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Stereochemically controlled syntheses of indole-substituted dihydrofuran-2-ones and a pyrrolidin-2-one

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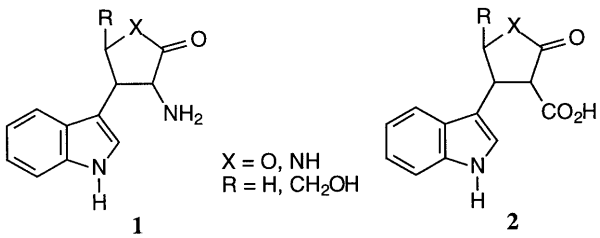
Abstract

In order to obtain constrained analogues of tryptophane, five-membered lactams and lactones bearing 4-indolyl and 3-carboxylic groups were prepared in a completely diastereoselective manner, resulting in a *trans* relationship. Furthermore, the use of chiral precursors in the synthesis yielded enantiomerically pure compounds with three contiguous chiral centres.

Keywords: indoles; lactams; lactones; stereocontrol.

3-Amino-4-indolyl-dihydrofuran-2-ones and pyrrolidin-2-ones **1** (Fig. 1) can be considered as constrained analogues of tryptophan[1] and serotonin.[2] They can also be useful building blocks for the synthesis of various heterocycles exhibiting potent pharmacological activities on the central nervous system[3–5] or show antitumor activity.[6,7]



1 **2**

Figure 1.

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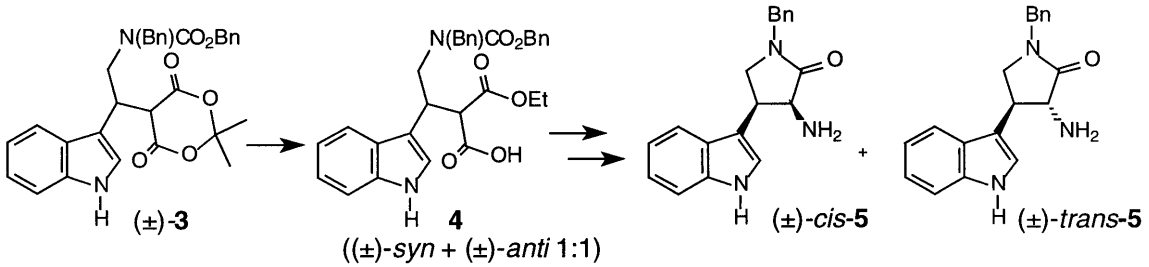
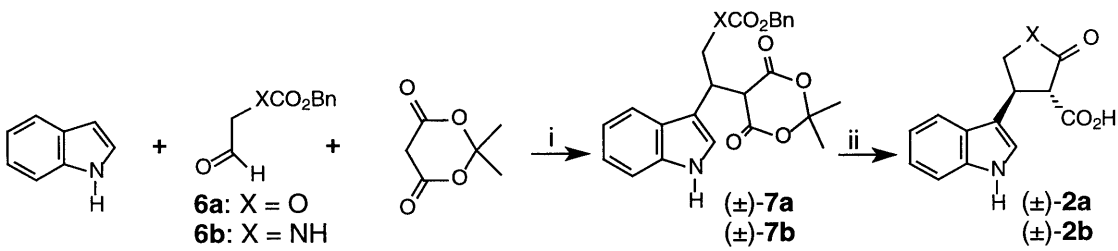
In the continuation of our programme on the synthesis of non-natural tryptophan derivatives,[8] we recently reported[9] a short approach to pyrrolidones **5** based on simple functional group transformations starting from compound **3**, as depicted in Scheme 1. Since **3** is racemic, and the ring opening of the Meldrum's acid core to **4** was not stereoselective, **5** was isolated as a separable mixture of racemic diastereomers.



Scheme 1.

In this regard, it was worth studying whether intramolecular nucleophilic attack on the cyclic malonic ester residue would improve the stereochemical outcome of the formation of the 5-membered ring. Herein, we wish to describe our preliminary results concerning a stereoselective route to compounds of general formula **2**.

Condensation of indole, Meldrum's acid, and protected 2-hydroxyacetaldehyde (**6a**)[10] or 2-aminoacetaldehyde (**6b**)[9] gave rise to racemic trimolecular adducts **7a** and **7b**, respectively (Scheme 2). Removal of the protecting group by hydrogenolysis, followed by spontaneous intramolecular ring closure afforded **2a** and **2b**[11] in one-pot reactions. In both cases, cyclisation resulted in the stereoselective formation of the respective (±)-*trans* disubstituted ring, while no *cis* diastereoisomer could be isolated. The *trans* relative stereochemistry was assigned with the aid of NOE experiments[‡] and of comparison with previous results.[§]



Scheme 2. Conditions: (i) CH_3CN, cat. D,L-proline, 75% (**6a**), 65% (**6b**); (ii) EtOH, H_2, Pd/C, 90% (**2a**), 80% (**2b**)

Nucleophilic attack of the internal hydroxy or amino groups seems to be dictated by steric factors. Fig. 2 shows the transition-state of the favoured equatorial approach, in which the bulky indole moiety is most remote from the carbonyl groups, leading to *trans* disubstituted products.

