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Scale-Up of an Enantioselective Overman Rearrangement for an Asymmetric Synthesis of a Glycine Transporter 1 Inhibitor

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Supporting Information

ABSTRACT: An enantioselective Overman 3,3-sigmatropic rearrangement on a quinuclidine skeleton was developed for the pilot-plant synthesis of a glycine transporter 1 inhibitor. The first stereocenter was produced by a Ru-catalyzed asymmetric transfer hydrogenation process followed by chirality transfer using the Overman rearrangement. The second stereocenter was generated by a diastereoselective hydrogenation reaction.

INTRODUCTION

The use of glycine transporter 1 (GlyT1) inhibitors for the treatment of schizophrenia and acute manic disorders continues to be an active area of research.[1] Recently, quinuclidine **1**, bearing two asymmetric centers, was being advanced, and a more expeditious and scalable synthesis was required.[2] We focused our attention on the readily available 3-quinuclidinone as the core skeletal starting material and envisioned an aldol condensation to an enone with asymmetric reduction to the allylic alcohol (Scheme 1). Subsequent stereoselective 3,3-sigmatropic Overman rearrangement[3] would provide the requisite diamine after diasteroselective olefin hydrogenation for conversion to the desired quinuclidine **1**. Herein, we describe the details of these studies for a practical asymmetric synthesis of quinuclidine **1** involving the first reported multikilogram scale-up of an Overman rearrangement.

RESULTS AND DISCUSSION

The overall eight-step process (Scheme 2) was developed for the second pilot campaign.[2] Our major objectives were to devise an efficient establishment of the two chiral centers, while maintaining the previously established final intermediate to minimize regulatory risks for a route change. We also desired a starting material that contained the quinuclidine functionality and found that quinuclidinone **2** was inexpensive and readily available. With this starting material, we quickly considered the feasibility of construction of a chiral allylic alcohol that could be converted to an enamide with subsequent reduction to the desired diamine. Many opportunities to utilize this intermediate for stereocontrol, including metal-catalyzed allylic aminations[4] and the Overman rearrangement, were considered. However, we believed that the thermal Overman rearrangement would be the most reliable as discrimination of the two secondary sites on the allylic system might be more problematic and time-consuming to develop. A stepwise description of the process development leading to the production of 24.2 kg of drug substance **1** is presented.

Aldol Condensation. The first step of the process was an adaptation of the literature protocol[5] for the aldol condensation of 3-quinuclidinone **2** and benzaldehyde for the synthesis of enone **3**. With the quinuclidinone more readily available as the hydrochloride salt, attention was focused on using this species in the aldol condensation. Initially, the use of 1.33−1.50 equiv of sodium hydroxide pellets in ethanol at 80 °C provided the desired aldol product in approximately 85% yield after 10−20 h. Switching to aqueous ethanolic sodium hydroxide provided a faster more efficient reaction with completion achieved in 2 h at 50 °C. Finally, increasing the dilution to aid in the mixing provided a robust process that was scaled for six batches of quinuclidinone **2** to provide 134.7 kg of aldol product **3** (Table 1).

Asymmetric Reduction of Enone 3. Although the simple reduction of enone **3** has been reported with sodium borohydride,[5,6] access to the enantiomerically enriched allylic alcohol **4** was required for enantiomeric control during the Overman rearrangement. After considering DIP-Cl based systems,[7] Ru-catalytic reductions,[8] oxazaborolidine reductions,[9] and biocatalytic reductions,[10] we decided to start with the CBS oxazaborolidine protocol (Scheme 3). Quite satisfactorily, immediate success was achieved as an 88% ee of alcohol *S*-**4** was obtained using BH_3·DMS in toluene and (*R*)-2-methyl CBS oxazaborolidine[11] as the catalyst at −20 °C with dosing of the enone **3** over 2 h. Recrystallization from a mixture of toluene and heptane gave 95% ee. Interestingly during the initial screening of conditions using diethylaniline−borane complex (DEANB)[12] and *S*-MeCBS catalyst in THF, the highest selectivitiy with 95% ee for alcohol *R*-**4** was obtained performing the reaction at 30 °C, whereas only 54% ee was observed at −20 °C. On a 25-g scale using DEANB, a 60% yield of *R*-**4** with 97% ee was obtained. However using catecholborane and performing the reaction at −20 °C, a

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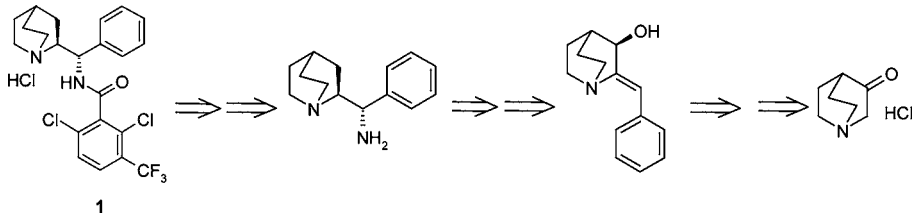
Scheme 1. Retrosynthetic analysis of GlyT1 inhibitor 1



Scheme 2. Process for the synthesis of GlyT1 inhibitor 1

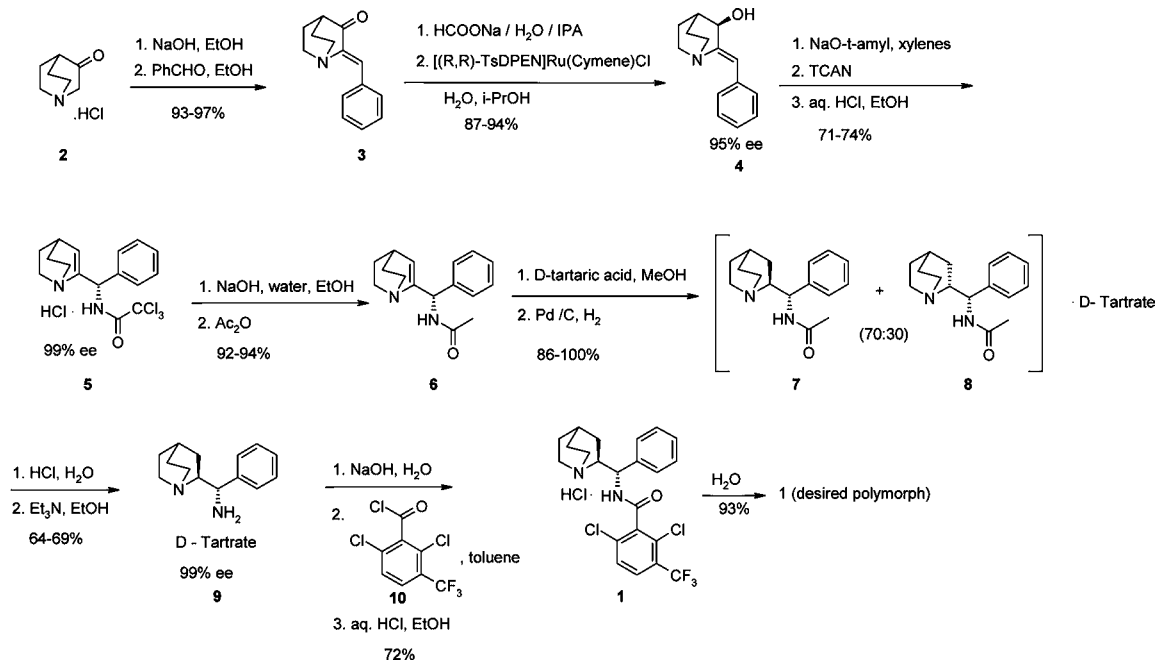
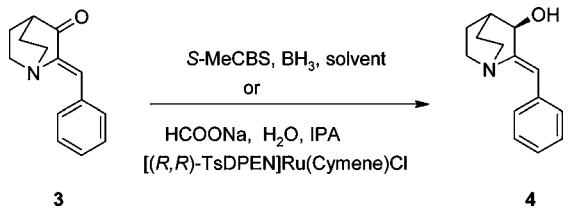


Table 1. Pilot-plant batches for synthesis of enone 3[a]

entry	alcohol **2** (kg)	yield (%)	enone **3** (kg)	purity (area %)	assay (wt %)
1	7.0	93	8.6	>99.9	n.d.[b]
2	20.0	97	25.7	>99.9	97.8
3	20.0	95	25.2	>99.9	98.1
4	20.0	94	24.7	>99.9	98.7
5	20.0	94	24.9	>99.9	98.4
6	19.8	95	24.8	>99.9	96.6

[a]Conditions: ketone **2**, PhCHO, NaOH, water, EtOH, 50 °C, 1 h. [b]n.d. = not determined.

