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Access to Oxetane-Containing *psico*-Nucleosides from 2-Methyleneoxetanes: A Role for Neighboring Group Participation?

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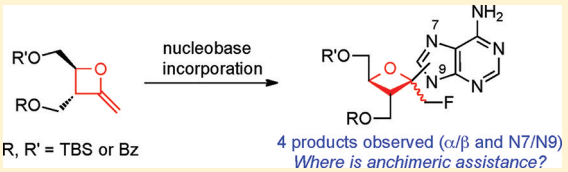
Supporting Information

ABSTRACT: The first *psico*-oxetanocin analogue of the powerful antiviral natural product, oxetanocin A, has been readily synthesized from *cis*-2-butene-1,4-diol. Key 2-methyleneoxetane precursors were derived from β-lactones prepared by the carbonylation of epoxides. F^+-mediated nucleobase incorporation provided the corresponding nucleosides in good yield but with low diastereoselectivity. Surprisingly, attempted exploitation of anchimeric assistance to increase the selectivity was not fruitful. A range of 2-methyleneoxetane and related 2-methylenetetrahydrofuran substrates was prepared to explore the basis for this. With one exception, these substrates also showed little stereoselectivity in nucleobase incorporation. Computational studies were undertaken to examine if neighboring group participation involving fused [4.2.0] or [4.3.0] intermediates is favorable.



INTRODUCTION

Oxetanocin A (OXT-A; Figure 1), an unusual nucleoside with an oxetanosyl sugar, was isolated in 1986 from the fermentation broth of *Baccilus megaterium*.[1] Because of its potent inhibition of HSV-1, HSV-2, HCMV, and HIV-1,[2] interest in the synthesis and biological evaluation of OXT-A and related analogues was intense over the next decade.[3] For example, base-modified OXTs, such as the thymine analogue, OXT-T, showed promising activity against VZV, HSV-1, and HSV-2,[4] while the guanine congener, OXT-G, inhibited HBV[5] and HCMV[6] replication. With the exception of cyclopropyl-containing carbocyclic nucleoside **1**, all of the oxetanocin analogues evaluated were derivatives of reducing sugars. We have become interested in exploring the biological potential of nonreducing (*psico*)-nucleosides containing an oxetanosyl sugar moiety.[7] Herein we report a straightforward route to the first *psico*-oxetanocin, 1′-fluoromethyl-OXT-A (**2**), and describe experimental and theoretical studies on the potential of using anchimeric assistance to enhance the diastereoselectivity in nucleobase incorporation.

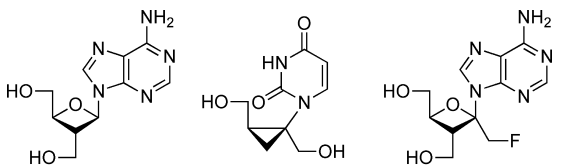


Figure 1. Structures of oxetanocin A and related *psico*-nucleosides.

Our interest in oxetane-containing *psico*-nucleosides grew out of our discovery that 1,5-dioxaspiro[3.2]hexanes **4** provided oxetane intact products **6** (Figure 2),[8] presumably via oxonium

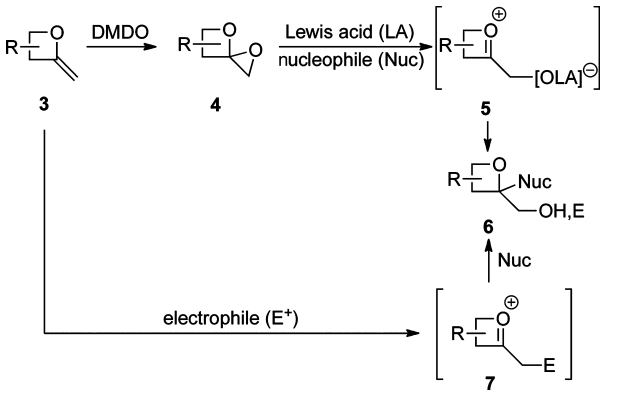


Figure 2. Pathways to oxetane-intact products from dioxaspirohexanes **4** or 2-methyleneoxetanes **3**.