Knowing that the ring closure proceeds with *trans* selectivity, it seemed attractive to investigate how the first chiral centre can be created in the trimolecular condensation. For this purpose, 2,3-*O*-isopropylidene-D-glyceraldehyde[13] [(*R*)-**8**], as chiral template, was condensed with indole and Meldrum's acid, affording the adduct **9**[14] as the sole diastereomer (Scheme 3).

[‡] A 6% NOE between the 'malonic' proton and those at positions 2 and 4 of the indole moiety was observed.[9,12]

[§] The ^{1}H NMR spectrum of **2b** showed a similar pattern to *trans*-**5**.[9]

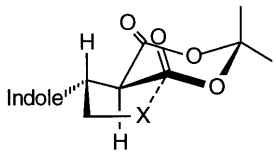
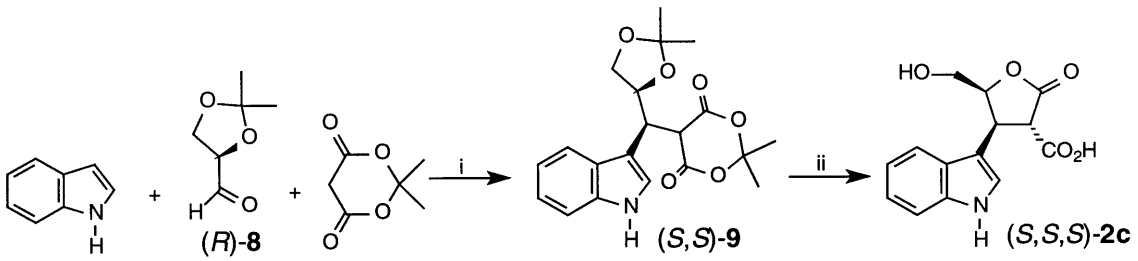


Figure 2.



Scheme 3. Conditions: (i) CH_3CN, cat. D,L-proline, 75%; (ii) CH_3CN, 10% HCl, 83%

The absolute configuration of the newly formed asymmetric carbon atom in **9** could not be determined by the usual spectroscopic methods. Hydrolysis of the isopropylidene protecting group followed by spontaneous cyclisation led to the lactone **2c**[15] in a regio- and stereoselective manner, as was elucidated from its ^1H and ^{13}C spectra. The absolute stereochemistry was assigned by single crystal X-ray analysis[16] (Fig. 3), which also permitted us to deduce the configuration of the newly created chiral carbon atom in **9**. Concerning the selective formation of this centre, according to recent work published by Ortuño and co-workers,[17] we assume that indole attacks the *Si* face of the Knoevenagel adduct formed from Meldrum's acid and the protected glyceraldehyde (Fig. 4).

This two-step sequence was also performed using 2,3-*O*-isopropylidene-L-glyceraldehyde [(*S*)-**8**][18] giving, as was expected, (*R*,*R*)-**9** and (*R*,*R*,*R*)-**2c**, whose physical and spectral characteristics were identical to those of their enantiomers, except for their specific rotations.[19]

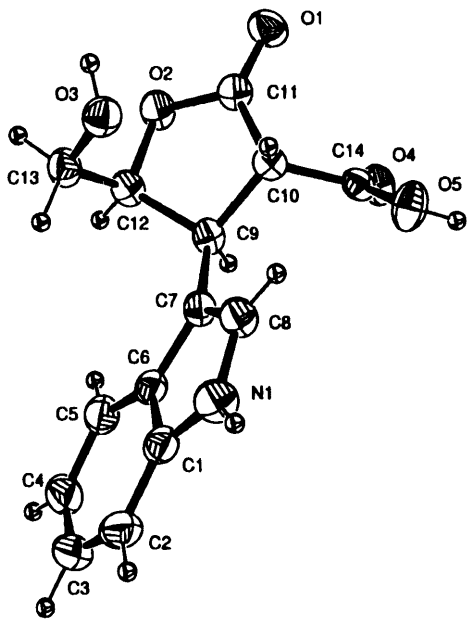


Figure 3.

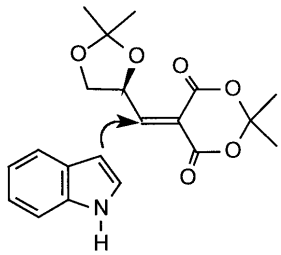


Figure 4.

