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Article

Development and Scale-Up of 7-COOH CBD Synthesis, a Key Cannabinoid Metabolite

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ABSTRACT: This article describes the process development required for the manufacture of a cannabidiol (CBD) metabolite, 7-carboxy cannabidiol (7-COOH CBD), starting from ∼0.5 mT of CBD. A laboratory-scale synthetic route to 7-COOH CBD was not scalable, primarily due to the reliance on chromatography. The route was shortened from 9 to 7 steps by altering the protecting group strategy. Byproduct formation was a major hurdle toward developing a robust process as was identifying points of purification. Chromatography was circumvented, and purification was achieved through base washes, resin treatment, dicyclohexylamine (DCHA) salt formation, and methanol slurry at the final step. Overall, a scalable process was developed for the conversion of CBD to 7-COOH CBD, with pilot-scale manufacturing processing of 30 kg of CBD delivering 1.99 kg of 7-COOH CBD. Further scaling was carried out to deliver 31.79 kg of 7-COOH CBD starting from ∼0.5 mT of CBD.

INTRODUCTION

Cannabis plants comprise of a highly complex mixture of compounds, with over 100 different cannabinoid molecules identified to date.[1] The cannabinoid class can be divided into three subcategories: phytocannabinoids found in the cannabis plant species, endocannabinoids that are endogenous cannabinoid molecules made in the human body and bind to cannabinoid receptors, and synthetic cannabinoids that can include examples of phytocannabinoids and endocannabinoids, as well as novel cannabinoid molecules.[2]

The medicinal properties of cannabis have been reported and researched for centuries.[3−5] Following the structural elucidation of cannabidiol (CBD)[6] and Δ9-tetrahydrocannabinol (THC) and the identification of the psychotropic effects of cannabis primarily due to THC content,[7] significant research into the pharmacological effects of the cannabis plant has continued to this day.

CBD is one of the major, nonpsychoactive constituents of the cannabis plant, and its metabolism has been studied in both animals and humans.[8] CBD is metabolized primarily by CYP450s, giving rise to several oxidative products, examples of which are shown in Figure 1.[8−10] The principal route of CBD metabolism in humans is via oxidation at the 7-position, driven by CYP3A4 and 2C19, to give 7-CH_2OH CBD.[9] This compound can be further oxidized to the 7-carboxy species, which is the main metabolite observed in circulation in human plasma.[8,11−13]

To establish CBD as a registered pharmaceutical agent, kilogram quantities of 7-COOH CBD were required for development activities. A lab-scale process for the synthesis of 7-COOH CBD had been developed by Butler *et al.* and is shown in Scheme 1. The process involved allyl protection of CBD, followed by epoxidation of **1** and acid-catalyzed ring-opening of epoxide **2** to produce allylic alcohol **3**. After switching the protecting group from allyl to acetate via $Pd(PPh_3)_4$/dimedone-mediated deprotection, allylic alcohol **5** was converted to aldehyde **7** by mesylation, bromination/allylic rearrangement, and then oxidation. The resulting aldehyde **7** underwent Pinnick oxidation to carboxylic acid **8**, which was deprotected to give the desired 7-COOH CBD.

The original synthetic route had been demonstrated at laboratory scale-up to 10 g input, with chromatographic purification required for 7 steps and gave an overall yield of 8.1%. Given the challenging timelines for delivery, the development of the lab-scale route was favored over further route scouting.

PROCESS DEVELOPMENT

Each step of the laboratory-scale synthesis of 7-COOH CBD had specific areas for development. General issues relevant to all steps concerned requirement for chromatographic purification (7 steps), large input of drying agents, dilute reactions, and complex workup protocols. Process development was carried out on the lab-scale route, targeting the delivery of a process demonstration at a pilot scale before scaling to multikilogram manufacture of 7-COOH CBD with the desired quality. Key highlights of the work performed for each step are outlined in turn in this section.

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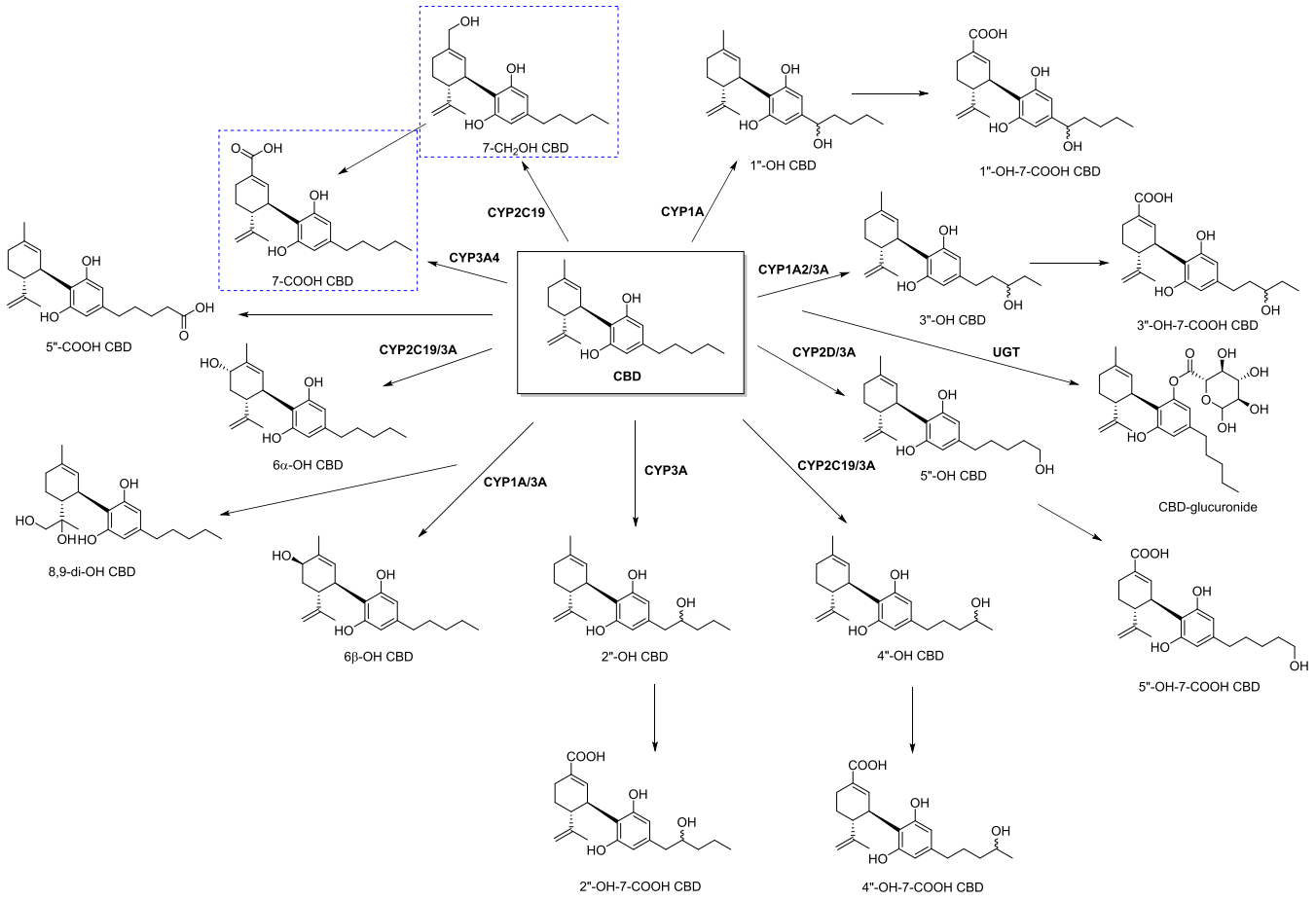
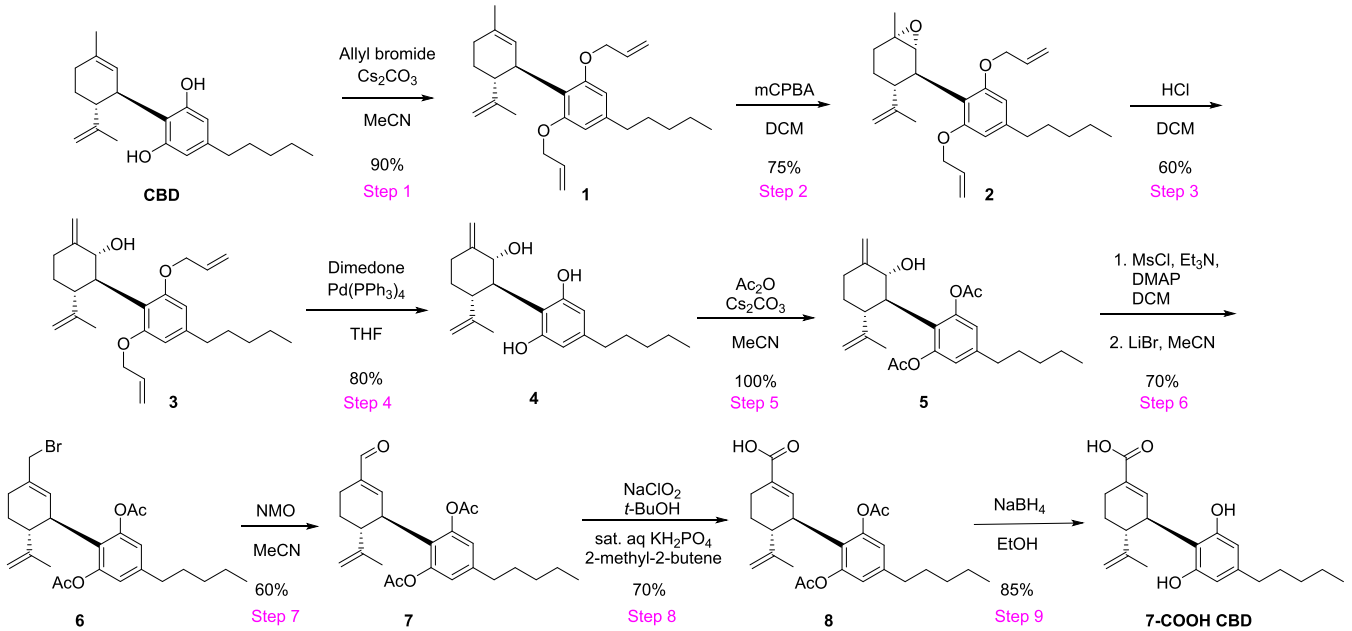


Figure 1. Chemical structure of several identified CBD metabolites.

Scheme 1. Lab-Scale Route to 7-COOH CBD



Step 1: Allyl Protection. Step 1 involved the bis-*O*-protection of CBD using allyl bromide and Cs_2CO_3 as shown in Scheme 2. Cs_2CO_3 can be difficult to agitate on scale because of its density. The reaction volumes were relatively large and needed to be reduced (target <10 vol). The product was an oil, and direct isolation was not possible due to the potential for major losses in product transfer.

