Tetrahedron Letters 61 (2020) 152447

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A fit for purpose synthesis of Bruton's tyrosine kinase inhibitor GDC-0852

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ARTICLE INFO

Article history:
Received 18 August 2020
Accepted 8 September 2020
Available online 11 September 2020

Keywords:
BTK inhibitor
Tetrahydroindolizine
Palladium-catalyzed
Regioselective
C—N coupling

ABSTRACT

The development of an expedient synthesis to GDC-0852 (**1**), a reversible BTK inhibitor drug candidate, is described. The key starting material tricyclic lactam **5** was prepared by an annulation reaction of unprotected piperidine-2-carbaldehyde HCl salt (**20**) and *N*-Boc piperidine-2,4-dione **21** in a safe and scalable manner. A highly selective Pd-catalyzed C—N coupling of lactam **5** and linker **2a**, followed by Suzuki–Miyaura coupling to fragment **8** subsequently provided a direct and convergent access to the penultimate **17**. A simple $NaBH_4$ aldehyde reduction completed the synthesis to GDC-0852 (**1**) in high yield (54% over 3 steps from **5**) and purity (99.0 A% HPLC).

Introduction

Bruton's tyrosine kinase (BTK) plays a crucial role in regulating the development, activation and signaling of B-cells, which are a subtype of lymphocytes critical to our body's adaptive immune system and its defense against pathogens [1,2]. Conversely an enhanced or overexpression of B-cell receptor signaling can lead to harmful lymphocytic malignancies or the pathogenesis of an autoimmune or inflammatory disorder [3]. Recent developments in this field have led to the discovery of ibrutinib [4] and acalabrutinib [5], approved as treatment for chronic lymphocytic leukemia (CLL) and mantle-cell lymphoma (MCL), as well as several new clinical drug candidates, such as fenebrutinib [6], evobrutinib [7], spebrutinib [8], and tirabrutinib [9], to address these aberrant B-cell development or signaling function.

GDC-0852 (**1**) is a small molecule drug candidate which targets inhibition of BTK in a reversible (non-covalent) manner to improve intended kinase target selectivity (Fig. 1) [2]. Herein we describe an expedient synthesis of GDC-0852 (**1**) to enable further development of this drug candidate.

The discovery synthesis of GDC-0852 (**1**) utilized successive Pd-catalyzed couplings to assemble fragment **5** and then **7** onto a linker molecule **4** to quickly furnish penultimate substrate **9** (Scheme 1). A simple saponification of the ester protecting group then reveals GDC-0852 (**1**), the target drug substance. This synthetic strategy serves as a divergent as well as streamlined protocol to multiple analogs around central linker **4** to support structure–activity relationship (SAR) studies. However, this approach suffers from protecting group manipulation, high reactant stoichiometry (3.0 equiv of **4**), poor yields in the endgame steps, and the requirement of silica gel column chromatographic purifications, making it unsuitable for longer term development.

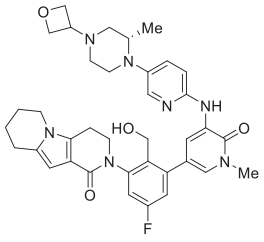

Fig. 1. GDC-0852 (**1**), a reversible BTK inhibitor drug candidate.

Another major drawback of the discovery synthesis is the long and challenging synthesis of fragment **5** [2,10]. The original route encompasses acetic anhydride mediated cyclization of Morita-Baylis-Hillman product **11** to generate indolizine **12**, followed by selective hydrogenation of the pyridine ring to form **13** [11], installation of ethylamine chain via Minisci type alkylation/nitrile reduction and finally base mediated lactam ring closure (Scheme 2). However, the combination of poor reproducibility, lack of robustness, safety concerns encountered in steps leading to **12** and **14** during scale up and tedious purifications resulted in <4% overall yield of tricyclic lactam **5**.

