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Review

Synthetic Approaches to a Key Pyridone-carboxylic Acid Precursor Common to the HIV-1 Integrase Strand Transfer Inhibitors Dolutegravir, Bictegravir, and Cabotegravir

Pankaj S. Mahajan* and Terrence R. Burke, Jr.

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ABSTRACT: Dolutegravir (DTG), Bictegravir (BIC), and Cabotegravir (CAB) are the second-generation integrase strand transfer inhibitors (INSTIs) that have been FDA-approved for the treatment of HIV-1 infection. Preparation of these INSTIs utilizes the common intermediate 1-(2,2-dimethoxyethyl)-5-methoxy-6-(methoxycarbonyl)-4-oxo-1,4-dihydropyridine-3-carboxylic acid (**6**). Presented herein is a literature and patent review of synthetic routes used to access the pharmaceutically important intermediate **6**. The review highlights the ways in which small fine-tuned synthetic modifications have been used to achieve good yields and regioselectivity of ester hydrolysis.

KEYWORDS: *pyridone-carboxylic acid, integrase strand transfer inhibitors, synthetic route, regioselectivity, ester hydrolysis, Dolutegravir, Bictegravir, Cabotegravir*

1. INTRODUCTION

The human immunodeficiency virus (HIV-1), the causative agent of acquired immunodeficiency syndrome (AIDS), has been a persistent threat to humanity for more than three decades.[1] In 2019 alone there were approximately 1.7 million new HIV-1 infections and 700 000 deaths.[2] In excess of 26 million HIV-infected people were under treatment with antiretroviral therapy (ART) in 2019,[2,3] and that number rose to 38.4 million in 2021.[4] A variety of drugs have been approved for the treatment of HIV-1, with many of these having mechanisms of action that target various phases of the replicative cycle of HIV.[3] The viral enzyme integrase (IN) is responsible for insertion of the viral genome into the host human's DNA. This renders it an attractive target for the drug development of anti-HIV-1 agents.[5] An important class of IN inhibitors that block the insertion process are known as integrase strand transfer inhibitors (INSTIs).[6−11] Five INSTIs have been approved for the treatment of AIDS by the U.S. Food and Drug Administration (FDA): Raltegravir (RAL, **1**) and Elvitegravir (EVG, **2**) are first-generation INSTIs, while Dolutegravir (DTG, **3**), Bictegravir (BIC, **4**), and Cabotegravir (CAB, **5**) are second-generation INSTIs (Figure 1).[3]

The second-generation INSTIs (**3**−**5**) share a bicyclic carbamoyl pyridone (BiCAP) moiety (highlighted in red in Figure 1) as well as a 5-halobenzyl amide group.[12] Preparation of these analogues utilizes the pyridone-carboxylic acid **6** as a common synthetic intermediate (Figure 1).[12−14] The syntheses of the these INSTIs using the acid **6** as a common intermediate has been reviewed recently.[12] Our current review is focused on the preparation of **6** as detailed in the patent and journal literature with an emphasis on minor modifications that distinguish these preparations.

2. SYNTHESIS

2.1. One-Pot Syntheses by GlaxoSmithKline (GSK). *2.1.1. Pyridone Synthesis via a Key Cyclization.* GSK developed a one-pot synthesis of the common intermediate pyridone-carboxylic acid **6** (Scheme 1) and further utilized it in the synthesis of Cabotegravir (**5**).[15,16] Methyl-4-methoxy acetoacetate (**7**, 20 mL) and dimethylformamide dimethyl acetal (**8**) (DMF-DMA, 24 mL excess) were reacted in the absence of solvent at room temperature for 1.5 h to obtain the *trans*-olefin product (*E*)-methyl 2-((2,2-dimethoxyethylamino)methylene)-4-methoxy-3-oxobutanoate (**9**). Reaction of **9** with a mixture of methanol and aminoacetaldehyde dimethyl acetal (**10**) with stirring for 1 h at room temperature provided the secondary vinylogous amide **11** following concentration. The key cyclization of the secondary vinylogous amide **11** to the target pyridone **13** was achieved by reacting **11** with dimethyl oxalate (**12**) in methanol with the portionwise addition of lithium hydride while maintaining the reaction temperature below 25 °C, followed by heating the resulting reaction mixture at 40 °C for 14 h. The regioselective hydrolysis of the pyridone bis-ester **13** was carried out at −5 °C using lithium hydroxide. A 90% selective hydrolysis at the C-5 position provided the pyridone-carboxylic acid **6** following a typical acid workup. This one-pot, four-step protocol avoids purification by column chromatog-

