JOC The Journal of Organic Chemistry

Article

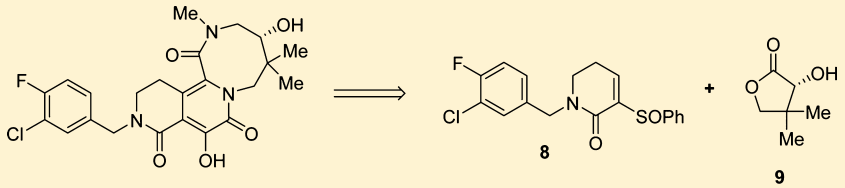
pubs.acs.org/joc

Asymmetric Synthesis of a Potent HIV-1 Integrase Inhibitor

Jeffrey T. Kuethe,*,† Guy R. Humphrey, Michel Journet, Zhihui Peng, and Karla G. Childers

Department of Process Chemistry, Merck & Co., Inc. P.O. Box 2000, Rahway, New Jersey 07065, United States

Supporting Information



ABSTRACT: The development of a practical asymmetric total synthesis of the potent HIV-1 integrase inhibitor **5** is described. Key transformations include construction of the naphthridine core in a highly efficient manner followed by cyclization of the 8-membered ring. Control of the atropisomers of intermediates and final compound **5** is also described.

INTRODUCTION

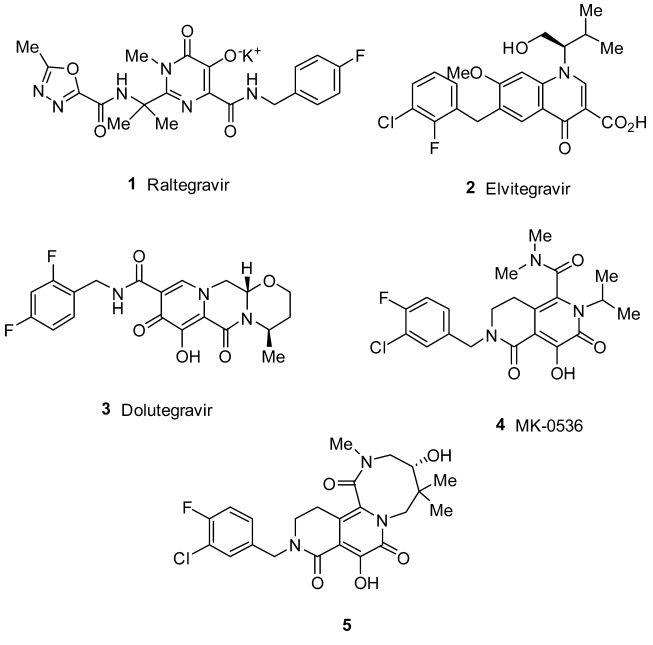
Replication of human immunodeficiency virus (HIV) involves three enzymes: reverse transcriptase, protease, and integrase. Current mainstay therapies for the treatment of HIV and acquired immunodeficiency syndrome (AIDS) involve inhibition of HIV reverse transcriptase[1] and HIV protease,[2] and a combination of these antiretroviral therapies has been used as an effective strategy to reduce viral loads.[3] While these important therapeutic targets have proven highly successful at reducing viral loads, drug resistance and side effects continue to fuel intensive efforts for new drug targets in HIV therapy. The third viral enzyme, HIV integrase, has become an especially attractive target given its critical role in HIV replication and viral infectivity.[4] Spanning nearly two decades, global research efforts to identify drugs that inhibit HIV integrase resulted in identification of Merck's Isentress (raltegravir) **1** as the first HIV integrase inhibitor approved for the treatment of HIV/AIDS (Scheme 1).[5] Several alternative structural classes[6] have emerged with the discoveries of elvitefravir **2**,[7] dolutegravir **3**,[8] and MK-0536 **4**.[9,10] As part of Merck's continuing effort to discover and develop novel HIV integrase inhibitors, compound **5** was identified as a potent and selective inhibitor of HIV integrase with substantially improved viral resistance and a robust pharmacokinetic profile.[11] Key obstacles for the synthesis of compound **5** included construction of the challenging 8-membered ring bearing a chiral hydroxy group and preparation of the core naphthyridine core. Herein, we report the development of a practical and efficient asymmetric synthesis of the HIV-1 integrase inhibitor **5**.

RESULTS AND DISCUSSION

Our retrosynthetic approach to inhibitor **5** is outlined in Scheme 2 and centered on construction of the formidable 8-membered ring via the combination of naphthyridine acid **6** and chiral amino alcohol **7**. Preparation of naphthyridine acid **6** was envisioned to arise from readily available unsaturated sulfoxide **8**. Construction of the naphthyridine ring being accomplished through a process similar to that utilized for the preparation of integrase inhibitor **4**.[10] Amino alcohol **7** could be derived from ring opening of D-(−)-pantolactone **9** by *N*-methylamine.

Our investigations began with the known unsaturated sulfoxide **8**.[10] Initial experiments were focused on application of the chemistry utilized in the synthesis of integrase inhibitor **4**

