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Scalable Synthesis of a Nonracemic α-Arylpropionic Acid via Ketene Desymmetrization for a Glucokinase Activator

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Supporting Information

ABSTRACT: Process research and development for a synthesis of the chiral carboxylic acid (*R*)-**2** as a key intermediate of the glucokinase activator (*R*)-**1** is described. The construction of the stereocenter at the α-carbon is a key point for the synthesis of (*R*)-**2**. The proposed process utilizes desymmetrization of a ketene in situ generated from the corresponding racemic carboxylic acid ***Rac*-2** with (*R*)-pantolactone as a chiral auxiliary followed by hydrolysis of the resulting ester. This key step has been successfully scaled up to 20 kg, which demonstrates that this synthetic approach is comparable with a previously reported approach via enantioselective hydrogenation.

INTRODUCTION

The world is now facing a huge increase in the number of people with diabetes, in particular, type 2 diabetes, because of aging population and rapidly rising numbers of overweight and obese people.[1] Many pharmaceutical companies are focusing their attention on diabetes, and have developed various small-molecule series as potential therapeutic agents for the treatment of type 2 diabetes. Among them, small-molecule glucokinase activators (GKAs) represent a new strategy.[2] (*R*)-2-[4-(Cyclopropylsulfonyl)phenyl]-*N*-pyrazin-2-yl-3-(tetrahydro-2*H*-pyran-4-yl) propanamide (*R*)-**1** has been regarded as a potent GKA.[3] For use in nonclinical studies and clinical trials, Prosidion developed a scalable methodology using the enantioselective hydrogenation of acrylic acid (*E*)-**3** as a key reaction for the construction of stereochemistry at the α-carbon center to give the key intermediate (*R*)-**2**, followed by amidation with 2-aminopyrazine, giving (*R*)-**1** (Scheme 1, route a).[3a,b] According to their reaction conditions, a high pressure (>700 psig) of hydrogen was required to promote the reaction. Lilly successfully reduced the hydrogen pressure to 70 psig using Et_3N as an additive, leading to improved reduction efficiency.[3d] We have reported another approach to (*R*)-**2** that employs the esterification of racemic carboxylic acid ***Rac*-2** via ketene formation followed by stereoselective protonation (route b).[3c,f] The intermediate ***Rac*-2** was easily synthesized by hydrogenation of (*E*)-**3** (route c); however, this route was not suitable for production at an industrial scale because it required more reaction steps than route a. Therefore, we reconstructed another synthetic route for ***Rac*-2** based on Merck's synthetic strategy (route d).[4] Herein, we describe our process research and development for a scalable synthesis of (*R*)-**2** via ketene desymmetrization.

RESULTS AND DISCUSSIONS

Scheme 2 illustrates the manufacturing results of our first campaign. At first, we selected readily available cyclopropylphenylsulfide **4** as a starting material for the multikilogram preparation of (*R*)-**1**.[5] A Friedel–Crafts reaction of **4** with ethyl chloroglyoxylate **12** followed by reduction of **5** produced secondary benzylic alcohol ***Rac*-6** in 75% yield after purification by crystallization. Subsequently, reduction of ***Rac*-6** with TMSCl and NaI in CH_3CN led to the corresponding α-aryl acetate **7**,[6] which was treated with oxone to give the crude sulfone. **8** was purified by crystallization (80% yield from ***Rac*-6**), alkylated with 4-THPCH_2I (**9**) in THF and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) using LHMDS as a base, and saponified with aq NaOH to give the sodium salt of ***Rac*-2**. ***Rac*-2** was isolated as a crystal in 57% yield through aqueous acid workup followed by repeated crystallization from toluene, a mixture of *i*-BuOAc and *n*-heptane, and *i*-BuOAc alone. Subsequently, (*R*)-**2** was obtained as a crystal in 80% yield by employing the diastereoselective esterification of a ketene generated from the corresponding acyl chloride with (*R*)-pantolactone followed by hydrolysis and crystallization from *i*-BuOAc. Finally, the amidation of (*R*)-**2** with 2-aminopyrazine gave the desired active pharmaceutical ingredient (*R*)-**1**. Our detailed investigations of this synthetic strategy are described below.

Friedel–Crafts Reaction for Benzyl Alcohol. Benzylic alcohol ***Rac*-6** was synthesized by a direct alkylation of **4** with ethyl glyoxalate **11** (route e) or by a Friedel–Crafts reaction with ethyl chloroglyoxylate **12** followed by reduction (route f), shown in Table 1. The reaction with **11** provided a mixture of *p*-adduct ***Rac*-6** and *o*-adduct ***Rac*-13** in the presence of $AlCl_3$. Crystallization from the mixture of toluene and *n*-heptane after aqueous workup gave purified ***Rac*-6** in 73% yield with a small amount of *o*-adduct and other impurities. This direct route using **11** as a reactant is favorable for the production of ***Rac*-6**; however, bulk availability and physical properties of **11** were limited.[7] Therefore, we ultimately chose a two-step sequence with **12** as the reactant for the synthesis of ***Rac*-6** in the first

