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Process Development for a Large Scale Stereoselective Synthesis of (*Z*)-(1-Bromobut-1-ene-1,2-diyl)dibenzene, a Key Intermediate of a Selective Estrogen Receptor Modulator

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Abstract:

Two efficient large scale syntheses of (*Z*)-(1-bromobut-1-ene-1,2-diyl)dibenzene are described. The first is a three-step synthetic sequence from trimethyl(phenylethynyl)silane in 63% overall yield. The key transformations involved the stereospecific carbometalation reaction of trimethyl(phenylethynyl)silane followed by a bromination. Subsequent Miyaura−Suzuki coupling with phenylboronic acid and transformation of the vinyltrimethylsilane to a vinyl bromide afforded the target. In an improved synthesis, a stereoselective nickel acetylacetonate catalyzed PhZnEt addition to but-1-ynylbenzene, generated an organozincate intermediate, which was brominated in 58−62% overall yield. A key feature of this work was the production of highly regiopure olefin. The optimization effort that resulted in the utilization of substoichiometric amounts of Ph_2Zn and the safety precautions taken to facilitate process scale-up are discussed.

Introduction

Breast cancer is the most common malignancy in women and it is estimated that nearly one in nine women will develop the disease within their lifetimes.[1] The current therapy for these patients include selective estrogen receptor modulators (SERMs)[2] with tamoxifen being the most widely prescribed medication for estrogen receptor (ER)-positive breast cancer.[3]

Tamoxifen is a partial estrogen agonist/antagonist SERM to which nearly 50% of hormone-induced breast cancer patients respond, but most patients eventually relapse with tamoxifen-resistant tumors.[4] Moreover, due to the estrogen agonistic activity of tamoxifen, postmenopausal patients undergoing long-term treatment with tamoxifen are prone to increased incidence of endometrial hyperplasia cancer.[5] There is, therefore, a substantial unmet medical need for the development of a pharmaceutical agent that inhibits estrogen induced metastatic breast cancer without stimulating uterine endometrial tissue growth.

(*Z*)-3-(4-((*Z*)-1,2-Diphenylbut-1-enyl)phenyl)acrylic acid (**1**), is a SERM that was originally discovered by Glaxo-Wellcome[6] and was later shown to be effective against estrogen induced cancers in animal studies. It was also shown to have a low potential to induce endometrial cancer growth. Further work demonstrated that **1** has attractive estrogen agonist and antagonist properties desirable for the treatment of breast cancer patients that have failed tamoxifen treatment.[7] Moreover, the low toxicity and the potent activity makes **1** a promising drug for the treatment of other hormone induced diseases.

As part of the development of a scalable synthesis of **1**,[8,9] a key issue was the control of isomeric impurities. The specification for the (*E*)-isomer **2**, a known estrogen agonist in rats,[10] was set at <0.15% for the drug substance. The Glaxo-Wellcome synthetic procedure[6a] relied on diastereomer control during the synthesis of vinyl bromide **3** to control the level of the isomeric

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(10) (a) The (*E*,*E*)-isomer of Tamoxifen is an estrogen agonist in rats. Jordan, V. C.; Haldemann, B.; Allen, K. E. *Endocrinology* **1981**, *108*, 1353–1361. (b) Harper, M. J.; Walpole, A. L. *Nature* **1966**, *212*, 87.

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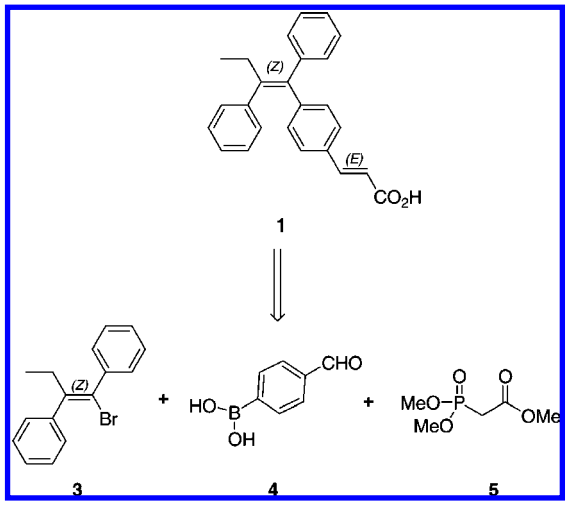
Scheme 1. **Retrosynthetic analysis**

