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Development of a Direct Photocatalytic C−H Fluorination for the Preparative Synthesis of Odanacatib

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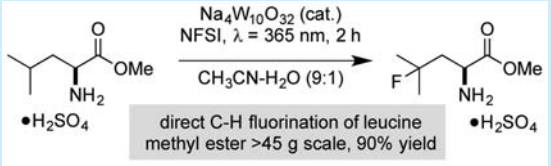
Supporting Information

ABSTRACT: Late-stage C−H fluorination is an appealing reaction for medicinal chemistry. However, the application of this strategy to process research appears less attractive due to the formation and necessary purification of mixtures of organofluorines. Here we demonstrate that γ-fluoroleucine methyl ester, an intermediate critical to the large-scale synthesis of odanacatib, can be accessed directly from leucine methyl ester using a combination of the decatungstate photocatalyst and *N*-fluorobenzenesulfonimide in flow. This efficient C−H fluorination reaction compares favorably with several generations of classical γ-fluoroleucine process syntheses.



The importance of fluorine to drug discovery cannot be overstated. Fluorination of drug leads is known to have profound effects on binding affinity, lipophilicity, and absorption, distribution, metabolism, excretion, and toxicity (ADME-tox).[1] While the vast majority of fluorinated pharmaceuticals are derived from commodity or readily prepared trifluoromethyl or fluoroaryl building blocks, the development of selective fluorination reagents and reactions have provided new and enabling tools for medicinal chemistry.[2] For example, C−H fluorination reactions reported by Sanford,[3] Groves,[4] Lectka,[5] Hartwig,[6] and others[2c,7] provide a means to directly fluorinate advanced drug candidates and attenuate metabolism. However, the increasing sophistication of these late-stage C−H fluorination processes can also present challenges that complicate or protract large-scale efforts required to support clinical studies and commercialization.[8] In fact, it has recently been perpended whether advances in late stage C−H fluorination are indeed useful or simply a "fancy novelty".[8] Thus, despite obvious promise, the practical application of late-stage C−H fluorination can be encumbered by poor conversion or selectivity and consequently complex and cost-prohibitive purifications. Here we report the direct synthesis of γ-fluoroleucine, a crucial intermediate in the synthesis of odanacatib.[9] Importantly, by pairing our photocatalytic late-stage C−H fluorination strategy[10] with high-throughput reaction optimization and flow photochemistry, γ-fluoroleucine was made readily available with dramatic reductions in cost, time, reactor space, and waste produced. While singular, the demonstration of this process on large-scale highlights a bright future for late-stage C−H fluorination in drug discovery and development.

Odanacatib (**2**) is a potent and selective cathepsin K inhibitor currently in clinical trials for the treatment of osteoporosis.[9] The unusual fluorinated amino acid (2*S*)-γ-fluoroleucine is an essential structural component of odanacatib, where fluorination prevents hydroxylation of the leucine subunit by CYP3A, significantly extending drug half-life when compared to the parent lead candidate **1**.[11] Considering the importance of (2*S*)-γ-fluoroleucine to the development of odanacatib, its synthesis has been studied extensively. In fact, several scalable and robust synthetic routes to this important amino acid have already been published,[12,13] five of which were developed at Merck and are highlighted in Figure 1. In general, the major challenges faced in each synthesis of γ-fluoroleucine are the controlled introduction and preservation of the α-chiral amine and tertiary alkyl fluoride functions. Consequently, syntheses of γ-fluoroleucine have relied on chiral catalysis,[13b,c] biocatalysis,[13d] the chiral pool,[13a] and chiral resolution[13e] to introduce the α-chiral amine function. However, incorporating the tertiary alkyl fluoride has only been possible using classical alkene or epoxide hydrofluorination reactions. A selective C−H fluorination of leucine that directly affords γ-fluoroleucine would clearly represent the most efficient approach to this key building block.

One of our laboratories has recently reported a photocatalytic fluorination of unactivated C−H bonds.[10] This reaction involves photoexcitation of a decatungstate catalyst to produce an excited state intermediate capable of hydrogen atom abstraction from various aliphatic substrates.[14] The resulting carbon-centered radical can then engage in fluorine atom transfer reactions with *N*-fluorobenzenesulfonimide (NSFI) in accordance with processes identified by Sammis and Paquin.[15] This reaction provides direct access to a range of fluorinated organics in modest to good yield and is unique among late-stage C−H fluorination reactions in the use of

