Organic Process Research & Development **2002**, *6*, 120–124

Research and Development of a Second-Generation Process for Bosentan, an Endothelin Receptor Antagonist

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Abstract:

A second-generation manufacturing process from 5-(2-methoxyphenoxy)-[2,2′-bipyrimidine]-4,6-(1*H*,5*H*)-dione to bosentan is based on the synthesis and deprotection of the *tert*-butyl ether of bosentan using available and inexpensive ethylene glycol mono-*tert*-butyl ether. This new strategy triggered a cascade of process improvements. Isolations are reduced from six to three, and drying operations, from five to two. Process solvents are reduced from six to two. The isolations of two sensitizers are eliminated. Toluene is used in place of methylene chloride. Two aqueous waste streams are eliminated by replacing DMF and ethylene glycol by toluene. Two methanol−isopropyl acetate recrystallizations of bosentan are replaced by the decantation of a suspension of bosentan formate monoethanolate in ethanol−toluene. Finally, the overall yield is increased from 67 to 84% and the final product purity improved from 99.3 to 99.7%.

Introduction

The endothelins are a family of structurally related 21-amino acid peptides with two cysteine−cysteine disulfide bridges, a hydrophobic C terminus, and a variety of N-terminal segments (Figure 1). These peptides are the most potent vasoconstrictors ever identified in vascular preparations from animals or humans. Endothelin receptor antagonists such as the promising non-peptide antagonist bosentan (**1**) (Figure 2) offer a new strategy for treatment of patients with cardiovascular pathology and, in particular, congestive heart failure.[1,2] In this well-established market, a competitive price will factor into commercial success. We sought to establish a more competitive market position for bosentan by reducing the bulk drug manufacturing cost.

The First-Generation Process. The first-generation process for bosentan manufacture is presented in Schemes 1 and 2.[3] In Part 1, amidine **4** is prepared in two steps from 2-chloropyrimidine (**2**) (87%). Reaction of dimethyl chloromalonate **5** with guaiacol affords malonate **6** (78%). Pyrimidinedione **7** is then constructed via an amidine−malonate condensation (76−83% based on **2**). In Part 2, the pyrimidinedione **7** is converted to the dichloropyrimidine **8** with phosphorus oxychloride (85−88%). One chlorine is replaced by *tert*-butylbenzenesulfonamide (**10**) (98%). The remaining chlorine is replaced by ethylene glycol (91%). Three crystallizations [two from methanol−isopropyl acetate, one from ethanol−water (83%)] provide specification grade bosentan (**1**) suitable for formulation.

Part I is convergent and requires only one isolation. While the yields are excellent in Part 2, an in-depth analysis uncovered several opportunities for improvement. There are six isolations and five drying operations. There are six process solvents. The potent sensitizer **8** is isolated. Methylene chloride is used in the workup of the phosphorus oxychloride reaction. The mild sensitizer **11** is isolated. *N*,*N*-Dimethylformamide (DMF) is used and aqueous DMF waste is generated in the first chloride displacement. Ethylene glycol is used and aqueous ethylene glycol waste is generated

