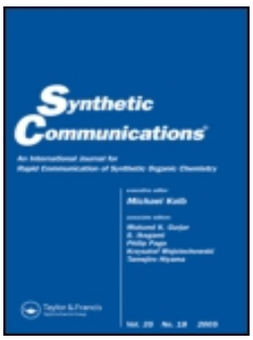

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A SHORT AND EFFICIENT STEREOSELECTIVE SYNTHESIS OF THE POTENT 5-LIPOXYGENASE INHIBITOR CMI-977

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Abstract: A short and efficient synthesis of the potent 5-lipoxygenase inhibitor CMI-977 is described using as the key step a stereoselective anomeric oxygen to carbon rearrangement of an alkynyl stannane tetrahydrofuranyl ether derivative mediated by boron trifluoride etherate.

Fully saturated oxygen heterocycles such as tetrahydropyrans and tetrahydrofurans bearing carbon substituents adjacent to the oxygen atom are common structural motifs found within numerous naturally occurring and

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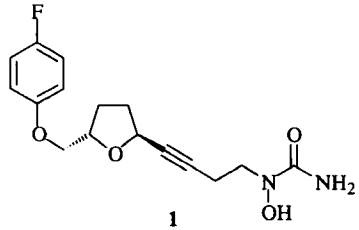
biologically important compounds. As a direct result of this abundance a wealth of methods have been devised for their synthesis over the years.[1] Recently we have introduced a new general method for the efficient synthesis of this type of structural motif which relies upon the oxygen to carbon rearrangement of an anomerically linked carbon centred nucleophile by mediation of Lewis acids. A range of nucleophiles, including electron rich alkenes,[2] silyl enol ethers[3] and alkynylstannanes[4] have been found to be compatible with the reaction conditions and lead efficiently to the carbon linked products in nearly all cases. We believe that this new methodology is a powerful addition to the existing protocols and is particularly effective for target orientated synthesis as it necessarily combines anomeric activation with side chain heteroatom protection.

Here we wish to report the utility of the anomeric oxygen to carbon rearrangement of an alkynyl stannane tetrahydrofuranyl ether derivative in the short and efficient synthesis of the potent 5-lipoxygenase inhibitor CMI-977 **1**.



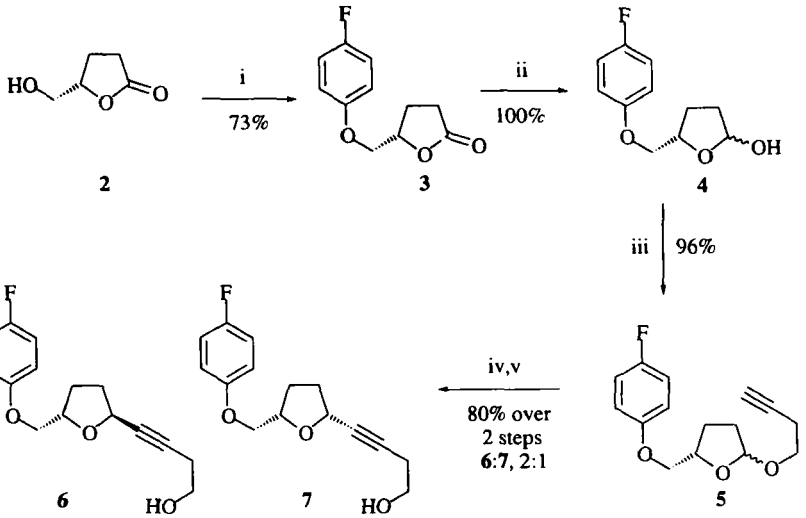
1
CMI-977

Figure 1

CMI-977 **1**[5] was recently discovered by CytoMed Industries and is presently being developed as an orally active treatment of chronic asthma. The compound contains a 2,5-disubstituted tetrahydrofuran ring in which a *para*-fluorophenoxymethyl group is disposed *trans* to a homopropargylic *N*-hydroxy urea side chain. It was this important biological activity combined with the ability to exploit the new methodology which made CMI-977 an ideal synthetic target (Figure 1).

The synthesis of **1** commenced from commercially available (*S*)-γ-hydroxymethyl-γ-butyrolactone **2**. The hydroxyl group of this material was converted directly into the desired *para*-fluorophenoxymethyl-γ-lactone **3** using a standard Mitsunobu protocol.[6] Thus, treatment of a mixture of alcohol **2** and *para*-fluorophenol (1.1 eq) with triphenylphosphine (1.15 eq) followed by diisopropylazodicarboxylate (DIAD) (1.15 eq) in THF at 0°C to reflux afforded **3** in good yield and on multigramme scale.

