Desymmetrization of Pibrentasvir for Efficient Prodrug Synthesis

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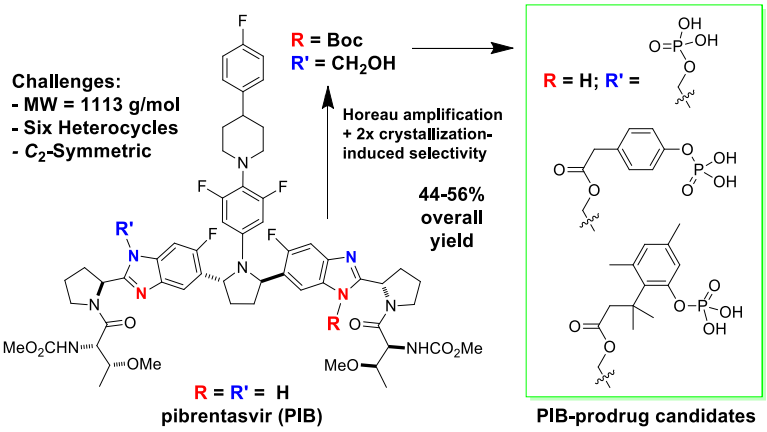
ABSTRACT: A novel and practical desymmetrization tactic is described to access a new class of pibrentasvir prodrugs. The homotopic benzimidazoles of pibrentasvir (PIB) are differentiated via a one-pot di-Boc/mono-de-Boc selective *N*-Boc protection and formaldehyde adduct formation sequence, both enabled by crystallization-induced selectivity. The first step represents the only known application of the Horeau principle of statistical amplification for C_2-symmetric polyheterocycle regioselective functionalization. The resulting versatile intermediate is employed in the high-yielding preparation of several pibrentasvir prodrug candidates.



INTRODUCTION

Mavyret® is a pan-genotype treatment for hepatitis C virus (HCV) containing glecaprevir, an NS3/4A protease inhibitor, and pibrentasvir (**1**, PIB), an NS5A inhibitor (Figure 1).[1] As the first pan-genotypic 8-week cure for people suffering from HCV, Mavyret® was approved by the U.S. Food and Drug Administration (FDA) in 2017 for the treatment of genotype 1-6 chronic HCV after a 98% 8-week cure rate was reported for treatment-naïve patients without cirrhosis or with compensated cirrhosis.[2] Enabling formulations were required for further improving bioavailability due to challenging physicochemical properties,[3] so a prodrug approach was pursued, resulting in the discovery of phosphates **2**, **3**, and **4**.[4]

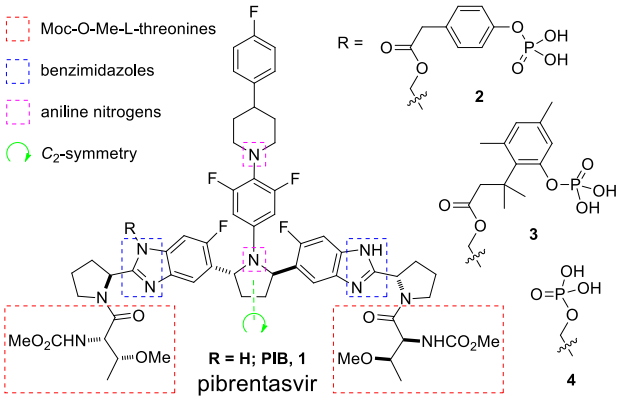


FIGURE 1. Pibrentasvir (**1**) structure, challenging features, and PIB prodrugs **2-4**

Pibrentasvir (**1**, PIB) is a large (MW 1113 g/mol) C_2-symmetric drug molecule which presents several uniquely challenging structural features when considering a solubility-enhancing prodrug approach (Figure 1). The end-cap amino acid fragments, methoxycarbonyl (Moc)-protected *O*-Me-L-threonines, are prone to epimerization, β-elimination, and facile Moc cleavage with nucleophiles and bases. For these reasons, preliminary attempts to attach cleavable prodrug moieties to the end-caps proved futile.[4] The four PIB benzimidazole nitrogen atoms initially appeared too similar in reactivity to be functionalized selectively, complicated by the two tertiary aniline nitrogens and the fact that PIB exists as a mixture of tautomers and rotamers in solution.[5] Finally, and most significantly when considering synthetic efficiency challenges, the C_2-symmetric nature of PIB renders each end homotopic. This feature facilitated efficient two-directional chain synthesis in the preparation of PIB[6] with stereochemical purity enhancement via the Horeau principle.[7] However, without a readily apparent internal functionalization or steric proximity effect to avoid bis(functionalization),[8] a statistical mixture of products was anticipated and observed in early syntheses of **2-4**.[4]