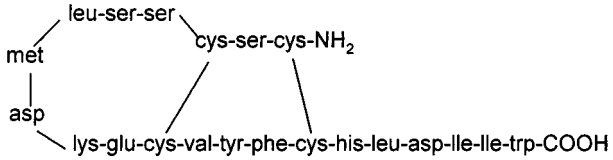

Figure 1. **Amino acid sequence for endothelin-1.**

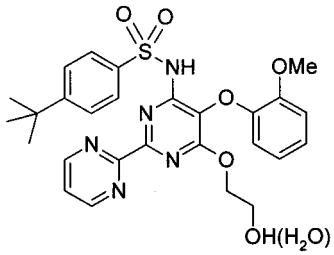

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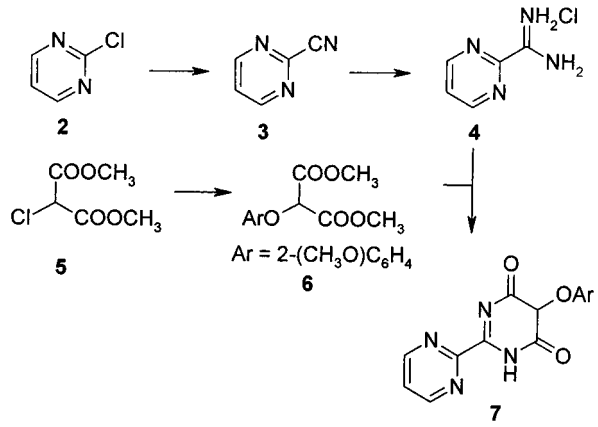
Figure 2. **Bosentan, an endothelin receptor antagonist.**

Scheme 1. **First-generation manufacturing process, part 1**



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(1) Neidhart, W.; Breu, V.; Bur, D.; Burri, K.; Clozel, M.; Hirth, G.; Muller, M.; Wessel, H. P.; Ramuz, H. *Chimia* **1996**, *50*, 519.

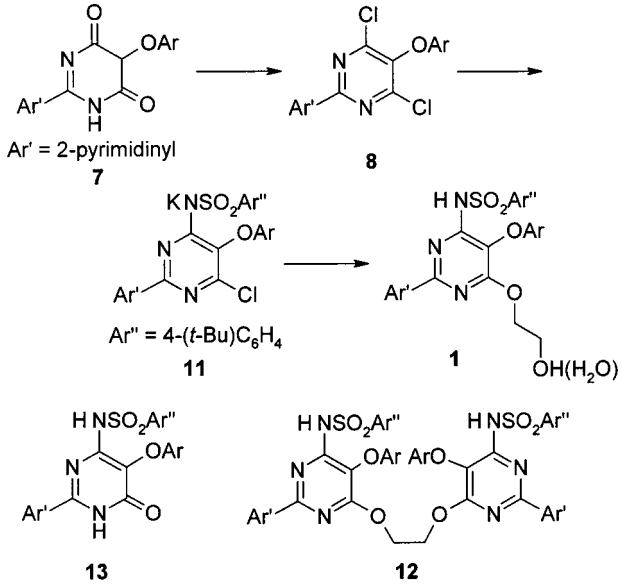
(2) Neidhart, W.; Breu, V.; Burri, K.; Clozel, M.; Hirth, G.; Klinkhammer, U.; Giller, T.; Ramuz, H. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2223.

(3) Burri, K.; Clozel, M.; Fischli, W.; Hirth, G.; Loffler, B.-M.; Neidhart, W.; Ramuz, H. U.S. Patent 5,292,740, 1994.

Published on Web 02/05/2002

10.1021/op010234i CCC: $22.00

Scheme 2. **First-generation manufacturing process, part 2**



in the second chloride displacement. A large excess (100 equiv) of ethylene glycol is required, resulting in a very low throughput for the second chloride displacement. Two final product recrystallizations from methanol−isopropyl acetate are required to lower the levels of dimer **12** and pyrimidinone **13**.

