A new synthesis of the amine fragment: an important intermediate to the anti-HIV drug lenacapavir
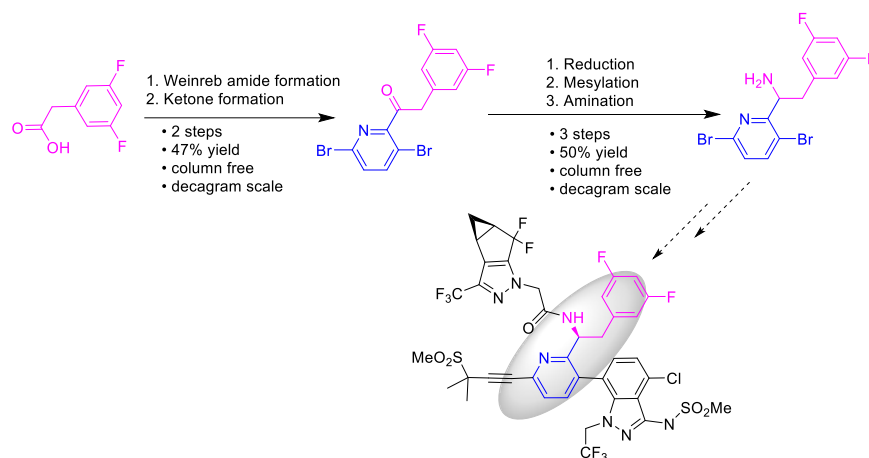
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TOC

ABSTRACT

Herein, we describe a new five-step approach to prepare 1-(3,6-dibromopyridin-2-yl)-2-(3,5-difluorophenyl)ethan-1-amine, an important intermediate in the synthesis of lenacapavir. The key step in the sequence is the Weinreb amide-based ketone synthesis, which provides an alternative entry point to the core structural component. Starting from the inexpensive 2-(3,5-

difluorophenyl)acetic acid, the Weinreb amide synthesis and the followed nucleophilic substitution afford the ketone in 47% yield. The subsequent functional group manipulation delivers the racemic amine which can be resolved with known mandelic acid resolution. This synthetic route has been demonstrated on decagram scale and affords the racemic amine in an overall isolated yield of 25%.

INTRODUCTION

The Human Immunodeficiency Virus (HIV) remains one of the most serious health threats in the world. With its progression to the Acquired Immunodeficiency Syndrome (AIDS), it is estimated that there are annually over 600,000 deaths worldwide from this disease and over 40 million deaths since the start of the epidemic.[1] There are currently about 40 million people globally that are infected by HIV - including 1.5 million children - and there are more than 1 million new infections annually.[2] Among the most promising therapies for the treatment of HIV infections, lenacapavir is a first-in-class drug that targets the HIV capsid protein.[3–5] It disrupts the functioning of the capsid protein across multiple steps in the viral life cycle. Remarkably, this substance has shown activity against all subtypes of HIV-1, including multi-drug resistant strains. This activity has been demonstrated at picomolar concentrations.[6] With its long-acting properties and bioavailability for oral and injectable dosing, lenacapavir is likely to become a first-line treatment for HIV infections.

Lenacapavir was first reported by Gilead Sciences in a family of patents and publications in 2018-2020.[7–10] The Gilead synthesis of lenacapavir involves the convergence of three major fragments and a propargyl sulfone (DMPS, in Figure 1). The central fragment of lenacapavir is Fragment A, which is joined to Fragment B using a Suzuki-Miyaura coupling and to Fragment C using a HATU-