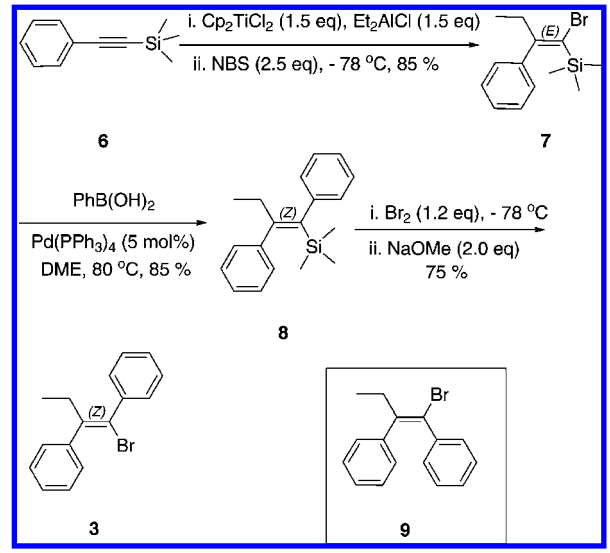


impurity **2**.[11] Vinyl bromide **3** was then elaborated via a Miyaura−Suzuki coupling followed by a Horner−Emmons homologation and hydrolysis to produce **1**. This general approach for assembling the tetrasubstituted core of **1** appeared to be a scalable process upon our consideration of alternative chemistry. If the proposed chemistry in Scheme 1 was ultimately successful as a commercial process, only the vinyl bromide **3** would require synthesis, as the other two synthons: (4-formylphenyl)boronic acid (**4**) and methyl 2-(dimethoxyphosphoryl)acetate (**5**) are commercially available. The key to the synthesis would be to develop an efficient, highly stereoselective synthesis of **3**.

The published[11,6] sequence to **3** was modified by our Discovery chemistry group.[12] The synthesis of **3** first entailed the attachment of an ethyl group to the benzyl position of trimethyl(phenylethynyl)silane (**6**) by treatment with a mixture of the diethylaluminum chloride and titanocene dichloride complex[13] (Scheme 2). The vinyl organometallic group was regiospecifically replaced by bromine by the reaction with *N*-bromosuccinimide (NBS) to produce (*E*)-(1-bromo-2-phenylbut-1-enyl)trimethylsilane (**7**) in 85% yield after column chromatography. The Negishi protocol was replaced by a Miyaura−Suzuki coupling[14] of the vinyl bromide with phenylboronic acid catalyzed by $Pd(PPh_3)_4$ to provide (*Z*)-(1,2-diphenylbut-1-enyl)trimethylsilane, **8**, in 85% yield after column chromatography. Finally, addition of bromine to the vinyl silane, **8**, followed by the elimination of TMSBr with sodium methoxide[15] produced **3**, which was purified by another column chromatography in 75% yield.

In addition to the elimination of the repeated column chromatography purifications, which are not solvent efficient processes and other nonscalable operations, a key challenge for the development of a viable chemical process was to produce

Scheme 2. **Discovery chemistry synthesis of vinyl bromide 3**



3 with no more than 0.3% of the (*E*)-isomer **9**, as we had demonstrated that this would result in **1** containing <0.15% of **2**, our required specification for the API. This paper describes the development of two efficient, large scale stereoselective syntheses of **3**, the key intermediate in the synthesis of our new SERM candidate.

Results and Discussion

Early Process. *Preparation of (E)-(1-Bromo-2-phenylbut-1-enyl)trimethylsilane, 7.* We perceived the most critical issue for the preparation of **7** to be the stability of the diethylaluminum chloride−titanocene dichloride complex. Extensive yield loss from decomposition occurred when the organometallic complex was held >3 h, which simulated the hold times we expected in the pilot plant implementation. This stability problem could be circumvented by the formation of the complex in the presence of the starting material. To accomplish this, the titanocene dichloride was combined with (trimethylsilyl)phenylacetylene (**6**) in methylene chloride and a heptane solution of diethylaluminum chloride was added. Under these conditions, the organometallic complex's existence was transitory as it rapidly reacted with the acetylene. It was then necessary to add NBS at −40 °C to limit decomposition from the heat of reaction as the calculated adiabatic temperature rise was 72 °C, a rather exothermic reaction.

A secondary problem was the volume efficiency of the reaction. The initial procedure had a V_{max} of ∼118 L/kg of starting material, primarily due to the volume of methylene chloride. This was improved by first quenching the reaction mass in a slurry of Celite, sodium hydroxide, and sodium bisulfite solution,[16] followed by distillation to remove most of the solvent. The addition of heptane then precipitated the inorganic byproduct, which was removed by filtration and the product-rich organic phase could be used directly in the next step once the aqueous layer was removed. These operational changes improved the V_{max} to ∼40 L/kg. Incorporating these improvements along with other optimization of reaction parameters, we converted 13 kg of the acetylene **6** into a total of

(11) Miller, R. B.; Al-Hassan, M. I. *J. Org. Chem.* **1985**, *50*, 2121–2123.
(12) Unpublished results of DuPont Pharmaceutical Company Discovery Chemistry group.
(13) (a) Snider, B. B.; Karras, M. *J. Organomet. Chem.* **1979**, *179*, C37–C41. (b) Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1984**, *43*, 4424–4431.
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(15) (a) Miller, R. B.; Reichenbach, T. *Tet. Lett.* **1974**, 543–546. (b) Miller, R. B.; McGarvey, G. *Synth. Commun.* **1977**, *7*, 475–482. (c) Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1978**, *43*, 4424–4431.
(16) Celite was added to aid the filtration of the inorganic by-products.