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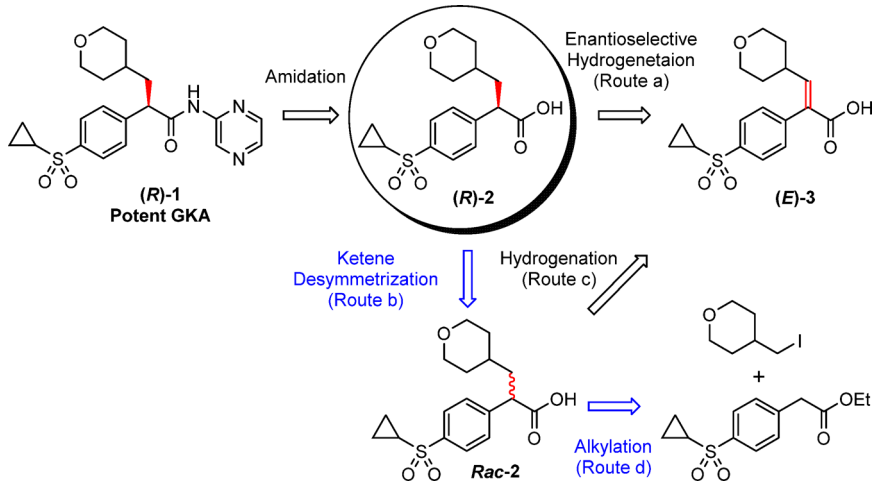
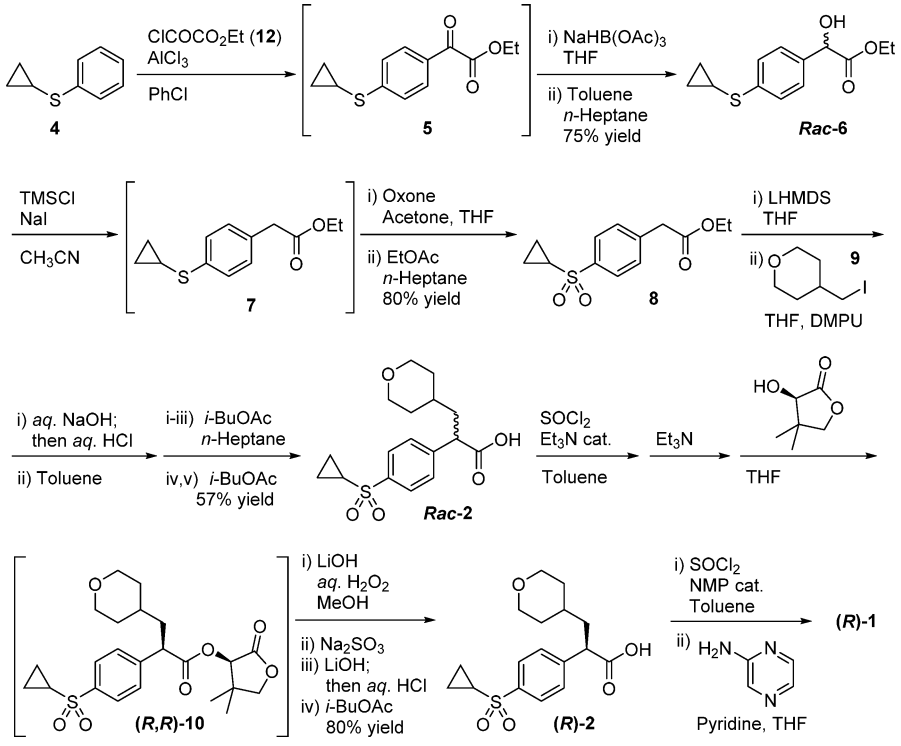
Scheme 1. Synthetic strategies for (*R*)-1 via (*R*)-2 as a key intermediate



Scheme 2. First campaign for (*R*)-1 on a multikilogram scale



campaign. Treatment of **4** with **12** in the presence of $AlCl_3$ gave the corresponding ketone **5** with almost exclusive para selectivity. This was followed by reduction with $NaBH(OAc)_3$ to give ***Rac*-6** in quantitative yield. PhCl as a solvent was also reacted with acyl chloride **12** to give the corresponding chlorobenzene adducts (5%−15% relative HPLC area %); however, the amount of these adducts was easily reduced below detectable limits by crystallization in the next step. Unfortunately, use of less expensive $NaBH_4$ as a reductant led to poor yield because of side reactions. The two-step sequence was reproducible in laboratory scale (up to 1.2 kg) to give the desired ***Rac*-6** in 85% crystallized yield; however, the yield decreased to 75% on a 27-kg scale. This unexpected decrease of yield could probably be attributed to the instability of **12** in the presence of $AlCl_3$ and PhCl. The prolonged stirring time of **12** and $AlCl_3$ in PhCl led to a poor HPLC profile of ***Rac*-6** in 1 h after adding **4** to the reaction mixture [84.1% relative HPLC area % (stirring time: 1 h) → 46.5% relative HPLC area % (stirring time: 3 h)], because the degradation and side reactions would be promoted. This scale-up problem was resolved by changing the addition order of reagents, i.e., **12** was added last to the reaction mixture of **4** and $AlCl_3$ in PhCl to give the reaction mixture containing ***Rac*-6** with the best HPLC profile in 1 h (92.5% relative HPLC area %).

Deoxygenation of α-Arylacetate. For the multikilogram preparation of **7**, a screen of acid-induced conditions in the presence of Et_3SiH for high conversion of ***Rac*-6** incorporating a variety of solvents and acids was undertaken (Table 2). Use of $BF_3{\cdot}OEt_2$ as an acid could not complete the reaction in any solvent even over a long duration (entries 1−3).[8,9] Unfortunately, an attempt with Brønsted acid TFA failed during the reduction (entry 4).[10] Only utilization of $TiCl_4$ as an acid gave

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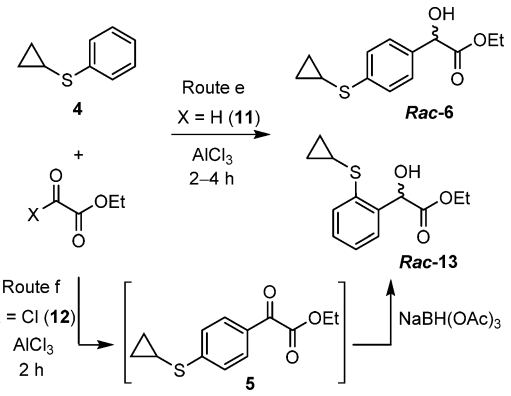
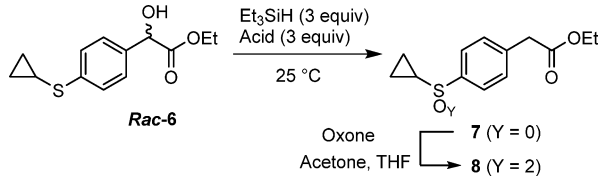
Table 1. Selective synthesis of 4



entry	reactant (X)	solvent	temp. (°C)	selectivity[a] *Rac*-6:*Rac*-13	yield (%)[a,b]
1	**11** (H)	CH_2Cl_2	30	25:1	78
2	**11** (H)	PhCl	30	11:1	80 (73)[c]
3	**11** (H)	PhCl	10	26:1	78
4	**12** (Cl)	CH_2Cl_2	10	73:1	90 (87)[c]
5	**12** (Cl)	PhCl	10	199:1	95 (86)[c]

[a]Determined by HPLC. [b]Assay yield of ***Rac*-6**. [c]Crystallized yield based on **4**.

Table 2. Acid-induced deoxygenation of *Rac*-6 with Et_3SiH



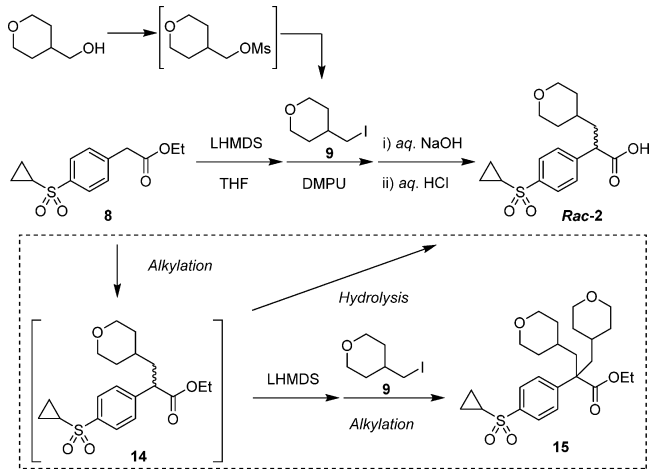
entry	solvent	acid	time (h)	conv.[a] (%)	yield[b] (%)
1	CH_2Cl_2	$BF_3{\cdot}OEt_2$	22	87	76
2	PhCl	$BF_3{\cdot}OEt_2$	22	88	68
3	CH_3CN	$BF_3{\cdot}OEt_2$	22	89	11
4	CH_2Cl_2	TFA	19	<5	<1
5	CH_2Cl_2	$TiCl_4$	6	>95	93

