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Development of a Flexible and Robust Synthesis of Tetrahydrofuro[3,4-*b*]furan Nucleoside Analogues

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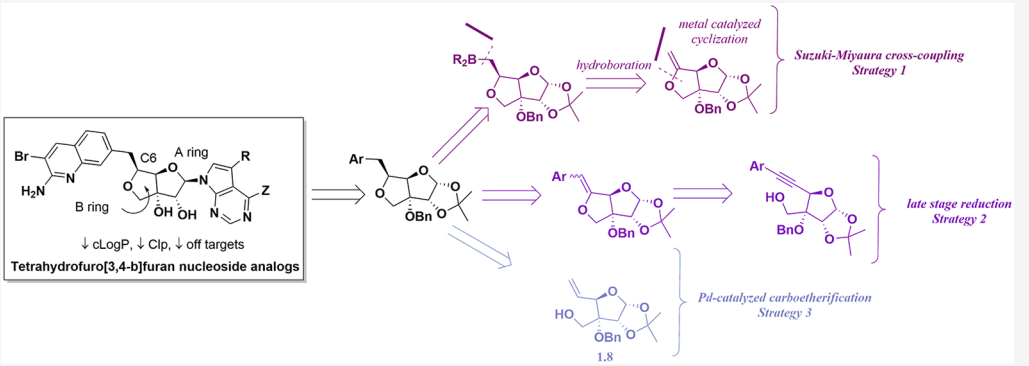

ABSTRACT: In the context of a PRMT5 inhibitor program, we describe our efforts to develop a flexible and robust strategy to access tetrahydrofuro[3,4-*b*]furan nucleoside analogues. Ultimately, it was found that a Wolfe type carboetherification from an alkenol derived from D-glucofuranose diacetonide was capable of furnishing the B-ring and installing the desired heteroaryl group in a single step. Using this approach, key intermediate **1.3-A** was delivered on a gram scale in a 62% yield and 9.1:1 dr in favor of the desired *S*-isomer. After deprotection of **1.3-A**, a late-stage glycosylation was performed under Mitsunobu conditions to install the pyrrolopyrimidine base. This provided serviceable yields of nucleoside analogues in the range of 31−48% yield. Compound **1.1-C** was profiled in biochemical and cellular assays and was demonstrated to be a potent and cellularly active PRMT5 inhibitor, with a PRMT5-MEP50 biochemical IC_{50} of 0.8 nM, a MCF-7 target engagement EC_{50} of 3 nM, and a Z138 cell proliferation EC_{50} of 15 nM. This work sets the stage for the development of new inhibitors of PRMT5 and novel nucleoside chemical matter for alternate drug discovery programs.

INTRODUCTION

Protein-a**R**ginine-**M**ethy**T**ransferase-5 (PRMT5) is a type-II methyl transferase that catalyzes the transfer of a methyl group from the cofactor *S*-adenosyl methionine (SAM) to the guanidino groups of arginine residues on histone and nonhistone proteins. Methylation is an important posttranslational modification in cell signaling and regulation. PRMT5 is known to be implicated in a number of diverse cellular functions, and it has emerged as a promising therapeutic target for the treatment of cancer.[1a,b]

As part of a lead optimization effort to develop high-quality PRMT5 inhibitors, we were initially inspired by the natural cofactor SAM and used this scaffold as a starting point to develop a series of SAM-competitive inhibitors (Figure 1, PDB ID: 7L1G). By joining the 5′- and 3′-carbons of SAM in a ring, a series of 5,5-bicyclic analogues were developed. Conformationally restricted nucleoside analogues can potentially improve binding by locking groups into a bioactive conformation and reduce metabolism by blocking hotspots or altering binding to CYP enzymes.[1c,d] As part of a systematic effort to explore the SAR of 5,5-bicyclic nucleoside analogues, a tetrahydrofuro[3,4-*b*]furan target was envisioned. It was hypothesized that the additional oxygen atom in the core would lower the LogP, which could lead to reduced metabolism, a cleaner off target profile, and potentially improved solubility.[2] There is a wealth of literature around the synthesis of conformationally constrained bicyclic nucleoside analogues. As is often the case, there were no-known examples with the substitution pattern we required.[1c,d]

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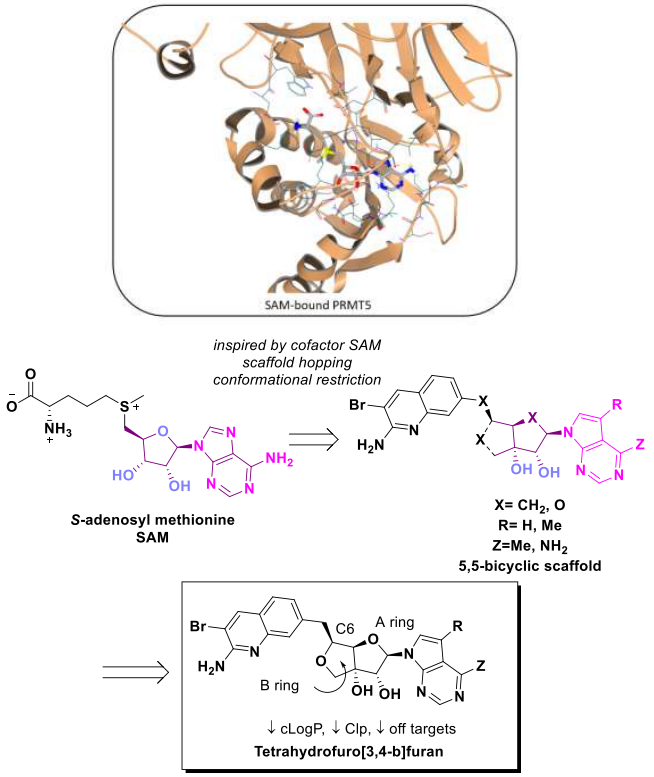

Figure 1. Inspiration and the design of tetrahydrofuro[3,4-*b*]furan PRMT5 Inhibitors.

Furthermore, our objective was to develop a synthetic approach capable of allowing for diversification, which required a different chemistry strategy than targeting a single compound. Herein, we describe our efforts toward enabling the synthesis of tetrahydrofuro[3,4-*b*]furan nucleoside analogues in the context of a PRMT5 inhibitor program.

RESULTS AND DISCUSSION

From previous studies, it was known that the 3-bromoquinolin-2-amine fragment was a privileged motif that made several key contacts with the protein,[2] so we needed to ensure that the chemistry we employed would be capable of installing that fragment. Another key consideration was the stereochemistry at C6. Both C6-stereoisomers of our target were docked into the receptor of PRMT5, the resulting poses were refined using MM-GBSA, allowing a flexible minimization for the ligand and the receptor sidechains within 5 Å of the ligand (Figure 2, see the Supporting Information for detailed methods). This resulted in a MMGBSA ΔG binding score difference of 9.02 kcal/mol favoring the S-configuration over the R-configuration at C6. Furthermore, we were interested in the conformational strain of the ligand in the bioactive conformation. Using a QM-based procedure (Supporting Information), the S-configuration was favored by 1 kcal/mol over the R-configuration. The energy values should not be taken as absolute; rather, they suggest a preference for the (*S*)-isomer. Given this stereochemical preference, our synthetic strategy would ideally deliver the desired isomer selectively.

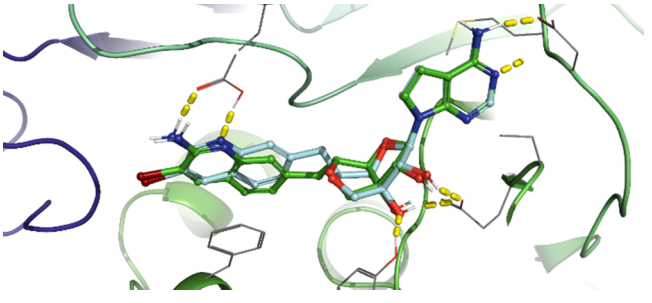

Figure 2. Docking and prediction of stereochemistry at C6.

Retrosynthetically, we envisioned a late-stage glycosylation of triol **1.2** (Scheme 1), which would allow us to readily explore SAR around the nucleobase. The problem was now reduced to finding a flexible synthesis of intermediate **1.3**. We explored three main strategies toward the synthesis of this key intermediate. Strategy 1 employed a palladium-catalyzed Suzuki−Miyaura cross-coupling to install the aryl group in a modular fashion. Borylations of exocyclic enol ethers are scarce in literature;[3] however, combined with some of the existing precedent and previous experience with a similar system, we felt that this was a viable approach.[2] Furthermore, we surmised that the electronics of the enol ether and the concavity of the molecule would provide the desired organoborane intermediate with the desired stereochemistry at C6. Strategy 2 was viewed as a complementary approach, whereby the aryl ring would be introduced earlier in the sequence by a Sonogashira reaction. Here, the key would be finding a reduction, which was highly selective and left the aryl bromide untouched, a challenging proposition. Finally, strategy 3 was envisioned whereby a palladium-catalyzed carboetherification would be employed to forge both the tetrahydrofuran ring and aryl-carbon bond in a single operation.[4] Strategy 3 was clearly the most attractive route on paper; however, given the short timelines in the drug discovery space, multiple strategies were pursued in parallel.

