A Versatile Approach to Anti-Asthmatic Compound CMI−977 and its Six-Membered Analogue

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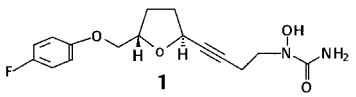
Abstract: The synthesis of the anti-asthmatic compound CMI−977 is described. The tetrahydrofuran ring was effectively constructed by involving olefin metathesis while the stereoselective introduction of the 1-*N*-hydroxyureidylbut-3-yn-4-yl side-chain was achieved by C-alkylation of the 2-benzenesulfonyl derivative.

Key words: anti-asthmatic, olefin metathesis, stereoselective synthesis, tetrahydrofuran, tetrahydropyran, nucleophilic displacement

The role of leukotrienes in inflammatory and allergic responses including arthritis, asthma, psoriasis, and thrombotic disease has been well recognized. The urge to develop antagonists or inhibitors of leukotriene biosynthesis to prevent inflammatory responses is an ongoing process.[1] Various 2,5-disubstituted tetrahydrofuran derivatives have been reported with lipoxygenase inhibitory activity.[2] However, (2*S*,5*S*)-5-(4-fluorophenoxylmethyl)-2-(1-*N*-hydroxyureidylbut-3-yn-4-yl)tetrahydrofuran (CMI−977) (**1**) is by far the most potent compound reported in this series.[3] In this communication, we report a new approach to 2,5-disubstituted tetrahydrofuran (CMI−977) as well as to the corresponding six-membered 2,6-disubstituted pyran analogue **2** based on (i) the olefin metathesis[4] and (ii) a stereoselective alkylation of 2-benzenesulfonyl derivatives.[5]



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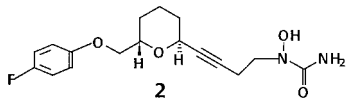

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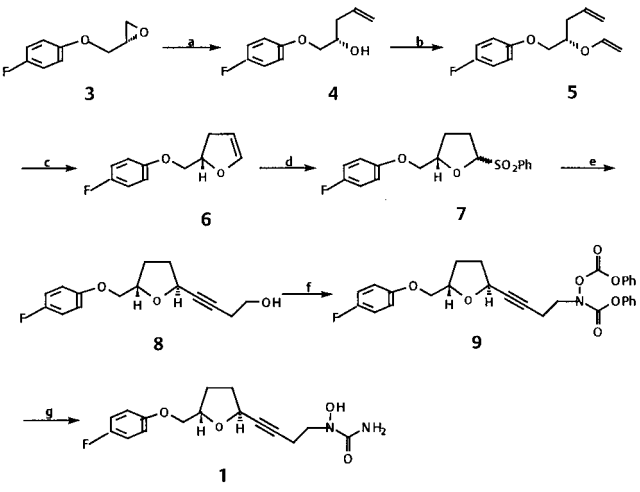
Recently we have reported an efficient approach to a *(S)*-glycidyl-4-fluorophenylether **3** in 92% ee by involving hydrolytic kinetic resolution technique.[6] Subsequent reaction of **3** with vinylmagnesium bromide in the presence of CuCN provided compound **4** in 78% yield. The conversion of free OH group into the vinyl ether[7] **5** was accomplished by treatment of **4** with ethyl vinyl ether and $Hg(OCOCF_3)_2$. The ring-closing metathesis of **5** in the presence of Grubb's catalyst (5 mol%) in refluxing benzene for 20 h gave the dihydrofuran derivative **6** in 52% yield.[8] The ^1H and ^{13}C NMR spectra of **6** were in complete agreement with the assigned structure.

