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Practical synthesis of a cell adhesion inhibitor by self-regeneration of stereocenters

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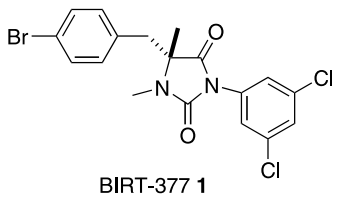
Abstract—An efficient enantiospecific synthesis of the cell adhesion inhibitor BIRT-377 by self-regeneration of stereocenters has been achieved in 38% overall yield in eight steps. The key transformations involve the stereoselective formation of the *trans* imidazolidinone **7**, subsequent alkylation, and the efficient hydrolysis of disubstituted imidazolidinone **9**. The process is practical, robust, and cost-effective; it has been successfully implemented in the pilot plant to produce multikilogram quantities of the drug BIRT-377 **1**.

1. Introduction

LFA-1 (lymphocyte function-associated antigen-1) belongs to the integrin family and is expressed solely on leukocytes (white blood cells) and is required for a variety of important functions in both killer and helper T cells. The counter receptor to LFA-1 on target cells is recognized to be ICAM-1 (intercellular cell adhesion molecule-1).[1] ICAM-1 belongs to the immunoglobulin family of receptors and can be expressed on cells from a variety of tissues, including endothelial, fibroblastic, and epithelial cells. Blocking the protein–protein interaction of cell adhesion molecules such as LFA-1 to ICAM-1 could prove beneficial to patients suffering from immune disorders, and an antisense polynucleotide molecule that blocks the expression of ICAM-1 is currently undergoing tests for the treatment of Crohn's disease.[2] With the realization that small molecules have an advantage over protein therapeutics, a high throughput screening was established by our Discovery team in an effort to identify low molecular-weight molecules that act as antagonists to the binding of LFA-1 to ICAM-1. The structure–activity relationship studies resulted in the discovery of BIRT-377 **1** (Fig. 1).[3,4] This small molecule selectively inhibits the association of LFA-1 to ICAM-1 in a reversible manner with a K_d of 25.8±6.3 nM. Additional binding site studies demonstrated that BIRT-377 binds to the β-subunit (CD11a chain) of LFA-1 and not to ICAM-1. Furthermore, it was shown in a mouse model that orally administered BIRT-377 inhibits the in vivo production of IL-2. Given the immense therapeutic potential that a small molecule such as BIRT-377 has to offer for the treatment of immunological disorders, we became involved in a program designed to develop an efficient, scalable, and cost-effective route for the synthesis of molecules like BIRT-377 and analogs. Herein, we report an efficient enantiospecific synthesis of BIRT-377 based on a modification of Seebach's self-regeneration of stereocenters strategy in which we extend the original protocol to achieve complete (>99.9%) overall stereoselectivity.[5]



BIRT-377 **1**

Figure 1.

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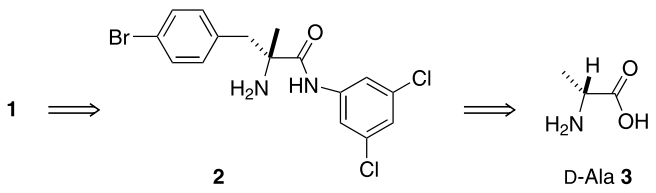


Scheme 1. Retrosynthetic strategy.

