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Synthesis of CMI-977, a Potent 5-Lipoxygenase Inhibitor†

Xiong Cai, Mukund S. Chorghade,* Aberra Fura, Gurmit S. Grewal, Karen A. Jauregui, Heather A. Lounsbury, Ralph T. Scannell, C. Grace Yeh, Michelle A. Young, and Shaoxia Yu

CytoMed, Inc., 840 Memorial Drive, Cambridge, Massachusetts 02139

Liang Guo, Robert M. Moriarty, Raju Penmasta, Munagala S. Rao, Rajesh K. Singhal, Zhengzhe Song, James P. Staszewski, Sudersan M. Tuladhar, and Sanmin Yang

Steroids, Ltd., 2201 West Campbell Park Drive, Chicago, Illinois 60612.

Abstract:

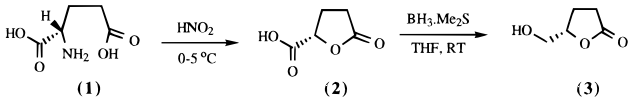
CMI-977 is a potent 5-lipoxygenase inhibitor that intervenes in the production of leukotrienes and is presently being developed for the treatment of chronic asthma. It is a single enantiomer with an *all-trans* (2*S*,5*S*) configuration. Of the four isomers of CMI-977, the *S*,*S* isomer was found to have the best biological activity and was selected for further development. The enantiomerically pure product was synthesized on a 2-kg scale from (*S*)-(+)-hydroxymethyl-γ-butyrolactone.

Introduction

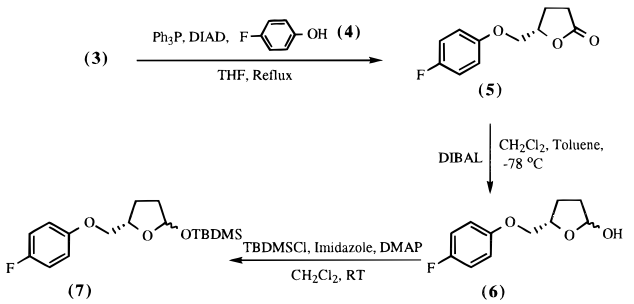
CMI-977 is a potent 5-lipoxygenase (5-LO) inhibitor that blocks the production of leukotrienes and is currently being developed for the prophylactic treatment of chronic asthma.[1] The 5-LO enzyme acts upon arachidonic acid, leading to the formation of leukotriene B_4 (LTB_4) and the cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4). The physiological effect of leukotrienes is to mimic the recognized pathophysiological features of asthma, including bronchoconstriction, increased airway responsiveness, increased microvascular permeability, and hypersecretion of mucus.[2]

CMI-977 is a single enantiomer with an *all-trans* (2*S*,5*S*) configuration. Inhibition of LTB_4 production in calcium ionophore-stimulated human whole blood was employed in the evaluation of the chiral isomers of CMI-977. Of the four isomers of CMI-977, the *S*,*S* isomer was found to have the best inhibitory activity and was selected for further development. For preclinical studies, it was necessary to prepare large quantities of the enantiomerically pure target compound.

(*S*)-(+)-Hydroxymethyl-γ-butyrolactone **(3)** was chosen as the chiral synthon. Due to delays encountered in procurement of commercial samples, it was prepared via appropriate modifications of a literature procedure from (*S*)−(+)-glutamic acid (**1**).[3] A two-step sequence involving diazotization of **1** followed by reduction of (*S*)-(+)-butyrolactone-carboxylic acid **(2)** with borane−dimethyl sulfide complex furnished, after column chromatography, the lactone **3** in excellent yield and purity. The reaction was, however, found



to be sensitive to the quality of the reducing reagent; fresh supplies of the the reagent afforded the best results. Diisopropylazadicarboxylate/triphenylphosphine-mediated Mitsunobu coupling[4] with 4-fluorophenol **(4)** yielded chiral lactone **5**. This material revealed a propensity to unravel to the open-chain derivative; dissolution of the material in toluene followed by treatment with pyridinium *p*-toluenesulfonate and chromatography led to the requisite lactone **5** as a white crystalline solid.