Scheme 1



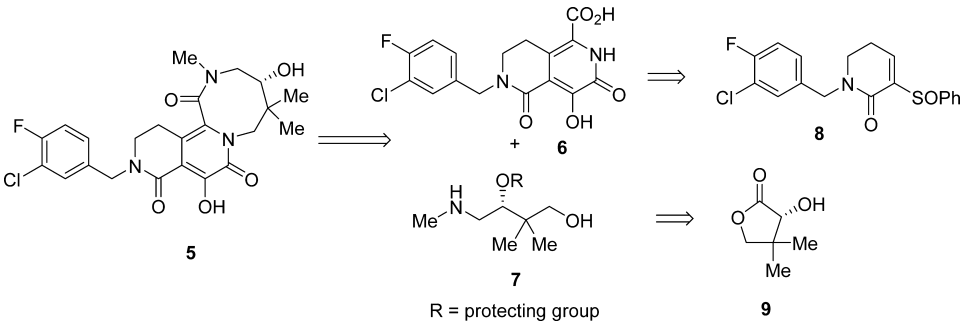
Special Issue: Heterocycles

Received: May 23, 2016
Published: July 29, 2016

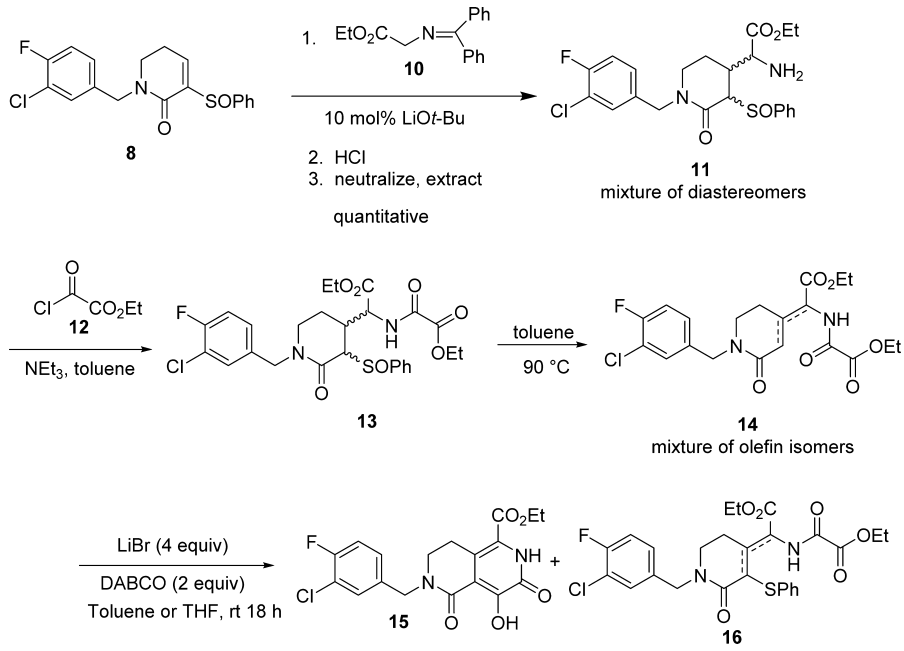
© 2016 American Chemical Society

DOI: 10.1021/acs.joc.6b01229
J. Org. Chem. 2016, 81, 10256−10265

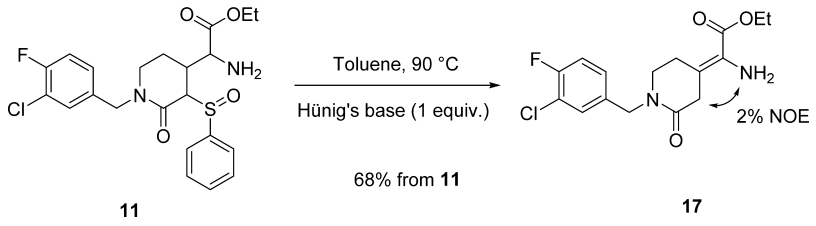
Scheme 2



Scheme 3



Scheme 4

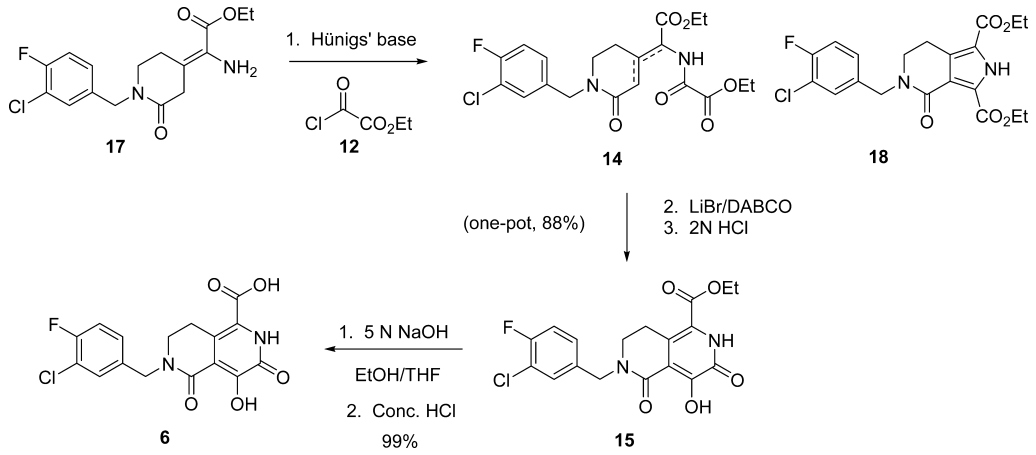


(Scheme 3). For example, reaction of *N*-(diphenylmethlene)-glycine ethyl ester **10** with sulfoxide **8** in the presence of 10 mol % of LiO*t*-Bu afforded intermediate **11** as an inseparable mixture of diastereomers in near-quantitative yield. Acylation using monoethyl oxalyl chloride **12** in the presence of NEt_3 furnished intermediate **13**, which was isolated in >95% yield following an aqueous workup. Heating intermediate **13** in toluene at 90 °C for 30 min afforded compound **14** as a mixture of olefin isomers together with PhSOH and Ph_2S_2. Crude compound **14** was not isolated but directly treated with 4 equiv of LiBr and 2 equiv of DABCO in order to affect cyclization to the naphthyridine ring **15**.[10] While the desired cyclization event occurred to provide compound **15** under these reaction conditions, the isolated yield was <25%. A large number of unidentified reaction impurities were formed under these conditions. The most significant impurity identified was sulfide **16**, presumably formed by reaction of **14** with Ph_2S_2. To prevent the formation of impurity **16**, it became necessary to resort to silica gel chromatography to remove the sulfur byproducts formed in the thermal elimination of sulfoxide **13** prior to cyclization. Treating the purified intermediate **14** with LiBr and DABCO resulted in an increased yield of **15** to ~80% with no formation of byproduct **16**. Unfortunately, all efforts to remove the sulfur impurities chemically from intermediate **14** were ineffective, rendering this approach not amenable for future development.

Having established that the general route to intermediate **15** employing the chemistry utilized for the manufacture of compound **4** (Scheme 3) was unsuitable for scale up due to low yields and the need for chromatography, our attention

DOI: 10.1021/acs.joc.6b01229
J. Org. Chem. 2016, 81, 10256−10265

Scheme 5

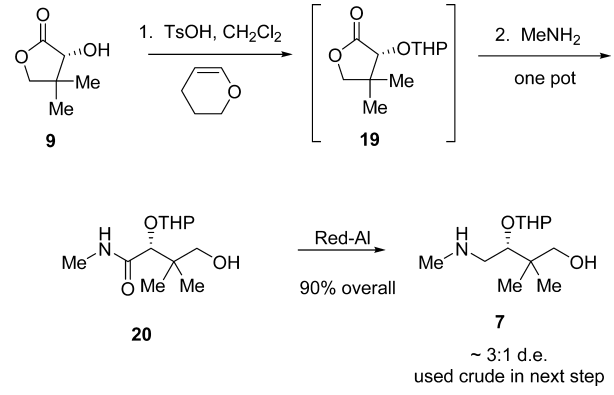


turned to identifying an alternative route. It was envisioned that reordering of the sequence of steps and removal of the sulfur byproducts formed in the thermal elimination step by crystallization would offer significant advantages in terms of controlling the product purity and yields.[12] To this end, compound **11** was prepared as described in Scheme 3. After an extractive workup, compound **11** was heated to 90 °C for 30 min (Scheme 4). Upon completion, the toluene was concentrated under reduced pressure to a small volume, and isopropyl acetate (IPAc) was added to aid in solubilizing sticky yellow impurities and sulfur residues. This resulted in a slurry of enamine **17** which was filtered and could be routinely isolated in 55−60% yield. In an effort to further optimize this step, it was discovered that the isolated yield of enamine **17** increased to 65−70% when 1 equiv of Hünig's base was added to the thermal elimination reaction mixture, resulting in a cleaner reaction profile. Under these conditions, compound **17** was isolated as a colorless solid in 68% yield. The *trans*-stereochemistry about the double bond of **17** was confirmed by NMR spectroscopy (COSY, NOESY, HMBC, ADEQUATE) where a 2% NOE was observed between the amine protons and the protons adjacent to the amide carbonyl. Compound **17** was also demonstrated to be chemically stable and not prone to isomerization.

Acylation of **17** with acid chloride **12** in THF was first performed at 5 °C in the presence of NEt_3 and afforded intermediate **16** in 91% HPLC assay yield (Scheme 5).[13] Also formed under these reaction conditions was a significant byproduct (5−10%) identified as pyrrole **18**.[14] In order to minimize the formation of pyrrole **18**, the preparation of naphthyridine ester **15** from enamine **17** was fully optimized in terms of base, temperature, and solvent resulting in a one-pot conversion of enamine **17** to naphthyridine **15**. The optimal conditions selected involved acylation of imine **17** with acid chloride **12** in the presence of the more bulky Hünig's base at −5 °C, which effectively reduced the formation of **18** to <1% as determined by HPLC analysis of the crude reaction mixture. Careful control of the addition of acid chloride **12** was required to maintain the internal reaction temperature <0 °C during the course of the addition. When the internal temperature was allowed to rise above 5 °C during the addition, increased amounts of pyrrole byproduct **18** (5−8%) were observed. Once the acylation was complete, direct addition of 4 equiv of LiBr and 2 equiv of DABCO to the reaction of mixture containing compound **16** was followed by allowing the reaction to warm to room temperature. Addition of aqueous HCl to the reaction mixture resulted in crystallization of naphthyridine **15**. Dilution with water and filtration gave **15** in analytically pure form in 88% overall yield for the one-pot process. Finally, saponification of **15** was conducted in EtOH/THF in the presence of 5 N NaOH. Upon completion, the reaction mixture was cooled to 15 °C and made acidic with concd HCl, which furnished a slurry that was filtered and dried to afford naphthyridine acid **6** as a highly crystalline solid in 99% yield.

The preparation of amino alcohol **7** started with commercially available D-(−)-pantolactone **9** (Scheme 6).

