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 antiasmático oralmente ativo, é descrita. As etapas chave envolveram uma ciclização oxidativa de Mukaiyama, fornecendo a unidade trans-THF (tetrahidrofuran) 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 (2S,5S) 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 C6, but a disappointing low degree of selectivity was observed. In a similar oxonium strategy, Ley and co-workers7 employed an anomic oxygen to promote the carbon rearrangement of an alkynytributylstannane 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
intramolecular substitution resulted in the creation of the key tetrahydrofuran ring intermediate 7. Ley and co-workers\textsuperscript{10} 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).\textsuperscript{9,10} The terminal acetylene 7 can be assembled via Seyferth-Gilbert homologation (using the Ohira-Bestmann protocol)\textsuperscript{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
protocol with homoallylic alcohol 15. The functional groups in fragment 15 could be installed starting from commercially available and inexpensive 4-fluorophenol 16, rac-epichlorohydrin 17 and allylbromomagnesium 18, in a strategy similar to that applied by Gurjar et al.

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). The epoxide rac-5 was resolved by hydrolytic kinetic resolution under Jacobsen conditions, using the catalyst (R,R)-(salen)CoIII(OAc) (19, 0.5 mol%) and H2O (0.57 equiv) in tert-butyl methyl ether, providing (S)-5 in a 48% yield.

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

Scheme 3. Preparation of epoxide (S)-5.
Mukaiyama protocol, mediated by the Co(modp)\textsubscript{2} (20) (30 mol%) catalyst, provided trans-THF 14 as the only observed diastereoisomer in an 84% yield. 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 homologation using the Ohira-Bestmann reagent, assembling the terminal acetylene 7 in a 75% yield over two steps (Scheme 5). The \(^1\)H NMR and \(^{13}\)C NMR spectra and the optical rotation of trans-THF 7 matched the reported values for this compound. Next, the treatment of 7 with \(n\)-BuLi and ethylene oxide 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, 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 \(\text{NH}_3\cdot\text{MeOH}\), 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.
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

((2S,5S)-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 l-PrOH (137 mL), followed by the addition of tert-ButOOH (1.7 mL, 9.1 mmol, 5.5 mol L−1 in nonane). 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 Na2S2O4 (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 (0.53 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 (CH3), 28.4 (CH3), 64.4 (CH3), 71.0 (CH3), 77.2 (CH), 79.7 (CH), 115.6 (CH), 115.9 (CH), 155.0 (C6), 155.5 (C6), 159.2 (C6); IR (film) νmax/cm−1 3300, 3076, 3055, 2982, 2951, 2927, 2876, 2114, 1863, 1734, 1601, 1506, 1456, 1335, 1294, 1250, 1098, 1072, 1043, 829, 758, 636; HRMS (EI-TOF) m/z [M]+ for C12H16F2O4 calcd. 226.1005, observed 226.0910.

((2S,5S)-2-(4-Hydroxy-1-butynyl)-5-((4-fluorophenoxy)methyl)tetrahydrofuran (4)

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 29.0 (c 0.7, CHCl3), [α]D20 30.0 (c 0.7, CHCl3).4

A solution of hexane/EtOAc (90:10) as the eluent, providing aldehyde 21 (2.37 g, 10.8 mmol) as a colorless oil in a 75% yield over two steps; [α]D20 29.0 (c 0.7, CHCl3), [α]D20 30.0 (c 0.7, CHCl3).4

H 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 (CH3), 33.2 (CH3), 68.6 (CH), 70.6 (CH3), 72.8 (C6), 77.0 (CH), 83.5 (CH), 115.6 (CH), 115.7 (CH), 115.9 (CH), 155.0 (C6), 155.5 (C6), 159.3 (C6); IR (film) νmax/cm−1 3300, 3076, 3055, 2982, 2951, 2927, 2876, 2114, 1863, 1734, 1601, 1506, 1456, 1335, 1294, 1250, 1098, 1072, 1043, 829, 758, 636; HRMS (EI-TOF) m/z [M]+ for C12H16F2O4 calcd. 226.1005, observed 226.0910.

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; [α]D20 −29 (c 1.8, CHCl3), [α]D −34.3 (c 1.8, CHCl3);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) νmax/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 C16H13FO4 calcld. 287.1060, observed 287.1048.

Phenyl hydroxy carbamate (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 exchanged 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) νmax/cm−1: 3302, 1711, 1688, 1512, 1491, 1285, 1207, 1105, 1026, 910, 795, 687.

Phenyl acetoxy carbamate (12)

To a solution of phenyl hydroxy carbamate 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 acetaldehyde 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 exchanged 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 quantitave 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) νmax/cm−1: 3259, 2941, 1796, 1749, 1591, 1477, 1458, 1369, 1246, 1180, 1084, 1024, 1005, 852, 756, 690.

Phenyl acetoxy(4-[(2S,5S)-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 acetoxy carbamate 12 (0.068 g, 0.35 mmol) in THF (1.5 mL) were added DIAD (disopropyl 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; [α]D20 −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 (CH3), 18.3 (CH3), 27.7 (CH3), 33.3 (CH3), 49.4 (CH3), 68.9 (CH3), 70.7 (CH3), 76.8 (CH), 81.2 (Cα), 81.6 (Cβ), 115.6 (CH), 121.4 (CH), 125.9 (CH), 129.4 (CH), 150.6 (Cγ), 153.2 (Cγ), 154.91 (Cα), 156.3 (Cβ), 158.2 (Cβ), 168.2 (Cβ), 165.5 (Cα), 168.2 (Cα); HRMS (ESI-TOF) m/z [M + H]+ for C29H23FN2O6 calcld. 442.1666, observed 442.1715.

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

To a round-bottomed flask, it was added 15 (85 mg, 0.19 mmol) at 0 °C. Then, NH2 (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; [α]D20 −40 (c 1.1, MeOH), [α]D −46.0 (c 1.1, MeOH); 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 (CH3), 27.7 (CH3), 33.3 (CH3), 48.7 (CH3), 69.1 (CH), 70.7 (CH3), 76.9 (CH), 80.7 (Cγ), 82.9 (Cα), 115.5 (CH), 115.7 (CH), 115.9 (CH), 154.8 (Cβ), 156.6 (Cγ), 158.2 (Cγ), 161.7 (Cα); IR (film) νmax/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 C16H15FN2O6 calcld. 323.1407, observed 323.1438.

Supplementary Information

Experimental details and supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.
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