Pergamon

Tetrahedron 54 (1998) 13391–13404

TETRAHEDRON

Synthesis and Biological Properties of a New Series of 5-Substituted-pyrimidine-L-Nucleoside Analogues†

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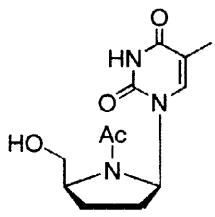
Received 27 March 1998; revised 27 August 1998; accepted 28 August 1998

Abstract: *trans*-4-hydroxy-L-proline (**5**) has been elaborated into a new series of pyrrolidine-L-nucleoside analogues incorporating non-standard 5-substituted-pyrimidine nucleobases, *via* the azidopyrrolidines **12** and **13**. Those analogues employing an acyl protecting group on the primary hydroxyl functionality underwent radical bromination of the ethyl side chain of the pyrimidine ring, to provide *E*-5-(2-bromovinyl)uracil-pyrrolidine-L-nucleosides **23-26**. Of the compounds assessed for potential antiviral activity only 5-ethyluracil-(benzoyloxymethyl)pyrrolidine **20** was found to be a specific inhibitor of vaccinia virus.

INTRODUCTION

Within the field of synthetic nucleoside chemistry, there have been many examples of nucleoside analogues possessing modified sugar moieties, some of which have proven to be potent antivirally active drugs such as AZT, 3TC and ddC. This has led to the investigation of the pyrrolidine ring as a possible replacement for the D-ribo sugar because it is a ubiquitously occurring structural motif with widespread applications in chemical synthesis together with diverse pharmacological uses.[1,2,3,4,5] However, of the pyrrolidine nucleoside analogues synthesised, where a protected nitrogen atom acts as a direct replacement for the furanosyl-oxygen atom such as in the 3′-deoxythymidine analogue **1** and 2′,3′-dideoxyuridine analogue **2**, antiviral activity was negligible or non-existent, which is probably in part the result of the necessity to protect the nitrogen atom in the pyrrolidine ring.[6,7,8,9] It is not possible to synthesise analogues of **1** and **2** without an electron withdrawing nitrogen protecting group, because a highly unstable geminal diamine system would exist resulting in the lone pair of electrons on the nitrogen atom eliminating the nucleobase. However, when the nitrogen atom of the pyrrolidine ring is displaced one atom away from the nucleobase in the C-3′ position, then it is possible to synthesise stable pyrrolidine nucleoside analogues such as **3** and **4**. These structures (**3**, **4**) also permit the preparation of compounds with or without nitrogen substitution.



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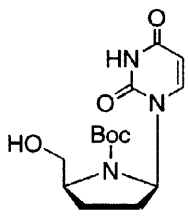

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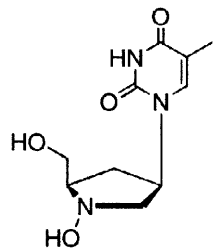

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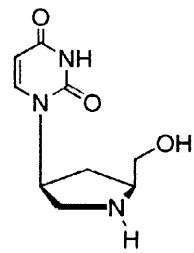

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PII: S0040-4020(98)00821-7

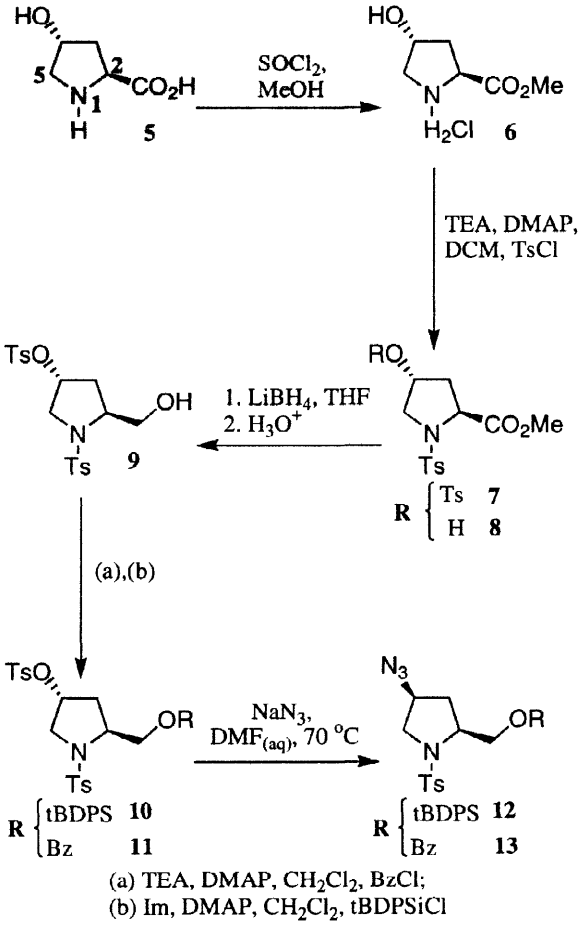
The thymidine analogue **3** was prepared by Ng and Orgel[10] and it was found to inhibit the growth of breast (MCF-7M), colon (HT-29) and lung (SK-MES-1) cancer cells. In the 1970's, Pandit *et al.*[11] synthesised some similar pyrrolidine nucleosides but these had the opposing configuration. Surprisingly, the L-nucleoside analogue **4** was found to exhibit weak inhibition of BHK cell growth. There has been a resurgence of interest in L-nucleosides in the current decade, which was triggered by the success of 3TC which is used extensively in HIV therapy and also the recognition that L-thymidine and *E*-5-(2-bromovinyl)-2′-deoxy-L-uridine (L-BVDU) are good substrates for herpes simplex virus type-1 thymidine kinase (HSV-1 TK).[12] Therefore, it was decided to prepare a series of stable pyrrolidine L-nucleoside analogues incorporating the non-standard nucleobase 5-ethyluracil and *E*-5-(2-bromovinyl)uracil and to evaluate them for antiviral activity against a variety of viruses.

RESULTS AND DISCUSSION

The strategy employed for the synthesis of the pyrrolidine L-nucleoside analogues was dependent on the preparation of the 4-azidopyrrolidine **13** (Scheme 1). Hydrogenation of the azido group could then be effected and the primary amine coupled with the butyramide **16** (Scheme 2) leading to a 5-ethyluracil-pyrrolidine-L-nucleoside derivative. The conversion of the ethyl side chain into an *E*-2-bromovinyl group could then be performed under radical conditions. Certain nucleoside analogues incorporating ethyl or *E*-2-bromovinyl sidechains on the 5-position of a pyrimidine moiety have historically produced potent anti-herpetic compounds.

Synthesis of the 4-Azidopyrrolidine Building Blocks.

The 4-azidopyrrolidine **13** (Scheme 1) was prepared from *trans*-4-hydroxy-L-proline (**5**) which was initially converted to its methyl ester **6** with thionyl chloride and dry methanol. The amino and hydroxyl functional groups of methyl ester **6** were simultaneously reacted with *p*-toluenesulfonyl chloride in a solution of dry triethylamine and dichloromethane to provide (2*S*,4*R*)-*N*-*p*-toluenesulfonyl-4-*p*-toluenesulfoxy-2-pyrrolidinecarboxylic acid methyl ester (**7**) together with a small quantity of the mono *N*-tosyl-pyrrolidine **8** which were separated by chromatography.[13] The ester **7** underwent quantitative reduction with lithium borohydride in tetrahydrofuran to provide hydroxymethylpyrrolidine **9** using the method described by Stille and co-workers.[14] The primary hydroxyl group of **9** was protected as either a *tert*-butyl-diphenyl silyl ether **10** or a benzoate ester **11** by its reaction with *tert*-butylchlorodiphenylsilane or benzoyl chloride under basic conditions. Compounds **10** and **11** were obtained in excellent yields. The displacement of the *p*-toluenesulfonate ester of silyl ether **10** and benzoate ester **11** with the azido nucleophile proceeded with inversion of stereochemistry to give the azidopyrrolidines **12** and **13**. The configuration was unequivocally confirmed in the case of the 4-azidopyrrolidine **12** which proved to be sufficiently crystalline for an X-ray diffraction analysis to be performed (Figure 1). In the case of **12** the nitrogen- and C-2, C-3, and C-4 carbon-atoms are structured in a plane. The C-4 carbon atom, which is attached to the azido group, is displaced above the plane of these atoms in an envelope conformation. This has been previously observed with carbocyclic thymidine whose crystal structure adopted a C-1′-*endo* conformation.[22]



