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Self-Regeneration of Stereocenters: A Practical Enantiospecific Synthesis of LFA-1 Antagonist BIRT-377

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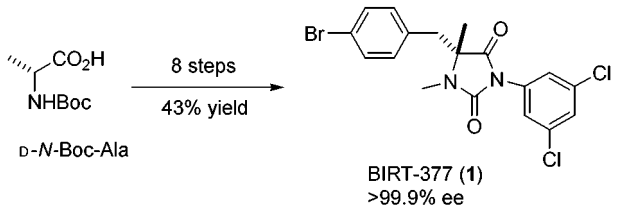
ABSTRACT



An efficient enantiospecific synthesis of the LFA-1 antagonist BIRT-377 has been achieved in 43% overall yield in eight steps. The key transformations involve the stereospecific 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).

In our drug discovery program, a series of *N*-aryl-substituted-hydantoins were identified as the first small molecule, nonpeptidic antagonists of the binding of intercellular adhesion molecules such as ICAM-1 with the leukointegrin LFA-1.[1,2] These LFA-1 antagonists have potential therapeutic utilities in treatment of a variety of inflammatory and immune disorders. In particular, BIRT-377 (**1**, Figure 1) was selected

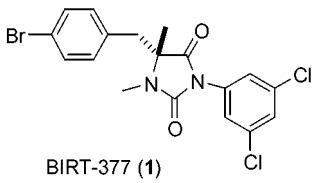
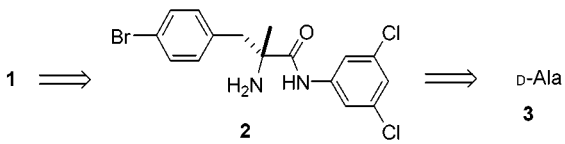


Figure 1.

as a candidate for further preclinical studies. Therefore, a large quantity of this drug substance was needed to support development activities.

The key structural feature of BIRT-377 (**1**) is the *N*-aryl-substituted-hydantoin bearing a quaternary stereogenic center. In our retrosynthetic analysis (Scheme 1), the hydantoin ring

Scheme 1



can be synthesized by cyclization of the corresponding acyclic α-substituted amino acid amide (**2**), which is derived from D- or L-alanine. In the literature, a variety of methodologies have been reported for the asymmetric synthesis of quaternary α-amino acids, and most recently this important

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(2) Woska , J. R., Jr.; Morelock, M. M.; Jeanfavre, D. D.; Bormann, B.-J. *J. Immunol.* **1996**, *156*, 4680.

