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Synthesis of Secondary Amines by Reductive Dimerization of Azides

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Abstract: Hydrogenolysis of azides using hydrogen over 5% palladium-on-charcoal at atmospheric pressure has provided a method for the preparation of symmetrical secondary amines by a reductive dimerization process. In this process, the azide carbons of two azides become attached to an amino nitrogen with concurrent expulsion of five nitrogen atoms.

Recently we have reported on stereoselective constructions of rigidified α-amino acids, both cyclic[1] and α-bridged bis(glycines).[2] In the present studies emphasis has been on the preparation of amines by way of intermediate azides. Conformationally restricted basic α-amino acids carrying an α-methyl substituent are of special interest as analogues of naturally occurring amino acids.[3] During this work we have discovered another route into α-bridged bis(glycines) connected by an ω-amino group (Scheme 1). Two products were formed in the reduction, *viz.* the primary amine and a secondary amine, the latter being the major product under the reaction conditions chosen.

The starting material for the syntheses was the bislactim ether, (2*R*,5*R*/*S*)-3,6-dimethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazine (**1**). The cyclic bislactim ether dipeptide was available from (*R*)-valine and racemic alanine.[4] Lithiation of the bislactim ether **1** at -78 °C was followed by alkylation with α,ω-dibromoalkanes in the presence of 1,3-dimethyl-2-imidazolidinone (DMEU). The conditions were chosen so as to favour monoalkylation, the product being the bromide **2**. The reactions were run both with straight addition of the alkylating reagent to the metalated bislactim ether and by inverse addition in which case the metalated bislactim ether was added to a large excess of the alkylating agent at -78 °C. The yields of monoalkylated products **2** were good. Invariably the inverse addition technique was superior both in product yields and in diastereoselectivity as seen by the diastereomeric (d.e) data. The d.e. figures given for the products from the inverse addition conditions mean that only one stereoisomer was seen by NMR. Capillary GLC was used to detect the second stereoisomer. After flash chromatography, a stereochemically homogenous product was obtained. No configurational change is assumed to take place in the subsequent reactions because the stereogenic center is quaternary.

High stereoselectivity at C-5 in the bislactim ether **1**, which already carries an alkyl group, seems to be a characteristic property of the 5-substituted bislactim system as both we and previous workers have reported.[1,4] This means that the 5-substituent in the metalated periplanar bislactim ether potentiates the shielding at the face of the isopropyl group with respect to the 5-unsubstituted parent compound. The increased sterical interaction

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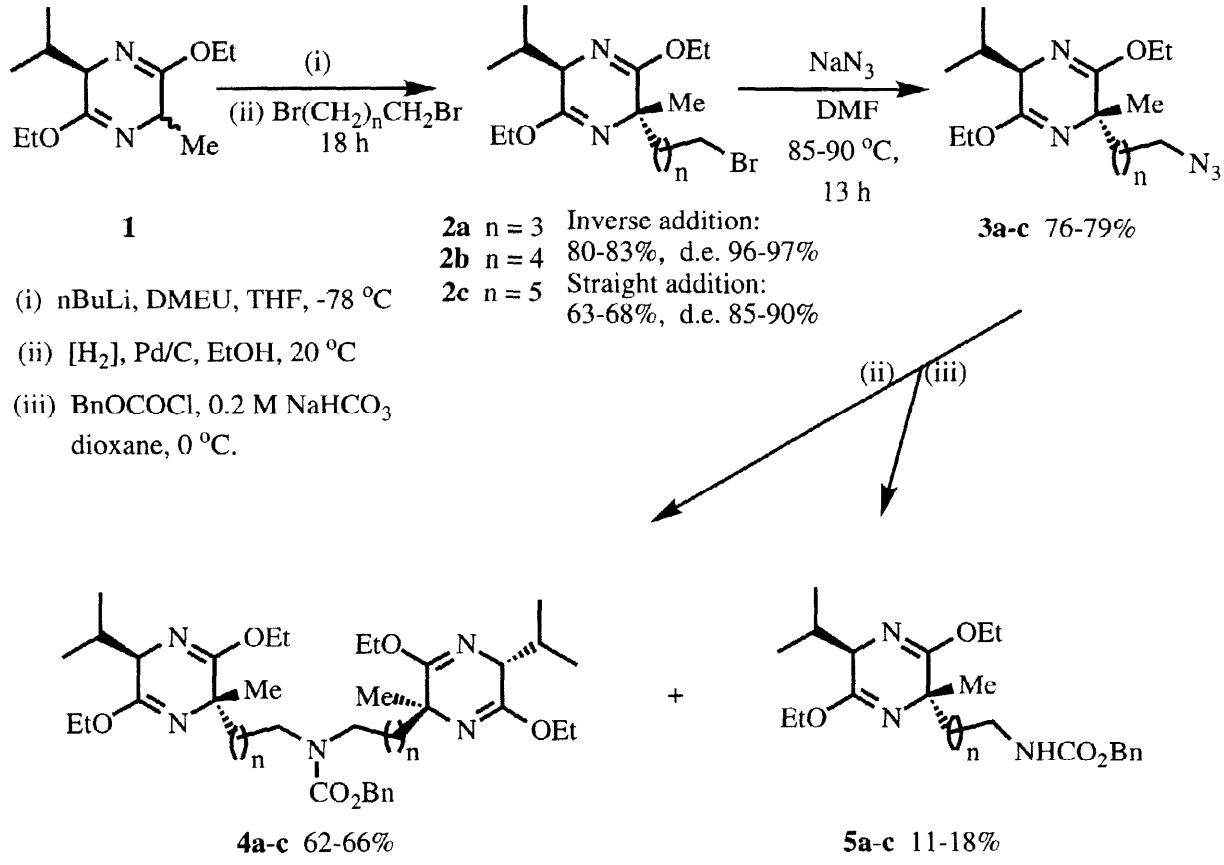
between the incoming electrophile and the isopropyl group directs the electrophile more strongly towards the unshielded face.

