

Stereoselective Total Synthesis of the Potent Anti-Asthmatic Compound CMI-977 (LDP-977)

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Neste trabalho, uma síntese curta e eficiente para o CMI-977 (LDP-977), um potente agente antiastmático oralmente ativo, é descrita. As etapas chave envolveram uma ciclização oxidativa de Mukaiyama, fornecendo a unidade *trans*-THF (tetrahidrofurano) e uma reação de homologação de Seyferth-Gilbert para construção da tripla ligação da molécula alvo. A síntese do bloco de construção chiral chave foi realizada a partir do emprego da resolução cinética hidrolítica de Jacobsen.

A short and efficient stereoselective total synthesis of CMI-977 (LDP-977), a potent and orally active anti-asthmatic compound, was developed. The key steps involve a highly diastereoselective Mukaiyama oxidative cyclization, which provides the *trans*-THF (tetrahydrofuran) unit and a Seyferth-Gilbert homologation to construct the triple bond in the target molecule. The synthesis of the key chiral building block was performed using Jacobsen hydrolytic kinetic resolution.

Keywords: total synthesis, CMI-977, Mukaiyama oxidative cyclization, Jacobsen hydrolytic kinetic resolution, Seyferth-Gilbert homologation

Introduction

Asthma is a chronic inflammatory disease of the respiratory system that results in the reduction or even the obstruction of air flow into the lungs.¹ Over the last 40 years, there have been sharp increases in the global prevalence of asthma and the mortality due to this condition. In 2006, approximately 300 million people worldwide developed asthma, and there are approximately 180,000 deaths annually.² In Brazil, asthma is the third most common cause of hospitalization in the Brazilian Unified Health System (SUS).³ The underdiagnosis and undertreatment of this disease have motivated the scientific community to search for new target-specific drugs to treat asthma and related respiratory diseases.⁴

The compound CMI-977 (LDP-977) (**1**) was discovered by Cyto-Med Inc., USA,⁵ and has been demonstrated to be a prominent candidate for the treatment of chronic asthma (Figure 1). This compound inhibits the 5-lipoxygenase pathway, thus blocking the production of leukotrienes.⁶ LDP-977 (**1**), containing a THF-2,5-*trans*-substituted ring with a (2*S*,5*S*) configuration, is orally active, and exhibits a good safety profile, a high degree of potency and excellent oral bioavailability relative to the three other stereoisomers.⁵