Scheme 3. Asymmetric reduction of enone 3



92% ee of alcohol **4** was obtained. Finally, using *S*-MeCBS catalyst (0.05 equivalents) with BH_3·DMS complex in toluene and scaling to 100−250 g, the desired alcohol *R*-**4** with 98% ee was obtained in >80% yield and provided initial quantities for development of the Overman rearrangement.

Because of the potential safety issues of using boranes in a plant setting,[13] the feasibility of employing a metal-catalyzed asymmetric transfer hydrogenation of enone **3** to enantiomerically enriched alcohol **4** was pursued.[8] Initially we reacted the commercially available (1*R*,2*R*)-(−)-*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine [(*R*,*R*)-TsDPEN] and $[RuCl_2(p\text{-cymene})]_2$ in a solvent at 40 °C for 1 h to prepare the precatalyst [(*R*,*R*)-TsDPEN]Ru(cymene)Cl. Enone **3** was added along with a reducing agent and heated at 65−75 °C (Table 2). The best conditions (Table 2, entries 8−10) for further optimization were using a mixture of H_2O and *i*-PrOH as the solvent with five equivalents of either HCOONa or HCOOH and Et_3N at 75 °C to provide excellent ee and complete conversion in two hours with 1 mol % catalyst. The use of HCOONa was preferred as the product alcohol *R*-**4** had less color. In addition, a nitrogen sweep to remove the formed CO_2 was essential to prevent stalling of the reaction. Finally the solvent mixture and equivalents of HCOONa were screened (Table 2, entries 11−16) on a 1−50 g scale with isolation of alcohol *R*-**4** in 91−94% yield containing approximately 2000 ppm Na and 900 ppm Ru in the isolated solid. The use of 0.2 mol % of catalyst and 5 equiv of HCOONa provided a reasonable conversion rate and minimized catalyst loading. After a final demonstration in the lab (Table 2, entry 17), the process was used for the first pilot batch (Table 3, entry 1). Ultimately the premade catalyst was purchased for simplicity, demonstrated in the lab (Table 2, entry 18) and used in the

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Table 2. Laboratory studies of asymmetric transfer hydrogenation of enone (3)[a]

entry	enone **3** (g)	cat. (mol %)	reducing agent (equiv)	solvent	temp (°C)	conv. (%)	time (h)	% ee
1	1	1	HCOOH (1.5)[b]	none	75	>99	4	90
2[c]	1	1	HCOOH (1.5)[b]	EtOAc	75	22	2	n.d.[d]
3[e]	1	1	HCOOH (1.5)[b]	THF	75	26	2	n.d.[d]
4	1	1	HCOOH (1.5)[b]	toluene	75	90	5	n.d.[d]
5	1	1	HCOOH (1.5)[b]	MeOH	75	70	2	n.d.[d]
6	1	1	HCOOH (1.5)[b]	EtOH	75	50	2	n.d.[d]
7	1	1	HCOOH (1.5)[b]	*i*-PrOH	75	83	5	95
8	1	1	HCOOH (5)[f]	*i*-PrOH	75	>99	2	95.6
9	1	1	HCOONa (5)	*i*-PrOH	65	>99	2	96
10	1	1	HCOONa (5)	H_2O, *i*-PrOH	65	>99	2	96
11	1	0.2	HCOONa (5)	H_2O, *i*-PrOH	65	>99	6	96
12	1	0.1	HCOONa (5)	H_2O, *i*-PrOH	65	96	6	96
13	10	0.2	HCOONa (5)	H_2O, *i*-PrOH[g]	65	94[h]	5	96
14	10	0.2	HCOONa (3)	H_2O, *i*-PrOH[g]	65	92[h]	5	96
15	50	0.2	HCOONa (3)	H_2O, *i*-PrOH[g]	65	91[h]	6	96
16	10	0.2	HCOONa (1.5)	H_2O, *i*-PrOH[g]	65	96	6	96
17	100	0.2	HCOONa (5)	H_2O, *i*-PrOH[i]	65	88[h]	6	95.5
18	50	0.2[j]	HCOONa (5)	H_2O, *i*-PrOH[i]	65	84[h]	6	95.6

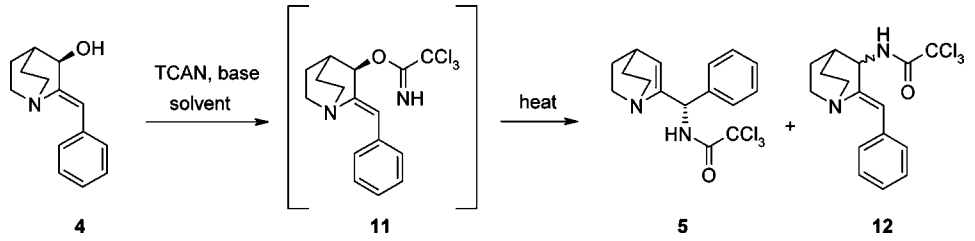
[a]Conditions: precatalyst from (*R*,*R*)-TsDPEN and $[RuCl_2(p\text{-cymene})]_2$ prepared in H_2O unless otherwise noted; enone and other components added with heating to 65−75 °C. [b]Et_3N (1.5 equiv) added. [c]Precatalyst prepared in EtOAc. [d]n.d. = not determined. [e]Precatalyst prepared in THF. [f]Et_3N (5 equiv) added. [g]7 parts at 5:2 ratio. [h]Isolated yield (>98% conversion). [i]8 parts at 5:3 ratio [j]Purchased [(*R*,*R*)-TsDPEN]Ru(cymene)Cl from Takasago.

Table 3. Pilot-plant batches of asymmetric reduction[a]

entry	enone **3** (kg)	Ru (ppm)	Na (ppm)	yield (%)	alcohol *R*-**4**(kg)	% ee	purity (area %)	assay (wt %)
1[b]	10.0	814	n.d.[c]	94	9.43	95.0	98	96
2	30.0	1253	107	89	27.0	95.6	99.2	100.3
3	30.0	1040	114	87	26.4	95.7	98.8	100.8
4	30.0	838	125	91	27.6	95.8	99.0	99.8
5	30.0	1020	108	88	26.6	95.2	96.5	96.6

[a]Conditions: enone **3**, [(*R*,*R*)-TsDPEN]Ru(cymene)Cl (0.2 equiv), *i*-PrOH, water, 65 °C, 6 h. [b]Catalyst prepared from (*R*,*R*)-TsDPEN and $[RuCl_2(p\text{-cymene})]_2$ in water. [c]n.d. = not determined.

Scheme 4. Overman rerrangement



4 **11** **5** **12**

Table 4. Laboratory experiments for Overman rearrangement[a]

entry	scale (*R*-**4**)	solvent	base	temperature[b] (°C)	yield of *S*-**5** HCl (%)	% ee
1	646 mg[c]	THF/*m*-xylene	NaH	140	93[d]	n.d.[e]
2	445 mg[f]	THF/*m*-xylene	NaH	140	74	98
3	445 mg	THF/*m*-xylene	NaHMDS	120	87	99
4	445 mg	THF/toluene	NaHMDS	105	86	n.d.
5	445 mg	THF/toluene	DBU	107	60[g]	n.d.
6	445 mg	toluene	NaO-*tert*-amyl	107	82	n.d.
7	50 g	toluene/THF	NaHMDS	107	84	>99
8	70 g	toluene	NaO-*tert*-amyl	107	83	>99
9	50 g	xylenes	NaO-*tert*-amyl	115	76	>99

[a]Conditions: alcohol *R*-**4**, base (0.1 equiv), TCAN (1.0 equiv) in solvent at 0 °C for 1 h; solvent exchanged and heated. [b]For Overman rearrangement of imidate **11**. [c]*rac*-**4** used. [d]Crude product as free base. [e]n.d. = not determined. [f]*S*-**4** used. [g]Not isolated, 60 area % of **5**; clean formation of the imidate with many impurities generated during rearrangement.

