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Stereoselective synthesis of (2*S*,7*S*)-7-(4-phenoxymethyl)-2-(1-*N*-hydroxyureidyl-3-butyn-4-yl)oxepane: a potential anti-asthmatic drug candidate

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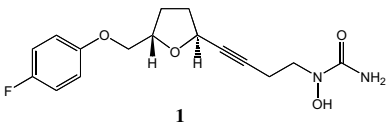
Abstract—We have achieved a short, efficient stereoselective synthesis of 7-membered oxepane derivatives with potential against asthma. Highlights of our synthetic strategy are regioselective oxidation of a hydroxyl group and efficient ring closure of an open chain aldehyde to a 2-benzenesulfonyl oxepane derivative with $PhSO_2H$. Surprisingly the *cis*-isomer showed better activity than the *trans*-isomer.

1. Introduction

Millions of people of every age group, all over the world, suffer the debilitating effects of chronic asthma. The occurrence of this disease keeps increasing at a phenomenal rate despite advances in molecular biology and asthma chemotherapy. Extensive research has been conducted on the clinical management of asthma; a paucity of effective medications and curative agents has led to patients exploring alternative therapies. A dramatic example is seen in the month of June in Hyderabad, a southern city of India. Millions of people flock to the city for a traditional medicine popularly known as 'fish medicine,' where for several years, a herbal concentrate has been administered through a small fish into the mouth of a patient.[1a]

2. Results and discussion

Intensive research is being conducted around the world for safer and target specific drugs for asthma.[1b–h] Various structural scaffolds and templates have been explored. Our attention was drawn to (2*S*,5*S*)-*trans*-5-[(4-fluorophenoxy)methyl]-2-(4-*N*-hydroxyureidyl-1-butynyl) tetrahydrofuran **1**, a compound that was initially studied as CMI-977 and later renamed as LDP-977. This compound was initially under clinical investigation[2] as a promising candidate for chronic asthma. It acts primarily by inhibiting the 5-lipoxygenase pathway, thereby blocking the production of inflammation mediatory leukotrienes. It had successfully been evaluated in animal models; and showed a high degree of potency, excellent oral bioavailability and an exceptionally



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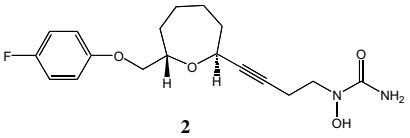

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favourable safety profile.[3] Several important structural features and biological activity of this compound prompted us to design additional analogues. As part of an extensive investigation of structure–activity relationships and preparation of designed combinatorial libraries we undertook the challenging synthesis of the seven membered analogue **2**.[4] Accordingly, the synthesis was initiated from (*S*)-4-fluorophenyl glycidyl ether, which was obtained from the hydrolytic kinetic resolution of (+)-4-fluorophenylglycidyl ether **3**.[4f] Regioselective opening of epoxide **3** with (4-benzyloxy) butylmagnesium bromide **4**, in the presence of cuprous cyanide in dry THF gave (2*S*)–7-benzyloxy-(4-fluorophenoxy)heptane-2-ol **5** in 73% yield.[5] Hydroxy compound **6** was obtained by the hydrogenolysis of **5** with 10% Pd–C in ethanol under a hydrogen atmosphere. The primary hydroxyl group in **6** was selectively oxidized by the slow addition of 2-iodoxy benzoic acid[6] in dry DMSO to furnish **7**. Surprisingly, the compound existed solely in the open chain form **7**, as evidenced by the presence of an aldehyde peak and the absence of any peaks pertaining to the tautomeric lactol in the ^{1}H NMR spectra.

The pivotal step of the synthetic strategy, that is, the diastereoselective installation of the side chain at the C-2 position was to be performed next. This might be possible only if hydroxy-aldehyde **7** isomerizes, at least during the reaction, into the corresponding lactol, which can then be captured as an oxenium ion in the presence of any acid by a nucleophile. This strategy is similar to Lewis acid mediated *C*-alkylation of glycals and their methyl derivatives. Recently, Ley et al. have demonstrated the utility of 2-arenesulfonyl cyclic ether derivatives as synthetic equivalents of less-stable glycal and its derivatives.[7]