The synthesis of key intermediate **1.5** began from readily available glucofuranose derivative **1.9** (Scheme 2). Dess−Martin oxidation followed by vinyl Grignard addition stereoselectively produced **1.11**. The protection of the tertiary alcohol to provide **1.12** was necessary for the success of subsequent chemistry. A benzyl-protecting group was chosen due to its common use in sugar chemistry and for its stability, which would allow for flexibility in the choice of conditions downstream. One of the acetonides was selectively cleaved with dilute sulfuric acid to provide **1.13**. A sequence of diol oxidative cleavage, alkynylation, ozonolysis, and reduction was effective in producing intermediate **1.16** on a multigram scale. The ozonolysis is noteworthy, as the olefin in **1.13** was uniquely hindered and failed to undergo dihydroxylation. With this key intermediate in hand, we could explore strategies to introduce the aryl ring and forge the second B-ring.

The cyclization of alkynols has been accomplished via a number of methods, including metal-catalyzed cyclization, halogenation, and Brønsted acid or base-catalyzed cyclization.[5] A limited exploration of gold and silver salts revealed that the silver-mediated cyclization performed well to provide the desired product **1.5** in 80% isolated yield.[5a,b] It was found that the quality of the silver carbonate is important for this transformation as variability was observed with different batches of reagent. It is also noteworthy that the enol ether **1.5** was found to be a stable colorless solid, which could be handled under ambient conditions and stored for an appreciable time at −20 °C. The key Suzuki−Miyaura reactions failed to provide the desired product **1.17**; rather,

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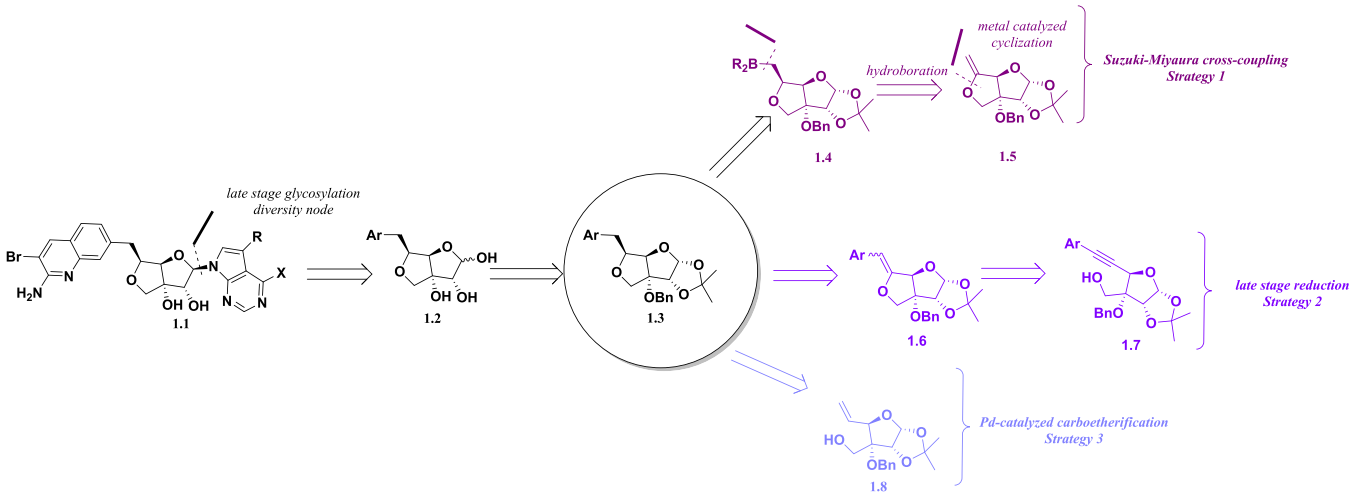
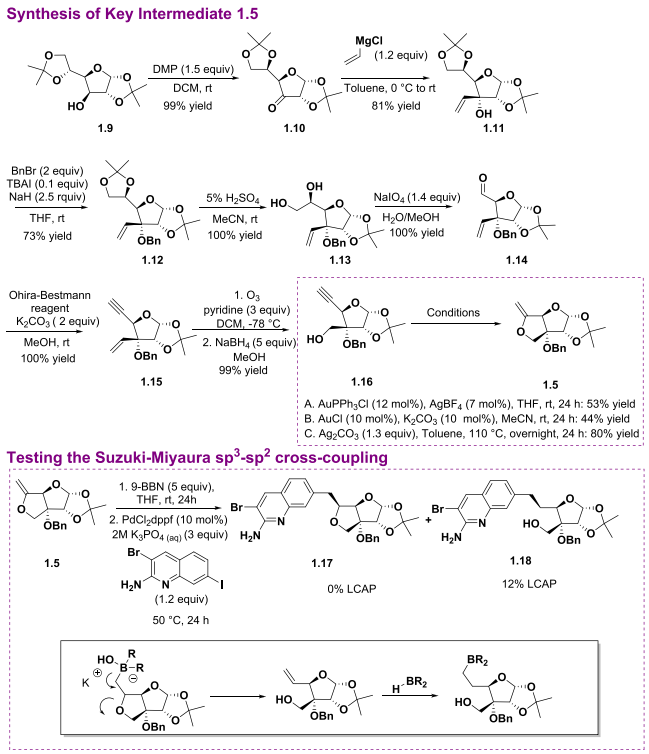
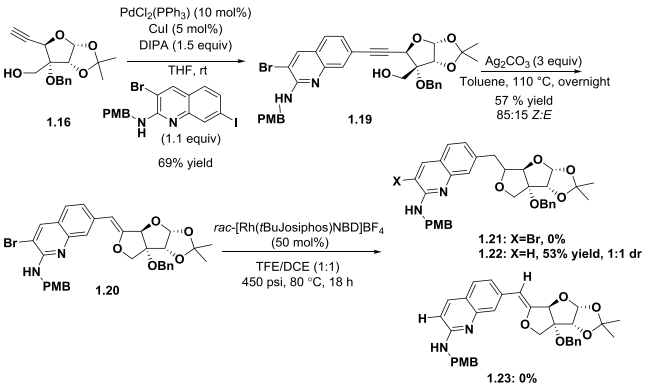
Scheme 1. Retrosynthesis



Scheme 2. Evaluation of Strategy 1



Scheme 3. Evaluation of Strategy 2



the ring-opened product **1.18** was formed in 12% LCAP (LC-area percent).[6] The formation of this byproduct is likely due to ring opening of the boronate species competing with transmetalation to the aryl palladium(II) species and is shown in Scheme 2.[6] Additional catalysts were screened, and the equivalents of 9-BBN were adjusted, but the desired product was not observed in all cases. While it is conceivable that with careful and thorough optimization, conditions could be found to affect a rapid transmetalation onto palladium and avoid ring opening; we felt that pursuing alternate strategies would be more fruitful.

We turned our attention to strategy 2 (Scheme 3). Sonogashira reaction with **1.16** under standard conditions provided a good yield of **1.19**, which could be cyclized under the same silver-mediated conditions used previously to afford **1.20** as an 85:15 mixture of *Z*:*E* isomers. We then went on to explore the reduction of the exocyclic enol ether. This was a very challenging feat as we required a selective reduction that would reduce a hindered electron-rich olefin in the presence of a heterocyclic aryl bromide. Several conditions were surveyed such as Pd/C, Rh/alumina, PtO_4, Crabtree's catalyst, Wilkinson's catalyst, diimide reduction, cobalt-mediated hydrogen atom transfer,[7b] and polar reduction with TFA/$HSiEt_3$.[7] However, most of the methods returned the starting material or afforded dehalogenated product **1.23** without reduction of the double bond. We then investigated a rhodium Josiphos catalyst system under higher pressures, which was able to cleanly afford product **1.22** in 95% LCAP in screening experiments. Scale up of the hit resulted in a 53% isolated yield of **1.22** as a 1:1 mixture of isomers at C6. Given the reluctance of the olefin to reduce under a number of alternate conditions, the reactivity of this catalyst system is truly remarkable. While this method could be useful in cases where both isomers at C6 are of interest and for compounds lacking a bromide substituent, it failed to meet our requirements, so we went on to explore an alternate strategy.

Finally, strategy 3 was inspired by the work of J. P Wolfe and co-workers who had done extensive work to develop intramolecular palladium-catalyzed carboetherification and carboaminations, whereby a carbon−carbon bond and carbo−heteroatom bond are formed in the same operation.[4] The mechanism is believed to proceed via coordination of the pendant alkoxide to the aryl palladium(II) intermediate,

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followed by a *syn*-insertion and reductive elimination (Figure 3).[4]

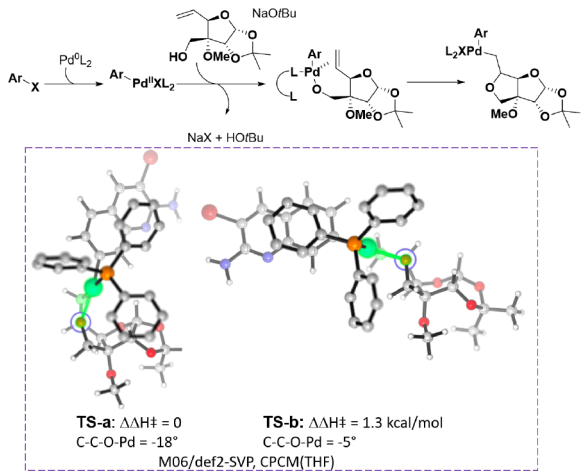


Figure 3. DFT transition structures for diastereoselective ring closure.

To get a sense for the diastereoselectivity, we computed the migratory insertion transition states (TSs) leading to the major (**TS-a**) and the minor (**TS-b**) diastereomer, using PPh_3 to model the monodentate coordination of dpe-phos and a methoxy group to model the benzyloxy group on the substrate. The energy difference between **TS-a** and **TS-b** of 1.3 kcal/mol predicted a diastereoselectivity of 7:1. The minor TS is slightly higher in energy due to more-eclipsing interactions associated with the alkene C−C bond and O−Pd bond involved in migratory insertion, as indicated by the torsional angles between these two partial bonds (−18° in the major TS vs −5° in the minor TS). The relatively small energy difference does not allow for a prediction to be made with confidence; however, encouraged by the models, we went forward to test out this strategy.

