Stereospecific Synthesis of (2*R*,5*R*)-Hept-6-yne-2,5-diamine: A Potent and Selective Enzyme-activated Irreversible Inhibitor of Ornithine Decarboxylase (ODC)

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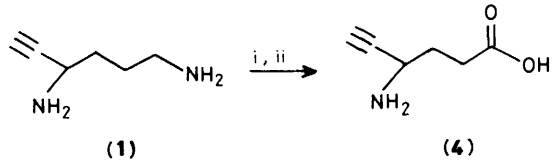
Hept-6-yne-2,5-diamine (**2**) and 2-methylhept-6-yne-2,5-diamine (**3**), while structurally related to the potent ornithine decarboxylase (ODC) inhibitor hex-5-yne-1,4-diamine (**1**), are stable to *in vivo* oxidation by monoamine oxidase (MAO). Although the methyl substitution is at a carbon relatively remote from the site of metabolic attack by ornithine decarboxylase (ODC), it has a critical influence on the potencies of these compounds as inhibitors of the enzyme. Of the four stereoisomers, (2*R*,5*R*)-(**2**) is the most active. Unambiguous syntheses of each isomer of (**2**) from the dianion of 3-trimethylsilyl-*N*-butoxycarbonylprop-2-ynylamine (**5**) are presented.

The polyamines spermidine and spermine and the diamine putrescine are believed to be involved in the regulation of growth processes.[1,2] In animal cells, these compounds are synthesized from ornithine according to the following sequence: ornithine → putrescine → spermidine → spermine, the first step being catalyzed by the enzyme ornithine decarboxylase (ODC; E.C. 4.1.1.17). Irreversible inhibitors of ODC, which cause a reduction in the cellular concentration of polyamines, have been shown to have potential for treating diseases associated with rapid cell proliferation.[3] In this context, we have recently reported that the product analogue, hex-5-yne-1,4-diamine (**1**), is one of the most potent known inhibitors of ODC.[4–6] Unfortunately, and somewhat surprisingly, (**1**) was found to be metabolized *in vivo* to 4-aminohex-5-ynoic acid (**4**), a potent, irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T); this results in undesirable side effects.[7,8] The diamine (**1**) is apparently a good substrate for monoamine oxidase (MAO), leading to an aldehyde which is subsequently oxidized by an alcohol dehydrogenase enzyme, to the amino acid (**4**) (Scheme 1). A solution to this problem relies on the



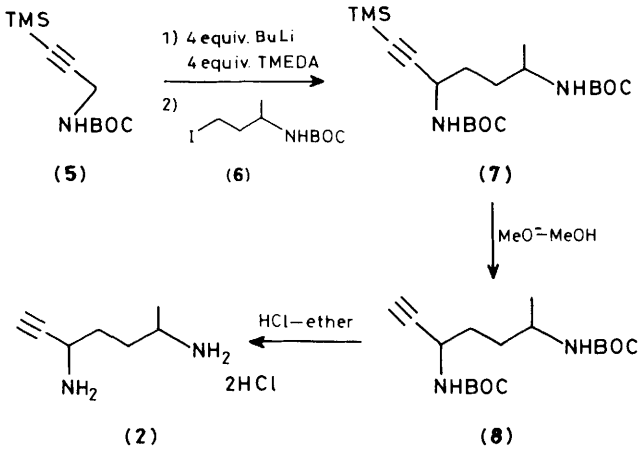
(**1**) (**4**)

Scheme 1. i, monoamine oxidase; ii, aldehyde dehydrogenase

knowledge that α-methyl-substituted amines are not good substrates of MAO.[9] We have thus undertaken the synthesis of some α-methyl derivatives of (**1**) in the hope that the methyl substitution would not be detrimental to the inhibitory potency towards ODC, while leading to greater metabolic stability.

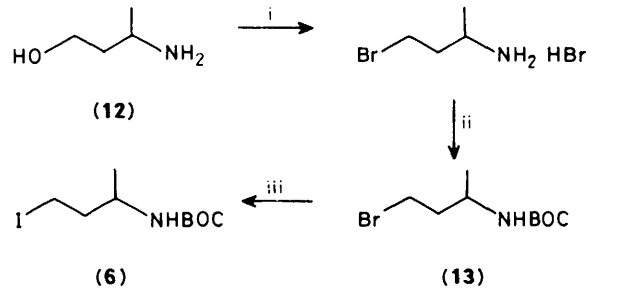
Results

The synthesis of the α-methyl derivative (**2**) is shown in Scheme 2. In the presence of an excess of base, the dianion prepared from compound (**5**)[10] was alkylated with the anion derived from compound (**6**) giving compound (**7**) in 60% yield. Attempts to use (**6**) directly were not successful because the alkylating species was rapidly protonated by the *N*-t-butoxycarbonyl (BOC) hydrogen. The iodide (**6**) was prepared in a straightforward manner from the amino alcohol (**12**)[11] as shown in Scheme 3. Deprotection of (**7**) was achieved in two



(**5**) (**6**) (**7**) (**2**) (**8**)

Scheme 2.



(**12**) (**6**) (**13**)

Scheme 3. *Reagents:* i, HBr (6M); ii, BOC_2O–NEt_3; iii, NaI–acetone

steps: removal of the trimethylsilyl group with sodium methoxide, followed by cleavage of the two *N*-BOC groups with ethereal hydrogen chloride to afford (**2**) as a mixture of stereoisomers. The composition of the isomeric mixture was determined by g.l.c. analysis (chiral polysiloxane type stationary phase Chirasil–Val) of the bis-*N*-trifluoroacetate derivatized substance.[12,13] A clean base line separation of the four stereoisomers of (**2**) [(**2a**$_1$), (**2a**$_2$), (**2b**$_1$), and (**2b**$_2$)] was thus obtained (Figure 1) indicating that one pair of enantiomers each accounted for 22% of the mixture, while the others accounted for 28% each (Table). The mixture of stereoisomers (**2**) was shown to be a potent inhibitor of ODC, the apparent dissociation constant (K_i = 13.5 μM) and the time of half

Table. Kinetic constants for inhibition of rat liver ODC, and g.l.c. analysis

	(1)	(2)	(3)	($2a_1$)	($2a_2$)	($2b_1$)	($2b_2$)	($2b'_1$)	($2b'_2$)
K_i(μM)	2.3	13.5	1 300	3	1 200	16	73	2 100	300
τ_{50}(min)	9.7	1.9	5.4	1.7	2.2	1.7	1.7	2.2	1.2
Configuration	(4R*S*)	(2R*S*,5R*S*)	(5R*S*)	(2*R*,5*R*)	(2*R*,5*S*)	(2*S*,5*S*)	(2*S*,5*R*)	(2*S*,5*S*)	(2*S*,5*R*)
Composition (g.l.c.)		22% ($2a_1$) 22% ($2a_2$) 28% ($2b_1$) 28% ($2b_2$)		99.4% ($2a_1$) 0.6% ($2a_2$)	99.7% ($2a_2$) 0.3% ($2a_1$)	83.7% ($2b_1$) 1.2% ($2b_2$) 14.3% ($2a_1$) 0.8% ($2a_2$)	83.2% ($2b_2$) 11.3% ($2b_1$) 0.8% ($2a_1$) 4.7% ($2a_2$)	99.8% ($2b_1$) 0.15% ($2b_2$)	91.5% ($2b_2$) 8.5% ($2b_1$)
M.p. (°C)	170	230	260	236	230	233	213	239	226
$[\alpha]_D^{25}$(°)				−13.6	+28	+9.5	−19.5	+12.8	−22.7

