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Practical Synthesis of a HIV Integrase Inhibitor

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Abstract:

A practical and efficient synthesis of the potent HIV integrase inhibitor 1 is described. Starting from readily available 3,4-dihydro-2*H*-pyran, the six-step synthesis features a through process without purification of any of the intermediates until the isolation of crystalline intermediate 7. After deprotection and classical resolution, amine 8 was isolated with excellent enantiopurity. A final amide coupling completed the synthesis of 1 in 7.6% overall yield from DHP. This chromatography-free route is more cost effective and increases the overall yield by nearly 3 times when compared with the original Med Chem synthethic route. This improved chemistry was used successfully to prepare multikilogram quantities of integrase inhibitor 1.

Introduction

Human immunodeficiency virus (HIV) type 1 encodes three enzymes, reverse transcriptase, protease, and integrase, that are implicated in the replication of the virus.[1] To date, antiretroviral therapies targeting two viral enzymes, reverse transcriptase and protease, have become widely available.[2] A combination of antiretroviral therapies has been approved to effectively reduce the viral load.[3] The development of potent and selective inhibitors of HIV integrase may provide additional long-term benefit, especially when used in a combination treatment of AIDS.[4]

As part of an ongoing drug discovery program in our laboratories, bicyclic hydroxypyrimidinone **1** has been identified as one such selective and potent inhibitor of HIV integrase.[5] Herein, we report a novel, chromatography-free synthesis, which is suitable for preparing multikilogram quantities of **1**.

The key features of our synthesis of **1** are outlined retrosynthetically in Scheme 1. Thus, **1** would be derived from racemic amine **(±)-8** by resolution followed by oxalamide formation. Further disassembly of compound **8** by cleavage of the seven-membered ring carbon−nitrogen bond would furnish the open-chain pyrimidone **5**, which in turn could be derived in one step from compound **4** through a rearrangement reaction. Compound **4** could be prepared in two steps from *N*-protected aminonitrile **2** through hydroxyamidine formation, followed by dimethyl acetylenedicarboxylate (DMAD) addition. Finally, compound **2** is readily available from 3,4-dihydro-2*H*-pyran (DHP) in a three-step sequence consisting of hydration, followed by a Strecker reaction and subsequent amine protection.

Results and Discussion

Synthesis of Bicyclic Hydroxypyrimidinone 7. The synthesis of **7** began with the hydration of DHP using aqueous

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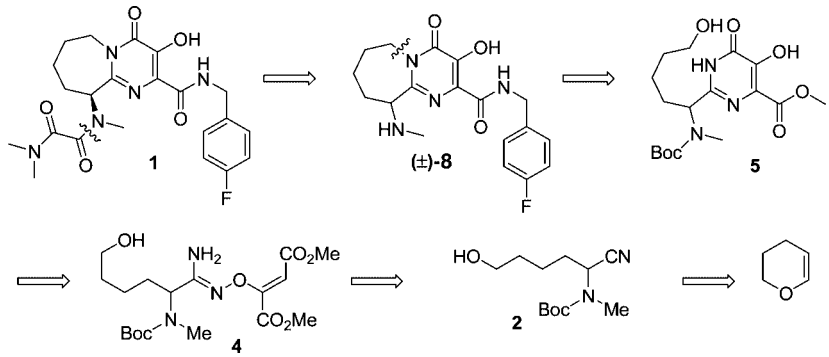
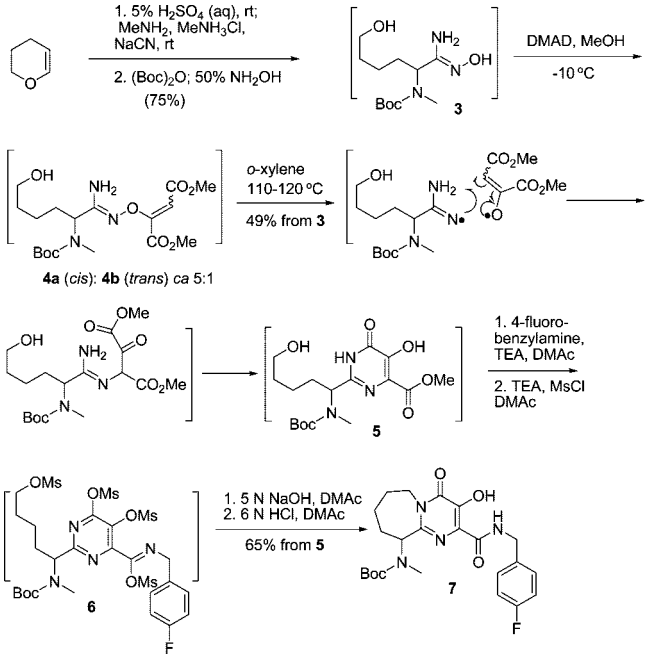
Scheme 1. **Retrosynthetic analysis of 1**



Scheme 2. **Through-process synthesis of bicyclic hydroxypyrimidinone 7**



sulfuric acid at 20−35 °C (Scheme 2).[6] The pH of the reaction mixture was adjusted to pH 6−7 with a 40% aqueous methylamine solution. A Strecker reaction was performed on the resulting hemiacetal using sodium cyanide and methylamine hydrochloride in water affording the corresponding *N*-methylaminonitrile. Selective Boc-protection of the secondary amine with di-*tert*-butyl dicarbonate, followed by treatment with 50% aqueous hydroxylamine gave compound **3** in 75% assay yield from DHP. The resulting reaction mixture was treated with DMAD at −10 °C overnight, then slowly warmed to room temperature to afford a mixture of *O*-alkene amidoximes **4a** (*cis*) and **4b** (*trans*) in 100% conversion. The thermal rearrangement[7] of the 5:1 mixture of **4a/4b** in *o*-xylene at 120 °C for 9 h afforded hydroxypyrimidinone **5** in 49% assay yield from compound **3**.

