A short and efficient stereoselective synthesis of the potent 5-lipoxygenase inhibitor, CMI-977

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A short and efficient synthesis of the potent 5-lipoxygenase inhibitor CMI-977 has been accomplished, utilising an oxygen to carbon rearrangement of an anomerically linked alkynyl stannane tetrahydrofuranyl ether derivative as the key step.

Asthma is a chronic inflammatory disease, typically featuring the symptoms of bronchoconstriction, increased airways responsiveness, increased microvascular permeability and hypersecretion of mucus; these effects being complicated by acute periodic inflammatory changes. Despite the complexity of the biochemical interactions involved in eliciting these varied symptoms, unexpectedly high efficacy has been observed in clinical trials that target a single group of pharmacological mediators. Specifically these drugs have been designed to block the synthesis or activity of the leukotrienes (LT).1-3

Leukotrienes are metabolites of arachidonic acid, produced by the activity of 5-lipoxygenase (5-LO). Certain classes of these leukotrienes, specifically the cysteinyl leukotrienes and LTB4, are produced by a variety of inflammatory cells and demonstrate physiological effects that mimic the recognised pathophysiological features of asthma listed above. CMI-977 1 is a potent 5-LO inhibitor that is known to block the generation of these leukotrienes. In particular, 1 was found to be a potent inhibitor of LTB4 production in ionophore human whole blood and on this basis was selected for further development for the prophylactic treatment of chronic asthma.4

We have recently introduced a new general method for the efficient synthesis of tetrahydropyran (THP) and tetrahydrofuran (THF) rings containing substituents adjacent to the oxygen atom (Scheme I). A range of anomerically linked carbon centred nucleophiles including electron rich alkenes,5-7 silyl enol ethers8-10 and alkynylstannanes11 have been shown to rearrange in the presence of Lewis acid to afford the carbon-linked products in good yields. This methodology is particularly suited to target oriented synthesis, as it necessarily combines anomeric activation with side chain heteroatom protection.

In this work we wish to report the utility of the anomeric oxygen to carbon rearrangement of an alkynylstannane tetrahydrofuranyl ether derivative in the short and efficient synthesis of the potent 5-LO inhibitor CMI-977.12

Results

Two different approaches to 1 were conceived, which differed in the timing of the introduction of the para-fluorophenol (pFP) substituent (Scheme II). Thus in route (i) it was envisaged that the bulky tert-butyldiphenylsilyl (TBDPS) protecting group in precursor 2 would bias the diastereoselectivity of the rearrangement reaction to favour formation of a trans-di-substituted THF ring, as had previously been observed in our synthesis of muricatetocin C.13 Conversely, route (ii) incorporates the pFP moiety (precursor 3) prior to the rearrangement step. This would allow a shorter route to 1 however, the diastereoselection of the key step is less predictable.
Initial investigations towards the synthesis of 1 concentrated on route (i). Lactol 5 was readily available in 70% yield over three steps starting from \((R)\)-glycidol 4. TBDPS protection of the free hydroxyl followed by copper mediated epoxide ring opening reaction with allyl magnesium bromide and subsequent ozonolysis of the terminal olefin with \textit{in situ} ring closing proceeded as previously reported (Scheme III).\(^{13}\) Heating 5 in the presence of \textit{homo}-propargylic alcohol and catalytic ambersyt\(^{10}\) A15 in benzene at reflux afforded the tetrahydrofuranyl ether 6 in 95% yield as a 3:2 mixture of anomers. With multigramme quantities of 6 available the anomeric oxygen to carbon rearrangement was attempted according to the original two step protocol.\(^{11}\) Thus deprotonation of 6 with butyllithium (1.2 eq) at \(-78^\circ\)C followed by treatment with tributyltin chloride (1.15 eq) afforded, after work up, the tributylstannylated material 3. This material was not purified, but was dissolved in dichloromethane, cooled to \(-10^\circ\)C and treated with boron trifluoride etherate (3.0 eq) for 5 minutes before the reaction mixture was quenched by the addition of sodium hydroxide. Aqueous work up and inspection of the crude \(^1\)H NMR indicated that the reaction had generated the carbon linked products 7 and 8 in a 5:1 ratio favouring the \textit{trans}-product. Unfortunately at this stage the diastereoisomers were not found to be separable by chromatography.

Introduction of the \textit{N}-hydroxy urea portion proceeded by displacement of the hydroxyl group released during the rearrangement step. Thus treatment of a mixture of 7 and 8 with \textit{N,O}-diphenoxycarbonyl hydroxylamine (1.1 eq),\(^{14}\) triphenyl phosphine (1.15 eq) and diisopropylazodicarboxylate (DIAD) (1.15 eq) according to a Mitsunobu protocol, delivered 9 and 10 in 87% yield (Scheme IV).\(^{15}\) Initial attempts at removing the TBDPS group using TBAF in THF failed, producing an intractable mixture of compounds. However, reaction in the presence of hydrofluoric acid-pyridine complex in THF slowly (60% conversion after 2 days) cleaved the silyl ether to afford 11 and 12 with no observable by-products. Unfortunately neither transformation permitted chromatographic separation of the epimeric mixture. At this stage introduction of the aryl unit followed by amidolysis was required to complete the synthesis. Thus, 11 and 12 were subjected to the Mitsunobu conditions in the presence of pFP however disappointingly, this failed to realise the desired aryl ether, resulting instead in complete decomposition of the starting material. Other attempts at this transformation focussed on the pre-preparation of an activated leaving group, which could subsequently be displaced by the phenol moiety. Functional groups incorporated included a mesylate (13 and 14), a bromide (15 and 16) and a triflate (17) however none of these compounds underwent displacement to afford any appreciable amounts of the aryl ether. It was also disappointing to find that in the preparation of these compounds no separation of the epimeric mixture was observed.

It appeared that the phenoxy carbonate protecting group of the \textit{N}-hydroxy urea was extremely base sensitive, and that as soon as this \textit{N}-hydroxyl was free it became a competitive nucleophile resulting in a failure to realise any conversion to the desired aryl ether. Although the potential existed for a change in the protecting group strategy, the lack of any observed separation of the epimeric mixture was also a concern. Thus, with these results in mind, it was decided to abandon route (i) and pursue the potentially more rewarding route (ii).
**Scheme III**—Reagents and Conditions: [i]. TBDPSCI, NEt3, DMAP, CH2Cl2, 24 hr, rt, (85%); [ii]. allylMgBr, CuLi2Cl4, (10 mol%), THF, 15 min, 2 hr, −30 °C, (89%); [iii]. O3, NaHCO3, CH2Cl2, 20 min, −78 °C; PPh3, 14 h, −78 °C → rt, (93%); [iv]. but-3-yn-1-ol, Amberlyst A-15®, benzene, 15 min, reflux, (95%); [v]. n-BuLi, THF, 30 min, −78 °C; Bu3SnCl, 30 min, −78 °C → rt; [vi]. BF3·OEt2, CH2Cl2, 5 min, −10 °C, (75%, 2 steps; 7/8, 5:1).

