Enantiopure *N*-protected α-amino glyoxals 1. Synthesis from α-amino acids and some condensation reactions with amines

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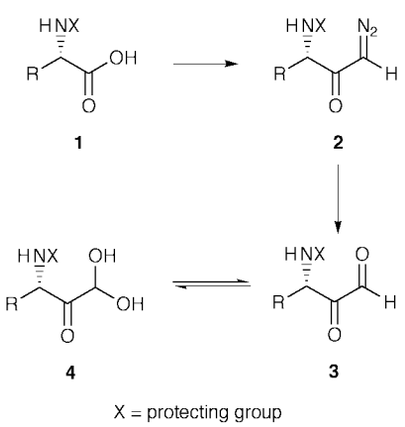
A series of *N*-protected α-amino diazoketones has been prepared from L-amino acids and dipeptides and used as precursors in the synthesis of novel *N*-protected α-amino glyoxals *via* oxidation with distilled dimethyldioxirane (DMD) in acetone. The glyoxals have been converted, without purification, into enantiopure imines, pyrazines, quinoxalines, and pyrido[2,3-*b*]pyrazines *via* condensation with the appropriate amine or diamine. The molecular structure of the pyrido[2,3-*b*]pyrazine derived from *N*-Cbz-L-phenylalanine has been determined by X-ray analysis.

When the research described below was initiated *N*-protected α-amino glyoxals of type **3** were unknown.[1] Without *N*-protection, α-amino glyoxals would be prone to spontaneous self-condensation. With *N*-protection, they should be much more stable yet amenable to a wide range of useful transformations through one or both carbonyl groups. Such transformations could provide access to numerous novel amino acid and peptide derivatives including potential protease inhibitors. We have developed a convenient synthesis of *N*-protected α-amino glyoxals from α-amino acids and dipeptides and have explored their conversion into ketomethylene amino pseudopeptides.[2] We have also tested their efficacy as inhibitors towards typical members of the serine and cysteine protease families.[3,4] Elsewhere, we will describe the elaboration of these glyoxals into polyfunctional amino acid and peptide derivatives *via* Wittig reactions.[5]

The synthesis, summarised in Scheme 1, is applicable to any



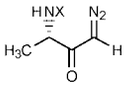
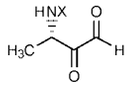
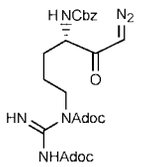
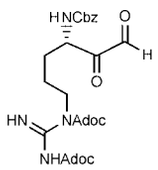
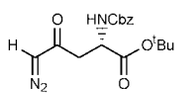
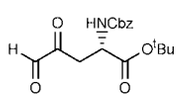
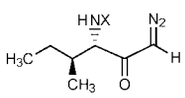
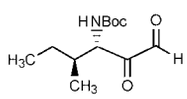
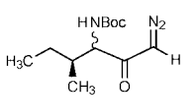
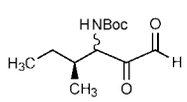
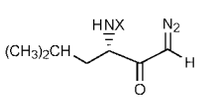
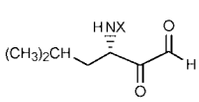
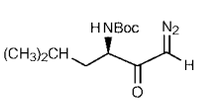
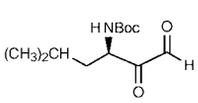
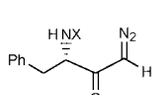
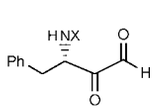
Scheme 1

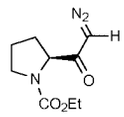
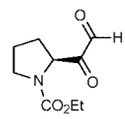
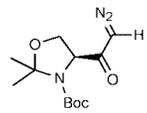
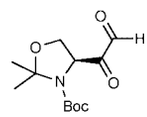
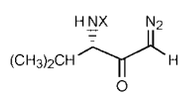
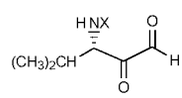
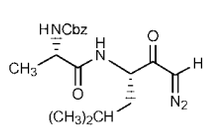
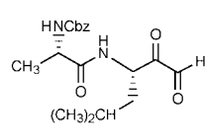
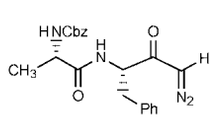
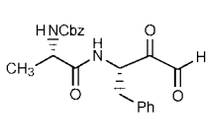
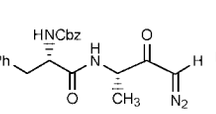
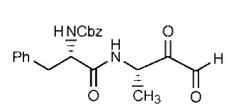
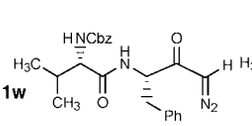
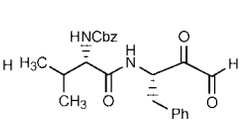
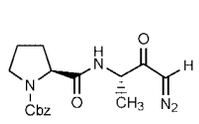
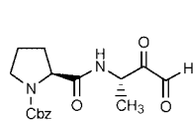
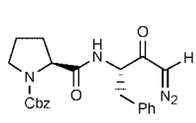
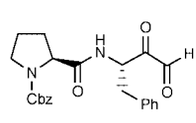
amino acid or peptide with a free carboxylic acid function and the reaction conditions tolerate most common forms of *N*-protection. We have successfully employed phthaloyl, benzyloxycarbonyl (Cbz), *tert*-butyloxycarbonyl (Boc), ethoxycarbonyl and 1-adamantyloxycarbonyl (Adoc) protecting groups. The two-step sequence involved conversion of the *N*-protected amino acids and peptides **1a**–**x** (all known compounds) into diazoketones **2a**–**x** (Table 1) which were then converted into the glyoxal by oxidation. Diazoketone formation was accomplished by the action of ethereal diazomethane on the acyl chloride or mixed anhydride of the amino acid, a well-documented route known to be free of racemization.[6,7] The transformation of diazoketone into glyoxal was accomplished using distilled dimethyldioxirane (DMD) in acetone as the oxidant.[8] Glyoxals **3a**–**x** were thus prepared: **3a**, **3b**, from L-alanine, **3c** from L-arginine, **3d** from L-aspartic acid, **3e**, **3f** from L-isoleucine, **3g** from D,L-isoleucine, **3h**, **3i**, **3j** from L-leucine, **3k** from D-leucine, **3l**, **3m**, **3n** from L-phenylalanine, **3o** from L-proline, **3p** from L-serine, **3q**, **3r**, **3s** from L-valine, **3t** from L-Ala-L-Leu, **3u** from L-Ala-L-Phe, **3v** from L-Phe-L-Ala, **3w** from L-Val-L-Phe, **3x** from L-Pro-L-Ala, and **3y** from L-Pro-L-Phe, respectively. These glyoxals were predominately, if not exclusively, in the hydrated form **4**, presumably from reaction with adventitious moisture present in the DMD solution. Although the glyoxal hydrate **3m** derived from Cbz-L-phenylalanine could be fully characterized, routinely the oxidation products were not scrutinised closely other than by TLC (to monitor the disappearance of the diazoketone) and ^{1}H NMR analysis which confirmed that product purity was >95% in each case. The ^{1}H NMR spectrum of **3m** exhibited, in addition to the normal Cbz-phenylalanine signals, a multiplet at δ 5.35 for the methine hydrogen atom of the $CH(OH)_2$ group and a doublet at δ 5.82 corresponding to the two hydroxylic protons.

To further characterize these glyoxals and explore their efficacy as *in situ* intermediates for amino acid and peptide elaboration, a number of reactions involving condensation with amines were examined. All of these reactions were conducted as one-pot procedures: the diazoketone was oxidized with DMD, acetone was removed at reduced pressure and replaced by another solvent, usually dichloromethane or ethanol, and the appropriate reagent was then added. These glyoxals condensed with simple 1,2-diamines to form dihydropyrazines (Scheme 2) which could be dehydrogenated to yield pyrazines on treatment with manganese dioxide in the presence of potassium hydroxide.[9] Representative examples of pyrazines formed in this way are **5f** and **5q** (Table 2) derived from 1,2-diaminoethane and glyoxals **3f** and **3q**. 1,2-Diaminopropane and glyoxal **3b** furnished pyrazine **6** as a 3 : 2 inseparable mixture of regioisomers. Reaction of 1,2-diaminoethane carboxylic acid methyl ester with glyoxal **3b** furnished a 1 : 1 mixture of pyrazines **7** and **8**, but these isomers could be separated by flash chromatography and the individual isomers could be distinguished by analysis of their HMBC and HMQC NMR spectra.

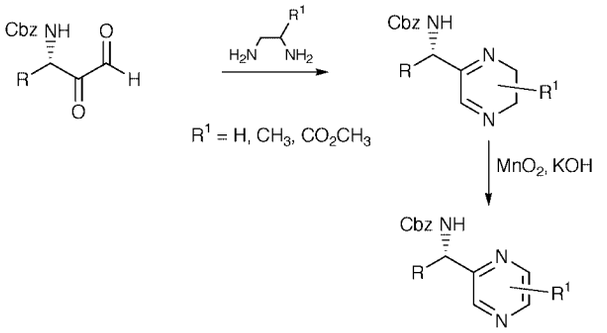
Reaction with freshly purified 1,2-diaminobenzene (Scheme 3) furnished a series of novel, optically active quinoxalines **9** (91–96% yield of microanalytically pure products) (Table 3) with the chiral aminoalkyl residue of an amino acid or peptide as a side chain. The quinoxalines, with the exception of the

Table 1 Preparation of glyoxals from *N*-protected amino acids and dipeptides

Amino acid/dipeptide	Diazoketone	Glyoxal
N-X-L-Alanine **1a** X = Boc **1b** X = Cbz	 **2a** **2b**	 **3a** **3b**
N^{α}-Cbz-N^{δ}, N^{ω}-bis-Adoc-L-Arginine **1c**	 **2c**	 **3c**
N-Cbz-L-Aspartic acid-O^{t}Bu **1d**	 **2d**	 **3d**
N-X-L-Isoleucine **1e** X = Boc **1f** X = Cbz	 **2e** X = Boc **2f** X = Cbz	 **3e** X = Boc **3f** X = Cbz
N-Boc-D,L-Isoleucine **1g**	 **2g**	 **3g**
N-X-L-Leucine **1h** X = Phthaloyl **1i** X = Cbz **1j** X = Boc	 **2h** X = Phthaloyl **2i** X = Cbz **2j** X = Boc	 **3h** X = Phthaloyl **3i** X = Cbz **3j** X = Boc
N-Boc-D-Leucine **1k**	 **2k**	 **3k**
N-X-L-Phenylalanine **1l** X = Box **1m** X = Cbz **1n** X = Phthaloyl	 **2l** X = Box **2m** X = Cbz **2n** X = Phthaloyl	 **3l** X = Box **3m** X = Cbz **3n** X = Phthaloyl

