# Asymmetric Synthesis of Oxygen Heterocycles via Pd-Catalyzed Dynamic Kinetic Asymmetric Transformations: Application to Nucleosides

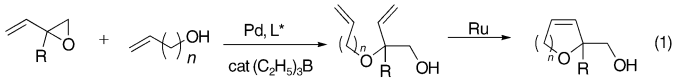
**Barry M. Trost,* Brian S. Brown, Ernest J. McEachern, and Oliver Kuhn[a]**

**Abstract:** Racemic butadiene and isoprene monoepoxide react with unsaturated alcohols in the presence of a chiral palladium catalyst and a boron co-catalyst to give 3-alkoxy-4-hydroxy-1-butene and 3-alkoxy-4-hydroxy-3-methyl-1-butene, respectively, with excellent regio- and enantioselectivity in a dynamic kinetic asymmetric transformation whereby both enantiomers of the starting epoxides provide the same enantiomeric product. In the case of 2-phenylbutadiene monoepoxide, easily available from phenacyl chloride and vinylmagnesium bromide, the reaction proceeds by kinetic resolution. A model to rationalize the result is presented. The bis-olefin products are ideal substrates for the Ru catalyzed ring closing metathesis. In this way, five-, six-, and seven-membered oxygen heterocycles are readily available enantiomerically pure. The value of this very simple two step process is demonstrated by the use of the five-membered ring heterocycles to form unnatural and unusual nucleosides that cannot be easily accessed by other means. The sequence involves a Ru catalyzed isomerization of the initial 2,5-dihydrofuran to a 2,3-dihydrofuran followed by a selenium promoted addition of a pyrimidine or purine base. One advantage of this strategy is the easy access to either enantiomeric series, both of which have important biological applications.

**Keywords:** asymmetric catalysis · asymmetric synthesis · metathesis · nucleosides · palladium

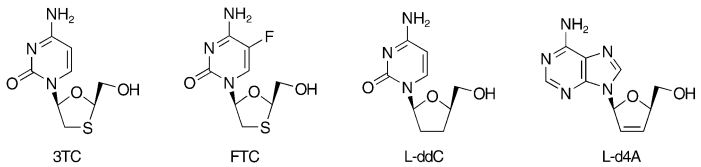
## Introduction

The asymmetric synthesis of oxygen heterocyles represents an important task because of the widespread occurrence of such structural motifs and their use as building blocks. The importance of nucleosides wherein the core ring is a tetrahydrofuran drew our attention especially to the case of five-membered rings. Nonetheless, larger rings are also of interest. Our strategy evolved from the ability to effect dynamic kinetic asymmetric transformations (DYKAT) of racemic epoxides with alcohol nucleophiles using Pd catalyzed asymmetric allylic alkylation (AAA). The intrinsic presence of a carbon-carbon double bond in such processes raised the question of a sequential Pd-catalyzed AAA and Ru-catalyzed metathesis sequence as shown in Equation (1). Simple variation of the chain length of the alcohol partner then would provide access to various ring sizes.



(1)

The case of five-membered rings holds special significance. In addition to the proven therapeutic potential of D-nucleoside analogues, a number of L-nucleoside analogues have recently demonstrated interesting biological activity as well.[1] Highlighting the need for enantioselective versatility, the "unnatural-like" compounds 3TC and FTC were found to be more potent and less toxic than their corresponding antipodes.[2] More traditional, furanyl analogues such as L-ddC and L-d4A[3] also show promise as anti-HIV and anti-HBV agents.




Non-racemic syntheses have generally utilized chiral pool starting materials, or a resolution of racemic material. The first method has the disadvantage of having easy access to only one enantiomer through occasionally lengthy sequences, while the second produces both enantiomers, but discards the unwanted half of the racemic mixture. The desymmetrization of a *meso*-diester provides a more flexible approach to non-

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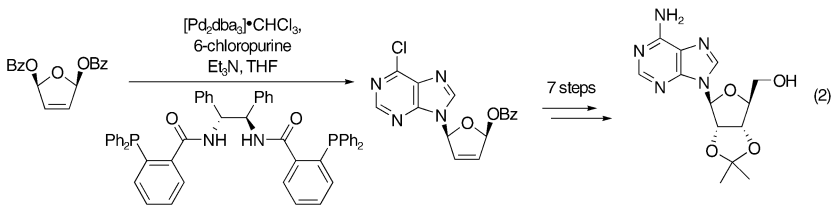
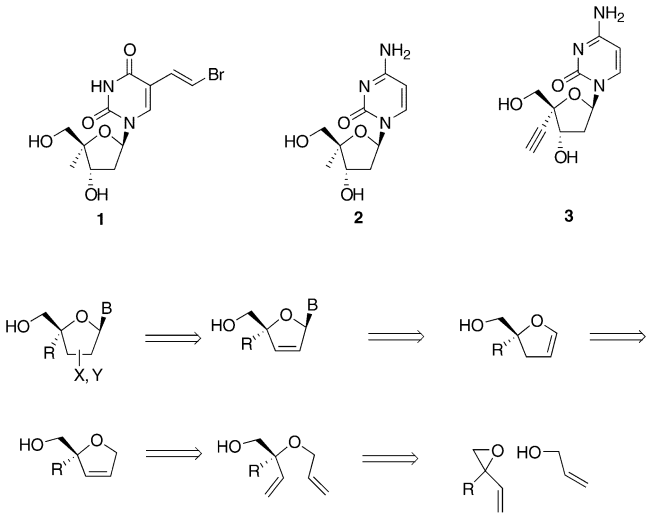
racemic material of either enantiomer in high optical purity and chemical yield [Eq. (2)].[4] One aspect that is an issue with respect to this approach, however, was the elaboration of the remaining benzoate to the desired hydroxymethyl group via a carboxylic acid moiety. A more direct synthesis of the hydroxymethyl series is desirable.




Additionally, a number of 4′-substituted analogues have been recently synthesized and found to display considerable biological activity. For example, the 4′-$\alpha$-methyl compounds **1**[5] and **2**[6] both possess antiviral activity against HSV, VZV, and HIV, although they also show considerable cytoxicity. While the 4′-ethynyl analogue **3**[7] retains potent activity against HIV, it is also much less cytotoxic than the others, offering results which encourage more investigation in this area. The synthesis of virtually all 4′-substituted analogues start from naturally-occurring sugars or nucleosides, generally proceeding through a 5′-oxo compound,[8] although methods using 4′,5′- or 3′,4′-didehydro compounds also exist.[9] Unfortunately, these routes tend to be lengthy and limit 4′-substitution to groups which can be installed by enolate chemistry. In an attempt to improve upon the known synthetic sequences, an alternative strategy was devised based on the construction of the sugar moiety by ring-closing metathesis of non-racemic diallyl ethers to form 2,5-dihydrofurans, which could then be elaborated to the desired nucleoside analogues as shown in Scheme 1.




Scheme 1. Retrosynthetic analysis.

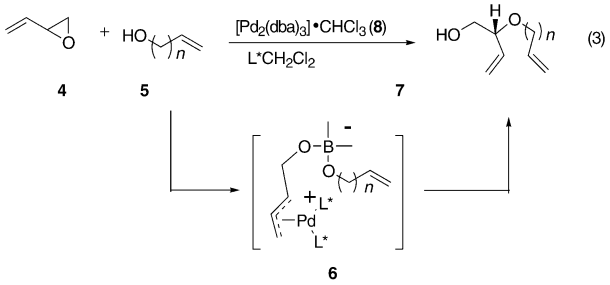
We, therefore, undertook a study of the use of unsaturated alcohols in the Pd-DYKAT process with three different vinyl epoxides. To demonstrate the utility of the new route, the syntheses of L-2′,3′-dideoxydidehydro nucleoside analogues possessing an H, Me, or Ph group in the 4′-$\beta$-position were examined, with the phenyl compounds being previously unreported and not easily accessible by traditional methods. This strategy then addresses the limitations previously mentioned by providing a succinct route to a wider range of 4′-substituted analogues in either enantiomeric series.

**DYKAT**: The Pd-DYKAT of racemic epoxides involves treatment of a 1:1 mixture of the alcohol and the vinyl epoxide with the chiral catalyst in the presence of 1 mol% triethylborane as a co-catalyst.[10] The reaction with commercial butadiene monoepoxide (epb, **4**) is depicted in Equation (3) and summarized in Table 1. For the reaction to succeed, the

Table 1. Pd-DYKAT of vinylepoxides.

| | Epoxide | Alcohol | Yield [%] | *ee* [%] |
|---|---|---|---|---|
| 1[a] | **4** | $n=1$ (**5a**) | 80 (**7a**) | 90 |
| 2[a] | **4** | $n=2$ (**5b**) | 82 (**7b**) | 90 |
| 3[a] | **4** | $n=3$ (**5c**) | 84 (**7c**) | 90 |
| 4[a] | **4** | $n=4$ (**5d**) | 80 (**7d**) | n.d.[e] |
| 5[b] | **10a** | $n=1$ (**5a**) | 86 (**11a**) | 94 |
| 6[b] | **10a** | $n=2$ (**5b**) | 83 (**11b**) | 96 |
| 7[b] | **10a** | $n=3$ (**5c**) | 86 (**11c**) | 91 |
| 8[c] | **10b** | $n=1$ (**5a**) | 33 (66)[d] (**12**, $n=1$) | 87 |

[a] Reaction performed with 0.5 mol% **8**, 1.5 mol% **9b**, 0.5 mol% triethylborane and 5 mol% DMAP in methylane chloride at RT. [b] Reaction performed with 1 mol% **8**, 3 mol% **9a**, and 1 mol% triethylborane in methylene chloride at RT. [c] Reaction with 1 mol% **8**, 3 mol% **9a**, and 20 mol% DMAP in dioxane at RT. [d] Yield in parentheses based upon 45% conversion. [e] n.d. = not determined.

