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Tetrahedron: *Asymmetry* 14 (2003) 1363–1370

TETRAHEDRON: *ASYMMETRY*

# A novel and simple asymmetric synthesis of CMI-977 (LDP-977): a potent anti-asthmatic drug lead

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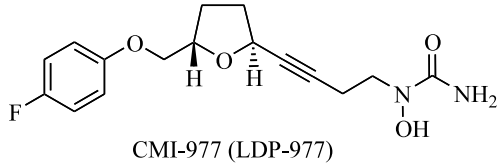
Received 31 January 2003; accepted 17 February 2003

**Abstract**—A practical gram scale asymmetric synthesis of CMI-977 is described. A tandem double elimination of an α-chloro-oxirane and concomitant intramolecular nucleophilic substitution was used as the key step. Jacobsen hydrolytic kinetic resolution and Sharpless asymmetric epoxidation protocols were applied for the execution of the synthesis of the key chiral building block.


## 1. Introduction

The alarming rise of asthma constitutes the biggest mystery in modern health care at the beginning of this century and the exact reasons still evade researchers despite the advances in molecular biology and asthma chemotherapy.[1a,b] This has led to the worldwide intense search for safer and target-specific drugs for asthma.[1c–g] CMI-977, (2*S*,5*S*)-*trans*-5-[(4-fluorophenoxy)methyl]-2-(4-*N*-hydroxyureidyl-1-butynyl)tetrahydrofuran **1** renamed later as LDP-977 is being developed by Cytomed Inc. USA, as a promising candidate for chronic asthma[2] (Fig. 1). It acts primarily by inhibiting the 5-lipoxygenase pathway and thus blocking the production of inflammatory mediatory leukotrienes. CMI-977 has successfully been evaluated in animal models. In guinea pigs, oral administration of CMI-977 effectively blocks ovalbumin-induced bronchoconstriction, airway eosinophil accumulation, and plasma extravasation. CMI-977 blocked LTB4 production with $IC_{50}$ of 117 nm and 10 mg/kg inhibited eosinophil influx by 63%. Data from phase IIa trial out of one randomized, double-blind, placebo-controlled analysis to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of a single dose of CMI-977 in normal subjects, showed that PK/PD profile is comparable with a single dose of zileuton, i.e. it may administered orally once or twice a day. Overall, CMI-977 has shown a high degree of potency, excellent oral bioavailability and exceptionally favorable safety profile.[3] CMI-977 belongs to the lignan family of 2,5-disubstituted tetrahydrofurans, featuring with diverse substitution and *trans*-juxtapositioned ring and is stereo specific (all other three stereoisomers have shown poor pharmacological profile). The unique structural ensemble, featured with diverse substitution and a *trans*-juxtapositioned ring invited the synthetic community to undertake a 'single enantiomer synthesis' that would deliver the target molecule with relevant stereochemistry and functionalities.[4,5]



CMI-977 (LDP-977)

**Figure 1.**

The inaugural synthetic route[4] for CMI-977, choosing (*S*)-(+)-hydroxymethyl-γ-butyrolactone as a chiron, was plagued with several problems such as poor selectivity and complicated separation of diastereomers which mitigated against efficient scale up and cost effective production of the target molecule. During the course of our efforts[5] to solve the problems encountered in the reported approach, we devised and exe-

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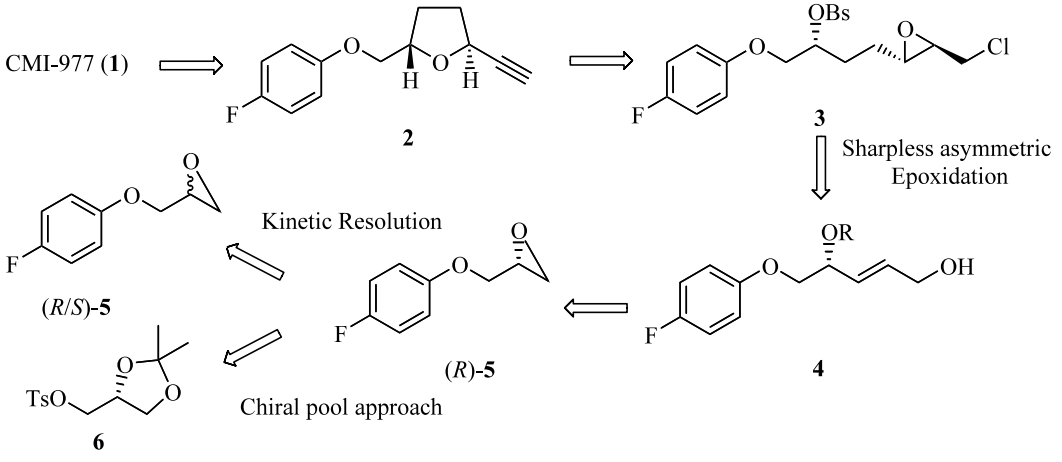
doi:10.1016/S0957-4166(03)00157-5

cuted three novel routes simultaneously in our laboratory that effectively addressed the aforesaid problems, resulting in the cost-effective syntheses of CMI-977, which are amenable for large scale production. Amongst these three approaches the first two approaches can be coined as second generation synthetic routes which addressed the diastereoselective problems encountered in the original synthetic route and our third report provides an alternative route for the synthesis of the key intermediate that had been used in the first generation as well in our previous two approaches.

