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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6722–6725

# Enantioselective synthesis of 2-[(3-ethyl-4-piperidyl)methyl]-indoles from a phenylglycinol-derived lactam: formal synthesis of *Strychnos* alkaloids

Mercedes Amat,* Núria Llor, Begoña Checa, Maria Pérez and Joan Bosch*

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

Received 25 May 2007; accepted 17 July 2007
Available online 21 July 2007

**Abstract**—A diastereodivergent synthesis of enantiopure *cis*- and *trans*-2-[(3-ethyl-4-piperidyl)methyl]indole (*cis*-**1b** and *trans*-**1b**) from a common phenylglycinol-derived oxazolopiperidone lactam **3** is reported. The key step is a stereocontrolled conjugate addition, either under kinetic or thermodynamic control, of the dilithium salt of 2-(2-indolyl)-1,3-dithiane to unsaturated lactam **3**.


*cis*- and *trans*-2-[(3-Ethyl-4-piperidyl)methyl]indoles **1** are key intermediates[1] in the synthesis of tetracyclic alkaloids of the uleine group[2] and pentacyclic *Strychnos* indole alkaloids[3] (Scheme 1). All these syntheses have been conducted in the racemic series, and no precedents for the enantioselective synthesis of (piperidylmethyl)-indoles **1** have been reported so far.

Taking into account that phenylglycinol-derived oxazolopiperidone lactams provide a general solution for the enantioselective synthesis of piperidines bearing virtually any type of substitution pattern,[4] we planned to take advantage of these chiral building blocks to develop a diastereodivergent synthesis of enantiopure *cis*- and *trans*-(piperidylmethyl)indoles *cis*-**1b**[5] and *trans*-**1b** (3,4-disubstituted piperidine derivatives). The former is a known synthetic precursor of the *Strychnos* alkaloids tubifoline, tubifolidine, and 19,20-dihydroakuammicine.[1a,b]

The key step of the synthesis is a stereocontrolled conjugate addition of a 2-indolylmethyl anion equivalent to an unsaturated oxazolopiperidone lactam that incorporates the ethyl substituent with the required absolute configuration.[6]

After some experimentation, the conjugate addition of the dilithium salt of 2-(2-indolyl)-1,3-dithiane[7,8] (**2**) to the easily accessible unsaturated lactam **3**[6c] was accomplished in excellent yield (90%) and good facial diastereoselectivity (4:1) to give the enantiopure *cis*-isomer *cis*-**4b** when the reaction was performed at −78 °C for 12 h using an excess (2 equiv) of the nucleophile in THF solution (Scheme 2).[9] The observed stereoselectivity can be explained by considering that the attack of the nucleophile takes place, under stereoelectronic control,[10] axial to the electrophilic carbon of the conjugated double bond of the conformationally rigid lactam **3**, and consequently, *cis* with respect to the ethyl substituent, as depicted in Figure 1.

In sharp contrast, when the conjugate addition of the dianion derived from **2** (1.2 equiv) was carried out at room temperature for a longer reaction time (16 h) in THF solution, the enantiopure isomer *trans*-**4b** was stereoselectively formed as the only product, also in excellent yield (93%).[9] This result makes evident that, under these conditions, the equilibration of the initially formed kinetic *cis*-isomer to the thermodynamic *trans*-isomer has occurred.

The conversion of *cis*-**4b** to the target *cis*-(piperidylmethyl)indole *cis*-**1b** was performed in three steps. Reductive desulfurization of *cis*-**4b** with nickel boride[11] ($NiCl_2{\cdot}H_2O$, $NaBH_4$, THF–MeOH, 0 °C, 4 h) gave (94% yield) oxazolopiperidone lactam *cis*-**5**, which bears the required ethyl and 2-indolylmethyl substituents at the piperidine 3 and 4 positions, respectively (Scheme 3).

*Keywords*: Phenylglycinol; *Strychnos* alkaloids; Piperidines; Indoles; Oxazolopiperidone lactams.
* Corresponding authors. Tel.: +34 93 4024538; fax: +34 93 4024539 (J.B.); e-mail addresses: amat@ub.edu; joanbosch@ub.edu

