ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D
Article
Cite This: Org. Process Res. Dev. XXXX, XXX, XXX−XXX
pubs.acs.org/OPRD

Process Development of an Efficient and Cost-Effective Telescoping Route to a Key Synthetic Precursor for the Preparation of a Renin Inhibitor

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Supporting Information

ABSTRACT: Here, we describe an efficient and cost-effective telescoping route to the pharmacologically active form (**2**), which is a key manufacturing precursor to a novel renin inhibitor for the treatment of hypertension. An efficient synthetic route to the target compound was established with 64% overall yield over nine steps with three isolations.

KEYWORDS: *renin inhibitor, prodrug, telescoping, C−N coupling, N/O chemoselectivity, oxazinone*

INTRODUCTION

Plasma renin activity[1] (PRA) plays an important role in the pathogenesis of hypertension (elevated blood pressure). In addition, high PRA is known to be a risk factor for myocardial infarction (heart attack) in patients suffering from hypertension.

During our screening study, the oxazinone derivative (**2**) was identified as a potential renin inhibitor. However, a parallel artificial membrane permeability assay showed that improvement in membrane permeability was required. Therefore, the medicinal team designed **1** as an optimized prodrug of **2**, which possessed immediate absorption and suitable physicochemical properties. **1** was transformed to its active metabolite **2** immediately in the body and showed powerful inhibition of PRA activity in human plasma (half-maximal inhibitory concentration (IC_{50}) = 0.73 nM).

The retrosynthetic pathway of **1** (Scheme 1) shows that **1** was derived from **2** and the prodrug[2] part (double esters;[3] **3**). Establishment of an efficient synthetic route for the structurally complex **2** will be essential for future commercial production. Here, we describe the history of synthetic development and present an efficient, cost-effective telescoping route to **2**.

RESULTS AND DISCUSSION

Discovery Route. The discovery route[4] to **2** used by the medicinal chemistry team is described in Scheme 2. Tetra-substituted benzene **4** was prepared from a commercially available derivative of benzoic acid over two steps in 41% yield in which only low regioselectivity was observed in nitration.[5] Benzylation of **4** and subsequent hydrolysis of **5** under a basic condition led to a tetra-substituted benzoic acid derivative **6**. Condensation with **14** gave **7** in 87% yield. Reduction of the nitro group and removal of the benzyl group on **7** was carried out simultaneously by hydrogenation in excellent yield. Subsequent amidation of **8** with **15** and intramolecular cyclization in the presence of cesium carbonate provided **10**, which required purification by silica-gel chromatography (overall yield over two steps, 47%). *N*-Alkylation of **10** with **16**, followed by deprotection of the Cbz group by hydrogenation and *N*-acylation with propionyl chloride, afforded **13** (overall yield over two steps, 66%). Finally, acid-mediated removal of the Boc group and purification by silica-gel chromatography delivered **2** in quantitative yield. The overall yield of the process to **2** was 10%. A 50 g synthesis of API was accomplished for the toxicity test through this synthetic route.

First- and Second-Generation Process Routes. The discovery route described above is not particularly attractive for large-scale manufacturing because of: (i) the requirement of several rounds of silica-gel column chromatography; (ii) a potentially explosive nitration reaction; (iii) a long linear route. We focused on these issues and planned the convergent route shown in Scheme 3.

We considered that **2** would be condensed between the corresponding carboxylic acid **29** and a secondary amine. We planned to introduce the carboxylic acid unit of **29** by Friedel−Crafts acylation of **26**, which would be prepared from the

Special Issue: Japanese Society for Process Chemistry

Received: November 30, 2018

DOI: 10.1021/acs.oprd.8b00414
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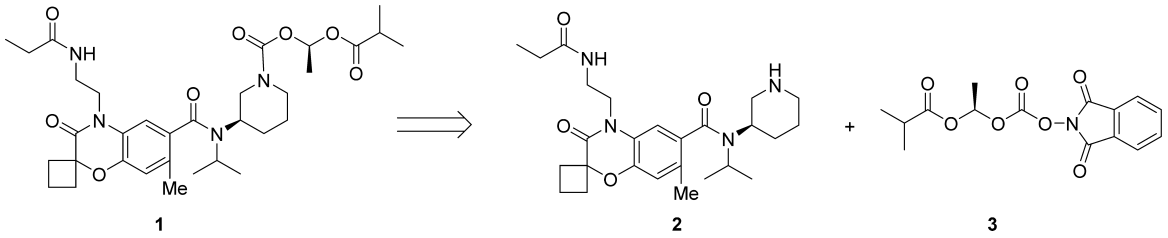
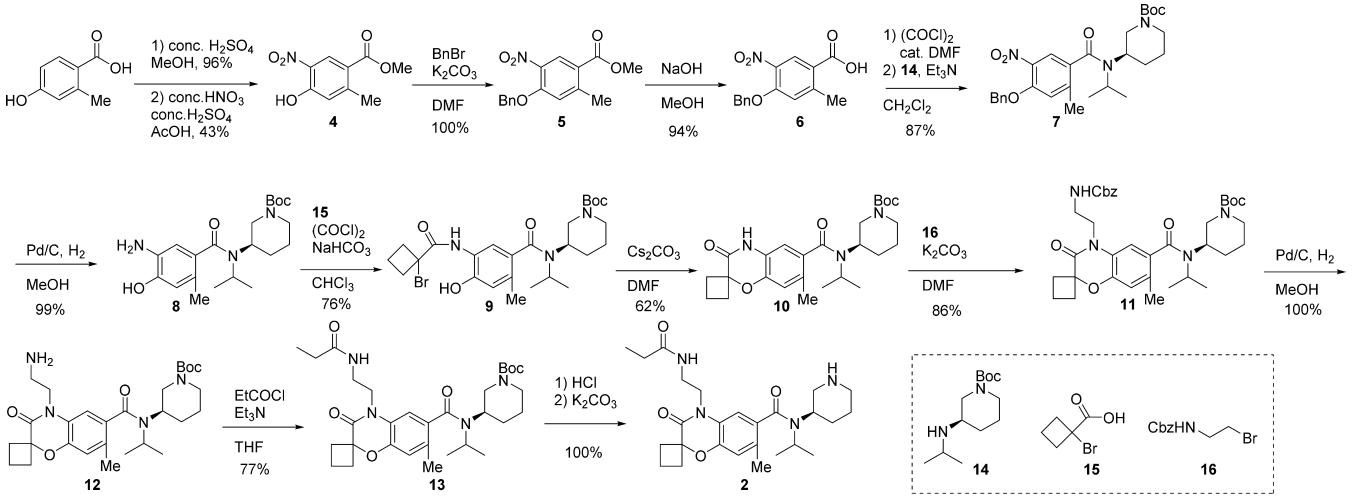
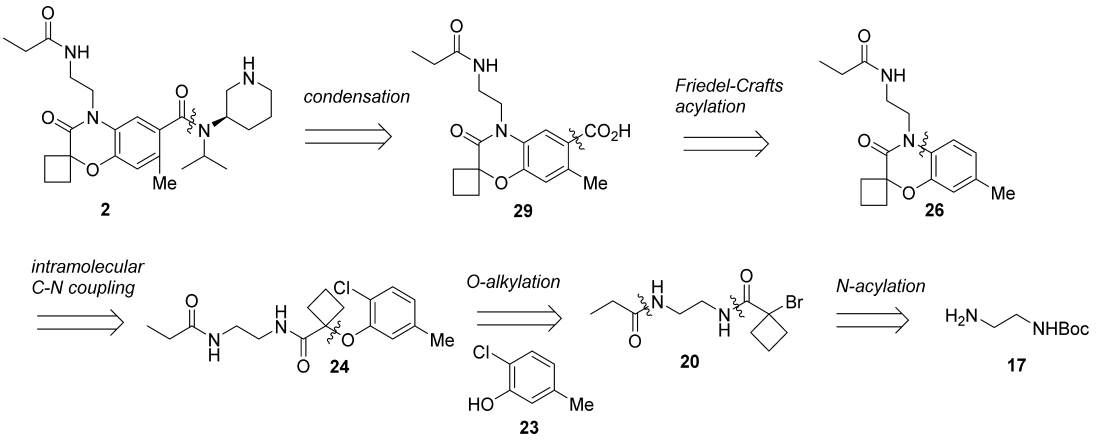
Scheme 1. Retrosynthetic Pathway of 1



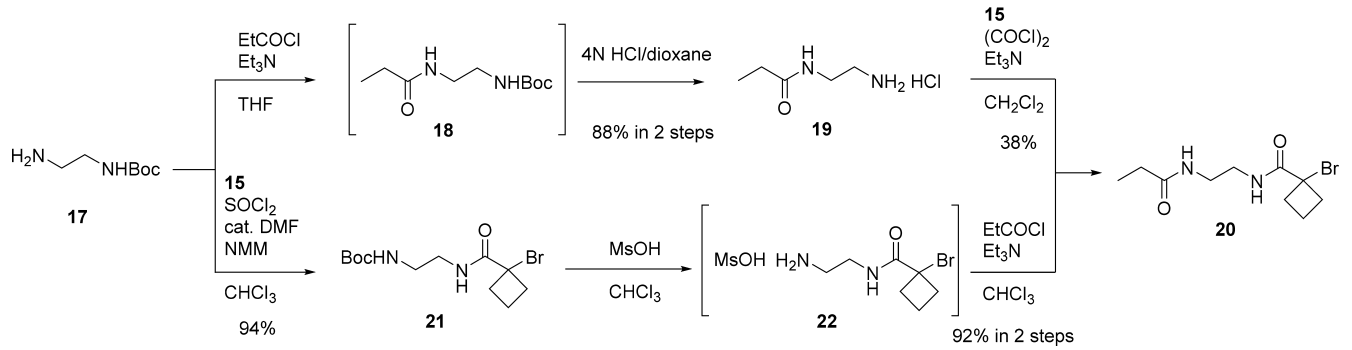
Scheme 2. Discovery Route of 2



Scheme 3. Retrosynthesis Analyses of 2



Scheme 4. Route Selection to 20



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Scheme 5. *O*-Alkylation and Byproduct via Smiles Rearrangement