During reaction familiarization, an impurity ranging from 13 to 22% HPLC PA was observed by HPLC and ^{1}H NMR. The impurity was shown to be the triallyl CDB derivative **9**

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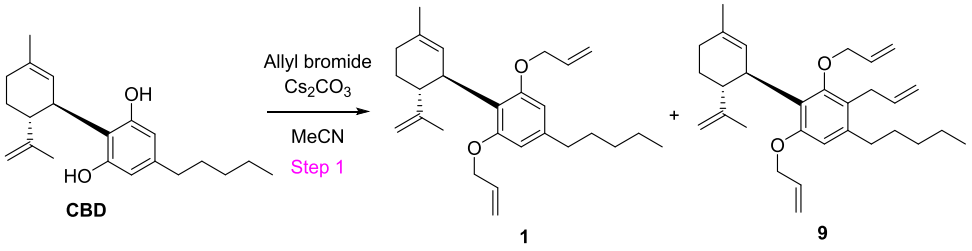
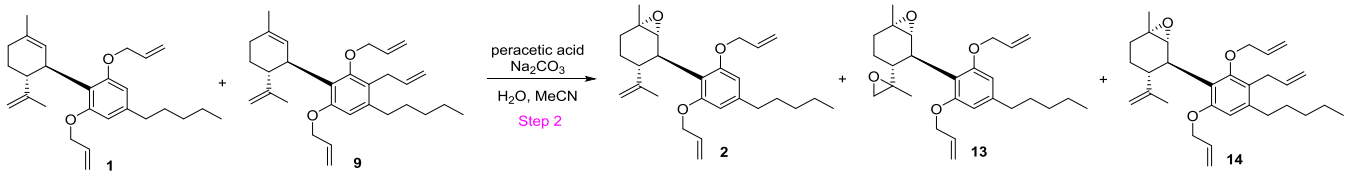
Scheme 2. Step 1 En Route to 7-COOH CBD



Scheme 3. Peracetic Acid Epoxidation for Step 2



(Scheme 2). The impurity was potentially formed either by Claisen rearrangement or Friedel−Crafts-type allylation of the electron-rich aromatic. The product solution after complete consumption of CBD was confirmed to be stable by HPLC post reaction completion over the course of 5 days, with no further allyl migration apparent. Since the Claisen rearrangement was not observed in the product, the triallyl impurity was likely formed via Friedel−Crafts-type allylation.

The best-identified procedure for step 1 involved adding a solution of CBD in MeCN (5 vol) over 15 min to a suspension of Cs_2CO_3 (4 equiv) and allyl bromide (2.2 equiv) in MeCN (5 vol) at 20−25 °C under N_2. The stability of the allyl bromide under basic conditions over the addition period was confirmed by HPLC analysis. Subsequent scale-up experiments with 100 and 500 g of CBD input successfully yield process-typical Step 1 product (~88:12 ratio of **1**:**9**).

Alternative less dense carbonate bases (K_2CO_3, Na_2CO_3) were screened; however, lower yields were obtained. To circumvent potential agitation issues associated with the use of Cs_2CO_3 on scale, the mode of addition was changed. Initially, MeCN (5 vol) was charged to a reactor under N_2 and then cooled to below the flash point of MeCN (−5−0 °C). Solid Cs_2CO_3 (4 equiv) was charged portionwise to the reactor with constant agitation to prevent settling of the solids at the bottom of the reactor. A well-agitated suspension was observed. After warming the suspension to 15−25 °C, allyl bromide followed by the substrate solution in MeCN was added. The altered mode of addition did not change the purity profile of the product.

Workup investigations were conducted to ascertain the best process for effective telescoping to step 2. The reaction mixture was filtered to remove inorganic salts and split into two portions. The first was concentrated *in vacuo* without quenching to yield a dark purple oil, and the second was worked up in accordance with the lab-scale route, which involved quenching with NH_4Cl. Phase splits were very slow for the latter workup, and oiling out of product in the organic layer was observed. Analysis of the products obtained by ^1H NMR and HPLC for both workup procedures showed similar product purities. Since quenching with NH_4Cl was not necessary, the process to be scaled would simply involve filtering the mixture to remove inorganic salts and telescoping the filtrate directly to step 2.

Step 2: Epoxidation. In the lab-scale route for step 2, mCPBA was used to perform the epoxidation with DCM as solvent. Chromatographic purification was required to remove diepoxide **13** and recover unreacted **1**. Development efforts were focused on improving the volumetric efficiency of both the reaction and workup and identifying an alternative (ICH class 2/3) solvent to DCM. Use of mCPBA on scale was not desirable due to difficulties associated with its use and shipment; therefore, the use of an alternative oxidant was investigated.

The initial focus of step 2 development was on peracetic acid-mediated epoxidation (Scheme 3). The use of peracetic acid (PAA) is often favored in industry, as it is an inexpensive oxidant that produces relatively benign byproducts and side products (acetic acid, oxygen, and water); however, there are still associated risks of fire and explosion incidents caused by the presence of flammable organic chemicals or the use of heat. An important factor for consideration was the ability to telescope the product from step 1 without the need for isolation. Efforts focused on the development of the epoxidation in MeCN, from which step 1 could be telescoped. The peracetic acid procedure involved the addition of a solution of **1** in MeCN (3.2 vol) to a solution of Na_2CO_3 (1 equiv) in H_2O (5 vol), followed by heating to 50 °C and subsequent controlled dropwise addition of peracetic acid (1 equiv). Vigorous gas evolution was observed upon peracetic acid addition. Analysis by HPLC indicated the formation of the desired monoepoxide **2** as the major product (54.9% HPLC PA), in addition to diepoxide **13** (5.5%) and triallyl epoxide **14** (12.9%) with unreacted **1** (22.1%) remaining. A further 2 × 0.2 equiv of peracetic acid charges were necessary to achieve reaction completion. Consumption of starting material was confirmed, and a final ratio of mono- to diepoxide of 73:27 by HPLC PA was obtained. The observed selectivity for epoxidation at the trisubstituted double bond of **1** is in line with the known reactivities of simple alkenes.[14]

Further work was carried out to ascertain the best conditions for step 2. Na_2CO_3 could be replaced by Cs_2CO_3, but telescoping step 1 product mixture (containing excess Cs_2CO_3) without filtration did not yield any desired epoxide. No major benefit to the product composition was apparent using Cs_2CO_3 in place of Na_2CO_3, so the latter base remained preferable. Performing the reaction in the absence of a base led

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to the formation of cyclic ether **15** as the major product (Figure 2).

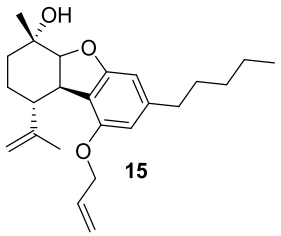

Figure 2. Proposed structure of the cyclic impurity.

Use of a MeCN/H_2O solvent mixture to maintain solubility of the inorganic base led to oiling out of the product, which did not occur when MeCN was the sole reaction solvent. With the aim to circumvent oiling out, organic bases (DBU, triethylamine) in MeCN were investigated, in addition to the use of Na_2CO_3 in MeCN, with either 1 vol or no H_2O added. The reaction proceeded very slowly with DBU (entry 1, Table 1),

Table 1. Strategies to Overcome Oiling Out

entry	base (equiv)	solvent (vol)	conv. (%)	ratio of **2**:**13** by HPLC PA (%)
1	DBU (1.2)	MeCN (10)	11	9.8:0
2	Et_3N (1.2)	MeCN (10)	0	-
3	Na_2CO_3 (1.2)	MeCN (10) + H_2O (1)	95	86:14
4	Na_2CO_3 (1.2)	MeCN (10)	98	81:19

and no desired product formed with triethylamine (entry 2, Table 1). The presence of minimum H_2O gave a good ratio of mono:diepoxide; however, the reaction stalled with 5% of **1** remaining (entry 3, Table 1). In the absence of H_2O (entry 4, Table 1), although the Na_2CO_3 was not fully solubilized, the reaction proceeded faster than those using a MeCN/H_2O solvent mixture, with less than 2% of **1** remaining after 2.5 h. Crucially, no oiling was observed. The best reaction conditions employing peracetic acid (1.2 equiv) with Na_2CO_3 (1.2 equiv) in MeCN (10 vol) provided a ratio of 81:19 **2**:**13**.

Step 3: Epoxide Ring-Opening. The lab-scale procedure for epoxide ring-opening employed methanolic HCl and DCM as a reaction solvent, with purification by column chromatography necessary to purge the cyclic ether byproduct **15** (Scheme 4). Development targets for step 3 involved improving the volumetric efficiency, replacement of DCM with a more environmentally benign solvent, and minimizing the formation of impurity **16** and telescoping product through to step 4 since **3** presented as an oil.

Reaction conditions involving base-catalyzed rearrangement as an alternative to acid-catalyzed reaction were investigated. No conversion was observed with LiHMDS, while LDA exclusively furnished the undesired cyclic ether **15**. The use of methylmagnesium *N*-cyclohexylisopropylamide, which had previously been reported to be effective in base-catalyzed epoxide ring-opening of cannabinoids, did not furnish allylic alcohol **3**.[15]

Reverting to the lab-scale route using HCl, the effect of increasing the quantity of HCl was investigated using purified epoxide **2** as substrate (Table 2). Using 0.2 equiv of methanolic HCl in DCM (10 vol) gave only a 50% conversion (entry 1, Table 2). Greater amounts of HCl (0.5, 1.0 equiv; entries 2 and 3, Table 2) led to higher conversion; however, the major product was the undesired cyclic ether **15**. This result contrasted with earlier experiments using step 2 product prepared via the lab-scale route with mCPBA, which yielded the desired alcohol in the majority. Greater quantities of H_2O were present in the step 2 product prepared using peracetic acid; therefore, it was hypothesized that H_2O was favoring the formation of **15**. Drying the epoxide via toluene azeotroping prior to reaction with HCl led to a reduction in **15** formation (entry 4, Table 2). It was therefore deemed critical to minimize the presence of H_2O prior to carrying out step 3.

Both trifluoroacetic and methanesulfonic acid (MSA; 0.6 equiv) were investigated as alternative anhydrous acids to mediate step 3 (entries 5 and 6, Table 3); however, neither yielded the desired product. To minimize **15** formation in the HCl-mediated ring-opening, HCl was generated *in situ* from the reaction of AcCl with IPA, and *i*PrOAc was used as the reaction solvent. A significantly more favorable ratio of 83:17 **3**:**15** was obtained (entry 7, Table 3). Investigation into alternative reaction solvents indicated that polar protic solvents mediated the undesired cyclization reaction and should be avoided for the desired epoxide rearrangement. A favorable ratio of 85:15 (**3**:**15**) was obtained using MeCN as a solvent (entry 9, Table 3).

To further minimize the presence of protic solvents in the reaction, a more concentrated (10 M) stock solution of HCl was generated *in situ* from AcCl with IPA and then diluted to 1 M with MeCN. An improved ratio of 90:10 **3**:**15** was obtained. Furthermore, reducing the quantity of HCl to 0.5 equiv further favored the desired product with a ratio of 93:7. The use of HCl gas in MeCN (0.5 equiv) instead of a solution generated from AcCl/IPA was found to moderately improve the ratio of **3**:**15** to 95:5. Use of a larger excess of gas (1.5 equiv) led to complete product degradation. As it would have been impractical to accurately weigh in the small quantity of gas required at pilot plant scale and above, it was decided to use a solution of HCl in MeCN (2.5% w/w to minimize fuming) for scale-up.

