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A New Synthetic Approach to the Polyoxins: Concise Stereoselective Preparation of Protected Thymine Polyoxin C

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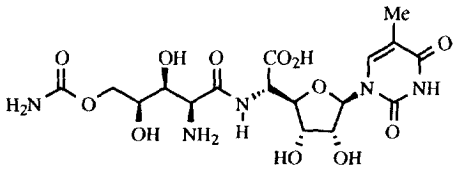
Abstract: A new approach to the synthesis of thymine polyoxin C has been devised, which uses the prochiral ketone 8-oxabicyclo[3.2.1]octan-3-one **8** as the starting material. An enol silane **12** derived from this ketone was reacted with TsN=Se=NTs in order to install the nitrogen functionality required in the final product, whilst retaining a reactive C=C in the product **13**. This compound was cleaved using ozone and, following protecting group manipulation, was subjected to an unusual one carbon side-chain degradation employing $Pb(OAc)_4$ to give an appropriate glycosyl donor **25**. Completion of the synthesis of a protected thymine polyoxin C was then carried out by reaction of **25** under Vorbrüggen conditions.

INTRODUCTION

The challenging array of functionality presented by the complex nucleoside antibiotics, such as polyoxin J **1**, combined with the notable biological activity of many members of this family, has stimulated intense synthetic activity in this area.[1] In particular, the polyoxins, exemplified by structure **1**, possess potent antifungal activity, which has been shown to be due to inhibition of chitin synthetase, whilst being non-toxic to animals, plants and bacteria.[2]



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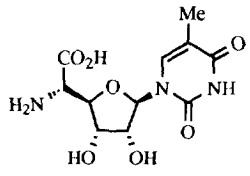

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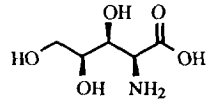
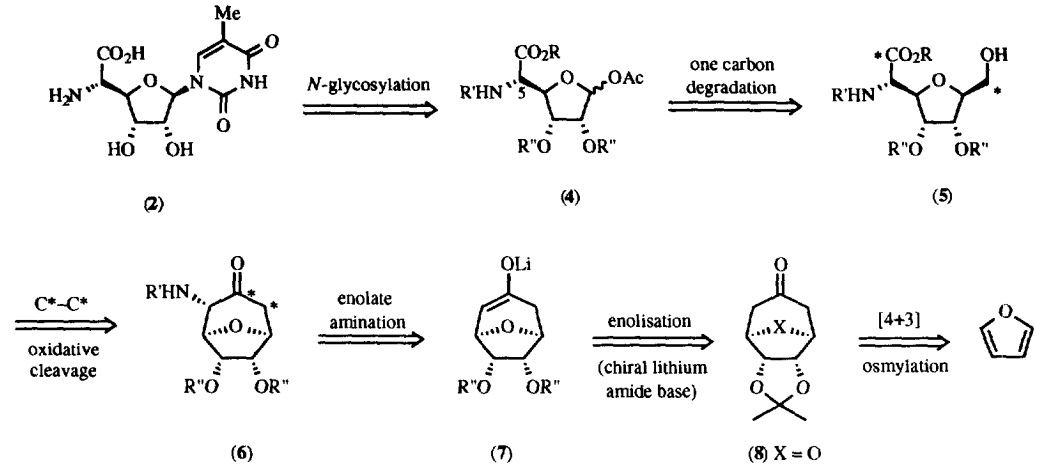


(3)

Total syntheses of polyoxin J have been recorded by four groups (one being a formal synthesis[6]),[3-6] whilst many others have reported syntheses, or partial syntheses, of either the nucleoside portion **2** (called thymine polyoxin C),[7] the side chain carboxylic acid **3** (polyoxamic acid),[8] or both.[9-11]

Despite the advances that have been made, many of these approaches involve a large number of synthetic steps or suffer from a lack of stereocontrol at some point. Furthermore, there are few approaches which do not involve manipulation of chiral pool starting materials.[12] We sought to develop a new approach to the nucleoside fragment of these targets which would be highly flexible, so as to allow the synthesis of unnatural analogues (e.g. carbocyclic derivatives), completely stereocontrolled, and reasonably concise. The retrosynthetic analysis for our chosen strategy is outlined in Scheme 1.



Scheme 1

Access to thymine polyoxin C **2** (in a protected form suitable for further manipulation) would be via *N*-glycosidation of a suitably protected donor, such as the acetate **4**, following well-established procedures (for example a Vorbrüggen protocol). This intermediate would be obtained by one-carbon degradation of the hydroxymethylene derivative **5**, itself the product of oxidative ring cleavage of bicyclic ketone **6**. The required nitrogen functionality (probably a protected amine) present in **6** would be installed by electrophilic amination of an enolate **7** derived from the symmetrical ketone **8**. This compound is readily available by a [4+3] cycloaddition approach from furan.

The perceived advantages of this approach are:

(i) In principle, bicyclo[3.2.1]ketones **8** having bridging atoms other than oxygen (e.g. X = C, N, S, etc.) could be employed, leading to interesting analogues.

(ii) The desired stereochemistry at C–5 (see compound **4**) would be established by *exo*-selective reaction of enolate **7** to give **6**.

(iii) A synthesis developed involving the enolisation of prochiral ketone **8** should be capable of asymmetric modification by the use of a chiral lithium amide base, according to our previously reported results.

(iv) The sequence shown appears rather concise, and should allow the conversion of furan into a suitably protected polyoxin C product in about 10 synthetic steps.

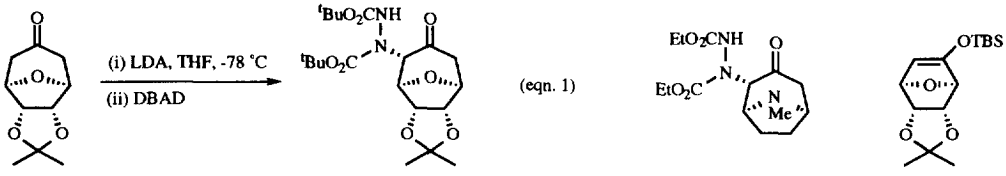
Herein we describe our results, which have resulted in the synthesis of a protected polyoxin C, in racemic form, according to the approach outlined above.

RESULTS AND DISCUSSION

(i) Enolate Amination

Since we had a plentiful supply of the required oxabicyclic ketone **8** in the form of the acetonide–protected diol shown,[13] the first real problem with which we were confronted was the selection

of an appropriate method of enolate amination. Initial interest focused on the reaction of the lithium enolate derived from **8** with di-*tert*-butylazodicarboxylate (DBAD),[14] which furnished the anticipated α-hydrazino ketone **9** as a single diastereoisomer and in reasonable chemical yield (eqn. 1).

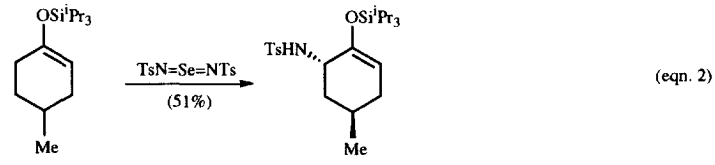


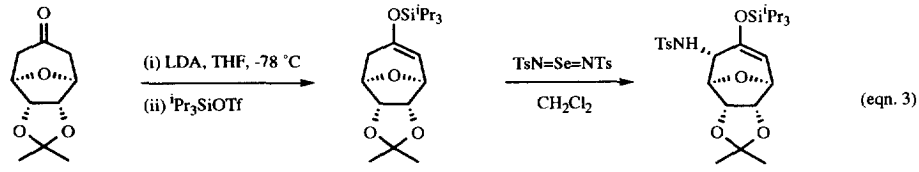
(**8**) (**9**) (66%) (**10**) (**11**)

Assignment of the *exo*-configuration at the new asymmetric centre formed was based on ample literature precedent, for example the related enolate amination to form **10** described by Majewski and Zheng.[15] In the case of **9**, we found that unambiguous assignment by analysis of ^{1}H NMR coupling constants was difficult due to the presence of rotamers associated with the amide linkages of the newly introduced hydrazino group. Unfortunately we were unable to progress this intermediate, since attempted oxidative cleavage via enol silane formation, or manipulation of the hydrazine to a more manageable derivative, for example by N–N cleavage, was not straightforward.

We briefly considered a number of alternative amination procedures including the use of 1-chloro-1-nitrosocyclohexane,[16] *N*-acyloxaziridines,[17] arylsulfonyl azide,[18] and the reaction between enol silanes and $BocN_3$, which had been used by the group of Vogel to convert enol silane **11** into the corresponding *N*-Boc α-amino ketone.[19]

Ultimately, we seized upon a report from the group of Magnus, which described the reaction of triisopropyl enol silanes, derived from cyclic ketones, with the Sharpless reagent, TsN=Se=NTs (eqn.2).[20]





(**8**) (**12**) (85%) (**13**) (84%)

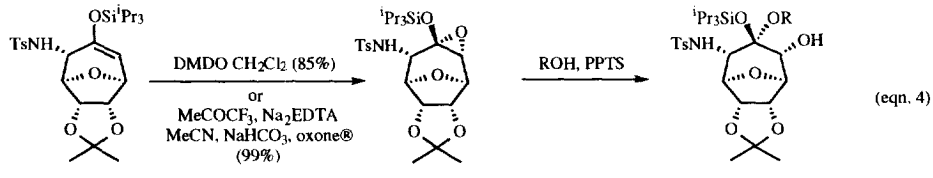
This reaction appeared especially attractive, since it proceeds via an ene–sigmatropic rearrangement sequence, which serves to install the protected amine functionality in a regiospecific and stereoselective fashion, and retains the useful enol silane group in the product. We were delighted to find that this method

was easily applied to our system. Enol silane formation, requiring the use of a reactive silyl triflate to form **12**, was followed by reaction with the selenodiimide reagent to furnish the desired sulfonamide product **13** in good overall yield (eqn. 3). Evidence that the nitrogen functionality had been installed, as expected, from the *exo*-face of the bicyclic enol silane came from the ^{1}H NMR spectrum, since the remaining methine proton α to nitrogen showed coupling only due to the sulfonamide N–H. This is diagnostic for an *endo*-orientated hydrogen in this type of system, since the dihedral angle with the bridgehead hydrogen approximates 90°.[21]

The Magnus variant of the Sharpless reaction clearly provides a superb solution to the enolate amination problem presented in Scheme 1, since it secures the required protected amine function whilst also retaining a double bond ideal for ring cleavage.