Scheme 1

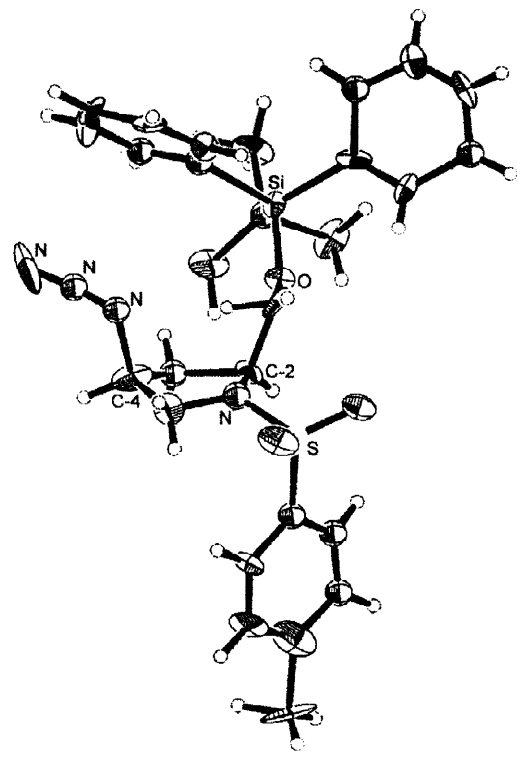
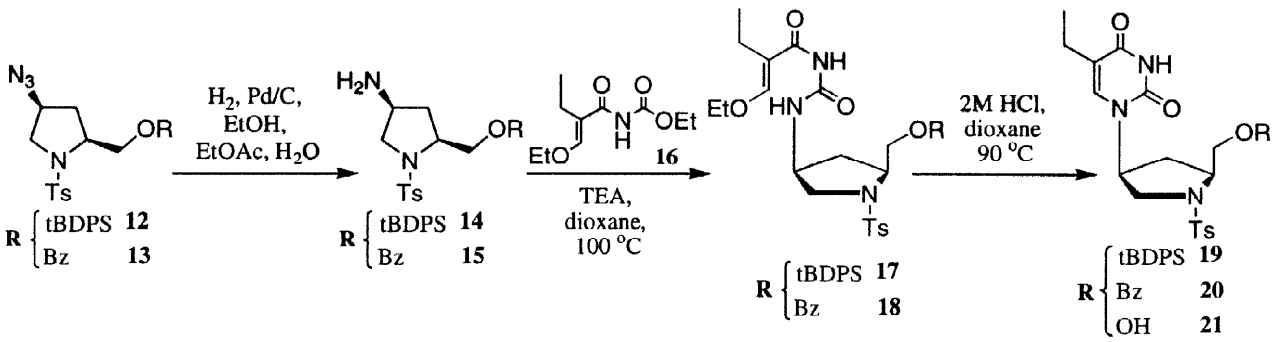


Figure 1

5-Ethyluracil-pyrrolidine-L-nucleoside Analogues.

Catalytic hydrogenation of the azido functionality of the 4-azidopyrrolidine **12** and 4-azido(benzoyloxymethyl)pyrrolidine **13** (Scheme 2) was performed in a solution of ethanol, ethyl acetate and water and efficiently produced the primary amines **14** and **15** in yields consistently greater than 90%. Typically, the primary amines produced were not characterized and their formation was monitored by TLC. They were then reacted directly with the butyramide **16**. The synthesis of this reagent was described by Wyatt *et al.*[16] where it was used in the preparation of carbocyclic BVDU. The condensation of the butyramide with either of the 4-aminopyrrolidines **14** or **15** required heating a solution of the reagents in dioxane at 100 °C for 10 hr in the presence of a slight excess of triethylamine, providing the urea derivatives **17** and **18**, which could be isolated and characterized prior to cyclisation to the pyrimidine. However, intermediate isolation is not usually necessary and the conversion of the urea intermediates **17** and **18** to the pyrimidine ring was performed by heating the solutions to 90 °C with 2M hydrochloric acid for 13.5 hr. The urea **18** produced **20** in a 67% yield from **15**. Compound **17** also underwent efficient cyclisation to the substituted-pyrimidine but the reaction conditions caused the concomitant removal of the silyl ether protecting group to produce the partially de-protected analogue **21** in yields of 70-80% together with ≤10% of the fully protected **19**. If the cyclisation of **17**

was induced with 2M sulfuric acid in dioxane, again with heating at 90 °C, then **21** was found to be the exclusive product.



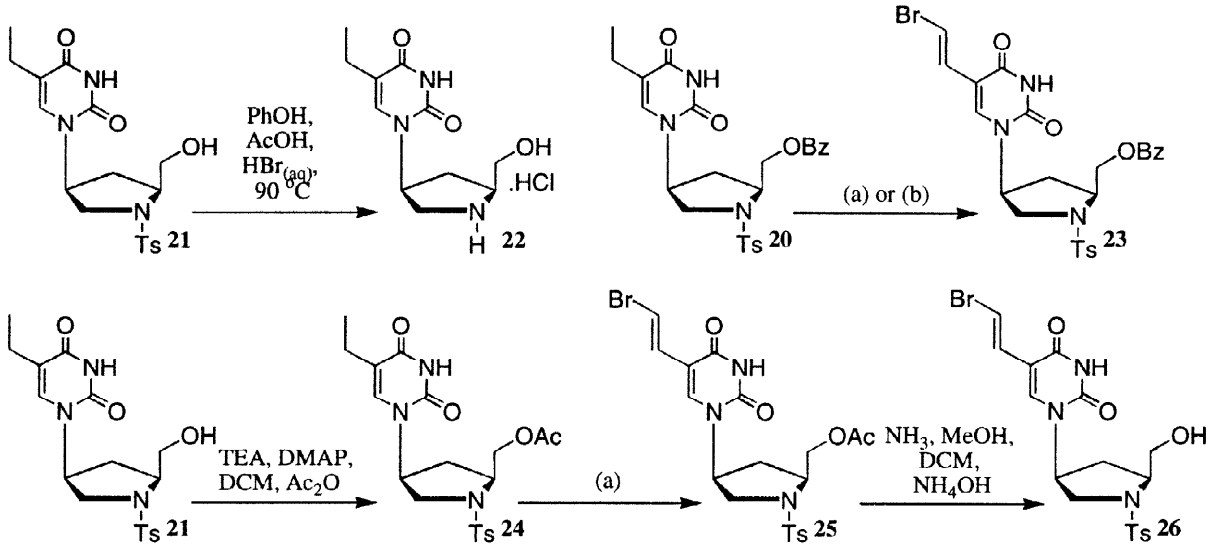
Scheme 2

The removal of the *p*-toluenesulfonamide protecting group from **21** (Scheme 3) required the use of phenol in acetic acid and hydrobromic acid at 90 °C for 18 hr. The molecule was remarkably resilient to these reaction conditions and gave the completely de-protected nucleoside analogue **22**, which was isolated as the hydrochloride salt in reproducible yields of 70%. Also, unreacted **21** could be recovered from the ether extracts that were employed to work up the reaction.

E-5-(2-Bromovinyl)uracil-pyrrolidine-L-nucleoside Analogues.

The conversion of the ethyl group of carbocyclic 5-ethyl-2′-deoxyuridine to an *E*-2-bromovinyl substituent by radical bromination has been extensively explored by Wyatt et al.[16] They found that the transformation was performed efficiently with either bromine or *N*-bromosuccinimide (NBS), in the presence of AIBN, using chloroform or dioxane as solvent. Therefore, these reaction conditions were used as a starting point to explore the same conversion with the 5-ethyluracil-pyrrolidine-L-nucleoside analogues. Limited success was found with the 5-ethyluracil-(benzoyloxymethyl)pyrrolidine **20** (Scheme 3). Using bromine with AIBN as a radical initiator, the *E*-5-(2-bromovinyl)uracil-(benzoyloxymethyl)pyrrolidine **23** was isolated in a yield of 17% together with some unreacted starting material. The use of *N*-bromosuccinimide/AIBN in dioxane proved to be slightly more rewarding, with compound **23** being formed in an improved, 28% yield but the reaction produced many more side products, as judged by TLC. The benzoyl protecting group was not ideal for the radical conditions being employed and previous work had suggested that the acetyl group was preferred.[16] Therefore, the partially de-protected **21** was reacted with acetic anhydride with triethylamine in dichloromethane to provide the acetate **24** in excellent yield. The radical bromination of **24** was conducted with bromine/AIBN in refluxing chloroform, as these conditions had previously produced a cleaner reaction. *E*-5-(2-Bromovinyl)uracil-(acetoxymethyl)pyrrolidine **25** was isolated in a 50% yield and no products other than unreacted starting material were observed. Further studies have revealed that this radical bromination is applicable to the synthesis of other *E*-5-(2-bromovinyl)uracil nucleoside analogues.[17] The de-acetylation of **25**

proceeded straightforwardly using ammonia in methanol and ammonium hydroxide to give **26** in quantitative yield. The removal of the *p*-toluenesulfonyl protecting group from the nitrogen atom of compound **26**, was not attempted because it was predicted that the bromovinyl side chain would prove to be too sensitive to survive the aggressive conditions necessary.



(a) i. Br_2, AIBN, $CHCl_3$, Δ, ii. TEA ;
(b) i. NBS, AIBN, dioxane, 60 °C, ii. TEA.

