ORGANIC PROCESS RESEARCH & DEVELOPMENT
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An Easy, Convenient, and Safe Process for the Synthesis of Lofexidine Hydrochloride

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Cite This: https://doi.org/10.1021/acs.oprd.0c00453 Read Online

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ABSTRACT: A very efficient, cost-effective, and easily scalable process for the synthesis of lofexidine hydrochloride (**1**), an alpha 2-adrenergic receptor agonist used for treating opioid withdrawal is presented. Process development allows the preparation of lofexidine hydrochloride (**1**) through a one-pot amidation/imidazoline ring formation reaction, starting from ethyl 2-(2,6-dichlorophenoxy)propionate (**13**) and ethylenediamine (**5**) by the action of titanium isopropoxide. The required intermediate ethyl 2-(2,6-dichlorophenoxy)propionate (**13**) can efficiently be obtained through *O*-alkylation of 2,6-dichlorophenol (**2**) with ethyl 2-chloropropionate (**12**) using potassium carbonate as an acid-scavenger agent.

KEYWORDS: *phenol O-alkylation, titanium isopropoxide, cyclization agents, imidazoline ring formation, process optimization*

1. INTRODUCTION

Lofexidine hydrochloride (**1**) (Figure 1) is an antihypertensive medication currently used to treat physical and psychological symptoms of opioid dependence.

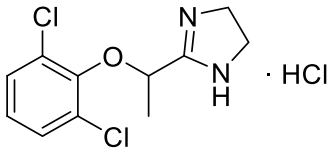

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Figure 1. Chemical structure of lofexidine hydrochloride.

Structurally similar to clonidine (Figure 2), it is a selective alpha 2-adrenergic receptor agonist that acts by reducing

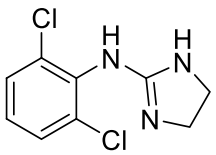

Figure 2. Chemical structure of clonidine.

norepinephrine release and by moderating the symptoms of noradrenergic hyperactivity triggered by opioid withdrawal.[1]

A limited number of synthetic strategies for the preparation of lofexidine hydrochloride (**1**) are described in the literature; these syntheses are multistep processes where the product is always obtained in rather low yields. In addition, the starting materials generally employed are both expensive and not easily available reagents[2,3] (Scheme 1); moreover, some of these reagents require special precautions while handling as they react violently with moisture and air[4,5] (Scheme 2).

Enantioselective syntheses have also been reported for the preparation of either the (*S*) or (*R*) form of lofexidine, but interest on the market in optically pure material has been close to nil thus far.

As can be inferred, unfortunately, the described synthetic pathways developed between the end of 60s and the beginning of 80s are applicable only on a small scale, and they are not suitable for scaling-up of the process for multi-kilogram productions.

Our R&D group was appointed to develop an improved process, when compared to prior literature examples, that is able to deliver lofexidine hydrochloride (**1**) in a scalable and safe manner with reduced costs.

To perform this task, we began by examining the already described procedures, and we focused in particular on the synthesis of Biedermann et al.,[6−8] which was a promising starting point.

The proposed synthetic pathway (Scheme 2) goes through the first intermediate, (*R*) or (*S*) ethyl 2-(2,6-dichlorophenoxy)propionate (**4**), isolated after *O*-alkylation of 2,6-dichlorophenol (**2**) with enantiopure ethyl 2-chloropropionate (**3*R*** or **3*S***) performed in methylethylketone (MEK) with potassium ethoxide or methoxide as the base, with a reported yield of approximately 56%. In the following step, this intermediate was reacted with ethylenediamine (**5**) at room temperature, and the resulting product was amide **6** with a yield of approximately 76%. Finally, the use of titanium tetrachloride ($TiCl_4$) as a cyclization reagent allowed for the isolation of enantiomerically pure lofexidine (**7*R*** or **7*S***) in 65%

