SYNTHESIS OF AND NUCLEOPHILIC ADDITION REACTIONS TO AN 8-ETHENYL-1,2,4-TRIAZOLO[4,3-a]PYRAZINE DERIVATIVE

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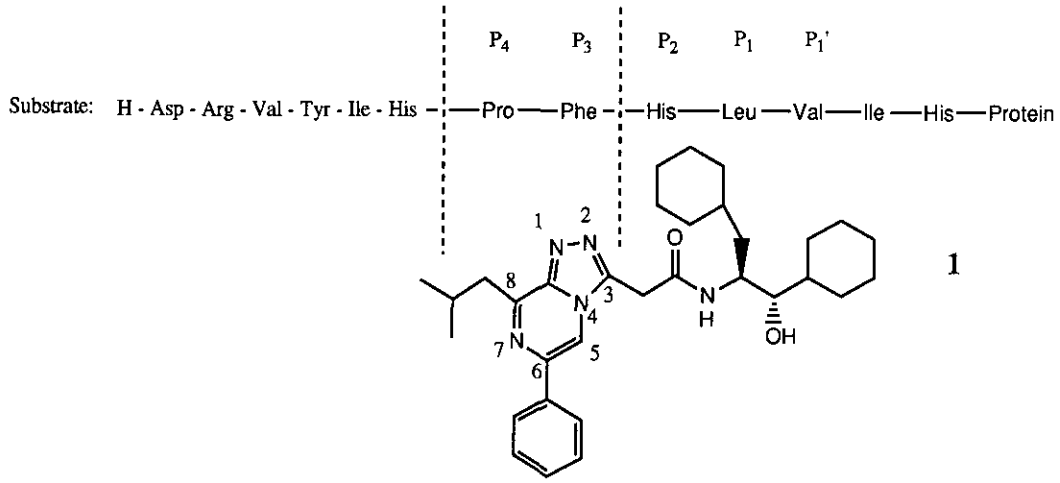
Abstract - Synthesis of and nucleophilic addition reactions to N-[(1S,2S)-1,3-dicyclohexyl-1-hydroxy-2-propyl]-8-ethenyl-6-phenyl-1,2,4-triazolo[4,3-a]pyrazine-3-acetamide are described.

We recently reported[1] the 1,2,4-triazolo[4,3-a]pyrazine derivative (1) (Figure 1) as a prototype of several series[1-3] of inhibitors of human renin, a key enzyme in the regulation of blood pressure.[4] Structure-activity relationships for these series of compounds were consistent with the 6,8-disubstituted 1,2,4-triazolo[4,3-a]pyrazine moiety acting as a non-peptidic replacement for the 'P_4' and 'P_3' residues[4] of the substrate. Since inhibitor (1) displayed only modest enzymic affinity (IC_{50} 1.1 μM), we sought ways of improving binding including, amongst other approaches,[1-3] variation of the two substituents in the 1,2,4-triazolo[4,3-a]pyrazine heterocycle. With respect to the 8-substituent, molecular modelling studies suggested a polar group linked to the heterocycle by a short alkyl chain could form a hydrogen bond with a donor in the enzyme.[5] To explore this possibility we chose to prepare the 8-ethenyl derivative (8) (Scheme 2) as a key intermediate, since, by analogy with typical electron deficient heterocycles such as pyridine,[6,7] the ethenyl group was expected to undergo addition reactions with hetero-nucleophiles. In this way a range of polar functions, linked to the heterocycle through an ethylene chain, could be introduced. Also, scope for longer linking chains could arise from homologation by carbon nucleophiles and subsequent manipulation of the resulting terminal functionality.

In designing a synthesis of 8 masking of the ethenyl group as the corresponding methyl thioether (compound 7a) was a key feature. By this means the 1,2,4-triazolo[4,3-a]pyrazine ring could be prepared starting from pyrazinone (2) (Scheme 1), readily obtained[8] by condensation of methioninamide with phenylglyoxal.[9] The latent double bond

Figure 1. Human renin substrate and the structure of inhibitor (**1**).



