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An improved synthesis of *N*-aryl-hydantoin LFA-1 antagonists via the enantiospecific alkylation of an isobutyraldehyde-derived imidazolidinone template

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Abstract—An improved and cost-effective process for the synthesis of *N*-aryl-hydantoin LFA-1 antagonists is described. Key transformations include the synthesis and stereospecific alkylation of the *trans*-isobutyraldehyde-derived template **4**, and the one-pot hydrolysis of intermediate **6**.

1. Introduction

In a search for novel therapeutic agents for ailments related to inflammation and immunology, our discovery group recently identified an important series of hydantoin small molecules that act as antagonists to the binding of intracellular adhesion molecules such as ICAM-1 with leukointegrin LFA-1.[1] The selection of BIRT377 **1** as a candidate for further pre-clinical studies gave rise to a program designed to develop a reliable and cost-effective process for their synthesis and the synthesis of similar chiral, non-racemic hydantoins. Of the synthetic methods investigated,[2–4] a modification of Seebach's self regeneration of stereocenters principle[5] resulted in a reliable process suitable for the multi kilogram synthesis of **1** and structurally related LFA-1 antagonists. This process development has been described in a previous report from our laboratories (Fig. 1).[6]

A key feature of molecules like **1** is the *N*-aryl-substituted hydantoin bearing a quaternary stereogenic center. The process originally developed for the synthesis of (+)-**1** relied on the stereospecific alkylation of the pivalaldehyde-derived imidazolidinone template **5** (Scheme 1).[6] Imidazolidinone **5** was prepared by the condensation of amino acid amide **2** and pivalaldehyde, followed by *N*-protection as the trifluoracetamide. Although all reactions in the eight-step process proceeded efficiently and in high-yield up to multi kilogram scale,[6] the major drawback of this process was the high cost of pivalaldehyde,[7] and more significantly, the limited number of bulk suppliers.[8] Anticipating the possibility that bulk commercial availability of pivalaldehyde could become an issue, and to reduce the cost of the process, we decided to investigate the use of the isobutyraldehyde-derived imidazolidinone template **4** for the synthesis of **1** and analogues.

2. Results and discussion

The alkylation of 2-isopropyl-imidazolidinones, which are derived from isobutyraldehyde and glycine, is reported to proceed with lower stereoselectivity than with the corresponding pivalaldehyde-derived analogues.[9] This is presumably due to the reduced bulk of the isopropyl group. As a result, 2-*tert*-butyl-imidazolidinones have become the templates of choice in the synthesis of amino acids and related compounds. How-

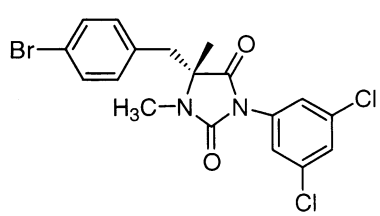

Figure 1. BIRT377 **1**.

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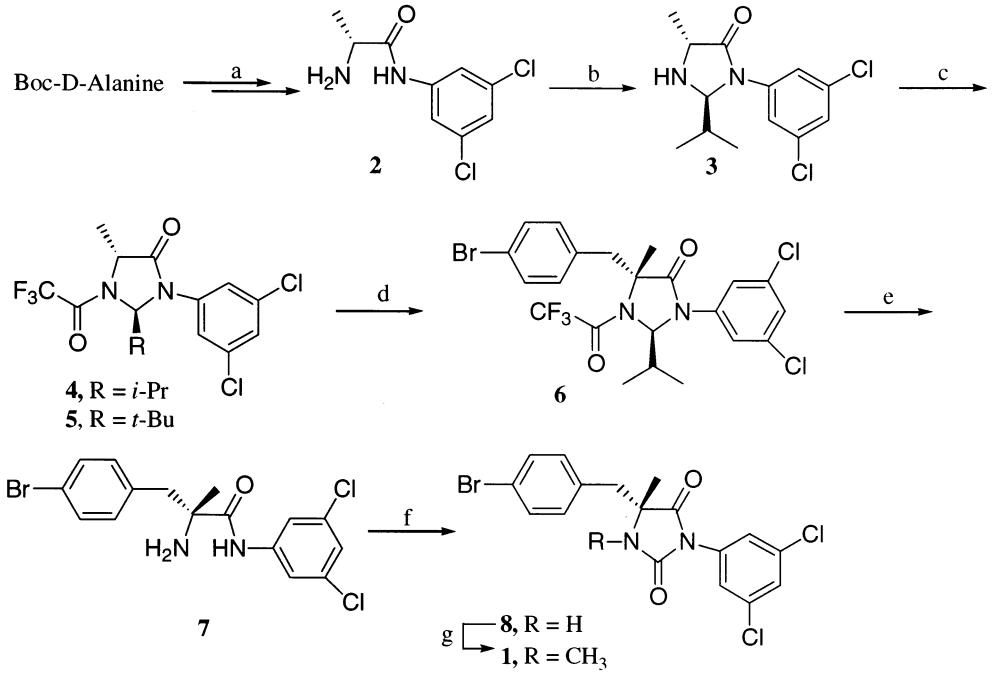