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Table 5. Overman rearrangement varying TCAN equivalents[a]

entry	alcohol *R*-**4** (g)	TCAN (equiv)	1,3-byproduct **12** (%)[b]	yield trichloroacetamide **5** (%)	% ee	Ru (ppm)
1	5	0.90	0.9	75	>99	265
2	5	0.95	1.0	76	>99	258
3	5	1.00	2.5	71	>99	186
4	5	1.10	10.5	58	77	83
5	5	1.20	17.4	46	62	n.d.[c]
6	5	1.46	21	42	56	n.d.[c]
7	5[d]	1.25	12.8	61	71	n.d.[c]
8	39.6	0.97	0.9	78	>99	172
9	89	0.95	1.8	73	>99	94
10	50	0.99	1.8	77	>99	n.d.[c]

[a]Conditions: alcohol *R*-**4** (approximately 700 ppm of Ru present), base (0.1 equiv), TCAN in xylenes at 0 °C for 1 h; heated to 115 °C for 6 h. [b]% in IPC compared to trichloroacetamide **5**. [c]n.d. = not determined. [d]Alcohol *R*-**4** used from CBS reduction.

Table 6. Pilot-plant batches of Overman rearrangement[a]

entry	alcohol *r*-**4** (kg)	trichloroacetamide **5** (kg)	yield (%)	% ee	Ru (ppm)	purity (area %)	assay (wt %)
1	4.6	6.2	76	>99.5	13.5	100.0	99.9
2	4.35	5.5	71	>99.5	9.1	100.0	98.9
3	26.8	36.8	74	>99.5	3.3	99.8	99.9
4	27.4	36.9	73	>99.5	4.4	99.8	98.9
5	26.2	35.6	73	>99.5	5.2	99.7	98.7
6	26.5	35.6	72	97.5	4.4	99.8	98.5

[a]Conditions: alcohol *R*-**4**, NaO-*tert*-amyl (0.1 equiv), TCAN (0.98 equiv) in xylenes at 0 °C for 1 h; heated 115 °C for 6 h.

remaining pilot batches (Table 3, entries 2−5) providing a total of 117 kg of alcohol *R*-**4** in 87−94% yield with >95% ee.

Overman Rearrangement. With the allylic alcohol *R*-**4** in hand, incorporation of the amine functionality in the appropriate position was undertaken. Although the well-established metal-catalyzed allylic amination processes were considered,[4] we decided to focus on a substrate control strategy to provide the necessary regio- and stereochemistry for the desired transformation. To this end, the thermal Overman rearrangement[3] occurring through a concerted [3,3] sigmatropic rearrangement seemed ideal for the desired transformation (Scheme 4). The process involves reaction of the alcohol *R*-**4** with trichloroacetontrile (TCAN) in the presence of catalytic base to generate intermediate imidate ester **11** that undergoes thermal rearrangement to the desired trichloroacetamide **5**. After confirmation that the Overman rearrangement was viable on milligram scale (Table 4, entries 1−2) to provide the desired trichloroacetamide, *rac*-**5**, in 93% isolated yield with standard protocols using catalytic sodium hydride[14] on the racemate, attention was focused on the development of a pilot-plant process using alcohol *R*-**4**.

Screening of bases (Table 4, entries 3−6) revealed that both NaHMDS and NaO-*tert*-amyl were suitable for scale-up providing the desired rearrangement amide, whereas DBU was not preferred due to substantial amounts of byproducts. Both NaHMDS (Table 4, entry 7) and NaO-*tert*-amyl (Table 4, entry 8) provided a good yield of trichloroacetamide *S*-**5** with a high ee. Although the reaction was complete in 3 h in *m*-xylenes at 140 °C versus 18 h in toluene at 107 °C, initial process safety concerns[15] prompted our focus on using toluene as the reaction solvent. However, after additional safety studies determined that the heat was the result of the rearrangement process, the final process was performed in xylenes at 115 °C (Table 4, entry 9), providing reaction completion in 6 h with a good impurity profile. Filtration of the mixture at the end of the reaction removed most of the Ru-containing impurities[16] and was conveniently done with a standard in-line filtration at scale. Trichloroacetamide **5** is conveniently isolated as the HCl salt by adding aqueous HCl and EtOH to the reaction mixture.

Most of the process development studies were performed using alcohol *R*-**4** originating from the *S*-MeCBS route so that we were surprised when lower yields and lower ee for trichloroacetamide **5** and a substantial increase in the level of the 1,3-rearrangement product **12** was obtained when using alcohol *R*-**4** from the Ru-transfer hydrogenation route. Initially, the presence of trace levels of Ru was believed to be the reason, but was found not to be the cause after using purified alcohol *R*-**4**.[17] Attention was focused on other parameters to assess the impact on the reaction performance. We found that excess TCAN was most detrimental to the reaction, as the amount of the 1,3-rearrangement product **12** increased from 1 to 21% as the excess of TCAN increased and the ee of trichloroacetamide **5** dropped to 77.2, 61.6, and 56.2% ee when 10, 20, and 46 mol % excesses of TCAN, respectively, were used (Table 5, entries 1−6). The wt % purity of alcohol *R*-**4** was typically lower, ranging from 95 to 98% from the Ru process compared to >98% from the CBS process, causing the TCAN to be in excess when alcohol *R*-**4** from the Ru process was used. Final confirmation of the TCAN impact rather than Ru content was demonstrated when *R*-**4** from the CBS process was treated with 1.25 equiv of TCAN and gave 12.8% 1,3-rearrangement product **12** and 71.4% ee (Table 5, entry 7), whereas *R*-**4** from the Ru process performed as expected when 0.95, 0.97, and even 1.0 equiv of TCAN were used (Table 5, entries 8−10). Others have postulated that the presence of trace acids can promote undesired side reactions and found that the inclusion of K_2CO_3[18] in the reaction will provide better reaction performance and may be important in our case as well when excess TCAN is used. Unfortunately, we did not have the resources to fully explore the mechanistic details in our system and consider that more experimentation is required to uncover the underlying features that cause erosion of both regiose-

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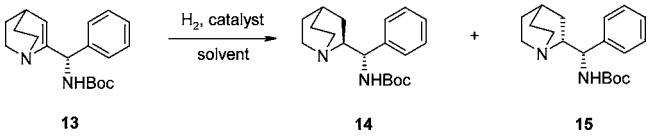
lectivity and stereoselectivity.[19] Nevertheless, a reproducible and scalable process was developed, using 0.98 equiv of TCAN to maximize yield and to minimize byproducts, and provided over 151 kg of trichloroacetamide **5** in six batches (Table 6). Of other note, the Ru content was reduced from 800−1200 ppm in alcohol *R*-**4** (Table 3) to <15 ppm in trichloroacetamide **5** (Table 6) in all batches.

Diastereoselective Olefin Reduction. In contrast to the successful rapid realization of the Overman rearrangement, we found difficulty with the diastereoselective olefin reduction. Direct reduction of the trichloroacetamide **5** had little success as the major products were removal of one or more chlorine atoms. Reduction of the allylic amine after removal of the trichloroacetyl group was also problematic as cleavage of the allylic carbon−nitrogen bond was preferred over olefinic reduction. In order to establish proof of concept for the synthetic strategy, the Boc-protected amine **13** was prepared, and then smooth reduction of the olefin occurred; however a 1:1 mixture of diastereomers **14** and **15** was generated (Scheme 5).

Scheme 5. Hydrogenation of Boc-protected amine 13



Extensive screening of the reduction of Boc-protected amine **13** was undertaken, exploring catalysts, solvents, and acid additives with the proximity of the tertiary nitrogen of the enamine anticipated to offer an additional control element. Different metal catalysts (Rh, Pt, and Pd) and supports were investigated with the best ratio (58:42 of **14** and **15**) achieved using a Degussa E3 catalyst (5% Pd/C wet). Interestingly, homogeneous catalysts such as the Wilkinson's catalyst gave very low conversions at low pressures (10 psi) and slightly better conversions at higher pressures (~ 150 psi) but favored the undesired diastereomer (**15**) (4:1 ratio).

Solvents, on the other hand, had a more pronounced influence on the conversion and the diastereoselectivity (Table 7). Protic solvents such as MeOH and EtOH gave the best conversion rates (Table 7, entries 1−4) with nonpolar solvents performing more poorly (Table 7, entries (5−10). Chlorinated solvents such as DCM with a 66:33 ratio (Table 7, entry 10) and DCE with a 73:27 ratio (Table 7, entry 11) provided slightly better diastereoselectivity, with DMSO and trifluoroethanol being unsuccessful.[20] Running the reactions at lower pressure did not improve the selectivity.

