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An Efficient Large-Scale Synthesis of Methyl 5-[2-(2,5-Dimethoxyphenyl)ethyl]-2-hydroxybenzoate

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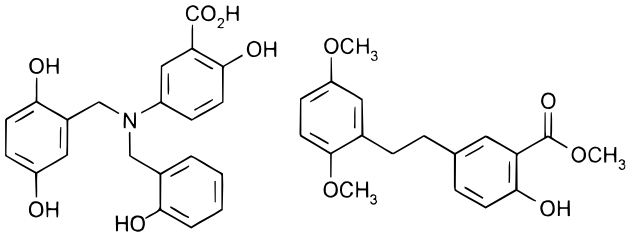
Abstract:

Methyl 5-[2-(2,5-dimethoxyphenyl)ethyl]-2-hydroxybenzoate (1) is a new chemical entity designed by Novartis Pharmaceuticals Corporation for the treatment of hyperproliferative and inflammatory disorders and cancer. Development of a prototype adequate process for its preparation is described. The finalized process was six steps in length and started with the commercially available compounds 2,5-dimethoxybenzaldehhyde and 5-formylsalicylic acid. The methyl ester of 5-formylsalicylic acid was condensed with dimethyl [(2,5-dimethoxyphenyl)-methyl]phosphonate, prepared from 2,5-dimethoxybenzaldehyde in three steps, to afford methyl 5-[2-(2,5-dimethoxyphenyl)-ethenyl]-2-hydroxy-(*E*)-benzoate. Without purification, this intermediate was hydrogenated using 10% Pd/C at 40 °C to afford 1, in >99.5% purity after recrystallization from absolute ethanol. The process research into the Horner−Wadsworth−Emmons-type olefination and a bromination reaction are also discussed; improvements in these transformations permitted elimination of column chromatography.

Introduction

Methyl 5-[2-(2,5-dimethoxyphenyl)ethyl]-2-hydroxybenzoate (**1**), a derivative of the EGF receptor tyrosine kinase inhibitor lavendustin A, is a potential therapeutic agent for the treatment of hyperproliferative and inflammatory disorders and cancer.[1] The original method for the preparation of **1**, shown in Scheme 1, was used to prepare material for the initial pharmacological screening.



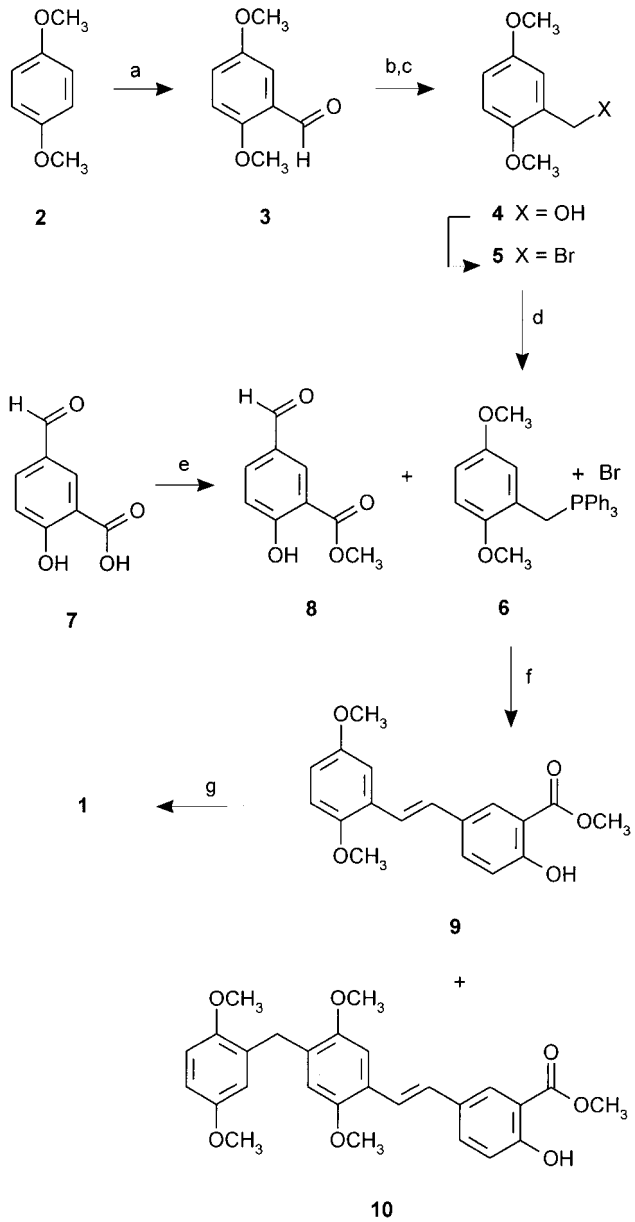
Lavendustin A

1

LAP 977

The synthesis started with the commercially available 1,4-dimethoxybenzene (**2**), and it involved formylation of **2** to afford aldehyde **3**, which was reduced to alcohol **4** with $NaBH_4$ and brominated using HBr gas to provide **5**. Bromide **5** was converted to phosphonium salt **6** using standard chemistry. This phosphonium salt was then coupled under Wittig conditions with aldehyde **8**, made from commercially available 5-formylsalicylic acid (**7**), to afford olefin **9**. At this stage, a large-scale column chromatography was needed