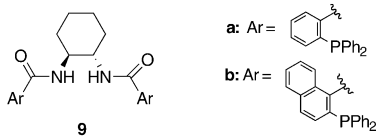



intermediate π-allylpalladium complex must interconvert between the two diastereomeric forms (when L* is chiral which become enantiomeric if L is achiral) faster than transfer of oxygen. Furthermore, the oxygen nucleophile must be preferentially transferred to the more substituted allyl terminus. The role of the boron co-catalyst is twofold, 1) to enhance the ability of alcohols to serve as good nucleophiles via formation of "ate" complexes and 2) to temporarily tether the

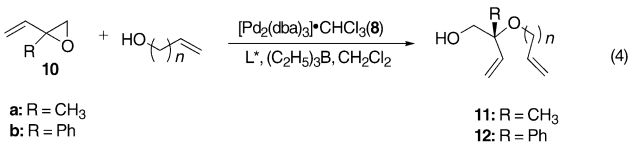
  

nucleophile to the epoxide oxygen to help deliver it to the proximal carbon as shown in **6**.

In the event, unsaturated alcohols **5a–d** reacted smoothly with **4** using 1 mol% Pd precatalyst **8**, 3 mol% ligand **9** and 1 mol% triethyl- or tri-*sec*-butyl borane to give good yields of the product **7a** but only in 64–69% *ee*. Switching to the more constrained naphthyl ligand **9b** increased the *ee* to 92%. Dropping the catalyst load to 0.5 mol% **8**, 1.5 mol% **9b** and 0.5 mol% triethylborane, gave comparable yield and *ee* (see Table 1, entry 1). Using homoallyl alcohol **5b**, a similar trend was observed. Thus, the latter conditions were adopted as our standard as summarized in Table 1 (entries 1–4). In the case of unsaturated alcohol **5d**, the *ee* of the product **7d** was not determined (see below) but we assume it will be similar. In all cases, only one regioisomer was observed.



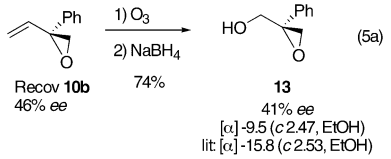

Switching to isoprene monoepoxide (**10a**) gave somewhat better results as summarized in Equation (4) and Table 1. At first glance, the requirement for attack to form a quarternary center might have been thought to be more difficult. Quite the contrary was the case. First, the "standard" ligand **9a** sufficed to give excellent results. Second, no DMAP was needed as a co-catalyst. Third, the enantioselectivities were slightly higher.




(4)

On the other hand, the phenyl substrate **10b** proved to be quite different. This substrate is easily accessed from phenacyl chloride and vinylmagnesium bromide in 91% isolated yield.[11] This epoxide reacted very sluggishly. Stoichiometric triallyl borate was required for any reasonable yields. Using 1 mol% **8** and 3 mol% of the "standard" ligand **9a** in methylene chloride gave only a 35% conversion to product of 34% *ee*. Using DMSO increased the conversion to 94% but the *ee* dropped to 10%. Ether solvents proved best for *ee*, 56% in $Et_2O$, 70% in THF, 81% in dioxane, and 84% in DME. Greater reproducibility in dioxane led to its being the solvent of choice; however, the conversion was still only 28%. Adding 20 mol% DMAP increased the conversion to 45% with an *ee* of 87%. Increasing the DMAP to 100 mol% gave a similar conversion, although somewhat lower yield, but enhanced the *ee* to 94%. Changing the palladium source to palladium acetate or π-allylpalladium chloride dimer, which normally give more kinetically active catalyst, decreased the conversion but maintained high *ee*, 93–94%. No beneficial effects were obtained by using chloride or fluoride salts.

Under conditions giving good enantioselectivity, the addition apparently occurs by a traditional kinetic resolution, as demonstrated by the low conversions and enhanced *ee* of the recovered starting material. Due to the considerable steric differences between the H, Me, and Ph substituents, the absolute stereochemistry of the product and recovered starting material was determined to confirm reaction in accord with the normal mnemonic [(*S*,*S*)-ligand reacting via the *syn* hydroxymethyl complex to give (*R*)-product for **7** and **11** but (*S*)-product for **12** because of change in priorities, not absolute configuration].[12] Treatment of recovered **10b** (46% *ee*) with ozone, followed by sodium borohydride reduction, provided the known alcohol **13**[13] in 73% yield and 41% *ee* [Eq. (5a)].

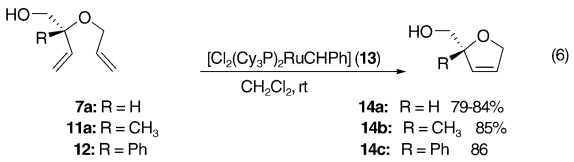



(5a)

Based upon the optical rotation, the major epoxide enantiomer was determined to possess the (*R*) configuration; this indicates preferential ionization of the (*S*)-**10b** in the addition reaction (any potential Payne rearrangement here results in retention of absolute stereochemistry and is not a concern). The increased reactivity of (*S*)-**10b** does not necessarily favor formation of (*S*)-**12** ($n=1$) due to the possibility of allyl interconversion under the Pd-catalyzed conditions. Therefore, **12** ($n=1$) was reconverted to starting **10b** to determine the absolute configuration of the newly created center, which was found to be the expected (*S*)-isomer [Eq. (5b)]. Overall, these results indicate selective ionization followed by a slower, but competitive, alkoxy transfer.


(5b)

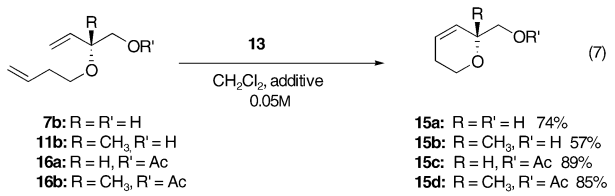
**Metathesis**: Ring-closing metathesis to form the five-membered rings as summarized in Equation (6) proceeded well with 2 mol% of Grubbs I catalyst **13**[14] to produce the 2,5-dihydrofurans **14a–c** of high enantiopurity. No loss of stereochemical integrity accompanied the RCM, that is, the enantiopurities of the products were identical to those of the acyclic precursors.




(6)

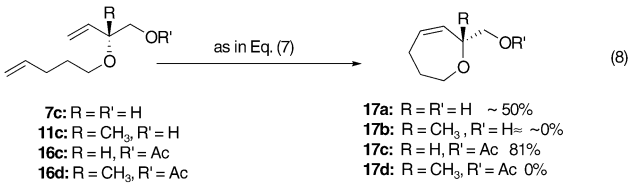
In contrast to the above, cyclization to the dihydropyrans proved more challenging. Conditions similar to those of Equation (6) with substrates **7b** and **11b** proceeded very

sluggishly and incomplete conversion persisted even upon heating. Speculating that the free hydroxyl group might be the culprit was counterintuitive since coordination to ruthenium in a carbene intermediate would have been anticipated to be a more severe problem for **7a**, **11a**, and **12**. Nevertheless, using 5 mol% of complex **13** and 30 mol% of titanium tetraisopropoxide,[15] presumably to coordinate the OH function, as well as elevated temperature (40 °C) and extended reaction times (18 h) gave good to moderate yields of dihydropyrans **15a** and **15b** as summarized in Equation (7).

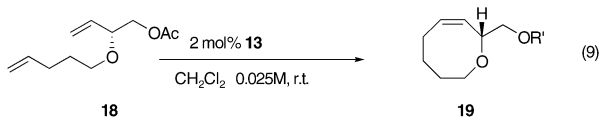



A more effective solution was employment of the corresponding acetates **16a**,**b**.[16] In the case of the unsubstituted substrate **16a**, cyclization proceeded very smoothly under the conditions of Equation (6) within 3 h. However, substrate **16b** only led to 43% conversion under the identical conditions even with 18 h reaction time. Increasing the catalyst load to 5 mol% increased the conversion to 61% which did not improve when the reaction was run at 40 °C. The best result was obtained by adding three portions of 2 mol% each of catalyst **13** over a 72 h period whereby conversion was 94% and the isolated yield of the product was 85%. Again, no loss of enantiopurity was observed.

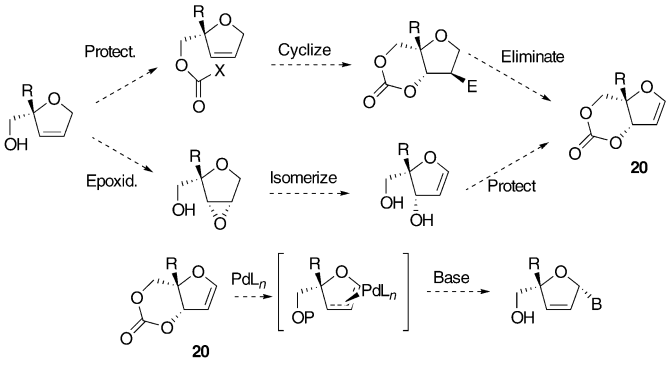
Extending the chain one more carbon led to even bigger problems. For the unsubstituted substrate **7c**, the best conditions found for substrate **7b** with titanium tetraisoproxide as a co-catalyst gave only a 50% conversion to alcohol **17a** [Eq. (8)]. The same conditions gave no conversion of diene alcohol **11c**. Using the monoacetate **16c**, however, gave an excellent yield of the oxepin **17c**. Unfortunately, diene acetate **16d** gave no cyclization to oxepin **17d**. Only intermolecular coupling to form the symmetrical 1,2-disubstituted alkene arising by metathesis of the monosubstituted olefin was observed.




A quick examination of the RCM of acetate **18** to the eight-membered ring **19** proceeded only in low yield (10%), with symmetrical 1,2-disubstituted alkene being the major product besides unreacted starting material [Eq. (9)]. Because of the failure of the RCM, establishing the *ee* of the alcohol precursor **7d** was not pursued.

