (0 °C) solution of (αS)-4b (100 mg, 0.25 mmol) in CH2Cl2 (3 mL), and the mixture was stirred at rt for 5 h, poured into saturated aqueous NaHCO3, and extracted with CH2Cl2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (EtOAc) to give (16S)-5b and (16R)-5b (60 mg, 69%, 58:42 ratio). Similarly, starting from (αR)-4b (125 mg, 0.31 mmol), CH2Cl2 (4 mL), and TiCl4 (50 µL, 0.46 mmol), tetracycles (16S)-5b and (16R)-5b (88 mg, 70%, 13:87 ratio) were obtained after flash chromatography (EtOAc).

(16S)-5b (lower R): IR (film) 3134, 1617 cm⁻¹; 1H NMR (300 MHz) 0.2717 (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), 2.33 (m, 1 H), 1.34 (m, 1 H), 1.37 (p, 3.0 Hz, 1 H), 3.78 (br s, 1 H), 3.83 (dm, J = 12.4 Hz, 1 H), 4.04 (dd, J = 12.4, 9.4, 6.2 Hz, 1 H), 4.57 (t, J = 3.0 Hz, 1 H), 4.48 (d, J = 6.2, 2.5 Hz, 1 H), 4.90 (m, 1 H), 7.10–7.50 (m, 5 H), 8.05 (br s, 1 H); 13C NMR (75.4 MHz) 57.3 (CH), 79.6 (CH), 81.0 (CH), 82.5 (CH), 84.8 (CH), 91.7 (CH), 95.2 (CH), 103.1 (CH), 110.1 (CH), 120.1 (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); [α]D² = 140.0 (c 1.0, CHCl3); MS-El m/z 418 (M+), 111, 357, 136.

(1R,5S,6S)-2-(1R,2-Hydroxy-1-phenylethyl)-6-(methoxycarbonyl)-3-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole (16S)-7. TiCl4 (35 mL, 0.32 mmol) was added to a solution of (αS)-6 (135 mg, 0.32 mmol) in CH2Cl2 (2 mL) at rt, and the resulting mixture was heated at reflux for 2 h. TiCl4 (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 NaHCO3 and extracted with CH2Cl2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (4:1 EtOAc–hexane) to give (16S)-7 (34 mg, 25%): IR (film) 3350, 1705, 1620 cm⁻¹; 1H NMR (300 MHz) 0.290 (d, 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, 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 (d, J = 3.6, 2.6 Hz, 1 H) 5.17 (d, J = 7.0 Hz, 1 H), 7.10–7.50 (m, 9 H); 13C NMR (75.4 MHz) 29.3 (CH), 31.7 (CH), 38.4 (CH), 46.2 (CH), 47.4 (CH), 52.6 (CH), 63.1 (CH), 102.9 (CH), 114.0 (CH), 117.0 (CH), 125.2 (CH), 127.5 (C), 127.6 (CH), 131.6 (C), 136.6 (C), 137.3 (C), 170.8 (C), 172.3 (C); mp 118 °C (EtO2-CH2Cl2); [α]D² = -4.1 (c 1.0, CHCl3).