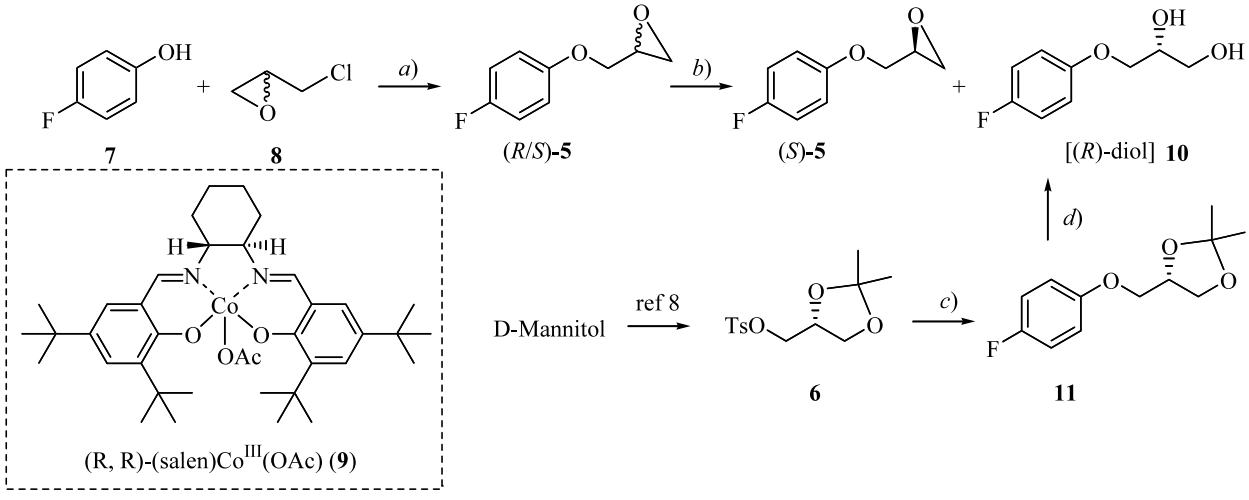
## 2. Results and discussion

Our general synthetic strategy (Scheme 1) toward the total synthesis of CMI-977 envisaged the synthesis of the key intermediate **2** following a tandem fragmentation/nucleophilic substitution sequence. Thus fragmentation of α-chlorooxirane **3** would lead to propargylalkoxide[6] and concomitant intramolecular substitution of suitably positioned leaving group would result in a tetrahydrofuran ring. It was envisaged that the functionality present in **3** could be installed using a combination of both Jacobsen's hydrolytic kinetic resolution on **5** and a Sharpless asymmetric expoxidation step.

Synthesis of key intermediate **5** began from the readily available 4-fluorophenol **7** and *rac*-epichlorohydrin **8**. Thus the reaction of 4-fluorophenol **7** with *rac*-epichlorohydrin in the presence of $K_2CO_3$ in refluxing acetone gave *rac*-4-fluorophenyl glycidyl ether **4** in 84% yield. The glycidyl ether **5** was subjected to HKR[7] conditions with 0.55 equiv. of water in *t*-butylmethyl ether using the catalyst (*R*,*R*)-(salen)$Co^{III}$(OAc) **9** (Scheme 2) to provide enantiomerically-pure (*S*)-**4** and (*R*)-diol **10** in 46% yield each. To confirm its absolute stereochemistry, **10** was obtained from the treatment of the known tosylate **6**[8] with 4-fluophenoxide, and subsequent hydrolysis of the resulting acetonide **11**. The physical data were identical in all respects ($^1$H NMR, specific rotation, etc.).




**Scheme 1.** Retrosynthetic analysis of **1**.



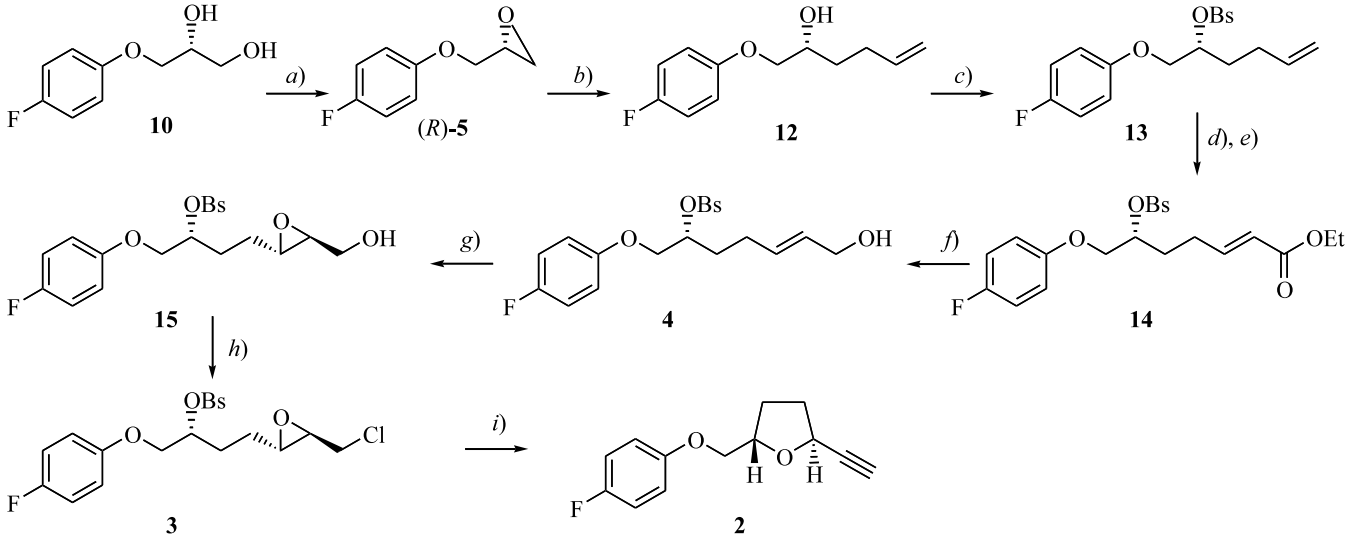

**Scheme 2.** *Reagents and conditions*: (a) $K_2CO_3$, acetone, reflux, 6 h, 84%; (b) **9**, *t*-BuOMe–$H_2O$, 0°C–rt, 5 h, 46% of each (*S*)-**5** and **10**; (c) NaH, THF–DMF, 0°C–rt, 12 h, 82%; (d) HCl, MeOH, rt, 12 h, 89%.

The diol **10** was converted to the desired epoxide (*R*)-**5** through the cyclic orthoester methodology of Sharpless et al.[9] in one pot. Accordingly, **10** was treated with a slight excess of trimethyl orthoacetate in the presence of TMSCl in dichloromethane (Scheme 3). The subsequent exposure of the chloroacetate to $K_2CO_3$ in methanol afforded the epoxide (*R*)-**5** in excellent yield.

