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Synthesis of A Homochiral α,α-Disubstituted α,β-Diamino-acid

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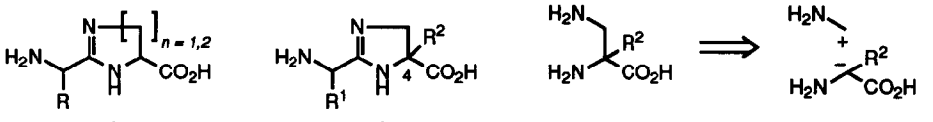
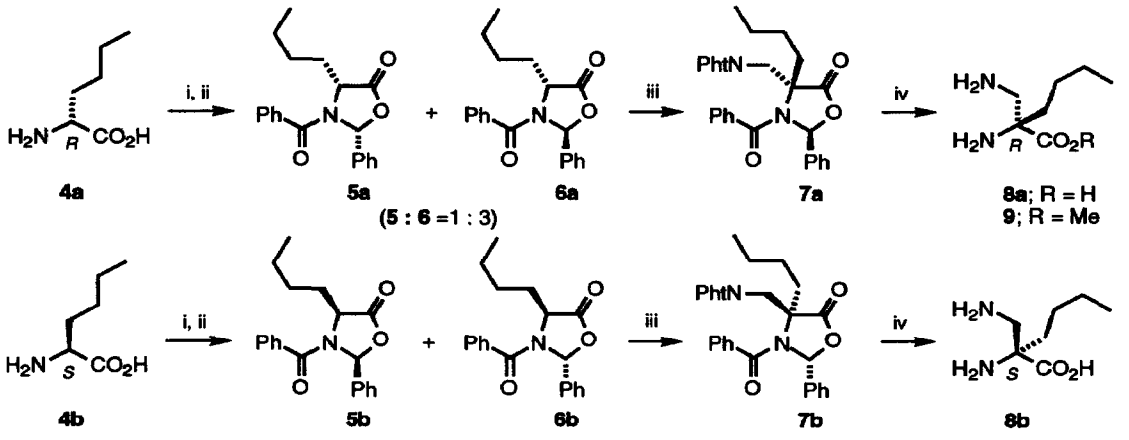
Abstract: The synthesis of a homochiral α,α-disubstituted α,β-diamino-acid is described from norleucine using stereospecific alkylation of a homochiral oxazolidinone enolate; an optically active pseudotetrapeptide analogue of CCK-4 is prepared to show an application of such diamino-acids.

We have reported on our programme of synthesis of cyclic amidine-containing amino-acids **1**, of interest both as pseudopeptides[1] (with amidine as an amide bond replacement) and as natural products (**1**; n = 2).[2] We wished to combine this strategy for peptide mimetics with the known ability of α,α-disubstituted amino-acids to limit conformational mobility,[3] for example to favour reverse turns, and thus defined cyclic amidines such as the 4(5)-substituted 4(5)-carboxyimidazolines **2** as targets. We further required these molecules to have a defined single configuration at the pseudo-α-centre, C-4. A preliminary target was therefore the stereodefined synthesis of α,α-disubstituted α,β-diamino-acids **3**. Our strategy, drawn out below, is the use of a homochiral amino-acid α-nucleophile synthon[4] with a C^+N electrophile. There is only one report of the use of these nucleophiles in α,β-diamino-acid preparation,[5] for the special case of proline with the very reactive iminium electrophile, $CH_2{=}N^+Me_2$. We report now our generally applicable preparation of an example of **3**, having $R^2 = (CH_2)_3Me$, as either pure enantiomer, and the application of one enantiomer for the assembly of a homochiral CCK-4 mimetic.



1 **2** **3**

We chose to use the oxazolidinone approach (Scheme 1). Thus *R*-norleucine **4a** was converted into the *N*-benzylidene imine (PhCHO, 1M NaOH aq.–EtOH; 95%), which on *N*-benzoylation (PhCOCl, CH_2Cl_2, –20°C) afforded the oxazolidinone (76%) as a mixture of two diastereoisomers **5a** and **6a** (1:3 by ^1H n.m.r. spectroscopic examination). Under these conditions of oxazolidinone assembly,[6,7] the major product is the *anti*-isomer **6a** which can be isolated pure (56%), $[\alpha]_D^{25}$ –201.4 (*c* 1.17 in $CHCl_3$) on recrystallisation of the



Scheme 1

Reagents: i, PhCHO, 1M NaOH aq.–EtOH; ii, PhCOCl, CH_2Cl_2, –20°C; then separate **5** and **6** by crystallisation; iii, 1M $LiN(SiMe_3)_2$, THF, –78°C → –65°C, N-bromomethylphthalimide; iv, 40% aq. HBr, reflux.