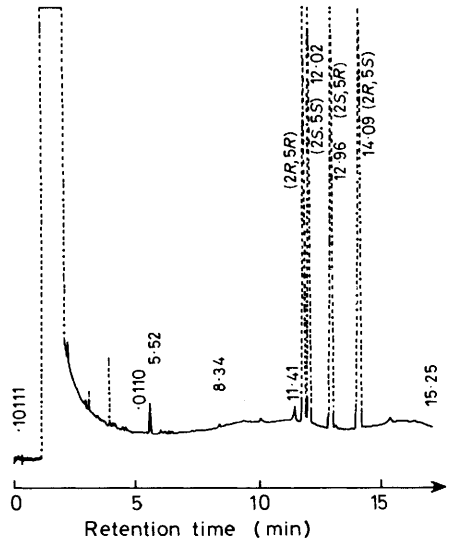
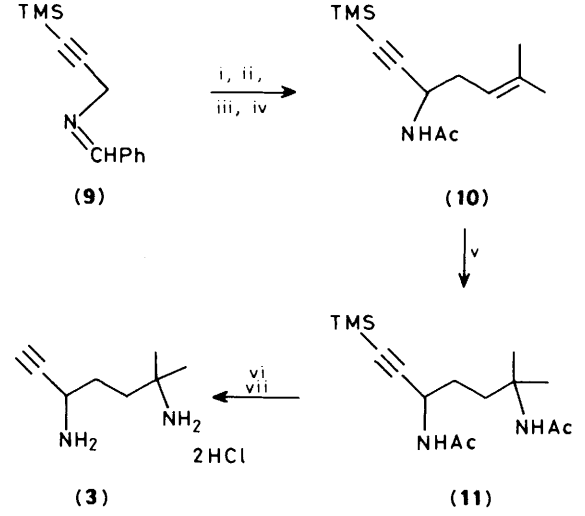


Figure 1: G.l.c. Analysis of (**2**) on Chirasil–Val capillary column



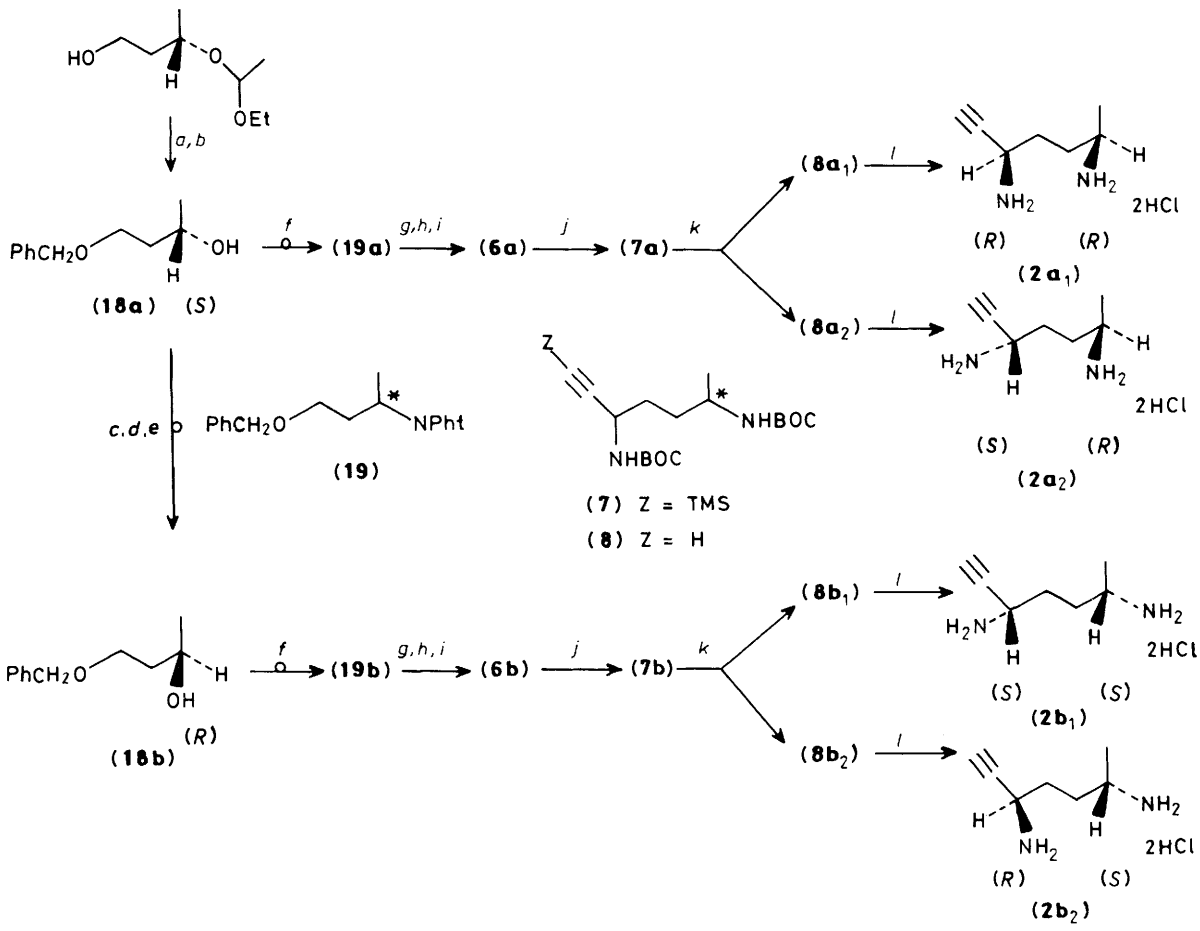
Scheme 4. *Reagents:* i, BuLi; ii, Br ; iii, $PhNHNH_2$; iv, AcCl–NEt_3; v, MeCN–H_2SO_4; vi, KOH–MeOH; vii, 6M HCl

inactivation of the enzyme (τ_{50} = 1.9 min) being comparable to the constants observed for (**1**) (Table), and, as expected, compound (**2**) is not a substrate for MAO.

In order to avoid the stereochemical problems owing to the presence of two asymmetric centres in compound (**2**), the *gem*-dimethyl derivative (**3**) was synthesized. An attempt to prepare compound (**3**) according to Scheme 2 was not successful owing to the instability of the dimethyl analogue of (**6**). However, a similar route (Scheme 4) avoided this problem. Thus, the anion derived from the Schiff base (**9**)[14] was readily alkylated with 3,3-dimethylallyl bromide leading to the olefin (**10**). The introduction of the second nitrogen function was achieved by a Ritter reaction affording compound (**11**), which was subsequently deprotected to give compound (**3**). When tested as an inhibitor of ODC, compound (**3**) was virtually inactive (Table), indicating that the stereochemistry about C-2 could play an important role in the affinity of these α-methyl-substituted amines for the enzyme. Thus it appeared likely that one of four stereoisomers of (**2**) would be a significantly more potent inactivator of ODC than the others. Moreover, it was expected that ODC would recognize the isomer(s) of (**2**) having the (5*R*) configuration, *i.e.* ($2a_1$) or ($2b_2$) (Scheme 5), in agreement with its stereochemical selectivity for the (*R*) enantiomer of (**1**).[6] In order to confirm this hypothesis and identify the active isomer, each of the isomers has been prepared according to Scheme 2, using the isomers of (**6**) [(*R*)-(**6a**); (*S*)-(**6b**)].

During the synthesis of (**2**) it was observed that the two racemic mixtures [(2*R*,5*R*)—(2*S*,5*S*)] and [(2*R*,5*S*)—(2*S*,5*R*)] could be considerably enriched by recrystallization of either of the *N*-BOC derivatives (**7**) or (**8**). Thus, alkylation of (**5**) with either (**6a**) or (**6b**) was expected to give a separate mixture of the diastereoisomers of (**7**) and/or (**8**). The enantiomers (**6a**) and (**6b**) were prepared by two routes; the first of these (Scheme 5) started from (*S*)-2-(1′-ethoxyethoxy)propan-1-ol, readily available from the enzyme reduction of ethyl acetoacetate using baker's yeast.[15] Benzylation of the alcohol followed by selective removal of the ethoxyethoxy group gave the key intermediate (*S*)-(**18a**). Conversion of (*S*)-(**18a**) into (*R*)-(**6a**) followed standard procedures while, to prepare (*S*)-(**6b**), it was necessary to invert the configuration of (*S*)-(**6a**) giving (*R*)-(**18b**), then subject (*R*)-(**18b**) to the same reaction sequence.