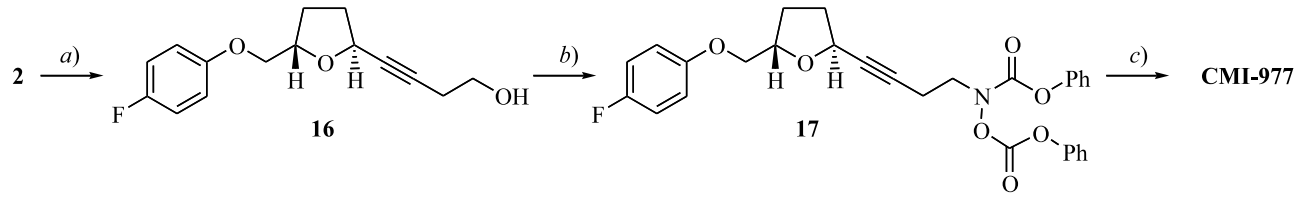
Epoxide (*R*)-**5** upon exposure to allylmagnesium bromide[10] gave the alcohol **12** in excellent yield. The alcohol was then converted to benzenesulphonate ester **13** with benzenesulphonyl chloride and $Et_3N$. The structure of product **13** was confirmed by the $^1H$ NMR spectrum with additional evidence from $^{13}C$ NMR, IR, EI and HRMS spectral data. The chemical shift of the methine proton bearing the sulphonate group moved downfield (compared to **12**) and appeared at 4.82 ppm and the protons in $PhSO_2$ group appeared as two sets, resonating between 7.44 and 7.91 ppm in the $^1H$ NMR spectrum. In the IR spectrum, two intense peaks at 1170 and 1339 $cm^{-1}$ characteristic of sulphonyl group were observed. The EI mass spectrum gave a molecular ion peak at (*m*/*z*) 350, which was subsequently confirmed by HRMS.

The olefin **13** was then submitted to reductive ozonolysis to provide the corresponding aldehyde, which was then elongated on reaction with a stable Wittig ylide to provide the corresponding α,β-unsaturated ester **14**. The predominant (*E*)-olefinic ester, obtained after chromatographic removal of minor (*Z*)-isomer, was characterized by $^1H$ and $^{13}C$ NMR spectroscopy. The coupling constant values ($J = 16.0$ Hz) of olefinic protons confirmed the (*E*)-geometry of olefin. The signals due to methyl group of -$OCH_2CH_3$ appeared at 1.30 ppm as triplet ($J = 7.1$ Hz) and the methylene at 4.17 ppm as a quartet whereas olefinic protons at 5.77 and 6.73–6.98 ppm. An intense IR adsorption at 1708 $cm^{-1}$ was characteristic for α,β-unsaturated ester. The allyl alcohol **4** was secured in excellent yield through the reduction of ester **14** with DIBAL-H at −78°C in advance of installing the second chiral centre. The structural identity was secured from the interpretation of $^1H$ and $^{13}C$ NMR, IR, EI and HRMS spectral data. The methylene group of allyl alcohol resonated between 3.84 and 4.13 ppm in the $^1H$ NMR spectrum.

The next phase of endeavor was Sharpless asymmetric epoxidation (SAE) of the allyl alcohol **4**. The epoxidation was performed with $Ti(O^iPr)_4$-(+)-DIPT[11] complex and cumene hydroperoxide. The product **15** was obtained after column chromatography in 92% yield. The spectral information from $^1H$ and $^{13}C$ NMR, IR, EI and HRMS studies proved the structure of **15** beyond doubt. The multiplet between 2.84 and 3.01 ppm revealed the identity of the epoxy protons, whereas the two olefinic protons disappeared in the region of 5.5–6.5 ppm. The rest of the protons resonated at the expected chemical shift regions. The elemental composition was confirmed by a molecular ion peak at (*m*/*z*) 396.1043 in HRMS (FAB) studies. Reaction of epoxymethanol **15** with triphenylphosphine (TPP) in refluxing $CCl_4$ gave the required epoxymethyl chloride **3** in poor yield, with the additional formation of ring-opened products in substantial ratio. The formation of side products was subdued considerably by addition of $CHCl_3$ to enable the solubility of starting material in reaction medium and the product **3** was obtained in 64% yield. The methylene group ($CH_2Cl$) moved upfield and resonated as two doublets of doublet at 3.43 ppm ($J = 5.5$, 8.0 Hz) and 3.58 ppm in the $^1H$ NMR spectrum.




**Scheme 3.** *Reagents and conditions*: (a) i. TMSCl, $CH_3C(OMe)_3$, $CH_2Cl_2$, 0°C–rt, 1 h, ii. $K_2CO_3$, MeOH, rt, 2 h, 91%; (b) allyl-MgBr, ether, CuCN, −22°C, 0.5 h, 84%; (c) $PhSO_2Cl$, $Et_3N$, DMA, $CH_2Cl_2$, 0°C–rt, 92%; (d) $O_3$, $CH_2Cl_2$, −78°C, 0.5 h, then $Me_2S$, rt, 12 h; (e) $Ph_3P{=}CHCO_2Et$, benzene, 60°C, 5 h, two steps, 70%; (f) DIBAL-H, $CH_2Cl_2$, −78°C, 45 min, 82%; (g) $Ti(O^iPr)_4$, (+)-disiopropyltartarate, cumene hydroperoxide, 4 Å sieves, $CH_2Cl_2$, −20°C, 2.5 h, 92%; (h) $PPh_3$, $NaHCO_3$, $CCl_4$, $CHCl_3$, reflux, 3 h, 64%; (i) LDA, THF, −40°C, 1 h, 60%.