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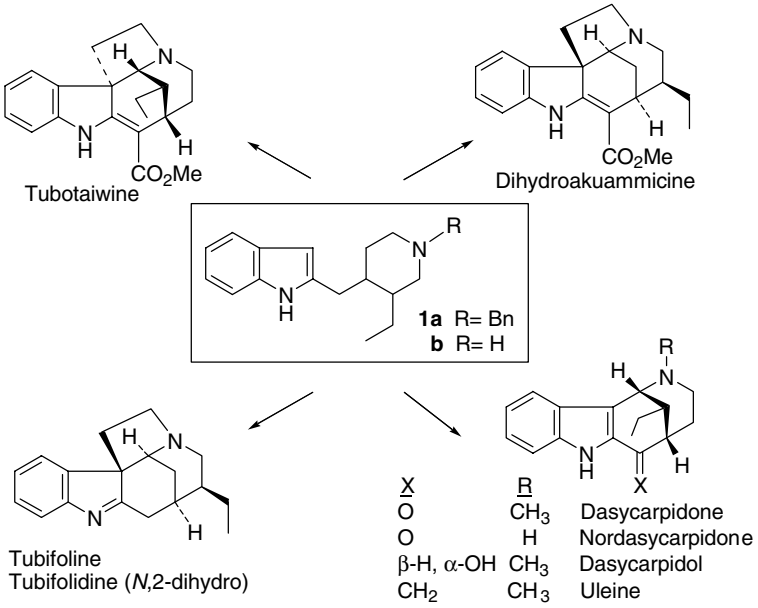
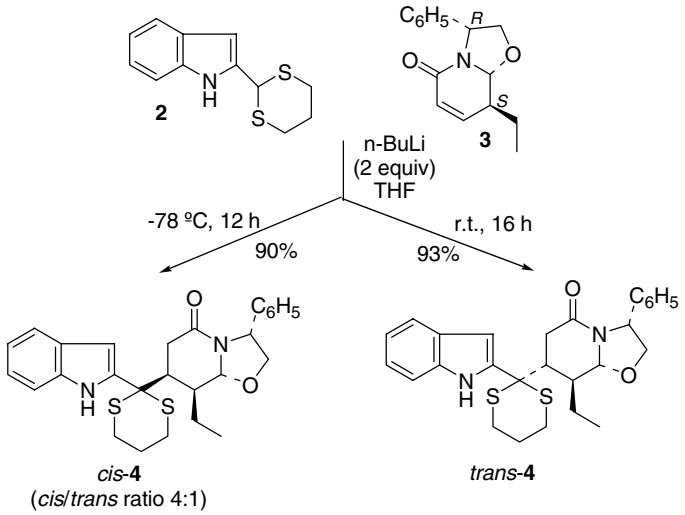
doi:10.1016/j.tetlet.2007.07.079




**Scheme 1.** Synthesis of uleine and *Strychnos* alkaloids from (piperidylmethyl)indoles **1**.




**Scheme 2.** Diastereodivergent synthesis of enantiopure *cis*-**4** and *trans*-**4**.

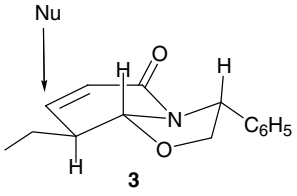


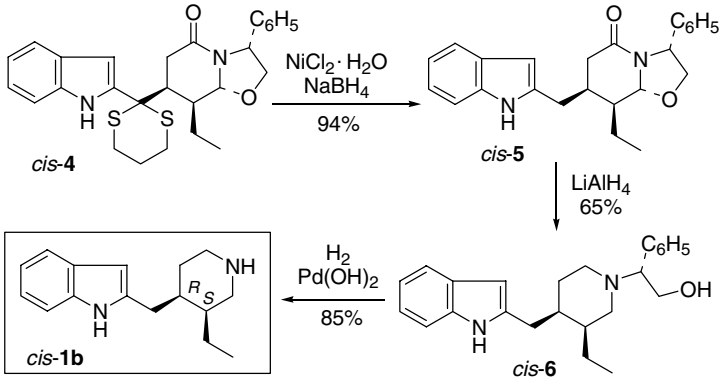

**Figure 1.** Stereoelectronic control in the conjugate addition to **3**.

Then, treatment of *cis*-**5** with $LiAlH_4$ (THF, reflux, 30 min) brought about both the reduction of the lactam carbonyl group and the reductive cleavage of the C–O bond of oxazolidine ring to give (65% yield) piperidine *cis*-**6**. A subsequent removal of the phenylethanol moiety by hydrogenolysis [$H_2$, $Pd(OH)_2$, EtOH, 400 psi] led to *cis*-(piperidylmethyl)indole *cis*-**1b** in 85% yield ($[\alpha]_D^{22}$ −11.6 (*c* 1.0, EtOH)). The NMR data of (−)-*cis*-**1b** were coincident with those reported for the racemic product.[1b]

