Stereoselective Synthesis of Alkynylglycines and α,α′-Alkynyl-Bridged Bis(glycines)

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Pd–Cul catalysis has been used to effect carbo-substitution with iodoarenes on the terminal alkynyl carbon in (2S,5R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-propargylpyrazine. Bridged structures were formed from diiodoarenes. Homocoupling with bridge formation between two alkynyl units was effected by the same catalyst system with air as the oxidant. Mild hydrolysis gave the corresponding unsaturated amino acids and esters. The dicoupled amino acids have two triple bonds in conjugation in the bridge between the α,α′-carbons in the two glycine units.

In drug design and development of bioactive small peptides and peptidomimetics, partially rigidified amino acid-like structures are sought for incorporation into peptides or peptidomimetics in order to induce conformational constraints which may be essential for spacing of the pharmacophoric region.1 We have previously reported the preparation of isosteric cystine analogues in which the –CH₂SSCH₂– bridge between the two glycine residues in cystine (Fig. 1, A) has been replaced by C₄ bridges. The rotational freedom and preferences for low-energy conformational states in isosteric amino acids is controlled by insertion of an aryl group, or by a carbon–carbon double bond in the C₄-bridge.2 A single bond in the bridge will give a particularly stretched bridge, and hence a conformationally highly constrained cystine analogue as indicated in structure B (n = 1) in Fig. 1.

In a recent report we described a synthesis of the triply bonded C₄-bridged cysteine substrate B (n = 1) in Fig. 1 in its S-configuration and its inclusion in bioactive peptides.3 We here report an extension of the bridge with inclusion of a second conjugated triple bond (B, n = 2; Fig. 1). In addition, aryl groups have been inserted between the triple bonds in the bridge. Also included are related conformationally restricted ‘monomeric’ α-amino acids. The new amino acids in this work belong to the R-series.

Results and discussion

The stereoselectivity in the alkylation at the α-carbon of glycine was effected by the use of a glycine equivalent in the form of the chiral auxiliary (S)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (1, Scheme 1) with the methodology pioneered by Schöllkopf.4 In the formation of a bridge structure two alkylations are involved, and two new stereogenic centers are generated in this process. In what might appear to be the most convenient method for the bridging of two glycines, the metallated glycine chiral auxiliary was reacted with electrophilic carbons at both termini in the chain, which was to become the bridge. The steric requirements of the propargyl moiety in the alkylation agent are relatively low, however, and therefore likely to give poor overall diastereoselectivity when two alkylation steps are involved. Accordingly the diastereomeric excess (d.e.) was low in the alkylation reaction with propargyl bromide (vide infra). Therefore we adopted a strategy involving the stereoselective preparation of appropriately substituted amino acid ‘monomers’ using the above chiral auxiliary. Subsequently, two stereochemically pure amino acid monomers were joined to furnish C₄-symmetrical bis(amino acids) by a palladium-catalyzed coupling operation. This concept parallels our previous construction of C₄-bridged bis-glycines in which the two central carbon atoms of the C₄-bridge were substituted by two methylene groups.5b

The method to be used for the palladium-mediated dimerization reaction over an aryl group, was initially studied as a carbo-substitution reaction on the terminal carbon of the monomeric propargyl derivative 2 (Scheme 1). Alkylation of lithiated (S)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (1) at –78 °C with pro-
pargyl bromide proceeded with low diastereoselectivity (4:1), which probably can be rationalized as being due to the low steric requirements of the electrophile. The major (5R)-isomer 2, however, was readily isolated in isomerically pure form (d.e. >98%) after flash chromatography on silica. Pd-catalysis in the presence of copper(I) iodide with triethylamine as both base and solvent was found to be particularly effective for the introduction of substituents on the terminal alkyne carbon in 2; the reaction proceeds over copper acetylide with subsequent transmetalation to palladium for the coupling reaction to occur. The reactions were run at ambient temperature to furnish the coupling products 3 with yields in the range 75–81%. Bromobenzene, 2-bromothiophene and phenyl triflate were inferior substrates in this reaction; heating was required and resulted in significantly lower yields of the coupling product.

Terminal stannylation in the pargyl derivative 2 was effected by lithiation at low temperature followed by quenching the lithium acetylide with tributylstannyl chloride which furnished the stannane 4. Subsequent palladium-catalyzed coupling with iodobenzene gave the phenyl derivative 3a, but the overall yield of 3a in this approach was far inferior to that from the direct coupling (vide supra).

