Supplementary Contents

A Succinct Synthesis of Bosentan by utilizing Glycol mono-THP ether

*Chung-Ryul Lee; Sang Yeul Lee and Tae-gyu Nam**

Department of Pharmacy and Institute of Pharmaceutical Science and Technology
Hanyang University, Ansan, Gyeonggi-do 426-791, South Korea

S1: Experimental

S3: Selected NMR Spectra of Compounds: **13**, **14**, and **1** (Bosentan)

S6: HPLC traces of new compounds: **13** and **14**

Experimental

General: Materials were purchased from commercial supplier and used without further purification. Progress of reaction was monitored by thin-layer-chromatography (TLC) using silica gel F₂₅₄ plates. Purification of the products was performed using silica gel chromatography with indicated solvents. NMR spectra were obtained using a Bruker-250 spectrometer 400 MHz for ¹H NMR and 100 MHz for ¹³C NMR and are reported as ppm from the internal standard tetramethylsilane (TMS). High-resolution mass spectra (HRMS) were obtained in Gyeonggi Institute of Science and Technology Promotion (GSTeP).

2-((Tetrahydro-2H-pyran-2-yl)oxy)ethan-1-ol (15). A stirred solution of ethylene glycol (10.0 mL, 118.5 mmol) and PPTS (450 mg, 1.8 mmol) in CH₂Cl₂ (250 mL) at ambient temperature was treated dropwise with a solution of 3,4-dihydro-2H-pyran (DHP; 10.8 mL, 179.0 mmol) in CH₂Cl₂ (50 mL) over 1 h. The reaction mixture was stirred for 18 h and washed with water and aqueous 10% NaCl. Resulting organic phase was dried over anhyd. MgSO₄ and concentrated under reduced pressure to provide the crude product. Flash chromatography (SiO₂, 1:1 EtOAc:hexanes) to provide **15** as a colorless oil (8.8 g, 51%): ¹H NMR (400 MHz, CDCl₃) δ 4.44-4.31 (m, 1H), 3.79 (m, 1H), 3.68-3.48 (m, 2H), 3.47-3.43 (m, 1H), 3.39-3.31 (m, 2H), 3.28-3.320 (m, 1H), 1.63-1.41 (m, 2H), 1.38-1.19 (m, 4H); CAS Registry Number: 2162-31-4.

4-tert-Butyl-N-(5-(2-methoxyphenoxy)-6-(2-(tetrahydro-2H-pyran-2-yloxy)ethoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (14). From (**6**): A solution of compound **15** (580 mg, 3.98 mmol) in anhydrous DMF (20 mL) at 0 °C was treated with NaH (60% in mineral oil, 191 mg, 4.78 mmol, washed with hexanes). The resulting mixture was stirred at 0 °C for 30 min under Ar and treated with a solution of commercially available **6** (purchased from Rovathin, 1990 mg, 3.79 mmol) in DMF (19 mL). The reaction mixture was stirred at 0 °C

for 1 h and then at ambient temperature for 5 h under Ar. The reaction mixture was diluted with EtOAc (500 mL), washed with aqueous 1 N HCl (3 x 30 mL), water (3x 50 mL) and saturated aqueous NaCl, dried over anhyd. MgSO₄, and concentrated under reduced pressure to provide the crude product. Flash chromatography (SiO₂, 3% MeOH–CH₂Cl₂) to provide **14** as green foam (1.64 g, 68%).

Bosentan (1). A solution of compound **14** (145 mg, 0.23 mmol) in MeOH (5 mL) at ambient temperature was treated with pyridinium *p*-toluenesulfonate (8 mg, 0.032 mmol). The reaction mixture was stirred for 24 h under Ar and concentrated under reduced pressure. The residue was dissolved in EtOAc (100 mL), washed with water (5 x 10 mL) and saturated aqueous NaCl, dried over anhyd. MgSO₄ and concentrated under reduced pressure to provide the crude product. Flash chromatography (SiO₂, gradient, 3 to 10% MeOH–CH₂Cl₂) to provide **1** as a white solid (107 mg, 84%): ¹H NMR (400 MHz, CDCl₃) δ 9.24 (s, 1H), 8.95 (d, *J* = 4.8 Hz, 2H), 8.41 (d, *J* = 6.8 Hz, 2H), 7.42-7.34 (m, 3H), 7.02-6.98 (m, 2H), 6.87 (d, *J* = 7.2 Hz, 1H), 6.75 (t, *J* = 7.4 Hz, 1H), 4.76 (s, 1H), 4.54-4.48 (m, 2H), 3.81 (s, 3H), 3.79-3.74 (m, 2H), 1.22 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 161.2, 157.6 (2C), 157.0, 155.1, 151.6, 149.4, 145.4, 136.1, 129.3 (2C), 125.3 (3C), 125.1, 124.4, 121.3, 121.0, 118.7, 112.3, 71.3, 62.1, 55.8, 35.0, 30.9 (3C); CAS Registry Number: 147536-97-8.

5-(2-Methoxyphenoxy)-6-(2-(tetrahydro-2H-pyran-2-yloxy)ethoxy)-4-amino-2,2'-bipyrimidine (13)

4-*tert*-Butyl-N-(5-(2-methoxyphenoxy)-6-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy)-2,2'-bipyrimidin-4-yl)benzenesulfonamide (14)

Bosentan (1)

HPLC Trace of Compound **13**

Time (min)	solvent A %
0	50
20	100
25	100

A: acetonitrile (0.1% formic acid)
B: water (0.1% formic acid)
Flow rate: 1 mL/min
Detection wave length: 280 nm
Column: INNO C18 [5 μm, 120 Å, 4.6 x 250 mm]

HPLC Trace of Compound **14**

Time (min)	solvent A %
0	50
20	100
25	100

A: acetonitrile (0.1% formic acid)
 B: water (0.1% formic acid)
 Flow rate: 1 mL/min
 Detection wave length: 280 nm
 Column: INNO C18 [5 µm, 120 Å, 4.6 x 250 mm]