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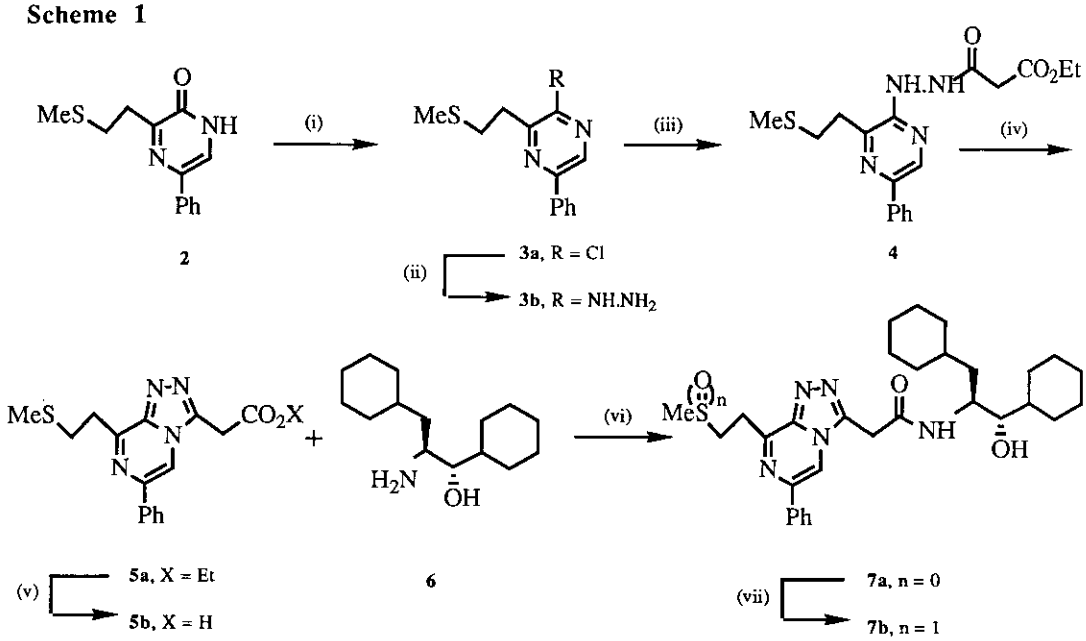
could then be carried through the relatively harsh procedures needed[1] to build on the triazole ring. Thus, essentially as described previously for the corresponding 8-isobutyl analogue,[1] **2** was converted in 50% overall yield to the 1,2,4-triazolo[4,3-*a*]pyrazine-3-acetic acid (**5b**). In the initial chlorination of **2** phosgene was found to be a superior reagent to phosphorus oxychloride.[10] Carbodiimide mediated coupling of **5a** with (1*S*,2*S*)-2-amino-1,3-dicyclohexylpropanol (**6**[1]) then gave the required thioether (**7a**), which, after oxidation and sulphoxide elimination, provided **8** (51% overall yield from **5b**).

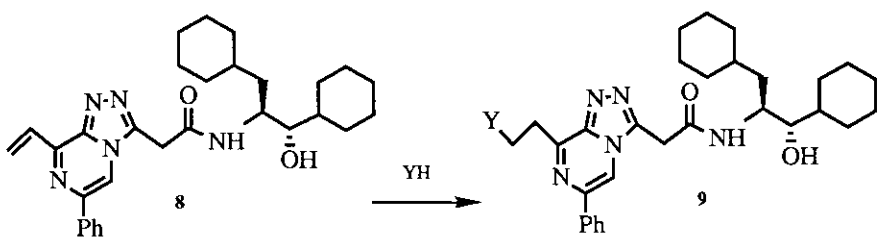
As anticipated, the ethenyl bond in **8** participated in addition reactions with hetero-nucleophiles, a selection of which are exemplified in Scheme 2. In a similar fashion to 2-vinylpyridine[11,12] primary and secondary amines underwent addition, either under neutral (e.g. compounds **9b,c**) or acidic conditions (e.g. **9d**). It is noteworthy that these transformations proceeded at ambient temperature. In the case of ammonia, however, under neutral conditions only a low yield of **9a** resulted.[13] The addition of heterocyclic and