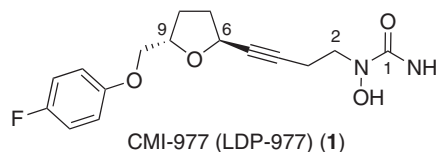
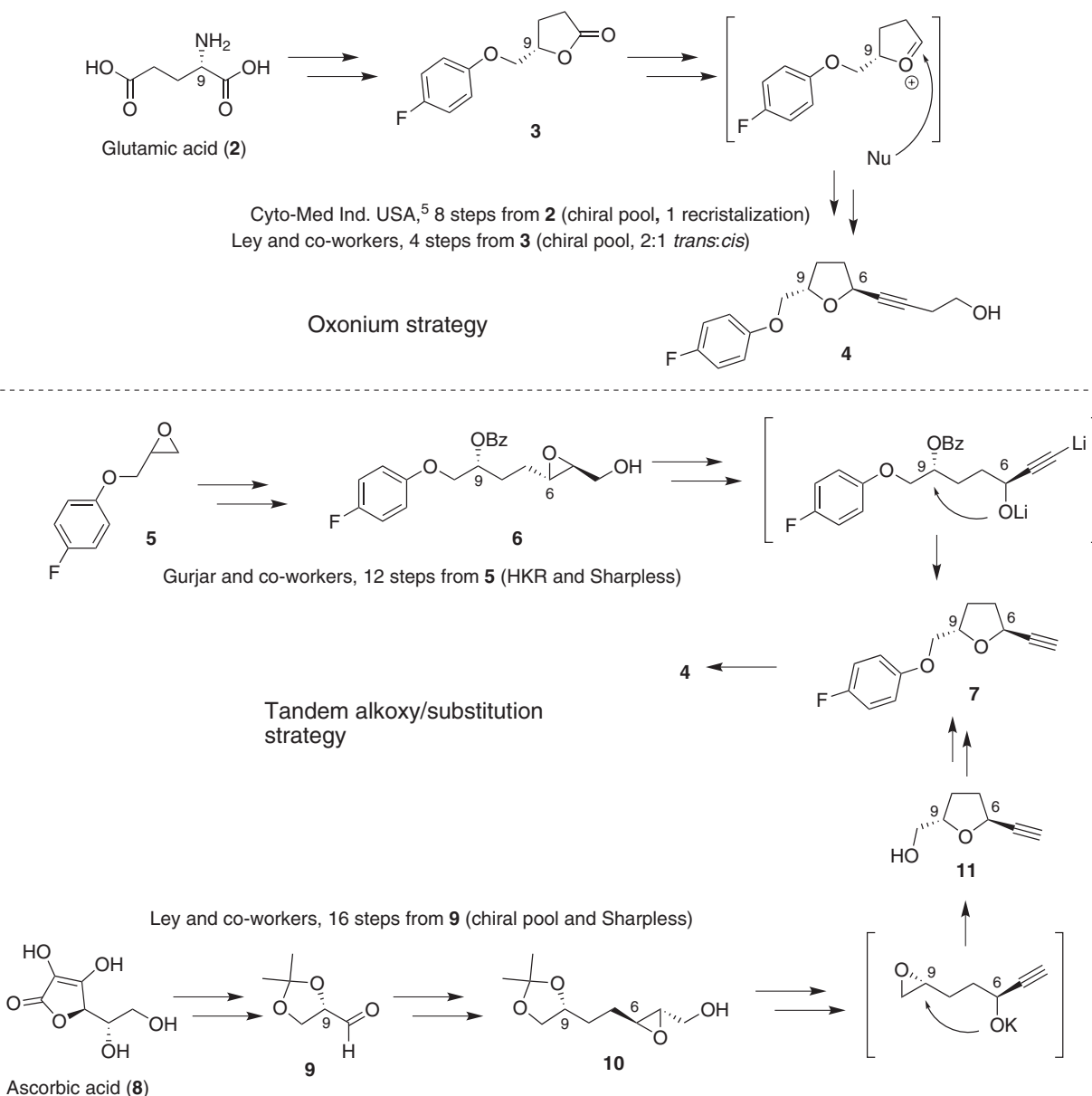


Figure 1. Chemical structure of CMI-977 (LDP-977) (**1**).

Over the years, several synthetic routes have been proposed for the stereoselective synthesis of the THF moiety present in CMI-977 (**1**) (Scheme 1).^{5,7,8} Intermediate **4** was prepared by Cyto-Med Inc., USA, using the first synthetic route developed,⁵ which involved a chiral pool approach for the creation of the C9 stereogenic center (Scheme 1). A nucleophilic attack involving an oxonium electrophile intermediate, obtained from **3**, produced **6**, but a disappointing low degree of selectivity was observed. In a similar oxonium strategy, Ley and co-workers⁷ employed an anomeric oxygen to promote the carbon rearrangement of an alkynyltributylstannane to access the THF unit, but their reaction also exhibited low selectivity (Scheme 1). Other similar strategies have led to similar results.⁸

Gurjar *et al.*⁹ reported a new stereoselective approach that installs the stereocenters at C6 and C9 in **6** using both Jacobsen hydrolytic kinetic resolution (HKR) and a Sharpless asymmetric epoxidation step (Scheme 1). The formation of a tandem propargyl alkoxide followed by

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Scheme 1. Synthetic approaches to the THF unit of CMI-977 (LDP-977) (**1**).

