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Conformationally Constrained Amino-Acids: Synthesis of Novel β, β-, 2,3-, and 3,4-Cyclised Tryptophans.

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Abstract: The synthesis of novel, conformationally constrained tryptophan mimetics is described.

The design and synthesis of unusual and unnatural amino-acids for incorporation into peptides and peptoids in order to confer conformational constraint, leading to potential improvements in biological activity, as well as increasing biostability, continues to be of great interest.[1-7]

We have previously published[8,9] the synthesis of a novel 3,4-cyclised tryptophan derivative for incorporation into a CCK-A antagonist.[10] We now wish to describe the synthesis of further tryptophan derivatives designed for incorporation into peptidomimetics.

Compounds **14** to **17** were synthesised by the route outlined in ***Scheme 1***. Protection of the indole nitrogen of commercially available 3-indoleacetonitrile using di-*tert*-butyl dicarbonate (Boc_2O) and DMAP in CH_2Cl_2 gave the precursor **1**. Ring-formation was carried out under two different conditions: dialkylation using sodium hydride in diethyl ether-DMSO with either 1,3-dibromopropane, 1,4-dibromobutane or 1,5-dibromopentane gave the 4-, 5- and 6- membered ring products respectively. However, for the 3-membered ring, use of NaH resulted in a very low yield of required product whereas use of LDA and 1,3-dichloroethane[11] was found to be more effective. In all cases, quenching with saturated ammonium chloride solution left the indole nitrogen protecting group intact, and this could be subsequently cleaved using either TFA in CH_2Cl_2 or by heating to 160°C. However, it was found to be more convenient to remove the Boc group *in situ* by quenching the dialkylation reaction with methanol and allowing to warm to room temperature to give compounds **2**, **3**, **4** and **5**.

Reduction of the nitrile to the corresponding imine by treatment with DIBAL-H at low temperature, followed by quenching (NH_4Cl) and hydrolysis with 2N H_2SO_4 gave the aldehydes **6**, **7**, **8** and **9** in good yields.[12]

Initial attempts to synthesise the amino-acids via the amino-nitriles formed by treatment[13] of aldehydes **6-9** with potassium cyanide in the presence of ammonium chloride and concentrated ammonia were not successful:

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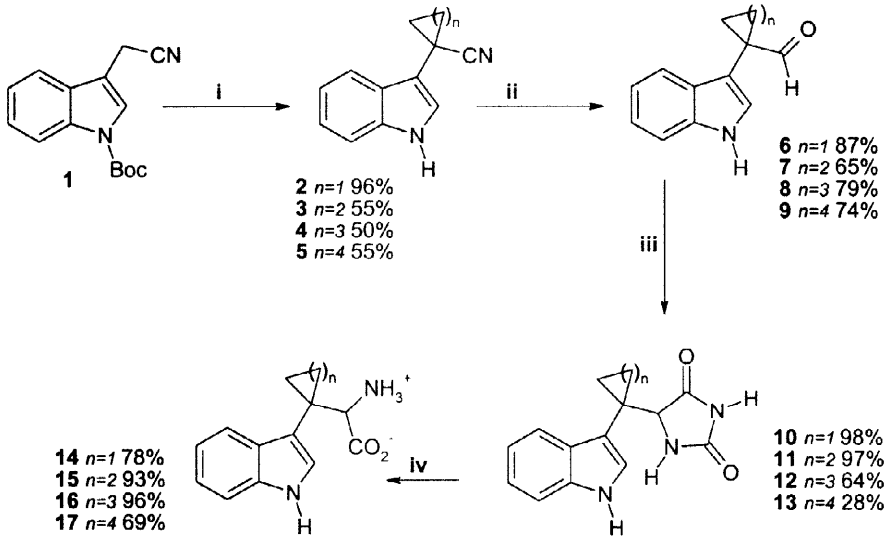
although the amino-nitriles were formed in good yield, the subsequent hydrolysis of the nitrile to the carboxylic acid was unsuccessful due to the degradation of the indole when subjected to the harsh conditions required.

Instead, compounds **6-9** were treated[13] with a mixture of ammonium carbonate and potassium cyanide in ethanol-water to give hydantoins **10, 11, 12** and **13** respectively.

Scheme 1.



Reagents and conditions: (i) see text; (ii) DIBAL-H, toluene, -50°C; then Et_2O-NH_4Cl (1:1) then 2N H_2SO_4; (iii) $(NH_4)_2CO_3$, KCN, ethanol-H_2O, 80°C; (iv) $Ba(OH)_2$, H_2O, 160°C, bomb; HCl; propylene oxide.