The approach to incorporate 4-*N*-hydroxyureidyl-1-butynyl side chain of CMI−977 was based on Ley's alkylation[5] of 2-benzenesulfonyl tetrahydrofuran. For this endeavour, compound **6** was treated with benzenesulfinic acid in CH_2Cl_2 to give 2-benzenesulfonyltetrahydro-2*H*-furan derivative **7** in 81% yield. Subsequent C-C bond formation at C-2 was carried out by treating compound **7** with dialkyl zinc reagent derived from BrMg-C≡C-CH_2-CH_2-OTHP and $ZnBr_2$ followed by deprotection with *p*-toluenesulfonic acid (PTSA) in methanol to give a 7:3 mixture of *trans-cis* isomers. The pure *trans* isomer **8** was isolated in 50% yield after crystallization from Et_2O/light petroleum. The spectral and analytical data were in complete agreement with reported values.[3b] Introduction of *N*-hydroxy urea group was achieved in two steps involving Mitsunobu reaction of **8** with *N*,*O*-bis(phenoxycarbonyl)hydroxylamine followed by treatment of **9** with ammonia in methanol to give CMI−977 **1**. The structure of **1** was proved by comparison of its ^1H NMR, mass spectra, $[\alpha]_D$ and melting point data with those of an authentic sample[3b] (Scheme 1).



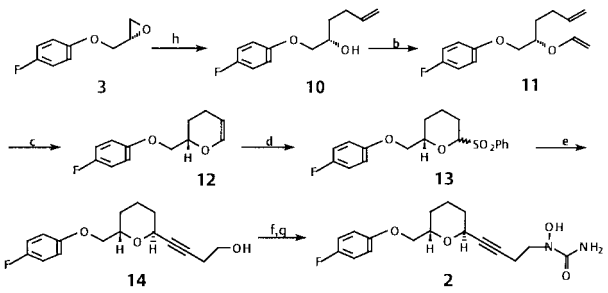
Reagents and conditions: (a) CH_2 = CHMgBr, CuCN, THF, 1.5 h; (b) $Hg(OCOCF_3)_2$, ethyl vinyl ether, 12 h; (c) Grubb's catalyst, C_6H_6, Δ, 20 h; (d) $PhSO_2H$, CH_2Cl_2, 2 h; (e) (i) *i*-PrMgBr, HC≡C-CH_2-CH_2-OTHP, $ZnBr_2$, THF, 4 h, (ii) PTSA, MeOH, 1 h; (f) Ph_3P, $PhOCONHOCO_2Ph$, DEAD, THF, 4 h; (g) NH_3/MeOH, 12 h

Scheme 1

Inspired by an efficient approach to 2,5-disubstituted tetrahydrofuran as described above, we sought to explore the versatility of this approach in the preparation of the so far

unknown six-membered 2,6-disubstituted tetrahydropyran analogue **2** of CMI−977. Availability of **2** and its biological profile is useful to evaluate the influence of ring size on the biological activity of these anti-asthmatic compounds.

Compound **3** was converted into the diene derivative **11** by first reacting with allylmagnesium bromide in the presence of CuCN to open the epoxide group followed by *O*-vinylation with ethyl vinyl ether-$Hg(OCOCF_3)_2$. The ring closing metathesis with Grubb's catalyst gave the dihydropyran derivative **12**, which was consequently converted into 2-benzenesulfonyltetrahydropyran derivative **13**. The carbon-carbon bond formation with BrMg-C≡C-CH_2-CH_2-OTHP and $ZnBr_2$ followed by deprotection gave *trans*-(2*S*,6*S*)-6-(4-fluorophenoxymethyl)-2-(1-hydroxybut-3-yn-4-yl)tetrahydropyran (**14**) as a single diastereomeric product. The formation of a single isomer during the C-C bond formation with tetrahydropyran sulfonyl derivative **13** compared to the tetrahydrofuran precursor **7** (with 7:3 selectivity) was indeed gratifying and this observation was attributed to the anomeric effect, favouring the axial bond formation.[5a] The all *trans* stereochemical assignment was provided by the extensive NOE studies carried out on this intermediate. The introduction of *N*-hydroxy urea was essentially carried out by the approach reported above for CMI−977 to give the six-membered analogue (2*S*,6*S*)-6-(4-fluorophenoxymethyl)-2-(1-*N*-hydroxyureidylbut-3-yn-4-yl)tetrahydropyran (**2**), whose structure was proved by ^1H and ^{13}C NMR spectral analysis. The lipoxygenase inhibitory activity of **2** is currently under investigation (Scheme 2).