We were pleased to find that hydroxypyrimidinone **5** could be successfully amidated with 4-fluorobenzylamine in *N*,*N*-dimethylacetamide (DMAc), followed by treatment with excess methanesulfonyl chloride to afford the tetra-mesylated intermediate **6**. Without workup, treatment of intermediate **6** with sodium hydroxide, followed by acidification to pH 2−3 using 6 N HCl, gave crystalline bicyclic hydroxypyrimidinone **7** in 24% overall yield from DHP.

Synthesis of Chiral Amine (−)-8 via Classical Resolution. Removal of the *N*-Boc protecting group from **7** was accomplished using hydrogen chloride (gas) in ethyl acetate, followed by neutralization with sodium hydroxide to provide racemic **8** (Scheme 3). After an initial screen of resolving agents and solvents, we found that the desired **(−)-8** could be selectively crystallized as the di-*p*-toluoyl-L-tartaric acid (L-DTTA) salt from DMF in 43% isolated yield. The salt was a 2:1 complex of **(−)-8**−L-DTTA. After a salt break of the chiral amine L-DTTA salt with sodium hydroxide, the desired amine **(−)-8** was isolated from an aqueous THF solution in 93% yield and 97% ee.

Synthesis of Chiral Amine (−)-8 via Classical Resolution/Racemization. As shown in Scheme 4, we attempted to directly racemize the undesired chiral amine **(+)-8**−L-DTTA salt

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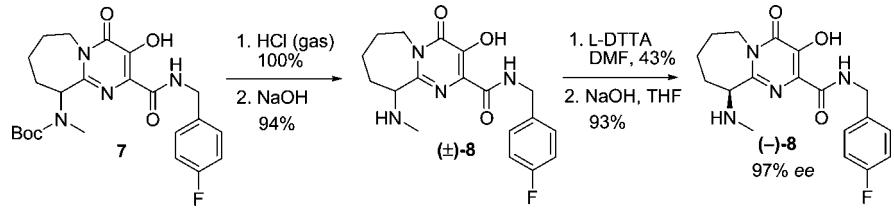
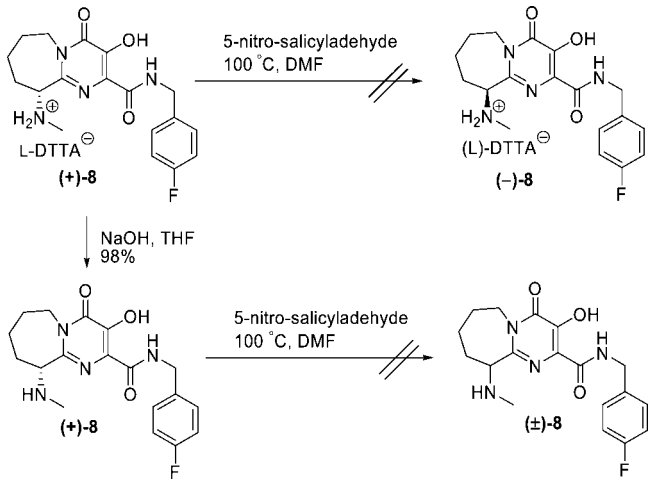
Scheme 3. **Synthesis of chiral amine (−)-8 via classical resolution**



Scheme 4. **Racemization of undesired (+)-8−L-DTTA salt and free amine (+)-8**



through a kinetic resolution/racemization process[8] which could be facilitated by a catalytic amount of an aldehyde catalyst (e.g., *p*-anisaldehyde, 5-nitro-salicyladehyde, etc.). Unfortunately, all attempts failed due to the poor thermal stability of the (+)-**8**−L-DTTA salt complex. Decomposition of the undesired chiral amine (+)-**8**−L-DTTA salt occurred at 70 °C without conversion to the desired chiral amine (−)-**8**−L-DTTA salt. The undesired free amine (+)-**8** also failed to racemize even at 150 °C in the presence of several reagents (e.g., *p*-anisaldehyde, 5-nitro-salicyladehyde, TMSCl/DBU, etc.).

We then postulated that the relative acidity of the phenolic hydroxyl group could be preventing epimerization at the amine center. Accordingly, compound **7** was protected as the methanesulfonate ester in high yield, and the amine was subsequently deprotected to give (±)-**10** (Scheme 5). Resolution of the amine with di-*p*-toluoyl-D-tartaric acid (D-DTTA) afforded desired chiral amine D-DTTA salt **11** in 51% isolated yield and 95% ee. After salt break of **11** and cleavage of the methanesulfonate ester with benzylamine, the desired chiral free amine (−)-**8** was isolated in 95% overall yield and without erosion of the ee.

Attempts to racemize the undesired antipode D-DTTA salt **12** to a mixture of **11** and**12** were not successful due to thermal instability. However, the undesired amine (+)-**10**, prepared from salt **12**, was successfully converted to (±)-**10** in 95% overall yield in the presence of 10 mol % of *p*-anisaldehyde at 70 °C for 35 h. The recycled racemic amine **10** could then undergo a second resolution using D-DTTA, thereby increasing the overall yield of the process. The epimerization mechanism, as shown in Scheme 6, likely proceeds via an azomethine ylide intermediate.[9]

Finally, attachment of the oxalamide side chain to amine (−)-**8** provided compound **1** (Scheme 7). Activation of dimethyloxamic acid by ethyl chloroformate in the presence of 4-methylmorpholine (4-NMM) gave the corresponding mixed anhydride as an intermediate, which was then coupled with amine (−)-**8**. Treatment of the reaction mixture with 40% aqueous dimethylamine effected cleavage of the small amount of *O*-acylated byproduct, to afford **1** in 86% overall yield and >99% ee after isolation by crystallization.

Conclusions

We have developed a practical, scaleable, and efficient synthesis of the potent HIV integrase inhibitor **1** in 7.6% overall from DHP. The route is highlighted by a six-step synthesis of the bicyclic hydroxypyrimidinone core **7** that does not require isolation of any of the intermediates. This chromatography-free route is more cost effective and increases the overall yield by nearly 3 times when compared with the original synthesis. This practical chemistry has been used successfully to prepare multikilogram quantities of HIV integrase inhibitor **1**.