The key alkenyl alcohol **1.8** was made by altering the strategy shown in scheme 2 and diverting intermediate **1.12**. Beginning from intermediate **1.12**, a sequence of ozonolysis, reduction, acetonide deprotection, and diol cleavage cleanly provided **1.26** as a mixture of cyclic acetals. Finally, olefination with methyltriphenylphosphonium bromide generated **1.8** in excellent overall yield (Scheme 4).

Gratifyingly, under standard conditions reported by the Wolfe group,[4f] reaction of **1.8** with 3-bromo-7-iodo-*N*-(4-methoxybenzyl)quinolin-2-amine delivered the desired product **1.3-A** in 64% yield and 9.1:1 dr in favor of the desired isomer, in good agreement with the predicted diastereoselectivity. The efficiency and functional group tolerance of this reaction were truly remarkable. We explored additional couplings with model substrates to inform on whether aryl bromides would also be suitable coupling partners and demonstrate that other aryl halides could be employed (Table 1). In general, aryl iodides and bromides can be used, and the selectivity is good, in line with studies from the Wolfe group.[4] Importantly, this reaction could be performed on a gram scale to provide ample amounts of intermediate **1.3-A** for further chemistry exploration and analogue synthesis.

Having found an efficient strategy to forge the B-ring and install our requisite aryl group, we proceeded to explore the end game of the synthesis (Scheme 5). Deprotection of **1.3-A** was accomplished under the action of boron trichloride. The

Scheme 4. Evaluation of Strategy 3

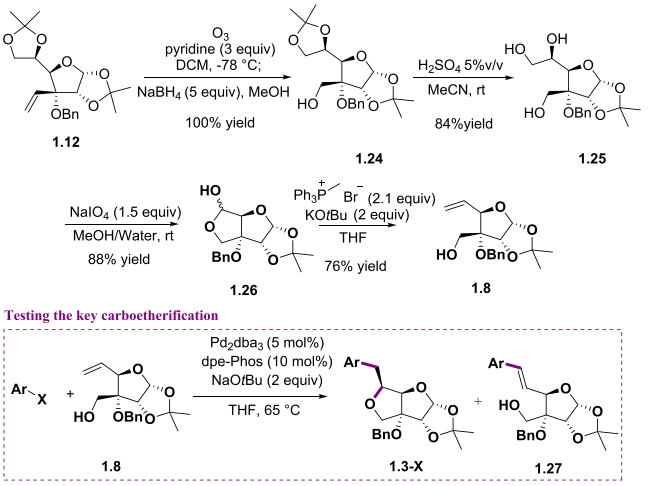
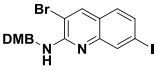
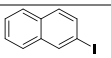
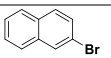
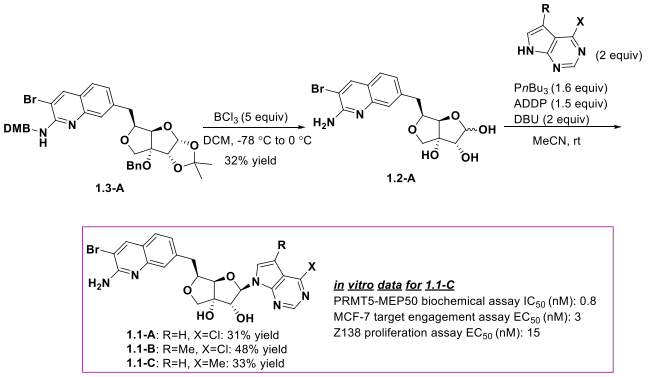


Table 1. Carboetherification of 1.8

Entry	ArX	Product label	1.3 Yield (%)[a]	1.27 Yield (%)[a]	dr[b]
1		A	62	-	9.1:1
2		B	52	4	-[c]
3		B	69	-	10.8:1
4		C	81	-	-[c]
5		C	69	-	-[c]

[a]Isolated yield of the major isomer, stereochemistry as drawn. [b]Determined by ^{1}H NMR. [c]Single isomer or alternate isomer not detected.

Scheme 5. End-Game Glycosylation



DMB-group on the aniline was reluctant to cleave and required warming to 0 °C. Despite a clean reaction profile, the recovery of the triol was only 32% yield likely due to its high polarity and aqueous solubility. Despite the lower yield, this chemistry could readily be scaled and provided enough material to go

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forward. With intermediate **1.2-A** in hand, we could begin to study the late-stage glycosylation. In general, the glycosylation of nucleosides remains a challenge in the field. Often harsh conditions are necessary, and yields can be low and substrate specific.[1b,8] We explored a number of different methods on related scaffolds, including the more traditional Vorbrüggen glycosylation. In many cases, low yields and multiple byproducts were observed. It was found that Mitsunobu conditions adapted from the work of Hocek, Mahrwald, and co-workers proved to be the most general and efficient approach for installing the base on these scaffolds.[9] It is thought that activation of the anomeric alcohol leads to displacement by the 2′-hydroxyl group of the ribose, yielding an epoxide intermediate; the backside attack guarantees the stereochemistry at the anomeric carbon. In general, moderate-to-low yields of the final nucleosides were obtained. It appeared that blocking the 3-position can provide a boost in yield likely because it discourages reaction at the 3-position of the pyrrolopyrimidine.

Despite the lower yields of the glycosylation, enough material could be made for biological testing. For example, compound **1.1-C** was submitted to our PRMT5-MEP50 biochemical assay, which is a direct measurement of the methylation activity of the enzyme complex on a short peptide substrate derived from the N-terminus of H4 histone. The biochemical IC_{50} was determined to be 0.8 nM, whereas the C6-diastereomer was 4-fold less potent, consistent with modeling predictions. Compound **1.1-C** also showed potent cellular activity in our cellular target engagement assay and our Z138 cell proliferation assays (see the Supporting Information) where it was found to have 3 and 15 nM potency values, respectively. Given the potency of these compounds and their mechanism of action, extreme care was taken when handling compounds such as **1.1-A−C** to limit exposure.

CONCLUSIONS

In conclusion, in the context of a program to identify PRMT5 inhibitors, our search led us to develop a flexible and robust synthetic strategy to access tetrahydrofuro[3,4-*b*]furan nucleoside analogues bearing aryl moieties at the 5′-position. The key to the success of this approach was the implementation of a Wolfe carboetherification reaction and a late stage glycosylation under Mitsunobu conditions. It is conceivable that, through modification of the intermediates or chemistry outlined herein, others can achieve novel scaffolds with substituents and properties tailored to their unique purpose.

EXPERIMENTAL SECTION

All reagents and solvents were purchased from commercial sources and used without further purification. Reactions were monitored by LCMS or thin-layer chromatography (TLC) on silica gel and visualized with UV light (254 nm). Flash chromatography was performed using prepacked RediSep R_f silica gel columns on a Teledyne Isco CombiFlash R_f automated chromatography system; column volumes are abbreviated as CV. All chemical shifts (δ) are reported in parts per million (ppm) and referenced to residual protium or the carbon resonance of the NMR solvent, respectively. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet), coupling constants (J) in Hertz (Hz), integration. HRMS data was collected on a Waters Acquity I Class UPLC with Xevo G2 XS Q Tof HRMS. The following compounds have previously been reported: **1.9−1.14**[10] and **1.24**.[11]

(3*aR*,5*R*,6*aS*)-5-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyldihydrofuro[2,3-*d*][1,3]dioxol-6(5*H*)-one (1.10). DMP (61.6 g, 145 mmol, 1.5 equiv) was added in portions to a solution of diacetone-D-glucose (25 g, 97 mmol, 1.0 equiv) in DCM (300 mL) at 0 °C. The reaction was then warmed to room temperature and stirred overnight. The reaction was then cooled to 0 °C, and a saturated solution of sodium bicarbonate was added (100 mL) followed by a saturated solution of sodium sulfite (100 mL). The reaction was stirred for 30 min at room temperature, and the layers were separated. The aqueous layers were extracted with DCM (1 × 200 mL); the combined organic layers were then dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford **1.10** (24.7 g, 99% yield) as a yellow oil. This material was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.09 (d, J = 4.2 Hz, 1H), 4.57−4.51 (m, 2H), 4.32−4.25 (m, 1H), 4.01−3.93 (m, 1H), 3.89−3.82 (m, 1H), 1.35 (s, 6H), 1.25 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 209.8, 113.0, 109.2, 102.5, 78.5, 76.6, 75.7, 63.9, 27.2, 27.0, 25.9, 25.0. HRMS (ESI) m/z: does not ionize as parent.$[\alpha]_D^{15}$ + 23° (c = 0.1, MeOH).