Scheme 3

Antiviral Testing Results

The pyrrolidine-L-nucleoside analogues at different levels of protection, together with synthetic intermediates, were tested in a broad antiviral assay encompassing: HSV-1 and -2, varicella zoster virus (VZV), human cytomegalovirus (HCMV), HIV-1 and -2, vaccinia virus and vesicular stomatitis virus.[20]

Of the intermediates tested, the azidopyrrolidines **12** and **13** both affected the replication of HCMV. The silyl ether-protected 4-azidopyrrolidine **12** was toxic at low concentrations (5 μM), whereas its benzoate ester **13** counterpart displayed some inhibition of replication (IC_{50} 22.6 μM) but toxicity (50 μM) was still pronounced. All of the nucleoside analogues tested were found to be cytotoxic.

None of the compounds tested proved to be capable of inhibiting the replication of HIV types 1 and 2 or vesicular stomatitis at sub-toxic concentrations. Compounds **21**, **22** and **26** with a free primary hydroxyl group, which might have been expected to exhibit antiviral properties were devoid of activity, which is probably not too surprising as compound **22** was shown not even to inhibit the phosphorylation of thymidine by HSV-1 TK.[19] Similar results were found with the fully protected pyrrolidine-L-nucleoside analogues (**19**, **24**, **25**) which were all inactive with the exception of 5-ethyluracil-(benzoyloxymethyl)pyrrolidine **20**, which was found to be a specific inhibitor of vaccinia virus (IC_{50} 40 μM, toxic at ≥201 μM) with comparable activity to

BVDU (IC_{50} 12 μM, toxic at ≥1200 μM).[21] The conversion of the ethyl side chain of **20** to an *E*-5-(2-bromovinyl) functionality as in **23**, resulted in a compound with no activity and increased toxicity (69 μM).[21]

EXPERIMENTAL SECTION

General Methods. Thin layer chromatography (TLC) was performed on pre-coated, aluminum-backed silica gel plates supplied by E. Merck A. G., Darmstadt, Germany. (Silica gel F_{254} thickness 0.2 mm). Development was by the ascending method. Detection was by quenching of the fluorescence at 254 nm and by the adsorption of iodine vapor. Flash Chromatography was performed on silica gel (Kiesegel 60/0 250 mesh, type 7734 supplied by E. Merck A. G.) using the indicated solvent mixtures (v/v).

MS: CI mass spectra were recorded on either a Kratos MS-80 or VG ProSpec using ammonia as a carrier gas; GCMS mass spectra (CI) were recorded on a Hewlett Packard 5989A using ammonia as a carrier gas coupled to a Hewlett Packard gas chromatography series 1050; EI mass spectra were recorded on either a VG ProSpec or a Kratos Profile; ES mass spectra were recorded on a VG ProSpec; FAB was carried out on either a Kratos MS80RF or a VG ZabSpec. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC300 (300 and 75 MHz) or Bruker AC250 (250 and 62.5 MHz) using the deuterated solvent as a lock and are reported in parts per million (δ) using the residual solvent signal as an internal reference. UV Spectrophotometry: measurements were taken on a Perkin-Elmer Lambda 2 spectrophotometer. EA: analyses were performed by GlaxoWellcome, Stevenage, Hertfordshire, UK. X-ray crystallographic data was recorded on a Rigaku X-ray diffractometer. The data was collected from the plates with a laser and processed on a Silicon Graphics workstation using R-axis 2ci, Texan and Shellx software.

Materials. All solvents were dried according to literature procedures and used immediately.[18] All reagents were purchased from the Aldrich Chemical Company Ltd. and used as supplied. Argon, hydrogen, and oxygen-free nitrogen gases were supplied by the British Oxygen Corporation.

(2*S*,4*R*)-4-Hydroxy-2-pyrrolidinecarboxylic acid methyl ester hydrochloride salt (6). Thionyl chloride (2.80 mL, 38.10 mmol) was added to an ice-cold solution of *trans*-4-hydroxy-L-proline (**5**) (5.00 g, 38.10 mmol) dissolved in methanol (50 mL, dry) under anhydrous conditions. The reaction was stirred at ambient temperature until complete dissolution of the amino acid had occurred and then the solution was concentrated *in vacuo*. Final traces of thionyl chloride were removed through co-evaporation with dichloromethane to give 6.92 g (100%) of **6** as a white crystalline solid: mp 160-161 °C; MS (CI) *m/z* 146$(M\text{-}Cl)^+$; δ_H (300 MHz, CD_3SOCD_3), 10.10-9.70(2H, br s, NH_2^+), 5.46(1H, br s, -OH), 4.52-4.39(2H, m, H-4/H-2), 3.75(3H, s, CO_2CH_3), 3.35(1H, dd $^2J_{AB}$ =4.50 Hz, $^3J_{AX}$ =12.50 Hz, H-5), 3.06(1H, dd $^2J_{BX}$ =5.00 Hz, $^3J_{AB}$ =12.50, Hz H-5), 2.26-1.98(2H, m, H-3); δ_C (75 MHz, CD_3SOCD_3), 169.0($\underline{C}O_2CH_3$), 68.4(C-4), 57.5($CO_2\underline{C}H_3$), 53.0(C-5), 53.0(C-2), 37.0(C-3).

(2*S*,4*R*)-*N*-*p*-Toluenesulfonyl-4-*p*-toluenesulfoxy-2-pyrrolidinecarboxylic acid methyl ester (7). A solution of *p*-toluenesulfonyl chloride (18.20 g, 95.30 mmol) in dichloromethane (50 mL, dry) was added dropwise over 30 min to an ice-cold solution/suspension of **6** (6.92 g, 38.10 mmol) in dichloromethane (50 mL, dry) with triethylamine (25 mL, dry) and 4,4-dimethylaminopyridine (DMAP) (0.01 g, 0.08 mmol) prepared 15 min earlier. After 48 hr at room temperature the solution was washed with water (200 mL), hydrochloric acid (2M, 200 mL), saturated sodium hydrogencarbonate (200 mL) and finally brine (100 mL). The recovered organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a dark-red crystalline solid (17.7 g)

which was purified (SiO_2: hexane-ethyl acetate 1:1) to give 14.49 g (84%) of **7** as a white solid and 1.06 g (9%) of (2*S*,4*R*)-4-*p*-toluenesulfoxy-4-hydroxy-2-pyrrolidinecarboxylic acid methyl ester (**8**). Compound **7**: mp 88-90 °C; MS (CI) *m/z* 453$(M)^+$; δ_H (300 MHz, $CDCl_3$), 7.71-7.63(2H, m, *N*-$O_2SC_6\underline{H}_4CH_3$), 7.61-7.51(2H, m, *N*-$O_2SC_6\underline{H}_4CH_3$), 7.36-7.20(4H, m, $O_2SC_6H_4CH_3$), 5.00-4.89(1H, m, H-4), 4.28-4.17(1H, pseudo-t, H-2), 3.70(3H, s, $CO_2C\underline{H}_3$), 3.65(1H, dd $^2J_{AB}$ =2.50 Hz, $^3J_{AX}$ =7.50 Hz, H-5), 3.58(1H, pseudo-d $^3J_{AX}$ =10.00 Hz, H-5), 2.41(3H, s, $O_2SC_6H_4C\underline{H}_3$), 2.39(3H, s, $O_2SC_6H_4C\underline{H}_3$), 2.36-2.25(1H, m, H-3), 2.22-2.10(1H, m, H-3); δ_C (75 MHz, $CDCl_3$), 171.6($\underline{C}O_2CH_3$), 145.4, 144.2, 134.0, 133.0(qC-$O_2S\underline{C}_6H_4CH_3$), 130.0, 129.8, 127.7(CH-$O_2S\underline{C}_6H_4CH_3$), 78.3(C-4), 59.2(C-2), 54.0(C-5), 52.7($CO_2\underline{C}H_3$), 37.3(C-3), 21.7, 21.6($O_2SC_6H_4\underline{C}H_3$). Analysis for $C_{20}H_{23}NO_7S_2$ C; 52.97, H; 5.11, N; 3.09 found: C; 53.15. H; 5.12, N; 3.00. Compound **8**: mp 103-104 °C MS (CI) *m/z* 300$(M+H)^+$; δ_H (300 MHz, $CDCl_3$) 7.82-7.73(2H, m, *N*-$SO_2C_6\underline{H}_4CH_3$), 7.36-7.29(2H, m, *N*-$SO_2C_6\underline{H}_4CH_3$), 4.49-4.41(1H, m, H-4), 4.25(1H, pseudo t $^3J_{AX}$ =9.00 Hz, H-2), 3.74(3H, s, $\underline{C}O_2CH_3$), 3.60(1H, dd $^2J_{AB}$ =4.00 Hz, $^3J_{AX}$ =7.50 Hz, H-5), 3.38(1H, pseudo-d $^3J_{AX}$ =11.50 Hz, H-5), 2.43(3H, s, *N*-$SO_2C_6\underline{H}_4CH_3$), 2.26-2.02(2H, m, H-3); δ_C (75 MHz, $CDCl_3$) 172.9($\underline{C}O_2CH_3$), 143.9, 134.4(qC-$O_2S\underline{C}_6H_4CH_3$), 129.7, 127.7(CH-$O_2S\underline{C}_6H_4CH_3$), 69.8(C-4), 59.6(C-2), 57.5(C-5), 52.6($CO_2\underline{C}H_3$), 39.1(C-3), 21.6($O_2SC_6H_5\underline{C}H_3$).