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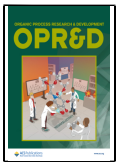

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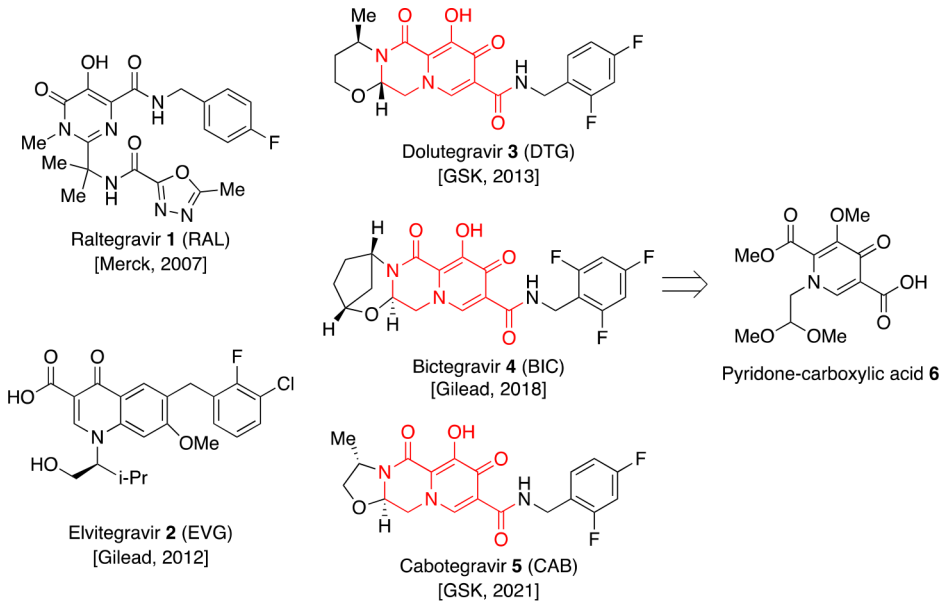
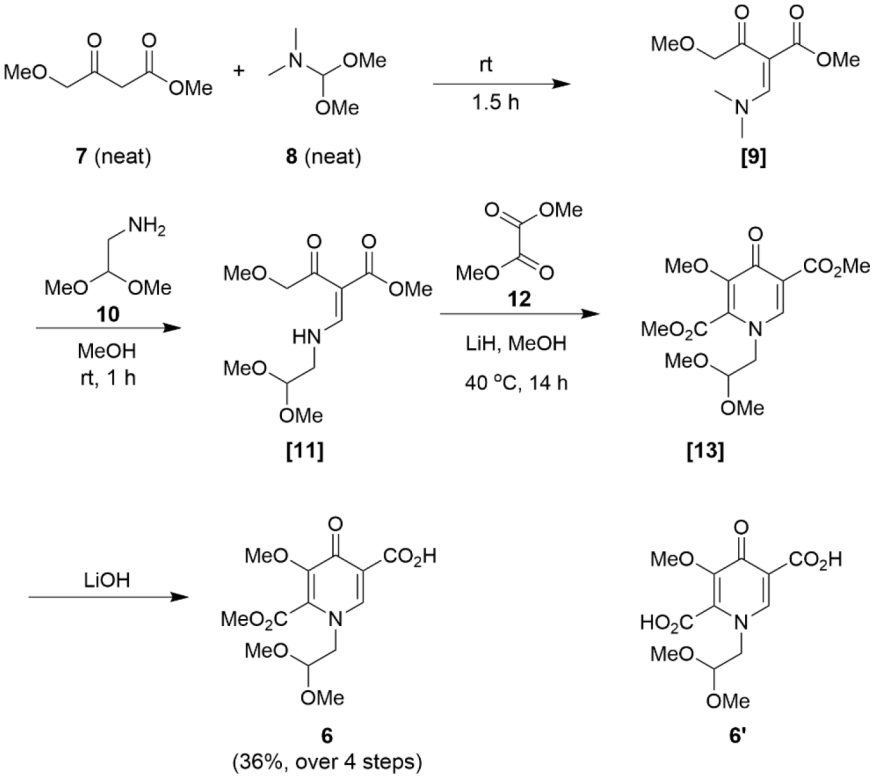


Figure 1. FDA-approved INSTIs with manufacturers, year of approval, and common intermediate precursor pyridone-carboxylic acid (**6**) used in the synthesis of INSTIs **3**–**5**. The bicyclic carbamoyl pyridone (BiCAP) moiety coming from the acid **6** is highlighted in red.

