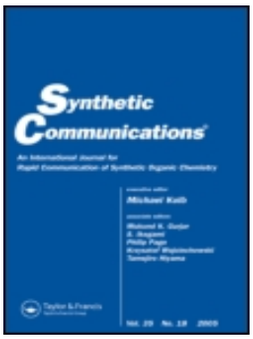

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SUCCINCT SYNTHESIS OF BOSENTAN UTILIZING GLYCOL MONO-THP ETHER

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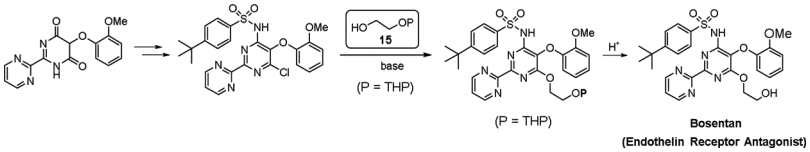
GRAPHICAL ABSTRACT



Abstract *A concise synthetic method for bosentan, a nonpeptide orally active dual endothelin ($ET\text{-}1_{A/B}$) receptor antagonist used for the treatment of pulmonary artery hypertension (PAH), was developed. We developed a new succinct synthetic route for bosentan by employing an acid-labile tetrahydropyran (THP)–protected glycol. THP group is advantageous over the previously known protection groups used in bosentan synthesis in that it provides a clean and quantitative deprotection. Bosentan was constructed via two parallel reaction pathways, yet the better product yield was obtained from a pathway via* ***6****. Deprotection of THP ether was achieved under a mild acidic condition to afford bosentan.*

Keywords Bosentan; endothelin receptor antagonist; pulmonary arterial hypertension; tetrahydropyran ether

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a devastating chronic disease characterized by vasoconstriction, remodeling of pulmonary arteries, progressive increase in pulmonary vascular resistance, and thrombosis.[1] Over the past decade, significant progress in the understanding of the pathogenesis has been achieved, and targeted therapies in the management of PAH have been developed.[2] One of the significant abnormalities in PAH is an overexpression of endothelin-1 (ET-1). The endothelins (ET-1, ET-2, and ET-3) are a family of 21 amino acid peptides and they play an important role in vascular homeostasis. ET-1 is the most important mediator of PAH. The action of ET-1 is complex and mediated via two cell-surface,

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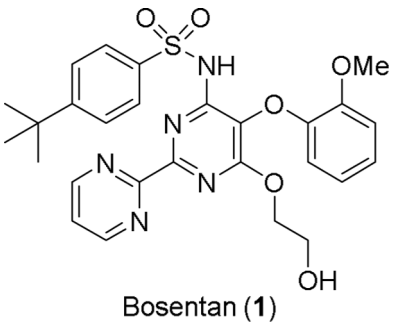


Bosentan (**1**)

Figure 1. Structure of bosentan (**1**).

G-protein-coupled receptors, ET_A and ET_B. Both receptors have been implicated in the pathological processes associated with PAH.[3] Orally active nonpeptide endothelin receptor antagonists might offer an opportunity to treat patients with PAH and congestive heart failure.[4]

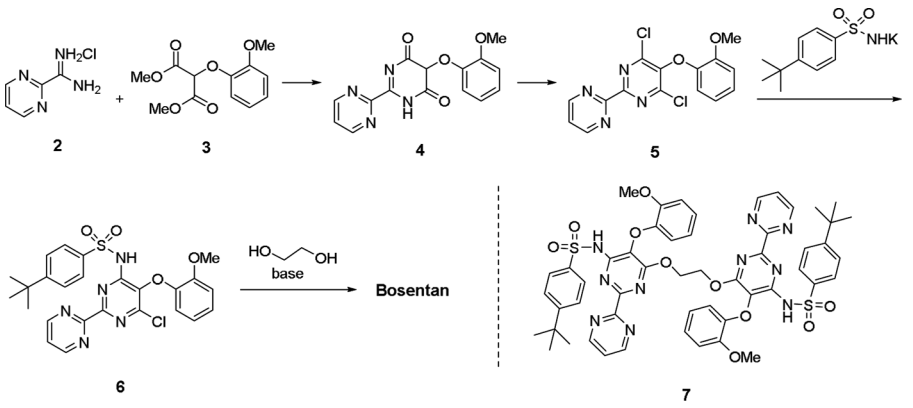
Bosentan is an orally active dual endothelin ($ET\text{-}1_{A/B}$) receptor antagonist (ERA) that competitively blocks the binding of endothelins to both ET_A and ET_B (Fig. 1).[5] Clinical trial data indicated an improvement of exercise capacity, PAH symptoms, and pulmonary hemodynamics.[6] Bosentan is the first nonpeptide ERA that was approved for the treatment of PAH and currently used in the clinical practice.[7] The development of bosentan including the initial process chemistry was conducted by Hoffmann–La Roche, but the clinical study was carried out by Actelion, which ultimately licensed the drug on the market.