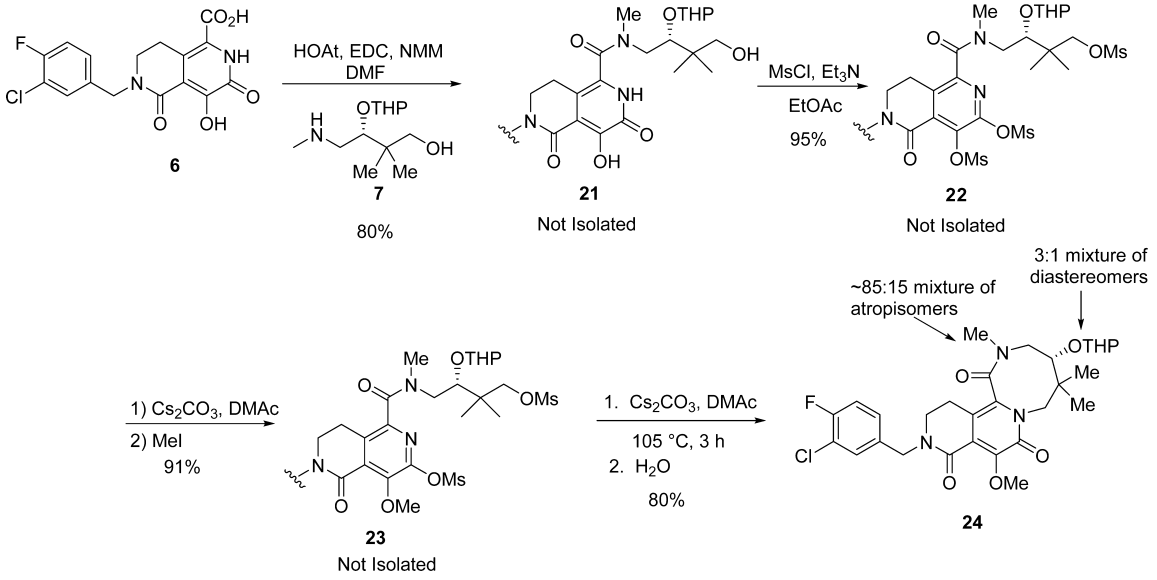
Scheme 6



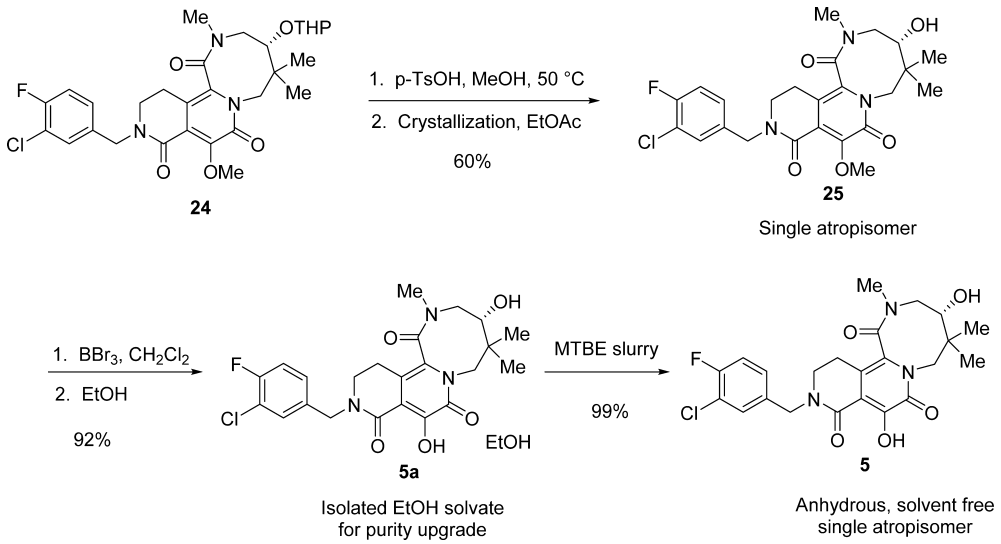
Protection of the hydroxyl group of pantolactone was required prior to ring opening with methylamine. While a number of protecting groups were evaluated, the THP protecting group proved to be the most robust in terms of downstream processing despite the fact that it added a layer of complexity by the introduction of diastereomeric mixtures. Treatment of lactone **9** with 3,4-dihydro-2*H*-pyran in CH_2Cl_2 in the presence of a catalytic amount of TsOH at room temperature gave the THP derivative **19** in quantitative yield. Compound **19** was not isolated and was followed by direct addition of 2.5 equiv of $MeNH_2$ (8 M in EtOH) at room temperature, resulting in ring opening of the lactone and the formation of amide **20** in >95% yield. After a solvent switch to toluene, the crude reaction mixture was treated with 2.5 equiv of Red-Al and heated to 90 °C for 4 h. After being quenched with 20 wt % aqueous KOH to remove the aluminum salts, the solvent was removed to give amino alcohol **7** as a 3:1 mixture of diastereomers, which were

DOI: 10.1021/acs.joc.6b01229
J. Org. Chem. 2016, 81, 10256−10265

Scheme 7



Scheme 8

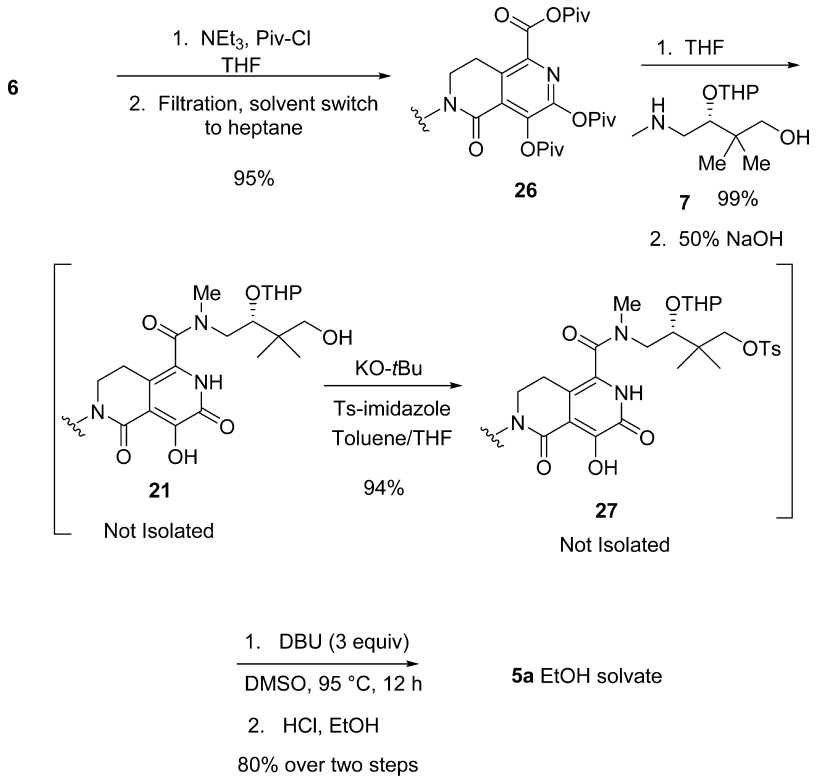


sufficiently pure for use in the next reaction without the need for further purification.

The first-generation synthesis of compound **24** involved a series of transformations where compound **24** was the first isolated intermediate (Scheme 7). This was necessary in order to avoid removal of minor diastereomers arising from the anomeric center of the THP group.[15] The coupling of naphthyridine acid **6** and amino alcohol **7** was carried out with 5 mol % of 1-hydroxy-7-azabenzotriazole (HOAt) and 1.2 equiv of EDC in the presence of 3 equiv of *N*-methylmorpholine (NMM) in DMF at room temperature for 2 days to afford intermediate **21** in 80% HPLC assay yield. Alternatively, the coupling could be achieved in a comparable yield by switching HOAt to HOBt; however, this required 1.1 equiv of HOBt in order to drive the reaction to completion and did not affect the reaction rate. Construction of the 8-membered ring at this point required activation of the primary alcohol and subsequent cyclization of the nitrogen onto the neopentyl center. Activation of intermediate **21** was accomplished by treatment with 5 equiv of NEt_3 and 5 equiv of MsCl to give tris-mesylate **22** in near-quantitative yield. After the mesylation was complete, quenching the reaction mixture with satd $NaHCO_3$ was necessary in order to effectively quench all of the excess MsCl. This operation was found to be crucial for good stability of tris-mesylate **22** since any trace of acid would cleave the THP protecting group. Tris-mesylate **22** was used in the next step without further purification. Attempted cyclization of tris-mesylate **22** in the presence of Cs_2CO_3 typically led to selective demesylation at the 3-position of the pyridine ring and no cyclization to **24**.[16] In order to address this issue, protection of this hydroxyl group was investigated. The selective mono-demesylation was conducted with 2 equiv of Cs_2CO_3 at 80 °C for 2 h. At this temperature, <5% of bis-demesylation was observed (i.e., removal of second mesylate adjacent to the pyridine nitrogen). After the solution was cooled to room temperature, 3 equiv of MeI was added to afford methoxy-bis-mesylate **23**. Protection of the hydroxyl group at this point was found to be critical for the subsequent cyclization to proceed to the 8-membered ring in the presence of Cs_2CO_3. When the hydroxyl group was unprotected, low conversions were