(3*aR*,5*R*,6*R*,6*aR*)-5-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-vinyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol (1.11). A 500 mL three-necked flask with a stir bar, temperature probe, dropping funnel, and septum was heated with a heat gun under vacuum; the glassware was cooled to room temperature and charged with **1.10** (20 g, 77 mmol, 1.0 equiv) and toluene (309 mL). The solution was cooled to 0 °C, and vinylmagnesium chloride (58 mL, 1.6 M in THF, 93 mmol, 1.2 equiv) was added dropwise at such a rate that the temperature did not exceed 5 °C. After the addition was complete, the reaction was warmed to room temperature and stirred for 3 h. The mixture was quenched with saturated aqueous ammonium chloride (250 mL) and then diluted with EtOAc (500 mL). The layers were separated, and the organic layer was washed with brine (2 × 250 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford **1.11** as a colorless solid (18 g, 81% yield). This material was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.86−5.77 (m, 1H), 5.70 (dd, J = 17.1, 11.0 Hz, 1H), 5.38 (d, J = 17.2 Hz, 1H), 5.28−5.24 (m, 1H), 5.21 (d, J = 10.8 Hz, 1H), 4.22−4.09 (m, 1H), 4.08−4.02 (m, 1H), 4.03−3.94 (m, 1H), 3.82−3.63 (m, 2H), 1.49 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H), 1.22 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 136.7, 115.4, 111.5, 107.4, 103.3, 82.7, 81.0, 79.3, 73.5, 64.2, 26.6, 26.3, 26.2, 25.0. HRMS (ESI) m/z: [M + Na] + calcd for $C_{14}H_{22}NaO_6$ 309.1314, found 309.1328. $[\alpha]_D^{20}$ + 101° (c = 0.126, MeOH).

(3*aR*,5*R*,6*R*,6*aR*)-6-(Benzyloxy)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-vinyltetrahydrofuro[2,3-*d*][1,3]-dioxole (1.12). A solution of **1.11** (18.0 g, 62.8 mmol, 1.0 equiv) in THF (165 mL) was cooled to 0 °C, and sodium hydride (6.28 g, 157 mmol, 2.5 equiv) was added in portions. The reaction was stirred for 30 min at 0 °C and then for 30 min at room temperature. Then, TBAI (2.32 g, 6.28 mmol, 0.1 equiv) was added followed by benzyl bromide (14.9 mL, 125 mmol, 2 equiv), and the reaction was stirred at room temperature overnight. The mixture was cooled to 0 °C and quenched with a saturated ammonium chloride solution (200 mL). The mixture was diluted with EtOAc (200 mL), and the layers were separated. The combined organic layers were washed with brine (2 × 200 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0−100% EtOAc/hexanes) to afford **1.12** as a colorless solid (17.2 g, 73% yield) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, J = 7.5 Hz, 2H), 7.37−7.32 (m, 2H), 7.31−7.26 (m, 1H), 5.89 (dd, J = 18.0, 11.4 Hz, 1H), 5.85 (d, J = 3.6 Hz, 1H), 5.49 (d, J = 11.4 Hz, 1H), 5.32 (d, J = 18.0 Hz, 1H), 4.71 (d, J = 11.4 Hz, 1H), 4.65 (d, J = 3.6 Hz, 1H), 4.63 (d, J = 11.4 Hz, 1H), 4.34 (d, J = 5.7 Hz, 1H), 4.19 (dd, J = 5.9 Hz, 1H), 4.01−3.94 (m, 2H), 1.64 (s, 3H), 1.45 (s, 3H), 1.41 (s, 3H), 1.36 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CD_3CN) δ 139.9, 136.4, 129.1, 128.3, 128.2, 119.7, 118.3, 113.3, 109.2, 105.5, 85.8, 83.1, 81.9, 74.8, 67.6, 66.6, 27.1, 26.8, 26.8, 25.4. HRMS (ESI) m/z: [M + Na] + calcd for $C_{21}H_{28}O_6Na$ 399.1784, found 399.1788. $[\alpha]_D^{20}$ + 142° (c = 0.197, MeOH).

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(*R*)-1-((3*aR*,5*R*,6*R*,6*aR*)-6-(Benzyloxy)-2,2-dimethyl-6-vinyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)ethane-1,2-diol (1.13). Sulfuric acid (5% v/v, 0.348 mL, 6.53 mmol, 0.4 equiv) was added to a solution of **1.12** (6.15 g, 16.34 mmol) in acetonitrile (82 mL) at room temperature. The reaction was stirred at room temperature for 3.75 h and monitored by TLC. The mixture was quenched with aqueous sodium hydrogen carbonate (saturated, 50 mL) and extracted with IPA/$CHCl_3$ (4 × 100 mL). The combined organic fractions were dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford **1.13** (5.50 g, 100% yield). This material was used in the next step without further purification. ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 7.46−7.25 (m, 5H), 6.03 (dd, J = 18.1, 11.5 Hz, 1H), 5.80 (d, J = 3.6 Hz, 1H), 5.53 (d, J = 11.5 Hz, 1H), 5.38 (d, J = 18.1 Hz, 1H), 4.80 (d, J = 3.7 Hz, 1H), 4.62 (d, J = 11.0 Hz, 1H), 4.56 (d, J = 11.0 Hz, 1H), 4.03 (d, J = 8.5 Hz, 1H), 3.66−3.51 (m, 2H), 3.51−3.39 (m, 1H), 2.80 (d, J = 4.1 Hz, 1H), 2.72−2.66 (m, 1H), 1.55 (s, 3H), 1.37 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, CD_3CN) δ 139.6, 136.2, 129.2, 128.6, 128.4, 119.5, 113.4, 105.3, 86.7, 81.8, 80.8, 71.4, 68.1, 64.7, 27.1, 26.8. HRMS (ESI) m/z: [M + Na] + calcd for $C_{18}H_{24}O_6Na$ 359.1471, found 359.1473. $[\alpha]_D^{20}$ + 181° (c = 0.280, MeOH).

(3*aR*,5*S*,6*R*,6*aR*)-6-(Benzyloxy)-2,2-dimethyl-6-vinyltetrahydrofuro[2,3-*d*][1,3]dioxole-5-carbaldehyde (1.14). A solution of sodium periodate (2.42 g, 11.3 mmol, 1.4 equiv) in water (25 mL) was cooled to 0 °C, a solution of **1.13** (2.72 g, 8.09 mmol, 1 equiv) in MeOH (25 mL) was added dropwise, and then the internal temperature was kept below 5 °C. The reaction was stirred for 1 h at 0 °C and then warmed to room temperature and stirred for 1.5 h. TLC indicated complete conversion. The reaction was cooled to 0 °C, ethylene glycol (2 mL, 36 mmol, 4.4 equiv) was added, the reaction was stirred for 5 min, a saturated sodium sulfite solution (50 mL) was added, and the mixture was allowed to warm to room temperature. The mixture was diluted with EtOAc (100 mL) and washed with brine (3 × 200 mL); the organic extracts were dried over sodium sulfate, filtered, and concentrated. This provided **1.14** as a yellow oil (2.5 g, 100% yield). This material was used without further purification. ^{1}H NMR (300 MHz, chloroform-d) δ 9.60 (s, 1H), 7.50−7.24 (m, 5H), 5.99 (d, J = 3.4 Hz, 1H), 5.80 (dd, J = 17.7, 11.2 Hz, 1H), 5.52 (d, J = 11.2 Hz, 1H), 5.43 (d, J = 17.7 Hz, 1H), 4.76−4.61 (m, 4H), 1.64 (s, 3H), 1.42 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 198.1, 138.0, 133.5, 128.5, 127.8, 127.6, 120.3, 113.9, 105.2, 86.3, 85.7, 81.8, 67.5, 27.2, 26.8. HRMS (ESI) m/z: [M + Na] + calcd for $C_{17}H_{20}O_5Na$ 327.1208, found 327.1209. $[\alpha]_D^{14}$ + 71° (c = 0.12, MeOH).

(3*aR*,5*R*,6*R*,6*aR*)-6-(Benzyloxy)-5-ethynyl-2,2-dimethyl-6-vinyltetrahydrofuro[2,3-*d*][1,3]dioxole (1.15). Dimethyl (1-diazo-2-oxopropyl)phosphonate (10% in MeCN, 25 mL, 10 mmol, 1.2 equiv) was added to a solution of **1.14** (2.6 g, 8.5 mmol, 1.0 equiv) and potassium carbonate (2.36 g, 17.1 mmol, 2 equiv) in MeOH (57 mL) at room temperature. The reaction was monitored by LCMS, and upon completion, the reaction was diluted with EtOAc (250 mL) and washed with saturated sodium bicarbonate solution (3 × 250 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated. This provided **1.15** as a colorless solid (2.6 g, 100% yield). This material was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42−7.19 (m, 5H), 6.00 (dd, J = 18.0, 11.4 Hz, 1H), 5.83 (d, J = 3.5 Hz, 1H), 5.59 (d, J = 11.4 Hz, 1H), 5.53 (d, J = 18.0 Hz, 1H), 4.90 (d, J = 3.5 Hz, 1H), 4.69 (d, J = 1.8 Hz, 1H), 4.55−4.43 (m, 2H), 3.60 (d, J = 1.9 Hz, 1H), 1.51 (s, 3H), 1.34 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 138.0, 134.5, 128.1, 127.4, 120.2, 112.0, 103.9, 84.5, 79.5, 78.8, 78.2, 72.2, 66.5, 26.5, 26.2. HRMS (ESI) m/z: [M + Na] + calcd for $C_{18}H_{20}O_4Na$ 323.1259, found 323.1259. $[\alpha]_D^{20}$ + 295° (c = 0.242, MeOH).

