cis- and *trans*-3-(3-Indolyl)proline Derivatives as Conformationally Restricted Analogues of Tryptophan

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Received 11 February 1999

Abstract: A method for the diastereoselective generation of 3-indolyl-3-proline derivatives has been developed. The [3+2] cycloaddition reaction of 3-vinylindoles with dimethyl *N*-ethoxycarbonyl-*N*-methoxymethylaminomalonate in the presence of $TiCl_4$, afforded the title compounds after acid hydrolysis and decarboxylation reactions. These new amino acids may be viewed as conformationally restricted mimetics of tryptophan.

Key words: constrained amino acids, tryptophan analogue, 3-(3-indolyl)prolines, cycloaddition, azomethine ylide

The incorporation of constrained α-amino acids into peptides is an important approach to understand their bioactive conformations.[1] The use of proline as a template in order to introduce conformational restrictions is well known.[2] In this vein, *cis*- and *trans*-3-substituted proline analogues have been investigated, which retain the side chain moieties of standard amino acids. Thus, 3-*n*-propylproline **1**, 3-phenylproline **2a,b** and 3-carboxyproline derivatives **3a-c** have been prepared as constrained analogues of norleucine (Nle), phenylalanine (Phe), tyrosine (Tyr), aspartic acid (Asp), glutamic acid (Glu) and glutamine (Glut) respectively (Fig.1).[3] To the best of our knowledge, some tryptophan mimetics have been already described, and five main modifications of tryptophan have been synthesized through a cyclisation between: a) the tryptophan α-carbon and the indole ring; [4a] b) the amino group and the indole ring; [4b] c) the carboxyl group and the β-position; [4c] d) the α- and β-positions; [4d] e) β- and β-positions.[4e] None of these tryptophan mimetics have a proline as template. In the present paper, we describe the synthesis of novel *cis*- and *trans*-3-(3-indolyl)proline derivatives **4** (Fig.1).

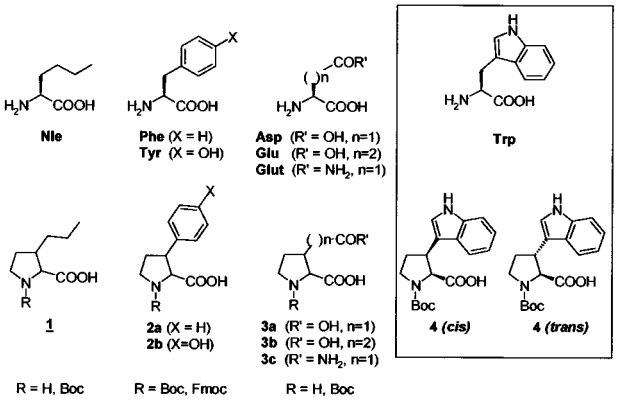
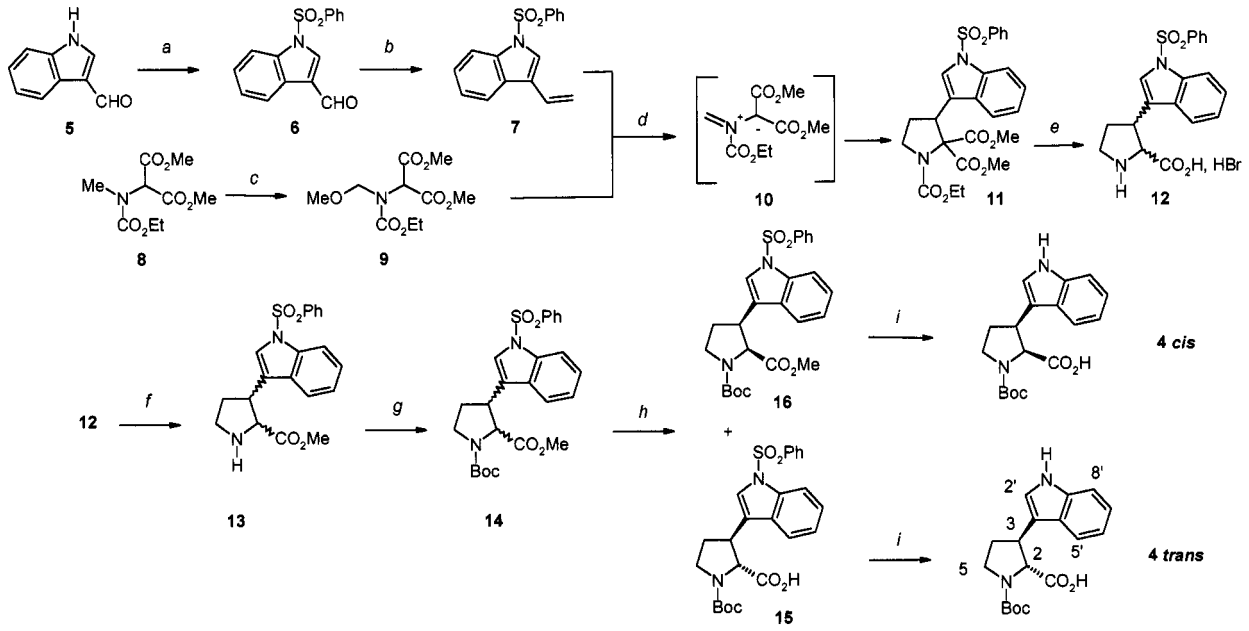