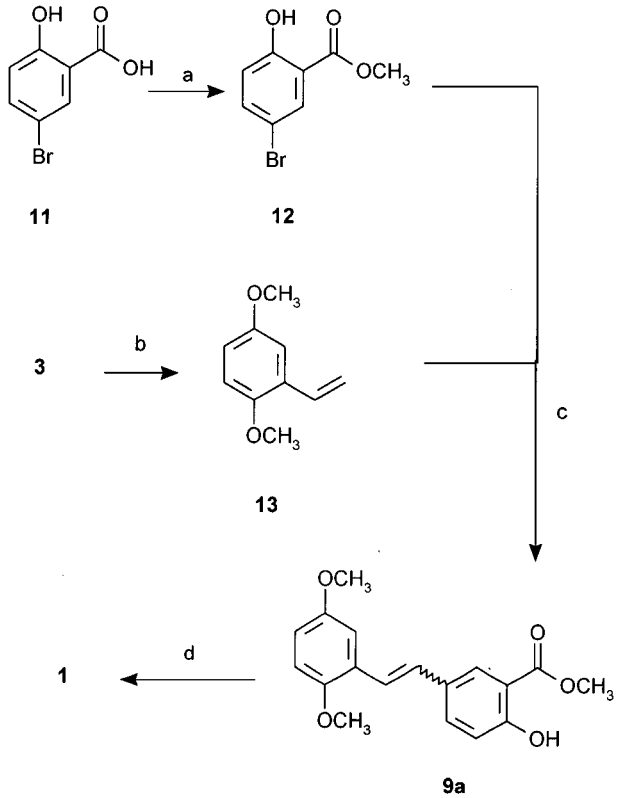
Scheme 1[a]



[a] (a) HexLi, THF, TMEDA, DMF, 0 °C (~90%); (b) toluene, hexane, THF, Bu_4NBr, H_2O, $NaBH_4$, 25 °C (95%); (c) toluene, hexane, THF, HBr(g), 0 °C (75%); (d) toluene, PPh_3, 60−75 °C (95%); (e) MeOH, H_2SO_4, heat (80%); (f) THF, LDA 0 °C (70%); (g) 10% Pd/C, H_2, EtOAc, 40 °C (60%).

(1) (a) Cammisuli, S.; Winiski, A. P.; Nussbaumer, P.; Hiestand, P.; Stutz, A.; Weckbecker, G. *Int. J. Cancer* **1996**, *65* (3), 351. (b) Ure, I.; Niederecker, C.; Nussbaumer, P.; Winiski, A. P.; Hegemann, L.; Stütz, A.; Wolff, K. *Skin Pharmacol.* **1996**, *9*, 166. (c) Nussbaumer, P.; Stütz, A. Eur. Patent 539326 A2 930428. (d) Nussbaumer, P.; Winiski, A. P.; Cammisuli, S.; Hiestan, P.; Weckbecker, G.; Stütz, A. *J. Med. Chem.* **1994**, *37* (24), 4079.

Scheme 2 [a]



[a] (a) MeOH, H_2SO_4, reflux; (b) $CH_3{}^+P(Ph)_3Br^-$, *n*-BuLi, THF, −10 °C to rt; (c) $Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N, CH_3CN, reflux; (d) H_2, EtOAc, 40 °C.

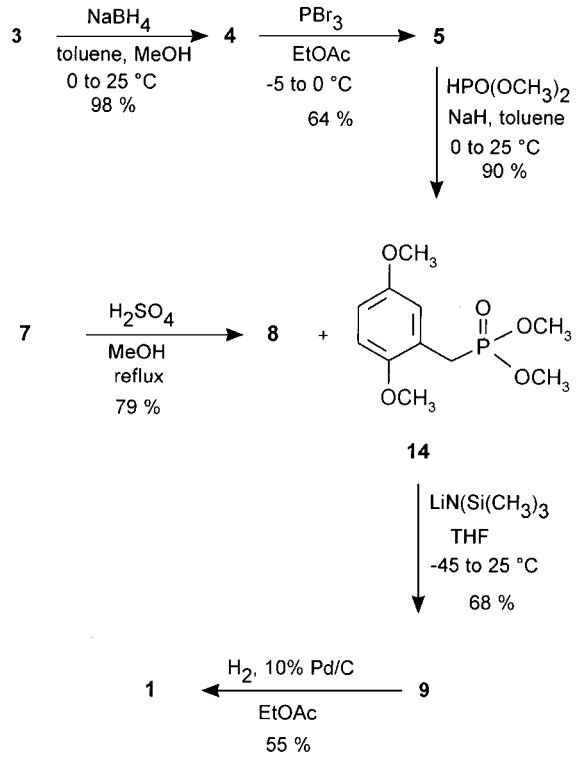
to eliminate the triphenyl byproduct **10**, so that the final drug substance specifications (>98% pure, with no single impurity >0.5%) could be achieved. Incorporation of the chromatography also eliminated the triphenylphosphine oxide byproduct of the Wittig reaction. Hydrogenation of purified (>97%) **9** afforded **1** as a white, crystalline material in an extremely pure state.

Results and Discussion

When the project was advanced, our first task was to evaluate critically the current synthetic route. Despite the generally high yields, the major obstacle to the further scale-up of this route was the necessity for a column chromatography of the penultimate intermediate **9**. In trying to avoid chromatography, we initially explored a new synthesis based on Heck chemistry for the preparation of olefin **9**, as delineated in Scheme 2. This route started with the commercially available 5-bromosalicyclic acid (**11**), which was esterified to give **12**. The styrene **13** was made from 2,5-dimethoxybenzaldehyde (**3**) via standard Wittig chemistry. Unfortunately, styrene **13**, which was an oil, had to be purified via chromatography to remove triphenylphosphine oxide and ancillary impurities so as to prevent polymerization. In our hands, this material had on several occasions polymerized when it had been left in the crude state. Several conditions for the Heck-type coupling[2] of bromide **12** with styrene **13** were investigated, with the best conditions being 3 mol % of $Pd(OAc)_2$ in refluxing acetonitrile containing tri-*o*-tolylphosphine and Et_3N. The yield was >90% of an

(2) (a) Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 308. (b) Heck, R. F. *Org. React. (N.Y.)* **1981**, *27*, 345.

Scheme 3



(*E*/*Z*) mixture of olefin **9a**, after isolation by chromatography. Hydrogenation of **9a** proceeded uneventfully to afford **1**, which was by NMR spectroscopy comparable with the drug substance made by the previous route.