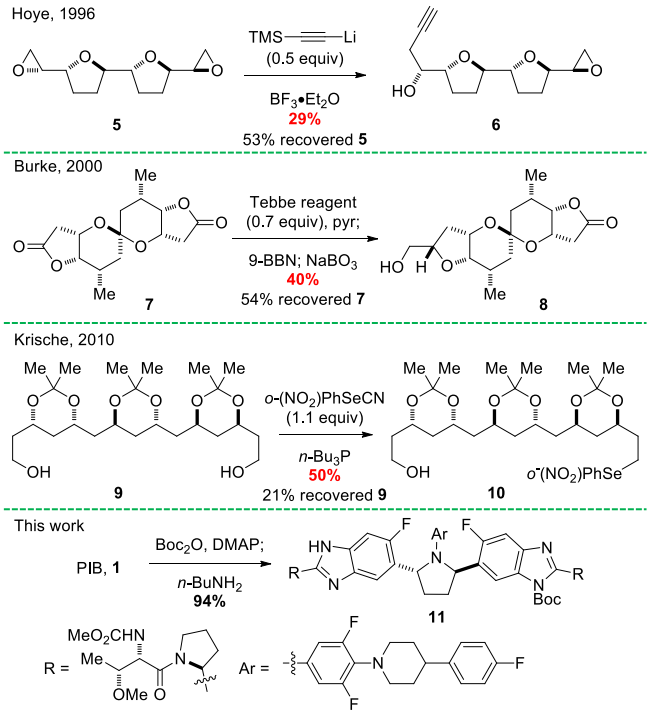


FIGURE 2. Examples of desymmetrization reactions of complex C_2-symmetric molecules in target-oriented syntheses

Since the seminal reviews by Schreiber[9] and Magnus[8] describing two-directional synthesis and terminus differentiation, this strategy has been used successfully in a number of additional complex molecule syntheses (Figure 2). For example, in Hoye's synthesis of the annonaceous acetogenin (+)-parviflorin, bis(epoxide) **5** was desymmetrized via reaction with a limited quantity of a lithium acetylide, giving alcohol **6** (29%) along with recovered **5** (53%).[10] Two syntheses from the Burke group utilized this approach, including a related annonaceous acetogenin, uvaricin (not shown), using a dihydroxylation,[11] and the C(37)-C(54) halichondrin B subunit, using an olefination/hydroboration/oxidation sequence to convert bis(lactone) **7** to desymmetrized primary alcohol **8** in 40% yield.[12] In a remarkably brief route to (+)-roxaticin that showcases this approach, the Krische group desymmetrized diol **9** via mono-selenide **10** formation in 50% yield.[13] In each example, a maximum yield of 50% was expected and observed due to the statistical mixtures of starting material/mono/di-functionalized products (1:2:1 ratio) obtained in homotopic termini differentiation, requiring starting material recovery and resubjection to improve material throughput. In contrast, this work describes a rare example of highly controlled mono-functionalization of a complex C_2-symmetric molecule via Horeau amplified di-Boc protection/crystallization-induced selective mono-Boc deprotection (de-Boc) with *n*-BuNH2, giving mono-*N*-Boc-PIB **11** in 94% yield from PIB. An overall yield of ~ 50% from PIB was a requirement for consideration of a pibrentasvir prodrug as a development candidate due to the high value of PIB, so this desymmetrization tactic was critical.