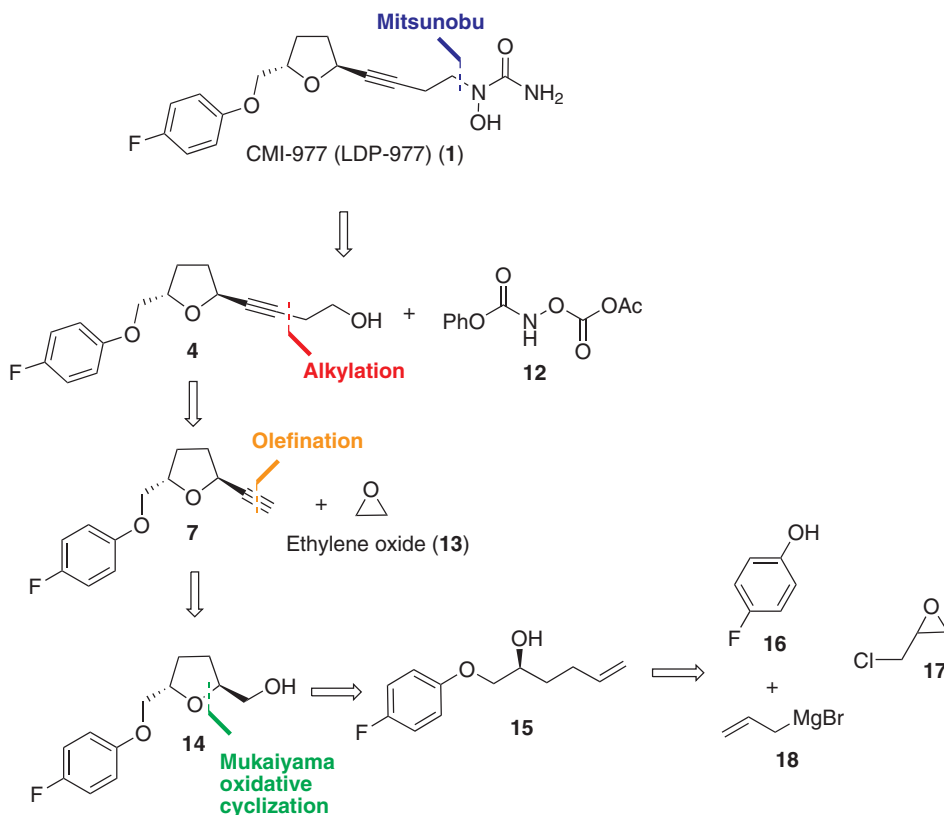
intramolecular substitution resulted in the creation of the key tetrahydrofuran ring intermediate **7**. Ley and co-workers¹⁰ also explored a similar tandem strategy providing the suitable intermediate **11**, which in turn afforded the key fragment **7**. These two new approaches were clearly superior for the construction of the 2,5-anti THF unit as higher levels of diastereoselectivity were achieved. However, numerous steps are involved in these synthetic routes.

In this paper, it is described our approach for the total synthesis of CMI-977 (LDP-977) (**1**). The biological importance of the target molecule and its structural features inspired us to devise a more concise and diastereoselective route to achieve the THF-2,5-*trans* ring of intermediate **7**.

Results and Discussion

Retrosynthetic analysis of CMI-977 (LDP-977) (**1**)

Our disconnection approach began with a long-established strategy for the insertion of the *N*-hydroxy urea moiety by alkylation involving acetylene **7** and epoxide **13**, followed by a Mitsunobu-like reaction involving alcohol **4** and hydroxycarbamate **12** (Scheme 2).^{9,10} The terminal acetylene **7** can be assembled via Seyferth-Gilbert homologation (using the Ohira-Bestmann protocol)¹¹ involving the aldehyde prepared from alcohol **14**. It was intended to create the *trans*-THF configuration in our key fragment **14** using a Mukaiyama oxidative cyclization



Scheme 2. Retrosynthetic analysis of CMI-977 (LDP-977) (1).

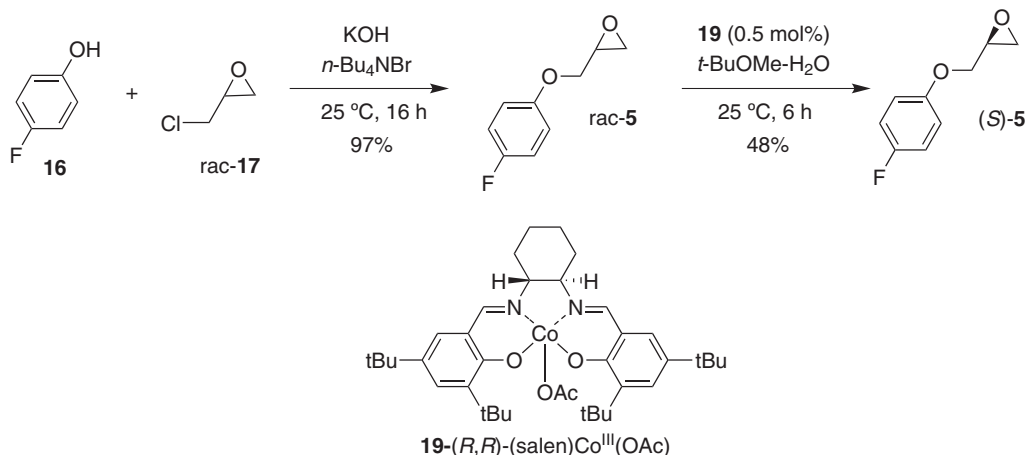
protocol with homoallylic alcohol **15**.¹² The functional groups in fragment **15** could be installed starting from commercially available and inexpensive 4-fluorophenol **16**, rac-epichlorohydrin **17** and allylmagnesium bromide **18**, in a strategy similar to that applied by Gurjar *et al.*⁹