While this approach looked promising, there were still several unanswered questions such as (a) how stable is styrene **13** to prolonged handling, (b) could the chromatographies be eliminated from this route, and (c) could all traces of palladium be removed[3] from the drug substance? Given these doubts and project time line constraints, we decided to pursue and develop the synthesis outlined in Scheme 3. This route differed from the original pathway in that it started with commercially available 2,5-dimethoxybenzaldehyde (**3**) and utilized a Horner−Wadsworth−Emmons reaction[4] for the construction of olefin **9**. The replacement of the phosphonium salt with a phosphonate in the olefination reaction offered the advantage of generating the water soluble dimethyl phosphoric acid byproduct instead of triphenylphosphine oxide. It was felt that this would remove one of the key obstacles in utilizing the original method for large-scale purposes.

The original conditions for the preparation of methyl ester **8** used 3 molar equiv of sulfuric acid and took 24 h to proceed to 95% conversion. Several alternative conditions such as $SOCl_2$/toluene followed by treatment with MeOH, TMSCl/toluene/MeOH, and H_2SO_4 (cat.)/MeOH/reflux were investigated in an effort to shorten the reaction time or lessen the amount of acid used. The Fisher-type esterification using excess H_2SO_4, however, proved to be the best when process economics and operations were considered.

(3) Specifications for Pd metal in a final drug substance at Novartis Pharmaceuticals are currently ≤4 ppm.

(4) (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Johnson, A. W. *Ylides and Imines of Phosphorus*; John Wiley & Sons, Inc.: New York, 1993.

Preparation of the alcohol **4** was straightforward and involved treatment of a toluene/methanol solution of the aldehyde **3** with sodium borohydride. An acid quench followed by an extractive workup afforded a 98% yield of 97% pure alcohol, as a nonviscous liquid. The benzyl bromide **5** was prepared in an approximately 85% yield (92−95% purity) as an off-white solid by treatment of **4** with phosphorus tribromide in toluene. This was converted to phosphonate **14** via the Michaelis−Becker reaction (NaH/dimethyl phosphite) in a 90% yield.[5] The phosphonate, which was an oil, was contaminated with mineral oil from the sodium hydride. As it was anticipated that the mineral oil would interfere in the purification of subsequent intermediates, a method was devised for its removal. The simple and efficient process we discovered involved partitioning the crude phosphonate between acetonitrile and heptane. The desired phosphonate remained in the acetonitrile phase while the mineral oil partitioned into the heptane layer. This operation removed the mineral oil quantitatively without loss of the desired phosphonate **14**.

A number of experimental conditions were investigated in the Horner−Wadsworth−Emmons olefination reaction between aldehyde−ester **8** and phosphonate **14**. Phase-transfer conditions (50% NaOH/toluene/*n*-Bu_4NHSO_4/reflux and KOH powder/THF/*n*-Bu_4NHSO_4/reflux)[6] were not amenable to our substrates. Use of butyllithium or hexyllithium as the base did provide the desired product but in low yields (∼50%). By far, the best conditions were those using lithium hexamethyldisilazane (generated *in situ* from *n*-butyllithium and HMDS) as the base in THF at −5 °C (∼65% yield).[7]

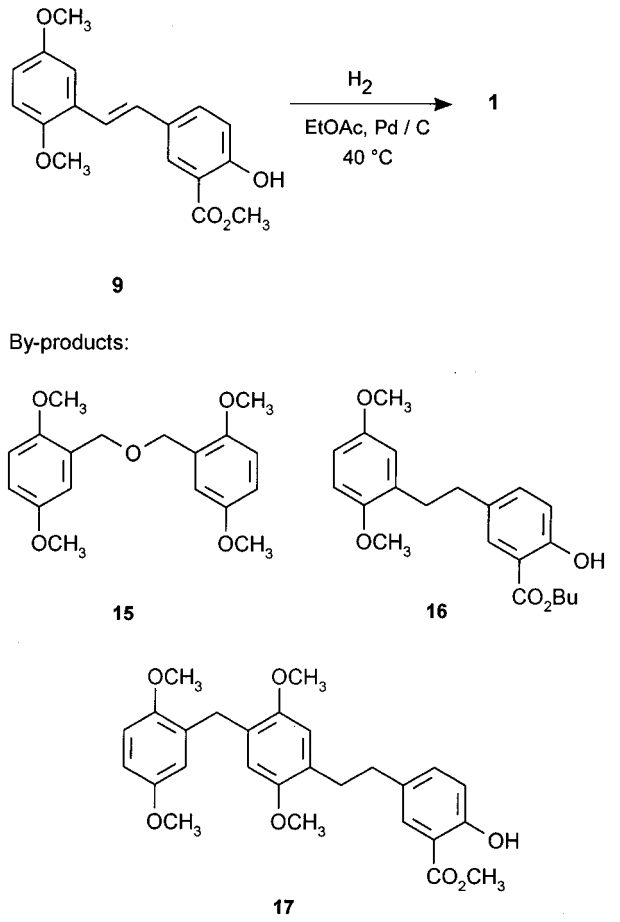
The olefin **9** did not readily crystallize, so the crude olefin was used without purification in the hydrogenation step to afford the desired drug substance **1**. The hydrogenation proceeded without difficulty; however, problems were encountered during our purification efforts (see Scheme 4). The crude drug substance contained two new byproducts: ether **15** and butyl ester **16**, in addition to **17**, a hydrogenated derivative of **10**.

The origin of the butyl ester impurity **16** was traced to the aldehyde−phosphonate coupling where trace amounts of lithium butoxide (generated by air oxidation of the butyllithium) transesterified the product **9** and/or the ester **8**. The amount of this impurity varied depending on the batch of butyllithium used. Fortunately, this impurity was found to be of less concern as it could be reduced to acceptable levels upon recrystallization of the drug substance.

