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Article

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Utilizing *o*-Quinone Methide Chemistry: Synthesis of d_9-Ivacaftor

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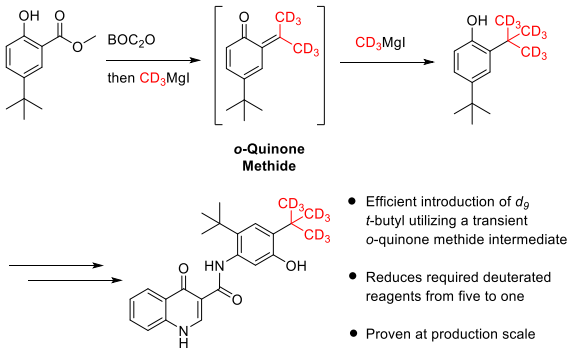


Abstract: Lead time and cost are important factors for any pharmaceutical API. However, these issues become even more important when the drug substance contains an isotope such as deuterium, which has a natural abundance of only ~0.016% of all hydrogen. Fewer suppliers and logistical barriers all play a role in driving up the cost. These factors would challenge the supply route used to manufacture d_9-ivacaftor (**17**), requiring investigation into alternative routes. By adapting the work from Pettus et al., a synthetic approach utilizing a transient *o*-quinone methide allowed access to the deuterium-labelled *o*-*tert*-butyl phenol moiety. This was developed and proven on pilot scale to significantly reduce the number of deuterated reagents used, leading to an overall reduction in cost by a factor of 10, while also providing the substantial benefit of applying prior process knowledge from the parent, non-isotopically enriched API ivacaftor (**7**).

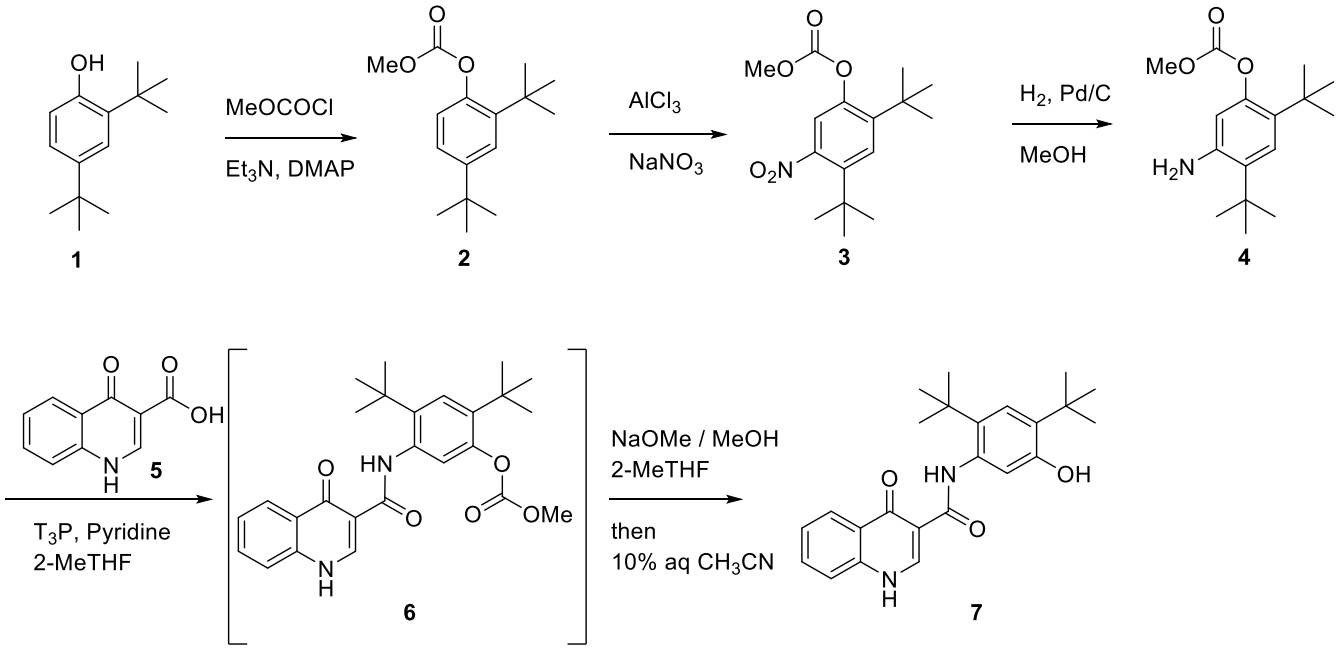
Introduction

Incorporating deuterium into clinical candidates has become more common over recent years.[1] While substituting hydrogen with deuterium in the proper location has its advantages,[2] there are also significant associated drawbacks; specifically, there are few suppliers of bulk sources of deuterium, deuterium is expensive relative to its hydrogen counterpart, and various region/country specific regulations exist, making it relatively difficult to move raw materials around the world. As a result, lead time and cost of APIs with deuterium will typically be negatively impacted. For these reasons, it is important to be as

efficient as possible with the source and use of deuterium reagents to mitigate these challenges and prevent the API price from being too high.

Ivacaftor (**7**) was commercialized in 2012 by Vertex Pharmaceuticals Incorporated under the trade name Kalydeco® for the treatment of Cystic Fibrosis (CF) patients with the G551D mutation.[3] It has since been used in combination with other agents to treat larger populations of CF patients.[4] The synthetic route to **7** is provided in Scheme 1.[5] Commercially available **1** is converted to its methyl carbonate **2**, setting the stage for a selective nitration using $AlCl_3$. Reduction of the nitro moiety, followed by coupling with the quinoline **5** gives the protected ivacaftor **6**, where treatment with sodium methoxide and crystallization from aqueous CH_3CN provides **7**. This route has provided ~45 MT since 2012.