20 kg of **7**, as a heptane solution of 42.9 wt/wt % potency in four batches with an overall solution yield of 90%.

Preparation of (Z)-(1,2-Diphenylbut-1-enyl)trimethylsilane, 8. Fortunately, the Miyaura−Suzuki reaction often allows a wide variety of reaction conditions. We were able to replace the suspected teratogen solvent dimethoxyethane with ethyl acetate. The $Pd(PPh_3)_4$ catalyst loading was reduced from 5 to 2 mol %, and the reaction was run under nitrogen pressure (~1020 mmHg) to enable the reflux temperature to reach 75 °C and thus drive the reaction to completion in only 3 h. The product mixture was cleaner as compared to the prior chemistry and allowed the worked-up heptane solution of **8** to be telescoped once more into the next step. This chemistry scaled up uneventfully into the plant, and we produced 17.8 kg of **8** as a heptane solution of 41.8 wt/wt % potency in two batches with an overall solution yield of 92%.

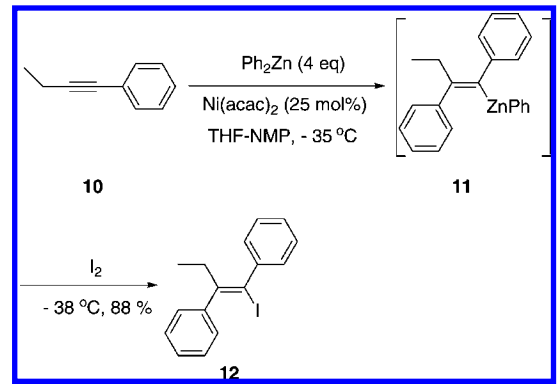
Preparation of (Z)-(1-Bromobut-1-ene-1,2-diyl)dibenzene, 3. To minimize operator exposure to bromine, we sought to change the original addition sequence of bromine addition to the substrate. Instead, the heptane solution of **8** produced in the last step was added to a −65 °C solution of bromine in methylene chloride, followed by elimination of TMSBr using a 25 wt % solution of sodium methoxide to regenerate the double bond. The bromide **3** was eventually isolated following workup by precipitation from 2-propanol. This crude product was subsequently recrystallized from an aqueous methanol solution to eliminate the last traces of the (*E*)-regio-impurity **9** as well as any impurities that were carried along the previous two telescoped steps. We successfully implemented this procedure in the pilot plant at 8.6 kg input scale in two batches to produce 13.2 kg of **3** with a yield of 76%.

Overall this three-reaction sequence with a single isolation step was sufficient to generate enough **3** in the pilot plant to meet our initial requirements for API. However, the scale of this campaign was about the largest that could be efficiently conducted for this process. For the production of larger quantities of **3**, we set as goals (i) the reduction of the length of the synthesis (three steps) and process cycle time, (ii) removal of the cryogenic conditions (steps 1 and 2), and (iii) an alternative for hazardous elemental bromine.

Second Preparative Process. The chemistry used by Knochel to prepare a closely related analogue, (*Z*)-(1-iodobut-1-ene-1,2-diyl)dibenzene (**12**)[17] (Scheme 3) suggested to us an alternative route that would allow the addition of both the ethyl and aryl groups over a single operation. The synthesis consisted of a $Ni(acac)_2$ catalyzed addition of diphenylzinc to phenylacetylenes in a stereospecific fashion at −35 °C to produce organozincate (**11**), which was subsequently quenched with iodine to produce vinyl iodide (**12**). This would preclude the necessity of conducting a separate Miyaura−Suzuki coupling and would leave functionality that could be exploited to append the final aryl ring.