Experimental Section

Analytical Methods. All reactions were carried out under nitrogen. Flash chromatography was carried out with EM Science silica gel 60 (neutral, 230−400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance NMR Spectrometer. Chemical shifts were reported in ppm relative to the residual deuterated solvent for ^{1}H and the deuterated solvent for ^{13}C. IR spectra were recorded on a Nicolet Margna FT-IR spectrometer 560. HPLC analysis was performed on a Hewlett-Packard 1100 MSD instrument. HRMS was recorded on a Micromass QT of Ultima API US mass spectrometer by ESI.

Preparation of *tert*-Butyl-(1-cyano-5-hydroxypentyl)methylcarbamate 2. To 5% w/v aqueous H_2SO_4 (120 mL) was added dropwise 3,4-dihydro-2*H*-pyran (42.06 g, 0.500 mol) over 30 min at 30−35 °C. The resulting solution was aged for 30 min at the same temperature. To the reaction mixture was added 0.2 equiv of 40% aqueous methylamine (8.6 mL, 0.100 mol) at 0−5 °C, and the pH was adjusted to 6−8 with 5 N aqueous NaOH. Methylamine hydrochloride (27.0 g, 0.400 mol, 0.8 equiv) and sodium cyanide (24.5 g, 0.500 mol, 1 equiv) were then added to the reaction mixture. The resulting solution was

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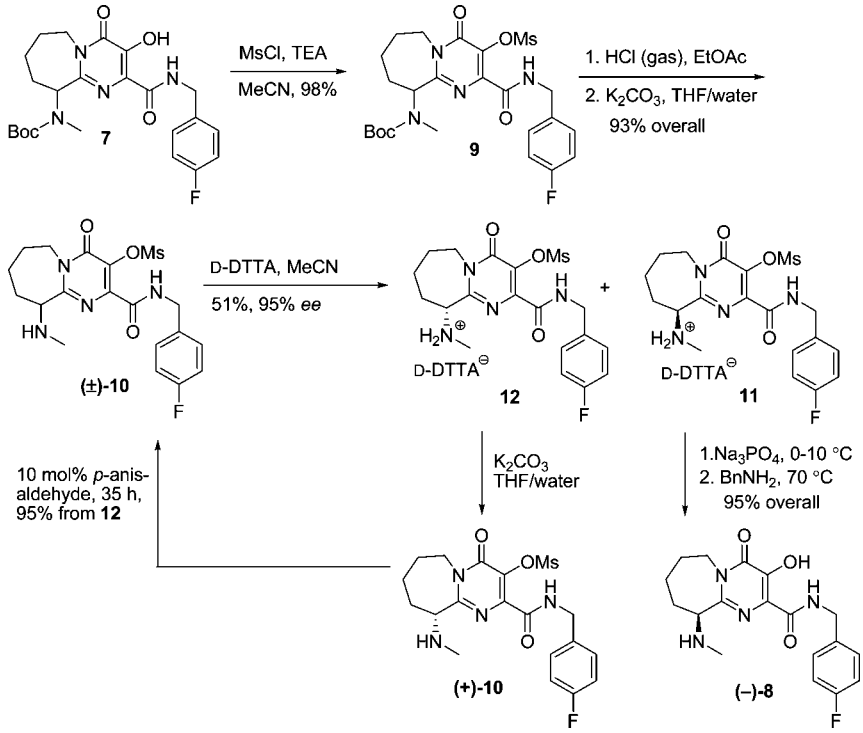
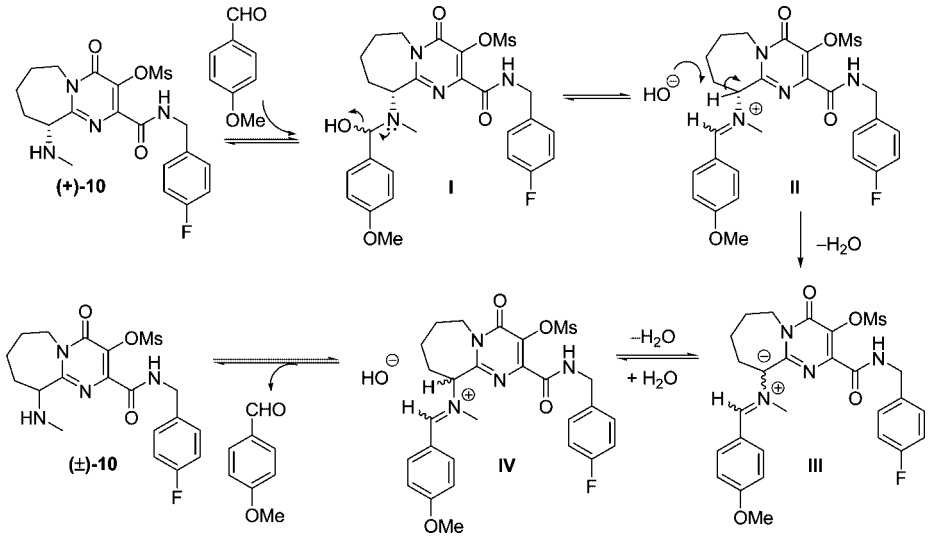
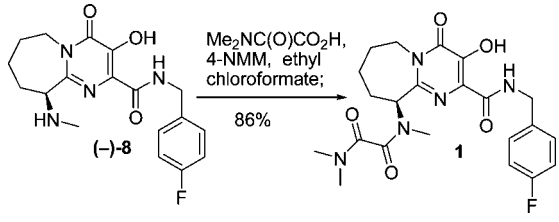
Scheme 5. **Alternative synthesis of amine (−)-8 via classical resolution and racemization**



Scheme 6. **Proposed mechanism for racemization of undesired free amine (+)-10**



Scheme 7. **Synthesis of HIV integrase inhibitor 1**



aged at room temperature for 4 h, and then the conversion was checked by ^{1}H NMR analysis (0.1 mL reaction mixture + 0.5 mL D_2O: 100% conversion, 80% assay yield). The reaction mixture was washed with heptane (2 × 85 mL), and the aqueous layer was extracted with IPAc (4 × 300 mL). The combined IPAc layers were concentrated to a total volume of about 420 mL (assay 0.40 mol).