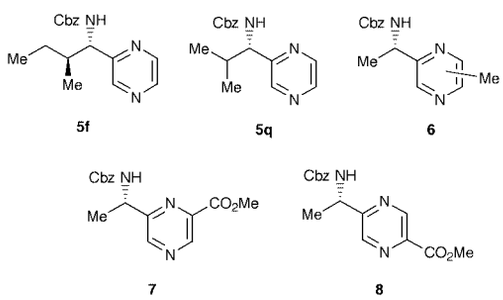
Amino acid/dipeptide	Diazoketone	Glyoxal
N-Ethoxycarbonyl-proline **1o**	 **2o**	 **3o**
i-Boc(*N*,*O*)-isopropylidene-L-serine **1p**	 **2p**	 **3p**
N-X-L-Valine **1q** X = Cbz **1r** X = EtO_2C **1s** X = Phthaloyl	 **2q** X = Cbz **2r** X = EtO_2C **2s** X = Phthaloyl	 **3q** X = Cbz **3r** X = EtO_2C **3s** X = Phthaloyl
N-Cbz-L-Ala-L-Leu **1t**	 **2t**	 **3t**
N-Cbz-L-Ala-L-Phe **1u**	 **2u**	 **3u**
N-Cbz-L-Phe-L-Ala **1v**	 **2v**	 **3v**
N-Cbz-L-Val-L-Phe **1w**	 **2w**	 **3w**
N-Cbz-L-Pro-L-Ala **1x**	 **2x**	 **3x**
N-Cbz-L-Pro-L-Phe **1y**	 **2y**	 **3y**

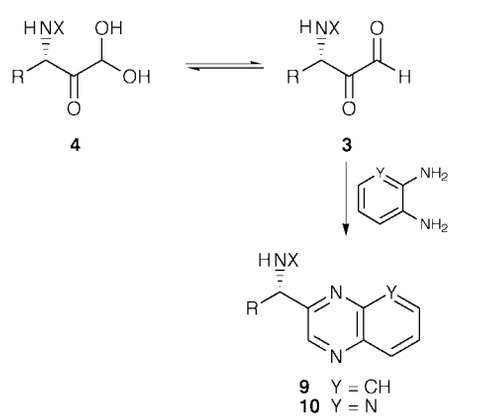
product derived from L-proline, which was an oil, were obtained as crystalline solids. All the spectral data were in agreement with the structural assignments, which were confirmed by H–H COSY, and H–C COSY NMR experiments. Confirmation of the enantiomeric purity of the quinoxalines was obtained by comparison of the ^{13}C NMR spectrum of the product derived



Scheme 2 Condensation of *N*-protected amino glyoxals with diamines.

Table 2 Derivatization of *N*-protected amino glyoxals as pyrazines





Scheme 3 Formation of quinoxalines and pyrido[2,3-*b*]pyrazines from *N*-protected amino glyoxals.

from L-isoleucine **3e** with that derived from D,L-isoleucine **3g**. Whereas the latter displayed two sets of signals, attributable to the presence of two diastereoisomers, the spectrum of the former indicated the presence of a single diastereoisomer, a distinction from which we could conclude that the two transformations leading from diazoketone to quinoxaline in the isoleucine series were free of racemization. We inferred, on the basis of these observations, that all the quinoxalines (and other amine condensation products) were produced in an enantiopure form.

In an extension of this approach to novel chiral nitrogen heterocycles we examined the condensation of several *N*-protected amino glyoxals with 2,3-diaminopyridine (Scheme 3) as a route to pyrido[2,3-*b*]pyrazines. Since the two amino functions are no longer equivalent, cyclization with the pyridine reagent could lead to regioisomeric products. In the event, condensation of glyoxals **3b**, **3i**, **3m**, **3o**, and **3q** (Table 3) with 2,3-diaminopyridine produced a single pyrido[2,3-*b*]pyrazine in each case, to which we assigned structures **10b**, **10i**, **10m**, **10o**, and **10q**, respectively, on mechanistic grounds. Arguing that the first condensation step should involve the more reactive aldehydic carbonyl group of the glyoxal and the more reactive

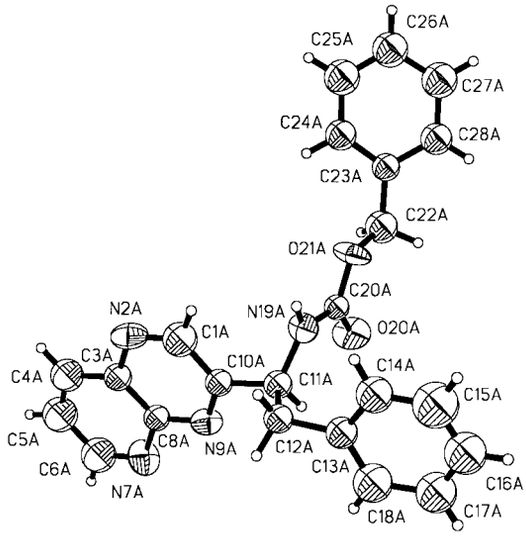


Fig. 1 A view of (1′*S*)-3-(2′-phenyl-1′-*N*-benzyloxycarbonylaminoethyl)pyrido[2,3-*b*]pyrazine **10m** showing the atom-labelling scheme for all non-hydrogen atoms. Thermal ellipsoids at 50% level.

3-amino group of the pyridine, we concluded that the pyrido-[2,3-*b*]pyrazines should have the regiochemistry depicted in structure **10** (Scheme 3). Crystallization of the pyrido[2,3-*b*]-pyrazine derivative of *N*-Cbz-L-phenylalanine (**10m**) enabled us to confirm by X-ray diffraction analysis[10] that the molecule does indeed possess structure **10** (Fig. 1).

In conclusion, we have demonstrated that *N*-protected α-amino glyoxals, which are readily available from α-amino acids and peptides, can be used to construct a range of monocyclic and bicyclic heteroaromatic products bearing chiral aminoalkyl residues as side chains.

Experimental

General procedures

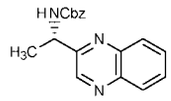
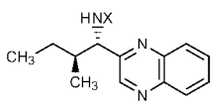
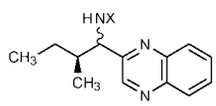
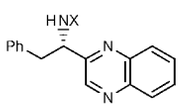
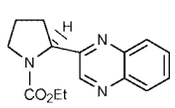
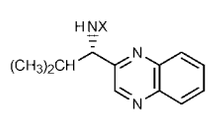
All the diazoketones used in this study were prepared from known *N*-protected amino acids and dipeptides by one of two well-established procedures both known not to cause racemization. For diazoketones with ethoxycarbonyl or phthaloyl protection, the amino acid was activated *via* the acyl chloride prior to exposure to ethereal diazomethane.[11] For all other forms of *N*-protection (Cbz, Boc, Adoc) the amino acid was activated *via in situ* mixed anhydride formation with isobutyl chloroformate.[6,7] The crude products from both routes were purified by flash chromatography over silica. Purity levels were ≥97% by ^{1}H NMR analysis.

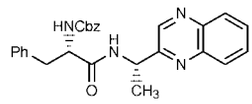
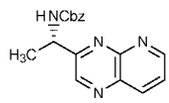
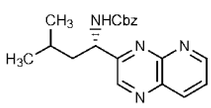
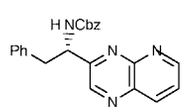
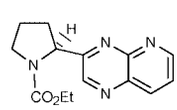
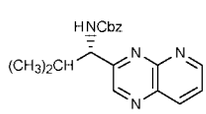
The following diazoketones were thus prepared: (*N*-*tert*-butoxycarbonyl-L-alanyl)diazomethane, **2a**;[6] (*N*-benzyloxycarbonyl-L-alanyl)diazomethane, **2b**;[12] [(3*S*,4*S*)-*N*-*tert*-butoxycarbonylisoleucyl]diazomethane, **1e**;[7] [(3*S*,4*S*)-*N*-benzyloxycarbonylisoleucyl]diazomethane, **1f**;[12] [(±)-*N*-*tert*-butoxycarbonylisoleucyl]diazomethane, **1g**;[7] (*N*-phthaloyl-L-leucyl)-diazomethane, **2h**;[14] (*N*-benzyloxycarbonyl-L-leucyl)diazomethane, **2i**;[13] (*N*-*tert*-butoxycarbonyl-L-leucyl)diazomethane, **2j**;[14] (*N*-*tert*-butoxycarbonyl-D-leucyl)diazomethane, **2k**;[13] (*N*-*tert*-butoxycarbonyl-L-phenylalanyl)diazomethane, **2l**;[7] (*N*-benzyloxycarbonyl-L-phenylalanyl)diazomethane, **2m**;[12] (*N*-phthaloyl-L-phenylalanyl)diazomethane, **2n**;[14] (*N*-ethoxycarbonyl-L-prolyl)diazomethane, **1o**;[7] (*N*-benzyloxycarbonyl-L-valyl)diazomethane, **1q**;[14] (*N*-ethoxycarbonyl-L-valyl)diazomethane, **1r**.[7]

N^{α}-Benzyloxycarbonyl-N^{δ},N^{ω}-bis(1-adamantyloxycarbonyl)-L-arginyldiazomethane, 2c

The title compound was prepared from the N-protected acid **1c** (15.0 g, 22.6 mmol) *via* the literature procedure. The crude

Table 3 Derivatization of *N*-protected amino glyoxals as quinoxalines and azaquinoxalines

Amino acid/ dipeptide gloxal	Quinoxaline/pyridopyrazine	Yield (%)
N-Cbz-L-Alanine		
	9b	93
N-X-L-Isoleucine		
3e X = Boc	**9e**	95
3f X = Cbz	**9f**	91
N-Boc-D,L-Isoleucine **3g**		
	9g	92
N-X-L-Phenylalanine		
3l X = Boc	**9l** X = Boc	93
3m X = Cbz	**9m** X = Cbz	92
N-Ethoxycarbonyl-L-proline **3o**		
	9o	90
N-X-L-Valine		
3q X = Cbz	**9q** X = Cbz	96
3r X = EtO_2C	**9r** X = EtO_2C	91
3s X = Phthaloyl	**9s** X = Phthaloyl	95