(1R,5R,6R)-2-(1R,2-Hydroxy-1-phenylethyl)-6-(methoxycarbonyl)-7-methyl-3-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole (16R)-7. TiCl4 (125 mL, 0.12 mmol) was added to a solution of (αR)-6 (190 mg, 0.45 mmol) in CH2Cl2 (10 mL), and the resulting mixture was heated at reflux 17 h. TiCl4 (50 µL, 0.45 mmol) was added, and the mixture was heated at reflux for an additional 4 h, poured into saturated solution NaHCO3, and extracted with CH2Cl2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (4:1 EtOAc–hexane).
hexane; 4.9:0.1 EtOAc–EtOH to afford (16R)-7 (38 mg, 20%); IR (film) 3375, 1739, 1624 cm⁻¹; ¹H NMR (300 MHz) δ 2.00 (dd, J = 11.0, 1.0 Hz, 1 H), 2.20 (dd, J = 11.0, 0.8 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); ¹³C NMR (75.4 MHz) δ 29.6 (CH), 29.8 (CH₃), 30.1 (CH), 38.5 (CH₂), 47.2 (CH), 47.5 (CH₂), 52.5 (CH₃), 63.3 (CH₂), 67.3 (CH), 109.2 (CH), 112.5 (C), 118.3 (CH), 119.6 (CH₂), 121.9 (CH), 124.5 (C), 127.6 (CH), 128.7 (CH), 130.6 (C), 136.4 (C), 137.3 (C), 137.5 (C), 140.1 (C), 140.1 (C), 141.7 (C), 141.7 (C); mp 166–169 °C (EtOAc–hexane) to give toluene (15 mL) was heated in the presence of NaCO₃ (1.0 g, 9.0 mmol) to give 10 (335 mg, 85%) after flash chromatography (7.5 EtOAc–hexane). IR (film) 1670 cm⁻¹; ¹H NMR (300 MHz) δ 0.93 (t, J = 7.2 Hz, 3 H), 3.37 (dd, J = 10.5, 7.6 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), 1.45 (d, J = 8.7, 1.1 Hz), 4.99 (d, J = 6.9 Hz, 1 H); ¹³C NMR (75.4 MHz) δ 10.7 (CH), 18.3 (CH₃), 23.9 (CH₂), 39.8 (CH), 59.6 (CH), 65.7 (CH), 73.6 (CH), 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 NaOH (10.0 mmol) to give 11 (280 mg, 85%) after flash chromatography (7:3 EtOAc–hexane) to afford 12 (140 mg, 81%): IR (KBr) 3375, 1739, 1628 cm⁻¹; ¹H NMR (300 MHz) δ 0.61 (t, J = 7.5 Hz, 3 H, CH₃), 1.39 (m, 1 H, CH₂), 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, CH₃N), 3.85 (s, 3 H, CH₃O), 3.91 (d, 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, 7.2 Hz, 1 H, H-1'), 4.90 (brs, 1 H, OH), 7.10–7.52 (m, 8 H, ArH), 7.65 (d, J = 7.8 Hz, 1 H, H-11); ¹³C NMR (75.4 MHz) δ 11.1 (CH₃), 23.7 (CH₃), 30.5 (CH₃N), 32.0 (C-4), 33.5 (C-5), 42.8 (C-12), 47.3 (C-6), 52.5 (CH₃O), 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-7p), 128.2, 128.3 (C-o, m), 131.3 (C-6a), 137.3 (C-7a), 137.8 (C-i), 169.9 (CNO, CO₂), 171.0 (COO); mp 115–117 °C; [α]₂⁰D = −10.5 (c 1.0, EtOH). Anal. Found: C 72.62; H 6.77; N 6.27. Found: C 72.74; H 6.83; N 6.28. Chapter C for C₂H₂N₂O₂CH₂Cl₂: C 68.23; H 6.44; N 5.84. Anal. Found: C 68.23; H 6.51; N 5.71.

