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Asymmetric Synthesis of LFA-1 Inhibitor BIRT2584 on Metric Ton Scale

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Supporting Information

ABSTRACT: The synthesis of LFA-1 inhibitor BIRT2584 on metric-ton scale was accomplished by means of a safe and robust process. Highlights of the process include the asymmetric synthesis of the key advanced intermediate by implementation of Seebach's self-regeneration of stereocenters principle, and a Ph_3PCl_2-induced dehydration of a critical urea followed by a regioselective bromination to give the elaborated 1*H*-imidazo[1,2-*a*]imidazol-2-one. A sulfonyl chloride intermediate was produced through Br/Mg exchange of iodoimidazole followed by addition to SO_2 in THF and subsequent oxidation. In a one-pot operation, the sulfonyl chloride was directly reacted with L-alaninamide using NaOH as base in aqueous DMF/THF to give BIRT2584.

INTRODUCTION

BIRT2584 is a small-molecule lymphocyte function-associated antigen-1 (LFA-1) inhibitor under investigation as a therapeutic agent in the treatment of immune ailments such as psoriasis, Crohn's disease, and rheumatoid arthritis.[1] To support late-stage development activities as well as clinical studies, the synthesis of BIRT2584 active pharmaceutical ingredient (API) in amounts exceeding one metric ton was needed, and a suitable scalable process had to be developed, optimized, and implemented. The previous syntheses of BIRT2584 followed approaches to structurally related LFA-1 inhibitors as shown in Scheme 1. Earlier routes proceeded through intermediates **B** or **C** and started from the pivalaldehyde-derived Seebach's template **A**.[2] Pivalaldehyde was a significant contributor to the overall API cost, and its commercial sources were limited. The conversion of **B** to intermediate **D** for the first route required a stoichiometric amount of CuCl that was not cost-effective.[3] The conversion of **C** to the common intermediate **D** for the second route required an excess of Me_3Al, which posed a safety concern.[4] Furthermore, the transformation of intermediate **D** to iodo-imidazole **E** involved iodination of a phosphate intermediate with HI, that produced side products that needed to be removed.[5] Although the previous two approaches were employed to produce up to 10 kg of BIRT2584 for early development activities, they were not sufficient to support a long-term development cycle. Herein, we report the optimization and implementation of a new process for the synthesis of LFA-1 inhibitor BIRT2584 on metric ton scale.[6]

RESULTS AND DISCUSSION

The BIRT2584 process began with the synthesis of intermediate **4** from Boc-D-alanine (**1**) as shown in Scheme 2. Boc-D-alanine was treated with isobutyl chloroformate/triethylamine and 3,5-dichloroaniline was added to the resulting mixed anhydride to give **2**. The crude **2** was hydrolyzed with *p*-toluenesulfonic acid in toluene to afford **3** as the *p*-TsOH salt in 85% yield from **1**. We had previously reported that an isobutyraldehyde derived imidazolidinone template (i.e., **5**) could be alkylated with high diastereoselectivity using Seebach's protocol and at a fraction of the cost of an analogous pivalaldehyde-derived template.[7] The synthesis of an isobutyraldehyde-derived template proceeded by the synthesis of intermediate **4**. Imidazolidinone **4** was initially obtained upon condensation of **3** with isobutyraldehyde in toluene with simultaneous azeotropic distillation of water. The above condensation afforded a mixture of both the *cis*- and *trans*-isomers of **4**, however, the pure *trans*-isomer **4** was obtained by a crystallization driven resolution in heptane in which the isomers interconverted in solution but the *trans*-isomer crystallized out of the mixture. This procedure was carried out successfully for the synthesis of **4** in multikilogram quantities. A subsequent, more streamlined process was developed in which the azeotropic distillation of water was performed with EtOAc instead of toluene. The use of EtOAc shortened the cycle time for the solvent exchange to heptane (<5% by volume of residual EtOAc), and the desired **4** crystallized in 75−79% yield in heptane at 50 °C.

Although **4** could be isolated in a promising 75−79% yield directly from the reaction mixture, approximately 20% of **4** and its *cis*-isomer **4a** remained in the filtrate as a 1:1 mixture. As a result, we sought to develop a practical process to recover **4** and **4a** by "recycling" the mother liquor, considering it contained no significant amount of impurities. As illustrated in Scheme 3, a more efficient synthesis of **4** was implemented by reusing the mother liquor from the initial reaction after collecting the first portion of **4**. Thus, the filtrate of the heptane solution from the first batch was added to the concentrate of the second batch (the same reaction at the same scale) after azeotropic distillation of water in EtOAc. A solvent exchange to heptane was then performed by distillation until the level of residual EtOAc in heptane was reduced to <5% by volume. The desired *trans*-isomer **4** was isolated in 95% yield for the second batch, and this process was repeated for up to four cycles as summarized in