Scheme 1



Reagents: (i) $COCl_2$ / THF / PhMe / Reflux; (ii) N_2H_4 / *n*-BuOH / Reflux; (iii) $ClOCCH_2CO_2Et$ / Et_3N / EtOAc / 0°C; (iv) PTSA / PhMe / Reflux; (v) NaOH / H_2O / EtOH; (vi) 1-Hydroxybenzotriazole / $Me_2N(CH_2)_3N{=}C{=}NEt$ / DMF; (vii) *m*-CPBA / CH_2Cl_2 / 0°C.

Scheme 2



9	Y	Yield (%)[a]	Conditions[b]
a	H_2N	12	N
b	$PhCH_2NH$	56	N
c	Me_2N	48	N
d		32	A
e		53	N
f	AcO	53	A

[a] Not optimised

[b] A = Acidic, N = Neutral (see Experimental Section)

oxygen nucleophiles is illustrated by the reaction of **8** with imidazole and acetate anion to give **9e** and **9f**, respectively.

By contrast with the addition of hetero-nucleophiles, the ethenyl group appeared to be inert to cyanide ion under a variety of conditions. In passing, however, it is worth mentioning that homologation could be achieved by oxidative cleavage of the double bond followed by Wittig reaction of the resulting aldehyde.

We were disappointed to find that none of the compounds (**9a-f**) showed improved affinity for human renin when compared with the reference inhibitor (**1**).

EXPERIMENTAL SECTION

All operations were carried out at ambient temperatures unless otherwise stated. All evaporations were done at below 50°C using a Buchi rotary evaporator. Flash chromatography was performed on silica gel (Merck Kieselgel: Art. 9385). Melting points were taken on a Büchi apparatus using glass capillary tubes and are uncorrected. ^{1}H Nmr spectra were recorded on Bruker WM200, WM250 or WM400 instruments and are reported as δ values (ppm) relative to Me_4Si as an internal standard. Electron impact mass spectra (eims) were recorded on a VG 12-12 Quadrapole or a VG 70-250 SE spectrometer. Positive fast atom bombardment mass spectra (fabms) were determined on a VG ZAB 2-SE or a VG modified AEl/Kratos MS9 spectrometer.

3-(2-Methylthioethyl-5-phenyl-2(1H)-pyrazinone (2). 12.5 M Sodium hydroxide solution (16.0 ml, 0.2 mol) was added to a stirred solution of phenylglyoxal monohydrate (15.2 g, 0.1 mol) and methioninamide hydrochloride (18.5 g, 0.1 mol) in methanol (250 ml) at -40°C under Ar. The solution was kept at -40°C for 2 h, warmed to ambient temperature over 0.5 h and left to stand for 1 h. Water (1 l) was added and the mixture was extracted with ether (2 x 500 ml). The aqueous phase was cooled to 0°C and acidified to pH 5 with conc. hydrochloric acid. The precipitated solid was collected and recrystallised from methanol to give **2** (10.0 g, 41%) as pale yellow needles, mp 174-176°C; ^{1}H nmr ($(CD_3)_2SO$): 2.1 (s, 3H), 2.8-3.1 (complex m, 4H), 7.25-7.55 (complex m, 3H), 7.8-7.9 (complex m, 3H); eims, m/z 247 $(M+H)^+$, 246, 231, 218, 199, 61; Found: C, 63.4; H, 5.7; N, 11.4; S, 13.0; $C_{13}H_{14}N_2OS$ requires: C, 63.4; H, 5.7; N, 11.2; S, 12.9.