((3*aR*,5*R*,6*R*,6*aR*)-6-(Benzyloxy)-5-ethynyl-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)methanol (1.16). A solution of **1.15** (581 mg, 1.93 mmol, 1 equiv) and pyridine (0.47 mL, 5.8 mmol, 3 equiv) in DCM (20 mL) was cooled to −78 °C, and a stream of ozone (Triogen Lab 2B ozone generator, using compressed air) was passed through for 10 min. The vessel was purged with air and warmed to room temperature. TLC (vanillin stain) and ^{1}H NMR were used to monitor the reaction. A small aliquot was removed and concentrated, ^{1}H NMR showed 90% conversion. The reaction was re-cooled to −78 °C, and ozone was passed through for another 10 min and then purged with air. The reaction was allowed to reach room temperature, diluted with DCM (20 mL), and washed with saturated sodium bicarbonate solution (1 × 30 mL); the organic layer was dried over sodium sulfate, filtered, and concentrated. The crude was diluted with MeOH (20 mL), and sodium borohydride (366 mg, 9.67 mmol) was added at 0 °C. The reaction was warmed to room temperature and stirred for 3 h. TLC indicated complete consumption of the starting material. The reaction was quenched by the addition of NaOH solution (1 M, 10 mL), stirred for 5 min, diluted with EtOAc (50 mL), and washed with brine (3 × 50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel RediSep Gold 40 g eluting with EtOAc/hexane (0% to 100%) to give **1.16** (581 mg, 99% yield) as a colorless wax. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43−7.30 (m, 4H), 7.31−7.22 (m, 1H), 5.79 (d, J = 3.7 Hz, 1H), 5.16 (t, J = 5.3 Hz, 1H), 4.89 (d, J = 3.7 Hz, 1H), 4.85 (d, J = 11.3 Hz, 1H), 4.69 (d, J = 11.3 Hz, 1H), 4.63 (d, J = 2.0 Hz, 1H), 4.01 (dd, J = 12.4, 5.4 Hz, 1H), 3.63−3.55 (m, 2H), 1.49 (s, 3H), 1.31 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 138.8, 128.0, 127.4, 127.3, 111.8, 103.9, 84.3, 79.2, 78.0, 77.8, 71.0, 67.6, 61.7, 26.7, 26.3. HRMS (ESI) m/z: [M + Na] + calcd for $C_{17}H_{20}O_5Na$ 327.1208, found 327.1199. $[\alpha]_D^{20}$ + 274° (c = 0.292, MeOH).

(3*aR*,4*aR*,7*aR*,7*bR*)-7*a*-(Benzyloxy)-2,2-dimethyl-5-methylenehexahydrofuro[3′,4′:4,5]furo[2,3-*d*][1,3]dioxole (1.5). Silver carbonate (1.25 g, 4.52 mmol, 1.27 equiv) and **1.16** (1.08 g, 3.56 mmol, 1 equiv) in dry toluene (18 mL) were heated to 80 °C overnight in an oil bath. TLC indicated complete conversion. The reaction was filtered through a pad of Celite with DCM and concentrated. The residue was purified by column chromatography on silica gel RediSep gold 40 g, eluting with EtOAc/isohexane (0% to 100%) to provide **1.5** (855 mg, 80% yield) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39−7.31 (m, 4H), 7.32−7.23 (m, 1H), 6.02 (d, J = 2.6 Hz, 1H), 4.81 (d, J = 2.7 Hz, 1H), 4.70−4.62 (m, 2H), 4.62−4.49 (m, 2H), 4.33 (s, 1H), 4.23 (s, 1H), 3.88 (d, J = 10.9 Hz, 1H), 1.53 (s, 3H), 1.33 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.2, 137.9, 128.2, 127.5, 127.5, 112.3, 106.4, 91.1, 86.4, 83.6, 77.9, 72.3, 67.1, 26.9, 26.9. HRMS (ESI) m/z: [M + H] + calcd for $C_{17}H_{21}O_5$ 305.1389, found 305.1382. $[\alpha]_D^{20}$ + 80° (c = 0.153, MeOH).

((3*aR*,5*R*,6*R*,6*aR*)-6-(Benzyloxy)-5-((3-bromo-2-((4-methoxybenzyl)amino)quinolin-7-yl)ethynyl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)methanol (1.19). 3-Bromo-7-iodo-*N*-(4-methoxybenzyl)quinolin-2-amine (933 mg, 1.99 mmol, 1.1 equiv), **1.16** (550 mg, 1.81 mmol, 1 equiv), cuprous iodide (17.2 mg, 0.090 mmol, 0.05 equiv), and bis-(triphenylphosphine)palladium(II) dichloride (127 mg, 0.181 mmol, 0.1 equiv) were charged in a 20 mL microwave vial, the vial was evacuated and backfilled with argon (3×), and tetrahydrofuran (7 mL) was added followed by diisopropylamine (0.386 mL, 2.71 mmol). The reaction was stirred at room temperature overnight. The residue was purified by column chromatography on silica gel RediSep Gold 12 g prepacked, eluting with EtOAc/hexane (0% to 100%) to provide **1.19** (807 mg, 69% yield) as a yellow solid. ^{1}H NMR (400 MHz, chloroform-d) δ 7.88 (s, 1H), 7.70 (s, 1H), 7.32−7.22 (m, 3H), 7.21−7.14 (m, 4H), 7.13−7.04 (m, 3H), 6.72 (d, J = 8.5 Hz, 2H), 5.69 (d, J = 3.7 Hz, 1H), 5.54−5.44 (m, 1H), 5.00 (s, 1H), 4.74−4.65 (m, 2H), 4.61 (d, J = 3.8 Hz, 1H), 4.59−4.52 (m, 2H), 4.03 (dd, J = 12.3, 5.2 Hz, 1H), 3.74 (dd, J = 12.3, 7.6 Hz, 1H), 3.63 (s, 3H), 1.48 (s, 3H), 1.23 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.2, 152.6, 146.4, 138.6, 138.5, 131.1, 130.3, 129.5, 128.6, 128.0, 127.8, 126.8, 125.6, 124.5, 123.0, 114.2, 113.2, 109.4, 104.3, 89.5, 85.2, 84.1, 80.4, 71.5, 68.1, 62.6, 55.5, 45.6, 27.1, 26.6. HRMS (ESI) m/z: [M + H] + calcd for $C_{34}H_{34}N_2O_6Br$ 645.1600, found 645.1596. $[\alpha]_D^{15}$ + 163° (c = 0.233, MeOH).

7-((*Z*)-((3*aR*,4*aR*,7*aR*,7*bR*)-7*a*-(Benzyloxy)-2,2-dimethyltetrahydrofuro[3′,4′:4,5]furo[2,3-*d*][1,3]dioxol-5-

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(4*aH*)-ylidene)methyl)-3-bromo-*N*-(4-methoxybenzyl)-quinolin-2-amine (1.20). Silver carbonate (9.36 g, 34.0 mmol, 3 equiv) and **1.19** (8.7 g, 11.3 mmol, 1 equiv) in dry toluene (139 mL) were heated to 110 °C overnight in an oil bath. The reaction was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with EtOAc/hexanes (0 to 100%) to provide **1.20** (4.6 g, 57% yield, 85:15 *Z*:*E*) of 1.20 as a white solid. (*Z*-Major isomer) ^{1}H NMR (499 MHz, DMSO-d_6) δ 8.28 (s, 1H), 7.75 (s, 1H), 7.62−7.53 (m, 1H), 7.44−7.21 (m, 6H), 7.15−7.06 (m, 1H), 6.86 (d, J = 8.4 Hz, 2H), 6.09 (d, J = 3.6 Hz, 1H), 5.78 (s, 1H), 4.95−4.83 (m, 2H), 4.75−4.56 (m, 5H), 4.19 (d, J = 11.1 Hz, 1H), 3.70 (s, 3H), 3.37 (s, 1H), 1.59 (s, 3H), 1.37 (d, J = 9.7 Hz, 3H). (Major isomer) ^{13}C{^{1}H} NMR (126 MHz, DMSO) δ 158.1, 155.4, 152.2, 146.4, 138.5, 137.8, 136.9, 132.2, 128.9, 128.7, 128.1, 127.6, 127.5, 123.9, 122.9, 122.2, 113.6, 113.5, 112.4, 106.9, 106.5, 102.9, 90.1, 85.8, 77.8, 74.0, 67.2, 55.0, 43.7, 27.0, 26.9. HRMS (ESI) m/z: [M + H] + calcd for $C_{34}H_{34}N_2O_6Br$ 645.1600, found 645.1610. $[\alpha]_D^{16.5}$ + 140° (c = 0.115, MeOH).

7-(((3*aR*,4*aR*,7*aR*,7*bR*)-7*a*-(Benzyloxy)-2,2-dimethylhexahydrofuro[3′,4′:4,5]furo[2,3-*d*][1,3]dioxol-5-yl)-methyl)-*N*-(4-methoxybenzyl)quinolin-2-amine (1.22). Catalyst preparation: A 50 mL three-necked round-bottomed flask was charged with rac-tBuJosiphos (0.378 g, 0.697 mmol) and bis(1,5-cyclooctadiene)rhodium (I) BF_4 (0.283 g, 0.697 mmol); the vessel was evacuated and backfilled with argon (3×), and DCM (20 mL) was added. The solution was stirred for 1 h and then concentrated. The residue was dissolved in DCM (3 mL), and MTBE (3 mL) was added causing precipitation. The slurry was stirred for 15 min, filtered, and washed with MTBE (3 × 3 mL). The solid was dried under a stream of nitrogen on the filter to provide a [Rh(tBuJosiphos)NBD]-BF_4 precatalyst (600 mg, 104% yield). A steel reactor was charged with the rac-[Rh(tBuJosiphos)NBD]BF_4 precatalyst (600 mg, 50 mol %), **1.20** (1.0 g, 1.4 mmol), and TFE:DCE (40 mL, 3:1). The reaction was stirred under 30 atm of hydrogen at room temperature for 3 days. The mixture was filtered, and the solid was washed with MeCN (2 × 10 mL); the filtrate was concentrated, and the residue was purified by reverse-phase HPLC (HP-Flash, MeCN/H2O/1% NH_4HCO_3). This provided **1.22** (465 mg, 53% yield, dr = 1:1) as a yellow solid.