ions **5**, in the presence of certain Lewis acids (including protons). In particular, we reported that aromatic heterocycles could be incorporated,[9] and extension to the coupling with nucleobases seemed logical. We have prepared hydroxymethyl-branched *psico*-nucleosides by this pathway, and results will be reported in due course. However, we also recognized that it should be possible to directly access oxonium ions **7**, related to **5**,

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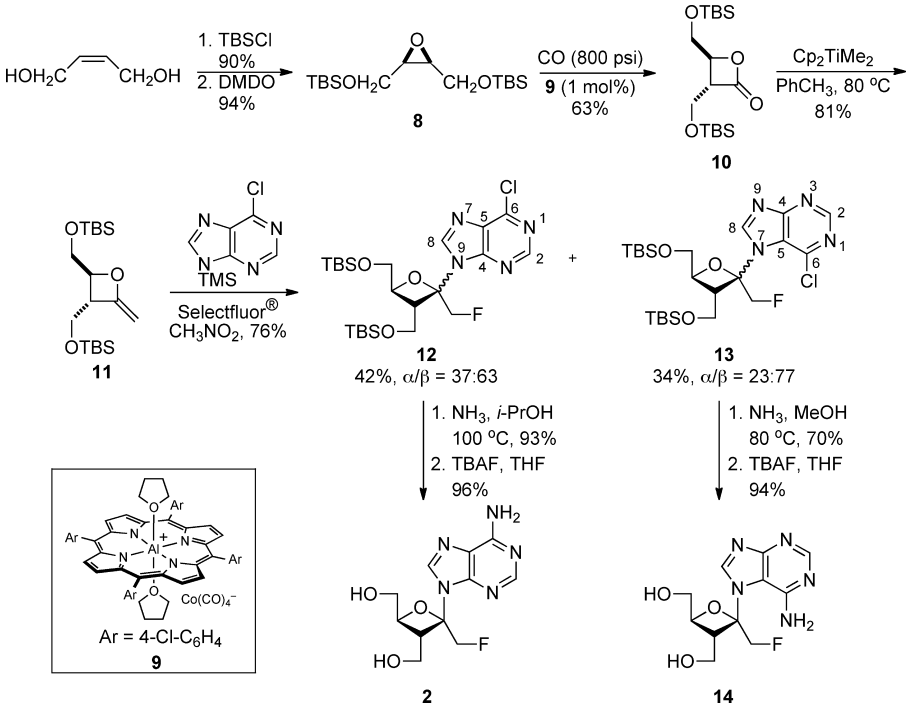
Scheme 1



from 2-methyleneoxetanes **3**, the precursors of the dioxaspirohexanes **4**. We decided to explore this option using an electrophilic fluorine source to prepare a direct analogue **2** of OXT-A. A related incorporation of a nucleobase onto a 2-methylenetetrahydrofuran using Selectfluor, a F^+ source, had been reported.[10]

RESULTS AND DISCUSSION

Silyl-protected 2-methyleneoxetane **11** was chosen as the substrate for exploring the feasibility of F^+-mediated generation of oxonium ions **7** (E = F). 2-Methyleneoxetane **11** was prepared in a straightforward, four-step procedure from *cis*-2-butene-1,4-diol (Scheme 1). Standard silyl protection and epoxidation by dimethyldioxirane (DMDO) of butenediol provided epoxide **8**. High-pressure carbonylation using catalyst **9** gave β-lactone **10** in good yield,[11] illustrating the significant practical utility of this approach to β-lactones. Methylenation[12] of **10** provided methyleneoxetane **11** efficiently.