Amino acid/ dipeptide gloxal	Quinoxaline/pyridopyrazine	Yield (%)
N-Cbz-L-Phe-L-Ala **3v**		
	9v	91
N-Cbz-L-Alanine **3b**		
	10b	92
N-Cbz-L-Leucine **3i**		
	10i	89
N-Cbz-L-Phenylalanine **3m**		
	10m	90
N-Ethoxycarbonyl-L-proline **3o**		
	10o	92
N-Cbz-L-Valine **3q**		
	10q	94

product was purified by recrystallization from dichloromethane–hexane to afford the pure α-diazoketone **2c** (9.3 g, 62%) as a pale yellow, crystalline solid, mp 80–82 °C (Found: C, 64.2; H, 7.3; N, 11.7. $C_{37}H_{48}N_6O_7$ requires: C, 64.5; H, 7.0; N, 12.2%); $[\alpha]_D^{20} = 4.1$ (*c*, 0.8 in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3377 (NH), 2105 (CHN_2), 1712, 1640, 1607 (COs); δ_H (300 MHz, $CDCl_3$) 1.53–1.67 (20H, m, Adam-H and $(CH_2)_2CH$), 2.02–2.19 (14H, m, Adam-H), 3.84 (2H, m, CH_2(N)CO), 4.35 (1H, m, $(CH_2)_2CH$), 5.12 (2H, s, OCH_2Ph), 5.98 (1H, s, CHN_2), 6.46 (1H, d, $J = 8.1$ Hz, NH), 7.33 (5H, m, Ar-H), 9.25 (1H, br s, HN=CNH), 9.41 (1H, br s, HN=CNH).

(*S*)-2-Benzyloxycarbonylamino-5-diazo-4-oxopentanoic acid *tert*-butyl ester, 2d

This compound was prepared from the diprotected acid **1d** (5.9 g, 18 mmol) according to the literature procedure. The crude product was purified by flash chromatography on silica (20% ethyl acetate–80% hexane) to afford pure α-diazoketone **2d** (3.8 g, 61%) as a yellow oil (Found: C, 58.5; H, 6.2; N, 11.8. $C_{17}H_{21}N_3O_5$ requires: C, 58.8; H, 6.1; N, 12.1%); $[\alpha]_D^{20}$ 37.1 (*c*, 3.64 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 2100 (CN_2), 1720 (NCO_2 and CO_2), 1630 ($COCHN_2$); δ_H (300 MHz, $CDCl_3$) 1.44 (9H, s, $(CH_3)_3C$), 2.83 (1H, m, CH_2CHNH), 2.98 (1H, m, CH_2-CHNH), 4.46 (1H, m, CH_2CHNH), 5.10 (2H, s, OCH_2Ph), 5.26 (1H, br s, CHN_2), 5.84 (1H, br d), 7.34 (5H, br s, Ar-H); δ_C (75 MHz, $CDCl_3$) 27.63 ($(CH_3)_3C$), 41.86, 50.91, 54.94, 66.65, 82.21 ($(CH_3)_3C$), 127.80, 127.89, 128.27, 136.12, 155.83 (CO of carbamate), 169.56 (CO of ester), 191.43 (CO of diazoketone).

(*N*-Butoxycarbonyl-*N*,*O*-isopropylidene-L-seryl)diazomethane, 2p

This compound was prepared from the diprotected acid **1p** (9.0 g, 37 mmol) *via* the literature procedure. The crude product was purified by flash chromatography on silica (20% ethyl acetate–80% hexane) to afford **2p** (6.1 g, 62%) as a pale yellow solid, mp 55–56 °C (Found: C, 53.7; H, 7.1; N, 15.7. $C_{12}H_{19}N_3O_4$ requires: C, 53.5; H, 7.1; N, 15.6%); $[\alpha]_D^{20}$ −145.8 (*c*, 1.1 in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 2115 (CN_2), 1703 (NCO_2), 1625 ($COCHN_2$); δ_H (300 MHz, $CDCl_3$) 1.45, 1.52 (12H, 2 × s, $C(CH_3)_3$ and CH_3CCH_3), 1.65 and 1.71 (3H, 2 × s, CH_3CCH_3), 4.11 (2H, m, OCH_2CH), 4.29, 4.40 (1H, 2 × m, CH(N)CO), 5.52 (1H, s, CHN_2).

(*N*-Benzyloxycarbonyl-L-alanyl-L-leucyl)diazomethane, 2t

The dipeptide acid **1t** (2.68 g, 7.96 mmol) was treated according to the literature procedure to give the title compound **2t** (1.87 g, 65%) as a yellow solid. The crude product was recrystallised from ethyl acetate–hexane–THF to give the pure α-diazoketone, mp 93–94 °C (Found: C, 60.2; H, 7.1; N, 15.3. $C_{18}H_{24}N_4O_4$ requires: C, 60.0; H, 6.7; N, 15.6%); $[\alpha]_D^{20}$ −57.5 (*c*, 0.6 in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3326 (NH), 2109 (CN_2), 1715

(NCO_2), 1645 (CONH), 1634 ($COCHN_2$); δ_H (300 MHz, $CDCl_3$) 0.90 (6H, m, $(CH_3)_2CH_2$), 1.37 (3H, d, $J = 8.1$ Hz, CH_3CH), 1.25–1.63 (3H, br m, $CH_2CH(CH_3)_2$), 4.31 (1H, br m, CH(N)CO), 4.94 (1H, br m, CH(N)CO), 5.10 (2H, s, OCH_2Ph), 5.50 (1H, s, CHN_2), 5.59 (1H, br d, $J = 6.9$ Hz, NH), 6.87 (1H, br d, $J = 7.4$ Hz, NH), 7.34 (5H, s, Ar-H); δ_C (75 MHz, $CDCl_3$) 18.44 (CH_3), 21.69 (CH_3), 22.85 (CH_3), 24.63, 40.84, 50.40, 53.95, 54.43, 66.89, 127.85, 128.07, 128.38, 135.94, 155.83 (CO of carbamate), 172.14 (CO of amide), 193.65 (CO of diazoketone); *m*/*z* 332 ($M^+ - N_2$, 34%), 91 ($PhCH_2^+$, 100).

(*N*-Benzyloxycarbonyl-L-alanyl-L-phenylalanyl)diazomethane, 2u

The dipeptide acid **1u** (3.88 g, 10.48 mmol) was treated according to the literature procedure to give the title compound **2u** (3.01 g, 73%) as a yellow solid. The crude product was recrystallized from ethyl acetate–hexane–THF to give the pure α-diazoketone, mp 113–115 °C (Found: C, 64.1; H, 5.5; N, 13.9. $C_{21}H_{22}N_4O_4$ requires: C, 64.0; H, 5.6; N, 14.2%); $[\alpha]_D^{20}$ −28.2 (*c*, 0.55 in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3309 (NH), 2105 (CN_2), 1689 (CO of carbamate), 1654 (CO of amide), 1625 (CO of diazoketone); δ_H (300 MHz, $CDCl_3$) 1.29 (3H, d, $J = 7.0$ Hz, CH_3), 3.02 (2H, br m, $PhCH_2$), 4.21 (1H, br m, CH(N)CO), 4.69 (1H, br m, CH(N)CO), 5.09 (2H, d, $J = 3.4$ Hz, OCH_2Ph), 5.29 (1H, s, CHN_2), 5.31 (1H, br s, NH), 6.78 (1H, br m, NH), 7.14–7.38 (10H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 18.17 (CH_3), 37.89, 50.54, 54.62, 56.89, 67.01, 126.93, 127.93, 128.15, 128.43, 128.48, 129.13, 135.88, 155.78 (CO of carbamate), 171.81 (CO of amide), 192.23 (CO of diazoketone); *m*/*z* 366 ($M^+ - N_2$, 66%), 91 ($PhCH_2^+$, 100).

(*N*-Benzyloxycarbonyl-L-phenylalanyl-L-alanyl)diazomethane, 2v

The dipeptide acid **1v** (1.70 g, 4.59 mmol) was treated according to the literature procedure to give the title compound **2v** (1.52 g, 84%) as an orange solid. The crude product was recrystallized from ethyl acetate–hexane–THF to give the pure α-diazoketone, mp 117–118.5 °C (Found: C, 64.1; H, 5.9; N, 14.1. $C_{21}H_{22}N_4O_4$ requires: C, 64.0; H, 5.6; N, 14.2%); $[\alpha]_D^{20}$ −13.2 (*c*, 0.58 in CH_2Cl_2); ν_{max} (KBr/cm^{-1}) 3304 (NH), 2113 (CN_2), 1692 (CO of carbamate), 1651 (CO of amide), 1629 (CO of diazoketone); δ_H (300 MHz, $CDCl_3$) 1.23 (3H, d, $J = 7.0$ Hz, CH_3), 3.07 (2H, d, $J = 6.8$ Hz, $PhCH_2$), 4.42–4.50 (2H, br m, CH(N)CO and CH(N)CO), 5.06 (2H, s, OCH_2Ph), 5.10 (1H, s, CHN_2), 5.50 (1H, d, $J = 7.8$ Hz, NH), 6.73 (1H, br d, $J = 5.2$ Hz, NH), 7.17–7.32 (10H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 17.73 (CH_3), 38.30, 51.85, 53.23, 55.98, 67.04, 126.96, 127.85, 128.10, 128.39, 128.55, 129.23, 135.93, 155.83 (CO of carbamate), 170.40 (CO of amide), 193.11 (CO of diazoketone); *m*/*z* 366 ($M^+ - N_2$, 75%), 91 ($PhCH_2^+$, 100).