(ii) C=C Cleavage

In previous work we had efficiently cleaved *trimethyl* enol silanes by conversion into the corresponding α-hydroxyketone followed by treatment with lead tetraacetate.[22] Therefore, we focused intially on establishing an analogous protocol for the oxidative cleavage of **13**. This did not proceed as anticipated. Under a variety of conditions we were unable to convert **13** into the desired α-hydroxyketone, although reaction with dimethyl dioxirane (DMDO),[23] or (trifluoromethyl)methyl dioxirane (using the in-situ generation protocol) gave excellent yields of the epoxide product **14** (eqn. 4).[24] This compound could not be converted into the desired ketone by either acidic treatment, which instead simply removed the acetonide, or reaction with TBAF in THF.



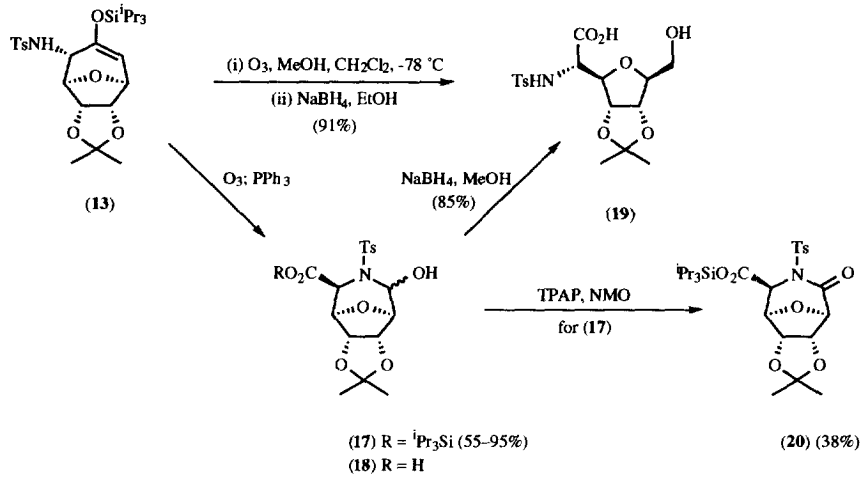
(13) (14) (15, R = Me) (84%) (16, R = allyl) (79%) (eqn. 4)

However, reaction with an alcohol (as solvent), in the presence of a catalytic amount of pyridinium *para*-toluenesulfonate (PPTS) readily yielded a number of mixed ketal derivatives, such as **15** and **16**. Unfortunately, it did not prove possible to transform these compounds further in a useful way, and we were forced to adopt alternative methods,

Ozonolysis of the enol silane C=C was an obvious option, but initial results were a little discouraging since reaction of **13** in CH_2Cl_2 solution with ozone at low temperature gave a mixture of two products in variable yield (55–95%). Neither of these products showed signals in the ^{1}H NMR in the region 9–10 ppm that could be attributed to aldehydic protons, but instead showed a signal at about 5.0–5.1 ppm along with a D_2O exchangable signal.

It became clear that the products of the ozonolysis were the epimeric *N*-tosyl hemiaminals **17**, unpredictable levels of hydrolysis to the corresponding acids **18** accounting for the variable yields obtained. This assignment was confirmed by reduction to the desired hydroxy-acid **19** (the reduction being

accompanied by loss of the somewhat labile silylester), and by oxidation to give the lactam **20**, using the Ley–Griffith TPAP protocol employing *N*-methylmorpholine-*N*-oxide, Scheme 2.[25]

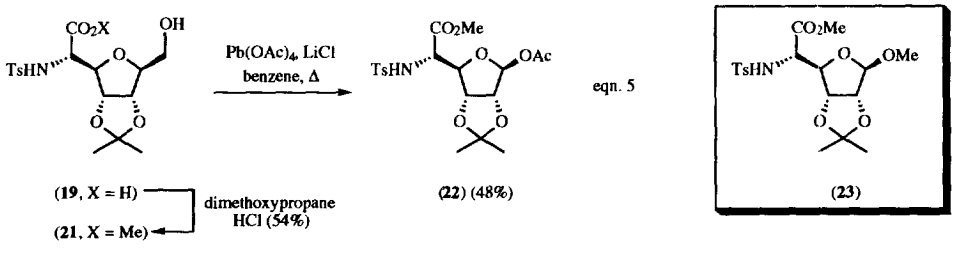


Scheme 2

With the ambiguity in the oxidation resolved we were able to apply a straightforward ozonolysis–$NaBH_4$ reduction sequence to furnish the desired hydroxy-acid **19** in excellent yield.

(iii) One-Carbon Degradation

A number of possibilities were considered for removal of the undesired carbon atom, present in **19** as a hydroxymethyl unit. For example, oxidation of similar compounds with PCC has been reported to give one-carbon degraded lactones.[26] Alternatively, oxidation to the carboxylic acid, followed by decarboxylation (for example using a Barton protocol) might be more convenient in providing a suitable glycoside donor.[27] Instead, we opted to examine reactions of several hydroxymethyl derivatives related to **19** with lead tetraacetate. Under such conditions we anticipated that the alcohol might be converted into the corresponding oxygen-centred radical, which could then undergo β-fragmentation, liberating formaldehyde,[28] and subsequent oxidation to give the required anomeric acetate. We were delighted to find that exactly such an outcome was observed on reaction of the methyl ester **21** with $Pb(OAc)_4$ and LiCl in benzene at reflux (eqn. 5).

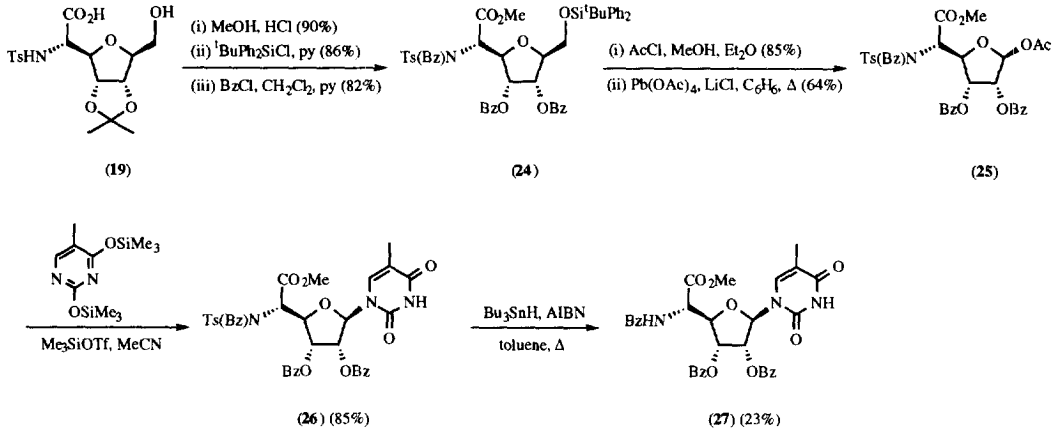


The anomeric acetate product **22** was isolated as a single diastereomer, comparison with the closely related compound **23**, described by Barrett and co-workers,[29] providing further reassurance of our stereochemical assignments.

(iv) Completion of the Synthesis

Unfortunately, the acetonide protecting group proved to be incompatible with the reaction conditions typically employed for introduction of the nucleobase. This problem, combined with the modest yields achieved for the sequence **19** → **21** → **22**, forced us to adopt a different protecting group strategy.

Following some preliminary studies, which probed the suitability of various protecting functions for primary and secondary alcohols, we devised the sequence shown in Scheme 3.



Scheme 3

The use of acetate or benzoate as secondary alcohol protection was suggested by their widespread use in previous syntheses of complex nucleosides, including polyoxin J. Therefore, esterification of **19**, with concomitant loss of the acetonide, and selective reprotection of the primary alcohol as a TBDPS ether was followed by treatment with excess BzCl, resulting in the formation of **24**. The *N*-benzoylation observed in this step could not be avoided, but subsequently turned out to be beneficial in opening up unexpected opportunities for *N*-desulfonylation.

Completion of our synthesis of a protected thymine-polyoxin C, **26**, then required deprotection of the primary hydroxyl, one-carbon degradation to give **25** as described above for the acetonide derivative **21**, and glycosidation using a Vorbrüggen protocol.[30]

As anticipated, the pyrimidine base was introduced with a high level of regioselectivity and diastereoselectivity, there being no evidence of α-nucleoside or *N*-3 nucleoside formation. The ^{1}H NMR data for **26** compare very well with those of closely related derivatives, and in particular, the *J* value of 5.5 Hz for the anomeric hydrogen is good evidence for the β-configuration shown.