promoted amide coupling. Fragment A is coupled to DMPS using a Pd-catalyzed Sonogashira reaction. Fragment A was prepared by Gilead from the chiral sulfinamide (**3**), which
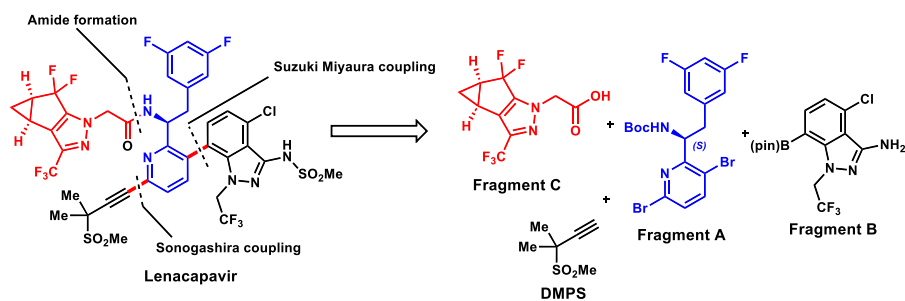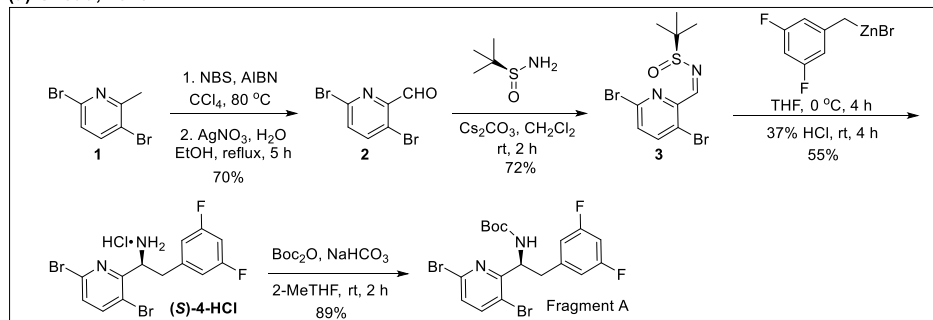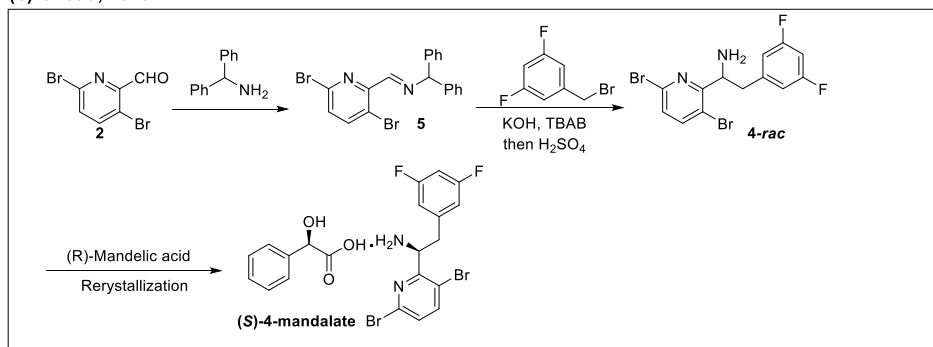

Figure 1. Retrosynthetic disconnections for lenacapavir and its simpler constituents for chemical synthesis.

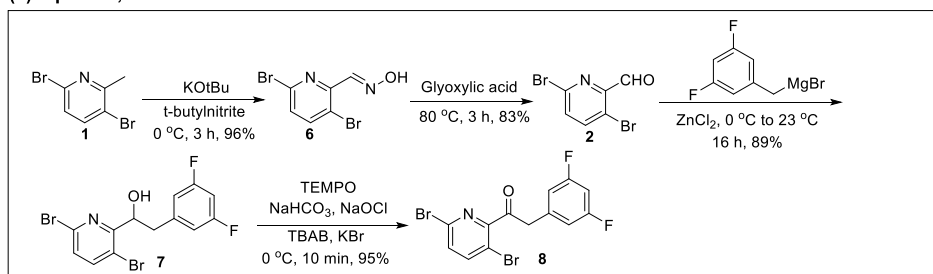**Scheme 1. Method for the synthesis of Fragment A and related conversions.**