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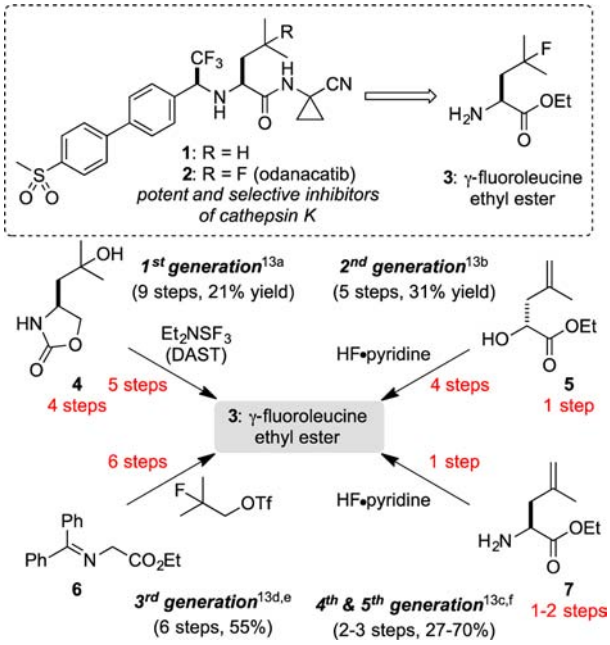
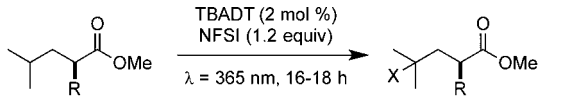


Figure 1. Five generations of large-scale γ-fluoroleucine syntheses developed at Merck.

NFSI.[3−7] Importantly, the decreased reactivity of NFSI relative to other fluorine transfer agents (e.g., Selectfluor)[16] also renders this reaction compatible with a wide range of functional groups.[10] Considering the importance of γ-fluoroleucine to the clinical development of odanacatib, we recognized that a direct fluorination of leucine would have a significant impact on the cost and ease of preparation of γ-fluoroleucine as well as the waste produced by this process.[17]

Table 1 highlights our initial attempts to effect the fluorination of (2*S*)-leucine. For simplicity, we first explored this reaction on the corresponding desamino compound **7** using our optimized reaction conditions.[10] As indicated in entry 1, we observed slow conversion to the 4-fluoro derivative **10**

Table 1. Fluorination of Analogues and Derivatives of Leucine



7: R = H
8: R = NH_2
9: R = NH_3Cl

10: R = H, X = F
11: R = NH_2, X = F
12: R = NH_3Cl, X = F
13: R = NH_3Cl, X = Cl

entry	reactant	solvent	concn	product (yield)[a]
1	7	CH_3CN[b]	1.0 M	**10** (28%)
2	7	CH_3CN-H_2O[c]	1.0 M	**10** (40%)[d]
3	8	CH_3CN	0.3 M	**11** (0%)[e]
4	9	CH_3CN	0.2 M	**12** (35%), **13** (43%)
5	9	CH_3CN	2 M	**12** (18%), **13** (37%)
6	9	CH_3CN-H_2O[f]	0.2 M	**12** (83%), **13** (<5%)

[a]Yield based on analysis of ^1H NMR spectra recorded on crude reaction mixtures using an internal standard. [b]0.1 equiv of $NaHCO_3$ was added. [c]Ratio of CH_3CN/H_2O = 2:1. [d]Combined yield of methyl ester and corresponding carboxylic acid. [e]The major isolated product was the *N*-benzenesulfonamide derivative of leucine methyl ester. [f]Ratio of CH_3CN/H_2O = 2:1.

over the course of 16 h. Repetition of this reaction in a mixture of CH_3CN and H_2O resulted in improved conversion, albeit to a mixture of the ester **10** and corresponding hydrolysis product (not shown). Unfortunately, reaction with (2*S*)-leucine methyl ester (**8**) failed to provide the desired γ-fluoro product **11** and instead delivered an *N*-benzenesulfonamide derivative (entry 3). In an effort to avoid side reactions between the free amine and NFSI, the fluorination was repeated with the HCl salt **9**, and we were delighted to find that small amounts of the γ-fluoroleucine·HCl salt **12** were produced along with the corresponding chloroleucine **13** (entries 4 and 5). The chlorination of **9** was surprising, and several experiments were carried out to gain further insight into this reaction. For example, when the reaction described in entry 4 was repeated without NFSI, no chloroleucine was produced. Replacing NFSI with $Na_2S_2O_8$ resulted in chlorination of leucine methyl ester in a similar yield (~30%). Notably, this latter reaction only returned starting material when repeated without TBADT and irradiation. Considering these facts, and the reduction potential of NFSI (E° = −0.78 V vs SCE)[2b] and TBADT (E° = 2.85 V vs SHE),[18] the formation of chloroleucine **13** may involve oxidation of chloride to molecular chlorine by photoexcited TBADT[18] and subsequent reaction of chlorine with the generated carbon radical. Alternatively, single electron transfer from the carbon radical to NFSI[15a] or oxidation of the carbon radical by TBADT[19] would lead to a carbocation intermediate that could react with associated chloride. In an effort to dissociate the chloride and avoid the formation of the chloroleucine analogue **13**, the fluorination reaction was repeated in a mixture of CH_3CN-H_2O (entry 6). Gratifyingly, under these conditions, the γ-fluoroleucine derivative **12** was produced as the major product in excellent yield. The reaction described in entry 6 was also repeated in a standard 5 mm NMR tube and monitored by ^1H NMR spectroscopy (Figure 2). As indicated in the stacked ^1H NMR spectra, after only 1.5