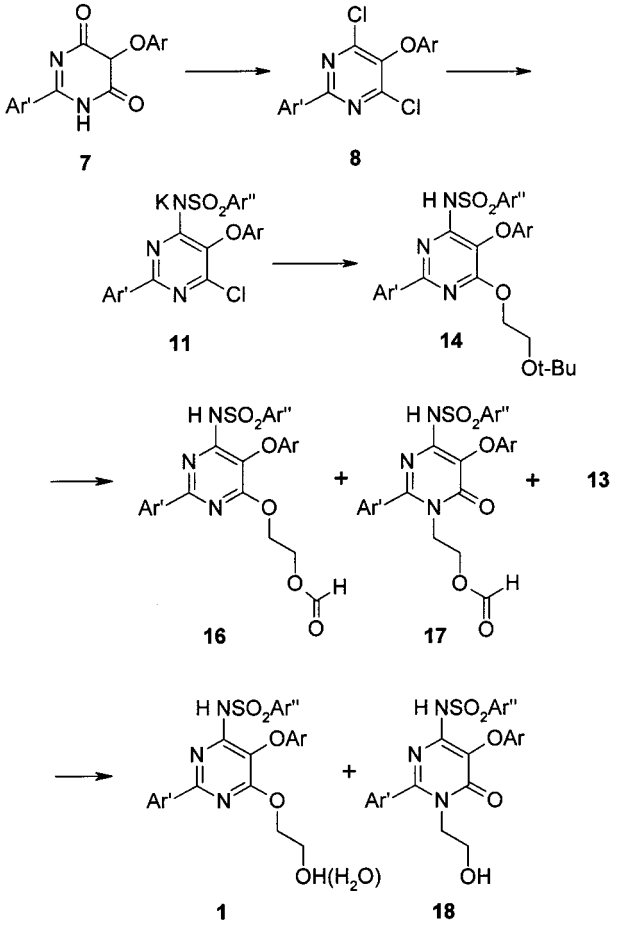
The Second-Generation Process.[4] The statistical problem associated with preparation of the monosubstituted ethylene glycol is a logical starting point for second-generation process design. The large excess of ethylene glycol could theoretically be replaced by one equivalent of a monoprotected ethylene glycol if the monoprotected glycol is available and the deprotection is clean and quantitative. Deprotection of a tetrahydropyranyl (THP) ether could be both clean and quantitative. However, ethylene glycol mono-THP ether is not available in bulk. On the other hand, ethylene glycol monobenzyl ether is readily available but heteroaromatic ring reduction complicates hydrogenolysis of the benzyl ether of bosentan. Ethylene glycol mono-*tert*-butyl ether (ETB) is available and inexpensive. We now report on a second-generation manufacturing process based on the synthesis and deprotection of bosentan *tert*-butyl ether (see Scheme 3). This single modification triggered a cascade of process improvements.

Replacement of DMF and Ethylene Glycol by Toluene and Elimination of the Isolation of Sulfonamide Salt 11. Since the second chloride displacement will not require ETB as a solvent, we first identified a solvent for this reaction. We established that the displacement using granular sodium hydroxide in toluene is rapid and efficient at 50−60 °C.

We next evaluated the first chloride displacement in toluene with the goal of eliminating isolation of the sulfonamide salt **11**. Only slow conversion was observed in a refluxing suspension of dichloride **8**, sulfonamide **10**, and anhydrous potassium carbonate in toluene. This displacement becomes rapid and efficient when 2 mol % of tetrabutylammonium bromide (TBAB) is added to the suspension. During the reaction, water is continuously separated using a Dean−Stark trap. This is consistent with the conversion of potassium bicarbonate to potassium carbonate, carbon dioxide, and water.

(4) Harrington, P. J.; Khatri, H. N.; DeHoff, B. S. U.S. Patent 6,136,971, 2000.

Scheme 3. **Second-generation manufacturing process**



The fluid viscosity of the thick suspension of sulfonamide salt **11** was measured at the end of the reaction. The fluid is non-Newtonian, with viscosity in an acceptable range (800−1200 cp). No agitation problems are anticipated on scale-up.

Replacement of Methylene Chloride by Toluene and Elimination of the Isolation of Pyrimidinedichloride 8. The pyrimidinedichloride **8** is known to be a potent sensitizer. The reaction of pyrimidinedione **7** with excess phosphorus oxychloride at reflux typically produces a product mixture containing the dichloride **8** and less than 1% of the monochloro intermediate **9**. In the current process, methylene chloride is added to this product mixture just prior to the aqueous quench. Since dichloride **8** is sufficiently soluble in toluene at 70 °C and toluene is inert to the vigorous quench conditions, we can replace methylene chloride by toluene and eliminate this isolation as well. The higher-boiling solvent also allows us to use a higher temperature during the exothermic quench or possibly to quench water-to-batch, avoiding transfer of dichloride **8** and the potential for a transfer line leak. Soluble phosphate in the aqueous waste stream can be reduced from over 40 000 to 1−4 ppm by treatment with excess lime.