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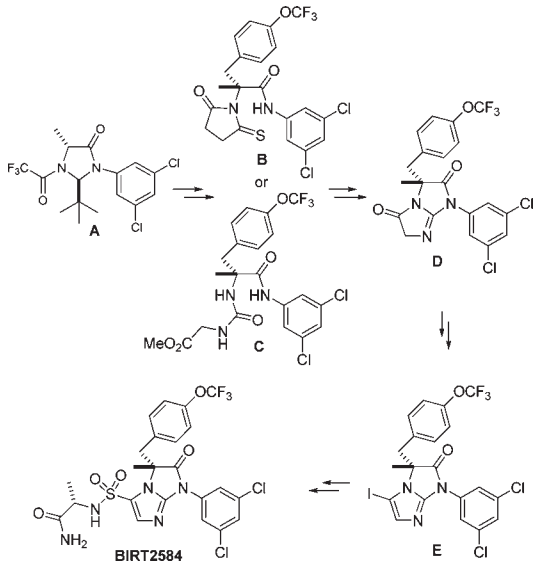
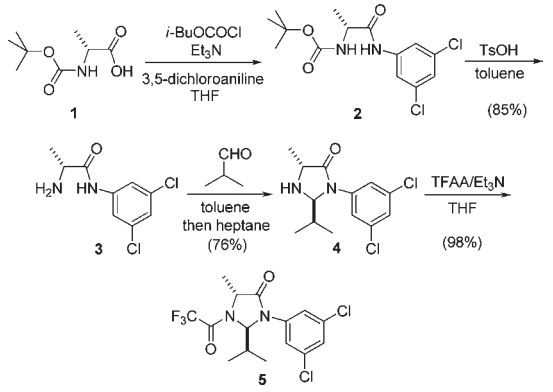
Scheme 1. Original synthesis of BIRT2584



Scheme 2. Initial synthesis of template 5



Scheme 3. Recycle of 4 in mother liquor

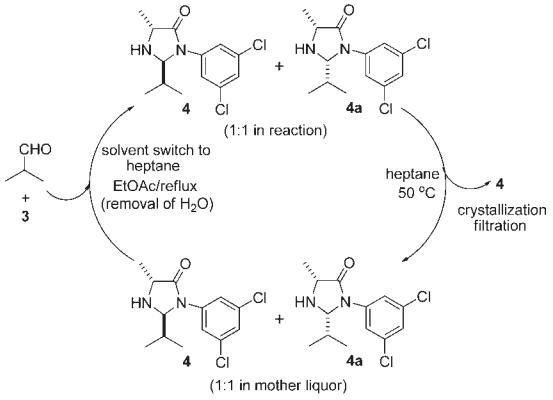
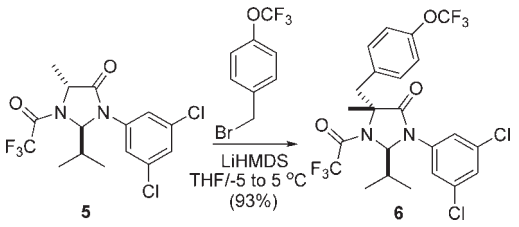


Table 1. The subsequent three cycles afforded a much higher recovery than the first. An average yield of about 90% for **4** was achieved by this method. This procedure was carried out successfully and reproducibly for the synthesis of **4** on production scale.

Table 1. Recycle of 4 in mother liquor

entry	recycle	scale (g)	yield of **4** (%)
1	initial batch	100	76
2	1	100	95
3	2	100	96
4	3	100	93
5	4	100	87

Scheme 4. Alkylation of 5 with 4-trifluoromethoxybenzyl bromide



A highly diastereoselective alkylation of template **5** with 4-trifluoromethoxybenzyl bromide was performed next to install the quaternary chiral center (Scheme 4). The desired diastereoisomer **6** was the sole product. Initially, LiHMDS was added to a solution of **5** in THF precooled to −15 °C to preform an enolate species. This process was exothermic and took a prolonged time (>2.5 h) to complete the addition of LiHMDS and keep the reaction temperature below 0 °C on 100-kg scale at one of our production facilities. During development activities for this reaction on a smaller scale this addition took a shorter time, and the stability of the enolate was not an issue. However, at production scale, significant decomposition of the enolate was observed over time, resulting in a moderate yield of **6** after isolation from a mixture of IPAc/heptane.

Therefore, this alkylation was further investigated as summarized in Table 2. The results demonstrated that formation of enolate at −5 to 0 °C (method A) over a longer time resulted in more decomposition with lower recoveries of **6**. The experiment in entry 3 was a simulation of our first production run on 100-kg scale, and the result was consistent with what we had previously experienced. We were pleased to find that addition of LiHMDS to a mixture of **5** and 4-trifluoromethoxybenzyl bromide in THF at a higher temperature of −5 to 5 °C in 3 h (method B) produced **6** in 93% yield. The rapid alkylation of the enolate as it was formed by benzyl bromide prevented decomposition. This procedure was implemented in our production facility and allowed the large-scale manufacturing of **6** under noncryogenic conditions.

Cleavage of the alkylated template was performed in one-pot by the successive treatment of **6** with KOH in IPA at 60 °C followed by 3 M sulfuric acid. Chiral amine **7** was isolated as the *p*-TSA salt from acetonitrile in 87% yield. Condensation of **7** with phenylcarbamate **8**[8] in the presence of TEA in DMSO at 60 °C followed by a crystallization in methanol gave urea **9** in 92% yield. Solvents such as MeOH or CH_3CN significantly slowed the reaction. This outcome was consistent with a literature report,[9] and a similar result was obtained using TEA as the solvent in the absence of DMSO (Scheme 5). With the urea **9** in hand, we next carried out the dehydration/cyclization to **11** which forms the core structure of the 1*H*-imidazo[1,2-*a*]imidazol-2-one system.

