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Adventures in Atropisomerism: Total Synthesis of a Complex Active Pharmaceutical Ingredient with Two Chirality Axes

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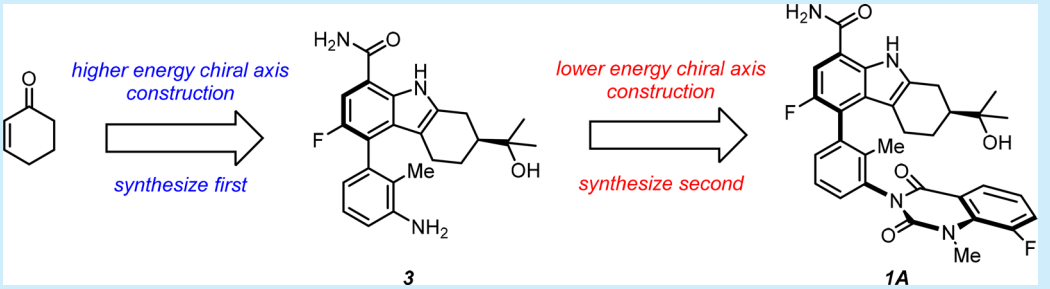
Supporting Information



ABSTRACT: A strategy to prepare compounds with multiple chirality axes, which has led to a concise total synthesis of compound **1A** with complete stereocontrol, is reported.

Bruton's tyrosine kinase (BTK) has been a target for the discovery and development of therapies to treat several disease types during the past decade.[1] Ibrutinib, which is a selective, irreversible inhibitor of the BTK enzyme is currently approved for the treatment of lymphoma and leukemia.[2] Acalabrutinib, is a second-generation BTK inhibitor that is more potent and selective than ibrutinib, is used in the treatment of a variety of cancer targets.[3] Inhibitors of BTK have also been investigated for the treatment of autoimmune diseases,[4] and compound **1A**,[5] is a reversible inhibitor of the BTK,[6] is currently in phase 2 clinical trials for the treatment of rheumatoid arthritis (see Figure 1).

Compound **1A** contains three chiral elements: a stereocenter at the hydroxyalkyl appendage of the carbazole ring, as well as the most striking structural features of **1A**, two bonds of hindered rotation that lead to diastereomeric axes of chirality.[7] Rotation about the hindered carbazole-aryl C−C bond was found to have a barrier to rotation of 28 kcal/mol (see Figure 2).[8] In contrast, the aryl-quinazolinedione C−N bond was found to have a lower rotational barrier of 26 kcal/mol. Rotation about these axes of chirality gives rise to four possible atropisomeric diastereomers. While the higher-energy C−C chirality axis is relatively stable, with little risk of epimerization under 90 °C and most chemical conditions, the lower-energy C−N bond, however, has a rotational half-life of hours to days, with a risk of slow epimerization.[7f,g,9] In this paper, we describe a straightforward strategy developed to prepare and control molecules with multiple axes of chirality. Implementation of this strategy led to the concise total synthesis of compound **1A** with complete diastereomeric and enantiomeric control.

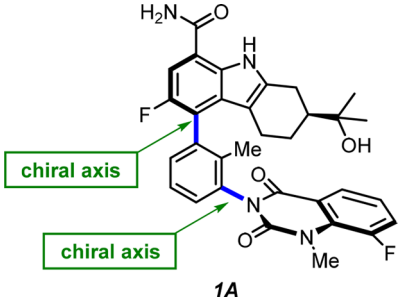


Figure 1. Chemical structure of compound **1A**.[5a]

In designing a robust and efficient chemical synthesis of **1A**, we sought to utilize the compound's physical properties and inherent stability profile to help guide the strategy. Based on computational predictions, we knew that the barrier of rotation about the C−C bond was 2 kcal/mol higher than the barrier for its C−N counterpart.[8] If constructed early in the synthesis, there would be a low risk of epimerizing the former in subsequent transformations used to install the latter. Synthesis of the carbazole-