**Scheme IV**—Reagents and Conditions: [i]. PPh3, DIAD, N,O-diphenoxycarbonyl hydroxylamine, THF, 0°C → rt, (87%); [ii]. HF·pyridine, THF, rt, (63%, 100% brsm); [iii]. MsCl, NEt3, CH2Cl2, 0 °C, (85%); [iv]. PPh3, CBr4, CH2Cl2, 0 °C → rt, (50%); [v]. Tf2O, NEt3, CH2Cl2, −78°C, (used crude).

Route (ii) began with commercially available (S)-γ-hydroxymethyl-γ-butyrolactone 18 (Scheme V). Conversion of the free hydroxyl to the para-fluorophenoxy ether proceeded by treatment with pFP (1.1 eq), DIAD (1.15 eq) and triphenylphosphine (1.15 eq) in THF at 0°C to reflux to afford 19 in 73%. Subsequent reduction with DIBAL-H (1.1 eq) in toluene at −78°C afforded lactol 20 as a 3:2 mixture of anomers in excellent yield. Preparation of the homopropargylic acetal 21 and the ensuing anomeric oxygen to carbon rearrangement step was achieved using the same protocol developed for route (i), to afford 22 and 23 in a 2:1 ratio in good combined yield.

As predicted, the trans-selectivity of the reaction decreased due to the reduced steric bulk of the aryl ether side chain. However, pleasingly in this case the rearrangement products were found to be completely separable by MPLC chromatography to afford diastereomerically pure 22 in 57% isolated yield. Furthermore single crystal X-ray diffraction of 22 was obtained providing unambiguous proof of the assigned trans-stereochemistry (Figure 2).

With 22 in hand conversion to CMI-977 was possible following a modification of a 2 step literature procedure (Scheme VI). Mitsunobu reaction with N,O-diphenoxycarbonyl hydroxylamine converted the free hydroxyl group of 22 to the protected N-hydroxy urea derivative 24, as described in route (i). Direct amination of this material by treatment with concentrated ammonium hydroxide at room temperature for 20 hours then gave 1 in 59% yield as a white amorphous solid. All physical and spectroscopic data (1H NMR, 13C NMR, IR and melting point) were in excellent agreement with the reported values and the specific
Scheme V—Reagents and Conditions: [i]. p-fluorophenol, PPh₃, DIAD, THF, 0°C → reflux, 3 hr, (73%); [ii]. DIBAL-H, toluene, -78°C, (100%); [iii]. but-3-yn-1-ol, Amberlyst A-15®, benzene, reflux, 15 min, (96%); [iv]. n-BuLi, Bu₃SnCl, -78°C → rt, 30 min; [v]. BF₃·OEt₂, CH₂Cl₂, -10°C, 5 min, (2 steps, 85%; 22/23, 2:1).

Scheme VI—Reagents and Conditions: [i]. PPh₃, DIAD, N,O-diphenoxycarbonyl hydroxylamine, THF, 0°C → rt, (91%); [ii]. Ammonia 0.88 specific gravity, rt, 12 hr, (59%).

Experimental Section

General. All reactions were carried out under an atmosphere of argon, and those not involving aqueous reagents were carried out in oven dried glassware, cooled under vacuum. Melting points were measured on a Reichert hot stage apparatus, and are uncorrected. Optical rotations were measured on an Optical Activity AA-1000 polarimeter, and [α]₀ values are reported in 10⁻¹ deg cm² g⁻¹; concentration (c) is in g/100 mL. IR spectra were obtained on a FTIR 1620 spectrometer, from a thin film deposited onto a sodium chloride plate or mixed with potassium bromide as a tablet. Microanalyses were performed in the microanalytical laboratories at the Department of Chemistry, Lensfield Road, Cambridge. Mass spectra and accurate mass data were obtained on a Micromass Platform LC-MS, Kratos MS890MS or Bruker BIOAPEX 4.7 T FTICR spectrometer, by electron ionisation, chemical ionisation or fast atom/ion bombardment techniques at the Department of Chemistry, Lensfield Road, Cambridge. ¹H NMR spectra were recorded in CDCl₃, on a Bruker DPX-400 spectrometer, at 400 MHz, with residual protic solvent CHCl₃ as the internal reference (δ_H = 7.26 ppm); Chemical

Conclusion

In summary a short and efficient synthesis of the potent 5-LO inhibitor CMI-977 has been achieved in 20% yield over 7 steps (79% average), using a stereoselective anomeric oxygen to carbon rearrangement of an alkynylstannane tetrahydrofuranyl ether derivative as the key step. We believe that this type of rearrangement involving both THF and THP ring systems will find further application in target orientated synthesis in the future.
shifts ($\delta$) are given in parts per million (ppm), and coupling constants ($J$) are given in Hertz (Hz). $^{13}$C NMR spectra were recorded in CDCl$_3$ on the same spectrometer at 100 MHz, with the central peak of NMR spectra were recorded in CDCl$_3$ on the same spectrometer at 100 MHz, with the central peak of NMR spectra were recorded in CDCl$_3$ on the same spectrometer at 100 MHz, with the central peak of NMR spectra were recorded in CDCl$_3$ on the same spectrometer at 100 MHz, with the central peak of NMR spectra were recorded in CDCl$_3$ on the same spectrometer at 100 MHz, with the central peak of.

The proton spectra are reported as follows: $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.73-7.71 (4H, m, Ph), 7.47-7.41 (6H, m, Ph), 5.89-5.78 (1H, m, CH=CH$_2$), 5.06-4.97 (2H, m, CH=CH$_2$), 3.82-3.75 (1H, m, CHO), 3.72 (1H, dd, J 10.1 and 3.4, CHHOSi), 3.56 (1H, dd, J 10.1 and 7.3, CHHOSi), 2.57 (1H, d, J 3.7, OH), 2.27-2.09 (2H, m, CH$_2$CH=CH$_2$), 1.64-1.47 (2H, m, CH$_2$CHOH) and 1.13 (9H, s, C(CH$_3$)$_3$); $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ = 138.3 (Ph), 135.6 (Ph), 133.2 (ipso C-Si), 129.9 (CH=CH$_2$), 127.8 (Ph), 114.8 (CH=CH$_2$), 71.4 (CHOH), 68.0 (CH$_2$OSi), 32.0 (CH$_2$), 29.8 (CH$_2$), 26.9 (C(CH$_3$)$_2$) and 19.3 (C(CH$_3$)$_2$); IR (film): 3430 (br, OH), 3072, 2931, 2858 (C-H), and 1640 (C=C) cm$^{-1}$. $m/z$ (EI) 337.2 (33%, M – OH), 207.7 (52%, M – C$_3$H$_7$) and 199.1 (100%, M = 2 × Ph). Anal. Found: C, 74.6; H, 8.48. C$_{22}$H$_{30}$O$_2$Si requires C, 74.5; H, 8.53%.

