SYNTHESIS OF 3-AMINO-4-INDOLYL-2-PIPERIDONES: TRYPTOPHAN-DERIVED PSEUDODIPEPTIDES

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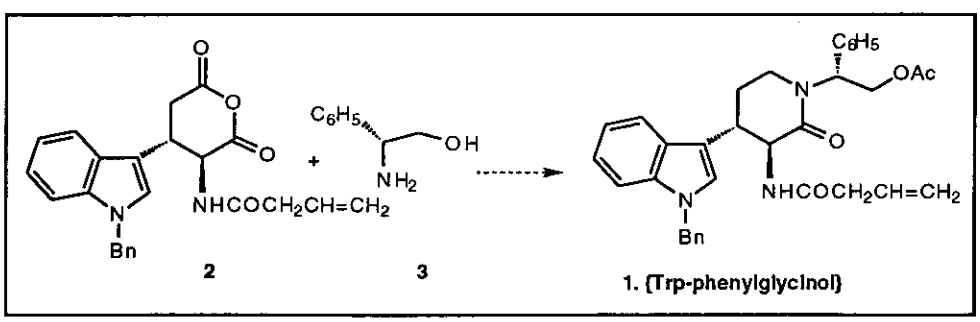
Abstract *– (αR,3R*,4R*)-N-*(2-Acetoxy-1-phenylethyl)-3-allyloxycarbonylamino-4-(1-benzyl-3-indolyl)-2-piperidone (**1**), a pseudodipeptide which contains a conformationally restricted analogue of tryptophan has been synthesized from anhydride (**2**) and (*R*)-(-)-phenylglycinol (**3**).

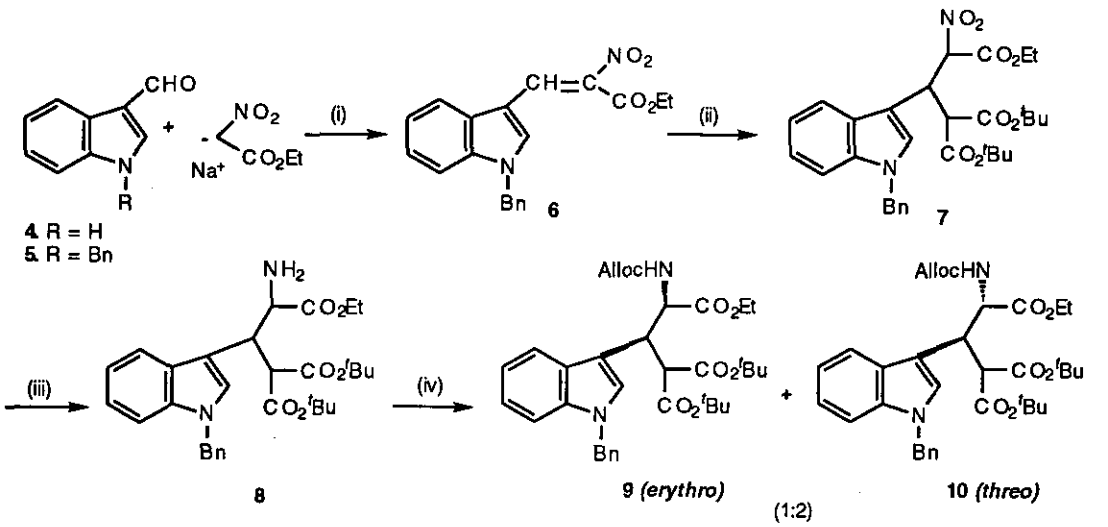
The study of pseudopeptides has two main goals: finding peptidomimetic molecules which can be used as drugs, and creating moieties, which once inserted in larger peptide chains of known activity, allow the study of the peptide structure-activity relationship.[1,2] Since several endogenous peptides involved in the regulation of key physiological processes such as somatostatin,[3] cholecystokinin (CCK),[4] or the luteinizing hormone-releasing hormone (LH-RH)[5] contain a tryptophan that is important in their receptor-binding site, we planned to prepare conformationally restricted analogues of this aminoacid. We thus designed structure (**1**), a Trp-phenylglycinol pseudodipeptide in which the tryptophan side chain (χ-l) is included in a 2-piperidone ring.[6]

In order to introduce a chiral center α with respect to the lactam nitrogen atom, the synthesis of compound



Scheme 1

(1) was planned by condensation of the conveniently functionalized anhydride (2) with *(R)*-(-)-phenylglycinol. Anhydride (2) was prepared from triester (10), which in turn was synthesized in four steps as indicated in Scheme 2. Thus, condensation of protected indole-3-carbaldehyde (5) with sodium ethyl nitroacetate gave indolylnitroacrylate (6), which was converted into the triester (7) by conjugate addition of the di-*tert*-butyl malonate monopotassium salt. At this point, the nitro group was reduced by hydrogenation in the presence of Raney Ni.[7] The resulting primary amines (8) were protected as the allyl carbamate (Alloc), and amino triesters *erythro*-9 and *threo*-10[8] were isolated by flash column chromatography in a 1:2 proportion.