2-Chloro-3-(2-methylthioethyl)-5-phenylpyrazine (3a). A 0.96 M solution of phosgene in toluene (208 ml, 0.2 mmol) was added to a solution of **2** (9.8 g, 40.0 mmol) in

tetrahydrofuran (200 ml) and the solution was heated under reflux for 4 h. Volatile material was removed by evaporation and the residue was dissolved in ether (200 ml). The solution was washed with 1 M sodium hydroxide (200 ml), water (200 ml) and saturated sodium chloride solution (200 ml). The organic phase was dried ($MgSO_4$) and the solvent was removed by evaporation to give **3a** (10.5 g, 99%) as an off-white solid, mp 65-66°C (from hexane); ^1H nmr ($CDCl_3$): 2.3 (s, 3H), 3.1 (t, J = 8.2 Hz, 2H), 3.4 (t, J = 8.2Hz, 2H), 7.45-7.6 (complex m, 3H), 8.0-8.1 (complex m, 2H), 8.7 (s, 1H); eims, m/z 265 $(M+H)^+$; Found: C, 58.9; H, 4.9; N, 10.4; Cl, 13.2; S, 12.5; $C_{13}H_{13}ClN_2S$ requires: C, 59.0; H, 4.9; N, 10.6; Cl, 13.4; S, 12.1.

3-(2-Methylthioethyl)-5-phenylpyrazine-2-hydrazine (3b). 55% hydrazine hydrate (38 ml, 0.76 mol) was added to a solution of **3a** (10.0 g, 38.0 mmol) in n-butanol (100 ml) and the mixture was heated under reflux for 4 h. Volatile material was removed by evaporation and the residue was partitioned between chloroform (300 ml) and water (300 ml). The aqueous phase was separated and extracted further with chloroform (2 x 300 ml). The combined extracts were washed with saturated sodium chloride solution (300 ml), dried ($MgSO_4$) and concentrated to give **3b** (9.1 g, 92%) as a purple solid, mp 107-109°C (from methanol); ^1H nmr ($CDCl_3$): 2.2 (s, 3H); 2.9-3.1 (complex m, 4H), 3.4 (br, 2H), 6.1 (br, 1H), 7.3-7.6 (complex m, 3H), 7.9-8.0 (m, 2H), 8.45 (s, 1H); eims, m/z 260 $(M+H)^+$, 245, 220, 213, 198, 183; Found: C, 59.9; H, 6.2; N, 21.3; S, 12.2; $C_{13}H_{16}N_4S$ requires: C, 60.0; H, 6.2; N, 21.5; S, 12.3.

N-(Ethoxycarbonylmethylenecarbonyl)-N'-[3-(2-methythioethyl)-5-phenylpyrazin-2-yl]-hydrazine (4). A solution of ethyl malonyl chloride (6.2 g, 41.2 mmol) in ethyl acetate (50 ml) was added to a stirred solution of **3a** (8.9g, 34.2 mmol) in ethyl acetate (150 ml) at 0°C. After stirring for 1 h, the precipitated solid was collected and suspended in chloroform (150 ml). A solution of sodium acetate (7.0 g, 85.5 mmol) in water (150 ml) was added. When all solid material had dissolved, the organic phase was separated, washed with water (150 ml) and saturated sodium chloride solution (150 ml), and then dried ($MgSO_4$). The solvent was removed by evaporation to give **4** (11.2 g, 87%) as a white powder, mp 130-131°C (from ethanol); ^1H nmr ($CDCl_3$): 1.3 (t, J = 6.7Hz, 3H), 2.2 (s, 3H), 3.1 (s, 4H), 3.5 (s, 2H), 4.3 (q, J = 6.7Hz, 2H), 7.3-7.5 (complex m, 3H), 7.9-8.0 (m, 2H), 8.4 (s, 1H); eims, m/z 375 $(M+H)^+$, 374, 327, 309, 281, 196; Found: C, 57.4; H, 6.0;

N, 14.8, S, 8.5; $C_{18}H_{22}N_4O_3S.0.25H_2O$ requires: C, 57.1; H, 6.0; N, 14.8; S, 8.4.