With the proximity of the basic quinuclidine nitrogen to the already generated asymmetric center, additives such as tartaric acid and its derivatives were also screened and provided a moderate impact on the diastereoselectivity (Table 8). Notably,

Table 7. Solvent choices screened for the reduction of 13[a]

entry	solvent	diastereoselectivity 14:15	conversion (%)
1	MeOH	52:48	98
2	EtOH	52:48	>99
3	BuOH	52:48	52
4	*i*-PrOH	58:42	81
5	ethyl acetate	52:48	59
6	THF	52:48	63
7	ACN	58:42	19
8	toluene	62:38	14
9	heptane	60:40	16
10	DCM	66:33	36
11	DCE	73:27	13
12	trifluoroethanol	n.d.[b]	<1
13	DMSO	n.d.[b]	<1

[a]Conditions: **13**, Degussa E3 catalyst (15%), 10 psi, 30 °C, 19 h, solvent. Not isolated. [b]n.d. = not determined.

Table 8. D-/L-Tartaric acids derivatives screened for hydrogenation of 13[a]

entry	additive	solvent	14:15	conversion (%)	temp (°C)	pressure (psi)
1	none	*i*-PrOH	58:42	81	30	10
2	none	DCM	66:33	36	30	10
3	D-tartaric acid	*i*-PrOH	60:40	>99	30	10
4	D-tartaric acid	DCM	68:32	>99	30	10
5	D-tartaric acid	DCM	68:32	>99	25	60
6	L-tartaric acid	*i*-PrOH	66:33	>99	30	60
7	L-tartaric acid	DCM	64:36	>99	30	60
8	ditolyl-D-tartaric acid	*i*-PrOH	52:48	97	25	60
9	ditolyl-D-tartaric acid	DCM	64:36	>99	25	60
10	ditolyl-L-tartaric acid	*i*-PrOH	70:30	56	25	10
11	ditolyl-L-tartaric acid	DCM	72:28	>99	25	10
12	ditolyl-L-tartaric acid	DCM	71:29	>99	30	10
13	dibenzoyl-D-tartaric acid	*i*-PrOH	64:36	98	30	60
14	dibenzoyl-D-tartaric acid	DCM	71:29	>99	30	60
15	dibenzoyl-L-tartaric acid	*i*-PrOH	64:36	>99	30	60
16	dibenzoyl-L-tartaric acid	DCM	73:27	>99	30	60

[a]Conditions: Degussa E3 catalyst (15%), solvent, additive, temp, pressure.

the use of di-*p*-tolyl-L-tartaric acid with the slight increased diastereoselectivity (Table 8, entry 5) was also an excellent resolving agent as near quantitative isolation of the desired diastereomer **14** was obtained as a crystalline salt. Intermediate **14** di-*p*-tolyl-L-tartrate was subsequently carried through the synthesis as the first verification of the viability of the process. A number of other, readily available α-hydroxycarboxylic acids such as mandelic acid and lactic acid as well as simpler carboxylic acids were also screened as additives but did not lead to diastereoselectivity enhancement. A brief screening of Lewis acids provided no benefit either.

At this point we synthesized a series of other substrates **16** (Scheme 6) by standard methods with various nitrogen protecting groups to explore the substrate control element on the diastereoselectivity (Table 9). In general aliphatic amides (Table 9, entries 1−7) gave higher selectivities than aromatic amides (Table 9, entries 8−13) and aliphatic carbamates (Table 9, entries 14−15). Compared to DCM, other solvents (MeOH, EtOH, IPA, THF, CF_3CH_2OH, toluene, trifluorotoluene, etc.) provided lower selectivity. In addition to low diastereoselectivity, reduction of the 2,6-dichloro-3-trifluoromethylphenyl

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Scheme 6. Diastereoselective hydrogenation of 16

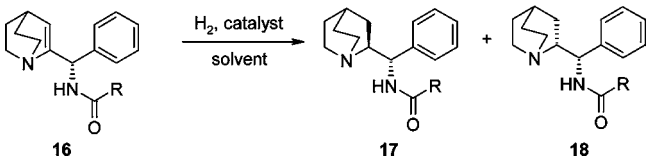
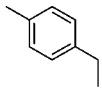
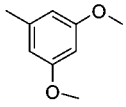
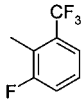
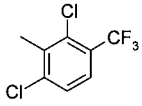


Table 9. Substrate screening of diastereoselective hydrogenation[a]

Entry	R=	17:18
1	CH_3[b]	87:13[c]
2	$CH_2CH_2CH_3$	87:13
3	$CH(CH_3)_2$	87:13
4	$C(CH_3)_3$	83:17
5	$CH(CH_2CH_3)_2$	83:17
6		73:27
7		93:7 (62:38 in EtOH)
8		82:18
9		81:19
10		78:22
11		76:24
12		75:25
13		1:1
14	OCH_3	75:25
15	OCH_2CH_3	75:25

[a]Conditions: **16**, Degussa E5, L-tartaric acid DCM, 100 psi H_2, 35 °C, 22 h. [b]Compound **6** with R = CH_3. [c]Compounds **7**, **8** with R = CH_3.

derivative (Table 9, entry 13) in an effort to give **1** directly provided dehalogenated byproducts.

At this juncture, a decision was made to develop a process for scale-up to the pilot plant. Acetamide **6**, prepared directly from the trichloroacetamide **5** by saponification with KOH and treatment with acetic anhydride, was chosen as the substrate because of its simplicity and low cost (Scheme 7). In addition, acetamide **7** was an intermediate in the original process, and the deprotection protocol had been developed and optimized previously so that we had no concerns about the stability of **9** under the strong acidic deprotection conditions. The transformation of trichloroacetamide to the simple acetamide performed as expected in the pilot plant (Table 10) to provide over 86 kg of acetamide **6**. Even though a lower ee of 97.2% was obtained for the final batch (Table 10, entry 3), this material was demonstrated to be suitable without reprocessing after use testing through the process.

Table 10. Pilot-plant batches for synthesis of acetamide 6[a]

entry	trichloroacetamide **5** (kg)	acetamide **6** (kg)	yield (%)	% ee	purity (area %)	assay (wt %)
1	54.0	31.9	92	>99.5	96.0	96.8
2	54.7	33.2	94	>99.5	95.5	95.7
3	35.4	21.2	93	97.2	97.1	98.0

[a]Conditions: trichloroacetamide **5**, NaOH, EtOH, water, 25 °C, 4 h; Ac_2O (1.2 equiv), 22 °C, 0.5 h

With the decision to focus on acetamide **6**, additional screening to improve further the diastereoselectivity of the hydrogenation was undertaken, but with little success. These conditions included homogeneous and heterogeneous catalysts (Pd/C, Pd/Al_2O_3, $[Rh(COD)_2]BF_4$, $RhH(CO)(PPh_3)_3$, PtO_2, $RuCl_2$, Ru $(OAc)_2$), additives (L-tartaric acid, D-tartaric acid, di-*p*-toluyl-L-tartaric acid, di-*p*-toluyl-D-tartaric acid, dibenzoyl-L-tartaric acid, dibenzoyl-D-tartaric acid, L-lactic acid, L-malic acid, citric acid, *R*-mandelic acid, methanesulfonic acid), phosphorus ligands for homogeneous conditions [(*S*,*S*′, *R*,*R*′)-Tangphos, (*R*)-(*S*)-PPF-P′Bu_2, CTH-Phane, CTH-P-phos, (*S*)-Phane-Phos, (*S*,*S*)- or (*R*,*R*)-Me-BPE, (*R*,*R*)-t-Bu-FerroTane, and other ligands from Josiphos family, phospholane family], solvents (MeOH, EtOH, IPA, THF, CF_3CH_2OH, DCM, DCE, toluene, trifluorotoluene), hydrogen pressures of 50–100 psi, and reaction temperatures from 0 to 50 °C.