Table 1. **Gas chromatographic analysis of commercial samples of ETB**

sample ID	ETB (%)	ethylene glycol (ppm)	ESB (ppm)
Maruzen	99.81	149	1207
spectrum MI0412	99.19	137	1245
TCI FGD 01	99.82	219	784
TCI OGF 01	99.74	238	778

Isolation of Bosentan *tert*-Butyl Ether 14. The gas chromatographic analysis of ETB (99+%) obtained from three commercial sources highlights only one impurity that could be problematic: ETB typically contains 0.07−0.13% ethylene glycol *sec*-butyl ether (ESB) (Table 1). This is converted to bosentan *sec*-butyl ether **15** which is not completely removed in the isolation of **14** nor cleaved during the *tert*-butyl ether deprotection. Removal of *sec*-butyl ether **15** must be included in the downstream sequence design.

After workup of the second chloride displacement with dilute hydrochloric acid, the toluene solution is concentrated and toluene replaced by ethanol. The ether **14** (99+% by LC) is isolated from the ethanol solution on cooling to 0 °C in 92% yield based on pyrimidinedione **7**. Significant amounts of residual sulfonamide salt **11**, pyrimidinone **13**, and *sec*-butyl ether **15** are removed in the ethanol liquors.

Unfortunately, with this workup procedure we are not yet able to direct the excess ETB to a single waste stream for recycle. To illustrate, we used 5 equiv of ETB (84.6 g) in an early nonoptimized procedure from 50 g of the dichoride **8** to the ether **14**. The fate of the ETB was the following: 20% (16.9 g) was used in the reaction, 19% (16.1 g) was recovered from the combined aqueous layer and water wash, 29% (24.4 g) was recovered from the toluene distillate, and the rest (32%) was apparently removed in the ethanol crystallization.

Deprotection to Bosentan Formate 16. Deprotection of a *tert*-butyl ether with protic[5,6] and Lewis acids ($FeCl_3$, $TiCl_4$, Me_3SiI)[7−9] is well precedented. Since the ether cleavage is at the end of the sequence to bosentan, we did not pursue a Lewis acid-mediated deprotection which might leave a trace-level of metal residue. We demonstrated ether cleavage with sulfuric acid in an alcohol solvent, hydrogen chloride in an alcohol solvent, methanesulfonic acid, trifluoroacetic acid, and formic acid. Deprotection with sulfuric acid at elevated temperature raised concerns about formation of sulfate esters, including the sulfate ester of bosentan. Deprotection with hydrogen chloride at elevated temperature raised concerns about corrosivity and formation of alkyl chlorides, including 2-chloroethanol and the chloride derived from bosentan. Deprotection with methanesulfonic acid at elevated temperature raised concerns about the formation of the methanesulfonate of bosentan. Since even trace quantities of a bosentan sulfate ester or bosentan-derived chloride would be unacceptable, we did not pursue these approaches beyond the initial demonstration of the ether cleavage.

The conversion of bosentan *tert*-butyl ether **14** to bosentan formate **16** with formic acid is efficient. The undesired ether cleavage to pyrimidinone **13** is not competitive. Despite the formation of bosentan formate **16**, necessitating an additional hydrolysis step, cleavage with formic acid was the best option.