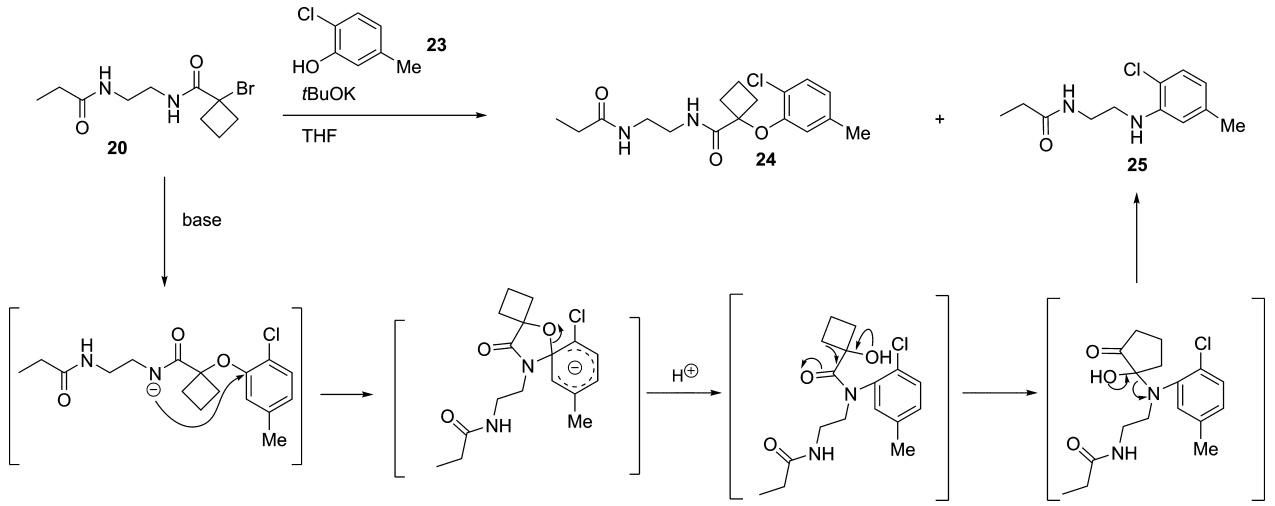
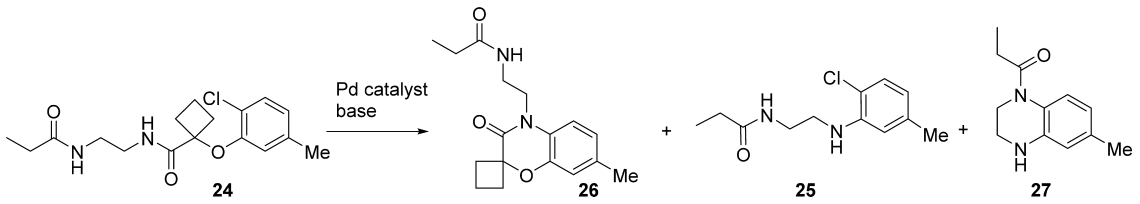


Table 1. Examination of C−N Coupling



entry	Pd cat.	mol %	base	solvent	temp [°C]	**24** [%][a]	**26** [%][a]	**25** [%][a]	**27** [%][a]
1	$Pd(PtBu_3)_2$	10	K_2CO_3	DMF	150	Nd	88 (69)[b]	3	9
2	$Pd(PtBu_3)_2$	10	K_3PO_4	DMF	150	Nd	78	Nd	22
3	$Pd(PtBu_3)_2$	10	Cs_2CO_3	DMF	150	Nd	60	Nd	40
4	$Pd(PtBu_3)_2$	2.5	K_2CO_3	DMF	150	Nd	98 (70)[b]	0.4	0.6
5	$Pd(PtBu_3)_2$	2.5	K_2CO_3	NMP	150	3	19	50	Nd
6	$Pd(PtBu_3)_2$	2.5	K_2CO_3	toluene	110	79	18	Nd	Nd
7	$Pd(PPh_3)_4$	2.5	K_2CO_3	DMF	150	10	1	44	Nd
8	NHC-Pd **1**[c]	2.5	K_2CO_3	DMF	150	Nd	52	32	Nd
9[d]	$Pd(PtBu_3)_2$	5	K_2CO_3	DMF	140	Nd	92 (75)[b]	Nd	4.8

[a]HPLC area%. [b]Isolated yield. [c]NHC-Pd **1**: allychloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-idinylidene]palladium(II). [d]Manufacturing condition for first-process generation route.

intramolecular C−N coupling of **24**. The latter would be synthesized via *O*-alkylation between the corresponding phenol **23** and diamide **20**, which would be prepared from the mono-Boc ethylenediamine **17**.

First, we evaluated the order of *N*-acylation for the synthesis of **20** from **17** (Scheme 4). The mono-Boc-protected **17** was prepared from the reaction between Boc anhydride and an excess amount of ethylenediamine[6] in 74% yield. In the first instance, *N*-acylation of **17** with propionyl chloride and subsequent deprotection of the Boc group were done in one pot to yield noncrystalline **19** in good yield.[7] Without further purification, secondary *N*-acylation of **19** with acyl chloride derived from **15** presented **20** in 38% isolated yield. The hydroscopic property of **19** led to degradation of the acid anhydride form of **15** to give the low yield. In the alternate sequence, amide **21** resulting from **17** and **15** could be isolated by crystallization from $CHCl_3$/*n*-heptane as white crystals in 94% yield with >98% high-performance liquid chromatography (HPLC) purity. One-pot Boc deprotection followed by the second *N*-acylation with propionyl chloride proceeded to provide **20** in high yield with >99% purity through crystallization.

With a synthesis of **20** secured, the final assembly was pursued. *O*-Alkylation of **23** was conducted with **20** by addition of *t*BuOK in THF (Scheme 5). The aniline compound (**25**) was formed as a byproduct that increased over time via Smiles rearrangement.[8] The aniline **25** was removed completely by crystallization to give the crystalline **24** in 79% isolated yield in 98% HPLC.

Formation of the benzoxazine core via intermolecular Pd-catalyzed carbon−nitrogen coupling reaction[9,10] was investigated (Table 1). The reaction proceeded with 10 mol % $Pd(PtBu_3)_2$[11] and K_2CO_3 in DMF at 150 °C in 69% isolated yield in 98% HPLC purity (entry 1). When using a stronger base such as K_3PO_4 or Cs_2CO_3, larger amounts of **25** or **27** via Smiles rearrangement were formed (entry 2, 3) as byproducts. A smaller amount of catalyst also showed excellent reactivity (entry 4). Employing this reaction in other solvents such as NMP or toluene did not elicit better results (entry 5, 6). Using other Pd catalysts such as $Pd(PPh_3)_4$ or Pd *N*-heterocyclic carbene catalysts such as NHC-Pd **1**[12] gave lower or moderate

DOI: 10.1021/acs.oprd.8b00414
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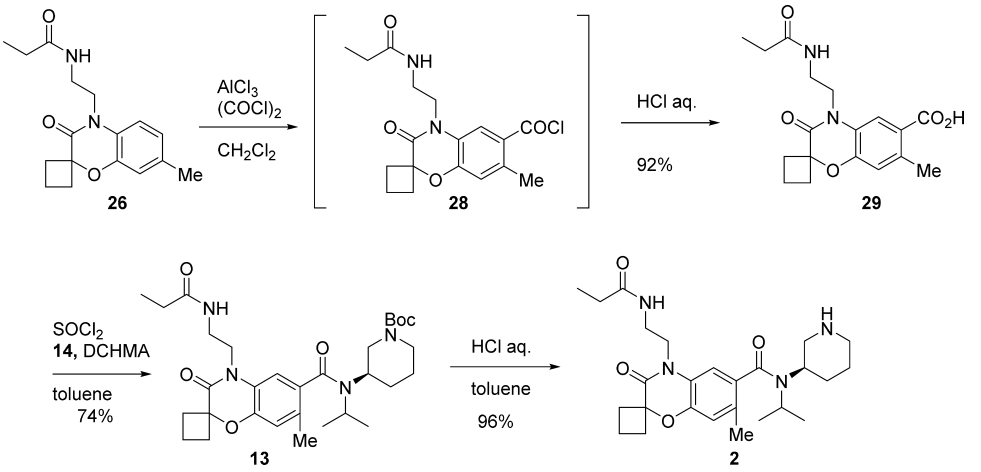
Scheme 6. Friedel–Crafts Acylation to 29 and Conversion to 2



yields (entry 7, 8). Consequently, $Pd(PtBu_3)_2$ and K_2CO_3 in DMF appeared to be the suitable condition for the reaction. Typically, this reaction consumed the starting material; however, when a different lot of $Pd(PtBu_3)_2$ was used in a kilogram-scale synthesis, the starting material was not consumed and a larger amount of byproducts were observed. This suggests that different lots of catalyst perform differently. In order to prepare needed material, 5 mol % of $Pd(PtBu_3)_2$ was used for the kilogram-scale campaign, and the reaction proceeded smoothly. Celite filtration, extraction with toluene/MTBE, and solvent switching to AcOEt were carried out. Crystallization from AcOEt/heptane delivered 6.4 kg of **26** in 75% yield with >99% HPLC purity as brown crystals.