The final process fine-tuning showed that the HCl equivalents could be lowered to 0.25, giving complete conversion of epoxide **2** to alcohol **3** and the solvent volumes

Scheme 4. Lab-Scale Step 3 Route

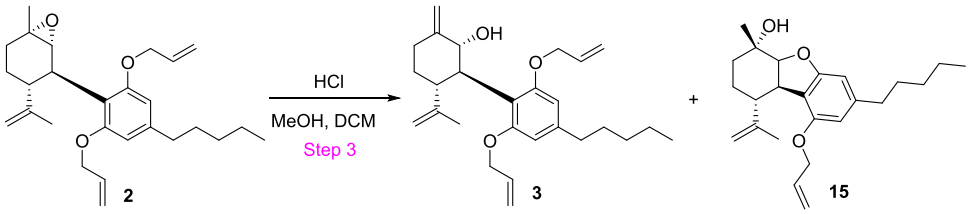

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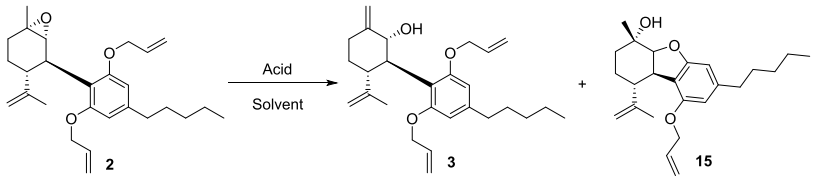
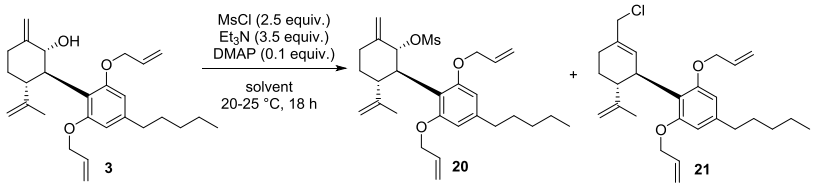
Table 2. Acidic Conditions Investigated for Step 3



entry	acid	equiv acid	solvent (10 vol)	conv. (%)	ratio of **3**:**15**
1	HCl (1 M in MeOH)	0.2	DCM	50	75:25
2	HCl (1 M in MeOH)	0.5	DCM	90	15:85
3	HCl (1 M in MeOH)	1.0	DCM	95	10:90
4[a]	HCl (1 M in MeOH)	0.5	DCM	90	80:20
5	TFA	0.6	DCM	0	-
6	MSA	0.6	DCM	0	-
7	HCl (1 M in IPA)[b]	1.0	*i*PrOAc	100	83:17
8	HCl (1 M in EtOH)[c]	1.0	EtOH	100	49:51
9	HCl (1 M in IPA)[b]	1.0	MeCN	100	85:15

[a]Substrate dried via toluene azeotroping prior to the reaction. [b]Generated via the reaction of AcCl with IPA. [c]Generated via the reaction of AcCl with EtOH.

Table 3. Solvent Screening Experiments for Step 4a



entry	solvent (vol)	conversion (%)	ratio of **20**:**21**
1	DCM (15)	100	0:100
2	toluene (10)	52	78:22
3	2-MeTHF (10)	64	63:37
4	EtOAc (10)	100	100:0
5	*i*PrOAc (10)	89	100:0
6	MeCN (10)	100	0:100
7[a]	MeCN (10)	100	0:100

[a]MsCl (1.5 equiv), Et_3N (2.0 equiv), and DMAP (0.05 equiv) were used.

could be lowered from 10 to 6. The Na_2CO_3 solution required for the quench was optimized at 2.5 volumes of 2.5% w/w solution to overcome the problem of precipitation of solids. A use test on 250 g scale with the telescoped step 2 product gave complete conversion to product in 90 min, and workup gave the product in a quantitative yield based on strip weight assay with an HPLC purity of 65.5%. The main impurity (12.3%) was determined to be triallyl derivative **16** (Figure 3).

Shortened Synthetic Strategy for Steps 4−9. In the original synthetic route, the protecting group was switched from allyl to acetate after step 3. To reduce the number of steps, a shortened seven-step route was devised in which the initial allyl protection was maintained until its removal in step 7a (Scheme 5). The viability of the proposed shortened synthetic route was proven at a small scale; however, further development of steps 4a−7a was necessary prior to scale-up.

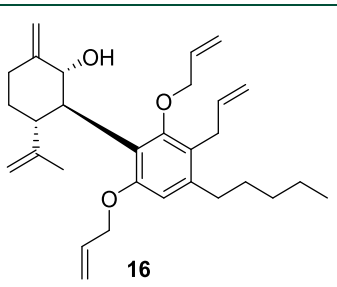


Figure 3. Proposed structure of the step 3 triallyl impurity.

Step 4a: Mesylation/Halogenation. Step 4a involved sequential mesylation and bromination of allyl alcohol **3** generated in step 3 (Scheme 6). Initial familiarization indicated that the intermediate mesylate (**20**) was readily converted to allyl chloride *in situ*, which underwent bromination in the presence of LiBr to yield a mixture of allyl bromide **17** and chloride **21**. Attempts to convert chloride **21** to aldehyde **18** without initial bromination yielded a product of HPLC purity lower than that obtained from oxidation of the chloride/bromide mixture. The overall targets for the development of step 4a included improvement in volumetric efficiency of the reaction, in addition to the replacement of DCM in the mesylation step, with a solvent more attractive for use at scale.

Initial development work investigated DMAP equivalents. The lab-scale route using 1.1 equiv of DMAP with Et_3N (3.5 equiv) and MsCl (2.5 equiv) in DCM (15 vol) yielded allyl chloride **21** as the major product, with mesylate **20** forming as a minor product. Reducing the quantity of DMAP to 0.1 equiv

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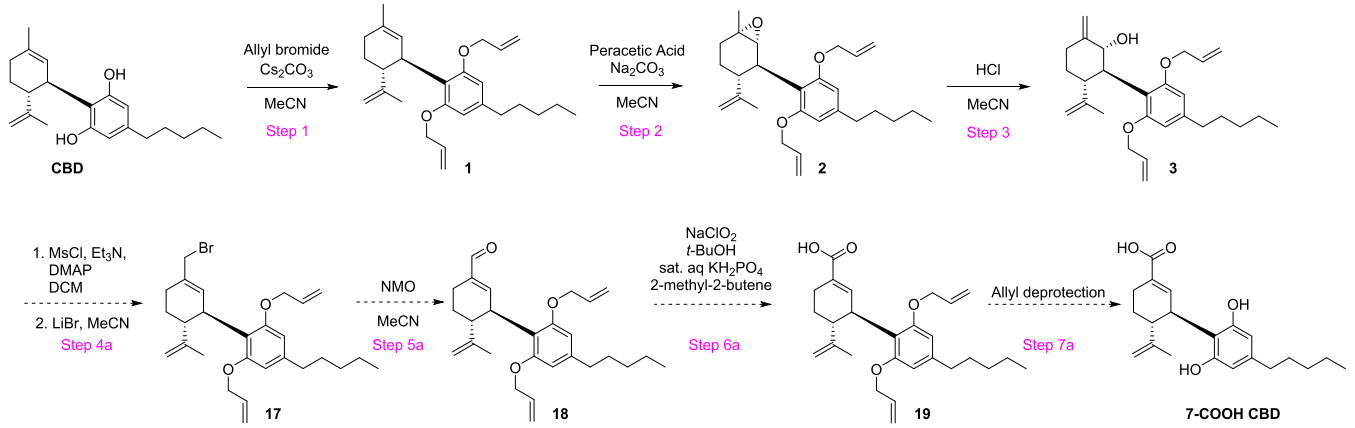
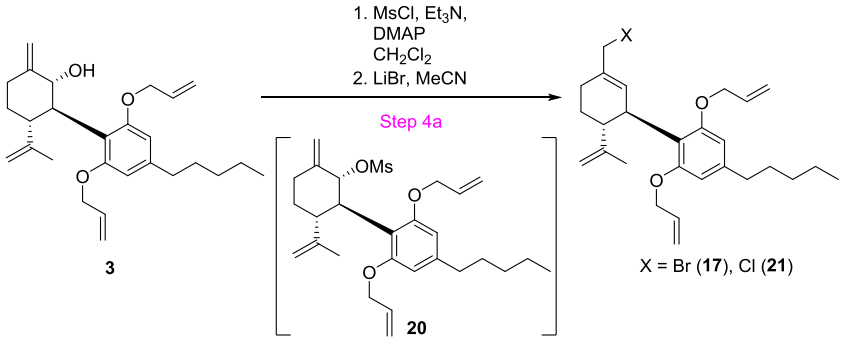
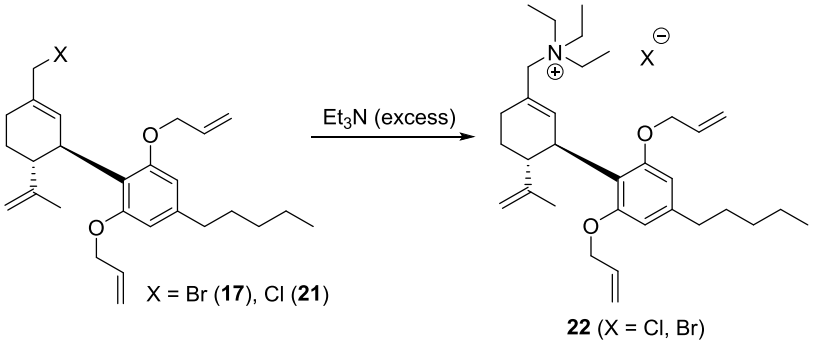
Scheme 5. Proposed Revised Shortened Synthetic Route



Scheme 6. Sequential Mesylation and Bromination



Scheme 7. Postulated Formation of Quaternary Ammonium Salt



resulted in initial exclusive mesylate formation within 1 h. Subsequent conversion of the mesylate to the chloride was observed after stirring for 60 h with complete consumption of **3**.

Toluene, 2-MeTHF, EtOAc, and *i*PrOAc (10 vol) were evaluated as alternative solvents to DCM (Table 3). Complete consumption of **3** was observed in EtOAc, and in contrast to previous experiments, the exclusive formation of mesylate **20** occurred in the absence of chlorination. No further reaction or decomposition occurred upon prolonged stirring (72 h). The mesylate was, however, found to decompose upon attempted isolation. In MeCN, complete conversion of **3** to chloride **21** was observed (entry 6, Table 3). A reduction in the number of equivalents of MsCl, Et_3N, and DMAP was investigated in parallel (entry 7, Table 3). Both reactions reached completion after stirring overnight. MeCN therefore was a viable alternative to DCM.

Since MeCN was the solvent to be employed for both steps 3 and 4a, telescoping of step 3 product mixture through the mesylation/halogenation was investigated. After the acid-catalyzed ring-opening, the step 3 reaction mixture was quenched using excess Et_3N, followed by mesylation of this mixture. However, this approach led to reaction stalling with multiple charges of MsCl and Et_3N required. Workup of step 3 ($NaHCO_3$ quench, brine wash, azeotropic distillation, then filtration to purge salts) was necessary prior to performing the mesylation/halogenation.

As facile chlorination occurred during the mesylation, one-pot mesylation/chlorination/bromination was attempted by running the mesylation in the presence of LiBr (5 equiv). Although this was found to yield a mixture of chloride **21** and bromide **17** after 1 h, 40% unreacted **3** remained. Addition of further portions of MsCl and Et_3N did not enable further conversion.

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Table 4. Attempts to Minimize Quaternary Ammonium Salt Formation in Step 4a

entry	solvent (vol)	MsCl equiv	Et_3N equiv	DMAP equiv	reaction time (h)	conversion (%)	HPLC PA **22** (%)
1[a]	MeCN (10)	1.3	2.0	0.05	18	100	20
2[b]	MeCN (10)	1.3	2.0	0.05	18	100	8
3[b]	MeCN (10)	1.8	1.75	0.05	18	72	0
4[b]	MeCN (10)	2.5	2.45	0.05	18	100	0

[a]Et_3N added prior to MsCl. [b]MsCl added prior to Et_3N.