(2*S*,4*R*)-*N*-*p*-Toluenesulfonyl-4-toluenesulfoxy-2-(hydroxymethyl)pyrrolidine (9).[14] Lithium borohydride in tetrahydrofuran (2.00 mL, 4.00 mmol) was added to an ice-cold solution of **7** (0.50 g, 1.10 mmol) in tetrahydrofuran (8 mL, dry). The solution was stirred at 0 °C for 1 hr followed by 1 hr at room temperature. The reaction was cooled to 0 °C and water (2.55 mL) was added followed by the careful addition of water-hydrochloric acid (1 mL, 1:1). The solution was extracted with dichloromethane (3×25 mL) and the combined organic layers were washed with sodium hydroxide (2M, 50 mL), hydrochloric acid (2M, 50 mL) and finally brine (50 mL). Combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 0.48 g (>100%) of slightly impure **9** as an opaque yellow tinged oil: MS (CI) *m/z* 426$(M+H)^+$ 443, $(M+NH_4)^+$; δ_H (300 MHz, $CDCl_3$) 7.71-7.62(2H, m, $O_2SC_6\underline{H}_4CH_3$), 7.57-7.50(2H, m, *N*-$O_2SC_6\underline{H}_4CH_3$), 7.34-7.24(4H, m, $O_3SC_6H_4CH_3$), 4.88-3.78(1H, m, H-4), 3.88(1H, dd $^2J_{AB}$ =3.00 Hz, $^3J_{AX}$ = 9.00 Hz, H-5), 3.76-3.58(4H, m, H-2/CH_2OH), 3.54(1H, dd $^2J_{AB}$ =4.00 Hz, $^3J_{AX}$ = 8.00 Hz, H-5), 2.76(1H, br s, $CH_2O\underline{H}$), 2.42(3H, s, $O_2SC_6H_4C\underline{H}_3$), 2.41(3H, s, $O_2SC_6H_4C\underline{H}_3$), 2.09-1.90(2H, m, H-3); δ_C (75MHz, $CDCl_3$) 145.3, 144.3, 134.5, 133.3(qC-$O_2S\underline{C}_6H_4CH_3$), 130.1, 130.0, 127.9, 127.7(CH-$O_2S\underline{C}_6H_4CH_3$), 79.0(C-4), 64.5($CH_2OH$), 60.5(C-2), 55.5(C-5), 35.3(C-3), 21.8($O_2SC_6H_4\underline{C}H_3$).

(2*S*,4*R*)-*N*-*p*-Toluenesulfonyl-4-toluenesulfoxy-2-(diphenyl-*tert*-butylsilyloxymethyl)pyrrolidine (10). *tert*-Butylchlorodiphenylsilane (3.63 g, 13.2 mmol) was added to an ice-cold solution of **9** (4.70 g, 11.00 mmol), imidazole (0.90 g, 13.2 mmol) and DMAP (0.16 g, 1.32 mmol) in dichloromethane (50 mL, dry) that had been prepared 15 min earlier. The cooling bath was removed and the reaction was stirred for 18 hr before it was washed with water (100 mL) and the organic layer was separated. The aqueous layer was extracted further with dichloromethane (3×100 mL), the combined organic layers were washed with brine (150 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a reddish brown oil (9.56 g) that was purified (SiO_2: hexane-ethyl acetate 1:1) to give 7.30 g (100%) of **10** as a clear oil: MS (FAB) *m/z* 664(M^+); δ_H (300 MHz, $CDCl_3$) 7.69-7.55(7H, m, C_6H_5/$O_2SC_6\underline{H}_4CH_3$), 7.49-7.35(7H, m, C_6H_5/$O_2SC_6\underline{H}_4CH_3$), 7.32-7.26(4H, m, C_6H_5/$O_2SC_6\underline{H}_4CH_3$), 5.02-4.92(1H, m, H-4), 3.86(1H, dd $^2J_{AB}$ =5.00 Hz, $^3J_{AX}$ =5.00 Hz, CH_2OSi), 3.82-3.68(2H, m, H-2/CH_2OSi), 3.77(1H, dd $^2J_{AB}$ =2.50 Hz, $^3J_{BX}$ =8.00 Hz, CH_2OSi), 3.64(1H, dd $^2J_{AB}$ =5.00 Hz, $^3J_{AX}$ =7.50 Hz, H-5), 3.46(1H, dd $^2J_{AB}$ =2.50 Hz, $^3J_{BX}$ =11.00 Hz, H-5), 2.44(3H, s, $O_2SC_6H_4C\underline{H}_3$), 2.43(3H, s,

$O_2SC_6H_4C\underline{H}_3$), 2.23-2.14(1H, m, H-3), 2.01-1.91(1H, m, H-3), 1.03(9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 145.2, 143.9(qC-$O_2S\underline{C}_6H_4CH_3$), 135.7, 135.6, 134.9(CH-$O_2S\underline{C}_6H_4CH_3$), 134.2, 132.9(qC-$C_6H_5$), 133.3, 132.9(qC-$O_2S\underline{C}_6H_4CH_3$), 130.0, 129.9(CH-$O_2S\underline{C}_6H_4CH_3$), 129.8, 129.6, 127.9, 127.7(CH-C_6H_5), 78.9(C-4), 66.7(CH_2*O*Si), 59.6(C-2), 54.5(C-5), 35.6(C-3), 27.0($C(\underline{C}H_3)_3$), 21.7, 21.6($O_2SC_6H_4\underline{C}H_3$), 19.3($\underline{C}(CH_3)_3$). Analysis for $C_{35}H_{41}NO_6S_2Si$ requires C; 63.32, H; 6.22, N; 2.11, S; 9.66, found C; 63.17, H; 6.34, N; 1.98, S; 9.42.

(2*S*,4*R*)-*N*-*p*-Toluenesulfonyl-4-toluenesulfoxy-2-(benzoyloxymethyl)pyrrolidine (11). Benzoyl chloride (0.66 mL, 5.64 mmol) was added to an ice-cold solution of **9** (2.00 g, 4.70 mmol), triethylamine (0.78 mL, 5.64 mmol) and DMAP (0.06 g, 0.24 mmol) in dichloromethane (20 mL, dry) that had been prepared 30 min earlier. The reaction was monitored (TLC: hexane-ethyl acetate 7:3). When no further changes were observed the solution was washed with water (50 mL) separated and the aqueous layer was extracted further with dichloromethane (3×50 mL). The combined organic extracts were washed with brine (100 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow/white solid that was re-crystallized from hexane-ethyl acetate to give 2.49 g (91%) of **11** as a white crystalline solid: mp 151-152 °C MS (CI) *m/z* 272$(M+H)^+$, 289$(M+NH_4)^+$; δ_H (300 MHz, CD_3SOCD_3) 7.94-7.87(2H, m, $O_2SC_6\underline{H}_4CH_3/O_2CC_6H_5$), 7.72-7.42(9H, m, $O_2SC_6\underline{H}_4CH_3/O_2CC_6H_5$), 7.37-7.30(2H, m, $O_2SC_6\underline{H}_4CH_3/O_2CC_6H_5$), 5.06-4.97(1H, m, H-4), 4.47(1H, dd $^2J_{AB}$ =4.00 Hz, $^3J_{AX}$ =7.50 Hz, CH_2*O*Bz), 4.37(1H, dd $^2J_{AB}$ =6.00 Hz, $^3J_{BX}$ =5.00 Hz, CH_2*O*Bz), 4.06-3.94(1H, m, H-2), 3.64(1H, dd $^2J_{AB}$ =4.00 Hz, $^3J_{AX}$ =9.00 Hz, H-5), 3.55-3.47(1H, m, H-5), 2.41(3H, s, $O_2SC_6H_4C\underline{H}_3$), 2.33(3H, s, $O_2SC_6H_4C\underline{H}_3$), 2.25-2.02(2H, m, H-3); δ_C (75 MHz, $CDCl_3$) 166.0($O_2\underline{C}C_6H_5$), 145.3, 144.2, 135.8, 133.1(qC-$O_2S\underline{C}_6H_4CH_3$), 130.0, 129.9, 129.6, 128.9, 128.5(CH-$O_2C\underline{C}_6H_5/O_2S\underline{C}_6H_4CH_3$), 78.3(C-4), 66.5($CH_2$*O*Bz), 56.9(C-2), 54.6(C-5), 36.0(C-3), 21.7, 21.6($O_2SC_6H_4\underline{C}H_3$). Analysis for $C_{26}H_{27}NO_7S_2$ requires C; 58.96, H; 5.14, N; 2.64, S; 12.11, found C; 59.21, H; 5.41, N; 2.36, S; 11.96.