Ethyl 8-(2-Methylthioethyl)-6-phenyl-1,2,4-triazolo[4,3-a]pyrazine-3-acetate (5a). A solution of 4 (11.0 g, 29.4 mmol) and p-toluenesulphonic acid hydrate (550 mg, 2.9 mmol) in toluene (150 ml) was heated under reflux for 3 h. The solvent was removed by evaporation and the residue was dissolved in ethyl acetate (200 ml). The solution was washed with saturated sodium hydrogen carbonate solution (200 ml), water (200 ml) and saturated sodium chloride solution (200 ml), and then dried ($MgSO_4$). The solvent was removed by evaporation and the residue was purified by flash chromatography, eluting with ethyl acetate/hexane (3:1 v/v), to give 5a (7.7 g, 74%) as an off-white solid, mp 120-122°C (from ethanol); ^1H nmr ($CDCl_3$): 1.3 (t, J = 6.7Hz, 3H), 2.25 (s, 3H), 3.2 (t, J = 7.7Hz, 2H), 3.7 (t, J = 7.7Hz, 2H), 4.25 (q, J = 6.7 Hz, 2H), 4.35 (s, 2H), 7.4-7.6 (complex m, 3H), 7.95-8.05 (m, 2H), 8.2 (s, 1H); eims, m/z 357 $(M+H)^+$, 341, 328, 309; Found: C, 60.3; H, 5.6; N, 15.4; S, 8.8; $C_{18}H_{20}N_4O_2S$ requires: C, 60.7; H, 5.6; N, 15.7; S, 9.0.

8-(2-Methylthioethyl)-6-phenyl-1,2,4-triazolo[4,3-a]pyrazine-3-acetic acid (5b). 1 M Sodium hydroxide solution (15 ml, 15.0 mmol) was added to a solution of 5a (1.78 g, 5.0 mmol) in dioxan (45 ml) and the mixture was stirred for 1 h. Volatile material was removed under high vacuum (bath temperature < 30°C) and the residue was dissolved in water (30 ml). The solution was filtered, cooled to 0°C and acidified to pH 2 with concentrated hydrochloric acid. The precipitated solid was collected and dried under vacuum to give **5b** (1.40 g, 85%) as a fawn powder, mp 120-121°C; ^1H nmr ($(CD_3)_2SO$): 2.2 (s, 3H), 3.2 (t, J = 7.7Hz, 2H), 3.6 (t, J = 7.7Hz, 2H), 4.4 (s, 2H), 7.4-7.6 (complex m, 3H), 8.05-8.15 (m, 2H), 9.0 (s, 1H); fabms, m/z 327 $(M-H)^-$, 283; Found: C, 58.1; H, 5.2; N, 17.3; S, 9.6; $C_{16}H_{16}N_4O_2S$ requires: C, 58.5; H, 4.9; N, 17.1; S, 9.8.

N-[(1S,2S)-1,3-Dicyclohexyl-1-hydroxy-2-propyl]-8-(2-methylthioethyl)-6-phenyl-1,2,4-triazolo[4,3-a]pyrazine-3-acetamide (7a). 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.96 g, 5.0 mmol) was added to a solution of **5b** (1.64 g, 5.0 mmol), (1S,2S)-2-amino-1,3-dicyclohexylpropanol (**6**[1]) (1.20 g, 5.0 mmol), 1-hydroxybenzotriazole hydrate (0.68 g, 5.0 mmol) and triethylamine (0.51 g, 5.0 mmol) in N,N-dimethylformamide (25 ml). The solution was left to stand overnight and then volatile material was removed under high vacuum (bath temperature < 40°C). The residue was partitioned between chloroform (100 ml) and water (100 ml). The organic layer was separated and washed with