Isomer 1: ^{1}H NMR (400 MHz, methanol-d_4) δ 7.73 (d, J = 8.9 Hz, 1H), 7.53−7.41 (m, 4H), 7.40−7.32 (m, 2H), 7.31−7.23 (m, 3H), 7.04 (d, J = 8.2 Hz, 1H), 6.85 (d, J = 8.5 Hz, 2H), 6.68 (d, J = 8.9 Hz, 1H), 5.89 (d, J = 3.6 Hz, 1H), 4.84 (s, 1H), 4.74−4.59 (m, 3H), 4.55 (s, 2H), 4.47 (s, 1H), 4.41 (d, J = 10.7 Hz, 1H), 4.34−4.25 (m, 1H), 3.73 (s, 3H), 3.61 (d, J = 10.7 Hz, 1H), 3.04 (dd, J = 13.6, 7.9 Hz, 1H), 2.95 (dd, J = 13.6, 7.3 Hz, 1H), 1.51 (s, 3H), 1.35 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, MeOD) δ 160.3, 158.9, 149.0, 140.9, 139.8, 138.1, 132.8, 130.0, 129.3, 128.7, 128.7, 128.6, 126.3, 124.6, 123.3, 114.9, 114.2, 113.3, 108.2, 94.5, 89.9, 86.6, 80.5, 72.5, 69.1, 55.7, 45.7, 39.9, 27.5, 27.3. HRMS (ESI) m/z: [M + H] + calcd for C34H37N2O6 569.2652, found 569.2654.

Isomer 2: ^{1}H NMR (400 MHz, methanol-d_4) δ 7.74 (d, J = 8.9 Hz, 1H), 7.54 (s, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.35−7.18 (m, 7H), 7.10 (dd, J = 8.1, 1.5 Hz, 1H), 6.87−6.81 (m, 2H), 6.68 (d, J = 8.9 Hz, 1H), 5.96 (d, J = 3.5 Hz, 1H), 4.85 (s, 2H), 4.74 (d, J = 3.5 Hz, 1H), 4.62 (d, J = 10.8 Hz, 1H), 4.55 (s, 1H), 4.47 (d, J = 10.8 Hz, 1H), 4.37 (d, J = 2.3 Hz, 1H), 4.21−4.14 (m, 1H), 4.08 (d, J = 10.5 Hz, 1H), 3.88 (d, J = 10.5 Hz, 1H), 3.72 (s, 3H), 3.10−2.96 (m, 2H), 1.52 (s, 3H), 1.38 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, MeOD) δ 160.3, 158.9, 149.0, 141.3, 139.4, 138.1, 132.9, 130.0, 129.2, 128.8, 128.7, 128.5, 126.0, 124.6, 123.2, 114.9, 114.7, 113.3, 108.2, 94.1, 87.4, 84.2, 82.6, 74.3, 68.9, 55.7, 45.7, 36.6, 27.8, 27.4. HRMS (ESI) m/z: [M + H] + calcd for $C_{34}H_{37}N_2O_6$ 569.2652, found 569.2652.

((3*aR*,5*R*,6*R*,6*aR*)-6-(Benzyloxy)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)methanol (1.24). A solution of **1.12** (1000 mg, 2.66 mmol, 1 equiv) and pyridine (0.645 mL, 7.97 mmol, 3 equiv) in DCM (20 mL) was cooled to −78 °C, and a stream of ozone (Triogen ozonator, using compressed air) was passed through the solution for 10 min. The vessel was purged with air and warmed to room temperature. The reaction was cooled to −78 ° C, and ozone was passed through for another 10−15 min. The vessel was purged with air and warmed to 0 °C. The crude was diluted with MeOH (20 mL), and sodium borohydride (502 mg, 13.3 mmol, 5 equiv) was added at 0 °C. The reaction was stirred at this temperature for 3 h. The reaction was quenched by the addition of NaOH solution (1 M, 50 mL), stirred for 5 min, and diluted with EtOAc (200 mL). The organic layer was washed with brine (3 × 50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford **1.24** as a colorless solid (1.1 g, 100% yield). This material was used in the next step without further purification. ^{1}H NMR (300 MHz, chloroform-d) δ 7.47−7.25 (m, 5H), 5.78 (d, J = 3.9 Hz, 1H), 4.76 (s, 2H), 4.51 (d, J = 3.9 Hz, 1H), 4.40 (dd, J = 6.4 Hz, 1H), 4.20 (d, J = 6.8 Hz, 1H), 4.15−4.02 (m, 2H), 3.92 (dd, J = 11.7, 4.5 Hz, 1H), 3.81 (dd, J = 11.8, 5.5 Hz, 1H), 3.14−3.00 (m, 1H), 1.62 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 138.7, 128.3, 127.7, 127.6, 112.9, 110.0, 104.2, 84.8, 82.1, 80.2, 73.8, 67.3, 66.9, 61.4, 27.1, 26.8, 26.4, 24.9. HRMS (ESI) m/z: [M + Na] + calcd for $C_{20}H_{28}O_7Na$ 403.1733, found 403.1731. $[\alpha]_D^{15}$ + 28° (c = 0.094, MeOH).

(*R*)-1-((3*aR*,5*R*,6*R*,6*aR*)-6-(Benzyloxy)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)ethane-1,2-diol (1.25). Sulfuric acid (1.2 mL, 5% v/v aqueous solution, 1.1 mmol, 0.4 equiv) was added to a solution of **1.24** (1.1 g, 2.8 mmol, 1 equiv) in MeCN (30 mL) at room temperature, and the reaction was stirred for 2 h. The reaction was made basic with a minimal amount of sodium hydroxide (1 mL, 2 mmol, 2 M), and then magnesium sulfate was added. The slurry was filtered and concentrated under reduced pressure to afford **1.25** as a yellow oil (800 mg, 84% yield). This material was used crude without further purification. ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 7.42 (d, J = 7.5 Hz, 2H), 7.39−7.32 (m, 2H), 7.32−7.26 (m, 1H), 5.69 (d, J = 3.8 Hz, 1H), 4.75 (d, J = 10.5 Hz, 1H), 4.60 (d, J = 10.5 Hz, 1H), 4.43 (d, J = 3.8 Hz, 1H), 3.97−3.87 (m, 2H), 3.86−3.78 (m, 2H), 3.66 (ddd, J = 26.5, 15.0, 5.2 Hz, 3H), 3.57−3.47 (m, 1H), 2.75−2.67 (m, 1H), 1.53 (s, 3H), 1.32 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CD_3CN) δ 139.8, 129.2, 128.7, 128.4, 113.2, 104.8, 86.2, 81.3, 80.1, 71.8, 67.5, 64.6, 60.0, 27.0, 26.8. HRMS (ESI) m/z: [M + Na] + calcd for $C_{17}H_{24}O_7Na$ 363.1420, found 363.1426. $[\alpha]_D^{17}$ + 67° (c = 0.099, MeOH).

(3*aR*,4*aS*,7*aR*,7*bR*)-7*a*-(Benzyloxy)-2,2-dimethylhexahydrofuro[3′,4′:4,5]furo[2,3-*d*][1,3]dioxol-5-ol (1.26). A solution of sodium periodate (277 mg, 1.30 mmol, 1.4 equiv) in water was cooled to 0 °C; then a solution of **1.25** (315 mg, 0.925 mmol, 1.0 equiv) in MeOH (2 mL) was added dropwise. The reaction was stirred for 1 h at 0 °C and then warmed to room temperature and stirred overnight. The reaction was cooled to 0 °C, and ethylene glycol (1 mL, 17.9 mmol) was added. The reaction was stirred for 5 min, saturated sodium sulfite (50 mL) was added, and then the reaction was warmed to room temperature. The mixture was diluted with EtOAc (100 mL), and the organic layer was washed with brine (3 × 200 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford **1.26** as a colorless solid (251 mg, 88% yield, 1.8:1 mixture at acetal carbon). This material was used without further purification. (spectra recorded as observed) ^{1}H NMR (400 MHz, chloroform-d) δ 7.46−7.30 (m), 6.02 (d, J = 3.4 Hz), 5.95 (d, J = 3.6 Hz), 5.37 (d, J = 14.3 Hz), 4.81 (d, J = 10.6 Hz), 4.75 (d, J = 10.6 Hz), 4.67 (dd, J = 5.8, 3.6 Hz), 4.61 (d, J = 10.6 Hz), 4.57 (s), 4.56−4.48 (m), 4.14 (d, J = 10.6 Hz), 3.88 (d, J = 11.6 Hz), 3.85−3.76 (m), 3.06 (bs, 1H), 1.66 (s), 1.46 (s), 1.43 (s). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 137.6, 128.6, 128.1, 127.9, 127.9, 114.7, 114.2, 107.3, 106.9, 101.4, 98.7, 91.9, 91.9, 88.2, 84.8, 82.1, 80.9, 73.1, 70.0, 69.0, 68.3, 27.6, 27.5, 27.4, 27.3. HRMS (ESI) m/z: [M + Na] + calcd for $C_{16}H_{20}O_6Na$ 331.1158, found 331.1155. $[\alpha]_D^{17}$ + 48° (c = 0.106, MeOH).

((3*aR*,5*R*,6*R*,6*aR*)-6-(Benzyloxy)-2,2-dimethyl-5-vinyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)methanol (1.8). Potassium *tert*-butoxide (183 mg, 1.63 mmol, 2.0 equiv) was added in portions to a suspension of methyltriphenylphosphonium bromide (611 mg, 1.71 mmol, 2.1 equiv) in THF (4 mL) at room temperature.