**Methyl (3R,7R,8S,8aR)-8-Ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine-7-aceta (11b).** A solution of 3b (155 mg, 8.22 mmol) in DMSO (25 mL) was added to a cooled solution of LDA (10.9 mg of 1.5 M solution in cyclohexane, 16.4 mmol) in THF (20 mL). After the mixture was stirred for 30 min at 0 °C for 1 h, the mixture was poured into saturated aqueous NaHCO₃, and extracted with CH₂Cl₂. The combined organic extracts were washed with water, dried, and concentrated to give an oil. Flash chromatography (EtOAc–hexane) afforded (αS)-11a and (αR)-11b (548 mg, 83%, 3:7 ratio). (αS)-11a (lower Rf): IR (film) 1736, 1661 cm⁻¹; ¹H NMR (300 MHz) δ 0.94 (t, J = 7.5 Hz, 3 H, 1H), 1.62 (m, 1 H, 1H), 1.70 (m, 1 H, 1H), 1.76 (m, 1 H, 1H), 2.44 (dd, J = 17.1, 7.0 Hz, 1 H, 1H), 2.60 (dd, J = 17.1, 4.2 Hz, 1 H, 1H), 2.59 (m, 1 H, 1H), 3.55 (s, 2 H), 3.57 (s, 2 H), 3.76 (d, J = 8.7 Hz, 1 H, 1H), 4.18 (m, 1 H, 1H), 4.20 (d, J = 4.0 Hz, 1 H, 1H), 4.30 (d, J = 4.0 Hz, 1 H, 1H), 5.70 (m, 1 H, 1H), 7.08 (m, J = 7.8 Hz, 1 H, 1H), 7.21 (m, J = 8.1 Hz, 1H), 7.28–7.44 (m, 6 H, 6 H), 7.56 (d, J = 7.8 Hz, 1 H, 1H); ¹³C NMR (75.4 MHz) δ 10.3 (CH₃), 25.1 (CH₂), 29.8 (CH₃), 35.0 (CH₂), 37.6 (CH₂), 42.8 (CH₂), 46.5 (CH₂), 52.3 (CH₃), 57.6 (CH₂), 73.9 (CH₂), 91.0 (CH), 101.6 (CH), 109.1 (CH), 119.7 (CH), 120.4 (CH), 121.6 (CH), 126.8 (CH), 126.8 (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); [α]₂⁰D = −70.0 (c 1.0, EtOH). Anal. C 72.62; H 6.77; N 6.27. Found: C 72.75; H 6.77; N 6.12. (αR)-11a (higher Rf): IR (KBr) 1751, 1676 cm⁻¹; ¹H NMR (300 MHz) δ 1.11 (t, J = 7.2, 3 H, 1H) (27) Amat, M.; Llor, N.; Hidalgo, J.; Bosch, J. Tetrahedron: Asymmetry 1997, 8, 2337.

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Calcd for C_{26}H_{28}N_{2}O_{4}: C, 70.73; H, 6.62; N, 6.34. Found: C, 71.05; H, 7.02; N, 6.05. (aR)-11b (higher R): IR (film) 3292, 2960, 2950, 1661 cm\(^{-1}\); \(\delta\) (500 MHz) 1.08 (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-1), 2.47 (m, 1 H, H-7), 3.65 (d, \(J = 10.0\) Hz, 1 H, CH\(_{2}\)COMe), 3.76 (3 H, 3 CH\(_3\)), 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-3), 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), 7.69 (m, 2 H, H-7), 7.22 (dd, \(J = 8.1, 4.8\) Hz, 1 H, H-5), 7.16 (m, 1 H, H-6) ind), 7.24–7.33 (m, 3 H, 6 H, Aryl), 10.31 (s, 1 H, \(OH\)), 1.1, 2.68 (2 H, 2 CH\(_2\)), 3.22 (d, \(J = 18.0, 8.4\) Hz, 1 H, H-11), 8.62 (br s, 1 H, \(OH\)); 13C NMR (75.4 MHz) 127.8 (CH), 128.8 (CH), 128.1 (CH), 132.0 (CH), 136.8 (C), 140.7 (OH), 140.5 (CH2), 146.3 (C=O), 146.6 (C=O), 146.7 (C=O), 171.3 (C=O), 171.5 (NCO); \([\alpha]_D^{22D} = -6.1 (c 0.56, EtOH); MS-EI m/z = 284 (M\(^+\), 47), 253 (41), 208 (41), 195 (100), 190 (60); HMRs calcd for C\(_{25}\)H\(_{28}\)N\(_{2}\)O\(_{3}\): 284.1525, found 284.1521. (bS)-11b (lower S) calcd for C\(_{26}\)H\(_{28}\)N\(_{2}\)O\(_{4}\): 299.1874, found 299.1875. (aS)-11b (lower S) calcd for C\(_{26}\)H\(_{28}\)N\(_{2}\)O\(_{4}\): 299.1874, found 299.1875.