Reagents and conditions: i) $TiCl_4$ (3 equivalents), pyridine (3 equivalents), THF, room temperature, 24 h (78%); ii) di-*tert*-butyl malonate (1.1 equivalents), ^tBuOK (1.1 equivalents), CH_2Cl_2, room temperature, 1 h, quenching with AcOH (87%); iii) W-2 Raney Ni, EtOH, H_2 (1 atm), 15 h (92%); iv) allyl chloroformate (1.2 equivalents), pyridine (1.2 equivalents), 0°C to room temperature, 1 h (87%).

Scheme 2

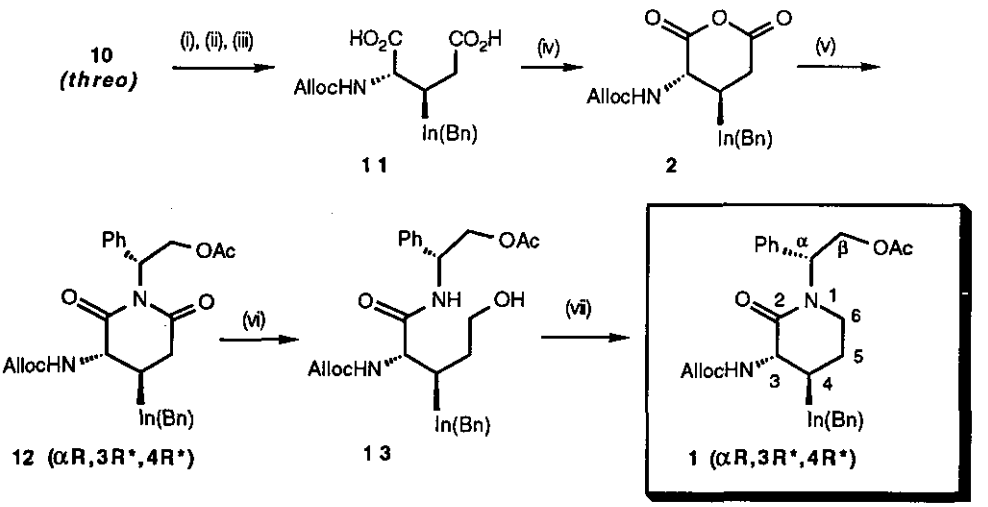
Treatment of triester (10) with TFA at 0°C allowed the selective hydrolysis of the *tert*-butyl esters in 80% yield (Scheme 3). The ethyl ester was cleaved subsequently with aqueous 5% KOH at room temperature and the decarboxylation was carried out by refluxing in 4N HCl to yield the *threo* diacid (11) (97% yield).[9] Further mesylation and Et_3N treatment of diacid (11) led to anhydride (2)[10] in 88% yield.

Condensation of racemic anhydride (2) with *(R)*-(-)-phenylglycinol[11] led to a complex mixture, from which only isomer (12)[12] was isolated by column chromatography, in 40% yield.[13] The structural assignment of compound 12 was confirmed by 2D nOe experiments, thus assuring the stereochemistry of the starting triester (10) and of anhydride (2).

The $NaBH_4$-2N HCl reduction of compound (**12**) occurred, as expected from glutarimides, in a regioselective manner upon the less hindered carbonyl group.[14] However, despite the reaction was carried out at low temperature, only hydroxy amide (**13**) was obtained, resulting from the reduction of the aldehyde generated by ring opening.

Finally, mesylation of hydroxyamide (**13**) and subsequent cyclisation using DBU led to the target lactam (**1**),[15] whose structural assignment was carried out by means of 2D nmr experiments.

With the synthesis of compound (**1**) as a model structure, a synthetic pathway which should be useful to prepare a great variety of tryptophan-derived pseudodipeptides has been established.



Reagents and conditions: i) TFA (5 equivalents), CH_2Cl_2, 0°C to room temperature, 48 h (white precipitate); ii) 5% aqueous KOH, dioxane, room temperature, 30 min; iii) 4N HCl, reflux, 4 h (78% in three steps); iv) MsCl (1 equivalent), Et_3N (3 equivalents), THF, -20°C, 2 h (88%); v) a. *(R)*-(-)-phenylglycinol (1 equivalent), reflux, 24 h. b. AcCl (excess) reflux, 4 h (40%); vi) $NaBH_4$ (5.5 equivalents), EtOH-THF, 2N HCl (3 drops every 15 min), -40°C, 2 h (70%); vii) a. MsCl (1 equivalent), Et_3N (1 equivalent), THF, -40°C, 2 h, hexane, filtration. b. DBU (1.2 equivalents), MeCN, room temperature, 1 h (26%).