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The reaction was stirred at room temperature for 3 h, the solution was cooled to 0 °C, a solution of **1.26** (251 mg, 0.814 mmol, 1.0 equiv) in THF (2 mL) was added, and then the reaction was stirred for 2 h. The mixture was quenched with saturated aqueous ammonium chloride (10 mL), and the mixture was extracted with EtOAc (1 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0−100% EtOAc/hexanes) to afford **1.8** (189 mg, 76% yield) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, J = 7.3 Hz, 2H), 7.37−7.33 (m, 2H), 7.31−7.27 (m, 1H), 5.94 (ddd, J = 17.2, 10.8, 5.3 Hz, 1H), 5.82 (d, J = 3.9 Hz, 1H), 5.49 (dt, J = 17.3, 1.6 Hz, 1H), 5.30 (dt, J = 10.8, 1.5 Hz, 1H), 4.79 (d, J = 11.1 Hz, 1H), 4.74 (d, J = 11.1 Hz, 1H), 4.73−4.70 (m, 1H), 4.68 (d, J = 3.9 Hz, 1H), 3.80 (d, J = 12.1 Hz, 1H), 3.69 (d, J = 12.1 Hz, 1H), 1.63 (s, 3H), 1.56 (bs, 1H), 1.39 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.8, 132.0, 128.3, 127.6, 127.6, 118.0, 112.7, 104.1, 84.9, 80.6, 80.0, 67.9, 62.2, 26.9, 26.6. HRMS (ESI) m/z: [M + Na] + calcd for $C_{17}H_{22}O_5Na$ 329.1365, found 329.1353. $[\alpha]_D^{20}$ + 48° (c = 7.085, CHCl3).

Carboetherification General Procedure. 7-(((3*aR*,4*aR*,7*aR*,7*bR*)-7*a*-(Benzyloxy)-2,2-dimethylhexahydrofuro[3′,4′:4,5]furo[2,3-*d*][1,3]dioxol-5-yl)methyl)-3-bromo-*N*-(2,4-dimethoxybenzyl)quinolin-2-amine (**1.3-A**): A schlenk flask was charged with 3-bromo-*N*-(2,4-dimethoxybenzyl)-7-iodoquinolin-2-amine (3.3 g, 6.5 mmol, 2.0 equiv), tris(dibenzylideneacetone)-dipalladium(0) (149 mg, 0.163 mmol, 0.05 equiv), sodium *tert*-butoxide (627 mg, 6.53 mmol, 2.0 equiv), and bis(2-diphenylphosphinophenyl)ether (176 mg, 0.326 mmol, 0.1 equiv), the flask was evacuated and backfilled with argon (3×), and then a solution of **1.8** (1.00 g, 3.26 mmol, 1.0 equiv) in THF (33 mL) was added. The reaction was heated to 65 °C overnight in an oil bath. The reaction was cooled to room temperature, diluted with EtOAc (200 mL), and washed with brine (2 × 200 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0−100% EtOAc/hexanes) to afford **1.3-A1** as a colorless solid (1.38 g, 62% yield major **1.3-A1**, 9.1:1 dr of crude mix).

Isomer 1 (**1.3-A1**): ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 8.16 (s, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.44 (s, 1H), 7.40−7.25 (m, 5H), 7.22 (d, J = 8.3 Hz, 1H), 7.15 (d, J = 8.1 Hz, 1H), 6.56 (s, 1H), 6.43 (d, J = 8.4 Hz, 1H), 6.17−6.07 (m, 1H), 5.96 (d, J = 3.1 Hz, 1H), 4.76 (d, J = 3.1 Hz, 1H), 4.65 (d, J = 5.8 Hz, 2H), 4.61 (d, J = 10.8 Hz, 1H), 4.52 (d, J = 11.0 Hz, 1H), 4.36 (s, 1H), 4.21−4.12 (m, 1H), 4.07 (d, J = 10.6 Hz, 1H), 3.88 (s, 3H), 3.87 (d, J = 9.3 Hz, 1H), 3.75 (s, 3H), 3.07−2.95 (m, 2H), 1.51 (s, 3H), 1.37 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 159.5, 157.8, 152.1, 146.2, 140.6, 138.5, 138.1, 128.4, 128.0, 127.4, 127.3, 126.5, 125.4, 123.9, 122.2, 119.3, 112.5, 106.9, 106.3, 104.3, 98.3, 92.2, 85.7, 81.9, 80.5, 72.3, 67.0, 55.4, 55.1, 35.1, 28.9, 27.1, 27.0. HRMS (ESI) m/z: [M + H] + calcd for $C_{35}H_{38}N_2O_7Br$ 677.1862, found 677.1868. $[\alpha]_D^{15}$ + 22° (c = 0.097, MeOH).

Isomer 2 (**1.3-A2**): ^{1}H NMR (300 MHz, methanol-d_4) δ 8.15 (s, 1H), 7.55−7.19 (m, 7H), 7.11 (d, J = 8.1 Hz, 1H), 6.56 (d, J = 2.2 Hz, 1H), 6.44 (dd, J = 8.3, 2.2 Hz, 1H), 5.93 (d, J = 3.7 Hz, 1H), 4.82 (s, 2H), 4.75−4.61 (m, 4H), 4.44 (d, J = 12.2 Hz, 2H), 4.36−4.26 (m, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 3.64 (d, J = 10.8 Hz, 1H), 3.06 (dd, J = 13.9, 7.7 Hz, 1H), 2.98 (dd, J = 13.9, 7.1 Hz, 2H), 1.53 (s, 3H), 1.37 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.5, 1598.0, 152.5, 147.2, 139.9, 138.4, 138.3, 130.8, 128.5, 127.8, 127.6, 126.6, 126.6, 124.1, 123.0, 119.8, 113.4, 108.1, 106.9, 104.1, 98.8, 93.4, 89.2, 85.3, 79.7, 71.9 68.3, 55.5, 55.5, 41.3, 39.0, 27.4, 27.3. HRMS (ESI) m/z: [M + H] + calcd for $C_{35}H_{38}N_2O_7Br$ 677.1862, found 677.1867. $[\alpha]_D^{15}$ − 15° (c = 0.13, MeOH).

(3*aR*,4*aR*,5*S*,7*aR*,7*bR*)-7*a*-(Benzyloxy)-2,2-dimethyl-5-(naphthalen-2-ylmethyl)hexahydrofuro[3′,4′:4,5]furo[2,3-*d*][1,3]dioxole (1.3-B1). Following the general procedure, **1.3-B1** (73 mg, 52% yield) was obtained. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.88−7.81 (m, 3H), 7.75 (s, 1H), 7.50−7.42 (m, 3H), 7.36−7.29 (m, 4H), 7.28−7.24 (m, 1H), 6.04 (d, J = 3.7 Hz, 1H), 4.85 (d, J = 3.6 Hz, 1H), 4.56 (q, J = 11.2 Hz, 2H), 4.35 (d, J = 2.3 Hz, 1H), 4.17 (ddd, J = 8.1, 6.0, 2.3 Hz, 1H), 4.05 (d, J = 10.6 Hz, 1H), 3.88 (d, J = 10.6 Hz, 1H), 3.15−2.96 (m, 2H), 1.50 (s, 3H), 1.36 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMSO) δ 138.6, 136.8, 133.5, 132.2, 128.6, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.6, 126.4, 125.8, 113.0, 106.8, 92.8, 86.2, 82.5, 81.0, 72.8, 67.5, 35.5, 27.7, 27.6. HRMS (ESI): [M + Na] + calcd for $C_{27}H_{28}O_5Na$ 455.1829, found 455.1820. $[\alpha]_D^{17}$ + 48° (c = 0.198, MeOH).

(3*aR*,4*aR*,5*R*,7*aR*,7*bR*)-7*a*-(Benzyloxy)-2,2-dimethyl-5-(naphthalen-2-ylmethyl)hexahydrofuro[3′,4′:4,5]furo[2,3-*d*][1,3]dioxole (1.3-B2 Minor Diaseteromer). ^{1}H NMR (600 MHz, DMSO) δ 7.89−7.83 (m, 3H), 7.69 (s, 1H), 7.51−7.44 (m, 4H), 7.43−7.38 (m, 3H), 7.33 (t, J = 7.3 Hz, 1H), 5.96 (d, J = 3.7 Hz, 1H), 4.77 (d, J = 3.7 Hz, 1H), 4.75−4.64 (m, 2H), 4.40−4.36 (m, 2H), 4.26 (t, J = 7.5 Hz, 1H), 3.59 (d, J = 10.8 Hz, 1H), 3.06−2.96 (m, 2H), 1.47 (s, 3H), 1.33 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMSO) δ 139.1, 136.3, 133.6, 132.2, 128.7, 128.3, 128.2, 127.9, 127.9, 127.8, 127.7, 127.6, 126.5, 125.9, 112.6, 106.8, 93.37, 88.68, 84.91, 79.18, 71.33, 67.79, 38.67, 27.51, 27.44. HRMS (ESI) m/z: [M + Na] + calcd for $C_{27}H_{28}O_5Na$ 455.1829, found 455.1817. $[\alpha]_D^{17}$ + 37° (c = 0.34, MeOH).