Accordingly, we exposed the hydroxy-aldehyde **7** to benzenesulfinic acid to obtain 2-benzenesulfinyloxepane derivative **8**. The acidity of the reaction medium and the stability of the benzenesulfonyl derivative may provide the driving force for the cyclization of **7** to the tautomeric glycal and the subsequent facile conversion of the latter to **8**. Nucleophilic displacement of sulfone **8** with tetrahydropyranyloxy-1-butynylmagnesium bromide, in the presence of anhydrous zinc bromide, gave the THP derivative **9**.[7a,b] Deprotection of the THP group furnished **10** as the major component in 75% yield (Scheme 1). This was confirmed as the *trans* derivative by NOE experiments in which irradiation of the H-2 proton did not show any enhancement of the H-7 proton and vice versa. The ^{1}H NMR spectrum of the enantiomerically pure *trans* product was amenable to first order splitting. For example, peaks corresponding to eight methylene protons were observed in the region of δ 1.40–2.12, whereas the oxepane ring protons H-2, H-7 were localized at δ 4.56 and 4.16, respectively. The molecular formula was confirmed by HRMS analysis with the observed molecular ion peak (M^+) at 292.1474 (calcd for $C_{17}H_{21}FO_3$: 292.1477). A Mitsunobu[8] reaction of **10** with *N*,*O*-bis(phenoxycarbonyl) hydroxylamine **11** gave compound **12**. Subsequent treatment of **12** with ammonia in methanol furnished the *trans*-isomer **2** as a colourless crystalline solid (Scheme 2).

During this work we were also able to synthesize the *cis* derivative by elaboration of the minor product obtained from nucleophilic displacement of the sulfone. These compounds were then tested for Leukotriene B4 inhibition in the human whole blood assay. Test compound activity was determined as per the Cayman LTD enzyme immunoassay (EIA) and evaluated as IC_{50} [nM]. The *cis*-isomer had an IC_{50} of 518 nM, whereas the *trans*-isomer had a value of 1339 nM. Surprisingly, the *cis*-isomer showed better activity than the *trans*-isomer. This could establish a new paradigm in the pathology of asthma, wherein generally, it has been proven that the *trans*-substituted compounds (mostly 5-membered) are more effective compounds with good inhibitory activity.

3. Conclusion

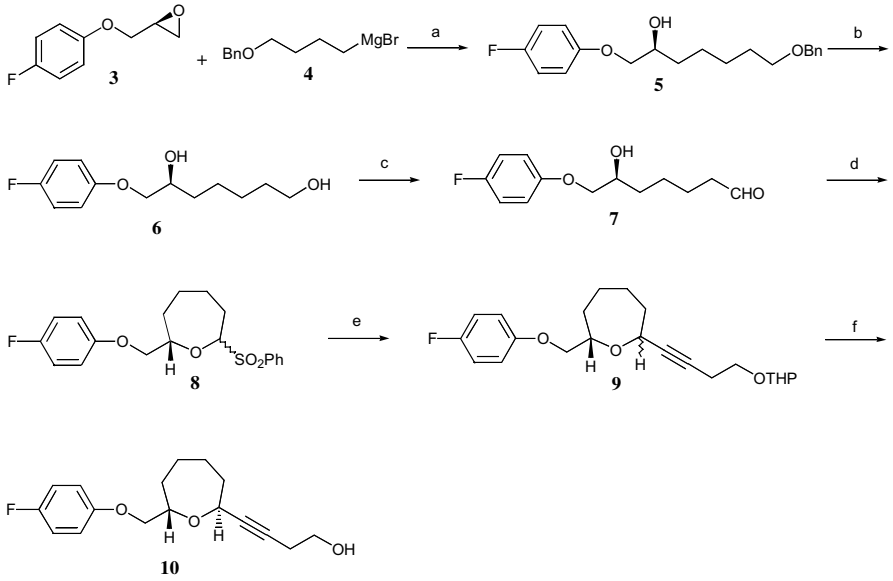
In summary, we have achieved a short, efficient, stereoselective synthesis of 7-membered oxepane derivatives with promise against asthma. Highlights of our synthetic strategy are the regioselective oxidation of a hydroxyl group and efficient ring closure of an open chain aldehyde to a 2-benzenesulfonyl oxepane derivative with $PhSO_2H$. Further efforts are being directed towards a combinatorial library of similar compounds.

4. Experimental

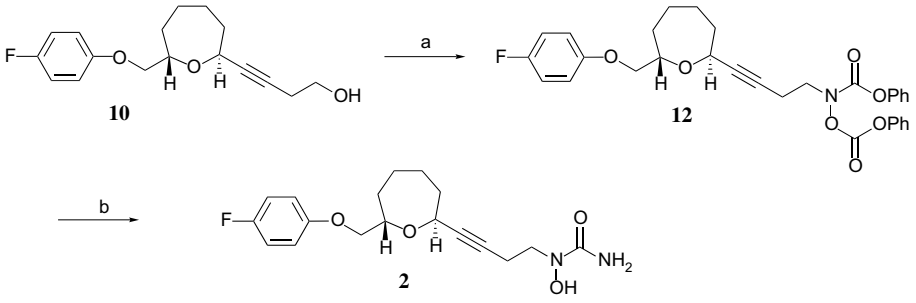
All solvents and reagents were purified and dried according to procedures described in Vogel's Text Book of Practical Organic Chemistry. Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP 370 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on Varian FT-200 MHz and Varian Unity-400 MHz spectrometers using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Finnigan Mat 1210 or MICRO MASS 7070 spectrometer at 70 eV using a direct inlet system. FABMS were recorded on a VG autospec mass spectrometer at 70 eV using a direct inlet system. Silica gel (60–120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.