saturated sodium hydrogen carbonate solution (100 ml), followed by water (100 ml) and saturated sodium chloride solution (100 ml). The solution was dried ($MgSO_4$) and the solvent was removed by evaporation. The residue was purified by flash chromatography, eluting with methanol/dichloromethane (1:19 v/v), to give **7a** (2.19 g, 80%) as a white powder, mp 200-204°C (after trituration with ether); ^1H nmr ($(CD_3)_2SO$): 0.5-1.8 (complex m, 24H), 2.0 (s, 3H), 2.8-2.9 (m, 1H), 3.0 (t, J = 6.7Hz, 2H), 3.4 (t, J = 6.7Hz, 2H), 3.8-3.9 (m, 1H), 4.2 (s, 2H), 4.55 (br s, 1H), 7.3-7.45 (complex m, 3H), 7.8 (d, J = 8.2 Hz, 1H), 7.9-8.0 (m, 2H), 8.7 (s, 1H); fabms, m/z 550 $(M+H)^+$; Found: C, 67.4; H, 8.0; N, 12.7; $C_{31}H_{43}N_5O_2S$ requires: C, 67.8; H, 7.8; N, 12.75.

N-[(1S,2S)-1,3-Dicyclohexyl-1-hydroxy-2-propyl]-8-(2-methylsulphinylethyl)-6-phenyl-1,2,4-triazolo[4,3-a]pyrazine-3-acetamide (7b). A solution of 85% m-chloroperoxybenzoic acid (0.75 g, 3.68 mmol) in dichloromethane (15 ml) was added dropwise over 10 min to a stirred solution of **7a** (2.02 g, 3.68 mmol) in dichloromethane (60 ml) at 0°C. After 1 h at 0°C the solution was concentrated (bath temperature < 30°C) and the residue was purified by flash chromatography, eluting with methanol/dichloromethane (7:93 v/v), to give **7b** (1.97 g, 95%) as a white powder, mp 107-112°C (after trituration with ether); ^1H nmr ($(CD_3)_2SO$): 0.6-2.0 (complex m, 24H), 2.7 (s, 3H), 3.0-3.1 (m, 1H), 3.35-3.7 (complex m, 4H), 3.9-4.1 (m, 1H), 4.3 (s, 2H), 4.7 (d, J = 5.6Hz, 1H), 7.4-7.6 (complex m, 3H), 7.9 (d, J = 8.2Hz, 1H), 8.0-8.1 (m, 2H), 8.7 (s, 1H); fabms, m/z 550, 502; Found: C, 64.4; H, 8.0; N, 11.9; $C_{31}H_{43}N_5O_3S$ requires: C, 64.8; H, 7.6; N, 12.1.

N-[(1S,2S)-1,3-Dicyclohexyl-1-hydroxy-2-propyl]-8-ethenyl-6-phenyl-1,2,4-triazolo[4,3-a]pyrazine-3-acetamide (8). A solution of **7b** (1.97 g, 3.50 mmol) in toluene (200 ml) was heated under reflux for 1 h. Volatile material was removed by evaporation and the residue was purified by flash chromatography, eluting with ethyl acetate/hexane (3:1 v/v) to give **8** (1.18 g, 67%) as an off-white powder, mp 185-188°C (after trituration with ether); ^1H nmr ($(CD_3)_2SO$): 0.6-2.0, (complex m, 24H), 3.0 (d, J = 8.2Hz, 1H), 3.9-4.1 (m, 1H), 4.35 (s, 2H), 6.15 (t, J = 5.0Hz, 1H), 7.2-7.3 (m, 2H), 7.4-7.6 (complex m, 3H), 8.0 (d, J = 8.2Hz, 1H), 8.1-8.2 (m, 2H), 8.9 (s, 1H); fabms, m/z 502 $(M+H)^+$; Found: C, 70.8; H, 7.9; N, 13.9; $C_{30}H_{39}N_5O_2.0.5H_2O$ requires: C, 70.6; H, 7.9; N, 13.7.