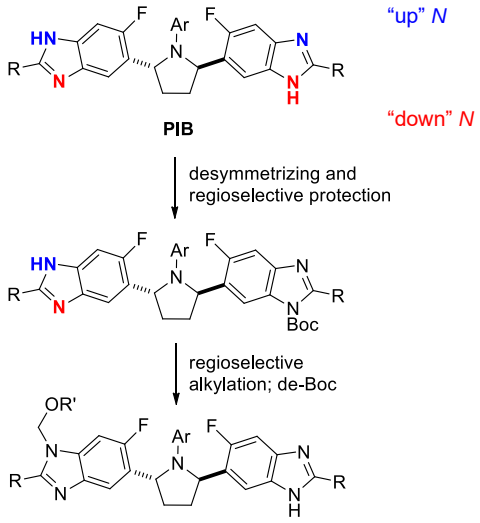
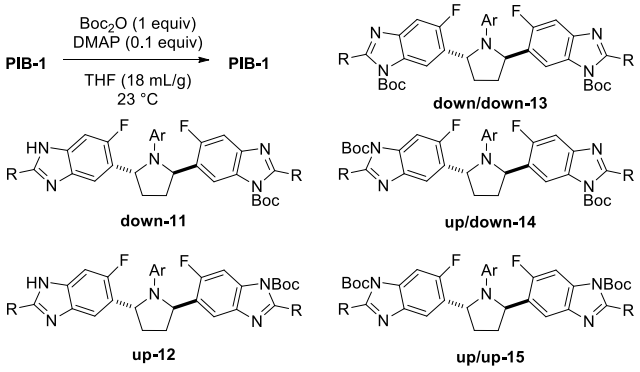


Figure 3. Benzimidazole nitrogen desymmetrizing and regioselective functionalization strategy

RESULTS AND DISCUSSION

Beyond homotopic terminus differentiation complexity, potential strategies to selectively functionalize PIB had to simultaneously address benzimidazole regioisomer selectivity (Figure 3). Since two equivalent PIB nitrogens are *para*-fluoro ("down" - red) and two are *meta*-fluoro ("up" - blue), some electronic bias was anticipated. However, early routes to PIB prodrugs demonstrated poor alkylation selectivities under a variety of conditions with challenging isomer separations further complicating the aforementioned statistical terminus differentiation issue.[4] Since no direct PIB alkylation appeared to provide any useful levels of selectivity or clear opportunities for efficient end differentiation, a selective and mild Boc protection strategy was envisioned to simplify the problem to a single benzimidazole regioselective alkylation. All reaction conditions would need to be mild enough to not degrade PIB and efficient enough to enable the 50% overall yield target. While considering the potential for biocatalytic or Miller peptide-based catalyst approaches for desymmetrization,[14] approaches using simple reagents which could benefit from inherent substrate bias and/or solubility properties were prioritized.

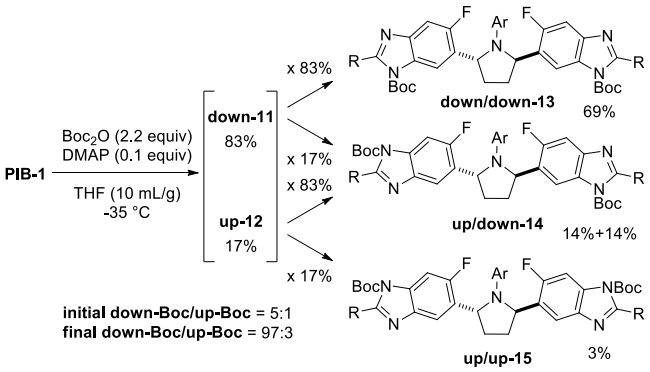


compound	1	11	12	13	14	15
peak area%	25.7	38.8	12.2	12.3	7.9	1.4

isolated: 48% yield, 3:1 **11**/**12**

Scheme 1. Initial attempt to mono-Boc protect PIB, **1**

Not surprisingly, initial attempts to mono-Boc protect PIB with 1 molar equivalent of di-*tert*-butyl dicarbonate (Boc_2O) gave a mixture of six compounds (Scheme 1), reflecting a 1:2:1 statistical ratio of starting material **1**, mono-Boc (**11** + **12**), and di-Boc (**13** + **14** + **15**) isomers with a 3:1 ratio of down-mono-Boc **11** (Boc *para* to fluoro) to up-mono-Boc **12** (Boc *meta* to fluoro). This ratio favoring **11** was presumably influenced by the more acidic nature of the nitrogens *para* to the fluorine. Following tedious chromatography, a 48% yield of mono-Boc isomers **11** and **12** was obtained. Slurrying the mixture in 3:1 MTBE/EtOAc gave a crystalline solid of **11** containing < 1% **12** (3:1 **12**/**11** in the filtrate), indicating a significant solubility difference between mono-Boc benzimidazole regiosiomers. This solubility difference would prove to be important in optimizing the formation of down-mono-Boc PIB **11**.