Reduction of lactone **5** to the corresponding lactol **6**[5] necessitated use of DIBAL; quenching the reaction with methanol followed by workup with aqueous potassium sodium tartrate furnished the product as a clear viscous oil that solidified on standing to a white solid. The anomeric hydroxyl group was conveniently protected by the formation of the *tert*-butyldimethylsilyl ether by treatment with *tert*-

† This paper is dedicated to Professor Y. Kishi on the occasion of his 60th birthday.

* Correspondence should be addressed to this author.

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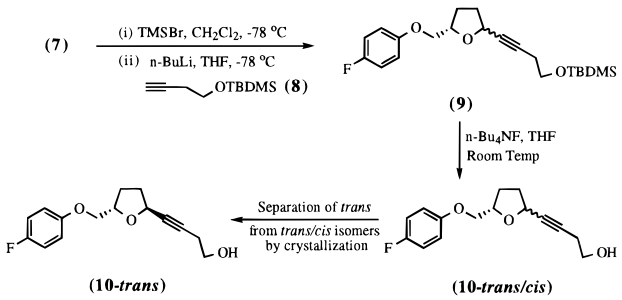
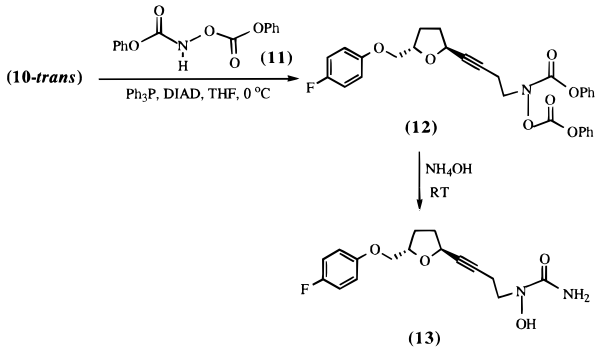
butyldimethylsilyl chloride, imidazole, and (*N*,*N*-dimethylamino)pyridine.[6] Further activation of the anomeric position in compound **7** with trimethylsilyl bromide[5] followed by treatment with 1-*tert*-butyldimethylsiloxy-3-butyne **(8)** and *n*-butyllithium[7] yielded a *trans/cis* mixture (1:1) of 9 that was used without further purification. Reaction of compound



9 with tetrabutylammonium fluoride led to deprotection of the hydroxy functionality. The resultant *trans/cis* mixture of the alkynols was subjected to extensive chromatography and repeated crystallization to obtain the desired trans alcohol **(10)** as a white crystalline solid.

Further elaboration to CMI-977 **(13)** was carried out by suitable modifications of a literature procedure;[8] it was deemed to be technically expedient to use aqueous ammonia instead of gaseous ammonia. The final product was crystal-



lized from ethyl acetate/hexanes to furnish a white crystalline solid that is highly soluble in methanol and ethanol but sparingly soluble in water. An analytical reference standard was obtained by recrystallization from methyl ethyl ketone. Enantiomeric purity was confirmed by chiral HPLC; analytical methods developed in our laboratories were adequate for evaluation of potency of the active pharmaceutical ingredient and the related process impurities. X-ray crystallographic studies have revealed the product to be highly crystalline; particles were seen to be platelike agglomerated crystals with a smooth surface texture. The substance is strongly cohesive in nature.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope apparatus and are uncorrected. Air- and moisture-sensitive reactions were carried out under an argon atmosphere. Evaporation or removal of solvents in vacuo implies that solvents were removed by means of a rotary evaporator using house vacuum (20−30 mmHg). Thin-layer chromatography (TLC) was performed on precoated silica gel glass plates (0.2 mm thickness) with 254-nm fluorescent indicator. Products were visualized with UV light and phosphomolybdic acid and heat. Column chromatography was carried out using silica gel (230−400 mesh) and appropriate eluants. All NMR spectra were recorded in deuteriochloroform unless specified otherwise. Proton NMR spectra were obtained on a Bruker AM-400 or a Varian VXR-300 spectrometer. Chemical shifts are reported in ppm (δ) relative to residual chloroform in deuteriochloroform (7.26 ppm), and signals are described as s, singlet, d, doublet, t, triplet, q, quartet, and m, multiplet. The abbreviation br is used to describe broad signals. Centers of complex multiplets are taken as chemical shifts. Infrared spectra were recorded on a Nicolet Impact 400D; samples were either embedded in KBr disks or thin films between sodium chloride plates as needed. UV−visible spectra were recorded on a Hitachi U-2000 spectrophotometer with solvents as indicated. Low-resolution mass spectra were recorded on a Finnigan MAT-90 mass spectrometer with chemical ionization mode using methane as the carrier gas. Optical rotations were obtained on a DigiPol-781 automatic polarimeter (Rudolph Instrument) at a wavelength of 589 nm (sodium D line) by a 1.0-dm cell with a total volume of 1 mL. Specific rotation, $[\alpha]_D$, was reported in degrees per decimeter at the specified temperature, and the concentration (*c*) was given in grams per 100 mL in the specified solvent. High-performance liquid chromatograms (HPLC) were obtained on a Waters LC Module I Plus equipped with a photodiode array detector (Waters 996), and Millennium version 2.15 software was used for data processing.