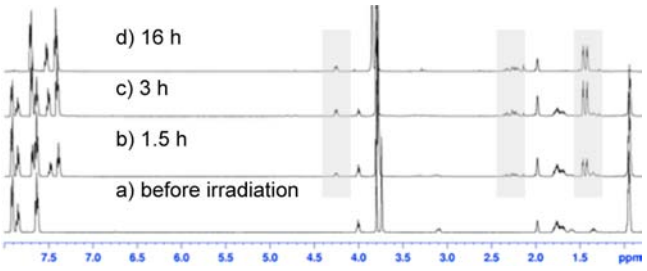


Figure 2. ^1H NMR spectra (600 MHz, CD_3CN/D_2O) of the C−H fluorination of leucine methyl ester·HCl salt (**9**) (Table 1, entry 6) taken at various time intervals. Resonances corresponding to the methyl ester of γ-fluoroleucine·HCl salt (**12**) are highlighted with gray boxes. The resonances that appear in the downfield region (δ > 7.0 ppm) indicate the conversion of (a) NFSI into (d) NHSI.

h the conversion reached ~25%, which doubled after 3 h. Finally, after 16 h, less than 5% of the starting material remained. Considering the efficiency of this process, production of minimal byproducts, and reliance on commodity chemicals, we were keen to evaluate whether this late-stage fluorination was indeed amenable to large-scale and could supplant existing process routes to γ-fluoroleucine (Figure 1).

Further optimization of the C−H fluorination reaction described in Table 1 (entry 6) involved high-throughput experimentation (HTE) using a recently developed photochemical screening platform[20] and MISER-LCMS analysis.[21] As

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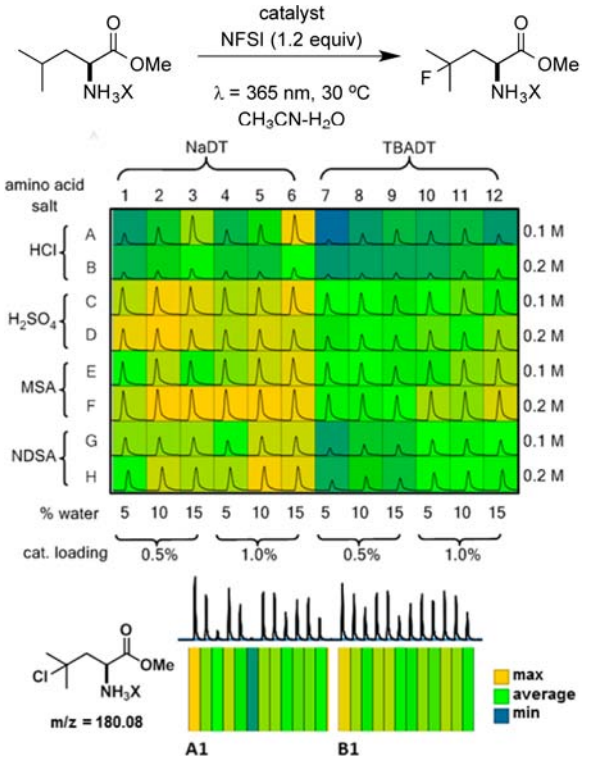

Figure 3. High-throughput optimization and MISER analysis of reaction conditions. Experiments performed on 10 μmol scale and irradiated with 365 nm LEDs for 16 h. Data are depicted as a heat map showing relative product concentrations based on integration of LCMS mass response. The standardized peaks displayed in the heat map are reproduced from the LCMS and correspond to the peak for the desired γ-fluoroleucine derivative.

depicted in Figure 3, we evaluated several reaction parameters in a 96 vial, 365 nm photoreactor on 10 μmol scale, including the amino acid salt, catalyst loading, concentration, and solvent composition. Additionally, we explored the effect of the catalyst counterion in hopes of replacing tetrabutylammonium with a less expensive sodium counterion.[22]