Following the conditions used to prepare racemic (**7**), the dianion derived from (**5**) was alkylated with either (**6a**) or (**6b**), affording mixtures of diastereoisomers ($7a_1$)–($7a_2$) and ($7b_1$)–($7b_2$), respectively. Separation of the diastereoisomers was not satisfactory at this stage but after selective removal of the trimethylsilyl group the resulting mixtures [($8a_1$)–($8a_2$) and ($8b_1$)–($8b_2$), respectively] were separable by fractional re-



Scheme 5. *Reagents:* a, $PhCH_2Cl$–NaOH; b, 1M HCl; c, TsCl–py; d, NBu_4OAc; e, NaOH; f, phtNH, PPh_3, $EtO_2CN{=}NCO_2Et$; g, 48% HBr; h, BOC_2O–NEt_3; i, NaI; j, (5) LDA, TMEDA; k, MeONa, MeOH; l, HCl gas, ether.

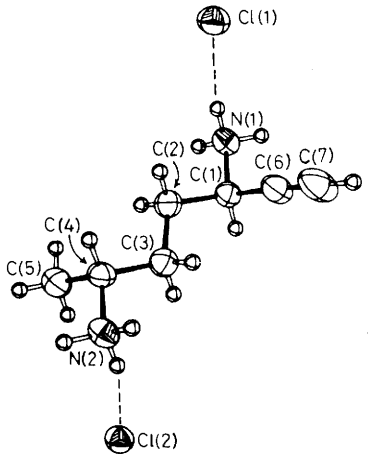
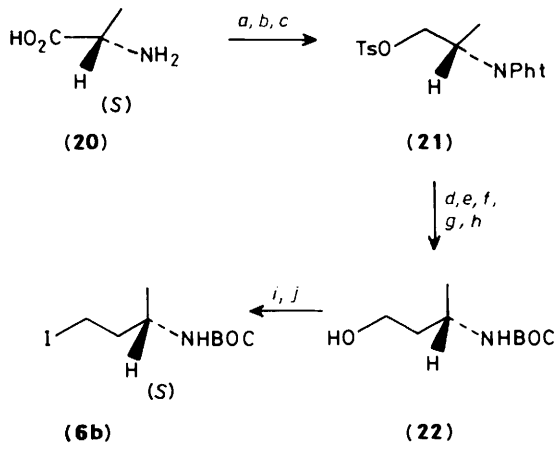


Figure 2: ORTEP representation of the three-dimensional *X*-ray structure of (**2a**$_1$)

crystallization. Each of the isomers was subsequently converted into (**2**) and their optical purity was determined by chiral-phase g.l.c. as described above. Whereas the isomers (**2a**$_1$) and (**2a**$_2$) were essentially pure (< 1% of the other isomer), the isomers (**2b**$_1$) and (**2b**$_2$) were not of satisfactory purity (Table), being contaminated with significant quantities of (**2a**$_1$) and (**2a**$_2$), respectively. Apparently partial racemization had occurred in the conversion of (**18a**) into (**18b**), eventually leading to optically impure (**6b**). When these compounds were tested as inhibitors of rat liver ODC some interesting results were obtained (Table). As shown by the K_I values, (**2a**$_1$) was the most active. This isomer was believed to have the (2*R*,5*R*) configuration and this was subsequently established by single crystal *X*-ray analysis (Figure 2).* The substance (**2a**$_2$), therefore, was the (2*R*,5*S*) isomer. Despite the low degree of optical purity of (**2b**$_1$) and (**2b**$_2$), the absolute configurations (2*S*, 5*S*) and (2*S*, 5*R*), respectively, could be assigned unambiguously from a comparison of their optical rotations with those of (**2a**$_1$) and (**2a**$_2$). As shown in the Table, the isomer (**2a**$_1$) is about four times more potent than the mixture of the four isomers (**2**). The activities of (**2b**$_1$) and (**2b**$_2$) were believed to be due in part to contamination with (**2a**$_1$). In order to support this argument, a second synthesis of (**6b**) was developed, starting in this case from (*S*)-alanine and following well-known procedures (Scheme 6). With essentially pure (**6b**) in hand, the synthesis (Scheme 5) was repeated leading to the (2*S*, 5*S*) isomer (**2b**$_1$′) and reasonably pure (**2b**$_2$′). The reason for the lower purity of (**2b**$_2$′) arose from the difficulties encountered in the fractional recrystallization of a small amount of material (**8b**$_2$) and was not related to the optical purity of (**6b**). These compounds were found to be weak inhibitors of ODC.

In conclusion, the work described in this paper represents a

* Carried out in the Laboratoire de Cristallochimie, Institut Le Bel, University Louis Pasteur, Strasbourg, under the supervision of Pr. R. Weiss.



Scheme 6. *Reagents: a*, phthalic anhydride; *b*, BH_3–Me_2S–THF; *c*, TsCl, py; *d*, NaCN–$(CD_3)_2SO$; *e*, 12N HCl, Heat; *f*, MeOH, HCl gas; *g*, BOC_2O, NEt_3, CH_2Cl_2; *h*, LAH, −78 °C, ether; *i*, MsCl, py, ether; *j*, MgI_2, ether.

case in which the potency of an enzyme-activated irreversible inhibitor is determined not only by the configuration of the carbon bearing the latent reactive species, but also by the stereochemistry of a remote asymmetric centre which is absent in both the natural substrate and product of the enzymatic catalysis. In addition, the weaker activity of the *gem*-dimethyl analogue (**3**) emphasizes the importance of the steric environment in this part of the molecule. Preliminary biological results obtained with the isomer (**2a**$_1$) have recently been reported.[16]

Experimental

Melting points were determined with a Büchi SMP-20 and are uncorrected as are boiling points. ^{1}H N.m.r. spectra (60 MHz) were recorded on a Varian Associates T-60, or on an EM-390 (90 MHz), spectrometer and are reported in p.p.m. from internal tetramethylsilane or 2,2-dimethyl-2-silapentane-5-sulphonate on the δ scale. I.r. spectra were recorded on a Perkin-Elmer IR-577 or IR-277 spectrophotometer. Mass spectra were taken from a Ribermag R 10-10 mass spectrometer. Microanalyses were conducted on a Perkin-Elmer 240 CHN analyser. Solvents and reagents were dried prior to use when necessary. Tetrahydrofuran (THF) was distilled from lithium aluminium hydride (LAH) and di-isopropylamine (DPA) and tetramethylethylenediamine (TMEDA) from KOH. Optical rotations were determined at 25 °C on a Perkin-Elmer 241 polarimeter. Ether refers to diethyl ether. Light petroleum has b.p. 35—60 °C.

3-*Trimethylsilyl*-N-*t*-*butoxycarbonylprop*-2-*ynylamine* (**5**).—A solution of di-t-butyl dicarbonate (109 g, 0.5 mol) in dichloromethane (200 ml) was added dropwise to a solution of prop-2-ynylamine (28 g, 0.5 mol) in dichloromethane (200 ml), cooled to 0 °C during the addition (30 min). The mixture was stirred for 2 h at room temperature and then concentrated under reduced pressure. The resulting protected amine was obtained after recrystallization from pentane (64 g, 84%); m.p. 43 °C; $\delta_H(CCl_4)$ 1.26 (9 H, s, BOC), 2.03 (1 H, t, *J* 2 Hz, HC≡C), 3.83 (2 H, dd, J_1 2 Hz, J_2 6 Hz, CCH_2N), and 4.8 (1 H, m, NH) (Found: C, 61.5; H, 8.3; N, 8.9. $C_8H_{13}NO_2$ requires C, 61.9; H, 8.4; N, 9.0%).

A solution of BuLi in hexane (1.3M; 0.2 mol, 160 ml) was added to a solution of *N*-t-butoxycarbonylprop-2-ynylamine (0.1 mol, 15.5 g) in THF (500 ml) at −78 °C. After 15 min a solution of MeSiCl (0.2 mol, 27 ml) in THF (100 ml) was added dropwise during 30 min. The mixture was stirred for an additional 1 h at room temperature after which a solution of AcOH (200 ml, 0.25M) was added. After 1h at room temperature the solution was concentrated under reduced pressure and extracted with ether. Work-up in the usual way followed by crystallization from pentane yielded (**5**) (22 g, 97%), m.p. 61 °C; $\delta(CDCl_3)$ 0.1 (9 H, s, TMS), 1.46 (9 H, s, BOC), 3.96 (2 H, d, *J* 6 Hz, CH_2), and 4.65 (1 H, m, NH) (Found: C, 58.3; H, 9.0; N, 6.1. $C_{11}H_{21}NO_2Si$ requires C, 58.1; H, 9.3; N, 6.1%).