[a]Determined by HPLC. [b]Isolated yield of **7** based on ***Rac*-6**.

complete and clean deoxygenation of ***Rac*-6** in a shorter time (entry 5).[11] However, abrupt exothermal behavior was observed with the addition of $TiCl_4$. Therefore, Lewis acid-induced deoxygenation with Et_3SiH was discontinued. Ultimately, for the effective reduction of ***Rac*-6** on a multikilogram scale, we employed TMSCl−NaI−CH_3CN conditions,[12] even though these conditions were accompanied by slight hydrolysis of ester (~10%).[13] Through a detailed optimization of this condition, high conversion (>99%) was achieved by using >3 equiv of both TMSCl and NaI with ***Rac*-6** in CH_3CN at 35−50 °C. **7** was easily converted to **8** using oxone as an oxidant in acetone and THF.[14] These reactions succeeded in 34-kg scale to give **8** in 80% yield (standard isolated yield on gram scale: 76%−87%). However, the use of $Na_2S_2O_3$ as a quenching agent was not acceptable for the next alkylation on a multikilogram scale, as shown below.

Alkylation for Racemic Carboxylic Acid. The alkylated acid ***Rac*-2** was obtained by treatment of **8** with LHMDS, followed by alkylation with 4-$THPCH_2I$ (**9**) and subsequent hydrolysis of ester **14** under basic conditions (85% assay yield).[15] Other alkylating analogues of **9** were briefly investigated; however, these led to low yields because of the formation of multiple byproducts arising from competing pathways (4-$THPCH_2OMs$: 57% assay yield, 4-$THPCH_2OTs$: 33% assay yield, and 4-$THPCH_2OTf$: 59% assay yield).[15] **9** was prepared from the corresponding alcohol in two reactions without special purification, such as distillation or column chromatography. DMPU as an additive enhanced the reactivity of lithium mixed aggregates (ratio of alkylation in 1 h after adding **9**: 15:81 → 4:87) (Scheme 3)[16] and accelerated the

Scheme 3. Alkylation of 8 with 9 via lithiation followed by hydrolysis



hydrolysis of **14** (conversion in 1 h: 42% → 90%). Dialkylation, as a result of additional lithiation and alkylation of **14**, was observed; however, the corresponding dialkylated ester **15** was effectively removed from the product-rich basic aqueous stream after hydrolysis by washing with toluene because it was not hydrolyzed under this basic condition.

Under the optimized conditions on a laboratory scale, the alkylated acid with desired purity was isolated as a crystal from the mixture of *i*-BuOAc and *n*-heptane (standard isolated yield: 75%−80%). However, the reaction mixture on the 29-kg scale failed to crystallize and purify to the desired quality. Through detailed investigations of the problematic factor, we discovered that contamination with a small amount of sulfur influenced the processing and profiles of this reaction.[17] **8** was obtained by oxidation of **7** using oxone as an oxidant. Oxone ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) is a weakly acidic triple salt. We chose $Na_2S_2O_3$ to quench the excess peroxides remaining in the resulting solution after removing the insoluble components of oxone from the reaction mixture by filtration. Under acidic conditions, $Na_2S_2O_3$ decomposed to elemental sulfur, i.e., on pilot scale, the prolongation of stirring and settling time would produce a large amount of sulfur as a byproduct. The participation of sulfur would affect the alkylation step in the presence of LHMDS to give various unexpected impurities. One impurity was isolated from the reaction mixture and identified as sulfide adduct **16** by spectroscopic analysis such as NMR, IR, MS, and elemental analysis.[18] The formation of **16** was detected in the presence of sulfur (0.2 equiv) as an additive to the usual reaction mixture (1.6% relative HPLC area %). Unfortunately, the contamination of ***Rac*-2** with a small amount of impurity **16** proved problematic in the downstream pharmaceutical ingredient; therefore, in the first campaign, ***Rac*-2** was rigorously purified by repeated crystallization from the mixture

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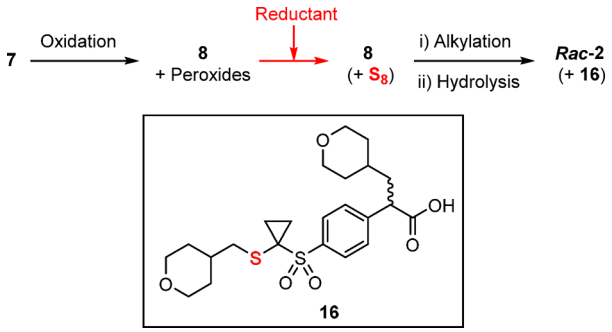
of *i*-BuOAc and *n*-heptane to reduce the residue level in ***Rac*-2** crystal to <0.05%. We investigated sodium bisulfite ($NaHSO_3$) as an alternative reductant and found that it did not lead to the formation of sulfur even in the presence of additional $KHSO_4$ over a long duration, and gave the desired **8** free from sulfur (Table 3, entry 4). Consequently, we will change the quenching agent for the previous oxidation step in the next large-scale campaign.

Table 3. Formation of impurity 16



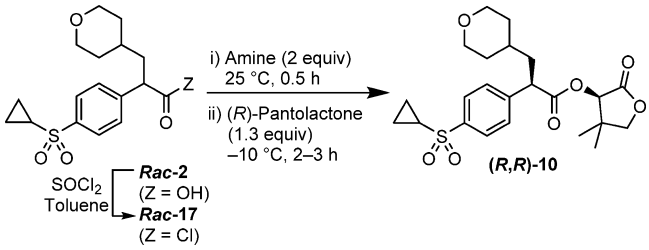
				Rac-2		
entry	scale	reductant	operation time[a]	yield (%)[b]	purity (%)[c]	**16** (%)[c]
1	>25 kg	$Na_2S_2O_3$	2 h	65[d]	97.0	0.51
2	5 g	$Na_2S_2O_3$	<15 min	79	98.6	<0.05
3[e]	5 g	$Na_2S_2O_3$	24 h	74	95.4	0.80
4[e]	5 g	$NaHSO_3$	24 h	78	98.6	<0.05

[a]Total time for stirring and settling in the presence of a reductant. [b]Crystallized yield based on **8**. [c]Relative HPLC area %. [d]Assay yield determined by HPLC. [e]$KHSO_4$ (0.87 w/w) was added to the filtrate before adding the reductant.