In summary, a convenient and stereoselective procedure has been worked out for the synthesis of indolyl-substituted lactams and lactones of type **2**. We have shown that the chirality of the glyceraldehydes ensured complete enantiocontrol of the trimolecular condensation and in this way that of three contiguous chiral centres in **2c**. Further work involving other chiral aldehydes as well as the transformation of compounds **2** into **1** is in progress in our laboratory.

Acknowledgements

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11. All new compounds gave satisfactory microanalyses or high resolution mass spectra and spectral data. Selected data: Compound **2a**: mp 157°C; IR (KBr) 3410, 1771, 1738 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.01 (d, $J=10.8$ Hz, 1H), 4.35 (m, 2H), 4.78 (m, 1H), 7.04 (t, $J=8.0$ Hz, 1H), 7.14 (t, $J=8.0$ Hz, 1H), 7.38 (d, $J=2.0$ Hz, 1H), 7.40 (d, $J=8.0$ Hz, 1H), 7.67 (d, $J=8.0$ Hz, 1H), 11.11 (s, 1H), 13.2 (br s, 1H); HRMS (EI): M^+ found 245.0679. $C_{13}H_{11}NO_4$ requires: 245.0685. Compound **2b**: mp 195°C; IR (KBr) 3385, 1721, 1684 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.39 (t, $J=9.0$ Hz, 1H), 3.52 (d, $J=10.0$ Hz, 1H), 3.75 (t, $J=9.0$ Hz, 1H), 4.18 (m, 1H), 7.02 (t, $J=8.0$ Hz, 1H), 7.12 (t, $J=8.0$ Hz, 1H), 7.30 (s, 1H), 7.41 (d, $J=8.0$ Hz, 1H), 7.60 (d, $J=8.0$ Hz, 1H), 7.98 (s, 1H), 10.88 (s, 1H), 12.5 (br s, 1H); HRMS (EI): M^+ found: 244.0848. $C_{13}H_{12}N_2O_3$ requires: 244.0840.

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14. Compound (*S*,*S*)-**9**: mp 65°C; $[\alpha]_D$ −33 ($c=1.22$, $CHCl_3$); IR (CH_2Cl_2) 3408, 1773, 1740 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.28 (s, 3H), 1.32 (s, 3H), 1.39 (s, 6H), 3.20 (s, 1H), 3.65 (t, $J=7.0$ Hz, 1H), 3.95 (t, $J=7.0$ Hz, 1H), 4.12 (d, $J=10.0$ Hz, 1H), 5.19 (m 1H), 6.87 (t, $J=8.0$ Hz, 1H), 6.98 (t, $J=8.0$ Hz, 1H), 7.18 (d, $J=2.0$ Hz, 1H), 7.28 (d, $J=8.0$ Hz, 1H), 7.68 (d, $J=8.0$ Hz, 1H), 10.52 (s, 1H); HRMS (EI): M^+ found 373.1549. $C_{20}H_{23}NO_6$ requires: 373.1525.
15. Compound (*S*,*S*,*S*)-**2c**: mp 82°C; $[\alpha]_D$ +139 ($c=0.82$, MeOH); IR (KBr) 3410, 1769, 1736 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.24 (dd, $J=2.4$ and 12.3 Hz, 1H), 3.40 (dd, $J=1.8$ and 12.3 Hz, 1H), 4.28 (d, $J=12.0$ Hz, 1H), 4.49 (dd, $J=8.1$ and 12.0 Hz, 1H), 5.00 (br s, 1H), 5.08 (m, 1H), 7.05 (t, $J=8.0$ Hz, 1H), 7.14 (t, $J=8.0$ Hz, 1H), 7.30 (d, $J=2.0$ Hz, 1H), 7.41 (d, $J=8.0$ Hz, 1H), 7.68 (d, $J=8.0$ Hz, 1H), 11.10 (s, 1H); HRMS (FAB): M^+ found: 275.0800. $C_{14}H_{13}NO_5$ requires: 275.0794.
16. Crystallographic data for (*S*,*S*,*S*)-**2c**: $C_{14}H_{13}NO_5$; orthorhombic; cell parameters ($T=20$°C) $a=7.837(4)$ Å, $b=12.003(3)$ Å, $c=14.732(10)$ Å; $V=1386(1)$ $Å^{-3}$; space group: $P2_12_12_1$, $Z=4$, $R=0.033$, $R_w=0.076$ for refinements based on 1451 observed [$I>2.0\sigma(I)$] reflections. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-144787. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, [Fax: +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk.
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19. Compound (*R*,*R*)-**9**: $[\alpha]_D$ +35 ($c=1.27$, $CHCl_3$). Compound (*R*,*R*,*R*)-**2c**: $[\alpha]_D$ −137 ($c=0.84$, MeOH).