

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

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Experimental

Unless noted, all reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Dichloromethane (CH₂Cl₂) and triethylamine (Et₃N) were distilled from CaH₂. Dimethyl sulfoxide (DMSO) was distilled under reduced pressure from CaH₂ and stored over molecular sieves. Tetrahydrofuran (THF) and diethylether (Et₂O) were distilled from Na/benzophenone. Purification of reaction products was carried out by flash column chromatography using silica gel (230-400 mesh). Analytical thin layer chromatography was performed on silica gel 60 and GF (5-40 µm thickness) plates. Visualization was accomplished with UV light and phosphomolybdic acid followed by heating. Optical rotations were measured on a Carl Zeiss LEP A2 with a sodium lamp and are reported as follows: $[\alpha]_{\lambda}^{T^{\circ}C}$ (c = g per 100 mL, solvent). ¹H and proton-decoupled ¹³C NMR (nuclear magnetic resonance) spectra were recorded in a Bruker spectrometer in DMSO or CDCl₃ at 250 MHz (1H) and 62.9 MHz (13C) or at 500 MHz (1H) and 125 MHz (¹³C). The chemical shifts (δ) are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm). Data are reported as: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sext = sextet, br = broadsinglet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, tt = triplet of triplets, m = multiplet; coupling constant(s) in Hz; integration. High-resolution mass spectrometry (HRMS) was recorded on a Waters Xevo Q-Tof using electrospray ionization (ESI) or on a GCT Premier Waters using electron ionization (EI). The parent ions $([M + H]^+, [M + Na]^+ \text{ and } [M]^+)$ are listed. Infrared spectra (IR) were recorded on a Bomem Hartman & Braun spectrometer. Wavelengths of maximum absorbance (max) are quoted in wavenumbers (cm⁻¹).

(±)-2,3-Epoxy-1-(4-fluorophenoxy)propane (rac-5)

Powdered KOH (26.8 g, 460 mmol) was added to a solution of p-fluorophenol **16** (10.0 g, 89.2 mmol) in rac-epichlorohydrin rac-17 (72 mL), followed by the addition of tetrabutylammonium bromide (6.24 g, 19.6 mmol). The mixture was stirred overnight at room temperature and the reaction was quenched with distilled water (50 mL). The phases were separated and the aqueous phase was extracted with Et₂O (3×30 mL). The organic layer was dried over Na2SO4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using a mixture of hexane/Et₂O (80:20) as eluent, providing 14.5 g (97%) of rac-5 as a colorless oil; ¹H NMR (CDCl₃, 250 MHz) δ 2.74 (dd, 1H, J 2.5 and 4.9 Hz), 2.85 (t, 1H, J 4.5 Hz), 3.30-3.36 (m, 1H), 3.90 (dd, 1H), J 5.7 and 11.1 Hz, 4.20 (dd, 1H, J 3.0 and 11.1 Hz), 6.8-7.2 (m, 4H); ¹³C NMR (CDCl₃, 62.9 MHz) δ 44.5 (CH₂), 50.1 (CH), 69.4 (CH₂), 115.6 (CH), 115.8 (CH), 116.0 (CH), 154.6 (C₀), 155.6 (C₀), 159.4 (C₀); IR (film) v_{max}/cm⁻¹ 3481, 3059, 3005, 2928, 2878, 2056, 1863, 1601, 1506, 1456, 1294, 1250, 1211, 1099, 1036, 916, 864, 829, 775, 750, 723.