Scheme 2. Selective di-Boc to a mixture of **13**, **14**, and **15**

Reasoning that selective de-Boc of a mixture of di-Boc benzimidazoles **13**, **14**, and **15** may facilitate selective protection, and that both **13** and **14** could undergo Boc deprotection to give mono-down-Boc isomer **11** if relative rates of Boc cleavage were favorable, a complete reaction to a mixture of di-Boc compounds **13**, **14**, and **15** was carried out (Scheme 2). Following initial optimization of solvent and temperature to minimize **15**,[15] treatment of PIB with Boc_2O in THF at -35 °C in the presence of catalytic DMAP gave a 69:28:3 ratio of **13**, **14**, and **15**, respectively. Since (up,down)-di-Boc isomer **14** contains both an up-Boc and a down-Boc, this result represents an 83 (69 + 28/2):17 (28/2 + 3) total down/up-*N*-Boc ratio (5:1). When considering all species containing at least one down-Boc benzimidazole (**13** and **14**), this mixture constitutes a 97 (69 + 28):3 ratio (32:1), provided all undesired up-Boc can be selectively removed. While the first Boc protection benefits from the electronic bias imparted by the fluorine atom, the enhancement observed in the second Boc protection can be considered an example of the Horeau principle of statistical amplification.[7]

The Horeau principle is typically invoked in asymmetric synthesis to, for example, explain the upgrade in optical purity of a low-ee scalemic sample through coupling to a bifunctional linker to form a C_2/*meso* mixture which can be more easily separated at the expense of yield. A review on this topic recently appeared.[7] Figure 4 shows Horeau's

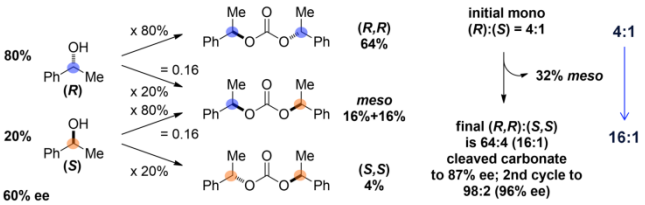
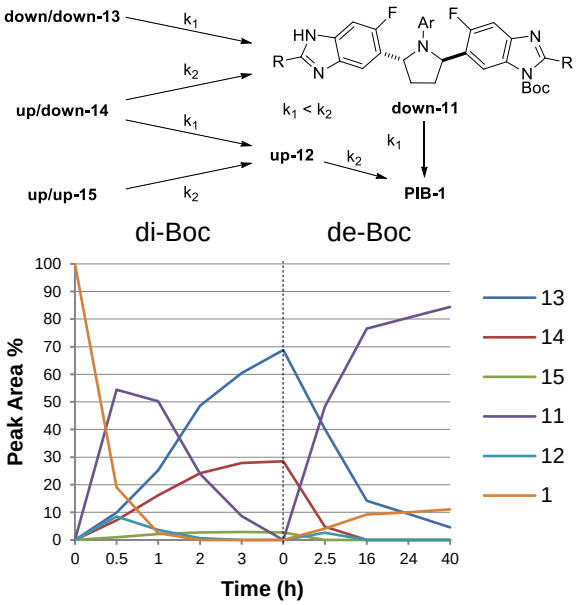