(2*S*,4*R*)-*N*-*p*-Toluenesulfonyl-4-azido-2-(diphenyl-*tert*-butylsilyloxymethyl)pyrrolidine (12). A solution of sodium azide (0.90 g, 13.84 mmol) in water (3 mL) was added to **10** (7.30 g, 11.13 mmol) dissolved in DMF (50 mL) and the mixture was heated at 70 °C for 5 hr then stirred at room temperature for 18 hr. The cooled solution was poured into a mixture of brine (500 mL) and water (100 mL), and extracted with dichloromethane (3×150 mL). The combined organic extracts were washed with brine (500 mL), dried ($MgSO_4$), filtered and the solvent was concentrated *in vacuo* to produce an orange oil that was purified (SiO_2: hexane-ethyl acetate 7:3) to give 5.19 g (87%) of **12** as an off-white crystalline solid which was re-crystallised from diethyl ether to give large opaque crystals: mp 89-91 °C; MS (FAB) *m/z* 535$(M)^+$; δ_H (300 MHz, $CDCl_3$) 7.70-7.63(5H, m, $C_6H_5/O_2SC_6\underline{H}_4CH_3$), 7.61-7.55(2H, m, $C_6H_5/O_2SC_6\underline{H}_4CH_3$), 7.50-7.34(8H, m, $C_6H_5/O_2SC_6\underline{H}_4CH_3$), 7.32-7.23(3H, m, $C_6H_5/O_2SC_6\underline{H}_4CH_3$), 3.96(1H, dd $^2J_{AB}$ =3.70 Hz, $^3J_{AX}$ =5.90 Hz, CH_2*O*Si), 3.84-3.63(3H, m, H-2/H-4/CH_2*O*Si), 3.49(1H, dd $^2J_{AB}$ =6.30 Hz, $^3J_{AX}$ =5.90 Hz, H-5), 3.28(1H, dd $^2J_{AB}$ =5.50 Hz, $^3J_{BX}$ =6.00 Hz, H-5), 2.42(3H, s, $O_2SC_6H_4C\underline{H}_3$), 2.25-2.11(1H, m, H-3), 2.06-1.92(1H, m, H-3), 1.07(9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 143.9, 134.4(qC-$O_2S\underline{C}_6H_4CH_3$), 135.8, 135.0(CH-$C_6H_5$), 133.7, 133.4(qC-$C_6H_5$), 130.1, 130.0(CH-$O_2S\underline{C}_6H_4CH_3$), 127.9, 127.6(CH-$C_6H_5$), 66.6($CH_2$*O*Si), 60.0(C-4), 59.1(C-2), 53.7(C-5), 33.4(C-3), 27.1($C(\underline{C}H_3)_3$), 21.7($O_2SC_6H_4\underline{C}H_3$), 19.5($\underline{C}(CH_3)_3$). Analysis for $C_{28}H_{34}N_4O_3SSi$ requires C; 62.89, H; 6.41, N; 10.48. S; 6.00 found C; 63.04, H; 6.19, N; 10.61, S; 6.27.

(2*S*,4*S*)-*N*-*p*-Toluenesulfonyl-4-azido-2-(benzoyloxymethyl)pyrrolidine (13).[15] A solution of sodium azide (0.20 g, 3.14 mmol) in water (1.50 mL) was added to **11** (1.29 g, 2.44 mmol) dissolved in DMF (15 mL) and

the mixture was heated at 70 °C for 18 hr then stirred at room temperature for a further 48 hr. The solution was washed with a solution of saturated brine (250 mL) and water (50 mL) and extracted with dichloromethane (3×75 mL). The combined organic extracts were washed with brine (200 mL) and dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a brown oil/solid which was purified (SiO_2: hexane-acetone 3:1) to give 0.77 g (78%) of **13** as a white solid: MS (CI) *m/z* 401$(M+H)^+$, 418$(M+NH_4)^+$; δ_H (300 MHz, $CDCl_3$) 8.08-8.01(2H, m, $O_2CC_6H_5$), 7.79-7.73(2H, m, $O_2CC_6H_5$), 7.62-7.54(1H, m, $O_2CC_6H_5$), 7.49-7.41(2H, m, $O_2SC_6H_4CH_3$), 7.34-7.28(2H, m, $O_2SC_6H_4CH_3$), 4.62(1H, dd $^2J_{AB}$ =4.50 Hz, $^3J_{AX}$ =5.50 Hz, CH_2OBz), 4.44(1H, dd $^2J_{AB}$ =7.50 Hz, $^3J_{BX}$ =4.00 Hz, CH_2OBz), 4.21-4.13(1H, m, H-2), 3.95-3.86(1H, m, H-4), 3.59(1H, dd $^2J_{AB}$ =5.50 Hz, $^3J_{AX}$ =6.00 Hz, H-5), 3.40 (1H, dd $^2J_{AB}$ =4.50, $^3J_{BX}$ =6.50 Hz, H-5), 2.41(3H, s, $O_2SC_6H_4CH_3$), 2.16-1.93(2H, m, H-3); δ_C (75 MHz, $CDCl_3$) 166.1($O_2CC_6H_5$), 144.2, 134.1(qC-$O_2SC_6H_4CH_3$), 133.5, 133.2, 130.0, 129.7, 129.0, 128.6, 128.4, 127.5(CH-$O_2CC_6H_5$/$O_2SC_6H_4CH_3$), 66.3(CH_2OBz), 59.1(C-2), 57.2(C-4), 53.5(C-5), 34.0(C-3), 21.6($O_2SC_6H_4CH_3$). Analysis for $C_{19}H_{20}N_4O_4S$ requires C; 56.99, H; 5.03, N; 13.99. S; 8.01 found C; 57.22, H; 4.98, N; 13.69, S; 7.86.

(2*S*,4*S*)-*N*-*p*-Toluenesulfonyl-4-amino-2-(diphenyl-*tert*-butylsilyloxymethyl)pyrrolidine (14). Palladium (10%, on carbon 0.15 g) was added to a solution of **12** (0.50 g, 0.93 mmol) dissolved in ethanol, water and ethyl acetate (26 mL, 10:1:2). The flask was evacuated and hydrogen was introduced. After 2.5 hr the flask was evacuated and placed under an inert atmosphere. The catalyst was filtered off using glass fiber pads (repeated if necessary) and the filtrate was concentrated *in vacuo* to give 0.44 g (100%) of **14** as a clear oil/solid: MS (CI) *m/z* 509$(M)^+$; δ_H (300 MHz, $CDCl_3$) 7.71-7.59(6H, m, C_6H_5/$O_2SC_6H_4CH_3$), 7.50-7.35(6H, m, C_6H_5/$O_2SC_6H_4CH_3$), 7.31-7.25(2H, m , C_6H_5/$O_2SC_6H_4CH_3$), 3.98(1H, dd $^2J_{AB}$ =2.50 Hz, $^3J_{AX}$ =7.50 Hz, CH_2OSi), 3.90(1H, dd $^2J_{AB}$ =10.00 Hz, $^3J_{AX}$ =2.50 Hz, CH_2OSi), 3.71-3.60(1H, m, H-2), 3.48(1H, dd $^2J_{AB}$ =10.00 Hz, $^3J_{AX}$ =2.50 Hz, H-5), 3.05(1H, dd $^2J_{AB}$ =7.50 Hz, $^3J_{AX}$ =5.00 Hz, H-5), 3.10-2.40(2H, m, H-5/H-4), 2.43(3H, s, $O_2SC_6H_4CH_3$), 2.17-2.05(1H, m, H-3), 1.79-1.67(1H, m, H-3), 1.45(~2H, br s, NH_2), 1.08(9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 143.5, 134.6(qC-$O_2SC_6H_4CH_3$), 135.7, 135.7(CH-C_6H_5), 133.6, 133.3(qC-C_6H_5), 129.8, 127.8(CH-$O_2SC_6H_4CH_3$), 127.5(CH-C_6H_5), 67.0(CH_2OSi), 60.3(C-2), 57.3(C-5), 50.5(C-4), 37.9(C-3), 27.0($C(CH_3)_3$), 21.6($O_2SC_6H_4CH_3$), 19.3($C(CH_3)_3$).