(2R/S, 5S)-5-(tert-Butyldiphenylsilyloxy)methyl-tetrahydrofuran-2-ol 5

(2S)-1-(tert-Butyldiphenylsiloxy)prop-2-enoxide.

Triethylamine (16.8 mL, 121 mmole) and dimethylaminopyridine (2.80 g, 22.6 mmole) were added to a stirred solution of (R)-(+)-glycidol 4 (5.60 g, 75.3 mmole) in dichloromethane (150 mL), and the reaction mixture was stirred for 24 hr. Hydrochloric acid solution (1.5 mL, 15 mmole) followed by sodium bicarbonate (1.50 g) at -78°C, was added and the reaction mixture became light blue (about 20 min). Triphenylphosphine (9.00 g, 34.4 mmole) was added and the reaction mixture was then warmed to rt and stirred for 14 hr, at which point the solvent was removed in vacuo. Purification by flash column chromatography, eluting with 40/60 petroleum ether-diethyl ether (10:1) afforded lactol (5.60 g, 75.3 mmole) in dichloromethane (250 mL) at -78°C. $\delta$ was then bubbled through until the reaction mixture became light blue (about 20 min). Triphenylphosphine (9.00 g, 34.4 mmole) was added and the reaction mixture, which was then warmed to rt and stirred for 14 hr, at which point the solvent was removed in vacuo. Purification by flash column chromatography, eluting with 40/60 petroleum ether-diethyl ether (10:1→10:1) afforded lactol 5 (9.47 g, 93%), an oil, as an inseparable mixture of anomers (3.2; assigned by integration of the peaks at $\delta_6$ (major) 5.59 (1H, t, br), J 3.2, (H-2) and $\delta_6$ (minor) 5.54 (1H, dd, J 6.6 and 3.6, H-2)]. $R_0$ 0.25 (40/60 petroleum ether-diethyl ether, 1:1); $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ (major) 7.73-7.69 (4H, m, Ph), 7.45-7.37 (6H, m, Ph), 5.59 (1H, t (br), J 3.2, (H-2), 4.41-4.35 (1H, m, H-5), 3.66 (2H, d, J 4.7, CH$_2$OSi), 3.27 (1H, d, J 2.3, OH), 2.20-1.70 (4H, m, H$_2$-3 and H$_2$-4) and 1.08 (9H, s, C(CH$_3$)$_2$); $^{13}$C NMR (400 MHz; CDCl$_3$): $\delta$ (minor) 7.73-7.69 (4H, m, Ph), 7.45-7.37 (6H, m, Ph), 5.48 (1H, dd, J 6.6 and 3.6, H-2), 4.27-4.22 (2H, m, H-5), 3.84 (1H, dd, J 10.8 and 3.6, CHHOSi), 3.63

To a stirred solution of (2S)-1-(tert-butyldiphenylsiloxymethyl)tetrhydrofuran-2-ol.

Sodium bicarbonate (1.50 g) was added to a stirred solution of (2S)-1-(tert-butyldiphenylsiloxymethyl)tetrhydrofuran-2-ol.

Sodium bicarbonate (1.50 g) was added to a stirred solution of (2S)-1-(tert-butyldiphenylsiloxymethyl)tetrhydrofuran-2-ol. Sodium bicarbonate (1.50 g) was added to a stirred solution of (2S)-1-(tert-butyldiphenylsiloxymethyl)tetrhydrofuran-2-ol. Sodium bicarbonate (1.50 g) was added to a stirred solution of (2S)-1-(tert-butyldiphenylsiloxymethyl)tetrhydrofuran-2-ol. Sodium bicarbonate (1.50 g) was added to a stirred solution of (2S)-1-(tert-butyldiphenylsiloxymethyl)tetrhydrofuran-2-ol.
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\text{\begin{align*}
\text{δ (major)} & : 7.56-7.52 (4H, m, \text{Ph}), 7.48-7.43 (4H, m, \text{Ph}), 7.41-7.37 (6H, m, \text{Ph}), 7.35-7.31 (1H, d, J = 10.3 \text{ Hz}), 7.03-6.99 (1H, m, C=CH) \\
\text{δ (minor)} & : 7.61-7.57 (2H, m, C=CH), 7.48-7.44 (1H, m, C=CH), 7.38-7.35 (1H, d, J = 7.5 \text{ Hz})
\end{align*}}
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2.49 (2H, td, J 6.3 and 1.8, C(CH$_3$)$_2$), 2.25-2.08 (3H, m, H$_2$-3 and OH$_2$), 2.00-1.85 (2H, m, H$_2$-4) and 1.06 (9H, s, (C(CH$_3$)$_2$)$_2$); $^1$H NMR (400 MHz; CDCl$_3$): δ (major) 7.72-6.66 (m, 4H, Ph), 7.44-7.36 (6H, m, Ph), 4.56 (1H, m, H-5), 4.07 (1H, m, H-2), 3.7 (1H, dd, J 10.5 and 4.7, CHHOSi), 3.67-3.63 (3H, m, CHHOSi and CH$_2$OH), 2.42 (2H, td, J 6.4 and 1.8, C=CCH$_2$), 2.25-2.08 (3H, m, H$_2$-3 and OH$_2$), 2.00-1.85 (2H, m, H$_2$-4) and 1.08 (9H, s, (C(CH$_3$)$_2$)$_2$); $^{13}$C NMR (100 MHz; CDCl$_3$): δ (major) 135.6 (Ph), 133.7 (ipso C-Si), 129.6 (Ph), 127.7 (Ph), 82.5 (CH=C), 81.5 (CH=CH$_2$), 79.2 (C-2), 68.8 (C-5), 66.0 (CH$_2$OSi), 61.0 (CH$_2$OH), 33.7 (C-3), 27.5 (C-4), 26.8 (C(CH$_3$)$_2$), 23.2 (C=CCH$_2$) and 19.2 (C(CH$_3$)$_2$); $^{13}$C NMR (100 MHz; CDCl$_3$): δ (minor) 135.6 (Ph), 133.7 (ipso C-Si), 129.6 (Ph), 127.6 (Ph), 82.5 (CH=C), 81.5 (CH=CH$_2$), 80.0 (C-2), 68.8 (C-5), 65.8 (CH$_2$OSi), 61.0 (CH$_2$OH), 33.4 (C-3), 28.2 (C-4), 26.8 (C(CH$_3$)$_2$), 23.2 (C=CCH$_2$) and 19.2 (C(CH$_3$)$_2$); IR (film): 3412 (br, O-H), 3060, 2932, 2857 (C-H) and 1589 cm$^{-1}$ (Ph); m/z (FAB) 431.4 (30%), M+Na, 199.1 (58%) and 135 (100%). Anal. Found: C, 73.4; H, 7.99. C$_2$H$_5$O$_2$Si requires C, 73.5; H, 7.89%.