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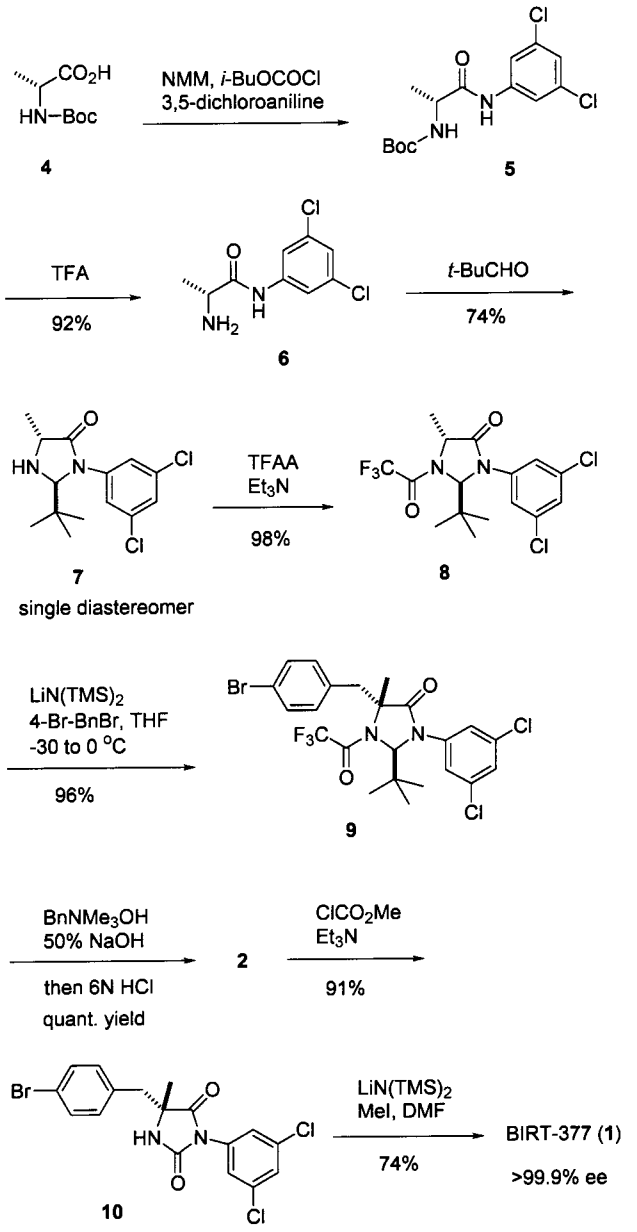
subject has been extensively reviewed by Cativiela.[3] Of these known methods, Seebach's self-regeneration of stereocenters principle[4] in preparation of α-substituted amino acid derivatives was most attractive to us due to its simplicity in terms of the easy access of the chiral template imidazolidinones (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 used, especially for industrial large-scale production, mainly due to the harsh conditions (aqueous HCl, 150−220 °C) required to hydrolyze the resulting 5,5-disubstituted imidazolidinone,[5−15] as well as its modest diastereoselectivities (70−90% ds) in the formation of the imidazolidinone template.[5] In this Letter, we wish to report an efficient enantiospecific synthesis of BIRT-377 (**1**) based on a modification of Seebach's strategy in which we extend the original protocol to achieve complete (>99.9%) overall stereoselectivity.

During our survey in the literature, it was found that the stereoselective formation of either the *trans* or *cis* imidazolidinones by Seebach's method was solely applied to the α-amino *N*-methyl amides as substrates, and other substitution (such as *N*-aryl) on the amide nitrogen atom was not reported.[3,4] 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.

The synthesis of BIRT-377 (**1**) is outlined in Scheme 2. The commercially available D-*N*-Boc-alanine (**4**) reacted with 3,5-dichloroaniline via a mixed anhydride intermediate (*i*-BuOCOCl, *N*-methylmorpholine, −10 °C to rt, THF) to give amide **5**. Deprotection of the crude amide **5** by TFA in dichloromethane afforded amino *N*-aryl amide **6** in 92% yield over two steps. This crude product was pure enough to carry on to next step without any purification.

In early laboratory studies, amino amide **6** was treated with pivalaldehyde in refluxing pentane in a manner similar to that described in Seebach's original procedure. A crystalline solid was directly formed from the reaction mixture and identified as the desired *trans* imidazolidinone **7**[16] 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

Scheme 2



base intermediate was actually obtained in this step and then cyclized only when treated with either HCl in MeOH at 0 °C or $(PhCO)_2O$ at 130 °C to generate stereoselectively either *trans* or *cis* imidazolidinones in 90% ds and 71% ds, respectively.[5] Later (Scheme 3), it was found that a mixture of *trans*/*cis* imidazolidinone **7**/**12** and Schiff base **11**, produced by treating amino amide **6** with pivalaldehyde in toluene or dichloromethane, was completely converted to the pure *trans* isomer **7** as a crystalline solid either when the neat mixture stood over a period of time, or when the mixture

(3) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517.
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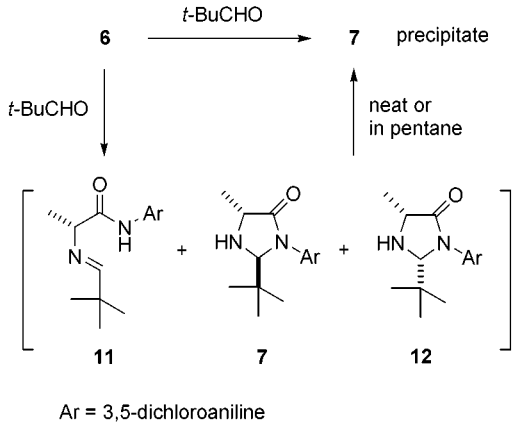
(14) Jaun, B.; Tanaka, M.; Seiler, P,; Kuehnle, F. N. M.; Braun, C.; Seebach, D. *Liebigs Ann. Chem.* **1997**, 1697.
(15) Damhaut, P.; Lemaire, C.; Plenevaux, A.; Brihaye, C.; Christiaens, L.; Comar, D. *Tetrahedron* **1997**, *53*, 5785.