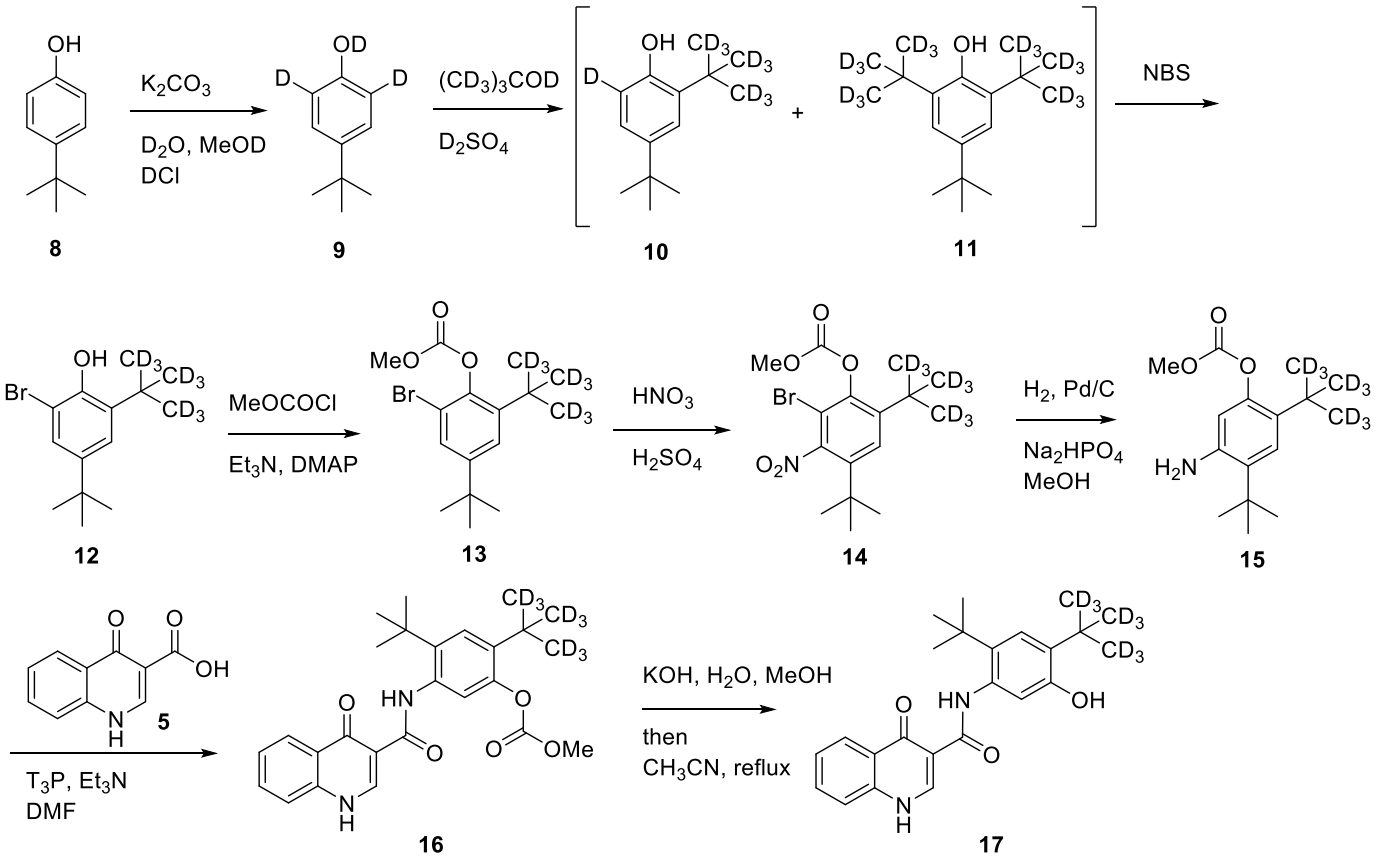
Scheme 1. **Synthesis of Ivacaftor**



d_9-Ivacaftor (**17**) presents potential advantages with respect to **7** that are being clinically evaluated.[6] Several synthetic pathways were identified to install the d_9-*t*-butyl,[7] with a clinical development supply route identified as shown in Scheme 2. Installation of the d_9-*t*-butyl is accomplished via Friedel-Crafts Alkylation using d_9-*t*-butanol. To minimize exchange of the deuteriums with protons, **8** is first converted to **9**. In both the protection step and alkylation step, deuterated reagents and solvents were required. The

reaction mixture of the alkylation step contained over alkylated by-product **11**, but this can be circumvented by brominating the mixture with NBS, leading to the bromination of both **10** and **11** to provide **12**. From here, a similar sequence is followed as in Scheme 1 to deliver **17**.

Scheme 2. **Supply Route for *d*$_9$-Ivacaftor**



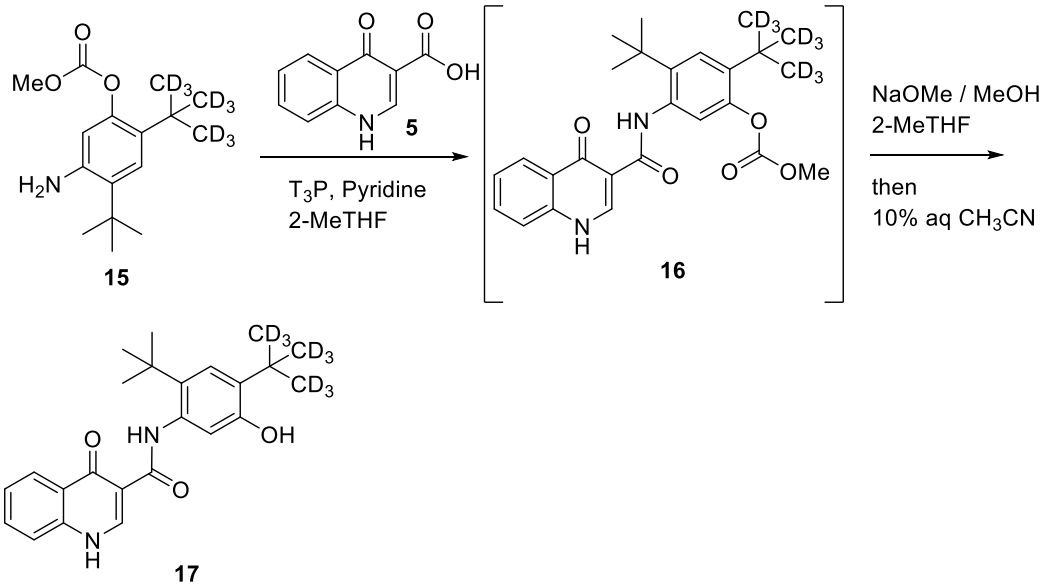
Although the initial supply route was successful in delivering the needed quantities of material for clinical use, the raw material costs associated with it were very high and sourcing the five required deuterated materials provided significant challenges. In addition, there was a desire to take advantage of the knowledge gained from the synthesis of **7**, leveraging the end-game chemistry and Quality by Design (QbD) work employed in generating its design spaces and specifications. The question therefore became: how can we best harmonize the synthesis of *d*$_9$-ivacaftor with the existing route to **7**?