Reagents and conditions: (b) $Hg(OCOCF_3)_2$, ethyl vinyl ether, 12 h; (c) Grubb's catalyst, C_6H_6, Δ, 20 h; (d) $PhSO_2H$, CH_2Cl_2, 2 h; (e) (i) *i*-PrMgBr, HC≡C-CH_2-CH_2-OTHP, $ZnBr_2$, THF, 6 h, (ii) PTSA, MeOH, 1 h; (f) Ph_3P, $PhOCONHOCO_2Ph$, DEAD, THF, 4 h; (g) NH_3/MeOH, 12 h; (h) CH_2 = $CHCH_2MgBr$, CuCN, Et_2O, 1.5 h

Scheme 2

In conclusion, we have reported a short and stereoselective approach to CMI−977 and its six-membered analogue. The extension of this approach to synthesize other diastereomers of CMI−977 and higher analogues are under progress.

Solvents were distilled before use. THF and Et_2O were dried over Na-benzophenone reagent. TLC was performed on precoated silica gel glass plates Merck 60 F_{254}. NMR spectra were recorded on Brucker spectrometers (AC-200, MSL-300 or DRX-500) with TMS as an internal standard. Mass spectra were recorded on Finnigan MAT-1020, and high-resolution mass spectra on VG Autospec spectrometer at 5 or 7 k resolution using perfluoro kerosene as an internal reference compound. Optical rotations were determined on JASCO 370 digital polarimeter with sodium light source. Mps were recorded on Mettler B-540 melting point apparatus.

(2*S*)-1-(4-Fluorophenoxy)pent-4-en-2-ol (4)

To a suspension of magnesium (1.63 g, 67.9 mmol) in dry THF (20 mL) at 0 °C was added a solution of vinyl bromide (3.6 g, 33.9 mmol) in dry THF (15 mL). After 0.5 h, CuCN (60 mg, 0.68 mmol) and (*S*)-4-fluorophenyl glycidyl ether (4.0 g, 23.8 mmol) were added. After stirring for 1 h at r.t., the mixture was quenched with sat. NH_4Cl, concentrated and the residue partitioned (EtOAc/H_2O). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel using EtOAC/light petroleum (1:4) to give **4** (3.64 g, 78%); $[\alpha]^{25}_D$ +15 (*c* 2.3, $CHCl_3$).

^1H NMR (200 MHz, $CDCl_3$): δ = 2.35 (dt, 2H, *J* = 7.3, 1.4 Hz), 2.51 (br s, 1H), 3.84 (dd, 1H, *J* = 9.3, 5.8 Hz), 3.92 (dd, 1H, *J* = 9.3, 4.4 Hz), 4.0 (m, 1H), 5.14 (m, 2H), 5.84 (m, 1H), 6.82 (m, 2H), 6.95 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.54, 69.06, 71.80, 115.28, 115.34 (2C), 115.52, 117.60, 133.61, 154.46, 157.99.

EI (MS): *m/z* (%) = 196 (M^+, 46), 137 (20), 112 (100), 95 (26).

Anal. Calcd for ($C_{11}H_{13}FO_2$): C, 67.35; H, 6.63. Found: C, 67.45; H, 6.73.

(2*S*)-2-(4-Fluorophenoxymethyl)-2,3-dihydro-2*H*-furan (6)

Compound **4** (3.6 g, 18.4 mmol), ethyl vinyl ether (350 mL) and $Hg(OCOCF_3)_2$ (0.8 g, 1.8 mmol) were stirred for 12 h at r.t. The reaction mixture was neutralized by addition of sat. $NaHCO_3$ and concentrated. The aqueous layer was extracted with Et_2O, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc/light petroleum (1:50) to give (2*S*)-2-(1-ethenoxy)-1-(4-fluorophenoxy)pent-4-ene (**5**) (2.85 g, 70%).

^1H NMR (200 MHz, $CDCl_3$): δ = 2.49 (dt, 2H, *J* = 7.3, 1.5 Hz), 3.97 (m, 2H), 4.04 (dd, 1H, *J* = 6.8, 1.9 Hz), 4.14 (m, 1H), 4.34 (dd, 1H, *J* = 14.2, 1.9 Hz), 5.15 (m, 2H), 5.84 (m, 1H), 6.38 (dd, 1H, *J* = 14.2, 6.8 Hz), 6.84 (m, 2H), 6.95 (m, 2H).