Scheme 1. (a) Ref. 6. (b) Isobutyraldehyde, toluene, 55°C; crystallization from methanol/hexanes (76%). (c) TFAA, Et_3N, THF (98%). (d) $LiN(TMS)_2$, 4-bromo-benzylbromide, THF, −20°C (95%). (e) *tert*-BuOK (2 equiv.), H_2O (1.3 equiv.), THF; conc. H_2SO_4 (3 equiv.), reflux (96%). (f) $ClCO_2CH_3$, Et_3N, NaOMe, THF (95%). (g) $KN(TMS)_2$, MeI, THF (74%).

ever, literature reports on the use of 2-isopropyl-imidazolidinone templates are few, and unlike **4**, the templates investigated do not have an aryl group at the 3-position.[9–11] Moreover, we were not aware of any studies related to the use of 2-isopropyl-imidazolidinones for the synthesis of α-disubstituted amino acids and related compounds. This was surprising, since the cost associated with the use of pivalaldehyde-derived templates is high, and a highly stereospecific alkylation of a novel isobutyraldehyde-derived template would make the synthesis of α-disubstituted amino acid derivatives significantly more affordable. Herein, we report our studies on the successful synthesis and alkylation of isopropyl-derived template **4**, and further manipulations of the alkylated product **6** that led to an improved synthesis of *N*-aryl-hydantoin LFA-1 antagonists such as **1**.

The alkylation of the isopropyl-derived imidazolidinone **4** was applied to the synthesis of **1**, as shown in Scheme 1. Amino amide **2** was prepared in two steps from Boc-D-alanine as previously reported by Yee.[6] Condensation of amino amide **2** with isobutyraldehyde in toluene at 55°C afforded imidazolidinone **3**[12] in good yield. Crude imidazolidinone **3** was initially obtained as a disappointing 3:2 mixture of *trans*- and *cis*-isomers.[13] However, under our crystallization conditions (reflux in methanol/hexanes, cooled to 4°C) the mixture was completely converted to the *trans*-isomer.[14] This is possible because an equilibrium mixture of both isomers exists in solution, but the *trans*-isomer selectively crystallizes out of the mixture, resulting in the complete formation of pure *trans*-**3**. Acylation of **3** (trifluoroacetic anhydride, Et_3N, THF, room temperature) afforded template **4**[15] as a crystalline solid in good yield, and alkylation of **4** with 4-bromobenzylbromide ($LiN(TMS)_2$, THF, −20°C) gave intermediate **6** in good yield as a single isomer. The enantiospecificity of the alkylation is noteworthy, because, as Seebach pointed out,[9] the isopropyl group is rather small with an 'A value' of 2.1 kcal/mol, much closer to a methyl group (1.7 kcal/mol) than a *tert*-butyl group (~5 kcal/mol). Nevertheless, our results clearly demonstrate that, under the right conditions, alkylation of a 2-isopropyl-imidazolidinone such as **4** can occur with the same degree of enantiospecificity as the corresponding *tert*-butyl analogue, such as **5** previously used by Yee.[6]

The next step of the synthesis involved hydrolysis of the imidazolidinone ring of **6**. However, this proved less easy than hydrolysis of the analogous pivalaldehyde-derived compound;[6] hence, treatment of **6** with $BnMe_3NOH$ and aqueous NaOH, followed by addition of 6N HCl, failed to give any of the hydrolysis product **7**. This observation was rather surprising since we initially expected the less sterically demanding isobutyraldehyde-derived intermediate **6** to be more susceptible to hydrolysis than the pivalaldehyde-derived analogue. We speculate that upon removal of the trifluoroacetate group from **6**, the resulting imidazolidinone ring could open and tautomerize to form a relatively stable tri-substituted enamine;[16] this is not possible with the pivalaldehyde-derived analogue, and could account for the difference in reactivity between the two substrates. Nevertheless, a one-pot hydrolysis sequence was developed based on the modified Gassman's procedure for the hydrolysis of amides.[17] Accordingly, treatment of **6** with potassium *tert*-butoxide (2 equiv.) and H_2O (1.3 equiv.) in THF resulted in the successful removal of the trifluoroacetate protecting group, and subsequent

addition of H_2SO_4 at reflux temperature resulted in the formation of the hydrolysis product **7** in good yield. Amino amide **7** was then converted to (+)-**1**[18] in two steps by reported procedures.[6]