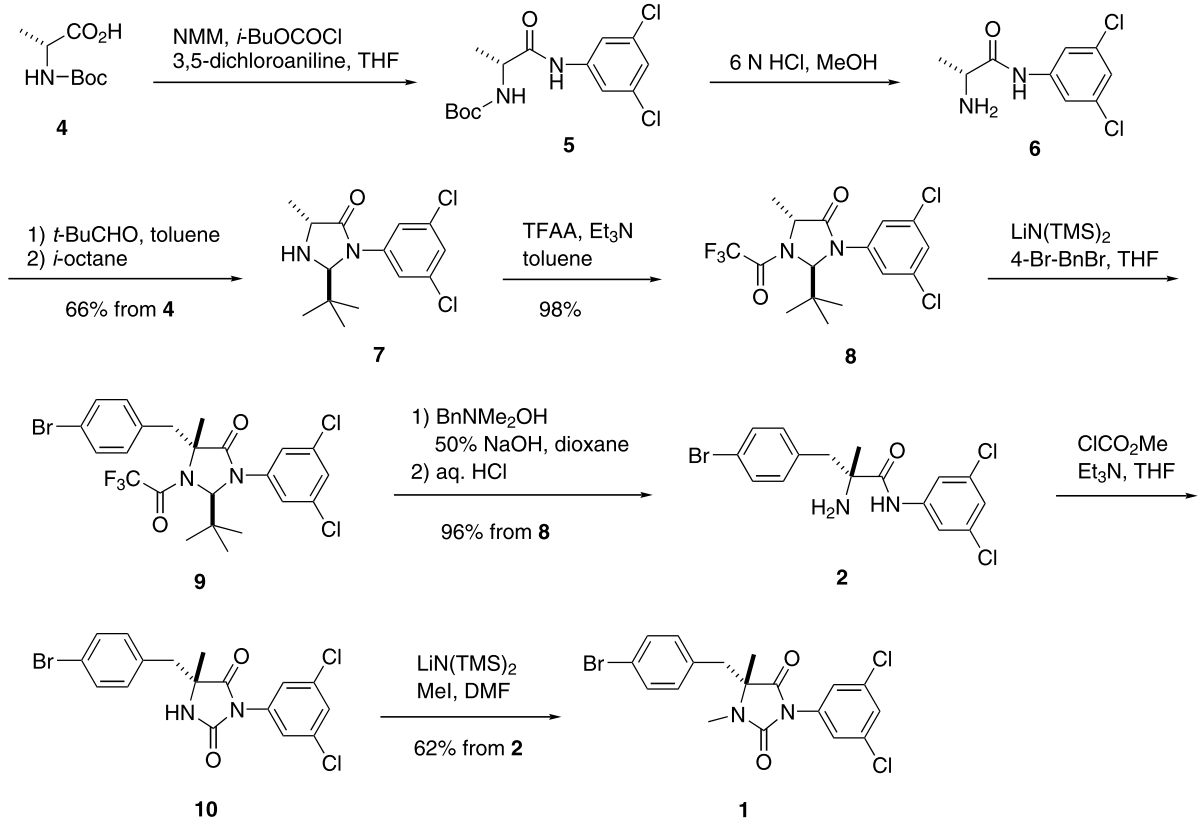
2. Results and discussion

2.1. Synthetic strategy

The key structural feature of BIRT-377 is the *N*-aryl-substituted hydantoin, which contains a quaternary stereogenic center. In our retrosynthetic analysis (Scheme 1), the hydantoin ring can be formed by cyclization of the corresponding α-substituted alanine amide **2**. In the literature, a variety of synthetic methodologies have been reported for the asymmetric synthesis of quarternary α-amino acids as well as their derivatives, and this important subject had been recently reviewed by Cativiela.[6] Of these known methods, Seebach's self-regeneration of stereocenters principle[7] in the preparation of α-substituted amino acid derivatives was most attractive to us due to its simplicity in terms of the easy access of the chiral template imidazolidinones (up to 90% ds), the stability of its enolate at higher temperature (up to 0°C), and the predictability of its stereochemical outcome. Unfortunately, this method has not been widely reported, especially for industrial large-scale production, probably due to the reported harsh conditions (aqueous HCl at 150–220°C) required to hydrolyze the resulting 5,5-disubstituted imidizolidinones,[8–18] as well as its modest diastereoselectivities (70–90% ds) in the formation of the imidazolidinone template. During our literature survey, it was found that the stereoselective formation of either the *trans*- or *cis*-imidazolidinones by Seebach's method was limited to the α-amino-*N*-methyl amides as substrates, and other substitution (such as *N*-aryl) on the amide nitrogen atom had not been reported. Therefore, the utilization of Seebach's principle to synthesize α-substituted amino *N*-aryl amide **2** (Scheme 1) for BIRT-377 **1** is intriguing in relation to the possible stereochemical outcome.

2.2. Stereoselective formation of *trans*-imidazolidinone

Since the complete diastereoselectivity (100% dr) for the alkylation of the *trans*-imidazolidinone such as **8** (Scheme 2) had been well documented in literature,[8–18] our efforts were first focused on the efficient formation of *trans*-*N*-aryl imidazolidinone **7** in Scheme 2. The synthesis of BIRT-377 **1** started with the commercially available D-*N*-Boc-alanine **4** (Scheme 2). The amide **5** was prepared by reacting **4** with 3,5-dichloroaniline via a mixed anhydride intermediate (*i*-BuOCOCl, *N*-methylmorpholine, −15°C to rt, THF). Deprotection of the crude amide **5** by HCl in methanol afforded amino *N*-aryl amide **6**. The crude product obtained after



Scheme 2. Synthesis of BIRT-377 **1**.