(S)-2,3-Epoxy-1-(4-fluorophenoxy)propane ((S)-5)

To the epoxide rac-**5** (14.5 g; 86.3 mmol) in *t*-BuOMe (30 mL), it was added (*R*,*R*)-(salen)Co^{III}(OAc)¹ (**19**) (300 mg, 0.453 mmol), and the mixture was stirred at 0 °C. Distilled water (0.91 mL, 49.6 mmol) was added dropwise over 1 h and the resulting mixture was stirred for 5 h at room temperature. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography using a mixture of hexane/ EtOAc (50:50) as eluent, providing 7.01 g (48%) of (*S*)-**5** as a colorless oil; $[\alpha]_D^{20}$ +13.0 (*c* 1.0, CHCl₃), $[\alpha]_D^{20}$ +5.0 (*c* 1.0, CHCl₃);^{1 1}H NMR (CDCl₃, 250 MHz) δ 2.74 (dd, 1H, *J* 2.5 and 4.9 Hz), 2.85 (t, 1H, *J* 4.5 Hz), 3.30-3.36 (m, 1H), 3.90 (dd, 1H, *J* 5.7 and 11.1 Hz), 4.20 (dd, 1H, *J* 3.0 and 11.1 Hz), 6.8-7.2 (m, 4H).

(S)-1-(4-Fluorophenoxy)hex-5-en-2-ol (15)

To a solution of allylmagnesium bromide (**18**) (17.8 mL, 17.8 mmol, 1 mol L⁻¹ in Et₂O), CuCN (22 mg, 0.25 mmol) was added and the solution was cooled to 0 °C. Then, a solution of (*S*)-**5** (1.50 g, 8.92 mmol) in Et₂O (18.3 mL)

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was added dropwise. The mixture was stirred for 30 min at 0 °C, quenched with a saturated aqueous solution of NH₄Cl (5 mL) and stirred for 30 min at room temperature. The mixture was then filtered and the precipitate rinsed with Et₂O. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography using a mixture of hexane/Et₂O (60:40) as eluent, providing the homopropargylic alcohol **15** (1.88 g, 8.92 mmol) as a colorless oil in a quantitative yield; $[\alpha]_D^{20}$ +20 (*c* 1.5, CHCl₃), $[\alpha]_D$ –16.5 (*c* 1.5, CHCl₃);¹ ¹H NMR (CDCl₃) 250 MHz) δ 1.61-1.76 (m, 2H), 2.11-2.33 (m, 2H), 2.41 (d, 1H, *J* 2.5 Hz), 3.76-4.10 (m, 2H), 4.98-5.11 (m, 2H), 5.76-5.93 (m, 1H), 6.80-6.99 (m, 2H); ¹³C NMR (CDCl₃, 62.9 MHz) δ 29.6 (CH₂), 32.2 (CH₂), 69.5 (CH), 72.8 (CH₂), 115.1 (CH₂), 115.5 (CH), 115.7 (CH), 116.0 (CH), 138.0 (CH), 154.7 (C₀), 155.5 (C₀), 159.3 (C₀).

Reference

 Gurjar, M. K.; Murugaiah, A. M. S.; Radhakrishna, P.; Ramana, C. V.; Chorghade, M. S.; *Tetrahedron: Asymmetry* 2003, 14, 1363.





Figure S2. ¹³C NMR spectrum (62.9 MHz, CDCl₃) of rac-5.



Figure S3. DEPT 135 NMR spectrum (62.9 MHz, CDCl₃) of rac-5.



Figure S4. DEPT 90 NMR spectrum (62.9 MHz, CDCl₃) of rac-5.



Figure S5. IR (film) spectrum of rac-5.

Lui "Lui-05" CDCI3/250 MHz jan19lcdH2



Figure S6. ¹H NMR spectrum (250 MHz, CDCl₃) of 15.

S5



Figure S7. ¹³C NMR spectrum (62.9 MHz, CDCl₃) of 15.

File Name Vrm.rsper.ci.gm.unicemp.br/espectros/oru/ker/250/2011/jan11/datalLuiz Cartos/mm/jan19lcdC/jan19lcdC/jan19lcdC 001000/tid Frequency (f/Hz) 62.90 Narcleus 130 Namber of Transients 256 Original Points Count 8192 Points Count 16384 Parke Segence dop/135 Solvent CHLOROFORM-D Sweep Width (Hz) 15000.24 Temperature (Fegree C) 25.160 9 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	4	
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Figure S8. DEPT 135 NMR spectrum (62.9 MHz, CDCl₃) of 15.



