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Article

Development of a Scalable Process for the Synthesis of Cyclopropyl-Methyl-Proline with Complex Stereochemistry: A Key Building Block of Factor D Inhibitors

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Cite This: https://doi.org/10.1021/acs.oprd.4c00223

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ABSTRACT: The development of a scalable process for a complex intermediate featuring a chiral, quaternary cyclopropane moiety presented significant challenges. We report two generations of synthetic strategies appropriate for the respective stages of development. The initial approach utilized a stereoselective Simmons−Smith cyclopropanation of (*R*)-pyroglutamic acid ester, which predominantly yielded the undesired stereoisomer. To circumvent this issue, we implemented a strategy that combined isomerization, recycling of the undesired isomer, and selective crystallization to improve the yield of the desired product. An important insight was that the Simmons−Smith cyclopropanation exhibited opposite stereoselectivity with a benzoyl ester of a prolinol substrate, resulting in the desired stereoisomer as the major product. This understanding enabled the development of a second-generation process that facilitated the large-scale production of the targeted intermediate, thus supporting the advancement of clinical trials.

KEYWORDS: *cyclopropanation, alkenes, diethylzinc, Bredereck, isomerization, diastereomer*

INTRODUCTION

The complement system, a fundamental component of the innate immune system, serves as an immediate and nonspecific defense against pathogens.[1] Unlike the adaptive immune system, which adapts over a lifetime, the complement system remains relatively static but plays a crucial role when activated alongside adaptive responses.[2] Several pathologies, from the atypical hemolytic uremic syndrome (aHUS) and neuromyelitis optica (NMO) to nonalcoholic steatohepatitis (NASH) and amyotrophic lateral sclerosis (ALS), have been implicated with disruptions in the complement cascade.[3] Factor D, critical in the alternative complement pathway, has emerged as a promising therapeutic target[4] for treating complement pathway-related diseases. Recently, the FDA approved Alexion's first small molecule Factor D inhibitor, danicopan,[5] marking a significant advancement in this field.

Recent trends in pharmaceutical research have shown a rise in drug candidates incorporating the cyclopropyl moiety.[6] In the context of Factor D inhibitors, the attachment of a fused cyclopropyl ring to a proline scaffold has been shown to greatly increase potency.[7] Our target compound **1**, a key building block of said investigational inhibitors, contains a cyclopropyl group with a quaternary carbon having chiral centers. This can give rise to four possible stereoisomers, as shown in Figure 1, which were all observed during our development efforts. The need for precise stereo control posed significant synthetic challenges.

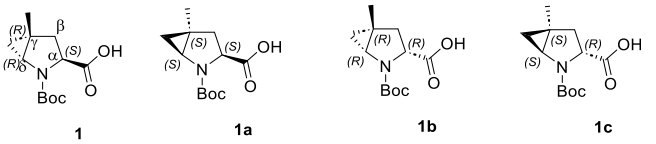


Figure 1. Desired compound **1** and the observed stereoisomers.

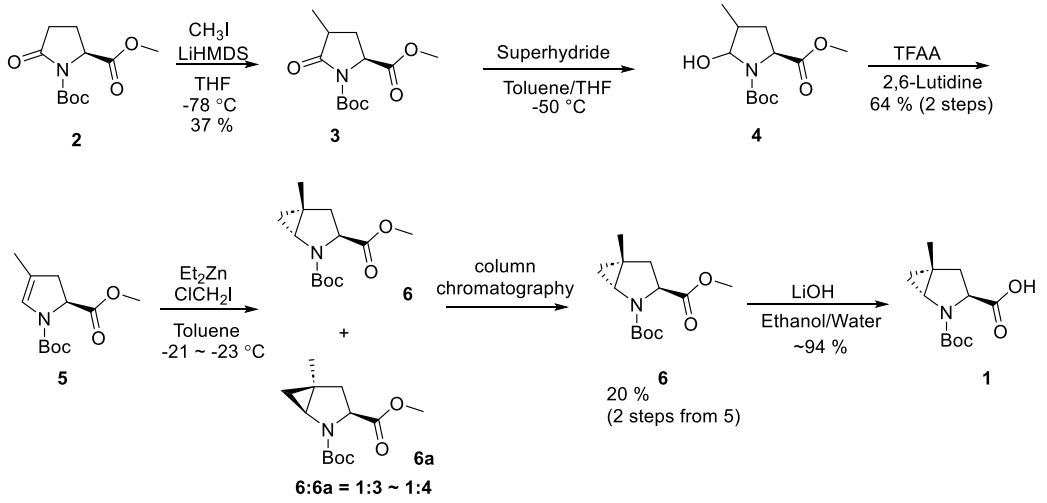
This manuscript details our journey through two generations of synthesis, each enhancing the efficiency and scalability of the process, ultimately leading to scale-up and multikilogram production of compound **1**.

RESULT AND DISCUSSION

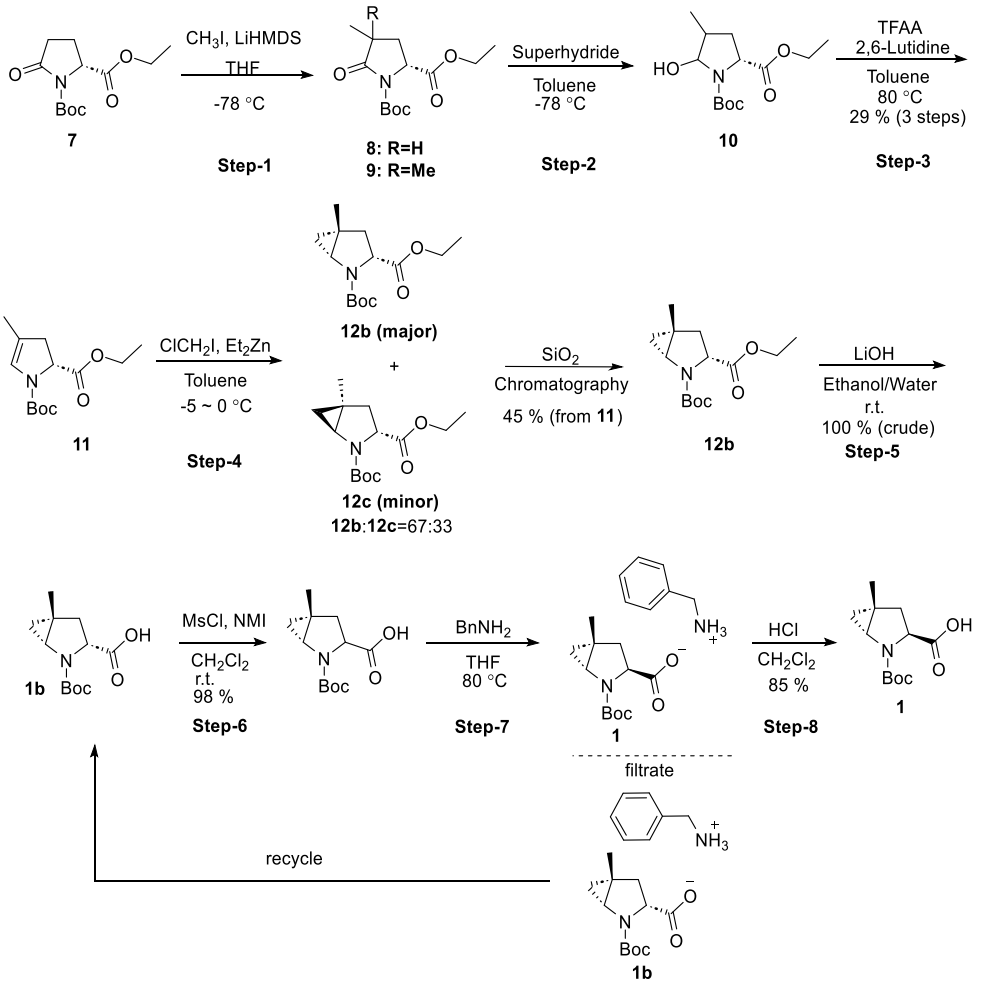
The key challenge in developing a process route for compound **1** is the installation of the desired stereochemistry, which is achieved during the cyclopropanation reaction. Cyclopropanation is an important transformation in organic chemistry, with several established methodologies,[8] including the classical Simmons−Smith reaction,[9] Simmons−Smith with the Furukawa modification,[10] and the utilization of sulfur ylides.[11]