Figure 4. Original application of the Horeau principle of statistical amplification[16]

first application of this principle in upgrading the enantiomeric purity of a 60% ee secondary alcohol to 87% ee by forming a mixture of C_2/*meso* carbonates, removing the *meso* isomer, and cleaving the carbonate.[16] In this example, since 20% (*R*) isomer becomes *meso* and 80% (*S*) isomer becomes *meso* (statistically), 32% of the carbonate mixture is readily removed, leaving a 64:4 (16:1) ratio of (*R*)/(*S*) after carbonate cleavage (87% ee). A second cycle further enhances the mixture to 96% ee at the further expense of yield. In the present case, rather than the minor/major (or equivalent major/minor) reaction product **14** being an undesirable *meso* isomer, the resulting up/down di-Boc **14** still contains a desired down-Boc (Scheme 2). Therefore, down/up-*N* regioselectivity is enhanced from 5:1 to 32:1 via the Horeau principle of statistical amplification, with 97% of the total mixture containing at least one down-*N*-Boc. This constitutes the first known application of this principle for the regioselective functionalization of a C_2-symmetric poly-heterocycle.[17] However, while both **13** and **14** contain at least one down-Boc benzimidazole, their simultaneous selective conversion to down-mono-Boc **11** without further de-Boc to PIB remained a significant hurdle to accomplishing PIB desymmetrization.

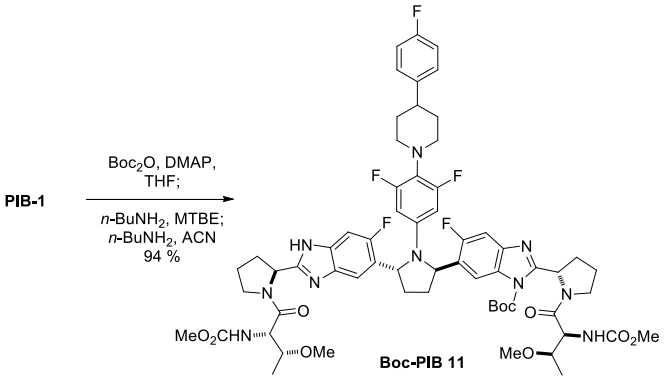


After 40 h: **13** (5 %), **11** (84 %), **1** (11 %); 75% isolated yield of **11**

Scheme 3. De-Boc of di-Boc mixture to give **11** selectively. De-Boc conditions: *n*-BuNH2 (1.5 equiv), MTBE (8 mL/g), 23 °C

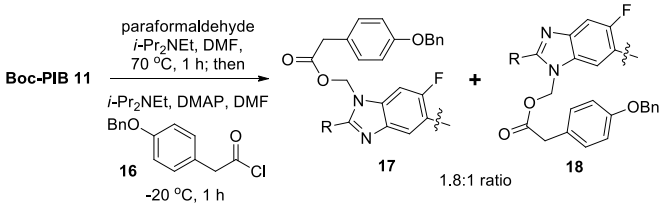
Since mono-Boc regioisomers **11** and **12** showed favorable solubility differences in MTBE (*vide supra*), and it was

anticipated that a primary aliphatic amine may deprotect the benzimidazoles at a slow enough rate that mono-Boc **11** could be protected from further de-Boc to PIB by crystallization,[18] the reaction solvent was switched from THF to MTBE and *n*-butylamine was added to the reaction mixture (Scheme 3). Much to our delight, under these conditions, up-Boc cleaved significantly faster than down-Boc, with **14** converting to **11** and **15** converting to **12** quite rapidly over the first 2.5 h while **13** converted more slowly to **11**. At this point, the solution was seeded with **11** (1 wt%), initiating a crystallization event. After 40 h at 23 °C, all mono-*N*-Boc and di-*N*-Boc isomers besides **13** and **11** were consumed, and a ratio of 5/84/11 for **13**/**11**/**1** was observed. Filtration gave a solid consisting of > 95% **11**.[19] Since product solubility in acetonitrile (ACN) was low, a re-slurry in ACN gave **11** with > 98% purity in 75% isolated yield.[19] Here, terminus differentiation of *C*2-symmetric di-Boc isomer **13**, the most significant component of the di-Boc mixture, was made possible through crystallization-induced protection of mono-Boc **11** against further de-Boc to PIB. Without crystallization of **11**, a statistical 1:2:1 ratio of di/mono/PIB would have been generated (Figure 2). Therefore, both Horeau amplification (di-Boc stage) and crystallization-induced protection (de-Boc stage) were required to deliver simultaneous regioselective benzimidazole functionalization and desymmetrization.