Received: October 7, 2020

https://doi.org/10.1021/acs.oprd.0c00453
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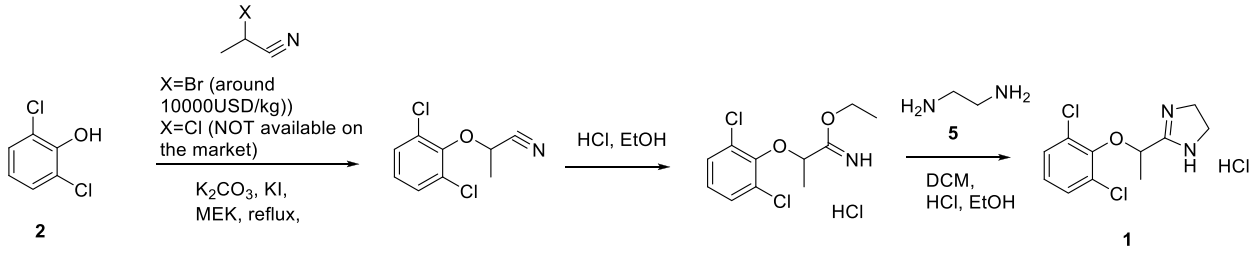
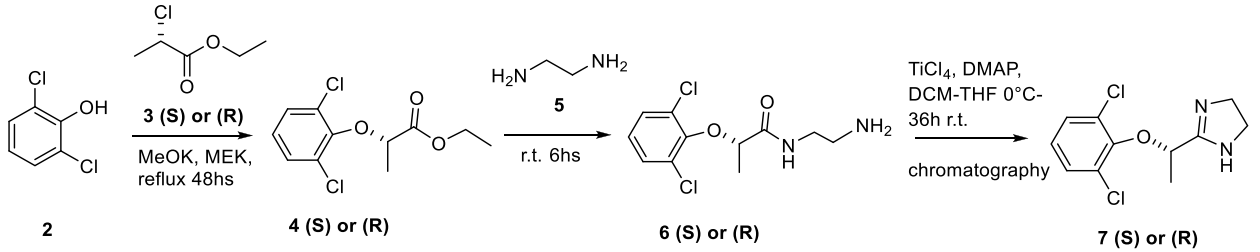
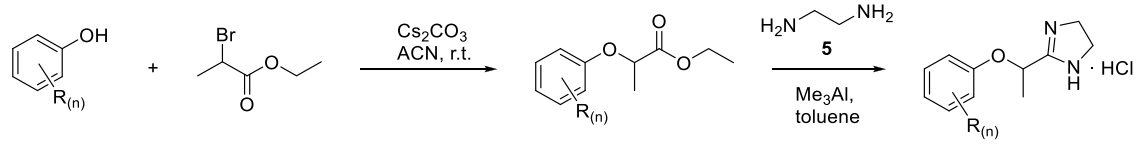
Scheme 1. First Published Synthetic Approach to Obtain Lofexidine Hydrochloride (Overall Yield of 35%)



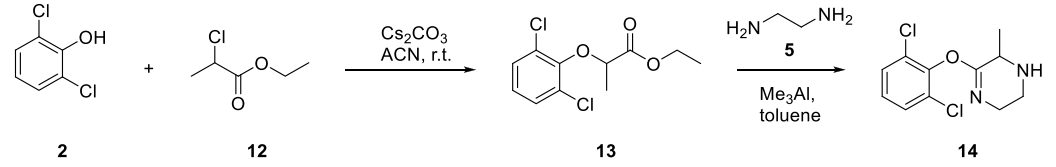
Scheme 2. Approaches of Biedermann et al.



Scheme 3. Alternative Synthetic Approach



Scheme 4. Application of the Alternative Route



yield (note that the process included purification by column chromatography).

This process, despite the low reported yields and the use of a corrosive cyclization agent ($TiCl_4$), is a valid starting point to develop an improved procedure to prepare lofexidine, especially when considering the cost of raw materials and ease of the synthetic pathway.