Preparation of the key fragment **14**

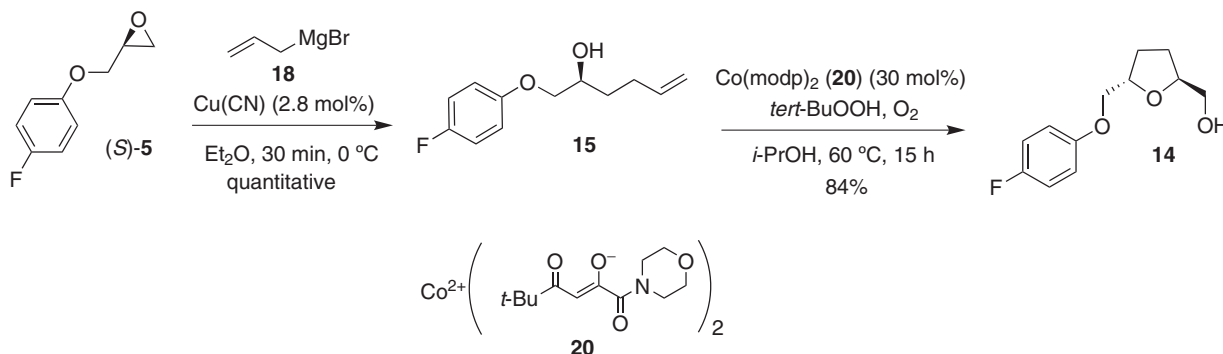
Our approach to the total synthesis of CMI-977 (LDP-977) (1) began with the reaction of *p*-fluorophenol **16**

with rac-epichlorohydrin **17** in the presence of KOH, providing rac-**5** in 97% yield (Scheme 3).¹³ The epoxide rac-**5** was resolved by hydrolytic kinetic resolution under Jacobsen conditions,¹⁴ using the catalyst (*R,R*)-(salen)Co^{III}(OAc) (**19**, 0.5 mol%) and H₂O (0.57 equiv) in *tert*-butyl methyl ether, providing (*S*)-**5** in a 48% yield.⁹

The next step involved the epoxide ring-opening of (*S*)-**5** with allylmagnesium bromide (**18**), providing homoallylic alcohol **15** in a quantitative yield (Scheme 4). The subsequent oxidative cyclization of **15** according to the



Scheme 3. Preparation of epoxide (*S*)-5.