All intermediates and the bridged target compounds in this report contain more than one stereogenic center. Epimerization at one of the centers will give rise to a diastereomeric mixture. Hence $^{13}$C and $^1$H NMR spectroscopy can be used as an analytical tool for stereocchemical information on the homogeneity of the product formed. Additional information can be gained from chromatography. Very mild acid conditions were used for liberation of the amino acid esters from their chiral auxiliary derived structures (Schemes 3 and 4). No indication of racemization in the bridged amino acid esters 10, 11 and 14 with two stereogenic centers (Scheme 4) was seen by NMR or chromatography. Similarly, no racemization was observed under the conditions used for hydrolysis of the esters to the acids 12, 13 and 15. The same stability is to be expected for the stereogenic centers in compounds 3 (Scheme 3) which therefore are assumed to yield enantiomERICALLY pure amino acid esters 8.

The bisglycines 5 and 6 (Scheme 2) have an aryl group inserted into the bridge between the two triple bonds. These compounds were prepared from 1,4-diiodobenzene or 2,5-diiodothiophene and the alkyne 2 in a coupling reaction using copper(I) iodide, triethylamine and Pd-catalysis under the above conditions. The reaction conditions used did not affect the stereogenic centers. The products 5 and 6 were isolated after simple flash chromatography on silica gel in yields of 59 and 53%, respectively.

Attempts to achieve oxidative homocoupling of the propargyl derivative 2 were unsatisfactory with copper(I) iodide, triethylamine and air as oxidant. However, in most of the above reactions small amounts of the homocoupled product 7, were observed as a by-product. Its formation is due to competitive transfer of two acetylene residues to the Pd-catalyst and subsequent reductive elimination. Adaptation of the above coupling conditions with Pd-catalysis in the presence of copper(I) iodide in triethylamine under mild oxidative conditions with air as the oxidant, has given us a process for homocoupling and formation of 7 in excellent yield. No coupling reaction was observed when an inert atmosphere with exclusion of air was used. Nor was there any coupling reaction in the absence of either copper iodide or the palladium catalyst.

Hydrolysis of the pyrazine ring in the 'monomeric' amino acid precursors (3) with liberation of the amino acid methyl esters (Scheme 3) was effected by adhering to the conditions described by Schöllkopf for the chemo selectivity of such reactions; $^4$ 0.25 M HCl in aqueous dioxiane yielded the new amino acids 8 in high yields. Further hydrolysis to the amino acids 9a and 9b was demonstrated from the corresponding methyl esters 8a and 8b by reaction with lithium hydroxide in aqueous dioxiane at ambient temperature.

The bridged amino acid precursors 5, 6 and 7 (Scheme 4) were all hydrolyzed to their respective amino acid methyl esters with 0.25 M HCl. The aryl-bridged
methyl esters 10 and 11 were further hydrolyzed to the respective diacids 12 and 13 using lithium hydroxide in aqueous dioxane at ambient temperature.

The simple dyne-bridged amino acid 15 was prepared from its ester under different hydrolytic conditions. We have found that hydrolysis with 6 M HCl at 40 °C for a short time led to clean cleavage of the ester group in 14 and formation of the amino acid 15 in high yield.

**Scheme 3.**

Experimental

The 1H NMR spectra were recorded at 200 MHz with a Varian Gemini 200 or a Bruker DPX 200 instrument; for 300 MHz spectra a Bruker DPX 300 was used. The 13C NMR spectra were recorded at 50 MHz with a Gemini 200 or a Bruker DPX 200, and the 75 MHz spectra on a Bruker DPX 300 instrument. NMR techniques such as DEPT, COSY, HETCOR, and proton–proton decoupling techniques were used in assignments and calculation of coupling constants. The mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing potential, and ammonia was used for chemical ionization (CI); the spectra are presented as m/z (% rel. int.).

Dry THF was distilled from sodium and benzophenone. 