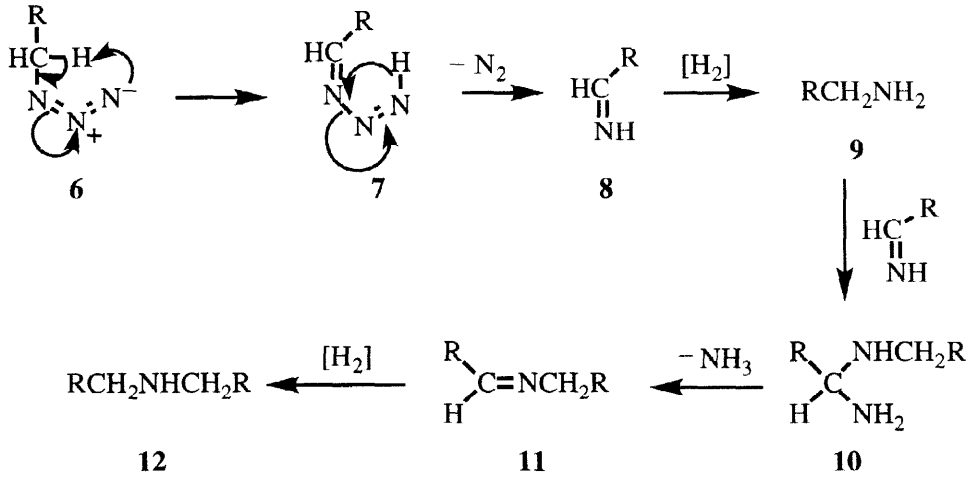
The bromide **2** was converted to the azide **3** by heating with sodium azide in DMF. Intramolecular competitive cyclization over *N*-4 was not observed. The azide **3** was subjected to hydrogenolysis using hydrogen over 5% palladium-on-charcoal in ethanol. Metal catalyzed hydrogenolysis reactions of azides with formation of primary amines are generally good reactions provided no other reducible groups are present.[5] Accordingly a primary amine was to be expected. The major product in this reaction, however, was a secondary amine. We are not aware of any other report describing formation of symmetrical secondary amines from azides in the reduction over palladium under related conditions. The secondary amine was isolated after *N*-benzyloxycarbonylation as the product **4** with yields in the range 62-66%. The minor product was the primary amine which was benzyloxycarbonylated and isolated as the derivativet **5** with yields in the range 11-18%. The same tendency for symmetrical secondary amine formation has also been observed in a higher homologue series.[6]



Scheme 1

A general methodology for the formation of secondary amines from azides is available by the reactions of boranes and dichloroboranes with azides.[7,8] In these reactions a carbosubstituent in the borane is transferred to the endo-azide nitrogen with expulsion of molecular nitrogen. The reductive amination in the present case

proceeds differently. The course of the reaction may be assisted by coordination of palladium to the bislactim ether system. A suggestion for the reaction path is provided in Scheme 2. Complexed palladium may facilitate α-proton abstraction by the terminal azide nitrogen (**6**) leading to N_2-expulsion. The resultant imine **8** may add either hydrogen to form the primary amine **9** or add a prior formed amine molecule resulting in aminal formation. Based on the product composition, the latter reaction seems to be the faster. Elimination of ammonia from the diamine **10** provides an *N*-substituted imine **11** which becomes the secondary amine **12** on addition of hydrogen. Support for this pathway has been found by running the reduction of the azide **3** in the presence of



Scheme 2

n-butylamine which led to the expected cross *N*-alkylation, *ie.* to the corresponding secondary butylamine (40%).[6] The suggested pathway bears a close resemblance to observations and explanations for product formation in the catalytic reduction of nitriles which may give primary amines, secondary amines or mixtures thereof depending on the conditions used in these the reactions.[9]

The amination products **4** and **5** can can be further converted into corresponding amino acid esters by mild acid cleavage of the bislactim ether rings.[2]

In conclusion, we have described a novel reductive dimerization process of azides to secondary amines effected by palladium-catalyzed hydrogenolysis.