Fluorine-mediated nucleobase incorporation of **11** gave a mixture of products. Initial purification provided a mixture of four *psico*-nucleosides in a ratio of 3:3:2:1 and in a total yield of 76%, demonstrating that the formation and capture of the oxonium ion from **11** was effective. The ratio of isomers was calculated from the ^{1}H NMR spectrum of the crude reaction mixture. In addition to the alternative facial diastereomers of **12**, the two other products were diastereomeric purine regioisomers **13** (connected at N7, rather than N9). Alkylation at N7 is known to take place in competition with N9 alkylation.[13] It is also possible that transglycosylation could occur, which could result in isomerization at the anomeric center.[14] However, we believe this is unlikely based on later results described in this paper. Further purification provided **12** (N9) as a 37:63 mixture and **13** (N7) as a 23:77 mixture, both favoring the desired β isomers. The assignment of regioisomers was determined based on purine ^{13}C NMR chemical shifts. It has been reported that the C4 and C5 chemical shifts are fairly characteristic and that they can be used to differentiate the two sets of isomers. C4 chemical shifts are less than 155 ppm, and C5 chemical shifts are greater than 120 ppm in N9-substituted isomers (the corresponding N7 isomer shifts are generally over 160 ppm and under 120 ppm).[15] On the basis of the ratio deduced from ^{1}H NMR and the quantity of material isolated, the desired nucleoside **12**-β was determined to have been formed in 27% yield. Mixtures **12** and **13** were subjected to amine substitution,[16] followed by TBS cleavage. Separation of the β isomers from their α/β mixtures was achieved either at the last stage or after amination, affording the target molecule **2** and its regioisomer **14** in good yields. The relative stereochemistry of both **2** and **14** was confirmed by NOESY studies.[17] This seven-step sequence provided rapid, straightforward access to the target *psico*-nucleoside **2** from the simple starting material, *cis*-2-butene-1,4-diol. More importantly, the approach suggested that nucleobase incorporation using F^+ to generate an oxetane oxonium ion was effective, with good conversion to nucleoside product.

Although encouraged by the efficiency of nucleobase incorporation, the diastereoselectivity of this step was not satisfying. We anticipated that a benzoyl group on the C3 hydroxymethyl moiety would provide anchimeric assistance, enhancing the desired stereoselectivity of the transformation. Although low yields were obtained, Yamamura and co-workers[18] proposed transition states with neighboring group participation for the key glycosyl bond formation step, in a synthesis of OXT-A.

To examine the potential of exploiting neighboring group participation, β-lactone **15a** (Table 1, entry 1) was prepared from dibenzoylated *cis*-2-buten-1,4-diol by the same sequence as had been used for TBS-protected β-lactone **10** (Scheme 1). It is noteworthy that the high-pressure carbonylation proceeded in lower yield (48%) and required higher catalyst loading (5%). Methylenation gave a moderate yield of 2-methyleneoxetane

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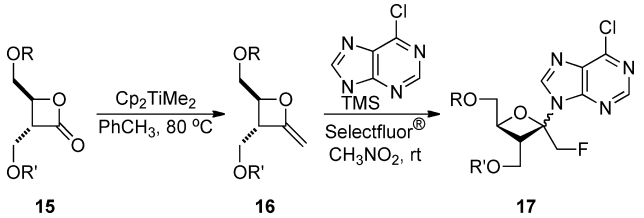
Table 1. Investigation of Anchimeric Assistance from C3 and/or C4 Benzoyl Groups of 2-Methyleneoxetanes



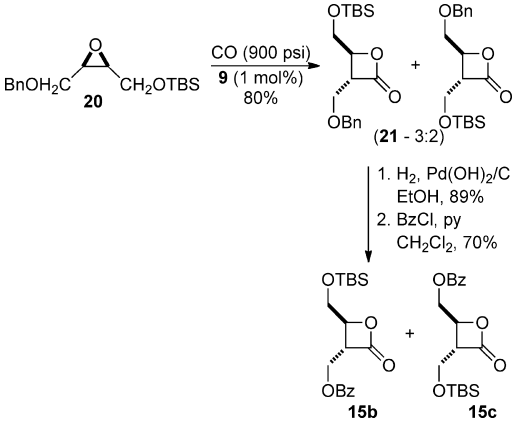
entry	R, R′	lactone	**16** (% yield)	**17** (% yield)	product ratio[a]
1	R, R′ = Bz	**15a**	**16a** (48)	**17a** (<20)	
2	R = TBS, R′ = Bz	**15b**	**16b** (75)	**17b** (53)	4:3:3:2
3	R = Bz, R′ = TBS	**15c**	**16c** (60)	**17c** (45)	4:2:1:1

[a]Product ratios were determined by a combination of the crude ^{1}H NMR and the masses of the products isolated. Both N7 and N9 nucleosides were isolated.

