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Enantioselective formal synthesis of uleine alkaloids from phenylglycinol-derived bicyclic lactams†

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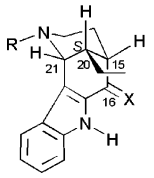
A two-step route for the enantioselective construction of the tetracyclic ring system of uleine alkaloids, involving the stereoselective conjugate addition of an appropriate indole-containing nucleophile to a chiral bicyclic δ-lactam and the subsequent cyclization on the indole 3-position of the resulting 4,5-disubstituted 2-piperidone, has culminated in the formal total synthesis of several alkaloids of this group.

The uleine alkaloids are characterized by the presence of a 1,5-methanoazocino[4,3-*b*]indole fragment bearing an ethyl chain at the bridge carbon. Although the alkaloids of the uleine group have received considerable synthetic attention,[1] their enantioselective synthesis has been little explored.[2] While the absolute configuration of the bridgehead C-15 position 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.



R	X	
CH_3	O	dasycarpidone
CH_3	CH_2	uleine
CH_3	α-OH, β-H	dasycarpidol
H	O	nordasycarpidone
H	CH_2	noruleine
CH_3	α-CH_2OH, β-H	17-hydroxydihydrouleine

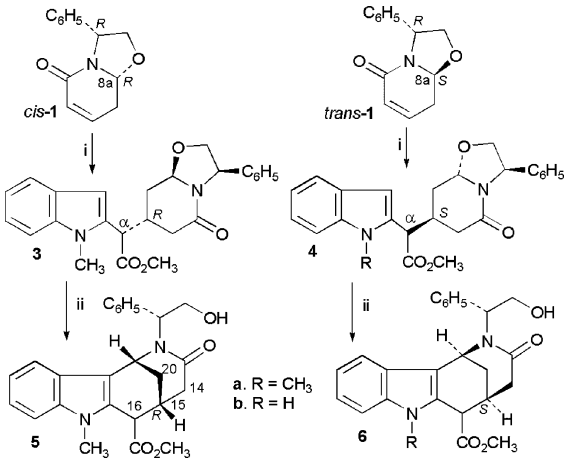
We report here a straightforward enantioselective entry to the tetracyclic ring system of uleine alkaloids, which has culminated in the formal synthesis of alkaloids of this group. The key steps are the stereoselective conjugate addition of an indole-containing nucleophile to a phenylglycinol-derived α,β-unsaturated δ-lactam and the intramolecular α-amidoalkylation on the indole 3-position taking advantage of the masked acyl iminium moiety present in the resulting 4,5-disubstituted 2-piperidone.

Taking into account that α,β-unsaturated lactams are poor Michael acceptors and that there are few examples of such 1,4-additions, in particular to δ-lactams lacking an additional electron-withdrawing group on the nitrogen and/or in conjugation with the double bond,[3] to check the viability of the proposed conjugate addition–cyclization sequence we used the model lactams *cis*-**1** and *trans*-**1**,[4] which lack the ethyl substituent present in the natural products. Reaction of these lactams with the enolate of methyl 1-methyl-2-indoleacetate (**2a**) gave the respective lactam esters **3** (53%) and **4a** (64%) as mixtures of epimers at the isomerizable stereocenter α to the ester group (Scheme 1), each epimer being separately cyclized by treatment with $TiCl_4$ to the corresponding tetracycles **5** (~25%) and **6a** (~50%). Similarly, the enolate of methyl 2-indoleacetate (**2b**) reacted with lactam *trans*-**1** to ultimately give tetracycles (16*R*)-**6b** and (16*S*)-**6b** in 36% overall yield.

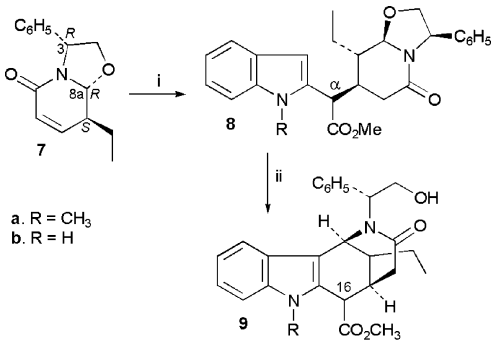
The relative configuration of C-16 in these tetracycles was deduced from the H_{15}-H_{16} *J* value and from the existence or absence of γ-gauche effects on C-14 and C-20 in the NMR spectra, whereas the absolute configuration was inferred by comparing the NMR data of tetracycles **6** with those of **9a**, whose configuration was known from the X-ray analysis of its precursor (α*R*)-**8a** (see below).