(*N*-Benzyloxycarbonyl-L-valyl-L-phenylalanyl)diazomethane, 2w

The dipeptide acid **1w** (0.61 g, 1.53 mmol) was treated according to the literature procedure to give the title compound **2w** (0.46 g, 72%) as a yellow solid. The crude product was recrystallized from ethyl acetate–hexane–THF to give the pure α-diazoketone, mp 191–195 °C (Found: C, 65.5; H, 6.4; N, 13.0. $C_{23}H_{26}N_4O_4$ requires: C, 65.4; H, 6.2; N, 13.3%); $[\alpha]_D^{20}$ −9.4 (*c*, 0.51 in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3317 (NH), 2111 (CN_2), 1695 (NCO_2), 1650 (CONH), 1630 ($COCHN_2$); δ_H (300 MHz, $CDCl_3$) 0.81 (3H, d, $J = 6.5$ Hz, $(CH_3)_2CH$), 0.90 (3H, d, $J = 6.6$ Hz, $(CH_3)_2CH$), 2.10 (1H, m, $(CH_3)_2CH$), 3.03 (2H, m, $PhCH_2$), 4.05 (1H, br m, CH(N)CO), 4.74 (1H, br m, CH(N)CO), 5.10 (2H, s, OCH_2Ph), 5.26 (1H, s, CHN_2), 5.42 (1H, br d, $J = 8.3$ Hz, NH), 6.87 (1H, br d, NH), 7.15–7.34 (10H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 17.41 (CH_3), 19.05 (CH_3), 30.67, 38.06, 54.68, 56.86, 60.27, 66.97, 126.90, 127.87, 128.08, 128.40, 128.48, 129.09, 135.90, 156.24 (CO of carbamate), 170.87 (CO of amide), 192.24 (CO of diazoketone); *m*/*z* 394 ($M^+ - N_2$, 16%), 352 (41), 91 ($PhCH_2^+$, 100).

(*N*-Benzyloxycarbonyl-L-prolyl-L-alanyl)diazomethane, 2x

The dipeptide acid **1x** (3.00 g, 9.36 mmol) was treated according to the literature procedure to give the title compound **2x** (2.37 g, 74%) as a yellow solid. The crude product was purified by recrystallization from ethyl acetate–hexane–THF to give the pure α-diazoketone, mp 59–61.5 °C (Found: C, 59.5; H, 6.0; N, 15.9. $C_{17}H_{20}N_4O_4$ requires: C, 59.3; H, 5.9; N, 16.3%); $[\alpha]_D^{20}$ −105.9 (*c*, 0.56 in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3311 (NH), 2128 (CN_2), 1694 (CO of carbamate), 1666 (CO of amide), 1626 (CO of diazoketone); δ_H (300 MHz, $CDCl_3$) 1.24 (3H, br d, $J = 10.6$ Hz, CH_3), 1.88–2.12 (4H, br m, CH_2CH_2), 3.48–3.55 (2H, br m, CH_2N), 4.33 (1H, br d, CH(N)CO), 4.43 (1H, br s, CH(N)CO), 5.14 (2H, s, OCH_2Ph), 5.37, 5.69 (1H, 2 × br s, CHN_2), 7.18 (1H, br s, NH), 7.30 (5H, br s, Ar-H); δ_C (50 °C, 125 MHz, $CDCl_3$) 16.93 (CH_3), 23.78 (br), 28.80, 30.64 (2 × br s), 46.70, 51.62, 52.64, 60.12, 66.65, 127.14, 127.45, 127.91, 135.98, 155.09 (br) (CO of carbamate), 171.44 (CO of amide), 193.61 (br) (CO of diazoketone); *m*/*z* 316 ($M^+ - N_2$, 24%), 275 ($M^+ - C_2N_2OH$, 25), 91 ($PhCH_2^+$, 100).

(*N*-Benzyloxycarbonyl-L-prolyl-L-phenylalanyl)diazomethane, 2y

The dipeptide acid **1y** (6.94 g, 17.5 mmol) was treated according to the literature procedure to give the title compound **2y** as a yellow solid. The crude product was purified by flash chromatography using 60% ethyl acetate–40% hexane as eluant, to give the pure α-diazoketone (4.92 g, 67%), mp 85–86.5 °C (Found: C, 65.5; H, 5.8; N, 12.7. $C_{23}H_{24}N_4O_4$ requires: C, 65.7; H, 5.8; N, 13.3%); $[\alpha]_D^{20}$ −97.0 (*c*, 0.76 in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3349 (NH), 2105 (CN_2), 1732 (CO of carbamate), 1661 (CO of amide), 1649 (CO of diazoketone); δ_H (500 MHz, $CDCl_3$) 1.35–1.48 (4H, br m, CH_2CH_2), 2.89–3.50 (4H, br m, CH_2N and $PhCH_2$), 4.31 (1H, br m, CH(N)CO), 4.60–4.80 (1H, br m, CH(N)CO), 5.13 (2H, s, $PhCH_2O$), 4.95, 5.51 (1H, 2 × s, CHN_2), 6.40, 6.81 (1H, 2 × br s, NH), 7.10–7.37 (10H, m, Ar-H); δ_C (50 °C, 125 MHz, $CDCl_3$) 24.16 (br), 28.61 (br), 37.58, 47.12, 53.97, 56.87, 60.87, 67.51, 126.94, 127.93, 128.23, 128.56, 129.15, 136.43, 156.00 (br) (CO of carbamate), 171.49 (CO of amide), 192.50 (br) (CO of diazoketone).

Oxidation of *N*-protected α-amino acid and dipeptide derived diazoketones using dimethyldioxirane: general procedure

The *N*-protected diazoketone (1 eq.) was dissolved in the minimum amount of dry, distilled acetone and 1.5 eq. of freshly dried (using anhydrous Na_2SO_4) DMD in acetone solution was added at room temp. and the reaction stirred. Evolution of nitrogen was observed. The reaction was followed by TLC and generally took approximately 10 min. The acetone was then removed under reduced pressure to yield the crude glyoxal and water. The crude glyoxal was dissolved in dry CH_2Cl_2, dried over Na_2SO_4 and the solvent removed by evaporation to give the glyoxal in quantitative yield.

(*S*)-1-(Benzyl-3,3-dihydroxy-2-oxopropyl)carbamic acid benzyl ester, 4m. Treatment of (*N*-benzyloxycarbonyl-L-phenylalanyl)diazomethane **2m** (311.2 mg, 0.96 mmol) in acetone (10 ml) with one equivalent of DMD (15 ml of a 0.065 M solution in acetone, 0.98 mmol) according to general procedure described above, after 10 min (TLC CH_2Cl_2) afforded the title compound **4m** (311.7 mg, 98%) as a pale yellow solid, mp 71–73 °C (Found: C, 65.8; H, 5.4; N, 4.2. $C_{18}H_{19}NO_5$ requires: C, 65.6; H, 5.8; N, 4.3%); $[\alpha]_D^{20}$ −10.8 (*c*, 0.7 in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3390, 3315 (OH and NH), 2949, 2925 (aldehydic C-H), 1736 (CO of carbamate), 1691 (COs of ketoaldehyde);

δ_H (300 MHz, CD_3COCD_3) 2.92 (1H, dd, $J_1 = 14.0$ Hz, $J_2 = 9.7$ Hz, $PhCH_2$), 3.32 (1H, dd, $J_1 = 14.1$ Hz, $J_2 = 4.2$ Hz, $PhCH_2$), 4.94 (1H, m, CH(N)CO), 5.00 (2H, s, OCH_2Ph), 5.36 (1H, m, $CH(OH)_2$), 5.82 (2H, d, $J = 7.9$ Hz, $CH(OH)_2$), 6.66 (1H, d, $J = 7.9$ Hz, NH), 7.18–7.30 (10H, m, Ar-H).

Assignment was also facilitated by H–H COSY, H–C COSY and decoupling experiments.

Oxidation of *N*-protected amino acid diazoketones and derivatization as pyrazines: general procedure

The diazoketone (1 eq.) was dissolved in acetone and stirred at 0 °C, under nitrogen. 1.5 equivalents of the acetone DMD solution were added in a single portion. Reactions were monitored by TLC. Upon completion (<10 min), the solvent was removed under reduced pressure. The crude glyoxal was then dissolved in dichloromethane (15 ml) and dried over anhydrous Na_2SO_4. 1 equivalent of the diamine and some $MgSO_4$ were added. The reaction mixture was allowed to stir for 2 hours at room temperature. The solid was then filtered and solvent evaporated to give the crude dihydropyrazine. Oxidation of the dihydropyrazine was achieved by dissolving the crude dihydropyrazine in EtOH and stirring at reflux for 6 hours in the presence of three equivalents of MnO_2 and 1.1 equivalents of KOH. The MnO_2 was filtered through a pad of Celite and the solvent evaporated. The crude reaction product was dissolved in EtOAc and washed with brine, dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to yield the crude pyrazine which was generally purified by flash chromatography on silica using EtOAc–hexane as eluant.

(1′*S*)-2-(2′-Methyl-1′-*N*-benzyloxycarbonylaminopropyl)-pyrazine, 5q. Oxidation of (*N*-benzyloxycarbonyl-L-valyl)-diazomethane **2q** (0.2 g, 0.73 mmol) in acetone (15 ml) with DMD (16 ml, 0.07 M, 1.5 eq.) according to the general procedure and subsequent condensation with diaminoethane (0.05 ml, 0.73 mmol) in CH_2Cl_2 (20 ml) yielded the crude dihydropyrazine as a yellow oil (Found: M^+, 287.1624. $C_{16}H_{21}N_3O_2$ requires: M^+, 287.1634); ν_{max} (KBr)/cm^{-1} 1710 (CO); δ_H (300 MHz, $CDCl_3$) 0.84 (3H, d, $J = 6.9$ Hz, $(CH_3)_2CH$), 1.00 (3H, d, $J = 6.7$ Hz, $(CH_3)_2CH$), 2.06 (1H, m, $(CH_3)_2CH$), 3.35 (2H, d, $J = 12.9$ Hz, NCH_2CH_2N), 3.57 (2H, d, $J = 12.3$ Hz, NCH_2CH_2N), 4.45 (1H, m, CH(N)CO), 5.10 (2H, s, OCH_2Ph), 5.79 (1H, d, $J = 8.1$ Hz, NH), 7.35 (5H, s, Ar-H), 7.78 (1H, s, CH=N); δ_C (75 MHz, $CDCl_3$) 16.87, 19.24, 31.18, 43.54, 44.61, 58.45, 66.65, 127.89, 128.28, 136.24, 152.57, 156.21, 159.08. The dihydropyrazine was then dehydrogenated according to the general procedure in the presence of MnO_2 (0.19 g, 2.2 mmol) and KOH (0.045 g, 0.8 mmol) to yield the crude pyrazine as a brown oil. Purification by flash chromatography on silica using EtOAc–hexane (40 : 60) gave the title compound **5q** as a pale yellow oil (0.11 g, 53%) (Found: M^+ 285.1477. $C_{16}H_{19}N_3O_2$ requires: M^+ 285.1476); $[\alpha]_D^{20}$ −54.4 (*c*, 1.9 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3329, 1716, 1608; δ_H (500 MHz, $CDCl_3$) 0.8 (3H, d, $J = 6.8$ Hz, $(CH_3)CH_3CHCH$), 0.95 (3H, d, $J = 6.8$ Hz, $(CH_3)CH_3CHCH$), 2.14 (1H, m, $(CH_3)_2CHCH$), 4.72 (1H, m, $(CH_3)_2CHCH$), 5.07 (1H, d, $J = 12.3$ Hz, PhCHHOCO), 5.12 (1H, d, $J = 12.1$ Hz, PhCHHOCO), 5.81 (1H, br d, $J = 8.6$ Hz, NH), 7.31 (5H, m, ArH), 8.47 (1H, s, N=CHC), 8.51 (2H, m, NCH=CHN); δ_C (125 MHz, $CDCl_3$) 18.24, 19.15, 33.79, 58.92, 66.91, 128.12, 128.15, 128.53, 136.42, 143.47, 144.07, 155.38, 156.19; *m*/*z* 285 (M^+), 91 ($PhCH_2$, 100%).