Figure S9. DEPT 90 NMR spectrum (62.9 MHz, CDCl₃) of 15.



Figure S10. ¹H NMR spectrum (250 MHz, CDCl₃) of 14.

Lui ago23LCDC1 LUI-4513C 250mhz CDCl3



Figure S11. ¹³C RMN spectrum (62.9 MHz, CDCl₃) of 14.



Figure S12. DEPT 135 NMR spectrum (62.9 MHz, CDCl₃) of 14.



Figure S13. DEPT 90 NMR spectrum (62.9 MHz, CDCl₃) of 14.



Figure S14. HRMS (EI-TOF) *m*/*z* [M]⁺ for C₁₂H₁₅FO₃ of 14.



Figure S15. IR (film) spectrum of 14.



Figure S16. ¹H RMN spectrum (250 MHz, CDCl₃) of 7.



Figure S17. ¹³C RMN spectrum (62.9 MHz, CDCl₃) of 7.

Acquisition Time (sec)	0.5439	Comment	Lui - LUI-33 - CDCI3/	250mhz - ago25lcdC1		Date	25 Aug 2	011 23:13:04
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Figure S18. DEPT 135 NMR spectrum (62.9 MHz, CDCl₃) of 7.

S11



Figure S19. DEPT 90 NMR spectrum (62.9 MHz, CDCl₃) of 7.



Figure S20. IR (film) spectrum of 7.



**Figure S21.** HRMS (EI-TOF) *m*/*z* [M]⁺ for C₁₃H₁₃FO₂ of **7**.



Figure S22. ¹H RMN spectrum (250 MHz, CDCl₃) of 4.



Figure S23. ¹³C RMN spectrum (62.9 MHz, CDCl₃) of 4.



Figure S24. IR (film) spectrum of 4.



Figure S25. HRMS (ESI-TOF) m/z [M + Na]⁺ for C₁₅H₁₇FO₃ of 4.



Figure S26. ¹H RMN spectrum (250 MHz, DMSO- $d_6$ ) of 26.



Figure S27. IR (film) spectrum of 26.



Figure S28. ¹H RMN spectrum (250 MHz, CDCl₃) of 12.



Figure S29. IR (film) spectrum of 12.



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Figure S30. ¹H RMN spectrum (500 MHz, CDCl₃) of 15.



Figure S31. ¹³C RMN spectrum (125.7 MHz, CDCl₃) of 15.



Figure S32. DEPT 135 NMR spectrum (125.7 MHz, CDCl₃) of 15.



Figure S33. DEPT 90 NMR spectrum (62.9 MHz, CDCl₃) of 15.



Figure S34. HRMS (ESI-TOF) m/z [M + H]⁺ for C₂₄H₂₅FNO₆ of 15.



Figure S35. ¹H RMN spectrum (250 MHz, CDCl₃) of 1.



Figure S36. ¹³C RMN spectrum (150.9 MHz, CDCl₃) of 1.

Acquisition Time (sec)	0.4544		Date	14 Aug 2012 15:49	:00						
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Nucleus	13C		Number of Transien	<b>ts</b> 448	Original Points Count	16384	Points Count	65536			
Pulse Sequence	deptsp135	6	Solvent	CHLOROFORM-D	Sweep Width (Hz)	36057.69	Temperature (degree	C) 25.199			
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176 168 16	0 152	144	136 128	120 112 104	96 88 8 Chemical Shift (ppm)	0 72	54 56 48	40 32	24	16	8

Figure S37. DEPT 135 NMR spectrum (150.9 MHz, CDCl₃) of 1.



Figure S8. DEPT 90 NMR spectrum (62.9 MHz, CDCl₃) of 1.



Figure S39. IR (film) spectrum of 1.



**Figure S40.** HRMS (ESI-TOF) m/z [M + H]⁺ for C₁₆H₁₉FN₂O₄ of **1**.