The only apparent problem with the route developed is the presence of the rather robust nitrogen protection in the form of a sulfonamide. Although we have been able to carry out little further work with our synthetic intermediates, we were prompted to explore possible *N*-desulfonylation by a recent report from

the group of Parsons.[31] Reaction of **26** under the free radical conditions described rewarded us with a low but promising yield of the desired benzamide **27**.

CONCLUSION

The objective of establishing a new route to the polyoxin family of nucleosides, according to Scheme 1, has been achieved largely as we planned at the outset. Although a degree of protecting group swapping was found to be necessary, the synthesis of the final protected derivative **26** proceeds in only 9 steps from the readily available ketone **8**, and is totally diastereocontrolled. Although we have not used a chiral lithium amide base to access these compounds in enantiomerically enriched form, this is clearly a viable and attractive option.[32]

ACKNOWLEDGEMENTS

We are grateful to the Engineering and Physical Sciences Research Council (EPSRC) and to British Biotech, Watlington Road, Cowley, Oxford OX4 5LY, U.K. for support of DG through the CASE scheme. We would also like to thank Dr Mark Whittaker and Dr Chris Blackwell of British Biotech for their interest in this work.

EXPERIMENTAL

General Details

Melting points for solid products were determined using a Kofler hot-stage apparatus. IR spectra were recorded on either Perkin-Elmer 1720-X FTIR or Perkin-Elmer 1600 Series FTIR instruments as either KBr discs or solutions in CCl_4 or $CHCl_3$. Signals are reported as w - weak, m - medium, s - strong, and b - broad. NMR spectra were recorded on Bruker AM 250, Jeol FX270, Bruker AM 400, or Bruker DRX 500 machines, with either Me_4Si or residual protic solvent as internal standard. *J* values are recorded in Hz and abbreviations used are br. - broad, s - singlet, d - doublet, t - triplet, q - quartet, qu - quintet, m - multiplet, dd - double doublet (abbreviations in inverted commas refer to multiplets having a simplified appearance due to identical couplings from non-equivalent protons, e.g. 'dd' = apparent t as two couplings are identical; 'ddd' = apparent dt as again two couplings are identical). Multiplicities indicated for ^{13}C NMR were obtained using a DEPT sequence. Mass spectra were recorded on VG Micromass 70E or VG Autospec spectrometers.

Microanalyses were performed at the microanalytical laboratory at the University of Nottingham using a Perkin-Elmer 240B elemental analyser. Analytical tlc. was performed on Merck precoated silica gel F_{254} plates and visualised by one or more of the following; ultra-violet light, iodine, potassium permanganate, acidic ammonium molybdate (IV) or phosphomolybdic acid. Preparative chromatography was carried out on columns of Merck Kieselgel 60 (230-400 mesh).

Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone ketyl; methanol from 3Å molecular sieves; pyridine and triethylamine from potassium hydroxide; acetonitrile and DCM were stored over 4Å molecular sieves. Light petroleum refers to petroleum ether b.p. 40-60 °C which was distilled prior to use.

Amination of the lithium enolate of ketone 8 to give hydrazide product 9

A solution of lithium diisopropylamide was prepared by treatment of a solution of diisopropylamine (0.175 cm^3, 1.25 mmol) in THF (10 cm^3) under nitrogen at -78 °C with ^{n}butyl lithium (1.6M in hexanes; 0.78 cm^3, 1.3 mmol). After stirring for 5 min the solution was allowed to warm to room temperature and then recooled to -78 °C when a solution of the ketone **8** (198 mg, 1 mmol) in THF (3 cm^3) was added dropwise to the mixture. The mixture was stirred at -78 °C for 1 h before the addition of a solution of di-*tert*-butylazodicarboxylate (250 mg, 1.2 mmol) in anhydrous dichloromethane (2 cm^3). After 30 min the reaction was quenched with glacial acetic acid (0.5 cm^3). The mixture was partitioned between pH7 phosphate buffer (10 cm^3) and dichloromethane (50 cm^3), the two phases were separated and the organic layer was dried ($MgSO_4$) and evaporated to dryness. Flash column chromatography with ether-dichloromethane (1:19) as the eluent afforded the *title compound* **9** as a cloudy oil (280 mg, 66%); (Found C, 55.78; H, 7.67. $C_{20}H_{32}N_2O_8$ requires C, 56.06; H, 7.53%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3401(w), 1728 (s), 1710 (s) and 1370; δ_H (250 MHz; $CDCl_3$) 6.66 and 6.39 (1H, 2 x br. s, N*H*), 5.17 and 4.84 (1H, 2 x m, 2-H), 4.59 (1H, d, *J* 5.3, 5-H), 4.63 (1H, m, 1-H), 4.54 (1H, *J* 5.8, 7-H), 4.46 (1H, d, *J* 5.8, 6-H), 2.72 (1H, 'ddd' *J* 5.3 and 15.8, 4-H_{exo}), 2.44 (1H, d, *J* 15.8, 4-H_{endo}), 1.47 (21H, m, 2 x $CO_2C(CH_3)_3$ and CH_3CCH_3), 1.23 (3H, m, CH_3CCH_3); δ_C (67.5 MHz; $CDCl_3$) 201.8 and 201.4 (C, C-3), 155.1 and 154.5 (2 x C, $CO_2{}^tBu$), 111.8, (C, $C(CH_3)_2$), 83.5 and 83.2 (CH, C-6), 82.4 (2 x C, $C(CH_3)_3$), 81.0 and 80.8 (CH, C-7), 79.8 and 79.7 (CH, C-5), 77.2 (CH, C-1), 65.5 and 64.9 (CH, C-2), 45.7 and 44.7 (CH_2, C-4), 28.0 (6 x CH_3, $C(CH_3)_3$), 25.9 (CH_3, CH_3CCH_3), 24.5 and 24.4 (CH_3, CH_3CCH_3); (Found: M^+, 428.2154. $C_{20}H_{32}N_2O_8$ requires M^+, 428.2159); *m/z* (EI) 428 (M^+, 1%), 272 (46), 228 (15), 196 (11), 154 (2), 127 (4), 102 (12), 57 (100).

Conversion of ketone 8 into the TIPS enol silane 12

A solution of lithium diisopropylamide was prepared by treatment of a solution of diisopropylamine (0.68 cm^3, 4.8 mmol) in THF (32 cm^3) under nitrogen at -78 °C with ^{n}butyl lithium (1.6M in hexanes; 3 cm^3, 5 mmol). A solution of the ketone **8** (750 mg, 4 mmol) in THF (10 cm^3) was added dropwise to the mixture which was then stirred at -78 °C for 1 h before the addition of triisopropylsilyl triflate (1.60 cm^3, 6 mmol). After 30 min the reaction was quenched with saturated aqueous $NaHCO_3$ (40 cm^3), the two phases were separated and the aqueous layer was extracted with ethyl acetate (3 x 75 cm^3). The combined organic

extracts were dried ($MgSO_4$) and evaporated to dryness. Flash column chromatography with ethyl acetate-light petroleum (1:9) as the eluent gave an oil which was further purified by distillation at 140 °C and 0.2 mmHg to afford the *title compound* **12** as a white solid (1.20 g, 87%); m.p. 51 °C; (Found C, 64.54; H, 9.80. $C_{19}H_{34}O_4Si$ requires C, 64.37; H, 9.67%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 1655, 1370, 1351, 865; δ_H (250 MHz; $CDCl_3$) 4.94 (1H, d, *J* 5.2, 2-H), 4.63 (1H, d, *J* 5.6, 7-H), 4.56 (1H, d, *J* 5.6, 6-H), 4.40 (1H, d, *J* 5.2, 1-H), 4.36 (1H, d, *J* 5.2, 5-H), 2.64 (1H, dd, *J* 5.2 and 17.4, 4-H_{exo}), 1.80 (1H, d, *J* 17.4, 4-H_{endo}), 1.50 (3H, s, CH_3CCH_3), 1.31 (3H, s, CH_3CCH_3), 1.07 (21H, m, $SiCH(CH_3)_2$); δ_C (67.5 MHz; $CDCl_3$) 148.8 (C, C-3), 112.0 (C, $C(CH_3)_2$), 102.8 (CH, C-2), 86.6 , 85.6 , 79.0 and 76.1 (CH, C-1, C-5, C-6 and C-7), 33.9 (CH_2, C-4), 26.3 and 25.0 (CH_3, isopropylidene CH_3), 17.7 (6 x CH_3, $SiCH(CH_3)_2$), 12.5 (3 x CH, SiCH); *m/z* (EI) 354 (M^+, 1%), 254 (34), 253 (100), 120 (23), 59 (43).