An immediate challenge to the utilization of the reaction on scale was the expense of diphenylzinc. We sought to reduce the cost of goods by preparing diphenylzinc in situ by the reaction of PhLi and $ZnCl_2$ in THF;[18] however, the subsequent reactions gave low yields with poor conversion as compared to those obtained using sublimed Ph_2Zn.[17a] We postulated the low reactivity of the in situ generated Ph_2Zn might be due to the residual chloride salts in the reaction mixture reacting with the $Ni(acac)_2$ to generate a less efficient $NiCl_2$ catalyst. An alternative protocol to generate the Ph_2Zn in situ by the reaction of triphenylborane and diethylzinc[19] also gave low yield. On the basis of these results, we concluded that a salt free Ph_2Zn reagent would be required and purchased the reagent as a THF solution.[20]

Scheme 3. **Ni(acac)$_2$ catalyzed Ph_2Zn addition to acetylenes**



As we had little latitude on the use of the expensive diphenylzinc, we explored the possibility for lowering the charge. Reduction of the equivalents of diphenylzinc from 4 to 1.5 did not impact the yield or purity. Another means to reduce the equivalents of diphenylzinc would be to utilize all of the phenyl ligands. As proposed by Knochel,[17a] the mechanism of this reaction suggests that only one phenyl group from Ph_2Zn is transferred to the product with the other phenyl group only serving as a spectator group. We considered the example of mixed alkyl−aryl−zinc reagents in asymmetric additions to aldehydes as these zinc reagents selectively transfer exclusively the phenyl group.[21] In analogy, we hypothesized that a mixture of Ph_2Zn and Et_2Zn would be effective in our case if an integrated species equivalent to the expected disproportionation product $EtZnPh$[21a] formed that would enable useful transfer of all of the phenyl groups.

We were pleased to observed only <3% of the corresponding diethyl analogue of **3**, when 1.5 equiv of Et_2Zn was added to our optimized reaction with 1.5 equiv of Ph_2Zn (Scheme 4). These encouraging results prompted us to further optimize the reaction, leading to a ~50% reduction of the zinc reagents (0.7 equiv Ph_2Zn and 0.7 equiv Et_2Zn) without loss of yield, thus significantly reducing our cost of goods.

We identified one challenge with this new reaction sequence; the subsequent bromination with NBS to produce **3** now generated a difficult to agitate gelatenous precipitate of the

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(19) Rottlander, M.; Palmer, N.; Knochel, P. *Synlett* **1996**, 573–575.

(20) The solution of the salt free diphenylzinc in tetrahydrofuran was supplied by Albemarle, Baton Rouge, LA, U.S.A.

(21) (a) Nehl, H.; Schmeidt, W. R. *J. Organomet. Chem.* **1985**, *289*, 1–8. (b) Bolm, C.; Muniz, K. *Chem. Commun.* **1999**, 1295–1296. (c) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muniz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465–3467. (d) Fontes, M.; Verdaguer, X.; Sola, L.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532–2543.

Scheme 4. **Addition of PhZnEt to 1-phenylbutyne**

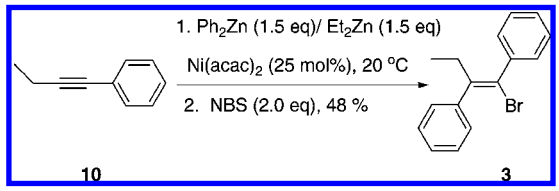
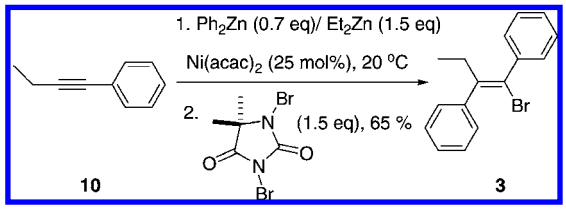


Table 1. **Screen of brominating reagents**

entry	electrophile	% conversion	ratio of *Z*:*E*
1	bromine	82%	98: 2
2	1,2-dibromo-1,1,2,2-tetrafluoroethane	2%	100: 0
4	pyridium tribromide	96%	97: 3
5	*N*-bromo acetamide	59%	93: 7
6	*N*,*N*′-dibromo-5,5-dimethylhydantoin	98%	97: 3
7	*N*-bromosuccinimide	85%	97: 3

Scheme 5. **Optimized reaction of PhZnEt with 1-phenylbutyne**



succinimide byproduct. Other brominating reagents were screened to avoid this issue and to further improve the yield of the bromination (Table 1).

N,*N*′-dibromo-5,5-dimethylhydantoin, a safe and inexpensive bromine source, proved to be a superior brominating reagent for this reaction, avoiding the gelling and also improving the yield of the reaction to 65−75%. Following the usual optimization of key reaction parameters, recrystallization led to **3** in 65% isolated yield and 99.3% purity with only <0.1% diethyl analogue and none of the (*E*)-isomer detected (Scheme 5).