(2S)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (1) was prepared as described.5a

(2S,5R)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(2-propyn-1-yl)pyrazine (2).5 Butyllithium (8.0 mL, 12.0 mmol, 1.5 M in hexane) was added to a solution of (2S)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (2.0 g, 10.9 mmol) in THF (7 mL) under nitrogen at −78 °C and the solution was stirred for 20 min. A solution of precooled (−78 °C) propargyl bromide (1.62 g, 10.9 mmol; 80% in toluene) in THF (7 mL) was added dropwise, and the mixture was stirred at this temperature for 5 h before being quenched by addition of phosphate buffer (pH 7). The THF was removed at reduced pressure, the residual material was extracted into diethyl ether (100 mL), and the ether solution was washed, dried (MgSO4) and evaporated. The diastereomeric ratio in the crude product was 4:1 (GLC).
Scheme 4.

major isomer of the title compound was isolated pure after flash chromatography on silica gel using hexane-EtOAc (10:1); yield 60% (1.45 g), d.e. >98%. 1H NMR (CDCl3): δ 0.66, 1.04 (Me2CH), 1.87 (1H, t, J 3.3, CH), 2.26 (1H, d sept, J 3.3 and 7.0 Hz, Me2CH), 2.69 (1H, m CH₂-CC), 3.69 and 3.70 (6H, 2s, 2 x MeO), 4.01 (1H, dd, J 3.3 Hz, H-2), 4.09 (1H, ddd, H-5). 13C NMR (CDCl3): δ 16.54 and 19.06 (CHMe), 25.07 (CH₂CC), 31.65 (CHMe₂), 52.52 and 52.56 (2 x MeO), 54.39 (C-5), 60.97 (C-2), 66.94 (CH₂CC), 80.56 (CH₂CC), 161.83 (C-3), 164.83 (C-6). The NMR assignments were based on HETCOR and COSY.

General procedure for the preparation of (2S,5R)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(3-phenyl-2-propyn-1-yl)pyrazine (3a) was obtained as above in 81% yield as an oily material. Anal. C₁₈H₂₃N₂O₃; C, H. 1H NMR (CDCl3): δ 0.70, 1.07 (Me₂CH), 2.20 (1H, d sept, J 3.3 and 7.0 Hz, Me₂CH), 2.90 (1H, dd, J 4.3 and 16.6 Hz CH₂-CC), 2.97 (1H, dd, J 4.6 and 16.6 Hz, CH₂-CC), 3.73 and 3.74 (6H, 2s, 2 x MeO), 4.05 (1H, dd, J 3.3 and 3.4 Hz, H-2), 4.22 (1H, ddd, J 3.4, 4.4 and 4.6 Hz, H-5), 7.22–7.33 (5H, m, Ph). 13C NMR (CDCl3): δ 16.50 and 19.08 (CHMe), 26.10 (CH₂CC), 31.52 (CHMe₂), 52.51 and 52.55 (2 x MeO), 54.64 (C-5), 60.85 (C-2), 82.36 and 86.15 (CH₂CC), 123.76 (ipsophenyl). MS (EI): 298 (15, M⁺), 284 (4), 283 (14), 184 (6), 183 (40), 182 (6), 167 (5), 142 (11), 141 (100), 140 (6), 115 (34).

(2S,5R)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(3-thienyl)-2-propyn-1-yl)pyrazine (3b) was obtained as above in 75% yield as an oily material. Anal. C₁₈H₂₃N₂O₃S; C, H. 1H NMR (CDCl3): δ 0.67 and 1.04 (Me₂CH), 2.28 (1H, d sept, J 3.3 and 7.0 Hz, Me₂CH), 2.90 (1H, dd, J 4.5 and 16.7 Hz CH₂-CC), 2.95 (1H, dd, J 4.7 and 16.7 Hz, CH₂-CC), 3.71 (6H, 2s, 2 x MeO), 4.02 (1H, dd, J 3.3 and 3.4 Hz, H-2), 4.18 (1H, ddd, J 3.4, 4.5 and 4.7 Hz, H-5), 6.91, 7.06, 7.15 (3H, thienyl). 13C NMR (CDCl3): δ 16.23 and 19.75 (CHMe), 26.96 (CH₂CC), 32.05 (CHMe₂), 52.84 (2 x MeO), 54.78 (C-2), 61.04 (C-5), 57.50 and 90.24 (CH₂CC), 123.30 (ipsothienyl), 125.51, 126.10, 130.43
(2S,5R)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-[3-(1-benzyl-2-oxo-1,2-dihydropyrrolin-5-yl)-2-propyn-1-yl]pyrazine (3e) was obtained as above in 79% yield as an oily material. Found: M 406.996. Calc. for C21H28N2O2: 406.2005. 1H NMR (CDCl3): δ 6.06, 1.02 (Me2CH), 2.24 (1H, d, J 3.4 and 7.0 Hz, Me2CH), 2.84 (2H, dd, J 4.8 Hz, CH2=CC), 3.67 and 3.68 (6H, 2 s, 2×MeO), 3.92 (1H, dd, J 3.4 and 3.4 Hz, H-2), 4.13 (1H, ddd, 3.4, and 4.8 Hz, H-5), 5.02 (1H, d, J 14.4, CH2Ph), 5.05 (1H, J 14.4 Hz, CH2Ph), 7.29–7.34 (Ph), 7.54 (1H, d, J 3.1 Hz, H-6), 8.56 (1H, d, J 3.1 Hz, H-4). 13C NMR (CDCl3): δ 16.49 and 19.05 (CHMe). 26.01 (CH2CC), 31.05 (CHMe2), 52.56 and 152.61 (2×Ome), 54.11 (C-2), 54.32 (CH2Ph), 61.00 (C-5), 74.04 and 90.31 (CH2CC), 102.62 (C-4), 128.80, 128.88 and 129.24 (Ph), 134.21 (ipsoPh), 148.69 (C-6), 154.67 (C-2’), 161.79 (C-3), 164.81 (C-3’), 167.76 (C-4). MS (EI): 406 (50, M+), 393 (111), 267 (13), 226 (8), 225 (24), 224 (77), 223 (20), 181 (7), 141 (58), 92 (7), 91 (100).