Reaction of the enol silane 12 with TsN=Se=NTs to give sulfonamide 13

A suspension of chloramine-T (dried at 80 °C *in vacuo*; 1.30 g, 5.74 mmol) and selenium (268 mg, 3.35 mmol) in dichloromethane (13 cm^3) was stirred under nitrogen for 36 h, during which time the dark grey slurry lightened in colour. A solution of the enol silane **12** (617 mg, 1.74 mmol) in dichloromethane (1.5 cm^3) was added and the mixture was stirred for 2 h, before it was diluted with ether (60 cm^3) and 2M NaOH (14 cm^3). After stirring for 30 min the brick red mixture was filtered through kieselguhr, the phases were separated and the aqueous layer was extracted with ether (2 x 70 cm^3). The combined organic extracts were washed with 1M NaOH, 0.1M HCl, water and brine (100 cm^3 each), and evaporated to dryness. Flash column chromatography with ethyl acetate-light petroleum (1:4) as the eluent afforded the *title compound* **13** as a white solid (810 mg, 81%); mp 141-142 °C; (Found C, 59.88; H, 8.05; N, 2.30. $C_{26}H_{41}NO_6SSi$ requires C, 59.63; H, 7.90; N, 2.68%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 1655, 1345, 1157, 1099 and 865; δ_H (270 MHz; $CDCl_3$) 7.77 (2H, d, *J* 8.0, aryl CH), 7.29 (2H, d, *J* 8.0, aryl CH), 4.98 (1H, d, *J* 5.0, 4-H), 4.98 (1H, d, *J* 8.3, NH), 4.51 (2H, s, 6- and 7-H), 4.42 (1H, d, *J* 5.0, 5-H), 4.27 (1H, s, 1-H), 3.41 (1H, d, *J* 8.3, 2-H_{endo}), 2.41 (3H, s, $ArCH_3$), 1.44 (3H, s, CH_3CCH_3), 1.29 (3H, s, CH_3CCH_3) and 0.99 (21H, m, $SiCH(CH_3)_2$); δ_C (67.5 MHz; $CDCl_3$) 146.5 (C, C-3), 143.2 (C, aryl CSO_2), 138.2 (C, aryl CCH_3), 129.6 and 126.8 (4 x CH, aryl CH), 113.1 (C, $C(CH_3)_2$), 105.3 (CH, C-4), 84.9 , 84.4 , 81.9 and 75.6 (4 x CH, C-1, C-5, C-6 and C-7), 54.2 (CH, C-2), 26.2 and 25.0 (2 x CH_3, isopropylidene CH_3), 21.4 (CH_3, $ArCH_3$), 17.7 (6 x CH_3, $SiCH(CH_3)_2$), 12.4 (3 x CH, SiCH); *m/z* (EI) 508 (M - CH_3, 1%), 480 (92), 422 (8), 284 (100), 267 (13), 73 (25), 59 (50).

Epoxidation of 13 with dioxirane reagents to give 14

To a solution of dimethyldioxirane in acetone[23] (0.073M, 4.5 cm^3) under nitrogen at room temperature was added a solution of the enol silane **13** (52 mg, 0.1 mmol) in anhydrous dichloromethane (1 cm^3). The

mixture was stirred for 10 h, then evaporated to dryness. The residue was partitioned between chloroform and water (25 cm^3 each), the phases were separated and the aqueous layer was extracted with chloroform (2 x 25 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated to dryness. Flash column chromatography with ethyl acetate-dichloromethane (3:97) as the eluent afforded the *title compound* **14** as a white solid (44 mg, 85%); m.p. 59-61 °C; (Found C, 57.82; H, 7.74; N, 2.83. $C_{26}H_{41}NO_6SSi$ requires C, 57.86; H, 7.66; N, 2.59%); $\upsilon_{max}(CCl_4)/cm^{-1}$ 2946, 2869, 1351, 1163, 1095, 866; δ_H (250 MHz; $CDCl_3$) 7.77 (2H, d, *J* 8.3, aryl C*H*), 7.28 (2H, d, *J* 8.3, aryl C*H*), 5.28 (1H, d, *J* 10.0, N*H*), 4.64 (1H, d, *J* 6.0, 7-H), 4.60 (1H, d, *J* 6.0, 6-H), 4.34 (1H, d, *J* 1.7, 1-H), 4.01 (1H, s, 5-H), 3.68 (1H, d, *J* 10.0, 4-H_{endo}), 3.17 (1H, d, *J* 1.7, 2-H), 2.41 (3H, s, ArCH_3), 1.44 (3H, s, CH_3CCH_3), 1.31 (3H, s, CH_3CCH_3), 0.94 (21H, m, 3 x Si$CH(CH_3)_2$); δ_C (67.5 MHz; $CDCl_3$) 143.3 (C, aryl CSO_2), 138.5 (C, aryl CCH_3), 129.6 and 126.8 (4 x CH, aryl CH), 113.3 (C, $C(CH_3)_2$), 83.4 , 82.1, 80.7 and 76.2 (4 x CH, C-1, C-5, C-6 and C-7), 77.8 (C, C-3), 58.0 (CH, C-2), 55.4 (CH, C-4), 26.0 and 24.8 (2 x CH_3, isopropylidene CH_3), 21.4 (CH_3, ArCH_3), 17.6 (6 x CH_3, SiCH(CH_3)$_2$) and 12.5 (3 x CH, SiCH); *m/z* (FAB) 540 (M + H^+, 68%), 496 (43), 154 (100), 136 (86), 59 (51).

Alternatively the *title compound* **14** was prepared as follows: To a homogenous solution of the enol silane **13** (131 mg, 0.25 mmol) in acetonitrile (2.5 cm^3) and aqueous Na_2·EDTA (1 cm^3, 4 mM) at 0 °C was added 1,1,1-trifluoropropanone (0.5 cm^3) dropwise.[24] To the solution at 0 °C was added in small portions over 35 min a mixture of $NaHCO_3$ (325 mg, 3.875 mmol) and oxone® (768 mg, 2.5 mmol). The mixture was stirred at 0 °C for 35 min and then partitioned between water (15 cm^3) and dichloromethane (30 cm^3). The two layers were separated and the aqueous layer was further extracted with dichloromethane (2 x 20 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated to dryness. Flash column chromatography with ethyl acetate-dichloromethane (3:97) as the eluent afforded the *title compound* **14** as a white solid (133 mg, 99%). The data were consistent with those described above.

Ring-opening of epoxide 14 to give methyl ether 15

A solution of the epoxide **14** (45 mg, 0.086 mmol) and pyridinium-*p*-toluenesulphonate (24 mg, 0.094 mmol) in methanol (1 cm^3) was stirred at room temperature for 3 h 30 min, before it was evaporated to dryness. Flash column chromatography with ethyl acetate-dichloromethane (4.5:95.5) as the eluent afforded the *title compound* **15** as a white solid (43 mg, 96%); m.p. 162-163 °C; (Found: C, 56.79; H, 8.26; N, 2.59. $C_{27}H_{45}NO_8SSi$ requires C, 56.72; H, 7.93; N, 2.45%); $\upsilon_{max}(CCl_4)/cm^{-1}$ 3331(w), 2948, 2870, 1382, 1338, 1168, 1061, 883; δ_H (270 MHz; $CDCl_3$) 7.75 (2H, d, *J* 8.1, aryl C*H*), 7.30 (2H, d, *J* 8.1, aryl C*H*), 5.17 (1H, d, *J* 4.0, N*H*), 4.79 (1H, d, *J* 5.5, 6-H), 4.50 (1H, d, *J* 5.5, 7-H), 4.31 (1H, s, 5-H), 4.23 (1H, d, *J* 2.0, 1-H), 3.39 (2H, m, 2- and 4-H_{endo}), 3.14 (3H, s, OCH_3), 2.64 (1H, d, *J* 8.9, O*H*), 2.42 (3H, s, ArCH_3), 1.44 (3H, s, CH_3CCH_3), 1.29 (3H, s, CH_3CCH_3), 1.08 (21H, m, 3 x Si$CH(CH_3)_2$); δ_C (67.5

MHz; $CDCl_3$) 143.6 (C, aryl CSO_2), 137.0 (C, aryl CCH_3), 129.8 and 127.0 (4 x CH, aryl *C*H), 111.7 (C, $C(CH_3)_2$), 96.0 (C, C-3), 83.6, 81.7, 80.8 and 80.6 (4 x CH, C-1, C-5, C-6 and C-7), 71.7 (CH, C-2), 54.0 (CH, C-4), 49.3 (CH_3, OCH_3), 26.0 and 24.6 (2 x CH_3, isopropylidene CH_3), 21.5 (CH_3, $ArCH_3$), 18.2 and 18.0 (6 x CH_3, $SiCH(CH_3)_2$), 13.0 (CH, 3 x SiCH); *m/z* (EI) 572 (M + 1, 2%), 496 (21), 398 (100), 280 (35), 243 (27), 154 (49), 136 (55), 91 (49), 73 (67), 59 (71).

Ring-opening of epoxide 14 to give allyl ether 16

A solution of the epoxide **14** (27 mg, 0.05 mmol) and pyridinium-*p*-toluenesulphonate (14 mg, 0.055 mmol) in allyl alcohol (1 cm^3) was stirred at room temperature for 1 h. The mixture was evaporated to dryness. Flash column chromatography with ethyl acetate-dichloromethane (4.5:95.5) as the eluent afforded the *title compound* **16** as a white solid (22.5 mg, 75%); (Found C, 58.13; H, 7.89; N, 2.21. $C_{29}H_{47}NO_8SSi$ requires C, 58.26; H, 7.92; N, 2.34%); $\upsilon_{max}(CCl_4)/cm^{-1}$ 2947, 2869, 1382, 1337, 1162, 1055, 882; δ_H (250 MHz; $CDCl_3$) 7.75 (2H, d, *J* 8.3, aryl C*H*), 7.31 (2H, d, *J* 8.0, aryl C*H*), 5.81 (1H, dddd, *J* 4.6, 6.0, 6.8 and 12.4, H_c), 5.24 (1H, dd, J_{ab} 1.2, J_{ac} 12.4, H_a), 5.19 (1H, dd, J_{ab} 1.2, J_{bc} 6.8, H_b), 5.18 (1H, br. d, N*H*), 4.83 (1H, d, *J* 5.5, 6-H), 4.52 (1H, d, *J* 5.5, 7-H), 4.32 (1H, s, 5-H), 4.24 (1H, d, *J* 1.5, 1-H), 3.98 (1H, dd, *J* 4.6 and 12.4, C*H*H), 3.75 (1H, dd, *J* 6.0 and 12.4, CH*H*), 3.44 (2H, m, 2 and 4-H_{endo}), 2.64 (1H, d, *J* 9.1, O*H*), 2.42 (3H, s, $ArCH_3$), 1.44 (3H, s, CH_3CCH_3), 1.24 (3H, s, CH_3CCH_3), 1.09 (21H, m, $SiCH(CH_3)_2$); δ_C (67.5 MHz; $CDCl_3$) 143.7 (C, aryl CSO_2), 137.1 (C, aryl CCH_3), 132.7 (CH, $CH=CH_2$), 129.9 and 127.1 (4 x CH, aryl *C*H), 117.3 (CH_2, $CH=CH_2$), 111.7 (C, $C(CH_3)_2$), 96.0 (C, C-3), 83.6, 81.7, 80.9 and 80.6 (4 x CH, C-1, C-5, C-6 and C-7), 71.9 (CH, C-2), 62.5 (CH_2, $OCH_2CH=CH_2$), 54.2 (CH, C-4), 25.9 and 24.3 (2 x CH_3, isopropylidene CH_3), 21.5 (CH_3, $ArCH_3$), 18.3 and 18.1 (6 x CH_3, $SiCH(CH_3)_2$), 13.4 (CH, SiCH); m/z (FAB, NBA) 494 (M^+ - 103, 10%), 423 (53), 306 (11), 266 (11), 207 (15), 155 (26), 147 (33), 136 (31), 115 (33), 91 (50), 73 (100), 59 (56).