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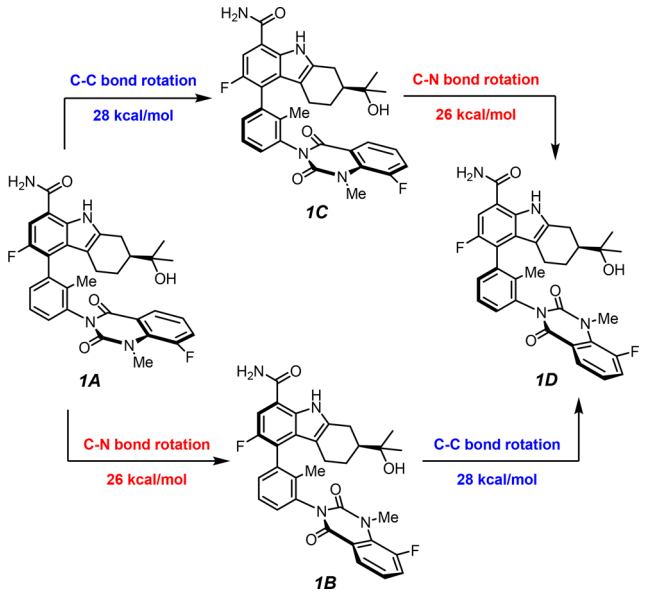


Figure 2. Atropisomeric diastereomers of compound **1A**.

aryl C−C bond with its associated chiral architecture first would serve two purposes: (1) act as a chiral template to direct the asymmetric construction of the lower barrier aryl-quinazolinedione axis of chirality and (2) broaden the available reaction conditions to construct the lower-barrier C−N atropisomer later in the synthesis without the risk of epimerizing the carbazole-aryl C−C chiral environment. Boger employed a similar strategy in his synthesis of the Vancomycin aglycon,[10] wherein the highest barrier CD fragment was constructed first to reduce the risk of epimerization in subsequent transformations. The lower barrier AB and DE chirality axes were then synthesized without perturbation of the high-barrier CD fragment.

Retrosynthetically, we envisioned constructing the aryl-quinazolinedione chiral C−N bond as the last step in the synthesis by reaction of enantiomerically and diastereomerically pure aniline **3** with 7-F-isatoic anhydride **2** to provide compounds **1A**/**1B**, epimeric about the C−N bond. Utilizing a dynamic crystallization, we hypothesized that **1A** could be selectively crystallized out of solution, while keeping the undesired diastereomer **1B** in solution, making it available for epimerization to form compound **1A** (see Figure 3).[11] However, this would require careful choice of solvent and temperature to ensure solubility differentiation between **1A** and **1B**, while avoiding epimerization of the C−C chiral axis. Aniline **3** would arise through a cross-coupling reaction of the corresponding electrophilic carbazole bromide **5** and commercially available arylboronic acid **4**. Either a Suzuki reaction combined with a crystallization could upgrade the diastereomeric purity of **3**, or an asymmetric Suzuki coupling variant could be developed through judicious choice of precatalyst and chiral ligand.

Carbazole **5** contains a hydroxyalkyl substituent and a highly functionalized arene core.[5a] Retrosynthetic disconnection of **5** into enantiomerically pure cyclohexanone **7** and tetra-substituted arene **6** was envisioned to arise from a convergent Fischer indolization.[12] Cyclohexanone **7** could be accessed through a myriad of sources, including the chiral pool and catalyst or chiral auxiliary-mediated transformations.

Although several methods of preparing **7** were explored, including conversion of natural product (*R*)-perillaldehyde to **7**,[13] we pursued the asymmetric rhodium-catalyzed conjugate