A final process scale up challenge became apparent when the thermochemical evaluation of the new reaction was performed. The heat of reaction of a solution of *N*,*N*′-dibromo-5,5-dimethylhydantoin in THF/NMP (12 L/kg of **10**) with the organozincate **11** was −846 kJ/mol with a calculated adiabatic temperature (T_{ad}) rise of 247 °C. Furthermore, the solution of *N*,*N*′-dibromo-5,5-dimethylhydantoin in THF/NMP itself would decompose with an onset temperature of 25 °C and heat of reaction of −284 kJ/mol. Subsequent ARC (accelerated reaction calorimetry) analysis showed the exothermic decomposition reached a maximum self-heat rate of 220 °C/min with a maximum rate of pressure increase of 100 psi/min occurring at 65 °C. Clearly these were unscalable reaction conditions. Instead of adding *N*,*N*′-dibromo-5,5-dimethylhydantoin as a solution, the process was changed whereby the *N*,*N*′-dibromo-5,5-dimethylhydantoin was added as a solid. The thermochemistry for the addition of solid *N*,*N*′-dibromo-5,5-dimethylhydantoin was only marginally better at −572 kJ/mol of **10** with a calculated T_{ad} rise of 88 °C; however, the heat flow measurements for this addition (Figure 2) indicated that portionwise addition did provide a dose controlled heat signature.

In addition, the thermochemical data indicated that no reagent accumulation occurred. To confirm this, HPLC analyses of the reaction mixture were performed with each *N*,*N*′-dibromo-5,5-dimethylhydantoin addition (figure 3). The data generated clearly showed the anticipated increase in product concentration, thus confirming that the *N*,*N*′-dibromo-5,5-dimethylhydantoin rapidly reacts under the reaction conditions and does not accumulate.

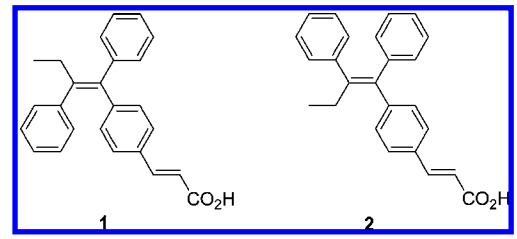


Figure 1. **Serm API, 1, and its (*E*)-isomer 2.**

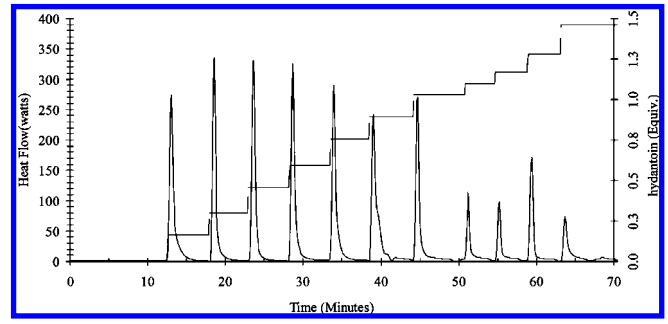


Figure 2. **Heat flow plot for solid *N*,*N*′-dibromo-5,5-dimethylhydantoin addition.**

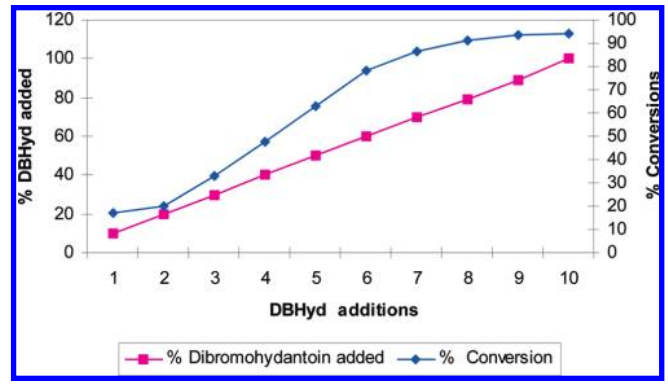


Figure 3. **Solid *N*,*N*′-dibromo-5,5-dimethylhydantoin addition and conversion.**

To safely implement the portionwise addition of the *N*,*N*′-dibromo-5,5-dimethylhydantoin into the plant, the following engineering controls were implemented: (i) an enclosed solids charging funnel was used to prevent exposure of *N*,*N*′-dibromo-5,5-dimethylhydantoin to water, which would generate bromine, known to be incompatible with THF;[22] (ii) the *N*,*N*′-dibromo-5,5-dimethylhydantoin was added in portions of 0.3 kg/kg of **10** per charge, which limited the potential heat production; (iii) HPLC analysis was performed during the addition to verify complete conversion and that there was no accumulation of reagent; (iv) the plant reactor was cooled to −10 °C between additions. The plant protocol began by the formation of the mixed zincate as described above. After the zincate formation was judged to be complete, the mixture was treated with toluene and was cooled to −10 °C. The solid *N*,*N*′-dibromo-5,5-dimethylhydantoin (1.5 equiv) was added via the solids addition funnel in ten equal portions with hold periods for the conversion to complete and also to allow the reaction mixture temperature to