Ketene Desymmetrization Followed by Hydrolysis for Non-Racemic Carboxylic Acid. ***Rac*-2** was effectively converted into (***R*)-2** via diastereoselective esterification of ketene in situ generated from the corresponding acyl chloride ***Rac*-17** with (*R*)-pantolactone followed by hydrolysis of the ester.[3c] We have previously reported that amines strongly affect the conversion of ***Rac*-17** to the activated species, such as a ketene, and an acyl ammonium salt;[3f] thereby, the diastereomeric ratio (dr) of the resulting ester (***R*,*R*)-10** was highly attributable to the size of the alkylamines (Table 4). Bulkier tertiary trialkylamines tend to prefer the path via the ketene rather than the path via the acyl ammonium salt (entries 1−6); however, bulkiness was likely limited. The bulkiest amines, such as (*i*-Pr)$_2$NEt and 1,2,2,6,6-pentamethylpiperidine (PMP), gave only a small amount of esters because their bulky chains disturbed the approach of the amine to a hydrogen atom on the α-carbon of acyl chloride (entries 7, 8). The less bulky secondary amine 2,2,6,6-tetramethylpiperidine (TMP) gave the ester with the highest selectivity because a nonselective path via an acyl ammonium salt led to the formation of an amide (~4%, entry 9). Finally, we selected the most inexpensive Et_3N as a base because its enantiomeric ratio (er) after crystallization was almost the same compared to *N*,*N*-dicyclohexylmethylamine ((*c*-Hex)$_2$NMe), which was the most effective amine in terms of diastereoselectivity.

The ketene-forming reaction was monitored by React IR (Figure 1),[19] which revealed that the treatment with Et_3N as a base below 0 °C successfully suppressed the degradation of

Table 4. Effect of amines on diastereoselectivity of (*R*,*R*)-10[a]



entry	amine	yield (%)[b]	dr[c]
1	Et_3N	81	91:9
2	Me_2NEt	89	85:15
3	*N*-methylmorpholine	86	90:10
4	(*n*-Pr)$_3$N	75	91:9
5	(*c*-Hex)$_2$NMe	75	92:8
6	(*n*-Bu)$_3$N	73	89:11
7	(*i*-Pr)$_2$NEt	<1[d]	–
8	PMP	<1[d]	–
9	TMP	82	93:7
10	none	0[e]	–

[a]An amine was added to a solution of ***Rac*-17** at 25 °C. After stirring for 0.5 h, a solution of (*R*)-pantolactone was added to the reaction mixture dropwise. After stirring for 2−3 h, the resulting mixture was purified by extraction and column chromatography. [b]Isolated yield based on ***Rac*-2**. [c]Determined by HPLC. [d]A slight amount of (***R*,*R*)-10** was detected in HPLC. [e]Formation of (***R*,*R*)-10** was not detected in HPLC. *c*-Hex = cyclohexyl, PMP = 1,2,2,6,6-pentamethylpiperidine, TMP = 2,2,6,6-tetramethylpiperidine.

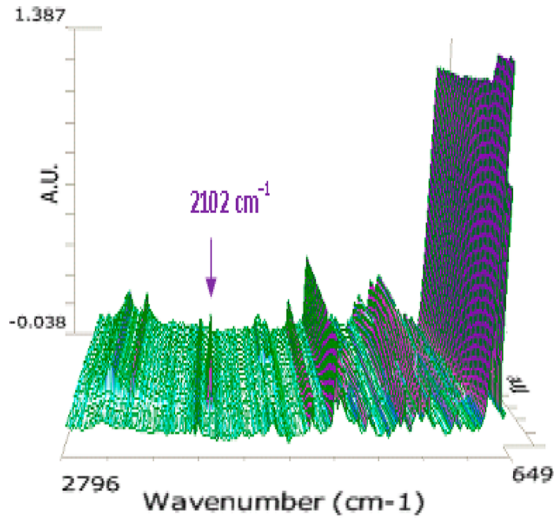


Figure 1. Monitoring the ketene intermediate by React IR.

ketene complexes, thereby resulting in high yield (>90%). Lower temperature in the addition step improved the diastereoselectivity of ester (***R*,*R*)-10** (up to 97:3 dr); however, (*R*)-pantolactone was sparingly soluble in toluene even at room temperature, and the reaction rate was determined by solution rate unless an (*R*)-pantolactone crystal was added without dissolving in a solvent. Therefore, we used THF as a cosolvent to dissolve (*R*)-pantolactone and performed the dropwise addition of this solution (room temperature) to the solution of **18** in toluene at <−70 °C. (***R*,*R*)-10** was hydrolyzed at 0−10 °C with less epimerization/racemization by aq H_2O_2 and LiOH (96:4 er);[20] however, this single treatment for hydrolysis led to a low crystallized yield (up to 65%). For (***R*,*R*)-10**, this

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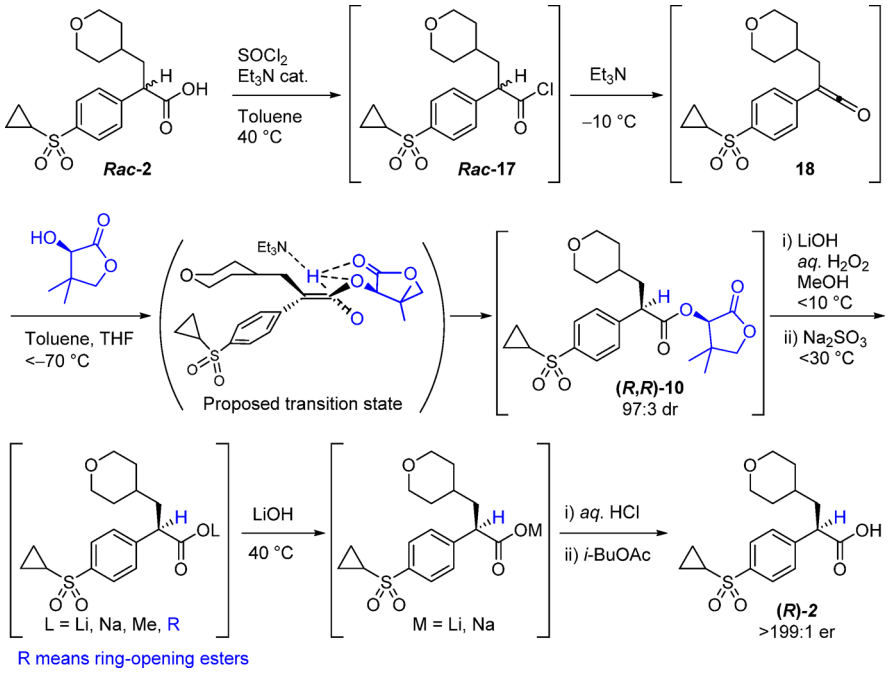
Scheme 4. Diastereoselective esterification of in situ ketene followed by hydrolysis



peroxide condition produces side esters such as methyl esters and ring-opening esters, which were removed by extraction because this condition alone cannot hydrolyze them. Therefore, the additional treatment of the resulting mixture with LiOH at 40 °C is a key requirement for high conversion of ester (*R*,*R*)-**10** to the corresponding carboxylate,[21] although the er of the crude ester was slightly decreased (94:6 er). Finally, acidification by aq HCl followed by crystallization from *i*-BuOAc gave the desired enantio-enriched carboxylic acid (*R*)-**2** as a colorless crystal with >99% purity and >199:1 er in 78%−80% yield (Scheme 4). These optimized conditions on laboratory scale were successfully applied to manufacture on a 20-kg scale, giving (*R*)-**2** with the desired quality in 80% yield.