(2S,5R)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-[3-(phenyl-2-propyn-1-yl)pyrazine (3a) by coupling between iodoobenzene and the stannane 4. Iodobenzene (0.045 ml, 0.4 mmol) was added to a solution of (2S,5R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(3-tributylstannyl-2-propyn-1-yl)pyrazine (0.213 g, 0.4 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.015 g, 0.002 mmol) in 1,2-dichloroethane (10 ml) under nitrogen, and the solution heated under reflux for 2 h. Diethyl ether was added to the cold solution and the resultant solution shaken with saturated aqueous potassium fluoride. The precipitated tributylstannyl fluoride was filtered off, the fluoride treatment was repeated and the filtrate was washed, dried (MgSO4) and evaporated. The product was isolated after flash chromatography on silica gel using hexane-EtOAc (10:1); yield oily product 0.045 g (45%).

(2S,5R)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-[3-(tributylstannyl-2-propyn-1-yl)pyrazine (4). Butyllithium (3.3 ml, 5.0 mmol, 1.5 M in hexane) was added to a solution of (2S,5R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-proparglypyrazine (1.0 g, 4.5 mmol) in THF (15 ml) under nitrogen at –78 °C. The solution was stirred for 30 min, then allowed to reach 0 °C and tributylstannyl chloride (1.2 ml, 4.5 mmol) was added dropwise with stirring. The reaction was allowed to proceed at ambient temperature for 16 h, dichloromethane was added and the solution was washed with brine, dried (Na2SO4), evaporated. The product was isolated after flash chromatography on silica gel using hexane-EtOAc-NEt3 (500: 12: 10); yield 1.13 (49%) of an oily material.

1H NMR (CDCl3): δ 6.06 and 1.03 (Me2CH), 0.83–0.92 and 1.19–1.62 (3 × Bu), 2.26 (1H, d, J 3.3 and 7.0 Hz, Me2CH), 2.69 (1H, dd, J 4.2 and 16.5 Hz, CH2=CC), 2.80 (1H, dd, J 4.4 and 16.5 Hz, CH2=CC), 3.68 (6H, 2 s, 2×MeO), 4.98 (1H, dd, J 3.3 and 3.4 Hz, H-2), 4.07 (1H, ddd, 3.4, 4.2 and 4.6 Hz, H-5). 13C NMR (CDCl3): δ 11.66, 14.35, 27.60 and 29.35 (3 × Bu), 17.27 and 19.83 (CHMe) 27.21 (CH2CC), 31.97 (CHMe2), 52.69 (2×OMe), 55.17 (C-5), 61.13 (C-2), 83.82 and 106.66 (CH2CC), 60.78 (C-3), 163.71 (C-6). MS (EI): 511/509/507 (3/2/1, M+), 445/453/451 (100/60/31), 177/175/173 (10/6/4).