EXPERIMENTAL

(2R,5S)-5-(4-Bromobut-1-yl)-2,5-dihydro-2-isopropyl-3,6-diethoxy-5-methylpyrazine (**2a**).

Method A. Inverse addition: A solution of nBuLi in hexane (14.5 ml, 23.21 mmol, 1.6 M) was added *via* a syringe over 5 min to a solution of *(2R,5RS)*-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazine (5.00 g, 22.10 mmol) and DMEU (5.05 g, 44.20 mmol) in dry THF (200 ml) at -78 °C. The mixture was stirred for 15 min at -78 °C before being gradually transferred via a teflon tubing to a solution of 1,4-dibromobutane (14.34 g,

66.30 mmol) in dry THF (100 ml). The solution was stirred at -78 °C for 10 h and the reaction quenched by addition of the mixture to phosphate buffer (pH 7; 150 ml). The mixture was extracted (3x) with diethyl ether (25 ml), the combined organic layers washed with brine, dried ($MgSO_4$), the solvent distilled off and the excess 1,4-dibromobutane removed by bulb-to-bulb distillation at 50 °C/0.2 torr. The product was further purified by flash chromatography using diethyl ether:hexane 1:20; yield 6.47 g (81 %). Crude product: d.e. > 97% (capillary GLC).

Method B Straight addition: A solution of nBuLi in hexane (14.5 ml, 23.21 mmol, 1.6 M) was added *via* a syringe over 5 min to a solution of *(2R,5RS)*-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazine (5.00 g, 22.10 mmol) and DMEU (5.05 g, 44.20 mmol) in dry THF (200 ml) at -78 °C. The mixture was stirred for 15 min before a solution of 1,4-dibromobutane (14.34 g, 66.30 mmol) in dry THF (25 ml) was added dropwise over 20 min. The solution was stirred for 8 h at -78 °C and the reaction quenched by addition of the reaction mixture to phosphate buffer (pH 7; 150 ml). The mixture was extracted (3x) with diethyl ether (25 ml), the combined organic layers washed with brine, dried ($MgSO_4$), the solvent distilled off and the excess 1,4-dibromobutane removed by bulb-to-bulb distillation at 50 °C/0.2 torr. The product was further purified by flash chromatography using diethyl ether:hexane 1:20; yield 5.03 g (63%) of a non-solid material. The d.e. (crude) was 90% (capillary GLC). Found: C, 53.22; H, 8.04; N, 7.72. Calc. for $C_{16}H_{29}BrN_2O_2$: C, 53.19; H, 8.08; N, 7.75%. HRMS: *M* 360.1412. Calc. for $C_{16}H_{29}N_2O_2Br$: 360.1412. IR: ν 1690 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ 0.69, 1.06 (2 d, *J* 7 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.40-1.90 (m, 6H, $(C\underline{H}_2)_3CH_2Br$), 1.26 (t, *J* 7 Hz, 6H, $OCH_2C\underline{H}_3$), 1.31 (s, 3H, 2-CH_3), 2.27 (dsp, J_1 7 Hz, J_2 3 Hz, $C\underline{H}(CH_3)_2$), 3.35 (t, *J* 7 Hz, 2H, $(CH_2)_3C\underline{H}_2Br$), 3.90 (d, *J* 3 Hz, 1H, H-2), 4.00-4.22 (m, 4H, $OC\underline{H}_2CH_3$).^{13}C NMR ($CDCl_3$): δ 14.29, 14.34 ($OCH_2\underline{C}H_3$), 16.89, 19.35 ($CH(\underline{C}H_3)_2$), 23.02, 23.72, 33.50, 40.24 ($(\underline{C}H_2)_4Br$), 28.60 (2-CH_3), 31.05 ($\underline{C}H(CH_3)_2$), 57.93 (C-2), 60.11, 60.18 ($O\underline{C}H_2CH_3$), 61.08 (C-5), 161.37, 164.48 (C=N).

(2*R*,5*S*)-5-(5-Bromopent-1-yl)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazine (**2b**).was prepared as above with 1,5-dibromopentane as alkylating agent.

Method A. Inverse addition:Yield 80%, d.e. 96%.

Method B. Straight addition: Yield 65%. d.e. 88%.

