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A diastereoselective synthesis of the tetrahydropyridazinone core of 2-oxo-1,6-diazobicyclo[4.3.0]nonane-9-carboxylate-based peptidomimetics starting from (*S*)-phenylalanine

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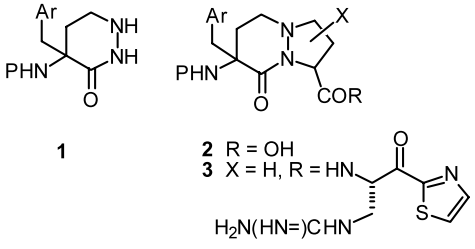
Abstract—A diastereoseletvive synthesis of a peptidic tetrahydropyridazinone **10** from (*S*)-phenylalanine is reported. This derivative was then converted to the bicyclic peptidomimetic **11**, an important class of β-strand mimetic.

The phenylalanine-based tetrahydropyridazinone ring system **1** is a synthetic precursor of 2-oxo-1,6-diazobicyclo[4.3.0]nonane-9-carboxylate dipeptidomimetic scaffolds **2** that are found in extended β-strand mimetics and other bioactives.[1–4] For example, bicycles **2** have been incorporated into peptide sequences to give extended β-strand mimetics of type **3** that inhibit serine proteases, including thrombin.[2–4] The idea of constraining a putative inhibitor molecule into an extended conformation in this way is an important and generic approach to protease inhibitor design.[5]



1

2 R = OH
3 X = H, R = HN

A preliminary report[3] suggests that the selectivity displayed by compounds of type **3**, for one protease over another, is influenced by the nature of the substituents (Ar and X) on the 2-oxo-1,6-diazobicyclo[4.3.0]nonane-9-carboxylate core. The recent screening of a library of such compounds against a range of serine proteases supports this observation with the identification of a number of potent and selective inhibitors.[4]

To date, key tetrahydropyridazinones of type **1** have only been synthesised as racemic mixtures.[2–4] The mixtures are then subjected to a regioselective 1,3-dipolar cycloaddition to give the racemic bicyclic peptidomimetics **2**.[2–4] A final extension of the peptide chain yields mixtures of diastereoisomeric β-strand mimetics that can be separated by HPLC.[2] This basic methodology has also recently been extended to the solid phase to provide access to small libraries of β-strand mimetics as mixtures of isomers. In this paper we present a diastereoseletvive synthesis of a peptidic tetrahydropyridazinone ring system of type **1** from (*S*)-phenylalanine (see compound **10**). This derivative was then converted to the bicyclic peptidomimetic **11** in what is the first enantioselective synthesis of this important class of β-strand mimetic.

The key to our synthesis is the use of chiral oxazolidinone chemistry pioneered by Seebach,[6] to generate the key α,α-dialkylated amino acid **7** (Scheme 1) which was then taken through the sequence shown in Scheme 2 to give **11**. The *N*-benzoyl protecting group was chosen for ease of access of the starting oxazolidinone **5**; however, it should be noted that Cbz-protected oxazolidinones of this type (albeit with the ring substituents *syn*) can also be prepared.[7,8]

The starting phenyloxazolidinone **5** was prepared in three steps from (*S*)-phenylalanine as previously described.[8] Deprotonation of **5** at C-4 with LiHMDS and alkylation of the resulting anion with allyl bromide gave the alkylated oxazolidinone **6**[9] as a single isomer by ^{1}H NMR and in excellent yield.[10] Subsequent hydrolysis of the oxazolidinone ring with NaOH in