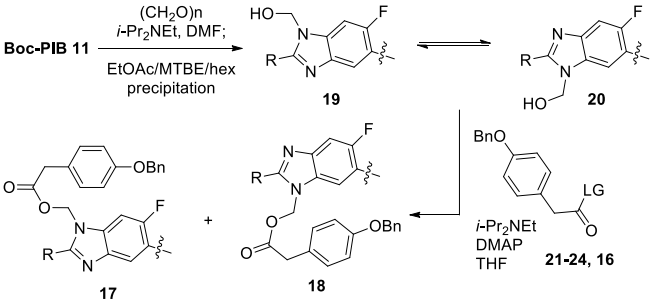
Scheme 4. One-pot di-Boc/mono-de-Boc with ACN solvent switch. Conditions: Boc_2O (1.9 equiv), DMAP (0.1 equiv), THF (5 mL/g), -40 °C, 3 h; *n*-$BuNH_2$ (0.8 equiv), MTBE (10 mL/g), 23 °C, 18 h; *n*-$BuNH_2$ (1 equiv), ACN (10 mL/g), 23 °C, 21 h; mother liquor resubjection

To further increase the yield of the desymmetrization reaction, the conditions in Scheme 4 were employed, taking advantage of the even lower solubility of Boc-PIB **11** in ACN compared to MTBE. Once di-Boc **14** was nearly consumed in MTBE where up/down Boc cleavage rate differences were optimal, a solvent switch to ACN was carried out to minimize crystallization losses and maximize protection of **11** from further de-Boc. Following product isolation in 84% yield, mother liquors were concentrated and resubjected to the reaction conditions to increase the yield to 94%. Overall, this di-Boc/mono-de-Boc PIB desymmetrization tactic provided a high isolated yield of a single down-mono-Boc product **11** out of the six species initially observed in attempted mono-Boc protection. While selective protection simplified the problem of PIB prodrug synthesis, regioselective functionalization of the remaining unprotected benzimidazole in **11** remained a formidable challenge (Figure 3).



Scheme 5. One-pot hydroxymethylation/acylation of **11**

Direct alkylation of Boc-PIB **11** with chloromethyl esters was feasible and used successfully for early syntheses of PIB prodrugs.[4] However, regioselectivities were poor and yields for the alkylation step variable after significant optimization efforts. Despite very limited precedent for regioselective benzimidazole formaldehyde adduct formation/acylation,[20] the reversible nature of such an adduct offered potential benefits that could prove advantageous. To probe this strategy, Boc-PIB **11** was treated with paraformaldehyde and *i*-Pr_2NEt in DMF for 1 h at 70 °C (Scheme 5), then cooled to -20 °C and acylated with acid chloride **16**.



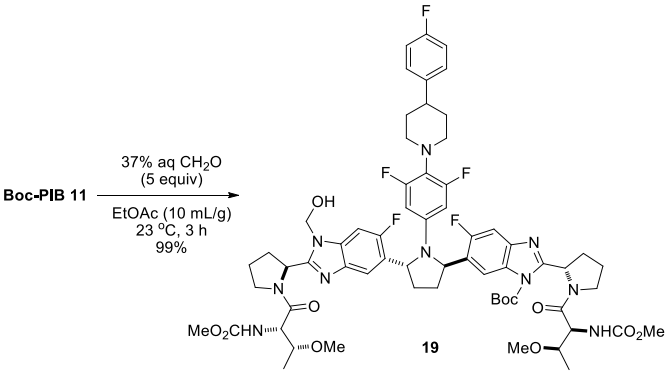
Reagent	Leaving Group (LG)	Temp (°C)	Time (h)	Conversion (%)	**17 : 18** ratio
21	OSu	23	18	20	1.8 : 1
22	4-NO_2PhO	23	2	35	1.7 : 1
23	OAt	0	1	35	4.5 : 1
24	C_6F_5O	-15	4	62	8 : 1
16	Cl	-15	1	95	20 : 1