Starting off with the project, a recent publication appeared useful to us:[9] a simplified procedure to obtain alkylate phenols is described (Scheme 3). In this paper, the formation of intermediates of general formula **10** is reported via an *O*-alkylation reaction of phenols (of general formula **8**) using 2-bromoethylpropionate (**9**) with cesium carbonate suspended in acetonitrile at room temperature. The reaction is very fast, and complete conversion can be achieved within 1 h at RT.

From an industrial point of view, a major drawback of this process is the use of cesium carbonate: it is not a common inorganic base and is quite expensive.

We tested this methodology in the alkylation of 2,6-dichlorophenol (**2**) with ethyl 2-chloropropionate (**12**), which is a less expensive (its cost is approximately 10 USD/kg) alternative to the bromo derivate. Unfortunately, we were not able to isolate or observe the formation of the desired product at room temperature over a short time (a few hours); nevertheless, increasing the reaction time to a few days yielded the expected product with a quantitative conversion.

Next, we explored the cyclization reagent, hoping to find an alternative to the use of $TiCl_4$. We found another interesting paper, reporting a one-pot reaction of alkylated phenols (of general formula **10**) with ethylenediamine (**5**) in the presence of trimethylaluminum.[9,10] The reaction is carried out in toluene at reflux and gives access to imidazoline rings (**11**) in a very high molar yield (>90%) (Scheme 3).

Unfortunately, trimethylaluminum is pyrophoric and reacts violently with water or moisture in the atmosphere, generating methane.[11] The use of this reactant on a production scale would be rather complex and would require some economical investments to implement a proper system to mitigate hazards related to the handling of the substance and its flammable byproducts.

Despite the apparent problems that may affect this chemistry, it was decided to follow the proposed synthetic step because it seemed to be the most promising and was characterized by an advantageous design. However, when applying these conditions to our system, much to our surprise, lofexidine could not be obtained from **13** using trimethylaluminum as a cyclization reagent, but the reaction quantitatively yields an unexpected product identified as (5-(2,6-dichlor-

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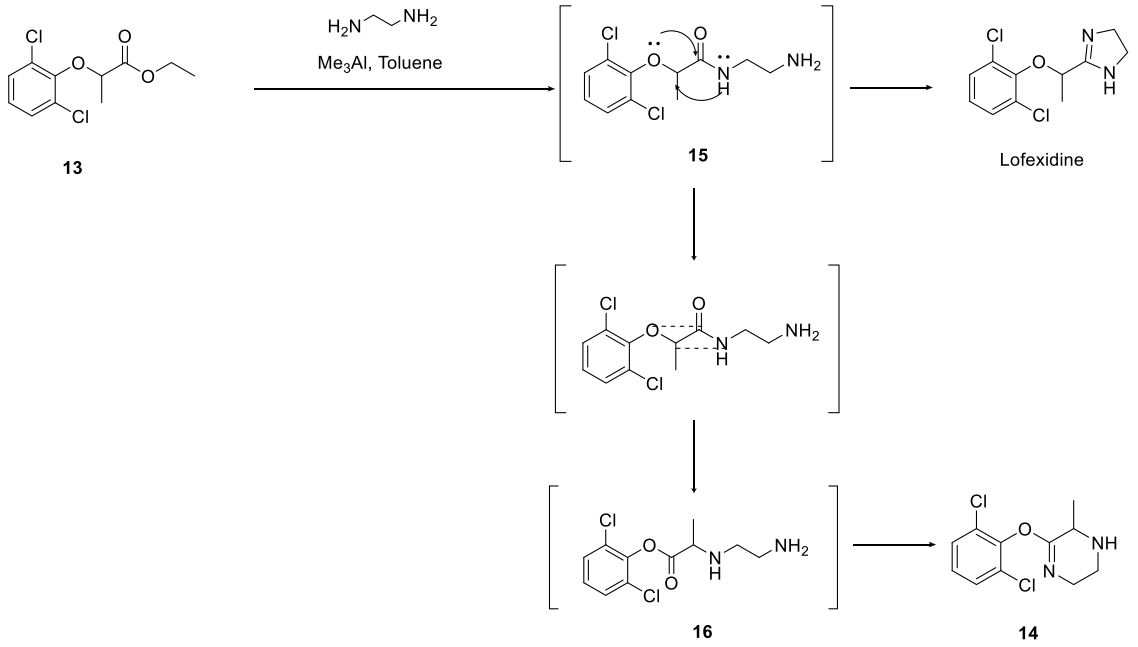
Scheme 5. Hypothetical Mechanism of the Formation of Byproduct 14



ophenoxy)-6-methyl-1,2,3,6-tetrahydropyrazine) (**14**) (Scheme 4).