The ether cleavage is carried out in neat formic acid at elevated temperature. Complete cleavage of the *tert*-butyl ether at 50 °C (0.2% residual by LC) requires a 5:1 (L/kg) formic acid−ether ratio and long reaction time (22 h). Complete cleavage of the *tert*-butyl ether is observed after just 3 h at 85 °C using a formic acid−ether ratio of 2:1. Complete cleavage of the *tert*-butyl ether but higher levels of pyrimidinone **13** (0.93%) are observed after 5 h at 85 °C using a 1:1 formic acid−ether ratio.

The formic acid is then removed as the toluene azeotrope. We observed some thermal rearrangement of **16** to pyrimidinone **17** when the azeotrope and residual toluene are distilled at atmospheric pressure and 85−105 °C. Rearrangement to pyrimidinone **17** is minimal (0.1−0.2%) when the azeotrope and residual toluene are distilled at 100 mmHg.

Meeting Purity Specifications via Decantation of Bosentan Formate 16. One of the major challenges we face in second-generation process design is to meet the FDA-filed purity specifications established by the first-generation process. Bosentan used in the clinical trials contained qualified impurities **11**, **12**, and **13**, and unqualified impurities totalling less than 0.2%. Thus, our second-generation material must also have total unqualified impurities less than 0.2%. *While the first-generation material is typically 99.3% pure, it is conceivable that we could produce 99.7% pure material which does not meet the unqualified impurity specification!*

Dilution of the toluene solution of formate **16** with absolute ethanol to produce a 4:1:1 mixture [ethanol (L): toluene (L):**16** (kg)], heating to produce a clear solution, then cooling to −5 °C affords large easily filtered crystals of bosentan formate monoethanolate. The low solubility of bosentan formate monoethanolate in ethanol−toluene, the efficient removal of unqualified impurities **14** and **15**, and the use of ethanol for the subsequent hydrolysis all suggested that the suspension should be decanted. The decantation is performed in the laboratory using a small gas dispersion tube (Ace Glass)connected via Teflon tubing to a receiver under vacuum (400−500 mmHg). The residual wet solid is redissolved in absolute ethanol at reflux and the solution assayed by LC to ensure that the impurity specification will be met before proceeding to the formate hydrolysis. An additional decantation can be added if necessary.

Hydrolysis of Bosentan Formate 16 and Isolation of Bosentan. Hydrolysis of formate **16** in ethanol using aqueous caustic is complete in less than 1 h at 25 °C. Some cleavage of bosentan to pyrimidinone **13** is observed at higher temperatures. Addition of 12 N HCl to adjust the pH to 5 affords bosentan crude as large near-colorless crystals. Formate **16** is not regenerated in the pH 5 suspension even after aging 20 h at 25 °C. A negligible yield increase and some regeneration of formate **16** is observed if the suspension pH is adjusted to 1. The pyrimidinone **17** (<0.2%) is

(5) Eder, U.; Haffer, G.; Neef, G.; Sauer, G.; Seeger, A.; Wiechert, R. *Chem. Ber.* **1977**, *110*, 3161.
(6) Halpern, B.; Nitecki, D. E. *Tetrahedron Lett.* **1967**, 3031.
(7) Ganem, B.; Small, V. R., Jr. *J. Org. Chem.* **1974**, *39*, 3728.
(8) Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.*, **1982**, *104*, 1116.
(9) Jung, M. E.; Lyster, M. A. *J. Org. Chem.*, **1977**, *42*, 3761.

simultaneously hydrolyzed to pyrimidinone **18**.

The final recrystallization provides specification grade material suitable for formulation. We can eliminate a drying operation by using the bosentan crude wet cake for the final crystallization. Alternatively, we can eliminate both an isolation and a drying operation by decantation of the bosentan crude suspension.