4.1. (2*S*)-7-Benzyloxy-1-(4-fluorophenoxy) heptan-2-ol 5

To a suspension of magnesium (1.4 g, 57.6 mmol) in dry THF (25 mL) was added 1,2-dibromoethane (0.2 mL) dropwise at room temperature followed by the slow addition of a solution of 4-benzyloxy-1-bromobutane **4** (7 g, 28.8 mmol) in dry THF (25 mL) under N_2 atmosphere. The reaction mixture was stirred for 1 h, cooled in an ice bath and CuCN (50.0 mg, 0.57 mmol) added followed by a solution of (*S*)-4-fluorophenyl glycidyl ether **3** (2.9 g, 17.3 mmol) in dry THF (30 mL). The reaction mixture was stirred for 15 min and then quenched with saturated aqueous ammonium chloride solution at 0 °C. The organic layer was successively



Scheme 1. Reagents and conditions: (a) 1,2-dibromoethane, CuCN, THF, 0 °C, 1.5 h, 73%; (b) 10% Pd–C, H_2, EtOH, rt, 3 h, 93%; (c) IBX, DMSO, THF, 0 °C–rt, 0.5 h, 62%; (d) $PhSO_2H$, $CaCl_2$, DCM, 0 °C–rt, 3 h, 80.8%; (e) Mg, *i*-PrBr, 4-tetrahydropyranoyl-1-butyne, $ZnBr_2$, 0 °C–rt, 12 h; (f) *p*-TSA, MeOH, rt, 1 h, **10A** 70%, **10B** 17.5%.



Scheme 2. Reagents and conditions: (a) **11**, PPh_3, DEAD, THF, rt, 4 h, 92%; (b) NH_3/MeOH, rt, 1 h, 65%.

washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified on silica gel column chromatography using EtOAc–hexane (1:6) as eluent to give **5** (5.8 g, 73%) as a colourless liquid. $[\alpha]_D$ = +12.0 (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.35–1.69 (m, 8H, $4\times CH_2$), 3.45 (t, J = 6.25 Hz, 2H, CH_2OBn), 3.71–3.95 (m, 3H, OCH_2, CHOH), 4.48 (s, 2H, OCH_2Ph), 6.82 (m, 2H, Ar), 6.95 (m, 2H, Ar), 7.27–7.35 (m, 5H, Ph); FABMS *m*/*z* (rel. intensity): 332 (M^+, 32), 261 (14), 207 (43), 181 (90), 125 (61), 112 (78), 107 (100); HRMS (FAB): calcd for ($C_{20}H_{25}FO_3$, M^+): 332.1787. Found 332.1803.

4.2. (6*S*)-7-(4-Fluorophenoxy) heptane-1,6-diol 6

A solution of **5** (5.8 g, 17.5 mmol) in ethanol (30 mL), containing 10% of Pd–C (100 mg) was stirred under an H_2 atmosphere for 3 h. The reaction mixture was filtered through Celite, washed with ethanol and concentrated. The residue was purified by silica gel column chromatography using EtOAc–hexane (1:1) to afford **6** (3.92 g, 93%) as a viscous liquid. $[\alpha]_D$ = +12.5 (*c* 3.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.29–1.69 (m, 8H, $4\times CH_2$), 3.65 (t, J = 6.8 Hz, 2H, CH_2OH), 3.82–4.02 (m, 3H, OCH_2, CHOH), 6.82 (m, 2H, Ar); EIMS *m*/*z* (rel. intensity): 242 (M^+, 9), 126 (13), 112 (100), 95 (31), 43 (78); HRMS (EI): calcd for ($C_{13}H_{19}FO_3$, M^+): 242.1318. Found 242.1319.