CONCLUSION

We developed a scalable route for multikilogram preparation of nonracemic carboxylic acid (*R*)-**2** with the desired quality. Our process utilizes desymmetrization of a ketene in situ generated from the corresponding racemic carboxylic acid ***Rac*-2** with (*R*)-pantolactone. This key step has been successfully scaled up to 20 kg, which demonstrates that this synthetic approach is comparable to the previously reported approach via enantioselective hydrogenation as a key step.[22]

EXPERIMENTAL SECTION

General. All air- and moisture-sensitive manipulations were performed under nitrogen atmosphere. All substrates, reagents, and solvents were used as received from suppliers without further purification.

Ethyl [4-(cyclopropylthio)phenyl](hydroxy)acetate (*Rac*-6) (CAS No.1196118-13-4). A reactor was charged with PhCl (241.05 kg) and $AlCl_3$ (36.20 kg; 271.5 mol), and cooled to −15−0 °C. The temperature was maintained between −15 and 0 °C, and ethyl chloroglyoxylate **12** (37.10 kg; 271.7 mol) was added to the mixture dropwise over a period of 1.5 h. After the addition, the mixture was stirred for 1 h. A solution of cyclopropylphenylsulfide **4** (27.20 kg; 181.0 mol) in PhCl (60.35 kg) was added to it dropwise over a period of 2.5 h at −15−0 °C. [The procedure on a pilot scale was not optimized. Our optimized procedure is as follows: A reactor was charged with PhCl and $AlCl_3$, and cooled to −15−0 °C. The temperature was maintained between −15 and 0 °C, and **4** was added to the mixture dropwise. After the addition, the mixture was stirred for 1 h. A solution of **12** in PhCl was added to it dropwise at −15−0 °C.] After addition, the mixture was warmed to 10−20 °C and stirred for 2 h. The resulting mixture was transferred to a second reactor that contained the purified water (326.00 kg) over a period of 2.5 h at 5−30 °C. The first reactor and the line were washed with PhCl (30.20 kg). After quenching the reaction mixture, the aqueous layer was separated and extracted with EtOAc (122.90 kg), while the first organic layer was concentrated under vacuum at 50−60 °C until no further distillate could be collected, and dissolved in EtOAc (172.05 kg). The organic layers were collected, washed with 24.6% aq NaCl (159.20 kg), 5.1% aq $NaHCO_3$ (139.10 kg), and 24.6% aq NaCl (159.20 kg) and concentrated under vacuum at 35−45 °C until no further distillate could be collected. The residue was dissolved in THF (72.45 kg) and concentrated under vacuum at 35−45 °C until no further distillate could be collected. The residue **5** was dissolved in THF (120.90 kg), and a suspension of $NaBH(OAc)_3$ in THF, which was prepared in another reactor with $NaBH_4$ (13.70 kg; 362.1 mol) and AcOH (87.00 kg; 1449 mol) in THF (133.05 kg), was added to it dropwise over a period of 1.5 h at 25−35 °C. Another reactor and the line were washed with THF (18.15 kg). The mixture was heated to 45−50 °C and stirred for 2 h. After cooling below 25 °C, the resulting mixture was washed with a 15% aq NaCl (136.40 kg) and concentrated under vacuum at 35−45 °C until no further distillate could be collected. The residue was dissolved in EtOAc (245.30 kg), washed with a mixture of NaCl (6.80 kg) and $NaHCO_3$ (13.60 kg) in purified water (116.00 kg) twice and a 15% aq NaCl (136.40 kg), and concentrated under vacuum at 45−55 °C until no further distillate could be collected. The residue was

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dissolved in toluene (47.10 kg) and concentrated under vacuum at 45−55 °C until no further distillate could be collected. The residue was diluted in toluene (71.50 kg) and heated to 50−60 °C. After dissolution, *n*-heptane (93.05 kg) was added to the solution and the resulting solution was cooled to 25−35 °C slowly over a period of 2 h. After crystallization, the resulting slurry was aged for 1 h at 25−35 °C, and cooled to 5−15 °C slowly over a period of 2 h. *n*-Heptane (93.05 kg) was added to the slurry dropwise over a period of 1 h. After aging for 5 h at 5−15 °C, the resulting slurry was filtered by centrifuge. The filter cake was washed with a cold mixture of toluene (12.00 kg) and *n*-heptane (28.00 kg). The cake was dried using conical dryer under vacuum at 45−55 °C for 13.5 h to give ***Rac*-6** as a pale-yellow crystal (34.15 kg; 75% yield; 97.20% HPLC area %). ^{1}H NMR ($CDCl_3$): δ 7.36 (d, $^3J_{HH}$ = 8.7 Hz, 2H), 7.33 (d, $^3J_{HH}$ = 8.7 Hz, 2H), 5.11 (d, $^3J_{HH}$ = 4.6 Hz, 1H), 4.32−4.13 (m, 2H), 3.43 (t, $^3J_{HH}$ = 5.1 Hz, 1H), 2.21−2.14 (m, 1H), 1.24 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.11−1.04 (m, 2H), 0.72−0.66 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 172.4, 137.9, 136.4, 127.1, 125.8, 72.0, 60.3, 13.9, 11.3, 8.2, 8.1. Anal. Calcd for $C_{13}H_{16}O_3S$: C, 61.88; H, 6.39; S, 12.71. Found: C, 61.87; H, 6.29; S, 12.53.