Ozonolysis of enol silane 13 to give a mixture of *N*-tosylhemiaminals 17 and 18

Ozone was bubbled through a solution of the enol silane **13** (52 mg, 0.1 mmol) in anhydrous dichloromethane (2.5 cm^3) at -78 °C for *ca.* 5 h until the Sudan V present as indicator decolourised. Nitrogen was then bubbled through the solution in order to dispel excess ozone, before triphenyl phosphine (52 mg, 0.2 mmol) was added as a solution in dichloromethane (0.5 cm^3). The solution was stirred at -78 °C for 1 h then at room temperature for 2 h, before the mixture was evaporated to dryness. Flash column chromatography with ethyl acetate-dichloromethane (4:96) as the eluent afforded the *title compound* **17** as a foam and as an approximate 4:1 mixture of *endo*:*exo* epimers (33 mg, 60%); (Found C, 55.82; H, 7.68; N, 2.47. $C_{26}H_{41}NO_8SSi$ requires C, 56.19; H, 7.44; N, 2.52%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 1722(s), 1365, 1289, 1171,

1085; δ_H (500 MHz; $CDCl_3$) for *exo* isomer - 7.79 (2H, d, *J* 8.3, aryl C*H*), 7.31 (2H, d, *J* 8.3, aryl C*H*), 5.04 (1H, dd, *J* 1.9 and 4.1, 2-H_{exo}), 4.94 (1H, d, *J* 5.7, 7-H), 4.65 (1H, d, *J* 2.5, 5-H), 4.40 (1H, d, *J* 2.5, 4-H), 4.30 (1H, d, *J* 5.7, 6-H), 4.29 (1H, d, *J* 1.9, 1-H), 4.06 (1H, d, *J* 4.1, O*H* exchanged with D_2O), 2.44 (3H, s, ArCH_3), 1.43 (3H, s, CH_3CCH_3), 1.22 (3H, s, CH_3CCH_3), 1.13 (21H, m, Si$CH(CH_3)_2$), for *endo* isomer - 5.07 (1H, m, 2-H_{endo}), 4.87 (1H, d, *J* 6.1, 7-H), 4.44 (1H, d, *J* 4.6, 4-H), 4.25 (1H, d, *J* 6.1, 6-H), 4.24 (1H, d, *J* 6.5, 1-H), 4.21 (1H, d, J 4.0, O*H* exchanged with D_2O); δ_C (100 MHz; $CDCl_3$) 167.3 (C, CO_2Si), 144.0 (C, aryl CSO_2), 137.6 (C, aryl CCH_3), 129.4 and 127.3 (4 x CH, aryl *C*H), 112.3 (C, $C(CH_3)_2$), 82.5, 80.0, 79.9, 79.0 and 77.6 (5 x CH, C-1, C-2, C-5, C-6 and C-7), 58.7 (CH, C-4), 25.9 and 24.7 (2 x CH_3, isopropylidene CH_3), 21.5 (CH_3, ArCH_3), 17.6 (CH_3, SiCH(CH_3)$_2$), 11.8 (CH, Si*C*H); *m/z* (FAB, NBA) 537 (M^+ - H_2O, 100%), 478 (56), 340 (15), 155 (61), 139 (36), 115 (59), 91 (74), 73 (51), 59 (76).

Elution of the column with methanol-dichloromethane (5:95) afforded the *title compound* **18** contaminated with triphenyl phosphine oxide which could not be purified further, either by chromatography or crystallisation. Analysis of the ^{1}H-nmr spectrum of the crude material allowed the assignment of the above structure.

Reduction of *N*-tosylhemiaminal 17 to give the hydroxyacid 19

A solution of the hemiaminal **17** (43 mg, 0.078 mmol) in anhydrous methanol (0.8 cm^3) under nitrogen at 0 °C was treated with sodium borohydride (7 mg, 0.17 mmol). The solution was allowed to slowly warm to room temperature overnight, then evaporated to dryness. Flash column chromatography with methanol-dichloromethane (1:4) as the eluent afforded the *title compound* **19** as a white solid (26 mg, 85%), m.p. 210-211 °C (Dec., from MeOH-Et_2O); υ_{max}(KBr disc)/cm^{-1} 3418 (b), 3266 (b), 1599 (s), 1384, 1329, 1163, 1090; δ_H (250 MHz; CD_3OD) 7.77 (2H, d, *J* 8.3, aryl C*H*), 7.38 (2H, d, *J* 8.3, aryl C*H*), 4.80 (1H, dd, *J* 2.9 and 6.4, 4-H), 4.62 (1H, dd, *J* 4.2 and 6.4, 5-H), 4.17 (1H, dd, *J* 2.9 and 6.0, 3-H), 3.99 (1H, dd, J 4.2 and 8.5, 6-H), 3.71 (1H, dd, *J* 5.0 and 12.2, C*H*HOH), 3.70 (1H, d, *J* 6.0, 2-H), 3.58 (1H, dd, *J* 5.0 and 12.2, CH*H*OH), 2.44 (3H, s, ArCH_3), 1.51 (3H, s, CH_3CCH_3), 1.34 (3H, s, CH_3CCH_3); δ_C (125 MHz; d_6-DMSO) 171.1 (C, C-1), 142.7 (C, aryl CSO_2), 137.9 (C, CCH_3), 129.6 and 126.7 (4 x CH, aryl *C*H), 112.2 (C, $C(CH_3)_2$), 85.7, 85.1, 82.3 and 81.4 (4 x CH, C-3, C-4, C-5 and C-6), 61.9 (CH_2, C-7), 59.7 (CH, C-2), 27.2 and 25.3 (2 x CH_3, isopropylidene CH_3), 21.1 (CH_3, ArCH_3); (Found: M + Na^+, 424.1647. $C_{17}H_{23}NNaO_8S$ requires M^+, 424.1042); *m/z* (FAB, glycerol) 446 (M + 2Na - H^+, 22%), 424 (M + Na^+, 59), 207 (40), 115 (98), 75 (29), 57 (21).

Ozonolysis of 13 with reductive work-up to give hydroxyacid 19 directly

Ozone was bubbled through a solution of the enol silane **13** (5.23 g, 10 mmol) in anhydrous 1:1 methanol-dichloromethane (200 cm^3) at -78 °C for *ca.* 5 h until the solution developed a permanent blue coloration. Nitrogen was then bubbled through the solution in order to dispel excess ozone, before a suspension of sodium borohydride (3 g, 80 mmol) in ethanol (20 cm^3) was cautiously added. The mixture was allowed to slowly warm to room temperature overnight and then was evaporated to dryness. Flash column chromatography over a short silica pad with first ethyl acetate-light petroleum (7:3) followed by methanol-dichloromethane (1:3) as the eluent afforded a crude white solid, which was taken up in methanol and precipitated with ether to afford the *title compound* **19** as a white solid (3.64 g, 91%). The data were consistent with those described above.

Oxidation of the *N*-Tosylhemiaminal 17 using TPAP to give the lactam 20

To a solution of the heminaminal **17** (124 mg, 0.22 mmol) and *N*-methylmorpholine-*N*-oxide (39 mg, 0.34 mmol) in anhydrous dichloromethane (1 cm^3) was added powdered 4Å molecular sieves (freshly dried in an oven, 500 $mgmmol^{-1}$) at 0 °C. The suspension was cooled to 0 °C and tetrapropylammonium perruthenate (3.8 mg, 5 mol%) was added. After 10 min the mixture was filtered through a short column of silica eluted with dichloromethane to afford the *title compound* **20** as a colourless oil (47 mg, 38 %); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 2943, 2865, 1746 (s), 1718 (s), 1366, 1084; δ_H (270 MHz; $CDCl_3$) 7.97 (2H, d, *J* 8.3, aryl C*H*), 7.32 (2H, d, *J* 8.2, aryl C*H*), 4.98 (1H, d, *J* 5.8, 4-H), 4.78 (1H, d, *J* 5.8, 5-H), 4.76 (1H, d, *J* 6.0, 6-H), 4.68 (1H, d, *J* 6.0, 7-H), 4.47 (1H, s, 1-H), 2.42 (3H, s, ArCH_3), 1.45 (3H, s, CH_3CCH_3), 1.22 (3H, s, CH_3CCH_3), 1.14 (21H, s, 3 x $SiCH(CH_3)_2$); δ_C (67.5 MHz; $CDCl_3$) 166.7 (C, C-2), 165.9 (C, CO_2Si), 145.5 (C, aryl CSO_2), 135.1 (C, aryl CCH_3), 129.8 and 129.2 (4 x CH, aryl *C*H), 113.7 (C, $C(CH_3)_2$), 82.8, 82.0, 80.0 and 78.8 (4 x CH, C-1, C-5, C-6 and C-7), 61.1 (CH, C-4), 25.7 and 24.5 (2 x CH_3, isopropylidene CH_3), 21.7 (CH_3, ArCH_3), 17.7 and 17.6 (6 x CH_3, $SiCH(CH_3)_2$), 12.2 and 11.9 (3 x CH, Si*C*H); (Found: M + H^+, 554.2233. $C_{26}H_{40}NO_8SSi$ requires M^+, 554.2244); *m/z* (FAB, NBA) 554 (9), 487 (15), 154 (100), 136 (84), 107 (35), 95 (29), 77 (28), 57 (52).