Results and Discussion

Modifying the End-Game Chemistry

In both syntheses (Schemes 1 & 2), an intermediate aniline (**4**, **15**) is produced. It was expected that there would be no deuterium exchange applying the ivacaftor **7** end-game chemistry starting with an appropriate deuterated intermediate aniline **15** (Scheme 3). There are significant logistical advantages with using the commercial chemistry, as the current **7** supply chain of other key intermediates could be utilized, as well as current procedures and analytical methods with specifications. During the development of **7**, QbD was utilized to establish design spaces for the hydrogenation, coupling and deprotection chemistry.

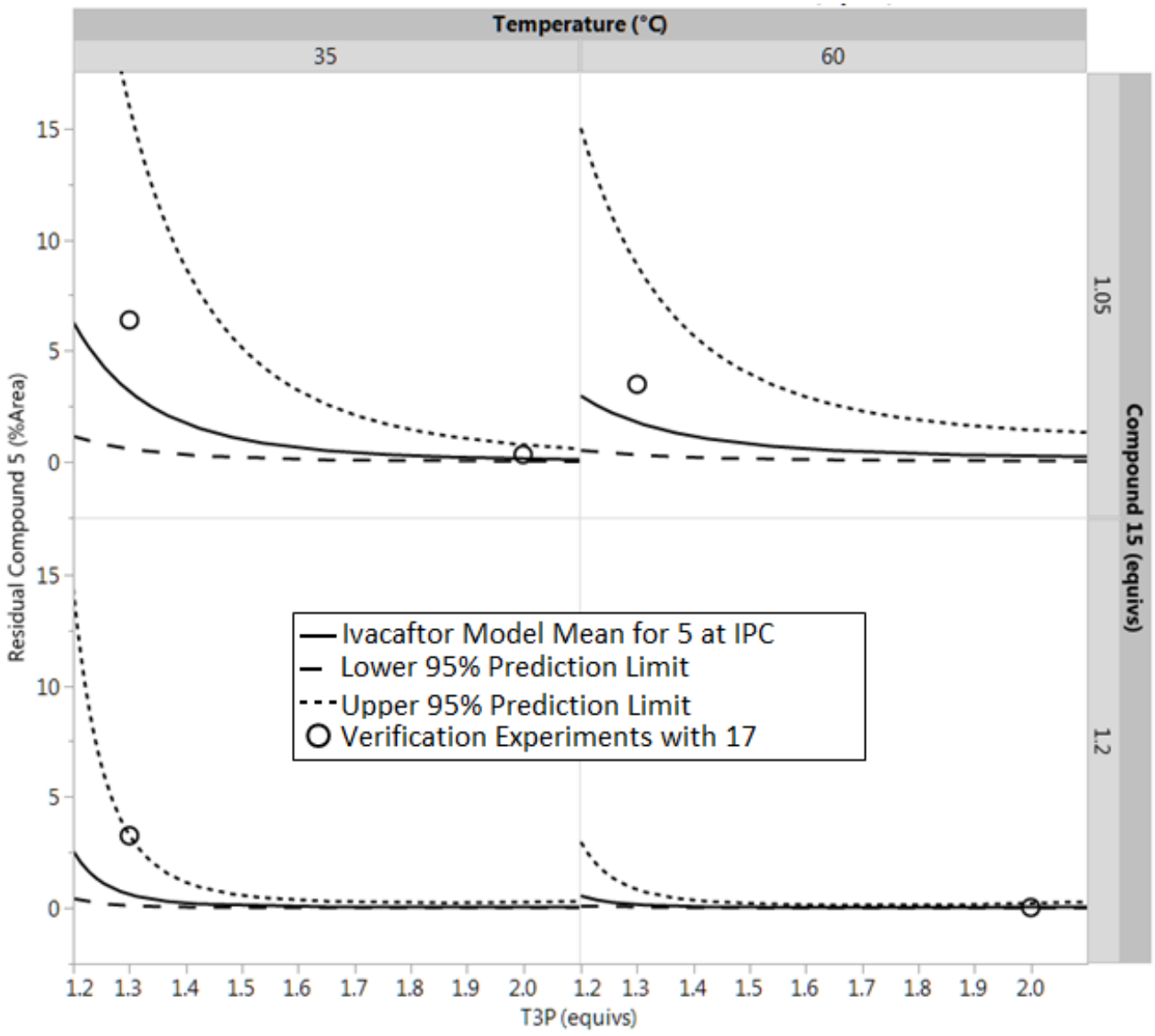
Scheme 3. **Modified Supply Route for d_9-Ivacaftor**



A familiarization run was performed using the center points of the coupling and deprotection steps starting with aniline **15**. After confirming the process was amenable, a series of verification experiments were performed as part of a comparability protocol with the aim of showing that the design spaces established for **7** would be applicable to the synthesis of **17**. Key to this is evaluating if our models from the design spaces of the ivacaftor commercial synthesis predict accurately the performance for the synthesis of d_9-ivacaftor **17**. Figure 1 shows that the data from verification experiments run on the coupling reaction of **15** and **5** (Scheme 3) align nicely with the in-process control model generated during enhanced

development studies of the reaction to **7**. Similarly, the models for other unit operations were verified, providing confidence that our established design spaces from the manufacture of **7** could be applied to the manufacture of **17**.