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2.7 Hz, 1 H), 7.26 (dd, \(J = 9.3\) Hz, 1 H), 7.04 (dm, \(J = 11.4, 4.8\) Hz, 1 H), 6.29 (dd, \(J = 9.3, 1.0\) Hz, 1 H), 7.04 (dm, \(J = 1.8, 1.2\) Hz, 1 H), 7.22 (dd, \(J = 9.3,\)

1.2 Hz, 1 H, H-3), 7.16 (m, 1 H, H-6), 7.24–7.33 (m, 3 H, 6 H, Aryl), 10.31 (s, 1 H, \(OH\)), 1.1, 2.68 (2 H, 2 CH\(_2\)), 3.22 (d, \(J = 18.0, 8.4\) Hz, 1 H, H-11), 8.62 (br s, 1 H, \(OH\)); 13C NMR (75.4 MHz) 127.8 (CH), 128.8 (CH), 128.1 (CH), 132.0 (CH), 136.8 (C), 140.7 (OH), 140.5 (CH2), 146.3 (C=O), 146.6 (C=O), 146.7 (C=O), 171.3 (C=O), 171.5 (NCO); \([\alpha]_D^{22D} = -6.1 (c 0.56, EtOH); MS-EI m/z = 284 (M\(^+\), 47), 253 (41), 208 (41), 195 (100), 190 (60); HMRs calcd for C\(_{25}\)H\(_{28}\)N\(_{2}\)O\(_{3}\): 284.1525, found 284.1521. (bS)-11b (lower S) calcd for C\(_{26}\)H\(_{28}\)N\(_{2}\)O\(_{4}\): 299.1874, found 299.1875. (aS)-11b (lower S) calcd for C\(_{26}\)H\(_{28}\)N\(_{2}\)O\(_{4}\): 299.1874, found 299.1875.

**General Procedure for Conglutinate Addition Reactions.**

-nBuLi (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 (ca. 2, cis or 10, trans; 0.9 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 NaHCl 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).

(2S,7S-and 7R,8S,8aR)-Ethyl-7-[2-(3-indolyl)-1,3-dioxide-2,6-dioxo-1,2,3,4,5,6-hexahydro-5H-oxazolo[3,2-]