1-*Iodo*-N-*t*-*butoxycarbonylbutan*-3-*ylamine* (**6**).—A solution of 3-aminobutanol[17] (8.8 g, 0.1 mol) in aqueous HBr (6M; 100 ml) was refluxed for 12 h. After cooling, the solution was washed with $CHCl_3$ (3 × 50 ml) and concentrated under reduced pressure. The crude 1-bromobutan-3-ylamine hydrobromide was suspended in CH_2Cl_2 (100 ml) with Et_3N (14 ml, 0.1 mol) and di-t-butyl dicarbonate (21.8 g, 0.1 mol) at room temperature overnight. The mixture was concentrated under reduced pressure and the residue was diluted with ether (150 ml) and washed with water (3 × 100 ml). After work-up the residue was purified by medium pressure chromatography on SiO_2 [AcOEt–light petroleum (5:95)] to give 1-bromo-*N*-t-butoxycarbonylbutan-3-ylamine (19 g, 75%), m.p. 55 °C; $\delta(CCl_4)$ 1.16 (3 H, d, *J* 6 Hz, Me), 1.36 (9 H, s, BOC), 1.93 (2 H, m, CH_2CHMe), 3.3 (2 H, t, *J* 7 Hz, $BrCH_2$), and 3.66 (1 H, m, CH).

A solution of this bromide (2.52 g, 0.01 mol) and NaI (1.65 g, 0.011 mol) in dry acetone (50 ml) was stirred overnight at room temperature in the dark. The precipitated salt (NaBr; 1 g) was filtered off and the solution was concentrated under reduced pressure. This residue was dissolved in ether (100 ml), washed with a solution of $NaHSO_3$ (0.1M; 50 ml), and then with water (2 × 50 ml). After drying ($MgSO_4$), the ether phase was evaporated and the essentially pure (**6**) was dissolved in THF (1M) and stored at 40 °C in the dark. The crystalline form of compound (**6**) decomposed slowly at room temperature; $\delta(CDCl_3)$ 1.16 (3 H, d, *J* 6 Hz, Me), 1.40 (9 H, s, BOC), 2 (2 H, m, CH_2CHMe), 3.2 (2 H, t, *J* 6 Hz, ICH_2), and 3.73 (1 H, m, CH).

7-*Trimethylsilyl*-N,N′-*di*-*t*-*butoxycarbonylhept*-6-*yne*-2,5-*diamine* (**7**).—A solution of BuLi in hexane (1M; 0.02 mol, 20 ml) was added at −78 °C to a solution of DPA (3 ml, 0.02 mol) and TMEDA (3.5 ml, 0.02 mol) in THF (50 ml). Subsequently, a solution of (**5**) (1.15 g, 5 mmol) in THF (10 ml) was added. The solution was stirred for 1 h at −78 °C and then a solution of (**6**) (1.5 g, 5 mmol) in THF (10 ml) was added. After 30 min at −78 °C, the solution was hydrolysed by glacial acetic acid (1.2 ml, 0.02 mol) followed by addition of water (100 ml) and ether (150 ml). The cooling bath was removed and the mixture was allowed to warm to room temperature and washed with water. The organic phase was washed with brine and dried ($MgSO_4$). The concentrated filtrate was purified by flash chromatography [SiO_2, AcOEt–light petroleum (1:9)] to give (**7**) (1.2 g, 60.5%), m.p. 116 °C (pentane) $\delta(CCl_4)$ 0.12 (9 H, s, TMS), 1.1 (3 H, d, *J* 6 Hz, Me), 1.36 (18 H, s, BOC), 1.50 [4 H, m, $(CH_2)_2$], 3.53 (1 H, m, CHMe), 4.33 (1 H, m, C≡CCH) and *ca.* 4.8 (2 H, m, NH) (Found: C, 60.6; H, 9.6; N, 7.3. $C_{20}H_{38}N_2O_4Si$ requires C, 60.2; H, 9.6; N, 7.0%).

N,N′-*Di*-*t*-*butoxycarbonyldiaminohept*-6-*yne*-2,5-*diamine* (**8**).—A solution of MeONa (1M; 1.1 ml, 1.1 mol) was added to a solution of (**7**) (0.4 g, 1 mmol) in MeOH (1 ml) at room temperature. After 1 h the mixture was concentrated and the residue was diluted with ether (50 ml). After work-up the product was recrystallized from pentane to afford (**8**) as colourless needles (0.28 g, 86%), m.p. 148 °C $\delta_H(CDCl_3)$ 1.1 (3 H, d, *J* 6 Hz, Me), 1.42 (18 H, s, BOC), 1.56 [4 H, m, $(CH_2)_2$],

2.23 (1 H, t, *J* 2 Hz, HC≡C), 3.53 (1 H, m, CHMe), and 4.3 (1 H, m, C≡CCH) (Found: C, 61.8; H, 8.9; N, 8.2. $C_{17}H_{30}N_2O_4$ requires C, 62.5; N, 9.2; H, 8.5%).

Hept-6-yne-2,5-diamine (**2**).—A solution of (**8**) (0.32 g, 1 mmol) in an excess of ethereal HCl (50 ml) was stirred for 24 h at room temperature whereupon the dihydrochloride salt of (**2**) crystallized as colourless needles (0.16 g, 80%), m.p. 230 °C; δ(D_2O) 1.33 (3 H, d, *J* 6 Hz, Me), 1.93 [4 H, m, $(CH_2)_2$], 3.06 (1 H, d, *J* 2 Hz, HC≡C), 3.43 (1 H, m, CHMe), and 4.16 (1 H, m, CCH); $\nu_{max.}$(Nujol) 2 100 (C≡C) and 3 250 cm^{-1} (HC) (Found: C, 42.3; H, 7.8; N, 13.8. $C_7H_{14}N_2$. 2HCl requires C, 42.2; H, 8.1; N, 14.0%).

N-*Acetyl-6-methyl-1-trimethylsilylhept-5-en-1-yn-3-ylamine*. (**10**).—A solution of BuLi (1.3M; 12.3 ml, 16 mmol) in hexane was added dropwise to a solution of (**9**) (3.45 g, 16 mmol) in THF (50 ml) at −78 °C. After 10 min, a solution of 1-bromo-3-methylbut-2-ene[18] (2.4 g, 16 mmol) in THF (10 ml) was added dropwise and the reaction mixture maintained at −78 °C for 30 min. The cooling bath was removed and the solution was quenched with water and then extracted with ether. The resulting imine was treated with a solution of phenylhydrazine (2 ml) in light petroleum (5 ml) for 30 min at room temperature. The resulting phenylhydrazone was filtered off and the filtrate was concentrated to give a residue was diluted with CH_2Cl_2 (50 ml). The resulting solution was cooled (*ca.* 0 °C) and treated with Et_3N (3 ml) followed by acetyl chloride (1.45 ml). After 1 h at 0 °C, the mixture was diluted with CH_2Cl_2 (200 ml), washed with 1M-HCl (3 × 50 ml) saturated aqueous $NaHCO_3$ (50 ml), and brine, and then dried ($MgSO_4$) and concentrated under reduced pressure. The residue, after chromatography on SiO_2 [ether–light petroleum (1:1)] followed by distillation gave (**10**) as a colourless liquid (2.2 g, 58%), b.p. 120 °C/30 mmHg; δ H ($CDCl_3$) 0.13 (9 H, s, TMS), 1.7 (6 H, d, *J* 6 Hz, $(Me)_2$), 2.0 (3 H, s, COMe), 2.36 (2 H, t, *J* 6 Hz, CH_2C), 4.8 (1 H, m, C≡CH), and 5.23 (1 H, m, CHC≡C); $\nu_{max.}$(film) 2 180 cm^{-1} (C≡C) (Found: C, 65.9; H, 9.4; N, 5.8. $C_{13}H_{23}NOSi$ requires C, 65.7; H, 9.7; N, 5.8%).