A second-generation process incorporating all these modifications has many significant advantages over the first-generation process. Isolations are reduced from six to three, and drying operations, from five to two. Process solvents are reduced from six to two. The potent sensitizer **8** is not isolated. Toluene is used in place of methylene chloride. The mild sensitizer **11** is not isolated. Two aqueous waste streams are eliminated by replacing DMF and ethylene glycol by toluene. Two methanol−isopropyl acetate recrystallizations of bosentan (**1**) are replaced by a decantation of the suspension of bosentan formate monoethanolate (**16**) in ethanol−toluene. Finally, the overall yield from dione **7** to bosentan (**1**) is increased from 67 to 84%, and the bosentan (**1**) purity increased from 99.3 to 99.7%.

Experimental Section

The preparation of pyrimidinedione **7** is described in ref 3. 4-*tert*-Butylbenzenesulfonamide **10** was purchased from Saurefabrik Schweizerhall and used as received. Phosphorus oxychloride, potassium carbonate, tetrabutylammonium bromide, sodium hydroxide beads, and formic acid were purchased from Aldrich Chemical Co. and used as received. Toluene was purchased from Burdick and Jackson and used as received. Ethylene glycol mono *tert*-butyl ether (ETB) was purchased from TCI America and used as received. Ethanol was purchased from Spectrum Chemical and used as received. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

Ethylene glycol mono *sec*-butyl ether (ESB) was prepared by a literature method.[10] A reference sample of bosentan *sec*-butyl ether **15** was then prepared using ESB and a procedure similar to the one described for bosentan *tert*-butyl ether **14**.

Heating bosentan formate monoethanolate **16**, toluene, and formic acid in a sealed tube at 150 °C for 5 h produced a mixture enriched in pyrimidinone **17**. Concentration in vacuo and preparative LC of the residue afforded **17** as an oil suitable for characterization by ^{1}H and ^{13}C NMR, IR, and mass spectrometry.

Hydrolysis of **17** using a procedure similar to the one described for preparing bosentan **1** afforded **18** as an oil suitable for characterization by ^{1}H and ^{13}C NMR, IR, and mass spectrometry.

4,6-Dichloro-5-(2-methoxyphenoxy)-2,2′-bipyridine (8). A mixture of 150.0 g (0. 480 mol) of pyrimidinedione **7** and 176 mL (290 g, 1.89 mol) of phosphorus oxychloride was heated to 90 °C. After the vigorous gas evolution subsided, the pot temperature was increased to 105 °C and maintained for 5 h. The mixture was cooled to 80−90 °C, diluted with 225 mL of toluene and then added via 12-gauge cannula to a mixture of 675 mL of toluene and 525 mL of H_2O over 15−30 min. External cooling was used to maintain the quench mixture temperature at less than 80 °C. Aqueous sodium hydroxide (400 mL of 30%) was added at 70−80 °C, and then the layers were separated. The toluene layer was washed with 500 mL of water containing 1 mL of 30% aqueous NaOH. [**NOTE**: After the caustic addition, the temperature must be kept above 70 °C to avoid precipitation of dichloropyrimidine **8**.] The combined aqueous layers were extracted with 500 mL of toluene. The combined organic phases were dried by distillation of the toluene azeotrope. The resulting solution was used directly in the next step.

***N*-[6-Chloro-5-(2-methoxyphenoxy)[2,2′-bipyrimidin]-4-yl]-4-(1,1-dimethylethyl)benzenesulfonamide, potassium salt (11).** 4-*tert*-Butylbenzenesulfonamide (**10**) (102.4 g, 0.480 mol), 79.6 g (0. 576 mol) anhydrous powdered (extra fine) potassium carbonate, 4.6 g (14 mmol, 2.9 mol %) of tetrabutylammonium bromide, and 1950 mL of toluene were added to the toluene solution of dichloropyrimidine (**8**) at 50 °C. The resulting suspension was refluxed with continuous removal of water using a Dean−Stark trap for 5−7 h. The suspension was cooled and then used directly in the next step.