(2*S*,4*S*)-*N*-*p*-Toluenesulfonyl-4-amino-2-(benzoyloxymethyl)pyrrolidine (15). The same procedure as described for the synthesis of **14** was used except that the reaction time extended to 4 hr. Compound **13** (0.35 g, 0.87 mmol) reacted to give 0.33 g (100%) of **15** as a clear oil/solid: GCMS (CI) *m/z* 375$(M+H)^+$; δ_H (300 MHz, CD_3COCD_3) 8.11-8.03(2H, m, $O_2CC_6H_5$), 7.86-7.80(2H, m, $O_2SC_6H_4CH_3$), 7.68-7.60(1H, m, $O_2CC_6H_5$), 7.55-7.47(2H, m, $O_2CC_6H_5$), 7.47-7.41(2H, m, $O_2SC_6H_4CH_3$), 4.62(1H, dd $^2J_{AB}$ =5.00 Hz, $^3J_{AX}$ =6.00 Hz, CH_2OBz), 4.50(1H, dd $^2J_{AB}$ =6.50 Hz, $^3J_{BX}$ =4.50 Hz, CH_2OBz), 4.24-4.13(1H, m, H-2), 3.67-3.57(1H, m, H-5), 3.37-3.27(2H, m, H-4/NH_2), 2.42(3H, s, $O_2SC_6H_4CH_3$), 2.13-2.02(1H, m, H-3), 1.93-1.80(1H, m, H-3); δ_C (75 MHz, CD_3COCD_3) 166.5($O_2CC_6H_5$), 144.5, 136.0(qC-$O_2SC_6H_4CH_3$), 133.8(CH-$O_2CC_6H_5$/$O_2SC_6H_4CH_3$), 131.0(qC-$O_2CC_6H_5$), 130.6, 130.3, 129.3, 128.3(CH-$O_2CC_6H_5$/$O_2SC_6H_4CH_3$), 67.8(CH_2OBz), 59.0(C-4/C-2), 58.5(C-2/C-4), 55.6(C-5), 36.2(C-3), 21.4($O_2SC_6H_4CH_3$).

(2*S*,4*S*)-*N*-*p*-Toluenesulfonyl-4-(5-ethylpyrimidin-1-yl)-2-(hydroxymethyl)pyrrolidine (21) and (2*S*,4*S*)-*N*-*p*-Toluenesulfonyl-4-(5-ethylpyrimidin-1-yl)-2-(diphenyl-*tert*-butylsilyloxymethyl)pyrrolidine (19). A solution of **14** (1.19 g, 2.34 mmol) and *N*-ethoxycarbonyl-*E*-2-ethoxyethylenebutyramide (**16**) (0.50 g, 2.34 mmol) in dioxane (6.00 mL) with triethylamine (0.32 mL, 2.44 mmol) was heated at 100 °C for 10 hr. At this

point the reaction could be concentrated *in vacuo* and purified (SiO_2: cyclohexane-ethyl acetate 3:7) to give **17**: MS (CI) 678$(M)^+$; δ_H (300 MHz, $CDCl_3$) 9.06-8.88(1H, m, N-H) 8.25(1H, s, C<u>H</u>-OCH_2CH_3), 7.80-7.53(6H, m, O_2SC_6<u>H_4</u>CH_3/C_6H_5), 7.50-7.20(8H, m, O_2SC_6<u>H_4</u>CH_3/C_6H_5), 4.21-4.00(3H, m, OC<u>H_2</u>CH_3/CH_2OSi), 4.01-3.59(4H, m, CH_2OSi/H-2′/H-4′/H-5′), 3.29-3.10(1H, m, H-5′), 2.41(3H, s, $O_2SC_6H_4C$<u>H_3</u>), 2.48-2.12(3H, m, C<u>H_2</u>CH_3/H-3′), 2.10-1.90(1H, m, H-3′), 1.33(3H, t $^3J_{AX}$= 7.50 Hz, OC<u>H_2</u>CH_3), 1.05(9H, s, $C(CH_3)_3$), 1.01(3H, t $^3J_{AX}$= 7.50 Hz, C<u>H_2</u>CH_3); δ_C (75 MHz, $CDCl_3$) 169.5(C-2), 157.1(<u>C</u>H-OCH_2CH_3), 154.7(C-4), 143.7, 134.6(qC-O_2S<u>C</u>$_6H_4CH_3$), 135.6(CH-O_2S<u>C</u>$_6H_4CH_3$), 133.5, 133.3(qC-C_6H_5), 129.9, 129.8, 128.0, 127.8, 127.5(CH-C_6H_5), 114.1(C-5), 70.3(CH_2OSi), 66.8(O<u>C</u>H_2CH_3), 59.6(C-4′), 54.1(C-5′), 48.3(C-2′), 35.0(C-3′), 27.0(C(<u>C</u>$H_3)_3$), 21.6($O_2SC_6H_4$<u>C</u>H_3), 19.3(<u>C</u>$(CH_3)_3$), 16.9(<u>C</u>H_2CH_3), 15.5(OCH_2<u>C</u>H_3), 13.5(CH_2<u>C</u>H_3). Normally, the solution was allowed to cool to room temperature and hydrochloric acid (2M, 3.00 mL) was added. Heating was continued at 90 °C for a further 13.5 hr (approx.). The cooled solution was washed with saturated sodium bicarbonate (100 mL) and extracted with dichloromethane (3×50 mL). The combined organic extracts were washed with brine (100 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford an orange oil/white solid (0.62 g) that was purified (SiO_2: cyclohexane-ethyl acetate 3:7 increasing to 100% ethyl acetate) to give 0.13 g (9%) of **19** as a white solid: MS (CI) *m/z* 632$(M+H)^+$, 650$(M+NH_4)^+$; δ_H (250 MHz, $CDCl_3$) 7.65-7.45(6H, m, O_2SC_6<u>H_4</u>CH_3/C_6H_5), 7.40-7.20(8H, m, O_2SC_6<u>H_4</u>CH_3/C_6H_5), 7.19(1H, s, H-6), 4.60-4.41(1H, m, H-4′), 3.88(1H, dd $^2J_{AB}$ = 2.00 Hz, $^3J_{AX}$ = 8.00 Hz, CH_2OSi), 3.64-3.45(2H, m, CH_2OSi/H-5′), 3.43-3.25(2H, m, H-2′/H-5′), 2.38(3H, s, $O_2SC_6H_4C$<u>H_3</u>), 2.20(2H, q $^3J_{AX}$ =7.00 Hz, C<u>H_2</u>CH_3), 2.25-2.00(4H, m, H-3′/C<u>H_2</u>CH_3), 1.01(3H, t $^3J_{AX}$ = 7.00 Hz, CH_2C<u>H_3</u>), 0.90(9H, s, $C(CH_3)_3$). Analysis for $C_{34}H_{41}N_3O_5SSi$ requires C; 64.63, H; 6.54, N; 6.65, S; 5.07, found C; 64.60, H; 6.51, N; 6.62, S; 4.92; and 0.67 g (73%) of **21** as a white solid: MS (CI) *m/z* 394$(M+H)^+$; δ_H (250 MHz, $CDCl_3$) 9.98(~1H, br s, N-H), 7.70-7.60(2H, m, O_2SC_6<u>H_4</u>CH_3), 7.35-7.26(2H, m, O_2SC_6<u>H_4</u>CH_3), 7.20(1H, s, H-6), 4.68-4.42(1H, m, H-4′), 3.98-3.90(1H, m, H-2′), 3.72-3.34(5H, m, CH_2OH/H-5′), 2.36(3H, s, $O_2SC_6H_4C$<u>H_3</u>), 2.30-2.06(4H, m, H-3′/C<u>H_2</u>CH_3), 2.23(2H, q $^3J_{AX}$= 7.00 Hz, C<u>H_2</u>CH_3), 1.00(3H, t $^3J_{AX}$= 7.00 Hz, CH_2C<u>H_3</u>); δ_C (62.5 MHz, $CDCl_3$) 163.5(C-2), 151.2(C-4), 144.6, 135.7(qC-O_2S<u>C</u>$_6H_4CH_3$), 132.8(C-6), 130.2, 127.6(CH-O_2S<u>C</u>$_6H_4CH_3$), 117.3(C-5), 64.0(CH_2OH), 60.4(C-4′), 52.5(C-5′), 51.7(C-2′), 32.6(C-3′), 21.5($O_2SC_6H_4$<u>C</u>H_3), 21.0(<u>C</u>H_2CH_3), 12.8(CH_2<u>C</u>H_3); UV λ_{max} (ethanol) 228.9 nm ε =13139. Analysis for $C_{18}H_{23}N_3O_5S$ requires C; 54.95, H; 5.89, N; 10.68, S; 8.15, found C; 54.67, H; 6.16, N; 10.42, S; 7.97.