Construction of the tetra-substituted benzene **29** was achieved through a Friedel–Crafts reaction (Scheme 6). The reaction required an excess amount of $AlCl_3$, $(COCl)_2$, and quenching with 1 N HCl aq. to provide **29**. During quenching, a considerable exothermic reaction (243 kcal/mol measured by super CRC) was observed. A slow addition of 1 N HCl over 3 h and a large amount of reaction solvent were therefore required. However, this led to low productive efficiency in the reaction (~17 g of target compound per L). After completion of quenching, 1-BuOH was added and the phases were allowed to separate. Insufficient water washing led to formation of the butyl ester of **29** in the crystallization step. Thus, the organic layer was washed until the pH of the water layer was above 2.5. Then, 6.8 kg of **29** was isolated by crystallization from 1-BuOH in 92% yield with >99% HPLC purity as white crystals. Acyl chloride formation was achieved by treating **29** with 1.9 equiv of $SOCl_2$ at 50 °C, followed by removal of excess $SOCl_2$ and gas under reduced pressure. Addition of a mixture of **14** and *N,N*-dicyclohexylmethylamine (DCHMA) at 50 °C afforded **13**. Importantly, the acid anhydride **30** (Figure 1) was generated readily in the presence of even small amounts of water. Thus, **14** and DCHMA were dried via a water–toluene azeotrope before being used. Variations in the reaction time and color (which required decoloration with active carbon) in the acyl chlorination step were observed, but 8 kg of amide **13** was delivered in 74% isolated yield with >99% HPLC purity. Finally, removal of the Boc group in **13** and desalting with NaOH aq. gave 6 kg of **2** in 96% yield. The overall yield of the entire process from ethylenediamine to **2** was 24%, and 5.9 kg of API by this first-generation process route was delivered for the preclinical and clinical test.

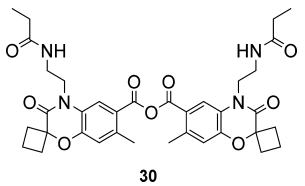


Figure 1. Structure of the acid anhydride **30**.

Further scale-up for the next campaign required minor optimization in each step (second-generation process route in Scheme 7). In the first-generation process route, generation of the impurity **25** was the cause of the lower yield in the *O*-alkylation step. We found that using *t*BuONa as a base and toluene/1-BuOH = 3/1 (w/w) as a solvent could suppress generation of this impurity. This optimized condition gave target compound **24** in 88% yield and >98% HPLC purity. The next stage of the synthesis was intermolecular carbon–nitrogen coupling in **24**. Through the previous campaign, variation of the catalytic activity between lots of $Pd(PtBu_3)_2$ was observed. Thus, in situ preparation of the catalyst was investigated, and it was achieved with 2 mol % $Pd(OAc)_2$ and 6 mol % $PtBu_3$[13] in xylene, which provided **26** in 96% yield and >99% HPLC purity. Use of excess $AlCl_3$ and $(COCl)_2$ resulted in considerable time for quenching, low production efficiency, and generation of hazardous CO, but reduction of these reagents or adaptation of another method was not found. Friedel–Crafts acylation was conducted without optimization, which resulted in 32 kg of **29** in 91% yield and >99% HPLC purity. This campaign revealed that further scale-up would be inadvisable because quenching with 1 N HCl led to considerable safety concerns for further scale-up. Acyl chlorination of **29** was accomplished with $SOCl_2$ in a previous manufacturing process, but variation in the reaction time and brown coloration of the target compound were noted. Through screening of acyl chlorination reagents, 1-chloro-*N,N*-2-trimethyl-1-propenylamine (CTPA)[14] was found to be suitable for the reaction, and this reagent can be obtained in bulk quantity at reasonable cost. Compared with $SOCl_2$, acyl chlorination with CTPA did not require removal of excess reagents and/or decoloration with activated carbon. The optimized procedure was scaled up to 1200 L, whereby 28 kg of **13** was prepared in 86% yield and >99% HPLC purity as white crystals. The final stage of the synthesis was scaled up

DOI: 10.1021/acs.oprd.8b00414
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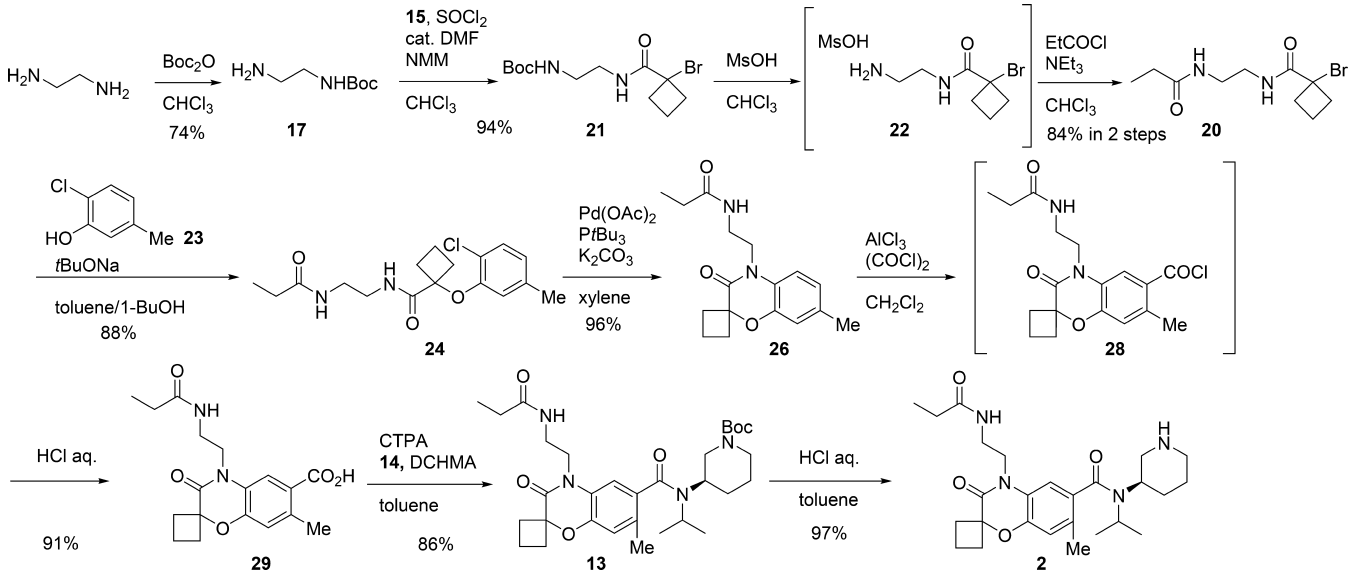
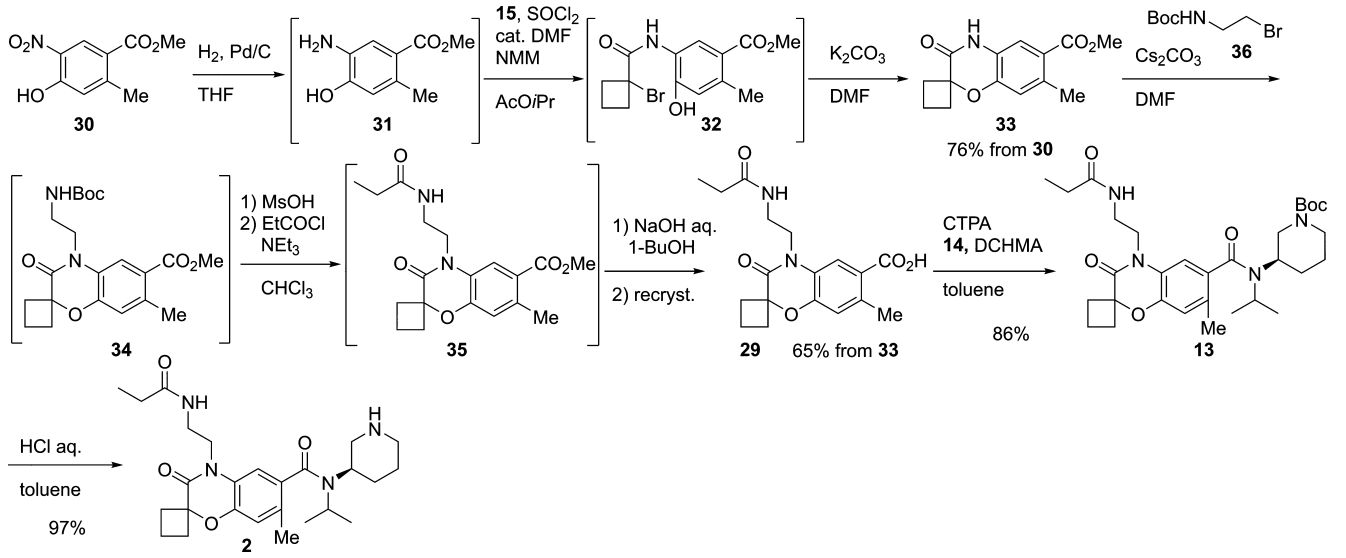
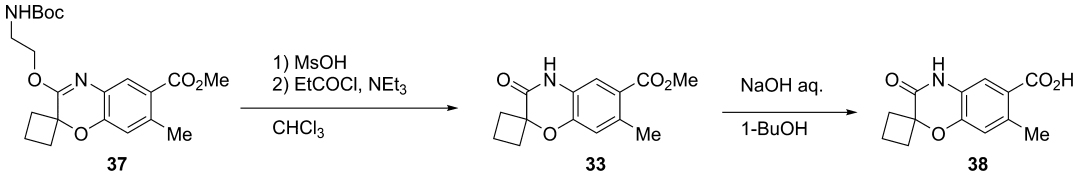
Scheme 7. Second-Generation Process Route of 2



Scheme 8. Third-Generation Process Route of 2



Scheme 9. Fate Analysis on *O*-Alkylated Byproduct 37



without optimization, which delivered 22 kg of **2**. In this campaign, the overall yield from ethylenediamine to **2** was 37%.

