Synthesis of Potential β-Turn Bicyclic Dipeptide Mimetics

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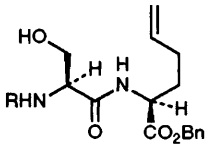
The syntheses of four diastereoisomeric bicyclic lactams, intended for analysis as β-turn-inducing mimetics, are described; the crystal structure of one derivative has been reported.

Several groups have shown an interest in conformationally restricted β-turn mimetics.[1–4] Studies have suggested that the conformations of many peptides bound to their receptors contain β-turns and some increases in potency and duration of action have been observed for bicyclic lactam β-turn-bearing (type II′ turn) analogues.[5] This communication reports the syntheses of four diastereoisomeric bicyclic dipeptide analogues (**3a,b, 6a,b, 9a,b, 12a,b**), from (*S*)-but-3-enylglycine,[6] and their derivatisation for analysis as β-turn dipeptide mimetics. On the basis of the previous studies by Nagai,[7] it was envisaged that **6** probably had most potential as a β-turn-inducing dipeptide mimetic; however, we wished to design a flexible synthesis to allow for the preparation of diastereoisomers of **6** for comparison.

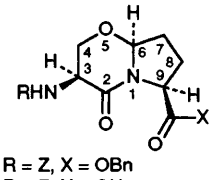
The precursor dipeptide **1a** was obtained from coupling Z-L-Ser-OH and(*S*)-but-3-enylglycine benzyl ester. Oxidative cleavage of the alkene **1a** with OsO_4 (cat.) and $NaIO_4$ (2 equiv.) gave a crude product mixture which was treated with acid [CF_3CO_2H (cat.), CH_2Cl_2, reflux] to give two isolated products (after chromatography) in a >8 : 1 mixture, assigned as **2a** and **5a** respectively on the basis of NOE studies (57% overall from **2a**). Substantial (>70%) conversion of the initially major product **2a** to the minor product **5a** could be effected by prolonged acid treatment (CF_3CO_2H).

Alkaline hydrolysis of **2a** [1 mol l^{-1} NaOH in tetrahydrofuran (THF)–H_2O (3 : 1)] gave two products assigned as **3a** and **12a**, on the basis of NOE studies and subsequent experiments. Thus, re-esterification of **3a** (benzyl bromide and Et_3N) gave **2a**, whilst re-esterification of **12a**, using the same conditions, gave a previously undetected diastereoisomer **11a**. Exposure of the free acid **3a** to base [1 mol l^{-1} NaOH in THF–H_2O (3 : 1)] resulted in conversion to its C-3 epimer **12a**. Further evidence for the assigned stereochemistry of **11a** was obtained by its synthesis from *Z*-D-serine-L-homoallylglycine **14a**. Thus, oxidative cleavage of **14a** with $NaIO_4$ (2 equiv.) and OsO_4 (cat.) followed by bicyclisation under acidic conditions afforded **8a** and **11a** in a >10 : 1 mixture (76% overall from **14a**). Again conversion of the initially major **8a** to the minor **11a** product could be effected by further acid treatment. The optical rotation of **11a**, prepared by this latter route {$[\alpha]_D$ = −69.4 (*c* = 0.9, $CHCl_3$)}, corresponded with that obtained from the product of re-esterification of **12a** {$[\alpha]_D$ = −71.0 (*c* = 1.1, $CHCl_3$)}, consistent with epimerisation (of **2a** or **3a**) at C-3 under basic conditions. Recrystallisation of **8a** from

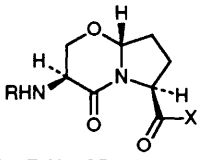
benzene allowed an X-ray crystal structure determination,† which confirmed the initial NOE assignments.



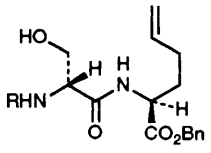
1a; R = Z
1b; R = Boc



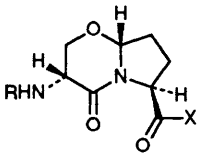
2a; R = Z, X = OBn
3a; R = Z, X = OH
2b; R = Boc, X = OBn
3b; R = Boc, X = OH
4; R = 2,4-$(NO_2)_2C_6H_4NHCOCH_2CO$, X = 4-$NO_2C_6H_4NH$



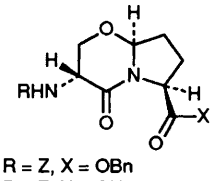
5a; R = Z, X = OBn
6a; R = Z, X = OH
5b; R = Boc, X = OBn
6b; R = Boc, X = OH
7; R = 2,4-$(NO_2)_2C_6H_4NHCOCH_2CO$, X = 4-$NO_2C_6H_4NH$