16a. Fluorine-mediated nucleobase incorporation of this provided a complex, low yielding mixture of products. Possible side reactions may include hydrolysis of **16a** or elimination of one benzoyloxy substituent, followed by ring expansion.[19] Complete separation of **17a** proved impossible; however, the purine-containing fractions were carried to the next stage, a one-pot deprotection/amine incorporation. Nucleoside **14** was the only clean product isolated in 4% yield from **16a**. The poor efficiency of this route suggested that the anchimeric assistance might not play a role in this substrate. Alternatively, it was possible that opposing participation pathways were in effect. Either fused oxonium ion **18** or bridged ion **19** could, in theory, be involved in the conversion of **16a** to nucleoside products (Figure 3).

In order to probe whether fused or bridged anchimeric assistance might be involved, 2-methyleneoxetanes **16b** and **16c**, with different protecting groups on the C3 and C4 hydroxymethyl groups, were prepared from β-lactones **15b** and **15c**. The lactones were prepared from known, differentially protected epoxide **20**[20] (Scheme 2). Carbonylation of **20**

Scheme 2



provided an inseparable 3:2 mixture of β-lactones **21**. Although the lactones were again inseparable after hydrogenolysis, benzoylation provided readily separated β-lactones **15b** and **15c**. Methylenation gave 2-methyleneoxetanes **16b** and **16c**, which were reacted with Selectfluor and 6-chloropurine under conditions identical to those used for **16a**. Although cleaner than that of **16a** and more efficient, the reaction of **16b** (Table 1, entry 2) provided multiple purine-containing products. Three nucleosides were isolated, and a fourth was contaminated with other byproducts. All four nucleosides clearly showed purine and fluorine incorporation. 2-Methyleneoxetane **16c**, which possesses a benzoyl group on the C4 position, would be expected to induce a bias to the opposite face through a bridged transition state (see Figure 3, **19**). However, nucleobase incorporation again

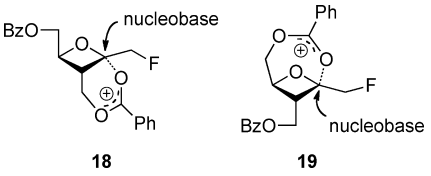


Figure 3. Plausible oxonium ions from **16a**.

proceeded in modest yield with multiple nucleoside products (Table 1, entry 3). Although the outcomes with **16b** and **16c** were somewhat better than that with **16a**, neither showed the high selectivity that is a hallmark of effective neighboring group participation.

In light of the conclusion that anchimeric assistance did not appear to play a role in the reactions of 2-methyleneoxetanes **16**, we wondered if this was because of ring strain in the four-membered ring in intermediates related to **18**/**19**. To probe whether releasing the ring strain from oxetanes by substituting tetrahydrofurans might propel the transition states toward closed forms (fused or bridged), 2-methylenetetrahydrofurans (THFs) **22**–**25** (Table 2) were prepared as THF analogues to access the types of oxonium ion intermediates we had anticipated for **16** (see Figure 3).

The γ-lactone precursors **26**–**29** of 2-methylene-THFs **22**–**25** were prepared as shown in Scheme 3. γ-Lactone **26** was synthesized from known γ-butyrolactone **30**,[21] while lactone **27** was prepared via benzoylation of known 4-hydroxy-γ-butyrolactone (**31**).[22] The synthesis of *cis*-γ-lactone **28** started with the alkylation of diester **32**,[23] which predominantly gave *anti*-product **33** in moderate yield. Chemoselective reduction provided diol **34**, which was cyclized to afford γ-lactone **35**. Deprotection followed by benzoylation of the resulting diol gave **28** in moderate yield.[24] The synthesis of *trans*-γ-lactone **29** involved direct alkylation of γ-butyrolactone **31**, which favored the desired diastereomer **36**. Standard deprotection/protection provided lactone **29**.