A solution of **5** (2.8 g, 12.6 mmol) and Grubb's catalyst (0.52 g, 0.63 mmol) in benzene (750 mL) was heated under reflux for 20 h, evaporated, and the residue chromatographed on silica gel using EtOAc/light petroleum (1:50) to give **6** (1.27 g, 52%); $[\alpha]^{25}_D$ +95 (*c* 2.3, $CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.48 (m, 1H), 2.82 (m, 1H), 3.89 (dd, 1H, *J* = 9.9, 6.6 Hz), 4.03 (dd, 1H, *J* = 9.9, 4.2 Hz), 4.90 (m, 2H), 6.29 (d, 1H, *J* = 2.2 Hz), 6.81 (m, 2H), 6.95 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.77, 70.68, 78.77, 98.85, 115.58, 115.79, 115.88 (2C), 145.24, 155.01, 159.10.

(2*S*,5*S*)-5-(4-Fluorophenoxymethyl)-2-(1-hydroxybut-3-yn-4-yl)tetrahydrofuran (8)

Compound **6** (1.2 g, 6.2 mmol) and benzenesulfinic acid (1.1 g, 7.4 mmol) in CH_2Cl_2 (20 mL) were stirred for 2 h at r.t., and filtered through Celite. The filtrate was washed with sat. $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using EtOAc/light petroleum (1:7) to give (2*S*,5*S*)-2-(benzenesulfonyl)-5-(4-fluorophenoxymethyl)tetrahydrofuran (**7**) (1.68 g, 81%).

To a solution of isopropylmagnesium bromide [prepared from magnesium (0.35 g, 14.7 mmol) and isopropyl bromide (1.2 g, 9.8 mmol) in THF] was added 4-tetrahydropyranoyl-1-butyne (1.5 g, 9.8 mmol) in THF (5 mL). After 30 min, a freshly prepared solution of $ZnBr_2$ (1 M, 5.9 mL, 5.9 mmol) in THF was introduced followed by, after 45 min, compound **7** (1.65 g, 4.9 mmol) in THF (5 mL). The reaction mixture was stirred for 3 h and then quenched with sat. NH_4Cl. THF was removed under reduced pressure and the residue partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The crude product was stirred with PTSA (0.02 g) in MeOH (10 mL) for 1 h, neutralized with Et_3N and concentrated. The residue was crystallized from Et_2O/light petroleum to yield **8** (0.65 g, 50%), mp 76 °C (Lit.[3b] mp 77−79 °C]; $[\alpha]^{25}_D$ −34.2 (*c* 1.3, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.88 (m, 1H), 2.05 (m, 1H), 2.24 (m, 2H), 2.48 (t, 2H, *J* = 6.2 Hz), 3.69 (t, 2H, *J* = 6.2 Hz), 3.91 (d, 2H, *J* = 4.7 Hz), 4.45 (m, 1H), 4.73 (m, 1H), 6.85 (m, 2H), 6.94 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.97, 27.68, 33.32, 60.74, 68.89, 70.64, 76.76, 81.13, 82.13, 115.35, 115.55, 115.80 (2C), 154.80, 159.55.

HRMS (FAB): *m/z* calc for $C_{15}H_{17}FO_3$ (M^+) 264.1161. Found: 264.1152.

Anal. Calc for $C_{15}H_{17}FO_3$: C, 68.18; H, 6.44. Found: C, 68.51; H, 6.35.

(2*S*,5*S*)-5-(4-Fluorophenoxymethyl)-2-(1-*N*-hydroxyureidyl-but-3-yn-4-yl)tetrahydrofuran (1)

A mixture of **8** (0.62 g, 2.3 mmol), Ph_3P (0.74 g, 2.8 mmol), *N,O*-bis(carbophenoxy)hydroxylamine (0.64 g, 2.8 mmol) and diethyl azodicarboxylate (DEAD) (0.49 g, 2.8 mmol) in THF (10 mL) was stirred at r.t. for 4 h, and concentrated. The residue was dissolved in EtOAc washed with H_2O, dried (Na_2SO_4) and concentrated. The product was purified on silica gel using EtOAc/light petroleum (1:6) to give (2*S*,5*S*)-5-(4-fluorophenoxymethyl)-2-(1-*N*,*O*-bis(phenoxycarbonyl)hydroxyaminobut-3-yn-4-yl)tetrahydrofuran (**9**) (1.1 g, 90%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.96 (m, 1H), 2.14 (m, 1H), 2.31 (m, 2H), 2.84 (t, 2H, *J* = 6.8 Hz), 4.0 (dd, 2H, *J* = 4.5, 2.0 Hz), 4.14 (t, 2H, *J* = 6.8 Hz), 4.53 (m, 1H), 4.82 (m, 1H), 7.0 (m, 4H), 7.25−7.55 (m, 10H).