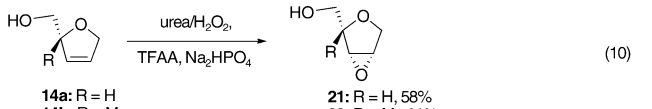



**Nucleoside synthesis**: Initially, the most direct route to the desired nucleoside analogues was considered to be one proceeding through cyclic carbonate **20**, which would then allow for nucleoside base installation by a palladium-catalyzed amination procedure. Two main paths to **20** are outlined in Scheme 2, and involve either alcohol activation followed by electrophilic cyclization and elimination, or an alcohol-directed epoxidation followed by epoxide opening. A variety of substrates prepared for the top route, including the Boc, *N*,*N*-dimethylcarbamate, *N*-tosylcarbamate,and pyrrolidinylcarbamate derivatives, failed to provide the desired cyclization products under a number of electrophilic cyclization conditions using selenium, iodine, or palladium. This route was therefore abandoned in favor of the epoxidation strategy.



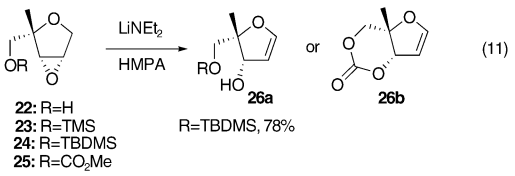

Scheme 2. Initial proposed nucleoside precursor.

After examination of several epoxidizing reagents, trifluoroperacetic acid was found to give significantly better results than the others, delivering the desired products **21** and **22** in reasonable yields [Eq. (10)]. Due to its easier handling, elaboration of **22** was initially examined.

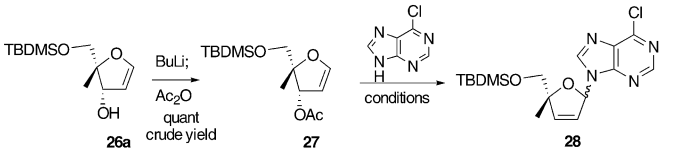


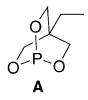

Base-mediated epoxide isomerization[17] attempts led only to decomposition, except in the case of LHMDS, which afforded 50% of the corresponding TMS-protected starting material (**23**). This result then led to preparation of the TBDMS ether **24** (TBDMS-Cl and **22**, 83% yield), reasoning that a silyl group protected against decomposition. Epoxide opening then occurred smoothly with $LiNEt_2$ giving allylic alcohol **26a** in 78% yield [Eq. (11)]. Attempted in situ formation of the corresponding cyclic carbonate **26b** starting from acyclic carbonate **25** (**22** and $ClCO_2CH_3$, 78% yield) failed.




The desired activation of alcohol **26a** was accomplished using *n*-butyllithium as base, followed by trapping to give the acetate, pivaloate, or benzoate [Eq. (12)]. These compounds had to be used as the crude materials since they were unstable to chromatography. Efforts to install more labile phosphate, carbonate, or even the originally sought cyclic carbonate leaving groups led only to decomposition. Therefore, nucleoside base introduction was examined using allylic acetate **27**.

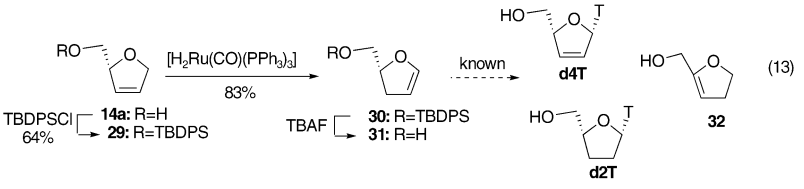



| Pd cat. | Ligand | Solvent | Yield (α:β) |
|---|---|---|---|
| $[Pd_2(dba)_3]$ | $P(O^iPr)_3$ | $CH_2Cl_2$ | 20 (3:1) |
| $[Pd_2(dba)_3]$ | $P(OPh)_3$ | $CH_2Cl_2$ | 35 (3:1) |
| $[Pd_2(dba)_3]$ | **A** | $CH_2Cl_2$ | 45 (2:1) |
| none | | DMF, 50 °C | 52 (0.8:1) |

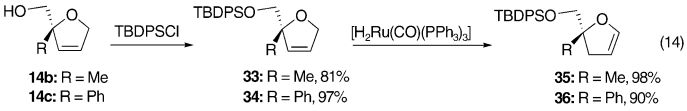
Under a variety of conditions, the planned Pd-catalyzed allylic amination proceeded very poorly, giving low yields, conversions, and diastereoselectivities. The reasons for this remain unclear, since similar π-allyl chemistry efficiently delivered nucleoside products.[4] The slight improvement in results using phosphite ligands indicates the problem may lie in the initial complexation of the enol ether, although examples of successful allylic alkylation in similar systems also exist. The most efficient conditions proved to be simple base-mediated $S_N2'$ displacement under thermal conditions, although these conditions were still unacceptable.

Therefore, a new route was devised involving alkene isomerization of the 2,5-dihydrofurans to the corresponding furanoid glycals. A number of literature precedents exist for the conversion of glycals to nucleoside analogues, with the enantiomer of **30** being a known intermediate in the syntheses of d4T and d2T via selenium-mediated electrophilic glycosylation.[18] Although conversion of unsubstituted 2,5-dihydrofuran to 2,3-dihydrofuran is known,[19] initial isomerization attempts met with disappointing results, giving either no reaction or decomposition. However, successful isomerizations of alkenes into conjugation with oxygen using ruthenium catalysts have been reported by Mori, Curran, and others,[20] although never specifically in the context of furanyl glycals.

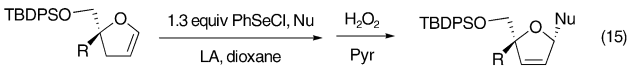



Indeed, reaction of silyl ether **29** with catalytic $[H_2Ru(CO)(PPh_3)_3]$ efficiently promoted the desired migration to dihydrofuran **30** [Eq. (13)].

Approximately 10% of the trisubstituted glycal **32** was observed, but fortunately analysis of the free alcohol **31**, obtained by TBAF-mediated desilylation, indicated that no racemization had occurred under the reaction conditions. This sequence therefore, represents a formal synthesis of the unnatural antipodes of d4T and d2T, and this material was not advanced further. The corresponding isomerization of the 2,2-disubstituted compounds **33** and **34**, where no alternative migration is possible, proceeded even more efficiently [Eq. (14)] to **35** and **36**, respectively.




Although successful glycal elaboration with a number of electrophiles has been reported, the silylated base/PhSeCl system[18] worked best here [Eq. (15)]. Modifications did lead to improvements. For example, changing from ether to dioxane increased the diastereoselectivity from 1.8:1 to 4.7:1 with bis-(trimethylsilyl)-thymine ($TMS_2T$) as a nucleophile and more dramatically, from 1.4:1 to 16:1 with bis-(trimethylsilyl)-uracil [$(TMS)_2U$] as a nucleophile. In all cases, $InCl_3$ proved to be the preferred Lewis acid, although the optimal



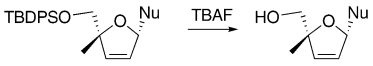

amount (catalytic or stoichiometric) varied from case to case (Table 2). Also, the amount of nucleophile did not generally affect the results much, except when using 6-chloropurine. The anomalous results here are not understood, but may be linked to variation in the quality of the in situ-formed silylated bases. Also not understood are the low yields in glycosylation with the 4′-methylglycal since this reaction is reported to work well in the unsubstituted case and gives the highest yield for any reaction in this study in the 4′-phenyl series. Another interesting difference between the Lewis acids is in the selectivity difference in entries 6 and 7. Although $SnCl_4$ gives a lower yield, it is much more selective. This selectivity trend is reversed however with the phenyl-substituted compound (entries 13–15). Optical purity remained unchanged by the glycosylation, as shown by chiral HPLC analysis of 4′-methyl-6-chloropurine analogue **44** and the 4′-phenyluridine analogue **45** after their conversions to free alcohols. This was true for both $InCl_3$ and $SnCl_4$.

The dihydrofuryl compounds were all deprotected to the free didehydronucleoside analogues [Eq. (16) and (17)]. This allowed the assignment of the major diastereomers of **37** and **39** based on conversion to, and comparison with, the known corresponding alcohols **42** and **47**.[6] The minor compounds in these reactions were assumed to be the

Table 2. Synthesis of nucleoside analogues.