Received: May 20, 2024
Revised: September 27, 2024
Accepted: October 4, 2024

Scheme 1. Medicinal Chemistry Synthesis of Compound 1



Scheme 2. Generation 1 Route to Compound 1



More recently, Co-catalyzed cyclopropanation has emerged as a powerful tool to achieve high stereoselectivities.[6e] In our research, after a review of the literature to identify synthetic strategies closely aligned with our target intermediates, we have selected the Simmons−Smith reaction using the Furukawa modification.[6,12]

The medicinal chemistry synthesis of compound **1** is shown in Scheme 1. The starting material methyl ester **2** was methylated by iodomethane and LiHMDS to afford a mixture of the monomethylated product **3**, a dimethylated side product, and unreacted **2**. Silica gel chromatography enabled the separation of **3**, which was reduced using lithium triethylborohydride (superhydride) to afford compound **4**.

https://doi.org/10.1021/acs.oprd.4c00223
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After a dehydration reaction, olefin **5** was obtained. A Simmons−Smith cyclopropanation reaction using Et_2Zn and $ClCH_2I$ was performed, followed by column chromatography to purify methyl ester **6**. After hydrolysis using LiOH, compound **1** was obtained.

This synthesis was used to obtain gram quantities of compound **1**, but it was not scalable. A major drawback was the stereoselectivity of the cyclopropanation reaction, as the desired product (compound **6**) was obtained as the minor component, while the major product was its stereoisomer (compound **6a**). The observed ratio of **6**:**6a** varied from 1:3 to 1:4. Despite the efforts to improve the stereoselectivity, the separation of compound **6** from **6a** via silica gel chromatography remained necessary for producing small quantities of compound **1**.

In response to these challenges, process development efforts initially aimed to address two main objectives: eliminating the need for full-scale column chromatography and developing a strategy to achieve the desired stereoselectivity. These efforts led to the generation 1 process, which successfully enabled the production of 350 g of compound **1**, meeting the immediate demands of preclinical studies. Subsequently, the generation 2 process incorporated key innovations, facilitating the synthesis of compound **1** on a multikilogram scale to meet the quantities required for advancing clinical development.

Generation 1 Process. The strategy employed for the generation 1 process relied on selecting a starting proline derivative with the opposite chirality of the α-position carbon (*R* instead of *S*), relative to the desired compound **1**. This deliberate choice aimed to leverage the stereoselective behavior of the Simmons−Smith reaction[6] to our advantage, as this would enable the installation of the desired stereochemistry for both the cyclopropyl and methyl groups. We then identified conditions conducive to the isomerization of the proline derivative's α-position carbon and devised a method for resolving the two isomers, through salt formation and crystallization. Subsequent recycling of the filtrate through isomerization, salt formation, and crystallization steps allowed the enhancement of the recovery and overall yield of the desired product.

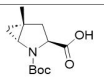
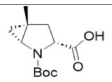
Scheme 2 illustrates the route that was developed and scaled-up as the generation 1 process. The commercially available starting material **7** was subjected to methylation using iodomethane and LiHMDS, resulting in a mixture comprising monomethylated compound **8**, dimethylated compound **9**, and unreacted starting material **7**. Compound **8** was separated via silica gel chromatography. The isolated product was then subjected to reduction using superhydride, followed by dehydration to yield olefin **11**. Olefin **11** was further reacted with $ClCH_2I$ and Et_2Zn, producing a mixture of a product of **12b** and **12c**, with **12b** as the major product (**12b**:**12c** = 67:33), which was purified through silica gel chromatography, followed by ester cleavage using LiOH.

The resulting compound, **1b**, was subjected to isomerization via mixed acid anhydride formation and subsequent hydrolysis. Isomerization conditions were identified during the development of a downstream amidation reaction, where it was found that the use of methanesulfonyl chloride and 1-methylimidazole to generate acid anhydride at room temperature led to the isomerization of the α-position carbon. While this result was unfavorable in the context of the amidation reaction, it provided a suitable path forward in our context. In the separation process, the mixture comprising compounds **1** and **1b** underwent selective crystallization facilitated by the formation of a benzylamine salt of **1**, which precipitated as a white solid. The filtrate, predominantly consisting of **1b** along with a minor amount of residual **1**, was recycled to enhance the overall yield.

The discovery of the benzylamine salt was critical to enable the effective separation of the desired stereoisomer in a reasonable yield. This was identified through a screening of five organic bases—pyridine, triethylamine, diisopropylethylamine, *tert*-butylamine, and benzylamine—using ethanol as the solvent. Using pyridine, triethylamine, and diisopropylethylamine did not yield solids. The *tert*-butylamine salt formed a solid with unfavorable physical properties that were difficult to isolate. In contrast, the benzylamine salt produced a favorable slurry and facilitated good resolution of the diastereomers. Based on these findings, we selected benzylamine for the isolation of the desired compound **1**.

The recycling protocol's performance during scale-up is summarized in Table 1. Isomerization of compound **1b** resulted in a 58:42 mixture of **1**:**1b**, reflecting the higher thermodynamic stability of the desired stereoisomer **1**. Benzylamine was added to the free acid solution to generate and crystallize the benzylamine salt in a 96:4 ratio with a recovery of 28%. The filtrate was predominantly the undesired stereoisomer (9:91), hence it was subjected to a second round of isomerization, followed by benzylamine salt formation, which allowed for an additional recovery of 12%. Upon a third isomerization attempt of the filtrate, it was observed that the chemical purity had diminished to levels considered unacceptable for further processing. Consequently, the total recovery of the benzylamine salt of compound **1** after all isomerization and benzylamine salt crystallization steps was ∼40%.

