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A New and Efficient Synthesis of 6-[(5*S*,9*R*)-9-(4-Cyanophenyl)-3-(3,5-dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]non-7-yl]nicotinic Acid, a Potent LFA-1/ICAM Inhibitor

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Abstract:

An efficient synthesis of 6-[(5*S*,9*R*)-9-(4-cyanophenyl)-3-(3,5-dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]non-7-yl]nicotinic acid 1 is described. This new process involves an *in situ* protection of 6-chloronicotinic acid as trimethylsilyl ester followed by coupling with spirocyclic hydantoin core 2 to give the target product in 89% overall yield after one-pot deprotection and final API recrystallization.

Introduction

During our efforts to identify small molecules that would interfere with the LFA-1/ICAM interaction, 6-[(5*S*,9*R*)-9-(4-cyanophenyl)-3-(3,5-dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]non-7-yl]nicotinic acid **1** was identified as a novel LFA-1 antagonist.[1] Compound **1** is a highly potent inhibitor of the LFA-1/ICAM interaction with an IC_{50} of 2.5 nM in an adhesion assay and an IC_{50} of 60 nM in a MLR cell proliferation assay.[1b] In addition to its optimal *in vitro* potency, compound **1** (Figure 1) had a desirable *in vitro* liability profile and was selected as our lead candidate for further evaluation. Herein, we describe a new and efficient scale up synthesis of **1** to support preclinical toxicology studies.

Results and Discussion

Original Synthesis. The original synthesis of 6-[(5*S*,9*R*)-9-(4-cyanophenyl)-3-(3,5-dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]non-7-yl]nicotinic acid **1** started with the protection of 6-nicotinic acid **2** as *tert*-butyl ester (Scheme 1).[1b] Treatment of **2** with thionyl chloride afforded 6-nicotinic acid chloride **3** in quantitative yield. Reaction of **3** with *tert*-butanol afforded the *tert*-butyl ester **4** in 70% yield. Heating of **4** with spirocyclic hydantoin intermediate **5**[2] at 112 °C in dimethylacetamide (DMA) in the presence of diisopropylethylamine (DIPEA) provided the coupling product **6** in 77% yield. The *tert*-butyl ester group in **6** was subsequently deprotected with trifluoroacetic acid to give **1** in 86% yield.

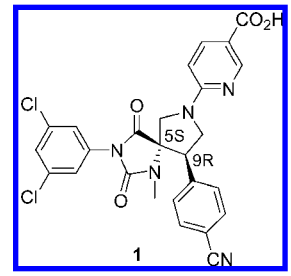
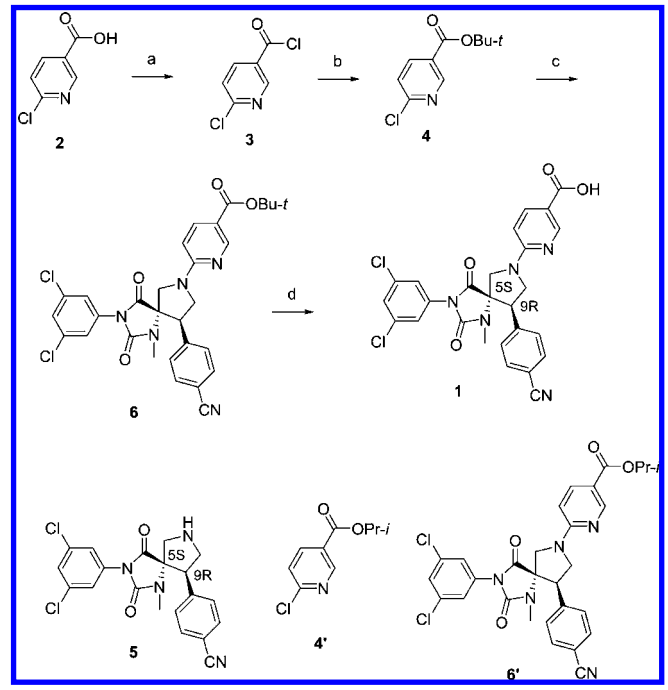


Figure 1. **6-[(5*S*,9*R*)-9-(4-Cyanophenyl)-3-(3,5-dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]non-7-yl]nicotinic acid.**

Scheme 1. **Original synthesis of 1**[a]



[a] Reagents and conditions: (a) $SOCl_2$, 90 °C, 100%; (b) *t*-BuOH, CH_2Cl_2, Et_3N, DMAP, 70%; (c) **5**, DIPEA, DMA, 112 °C, 77%; (d) TFA, DCM, 86%.