DOI: 10.1021/acs.joc.6b01229
J. Org. Chem. 2016, 81, 10256−10265

Scheme 9



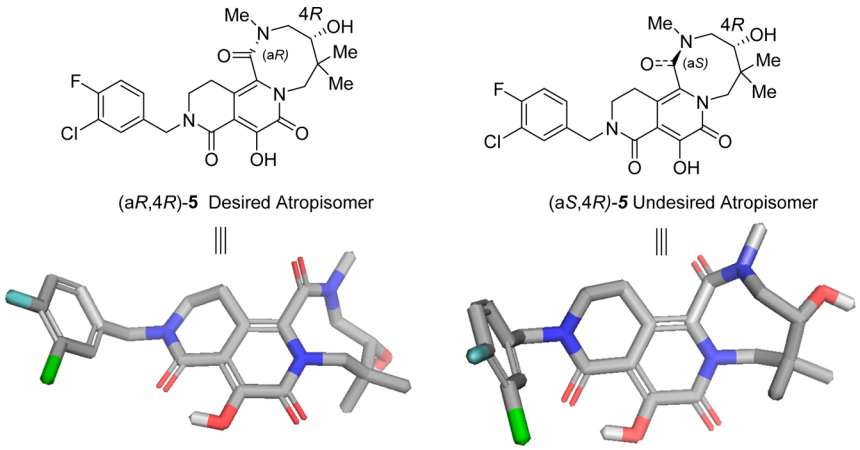
observed, presumably due to the precipitation of the cesium salt of the hydroxyl group. The original route for cyclization of the 8-memebered ring involved intramolecular cyclization of a primary mesylate in the presence of Cs_2CO_3 in DMF at 150 °C in a microwave.[17] The cyclization of our bis-mesylate **23** to compound **24** was fully optimized with respect to solvent and temperature. Methoxy-bis-mesylate **23** was treated with 3 equiv of Cs_2CO_3 at 105 °C in dimethylacetamide (DMAc) for 5 h to affect cyclization to the 8-membered ring. After the cyclization was complete, the reaction mixture was cooled to room temperature, and water was added to precipitate compound **24**, which was isolated in 80% yield. Compound **24** exists as a complex mixture of both THP diastereomers (~3:1) and an approximate 85:15 mixture of atropisomers about the amide bond due to restricted amide bond rotation (vide infra).

The end-game synthesis of the final compound is depicted in Scheme 8. The mixture of both diastereomers and atropisomers of **24** was treated with a catalytic amount of *p*-TsOH in MeOH at 50 °C for 2 h to cleave the THP protecting group and initially afford **25** as an 85:15 mixture of atropisomers. Compound **25** crystallized from EtOAc and was isolated as a single atropisomer in 56% isolated yield. The final synthetic step required removal of the methoxy group with BBr_3. Treatment of **25** with 2.1 equiv of BBr_3 at 5 °C resulted in smooth deprotection leading to crude **5**. After an aqueous workup, the solvent was switched from CH_2Cl_2 to EtOH, which resulted in crystallization of compound **5a** as an ethanol solvate in 92% isolated yield and as a single atropisomer. The choice to isolate the crystalline ethanol solvate offered the advantage of a final purity upgrade before the final isolation of the more stable anhydrous/solvent-free phase of compound **5**. Conversion of compound **5a** to the final API was accomplished by slurrying compound **5a** in MTBE for 20 h followed by filtration to give final compound **5** in 98% yield as a single atropisomer.

Although the synthesis of **5** was effectively demonstrated on a multikilogram scale, key aspects of the conversion of naphthyridine acid **6** to final product **5** still needed to be addressed, including streamlining the route, eliminating the need for protection/deprotection of the pyridine hydroxyl group, and further optimization of the 8-membered ring-closure reaction. Thus, a second-generation synthesis was required and is highlighted in Scheme 9. Reaction of naphthyridine acid **6** with 3.5 equiv of pivaloyl chloride in the presence of 5 equiv of NEt_3 in THF followed by filtration of the triethylamine hydrochloride and switching the solvent to heptane afforded crystalline trispivalate **26** in 94% isolated yield. While compound **26** was discovered to be somewhat unstable to open air, it maintained good stability when stored under inert conditions. Reaction of **26** with amino alcohol **7** initially formed the amide bond, displacing the ester pivalate quantitatively in <30 min. Hydrolysis of the corresponding bispivalate intermediate was then accomplished by direct addition of 50% NaOH to furnish intermediate **21** in near-quantitative yield. As in the first-generation synthesis, compounds **21** and **27** were not isolated and were carried crude into the next step without purification. Treatment of **21** with an excess of potassium *tert*-butoxide in the presence of 1-(*p*-toluenesulfonyl)imidazole in toluene gave the monotosylated intermediate **27** in 94% yield. There was no evidence of tosylation of the hydroxyl groups on the pyridine ring under these conditions as the excess potassium *tert*-butoxide effectivly cleaved these potential intermediates.[18] After an aqueous workup, monotosylate **27** was used directly in the next step as a solution in DMSO. The cyclization step was extensively examined in terms of both base and solvent combinations. The optimal conditions involved slow addition of DBU in DMSO to

DOI: 10.1021/acs.joc.6b01229
J. Org. Chem. 2016, 81, 10256−10265

Scheme 10



a solution of **27** in DMSO at 95 °C to afford crude **24** as a 87:13 mixture of atropisomers. Treatment of **24** with HCl at 40 °C and cooling to room temperature resulted in the crystallization of **5a** as an ethanol solvate which was isolated in 80% yield over the two steps and as a single atropisomer.

Atropisomerism is often observed when the free rotation about a bond is sufficiently restricted to result in stereoisomers called atropisomers whose interconversion is slow enough to allow for their separation and characterization.[19] Typically, atropisomerism is thought of in terms of restricted rotation about biaryl systems with BINAP serving as a representative example of molecules exhibiting this property. Tertiary aromatic amides also may be susceptible to restricted bond rotation and exhibit atropisomerization.[20,21] In a system structurally related to **5**, a similar naphthyridine displayed atropisomerism where the atropisomers were easily separated due to highly restrictive amide bond rotation.[22] Compounds **24**, **25**, **5a**, and final product **5** all have sufficient hindrance to rotation about the amide bond to permit separation of the atropisomers. The two atropisomers for compound **5** are depicted in Scheme 10. The desired atropisomer (a*R*,4*R*)-**5** has the carbonyl of the amide bond pointing up, whereas the undesired (a*S*,4*R*)-**5** has the carbonyl pointing back.[23,24] The undesired atropisomer of compound **5** demonstrated significantly less antiviral activity and had a markedly different pharmacokinetic profile from compound **5**. Compounds **24**, **25**, **5a**, and final product **5** all exist as an interconverting mixture of atropisomers when in solution. This is due to the fact that the methyl group is not sufficiently large enough to prevent this interconversion. Re-equilibration of the atropisomers occurs in solution at a rate of ∼2% per day depending on the solvent and temperature. For example, in EtOH, conversion of pure atropisomer **5** proceeds to a ∼ 85:15 mixture of atropisomers after stirring for 8 days at room temperature. However, at 37 °C, after just 3 days, the ratio of atropisomers was observed to be 85:15. Fortunately, the desired atropisomer of **5** was the thermodynamically more stable. In the solid state as a pure atropisomer, compounds **24**, **25**, **5a**, and final product **5** all proved to be chemically and conformationally stable, and no interconversion was observed when stored at room temperature.

CONCLUSION

In conclusion we have developed a practical, efficient asymmetric first-generation synthesis of the potent HIV-1 integrase inhibitor **5**, which proceeded in 10 synthetic steps and 14% overall yield from readily available unsaturated sulfoxide **8**. The route was robust, required no chromatography, and was scalable to multikilogram scale. The second-generation synthesis also proceeded in 10 synthetic steps, but in an improved 28% overall yield. These synthetic routes were highlighted by a 5-step synthesis of the challenging 8-membered ring that does not require isolation of any intermediates. The additional hurdle of controlling atropisomerization presented an added layer of complexity that was solved via crystallization of the desired atropisomer.

EXPERIMENTAL SECTION

All reagents were purchased from commercial sources and used as received. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, with chemical shifts given in ppm relative to TMS at δ = 0. Reaction mixtures and products were analyzed by reversed-phase HPLC using a 4.6 × 250 mm RP18 column. Solvent compositions consisted of 0.1% H_3PO_4 and acetonitrile with a flow rate of 1.5 mL/min.

Preparation of Ethyl 2-Amino-2-(1-(3-chloro-4-fluorobenzyl)-2-oxo-3-(phenylsulfinyl)piperidin-4-yl)acetate (11). In a 100 L round-bottom flask equipped with a mechanical stirrer, nitrogen inlet, thermocouple, and a 2 L addition funnel was added 5.00 kg (13.7 mol) of unsaturated sulfoxide **8**, 4.00 kg (15.1 mol) of glycine imine **10**, and 40 L of THF. The resulting slurry was stirred at room temperature until all the solids dissolved and was then cooled in an ice bath to an internal temperature of 0 °C. To the homogeneous solution was then added dropwise 1.4 L (1.4 mol) of a 1 M solution of lithium *tert*-butoxide while the internal temperature was maintained at <15 °C. The solution was cooled to 0 °C and was stirred at this temperature for 45 min, at which point HPLC indicated complete consumption of the starting material. To the cooled reaction mixture was added 35 L of 2 N HCl at such a rate that the internal temperature warmed gradually to room temperature. The hazy yellow solution was stirred at room temperature for 45 min and transferred to a 200 L extractor. The mixture was diluted with 25 L of MTBE, and the layers were separated. The organic layer was back extracted with 5 L of 2 N HCl. The combined aqueous layers were washed with MTBE (2 × 25 L) to completely remove residual benzophenone. The acidic aqueous layer was charged into a 100 L round-bottom flask, diluted with 25 L of isopropyl acetate (IPAc), and cooled to 0 °C. To the solution was added dropwise 25 L of 5 N NaOH, keeping the internal temperature <5 °C, and the final pH was 8.5. The layers were separated, and the aqueous layer was back extracted with 8 L of IPAc. The IPAc solution was utilized directly in the next step without further purification.