1,4-Bis-[3-{(2S,5R)-2,5-dihydro-2-isopropyl-5-pyrazinyl-1-propyn-1-yl}benzene (5). 1,4-Diodobenzene (0.362 g, 1.10 mmol) was added to a stirred suspension of (2S,5R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-proparglypyrazine (0.731 g, 3.30 mmol), copper(I) iodide (0.030 g, 0.16 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.056 g, 0.08 mmol) in dry, freshly distilled dichloromethane (12 ml) and triethylamine (0.485 ml, 3.50 mmol) under nitrogen. The mixture was stirred at ambient temperature for 24 h, after which the solvent was distilled off at reduced pressure, the residue was dissolved in chloroform (70 ml) and the solution was washed, dried (MgSO4) and evaporated. The product was purified by flash chromatography on silica gel using hexane–EtOAc (5:1), and recrystallized from ethyl acetate; yield 0.336 g (59%), m.p. 95 °C. Anal. Calcd for C26H23N2O2: C, H, 13.49 (CHMe). 28.21 (CH2CC), 31.05 (CHMe2), 52.56 and 152.61 (2×Ome), 54.11 (C-2), 54.32 (CH2Ph), 61.00 (C-5), 74.04 and 90.31 (CH2CC), 102.62 (C-4), 128.80, 128.88 and 129.24 (Ph), 134.21 (ipsoPh), 148.69 (C-6), 154.67 (C-2’), 161.79 (C-3), 164.81 (C-3’), 167.76 (C-4). MS (EI): 519 (49, M+), 487 (12), 335 (13), 211 (14), 184 (16), 183 (100), 182 (16), 169 (17), 168 (11), 167 (18), 141 (48). The NMR assignments were based on HETCOR and COSY.

2,5-Bis-[3-{[(2S,5R)-2,5-dihydro-2-isopropyl-5-pyrazinyl-1-propyn-1-yl]thiophene (6). 2,5-Diodothiophene (0.350 g, 1.04 mmol) was added to a stirred suspension of (2S,5R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(2-propyn-1-yl)pyrazine (0.693 g, 3.12 mmol), copper(I) iodide (0.030 g, 0.16 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.057 g, 0.08 mmol) in dry, freshly distilled dichloromethane (12 ml) and triethylamine (0.485 ml, 3.50 mmol) under nitrogen. The mixture was stirred at ambient temperature for 24 h, after which the solvent was distilled off at reduced pressure and the residue dissolved in chloroform (70 ml). The solution was washed, dried (MgSO4) and evaporated and the product was purified by flash chromatography on silica gel using hexane–EtOAc (15:1); yield 0.336 g.
amino acid ester was isolated from the residue after flash chromatography on silica gel using Et$_2$O-MeCN-aq.NH$_3$ (100:5:1).

(R)-Methyl 2-amino-5-phenyl-4-pentanoate (8a) was obtained in 88% yield; non-crystalline material. Anal. C$_{15}$H$_{24}$NO$_2$: C, H. [a]. +3.5 (c=1,07, EtOH). 1H NMR (CDCl$_3$): δ 1.71 (NH$_2$), 2.83 (1 H, dd, J 6.4 and 16.8 Hz, CH$_2$-CC), 2.85 (1 H, dd, J 5.1 and 16.8 Hz, CH$_2$-CC), 3.70 (1 H, dd, J 5.1 and 6.4 Hz, CH$_2$-CH$_2$), 3.76 (OMe), 7.24-7.51 (Ph). 13C NMR (CDCl$_3$): δ 26.54 (CH$_2$-CC), 52.55 (OMe), 53.73 (CH), 83.27 and 84.66 (CH$_2$-CC), 122.51 (ipso-Ph), 127.35, 127.55 and 130.97 (Ph), 173.16 (CO). MS (EI): 203 (M$^+$, 18), 131 (7), 128 (4), 117 (9), 116 (4), 89 (13), 88 (100).

(R')-Methyl 2-amino-5-(2-thienyl)-4-pentanoate (8b) was obtained in 86% yield; non-crystalline material. Anal. C$_{15}$H$_{14}$NO$_2$: C, H. [a]. +5.4 (c=0.5, EtOAc). 1H NMR (CDCl$_3$): δ 1.40 (NH$_2$), 2.81 (1 H, dd, J 6.0 and 16.7 Hz, CH$_2$-CC), 2.86 (1 H, dd, J 5.0 and 16.7 Hz, CH$_2$-CC), 3.69 (1 H, dd, J 5.0 and 6.0 Hz, CH$_2$-CH$_2$), 3.74 (OMe), 6.90, 7.11 and 7.16 (thienyl). 13C NMR (CDCl$_3$): δ 26.23 (CH$_2$-CC), 52.26 (OMe), 53.15 (CH), 76.43 and 88.94 (CH$_2$-CC), 123.10 (2-thienyl), 126.30, 126.74, 131.65 (Ph), 174.20 (CO). MS (Cl): 210 (M$^+$, 1), 209 (19), 194 (3), 193 (3), 178 (8), 177 (18), 152 (7), 151 (1), 150 (100).