The original synthesis was fairly straightforward and worked well on a smaller scale. However, on a larger scale we were quite surprised to find that the penultimate ester **6** was contaminated by 1−3% of isopropyl ester **6′**. Careful flash column chromatographic separation was needed to purge this impurity **6′** prior to final deprotection by TFA. After screening a number of solvents, crystalline material could be obtained

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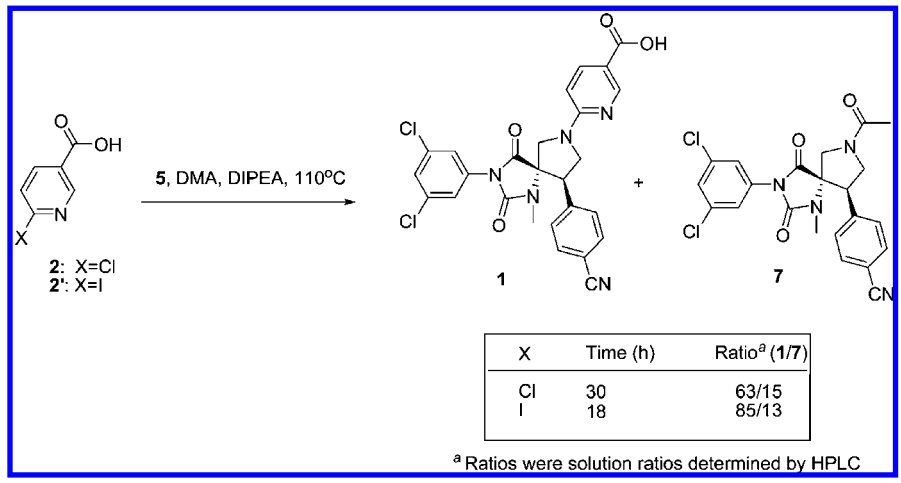
Scheme 2. **Direct coupling using 6-halonicotinic acid**



X	Time (h)	Ratio[a] (1/7)
Cl	30	63/15
I	18	85/13

[a] Ratios were solution ratios determined by HPLC

from crude **1** using $CHCl_3$; however, the recrystallized **1** was contaminated with residual solvent $CHCl_3$ (0.04%), a level that did not meet our quality criteria for toxicology studies.

Careful examination of the source of the isopropyl ester, impurity **6′**, revealed that it originated from the *tert*-butanol used during the *tert*-butyl ester formation with **3**. Although a high-quality source of *tert*-butanol was used, trace amounts of isopropanol present in the reagent also reacted with 6-chloronicotinic acid chloride **3** to give 4% of impurity **4′** which was enriched during the esterification process due to the enhanced reactivity of the isopropanol relative to the more sterically incumbered tert-butanol. Iso-propyl impurity could be partially removed by column chromotagraphy and was carried through to the next step coupling reaction with spirocyclic hydantoin intermediate **5**. While we were searching for vendors with *tert*-butanol completely free of isopropanol, we decided to develop an alternative synthesis which would avoid the aforementioned issues completely.

Alternative Synthesis. Our initial focus in the development of an alternative synthesis was on the direct coupling of spirocyclic hydantoin **5** with 6-chloronicotinic acid **2** (Scheme 2). Thus, heating **5** with 1.5 equiv of **2** in DMA in the presence of 2.5 equiv of DIPEA at 110 °C for 30 h gave a 63% yield of the desired product **1** and a 22% yield of unreacted **5**, as determined by LC/MS. Under these reaction conditions, however, a new impurity (15%) was also observed. This new impurity **7** had an M + 1 mass of 457, resulting from the reaction of **5** with DMA. Other solvents such as DMPU, NMP, DMSO, and toluene were then screened instead of DMA to see if the yield of the direct coupling reaction could be improved. Unfortunately, they all gave inferior results to DMA. The reactions in these solvents were more sluggish and generated more impurities as seen by LC/MS.