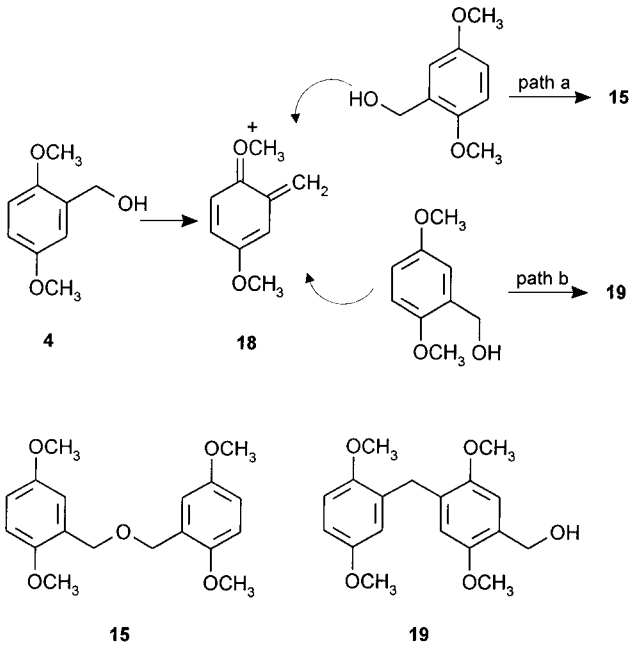
The byproducts **15** and **17**, however, could not be decreased to acceptable levels by simple recrystallization. This necessitated an investigation to identify the origin of this set of byproducts and try to eliminate them by adjusting the reaction conditions. On the basis of the structures of these two byproducts, we linked their origin to the bromination step (see Scheme 5).

Under the acidic bromination conditions, the stabilized benzylic cation **18** is attacked by a molecule of benzyl alcohol **4**. The O-alkylation pathway (path a) provides the ether **15**, while the C-alkylation pathway (path b) affords alcohol **19**. Ether **15** remains unchanged throughout the subsequent reaction sequences while alcohol **19** is bromi-

Scheme 4



Scheme 5

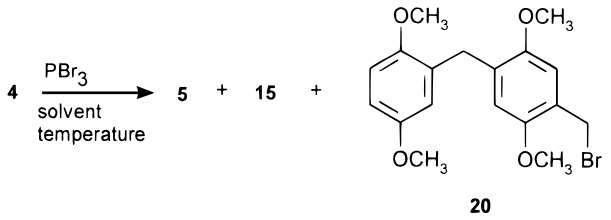


(5) The classical approach to phosphonates using the Michaelis−Arbuzov reaction (trialkyl phosphite, heat) is less desirable for large-scale production due to the odiferous nature of the trialkyl phosphite. For lead references using Michaelis-Becker conditions, see: (a) Johnson, A. W. *Ylides and Imines of Phosphorus*; John Wiley & Sons, Inc.: New York, 1993; p 309. (b) Ley, S. V.; Woodward, P. R. *Tetrahedron Lett.* **1987**, *28*, 345. (c) Kim, C. U.; Misco, P. F.; Luh, B. Y.; Martin, J. C. *Heterocycles* **1990**, *31*, 1571.

(6) (a) Piechucki, C. *Synthesis* **1976**, 187. (b) Texier-Boullet, F.; Foucaud, A. *Synthesis* **1979**, 884. (c) Piechucki, C. *Synthesis* **1974**, 869.

(7) Bojin, M. L.; Barkallah, S.; Evans, S. A., Jr., *J. Am. Chem. Soc.* **1996**, *118*, 1549.

Table 1. **Optimization of bromide 5 formation**



20

		yield, %		
entry	conditions	15	20	5
1	toluene/0 to 15 °C	5.5	2.3	89
2	toluene/−5 °C	2.9	2.1	87
3[a]	toluene/−5 °C	<0.5	∼1	88
4[b]	EtOAc/−5 °C	0	0	64

[a] Inverse addition (alcohol to PBr_3 solution). [b] Yield and purity after recrystallization from EtOAc/heptane.

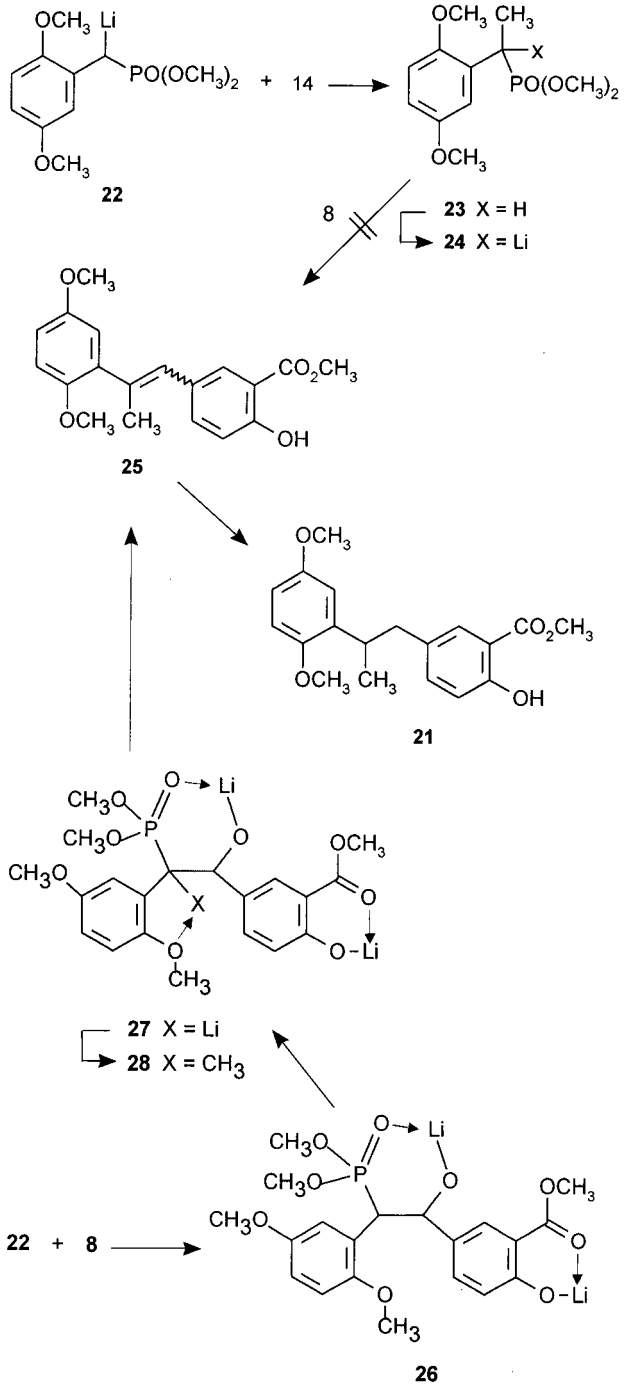
nated, converted to its corresponding phosphonate, and then coupled with aldehyde **8** in the Horner−Wadsworth−Emmons reaction, and after hydrogenation it is isolated in the drug substance as compound **17**. To prove this hypothesis, we started the synthesis from a chromatographically purified sample of bromide **5**. The drug substance obtained after completion of the sequence **5** → **14** → **9** → **1** did not contain either impurity **17** or **15**. On the basis of this result, we directed our efforts toward the preparation of *pure* bromide **5**.