Esterification of hydroxy acid 19 to give ester 21

To a suspension of the acid **19** (200 mg, 0.5 mmol) in 2,2-dimethoxypropane (5 cm^3) was added concentrated hydrochloric acid (0.5 cm^3) and the mixture was heated to 56 °C for 16 h, before it was evaporated to dryness. Flash column chromatography with ethyl acetate-light petroleum (4:3) as the eluent afforded *title compound* **21** as a colourless oil (138 mg, 54%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3539 (b), 3345 (b), 1741 (s), 1598 (w), 1348, 1157, 1113, 1093, 976; δ_H (400 MHz; $CDCl_3$) 7.73 (2H, d, *J* 8.2, aryl C*H*), 7.31 (2H,

d, *J* 8.2, aryl C*H*), 5.74 (1H, d, *J* 7.6, N*H*), 4.69 (1H, dd, *J* 3.3 and 6.4, 5-H), 4.65 (1H, dd, *J* 3.4 and 6.4, 4-H), 4.14 (1H, dd, *J* 3.4 and 5.8, 3-H), 4.11-4.09 (2H, m, 2-H and 6-H), 3.77 (1H, m, C*H*HOH), 3.62 (1H, m, CH*H*OH), 3.54 (3H, s, CO_2CH_3), 2.73 (1H, br.s, O*H*), 2.42 (3H, s, $ArCH_3$), 1.49 (3H, s, CH_3CCH_3), 1.32 (3H, s, CH_3CCH_3); δ_C (100 MHz; $CDCl_3$) 169.6 (C, C-1), 143.9 (C, aryl CSO_2), 136.2 (C, aryl CCH_3), 129.7, 129.6, 127.3 and 127.2 (4 x CH, aryl *C*H), 113.9 (C, $C(CH_3)_2$), 85.6, 84.6, 81.7 and 81.1 (4 x CH, C-3, C-4, C-5 and C-6), 62.4 (CH_2, C-7), 57.6 (CH, C-2), 52.7 (CH_3, CO_2CH_3), 27.2 and 25.3 (2 x CH_3, isopropylidene CH_3), 21.5 (CH_3, $ArCH_3$); (Found: M + H^+, 416.1395. $C_{18}H_{26}NO_8S$ requires M^+, 416.1379); *m/z* (FAB, glycerol) 416 (M + H^+, 100%), 358 (18), 298 (18), 155 (23), 91 (20), 59 (5).

One carbon degradation of alcohol 21 to give the anomeric acetate 22

To a degassed solution of the alcohol **21** (63 mg, 0.152 mmol) in benzene (2 cm^3) under nitrogen was added lithium chloride (26 mg, 0.628 mmol) and lead (IV) acetate (306 mg, 0.691 mmol). The brown solution was heated at reflux for 17 h during which time the solution decolourised and a white precipitate formed. The cooled mixture was filtered through a pad of kieselguhr, washed with acetone (20 cm^3) and the filtrate was evaporated to dryness. Flash column chromatography with ethyl acetate-light petroleum (1:9) as the eluent afforded the β-anomer of the *title compound* **22** as a colourless oil (32 mg, 48%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 1747 (s), 1599 (w), 1351, 1164, 1110, 976; δ_H (250 MHz; $CDCl_3$) 7.68 (2H, d, *J* 8.2, aryl C*H*), 7.30 (2H, d, *J* 8.2, aryl C*H*), 6.15 (1H, s, 6-H), 5.53 (1H, d, *J* 10.6, N*H*), 4.99 (1H, d, *J* 5.9, 5-H), 4.74 (1H, d, *J* 5.9, 4-H), 4.14 (1H, d, *J* 10.6, 3-H), 3.88 (2H, 'dd', *J* 10.6, 2-H), 3.32 (3H, s, CO_2CH_3), 2.41 (3H, s, $ArCH_3$), 2.07 (3H, s, $OC(O)CH_3$), 1.45 (3H, s, CH_3CCH_3), 1.33 (3H, s, CH_3CCH_3); δ_C (67.5 MHz; $CDCl_3$) 169.8 (C, C-1), 144.2 (C, aryl CSO_2), 136.1 (C, aryl CCH_3), 129.6 and 127.2 (4 x CH, aryl C*H*), 111.3 (C, $C(CH_3)_2$), 101.4 (CH, C-6), 87.2, 84.2 and 81.6 (3 x CH, C-3, C-4 and C-5), 57.7 (CH, C-2), 52.4 (CH_3, CO_2CH_3), 26.2 and 24.9 (2 x CH_3, isopropylidene CH_3), 21.5 (CH_3, $ArCH_3$), 21.1 (CH_3, O_2CCH_3); (Found: M - OAc^+, 384.1118. $C_{17}H_{22}NO_7S$ requires M^+, 384.1117); *m/z* (FAB, glycerol) 428 (M - CH_3^+, 4%), 384 (M - OAc^+, 46%), 347 (6), 298 (3), 266 (10), 184 (34), 155 (100), 139 (28), 115 (12), 91 (80), 57 (21).

Protecting group manipulation to convert hydroxyacid 19 into the ester 24

(i) Acetonide removal using HCl in MeOH

To a suspension of the acid **19** (400 mg, 1.0 mmol) in anhydrous methanol (10 cm^3) under nitrogen at 0 °C was added acetyl chloride (0.8 cm^3) dropwise over 2-3 min. The mixture was allowed to slowly warm to room temperature overnight and then was evaporated to dryness. The residue was taken up in ethyl acetate (50 cm^3) and washed with water (2 x 2 cm^3). The aqueous layer was further extracted with ethyl acetate (2

x 20 cm^3) and the combined organic layers were dried ($MgSO_4$), and evaporated to dryness to afford an intermediate triol as a hygroscopic solid (340 mg, 90%); m.p. 94-96 °C; (Found C, 45.87; H, 6.32; N, 3.73. $C_{15}H_{21}NO_8S.H_2O$ requires C, 45.80; H, 5.89; N, 3.56%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3340 (b), 1742 (s), 1345, 1162, 1094; δ_H (250 MHz; $CDCl_3$) 7.74 (2H, d, *J* 8.2, aryl C*H*), 7.30 (2H, d, *J* 8.2, aryl C*H*), 6.85 (1H, d, *J* 8.0, N*H*), 4.36 (1H, dd, *J* 5.7 and 4.7, 5-H), 4.27 (1H, dd, *J* 4.1 and 4.7, 4-H), 4.21 (1H, 'dd', *J* 4.1, 3-H), 4.07 (1H, dd, *J* 4.1 and 8.0, 2-H), 3.96 (1H, d, *J* 5.7, 6-H), 3.93 (1H, d, *J* 12.3, C*H*HOH), 3.70 (1H, d, *J* 12.3, CH*H*OH), 3.54 (3H, s, CO_2CH_3), 2.42 (3H, s, $ArCH_3$); δ_C (100 MHz; $CDCl_3$) 169.7 (C, C-1), 143.9 (C, aryl CSO_2), 136.1 (C, aryl CCH_3), 129.7 and 127.3 (4 x CH, aryl *C*H), 83.7 and 82.9 (2 x CH, C-3 and C-6), 71.9 and 71.2 (2 x CH, C-4 and C-5), 61.9 (CH_2, C-7), 57.6 (CH, C-2), 52.8 (CH_3, CO_2CH_3), 21.5 (CH_3, $ArCH_3$); *m/z* (FAB, glycerol) 749 (2M - H^+, 9%), 376 (M + H^+, 38), 242 (11), 155 (54), 139 (25), 91 (100), 88 (29), 57 (21).

