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Development of a Practical and Scalable Synthesis of (*R*)- and (*S*)-3-Amino-2-[(benzyloxy)methyl]propan-1-ol Monohydrochloride: A Useful C-4 Chiral Building Block

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ABSTRACT: The development of a practical and scalable synthesis of a C-4 chiral amine building block (*R*)-**1·HCl** and (*S*)-**1·HCl** is described. This important chiral intermediate (*R*)-**1·HCl** is efficiently synthesized from the commercially available, inexpensive, and simple 2-(hydroxymethyl)-1,3-propanediol (**31**) using lipase-catalyzed enantioselective hydrolysis as a key reaction. Development resulted in a telescoped process that was operated successfully and reproducibly in a pilot-plant-scale synthesis, and 22 kg of chiral amine (*R*)-**1·HCl** was prepared in the first scale-up synthesis. This synthetic method is also useful for preparation of the important chiral building block (*S*)-**1·HCl**, which is the enantiomer of (*R*)-**1·HCl**.

1. INTRODUCTION

The C-4 chiral amine unit (*R*)-3-amino-2-[(benzyloxy)methyl]-propan-1-ol monohydrochloride ((*R*)-**1·HCl**) and (*S*)-3-amino-2-[(benzyloxy)methyl]propan-1-ol monohydrochloride ((*S*)-**1·HCl**) (Figure 1) should be useful as chiral building

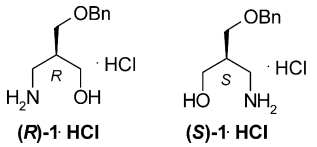

Figure 1. C-4 chiral amine building blocks.

blocks.[1] In particular, it should likely be a key intermediate for a potent p38 MAP kinase inhibitor.[2a] Further, this chiral building block is also likely to be useful for the synthesis of chiral pharmaceutical intermediates.[2b] A number of practical methods for the synthesis of C-3 chiral building blocks have been reported,[3] including many cases for the preparation of 2-substituted-1,3-propanediol chiral derivatives.[4] However, few reports have described C-4 chiral building block synthesis, and these methods have many possible issues in scale-up synthesis.[1] Against this background, we needed to develop a practical and scalable synthesis method for the promising chiral amine unit (*R*)-**1·HCl**. Herein, we report our efforts to develop a practical and scalable synthetic method for (*R*)-**1·HCl** capable of being operated on a 22-kg-scale synthesis. This was accomplished by the development of key enantioselective hydrolysis with lipase that could be performed under environmentally friendly conditions. This method is also useful for the preparation of the (*S*)-form chiral amine building block (*S*)-**1·HCl**. The preparation of (*S*)-**1·HCl** was also achieved in good yield and high enantiopurity.

2. RESULTS AND DISCUSSION

The asymmetric synthetic studies were performed by the Medicinal Chemistry group as shown in Schemes 1 and 2.

Basically, synthesis was accomplished by reference to a reported method (Scheme 1).[1a] This method had many problematic issues in scale-up synthesis, however, as listed below.

- Purification using SiO_2 column chromatography in many steps is not practical in pilot-plant-scale synthesis.
- Distillation steps were needed because not all intermediates were solid or crystalline compounds.
- Reduction of ethyl ester with lithium aluminum hydride (LAH) should be avoided in a large-scale synthesis from the point of view of safety.
- Ozonolysis of alkene compound **9** was not practical in a pilot-plant synthesis.
- The use of sodium azide and small-molecule azide compound **12** should be avoided for a large-scale synthesis from the point of view of safety and toxicity.[5]
- The overall yield was low (5.8% from commercially available diethyl malonate (**2**) in 14 steps).
- Enantiomeric purity was unacceptable (97.8% ee on HPLC), meaning that further purification would be required to meet our desired level.

This chiral auxiliaries method was performed by reference to the reported method (Scheme 2).[1b] However, it also had many

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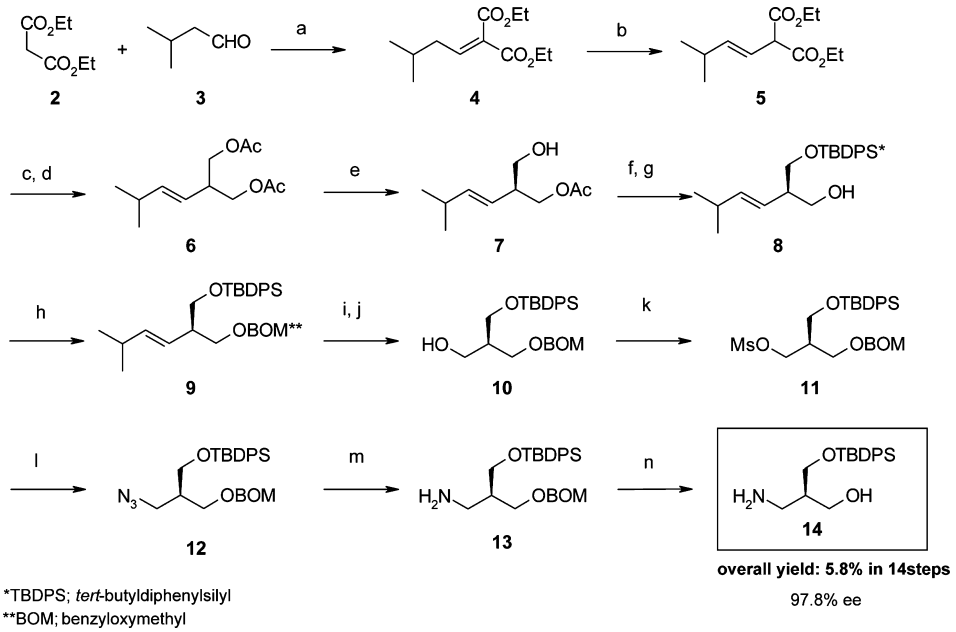
Scheme 1. Asymmetric synthetic route I (Medicinal Chemistry route I)[a]



[a]Reagents and conditions: (a) piperidine, AcOH, toluene, reflux, distilled (93% yield); (b) sodium hydride, THF, 0 to 40 °C, distilled (99.1% yield); (c) $LiAlH_4$, Et_2O, rt; (d) Ac_2O, pyridine, 0 °C, distilled (60.1% yield in 2 steps); (e) porcine pancreatic lipase, 1 M NaOH aq, phosphate buffer (pH 7)/IPE, rt, SiO_2 column chromatography (44.0% yield, $[\alpha]_D = -28.2°$ ($c = 2$, $CHCl_3$, ref 1a −25.3°), 97% ee on NMR); (f) TBDPSCl, imidazole, rt; (g) KOH, MeOH, 0 °C to rt, SiO_2 column chromatography (99.1% yield in 2 steps); (h) BOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, SiO_2 column chromatography (68.1% yield); (i) O_3, MeOH, CH_2Cl_2, −78 °C; (j) $NaBH_4$, MeOH, rt (64.3% yield in 2 steps); (k) MsCl, Et_3N, CH_2Cl_2, rt (98.1% yield); (l) NaN_3, DMF, 75 °C (74.0% yield); (m) H_2, Pd−C, MeOH, 1 atm, rt (78.4% yield); (n) H_2, $Pd(OH)_2$-C, EtOAc, MeOH, 3 atm, rt (99.1% yield).

problematic issues with regard to scale-up synthesis, listed below.

- Purification using SiO_2 column chromatography in many steps is not practical in pilot-plant-scale synthesis.
- Commercially available chiral auxiliary reagent **19** is expensive.[6]
- The overall yield was low (3.8% from commercially available *β*-alanine (**15**) in 10 steps).
- The level of enantiomeric purity was almost the same as that of the method of Medicinal Chemistry route I.

2.1. Our New Synthetic Strategy for the Chiral Amine Unit. Under these circumstances, there has been a strong demand for the development of a worthwhile production process for (*R*)-**1**·**HCl** with higher overall yield which does not require column chromatography purification and/or distillation steps. We therefore focused on three synthesis routes for the chiral amine unit (Figure 2).

We describe three strategies (route A, B, and C) for the preparation of (*R*)-**1** in Figure 2. Route A: the key chiral amine unit would be synthesized from chiral carboxylic acid (*R*)-**30** derived from compound **29**. In route A, one of the reasons for the selection of TBDPS for the protection of alcohol was that it has the possibility to work well in enzyme reactions because of its bulky structure. Compound **29** would be prepared from commercially available diethyl bis(hydroxymethyl) malonate (**28**). In routes B and C, the key intermediate chiral monoacetylated alcohol compound (*S*)-**34** would be synthesized from compound **32** or **33** using an enzyme reaction. According to the similar reaction reported previously, a *Bn* group was selected for the protection of alcohol.[1a] Additional reasons for the selection of a *Bn* group for the protection of the OH group is that it is advantageous in subsequent steps from the point of view of stability, and its manageability for HPLC analysis (detectable at ultraviolet wavelengths). These units would be prepared from commercially available 2-(hydroxymethyl)-1,3-propanediol (**31**). In the following sections, we report details of our study for the preparation of the desired chiral amine unit.