Figure 1. **Location and Results of Verification Experiments (Denoted with O) Relative to Coupling Model Mean and Prediction Intervals**

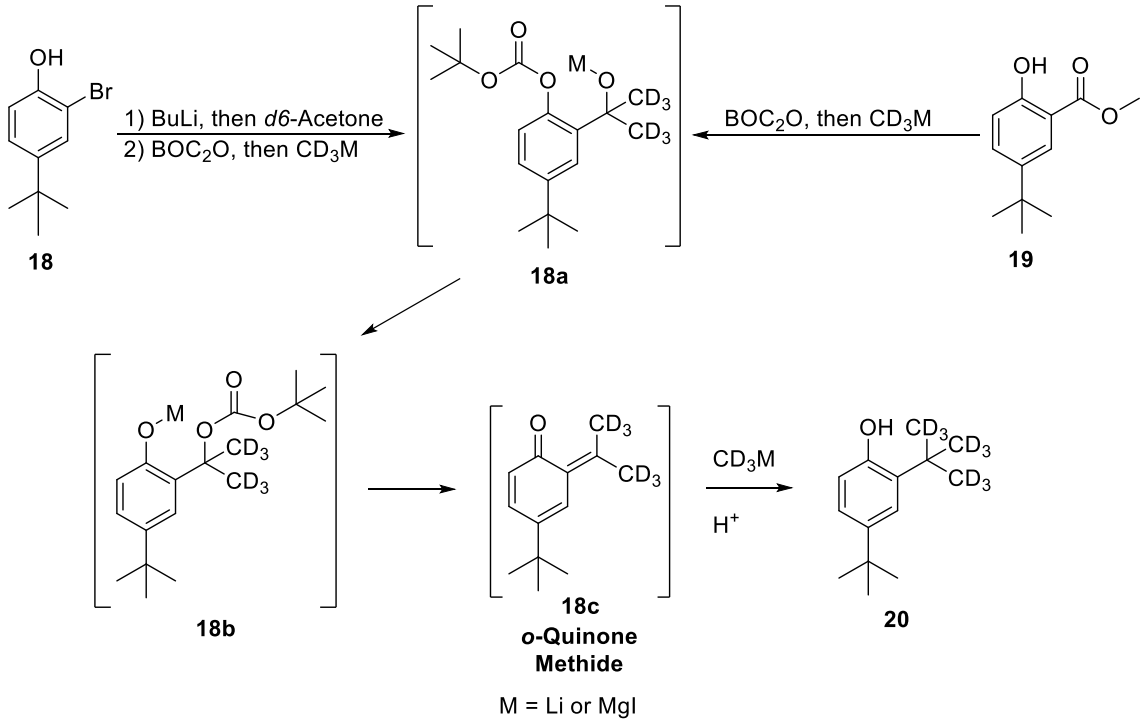


This modified supply route was used to produce >200 kg of **17** to support clinical studies. However, there was still room for improvement, especially with respect to cost effectiveness.

Screening for and Optimizing an Alternative Route

Phenols **18** and **19** were identified as abundant and inexpensive commercially available raw materials for an alternative route to **15**. As Pettus and colleagues have shown,[8] a disconnection involving a transient *o*-quinone methide intermediate, that can be used to capture a nucleophile, is an excellent way of converting an aromatic ester to its *t*-butyl derivative. Utilizing d_6-acetone addition to **18** provides an alternative pathway to the same *o*-quinone methide intermediate by way of the tertiary alcohol as disclosed in this paper. If either was successful, this would allow entry of the d_9 version of 2,4-di-*t*-butylphenol (the raw material used in the synthesis of **7**), allowing us to take full advantage of our knowledge of the ivacaftor commercial route (Scheme 1). It would also decrease the number of required deuterated reagents from five (Scheme 2) to one or two (Scheme 4).

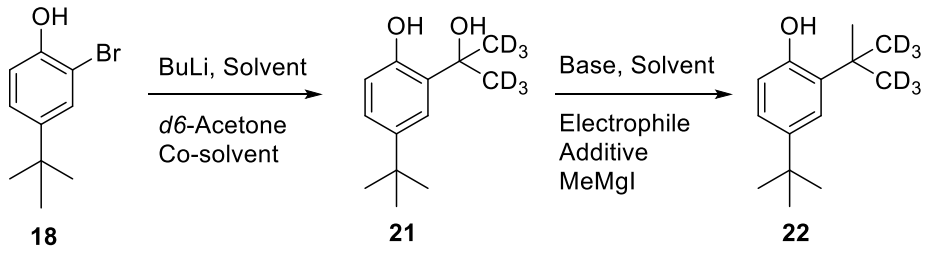
Scheme 4. **Potential Access to d_9 Phenol 20 from Commercially Available Raw Materials**



Screening studies were initiated to investigate the conversion of **18** to **21**, followed by a separate study examining the conditions required to convert the tertiary alcohol to **22** (Scheme 5). The more conveniently available MeMgI was used for this study in place of CD_3MgI. Using *n*BuLi (in hexanes) as the lithium

source, and varying equivalents, solvent, co-solvent and the amount of d_6-acetone, the results in Table 1 were obtained.

Scheme 5. **Screening the Viability of the d_6-Acetone Route**



18 21 22

Table 1. **Screening Studies for the Lithiation and Addition of d_6-Acetone**

Exp #	*n*BuLi (equiv)	d_6-Acetone (equiv)	Co-solvent	% Product
1	2.0	1.05	None	67
2	2.0	1.05	Et_2O	71
3	2.0	1.05	THF	33
4	2.0	1.05	2-MeTHF	44
5	2.0	1.05	CPME	70
6	2.0	1.05	1,4-Dioxane	27
7	2.0	1.05	MTBE	82
8	2.0[a]	1.05	MTBE	65
9	2.0	1.5	MTBE	81

[a] For entry 8, *n*BuLi was sourced as a solution in cyclohexane

This initial data set indicated that MTBE provided good results as a co-solvent (entries 1 – 7). Increasing the equivalents of electrophile had no impact (entry 9). With a strong desire to minimize the d_6-acetone used, we began to investigate the downstream chemistry using the conditions of entry 7. Although telescoping into the next step made sense to evaluate, for screening purposes, intermediate **21** was isolated and subjected to further conditions to install the final methyl moiety (Table 2). In each experiment, 2 eq *n*BuLi (in hexanes) was used as base with 10 vol solvent as indicated.

***Table 2*. Screening Studies for Conversion of 21 to 22**

Exp #	Solvent	Electrophile (equiv)	Additive (equiv)	MeMgI (equiv)	% Product
1	THF	PivCl (1.3)	None	1.5	43
2	THF	BzCl (1.3)	None	1.5	40
3	THF	TFAA (1.0)	None	1.3	40
4	THF	TFAA (1.0)	CuBr-SMe_2 (0.1)	1.3	63
5	THF	TFAA (1.2)	CuBr-SMe_2 (0.1)	1.5	52
6	THF	TFAA (1.2)	CuBr-SMe_2 (0.5)	1.5	56
7	THF	TFAA (1.2)	CuBr-SMe_2 (1.0)	1.5	51
8	THF	TFAA (1.2)	$MgBr_2$ (0.1)	1.5	9
9	THF	TFAA (1.2)	$Pd(PPh_3)_4$ (0.1)	1.5	27
10	THF	TFAA (1.2)	$Pd(PPh_3)_4$ (0.5)	1.5	17
11	THF	TFAA (1.2)	DMAP (1.1)	1.5	5
12	1:1 THF/heptane	TFAA (1.2)	None	1.5	2
13	1:1 THF/DCM	TFAA (1.2)	None	1.5	16
14	MTBE	TFAA (1.2)	None	1.5	9

Trifluoroacetic anhydride (TFAA) furnished the best conversion, but other electrophiles also gave appreciable product (entries 1 & 2). Several additives were evaluated under the hypothesis they might stabilize an *o*-quinone methide. Copper bromide dimethyl sulfide complex did show a positive effect on the yield (entries 4 – 7). There is some discussion in the literature that an *o*-quinone methide might react as a diradical, [9] so it was hypothesized that solvent could have an effect. However, efforts to try mixed solvent systems and/or changing solvent polarity only led to lower yields (entries 12 – 14).