Table 1. Evolution of Diastereomeric Purity (DP) toward the Purification of Compound 1 during the Scale-Up. Detailed Procedure Provided in the Experimental Section

	DP Desired 	DP Undesired 	Recovery
Post Step 5	1	99	100 %
After isomerization (step-6)	58	42	98%
After 1st benzylamine formation (solids)	96	4	28 %
After 1st benzylamine formation (filtrate)	9	91	
After isomerization (1st recycle)	55	45	-
After 2nd benzylamine formation (solids)	95	5	12 %
After 2nd MLR isomerization (2nd recycle)	57	43	-

The process to carry out the benzylamine salt break initially employed a 10% aqueous citric acid solution, maintaining a pH between 2 and 3. However, upon further evaluation, it was determined that adjusting the pH to a 1 to 2 range using a 1.5 M hydrochloric acid (HCl) aqueous solution did not induce Boc-deprotection and was effective in substantially reducing the impurity levels of the residual benzylamine, from 2.5% to negligible levels. Upon salt break, the diastereomeric purity remained at 96:4. If necessary, another benzylamine treatment would have further purified compound **1**; however, this was not performed as the purity was sufficient for toxicological studies (target: stereochemical purity of >95%).

The first-generation process was successful in producing compound **1** on an ∼350 g scale; however, it exhibited significant limitations that hindered its use in larger-scale

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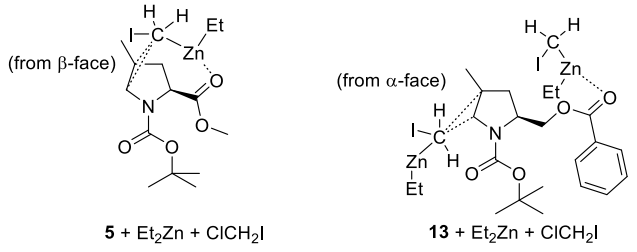
production. The process was very inefficient, demanding multiple isomerization and recycling cycles to achieve satisfactory yields. A key issue was that the cyclopropanation reaction did not allow the installation of the correct stereochemistry on the desired substrate. Furthermore, two column chromatographic operations were needed following the methylation and cyclopropanation steps. These challenges informed our subsequent research efforts, culminating in the development and implementation of a scalable second-generation process.

Generation 2 Process. The development of a second-generation process capable of multikilogram production focused initially on establishing cyclopropanation conditions that predominantly yielded the desired stereoisomer. Notably, a study by Asano et al.[13] revealed that the use of a larger silyl ether altered the stereoselectivity of the cyclopropanation reaction. They proposed that in their system, zinc coordination with the carbonyl oxygen of the methyl ester group preferentially facilitated the attack on the β-face over the α-face of the proline derivative. Conversely, the steric hindrance introduced by the silyl ether and the absence of a coordinating carbonyl oxygen could account for the observed reversal in stereoselectivity.

We deliberated the use of silyl ethers and anticipated potential challenges during workup and deprotection. Instead, we outline key criteria for identifying a new functional group capable of inducing the desired stereoselectivity. The functional group would need to (1) be sufficiently bulky to cover the β-face to block approaching carbene species, (2) lack a carbonyl proximal to the proline ring, (3) be readily available and easy to install, (4) be easy to remove, and (5) contain a chromophore to facilitate analytical measurements and aid in monitoring the purification of stereoisomers in the cyclopropanation and subsequent steps. We identified the benzoyl ester as fitting all of these criteria. Scheme 3 illustrates the

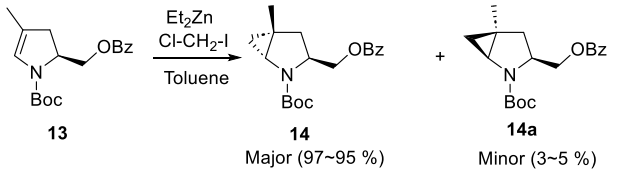
Scheme 3. Proposed Mechanism of Cyclopropanation Face Selectivity



proposed mechanism of cyclopropanation face selectivity for both the methyl ester and the benzoyl ester substrates. The latter gratifyingly yielded the desired product with a remarkable 95:5−97:3 selectivity, as depicted in Scheme 4. This key result provided a foundation for our synthetic strategy, culminating in the generation 2 process shown in Scheme 5.

The new route started from an inexpensive, commercially available (*S*)-prolinol derivative **15**. A benzoylation reaction with BzCl in dichloromethane, followed by Boc protection, generated compound **17**. Bredereck's reaction (Bredereck's reagent: *tert*-butoxybis(dimethylamino)methane) using DME as a solvent, followed by hydrogenation, enabled the generation of the monomethylated **19**, which was then reduced under cryogenic conditions. A subsequent dehydration afforded olefin **13**, followed by Simmons−Smith cyclopropanation to generate compound **14**. Subsequent ester hydrolysis to compound **21** was followed by oxidation, benzylamine salt isolation, salt break, and crystallization to obtain compound **1**.

Scheme 4. Stereoselectivity Obtained Using the Benzoyl Ester Substrate



Key outcomes of the generation 2 route optimization were: (i) the Bredereck's/hydrogenation sequence[14] was found to be critical to ensure the selective formation of the monomethylated product and prevent the need for column chromatographic separation; (ii) the use of the benzoyl ester substrate for the cyclopropanation enabled obtaining the desired stereoisomer as the major product; (iii) a robust oxidation step using TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) as the oxidant was developed; (iv) salt formation through a benzylamine salt to remove the undesired stereoisomers was optimized.

A robust procedure for Bredereck's reaction was developed, starting from a solution of compound **17** in 2-dimethoxyethane, with 1.5 equiv of Bredereck's reagent at 75 ± 5 °C for 14 h. The reaction is high-yielding (~90%), producing a high-purity product (>98%). We observed high variability in reaction performance depending on the source of Bredereck's reagent, despite equivalent quality testing from the vendors (Table 2). Hence, a use-test prior to utilization was incorporated.

The Simmons−Smith cyclopropanation process was executed under identical conditions employed during generation 1. This reaction involves the in situ formation of a carbenoid through the reaction of diethylzinc and a carbene source, which then reacts with the double bond of the olefin to form the cyclopropane ring. In our process, diethylzinc was added to a solution containing olefin **13** in dry toluene at −25 °C. After warming the reaction mixture to 0 °C, a solution of chloroiodomethane in toluene was added in four separate portions. After completion of the reaction, the reaction mixture was quenched with aqueous $NaHCO_3$. We observed a selectivity of 95:5−97:3 for **14**:**14a**, a ratio maintained during scale-up as well.

As a common practice, process safety data were collected on all processes before scale-up. The cyclopropanation step was particularly scrutinized because of the safety challenges involved in the use of diethylzinc and the exothermic character of this reaction. Heat evolution was monitored by reaction calorimetry relative to the diethylzinc addition, the chloroiodomethane addition (in three equal portions), and the quench procedure. The data are presented in Table 3. DSC screening was also conducted. The data showed that the adiabatic temperature rises associated with each reaction stage are mild and these process steps can be scaled-up safely.[15] Great care needs to be taken for handling of the diethylzinc. In the reaction, it reacts with excess chloroiodomethane, and therefore, diethylzinc is not present in its free form. Any

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Scheme 5. Generation 2 Route to Compound 1