Scheme 1. One-Pot Synthesis of Pyridone-carboxylic Acid 6 by GSK[a]



[a]Brackets indicate that the compound has not been isolated from the reaction mass, but solvent was substantially removed to provide product as a nonsolid residue.[15,16]

raphy, with the final product **6** being collected by filtration in 36% overall yield. However, the authors did not provide data on the presence of pyridone bis-carboxylic acid **6′**, which is a possible side product arising from ester hydrolysis at both the C-2 and C-5 positions despite claiming that regioselectivity for ester hydrolysis of **13** is 90% at the C-5 position.

2.1.2. Modified Temperature-Controlled Synthesis. GSK modified the one-pot synthesis described in Scheme 1 to improve overall yields of the acid **6**.[17] The first step of the modified protocol is similar to the previous synthesis (on 12 mL scale of **7**), except that the reaction is performed overnight at ambient temperature with excess DMF-DMA being removed under vacuum to provide the crude product **9** from

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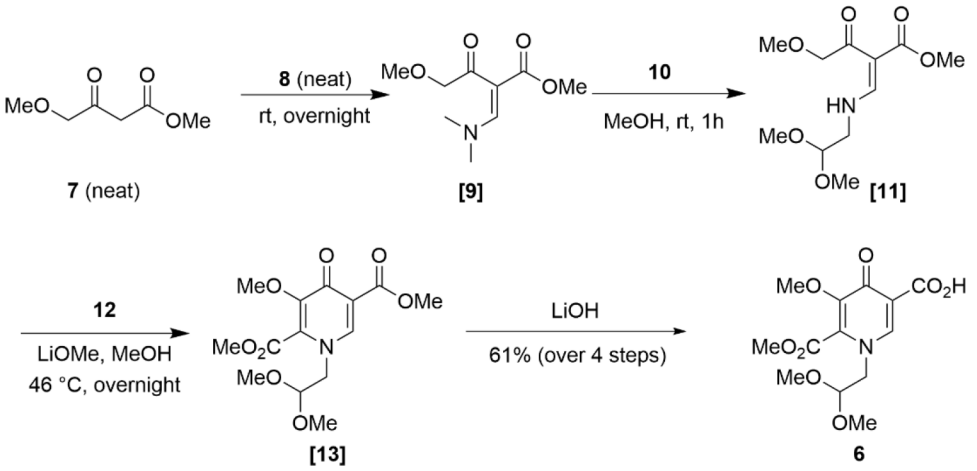
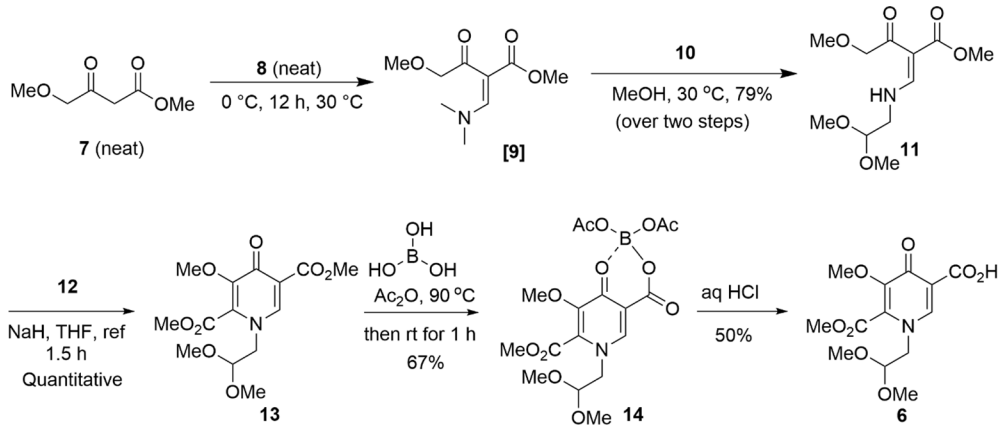
Scheme 2. Modified One-Pot Synthesis of Pyridone-carboxylic Acid 6 by GSK[17]