**Scheme 4.** *Reagents and conditions*: (a) *n*-BuLi, $BF_3{\cdot}OEt_2$, ethylene oxide, THF, −78°C, 0.5 h, 90%; (b) $PPh_3$, DIAD, bis(phenoxycarbonyl)hydroxylamine, THF, 0°C–rt, 5 h, 80%; (c) $NH_3$, MeOH, 0°C, 0.5 h, 70%.

The key transformation was next effected by exposure of **3** to 3 equiv. of LDA,[6] which resulted in the generation of propargyl alkoxide through double elimination followed by concomitant intramolecular $S_N2$ cyclization to provide the THF–acetylene derivative **2**. In the $^1H$ NMR spectrum, the resonances of two ring-junction protons at C-5 and C-2 appeared between $\delta$ 4.38–4.53 and 4.74 ppm, respectively, the acetylenic proton as a doublet at $\delta$ 2.39 ppm and the rest of the protons at the relevant positions. Thus, this central key transformation expediently framed the main skeleton in one pot with appropriate substitution and crucial stereochemistry.

Two carbon homologation of **2** was successfully achieved through $BF_3{\cdot}OEt_2$ facilitated opening of ethyleneoxide at −78°C with incipient acetylide generated from **2** with *n*-butyllithium (Scheme 4). The poor NOE enhancement observed during the double irradiation of protons at C-2 and C-5 suggested that these protons are not in close proximity, i.e. the relative stereochemistry of the junction is *trans*. The chiral homogenity of **16** was checked by matching the specific rotation with the authentic sample supplied by M/S Steroids, Chicago, USA {$[\alpha]_D = -34.3$ (*c* 1.4, $CHCl_3$), lit.[4] $[\alpha]_D = -34$ (*c* 1, $CHCl_3$)}. The final endeavor was attachment of the *N*-hydroxyuriedyl moiety to **16**, which was effectively accomplished through Abbott technology,[12] using *N*-hydroxyurea equivalent *N*,*O*-bis(phenoxycarbonyl)hydroxylamine. Thus, Mitsunobu reaction of **15** with Abbott reagent in the presence of TPP and DIAD gave the fully-protected derivative **17** whose structure was deduced from the $^1H$ NMR, FABMS and HRMS spectral data. Ammonolysis of urethane derivative **17** on exposure to methanolic ammonia solution culminated in the total synthesis of target compound **1**, which was identical in all respects, viz. $^1H$ and $^{13}C$ NMR, IR, EI spectra, specific rotation and melting point with that of authentic sample.

## 3. Conclusion

In conclusion, we have described a total synthesis of CMI-977 in a completely stereocontrolled fashion. The assembly of tetrahydrofuran ring with suitable appendages of appropriate stereochemistry through the central transformation 'double elimination and intramolecular $S_N2$ ring closure'. Our enantioselective synthesis of CMI-977 is characterized by a linear approach with absolute structure authentification of key intermediates by alternatively deriving it from conventional chiral pool approach and considerable flexibility for substitution tuning at any position with required stereochemistry.

## 4. Experimental

### 4.1. (±)-2,3-Epoxy-1-(4-fluorophenoxy)propane, 5

A mixture of *p*-fluorophenol, **7** (5.0 g, 44.6 mmol), *rac*-epichlorohydrin, **8** (16.5 g, 178.4 mmol) and $K_2CO_3$ (24.6 g, 178.4 mmol) in anhydrous acetone (100 mL) was heated under reflux for 6 h with vigorous stirring. The reaction mixture was filtered, evaporated and excess epichlorohydrin was removed by distillation at 120–130°C and the residue was distilled under reduced pressure (bp 100°C at 4 mmHg) to give *rac*-**5** (6.3 g, 84%) as a colorless oil.

**4.1.1. Spectral data for *rac*-5**. $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 2.68 (dd, $J=2.2$, 4.5 Hz, 1H, H-3), 2.85 (t, $J=4.5$ Hz, 1H, H-3′), 3.27 (m, 1H, H-2), 3.89 (dd, $J=6.7$, 15.7 Hz, 1H, H-1), 4.11 (dd, $J=4.5$, 15.7 Hz, 1H, H-1′), 6.74–7.02 (m, 4H). EIMS at (*m*/*z*): 57 (100), 73 (23), 83 (80), 95 (31), 112 (98), 125 (20), 168 (54). HRMS calcd for $C_9H_9FO_2$: 168.0586. Found: 168.0581.

### 4.2. Hydrolytic kinetic resolution of *rac*-5

The compound *rac*-**5** (10 g, 59.5 mmol) and (*R*,*R*)-(salen)$Co^{III}$(OAc) catalyst **9** (215 mg, 0.32 mmol) were taken in *t*-butyl methyl ether (20 mL) and cooled to 0°C. Conducting water (0.6 mL, 32.7 mmol) was then added dropwise for 1 h and stirred for an additional 5 h at rt (monitored by HPLC). The reaction mixture was eluted through a short silica gel column to obtain epoxide (*S*)-**5** (4.6 g, 46%) and diol **10** (5.06 g, 46%, 1:1 ethyl acetate:hexane).

**4.2.1. Physical data of (2*S*)-2,3-epoxy-1-(4-fluorophenoxy)propane, (*S*)-5**. $[\alpha]_D = +5.0$ (*c* 1.0, $CHCl_3$).

**4.2.2. Physical data of (2*R*)-1-(4-fluorophenoxy)propane-2,3-diol, 10**. Mp 58–59°C. $[\alpha]_D = -10$ (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): 3200 (br), 3020, 1493, 1044, 846 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 2.09 (br s, 1H, OH, $D_2O$ exchangeable), 2.65 (d, 1H, $J=3.4$ Hz, OH), 3.60–3.87 (m, 2H), 3.91–4.12 (m, 3H), 6.73–7.03 (m, 4H). $^{13}C$ NMR ($CDCl_3$, 50 MHz): $\delta$ 63.6, 69.6, 70.4, 115.4, 115.6, 116.1, 154.4 and 155.0, 159.8. EIMS at (*m*/*z*): 43 (21), 57 (34), 83 (34), 95 (21), 112 (100), 186 (9) [$M^+$]. HRMS calcd for $C_9H_{11}FO_3$: 186.0692. Found: 186.0693.