neutralization was pure enough to carry on to the next step without further purification. In our preliminary laboratory studies,[5] amino amide **6** was treated with pivalaldehyde in refluxing pentane in a manner similar to that described by Seebach's original procedure. A crystalline solid was directly formed from the reaction mixture and identified as the desired *trans*-imidazolidinone **7**[19] as a single diastereomer in 74% yield. This observation is in contrast with Seebach's case for the corresponding amino acid *N*-methyl amide. Seebach reported that the acyclic Schiff base intermediate was actually obtained as an oil in this step and then cyclized only when treated with HCl in methanol at 0°C or with $(PhCO)_2O$ at 130°C to generate stereoselectively either *trans*- or *cis*-imidazolidinones in 90% ds and 71% ds, respectively.[8]

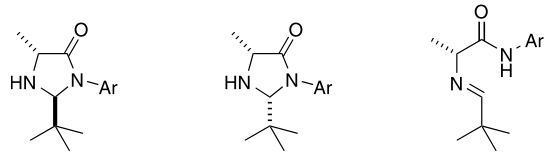
In our later experiments, it was found that a mixture of *trans*- and *cis*-imidazilidinones **7** and **11** and Schiff base **12** (Table 1) was readily formed by treating amino amide **6** with pivalaldehyde in toluene or dichloromethane. However, when this oily mixture (with various **7**/**11**/**12** ratios) was allowed to stand neat over a period of time, or when the mixture of **7**/**11**/**12** was stirred in nonpolar solvents such as pentane or *i*-octane, it was completely converted to the pure *trans*-isomer **7** as a crystalline solid.

This observation was intriguing and led us to conduct some equilibration experiments for the mixture of **7**/**11**/**12** in solution. Pure *trans*-imidazolidinone **7** was dissolved in deuteriated solvents such as $CDCl_3$, benzene-d_6, DMSO-d_6, and MeOH-d_4. These samples were allowed to equilibrate at ambient temperature and led to the formation of four related compounds, which are the *trans*- and *cis*-imidazolidinones **7** and **11**, acyclic Schiff base **12**, and some hydrolyzed free amine **6** (Table 1). The ratio of **7**/**11**/**12**/**6** was monitored by ^{1}H NMR spectroscopy over a period of time. The results are summarized in Table 1.

It is interesting that pure *trans*-**7** was equilibrated to a mixture of **7**/**11**/**12**/**6** in these solutions over time. However, both the equilibrium ratios and the rates of equilibration were different in different solvents. In polar solvents, the ratios of **7**/**11** (91:9 in DMSO-d_6 and 80:20 in MeOH-d_4) were reached instantaneously and no change of this ratio was observed over days. In less polar solvents $CDCl_3$ and benzene-d_6, the rate of equilibration was much slower. The amount of *cis*-isomer **11** was slowly increased, in chloroform **7**/**11** to 77:23 at 22 days and in benzene **7**/**11** to 88:12 at 3 days. Most importantly, these apparent equilibration data indicated that there is no overwhelming thermodynamic factor in favor of the *trans*-isomer **7** over the *cis*-isomer **11**. Therefore, formation of the single *trans*-isomer **7** during the crystallization of a mixture of *trans*- and *cis*-imidazolidinones **7** and **11** in non-polar solvents such as alkanes is not attributable to the inherent thermodynamic properties of these *trans*/*cis* isomers. Instead, the phenomenon observed in this case is more consistent with a crystallization-driven dynamic transformation,[20] in which the crystallinity of the *trans*-isomer **7** is the driving force for the stereoselective formation of the single diastereomer. The possible factors contributing to the stereoselective formation of *trans*-**7** include the different crystallinity of the respective compounds **7**/**11**/**12** and the lower pK_a of the NH group in the *N*-aryl amide **6** in comparison with those of the corresponding *N*-methyl amide, which facilitates the equilibration among **7**/**11**/**12**.

After the unique behavior of these *trans*- and *cis*-isomers **7** and **11** was identified, the desired *trans* isomer **7** was easily formed stereoselectively. A solution of amino amide **6** and pivalaldehyde in toluene was heated at 50°C and a mixture of *trans*- and *cis*-**7** and **11**, and Schiff base **12** was obtained. Regardless of the **7**/**11**/**12** ratio in this mixture, pure *trans*-**7** was selectively precipitated as a crystalline solid from *i*-octane (Scheme 2). It should be noted that this chiral template **7** was the