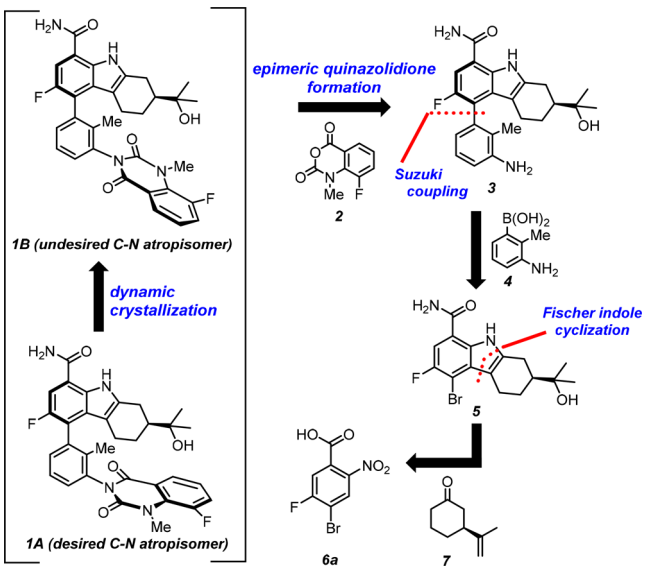
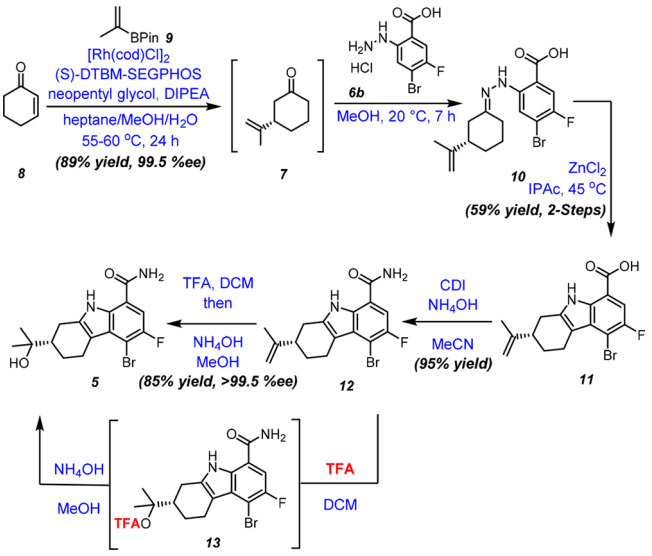


Figure 3. Retrosynthetic analysis of compound **1A**.

addition of isopropenylboronic acid pinacol ester **9** to cyclohexenone **8** for its direct, one-step access to cyclohexanone **7** (see Scheme 1).[14] A combination of 0.3 mol % of $[Rh(COD)Cl]_2$ with 0.66 mol % (S)-DTBM-SEGPHOS in a mixture of heptane, methyl alcohol (MeOH), and water delivered **7** in 89% yield and >99.5% enantiomeric excess (ee).[15] Critical to the success of this reaction was the use of 1,3-diol neopentyl glycol as a key additive, and rigorous exclusion of oxygen to below 400 ppm to preserve both high reaction conversion and enantioselectivity.

Scheme 1. Synthesis of Carbazole 5



Without isolation, ketone **7** was carried into the next step as a solution in heptane and MeOH and was condensed with aryl hydrazine **6b** (formed in two steps from **6a**)[5a] to afford hydrazone **10** in 98% isolated yield by collection of the solids directly from the reaction mixture. Treatment of **10** with $ZnCl_2$ induced the Fischer indolization to afford the carboxylic acid containing carbazole **11** in 61% isolated yield. Two main impurities arose from the reaction: the decarboxylation byproduct of **11** and the carbazole resulting from regioisomeric cyclization. However,

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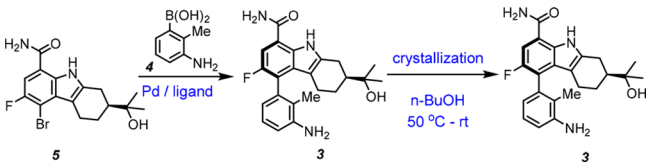
both of these impurities were purged to <0.05% upon crystallization from acetonitrile. Treatment of carbazole **11** with CDI and NH_4OH delivered the corresponding amide **12** in 95% yield. Conversion of the pendent olefin to the Markovnikov hydration product under known sulfuric or phosphoric acid hydration conditions delivered a complex mixture of the desired alcohol and elimination products.[16] However, treatment with trifluoroacetic acid[17] was found to cleanly convert olefin **12** to the corresponding TFA ester **13**. Without isolation, reaction of **13** with NH_4OH in MeOH induced ester hydrolysis to deliver the desired alcohol **5** in 85% isolated yield.

With access to carbazole **5**, we began to execute our strategy of establishing the higher-energy barrier chirality axis in compound **3**. Achiral catalyst $PdCl_2$(dppf) was first utilized to evaluate the reactivity of **5** with commercially available arylboronic acid **4** (see Table 1). Pleasingly, aniline **3**, which is epimeric about the carbazole-aryl bond, was formed with >98% conversion. Upon crystallization from *n*-BuOH, we discovered that the undesired atropisomeric diastereomer could be purged to provide **3** in 13:1 diastereomeric ratio (dr). Impressively, a second crystallization from *n*-BuOH delivered **3** with >60:1 dr, albeit in 64% yield.[18] With the success of the achiral Suzuki–Miyaura coupling and *n*-BuOH crystallization procedure, we turned our attention to the development of an asymmetric variant with the target of delivering a higher yield of **3** and, thus, better material throughput through improved chiral control.[19]