### 4.3. Preparation of (2*R*)-1-(4-fluorophenoxy)propane-2,3-diol, 10 from 6

Sodium hydride (1.9 g, 80 mmol) was added slowly to a solution of 4-fluorophenol (6.54 g, 58 mmol) in a mixture of THF and DMF (4:1, 60 mL) at 0°C. After being stirred for 30 min, a solution of **6** (15.5 g, 54 mmol) in THF (40 mL) was added at rt. The reaction mixture was stirred overnight and quenched with water. After the removal of solvent, the residue was partitioned between ether (200 mL) and water (200 mL). The organic layer was dried ($Na_2SO_4$), concentrated, and the residue purified by silica gel chromatography (10% ethyl acetate in hexane) to give **11** (10.8 g, 82%) as a colorless oil. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 1.32, 1.38 (2s, 6H, 2×$CH_3$), 3.73–3.88 (m, 2H, H-3, 3′), 3.95 (dd, $J$=5.0, 10.0 Hz, 1H, H-1), 4.06 (t, $J$=10.0 Hz, 1H, H-1′), 4.33 (quint., $J$=6.0 Hz, 1H), 6.68–6.81 (m, 2H), 6.89 (t, $J$=8.8 Hz, 2H). A solution of **6** (4.26 g, 18.8 mmol) in methanolic HCl (10%, 25 mL) was stirred overnight, quenched with solid $NaHCO_3$, filtered and evaporated. The residue on silica gel chromatographic purification (50% ethyl acetate in hexane) gave **10** (8.14 g, 89%) as a solid. The characterization data from $^1$H NMR, IR, EI and HRMS spectra were identical in all respects with that of **10** obtained in Section 4.2.

### 4.4. (2*R*)-2,3-Epoxy-1-(4-fluorophenoxy)propane, (*R*)-5

Trimethylsilyl chloride (3.0 mL, 20 mmol) was added to a solution of diol **10** (3.72 g, 20 mmol) and trimethyl orthoacetate (3.0 mL, 20 mmol) in $CH_2Cl_2$ (60 mL) at 0°C. The solution was stirred for 60 min, then evaporated to obtain crude chloroacetate. The crude product was dissolved in dry methanol (40 mL) and $K_2CO_3$ (6.80 g, 49 mmol) was added. The suspension was stirred vigorously for 2 h, then filtered and the residue washed with $CH_2Cl_2$. The filtrate was evaporated and the residue was distilled under vacuum to obtain (*R*)-**5** as a colorless liquid (3 g, 91%).

**4.4.1. Physical data of (*R*)-5**. Bp 102°C at 4 mmHg. $[\alpha]_D$=−5.2 (*c* 1.1, $CHCl_3$). IR (neat): 831, 1215, 1493, 2892 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 2.73 (m, 1H, H-3), 2.88 (t, $J$=4.5 Hz, 1H, H-3′), 3.30 (m, 1H, H-2), 3.92 (dd, $J$=6.7, 15.7 Hz, 1H, H-1), 4.16 (dd, $J$=4.5, 15.7 Hz, 1H, H-1′), 6.78–7.09 (m, 4H). EIMS (*m*/*z*): 51 (100), 75 (23), 83 (80), 95 (31), 112 (98), 125 (20), 168 (54) [M$^+$]. HRMS calcd for $C_9H_9FO_2$: 168.0586. Found: 168.0580.

### 4.5. (2*R*)-2-Benzenesulphonyloxy-1-(4-fluorophenoxy)-5-hexene, 13

To a mixture of magnesium (0.89 g, 36.6 mmol) and iodine (a crystal) in ether (15 mL), a solution of allyl bromide (3.0 g, 24.8 mmol) in ether (10 mL) was slowly added. After stirring for 30 min at rt, cuprous cyanide (22 mg) was then added in one portion, resulting with color change of reaction mixture into dark brown. After cooling to −22°C, epoxide (*R*)-**5** (2.05 g, 12.2 mmol) in ether (25 mL) was added dropwise. The reaction mixture was stirred for 30 min at −22°C, quenched with saturated $NH_4Cl$ solution and the resulting suspension stirred for another 30 min. Inorganic solid material was filtered off and washed with ether. The combined ether layer were dried ($Na_2SO_4$) and concentrated to furnish the residue, which on filtration over silica gel column (20% ethyl acetate in hexane) gave **12** (2.2 g, 84%) as a colorless oil.

**4.5.1. Physical data of 12**. $[\alpha]_D$=−16.3 (*c* 1.5, $CHCl_3$). IR ($CHCl_3$): 3400, 2930, 1530, 1215, 830 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.58–1.73 (m, 2H, H-3, 3′), 2.16–2.40 (m, 2H, $CH_2$-C), 3.80 (t, $J$=8.4 Hz, 1H, H-1), 3.91 (d, $J$=11.0 Hz, 1H, H-1′), 3.96–4.03 (m, 1H), 5.0 (d, $J$=10.2 Hz, 1H, one of $CH_2$=), 5.07 (d, $J$=17.4 Hz, 1H, one of $CH_2$=), 5.76–5.91 (m, 1H, CH=), 6.78–6.88 (m, 2H), 6.98 (t, $J$=9.0, 2H). $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$ 29.6, 32.1, 69.4, 72.7, 115.0, 115.5, 115.6, 116.0, 138.0, 154.6 and 154.9, 159.7. EIMS (*m*/*z*): 43 (34), 57 (22), 112 (110), 210 (12) [M$^+$].

A solution of **12** (7.4 g, 35.2 mmol), triethylamine (10 mL, 71.7 mmol) and 4-*N*,*N*′-dimethylaminopyridine (0.43 g) in dry $CH_2Cl_2$ (50 mL) at 0°C was treated with a solution of benzenesulphonyl chloride (5 mL, 38.9 mmol) in $CH_2Cl_2$ (10 mL). After stirring at rt for 6 h, the reaction mixture was concentrated and the residue passed through short silica gel column (1:4 ethyl acetate:hexane) to afford **13** (11.3 g, 92% yield) as a colorless solid.