We developed a new succinct synthetic route for bosentan by employing an acid-labile tetrahydropyran (THP)–protected glycol **15**. Bosentan was constructed via two parallel reaction pathways, yet the better product yield was obtained from a pathway via **6**. THP ether could be removed under a mild condition to afford bosentan.

RESULTS AND DISCUSSION

The initial bosentan synthesis began with a condensation reaction between an amidine **2** and a malonate **3** to provide a pyrimidinedione **4** (Scheme 1).[7] Treating **4** with $POCl_3$ afforded a dichloropyrimidine **5**, where one of two chloro substituents was displaced by potassium *tert*-butylbenzenesulfonamide to afford a sulfonamide **6**. Remaining chloride in **6** was replaced with ethylene glycol to afford the desired bosentan **1**. Disadvantages associated with the original route include the formation of undesired dimeric compound **7,** which was hard to remove, and the use of excess amount (100 equiv) of ethylene glycol in the last step, which resulted in poor throughput.

Since successful establishment of the pharmaceutical market, several cost-effective synthetic routes for bosentan have been developed in pursue of more competitive market position. The second synthetic route was designed to eliminate problems in the original route (Scheme 2).[8] The main idea was the displacement of a chloride in sulfonamide **6** with stoichiometric amount of glycol mono-*tert*-butyl ether, avoiding the use of excess amount of ethylene glycol, to afford bosentan

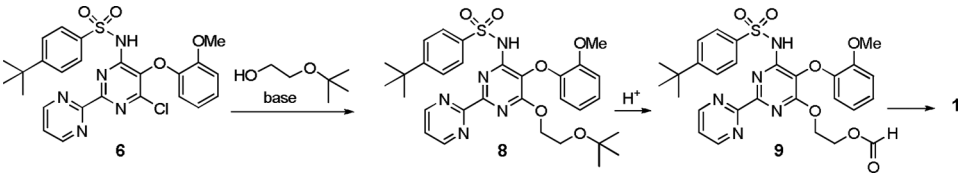


Scheme 1. Original synthetic route for bosentan.

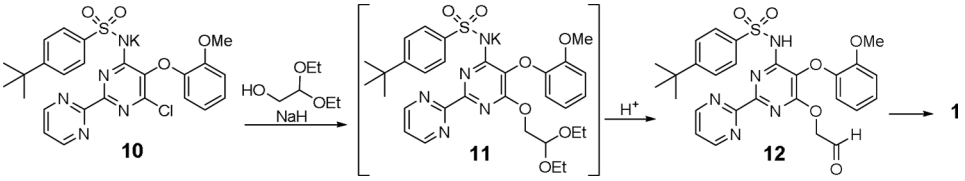
tert-butyl ether **8**. In this modified scheme, the formation of dimeric **7** could be circumvented, but deprotection of **8** resulted in bosentan formate ester **9**. Although hydrolysis of **9** afforded bosentan, this route required an additional deprotecting step.

Several synthetic procedures for bosentan were reported subsequently, and one of the elegant works is depicted in Scheme 3.[9] In this process, the chloro substituent on compound **10**, a potassium salt of **6**, was displaced by glycolaldehyde diethylacetal to form an acetal **11**, where diethylacetal protecting group was in situ removed in an acidic environment to afford an aldehyde **12**. Reduction of the aldehyde functionality to an alcohol produced bosentan.

