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Regiocontrolled synthesis of highly-functionalized fused imidazoles: a novel synthesis of second generation LFA-1 inhibitors

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Abstract—A new and reliable route to a new class of LFA-1 inhibitors such as (**2**) has been developed. A key aspect of this route is the transformation of amino amide **5** into iodide **3** in four steps. Iodide **3** is a key advanced intermediate used in the synthesis of all second-generation 1*H*-imidazo[1,2-α]imidazol-2-one LFA-1 inhibitors.

Lymphocytes are cells of the immune system that must balance their dual role of surveillance and responsiveness as they patrol the body in search of foreign antigens. In their surveillance role, they must circulate freely in the blood and lymph in a non-adherent (unactivated) state. In the presence of a foreign antigen, however, these cells must become activated quickly, cross membrane walls, congregate at the site of infection and adhere to and destroy the invading cells bearing the foreign antigen. The interactions between cells that direct lymphocyte activation, migration and localization are mediated by cell-surface molecules known as adhesion receptors.[1] LFA-1 (lymphocyte function-related antigen) belongs to the integrin family of receptors associated with the role of regulating adhesion and migration of lymphocytes, and the counter receptor to LFA-1 on target cells is recognized to be ICAM-1 (intercellular cell adhesion molecule).

Blocking the protein–protein interaction of cell adhesion molecules such as LFA-1 to ICAM-1 has the potential to benefit patients suffering from immune disorders. Accordingly, a program to find small molecule inhibitors of LFA-1 was initiated by our discovery team and resulted in the finding of series of hydantoins inhibitors such as BIRT377 (**1**).[2] Further SAR studies led to a series of structurally related 1*H*-imidazo[1,2-α]imidazol-2-ones such as compound **2** with improved pharmacological properties (Fig. 1).[3]

The selection **2** and related compounds for further pre-clinical studies created the need to develop a safe, robust, reliable and scalable process suitable for the synthesis of large amounts of these compounds. The development of such process presented us with a number of challenges, as certain aspects of the original discovery route were not ideal for scale-up due to the use of potentially dangerous azide reagents and the extensive use of silica gel chromatography.[4] In addition, a key step of the discovery route involved the direct iodination of **4** to afford **3**, and this reaction was not regioselective and resulted in the formation of a mixture of regioisomers that had to be separated by chromatography.[4,19]

We focused our attention on the highly functionalized vinyl iodide **3** (Scheme 1), as this compound is a key precursor to all second generation 1*H*-imidazo[1,2-α]imidazol-2-one LFA-1 inhibitors such as **2**. Therefore, a safer, efficient and scalable route to iodide **3** would not only make it possible to synthesize large

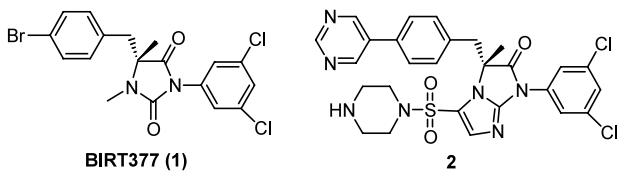

Figure 1.

Keywords: imidazoles; LFA-1 inhibitors; vinyl iodides.
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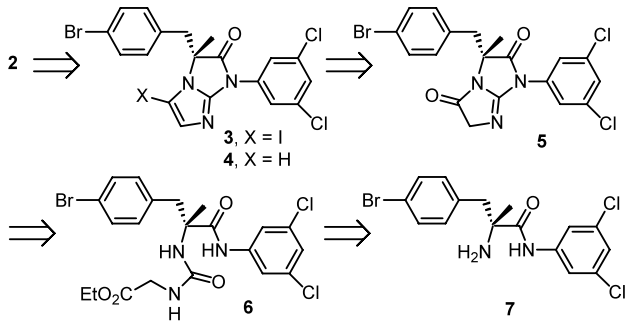
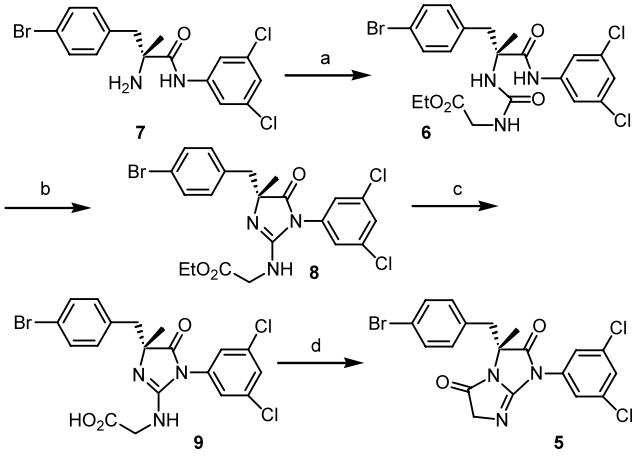