Table 1. Acylation leaving group screen results

While good conversion to desired product was observed (85% overall yield), a disappointing 1.8:1 ratio of benzimidazole regioisomers **17** and **18** resulted, suggesting poor selectivity in the hydroxymethylation step and/or equilibration during the acylation. Undeterred by this preliminary result, Boc-PIB formaldehyde adduct **19**/**20** mixture was isolated by precipitation from EtOAc/MTBE/hexanes for investigation of acylation leaving group identity (Table 1).[21] Standard acylating conditions (*i*-Pr_2NEt, DMAP) were chosen as a basis for comparison between the acylating reagents, resulting in a wide range of reaction rates and product ratios. Reaction temperature was chosen for each acylating reagent to afford some conversion to product in order to measure the product isomer ratios. An increase in leaving group propensity resulted in greater conversion

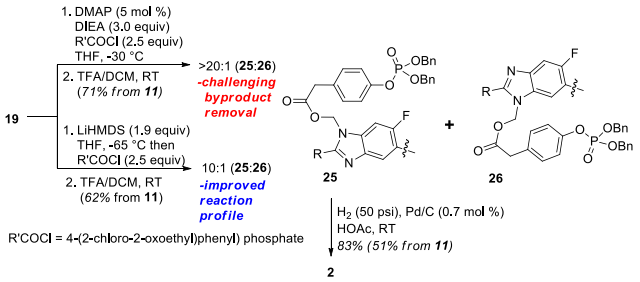
to the product isomer mixture as well as higher regioselectivity. With a relatively poor leaving group (OSu) in **21**, the reaction reached 20% conversion after 18 h at 23 °C, and a similar product ratio was observed as in the 1-pot reaction (1.8:1). Employing the original highly electrophilic acid chloride **16** vastly improved rate (95% conversion after 1 h at -15°C) and surprisingly improved the isomer ratio to 20:1 in favor of the desired product. Since conditions for the acylation were nearly identical to the one-pot reaction, the improved regioselectivity clearly resulted from isolation of the solid formaldehyde adduct. Therefore, the hydroxymethylation constituted a second consecutive crystallization-induced selective reaction.[21]

While the DMF/paraformaldehyde conditions provided adequate material for preliminary studies, a more convenient formaldehyde adduct formation was desired to avoid DMF distillation on larger scale (Scheme 6). Reaction of Boc-PIB **11** with 37% aqueous formaldehyde in EtOAc for 3 h in the absence of base was found to give a high mass balance of hydroxymethylation product (>10:1 **19**/**11** ratio by ^{1}H NMR in DMSO).[22] Efficient isolation was achieved by partial concentration and slow addition of heptanes with product seeding to facilitate crystallization. After filtration and drying, key intermediate **19** was isolated as a white solid in 99% yield.



Scheme 6. Preparation of key intermediate **19**

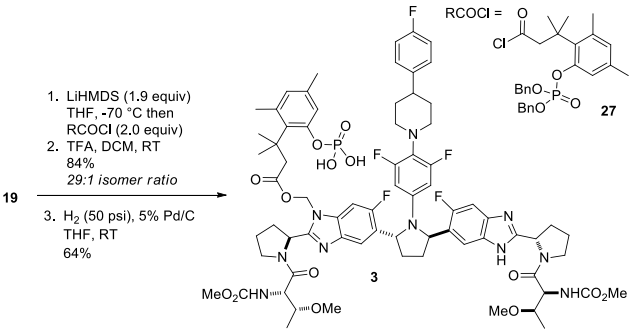
Having secured a robust and scalable procedure for the synthesis of compound **19**, we proceeded to investigate its use in the preparation of lead prodrugs of PIB.[4] The encouraging results observed in the model system (Table 1) provided a useful starting point for the acylation of **19** with more complex structures. We were pleased to find that treatment of a solution of **19** with dibenzyl (4-(2-chloro-2-oxoethyl)phenyl) phosphate (Scheme 7, R'COCl) in the presence of DMAP and *i*-Pr$_2$NEt in THF at -30 °C rapidly afforded a mixture of isomers with high conversion (> 90%) and selectivity (> 20:1 isomer ratio). Nevertheless, we encountered difficulties in the removal of byproducts from these initial reactions, which led us to investigate stronger bases under cryogenic conditions.[23] Fortunately, treatment of **19** with lithium hexamethyldisialazide (LiHMDS) and the acid chloride at -65 °C rapidly afforded the desired product with a significantly improved reaction profile, albeit with slightly reduced conversion and selectivity (85% conv., 10:1 isomer ratio). After Boc-deprotection of the crude material with TFA in CH_2Cl_2, the regioisomers were efficiently separated via flash silica gel chromatography, affording the penultimate dibenzylphosphate intermediate **25** in 62% yield over 3 steps from 11.