Figure 1. Conformationally constrained analogues of norleucine, phenylalanine, tyrosine, aspartic acid, glutamic acid and glutamine.

As depicted in Scheme 1, the synthetic approach is based on a [3+2] cycloaddition reaction of the 3-vinylindole derivative **7** with azomethine ylide **10** which was generated by acid treatment (Lewis acid) in the presence of the dimethyl *N*-ethoxycarbonyl-*N*-methoxymethylaminomalonate **9**.[5] Among the several methods examined with the aim to construct 3-(3-indolyl)proline skeleton, the [3+2] cycloaddition of **10** with the adequate olefinic dipolarophile **7** has been chosen due to its high regioselectivity in multigram scale preparation.

According to the procedure described by Pindur *et al.*,[6] treatment of the commercially available indolyl-3-carboxaldehyde **5** with sulfonyl chloride gave **6** in 98% yield which was then treated with triphenylmethylphosphonium bromide through a Wittig-olefination reaction under standard reaction conditions affording pure **7** in 93% yield. With **7** in hand, we turned our attention to the synthesis of the pyrrolidine derivative **11** by regioselective [3+2] cycloaddition reaction with the betaine **10** which was generated *in situ* from **9** in the presence of $TiCl_4$ and TEA at reflux in 99% yield in a ~50g scale. The synthesis of the malonate derivative **9** was achieved through an anodic oxidation of **8** [7] in presence of methanol under the experimental conditions reported by Shono *et al.*[5,8] in 65% yield. We have found that the yield of the synthesis of **9** increases highly when the concentration of **8** is close to 0.8M in a mixture of methanol and acetic acid 98/2. Then, tandem deesterification-decarboxylation reaction of **11** was performed using conc. HBr (47%) in acetic acid to give **12** as a *cis*/*trans* epimeric mixture in a ~6/4 ratio (determined by ^{1}H-NMR, 300 MHz) in 97% yield. After esterification of **12** using a methanolic HCl solution (giving **13** with 63% yield) followed by *N*-Boc protection under standard experimental conditions afforded **14** as a mixture of the *cis*- and *trans*-3-(3-indolyl)proline methyl esters (~7/3 ratio, determined by ^{1}H-NMR, 300 MHz) in 72% yield. Selective saponification of **14** using 0.5N NaOH allowed separation into pure *cis*-3-(3-indolyl)proline methyl ester **16** and *trans*-3-(3-indolyl)proline **15** in 66% and 29% yield respectively. Finally, the target compounds were obtained by treatment with 3N NaOH affording pure **4** ***trans*** and **4** ***cis*** both in 99% yields.[9]



Scheme 1. Synthesis of 3-(3-indolyl)proline derivatives **4** ***trans*** and **4** ***cis***.