Scheme 1. Retrosynthesis analysis of iodides **3** and **2**.

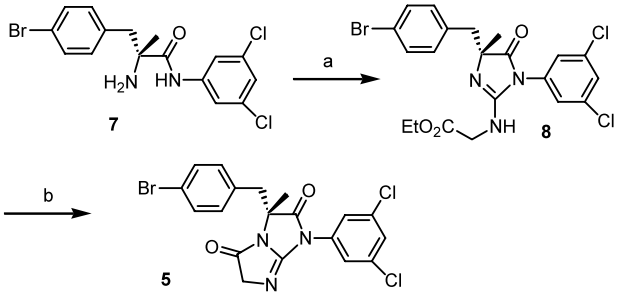
amounts of compounds such as **2**, but it would also facilitate the synthesis of analogs and expedite SAR studies. Key objectives of our new synthesis of **3** (Scheme 1) would be to eliminate the use of azide reagents and to replace the non-selective iodination of **4**. Accordingly, our proposed synthesis of **3** is shown in Scheme 1. Iodide **3** would be synthesized from intermediate **5**, which has the same oxidation state as **3**. Intermediate **5** would be prepared from intermediate urea **6**, and **6** would come from amino amide **7**, for which a well-established synthetic route from D-alanine already exists.[5]

Our first generation synthesis of intermediate **5** is shown in Scheme 2. Treatment of **7** with commercially available ethyl isocyanoacetate afforded urea **6** in excellent yield as a crystalline compound. Dehydration of urea **6** upon treatment with $Ph_3P{\cdot}CCl_4/Et_3N$[6] gave intermediate **8** in good yield, presumably through a transient carbodiimide that cyclizes spontaneously.[7] Subsequent hydrolysis of **8** with LiOH gave carboxylic acid **9**, which was converted to its acyl chloride with oxalyl chloride and triethylamine and cyclized under the reaction conditions to afford **5** in 57% yield.

Further optimization led to a more streamlined synthesis of **5** (Scheme 3). We were able to combine the



Scheme 2. *Reagents and conditions*: (a) ethyl isocyanoacetate, CH_2Cl_2, rt, 2.5 h; (b) Ph_3P, CCl_4, Et_3N, rt, 12 h (81%); (c) 1 M LiOH, THF, rt, 1 h; (d) $(COCl)_2$, Et_3N, THF, –20°C (57% for two steps).



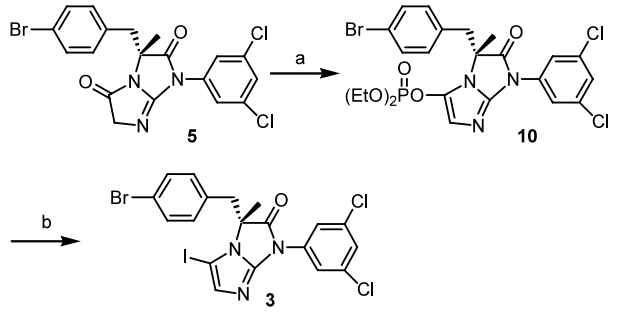
Scheme 3. *Reagents and conditions*: (a) i. ethyl isocyanoacetate, CH_2Cl_2, rt, 2.5 h; ii. Ph_3P, CCl_4, Et_3N, rt, 12 h (81%); (b) Me_3Al, Ph_3PO, toluene, 25°C (91%).