Scheme 3. Synthesis of Pyridone-carboxylic Acid 6 by the Mylan Lab[18,19]



DMF-DMA (Scheme 2). The secondary vinylogous amide **11** was obtained by adding 2,2-dimethoxyethan-1-amine (**10**) into a solution of **9** in methanol, while maintaining the reaction temperature below 10 °C with stirring (1 h), and then warming to room temperature and concentrating. The key cyclization reaction was performed by adding lithium methoxide (2 M in methanol) to a solution of **11** and dimethyl oxalate (**12**) in methanol under an inert atmosphere and heating to 46 °C overnight (the reaction time was not indicated). This yielded the pyridone bis-ester **13**. Regioselective ester hydrolysis of **13** was performed as in the previous synthesis but at −2 °C with a typical acid workup at 0 °C. The authors observed the regioselectivity ratio during ester hydrolysis of **13** as ∼10:1 or 90% selectivity at C-5 when lithium hydroxide was used, while NaOH and KOH provided 3:1 selectivity. It is possible that the bis-carboxylic acid **6′** went into the mother liquor after filtration. This one-pot reaction sequence produced the final target acid **6** in 61% overall yield.

2.2. Mylan Lab Approach via a Boron-ate Intermediate. The Mylan lab developed a new hectogram-scale process to prepare the acid **6** via the boron-ate complex **14** (Scheme 3). This yielded the target acid **6** (monoacid) as the sole product, avoiding the potential formation of the side product bis-carboxylic acid **6′**.[18,19] In the first step, addition of DMF-DMA (**8**) to methyl-4-methoxy acetoacetate (**7**) was performed at 0 °C, the reaction mixture was then stirred at ambient temperature (12 h), and the product **9** was taken forward for the next reaction without purification. Amino-acetaldehyde dimethyl acetal (**10**) was added to a precooled solution of **9** in methanol at 20 °C. Progress of the reaction was monitored, and upon completion the solvent was evaporated and the residue was dissolved in DCM followed by aqueous washing and concentration. The crude product **11** was then stirred with hexane and pure product was obtained by filtration; no purification was required. The pyridone bis-ester **13** was obtained quantitatively by cyclization of the *trans* secondary vinylogous amide **11** with dimethyl oxalate (**12**) using sodium hydride in THF under reflux with purification by column chromatography. To a heated solution of acetic anhydride and boric acid was added a solution of **13** in toluene, and the reaction mixture was stirred at 50 °C (1 h) to give the boron-ate complex **14**. This was hydrolyzed in methanol with cooling at 10 °C using aqueous HCl. Acid **6** was obtained as the sole product following the addition of H_2O and collection by filtration with 100% regioselectivity. This protocol avoids formation of the bis-carboxylic acid **6′**, but the overall yield is 26% following a single column purification step. The authors did not explain why the hydrolysis of boron-ate complex is low yielding (Scheme 3).

2.3. Divi Lab Benzyl Ester Approach. A report from the Divi lab claims that the regioselective ester hydrolysis described by GSK[15−17] (Schemes 1 and 2) does not occur with complete regioselectivity and that it results in at least 10% formation of bis-carboxylic acid **6′**.[20] The selectivity for ester