Found: C, 54.36; H, 8.34; N, 7.40. Calc. for $C_{17}H_{31}BrN_2O_2$: C, 54.40; H, 8.32; N, 7.46%. HRMS: *M* 374.1569. Calc. for $C_{17}H_{31}N_2O_2Br$: 374.1569. IR: ν 1690 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ 0.69, 1.06 (2 d, *J* 7 H, 6H, $CH(C\underline{H}_3)_2$), 0.97-2.00 (m, 8H, $(C\underline{H}_2)_4CH_2Br$), 1.26 (t, *J* 7 Hz, 6H, $OCH_2C\underline{H}_3$), 1.30 (s, 3H, 2-CH_3), 2.23 (dsp, J_1 7 Hz, J_2 3 Hz, $C\underline{H}(CH_3)_2$), 3.36 (t, *J* 7 Hz, 2H, $(CH_2)_4C\underline{H}_2Br$), 3.89 (d, *J* 3 Hz, 1H, H-2), 4.00-4.40 (m, 4H, $OC\underline{H}_2CH_3$). ^{13}C NMR ($CDCl_3$): δ 14.28, 14.35 ($OCH_2\underline{C}H_3$), 16.86, 19.34 ($CH(\underline{C}H_3)_2$), 23.42, 27.98, 32.56, 33.72, 40.95 ($(\underline{C}H_2)_5Br$), 28.60 (2-CH_3), 31.05 ($\underline{C}H(CH_3)_2$), 58.06 (C-2), 60.06, 60.15 ($O\underline{C}H_2CH_3$), 61.06 (C-5), 161.22, 164.66 (C=N).

(2*R*,5*S*)-5-(6-Bromohex-1-yl)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazine (**2c**) was prepared as above with 1,6-dibromohexane as alkylating agent.

Method A. Inverse addition:Yield 83%, d.e. 97%.

Method B. Straight addition: Yield 68%. d.e. 85%.

Found: C, 55.54; H, 8.51; N, 7.19. Calc. for $C_{18}H_{33}BrN_2O_2$: C, 55.52; H, 8.54; N, 7.19%. HRMS: *M* 388.1725. Calc. for $C_{18}H_{33}N_2O_2Br$: 388.1725. IR: ν 1690 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ 0.69, 1.06 (2 d,

J 7 Hz, 6H, $CH(C\underline{H}_3)_2$), 0.90-2.00 (m, 10H, $(C\underline{H}_2)_5CH_2Br$), 1.26 (t, *J* 7 Hz, 6H, $OCH_2C\underline{H}_3$), 1.30 (s, 3H, 2-CH_3), 2.23 (dsp, J_1 7 Hz, J_2 3 Hz, $C\underline{H}(CH_3)_2$), 3.38 (t, *J* 7 Hz, 2H, $(CH_2)_5C\underline{H}_2Br$), 3.89 (d, *J* 3 Hz; 1H, H-2), 4.00-4.20 (m, 4H, $OC\underline{H}_2CH_3$). ^{13}C NMR ($CDCl_3$): δ 14.28, 14.35 ($OCH_2\underline{C}H_3$), 16.84, 19.34 ($CH(\underline{C}H_3)_2$), 24.04, 27.96, 28.59, 32.66, 33.78, 41.11 ($(\underline{C}H_2)_6Br$), 28.60 (2-CH_3), 31.03 ($\underline{C}H(CH_3)_2$), 58.09 (C-2), 60.01, 60.11 ($O\underline{C}H_2CH_3$), 61.06 (C-5), 161.13, 164.73 (C=N).

(2*R*,5*S*)-5-(4-Azidobut-1-yl)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazine (**3a**). Sodium azide (1.08 g, 16.7 mmol) was added to a solution of *(2R,5S)*-5-(4-bromobut-1-yl)-2,5-dihydro-2-isopropyl-3,6-diethoxy-5-methylpyrazine (2.0 g, 5.54 mmol) in DMF (40 ml) and the mixture heated with stirring at 85-90 °C for 13 h when TLC monitoring (Et_2O:hexane 1:5, R_f 0.40) showed the reaction to be complete. The mixture was poured into water (70 ml), extracted (3x) with diethyl ether (20 ml), the combined organic layers washed with brine, dried ($MgSO_4$) and the solution evaporated at reduced pressure. The residual material was subjected to flash chromatography using hexane:Et_2O 5:1 (R_f : 0.40); yield 1.40 g (78%) of a non-solid material. Found: C, 59.43; H, 9.00; N, 21.61. Calc. for $C_{16}H_{29}N_5O_2$: C, 59.42; H, 9.04; N, 21.65%. HRMS: M 323.2321. Calc. for $C_{16}H_{29}N_5O_2$: 323.2321. IR: ν 2080 cm^{-1} (N_3) and 1680 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ 0.70, 1.06 (2 d, *J* 7 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.00-1.90 (m, 6H, $(C\underline{H}_2)_3CH_2N_3$), 1.26 (t, *J* 7 Hz, 6H, $OCH_2C\underline{H}_3$), 1.31 (s, 3H, 2-CH_3), 2.27 (dsp, J_1 7 Hz, J_2 3 Hz, $C\underline{H}(CH_3)_2$), 3.21 (t, *J* 7 Hz, 2H, $(CH_2)_3C\underline{H}_2N_3$), 3.91 (d, *J* 3 Hz, 1H, H-2), 4.00-4.23 (m; 4H, $OC\underline{H}_2CH_3$). ^{13}C NMR ($CDCl_3$): δ 14.27, 14.34 ($OCH_2\underline{C}H_3$), 16.88, 19.35 ($CH(\underline{C}H_3)_2$), 21.60, 28.71, 40.70, 51.21 ($(\underline{C}H_2)_4N_3$), 28.60 (2-CH_3), 31.05 ($\underline{C}H(CH_3)_2$), 57.97 (C-2), 60.10, 60.17 ($O\underline{C}H_2CH_3$), 61.08 (C-5), 161.35, 164.49 (C=O).