Because of the reactivity of the transient *o*-quinone methide, the nucleophilic trap needed to be immediately available, and that was a challenge to this approach using d_6-acetone. This raised concerns about the route's reproducibility upon scale-up. Thus, attention was turned to screening the process as described by Pettus starting with ester **19**.[8] Toward that end, BOC protection of **19** provided **23** without incident (Scheme 6). A screening study was setup to evaluate equivalents of CD_3MgI, Grignard reagent solvent choice and co-solvent. The results are shown in Table 3. Note: in all cases, addition of substrate to Grignard was performed to achieve high concentrations of Grignard to substrate over the course of the reaction, consistent with the findings of Pettus.

Scheme 6. **Screening the Viability of the Conversion of 19 to 20**

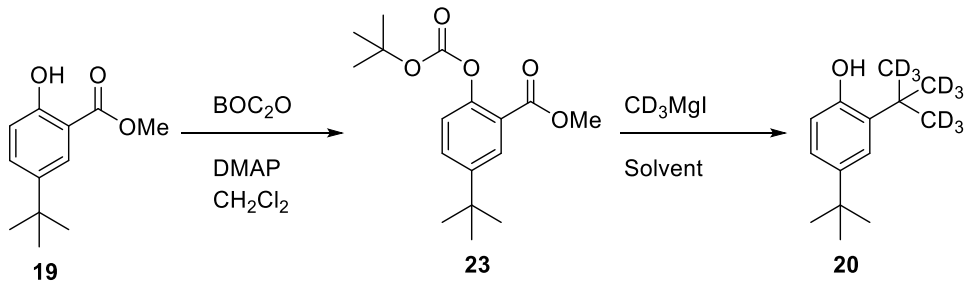


Table 3. **Screening Studies for Conversion of 23 to 20**

Exp #	CD_3MgI (equiv)	Grignard (Reagent Solvent, Molarity)	Co-Solvent (volumes)	% Product
1	5.0	2-MeTHF (3.4M)	None	62
2	5.0	Toluene (1.4M)	THF (11)	72
3	5.0	Et_2O (3.0M)	None	51
4	5.0	Et_2O (3.0M)	THF (10)	73
5	5.0	Et_2O (3.0M)	MTBE (6)	50
6	5.0	*n*-Bu2O (2.7M)	THF (8)	82
7	5.0	*n*-Bu2O (1.0M)	*n*-Bu2O (10)	48
8	5.0	*n*-Bu2O (2.1M)	Toluene (15)	6

9	5.0	*n*-Bu2O (2.1M)	1,4-Dioxane (15)	6
10	5.0	*n*-Bu2O (2.7M)	Toluene/THF 3:1 (11.6)	40
11	5.0	*n*-Bu2O (2.7M)	Toluene/THF 1:1 (11.6)	70
12	3.2	*n*-Bu2O (2.5M)	THF (3)	44
13	3.5	*n*-Bu2O (2.7M)	THF (6)	61
14	4.1	*n*-Bu2O (2.4M)	THF (10)	75
15	4.3	*n*-Bu2O (2.7M)	THF (9)	74
16	4.6	*n*-Bu2O (2.5M)	THF (10)	77
17	6.0	*n*-Bu2O (2.5M)	THF (11)	79

While the Grignard could be sourced in several solvents, ethereal solvents were desired due to commercial availability. THF as a co-solvent led to higher yields and more consistent results (entries 2, 4 and 6). A clear shift in the Schlenck equilibrium occurred with THF as co-solvent, [10] as a MgI_2-THF insoluble complex formed, leading to a beneficial system containing the more reactive $(CD_3)_2Mg$. [11] The volume of THF was important, though, because too little THF created a problematic thick slurry. Other additional solvents that were tried did not prove as fruitful. In choosing between Et_2O and *n*-Bu_2O as the solvent source of the Grignard solution (for example, entries 4 & 6), *n*-Bu_2O was more attractive due to less risk with flammability.

While both alternative routes provide a viable pathway to **20**, the approach as described in Scheme 6 using the screening conditions from Table 3 entry 6 were taken forward for further development. Prior to conducting a proof of concept on pilot scale, a few key questions remained, namely around the ideal temperature of the reaction and whether the process could be telescoped into the downstream chemistry.

An evaluation of reaction temperature was warranted to understand what temperature the reaction requires and understand if the impurity profile can be impacted. A Mettler Toledo React-IR 15 instrument running iC IR software version 7.0297 was used to effectively evaluate in a single experiment the

temperature at which the reaction takes place. Figure 2 outlines the experiment and key changes in the IR as the temperature was stepped up from -60 °C to -20 °C. In this case, the entire substrate solution was added to the Grignard at -60°C and monitored for changes in the IR spectrum as the temperature was raised in stages. The iC IR software has a feature to automatically identify wavenumbers of interest that correlate to statistical variation in the spectra over time during the experiment. This feature, built upon the ConcIRT algorithm, was utilized to identify several trends in the spectra during a period at the end of the experiment where substrate was reacting at a constant temperature and concentration (>1.5 hours). Once identified, the useful wavenumbers (1625 cm^{-1} is believed to correlate with the product and 1762 cm^{-1} with the substrate) could be tracked throughout the experiment. It was noted that the reaction does start to proceed around -40°C. Separate experiments were performed at selected temperatures from -30°C to +20°C to evaluate differences in impurity profile. All reactions provided similar product and impurity profiles, with major impurities analogous to those previously described by Pettus (tertiary alcohol **24** and styrene **25**, Figure 3). Due to simplicity and logistical preference, a temperature of 15 – 25°C was selected avoiding the need for low-temperature conditions.