The original bromination conditions we employed involved addition of phosphorus tribromide to a toluene solution of the alcohol while the reaction was allowed to exotherm (see Table 1, entry 1), and it produced an 89% isolated yield of bromide **5** containing roughly 8% of the ether **15** and bromide **20** combined.

Attempts to recrystallize the material of this quality were not promising; repeated recrystallizations from EtOAc/heptane were necessary to remove these impurities with an unacceptable loss in yield. Lowering the reaction temperature and maintaining it throughout the addition improved the byproduct spectrum, but maintaining a low reaction temperature in conjunction with an inverse addition (alcohol to PBr_3) almost completely suppressed the ether formation and reduced the amount of bromide **20** formed by about one-half (see Table 1, entry 3). Fortunately, the crude product could be further purified by distillation of the toluene and precipitation from ethyl acetate/heptane to obtain pure (100% by HPLC) bromide **5**. For the process, ethyl acetate was substituted for toluene as the reaction medium (see Table 1, entry 4). This was done to streamline the isolation (avoids solvent exchange) and to eliminate a safety issue associated with the product isolation; the bromide showed some thermal instability near the distillation temperature of toluene. The isolated yield of pure bromide **5** was 64%.

With a new process in hand for the preparation of **5**, we proceeded to finalize the processes for the preparation of phosphonate **14**, olefin **9,** and drug substance **1**. The final procedures for the preparation of **14** and **9** proceeded smoothly; however, last-minute modifications in the analytical method picked up a new trace level impurity (ap-

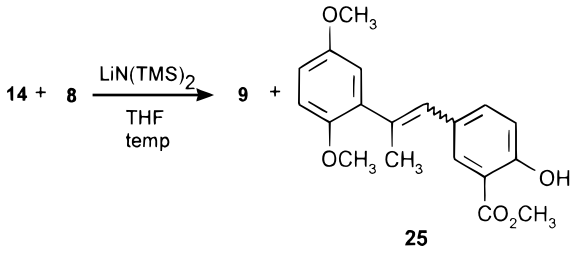
Scheme 6



proximately 0.6−0.7%; maximum limit 0.5%) in the recrystallized drug substance. Isolation of the peak in question by preparative HPLC combined with characterization by NMR and MS identified the impurity as the methylated analog of the drug substance, compound **21**.

Two hypotheses existed for the formation of this impurity (see Scheme 6). In one pathway, phosphonate anion **22** is methylated by phosphonate **14** (methyl phosphonate acts as a methylating agent) to afford the methylated compound **23**. Upon deprotonation of **23** and subsequent reaction of the lithio species **24** with aldehyde **8**, olefin **25** (possible mixture of geometric isomers) is generated, which provides **21** after hydrogenation. Alternatively, phosphonate anion **22** condenses with aldehyde **8** to afford the betaine intermediate **26**. This intermediate is deprotonated to the stabilized lithio

Table 2. **Studies towards reducing the amount of impurity 25 in the Wadsworth−Emmons reaction**



25

entry	temp, °C	yield of **25**, %
1	20	9.7
2	−5	3.5
3	−20	2.5
4	−75	not detected

species **27**, which is methylated to afford betaine **28** and collapses to afford olefin **25**, the precursor to **21**.

Subjecting pure phosphonate **23** to the Horner−Wadsworth−Emmons reaction conditions (THF/*n*-BuLi/HMDS/−20 °C), followed by treatment of the ylide with aldehyde **8**, gave only trace amounts of the desired olefin **25**. Mostly unreacted starting materials were recovered. It is, therefore, more likely that **21** results *via* the intermediacy of lithio species **27**.[8]

In an effort to minimize this recently identified methylated byproduct **21** to <0.5% in the drug substance, we investigated several reaction temperatures for the condensation of phosphonate **14** with aldehyde **8** (see Table 2).

The results reported in Table 2 showed that the reaction temperature plays a crucial role in the generation of impurity **25**; in the crude product, impurity **25** ranges from a high of 9.7% at 20 °C to nondetectable at −75 °C (see Table 2, entries 1 and 4, respectively). While the result of entry 4 was excellent, from a manufacturing perspective this was not ideal since the low reaction temperature presented operational problems. Fortunately, laboratory experiments indicated that olefin **9** containing 2−3% of **25** could produce acceptable drug substance (<0.5% of **21**) if the drug substance **1** was twice recrystallized from ethanol. As a consequence, the lower reaction temperature of −20 °C (easily obtainable in a plant vessel) was incorporated into the plant process.

Upon implementation in the development plant, this reaction did not give reproducible yields. In order to make the condensation reaction between phosphonate **14** and aldehyde **8** more robust, we modified the process slightly. The modified process varied from the previous process in that the reaction utilized simultaneous addition of the aldehyde and phosphonate to the base, and the reaction temperature was lowered to −45 °C. These modifications successfully limited the phosphonate anion to any competing side reactions (methylation, oxidation, or protonation) in the pilot plant. This new process afforded penultimate **9** in a 68% yield with 2% of methylated compound **25**.

Hydrogenation of the crude olefin **9** produced by the new process occurred uneventfully and afforded a 55% yield of drug substance after two recrystallizations from ethanol. The product **1** contained 0.32% of the methylated analog **25** as the only impurity.