Table 1. Equilibration of *trans*-imidazolidinone **7** in organic solvents

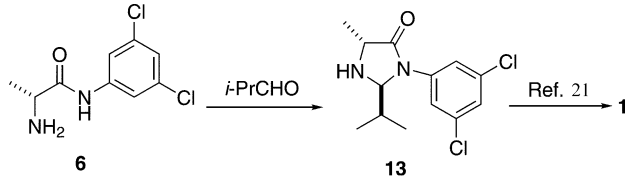


7 **11** **12**

Entry	Solvent	Time	**7** (%)	**11** (%)	**12** (%)	**6** (%)
1	$CDCl_3$	0	100	0	0	0
2		3 h	95.0	0.5	4.0	0.5
3		6 h	90.0	1.0	8.0	1.0
4		22 days	48.0	14.0	29.0	9.0
5	C_6H_6-d_6	0	100	0	0	0
6		5 h	93.4	0.2	4.7	1.7
7		2 days	68.1	4.8	23.5	3.6
8		3 days	61.0	8.3	26.8	3.9
9	DMSO-d_6	0 to days	82.0	8.0	10.0	0
10	MeOH-d_4	0 to days	69.0	17.1	13.9	0

first isolated crystalline intermediate and it served as the first purification point from the beginning of the synthesis and the overall yield of **7** was 66% for the first three steps from **4**.

Interestingly, when isobutyraldehyde was used to replace the much more expensive pivalaldehyde, similar phenomenon in terms of stereoselective formation of the *trans*-isomer **13** was also observed (Scheme 3).[21] Even though such a change may seem trivial, it has not been previously documented in the literature that aldehyde bearing α-hydrogen can be used in this protocol.



Scheme 3. Isobuyyraldehyde-derived *trans*-imidazolidinone **13**.

2.3. Synthesis of BIRT-377

The enantiomerically pure *trans*-imidazolidinone **7** was *N*-protected (TFAA, TEA, toluene, rt, 98% yield). The resulting imidazolidinone **8** was deprotonated at −5°C and the resulting enolate was alkylated with bromobenzyl bromide from the opposite face to the *tert*-butyl group to give α.α-disubstituted imidazolidinone **9** as a single diastereomer.[22]

As reported by Seebach and others,[8–18] hydrolysis of dialkylated imidazolidinone **9** was not trivial, presumably due to steric hindrance of the substrate and its low solubility in aqueous media. The substrate remained unreacted under most of the traditional hydrolysis conditions (aqueous HCl/MeOH at reflux; aqueous NaOH/MeOH at reflux; or H_2NNH_2/EtOH at reflux). After considerable efforts, a practical one-pot hydrolysis procedure was developed. The trifluoroacetamide moiety of **9** was first hydrolyzed (1.5 equiv. of $BnNMe_3OH$, 2.0 equiv. of 50% NaOH, rt to 40°C, dioxane) to give a mixture of the corresponding partially hydrolyzed *N*-unsubstituted aminal of **9**, Schiff base of **2**, and **2** itself. Subsequent direct addition of 6 M HCl to the above mixture resulted in complete hydrolysis to afford amino amide **2** in 96% overall yield from **8**. The smooth hydrolysis of **9** by $BnNMe_3OH$ may be attributed to its unique features acting as a potent base and a phase transfer catalyst.

Treatment of crude **2** with methyl chloroformate in the presence of triethylamine gave crude hydantoin **10**. Methylation [$LiN(TMS)_2$, MeI, DMF, rt] of the crude **10** followed by a single crystallization of the crude product from EtOAc/hexane afforded BIRT-377 **1** in 62% overall yield from **2**. The drug substance possessed excellent chemical purity (>99.9% by HPLC[23]) and enantiomeric excess (>99.9% ee by chiral HPLC[24]).

3. Conclusion

In conclusion, an efficient enantiospecific synthesis of a cell adhesion inhibitor BIRT-377 **1** has been achieved in 38% overall yield in eight steps. The key transformations involve the stereoselective formation of the *trans*-imidazolidinone **7**, subsequent alkylation, and the efficient hydrolysis of **9**. The crude intermediates were used directly in all steps in this synthetic scheme and there was no purification step needed in the entire sequence. A single crystallization of the final product gave the drug substance in high purity. This process is practical, robust, and cost-effective, and it has been successfully implemented in the pilot plant to produce multikilogram quantities of BIRT-377 **1**.