(2*R*,5*S*)-5-(5-Azidopent-1-yl)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazine (**3b**) was prepared as above from (2*R*,5*S*)-5-(5-bromopent-1-yl)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazine in 76% yield; a non-solid. Found: C, 60.54; H, 9.29; N, 20.69. Calc. for $C_{17}H_{31}N_5O_2$: C, 60.51; H, 9.26; N, 20.75%. HRMS: *M* 337.2478. Calc. for $C_{17}H_{31}N_5O_2$: 337.2477. IR: ν 2080 cm^{-1} (N_3) and 1690 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ 0.69, 1.06 (2 d, *J* 7 Hz, 6H, $CH(C\underline{H}_3)_2$), 0.90-1.62 (m, 6H, $(C\underline{H}_2)_4CH_2N_3$), 1.26 (t, *J* 7 Hz, 6H, $OCH_2C\underline{H}_3$), 1.31 (s, 3H, 2-CH_3), 2.27 (dsp, J_1 7 Hz, J_2 3 Hz, $C\underline{H}(CH_3)_2$), 3.21 (t, *J* 7 Hz, 2H, $(CH_2)_4C\underline{H}_2N_3$), 3.90 (d, *J* 3 Hz, 1H, H-2), 4.00-4.23 (m, 4H, $OC\underline{H}_2CH_3$).^{13}C NMR ($CDCl_3$): δ 14.28, 14.35 ($OCH_2\underline{C}H_3$), 16.86, 19.35 ($CH(\underline{C}H_3)_2$), 23.83, 26.54, 28.62, 41.03, 51.31 ($(\underline{C}H_2)_5N_3$), 28.62 (2-CH_3), 31.05 ($\underline{C}H(CH_3)_2$), 58.02 (C-2), 60.06, 60.14 ($O\underline{C}H_2CH_3$), 61.06 (C-5), 161.20, 164.66 (C=N).

(2*R*,5*S*)-5-(6-Azidohex-1-yl)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazine (**3c**) was prepared as above from (2*R*,5*S*)-5-(6-bromohex-1-yl)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazine in 79% yield; non-solid material. Found: C, 61.59; H, 9.43; N, 19.91. Calc. for $C_{18}H_{33}N_5O_2$: C, 61.51; H, 9.46; N, 19.92%. HRMS: *M* 351.2634. Calc. for $C_{18}H_{33}N_5O_2$: 351.2634. IR: ν 2080 cm^{-1} (N_3) and 1680 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ 0.69, 1.06 (2 d, *J* 7 Hz, 6H, $CH(C\underline{H}_3)_2$), 0.80-2.00 (m, 6H, $(C\underline{H}_2)_5CH_2N_3$), 1.26 (t, *J* 7 Hz, 6H, $OCH_2C\underline{H}_3$), 1.30 (s, 3H, 2-CH_3), 2.25 (dsp, J_1 7 Hz, J_2 3 Hz, $C\underline{H}(CH_3)_2$), 3.23 (t, *J* 7 Hz, 2H, $(CH_2)_5C\underline{H}_2N_3$), 3.91 (d, *J* 3 Hz, 1H, H-2), 4.00-4.20 (m, 4H, $OC\underline{H}_2CH_3$). ^{13}C NMR ($CDCl_3$): δ 14.28, 14.35 ($OCH_2\underline{C}H_3$), 16.84, 19.34 ($CH(\underline{C}H_3)_2$), 24.09, 26.49, 28.68, 28.98, 41.12, 51.42 ($(\underline{C}H_2)_6N_3$), 28.60 (2-CH_3), 31.03 ($\underline{C}H(CH_3)_2$), 58.08 (C-2), 60.00, 60.10 ($O\underline{C}H_2CH_3$), 61.05 (C-5), 161.12, 164.69 (C=N).