a) 5 (0.5 mol), $PhSO_2Cl$ (0.75 mol), K_2CO_3 (2 mol), MEC (1.5L), reflux, 2 h, 98% **b)** $(Ph_3)_3PCH_3^+Br^-$ (0.19 mol), THF (1L), *n*BuLi (1.6 M, 0.19 mol), -10°C to rt for 3.5 h then **6** (0.17 mol), rt, 12 h then flash chromatography on silica gel[10] (CH_2Cl_2), 93% **c) 8** (38 mmol), undivided cell, platinum-plate anode (cylinder surface : 47cm^2), carbon rod cathode (diameter : 1cm), solvent : MeOH/AcOH 98/2 (50mL), supporting electrolyte : 0.1M TFBTBA, 15 F/mol with constant current : 2.5A, 9 h, rt, then 0.1M $NaHCO_3$ (35mL), flash chromatography on silica gel (cyclohexane/AcOEt 85/15), 65% **d) 9** (0.34 mol), $TiCl_4$ (0.34 mol), **7** (0.17 mol), TEA (0.17 mol), CH_2Cl_2 (2L), reflux, 1.5 h then flash chromatography on silica gel[10] (cyclohexane/CH_2Cl_2/AcOEt 45/45/10), 99% **e) 11** (92 mmol), HBr (47%)/AcOEt 1/1 v/v (1L), reflux, 12 h, 97% (*cis*/*trans* isomer ratio ~6/4, ^{1}H-NMR, 300 MHz, DMSO-d_6) **f) 12** (0.13 mol), MeOH (2L), H_2SO_4 (95%) (31 mL), reflux, 12 h, flash chromatography on silica gel[10] (CH_2Cl_2/MeOH 95/5), 63% (*cis*/*trans* isomer ratio 7/3, ^{1}H-NMR, 300 MHz, DMSO-d_6) **g) 13** (0.1mol), Boc_2O (0.14 mol), MeOH (1.8 L), $NaHCO_3$ (0. 36 mol), rt, 12 h, flash chromatography on silica gel[10] (cyclohexane/AcOEt 70/30), 72% (*cis*/*trans* isomer ratio 7/3, ^{1}H-NMR, 300 MHz, DMSO-d_6) **h) 14** (78 mmol), 0.5N NaOH (154 mL), THF (154 mL), precipitation of **16** (66%) then acidification of the aq. phase (1N HCl, pH = 4) and extraction with AcOEt: **15** (29%) **i) 15** or **16** (48 mmol), 3N NaOH (350 mL), MeOH (700 mL), reflux, 12 h, **4** ***trans*** , **4** ***cis***: 99%.

In conclusion, we describe herein a new approach for the construction of original *cis*- and *trans*-3-(3-indolyl)proline derivatives **4** ***cis*** and **4** ***trans*** that utilises the [3+2] cycloaddition reaction of the 3-vinylindole derivative **7** with azomethine ylide **10** as the key step. These two proline derivatives are the first two conformationally constrained tryptophan analogues. Preparation of a variety of 3-substituted proline derivatives may be envisioned using this route.

Acknowledgement

We wish to thank G. Doerflinger, I. Gozzi, P. Hubert, R. Poulain, A. Renaudon and J-C. Szmigel for technical assistance.

References and Notes

(1) For excellent reviews, see: Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bös, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Khan, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. E., *J. Med. Chem.*, **1993**, *36*, 21, 1 ; Khan, M., *Tetrahedron*, **1993**, *49*, 17, 3432 ; Abell, A. *Advances in Amino acid mimetics and Peptidomimetics*, Eds : Jai Press Inc., **1997** and references cited therein.

(2) For reviews, see: Hirschmann, R. ; Veber, D. F. *Bioorg. Chem.* **1978**, *7*, 447 ; Toniolo, C. *Int. J. Protein Res.*, **1990**, *35*, 287 ; Arison, B. H. and references cited therein.

(3)a) For conformationally restricted proline analogues of norleucine, see: Chung, J. Y. L.; Wasicak, J. T.; Arnold, W. A.; May, C. S.; Nadzan, A. M.; Holladay, M. W.; *J. Org. Chem.*, **1990**, *55*, 270; Moss, W. O.; Bradbury, R. H. ; Hales, N. J.; Gallagher, T. ; *Tetrahedron Lett.*, **1990**, *31*, 39, 5653; utilisation of *trans*-3-*n*-propyl-L-proline as a methionine analogue, see : : Holladay, M. W.; Lin, C. W.; May, C. S.; Garvey, D. S.; Witte, D. G.; Miller, T. R.; Wolfram, C. A. W.; Nadzan, A. M.; *J. Med. Chem.*, **1991**, *34*, 455 ; Sasaki, N. A. ; Dockner, M. ; Chiaroni, A. ; Riche, C. ; Potier, P.; *J. Org. Chem.*, **1997**, *62*, 765.