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https://doi.org/10.1016/j.tetlet.2020.152447
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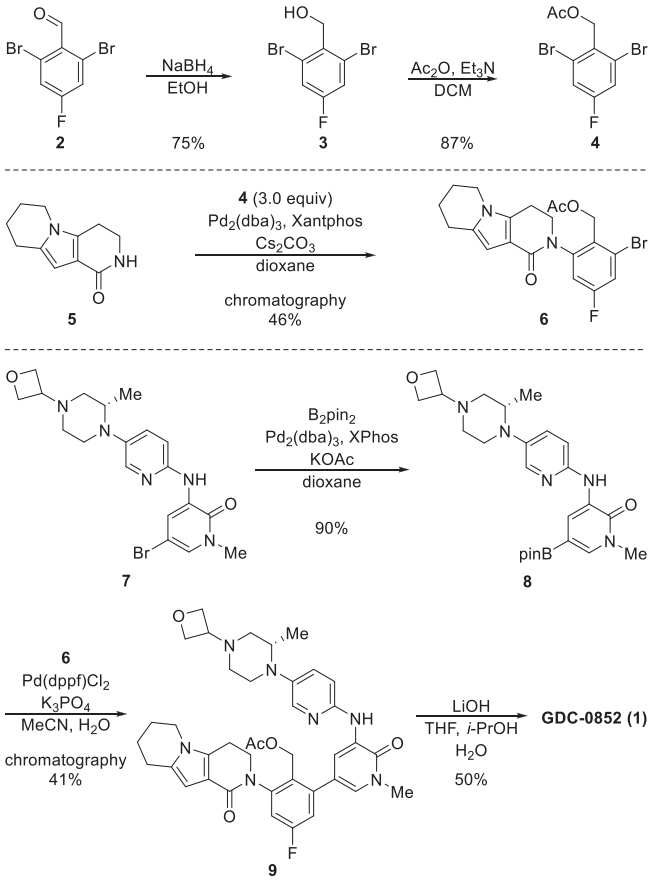
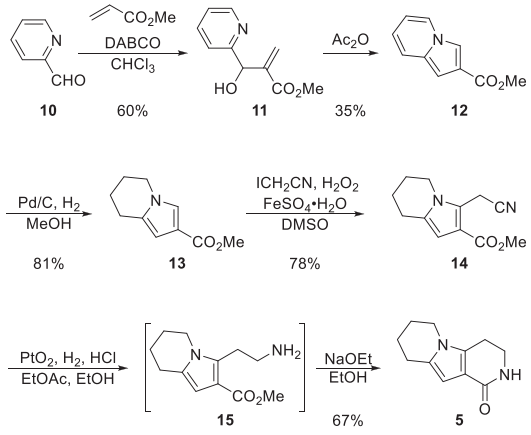


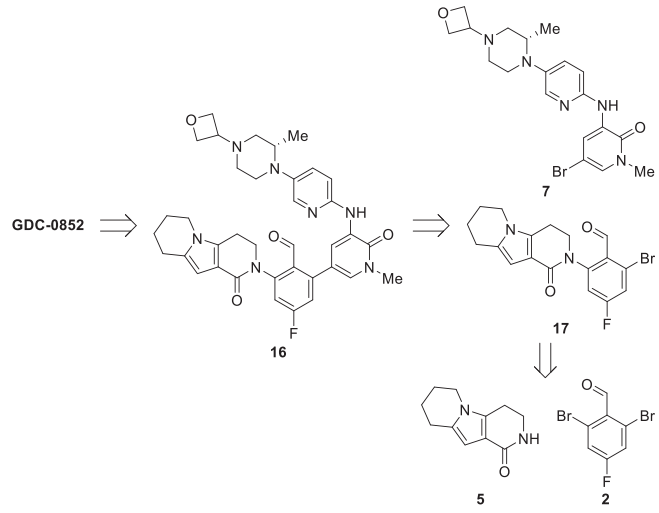
Scheme 1. Discovery synthetic approach to GDC-0852 (1).



Scheme 2. Original synthesis to fragment 5.

Results and discussion

After evaluating of the structure of GDC-0852 (**1**), we proposed a retrosynthesis shown in Scheme 3, which would bypass inefficient alcohol protection/deprotection steps in the discovery route and shorten the overall synthesis sequence. In this alternate route, the active pharmaceutical ingredient (API) would be derived from penultimate aldehyde **16**, which could be assembled through a Suzuki–Miyaura coupling of the boronic ester (**8**) of fragment **7** with bromide **17.** Intermediate **17** would be directly generated through palladium-catalyzed C—N coupling of fragment **5** with linker **2**.

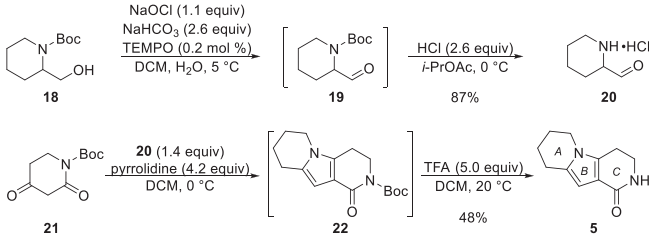


Scheme 3. Retrosynthetic analysis for assembly of GDC-0852.