2.2. Results for Route A. To produce the chiral amine unit, we first aimed to synthesize compound **29** (Scheme 3). After acetonide protection of diethyl bis(hydroxymethyl)-malonate (**28**), the Krapcho reaction of diester **36** was attempted, and the desired decarboxylated compound **37** was obtained. After subsequent deprotection, the desired diol compound **38** was prepared.[7] Following mono-silylation was performed with TBDPSCl and Et_3N, and the desired compound **29** was prepared from **38** in 60.0% yield.

2.3. Enantioselective Hydrolysis of Compound 29 with Enzyme. Enantioselective hydrolysis of **29**[1c] by use of different enzymes was attempted (Table 1).

The use of lipase *B* (*Rhizopus arrhizus*), lipase *C* (*Rhizopus niveus*), Lipase M Amano 10 (*Mucor javanicus*, *F*), and Lipase F-AP15 (*Rhizopus oryzae*, *G*) gave positive tendencies (entries 2, 3, 6, and 7). Next, we screened the concentration ratio of DMSO to increase the enantioselectivity, but unfortunately obtained no further improvement. As shown above, we were unable to prepare the desired chiral unit in route A. We therefore focused on routes B and C to obtain the desired chiral unit.

2.4. Results for Route B. To achieve a highly enantioselective reaction, we investigated another approach, enantioselective acetylation with enzyme, as shown in Scheme 4.

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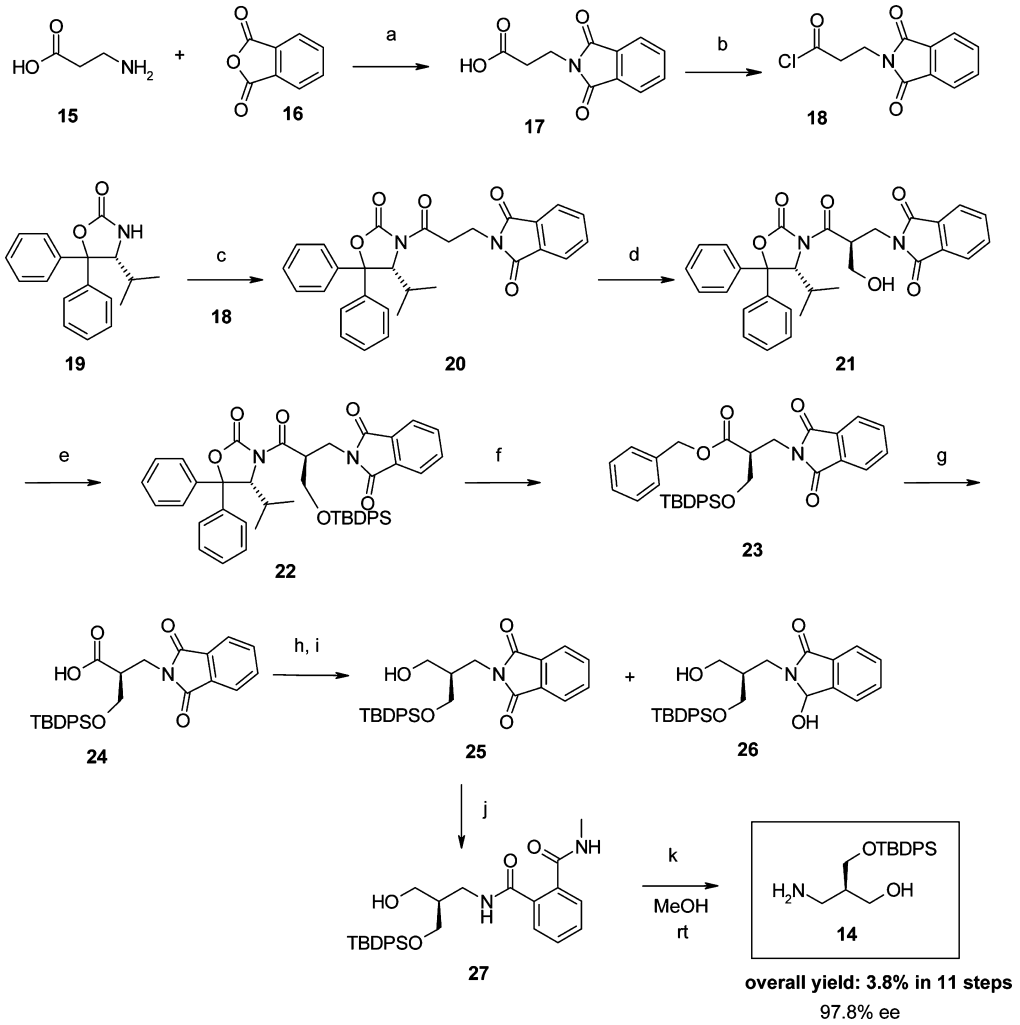
Scheme 2. Asymmetric synthetic route II (Medicinal Chemistry route II)[a]



[a]Reagents and conditions: (a) neat, 150 °C (92.2% yield); (b) $(COCl)_2$, DMF (cat.), CH_2Cl_2 (quant); (c) *n*-BuLi, THF, 0 °C to rt, SiO_2 column chromatography (88.1% yield); (d) 1,3,5-trioxane, $TiCl_4$, Et_3N, CH_2Cl_2, −10 to 0 °C, SiO_2 column chromatography (56.1% yield); (e)TBDPSCl, imidazole, CH_2Cl_2, rt (86.1% yield); (f) BnOH, *n*-BuLi, THF, −35 to −30 °C (46.0% yield); (g) H_2, Pd−C, MeOH, rt (94.1% yield); (h) isobutyl chloroformate, *N*-methylmorpholine, DME, −10 °C; (i) $NaBH_4$, DME, H_2O, −10 °C (**25**: 54.0% yield, **26**: 42.1% yield); (j) $MeNH_2$, MeOH, rt, SiO_2 column chromatography (56.0% yield); (k) $MeNH_2$, MeOH, rt (74.0% yield).

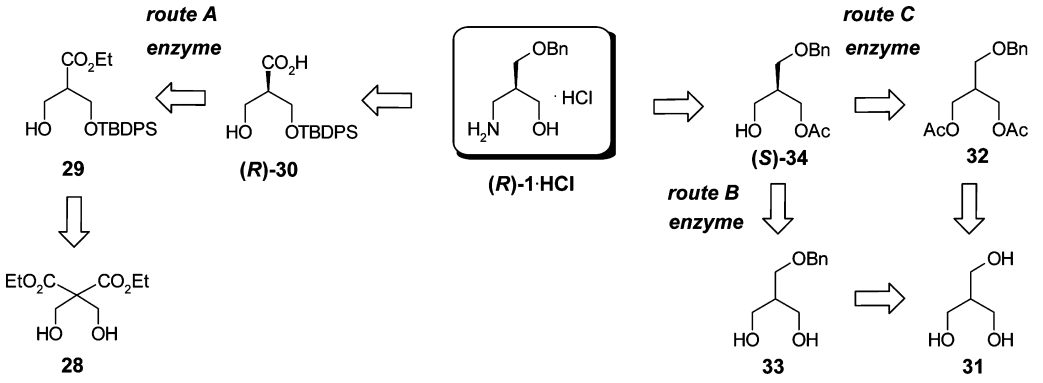


Figure 2. Retrosynthetic analysis of chiral amine unit (*R*)-**1**·**HCl**.

Our synthetic plan for compound **33** is shown in Scheme 5. The target compound **33** should be prepared from commercially available 2-(hydroxymethyl)-1,3-propanediol (**31**) in three steps. Consequently, the acetonide protection of triol **31**, benzylation of alcohol **39**, and deprotection of compound **40** were performed as shown in Scheme 5 in 73.0% yield with a good procedure. One of the keys to success was that diol **33** could be isolated as white crystals in diisopropylether in high purity (typically >98% on HPLC).[8] After optimization, we developed a scalable synthetic method

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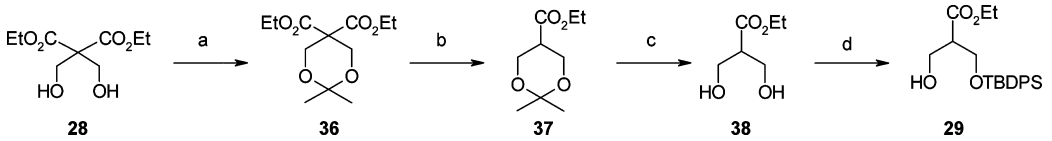
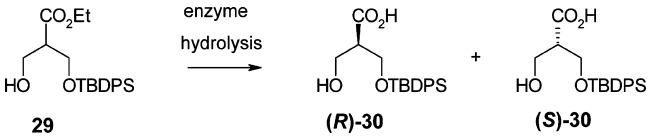
Scheme 3. Synthesis of compound 29[a]



[a]Reagents and conditions: (a) TsOH·H_2O (0.1 equiv), 2,2-dimethoxypropane, 25 °C, 1 h (85.1% yield); (b) LiCl (2 equiv), H_2O (1 equiv), DMSO, 160 °C, 2 h (46.0% yield); (c) 6 M HCl aq (0.56 equiv), MeOH, 25 °C, 12 h (98.1% yield); (d) Et_3N (1 equiv), TBDPSCl (1 equiv), CH_3CN, −30 °C then 25 °C, 12 h (60.0% yield).