**4.5.2. Physical data of 13**. Mp 63–64°C. $[\alpha]_D$=+5.4 (*c* 2.6, $CHCl_3$). IR ($CHCl_3$): 3415 (br), 1493, 1339, 1170, 923 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 1.88 (q, $J$=7.7 Hz, 2H, H-3, 3′), 2.0–2.23 (m, 2H, H-4, 4′), 3.88–4.08 (m, 2H, $OCH_2$), 4.82 (quint., $J$=6.4 Hz, 1H, H-5), 4.90–5.05 (m, 2H, $CH_2$=), 5.59–5.82 (m, 1H, CH=), 6.64 (m, 2H), 6.90 (t, $J$=9.1 Hz, 2H), 7.44–7.68 (m, 3H, $PhSO_2$), 7.91 (d, $J$=6.4 Hz, 2H, $PhSO_2$). $^{13}$C NMR ($CDCl_3$, 50 MHz): 28.7, 30.6, 69.1, 80.2, 115.4, 115.5, 115.7 and 116.0, 127.7, 129.1, 133.6, 136.6, 137.0, 154.1, 155.1, 159.8. EIMS (*m*/*z*): 77 (100), 112 (16), 141 (48), 162 (12), 234 (12), 350 (10) [M$^+$]. HRMS calcd for $C_{18}H_{19}FO_4S$: 350.0988. Found: 350.0996.

### 4.6. Ethyl (2*E*,6*R*)-6-benzenesulphonyloxy-7-(4-fluorophenoxy)hept-2-en-1-oate, 14

Ozone was purged through a solution of **13** (11.3 g, 32.2 mmol) in dry $CH_2Cl_2$ (100 mL) at −78°C, until the blue color persisted (∼30 min). The reaction mixture was brought to rt and then a stream of $N_2$ gas passed to remove excess of ozone. After cooling again to −78°C, dimethyl sulfide (13.9 mL, 32.5 mmol) was added. The reaction mixture was brought to rt, stirred further for 12 h, washed with water and brine, and concentrated to afford the crude aldehyde (10.8 g), which was treated with ethoxycarbonyl methylenetriphenylphosphorane (11.5 g, 33 mmol) in benzene (100 mL). After being stirred for 5 h at 60°C, the reaction mixture was concentrated and the residue chromatographed on silica gel (1:3 ethyl acetate:hexane) to afford **14** (9.6 g, 70%) as a colorless oil.

**4.6.1. Physical data of 14**. $[\alpha]_D = +5.8$ (*c* 1.5, $CHCl_3$). IR ($CHCl_3$): 2923, 1708, 1493, 1339, 1170, 830 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 1.30 (t, $J = 7.1$ Hz, 3H, $CH_3$), 1.94 (q, $J = 6.6$ Hz, 2H, H-5, 5′), 2.10–2.40 (m, 2H, H-4, 4′), 3.89–4.10 (m, 2H, $CH_2O$), 4.17 (q, $J = 7.1$ Hz, 2H, $OCH_2$), 4.82 (quint., $J = 6.6$ Hz, 1H, H-6), 5.77 (d, $J = 16.0$ Hz, 1H, H-3), 6.60–6.90 (m, 5H, aromatic and H-2), 7.47–7.98 (m, 5H). $^{13}C$ NMR ($CDCl_3$, 50 MHz): $\delta$ 14.0, 27.0, 29.8, 60.1, 69.0, 79.5, 115.4, 115.5, 116.0, 122.3, 127.7, 129.1, 133.7, 136.7, 146.4, 153.9, 155.1, 160.0, 166.1. EIMS (*m*/*z*): 41 (34), 43 (52), 55 (30), 57 (36), 77 (100), 96 (28), 125 (40), 142 (37), 152 (21), 422 (3) [$M^+$]. HRMS calcd for $C_{21}H_{23}FO_6S$: 422.1199. Found: 422.1180.

### 4.7. (2*E*,6*R*)-6-Benzenesulphonyloxy-7-(4-fluorophenoxy)-hept-2-en-1-ol, 4

DIBAL-H (14.2 mL, 14.2 mmol, 1 M solution in toluene) was added dropwise over 5 min to a solution of **14** (3 g, 7.1 mmol) in $CH_2Cl_2$ (30 mL) under $N_2$ at −78°C. The solution was stirred at the same temperature for 45 min, quenched with saturated $NH_4Cl$ solution. The reaction mixture was filtered through a pad of Celite, dried ($Na_2SO_4$) and concentrated. The residue was eluted through a column of short silica gel (50% ethyl acetate in hexane) to obtain **4** (2.23 g, 82%) as a colorless solid.

**4.7.1. Physical data of 4**. Mp 76–77°C. $[\alpha]_D = +19.5$ (*c* 0.6, $CHCl_3$). IR ($CHCl_3$): 3562, 2923, 1493, 1323, 1177, 1170, 923 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 1.30–1.46 (br s, 1H, OH), 1.82–2.0 (m, 4H, H-4, 4′, 5, 5′), 3.84–4.13 (m, 4H, H-1, 1′, 7, 7′), 4.88 (quint., $J = 5.6$ Hz, 1H, H-6), 5.5–5.73 (m, 2H, H-2, H-3), 6.57–6.72 (m, 2H), 6.92 (t, $J = 8.1$ Hz, 2H), 7.46–7.70 (m, 3H), 7.88–8.01 (d, $J = 7.7$ Hz, 2H). $^{13}C$ NMR ($CDCl_3$, 50 MHz): $\delta$ 27.3, 30.8, 63.2, 69.1, 80.3, 115.4, 115.5, 115.6, 116.0, 127.8, 129.1, 130.4, 133.7, 137.0, 154.0, 155.1, 160.1. EIMS (*m*/*z*): 41 (40), 55 (25), 67 (46), 77 (100), 93 (91), 112 (52), 141 (22), 152 (16), 380 (3) [$M^+$]. HRMS calcd for $C_{19}H_{21}FO_5S$: 380.1094. Found: 380.1098.