provides the desired amine enantiomer **(S)-4-HCl** (as an HCl salt) after the addition and hydrolysis steps. Boc protection then provides Fragment A in 25% overall yield from 3,6-dibromo-2-methylpyridine (**1**). (Scheme 1a).[9,10] A racemic synthesis of amine **4-rac** was also described from imine **5** using an alkylation strategy and 3,5-difluorobenzyl bromide. Resolution of **4-rac** with (R)-mandelic acid afforded the desired amine enantiomer **(S)-4-mandalate** (Scheme 1b).[8] Recently, Lipshutz and coworkers disclosed an efficient route to the ketone intermediate **7** (Scheme 1c).[11] The sequence involves the reaction of aldehyde **2** with the organozinc reagent to provide the alcohol intermediate (**6**). These synthetic methods, while successful, all invoke the use of one or

more expensive raw material or reagent.[12] To advance the performance and cost-effectiveness of the chiral resolution route to Fragment A (en route to lenacapavir), we have sought to prepare **4-rac** from more economical reagents, using a route that supplants column chromatographic purifications with cheaper, scalable alternatives. Herein, we describe a novel five-step sequence for the synthesis of **4-rac** from inexpensive raw material and reagents.[13] The chemistry has been demonstrated on decagram scale (Scheme 2). The detailed results of these studies are reported herein.

Scheme 2. Five-step route for synthesis of amine **4-rac**.
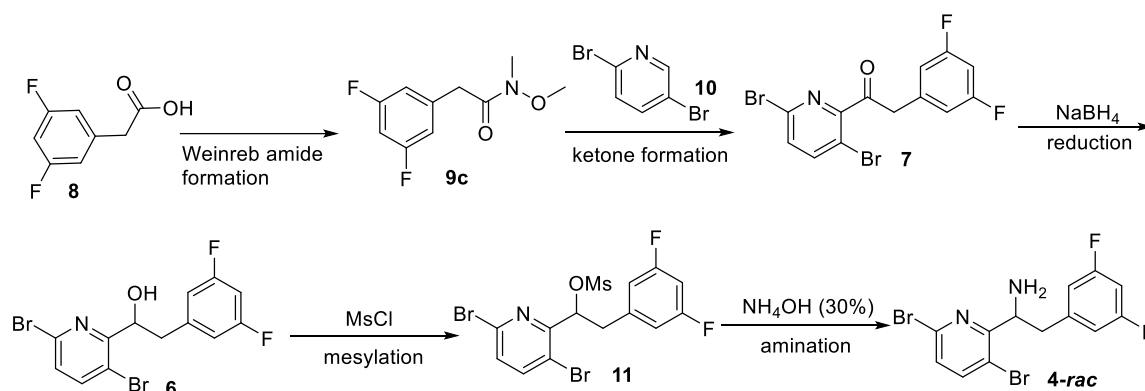
RESULTS AND DISCUSSION

The synthesis of ketone **7** is imperative to the success of the chemistry shown in Scheme 2.[14] Our initial efforts to make ketone **7** involved the nucleophilic substitution of 3,5-difluorobenzylnitrile **9a** with organomagnesium reagent **10-Mg** (Table 1). Organomagnesium reagent **10-Mg** was prepared by deprotonation of **10** with Knochel-Hauser base (TMPMgCl·LiCl), according to the reported protocol.[8] Treatment of **10-Mg** with **9a** failed to generate any desired product (Table 1, entry 1). Efforts to access ketone **7** by activating **9a** for **10-Mg** addition, with ZnCl₂ were not successful (Table 1, entry 2). Switching the organomagnesium reagent to organolithium salt **10-**

Li also failed to afford ketone **7**; partial scrambled lithiation and debromination were observed. Neither lowering the reaction temperature, nor the addition of organometal disaggregating additives such as HMPA and TMEDA resulted in no improvement. All these attempts resulted in main recovery of **10** (Table 1, entries 3-4). We postulated that these results may indicate that the organometallic reagent **10-Mg** or **10-Li** was quenched by the acidic benzylic C-H bonds of **9a** (pKa ~ 19-20)[15] negating the desired 1,2-addition at the nitrile.