Scheme 3

ACKNOWLEDGEMENTS

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5. F. Haviv, C. A. Palabrica, E.N. Bush, G. Diaz, E.S. Johnson, S. Love, and J. Greer, *J. Med. Chem.*, 1989, **32**, 2340.

6. A similar variation had been described for phenylalanine rigidified analogues used in a study of renin inhibitors: S.E. Laszlo, B.L. Bush, J.J. Doyle, W.J. Greenlee, D.G. Hangauer, T.A. Halgren, R.J. Lynch, T.W. Schorn, and P.K.S. Siegl, *J. Med. Chem.*, 1992, **35**, 833.

7. When the reduction was carried out on the triethyl triester analogue of **7**, spontaneous intramolecular lactamization was observed.

8. (**10**): Ir (NaCl) 3430 (NH), 1740 and 1728 (C=O) cm^{-1}. ^1H Nmr 0.95 (s, 9H, CCH_3), 1.05 (t, J = 7 Hz, 3H, CH_3CH_2), 1.50 (s, 9H, CCH_3), 3.49 (d, J = 5.3 Hz, 1H, CHCO), 3.98 (q, J = 7 Hz, 2H, CH_3CH_2), 4.23 (dd, J = 12 and 6 Hz, 1H, CH-In), 4.58 (d, J = 5.6 Hz, 2H, CH_2CH=), 4.99 (dd, J = 8.2 and 6.4 Hz, 1H, CHNH), 5.27 (s, 2H, CH_2Ph), 5.20-5.40 (m, 2H, CH=CH_2), 5.90 (m, 1H, CH=CH_2), 7.0-7.4 (m, 9H, Ar-H), 7.76 (m, 1H, In-4H). ^{13}C Nmr 13.8 (CH_3), 27.1 and 27.8 (CCH_3), 37.9 (CH-In), 50.1 (CH_2Ph), 56.9 and 57.2 (*C*HNH and *C*HCO), 61.2 (CH_2CH_3), 65.7 (CH_2CH=), 81.2 and 81.9 ($C(CH_3)_3$), 109.6 (In-C7), 117.7 (In-C3a), 119.4 (In-C4), 119.6 (In-C5), 121.9 (In-C6), 126.8, 127.3, 127.6, 128.4, 128.6, 132.6, 135.8 (In-C7a), 137.1, 155.4 (CONH), 166.6 and 167.5 (COO), 171 (*C*OOEt). Ms (EI) *m/z* (%) 620 (M^+, 2), 562 (6), 491 (12), 434 (59), 278 (100), 91 (99), 57 (65). Anal. Calcd for $C_{35}H_{44}N_2O_8$: C, 67.72; H, 7.14; N, 4.51. Found : C, 67.82; H, 7.13; N, 4.26.

9. When the hydrolysis of triester (**10**) was assayed directly with 5% aqueous KOH, heating was necessary, and a diastereomeric mixture of the *threo* and *erythro* diacids (**11**) was obtained.

10. (**2**): Ir (NaCl) 1720 (C=O), 1650 cm^{-1} (C=C). ^1H Nmr 3.00-3.40 (m, 2H, CH_2CO), 3.95 (m, 1H, CH-In), 4.23 (d, J= 7 Hz, 2H, CH_2CH=), 4.68 (d, J = 6 Hz, 1H, CHNH), 5.00-5.50 (m, 4H, CH_2=CH and CH_2Ph), 5.80 (m, 1H, CH_2=CH), 6.90-7.30 (m, 9H, Ar-H), 7.60 (d, J = 8 Hz, 1H, In-4H). ^{13}C Nmr 31.8 (CHIn), 37.2 (CH_2CO), 49.9 (CH_2Ph), 55.8 (CHNH), 65.8 (CH_2CH=), 110.1 (In-C3a), 111.2 (In-C7), 117.4 (CH=CH_2), 118.5 (In-C4), 119.6 (In-C5), 122.14 (In-C6), 126.6, 127.3, 127.5, 128.5, 128.6 and 132.1 (Ph), 137.0 (In-C7a), 156.1 (CONH), 173.1 (CO), 174.2 (CO). Ms (EI) *m/z* (%) 418 (M^+, 7), 334 (14), 278 (58), and 91 (100). Ms (CI) 447 (M^++29) 432 (M^++14), 419 (M^++1).