To the resulting solution was added a solution of Boc_2O (91.7 g, 0.42 mol, 1.05 equiv) in IPAc (42 mL) dropwise over 30 min at 30−35 °C. The resulting solution was stirred at the same temperature for 1.5 h (100% conversion by ^{1}H NMR). To the reaction mixture was added 4.5% NH_4OH/10% NH_4Cl (70 g)[10] at 20−25 °C. The resulting mixture was stirred at the same temperature overnight. After phase separation, the aqueous layer was extracted with IPAc (1 × 1 L). The combined organic layers were washed sequentially with 1 N aqueous NaOH (3 × 100 mL) at 0−5 °C, 10% aqueous NH_4Cl (1 × 100 mL), and 20% aqueous NaCl (1 × 100 mL) at the same temperature. The yield of *N*-Boc-*N*-methyl-aminonitrile was assayed by

(10) The 4.5% NH_4OH/10% NH_4Cl (aq) was prepared by mixing 12.5 g of 28% aqueous NH_4OH, 7 g of NH_4Cl (solid), and 50.5 g of water.
(11) In order to sharpen the peaks, the ^{1}H NMR spectra of compopunds **3**, **7**, and **9** were obtained at 350 K in a pressure-capable sealed tube.

HPLC (121.2 g, 80% from DHP). The solution was then concentrated to afford the crude *N*-Boc-*N*-methyl-aminonitrile **2**, which was used directly in the next step. For characterization, a small sample was purified by flash chromatography (silica gel, hexane/EtOAc = 1: 1) to afford *N*-Boc-*N*-methyl-aminonitrile as a colorless oil. IR (thin film) ν_{max} 3445, 2976, 2936, 2869, 2230, 1696, 1654, 1387, 1148 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (at 350 K): 5.18 (m, 1 H), 3.64 (q, J = 5.7 Hz, 2 H), 2.88 (s, 3 H), 1.88−1.75 (m, 3 H), 1.65−1.61 (m, 2 H), 1.49−1.46 (m, 1 H), 1.18 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 155.0, 117.9, 81.5, 62.2, 47.2, 31.6, 31.2, 30.1, 28.3, 21.8. HRMS (ESI) calculated for $C_{12}H_{22}N_2O_3Na$ $(M + Na)^+$ 265.1528, found 265.1525.

Preparation of Hydroxyamidine 3. To a solution of crude *N*-Boc-*N*-methylaminonitrile **2** (121.2 g, 0.400 mol) in methanol (185 mL) was added 1.05 equiv of 50% aqueous NH_2OH solution (25.7 mL, 0.42 mol) at room temperature. The resulting solution was then stirred at a 60 °C. After 3 h, HPLC analysis indicated > 98% conversion to **3** (assay yield 110.2 g, 94% from *N*-Boc-*N*-methylaminonitrile). Excess hydroxylamine was then removed by repeated distillation/methanol flushing until the assay of the remaining NH_2OH in the solution was less than 1 mol % relative to hydroxyamidine **3**. The resulting solution was adjusted to a total volume of about 450 mL, to afford crude **3**, which was used without further purification in the next step. For characterization, a small sample was purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc = 1:1) to afford compound **3** as a colorless oil. IR (thin film) ν_{max} 3356, 2933, 1663, 1393, 1148 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (at 350 K[11]): 5.25 (br s, 1 H), 4.80 (br s, 3 H), 4.55 (dd, J = 8.5, 6.6 Hz, 1 H), 3.59 (t, J = 6.0 Hz, 2 H), 2.61 (s, 3 H), 1.83 (m, 1 H), 1.67 (m, 1 H), 1.61−1.53 (m, 2 H), 1.45 (s, 9 H), 1.37 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (at 350 K): 156.7, 152.8, 80.2, 62.2, 56.3, 32.0, 29.4, 28.3, 27.3, 22.2. HRMS (ESI) calculated for $C_{12}H_{26}N_3O_4$ $(M + H)^+$ 276.1918, found 276.1921.

Preparation of Hydroxypyrimidinone 5. To a solution of hydroxyamidine **3** (110.2 g, 0.376 mol) in methanol was added DMAD (56.1 g, 0.395 mol) at −10 °C. The resulting solution was stirred at the same temperature for 14 h and then allowed to warm to room temperature over 10 h (>98% conversion by HPLC analysis at this point). The reaction mixture was then concentrated to give a crude mixture of compounds **4a** (*cis*) and **4b** (*trans*) in a 5:1 ratio.

The crude adducts **4a/4b** (150.3 g, 0.36 mol) were dissolved in *o*-xylene (1.5 L), and the resulting solution was heated at 110−120 °C for 12 h. After cooling to 50 °C, EtOAc (215 mL) was added, and the resulting reaction mixture was extracted with 5% aqueous $NaHCO_3$ (1 × 454 mL, 0.27 mol) at 37 °C, and again with 5% aqueous $NaHCO_3$ (1 × 454 mL, 0.27 mol) at room temperature. To the combined aqueous solutions were added EtOAc (576 mL). To the resulting two-phase mixture was slowly added 6 N HCl aqueous solution (95 mL, 0.57 mol) to adjust the pH of aqueous solution to 2.5−3.5. NaCl (90 g) was then added, and the mixture was stirred at room temperature until complete dissolution of the NaCl (about 0.5 h). After phase separation, the aqueous layer was extracted with EtOAc (1 × 160 mL). The combined organic layers were washed with brine (1 × 110 mL) and concentrated to afford crude hydroxypyrimidinone **5** (assay 63.8 g, 49% overall yield from **3**). For characterization, a small sample was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH = 100:1, 100:1.5, 100:2) to afford compound **5** as a white solid, mp 62.0−63.5 °C. IR (thin film) ν_{max} 3350, 3100, 2934, 1695, 1615, 1450, 1159 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 10.66 (br s, 2 H), 4.77 (m, 1 H), 4.01 (s, 3 H), 3.72−3.67 (m, 2 H), 2.77 (s, 3 H), 2.20−1.55 (m, 5 H), 1.48 (s, 9 H), 1.43−1.35 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.4, 158.6, 157.3, 150.3, 148.9, 126.0, 81.4, 62.2, 58.1, 53.3, 31.9, 31.1, 28.4 (2 C), 22.2. HRMS (ESI) calculated for $C_{17}H_{27}N_3O_7Na$ $(M + Na)^+$ 408.1747, found 408.1751.