A plausible mechanism for the formation of product **14** is described in Scheme 5. The substrate undergoing cyclization is ester **16**, which is generated in turn from amide **15** as a result of a dyotropic rearrangement.[12] In these types of reactions, two sigma bonds simultaneously migrate intramolecularly; in our case, this rearrangement results in a different cyclization substrate. Intermediate **16** has not been isolated or characterized; therefore, its formation can only be considered a hypothesis.

Despite these drawbacks, the proposed process flow, very similar to the Biedermann et al. process that uses $TiCl_4$, was considered a potentially valid methodology to prepare lofexidine. Therefore, we set out to optimize the synthetic pathway, both the alkylation and the cyclization step, to obtain the target compound in a scalable fashion.

2. PROCESS DEVELOPMENT

2.1. First Step. Considering the limitations already discussed on the use of cesium carbonate on a large scale, a more common and cheaper alkaline carbonate salt, i.e., potassium carbonate, was considered as an alternative.

However, the first attempt at reproducing the alkylation step of 2,6-dichlorophenol (**2**) with ethyl 2-chloropropionate (**12**) with potassium carbonate in acetonitrile again resulted in very slow kinetics (just as with cesium carbonate). We verified that, to quantitatively convert to alkylated phenol, several days are needed at high temperature, close to the solvent boiling point. Some experiments were performed to determine an alternative solvent (a polar aprotic solvent) to replace acetonitrile, which could speed up the reaction (Table 1). Ketones were found to give good results when applying the procedure with potassium carbonate used as an acidity scavenger. On the other hand, hydrocarbons (both aliphatic and aromatic) did not give acceptable results when tested as alternatives. Taking into account these results, we selected methylisobutylketone (MIBK) as the solvent, with K_2CO_3 as the base (entry 4).

Table 1. Preliminary Screening Experiments

entry	inorganic base	solvent	T (°C)/ time	% of conversion
1	Cs_2CO_3	acetonitrile	25 °C/6 days	quantitative (>95%)
2	K_2CO_3	acetone	56 °C/48 h	45%
3	K_2CO_3	methyl isobutyl ketone	60 °C/48 h	50%
4	K_2CO_3	methyl isobutyl ketone	116 °C/5 h	quantitative (>95%)
5	K_2CO_3	methyl ethyl ketone	79 °C/18 h	70%

MIBK is advantageous because of its high boiling point (116 °C), which allows the reaction to be run at a higher temperature than other commonly examined ketones (acetone and methylethyl ketone) (Table 1).

Furthermore, due to a low miscibility with water, the use of MIBK allows for an easy work-up procedure. In particular, it is possible to remove the salinity from the reaction mixture by simple phase separation with neutral water and finally obtain the alkylated product by an easy concentration to dryness of the organic phases.

We also observed that, by performing the reaction under reflux in MIBK, only a few hours were enough to obtain the first intermediate in a quantitative yield (conversion >95%) starting from 2,6-dichlorophenol (**2**) and ethyl 2-chloropropionate (**12**). It is important to note that all chemical species involved in the reaction are stable at the refluxing temperature of MIBK. Another good reason to use MIBK is that the removal of water from the reaction mixture can be performed quite easily; this turns out to be a key factor for the following step. Indeed, water, if present in a relevant amount during the following reaction, can react with ester moieties and yield the corresponding hydrolyzed carboxylic acid. These acidic salt species cannot be recovered by the designed work-up, and the consequence would be a loss of material.