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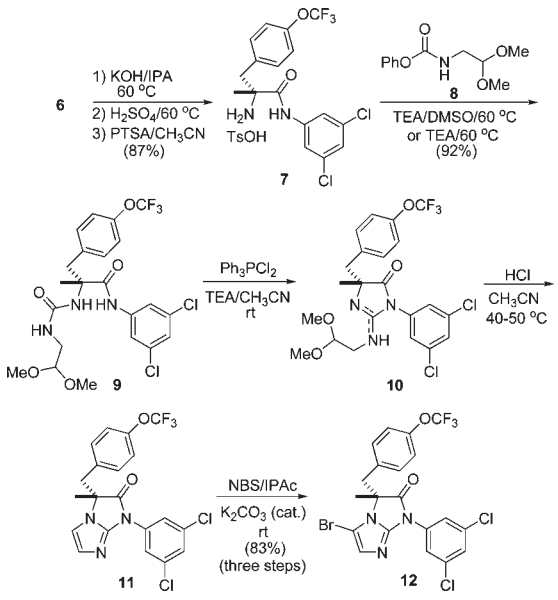
Table 2. Alkylation of 5 with 4-trifluoromethoxybenzyl bromide

entry	scale (kg)	method[a]	time for addition of LiHMDS (h)	yield of **6** (%)[b]
1	**0.1**	A	0.5 (−10 to 0 °C)	89
2	**0.1**	A	1.5 (−5 to 0 °C)	80
3	**0.1**	A	2.5 (−5 to 0 °C)	65
4	**0.1**	B	2.5 (−5 to 5 °C)	94
5	**200**	B	3.0 (−5 to 5 °C)	93

[a] A: addition of LiHMDS to **5** in THF followed by bromide. B: addition of LiHMDS to a mixture of **5** and bromide in THF. [b] Isolated from a mixture of IPAc/heptane.

Scheme 5. Synthesis of bromoimidazole 12



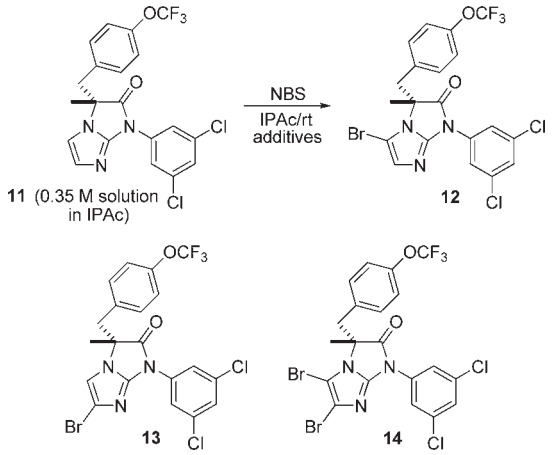
We originally performed the dehydration/cyclization of urea **9** using a combination of Ph_3P, CCl_4, and TEA[10] which was demonstrated to be effective in the synthesis of a similar guanidine derivative.[4] The reaction produced **10** (as a 1:1 mixture of two endo- and exoisomers) in 94% isolated yield. Considering that the use of toxic CCl_4 as reagent in production was not desirable, we searched for alternative dehydration conditions. The combination of Ph_3P and CCl_4 has been used for the preparation of Ph_3PCl_2 which is now commercially available and inexpensive, and it is often used for *N*-ylide formation.[11] We therefore studied the possibility of employing this reagent for our key dehydration. We were pleased to find that a slow addition of 1.7 equiv of Ph_3PCl_2 to **9** and 3.5 equiv of TEA in acetonitrile at 20−25 °C, gave **10** in quantitative yield (Scheme 5). Without a workup, the resulting mixture was treated with concentrated HCl at 40−50 °C to give crude bicyclic imidazole **11**, which contained Ph_3PO, in 95% yield (HPLC assay) over two steps. The HPLC assay yield was consistent with small-scale experiments in which **11** was purified by silica gel chromatography. Intermediate **11**, crude or purified through chromatography, was an oil that was used directly in the subsequent bromination after a simple aqueous workup of the IPAc solution[12] of crude **11**.

The subsequent bromination was performed directly on the crude IPAc solution of **11** from the previous step which simplified the process greatly. Similar brominations of *N*-alkylimidazoles,[13] imidazo[1,2-*a*]pyrimidines,[14] and imidazo[1,2-*a*]pyridine derivatives[15] are known to be very regio- and chemoselective, but the bromination of **11** was not straightforward and required some optimization. Table 3 outlines the results of some typical experiments. Treatment of **11** by slow addition of a suspension of 1.05 equiv of NBS in IPAc gave bromoimidazole **12** in 57% yield with only a trace amount of regioisomer **13** and <2% of dibromide **14**. A similar result was obtained when chromatographically pure **11** was used under the same conditions (entry 2, Table 3). While the regio- and chemoselectivity were promising, bromide **12** was obtained only in moderate yield because several byproducts were obtained which diminished the yield by more than 10%. Isolation and/or identification of these byproducts were not successful since they rapidly interconverted. On the basis of preliminary MS data, these byproducts are possibly products of imidazole-dimerization.[16] Interestingly, in the presence of Lewis acids such as PPTS and $ZnBr_2$, the bromination resulted in significantly increased formation of these byproducts, accounting for up to 22% of the mixture (entries 3−4, Table 3). These experiments suggested that the proposed dimerization of **11** may be promoted by acids, which is consistent with literature reports of Lewis acid-promoted dimerization of imidazole-related heterocycles.[17] As expected, the same bromination of **11** in the presence of TEA significantly suppressed the formation of dimer-derivatives (entry 5, Table 3), leading to a much improved 83% yield of **12**. In this case about 1.4 equiv of NBS was needed for a complete reaction due to the reaction between TEA and NBS.[18] Subsequently, the inorganic base K_2CO_3 was used to replace TEA, and indeed, the bromination of **11** produced **12** in 86% isolated yield with no need for excess NBS. Crystallization from IPA/water provided clean **12** and also removed the residual Ph_3PO carried over from the previous step. Controlling the amount of NBS based on the HPLC assay of the crude IPAc solution of **11** was critical. Excess NBS led to an increased amount dibromide **14** and a low overall yield of BIRT2584 in the subsequent step.