N,N′-*Diacetyl-2-methyl-7-trimethylsilylhept-6-yne-2,5-diamine* (**11**).—A solution of (**10**) (4.7 g, 20 mmol) and acetonitrile (0.94 ml) was treated with a mixture of glacial acetic acid (4 ml) and H_2SO_4 (1 ml) for 24 h at room temperature. The resulting solution was hydrolysed with water (15 ml), neutralized by Na_2CO_3, then extracted with ether. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on SiO_2 (5% MeOH in $CHCl_3$) to give (**11**) (1.6 g, 27%), δ($CDCl_3$) 0.13 (9 H, s, TMS), 1.23 (6 H, s, Me_2), 1.73 [4 H, m, $(CH_2)_2$], 2.00 and 2.06 [6 H, $(COMe)_2$], 4.7 (1 H, m, CCHN); $\nu_{max.}$($CHCl_3$) 1 740, (CO) and 2 160 cm^{-1} (C≡C) (Found: C, 60.2; H, 9.3; N, 9.1. $C_{15}H_{28}N_2O_2Si$ requires C, 60.7; H, 9.5; N, 9.4%).

2-*Methylhept-6-yne-2,5-diamine* (**3**).—A solution of (**11**) (1.27 g, 4.3 mmol) in methanol (4.5 ml) was added to a solution of KOH (0.38 g) in water (4.5 ml) and then stirred for 30 min at room temperature. The mixture was concentrated, diluted with brine, and extracted with CH_2Cl_2. The resulting product was refluxed in aqueous HCl (6M; 100 ml) overnight and then evaporated to dryness; the residue was recrystallized from methanol to give (**3**) as colourless *needles*, m.p. 260 °C; δ(D_2O) 1.38 [6 H, s, $(Me)_2$], 2.00 [4 H, m, $(CH_2)_2$], 3.06 (1 H, d, *J* 2.4 Hz, HC≡C), and 4.20 (1 H, m, HCC≡C); *M* + 1 141 (Found: C, 43.2; H, 7.9; N, 12.1. $C_8H_{16}N_2$·2HCl·0.5H_2O requires C, 43.2; H, 8.6; N, 12.6%). G.l.c. analysis on Chirasil Val capillary column: 48.7 and 49.4% of each enantiomer.

(3S)-1-*Benzyloxybutan-3-ol* (**18a**).—Benzyl chloride (12.6 g, 0.1 mol) was added dropwise to a mixture of (*S*)-3-(1-ethoxyethoxy)butan-1-ol[15] (16.3 g, 0.1 mol) and tetrabutylammonium hydrogen sulphate (1.7 g, 0.005 mol) in 50% aqueous sodium hydroxide (40 ml). The reaction mixture was vigorously stirred at room temperature for 4 h and then diluted with water (50 ml) and extracted with ether. The organic phase was washed with saturated aqueous ammonium chloride and dried ($MgSO_4$). The crude (3*S*)-1-benzyloxy-3-(1-ethoxyethoxy)butane was diluted with THF (100 ml) and hydrolysed with aqueous HCl (1M; 100 ml) at room temperature overnight. The mixture was concentrated under reduced pressure, extracted with water, dried ($MgSO_4$), and evaporated. The residue was distilled to give (**18a**) as a colourless *oil* (15.6 g, 86%), b.p. 145 °C/100 mmHg; δ($CDCl_3$) 1.16 (3 H, d, *J* 6 Hz, Me), 1.66 (2 H, q, *J* 6 Hz, CH_2CH), 2.9 (1 H, s, OH), 3.56 (2 H, t, *J* 6 Hz, OCH_2CH_2), 3.9 (1 H, q, *J* 6 Hz, CHOH), 4.26 (2 H, s, OCH_2Ph), and 6.9 (5 H, s, Ph) (Found: C, 72.9; H, 8.6. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.9%).

(3R)-1-*Benzyloxybutan-3-ol* (**18b**).—Toluene-*p*-sulphonyl chloride (19 g, 0.1 mol) was added in portions to a cold solution (*ca.* 0 °C) of (**18a**) (18 g, 0.1 mol) in a mixture of pyridine (50 ml) and dichloromethane (200 ml). After completion of the addition the mixture was stirred for 1 h at 0 °C and then overnight at room temperature. Water was added and then the mixture was extracted with dichloromethane and the extract dried ($MgSO_4$). Evaporation gave the crude tosylate which was used for the next step without further purification; δ($CDCl_3$) 1.2 (3 H, d, *J* 6 Hz, MeCH), 1.73 (2 H, q, *J* 6 Hz, CH_2CH), 2.33 (3 H, s, $MePhSO_3$), 3.3 (2 H, t, *J* 6 Hz, OCH_2CH_2), 4.2 (2 H, s, OCH_2Ph), 4.73 (1 H, q, *J* 6 Hz, CHOTs), 7.16 (5 H, s, Ph), and 7.60 (4 H, m, C_6H_4).

The tosylate was diluted with acetone (300 ml) containing tetrabutylammonium acetate (62 g, 0.2 mol) and the mixture was heated under reflux for 8 days. It was then concentrated under reduced pressure, hydrolysed and extracted with ether; evaporation of the extract gave the product which was distilled to give (3*R*)-1-*benzyloxybutan-3-yl acetate* as an oil (17 g, 78%), b.p. 85 °C/0.3 mmHg; δ($CDCl_3$) 1.23 (3 H, d, *J* 6 Hz, MeCH), 1.76 (2 H, t, *J* 6 Hz, CH_2CH), 1.93 (3 H, s, MeCO), 3.33 (2 H, t, *J* 6 Hz, OCH_2Me), 4.33 (2 H, s, OCH_2Ph), 4.9 (1 H, q, *J* = 6 Hz, CH_2OAc), and 6.96 (5 H, s, Ph) (Found: C, 70.3; H, 7.9. $C_{13}H_{18}O_3$ requires C, 70.5; H, 8.0%), $[\alpha]_D$ − 13.5° (*c* 1, $CHCl_3$).

This acetate (10 g, 0.045 mol) was stirred at room temperature in an aqueous solution of NaOH (1M; 100 ml) and methanol (20 ml). After 4 h, the mixture was concentrated, diluted with water (100 ml), and extracted with ether. After work-up the residue was distilled to give (**18b**) as an *oil* (6.5 g, 84%), b.p. 85 °C/0.3 mmHg: δ(CCl_4) 1.15 (3 H, d, *J* 6 Hz, Me), 1.66 (2 H, q, *J* 6 Hz, CH_2CH), 2.7 (1 H, s, OH), 3.55 (2 H, t, *J* 6 Hz, OCH_2CH_2), 3.9 (1 H, q, *J* 6 Hz, CHOH), 4.25 (2 H, s, CH_2Ph), and 6.5 (5 H, s, Ph) (Found: C, 72.9; H , 8.4. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.9%).

(3R)- *or* (3S)-1-*Benzyloxy-3-phthalimidobutane* (**19a**) *or* (**19b**).—A solution of diethyl azodicarboxylate (9 g, 0.05 mol) in THF (20 ml) was added dropwise to a solution of (**18**) (9 g, 0.05 mol), phthalimide (7.5 g, 0.05 mol), and triphenylphosphine (13.5 g, 0.05 mol) in THF (100 ml) at 0 °C over 30 min and the mixture was then stirred at room temperature overnight. The solution was concentrated under reduced pressure, filtered to remove diethyl hydrazine-1,2-dicarboxylate (6.6 g), and re-evaporated. The residue was mixed with ether, filtered to remove triphenylphosphine oxide (13.5 g), and re-evaporated. Purification of the mixture by flash chromatography [SiO_2; AcOEt–light petroleum (1:9)] afforded the *title compounds* (**19**).