Scheme 7. Preparation of Prodrug **2**

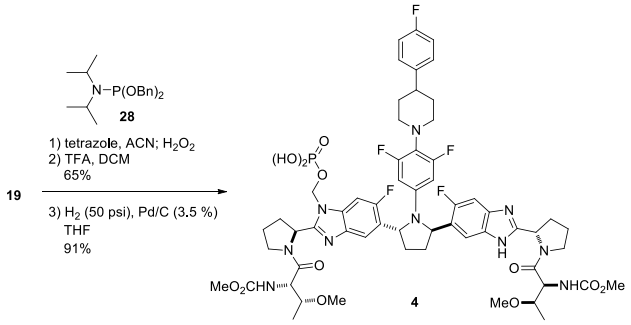
The final hydrogenolysis step revealed some inherent solubility and isolation challenges with the phosphate prodrug **2**. Initial reactions in THF or mixtures of THF and protic solvents (e.g. HOAc, MeOH, H2O) resulted in incomplete conversion and aggregation of the product with the catalyst; however, reactions in neat HOAc as solvent with 0.7 mol% Pd/C and 50 psi H_2 were complete in < 2 h. After removal of the catalyst bed and concentration in vacuo, a final slurry of the crude material in IPA (10 mL/g) afforded compound **2** in 83% yield (Scheme 7, 51% from Boc-PIB **11**).[24]

Preliminary observations made during the synthesis of compound **2** informed the subsequent preparation of prodrug **3** (Scheme 8). Cryogenic treatment of **19** with LiHMDS in THF was followed by rapid addition of a preformed solution of the acid chloride **27** in THF to give nearly quantitative acylation in < 5 min.[24] Boc-deprotection of the crude material gave a mixture of products with a 29:1 regioisomer ratio. The major isomer was then efficiently separated using silica gel chromatography to give the penultimate dibenzylphosphate in 84% yield from **11**. Optimization studies of the final phosphate deprotection to generate compound **2** indicated that THF instead of HOAc was the preferred solvent in this case, giving complete debenzylation in 20 h at ambient temperature with 5% Pd/C and 50 psi H_2. Crude material was purified via hot IPA crystallization and a final slurry in acetone to give **3** in 64% isolated yield.[24]



Scheme 8. Preparation of Prodrug **3**

To prepare phosphonoxymethyl prodrug **4** from key intermediate **19**, a new strategy was required that would rapidly and selectively forge a P-O bond (Scheme 9). After several failed attempts to directly form this bond at the phosphate oxidation state, an efficient phosphite formation was realized by employing dibenzylphosphoramidite reagent **28** with tetrazole as base.[25] Following addition of hydrogen peroxide and de-Boc of the resulting crude phosphate, dibenzylphosphonoxymethyl product **29** was obtained in good yield (65%). Finally, benzyl hydrogenolysis proceeded without incident, giving PIB prodrug **4**.



Scheme 9. Preparation of Prodrug **4**

CONCLUSION

The initial synthetic routes to prodrugs **2** - **4** employed unselective direct alkylations of PIB **1** or Boc-PIB **11** with the requisite chloromethyl esters, where tedious separation of mixtures resulted in low overall yields.[4] Ultimately, the development of a scalable route to key intermediate **19** facilitated regioselective preparation of these lead prodrugs from PIB **1** and suitably positioned them for consideration as clinical candidates. The identification of high-yielding functionalization reactions of **19** and subsequent phosphate deprotection completed the syntheses of prodrugs **2** – **4**, improving overall yields from 6-11% to 44-56% from PIB **1**. The desymmetrization tactic employed here to differentiate the homotopic termini of PIB **1** also highlights the importance of considering classical and perhaps under-utilized strategies such as statistical amplification and exploitation of solubility differences for selectivity in even the most complex chemical settings.

ASSOCIATED CONTENT

Supporting Information. Experimental details and characterization data for all new compounds. This material is available free of charge via the internet at http://pubs.acs.org

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ACKNOWLEDGMENT

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ABBREVIATIONS

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1) See www.mavyret.com
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