14a; R = Z
14b; R = Boc



8a; R = Z, X = OBn
9a; R = Z, X = OH
8b; R = Boc, X = OBn
9b; R = Boc, X = OH
10; R = 2,4-$(NO_2)_2C_6H_4NHCOCH_2CO$, X = 4-$NO_2C_6H_4NH$



11a; R = Z, X = OBn
12a; R = Z, X = OH
11b; R = Boc, X = OBn
12b; R = Boc, X = OH
13; R = 2,4-$(NO_2)_2C_6H_4NHCOCH_2CO$, X = 4-$NO_2C_6H_4NH$

Bn = $PhCH_2$; Z = $PhCH_2OC(:O)$, Boc = $Bu^tOC(:O)$

† *Crystal Data*, **8a**, $C_{23}H_{24}N_2O_6$, M_r = 424.452, orthorhombic, space group $P2_12_12_1$(No. 19), a = 6.334(1), b = 14.368(1), c = 23.608(2) Å, V = 2148.5 Å^3, Z = 4, D_c = 1.312 g cm^{-3}, Cu-Kα radiation, colourless transparent needle 0.3 × 0.3 × 0.6 mm, μ = 7.523 cm^{-1}. Data were collected on a CAD-4F diffractometer in ω–2θ mode, $0 < 2\theta \leq 144°$. 3992 unique reflections, of which 3292 were observed [$I \geq 3\ \sigma(I)$]. Data were corrected for absorption. Full-matrix least-squares refinement of positional and anisotropic thermal parameters for all non-hydrogen atoms; H-atom coordinates were calculated. A Flack enantiopole converged to a value of −0.3(3), consistent with the reported stereochemistry. At convergence R = 0.048, R_w = 0.065 for 281 parameters. The model reported gives only a single site for each of the atoms O(22), O(23) and C(21)–C(30), which have unusually high thermal parameters due to disorder over *at least* two sites. Further work is being undertaken to resolve the disorder.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

Deprotections of **2a** and **5a** under neutral conditions [$(Bu_3Sn)_2O$, toluene, reflux[8]] gave **3a** and **6a** respectively, apparently without epimerisation at C-3, albeit in low yield (*ca.* 35%). Saponification of both **8a** and **11a** with 1 mol l^{-1} NaOH in THF–H_2O (3:1) gave their free acids **9a** and **12a**, respectively (>95%). The low yielding deprotections of **2a** and **5a** were circumvented by use of a Boc protecting group. Thus, oxidative cleavage of **1b** and cyclisation of the resultant products, under acidic conditions, furnished the two bicyclic diasterioisomers **2b** and **5b** as a *ca.* 10:1 mixture (77% overall from **1b**), which on hydrogenolysis gave **3b** and **6b** respectively (>90%). Similarly, Boc-D-Ser-L-homoallylglycine **14b** was synthesised from Boc-D-Ser-OH and (*S*)-but-3-enylglycine benzyl ester. Oxidative cleavage of the double bond and cyclisation under acidic conditions furnished **8b** and **11b** in a >7:1 ratio, which on hydrogenolysis gave **9b** and **12b** respectively.

Previous studies have reported that tetrapeptides functionalised with Dnp (dinitrophenyl) and pNA (*para*-nitroanilide) at the N and C-termini respectively, which adopt a β-turn conformation, display a 'Cotton effect' in their CD spectra.[9] The bicyclic structures **3, 6, 9** and **12** were therefore similarly functionalised according to literature procedures.[7] Thus, for example the acid **6b** was coupled with glycine *para*-nitroanilide using diphenylphosphoryl azide. After removal of the Boc group the resultant N-terminus was functionalised with *N*-2,4-dinitrophenylglycine to give **7** (52% from **2b**). Similar procedures were followed for the functionalisation of mimetics **3, 9** and **12** to give **4, 10** and **13** respectively.

In summary, this communication describes the synthesis of the dipeptide mimetics **3, 6, 9** and **12** and their derivatisation for CD analysis. These diastereoisomers should be amenable to functionalisation by the use of modified amino acids. The evaluation of the potential of compounds **4, 7, 10** and **13** as β-turn dipeptide mimetics using the dichromophoric assay technique is presently in progress. In addition, incorporation of the dipeptide mimetics into biologically active peptides known to contain β-turns, *e.g.* gramicidin S, *via* solid phase synthesis will be the subject of future investigations.

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