(2S, 5S)-2-(tert-Butyldiphenylsilyloxy)methyl)-5-(1-N, O-bis(phenoxycarbonyl)hydroxyaminobut-3-ynyl)tetrahydrofuran 10 and (2S, 5R)-2-(tert-Butyldiphenylsilyloxy)methyl)-5-(1-N, O-bis(phenoxycarbonyl)hydroxyaminobut-3-ynyl)tetrahydrofuran 9. A solution of disopropyl azodicarboxylate (DIAD) (0.82 mL, 4.16 mmole) in THF (1.5 mL) was added dropwise via syringe to a stirred solution of 7 and 8 (1.48 g, 3.65 mmole), N,O-bis(phenoxycarbonyl)hydroxylamine (1.09 g, 9.89 mmole) and triphenylphosphine (1.09 g, 4.16 mmole) in THF (15 ml) at 0°C. The reaction mixture was allowed to warm to rt, stirred for 30 min and then concentrated in vacuo. The resulting residue was purified by flash column chromatography, eluting with 40/60 petroleum ether-diethyl ether (10:1→4:1) to afford the fully protected N-hydroxy amines 9 and 10 (2.09 g, 87%) as an oil, in an inseparable mixture of trans and cis isomers 9/10, 1:5; assigned by integration of the peaks at δ$_H$ (major) 4.70 (1H, t, br, J 6.0, H-5) and δ$_H$ (minor) 4.58 (1H, t, br, J 6.2, H-5). R$_f$ 0.28 (40-60 petroleum ether-diethyl ether, 2:1); $^1$H NMR (400 MHz; CDCl$_3$): δ (major) 7.74-7.67 (4H, m, Ph), 7.45-7.36 (10H, m, Ph), 7.31-7.24 (4H, m, Ph), 7.23-7.18 (2H, m, Ph), 4.70 (1H, t, br, J 6.0, H-5), 4.29-4.23 (1H, m, H-2), 4.05 (2H, t, J 7.2, CH$_2$N), 3.68 (2H, d, J 4.4, CH$_2$OSi), 2.76 (2H, td, J 7.2 and 1.3, C=CCH$_2$), 2.25-2.09 (2H, m, H$_2$-3), 2.03-1.88 (2H, m, H$_2$-4) and 1.08 (9H, s, C(CH$_3$)$_2$); $^1$H NMR (400 MHz; CDCl$_3$): δ (minor) 7.74-7.67 (4H, m, Ph), 7.45-7.36 (10H, m, Ph), 7.31-7.24 (4H, m, Ph), 7.23-7.18 (2H, m, Ph), 4.58 (1H, t, br, J 6.2, H-5), 4.29-4.23 (1H, m, H-2), 3.97 (2H, t, J 7.2, CH$_2$N), 3.81 (1H, dd, J 10.4 and 4.7, CHHOSi), 3.71-3.66 (1H, m, CHHOSi), 2.69 (2H, td, J 7.2 and 1.3, C=CCH$_2$), 2.25-2.09 (2H, m, H$_2$-3), 2.03-1.88 (2H, m, H$_2$-4) and 1.09 (9H, s, C(CH$_3$)$_2$); $^{13}$C NMR(100 MHz; CDCl$_3$): δ (major) 153.4 (CO$_2$Ph), 152.7 (CO$_2$Ph), 150.9 (ipso C-O), 150.6 (ipso C-O), 153.6 (Ph), 133.8 (ipso C-Si), 129.7 (Ph), 129.6 (Ph), 129.5 (Ph), 127.9 (Ph), 126.9 (Ph), 126.2 (Ph), 121.4 (Ph), 120.6 (Ph), 82.4 (CH=C), 80.5 (CH=CH$_2$), 79.2 (C-2), 68.8 (C-5), 66.0 (CH$_2$OSi), 49.7 (CH$_2$N), 33.6 (C-3), 27.5 (C-4), 26.9 (CH$_2$OSi), 19.3 (C(CH$_3$)$_2$) and 17.8 (C=CCH$_2$); IR (film): 3071, 2932, 2846 (C-H), 1808 (C=O), 1750 (C=O), 1584 and 1494 cm$^{-1}$ (Ph); m/z (FAB) 686.2535 (C$_{35}$H$_{46}$NO$_2$SiNa requires 686.2544); m/z (FAB) 687 (100%, M+Na), 664 (25%, M), 606 (66%, M-C$_6$H$_4$), 586 (82%, M-Ph), and 356 (48%).