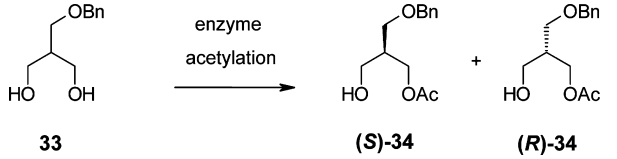
Table 1. Enzyme-catalyzed enantioselective hydrolysis[a]



entry	enzyme (derivation)	tentative symbol in this article	conversion (%)[b]	% ee[b]
1	esterase (*Streptomyces rokkei*)	*A*	0	–
2	lipase (*Rhizopus arrhizus*)	*B*	50	36
3	lipase (*Rhizopus niveus*)	*C*	25	36
4	lipase (wheat germ)	*D*	0	–
5	Lipase AS Amano (*Aspergillus niger*)	*E*	0	–
6	Lipase M Amano 10 (*Mucor javanicus*)	*F*	29	31
7	*Lipase F-AP15* (*Rhizopus oryzae*)	*G*	53	35
8	Lipase G Amano 50 (*Penicillium camembertii*)	*H*	1	–
9	Lipase AYS Amano (*Candida rugosa*)	*I*	20	10
10	Lipase PS Amano (*Burkholderia cepacia*)	*J*	0	–
11	Lipase AK Amano (*Pseudomonas fluorescens*)	*K*	0	–
12	lipase (porcine pancreas)	*L*	0	–

[a]Reaction temp: 37 °C; reaction time: 20 h; 100 mM Tris·HCl buffer (Tris = tris(hydroxymethyl)aminomethane): pH 7.5; ester: 0.5 mg/mL; enzyme: 1 mg/mL in 5% aqueous DMSO. [b]Determined by HPLC; DAICEL CHIRALCEL OJ-RH, 5 μm, 4.6 mm × 150 mm column, elution 0.02 M KH_2PO_4 aq (adjust pH 2.0 by aq H_3PO_4)/CH_3CN = 13/7, over 40 min, 1.0 mL/min, at 25 °C, with UV detection at 220 nm. Retention time: one isomer: 31 min, another isomer: 33 min.

Scheme 4. Another approach for chiral unit (route B)



for **33** as shown in the Experimental Section. On the other hand, direct monobenzylation of **31** with benzyl bromide or benzyl chloride was unsuccessful, even though in various kinds of basic conditions, including Schotten−Baumann-like conditions,[9] these conditions gave such low selectivity that a large percentage of dibenzylated impurity was observed. Next, the following enantioselective acylation using enzyme was attempted (Table 2).

As shown in Table 2, the use of enzyme *K* (Lipase AK Amano[10]) gave good enantioselectivity (entry 11). However, diacylated compound **32** was observed at about 68% in HPLC analysis. Next, to increase the yield of **34**, solvent screening tests were performed. Unfortunately, however, yield could not be improved and optical purity was less than 88% ee. We concluded that the enantioselective acetylation method has a low possibility of success in preparation of the desired compound in a good yield.

2.5. Results for Route C. Enantioselective hydrolysis of diacetate compound **32** was attempted (Scheme 6). Compound **32** was prepared from diol **33** with the acetic anhydride, DMAP, in EtOAc solvent in a good yield. Next, we attempted enantioselective hydrolysis using various types of enzymes (Table 3). Consequently, the use of *Pseudomonas* series gave good enantioselectivity (entries 10, 11). *Pseudomonas fluorescens* (Lipase AK Amano,[11] 85% ee, entry 11), and *Burkholderia cepacia* (previously called *Pseudomonas cepacia*) (Lipase PS Amano, 76% ee, entry 10) are related species. However, this result was not sufficient to meet our goal (>98% ee).

To improve enantioselectivity, we screened cosolvents using Lipase AK Amano (Table 4).

As shown in Table 4, 40% or 60% aqueous DMSO (entries 3, 4) and 10% aqueous IPE (entry 9) gave good results, and enantiopurity was improved to around 90% ee. As another approach, we focused on the chain length. The enantioselective hydrolysis of dibutanoate **41**, bis(2-methylpropanoate) **42**, and dihexanoate **43** were tested as shown in Scheme 7. Various kinds of lipase and esterase were tested for these reactions, but the results were not good in comparison with those of the enantioselective hydrolysis of diacetate in terms of both enantioselectivity and yield of (*S*)-**34**.

2.6. Scale-Up Study for Enantioselective Hydrolysis Using Lipase AK Amano. As shown above, a good enantioselective hydrolysis reaction condition using Lipase AK was discovered. However, this hydrolysis method using Lipase AK had several possible issues in scale-up synthesis, as described below.

- The reaction speed is so fast that it would be difficult to control overhydrolysis to the diol compound **33**.
- The reaction was performed in a highly diluted condition (0.5 mg/mL). Productivity for a 20-kg synthesis campaign required improvement.

To solve these problems in scale-up synthesis, we screened the conditions of (1) effect of cosolvent and (2) effect of pH of the buffer and amount of lipase.

2.6.1. Effect of Cosolvent. To increase concentration and productivity, screening of the cosolvent was performed under high concentration conditions (50 mg/mL) as shown in Table 5. In this highly concentrated condition, DMSO as cosolvent did not work well, and reaction speed was too fast for control (entry 1). In contrast, *i*-PrOH or DME gave high optical purity (>90% ee) in highly concentrated conditions (entries 2, 7).

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Scheme 5. Synthesis of diol compound 33

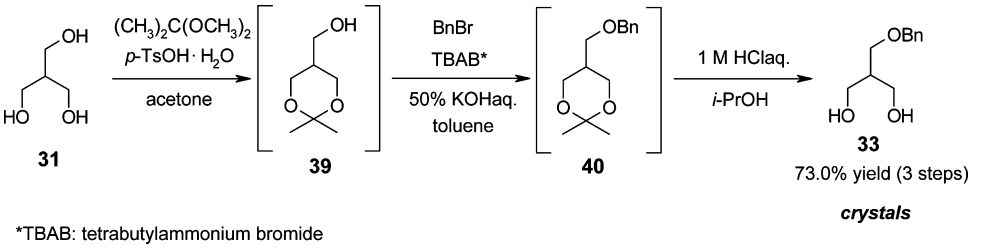
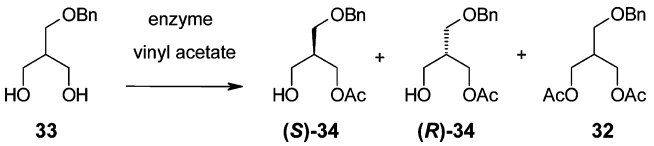


Table 2. Enantioselective acetylation with enzyme (route B)[a]



		HPLC area %[b]				
entry	enzyme	33	(S)-34	(R)-34	32	% ee[b]
1	*A*	6	17	20	57	8
2	*B*	73	19	5	3	58
3	*C*	63	18	14	5	13
4	*D*	97	1	1	1	0
5	*E*	62	26	8	4	53
6	*F*	81	15	3	1	67
7	*G*	81	13	5	1	44
8	*H*	47	37	15	1	42
9	*I*	6	30	20	44	20
10	*J*	0	22	33	45	20
11	*K*	0	2	30	68	88
12	*L*	58	15	13	14	7

[a]Reaction temp: 37 °C; reaction time: 24 h; solvent: 1% water in vinyl acetate; **33**: 0.5 mg/mL; enzyme: 1 mg/mL. [b]Determined by HPLC methods A and B (see Experimental Section).

2.6.2. Effect of pH of the Buffer and Amount of Lipase (Optimization of the Reaction). The lipase reaction under a highly concentrated condition was optimized (Table 6).

Results showed the tendency for the lower pH 4.4 to give a slower reaction (entry 1), whereas a higher pH such as 5.8 or 6.5 accelerated the hydrolysis reaction (entries 2, 3). A pH of approximately 5.8 gave the best result from the standpoint of ease of controlling the reaction in large-scale synthesis. Furthermore, the use of 10 wt % of lipase was sufficient to carry out the reaction. From these results, we developed a way to scale-up this synthesis reaction. The reaction time was approximately 24 h, meaning that the control of overhydrolysis to diol was easier than with the previous method. Additionally, the substrate concentration was improved to 50 mg/mL from 0.5 mg/mL (i.e., hundred-fold). Removal of the overhydrolysed diol compound **33** was possible without SiO_2 column chromatography as the product could be selectively extracted into the aqueous layer during phase separation between toluene and water. This promising method was verified in a pilot-plant 36-kg synthesis, and the results were the same as those from the lab-scale operations. Details of the procedure are provided in the Experimental Section. Nevertheless, enantiopurity at this stage was still insufficient (91% ee). Furthermore, we

Table 3. Enzyme evaluation[a]

			HPLC area %[b]				
entry	enzyme	time (h)	33	(S)-34	(R)-34	32	% ee[b]
1	*A*	0.5	84	3	13	0	63
2	*B*	20	0	20	34	46	26
3	*C*	20	3	30	57	10	31
4	*D*	2	12	42	26	20	24
5	*E*	20	78	16	4	2	60
6	*F*	20	2	39	50	9	12
7	*G*	20	21	24	55	0	39
8	*H*	20	0	26	40	34	21
9	*I*	20	90	6	4	0	20
10	*J*	2	12	65	9	14	76
11	*K*	2	20	74	6	0	85
12	*L*	20	10	40	38	12	3

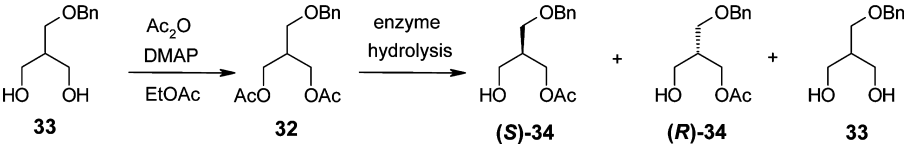
[a]Reaction temp: 37 °C; 5% DMSO−Tris·HCl buffer (pH 7.5); **32**: 0.5 mg/mL; enzyme: 1 mg/mL. [b]Determined by HPLC methods A and B (see Experimental Section).