Table 1. Synthesis of ketone **7**
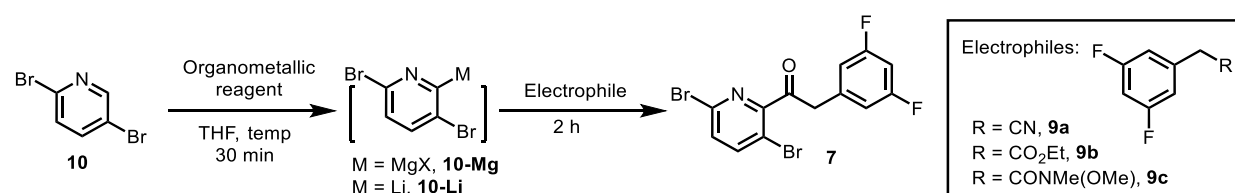
Entry[a]	Base (equiv)	Electrophile(equiv)	Temp (°C)	Yield/%
1	TMPMgCl·LiCl (1.5)	**9a** (1.5)	-20	ND
2	TMPMgCl·LiCl (2.5) / ZnCl$_2$ (1.1)	**9a** (1.1)	-20	ND
3	LDA (1.0) / HMPA (10%)	**9a** (1.2)	-40	ND
4	LiHMDS (1.0) / HMPA (10%)	**9a** (1.2)	-40	ND
5[b]	TMPMgCl·LiCl (1.5)	**9b** (1.5)	-20	15[c]
6	TMPMgCl·LiCl (1.1)	**9c** (1.1)	-10	45[c]
7	TMPMgCl·LiCl (1.0)	**9c** (1.1)	-20	40[c]
8	**TMPMgCl·LiCl (1.1)**	**9c (1.1)**	**-20**	**66[c]**
9[d]	**TMPMgCl·LiCl (1.1)**	**9c (1.1)**	**-20**	**50[e]**

[a]All reactions were carried out with **10** (0.25 g, 1 equiv) and organometallic reagent in THF (10 V) for 30 min, followed by addition of electrophile and stirring at the same temperature for 2 h under the condition shown in the table unless otherwise stated, solvent volume (V) = mL/g of **10**. [b]4 h. [c]Isolated yield with column chromatographic purification. [d]Reaction was conducted on 30 g scale. [e]Extractive workup and subsequential trituration for purification, the product was obtained with 93% purity (qNMR) after trituration from 5% ethyl acetate in heptanes. ND: the desired product was not detected.

We envisioned that a decrease of acidity of the benzylic C-H bonds of the electrophile might mitigate deprotonation and thus favor the addition reaction. In this regard, the reaction of **10-Mg** with ester **9b** (pKa ~ 22 -23)[15] afforded the desired product in 15% isolated yield (Table 1, entry 5). The positive results inspired our further investigation of other electrophiles. Weinreb amide **9c** (pKa ~ 26) was identified as optimal electrophile to afford ketone **7**. The reaction of **10-Mg** with Weinreb amide **9c** afforded ketone **7** in 45% isolated yield with 95% qNMR purity after column chromatography purification (Table 1, entry 6). We posit that the cumulative factors - less acidic benzylic C-H bonds and exceptional metal chelation capability of the Weinreb amide - facilitate ketone formation.[16] THF was the optimal solvent choice for this transformation. Further optimization of equivalents of Knochel-Hauser base and reaction temperature revealed that 1.1 equivalent of Knochel-Hauser base (TMPMgCl·LiCl) and -20 °C delivered the best result of ketone **7** (Table 1, entries 7-8). Under this best condition, the reaction of **10-Mg** with Weinreb amide **9c** afforded ketone **7** in 66% isolated yield after column chromatography purification (Table 1, entry 8). To eliminate column purification, a process of an extractive workup and subsequential trituration was identified to allow isolation of **7**. The protocol was demonstrated on a 30g scale, affording **7** in 50% of isolated yield with 93% purity (qNMR) (Table 1, entry 9). Weinreb amide **9c** was readily synthesized from commercially available acid **8** in a one-pot process. As shown in Scheme 3, conversion of acid to acetyl chloride followed by reaction with N,O-dimethylhydroxyl-amine afforded Weinreb amide **9c** in 96% isolated yield. As an alternative, **8** was also prepared from readily available 1-bromo-3,5-difluorobenzene in two steps in 32% overall isolated yield (see SI).[17]