### 4.8. (2*S*,3*S*,6*R*)-6-Benzenesulphonyloxy-2,3-epoxy-7-(4-fluorophenoxy)heptan-1-ol, 15

Titanium tetrakis(isopropoxide) (1.9 g, 6.67 mmol) and (+)-diisopropyl tartrate (1.08 mL, 6.7 mmol) were sucessively added to a suspension of powdered molecular sieves (4 Å, 3 g), in $CH_2Cl_2$ (15 mL). After stirring for 5 min, cumene hydroperoxide (22.1 mL, 10.94 mmol, 80% solution in cumene) was added dropwise. After stirring for 15 min, the allyl alcohol **4** (2.54 g, 6.67 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise. The reaction mixture was stirred for 2.5 h at −20°C, left refrigerated overnight, quenched with 10% tartaric acid solution (1 mL) at −20°C, and allowed to warm to rt. After filtration of the reaction mixture over a Celite pad, the filtrate was dried (anhydrous sodium sulphate), and concentrated. The chromatographic purification of the residue on silica gel (1:1 ethyl acetate:hexane) afforded pure epoxy alcohol **15** (2.41 g, 92%) as a colorless solid.

**4.8.1. Physical data of 15**. Mp 109–110°C. $[\alpha]_D = +2.1$ (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): 3546, 2923, 1508, 1360, 1170, 908, 831, 754 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 1.39–2.07 (m, 4H, H-4, 4′, 5, 5′), 2.84–3.01 (m, 2H, H-2, 3), 3.54–3.72 (m, 1H, H-1), 3.82–4.08 (m, 3H, H-1, 7, 7′), 4.88 (quint., $J = 6.0$ Hz, 1H, H-6), 6.63 (dd, $J = 4.0$, 9.0 Hz, 2H) and 6.92 (t, $J = 9.0$ Hz, 2H), 7.47–7.72 (m, 3H) and 7.93 (d, $J = 7.5$ Hz, 2H). $^{13}C$ NMR ($CDCl_3$, 50 MHz): $\delta$ 27.0, 28.1, 55.1 and 58.2, 61.4, 69.1, 80.3, 115.45, 115.54, 116.0, 127.7, 129.1, 133.7, 136.9, 154.0, 155.1, 160.0. EIMS (*m*/*z*): 41 (28), 43 (40), 67 (43), 77 (100), 84 (39), 96 (39), 114 (42), 142 (27), 152 (34), 196 (13), 272 (9), 396 (8) [$M^+$]. HRMS calcd for $C_{19}H_{21}FO_6S$: 396.1043. Found: 396.1024.

### 4.9. (2*R*,3*S*,6*R*)-6-Benzenesulphonyloxy-1-chloro-2,3-epoxy-7-(4-fluorophenoxy)heptane, 3

A solution of **15** (2.25 g, 5.7 mmol) and triphenylphosphine (1.5 g, 5.7 mmol) in a solvent mixture of $CHCl_3$ and $CCl_4$ (40 mL, 1:1 ratio) containing $NaHCO_3$ (0.3 g) was refluxed for 3 h. Removal of the solvent and subsequent purification of the residue by silica gel column chromatography (1:4 ethyl acetate:hexane) afforded **3** (1.51 g, 64%) as a colorless solid.

**4.9.1. Physical data of 3**. Mp 59–60°C. $[\alpha]_D = -5.5$ (*c* 0.6, $CHCl_3$). IR ($CHCl_3$): 2939, 1493, 1369, 1185, 923 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 1.53 (q, $J = 6.8$ Hz, 1H, H-5), 1.72–2.09 (m, 3H, H-4, 5, 5′), 2.83 (td, $J = 2.3$, 5.5 Hz, 1H, H-3), 2.92 (td, $J = 2.3$, 5.5 Hz, 1H, H-2), 3.43 (dd, $J = 5.5$, 8.0 Hz, 1H, H-1), 3.58 (dd, $J = 5.5$, 8.0 Hz, 1H, H-1′), 3.87–4.10 (m, 2H, H-7, 7′), 4.86 (q, $J = 6.8$ Hz, 1H, H-6), 6.58–6.74 (m, 2H), 6.92 (t, $J = 9.0$ Hz, 2H), 7.47–7.73 (m, 3H) and 7.92 (d, $J = 7.3$ Hz, 2H, $PhSO_2$). EIMS (*m*/*z*): 41 (19), 67 (31), 77 (100), 81 (24), 83 (31), 95 (25), 125 (25), 141 (55), 145 (55), 414 (10) [$M^+$]. HRMS calcd for $C_{19}H_{20}ClFO_5S$: 414.0704. Found: 414.0721.

### 4.10. (2*S*,5*S*)-2-Ethynyl-5-[(4-fluorophenoxy)methyl]-tetrahydrofuran, 2

A solution of **3** (1.0 g, 2.41 mmol) in dry THF (8 mL) was added to lithium diisopropylamide (7.2 mmol) [generated in situ by the addition of *n*-BuLi (7.2 mL, 7.2 mmol) to a solution of diisopropylamine (1.12 mL, 8.6 mmol) in dry THF (6 mL) at −40°C and stirring for 15 min] at −40°C. The reaction was stirred for 1 h at −40°C, gradually warmed to rt and quenched with aqueous $NH_4Cl$ (1 mL). The reaction mixture was evaporated under reduced pressure and the residue taken in ethyl acetate, washed with water and brine, dried (anhydrous sodium sulphate) and concentrated. The residue after silica gel chromatographic purification (1:9 ethyl acetate:hexane) afforded **2** (0.32 g, 60%) as a colorless liquid.