Table 4. Screening of co-solvent[a]

		HPLC area %[b]				
entry	solvent	33	(S)-34	(R)-34	32	% ee[b]
1	5% DMSO	20	74	6	0	85
2	20% DMSO	21	75	4	0	90
3	40% DMSO	16	75	4	5	90
4	60% DMSO	3	74	4	19	90
5	80% DMSO	0	2	0	98	–
6	10% DMF	14	77	7	2	83
7	10% THF	28	63	9	0	75
8	10% *t*-BuOH	15	76	7	2	83
9	10% IPE	33	35	2	30	89
10	10% toluene	15	13	1	71	86

[a]Reaction temp: 37 °C; reaction time: 2 h; Tris·HCl buffer, pH 7.5; **32**: 0.5 mg/1 mL; Lipase AK: 1 mg/mL. [b]Determined by HPLC methods A and B (see Experimental Section).

Scheme 6. Enantioselective hydrolysis of diacetate 32



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Scheme 7. Enantioselective hydrolysis of compounds of various chain lengths with enzyme

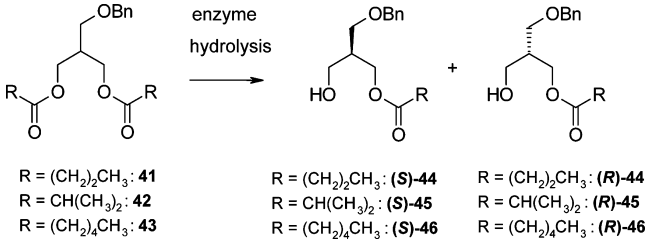

Table 5. Effect of co-solvent[a]

		HPLC area %[d]			
entry	cosolvent	33	34	32	% ee[d]
1	DMSO[c]	88.7	11.2	0.1	48
2	*i*-PrOH[b]	28.6	65.9	5.5	91
3	IPE[c]	47.9	44.9	7.2	30
4	toluene[c]	19.5	35.9	44.6	39
5	DMF[c]	31.4	64.1	4.5	86
6	THF[c]	5.9	23.3	70.8	79
7	DME[c]	23.9	68.5	7.6	91
8	CPME[c]	35.7	45.5	18.8	71
9	MeCN[c]	1.0	7.4	91.6	72

[a]Reaction temp: 25 °C; 0.5 M phosphate buffer (pH 6.0): cosolvent = 1:1 (1 g/20 mL); lipase: 24 wt %. [b]Reaction time; 24 h. [c]Reaction time; 14 h. [d]Determined by HPLC methods A and B (see Experimental Section).

Table 6. Optimization of the pH of buffer and amount of Lipase AK Amano[a]

			HPLC area %[b]			
entry	pH of buffer	time (h)	33	34	32	% ee[b]
1	4.4	24	11.3	68.3	20.4	90
		45	13.6	67.7	18.7	87
2	5.8	17	15.1	73.7	11.2	90
		24	18.2	76.2	5.6	91
		45	20.6	75.5	3.9	91
3	6.5	17	20.1	71.8	8.1	90
		24	24.1	72.0	3.9	91
		45	33.0	65.3	1.7	90

[a]Reaction temp: 25 °C; phosphate buffer: DME = 1:1 (1 g/20 mL); lipase: 10 wt %. [b]Determined by HPLC methods A and B (see Experimental Section).

considered that it would not be efficient to purify this intermediate (*S*)-**34** because of its characteristics as an oily product. We therefore went ahead with the following steps without purification.

Next, we proceeded to the synthesis of chiral amine unit (*R*)-**1** from chiral alcohol (*S*)-**34** (Scheme 8). Primary alcohol (*S*)-**34** was converted to mesylate **47** using MsCl with Et_3N in good yield. For the preparation of (*R*)-**1** from mesylate **47**, we focused on two methods, the phthalimide method (Gabriel amine synthesis) and the diboc amine method using di-*tert*-butyl iminodicarboxylate.[12] The phthalimide intermediate **48** was easily prepared from mesylate **47** and potassium phthalimide in good yield. However, the deprotection reaction gave a poor yield. Treatment with methylamine or hydrazine did not give a clean reaction profile, and column chromatography purification was needed to prepare the pure chiral amine compound (*R*)-**1**. Meanwhile, the reaction of mesylate **47** and di-*tert*-butyl iminodicarboxylate with cesium carbonate in DMI solvent and deprotection of the di-Boc and *O*-acetyl compound **49** in acidic conditions proceeded smoothly. After the reaction, the chiral amine compound (*R*)-**1·HCl** was crystallized as a salt of hydrochloric acid in *i*-PrOH−*i*-PrOAc. The purity of the chiral amine compound was >99.5 area % and >99.0% ee. The enantiomer was efficiently removed to the filtrate. The yield from diol compound **33** was 51.6% in five steps, and the overall yield from triol compound **31** was 37.7% in eight steps. This means that we were able to develop a practical method for an enantiopure chiral amine unit, and we in fact prepared 22.0 kg of desired chiral amine (*R*)-**1·HCl** in large-scale.

2.7. Preparation of Enantioisomer (*S*)-1·HCl. This useful chiral acetyl alcohol (*S*)-**34** was converted to the *S*-amine unit (*S*)-**1** also as shown in Scheme 9. The TBDMS protection of primary alcohol (*S*)-**34** was achieved with TBDMSOTf in the presence of 2,6-lutidine, and the following deacetylation of **50** was easily accomplished by using potassium carbonate in MeOH. Mesylation of **51**, preparation of **53**, and desilylation of **53** were performed in good yield. Next, the deprotection of the primary amine was accomplished in an excellent procedure. The desired (*S*)-**1·HCl** was isolated as a monohydrochloride in a high enantiopurity (99.5% ee). The overall yield of (*S*)-**1·HCl** from **31** was 35.9% in eleven steps.

3. CONCLUSION

In summary, we developed a practical and scalable synthetic method for the preparation of useful C-4 chiral amine building blocks. The key asymmetric construction was achieved using lipase-catalyzed enantioselective hydrolysis as a key reaction that was performed with marked efficiency under environmentally friendly conditions. Finally, this process was conducted in large-scale and yielded 22 kg of the target chiral amine (*R*)-**1·HCl** for the first GMP delivery. The enantioisomer (*S*)-**1·HCl** was also prepared in high enantiopurity. These promising chiral amine units (*R*)-**1·HCl** and (*S*)-**1·HCl** would be useful for the preparation of various kinds of chiral compounds.

4. EXPERIMENTAL SECTION

General. Starting materials, reagents, and solvents were obtained from commercial suppliers and used without further purification. ^1H and ^{13}C NMR spectra were recorded in the specified deuterated solvent. Chemical shifts of ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual solvent ($CHCl_3$ 7.26 ppm; DMSO-d_6 2.50 ppm) or TMS. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet doublet, t = triplet, m = multiplet and br = broad), coupling constant (Hz), and integration. Chemical shifts of proton-decoupled ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.0 ppm), DMSO-d_6 (39.5 ppm) on the δ scale. IR spectra were measured using the KCl disk method (JP16). HPLC was performed using the HITACHI D-2500 or D-7500 system. HPLC methods are described below.

HPLC Methods. *Method A:* YMC-Pack ODS-A, 5 μm, 4.6 mm × 150 mm column, elution 0.01 M KH_2PO_4 aq/CH_3CN = 1/1, over 30 min, 1.0 mL/min, at 40 °C, with UV detection at 220 nm.