(1′*S*,2′*S*)-2-(2′-Methyl-1′-*N*-benzyloxycarbonylaminobutyl)-pyrazine, 5f. Treatment of (*N*-benzyloxycarbonyl-L-isoleucyl)-diazomethane **2f** (0.15 g, 0.52 mmol) in acetone (15 ml) with DMD (11 ml, 0.07 M, 1.5 eq.) according to the general procedure and subsequent condensation with diaminoethane (0.035 ml, 0.52 mmol) in CH_2Cl_2 (20 ml) yielded the crude dihydropyrazine as a yellow oil. The dihydropyrazine was dehydrogenated according to the general procedure in the presence of MnO_2 (0.135 g, 1.56 mmol) and KOH (0.032 g, 0.57 mmol) to yield the crude pyrazine as a brown oil. Purification by flash chromatography on silica using EtOAc–hexane (40 : 60) gave the title compound **5f** as a pale yellow waxy solid (70 mg, 45%) (Found: C, 68.3; H, 7.2; N, 13.8%. $C_{17}H_{21}N_3O_2$ requires: C, 68.2; H, 7.0; N, 14.0%); $[\alpha]_D^{20}$ −51.3 (*c*, 1.92 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3357, 1689; δ_H (500 MHz, $CDCl_3$) 0.77 (3H, d, $J = 6.75$ Hz, CH_3CH), 0.91 (3H, t, $J = 7.4$ Hz, CH_3CH_2-CH), 1.16 (1H, m, CH_3CHHCH), 1.55 (1H, m, CH_3CHHCH), 1.91 (1H, m, CH_3CH_2CHCH), 4.77 (1H, m, CHNH), 5.07, 5.11 (2H, 2 × d, $J = 12.3$ Hz, $PhCH_2OCO$), 5.84 (1H, br d, $J = 8.6$ Hz, NH), 7.31 (5H, m, ArH), 8.46 (1H, s, N=CHC), 8.51 (2H, m, NCH=CHN); δ_C (125 MHz, $CDCl_3$) 11.37, 14.57, 15.36, 25.13, 40.07, 57.91, 66.89, 128.12, 128.14, 128.38, 128.52, 136.42, 142.38, 143.47, 144.04, 155.34, 156.06; *m*/*z* 299 (M^+), 91 ($PhCH_2$, 100%).

(1′*S*)-2-(1′-*N*-Benzyloxycarbonylaminoethyl)-5-methyl-pyrazine and (1′*S*)-2-(1′-*N*-benzyloxycarbonylaminoethyl)-6-methylpyrazine, 6. Treatment of (*N*-benzyloxycarbonyl-L-alanyl)diazomethane **2b** (0.2 g, 0.81 mmol) in acetone (15 ml) with DMD (17 ml, 0.07 M, 1.5 eq.) according to the general procedure and subsequent condensation with 1,2-diaminopropane (0.07 ml, 0.52 mmol) in CH_2Cl_2 (20 ml) for 4 hours yielded the crude dihydropyrazine as a pale yellow oil. The dihydropyrazine was dehydrogenated according to the general procedure in the presence of MnO_2 (0.21 g, 2.4 mmol) and KOH (0.05 g, 0.89 mmol) to yield the crude pyrazines as a brown oil. Purification by flash chromatography on silica using EtOAc–hexane (40 : 60) gave the title compounds as an inseparable mixture of regioisomers (3 : 2) as a colourless oil **6** (0.12 g, 55%) (Found: M^+ 271.1326. $C_{15}H_{17}N_3O_2$ requires: M^+ 271.1321); δ_H (500 MHz, $CDCl_3$) 1.48 (2 × 3H, d, CH_3CH-(NH)), 2.52, 2.54 (2 × 3H, s, Het-CH_3), 4.97 (2 × 1H, CH_3CH-(NH)), 5.10 (2 × 2H, m, $PhCH_2OCO$), 5.83, 5.94 (2 × 1H, br s, NH), 7.31 (2 × 5H, m, Ph-H), 8.34, 8.36, 8.46 (2 × 2H, s, Het-H).

(1′*S*)-2-(1′-*N*-Benzyloxycarbonylaminoethyl)-5-methoxycarbonylpyrazine, 7, and (1′*S*)-2-(1′-*N*-benzyloxycarbonylaminoethyl)-6-methoxycarbonylpyrazine 8. Treatment of (*N*-benzyloxycarbonyl-L-alanyl)diazomethane **2b** (0.2 g, 0.81 mmol) in acetone (15 ml) with DMD (17 ml, 0.07 M, 1.5 eq.) according to the general procedure and subsequent condensation with 2,3-diaminopropionic acid methyl ester dihydrochloride (0.15 g, 0.81 mmol) in the presence of NEt_3 (0.23 ml, 1.6 mmol) in MeOH (20 ml) overnight, yielded the crude pyrazine as a mixture of regioisomers which was purified by flash chromatography on silica using EtOAc–hexane (50 : 50) as eluant to give regioisomer **7** as a colourless oil (65 mg, 25%), $[\alpha]_D^{20}$ −48.6 (*c*, 1.68 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3330, 1723; δ_H (500 MHz, $CDCl_3$) 1.46 (3H, d, $J = 6.9$ Hz, CH_3CHNH), 3.95 (3H, s, CO_2CH_3), 4.69 (1H, m, CH_3CHNH), 5.07 (2H, s, $PhCH_2OCO$), 5.72 (1H, br d, $J = 4.35$ Hz, NH), 7.27 (5H, m, Ar-H), 8.69 (1H, s, Het-H), 9.11 (1H, s, Het-H); δ_C (125 MHz, $CDCl_3$) 22.07, 47.87, 51.13, 65.10, 126.26, 126.35, 126.55, 126.67, 126.85, 134.35, 142.79, 144.00, 163.50. Further elution of the column gave regioisomer **8** as a colourless oil (72 mg, 28%), $[\alpha]_D^{20}$ −57.4 (*c*, 0.86 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3336, 1724; δ_H (500 MHz, $CDCl_3$), 1.44 (3H, d, $J = 6.9$ Hz, CH_3CHNH), 3.97 (3H, s, CO_2CH_3), 5.03 (3H, m, $PhCH_2OCO + CH_3CHNH$), 5.62 (1H, br s, NH), 7.29 (5H, Ar-H), 8.63 (1H, s, Het-H), 9.15 (1H, s, Het-H); δ_C (125 MHz, $CDCl_3$), 20.98, 48.78, 52.09, 66.03, 127.14, 127.24, 127.55, 140.95, 141.50, 144.34, 163.29 (Found: C, 60.6; H, 5.4; N, 12.9. $C_{16}H_{17}N_3O_4$ requires: C, 60.9; H, 5.4; N, 13.3%). Regioisomers assigned by HMBC and HMQC NMR spectra.

Oxidation of *N*-protected amino acid diazoketones and derivatization as quinoxalines and pyrido[2,3-*b*]pyrazines: general procedure

The diazoketone (1 eq.) was dissolved in acetone and stirred at 0 °C, under an atmosphere of nitrogen. One equivalent of dimethyldioxirane was added in a single portion. Reactions were monitored by TLC and if more DMD was required it was added. The crude glyoxal was then dissolved in ethanol and stirred at room temperature. 1.05 equivalents of freshly reduced *o*-phenylenediamine† or 2,3-diaminopyridine‡ was added and the solution stirred overnight at room temperature. The solvent was then removed under reduced pressure and the crude material purified by flash chromatography or PLC on silica.

(1′*S*)-2-(1′-*N*-Benzyloxycarbonylaminoethyl)quinoxaline, 9b. Treatment of (*N*-benzyloxycarbonyl-L-alanyl)diazomethane **2b** (61.9 mg, 0.25 mmol) in acetone (40 ml) with 1 equivalent DMD (3.0 ml of a 0.089 M solution in acetone, 0.27 mmol) according to the general procedure and subsequent condensation with *o*-phenylenediamine (27.9 mg, 0.26 mmol) yielded the crude product as a brown oil (81.3 mg). The crude material was purified by PLC on silica, using 50% ethyl acetate–hexane as eluant, to give the pure quinoxaline **9b** (71.6 mg, 93%) as a white solid, mp 124–125 °C (Found: C, 70.2; H, 5.7; N, 13.7. $C_{18}H_{17}N_3O_2$ requires: C, 70.3; H, 5.6; N, 13.7%); $[\alpha]_D^{20}$ −111.2 (*c*, 2.2 in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3324 (NH), 1684 (CO of carbamate); δ_H (500 MHz, $CDCl_3$) 1.61 (3H, d, J = 6.6 Hz, CH_3CH), 5.14 (2H, dd, J_1 = 17.2 Hz, J_2 = 12.1 Hz, OCH_2Ph), 5.22 (1H, m, CH(N)CO), 6.30 (1H, d, J = 7.0 Hz, NH), 7.31–7.38 (5H, m, Ar-H), 7.74 (2H, m, Ar-H), 8.07 (2H, m, Ar-H), 8.84 (1H, s, CH=N).