Conclusion

In conclusion, we achieved a reproducible plant process for the preparation of **1** without using a column chromatography. This objective was accomplished by critically evaluating the origin of byproducts at various stages of the synthesis and adjusting the chemistry as necessary. In addition, we discovered an extremely efficient protocol to remove mineral oil from the crude phosphonate. The route as outlined in Scheme 3 was used to produce approximately 40 kg of **1**.

Experimental Section

Materials and Methods. The 2,5-dimethoxybenzaldehyde (**2**) was obtained from Upjohn, and 5-formylsalicylic acid (**7**) was supplied by SEAC *via* Davos Chemical Corporation. All other reagents came from Aldrich.

Reaction monitoring and chromatographic analysis of methyl ester **8** was performed on an ODS Hypersil column (100 mm × 4.6 mm, 5 μm). The mobile phase (isocratic) was 80% water/20% acetonitrile/0.1% trifluoroacetic acid (TFA) at a flow rate of 1 mL/min. For alcohol **4**, bromide **5**, and phosphonate **14**, a HALsil 120, C18 column (100 mm × 4.6 mm, 5 μm) was used with mobile phase A = 0.1% TFA/acetonitrile, B = 0.1% TFA/MeOH, C = 0.1% TFA/water at a flow rate of 2 mL/min. A gradient from 25% A/75% C to 25% A/40% B/35% C was used. For olefin **9** a LiChrosphere 60 RP-Select B column (125 mm × 4 .0 mm, 5 μm) was used with mobile phase A = 90% MeOH/10% 0.05 M phosphate buffer, pH 2.5, and B = 10% MeOH/90% 0.05 M phosphate buffer, pH 2.5, at a flow rate of 1.5 mL/min. A gradient from 50% A/50% B to 100% A was used. For **1** a Liphosphere 5 RP-Select B column (125 mm × 4.0 mm, 5 μm) was used with mobile phase A = 90% MeOH/10% 0.05 M phosphate buffer, pH 2.5, and B = 10% MeOH/90% 0.05 M phosphate buffer, pH 2.5, at a flow rate of 1.5 mL/min. A gradient from 70% A/30% B to 100% A and back to 70% A/30% B was used. All products were analyzed at 230 nm using a Waters 484 detector.

Melting points are uncorrected. ^{1}H and ^{13}C NMR sprectra were recorded on a Bruker DPX 300 instrument; coupling constants *J* are given in hertz.

2-Ethenyl-1,4-dimethoxybenzene (13). A solution of 112.5 g (0.315 mol) of methyltriphenylphosphonium bromide in 800 mL of THF was cooled to −20 °C and treated with 126 mL (0.315 mol) of *n*-butyllithium (2.5 M in hexanes). The internal temperature was maintained at −10 to −15 °C throughout the addition. After the orange-yellow suspension was stirred at −10 °C for 30 min, a solution of 50 g (0.301 mol) of 2,5-dimethoxybenzaldehyde **(3)** in 200 mL of THF was added over 30 min while the temperature was maintained between −5 and −10 °C. Cooling was removed, and the

(8) Phosphorus betaines derived from phosphonium salts are known to react with base to afford β-oxido phosphonium ylides which can react with various electrophiles. See: (a) Corey, E. J.; Yamamoto, H. *J. Am. Chem. Soc.* **1970**, *92*, 226. (b) Corey, E. J.; Shulman, J. I.; Yamamoto, H. *Tetrahedron Lett.* **1970**, 447. (c) Schlosser, M.; Christmann, F. K.; Piskala, A.; Cofhnet, D. *Synthesis* **1971**, 29.

reaction mixture was stirred with warming to ambient temperature over 6 h. The reaction mixture was vacuum filtered through a Buchner funnel/polypropylene filter pad, and the filter cake was rinsed with 200 mL of hexane. The filtrate was concentrated *in vacuo* and subjected to chromatography on silica gel (500 g, 230−400 mesh). Elution with 40−50% EtOAc/hexane followed by concentration of product-containing fractions afforded 46 g of **13** (95%), as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3H), 3.80 (s, 3H), 5.26 (dd, J = 1.5, 11.2, 1H), 5.74 (dd, J = 1.5, 17.8, 1 H), 6.75−7.1 (m, 4H); MS (CI/isobutane) 165 (MH^+), 151.

Methyl 5-[2-(2,5-Dimethoxyphenyl)ethenyl]-2-hydroxy-(*E*/*Z*)-benzoate (9a). To a solution of 2.02 g (8.7 mmol) of bromo ester **12** and 2.13 g (13 mmol) of styrene **13** in 35 mL of acetonitrile were added 3.6 mL (26 mmol) of triethylamine, 264 mg (0.87 mmol) of tri-*o*-tolylphosphine, and 97 mg (0.44 mmol) of $Pd(OAc)_2$. Nitrogen was bubbled through the reaction mixture for 5 min, and then the mixture was heated at reflux for 4 h. The mixture was filtered to remove precipitated palladium and then concentrated *in vacuo*. The residue was subjected to chromatography on silica gel (80 g, 230−400 mesh) eluting with 10−20% EtOAc/hexane. Concentration *in vacuo* of the product-containing fractions afforded 2.74 g (100% mass recovery, approximately 90% pure by NMR) of olefin **9a**, as an off-white solid containing a mixture of *E* and *Z* (minor) isomers: MS (CI/isobutane) 315 (MH^+), 165, 151.