Preparation of Bicyclic Hydroxypyrimidinone 7. To a solution of hydroxypyrimidone **5** (12.7 g, 0.0330 mol) in DMAc (95.3 mL) was added 2 equiv of Et_3N (9.15 mL, 0.0657 mol) and 1.5 equiv of 4-fluorobenzylamine (5.63 mL, 0.0493 mol) at 0 °C. The resulting mixture was warmed to 78−82 °C and aged overnight at the same temperature. After cooling to 0−5 °C, Et_3N (27.6 mL, 0.198 mol) was added in one portion. MsCl (15.3 mL, 0.198 mol) was then added dropwise, maintaining the temperature below 10 °C. The resulting slurry was stirred for 2.5 h at 0−5 °C to give intermediate **6**. NaOH aqueous solution (5 N, 47.1 mL, 0.236 mol) was then added dropwise, and the reaction mixture was then warmed to 78−82 °C and stirred for 22 h. After cooling to 50 °C, 6 N HCl aqueous solution (96.4 mL, 0.578 mol) was added dropwise over 1 h to adjust the pH to 2−3. The resulting crystalline slurry was stirred for 1 h at 50 °C, water (28 mL) was then added dropwise at the same temperature over 1 h, and the mixture was stirred at room temperature overnight. The crystalline solid was filtered and washed with 1:1 MeOH/H_2O (25.4 mL). The crude product was recrystallized from 1:1 methanol/water (100 mL) to afford bicyclic hydroxypyrimidinone **7** (9.88 g, 65%) as white cubes, mp 183.3−183.8 °C. IR (thin film) ν_{max} 3384, 2936, 1689, 1647, 1604, 1536, 1512, 1241, 1222, 1145 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (at 350 K): 11.70 (s, 1 H), 7.71 (br s, 1 H), 7.30 (m, 2 H), 7.02 (m, 2 H), 5.26 (br d, J = 12.9 Hz, 1 H), 5.10 (d, J = 10.0 Hz, 1 H), 4.53 (m, 2 H), 3.32 (t, J = 12.9 Hz, 1 H), 2.87 (s, 3 H), 2.15−2.03 (m, 3 H), 1.86−1.67 (m, 2 H), 1.43 (m, 1 H), 1.31 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (at 350 K): 168.2, 162.5 (d, J = 247 Hz), 158.0, 156.2, 151.9, 146.9, 133.1 (d, J = 3 Hz), 129.4 (d, J = 8 Hz), 124.6, 115.6 (d, J = 22 Hz), 80.1, 58.5, 42.8, 42.4, 30.8, 30.7, 28.2, 28.0, 27.0. HRMS (ESI) calculated for $C_{23}H_{29}FN_4O_5Na$ $(M + Na)^+$ 483.2020, found 483.2021.

Preparation of Amine HCl salt (±)-8·HCl. Through a solution of ethyl acetate (420 mL) was bubbled HCl gas (79.2 g) at −30 to −20 °C. Bicyclic hydroxypyrimidinone **7** (100.6 g, 0.218 mol) was slowly portion-wise charged to the HCl/EtOAc solution at −30 to −20 °C. The resulting solution was stirred at −15 to −10 °C for 2 h, at −10 to 0 °C for 1.5 h, and then slowly warmed to 25 °C over 1.5 h, then stirred at 25 °C for 4 h. To the reaction mixture was slowly added EtOAc (700 mL) over 1 h at 25 °C. The resulting slurry was stirred at 25 °C for 4 h. The product was collected by filtration, washed with EtOAc (1 × 200 mL) and heptane (1 × 200 mL), and

then dried under vacuum with nitrogen sweep to afford the desired product (±)-**8**·HCl (86.7 g, 100%) as a white crystalline solid, mp >290 °C dec. IR (thin film) ν_{max} 3258, 3059, 2938, 2731, 2468, 1698, 1638, 1600, 1545, 1510, 1461, 1332, 1251, 1214, 829 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 12.35 (br s, 1 H), 9.96 (t, J = 6.3 Hz, 1 H), 9.51 (br s, 1 H), 9.19 (br s, 1 H), 7.42 (m, 2 H), 7.19 (m, 2 H), 4.92 (dd, J = 14.5, 5.1 Hz, 1 H), 4.71 (m, 1 H), 4.47 (m, 2 H), 3.52 (t, J = 14.5 Hz), 2.65 (s, 3 H), 2.30 (br d, J = 12.6 Hz, 1 H), 1.95 (m, 1 H), 1.90−1.75 (m, 2 H), 1.64 (m, 1 H), 1.33 (m, 1 H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 168.5, 161.8 (d, J = 243 Hz), 157.5, 148.0, 147.4, 135.1 (d, J = 3 Hz), 130.1 (d, J = 8 Hz), 124.9, 115.5 (d, J = 21 Hz), 60.0, 41.8, 41.7, 32.6, 29.3, 26.3, 26.0. HRMS (ESI) calculated for $C_{18}H_{22}FN_4O_3$ (free base + H)$^+$ 361.1676, found 361.1679.