(R')-Methyl 2-amino-5-(1-benzyl-2-oxo-1,2-dihydropyrindin-5-yl)-4-pentanoate (8c) was obtained in 76% yield; non-crystalline material. Anal. C$_{17}$H$_{15}$NO$_2$: C, H. [a]. +2.6 (c=0.39, EtOH). 1H NMR (CDCl$_3$): δ 1.77 (NH$_2$), 2.71 (1 H, dd, J 6.2 and 16.8 Hz, CH$_2$-CC), 2.76 (1 H, dd, J 5.1 and 16.8 Hz, CH$_2$-CC), 3.63 (1 H, dd, J 5.1 and 6.2 Hz, CH$_2$-CH$_2$), 3.68 (OMe), 5.01 (CH$_2$Ph), 7.26-7.36 (Ph), 7.67 (1 H, dd, J 3.1 Hz, H-6'), 8.49 (1 H, d, J 3.1, H-4'). 13C NMR (CDCl$_3$): δ 25.26 (CH$_2$-CC), 52.27 (OMe), 53.63 (CH), 54.04 (CH$_2$Ph), 76.96 and 88.83 (CH$_2$-CC), 101.95 (C-5'), 128.62, 128.74, 129.11 and 134.15 (Ph), 149.22 (C-6'), 154.51 (C-2') 167.55 (C-4'), 174.01 (CO). MS (EI): 311 (15, M$^+$), 253 (4), 252 (21), 226 (5), 225 (14), 224 (100), 223 (10), 92 (14), 91 (97). The assignments were based on HETCOR and COSY.

General procedure for the preparation of (R)-methyl 2-amino-5-aryly-4-pentanoate (9). 0.5 M HCl (4.5 ml, 2.25 mmol) was added to a solution of (2S,5R)-2,5-dihydro-3,6-dimethyl-2-isopropyl-5-(3-aryl-2-propynyl)pyrazine (3) (1.07 mmol) in dioxane (4.5 ml). The mixture was stirred at ambient temperature for 5 h and the pH adjusted to 10 by addition of aqueous NaOH. The mixture was then extracted with dichloromethane (3 × 15 ml), and the extracts were dried (MgSO$_4$) and evaporated. Methyl valinate was removed at reduced pressure by slow bulb-to-bulb distillation. The desired
3.20 (1 H, dd, J 5.7 and 18.0 Hz, CH₂-CC), 4.21 (1 H, dd, J 4.7 and 5.7 Hz, CH₂CH₂), 7.31-7.45 (Ph). ¹³C NMR (CD₂OD): δ 22.30 (CH₂-CC), 52.94 (CH), 83.59 and 85.73 (CH₂-CC), 123.93 (ipso-Ph), 129.37, 129.57 and 132.82 (Ph). 170.57 (CO). MS (EI): 189 (M⁺), 173 (4), 172 (35), 171 (6), 145 (20), 144 (56), 143 (25), 117 (148), 116 (39), 115 (74), 91 (12), 89 (18), 74 (100).

(2R)-2-Amino-5-(2-thienyl)-4-pentyonoic acid (9b) hydrochloride. ¹H NMR (CD₂OD): δ 3.13 (1 H, dd, J 5.4 and 18.1 Hz, CH₂-CC), 3.20 (1 H, dd, J 5.4 and 18.1 Hz, CH₂CH₂), 4.19 (1 H, dd, J 5.4 and 5.4 Hz, CHCH₂), 6.96, 7.24 and 7.37 (thienyl). ¹³C NMR (CD₂OD): δ 23.07 (CH₂-CC), 53.36 (CH), 73.31 and 86.69 (CH₂-CC), 122.86 (2'-thienyl), 127.05, 127.54 and 132.54 (Ph), 169.76 (CO). MS (EI): 195 (10, M⁺), 178 (31), 151 (9), 150 (30), 149 (13), 123 (10), 122 (45), 121 (100), 117 (12).