The presence of water can be due to either the nondry solvents or nondry potassium carbonate used; in addition, it can be formed during the reaction itself: when potassium

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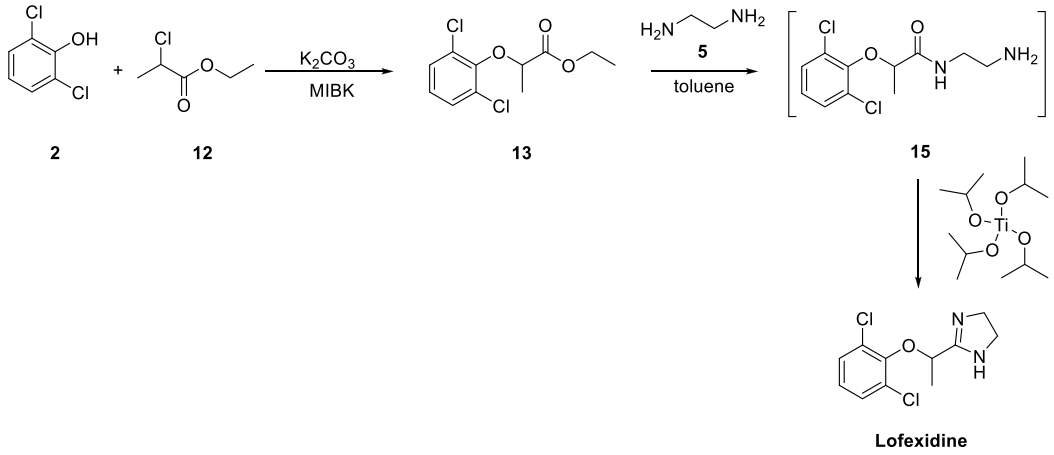
Scheme 6. Final Optimized Synthesis of Lofexidine



carbonate is used as an acid scavenger, it is known that its degradation gives a molecule of water and carbon. This reactivity is maximized if the carbonate is not completely solubilized in the reaction medium, and in our system, it is present as a solid as it is insoluble in MIBK. The use of MIBK at refluxing temperature allows for the removal of formed water by using a Dean−Stark apparatus.

2.2. Second and Third Steps. Moving to the cyclization reaction, as previously mentioned, it was already experimentally demonstrated that the usage of trimethylaluminum promotes a side reaction and that the use of $TiCl_4$ should be avoided due to its difficult handling.

Titanium tetrachloride is used in some procedures[6−8] to form imidazoline rings, but unfortunately, $TiCl_4$ (a liquid) is usually sold in special cylinders because it is very reactive with moisture and quite corrosive. It is also not easy to find on the market because of restrictions on transportation, which could make it unavailable or difficult to retrieve in some areas of the world.

To overcome this problem, we screened more cyclization reagents, such as trimethylsilyl chloride and phosphorus oxychloride. The former shows no reactivity, while with the highly reactive phosphorus oxychloride ($POCl_3$), it was possible to reach a conversion >90% in toluene at high temperatures. Unfortunately, $POCl_3$ is a very toxic and corrosive compound, and in contact with water, it causes a very violent exothermic reaction with conspicuous gas evolution that can lead to pressure build-up.

Dismayed by these results, we turned back to titanium complexes. Other titanium compounds that can be used in place of homoleptic tetrachloride are alkoxide derivates, such as titanium tetramethoxide, tetraethoxide, and tetraisopropoxide. These compounds are all commercially available, and of them, titanium isopropoxide is the most common and the cheapest. For that reason, it was chosen as the best candidate to be tested for the purpose. Despite being a liquid at room temperature similar to $TiCl_4$, it is not stored in cylinders because its reaction with moist air is not as vigorous as in the case of titanium tetrachloride. Moreover, this reagent is not corrosive on metals.

Initially, the reaction from ester **13** to lofexidine was performed in two steps, going through the isolation of amide **15**, as described in Scheme 6, and then performing the cyclization using titanium isopropoxide. However, we observed that, during the formation of intermediate **15**, at the end of the reaction, dimeric impurity **17** (Figure 3) was present at 5−10%, w/w.