(1′*S*,2′*S*)-2-(1′-*N*-*tert*-Butoxycarbonylamino-2′-methylbutyl)-quinoxaline, 9e. Treatment of [(3*S*,4*S*)-*N*-*tert*-butoxycarbonylisoleucyl]diazomethane **2e** (109.7 mg, 0.43 mmol) in acetone (50 ml) with 1 equivalent DMD (4.6 ml of a 0.093 M solution in acetone, 0.43 mmol) according to the general procedure and subsequent condensation with *o*-phenylenediamine (54 mg, 0.50 mmol) yielded the crude product as a brown oil. Purification by PLC on silica, using 25% ethyl acetate–75% hexane as eluant, yielded the pure product **9e** (128.9 mg, 95%) as a white solid, mp 131–133 °C (Found: C, 68.4; H, 8.2; N, 13.4. $C_{18}H_{25}N_3O_2$ requires: C, 68.5; H, 8.0; N, 13.3%); $[\alpha]_D^{20}$ −96.4 (*c*, 2.7 in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3255 (NH), 1713 (CO of carbamate); δ_H (300 MHz, $CDCl_3$) 0.86 (3H, d, J = 6.8 Hz, CH_3CH), 0.93 (3H, t, J = 7.3 Hz, CH_3CH), 1.19–1.26 (1H, br m, CH_3CH_2), 1.45 (9H, s, $(CH_3)_3C$), 1.50–1.60 (1H, br m, CH_3CH_2), 2.03 (1H, br m, CH_3CH_2), 4.97 (1H, br t, CH-(N)CO), 5.82 (1H, br d, NH), 7.75 (2H, m, Ar-H), 8.10 (2H, m, Ar-H), 8.80 (1H, s, CH=N); δ_C (75 MHz, $CDCl_3$) 11.40 (CH_3CH_2), 15.39 (CH_3CH), 24.88 (CH_2), 28.24 (($CH_3)_3C$), 40.39 ($CHCH_3$), 57.84 (CH(N)CO), 79.41 (($CH_3)_3C$), 128.96, 129.11, 129.34, 129.90, 141.64 (Ar-C-N), 141.70 (Ar-C-N), 144.74 (HC=N), 155.32, 155.47 (CO of carbamate and CC=N).

(1′*S*,2′*S*)-2-(2′-Methyl-1′-*N*-benzyloxycarbonylaminobutyl)-quinoxaline, 9f. Treatment of [(3*S*,4*S*)-*N*-benzyloxycarbonylisoleucyl]diazomethane **2f** (93.8 mg, 0.32 mmol) in acetone (50 ml) with 1 equivalent DMD (4.0 ml of a 0.086 M solution in acetone, 0.34 mmol) according to the general procedure and subsequent condensation with *o*-phenylenediamine (37 mg, 0.34 mmol) yielded the crude product as a brown solid. Purification by PLC on silica, using 25% ethyl acetate–75% hexane as eluant, yielded the pure product **9f** (102.8 mg, 91%) as a yellow solid, mp 116–118 °C (Found: C, 71.7; H, 6.9; N, 11.8. $C_{21}H_{23}N_3O_2$ requires: C, 72.2; H, 6.6; N, 12.0%); $[\alpha]_D^{20}$ −117.2 (*c*, 2 in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3210 (NH), 1700 (CO of carbamate); δ_H (300 MHz, $CDCl_3$) 0.87 (3H, d, J = 6.7 Hz, CH_3CH), 0.92 (3H, t, J = 7.4 Hz, CH_3CH_2), 1.17–1.28 (1H, br m, CH_3CH_2), 1.54–1.61 (1H, br m, CH_3CH_2), 2.03–2.07 (1H, br m, CH_3CH), 5.05 (1H, overlapping dd, J = 8.1 Hz, CH(N)CO), 5.12 (2H, d, J = 2.5 Hz, OCH_2Ph), 6.18 (1H, d, J = 8.4 Hz, NH), 7.26–7.35 (5H, m, Ar-H), 7.71–7.77 (2H, m, Ar-H), 8.03–8.13 (2H, m, Ar-H), 8.80 (1H, s, CH=N); δ_C (75 MHz, $CDCl_3$) 11.33 (CH_3CH_2), 15.31 (CH_3CH), 24.87 (CH_2), 40.38 ($CHCH_3$), 58.23 (CH(N)CO), 66.76 (OCH_2), 127.97, 128.34, 128.90, 129.12, 129.43, 129.97, 136.22 (Ar-CCH_2O), 141.60 (Ar-C-N), 141.69 (Ar-C-N), 144.62 (HC=N), 154.76, 156.00 (CO of carbamate and CC=N).

(±)-2-(2′-Methyl-1′-*N*-*tert*-butoxycarbonylaminobutyl)quinoxaline, 9g. Treatment of (±)-(*N*-*tert*-butoxycarbonylisoleucyl)-diazomethane **2g** (85.9 mg, 0.34 mmol) in acetone (50 ml) with 1 equivalent DMD (3.7 ml of a 0.093 M solution in acetone, 0.34 mmol) according to the general procedure and subsequent condensation with *o*-phenylenediamine (42 mg, 0.39 mmol) yielded the crude product as a brown oil. Purification by PLC on silica, using 25% ethyl acetate–75% hexane as eluant, yielded the pure product **9g** (97.5 mg, 92%) as a white solid; δ_H (300 MHz, $CDCl_3$) 0.87 (3H, m, CH_3CH_2), 0.97 (3H, m, CH_3CH), 1.14–1.25 (1H, br m, CH_3CH_2), 1.45 (9H, s, $(CH_3)_3C$), 1.40–1.57 (1H, br m, CH_3CH_2), 1.98–2.04 (1H, br m, CH_3CH), 4.96, 5.07 (1H, 2 × br m, CH(N)CO), 5.77 (1H, br m, NH), 7.74 (2H, m, Ar-H), 8.09 (2H, m, Ar-H), 8.78 (1H, s, CH=N); δ_C (75 MHz, $CDCl_3$) 11.41, 11.64 (CH_3CH_2), 13.95, 15.39 (CH_3CH), 24.88, 26.36 (CH_3CH_2), 28.24 (($CH_3)_3C$), 40.39, 40.59 (CH_3CH), 57.12, 57.40 (CH(N)CO), 79.41 (($CH_3)_3C$), 128.96, 129.10, 129.30, 129.33, 129.89, 141.57, 141.64, 141.70 (Ar-C-N), 144.52, 144.55 (HC=N), 155.33, 155.69 (CO of carbamate and CC=N).

(1′*S*)-2-(1′-*N*-*tert*-Butoxycarbonylamino-2′-phenylethyl)quinoxaline, 9l. Treatment of (*N*-*tert*-butoxycarbonyl-L-phenylalanyl)diazomethane **2l** (78.8 mg, 0.27 mmol) in acetone (40 ml) with 1 equivalent DMD (3.2 ml of a 0.089 M solution in acetone, 0.28 mmol) according to the general procedure and subsequent condensation with *o*-phenylenediamine (30.5 mg, 0.28 mmol) yielded the crude product as a brown oil. Purification by PLC on silica, using 50% ethyl acetate–50% hexane as eluant, yielded the pure product **9l** (95.2 mg, 93%) as a white solid, mp 108–110 °C (Found: C, 71.8; H, 6.8; N, 11.8. $C_{21}H_{23}N_3O_2$ requires: C, 72.2; H, 6.6; N, 12.0%); $[\alpha]_D^{20}$ +16.1 (*c*, 4.8 in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3201 (NH), 1700 (CO of carbamate); δ_H (500 MHz, $CDCl_3$) 1.45 (9H, s, $(CH_3)_3C$), 3.16 (1H, dd, J_1 = 12.9 Hz, J_2 = 8.1 Hz, $PhCH_2$), 3.37 (1H, dd, J_1 = 13.3 Hz, J_2 = 5.6 Hz, $PhCH_2$), 5.15, 5.30 (1H, br s and m, CH(N)CO), 5.70, 5.94 (1H, br s and d, J = 7.3 Hz, NH), 7.02 (2H, s, Ar-H), 7.19 (3H, s, Ar-H), 7.75 (2H, m, Ar-H), 8.07 (2H, dd, J_1 = 7.3 Hz, J_2 = 1.3 Hz, Ar-H), 8.40 (1H, s, CH=N).

(1′*S*)-2-(1′-*N*-Benzyloxycarbonylamino-2′-phenylethyl)quinoxaline, 9m. Treatment of (*N*-benzyloxycarbonyl-L-phenylalanyl)diazomethane **2m** (79.5 mg, 0.24 mmol) in acetone (20 ml) with 1 equivalent DMD (3.7 ml of a 0.065 M solution in acetone, 0.24 mmol) according to the general procedure and subsequent condensation with *o*-phenylenediamine (31 mg, 0.28 mmol) yielded the crude product as a brown oil. The crude material was purified by PLC on silica, following multiple elution, using 70% ether–30% hexane as eluant. The resulting product was then recrystallized from methanol to give the pure quinoxaline **9m** (86.7 mg, 92%) as a pale yellow solid, mp 110–

† The crude *o*-phenylenediamine (25 g) was dissolved in hot water (90 ml) containing sodium hydrosulfite (2 g), clarified with decolorizing charcoal. After cooling, the crystals were filtered and stored in a vacuum desiccator. L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Wiley, New York, 1967, vol. 1, p. 835.

‡ The crude 2,3-diaminopyridine was purified by dissolution in boiling benzene and clarifying with decolorizing charcoal followed by crystallization from benzene to give purple needle-like crystals.

111.5 °C (Found: C, 75.2; H, 5.6; N, 10.7. $C_{24}H_{21}N_3O_2$ requires: C, 75.2; H, 5.5; N, 11.0%); $[\alpha]_D^{20}$ + 18.9 (*c*, 0.8 in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3329 (NH), 1717 (CO of carbamate); δ_H (500 MHz, $CDCl_3$) 3.16 (1H, dd, J_1 = 13.4 Hz, J_2 = 8.0 Hz, $PhCH_2$), 3.40 (1H, dd, J_1 = 13.6 Hz, J_2 = 5.7 Hz, $PhCH_2$), 5.13 (2H, dd, J_1 = 18.6 Hz, J_2 = 12.3 Hz, OCH_2Ph), 5.35 (1H, dd, J_1 = 14.0 Hz, J_2 = 7.8 Hz, CH(N)CO), 6.21 (1H, d, *J* = 7.8 Hz, NH), 6.98 (2H, m, Ar-H), 7.19 (4H, m, Ar-H), 7.36 (4H, d, *J* = 4.1 Hz, Ar-H), 7.76 (2H, m, Ar-H), 8.06 (2H, dd, J_1 = 18.1 Hz, J_2 = 7.4 Hz, Ar-H), 8.38 (1H, s, CH=N); δ_C (125 MHz, $CDCl_3$) 42.57 ($PhCH_2$), 55.58 (CH(N)CO), 66.96 (OCH_2Ph), 126.95, 128.18, 128.21, 128.57, 129.00, 129.35, 129.46, 129.74, 130.22, 136.23 (Ar-C), 136.37 (Ar-C), 141.70 (Ar-C-N), 141.91 (Ar-C-N), 144.47 (CH=N), 154.42, 155.74 (CO of carbamate and CC=N).