2-Methylene-THFs **22**–**25**, obtained from chemoselective methylenation of the corresponding lactones **26**–**29**, were subjected to the Selectfluor-mediated nucleobase incorporation conditions used for the 2-methyleneoxetanes, and the outcomes are summarized in Table 2. 2-Methylenetetrahydrofuran **22** underwent F^+-mediated purine incorporation in 43% yield, with the isolation of four nucleoside products in a ratio of 5:3:3:1 (entry 1). The ratios were determined from ^{1}H NMR of the crude reaction mixture, where product purine protons can be clearly distinguished. The identification of product purine peaks in the crude NMR was based on the isolation of two sets of product mixtures in an analogous fashion to the oxetanosyl nucleosides. This result indicated that the six-membered closed-ring transition state might again not be an important contributor in the case of the 2-methylene-THFs. An important role for the bridged transition state (analogous to **19**) was also discounted due to the low facial

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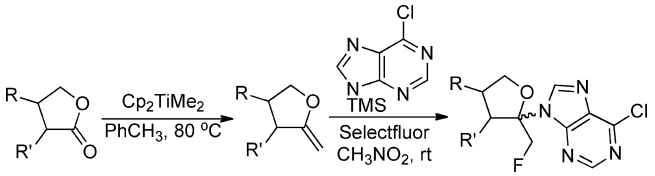
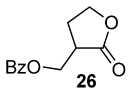
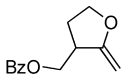
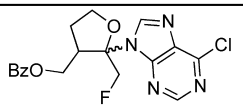
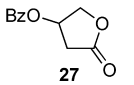
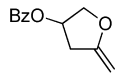
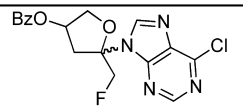
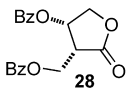
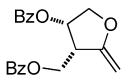
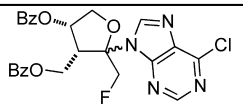
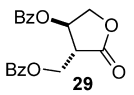
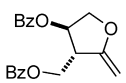
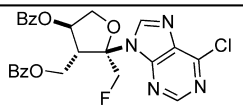
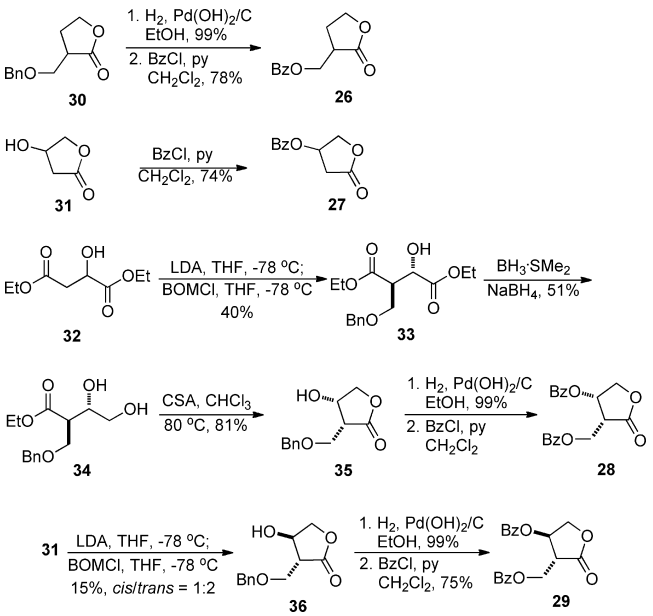
Table 2. Investigation of Anchimeric Assistance in 2-Methylenetetrahydrofurans



entry	lactone	2-methylene THF (%yield)	product (%yield, product ratio)[a]
1	 **26**	 **22** (54%)	 (43%, ca. 5:3:3:1 dr)
2	 **27**	 **23** (48%)	 (76%, ca. 1:1 dr)
3	 **28**	 **24** (22%)[b]	 (66%)[c]
4	 **29**	 **25** (58%)	 **37** (72%, >20:1 dr)

[a]See text for discussion. [b]Yield calculated over three steps from **35** (see ref 24 for details). [c]Crude ^{1}H NMR showed multiple products.