Practical supply routes to fragments **2** [2,12] and **7** [13] are known and were adopted without changes to enable faster development for early phase delivery of GDC-0852 (**1**). We turned our attention to developing a concise synthesis of heterocycle **5** via the annulation of unprotected α-amino aldehyde **20** and diketone **21** [14,15]. This approach drastically reduced the number of key bond forming steps to tricyclic lactam **5** since a more advanced starting material piperidine-2,4-dione (**21**) could be utilized to form ring B convergently (Scheme 4).

Due to the unavailability of piperidine-2-carbaldehyde **20** on scale, we commenced our synthesis with the oxidation of commercially available **18** using TEMPO/NaOCl condition in DCM/water to give **19**, which was carried directly into the subsequent step. The Boc-deprotection was performed with HCl in *i*-PrOAc to facilitate the isolation of **20** as a crystalline HCl salt in high yield of 87%. Treatment of **20** with key fragment **21** in DCM and pyrrolidine furnished the desired tricyclic lactam **22**, which was unfortunately not stable under work-up and isolation conditions. The crude reaction mixture was therefore telescoped to the next step, in which TFA was employed to complete the Boc-deprotection. A crystallization condition in ethanol was developed to purify and isolate **5** in modest yield of 48% over two steps. This four-step synthesis provided a fit-for-purpose means to prepare multiple kilogram quantities of **5** safely and rapidly to support the material need for the endgame process.

With the key fragments (**2**, **5** and **7**) in hand, we began to evaluate the endgame chemistry to assemble GDC-0852 (**1**). A preliminary proof-of-concept for the direct C—N coupling of **5** to linker **2** was first achieved. The reaction employing 5 mol% $Pd_2(dba)_3$/Xantphos (1:2) as the catalyst and K_2CO_3 as the base in 1,4-dioxane proceeded encouragingly in 99% conversion at 95 °C (Fig. 2). However, despite high excess of bromide **2** (2.5 equiv), the selectivity of the



Scheme 4. Large scale preparation of 5 via new synthesis route.

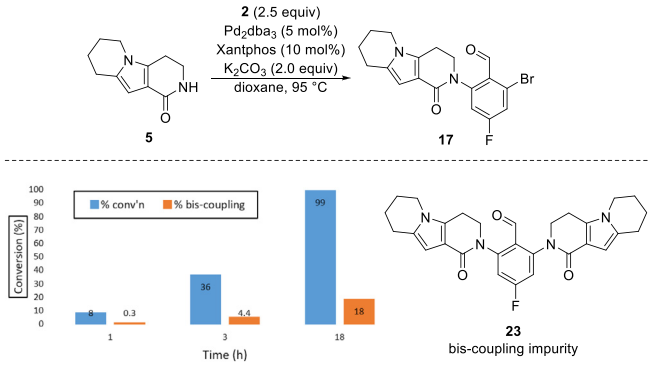


Fig. 2. Proof of concept for direct C—N coupling of **5** to linker **2.**

desired product **17** versus bis-coupling impurity **23** was poor (82:18) [16]. As the concentration of **17** grew during the reaction, the side reaction forming the bis-coupling impurity (<1% initially) turned into a major competitor due to limited bias of reactivity between bromides **2** and **17**.

We evaluated the Pd catalyzed C—N coupling through a microscale high-throughput experimentation (HTE) approach using a moderate stoichiometry of **2** (1.5 equiv) and K_2CO_3 (3.0 equiv) as base at 70 °C [17] confirmed Xantphos as one of the best ligands for this transformation (Fig. 3) [18]. Validation experiments on laboratory scale (0.50 g) showed that lower catalyst loading (5 mol%) in toluene at 80 °C could provide **17** in 97% conversion. A slightly improved selectivity (13% of bis-coupling impurity **23**) was observed when compared to the starting 1,4-dioxane conditions (Table 1, entries 1 and 2). However, reduction of linker stoichiometry (to 1.5 equiv) unfortunately led to higher bis-coupling impurity (19% of **23**, Table 1, entry 3). Further fine-tuning of temperature (70 °C) and linker stoichiometry (1.2 equiv) did not provide better outcome (Table 1, entries 4 and 5). Instead, poor