A solution of **9** (1.0 g, 1.9 mmol) in sat. methanolic ammonia (10 mL) was stirred for 12 h at r.t., and concentrated. The residue was purified on silica gel using EtOAc/light petroleum (1:1) to give **1** (0.39 g, 64%); mp 107 °C (Lit.[3b] mp 113−114 ºC) $[\alpha]^{25}_D$ −47 (*c* 1, MeOH); [Lit.[3b] $[\alpha]^{25}_D$ −47.8 (*c* 0.3, CD_3OD)].

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.82 (m, 1H), 2.01 (m, 1H), 2.22 (m, 2H), 2.54 (t, 2H, *J* = 7.9 Hz), 3.68 (t, 2H, *J* = 7.9 Hz), 3.91 (m, 2H), 4.46 (m, 1H), 4.73 (m, 1H), 5.68 (br s, 2H), 6.78−7.02 (m, 4H), 8.95 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): = δ 17.13, 27.66, 33.28, 48.62, 69.08,76.36, 76.72, 80.72, 82.80, 115.50 (2C), 115.63, 115.97, 154.98, 159.70, 161.84.

HRMS (FAB): *m/z* calc for $C_{16}H_{20}N_2O_4F$ ($M+H^+$) 323.1407. Found: 323.1424.

(2*S*)-1-(4-Fluorophenoxy)hex-5-en-2-ol (10)

To a solution of allylmagnesium bromide [prepared from magnesium (1.23 g, 51.4 mmol) and allyl bromide (3.1 g, 25.7 mmol) in dry Et_2O (10 mL)] was successively added CuCN (45 mg) and *(S)*-4-fluorophenyl glycidyl ether (3.0 g, 18.0 mmol). The reaction mixture was stirred for 15 min at r.t., quenched with sat. NH_4Cl and concentrated. The residue was dissolved in EtOAc, washed with H_2O, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel using EtOAc/light petroleum (1:4) to give **10** (3.0 g, 80%); $[\alpha]^{25}_D$+21.4 (*c* 2.1, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.65 (m, 2H), 2.18 (m, 2H), 2.65 (br s, 1H), 3.85 (m, 2H), 4.0 (m, 1H), 5.02 (m, 2H), 5.83 (m, 1H), 6.85 (m, 2H), 6.95 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.55, 32.11, 69.40, 72.75, 115.01, 115.42, 115.50, 115.57, 115.96, 137.91, 154.64, 159.69.

EI (MS): *m/z* (%) = 210 (M^+, 17), 126 (19), 112 (100), 95 (18).

Anal. Calc for $C_{12}H_{15}O_2F$: C, 68.57; H, 7.14. Found: C, 68.35; H, 7.23.

(2*S*)-2-(4-Fluorophenoxymethyl)-3,4-dihydro-2*H*-pyran (12)

Compound **10** (2.95 g, 14.0 mmol), ethyl vinyl ether (250 mL), and $Hg(OOCCF_3)$ (0.6 g, 1.4 mmol) were stirred for 12 h and worked-up as described earlier for **5**. The residue was purified on silica gel using EtOAc/light petroleum (1:50) to give (2*S*)-2-(1-ethenoxy)-1-(4-fluorophenoxy)hex-5-ene (**11**) (2.32 g, 70%).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.82 (m, 2H), 2.23 (m, 2H), 3.9−4.2 (m, 4H), 4.34 (dd, 1H, *J* = 14.2, 1.4 Hz), 5.05 (m, 2H), 5.83 (m, 1H), 6.39 (dd, 1H, *J* = 14.2, 6.4 Hz), 6.85 (m, 2H), 6.95 (m, 2H).