Scheme 3



diastereoselectivity (~1:1 dr of N9 isomers only; no N7 isomers observed) of the reaction with **23** (entry 2). This lack of observation of N7 isomers is a clear indication that the formation of the *psico*-nucleosides was irreversible and suggests that their presence in other reactions was not due to transglycosylation under these reaction conditions. Although the reaction of 2-methylene-THF **24**, having *cis*-substituents, proceeded in good overall yield, there were multiple nucleoside products, again suggesting that anchimeric assistance had not played a major role (entry 3). Surprisingly, the *trans*-isomer **25** produced predominantly **37** in 72% yield (entry 4). Thus, with the exception of 2-methylenetetrahydrofuran **25**, which will be discussed further below, it appeared that neither the 2-methyleneoxetanes nor the 2-methylene-THFs reacted along pathways that had significant involvement of oxonium ions stabilized by neighboring groups. We decided to examine this further from a quantum mechanics standpoint.

With the possible exception of compound **25**, anchimeric assistance apparently does not govern the outcome of these fluorine-mediated nucleobase incorporation reactions. One potential explanation is that the invocation of anchimeric assistance rests on the assumption that the oxonium ions shown in Figure 3 are more stable than the corresponding open forms of these cations. However, if that were not the case (i.e., if the cations were only equally stable to the open carbocations, or even less stable), then anchimeric assistance would not dictate the stereochemical outcome. The fluorination reactions would proceed partially or entirely through open carbocations that would not be expected to show a strong stereochemical preference in their reactivity. Since there is no convincing literature evidence for remote neighboring group participation (e.g., **19**),[25] we decided to focus on the more likely fused intermediate **18**.

Electronic structure calculations were used to evaluate the relative stability of open and fused carbocations. In order to

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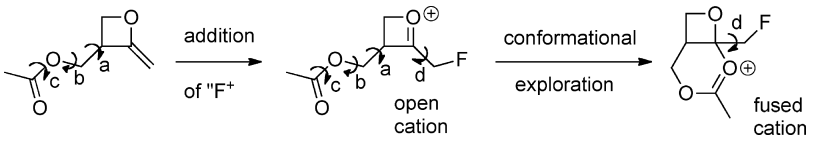

Figure 4. Rotatable bonds in oxetane precursor and in corresponding open and fused oxonium ions.

reduce computational time, the benzoyl group was replaced with an acetyl group in the system shown in Figure 4. If the fused structure were more stable than the open structure, anchimeric assistance would be expected to yield a strong stereochemical effect on the outcome of the reaction. On the other hand, if the open form were more stable, no such behavior would be expected.

Referring to "the open form" in fact oversimplifies the matter since different conformations are possible about the four dihedral angles marked a, b, c, and d in Figure 4. In order to address the matter in a thorough fashion, calculations were performed on all possible structures. The three dihedral angles a, b, and d were given starting values of ±60 and 180° and the dihedral angle c starting values of 0 (*Z*) and 180° (*E*), for a total of 54 (3 × 3 × 3 × 2) starting structures. The starting material was treated in like fashion (18 starting structures), as was the fused cation (3 starting structures).

The calculations indicated that, indeed, as one would expect, the fused cation is more stable than the open structure, and by a large amount (~10 kcal/mol), for both the four-membered ring system shown above and also for the corresponding five-membered ring system. The calculations thereby reject lack of stability of the fused cations as an explanation for the lack of stereospecificity. The involvement of *trans*-fused cations was also considered. For the oxetane system, the most stable *trans*-fused intermediate is some 21 kcal/mol higher in energy than the most stable *cis*-fused intermediate (Figure 5a). Further-