Table 1. Asymmetric Suzuki–Miyaura Coupling Ligand Screening[a]



entry	metal/ligand	product yield	diastereomeric ratio, dr
1	$PdCl_2$(dppf)	91.7	1.4:1.0
2	$Pd(OAc)_2$/(*R*)-Et-DuPhos	9.3	3.2:1.0
3	$Pd(OAc)_2$/(*R*)-Et-Ferrotane	42.1	2.5:1.0
4	$Pd(OAc)_2$/(*S*)-Xyl-SDP	51.7	5.4:1.0
5	$Pd(OAc)_2$/(*S*)-Ph-SDP	93.3	3.8:1.0
6	$Pd(OAc)_2$/(*R*)-BINAP	92.3	2.0:1.0

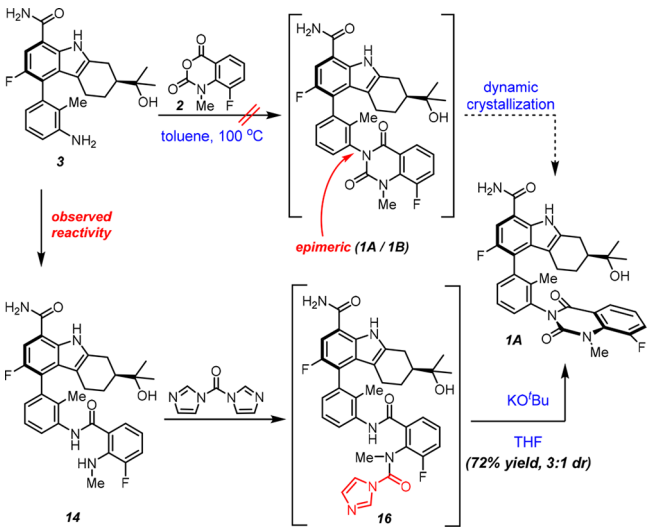
[a]Reaction conditions: **5** (10 μmol), **4** (1.1 equiv), Pd (5 mol %), ligand (5 mol %), K_3PO_4 (2.0 equiv), 5:1 THF/H_2O, 65 °C, 14 h.

The asymmetric Suzuki–Miyaura cross-coupling of **5** and commercially available arylboronic acid **4** was first evaluated by high-throughput screening against a library of chiral ligands (see Table 1). Both (*S*)-Xyl-SDP and (*S*)-Ph-SDP ligands (Table 1, entries 4 and 5) were found to provide the highest level of diastereoselectivity, with up to 5.4:1 dr and with good conversion.[20] However, the (*S*)-Xyl and (*S*)-Ph-SDP ligands are not widely available and extremely expensive on a manufacturing scale. Therefore, we optimized the reaction employing readily available (*R*)-BINAP (Table 1, entry 6), which provided excellent conversion to **3**, albeit with modest 2:1 diastereoselectivity in these initial experiments.

Both the reaction temperature and the solvent were found to affect the reaction diastereoselectivity. Lowering the reaction temperature to 5 °C and including a MeOH cosolvent to improve the arylboronic acid solubility increased the reaction diastereoselectivity to 16:1 dr, while maintaining the high reaction conversion. When combined with the *n*-BuOH crystallization, compound **3** was isolated in 87% isolated yield with a 65:1 dr about the carbazole-aryl C–C bond.

With the higher-barrier carbazol-aryl bond constructed, we evaluated the introduction of the lower-barrier aryl-quinazolinedione chiral axis by reaction of **3** with 7-F-isatoic anhydride **2** (see Scheme 2). However, treatment of aniline **3** with **2** did not deliver

Scheme 2. Proof of Concept Synthesis of 1A



the desired quinazolinedione, but rather noncyclized amide **14**, resulting from the expulsion of carbon dioxide. However, compound **14** was not a dead end, but rather a viable intermediate to complete the synthesis of **1A** and understand the reactivity and diastereoselectivity of the system at this late stage of the synthesis. To that end, treatment of **14** with CDI, in conjunction with 1 equiv of KO*t*-Bu, afforded **1A** through the intermediacy of the activated imidazole amide **16**. Upon further examination of the reaction, the desired diastereomer was found to be favored during the cyclization with 3:1 dr about the aryl–quinazolinedione bond.