(5*S*)-(+)-γ-Butyrolactone-5-carboxylic Acid (2). A solution of sodium nitrite (1525 g, 27 mol) in water (6000 mL) was added dropwise to a mixture of (S)-(+)-glutamic acid **(1)** (2500 g, 17 mol) in water (8000 mL) and concentrated hydrochloric acid (2200 mL, 26.4 mol) at 0−5 °C under vigorous stirring (8−10 h). The clear solution was stirred at room temperature overnight. Evaporation of water to dryness (40−45 °C/1 mmHg) gave a pale yellow oil along with colorless crystals, and then ethyl acetate (6000 mL) was added. The insoluble material was filtered by suction, and the filtrate (organic phase) was dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated in vacuo to give a viscous oil, which was crystallized from ethyl acetate to afford **2** as a white solid (1200 g): mp 71−73 °C; $[\alpha]^{20}_D = +13.5°$ (c = 5, CH_3OH).

(5*S*)-(+)-5-Hydroxymethyl-γ-butyrolactone (3). To a stirred solution of **2** (1080 g, 8.3 mol) in dry tetrahydrofuran (7000 mL) was added borane−dimethyl sulfide complex (1.0 M, 950 mL, 10.0 mol) dropwise over a period of 3 h at room temperature. After being stirred for additional 3 h, the reaction mixture was quenched by cautious addition of anhydrous methanol (6000 mL). The mixture was concentrated in vacuo to give the crude product. The crude product

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was purified by chromatography on silica gel using ethyl acetate/hexanes (1:1) to give **3** as a colorless oil (800 g): $[\alpha]^{20}_{D} = +51°$ ($c = 0.5$, $CHCl_3$). TLC $R_f = 0.21$ (ethyl acetate/hexanes, 4:1); IR (neat) 3430, 2943, and 1747 cm^{-1}.

(5*S*)-5-(4-Fluorophenoxymethyl)-γ-butyrolactone (5). To a mixture of **3** (1000 g, 8.62 mol), 4-fluorophenol **(4)** (1013 g, 9.05 mol), and triphenylphosphine (2371 g, 9.05 mol) in dry tetrahydrofuran (10 000 mL) was added dropwise diisopropylazodicarboxylate (1776 g, 9.05 mol) at room temperature. The mixture was heated at reflux for 5 h. The solvent was removed in vacuo to give the solid residue. The solid residue was triturated with 20% ethyl acetate in hexanes. The solid was removed by filtration and washed with 20% ethyl acetate in hexanes. The filtrate was concentrated in vacuo to give a viscous liquid. The viscous liquid was dissolved in ethyl acetate (5000 mL) and washed with 5% aqueous sodium hydroxide solution (2 × 1000 mL), and the organic extract was concentrated in vacuo to give a viscous oil. The oil was dissolved in dichloromethane (6000 mL), and sodium hydroxide solution (5 M, 2500 mL) was added. The resultant solution was stirred at room temperature for 1 h. The basic aqueous phase was acidified with 6 M hydrochloric acid and extracted with ethyl acetate (2 × 2000 mL). The organic phase was concentrated in vacuo to give the residue, which was dissolved in toluene (6000 mL). Pyridinium *p*-toluenesulfonate (10 g) was added and the mixture heated under reflux, using a Dean−Stark apparatus, for 1 h. The cold solution was then passed through a silica gel column and eluted with ethyl acetate in hexane (1:1). The eluants were concentrated in vacuo to give the lactone, which was recrystallized from ethyl acetate and hexanes mixture to afford **5** as white crystalline solid (1207 g): TLC $R_f = 0.55$ (ethyl acetate/hexanes, 4:1); IR (KBr) 3120, 3073, 2958, 2928, and 1770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (m, 2H), 2.65 (m, 2H), 4.07 (dq, 2H), 4.83 (m, 1H), 6.83 (m, 2H), and 6.95 (m, 2H); MS (CI) 211 ($M^+ + 1$, 100%).