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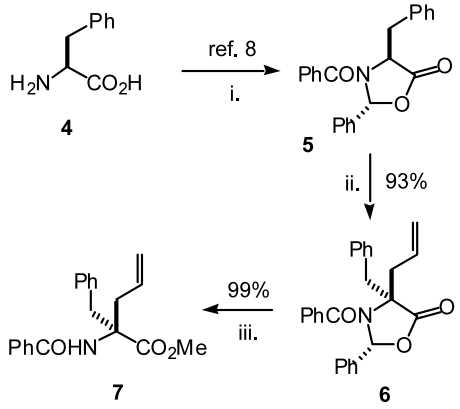
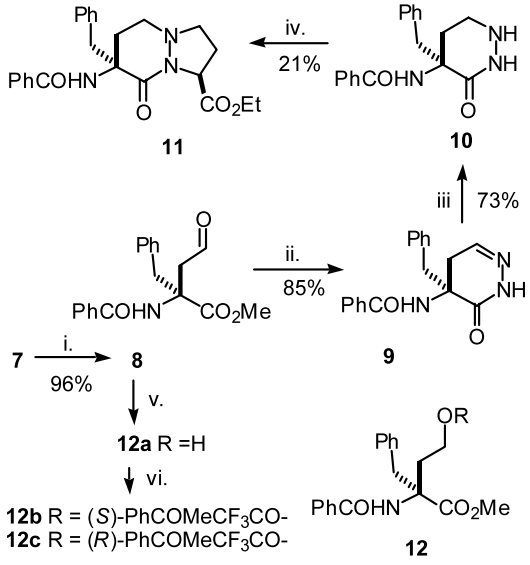
methanol, followed by the addition of an excess of diazomethane gave optically active (–)-**7**[11] in excellent overall yield.[12] The oxazolidinone **5** and the α,α-dialkylated amino acid **7** have been used previously by us to construct a 1,2,3,6-tetrahydropyridine-based peptidomimetic, the absolute configuration of which was determined by X-ray crystallography.[13]

With an adequate supply of (–)-**7** in hand we set about synthesising (Scheme 2) the heterocyclic core of the dipeptidomimetic in a similar manner to that previously reported for racemic **2**.[2] Ozonolysis of the olefin gave the corresponding aldehyde (–)-**8**,[14] which upon refluxing for 3 days with hydrazine in THF, gave the cyclic hydrazone (–)-**9**[14] in good yield. Hydrogenation of (–)-**9** over Adam's catalyst (PtO_2), as reported for the preparation of **2** (P = Boc),[2] gave variable results in our hands. However, reduction of (–)-**9** with sodium cyanoborohydride gave the desired tetrahydropyridazinone (–)-**10**[15] cleanly and in good yield (Scheme 2). We decided to establish the enantiomeric purity of the key intermediate (–)-**7**, and hence subsequent derivatives, by reduction to the alcohol **12a** and subsequent reaction with (*S*)- and (*R*)-methoxy-α-trifluoromethylphenyl acetyl chlorides[16] (Scheme 2). An analysis of the product MTPA esters from these two reactions by ^1H NMR revealed a diastereomeric excess of >95%. This is a key finding since it also establishes the enantiomeric purity of **5**, which has found use elsewhere.



Scheme 1. *Reagents and conditions*: (i) NaOH, then PhCHO, DCM, reflux, then PhCOCl, DCM, –20°C, then 0°C for 3 days; (ii) LiHMDS, –78°C, THF, allyl bromide; (iii) NaOH/MeOH, reflux, followed by CH_2N_2.



Scheme 2. *Reagents and conditions*: (i) O_3, CH_2Cl_2/MeOH (3:1), –78°C; (ii) hydrazine, reflux, 2 days; (iii) $NaB(CN)H_3$, MeOH/HCl, 0°C–rt, 18 h; (iv) CH_2O, reflux, ethyl acrylate; (v) $LiBH_4$, DCM; (vi) DMAP, Et_3N and (*S*)- or (*R*)-MTP-Cl, 10 min, rt.

Finally, treatment of (–)-**10** with formaldehyde and subsequent heating with an excess of ethyl acrylate gave rise to a 1,3 dipolar cycloaddition as reported[2] for the preparation of **2** (P = Boc). Purification of this product by chromatography gave the desired bicyclic template **11**[14] in modest yield. The absolute configuration of **11** was assigned as shown on the basis of the previously determined absolute configuration of **5** and also the relative configuration of **2** as reported by Takahashi and Kahn.[2–4] This is consistent with the assignment of relative configuration to related compounds.[1,17]

In conclusion, we have presented the first enantioselective synthesis of the phenylalanine-based tetrahydropyridazinone **10**, and its conversion to the 2-oxo-1,6-diazobicyclo[4.3.0]nonane-9-carboxylate dipeptido-mimetic scaffold **11**, an important component of extended β-strand mimetics. The nature and absolute configuration of the starting amino acid can be varied to give a versatile and potentially general method for the preparation of compounds of type **1**. In addition, the enantiomeric purity of the key intermediate **7**, and hence previously reported **5**,[7,8] has been shown to be >95%.