(**19a**) (12 g, 78%), m.p. 52 °C $[\alpha]_D$ − 38.5° (*c* 1, $CHCl_3$); δ($CDCl_3$) 1.33 (3 H, d, *J* 7 Hz, MeCH), 1.83 (2 H, m, CH_2CH),

3.26 (2 H, t, *J* 6 Hz, OCH_2CH_2), 4.13 (2 H, s, CH_2Ph), 4.6 (1 H, m, C*H*Me), 6.96 (5 H, s, Ph), and 7.46 (4 H, m, C_6H_4) (Found: C, 73.7; H, 6.0; N, 4.5. $C_{19}H_{18}NO_3$ requires C, 73.3; H, 6.1; N, 4.5%).

(**19b**) (12.5 g, 80.5%), m.p. 56 °C; $[\alpha]_D$ + 26° (*c* 1, $CHCl_3$); ^1H n.m.r. spectrum similar to that of (**19a**) (Found: C, 73.7; H, 6.1; N, 4.4%).

(3R)- *or* (3S)-1-*Bromo-t-butoxycarbonylbutan*-3-*ylamine* (**13a**) *or* (**13b**).—A solution of (**19**) (**a** or **b**) (15 g, 0.05 mol) in HBr 48% (50 ml) was refluxed overnight, after which it was cooled and the precipitated phthalic acid filtered off. The filtrate was washed with $CHCl_3$ and concentrated under reduced pressure. The 1-bromobutan-3-ylamine crystallized spontaneously (9.5 g, 78%), m.p. 130 °C, and was used without further purification; δ(D_2O) 1.28 (3 H, t, *J* 6 Hz, *Me*CH), 2.18 (2 H, t, *J* 6 Hz, CH_2CH), 3.48 (2 H, t, *J* 6 Hz, CH_2Br), 3.6 (1 H, m, C*H*Me). A mixture of 1-bromobutan-3-ylamine (4.7 g, 0.02 mol), di-t-butyl dicarbonate (4.4 g, 0.02 mol), and $NaHCO_3$ (1.7 g, 0.02 mol) in $CHCl_3$ (20 ml) and water (15 ml) was refluxed overnight. $CHCl_3$ extraction followed by flash chromatography [SiO_2; AcOEt–light petroleum (1:9)] afforded the pure *title compounds* (**13**).

(**13a**) (3.2 g, 64%), m.p. 59 °C; $[\alpha]_D$ − 20.3° (*c* 0.76, EtOH); $\nu_{max.}$(KBr), 1 680 cm^{-1} (CO_2) and 3 385 cm^{-1} (NH); δ($CDCl_3$) 1.1 (3 H, d, *J* 6 Hz, *Me*CH), 1.41 (9 H, s, BOC), 1.96 (2 H, q, *J* 6 Hz, CH_2CH), 3.36 (2 H, t, *J* 6 Hz, CH_2Br), 3.75 (1 H, m, C*H*Me), and 4.30 (1 H, m, NH) (Found: C, 43.1; H, 7.0; N, 5.45. $C_9H_{18}BrNO_2$ requires C, 42.87; H, 7.19; N, 5.55%).

(**13b**) (4 g, 80%), m.p. 55 °C; $[\alpha]_D$ + 14.7° (*c* 0.42, EtOH); i.r. and ^1H n.m.r. spectra similar to (**13a**) (Found: C, 43.0; H, 7.0; N, 5.7%).

(3R)- *or* (3S)-1-*Iodo*-N-*t-butoxycarbonylbutan*-3-*ylamine* (**6a**) *or* (**6b**).—A solution of (**13**) (**a** or **b**) (2.5 g, 0.01 mol) and NaI (1.65 g, 0.011 mol) in dry acetone (50 ml) was left overnight at room temperature in darkness. The precipitated NaBr (*ca.* 1 g) was filtered off and the solution was concentrated under reduced pressure to give (**6a**) or (**6b**) (3 g) which was used for the next step without further purification; δ($CDCl_3$) 1.23 (3 H, d, *J* 6 Hz, *Me*CH), 1.46 (9 H, s, BOC), 2.11 (2 H, q, *J* 6 Hz, CH_2CH), 3.23 (2 H, t, *J* 6 Hz, CH_2I), 3.76 (1 H, m, C*H*Me) and 4.7 (1 H, m, NH).

(2R,5RS)- *or* (2S,5RS)-N,N′-*Di-t-butoxycarbonyl*-1-*trimethylsilylhept*-1-*yne*-2,5-*diamine* (**7a**) *or* (**7b**).—To a solution of LDA (0.04 mol) and TMEDA (6 ml, 0.04 mol) in THF (100 ml) at −78 °C was added a solution of (**5**) (2.3 g, 0.01 mol) in THF (10 ml) followed, after 1 h, by an addition of (**6a**) or (**6b**) (3 g, 0.01 mol) in THF (10 ml). After a further 30 min at −78 °C, AcOH (2.5 ml), water (200 ml), and ether (300 ml) were added consecutively. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give (**7a**) or (**7b**) which was used without further purification for the next step.

(2R,5R)- *and* (2R,5S)-N,N′-*Di-t-butoxycarbonylhept*-6-*yne*-2,5-*diamine* (**8a**$_1$) *and* (**8a**$_2$) *or* (2S,5S) *and* (2S,5R)-N,N′-*di-t-butoxycarbonylhept*-6-*yne*-2,5-*diamine* (**8b**$_1$) *and* (**8b**$_2$).—A solution of MeONa in MeOH (1M; 12 ml, 0.012 mol) was added to a solution of (**7a**) or (**7b**) in MeOH (5 ml) at room temperature. The mixture was stirred for 1 h at room temperature and then concentrated and the residue diluted with ether (100 ml). The solution was washed with water (2 × 25 ml), dried ($MgSO_4$), and concentrated. The residue was crystallized from ether–pentane to give (**8a**$_1$) from (**7a**) (700 mg); m.p. 151 °C $[\alpha]_D$ + 28° (*c* 0.52, $CHCl_3$); δ($CDCl_3$) the same as that described for (**8**); $\nu_{max.}$(KBr), 3 350 (NH), and 1 680 cm^{-1} (CO_2); C≡C not visible (Found: C, 62.7; H, 9.0; N, 8.5. $C_{17}H_{30}N_2O_4$ requires C, 62.6; H, 9.2; N, 8.5%), and (**8b**$_1$) from (**7b**) (800 mg): m.p. 157 °C; $[\alpha]_D$ − 11.4° (*c* 0.545, $CHCl_3$); ^1H n.m.r. and i.r. spectra were similar to those of (**8**). (Found: C, 62.7; H, 8.9; N, 8.5%).

The mother liquors were purified by flash chromatography [AcOEt–light petroleum (1:9) as eluant to give (**8a**$_2$) from (**7a**) (800 mg); m.p. 106 °C; $[\alpha]_D$ − 6° (*c* 0.6, $CHCl_3$); ^1H n.m.r. and i.r. spectra similar to those of (**8**) (Found: C, 62.7; H, 9.1; N, 8.4%), and (**8b**$_2$) from (**7b**) (750 mg): m.p. 99 °C $[\alpha]_D$ + 6.2° (*c* 0.535, $CHCl_3$); ^1H n.m.r. and i.r. spectra similar to those of (**8**) (Found: C, 62.8; H, 8.8; N, 8.4%).

(2R,5R)-(**2a**$_1$), (2R,5S)-(**2a**$_2$) (2S,5S)-(**2b**$_1$), *and* (2S,5R)-*hept*-6-*yne*-2,5-*diamine* (**2b**$_2$).—A solution of (**8a**$_1$, **a**$_2$, **b**$_1$, or **b**$_2$) (0.32 g, 1 mmol) in an excess of ethereal HCl was stirred for 24 h at room temperature. The dihydrochloride of (**2**) (**a**$_1$, **a**$_2$, **b**$_1$, or **b**$_2$), which crystallized directly was filtered off and dried *in vacuo*.