N,N-bis[4-((2*R*,5*S*)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazin-5-yl)butyl]-*N*-benzyloxcarbonyl-amine (**4a**) and (2*R*,5*S*)-5-(4-Benzyloxycarbonylaminobut-1-yl)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazine (**5a**). A solution of ((2*R*,5*S*)-5-(4-azidobut-1-yl)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazine (0.63 g, 1.95 mmol) in ethanol (12 ml) containing the catalyst 5% palladium-on-charcoal (0.25 g) was purged with nitrogen, hydrogen bubbled through the solution and the mixture kept under hydrogen at atmospheric pressure (baloon) overnight. After removal of hydrogen, the mixture was filtered through a pad of celite and the ethanol distilled off from the filtrate at reduced pressure. The residue was dissolved in dioxane (10 ml) and benzyloxycarbonyl chloride (0.35 ml, 2.50 mmol) added to the dioxane solution at 0 °C followed by dropwise addition of 1 M $NaHCO_3$ (2.90 ml, 2.90 mmol). The mixture was stirred for 2 h, diluted with water and extracted with chloroform (4x25 ml). The pooled organic layers were dried ($MgSO_4$), the solvents removed at reduced pressure and the residual material subjected to flash chromatography using hexane:EtOAc 5:1.The monomeric product **5a** was first eluted (TLC; R_F 0.31); yield 1.51 g (18 %). The dimeric product **4a** was subsequently eluted (TLC; R_F 0.20); yield 0.437 g (63%).

N,N-bis[4-((2*R*,5*S*)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazin-5-yl)butyl]-*N*-benzyloxy-carbonylamine (**4a**). Found: C, 67.52; H, 9.22; N, 9.77. Calc. for $C_{40}H_{65}N_5O_6$: C, 67.48; H, 9.20; N, 9.84%. HRMS: *M* 711.4934. Calc. for $C_{40}H_{65}N_5O_6$: 711.4934 IR: ν 1670 cm^{-1} (C=N, C=O). ^1H NMR ($CDCl_3$): δ 0.69, 1.04 (2 d, *J* 7 Hz, 12H, $CH(CH_3)_2$), 0.90-2.00 (m, 12H, $(CH_2)_3CH_2NHCO$), 1.24 (t, *J* 7 Hz, 12H, OCH_2CH_3), 1.30 (s, 6H, 2-CH_3), 2.25 (dsp, J_1 7 Hz, J_2 3 Hz, 2H, $CH(CH_3)_2$), 3.18 (q, *J* 7 Hz, 4H, $(CH_2)_3CH_2NHCO$), 3.88 (d, *J* 3 Hz, 2H, H-2), 3.92-4.22 (m, 8H, OCH_2CH_3), 5.06 (s, 2H, CH_2-C_6H_5), 7.22-7.38 (m, 5H, CH_2-C_6H_5). ^{13}C NMR ($CDCl_3$): δ 14.31, 14.38 (OCH_2CH_3), 16.96, 19.39 ($CH(CH_3)_2$), 21.67, 40.13, 47.00, 47.85 ($(CH_2)_4NHCO$), 28.61 (2-CH_3), 31.14 ($CH(CH_3)_2$), 58.06 (C-2), 60.14, 60.22 (OCH_2CH_3), 61.11 (C-5), 66.66 (CH_2-C_6H_5), 127.54, 127.62, 128.37, 137.11 (CH_2-C_6H_5), 155.92 (NHCO), 161.24, 164.61 (C=N).

(2*R*,5*S*)-5-(4-Benzyloxycarbonylaminobut-1-yl)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazine (**5a**): Found: C, 66.63; H, 8.61; N, 9.71. Calc. for $C_{24}H_{37}N_3O_4$: C, 66.79; H, 8.64; N, 9.74%. HRMS: *M* 431.2783. Calc. for $C_{24}H_{37}N_3O_4$: 431.2786. IR: ν 1680 cm^{-1} (C=N, C=O). ^1H NMR ($CDCl_3$): δ 0.69, 1.06 (2 d, *J* 7 Hz, 6H, $CH(CH_3)_2$), 0.90-2.00 (m, 6H, $(CH_2)_3CH_2NHCO$), 1.24 (t, *J* 7 Hz, 6H, OCH_2CH_3), 1.30 (s, 3H, 2-CH_3), 2.25 (dsp, J_1 7 Hz, J_2 3 Hz; 1H, $CH(CH_3)_2$), 3.14 (q, *J* 7 Hz, 2H, $(CH_2)_3CH_2NHCO$), 3.89 (d, *J* 3 Hz; 1H, H-2), 3.99-4.20 (m, 4H, OCH_2CH_3), 4.74 (s, 1H, NHCO), 5.07 (s, 2H, CH_2-C_6H_5), 7.30-7.36 (m, 5H, CH_2-C_6H_5). ^{13}C NMR ($CDCl_3$): δ 14.33, 14.39 (OCH_2CH_3), 16.92, 19.41 ($CH(CH_3)_2$), 21.58, 29.72, 40.79, 40.94 ($(CH_2)_4NHCO$), 28.68 (2-CH_3), 31.09 ($CH(CH_3)_2$), 58.06 (C-2), 60.14, 60.22 (OCH_2CH_3), 61.11 (C-5), 66.54 (CH_2-C_6H_5), 127.48, 127.96, 128.41, 136.69 (CH_2-C_6H_5), 156.29 (NHCO), 161.37, 164.64 (C=N).