(2*S*,4*S*)-*N*-*p*-Toluenesulfonyl-4-(5-ethylpyrimidin-1-yl)-2-(benzoyloxymethyl)pyrrolidine (20). The same procedure as described for the synthesis of compounds **19** and **21** was employed: **15** (0.18 g, 0.49 mmol) and **16** (0.10 g, 0.49 mmol) in dioxane (3.00 mL) with triethylamine (0.12 mL, 0.90 mmol). An orange oil/white solid (0.62 g) was recovered and purified (SiO_2: cyclohexane-ethyl acetate 3:7) to give 0.16 g, (67%) of **20** as a white solid: MS (CI) *m/z* 498$(M+H)^+$; δ_H (250 MHz, $CDCl_3$) 9.50(~1H, br s, N-H), 8.03-7.94(2H, m, $O_2CC_6H_5$), 7.83-7.74(2H, m, O_2SC_6<u>H_4</u>CH_3), 7.64-7.54(1H, m, $O_2CC_6H_5$), 7.49-7.33(4H, m, $O_2CC_6H_5/O_2SC_6$<u>H_4</u>CH_3), 7.02(1H, s, H-6), 4.76(1H, dd $^2J_{AB}$= 4.00 Hz, $^3J_{AX}$= 8.00 Hz, CH_2OBz), 4.68-4.57(1H, m, H-4′), 4.52(1H, dd $^2J_{AB}$= 8.00 Hz, $^3J_{BX}$= 5.00 Hz, CH_2OBz), 4.07-4.40(1H, m, H-2′), 3.75(1H, dd $^2J_{AB}$= 7.00 Hz, $^3J_{AX}$= 4.00 Hz, H-5′), 3.52(1H, dd $^2J_{AB}$= 4.0 Hz, $^3J_{BX}$= 8.0 Hz, H-5′), 2.52-2.36(4H, m, H-3′/$O_2SC_6H_4$C<u>H_3</u>), 2.43(3H, s, $O_2SC_6H_4C$<u>H_3</u>), 2.30-2.07(4H, m, H-3′/C<u>H_2</u>CH_3), 2.24(2H, q $^3J_{AX}$= 7.00 Hz, C<u>H_2</u>CH_3), 1.03(3H, t $^3J_{AX}$= 8.00 Hz, CH_2C<u>H_3</u>); δ_C (62.5 MHz, $CDCl_3$) 163.5(C-2), 151.2(C-4), 144.6, 135.7(qC-O_2S<u>C</u>$_6H_4CH_3$), 132.8(C-6), 130.2, 127.6(CH-O_2S<u>C</u>$_6H_4CH_3$), 117.3(C-5), 64.0(CH_2OBz), 60.4(C-4′),

52.5(C-5′), 51.7(C-2′), 32.6(C-3′), 21.5($\underline{C}H_2CH_3$), 21.0($O_2SC_6H_4C\underline{H}_3$), 12.8($CH_2\underline{C}H_3$); UV λ_{max} (ethanol) 228.9 nm ε =23139. Analysis for $C_{25}H_{27}N_3O_7S$ requires C; 60.35, H; 5.47, N; 8.45, S; 6.44, found C; 60.52, H; 5.68, N; 8.67, S; 6.31.

(2*S*,4*S*)-4-(5-Ethylpyrimidin-1-yl)-2-(hydroxymethyl)pyrrolidine Hydrochloride (22). **21** (0.20 g, 0.50 mmol) and phenol (0.15 g, 1.52 mmol) were dissolved in a solution of acetic acid (5.10 mL) and hydrobromic acid (48%, 4.40 mL). The solution was heated at 90 °C for 16 hr and then poured into water and extracted with diethyl ether. The aqueous solution was applied to an AG50W-X8 (H^+ form) column (6.20 mL) and eluted first with water (25 mL) and then ammonium hydroxide (0.5M, 50 mL). The ammonium hydroxide fractions were evaporated to dryness to provide a viscous oil that was dissolved in hydrochloric acid (2M, 10 mL) and concentrated *in vacuo* to give 0.10 g (71%) of **22** as an off-white solid: MS (FAB) *m/z* 240(M+H)$^+$; δ_H (300 MHz, CD_3SOCD_3) 11.50-11.26(~1H, m, N-H), 9.16(~1H, br s, N-H), 7.80-7.70(~1H, m, N-H), 7.57(1H, s, H-6), 5.21-5.05(1H, m, H-4′), 3.80-3.26(5H, m, CH_2OH/H-5′), 2.41-2.14(3H, m, H-3′/$C\underline{H}_2CH_3$), 2.22(2H, q $^3J_{AX}$ =7.40 Hz, $C\underline{H}_2CH_3$), 2.12-1.86(1H, m H-3′), 1.06(3H, t $^3J_{AX}$ =7.40 Hz, $CH_2C\underline{H}_3$); δ_C (75 MHz, CD_3OD) 166.6(C-2), 153.4(C-4), 142.9(C-6), 117.9(C-5), 64.2(C-2′), 61.4(CH_2OH), 61.0(C-2′), 50.4(C-5′), 32.2(C-3′), 21.6($C\underline{H}_2CH_3$), 14.0($CH_2C\underline{H}_3$); UV λ_{max} (ethanol) 272 nm ε =12845. Analysis for $C_{11}H_{18}ClN_3O_3$ requires C; 47.95, H; 6.58, N; 15.24, found C; 47.81, H; 6.29, N; 15.50.

(2*S*,4*S*)-*N*-*p*-Toluenesulfonyl-4-[*E*-5-(2-bromovinyl)-pyrimidin-1-yl]-2-(benzoyloxymethyl)pyrrolidine (23).[16] **Method 1:** Bromine (12 μL, 0.21 mmol) was added at a rate that maintained a pale orange solution to **20** (53 mg, 0.11 mmol) and AIBN (0.001 g) in chloroform (2.50 mL, dry) that was being heated under reflux under an atmosphere of nitrogen. After the addition was complete, the reaction was heated for a further 10 min, cooled and triethylamine (37 μL, 0.28 mmol) was added over 5 min, maintaining the solution temperature below 50 °C. After 30 min the reaction was washed with water (10 mL), the aqueous layer extracted with dichloromethane (3×25 mL), and the combined organic extracts were washed with hydrochloric acid (2M, 10 mL) and water (10 mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil that was purified (SiO_2: cyclohexane-ethyl acetate 3:7) to give 10 mg (17%) of **23** as a yellow solid. **Method 2:** A solution of *N*-bromosuccinimide (55 mg, 0.31 mmol) in dioxane (0.50 mL) was added over 35 min to a solution of **20** (0.05 g, 0.10 mmol) in dioxane (0.50 mL) at 60 °C under an atmosphere of nitrogen. After 1 hr, triethylamine (44 μL, 0.44 mmol) was added and the reaction was heated at 60 °C for a further 20 min and then stirred at room temperature for 18 hr. The solution was diluted with dichloromethane (10 mL), washed with hydrochloric acid (2M, 10 mL), sodium metabisulfite (5%, 10 mL) and saturated sodium bicarbonate (10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford an orange oil/solid (100 mg) that was purified (SiO_2: cyclohexane-ethyl acetate 3:7) to give 16.3 mg (28%) of **23** as a white solid: GCMS (CI) *m/z* 575, 576(M+H)$^+$(isotopes); δ_H (250 MHz, $CDCl_3$) 8.70(~1H, br s, N-H), 8.00-7.92(2H, m, $O_2CC_6H_5$), 7.84-7.75(2H, m, $O_2SC_6\underline{H}_4CH_3$), 7.51-7.30(5H, m, $O_2CC_6H_5$/$O_2SC_6\underline{H}_4CH_3$/vinylic-H), 7.02(1H, s, H-6), 6.35(1H, d $^2J_{AX}$= 14.00 Hz, vinylic-H), 4.89-4.65(2H, m, H-4′/CH_2OBz), 4.60(1H, dd $^2J_{AB}$= 8.00 Hz, $^3J_{BX}$= 6.00 Hz, CH_2OBz), 4.07-3.96(1H, m, H-2′), 3.74(1H, dd $^2J_{AB}$= 7.00 Hz, $^3J_{AX}$= 4.00 Hz, H-5′), 3.51(1H, dd $^2J_{AB}$= 6.00 Hz, $^3J_{AX}$= 4.00 Hz, H-5′), 2.56-2.40(4H, m, H-3′/$O_2SC_6H_4C\underline{H}_3$), 2.44(3H, s, $O_2SC_6H_4C\underline{H}_3$), 2.20-2.04(1H, m, H-3′). δ_C (300 MHz, $CDCl_3$) 166.2($O_2\underline{C}C_6H_5$), 160.7(C-2), 149.5(C-4), 144.9, 130.3(qC-$O_2S\underline{C}_6H_4CH_3$), 137.6(C-6), 133.7, 133.3, 129.6, 129.4, 128.7, 127.7(CH- $O_2C\underline{C}_6H_5$/$O_2S\underline{C}_6H_4CH_3$/vinylic-C),

112.3(C-5), 110.9(vinylic-C), 65.8(CH_2OBz), 57.0(C-4′), 53.4(C-2′), 51.9(C-5′), 33.7(C-3′), 21.6($O_2SC_6H_4\underline{C}H_3$); HRMS (FAB) found 596.048657 requires 596.046688 for $C_{25}H_{24}N_3O_6NaSBr$.