4. Experimental[25]

4.1. (1*R*)-[1-(3,5-Dichloro-phenylcarbamoyl)-ethyl]-carbamic acid *tert*-butyl ester 5

A solution of D-*N*-Boc-alanine **4** (8.83 kg, 46.7 mol) in 90 L of anhydrous THF was prepared in a 50 gallon reactor. The reaction mixture was cooled to approximately −15°C and *N*-methyl-morpholine (4.96 kg, 49.0 mol) was added at a rate to keep the internal temperature at −15°C. Isobutyl chloroformate (6.67 kg, 48.8 mol) was added into the reaction mixture over a 45 min period to keep the internal temperature at −15°C. The resulting mixture was then agitated at this temperature for 30 min. A solution of 3,5-dichloroaniline (7.57 kg, 46.7 mol) in 25 L of THF was added at a rate to keep the internal temperature between −15°C and −20°C over 30 min. THF (5 L) was used to rinse the transfer line and added to the reaction mixture. The reaction mixture was then warmed to 20°C over 6 h. The resulting suspension was filtered and the solids were washed with THF (2×8 L). The combined filtrate was stored in a cold room (∼4°C).

The above procedure was repeated in the identical manner to produce another batch of this compound. The combined filtrate from these two batches was concentrated under reduced pressure (∼200 torr) with jacket temperature at 30–40°C. After collecting approximate 235 L of the distillate, MeOH (70 L) was added to the mixture. The mixture was subjected to vacuum distillation (jacket temp. <60°C). After 50 L of the distillate were collected, the crude product **5** solution was transferred to a container with aid of 20 L of MeOH (total weight: 73.4 kg) and used for next step directly. An analytically pure sample was obtained by flash chromatography. Mp 146°C; $[\alpha]_D^{20} = +72.0$ (*c* 1.07, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.81 (br.s, 1H), 7.46 (s, 2H), 7.06 (s, 1H), 4.93 (br. d, $J = 6.6$ Hz, 1H), 4.28 (br. dt, $J = 7.0$ Hz, 1H), 1.47 (s, 9H), 1.42 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 156.5, 139.6, 134.9, 123.8, 117.6, 81.0, 50.9, 17.4. Anal. calcd for $C_{14}H_{18}Cl_2N_2O_3$: C, 50.46; H, 5.44; N, 8.41. Found: C, 50.40; H, 5.42; N, 8.27.

4.2. (2*R*)-2-Amino-*N*-(3,5-dichlorophenyl)-propionamide 6

Hydrochloric acid (12 M, 39 L, 468 mol) was charged into a 50 gallon reactor and diluted with water (39 L) and MeOH (20 L). The internal temperature rose to ~30°C. The above solution of crude amide **5** (73.4 kg, max. 93.4 mol) obtained from the last step was added into the reaction mixture in two portions over 1 h and gas evolution started at this point. The reactor jacket temperature was set to 25°C and the reaction mixture was agitated for 18 h. The reaction mixture was then subjected to vacuum distillation with jacket temperature <60°C. After ~70 L of distillate was collected, the reaction mixture was cooled to ~15 to 20°C and 60 L of toluene was added. 50% NaOH solution (~40 kg) was added at a rate to keep the internal temperature below 25°C until the pH reached 13–14 in the aqueous layer. The layers were separated and the aqueous layer was extracted with toluene (2×35 L). The combined organic layers were washed with water (2×30 L) and concentrated under reduced vacuum (jacket temp. <50°C). After ~110 L of distillate was collected, the crude product **6** solution was transferred to a container with aid of 10 L of toluene (total weight: 40.3 kg) and used for next step directly. Analytically pure sample was obtained by flash chromatography. Oil; $[\alpha]_D^{20}=+0.4$ (*c* 1.10, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.66 (br. s, 1H), 7.56 (s, 2H), 7.06 (s, 1H), 3.60 (q, $J=7.0$ Hz, 1H), 1.62 (br. s, 2H), 1.41 (d, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0, 139.5, 135.1, 123.8, 117.4, 51.0, 21.4. Anal. calcd for $C_9H_{10}Cl_2N_2O$: C, 46.37; H, 4.32; N, 12.02. Found: C, 46.14; H, 4.32; N, 11.89.

4.3. (2*S*,5*R*)-2-*tert*-Butyl-3-(3,5-dichlorophenyl)-5-methyl-imidazolidin-4-one 7