Third-Generation Process Route. We achieved kilogram-scale synthesis of **2** through the second-generation process route. However, inherent issues in Friedel–Crafts acylation and modest overall yield were important bottlenecks in terms of a cost-effective, efficient commercial manufacturing route. Thus, we attempted to find an alternate route for the synthesis of **2**. Intensive survey of materials revealed that the tetra-substituted benzene derivative **30** could be obtained in bulk quantity from suppliers at reasonable cost. Hence, Friedel–Crafts acylation could be avoided, and the synthetic route was shortened.

The nitro compound **30** was reduced to the corresponding amine **31** by hydrogenation in the presence of Pd/C in quantitative yield (Scheme 8). After removal of Pd/C through filtration, treatment of **31** with acyl chloride derived from **15** gave amide **32**. The latter was extracted with AcO*i*Pr, and the solvent exchanged into DMF in preparation for the next step. The solution was heated to 80 °C in the presence of potassium carbonate to afford **33**, which was isolated by crystallization

DOI: 10.1021/acs.oprd.8b00414
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from DMF/water and resulted in preparation of a three-step telescoped approach in 76% overall yield. Treatment of **33** with **36** in the presence of cesium carbonate as a base in DMF was converted to **34** contaminated with ca. 10% of the *O*-alkylated compound **37** as a major byproduct.[15] Then, **34** was extracted with $CHCl_3$ and reacted with 5 equivalents of methanesulfonic acid to prompt deprotection of the Boc group. Subsequent *N*-acylation with propionyl chloride in the presence of triethylamine was carried out in one pot to produce **35**. After washing with water, $CHCl_3$ was displaced to 1-BuOH, hydrolysis was carried out in two phases, and **29** was isolated by crystallization from 1-BuOH. Although crystalline **29** had >98% purity, it contained 1.4% of **38** derived from **37**[16] (Scheme 9). This amount of **38** was too high to permit isolation of acceptable API. Therefore, further purification of **29** by recrystallization was required, which reduced impurities to an acceptable level (<0.3%). The four-step telescoped synthesis and single recrystallization from **33** to **29** led to a yield of 65%. Conversion to **2** through **13** was achieved by the same manner as the second-generation process route. The overall yield to **2** was improved to 41% over nine steps.

Fourth-Generation Process Route. The following three issues still remained in the third generation synthesis: (i) there are a high number of intermediates isolated, which causes product loss and poor process efficiency; (ii) there is a high formation of impurities, which causes poor yield; (iii) undesirable solvents such as $CHCl_3$ and DMF needed to be avoided considering the environmental, toxicological, and quality concerns. We began to explore a more efficient synthetic route by improving the third generation process route. Analysis of **32** revealed that the *N*,*O*-bisacyl compound **39** (HPLC area%: 1.1%) was a major byproduct (Figure 2). By

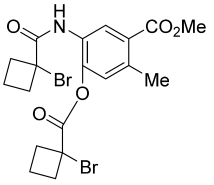

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Figure 2. Structure of the bisacyl **39**.

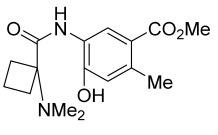
secondary addition of *N*-methyl moropholine (NMM) and heating the reaction mixture to 45 °C in the step, the impurity **39** was reacted with the substrate **31** to give target compound **32**.

In the next intramolecular *O*-alkylation, DMF-derived byproduct **40** and intermolecular alkylation reaction-derived byproducts **41** and **42** were identified (Figure 3). Hanging the solvent from DMF to NMP and dilute conditions could suppress formation of these byproducts, and **33** was isolated by crystallization from NMP/water with >99% purity. This optimized processes increased the yield from 76% to 87% over the initial three steps.

As mentioned above, contamination of **38** into **29** derived from the *O*-alkylated compound **37** required recrystallizations to gain **29** with satisfactory purity in the third-generation process route. To ameliorate this situation, we scrutinized the reaction conditions from **33** to **34** closely (Table 2). Less expensive K_3PO_4 and less toxic DMA showed almost identical reactivity and N/O selectivity compared with the original procedure (entries 1 and 2). Heating to 70 °C increased reactivity, although regioselectivity was decreased slightly (entry 3). No reaction took place with K_2HPO_4 or Li_3PO_4 (entries 4 and 5). K_2CO_3 elicited lower reactivity and selectivity (entry 6). Tertiary alkoxides such as *t*BuOK, *t*BuONa, or *t*BuOLi presented higher selectivity, but a larger amount of starting material remained unreacted (entries 7, 8, and 9). Other solvents such as THF or acetonitrile did not give satisfactory results (entries 10 and 11). Consequently, the less expensive K_3PO_4 and less toxic DMA at 70 °C was chosen as the best condition (entry 2) from the perspective of reactivity and selectivity.

To improve purity, undissolved salt was removed through filtration, and then, toluene (instead of $CHCl_3$) was used for extraction at 70 °C to afford **34** in toluene solution. Treatment of **34** with methanesulfonic acid resulted in a Boc-deprotected methanesulfonic acid salt **43**, but the *O*-alkylated compound **37** was transformed to **33** (Scheme 10). The latter remained in the organic layer of combined solvents (toluene/THF = 9/1) efficiently, but additional extraction with toluene ensured that the methanesulfonic acid salt **43** was extracted into the water layer exclusively. An aqueous solution of sodium hydroxide was added in the presence of propionic anhydride in two phases to invoke neutralization and *N*-acylation consecutively. Subsequent hydrolysis of **35** gave **29** after crystallization from 1-BuOH, which provided the compound in >99.5% purity without further purification. The yield from **33** to **29** was increased from 65% to 80% over four steps.

The main reason for isolation of **13** was to remove **44** (Figure 4), and therefore, it was thought that control of **44** would allow for one less isolation. To suppress this formation of **44**, initially, we attempted an inverse addition such that the acid chloride **28** solution was added dropwise to a mixture of amine **14** and DCHMA. This inverse addition could reduce formation of dimer **44** from 4.2% to 0.5%, but the acid chloride **28** solution in toluene was supersaturated, and the precipitated acyl chloride was clogged during transfer. However, it was proposed that precipitation of the acid chloride **28** reduced its concentration in the supernatant, which could lead to suppression of dimer formation. This was explored by modifying the temperature described in Table 3. Addition of the amine **14** into acid chloride **28** without precipitation of **28**



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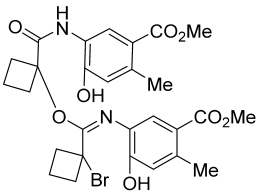

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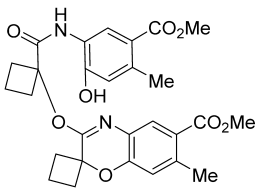

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Figure 3. Structure of impurities in the intramolecular *O*-alkylation.

DOI: 10.1021/acs.oprd.8b00414
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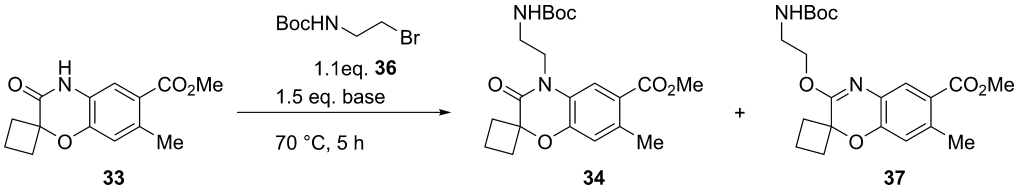
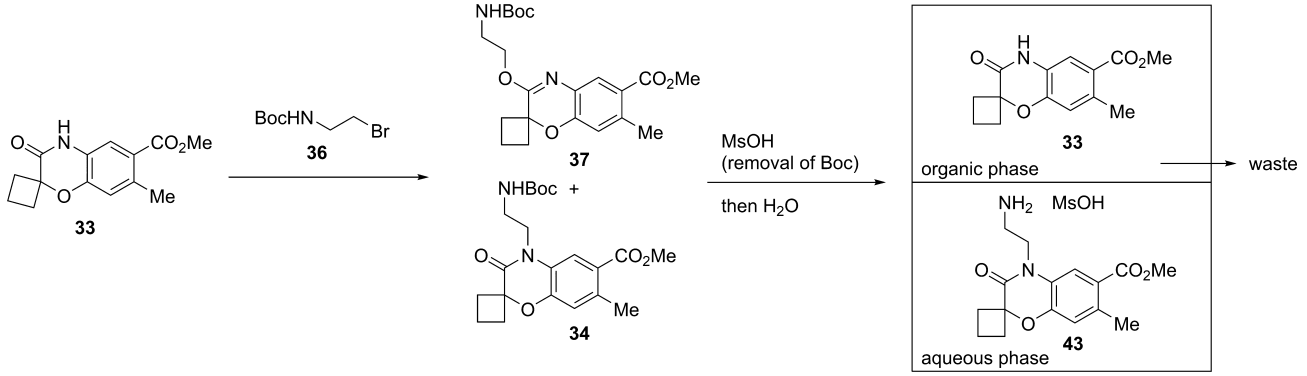
Table 2. Optimization of the Reaction Condition for *N*-Alkylation



entry	base	solvent	temp [°C]	34/(34 + 33) [%][a]	34/37[a]
1	Cs_2CO_3	DMF	50	96.8	12.1/1
2	K_3PO_4	DMA	50	92.2	12.7/1
3	K_3PO_4	DMA	70	98.9	11.6/1
4	K_2HPO_4	DMA	70	NR	NR
5	Li_3PO_4	DMA	70	NR	NR
6	K_2CO_3	DMA	70	60.5	10.9/1
7	*t*BuOK	DMA	70	92.3	17.4/1
8	*t*BuONa	DMA	70	81.1	15.7/1
9	*t*BuOLi	DMA	70	74.4	19.5/1
10	K_3PO_4	THF	70	28.8	11.8/1
11	K_3PO_4	CH_3CN	70	82.4	14.5/1

[a]Calculated on the basis of HPLC area%.