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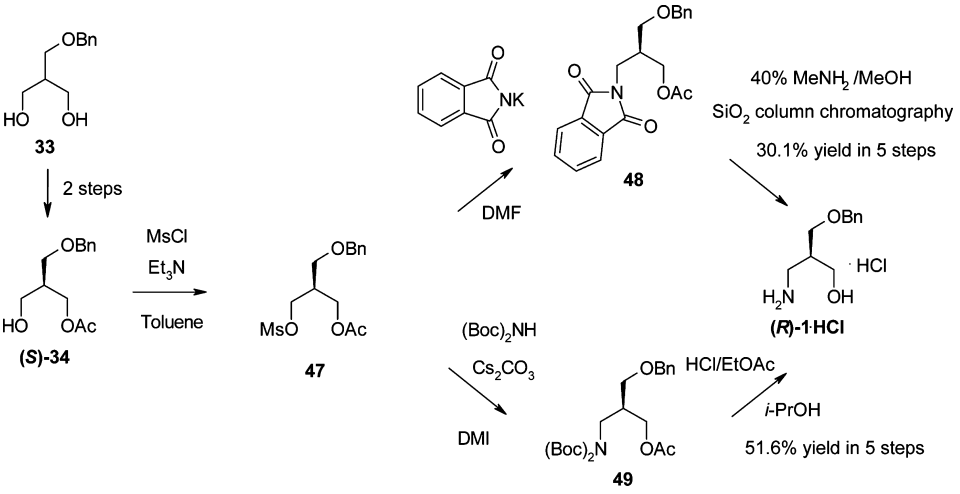
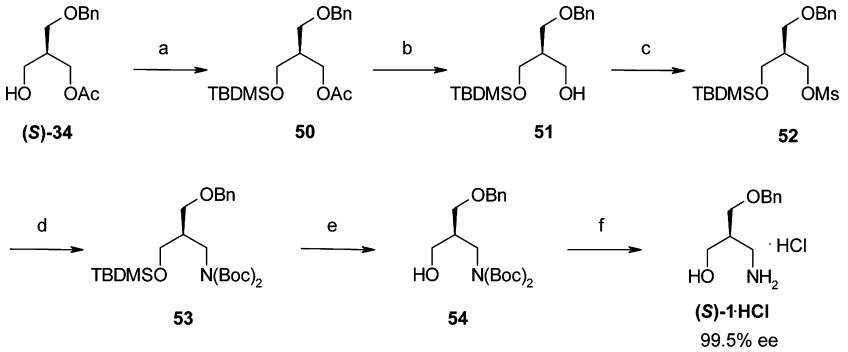
Scheme 8. Preparation of the chiral amine unit from chiral alcohol



Scheme 9. Synthesis of *S*-form chiral amine (*S*)-1·HCl[a]



[a]Reagents and conditions: (a) TBDMSOTf (1.04 equiv), 2,6-lutidine (1.2 equiv)/THF, −20 °C (95.1% yield); (b) K_2CO_3 (2.04 equiv)/MeOH, 25 °C (97.2% yield); (c) Et_3N (1.45 equiv), MsCl (1.07 equiv)/toluene, −5 °C then 5 °C (97.0% yield); (d) Boc_2NH (1.1 equiv), Cs_2CO_3 (2.4 equiv)/DMI, 75 °C (99.2% yield); (e) tetrabutylammonium fluoride 1 M in THF (1.15 equiv)/THF, 0 °C then 25 °C (97.1% yield); (f) 4 M HCl/EtOAc (2.5 equiv)/MeOH, 40 °C (80.1% yield).

40: 8.0 min, benzylbromide: 9.4 min, toluene: 9.9 min, dibenzylether: 19.9 min, **33**: 2.1 min, EtOAc: 2.8 min, **34**: 3.4 min, **32**: 7.4 min, **47**: 5.8 min.

Method B: DAICEL CHIRALPAK AD-RH, 5 μm, 4.6 mm × 150 mm column, elution 0.02 M KH_2PO_4 aq (adjust pH 2.0 by aq H_3PO_4)/CH_3CN = 3/1, over 40 min, 1.0 mL/min, at 40 °C, with UV detection at 220 nm.

(*S*)-**34**: 11.7 min, (*R*)-**34**: 12.9 min.

Method C: YMC-Pack ODS-A, 5 μm, 4.6 mm × 150 mm column, elution 0.01 M KH_2PO_4 aq/CH_3CN = 3/7, over 30 min, 1.0 mL/min., at 40 °C, with UV detection at 220 nm.

(*R*)-**1**: 1.5 min, DMI: 1.8 min, **47**: 2.7 min, toluene: 4.1 min, **49**: 10.1 min.

Method D: YMC-Pack ODS-A, 5 μm, 4.6 mm ×150 mm column, elution 0.01 M KH_2PO_4 aq/CH_3CN = 8/2, over 30 min, 1.0 mL/min, at 40 °C, with UV detection at 220 nm.

(*R*)-**1**: 3.2 min.

Method E: DAICEL CROWNPAK CR(+), 5 μm, 4.0 mm ×150 mm column, elution 0.02 M $NaClO_4$ aq (adjust pH 2.0 by aq $HClO_4$)/MeOH = 85/15, over 30 min, 1.0 mL/min, at 40 °C, with UV detection at 220 nm.

(*R*)-**1**: 12.5 min, (*S*)-**1**: 15.9 min.

Method F: YMC-Pack ODS-A, 5 μm, 4.6 mm × 150 mm column, elution 0.01 M KH_2PO_4 aq/CH_3CN = 3/7, over 30 min, 1.5 mL/min, at 40 °C, with UV detection at 220 nm.

34: 2.6 min, **50**: 20 min, **51**: 6.9 min, **52**: 9.7 min.

Method G: YMC-Pack ODS-A, 5 μm, 4.6 mm × 150 mm column, elution 0.01 M KH_2PO_4 aq./CH_3CN = 2/8, over 30 min, 1.5 mL/min., at 40 °C, with UV detection at 220 nm.

52: 4.4 min, **53**: 25 min, **54**: 2.9 min.

Method H: YMC-Pack ODS-A, 5 μm, 4.6 mm ×1 50 mm column, elution 0.01 M KH_2PO_4 aq/CH_3CN = 2/8, over 30 min, 1.0 mL/min., at 40 °C, with UV detection at 220 nm.

(*S*)-**1**: 1.7 min, **54**: 4.4 min.

(2,2-Dimethyl-1,3-dioxan-5-yl)methanol (39). To a solution of 2-(hydroxymethyl)-1,3-propanediol **31** (38.1 kg, 359 mol) and *p*-toluenesulfonic acid monohydrate (0.683 kg, 3.59 mol) in acetone (301 kg) was added 2,2-dimethoxypropane (44.9 kg, 431 mol) at 25 °C. After the reaction mixture was aged for 2 h, to the batch was added triethylamine (3.63 kg, 35.9 mol), and the batch was concentrated *in vacuo* . To the residue was added toluene (99 kg) and concentrated *in vacuo* to afford the desired **39**, to which was added toluene (330 kg). The solution was used in the next step without purification. An analytical sample of **39** was purified by SiO_2 column chromatography ($CHCl_3$ /MeOH = 10/1).

MS (ESI, pos.) *m*/*z*: 147.0, MS (GC, pos.) *m*/*z*: 147.1.

^{1}H NMR (400 MHz, DMSO-d_6): δ 4.52 (1H, t, *J* = 5.2 Hz), 3.82 (2H, dd, *J* = 11.8, 4.4 Hz), 3.61 (2H, d, *J* = 11.8, 7.2 Hz),

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3.38 (2H, dd, J = 6.8, 5.2 Hz), 1.65−1.73 (1H, m), 1.30 (3H, s), 1.29 (3H, s).

^{13}C NMR (100 MHz, DMSO-d_6): δ 97.1, 60.8 (2 carbons), 59.6, 36.5, 24.7, 23.1.

Process mass intensity (from **31** to **39**) = 15.6.

(38.1 + 0.683 + 301 + 44.9 + 3.63 + 99 + 330)/52.5 (theoretical yield) = 15.6.

5-[(Benzyloxy)methyl]-2,2-dimethyl-1,3-dioxane (40). To a solution of **39** in toluene were added an aqueous solution of potassium hydroxide (85.5 kg/water 85.5 L, 1527 mol) and tetrabutylammonium bromide (11.6 kg, 36.0 mol) and benzylbromide (64.5 kg, 377 mol) at 25 to 40 °C. The reaction mixture was heated to 50 °C and aged for 10 h with vigorous stirring, after which time HPLC analysis indicated <1% benzyl bromide remained (HPLC method A). In fact, benzyl bromide was not detected on HPLC analysis. To the batch was then added water (267 kg), and the resulting organic layer was washed with water (381 kg) and concentrated *in vacuo* to afford desired **40**, to which was added *i*-PrOH (150 kg). The solution was used in the next step without purification. An analytical sample of **40** was purified by SiO_2 column chromatography (*n*-heptane/EtOAc = 9/1).

MS (ESI, pos.) m/z: 237.1, MS (GC, pos.) m/z: 237.2.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.25−7.38 (5H, m), 4.46 (2H, s), 3.86 (2H, dd, J = 11.8, 4.4 Hz), 3.64 (2H, dd, J = 11.8, 6.9 Hz), 3.44 (2H, d, J = 6.9 Hz), 1.87−1.95 (1H, m), 1.31 (3H, s), 1.29 (3H, s).

^{13}C NMR (100 MHz, DMSO-d_6): δ 138.4, 128.2 (2 carbons), 127.3 (2 carbons), 127.2, 97.2, 72.1 68.4, 60.7 (2 carbons), 34.1, 24.4, 23.4.