N,N-bis[5-((2*R*,5*S*)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazin-5-yl)pentyl]-*N*-benzyloxy carbonylamine (**4b**) and (2*R*,5*S*)-5-(5-Benzyloxycarbonylaminopent-1-yl)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazine (**5b**) were prepared as above from (2*R*,5*S*)-2-(5-azidopent-1-yl)-3,6-diethoxy-2,5-

dihydro-2-isopropyl-5-methylpyrazine. The products were separated by flash chromatography under the same conditions as used above.

N,N-bis[5-((2*R*,5*S*)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazin-5-yl)pentyl]-*N*-benzyloxycarbonylamine (**4b**). Found: C, 68.15; H, 9.34; N, 9.49. Calc. for $C_{42}H_{69}N_5O_6$: C, 68.17; H, 9.40; N, 9.46%. HRMS: *M* 739.5248. Calc. for $C_{42}H_{69}N_5O_6$: 739.5247. IR: ν 1690 cm^{-1} (C=N, C=O). ^1H NMR ($CDCl_3$): δ 0.68, 1.05 (2 d, *J* 7 Hz, 12H, $CH(CH_3)_2$), 0.82-1.86 (m, 16H, $(CH_2)_3CH_2NHCO$), 1.24 (t, *J* 7 Hz, 12H, OCH_2CH_3), 1.29 (s, 6H; 2-CH_3), 2.26 (dsp, J_1 7 Hz, J_2 3 Hz, 2H, $CH(CH_3)_2$), 3.13 (q, *J* 7 Hz, 4H, $(CH_2)_3CH_2NHCO$), 3.89 (d, *J* 3 Hz, 2H, H-2), 3.97-4.22 (m, 8H, OCH_2CH_3), 5.08 (s; 2H, CH_2-C_6H_5), 7.25-7.38 (m, 5H, CH_2-C_6H_5). ^{13}C NMR ($CDCl_3$): δ 14.33, 14.40 (OCH_2CH_3), 16.87, 19.40 ($CH(CH_3)_2$), 24.19, 26.91, 41.28, 47.02, 47.86 ($(CH_2)_5NHCO$), 28.65 (2-CH_3), 31.03 ($CH(CH_3)_2$), 58.08 (C-2), 60.03, 60.13 (OCH_2CH_3), 61.06 (C-5), 66.65 (CH_2-C_6H_5), 127.64, 127.72, 128.38, 137.17 (CH_2-C_6H_5), 156.06 (NHCO), 161.16, 164.75 (C=N).

(2*R*,5*S*)-5-(5-Benzyloxycarbonylaminopent-1-yl)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazine (**5b**): Yield 11%. Found: C, 67.44; H, 8.87; N, 9.47. Calc. for $C_{25}H_{39}N_3O_4$: C, 67.39; H, 8.82; N, 9.43%. HRMS: *M* 445.2941. Calc. for $C_{25}H_{39}N_3O_4$: 445.2942. IR: ν 1670 cm^{-1} (C=N, C=O). ^1H NMR ($CDCl_3$): δ 0.68, 1.05 (2 d, J 7 Hz, 6H, $CH(CH_3)_2$), 0.82-1.86 (m, 8H, $(CH_2)_3CH_2NHCO$), 1.24 (t, *J* 7 Hz, 6H, OCH_2CH_3), 1.29 (s, 3H, 2-CH_3), 2.26 (dsp, J_1 7 Hz, J_2 3 Hz, 1 H, $CH(CH_3)_2$), 3.13 (q, *J* 7 Hz, 2H, $(CH_2)_3CH_2NHCO$), 3.89 (d, *J* 3 Hz, 1H, H-2), 3.97-4.22 (m, 4H, OCH_2CH_3), 4.72 (s, 1H; NHCO), 5.08 (s, 2H, CH_2-C_6H_5), 7.25-7.38 (m, 5H, CH_2-C_6H_5). ^{13}C NMR ($CDCl_3$): δ 14.34, 14.41 (OCH_2CH_3), 16.90, 19.41 ($CH(CH_3)_2$), 24.03, 26.71, 29.86, 41.08, 41.19 ($(CH_2)_5NHCO$), 28.68 (2-CH_3), 31.07 ($CH(CH_3)_2$), 58.10 (C-2), 60.09, 60.19 (OCH_2CH_3), 61.09 (C-5), 66.55 (CH_2-C_6H_5), 128.04, 128.08, 128.48, 136.69 (CH_2-C_6H_5), 156.34 (NHCO), 161.24, 164.76 (C=N).