N-[(1S,2S)-1,3-Dicyclohexyl-1-hydroxy-2-propyl]-8-(2-dimethylaminoethyl)-6-phenyl-1,2,4-triazolo[4,3-a]pyrazine-3-acetamide (9c). Compound **8** (100 mg, 0.20 mmol) was dissolved in

a 7.3 M solution of dimethylamine in ethanol (2 ml, 14.6 mmol) and the solution was left to stand for 1.5 h. Volatile material was removed by evaporation and the residue was purified by flash chromatography, eluting with methanol/dichloromethane (3:17 v/v) to give **9c** (52 mg, 48%) as a white powder, mp 149-153°C (after trituration with hexane); ^{1}H nmr ($(CD_3)_2SO$): 0.6-2.0 (complex m, 24H), 2.3 (s, 6H), 3.0-3.1 (m 3H), 3.45 (t, J = 6.7Hz, 2H), 3.9-4.1 (m, 1H), 4.3 (s, 2H), 4.7 (d, J = 5.6Hz, 1H), 7.4-7.6 (complex m, 3H), 7.9 (d, J = 8.2Hz, 1H), 8.0-8.1 (m, 2H), 8.8 (s, 1H); fabms, m/z 547 $(M+H)^+$; Found: C, 69.4; H, 8.4; N, 14.9; $C_{32}H_{46}N_6O_2.0.5H_2O$ requires: C, 69.1; H, 8.5; N, 15.1.

Compounds (**9a,b,d,e**) were obtained by analogous procedures:

9a (from **8** and ammonia): yield 12%; mp 130-135°C (after trituration with hexane); ^{1}H nmr ($(CD_3)_2SO$ + CD_3CO_2D): 0.6-1.9 (complex m, 24H), 3.0-3.1 (m, 1H), 3.5-3.7 (m, 4H), 3.9-4.1 (m, 1H), 4.4 (s, partially exchanged with CD_3CO_2D), 7.5-7.7 (complex m, 3H), 8.0-8.1 (m, 2H), 8.8 (s, 1H); fabms, m/z 519 $(M+H)^+$, 490, 472, 268, 251; Found: C, 68.2; H, 7.8; N, 15.5; $C_{30}H_{42}N_6O_2.0.5H_2O$ requires: C, 68.3; H, 8.0; N, 15.9.

9b (from **8** and 5 eq. benzylamine): yield 56%; mp 88-92°C (after trituration with hexane); ^{1}H nmr ($(CD_3)_2SO$): 0.6-2.0 (complex m, 24H), 3.0-3.1 (m, 1H), 3.2 (t, J = 6.7Hz, 2H), 3.5 (t, J = 6.7Hz, 2H), 3.9-4.1 (m, 1H), 4.3 (s, 2H), 4.65 (d, J = 5.6Hz, 1H), 7.2-7.6 (complex m, 8H), 7.9 (d, J = 8.2Hz, 1H), 8.0-8.1 (m, 2H), 8.8 (s, 1H); fabms, m/z 609 $(M+H)^+$, 490, 268, 251, 91; Found: C, 71.4; H, 8.0; N, 13.5; $C_{37}H_{49}N_6O_2.H_2O$ requires: C, 70.9; H, 7.8; N, 13.4.