Preparation of Amino-[1-(3-chloro-4-fluorobenzyl)-2-oxopiperidin-(4*Z*)-ylidene]acetic Acid Ethyl Ester (17). A 100 L round-bottom flask equipped with a mechanical stirrer, nitrogen inlet,

DOI: 10.1021/acs.joc.6b01229
J. Org. Chem. 2016, 81, 10256−10265

thermocouple, and water-cooled condenser was charged with 6.4 kg (13.7 mol) of crude **11** as a solution in IPAc. The solvent was concentrated under reduced pressure with a constant feed of toluene, and the volume was adjusted to a total volume of 65 L (KF = 200 ppm). To the solution was added 2.4 L (13.8 mol) of Hünig's base, and the slurry was heated to 90 °C. After 30 min at 90 °C, the reaction was assayed for conversion and then cooled to ∼70 °C. The reaction mixture was concentrated under reduced pressure, and volume was reduced to ∼18 L, upon which a slurry formed. To the slurry was added 2 L of IPAc and the slurry allowed to cool to room temperature and stirred for 3 h. The slurry was filtered, rinsed with a mixture of 12L of 5:1 heptane/IPAC, and dried overnight under vacuum/N_2 sweep to give 3.0 kg (99 wt %, 65%) of **17** as a fluffy white solid: mpp 109−110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (t, 3H, J = 7.1 Hz), 2.97 (t, 2H, J = 5.6 Hz), 3.18 (s, 2H), 3.26 (t, 2H, J = 5.6 Hz), 3.44 (s, 2H), 4.25 (q, 2H, J = 7.1 Hz), 4.57 (s, 2H), 7.10 (m, 2H), 7.33 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 27.6, 36.2, 46.1, 49.3, 61.2, 116.3, 116.8 (d, J = 21 Hz), 121.5 (d, J = 17 Hz), 127.5, 127.8 (d, J = 7 Hz), 130.3, 134.2, 157.4 (d, J = 241 Hz), 164.4, 168.1. Anal. Calcd For $C_{16}H_{18}ClFN_2O_3$: C, 56.39; H, 5.32; N, 8.22. Found: C, 56.42; H, 5.29; N, 8.17.

Preparation of Ethyl 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (15). A 100 L round-bottom flask equipped with a mechanical stirrer, nitrogen inlet, thermocouple, and 2 L addition funnel was charged with 3.50 kg (8.80 mol) of imine **17** and 45 L of THF. The solution was cooled to 0 °C, and 1.70 L (9.68 mol) of Hünig's base was added in one portion. To the resulting solution was added dropwise, via the addition funnel, 1.20 L (9.24 mol) of monoethyl oxalyl chloride **12** at such a rate that the temperature was maintained below 3.5 °C. The reaction mixture was stirred for 30 min below 3.5 °C, at which point 3.06 kg (35.2 mol) of LiBr and1.97 kg (17.60 mol) of DABCO were introduced as solids. The resulting mixture was allowed to warm to room temperature and stirred for 16 h at room temperature. The reaction mixture was quenched with 35 L of 2 N aq HCl (35 L) and stirred at room temperature for 30 min. The mixture was then concentrated under reduced pressure in order to remove approximately one-half to three-fourths of the total THF charge. The resulting slurry was diluted to the original quench volume with water. The approximate amount of THF removed was 36−38 L. The slurry was stirred at room temperature for 30 min and filtered. The wet cake was slurry washed with water (2 × 12 L) and then with MTBE (3 × 12 L) and dried under vacuum/N_2 sweep to afford 2.95 kg (85%) of ester **15** as a colorless solid: mp 198−199 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, 3H, J = 7.1 Hz), 3.13 (t, 2H, J = 5.7 Hz), 3.48 (t, 2H, J = 5.7 Hz), 4.21 (q, 2H, J = 7.1 Hz), 4.65 (s, 2H), 7.33 (m, 2H), 7.54 (m, 1H), 11.35 (br s, 1H), 13.8 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 23.5, 45.6, 49.1, 61.9, 113.1, 117.5 (d, J = 21 Hz), 119.9 (d, J = 17 Hz), 120.1, 120.6, 129.0 (d, J = 7 Hz), 130.5, 134.7, 155.8, 156.1, 157.3 (d, J = 241 Hz), 161.8, 167.6; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −115.7. Anal. Calcd For $C_{18}H_{16}ClFN_2O_5$: C, 54.76; H, 4.09; N, 7.10. Found: C, 54.83; H, 4.06; N, 6.99.

Preparation of Ethyl 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid (6). To a 100 L flask equipped with a mechanical stirrer, nitrogen inlet, and thermocouple were added 3.08 kg (7.80 mol) of ester **15** and 37 L of a 1:1 mixture of EtOH/THF. To the resulting slurry was added 9.4 L of 5 N aq NaOH, and the mixture was warmed to 50−53 °C for 45 min. The slurry was then diluted with 10 L of water (∼3.33 L/kg) and stirred for an additional 1 h at 50−53 °C. Upon completion of the hydrolysis, the slurry was cooled to 15 °C, acidified with 6 L of concd HCl, and stirred at room temperature for 12 h. The slurry was filtered, washed with water (3 × 12 L), and dried under vacuum/N_2 sweep at +35 °C to afford 2.82 kg (99% yield) of naphthyridine acid **6** as a colorless solid: mp 275 °C dec; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.17 (t, 2H, J = 6.4 Hz), 3.47 (t, 2H, J = 6.4 Hz), 4.65 (s, 2H), 7.32 (m, 2H), 7.54 (m, 2H), 13.84 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 23.6, 45.7, 49.1, 112.9, 117.5 (d, J = 21 Hz), 119.7, 119.9 (d, J = 21 Hz), 120.1, 129.0 (d, J = 7 Hz), 134.7, (d, J = 3 Hz), 155.9, 156.8, 157.1 (d, J = 241 Hz), 163.3, 167.7; ^{19}F NMR (DMSO-d_6, 75 MHz) δ −118.7. Anal. Calcd For $C_{16}H_{12}ClFN_2O_5$: C, 52.40; H, 3.30; N, 7.64. Found: C, 52.38; H, 3.25; N, 7.59.

Preparation of (3*R*)-2,2-Dimethyl-4-(methylamino)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)butan-1-ol (7). In a 100 L flask equipped with a mechanical stirrer, nitrogen inlet, and thermocouple were added 5.20 kg (40 mol) of D-(−)-pantolactone **9**, 15.6 L of dichloromethane, and 19.8 g (0.1 mol) of $TsOH·H_2O$. The solution was cooled to −5 °C utilizing a dry ice/acetone bath, and 3.69 kg (44.0 mol) of 3,4-dihydro-2*H*-pyran was added over 30 min while keeping the internal temperature below 20 °C. The resulting solution was stirred at room temperature for 1 h, and 12.4 L (100 mol) of a 33 wt % solution of methylamine in EtOH was added in one portion. The resulting yellow solution was stirred at room temperature for 18 h. The reaction mixture was diluted with 15 L of toluene and concentrated under reduced pressure to near dryness and then reconcentrated under reduced pressure to remove residual methylamine and EtOH. The solvent was adjusted to a final volume of ∼90 L of toluene and used in the next step without purification.