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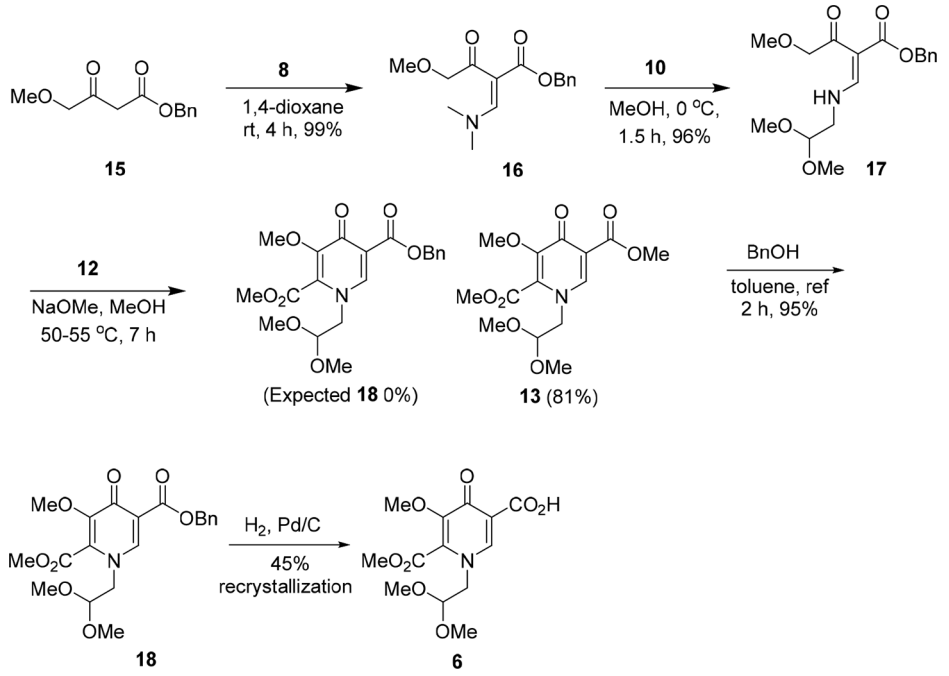
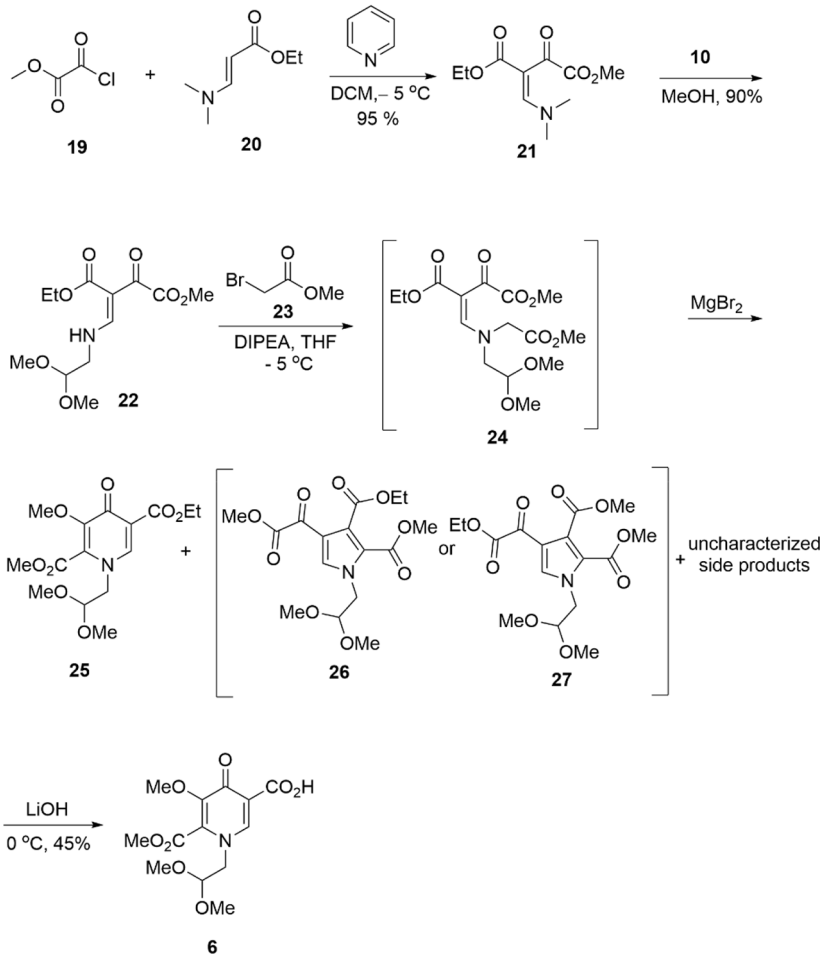
Scheme 4. Synthesis of Pyridone-carboxylic Acid 6 by the Divi Lab Involving Transesterification[20]



Scheme 5. Synthesis of Pyridone-carboxylic Acid 6 by Yu and Co-workers[21]



hydrolysis at the C-5 position is even poorer if sodium hydroxide or potassium hydroxide is used. To overcome this issue, they developed a new gram-scale synthetic route to the target acid **6** via benzyl ester **18** and utilized this in the