***N*-[6-[2-(1,1-Dimethylethoxy)ethoxy]-5-(2-methoxyphenoxy)[2,2′-bipyrimidin]-4-yl]-4-(1,1-dimethylethyl)benzenesulfonamide (Bosentan *tert*-Butyl Ether) (14)**. Ethylene glycol mono-*tert*-butyl ether (ETB) (189 mL, 170 g, 1.44 mol) and 38.4 g (0.960 mol) of granular sodium hydroxide were added to the sulfonamide salt (**11**) suspension in toluene. The suspension was then heated at 55 °C for 3−7 h. The mixture changed from a suspension to a near solution to a suspension during this time. The resulting suspension was cooled and 80 mL of 12 N HCl in 720 mL of water was added. More acid (10−15 mL) was added to adjust the pH to 3−4 and produce two clear layers. The layers were separated. The organic layer was washed twice with 500 mL of water. The toluene−water azeotrope and toluene were distilled at atmospheric pressure (3200 mL collected). The flask was cooled, and distillation was continued under reduced pressure until approximately 50 mL of toluene remained. The pot solution was cooled and diluted with 1500 mL of denatured ethanol. Toluene was removed as the ethanol azeotrope (500−750 mL collected) and the suspension were allowed to cool to 25 °C overnight. After cooling to 2−5 °C, the suspension was stirred for 2 h. The precipitate was suction-filtered, washed with 500 mL cold denatured ethanol, and then dried in a vacuum oven at 40−50 °C to afford 268 g (91.8%) of near colorless powder.

Recrystallization from toluene and then ethyl ether provided material for elemental analysis: mp 156−156.5 °C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 9H), 1.28 (s, 9H), 3.62 (t, 2H, J = 4.9 Hz), 3.99 (s, 3H), 4.62 (t, 2H, J = 4.9 Hz), 6.83−6.88 (m, 1H), 6.96−6.99 (d, 1H, J = 8.1 Hz), 7.08−7.13 (m, 1H), 7.29 (d, 1H, J = 8.1 Hz), 7.38−7.42 (m, 3H), 8.38 (d, 2H, J = 8.6 Hz), 8.98 (d, 2H), 9.1 (br, 1H); IR (KBr pellet) 3300−3200, 2975, 2890, 2840, 1575, 1500 cm^{-1}. Anal. Calcd for $C_{31}H_{37}N_5O_6S$: C, 61.27; H, 6.14; N, 11.52. Found: C, 61.53; H, 6.37; N, 11.42.

(10) Zakharkin, L. I.; Khorlina, I. M. *Izv. Akad. Nauk SSR, Otd. Khim. Nauk* **1959**, 2255.

4-(1,1-Dimethylethyl)-N-[6-[2-formyloxy)ethoxy]-5-(2-methoxyphenoxy)[2,2′-bipyrimidin]-4-yl]benzenesulfonamide, Compd. with Ethanol (1:1) (Bosentan Formate Monoethanolate) (16). A mixture of 250.82 g (0.413 mol) of bosentan *tert*-butyl ether (**14**) and 500 mL 95−97% formic acid was heated at 85 °C for 4 h. The resulting yellow solution was cooled and diluted with 800 mL toluene. Formic acid and toluene were distilled as the azeotrope by using a 1000-mL distillation storage head (Ace Glass) as a layer-separating collector at 35−39 °C and 97−102 mmHg (collected 680 mL top phase and 450 mL bottom phase). At this point GC analysis indicated the toluene distillate contained only trace formic acid and that the product−toluene ratio (LC area %) in the pot was ∼92:4. The suspension was cooled to 50 °C, diluted with 615 mL of absolute ethanol, and then heated to reflux. The solution was allowed to cool to 25 °C at ∼150 rpm over 18 h. The resulting suspension was cooled to −5 °C, stirred for 2 h, and then decanted (collected 400 mL in 75 min). The wet solid was taken up in 500 mL of absolute ethanol at reflux. The solution was allowed to cool to 25 °C at ∼150 rpm over 4 h, and then the suspension was decanted (585 mL in 40 min). The wet solid was used directly in the next step.