From thorough analysis of reported processes, we could envisage a succinct synthetic pathway to bosentan by introducing a monoprotected glycol where its hydroxyl protecting group should be stable in basic condition yet labile in mild acidic environment. Herein, we report our effort to synthesize bosentan by utilizing glycol mono-THP ether **15** (Scheme 4). Although THP ether has an advantage as a protection group in that it provides a clean and quantitative deprotection, difficulty in the preparation of glycol mono-THP ether on a mass production scale hampered its use in bosentan synthesis.[8] THP was selected as a protection group in our synthesis for the following reasons. First of all, the use of THP ether as the protecting group can reduce one step in synthesis (Scheme 2) and its mild acidic removal condition is likely to improve the impurity profile. Second, the structure of bosentan does not tolerate basic deprotection conditions because of the possible deprotonation of the sulfonamide group or a possible attack on pyrimidine core if fluoride ion is involved in



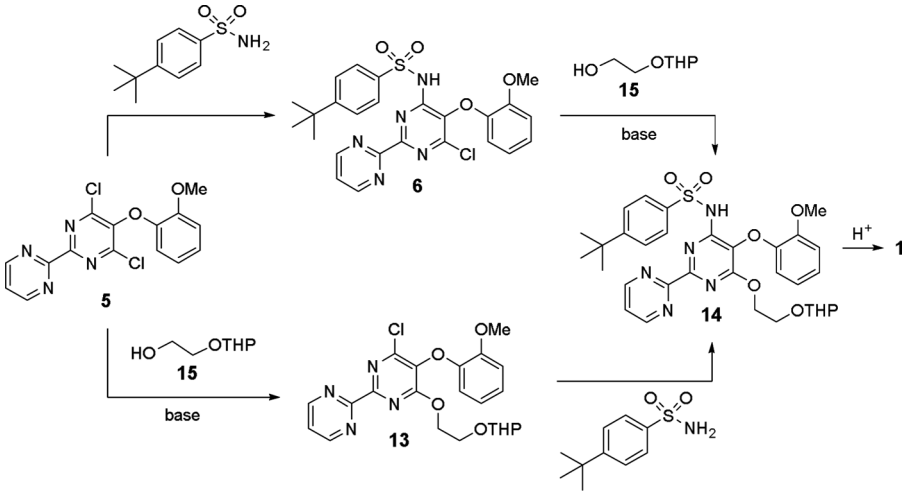
Scheme 2. Second synthetic route for bosentan.



Scheme 3. Preparation of bosentan from glycolaldehyde.

deprotection step. Thus, an acid-labile protecting group should be used in the synthesis. Of acids, Lewis acids are not recommendable because the removal of metal from the final bosentan active pharmaceutical ingredient (API) can be a challenging task. Strong acids such as sulfuric acid or formic acid are not suitable because of the possible formation of corresponding sulfate or formate esters (Scheme 2). At an elevated temperature, even a mild acidic condition can convert the pyrimidine core to the isomeric pyrimidinone form. Thus, the ideal protecting group should be acid labile and robust under basic conditions.

Therefore, the synthesis began with the preparation of ethylene glycol mono-THP ether **15** following a literature procedure.[10] With **15** in hand, two possible synthetic pathways toward the bosentan–THP ether **14** from commercially available compounds **5** and **6** were pursued in a parallel manner. In one method, the chloro substituent in **6** (the conversion from **5** to **6** was well established in literature[7–9]) was displaced with **15** to produce bosentan–THP ether **14** (68%). In another pathway, one of two chlorines on **5** was displaced with **15** to provide **13** (62%), which was converted to **14** by treating with *tert*-butylbenzenesulfonamide in basic conditions (63%). Successful construction of **14** from both pathways might be evidence for the robustness of our approach. Deprotection of THP ether with pyridinium p-toluenesulfonate (PPTS) afforded bosentan **1** in good yield (84%).[10]



Scheme 4. Synthesis of bosentan from glycol mono-THP ether.