As highlighted in the heat map (Figure 3) we were pleased to find that the sodium salt of decatungstate (rows 1–6) is superior to TBADT in catalyzing the fluorination of all salts of leucine methyl ester. Additionally, the HCl salt **9** is least compatible with the desired process due to competitive chlorination (see separate MISERgram for production of chloroleucine, bottom of Figure 3). While the addition of water improved the outcome of reactions involving the HCl salt **9** (e.g., A3 and A6 in heat map), owing to the limited solubility of NFSI in aqueous acetonitrile, a highly solvent intensive process would be required to both maintain a homogeneous reaction and sufficiently limit the production of chloroleucine. Alternatively, chloroleucine byproducts were avoided through the use of either bisulfate or mesylate (MSA) salts, which also proved to be relatively insensitive to solvent composition or concentration (rows C–F in heat map). As highlighted in rows G and H, reactions involving the napthalene disulfonic acid (NDA) salt proved problematic due to decreased solubility and required both a higher catalyst loading and water content to reach reasonable levels of conversion. Considering these results as well as ease of isolation and downstream processing, the bisulfate salt was ultimately selected as the preferred salt. The optimal reaction conditions (row C, column 2) were reproduced on a 20 mg scale and provided a 97% assay yield after 18 h of irradiation.

In order to evaluate the utility of this direct fluorination for the large-scale production of odanacatib, a 365 nm flow photoreactor was built following the basic design principles described by Booker-Milburn.[23] The reactor was calculated to have a total light output of 32 W (λ_{max} = 365 nm) and consists of 100 ft of 1/16″ I.D. PFA tubing (total reactor volume = 60 mL).[22] Using the optimized reaction conditions (*vide supra*) fluorination was performed on 190 mmol scale (46.5 g), at 0.2 M (9:1 MeCN/water), and pumped through the reactor at 0.5 mL/min (2 h residence time). After the total volume was collected, the mixture was concentrated under reduced pressure followed by azeotropic distillation with 2-MeTHF. Following this process, (*S*)-γ-fluoroleucine methyl ester bisulfate could be isolated by direct precipitation from 2-MeTHF (44.7 g, 90%) (Figure 4).

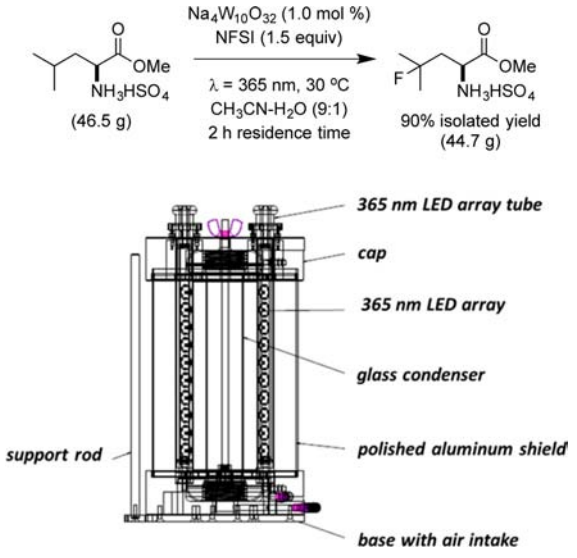

Figure 4. Scalable flow synthesis of γ-fluoroleucine and reactor design.

In conclusion, a robust, one-step synthesis of (*S*)-γ-fluoroleucine methyl ester has been developed that relies on a direct photocatalytic C–H fluorination reaction and compares well to previous, large-scale syntheses of (*S*)-γ-fluoroleucine esters (Figures 1 and 5). This process has been executed on multigram scale with little deviation in conversion or yield from exploratory small-scale reactions (<100 mg). This investigation

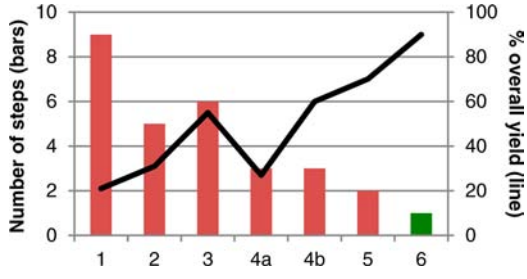

Figure 5. Comparison of overall yield and number of steps for the previous (Figure 1) and present syntheses of (*S*)-γ-fluoroleucine esters. Numbers on horizontal axis represent individual large-scale synthesis campaigns for (*S*)-γ-fluoroleucine esters (see Figure 1) with the present synthesis represented by a green bar (6).

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highlights the remarkable efficiency and selectivity of the decatungstate-catalyzed fluorination reaction,[10] where the final purification of (*S*)-γ-fluoroleucine methyl ester could be accomplished by straightforward precipitation and filtration. Importantly, this first demonstration of late-stage fluorination of an unactivated C−H bond for process research purposes further emphasizes the important role new C−H fluorination strategies can play in drug discovery and development.[8]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02532.

Experimental procedures, high throughput experimentation, and photochemical flow reactor design (PDF)

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Notes

The authors declare no competing financial interest.

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