The above solution of **20** in toluene was transferred to a 200 L jacketted reactor, and the solution was cooled to an internal temperature of −5 °C. To the solution was added dropwise 30.2 L (100 mol) of a ∼65 wt % solution of Red-Al in toluene over a period of 45 min while keeping the internal temperature below 20 °C. Hydrogen off-gassing was observed during the first 10 L addition of Red-Al. The resulting mixture was then heated to 90 °C for 4 h and allowed to cool to room temperature. The mixture was further cooled to −5 °C and quenched with 8.7 L of isopropyl alcohol keeping the internal temperature below 20 °C. The solution was inversely quenched into a 52 L of a 20 wt % aqueous KOH solution, and the layers were separated. The organic phase was washed with water (2 × 35 L) and was concentrated under reduced pressure to provide 8.96 kg a crude oil (8.25 kg) 92 wt % by NMR assay (90% overall yield from 7) as a light yellow oil and as a 3:1 mixture of THP diastereomers that were used in the next step without further purification. Major diastereomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (s, 3H), 0.97 (s, 3H), 1.55 (m, 4H), 1.78 (m, 1H), 1.84 (m, 1H), 2.44 (s, 3H), 2.66 (m, 1H), 2.81 (dd, 1H, J = 12.8 and 4.5 Hz), 3.21 (d, 1H, J = 11.5 Hz), 3.46 (d, 1H, J = 11.5 Hz), 3.52 (m, 1H), 3.59 (t, 1H, J = 4.5 Hz), 3.96 (m, 1H), 4.70 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.3, 21.4, 23.94, 25.2, 31.3, 36.1, 39.3, 49.5, 63.7, 67.1, 79.6, 97.4. Minor diastereomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (s, 3H), 0.98 (s, 3H), 1.55 (m, 4H), 1.78 (m, 1H), 1.84 (m, 1H), 2.43 (s, 3H), 2.66 (m, 1H), 2.89 (m, 1H), 2.99 (d, 1H, J = 11.5 Hz), 3.36 (m, 1H), 3.52 (m, 1H), 3.60 (d, 1H, J = 11.5 Hz), 3.88 (m, 1H), 4.51 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 22.1, 23.9, 25.2, 30.9, 35.7, 40.1, 51.3, 64.1, 66.0, 85.5, 102.8.

First-Generation Synthesis of 5a. *Preparation of (4R)-11-(3-Chloro-4-fluorobenzyl)-9-methoxy-2,5,5-trimethyl-4-((tetrahydro-2H-pyran-2-yl)oxy)-3,4,5,6,12,13-hexahydro-2H-[1,4]diazocino[2,1-a][2,6]naphthyridine-1,8,10(11H)-trione (**25**).* To a 75 L round-bottom flask equipped with a mechanical stirrer, nitrogen inlet, and thermocouple was added 4.00 kg (10.91 mol) of naphthyridine acid **6**, 3.29 kg (13.09 mol) of 92 wt % amino alcohol **7**, 3.61 L (32.73 mol) of *N*-methylmorpholine, 74 g (0.55 mol) of HOAt, and 2.51 kg (13.09 mol) of EDC. The mixture was dissolved in 28 L of DMF and stirred at room temperature for 60 h. The reaction mixture was diluted with 40 L of EtOAc and 28 L of water. The mixture was transferred to an extractor, and the layers were separated. The aqueous layer was back extracted with an additional 40 L of EtOAc. The combined extracts were washed with water (2 × 40 L) and concentrated in a 100 L round-bottom flask under reduced pressure while azeotropically drying with a feed of EtOAc during the concentration. The volume was adjusted to ∼50 L (KF < 300 μg/g) to provide 5.06 kg by HPLC assay (80% yield) of amide **21**, which was used in the next step without further purification.

To the above solution of 5.06 kg (8.72 mol by assay) of amide **21** was added 6.08 L (43.62 mol) of NEt_3, and the solution was cooled in an ice bath to an internal temperature of 5 °C. To the mixture was slowly added dropwise 3.38 L (43.62 mol) of MsCl while maintaining the internal temperature below 20 °C. After the addition, the slurry

DOI: 10.1021/acs.joc.6b01229
J. Org. Chem. 2016, 81, 10256−10265

was stirred at room temperature for 1 h and was quenched into a 50 L solution of saturated aqueous $NaHCO_3$. The biphasic solution was stirred at room temperature for 1 h, and the layers were separated. The organic layer was washed with 50 L of water, and the solvent was switched to DMAc under reduced pressure in a 100 L round-bottom flask to give a final volume of ∼50 L (KF < 300 μg/g) and provided 6.75 kg by assay (95%) of **22** which was used in the next step without further purification.

To the above solution of 6.75 kg by assay (8.29 mol) of trismesylate **22** in DMAc was added 5.40 kg (16.58 mol) of Cs_2CO_3, and the mixture was heated to 80 °C. After 2 h at 80 °C, the mixture was cooled to room temperature, and 1.55 L (24.88 mol) of MeI was added. The mixture was stirred at room temperature for 15 h and diluted with 40 L of water. The mixture was transferred to a 200 L extractor and further diluted with 50 L of EtOAc. The layers were separated, and the organic layer was washed with 40 L of water. The solvent was concentrated under reduced pressure in a 50 L round-bottom flask while first azeotropically drying by EtOAc distillation and finally solvent switching to DMAc to provide a final volume of ∼9 L (KF < 300 μg/g) and 5.66 kg by assay (91% assay yield) of **23** that was used in the next step without further purification.

To a 100 L round-bottom flask equipped with a mechanical stirrer, nitrogen inlet, addition funnel, and thermocouple was added 7.37 kg (22.63 mol) of Cs_2CO_3 and 31 L of DMAc, and the slurry was heated to an internal temperature of 105 °C. To this slurry was slowly added via the addition funnel over 4 h the above solution of 5.66 kg by assay (7.54 mol) of **23** in 9 mL of DMAc. After the addition was complete, the mixture was stirred at the same temperature for an additional 3 h and cooled to room temperature. To the mixture was added 50 L of water over the course of 1 h, and the resulting slurry was stirred at room temperature for 15 h. The slurry was filtered, and the wet cake was washed with water (2 × 20 L) and dried under vacuum/N_2 sweep for 24 h at room temperature to give a brown solid (6.94 kg, ∼ 50 wt %, 3.47 kg by assay, 80% assay yield) of **24** as an 85:15 mixture of amide atroisomers and 3:1 mixture of diastereomers which was used directly in the next step without further purification.

*Preparation of (R)-11-(3-Chloro-4-fluorobenzyl)-4-hydroxy-9-methoxy-2,5,5-trimethyl-3,4,5,6,12,13-hexahydro-2H-[1,4]diazocino-[2,1-a]naphthridine-1,8,10(11H)-trione (**25**).* To a 100 L round-bottom flask equipped with a mechanical stirrer, nitrogen inlet, and thermocouple was added 3.47 kg by assay (6.02 mol) as a 85:15 mixture of amide atropisomers of **24**, 30 L of MeOH, and 343 g (1.81 mol) of $TsOH·H_2O$. The mixture was heated to 50 °C for 2 h and cooled to room temperature. The solvent was switched to EtOAc under reduced pressure with a constant feed of EtOAc while the volume was maintained at ∼30 L. During concentration, the product crystallized. The final volume was adjusted to ∼25 L, the resulting slurry was stirred at room temperature for 2 h and filtered, and the wet cake was washed with EtOAc (2 × 5 L). The cake was dried under vacuum/N_2 sweep at room temperature for 24 h to provide 1.66 kg (56%) of **25** as a colorless solid and a single amide atropisomer: mp 190−192 °C (DSC); $[\alpha]_D$ +1.60 (*c* 1.0, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.72 (s, 3H), 1.08 (s, 3H), 2.40 (m, 1H), 2.60 (m, 1H), 2.91 (d, 1H, *J* = 15.1 Hz), 3.07 (s, 3H), 3.18 (d, 1H, *J* = 15.1 Hz), 3.34 (m, 1H), 3.44 (m, 2H), 3.59 (dd, 1H, *J* = 15.2 and 9.8 Hz), 3.82 (s, 3H), 4.55 (d, 1H, *J* = 15.2 Hz), 4.57 (d, 1H, *J* = 15.2 Hz), 4.74 (d, 1H, *J* = 15.2 Hz), 5.10 (d, 1H, *J* = 4.6 Hz), 7.35 (m, 1H), 7.40 (t, 1H, *J* = 9.0 Hz), 7.54 (dd, 1H, *J* = 7.3 and 2.0 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 14.9, 25.2, 27.2, 33.7, 38.7, 45.9, 49.2, 51.0, 53.4, 60.1, 72.7, 111.7, 117.4 (d, *J* = 20.8 Hz), 119.9 (d, *J* = 18.4 Hz), 127.7, 128.7 (d, *J* = 7.5 Hz), 130.1, 134.0, 136.0 (d, *J* = 3.7 Hz), 149.5, 157.0 (d, *J* = 245.1 Hz), 159.3, 160.6, 162.4; ^{19}F NMR (DMSO-d_6, 75 MHz) δ −118.6. Anal. Calcd For $C_{24}H_{27}ClFN_3O_5$: C, 58.60; H, 5.53; N, 8.54. Found: C, 58.30; H, 5.54; N, 8.45.

