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Synthesis of chiral 2′,3′-pyranone(pyrrolidinone)-fused tryptamines

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Abstract—Chiral pyrano- and pyrrolidino-fused tryptamines were prepared by a diasteroselective trimolecular condensation between indole, Garner's aldehyde and Meldrum's acid, followed by selective functional group transformations.

The trimolecular condensation between indole, aldehydes and Meldrum's acid proved to be a versatile method for the preparation of conformationally constrained β-substituted tryptophans.[1]

When a chiral aldehyde, bearing a masked nucleophile function (e.g. 2,3-*O*-isopropylidene-D-glyceraldehyde) was used, trimolecular condensation and a subsequent deprotection–spontaneous cyclization sequence afforded the corresponding lactone acid (Scheme 1, **B**: X = Y = O) enabling the creation of two novel stereocenters with complete diastereocontrol.[2]

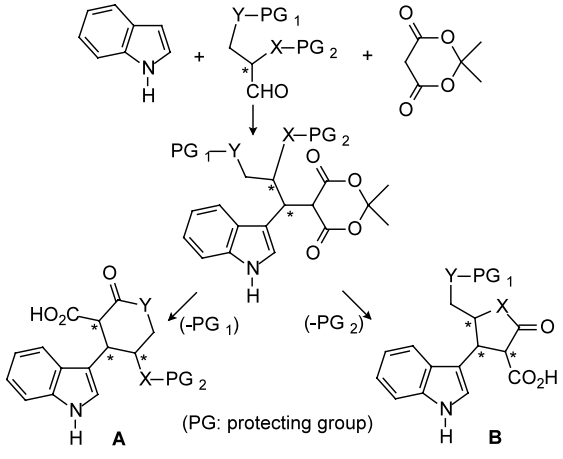
In continuation of our program toward non-natural tryptophan, tryptamine derivatives, we decided to investigate the control of newly created stereocenters by using orthogonally protected bifunctional chiral aldehydes. Depending on the conditions of deprotection chemoselective internal nucleophile ring opening of the Meldrum's acid core could be envisaged (Scheme 1).

Herein, we disclose an efficient enantioselective access to pyrano- **1** and pyrrolidino ring-substituted tryptamines **2**, based on a trimolecular condensation, followed by selective functional group transformations strategy (Scheme 2).

Such chiral, heterocycle fused tryptamines can be considered as valuable intermediates for the preparation of functionalized, conformationally restricted serotonin[3] and β-carboline[4] analogs of biological interest.

In accord with our synthetic objectives Garner's aldehyde **3**[5] and its modified analog **4**,[6] both readily available from L-serine, were chosen as chiral aldehydes.

Trimolecular condensation of indole **5**, with Meldrum's acid **6**, and Garner's aldehyde **3**, under standard conditions,[7] smoothly afforded the corresponding adduct **7**,[8] isolated by flash chromatography in 90% yield. ^{1}H



Scheme 1.

Keywords: multicomponent reaction; trimolecular condensation; Garner's aldehyde; diastereoselective synthesis; chiral tryptamine derivatives.