Acknowledgements

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9. To a solution of oxazolidinone **5** (2.11 g, 5.91 mmol, 1 equiv.) in dry THF (15 mL) cooled to −78°C under argon was added LiHMDS (6.501 mL of 1 M solution in THF/hexanes, 6.5 mmol, 1.1 equiv.). The solution was stirred at −78°C for 7 min whereupon allyl bromide (0.768 mL, 8.87 mmol, 1.5 equiv.) was added and the mixture stirred at −78°C for 2 h before being allowed to warm to room temperature overnight. Saturated aqueous NH_4Cl solution (20 mL) was added and the solution extracted with ether (3×20 mL). The ether extracts were combined, dried over Na_2SO_4 and the solvent removed to give (−)-**6** as a white solid. Recrystallisation from ether gave white needles (2.342 g, 93%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.82 (dd, J=13.7 and 5.4 Hz, 1H, C**H**$_a$CH=CH$_2$), 3.45 (d, J=13.7 Hz, 1H, C**H**$_a$Ph), 3.59 (dd, J=13.7 and 10.1 Hz, 1H, C**H**$_b$CH=CH$_2$), 4.09 (d, J=13.7 Hz, 1H, PhC**H**$_b$), 5.50 (m, 4H, CH=C**H**$_2$ and Ph**H**), 5.98 (m, 1H, C**H**=CH$_2$), 6.03 (s, 1H, **H2**), 6.66 (t, J=7.8 Hz, 2H, Ph**H**), 6.77 (d, J=7.3 Hz, 2H, Ph**H**), 6.95 (t, J=7.3 Hz, 1H, Ph**H**), 7.02 (t, J=7.5 Hz, 2H, Ph**H**), 7.14 (t, J=7.5 Hz, 1H, Ph**H**), 7.38–7.45 (m, 5H, Ph**H**). ^{13}C NMR ($CDCl_3$): δ 39.7, 41.6, 69.8, 91.0, 122.2, 125.2, 127.4, 127.6, 127.8, 128.2, 129.0, 129.1, 129.1, 130.8, 131.3, 135.0, 136.2, 136.6, 169.9, 173.3. FTIR (KBr) 3026, 1792, 1653 cm^{-1}. m/z (EI) calcd for $C_{26}H_{23}NO_3$ 397.1678, found 397.1672. $[\alpha]_D$=−2.9° (c 1.0, $CHCl_3$). Mp 141–143°C.
10. Note that the C-4 configuration of **5** has been inverted in this sequence.
11. To a solution of (−)-**6** (2.3 g, 5.79 mmol, 1 equiv.) dissolved in methanol (30 mL) under argon was added NaOH (11.587 mL of 1 M aqueous solution, 11.59 mmol, 2 equiv.). The solution was refluxed under argon for 1 h. The solution was then cooled and concentrated under reduced pressure. The residue was taken up in water (10 mL) and acidified to pH 2 with 10% aqueous HCl. The aqueous solution was extracted with ether (3×20 mL) and the combined ether extracts washed with brine (2×20 mL), dried over Na_2SO_4 and filtered. The resulting solution was then cooled to 0°C and an ethereal solution of diazomethane added until the bright yellow colour persisted over an extended period. The solution was stirred at rt for 2 h whereupon the reaction was quenched with the addition of a few drops of acetic acid. The solvent was removed to give (−)-**7** as a colourless oil (1.864 g, 99%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.72 (dd, J=7.3 Hz, 1H, C**H**$_a$CH=CH$_2$), 3.21 (d, J=13.7 Hz, 1H, PhC**H**$_a$), 3.60 (dd, J=7.3 Hz, 1H, C**H**$_b$CH=CH$_2$), 3.83 (s, 3H, O**Me**), 3.95 (d, J=13.7 Hz, 1H, PhC**H**$_b$), 5.10 (m, 2H, CH=C**H**$_2$), 5.65 (m, 1H, C**H**=CH$_2$), 6.93 (br s, 1H, N**H**), 7.19 (m, 2H, Ph**H**), 7.41 (m, 3H, Ph**H**), 7.41 (t, J=7.3 Hz, 2H, Ph**H**), 7.49 (t, J=7.3 Hz, Ph**H**), 7.68 (m, 2H, Ph**H**). ^{13}C NMR ($CDCl_3$): δ 39.3, 40.1, 52.6, 66.2, 119.1, 126.6, 126.8, 128.1, 128.4, 129.5, 131.3, 132.1, 135.1, 136.1, 166.7, 173.2. FTIR (KBr) 3414, 2953, 1738, 1666, 1603, 1580, 1516, 1487, 1448 cm^{-1}. m/z calcd for $C_{20}H_{21}NO_3$ 323.1521, found 323.1525. $[\alpha]_D$=−56.8° (c 1.0, $CHCl_3$).