Figure 2. **React-IR Profile in which a Half-portion of Ester 23 was Added and the Reaction Warmed in Stages Prior to Adding the Remaining Substrate.**

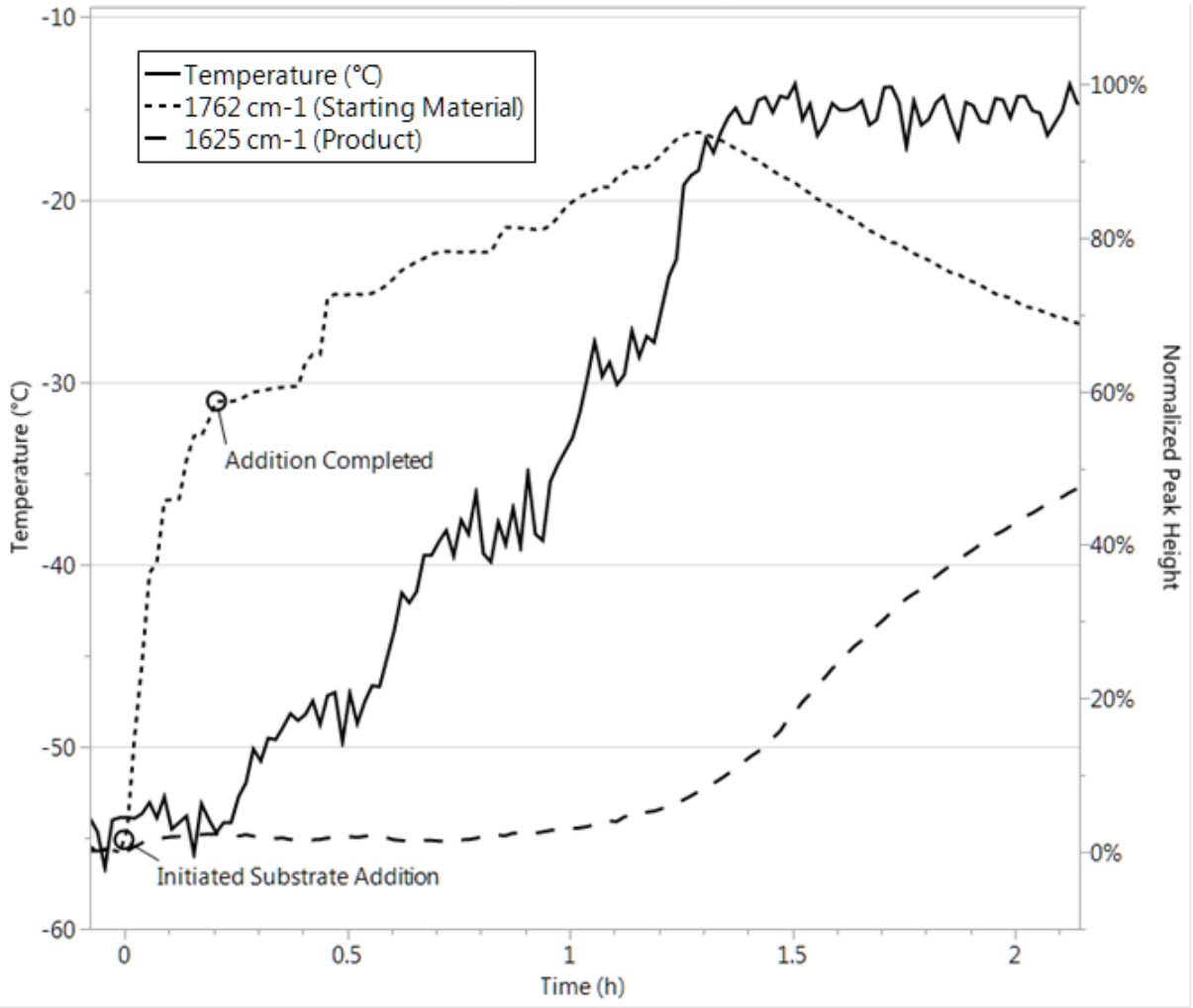
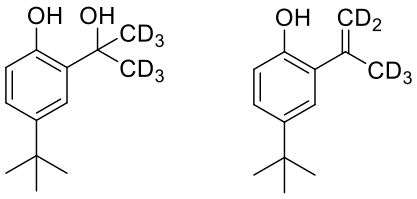


Figure 3. **Major Impurities Formed During Grignard Reaction**



21 **24**

A simple quench/workup sequence was identified. Addition of the reaction to 6N HCl, followed by aqueous washes and a thiosulfate wash, produced the crude product, which was assessed in the downstream chemistry without further purification. Towards this end, subjection of crude **20** to the

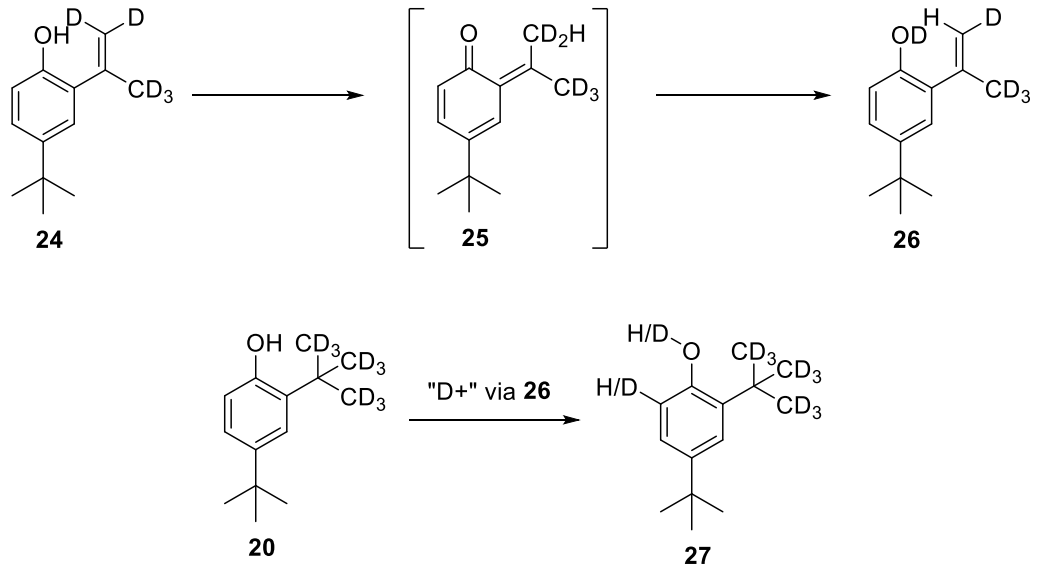
manufacturing process according to Scheme 1 led to nitro aromatic **3** meeting all specifications. While using crude **20** was proven viable, a purification of **20** by distillation was developed to establish a clear breakpoint in the supply chain. It was advantageous to our supply chain to source the phenol and ship this to our desired manufacturing locations as needed, rather than back integrate the nitration chemistry where **20** was being made.