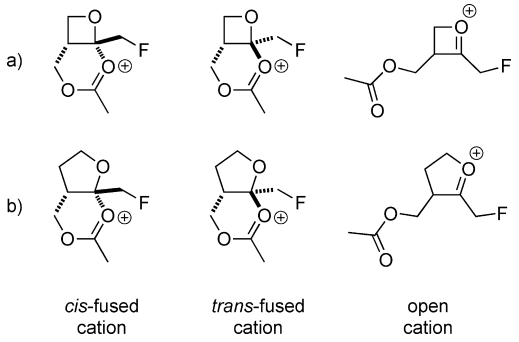

Figure 5. Plausible *cis*-fused, *trans*-fused, and open monocyclic intermediates.

more, the most stable *trans*-fused intermediate is 2.5 kcal/mol higher in energy than even the LEAST stable conformation of the open (non-anchimerically assisted) cation. In the five-membered ring (THF) system, the most stable *trans*-fused intermediate is 11 kcal/mol higher in energy than the most stable *cis*-fused structure (Figure 5b). In this case, it is more stable than most of the conformations of the open cation and only 0.5 kcal/mol higher in energy than the most stable monocyclic conformation. Thus, it is not entirely unreasonable to imagine that the *trans*-fused structure might participate if there were some kinetic barrier that hindered formation of the much more stable *cis*-fused structure. Nevertheless, it does not seem likely that a competition between *cis*- and *trans*-fused cations explains the lack of stereoselectivity in most of the THF cases. A full tabulation of the calculated energies for the starting compounds and for the cation intermediates appears in the Supporting Information.

It is possible that solvent plays a major role in relative stabilization of the oxonium ion intermediates or in the efficiency of formation of the fused species. The calculations were conducted without taking solvent into account. The nucleobase incorporation reaction of 2-methyleneoxetane **15b** was repeated in acetonitrile, DMF, and 1,2-dichloroethane. The outcomes were essentially unchanged in comparison to that in nitromethane.

What else might explain the experimentally observed behavior? Anchimeric assistance is a well-documented phenomenon and is used extensively to guide stereochemistry in the synthesis of carbohydrates and similar structures. However, the commonly used cases differ from the structures considered here in one important way: normally, the fused ions are five-membered rings, not six- or seven-membered rings.

In the more usual case, illustrated in Figure 6, only two dihedral angles, a and c, describe the conformational space

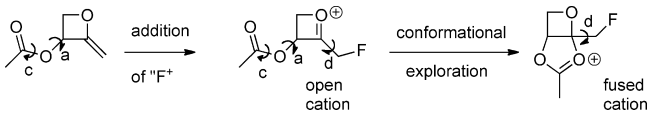

Figure 6. Rotatable bonds in oxetane precursor and in the corresponding open and fused oxonium ions for five-membered systems.

available to the starting material and to the "open" cation. In the oxetanocin-type systems, however (Figure 4), three dihedral angles—a, b, and c—describe the space. This difference might matter if the carbocationic intermediate is very short-lived. Normally, one assumes that an intermediate exists sufficiently long that it will adopt the most favorable conformation before reacting. However, the intermediate carbocation might in fact be so reactive that the time scale for its reaction with a nucleophile is of the same order as the time scale for conformational exploration of the dihedral angles a, b, and c. The more traditional systems that form a five-membered cycle have an advantage, essentially entropic in nature, in that the cation needs only to explore rotation around two dihedral angles, a and c, in order to find the most stable cyclic structure. In fact, it is really only one dihedral angle because the angle marked c has a very strong preference for a *Z* arrangement, such that the *E* conformations can for most practical purposes be neglected.

The systems we examined, however, require exploration around both the angles marked a *and* b (c can be neglected, again, because of the strong preference for a *Z* conformation). Crudely speaking, nine conformations (3 × 3) need to be explored, instead of just three. It is worth noting that, in the neutral starting materials, the most stable conformations are

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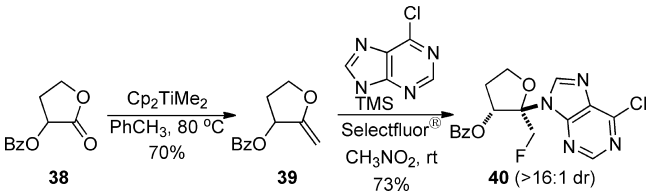
ones in which the acetoxy oxygen is far from the carbon to which a bond must be formed in the fused carbocation structure.