(5*S*)-5-(4-Fluorophenoxymethyl)-2-hydroxytetrahydrofuran (6). To a solution of **5** (1000 g, 4.74 mol) in dichloromethane (6000 mL) at −78 °C was added a solution of diisobutylaluminum hydride in toluene (1.5 M, 3490 mL, 5.23 mol) in a period of 2 h. The reaction mixture was stirred at −78 °C for 2 h more until the reaction was complete (TLC, silica gel, dichloromethane). Methanol (1000 mL) was added dropwise at −78 °C to quench the reaction. To that mixture was then added a saturated aqueous solution of potassium sodium tartrate (2000 mL), and the mixture was allowed to warm to room temperature overnight. The reaction mixture was concentrated in vacuo to remove most of dichloromethane, and the white residue was dissolved in warm water and extracted with toluene (3 × 2500 mL). The organic phase was washed with water (3 × 3000 mL) and saturated sodium chloride solution (1 × 2000 mL), dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to give **6** as a clear viscous oil, which solidified on standing to give a white solid (1006 g): TLC $R_f = 0.06$ (dichloromethane); IR (KBr) 3406, 2936, and 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.8 (m, 1H), 2.05 (m, 2H), 2.26 (m, 1H), 3.93 (m, 2H), 4.01 (m, 0.5H), 4.47 (m, 0.5H), 4.61 (m, 0.5H), 5.57 (m, 0.5H), 5.66 (m, 0.5H), 6.88 (m, 2H), and 6.98 (m, 2H); MS (CI) 212 ($M^+ + 1$, 100%).

(5*S*)-5-(4-Fluorophenoxymethyl)-2-(*tert*-butyldimethylsiloxy)tetrahydrofuran (7). To a solution of **6** (1000 g, 4.72 mol) in dichloromethane (5000 mL) were added, at room temperature, imidazole (482 g, 7.08 mol), (*N*,*N*-dimethylamino)pyridine (8.65 g, 0.71 mol), and *tert*-butyldimethylsilyl chloride (1067 g, 7.08 mol). The mixture was stirred at room temperature overnight. The white solid was filtered and washed with dichloromethane (3 × 1000 mL). The filtrate was concentrated in vacuo to give a residue which was dissolved in ethyl acetate (4000 mL), washed with water (3 × 1000 mL) and saturated sodium chloride solution (1 × 1000 mL), dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to give **7** as a viscous colorless liquid (1510 g). TLC $R_f = 0.60/0.61$ (ethyl acetate/hexanes, 1:1); IR (neat) 2954, 2924, 2857, and 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.9 (s, 9H), 1.80−2.10 (m, 3H), 2.22 (m, 1H), 3.91 (m, 2H), 4.38 (m, 0.33H), 4.50 (m, 0.67H), 5.52 (m, 0.33H), 5.09 (m, 0.67H), 6.86 (m, 2H), and 6.96 (m, 2H).

Preparation of 1-*tert*-Butyldimethylsiloxy-3-butyne (8). To a stirred solution of 3-butyn-1-ol (1000 g, 14.2 mol) in dichloromethane (9000 mL) was added imidazole (970 g, 14.25 mol) followed by *tert*-butyldimethylsilyl chloride (2140 g, 14.2 mol) at room temperature. The reaction mixture was stirred at room temperature overnight and then filtered, and the white solid residue was extracted with dichloromethane (3 × 1500 mL). The combined filtrates were concentrated in vacuo to remove dichloromethane, and the crude oil (2609 g) was distilled under reduced pressure to give **8** as a colorless liquid (2305 g): bp = 98−105 °C at ca. 60 mmHg; TLC $R_f = 0.80$ (ethyl acetate/hexanes, 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.87 (s, 9H), 1.95 (m, 2H), 2.07 (s, 1H), and 2.42 (m, 2H).