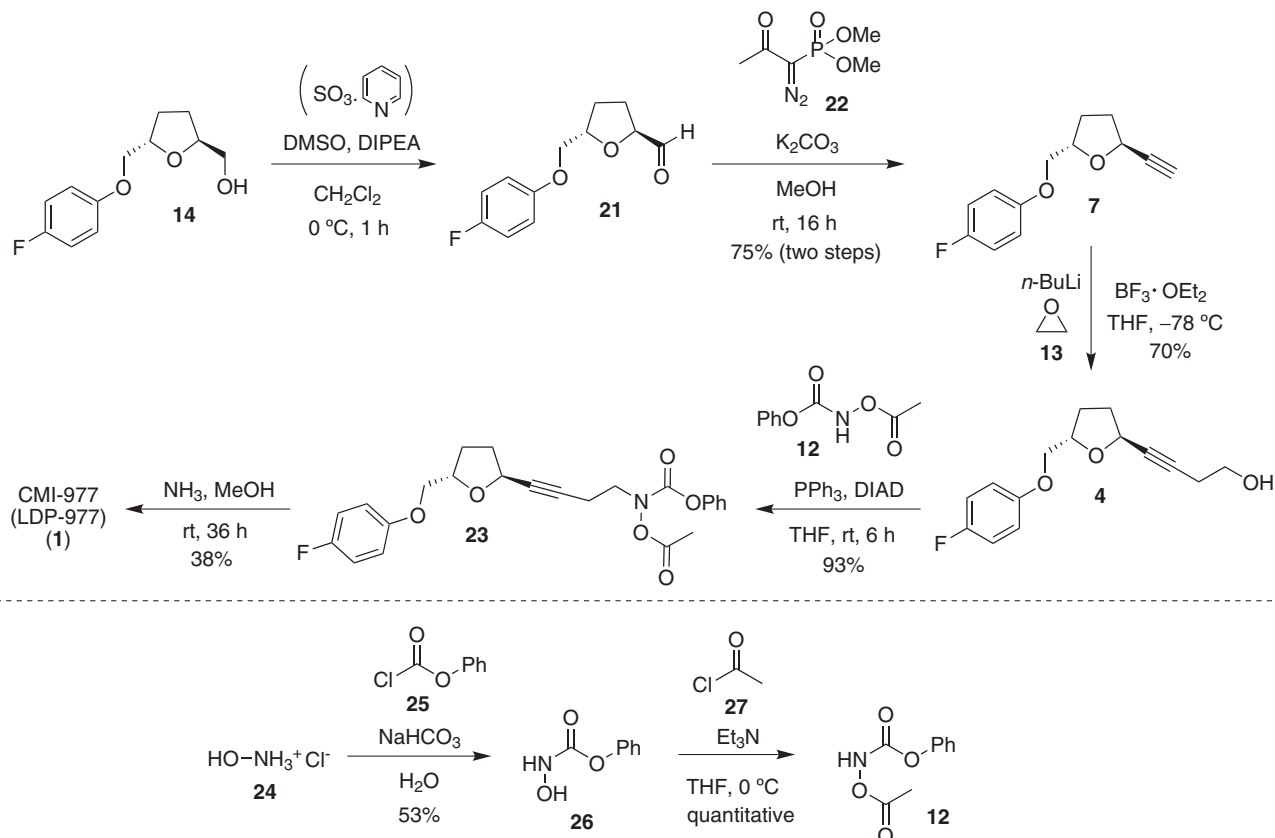
Scheme 4. Preparation of 2,5-*trans*-THF **14**.

Mukaiyama protocol,¹² mediated by the Co(modp)_2 (**20**) (30 mol%) catalyst,¹⁵ provided *trans*-THF **14** as the only observed diastereoisomer in an 84% yield.⁸ This approach has proven to be a powerful strategy for accessing the 2,5-*trans*-THF unit in a highly diastereoselective fashion.

Preparation of the key fragment **4** and conclusion of the synthesis

The alcohol **14** was then oxidized to aldehyde **21** under Parikh-Doering conditions, followed by Seyferth-Gilbert homologation¹⁶ using the Ohira-Bestmann reagent **22**,¹¹ assembling the terminal acetylene **7** in a 75% yield

over two steps (Scheme 5). The ¹H NMR and ¹³C NMR spectra and the optical rotation of *trans*-THF **7** matched the reported values for this compound.⁹ Next, the treatment of **7** with *n*-BuLi and ethylene oxide **13** led to alcohol **4** in a 70% yield. As shown in Scheme 5, the preparation of hydroxycarbamate **26** (53% yield), followed by its acetylation using acetyl chloride **27**, provided **12** in a quantitative yield. A Mitsunobu-like reaction between alcohol **4** and *N*-hydroxycarbamate **12** provided **23** in a 93% yield. Finally, **23** was ammonolysed with $\text{NH}_3\text{-MeOH}$, yielding CMI-977 as a white solid in a 38% yield. The spectral and physical data of the synthetic sample were in complete agreement with those reported in the literature.^{5,7-9}



Scheme 5. Preparation of alcohol **4** and conclusion of the synthesis of CMI-977 (LDP-977) (**1**).

Conclusions

In conclusion, it was developed a novel total synthesis of CMI-977 (LDP-977) (**1**) involving 9 steps from fluorophenol **16**. This route is more concise than the previous synthetic routes reported for CMI-977 (LDP-977) (**1**). Our synthetic strategy employed a high diastereoselective Mukaiyama oxidative cyclization provide the *trans*-THF ring, and this approach reduced the number of reaction steps necessary to achieve the acetylenic intermediate **4**. This intermediate was obtained in a highly stereoselective fashion using amenable and easily scalable reactions. Moreover, the key chiral epoxide was prepared by Jacobsen hydrolytic kinetic resolution, and the starting reagents are commercially and readily available.