A solution of the crude amino amide **6** (40.3 kg, max. 93.4 mol) was added into a 50-gallon reactor and diluted with 48 L of toluene. A solution of pivalaldehyde (8.17 kg, 94.86 mol) in 10 L of toluene was added to the reaction mixture over 30 min and the internal temperature rose from 21°C to 27°C. The transfer line was rinsed with 15 L of toluene. After the reaction mixture was heated to 50°C and agitated at this temperature for ~20 h, the reaction mixture was subjected to vacuum distillation (jacket temp. <65°C) to collect ~95 L of distillate over ~4 h. The vacuum was released and *i*-octane (77 L) was added to the mixture. The reaction mixture was cooled to ~0°C and stirred for 2 h during which crystalline solids were formed in the reaction mixture. The solids were collected by filtration and the cake was rinsed with *i*-octane (2×12 L) to give 17.65 kg of pure **7** as first crop. The combined filtrate was concentrated to dryness and then treated with 16 L of *i*-octane. The crystalline solids were formed and filtered. The solids were rinsed with *i*-octane (2×1.5 L) to give 0.91 kg of pure **7** after drying. The total yield of **7** was 18.56 kg (66%). Mp 126°C; $[\alpha]_D^{20}=-12.1$ (*c* 1.30, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32 (s, 2H), 7.19 (s, 1H), 4.85 (s, 1H), 3.76 (q, $J=6.8$ Hz, 1H), 2.05 (br. s, 1H), 1.36 (d, $J=6.8$ Hz, 2H), 0.84 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.3, 140.5, 135.1, 126.0, 122.8, 82.0, 55.5, 39.5, 26.1, 18.2. Anal. calcd for $C_{14}H_{18}Cl_2N_2O$: C, 55.82; H, 6.02; N, 9.30. Found: C, 55.80; H, 6.05; N, 9.15.

4.4. (2*R*,5*R*)-2-*tert*-Butyl-3-(3,5-dichlorophenyl)-5-methyl-1-trifluoroacetyl-imidazolidin-4-one 8

Imidazolidinone **7** (18.3 kg, 60.7 mol) was charged into a 50 gallon reactor followed by 130 L of toluene. The resulting solution was subjected to vacuum distillation to collect ~20 L of distillate in order to ensure the dryness of the material. The reaction mixture was cooled to 0°C and triethylamine (7.07 kg, 69.9 mol) was added over 15 min at this temperature. Trifluoroacetic anhydride (14.68 kg, 69.9 mol) was added to the reaction mixture over 1 h at a rate to keep the internal temperature at −5°C. The reaction mixture was agitated at ~0°C for 1 h and then warmed to 20°C over 1 h. The reaction was complete and the reaction mixture was cooled to 10°C and water (20 L) was added at this temperature. The layers were separated and the organic layer was washed with water (20 L and then 10 L). The organic layer was concentrated under reduced pressure (jacket temp. <65°C). After ~110 L of distillate was collected. *i*-Octane (150 L) was added and the distillation continued until ~100 L of distillate was collected. The crystalline solids were collected by filtration and washed with *i*-octane (2×12 L) to give 22.30 kg of pure **8**. Concentration of the filtrate to dryness and treating the residue with 5 L of *i*-octane afforded additional 1.20 kg of **8**. The total yield of **8** was 23.50 kg (98%). Mp 131°C; $[\alpha]_D^{20}=+119.1$ (*c* 1.25, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.48 (s, 2H), 7.28 (s, 1H), 6.20 (br. s, 1H), 4.52 (q, $J=6.6$ Hz, 1H), 1.68 (d, $J=6.3$ Hz, 3H), 0.87 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.5, 138.6, 135.6, 127.0, 122.2, 117.3, 114.5, 79.0, 57.8, 42.1, 26.3. Anal. calcd for $C_{16}H_{17}Cl_2F_3N_2O_2$: C, 48.38; H, 4.31; N, 7.05. Found: C, 48.31; H, 4.36; N, 6.79.

4.5. (2*R*,5*R*)-5-(4-Bromo-benzyl)-2-*tert*-butyl-3-(3,5-dichlorophenyl)-5-methyl-1-trifluoroacetyl-imidazolidin-4-one 9

A solution of **8** (12.74 kg, 32.07 mol) in 48 kg of anhydrous THF was prepared in a 50-gallon reactor. The solution was subjected to vacuum distillation to collect ~20 L of distillate to ensure the anhydrous conditions. The reaction mixture was cooled at −5°C to +5°C and a solution of LiHMDS (1.0 M, 29.65 kg, 33.3 mol) was added at this temperature over 45 min. After the addition, the reaction mixture was agitated at −5°C to 0°C for 1 h. A solution of 4-bromobenzyl bromide (8.34 kg, 33.4 mol) in 18 L of THF was added at −5°C to 0°C over 40 min. The reaction mixture was agitated at this temperature for 2 h. Saturated ammonium chloride solution (9 L) was added to quench the reaction. The reaction mixture was subjected to vacuum distillation. After collecting ~55 L of distillate, a slurry was formed in the mixture and water (40 L) was added to dilute the slurry. Additional 30 L of distillate was collected by vacuum distillation. At this point, toluene