The above product **11** (2.3 g, 9.7 mmol), Grubb's catalyst (0.4 g, 0.48 mmol) in benzene (600 mL) were heated under reflux for 20 h and processed as described earlier for **6**, to give **12** (1.11 g, 55%); $[\alpha]^{25}_D$ +47.3 (*c* 1.6, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.65−2.4 (m, 4H), 3.83 (dd, 1H, *J* = 5, 9.3 Hz), 3.95 (dd, 1H, *J* = 9.3, 6.1 Hz), 4.16 (m, 1H), 4.71 (m, 1H), 6.39 (d, 1H, *J* = 5 Hz), 6.8−7.0 (m, 4H).

EI (MS): *m/z* (%) = 208 (M^+, 40), 125 (19), 112 (100), 95 (27), 83 (45).

Anal. Calc for $C_{12}H_{13}O_2F$: C, 69.23; H, 6.25. Found C, 68.97; H, 6.42.

(2*S*,6*S*)-6-(4-Fluorophenoxymethyl)-2-(1-hydroxybut-3-yn-4-yl)tetrahydropyran (14)

A solution of **12** (1.1 g, 5.3 mmol) and benzenesulfinic acid (0.9 g, 6.3 mmol) in CH_2Cl_2 (20 mL) were stirred for 2 h at r.t. and processed as described earlier for **7**. The resulting product (2*RS*,6*S*)-2-(benzenesulfonyl)-6-(4-fluorophenoxymethyl)tetrahydropyran (**13)** (1.52 g) was reacted with isopropylmagnesium bromide prepared from magnesium (0.3 g) and isopropyl bromide (1.05 g), 4-tetrahydropyranoylbut-1-yne (1.32 g, 8.6 mmol), $ZnBr_2$ solution (1 M, 5.14 mL, 5.14 mmol) in THF (20 mL). After usual processing, the product was treated with PTSA (25 mg) in MeOH (10 mL) to cleave the THP group, neutralized with Et_3N and concentrated. The crude product was chromatographed on silica gel using EtOAc/light petroleum (1:8) to obtain **14** (0.83 g, 70%); $[\alpha]^{25}_D$ −32 (*c* 1.1, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.5−2.1 (m, 6H), 2.55 (m, 2H), 3.73 (t, 2H, *J* = 6.3 Hz), 3.82 (dd, 1H, *J* = 9.7, 6.4 Hz), 3.98 (dd, 1H, *J* = 9.7, 4.7 Hz), 4.22 (m, 1H), 4.8 (s, 1H), 6.83 (m, 2H), 6.93 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.88, 23.18, 27.04, 30.38, 61.11, 65.52, 69.96, 71.92, 80.08, 84.02, 115.12, 115.63, 115.72, 115.79, 154.97, 158.28.

EI (MS): *m/z* (%) = 278 (M^+, 18), 153 (28), 125 (37), 112 (100), 95 (75), 79 (73).

Anal. Calc for $C_{16}H_{19}O_3F$: C, 69.06; H, 6.83. Found: C, 68.98; H, 7.05.

(2*S*,6*S*)-6-(4-Fluorophenoxymethyl)-2-(1-*N*-hydroxyureidyl -3-butyn-4-yl)tetrahydropyran (2)

Compound **2** (65%) was obtained from **14** by the same procedure as described for compound **1**.

$[\alpha]^{25}_{D}$ −28.6 (*c* 1.2, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.5−2.0 (m, 6H), 2.52 (t, 2H, *J* = 7.3 Hz), 3.65 (t, 2H, *J* = 7.3 Hz), 3.83 (m, 2H), 4.2 (m, 1H), 4.75 (s, 1H), 5.77 (br s, 2H), 6.75−7.0 (m, 4H), 9.0 (br s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.15, 18.71, 27.80, 30.40, 48.95, 65.43, 69.98, 72.24, 79.53, 84.54, 115.52, 115.82, 115.94, 116.03, 155.01, 159.01, 161.84.

Anal. Calc for $C_{17}H_{21}N_2O_4F$: C, 60.71; H, 6.25, N, 8.33. Found: C, 60.60; H, 6.42; N, 8.25.

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