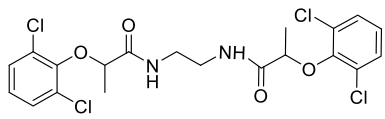


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Figure 3. Chemical structure of the dimer impurity.

After a deeper investigation, we proved that imidazoline ring formation is better performed in a one-pot way, charging ethylenediamine (**5**), titanium isopropoxide, toluene (used as the solvent), and ester intermediate **13** and allowing the reaction to take place under reflux (110 °C). Applying this procedure, we observed a quantitative conversion (>95%) of **13** to lofexidine over a few hours of reaction (Scheme 6).

Using this method, lofexidine can be obtained in high purity without the formation of byproducts, and the reaction time is short enough to allow the production of several batches per week in a production plant. Moreover, dimer impurity **17** formed in the two-step sequence, when using this improved method, is present at the end of the reaction in only marginal quantities and can be completely removed during the work-up. Impurity **14** was also present in low percentages (below 0.10%, w/w).

To complete the synthesis of API, the final lofexidine hydrochloride salt (**1**) was isolated by the addition of HCl to an alcoholic solution of the free base.

Some preliminary experiments were carried out starting from the methods reported in the literature[2,4,8] in which the techniques describe dissolution in alcoholic or mixed alcoholic/ethereal systems of lofexidine and its precipitation as salt by the addition of aqueous HCl, with the formation of gummy solids that are difficult to filter.

To avoid both the formation of these kinds of gummy solids of the hydrochloride salt and yield losses due to the presence of water, in which lofexidine hydrochloride (**1**) is very soluble, we turned to use an alcoholic system to dissolve the lofexidine-free base and then precipitate it by saturating the solution with gaseous HCl. This operation is very common in the case of scaling-up reactions and allows us to reduce the volumes involved and to optimize yields.

https://doi.org/10.1021/acs.oprd.0c00453
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2.3. Notes about Thermal Safety. Before proposing the implementation of a new process in a production plant, a complete thermal safety study must be performed to ensure that no risks at any time are associated with the new procedure.

The reaction to obtain the first intermediate ester **13** is exothermic (the resulting adiabatic temperature rise of the system obtained by an adiabatic calorimeter experiment in a closed vessel is approximately 38 K, 108 kJ/$mol_{Dichlorophenol}$), but the reaction kinetics are slow enough that even an instantaneous power output is manageable by any reactor installed in the production plant (the resulting maximum power is lower than 5 W/kg; for reference, a typical manageable power by a production reactor is approximately 20 W/kg). This reaction is performed under reflux, so the adiabatic temperature rise has no meaning since isothermal conditions are assured by the physical effect of boiling. In the case of failure in the cooling power of the condenser, the amount of uncondensed solvent would be less than one-third of the overall amount and would not cause a critical concentration of the mass. The possible evolution of carbon dioxide is quantitatively negligible.

The one-pot reaction for producing the final lofexidine from ester intermediate **13**, ethylenediamine (**5**), and $Ti(OiPr)_4$ is endothermic, and the final reaction mixture is thermally stable at least up to 180 °C (maximum tested temperature).

The overall process results are compliant with our safety policy.

3. CONCLUSIONS

Through the described process development, we solved most of the drawbacks that affected the procedures for the synthesis of lofexidine hydrochloride (**1**) found in the literature. The procedure reported in this manuscript offers practical advantages with respect to the known prior art.

In particular, a great advantage of this new process is that it is possible to obtain the targeted compound starting from very inexpensive raw materials (ethyl 2-chloropropionate **12**, potassium carbonate, and titanium isopropoxide) that are largely available on the market and easy to use on scale. The process flow was optimized and adjusted according to the peculiar properties of these new and generally less reactive reagents. Methods for performing the reactions have been set up through a very extensive screening of conditions.

This new optimized procedure meets the requirements of scalability, safety, and target price, which allows us to be competitive in the market when proposing the product.