Scheme 8. NMO-Mediated Oxidation of Allyl Halides to Aldehyde 18

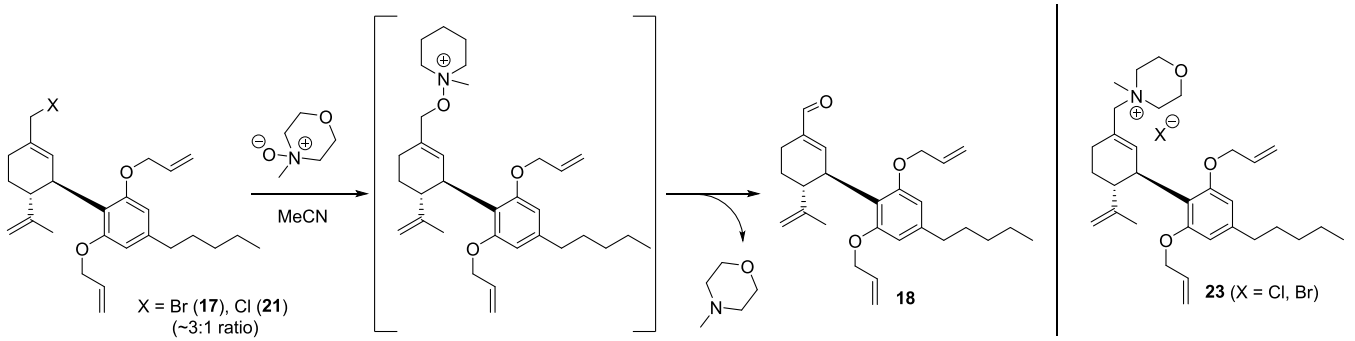
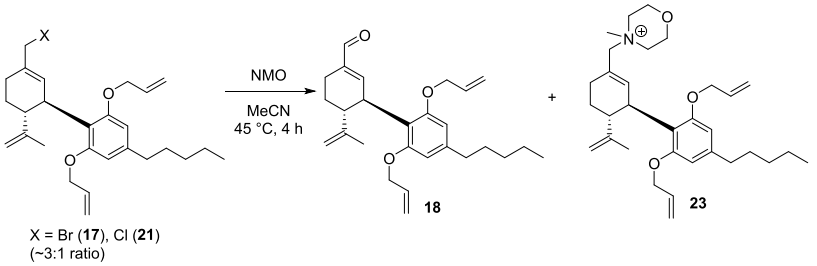


Table 5. Step 5a Process Improvements



entry	MeCN (vol)	NMO equiv	mode of NMO addition	ratio of **18**:**23** by HPLC PA
1	10	2.5	solid	60:40
2	5	3.5	solid	86:14
3	5	3.5	solution in MeCN (2.5 vol)	88:12

The process was reverted to performing the mesylation/chlorination and then bromination steps sequentially. Allylic alcohol **3** initially underwent one-pot mesylation and chlorination using MsCl (1.5 equiv), Et_3N (2 equiv), and DMAP (0.05 equiv) in MeCN (10 vol). After the mixture was stirred for 1 h at 20−25 °C, complete conversion of **3** was achieved. LiBr (5 equiv) was added to the mixture and heated to 60 °C. Stirring the mixture for 18 h yielded a ∼3:1 mixture of allyl bromide **17** and chloride **21**.

Significant quantities (20% by HPLC PA) of an early eluting byproduct were observed. A product with the same retention time had formed in a reaction where a large excess (5 equiv) of Et_3N was used to quench step 3, followed by telescoping directly to step 4a. It was postulated that the byproduct was the ammonium salt formed by the substitution of Et_3N for the halide (Scheme 7). To confirm that the observed byproduct was the ammonium salt, isolated allyl bromide **17** was reacted with Et_3N (3 equiv) at 60 °C for 2 h. Complete consumption of **17** was observed, and a major product was formed with an equivalent retention time to that of the impurity peak from previous experiments, supporting the hypothesis of the quaternary ammonium salt as a byproduct.

Further development work focused on minimizing the ammonium salt **22** formation (Table 4). The existing procedure involved the addition of Et_3N (2 equiv) and then MsCl (1.3 equiv). A reduction in the quantity of **22** from 20 to 8% by HPLC PA was achieved by reversing the order of addition of Et_3N and MsCl (entry 2, Table 4). Employing the reverse order of addition, the use of excess MsCl (1.8 equiv) with Et_3N (1.75 equiv) was found to eliminate the formation of **22** (entry 3, Table 4). However, incomplete conversion was achieved. Use of 2.5 equiv of MsCl and 2.45 equiv of Et_3N mediated the complete consumption of **3**, and critically no ammonium salt **22** was generated. Scale-up of the process (initially up to 30 g) under the improved conditions provided full conversion to the allylic mixture with no formation of the ammonium salt side product.

Step 5a: N-Methylmorpholine-N-oxide (NMO) Oxidation. Step 5a involved the oxidation of the alkyl halides generated in step 4a to aldehyde **18**. The ∼1:3 mixture of chloride **21** and bromide **17** obtained from step 4a underwent NMO-mediated oxidation to the aldehyde (Scheme 8). However, an impurity peak was observed, which had a retention time similar to that of the ammonium salt observed in step 4a. The reaction proceeds via substitution of NMO for the halide, which undergoes subsequent elimination of *N*-methylmorpholine (NMM) to generate the aldehyde (Scheme 8). Substitution of the liberated NMM for the halide was likely the cause of

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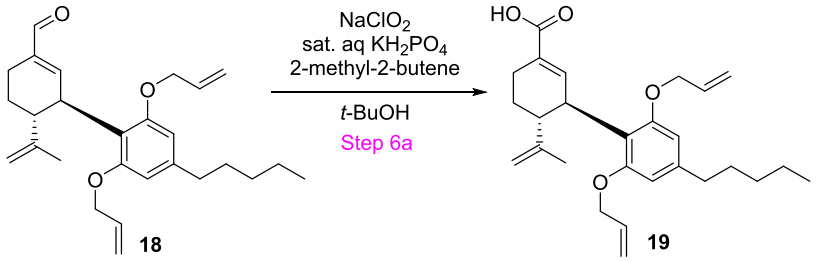
Scheme 9. Pinnick Oxidation (Step 6a)



byproduct salt **23** formation. Promoting quicker formation of the alkoxyamine intermediate by reducing the volumes of MeCN from 10 to 5 and increasing the NMO equivalents from 2.5 to 3.5 improved the ratio of **18**:**23** from 60:40 to 86:14 (entries 1 and 2, Table 5).

Initial experiments were carried out by adding solid NMO in one portion. From a safety perspective, introducing the NMO in a more controlled fashion was necessary. Addition of a solution of the telescoped step 4a product in MeCN (2.5 vol) to a suspension of NMO (3.5 equiv) in MeCN (2.5 vol) at 45 °C over the course of 20 min was found to mediate complete conversion, with an 88:12 ratio of **18**:**23** (entry 3, Table 5).

Step 6a: Pinnick Oxidation. The lab-scale procedure for the Pinnick oxidation of aldehyde **18** to carboxylic acid **19** employed $NaClO_2$ (4.3 equiv) with satd. aq KH_2PO_4 and a large excess of 2-methyl-2-butene (25 equiv) as hypochlorous acid (HOCl) scavenger in *t*-BuOH (50 vol) (Scheme 9). Reduction in the solvent volumes and equivalents of $NaClO_2$ and HOCl scavenger were priorities for the development work. Additionally, given that all steps had been telescoped to this point of the synthesis, it was critical to identify potential points of purification, including salt formation and/or performing an ion-exchange catch-and-release strategy.

Reduction in the equivalents of HOCl scavenger and $NaClO_2$, and solvent volumes, was initially investigated. DMSO was evaluated as an alternative scavenger to 2-methylbutene. Using DMSO (2 equiv) with $NaClO_2$ (1.5 equiv) in a mixture of *t*-BuOH (10 vol), KH_2PO_4 (satd. aq; 2 vol), and H_2O (1 vol) was found to mediate the complete conversion of aldehyde **18** (Table 6), with a purity profile similar to that obtained using the lab-scale procedure.

Table 6. Investigation of Solvents, HOCl Scavengers, and $NaClO_2$ Equivalents for Pinnick Oxidation

entry	solvent (vol)	HOCl scavenger (equiv)	Rxn time (h)	conv (%)
1[a]	*t*-BuOH (50)	2-methyl-2-butene (25)	18	24
2[b]	*t*-BuOH (10)	DMSO (2)	18	100
3[b]	MeCN (6)/*t*-BuOH (2)	DMSO (2)	8	100

[a]$NaClO_2$ (4.3 equiv) used. [b]$NaClO_2$ (1.5 equiv) used.

At this point in the development of step 6a, hazard evaluation by Advanced Reactive System Screening Tool (ARSST) indicated that **18** had a low-temperature onset of decomposition (53 °C). This meant distillation of the step 5a product mixture to solvent swap from MeCN to *t*-BuOH was not feasible. Use of MeCN as a sole reaction solvent for step 6a led to oiling out upon the addition of aqueous KH_2PO_4. A mixed MeCN/*t*-BuOH (6:2 vol) solvent system yielded a homogeneous mixture, and a 99% conversion was achieved within 8 h, with quantitative yield based on strip weight assay. The mixed solvent system would be used for scale-up, and step 5a workup was revised, whereby the crude product solution in MeCN was washed with HCl (4%, 2.5 vol) and brine (2 × 2 vol), and then taken through to step 6a where *t*-BuOH (2 vol) would be added.

Given the priority of achieving purity improvement, salt formation was attempted on step 6a product. Formation of sodium, potassium, or dicyclohexylamine salts all proved unsuccessful, either yielding no solid salt or very low (<30%) recovery. The potential to use a basic ion-exchange resin (Amberlyst A26 (OH-form)) for purification of step 6a product was also evaluated. Both 100 and 200 wt % of the resin were added to solutions of **19**, but analysis of the liquors by HPLC indicated no absorption of the desired product onto the resin.

With the likelihood that subsequent allyl deprotection would require the use of a palladium catalyst, reducing the weight of crude step 6a product would significantly reduce the costs associated with step 7a. TLC analysis (3:1 heptane/2-MeTHF) showed that baseline impurities were present in the crude step 6a product mixture, so a slurry with silica, alumina, or charcoal was proposed as a means of purging those impurities. In a 3:1 heptane/2-MeTHF solvent mixture, silica (entry 4, Table 7) yielded better purity uplift than alumina (entry 3, Table 7), while charcoal did not significantly improve the purity (entry 2, Table 7). Alternative solvent systems were evaluated, and the best balance between recovery and purity uplift was achieved in an EtOAc/heptane mixture with silica as the adsorbent (entry 7, Table 7). The treatment successfully adsorbed 34% of nonvolatile impurities, with a 99% recovery of **19**.

Despite the promising results obtained using silica in EtOAc/heptane, multiple distillations were necessary for the solvent swap from the MeCN/*t*-BuOH solvent mixture. The indicated onset of decomposition occurring at 53 °C and with an adiabatic temperature increase of 181 °C meant multiple distillations were therefore undesirable. To overcome this issue, crude step 6a product was distilled to 2 vol, and heptane (3 vol), EtOAc (1 vol), and silica (200% by wt) were added. This procedure yielded a result analogous to that using a pure EtOAc/heptane (1:3) mixture and was feasible on scale.

Step 7a: Allyl Deprotection. The final step in the synthesis of 7-COOH CBD was allyl deprotection (Scheme 10). The lab-scale deprotection procedure employed $Pd(PPh_3)_4$ with dimedone as an allyl scavenger. Since no significant purification had been achieved in any of the previous steps in the synthesis, a primary target for the development of step 7a involved identifying a means of isolating pure 7-COOH CBD. Salt

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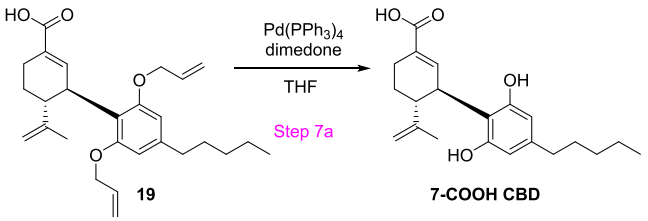
Table 7. Purification Experiments for Step 6a Crude Product

entry	adsorbent	elution solvent (vol)	adsorbent input (% by wt)	recovery by SWA[a] (%)	adsorbed (%)	mass balance (%)	recovery by HPLC Assay (%)	HPLC purity (%)
1	no treatment	2-MeTHF (1)/heptane (3)	-	100	N/A	100	97	40.1
2	charcoal	2-MeTHF (1)/heptane (3)	20	96	not checked	-	76	40.5
3	neutral alumina	2-MeTHF (1)/heptane (3)	150	82	not checked	-	90	41.4
4	silica	2-MeTHF (1)/heptane (3)	150	62	30	92	93	47.5
5	silica	2-MeTHF (1)/heptane (4.5)	200	60	39	99	91	46.1
6	silica	heptane (3)	150	65	35	100	89	45.7
7	silica	EtOAc (1)/heptane (3)	200	63	34	97	99	47.9
8	neutral alumina	EtOAc (1)/heptane (3)	200	75	not checked	-	84	21.5

[a]Strip weight assay (SWA).