Experimental

((2*S*,5*S*)-5-((4-Fluorophenoxy)methyl)tetrahydrofuran-2-yl) methanol (**14**)

Co(modp)₂ (**20**) (1.37 g, 2.80 mmol)¹⁵ was added to a solution of **15** (1.91 g, 8.45 mmol) in *i*-PrOH (137 mL), followed by the addition of *tert*-BuOOH (1.7 mL, 9.1 mmol, 5.5 mol L⁻¹ in nonane).⁸ The mixture was heated to 60 °C and stirred overnight under an O₂ atmosphere at this temperature. The solution was cooled to 25 °C and quenched with a saturated aqueous solution of Na₂S₂O₃ (15 mL). The mixture was concentrated, and the residue was diluted with a saturated aqueous solution of NH₄Cl (20 mL) followed by extraction with EtOAc (20 mL). The organic layer was concentrated under reduced pressure, and the residue was purified by flash column chromatography using a mixture of hexane/EtOAc (60:40) as the eluent, providing **14** (0.532 g, 2.35 mmol) as a colorless oil in an 84% yield; [α]_D²⁰ +18 (*c* 1.5, CHCl₃); ¹H NMR (CDCl₃, 250 MHz) δ 1.70-1.89 (m, 2H), 1.97-2.19 (m, 3H), 3.52 (dd, 1H, *J* 6.0 and 11.0 Hz), 3.68-3.72 (m, 1H), 3.86-3.96 (m, 2H), 4.13-4.22 (m, 1H), 4.32-4.42 (m, 1H), 6.81-6.98 (m, 4H); ¹³C NMR (CDCl₃, 62.9 MHz) δ 27.0 (CH₂), 28.4 (CH₂), 64.4 (CH₂), 71.0 (CH₂), 77.2 (CH), 79.7 (CH), 115.6 (CH), 115.9 (CH), 155.0 (C₀), 155.5 (C₀), 159.2 (C₀); IR (film) ν_{max}/cm⁻¹ 3447, 3055, 2979, 2930, 2876, 2306, 1507, 1455, 1266, 1211, 1098, 1073, 1043, 830, 738; HRMS (EI-TOF) *m/z* [M]⁺ for C₁₂H₁₃FO₃ calcd. 226.1005, observed 226.1019.

(2*S*,5*S*)-2-Ethynyl-5-((4-fluorophenoxy)methyl) tetrahydrofuran (**7**)

A solution of **14** (3.315 g, 14.7 mmol) in CH₂Cl₂ (180 mL) was cooled to 0 °C. DMSO (dimethyl sulfoxide,

10.5 mL, 148.5 mmol) and DIPEA (diisopropylethylamine, 12 mL, 75 mmol) were added to the mixture, which was then stirred for 5 min, followed by the addition of SO₃·pyridine (7.05 g, 45 mmol). After stirring for 1 h at 0 °C, the reaction was diluted in CH₂Cl₂, quenched with a saturated aqueous solution of NaHCO₃ (150 mL) and extracted with CH₂Cl₂ (3 × 150 mL). The organic phase was washed with water (150 mL) and brine (150 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure, providing aldehyde **21** (3.3 g), which was used in the next step without further purification.

To a solution of **21** (3.2 g, 14.7 mmol) in methanol (335 mL), it was added the Ohira-Bestmann reagent¹¹ (3.9 g, 30 mmol), followed by the addition of K₂CO₃ (3.4 g, 33 mmol). The mixture was stirred at room temperature overnight and quenched with a saturated aqueous solution of NH₄Cl (50 mL). The mixture was then extracted with Et₂O (2 × 300 mL), and the organic layer dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel 200-400 mesh) using a mixture of hexane/EtOAc (90:10) as the eluent, providing alkyne **7** (2.37 g, 10.8 mmol) as a colorless oil in a 75% yield over two steps; [α]_D²⁰ -29 (*c* 0.7, CHCl₃), [α]_D -23.0 (*c* 0.7, CHCl₃);⁹ ¹H NMR (CDCl₃, 250 MHz) δ 1.84-2.28 (m, 4H), 2.45 (d, 1H, *J* 2.5 Hz), 3.93 (d, 2H, *J* 5.0 Hz), 4.43-4.50 (m, 1H), 4.72-4.78 (m, 1H), 6.82-6.99 (m, 4H); ¹³C NMR (CDCl₃, 62.9 MHz) δ 27.7 (CH₂), 33.2 (CH₂), 68.6 (CH), 70.6 (CH₂), 72.8 (C₀), 77.0 (CH), 83.5 (CH), 115.6 (CH), 115.7 (CH), 115.9 (CH), 155.0 (C₀), 155.5 (C₀), 159.3 (C₀); IR (film) ν_{max}/cm⁻¹ 3300, 3076, 3055, 2982, 2951, 2928, 2876, 2114, 1863, 1734, 1601, 1506, 1456, 1335, 1294, 1250, 1209, 1097, 1072, 1043, 1009, 887, 829, 758, 636; HRMS (EI-TOF) *m/z* [M]⁺ for C₁₃H₁₃FO₂ calcd. 220.0900, observed 220.0910.