(22) Tayim, H. A.; Absi, M. *Chem. Ind.* **1973**, 347–349.

cool back to −10 °C. At the end of the addition, the reaction mixture was warmed to 20 °C and stirred for 2 h to consume any remaining starting material followed by aqueous work up and crystallization. The process was scaled up in the pilot plant to produce 70.3 kg of **3** in two batches with an average yield of 58% and 99.6% purity. The process was later transferred to a vendor to produce an additional 156 kg of (*Z*)-(1-bromobut-1-ene-1,2-diyl)dibenzene, **3**, in comparable yield and purity. The production of multiple batches by different plants provided us with sufficient confirmation that our process for producing **3** was robust.

Conclusion

Two processes have been developed to prepare multikilogram quantities of the vinyl bromide **3**, the key intermediate for the synthesis of **1**. The early process involved a three-step sequence starting with trimethyl(phenylethyl-1-nyl)silane (**6**). The stereochemistry of the tetrasubstituted olefin was established by the stereoselective carbometalation reaction with a mixture of Cp_2TiCl_2 and Et_2AlCl followed by NBS quench of the organometallic intermediate to generate (*E*)-(1-bromo-2-phenylbut-1-enyl)trimethylsilane (**7**). Subsequent Miyaura−Suzuki coupling with phenylboronic acid produced (*Z*)-(1,2-diphenylbut-1-enyl)trimethylsilane (**8**). An addition−elimination sequence with bromine followed by sodium methoxide produced the key intermediate **3**. This three-step sequence was later replaced with a one-step reaction based on the $Ni(acac)_2$ catalyzed substoichiometric diphenylzinc/diethylzinc addition to but-1-ynylbenzene (**10**). The generated organozincate was brominated with *N*,*N*′-dibromo-5,5-dimethylhydantoin under well-defined conditions to ensure safety to form **3**. The two processes supported the generation of sufficient amounts of **1** to support pharmaceutical development activities and clinical trials.

Experimental Section

All the chemicals and solvents obtained from commercial sources were used as received without further purification. All the reactions were performed under a nitrogen atmosphere. The reversed-phase HPLC technique was utilized to analyze the chemical and isomeric purities of the compounds. The HPLC purity of the compounds was performed using a Zorbax SB-Phenyl, 150 × 4.6 mm column; the mobile phase was 10 mM NaH_2PO_4, pH 3.0 buffer (solvent A) and 100% acetonitrile (solvent B), flow rate 1 mL/min, temperature 40 °C, and detection at 265 nm. The isomeric purity of the compounds was analyzed with a Hypersil Hypercarb, 100 × 4.6 mm column; the mobile phase was 80% acetonitrile/20% water/0.1% trifluoroacetic acid solution (solvent A) and 100% tetrahydrofuran/0.1% trifluoroacetic acid solution (solvent B), flow rate 1.5 mL/min, temperature 40 °C, and detection at 265 nm.

(*E*)-(1-Bromo-2-phenylbut-1-enyl)trimethylsilane (7). A mixture of methylene chloride (88 kg), bis(cyclopentadienyl)titanium dichloride (Cp_2TiCl_2, 7.2 kg, 28.7 mol, 1.5 equiv) and trimethyl(phenylethynyl)silane (**6**) (3.25 kg, 18.6 mol, 1 equiv) was cooled to 15 °C, and a 25 wt % heptane solution of diethylaluminium chloride (13.85 kg, 18.6 mol, 1.5 equiv) was added over 1 h at <20 °C. The reaction mixture was warmed to 20 °C and was stirred for 2 h. HPLC indicated all **6** had reacted. The reaction mixture was cooled to −40 °C, and solid NBS (6.5 kg, 36.5 mol, 2 equiv) was added in portions over 1 h at <−35 °C. The reaction mixture was warmed to 0 °C over 2 h and was stirred for 1 h at 20 °C. The reaction mixture was transferred into a quench solution, which was prepared by combining water (22 kg), 30% aqueous sodium hydroxide solution (12 kg, 86.7 mol, 4.66 equiv), sodium sulfite (2.82 kg, 23.3 mol, 1.2 equiv), and Celite 560 (1.6 kg) at 20 °C (**caution: ethane is evolved**). The mixture was heated to 50 °C to remove methylene chloride by distillation. Heptane (41 kg) was added, and the mixture was cooled to 20 °C. The slurry was stirred for 15 min and was filtered. The cake was washed with heptane (10.4 kg) and the combined filtrates were transferred back to the reactor. The filtrates were allowed to settle and the bottom aqueous phase was removed. The product rich organic phase was concentrated by vacuum distillation at 100 mmHg with the jacket temperature at 60 °C to produce a heptane solution of **7** (57.5 kg of solution, 8.87 wt % of **7**, 90% solution yield).