(16) The corresponding *cis* isomer of **8** was independently prepared by deprotonation of *trans* **8** with $LiN(TMS)_2$ at 0 °C followed by quenching the enolate with saturated aqueous NH_4Cl at the same temperature. The *trans*/*cis* stereochemistry was determined by NOESY experiment. The chemical shifts for the *N*,*N*-acetal methine protons at the C-3 position in *trans* and *cis* **8** are characteristically different: δ 6.39 ppm (for *trans* isomer); δ 6.20 ppm (for *cis* isomer).

Scheme 3



of **7**/**12**/**11** was stirred in a nonpolar solvent such as pentane. These experiments suggest that the crystallinity of the *trans* **7** is the driving force for the stereospecific formation of a single diastereomer. The mechanistic aspects of these observations are not clearly understood at this moment and will be the subject of future investigations. The possible factors contributing to the stereospecific formation of **7** include the different crystallinity of the respective compounds **7**/**12**/**11** and the lower pK_a of the NH group in the *N*-aryl amide **11** in comparison with those of the corresponding *N*-methyl amide, which may facilitate the equilibration among **7**/**12**/**11**.

After protection of **7** (TFAA, Et_3N, 0 °C to rt, CH_2Cl_2, 98% yield), crude **8** in THF was deprotonated with $LiN(TMS)_2$ at −30 to −20 °C and then the resulting enolate was alkylated at −30 to 0 °C with 4-bromobenzyl bromide from the opposite face of the *tert*-butyl group to give 5,5-disubstituted **9** as a single diastereomer[17] in 96% yield.

As reported by Seebach and others,[5−15] hydrolysis of dialkylated imidazolidinone **9** was not trivial, presumably due to the hindrance of the substrate. The substrate remained intact under most of the traditional hydrolysis conditions (aqueous HCl/MeOH, reflux; aqueous NaOH/MeOH, reflux; or H_2NNH_2/EtOH, reflux). After considerable effort, a practical one-pot hydrolysis procedure was developed. The trifluoroacetamide group 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 acetal of **9**, Schiff base of **2**, and **2** itself. Subsequent direct addition of 6 N HCl to the above mixture resulted in complete hydrolysis to afford amino amide **2** in quantitative yield. 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** in 91% yield. Methylation [$LiN(TMS)_2$, MeI, DMF, rt] of **10** followed by a single crystallization of the crude product from EtOAc/hexane afforded BIRT-377 (**1**) in 74% yield. This drug substance possessed excellent chemical purity (>99.9% by HPLC)[18] and optical purity (>99.9% ee by chiral HPLC).[19]

In summary, an efficient enantiospecific synthesis of the LFA-1 antagonist BIRT-377 (**1**) has been achieved in 43% overall yield in eight steps. The key transformations involve the stereospecific formation of the *trans* imidazolidinone **7**, subsequent alkylation, and the efficient hydrolysis of **9**. It should be noted that 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**). To the best of our knowledge, this is the first reported example to utilize Seebach's self-regeneration of stereocenters principle to synthesize α,α-disubstituted amino acid derivatives on an industrial scale.

Further reports related to this subject will address the experimental details of the overall process, the study of kinetic/thermodynamic factors affecting the diastereoselectivity in the formation of **7**, and the application of highly crystalline template **7** to the general synthesis of α,α-disubstituted amino acids.

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Supporting Information Available: Spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http:/pubs.acs.org.

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(17) In ^1H NMR spectrum, the disubstituted imidazolidinone **9** exists as a mixture of two rotamers, as reported by Seebach. See ref 4 and cited references.

(18) 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.

(19) 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.