We chose the more readily available tartaric acid derivatives as additives (Table 11) and found a slight superiority for the L-tartaric acid with an 87:13 ratio of diastereomers being generated (Table 11, entry 3). Interestingly, citric acid was also a suitable additive providing reasonable selectivities (Table 11, entries 5, 8, 9). With these results, we proposed the use of the Degussa E5 catalyst (Pd–C) and 1 equiv L-tartaric acid, with 60 psi H_2, at 40 °C in DCM solvent for the reduction of **6**. However, a switch to MeOH as the solvent was made[21] to avoid the health, safety, and environmental concerns of potential DCM release during the venting of the hydrogenation reactor. In addition the reaction components had better solubility in MeOH than in the other solvents screened and increased the throughput in our hydrogenator. A demonstration batch was performed in the pilot plant with L-tartaric acid

Scheme 7. Diastereoselective hydrogenation of acetamide 6

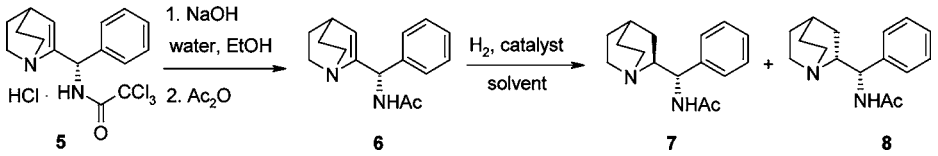


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Table 11. Screening conditions for reduction of acetamide 6[a]

entry	catalyst[b]	additive	solvent	7:8
1	Degussa E5	D-tartaric acid	MeOH	65:35
2	Degussa E5	L-tartaric acid	MeOH	66:34
3	Degussa E5	L-tartaric acid	DCM	87:13
4	Degussa E5	D-tartaric acid	DCM	80:20
5	Degussa E5	citric acid	MeOH	70:30
6	JM Pd/Al_2O_3	D-tartaric acid	MeOH	72:28
7	JM Pd/Al_2O_3	D-tartaric acid	IPA	62:38
8	JM Pd/Al_2O_3	citric acid	MeOH	75:25
9	JM Pd/Al_2O_3	citric acid	CF_3CH_2OH	78:22

[a]Conditions: catalyst (15%), solvent, additive, 60 psi H_2, 40 °C. [b]JM = Johnson Matthey

as the additive (Table 12, entry 1) to establish the viability of the process.

Table 12. Pilot-plant batches for hydrogenation of acetamide 6[a]

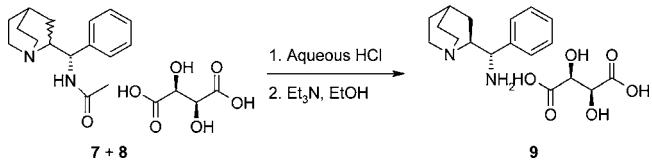
entry	acetamide 6 (kg)	ratio of 7:8	yield (%)
1[b]	3.7	70:30	94
2	15.0	71:29	97
3	15.0	70:30	100
4	15.0	71:29	98
5	9.2	69:31	86
6	9.5	69:31	98
7	10.6	69:31	96
8	10.5	69:31	100

[a]Conditions: Degussa E5 catalyst MeOH, D-tartaric acid, 1020 mmHg of H_2, 33 °C, 4 h. [b]L-Tartaric acid used as additive.

Following the change to MeOH, it became apparent that there was no longer an advantage to using L-tartaric acid as the additive (Table 11). The downstream process uses D-tartaric acid for the final purification of diamine tartrate **9**, and we had clearly demonstrated that excellent recovery (>95%) of the desired diastereomer occurs, even with a 2:1 mixture. In addition, this salt is the same final intermediate as the previous process and aids in the regulatory aspects of the process change. We decided to explore performing the olefin reduction with D-tartaric acid as the additive and to telescope the process to produce the final intermediate tartrate **9**. For this process change, more of the costlier D-tartaric acid would be required for removal of the undesired 30% *R,S*-diastereomer, but the overall process would be greatly simplified. The final process for the catalytic hydrogenation used the following conditions: 1.0 equiv of the acetamide **6** in MeOH (10 parts) in the presence of 5 wt % of Pd/C and 1.0 equiv of D-tartaric acid at 52−55 psi H_2, 35 °C for 4−6 h. This process using D-tartaric acid with MeOH as the solvent was considered the most expedient and environmentally friendly, even though the selectivity was lower compared with that using DCM as the solvent. A total of seven batches (Table 12, entries 2−9) were performed in the pilot plant on a 10−15-kg scale to provide a MeOH solution of **7** and **8** that was used directly in the next step.

Hydrolysis and Resolution of Mixture of Acetamides of 7 and 8 to Final Intermediate 9. The hydrolysis of the acetamide could be achieved with either HCl or methanesulphonic acid (MSA) (Scheme 8). However, because of the potential for GTI formation using MSA in alcohol solvents, hydrolysis with HCl was further developed. The MeOH solution of a mixture of acetamides **7** and **8** from the hydrogenation reaction was solvent exchanged into water for the acidic hydrolysis using 3.0 equiv of HCl. Use of lower acid strengths resulted in prolonged reaction times. Upon completion, the reaction was neutralized with a base to a pH of 5−6 to produce diamine tartrate **9** as a crystalline EtOH solvate. A few bases such as NaOH, NH_4OH, and Et_3N were explored, with Et_3N providing the best chiral purity and yield of diamine tartrate **9** (Table 13). The final process was performed in the plant to produce over 78 kg of diamine tartrate **9** with <0.2% of any other stereoisomer in a satisfactory yield of over 60% considering the starting isomeric mixture of acetamides **7** and **8**. In addition, both the Ru- and Pd levels were reduced below 4 ppm so that additional metal-scavenging processes were not required.

Scheme 8. Hydrolysis of acetamides 7 and 8 to final intermediate 9



Drug Substance Preparation. The final synthetic step in the process involved the coupling of diamine **9** with acid **19** (Scheme 9). For the preparation of early scale-up batches oxalyl chloride had been used to generate acid chloride **10**, and the reaction solvent was DCM. A more suitable process for the scale-up batches used thionyl chloride with a catalytic amount of DMF in toluene as solvent for 2−3 h at 80 °C. A single 35.2-kg batch of acid chloride **10** was prepared and used as a toluene solution. The coupling reaction was conducted efficiently under Schotten−Baumann conditions using aqueous NaOH as base. After water washing and solvent exchange to ethanol and addition of aqueous HC1, smooth crystallization of drug substance **1** as the HCl salt was achieved. The initial isolated material was present as the undesired polymorph, but simply suspending the solid in water and heating to 55 °C for about 2 h prompted smooth conversion, providing 24.2 kg of **1** (100 A % purity, 99.9 wt %% purity with <0.05% achiral impurities and <0.10% chiral impurities) in the desired polymorphic form.[22]

■ CONCLUSION

In conclusion, we have demonstrated an efficient and scalable eight-step synthesis of drug substance **1** in 20% overall yield. More significantly, this process used a catalytic, enantioselective reduction to set the first stereogenic center for a subsequent chirality transfer process involving a stereoselective Overman rearrangement to produce the desired functional groups and substitution on the quinuclidine system. The second center was generated via a diastereoselective hydrogenation reaction. Finally, we consider this chemistry to be one of the most practical approaches to quinuclidine derivatives and should have great utility for the preparation of novel cinchona-type derivatives for many applications to organocatalysis.[23]

■ EXPERIMENTAL SECTION

General. HPLC was conducted on either Xterra RP18 4.6 mm × 150 mm × 3.5 μm, YMC-Pack Pro C18 4.6 mm × 150

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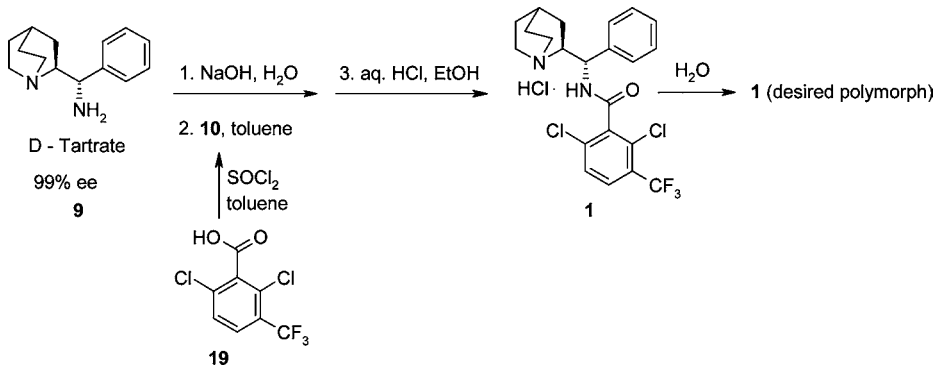
Table 13. Acid hydrolysis of acetamides 7 and 8 to final intermediate[a]

entry	7 and 8 (kg)	diamine 9[b] (kg)	yield (%)	chiral purity (%)	purity (area %)	assay (wt %) as free base[c]	Ru level (ppm)	Pd level (ppm)
1	5.3[d]	3.8	44	*SS*: 99.79 *SR*: 0.16 *RR*: 0.05	99.9	50.2	1.9	<1
2	22.5	13.8	69	*SS*: 99.84 *SR*: 0.07 *RR*: 0.09	99.7	51.9	1.2	<1
3	23.1	13.8	67	*SS*: 99.84 *SR*: 0.07 *RR*: 0.09	99.7	52.8	1.2	<1
4	22.4	12.6	64	*SS*: 99.88 *SR*: 0.06 *RR*: 0.06	99.8	51.5	1.0	<1
5	26.3	15.9	68	*SS*: 99.81 *SR*: 0.13 *RR*: 0.06	99.4	54.9	1.5	3.9
6	32.3	18.5	64	*SS*: 99.75 *SR*: 0.10 *RR*: 0.15	99.7	52.8	1.5	2.6