Ethyl [4-(cyclopropylsulfonyl)phenyl]acetate (8) (CAS No. 1058167−40−0). A reactor was charged with CH_3CN (79.85 kg), ***Rac*-6** (33.95 kg; 134.5 mol) and NaI (64.50 kg; 430.3 mol), and it was warmed to 30−35 °C. TMSCl (58.40 kg; 537.6 mol) was added to the mixture dropwise over a period of 0.5 h. After the addition, the mixture was stirred for 11 h. The resulting mixture was quenched with 20% aq $NaHSO_3$ (81.30 kg). The resulting solution was extracted with EtOAc (122.00 kg, 122.10 kg) twice. The organic layers were collected, washed with a 10% aq NaCl (169.00 kg), 10% aq Na_2CO_3 (169.00 kg), 10% aq Na_2CO_3 (169.00 kg), and 10% aq NaCl (169.00 kg), and concentrated under vacuum at 45−55 °C until no further distillate could be collected. The residue **7** was dissolved in acetone (53.75 kg) and THF (151.10 kg), and a 23.4% aq oxone (531.00 kg; 404.2 mol) was added to it dropwise over a period of 3.5 h at 15−25 °C. After stirring for 2 h, EtOAc (245.00 kg) was added to the resulting mixture. The resulting suspension was filtered by centrifuge, and the filter cake was washed with EtOAc (61.80 kg). The filtrate was transferred to a reactor, and 9.5% aq $Na_2S_2O_3$ (143.30 kg) was added to it over a period of 45 min at 15−30 °C, and the resulting mixture was stirred for 40 min. [The procedure on a pilot scale was not optimized. Our optimized procedure is as follows: The filtrate was transferred to a reactor, and 9.5% aq $NaHSO_3$ was added to it at 15−30 °C, and the resulting mixture was stirred for 0.5−1 h.] After settling for 35 min, the aqueous layer was separated, and extracted with EtOAc (122.10 kg). The organic layers were collected, washed with a 10% aq Na_2CO_3 (135.50 kg) and 10% aq NaCl (135.50 kg), and concentrated under vacuum at 35−45 °C until no further distillate could be collected. The residue was dissolved in toluene (47.10 kg), and concentrated under vacuum at 45−55 °C until no further distillate could be collected. The residue was diluted in EtOAc (76.55 kg), and heated to 50−70 °C. After dissolution, the resulting solution was cooled to 40−45 °C slowly over a period of 1 h. After crystallization, the resulting slurry was aged for 1.5 h at 40−50 °C, cooled to 5−15 °C slowly over a period of 3.5 h, and stirred for 3 h. *n*-Heptane (116.05 kg) was added to the slurry dropwise over a period of 1 h. After aging for 1 h at 5−15 °C, the resulting slurry was filtered by centrifuge, and the filter cake was washed with a cold mixture of EtOAc (21.60 kg) and *n*-heptane (32.55 kg). The cake was dried using conical dryer under vacuum at 45−55 °C for 6.5 h to give **8** as a pale-yellow crystal (28.90 kg; 80% yield; 99.89% HPLC area %). ^{1}H NMR ($CDCl_3$): δ 7.86 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.48 (d, $^3J_{HH}$ = 8.7 Hz, 2H), 4.18 (quartet, $^3J_{HH}$ = 7.2 Hz, 2H), 3.71 (s, 2H), 2.49−2.42 (m, 1H), 1.38−1.33 (m, 2H), 1.27 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.06−1.00 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 170.4, 140.4, 139.1, 130.4, 127.2, 60.5, 39.8, 32.0, 14.0, 5.3. Anal. Calcd for $C_{13}H_{16}O_4S$: C, 58.19; H, 6.01; S, 11.95. Found: C, 58.11; H, 5.92; S, 11.89 (laboratory-scale sample), C, 57.78; H, 5.92; S, 13.61 (pilot-scale sample).

4-(Iodomethyl)tetrahydro-2*H*-pyran (9) (CAS No.101691−94−5). A reactor was charged with tetrahydro-2*H*-pyran-4-ylmethanol (22.75 kg; 195.9 mol), toluene (137.00 kg) and Et_3N (22.70 kg; 224.3 mol), and it was cooled to 0−10 °C. A solution of methanesulfonyl chloride (24.60 kg; 214.8 mol) in toluene (59.00 kg) was added to the mixture dropwise over a period of 0.5 h. After the addition, the mixture was warmed to 20−30 °C. After stirring for 1.5 h, purified water (114.00 kg) was added to the resulting mixture. The aqueous layer was separated, and extracted with toluene (58.80 kg). The organic layers were collected and concentrated under vacuum at 45−55 °C until no further distillate could be collected. The residue was dissolved in acetone (53.75 kg), NaI (73.20 kg; 488.4 mol) was added to it portionwise over a period of 45 min, and warmed to 55−65 °C. After stirring for 5 h, purified water (182.00 kg) was added to the resulting mixture. The resulting solution was concentrated under vacuum at 45−55 °C until no further distillate could be collected. The residue was dissolved in EtOAc (163.80 kg), washed with 17.9% aq $Na_2S_2O_3$ (101.25 kg), dried over $MgSO_4$ (2.30 kg), and filtered by centrifuge. The filter cake was washed with EtOAc (27.30 kg). The filtrate was concentrated under vacuum at 25−35 °C until no further distillate could be collected. The residue **9** was taken directly into the next step without further purification (93% assay yield). ^{1}H NMR ($CDCl_3$): δ 4.00−3.94 (m, 2H), 3.37 (td, $^3J_{HH}$ = 11.8 Hz, 2.0 Hz, 2H), 3.10 (d, $^3J_{HH}$ = 6.7 Hz, 2H), 1.82−1.75 (m, 2H), 1.75−1.66 (m, 1H), 1.36−1.25 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 67.6, 37.7, 33.6, 13.9. Anal. Calcd for $C_6H_{11}IO$: C, 31.88; H, 4.90. Found: C, 31.76; H, 4.72.

2-[4-(Cyclopropylsulfonyl)phenyl]-3-(tetrahydro-2*H*-pyran-4-yl)propanoic acid (*Rac*-2) (CAS No. 745052−93−1). A reactor was charged with **8** (28.70 kg; 107.0 mol) and THF (128.05 kg) and cooled to −10−0 °C. The temperature was maintained between −10 and 0 °C, and a 20.5% solution of LHMDS in THF (93.30 kg; 114.3 mol) was added to the mixture dropwise over a period of 1.5 h. After the addition, the mixture was stirred for 1 h. A solution of **9** (33.90 kg; 139.5 mol) in THF (51.10 kg) and DMPU (20.55 kg; 160.3 mol) was added to the mixture dropwise over a period of 1 h at −10−0 °C. After addition, the mixture was warmed to 15−25 °C and stirred for 2 h. An 8% aqueous solution of NaOH (100.15 kg) was added to the resulting mixture, and the resulting solution was warmed to 45−55 °C. After stirring for 4 h, the organic layer was separated and extracted with 10% aq NaCl (143.40 kg). The aqueous layers were collected, acidified by 35% aq HCl (34.20 kg), and extracted with EtOAc (131.25 kg, 130.05 kg) twice. The organic layers were collected, washed with a 10% aq $NaHSO_3$ (143.40 kg), dried over $MgSO_4$ (2.85 kg), and filtered on activated charcoal (1.45 kg). The filter cake was washed with EtOAc (80.80 kg). The filtrate was transferred to a reactor and concentrated under vacuum at 45−55 °C until no further distillate could be collected. The residue was dissolved