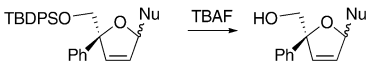
| | R | Nu (equiv) | L.A. (equiv) | Product | Yield [%] ($\alpha$:$\beta$) |
|---|---|---|---|---|---|
| 1 | Me (**35**) | $(TMS)_2T$ (2) | $SnCl_4$(1.2) | **37** | 42 (4.7:1) |
| 2 | | (2) | $SnCl_4$ (0.1) | **37** | 58 (3.5:1) |
| 3 | | (2) | $InCl_3$ (1.5) | **37** | 59 (5.0:1) |
| 4 | | (4) | $InCl_3$ (1.5) | **37** | 73 (7.1:1) |
| 5 | | (2) | $InCl_3$ (0.1) | **37** | 70 (7.1:1) |
| 6 | | $(TMS)_2U$ (2) | $SnCl_4$ (1.2) | **38** | 39 (16:1) |
| 7 | | (2) | $InCl_3$ (1.5) | **38** | 60 (5.0:1) |
| 8 | | (TMS)6-ClPur (2) | AgOTf (1.2) | **39** | 38 (1.4:1) |
| 9 | | (2) | $SnCl_4$ (1.2) | **39** | 32 (2.3:1) |
| 10 | | (1.3) | $InCl_3$ (0.1) | **39** | 14 (1.1:1) |
| 11 | | (2) | $InCl_3$ (1.2) | **39** | 21 (1.3:1) |
| 12 | | (2) | $InCl_3$ (0.1) | **39** | 40 (2.5:1) |
| 13 | Ph (**36**) | $(TMS)_2U$ (2) | $SnCl_4$ (1.2) | **40** | 60 (6.0:1) |
| 14 | | (2) | $InCl_3$ (0.1) | **40** | 67 (9:1) |
| 15 | | (1.3) | $InCl_3$ (0.1) | **40** | 66 (10:1) |
| 16 | | (TMS)6-ClPur (2) | $SnCl_4$ (1.2) | **41** | 62 (5.3:1) |
| 17 | | (2) | $InCl_3$ (1.2) | **41** | 83 (4.4:1) |
| 18 | | (1.3) | $InCl_3$ (0.1) | **41** | 49 (5:1) |
| 19 | | (2) | $InCl_3$ (0.1) | **41** | 15 (4.5:1) |

C1′-epimers, although this has not been rigorously established. Preferential formation of the $\alpha$-anomers in the 4′-phenyl system was assumed based on analogy to the methyl series. This is supported by the large difference in $^1$H NMR shifts of the C6 proton between the epimers of **45**. While the major isomer, presumed ***45α***, shows the usual shift at 8.11 ppm, the minor ***45β*** displays this proton at 6.82 ppm, most likely due to anisotropic shielding by the *cis* phenyl ring. (The use of $\alpha$ and $\beta$ refers to the stereochemistry as drawn in Equation (17) wherein $\alpha$ refers to the enantiomer of the natural nucleosides). For the 6-chloropurine substitutions, no significant amounts of N7-products were detected (again, assuming the reported isomers to be C1′-epimers).




(16)

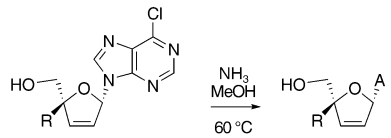
**37:** Nu = T **42:** 95%
**38:** U **43:** 95%
**39:** 6-ClPur (1:1 α:β) **44:** 75%, 90% *ee*




(17)

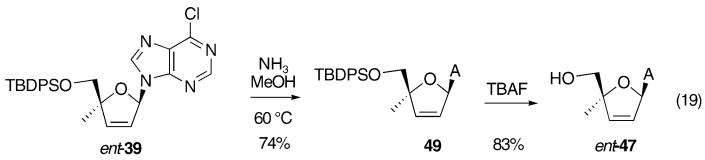
**40:** Nu = U (6:1 α:β) **45:** 98%, 87% *ee*
**41:** 6-ClPur (5:1 α:β) **46:** 100%

Conversion of the 6-chloropurines to the adenines was accomplished by heating in $NH_3$ saturated MeOH [Eq. (18)]. For the 4′-methyl analogues, amination prior to silyl deprotection proceeded more efficiently than when these steps were reversed. For example, amination of silyl ether *ent*-**39** proceeds in 74% yield while amination of alcohol **44** occurs in only 36% yield [Eq. (19)]. Small but appreciable amounts (up to 20%) of the corresponding 6-methoxy compounds were also observed in the amination reaction.




**44:** R = $CH_3$ **47:** 36%
**46:** R = Ph **48:** 68%

(18)




*ent*-**39** 74% **49** 83% *ent*-**47**

(19)

## Discussion and Conclusion

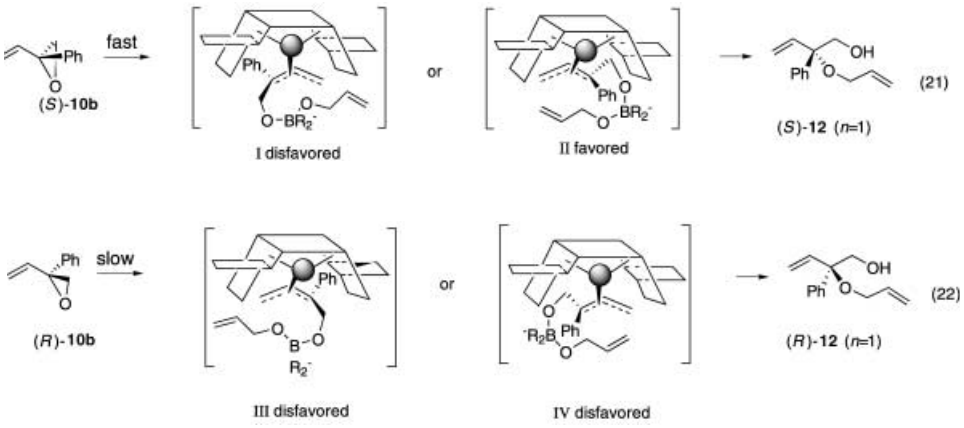
The palladium catalyzed AAA reactions of vinyl epoxides provides a simple and powerful atom economical approach to very flexible building blocks wherein a tetrasubstituted carbon has three quite distinct functional groups for individual manipulation—one of which is an alkene [Eq. (20)].


(20)

Thus, incorporating a double bond into the pronucleophile sets the stage for ring formation. When the pronucleophile is an alcohol then the ring being formed is an oxygen heterocycle. Indeed, five to seven-membered oxygen heterocycles are now easily accessed asymmetrically by this strategy. The fact that both enantiomers of racemic epoxide can be converted to the same enantiomer of the product and that the enantiodiscriminating event simultaneously builds more of the structure of the desired final target (and does not just simply introduce chirality) provides increased practicality.

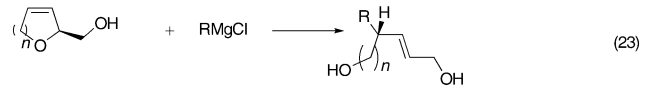
While the DYKAT worked well for small R groups in the epoxide, phenyl was a problem. Clearly, the nature of the chiral space restricts formation of both diastereomeric palladium complexes with these chiral ligands. We have previously demonstrated that a phenyl substitutent has no particular bias to go *syn* or *anti* relative to methyl in the π-allylpalladium intermediate during ionization with these chiral ligands.[21] The source of this behavior may be the duality of steric size of the phenyl group, that is, it is bulky in the plane of the ring but relatively non-bulky if rotated so that interactions occur above or below the plane of the ring. This reasoning favors ionization to form the π-allylpalladium complexes wherein the alkoxymethyl group is preferentially *syn* as shown in structures II and IV [Eq. (21) and (22)]. Therefore, structures I and III are labelled as disfavored. Whereas, ionization from (*S*)-**10b** meets this requirement and places this group in the sterically uncongested "flap" region of the ligand forming the favored II, ionization from (*R*)-**10b** makes this group butt against a "wall" of one of the aromatic rings on the ligand forming the disfavored IV. The sterically bulky phenyl ring on the same carbon as the alkoxymethyl



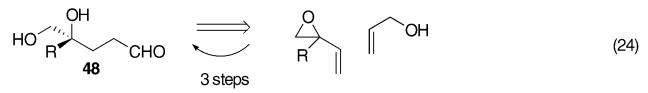

group then prevents minimization of the unfavorable steric interactions of IV to the extent that it is even difficult to form. Thus, a true DYKAT becomes more difficult as observed in the present case.

The metathesis also demonstrates a strong steric dependence.[22] Thus, while the favorability of five-membered ring formation minimizes such issues, they arise with increasing dominance in forming six-membered rings and, in the case of the seven-membered ring bearing a tetrasubstituted carbon, completely inhibited the reaction. The hydroxyl group has a similar kinetic effect; however, it can be easily circumvented by the use of the acetate derivatives. It should be noted that these type of allylic ethers have been used for chelate controlled additions of Grignard reagents [Eq. (23)].[23] In that report, the substrates were obtained enantiomerically pure by kinetic resolutions. The current method provides a more efficient approach.



(23)

The synthesis of the nucleosides provides further demonstration of the value of these oxygen heterocycles available by this methodology. Unlike starting from the chiral pool, either enantiomer is easily accessed simply by switching the ligand. Indeed, *ent*-**39** was prepared exactly in the same manner as **39** and in comparable efficiency and yields. The efficient isomerization of the 2,5-dihydrofurans to the 2,3-dihydrofurans provides two valuable intermediates in a reasonably atom economic manner where the only mass loss is a molecule of ethylene from the starting epoxide and unsaturated alcohol.[24] The 2,3-dihydrofuran is also an equivalent of the aldehyde **48**,



(24)

which derives in only 3 steps and possesses diverse functionality [Eq. (24)]. The method of Castillon et al proved quite efficient for diastereoselective introduction of the nucleoside bases.

The unsaturated dideoxy nucleosides formed in this work are of interest in their own right but also as intermediates for introduction of various substituents at the 2- and 3-positions. Thus, unusual nucleosides of high diastereo- and enantiopurity are available in 5 steps from vinyl epoxides and allyl alcohol.

## Experimental Section

**Preparation of 2-(*R*)-2-methyl-2-allyloxybut-3-en-1-ol (11a)**: Freshly distilled allyl alcohol (0.86 mL, 10.0 mmol) and a solution of $Et_3B$ (1M in THF, 0.10 mL, 0.10 mmol) were added to a solution of $[Pd_2dba_3]\cdot CHCl_3$ (53.3 mg, 0.0515 mmol) and (1*S*,2*S*)-(**9a**) (0.107 g, 0.154 mmol) in $CH_2Cl_2$ (100 mL) to give an orange solution. After stirring for 5 min, neat epoxide **10a** (1.00 mL, 10.2 mmol) was added giving a light yellow solution. The mixture was stirred for 9.5 h, concentrated at 25 mm Hg, and purified by Kugelrohr distillation (125 °C at 25 mm Hg) to provide **11a** as a clear oil (1.22 g, 8.58 mmol, 86 %) in 94 % *ee* by chiral GC analysis (Cyclosil-B, 90 °C, $t_R$(*R*-(−)-isomer) = 16.5 min, $t_R$(*S*-(+)-isomer) = 17.8 min); $[\alpha]_D^{24} = -7.9$ ($c = 1.4$, $CHCl_3$); IR (film): $\tilde{\nu} = 3441, 1727, 1646, 1461, 1415, 1122, 1059, 924\ cm^{-1}$; $^1H$ NMR (300 MHz): $\delta = 5.92-5.75$ (m, 2H), 5.26–5.19 (m, 3H), 5.10 (dd, $J = 1$, 10 Hz, 1H), 3.85 (dd, $J = 1$, 4 Hz, 2H), 3.48 (d, $J = 11$ Hz, 1H), 3.41 (d, $J = 11$ Hz, 1H), 2.16 (br s, 1H), 1.27 (s, 3H); $^{13}C$ NMR (75 MHz): $\delta = 139.6, 135.4, 116.8, 115.9, 78.2, 69.3, 63.8, 18.5$; elemental analysis calcd (%) for $C_8H_{14}O_2$: C 67.57, H 9.92; found: C 67.45, H 9.79.