4. EXPERIMENTAL SECTION

The reaction conversion and purity of each intermediate were checked by ultra performance liquid chromatography (UPLC) analysis, typically using an ACQUITY UPLC BEH C18 column (1.7 μm, 2.1 × 50 mm) with a water/acetonitrile/0.1% formic acid mixture as the eluent phase.

Melting points were determined in glass capillary tubes on a Buchi B-540 apparatus.

Mass spectroscopy (MS) analysis was carried out using Waters Acquity UPLC equipped with a QDA spectrometer detector. Ion generation was obtained by electrospray ionization (ESI) in positive mode. The sample was dissolved in methanol (approximately 1 mg/mL) and injected into the LC.

NMR spectra were acquired on a Bruker AV400 instrument. Chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane (TMS), and spin multiplicities were given as "s" (singlet), "d" (doublet), "t" (triplet), "q" (quartet), and "m" (multiplet).

Elemental analysis (CHN) was carried out by Thermo Flash 2000 equipment under the following conditions: sample weight: 0.1−10 mg; furnace temperature: 1010 °C; column temperature: 70−75 °C; carrier gas: He; flow: 130 mL/min.

4.1. Synthesis of Ethyl 2-(2,6-Dichlorophenoxy)-propionate (13). Potassium carbonate (2.32 kg, 16.8 moles) and MIBK (5.9 L) were charged at 25 °C into a 50 L Kilolab Hastelloy reactor under a N_2 flow. A solution of 2,6-dichlorophenol (**2**) (1.96 kg, 12.0 moles) in MIBK (5.88 L, 3 volumes vs 2,6-dichlorophenol) prepared in a 25 L Kilolab Hastelloy reactor was added to the suspension. The suspension was stirred at 25 °C for 10−15 min, and ethyl 2-chloropropionate (**12**) (2.29 kg, 2.1 L, 16.8 moles) was then slowly added. The suspension was heated to reflux (116 °C) for 5 h. The reaction was checked by UPLC: conversion >99%. The suspension was left to stand at 25 °C, and salts were dissolved by adding water (7.8 L, 4 volumes vs 2,6-dichlorophenol). The layers were separated, and the aqueous layer was washed with MIBK (5.88 L, 3 volumes vs 2,6-dichlorophenol). The reunited organic phases were washed with a 5% solution of aqueous sodium hydroxide (3.9 L, 2 volumes vs 2,6-dichlorophenol) previously prepared in a 10 L Kilolab glass-lined reactor and then with water (7.8 L, 4 volumes vs 2,6-dichlorophenol). The final organic phase was concentrated to a low volume, and fresh toluene (7.8 L, 4 volumes vs 2,6-dichlorophenol) was added and evaporated again to a low volume. This operation was repeated three times to eliminate the residue of MIBK and to isolate intermediate **13** as a toluene solution, used as is in the next step (14.16 kg, 12.0 moles). Purity >95% (as UPLC Area%).

^{1}H NMR characterization of **13** (400 MHz, chloroform-d) δ 7.29 (d, J = 8.1 Hz, 2H Arom), 6.99 (t, J = 8.1 Hz, 1H Arom), 4.83 (q, J = 6.8 Hz, 1H, CH), 4.24 (q, J = 7.2 Hz, 2H, CH2), 1.63 (d, J = 6.7 Hz, 3H, CH3), 1.28 (t, J = 7.1 Hz, 3H, CH3).

^{13}C NMR characterization of **13** (400 MHz, chloroform-d) δ 170.7, 150.3, 129.4, 129.1, 125.2, 78.0, 61.4, 18.2, 14.1.