Compound (**2a**$_1$) was obtained from (**8a**$_1$) (0.2 g); m.p. 236 °C; $[\alpha]_D$ − 13.6° (*c* 1.51, H_2O); ^1H n.m.r. and i.r. spectra were similar to those of (**2**) (Found: C, 42.0; H, 7.8; N, 13.9. $C_7H_{14}N_2$·2HCl requires C, 42.2; H, 8.1; N, 14.0%). G.l.c. analysis showed 99.4% of (**2a**$_1$) and 0.6% of (**2a**$_2$). The structure (2*R*,5*R*) of (**2a**$_1$), the biologically active stereoisomer of hept-6-yne-2,5-diamine was confirmed by *X*-ray diffraction analysis. Suitable single crystals of (**2a**$_1$) were obtained by slow evaporation of an ethanolic solution at room temperature. $C_7H_{16}Cl_2N_2$ *M* = 199. Orthorhombic, *a* = 7.895 (1), *b* = 10.741 (1), *c* = 13.153 (1), Å, *V* = 1 115 Å^3, $d_{obs.}$ = 1.10 ± 0.02 g cm^{-3}, *Z* = 4, $d_{calc.}$ = 1.186 g cm^{-3}, F_{000} = 424, *e* = 48.144 cm^{-1}, space group $P2_12_12_1$. Figure 2 shows an ORTEP plot of the molecule.

Compound (**2a**$_2$) (2*R*,5*S*) was obtained from (**8a**$_2$) (0.2 g); m.p. 230 °C; $[\alpha]_D$ + 28° (*c* 0.515, H_2O); ^1H n.m.r. and i.r. spectra were similar to those of (**2**) (Found: C, 41.9; H, 7.8; N, 13.9. $C_7H_{14}N_2$·2HCl requires C, 42.2; H, 8.1; N, 14.0%). G.l.c. analysis 99.7% or (**2a**$_2$) and 0.3% of (**2a**$_1$). The (*S*)-configuration at C(5) was deduced from the structure of (**2a**$_1$).

Compound (**2b**$_1$) (2*S*,5*S*) was obtained from (**8**) (0.2 g); m.p. 233 °C; $[\alpha]_D$ + 9.5° (*c* 0.62, H_2O); ^1H n.m.r. and i.r. spectra were similar to those of (**2**) (Found: C, 41.9; H, 7.7; N, 14.0. $C_7H_{14}N_2$·2HCl requires C, 42.2; H, 8.1; N, 14.0%). G.l.c. analysis showed 83.7% of (**2b**$_1$), 14.3% of (**2a**$_1$), 0.8% of compound (**2a**$_2$) and 1.2% of (**2b**$_2$). The (*S*)-configuration at C(5) of (**2b**$_1$) was deduced by comparison of these physical constants with those of (**2a**$_1$).

Compound (**2b**$_2$) (2*S*,5*R*) was obtained from (**8b**$_2$) (0.2 g); m.p. 213 °C; $[\alpha]_D$ − 19.5° (*c* 0.5, H_2O); ^1H n.m.r. and i.r. spectra were similar to those of (**2**) (Found: C, 41.9; H, 7.7; N, 14.0. $C_7H_{14}N_2$·2HCl requires C, 42.2; H, 8.1; N, 14.0%). G.l.c. analysis showed 83.2% of (**2b**$_2$), 4.7% of (**2a**$_2$), 0.8% of (**2a**$_1$) and 11.3% of (**2b**$_1$). The (*R*)-configuration at the C(5) of (**2b**$_2$) was deduced by comparison of these physical constants with those of (**2a**$_2$).

2(*S*)-2-*Phthalimidopropyl Toluene*-p-*sulphonate* (**21**).—A mixture of (S)-alanine (0.3 mol, 26.7 g) and phthalic anhydride (0.3 mol, 45 g) in benzene (300 ml) was refluxed (Dean-Stark) overnight, cooled, and the solution acidified with aqueous HCl (6M). The precipitated phthaloylalanine (55 g) was collected and dried. A portion of this substance (0.05 mol, 11 g) was dissolved in THF (150 ml) and the solution cooled to −78 °C and then treated with BH_3–Me_2S complex (10M; 6 ml). The mixture was stirred overnight at room temperature and then extracted with CH_2Cl_2 to afford essentially pure (*S*)-2-phthalimidopropanol (10 g, 97%), m.p. 77 °C; δ($CDCl_3$) 1.43 (3 H, d, *J* 6 Hz, MeCH), 2.65 (1 H, m, OH), 3.91 (2 H, d, *J* 6 Hz, CH_2OH), 4.46 (1 H, m, C*H*Me), and 7.66 (4 H, m, C_6H_4) (Found: C, 64.3; H, 5.5; N, 6.7. $C_{11}H_{11}NO_3$ requires C, 64.3; H, 5.4; N, 6.8%), $[\alpha]_D$ + 7.2° (*c* 0.5, $CHCl_3$).

A solution of (*S*)-2-phthalimidopropanol (10.25 g, 0.05 mol),

tosyl chloride (11.4 g, 0.06 mol), and pyridine (15 ml) in dichloromethane (100 ml) was stirred overnight at room temperature. The mixture was washed with AcOH (1M), and the CH_2Cl_2 layer dried ($MgSO_4$) and evaporated. The residue was crystallized from ether–CH_2Cl_2 to give (**21**) (12 g, 56%), m.p. 135 °C; $\delta_H(CDCl_3)$ 1.4 (3 H, d, *J* 6 Hz, *Me*CH), 2.3 (3 H, s, *Me*C_6H_4), 4.16 (1 H, m, CH), 4.56 (2 H, d, *J* 5 Hz, CH_2), 7.33 (4 H, m, C_6H_4 Tosyl), and 7.6 (4 H, s, C_6H_4, phthaloyl) (Found: C, 60.1; H, 4.8; N, 3.9. $C_{18}H_{17}NO_5S$ requires C, 60.1; H, 4.7; N, 3.8%), $[\alpha]_D$ + 20.0° (*c* 0.504, $CHCl_3$).

(S)-3-*Phthalimidopropionitrile*.—A suspension of the tosylate (**21**) (11 g, 0.03 mol) and sodium cyanide (1.5 g, 0.03 mol) in DMSO (50 ml) was heated at 100 °C for 48 h. The mixture was cooled, diluted with water (100 ml) and CH_2Cl_2 (200 ml) and the organic layer then separated, washed with water (5 × 100 ml) dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography [SiO_2, ether–light petroleum (1:1)] to give the nitrile (3 g, 42%), m.p. 91 °C; $\delta(CDCl_3$; 90 MHz) 1.50 (3 H, d, *J* 6 Hz, Me), 3.0 (ABX, 2 H, qd, CH_2CN, J_{AB} 15 Hz, J_{AX} 9 Hz, J_{BX} 7.5 Hz), 4.66 (1 H, tq, *CH*Me), and 7.66 (4 H, m, C_6H_4) (Found: C, 67.3; H, 5.0; N, 12.9. $C_{12}H_{10}N_2O_2$ requires C, 67.2; H, 4.6; N, 13.0%), $[\alpha]_D$ + 38° (*c* 0.24, $CHCl_3$).

(*S*)-3-*t-Butoxycarbonylaminobutan*-1-*ol* (**22**).—A suspension of (*S*)-3-phthalimidopropionitrile (4.3 g, 0.02 mol) in concentrated HCl (100 ml) was refluxed overnight. After cooling, the precipitated phthalic acid was removed and the solution was concentrated and dried under reduced pressure. The crude amino acid was dissolved in methanol (100 ml) containing a catalytic amount of TsOH (0.1 g) and left overnight. The solvent was then evaporated off and the residue, with di-t-butyl dicarbonate (4.4 g, 0.02 mol) and Et_3N (2.8 ml, 0.02 mol) in CH_2Cl_2 (100 ml) was stirred for 4 h at room temperature. CH_2Cl_2 extraction, followed by flash chromatography [SiO_2, ether–light petroleum ether (1:3)] afforded (*S*)-methyl-3-t-butoxycarbonylaminobutanoate which was recrystallized from pentane (4 g, 97%), m.p. 42 °C; $\delta_H(CDCl_3)$ 1.16 (3 H, d *J* 6 Hz, MeCH), 1.36 (9 H, s, BOC), 2.4 (2 H, d, *J* 6 Hz, CH_2), 3.6 (3 H, s, MeO), 3.83 (1 H, m, C*H*Me), and 5.1 (1 H, m, NH) (Found: C, 55.5; H, 8.4; N, 6.3. $C_{10}H_{19}NO_4$ requires C, 55.2; H, 8.8; N, 6.4%), $[\alpha]_D$ − 20.2° (*c* 0.54, $CHCl_3$).