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| 34a | 34b |
| --- | --- |

| 34a | IR (film) 3280, 1650 cm−1;1H NMR (300 MHz) δ 0.87 (t, J = 7.2 Hz, 3 H, CH3), 1.26 (m, 1 H, CH2), 1.58 (m, 1 H, CH2), 1.86 (m, 2 H, CH2-CH(Si)(Me)2), 2.03 (m, 1 H, H-7a), 2.64 (m, 3 H, CH2-CH(Si)(Me)2), 2.79 (m, 1 H, H-7), 2.88 (masked, 2 H, CH2-CH(Si)(Me)2), 2.90 (dd, J = 15.6, 6.0 Hz, 1 H, H-1, H-7), 3.96 (dd, J = 9.0, 1.5 Hz, 1 H, H-1, H-7), 4.13 (dd, J = 9.0, 1.5 Hz, 1 H, H-1, H-7), 7.21 (d, J = 7.2 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-4 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);13C NMR (75.4 MHz) δ 12.5 (CH3), 21.0 (CH2), 24.2 (CH2-CH(Si)(Me)2), 27.9, 28.5 (CH(Si)(Me)2), 35.3 (C-6), 44.8 (C-8), 46.9 (C-7a), 57.5 (Cs2), 58.5 (C-5), 74.0 (C-2), 91.0 (C-8), 106.4 (C-3 ind), 120.6 (C-4 ind), 122.4 (C-5 ind), 122.6, 126.4 (C-8a ind), 127.1 (C-9), 128.5 (Cs ind), 130.6 (C-2 ind), 136.9 (C-14 ind), 141.3 (C-7a ind), 167.5 (COO); [α]22D +12.4 (+ 0.5, MeOH). Analytical data for C27H33N2S2O2: C, 66.50; H, 6.41; N, 5.74. Found: C, 66.63; H, 6.38; N, 4.97. 34b: 1H NMR (300 MHz) δ 0.88 (t, J = 7.7 Hz, 3 H, CH3), 1.19 (m, 1 H, CH2), 1.40 (m, 1 H, CH2), 1.57 (m, 1 H, CH2-CH(Si)(Me)2), 2.23 (m, 2 H, CH2-CH(Si)(Me)2), 2.53 (m, 5 H, CH2-CH(Si)(Me)2), 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 = 5.7 Hz, 1 H, H-6), 5.81 (dd, J = 9.0, 1.9 Hz, 1 H, H-7 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-1 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-1 ind), 8.71 (br s, 1 H, NH);13C NMR (75.4 MHz) δ 10.3 (CH3), 24.1 (CH2-CH(Si)(Me)2), 26.5 (CH3), 27.5, 27.6 (CH2-CH(Si)(Me)2), 34.3 (C-6), 41.6 (C-8), 48.2 (C-7a), 58.1 (C-5), 60.9 (Cs2), 74.4 (C-4), 90.7 (Cs a), 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), 127.9 (C-o, m), 128.5 (C-3a ind), 139.5 (C-2 ind), 137.5 (C-o), 140.0 (C-7a ind), 167.5 (COO); [α]22D +99.3 (+ 0.5, MeOH). Analytical data for C27H33N2S2O2: C, 67.71; H, 6.32; N, 5.85. Found: C, 67.71; H, 6.62; N, 5.62. General Procedure for Desulfurization Reactions. NiCl2·6H2O (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, NaBH4 (21−30 mmol) was added portionwise, and the mixture was stirred at −30 °C for 2 h and then filtered through Celite. The filtrate was concentrated and partitioned between saturated aqueous NaCl and CH2Cl2. The combined organic extracts were dried and concentrated to give the desired product 35−42 (see the Supporting Information for details).

(2R,7S,8S,8aR)-Ethyl-7-[2-(3-indolylmethyl)5-oxo-3-phenyl-2,3,5,6,7,8a-hexahydro-5H-oxazolo[3,2-a]pyri-
 mixture was stirred at rt for 1 h, poured into saturated aqueous NaHCO₃, and extracted with CH₂Cl₂. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (99:1 CH₃Cl–MeOH) to
give tetracycles 53 (55 mg, 35%) and 54 (10 mg, 6%). 53: IR (film) 3256, 1650 cm⁻¹; ¹H NMR (400 MHz) 0.96 (t, J = 7.5 Hz, 3 H, CH₃), 1.36 (m, 2 H, CH₂), 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-1, 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); ¹³C NMR (100.6 MHz) 25.4 (CH₃), 36.1 (CH₂), 53.0 (C₂), 68.8 (CH), 111.6 (CH), 112.4 (CH), 117.0 (CH), 121.5 (CH), 126.2 (CH), 130.9 (CH), 136.0 (CH), 137.5 (NCO), [α]₂⁵D +82.2 (c 0.3, CHCl₃); MS-El m/z 254 (M⁺, 75), 195 (76), 180 (100), 168 (51); HMRS calsd for C₁₆H₁₈N₂O 254.1419, found 254.1416.

The energies of the conjugate addition of the anion derived from 18 to the lactams was examined from B3LYP 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-11a, 26a, 26b, and 31b (CIF), computational details of the 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.

The generalized molecular interaction potential with polarization (GMIPp) 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 diatomic dispersion correction based on the H2 model. In eq 1, R, and ρ are defined for the positions of the nuclei (Z) in the molecule and of the atoms in the classical probe, C denotes the coefficient of atomic orbitals in the molecular orbit–linear combination of atomic orbitals, ρ is the first-order density matrix, ϕ is the set of atomic orbitals, ξ denotes the energy of molecular orbitals, and e 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 de-