N,N-bis[6-((2*R*,5*S*)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazin-5-yl)hexyl]-*N*-benzyloxycarbonylamine (**4c**) and (2*R*,5*S*)-5-(6-Benzyloxycarbonylaminohex-1-yl)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazine (**5c**) were prepared as above from (2*R*,5*S*)-2-(6-azidohex-1-yl)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazine. The products were separated by flash chromatography under the same conditions as above.

N,N-bis[6-((2*R*,5*S*)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazin-5-yl)hexyl]-*N*-benzyloxycarbonylamine (**4c**). Yield 62%. Found: C, 68.76; H, 9.52; N, 9.17. Calc. for $C_{44}H_{73}N_5O_6$: C, 68.80; H, 9.58; N, 9.12%. HRMS: *M* 767.5560. Calc. for $C_{44}H_{73}N_5O_6$: 767.5560. IR: ν 1680 cm^{-1} (C=N, C=O). ^1H NMR ($CDCl_3$): δ 0.68, 1.05 (2 d, *J* 7 Hz, 12H, $CH(CH_3)_2$), 0.82-1.86 (m, 20H, $(CH_2)_3CH_2NHCO$), 1.24 (t, *J* 7 Hz, 12H; OCH_2CH_3), 1.29 (s, 6H, 2-CH_3), 2.25 (dsp, J_1 7 Hz, J_2 3 Hz, 2 H, $CH(CH_3)_2$), 3.17 (q, *J* 7 Hz, 4H, $(CH_2)_3CH_2NHCO$), 3.89 (d, *J* 3 Hz, 2H, H-2), 3.95-4.22 (m, 8H, OCH_2CH_3), 5.09 (s, 2H, CH_2-C_6H_5), 7.23-7.38 (m, 5H; CH_2-C_6H_5). ^{13}C NMR ($CDCl_3$): δ 14.34, 14.41 (OCH_2CH_3), 16.88, 19.41 ($CH(CH_3)_2$), 24.34, 26.77, 29.41, 41.28, 46.86, 47.86 ($(CH_2)_6NHCO$), 28.67 (2-CH_3), 31.04 ($CH(CH_3)_2$), 58.14 (C-2), 60.01, 60.13 (OCH_2CH_3), 61.07 (C-5), 66.70 (CH_2-C_6H_5), 127.66, 127.74, 128.38, 137.15 (CH_2-C_6H_5), 156.10 (NHCO), 161.12, 164.81 (C=N).

(2*R*,5*S*)-5-(6-Benzyloxycarbonylaminohex-1-yl)-3,6-diethoxy-2,5-dihydro-2-isopropyl-5-methylpyrazine (**5c**): Yield 11%. Found: C, 67.90; H, 8.94; N, 9.10. Calc. for $C_{26}H_{41}N_3O_4$: C, 67.94; H, 8.99; N, 9.14%. HRMS: *M* . 459.3097. Calc. for $C_{26}H_{41}N_3O_4$: 459.3099. IR: ν 1680 cm^{-1} (C=N, C=O). ^1H NMR ($CDCl_3$): δ 0.68, 1.05 (2 d, *J* 7 Hz, 6H, $CH(CH_3)_2$), 0.82-1.86 (m, 10H, $(CH_2)_3CH_2NHCO$), 1.24 (t, *J* 7 Hz, 6H, OCH_2CH_3), 1.29 (s; 3H, 2-CH_3), 2.25 (dsp, J_1 7 Hz, J_2 3 Hz, 1H, $CH(CH_3)_2$), 3.14 (q, *J* 7 Hz, 2H, $(CH_2)_3CH_2NHCO$), 3.89 (d, *J* 3 Hz, 1H, H-2), 3.96-4.22 (m, 4H, OCH_2CH_3), 4.76 (s, 1H, NHCO), 5.08 (s, 2H, CH_2-C_6H_5), 7.25-7.38 (m, 5H; CH_2-C_6H_5). ^{13}C NMR ($CDCl_3$): δ 14.34, 14.41 (OCH_2CH_3), 16.90, 19.41 ($CH(CH_3)_2$), 24.23, 26.61, 29.21, 29.88, 41.09, 41.23 ($(CH_2)_6NHCO$), 28.68 (2-CH_3), 31.07 ($CH(CH_3)_2$), 58.14 (C-2), 60.05, 60.16 (OCH_2CH_3), 61.08 (C-5), 66.54 (CH_2-C_6H_5), 128.03, 128.07, 128.48, 136.70 (CH_2-C_6H_5), 156.35 (NHCO), 161.17, 164.81 (C=N).

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