(ii) Selective primary alcohol protection using ^{t}BuPh$_2$SiCl

To a solution of the triol (1.371 g, 3.656 mmol) in anhydrous pyridine (7 cm^3) under nitrogen at 0 °C was added *tert*-butylchlorodiphenylsilane (1 cm^3, 3.84 mmol) dropwise over 5 min. The mixture was allowed to stir at room temperature for 2 d, befrore it was evaporated to dryness. Flash column chromatography with methanol-dichloromethane (2:96) as the eluent afforded the desired silyl ether as a hygroscopic solid (1.92 g, 86%); (Found C, 61.13; H, 6.74; N, 2.24. $C_{31}H_{39}NO_8SSi$ requires C, 60.66; H, 6.40; N, 2.28%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3544 (b), 3330 (b), 2359, 1739 (s), 1346, 1113; δ_H (250 MHz; $CDCl_3$) 7.71-7.65 (6H, m, aryl C*H*), 7.45-7.36 (6H, m, aryl C*H* SiPh_2), 7.24 (2H, d, *J* 8.1, aryl C*H* SO_2Tol), 5.80 (1H, d, *J* 8.4, N*H*), 4.27 (1H, 'dd', *J* 5.3, 3-H), 4.20 (1H, 'dd', *J* 5.3, 4-H), 4.07 (1H, m, 5-H), 4.00 (1H, dd, *J* 5.3 and 8.4, 2-H), 3.94 (1H, m, 6-H), 3.67 (1H, d, *J* 4.2, CH_2OSi), 3.40 (3H, s, CO_2CH_3), 2.39 (3H, s, $ArCH_3$), 1.06 (9H, s, $C(CH_3)_3$); δ_C (67.5 MHz; $CDCl_3$) 170.0 (C, CO_2CH_3), 143.9 (C, aryl CSO_2), 136.2 (C, aryl CCH_3), 135.5 (2 x CH, *p*-aryl *C*H Ph_2 Si), 133.0 and 132.9 (2 x C, aryl *C*Si), 129.9 and 129.8 (4 x CH, aryl *C*H Ph_2 Si), 129.6 (2 x CH, aryl *C*H SO_2Tol), 127.8 and 127.7 (4 x CH, aryl *C*H Ph_2 Si), 127.3 (2 x CH, aryl *C*H SO_2Tol), 84.5, 82.5, 72.8 and 72.0 (4 x CH, C-3, C-4, C-5 and C-6), 63.8 (CH_2, C-7), 57.8 (CH, C-2), 52.5 (CH_3, CO_2CH_3), 26.8 (CH_3, $C(CH_3)_3$), 21.5 (CH_3, $ArCH_3$), 19.2 (C, $C(CH_3)_3$); (Found: M + H^+, 614.2250. $C_{31}H_{40}NO_8SSi$ requires M^+, 614.2244); *m/z* (FAB, NBA) 614 (M + H^+, 7%), 556 (62), 536 (100), 197 (82), 155 (53), 135 (92), 91 (60).

*(iii) Diol benzoylation to give **24***

To a solution of the silyl ether (525 mg, 0.855 mmol) in dichloromethane-pyridine (6:1, 8.5 cm^3) under nitrogen at 0 °C was added benzoyl chloride (975 mg, 655 µl, 5.64 mmol). The mixture was stirred overnight before it was hydrolysed with ice (10 g). After 1 h, the phases were separated and the aqueous

layer was extracted with dichloromethane (3 x 50 cm^3). The combined organic layers were washed with water and brine (5 cm^3 each) and evaporated to dryness. Flash column chromatography with ether-light petroleum (2:3) as the eluent afforded the *title compound* **24** as a foam (646 mg, 82%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 1732 (s), 1688, 1601 (w), 1361, 1316, 1113; δ_H (400 MHz; $CDCl_3$) 8.01 (2H, d, *J* 7.1, *o*-aryl C*H* *Ph*CO_2), 7.94 (2H, d, *J* 7.1, *o*-aryl C*H* *Ph*CO_2), 7.87-7.82 (4H, m, *o*-aryl C*H* Si^{t}Bu*Ph*$_2$), 7.50-7.22 (15H, m, aryl C*H*), 7.07-7.04 (4H, m, *m*-aryl C*H* Si^{t}Bu*Ph*$_2$), 6.98 (2H, t, *J* 7.8, *p*-aryl C*H* Si^{t}Bu*Ph*$_2$), 6.16 (1H, 'dd', *J* 5.7, 4-H), 5.98 (1H, 'dd', *J* 5.7, 5-H), 5.46 (1H, d, *J* 7.9, 2-H), 5.39 (1H, dd, *J* 7.9 and 5.7, 3-H), 4.53 (1H, d, *J* 5.7, 6-H), 4.08 (2H, br.s, CH_2OSi), 3.85 (3H, s, CO_2CH_3), 2.33 (3H, s, ArCH_3), 1.21 (9H, s, SiC(CH_3)$_3$); δ_C (67.5 MHz; $CDCl_3$) 170.6 (C, CO_2CH_3), 168.3 (C, Ph*C*(O)N), 165.0 and 164.9 (2 x C, PhCO_2), 144.7 (C, aryl CSO_2), 135.5 (C, aryl CCH_3), 135.1, 133.7, 133.0, 132.8, 130.2, 129.6, 129.5, 129.4, 129.1, 129.0, 128.9, 128.5, 128.0, 127.6 and 127.0 (22 x C and CH, aryl *C* and aryl *C*H), 83.3, 77.8, 74.1 and 71.5 (4 x CH, C-3, C-4, C-5 and C-6), 63.1 (CH_2, C-7), 61.7 (CH, C-2), 52.6 (CH_3, CO_2CH_3), 26.7 (CH_3, C(CH_3)$_3$), 21.3 (CH_3, ArCH_3), 19.0 (C, $C(CH_3)_3$); (Found: M + H^+, 926.2867. $C_{52}H_{52}NO_{11}SSi$ requires M^+, 926.2952); *m/z* (FAB, glycerol) 901 (M^+ - 24, 3%), 735 (7), 391 (4), 317 (9), 261 (7), 223 (21), 131 (22), 75 (33), 57 (23).

Deprotection of 24 and one carbon degradation of the resulting alcohol to give anomeric acetate 25

(i) Removal of the silyl protecting group

To a solution of the silyl ether **24** (526 mg, 0.57 mmol) in methanol-ether (1:1, 20 cm^3) under nitrogen at 0 °C was added acetyl chloride (0.38 cm^3, 5.35 mmol). The mixture was stirred at room temperature overnight before it was evaporated to dryness. The residue was partitioned against dichloromethane (75 cm^3) and aqueous $NaHCO_3$ (10 cm^3), the phases were separated and the organic layer was dried ($MgSO_4$) and evaporated to dryness. Flash column chromatography with ether-light petroleum (6:1) as the eluent afforded an intermediate primary alcohol as a foam (332 mg, 85%); (Found C, 63.00; H, 4.87; N, 2.13. $C_{36}H_{33}NO_{11}S$ requires C, 62.87; H, 4.84; N, 2.04%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3535 (b), 1731 (s), 1601 (w), 1353, 1316, 1125; δ_H (250 MHz; $CDCl_3$) 7.98 (2H, dd, *J* 8.5 and 1.4, *o*-aryl C*H* *Ph*CO_2), 7.97 (2H, dd, *J* 8.4 and 1.3, *o*-aryl C*H* *Ph*CO_2), 7.54-7.47 (2H, m, aryl C*H*), 7.44 (2H, d, *J* 8.4, aryl C*H* SO_2*Tol*), 7.38-7.28 (5H, m, aryl C*H*), 7.10 (2H, d, *J* 8.4, aryl C*H* SO_2*Tol*), 7.08 (4H, m, aryl C*H*), 5.79 (1H, 'dd', *J* 5.8, H-4), 5.77 (1H, 'dd', *J* 5.8, H-5), 5.55 (1H, d, *J* 5.8, H-2), 5.19 (1H, 'dd', *J* 5.8, H-3), 4.40 (1H, dd, *J* 3.0 and 5.8, H-6), 4.03 (1H, ddd, *J* 12.5, 4.9 and 3.0, C*H*HOH), 3.90 (1H, ddd, *J* 12.5, 8.3 and 3.0, CH*H*OH), 3.85 (3H, s, CO_2CH_3), 2.79 (1H, dd, *J* 8.3 and 4.9, O*H*, exchanged with D_2O), 2.38 (3H, s, ArCH_3); δ_C (67.5 MHz; $CDCl_3$) 170.5 (C, CO_2CH_3), 167.9 (C, Ph*C*(O)N), 165.2 and 164.9 (2 x C, PhCO_2), 144.9 (C, aryl CSO_2), 134.9 (C, aryl CCH_3), 133.6 (C, aryl *C* *Ph*C(O)N), 133.0, 132.9, 130.4,

129.5, 129.3, 129.0, 128.9, 128.3, 128.0, 127.3 and 127.2 (18 x C and CH, aryl *C* and aryl *C*H), 83.6 and 79.0 (2 x CH, C-3 and C-6), 73.5 and 72.2 (2 x CH, C-4 and C-5), 61.7 (CH_2, C-7), 60.8 (CH, C-2), 52.5 (CH_3, CO_2CH_3), 21.2 (CH_3, ArCH_3); *m/z* (CI, methane) 688 ($M + H^+$, 6%), 534 (21), 341 (4), 157 (64), 139 (24), 123 (100), 105 (62), 91 (13), 79 (25), 57 (11).