Scheme 10. Allyl Deprotection (Step 7a)



formation and ion-exchange catch-and-release were the most likely methods of purification.

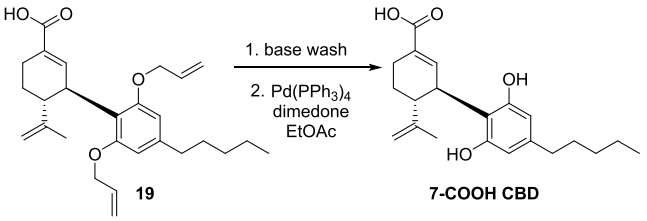
Further development required for step 7a entailed investigating alternative conditions to $Pd(PPh_3)_4$/dimedone, given the costs associated with $Pd(PPh_3)_4$ and potential challenges with purging dimedone-related impurities. Extensive investigations were carried out, employing alternative literature conditions, including $Pd(PPh_3)_4$-catalyzed deprotection with alternative scavengers (piperidine,[16] barbituric acid[17]), reductive deprotection ($NaBH_4$) with $Pd(PPh_3)_4$,[18] catalytic I_2 in PEG-400,[19] $CeCl_3$/NaI,[20] Pd/C with KOH,[21] or ammonium formate.[22] However, none of these alternative conditions successfully deprotected allyl acid **19**.

With alternative methods to $Pd(PPh_3)_4$/dimedone failing to yield satisfactory results, the focus of development work returned to improvement of the lab-scale procedure. Reaction completion was achieved on reducing the equivalents of dimedone from 3.5 to 2.5. Furthermore, both 2-MeTHF and EtOAc were shown to be feasible alternative solvents to THF. Since the workup employed EtOAc as a solvent, this was chosen as a solvent for further reaction development.

Challenges were encountered with achieving reaction completion using the best conditions on a fresh batch of allyl 7-COOH CBD **19**. Initially adding 3 mol % of $Pd(PPh_3)_4$ to a solution of **19** and dimedone (2.5 equiv) in EtOAc (15 vol) yielded trace amounts of monodeprotected product after stirring at 60 °C, and a further 6 mol % $Pd(PPh_3)_4$ was required to achieve reaction completion. These results did not align with those seen for the previously used batch of acid **19**. The former batch had undergone attempted salt formation *via* the addition of base. It was hypothesized that the basification of step 6a product was crucial to achieving reaction completion for the deprotection. To confirm this hypothesis, a freshly prepared batch of **19** was dissolved in EtOAc and washed with NaOH (1 M). Analysis by HPLC revealed that **19** remained in the organic phase. The allyl deprotection conditions were applied to the basified step 6a material, and reaction completion was achieved within 90 min using 5 mol % of $Pd(PPh_3)_4$. No conversion was observed in a parallel reaction using nonbasified **19**, suggesting that it was critical to basify acid **19** prior to step 7a.

A series of experiments were carried out to further develop the allyl deprotection for scale-up (Table 8). Several different bases were used for the initial base wash of **19**, while variation in base equivalents, catalyst loadings, and order of addition of dimedone and catalyst were investigated. Overall, where no

Table 8. Summary of Step 7a Base Wash and Catalyst Loading Investigations[a]



entry	base	base (equiv)	$Pd(PPh_3)_4$ (mol %)	Rxn time (h)	conv (%)	HPLC purity (%)
1	none	-	5.0	16	68	5.6
2	none (H_2O wash)	-	5.0	16	73	9.9
3	NaOH (5%)	1.0	5.0	16	100	29.8
4	NaOH (10%)	2.0	5.0	16	100	29.4
5	$NaHCO_3$ (7.5%)	1.0	5.0	16	100	28.6
6	K_2CO_3 (15%)	1.0	5.0	16	100	31.7
7	K_2CO_3 (15%)	1.0	3.5	16	100	31.9
8	K_2CO_3 (15%)	1.0	2.0	16	100	32.8
9[b]	K_2CO_3 (15%)	1.0	5.0	16	100	32.8
10	K_2CO_3 (15%)	0.5	5.0	16	100	33.9

[a]$Pd(PPh_3)_4$ was added to solution of **6**, then heated to 60 °C, prior to dimedone addition. [b]Dimedone was added to solution of **6**, then heated to 60 °C, prior to $Pd(PPh_3)_4$ addition.

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base was used (with or without a prior H_2O wash), the reaction did not go to completion (entries 1 and 2, Table 8). In all other experiments, the complete conversion of diallyl acid **19** was observed. K_2CO_3 wash (entries 6−9, Table 8) gave slightly cleaner reactions than NaOH (entries 3 and 4, Table 8) or $NaHCO_3$ (entries 5 and 6, Table 8). K_2CO_3 could be used at 1.0 equiv or 0.5 equiv (entry 10, Table 8), giving complete conversion and similar purity. Reduced catalyst loading of 3.5 mol % (entry 7, Table 8) or 2.0 mol % (entry 8, Table 8) also gave complete conversion. Inverting the addition sequence (adding dimedone, heating to 60 °C, and then adding catalyst) also gave complete conversion (entry 9, Table 8). Reducing the dimedone loading from 2.5 to 1.5 equiv did not have a detrimental effect on the reaction.

A priority for development of the workup of step 7a was to purge dimedone and related impurities. An initial charcoal filtration through a lenticular charcoal filter was incorporated into the workup to remove solids upon cooling the reaction mixture. Washing the filtrate with a weak base was investigated as a means of improving the purity. A $NaHCO_3$ (5% aq, 10 vol) wash was found to selectively extract dimedone and related impurities into the aqueous phase, while 7-COOH CBD remained in the organic phase.

With successful purging of the dimedone-related impurities achieved by the $NaHCO_3$ wash, further purification was necessary to remove catalyst-related impurities. Attempts to extract the 7-COOH CBD using a stronger base (NaOH) led to product degradation. Adding a basic ion-exchange resin (Purolite A500OH Plus; 250 wt %) to the organic phase after $NaHCO_3$ wash trapped the 7-COOH CBD. Reconstituting the resin in citric acid (10% aq, 3 vol) and EtOAc (3 vol) then filtering and concentrating the organic phase from filtrate to dryness yielded a 93% recovery of 7-COOH CBD, while the HPLC assay increased from 13.3 to 67.3%.

Dicyclohexylamine (DCHA) salt formation was investigated as a method of further purification. Addition of DCHA (1.2 equiv) to a solution of crude 7-COOH CBD in EtOAc (5 vol) yielded a high-viscosity oil, which could not be agitated. Addition of IPA (1 vol) solubilized the oil, and solid formation was observed after 16 h. A 97% yield of DCHA salt was obtained upon isolation of the off-white solid with an 85.1% HPLC purity. For the first time in the synthesis, solid product could reliably be obtained with concurrent purity uplift. Attempts to generate the DCHA salt without prior resin catch−release were unsuccessful.

A further purity uplift was required to achieve the target of ≥95.0% purity of 7-COOH CBD. A solvent screen for the DCHA salt indicated that MeOH was the sole candidate solvent investigated; however, 25 vol was required for complete solubilization at reflux. The salt was insoluble in MTBE, heptane, and H_2O. Crystallization was attempted using various antisolvents in combination with MeOH (25 vol) at 60 °C. Mixtures of MeOH/organic solvent (MeCN, EtOAc, heptane, MTBE) failed to yield solid. A MeOH/H_2O mixture yielded solid with the addition of 2 vol H_2O. However, despite an uplift in purity from 78.9 to 93.7%, only a 56% recovery was achieved. The low recovery likely resulted from the large volumes of MeOH required for initial solubilization of the DCHA salt. Attempts at crystallizing the 7-COOH CBD free acid using solvent/antisolvent combinations were also unsuccessful, with very low yields or negligible purity uplifts achieved.

MeOH/H_2O slurries of the DCHA salt using various ratios of both solvents (10 vol total) were investigated as an alternative to crystallization. Portions of the DCHA salt were suspended in the MeOH/H_2O mixtures, heated to 60 °C, stirred for 10 min, and then allowed to cool overnight. The precipitates were filtered and dried under vacuum. The results are summarized in Table 9. Overall, a better purity uplift was achieved with a greater proportion of MeOH than H_2O but with lower recovery.

Table 9. Results from MeOH/H_2O Slurries of 7-COOH CBD-DCHA Salt

entry	ratio of MeOH/H_2O	recovery (%)	purity before slurry (%)	purity after slurry (%)
1	90:10	57	78.9	93.4
2	70:30	64	78.9	85.2
3	50:50	86	78.9	83.3
4	30:70	89	78.9	80.5
5	10:90	93	78.9	79.6

A series of hot slurries were performed on the DCHA salt using MeOH, EtOH, and MeOH/H_2O mixtures (Table 10).

Table 10. Slurry Experiments for Purification of the 7-COOH CBD-DCHA Salt

entry	solvent (vol)	yield (%)	HPLC purity (%)
1	MeOH (5), H_2O (5)	93	86.3
2	MeOH (5), H_2O (5)	85	89.4
3	MeOH (5)	60	95.4
4	MeOH (2)	66	94.8
5	EtOH (3)	84	90.4

MeOH/H_2O mixtures and EtOH gave products that did not meet the target specifications of ≥95.0% (entries 1, 2, and 5, Table 10). Better results were achieved with MeOH, where purities of 94.8−95.4% were achieved (entries 3 and 4, Table 10). The only significant purity uplift was achieved using neat MeOH. Using 5 vol of MeOH gave a 60% yield of DCHA salt with an HPLC purity of 95.4%. Reducing to 2 vol MeOH improved the yield to 66%, with a HPLC purity of 94.8%. The latter yield and purity combined resulted in a 77% recovery of active 7-COOH CBD and represented the best balance between recovery and purity uplift.

Salt dissociation was performed on the slurry-purified DCHA salt by suspending the precipitate in a biphasic mixture of EtOAc (6 vol) and citric acid (10% aq, 6 vol), stirring for 10 min at 20−25 °C, and then separating the phases. The organic phase was concentrated back to ∼2 vol, codistilled with heptane to ∼2 vol, and then resuspended in heptane (4 vol). A white precipitate was obtained, which was filtered and dried under vacuum. The HPLC purity of the solid was 95.7%, and a quantitative yield of 7-COOH CBD was obtained. The QNMR assay of the 7-COOH CBD was 91.4%, with 6.5% EtOAc present. Further drying removed negligible amounts of EtOAc. Analysis by TGA showed a weight loss of 0.8% between 30 and 105 °C, which is likely due to the loss of solvent and/or volatile components. A weight loss of 4.6% was also observed between 105 and 158 °C. The stepwise weight loss and associated endotherm suggested that the material was solvated/hydrated.

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Table 11. Alternative Solvents for Salt Dissociation and Product Isolation

entry	solvent	procedure	outcome	HPLC purity (%)	QNMR assay (%)	residual solvent by QNMR (%)
1	EtOAc	concentrate solution of free acid to 2 vol, add heptane, concentrate to 2 vol, then add heptane	off-white solid obtained	95.7	91.4	5.1
2	*i*PrOAc		off-white solid obtained	95.0	97.8	1.6
3	MTBE		oiling out occurred upon initial concentration	-	-	-
4	MTBE	add heptane to a solution of free acid in MTBE, concentrate to 5 vol, cool and filter	off-white solid obtained	95.6	97.4	2.1

To reduce the residual EtOAc present in the isolated 7-COOH CBD, a heptane slurry was trialed, but 5.1% of EtOAc remained by QNMR. Isopropyl acetate was investigated as an alternative solvent to EtOAc for salt dissociation and product isolation (entry 2, Table 11). A quantitative yield of 7-COOH CBD was obtained, and the HPLC purity at 95.0% was slightly lower than that from EtOAc. Promisingly, however, the QNMR assay for the 7-COOH CBD obtained from *i*PrOAc was 97.8%, with only 1.6% *i*PrOAc remaining.