Preparation of Racemic Amine (±)-8. To a slurry of (±)-**8**·HCl (71.6 g, 0.180 mol) in water (525 mL) was added a solution of 5 N sodium hydroxide (36.0 mL) in water (175 mL) via an addition funnel over 2 h. The mixture was stirred at room temperature for 24 h with vigorous stirring. The product was collected by filtration, washed with water (1 × 500 mL) and 1:1 MTBE/heptane (1 × 140 mL), and dried under vacuum with a nitrogen sweep to give racemic free amine (±)-**8** (61.2 g, 94%) as a white crystalline solid, mp 150.6−152.2 °C. IR (thin film) ν_{max} 3625, 3134, 1653, 1625, 1540, 1507, 1457 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.47 (br s, 1 H), 7.30 (m, 2 H), 7.08 (m, 2 H), 4.82 (d, J = 9.0 Hz, 1 H), 4.44 (m, 2 H), 4.19 (d, J = 9.0 Hz, 1 H), 3.59 (m, 1 H), 2.38 (s, 3 H), 2.06 (m, 1 H), 1.81 (m, 1 H), 1.68 (m, 2 H), 1.46 (m, 1 H), 1.25 (m, 1 H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 168.9, 161.7 (d, J = 243 Hz), 160.7, 151.7, 145.7, 135.9 (d, J = 3 Hz), 129.6 (d, J = 8 Hz), 124.4, 115.5 (d, J = 22 Hz), 61.6, 41.8, 41.3, 34.0, 32.0, 27.2, 26.4. HRMS (ESI) calculated for $C_{18}H_{22}FN_4O_3$ (M + H)$^+$ 361.1676, found 361.1674.

Preparation of Chiral Amine (−)-8−L-DTTA Salt. To a slurry of (±)-**8** (30.0 g, 0.0832 mol) in DMF (140 mL) was added a solution of di-*p*-toluoyl-L-tartaric acid (32.5 g, 0.0832 mol) in DMF (70 mL) over 10 min via an addition funnel at 50 °C. The reaction mixture was seeded (the reaction mixture is a slurry throughout the salt formation) and then cooled to 20 °C over 1 h. Isopropyl alcohol (140 mL) then heptane (140 mL) were added successively to the slurry, which was stirred at 20 °C for 2 h. The product was collected by filtration, washed with 1:1 isopropanol/heptane (1 × 150 mL), and dried at 40 °C under vacuum with a nitrogen sweep to afford chiral amine (−)-**8**−L-DTTA salt (39.6 g, 43% isolated yield, 97% ee) as a colorless crystalline solid, mp 201.5−202.5 °C. ^1H NMR (400 MHz, CD_3OD) δ: 7.96 (m, 2 H), 7.37 (m, 2 H), 7.23 (m, 2 H), 7.02 (m, 2 H), 5.87 (s, 1 H), 5.09 (dd, J = 14.4, 5.6 Hz, 1 H), 4.55 (s, 2 H), 4.48 (dd, J = 10.8, 1.2 Hz, 1 H), 3.46 (dd, J = 14.4, 11.6 Hz, 1 H), 2.76 (s, 3 H), 2.39 (s, 3 H), 2.26 (br d, J = 13.3 Hz, 1 H), 2.08−1.84 (m, 3 H), 1.69 (m, 1 H), 1.37 (m, 1 H).^{13}C NMR (DMSO-d_6, 100 MHz) δ: 169.9, 168.6, 165.2, 162.8, 161.8 (d, J = 243 Hz), 157.9, 157.3, 148.7, 147.7, 143.9, 135.3, 135.2 (d, J = 3 Hz), 130.0, 129.9, 129.7, 129.5, 127.8 (d, J = 8 Hz), 124.9, 115.6 (d, J = 21 Hz), 74.1, 60.3, 41.9, 41.7, 36.3, 32.8, 31.3, 29.8, 26.3, 26.2, 21.6. HRMS (ESI) calculated for $C_{18}H_{22}FN_4O_3$ (free base + H)$^+$ 361.1676, found 361.1685.

Preparation of Chiral Free Amine (−)-8. Aqueous sodium hydroxide (4.91 N, 15.4 mL) was added in one portion to a slurry of (−)-**8**-L-DTTA salt (42.0 g, 0.0757 mol) in THF (230 mL) and water (63 mL). The addition of NaOH is exothermic, and the thick slurry briefly becomes a thin slurry/solution prior to the crystallization of the free amine. After a 15 min age, water (525 mL) was added via an addition funnel. The resulting slurry was stirred for 2.5−3 h and cooled to 2−4 °C. The product was collected by filtration, washed with water (160 mL) and 1:1 MTBE/heptane (1 × 160 mL), and dried under vacuum with nitrogen sweep to give chiral free amine (−)-**8** (25.7 g, 94%, 97% ee) as a crystalline solid. $[\alpha]_D$ −29.2 ° (*c* 1.1, DMSO).

Chiral SFC conditions: Chiralpak AD column (250 mm × 4.6 mm); 25% MeOH/CO_2 @ 1.5 mL/min.; UV @ 210 nm. The retention time for (−)-**8** is 10.27 min. The retention time for (+)-**8** is 6.67 min.