Pilot Scale Proof of Concept and a Key Finding

With a process in hand, an evaluation was sought at pilot scale to assess robustness, produce material for required project studies and ensure viability for future production. Starting with 21.6 kg of **19**, the protection chemistry to manufacture **23** ran smoothly, producing a THF solution containing 31.3 kg **23** (97.7% yield) that met specifications. This solution was charged into the mixture of CD_3MgI/*n*-Bu_2O (5.0 eq at 2.7 M) and THF (8 vol), achieving the desired conversion (no detected **23**) and impurity profile (>80% product **20**) at the end of reaction. After quenching and aqueous washes, the product was distilled to provide 13.9 kg **20** (64% yield). Analytical data of the purified product (two fractions via the distillation) showed an overall combined purity of >95% with a d_9 incorporation in the *t*-butyl of >98%, as determined by mass spectrometry.

Examination of the ^{1}H NMR led to an interesting discovery. The integration of the proton *ortho* to the phenol was lower than expected. Further investigation showed that in fact, we had ~20% deuterium incorporation (compound **27**). This is likely due to exchange chemistry occurring during the distillation.[12] The source of the deuterium is styrene impurity **24**, produced during the conversion of **23** to **20** by way of a [1,5] sigmatropic shift competing with the desired addition of the third methyl Grignard. During the high-temperature distillation, deuterium can be incorporated into the system by way of additional [1,5] shifts involving styrene impurity **24** (Scheme 7), providing deuterium incorporation on the phenol of **26** by way of *o*-quinone methide intermediate **25**.[13] Any deuterium incorporated on the exchangeable phenol of **26** or its isotopologues would also be distributed among the phenol and *ortho* positions of **20** via exchange chemistry.

Scheme 7. **[1,5] Sigmatropic Shift of Styrene Impurity During Purification Allowing Deuterium into the System**



Due to this discovery, an HCl wash sequence was installed as the first unit operation of the next step in the downstream chemistry (refer to Scheme 1, preparation of the methyl carbonate) to remove the exchangeable deuterium from **27**, converting back to **20**. This process was proven to provide **20** with no detectable *ortho* or phenolic deuterium.

Conclusion

An alternative route to d_9-ivacaftor **17** was identified and developed to reduce the number of required deuterated reagents from five to one, while harmonizing the synthetic routes to **17** and **7** to start from the analogous 2,4-di-*t*-butylphenol. The cost of API production was reduced by a factor of 10. The new synthetic route took advantage of work by Pettus et al., using a transient *o*-quinone methide to produce the deuterium-labelled *o-tert*-butyl phenol. The product **20** contained high levels of deuterium incorporation (>98% d_9) in the *t*-butyl, with no detectable deuterium elsewhere in the molecule once understanding was gained of the exchange that occurs during the distillation. This project was a good reminder of the exchangeability of protons and alkyl groups under acidic conditions (and especially during a Friedel-Crafts alkylation) with electron rich aromatics. This should be kept in mind regarding stable label API's and preparation of deuterated reference standards.

Experimental

General. HPLC conditions: Analyses were performed using a Waters Symmetry Shield RP-18, 50 x 4.6mm, 3.5µm column (Part #186000177). Mobile phase consisted of a gradient method using A: 0.1% (v/v) phosphoric acid (85%) / water and B: 0.1% (v/v) phosphoric acid (85%) / acetonitrile. Assays were determined using high purity reference standards. NMR spectra were collected using a Bruker 400 MHz spectrometer. Solvents and reagents were obtained from commercial sources and used as is without further purification, unless otherwise noted. All reactors are standard multi-purpose equipment, either glass-lined or stainless steel, unless otherwise noted. All reactions were carried out under an atmosphere of nitrogen, unless otherwise noted.

4-(*Tert*-butyl)-2-(2-hydroxypropan-2-yl-1,1,1,3,3,3-d6)phenol (21). To an oven dried J-Kem culture tube was charged a magnetic stir bar. The tube was capped with a septa. The reactor was purged with nitrogen and dropped in a -78°C bath. To the reactor was charged *n*BuLi (5.0 ml, 8.0 mmol, 1.6 M in hexanes), followed by a solution of **18** (0.94 g, 4.0 mmol) in MTBE (2.5 ml). The mixture was stirred for 2 hrs. To the reaction was charged d_6-acetone (0.46 g, 8.0 mmol) dropwise over 30 min. The reaction was allowed to slowly warm to ambient temperature overnight. The reaction was quenched and washed sequentially with saturated NH_4Cl, water and then saturated NaCl. The organic phase was concentrated to dryness to provide an oil that was a mixture of products. This mixture was purified by SFC chromatography to provide the title compound as an oil with a yield of 70% (0.62 g (99.1% purity): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 1H), 7.22 (dd, J = 8.5, 2.5 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 2.40 (s, 1H), 1.31 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.3, 142.1, 130.1, 125.8, 121.9, 117.0, 76.0, 34.1, 31.6, 29.3 (m, $2CD_3$). HRMS (ESI/Q-TOF) m/z: $[M - H]^-$ Calcd for $C_{13}H_{13}D_6O_2$ 213.1767; Found 213.1840.