3. Conclusions

In conclusion, we have developed a more effective process for the synthesis of *N*-aryl-hydantoin LFA-1 inhibitors such as BIRT377 **1** via the enantiospecific alkylation of 2-isopropyl-imidazolidinone **4**. To the best of our knowledge, this is the first successful use of an isobutyraldehyde-derived imidazolidinone template for the asymmetric stereospecific synthesis of an α-disubstituted amino acid derivative. Furthermore, our results argue against current conventional wisdom, which suggests that 2-*tert*-butyl-imidazolidinones are always superior templates for alkylation than the corresponding 2-isopropyl analogues. In addition, a relatively mild one-pot hydrolysis method for the hydrolysis of **6** was implemented.[19] Finally, the process described herein is more cost effective than the previous process[6] due to the lower cost of isobutyraldehyde, which is available in bulk from a number of suppliers.[20] The scope and limitations of the use of isobutyraldehyde-derived templates for the synthesis of analogues of **1**, as well as other quaternary α-amino acid derivatives, is currently under investigation and will be reported in due course.

4. Experimental

Unless otherwise specified, all reactions were carried out in oven-dried glassware under an atmosphere of nitrogen. NMR spectra were recorded on a Bruker DPX-400 NMR spectrometer. Shifts are reported in ppm relative to trimethylsilane; coupling constants (J) are reported in hertz, refer to apparent peak multiplicities, and may not necessarily be true coupling constants. The commercially available starting materials were used as received without further purification and all solvents were dried by standard methods prior to use. All melting points were recorded using a Fisher–Johns melting point apparatus and are uncorrected.

4.1. Preparation of (2*S*,5*R*)-3-(3,5-dichloro-phenyl)-2-isopropyl-5-methyl-imidazolidin-4-one 3

Isobutyraldehyde (40.1 mL, 442 mmol) was added dropwise over a period of 30 min to a stirred solution of amino amide **2**[6] and toluene (420 mL) at room temperature. The mixture was heated to 50°C and stirred for 12 h. Concentration under reduced pressure afforded 123 g of crude product as a solid. Recrystallization from methanol (28 mL) and hexanes (570 mL) afforded 80.6 g (76%) of product as a yellow solid: mp 123–125°C; $[\alpha]_D^{20}=+19$ ($c=5.1$, CH_2Cl_2). ^{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, $J=1.96$, 1H), 7.17 (m, 1H), 7.41 (d, $J=1.96$ Hz, 2H); ^{13}C NMR (100 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%.

4.2. Preparation of (2*R*,5*R*)-3-(3,5-dichloro-phenyl)-2-isopropyl-5-methyl-1-(2,2,2-trifluoro-acetyl)-imidazolidin-4-one 4

Trifluoroacetic anhydride (40 mL, 283 mmol) was added dropwise to a stirred solution of **3** (79.6 g, 277 mmol), triethylamine (39.4 mL, 283 mmol) and THF (600 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 afford 185 g of an orange oil. The above oil was dissolved in ethyl acetate (1 L) and washed sequentially with 0.5N HCl, 0.5N NaOH, water and brine. The organic portion was concentrated under reduced pressure to afford 129 g (98%) of a colorless oil that solidified upon standing: mp 87–89°C; $[\alpha]_D^{20}=+87$ ($c=7.15$, CH_2Cl_2); ^{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, 1H), 7.30 (m, 1H), 7.45 (br s, 2H); ^{13}C NMR (100 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 $C_{15}H_{15}C_{12}F_3N_2O_2$: C, 47.02; H, 3.95; N, 7.31. Found C, 47.16; H, 3.82; N, 7.24%.

4.3. Preparation of (2*R*,5*R*)-5-(4-bromo-benzyl)-3-(3,5-dichloro-phenyl)-2-isopropyl-5-methyl-1-(2,2,2-trifluoro-acetyl)-imidazolidin-4-one 6