Three additional batches were performed, and the heptane solutions of the four batches were combined. The combined heptane solution was concentrated by distillation to produce 46.6 kg of a heptane solution containing 20.0 kg of **7**. A sample was concentrated in vacuo for characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 9H), 1.08 (t, J = 7.5 Hz, 3H), 2.80 (q, J = 7.6 Hz, 2H), 7.25−7.27 (m, 2H), 7.42−7.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.04, 11.15, 34.32, 127.40, 127.52, 127.99, 128.68, 141.85, 156.66. HRMS Calcd for $C_{13}H_{19}SiBr$: 282.0439 [M^+]. Found: 282.0432 [M^+].

(*Z*)-(1,2-Diphenylbut-1-enyl)trimethylsilane (8). A mixture of potassium carbonate (15.0 kg, 108.53 mol, 3.07 equiv) and water (31 kg) was stirred for 30 min to dissolve all the solids. The heptane solution of **7** (23.3 kg solution containing 10.0 kg of **7**, 35.3 mol, 1 equiv) and ethyl acetate (55.0 kg) were added to the solution. The mixture was cooled to 5 °C, was first inerted with nitrogen, and was then inerted with argon. Phenylboronic acid (6.5 kg, 53.3 mol, 1.51 equiv) and tetrakis(triphenylphosphine)palladium(0) (0.84 kg, 0.73 mol, 0.02 equiv) were added; the reaction mixture was inerted again with argon and was sparged with nitrogen for 15 min. The reaction mixture was heated under a pressure of 1020 mmHg to 78 °C and was held for 3 h. HPLC indicated the reaction was complete. All ethyl acetate was removed by distillation at 760 mmHg with a jacket set point of 95 °C. The concentrated mixture was cooled to 50 °C and heptane (55.5 kg), methanol (16.1 kg), and water (20 kg) were sequentially added. The mixture was stirred for 20 min and was filtered through a 24 in. plate filter containing a 2−3 in. bed of Celite (3.0 kg) to remove insoluble residues. The reactor and the filter cake were rinsed with heptane (17.5 kg), and the rinse was combined with the filtrate. The combined filtrates were allowed to settle for 20 min, and the bottom aqueous phase was separated. Water (23 kg) and methanol (41.0 kg) were added to the heptane layer. The mixture was stirred for 20 min and allowed to settle for 20 min, and the bottom aqueous layer was separated. The heptane layer was washed again with water (23 kg) and methanol (41 kg) and was concentrated by vacuum distillation to produce a heptane solution of (*Z*)-(1,2-diphenylbut-1-enyl)trimethylsilane (**8**), (80.0 kg of solution, 12.13 wt % of **8**, 92% solution yield).

A second batch was performed, and the heptane solutions were combined and concentrated by distillation to produce 42.6 kg of a heptane solution containing 17.8 kg of **8**. A sample was concentrated in vacuo for characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 9H), 1.05 (t, J = 7.5 Hz, 3H), 2.47 (q, J = 7.6 Hz, 2H), 7.34−7.36 (m, 2H), 7.49−7.56 (m, 5H) 7.59−7.68 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.12, 12.82, 30.14, 125.04, 126.74, 127.69, 127.91, 128.08, 128.99, 140.87, 143.92, 144.59, 155.35. HRMS Calcd for $C_{19}H_{24}Si$: 280.1647 [M^+]. Found: 280.1653 [M^+].

(*Z*)-(1-Bromobut-1-ene-1,2-diyl)dibenzene (3). *Process A.* A solution of methylene chloride (95 kg) and bromine (7.68 kg, 48 mol, 1.5 equiv) was cooled to −65 °C, and a heptane solution of **8** (21.3 kg of solution, 8.6 kg of 9, 32.0 mol, 1.0 equiv) was added over 1 h at <−55 °C. The reaction mixture was held at −55 °C for 30 min at which time HPLC indicated the bromination was complete. A 25 wt % solution of sodium methoxide in methanol (13.89 kg of solution, 3.47 kg of NaOMe, 64.0 mol, 2 equiv) was added over 2 h at <−55 °C. The reaction mixture was stirred at −55 °C for 1 h and was warmed to 0 °C over 30 min. The reaction mixture was diluted with water (24 kg) over 30 min at <10 °C. The mixture was warmed to 20 °C over 30 min and was stirred for 1 h. The mixture was allowed to settle, and the phases were separated. The product rich organic phase was heated to 60 °C to remove methylene chloride by distillation and exchange the solvent to 2-propanol. The solution was further diluted with 2-propanol (141 kg) to a final volume of 87 L. After GC analysis indicated the solvent exchange was complete, the solution was cooled to 35 °C over 3 h. Water was added over 15 min, and the slurry was stirred for 2 h at 20 °C. The crude product was filtered, and the cake was dried for 16 h on a Nutsche filter under vacuum with a nitrogen purge. The crude product was charged back to the reactor and methanol (85 kg) was added over 15 min. The mixture was heated to 65 °C over 1 h to dissolve the solids. Water (12 kg) was added over 30 min at >50 °C, and the solution was cooled to 30 °C over 2 h to effect crystallization. Additional water (15 kg) was added, and the slurry was cooled to 20 °C and aged for 1 h. The slurry was filtered, and the cake was washed with 50% aqueous methanol (36 kg). The wet cake was dried under vacuum at 50 °C to produce **3** (6.8 kg, 76% yield, 99.65 area %, 100.2 wt % and 100% (*Z*)-isomer).