b) For conformationally restricted proline analogues of phenylalanine, see: Belokon, Y. N.; Bulychev, A. G.; Pavlov, V. A.; Fedorova, E. B. ; Tsyryapkin, V. A.; Belikov, V. M.; *J. Chem. Soc. Perkin Trans 1*, **1988**, 2075; Sarges, R. ; Tretter, J. R. *J. Org. Chem.* **1974**, *39*, 12, 1710 ; Chung, J. Y. L.; Wasicak, J. T.; Arnold, W. A.; May, C. S.; Nadzan, A. M.; Holladay, M. W.; *J. Org. Chem.*, **1990**, *55*, 270; Holladay, M. W. ; Lin, C. W.; May, C. S.; Garvey, D. S.; Witte, D. G.; Miller, T. R.; Wolfram, C. A.; Nadzan, A. M.; *J. Med. Chem.*, **1991**, *34*, 457.

c) For conformationally restricted proline analogues of tyrosine, see : Waid, P. P.; Flyn, G. A.; Huber, E. W.; Sabol, J. S.; *Tetrahedron Lett.*, **1996**, *37*, 24, 4091.

d) For conformationally restricted proline analogues of aspartic acid and glutamic acid, see: Chung, J. Y. L.; Wasicak, J. T.; Arnold, W. A.; May, C. S.; Nadzan, A. M.; Holladay, M. W.; *J. Org. Chem.*, **1990**, *55*, 270 ; Moss, W. O.; Bradbury, R. H. ; Hales, N. J.; Gallagher, T. ; *Tetrahedron Lett.*, **1990**, *31*, 39, 5653 ; Hashimoto, K. ; Yamamoto, O. ; Horikawa, M. ; Ohfune, Y. ; Shirahama, H. ; *Bioorg. & Med. Chem. Lett.*, **1994**, *4*, 15, 1851; Sasaki, N. A.; Pauly, R.; Fontaine, C.; Chiaroni, A.; Riche, C.; Potier, P.; *Tetrahedron Lett.*, **1994**, *35*, 2, 241 ; Carpes, M. J. S.; Miranda, P. C.; Correia, C. R.; *Tetrahedron Lett.*, **1997**, *38*, 11, 1869.

e) For conformationally restricted proline analogues of glutamine, see: Sabol, J. S. S.; Flynn, G. A.; Friedrich, D.; Huber, E. W.; *Tetrahedron Lett.*, **1997**, *38*, 21, 3687.