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in *i*-BuOAc (99.40 kg) and concentrated under vacuum at 45−55 °C until no further distillate could be collected. The residue was diluted in *i*-BuOAc (124.30 kg) and heated to 90−110 °C. After dissolution, the resulting solution was cooled to 35−45 °C slowly over a period of 1 h. After crystallization, the slurry was aged for 1 h at 35−45 °C, warmed to 73−83 °C, and cooled to 5−15 °C slowly over a period of 4.5 h. *n*-Heptane (98.25 kg) was added to the slurry dropwise over a period of 3.5 h. (After the addition, the slurry was emulsified immediately.) The emulsion was concentrated under vacuum at 45−55 °C until no further distillate could be collected. Toluene (124.10 kg) was added to the residue in the reactor, and the mixture was warmed to 85−95 °C. After dissolution, the resulting solution was cooled to 45 °C over a period of 4 h and stirred for 0.5 h at 40−45 °C. After cooling to 15 °C, the resulting slurry was aged at 10−15 °C for 2 h, filtered by centrifuge. The filter cake was washed with cold toluene (49.70 kg). The cake was dried using a conical dryer under vacuum at 45−55 °C for 4 h to give crude ***Rac*-2** as a pale-yellow crystal containing toluene with a weight of 32.25 kg (65% assay yield, 96.97% HPLC area %). A reactor was charged with *i*-BuOAc (49.85 kg) and the dry crude ***Rac*-2** (32.25 kg) and heated to 110 °C. After dissolution, the solution was cooled to 45 °C slowly over a period of 4.5 h. After the resulting slurry was aged at 40−45 °C for 0.5 h, *n*-heptane (39.30 kg) was added to it dropwise over 1 h, and the resulting slurry was cooled to 15 °C slowly over a period of 2 h. After stirring at 10−15 °C for 1 h, the resulting slurry was filtered by centrifuge, and the filter cake was washed with a cold mixture of *i*-BuOAc (24.90 kg) and *n*-heptane (19.60 kg). The wet cake (28.70 kg) was transferred to a reactor that contained *i*-BuOAc (50.05 kg), and the mixture was heated to 110 °C. After dissolution, the solution was cooled to 45 °C slowly over a period of 3 h. The resulting slurry was aged at 40−45 °C for 0.5 h, *n*-heptane (39.30 kg) was added to it dropwise over 1 h, and the resulting slurry was then cooled to 15 °C slowly over a period of 1 h. After stirring at 40−45 °C for 1 h, the resulting slurry was filtered by centrifuge, and the filter cake was washed with a cold mixture of *i*-BuOAc (24.90 kg) and *n*-heptane (19.60 kg). The wet cake (27.25 kg) was transferred to a reactor that contained *i*-BuOAc (49.80 kg), and the mixture was heated to 110 °C. After dissolution, the solution was cooled to 45 °C slowly over a period of 4.5 h. After the resulting slurry was aged at 40−45 °C for 0.5 h, *n*-heptane (39.35 kg) was added to it dropwise over 1 h, and the resulting slurry was cooled to 15 °C slowly over a period of 2 h. After stirring at 10−15 °C for 1.5 h, the resulting slurry was filtered by centrifuge, and the filter cake was washed with a cold mixture of *i*-BuOAc (24.95 kg) and *n*-heptane (19.65 kg). The wet cake (26.50 kg) was transferred to a reactor that contained *i*-BuOAc (49.85 kg), and the mixture was heated to 110 °C. After dissolution, the solution was cooled to 45 °C slowly over a period of 3.5 h. The resulting slurry was warmed to 78 °C slowly over a period of 1 h. After stirring at 78 °C for 0.5 h, the slurry was cooled to 15 °C slowly over a period of 5.5 h. After stirring at 10−15 °C for 1.5 h, the resulting slurry was filtered by centrifuge, and the filter cake was washed with cold *i*-BuOAc (24.90 kg). The wet cake (23.95 kg) was transferred to a reactor that contained *i*-BuOAc (49.75 kg), and the mixture was heated to 110 °C. After dissolution, the solution was cooled to 45 °C slowly over a period of 4 h. The resulting slurry was warmed to 73 °C slowly over a period of 0.5 h. After stirring at 73−76 °C for 0.5 h, the slurry was cooled to 15 °C slowly over a period of 5.5 h. After stirring at 10−15 °C for 1.5 h, the resulting slurry was filtered by centrifuge, and the filter cake was washed with cold *i*-BuOAc (24.85 kg). The cake was dried using a conical dryer under vacuum at 45−55 °C for 4.5 h to give ***Rac*-2** as a colorless crystal (20.50 kg; 57% yield; 99.94% HPLC Area %). ***Rac*-2:** ^{1}H NMR ($CDCl_3$): δ 7.87 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.51 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 3.96−3.90 (m, 2H), 3.80 (t, $^3J_{HH}$ = 7.8 Hz, 1H), 3.30 (tdd, $^3J_{HH}$ = 11.8 Hz, 5.1 Hz, 2.0 Hz, 2H), 2.46 (tt, $^3J_{HH}$ = 7.9 Hz, 4.9 Hz, 1H), 2.12−2.04 (m, 1H), 1.81−1.72 (m, 1H), 1.64−1.55 (m, 2H), 1.46−1.25 (m, 5H), 1.08−1.01 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 174.1, 145.5, 139.1, 128.9, 127.4, 66.8, 47.5, 39.7, 32.5, 32.3, 32.1, 31.9, 5.3. Anal. Calcd for $C_{17}H_{22}O_5S$: C, 60.33; H, 6.55; S, 9.47. Found: C, 60.26; H, 6.52; S, 9.45. **14**: ^{1}H NMR ($CDCl_3$): δ 7.86 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.50 (d, $^3J_{HH}$ = 8.0 Hz, 2H), 4.22−4.06 (m, 2H), 3.97−3.90 (m, 2H), 3.77 (t, $^3J_{HH}$ = 7.8 Hz, 1H), 3.36−3.26 (m, 2H), 2.51−2.43 (m, 1H), 2.12−2.03 (m, 1H), 1.77−1.69 (m, 1H), 1.64−1.54 (m, 3H), 1.45−1.25 (m, 5H), 1.23 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.08−1.01 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 172.8, 144.8, 139.5, 128.7, 127.8, 67.6, 67.5, 61.1, 48.3, 40.3, 32.7, 32.7, 32.6, 32.5, 14.0, 5.8. Anal. Calcd for $C_{19}H_{26}O_5S$: C, 62.27; H, 7.15; S, 8.75. Found: C, 62.10; H, 7.13; S, 8.84. **15**: ^{1}H NMR ($CDCl_3$): δ 7.85 (d, $^3J_{HH}$ = 8.8 Hz, 2H), 7.53 (d, $^3J_{HH}$ = 8.8 Hz, 2H), 4.16 (d, $^3J_{HH}$ = 7.2 Hz, 1H), 4.12 (d, $^3J_{HH}$ = 7.2 Hz, 1H), 3.86−3.78 (m, 4H), 3.30−3.18 (m, 4H), 2.47 (tt, $^3J_{HH}$ = 8.0 Hz, 4.8 Hz, 1H), 2.11 (dd, $^2J_{HH}$ = 14.4 Hz, $^3J_{HH}$ = 5.6 Hz, 2H), 2.02 (dd, $^2J_{HH}$ = 14.4 Hz, $^3J_{HH}$ = 5.6 Hz, 2H), 1.46−1.32 (m, 4H), 1.32−1.17 (m, 11H), 1.08−1.00 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 175.0, 148.8, 138.9, 127.5, 127.3, 67.7, 61.0, 52.9, 43.4, 34.3, 33.9, 32.8, 31.5, 13.8, 5.8. Anal. Calcd for $C_{25}H_{36}O_6S$: C, 64.63; H, 7.81; S, 6.90. Found: C, 64.62; H, 7.80; S, 6.78. **16**: ^{1}H NMR ($CDCl_3$): δ 7.91 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.53 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 5.27 (bs, 1H), 3.98−3.90 (m, 4H), 3.81 (t, $^3J_{HH}$ = 7.8 Hz, 1H), 3.39−3.26 (m, 4H), 2.63 (dd, $^3J_{HH}$ = 11.6 Hz, 6.6 Hz, 1H), 2.58 (dd, $^3J_{HH}$ = 11.6 Hz, 7.0 Hz, 1H), 2.15−2.06 (m, 1H), 1.98−1.92 (m, 2H), 1.81−1.72 (m, 1H), 1.72−1.56 (m, 5H), 1.50−1.38 (m, 1H), 1.38−1.13 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 176.7, 144.7, 137.1, 129.9, 128.5, 67.6, 67.6, 67.6, 48.2, 45.1, 40.3, 40.0, 34.4, 32.7, 32.6, 32.5, 32.3, 32.3, 30.9, 17.1, 17.0. Anal. Calcd for $C_{23}H_{32}O_6S_2$: C, 58.95; H, 6.88; S, 13.68. Found: C, 58.95; H, 6.83; S, 13.52.