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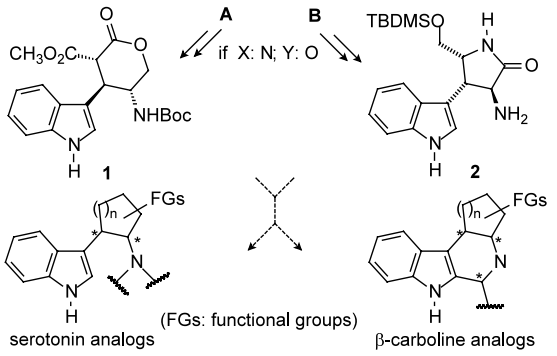
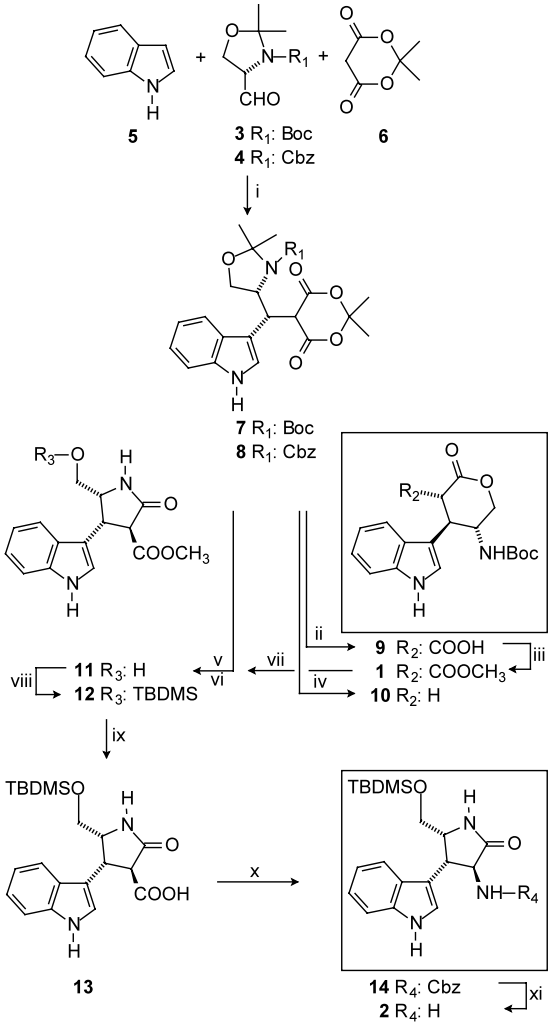


Scheme 2.



Scheme 3. *Reagents and conditions*: (i) CH_3CN, D,L-proline; (ii) CH_3OH, p-$TsOH_{(cat)}$; (iii) CH_2N_2, ether; (iv) AcOH–H_2O, reflux; (v) from **7**: (a) CH_3OH–HCl, reflux, (b) Et_3N; (vi) from **8**: H_2, Pd–C, EtOAc, AcOH; (vii) (a) TFA, CH_2Cl_2, (b) Et_3N; (viii) TBDMSCl, imidazole, CH_2Cl_2, DMF; (ix) (a) KOH_{aq}, THF, 0°C, (b) citric acid; (x) (a) DPPA, Et_3N, (b) BnOH, THF, reflux; (xi) H_2, Pd–C, EtOAc.

NMR analysis of **7** showed that the condensation step underwent with a high (>90%) diastereoselectivity (Scheme 3).

The absolute configuration of the newly created stereocenter was determined at a later stage of the synthesis, whereas the observed good diasteroselectivity could result from a selective *Re* face approach of indole on the Knoevenagel adduct (Fig. 1).

Similarly, modified Garner's aldehyde **4**, under the same conditions, gave the appropriate adduct **8** diastereoselectively (diastereomer ratio 95:5) in 68% yield.

Initially, selective isopropylidene deprotection of **7** was attempted in methanol containing catalytic amount of p-TsOH. After diazomethane-assisted esterification of the intermediate lactone acid **9**, diastereomerically pure N_b-protected pyrano-annulated tryptamine **1**[9] was isolated. For its formation an internal nucleophile attack of the primary alcohol on the Meldrum's acid moiety could be accounted. By longer heating in aqueous acetic acid the decarboxylated counterpart **10** was also prepared in 82% yield.

The configuration of **1** was determined by usual combination of NMR experiments. The observed coupling constant, $J_{H\text{-}3}$–$J_{H\text{-}4}$ = 11.6 Hz in **1** was in accordance with the H-3/H-4 *trans* relative stereochemistry, while the absolute configuration of C-4 carbon, created during the trimolecular condensation, was evidenced by NOE measurements. The strong interaction between irradiated NH and H-4, H-6 protons supported all equatorial positions for the three substituents and (*R*) absolute configuration of C-4 carbon (Fig. 2).

Treatment of **7** in boiling methanol–HCl led to diastereomerically pure lactam ester **11**, isolated by chromatography in 73% yield. Its formation can be explained by a full deprotection, selective internal nitrogen nucleophile ring closure sequence, followed by esterification of the resulting carboxylic acid.