Scheme 10. Removal of the *O*-Alkylated Byproduct



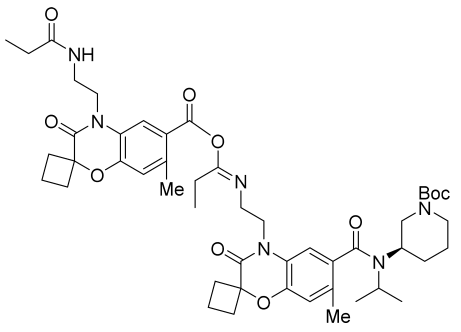


Figure 4. Structure of dimer **44**.

provided 4.2% of dimer **44** at 40 °C (entry 1). A lower temperature enabled suppression of the amount of dimer **44** (entries 2 and 3) due to the precipitated acid chloride **28** (0.33% and 0.22%, respectively). Eventually, the equivalent of amine **14** could be decreased to 1.05 equiv without extension of the reaction time (entry 4).

Final acid-mediated deprotection of the Boc group in **13** gave **2** in excellent yield. For expediency, the chemistry mentioned above was telescoped such that **13** was not isolated but instead was converted directly to **2**, which resulted in 92% yield with >99% HPLC purity over two steps. The overall yield of the fourth-generation process route was 64% over nine steps (Scheme 11).

SUMMARY

We developed an efficient and cost-effective telescoping route to **2**, which is the key precursor for a novel renin inhibitor (**1**). In the first steps, optimization of the reaction and workup condition in each step through the physicochemical properties of impurities and development of a telescoped process were accomplished. For the following four steps and final two steps, we developed telescoped processes to avoid the isolation of intermediates. The overall yield to **2** approached 64% over nine steps. The route comparison is shown in Table 4. Compared with the discovery route, the number of steps and isolations improved from 12 to 9 and 12 to 3, respectively, and the overall yield increased from 10% to 64%.

EXPERIMENTAL SECTION

General. ^1H and ^{13}C NMR spectra were recorded on a Bruker Ultrashield 400 Plus spectrometer at 400 and 100.6 MHz, respectively. Chemical shifts (δ) are given in parts per million, and tetramethylsilane was used as the internal standard for spectra obtained in DMSO-d_6, Methanol-d_4 and $CDCl_3$. High-resolution mass spectra were measured on a Thermo Fisher Scientific LTQ Orbitrap Discovery. HPLC was

DOI: 10.1021/acs.oprd.8b00414
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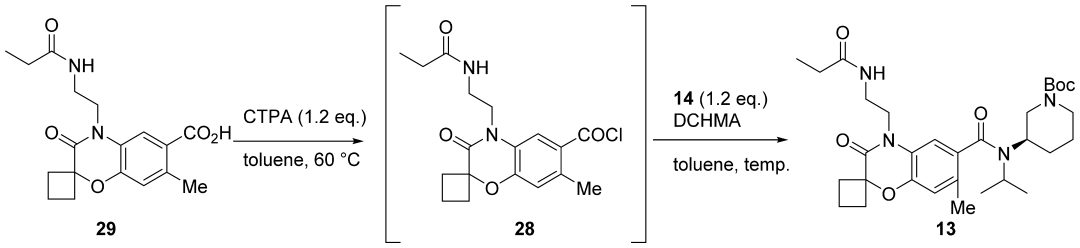
Table 3. Temperature Examination during Amidation



entry	temp [°C]	acyl chloride precipitate	time [h]	**29** [%][a]	**13** [%][a]	**44** [%][a]
1	40	–	3	0.09	90.32	4.21
2	30	+	3	0.18	96.29	0.33
3	20	+	4	0.41	96.22	0.22
4[b]	25	+	4	0.50	95.59	0.42

[a]HPLC area%. [b]1.05 eq. of **14** was used.

Scheme 11. Fourth-Generation Process Route

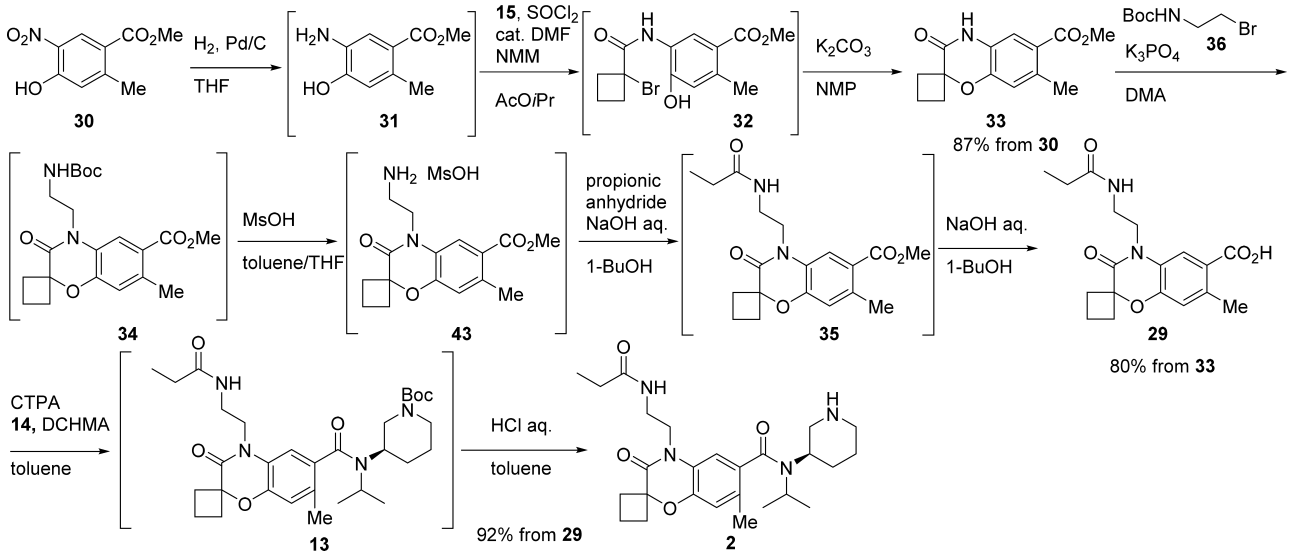


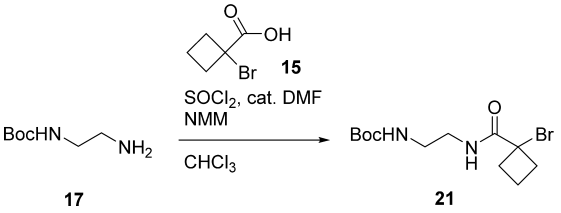
Table 4. Comparison of Synthetic Route

route	discovery route	second generation	third generation	fourth generation
number of reaction steps[a]	12	9	10	9
number of isolations[a]	12	8	5	3
overall yield (%)[a]	10	37	41	64
manufacturing cost[b]		100[c]	31[c]	19[c]

[a]From SM to **2**. [b]Manufacturing cost is calculated on the basis of variable cost and fixed for the synthetic route from SM to **1**. [c]Relative cost when the 2nd generation process route is set to 100.

performed on a Shimazu LC-20A; Sumipax ODS C-217 column (4.6 mm i.d. × 150 mm, 5 μm); eluent: (a) 0.1% TFA aq. and (b) MeOH; flow rate = 1.0 mL/min; temperature: 30 °C; UV detection at 220 nm; gradient: (b/a) 50/50 (0 min)−90/10 (0−30 min)−90/10 (30−35 min)−10/90 (35.01 min)−10/90 (35.1−45 min). The purity listed is determined by area %. All reactions were carried out under nitrogen unless otherwise mentioned. Reagents and solvents were used as obtained from commercial suppliers without further purification.

Second Generation Process Route (Scheme 7).



***tert*-Butyl (2-(1-bromocyclobutane-1-carboxamido)-ethyl)carbamate (21).** To a solution of **15** (28.0 kg, 156.4 mol, 1.0 equiv) dissolved in $CHCl_3$ (269.0 kg) and DMF (2.8 kg) was added thionyl chloride (22.3 kg, 187.4 mol, 1.2 equiv) dropwise over 1 h at 50 °C under a nitrogen atmosphere. The reaction was monitored by HPLC until completion (10 h) at the same temperature to give a solution of carboxylic acid chloride.