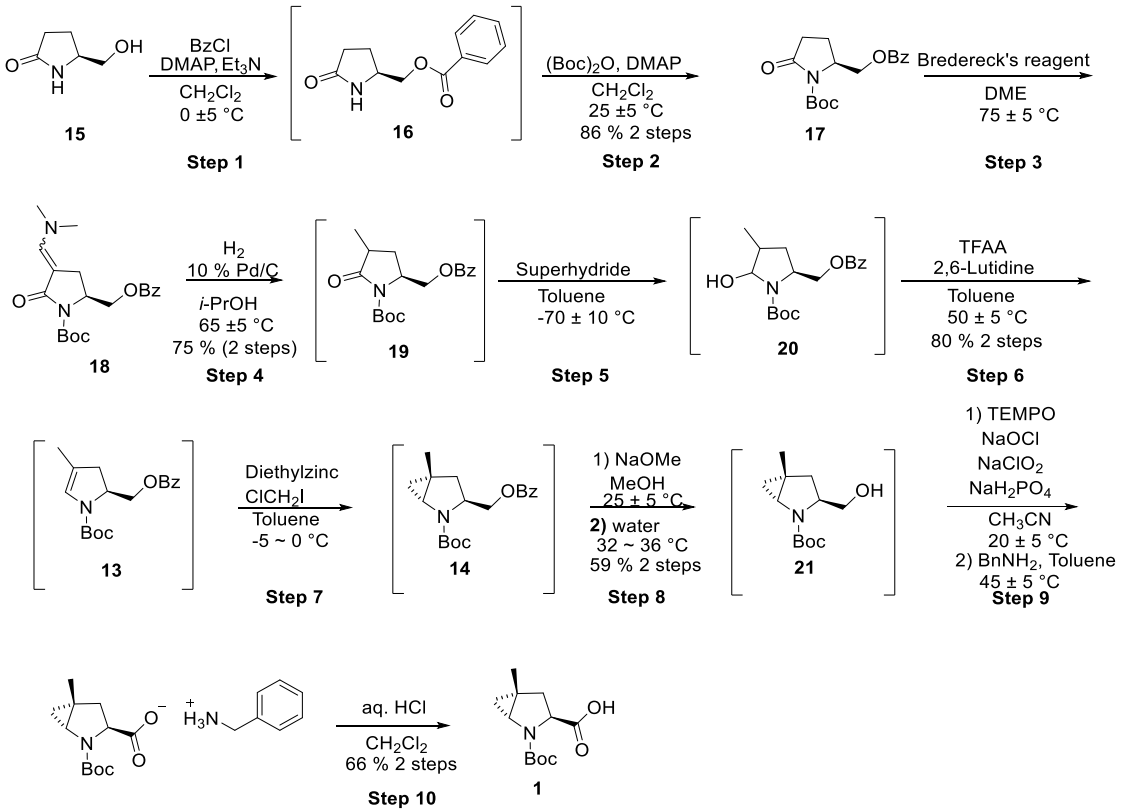


Table 2. Bredereck's Reaction Performance Using Bredereck's Reagent Obtained from Different Sources (A, B, C)

Source	Yield	Final purity
A (n = 2)	52%	62%
B	83%	88%
C (n = 8)	91%	99%

Table 3. Process Safety Data on the Cyclopropanation Step[a]

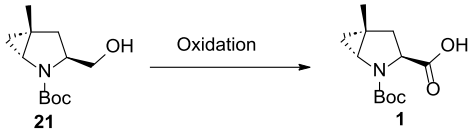
Process step	T_p (°C)	ΔH_r [kJ/kg]	ΔT_{ad} (°C)	MTSR (°C)
1.5 M diethylzinc addition	−25	569.4	6	−19
addition of chloroiodomethane (three portions)	0	1125.0	20.4	20.4
sodium bicarbonate solution addition	5	1323.5	23.1	28.1

[a] T_p: process temperature. ΔT_{ad}: adiabatic temperature rise. MTSR: maximum temperature of the synthesis reaction.

residual reagents are safely quenched with aqueous $NaHCO_3$ at the end of the reaction.

Following cyclopropanation and hydrolysis, an oxidation reaction was developed, as shown in Table 4. We investigated a range of oxidation conditions to convert the hydroxy methyl group to the carboxylic acid. We found that TPAP (tetrapropylammonium perruthenate) and CrO_3 (entries 10 and 11, respectively) as oxidants gave the best results in terms of overall yield. However, to avoid the higher costs associated with metals and the complexities of developing a control strategy to remove them, we selected TEMPO as the oxidizing agent for further development. In this reaction, TEMPO is a stable nitroxyl radical that acts as a catalyst in the oxidation

Table 4. Screening of Oxidation Conditions



Entry	Oxidation conditions	Yield
1	Jones oxidation (CrO_3, H_2SO_4 in acetone)	0%
2	$KMnO_4$, K_2CO_3, ^tBuOH	0%
3	Bi_2O_3, tBuOOH, AcOEt	0%
4	1,3,5,7-tetraazatricyclo(3.3.1.13,7)decane-2-ol, NaClO, $NaClO_2$	0%
5	oxone, CH_3CN, H_2O	0%
6	pyridinium chlorochromate (PyH^+, CrO_3^-, PCC), H_5IO_6, CH_3CN)	0%
7	TEMPO, NaClO, $NaClO_2$	75%
8	TEMPO, Bu_4NSO_4H, NaClO, $NaClO_2$	70−80%
9	TEMPO, Bu_4NBr, KBr, NaClO, $NaClO_2$	75%
10	TPAP, N-methylmorpholine-N-oxide, CH_3CN	90%
11	CrO_3, HIO_4, CH_3CN	90%

process, NaClO serves as the primary oxidizing agent in the reaction, and $NaClO_2$ is used to regenerate the TEMPO radical from its reduced form, allowing the catalyst to be recycled back. The optimized process required simultaneous addition of NaClO and $NaClO_2$ at a controlled rate.[16] We observed that a departure from the optimized relative rate of addition would lead to the generation of two unknown impurities at levels that approached ∼5%.

The oxidation reaction was followed by the formation of a benzylamine salt which was isolated as a white solid. The benzylamine salt formation was a purification step that was key to achieving the desired chemical purity and eliminating

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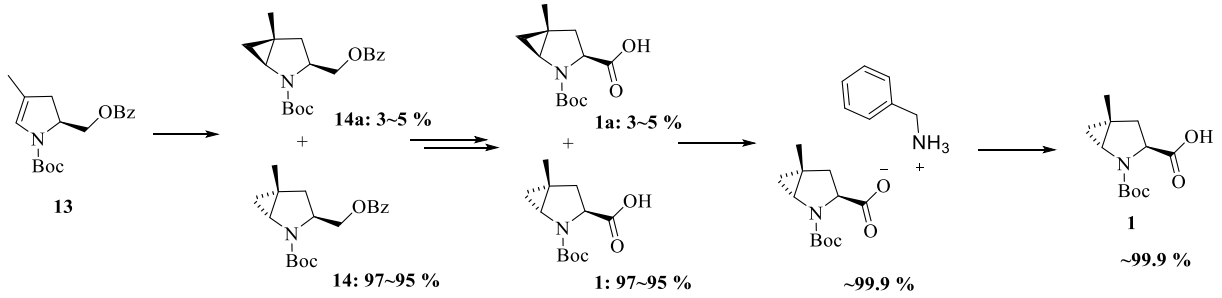
Scheme 6. Isomer Generation During the Cyclopropanation Reaction and Subsequent Purification



undesired stereoisomers. Scheme 6 shows the evolution of observed stereoisomers in the generation 2 process. The cyclopropanation generated the desired product **14** as the major product with a 95:5 to 97:3 stereoselectivity. The two stereoisomers reacted in the two downstream steps and maintained a **1**:**1a** ratio of ∼95:5 to 97:3. The benzylamine salt formation effectively purified the desired compound, rejecting the undesired stereoisomer to levels ∼0.1%.