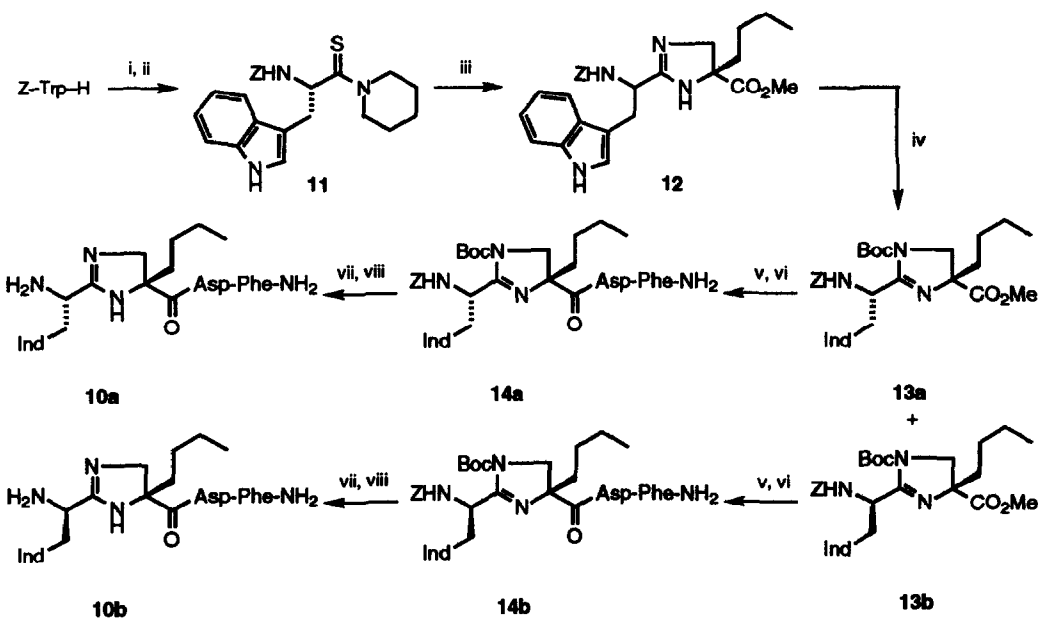
mixture.[8] The *anti* relative configuration of **6a** was confirmed by observation in the ^1H n.m.r. spectrum of n.O.e. enhancements of the signals at δ 1.45 and 1.75, CH_2, on irradiation of the signal at δ 6.9, C-2(H), and of the signal at δ 5.15, C-4(H), on irradiation at δ 7.4, Ar-H. The pure enantiomeric oxazolidinone **6b**, $[\alpha]_D^{23}$ +201.4 (*c* 1.02 in $CHCl_3$), was similarly prepared from *S*-norleucine **4b** *via* the imine (99%), acylation (75%) and crystallisation of **6b** (56%) from the 3:1 mixture with its epimer **5b**.

C(α)-Alkylation of the oxazolidinones was achieved under strongly basic conditions (lithium hexamethyldisilazide, THF, –78° → –65°C to ensure solution of the anion) with *N*-bromomethylphthalimide as electrophile; loss of the enolate orange colour evidenced alkylation. Thus oxazolidinone **6a** afforded 4,4-disubstituted derivative **7a** (89%), $[\alpha]_D^{23}$ –174.8 (*c* 1.0 in $CHCl_3$), whilst **6b** gave **7b** (88%), $[\alpha]_D^{25}$ +174.9 (*c* 0.55 in $CHCl_3$). That alkylation occurs *anti* to the 2-phenyl substituent[6] was confirmed by observation in the ^1H n.m.r. spectrum of, *inter alia*, an n.O.e. enhancement of the signals at δ 4.3 and 4.7 for the CH_2-phthaloyl protons on irradiation of the signal at δ 6.4, C-2(H), and *vice versa*. Thus aminoalkylation of the original norleucine residue has been accomplished with overall inversion. The α,α-disubstituted α,β-diamino-acid was liberated in one step by an acidic hydrolysis [40% w/v aq. HBr at reflux, 3h; then Amberlite IR-120(H)] that cleaved the heterocyclic ring and the *N*-benzoyl and *N*-phthaloyl protecting groups to give, respectively, *R*-enantiomer **8a** (86%), $[\alpha]_D^{25}$ +5.9 (*c* 1.01 in H_2O),[9] from **7a**, and *S*-enantiomer **8b** (86%), $[\alpha]_D^{27}$ –5.7 (*c* 0.28 in H_2O), from **7b**. The pure *R*-enantiomer **8a** was converted into the methyl ester hydrochloride salt (AcCl, MeOH, reflux 16 h; 2-3 successive treatments were required), and thence by basification ($NaHCO_3$ aq.) into the free diamino ester **9** (75%).[9]

The application of the optically pure α,α-disubstituted α,β-diamino-acid was illustrated by the conversion of *R*-enantiomer **8a** into an optically active pseudotetrapeptide Z-Trp-ψ[Im]Nle-Asp-Phe-NH_2 **10**, of interest as an analogue of CCK-4, the C-terminal tetrapeptide H-Trp-Met-Asp-Phe-NH_2 of cholecystokinin.[1b,10].