Dimethyl 5,5'-[p-phenylene] bis[(2R)-2-amino-4-pentyonoate] (10). 0.5 M HCl (3.6 ml, 1.76 mmol) was added to a solution of 1,4-bis[3-[(2S,5R)-2,5-dihydro-2-isopropyl-5-pyrazinyl]propynyl-1-yl]benzene (0.42 mmol) in dioxane (3.6 ml) and the mixture was stirred at ambient temperature for 5 h. The pH was adjusted to 10 by addition ofaq. ammonia, the mixture was extracted with dichloromethane (3 × 15 ml) and the extracts were dried (MgSO₄) and evaporated. Methyl valinate was removed at reduced pressure by slow bulb-to-bulb distillation. The title amino acid ester was isolated from the residue after flash chromatography on silica gel using CH₂Cl₂-CH₂Cl₂-EtOHaq-NH₃ (200:10:1); yield 0.106 (77%) as an oily material. Found: M 328.1432. Calc. for C₁₈H₁₈N₂O₄: 328.1423. ¹H NMR (CDCl₃): δ 1.74 (NH₃), 2.78 (1 H, dd, J 6.2 and 16.8 Hz, CH₂-CC), 2.81 (1 H, dd, J 5.3 and 16.8 Hz, CH₂-CC), 3.66 (1 H, dd, J 5.3 and 6.2 Hz, CHCH₂), 3.71 (OMe), 7.25 (s, Ph). ¹³C NMR (CDCl₃): δ 26.00 (CH₂-CC), 53.33 (OMe), 53.42 (CH), 83.04 and 86.59 (CH₂-CC), 122.79 (ipso-Ph), 131.51 (Ph), 174.31 (CO). MS (EI): 328 (M⁺), 270 (17), 269 (82), 242 (18), 241 (100), 210 (12), 209 (14), 182 (18), 181 (61), 180 (21).

Dimethyl 5,5'-[thiophene-2,5-diy] bis[(2R)-2-amino-4-pentyonoate] (11). 0.5 M HCl (3.6 ml, 1.76 mmol) was added to a solution of 2,5-bis[3-[(2S,5R)-2,5-dihydro-2-isopropyl-5-pyrazinyl]propynyl]thiophene (0.22 g 42 mmol) in dioxane (3.6 ml) and the mixture was stirred at ambient temperature for 5 h. The pH was adjusted to 10 by addition ofaq. ammonia and the mixture was extracted with dichloromethane (3 × 15 ml). The extracts were dried (MgSO₄) and evaporated and methyl valinate was removed at reduced pressure by slow bulb-to-bulb distillation. The title amino acid ester was isolated from the residue after flash chromatography on silica gel using CH₂Cl₂-CH₂Cl₂-EtOHaq-NH₃ (200:10:1); yield 0.102 g (73%) as an oily material. Found: M 334.0981. Calc. for C₂₁H₁₈N₂O₄S: 334.0987. [α]D₂⁵ +2.5° (c = 0.63, EtOH). ¹H NMR (CDCl₃): δ 1.74 (NH₃), 2.79 (1 H, dd, J 6.3 and 16.9 Hz, CH₂-CC), 2.83 (1 H, dd, J 5.3 and 16.9 Hz, CH₂-CC), 3.67 (1 H, dd, J 5.3 and 6.3 Hz, CHCH₂), 3.73 (OMe), 6.92 (s, thienyl). ¹³C NMR (CDCl₃): δ 26.22 (CH₂-CC), 52.31 (OMe), 53.25 (CH), 76.02 and 89.76 (CH₂-CC), 123.82 (2'-thienyl), 131.36 (thienyl), 174.10 (CO). MS (EI): 334 (10, M⁺), 249 (6), 248 (19), 247 (100), 246 (6), 216 (13), 215 (6), 188 (21), 187 (57), 185 (14).

5,5'-[p-Phenylene] bis[(2R)-2-amino-4-pentyonoic acid] (12) dihydrochloride. 0.5 M LiOH (0.22 ml, 0.40 mmol) was added to a solution of dimethyl 5,5'-[p-phenylene] bis[(2R)-2-amino-4-pentyonoate] (0.072 g, 0.22 mmol) in dioxane (0.2 ml). The mixture was stirred at ambient temperature for 24 h, after which it was acidified by dropwise addition of conc. HCl and evaporated to dryness at reduced pressure. The residue was repeatedly triturated with diethyl ether; the hydrochloride of the amino acid remained essentially pure; yield >95%, white solid. ¹H NMR (D₂O): δ 2.96 (1 H, dd, J 5.0 and 18.0 Hz, CH₂-CC), 3.02 (1 H, dd, J 5.8 and 18.0 Hz, CH₂-CC), 4.08 (1 H, dd, J 5.0 and 5.8 Hz, CHCH₂), 7.27 (Ph). ¹³C NMR (CD₂OD): δ 22.02 (CH₂-CC), 52.82 (CH), 84.77 and 85.10 (CH₂-CC), 123.79 (ipso-Ph), 132.71 (Ph), 171.83 (CO).