(*R*)-2-[4-(Cyclopropylsulfonyl)phenyl]-3-(tetrahydro-2*H*-pyran-4-yl)propanoic acid ((*R*)-2) (CAS No. 745053-49-0). A reactor was charged with toluene (87.85 kg), ***Rac*-2** (20.25 kg; 59.84 mol) and Et_3N (182.0 g; 1.798 mol), and it was warmed to 35−40 °C. $SOCl_2$ (9.25 kg; 77.8 mol) was added to the reaction mixture under a scrubber system. After stirring at 40−45 °C for 3 h, the reaction mixture was concentrated under vacuum at 45−46 °C until no further distillate could be collected. The residue was dissolved in toluene (35.35 kg), and the solution was concentrated under vacuum at 46 °C until no further distillate could be collected. The residue was dissolved in toluene (141.15 kg) and cooled to −6 °C. Et_3N (12.14 kg; 120.0 mol) was added to the solution and stirred at −10−0 °C for 12 h. After cooling to −77 to −74 °C, a solution of (*R*)-pantolactone (9.40 kg; 72.2 mol) in THF (73.25 kg) was added dropwise to the yellow solution over a period of 2.5 h, and the resulting mixture was stirred for 2 h. After warming to −5 °C, citric acid monohydrate (22.20 kg) and purified water (40.60 kg) were added to the reaction solution. After warming to 20 °C, the resulting solution was separated. The organic layer was washed with purified water (40.60 kg) and 10% aq NaCl (81.60 kg), and concentrated

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under vacuum at 48−51 °C until no further distillate could be collected. The residue was dissolved in MeOH (48.25 kg) and concentrated under vacuum at 50−51 °C until no further distillate could be collected, to give the residue (*R*,*R*)-**10**. Another reactor was charged with 35.4% H_2O_2 (8.05 kg; 83.8 mol) and purified water (40.65 kg), and was cooled to 5 °C. A solution of lithium hydroxide monohydrate (3.00 kg, 71.4 mol) in purified water (20.30 kg) was added dropwise. The resulting lithium peroxide solution was transferred to a second reactor containing a solution of (*R*,*R*)-**10** in MeOH (96.50 kg) dropwise over 1 h at 0−3 °C. After stirring at −1−3 °C for 1.5 h, a solution of Na_2SO_3 (18.30 kg; 145.2 mol) in purified water (163.50 kg) was added dropwise to the resulting solution over a period of 1.5 h at 8−9 °C. After warming to 35 °C, lithium hydroxide monohydrate (3.80 kg; 90.6 mol) was added to the solution. After stirring at 38−40 °C for 2.5 h, the resulting solution was washed with toluene (87.90 kg), and acidified by 35% aq HCl (27.50 kg). The aqueous layer was extracted with EtOAc (91.35 kg, 91.35 kg, 91.25 kg) three times, and the collected organic layers were washed with 10% aq NaCl (81.75 kg), dried over $MgSO_4$ (4.05 kg), and filtered. After the filtrate was concentrated at 50 °C under vacuum, the residue was dissolved in *i*-BuOAc (70.30 kg), and the solution was concentrated at 50−51 °C under vacuum. The residue was dissolved in *i*-BuOAc (87.95 kg) at 110 °C. The solution was cooled slowly to 85 °C for crystallization. After crystallization, the suspension was stirred at 85−81 °C for 1.5 h, and cooled slowly to 15 °C over a period of 8 h. After stirring at 15−11 °C for 3 h, a crystal was filtered, washed with *i*-BuOAc (35.20 kg), and dried at 46−51 °C for 6 h under vacuum to give (*R*)-**2** as a colorless crystal (16.20 kg; 80.0% yield from ***Rac*-2**, 99.84:0.16 er). (*R*)-**2**: ^{1}H NMR ($CDCl_3$): δ 7.87 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.51 (d, $^3J_{HH}$ = 8.2 Hz, 2H), 3.97−3.90 (m, 2H), 3.80 (t, $^3J_{HH}$ = 7.8 Hz, 1H), 3.30 (tdd, $^2J_{HH}$ = 11.8 Hz, $^3J_{HH}$ = 5.1 Hz, 2.0 Hz, 2H), 2.46 (tt, $^3J_{HH}$ = 7.9 Hz, 4.9 Hz, 1H), 2.12−2.04 (m, 1H), 1.81−1.72 (m, 1H), 1.64−1.55 (m, 2H), 1.46−1.25 (m, 5H), 1.08−1.01 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 174.1, 145.5, 139.1, 128.9, 127.4, 66.8, 47.5, 39.7, 32.5, 32.3, 32.1, 31.9, 5.3. Anal. Calcd for $C_{17}H_{22}O_5S$: C, 60.33; H, 6.55; S, 9.47. Found: C, 60.08; H, 6.50; S, 9.49. $[\alpha]^{20}_D$ −53.4 (*c* 1.06, MeOH).

■ ASSOCIATED CONTENT

Supporting Information

Spectra of all new compounds, such as intermediate **14**, impurities **15** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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