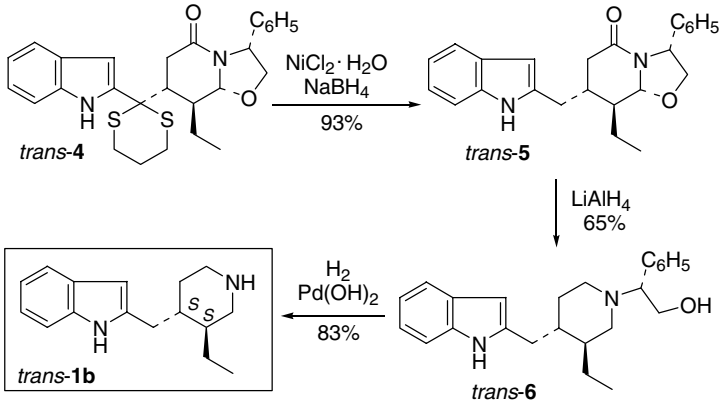
Taking into account previous correlations[1,12] and that the stereogenic centers at the piperidine 3 and 4 positions in *cis*-**1b** are configurationally stable, the above synthesis of *cis*-**1b** also represents a formal synthesis of the alkaloids (−)-tubifoline, (−)-tubifolidine, and (−)-19,20-dihydroakuammicine.

Following a similar reaction sequence, *trans*-**4b** was converted to *trans*-(piperidylmethyl)indole *trans*-**1b**[13] ($[\alpha]_D^{22}$ −77.8 (*c* 0.09, EtOH)) via the enantiopure intermediates *trans*-**5** and *trans*-**6** (Scheme 4).

The concise routes (four synthetic steps) developed herein further illustrate the potential of phenylglycinol-derived




**Scheme 3.** Enantioselective synthesis of (piperidylmethyl)indole *cis*-**1b**.




**Scheme 4.** Enantioselective synthesis of (piperidylmethyl)indole *trans*-**1b**.

oxazolopiperidone lactams for the enantioselective synthesis of diversely substituted piperidine derivatives.

## Acknowledgments

Financial support from the Ministry of Science and Technology (Spain)-FEDER (Project CTQ2006-02390/BQU) and the DURSI, Generalitat de Catalunya (Grant 2005-SGR-0603) is gratefully acknowledged. Thanks are also due to the Ministry of Science and Technology (Spain) for a fellowship to B.C.

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9. *Experimental procedure for the preparation of cis*-**4** *and trans*-**4**: A solution of *n*-BuLi in hexane (21 mL of a 1.6 M solution, 32.8 mmol) was slowly added at −78 °C to a solution of 2-(2-indolyl)-1,3-dithiane (**2**; 3.86 g, 16.4 mmol) in anhydrous THF (50 mL). The mixture was stirred at −30 °C for 2 h and added at −78 °C, via a canula, to a solution of lactam **3** (2 g, 8.2 mmol) in anhydrous THF (20 mL). The resulting mixture was stirred at −78 °C for 12 h, poured into saturated aqueous $NH_4Cl$, and extracted with EtOAc. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (9:1 to 1:4 hexane–EtOAc) to give compounds *cis*-**4** (2.58 g, 73%) and *trans*-**4** (0.60 g, 17%). Operating as above (reaction conditions: 16 h at room temperature), from dithiane **2** (2.33 g, 9.9 mmol) and lactam **3** (2 g, 8.2 mmol) was obtained *trans*-**4** (3.6 g, 93%) after flash chromatography.
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13. *Spectroscopic data of trans*-**1b**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.92 (t, $J = 7.2$ Hz, 3H, $CH_3$), 1.26–1.39 (m, 1H, H-3), 1.50–1.79 (m, 5H, $CH_2$, H-5 and H-4), 2.35–2.64 (m, 3H, $CH_2$ ind, H-2 and H-6 ax), 3.11–3.33 (m, 3H, $CH_2$ ind, H-2 and H-6 eq), 4.20 (br s, 1H, NH), 6.21 (s, 1H, H-3 ind), 7.04–7.14 (m, 2H, H-5 and H-6 ind), 7.29–7.33 (m, 1H, H-4 ind), 7.52 (dd, $J = 7.3$, 1.2 Hz, H-7 ind), 8.49 (br s, 1H, NH ind). $^{13}$C NMR (75.4 MHz, $CDCl_3$) $\delta$ 10.0 ($CH_3$), 23.0 ($CH_2$), 27.7 (C-5), 31.2 ($CH_2$ ind), 38.9 (C-4), 39.1 (C-3), 43.5 (C-6), 47.0 (C-2), 100.3 (C-3 ind), 110.6 (C-7 ind), 119.4 and 119.6 (C-4 and C-5 ind), 120.8 (C-6 ind), 128.7 (C-3a ind), 135.9 (C-2 ind), 136.7 (C-7a ind).