4-(*Tert*-butyl)-2-(2-methylpropan-2-yl-1,1,1,3,3,3-d6)phenol (22). To a 250 ml round bottom flask equipped with a magnetic stir bar, temperature probe and nitrogen bubble was charged **21** (4.3 g, 20.06

mmol), followed by THF (86 ml). The mixture was cooled to -70°C in a dry ice/acetone bath. To the reactor was charged dropwise *n*BuLi (25.01 ml, 40.1 mmol, 1.6 M in hexanes), and stirred for 20 min. To the reactor was charged dropwise trifluoroacetic anhydride (2.80 ml, 20.1 mmol), and stirred for 35 min. To the reactor was charged CuBr DMS (0.41 g, 2.00 mmol), followed by dropwise addition of CH_3MgI (8.69 ml, 26.1 mmol, 3.0 M in Et_2O). The reaction mixture was allowed to warm slowly to ambient temperature. The reaction was quenched with saturated NH_4Cl and transferred to a separatory funnel. The mixture was extracted with IPAc (86 ml), and the aqueous phase back extracted with an additional IPAc (86 ml). The combined organics were washed with water, then saturated NaCl and dried over Na_2SO_4. After filtration, the mixture was concentrated to dryness to provide an oil that was a mixture of products. This mixture was purified by SFC chromatography to provide the title compound as an oil with a yield of 51% (2.2 g (98.0% purity): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 2.5 Hz, 1H), 7.08 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 4.59 (bs, 1H), 1.41 (s, 3H), 1.30 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.9, 143.1, 135.3, 124.2, 123.7, 116.0, 34.4, 31.8, 29.6, 28.8 (m, $2CD_3$). HRMS (ESI/Q-TOF) m/z: $[M - H]^-$ Calcd for $C_{14}H_{15}D_6O$ 211.1974; Found 211.2033.

Methyl 2-((*tert*-butoxycarbonyl)oxy)-5-(*tert*-butyl)benzoate (23). **19** (21.6 kg, 103.7 mol) was charged to a reactor, followed by 4-dimethylaminopyridine (62.1 g, 0.5 mol) and dichloromethane (170.3 kg). The reaction was stirred to dissolve while maintaining a temperature of 25 °C +/- 5.0 °C. Di-*t*-butyldicarbonate (23.1 kg, 105.8 mol) as a solution in dichloromethane (53.9 kg) was charged over 1 hour maintaining a temperature of 25 °C +/- 5.0 °C. The reaction was stirred for 1 hour. IPC confirmed complete conversion (residual **19** NMT 0.50% area). Ammonium chloride (6.7 kg, 125.3 mol) as a solution in water (58.1 kg) was charged to the reaction, and the mixture was stirred for 1 hour. The layers were separated, and the organic retained. To the organic layer was charged water (64.1 kg), and the mixture was stirred for 1 hour. The layers were separated, and the organic retained. This water wash was repeated a 2nd time. The organic layer was solvent swapped to THF with successive distillations and additions of THF. A final solution (84.7 kg) was obtained in THF containing the title compound (31.3 kg, 97.7% yield and 99.2% area purity) which was used as-is in the next reaction: ^{1}H NMR (400 MHz, $CDCl_3$):

δ 8.02 (d, *J* = 2.5 Hz, 1H), 7.58 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 3.90 (s, 3H), 1.59 (s, 9H), 1.34 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 165.5, 151.9, 149.1, 148.3, 130.9, 128.7, 123.0, 122.7, 83.6, 52.3, 34.6, 31.2, 27.7. HRMS (HESI-QEHF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{25}O_5$ 309.16965; Found 309.1685.

4-(Tert-butyl)-2-(2-(methyl-d3)propan-2-yl-1,1,1,3,3,3-d6)phenol (20). THF (212.5 kg) was charged to a reactor. CD_3MgI in dibutyl ether (2.7M, 202.2 kg, 482.0 mol) was charged over 4 hours while maintaining a temperature of 25 °C +/- 5.0 °C. **23** as a solution in THF from the previous reaction (32.0 kg, 103.7 mol) was charged over 5 hours while maintaining a temperature of NMT 30 °C, rinsing the source drum for **23** with THF (6 kg). The reaction was stirred for 2 hours. IPC confirmed complete conversion (residual **23** NMT 0.20% area). The reaction was cooled to 10 °C +/- 5.0 °C. *t*-Butanol (14.4 kg, 194.3 mol) in dibutyl ether (23.1 kg) was charged over 1.5 hours maintaining a temperature of 10 °C +/- 5.0 °C and stirred for 20 minutes. To the reaction was charged 6N HCl (163.4 kg) over 2 hours while maintaining a temperature of NMT 20 °C. The reaction was stirred for 30 minutes. The layers were separated, drumming off both the lower aqueous and upper organic layers. The aqueous layer was charged back into the reactor and back extracted with dibutyl ether (137.0 kg), stirring for 30 minutes. The layers were separated, and the lower aqueous layer removed. The previously drummed organic phase was charged to the reactor to combine both organics. To the reactor was charged water (27.6 kg), and the mixture was stirred for 45 minutes. The layers were separated, and the organic retained. This water wash was repeated a 2nd time. To the reactor was charged 5% sodium thiosulfate (126 kg), and the mixture was stirred for 45 minutes. The layers were separated, and the organic retained. To the reactor was charged water (27.6 kg), and the mixture was stirred for 45 minutes. The layers were separated, and the organic retained. The organic was distilled to minimal volume and transferred to a reactor setup to perform fractional distillation. Purification was performed using fractional distillation, collecting the product at a pot temperature of 135 – 155 °C and a head temperature of 118 – 120 °C. The title compound was isolated as a low melting solid in two batches with a total yield of 64% (11.0 kg (96.8% purity) and 2.9 kg (89.0% purity)): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 2.4 Hz, 1H), 7.14 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.64 (d,

J = 8.2 Hz, 1H), 1.36 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 151.8, 143.0, 135.2, 124.1, 123.6, 115.9, 34.3, 31.7, 28.6 (m, $3CD_3$). Deuterated purity by LC-MS: >98% d_9. HRMS (HESI-QEHF) m/z: $[M]^+$ Calcd for $C_{14}H_{13}D_9O$ 215.22301; Found 215.2226.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

- ^{1}H and ^{13}C NMR of compounds **20**, **21**, **22** and **23**
- HRMS data for compounds **20**, **21**, **22** and **23**

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(13) (a) Hansen, H.J. "Aromatic Sigmatropic Hydrogen-Shifts in 2-Vinyl- and 2-Allyl-phenols". *Helv. Chim. Acta* **1977**, *60*, 2007. (b) Note: another pathway to deuterium incorporation in the ring is via **18c** during the reaction sequence. Conversion of **18c** to known impurity styrene **24**, can allow "free" deuterium into the system during reaction. However, with the aqueous workup of the reaction it is believed that this deuterium is exchanged prior to distillation, rendering this pathway an in-significant contributor.