5-Formyl-2-hydroxybenzoic Acid Methyl Ester (8). A suspension of 125 g (0.750 mol) of 5-formyl-2-hydroxybenzoic acid **(7)** in 2.50 L of methanol was heated to 60 °C, and to the resulting solution was added over 25 min 219 g (2.15 mol) of concentrated sulfuric acid. The temperature was maintained at 60−63 °C throughout the addition (exothermic). The resulting red solution was stirred at 60 °C for 24 h, cooled to approximately 40 °C, and concentrated under reduced pressure (100 Torr) to a final volume of 700 mL (approximately 2 L of methanol was distilled out). The solution was cooled to 15 °C and diluted with 1.50 L of water and 2.25 L of toluene. After 30 min of stirring, 100 g of cellulose was added, and the suspension was stirred for an additional 5 min and then vacuum filtered through a Buchner funnel/polypropylene filter pad. The filter cake was rinsed with 0.25 L of toluene. The phases were separated, and the organic phase was washed with a solution of 100 g of sodium bicarbonate in 1.15 L of water followed by 1.0 L of water. The solution was concentrated under reduced pressure (50 °C/60−70 Torr) to a final volume of 0.35 L (2.05 L of distillate was collected). While the temperature of the mixture was approximately 45−50 °C, 1.15 L of heptane was added, and the mixture was cooled to 3−5 °C over 15 min and stirred for 30 min. Vacuum filtration through a Buchner funnel/ polypropylene filter pad followed by rinsing of the filter cake with 0.25 L of chilled heptane (approximately 0−5 °C) and vacuum drying at 40 °C afforded 107.3 g (79%) of **8**, as a yellowish-tan solid: mp 80−81 °C; ^{1}H NMR ($CDCl_3$) δ 4.01 (s, 3H), 7.11 (d, J = 8.7, 1H), 8.0 (dd, J = 2.1, 8.7, 1H), 8.39 (d, J = 2.1, 1H), 9.89 (s, 1H), 11.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 189.84, 169.93, 166.40, 135.66, 133.79, 128.69, 118.78, 112.67, 52.79 ppm; IR (KBr) 3436, 1681, 1614, 1586, 1446, 1350, 1272, 1206, 1086 cm^{-1}; MS (CI/isobutane) 181 (MH^+), 180, 175, 161, 148.

2,5-Dimethoxybenzenemethanol (4). To a 0 °C solution of 500.5 g (3.01 mol) of 2,5-dimethoxybenzaldehyde **(3)** in 2.0 L of toluene and 0.33 L of methanol was added over 1 h 31.9 g (0.84 mol) of powdered sodium borohydride in six portions of 5.32 g each. The internal temperature was maintained at 15−25 °C throughout the addition (exothermic). The mixture was stirred at 25 °C for 30 min and then quenched by addition of a solution of 100 g (1.02 mol) of sulfuric acid in 0.8 L of water while the temperature was maintained below 30 °C. After the biphasic mixture was stirred for 30 min, the phases were separated, and the water layer was reextracted with 0.4 L of toluene. The combined organic phase was washed with a solution of 50 g of sodium bicarbonate in 0.75 L of water. Concentration (50 °C/38 Torr) of the organic phase afforded 509.7 g (98%) of **4**, as a clear, slightly yellow liquid (HPLC purity 97%), which was used directly in the next transformation: ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3H), 3.78 (s, 3H), 4.62 (s, 2H), 6.76 (s, 2H), 6.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 153.66, 151.41, 130.32, 114.60, 112.93, 111.18, 61.54, 55.76, 55.72 ppm; IR (film) 3407, 2999, 2944, 2834, 1499, 1465, 1219, 1046 cm^{-1}; MS (CI/isobutane) 169 (MH^+), 168, 152, 151, 139.

2-(Bromomethyl)-1,4-dimethoxybenzene (5). To a −5 °C solution of 169 g (0.62 mol) of phosphorus tribromide in 1.0 L of ethyl acetate was added over 40 min a solution of 300 g (1.78 mol) of 2,5-dimethoxybenzenemethanol **(4)** in 0.5 L of ethyl acetate. Throughout the addition, the internal temperature was maintained between −5 and 0 °C. The slightly opaque, yellow reaction mixture was stirred at 0 °C for 30 min and then was quenched with a solution of 66 g (0.62 mol) of sodium carbonate in 0.8 L of water. The biphase was stirred at 25 °C for 30 min, the phases were separated, and the organic phase was concentrated under reduced pressure (30 °C/120 Torr) to approximately half the original volume. To the distillation residue was added 2.5 L of heptane, and the mixture was cooled to 0 °C and stirred for 2 h. Vacuum filtration through a Buchner funnel/ polypropylene filter pad followed by rinsing of the filter cake with 1 L of heptane and vacuum drying at 30 °C afforded 265 g (64%) of **5**, as a white solid: mp 74−75 °C; ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3H), 3.82 (s, 3H), 4.52 (s, 2H),6.8 (br s, 2 H), 6.9 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 153.36, 151.58, 126.86, 116.32, 114.94, 112.13, 56.10, 55.65, 28.79 ppm; IR (KBr) 2946, 2843, 1504, 1461, 1287, 1238, 1209, 1047, 813 cm^{-1}; MS (CI/NH_3) 201, 200, 185, 182, 169, 168, 151.

Dimethyl [(2,5-Dimethoxyphenyl)methyl]phosphonate (14). A suspension of 29.3 g (0.73 mol) of 60% sodium hydride in mineral oil in 0.5 L of toluene was cooled to −10 °C. To this mixture was added carefully over 40 min, while the internal temperature was maintained below 0 °C (exothermic), 86.7 g (0.79 mol) of dimethyl phosphite. After 10 min, 130 g (0.56 mol) of 2-(bromomethyl)-1,4-dimethoxybenzene **(5)** as a solution in 0.6 L of toluene was added over 30 min. The temperature was allowed to rise to 15 °C throughout the course of the addition. The mixture was stirred for 1.5 h and quenched by the addition of 10 mL of

2-propanol followed by 0.4 L of water. After 40 min of stirring, the phases were separated, and the organic phase was concentrated under reduced pressure (50 °C/35 Torr). To the distillation residue was added 0.25 L of acetonitrile and 0.125 L of heptane. The biphasic mixture was stirred for 10 min and allowed to settle, and the upper heptane layer was removed. The lower acetonitrile layer was treated with heptane as above, one more time. The acetonitrile layer was concentrated under reduced pressure (50 °C/35 Torr), diluted with 0.05 L of toluene, and reconcentrated (50 °C/25 Torr) to afford 142 g (90%) of phosphonate **14**, as a clear yellow oil (HPLC purity 93%), which was used directly in the next transformation: ^{1}H NMR ($CDCl_3$) δ 3.25 (d, J = 21.82, 2H), 3.65 (s, 3H), 3.71 (s, 3H), 3.76 (s, 3H), 3.81 (s, 3H), 6.74−6.89 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 153.24, 151.36, 151.27, 128.79, 127.99, 125.07, 120.83, 120.70, 116.89, 116.82, 112.72, 112.67, 111.57, 55.95, 55.43, 52.47, 52.38, 26.69, 24.85 ppm; IR (film) 2953, 1505, 1465, 1254, 1227, 1048, 1031, 808 cm^{-1}; MS (CI/isobutane) 261 (MH^+).