***trans/cis*-(5*S*,2*SR*)-2-(1-*tert*-Butyldimethylsiloxy-3-butyn-4-yl)-5-(4-fluorophenoxymethyl)tetrahydrofuran (9).** To a stirred solution of **7** (1026 g, 3.14 mol) in dry dichloromethane (8000 mL) at −78 °C was added trimethylsilyl bromide (456 mL, 3.46 mol) over 5 min under argon. The mixture was stirred at −78 °C for 4 h. In a separate flask containing 1-*tert*-butyldimethylsiloxy-3-butyne **(8)** (695 g, 3.77 mol) in tetrahydrofuran (3500 mL) was added dropwise a solution of *n*-butyllithium in hexane (2.5 M, 1445 mL, 3.61 mol) at −78 °C. After being stirred at −78 °C for 1 h, the solution was transferred via cannula to the solution from above. After 2 h at −78 °C, the reaction was checked by TLC using silica gel, ethyl acetate/hexanes (1:9) to ensure completion of the reaction. The reaction was quenched by the addition of saturated aqueous sodium chloride solution (1000 mL) and extracted with ethyl acetate (3 × 1000 mL). The organic extracts were washed with saturated sodium chloride solution (3 × 1000 mL), dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to give the crude *trans/cis* alkyne **9** (1185 g): TLC $R_f = 0.38/0.39$ (ethyl acetate/hexanes, 1:9). The crude product was used without further purification.

trans*-(5*S*,2*S*)-2-(1-Hydroxy-3-butyn-4-yl)-5-(4-fluorophenoxymethyl)tetrahydrofuran (10-*trans*).** To a stirred solution of crude *trans/cis* alkyne **9** (1185 g, 3.14 mol) in tetrahydrofuran (5000 mL) was added tetrabutylammonium fluoride (1.0 M, 3130 mL, 3.13 mol) at room temperature. The reaction was stirred at room temperature until completion (checked by TLC using silica gel, ethyl acetate/hexanes, 1:9), quenched with water, and extracted with ethyl acetate. The organic phase was washed with water (3 × 1000 mL) and saturated sodium chloride solution (1 × 1000 mL), dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to give an oil. The oil was filtered through silica gel using ethyl acetate/hexanes (1:4). The fractions containing the trans and cis isomers were evaporated in vacuo, and the resulting oil (**10-*trans/cis) (495 g) was dissolved in warm ether, and then hexane was added to the point of turbidity, followed by the addition of a few drops of ether to obtain a clear solution. This solution was then seeded with pure trans compound and refrigerated. The resultant crystals were recrystallized two or three times with ether/hexanes to give the pure trans isomer (**10-*trans***) as a white crystalline solid (200 g): TLC $R_f = 0.22$ (ethyl acetate/hexanes, 1:1); mp = 77−79 °C (ether/hexanes); IR (KBr) 3487, 2915, 2236, 1599, 1501, 1245, 1215, 1057, 835, and 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.88 (m, 1H), 2.02 (m, 1H), 2.25 (m, 2H), 2.50 (m, 2H), 3.72 (t, 2H), 3.93 (d, 2H), 4.48 (m, 1H), 4.76 (m, 1H), 6.84 (m, 2H), and 6.96 (t, 2H).

Preparation of *N*,*O*-Bis-(phenoxycarbonyl)hydroxylamine (11). To a stirred solution of sodium bicarbonate (430 g, 5.12 mol) in water (3000 mL) was added hydroxylamine hydrochloride (176 g, 2.54 mol) at 0 °C (ice bath). The mixture was stirred for 30 min at 0 °C, and then phenylchloroformate (1200 g, 7.66 mol) was added. A solution of sodium bicarbonate (646 g, 7.70 mol) in water (5400 mL) was added, followed by an additional quantity of water (600 mL) to wash the remaining sodium bicarbonate into the reaction mixture. The mixture was stirred for 30 min at 0 °C and then for 2 h at room temperature. The resulting precipitate was filtered and washed with hexanes (3 × 500 mL). The solid was then dissolved in warm ether (2200 mL), and hexanes (1500 mL) were added. The solution was cooled to room temperature to precipitate the product. Additional hexanes (5000 mL) were added, and the suspension was allowed to stand overnight. The solid was collected by filtration to give **11** as a white solid (475 g). TLC $R_f = 0.51$ (ethyl acetate/hexanes, 1:2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 5H), 7.39 (m, 5H), and 8.67 (br s, 1H).