In order to increase the reactivity of the nicotinic acid component for the coupling reaction with spirocyclic hydantoin **5** (Scheme 2), we decided to use 6-iodonicotinic acid **2′**. Compound **2′** could be readily prepared in almost quantitative yield by heating 6-chloronicotinic acid **2** with 2 equiv of sodium iodide in ethyl methyl ketone at 110 °C for 12 h.[3] The coupling of 6-iodonicotinic acid **2′** with **5** was much faster, as expected.

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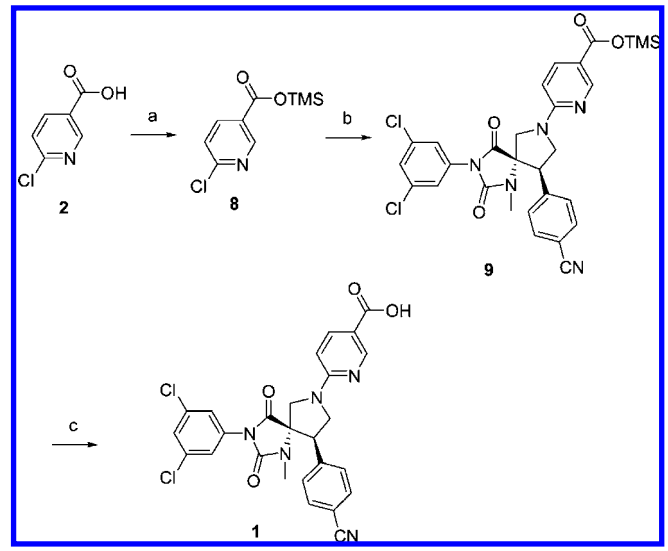
Scheme 3. **Alternative synthesis of 1**[a]



[a] Reagents and conditions: (a) $(CH_3)_3SiNHSi(CH_3)_3$, cat. TMSCl, 78 °C, 3 h, 100%; (b) **5**, cat. DMAP, DMA, DIPEA, 95 °C, 18 h; (c) MeOH, 25 °C, 2 h, 98%.

The reaction was over within 16 h at 110 °C as indicated by complete disappearance of the starting material. However, in addition to 85% of the desired product **1**, a substantial amount of impurity **7** (13%) was seen in the reaction mixture by LC/MS.

We next turned our attention to an *in situ* silyl protection strategy using the known silyl protected 6-chloronicotinic acid **8** (Scheme 3).[4] Thus, refluxing 6-chloronicotinic acid **2** with hexamethyldisilazane in dichloromethane (DCM) in the presence of cat. TMSCl afforded the silylated product **8** in quantitative yield. The reaction mixture began as a slurry, but as it progressed, the mixture became homogeneous. After the volatiles were removed and after a subsequent solvent swap with DMA, the *in situ* generated **8** was reacted with the spirocyclic hydantoin **5**. The coupling reaction went very

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smoothly and cleanly. After the reaction mixture stirred at 90 °C for 18 h, the reaction was complete. Quenching the reaction mixture with methanol followed by water gave the target molecule **1** in 98% yield as a first drop. Final API recrystallization using EtOH/H_2O gave **1** with 90% recovery and 99.9% HPLC purity. Moreover, while the starting material **5** had an ee of 98.5%, the optical purity of API **1** was raised to 100% ee after the recrystallization.

In summary, we have developed an efficient alternative synthesis for 6-[(5*S*,9*R*)-9-(4-cyanophenyl)-3-(3,5-dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]non-7-yl]nicotinic acid**1**. This new process features an *in situ* protection of 6-chloronicotinic acid as trimethylsilyl ester **8** followed by coupling with the spirocyclic hydantoin core (**5**) to give the target product **1** in 89% overall yield after a one-pot deprotection and final API recrystallization.

Experimental Section

All reagents were obtained from Aldrich Chemical Co. and used without further purification unless otherwise stated. Spirocyclic hydantoin **5** was obtained from Bristol-Myers Squibb Company. All reactions were performed under a nitrogen atmosphere. All glassware was dried and purged with nitrogen or argon before use. All reactions were monitored by HPLC using the following conditions: Combi-Screen ODS column 5 μm, 4.6 mm × 50 mm. Solvent: A = 10% methanol/90% water with 0.2% H_3PO_4; B = 90% Methanol/10% water with 0.2% H_3PO_4. Gradient: 0−100% B over 4 min. Flow: 1 mL/min, wavelength: 220 nm). HPLC analyses were performed using a Shimadzu system (model SPD 10AV). All ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer using DMSO-d_6 as the solvent.