Process mass intensity (from **39** to **40**) = 12.3.

(85.5 + 85.5 + 11.6 + 64.5 + 267 + 381 + 150)/84.9 (theoretical yield) = 12.3.

2-[(Benzyloxy)methyl]propane-1,3-diol (33). To a solution of **40** in *i*-PrOH was added an aqueous hydrochloric acid (35 wt % HCl 3.72 kg/water 32.8 kg) at 25 °C and aged for 3 h, after which time HPLC analysis indicated <1% **40** remained (HPLC method A). The batch was then concentrated *in vacuo*. To the residue were added EtOAc (344 kg) and aqueous NaCl (NaCl 43.8 kg/water 175 kg), and the organic layer was concentrated *in vacuo* again. To the resulting residue was added diisopropylether (138 kg), and the solution was seeded (3.81 g) at 28 °C. After aging for 1 h at 30 °C, the batch was cooled to between −10 and −5 °C and aged for 14 h. The slurry was filtered and washed with diisopropylether (27.6 kg, precooled to 0 °C). The wet cake was dried *in vacuo* at 30 °C to afford the desired **33** with 99.5% purity via HPLC method A (51.4 kg, 73.0% yield from **31** in three steps).

MS (ESI, pos.) m/z: 197.1.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.24−7.37 (5H, m), 4.49 (2H, s), 4.35 (2H, br), 3.41−3.46 (6H, m), 1.76−1.85 (1H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ 138.8, 128.2 (2 carbons), 127.3 (2 carbons), 127.1, 72.1, 68.6, 59.5 (2 carbons), 44.3.

Anal. Calcd for $C_{11}H_{16}O_3$. Calc: C (67.32%), H (8.22%). Found: C (67.06), H (8.30%).

Process mass intensity (from **40** to **33**) = 14.9.

(3.72 + 32.8 + 344 + 43.8 + 175 + 138 + 27.6)/51.4 = 14.9.

2-[(Benzyloxy)methyl]propane-1,3-diyl Diacetate (32). The solution of **33** (36.2 kg, 184 mol), DMAP (2.25 kg, 18.4 mol) in EtOAc (327 kg) was cooled to 0 °C. Acetic anhydride (39.4 kg, 386 mol) was then added below 30 °C. The reaction mixture was aged for 3 h at 30 °C, after which time HPLC analysis indicated <1% **33** and <1% mono-acetylated intermediate remained (HPLC method A). To the batch was added water (362 kg), and the resulting organic layer was washed with aqueous sodium bicarbonate ($NaHCO_3$ 18.1 kg/water 362 kg). The organic layer was washed with water (362 kg), and the resulting organic layer was concentrated *in vacuo* to afford desired **32** with 98% purity via HPLC method A. The theoretical yield is 51.7 kg. This was then mixed with 1,2-dimethoxyethane (448 kg), and the solution was used in the next step without purification. An analytical sample of **32** was purified by SiO_2 column chromatography (*n*-heptane/EtOAc = 2/1).

MS (ESI, pos.) m/z: 281.1, MS (GC, pos.) m/z: 281.1.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.26−7.38 (5H, m), 4.47 (2H, s), 4.00−4.10 (4H, m), 3.46 (2H, d, J = 5.9 Hz), 2.26−2.31 (1H, m), 1.99 (6H, s).

^{13}C NMR (100 MHz, DMSO-d_6): δ 170.2 (2 carbons), 138.2, 128.2 (2 carbons), 127.4, 127.3 (2 carbons), 72.1, 67.1, 61.8, 59.7, 37.7, 20.5 (2 carbons).

Process mass intensity (from **33** to **32**) = 37.2.

(2.25 + 327 + 39.4 + 362 + 18.1 + 362 + 362 + 448)/51.7 (theoretical yield) = 37.2.

(*S*)-3-(Benzyloxy)-2-(hydroxymethyl)propyl Acetate ((*S*)-34). To a solution of **32** in 1,2-dimethoxyethane were added phosphate buffer (KH_2PO_4; 7.02 kg, K_2HPO_4; 0.90 kg/water 516 kg, pH 5.8) and Lipase AK Amano (Amano enzyme, 5.16 kg) at around 25 °C. The batch was aged for approximately 26 h at 25 °C, after which time HPLC analysis indicated <6% **32** remained (HPLC method A). In this stage, the reaction mixture contained overhydrolyzed diol **33** at 18% (HPLC method A). To the batch was added toluene (893 kg), and the resulting organic layer was mixed with filter aid (Radiolite, 10.3 kg). After filtration of the batch, the resulting cake was washed with toluene (45 kg). The filtrate was then washed with aqueous sodium bicarbonate ($NaHCO_3$ 25.8 kg/water; 516 kg) and aqueous NaCl (NaCl; 25.8 kg/water; 516 kg) five times to remove compound **33**. The resulting organic layer was analyzed by HPLC and showed 91.6% purity (HPLC method A) and 91% ee (HPLC method B). The organic layer was concentrated *in vacuo* to afford the desired **(*S*)-34**. After the addition of toluene (285 kg) to the residue, the resulting solution was used in the next step without purification. An analytical sample of **(*S*)-34** was purified by SiO_2 column chromatography (*n*-heptane/EtOAc = 1/1).

MS (ESI, pos.) m/z: 239.1, MS (GC, pos.) m/z: 229.1.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.27−7.37 (5H, m), 4.58 (1H, t, J = 5.3 Hz), 4.45 (2H, s), 4.04 (2H, d, J = 6.2 Hz), 3.32−3.49 (4H, m), 1.98−2.04 (1H, m), 1.97 (3H, s).

^{13}C NMR (100 MHz, DMSO-d_6): δ 170.4, 138.5, 128.2, 127.3 (4 carbons), 72.1, 67.8, 62.3, 58.8, 41.0, 20.6.

Process mass intensity (from **32** to **(*S*)-34**) = 147.3.

(7.02 + 0.90 + 516 +5.16 + 893 + 10.3 + 45 + 25.8 + 516 + 25.8+(516 + 285)5 + 285)/34.2 = 147.3.

(*S*)-3-(Benzyloxy)-2-[(mesyloxy)methyl]propyl Acetate (47). A solution of **(*S*)-34** in toluene was cooled to −5 °C, and triethylamine (20.9 kg, 207 mol) was added to the solution; then methanesulfonyl chloride (19.0 kg, 166 mol) was added at 0 °C. The reaction mixture was aged for 1 h at 0 °C, after which time HPLC analysis indicated <1% **34** remained (HPLC method A). To the mixture was added water (330 kg), and the resulting organic layer was concentrated *in vacuo* to afford the desired **47** with 91% purity via HPLC method A. To this was

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then added DMI (231 kg), and the solution was used in the next step without purification.

An analytical sample of **47** was purified by SiO_2 column chromatography (*n*-heptane/EtOAc = 3/2).

MS (ESI, pos.) *m*/*z*: 317.1, MS (GC, pos.) *m*/*z*: 317.1.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.27−7.38 (5H, m), 4.49 (2H, s), 4.22−4.30 (2H, m), 4.05−4.13 (2H, m), 3.50 (2H, d, *J* = 6.0 Hz), 3.17 (3H, s), 2.34−2.41 (1H, m), 2.00 (3H, s).

^{13}C NMR (100 MHz, DMSO-d_6): δ 170.2, 138.1, 128.3, 128.2, 127.5, 127.4, 127.3, 72.2, 68.0, 66.6, 61.2, 38.1, 36.4, 20.5.

Process mass intensity (from **(*S*)-34** to **47**) = 13.2.

(20.9 + 19.0 + 330 + 231)/45.6 = 13.2.

(*S*)-3-(Benzyloxy)-2-{[bis(*tert*-butoxycarbonyl)amino]-methyl}propyl Acetate (49). To a solution of **47** in DMI were added di-*tert*-butyl iminodicarboxylate (31.5 kg, 145 mol) and Cs_2CO_3 (49.5 kg, 152 mol). The batch was then heated to 75 °C and aged for 8 h, after which time HPLC analysis indicated <1% **47** remained (HPLC method C). To the batch were added EtOAc (394 kg) and water (219 kg) after cooling to 25 °C, and the resulting organic layer was washed with water (219 kg) three times. The resulting organic layer was concentrated *in vacuo* to afford the desired **49** with 85% purity via HPLC method A. This was mixed with MeOH (143 kg), and the solution was used in the next step without purification. An analytical sample of **49** was purified by SiO_2 column chromatography (*n*-heptane/EtOAc = 9/1).

MS (FAB, pos.) *m*/*z*: 438.3.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.27−7.37 (5H, m), 4.45 (2H, s), 4.01 (2H, dd, *J* = 5.7, 1.7 Hz), 3.61 (2H, d, *J* = 7.7 Hz), 3.38−3.42 (2H, m), 2.25−2.32 (1H, m), 1.96 (3H, s), 1.42 (18H, s).

^{13}C NMR (100 MHz, DMSO-d_6): δ 170.2, 152.1 (2 carbons), 138.2, 128.1 (2 carbons), 127.3 (2 carbons), 127.2, 81.8, 72.1, 68.1, 62.9, 45.3, 37.9, 27.7, 27.5 (6 carbons), 20.5.