4.3. (6*S*)-7-(4-Fluorophenoxy)-6-hydroxyheptanal 7

To a solution of **6** (3.6 g, 14.8 mmol) in dry THF (60 mL) was added, dropwise, a solution of IBX (5.0 g, 17.8 mmol) in dry DMSO (4.0 mL) over a period of 15 min at 0 °C temperature. After 15 min, the reaction mixture was diluted with iced water, filtered through Celite and concentrated. The residue was extracted with dry ether, washed with brine, dried over Na_2SO_4 and the organic solvent removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc–hexane (1:9) to give **7** (2.2 g, 62%) as a viscous liquid. $[\alpha]_D$ = +12.0 (*c* 3.77, $CHCl_3$); IR (neat): 3694–3200 (br), 2941, 1684, 1498, 1208, 824 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ. 4–1.8 (m, 6H, $3\times CH_2$), 2.49 (t, J = 5.47 Hz, 2H, CH_2CHO), 3.71–4.05 (m, 4H, OCH_2, CHOH), 6.85 (m, 2H, Ar), 6.94 (m, 2H, Ar), 9.8 (s, 1H, CHO); FABMS *m*/*z* (rel. intensity): 240 (M^+, 37), 223 (80), 205 (18), 154 (37), 136 (65), 125 (58), 109 (100); HRMS (FAB): calcd for ($C_{13}H_{17}FO_3$, M^+): 240.1161. Found 240.1164.

4.4. (2*RS*,7*S*)-2-(Benzenesulfonyl)-7-(4-fluoromethyl) oxepane 8

To an ice cold mixture of benzenesulfinic acid (1.8 g, 12.4 mmol) and $CaCl_2$ (1.4 g, 12.5 mmol) in dry CH_2Cl_2 (50 mL) was added, dropwise, a solution of **7** (2 g, 8.3 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 3 h at room temperature, filtered through Celite and washed with CH_2Cl_2. The combined organic layer was washed with saturated aqueous Na_2CO_3, water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using EtOAc–hexane (1:6) as eluent to furnish **8** (2.45 g, 80.8%) as a white solid. Mp 126–128 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.430–2.20 (m, 7H, $3\times CH_2$, 1/2 CH_2), 2.5 (m, 1H, 1/2 CH_2), 3.62 (dd, $J = 5.84$, 10.75 Hz, 1H, OCH_2), 3.82 (dd, $J = 4.49$, 10.75, 1H, OCH_2), 4.45 (m, 1H, H-7), 4.72 (dd, $J = 6.6$, 10.75 Hz, 1H, H-2), 6.75 (m, 2H, Ar), 6.95 (m, 2H, Ar), 7.49 (m, 3H, Ph), 7.91 (m, 2H, Ph).

4.5. (2*S*,7*S*)-7-(Fluorophenoxymethyl)-2-(1-hydroxy-3-butyn-4-yl) oxepane 10

To a suspension of magnesium (0.58 g, 24.2 mmol) in dry THF (10 mL) was added 1,2-dibromoethane (catalytic amount). This was followed by the dropwise addition of a solution of isopropyl bromide (1.85 g, 15.1 mmol) in THF (5 mL). The reaction mixture was stirred for 1 h and the resulting isopropyl magnesium bromide cannulated into a 50 mL two-necked flask. A solution of 4-tetrahydropyranoyl-1-butyne (1.86 g, 12.0 mmol) in THF (5 mL) was added and the mixture was stirred for 30 min. This was followed by the addition of a freshly-prepared $ZnBr_2$ solution (1 M, 7.25 mL, 7.2 mmol) in THF at 0 °C. After 45 min, (2*RS*,7*S*)-2-(benzenesulfinyl)-7-(4-fluorophenoxymethyl) oxepane (2.2 g, 6.0 mmol) in THF (10 mL) was added and the mixture stirred for 12 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. THF was removed under reduced pressure and the residue was partitioned and concentrated to give (2*RS*,7*S*)-7-(4-fluorophenoxymethyl)-2-(4-tetrahydropyranoyl-1-butynyl) oxepane **9**. The crude product was dissolved in MeOH (25 mL) and *p*-TSA added. After 1 h, the reaction mixture was neutralized with saturated Na_2CO_3 solution and concentrated. The crude product was purified by silica gel chromatography using EtOAc–hexane (1:8) to give (2*S*,7*S*)-7-(4-fluorophenoxymethyl)-2-(4-hydroxybutynyl) oxepane **10** (1.32 g, 70%): $[\alpha]_D = -74.0$ (*c* 3.63, $CHCl_3$); IR (neat): 3634–3200 (br), 2909, 1498, 824 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.50 (m, 2H, CH_2), 1.76 (m, 2H, CH_2), 1.89 (m, CH_2), 2.12 (m, 2H, CH_2), 2.48 (dt, $J = 7.17$, 1.4 Hz, 2H, $=CH_2$), 3.68 (t, $J = 7.17$ Hz, CH_2OH), 3.81 (dd, $J = 6.04$, 9.32 Hz, 1H, OCH_2), 3.92 (dd, $J = 5.11$, 9.32 Hz, 1H, OCH_2), 4.16 (m, 1H, H-7), 4.56 (m, 1H, H-2), 6.84 (m, 2H, Ar), 6.95 (m, 2H, Ar); EIMS *m*/*z* (rel. intensity): 292 (M^+, 32), 123 (85), 112 (88), 95 (70), 41 (100); HRMS (E1): calcd for ($C_{17}H_{21}FO_3$, M^+): 292.1477. Found 292.1474.