(50 L) was added to the mixture for extraction. The layers were separated, the organic layer was washed with water (40 L), and concentrated under reduced pressure. After collecting ~30 L of distillate, the mixture became a slurry. Toluene (20 L) was added to dissolve the slurry and the solution was then transferred into a container with aid of 12 L of toluene. The total weight of this solution was 75.45 kg and this material was used for next step directly. The crude alkylated product **9** was estimated to be 17.50 kg (96%). Analytically pure sample was obtained by flash chromatography. Mp 164°C; $[\alpha]_D^{20}=+89.8$ (*c* 1.01, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) two rotamers δ 7.23–7.29 (m, 3H), 6.93 (s, 1H), 6.76–6.79 (m, 3H), 5.66 (s, 0.4H), 5.40 (s, 0.6H), 3.72 (d, $J=14$ Hz, 0.6H), 3.26 (d, $J=14$ Hz, 0.4H), 3.08 (t, $J=15$ Hz, 1H), 1.96 (s, 0.6H), 1.93 (s, 0.4H), 0.86 (s, 6.4H), 0.73 (s, 3.6H). Anal. calcd for $C_{23}H_{22}BrCl_2F_3N_2O_2$: C, 48.79; H, 3.92; N, 4.95. Found: C, 49.02; H, 3.95; N, 4.88.

4.6. (2*R*)-2-Amino-3-(4-bromophenyl)-*N*-(3,5-dichlorophenyl)-2-methyl-propionamide 2

A solution of **9** in toluene (75.45 kg, max. 32.07 mol) from last step was transferred into a 50-gallon reactor with aid of 15 L of toluene. The solution was subjected to vacuum distillation (jacket temp. <65°C) to collect ~80 L of distillate. At this point, 1,4-dioxane (80 L) was added and distillation continued to collect ~16 L of distillate. At 20°C, an aqueous 40% (w/w) $BnMe_3NOH$ (20.15 kg, 48.2 mol) was added to the reaction mixture followed by 50% NaOH (5.13 kg, 64 mol). The reaction mixture was then heated to 40°C and vigorously agitated at this temperature for 12 h. An HCl solution (prepared by mixing 19.40 kg of conc. HCl and 10 L of water) was added to the reaction mixture. The reaction mixture was then heated to 50°C and stirred for 4 h. The reaction mixture was subjected to vacuum distillation (jacket temp. <65°C). After ~65 L of distillate was collected, toluene (50 L) was added and the mixture was cooled to ~10°C. A 50% NaOH solution was added at a rate to keep the internal temperature below 20°C until the pH of aqueous layer reached 13–14 (~10.5 kg of 50% NaOH was used). The layers were separated, the organic layer was washed with water (2×40 L) and concentrated under reduced pressure to give 13.33 kg of crude **2** which contained 7% by weight of residual toluene. The yield of **2** was 12.4 kg (96%). Analytically pure sample was obtained by flash chromatography. Mp 81°C; $[\alpha]_D^{20}=+176.6$ (*c* 1.07, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.74 (br. s, 1H), 7.52 (d, $J=1.9$ Hz, 2H), 7.41 (d, $J=8.3$ Hz, 2H), 7.08 (t, $J=1.9$ Hz, 1H), 7.05 (d, $J=8.3$ Hz, 2H), 3.47 (d, $J=13$ Hz, 1H), 2.61 (d, $J=13$ Hz, 1H), 1.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.7, 139.4, 135.3, 135.1, 131.8, 131.6, 123.9, 121.2, 117.5, 58.8, 45.6, 28.0. Anal. calcd for $C_{16}H_{15}BrCl_2N_2O$: C, 47.79; H, 3.76; N, 6.97. Found: C, 47.89; H, 3.81; N, 6.75.

4.7. (5*R*)-5-(4-Bromobenzyl)-3-(3,5-dichlorophenyl)-5-methyl-imidazolidine-2,4-dione 10