It has been reported[14,15] that hydantoins can be difficult to hydrolyse to the corresponding amino-acids and, considering the potential sensitivity of the indole nucleus to harsh hydrolytic conditions, several attempts to derivatise the hydantoin in order to make it more susceptible to mild hydrolysis were carried out. These involved appending tosyl[16] groups or Boc[17] groups to the hydantoin nitrogen atoms. However, these gave mixtures on which hydrolysis attempts proved to be low yielding. It was found that the best results were obtained by heating the hydantoin with water and $Ba(OH)_2$ at 160°C in a bomb for 12 hours. Converting the amino-acids to the HCl salts allowed for the easy separation of inorganic material, and the resulting compounds were then converted to the zwitterionic species **14, 15, 16** and **17** by treatment with propylene oxide.

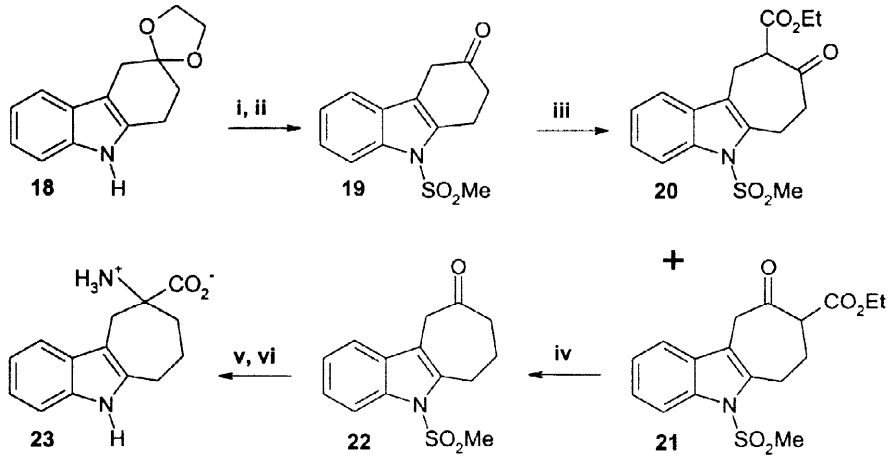
Having completed a successful route to the β,β-disubstituted tryptophan derivatives **14-17**, our attention focussed on the synthesis of the 2,3-cyclised tryptophan mimetic **23** (***Scheme 2***). The route to this amino-acid required the synthesis of a 7-membered ring ketone, and this was envisaged as coming from the corresponding 6-membered ring ketone by means of a ring-expansion reaction.

A Fischer-Indole[18] synthesis using commercially available 1,4-cyclohexanone monoethylene ketal gave indole **18** in 90% overall yield. Protection of the indole nitrogen with the methanesulfonyl group using ^{n}BuLi as base (78%), followed by hydrolysis of the acetal functionality (79%) gave cyclohexanone **19**, our precursor for the ring-expansion. The methanesulfonyl group was chosen as it was found that the more commonly used benzenesulfonyl protecting group was too stable to hydrolytic conditions at the end of the synthesis.

Additionally, leaving the indole nitrogen unprotected gave rise to complicated mixtures when the ring expansion was attempted.

The ring-expansion was carried out using ethyl diazoacetate with triethyloxonium tetrafluoroborate as Lewis acid catalyst to yield the regioisomers **21** (42%) and **20** (28%). Use of $TMSCHN_2$ gave mixtures of compounds, including exocyclic epoxides and multiple ring expansion products. Decarboxylation gave ketone **22,** which was then treated in an identical manner to the aldehydes **6-9** to yield, after N-deprotection, the amino-acid **23**.

Scheme 2.



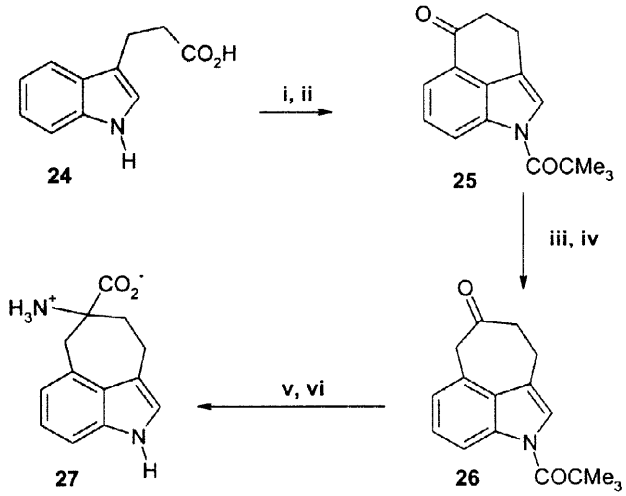
Reagents and conditions: (i) ^{n}BuLi, THF, -78°C; then $MeSO_2Cl$; 78% (ii) pTsOH, acetone-H_2O, reflux, 79%; (iii) $EtO_2CCH(N_2)$, $Et_3O^+BF_4^-$, CH_2Cl_2, 0°C, 42%; (iv) 10% H_2SO_4, reflux, 59%; (v) $(NH_4)_2CO_3$, KCN, ethanol-H_2O, 80°C, 80%; (vi) $Ba(OH)_2$, H_2O, 160°C, bomb; HCl; propylene oxide, 82%.