Similarly, deprotection of the Cbz group by hydrogenolysis in ethanol containing acetic acid led to the same lactam ester **11**, isolated in 63% yield after methylation with diazomethane. The preferred lactamisation over lactonisation permitted to establish stereo-

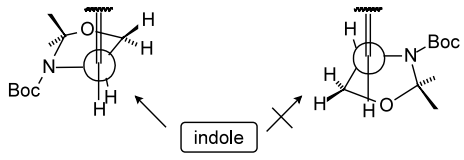


Figure 1.

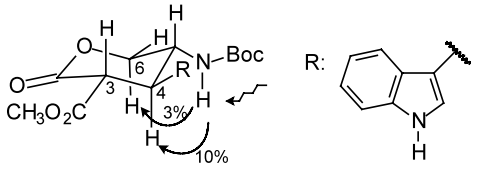


Figure 2. NOE measurements of **1**.

chemical correlation between the pyrano- and pyrrolidino-substituted series. Indeed, TFA-mediated cleavage of NBoc protection of **1** of known stereochemistry afforded the formerly prepared lactam ester **11**. Its depicted stereochemistry was confirmed on the basis of NOE experiments.

Prior to the classical conversion of carboxylic acid into carbamate some functional group transformations, e.g. protection of the primary alcohol to afford **12**, followed by hydrolysis of the ester function, were achieved. Acid function of **13** was transformed into carbamate **14** by diphenylphosphoryl azide assisted acyl azide formation, followed by Curtius rearrangement in the presence of benzyl alcohol, providing benzyl carbamate **14** in 80% overall yield. Final deprotection of **14** by hydrogenolysis led almost quantitatively to the aimed pyrrolidino tryptamine **2**.[10]

In conclusion, a highly enantioselective synthesis, based on a trimolecular condensation as a key-step, has been developed for the preparation of pyrano- and pyrrolidino-fused tryptamines (*R*,*R*,*R*)-**1** and (*S*,*S*,*R*)-**2**. We have shown that the chirality of the Garner's aldehyde ensured a complete and predictable enantiocontrol of the two newly created stereocenters. Application of functionalized tryptamines (**1** and **2**) to the synthesis of biologically active polycyclic compounds is in progress.

Acknowledgements

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8. All new compounds gave satisfactory spectral data. Selected data for **7**: $[\alpha]_D^{23}$ −1 (*c* 3.66, CH_2Cl_2); ^{1}H NMR (C_6D_6, 343 K): δ 1.20 (s, 3H), 1.47 (s, 3H), 1.71 (s, 9H), 1.83 (s, 3H), 2.05 (s, 3H), 4.17 (dd, 1H, J=9.3, 6.3 Hz), 4.46 (s, 1H), 4.98 (brs, 1H), 5.12 (brs, 1H), 5.34 (d, 1H, J=4.0 Hz), 7.38–7.52 (m, 4H), 7.86 s, 1H), 8.32 (d, 1H, J=5.2 Hz).
9. Selected data for (*R*,*R*,*R*)-**1**: $[\alpha]_D^{22}$ −19 (*c* 1.00, $CHCl_3$); mp 147–149°C; ^{1}H NMR (acetone-d_6): δ 1.26 (s, 9H), 3.51 (s, 3H), 3.95 (dd, 1H, J=11.6, 8.6 Hz), 4.22 (d, 1H, J=11.6 Hz), 4.30–4.38 (m, 2H), 4.63 (dd, 1H, J=10.8, 3.8 Hz), 6.46 (d, 1H, J=7.2 Hz), 7.03 (t, 1H, J=7.9 Hz), 7.11 (t, 1H, J=7.9 Hz), 7.31 (d, 1H, J=2.3 Hz), 7.39 (d, 1H, J=7.9 Hz), 7.70 (d, 1H, J=7.9 Hz), 10.23 (brs, 1H).
10. Selected data for (*S*,*S*,*R*)-**2**: $[\alpha]_D^{22}$ −211 (*c* 0.89, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ −0.13 (s, 6H), 0.81 (s, 9H), 2.23 (brs, 2H), 3.26 (m, 2H), 3.70 (dd, 1H, J=11.1 and 8.0 Hz), 3.90 (m, 1H), 3.98 (d, 1H, J=11.1 Hz), 6.58 (brs, 1H), 7.05–7.25 (m, 3H), 7.37 (d, 1H, J=7.9 Hz), 7.51 (d, 1H, J=7.8 Hz), 8.93 (brs, 1H).