[a]Conditions: acetamide 7 and 8 in MeOH, solvent exchange to water; aq HCl, 103 °C; Et_3N, EtOH. [b]Isolated as D-tartrate EtOH solvate. [c]Contains ~6% water and ~6% EtOH. [d]Demonstration batch using L-tartrate salt, free-basing step, and isolation as D-tartrate salt

Scheme 9. Final conversion to GlyT1 inhibitor 1



mm × 3 μm, YMC-ODS AQ 4.6 mm × 150 mm × 3 μm or a Waters Atlantis T3 4.6 mm × 150 mm × 3 μm column as follows: HPLC Method 1: conducted on a Xterra RP18 4.6 mm × 150 mm × 3.5 μm column at 30 °C, wavelength = 225 nm; flow rate 1 mL/min; solvent A: (30:70) ACN/water with 0.1% NH_4OH; B: (70:30) ACN/water with 0.1 NH_4OH; gradient 100% A to 100% B over 20 min: (compound, retention time), (benzaldehyde, 5.42 min), (enone **3**, 12.03 min); HPLC Method 2: conducted on a Xterra RP18 4.6 mm × 150 mm × 3.5 μm column at 30 °C, wavelength = 225 nm; flow rate 1 mL/min; solvent A: (40:60) ACN/water with 0.1% NH_4OH; B: water with 0.1 NH_4OH; gradient 100% A to 100% B over 20 min: (compound, retention time), (alcohol *R*-**4**, 5.36 min), (enone **3**, 7.44 min), (trichloroacetamide **5**, 9.43 min), (imidate **11**, 14.29 min); HPLC Method 3: conducted on a YMC-Pack Pro C18 4.6 mm × 150 mm × 3 μm at 30 °C, wavelength = 210 nm; flow rate 1 mL/min; solvent A: (5:95) ACN with 0.1% TFA/water with 0.1% TFA; B: (60:40) ACN with 0.1% TFA/water with 0.1% TFA; gradient 100% A to 100% B over 20 min: (compound, retention time), (acetamide **6**, 7.87 min), (trichloroacetamide **5**, 12.85 min); HPLC Method 4: conducted on a YMC-ODS AQ 4.6 mm × 150 mm × 3 μm at 30 °C, wavelength = 210 nm; flow rate 1 mL/min; solvent A: ACN; B: water with 0.1% *o*-phosphoric acid; 100% B for 2 min, gradient 100% B to (60:40) A/B over 20 min: (compound, retention time), (diamine **9**, 6.9 min), (acetamide **8**, 7.82 mini), (acetamide **6**, 9.29 min), (acetamide **7**, 10.59 min). Chiral separations for ee determinations were conducted on Chiralpak IA 4.6 mm × 250 mm × 5 μm, Chiralpak AD-H, 4.6 mm × 150 mm × 5 μm, Regis Chirosil RCA (+) 4.6 mm × 250 mm × 5 μm or Chirobiotic V, 250 × 4.6 mm × 5 μm column as described in the Supporting Information. GC was conducted on a Rtx-5 30 m × 0.53 mm × 3 μm column with the following temperature gradient: 50 °C for 5 min, then 15 °C/min to 260 °C, hold 2 min. IR spectra were recorded as a KBr disk. Demineralized water is referred to as water. The following were purchased as indicated: EtOH SDA-3C denatured with *i*-PrOH (4.76%) (Pharmco), quinuclidinone hydrochloride (Orgasynth Industries), RuCl[(*R*,*R*)-Tsdpen](*p*-cymene) (Takasago), trichloroacetonitrile (Zandu Chemicals Limited), solution of NaO-*tert*-amyl (25% in toluene) (BASF), xylenes (mixture of xylene isomers and ethylbenzene) (Pharmco), D-tartaric acid (Aldrich) and 2,6-dichloro-3-(trifluoromethyl)benzoic acid (Ash Ingredients). All vessels were inerted with N_2, and reaction temperatures were ±3 °C, unless otherwise stated.

*2-Z-Benzylidene-1-azabicyclo[2.2.2]octan-3-one (**3**).* To a 30-gal glass-lined reactor was charged 3-quinuclidinone hydrochloride **2** (20.0 kg, 123 mol) and EtOH SDA-3C (22.0 kg). A

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50% aqueous NaOH solution (13.0 kg, 163 mol) was added over 15 min, causing a slight exotherm to 25 °C. The batch temperature was adjusted to 30 °C. In a separate 30-gal Hastelloy reactor was added benzaldehyde (13.0 kg, 123 mmol) and EtOH SDA-3C (10.0 kg). The benzaldehyde solution was added to the first solution over 20 min using EtOH SDA-3C (5.2 kg) to rinse the reactor, while maintaining the temperature at 30 °C. The batch was heated to 50 °C. After 1 h, a sample was analyzed to determine reaction completion (criteria: HPLC, <5% of benzaldehyde; results: 0.05−0.2%). Water (26 kg) was charged to the reactor at 50 °C and held for 1 h. The batch was then cooled to 22 °C over 2 h. After1 h, the product was filtered and washed with EtOH SDA-3C (24.0 kg) and water (20 kg). The solid was dried in a tray dryer under vacuum at 50 °C for 1 day to give 25.7 kg (97%) of **3**: IR 1703, 1624 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.03 (m, 2), 7.36 (m, 3), 7.02 (s, 1), 3.16 (m, 2), 3.00 (m, 2), 2.64 (m, 1), 2.03 (m, 4); ^{13}C NMR ($CDCl_3$) δ 206.64, 134.19, 132.37, 129.77, 128.64 (2), 125.35, 123.37, 114.94, 74.70, 47.70, 40.51, 26.12 (2); LC−MS, *m/z* 214.11 [M + H]. Anal. Calcd for $C_{14}H_{15}NO$ C 78.84; H 7.09; N 6.57. Found: C 78.68; H 6.96; N 6.51.[24]

R-2-Benzylidene-1-azabicyclo[2.2.2]octan-3-ol (R-4) Using (S)-2-Methyl-CBS-oxazaborolidine. To a 2.0 M toluene solution of BH_3·DMS (250 mL, 500 mmol) at −10 °C was added a 1 M toluene solution of (*S*)-2-methyl-CBS-oxazaborolidine (25 mL, 25 mmol). After 0.5 h, the solution was cooled to −20 °C, and a solution of enone **3** (107 g, 500 mmol) in toluene (1.5 L) was added over 2 h, while maintaining the temperature <−10 °C. After 1 h, HPLC showed complete conversion to alcohol *R*-**4** (89% ee). MeOH (100 mL) was carefully added (NOTE: hydrogen gas evolution occurs) while keeping the reaction temperature <0 °C. The mixture was concentrated, MeOH (750 mL) was added, and the mixture was heated to 60 °C for 1 h and then concentrated. Toluene (1.5 L) was added, and the solution was concentrated to one-third volume (~500 mL). The resulting toluene solution was heated to 60 °C, and heptane (1.5 L) was added slowly over 0.5 h to induce crystallization. The resulting slurry was allowed to cool to 20 °C overnight. The mixture was cooled to 0 °C. After 1 h, the solid was collected and washed with a heptane mixture (200 mL). After drying at 30 °C for 16 h, 88.0 g (82%) of alcohol *R*-**4** (98% ee) was obtained.