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

A solution of *n*-BuLi (0.25 mL, 0.625 mmol, 2.5 mol L⁻¹ in hexane) was added to a solution of **7** (0.10 g, 0.45 mmol) in THF (1.9 mL) at -78 °C. BF₃·OEt₂ (0.18 mL, 1.4 mmol) in THF (0.25 mL) was added to the mixture, followed by the addition of a solution of ethylene oxide (0.27 mL, 0.68 mmol, 2.5 mol L⁻¹ in THF). The mixture was stirred at -78 °C for 30 min, quenched with a saturated aqueous solution of NH₄Cl, and concentrated under reduced pressure. The residue was dissolved in EtOAc (10 mL), washed with H₂O (5 mL) and brine (5 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Finally, the residue was purified by flash column chromatography using a mixture of hexane/EtOAc (1:1) as the eluent,

providing **4** (0.081 g, 30.6 mmol) as a white solid in a 70% yield; mp 62–68 °C; $[\alpha]_D^{20}$ –29 (*c* 1.8, CHCl₃), $[\alpha]_D$ –34.3 (*c* 1.8, CHCl₃);⁹ ¹H NMR (CDCl₃, 250 MHz) δ 1.57–2.32 (m, 6H), 2.49 (dt, 2H, *J* 1.6 and 6.2 Hz), 3.36–3.59 (m, 1H), 3.71 (m, 2H), 3.92 (d, 2H, *J* 4.7 Hz), 4.41–4.51 (m, 1H), 4.72–4.77 (m, 1H), 6.81–6.98 (m, 4H); ¹³C NMR (CDCl₃, 62.9 MHz) δ 23.1, 27.8, 33.5, 60.9, 61.8, 69.0, 70.7, 76.9, 81.5, 82.0, 115.5, 115.9, 154.9, 155.4, 159.2; IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3479, 3078, 2920, 2872, 2237, 1601, 2506, 1456, 1350, 1296, 1248, 1209, 1099, 1074, 1057, 1040, 1003, 928, 833, 760; HRMS (ESI-TOF) *m/z* [M + Na]⁺ for C₁₅H₁₇FO₃ calcd. 287.1060, observed 287.1048.

Phenyl hydroxycarbamate (**26**)

To a solution of hydroxylammonium chloride **24** (2.0 g, 28.8 mmol) in H₂O (60 mL), it was added NaHCO₃ (4.3 g, 50.8 mmol) at 25 °C, and the mixture stirred for 10 min. Then, the reaction was cooled to 0 °C, and phenyl chloroformate **25** (3.54 mL, 28.2 mmol) was added dropwise. The mixture was stirred for 5 h at 25 °C, and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (2 × 30 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Finally, the residue was purified by flash column chromatography using a mixture of CH₂Cl₂/MeOH (10:1) as the eluent, providing **26** (2.30 g, 14.9 mmol) as a white solid in a 53% yield; mp 104–106 °C; ¹H NMR (250 MHz, DMSO) δ 7.05–7.42 (m, 5H), 9.05 (s, 1H), 10.23 (bs, 1H); IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3302, 1711, 1688, 1512, 1491, 1285, 1207, 1105, 1026, 910, 795, 687.

Phenyl acetoxycarbamate (**12**)

To a solution of phenyl hydroxycarbamate **26** (1.8 g, 6.5 mmol) in THF (100 mL) at 0 °C, it was added Et₃N (1.6 mL, 6.2 mmol) and acetyl chloride **27** (0.47 mL, 6.6 mmol). The solution was left standing until the starting material could not be detected by TLC. H₂O (5 mL) was then added, and the mixture was extracted with CH₂Cl₂ (3 × 5 mL), dried over Na₂SO₄ and concentrated under reduced pressure, providing **12** (1.27 g, 6.5 mmol) as a white solid in quantitative yield; mp 79–82 °C; ¹H NMR (CDCl₃, 250 MHz) δ 2.23 (s, 3H), 7.12–7.43 (m, 5H), 8.57 (s, 1H); IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3259, 2941, 1796, 1749, 1591, 1477, 1458, 1369, 1246, 1180, 1084, 1024, 1005, 852, 756, 690.