To a solution of **17** (27.6 kg, 172.3 mol, 1.1 equiv) dissolved in $CHCl_3$ (89.1 kg) and *N*-methyl morpholine (NMM) (34.8 kg, 344.0 mol, 2.2 equiv) was added the solution of carboxylic acid chloride over 2 h at −5 °C, and the reaction was monitored by HPLC until completion (1 h). To the mixture was added water (280.0 kg) and $CHCl_3$ (168.0 kg), followed by warming to 25 °C and stirring for 15 min. The separated

DOI: 10.1021/acs.oprd.8b00414
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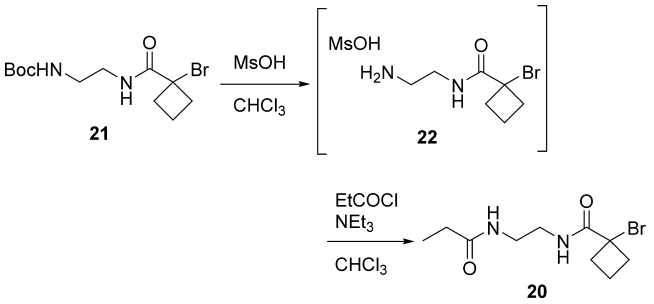
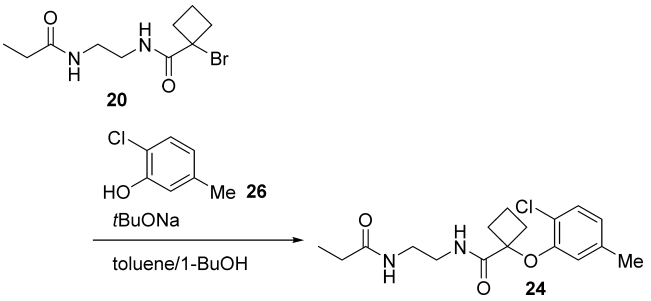
organic phase was washed with water (280.0 kg) with stirring for 15 min, and the organic phase obtained was concentrated by evaporation to give a suspension (164.0 kg). To this suspension was added $CHCl_3$ (61.2 kg), followed by heating to 50 °C to give a solution, and *n*-heptane (87.9 kg) was added dropwise over 40 min. The mixture was cooled to 43 °C; then, a precipitate was observed. After heating to 50 °C, *n*-heptane (87.9 kg) was added, and the mixture was cooled to 0 °C over 4 h; the precipitate obtained was filtered, washed with a mixture of $CHCl_3$ and *n*-heptane, and dried to give **21** (47.1 kg, 146.7 mol, 93.8% yield) as a white solid.

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (brs, 1H), 5.00 (brs, 1H), 3.37−3.31 (m, 2H), 3.30−3.23 (m, 2H), 2.97−2.88 (m, 2H), 2.57−2.48 (m, 2H), 2.28−2.16 (m, 1H), 1.95−1.84 (m, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 156.8, 79.7, 59.5, 41.5, 39.7, 37.8 (2C), 28.3 (3C), 16.9; HRMS (ESI) calcd. for $C_{12}H_{21}BrN_2O_3$ *m*/*z* 321.0808 [M + H]$^+$, found 321.0811.



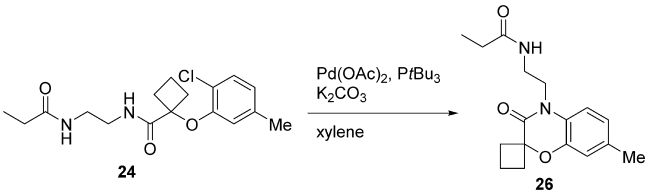
1-Bromo-*N*-(2-propionamidoethyl)cyclobutane-1-carboxamide (20). To a solution of **21** (47.1 kg, 146.6 mol, 1.0 equiv) in $CHCl_3$ (462.0 kg) was added methanesulfonic acid (21.1 kg, 220.0 mol, 1.5 equiv) over 15 min at 50 °C. The reaction was monitored by HPLC until completion (2 h), and the mixture was cooled to 25 °C. After addition of triethylamine (40.1 kg, 395.9 mol, 2.7 equiv) over 1 h at the same temperature, propionyl chloride (14.9 kg, 161.3 mol, 1.1 equiv) was added dropwise over 1 h at the same temperature. The reaction was monitored by HPLC until completion (1 h 10 min); then, water (236.0 kg) was added. A separated aqueous phase was extracted with $CHCl_3$ (405.0 kg) with stirring for 15 min. Combined organic phases were concentrated by evaporation to give a suspension in $CHCl_3$ (150.0 kg). To this suspension was added $CHCl_3$ (134.0 kg), followed by heating to 50 °C to give a solution, and *n*-heptane (91.4 kg) was added dropwise over 30 min. After cooling to 43 °C over 15 min, a precipitate was observed. The suspension was heated to 50 °C, and *n*-heptane (91.4 kg) was added over 20 min at the same temperature. After cooling to 0 °C over 3 h 30 min, the precipitate obtained was filtered, washed with a mixture of $CHCl_3$ and *n*-heptane, and dried to give **20** (34.0 kg, 122.8 mol, 83.8% yield) as a white solid.

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (brs, 1H), 6.17 (brs, 1H), 3.43−3.38 (m, 4H), 2.97−2.88 (m, 2H), 2.60−2.51 (m, 2H), 2.20 (q, *J* = 7.2 Hz, 2H), 2.30−2.19 (m, 1H), 1.96−1.85 (m, 1H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 172.5, 59.4, 40.8, 39.6, 37.8 (2C), 29.6, 16.9, 9.8; HRMS (ESI) calcd. for $C_{10}H_{17}BrN_2O_2$ *m*/*z* 277.0546 [M + H]$^+$, found 277.0548.



1-(2-Chloro-5-methylphenoxy)-*N*-(2-propionamidoethyl)cyclobutane-1-carboxamide (24). To a solution of *t*BuONa (14.2 kg, 147.3 mol, 1.2 equiv) in toluene (523.0 kg) and 1-BuOH (187.0 kg) was added **26** (17.5 kg, 122.7 mol, 1.0 equiv) with stirring under a nitrogen atmosphere. The mixture was stirred at 20 °C for 1 h. To the mixture was added **20** (34.0 kg, 122.7 mol, 1.0 equiv) over 40 min and stirred at the same temperature. The mixture was heated to 45 °C, and the reaction was monitored by HPLC until completion (2.5 h). After cooling to 25 °C, water (250.0 kg) was added with stirring for 15 min. The separated organic phase was washed with water (84.0 kg) and concentrated to give a suspension (245.0 kg). The suspension was heated to 45 °C and stirred at the same temperature for 30 min and then cooled to 0 °C over 2 h. *n*-Heptane (84.0 kg) was added dropwise to the cooled suspension, and the resulting suspension was stirred at the same temperature for 2.5 h. The precipitate was filtered, washed with a mixture of toluene and *n*-heptane twice, and dried to give **24** (36.4 kg, 107.6 mol, 87.6% yield) as a white solid.

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 8.0, 1.2 Hz, 1H), 6.59 (t, *J* = 5.6 Hz, 1H), 6.29 (d, *J* = 1.2 Hz, 1H), 5.81 (t, *J* = 5.6 Hz, 1H), 3.47−3.31 (m, 2H), 3. 25−3.19 (m, 2H), 2.73−2.65 (m, 2H), 2.41−2.32 (m, 2H), 2.21 (s, 3H), 2.03 (q, *J* = 8.0 Hz, 2H), 2.00−1.84 (m, 2H), 1.03 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 173.8, 150.1, 137.8, 130.2, 123.3, 120.7, 116.5, 81.9, 40.0, 39.1, 31.7 (2C), 29.4, 21.3, 13.7, 9.7; HRMS (ESI) calcd. for $C_{17}H_{23}ClN_2O_3$ *m*/*z* 339.1470 [M + H]$^+$, found 339.1471.



***N*-(2-(7-Methyl-3-oxospiro[benzo[*b*][1,4]oxazine-2,1′-cyclobutan]-4(3*H*)-yl)ethyl)propionamide (26).** To a suspension of $Pd(OAc)_2$ (482.0 g, 2.15 mol, 0.02 equiv), potassium carbonate (297.0 kg, 2.15 mol, 0.02 equiv), and xylene (313.0 kg) was added P*t*Bu$_3$ 50% toluene solution (2.5 kg, 6.5 mol, 0.06 equiv) at 25 °C under nitrogen atmosphere. The mixture was heated to 80 °C and stirred for 1 h at the same temperature. After cooling to 40 °C, potassium carbonate (29.4 kg, 212.7 mol, 2.0 equiv) and **24** (36.4 kg, 107.4 mol, 1.0 equiv) were added, and the mixture was heated to 130 °C. The reaction was monitored by HPLC until completion (3 h), and the reaction mixture was cooled to 45 °C. THF (72.8 kg) and water (182.0 kg) were added, and the separated organic phase was washed with water (72.8 kg) and concentrated to give a suspension (178.0 kg). The suspension was heated to 75 °C to give a clear solution. After cooling to 0 °C over 8 h, the precipitate was filtered, washed with a mixture of toluene and

DOI: 10.1021/acs.oprd.8b00414
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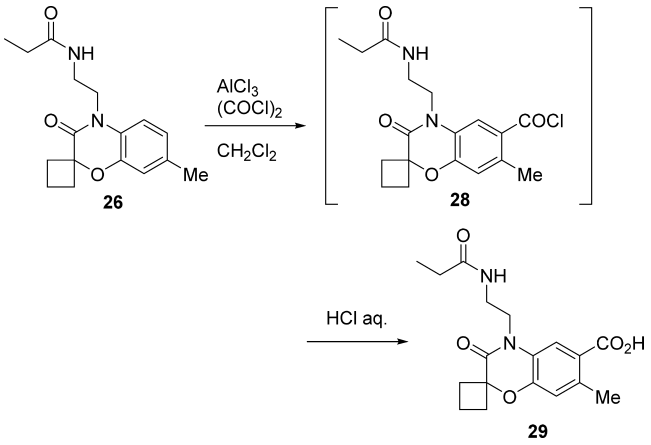
n-heptane twice, and dried to give **26** (31.2 kg, 103.3 mol, 96.1% yield) as a white solid.