(2*S*,5*S*)-*trans*-5-(4-Fluorophenoxymethyl)-5-(4-*N*,*O*-bis-(phenoxycarbonyl)hydroxylamino-3-butyn-4-yl)tetrahydrofuran (12). To the stirred and cooled solution of **10-*trans*** (450 g, 1.70 mol), *N*,*O*-bisphenoxycarbonylhydroxylamine (698 g, 2.60 mol), and triphenylphosphine (715 g, 2.72 mol) in dichloromethane (9000 mL) was added dropwise diisopropylazodicarboxylate (551 g, 2.72 mol), at 0 °C (ice bath). The ice bath was removed, and the reaction was warmed to room temperature and stirred for 30 min (checked the reaction by TLC using silica gel, ethyl acetate/hexanes, 1:1). The reaction mixture was filtered through a silica gel column and eluted with dichloromethane. The fractions containing the compound were concentrated in vacuo to give **12** as a pale yellow viscous oil (880 g): TLC $R_f = 0.52$ (ethyl acetate/hexanes, 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 1.85 (m, 1H), 2.03 (m, 1H), 2.22 (m, 2H), 2.75 (m, 2H), 3.92 (d, 2H), 4.05 (m, 2H), 4.47 (m, 1H), 4.76 (m, 1H), 6.84 (m, 2H), 6.95 (m, 2H), 7.26 (m, 5H), and 7.41 (m, 5H).

(2*S*,5*S*)-*trans*-5-(4-Fluorophenoxymethyl)-2-(1-*N*-hydroxyureidyl-3-butyn-4-yl)tetrahydrofuran (13) (CMI-977). To a stirred solution of **12** (880 g, 1.69 mol) in methanol (3600 mL) was added ammonium hydroxide solution (9000 mL) at room temperature. The reaction mixture was stirred at room temperature for 6 h and then extracted with dichloromethane (3 × 4000 mL). The organic phase was washed with 5% sodium hydroxide solution (3 × 1500 mL). The aqueous phase was cooled and acidified with concentrated hydrochloric acid to pH 7−8. The resulting solid was filtered and washed with water. The crude product (solid) was dissolved in methanol and refluxed with carbon (100 g) for 1 h. The solution was filtered and concentrated in vacuo to give a white solid (338 g) and recrystallized from ethyl acetate in hexanes to produce **13** (CMI-977) as a white crystalline solid (325 g): TLC $R_f = 0.48$ (ethyl acetate/methanol, 9:1); mp = 113−114 °C (ethyl acetate/hexanes); $[\alpha]^{25}_D = -47.8°$ ($c = 0.3$, CD_3OD); IR (KBr) 3438, 3193, 2914, 1626, and 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ δ 1.84 (m, 1H), 2.01 (m, 1H), 2.22 (m, 2H), 2.55 (t, 2H), 3.75 (t, 2H), 3.94 (m, 2H), 4.48 (m, 1H), 4.74 (t, 2H), 5.25 (br s, 2H), 6.86 (m, 2H), and 6.98 (m, 2 H); MS (CI) 323 ($M^+ + 1$, 7.4%), 280 (100%), 264 (55.5%). CMI-977 drug was characterized by ultraviolet spectroscopy (absorbance of a 1 cm, 1% w/v solution methanol at 210 nm, 217, and at 280 nm, 72). Microanalysis after complete combustion was as follows. Synthesized: calcd C, 59.62; H, 5.94; N, 8.69; and obsd, C, 59.50; H, 6.01; N, 8.69. Reference standard: calcd C, 59.62; H, 5.94; N, 8.69; and obsd, C, 59.68; H, 5.89; N, 8.74. Partition coefficients were as follows: chloroform/water = 34.7:1.0 and ethyl acetate/water = 98.7:1.3. Chromatographic conditions used for determination of chemical purity were as follows: column, Zorbax ODS 4.6 × 250 mm; mobile phase, 58% methanol, 42% K_2HPO_4 (10 mM, pH 3, prepared by adding 1.74 g of K_2HPO_4 in 1 L of water and adjusting the pH with orthophosphoric acid); flow rate, 1 mL/min; detection, 254 nm; detection volume, 50 μL; analysis time, 30 min; concentration, ~2 mg in 3 mL. HPLC conditions used for the determination of chiral purity were as follows: column, Chiral Technologies, Chiral OD-H, 4.6 × 250 mm; mobile phase, 89% hexanes, 8% 2-propanol, 3% ethanol; flow rate, 0.75 mL/min; detection, 215 nm; injection volume, 50 μL; analysis time, 40 min.

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