During the pilot-plant production of **12**, we had one occasion when the bromination of crude **11** in IPAc gave only 40% of **12** on 50-kg scale due to the formation of a byproduct identified as the ring-cleavage product **18**. We found that the presence of water in the crude IPAc solution of **11** led to the ring cleavage of imidazole to **18**. As demonstrated in Table 4, a significant amount of **18** was found when the water content in the IPAc solution reached 1%. For the pilot-plant incident, we concluded that an inefficient phase cut during the aqueous workup and insufficient removal of water by azeotropic distillation of the IPAc solution of **11** resulted in the water levels that in the presence of NBS cleaved the imidazole ring. Since this side reaction was not significant when the water content was <1000 ppm, a specification was set for this particular step and this failure mode was not observed in all subsequent batches.

The final stage of the process, namely the transformation of **12** to BIRT2584, was executed next. Br/Mg exchange of **12** was performed by addition of *i*PrMgCl (1.05 equiv) in THF at −5 °C. Upon completion of the charge of *i*PrMgCl, successive addition of SO_2 (1.1 equiv) as a THF solution and a suspension of NCS (1.1 equiv) in THF to the reaction mixture at −5 °C produced sulfonyl chloride **19**. Without a workup, coupling of **19** with L-alaninamide was then carried out. A screening of conditions

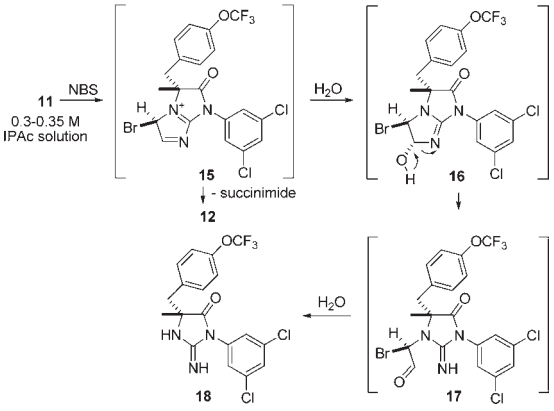
Table 3. Bromination of 11 with NBS to bromoimidazole 12



entry	additive (0.1 equiv)	dimerization derivatives (area %)[a]	time (h)	isolated yield of **12**[b]
1	/	11	1	63
2[c]	/	11	1	64
3	PPTS	13	1	58
4	$ZnBr_2$	22	0.5	45
5	TEA	2	1	83
6	K_2CO_3	1	1	86

[a] Area purity by HPLC. [b] Isolated yield by crystallization from IPA/water. [c] Chromatographically pure **11** used.

Table 4. Water impact for bromination of 11



entry	scale (g)	water (%)	HPLC wt % assay yield of **12**(%)	HPLC wt % assay yield of **18**(%)
1	100	0.02	93	<1
2	100	0.05	93	<1
3	100	0.10	90	4
4	100	0.50	84	8
5	100	1.00	69	15
6	100	2.00	65	18

revealed that the choices of solvents and bases had a significant impact on the reaction, as shown in Table 5. Without a cosolvent, the coupling of **19** with L-alaninamide in the presence of TEA was sluggish, probably due to the poor reactivity and solubility of L-alaninamide in THF (entry 1). Addition of a mixture of L-alaninamide and TEA or pyridine in DMF (as cosolvent) to the reaction mixture of **19** produced BIRT2584 in only 40−50% yield due to the formation of a large amount of sulfonic acid **20** over the prolonged reaction times required (entries 2−3). Addition of inorganic bases such as K_2CO_3 under the same conditions gave a similar result (entry 4). While the coupling reaction using a combination of DMF and water as cosolvent and TEA as base gave an improved yield of BIRT 2584 (entry 5), the use of either K_2CO_3 or Cs_2CO_3 significantly reduced the formation of **20** with a complete reaction in 6 h, resulting in 85−86% yield of BIRT 2584 after crystallization from ethanol/water (entries 6−7). In the absence of DMF, the reaction rate was dramatically reduced, and 24 h were required for a complete reaction. Under these conditions more hydrolysis of the sulfonyl chloride was also observed (entry 8).

During production in the pilot plant, we experienced a yield fluctuation of BIRT2584 using K_2CO_3 as base with different levels of **20**, presumably formed due to the poor solubility of the base in a multiphase reaction system. The search for an alternative base other than Cs_2CO_3 which gave consistent results revealed that aq NaOH produced a result similar to those of K_2CO_3 and Cs_2CO_3 (entry 9). It was interesting to notice that the pH values at the end point for all reactions with >85% of BIRT 2584 were between 9 and 10.5 which we believe to be critical for a satisfactory reaction (such as entries 6, 7, and 9). This observation is in agreement with the fact that both excess and substoichiometric NaOH produced BIRT2584 in diminished yield along with increased amounts of **20** (entries 10 and 11). In general, the byproduct **20** was totally rejected after initial isolation of crude BIRT2584 from a 1:5 mixture of EtOAc/heptane. The final crystallization was performed in a 10:1 mixture of EtOH/water to produce the desired polymorph in 92% yield.