*Preparation of (R)-11-(3-Chloro-4-fluorobenzyl)-4,9-hydroxy-2,5,5-trimethyl-3,4,5,6,12,13-hexahydro-2H-diazocino[2,1-a][2,6]-naphthyridine-1,8,10(11H)-trione EtOH Solvate (**5a**).* In a 50 L round-bottom flask equipped with a mechanical stirrer, nitrogen inlet, and thermocouple were added 1.66 kg (3.37 mol) of **25** and 15 L of CH_2Cl_2, and the mixture was cooled to an internal temperature of 5 °C. To this solution was added 7.1 L (7.1 mol) of a 1 M solution of BBr_3 over 1 h while maintaining the internal temperature <20 °C. The resulting slurry was stirred at room temperature for 1 h and cooled to 5 °C. To the slurry was added dropwise 2.5 L of MeOH followed by the addition of 20 L of water in one portion. The mixture was stirred at room temperature for 1 h, and the layers wre separated. The organic layer was washed with 20 L of a 1% aqueous solution of $NaHCO_3$ followed by 20 L of water. The solvent was concentrated under reduced pressure with the constant addition of ethanol and a final volume of ∼16 L. The resulting slurry was stirred at room temperature of 2 h and filtered, and the wet cake was washed with 5 L of EtOH. The solid was dried under vacuum/N_2 sweep for 24 h to give 1.62 kg (92%) of **5a** as an EtOH solvate and as a pure atropisomer and a colorless solid: mp 145−147 °C (DSC); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.72 (s, 3H), 1.06 (t, 3H, *J* = 7.3 Hz); 1.08 (s, 3H), 2.44 (dt, 1H, *J* = 15.4 and 5.4 Hz), 2.71 (m, 1H), 2.91 (d, 1H, *J* = 15.2 Hz), 3.07 (s, 3H), 3.16 (d, 1H, *J* = 15.2 Hz), 3.33 (m, 1H), 3.42−3.56 (m, 4H), 3.61 (dd, 1H, *J* = 15.1 and 9.5 Hz), 4.34 (t, 1H, *J* = 4.8 Hz), 4.54 (d, 1H, *J* = 14.2 Hz), 4.62 (d, 1H, *J* = 15.2 Hz), 4.75 (d, 1H, *J* = 15.2 Hz), 5.08 (d, 1H, *J* = 4.8 Hz), 7.41 (m, 2H), 7.60 (dd, 1H, *J* = 7.2 and 2.0 Hz), 13.1 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 14.9, 19.0, 23.9, 27.2, 33.7, 38.8, 46.0, 49.1, 51.1, 53.5, 56.5, 109.9, 111.8, 117.4 (d, *J* = 20.8 Hz), 120.1 (d, *J* = 18.0 Hz), 128.7, 129.0 (d, *J* = 8.3 Hz), 130.4, 134.7 (d, *J* = 3.5 Hz), 152.2, 157.0, 157.1 (d, *J* = 246.0 Hz), 162.4, 167.4; ^{19}F NMR (DMSO-d_6, 75 MHz) δ −118.1. Anal. Calcd For $C_{25}H_{31}ClFN_3O_6$: C, 57.31; H, 5.96; N, 8.02. Found: C, 57.09; H, 5.93; N, 7.96.

*Preparation of (R)-11-(3-Chloro-4-fluorobenzyl)-4,9-hydroxy-2,5,5-trimethyl-3,4,5,6,12,13-hexahydro-2H-diazocino[2,1-a][2,6]-naphthyridine-1,8,10(11H)-trione (**5**).* In a 50 L round-bottom flask equipped with a mechanical stirrer and thermocouple was added 2.80 kg (5.34 mol) of the above EtOH solvate **5a** and 28 L of MTBE. The resulting slurry was stirred at room temperature of 20 h. The slurry was filtered, and the wet cake was washed with 5 L of MTBE and dried under vacuum/N_2 sweep for 24 h at room temperature to provide 2.50 kg (98%, > 99 wt %) of **5** as a colorless solid containing 0.5 wt % of MTBE that could not be further removed: mp 242−243 °C (DSC); $[\alpha]_D$ +1.19 (*c* 1.0, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.72 (s, 3H), 1.10 (s, 3H), 2.44 (dt, 1H, *J* = 15.4 and 5.4 Hz), 2.71 (m, 1H), 2.91 (d, 1H, *J* = 15.1 Hz), 3.06 (s, 3H), 3.16 (d, 1H, *J* = 15.1 Hz), 3.33 (m, 1H), 3.51 (m, 2H), 3.61 (dd, 1H, *J* = 15.1 and 9.5 Hz), 4.54 (d, 1H, *J* = 14.2 Hz), 4.62 (d, 1H, *J* = 15.1 Hz), 4.76 (m, 1H, *J* = 15.1 Hz), 5.10 (d, 1H, *J* = 4.6 Hz), 7.40 (m, 2H), 7.60 (d, 1H, *J* = 7.2 and 2.0 Hz), 13.1 (s, 1H);); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 14.9, 23.9, 27.2, 33.7, 38.9, 46.0, 49.1, 51.0, 53.5, 75.8, 109.9, 111.9, 117.5 (d, *J* = 21.4 Hz), 120.0 (d, *J* = 18.2 Hz), 128.7, 129.0 (d, *J* = 7.3 Hz), 130.5, 134.8 (d, *J* = 3.76 Hz), 152.2, 157.0, 157.1 (d, *J* = 243.o Hz), 162.4, 167.4; ^{19}F NMR (DMSO-d_6, 75 MHz) δ −118.1. Anal. Calcd For $C_{23}H_{25}ClFN_3O_5$: C, 57.80; H, 5.27; N, 8.79. Found: C, 57.72; H, 5.13; N, 8.76.

Second-Generation Synthesis of 5a. *Preparation of 6-(3-Chloro-4-fluorobenzyl)-5-oxo-3,4-bis(pivalyloxy)-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylic Pivalic Anhydride (**26**).* A 100 mL flask was charged with 15 mL of THF, 1.0 g (2.73 mmol) of naphthyridine acid **6** (1.0 g, 2.73 mmol), and 1.90 mL (13.65 mmol) of NEt_3, and the resulting slurry was cooled to 10 °C. To the slurry was added dropwise 1.18 mL (9.56 mmol) of trimethylacetyl chloride, and the mixture was stirred at room temperature for 5 h. The resulting slurry was filtered, and the solids were washed with 5 mL of dry THF. The filtrate was concentrated under reduced pressure with a constant feed of heptane to a final volume of ∼15 mL. The resulting slurry was stirred at room temperature of 1 h, filtered, washed with 10 mL of heptane, and dried at 40 °C in a vacuum oven for 12 h to afford 1.59 g (95%) of trispivalate **26** as a colorless solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0 1.36 (s, 9H), 1.40 (s, 9H), 1.41 (s, 9H), 3.42 (br m, 2H), 3.52 (br m, 2H), 4.71 (br m, 2H), 7.13 (t, 1H, *J* = 8.5 Hz), 7.20 (m, 1H), 7.40 (dd, 1H, *J* = 7.1 and 2.3 Hz);); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.6, 26.4, 26.7, 27.0, 27.1, 39.3, 39.6, 44.9, 45.8, 49.3, 116.8 (*J* = 21.7 Hz), 121.3, (*J* = 17.0 Hz), 127.7 (*J* = 7.3 Hz), 130.2, 133.5 *J* = 4.4 Hz), 133.5, 137.3, 137.9, 141.2, 149.9, 157.7 (*J* = 255 Hz), 159.7,

DOI: 10.1021/acs.joc.6b01229
J. Org. Chem. 2016, 81, 10256−10265

162.0, 174.8, 175.0, 175.2. Anal. Calcd for $C_{31}H_{36}ClFN_2O_8$: C, 60.14; H, 5.86; N, 4.53. Found: C, 59.81; H, 5.87; N, 4.49.

*Preparation of (R)-11-(3-Chloro-4-fluorobenzyl)-4,9-hydroxy-2,5,5-trimethyl-3,4,5,6,12,13-hexahydro-2H-diazocino[2,1-a][2,6]-naphthyridine-1,8,10(11H)-trione EtOH Solvate (**5a**).* To a solution of 1.0 g (1.62 mol) of trispivalate **26** in 7 mL of THF was added 0.41 g (1.62 mmol) of a 92 wt % solutoin of amino alcohol **7** in 1 mL of THF. After being stirred for 15 min at room temperature, the mixture was cooled to 5 °C, and 2 mL of MeOH was added followed by the addition of 0.52 mL (9.72 mmol) of a 50 wt % solution of aqueous NaOH while keeping the internal temperature <15 °C. The clear solution is stirred for 1 h, and 5 mL of a 2 N solution of HCl was added slowly while keeping the internal temperature <15 °C to give a pH of 6−6.5. The mixture was extracted with 5 mL of toluene, and the organic layer was washed with 10 mL of a 15 wt % solution of brine. The organic layer is azeotropically dried with a constant feed of toluene and the final volume adjusted to ∼6 mL to give amide **21** that was used in the next step without further purification.