Conversion of lactone **3** to the rearrangement precursor **5** was then possible through a two step high yielding sequence. Standard lactone **3** to lactol **4** reduction using a slight excess of diisobutylaluminium hydride in toluene at -78°C followed by treatment of the crude material with an excess of 3-butyn-1-ol and a catalytic amount of Amberlyst® A15 in refluxing benzene afforded the tetrahydrofuranyl ether **5** in 96% yield and as a 1:1 mixture of anomers.



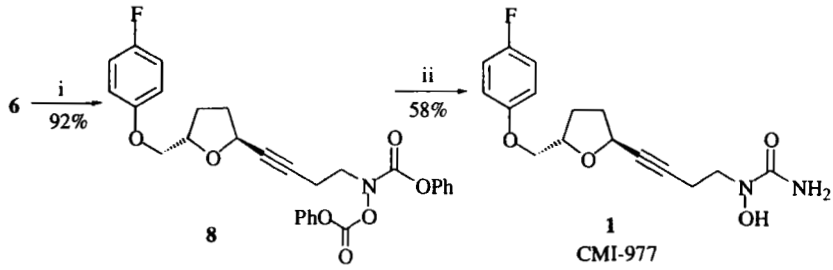
Scheme 1 *Reagents and conditions*: i, *p*-fluorophenol (1.1 eq), PPh_3 (1.15 eq), DIAD (1.15 eq), THF, 0°C then reflux 3h; ii, DIBALH (1.1 eq) toluene, -78°C; iii, 3-butyn-1-ol (11.0 eq), Amberlyst® A15 (cat), benzene, azeotrope; iv, BuLi (1.2 eq), THF, -78°C then Bu_3SnCl (1.15 eq), -78°C to RT, 30 min; v, $BF_3.OEt_2$ (3.0 eq), CH_2Cl_2, -10°C, 5 min.

With multigramme quantities of the homopropargylic tetrahydrofuranyl ether **5** in hand, the anomeric oxygen to carbon rearrangement was attempted following the original two step protocol. Thus deprotonation of alkyne **5** with butyllithium (1.2 eq) in tetrahydrofuran at -78°C followed by treatment with tributyltin chloride (1.15 eq) at -78°C to room temperature afforded the crude tributylstannylated material on work up. This material was not purified but was dissolved in dichloromethane, cooled to -10°C, and then treated with boron trifluoride etherate (3.0 eq) for 5 minutes before the reaction mixture was quenched with sodium hydroxide. Aqueous work up and inspection of the crude ^1H nmr indicated that

the reaction had produced the carbon linked products **6** and **7** in a ratio of 2:1 favouring the *trans* product **6**. Purification by MPLC chromatography allowed separation of the diastereomeric products which were isolated in a combined yield of 80%. The stereochemistry of the major product **6** was unambiguously determined by single crystal X-ray diffraction[7] (Scheme 1).

Conversion of alcohol **6** into CMI-977 **1** was possible following a modification of a two step literature procedure.[8] In the first step, the hydroxyl group of **6** was converted directly to the *N,O*-diphenoxycarbonyl hydroxylamine derivative using a Mitsunobu protocol. Thus treatment of a mixture of alcohol **6** and *N,O*-diphenyloxycarbonyl hydroxylamine (1.1 eq) with triphenylphosphine (1.15 eq) followed by diisopropylazodicarboxylate (1.15 eq) in THF at 0°C to room temperature gave **8** in good yield (92%) after purification *via* column chromatography. Direct ammonolysis of this material by treatment with concentrated ammonium hydroxide at room temperature for 20 hours then gave the target material **1** in 58% yield as a white amorphous solid. The ^{1}H nmr, ^{13}C nmr, Ir, melting point and MS were in excellent agreement with the reported data.[5] The specific rotation $[\alpha]_D^{31}$ –40.7 (*c* 0.95, CH_2Cl_2) of the synthesised material was in excellent agreement with that of an authentic sample[9] $[\alpha]_D^{31}$ –40.5 (*c* 1.00, CH_2Cl_2) (Scheme 2).

In summary, a short and efficient synthesis of the potent 5-lipoxygenase inhibitor CMI-977 has been achieved in 20% yield over 7 steps (79% per step average),



Scheme 2 *Reagents and conditions*: i, *N,O*-Bis-(phenoxycarbonyl)-hydroxylamine (1.1 eq), PPh_3 (1.15 eq), DIAD (1.15 eq), THF, 0°C then RT 1h; ii, NH_4OH (0.88 sp g), RT, 20 h.

using a stereoselective anomeric oxygen to carbon rearrangment of an alkynyl stannane tetrahydrofuranyl ether derivative as the key step. We believe that this type of rearrangement will find further application in target oriented syntheses in the future.

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