**Preparation of 2-(*S*)-2-phenyl-2-allyloxybut-3-en-1-ol (12, $n = 1$)**: A flask containing $[Pd_2dba_3]\cdot CHCl_3$ (0.222 g, 0.215 mmol), (1*S*,2*S*)-(**9a**) (0.445 g, 0.644 mmol), and DMAP (0.526 g, 4.30 mmol) was evacuated and filled with $N_2$ three times, and filled with dioxane (100 mL). To this was added triallyl borate (4.26 mL, 21.5 mmol), and the resulting solution was stirred for 10 min. Epoxide **10b** (3.15 g, 21.5 mmol) was then added, and allowed to react for 19 h. The reaction mixture was concentrated, diluted with sat aq $NaHCO_3$ (50 mL) and extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organic layers were dried ($Na_2SO_4$), concentrated, and purified by flash chromatography (15 % $Et_2O$/PE) to provide recovered **10b** as a yellow oil [1.38 g, 9.44 mmol, 44 %, 46 % *ee* by chiral GC analysis (Cyclosil-B, 110 °C, $t_R$(*R*-(+)-minor isomer) = 14.0 min, $t_R$(*S*-(−)-major isomer) = 14.6 min)], and product **12**($n = 1$) as a yellow oil [1.45 g, 7.11 mmol, 33 %, 87 % *ee* by chiral GC analysis (Cyclosil-B, 140 °C $t_R$(*R*-(+)-isomer) = 26.7 min; $[\alpha]_D^{24} = -10.4$ ($c = 1.49$, $CH_2Cl_2$). $t_R$(*S*-(−)-isomer) = 28.0 min)]; IR (film): $\tilde{\nu} = 3450, 3085, 2923, 1645, 1492, 1408, 1059, 925\ cm^{-1}$; $^1H$ NMR (300 MHz): $\delta = 7.41-7.27$ (m, 5H), 6.12 (ddd, $J = 1.2$, 11.1, 17.8 Hz, 1H), 5.96 (m, 1H), 5.50–5.30 (m, 3H), 5.17 (d, $J = 10.2$ Hz, 1H), 3.96–3.83 (m, 4H), 2.00 (br s, 1H); $^{13}C$ NMR (75 MHz): $\delta = 140.0, 137.2, 135.0, 128.4, 127.7, 127.0, 118.2, 116.0, 82.3, 67.8, 64.5$; elemental analysis calcd (%) for $C_{13}H_{16}O_2$: C 76.43, H 7.91; found: C 76.20, H 7.98.

**Metathesis to (2-(*R*)-2,5-dihydrofuran-2-yl)methanol (14a)**: A solution of **7a** (1.37 g, 10.7 mmol) and $[Cl_2(PCy_3)_2RuCHPh]$ (0.176 g, 0.214 mmol) in $CH_2Cl_2$ (110 mL) was stirred for 3 h. The mixture was concentrated (80 mmHg), and purified by flash chromatography (67 % $Et_2O$/pentane) and Kugelrohr distillation (140 °C at 25 mmHg) to provide **14a** as a clear oil (0.847 g, 8.46 mmol, 79 %) in 87–90 % *ee* by chiral GC analysis (Cyclosil-B, 80 °C, $t_R$(*S*-(−)-isomer) = 20.2 min, $t_R$(*R*-(+)-isomer) = 20.7 min); $[\alpha]_D^{24} = 123.8$ ($c = 1.0$, $CH_2Cl_2$); IR (film): $\tilde{\nu} = 3396$, 2859, 1654, 1356, 1074, 1038 $cm^{-1}$; $^1H$ NMR (300 MHz): $\delta = 6.02$ (dq, $J = 2.0$, 6.2 Hz, 1H), 5.76 (m, 1H), 4.92 (br s, 1H), 4.76–4.63 (m, 2H), 3.74 (ddd, $J = 2.9$, 6.4, 11.4 Hz,

1H), 3.58 (ddd, $J = 4.9, 6.4, 11.4$ Hz, 1H), 1.84 (t, $J = 6.4$ Hz, 1H); $^{13}$C NMR (75 MHz): $\delta = 128.4, 126.2, 86.9, 75.4, 64.8$; elemental analysis calcd (%) for $C_5H_8O_2$: C 59.97, H 8.07; found: C 60.02, H 7.95.

**Metathesis to (2-(*R*)-2-methyl-2,5-dihydrofuran-2-yl)methanol (14b)**: A solution of **11a** (1.22 g, 8.58 mmol) and $[Cl_2(PCy_3)_2RuCHPh]$ (0.141 g, 0.171 mmol) in $CH_2Cl_2$ (190 mL) was stirred for 5.5 h. The mixture was concentrated (30 mmHg), and purified by Kugelrohr distillation (125 °C at 25 mmHg) to provide **14b** as a clear oil (0.834 g, 7.30 mmol, 85%). $[\alpha]_D^{24} = 25.3$ ($c = 0.60$, $CHCl_3$); IR (film): $\tilde{\nu} = 3418, 1646, 1454, 1350$ cm$^{-1}$; $^1$H NMR (300 MHz): $\delta = 5.91$ (br d, $J = 6.0$ Hz, 1H), 5.65 (dt, $J = 2.0, 6.0$ Hz, 1H), 4.64 (br s, 2H), 3.54–3.46 (m, 2H), 2.12 (br s, 1H), 1.22 (s, 3H); $^{13}$C NMR (75 MHz): $\delta = 131.1, 127.4, 90.7, 75.1, 68.3, 22.3$; elemental analysis calcd (%) for $C_6H_{10}O_2$: C 63.14, H 8.83; found: C 62.95, H 8.65.

**Metathesis to (2-(*R*)-2-phenyl-2,5-dihydrofuran-2-yl)methanol (14c)**: A solution of **12** (1.67 g, 8.17 mmol) and $Cl_2(PCy_3)_2RuCHPh$ (133 mg, 1.61 mmol) in $CH_2Cl_2$ (4.5 mL) was stirred for 7 h. Additional $[Cl_2(PCy_3)_2RuCHPh]$ (66.3 mg, 0.0806 mmol) was then added, and the mixture was stirred for 4 h, concentrated, and purified by flash chromatography (60% $Et_2O$/PE) to provide **14c** as a tan oil (1.24 g, 7.04 mmol, 86%) which solidified. M.p. 47–50 °C; $[\alpha]_D^{24} = -102.8$ ($c = 1.0$, $CH_2Cl_2$); IR (film): $\tilde{\nu} = 3440, 2855, 1602, 1448, 1088, 1061, 1009$ cm$^{-1}$; $^1$H NMR (300 MHz): $\delta =$ 7.40–7.25 (m, 5H), 6.05 (s, 2H), 4.85 (d, $J = 13.0$ Hz, 1H), 4.74 (d, $J =$ 13.0 Hz, 1H), 3.79 (s, 1H), 2.00 (s, 1H); $^{13}$C NMR (75 MHz): $\delta = 142.3, 129.7, 128.4, 128.0, 127.4, 125.0, 94.3, 75.5, 68.6$; elemental analysis calcd (%) for $C_{11}H_{12}O_2$: C 74.96, H 6.88; found: C 75.01, H 7.02.

**Preparation of (2-(*R*)-5,6-dihydro-2*H*-pyran-2-yl)-methanol (15a)**: Following the normal metathesis procedure, the allyl ether **7b** was converted into the cyclic ether **15a** using the following quantities of reagents and solvents: compound **7b** (100 mg, 0.70 mmol), $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (29 mg, 0.035 mmol), $[Ti(i\text{PrO})_4]$ (58 μL, 0.21 mmol), $CH_2Cl_2$ (14 mL). The reaction time in this case was 18 h, while the reaction temperature was 40 °C. Flash chromatography of the crude material (silica gel, pentane/$Et_2O$ 2:1) afforded **15a** as a colorless oil (59 mg, 74%) in 90% *ee* (separated by chiral GLC, Cyclosil B column, isothermal 100 °C, $t_R$(*R*-(−)-isomer) = 19.49 min, $t_R$(*S*-(+)-isomer) = 20.31 min); $[\alpha]_D = -13.9°$ ($c = 1.28$, $CHCl_3$); IR: $\tilde{\nu} =$ 3418, 1653, 1462, 1430, 1371, 1185, 1093, 1056, 770 cm$^{-1}$; $^1$H NMR (300 MHz): $\delta = 5.95–5.90$ (m, 1H), 5.56–5.54 (d, 1H, $J = 10$ Hz), 4.18 (br s, 1H), 4.00–3.94 (m, 1H), 3.70–3.53 (m, 3H), 3.40–2.38 (m, 1H), 2.36–2.21 (m, 1H), 1.94 (br d, 1H, $J = 18$ Hz), $^{13}$C NMR (75.5 MHz): $\delta =$ 93.2, 81.0, 74.6, 64.0, 63.0, 25.2; elemental analysis calcd (%) for $C_6H_{10}O_2$: C 63.14, H 8.83; found C 62.91, H 8.78.