Lithium bis(trimethylsilyl)amide (282 mL of a 1 M solution in THF, 282 mmol) was added dropwise to a stirred solution of **4** (128 g, 268 mmol), 4-bromo-benzyl bromide (68.5 g, 268 mmol) and THF (585 mL) at −20°C over a period of 1 h. The mixture was allowed to reach ambient temperature and concentrated under reduced pressure to afford 280 g of an oil. The crude product was partitioned between ethyl acetate (1.2 L) and water (400 mL). The organic layer was stored and the aqueous layer was extracted further with ethyl acetate (2×200 mL). The combined organic extract was washed with brine (200 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford 155 g of **6** as a yellow oil that solidified upon standing: $[\alpha]_D^{20}=+95$ ($c=9.5$, CH_2Cl_2); mp 143–145°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (d, $J=7.0$ Hz, 3H), 0.92 (d, $J=7.0$ Hz, 3H), 1.95 (s, 3H), 2.07 (m, 1H), 3.02 (d, $J=13.7$ Hz, 1H), 3.72 (d, $J=13.7$ Hz, 1H), 5.10 (br, 1H), 6.76 (d, $J=1.6$ Hz, 2H), 6.81 (d, $J=8.3$ Hz, 2H), 7.3 (br, 1H), 7.37 (d, $J=8.3$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 20.1, 22.3, 36.3, 39.1, 70.2, 78.2, 121.8, 123.9, 128.1, 131.2, 131.8, 134.0, 135.6, 137.3, 169.9; anal. calcd for $C_{22}H_{20}BrCl_2F_3N_2O_2$: C, 47.85; H, 3.65; N, 5.07. Found C, 47.69; H, 3.68; N, 4.87%.

4.4. Preparation of (*R*)-2-amino-3-(4-bromo-phenyl)-*N*-(3,5-dichloro-phenyl)-2-methyl-propionamide 7

Potassium *tert*-butoxide (343 mL of a 1 M solution in THF, 343 mmol) was added to a stirred solution of **5**

g, 267 mmol), THF (290 mL) and water (5.3 mL) at room temperature and the resulting mixture was stirred for 30 min. The resulting mixture was filtered and concentrated under reduced pressure to afford 238 g of an amber oil. The above oil was dissolved in ethanol (1.2 L) and conc. sulfuric acid (54 mL, 972 mmol) was added over a period of 10 min at ambient temperature. The mixture was then refluxed for 30 min and allowed to reach room temperature. The mixture was placed over an ice bath and 50% NaOH (1.63 mol) was added dropwise. The mixture was filtered and concentrated under reduced pressure to afford an oil. The crude oil was partitioned between ethyl acetate (700 mL) and water (250 mL). The organic layer was set aside and the aqueous layer was extracted with ethyl acetate (2×200 mL). The combined organic portions were washed sequentially with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford 111 g of product as an oil.[21]

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7. As a rough price comparison, one can look at the prices quoted by the Aldrich Chemical Co. At the time this manuscript was written the cost for 100 mL of pivalaldehyde was $321.90, whereas 100 mL of isobutyraldehyde costs only $40.00.
8. We were unable to purchase multi kilogram quantities of pivalaldehyde from companies listed in previous reports[5] as suppliers of bulk pivalaldehyde. To the best of our knowledge, the only supplier of bulk pivalaldehyde available when this manuscript was prepared was Inspec Fine Chemicals, Ltd. in England.
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12. All new compounds were characterized by ^1H and ^{13}C NMR, mass spectra and elemental analysis. The structure of intermediate **5** was confirmed by X-ray analysis.
13. The *cis*/*trans* ratio was determined by ^1H NMR.
14. The *cis*- and *trans*-imidazolidinone isomers of **3** are epimers at the C-2 position. The stereogenic center bearing the methyl group does not epimerize under the crystallization conditions; otherwise, epimerization at the C-5 position would result in racemic **3**. Therefore, conversion to the *trans*-isomer must occur by opening of the imidazolidinone and condensation. Please see Ref. 6 for a similar preparation of the pivalaldehyde-derived imidazolidinone analogue as a single enantiomer.
15. The e.e. of (+)-**4** was determined to be >99%. Chiral HPLC column, Chiralpak OD (250×4.6 mm); mobile phase, 7% EtOH and 0.1% trifluoroacetic acid in hexane; flow rate 1.0 mL/min; ambient temperature; retention time, (+)-**4** = 4.08 min; (−)-**4** = 5.07 min.
16. No attempts were made to isolate and characterize any intermediates resulting from the removal of the trifluoroacetate group.
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18. The e.e.s of (−)-**8** and (+)-**1** were determined by chiral HPLC to be >99%. See Ref. 6 for details on the HPLC methods.
19. The standard hydrolysis method involves heating the hydantoin in concentrated acid at 175–180°C in a sealed tube.
20. At the time this manuscript was written, isobutyraldehyde was offered in multi kilogram quantities by a number of suppliers, including the Aldrich Chemical Company Inc., Acros Organics, Alfa Aesar, EM Science, Fluka, Pfaltz & Bauer, Inc. and Crescent Chemical Co., Inc.
21. The analytical data of intermediate **7** were identical to data previously reported for that compound. See Ref. 6 for details.