4.6. (2*S*,7*S*)-7-(Fluorophenoxymethyl)-2-[*N*,*O*-bis(phenoxycarbonyl)-3-butyn-4-yl) oxepane 12

A mixture of (2*S*,7*S*)-7-(4-fluorophenoxymethyl)-2-(4-hydroxybutynyl) oxepane, **10A** (0.9 g, 3.1 mmol), TPP (1.0 g, 3.7 mmol) and *N*,*O*-bis(carbophenoxy)hydroxylamine **11** (1.0 g, 3.7 mmol) in dry THF (20.0 mL) was cooled to 0 °C. Diethylazadicarboxylate (0.64 g, 3.7 mmol) was added dropwise and the reaction mixture stirred at room temperature for 4 h. The solvent was removed on a rotary evaporator. The residue was partitioned between EtOAc and water, washed with brine, dried over Na_2SO_4 and concentrated. The product was purified by silica gel chromatography using EtOAc–hexane (1:9) to give pure **12** (1.55 g, 92%). $[\alpha]_D = -46.0$ (*c* 2.4, $CHCl_3$); IR (neat) 3600–3200 (br), 2941, 1678, 1502, 1215, 824 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.39–2.18 (m, 8H, $4\times CH_2$), 2.70 (t, $J = 6.9$ Hz, 2H, $=CH_2$), 3.70–4.05 (m, 4H, CH_2OH, OCH_2), 4.13 (m, 1H, H-7), 4.51 (m, 1H, H-2), 6.76–6.96 (m, 4H, Ar), 7.13-7.44 (m, 10H, $2\times$ Ph); FABMS *m*/*z* (rel. intensity): 547 (M^+, 23), 410 (5), 300 (10), 206 (19), 151 (19), 95 (42), 77 (100).

4.7. (2*S*,7*S*)-2-(4-Fluorophenoxymethyl)-7-(1-*N*-hydroxyureidyl-3-butyn-4-yl) oxepane 2

A solution of (2*S*,7*S*)-7-(4-fluorophenoxymethyl)-2-[4-(*N*,*O*-biscarbophenoxy)-1-butynyl] oxepane **12** (1.3 g, 2.44 mmol) in MeOH (25 mL) was cooled to 0 °C, after which saturated methanolic ammonia solution was added and the reaction mixture stirred at room temperature for an hour. The solvent was removed and the residue purified by silica gel chromatography using EtOAc–hexane (1:1) to provide **2** (0.55 g, 65%) as a colourless solid. $[\alpha]_D = -56.0$ (*c* 2.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.41–2.18 (m, 8H, $4\times CH_2$), 2.51 (dt, $J = 1.1$, 7.1 Hz), 2H, $=CH_2$), 3.69 (t, $J = 7.1$ Hz, 2H, CH_2N), 3.81 (dd, $J = 9.52$, 4.76 Hz, 1H, OCH_2), 3.9 (dd, $J = 5.71$, 9.52 Hz, 1H, OCH_2), 4.13 (m, 1H, H-7), 4.51 (m, 1H, H-2), 5.25 (s, 2H, $CONH_2$), 7.02 (m, 4H, Ar), 7.69 (s, 1H, N–OH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 17.19 (CH_2), 24.59 (CH_2), 27.45 (CH_2), 32.0 (CH_2), 37.13 ($=CH_2$), 48.89 (CH_2N), 72.03 (C-7), 72.31 (C-2), 81.57, 82.41 (C=C), 115.51 ($2\times$ CH, Ar), 115.66 (CH, Ar), 115.81 (CH, Ar), 115.97 (CH, Ar), 154.90 (F–C, Ar), 159.66 (O–C, Ar), 161.78 ($NCONH_2$); FABMS *m*/*z* (rel. intensity): 351 (M^+1, 100), 308 (8), 291 (6), 154 (27), 111 (6), 95 (17); HRMS (FAB): calcd for ($C_{18}H_{24}FN_2O_4$, M^++1): 351.1720. Found 351.1736.

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