(2*S*,4*S*)-*N*-*p*-Toluenesulfonyl-4-(5-ethylpyrmidin-1-yl)-2-(acetoxymethyl)pyrrolidine (24). Under an atmosphere of argon, acetic anhydride (72 μL, 0.76 mmol) was added to an ice-cold solution of **21** (0.25 g, 0.64 mmol), triethylamine (0.11 mL, 0.76 mmol) and DMAP (20 mg) dissolved in dichloromethane (15 mL, dry) that was prepared 15 min earlier. The cooling bath was removed and the reaction was stirred at room temperature. After 18 hr, the solution was diluted with dichloromethane (50 mL) washed with water (50 mL) and the organic layer separated. The aqueous layer was extracted further with dichloromethane (3×50 mL) and the combined organic extracts were washed with brine (100 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a viscous yellow oil (0.32 g) that was purified (SiO_2: cyclohexane-ethyl acetate 3:7) to give 0.23 g (82%) of **24** as a white foam: MS (CI) *m/z* 436$(M+H)^+$; δ_H (300 MHz, $CDCl_3$) 9.20(~1H, br s, N-H), 7.78-7.68(2H, m, $O_2SC_6\underline{H}_4CH_3$), 7.43-7.33(2H, m, $O_2SC_6\underline{H}_4CH_3$), 7.07(1H, s, H-6), 4.62-4.49(1H, m, H-4′), 4.42(1H, dd $^2J_{AB}$= 4.40 Hz, $^3J_{AX}$= 7.00 Hz, CH_2OAc), 4.25(1H, dd $^2J_{AB}$= 6.60 Hz, $^3J_{BX}$= 4.80 Hz, CH_2OAc), 3.85-3.73(1H, m, H-2′), 3.63(1H, dd $^2J_{AB}$= 7.40 Hz, $^3J_{AX}$= 4.80 Hz, H-5′), 3.50(1H, dd $^2J_{AB}$= 6.20 Hz, $^3J_{BX}$= 5.20 Hz, H-5′), 2.45(3H, s, $O_2SC_6H_4C\underline{H}_3$), 2.41-2.08(3H, m, H-3′/$C\underline{H}_2CH_3$), 2.07-1.91(4H, m, H-3′/$O_2CC\underline{H}_3$), 1.11(3H, t $^3J_{AX}$= 7.40 Hz, $CH_2C\underline{H}_3$). δ_C (75 MHz, $CDCl_3$) 170.6($O_2\underline{C}CH_3$), 163.4(C-2), 151.0(C-4), 144.7, 133.0(qC-$O_2S\underline{C}_6H_4CH_3$), 135.5(C-6), 129.8, 127.8(CH-$O_2S\underline{C}_6H_4CH_3$), 117.4(C-5), 65.9($CH_2OAc$), 56.6(C-4′), 52.8(C-2′), 51.6(C-5′), 33.7(C-3′), 21.6($O_2SC_6H_4\underline{C}H_3$), 20.8($O_2C\underline{C}H_3$), 20.3($\underline{C}H_2CH_3$), 12.9($CH_2\underline{C}H_3$). Analysis for $C_{20}H_{25}N_3O_6S$ requires C; 55.16, H; 5.79, N; 9.65. S; 7.36 found C; 54.93, H; 5.55, N; 9.72, S 7.52.

(2*S*,4*S*)-*N*-*p*-Toluenesulfonyl-4-[*E*-5-(2-bromovinyl)-pyrimidin-1-yl]-2-(acetoxymethyl)pyrrolidine (25). A solution of bromine (25 μL, 0.46 mmol) and AIBN (2 mg) in chloroform (3 mL, dry) was added at a rate that maintained a pale orange solution to **24** (0.10 g, 0.23 mmol) dissolved in chloroform (3 mL, dry) that was being heated under reflux under an atmosphere of nitrogen. After the addition, the reaction was heated for a further 20 min and then cooled. Triethylamine (78 μL, 0.57 mmol) was added over 5 min maintaining solution temperature below 50 °C. After 90 min the reaction was diluted with dichloromethane (15 mL), washed with water (15 mL) and the organic layer was separated. The aqueous layer was extracted further with dichloromethane (3×25 mL) and the combined organic extracts were washed with hydrochloric acid (2M, 10 mL) and water (10 mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a brown foam (0.11 g) that was purified (SiO_2: cyclohexane-ethyl acetate 3:7) to give (0.06 g, 51%) of **25** as an opaque solid together with **24** (20 mg): MS (CI) *m/z* 513, 514$(M+H)^+$, 529, 530$(M+NH_4)^+$ (isotopes); δ_H (300 MHz, $CDCl_3$) 9.20(~1H, br s, N-H), 7.80-7.66(2H, m, $O_2SC_6\underline{H}_4CH_3$), 7.52-7.29(4H, m, H-6/vinylic-H/$O_2SC_6\underline{H}_4CH_3$), 6.62(1H, d $^2J_{AX}$ =14.40 Hz, vinylic-H), 4.71-4.54(1H, m, H-4′), 4.45-4.24(2H, m, CH_2OAc), 3.88-3.72(1H, m, H-2′), 3.68-3.43(2H, m, H-5′), 2.58-2.31(4H, m, H-3′/$O_2SC_6H_4C\underline{H}_3$), 2.13-1.90(4H, m, H-3′/$O_2CC\underline{H}_3$); δ_C (75 MHz, $CDCl_3$) 170.6($O_2\underline{C}CH_3$), 161.2(C-2), 149.7(C-4), 144.9, 132.7(qC-$O_2S\underline{C}_6H_4CH_3$), 138.4(C-6), 130.3, 127.9(CH-$O_2S\underline{C}_6H_4CH_3$), 128.0(vinylic-C), 11.9(C-5), 110.7(vinylic-C), 65.6(CH_2OAc), 56.7(C-4′), 53.2(C-2′), 52.1(C-5′), 34.1(C-3′), 21.7($O_2SC_6H_4\underline{C}H_3$), 20.8($O_2C\underline{C}H_3$). Analysis for $C_{20}H_{22}BrN_3O_6S$ requires C; 46.88, H; 4.33, N; 8.20, S; 6.26 found C; 47.02, H; 4.30, N; 7.96, S 6.00.

(2*S*,4*S*)-*N*-*p*-Toluenesulfonyl-4-[*E*-5-(2-bromovinyl)-pyrimidin-1-yl]-2-(hydroxymethyl)pyrrolidine (26). A solution of ammonia in methanol (2M, 6.00 mL) followed by concentrated aqueous ammonia (2.50 mL) was

added to **25** (0.10 g, 0.20 mmol) dissolved in dichloromethane (2.00 mL). The de-acetylation was followed (TLC: cyclohexane- ethyl acetate 3:7) and when no further changes were observed (TLC), the reaction was concentrated *in vacuo* to give 0.10 g (100%) of **26** as a brown solid: MS (FAB) 470, 472$(M+H)^+$, 492, 494$(M+Na)^+$ (isotopes); δ_H (300 MHz, $CDCl_3$) 7.78-7.61(3H, m, $O_2SC_6\underline{H}_4CH_3$/H-6), 7.45-7.29(3H, m, $O_2SC_6H_4CH_3$/vinylic-H), 6.65(1H, d $^3J_{AX}$ =13.6 Hz, vinylic-H), 4.70-4.59(1H, m, H-4′), 4.20-4.07(1H, m, CH_2OH), 3.80-3.40(5H, m, CH_2OH/H-5′/H-2′), 2.48-2.11(5H, m, H-3′/$O_2SC_6H_4C\underline{H}_3$); δ_C (75 MHz, $CDCl_3$) 161.6(C-2), 150.1(C-4), 144.9, 132.3(qC-$O_2S\underline{C}_6H_4CH_3$), 139.1(C-6), 130.3, 127.8(CH-$O_2S\underline{C}_6H_4CH_3$), 128.4(vinylic-C), 11.7(C-5), 109.9(vinylic-C), 63.7(CH_2OH), 60.3(C-4′), 53.3(C-5′), 52.0(C-2′), 33.1(C-3′), 21.7($O_2SC_6H_4\underline{C}H_3$); UV (ethanol) λ_{max} =275.0 nm ε =80128. Analysis for $C_{18}H_{20}BrN_3O_5S$ requires C; 45.97, H; 4.29, N; 8.93, S; 6.82, found C; 46.21, H; 4.36, N; 8.67, S; 6.79.

ACKNOWLEDGMENTS

The authors wish to thank the EPSRC and GlaxoWellcome PLC for providing funding (CASE ward to NBW) for this project. Antiviral testing was conducted by GlaxoWellcome PLC, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts. SG1 2NY, UK and Professor E. De Clercq, Rega Institute for Medical Research, Katholieke Universiteit, Leuven, Belgium. The thymidine kinase study performed on **22** was carried out by Professor S. Spadari, Istituto di Genetica Biochemica ed Evoluzionistica, Pavia, Italy. Useful discussions were had with Dr. G. W. Hardy and Dr. S. G. Rahim of GlaxoWellcome PLC. We are grateful to Dr. T. A. Hamor and co-workers for the X-ray crystallography.

REFERENCES AND NOTES

† This paper is dedicated to the memory of Professor R. T. Walker who died in November 1997.

‡ Currently undertaking a postdoctoral position with Professor Marvin H. Caruthers at the University of Colorado at Boulder.

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