11. J. Royer, H.-P. Husson, *Heterocycles*, 1993, **36**, 1493.

12. (**12**): $[\alpha]_D$ = -22.4 (c = 0.8, $CHCl_3$), Ir (NaCl) 1744 and 1696 (CO), 1539 (C=C) cm^{-1}. ^1H Nmr 2.01 (s, 3H, $COCH_3$), 2.75 (dd, *J* = 17.5 and 4 Hz, 1H, 5-H), 3.21 (dd, *J* = 17.5 and 8.5 Hz, 1H, 5-H), 3.88 (m, 1H, 4-H), 4.24 (dd, *J* = 11.5 and 4.5 Hz, 1H, β-H_A), 4.38 (dd, *J* = 11.5 and 7.5 Hz, 1H, β-H_B), 4.59 (d, *J* = 3 Hz, 1H, 3-H); 4.68 (dd, *J* = 5.5 and 1 Hz, 2H, CH_2CH=), 5.22 (m, 1H, CH_2=CH), 5.24 (s, 2H, CH_2Ph), 5.34 (m, 2H, α-H and CH_2=CH), 5.83 (m, 1H, CH=CH_2), 6.95 (s, 1H, In-2H), 7.00-7.30 (m, 13H, Ar-H) and 7.55 (d, *J* = 8 Hz, 1H, In-4H). ^{13}C Nmr 20.8 ($COCH_3$), 32.5 (C-4), 38.3 (C-5), 50.1 (CH_2Ph), 52.9 (C-3), 65.9 (C-β), 67.0 (C-α), 67.6 (CH_2CH=), 110.3 (In-C7), 118.6 (CH=CH_2), 119.2 (In-C4), 119.9(In-C5), 122.7 (In-C6), 125.0 (In-C2), 126.7, 126.8, 127.8, 128.1, 128.8, 130.9 (CH=CH_2), 151.5 (CONH), 169.6 (CO), 171.4 (CO) and 173.1 (CO). Ms (EI) *m/z* (%) 579 (M^+, 4), 418 (4), 233 (7), 331 (8), 521 (11), 289 (13), 260 (35), 91 (100). Anal. Calcd for $C_{34}H_{33}N_3O_6$: C, 70.45; H, 5.74; N, 7.25. Found : C, 70.38; H, 5.65; N, 7.15.

13. The diastereomer of compound **12** was detected in the crude reaction mixture by nmr, but we could never isolate it.

14. W.N. Speckamp and H. Hiemstra, *Tetrahedron*, 1985, **41**, 4367.

15. (**1**): $[\alpha]_D$ = -19.6 (c = 0.5, $CHCl_3$), Ir ($CHCl_3$) 3450-3200 (OH), 1750, 1700 and 1620 (CO) cm^{-1}. ^1H Nmr (500 MHz) 1.62 (s, 3H, CH_3CO), 2.19-2.28 (m, 1H, 5-H), 2.70 (br t, *J* = 10.5 Hz, 1H, 5-H), 2.77 (dd, *J* = 10.5 and 7 Hz, 1H, β-H_A), 3.57 (td, *J* = 10.5 and 6.5 Hz, 1H, 6-H), 3.66 (dd, *J* = 10.5 and 2.5 Hz, 1H, β-H_B), 3.84-3.98 (m,2H, 4-H and 6-H), 4.50-4.60 (m, 3H, α-H and CH_2CH=), 4.68 (d, *J* = 8 Hz, 1H, 3-H), 5.26 and 5.35 (2d, *J* = 14 Hz, 1H each, CH_2Ph), 5.00-5.50 (m, 2H, CH_2=CH), 5.88-5.98 (m, 1H, CH_2=CH), 6.78 (br s, 2H, Ph-H), 7.01 (s, 1H, In-2H), 7.11-7.31 (m, 10H, Ar-H), 7.34 (d, *J* = 7 Hz, 1H, In-7H), 7.62 (d, *J* = 7 Hz, 1H, In-4H). ^{13}C Nmr 20.5 (CH_3), 27.3 (C-5), 39.0 (C-4), 45.8 (C-6), 50.1 (CH_2Ph), 51.6 (C-3), 63.9 (C-α), 64.9 (C-β), 65.9 (CH_2CH=), 110.6 (In-C7), 117.3 (CH_2=CH), 118.2 (In-C4), 119.9 (In-C5), 122.4 (In-C6), 126.1 (In-C2), 126.5, 126.9, 127.6, 127.7, 128.5, 128.5 and 128.6 (Ar and CH=), 169.5, 169.6 and 170.2 (CO). Ms (EI) *m/z* (%) 565 (M^+,8), 374 (8), 359 (30), 318 (41), 246 (15), 163(9), 91(100). Anal. Calcd for $C_{34}H_{35}N_3O_5$: C, 72.18; H, 6.24; N, 7.43. Found: C, 72.21; H, 5.98; N, 7.21.

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