(ii) One-carbon degradation to give ***25***

To a degassed solution of the primary alcohol (118 mg, 0.172 mmol) in benzene (2.5 cm^3) under nitrogen was added lithium chloride (3 mg) and lead (IV) acetate (excess acetic acid removed under high-vacuum, 191 mg, 0.43 mmol). The brown solution was heated at reflux for 8 h 30 min during which time the solution decolourised and a white precipitate formed. The mixture was cooled, filtered through a pad of kieselguhr and washed with acetone (25 cm^3). The filtrate was filtered again to remove further precipitate, once more washing with acetone, and the colourless filtrate was evaporated to dryness. Flash column chromatography with ether-light petroleum (7:3) as the eluent afforded the β-anomer of the *title compound* **25** as a foam (78 mg, 64%); (Found C, 61.46; H, 4.93; N, 1.95. $C_{37}H_{33}NO_{12}S$ requires C, 62.09; H, 4.65; N, 1.96%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 1738 (s), 1684, 1601 (w), 1362, 1317, 1124, 1105; δ_H (400 MHz; $CDCl_3$) 7.93 (2H, d, *J* 8.8, *o*-aryl C*H* *Ph*CO_2), 7.92 (2H, d, *J* 8.0, *o*-aryl C*H* *Ph*CO_2), 7.52 (1H, t, *J* 6.8, *p*-aryl C*H* *Ph*CO_2), 7.45 (1H, t, *J* 6.8, *p*-aryl C*H* *Ph*CO_2), 7.38 (2H, d, *J* 8.2, aryl C*H* SO_2*Tol*), 7.35-7.25 (4H, m, aryl C*H*), 7.21 (1H, t, *J* 6.6, *o*-aryl C*H* *Ph*C(O)N), 7.07 (2H, d, *J* 8.2, aryl C*H* SO_2*Tol*), 6.96-6.89 (4H, m, aryl C*H*), 6.51 (1H, s, 6-H), 6.01 (1H, dd, *J* 7.6 and 4.8, 4-H), 5.89 (1H, d, *J* 4.8, 5-H), 5.56 (1H, 'dd', *J* 7.6, 3-H), 5.37 (1H, d, *J* 7.6, 2-H), 3.88 (3H, s, CO_2CH_3), 2.35 (3H, s, ArCH_3), 2.19 (3H, s, CH_3CO_2); δ_C (67.5 MHz; $CDCl_3$) 170.5 (C, C-1), 168.9 (C, CH_3CO_2), 168.5 (C, Ph*C*(O)N), 165.0 and 164.9 (2 x C, PhCO_2), 145.1 (C, aryl CSO_2), 134.9 (C, aryl CCH_3), 133.4, 133.3, 130.5, 129.8, 129.5, 129.1, 129.0, 128.8, 128.7, 128.6, 128.3, 128.2, 127.9, 127.6 and 127.3 (22 x C and CH, aryl *C* and aryl *C*H), 98.3 (CH, C-6), 78.7 (CH, C-3), 74.4 (CH, C-5), 73.2 (CH, C-4), 62.8 (CH, C-2), 53.0 (CH_3, CO_2CH_3), 21.5 (CH_3, ArCH_3), 21.1 (CH_3, CH_3CO_2); *m/z* (CI, methane) 730 ($M - H + CH_4^+$, 5%), 656 ($M - OAc^+$, 52%), 576 (9), 502 (20), 378 (28), 259 (77), 157 (94), 139 (53), 123 (100), 105 (90), 93 (28), 79 (39), 57 (24).

Vorbrüggen glycosidation to give the protected thymine polyoxin C 26

To a solution of the β-acetate **25** (84 mg, 0.117 mmol) in anhydrous acetonitrile (1 cm^3) under nitrogen at 0 °C was added trimethylsilyl trifluoromethanesulfonate (28 μl, 0.142 mmol) dropwise. After 1 min a solution of 2,4-bis(trimethylsilyloxy)-5-methylpyrimidine[33] (70 mg, 0.293 mmol) in acetonitrile (1.5 cm^3) was added dropwise and the mixture was stirred at 0 °C for 2 h. A second addition of trimethylsilyl trifluoromethane-sulfonate (100 μl) was made and the mixture was stirred for a further 1 h. The mixture

was quenched with aqueous $NaHCO_3$ (2 cm^3), extracted with chloroform (3 x 10, cm^3) and the combined organic layers were dried ($MgSO_4$) and evaporated to dryness. Flash column chromatography with methanol-chloroform (1:99) as the eluent afforded only the *N*-1 β-anomer of the *title compound* **26** as a colourless oil (78 mg, 85%); υ_{max}(film)/cm^{-1} 3686, 3625, 1728 (s), 1697 (s), 1604, 1463, 1019; δ_H (250 MHz; $CDCl_3$) 8.95 (1H, br.s, pyrimidinyl N*H*), 7.97 (2H, dd, *J* 1.3 and 8.4, *o*-aryl C*H* *Ph*CO_2), 7.87 (2H, dd, *J* 1.3 and 8.4, *o*-aryl C*H* *Ph*CO_2), 7.55 (2H, d, *J* 8.3, aryl C*H* SO_2*Tol*), 7.48 (2H, m, *p*-aryl C*H* *Ph*CO_2), 7.40-7.27 (7H, m, aryl C*H*), 7.16 (2H, d, *J* 8.3, aryl C*H* SO_2*Tol*), 7.13 (1H, s, 6-H), 7.11 (2H, d, *J* 1.4, aryl C*H*), 6.27 (1H, d, *J* 5.5, 1'-H), 6.09 (1H, dd, *J* 5.1 and 6.6, 3'-H), 5.99 (1H, dd, *J* 5.5 and 6.6, 2'-H), 5.60, (1H, d, *J* 5.8, 5'-H), 5.09 (1H, 'dd', *J* 5.4, 4'-H), 3.84 (3H, s, CO_2CH_3), 2.38 (3H, s, ArCH_3), 1.98 (3H, s, pyrimidinyl CH_3); δ_C (67.5 MHz; $CDCl_3$) 171.3 (C, C-6'), 168.5 (C, Ph*C*(O)N), 165.6 and 165.5 (2 x C, PhCO_2), 164.0 (C, C-4), 150.6 (C, C-2), 145.7 (C, aryl CSO_2), 137.1 (CH, C-6), 135.4 (C, aryl CCH_3), 134.3, 133.9, 133.8, 131.4, 130.2, 129.7, 129.2, 129.1, 128.8, 128.7, 128.1 and 128.0 (20 x C and CH, aryl *C* and aryl *C*H), 112.2 (C, C-5), 89.3 (CH, C-1'), 81.8 (CH, C-4'), 73.4 (CH, C-2') 72.3 (CH, C-3'), 61.1 (CH, C-5'), 53.4 (CH_3, CO_2CH_3), 22.0 (CH_3, ArCH_3), 12.8 (CH_3, pyrimidinyl CH_3); (Found: M + H^+, 782.0097. $C_{40}H_{36}N_3O_{12}S$ requires M^+, 782.2020); *m/z* (CI, methane) 782 (M + H^+, 1%), 623 (4), 502 (8), 459 (17), 380 (5), 258 (15), 157 (67), 127 (93), 123 (100), 105 (87), 79 (27), 57 (10).

N-Desulfonylation of 26 under free radical conditions to give 27

To a degassed solution of the β-nucleoside **26** (70 mg, 0.09 mmol) in toluene (4 cm^3) under nitrogen at reflux was added a solution of tributyltin hydride (27 μl, 0.1 mmol) and AIBN (2.8 mg, 0.017 mmol) in toluene (1 cm^3) dropwise. After 5 h, a further addition of tributyltin hydride (60 μl) was made together with additions of AIBN (~2 mg) every 30 min for 6 h. The mixture was cooled, evaporated to dryness and partitioned against ether and 8% aqueous potassium fluoride solution (5 cm^3 each). After stirring for 2 h, the aqueous phase was extracted with ether (3 x 20 cm^3) and the combined organic layers were washed with water and brine (2 cm^3 each), dried ($MgSO_4$) and evaporated to dryness. Flash column chromatography with ethyl acetate-dichloromethane (3:7) as the eluent afforded the *title compound* **27** as a white solid (13 mg, 23%); (Found C, 62.87; H, 4.90; N, 6.83. $C_{33}H_{29}N_3O_{10}$ requires C, 63.15; H, 4.66; N, 6.70%); υ_{max}($CHCl_3$)/cm^{-1} 3387, 1729 (s), 1695 (s), 1602, 1463, 1316, 1124; δ_H (400 MHz; $CDCl_3$) 8.80 (1H, br. s, pyrimidinyl N*H*), 7.98 (2H, dd, *J* 1.3 and 8.3, *o*-aryl C*H* *Ph*CO_2), 7.94 (2H, dd, *J* 1.2 and 8.3, *o*-aryl C*H* *Ph*CO_2), 7.91 (2H, dd, *J* 1.2 and 8.4, *o*-aryl C*H* *Ph*C(O)N), 7.61-7.32 (9H, m, *m*-and *p*-aryl C*H*), 7.16 (1H, d, *J*, 1.1, 6-H), 6.04 (1H, 'dd', *J* 6.1, 5'-H), 5.99 (1H, d, *J* 4.3, 1'-H), 5.75 (1H, dd, *J* 4.5 and 6.6, 3'-H), 5.31 (1H, 'dd', *J* 4.3 and 6.6, 2'-H), 4.88 (1H, dd, *J* 4.5 and 6.1, 4'-H), 3.77 (3H, s, CO_2CH_3), 1.90 (3H, d, *J* 1.1, 5-CH_3); δ_C (100 MHz; $CDCl_3$) 169.3 (C, C-6'), 167.6 (C, Ph*C*(O)N), 165.5 and 165.4 (2 x

C, Ph*C*O_2), 163.2 (C, C-4), 150.3 (C, C-2), 136.9 (CH, C-6), 133.8, 133.0, 132.2, 129.8, 128.6, 128.5, 128.3, 127.4 and 127.3 (18 x C and CH, aryl *C* and aryl *C*H), 112.2 (C, C-5), 90.6 (CH, C-1'), 81.6 (CH, C-4'), 73.8 (CH, C-2') 70.4 (CH, C-3'), 54.2 (CH, C-5'), 53.0 (CH_3, CO_2CH_3), 12.3 (CH_3, pyrimidinyl *C*H_3); (Found: M + H^+, 628.1993. $C_{33}H_{29}N_3O_{10}$ requires M^+, 628.1931); *m/z* (CI, methane) 628 (M + H^+, 7%), 502 (11), 380 (7), 258 (34), 127 (93), 123 (90), 105 (100), 79 (39), 57 (7).

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