In order to further investigate the use of ring-expansion reactions in the synthesis of tryptophan mimetics, we also synthesised the novel 3,4-cyclised amino-acid **27** from the corresponding 3,4-cyclised 6-membered ring ketone (***Scheme 3***).

The precursor for the ring-expansion, ketone **25,** was synthesised by means of an intramolecular Friedel-Crafts acylation.[19,20] Thus, protection of 3-indole propionic acid **24** with the pivaloyl group was followed by conversion of the carboxylic acid to the acid chloride with thionyl chloride. Treatment with aluminium chloride and chloroacetyl chloride resulted in an intramolecular Friedel-Crafts acylation reaction at C-4 of the indole ring. Under these conditions, importantly, no product was detected from the competing acylation at C-2.[20] Ring expansion with $TMSCHN_2$ was now successful in the presence of triethyloxonium tetrafluoroborate to give ketone **26** (63%). After removal of the pivaloyl protecting group, ketone **26** was treated in an identical manner to the aldehydes **6-9** to yield amino acid **27**.

In conclusion, we report here the synthesis of novel mimetics of the amino-acid tryptophan: compounds **14-17** comprise a novel set of β,β-disubstituted tryptophan derivatives; and **23** and **27** as novel 2,3- and 3,4-cyclised tryptophan derivatives. Their incorporation into peptidomimetics of interest and the biological activity of such compounds will be reported shortly.

Scheme 3.



Reagents and conditions: (i) ^{n}BuLi, Me_3COCl, -78°C, 89%; (ii) $SOCl_2$, then $AlCl_3$, $ClCH_2COCl$, 88%; (iii) Me_3SiCHN_2, $Et_3O^+ BF_4^-$, 63%; (iv) 0.1N NaOMe, 0°C, 19% (v) KCN, $(NH_4)_2CO_3$, ethanol-H_2O, 33%; (vi) $Ba(OH)_2$, H_2O, 160°C, bomb, 82%.

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References and Notes.

1. Han, Y.; Liao, S.; Qiu, W.; Cai, C.; Hruby, V.J., *Tetrahedron Lett.*, **1997**, *38*, 5135.
2. Gibson, S.E.; Guillo, N.; Kalindjian, S.B.; Tozer, M.J., *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1289.
3. Gibson, S.E.; Guillo, N.; Middleton, R.J.; Thuillie, A.; Tozer, M.J., *J. Chem. Soc., Perkin Trans. I*, **1997**, 447.
4. Gibson, S.E.; Middleton, R.J., *J. Chem. Soc., Chem. Commun.*, **1995**, 1743.
5. Haskell-Luevano, C.; Boteju, L.W.; Miwa, H.; Dickinson, C.; Gantz, I.; Yamada, T.; Hadley, M.E.; Hruby, V.J., *J. Med. Chem.*, **1995**, *38*, 4720.
6. Bruncko, M.; Crich, D., *J. Org. Chem.*, **1994**, *59*, 4239.
7. Eden, J.M.; Hall, M.D.; Higginbottom, M; Horwell, D.C.; Howson, W.; Hughes, J.; Jordan, R.E.; Lewthwaite, R.A.; Martin, K.; McKnight, A.T.; O'Toole, J.C.; Pinnock, R.D.; Pritchard, M.C.; Suman-Chauhan N.; Williams, S.C. *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 2617.
8. Horwell, D.C.; Nichols, P.D.; Roberts, E., *Tetrahedron Lett.*, **1994**, *35*, 939.
9. Horwell, D.C.; Nichols, P.D.; Ratcliffe, G.S.; Roberts, E., *J. Org. Chem.*, **1994**, *59*, 4418.
10. Nichols, P.D.; PhD Thesis, Cambridge University, **1994**.
11. Agawa, T., *J. Chem. Soc., Perkin Trans. I*, **1981**, 751.
12. Hayashi, M.; Yoshiga, T.; Oguni, N., *Synlett*, **1991**, 479.
13. Taylor, J.B.; Lewis, J.W.; Jacklin, M., *J. Med. Chem.*, **1970**, *13*, 1226.
14. Klosterman, H.J.; Painter, E.P., *J. Am. Chem. Soc.*, **1947**, *69*, 2009
15. Nyberg, D.D.; Christensen, B.E., *J. Am. Chem. Soc.*, **1957**, *79*, 1222.
16. Hiroi, K.; Achiwa, K.; Yamada, S-I., *Chem. Pharm Bull.*, **1968**, *16*, 444.
17. Kubik, S.; Meissner, R.S.; Rebek, J., *Tetrahedron Lett.*, **1994**, *35*, 6635.
18. Britten, A.; Lockwood, G., *J. Chem. Soc., Perkin I*, **1974**, 1824.
19. Teranishi, K.; Hayashi, S.; Natasuka, S-I.; Goto, T., *Tetrahedron Lett.*, **1994**, *35*, 8173.
20. Teranishi, K.; Hayashi, S.; Natasuka, S-I.; Goto, T., *Synthesis*, **1995**, 509.