Phenyl acetoxyl(4-((2*S*,5*S*)-5-((4-fluorophenoxy)methyl)tetrahydrofuran-2-yl)but-3-ynyl)carbamate (**23**)

To a solution of **4** (88 mg, 0.33 mmol), PPh₃ (0.10 g, 0.35 mmol) and phenyl acetoxycarbamate **12** (0.068 g,

0.35 mmol) in THF (1.5 mL) were added DIAD (diisopropyl azodicarboxylate, 0.070 mL, 71 mg, 0.35 mmol), and the mixture was stirred for 30 min at 0 °C. The reaction was then stirred at room temperature for 6 h. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography using a mixture of hexane/EtOAc (7:3) as the eluent, providing **23** (0.136 g, 0.310 mmol) as a colorless oil in 93% yield; $[\alpha]_D^{20}$ –14 (*c* 0.8, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 1.81–1.88 (m, 1H), 1.96–2.03 (m, 1H), 2.22 (s, 3H), 2.63 (dt, 2H, *J* 1.7 and 7.2 Hz), 3.92 (d, 4H, *J* 4.8 Hz), 4.43–4.47 (m, 1H), 4.71–4.75 (m, 1H), 6.82–6.86 (m, 2H), 6.93–6.97 (m, 2H), 7.13–7.17 (m, 3H), 7.20–7.26 (m, 1H), 7.34–7.39 (m, 3H); ¹³C NMR (CDCl₃, 125.7 MHz) δ 17.8 (CH₂), 18.3 (CH₃), 27.7 (CH₂), 33.3 (CH₂), 49.4 (CH₂), 68.9 (CH), 70.7 (CH₂), 76.8 (CH), 81.2 (C₀), 81.6 (C₀), 115.6 (CH), 121.4 (CH), 125.9 (CH), 129.4 (CH), 150.6 (C₀), 153.2 (C₀), 154.91 (C₀), 156.3 (C₀), 158.2 (C₀), 168.2 (C₀), 165.5 (C₀), 168.2 (C₀); HRMS (ESI-TOF) *m/z* [M + H]⁺ for C₂₄H₂₅FNO₆ calcd. 442.1666, observed 442.1715.

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

To a round-bottomed flask, it was added **15** (85 mg, 0.19 mmol) at 0 °C. Then, NH₃ (2 mL, 14 mmol, 7 mol L⁻¹ in MeOH) was added, and the mixture was stirred at 0 °C for 36 h. The reaction was concentrated under reduced pressure and purified by flash column chromatography using a mixture of CHCl₃/MeOH (20:1) as the eluent, providing the compound CMI-977 (**1**) (24 mg, 0.074 mmol) as a colorless solid in a 38% yield; mp 106–107 °C, 106–107 °C; $[\alpha]_D^{20}$ –40 (*c* 1.1, MeOH), $[\alpha]_D$ –46.0 (*c* 1.1, MeOH);⁹ ¹H NMR (CDCl₃, 250 MHz) δ 1.19 (s, 1H), 1.67–1.81 (m, 1H), 1.86–1.98 (m, 1H), 2.08–2.21 (m, 2H), 2.46 (t, 2H, *J* 6.5 Hz), 3.60 (t, 2H, *J* 6.8 Hz), 3.77–3.89 (m, 2H), 4.34–4.43 (m, 1H), 4.63–4.67 (m, 1H), 5.48 (s, 2H), 6.74–6.92 (m, 4H), 8.60 (br, 1H); ¹³C NMR (CDCl₃, 150.9 MHz) δ 17.2 (CH₂), 27.7 (CH₂), 33.3 (CH₂), 48.7 (CH₂), 69.1 (CH), 70.7 (CH₂), 76.9 (CH), 80.7 (C₀), 82.9 (C₀), 115.5 (CH), 115.7 (CH), 115.9 (CH), 154.8 (C₀), 156.6 (C₀), 158.2 (C₀), 161.7 (C₀); IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3445, 3331, 3178, 2918, 2878, 1639, 1583, 1512, 1454, 1362, 1302, 1229, 1097, 1078, 1038, 937, 827, 762; HRMS (ESI-TOF) *m/z* [M + H]⁺ for C₁₆H₂₀FN₂O₄ calcd. 323.1407, observed 323.1438.

Supplementary Information

Experimental details and supplementary data are available free of charge at <http://jbc.sqb.org.br> as PDF file.

Acknowledgments

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