SUMMARY AND CONCLUSION

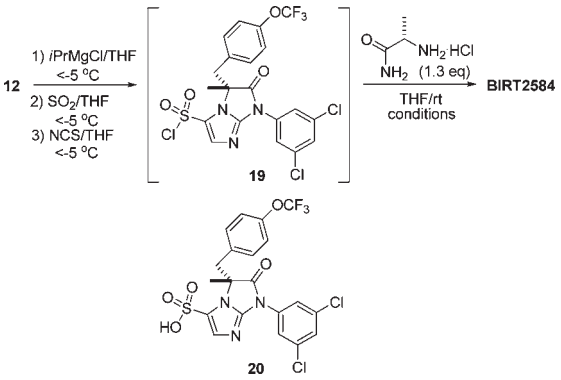
We developed and implemented a concise and robust process for the production of LFA-1 inhibitor BIRT2584 on metric ton scale. The process features an efficient synthesis of Seebach's template, a new methodology for the dehydration of a urea intermediate with Ph_3PCl_2 and a regioselective bromination of imidazo[1,2-*a*]imidazol-2-one derivatives. Furthermore, an efficient one-pot process for the preparation of the sulfonamide from a bromoimidazole using SO_2 solutions was also developed involving four *in situ* chemical transformations.

EXPERMENTAL SECTION

General. All raw materials were used as received from commercial sources without pretreatment. HPLC monitoring for all reactions was carried out with the use of commercially available reverse-phase columns (Zorbax Eclipse XDB-C8) eluted with 0.05% TFA (aq) and 0.05% TFA in acetonitrile. The chiral purity of **7** was determined using a Chiralpak AD-3, 3.0 μm, 150 mm × 3.0 mm column, eluting with 2% IPA in hexane.

(2*S*,5*R*)-3-(3,5-Dichlorophenyl)-2-isopropyl-5-methylimidazolidin-4-one (4). First Batch: *p*-Toluenesulfonic acid salt of **3** (2578 g, 5.10 mol) in EtOAc (7.0 L) was stirred with 2 N NaOH (2.8 L, 5.60 mol) for 30 min, and the separated organic layer was washed with water (2.0 L). Isobutyraldehyde (571 mL, 6.00 mol) was added to this stirred EtOAc solution at 17−23 °C over a period of 30 min. Azeotropic distillation was performed at reflux with a Dean−Stark until no more water was collected (~10 h).

Table 5. One-pot synthesis of LFA-1 BIRT2584 from 12



entry	base[a]	cosolvent[b] (vol % to THF)[c]	time (h)	yield of BIRT 2584[d] (wt % of **20**)[e]
1	TEA	/	20	<10%
2	TEA	DMF (10)	17	45% (23%)
3	py	DMF (10)	15	40% (25%)
4	K_2CO_3	DMF (10)	20	51% (20%)
5	TEA	DMF (10)/H_2O (10)	6	64% (13%)
6	K_2CO_3	DMF (10)/H_2O (10)	6	85% (6%)
7	Cs_2CO_3	DMF (10)/H_2O (10)	6	86% (5%) (pH ≈ 9.8)[f]
8	K_2CO_3	H_2O (10)	24	72% (11%)
9	NaOH (2.4 equiv)	DMF (10)/H_2O (10)	6	86% (4%) (pH: ~10)[f]
10	NaOH (2.6 equiv)	DMF (10)/H_2O (10)	6	79% (9%) (pH > 11)[f]
11	NaOH (2.2 equiv)	DMF (10)/H_2O (10)	10	76% (10%) (pH ≈ 8)[f]

[a] 3 equiv for TEA, pyridine and 1.5 equiv for K_2CO_3 and Cs_2CO_3 used. [b] Added as L-alaninamide HCl salt solution. [c] Volume % to all THF used in the first three chemical transformations. [d] Isolated by crystallization from EtOH/water. [e] Weight % assay of the reaction mixture by HPLC. [f] pH value at the end point.

The mixture was then concentrated to a low volume (~1.5 L), and heptane (6.0 L) was added. Distillation was performed under reduced pressure at 50−60 °C to a low volume (~1.5 L). To the concentrate was added heptane (6.0 L), and the solution was stirred at 50 °C for 12 h while crystallization occurred. The mixture was cooled to 20−25 °C and filtered, and the filter cake was washed with heptane (1.0 L) to give **4** (1113 g, 76%) as a light-yellow solid.