(2S, 5S)-2-(hydroxymethyl)-5-(1-N, O-bis(phenoxycarbonyl)hydroxyaminobut-3-ynyl)tetrahydrofuran 12 and (2S, 5R)-2-(hydroxymethyl)-5-(1-N, O-bis(phenoxycarbonyl)hydroxyaminobut-3-ynyl)tetrahydrofuran 11. Hydrofluoric acid pyridine complex (2.4 M in THF, 3.50 mL, 8.40 mmole) was added dropwise to a stirred solution of 9 and 10 (1.85 g, 2.80 mmole) in THF (3.5 mL) at rt. After 48 hr, the reaction mixture was diluted with diethyl ether (50 mL) and washed with saturated copper sulfate solution (2 x 30 mL), water (30 mL) and saturated sodium chloride solution (30 mL), dried (MgSO$_4$), filtered and concentrated in vacuo. Purification by flash column chromatography eluting with 40/60 petroleum ether-diethyl ether (1:1→1:2) then neat diethyl ether afforded primary alcohols 11 and 12 [750 mg, 63% (100% brsn)] as an oil, in an inseparable mixture of trans and cis isomers [11/12, 1:5; assigned by integration of the peaks at δ$_H$ (major) 4.68 (1H, t, br, J 6.2, H-5) and δ$_H$ (minor) 4.62 (1H, m, H-5)]. R$_f$ 0.28 (di-
ethyl ether); \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) (major) 7.43-7.37 (4H, m, Ph), 7.31-7.24 (4H, m, Ph), 7.18 (2H, d, J 7.8, Ph), 4.68 (1H, t (br), J 6.2, H-5), 4.25-4.19 (1H, m, H-2), 4.03 (2H, t, J 7.2, CH\(_2\)N), 3.68 (1H, dd, J 11.7 and 2.9, CH\(_2\)OH), 3.48 (1H, dd, J 11.7 and 5.5, CH\(_2\)OH), 2.74 (2H, td, J 7.2 and 1.4, C=CCH\(_3\)), 2.20-2.12 (1H, m, H-3), 2.10-1.90 (3H, m, H-3, H-4 and OH) and 1.75-1.67 (1H, m, H-4); \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) (minor) 7.43-7.37 (4H, m, Ph), 7.31-7.24 (4H, m, Ph), 7.18 (2H, d, J 7.8, Ph), 4.62 (1H, m, H-5), 4.09-4.04 (1H, m, H-2), 4.04-4.01 (2H, m, CH\(_2\)N), 3.71 (1H, dd, J 11.7 and 3.0, CH\(_2\)OH), 3.57 (1H, dd, J 11.7 and 5.2, CH\(_2\)OH), 2.75-2.72 (2H, m, C=CCH\(_3\)), 2.20-2.12 (1H, m, H-3), 2.10-1.90 (3H, m, H-3, H-4 and OH) and 1.75-1.67 (1H, m, H-4); \(^13\)C NMR (100 MHz; CDCl\(_3\)): \(\delta\) (major) 155.4 (CO\(_2\)Ph), 152.6 (CO\(_2\)Ph), 150.9 (ipso \(\text{C}_\text{o}-\text{O}\)), 150.5 (ipso \(\text{C}_\text{o}-\text{O}\)), 129.7 (Ph), 129.5 (Ph), 126.7 (Ph), 126.2 (Ph), 121.4 (Ph), 120.5 (Ph), 82.5 (CHC=C), 80.9 (CHC=C), 79.2 (C-2), 68.7 (C-5), 64.6 (CH\(_2\)OH), 49.6 (CH\(_2\)N), 33.7 (C-3), 26.8 (C-4) and 17.8 (C=CCH\(_3\)); \(^13\)C NMR (100 MHz; CDCl\(_3\)): \(\delta\) (minor) = 155.4 (CO\(_2\)Ph), 152.6 (CO\(_2\)Ph), 150.9 (ipso \(\text{C}_\text{o}-\text{O}\)), 150.5 (ipso \(\text{C}_\text{o}-\text{O}\)), 129.7 (Ph), 129.5 (Ph), 126.7 (Ph), 126.2 (Ph), 121.4 (Ph), 120.5 (Ph), 82.5 (CHC=C), 80.9 (CHC=C), 80.5 (C-2), 68.8 (C-5), 64.7 (CH\(_2\)OH), 49.6 (CH\(_2\)N), 33.7 (C-3), 26.7 (C-4) and 17.8 (C=CCH\(_3\)); m/z (FAB) 426.2 (100%, M+H), 136.1 (93%) and 107.1 (60%). Anal. Found: C, 65.0; H, 5.44; N, 3.3. C\(_6\)H\(_5\)NO\(_2\) requires C, 64.9; H, 5.45; N, 3.3%.

(2S, 5S)-2-(Bromomethyl-5-(1-N-\(O\)-bis(phenoxycarbonyl) hydroxyaminobut-3-ynyl) tetrahydrofuran 15 and (2S, 5R)-2-(Bromomethyl)-5-(1-N-\(O\)-bis(phenoxycarbonyl) hydroxyaminobut-3-ynyl) tetrahydrofuran 16. A solution of triphenylphosphine (35 mg, 0.13 mmole) in dichloromethane (0.2 mL) was added dropwise via syringe to a solution of \(11 + 12\) (51 mg, 0.12 mmole) and tetrabromomethane (44 mg, 0.13 mmole) in dichloromethane (0.4 mL) at 0°C. The reaction mixture was then allowed to warm to rt, stirred for 14 hr, passed through a small pad of silica (eluting with dichloromethane) and concentrated in vacuo. Purification by flash column chromatography eluting with 40/60 petroleum ether-diethyl ether (20:1 then 1:1) afforded bromides 15 and 16 (31 mg, 50%) as an oil, as an inseparable mixture of trans and cis isomers [15/16, 5:1; assigned by integration of the peaks at \(\delta_{\text{h}}\) (major) 4.71 (1H, t (br), J 5.9, H-5) and \(\delta_{\text{h}}\) (minor) 4.63 (1H, dd, J 6.5 and 4.4, H-5)]. \(R_f\) 0.28 (diethyl ether); \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) (major) 7.43-7.37 (4H, m, Ph), 7.31-7.24 (4H, m, Ph), 7.18 (2H, d, J 7.8, Ph), 4.71 (1H, t (br), J 5.9, H-5), 4.39-4.34 (1H, m, H-2), 4.24 (1H, dd, J 11.2 and 3.4, CH\(_2\)OHOSO\(_2\)), 4.15 (1H, dd, J 11.2 and 5.5, CH\(_2\)OHOSO\(_2\)), 4.02 (2H, t, J 7.0, CH\(_2\)N), 3.02 (3H, s, CH\(_3\)SO\(_2\)), 2.72 (2H, td, J 7.0 and 1.2, C=CCH\(_3\)), 2.22-2.11 (2H, m, H-3), 2.06-1.97 (1H, m, H-4) and 1.79-1.70 (1H, m, H-4); \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) (minor) 7.43-7.37 (4H, m, Ph), 7.31-7.24 (4H, m, Ph), 7.18 (2H, d, J 7.8, Ph), 4.63 (1H, dd, J 6.5 and 4.9, H-5), 4.39-4.34 (1H, m, H-2), 4.29-4.25 (2H, m, CH\(_2\)OSO\(_2\)), 4.02 (2H, t, J 7.0, CH\(_2\)N), 3.05 (3H, s, CH\(_3\)SO\(_2\)), 2.72 (2H, t, J 7.5 and 1.2, C=CCH\(_3\)), 2.22-2.11 (2H, m, H-3), 2.06-1.97 (1H, m, H-4) and 1.79-1.70 (1H, m, H-4); \(^13\)C NMR (100 MHz; CDCl\(_3\)): \(\delta\) (major) 153.4 (CO\(_2\)Ph), 152.6 (CO\(_2\)Ph), 150.9 (ipso \(\text{C}_\text{o}-\text{O}\)), 150.5 (ipso \(\text{C}_\text{o}-\text{O}\)), 129.7 (Ph), 129.5 (Ph), 126.7 (Ph), 126.2 (Ph), 121.4 (Ph), 120.5 (Ph), 81.5 (CHC=C), 81.4 (CHC=C), 76.0 (C-2), 70.9 (CH\(_2\)OSO\(_2\)), 69.1 (C-5), 49.6 (CH\(_2\)N), 37.6 (SO\(_2\)CH\(_3\)), 33.2 (C-3), 27.1 (C-4) and 17.7 (C=CCH\(_3\)); \(^13\)C NMR (100 MHz; CDCl\(_3\)): \(\delta\) (minor) 153.4 (CO\(_2\)Ph), 152.6 (CO\(_2\)Ph), 150.9 (ipso \(\text{C}_\text{o}-\text{O}\)), 150.5 (ipso \(\text{C}_\text{o}-\text{O}\)), 129.7 (Ph), 129.5 (Ph), 126.7 (Ph), 126.2 (Ph), 121.4 (Ph), 120.5 (Ph), 81.5 (CHC=C), 81.4 (CHC=C), 76.0 (C-2), 71.9 (CH\(_2\)OSO\(_2\)), 69.1 (C-5), 49.6 (CH\(_2\)N), 37.7 (SO\(_2\)CH\(_3\)), 33.2 (C-3), 27.4 (C-4) and 17.7 (C=CCH\(_3\)).
H-3) and 1.83-1.75 (1H, m, H-3); 1H NMR (400 MHz; CDCl3); δ (minor) 7.43-7.37 (4H, m, Ph), 7.31-7.24 (4H, m, Ph), 7.18 (2H, d, J 7.8, Ph), 4.64-4.61 (1H, m, H-5), 4.21-4.15 (1H, m, H-2), 4.02 (2H, m, CH2N), 3.51 (1H, dd, J 10.1 and 5.1, CHHBr), 3.37 (1H, dd, J 10.1 and 7.3, CHHBr), 2.73 (2H, m, C=CCH2), 2.27-2.16 (2H, m, H-4), 2.04-1.95 (1H, m, H-3) and 1.83-1.75 (1H, m, H-3); 1C NMR (100 MHz; CDCl3): δ (major) 153.4 (CO2Ph), 152.6 (CO2Ph), 150.9 (ipso C-O), 150.5 (ipso C-O), 129.7 (Ph), 129.5 (Ph), 126.7 (Ph), 126.2 (Ph), 121.4 (Ph), 120.5 (Ph), 81.9 (CH=CH=O), 81.2 (CHC=CH=), 77.7 (C-2), 69.3 (C-3), 49.6 (CH3N), 35.4 (CH3Br), 33.4 (C-3), 30.0 (C-4) and 17.8 (C=CH2); 13C NMR (100 MHz; CDCl3): δ (minor) 153.4 (CO2Ph), 152.6 (CO2Ph), 150.9 (ipso C-O), 150.5 (ipso C-O), 129.7 (Ph), 129.5 (Ph), 126.7 (Ph), 126.2 (Ph), 121.4 (Ph), 120.5 (Ph), 81.9 (CH=CH=O), 81.2 (CHC=CH=), 79.4 (C-2), 69.3 (C-3), 49.6 (CH3N), 35.4 (CH3Br), 33.4 (C-3), 30.3 (C-4) and 17.8 (C=CH2).