A second batch was performed on an 8.6 kg input scale to generate a total of 7.2 kg of **3** in 72% yield and 99.7% HPLC purity area or wt/wt with no (*E*)-isomer detected.

Process B. A solution of 8.3 wt % THF solution of diphenylzinc (626.5 kg of solution, 52.0 kg of diphenylzinc, 236.7 mol, 0.7 equiv) was concentrated by distillation at atmospheric pressure to a final volume of 145 L. NMP (90 kg) was added to the concentrated solution, and the mixture was cooled to 15 °C. A 20 wt % toluene solution of diethylzinc (146 kg of solution, 29.2 kg of diethylzinc, 236.7 mol, 0.7 equiv) was added. The mixture was warmed to 20 °C, stirred at 20 °C for 30 min, and cooled to −5 °C. To a separate reactor was charged nickel acetylacetonate (2.2 kg, 8.45 mol, 0.025 equiv), but-1-ynylbenzene (**10**) (44 kg, 338 mol, 1 equiv), and tetrahydrofuran (78 kg) sequentially. The mixture was stirred for 30 min to generate a solution. The solution of **10** and nickel acetylacetonate was transferred to the cold diphenylzinc/diethylzinc solution over 30 min at <5 °C. The reaction mixture was warmed to 20 °C and was stirred over a period of 4 h. HPLC indicated the reaction was complete. Toluene (458 kg) was charged, and the reaction mixture was cooled to −10 °C. *N*,*N*′-Dibromo-5,5-dimethylhydantoin (145 kg, 507 mol, 1.5 equiv) was charged in 10 portions over 5 h at <10 °C. The mixture was warmed to 20 °C and was stirred for 2 h. The mixture was cooled to −5 °C, and a solution of concentrated hydrochloric acid (106 kg) and water (220 L) was added over 30 min at <10 °C (**caution: ethane is evolved**). The mixture was warmed to 20 °C and stirred for 30 min. The phases were separated, and the organic phase was cooled to −5 °C. A solution of sodium sulfite (106 kg) and water (420 L) was added at <10 °C. The mixture was warmed to 20 °C and stirred for 30 min. The phases were allowed to settle, and the bottom aqueous phase was separated. The product rich organic phase was washed with 15% aqueous sodium chloride solution (580 kg). The organic solvent was exchanged to 2-propanol by distillation and addition of a total of 2-propanol (1030 kg) to a final volume of 420 L. GC analysis indicated the toluene was 0.8 v/v % and the solution was cooled to 20 °C over 2 h to effect crystallization. Water (160 L) was added over a period of 30 min, and the slurry was stirred for 1 h. The slurry was filtered, and the cake was washed with 45% aqueous 2-propanol (154 kg). The crude product was filtered, and the cake was dried for 16 h on a Nutsche filter under vacuum with a nitrogen purge. The crude **3** was charged back to the reactor, 2-propanol (370 kg) was added, and the mixture was heated to 70 °C to generate a solution. The solution was cooled to 20 °C over 2 h to effect crystallization, and water (123 kg) was added over 30 min. The slurry was stirred for 1 h and was filtered, and the cake was washed with 55% aqueous 2-propanol (220 kg). The wet cake was dried under vacuum at 70 °C to produce **3** (57.4 kg, 58% yield, 99.6 area %, 97.8 wt % and 100% (*Z*)-isomer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.3 Hz), 2.39 (q, 2H, J = 7.3 Hz), 7.32−7.38 (m, 5H), 7.41−7.48 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.03, 29.46, 118.62, 127.17, 128.15, 128.29, 128.33, 128.88, 140.80, 142.33, 144.73. HRMS Calcd for $C_{16}H_{15}Br$: 286.0357 [M^+]. Found: 286.0363 [M^+].

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Supporting Information Available

^{1}H and ^{13}C NMR spectra. HRMS analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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