Process mass intensity (from **47** to **49**) = 16.8.

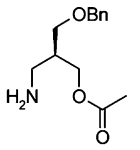
(31.5 + 49.5 + 394 + 219 + 219 + 143)/63.0 = 16.8.

(*R*)-3-Amino-2-[(benzyloxy)methyl]propan-1-ol Monohydrochloride (*R*)-1·HCl. To a solution of **49** in MeOH, was added 4 M HCl in EtOAc (87 L, 348 mol) at around 25 °C and heated to 40 °C. The batch was aged for 20 h, after which time HPLC analysis indicated <1% of **49** and intermediate X remained (HPLC method C). The batch was then concentrated *in vacuo* to about 60 L. To the resulting residue was added *i*-PrOH (143 kg), and the resulting mixture was concentrated *in vacuo* to about 60 L. To the residue was added *i*-PrOH (95 kg), and the batch was heated to 77 °C, filtered, and washed with *i*-PrOH (24 kg). The filtrate was cooled and seeded (6.0 g) at 30 °C. After aging for 1 h at 30 °C, isopropyl acetate (132 kg) was added to the batch, and the mixture was cooled to 0 °C and aged for 17 h. The resulting slurry was filtered and washed with isopropyl acetate (53 kg, precooled to 5 °C). The wet cake was dried *in vacuo* at 40 °C to afford the desired **(*R*)-1·HCl** with >99.5% purity via HPLC method D (22.04 kg, 51.6% yield from **33** in 5 steps). An enantiomer was detected at 0.5% (HPLC method E). Overall yield: 37.7% from **31** in eight steps.

MS (ESI, pos.) *m*/*z*: 196.1.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.10 (2H, br), 7.26−7.38 (5H, m), 4.89 (1H, br), 4.48 (2H, d, *J* = 2.8 Hz), 3.36−3.55 (4H, m), 2.85 (2H, d, *J* = 6.6 Hz), 2.06−2.12 (1H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ 138.4, 128.2 (2 carbons), 127.4 (2 carbons), 127.3, 72.1, 68.5, 59.2, 39.4, 38.3.



intermediate X

Anal. Calcd for $C_{11}H_{17}NO_2$·HCl. Calc: C (57.02), H (7.83), N (6.04), Cl (15.30). Found: C (57.03), H (7.88), N (5.83), Cl (15.28).

IR (KCl): 3141, 2963, 2846, 1619, 1505, 1354, 1118, 1024, 1016, 737.

Mp 96.5 °C (by DSC).

$[\alpha]^{20}_D$ = +3.0 ° (*c* = 1.0, DMF).

Process mass intensity (from **49** to **(*R*)-1·HCl**) = 24.2.

(87 + 143 + 95 + 24 + 132 + 53)/22.04 = 24.2.

(*S*)-3-(Benzyloxy)-2-({[*tert*-butyl(dimethyl)silyl]oxy}-methyl)propyl Acetate (50). To a solution of **(*S*)-34** (8.50 g, 35.7 mmol, 91% ee, HPLC method B) in THF (300 mL) was added 2.6-lutidine (4.59 g, 42.8 mmol), and the mixture was cooled to −20 °C. To the batch was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (9.8 g, 37.1 mmol) at −20 °C and aged for 1 h, after which time HPLC analysis indicated <1% of **34** remained (HPLC method F). A 4% (w/v) aqueous solution of $NaHCO_3$ (200 mL) was then added, and the batch was concentrated *in vacuo*. To the residue were added EtOAc (400 mL) and a 5% (w/v) aqueous solution of NaCl (100 mL), and the organic layer was washed with a 5% (w/v) aqueous solution of NaCl (100 mL). The resulting organic layer was concentrated *in vacuo* to afford the desired **50** with 94% purity via HPLC method F: 11.95 g (95.1% yield).

An analytical sample of **50** was purified by SiO_2 column chromatography (*n*-heptane/EtOAc = 8/2).

MS (ESI, pos) *m*/*z*: 353.2.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30−7.41 (5H, m), 4.49 (2H, s), 4.07 (2H, d, *J* = 6.1 Hz), 3.67 (2H, dd, *J* = 5.6, 3.1 Hz), 3.48 (2H, t, *J* = 5.6 Hz), 2.10−2.14 (1H, m), 2.02 (3H, s), 0.88 (9H, s), 0.05 (6H, s).

^{13}C NMR (100 MHz, DMSO-d_6): δ 170.3, 138.3, 128.2 (2 carbons), 127.4, 127.3 (2 carbons), 72.1, 67.3, 61.9, 60.3, 40.7, 25.7 (3 carbons), 20.7, 17.8, −0.57 (2 carbons).

Process mass intensity (from **(*S*)-34** to **50**) = 87.1.

(267 + 4.59 + 9.8 + 200 + 360 + 100 + 100)/11.95 = 87.1.

(*R*)-3-(Benzyloxy)-2-({[*tert*-butyl(dimethyl)silyl]oxy}-methyl)propan-1-ol (51). To a solution of **50** (10.0 g, 28.4 mmol) in MeOH (200 mL) was added potassium carbonate (4.0 g, 28.9 mmol) at 25 °C, and the batch was aged for 1 h at the same temperature, after which time HPLC analysis indicated <1% of **50** remained (HPLC method F). To the batch were added EtOAc (400 mL) and a 20% (w/v) aqueous solution of NaCl (100 mL), and the organic layer was washed with a 20% (w/v) aqueous solution of NaCl (100 mL). The resulting organic layer was concentrated *in vacuo* to afford the desired **51** with 97% purity via HPLC method F: 8.54 g (97.2% yield).

An analytical sample of **51** was purified by SiO_2 column chromatography (*n*-heptane/EtOAc = 8/2).

MS (ESI, pos) *m*/*z*: 311.2.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.26−7.37 (5H, m), 4.44 (2H, s), 4.39 (1H, t, *J* = 5.1 Hz), 3.60−3.64 (2H, m), 3.40−3.45 (4H, m), 1.82−1.86 (1H, m), 0.85 (9H, s), 0.01 (6H, s).

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^{13}C NMR (100 MHz, DMSO-d_6): δ 138.6, 128.1 (2 carbons), 127.3, 127.2 (2 carbons), 72.1, 67.9, 60.8, 59.1, 44.2, 25.7 (3 carbons), 17.9, −5.53 (2 carbons).

Process mass intensity (from **50** to **51**) = 84.5.

(158 + 4.0 + 360 + 100 + 100)/8.54 = 84.5.

(*R*)-3-(Benzyloxy)-2-({[*tert*-butyl(dimethyl)silyl]oxy}-methyl)propyl Methanesulfonate (52). To a solution of **51** (7.0 g, 22.5 mmol) in toluene (250 mL) was added triethylamine (3.3 g, 32.6 mmol), and the batch was cooled to −5 °C. Methanesulfonyl chloride (2.75 g, 24.0 mmol) was added to the batch below 5 °C. The reaction mixture was aged for 1 h at 5 °C, after which time HPLC analysis indicated <1% **51** remained (HPLC method F). To the batch was added water (100 mL), and then the resulting organic layer was washed with a 5% (w/v) aqueous solution of NaCl (100 mL). The resulting organic layer was concentrated *in vacuo* to afford the desired **52** with 95% purity via HPLC method F: 8.49 g (97.0% yield).

An analytical sample of **52** was purified by SiO_2 column chromatography (*n*-heptane/EtOAc = 8/2).

MS (ESI, pos) *m*/*z*: 389.2.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.28−7.36 (5H, m), 4.47 (2H, s), 4.23 (2H, d, *J* = 6.0 Hz), 3.63−3.66 (2H, m), 3.45−3.49 (2H, m), 3.15 (3H, s), 2.14−2.20 (1H, m), 0.85 (9H, s), 0.03 (6H, s).

^{13}C NMR (100 MHz, DMSO-d_6): δ 138.2, 128.2 (2 carbons), 127.4, 127.3 (2 carbons), 72.2, 68.1, 66.7, 59.7, 41.1, 36.4, 25.7 (3 carbons), 17.8, −5.61 (2 carbons).

Process mass intensity (from **51** to **52**) = 49.8.

(217 + 3.3 + 2.75 + 100 + 100)/8.49 = 49.8.

Di-*tert*-butyl (*R*)-2-[3-(Benzyloxy)-2-({[*tert*-butyl-(dimethyl)silyl]oxy}methyl)propyl]-2-imidodicarbonate (53). To a solution of **52** (8.0 g, 20.6 mmol) in DMI (40 mL) were added di-*tert*-butyl iminodicarboxylate (4.92 g, 22.6 mmol) and Cs_2CO_3 (8.05 g, 24.7 mmol) at 25 °C. The batch was then heated to 75 °C and aged for 6 h, after which time HPLC analysis indicated <1% **52** remained (HPLC method G). After cooling to 25 °C, EtOAc (300 mL) and a 5% (w/v) aqueous solution of NaCl (100 mL) were added to the batch. The organic layer was then washed with a 5% (w/v) aqueous solution of NaCl (100 mL), and the resulting organic layer was concentrated *in vacuo* to afford the desired **53** with 96% purity via HPLC method G: 10.4 g (99.2% yield).