Scheme 3. Synthesis of Weinreb amide **9c**.
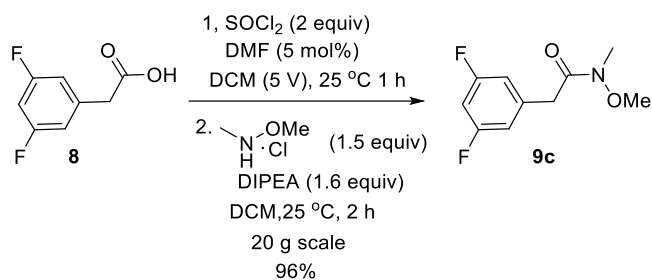
Ketone **7** is an important intermediate to access chiral amine **4**. Several chemical transformations including transition metal catalyzed hydrogenation have been disclosed by Gilead (Scheme 4).[8] For instance, asymmetric hydrogenation of a vinyl acetamide using a chiral iridium catalyst afforded **(S)-4-Ac**. Reductive amination of ketone **7** with a chiral ruthenium catalyst yielded **(S)-4**. Ketone **7** could be reduced to chiral alcohol with a chiral ruthenium catalyst and then converted to **(S)-4-HCl** under Staudinger reaction conditions. The chiral amine **(S)-4** could also be prepared through transaminase catalyzed amination. While the yield and enantioselectivity of these respective methodologies was not directly disclosed, all relied on expensive chiral metal catalyst/ligand systems or transaminase enzyme.

Scheme 4. Reported transformations of ketone **7** to chiral amine and derivatives.[8]
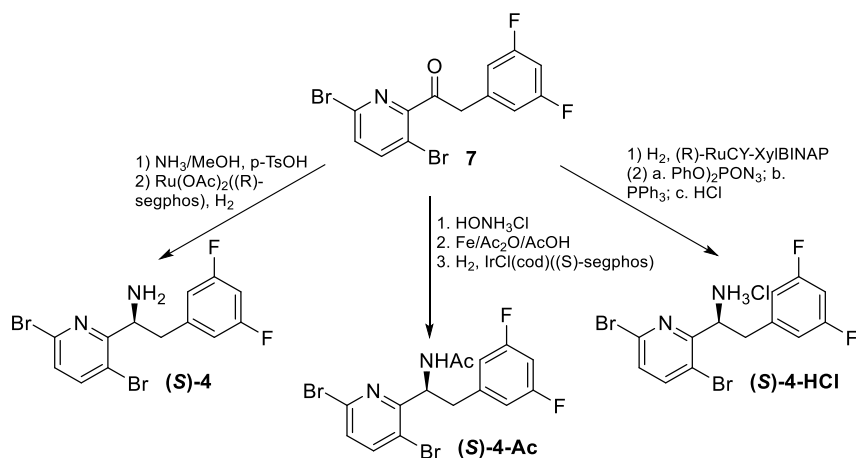
To achieve more cost-effective access to chiral amine **4**, our effort was focused on the synthesis of **4-rac**, a key precursor for the chiral resolution to afford the chiral amine. Initial attempts to achieve **4-rac** were performed by Leuckart amination of **7** with NH_4HCO_2,[18] but resulted in recovery of the starting material **7**. Other amines, such as Boc-NH_2[19]/$^tBuS(O)NH_2$[20] also failed to react with ketone **7**. Ultimately, reduction of ketone **7**, mesylation of the incipient alcohol, then amination of mesylate **11** successfully afforded **4-rac** (Table 2). Mesylate **11** was prepared in two steps from ketone **7** in >95% isolated yield (Scheme 5). Reduction of ketone **7** with $NaBH_4$ proceeded smoothly,[22] and afforded alcohol **6** in >95% isolated yield (95% qNMR purity). The subsequent mesylation of alcohol **6** with mesyl chloride furnished **11** in >99% isolated yield (93% qNMR purity). Simple aqueous workup was in both the reduction and mesylation reactions.