Buoyed by achieving proof-of-concept on the total synthesis of **1A** and the favorable cyclization diastereoselectivity, we set off to streamline the synthetic sequence and improve upon the aryl–quinazolinedione diastereoselectivity. We envisioned that chirally pure aniline **3** could be coupled with an isatoic anhydride analogue of **2** containing the embedded functionality to enable closure to the quinazolinedione ring (see Table 2). 3-Fluoro anthranilic acid with a carbamate functional group mapped perfectly onto the quinazolinedione ring system; however, the role that the carbamate R-group would play in the cyclization was unclear. At the outset, a library of functionalized anthranilic acid carbamates were prepared to evaluate the cyclization step. A simple EDAC (1-ethyl-3-(3-(dimethylamino)propyl)-carbodiimide)-mediated coupling of aniline **3** with the anthranilic acid-carbamate derivatives (**17**–**22**) delivered advanced carbamates (**23**–**28**).[21] Treatment of each carbamate with KO*t*-Bu in THF showed surprising results.

Advanced carbamates containing aromatic R groups (**23** and **24**, entries 1 and 2 in Table 2) showed high conversion; however, poor diastereoselectivity was observed and in the case of phenylcarbamate **24**, the undesired diastereomer (**1B**) was favored (1:1.5 dr). Small straight-chain alkyl substitution delivered the highest cyclization diastereoselectivity with *n*-

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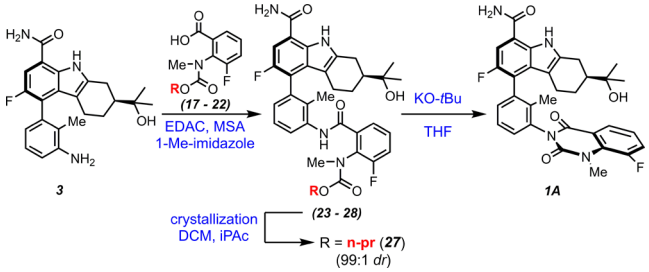
Table 2. Effect of the Leaving Group on the Diastereoselectivity of the C−N Forming Cyclization[a]



entry	carbamate R group	reaction dr
1	benzyl (**23**)	2.7:1.0
2	phenyl (**24**)	1.0:1.5
3	methyl (**25**)	3.8:1.0
4	ethyl (**26**)	5.0:1.0
5	*n*-propyl (**27**)	6.0:1.0
6	*i*-propyl (**28**)	4.7:1.0

[a]Reaction conditions: KO*t*-Bu (1.0 equiv), THF, 20 °C.

propylcarbamate **27** (entry 5 in Table 2) providing **1A** with 6:1 dr. The improved diastereoselectivity observed by changing the length of the carbamate R-group alkyl chain from methyl **25** to ethyl **26** to *n*-propyl **27** led us to target the *n*-propylcarbamate **27** as the penultimate intermediate in the total synthesis of **1A**. Importantly, upon the crystallization of *n*-propylcarbamate **27** from a dichloromethane and *iso*-propylacetate mixture, **27** could be isolated in 88% yield with an upgrade in the diastereomeric ratio about the carbazole-aryl bond to 99:1 dr.

Although KO*t*-Bu afforded product **1A** with 6:1 dr, further study of the cyclization revealed that bases with a lithium counterion provided diastereoselectivities on the order of 25:1 dr, when paired with dioxane or chloroform as a solvent (Figure 4). A

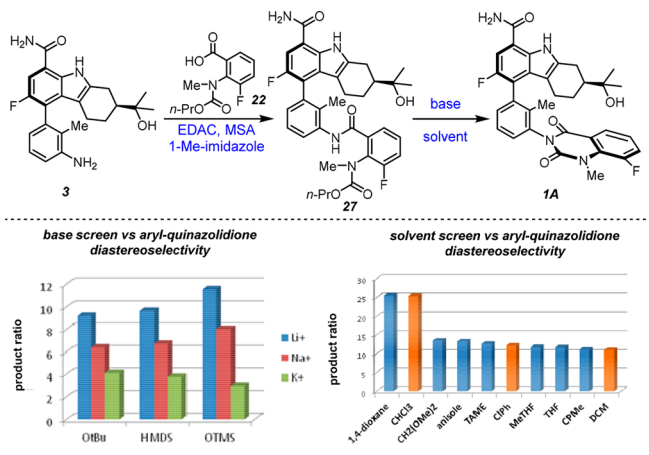


Figure 4. Impact of base and solvent on aryl−quinazolidione diastereoselectivity.

general trend of higher selectivity with counterions of Li > Na > K was evident across various bases, regardless of the anion. The diastereoselectivity values observed across lithium bases were almost identical, and, therefore, 1 M LiO*t*-Bu in THF was chosen because of its relative ease of handling, availability, and low cost.