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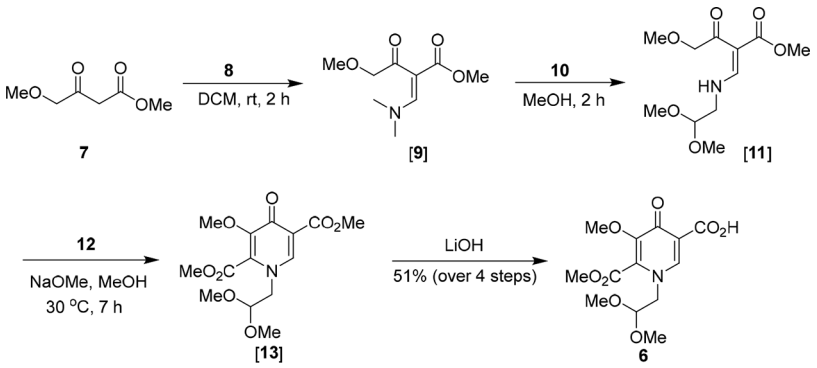
Scheme 6. Synthesis of Pyridone-carboxylic Acid 6 by Solara Active Pharma[22]



syntheses of Dolutegravir (**3**) and Cabotegravir (**5**) (Scheme 4).

Benzyl 4-methoxy-3-oxobutanoate **15** and DMF-DMA **8** were reacted in 1,4-dioxane to afford benzyl (*Z*)-2-((dimethyl)methylene)-4-methoxy-3-oxobutanoate (**16**) in quantitative yield. This was then reacted with **10** in the usual fashion to provide the *trans* secondary vinylogous amide benzyl ester **17** in 96% yield. The bis-methyl ester product **13** was observed during the cyclization reaction of **17** with dimethyl oxalate (**12**), and the expected benzyl ester product **18** was not observed (Scheme 4). The possible reasons for the trans-esterification were not discussed. The desired benzyl ester **18** was obtained in excellent yield by refluxing a solution of the bis-methyl ester **13** with benzyl alcohol in toluene. Catalytic hydrogenation of **18** yielded the target pyridone-carboxylic acid **6** in 45% yield after a single recrystallization from methanol/H_2O. The overall yield of this approach is 33%; however, a lower yield might have resulted from the loss of some final product during recrystallization. This methodology provides an alternate means of achieving 100% regioselective ester hydrolysis at the C-5 position. The bis-methyl ester product **13** can be directly converted to the corresponding mixed benzyl ester **18** and carried forward to the acid **6** without purification following catalytic hydrogenation.

2.4. $MgBr_2$-Promoted Intramolecular Cyclization Approach. Yu and co-workers developed a new hectogram-scale synthetic route to the acid **6** via $MgBr_2$-promoted intramolecular cyclization.[21] The synthesis reacts commercially available methyl oxalyl chloride (**19**) with ethyl 3-(*N*,*N*-dimethylamino)acrylate (**20**) using pyridine as a base in DCM at −5 °C to afford the vinylogous amide **21** (Scheme 5). The authors standardized these conditions by varying the base and reaction temperature. Subsequent coupling with amino-acetaldehyde dimethyl acetal (**10**) under standard conditions provided the vinylogous amide **22**. The authors performed an extensive investigation of the intramolecular regioselective cyclization (a key step) to achieve the mixed pyridone bis-ester **25**. The study revealed that, by utilizing $MgBr_2$ as an additive and *N*,*N*-diisopropylethylamine as a base at −5 °C, the cyclization proceeded via intermediate **24**. This gave an optimized 55% yield of the desired pyridone bis-ester **25** along with a mixture of pyrrole side product **26** or **27** (total 10%) and additional unidentified side products (35%). The claimed yields of **25**, pyrrole isomers **26** and **27**, and other side products were based on chromatographic analysis (TLC or HPLC) of the organic phase of the reaction mixture after workup. Regioselective ester hydrolysis of **25** at the C-5 ethyl ester was accomplished directly by treating the organic phase containing a mixture of products **25** and **27** with the addition of H_2O and 2 equiv of lithium hydroxide at 0 °C. This afforded the expected pyridone-carboxylic acid **6** in 45% yield over two steps. The authors also purified and characterized the mixed pyridone bis-ester **25** from the key cyclization reaction.

The authors studied ester hydrolysis by varying base composition and reaction temperature and found that the best condition was 2 equiv of lithium hydroxide at 0 °C, which provided a 90% yield of the acid **6** with 8% of the bis-carboxylic acid **6′**. The authors claimed that sodium hydroxide and potassium hydroxide did not provide considerable selectivity at C-5 for ester hydrolysis of mixed ester **25**. The overall yield for the entire sequence of reactions was 38%. Although the key step was not regioselective and gave moderate yields of the expected product **25**, the study provides encouragement to synthetic chemists to further investigate the transformation.