Second Batch: *p*-Toluenesulfonic acid salt of **3** (2578 g, 5.10 mol) in EtOAc (7.0 L) was stirred with 2 N NaOH (2.8 L, 5.60 mol) for 30 min, and the separated organic layer was washed with water (2.0 L). Isobutyraldehyde (571 mL, 6.00 mol) was added to this stirred EtOAc solution at 17−23 °C over a period of 30 min. Azeotropic distillation was performed at reflux with a Dean−Stark until no more water was collected (~10 h). After the mixture was concentrated to a low volume (~1.5 L) by distillation, the filtrate from the first batch was added to the concentrate of the second batch. Distillation was performed under reduced pressure at 50−60 °C to a low volume (~1.8 L). To the concentrate was added heptane (6.5 L), and the solution was stirred at 50 °C for 12 h while crystallization occurred. The mixture was cooled to 20−25 °C and filtered, and the filter cake was washed with heptane (1.0 L) to give **4** (1391 g, 95%) as a light-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 1.38 (d, J = 6.8 Hz, 3H), 2.02−1.95 (m, 2H), 3.72 (q, J = 6.1 Hz, 1H), 5.02 (d, J = 1.96 Hz, 1H), 7.17 (m, 1H), 7.41 (d, J = 1.96 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.1, 18.1, 18.4, 30.5, 56.2, 78.1, 120.8, 125.5, 135.4, 138.7, 174.9; Anal. calcd for $C_{13}H_{16}Cl_2N_2O$: C, 54.37; H, 5.62; N, 9.75. Found C, 54.44; H, 5.43; N, 9.63%.

(2*R*,5*R*)-3-(3,5-Dichlorophenyl)-2-isopropyl-5-methyl-1-(2,2,2-trifluoroacetyl)imidazolidin-4-one (5). Trifluoroacetic anhydride (400 mL, 2.83 mol) was added dropwise to a stirred solution of **4** (796 g, 2.77 mol), triethylamine (394 mL, 2.83 mol), and THF (6000 mL) at 0 °C over a period of 90 min. The resulting solution was allowed to reach ambient temperature and stirred for 90 min. The mixture was concentrated under reduced pressure to a low volume (~1.5 L), and water (6000 mL) was added over 60 min while seed crystals of **5** were added. The resulting slurry was filtered to afford 1290 g (98%) of a white solid: mp 87−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (d, J = 7.2 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 1.68 (d, J = 6.4 Hz, 3H), 2.42 (m, 1H), 4.57 (q, J = 6.6 Hz, 1H), 6.18 (s, 1 H), 7.30 (m, 1 H), 7.45 (br s, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.8, 18.1, 20.2, 57.0, 78.0, 122.4, 127.3, 135.7, 137.4, 168.7; Anal. calcd for $C_{15}H_{15}C_{l2}F_3N_2O_2$: C, 47.02; H, 3.95; N, 7.31. Found C, 47.16; H, 3.82; N, 7.24

(2*R*,5*R*)-5-(4-Trifluoromethoxybenzyl)-3-(3,5-dichlorophenyl)-2-isopropyl-5-methyl-1-(2,2,2-trifluoroacetyl)imidazolidin-4-one (6). To a mixture of **5** (750 g, 1.96 mol) and *p*-trifluoromethoxybenzyl bromide (513 g, 2.01 mol) in THF (2.0 L) was added a 1 M solution of $LiN(TMS)_2$ in THF (2030 mL, 2.03 mol) at 0−5 °C over 1 h. The mixture was then stirred at this temperature for an additional 30 min and quenched with 5% NH_4Cl (3 L). A distillation was performed to remove THF followed by addition of a 10:1 mixture of heptane and ethyl acetate (3 L). The resulting slurry was filtered, and the cake was washed with water (1 L). The filter cake was dried under vacuum at 40 °C to give **6**

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as a white solid (1016 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) For the major rotamer: δ 7.29 (d, J = 2.0 Hz, 1H), 7.10 (ABq, J = 8,0 Hz, 2H), 6.98 (ABq, J = 8,0 Hz, 2H), 6.83 (d, J = 2.0 Hz, 2H), 5.08 (s, 1H), 3.76 (d, J = 14.0 Hz, 1H), 3.12 (d, J = 14.0 Hz, 1H), 2.12−2.03 (m, 1H), 1.96 (s, 3H), 0.92 (d, J = 6.4 Hz, 3H), 0.55 (d, J = 6.4 Hz, 3H). For the minor rotamer: δ 7.26 (s, 1H), 7.10 (ABq, J = 8,0 Hz, 2H), 6.98 (ABq, J = 8,0 Hz, 2H), 6.75 (s, 2H), 5.14 (s, 1H), 3.33 (d, J = 14.4 Hz, 1H), 3.17 (d, J = 14.4 Hz, 1H), 2.30−2.22 (m, 1H), 1.92 (s, 3H), 0.79 (d, J = 6.4 Hz, 3H), 0.55 (d, J = 6.4 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) for the major rotamer only: δ 169.9, 155.7 (q, J = 37.0 Hz), 148.8 (d, J = 2.0 Hz), 137.3, 135.7, 133.8, 131.0, 128.1, 123.7, 121.0, 120.4 (q, J = 256.0 Hz), 115.6 (q, J = 287.0 Hz), 78.0 (q, J = 5.0 Hz), 70.1, 39.2, 36.5 (d, J = 1.0 Hz), 22.4, 20.2, 14.4; HRMS calculated for $C_{23}H_{20}Cl_2F_6N_2O_3$ $[M + H]^+$: 557.0827, Found: 557.0838.