Preparation of *O*-Mesylated Bicyclic Hydroxypyrimidinone 9. To a solution of bicyclic hydroxypyrimidinone **7** (36.8 g, 0.0800 mol) in acetonitrile (200 mL) was added TEA (12.3 mL, 0.0880 mol) at room temperature. The resulting slurry was cooled to 0−5 °C, and methanesulfonyl chloride (6.5 mL, 0.0840 mol) was added slowly, maintaining the temperature below 15 °C. The resulting slurry was stirred at 5−15 °C for 2 h. To the reaction mixture was slowly added water (450 mL) over 1 h. The resulting slurry was stirred at 0 °C for 2 h. The product was collected by filtration, and washed with water (1 × 200 mL) and heptane (1 × 100 mL), and dried under vacuum with nitrogen sweep to afford *O*-mesylated bicyclic hydroxypyrimidinone **9** (42.09 g, 98%) as a white crystalline solid, mp 190.0−190.9 °C. IR (thin film) ν_{max} 3395, 3011, 2937, 1693, 1605, 1557, 1510, 1367, 1200, 1164 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ (at 350 K): 7.69 (br s, 1 H), 7.31 (m, 2 H), 7.03 (m, 2 H), 5.24 (dd, J = 14.2, 5.0 Hz, 1 H), 4.53 (m, 2 H), 3.53 (s, 3 H), 3.43 (m, 1 H), 2.86 (s, 3 H), 2.20−2.10 (m, 3 H), 1.89 (m, 1 H), 1.78 (m, 1 H), 1.43 (m, 1 H), 1.31 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (at 350 K): 163.7, 160.1 (d, J = 238 Hz), 160.9, 160.2, 156.1, 141.9, 135.0, 133.6 (d, J = 3 Hz), 129.5 (d, J = 8 Hz), 115.5 (d, J = 22 Hz), 80.6, 59.7, 43.4, 42.9, 41.0, 30.8, 30.0, 28.2, 27.9, 26.5. HRMS (ESI) calculated for $C_{24}H_{32}FN_4O_7S$ (M + H)$^+$ 539.1970, found 539.1971.

Preparation of *O*-Mesylated Free Amine (±)-10. To a 1 L round-bottom flask was charged ethyl acetate (160 mL). To the solution of ethyl acetate was bubbled HCl gas (33.44 g, 0.916 mol) at −30 to −20 °C. *O*-Mesylated bicyclic hydroxypyrimidinone **9** (49.34 g, 0.0916 mol) was slowly portion-wise charged to the HCl/EtOAc solution at −30 to −20 °C. The resulting solution was stirred at −30 to −20 °C for 1 h, slowly warmed to 0 °C over 2.5 h, then stirred from 0 °C to room temperature over 2 h. The reaction mixture was diluted with EtOAc (188 mL), and then heptane (376 mL) was slowly added over 1 h. The resulting slurry was stirred at room temperature

for 1−2 h. The product was collected by filtration, washed with heptane (1 × 100 mL), and dried under vacuum with nitrogen sweep to afford (±)**-10**·HCl salt (43.2 g, 99%) as a white crystalline solid.

To a solution of (±)−**10**·HCl salt (36.74 g, 0.0782 mol) in 1:1 THF/water (120 mL) was slowly added 1 M potassium carbonate (93.8 mL, 0.0938 mol) at 0−5 °C. The resulting slurry was stirred at 0−5 °C for 10 min. To the slurry was added water (300 mL), and the slurry was stirred at 0−5 °C for 0.5 h. The product was collected by filtration, washed with water (1 × 200 mL), heptane (1 × 50 mL), and dried under vacuum with nitrogen sweep to give (±)**-10** (32.2 g, 94%) as a white crystalline solid, mp 81.0−83.0 °C. IR (thin film) ν_{max} 3347, 3019, 2938, 2861, 2801, 1684, 1604, 1552, 1510, 1369, 1199, 1163 cm^{-1}. ^1H NMR (CD_3CN, 400 MHz) δ: 8.41 (br s, 1 H), 7.38 (m, 2 H), 7.09 (m, 2 H), 4.92 (dd, J = 14.2, 4.8 Hz, 1 H), 4.57−4.47 (m, 2 H), 3.90 (br d, J = 10.9 Hz, 1 H), 3.83 (d, J = 9.5 Hz, 1 H), 3.44 (s, 3 H), 2.36 (s, 3 H), 2.20−2.12 (m, 1 H), 1.88−1.79 (m, 3 H), 1.65−1.50 (m, 2 H). ^{13}C NMR (CD_3CN, 100 MHz) δ: 162.0, 161.8, 161.7 (d, J = 243 Hz), 169.0, 142.5, 135.1 (d, J = 3 Hz), 134.2, 129.3 (d, J = 8 Hz), 115.0 (d, J = 22 Hz), 63.1, 42.2, 41.8, 40.3, 34.0, 32.0, 25.9, 25.6. HRMS (ESI) calculated for $C_{19}H_{24}FN_4O_5S$ $(M + H)^+$ 439.1451, found 439.1451.

Preparation of Chiral Amine (−)-10−D-DTTA 11. To a solution of di-*p*-toluoyl-D-tartaric acid (8.81 g) in 98:2 acetonitrile/water (80 mL) was slowly added a solution of free amine (±)**-10** (10.0 g, 0.0228 mol) in 98:2 acetonitrile/water (40 mL) at 50 °C. The resulting slurry was stirred at 45−50 °C for 6 h, and then at room temperature for 10 h. The product was collected by filtration, washed with acetonitrile (1 × 50 mL), and dried under vacuum with nitrogen sweep to afford desired product **11** (9.57 g, 95.0% ee, 51% isolated yield) as a colorless crystalline solid, mp 184.0−185.0 °C. IR (thin film) ν_{max} 1718, 1653, 1507, 1359, 1230, 1200, 1165, 1087 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 11.31 (br s, 2 H), 9.51 (s, 1 H), 7.90−7.78 (m, 4 H), 7.40−7.18 (m, 6 H), 7.15−7.00 (m, 2 H), 5.69 (s, 2 H), 4.80 (4.80 (br d, J = 12.6 Hz, 1 H), 4.65 (d, J = 10.0 Hz, 1 H), 4.37 (m, 2 H), 3.58 (t, J = 12.6 Hz, 1 H), 3.48 (s, 3 H), 2.54 (s, 3 H), 2.34 (s, 6 H), 2.16 (m, 1 H), 1.82 (m, 1 H), 1.72−1.46 (m, 3 H), 1.20 (m, 1 H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 169.1, 165.5, 161.7 (d, J = 243 Hz), 161.5, 158.4, 156.7, 144.4, 142.6, 135.6 (d, J = 3 Hz), 134.5, 129.8, 129.7, 129.6, 127.3, 115.4 (d, J = 22 Hz), 73.3, 60.0, 42.7, 42.0, 41.0, 32.1, 28.3, 26.4, 25.2, 21.7. HRMS (ESI) calculated for $C_{19}H_{24}FN_4O_5S$ (free base + H)$^+$ 439.1451, found 439.1449.