An analytical sample of **53** was purified by SiO_2 column chromatography (*n*-heptane/EtOAc = 8/2).

MS (ESI, pos) *m*/*z*: 510.3.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.26−7.34 (5H, m), 4.43 (2H, s), 3.55−3.60 (4H, m), 3.30−3.43 (2H, m), 2.48−2.51 (1H, m), 1.41 (18H, s), 0.85 (9H, s), 0.01 (6H, s).

^{13}C NMR (100 MHz, DMSO-d_6): δ 152.2 (2 carbons), 138.4, 128.1 (2 carbons), 127.3, 127.2 (2 carbons), 81.6 (2 carbons), 72.2, 68.1, 61.2, 45.4, 41.4, 27.5 (6 carbons), 25.7 (3 carbons), 17.9, −5.04 (2 carbons).

Process mass intensity (from **52** to **53**) = 50.5.

(42 + 4.92 + 8.05 + 270 + 100 + 100)/10.4 = 50.5.

Di-*tert*-butyl (*S*)-2-[3-(benzyloxy)-2-(hydroxymethyl)-propyl]-2-imidodicarbonate (54). To a solution of **53** (8.0 g, 15.7 mmol) in THF (250 mL) was added tetrabutylammonium fluoride 1 M in THF (18 mL, 18.0 mmol) at 0 °C, and the mixture was warmed to 25 °C. The batch was aged for 2 h, after which time HPLC analysis indicated <1% **53** remained (HPLC method G). To the batch were added a 5% (w/v) aqueous solution of NaCl (50 mL) and EtOAc (200 mL). The resulting organic layer was washed with a 5% (w/v) aqueous solution of NaCl (50 mL), and the resulting organic layer was concentrated *in vacuo* to afford the desired **54** with 97% purity via HPLC method G: 6.0 g (97.1% yield).

An analytical sample of **54** was purified by SiO_2 column chromatography (*n*-heptane/EtOAc = 9/1 then 6/4).

MS (ESI, pos) *m*/*z*: 396.3.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30−7.41 (5H, m), 4.49 (2H, s), 4.04 (2H, d, *J* = 5.8 Hz), 3.40−3.44 (2H, m), 3.00−3.06 (2H, m), 2.01−2.12 (1H, m), 1.44 (9H, s), 1.41 (9H, s), 1.28 (1H, br).

^{13}C NMR (100 MHz, DMSO-d_6): δ 155.7, 152.9, 138.4, 128.1 (2 carbons), 127.3 (3 carbons), 81.2 (2 carbons), 77.5, 72.1, 68.1, 65.3, 28.1, 27.3 (6 carbons).

Process mass intensity (from **53** to **54**) = 86.3.

(222 + 16 + 50 + 180 + 50)/6.0 = 86.3.

(*S*)-3-Amino-2-[(benzyloxy)methyl]propan-1-ol Monohydrochloride (*S*)-1·HCl. To a solution of **54** (5.0 g, 12.6 mmol) in MeOH (15 mL), 4 M HCl in EtOAc (10 mL, 40 mmol) was added at around 25 °C and the mixture was heated to 40 °C. The batch was aged for 3 h, after which time HPLC analysis indicated <1% of **54** remained (HPLC method H). The batch was then concentrated *in vacuo* to about 6.6 mL. To the resulting residue, *i*-PrOH (15 mL) was added and concentrated *in vacuo* to about 6.6 mL. To the residue, *i*-PrOH (12.5 mL) was added and the batch was heated to 77 °C and then cooled to 30 °C. After aging for 1 h at 30 °C, the resulting slurry was added isopropyl acetate (12.5 mL) and aged for 5 h at 30 °C. The slurry was filtered and washed with isopropyl acetate (5 mL). The wet cake was dried *in vacuo* at 40 °C to afford the desired **(*S*)-1·HCl** with 99% purity via HPLC method H (2.34 g, 80.1% yield). Enantiomer was detected at 0.24% (HPLC method E). Overall yield: 35.9% from **31** in eleven steps.

MS (ESI, pos.) *m*/*z*: 196.1.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.10 (2H, br), 7.26−7.38 (5H, m), 4.90 (1H, br), 4.48 (2H, d, *J* = 2.8 Hz), 3.36−3.56 (4H, m), 2.85 (2H, d, *J* = 6.6 Hz), 2.06−2.12 (1H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ 138.4, 128.2 (2 carbons), 127.4 (2 carbons), 127.3, 72.1, 68.5, 59.2, 39.4, 38.3.

Anal. Calcd for $C_{11}H_{17}NO_2$·HCl. Calc: C (57.02), H (7.83), N (6.04), Cl (15.30). Found: C (57.01), H (7.87), N (5.81), Cl (15.29).

IR (KCl): 3141, 2962, 2846, 1619, 1506, 1354, 1118, 1024, 1016, 737.

Mp 96.8 °C (by DSC).

$[\alpha]^{20}_D$ = −3.0 ° (*c* = 1.0, DMF).

Process mass intensity (from **54** to **(*S*)-1·HCl**) = 24.7.

(11.9 + 9 + 11.7 + 9.8 + 11 + 4.4)/2.34 = 24.7.

Diethyl 2,2-Dimethyl-1,3-dioxane-5,5-dicarboxylate (36). To a solution of diethyl bis(hydroxymethyl)malonate **28** (100 g, 454 mmol) in 2,2-dimethoxypropane (300 g, 2880 mmol) was added *p*-toluenesulfonic acid monohydrate (8.6 g, 45.2 mol) at 25 °C. After the reaction mixture was aged for 1 h, the batch was poured into a 5% (w/v) aqueous solution of $NaHCO_3$ (500 mL) and toluene (500 mL). The resulting organic layer was washed with brine (500 mL), and the organic layer was concentrated *in vacuo* to afford the desired crude **36** (100 g, 85.1% yield), which was used in the next step without purification.

MS (ESI, pos) *m*/*z*: 261.3.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.28 (4H, s), 4.20−4.27 (4H, m), 1.40 (6H, s), 1.20−1.28 (6H, m).

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Ethyl 2,2-dimethyl-1,3-dioxane-5-carboxylate (37). To a solution of **36** (30 g, 115.3 mmol) in DMSO (50 mL), LiCl (9.8 g, 231 mmol) and water (2.1 g, 117 mmol) were added. The batch was heated to 160 °C and aged for 2 h, then cooled to 0 °C. To the batch were added water (150 mL) and EtOAc (300 mL), and the batch was then filtered. To the resulting filtrate was added EtOAc (50 mL), and the organic layer was washed with brine (50 mL) and concentrated *in vacuo* to afford the desired crude **37** compound (10.1 g, 46.0% yield), which was used in the next step without purification.

MS (GC, pos.) *m*/*z*: 189.0.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.22−4.28 (2H, m), 4.14−4.20 (2H, m), 4.01−4.08 (2H, m), 2.27−2.80 (1H, m), 1.44 (3H, s), 1.41 (3H, s), 1.24−1.30 (3H, m).

Ethyl 3-Hydroxy-2-(hydroxymethyl)propanoate (38). To a solution of **37** (8.0 g, 42.5 mmol) in MeOH (58 mL) was added 6 M HCl (4 mL, 24 mmol) at 25 °C. The batch was aged for 12 h at 25 °C, and then to the batch was added $NaHCO_3$ (23 g, 274 mmol). The batch was then filtered and washed with EtOAc (50 mL) twice. The filtrate was concentrated *in vacuo* to afford the desired crude **38** (6.19 g, 98.1% yield), which was used in the next step without purification.

MS (GC, pos.) *m*/*z*: 148.9.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.22 (2H, dd, J = 14.0, 7.2 Hz), 3.93−3.99 (4H, m), 2.73−2.78 (2H, m), 2.69−2.72 (1H, m), 1.30 (3H, t, J = 7.2 Hz).

Ethyl (*R,S*)-3-{[*tert*-Butyl(diphenyl)silyl]oxy}-2-(hydroxymethyl)propanoate (29). To a solution of **38** (0.76 g, 5.13 mmol) in acetonitrile (15 mL) was added triethylamine (0.52 g, 5.14 mmol), and the mixture was cooled to −10 °C. To the batch was added *tert*-butylchlorodiphenylsilane (1.37 g, 4.98 mmol), and the batch was aged for 12 h at 25 °C. After concentration *in vacuo*, diisopropylether (40 mL) and water (30 mL) were added to the batch, and the resulting organic layer was washed with brine (10 mL) and concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography (*n*-heptane/EtOAc = 8/1 then 2/1) to afford the desired **29**, 1.19 g (60.0% yield).

MS (FAB, pos.) *m*/*z*: 387.1, MS (FAB, neg.) *m*/*z*: 385.2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52−7.70 (4H, m), 7.37−7.50 (6H, m), 4.10−4.20 (2H, m), 3.80−4.05 (4H, m), 2.77−2.83 (1H, m), 2.29−2.34 (1H, m), 1.23−1.30 (3H, m), 1,04 (9H, s).

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Notes

The authors declare no competing financial interest.

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