(5S)-5-(4-Fluorophenoxy)methyl)-2-hydroxytetrahydrofuran 19. Di-iso-propyl azodicarboxylate (3.87 mL, 19.7 mmole) was added dropwise via syringe to a stirred solution of 18 (1.99 g, 17.0 mmole), triphenylphosphine (6.74 g, 25.7 mmole) and 4-fluorophenol (2.11 g, 18.8 mmole) in toluene (44 mL). The solution was heated at reflux for 3 hr and the solvent was then removed in vacuo. Purification by flash column chromatography eluting with 40/60 petroleum ether-diethyl ether (1:1) gave an inseparable mixture of anomers (57:43; assigned by integration of the peaks at δH 5.58 (1H, s (br), H-2) and δH 5.51 (1H, t, J 3.6, H-2)). Rf 0.44 (diethyl ether); 1H NMR (400 MHz; CDCl3): δ (mixture): 9.72 (trace tautomeric CHO), 6.94-6.89 (4H, m, CHCF), 6.84-6.79 (4H, m, CHCO), 5.58 (1H, s (br), H-2), 5.51 (1H, t, J 3.6, H-2), 4.57-4.52 (1H, m, H-5), 4.42-4.38 (1H, m, H-5), 4.01-3.94 (2H, m, CH2OAr), 3.91-3.84 (2H, m, CH2OAr), 3.52-3.49 (1H, m, OH), 3.45-3.43 (1H, m, OH), 2.25-2.21 (2H, m, H-3), 2.08-1.83 (4H, m, H-3 and H-4) and 1.79-1.71 (2H, m, H-4); 13C NMR (100 MHz; CDCl3) δ = 157.3 (d, J 244, 2 ipso C-F), 154.9 (d, J 2, 2 ipso C-O), 115.6 (3 Ar), 115.5 (Ph), 99.0 (C-2), 98.8 (C-2), 77.4 (C-5), 76.3 (C-5), 72.2 (CH2OAr), 70.8 (CH3OAr), 33.8 (C-3), 32.7 (C-3), 25.8 (C-4) and 25.5 (C-4); m/z (FAB) 235.0750; C11H13O2NaF requires 235.0767.