(4) For a recent review on conformationally constrained analogues of Phe, Tyr, Trp and His, see: Gibson, S. E. ; Guillo, N. ; Tozer, M. J. *Tetrahedron*, **1999**, *55*, 585 and references cited therein a) Horwell, D. C. ; Nichols, P. D. ; Roberts, E. ; *Tetrahedron Lett.*, **1994**, *35*, 939 ; Horwell, D. C. ; Nichols, P. D. ; Ratcliffe, G. S. ; Roberts, E., *J. Org. Chem.*, **1994**, *59*, 4418 ; Irie, K. ; Iguchi, M., Oda, T. ;Suzuki, Y. ; Okuno, S. ; Ohigashi, H. ; Koshimizu, K. ; *Tetrahedron*, **1995**, *51*, 6255 ; Horwell, D.C. ; McKiernan, M. J. ; Naylor, D. ; Osborne, S. A. ; *Lett. Pept. Sci.*, **1998**, *5*, 143 b) Bruncko, M. ; Crich, D. ; *Tetrahedron Lett.*, **1992**, *33*, 6251 ; Chung, J. Y. L. ; Wasicak, J. T. ; Nadzan, A. M. ; *Synth. Commun.*, **1992**, *22*, 1039 ; Kozikowski, A. P. ; Ma, D. ; Pang, Y. P. ; Schum, P. ; Likic, V. ; Mishra, P. K. ; Macura, S. ; Basu, A. ; Lazo, J. S. ; Ball, R. G. ; *J. Am. Chem. Soc.*, **1993**, *115*, 3957 ; Zembower, D. E., Ames, M. M. ; *Synthesis*, **1994**, 1433 c) Rodriguez, R. ; Vinets, I. ; Diez, A. ; Rubiratta, M. ; *Synth. Commun.*, **1996**, *26*, 3029 ; Rodriguez, Diez, A. ; Rubiralta M., Giralt, E. ; *Heterocycles*, **1996**, *43*, 513 ; Dubois, L. ; Metha, A. ; Tourette, E. ; Dodd, R. H. ; *J. Org. Chem. ;* **1994**, *59*, 434 ; Hofmann, B. ; Dauban, P. ; Biron, J-P. ; Potier, P. ; Dodd, R. H. ; *Heterocycles*, **1997**, *46*, 473 d) Donati, D. ; Garzon-Aburbeh, A. ; Natalini, B. ; Marchioro, C. ; Pellicciari, R. ; *Tetrahedron*, **1996**, *52*, 9901 e) Horwell, D. C. ; McKiernan, M. J. ; Osborne, S. ; *Tetrahedron Lett.;* **1998**, *39*, 8729.
(5) Shono, T.; Terauchi, J.; Matsumura, Y.; *Chem. Lett.*, **1989**, 1963 and references cited therein
(6) Pindur, U.; Pfeuffer, L.; *Monatsh. Chem.*, **1989**, *120*, 157.
(7) Dimethyl-*N*-ethoxycarbonyl-*N*-methylaminomalonate **8** was prepared in two steps in 67% overall yield by the action of *N*-methylbenzylamine with diethylbromomalonate (EtOH, TEA, reflux, 3h) followed by hydrogenation (EtOH, $AcONH_4$, Pd(C), 40°C, 1h).
(8) Shono, T.; Matsumura, Y.; Onomura, O.; Yamada, Y.; *Synthesis*, **1987**, 1099.
(9) All new compounds gave satisfactory analytical and spectroscopic data (^{1}H NMR, IR, MS and elemental analysis). Representative data for the selected products obtained: **4** ***trans***: pale yellow solid; m.p. 212 °C ; IR (KBr) 3410 and 3275 (indole), 1725 (CO acid), 1675 (CO carbamate), 740 (indole) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz, 393 K) δ 7.6 (dd, J = 8 and 2, 1H, Hz, H5'), 7.35(dd, J = 8 and 2 Hz, 1H, H8'), 7.15 (s, 1H, H2'), 6.95-7.15 (m, 2H, H6' and H7'), 4.3 (d, J = 5 Hz, 1H, H2), 3.7 (m, 1H, H3), 3.40-3.65 (m, 2H, H5), 2.0-2.4 (two m, 2H, H4), 1.40 (s, 9H, *t*-Bu) ; MS (EI, 70ev) 330 (M^+), 286, 274, 229; Anal. Calc. $C_{18}H_{22}N_2O_4$: C, 65.43; H,6.71; N, 8.48; O, 19.37. Found : C, 65.1; H, 7.1; N, 8.2. **4** ***cis***: white solid; m. p. 229 °C ; IR (KBr) 3350 (indole), 1725 (CO acide), 1635 (CO carbamate), 737 (indole) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz, 393 K) δ 7.6 (dd, J = 8 and 2, 1H, Hz, H5'), 7.35 (dd, J = 8 and 2 Hz, 1H, H8'), 7.15 (s, 1H, H2'), 6.95-7.15 (m, 2H, H6' and H7'), 4.5 (d, J = 8.5 Hz, 1H, H2), 4.0 (m, 1H, H3), 3.75 (m, 1H, H5), 3.50 (m, 1H, H5), 2.(0 (m, 1H, H4), 2.30 (m, 1H, H4), 1.40 (s, 9H, *t*-Bu) ; MS (EI, 70ev) 330 (M^+), 286, 274, 229; Anal. Calc. $C_{18}H_{22}N_2O_4$: C, 65.43; H,6.71; N, 8.48; O, 19.37. Found : C, 65.1; H, 6.7; N, 8.2; O, 19.3. NMR assignments were secured by 2D COSY experiments while the relative stereochemistry was confirmed by nOe experiments performed on compounds **4** ***trans*** and **4** ***cis***: larger effects were observed between H2, H3 and H2' for the *trans* arrangement compared to the *cis* derivative.
(10) Silica gel 60 (0.063-0.2 mm), Merck.

Article Identifier:
1437-2096,E;1999,0,06,0786,0788,ftx,en;G07499ST.pdf