Chiral SFC conditions: Chiralpak AD column (250 mm × 4.6 mm); 25% MeOH/CO_2 @ 1.5 mL/min.; UV @ 210 nm. The retention time for (−)**-10** is 9.43 min. The retention time for (+)**-10** is 6.15 min.

Racemization of Undesired Enantiomer (+)-10 to Racemic Amine (±)-10. To the mother liquors from the above classical resolution, which contained undesired amine D-DTTA salt **12** (~0.0114 mol), was slowly added 1 M potassium carbonate (28.5 mL, 0.0285 mol) at 0−5 °C. The resulting solution was stirred at 0−5 °C for 10 min. IPAc (50 mL) was then added and stirring continued for 10 min. The organic layer was separated, and the aqueous layer was back extracted with IPAc (1 × 30 mL). The combined organic layers were washed with brine (2 × 20 mL), then concentrated and solvent-switched to acetonitrile (total volume 38 mL). Water (2 mL), and 0.1 equiv of *p*-anisaldehyde (0.16 g, 0.00114 mol) were added, and the resulting solution was degassed and heated at 70 °C for 30−40 h. The resulting solution of **10** (0−3% ee) could be resubmitted to the D-DTTA-classical resolution.

Hydrolysis of *O*-Mesylated Amine (−)-10 to Hydroxyl Amine (−)-8. To a solution of chiral amine (−)**-10**−D-DTTA **11** (3.00 g, 3.64 mmol) in acetonitrile (6 mL) was added 0.76 M aqueous sodium phosphate (12 mL, 9.12 mmol) at 0−10 °C. The resulting slurry was stirred at room temperature for 0.5 h, then diluted with water (12 mL). The solution was extracted with IPAc (2 × 15 mL). The combined organic layers were washed with brine (2 × 8 mL), and concentrated to gave chiral free amine (−)**-10** (1.58 g, 99%), $[\alpha]_D$ −72.7 ° (*c* 1.1, MeOH), which was dissolved in acetonitrile (19 mL) and treated with benzylamine (0.78 g, 7.28 mmol) at 70 °C for 6 h. The reaction was cooled to room temperature, and adjusted to pH 2−3 with 2.5 N HCl. The reaction mixture was then concentrated, and the residue was recrystallized from 1:2 THF/water (45 mL) to afford desired free chiral amine (−)**-8** (1.25 g, 96% yield, 97% ee).

Preparation of HIV Integrase Inhibitor 1. A slurry of chiral free amine (−)**-8** (24.0 g, 0.0666 mol) in THF (360 mL) was dried azeotropically with continuous distillation of THF at 60 °C until the water level detected by Karl Fisher titration of the solution was less than 100 ppm. The resulting slurry was adjusted to a total volume of 240 mL, which was kept at room temperature under nitrogen.

To a separate flask was charged THF (360 mL) and the side chain acid (13.3 g, 0.113 mol). The resulting solution was cooled to 0 °C, and ethyl chloroformate (9.56 m L, 0.100 mol) was added. To the reaction mixture was dropwise added 4-NMM (11.7 mL, 0.107 mol) at −3 to 0 °C over a period of 0.5 h, and the mixture was aged for 2 h at the same temperature.

The resulting slurry of mixed-anhydride in THF (−5 °C) was transferred to the precooled (−5 to −8 °C) slurry of chiral free amine (−)**-8** in THF. The reaction mixture was stirred at 0−5 °C for 1 h. At this point, additional 4-NMM (11.0 mL, 0.100 mol) was charged, and the mixture was stirred for 1.5 h at 0−10 °C. Aqueous dimethylamine solution (40 wt %, 29.6 mL) was added at 5−10 °C, and the mixture was stirred for 2 h at 10−23 °C. The reaction mixture was acidified to pH 3−4 by the addition of 2 N HCl at 5−15 °C. To the resulting reaction mixture was added degassed brine (120 mL). After phase separation, the aqueous layer was back-extracted with EtOAc (1 × 360 mL). The combined organic layers were further washed with brine (1 × 240 mL), and concentrated to a volume of 240 mL for crystallization. To the resulting slurry was slowly added heptane (720 mL) at room temperature. The resulting slurry was cooled to −3 to 2 °C over 0.5 h, and stirred for 1 h. The product was collected by filtration, washed with 1:3 EtOAc/heptane

(120 mL), and dried under vacuum with nitrogen sweep to give crude product **1**. The crude product was recrystallized from 1:2 methanol/water (210 mL) to afford pure product **1** (26.3 g, 86% overall yield from (−)-**8**, >99.9% ee) as colorless cubes, mp 279.0−280.0 °C. $[\alpha]_D$ −86.3 ° (*c* 1.8, DMSO). IR (thin film) ν_{max} 3280, 2937, 1685, 1640, 1603, 1537, 1510, 1244, 1086 cm^{-1}. Both of the ^1H and ^{13}C NMR data are matched with previous literature reports.[5b] HRMS (ESI) calculated for $C_{22}H_{27}FN_5O_5$ $(M + H)^+$ 460.1996, found 460.1999.

Chiral HPLC conditions: Chiralpak AD-H column (250 mm × 4.6 mm); 30% isopropyl alcohol/70% heptane @ 1.0 mL/min.; UV @ 210 nm. The retention time for HIV integrase inhibitor**1** is 22.14 min. The retention time for the undesired enantiomer is 17.47 min.

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Supporting Information Available

General experimental details and copies of ^1H NMR, ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http: //pubs.acs.org.

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