We conducted a series of optimization experiments to determine the most effective solvent combination for the benzylamine salt preparation of compound **1** to maximize the yield and selectivity. As shown in Table 5, acetonitrile and toluene were found to have the most favorable combination in terms of rejecting the undesired stereoisomer and achieving a high yield. Toluene was selected as it could be used effectively in the upstream extractions.

Table 5. Screening of Benzylamine Salt Preparation of Compound 1[a]

Solvent	% Yield	HPLC (% area)	Chiral HPLC
THF/*n*-heptane (1:1)	49.0	96.88	99.17
THF/*n*-heptane (1:2)	58.5	97.51	99.35
i-PrOH/*n*-heptane (1:1)	58.5	99.29	99.84
2-MeTHF/*n*-heptane (1:2)	56.6	97.63	99.62
acetonitrile	66.0	98.47	99.64
[b]toluene	66.0	97.98	99.51

[a]Screening was conducted at a temperature of 20−30 °C. The starting ratio of **1** to **1a** was 95:5. Screening time: 8 h; solvent volume: 7 mL/g. [b]Current manufacture scale using toluene, extraction using CH_2Cl_2: yield, 66% (two steps); HPLC purity, 99.44%; chiral purity, 99.90%.

The main identified impurities were derivatives of unreacted intermediates, stereoisomers, and modifications of the Boc-protecting group. Recent optimization efforts have shown that performing the benzylamine isolation process twice consistently enhances the chemical purity to above 99.5%, with compound **1a** remaining as the major low-level impurity.

In summary, the second generation synthesis of compound **1** represented a significant advancement, facilitating the scale-up of production to tens of kilograms per batch of compound **1** and achieving cumulative production exceeding 800 kg of compound **1**, all while maintaining consistent high quality. Despite these advancements, the production process still presents several opportunities for improvement. Among the main drawbacks, the efficiency of Bredereck's reaction was found to be critically dependent on the source of the reagent, a variable which has eluded clear characterization by our current analytical techniques. The technical requirements for the overall synthesis included the utilization of specialized equipment for hydrogenation as well as cryogenic conditions for the carbonyl reduction by superhydride. The cyclopropanation involves the use of diethylzinc, which presents significant safety challenges in terms of material handling. The oxidation relies on the simultaneous addition of reagents, requiring tight control of the relative rates of addition, potentially leading to the generation of significant amounts of impurities. The selection of solvents was not optimized to incorporate greener options. Above all, the synthesis is characterized by a long sequence of nine linear chemical steps, resulting in extended lead times and poor sustainability metrics. Acknowledging these significant challenges, we are actively pursuing the development of a next-generation synthesis that addresses all of these challenges.

CONCLUSION

The journey toward a robust and scalable synthesis of compound **1**, a molecule that features a quaternary chiral cyclopropane group, was a challenging endeavor spread across two distinct generations of methodologies. Our initial process utilized a Simmons−Smith cyclopropanation on an (*R*)-proline ester derivative, which generated the undesired stereoisomer. We devised a strategy wherein, through isomerization, selective crystallization, and recycling, we could generate hundred-gram quantities of compound **1**. While this route was critical in providing initial supplies to conduct early studies, it was extremely inefficient, low-yielding, and required several column chromatographic purifications. Given these limitations, we developed our second-generation approach, leveraging the use of a benzoyl ester that enabled the desired stereoselectivity for cyclopropanation. By judiciously reevaluating and refining our synthetic strategies, we successfully optimized the synthesis of compound **1** via the generation 2 route, enabling production at a multikilo scale per batch. Several challenges in the synthesis of compound **1** remain, as the nine-step linear route is long and inefficient. We are actively developing a next-generation synthesis route that addresses the drawbacks described herein. Our goal is to create a process that enables a step-change improvement in terms of efficiency, cost, and sustainability. We look forward to reporting our findings in due course.

EXPERIMENTAL SECTION

General Information. All starting materials were commercially available and used without further purification. Large-scale reactions were carried out in stainless steel or glass-lined steel reactors fitted with heat transfer jackets and serviced with the appropriate ancillary equipment.

NMR spectra were recorded on a Bruker 400 MHz Avance Neo console spectrometer. LC-MS spectra were recorded on an Agilent 1260 HPLC system coupled to an Agilent Triple Quad-6420 mass detector. HRMS spectra were recorded on a

https://doi.org/10.1021/acs.oprd.4c00223
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Thermo Exactive+ EMR instrument. HPLC chromatograms were recorded on an Agilent 1260 series HPLC system.

*First Generation Manufacturing Route. Step-1: 1-(tert-butyl)-2-ethyl-(2R)-4-methyl-5-oxopyrrolidine-1,2-dicarboxylate (**8**).* To a solution of 1-(*tert*-butyl)-2-ethyl-(*R*)-5-oxopyrrolidine-1,2-dicarboxylate **7** (3.8 kg, 14.8 mol) in dry THF (27 kg) at −78 °C, LiHMDS (15.2 L, 15.2 mol, 1.0 M in THF, Sigma-Aldrich) is added. The reaction mixture is stirred at −78 °C for 1 h, after which methyl iodide (4.1 kg, 28.9 mol) is added. The mixture is stirred at −78 °C for an additional 2 h. Water is then added, and the resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue is passed through a silica gel plug using *n*-hexane/ethyl acetate to give a mixture of **8** [89% pure* by HPLC (two stereoisomer mixture)]. [Yield: 3.7 kg, 13.6 mol (92% crude)].

*Including **7** and **9**. Purification occurs in Step-3.

*Step-2: 1-(tert-butyl)-2-ethyl-(2R)-5-hydroxy-4-methylpyrrolidine-1,2-dicarboxylate (**10**).* To the above solution of compound **8** (3.7 kg, 13.6 mol, crude) in dry toluene (32 kg) at −78 °C, lithium triethylborohydride (17.7 L, 17.7 mol, 1.0 M in THF, Sigma-Aldrich) is added. The reaction mixture is stirred at −78 °C for 2 h. Water is then added, and the resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na_2SO_4, filtered, and concentrated to yield compound **10**. [Yield: 3.2 kg, 11.7 mol (86% crude)]

*Step-3: 1-(tert-butyl)-2-ethyl-(R)-4-methyl-2,3-dihydro-1H-pyrrole-1,2-dicarboxylate (**11**).* To a solution of compound **10** (3.2 kg, 11.7 mol) in dry toluene (28 kg) at 0 °C, 2,6-lutidine (1.9 kg, 17.6 mol) and trifluoroacetic anhydride (2.4 kg, 11.5 mol) are added. The resultant mixture is stirred at 80 °C for 1 h, then cooled to 0 °C and quenched with water. The reaction mixture is then extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue is purified by column chromatography on silica gel using *n*-hexane/ethyl acetate to yield compound **11**. [Yield: 1.1 kg, 4.3 mol (29%) over three steps]

11: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.30 (d, 1H), 4.66−4.54 (m, 1H), 4.29−4.17 (m, 2H), 3.03−2.92 (m, 1H), 2.57−2.47 (m, 1H), 1.70 (s, 3H), 1.49−1.44 (m, 9H), 1.31−1.29 (m, 3H) ppm. LC-MS: MS (ESI+): $[(M + H)\text{-Boc}]^+$ m/z calcd for $C_8H_{14}NO_2$, 156.1; found, 156.2.