2.5. Solara Active Pharma Approach. Solara Active Pharma developed a slightly modified route to the acid **6** relative to what is shown in Schemes 1 and 2 (Scheme 6). They used this for the synthesis of Dolutegravir (**3**).[22] The company performed the synthesis on a 100 g scale. The first step employed DCM with removal of solvent *in vacuo* after synthesis of the *tert*-vinylogous amide **9**. Conversion to the vinylogous amide **11** was achieved by reaction with amino-acetaldehyde dimethyl acetal (**10**) in methanol. Cyclization to the pyridone bis-ester **13** was carried out at 30 °C in the presence of dimethyl oxalate (**12**) and lithium methoxide. The product pyridone-carboxylic acid **6** was obtained by regioselective ester hydrolysis using lithium hydroxide at 0 °C after acidification with 2 N HCl followed by recrystallization in isopropanol. In this way the final acid **6** was obtained in four steps with an overall 51% yield. The authors did not discuss the formation of pyridone bis-carboxylic acid **6′** or the regioselectivity of hydrolysis.

2.6. Cipla Continuous Flow Approach. A continuous flow approach to the pyridone-carboxylic acid **6** was developed by Cipla.[23] The process is a straightforward, economical, and cost-effective method that is suitable for industrial scale-up (Scheme 7). Advantages include high yields with reduced reaction times. The process is effective and requires only 20 min for four steps to achieve an overall yield of approximately 80% with 99.5% purity. The synthesis was successfully conducted on a kilogram scale.

Methyl-4-methoxy acetoacetate **7** and DMF-DMA (**8**) were reacted in a microchannel reactor at 30 °C for 40 s to give the condensation product **9**. This was continuously moved from the first reactor to the next microchannel reactor. Amino

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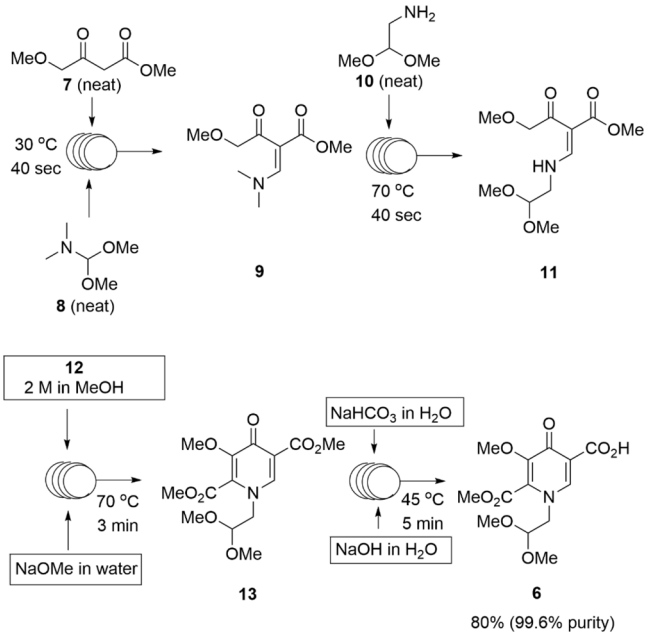
Scheme 7. Cipla's Continuous Flow Preparation of Pyridone-carboxylic Acid 6[23]



acetaldehyde dimethyl acetal (**10**) was added at 70 °C with a residence time of 40 s to yield the secondary vinylogous amide **11**. The mixture was then continuously flowed through a tube flow reactor in which a 2 M solution of dimethyl oxalate (**12**) in methanol was added in the presence of sodium methoxide at 70 °C. After a residence time of 3 min the cyclized product pyridone bis-ester **13** was obtained. This was introduced continuously in a tube flow reactor to which was added a solution of sodium bicarbonate and sodium hydroxide in H_2O at 45 °C and a residence time of 5 min to give crude pyridone-carboxylic acid **6** (90% yield). This was further purified by crystallization from isopropanol to give the acid in 80% overall yield and >99% purity.