The above results made evident that the conjugate addition had taken place stereoselectively on the *Re* face of lactam *cis*-**1**, whereas lactam *trans*-**1** had reacted with *Si* facial selectivity. This is in agreement with the stereochemical outcome of other conjugate additions to these and related lactams, and can be accounted for by considering that the process is kinetically controlled.[4,5]

Once it was demonstrated that the above approach can provide access to the tetracyclic ring system of uleine alkaloids with the natural configuration at the bridgehead carbons (*e.g.* **5**), we extended our studies using the unsaturated lactam **7**,[4] which has the same *cis*-3,8a configuration as *cis*-**1** but incorporates the ethyl substituent present in the natural products with the required absolute configuration for the synthesis of alkaloids in the normal C-20 series. The addition of the enolate of ester **2a** to lactam **7** led to a 3 : 7 epimeric mixture of lactam esters **8a** in excellent yield (83%) and complete facial selectivity (Scheme 2). Cyclization of the major isomer also took place in excellent yield (81%) to give



Scheme 1 *Reagents and conditions*: (i) **2a** or **2b**, LDA, THF, −78 °C, then **1**, 0 °C. (ii) $TiCl_4$, CH_2Cl_2, rt (reflux from **3**).



Scheme 2 *Reagents and conditions*: (i) **2a** or **2b**, LDA, THF, −78 °C, then **7**, HMPA, CuCN (from **2b**), rt. (ii) $TiCl_4$, CH_2Cl_2, reflux.

† Electronic supplementary information (ESI) available: full crystallographic details and ^1H and ^{13}C NMR spectra for all new compounds. See http://www.rsc.org/suppdata/cc/b4/b400987h/

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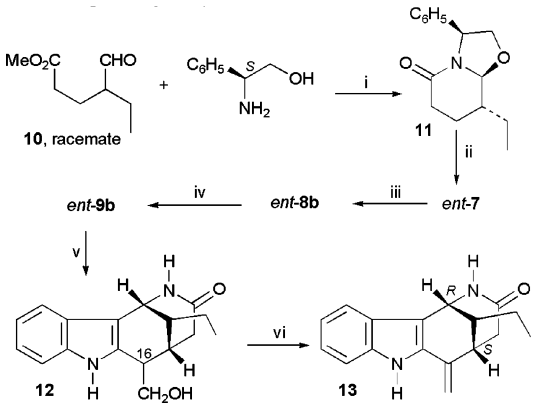
tetracycle **9a**. The same stereoselectivity was observed from the enolate of the *N*-unsubstituted 2-indoleacetate **2b**, although in this case the conjugate addition only took place in acceptable yield (40%) in the presence of CuCN. The resulting epimeric esters **8b** were separately cyclized (~50%) to give the same enantiopure tetracycle **9b**, thus indicating that epimerization at C-16 had occurred during cyclization.

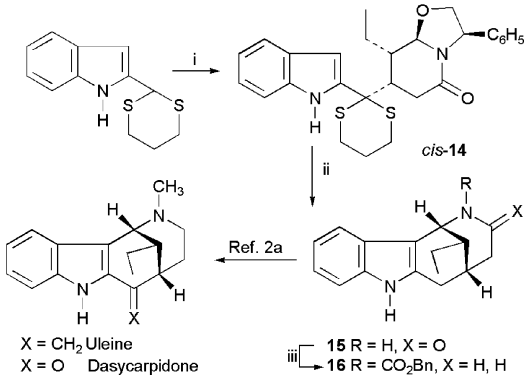
The relative configuration of (α*R*)-**8a** was unambiguously established by X-ray crystallography†‡, indicating that the ethyl substituent had exerted a dramatic influence on the stereochemical course of the conjugate addition since it had occurred on the *Si* face of the carbon–carbon double bond to give an all-*trans* piperidine derivative as a consequence of the thermodynamic control.[6] Consequently, the absolute configuration at the bridgehead carbons of tetracycles **9** is the opposite of that present in the uleine alkaloids.