MTBE was also examined as an alternative solvent. Oiling out of the product occurred during product isolation upon concentrating a solution of 7-COOH CBD in MTBE to ∼2 vol, adding heptane, and concentrating back to 2 vol (entry 3, Table 11). To overcome the oiling out, heptane (4 vol) was added to the solution in 6 vol MTBE, followed by concentrating back to ∼5 vol (entry 4, Table 11). A white solid precipitated upon concentrating, and cooling to 0−5 °C yielded an off-white solid with analogous HPLC purity and QNMR assay to that from the *i*PrOAc experiment, and 2.1% MTBE remained. Overall, the MTBE procedure was the simplest and offered a good balance between product purity and minimization of residual solvent.

It was important to ensure that Pd levels of the final product were within ICH Q3D specification (<100 ppm). Analysis by ICP-MS indicated that 3266 ppm Pd remained after step 7a resin treatment, which reduced to 84.2 ppm Pd after salt formation and dissociation, and final product isolation.

Pilot Plant Campaign. Prior to scale-up to deliver the required 30 kg of 7-COOH CBD, a pilot-scale run-through of the process was carried out. A total input of 31 kg of CBD was processed. Since no standards of products for steps 1−5 had been isolated, quantitative yields could not be determined. All steps proceeded in near-quantitative uncorrected yields based on strip weight assay (Table 12), with telescoping of each step.

Table 12. Summary of Steps 1−5 Pilot Plant Campaign

step	crude input based on strip weight (kg)	uncorrected yield (%)	HPLC purity (% PA)
1	30.8	96	82−84
2	37.0	100	64−67
3	38.2	96	62−63
4	36.6	100	59[a]
5	43.0	107	34−35

[a]As mixtures of bromide **17** (34−35%) and chloride **21** (24−25%).

For step 1, typical product purities were 82−84%, with the remainder being composed of triallyl impurity **9**. Step 2 product was generated in a 64−67% purity, with ∼14% bis-epoxide **13** and ∼11% triallyl epoxide **14** formed. Epoxide ring-opening yielded allylic alcohol **3** with a 62−63% HPLC purity. The sequential mesylation/halogenation yielded a mixture of bromide **17** and chloride **21** with an overall purity of 59% in a 59:41 ratio of **17**:**21**.

Step 6a Pinnick oxidation also proceeded in a quantitative uncorrected yield. Purification by silica slurry removed ∼45% of the nonvolatile impurities, and a 94% recovery of diallyl acid **19** was achieved. Allyl deprotection proceeded in a quantitative uncorrected yield, with a >99% conversion. Purification of the crude 7-COOH CBD involved filtration through a lenticular carbon filter, which was washed with EtOAc (2.0 vol). After charcoal treatment, the mixture was concentrated to 3.5 vol and washed with $NaHCO_3$. Some 7-COOH CBD was still detected in the EtOAc (8.7% by peak area) after treatment with 250% by weight of resin, and additional resin (80% by weight) was added to further extract the product (1.8% by peak area remained). The resin was then agitated in a mixture of EtOAc−citric acid in the reactor, and after filtration, the resin was washed with EtOAc. After phase separation, the combined organics were assayed. Based on HPLC assay, the 7-COOH CBD content was 3.28 kg (81%) and the product had an HPLC purity of 57.8%. Based on strip weight assay, the solution contained 10.6 kg of nonvolatile material; therefore, the assayed weight of 7-COOH CBD as a percentage of nonvolatiles was 34.5% w/w. The purification procedure removed 35.8 kg (79%) of nonvolatile components from the crude product with a loss of 0.76 kg (19%) of the 7-COOH CBD.

For DCHA salt formation, the solution after ion-exchange purification was concentrated to ∼5 vol and diluted with IPA (1.0 vol). However, upon attempting to charge the DCHA, an immediate crystallization of an abundant white solid occurred in the feed vessel and lines that had previously been used to charge the IPA. A lab-scale experiment confirmed that adding DCHA to a vial containing IPA results in solid formation. The solid was potentially a solvate that redissolved in EtOAc.

As the feed line clogged with solid resulting from the reaction of DCHA with IPA, no DCHA had reached the reactor containing the solution of crude 7-COOH CBD. The solution was transferred to a clean reactor vessel, and DCHA (1.2 equiv) was charged. The mixture was stirred overnight at 20−25 °C, and the product was filtered off, washing with EtOAc (3 × 5 vol). The crude product was isolated in a 98% yield based on the HPLC assayed input of 7-COOH CBD. The recovery of the 7-COOH CBD based on the HPLC assay was 84%, and the product had an HPLC purity of 85.4%.

The purification of the DCHA salt using MeOH (2 vol) yielded 3.36 kg of solid with a 94.5% HPLC purity. After salt cracking using MTBE/citric acid, the solvent was switched to heptane (7 vol) for crystallization. The isolated product was dried at 30 °C. Although the main crystallization solvent was heptane, the removal of residual MTBE on drying was problematic and took 7 days to reach specification. A total of 1.99 kg of 7-COOH CBD was isolated with a 97.0% w/w

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QNMR assay and 95.1% HPLC purity. The yield of 7-COOH CBD from the purified DCHA salt was 90%.

For step 6a, a standard had been isolated for diallyl acid **19**, allowing quantitative HPLC analysis for yield determination through steps 1−6. A yield summary for step 6a onward is given in Table 13. For simplicity, the yields are based on the 7-COOH CBD contents of the products from each stage (correcting the content in the step 6a diallyl acid **19** for molecular weight). In summary, after the first 6 reaction steps (from an initial CBD input of 30.8 kg), the product contained 4.15 kg (12%) of 7-COOH CBD (corrected for molecular weight) along with approximately 40 kg of nonvolatile impurities. A further 18.5 kg of nonvolatile impurities were added after allyl deprotection (dimedone and catalyst-related). Therefore, the various purification steps gave a 48% recovery of the available 7-COOH CBD (1.99 kg from 4.15 kg) while removing 58 kg of other nonvolatile impurities.

Table 13. Summary of Pilot Plant Campaign

step	crude strip weight (kg)	7-COOH CBD HPLC assayed (kg)	yield (%)	HPLC purity (%)
steps 1−6a crude diallyl acid **19**	44.3	4.15[a]	12	39.7−44.2
diallyl acid **19** after silica repeat slurrying	26.8	3.85[a]	93	35.6−46.6
step 7a reaction	45.3	4.04	105	35.9
7-COOH CBD after resin treatment	9.48	3.28	81	57.8
7-COOH CBD crude DCHA salt	-	2.75	84	85.4
7-COOH CBD-DCHA salt after MeOH repeat slurrying	-	2.20	80	94.5
7-COOH CBD after salt dissociation	-	1.99	90	95.1
overall			6	

[a]Corrected for the molecular weight of the diallyl acid.

Production Campaign. For the production campaign to generate 30 kg of 7-COOH CBD, a total CBD input of 455.8 kg was processed. In step 1, the target addition temperature for allyl bromide was 20−25 °C and maintaining the mixture in this range led to extended addition times (8−13 h) compared with previous campaigns. Despite this, the level of triallyl CBD **9** in these batches (8−10%) was lower than in the pilot plant campaign (16−18%) (Table 14). The extended addition times were potentially beneficial in reducing the impurity level. The crude products were isolated in 97−100% yields based on the strip weight assay. Products showed HPLC purities of 89−90%, with the main impurity being triallyl adduct **9** (9−10%). For step 2 epoxidation, the product was isolated in a 97% yield based on crude strip weight. Diepoxide **13** (13.8−15.3%) and triallyl monoepoxide **14** (7.0−8.2%) were the main impurities. In the step 3 ring-opening, >99.0% conversion was achieved in 15 min. Allylic alcohol **3** was isolated in a 96−99% yield based on crude strip weight with HPLC purities of 66.7−67.5%. Yields were similar to those achieved in the pilot plant, while HPLC purities were higher, probably reflecting the higher input purity of the epoxide. Steps 4 (mesylation/halogenation) and 5 (NMO oxidation) also proceeded in quantitative uncorrected crude yields, with a 39−43% HPLC purity of aldehyde **18** generated.

Table 14. Summary of Steps 1−5 Production Campaign

step	crude input (kg)	uncorrected yield (%)	HPLC purity (% PA)
1	455.8	99	89−90
2	563.6	97	71−72
3	567.6	98	67−68
4	554.7	101	58−59[a]
5	645.2	100	39−43

[a]As a mixture of bromide **17** and chloride **21** (~56:44 ratio).

The step 6a oxidation and purification process was scaled up to the production plant in two batches (Table 15). Both batches gave acceptable conversions (98.5%, specification NLT = 98.0%) after 10−16 h. Post silica treatment, the weight of nonvolatiles in the first batch of product (198.3 kg) was significantly lower than the input weight (279.4 kg), indicating that the silica gel treatment had been effective in removing impurities. In the second batch, the weight of nonvolatiles in the product (251.0 kg) was only slightly lower than that in the input material (278.2 kg), indicating that the purification was less successful, possibly due to poorer mixing of the silica with the product solution in the second batch. Both batches showed similar HPLC assayed weights of product (35.4:38.9 kg). The combined assayed weight (74.3 kg) was higher than the anticipated weight extrapolated from the pilot plant results (70.3 kg), indicating that the first six steps of the full production campaign had gone well. Dividing the HPLC assay by the strip weight assay gave an assay result for product **19** as a percentage of nonvolatile components. In the production batches, the overall assay was 16.5% w/w compared to the 17.7% w/w achieved in the pilot plant, indicating that the purification had been somewhat less successful in the production batches. Both batches showed similar purities by HPLC analysis (36.8:39.6%).

Table 15. Production Campaign Summary of Step 6 Pinnick Oxidation

batch	input by SWA[a] (kg)	output by SWA (kg)	yield (%)	HPLC purity (%)	HPLC assay (% w/w)	assayed wt of **19** (kg)
1	279.4	198.3	68	36.8	3.71	35.4
2	278.2	251.0	87	39.6	3.99	38.9
total	557.6	449.3	78			74.3

[a]Strip weight assay (SWA).

Step 7a deprotection proceeded in quantitative yield in the pilot plant batches, while subsequent purification successfully removed ~65% of nonvolatile impurities at the loss of ~19% 7-COOH CBD. In the production campaign, the process was carried out in two batches, and the results are summarized in Table 16. Both batches gave complete conversion of **19** to 7-COOH CBD in 8−14 h. The total input to the step 7 reaction and purification batches was 449.3 kg based on the strip weight assay, and the total output was 170.6 kg. The purification process (charcoal filtration, $NaHCO_3$ wash, resin treatment) therefore removed 279 kg (62%) of nonvolatile impurities carried through from steps 1 to 6 and removed the dimedone and catalyst-related impurities generated in step 7. Based on the HPLC assay, the input material contained 74.3 kg of **19** and the product contained 57.9 kg of 7-COOH CBD, representing a 96% yield on reaction and purification. This

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Table 16. Production Campaign Step 7a Allyl Deprotection

	assayed input		reaction and workup				DCHA salt		MeOH reslurry		salt crack	
batch	SWA[a] (kg)	HPLC (kg)	crude output (kg)	yield (%)	HPLC purity (%)	assayed wt (kg)	output (kg)	HPLC purity (%)	output (kg)	HPLC purity (%)	output (kg)	HPLC purity (%)
1	198.3	35.4	80.1	49.8	59.8	29.4	73.8	88.2	52.9	96.2	32.8	96.8
2	251.0	38.9	90.5	44.5	57.0	28.6						

[a]Strip weight assay (SWA).