To the solution of 1.0 g (1.72 mmol) of amide **21** in 6 mL of toluene was added 12 mL of THF, and the solution was cooled to 5 °C. To the solution was added 1.16 g (10.32 mmol) of solid potassium *tert*-butoxide in one portion. The resulting mixture was stirred at 10−15 °C for 1 h, and 0.73 g (3.27 mmol) of 1-(*p*-toluenesulfonyl)-imidazole was added in one portion. The resulting mixture was stirred at the same temperature for 1 h, cooled to <10 °C, and quenched with 6 mL of a 2 N solution of HCl to give a pH of 6−6.5. The layers were separated, and the organic layer was washed with 10 mL of water. The solution was azeotropically dried with a constant feed of toluene until the KF was <500 μg/g of water and then solvent switched to DMSO and a final volume of 4 mL of **27** which was used in the next reaction without further purification.

To a solution of 0.61 mL (4.08 mmol) of DBU (0.61 mL, 4.08 mmol) in 6 mL of at 95 °C was slowly added a solution of 1.00 g (by assay, 1.36 mmol) of the monotosylate **27** in 4 mL of DMSO, and the mixture was stirred at 95 °C for additional 6 h. The mixture was cooled to 15 °C and diluted with 10 mL of EtOAc, and 6 mL of 0.4 N aqueous HCl (0.4 N, ∼ 6 mL) was added to give a final pH = 6.5−7.0. The layers were separated, and the aqueous layer was back extracted with 8 mL of EtOAc. The combined organic extracts were washed with 10 mL of water (2×), treated with 0.27 g of Darco-G60 at room temperature for 1 h, and filtered through a pad of cellulose. The filtrated was concentrated under reduced pressure and solvent switched to EtOH by the constant addition of EtOH during the concentration. The final volume was 5 mL of **24** which contained 0.54 g (70%) which was used in the next step without further purification.

To a solution of the 1.0 g (1.78 mmol) of intermediate **24** in 10 mL of EtOH was added 0.18 mL (0.89 mmol) of a 5 N solution of HCl in 2-propanol. The mixture was stirred at 40 °C for 2 h. During the course of the reaction, the EtOH solvate of **5a** crystallized. The resulting slurry was cooled to room temperature and stirred for 3 h. The slurry was filtered and washed with 5 mL of EtOH and dried in a vacuum oven at 40 °C for 12 h to afford 0.75 g (80%) of **5a** as a colorless solid, and a single atropisomer that was identical to that prepared in the first-generation synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01229.

Spectroscopic data for compounds **5**, **5a**, **6**, 7, **15**, **17**, and **25** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jeffrey_kuethe@merck.com.

Notes

The authors declare no competing financial interest.

[†](J.T.K.) ISHC member.

■ ACKNOWLEDGMENTS

We thank Lisa DiMichele, Robert Reamer, Alexei Buevich, and Peter G. Dormer of Merck & Co., Inc. for valuable NMR assistance and Dr. Edward Sherer for computational asistance. We also thank former Merck & Co., Inc., employees Danny Mancheno, Dr. Remy Angelaud, and Dr. Philip Pye for experimental assistance.

■ REFERENCES

(1) For a leading reference, see: Seeney, Z. K.; Klumpp, K. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 458−470.

(2) For a leading reference, see: von Hentig, N. *Drugs Today* **2008**, *44*, 103−132.

(3) For a review, see: *HIV Chemotherapy: A Critical Review*; Butera, S. T., Ed.; Caister Academic Press: Norfolk, UK, 2005.

(4) For a leading reference, see: Pace, P.; Rowley, M. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 471−479.

(5) (a) Cabrera, C. *Curr. Opin. Invest. Drugs* **2008**, *31*, 310. (b) Rowley, M. *Prog. Med. Chem.* **2008**, *46*, 1−28. (c) Markowitz, M.; Evering, T. H. *Drugs Today* **2007**, *43*, 865−877. (d) Dayam, R. G. R.; Al-Mawsawi, L. Q.; Neamati, N. *Med. Res. Rev.* **2008**, *28*, 118−154.

(6) Karmon, S. L.; Markowitz, M. *Drugs* **2013**, *73*, 213−228.

(7) Klibanov, O. M. *Curr. Opin. Investig. Drugs.* **2009**, *10*, 190−200. (b) Reviriego, C. *Drugs Today* **2014**, *50*, 209−217.

(8) Katlama, C.; Murphy, R. *Expert Opin. Invest. Drugs* **2012**, *21*, 523−530.

(9) Métifiot, M.; Johnson, B.; Smith, S.; Zhao, X. Z.; Marchand, C.; Burke, T.; Hughes, S.; Pommier, Y. *Antimicrob. Agents Chemother.* **2011**, *55*, 5127−5133.

(10) Egbertoson, M. S.; Wai, J. S.; Cameron, M.; Hoerrner, R. S. In *Antiviral Drugs: From Basic Discovery through Clinical Trials*; Kazmierski, W. M., Ed.; John Wiley & Sons, Inc.: New York, 2011; pp 163−180.

(11) Vacca, J. P.; Wai, J. S.; Payne, L. S.; Isaacs, R. C. A.; Han, W.; Egbertson, M.; Pracitto, R. PCT Int. Appl. WO2006121831 A2, 2006, 1116.

(12) For an initial disclosure for the synthesis of compound **6** that doesn't describe synthetic details, see: Raheem, I. T.; Walji, A. M.; Klein, D.; Sanders, J. M.; Powell, D. A.; Abeywickrema, P.; Barbe, G.; Bennet, A.; Childers, K.; Christensen, M.; Clas, S.-D.; Dubost, D.; Embrey, M.; Grobler, J.; Hafey, M. J.; Hartingh, T. J.; Hazuda, D. J.; Kuethe, J. T.; Dunn, J. M.; Miller, M. D.; Moore, K. P.; Nolting, A.; Pajkovic, N.; Patel, S.; Peng, Z.; Rada, V.; Rearded, P.; Schreier, J. D.; Sisko, J.; Steele, T. G.; Truchon, J.-F.; Wai, J.; Xu, M.; Colemen, P. J. *J. Med. Chem.* **2015**, *58*, 8154−8165.

(13) HPLC assay yield refers to quantitative HPLC analysis employing an analytical standard.

(14) Byproduct **20** was not isolated, but was identified by NMR analysis of the crude reaction mixture.

(15) Intermediates leading to compound **24** were not crystalline, making their isolation problematic.

(16) Selective demesylation was confirmed by NMR analysis of the crude reaction mixture.

(17) For the synthesis of this precursor, see ref 11.

(18) Aryl sulfonate esters are readily cleaved under basic conditions; for some leading references, see: Wuts, P. G. M. *Greene's Protective Groups in Organic Chemistry*, 5th ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2014; pp 541−545.

(19) For a leading reference, see: Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, C.; Pink, J. H.; Westlund, N.; Yasin, S. A. *Tetrahedron* **1998**, *54*, 13277−13294.

(20) For leading examples, see: (a) Barrett, K. T.; Miller, S. J. *J. Am. Chem. Soc.* **2013**, *135*, 2963−2966. (b) Tabata, H.; Wada, N.; Takada, Y.; Oshitari, T.; Takahashi, H.; Natsugari, H. *J. Org. Chem.* **2011**, *76*, 5123−5131. (c) Tabata, H.; Suzuki, H.; Akiba, K.; Takahashi, H.; Natsugari. *J. Org. Chem.* **2010**, *75*, 5984−5993. (d) Clayden, J.;

DOI: 10.1021/acs.joc.6b01229
J. Org. Chem. 2016, 81, 10256−10265

Johnson, P.; Pink, J. H.; Helliwell, M. *J. Org. Chem.* **2000**, *65*, 7033−7040.
(21) For references on amide atropisomers in manufactured pharmaceuticals, see: (a) Parker, J. S.; Smith, N. A.; Welham, M. J.; Moss, W. O. *Org. Process Res. Dev.* **2004**, *8*, 45−50. (b) Friary, R. J.; Spangler, M.; Osterman, R.; Schulman, L.; Schwerdt, J. H. *Chirality* **1996**, *8*, 364. (c) Chenard, B. L.; Devries, K. M.; Welch, W. M. WO09838187, 1998.
(22) For an account of atroisomers within a structurally related naphthyridine, see: Natsugari, H.; Ikeura, Y.; Kamo, I.; Ishimaru, T.; Ishichi, Y.; Fujishima, A.; Tanaka, T.; Kasahara, F.; Kawada, M.; Doi, T. *J. Med. Chem.* **1999**, *42*, 3982−3993.
(23) The stereochemical assignment was based on similar assigmments in ref 19 where the letter *a* before *R* and *S* denotes axial chirality, see: Cahn, R. S.; Ingold, C.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385−415.
(24) The 3-D representations in Scheme 10 were calculated using the program PyMOL.

DOI: 10.1021/acs.joc.6b01229
J. Org. Chem. 2016, 81, 10256−10265