6-[(5*S*,9*R*)-9-(4-Cyanophenyl)-3-(3,5-dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]non-7-yl]nicotinic Acid (1). *Direct Coupling.* A 250-mL round-bottom flask was charged with 6-iodonicotinic acid **2′** (373.3 mg, 1.5 mmol), **5** (414 mg, 1 mmol), dimethylacetamide (2 mL), and diisopropylethylamine (320 mg, 2.5 mmol). After the reaction mixture was stirred at 110 °C for 16 h under nitrogen, it was cooled to rt and was slowly added to ice water (2 mL) with stirring. The resulting white slurry was filtered by vacuum filtration, and the crude product was washed with water (3 × 2 mL). The crude product was dried *in vacuo* at 60 °C for 18 h and was redissolved in chloroform (25 mL) and stirred overnight at room temperature and then at 4 °C for 30 min. The white crystals were collected by vacuum filtration, washed with cold chloroform (2 × 5 mL), and dried *in vacuo* at 60 °C to give **3** (347 mg, 75% yield, 98% HPLC area purity). LC/MS (ESI) *m*/*z* 536 (M + H).

Scale-Up Synthesis. A 2-L three-neck round-bottom flask was charged with 6-chloronicotinic acid **2** (37.8 g, 0.24 mol), dichloromethane (360 mL), hexamethyldisilazane (28.61 g, 0.177 mol), and TMSCl (1.11 g, 10 mmol). The slurry was refluxed under N_2 atmosphere for 3 h until a light-brown solution was obtained. The reaction mixture was cooled to rt, and the solvent was removed under reduced pressure to afford a light-brown syrup which solidified upon cooling. To this flask was added **5** (49.68 g, 0.119 mol), dimethylacetamide (500 mL), and diisopropylethylamine (38.73 g, 0.299 mmol). After the reaction mixture was stirred at 90 °C for 18 h under nitrogen, it was cooled to rt. MeOH (100 mL) was added while stirring. The temperature was raised from 25 to 35 °C. The resulting volatile solvents (MeOH and methoxytrimethylsilane) were removed *in vacuo*, and the resulting mixture was slowly added to H_2O (600 mL) with stirring. The resulting white slurry was filtered by vacuum filtration, and the product was washed with water (3 × 20 mL) and dried to afford **1** as a white solid (62.88 g, 98% yield). LC/MS (ESI) *m*/*z* 536 (M + H).

Recrystallization from EtOH/H_2O. Compound **1** (49 g) from above was dissolved in EtOH (390 mL) at 90 °C, and H_2O (120 mL) was added at this temperature. The mixture was cooled slowly to room temperature and then at 4 °C for 30 min. The white crystals were collected by vacuum filtration, washed with EtOH/H_2O (1/3 ratio, 2 × 100 mL) and then H_2O (3 × 300 mL). The solid was dried *in vacuo* at 60 °C for 16 h and then at 90 °C for additional 18 h to give **1** (44.5 g, 90% recovery yield, 99.9% HPLC area purity, and 100% ee). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.68 (s, 1H), 8.31 (s, 1H), 8.00 (s, 2H), 7.90 (s, 2H), 7.63 (s, 2H), 6.84 (s, 2H), 4.37 (t, J = 9.9 Hz, 1H), 4.16 (d, J = 9.9 Hz, 3H), 4.00 (d, J = 12.1 Hz, 1H), 3.19 (s, 3H); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 170.81, 166.46, 158.01, 152.81, 150.37, 139.08, 137.81, 133.65, 132.88, 132.15, 128.83, 127.64, 124.46, 114.62, 110.73, 105.48, 48.03, 46.75, 45.24, 24.73. Anal. Calcd for $C_{26}H_{19}C_{l2}N_5O_4 \cdot 0.62\ H_2O$: C, 57.03; H, 3.73; N, 12.79; Cl, 12.95. Found: C, 57.01; H, 3.34; N, 12.78; Cl, 13.00.

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