4.2. Synthesis of Lofexidine. Titanium isopropoxide (2.57 kg, 9.00 moles) and toluene (9.5 L, 6 volumes vs intermediate **13**) were charged at 25 °C into a 50 L Kilolab Hastelloy reactor blanketed by a N_2 flow. A solution of ethylenediamine (**5**) (0.55 kg, 9.00 moles) in toluene (4 L, 2.5 volumes vs intermediate **13**) was then added. The reaction mixture was stirred at 25 °C for 1 h, and a toluene solution of ethyl 2-(2,6-dichlorophenoxy)propionate (**13**) (7.08 kg, 6.000 moles) was added. The reaction mixture was heated to reflux (110 °C) and stirred for 18 h. The reaction was checked by UPLC (conversion: 98%). The mixture was then cooled to 25 °C, and the yellow-orange solution was added to a 30% tartaric acid solution (23.8 L, 15 volumes vs intermediate **13**) previously prepared in a 50 L Kilolab glass-lined reactor (titanium isopropoxide reacted with tartaric acid in an aqueous environment, forming a soluble Ti species; in this case, no TiO_2 was formed, and Ti salts were completely soluble).

The organic layer was discarded, and toluene was added to the aqueous acidic layer containing titanium salts and the product as tartrate (8.9 L, 5.6 volumes vs intermediate **13**). The mixture was basified by adding 30% sodium hydroxide until reaching pH 12. The layers were separated, and the

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aqueous layer was washed with toluene (14.3 L, 9 volumes vs intermediate **13**). The mixed organic phases were washed with water (8.9 L, 5.6 volumes vs intermediate **13**) and concentrated to a low volume. The obtained suspension was filtered at 25 °C, and the needles were dried at 40 °C to yield the crude lofexidine-free base as a yellowish solid. Yield >90% was calculated from the starting material (2,6-dichlorophenol) of the previous step. Purity >95% (Area %).

The resulting product could be used for the precipitation of hydrochloride salt **1** or could be further purified by crystallization with heptane or hexane or by pulping at room temperature in methylisobutylketone or methylethylketone.

^{1}H NMR characterization of lofexidine-free base (400 MHz, chloroform-d) δ 7.31 (d, J = 8.1 Hz, 2H Arom), 7.01 (t, J = 8.1 Hz, 1H Arom), 5.16 (q + s (broad), J = 6.6 Hz, 2H, CH, NH), 3.65 (dd, J = 25.5, 8.6 Hz, 4H, CH2-CH2), 1.59 (d, J = 6.6 Hz, 3H, CH3).

^{13}C NMR of lofexidine-free base (400 MHz, chloroform-d) δ 167.9, 149.5, 129.6, 129.2, 125.3, 77.0, 51.7, 18.9.

4.3. Synthesis of Lofexidine Hydrochloride (1). Crude lofexidine-free base (2.3 kg, 8.90 moles) was dissolved in isopropanol (6.9 L, 3 volumes vs lofexidine) at 50 °C. A solution of HCl in isopropanol (3.22 L, 1.4 volumes vs lofexidine) was charged by dropping at this temperature until acidic pH was reached. The obtained suspension was cooled to 0 °C, and after overnight aging, the white solid was collected by filtration and dried (yield: 80−85%).

^{1}H NMR of lofexidine hydrochloride (**1**) (400 MHz, DMSO-d_6) δ 10.72 (s, 2H, NH, H+), 7.58 (d, J = 8.1 Hz, 2H Arom), 7.28 (t, J = 8.1 Hz, 1H Arom), 5.22 (q, J = 6.7 Hz, 1H, CH), 3.85−3.96 (m, 4H, CH2-CH2), 1.69 (d, J = 6.7 Hz, 3H, CH3).

^{13}C NMR of lofexidine hydrochloride (**1**) (400 MHz, DMSO-d_6) δ 169.4, 149.0, 130.2, 128.9, 127.6, 73.7, 45.0, 19.1. mp: 236 °C; elemental analysis (theoretical): C, 44.70; H, 4.43; N, 9.48; (experimental): C, 44.71; H, 4.44; N, 9.34. MS: 259.1[MH$^+$].

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00453.

NMR spectra for structure determinations of intermediates and the final product (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge Benedetta C. Pediglieri for the analytical support and performance of all analytical tests and Dr. Alberto Oppedisano for the consultancy and final revision of the manuscript.

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