**4.10.1. Physical data of 2**. $[\alpha]_D = -23.0$ (*c* 0.7, $CHCl_3$). IR ($CHCl_3$): 3308, 2923, 2123, 1600, 1493, 1212, 1046, 838 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 1.81–2.37 (m, 4H, H-3, 3′, 4, 4′), 2.39 (d, $J = 2.3$ Hz, 1H, acetylenic), 3.86–4.01 (m, 2H, $OCH_2$), 4.38–4.53 (m, 1H, H-5), 4.74

(dt, $J=3.0$, 5.6 Hz, 1H, H-2), 6.76–7.02 (m, 4H). EIMS ($m/z$): 43 (37), 55 (19), 81 (65), 95 (100), 112 (32), 125 (11), 220 (35) [$M^+$]. HRMS calcd for $C_{13}H_{13}FO_2$: 220.0899. Found: 220.0899.

### 4.11. (2*S*,5*S*)-2-(4-Hydroxyl-1-butynyl)-5-[(4-fluorophenoxy)methyl]tetrahydrofuran, 16

*n*-BuLi (5 mL, 1 M solution in hexane) was added to a solution of **15** (0.8 g, 3.6 mmol) in THF (15 mL) at −78°C. Freshly distilled $BF_3{\cdot}OEt_2$ (1.4 mL, 11.0 mmol) in THF (2 mL) was then added followed by excess of ethylene oxide in THF (5 mL). The reaction mixture was stirred at −78°C for 30 min, quenched with aqueous $NH_4Cl$ solution, and concentrated on rotary evaporator. The residue was taken in ethyl acetate, washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude product was purified by column chromatography to afford **16** (0.86 g, 90% yield) as a colorless solid.

**4.11.1. Physical data of 16**. Mp 72–73°C; lit.[4] 77–79°C. $[\alpha]_D=-34.3$ ($c$ 1.8, $CHCl_3$); lit.[4] $[\alpha]_D=-34.0$ ($c$ 1.8, $CHCl_3$). $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 1.67–1.77 (br s, 1H, OH), 1.78–2.37 (m, 4H, H-3, 4, 4′), 2.52 (dt, $J=1.7$, 6.4 Hz, 2H, ≡-$CH_2$), 3.74 (t, $J=6.4$ Hz, 2H, $CH_2OH$), 3.94 (d, $J=5.0$ Hz, 2H, $ArOCH_2$), 4.40–4.54 (m, 1H, H-5), 4.72–4.83 (m, 1H, H-2), 6.80–7.06 (m, 4H). $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$ 23.0, 17.7, 33.3, 60.7, 68.9, 70.6, 76.8, 81.1, 82.1, 115.4, 115.6, 115.8, 154.8, 159.6. EIMS ($m/z$): 65 (33), 67 (42), 69 (92), 77 (100), 79 (84), 81 (48), 83 (48), 111 (46), 112 (67), 121 (45), 125 (28), 139 (55), 152 912), 264 (8) ($M^+$+1).

### 4.12. (2*S*,5*S*)-5-[(4-Fluorophenoxyl)methyl]-2-(4-*N*,*O*-bis(phenoxycarbonyl)hydroxylamino)-1-butynyl] tetrahydrofuran, 17

To a solution of **16** (1.0 g, 3.8 mmol), triphenylphosphine (1.17 g, 4.05 mmol) and *N*,*O*-bis(phenoxycarbonyl)hydroxylamine (1.24 g, 4.05 mmol) in THF (15 mL), was added diisopropylazodicarboxylate (0.82 g, 4.05 mmol) dropwise at 0°C for 5 min. The reaction mixture was stirred at 0°C for 30 min and at rt for 6 h. Concentration of the reaction mixture and purification of the residue by silica gel chromatography (1:7 ethyl acetate:hexane) provided **17** (1.6 g, 80%).

**4.12.1. Physical data of 17**. $[\alpha]_D=-18.4$ ($c$ 0.9, $CHCl_3$). $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 1.76 (m, 1H), 1.95 (m, 1H), 2.13 (m, 2H), 2.64 (t, $J=6.8$ Hz, 2H, $CH_2N$), 3.79 (dd, $J=2.0$, 4.5 Hz), 3.95 (t, 2H, $J=6.8$ Hz, ≡-$CH_2$), 4.33 (m, 1H), 4.63 (m, 1H, H-2), 6.63–6.93 (m, 4H), 7.13–7.50 (m, 10H). FABMS at ($m/z$): 520. HRMS calcd for $C_{29}H_{27}FNO_7-M^+$+1: 520.1771. Found: 520.1770.

### 4.13. (2*S*,5*S*)-*trans*-5-[(4-Fluorophenoxy)methyl]-2-(4-*N*-hydroxyureidyl-1-butynyl)tetrahydrofuran, CMI-977, 1

Ammonia gas was purged into a solution of **17** (3.0 g, 5.8 mmol) in methanol (10 mL) at 0°C for 30 min. The reaction mixture was stirred at ambient temperature for 1 h. Rotary evaporation of the solvent, followed by purification of the residue on elution through a short silica gel pad ($CHCl_3$:MeOH, 20:1) afforded **1** (1.3 g, 70%) as a colorless solid.

**4.13.1. Physical data of 1**. Mp 106–107°C; lit.[4] 113–114°C. $[\alpha]_D=-46.8$ ($c$ 1.1, MeOH); lit.[4] $[\alpha]_D=-47.8$ ($c$ 0.3, $CD_3OD$). $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 1.83 (m, 1H, H-4), 2.01 (m, 1H, H-4′) 2.22 (m, 2H, H-3, 3′), 2.54 (t, $J=7.8$ Hz, 2H, ≡-$CH_2$), 3.68 (t, $J=7.8$ Hz, 2H, $CH_2N$), 3.91 (m, 2H, $CH_2O$), 4.46 (m, 1H, H-5), 4.73 (m, 1H, H-2), 5.68 (br s, 2H, $NH_2$), 6.78–7.02 (m, 4H), 8.95 (s, 1H, N-OH). $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$ 17.13, 27.66, 33.28, 48.62, 69.08, 70.72, 76.36, 80.72, 82.80, 115.50, 115.63, 115.97, 154.98, 159.70, 161.84. FABMS at ($m/z$): 137 (42), 154 (54), 280 (11), 324 (100) [$M^+$+1].

## Acknowledgements

A.M.S.M. thanks the CSIR for financial support in the form of a research fellowship.

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