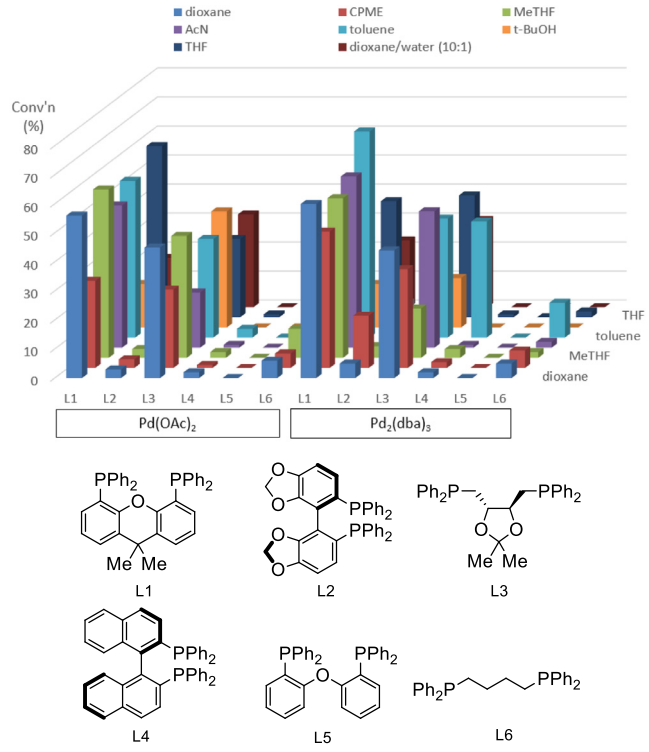
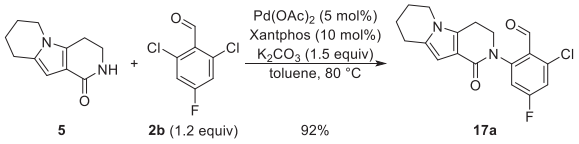


Fig. 3. Subset of HTE results for C—N coupling.

conversions (46–47%) were obtained in toluene as well as MeTHF. On the other hand, the reaction in toluene at 80 °C with 1.2 equiv linker **2** and 5 mol% catalyst achieved high conversion (97%), but bis-coupling impurity **23** (>15%) remained stubbornly high (Table 1, entry 6).

In order to achieve higher selectivity, a greater bias between the reactivity of the halides on linker **2** and the C—N coupling product was believed to be essential [19]. This hypothesis was tested and later validated by the reaction using 2-bromo-6-chloro-4-fluorobenzaldehyde **2a**. Even when the linker stoichiometry was reduced to 1.2 equiv, only 0.5% of **23** was observed. Additionally, the reaction produced excellent isolated yield (93%) on 10.0 g scale (Table 1, entry 7). Preferential amidation of bromide over chloride was evident. To our pleasant surprise, 2,6-dichloro-4-fluorobenzaldehyde (**2b**), a symmetrical substrate, could also provide high selectivity (97:3) and yield (90%) in favor of mono amidation product **17a** (Table 1, entry 8).

Due to the cost advantage and broader commercial availability, linker **2b** was selected for further development. On implementation to kilogram scale, the C—N coupling of **5** and **2b** provided **17a** in excellent selectivity (99:1) and clean reaction profile. Furthermore, crystallization in toluene purged side product **23** to <0.5% and afforded **17a** in 92% isolated yield and 98.0 A% HPLC purity (Eq. (1)).



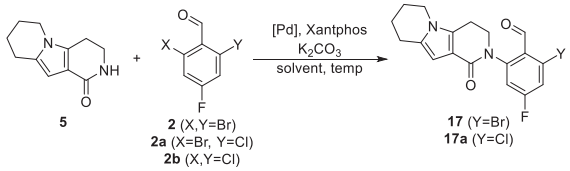
(1)

Next, we switched our focus to the Suzuki–Miyaura coupling to form penultimate intermediate **16** (Scheme 5). In order to further streamline the process, we explored and quickly adapted a telescoped borylation/Suzuki–Miyaura cross-coupling strategy using **7** and **17a**. This protocol circumvented the practice of preparing and isolating pinacol boronate **8** in a separate step. An active, dual-purpose catalyst $PdCl_2[P(t\text{-}Bu)_2Ph]_2$ was identified to accommodate both the borylation and Suzuki–Miyaura reactions in the same reactor. The telescoped reactions proceeded smoothly on kilogram scale with only minor impurities being observed. Subsequent aqueous work up and crystallization of Suzuki–Miyaura product in ethanol gave **16** in 71% yield and 98.0 A% HPLC purity. It should be noted that the purifications of **16** and **17a** by crystallization prior to the final API step were critical to control the residual Pd in the isolated API, which also enabled removal of chromatographic purifications from the endgame process.