However, the *trans* stereoselectivity of the above additions makes accessible tetracyclic derivatives with the natural configuration in the 20-epi series. It is simply a matter of starting from the enantiomer of **7**, taking advantage of the fact that both enantiomers of phenylglycinol are commercially available. The required unsaturated lactam *ent*-**7** was prepared in 55% overall yield by cyclodehydration of (*S*)-phenylglycinol with racemic methyl 4-formylhexanoate (**10**), in a process involving a dynamic kinetic resolution, followed by generation of the carbon–carbon double bond *via* a β-ketosulfoxide as in the above *R*-series (Scheme 3). As expected, conjugate addition of the enolate derived from **2b** to *ent*-**7**, followed by cyclization of the resulting epimeric mixture of lactam esters *ent*-**8b**, led to tetracycle *ent*-**9b**, which was chemoselectively reduced with Na/liq NH_3, to alcohols **12** (64%; 16*R*/16*S* 1 : 2 epimeric mixture) and then converted (53%) to the nor-20-epiuleine derivative **13** *via* the corresponding mesylate.

The enantioselective access to the more abundant alkaloids with a *cis* H_{15}–H_{20} relationship required the preparation of an appropriate *cis*-4,5-disubstituted 2-piperidone by stereocontrolled conjugate addition to unsaturated lactam **7**, avoiding the undesired equilibration to the more stable *trans* isomers. For this purpose we selected the dianion derived from 2-(2-indolyl)-1,3-dithiane[7] as the nucleophile. To our delight, the reaction took place in extraordinarily high yield (90%) and good stereoselectivity (*cis*/*trans* ratio 4 : 1), affording the desired enantiopure piperidone *cis*-**14** in 72% yield after column chromatography (Scheme 4). Treatment of *cis*-**14** with sodium in liquid ammonia brought about the reductive desulfurization and cleavage of the benzylic C–N bond to give a 6-oxylactam, which was cyclized with $TiCl_4$ to the tetracyclic lactam **15** in 35% overall yield. Finally, borane reduction of the lactam carbonyl group followed by treatment of the resulting secondary amine with



Scheme 3 *Reagents and conditions*: (i) Et_2O, anh. Na_2SO_4, 0 °C, 1 h, then 70 °C, 10–15 mm Hg. (ii) $C_6H_5S(O)OMe$, KH, THF, reflux, then toluene, Na_2CO_3, reflux. (iii) **2b**, LDA, THF, −78 °C, then *ent*-**7**, HMPA, CuCN, rt. (iv) $TiCl_4$, CH_2Cl_2, reflux. (v) Na, liq NH_3, −33 °C. (vi) MsCl, Et_3N, CH_2Cl_2, 0 °C, then DBU, THF, reflux.



Scheme 4 *Reagents and conditions*: (i) *n*-BuLi, THF, −78 °C, then **7**. (ii) Na, liq, NH_3, −33 °C, then $TiCl_4$, CH_2Cl_2, 25 °C. (iii) $BH_3{\cdot}Me_2S$, toluene, reflux, then $ClCO_2Bn$, K_2CO_3.

benzyl chloroformate gave (40% overall yield) carbamate **16** {$[\alpha]^{25}_D$ + 89.0 (*c* 0.3, $CHCl_3$); lit.[2a] $[\alpha]^{28}_D$ + 89.4 (*c* 0.4, $CHCl_3$)}, which had previously been converted[2a] into the alkaloids (+)-dasycarpidone and (+)-uleine. Taking into account previous correlations,[8,9] the above synthesis also represents a formal total synthesis of nordasycarpidone, (+)-dasycarpidol and (−)-17-hydroxydihydrouleine.

Conjugate addition reactions to phenylglycinol-derived unsaturated δ-bicyclic lactams[10] allow the stereocontrolled formation of C–C bonds at the piperidine 4-position and open short and efficient routes for the enantioselective construction of the bridged tetracyclic ring system of uleine alkaloids, both in the normal and 20-epi series.

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Notes and references

‡ *Crystal data* for $C_{27}H_{30}N_2O_4$ (α*R*)-**8a** at 294(2) K: M = 446.53, orthorhombic, space group $P2_12_12_1$, a = 8.931(2), b = 5.990(10), c = 28.080(9) Å, V = 2407.3(10) Å^3, Z = 4, μ(Mo Kα) = 0.083 mm^{-1}, 3440 reflections collected. The final $R1$ and $wR2$ were −0.0485 and 0.0981 [$I > 2\sigma(I)$] and 0.1321 and 0.1451 (all data, respectively). CCDC 263283. See http://www.rsc.org/suppdata/cc/b4/b400987h/ for crystallographic data in .cif or other electronic format.

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