Table 17. Yield Summary for the Production Campaign of 7-COOH CBD Manufacture

step	input	wt (kg)	output	wt (kg)	yield (%)	HPLC purity (%)
1	CBD	455.8	1	563.6	99	88.9−90.1
2	1	563.6	2	567.6	97	71.2−72.3
3	2	567.6	3	554.7	98	66.7−67.5
4a	3	554.7	17/21 (bromide/chloride mixture)	645.2	101	57.9−59.0
5a	17/21 (bromide/chloride mixture)	645.2	18	557.6	100	39.3−43.3
6a	18	557.6	19	449.3	78	36.8−39.6
7a	19	449.3	crude 7-COOH CBD	170.6	47	57.0−59.8
DCHA salt	crude 7-COOH CBD	170.6	crude 7-COOH CBD-DCHA	73.8	28	88.2
MeOH reslurry	crude 7-COOH CBD-DCHA	73.8	purified 7-COOH CBD-DCHA	52.9	72	96.2
salt crack	purified 7-COOH CBD-DCHA	52.9	7-COOH CBD	32.8	95	96.8
total					6.6	

was higher than the 88% yield recorded in the pilot plant batch. Products had HPLC purities of 57.0−59.8%.

Further purification of the 7-COOH−CBD via salt formation with DCHA was performed, and from the production campaign, the two batches of crude 7-COOH CBD were combined for the salt formation step. Prior to the production-scale batch, a series of use-test experiments were carried out. From the previous pilot plant campaign, a 34% yield based on strip weight assayed input of 7-COOH CBD was anticipated. In the lab use tests, using 7-COOH CBD solutions from the production batches (weighted average), a lower yield was achieved (27%), even when lowering the IPA input to the crystallization mixture. Increasing the DCHA input from 1.2 to 1.4 equiv did increase the yield to 30%, but a further increase to 1.6 equiv led to a decrease in yield (27%). Based on these results, 1.4 equiv of DCHA was used in the bulk batch.

The two batches of crude 7-COOH CBD were combined in the plant vessel, concentrated to 5 vol, diluted with IPA, and treated with DCHA (1.4 equiv). No difficulties were encountered with the operability of the process, although the yield (28% based on wet weight and LOD) was slightly lower than anticipated from the lab use test (30%). As expected, a significant uplift in HPLC purity was achieved (from ∼58 to 88%).

After MeOH slurry, the isolated yield (72%) was slightly higher than that in the pilot-scale campaign (70%) and the HPLC purity of the product (96.2%) was also higher than anticipated, which exceeded the specification for the final product purity (≥95.0%). After salt crack and solvent swap into heptane, crystallization led to a mixture that was very slow to filter and wash with heptane. Despite being left in the filter overnight with the vacuum on to remove as much mother liquor as possible, the wet weight of the product was very high (184.6 kg). The product was dried at 30 °C/4 mbar for 8 days, yielding 32.79 kg (95%) of 7-COOH CBD with a final MTBE content of 0.94%w/w by QNMR (specification ≤2.0%w/w). The yield was higher than that achieved in the previous pilot plant-scale campaign (90%) but matched those of previous laboratory experiments.

The yield summary given in Table 17 is based on the strip weight assayed outputs of steps 1−7 and on the isolated yields after purification. As no reference standards for intermediates from steps 1 to 5 were available, quantitative HPLC analysis of the products from these steps was not possible. Based on the strip weight assay, the yields from these steps were effectively quantitative. An HPLC assay of **19** gave an overall yield for the first six steps of 74.3 kg (12.1%), which compares to the 11.4% achieved in the pilot plant campaign. The HPLC reference standard for 7-COOH CBD appeared to have partially decomposed, and therefore HPLC assayed yields for step 7 were not possible. Based on the assayed weight of **19** (74.3 kg) and the final weight of 7-COOH CBD (32.79 kg), the yield for these last steps (deallylation and purification) was 54%. The overall yield from the production campaign (32.79 kg of 7-COOH CBD from 455.8 kg of CBD, 6.6%) was slightly higher than that achieved in the previous pilot plant campaign (1.987 kg of 7-COOH CBD from 30.8 kg of CBD, 5.9%).

CONCLUSIONS

The synthesis of CBD metabolite 7-COOH CBD was achieved with high purity at a multikilogram scale. Successful demonstration of a single protecting group strategy meant that a laboratory-scale synthetic route could be reduced from 9 to 7 steps. After extensive development work, all steps of the process were successfully scaled to both the pilot and production scales. On the production scale, 456 kg of CBD was processed, and all steps proceeded in quantitative uncorrected yield. As purification was not feasible for steps 1−5a, isolation of pure 7-COOH CBD was a major challenge. Silica slurry after the Pinnick oxidation reduced the crude weight of product, and the developed workup procedure post allyl deprotection involving sequential charcoal filtration, base wash, and resin treatment gave a 96% yield of the available 7-COOH CBD while removing 279 kg of nonvolatile impurities. A further purity uplift via DCHA salt formation, MeOH repeat

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slurrying, and salt dissociation yielded 32.8 kg of 7-COOH CBD with a 96.8% HPLC purity.

EXPERIMENTAL SECTION

Unless otherwise indicated, all reagents and solvents were purchased from commercial suppliers and used without further purification. For steps 1−7a, equivalents and solvent volumes were relative to the uncorrected input mass of the limiting reagent determined by strip weight assay (SWA). HPLC analysis was performed using a Phenomenex Luna 3 μm C18(2) T 150 mm × 4.6 mm column with H_2O + 0.1% HCO_2H and MeCN + 0.1% HCO_2H as mobile phases. ^1H NMR spectra were obtained on a Bruker Avance NEO 500 MHz NMR spectrometer.

Synthesis of (1*R*,2*R*)-2′,6′-Bis(allyloxy)-5-methyl-4′-pentyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-1,1′-biphenyl (1). CBD (227.59 kg, 724 mol, 1.0 equiv) in MeCN (1140 L, 5.0 vol) was added to a stirred suspension of Cs_2CO_3 (942 kg, 2.89 mol, 4.0 equiv) and allyl bromide (193.4 kg, 1600 mol, 2.2 equiv) in MeCN (910 L, 4.0 vol), ensuring the temperature remained between 20 and 25 °C. The mixture was stirred at 20−25 °C for 3 h and then filtered. The precipitate was washed with MeCN (600 L, 2.6 vol), and the filtrate was concentrated *in vacuo* to 1.25 vol (280 L). The solution was codistilled with MeCN (460 L, 2.0 vol) *in vacuo* to 1.25 vol (280 L), the solution was drummed off, and the reactor was rinsed with MeCN (230 L, 1.0 vol) and then combined with the bulk solution. The solution (39.6% w/v by SWA, 285.1 kg nonvolatiles, 100% uncorrected yield, 88.9% HPLC purity) was used without purification.

Synthesis of (1*S*,4*R*,5*R*,6*R*)-5-(2,6-Bis(allyloxy)-4-pentylphenyl)-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo-[4.1.0]heptane (2). The crude solution of **1** in MeCN (720 kg@39.6% w/v by SWA = 285.1 kg, 723 mol, 1.0 equiv) and MeCN (2280 L, 8 vol) was charged to a reactor containing Na_2CO_3 (91.8 kg, 866 mol, 1.2 equiv). Peracetic acid (40% w/w in AcOH, 165.4 kg, 870 mol, 1.2 equiv) was added, ensuring the internal temperature did not exceed 30 °C. The mixture was stirred for 6 h, and then H_2O (1140 L, 4 vol) and sodium metabisulfite (40% aq, 570 L, 2.0 vol) were added at 20−22 °C. The biphasic mixture was stirred for 15 min at 20−25 °C, and then the phases were separated. The organic phase was washed with NaOH (10% w/w aq, 570 L, 2 vol) and brine (25% w/w aq, 570 L, 2 vol) and then concentrated to a minimum volume. After codistilling with MeCN (2 × 570 L, 2 × 5 vol) back to a minimum volume, MeCN (2 vol) was added, and the solution (34.5% w/w by SWA, 292 kg nonvolatiles, 98% uncorrected yield, 71.3% HPLC purity) was used without purification.

Synthesis of (1*R*,2*R*,3*R*)-2-(2,6-Bis(allyloxy)-4-pentylphenyl)-6-methylene-3-(prop-1-en-2-yl)cyclohexanol (3). A solution of HCl in MeCN (231 kg@2.80% w/w, 177 mol, 0.25 equiv) was added to a reactor containing MeCN (730 L, 2.5 vol) and the solution of **2** in MeCN (843 kg@34.5% w/w by SWA = 290.8 kg, 708 mol, 1.0 equiv) at 20−25 °C. The mixture was stirred for 15 min and then quenched with $NaHCO_3$ (2.5% w/w aq, 730 L, 2.5 vol). The organic phase was washed with brine (25% w/w aq, 580 L, 2 vol) and then concentrated to a minimum volume. MeCN (580 L, 2.0 vol) was added, and the solution was concentrated to a minimum volume. MeCN (580 L, 2.0 vol) was added, and the solution (38.4% w/w by SWA, 279.6 kg nonvolatiles, 96% uncorrected yield, 66.7% HPLC purity) was used without purification.

Synthesis of (1*R*,2*R*)-2′,6′-Bis(allyloxy)-5-bromomethyl-4′-pentyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-1,1′-biphenyl (17) and (1*R*,2*R*)-2′,6′-Bis(allyloxy)-5-chloromethyl-4′-pentyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-1,1′-biphenyl (21). DMAP (4.2 kg, 34 mol, 0.05 equiv), MeCN (1400 L, 5.0 vol), and the solution of **3** in MeCN (728 kg@38.4% w/w SWA = 279.6 kg, 681 mol, 1.0 equiv) were charged to a reactor and then cooled to 0−5 °C. MsCl (195.2 kg, 1704 mol, 2.5 equiv) and then Et_3N (168.9 kg, 1669 mol, 2.45 equiv) were added, maintaining the temperature below 5 °C. After holding for 15 min, the mixture was warmed to 20−25 °C and stirred for 4 h. LiBr (295.8 kg, 4406 mol, 5.0 equiv) was added, and the mixture was heated to 60−65 °C. After stirring for 13 h, the mixture was cooled to 20−25 °C. EtOAc (560 L, 2 vol) was added, and the mixture was washed with H_2O (3 vol) and brine (25% w/w aq, 2 × 560 L, 2 × 2 vol) and then concentrated to a minimum volume. MeCN (420 L, 1.5 vol) was added, and the mixture was concentrated to a minimum volume. MeCN (560 L, 2.0 vol) was added, and the solution (36.1% w/w by SWA, 324.2 kg nonvolatiles, 101% uncorrected yield, 27.7% bromide **17** and 30.2% chloride **21** by HPLC) was used without purification.

Synthesis of (1*R*,2*R*)-2′,6′-Bis(allyloxy)-5-formyl-4′-pentyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydro-1,1′-biphenyl (18). Anhydrous NMO (281 kg, 2399 mol, 3.5 equiv) and MeCN (810 L, 2.5 vol) were charged to a reactor and then heated to 40−45 °C. The MeCN solution of **17**/**21** mixture (898 kg@36.1% w/w by SWA = 324.2 kg, 685 mol, 1.0 equiv) was charged for 7 h at 40−45 °C, and the charge line was rinsed with MeCN (160 L, 0.5 vol). The mixture was stirred at 40−45 °C for 18 h and then cooled to 15−20 °C. The solution was washed with HCl (4% w/w aq, 810 L, 2.5 vol) and brine (25% w/w aq, 2 × 650 L, 2 × 2 vol), and the organic phase (35.8% w/w by SWA, 278.2 kg nonvolatiles, 99% uncorrected yield, 43.3% HPLC purity) was used without purification.