**Preparation of (2-(*R*)-2-methyl-5,6-dihydro-2*H*-pyran-2-yl)methanol (15b)**: Following the metathesis protocol, the allyl ether **11b** was converted into the cyclic ether **15b** using the following quantities of reagents and solvents: compound **11b** (100 mg, 0.64 mmol), $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (26 mg, 0.032 mmol), $[Ti(i\text{PrO})_4]$ (57 μL, 0.19 mmol), $CH_2Cl_2$ (13 mL). The reaction time in this case was 18 h, while the reaction temperature was 40 °C. Flash chromatography of the crude material (silica gel, pentane/$Et_2O$ 2:1) afforded starting material **11b** (22 mg, 22%) and **15b** (47 mg, 57%) as a colorless oil in 90% *ee* (separated by chiral GLC, Cyclosil B column, isothermal 120 °C, $t_R$(*R*-(−)-isomer) = 10.08 min, $t_R$(*S*-(+)-isomer) = 10.58 min); $[\alpha]_D = -24.3°$ ($c = 2.07$, $CHCl_3$); IR: $\tilde{\nu} = 3441, 1652, 1453, 1428, 1365, 1216, 1080, 999, 722$ cm$^{-1}$; $^1$H NMR (300 MHz): $\delta = 5.95–5.89$ (m, 1H), 5.53 (d, 1H, $J = 10$ Hz), 3.85–3.72 (m, 2H), 3.51 (d, 1H, $J =$ 11 Hz), 3.39 (d, 1H, $J = 11$ Hz), 2.19–1.94 (m, 2H), 1.18 (s, 3H); $^{13}$C NMR (75.5 MHz): $\delta = 131.0, 126.1, 74.5, 68.4, 59.4, 25.0, 21.5$; elemental analysis calcd (%) for $C_7H_{12}O_2$: C 65.60, H 9.44; found: C 65.45, H 9.22.

**Preparation of 2-(*R*)-5,6-dihydro-2*H*-pyran-2-ylmethyl acetate (15c)**: Following the metathesis protocol, the allyl ether **16a** was converted into the cyclic ether **15c** using the following quantities of reagents and solvents: compound **16a** (131 mg, 0.71 mmol), $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (12 mg, 0.014 mmol), $CH_2Cl_2$ (14 mL). The reaction time in this case was 3 h. Flash chromatography of the crude material (silica gel, pentane/$Et_2O$ 2:1) afforded **15c** as a colorless oil (99 mg, 89%) in 90% *ee* (separated by chiral GLC, Cyclosil B column, isothermal 120 °C, $t_R$(*S*-(−)-isomer) = 11.78 min, $t_R$(*R*-(+)-isomer) = 12.14 min); $[\alpha]_D = +20.4°$ ($c = 1.54$, $CHCl_3$); IR: $\tilde{\nu} =$ 1743, 1654, 1431, 1368, 1234, 1188, 1100, 1041, 770 cm$^{-1}$; $^1$H NMR (300 MHz): $\delta = 5.94–5.88$ (m, 1H), 5.53 (dd, 1H, $J = 2$, 10 Hz), 4.27 (br s, 1H), 4.09–3.90 (m, 3H), 3.67–3.58 (m, 1H), 2.26–2.15 (m, 1H), 2.03 (s, 3H), 1.97–1.88 (m, 1H); $^{13}$C NMR (75.5 MHz) $\delta = 170.9, 127.4, 125.3, 71.9,$ 65.9, 62.8, 24.9, 20.8; elemental analysis calcd (%) for $C_8H_{12}O_3$: C 61.52, H 7.74; found: C 61.70, H 7.61.

**Preparation of 2-(*R*)-2-methyl-5,6-dihydro-2*H*-pyran-2-ylmethyl acetate (15d)**: Following the metathesis protocol, the allyl ether **16b** was converted into the cyclic ether **15d** using the following quantities of reagents and solvents: compound **16b** (150 mg, 0.77 mmol), $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (38 mg, 0.046 mmol), $CH_2Cl_2$ (15 mL). The reaction time in this case was 3 d, and the Grubbs catalyst was added in three portions of 13 mg at 24 h intervals. Flash chromatography of the crude material (silica gel, pentane/$Et_2O$ 2:1) afforded **15d** (110 mg, 85%) as a colorless oil in 96% *ee* (separated by chiral GLC, Cyclosil B column, isothermal 120 °C, $t_R$(*R*-(+)-isomer) = 10.26 min, $t_R$(*S*-(−)-isomer) = 10.66 min); $[\alpha]_D = +49.8°$ ($c =$ 1.50, $CHCl_3$); IR: $\tilde{\nu} = 1744, 1430, 1381, 1368, 1242, 1083, 1043, 737$ cm$^{-1}$; $^1$H NMR (300 MHz): $\delta = 5.92–5.86$ (m, 1H), 5.52 (dt, 1H, $J = 10$, 2 Hz), 4.11 (d, 1H, $J = 11$ Hz), 3.88 (d, 1H, $J = 11$ Hz), 3.85–3.71 (m, 2H), 2.10–2.02 (m, 5H), 1.20 (s, 3H); $^{13}$C NMR (75.5 MHz): $\delta = 170.9, 130.1, 126.3,$ 72.7, 68.3, 59.5, 24.8, 22.5, 20.9; elemental analysis calcd (%) for $C_9H_{14}O_3$: C 63.51, H 8.29; found: C 63.70, H 8.47.

**Preparation of 2-(*R*)-2,5,6,7-tetrahydro-oxepin-2-ylmethyl acetate (17c)**: Following the methathesis protocol, the allyl ether **16c** was converted into the cyclic ether **17c** using the following quantities of reagents and solvents: compound **16c** (93 mg, 0.47 mmol), $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (8 mg, 0.009 mmol), $CH_2Cl_2$ (9 mL). The reaction time in this case was 3 h. Flash chromatography of the crude material (silica gel, pentane/$Et_2O$ 2:1) afforded **17c** (65 mg, 81%) as a colorless oil in 90% *ee* (separated by chiral GLC, Cyclosil B column, isothermal 120 °C, $t_R$(*R*-(+)-isomer) = 19.87 min, $t_R$(*S*-(−)-isomer) = 20.49 min); $[\alpha]_D = +56.1°$ ($c = 2.39$, $CHCl_3$); IR: $\tilde{\nu} =$ 1743, 1435, 1367, 1235, 1137, 1044, 692 cm$^{-1}$; $^1$H NMR (300 MHz): $\delta =$ 5.90–5.82 (m, 1H), 5.46 (d, 1H, $J = 11$ Hz), 4.25 (br s, 1H), 4.11–3.99 (m, 3H), 3.70–3.62 (m, 1H), 2.37–2.31 (m, 1H), 2.20–2.12 (m, 1H), 2.03 (s, 3H), 1.82–1.72 (m, 2H); $^{13}$C NMR (75.5 MHz): $\delta = 170.9, 133.8, 129.4,$ 75.8, 71.3, 66.5, 28.7, 26.8, 20.8; elemental analysis calcd (%) for $C_9H_{14}O_3$: C 63.51, H 8.29; found: C 63.65, H 8.40.

**Preparation of (2*R*)-2-methyl-2-*tert*-butyldiphenylsiloxymethyl-2,5-dihydrofuran (33)**: TBDPSCl (0.79 mL, 3.0 mmol) was added to a solution of alcohol **14b** (0.314 g, 2.75 mmol), imidazole (0.247 g, 3.63 mmol), and DMAP (33.2 mg, 0.272 mmol) in DMF (5 mL). The reaction mixture was stirred 30 min, diluted with ether (50 mL), washed with water (30 mL) and brine (20 mL), dried ($Na_2SO_4$), and concentrated to give a clear oil. Flash chromatography (2 to 4% $Et_2O$/PE) provided **33** as a clear oil (0.781 g, 2.21 mmol, 81%). $[\alpha]_D^{24} = 35.7$ ($c = 1.35$, $CH_2Cl_2$); IR (film): $\tilde{\nu} = 3072, 2930, 2857, 1590, 1472, 1428$ cm$^{-1}$; $^1$H NMR (500 MHz): $\delta = 7.69–7.66$ (m, 4H), 7.42–7.34 (m, 6H), 5.88 (dt, $J = 1.4, 6.1$ Hz, 1H), 5.75 (dt, $J = 2.4, 6.1$ Hz, 1H), 4.70–4.62 (m, 2H), 3.61 (d, $J = 10.0$ Hz, 1H), 3.55 (d, $J = 10.0$ Hz, 1H), 1.30 (s, 3H), 1.05 (s, 9H); $^{13}$C NMR (125 MHz): $\delta = 135.7, 135.6, 133.6,$ 131.9, 129.5, 127.6, 126.7, 90.5, 75.1, 69.8, 26.8, 22.8, 19.2.

**Preparation of (2*S*)-2-*tert*-butyldiphenylsiloxymethyl-2-phenyl-2,5-dihydrofuran (34)**: TBDPSCl (1.96 mL, 7.54 mmol) was added to a solution of alcohol **14c** (1.21 g, 6.86 mmol), imidazole (0.606 g, 8.90 mmol), and DMAP (25 mg, 0.20 mmol) in DMF (15 mL). The reaction mixture was stirred 45 min, diluted with $Et_2O$ (100 mL), washed with water (125, 50 mL) and brine (50 mL), dried ($Na_2SO_4$), and concentrated to give a tan oil. Flash chromatography (3 to 4% $Et_2O$/PE) provided **34** as a clear oil (2.76 g, 6.66 mmol, 97%). $[\alpha]_D^{24} = -17.9$ ($c = 1.25$, $CH_2Cl_2$); IR (film): $\tilde{\nu} = 3071,$ 2936, 2857, 1590, 1428, 1113, 1081, 701 cm$^{-1}$; $^1$H NMR (500 MHz): $\delta =$ 7.65–7.62 (m 2H), 7.59–7.56 (m, 2H), 7.41–7.18 (m, 11H), 6.06 (dt, $J = 2.4,$ 6.1 Hz, 1H), 5.99 (dt, $J = 1.2, 6.1$ Hz, 1H), 4.85 (dt, $J = 2.0, 12.9$ Hz, 1H), 4.73 (dt, $J = 2.0, 12.9$ Hz, 1H), 3.84 (s, 2H), 1.01 (s, 9H); $^{13}$C NMR (125 MHz): $\delta = 143.1, 135.6, 133.5, 130.0, 129.5, 128.0, 127.5, 127.0, 125.6,$ 94.0, 75.6, 70.2, 26.7, 19.2; elemental analysis calcd (%) for $C_{27}H_{30}O_2Si$: C 78.20, H 7.31; found: C 78.35, H 7.25.