S-2-Benzylidene-1-azabicyclo[2.2.2]octan-3-ol (R-4). To a 100-gal stainless steel reactor was charged RuCl[(*R*,*R*)-Tsdpen](*p*-cymene) (0.22 kg, 0.35 mol), water (30.0 kg), and 2-propanol (24.0 kg). The temperature was adjusted to 40 °C and held for 1 h. In a separate 100-gal Hastelloy reactor was charged sodium formate (48 kg, 706 mol), water (120.0 kg), enone **3** (30.0 kg, 141 mol), and 2-propanol (48 kg). A nitrogen sparge of the mixture was performed through a dip tube to degas carbon dioxide generated to keep the reaction from stalling. The mixture was heated to 40 °C. The catalyst solution was added into the heterogeneous enone **3** solution. The resulting mixture was heated to 67 °C and held for 5 h. A sample was analyzed for reaction completion (criteria: HPLC, <2.1 A% of **3**; results: 0.23−1.2%). The reaction was cooled to 37 °C, and a slight vacuum (100 mmHg) was applied to degas any residual carbon dioxide. Agitation was stopped, and the aqueous layer was removed. Water (180 kg) was added to the reaction mixture, and the temperature was adjusted to 22 °C and held overnight. The crystallized product was collected on a 50-gal Hastelloy filter and washed twice with water (90.0 kg each). The solid was dried in a tray dryer under vacuum at 60 °C for 1 day to give 26.6 kg (88%) of *R*-**4**: ^1H NMR ($CDCl_3$) δ 7.78 (m, 2), 7.27 (m, 2), 7.16 (m, 1), 6.23 (s, 1), 4.24 (s, 1), 2.95 (m, 3), 2.75 (m, 1), 2.52 (s, 1), 1.98 (m, 1), 1.90 (m, 1), 1.67 (m, 1), 1.42 (m, 2); ^{13}C NMR ($CDCl_3$) δ 153.59, 136.20, 128.99 (2), 127.92 (2), 126.35, 120.27, 69.64, 47.60, 46.52, 30.94, 24.91, 18.98; LC−MS, *m/z* 216.13 [M + H]. Anal. Calcd for $C_{14}H_{17}NO$ C 78.10; H 7.96; N 6.51. Found: C 77.95; H 8.11; N 6.50.

(S)-N-[(1-Azabicyclo[2.2.2]oct-2-en-2-yl)phenyl-methyl]-2,2,2-trichloroacetamide Hydrochloride Salt (5). To a 200-gal Hastelloy reactor was charged alcohol *R*-**4** (26.8 kg, 125 mol) and xylenes (230.0 kg). To the resulting slurry was added a solution of NaO-*tert*-amyl (25%) in toluene (5.4 kg, 12.3 mol) over 10 min to maintain the temperature below 25 °C. After cooling to 15 °C, trichloracetonitrile (18.0 kg, 125 mol) in a prefilled pressure tank was added slowly over 1.5 h, while maintaining the reaction temperature below 15 °C. Upon complete addition, the reaction mixture was adjusted to 23 °C and held for 1 h. A sample was analyzed for reaction completion with conversion to intermediate imidate **11** (criteria: HPLC, ≤5% of *R*-**4**; result 1.1−2.0%). The reaction mixture was heated to 114 °C and held for 6 h. The batch was cooled to 23 °C, and a sample was checked for disappearance of the imidate intermediate (criteria: HPLC, ≤2% of **11**; result 0.1−0.3%). The batch was filtered through two 0.8 μm filters using EtOH (170 kg) to rinse the reactor. The filtrate and the rinse were returned to the reactor. After heating to 76 °C, a solution of 37% aqueous HCl (13.0 kg, 132 mol) in EtOH SDA-3C (43 kg) premixed in a pressure tank was added. After 0.5 h, the mixture was cooled to 20 °C and held for 1 h. The crystallized product was collected on a 50-gal Hastelloy filter and washed twice with a premade mixture of EtOH SDC-3A (9.1 kg) and xylenes (27.0 kg). The solid was dried in a tray dryer under vacuum at 50 °C for 1 day to give 36.8 kg (74%) of trichloroacetamide **5** hydrochloride: ^1H NMR (DMSO-d_6) δ 12.02 (s, 1), 9.98 (m, 1), 7.48 (m, 2), 7.42 (m, 2), 7.31 (m, 1), 6.21 (m, 1), 5.94 (m, 1), 3.56 (m, 2), 3.18 (m, 1), 3.04 (m, 1), 2.96 (m, 1), 1.88 (m, 2), 1.57 (m, 2); ^{13}C NMR (DMSO-d_6) δ 161.09, 140.27, 135.73, 133.45, 128.45 (2), 128.18, 127.56 (2), 92.69, 53.77, 49.91, 49.64, 25.98, 23.34, 23.08; LC−MS, *m/z* 359.02, 361.02 [M + H]. Anal. Calcd for $C_{16}H_{17}Cl_3N_2O$·HCl: C 48.51; H 4.58; N 7.07; Cl 35.80. Found: C 48.54; H 4.43; N 7.07; Cl 35.69.

(S)-N[(1-Azabicyclo[2.2.2]oct-2-en-2-yl)phenylmethyl]-acetamide (6). To a 100-gal glass-lined reactor was added trichloroacetamide **5** (54.7 kg, 138 mol) and EtOH (66.0 kg). To the resulting slurry was added a 50% aqueous solution of NaOH (24 kg, 300 mol) over 0.5 h, while maintaining the temperature below 25 °C. A thick-slurry was obtained that became thinner as the reaction proceeded. After 4 h, a sample was analyzed for the consumption of trichloroacetamide **5** (criteria: HPLC, <2 A% of **5**; result: 0.2−0.4%). Water (55.0 kg) was added to give a homogeneous solution. Acetic anhydride (17.0 kg, 167 mol) was charged from a pressure tank over 1 h, while maintaining the reaction temperature at 22 °C. After 0.5 h, a sample was analyzed for the consumption of the intermediate unsaturated diamine (criteria: HPLC <2 A% of intermediate unsaturated diamine; result: 0.05−0.3%). Water (82.0 kg) was added. Vacuum distillation was performed at 60 mmHg keeping the batch temperature below 60 °C to remove EtOH (criteria: GC, <2 wt % EtOH; result: 0.03−0.4%). After cooling to 20 °C, a 50% aqueous solution of NaOH (7.0 kg, 88 mol) was added until pH > 13. After 0.5 h, the solid was

collected on a 50-gal Hastelloy filter and washed with twice with water (55.0 kg each). The solid was dried in a tray dryer under vacuum at 50 °C for 1 day to give 33.2 kg (94%) of acetamide **6**: ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 4), 7.20 (tt, 1, J = 7.8, 1.4), 6.57 (d, 1, J = 8.8), 5.57 (d, 1, J = 8.8), 6.43 (d, 1, 7.2), 2.89 (ddd, 1, J = 4.7, 8.9, 13.0), 2.79 (ddd, 1, J = 4.7, 8.9, 13.0), 2.38 (dddd, 1, J = 2.5, 5.1, 10.7, 13.0), 2.60 (m, 1), 2.17 (dddd, 1, J = 2.5, 5.1, 10.7, 13.0), 1.58 (dddd, 1, J = 2.6, 5.0, 6.5, 14.3), 2.02 (s, 3), 1.53 (dddd, 1, J = 2.6, 5.0, 6.5, 14.3), 1.33 (m, 1), 1.45 (m, 1); LC−MS, m/z 257.17 [M + H]. Anal. Calcd for $C_{16}H_{17}N_2O$ C 74.97; H 7.86; N 10.93. Found: C 74.87; H 8.14; N 10.91.

*(S)-[(S)-1-Azabicyclo[2.2.2]oct-2-yl]phenylmethylamine (2S,3S)-2,3-dihydroxy-succinic Acid Salt (**9**).* To a 50-gal Hastelloy reactor was charged Pd/C Degussa E-5 catalyst (0.75 kg, 0.35 mol), acetamide **6** (15 kg, 58.5 mol), D-tartaric acid (8.9 kg, 59.3 mol) and MeOH (120 kg) at a temperature of 20−25 °C. Nitrogen purging was done twice. Hydrogen gas was charged with a set point for the maximum pressure of 3500 mmHg with a reaction pressure set to 1020 mmHg. The mixture was heated to 33 °C. The pressure, temperature, and hydrogen flow rates were observed, and the hydrogenation was continued until hydrogen uptake ceased. After 4 h, the reaction was cooled to 23 °C, hydrogen pressure was released, and the mixture was purged with N_2. A sample was analyzed for reaction completion (criteria: HPLC, < 1.0% of **6**; results: 0.1−0.7%). The reaction mixture was filtered through a multiplate reverse flow sparkler filter with an additional 0.8 μm guard filter on the outlet. Two charges of MeOH (36.0 kg each) were used to rinse the reactor and transfer lines. The resulting MeOH solution of the mixture of **7** and **8** was analyzed for wt/wt assay (15.4%, 94% yield) as an approximate 70:30 mixture of diastereomers and used for next step without any purification.