12. It should be noted that while this sequence gives rise to the (*R*)-enantiomer the methodology lends itself equally well to the synthesis of the corresponding (*S*) isomer. This can be achieved by either starting with an (*R*)-amino acid or alternatively using a *syn* oxazolidinone, methods for the preparation of which are known (see Refs. 7 and 8).
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14. Prepared using the method described in Ref. 2.
    Compound **8**: ^{1}H NMR ($CDCl_3$): δ 3.06 (d, J=13.7 Hz, 1H, C**H**$_a$CHO), 3.23 (d, J=18.1 Hz, 1H, PhC**H**$_a$), 3.79 (s, 3H, O**Me**), 3.91 (d, J=13.7 Hz, 1H, C**H**$_b$CHO), 4.29 (d, J=18.1 Hz, 1H, PhC**H**$_b$), 7.00 (m, 2H, Ph**H**), 7.16 (d, J=6.8 Hz, 1H, N**H**), 7.21 (m, 3H, Ph**H**), 7.40 (t, J=7.3 Hz, 2H, Ph**H**), 7.49 (t, J=7.3 Hz, 1H, Ph**H**), 7.65 (d, J=7.3 Hz, 2H, Ph**H**), 9.67 (s, 1H, C**H**O). ^{13}C NMR ($CDCl_3$): δ 40.6, 48.4, 52.7, 61.4, 126.7, 127.1, 128.1, 128.4, 129.5, 131.5, 134.4, 134.5, 166.9, 172.1, 198.7. FTIR (KBr) 3406, 3032, 2955, 1744, 1659, 1601, 1582, 1516, 1489 cm^{-1}. m/z (ES) calcd for $C_{18}H_{17}KN_3O_2$ (M+K) 348.1212, found 348.1220. $[\alpha]_D$=−83.6° (c 1.0, $CHCl_3$).
    Compound **9**: ^{1}H NMR ($CDCl_3$): δ 2.90 (d, J=18.2 Hz, 1H, C**H**$_a$CH), 3.04 (d, J=13.7 Hz, 1H, PhC**H**$_a$), 3.58 (d, J=13.7 Hz, 1H, PhC**H**$_b$), 3.90 (dd, J=4.6 and 18.2 Hz, 1H, C**H**$_b$CH), 7.07 (m, 2H, Ph**H**), 7.19 (s, 1H, C**H**=N), 7.21–7.26 (m, 4H, PhCON**H** and Ph**H**), 7.42 (t, J=7.6 Hz, 2H, Ph**H**), 7.51 (t, J=7.3 Hz, 1H, Ph**H**), 7.70 (d, J=7.8 Hz, 2H, Ph**H**), 8.79 (brs, 1H, N=N**H**). ^{13}C NMR ($CDCl_3$): δ 34.1, 39.0, 56.3, 126.9, 127.3, 128.2, 128.5, 130.0, 131.8, 134.1, 134.4, 145.6, 167.1, 167.2. FTIR (KBr) 3387, 3229, 3125, 2878, 1686, 1647, 1601, 1582, 1516, 1489 cm^{-1}. m/z (ES) calcd for $C_{18}H_{17}N_3O_2$ (M+1) 308.1399, found 308.1395. $[\alpha]_D$=−128.4° (c 1.0, $CHCl_3$). Mp 189–192°C.
    Compound **11**: ^{1}H NMR ($CDCl_3$): δ 1.28 (t, J=7.3 Hz, 3H, $CO_2CH_2CH_3$), 2.25 (m, 1H, C**H**$_a$CHCO$_2$Et), 2.55 (m, 2H, C**H**$_b$CHCO$_2$Et and CC**H**$_a$CH$_2$N), 3.00 (ddd, J=6.3, 9.3 and 18.6 Hz, 1H, C**H**$_a$CH$_2$CHCO$_2$Et), 3.04 (m, 3H, CC**H**$_b$CH$_2$N and CCH$_2$C**H**$_2$N), 3.21 (m, 1H, C**H**$_b$CH$_2$CHCO$_2$Et), 3.57 (d, J=13.2 Hz, 1H, PhC**H**$_a$), 3.68 (d, J=13.2 Hz, 1H, PhC**H**$_b$), 4.22 (q, J=7.3 Hz, 2H, CO$_2$C**H**$_2$CH$_3$), 4.60 (dd, J=2.6 and 9.0 Hz, 1H, C**H**CO$_2$CH$_2$CH$_3$), 7.05 (m, 2H, Ph**H** and N**H**), 7.20 (m, 3H, Ph**H**), 7.38 (m, 3H, Ph**H**), 7.47 (t, J=7.3 Hz, 1H, Ph**H**), 7.72 (d, J=7.3 Hz, 2H, Ph**H**). ^{13}C NMR ($CDCl_3$): δ 14.1, 28.9, 34.0, 41.2, 52.1, 54.3, 57.5, 59.5, 61.8, 126.9, 127.0, 128.1, 128.4, 130.0, 131.4, 134.8, 136.5, 165.5, 166.7, 170.2. FTIR (KBr) 2939, 1736, 1649 cm^{-1}. m/z (ES) calcd for $C_{24}H_{27}N_3O_4$ (M+1) 422.2080, found 422.2075.
15. A small crystal of methyl orange was added to a solution of the hydrazone (−)-**9** (1.55 g, 5.05 mmol) dissolved in methanol (40 mL) at 0°C. The solution turned yellow. Drops of 2N aqueous HCl in MeOH were added until the solution turned red. $NaBH_3CN$ (330 mg, 5.3 mmol, 1.05 equiv.) was added slowly. Whenever the colour of the reaction mixture started to turn yellow during addition,