Structural assignment was facilitated by H–H COSY and H–C COSY experiments.

(*S*)-2-(*N*-Ethoxycarbonylpyrrolidin-2-yl)quinoxaline, 9o. Treatment of (*N*-ethoxycarbonyl-L-prolyl)diazomethane **2o** (100.9 mg, 0.48 mmol) in acetone (40 ml) with 1 equivalent DMD (6 ml of a 0.089 M solution in acetone, 0.53 mmol) according to the general procedure and subsequent condensation with *o*-phenylenediamine (52.0 mg, 0.48 mmol) yielded the crude product as a brown oil. Purification by PLC on silica, using 50% ethyl acetate–50% hexane as eluant, yielded the pure product **9o** (116.5 mg, 90%) as an oil (Found: C, 66.2; H, 6.5; N, 15.3. $C_{15}H_{17}N_3O_2$ requires: C, 66.4; H, 6.3; N, 15.5%); $[\alpha]_D^{20}$ −140.4 (*c*, 0.9 in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 1695 (CO of carbamate); δ_H (500 MHz, $CDCl_3$) 0.88, 1.23 (3H, 2 × t, *J* = 7.0 Hz, CH_2CH_3), 1.93–2.47 (4H, br m, CH_2CH_2), 3.62–3.78 (2H, br m, CH_2N), 3.94, 4.09 (2H, q, *J* = 7.0 Hz and m, OCH_2CH_3), 5.11, 5.19 (1H, dd, J_1 = 8.1 Hz, J_2 = 4.4 Hz and dd, J_1 = 7.7 Hz, J_2 = 4.0 Hz, CH(N)CO), 7.65–7.74 (2H, m, Ar-H), 8.00–8.07 (2H, m, Ar-H), 8.75, 8.81 (1H, 2 × s, CH=N).

(*S*)-2-(1′-*N*-Benzyloxycarbonylamino- 2′-methylpropyl)quinoxaline, 9q. Treatment of (*N*-benzyloxycarbonyl-L-valyl)-diazomethane **2q** (2.29 g, 8.32 mmol) in acetone (60 ml) with 1 equivalent DMD (100 ml of a 0.084 M solution in acetone, 8.4 mmol) according to the general procedure and subsequent condensation with *o*-phenylenediamine (0.91 g, 8.42 mmol) yielded the crude product as a yellow solid. Flash chromatography on silica using 20% ethyl acetate–80% hexane as eluant yielded the pure product **9q** (2.67 g, 96%) as a white solid, mp 99–100.5 °C (Found: C, 71.5; H, 6.2; N, 12.5. $C_{20}H_{21}N_3O_2$ requires: C, 71.6; H, 6.3; N, 12.5%); $[\alpha]_D^{20}$ −129.6 (*c*, 3.5 in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3287 (NH), 1688 (CO of carbamate); δ_H (500 MHz, $CDCl_3$) 1.06 (6H, overlapping d, *J* = 7.2 Hz, $(CH_3)_2CH$), 2.38 (1H, m, $(CH_3)_2CH$), 5.10 (1H, dd, J_1 = 8.6 Hz, J_2 = 6.0 Hz, CH(N)CO), 5.23 (2H, dd, J_1 = 21.8 Hz, J_2 = 12.3 Hz, OCH_2Ph), 7.42–7.49 (5H, m, Ar-H), 7.85–7.89 (2H, m, Ar-H), 8.18 (2H, m, Ar-H), 8.90 (1H, s, CH=N).

(*S*)-2-(1′-*N*-Ethoxycarbonylamino-2′-methylpropyl)quinoxaline, 9r. Treatment of (*N*-ethoxycarbonyl-L-valyl)diazomethane **2r** (81.9 mg, 0.38 mmol) in acetone (40 ml) with 1 equivalent DMD (4.5 ml of a 0.089 M solution in acetone, 0.40 mmol) according to the general procedure and subsequent condensation with *o*-phenylenediamine (43.0 mg, 0.40 mmol) yielded the crude product as a brown oil. Purification by PLC on silica, using 50% ethyl acetate–50% hexane as eluant, yielded the pure product **9r** as a white solid, mp 62–65 °C (Found: C, 65.5; H, 7.2; N, 15.1. $C_{15}H_{19}N_3O_2$ requires: C, 65.9; H, 7.0; N, 15.4%); $[\alpha]_D^{20}$ −163.5 (*c*, 2.9 in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3323 (NH), 1681 (CO of carbamate); δ_H (500 MHz, $CDCl_3$) 0.91 (3H, d, *J* = 6.6 Hz, $(CH_3)_2CH$), 0.93 (3H, d, *J* = 7.0 Hz, $(CH_3)_2CH$), 1.22 (3H, t, *J* = 7.0 Hz, CH_3CH_2), 2.24 (1H, m, $(CH_3)_2CH$), 4.10 (2H, m, CH_2CH_3), 4.94 (1H, dd, J_1 = 8.6 Hz, J_2 = 6.6 Hz, CH(N)CO), 6.03 (1H, d, *J* = 8.4 Hz, NH), 7.72 (2H, m, Ar-H), 8.03 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.2 Hz, Ar-H), 8.08 (1H, dd, J_1 = 7.7 Hz, J_2 = 1.8 Hz, Ar-H), 8.77 (1H, s, Ar-H).

(*S*)-2-(1′-*N*-Phthaloylamino-2′-methylpropyl)quinoxaline, 9s. Treatment of (*N*-phthaloyl-L-valyl)diazomethane **2s** (74.0 mg, 0.27 mmol) in acetone (40 ml) with 1 equivalent DMD (3.5 ml of a 0.089 M solution in acetone, 0.31 mmol) according to the general procedure and subsequent condensation with *o*-phenylenediamine (31.0 mg, 0.29 mmol) yielded the crude product as a brown oil. Purification by PLC on silica, using 50% ethyl acetate–50% hexane as eluant, yielded the pure product **9s** as a white solid, mp 101–103 °C (Found: C, 72.1; H, 5.1; N, 12.4. $C_{20}H_{17}N_3O_2$ requires: C, 72.5; H, 5.2; N, 12.7%); $[\alpha]_D^{20}$ −90.0 (*c*, 0.12 in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 1715 (carbonyls); δ_H (500 MHz, $CDCl_3$) 1.03 (3H, d, *J* = 6.7 Hz, $(CH_3)_2CH$), 1.09 (3H, d, *J* = 6.7 Hz, $(CH_3)_2CH$), 3.47 (1H, m, $(CH_3)_2CH$), 5.32 (1H, d, *J* = 11.2 Hz, CH(N)CO), 7.70–7.76 (4H, m, Ar-H), 7.84 (2H, dd, J_1 = 5.4 Hz, J_2 = 3.2 Hz, Ar-H), 8.09 (2H, m, Ar-H), 9.23 (1H, s, CH=N).

(1′*S*,2″*S*)-2-[1′-(2″-*N*-Benzyloxycarbonylamino-3″-phenylpropanoylamino)ethyl]quinoxaline, 9v. Treatment of (*N*-benzyloxycarbonyl-L-phenylalanyl-L-alanyl)diazomethane **2v** (267.0 mg, 0.68 mmol) in acetone (30 ml) with 1 equivalent DMD (15.0 ml of a 0.045 M solution in acetone, 0.68 mmol) according to the general procedure and subsequent condensation with *o*-phenylenediamine (73.2 mg, 0.68 mmol) yielded the crude product as a yellow solid. Purification by flash chromatography on silica yielded the pure product **9v** (279.5 mg, 91%) as a white solid. A microanalytically pure sample was obtained by recrystallization from ethyl acetate–hexane (Found: C, 71.2; H, 5.6; N, 12.5. $C_{27}H_{26}N_4O_3$ requires: C, 71.3; H, 5.8; N, 12.3%); $[\alpha]_D^{20}$ −106.2 (*c*, 1.2 in CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3264 (NH), 1687 (CO of carbamate), 1647 (CO of amide); δ_H (500 MHz, $CDCl_3$) 1.51 (3H, d, *J* = 6.6 Hz, CH_3CH), 2.97 (1H, m, $PhCH_2$), 3.16 (1H, dd, J_1 = 13.7 Hz, J_2 = 5.7 Hz, $PhCH_2$), 4.50 (1H, m, CH(N)CO), 5.12 (2H, s, OCH_2Ph), 5.30 (1H, quintet, *J* = 7.0 Hz, CH(N)CO), 5.52 (1H, br d, *J* = 7.3 Hz, NH), 6.70 (1H, br m, NH), 6.99 (3H, br d, Ar-H), 7.10 (3H, d, *J* = 7.3 Hz, Ar-H), 7.35 (4H, s, Ar-H), 7.77 (2H, dd, J_2 = 6.4 Hz, J_2 = 3.5 Hz, Ar-H), 7.91 (1H, dd, J_1 = 6.2 Hz, J_2 = 3.3 Hz, Ar-H), 8.12 (1H, dd, J_1 = 6.0 Hz, J_2 = 3.8 Hz, Ar-H), 8.73 (1H, s, CH=N); δ_C (125 MHz, $CDCl_3$) 21.92 (*C*H_3), 39.12 (Ph*C*H_2), 48.23 (*C*HNCO), 56.50 (*C*H(N)CO), 67.04 (O*C*H_2Ph), 128.48, 128.51, 128.99, 129.09, 129.24, 129.73, 130.23, 136.11 (Ar-C), 141.93 (Ar-C-N), 143.93 (HC=N), 155.13, 155.80 (CO of carbamate and C*C*=N), 170.11 (CO of amide).