(2R/S, 5S)-5-(4-Fluorophenoxy)methyl)-2-(but-3-yn-1-oxo)tetrahydrofuran 21 Amberlyst A-15® (100 mg) was added to a stirred solution of 20 (2.50 g, 11.9 mmole) and 3-butyn-1-ol (5 mL, 66 mmole) in benzene (80 mL) in a round bottomed flask fitted with a distillation head and condenser. The reaction mixture was heated to 80 °C and 15 mL of benzene/water azetropes removed through distillation. Cooling to rt, filtration and removal of volatiles in vacuo afforded homo-propargylic ether 21 (3.01 g, 96%), an oil, as an inseparable mixture of anomers (57:43; assigned by integration of the peaks at δH 5.24 (1H, d, J 4.5, H-2) and δH 5.17 (1H, d, J 4.4, H-2)). Rf 0.64 (40/60 petroleum ether-diethyl ether, 1:1); 1H NMR (400 MHz; CDCl3): δ (major) 6.98-6.93 (2H, m, Ar), 6.88-6.83 (2H, m, Ar), 5.24 (1H, d, J 4.5, H-2), 4.49-4.40 (1H, m, H-5), 3.93 (2H, d, J 4.8, CH2OAr), 3.84-3.73 (1H, m, OCHHCH2), 3.61-3.50 (1H, m, OCHHCH2), 2.47 (2H, td, J 6.9 and 2.6, 4.37-4.31 (1H, m, H-2), 4.02 (2H, t, J 7.0, CH2N), 3.42 (1H, dd, J 10.3 and 4.6, CHHBr), 3.36 (1H, dd, J 10.3 and 6.3, CHHHBr), 2.73 (2H, td, J 7.1 and 1.4, CH=CH2), 2.27-2.16 (2H, m, H-2), 2.04-1.95 (1H, m, H-3) and 1.83-1.75 (1H, m, H-3); 1H NMR (400 MHz; CDCl3); δ (minor) 7.43-7.37 (4H, m, Ph), 7.31-7.24 (4H, m, Ph), 7.18 (2H, d, J 7.8, Ph), 4.64-4.61 (1H, m, H-5), 4.21-4.15 (1H, m, H-2), 4.02 (2H, m, CH2N), 3.51 (1H, dd, J 10.1 and 5.1, CHHBr), 3.37 (1H, dd, J 10.1 and 7.3, CHHBr), 2.73 (2H, m, C=CCH2), 2.27-2.16 (2H, m, H-4), 2.04-1.95 (1H, m, H-3) and 1.83-1.75 (1H, m, H-3); 1C NMR (100 MHz; CDCl3): δ (major) 153.4 (CO2Ph), 152.6 (CO2Ph), 150.9 (ipso C-O), 150.5 (ipso C-O), 129.7 (Ph), 129.5 (Ph), 126.7 (Ph), 126.2 (Ph), 121.4 (Ph), 120.5 (Ph), 81.9 (CH=CH=O), 81.2 (CHC=CH=), 77.7 (C-2), 69.3 (C-3), 49.6 (CH3N), 35.4 (CH3Br), 33.4 (C-3), 30.0 (C-4) and 17.8 (C=CH2); 13C NMR (100 MHz; CDCl3): δ (minor) 153.4 (CO2Ph), 152.6 (CO2Ph), 150.9 (ipso C-O), 150.5 (ipso C-O), 129.7 (Ph), 129.5 (Ph), 126.7 (Ph), 126.2 (Ph), 121.4 (Ph), 120.5 (Ph), 81.9 (CH=CH=O), 81.2 (CHC=CH=), 79.4 (C-2), 69.3 (C-3), 49.6 (CH3N), 35.4 (CH3Br), 33.4 (C-3), 30.3 (C-4) and 17.8 (C=CH2).
CH₂C≡C), 2.24-1.73 (4H, m, H₂-3 and H₂-4) and 1.97 (1H, t, J = 2.6, C≡CH); ¹H NMR (400 MHz; CDCl₃): δ (minor) 6.98-6.93 (2H, m, Ar), 6.88-6.83 (2H, m, Ar), 5.17 (1H, d, J = 4.4, H-2), 4.49-4.40 (1H, m, H-5), 4.02 (1H, dd, J = 9.5 and 6.9, CHHOAr), 3.94-3.91 (1H, m, CHHOAr), 3.84-3.73 (1H, m, OCH₂CH₂), 3.61-3.50 (1H, m, OCH₂CH₂), 2.42 (2H, td, J = 6.8 and 2.6, C₃H₂C≡C), 2.24-1.73 (4H, m, H₂-3 and H₂-4) and 1.93 (1H, t, J = 2.6, C≡CH); ¹³C NMR (100 MHz; CDCl₃): δ (major) = 157.3 (d, J = 233, ipso C-F), 155.0 (d, J = 2, ipso C-O), 115.6 (Ar), 115.6 (Ar), 104.5 (C-2), 81.4 (C≡CH), 76.3 (C-5), 70.8 (CH₂OAr), 69.1 (C≡CH), 65.4 (OCH₂CH₂), 32.0 (C₃H₂C≡C), 25.8 (C₅-3) and 19.9 (C-4); ¹³C NMR (100 MHz; CDCl₃): δ (minor) 157.3 (d, J = 233, ipso C-F), 155.0 (d, J = 2, ipso C-O), 115.6 (Ar), 115.6 (Ar), 104.4 (C-2), 81.5 (C≡CH), 78.3 (C-5), 72.6 (CH₂OAr), 69.2 (C≡CH), 65.2 (OCH₂CH₂), 32.8 (CH₂C≡C), 26.3 (C₃-3) and 20.0 (C-4); IR (film): 3300 (C=C-H), 2920, 2854 (C-H), 2120 cm⁻¹ (C≡C); IH NMR (400 MHz; CDCl₃): δ (major) 4.49-4.43 (1H, m, H-5) and δₘₙ₁ (minor) 4.31-4.25 (1H, m, H-5) in the crude ¹H NMR were further purified by MPLC eluting with 40/60 petroleum ether-diethyl ether (1:1) to give alcohol 22 as white cubes (1.66 g, 57%); m.p.: 77-79°C; Rᵣ (major) 0.22 (hexane-ethyl acetate, 1:1); [α]°D (major) = -42.3 (c 1.35 in CH₂Cl₂); ¹H NMR (400 MHz; CDCl₃): δ (major) 6.98-6.92 (2H, m, CHCF), 6.85 (2H, dd, J = 9.1 and 4.3, CHCO), 4.76-4.73 (1H, m, H-2), 4.49-4.43 (1H, m, H-5), 3.93 (2H, d, J = 4.8, CH₂OAr), 3.71 (2H, q, J = 6.3, CH₂OH), 2.49 (2H, td, J = 6.3 and 1.8, C≡CCH₂), 2.28-2.18 (2H, m, H-3 and H-4), 2.05-1.97 (1H, m, H-3), 1.93 (1H, t, J = 6.3, OH) and 1.91-1.82 (1H, m, H-4); ¹H NMR (400 MHz; CDCl₃): δ (minor) 6.98-6.92 (2H, m, CHCF), 6.85 (2H, dd, J = 9.1 and 4.3, CHCO), 4.64-4.62 (1H, m, H-2), 4.31-4.25 (1H, m, H-5), 4.05 (1H, dd, J = 9.6 and 5.9, CHHOAr), 3.94 (1H, dd, J = 9.6 and 5.1, CHHOAr), 3.71 (2H, q, J = 6.3, CH₂OH), 2.49 (2H, td, J = 6.3 and 1.8, C≡CCH₂), 2.28-2.18 (2H, m, H-3 and H-4), 2.05-1.97 (1H, m, H-3), 1.75 (1H, s (br), OH) and 1.91-1.82 (1H, m, H-4); ¹³C NMR (100 MHz; CDCl₃): δ (major) 157.4 (d, J = 237, ipso C-F), 154.9 (d, J = 2, ipso C-O), 115.7 (d, J = 21, CHCF), 115.6 (d, J = 6, CHCO), 81.9 (CH₂C≡C), 81.6 (CH₂C≡C), 76.9 (C-2), 70.8 (CH₂OAr), 69.0 (C-5), 61.0 (CH₂OH), 33.5 (C-3), 27.9 (C-4) and 23.2 (C≡CCH₂); ¹³C NMR (100 MHz; CDCl₃): δ (minor) 157.4 (d, J = 237, ipso C-F), 154.9 (d, J = 2, ipso C-O), 115.7 (d, J = 21, CHCF), 115.6 (d, J = 6, CHCO), 81.8 (CH₂C≡C), 81.6 (CH₂C≡C), 77.8 (C-2), 71.2 (CH₂OAr), 69.0 (C-5), 60.9 (CH₂OH), 33.3 (C-3), 28.3 (C-4) and 23.2 (C≡CCH₂); IR (KBr) (major): 3490 (O-H), 2978, 2920, 2854 (C-H), 2235 (C≡C), 1646, 1599 and 1507 (Ar). Anal Found (major): C, 68.0; H, 6.45. C₁₅H₁₇O₅F requires C, 68.1; H, 6.48%.