_p_-Toluenesulfonic Acid Salt of (_R_)-2-Amino-3-(4-trifluoromethoxyphenyl)-_N_-(3,5-dichlorophenyl)-2-methylpropionamide (7). A mixture of **6** (1000 g, 1.79 mol) and KOH (111 g, 1.97 mol) in IPA (3.6 L) was heated to 60 °C for 1 h, and then 3 M sulfuric acid (750 mL, 2.27 mol) was added. After agitating at 60 °C for 3 h, a distillation of IPA was performed to a low volume (∼1.5 L). IPAc (4 L) was then added followed by a slow addition of 0.2 N KOH in water (3 L, 0.60 mol). The layers were separated, the organic layer was distilled to a low volume (∼1.7 L), and acetonitrle (2 L) was then charged. To this solution was added a solution of _p_-toluenesulfonic acid monohydrate (358 g, 1.88 mol) in acetonitrile (1.5 L), causing a slurry of the salt to form. The product was then collected by filtration and dried under vacuum at 40 °C to give **7** as light-yellow crystals (902 g, 87%). ^{1}H NMR (400 MHz, MeOD-d_4) δ 7.76 (ABq, J = 8.0 Hz, 2H), 7.71 (d, J = 2.0 Hz, 2H), 7.33 (ABq, J = 8.8 Hz, 2H), 7.23−7.19 (m, 5H), 3.44 (d, J = 14.4 Hz, 1H), 3.31 (d, J = 14.4 Hz, 1H), 2.35 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (400 MHz, MeOD-d_4) δ 170.5, 150.3 (d, J = 1.0 Hz), 143.4, 141.9, 141.1, 136.2, 133.5, 133.2, 130.0, 127.0, 125.5, 122.5, 121.9 (q, J = 254.0 Hz), 120.3, 62.7, 42.8, 21.9, 21.4; HRMS calculated for $C_{17}H_{15}Cl_2F_3N_2O_2$ $[M + H]^+$: 407.0535, Found: 407.0538.

(_R_)-_N_-(3,5-Dichlorophenyl)-2-[3-(2,2-dimethoxyethyl)ureido]-2-methyl-3-(4-trifluoro-methoxyphenyl)propionamide (9). To a solution of **7** (850 g, 1.47 mol) in DMSO (1.5 L) was added **8** (365 g, 1.61 mol) in MTBE (1.5 L). After a distillation was performed to remove MTBE, TEA (223 g, 2.21 mol) was added. The resulting mixture was heated to 60 °C for 3 h and quenched with addition of EtOAc (3.5 L) and water (3 L). The layers were separated, and the organic phase was washed with water (1 L). A distillation of EtOAc was performed to a low volume (∼1.5 L) followed by addition of MeOH (4 L). The solution was again distilled to a low volume (∼3.5 L), and the solids that precipitated were collected by filtration. The filter cake was washed with MeOH (500 mL) and dried under vacuum at 40 °C to give **9** (728 g, 92%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.93 (s, 1H), 7.78 (d, J = 2.0 Hz, 2H), 7.28−7.22 (m, 5H) 6.21 (s, 1H), 6.13 (t, J = 6.0 Hz, 1H), 4.36 (t, J = 5.6 Hz, 1H), 3.41 (d, J = 13.2 Hz, 1H), 3.30 (s, 6H), 3.27−3.21 (m, 1H), 3.12 (d, J = 13.2 Hz, 1H), 3.12−3.05 (m, 1H), 1.26 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6) δ 173.9, 156.8, 147.1 (d, J = 2 Hz), 141.7, 136.7, 133.8, 132.4, 122.0, 120.3, 120.1 (q, J = 254.0), 117.9, 102.7, 59.0, 53.3, 53.2, 40.7, 23.1; HRMS calculated for $C_{22}H_{24}Cl_2F_3N_3O_5$ $[M + H]^+$: 538.1117, Found: 538.1127.

(_R_)-3-(4-Trifluoromethoxybenzyl)-1-(3,5-dichlorophenyl)-5-bromo-3-methyl-1_H_-imidazo[1,2-_a_] imidazole-2-one (12). To a suspension of **9** (1200 g, 2.23 mol) and TEA (790 g, 7.81 mol) in acetonitrile (3 L) was slowly added a solution of Ph_3PCl_2 (1263 g, 3.79 mol) in acetonitrile (2 L) at 10−20 °C over 30 min. The resulting mixture was stirred at rt for 2 h (to give **10**), and concentrated HCl (50 mL, 0.60 mol) was then added. After being stirred at 40−50 °C for 2 h, the mixture was quenched with the addition of K_2CO_3 (85 g, 0.61 mol) in water (3 L). A partial distillation of CH_3CN was next performed to a volume of about 5 L, and IPAc (4 L) was then charged. The mixture was filtered to remove some solids (TPPO), and the layers were separated. The organic layer was washed with water (1 L), and an azeotropic distillation was performed until KF analysis of the solution showed <1000 ppm water. An estimated 0.5 M solution of **11** was used for the next bromination. To the above IPAc solution of **11** was added K_2CO_3 (15 g, 0.11 mol) followed by a suspension of NBS (395 g, 2.22 mol) in IPAc (2 L) at 10−20 °C over 30 min. The resulting mixture was stirred at rt for 1 h. The mixture was filtered, and the filtrate was distilled to a low volume (2 L). IPA (4 L) was added, and a distillation was again performed to a low volume (2 L, 2×). After addition of IPA (4 L), water (600 mL) was slowly added. The resultant slurry was stirred for an additional 1 h, and the product was collected by filtration. The filter cake was washed with IPA (500 mL), and dried under vacuum at 40 °C to give **12** as a light-yellow solid (990 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 2.0 Hz, 1H), 7.28 (m, 1H), 7.03 (ABq, J = 8.4 Hz, 2H), 6.97 (ABq, J = 8.4 Hz, 2H), 6.87 (s, 1H), 3.55 (d, J = 14.0 Hz, 1H), 3.35 (d, J = 14.0 Hz, 1H), 1.94 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 173.8, 149.9 (d, J = 1.0 Hz), 146.4, 135.4, 134.1, 131.8, 130.9, 128.8, 127.4, 121.0, 120.4, 120.3 (q, J = 256.0 Hz), 95.2, 68.3, 41.9, 22.0; HRMS calculated for $C_{20}H_{13}BrCl_2F_3N_3O_2$ $[M + H]^+$: 533.9593, Found: 533.9599.