2.7. Miscellaneous. Zhao and Wang employed GSK's approach[15] to synthesize acid **6** and used this in the preparation of the Dolutegravir tricyclic intermediate. They studied epimerization of the newly formed chiral center in this pharmaceutically important tricycle catalyzed by EDCI/DMAP. The authors also presented a detailed study of the diastereomer formation and proposed the mechanism for the observed diastereoselectivity.[24] Aurabindo Pharma synthesized Dolutegravir using GSK's approach[15] to prepare the intermediate acid **6**[25] and studied the regioselective ester hydrolysis of **13** using various bases. Lithium hydroxide monohydrate (2 equiv) provided an 85% yield of acid **6** and only 3% formation of bis-acid **6′**, while sodium hydroxide and potassium hydroxide were not selective and produced high yields of the unwanted bis-carboxylic acid **6′**.[26] Absolute purity of acid **6** was obtained by recrystallization from H_2O. Gilead Sciences also utilized GSK's[15] methodology in its development of new INSTIs.[27] We have also taken advantage of GSK's modified approach[17] in our development of new *N*-substituted bicyclic carbamoyl pyridone (BiCAPs) based INSTIs.[28]

3. SUMMARY

The importance of the precursor **6** has prompted academics and pharma to develop new synthetic routes for its preparation that are practical and inexpensive; see Table 1 for a comparison of reported syntheses. The following summarizes highlights of the current literature survey:

Table 1. Comparison of Reported Syntheses of Acid 6

approach	reaction scale	synthetic steps	overall yield (%)	regioselectivity ratio (C-5:C-2)
GSK's synthesis[15,16]	20 mL	four steps (one pot)	36	~90:10
GSK's modified synthesis[17]	12 mL	four steps (one pot)	61	~90:10
Mylan lab[18,19]	200 g	five steps	26	100%
Divi lab[20]	25 g	five steps	33	100%
Yu et al.[21]	143 g	five steps	45	90:8
Solara Active Pharma[22]	100 g	four steps	51	not discussed
Cipla's continuous flow[23]	5 kg	four steps	80	not discussed
Aurobindo Pharma[26]	50 g	four steps (one pot)	70	85:3

- GSK has developed an effective one-pot synthesis of the acid precursor **6** and applied this to the synthesis of Cabotegravir, which was approved for the treatment of HIV/AIDS in 2021 (Schemes 1 and 2).[15−17]
- Inspired by GSK's one-pot development of the acid **6**, industrial sources advanced the field through modification of the synthetic routes.
- The Mylan lab used the boron-ate intermediate **14** to achieve 100% selectivity for the regioselective ester hydrolysis at C-5, which would otherwise not be possible (Scheme 3).[18]
- The Divi lab used the benzyl ester derivative **18** for ester hydrolysis to obtain the desired acid product. They discovered transesterification during their development (Scheme 4).[20]
- Cipla developed a fast and very effective continuous flow synthesis of **6** with high yields and selectivity for regioselective ester hydrolysis. The entire synthesis requires only 20 min only with 80% overall yield (Scheme 7).[23]
- An absolute purity of acid **6** could be achieved via recrystallization from isopropanol[22] or H_2O[26] if a mixture of **6** and **6′** arises from the ester hydrolysis step.

4. CONCLUSION

The pyridone-carboxylic acid **6** is an essential precursor for the synthesis of all three second-generation INSTI drugs used in the therapy of HIV/AIDS. These can be synthesized from the common precursor pyridone-carboxylic acid **6** with two additional steps, depending on the choice of fluorinated benzyl amines and amino alcohols. This article covers the detailed synthetic development of the common acid precursor **6**. A central challenge in the synthesis of the acid **6** is to achieve 100% regioselectivity for ester hydrolysis at the C-5 position. Ester hydrolysis of **13** can be addressed, either by converting **13** to **18** or by creating a labile ester at the C-5 position. If a mixture of the acid **6** and bis-acid **6′** is observed in the designed synthesis, the bis-acid can be removed via recrystallization with isopropanol or H_2O, wherein it goes into the mother liquor. In our current report we cover detailed aspects in the developed synthetic routes for the acid **6**. We believe that the current review will be useful for synthetic, medicinal, and process chemists in choosing the most appropriate synthetic route to access medicinal and biologically active compounds having the pyridone-carboxylic acid moiety.

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AUTHOR INFORMATION

Corresponding Author

Pankaj S. Mahajan − *Chemical Biology Laboratory, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Frederick, Maryland 21702, United States*; Phone: 301-846-5910; Email: pankaj.mahajan@nih.gov; Fax: 301-846-6033

Author

Terrence R. Burke, Jr. − *Chemical Biology Laboratory, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Frederick, Maryland 21702, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.oprd.3c00063

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Notes

The authors declare no competing financial interest.

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