A solution of intermediate **2** (7.90 kg, 19.65 mol) in dichloromethane (72 L) was concentrated under reduced pressure to remove dichloromethane, which was replaced with THF. The resulting solution of **2** in THF (40 L) was cooled to 10°C and triethylamine (4.32 kg, 42.7 mol) was slowly added. The internal temperature was then adjusted to 0°C and methyl chloroformate (3.054 kg, 32.3 mol) was added at a rate to keep the internal temperature below 10°C. The temperature was then increased and the mixture was stirred at reflux (68°C) for 14 h and quenched with water (3.5 L). The mixture was then concentrated under reduced pressure keeping the jacket temperature at 57–60°C until approximately 43 L of distillate was collected. Water (28 L) was added and the internal temperature was adjusted to 20–23°C. The product was extracted with dichloromethane (2×19 L), the combined organic portions were washed with water (14 L) and concentrated under reduced pressure. Methanol (30 L) was added and the mixture was again concentrated under reduced pressure keeping the jacket temperature at 60–65°C until 43 L of distillate was collected. Afterwards, triethylamine (4.34 kg, 42.9 mol) and methanol (19 L) were added and the mixture was stirred and heated at reflux for 14 h. The mixture was concentrated under reduced pressure keeping the jacket temperature at 60°C. After 39 L of distillate were collected, the distillation was stopped and mixture was cooled to 20°C. The total weight of the crude **10** solution was 20.05 kg and used for next step directly. An analytically pure sample was obtained by flash chromatography. foam; $[\alpha]_D^{20}=-120.0$ (*c* 1.02, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, $J=8.3$ Hz, 2H), 7.34 (s, 1H), 7.06 (d, $J=8.3$ Hz, 2H), 6.98 (s, 2H), 6.84 (br. s, 1H), 3.13 (d, $J=13$ Hz, 1H), 2.91 (d, $J=13$ Hz, 1H), 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.1, 154.7, 135.2, 132.8, 132.7, 131.7, 128.5, 124.5, 122.0, 62.7, 43.5, 23.3. Anal. calcd for $C_{17}H_{13}BrCl_2N_2O_2$: C, 50.46; H, 5.44; N, 8.41. Found: C, 50.40; H, 5.42; N, 8.27.

4.8. (5*R*)-5-(4-Bromobenzyl)-3-(3,5-dichlorophenyl)-1,5-dimethyl-imidazolidine-2,4-dione 1

The above solution containing crude hydantoin **10** (20.05 kg, max. 19.65 mol) was concentrated under reduced pressure to remove methanol. Toluene (60 L) was added and distilled to remove the residual methanol. DMF (25 L) was added and the internal temperature was adjusted to 7.5±2.5°C as lithium bis(trimethylsilyl)amide (21.03 kg, 1.0 M in THF, 20.4 mol) was slowly added. The internal temperature was adjusted to 15±2°C and a solution of iodomethane (3.82 kg, 29.9 mol) in DMF (5.0 L) was slowly added at a rate to keep the internal temperature at 15–20°C. The mixture was then stirred at 20°C for 3 h. The reaction was then quenched with water (105 L) at 25°C. The product was extracted from the above aqueous mixture with ethyl acetate (3×15 L) and the combined organic layers were then washed with water (60 L). The resulting solution was filtered to remove any solid particle The resulting solution was concentrated under reduced pressure with a jacket temperature at 55-60°C until 32 L of distillate was collected. Crystallization was carried

out by heating the above ethyl acetate solution of the product to reflux and then slowly adding hexane (60 L). The temperature of the resulting slurry was adjusted to 0°C and the mixture was stirred for 1 h. The product was collected by filtration and the filter cake was washed twice with a 4:1 ethyl acetate/hexane solution and once with hexane (6 L). The crystalline material 1 was then dried in a vacuum oven at ambient temperature for 24 h to afford 5.35 Kg (62% yield from 2) of BIRT-377 **1** as a white solid. Both chemical purity and enantiomeric excess were >99.9%.[23,24] Mp 135–136°C; $[\alpha]_D^{25}=+127.3$ (*c* 0.78, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (br. d, $J=8.3$ Hz, 2H), 7.28 (t, $J=1.8$ Hz, 1H), 6.94 (br. d, $J=8.3$ Hz, 2H), 6.84 (d, $J=1.8$ Hz, 2H), 3.08 (d, $J=14$ Hz, 1H), 3.06 (s, 3H), 2.96 (d, $J=14$ Hz, 1H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.3, 153.4, 135.0, 132.9, 132.8, 131.8, 131.0, 128.3, 124.4, 121.9, 65.6, 40.6, 25.2, 21.0. Anal. calcd for $C_{18}H_{15}BrCl_2N_2O_2$: C, 48.90; H, 3.42; N, 6.34; Br, 18.07; Cl, 16.04. Found: C, 48.98; H, 3.40; N, 6.38; Br, 18.33; Cl, 16.07.

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23. HPLC column, Novapak C18 (30 cm×3.0 mm); mobile phase, 70% MeCN in aqueous 0.1% TFA; flow rate, 1.0 mL/min; ambient temperature.
24. Chiral HPLC column, Chiralpak AD (30 cm×4.6 mm); mobile phase, 5% EtOH and 0.5% Et_2NH in hexane; flow rate, 1.0 mL/min; ambient temperature; retention time, (+)-**1** (BIRT-377), 11.38 min; (−)-**1**, 13.36 min.
25. For general experimental procedure, see: Ref. 21.