Recrystallization from anhydrous ethanol provided material for elemental analysis: mp 138.5−140 °C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.21 (t, 3H, J = 7.0 Hz), 1.29 (s, 9H), 1.67 (br, 1H), 3.70 (m, 2H), 3.90 (s, 3H), 4.35 (m, 2H), 4.71 (m, 2H), 6.80−6.85 (m, 1H), 6.95 (d, 1H, J = 7.5 Hz), 7.03−7.11 (m, 2H), 7.40−7.44 (m, 3H), 7.89 (s, 1H), 8.41 (d, 2H, J = 8.4 Hz), 8.93 (br, 1H), 8.99 (d, 2H); IR (KBr pellet) 3600−3240, 2970, 2910, 2870, 1725, 1685, 1580, 1560 cm^{-1}. Anal. Calcd for $C_{30}H_{35}N_5O_8S$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.40; H, 5.51; N, 11.43.

Bosentan Crude (1). Absolute ethanol (600 mL), 165.2 g of 30% sodium hydroxide (1.239 mol NaOH), and 175 mL of water were added to the wet bosentan formate monoethanolate (**16**). The resulting solution was stirred at 25 °C for 60 min. The suspension was slowly acidified with 77 mL of 12 N HCl to pH 5 cooling with ice to maintain 25 °C. Water (350 mL) was added dropwise, and then the suspension was stirred at 25 °C for 3 h. The precipitate was suction-filtered, washed with 250 mL of 1:1 ethanol−water, and then briefly air-dried at 25 °C.

Bosentan Pure (1). The wet bosentan crude (**1**) was taken up in 650 mL of anhydrous ethanol at reflux. Water (650 mL) was added dropwise at reflux. The resulting suspension was allowed to cool to 25 °C at ∼150 rpm over 6 h. The precipitate was suction-filtered and air-dried at 25 °C for 16 h to afford 214.47 g of near colorless crystals (91.2% from bosentan *tert*-butyl ether **14**).

Precipitation of Phosphate from Pyrimidinedichloride 8 Aqueous Waste. The aqueous layers from a 50-g-scale pyrimidinedichloride **8** workup were combined and then filtered though 0.45 μm media to yield 650 mL of a clear, light yellow solution containing about 0.985 M phosphate (as PO_4^{-2}). The filtrate (100 mL) was charged to a 500-mL flask equipped with an overhead stirrer. After calcium oxide (3, 4, or 5 equiv) was added, the white slurry was agitated vigorously for 30−60 min at 20−22 °C and then filtered through a coarse sintered glass funnel. The slurries produced using 3 or 4 equiv of calcium oxide both filtered well. Soluble phosphate was reduced from over 40 000 ppm to 4 ppm using 3 equiv of calcium oxide. Soluble phosphate was reduced to just 1 ppm using 4 equiv of calcium oxide.[11]

Viscosity Measurement of Suspension of Sulfonamide Salt 11 in Toluene. The fluid viscosity was measured with the use of the Brookfield model DVII viscometer. A 300-mL sample of the reaction slurry was withdrawn, placed in an agitated beaker, and heated on a hot plate at 85−90 °C. Viscosity was measured using a no. 2 spindle at speeds ranging from 3 to 12 rpm. The slurry was quickly suspended at 600 rpm, and and then agitation was stopped to record the viscosity.

Supporting Information Available

Structure elucidation for compounds **17** and **18** (^{1}H NMR, ^{13}C NMR, IR, APCI/MS), reaction-monitoring and impurity-profile HPLC methods, solubility study for bosentan formate monoethanolate **16** in ethanol−toluene, and GC method for ETB. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review October 15, 2001.

OP010234I

(11) For phosphate analysis, see: *Official Methods of Analysis of the Association of Official Analytical Chemists*, 14th ed.; Williams, S., Ed.; Association of Official Analytical Chemists: Arlington, VA, 1984; pp 632−633.