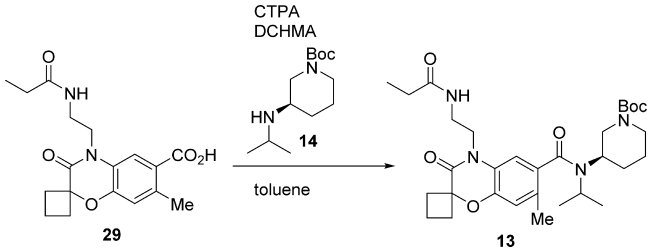
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, J = 8.8 Hz, 1H), 6.83−6.78 (m, 2H), 6.12 (brs, 1H), 4.04 (t, J = 6.4 Hz, 2H), 3.51 (dd, J = 6.8, 6.4 Hz, 2H), 2.58−2.49 (m, 2H), 2.31−2.21 (m, 2H), 2.26 (s, 3H), 2.16 (q, J = 8.0 Hz, 2H), 2.01−1.82 (m, 2H), 1.10 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 168.4, 143.2, 134.1, 126.4, 123.5, 118.5, 114.4, 79.4, 40.8, 38.3, 31.3 (2C), 29.5, 20.7, 13.2, 9.6; HRMS (ESI) calcd. for $C_{17}H_{22}N_2O_3$ m/z 303.1703 $[M + H]^+$, found 303.1704.



7-Methyl-3-oxo-4-(4-oxohexyl)-3,4-dihydrospiro-[benzo[*b*][1,4]oxazine-2,1′-cyclobutane]-6-carboxylic Acid (29). To a suspension of $AlCl_3$ (68.8 kg, 516.3 mol, 5.0 equiv) and oxalyl chloride (39.3 kg, 309.8 mol, 3.0 equiv) in CH_2Cl_2 (306.9 kg) was added **26** (31.2 kg, 103.3 mol, 1.0 equiv) in CH_2Cl_2 (306.9 kg) at −5 °C over 2.5 h. The reaction mixture was stirred for 2.5 h at the same temperature, allowed to warm to 25 °C, and stirred for 1 h at the same temperature. The reaction mixture was cooled to −5 °C. 1 N HCl aq. (466.8 kg) was added over 4 h with maintenance of the internal temperature below 25 °C, and the mixture was stirred for 10 h at the same temperature.

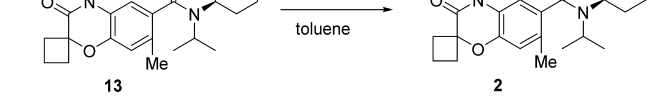
1-BuOH (624.0 kg) was added, and the separated organic phase was washed with water (446.0 kg). The separated organic phase was washed with water (112.0 kg) and concentrated to give a suspension (129.0 kg). 1-BuOH (14.2 kg) was added, and the suspension was heated to 110 °C to give a clear solution. After cooling to 0 °C over 18 h, the precipitate was filtered, washed with a mixture of 1-BuOH and *n*-heptane twice, and dried to give **29** (32.5 kg, 93.7 mol, 90.7% yield) as a white solid.

White solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (s, 1H), 7.96 (t, J = 6.0 Hz, 1H), 7.64 (s, 1H), 6.97 (s, 1H), 3.93 (t, J = 6.0 Hz, 2H), 3.29 (q, J = 6.0 Hz, 2H), 2.57−2.49 (m, 2H), 2.46 (s, 3H), 2.27−2.17 (m, 2H), 1.99 (q, J = 7.6 Hz, 2H), 1.95−1.85 (m, 1H), 1.83−1.70 (m, 1H), 0.92 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.4, 168.0, 166.2, 145.5, 135.8, 126.9, 124.9, 120.3, 117.2, 79.1, 41.3, 36.2, 31.0 (2C), 28.6, 20.9, 12.8, 9.8; HRMS (ESI) calcd. for $C_{18}H_{22}N_2O_5$ m/z 347.1601 $[M + H]^+$, found 347.1600.



***tert*-Butyl (*R*)-3-(*N*-Isopropyl-7-methyl-3-oxo-4-(2-propionamidoethyl)-3,4-dihydrospiro[benzo[*b*][1,4]-oxazine-2,1′-cyclobutane]-6-carboxamido)piperidine-1-carboxylate (13).** To a solution of **29** (20.0 kg, 57.7 mol, 1.0 equiv) in toluene (160.0 kg) was added 1-chloro-*N*,*N*-2-trimethyl-1-propenylamine (CTPA) (9.3 kg, 69.3 mol, 1.2 equiv) at 60 °C, and the mixture was stirred. The reaction was monitored by HPLC until completion (2 h). After cooling to 40 °C, to the mixture was added a mixture of **14** (16.8 kg, 69.3 mol, 1.2 equiv) and *N*,*N*-dicyclohexylmethylamine (DCHMA) (13.5 kg, 69.3 mol, 1.2 equiv) in toluene (77.1 kg) over 40 min, and the reaction mixture was stirred at the same temperature. The reaction was monitored by HPLC until completion (2 h). After cooling to 20 °C, 3.65% AcOH aq. (171.2 kg) was added. The separated organic phase was washed with 3.65% AcOH aq. (171.2 kg) and water (25.6 kg) and then concentrated to give a suspension (97.0 kg). Toluene (17.0 kg) was added, and the suspension was heated to 60 °C to give a clear solution. *n*-Heptane (81.4 kg) was added, and a tiny amount of **13** was added. After cooling to 0 °C over 4 h, the precipitate was filtered, washed with a mixture of toluene and *n*-heptane, and dried to give **13** (28.2 kg, 49.4 mol, 85.5% yield) as a white solid.

White solid; $[\alpha]_D^{22}$ = −33.1 (c 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, major rotamer) δ 6.83 (s, 1H), 6.81 (s, 1H), 6.12−5.92 (m, 1H), 4.23−3.81 (m, 5H), 3.80−3.63 (m, 1H), 3.62−3.34 (m, 2H), 3.11−2.94 (m, 1H), 2.93−2.79 (m, 1H), 2.79−2.58 (m, 1H), 2.48−2.36 (m, 1H), 2.37−2.17 (m, 5H), 2.15 (q, J = 7.2 Hz, 2H), 2.03−1.65 (m, 4H), 1.62−1.47 (m, 1H), 1.45 (s, 9H), 1.41−1.27 (m, 1H), 1.14−1.20 (m, 3H), 1.10 (d, J = 8.0 Hz, 3H), 1.08 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer) δ 174.2, 170.3, 167.9, 154.7, 143.0, 132.5, 129.8, 129.4, 126.7, 119.6, 111.0, 79.3, 51.8, 51.2, 43.6, 41.0, 37.6 (2C), 31.7, 30.8, 29.2, 28.3 (3C), 27.3, 25.5, 20.7, 20.3, 18.2, 13.0, 9.5; HRMS (ESI) calcd. for $C_{31}H_{46}N_4O_6$ m/z 571.3490 $[M + H]^+$, found 571.3492.



***(R)*-*N*-Isopropyl-7-methyl-3-oxo-*N*-(piperidin-3-yl)-4-(2-propionamidoethyl)-3,4-dihydrospiro[benzo[*b*][1,4]-oxazine-2,1′-cyclobutane]-6-carboxamide (2).** To a suspension of **13** (27.9 kg, 48.9 mol, 1.0 equiv) in toluene (55.9 kg) and water (28.0 kg) was added 35% HCl aq. (40.3 kg, 391.9 mol, 8.0 equiv) at 10 °C. The reaction was monitored by HPLC until completion (3 h), and the separated organic phase was extracted with water (10.3 kg). Toluene (336.0 kg) was added to the collected aqueous phase, and 24% NaOH aq. (65.1 kg, 391.9 mol, 8.0 equiv) was added at 10 °C. After heating to 75 °C, the organic phase was separated and

DOI: 10.1021/acs.oprd.8b00414
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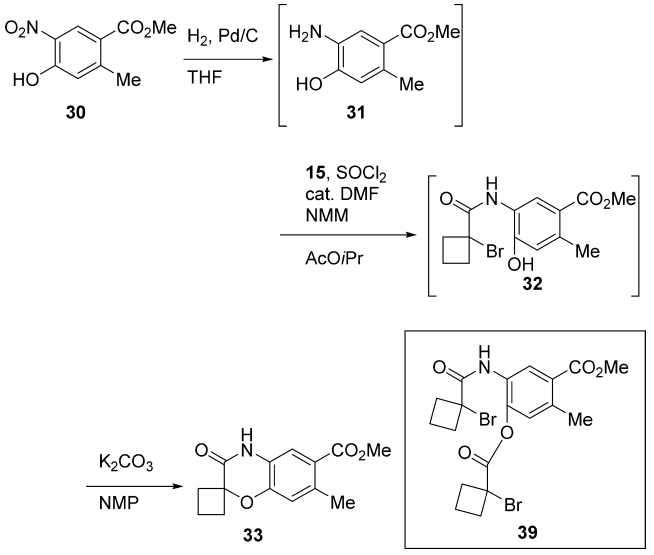
washed with water (28.9 kg). The organic phase obtained was concentrated, and the suspension was heated to 80 °C, followed by addition of *n*-heptane (76.9 kg) over 1 h. After addition of a tiny amount of **2**, the mixture was cooled to 15 °C over 5 h. The precipitate was collected, washed with a mixture of toluene and *n*-heptane, and dried to give **2** (22.4 kg, 47.6 mmol, 97.3% yield) as a white solid.

White solid; $[\alpha]_D^{22} = -4.63$ (*c* 1.08, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, major rotamer) δ 6.82 (s, 1H), 6.78 (s, 1H), 6.11−5.97 (m, 1H), 4.10−4.02 (m, 1H), 3.98−3.92 (m, 1H), 3.89−3.75 (m, 1H), 3.75−3.65 (m, 1H), 3.52−3.40 (m, 2H), 3.18−3.06 (m, 1H), 2.98−2.90 (m, 1H), 2.89−2.59 (m, 3H), 2.44−2.24 (m, 3H), 2.20 (s, 3H), 2.14 (q, *J* = 7.6 Hz, 2H), 2.01−1.64 (m, 5H), 1.60−1.48 (m, 3H), 1.32−1.20 (m, 1H), 1.10 (d, *J* = 7.6 Hz, 3H), 1.07 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD, measured at 328 K, major rotamer) δ 177.1, 172.6, 169.0, 144.8, 133.8, 130.9, 128.5, 120.7, 112.7, 80.8, 54.4, 53.0, 46.4, 42.1, 37.7 (2C), 32.4, 31.8, 30.1, 28.9, 27.8, 20.9 (2C), 18.5, 13.9, 10.2; HRMS (ESI) calcd. for $C_{26}H_{38}N_4O_4$ *m/z* 471.2966 $[M + H]^+$, found 471.2964.