**Preparation of (2*R*)-2-*tert*-butyldiphenylsiloxymethyl-2-methyl-2,3-dihydrofuran (35)**: A solution of **33** (0.775 g, 2.20 mmol) and $[H_2Ru(CO)(PPh_3)_3]$ (39.9 mg, 0.0435 mmol) in toluene (6.6 mL) was heated from rt to 80 °C for 1 h. The reaction mixture was concentrated and purified by flash chromatography (3% $Et_2O$/PE) to provide **35** as a clear film (0.759 g, 2.15 mmol, 98%). $[\alpha]_D^{24} = -48.3$ ($c = 1.0$, $CH_2Cl_2$); IR (film): $\tilde{\nu} = 2930, 2858,$ 1622, 1428, 1113, 1059, 701 cm$^{-1}$; $^1$H NMR (500 MHz): $\delta = 7.69–7.66$ (m, 4H), 7.44–7.36 (m, 6H), 6.20 (q, $J = 2.4$ Hz, 1H), 4.77 (q, $J = 2.4$ Hz, 1H), 3.59 (d, $J = 10.1$ Hz, 1H), 3.57 (d, $J = 10.1$ Hz, 1H), 2.68 (dt, $J = 2.4,$

15.1 Hz, 1H), 2.28 (dt, $J = 2.4$, 15.1 Hz, 1H), 1.36 (s, 3H), 1.06 (s, 9H); $^{13}$C NMR (125 MHz): $\delta = 144.4$, 135.7, 133.6, 129.6, 128.6, 98.6, 86.6, 68.9, 37.8, 26.8, 23.7, 19.4; elemental analysis calcd (%) for $C_{22}H_{28}O_2Si$: C 74.94, H 8.02; found: C 75.15, H 7.89.

**Preparation of (2*S*)-2-*tert*-butyldiphenylsiloxymethyl-2-phenyl-2,3-dihydrofuran (36)**: A solution of **34** (2.73 g, 6.58 mmol) and $[H_2Ru(CO)(PPh_3)_3]$ (125 mg, 0.136 mmol) in toluene (20 mL) was heated from rt to 70 °C for 4 h. The reaction mixture was concentrated and purified by flash chromatography (5% $Et_2O$/PE), and re-subjected to the reaction conditions except at 80 °C for 9 h. The reaction mixture was concentrated and purified by flash chromatography (3% $Et_2O$/PE) to provide **36** as a clear film (2.46 g, 5.94 mmol, 90%); $[\alpha]_D^{24} = -39.9$ ($c = 1.54$, $CH_2Cl_2$); IR (film): $\tilde{\nu} = 2930$, 2858, 1625, 1428, 1153, 1113, 1058, 700 cm$^{-1}$; $^1$H NMR (300 MHz): $\delta = 7.58$ (m, 2H), 7.51 (m, 2H), 7.43–7.16 (m, 11H), 6.39 (q, $J = 2.4$ Hz, 1H), 4.86 (q, $J = 2.4$ Hz, 1H), 3.81 (d, $J = 10.2$ Hz, 1H), 3.75 (d, $J = 10.2$ Hz, 1H), 3.15 (dt, $J = 2.4$, 15.0 Hz, 1H), 2.77 (dt, $J = 2.4$, 15.0 Hz, 1H), 1.00 (s, 9H); $^{13}$C NMR (75 MHz): $\delta = 144.5$, 144.4, 135.7, 135.6, 133.5, 133.3, 129.6, 129.5, 128.0, 127.6, 127.1, 125.7, 98.9, 89.8, 69.7, 38.5, 26.7, 19.3; elemental analysis calcd (%) for $C_{27}H_{30}O_2Si$: C 78.22, H 7.29; found: C 78.40, H 7.18.

**Preparation of thymidine analogue 37**: PhSeCl (17.1 mg, 0.0893 mmol) was added to a solution of **35** (24.4 mg, 0.0692 mmol) in dioxane (0.5 mL), and allowed to react for 45 min. To the resultant solution was added bis(trimethylsilyl)thymine (37.2 g, 0.138 mmol), followed by $InCl_3$ (1.7 mg, 0.0077 mmol). The reaction mixture was stirred for 3 h, diluted with sat aq $NaHCO_3$ (7 mL), and extracted with $CH_2Cl_2$ (2 × 8 mL). The combined organic layers were dried ($Na_2SO_4$), concentrated, and purified by flash chromatography (30% $Et_2O$/PE) to give an impure mixture of selenides as a clear film (35 mg). This mixture was dissolved in THF (0.8 mL), and pyridine (12 μL) and 30% $H_2O_2$ (16 μL) was added. The mixture was stirred for 45 min, concentrated, and and purified by flash chromatography (40% $Et_2O$/PE) to afford a 7:1 mixture of isomeric products as a clear film (23.0 mg, 0.0483 mmol, 70%). Material from other runs was combined and re-purified by flash chromatography (15% $Et_2O$/PE, 2.5% IPA) to provide pure **37*α*** and tentatively identified **37*β*** as a clear films. Both could be crystallized from EtOAc/PE. **37*β***: m.p. 97–102 °C; $[\alpha]_D^{24} = 74.1$ ($c = 1.0$, $CH_2Cl_2$); IR (film): $\tilde{\nu} = 3182$, 1694, 1471, 1428, 1252, 1113, 1082, 703 cm$^{-1}$; $^1$H NMR (500 MHz): $\delta = 8.52$ (br s, 1H), 7.67–7.64 (m, 4H), 7.44–7.38 (m, 6H), 7.03 (s, 2H), 6.25 (d, $J = 6.0$ Hz, 1H), 5.80 (d, $J = 6.0$ Hz, 1H), 3.64 (d, $J = 10.3$ Hz, 1H), 3.58 (d, $J = 10.3$ Hz, 1H), 1.92 (s, 3H), 1.40 (s, 3H), 1.06 (s, 9H); $^{13}$C NMR (125 MHz): $\delta = 163.6$, 150.6, 139.2, 135.6, 135.4, 133.0, 132.9, 129.8, 127.7, 125.4, 111.1, 91.7, 90.0, 69.5, 26.8, 22.7, 19.2, 12.6.

**37*α***: m.p. 137–141 °C; $[\alpha]_D^{24} = 4.30$ ($c = 1.0$, $CH_2Cl_2$); IR (film): $\tilde{\nu} = 3184$, 1691, 1113, 1081, 703 cm$^{-1}$; $^1$H NMR (300 MHz): $\delta = 8.25$ (br s, 1H), 7.66–7.60 (m, 4H), 7.45–7.34 (m, 6H), 7.13 (s, 1H), 6.99 (s, 1H), 6.34 (dd, $J = 1.8$, 6.0 Hz, 1H), 5.78 (d, $J = 6.0$ Hz, 1H), 3.77 (d, $J = 10.7$ Hz, 1H), 3.72 (d, $J = 10.7$ Hz, 1H), 1.41 (s, 3H), 1.35 (s, 3H), 1.07 (s, 9H); $^{13}$C NMR (75 MHz): $\delta = 163.9$, 151.0, 139.5, 135.6, 135.4, 135.3, 133.3, 132.7, 130.0, 129.9, 127.8, 127.7, 124.8, 111.0, 91.7, 89.1, 69.2, 26.9, 23.2, 19.4, 11.8; elemental analysis calcd (%) for $C_{27}H_{32}N_2O_4Si$: C 68.02, H 6.78, N 5.88; found: C 67.81, H 6.75, N 5.84.

**Preparation of thymidine analogue 42**: TBAF (1.0 M in THF, 57 μL, 0.057 mmol) was added to a solution of **37** (22.7 mg, 0.0476 mmol) in THF (0.40 mL). The resultant solution was stirred 2.5 h, concentrated, and purified by flash chromatography (80% EtOAc/PE) to afford **42** as a white solid (10.8 mg, 0.0453 mmol, 95%). M.p. 180–182 °C; $[\alpha]_D^{24} = -64.3$ ($c = 1.0$, MeOH); IR (film): $\tilde{\nu} = 3420$, 1694, 1472, 1083 cm$^{-1}$; $^1$H NMR ($D_2O$, 300 MHz): $\delta = 7.61$ (s, 1H), 6.89 (s, 1H), 6.37 (dd, $J = 1.6$, 6.0 Hz, 1H), 5.85 (d, $J = 6.0$ Hz, 1H), 3.66 (d, $J = 12.7$ Hz, 1H), 3.51 (d, $J = 12.7$ Hz, 1H), 1.79 (s, 3H), 1.25 (s, 3H); $^1$H NMR ($CD_3OD$, 500 MHz): $\delta = 7.82$ (d, $J = 1.2$ Hz, 1H), 6.95 (d, $J = 1.5$ Hz, 1H), 6.35 (dd, $J = 2.0$, 6.1 Hz, 1H), 5.84 (dd, $J = 1.2$, 6.1 Hz, 1H), 3.65 (d, $J = 12.0$ Hz, 1H), 3.57 (d, $J = 12.0$ Hz, 1H), 1.83 (d, $J = 1.5$ Hz, 1H), 1.26 (s, 3H); $^{13}$C NMR ($CD_3OD$, 125 MHz): $\delta = 166.7$, 153.0, 140.8, 139.2, 126.2, 110.9, 93.6, 90.5, 67.7, 23.3, 12.4.