The final aldehyde reduction to convert **16** to GDC-0852 API was subsequently achieved by performing the reaction in methanol with a slow addition of a solution of $NaBH_4$ in aqueous 1.0 N NaOH. The crude product, after work up, was then treated with Si-Thiol/Si-TMT to control residual Pd to <20 ppm, followed by recrystallization in IPA/water to furnish GDC-0852 (**1**) in 81% yield and 99.0 A% HPLC purity.

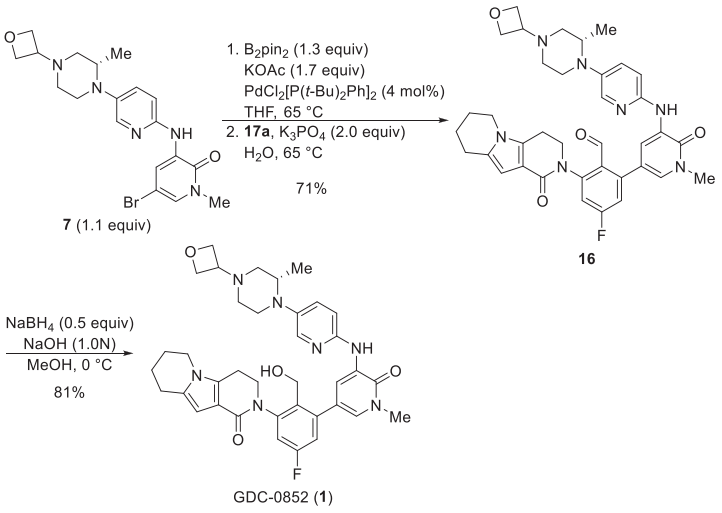
In conclusion, we have developed an enabling process for the delivery of kilogram quantities of GDC-0852 (**1**). Key starting material **5** was successfully prepared on scale via an efficient annulation of piperidine-2-carbaldehyde HCl salt (**20**) and *N*-Boc piperidine-2,4-dione (**21**). The endgame chemistry features a Pd-catalyzed C—N coupling of tricyclic lactam **5** and dichloride **2b** to assemble key intermediate **17a** and a telescoped borylation/Suzuki–Miyaura reaction to furnish the penultimate aldehyde intermediate **16**. $NaBH_4$ reduction of aldehyde **16** completed the synthesis of GDC-0852 (**1**) and afforded the API in 54% over 3 steps from **5** and 99.0 A% HPLC purity.

Table 1
C—N coupling selectivity of different linker substrates.



entry[a]	linker (equiv)	solvent / temp (°C)	% conv	23 (%)[b]
1[c]	**2** (2.5)	dioxane, 95	99	18
2	**2** (2.5)	toluene, 80	97	13
3	**2** (1.5)	toluene, 80	100	19
4[d]	**2** (1.2)	toluene, 70	47	11
5[d]	**2** (1.2)	MeTHF, 70	46	10
6[e]	**2** (1.2)	toluene, 80	97	19
7[e]	**2a** (1.2)	toluene, 80	100 (93)[f]	0.5
8[e]	**2b** (1.2)	toluene, 80	99 (90)[f]	2.9

[a] All reactions were conducted by heating **5** (0.50 g, 2.6 mmol), 120, 150 or 250 mol% linker **2**, 200 mol% K_2CO_3, 5 mol% $Pd(OAc)_2$ and 10 mol% Xantphos in solvent (4.0 mL) at 80 or 95 °C; [b]Normalized percent value to product by HPLC at 220 nm; [c]$Pd_2(dba)_3$ (5 mol%) and 5.0 mL solvent employed; [d]3.0 mL solvent employed; [e]150 mol% K_2CO_3 employed; [f]1solated yield for 10.0 g reaction.



Scheme 5. Improved endgame synthesis to GDC-0852.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors thank Anny Tangkilisan, Colin Masui, Theresa Cravillion and Scott Savage for assistance with high-throughput experimentations, Tina Nguyen and Drs. Sam Yang, Kenji Kurita and Chris Crittenden for analytical support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152447.

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[17] HTE was performed at 70 °C to accommodate lower boiling solvents.
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[19] The approach to use a differentiated linker was also described and successfully implemented on scale by Hong and co-workers (ref. 16).