Fourth Generation Process Route (Scheme 11).

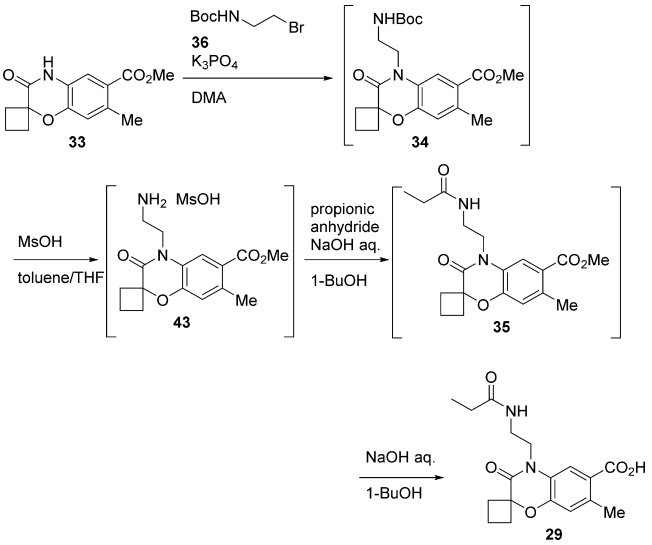


1-Bromo-*N*-(2-propionamidoethyl)cyclobutane-1-carboxamide (33). To a solution of **30** (10.0 g, 47.4 mmol) in THF (80.0 g) was added 10% Pd/C (50% wet, 0.5 g), and the mixture was stirred at 30 °C under hydrogen atmosphere. The reaction was monitored by HPLC until completion (6 h); then, the suspension was filtered to give **31** solution in THF. The solution was used for the following reaction without isolation.

To a solution of **15** (8.07 g, 45.1 mmol) in AcO*i*Pr (48.4 g) was added DMF (0.81 g), and the mixture was heated to 60 °C. Thionyl chloride (6.17 g, 51.9 mmol) was added at the same temperature, and the reaction was monitored by HPLC until completion (1 h). The mixture was cooled to 20 °C and added to a solution of **31** and NMM (10.95 g, 108.2 mmol) over 2 h at 2 °C. Secondary NMM (10.95 g, 108.2 mmol) was added, and the reaction mixture was heated to 45 °C to transform **39** to **32**. After addition of water (40.37 g), separated organic phase was washed with 7.2% HCl aq. (40.37 g) and water (40.37 g) twice. The solvent was displaced with NMP (123.46 g) to give a **32** solution in NMP. The solution was used for the following reaction without isolation.

To the solution of **32** in NMP was added potassium carbonate (6.86 g, 49.6 mmol) and water (6.17 g), and the mixture was heated to 80 °C under nitrogen atmosphere. The reaction was monitored by HPLC until completion (3 h); the mixture was cooled to 50 °C. Water (169.73 g) was added over 1 h, and the mixture was stirred for 1 h. The resulting suspension was cooled to 25 °C over 2 h, and the precipitate was filtered. The filter cake was washed with water (46.29 g) twice and dried to give **33** as a white solid (10.27 g, 39.3 mmol, 87.2% yield in 3 steps based on **15**).

White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.47 (s, 1H), 6.86 (s, 1H), 3.87 (s, 3H), 2.73−2.62 (m, 2H), 2.55 (s, 3H), 2.35 (q, *J* = 9.2 Hz, 2H), 2.08−1.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 167.0, 145.5, 137.4, 124.4, 123.4, 120.3, 118.0, 80.1, 51.8, 31.8 (2C), 21.6, 13.3; HRMS (ESI) calcd. for $C_{14}H_{15}NO_4$ *m/z* 262.1074 $[M + H]^+$, found 262.1075.



7-Methyl-3-oxo-4-(4-oxohexyl)-3,4-dihydrospiro-[benzo[*b*][1,4]oxazine-2,1′-cyclobutane]-6-carboxylic acid (29). To a solution of **33** (10.00 g, 38.3 mmol) in DMA (50.00 g) was added tripotassium phosphate (12.19 g, 57.4 mmol) and **36** (9.44 g, 42.1 mmol) under nitrogen atmosphere. The mixture was heated to 70 °C and stirred at the same temperature. The reaction was monitored by HPLC until completion (6 h); then, the mixture was cooled to 30 °C. The suspension was filtered to remove an undissolved inorganic substance, and the filter cake was washed with DMA (15.00 g). The filtrate was heated to 70 °C; toluene (200.00 g) and water (70.00 g) were added, and separated organic phase was washed with water (70.00 g). The toluene solution was used for the following reaction without isolation.

To the **34** solution in toluene was added methanesulfonic acid (18.39 g, 191.4 mmol). The reaction was monitored by HPLC until completion (4 h). After addition of water (60.00 g), the separated aqueous phase was washed with toluene (50.00 g), and water (10.00 g) was added to give a **34** solution in water. The solution was used for the following reaction without isolation.

To the **43** solution in water was added 1-BuOH (120.00 g), and the mixture was cooled to 5 °C. Propionic anhydride (7.47 g, 57.4 mmol) was added at the same temperature; then, 24% NaOH aq. (41.46 g, 248.8 mmol) was added at the same temperature. The reaction was monitored by HPLC until completion (1 h). The aqueous phase was separated to give a **35** solution in 1-BuOH. The solution was used for the following reaction without isolation.

DOI: 10.1021/acs.oprd.8b00414
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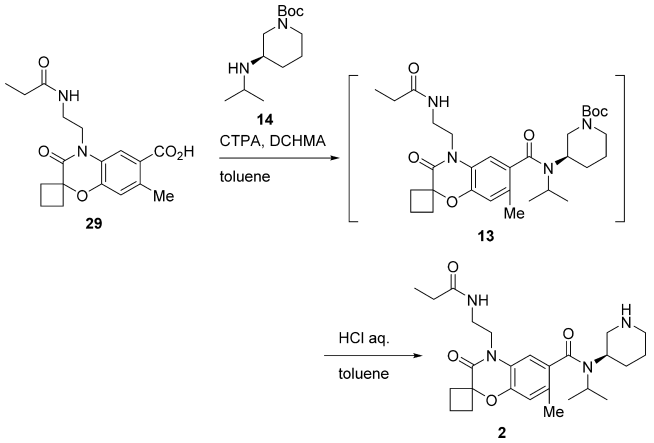
To the **35** solution in 1-BuOH was added 1-BuOH (60.0 g), and the mixture was heated to 55 °C.

24% NaOH aq. (19.14 g, 114.8 mmol) was added, and the reaction mixture was stirred at the same temperature. The reaction was monitored by HPLC until completion (3 h). After cooling to 20 °C, 35% HCl aq. (15.97 g, 153.1 mmol) was added, and the separated organic phase was washed with water (50.00 g) repeatedly until pH of the aqueous phase was 2.5 or more. The obtained organic phase was concentrated to give the suspension (47.70 g). After heating to 110 °C, the mixture was cooled to 0 °C over 6 h. The precipitate was collected and washed with 1-BuOH twice and dried to give **29** (10.61 g, 30.6 mmol, 80.0% yield in 4 steps) as a white solid.



(*R*)-*N*-Isopropyl-7-methyl-3-oxo-*N*-(piperidin-3-yl)-4-(2-propionamidoethyl)-3,4-dihydrospiro[benzo[*b*][1,4]-oxazine-2,1′-cyclobutane]-6-carboxamide (2). To a solution of **29** (24.02 g, 69.4 mmol, 1.0 equiv) in toluene (192.20 g) was added CTPA (11.12 g, 83.2 mmol, 1.2 equiv), and the mixture was stirred at 60 °C. The reaction was monitored by HPLC until completion (2 h). After cooling to 25 °C, the mixture of **14** (17.65 g, 72.8 mmol, 1.05 equiv) and DCHMA (16.26 g, 83.2 mmol, 1.2 equiv) in toluene (114.71 g) was added over 1 h at the same temperature. The reaction was monitored by HPLC until completion (4 h). After addition of 3.65% AcOH aq. (205.39 g), the separated organic phase was washed with 3.65% AcOH aq. (205.39 g) and water (30.75 g) and then concentrated to give a toluene solution (369.42 g). The solution was used for the following reaction without isolation.

To the solution of **13** in toluene was added 35% HCl aq. (44.61 g) at 10 °C. The reaction was monitored by HPLC until completion (2 h). After addition of water (43.37 g), the separated organic phase was extracted with water (43.37 g). Toluene (451.20 g) was added to the collected aqueous phase, and 24% NaOH aq. (71.37 g) was added at 10 °C. After heating to 75 °C, the organic phase was separated and washed with water (38.78 g). The organic phase obtained was concentrated, and the suspension was heated to 80 °C, followed by addition of *n*-heptane (103.37 g) over 1 h. After addition of a tiny amount of **2**, the mixture was cooled to 15 °C over 5 h. The precipitate was collected, washed with a mixture of toluene and *n*-heptane, and dried to give **2** (29.88 g, 63.5 mmol, 91.6% yield in 2 steps) as a white solid.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.8b00414.

NMR spectra for compounds (PDF)

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Notes

The authors declare no competing financial interest.

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