9d (from **8** and 5 eq. morpholine in the presence of 5 eq. of acetic acid): yield 32%; mp 149-152°C (after trituration with ether); ^{1}H nmr ($(CD_3)_2SO$): 0.6-2.0 (complex m, 24H), 2.9-3.1 (m, 3H), 3.2-3.3 (m, 4H), 3.6-3.8 (complex m, 6H), 3.9-4.1 (m, 1H), 4.3 (s, 2H), 4.7 (d, J = 5.6Hz, 1H), 7.4-7.6 (complex m, 3H), 7.9 (d, J = 8.2Hz, 1H), 8.0-8.1 (m, 2H), 8.8 (s, 1H); fabms, m/z 589 $(M+H)^+$, 100; Found: C, 67.4; H, 7.9; N, 13.8; $C_{34}H_{48}N_6O_3.H_2O$ requires: C, 67.3; H, 8.25; N, 13.9.

9e (from **8** and 5 eq. imidazole in refluxing ethanol): yield 53%; mp 120-125°C (after trituration with ether); ^{1}H nmr ($(CD_3)_2SO$): 0.6-2.0 (complex m, 24H), 2.9-3.0 (m, 1H), 3.8 (t, J = 6.7Hz, 2H), 3.9-4.1 (m, 1H), 4.3 (s, 2H), 4.6-4.8 (m, 3H), 6.8 (s, 1H), 7.2 (s, 1H), 7.4-7.6 (complex m, 3H), 7.7 (s, 1H), 7.9 (d, J = 8.2Hz, 1H), 8.0-8.1 (m, 2H), 8.8 (s, 1H); fabms, m/z 570 $(M+H)^+$; Found: C, 67.5; H, 7.6; N, 16.4; $C_{33}H_{43}N_7O_2.H_2O$

requires: C, 67.4; H, 7.7; N, 16.7.

N-[(1S,2S)-1,3-Dicyclohexyl-1-hydroxy-2-propyl]-8-(2-acetoxyethyl)-6-phenyl-1,2,4-triazolo[4,3-a]pyrazine-3-acetamide (9f). A solution of **8** (147 mg, 0.29 mmol) and sodium acetate (238 mg, 2.90 mmol) in acetic acid (5 ml) was left to stand overnight. Volatile material was removed by evaporation and the residue was dissolved in ethyl acetate (20 ml). The solution was washed with sodium hydrogen carbonate solution (20 ml), water (20 ml) and saturated sodium chloride solution (20 ml). The dried ($MgSO_4$) solution was concentrated and the residue was purified by flash chromatography, eluting with methanol/dichloromethane (1:19 v/v), to give **9f** (87 mg, 53%) as a white powder, mp 181-183°C (after trituration with hexane); ^1H nmr ($(CD_3)_2SO$): 0.6-1.8 (complex m, 24 H), 2.0 (s, 3H), 3.0-3.1 (m, 1H), 3.6 (t, J = 6.7Hz, 2H), 3.9-4.1 (m, 1H), 4.3 (s, 2H), 4.7-4.8 (m, 3H), 7.4-7.6 (complex m, 3H), 7.9 (d, J = 8.2 Hz, 1H), 8.0-8.1 (m, 2H), 8.8 (s, 1H); fabms, m/z 562 $(M+H)^+$, 502; Found: C 68.0; H, 7.8; N, 12.1; $C_{32}H_{43}N_5O_4$ requires: C, 68.4; H, 7.7; N, 12.5.

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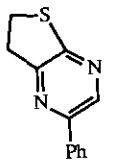
10. When phosphorus oxychloride was used **3a** was obtained only in low yield and contaminated by an impurity provisionally assigned structure (**10**) on the basis of *spectroscopic data*.



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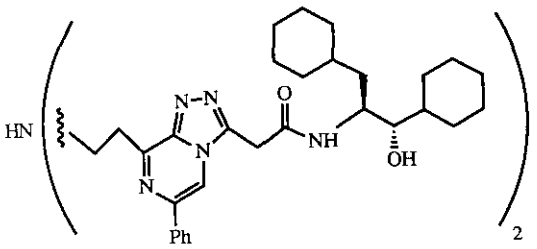
13. A significant amount of the bis-adduct (**11**) was also isolated.



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