two-step synthesis of **8** into a one-pot procedure without isolation of **6**, and accomplished the direct synthesis of **5** from **8** without going through intermediate **9**. Accordingly, treatment of **7** with ethyl isocyanoacetate followed by in situ dehydration and cyclization of the intermediate urea (**6**) afforded **8** in 81% yield. Heating **8** in the presence of acids or bases failed to produce **5**, but intermediate **8** could be converted to **5** using a modification of Weinreb's procedure for the conversion of esters to amides.[8,9]

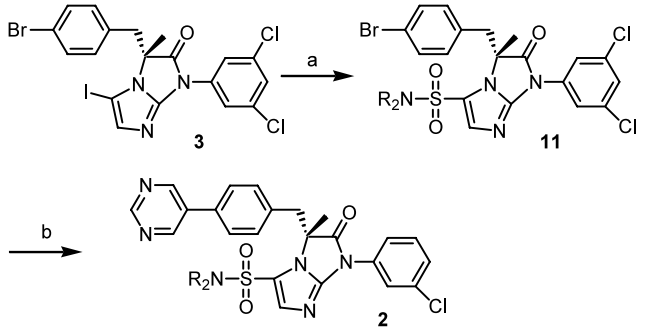
With a reliable source of **5** now available, we turned our attention to the transformation of **5** into iodide **3**. The direct synthesis of vinyl halides such as chlorides and bromides from amides and ketones with reagents such as $POCl_3$ or $POBr_3$[10] is well known,[11] but the synthesis of vinyl iodides from carbonyl compounds is far less common, and we could not find a literature precedent for the direct or indirect transformation of amides into vinyl iodides. There exist a number of methods for the indirect synthesis of vinyl iodides from ketones through intermediates such as hydrazones,[12] vinyl trimethyltin compounds,[13] triflates[14] and vinyl phosphates,[15] and we decided to pursue the use of a vinyl phosphate intermediate due to the reported higher stability of such compounds relative to similar triflates.[16]

Phosphate **10** was easily prepared from **5** in good yield using standard conditions ($KN(TMS)_2$, $(EtO)_2POCl$, THF), and could be purified by filtration through a short plug of silica gel and stored for several weeks without noticeable decomposition (Scheme 4). Phosphate **10** was then converted to **3** in 75% yield upon treatment with NaI/TMSCl according to a modification of the procedure described by Wiemer and co-workers[15] in their synthesis of vinyl iodides from ketone-derived vinyl phosphates. Interestingly, the formation of **3** was faster and more reproducible when 0.7 to 1 equiv. of water were added to the reaction mixture. There is very little known about the mechanism for this transformation, but it is very likely that at least in our case, the presence of hydrogen iodide generated by the TMSCl/NaI/water[17] system is crucial for the reaction.[18]

With a reliable and convenient route to intermediate **3** at hand, the preparation of second generation 1*H*-imi-



Scheme 4. *Regents and conditions*: (a) $KN(TMS)_2$, $(EtO)_2POCl$, THF, –20°C (92%); (b) NaI, TMSCl, H_2O, CH_2Cl_2 (75%).



Scheme 5. *Reagents and conditions*: (a) *c*-PentMgCl, SO_2, NCS, R_2NH, THF (89%); (b) $ArB(OH)_2$, $(dppf)PdCl_2$, K_3PO_4, DME (80–85%).

dazo[1,2-α]imidazol-2-one LFA-1 inhibitors such as **2** in large quantities was accomplished using the procedure described by Wu and co-workers[4,19] (Scheme 5).

In conclusion, we have developed a new, reliable, regiocontrolled and safe route to a new class of LFA-1 inhibitors such as **2**. The novel aspect of this route is the transformation of amino amide **7** into iodide **3** in four steps. Development of a reliable synthesis of **3** is important because **3** is a key advanced intermediate used in the synthesis of second-generation 1*H*-imidazo[1,2-α]imidazol-2-one LFA-1 inhibitors.

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