Methyl 5-[2-(2,5-Dimethoxyphenyl)ethenyl]-2-hydroxy-(*E*)-benzoate (9). To a solution of 47.6 g (0.295 mol) of 1,1,1,3,3,3-hexamethyldisilazane in 0.7 L of THF at −10 °C was added over 30 min 0.10 L (0.25 mol) of *n*-butyllithium (2.5 M in hexanes). The internal temperature was maintained below −5 °C throughout the addition. The mixture was stirred briefly at −5 °C and then cooled to −45 °C, whereupon a solution of 31.4 g (0.241 mol) of dimethyl [(2,5-dimethoxyphenyl)methyl]phosphonate **(14)** and 18.9 g (0.105 mol) of 5-formyl-2-hydroxybenzoic acid methyl ester **(8)** in 0.25 L of THF was added over 30 min. The internal temperature was maintained at −45 °C throughout the addition. After the addition was complete, the mixture was stirred at −45 to −50 °C for 1 h, then warmed to 25 °C over 2 h, and stirred for 12 h. After the mixture was cooled to 0 °C, a solution of 25.4 g (0.25 mol) of sulfuric acid in 0.25 L of water was added to adjust the pH to 3−4. The phases were separated, and the aqueous layer was extracted with 0.15 L of toluene. The combined organic phase was washed with a solution of 40 g of sodium bicarbonate in 0.25 L of water and concentrated under reduced pressure (50 °C/30 Torr) to afford 34.6 g (HPLC purity 64.7%; 68% yield) of crude **9**, as an orange oil. This oil was diluted with 40 mL of ethyl acetate and used in the following transformation. An aliquot was purified by chromatography on 230−400 mesh silica gel using 10−25% EtOAc/hexane to afford the following spectroscopic data: ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 3.85 (s, 3H), 3.98 (s, 3H), 6.75−7.36 (m, 6 H), 7.70 (dd, J = 2.22, 8.69, 1H), 7.98 (d, J = 2.14, 1H), 10.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 170.40, 160.98, 153.72, 151.30, 133.35, 129.32, 128.05, 127.96, 127.14, 122.04, 117.85, 113.51, 112.23, 111.55, 56.17, 55.68, 52.23 ppm; IR (KBr) 3439, 2953, 2833, 1677, 1588, 1497, 1443, 1218, 1045 cm^{-1}; MS (CI/ isobutane) 315 (MH^+), 314, 282, 184, 165, 151, 141.

Methyl 5-[2-(2,5-Dimethoxyphenyl)ethyl]-2-hydroxybenzoate (1). A 2-L Paar hydrogenation flask was flushed with nitrogen and charged with 39.1 g of 10% palladium on carbon (wet catalyst; water ∼50%) and 1.30 kg of an ethyl acetate solution of methyl 5-[2-(2,5-dimethoxyphenyl)-ethenyl]-2-hydroxy-(*E*)-benzoate **(9)** (contains 185.9 g (0.59 mol) of olefin **9**). The mixture was hydrogenated at 40 °C and 30 psi for 4 h. The solution was vacuum filtered through a Buchner funnel/polypropylene filter pad containing 40 g of Celite, and the filter cake was rinsed with 0.1 L of ethyl acetate. Concentration under reduced pressure (45 °C/45 Torr) afforded a brown oil, which was diluted with 0.9 L of toluene and washed with a solution of 294 g of sodium bicarbonate in 1.8 L of water in two 0.9-L portions. The aqueous layers were reextracted with 0.4 L of toluene, and the combined toluene phase was stirred with 50 g of cellulose and a solution of 30 g of sulfuric acid in 0.8 L of water. Vacuum filtration through a Buchner funnel/polypropylene filter pad followed by phase separation and concentration of the organic phase under reduced pressure (50 °C/45 Torr) afforded 250 g of a brown oil. The oil was dissolved in 0.23 L of 95% ethanol and stirred at 0 °C for 1 h. The solids were collected *via* vacuum filtration through a Buchner funnel/polypropylene filter pad and rinsed with 0.1 L of 190-proof ethanol. The damp, off-white solid was dissolved in 0.325 L of ethyl acetate and 0.325 L of hepane and stirred with 110 g of 70−230 mesh silica gel for 30 min. Vacuum filtration of the mixture through a Buchner funnel/polypropylene filter pad followed by concentration of the mixture under reduced pressure (50 °C/70 Torr) afforded an oil, which was dissolved in 0.14 L of absolute ethanol. The ethanol solution was cooled to 10 °C and stirred for 1.5 h. Vacuum filtration through a Buchner funnel/polypropylene filter pad followed by rinsing of the solids with 0.1 L of absolute ethanol and drying in a vacuum oven at 35 °C afforded 103 g (55%) of **1**, as a white solid: mp 67.4 °C; HPLC purity 99.68%; ^{1}H NMR ($CDCl_3$) δ 2.80 (m, 4H), 3.74 (s, 3H), 3.78 (s, 3 H), 3.95 (s, 3H), 6.61−6.91 (m, 4H), 7.27 (dd, J = 2.34, 8.57, 1H), 7.66 (d, J = 2.25, 1H), 10.64 (s,1H); ^{13}C NMR (75 MHz, $CDCl_3$) 170.64, 159.83, 153.45, 151.79, 136.25, 132.97, 131.12, 129.17, 117.32, 116.38, 111.94, 111.26, 111.22, 55.92, 55.71, 52.17, 35.19, 32.60 ppm; IR (KBr) 3201, 2955, 2843, 1675, 1588, 1503, 1440, 1222, 1085, 1051, 1028, 793 cm^{-1}; MS (CI/isobutane) 317 (MH^+), 316, 286, 285, 165, 151, 133.

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