Synthesis of (1*R*,6*R*)-2′,6′-Diallyloxy-4′-pentyl-6-(prop-1-en-2-yl)-1,4,5,6-tetrahydro-[1,1′-biphenyl]-3-carboxylic Acid (19). To the solution of **18** in MeCN (587 kg@47.6% w/w SWA = 279.4 kg, 684 mol, 1.0 equiv) was added *t*-BuOH (560 L, 2 vol), DMSO (80.2 kg, 1026 mol, 1.5 equiv), and KH_2PO_4 (20% w/w aq, 560 kg, 2 vol). $NaClO_2$ (25% w/w aq, 371 kg, 1026 mol, 1.5 equiv) was added at 15−35 °C. The mixture was stirred at 20−25 °C for 11.5 h and then quenched with sodium metabisulfite (40% w/w aq, 377 kg, 1 vol) at 15−35 °C. The phases were separated, and the organic phase was washed with brine (25% w/w aq, 2 × 560 L, 2 × 2 vol) and then concentrated *in vacuo* to 2 vol (∼560 L). EtOAc (280 L, 1 vol) and heptane (840 L, 3 vol) were added, followed by silica gel (40−63 μm, 560 kg, 200 wt %). The slurry was stirred for 2 h at 15−25 °C and then filtered, and the filter cake was washed with a heptane/EtOAc mixture (3:1, 3.9 vol, 1080 L). The filtrate was concentrated to ∼1.3 vol, EtOAc (2 vol) was added, and the solution (20.8% w/w by SWA, 198.3 kg nonvolatiles, 68% uncorrected yield, 36.8% HPLC purity) was used without further purification.

Synthesis of 7-COOH CBD. The EtOAc solution of **19** (954 kg@20.8% w/w SWA = 198.3 kg (35.4 kg active **19**), 467 mol, 1.0 equiv) and EtOAc (400 L, 2.0 vol) were charged to a dry reactor under N_2. K_2CO_3 (15% w/w aq, 190 L, 234 mol, 0.5 equiv) was added, and the mixture was agitated for 25 min at 15−20 °C. The aqueous phase was separated, and then

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$Pd(PPh_3)_4$ (10.7 kg, 9.259 mol, 2 mol %) was charged to the organic phase, and the mixture was agitated at 15−20 °C for 20 min. Dimedone (99.2 kg, 708 mol, 1.5 equiv) was charged, and the mixture was warmed to 60−65 °C for 6 h. After 14 h, reaction completion was confirmed before the solution was cooled to 0−5 °C and circulated through a lenticular carbon filter for 1 h. The filter was washed with EtOAc (400 L, 2.0 vol), and the filtrate was concentrated *in vacuo* to 3.5 vol (∼700 L). The solution was warmed to 60−65 °C, and aqueous $NaHCO_3$ (7.5% w/w aq, 1,500 L, 3.5 equiv) was added for 9 h. The mixture was agitated at 60−65 °C for 1 h and then cooled to 20−25 °C. The phases were separated, and the organic phase was washed with a further portion of $NaHCO_3$ (7.5% w/w aq, 1500 L, 3.5 equiv). Purolite A500OH Plus Resin (500 kg, 250% w/w) and EtOAc (600 L) were charged to the organic phase and stirred at 15−20 °C. After 7 h, the suspension was filtered, and the solids were washed with EtOAc (1440 L, 7.2 vol). The resin was returned to the reactor, and citric acid (10% w/w aq, 600 L, 3.0 vol) and EtOAc (1200 L, 6.0 vol) were charged. The mixture was agitated at 15−20 °C for 30 min and then filtered, and the solids were washed with EtOAc (960 L, 4.8 vol). The phases were separated in the mother liquor to yield the crude 7-COOH CBD as a solution in EtOAc (29.4 kg assayed 7-COOH CBD, quant. yield, 59.8% HPLC purity).

The preparation of 7-COOH CBD was repeated in a second batch starting from 228.25 kg of CBD and yielding 28.6 kg (assayed) of 7-COOH CBD with an HPLC purity of 57.0%.

The combined batches of crude 7-COOH CBD solution (170.6 kg by strip weight assay, 495 mol, 57.9 kg active 7-COOH CBD by HPLC assay) in EtOAc were concentrated *in vacuo* to 4.5 vol (770 L), and then IPA (170 L, 1.0 vol) was charged. DCHA (125.7 kg, 693 mol, 1.4 equiv) was added for 60 min at 10−21 °C, and the mixture was agitated for 18 h at 20−25 °C. The product was filtered, and the filter cake was washed with EtOAc (1850 L, 10.8 vol). The filter cake (73.8 kg) and MeOH (148 L, 2 vol) were charged to a clean reactor, and the suspension was heated to 60−65 °C for 3 h and then held for 4 h. The mixture was cooled to 20−25 °C for 2 h and then to 0−5 °C for a further 2 h. After holding at 0−5 °C for 1 h, the product was filtered, washed with MeOH (2 × 74 L, 2 × 1 vol), and dried at 30 °C for 16 h. The dried, purified 7-COOH CBD-DCHA salt (52.9 kg, 100.6 mol, 1.0 equiv), MTBE (317 L, 6.0 vol), and aqueous citric acid (10% w/w aq, 317 L, 6.0 vol) were charged to a clean reactor and agitated at 20−25 °C for 80 min. The phases were separated, and the organic phase was washed with H_2O (2 × 106 L, 2 × 2 vol) and then polish-filtered. Heptane (423 L, 8.0 vol) was charged, and the mixture was concentrated *in vacuo* to 6 vol (320 L). Heptane (106 L, 2.0 vol) was charged, and the mixture was cooled to 15−25 °C, held for 90 min, and then cooled to 0−5 °C. The mixture was held at 0−5 °C for 1.5 h and then filtered and washed with heptane (2 × 106 L, 2 × 2 vol). The solid was dried for 8 days at 30 °C and 3 mbar to give 7-COOH CBD (32.79 kg, 54% yield from the total input of **19**, 96.8% HPLC purity) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.2−11.6 (br s, 1H), 8.93 (s, 1H), 6.61 (s, 1H), 6.06 (s, 1H), 4.48 (d, J = 17.0 Hz, 2H), 3.99−3.91 (m, 1H), 3.02−2.93 (m, 1H), 2.42−2.28 (m, 3H), 2.23−2.13 (m, 1H), 1.82−1.74 (m, 1H), 1.66−1.55 (m, 4H), 1.48 (quint., J = 7.5 Hz, 2H), 1.34−1.21 (m, 4H), 0.86 (t, J = 7.1 Hz, 3H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.4c00093.

HPLC methods, example traces, ^{1}H NMR of 7-COOH CBD, and TGA thermogram (PDF)

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) ElSohly, M. Chemical Constituents of Cannabis. In *Cannabis and Cannabinoids: Pharmacology, Toxicology and Therapeutic Potential*; Haworth Press: New York, 2002.

(2) Price, K. N.; Thompson, A. M.; Shi, V. Y. 28 - Complementary and Alternative Medicine. In *A Comprehensive Guide to Hidradenitis Suppurativa*; Shi, V. Y.; Hsiao, J. L.; Lowes, M. A.; Hamzavi, I. H., Eds.; Elsevier: Philadelphia, 2022; pp 273−282.

(3) Bonn-Miller, M. O.; ElSohly, M. A.; Loflin, M. J. E.; Chandra, S.; Vandrey, R. Cannabis and cannabinoid drug development: evaluating botanical versus single molecule approaches. *Int. Rev. Psychiatry* **2018**, *30*, 277−284.

(4) Mechoulam, R. *Cannabinoids as Therapeutic Agents*; CRC Press: FL, 2019.

https://doi.org/10.1021/acs.oprd.4c00093
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

(5) Mechoulam, R.; Hanuš, L. R. A Historical Overview of Chemical Research on Cannabinoids. *Chem. Phys. Lipids* **2000**, *108*, 1−13.
(6) Mechoulam, R.; Shvo, Y. Hashish—I: The Structure of Cannabidiol. *Tetrahedron* **1963**, *19*, 2073−2078.
(7) Mechoulam, R.; Gaoni, Y. The Absolute Configuration of Delta-1-tetrahydrocannabinol, the Major Constituent of Hashish. *Tetrahedron Lett.* **1967**, *8*, 1109−1111.
(8) Ujváry, I.; Hanuš, L. Human Metabolites of Cannabidiol: A Review on Their Formation, Biological Activity, and Relevance in Therapy. *Cannabis Cannabinoid Res.* **2016**, *1*, 90−101.
(9) Jiang, R.; Yamaori, S.; Takeda, S.; Yamamoto, I.; Watanabe, K. Identification of Cytochrome P450 Enzymes Responsible for Metabolism of Cannabidiol by Human Liver Microsomes. *Life Sci.* **2011**, *89*, 165−170.
(10) Beers, J. L.; Fu, D.; Jackson, K. D. Cytochrome P450-Catalyzed Metabolism of Cannabidiol to the Active Metabolite 7-Hydroxy-Cannabidiol. *Drug Metab. Dispos.* **2021**, *49*, 882−891.
(11) Beers, J. L.; Authement, A. K.; Isoherranen, N.; Jackson, K. D. Cytosolic Enzymes Generate Cannabinoid Metabolites 7-Carboxycannabidiol and 11-Nor-9-carboxytetrahydrocannabinol. *ACS Med. Chem. Lett.* **2023**, *14*, 614−620.
(12) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000OtherR.pdf.
(13) Whalley, B.; Stott, C.; Gray, R.; Jones, N. The Human Metabolite of Cannabidiol, 7-Hydroxyl Cannabidiol, but not 7-Carboxy Cannabidiol, is Anticonvulsant in the Maximal Electroshock Seizure Threshold Test (MEST) in Mouse *American Epilepsy Society Meeting Abstract* 2017, p 435.
(14) Shea, K. J.; Kim, J.-S. Influence of Strain on Chemical Reactivity. Relative Reactivity of Torsionally Distorted Double Bonds in MCPBA Epoxidations. *J. Am. Chem. Soc.* **1992**, *114*, 3044−3051.
(15) Hanuš, L. O.; Tchilibon, S.; Ponde, D. E.; Breuer, A.; Frideb, E.; Mechoulam, R. Enantiomeric Cannabidiol Derivatives: Synthesis and Binding to Cannabinoid Receptors. *Org. Biomol. Chem.* **2005**, *3*, 1116−1123.
(16) Déziel, R. Deprotection of Allylic Esters and Ethers. U.S. Patent US4788282A, 1985.
(17) Tsukamoto, H.; Suzuki, T.; Kondo, Y. Remarkable Solvent Effect on Pd(0)-Catalyzed Deprotection of Allyl Ethers Using Barbituric Acid Derivatives: Application to Selective and Successive Removal of Allyl, Methallyl, and Prenyl Ethers. *Synlett* **2007**, *2* (20), 3131−3136.
(18) Beugelmans, R.; Bourdet, S.; Bigot, A.; Zhu, J. Reductive Deprotection of Aryl Allyl Ethers with $Pd(PPh_3)_4/NaBH_4$. *Tetrahedron Lett.* **1994**, *35*, 4349−4350.
(19) Konda, S. G.; Humne, V. T.; Lokhande, P. D. Rapid and Selective Deallylation of Allyl Ethers and Esters using Iodine in Polyethylene Glycol-400. *Green Chem.* **2011**, *13*, 2354−2358.
(20) Thomas, R. M.; Reddy, G. S.; Iyengar, D. S. An Efficient and Selective Deprotection of Allyl Ethers by a $CeCl_3.7H_2O$-NaI System. *Tetrahedron Lett.* **1999**, *40*, 7293−7294.
(21) Ishizaki, M.; Yamada, M.; Watanabe, S.; Hoshino, O.; Nishitani, K.; Hayashida, M.; Tanaka, A.; Hara, H. Palladium Charcoal-Catalyzed Deprotection of O-Allylphenols. *Tetrahedron* **2004**, *60*, 7973−7981.
(22) Ganguly, N. C.; Dutta, S.; Datta, M. Mild and Efficient Deprotection of Allyl Ethers of Phenols and Hydroxycoumarins using a Palladium on Charcoal Catalyst and Ammonium Formate. *Tetrahedron Lett.* **2006**, *47*, 5807−5810.

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