A small sample of **10** was isolated as an oil (a 1:1 mixture of endo- and exo-isomers) by chromatography on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.44 (m, 2H), 6.80 (m, 1H), 4.51 (s, 2H), 4.17 (q, J = 7.2 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 191.9 (d, J = 2.0 Hz), 167.5, 162.4 (d, J = 249.0 Hz), 161.1, 140.3 (d, J = 7.0 Hz), 132.7 (dq, J = 7.5, 33.6 Hz), 132.6, 130.1, 129.0, 127.4, 122.9 (q, J = 272.0 Hz), 122.2 (m), 120.1 (d, J = 22.0 Hz), 117.0 (m), 113.7, 65.5, 61.6, 14.0; HRMS calculated for $C_{22}H_{22}Cl_2F_3N_3O_4$ $[M + H]^+$: 520.1012, Found: 520.1034.

A small sample of **11** was isolated as an oily residue by chromatography on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 2.0 Hz, 2H), 7.26 (t, J = 1.6 Hz, 1H), 7.03 (ABq, J = 8.0 Hz, 2H), 6.98 (d, J = 2.0 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 6.92 (ABq, J = 8.0 Hz, 2H), 3.33 (d, J = 14.0 Hz, 1H), 3.21 (d, J = 14.0 Hz, 1H), 1.79 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 174.9, 148.8 (d, J = 2.0 Hz), 145.8, 135.3, 134.8, 131.8, 131.0, 129.2, 127.0, 120.9, 120.3 (q, J = 256.0 Hz), 120.1, 111.1, 66.1, 43.9, 23.1; HRMS calculated for $C_{20}H_{14}Cl_2F_3N_3O_2$ $[M + H]^+$: 456.0487, Found: 456.0508.

(_S_)-2-[(_R_)-7-(3,5-Dicholrophenyl)-5-methyl-6-oxo-5-(4-trifluoromethoxybenzyl)-6,7-dihydro-5_H_-imidazo[1,2-_a_]imidazole-3-sulfonylamino]propionamide (BIRT2584). To a solution of **12** (1000 g, 1.87 mol) in THF (2.0 L) was added a 2.0 M solution of _i_PrMgCl (1968 mL, 1.97 mol) at −15 to −5 °C over 45 min. After agitating at this temperature for an additional 10 min, a prepared SO_2 solution (133 g, 2.06 mol) in THF (400 mL) was added at −15 to −5 °C over 45 min, followed immediately by the addition of a suspension of NCS (292 g, 2.19 mol) in THF (1200 mL) over 30 min. The resultant mixture was aged at −5 °C for 10 min, then NaOH (176 g, 4.40 mol) was charged

to the reaction mixture followed by the addition of L-alaninamide HCl salt (302 g, 2.42 mol) in DMF (550 mL) and water (550 mL) over 15 min, keeping the internal temperature −20 °C. After having stirred at 18 to 23 °C for 6 h, the mixture was quenched with water (4 L) and ethyl acetate (2.4 L). The layers were separated, and the organic layer was distilled to a low volume (~2.3 L), and EtOAc (5.0 L) was then added. The solution was then washed with water (3.0 L) and distilled to a low volume (2.0 L). A slow addition of heptane (6.0 L), antisolvent to the organic solution, was then made, and the resulting slurry was stirred at rt for 2 h. The crude product was collected by filtration to give BIRT 2584 as white crystals (975 g, 86%) after drying. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.0 (s, 1H), 7.63 (t, J = 1.6 Hz, 1H), 7.46 (d, J = 2.0 Hz, 2H), 7.44 (s, 1H), 7.42 (s, 1H), 7.16 (ABq, J = 8.0 Hz, 2H), 7.14 (s, 1H), 6.99 (ABq, J = 8.0 Hz, 2H), 3.84 (q, J = 7.2 Hz, 1H), 3.77 (d, J = 14.0 Hz, 1H), 3.28 (d, J = 14.0 Hz, 1H), 1.96 (s, 3H), 1.22 (d, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, MeOD-d_4) δ 177.1, 175.4, 150.3, 150.1 (d, J = 2.0 Hz), 136.5, 135.9, 135.3, 134.4, 132.3, 128.7, 128.3, 122.6, 122.0, 121.8 (q, J = 254.0 Hz), 71.6, 53.5, 43.4, 22.2, 19.6; HRMS calculated for $C_{23}H_{20}Cl_2F_3N_5O_5S$ $[M + H]^+$: 606.0587, Found: 606.0590.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H/^{13}C NMR spectra for **4**−**7**, **9**−**14**, **18**, **20**, **BIRT2584**. This material is available free of charge via the Internet at http://pubs.acs.org.

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