*Step-4: 2-(tert-butyl)-3-ethyl-(1R,3R,5R)-5-methyl-2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (**12b**).* To a solution of compound **11** (1.07 kg, 4.2 mol) in dry toluene (1.7 kg) at −20 °C, diethylzinc (9.8 L, 10.8 mol, 1.1 M in toluene, Sigma-Aldrich) is added. The reaction mixture is stirred at −20 °C for 30 min. Chloroiodomethane (4.1 kg, 23.2 mol) is then added, and the mixture is stirred at −20 °C, followed by stirring at −5 to 0 °C for 6 h. After the reaction is complete, saturated aqueous $NaHCO_3$ is added to the reaction mixture at −20 °C, and the temperature is allowed to rise to 25 °C. The resulting mixture is stirred at 25 °C for 20 min, then filtered through Celite and washed with ethyl acetate. The organic layer is separated, dried over anhydrous Na_2SO_4, filtered, and concentrated to yield compounds **12b** and **12c**. The residue is purified by repeated column chromatography on silica gel using *n*-hexane/ethyl acetate to obtain compound **12b**. [Yield: 0.51 kg, 1.9 mol (45%)]

12b: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.61−4.49 (m, 1H), 4.21−4.11 (m, 2H), 3.28−3.16 (m, 1H), 2.42−2.31 (m, 1H), 2.15−2.09 (m, 1H), 1.49−1.20 (m, 15H), 1.10−0.58 (m, 2H) ppm. LC-MS: MS (ESI+): $[(M + H)\text{-Boc}]^+$ m/z calcd for $C_9H_{16}NO_2$, 170.1; found, 170.4.

*Step-5: (1R,3R,5R)-2-(tert-butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (**1b**).* To a solution of compound **12b** (1.0 kg, 3.7 mol) in EtOH/water (2.2 kg/1.1 kg) at 0 °C, $LiOH{\cdot}H_2O$ (171 g, 4.1 mol) is added. The reaction mixture is stirred at room temperature for 5 h and then concentrated. Water is added to the resulting mixture, and the aqueous layer is washed with dichloromethane. The aqueous layer is then acidified with 1.5 N HCl and extracted with dichloromethane. The organic layer is separated, dried over anhydrous Na_2SO_4, filtered, and concentrated to yield compound **1b**. [Yield: 895 g, 3.7 mol (100% crude)]

1b ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.57 (bs, 1H), 4.37 (m, 1H), 3.10 (m, 1H), 2.35 (m, 1H), 1.98 (m, 1H), 1.41−1.32 (m, 9H), 1.17 (s, 3H), 0.91 (m, 1H), 0.57 (m, 1H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ: 174.3, 153.3, 78.8, 58.8, 42.5, 36.3, 28.0, 22.1, 20.3, 18.5 ppm. HRMS (negative mode): calculated for $C_{12}H_{18}NO_4$ $(M - H)^-$: 240.1236; found: 240.1238.

1c is prepared using the same method as in Step-5 with **12c**.

1c: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.46 (bs, 1H), 3.84 (m, 1H), 3.08−3.04 (m, 1H), 2.42−2.36 (m, 1H), 1.84 (bs, 1H), 1.39−1.33 (m, 9H), 1.17 (s, 3H), 0.64 (s, 2H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ: 173.1, 154.3, 78.9, 59.8, 42.7, 37.9, 28.0, 22.1, 21.3, 20.6 ppm. HRMS (negative mode): calculated for $C_{12}H_{18}NO_4$ $(M - H)^-$: 240.1236; found: 240.1238.

*Step-6: (1R,5R)-2-(tert-butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (**1**) and **1b**.* To a solution of compound **1b** (893 g, 3.7 mol) in dichloromethane (11 kg) at 0 °C, 1-methylimidazole (827 g, 10.1 mol) is added. The reaction mixture is stirred at 0 °C for 30 min. Methanesulfonyl chloride (480 g, 4.2 mol) is then added, and the mixture is stirred at room temperature for 16 h. Aqueous $LiOH{\cdot}H_2O$ (543 g, 12.9 mol) is added to the resulting mixture. The aqueous layer is washed with dichloromethane, acidified with 1.5 N HCl, and then extracted with dichloromethane. The organic layer is separated, dried over anhydrous Na_2SO_4, filtered, and concentrated to yield compounds. [Yield: 879 g, 3.6 mol (98%), mixture of **1** and **1b** (58:42)]

*Step-7 and recycle: (1R,3S,5R)-2-(tert-butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hexane-3-carboxylic acid benzylamine salt (**1**·benzylamine salt).* To a solution of the mixture of compounds **1** and **1b** (870 g, 3.61 mol), THF (1.5 kg) is added, and the mixture is stirred at 80 °C. THF (17.0 kg) is then added slowly, followed by benzylamine (405 g, 3.8 mol). The reaction mixture is stirred at 80 °C for 30 min until a clear solution is obtained. The mixture is then cooled slowly to 20−30 °C and stirred for 30 min. Further cooling to 0−5 °C is performed, and the mixture is stirred for an additional 30 min. The solid is filtered and dried below 40 °C to yield the benzylamine salt of compound **1**. [Yield: 352 g (benzylamine salt), 1.01 mol (28%), **1**:**1b** (96:4)]

The filtered mother liquor is reprocessed for isomerization as described above (**1b** and **1**). The isolated benzylamine salt from this reprocessing has a yield of 146 g (benzylamine salt), 0.42 mol (12%), **1**:**1b** (95:5).

*Step-8: (1R,3S,5R)-2-(tert-butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (**1**).* All of the **1**·benzylamine salt (593 g, 1.70 mol) previously produced is dissolved in dichloromethane (17 kg) and acidified with a 1.5

https://doi.org/10.1021/acs.oprd.4c00223
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M HCl solution. The organic layer is then washed with 5% brine, separated, and extracted three times before being concentrated to obtain **1** as a white solid [yield: 350 g, 1.45 mol (85%), **1**:**1b** (96:4)].

1: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.47 (bs, 1H), 3.84 (m, 1H), 3.08−3.03 (m, 1H), 2.42−2.36 (m, 1H), 1.84 (bs, 1H), 1.45−1.33 (m, 9H), 1.15 (s, 3H), 0.62 (s, 2H) ppm, ^{13}C NMR (DMSO-d_6, 101 MHz) δ 173.2, 154.4, 79.2, 59.8, 42.7, 37.9, 28.0, 22.8, 21.1, 20.5 ppm.