Scheme 5. Synthesis of mesylate **11** from ketone **7**.
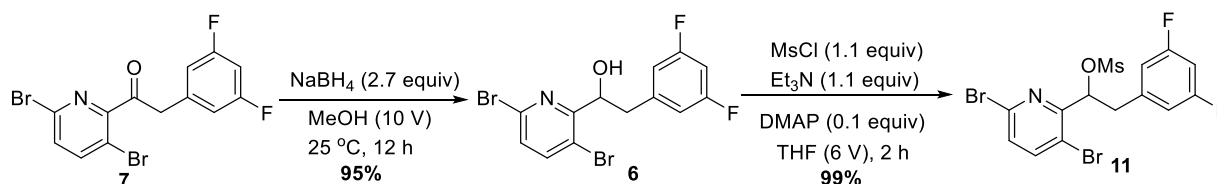
Treatment of **11** with NH_4OH in a heavy wall pressure vessel at 70 °C afforded **4-rac** in 48% isolated yield with 99A% purity (GC-MS), after column purification (Table 2, entry 1). Similarly, conducting the amination with a solution of NH_3 in MeOH provided **4-rac** in 46% isolated yield with 99A% purity (GC-MS) after column purification (Table 2, entry 2). The amination with NH_3 in MeOH scaled up to a 10 g scale, affording the **4-rac** in 56% isolated yield after column chromatography purification (Table 2, entry 3). Notably, 40 h of reaction time was needed to achieve a full conversion in this reaction. Under these conditions, the mesylate elimination

product, olefin **12**, was concurrently formed. Conducting experiments in conventional glass reactors, at ambient pressure, resulted in no reaction (Table 2, entries 4-5). To eliminate column purification, an aqueous pH-attuned workup process was developed. The protocol was demonstrated on a 10g scale with NH$_4$OH as aminating reagent. For example, after completion of the amination in a Parr reactor, the reaction mixture was treated with aq. HCl allowing complete elimination of the side-product **12** by ethyl acetate extraction, leaving **4-*rac*-HCl** in the aqueous phase. Adjusting the **4-*rac*-HCl** -enriched aqueous layer to an alkaline pH with aq. NaOH afforded pure **4-*rac*** as a solid, after crystallization in 54% isolated yield with 99% purity by qNMR (Table 2, entry 6).

Table 2. Optimization of amination **11** for synthesis of **4-*rac***
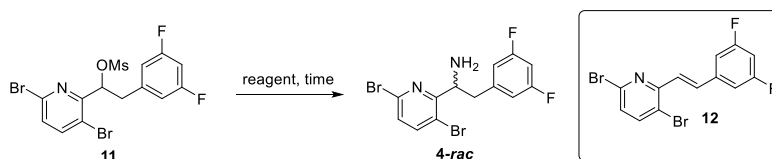
Entry[a]	Reagents (20 V)	Time	Isolated Yield
1	aq. 30% NH$_4$OH	24 h	48%[b]
2	7M NH$_3$ in MeOH	24 h	46%[b]
3	7M NH$_3$ in MeOH	40 h	56%[d]
4	7M NH$_3$ in MeOH	18 h	-[c]
5	aq. 30% NH$_4$OH	18 h	-[c]
6	aq. 30% NH$_4$OH	24 h	54%[e]

 [a]All reactions were carried out at 70 °C with 20 volumes of aminating solution as shown in table, volume = mL/g of **11**. [b]The reaction was performed on 100 mg of **11** in a heavy wall reactor; purification by column chromatography. [c]Reaction was performed in conventional glass reactors, at ambient pressure. [d]Reaction was performed with **11** (10 g, 20.7 mmol) and 7M NH$_3$ in MeOH (200 mL) in a Parr reactor; the inside pressure was recorded as 49 psi; the product was purified with column chromatography; olefin **12** was isolated in 22% yield. [e]Reaction was performed with **11** (10 g, 20.7 mmol), 30% aq. NH$_4$OH (200 mL) and MeOH (40 mL) in a Parr reactor; the inside pressure was recorded as 50 psi; the product was purified with an aqueous pH-attuned workup process.