A solution of this ester (3.8 g, 0.018 mol) in ether (50 ml) was added to a suspension of LAH (0.8 g, 0.02 mol) in anhydrous ether (50 ml) at − 78 °C. After 1 h, the mixture was hydrolysed by successive addition of water (0.8 ml), 15% aqueous NaOH (0.8 ml), and water (2.5 ml) followed by stirring at room temperature for 1 h. The granulated mineral salts were filtered off and, the filtrate dried ($MgSO_4$) and concentrated under reduced pressure. The residue was recrystallized from pentane–ether to give the *alcohol* (**22**) (3 g, 88%), m.p. 56 °C; $\delta_H(CDCl_3)$ 1.25 (3 H, d, *J* 6 Hz, Me), 1.4 (9 H, s, BOC), 1.8 (2 H, m, CH_2CH), *ca.* 3 (1 H, m, OH), 3.56 (2 H, dd, *J* 4 Hz, CH_2O), 3.9 (1 H, m, C*H*Me), and 4.33 (1 H, m, NH) (Found: C, 57.3; H, 9.6; N, 7.4. $C_9H_{19}NO_3$ requires C, 57.1; H, 10.1; N, 7.4%), $[\alpha]_D$ + 10.2° (*c* 0.5, $CHCl_3$).

(S)-1-*Iodo*-N-*t-butoxycarbonylbutan*-3-*ylamine* (**6b**).—A solution of the alcohol (**22**) (1.9 g, 0.01 mol), methanesulphonyl chloride (1.2 ml, 0.011 mol), and NEt_3 (3 ml) in CH_2Cl_2 (50 ml) was stirred overnight at room temperature. The mixture was diluted with CH_2Cl_2 (100 ml) washed with AcOH (1M; 2 × 50 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was used for the next step without further purification (2.7 g); $\delta_H(CDCl_3)$ 1.1 (3 H, d, *J* 6 Hz, *Me*CH), 1.33 (9 H, s, BOC), 1.75 (2 H, m, CH_2CH), 2.85 (3 H, s, *Me*SO_3), 3.6 (1 H, m, C*H*Me), 4.1 (2 H, t, *J* 6 Hz, CH_2) and *ca.* 4.5 (1 H, m, NH).

This product (2.7 g), dissolved in anhydrous ether (20 ml) at 0 °C, was treated with a solution of MgI_2 in ether (2M; 50 ml, 0.01 mol). The mixture was stirred for 2 h at 0 °C, hydrolysed and then extracted with ether. The organic layer was washed with aqueous $Na_2S_2O_3$ (1M), dried ($MgSO_4$), and concentrated under reduced pressure to give (**6b**) (2.8 g) which was kept in THF at 0 °C and used without further purification for the next step: $\delta_H(CDCl_3)$ 1.1 (3 H, d, *J* 6 Hz, Me), 1.33 (9 H, s, BOC), 1.9 (2 H, q, *J* 7 Hz, CH_2CH), 3.06 (3 H, t, *J* 7 Hz, CH_2I), 3.5 (1 H, m, C*H*Me), and 3.8 (1 H, m, NH).

(2S,5S)- *and* (2S,5R)-N,N′-*Di*-t-*butoxycarbonylhept*-6-*yne*-2,5-*diamine* (**8b′**$_1$) *and* (**8b′**$_2$).—These compounds were obtained from (**6b**) [prepared from (**22**)] by the procedure described for the isomers (**8a**$_1$) and (**8a**$_2$).

(**8b′**$_1$) (0.73 g), m.p. 151 °C; $[\alpha]_D$ − 28.2° (*c* 0.5, $CHCl_3$) (Found: C, 62.8; H, 9.1; N, 8.6. $C_{17}H_{30}NO_4$ requires C, 62.6; H, 9.2; N, 8.5%).

(**8b′**$_2$) (0.6 g), m.p. 105 °C; $[\alpha]_D$ + 7.3° (*c* 0.6, $CHCl_3$) (Found: C, 62.6; H, 9.0; N, 8.4. $C_{17}H_{30}NO_4$ requires C, 62.6; H, 9.2; N, 8.5%).

(2S,5S)- *and* (2S,5R)-*Hept*-6-*yne*-2,5-*diamine* (**2b′**$_1$) *and* (**2b′**$_2$).—Following the procedure described for the preparation of (**2a**$_1$) and (**2a**$_2$), (**8b′**$_1$) and (**8b′**$_2$) (0.32 g, 1 mmol) were deprotected to afford: (**2b′**$_1$) (0.2 g), m.p. 239 °C; $[\alpha]_D$ + 12.8° (*c* 1, H_2O); ^1H n.m.r. and i.r. spectra were similar to those of (**2**) (Found: C, 42.1; H, 7.9; N, 14.2. $C_7H_{14}N_2$·2HCl requires C, 42.2; H, 8.1; N, 14.0%); g.l.c. analysis showed 99.8% of (**2b**$_1$), 0.15% of (**2b**$_2$); and (**2b′**$_2$) (0.2 g), m.p. 226 °C; $[\alpha]_D$ − 22.7° (*c* 1, H_2O); ^1H n.m.r. and i.r. spectra were similar to those of (**2**) (Found: C, 41.9; H, 7.9; N, 14.2. $C_7H_{14}N_2$·2HCl requires C, 42.2; H, 8.1; N, 14.0%); g.l.c. analysis showed 91.4% of (**2b**$_2$) and 8.3% of (**2b**$_1$).

References

1 D. H. Russell, 'Polyamines in Normal and Neoplastic Growth', Raven Press, New York, 1975.
2 J. Jänne, H. Pösö, and A. Raina, *Biochem. Biophys. Acta*, 1978, **473**, 241.
3 A. Sjoerdsmar and P. J. Schechter, *Clin. Pharmacol. Ther.*, 1984, **35**, 287.
4 B. W. Metcalf, P. Bey, C. Danzin, M. J. Jung, P. Casara, and J. P. Vevert, *J. Am. Chem. Soc.*, 1978, **100**, 2551.
5 C. Danzin, M. J. Jung, B. W. Metcalf, J. Grove and P. Casara, *Biochem. Pharmacol.*, 1979, **28**, 627.
6 P. Casara, C. Danzin, B. W. Metcalf, and M. J. Jung, *J. Chem. Soc., Chem. Commun.*, 1982, 1190.
7 C. Danzin, M. J. Jung, N. Seiler, and B. W. Metcalf, *Biochem. Pharmacol.*, 1979, **28**, 633.
8 C. Danzin, P. Casara, N. Claverie, and J. Grove, *Biochem. Pharmacol.*, 1983, **32**, 941.
9 (*a*) H. Blaschko, *Pharmacol. Rev.*, 1952, **4**, 415; (*b*) R. B. Silverman, *Biochemistry*, 1984, **23**, 5206.
10 B. W. Metcalf and P. Casara, *J. Chem. Soc., Chem. Commun.*, 1979, 119.
11 H. Schoenenberger, H. Vogel, and E. Bamann, *Arch. Pharm.*, 1965, **298** (**6**), 371.
12 H. Franck, G. J. Nicholson, and E. J. Bayer, *Chromatographia*, 1978, 146.
13 J. Wagner and J. P. Hinckel, unpublished results.
14 B. W. Metcalf and P. Casara, *Tetrahedron Lett.*, 1975, **38**, 3337.
15 B. Seuring and D. Seebach, *Helv. Chim. Acta*, 1977, **60**, 1175.
16 (*a*) C. Danzin, P. Casara, N. Claverie, B. W. Metcalf, and M. J. Jung, *Biochem. Biophys. Res. Commun.*, 1983, **116**, 237; (*b*) P. Mamont, M. Siat, A. M. Joder-Ohlenbusch, A. Bernhardt, and P. Casara, *Eur. J. Biochem.*, 1984, **142**, 457.
17 R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.*, 1962, 2215.
18 H. Simon, Ad. Kaufmann, and H. Schinz, *Helv. Chim. Acta*, 1946, **29**, 1133.

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