*Second Generation Manufacturing Route. Step-1 and Step-2: tert-butyl-(S)-2-((benzoyloxy)methyl)-5-oxopyrrolidine-1-carboxylate (**17**).* To a solution of (*S*)-5-(hydroxymethyl)-2-pyrrolidinone **15** (95.84 kg, 832.5 mol) in dichloromethane (767 kg) at 0 ± 5 °C, 4-(dimethylamino)-pyridine (10.54 kg) and triethylamine (101.59 kg) are added under a nitrogen atmosphere. Benzoyl chloride (118.84 kg) is then added to the reaction mixture, which is stirred at 0 ± 5 °C for an additional hour. After completion of the reaction, the mixture is quenched with 5% sodium bicarbonate solution (579 L), and the temperature is raised to 25 ± 5 °C. The layers are separated, and the aqueous layer is extracted with dichloromethane (767 kg). The combined organic layers are washed with 10% brine solution (432 L) and then separated. The organic layer (including **16**) is treated with 4-(dimethylamino)pyridine (45.04 kg) and di-*tert*-butyl dicarbonate (308.60 kg, 1414 mol) at 25 ± 5 °C under a nitrogen atmosphere. The reaction mixture is stirred at 25 ± 5 °C for 2.5 h. Additional di-*tert*-butyl dicarbonate (36.40 kg, 167 mol) is then added. The mixture is stirred at 25 ± 5 °C until compound **16** is consumed (HPLC shows less than 5% remaining). Water (959 kg) is added to the reaction mixture, which is then stirred, and the layers are separated. The organic layer is washed with 5% aqueous HCl solution (537 kg × 2), followed by 10% brine (432 L). The organic layer is concentrated and crystallized using 5% ethyl acetate in *n*-heptane (334 kg), then filtered and dried to give compound **17**. [Yield: 227.87 kg, 713.5 mol (86%, over two steps)]

17: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.95−7.93 (m, 2H), 7.70−7.66 (m, 1H), 7.56−7.52 (m, 2H), 4.64−4.60 (m, 1H), 4.47−4.45 (m, 1H), 4.40−4.36 (m, 1H), 2.64−2.57 (m, 1H), 2.40−2.33 (m, 1H), 2.21 (m, 1H), 1.95 (m, 1H), 1.42 (s, 9H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ: 173.5, 165.5, 149.3, 133.6, 129.3, 129.2, 128.9, 82.0, 65.2, 55.8, 31.4, 27.6, 20.3 ppm. HRMS (positive mode): calculated for $C_{12}H_{14}NO_3$ (M − Boc + H)$^+$: 220.0974; found: 240.0965.

*Step-3 and Step-4: tert-butyl (5S)-5-((benzoyloxy)methyl)-3-methyl-2-oxopyrrolidine-1-carboxylate (**19**).* To a solution of compound **17** (100.0 kg, 313.1 mol) in 2-dimethoxyethane (130 kg), Bredereck's reagent [*tert*-butoxy bis-(dimethylamino)methane (82.00 kg, 470.5 mol)] is added at 25 ± 5 °C. The reaction mixture is stirred for 14 h at 75 ± 5 °C. After completion of the reaction, the reaction mixture is cooled to 25 ± 5 °C, and water (1262 kg) is added. The suspension is stirred for 1 h, then the solid is filtered and washed with water (500 kg), and vacuum-dried on the filter for 3 h. The partially dried solid is transferred to a reaction vessel and washed with *n*-heptane (137 kg). The mixture is stirred, and the solid is collected by filtration and vacuum-dried on the filter for 5 h, followed by additional vacuum drying at 75 ± 5 °C for 8 h. 10% palladium on carbon (10.00 kg, 50% water wet) is added to the vessel under a nitrogen atmosphere, and 2-propanol (134 kg) is then added to form a slurry. This slurry is transferred to an autoclave hydrogenator. [Additional 2-propanol (100 kg) is used to wash the palladium on a carbon slurry preparation tank and transfer line]. The slurry of dried compound **18** (a mixture of *E* and *Z*, 102.20 kg) with 2-propanol (393 kg) is transferred into the autoclave, which contains the palladium catalyst, under a nitrogen atmosphere. [Additional 2-propanol (24 kg) is used for the preparation tank and transfer line]. The autoclave hydrogenator is pressurized with nitrogen (∼1 kg/cm^2) at 25 ± 5 °C, then replaced with hydrogen. The reaction mixture is stirred for 28 h at 65 ± 5 °C under 5−6 kg/cm^2 hydrogen pressure. After the reaction is complete, the mixture is cooled to 25 ± 5 °C, and the hydrogen pressure is slowly released. The mixture is then filtered using a sparkler filter and washed with 2-propanol (236 kg). The filtrate is concentrated, and 20% ethyl acetate in *n*-heptane (720 kg) is added. Silica gel (30 kg) and Celite (20 kg) are added, and the mixture is stirred for 2 h and then filtered. The bed is washed with 20% ethyl acetate in *n*-heptane (362 kg). The silica gel−Celite purification is repeated once more, with the bed washed again with 20% ethyl acetate in *n*-heptane (362 kg). The filtrate is concentrated completely to obtain compound **19** (mixture of CH_3 α and β) as a thick liquid. Toluene (87 kg) is added, and the toluene is distilled below 5 °C until no further distillation is observed. Additional toluene (∼100 kg) is used for washing the vessel walls to give a solution of **19** (mixture). [Yield: 77.94 kg, 233.8 mol (75%, over two steps), corrected by HPLC assay]

*Step-5 and Step-6: tert-butyl 2-((benzoyloxy)methyl)-4-methyl-2,3-dihydro-1H-pyrrole-1-carboxylate (**13**).* To a solution of **19** (mixture) (120.0 kg, 360.0 mol, corrected by HPLC assay) in toluene (293 kg), additional toluene (1040 kg) is added. Lithium triethylborohydride (∼20% in THF, 215.0 kg) is then added at −70 ± 10 °C under a nitrogen atmosphere, and the mixture is stirred for 1.5 h. After completion of the reaction, the mixture is quenched with acetic acid (26.4 kg) in toluene (208 kg) at −70 ± 10 °C. The reaction temperature is then raised to −25 ± 10 °C, followed by the addition of sodium hypochlorite solution (1740 kg). The organic layer is separated and washed with sodium hypochlorite solution (1200 kg). This washing process is repeated two more times, followed by washing with 10% brine solution (660 kg). The organic layer is then separated and concentrated in 8−10 volume stages to obtain solution **20**, which then proceeds to the next step. To a solution of **20**, 2,6-lutidine (84 kg) and trifluoroacetic anhydride (83 kg) are added at 0 ± 5 °C. The resultant mixture is stirred at 50 ± 5 °C for 4 h, then cooled to 25 ± 5 °C. Next, 10% sodium bicarbonate solution (600 kg) is added. The layers are separated, and the organic layer is washed with 10% aqueous citric acid solution (1200 L), followed by 5% brine solution (570 kg). The organic layer is separated and concentrated at a temperature below 60 °C to obtain **13** as a thick oily reaction mixture. [*Yield: 91.2 kg, 287.3 mol (80%, over two steps), corrected by HPLC assay]

*Including a small amount of residual toluene.