EXPERIMENTAL

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

A solution of compound **15** (604 mg, 4.12 mmol) in anhydrous dimethylformamide (DMF; 20 mL) at 0 °C was treated with NaH (60% in mineral oil, 198 mg, 4.95 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 **5** (purchased from TCI, 1872 mg, 5.36 mmol) in DMF (20 mL). The reaction mixture was stirred at 0 °C for 1 h and then at ambient temperature for 3 h under Ar. The reaction mixture was diluted with EtOAc (500 mL); washed with aqueous 1 N HCl (3 × 30 mL), water (3 × 50 mL), and saturated aqueous NaCl; dried over anhydrous $MgSO_4$; and concentrated under reduced pressure to provide the crude product. Flash chromatography (SiO_2, 5% MeOH–CH_2Cl_2) afforded **13** as a white semi solid (1170 mg, 62%) along with a trace amount of undesired bis-alkylated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, $J = 5.0$ Hz, 2H), 7.38 (t, $J = 5.0$ Hz, 1H), 7.02–6.97 (m, 1H), 6.91 (dd, $J = 8.0$, 1.2 Hz, 1H), 6.78–6.747 (m, 1H), 6.64 (dd, $J = 8.0$, 1.2 Hz, 1H), 4.72–4.62 (m, 2H), 4.42 (t, $J = 3.2$ Hz, 1H), 3.86–3.80 (m, 1H), 3.84 (s, 3H), 3.65–3.58 (m, 1H), 3.56–3.49 (m, 1H), 3.35–3.28 (m, 1H), 1.64–1.30 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 161.3, 158.0 (2C), 156.1, 153.1, 149.3, 145.6, 134.8, 124.0, 121.4, 120.7, 115.7, 112.8, 98.3, 67.5, 64.7, 61.5, 56.3, 30.3, 25.4, 18.9. HRMS (ESI) m/z $[M + H]^+$ calcd. for $C_{22}H_{24}O_5N_4$ Cl 459.1430; found 459.1444.

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

A solution of compound **13** (2.0 g, 4.36 mmol) and commercially available 4-*tert*-butylbenzenesulfoamide (1.0 g, 4.79 mmol) in toluene (30 mL) was treated with K_2CO_3 (723 mg, 5.23 mmol) and tetra-n-butylammonium bromide (142 mg, 0.44 mmol). The reaction mixture was warmed at 100 °C for 18 h and cooled down to ambient temperature. The resulting mixture was filtered through a pad of Celite, and the filtrate was diluted with EtOAc (100 mL); washed with aqueous 1 N HCl, water, and brine; dried over anhydrous $MgSO_4$; and concentrated under reduced pressure to provide the crude product. Flash chromatography (SiO_2, 3% MeOH–CH_2Cl_2) to provide **14** as a green foam (1.75 g, 63%): mp = 75–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (d, $J = 4.0$ Hz, 2H), 8.99 (m, 1H), 8.44–8.31 (m, 2H), 7.45 (m, 1H), 7.42 (d, $J = 8.4$ Hz, 2H), 7.22 (m, 1H), 7.09 (t, $J = 7.4$ Hz, 1H), 6.97 (d, $J = 8.0$ Hz, 1H), 6.86–6.80 (m, 1H), 4.78–4.66 (m, 2H), 4.60–4.55 (m, 1H), 4.06–3.90 (m, 4H), 3.79–3.60 (m, 2H), 3.48–3.43 (m, 1H), 1.78–1.38 (m, 6H), 1.28 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.0, 161.4, 157.8 (2C), 157.1, 156.1, 151.6, 149.8, 146.0, 136.3, 129. 6, 129.5 (2C), 125.5, 125.4 (2C), 121.4, 121.2, 120.1, 112.4, 98.5, 66.9, 65.1, 61.8, 56.1, 35.2, 31.1 (3C), 30.5, 25.5, 19.1. HRMS (ESI) m/z $[M + H]^+$ calcd. for $C_{32}H_{38}O_7N_5S$ 636.2486; found 636.2490.

CONCLUSION

We developed new succinct synthetic routes for bosentan by employing acid labile THP-protected ethylene glycol **15**.[11] Bosentan was constructed via two parallel reaction pathways, yet pathway through **6** afforded the better product yield. THP ether could be removed in a mild acidic condition to afford bosentan.

FUNDING

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SUPPORTING INFORMATION

Full experimental details, ^{1}H and ^{13}C NMR spectra, and HPLC tracers for this article can be accessed on the publisher's website.

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