(*S*)-3-(1′-*N*-Benzyloxycarbonylaminoethyl)pyrido[2,3-*b*]-pyrazine, 10b. Oxidation of (*N*-Cbz-L-alanyl)diazomethane **2b** (0.15 g, 0.61 mmol) in acetone (10 ml) with DMD (13 ml, 0.07 M, 1.5 eq.) according to the general procedure and subsequent condensation with 2,3-diaminopyridine (66 mg, 0.61 mmol) in EtOH (15 ml) yielded the crude product as a brown oil which was purified by flash chromatography on silica using EtOAc as eluant to give the title compound as a pale yellow oil **10b** (0.172 g, 92% yield) (Found: M^+, 308.1273. $C_{17}H_{16}N_4O_2$ requires: *M*, 308.1273); $[\alpha]_D^{20}$ −73.3 (*c*, 0.93, $CHCl_3$); ν_{max} (film)/cm^{-1} 3313, 1716, 1602; δ_H (500 MHz, $CDCl_3$) 1.67 (3H, d, *J* = 6.9 Hz, CH_3CH), 5.12 (2H, dd, J_1 = 18.6 Hz, J_2 = 12.4 Hz, OCH_2Ph), 5.32 (1H, m, CH_3CH), 6.49 (1H, d, *J* = 6.9 Hz, N-H), 7.28–7.33 (5H, m, Ar-H), 7.68 (1H, m, Ar-H), 8.47 (1H, m, Ar-H), 9.03 (1H, s, CH=N), 9.14 (1H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 22.74, 51.06, 67.72, 126.00, 128.85, 128.94, 129.35, 137.25, 137.99, 139.36, 146.50, 151.07, 155.14, 156.78, 160.95; *m*/*z* 308 (M^+), 159 (M^+ − Cbz, 100%).

(*S*)-3-(3′-Methyl-1′-*N*-benzyloxycarbonylaminobutyl)pyrido-[2,3-*b*]pyrazine, 10i. Oxidation of (*N*-Cbz-L-leucyl)diazomethane **2i** (50 mg, 0.17 mmol) in acetone (5 ml) with DMD

(4 ml, 0.07 M, 1.5 eq.) according to the general procedure and subsequent condensation with 2,3-diaminopyridine (20 mg, 0.17 mmol) in EtOH (10 ml) yielded the crude product as a brown oil which was purified by flash chromatography on silica using EtOAc–hexane (60:40) as eluant to give the title compound as a yellow oil **10i** (64 mg, 90%) (Found: C, 68.3; H, 6.2; N, 15.9. $C_{20}H_{22}N_4O_2$ requires: C, 68.5; H, 6.3; N, 16.0); $[\alpha]_D^{20}$ −133 (*c*, 1.0 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3440, 1716; δ_H (500 MHz, $CDCl_3$) 0.97 (3H, d, J = 6.6 Hz, $CH_3CH(CH_3)$), 1.01 (3H, d, J = 6.4 Hz, $CH_3CH(CH_3)$), 1.17 (1H, m, $(CH_3)_2CH$), 1.81 (2H, m, $(CH_3)_2CHCH_2$), 5.00 (2H, dd, J_1 = 20.3 Hz, J_2 = 12.4 Hz, OCH_2Ph), 5.28 (1H, m, $(CH_3)_2CHCH_2CH$), 6.07 (IH, d, J = 8.6 Hz, N-H), 7.17–7.35 (5H, m, Ar-H), 7.70 (1H, m, Ar-H), 8.48 (1H, m, Ar-H), 9.00 (1H, s, CH=N), 9.15 (1H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 20.05, 21.62, 22.33, 24.35, 44.67, 45.75, 52.09, 59.75, 66.27, 67.51, 124.46, 126.19, 126.70, 127.32, 127.42, 127.83, 128.05, 135.68, 136.57, 137.94, 143.84, 144.49, 145.26, 149.83, 153.58, 154.68, 155.33, 155.50, 159.67; *m*/*z* 350 (M^+).

(*S*)-3-(2′-Phenyl-1′-*N*-benzyloxycarbonylaminoethyl)pyrido-[2,3-*b*]pyrazine, 10m. Oxidation of (*N*-Cbz-L-phenylalanyl)-diazomethane **2m** (0.15 g, 0.46 mmol) in acetone (10 ml) with DMD (10 ml, 0.07 M, 1.5 eq.) according to the general procedure and subsequent condensation with 2,3-diaminopyridine (50 mg, 0.46 mmol) in EtOH (15 ml) yielded the crude product as a brown oil which was purified by flash chromatography on silica using EtOAc–hexane (80:20) as eluant to give the title compound as a pale brown solid **10m** (0.16 g, 90% yield); mp 115–117 °C (Found: C, 71.8; H, 5.5; N, 14.8. $C_{23}H_{20}N_4O_2$ requires: C, 71.8; H, 5.2; N, 14.6); $[\alpha]_D^{20}$ +65.56 (*c*, 0.9, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3347, 1686; δ_H (500 MHz, $CDCl_3$) 3.21 (1H, dd, J_1 = 13.4 Hz, J_2 = 8.4 Hz, $PhCH_2CH$), 3.44 (1H, dd, J_1 = 13.3 Hz, J_2 = 6.1 Hz, $PhCH_2CH$), 5.09 (2H, dd, J_1 = 20.9 Hz, J_2 = 12.4 Hz, OCH_2Ph), 5.42 (1H, m, $PhCH_2CH(NH)$), 6.30 (1H, br d, J = 7.65, N-H), 7.01–7.32 (5H, m, Ar-H), 7.71 (1H, m, Ar-H), 8.44 (1H, m, Ar-H), 8.49 (1H, s, CH=N), 9.16 (1H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 41.46, 54.74, 65.90, 124.23, 126.09, 126.95, 127.09, 127.50, 127.71, 128.38, 135.17, 136.17, 137.63, 144.90, 149.35, 153.27, 154.87, 157.56; *m*/*z* 384 (M^+), 91 ($PhCH_2$, 100%).

(*S*)-3-(*N*-Ethoxycarbonylpyrrolidin-2-yl)pyrido[2,3-*b*]pyrazine, 10o. Oxidation of (*N*-ethoxycarbonyl-L-prolyl)diazomethane **2o** (50 mg, 0.24 mmol) (5 ml) with DMD (5 ml, 0.07 M, 1.5 eq.) according to the general procedure and subsequent condensation with 2,3-diaminopyridine (26 mg, 0.24 mmol) in EtOH (10 ml) yielded the crude product as a brown oil which was purified by flash chromatography on silica using EtOAc as eluant to give the title compound as a brown oil **10o** (60 mg, 92%) (Found: M^+, 272.1271; $C_{14}H_{16}N_4O_2$ requires: M^+, 272.1273); $[\alpha]_D^{20}$ −102 (*c*, 3.2 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3475, 1694, 1601; δ_H (500 MHz, $CDCl_3$) 0.94, 1.26 (3H, 2 × t, J = 6.8 Hz, CH_3CH_2), 2.01–2.35 (4H, br m, CH_2CH_2), 3.66–3.79 (2H, br m, CH_2CH_2N), 3.99, 4.12 (2H, 2 × m, $CO_2CH_2CH_3$), 5.24, 5.28 (1H, 2 × m, CH_2CHN), 7.74 (1H, m, Ar-H), 8.50 (1H, m, Ar-H), 8.91, 8.96 (1H, 2 × s, CH=N), 9.18 (1H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 14.41, 14.62, 23.69, 24.48, 32.51, 34.02, 47.16, 47.66, 60.84, 61.10, 61.30, 104.55, 124.75, 124.86, 136.87, 138.31, 144.68, 144.75, 150.33, 153.87, 154.18, 160.98.

(*S*)-3-(2′-Methyl-1′-*N*-benzyloxycarbonylaminopropyl)-pyrido[2,3-*b*]pyrazine, 6q. Oxidation of (*N*-Cbz-L-valyl)-diazomethane **2q** (0.15 g, 0.54 mmol) in acetone (10 ml) with DMD (12 ml, 0.07 M, 1.5 eq.) according to the general procedure and subsequent condensation with 2,3-diaminopyridine (59 mg, 0.54 mmol) in EtOH (15 ml) yielded the crude product as a pale brown oil which was purified by flash chromatography on silica using EtOAc as eluant to give the title compound as a yellow oil **10q** (0.17 g, 94%) (Found: C, 67.9; H, 6.1; N, 16.8. $C_{19}H_{20}N_4O_2$ requires: C, 67.8; H, 5.9; N, 16.6); $[\alpha]_D^{20}$ −125 (*c*, 1.48 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3317, 1716, 1602; δ_H (500 MHz, $CDCl_3$) 0.96 (3H, d, J = 6.9 Hz, $CH_3CH(CH_3)$), 1.00 (3H, d, J = 6.8 Hz, $CH_3CH(CH_3)$), 2.35 (1H, m, $(CH_3)_2CH$), 5.06 (1H, m, $(CH_3)_2CHCH$), 5.09 (2H, dd, J_1 = 17.7 Hz, J_2 = 12.4 Hz, OCH_2Ph), 6.30 (IH, d, J = 8.8 Hz, N-H), 7.27–7.33 (5H, m, Ar-H), 7.71 (1H, m, Ar-H), 8.49 (1H, m, Ar-H), 8.96 (1H, s, CH=N), 9.17 (1H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 18.03, 19.46, 34.07, 59.30, 66.85, 125.09, 127.90, 127.99, 128.41, 136.33, 137.08, 138.52, 146.16, 150.33, 154.23, 156.38, 159.03; *m*/*z* 336 (M^+).

X-Ray crystal structure determination

Data were collected using a Siemens P3 four circle diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at room temperature. The structure was solved by direct methods all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atom positions were added at idealized positions and a riding model with fixed thermal parameters (U_{ij} = 1.2 U_{ij} (eq)) was used for subsequent refinement. The absolute configuration of **10m** was defined by the use of pure (L-phenylalanyl)glyoxal in the preparation of **10m**. The SHELXTL PC[15] and SHELXL-93[16] packages were used for structure solution and refinement. Additional material, available from the Cambridge Crystallographic Data Centre includes atomic coordinates, thermal parameters, remaining bond lengths and angles, and structure factors.[10]

Crystal data for $[C_{23}H_{20}O_2N_4]$ (**10m**): M = 384.43, monoclinic, space group $P2_1$, a = 5.119(1) Å, b = 9.171(2) Å, c = 21.063(4) Å, β = 92.94(3)°, U = 987.6(3) Å^{-3}, Z = 2, D_c = 1.293 Mg m^{-3}, $F(000)$ = 404, μ = 0.685 mm^{-1}, crystal dimensions = 0.54 × 0.35 × 0.15 mm. A total of 1940 reflections were measured for $4 < 2\theta < 110$ and 1720 unique reflections were used in the refinement. The final parameters were wR_2 = 0.1196 and R_1 = 0.0483 [$I > 2\sigma(I)$].

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