13: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.95−7.92 (m, 2H), 7.67−7.64 (m, 1H), 7.54−7.50 (m, 2H), 6.22−6.18 (m, 1H), 4.42−4.39 (m, 1H), 2.91−2.89 (m, 1H), 2.84−2.77 (m, 1H), 2.41−2.27 (m, 1H), 1.67 (s, 3H), 1.41 (s, 9H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ: 165.6, 150.8, 133.3, 129.6, 129.3, 128.6, 123.6, 115.1, 79.3, 65.0, 55.4, 36.9, 31.2, 28.1, 22.1, 13.5 ppm. HRMS (positive mode): calculated for $C_{13}H_{16}NO_2$ (M − Boc + H)$^+$: 218.1181; found: 218.1171.

https://doi.org/10.1021/acs.oprd.4c00223
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*Step-7: tert-butyl 3-((benzoyloxy)methyl)-5-methyl-2-azabicyclo[3.1.0]hexane-2-carboxylate (**14**).* To a solution of **13** (50.0 kg, 157.5 mol, corrected by HPLC assay) in toluene (1000 kg) at −25 °C, diethylzinc (1.0 M in toluene, 287.85 kg, 319.8 mol) is added. The reaction mixture is stirred at −25 °C for 30 min. The temperature of the reaction mixture is then allowed to rise to 0 °C to −5 °C, and a solution of chloroiodomethane (193.4 kg, 1096.5 mol) in toluene (173 kg) is added in four portions. The mixture is stirred at 0 °C to −5 °C for 6 h. After completion of the reaction, the mixture is quenched with aqueous $NaHCO_3$ (50 kg of $NaHCO_3$ dissolved in 500 kg of water). The resulting mixture is stirred at room temperature for 30 min and then filtered through Celite, and the bed is washed with toluene (217 kg). The organic layer is separated from the filtrate. The product is extracted from the aqueous layer using toluene (217 kg). The combined organic layers are washed with water (500 kg), followed by a brine solution (250 kg), and then concentrated to two volume stages before proceeding to the next step.

*Step-8: tert-butyl 3-(hydroxymethyl)-5-methyl-2-azabicyclo[3.1.0]hexane-2-carboxylate (**21**).* To the crude compound **14** (**14**:**14a** = 97:3) from Step-7 (100 kg, 315.1 mol, calculated from compound **13**: two combined crude batches from Step-7), methanol (792 kg) is added, and the mixture is stirred at 0 ± 5 °C. Then, 25% sodium methoxide in methanol (67 kg) is added. The reaction mixture is stirred at 25 ± 5 °C for 2 h. The mixture is then cooled to 0 ± 5 °C, and water (1000 kg) is added. The temperature is raised to 32−36 °C and maintained for 34 h. The reaction mixture is concentrated below 45 °C until no distillate is observed (leaving an aqueous layer in the vessel). The mixture is then cooled to 25 ± 5 °C, and the product is extracted with *n*-heptane (684 kg). The organic layer is separated, and the aqueous layer is extracted again with *n*-heptane (342 kg), with the *n*-heptane extraction repeated once more. The combined organic layers are washed with 5% citric acid (525 kg), followed by water (500 kg), and then with 10% brine (550 kg). The organic layer is concentrated below 45 °C until no distillate is observed, yielding a mixture of compounds **21** and **21a** as a thick semisolid. [Yield: 42.06 kg, 185.0 mol (59%, over two steps: Step-7 and Step-8), corrected by HPLC assay]

*Step-9 and Step-10: (1R,3S,5R)-2-(tert-butoxycarbonyl)-5-methyl-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (**1**).* To a solution of a compound mixture of **21** and **21a** (49.22 kg, 216.5 mol, corrected by HPLC assay) in acetonitrile (50 kg), monosodium phosphate (49.22 kg) in water (123 kg) and TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) (4.04 kg) are added at 25 ± 5 °C. After stirring the reaction mixture for 30 min, the temperature is cooled to 20 ± 5 °C. Sodium chlorite (29.53 kg) in water (49.22 kg) and a diluted solution of sodium hypochlorite (4.92 kg) in water (15.75 kg) are then added simultaneously (note: if not added simultaneously, two unknown impurities, each approximately 5%, will be generated) at below 35 °C. The reaction mixture is stirred for 9 h at below 35 °C. After completion of the reaction, the mixture is quenched with a sodium sulfite solution (49.22 kg in 492 kg water, total 541 kg). The product is extracted with toluene (214 kg). The organic layer is cooled to 15 ± 5 °C, and the aqueous layer is adjusted to pH 2.5−3.5 with 1.5 M HCl solution, then stirred for 30 min. The organic layer is separated. Toluene (128 kg) is added, and the extraction is repeated from the aqueous layer. The combined organic layers are washed with water (492 kg) and separated. This washing step is repeated once more. The organic layer is then washed with 10% brine (492 kg) and separated, and the solvent is removed in vacuo below 55 °C until a volume of approximately 5 times the initial volume remains. Benzylamine (24.61 kg) in toluene (86 kg) is added at 25 ± 5 °C, and the reaction mixture is stirred for 1 h at 45 ± 5 °C. The mixture is then cooled to 25 ± 5 °C, and the solid is filtered. The slurry is washed with toluene (85.64 kg). The solids are suspended in dichloromethane (655 kg), the reaction mixture is cooled to 15 ± 5 °C, and the pH is adjusted to approximately 1−2 with 1.5 M HCl solution. The aqueous layer is back-extracted with dichloromethane (327 kg), and this extraction is repeated once more. The combined organic layers are washed with water (246 kg), then with 10% brine (246 kg), separated, and concentrated to approximately 1−2 times the initial volume. *n*-Heptane (100 kg) is added to the concentrated reaction mixture, and the solvent is removed in vacuo at a temperature below 55 °C until approximately 1−2 times the initial volume remains. This process is repeated once more. *n*-Heptane (67 kg) is added, and the reaction mixture is cooled to 25 ± 5 °C and stirred for 2 h to precipitate the solids. The solids are filtered, washed with *n*-heptane (67 kg), and dried under vacuum at 35 ± 5 °C for 8 h to afford compound **1** as white solids. [Yield: 34.32 kg, 142.2 mol (66%, over two 2 steps)]

1: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.47 (bs, 1H), 3.84 (m, 1H), 3.08−3.03 (m, 1H), 2.42−2.36 (m, 1H), 1.84 (bs, 1H), 1.45−1.33 (m, 9H), 1.15 (s, 3H), 0.62 (s, 2H) ppm, ^{13}C NMR (DMSO-d_6, 101 MHz) δ 173.2, 154.4, 79.2, 59.8, 42.7, 37.9, 28.0, 22.8, 21.1, 20.5 ppm. HPLC chiral purity: 99.90%. HRMS (negative mode): calculated for $C_{12}H_{18}NO_4$ $(M - H)^-$: 240.1236; found: 240.1239. Chemical purity (by HPLC): 99.4% (major impurities: $BnNH_2$, benzoic acid, and **1a**). Chiral purity (by chiral HPLC): 99.9%.

1a is prepared following the procedure in ref 5.

1a: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.57 (bs, 1H), 4.37 (m, 1H), 3.10 (m, 1H), 2.37 (m, 1H), 1.98 (m, 1H), 1.41−1.32 (m, 9H), 1.17 (s, 3H), 0.91 (m, 1H), 0.56 (m, 1H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz) δ: 174.3, 153.3, 78.8, 58.8, 42.3, 36.3, 28.0, 22.1, 20.3, 18.5 ppm. HRMS (negative mode): calculated for $C_{12}H_{18}NO_4$ $(M - H)^-$: 240.1236; found: 240.1238.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.4c00223.

Characterization data for isolated compounds, including ^{1}H and ^{13}C NMR spectra, NOE charts, purity, and LC-MS and HRMS data (PDF)

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https://doi.org/10.1021/acs.oprd.4c00223
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The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Polisetty Kartik, Process Engineering, Syngene International Ltd., for generating chemical manufacturing process safety data.

■ ABBREVIATIONS

MLR mother liquor
DP diastereomeric purity

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https://doi.org/10.1021/acs.oprd.4c00223
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