(2S,5S)-2-(4-Fluorophenoxymethyl)-5-(1-hydroxy-3-butyln-3-yl)tetrahydrofuran 22 and (2S,5S)-2-(4-Fluorophenoxymethyl)-5-(1-hydroxy-3-butyln-4-yl)tetrahydrofuran 23. n-Butyllithium (1.6 M in hexanes, 8.50 mL, 13.6 mmole) was added dropwise via syringe to a solution of 21 (3.00 g, 11.0 mmole) in THF (8.5 mL) at -78 °C. After 30 min at -78 °C tributylin chloride (3.54 mL, 13.1 mmole) was added dropwise via syringe and the reaction allowed to warm to rt. The reaction mixture was then diluted with diethyl ether (50 mL) and washed with water (30 mL) and saturated sodium chloride solution (30 mL). Drying (MgSO₄) and evaporation of volatiles in vacuo gave the stannylated material as a viscous oil, which was used without purification in the subsequent step.

Boron trifluoride etherate (4.19 mL, 33 mmole) was added dropwise via syringe to a vigorously stirred solution of the crude stannane (6.10 g) in dichloromethane (3 mL) at -10°C. After 10 min at -10°C, 10% sodium hydroxide solution (2 mL) was added. Following dilution of the reaction mixture with dichloromethane, the organic phase was separated, washed with saturated sodium chloride solution (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. The resulting oil was purified by flash column chromatography eluting with 40/60 petroleum ether-diethyl ether (20:1, 1:1, 1:2). The fractions containing a mixture of cis and trans isomers [22/23, 2:1; asigned by integration of the peaks at δₘₙ₁ (major) 4.49-
\[ \delta 7.43-7.36 \text{ (4H, m, Ph), 7.32-7.23 (4H, m, Ph), 7.19 (2H, d, J 7.8, Ph), 7.00-6.92 (2H, m, CHCF), 6.85-6.81 (2H, m, CHCO), 4.74 (1H, t (br), J 5.9, H-5), 4.49-4.43 (1H, m, H-2), 4.03 (2H, t, J 7.1, CH$_2$N), 3.92 (2H, d, J 4.8, CH$_2$OAr), 2.74 (2H, td, J 7.1 and 1.4, C=CCH$_2$), 2.27-2.17 (2H, m, H-3 and H-4), 2.07-1.97 (1H, m, H-3) and 1.90-1.80 (1H, m, H-4); $^{13}$C NMR (100 MHz; CDCl$_3$): \delta 157.3 (d, J 238, ipso C-F), 155.0 (ipso C-O), 153.4 (CO$_2$Ph), 152.6 (CO$_2$Ph), 150.9 (ipso C-O), 150.5 (ipso C-O), 129.7 (Ph), 129.5 (Ph), 126.7 (Ph), 126.2 (Ph), 121.4 (Ph), 120.5 (Ph), 115.7 (d, J 23, CHCF), 115.6 (d, J 5, CHCO), 82.0 (C=CCH$_2$), 80.9 (C=CCH$_2$), 76.9 (C-2), 70.7 (CH$_2$OAr), 68.9 (C-5), 49.7 (CH$_2$N), 33.4 (C-3), 27.8 (C-4) and 17.8 (C=CCH$_2$); IR (film): \nu 2854, 2842, 2785, 2931, 2978, 2931, 2854 (C-H), 1806, 1747 (C=O), 1591 and 1506 cm$^{-1}$ (Ar). Anal. Found: C, 81.5; H, 5.15; N, 2.6. C$_{29}$H$_{26}$O$_7$NF requires C, 81.7; H, 5.04; N, 2.7%.

(2S,5S)-2-(4-Fluorophenoxymethyl)-5-(1-N-hydroxyureido)-3-yltetrahydrofuran, CMI-977 1. Ammonia solution (0.88 specific gravity, 4 mL) was added to 24 (50 mg, 0.10 mmole), the solution stirred at rt for 12 hr and then the volatiles removed in vacuo. Purification by flash column chromatography eluting with dichloromethane-methanol (100:0→95:5) afforded CMI-977 1 (19 mg, 59%) as a white amorphous solid. m.p. 112-114°C; $R_f$ 0.25 (dichloromethane-methanol, 95:5); $[\alpha]_D^{29}$ = -40.7 (c 0.95 in CH$_2$Cl$_2$), authentic sample $[\alpha]_D^{29}$ = -40.5 (c 1.00 in CH$_2$Cl$_2$); $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 8.24 (1H, s (br), OH), 7.00-6.93 (2H, m, CH$_2$OAr), 6.84 (2H, dd, J 9.1 and 4.3, CH$_2$O), 5.42 (2H, br s, NH$_2$), 4.73 (1H, t, J 5.8, H-5), 4.49-4.43 (1H, m, H-2), 3.93 (1H, dd, J 9.9 and 4.0, CH$_2$OAr), 3.88 (1H, dd, J 9.9 and 5.7, CH$_2$OAr), 3.69 (2H, t, J 6.2, CH$_2$N), 2.54 (2H, t, J 6.2, C=CCH$_2$), 2.27-2.18 (2H, m, H-3 and H-4), 2.06-1.96 (1H, m, H-4) and 1.84-1.78 (1H, m, H-3); $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 161.8 (C=O), 157.4 (d, J 237, ipso C-F), 154.8 (d, J 2, ipso C-O), 115.8 (d, J 23, CHCF), 115.6 (d, J 12, CH$_2$O), 83.0 (C=CCH$_2$), 80.7 (C=CCH$_2$), 76.9 (C-2), 70.7 (CH$_2$OAr), 69.2 (C-5), 48.7 (CH$_2$N), 33.3 (C-4), 27.7 (C-3) and 17.3 (C=CCH$_2$); IR (KBr): 3448 (O-H), 3335, 3259 (H-N-H), 2921, 2854 (C=O), 1576 and 1508 cm$^{-1}$ (Ar). Anal. Found: C, 59.6; H, 5.86; N, 8.6. C$_{16}$H$_{10}$O$_7$NF requires C, 59.6; H, 5.94; N, 8.7%.

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References

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