drops of 2N aqueous HCl in MeOH were added immediately to restore to red colour. The reaction was stirred at 0°C for 3 h then allowed to warm to room temperature overnight. The solvent was removed under reduced pressure, the red residue taken up in ethyl acetate and washed with saturated aqueous $NaHCO_3$ (2×20 mL), water (2×20 mL) and dried over $MgSO_4$. The solvent was removed to give the product as a white foam. Purification by radial chromatography eluting with 1:3 ethyl acetate/petroleum ether gave (−)-**10** as a sticky white solid (1.135 g, 73%). ^{1}H NMR ($CDCl_3$): δ 2.51 (m, 2H, C**H**$_2$N), 2.83 (m, 1H, C**H**$_a$CH$_2$N), 3.15 (m, 1H, C**H**$_b$CH$_2$N), 3.19 (d, J=13.2 Hz, 1H, PhC**H**$_a$), 3.53 (d, J=13.2 Hz, 1H, PhC**H**$_b$), 6.99 (brs, 1H, N**H**), 7.23 (s, 1H, N**H**), 7.26 (m, 2H, Ph**H**), 7.31–7.35 (m, 3H, Ph**H**), 7.42 (t, J=7.5 Hz, 2H, Ph**H**), 7.50 (m, 1H, Ph**H**), 7.20 (d, J=8.3 Hz, 2H, Ph**H**). ^{13}C NMR ($CDCl_3$): δ 34.4, 43.6, 44.5, 57.7, 127.0, 127.3, 128.3, 128.5, 130.3, 131.6, 133.8, 134.8, 166.8, 173.2. FTIR (KBr) 3248, 3063, 2936, 1649, 1638, 1580, 1508, 1483 cm^{-1}. m/z (ES) calcd for $C_{18}H_{19}N_3O_2$ (M+1) 310.1556, found 310.1549. $[\alpha]_D$=−25.7° (c 1.0, $CHCl_3$).

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