To a 100-gal Hastelloy reactor was added the MeOH solution of acetamide **7** and **8** (260.4 kg, 9−11 wt %). Vacuum distillation (200 mmHg) keeping the jacket temperature below 50 °C was performed until minimum stir volume was achieved. The batch was cooled to room temperature and held overnight. Water (66.0 kg) was added, and vacuum distillation (200 mmHg) keeping the jacket temperature below 85 °C was performed until minimum stir volume was achieved. The reaction mixture was cooled to 23 °C, and an IPC was performed to ensure completion of distillation (criteria: GC, <3.0 wt % of MeOH; results: 0.5−2.4%). In some instances two distillations were performed. Concentrated HCl (25 kg, 686 mol) was added, and the resulting mixture was heated to 103 °C. After 6 h, a sample was analyzed for reaction completion (criteria: HPLC, ≤1.0% of **7** and ≤1.0% of **8**; results: **7**, 0.1−0.9%, and **8**, 0.1−0.9%). Typical total heating time was 12−14 h. The reaction mixture was cooled to 20 °C, and Et_3N (28.7 kg, 284 mol) was slowly added, keeping the reaction temperature below 40 °C until pH = 5.0−5.5. The reaction temperature was adjusted to 22 °C, and EtOH SDA-3C (120.0 kg) was added. The reaction mixture was cooled to 0 °C. After 1 h, the slurry was filtered onto an 18-in. single plate Hastelloy filter and washed twice with premade mixtures of EtOH SDA-3C (37.0 kg) and water (5.2 kg). The solid was dried in a tray dryer under vacuum at 50 °C for 4−5 days (Note: it was determined that an EtOH solvate is formed and not detrimental to the next step.) to give 15.9 kg (68%) of diamine tartrate salt **9** as an ethanol solvate (6.4 wt % by ^{1}H NMR): ^{1}H NMR (DMSO-d_6) δ 7.53 (m, 2), 7.41 (m, 2), 7.36 (m, 1), 6.00 (m, 6), 4.15 (m, 1), 3.85 (s, 2), 3.22 (m, 1), 3.18 (m, 1), 2.99 (m, 2), 2.81 (m, 1), 1.74 (m, 1), 1.52 (m, 4), 1.17 (m, 1), 0.99 (m, 1); ^{13}C NMR (DMSO-d_6) δ 174.38 (2), 137.67, 128.63 (2), 128.41, 128.24 (2), 71.28 (2), 58.98, 55.59, 48.70, 40.89, 29.17, 25.17, 24.17, 20.92; LC−MS, m/z 217.18 [M + H].

***N*-[(*S*)-(*S*)-1-Azabicyclo[2.2.2]oct-2-yl-phenylmethyl]-2,6-dichloro-3-trifluoromethylbenzamide Hydrochloride (1).** *Preparation of 2,6-Dichloro-3-trifluoromethylbenzoic Acid Chloride **10**.* To a 50-gal Hastelloy reactor was added 2,6-dichloro-3-(trifluoromethyl)benzoic acid (**19**) (33.0 kg, 128 mol), toluene (140 kg), a catalytic amount of DMF (779 g, 10.7 mol), and thionyl chloride (18.0 kg, 151 mol). The resulting solution was heated to 70−75 °C for 1 h, then heated to 75 °C for 2 h. (CAUTION: significant gas evolution observed. The two-stage heating was done after process safety studies demonstrated that the rate of gas evolution was better controlled under these conditions. If gas evolution occurs too fast, the reactor should be cooled.) The reaction was cooled to 20 °C, and the toluene solution of acid chloride **10** was used in the coupling step.

*Coupling of Diamine **9** and Acid Chloride **10**.* To a 100-gal stainless steel reactor was added diamine tartrate salt **9** (36.2 kg, 91 mol) and water (181.0 kg). To this solution was added a 50% aqueous NaOH solution (24.3 kg, 304 mol), keeping the temperature below 25 °C. To the resulting suspension was added a toluene solution of acid chloride **10** (118.3 kg, 19.7 wt %, 90 mol) over 3 h, maintaining the reaction temperature below 27 °C. After 1 h, the pH was 6−7, and thus additional 50% aqueous NaOH solution (4.0 kg, 50 mol) was added. After 2 h, a sample was taken from the organic layer to measure consumption of acid chloride **10** (criteria: HPLC, ≤2.0% of **10**; result: 0.5%). The aqueous layer was removed. Water (74.0 kg) and 50% aqueous NaOH solution (18 kg, 225 mol) were added. After 0.5 h, the aqueous layer was removed. The organic phase was washed with water (3 × 74.0 kg each). Vacuum distillation was performed on the resulting solution (107 mmHg) while keeping the jacket temperature below 80 °C to reach minimum stir volume. Absolute EtOH (160.0 kg) was added, and vacuum distillation was performed (156 mmHg) while keeping the jacket temperature below 80 °C to reach a final volume one-third of the original. A sample was removed to check the completion of distillation (criteria: GC, ≤5 wt % of toluene and ≤60 wt % of EtOH; result: toluene 5%, EtOH 50%). The reaction mixture was transferred through a 0.8 μm filter into a 100-gal Hastelloy reactor. The batch temperature was adjusted to 55 °C, and conc. HCl (11.0 kg, 112 mol) filtered through an 0.8 μm inline filter was added. After 2 h, the temperature was adjusted to 48 °C, and 0.5 kg of seeds suspended in approximately 0.5 L of the reaction mixture was charged to induce crystallization. The reaction was cooled to −10 °C over 2.5 h. The solid was collected on an 18-in single plate Hastelloy filter and washed with absolute EtOH (14.0 kg).

The solid was dried in a tray dryer under vacuum at 60 °C for 2 days to give 31.0 kg (72%) of **1** as the undesired polymorph.

*Polymorph Conversion of **1**.* Water (52.2 kg) filtered through an 0.8 μm inline filter was added to a 30-gal glass-lined reactor and heated to 55 °C. Drug candidate **1** (26.1 kg, 52.9 mol) was added in portions. Crystallization of **1** as the desired polymorph occurred without seeding. The reaction was cooled to 4 °C. After 18 h, water (18.2 kg) was added. The solid was collected on an 18-in. single plate Hastelloy filter and washed with water (13.1 kg). The solid was dried in a tray dryer under vacuum at 60 °C for 1 day to give 24.2 kg (93%) of **1** (100 A%

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purity, 99.9 wt %% purity with <0.05% achiral impurities and <0.10% chiral impurities) as the desired polymorph: IR 1670 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.68 (s, 1), 9.93 (s, 1), 7.63 (d, 1, J = 8.3), 7.55 (d, 1, J = 7.6), 7.45−7.35 (m, 3), 5.25 (dd, 1, J = 8.9, 11.4), 4.08 (dt, 1, J = 4.7, 11.1), 3.78 (t, 1, J = 11.4), 3.61 (m, 1), 3.48 (m,1), 3.28 (m, 1), 2.27 (quint, 1, J = 3.1), 2.15 (m, 1), 2.03 (m, 1), 1.93 (m, 1), 1.82 (m, 1), 1.72 (m,1); ^{13}C NMR (DMSO-d_6) δ 163.60, 137.51, 136.10 (2), 130.91, 129.07 (2), 128.96, 128.59, 128.50 (2), 128.02, 122.28, 58.60, 56.76, 49.29, 41.80, 29.08, 23.33, 22.54, 20.57 (*Note*: =*C*−CF_3 not observed); ^{19}F NMR δ 273, 5.1; LC−MS, m/z 457.14 [M + H]. Anal. Calcd for $C_{22}H_{21}Cl_2F_3N_2O$·HCl: C 53.51; H 4.49; N 5.67. Found: C 53.57; H 4.53; N 5.77.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra and HPLC chromotagrams for ee determinations of intermediates. 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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(15) Imidate ester **11** has an exothermic onset with an energy of 789 kJ/kg at 113 °C that was subsequently shown to be the energy generated from the rearrangement and not from decomposition. Trichloroacetamidate **5** as the free base shows no exothermic thermal activity under isothermal conditions at 120 °C for 30 h. The solvent provides an additional barrier to any catastrophic decomposition. Thus, the reaction is considered safe to scale up.

(16) Ru level was approximately 700 ppm in alcohol *R*-**4**, 100 ppm in isolated *S*-**5** without filtration, and 20 ppm in isolated *S*-**5** with filtration.

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