5,5'-[Thiophene-2,5-diy] bis[(2R)-2-amino-4-pentyonoic acid] (13) dihydrochloride. 0.5 M LiOH (0.24 ml, 0.48 mmol) was added to a solution of dimethyl 5,5'-[thiophene-2,5-diy] bis[(2R)-2-amino-4-pentyonoate] (0.080 g, 0.24 mmol) in dioxane (0.24 ml) and the mixture was stirred at ambient temperature for 24 h, after which it was acidified by dropwise addition of conc. HCl and evaporated to dryness at reduced pressure. The residue was repeatedly triturated with diethyl ether; the hydrochloride of the amino acid remained essentially pure; yield 0.089 g (95%), white solid. ¹H NMR (CD₂OD): δ 3.18 (1 H, dd, J 4.7 and 18.0 Hz, CH₂-CC), 3.20 (1 H, dd, J 5.47 and 18.0 Hz, CH₂-CC), 4.25 (1 H, dd, J 4.7 and 5.7 Hz, CHCH₂), 7.2 (s, thienyl). ¹³C NMR (CD₂OD): δ 22.47 (CH₂-CC), 52.52 (CH), 778.19 and 87.80 (CH₂-CC), 125.12 (2'-thienyl), 133.60, (thienyl), 170.16 (CO).

(2R,9R)-Dimethyl 2,9-diamo-no-4,6-decadinyldiace (14). 0.5 M HCl (3.6 ml, 1.76 mmol) was added to a solution of 1,6-bis[(2S,5R)-2,5-dihydro-2-isopropyl-3,6-dimethoxy-5-pyrazinyl]-2,4-hexadiyne (0.390 g, 0.42 mmol) in dioxane (3.6 ml) and the mixture was stirred at ambient temperature for 5 h. The pH was adjusted to 10 by addition ofaq. ammonia and the mixture was extracted with dichloromethane (3 × 15 ml). The extracts were dried (MgSO₄) and evaporated and valine methyl ester was removed at reduced pressure by slow bulb-to-bulb distillation. The title amino acid ester was isolated from the residue after flash chromatography on silica gel using CH₂Cl₂-CH₂Cl₂-EtOHaq-NH₃ (200:10:1); yield 0.098 g (88%) as an oily non-crystalline material. Found: M 252.1104.
Calc. for C_{12}H_{16}N_{2}O_{4}: 252.1110. [α]_{D}^{25} + 12.2° (c = 0.51, EtOH). \(^1\)H NMR (CDCl₃): δ 1.69 (NH₂), 2.63 (1 H, dd, J 6.7 and 16.9 Hz, CH₂CC), 2.70 (1 H, dd, J 5.2 and 16.9 Hz, CH₂CC), 3.61 (1 H, dd, J 5.2 and 6.7 Hz, CHCH₂), 3.72 (OMe). \(^13\)C NMR (CDCl₃): δ 25.46 (CH₂CC), 52.15 (OMe), 52.87 (CH), 67.32 and 73.13 (CH₂CC), 173.65 (CO). MS (EI): 252 (1, M⁺), 193 (39), 166 (10), 165 (82), 133 (30), 106 (75), 105 (25), 104 (31), 89 (8), 88 (100), 79 (14).

(2R,9R)-2,9-Diamo-4,6-decadiynedioic acid (15) dihydrochloride. (2R,9R)-Dimethyl 2,9-diamo-4,6-decadiynedioate (0.090 g, 0.36 mmol) was added to 6 M HCl (4 ml). The mixture was stirred at 40 °C for 1 h before being evaporated to dryness at reduced pressure. The residual material was triturated with diethyl ether which left a white solid, yield > 95%. \(^1\)H NMR (D₂O): δ 2.85 (1 H, dd, J 5.0 and 18.1 Hz, CH₂CC), 2.89 (1 H, dd, J 5.5 and 18.1 Hz, CH₂CC), 4.10 (1 H, dd, J 5.0 and 5.5 Hz, CHCH₂). \(^13\)C NMR (CD₂OD): δ 21.65 (CH₂CC), 52.17 (CH), 69.29 and 72.41 (CH₂CC), 171.04 (CO).

References


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