To further showcase the synthetic utility of our five-step protocol for preparation of **4-*rac***, decagram-scale batches were carried out (Scheme 6). Starting with 50 g of 2-(3,5-difluorophenyl)acetic acid **8**, the Weinreb amide **9c** was isolated with 95% yield. Treatment of the Weinreb amide **9c** with 0.9 eq of 2,5-dibromopyridine (**10**) in the presence of 1.1 eq of TMPMgCl furnished the ketone **7** in 50% isolated yield with >99% qNMR purity. The ketone **7** was then reduced with NaBH$_4$ to afford alcohol **6** in 95% isolated yield. Mesylate **11** was obtained in almost quantitative yield by mesylation of alcohol **6**. Amination of mesylate **11** with NH$_4$OH in a Parr reactor delivered **4-*rac*** in 54% isolated yield with >99% qNMR purity after acid followed by base treatment. The overall isolated yield of the process from **8** to make **4-*rac*** was ~25% without the need of column chromatography purification.

Scheme 6. Decagram-scale demonstration of synthesis of **4-*rac***
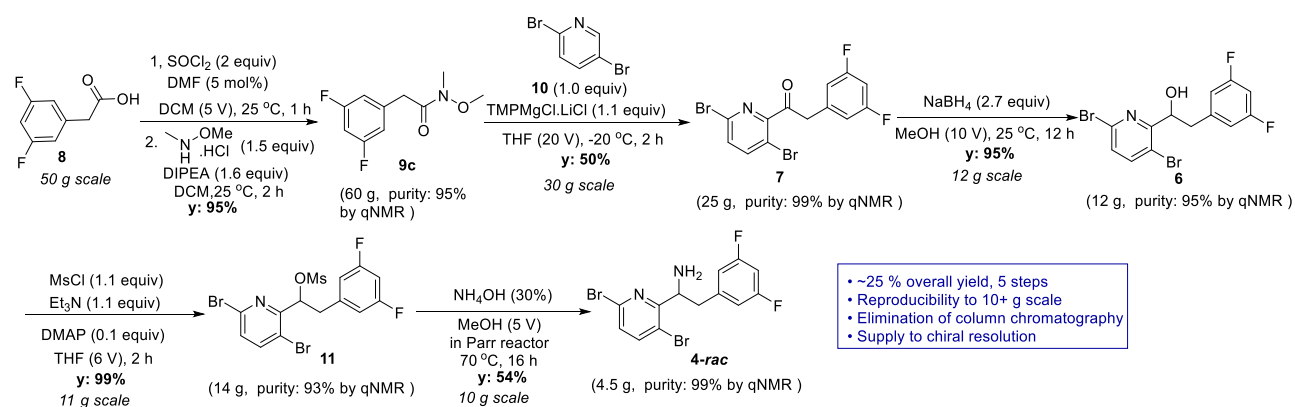
CONCLUSIONS

In conclusion, a new synthetic route has been disclosed to access the racemic amine **4-*rac***, advancing the synthesis of lenacapavir. This strategy featured ketone synthesis, reduction, mesylation and nucleophilic amination as key steps, utilizing readily available and inexpensive raw material and reagents. These findings will hopefully provide a cost-effective supply of racemic amine for use in chiral resolution to access the chiral amine in the synthesis of lenacapavir. We

hope that this new approach will inspire further efforts to optimize the process toward affordable commercial manufacture of lenacapavir for low and middle-income countries.

SUPPORTING INFORMATION

The Supporting Information is available free of charge at https://pubs.acs.org/doi/SOMEJOURNALLINK These data include additional experimental details and analytical methods.

ACKNOWLEDGEMENTS

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(12) Typical raw material cost: 3,5-Difluorobenzylzinc Bromide Solution (0.5 M in THF, 50 mL): $321.3 (Sigma-Aldrich); 3,5-Difluorobenzylmagnesium Bromide (0.25 M Ethyl Ether, 100 mL): $555.1 (Sigma-Aldrich); 2,5-Dibromo-6-Methylpyridine (100 g): $60 (AK Scientific).

(13) Major raw material cost in this route: 2,5-Dibromopyridine (100 g): $31 (AK Scientific);3,5-Difluorophenylacetic Acid (100 g): $240 (AK Scientific).

(14) When we draft the manuscript, Lipshutz disclosed a synthetic route to make the ketone, See Ref 7.

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