Thus the piperidine thioamide **11** was prepared (Scheme 2) from N^{α}-benzyloxycarbonyl-*S*-tryptophan as reported previously (72% overall). S-Methylation (MeI, neat, reflux 16 h) afforded a thioimidate that was treated directly with *R*-diamino-ester **9** (MeOH, reflux) to give the dihydroimidazole **12** as an inseparable 1:1 mixture of diastereoisomers, epimeric at the α-carbon centre of the tryptophan residue. Proton exchange at the C-atom attached to C-2 of dihydroimidazoles is well precedented.[1,11] Protection of the amidine ring (Boc_2O, $NaHCO_3$, aq. THF) to remove its basic/nucleophilic properties, was necessary for further reactions; chromatographic separation of the two diastereoisomers **13a/b** was then possible, and they were thereafter taken forward separately.[12,13] Quantitative hydrolysis at the C-terminus (0.1M LiOH aq.–THF) was followed by generation of an active ester (pentafluorophenol, DCC, EtOAc; 86% in each series) and coupling with H-Asp-Phe-NH_2 (Et_3N, DMF) to afford the separate protected pseudotetrapeptide diastereoisomers **14a/b** (97 and 62%, not necessarily respectively). Deprotection at the N-terminus (H_2, $Pd(OH)_2$, 50 psi; 98% in each series) and of the cyclic amidine (TFA, thioanisole & EtSH as cation scavengers; 84% in each series) afforded the separate pseudotetrapeptide isomers **10a** and **10b** as trifluoroacetate salts.[14]

We have thus demonstrated a stereoselective route to α-quaternary α,β-diamino-acids, useful in the assembly of modified peptides and analogues. The support of SERC and Parke-Davis Neuroscience Research Centre (studentship to A.K.C.) is gratefully acknowledged.



(Z = benzyloxycarbonyl; Boc = t-butoxycarbonyl; Ind = 3-indolyl)

Scheme 2

Reagents: i, pentafluorophenol, DCC, CH_2Cl_2, 0°C; then piperidine, 0°C; ii, Lawesson's reagent, toluene reflux; iii, MeI neat, reflux 16h; then diamino-ester **9**, MeOH, reflux 16h; iv Boc_2O, $NaHCO_3$, aq.–THF; then separation by column chromatography; v, 0.1M LiOH aq.–THF; vi, pentafluorophenol, DCC, EtOAc; then H-Asp-Phe-NH_2 Et_3N, DMF; vii, H_2, 50 psi, $Pd(OH)_2$ on C, MeOH; viii, TFA, thioanisole & ethanedithiol, 0°C → 25°C.

REFERENCES AND NOTES:

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3. See for example: Toniolo, C. *Janssen Chimica Acta*, **1993**, *11*, 10-16, and references therein.
4. For a survey of amino-acid enolate equivalents, see: Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford. 1989; pp. 1-95.
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7. The relative stereochemistry of the major oxazolidinone diastereoisomer in such cyclizations varies with the aldehyde, the acylating agent and the order of assembly of the components: *cf.* Seebach, D.; Fadel, A. *Helv. Chim. Acta*, **1985**, *68*, 1243-1250; Karady, S.; Amato, J. S.; Weinstock, L. M. *Tetrahedron Lett.*, **1984**, *25*, 4337-4340.
8. All new compounds gave spectral data (IR, UV, NMR, MS) in accord with the assigned structure, and satisfactory combustion analysis or accurate mass measurement.
9. Selected data for **8a**: ν_{max}/cm^{-1} 1600; δ_H (300MHz; D_2O) 1.1 (3H, t, CH_3), 1.4-1.6 (4H, m, 2 x CH_2), 1.85 (1H, m, CH_2CHHCN), 2.05 (1H, m, CH_2CHHCN), 3.25 (2H, dd, CH_2NH_2). For **9**: ν_{max}/cm^{-1} 3504 (NH), 2958, 1723 (CO); δ_H (300MHz; D_2O) 0.89 (3H, t, CH_3), 1.1-1.6 (6H, m, 3 x CH_2), 2.8 (2H, dd, CH_2NH_2), 3.75 (3H, s, OCH_3).
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12. The two isomers **13a** and **13b** were *diastereo*isomers, and a single *regio*isomer was formed with respect to the t-butoxycarbonyl (Boc) group. This was confirmed by acidic removal (TFA) of the Boc function from the separated isomers **13a** and **13b** which gave in each case a single product dihydroimidazole salt distinct from the other, i.e. the separate diastereoisomers of **12** (*cf.* also ref. 14). The location of the Boc protecting group (N-1 vs. N-3) is not yet known, and is drawn arbitrarily in Scheme 2 on the least hindered nitrogen atom.
13. It was not possible to determine which of the separated diastereoisomers **13a** and **13b** had the *S* and which the *R* configuration, at the tryptophan α-carbon centre.
14. Whilst the dihydroimidazoles **10** are kept as salts, no epimerisation takes place at the tryptophan α-carbon centre.

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