Further studies to understand the impact of lithium on cyclization diastereoselectivity are currently underway and will be reported in due course. However, B3LYP calculations indicated a favorable transition-state interaction between the carbazole fluorine and the lithium counterion of the quinazolinedione tetrahedral intermediate **31**, before collapse, leading to the desired diastereomer **1A** (see Figure 5). Formation of the undesired diastereomer **1B** was predicted to proceed through transition state **30**, where the lithium alkoxide intermediate encounters steric repulsion with the carbazole and cannot engage in coordination to the fluorine, resulting in a higher energy reaction pathway.

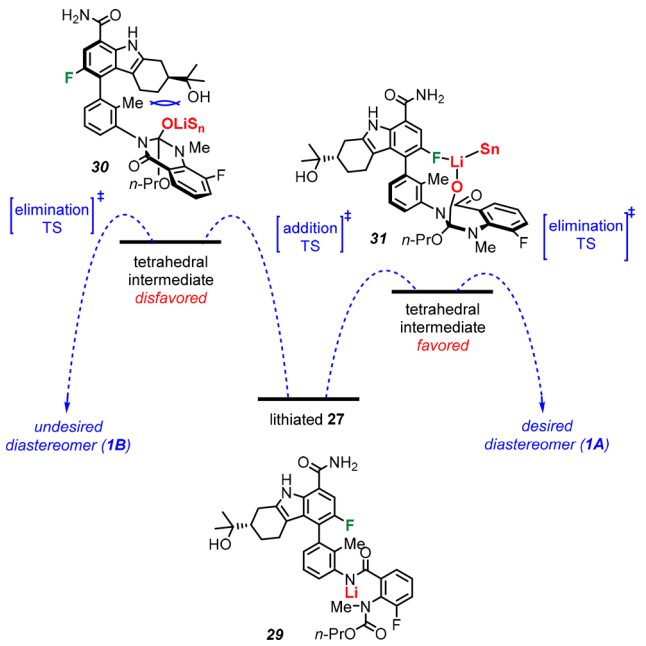


Figure 5. B3LYP modeling of the diastereoselective cyclization leading to compound **1A**.

Under the optimized conditions, compound **27** was slowly added to a mixture of 5 mol % of LiO*t*-Bu in dioxane at 25 °C to afford quantitative conversion to 96% of **1A** with only 4.0% of the undesired diastereomer **1B**. Upon crystallization from a mixture of MeTHF, MeOH, and acetone, compound **1A** was isolated in 90% yield with <0.5% of **1B**.

In summary, we have developed a strategy to synthesize an architecturally complex API with multiple chirality axes. The strategy relies upon establishing the stereochemical configuration of the highest energy barrier axially chiral diastereomer first, thereby reducing the risk of epimerization in downstream chemistry. Also, the higher barrier diastereomer acts as a chiral template to construct the stereochemical configuration of the lower barrier axially chiral bond. A concise enantioselective and diastereoselective synthesis of compound **1A** was achieved in eight longest linear steps, 28.3% overall yield, and led to the manufacture of >200 kg of **1A**. As more diverse and complex chemical space is explored in the pharmaceutical industry, our strategy can be useful to quickly and efficiently prioritize synthetic routes to bring medicines to patients.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01218.

Experimental procedures and characterization/NMR spectra for all intermediates and **1A** (PDF)

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Notes

The authors declare no competing financial interest.

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(8) Estimation of rotational barriers was carried out at the B3LYP/6-31+G(d,p) level of theory using a relaxed PES scan with geometry optimization at each point. The dihedral angle coordinate associated to a given bond rotation was incremented by a step size of 10° and a total of 36 steps. All calculations were executed using Gaussian 09, Revision B.01.

(9) The rate of C−N bond epimerization at 25 °C was found to be 0.0018%/h and independent of solvent.

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