3-(((3*aR*,4*aR*,5*S*,7*aR*,7*bR*)-7*a*-(Benzyloxy)-2,2-dimethylhexahydrofuro[3′,4′:4,5]furo[2,3-*d*][1,3]dioxol-5-yl)methyl)pyridine (1.3-C). Following the general procedure, **1.3-C**(101 mg, 81% yield) was obtained. ^{1}H NMR (500 MHz, DMSO) δ 8.47 (d, J = 1.8 Hz, 1H), 8.42 (dd, J = 4.8, 1.5 Hz, 1H), 7.68 (dt, J = 7.8, 1.7 Hz, 1H), 7.39−7.25 (m, 6H), 6.02 (d, J = 3.6 Hz, 1H), 4.85 (d, J = 3.6 Hz, 1H), 4.61−4.52 (m, 2H), 4.34 (d, J = 2.4 Hz, 1H), 4.08 (td, J = 5.6, 2.8 Hz, 1H), 4.05 (d, J = 10.6 Hz, 1H), 3.87 (d, J = 10.6 Hz, 1H), 2.97−2.81 (m, 2H), 1.51 (s, 3H), 1.36 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO) δ 150.6, 147.9, 138.6, 137.0, 134.7, 128.6, 128.0, 127.9, 123.8, 113.1, 106.8, 92.9, 86.1, 82.1, 80.9, 72.8, 67.5, 32.6, 27.7, 27.5. HRMS (ESI) m/z: [M + H] + calcd for $C_{22}H_{26}NO_5$ 384.1811, found 384.1804. $[\alpha]_D^{17}$ + 44° (c = 0.448, MeOH).

(3*R*,3*aS*,6*aR*)-6-((2-Amino-3-bromoquinolin-7-yl)methyl)-tetrahydrofuro[3,4-*b*]furan-2,3,3*a*(4*H*)-triol (1.2A). Boron trichloride (0.79 mL, 0.79 mmol, 5 equiv) was added to a solution of **1.3-A1** (107 mg, 0.16 mmol, 1.0 equiv) in DCM (8 mL) at −78 °C. The reaction was stirred for 15 min, warmed to 0 °C, and then stirred for 30 min. The reaction was quenched by the addition of THF and saturated aqueous $NHCO_3$ (4:1, 3 mL). The mixture was concentrated under reduced pressure, and the crude was purified by mass-triggered reverse-phase HPLC (MeCN/water with 0.1% NH_4OH modifier) to afford **1.2-A** as a colorless solid (34 mg, 32% yield) as a 1.25:1 mixture at the anomeric carbon. (Reported as observed). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.25 (s, 1H (isomer 1 + isomer 2)), 7.59−7.44 (m, 2H (isomer 1 + isomer 2)), 7.25 (dd, J = 7.7, 3.9 Hz, 1H (isomer 1 + isomer 2)), 5.38 (d, J = 3.8 Hz, 1H (isomer 1)), 5.19 (d, J = 2.8 Hz, 1H (isomer 2)), 4.24 (d, J = 3.3 Hz, 1H (isomer 1)), 4.13−4.02 (m, 2H (isomer 1 + isomer 2)), 3.91 (d, J = 9.4 Hz, 1H (isomer 1)), 3.81 (d, J = 3.8 Hz, 1H (isomer 2)), 3.69 (d, J = 2.7 Hz, 1H (isomer 2)), 3.59 (d, J = 9.5 Hz, 1H (isomer 2)), 3.50 (d, J = 9.4 Hz, 1H (isomer 1)), 3.07 (m, 2H (isomer 1 + isomer 2)). ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 154.4, 146.6, 140.7, 140.5, 139.0, 126.5, 124.9, 124.0, 124.0, 122.4, 105.9, 102.9, 97.6, 86.1, 86.0, 84.4, 84.0, 82.3, 82.2, 78.8, 76.2, 76.0, 75.3, 35.0, 35.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{18}N_2O_5Br$ 397.0399, found 397.0395. $[\alpha]_D^{15}$ + 65° (c = 0.28, MeOH).

End-Game Glycosylation General Procedure. Synthesis of (2*R*,3*R*,3*aS*,6*S*,6*aR*)-6-((2-amino-3-bromoquinolin-7-yl)methyl)-2-(4-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)tetrahydrofuro[3,4-*b*]-furan-3,3*a*(4*H*)-diol (**1.1-C**): To a vial containing **1.2-A** (100 mg, 0.25 mmol, 1 equiv) in anhydrous acetonitrile (4 mL) was added 1,1′-(azodicarbonyl)dipiperidine (95 mg, 0.38 mmol, 1.5 equiv) followed by tri-*n*-butylphosphine (81 mg, 0.40 mmol, 1.6 equiv) at room temperature. The mixture was stirred for 1 h. In a separate oven-dried vial containing 4-methyl-7*H*-pyrrolo[2,3-d]pyrimidine (67 mg, 0.50 mmol, 2 equiv) suspended in dry MeCN (4 mL) was added DBU (76 μL, 0.50 mmol, 2 equiv). This mixture was stirred for 1 h at room

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temperature and was then added to the above mixture containing the triol. The final reaction mixture was then stirred at room temperature overnight. The reaction mixture was filtered and purified by Prep-HPLC (MeCN/water with 0.1% TFA modifier) to afford 53 mg (33% yield) of **1.1-C** as a TFA salt. **Caution** when handling compounds **1.1-A–C** manipulations such as drying, concentrating, or weighing of final compounds was performed in an isolator to reduce potential exposure. A disposable lab coat over a regular lab coat should be worn in addition to double gloves. Ensure that your institution has the proper procedures, PPE, and equipment to handle extremely potent compounds. ^{1}H NMR (499 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.85 (s, 1H), 8.12 (d, J = 3.9 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.57–7.50 (m, 1H), 7.46–7.42 (m, 1H), 7.19 (d, J = 3.8 Hz, 1H), 6.26 (d, J = 7.9 Hz, 1H), 4.36 (d, J = 8.0 Hz, 1H), 4.33 (d, J = 4.2 Hz, 1H), 4.13–4.08 (m, 1H), 3.96 (d, J = 9.1 Hz, 1H), 3.38 (d, J = 9.2 Hz, 1H), 3.08–3.03 (m, 2H), 2.89 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO) δ 156.1, 152.5, 150.5, 145.0, 144.6, 136.2, 129.4, 127.7, 126.9, 120.1, 117.8, 117.4, 117.0, 105.7, 103.1, 88.0, 86.6, 83.4, 81.5, 75.1, 34.6, 18.4. HRMS (ESI) m/z: [M + H] + calcd for $C_{23}H_{23}N_5O_4Br$ 512.0933, found 512.0908.

(2*R*,3*R*,3*aS*,6*S*,6*aR*)-6-((2-Amino-3-bromoquinolin-7-yl)-methyl)-2-(4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-tetrahydrofuro[3,4-*b*]furan-3,3*a*(4*H*)-diol (1.1-A). Following the glycosylation general procedure, **1.1-A** (10 mg, 31% yield) was obtained. ^{1}H NMR (499 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.71 (s, 1H), 8.19 (s, 2H), 8.00 (d, J = 3.7 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.49 (s, 1H), 7.35 (d, J = 8.2 Hz, 1H), 6.81 (d, J = 3.7 Hz, 1H), 6.21 (d, J = 7.9 Hz, 1H), 4.38 (d, J = 7.9 Hz, 1H), 4.28 (d, J = 4.1 Hz, 1H), 4.12–4.06 (m, 1H), 3.95 (d, J = 9.1 Hz, 1H), 3.37 (d, J = 9.1 Hz, 1H), 3.09–2.99 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO) δ 152.0, 151.5, 151.3, 143.8, 139.0, 128.9, 127.8, 126.5, 121.3, 120.2, 117.9, 106.1, 100.8, 88.2, 87.2, 83.8, 82.0, 77.3, 75.1, 35.0.HRMS (ESI) m/z: [M + H] + calcd for $C_{22}H_{20}N_5O_4ClBr$ 532.0387, found 532.0380.

(2*R*,3*R*,3*aS*,6*S*,6*aR*)-6-((2-Amino-3-bromoquinolin-7-yl)-methyl)-2-(4-chloro-5-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)tetrahydrofuro[3,4-*b*]furan-3,3*a*(4*H*)-diol (1.1-B). Following the glycosylation general procedure, **1.1-B** (16 mg, 48% yield) was obtained. ^{1}H NMR (499 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.63 (s, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.73 (s, 1H), 7.52 (s, 1H), 7.42 (dd, J = 8.3, 1.1 Hz, 1H), 6.17 (d, J = 8.1 Hz, 1H), 4.31–4.25 (m, 2H), 4.12–4.05 (m, 1H), 3.94 (d, J = 9.1 Hz, 1H), 3.36 (d, J = 9.2 Hz, 1H), 3.09–3.00 (m, 2H), 2.47–2.44 (m, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO) δ 159.3, 159.1, 152.5, 152.0, 151.1, 150.6, 144.8, 144.5, 126.8, 125.3, 120.1, 116.5, 114.9, 110.8, 105.6, 87.6, 86.0, 83.2, 81.5, 76.8, 74.8, 34.6, 11.2. HRMS (ESI): [M + H]$^+$ calcd for $C_{23}H_{22}N_5O_4ClBr$ 546.0544, found 546.0529.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02969.

Modeling and computational results, biological assays, copies of ^{1}H NMR and ^{13}C NMR spectra, and X-ray crystallography (PDF)

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Notes

The authors declare no competing financial interest.

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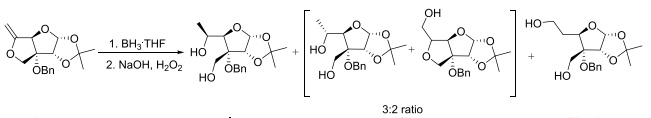

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