**Preparation of uridine analogue 45**: PhSeCl (26.5 mg, 0.138 mmol) was added to a solution of **36** (44.2 mg, 0.107 mmol) in dioxane (0.5 mL) and allowed to react for 45 min. To the resultant solution was added bis(trimethylsilyl)uracil (54.5 mg, 0.213 mmol), followed by $InCl_3$ (2.7 mg, 0.012 mmol). The reaction mixture was stirred for 3 h, diluted with sat aq $NaHCO_3$ (5 mL), and extracted with $CH_2Cl_2$ (2 × 7 mL). The combined organic layers were dried ($Na_2SO_4$), concentrated, and purified by flash chromatography (25% EtOAc/PE) to give an impure mixture of selenides as a yellow film (50 mg). This mixture was dissolved in THF (0.5 mL), and pyridine (18 μL) and 30% $H_2O_2$ (25 μL) were added. The mixture was stirred for 1 h, concentrated, and purified by flash chromatography (33% EtOAc/PE) to afford a 9:1 mixture of C-1′ isomeric products **40*α*:*β*** as a clear film (37.3 mg, 0.0711 mmol, 67%). **40*α***: $^1$H NMR (500 MHz): $\delta = 8.63$ (br s, 1H), 7.96 (d, $J = 8.0$ Hz, 1H), 7.68 (m, 2H), 7.62 (m, 2H), 7.57–7.29 (m, 11H), 7.08 (s, 1H), 6.57 (dd, $J = 2.0$, 5.8 Hz, 1H), 5.87 (dd, $J = 1.3$, 5.8 Hz, 1H), 4.02 (s, 2H), 1.11 (s, 9H). A solution of TBAF (1 M in THF, 0.34 mL, 0.34 mmol) was added to a solution of a 6:1 mixture of C-1′ isomeric ethers **40*α*:*β*** (0.150 g, 0.285 mmol) in THF (1.5 mL), and stirred for 90 min. The mixture was concentrated and purified by flash chromatography (EtOAc to 7% MeOH/$CH_2Cl_2$ gradient elution) to afford a 6:1 mixture of **45*α*:*β*** as a white foam. Further purification by preparative HPLC (5% to 95% 0.1% TFA/$H_2O$/MeOH over 35 min, 20 mL min$^{-1}$) gave C-1′ **45*β*** (10.3 mg, 0.0360 mmol, 13%) as a white solid, and **45*α*** (69.1 mg, 0.241 mmol, 85%) as a white foam.

**45*α***: m.p. 173–177 °C (decomp); $[\alpha]_D^{24} = -60.1$ ($c = 0.5$, acetone); IR (film): $\tilde{\nu} = 3424$, 3060, 1694, 1466, 1377, 1263 cm$^{-1}$; $^1$H NMR ([D$_6$]acetone, 500 MHz): $\delta = 10.07$ (br s, 1H), 8.11 (d, $J = 8.1$ Hz, 1H), 7.50–7.47 (m, 2H), 7.38–7.34 (m, 2H), 7.29–7.26 (m, 1H), 7.01 (t, $J = 1.4$ Hz, 1H), 6.80 (dd, $J = 2.0$, 6.0 Hz, 1H), 5.97 (ddd, $J = 0.5$, 1.4, 6.0 Hz, 1H), 5.59 (d, $J = 8.1$ Hz, 1H), 4.50 (br s, 1H), 3.97 (d, $J = 12.0$ Hz, 1H), 3.72 (d, $J = 12.0$ Hz, 1H); $^{13}$C NMR (125 MHz): $\delta = 163.9$, 151.8, 142.8, 142.5, 138.9, 129.2, 128.2, 126.3, 126.1, 102.2, 96.6, 90.1, 68.4; elemental analysis calcd (%) for $C_{15}H_{14}N_2O_4$: C 62.92, H 4.94, N 9.79; found: C 62.75, H 5.19, N 9.53; chiral HPLC analysis indicates 87% *ee* (Chiralcel OJ, 70:30 hept/IPA, 0.2 mL min$^{-1}$, $t_R$((+)-isomer) = 52.0 min, $t_R$((−)-isomer) = 57.8 min). **45*β***: $^1$H NMR ([D$_6$]acetone, 500 MHz): $\delta = 7.45–7.43$ (m, 2H), 7.37–7.34 (m, 2H), 7.30–7.27 (m, 1H), 7.14 (t, $J = 1.5$ Hz, 1H), 6.84 (dd, $J = 2.0$, 5.9, Hz, 1H), 6.82 (d, $J = 8.0$ Hz, 1H), 6.03 (dd, $J = 1.5$, 5.9 Hz, 1H), 5.39 (d, $J = 8.0$ Hz, 1H), 3.75 (d, $J = 11.7$ Hz, 1H), 3.68 (d, $J = 11.7$ Hz, 1H).

**Preparation 6-chloropurine analogue 46**: Neat PhSeCl (58.5 mg, 0.305 mmol) was added to a solution of **36** (98.0 mg, 0.236 mmol) in dioxane (1.0 mL), and stirred 15 min. A solution of (TMS)-6-chloropurine (0.32 M in dioxane, 1.5 mL, 0.48 mmol) was added, followed by addition of $InCl_3$ (63.3 mg, 0.286 mmol). The reaction mixture was stirred 3 h, diluted with sat aq $NaHCO_3$ (7 mL), and extracted with $CH_2Cl_2$ (3 × 6 mL). The combined organic layers were dried ($Na_2SO_4$), concentrated, and purified by flash chromatography (25% EtOAc/PE) to give an impure mixture of selenides as a yellow oil (0.33 g). This mixture was dissolved in THF (1 mL), and pyridine (30 μL) and 30% $H_2O_2$ (41 μL) were added. The mixture was stirred for 1 h, concentrated, and purified by flash chromatography (33% EtOAc/PE) to afford a 4.4:1 mixture of C-1′ isomeric products **41*α*:*β*** as a clear film (111 mg, 0.196 mmol, 83%). **41*α***: $^1$H NMR (300 MHz): $\delta = 8.75$ (s, 1H), 8.42 (s, 1H), 7.60–7.25 (m, 15H), 7.20 (s, 1H), 6.70 (dd, $J = 1.9$, 6.0 Hz, 1H), 6.10 (dd, $J = 1.0$, 6.0 Hz, 1H), 3.99 (d, $J = 11.0$ Hz, 1H), 3.94 (d, $J = 11.0$ Hz, 1H), 1.02 (s, 9H).

A solution of TBAF (1 M in THF, 61 μL, 0.061 mmol) was added to a solution of a 5:1 mixture of **41*α*:*β*** (31.8 mg, 0.0560 mmol) in THF (0.5 mL), and stirred for 90 min. The mixture was concentrated and purified by flash chromatography (2% MeOH/$CH_2Cl_2$) to afford a 5:1 mixture of **46*α*:*β*** as a white foam (18.4 mg, 0.560 mmol, 100%). Repurification of a sample of this mixture by flash chromatography (80% EtOAc/PE) afforded pure alcohol **46*α*** as a clear film: $[\alpha]_D^{24} = -152.9$ ($c = 1.0$, $CH_2Cl_2$); IR (film): $\tilde{\nu} = 3356$, 2924, 1592, 1565, 1488, 1397, 1336, 1197, 1088 cm$^{-1}$; $^1$H NMR (500 MHz): $\delta = 8.77$ (s, 1H), 8.56 (s, 1H), 7.47–7.33 (m, 5H), 7.15 (s, 1H), 6.80 (dd, $J = 2.1$, 6.1 Hz, 1H), 6.06 (d, $J = 6.1$ Hz, 1H), 4.39 (br s, 1H), 4.00 (m, 2H); $^{13}$C NMR (125 MHz): $\delta = 152.0$, 151.4, 151.2, 144.7, 140.1, 138.3, 132.2, 128.7, 128.1, 125.1, 124.6, 97.3, 89.5, 68.5; HRMS: *m*/*z*: calcd for $C_{11}H_{11}O_2$: 175.0759; found: 175.0762 [$M^+ - C_5H_2ClN_4$].

**Preparation of adenosine analogue 48**: A solution of **46*α*** (13.9 mg, 0.423 mmol) in $NH_3$/MeOH (satd at 0 °C, 0.5 mL) was heated in a sealed vial to 60 °C for 26 h. M.p. 196–199 °C (decomp); $[\alpha]_D^{24} = -176.7$ ($c = 0.5$, MeOH); IR (film): $\tilde{\nu} = 3176$, 2922, 1651, 1600, 1472, 1418, 1205, 1089, 1061 cm$^{-1}$; $^1$H NMR (500 MHz): $\delta = 8.31$ (s, 1H), 8.00 (s, 1H), 7.48–7.45 (m, 2H), 7.43–7.39 (m, 2H), 7.36–7.32 (m, 1H), 7.03 (m, 1H), 6.78 (dd, $J = 1.8$, 5.9 Hz, 1H), 6.01 (dd, $J = 1.2$, 5.9 Hz, 1H), 5.82 (br s, 2H), 4.03 (d, $J = 12.9$ Hz, 1H), 3.99 (d, $J = 12.9$ Hz, 1H); $^{13}$C NMR (125 MHz): $\delta = 155.4$, 152.9, 149.1, 140.5, 140.0, 138.0, 128.7, 128.0, 125.1, 124.7, 120.0, 97.6, 89.6,

68.8; elemental analysis calcd (%) for $C_{16}H_{15}N_5O_2$: C 62.12, H 4.90, N 22.64; found: C 62.33, H 4.86, N 22.39.

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