To examine experimentally if a five-membered oxonium-fused cation is involved in fluorine-mediated nucleobase incorporation of α-methylene cyclic ethers, methylene-THF **39**, derived from readily prepared γ-lactone **38**, was treated with Selectfluor and 6-chloropurine. Diastereomer **40** was isolated in very good yield (Scheme 4). This outcome supports an

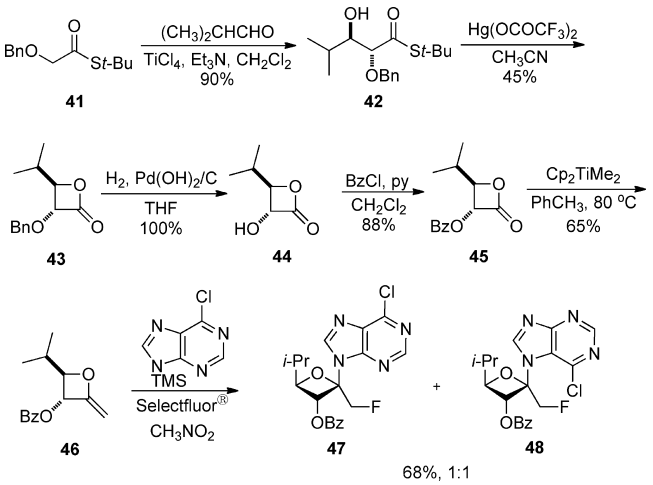
Scheme 4



important role for anchimeric assistance in methylene-THF systems.

In order to further investigate if a five-membered oxonium bridge can be also formed in methyleneoxetane systems, the preparation of a β-lactone related to γ-lactone **38** was attempted. Several synthetic strategies were explored, including [2 + 2] reaction of aldehydes and ketene precursors, direct hydroxylation of β-lactones, the synthesis of α-silyl-β-lactones for Fleming–Tamao oxidation, and the preparation of α-benzoyloxy-β-hydroxy acids for lactonization. None of these provided adequate materials for further transformations to the desired α-benzoyloxy-β-lactones. Finally, a titanium enolate aldol condensation using thioester **41** and isobutyraldehyde provided *anti*-α-benzyloxy-β-hydroxy thioester **42** as a single diastereomer (Scheme 5).[26] Compound **42** was then lactonized

Scheme 5



by mercury trifluoroacetate to afford α-benzyloxy-β-lactone **43** in moderate yield. Isobutyraldehyde was used in this sequence due to unsuccessful lactonization of substrates derived from other aldehydes (e.g., acetaldehyde). Upon hydrogenolysis[27] and benzoylation, the desired α-benzoyloxy-β-lactone **45** was obtained in good yields. Methylenation of **45** provided methyleneoxetane **46**, which underwent F^+-mediated nucleobase incorporation. Crude NMR showed a 1:1 mixture of two *psico*-nucleoside products, with clear signs of fluorine and nucleobase incorporation. Purification provided β-nucleosides **47** and **48** in good yields. The relative stereochemistry was confirmed by NOESY studies.[17] The reaction rate was slower in this reaction than in the nucleobase incorporation of 2-methylene-THF **39**. Considering the bulkiness of the neighboring isopropyl group, the rate of the nucleophilic addition of the nucleobase to the fluorinated five-membered oxonium intermediate is likely to be decreased, facilitating the formation of both N9 and N7 products. Only β-face nucleosides **47** and **48** were isolated, strongly indicating the involvement of anchimeric assistance via a five-membered oxonium intermediate for the methyleneoxetane system.

While logically possible that entropic effects related to exploration of conformational space account for the general lack of neighboring group participation for the six-membered transition states, such an explanation does not seem likely. The concentration of nucleophile in these experiments is not particularly high, which further decreases the likelihood that the intermolecular reaction could compete with conformational exploration. Furthermore, a reaction run at a 10-fold dilution on 2-methyleneoxetane **16b** gave nucleosides **17b** in essentially the same ratio as the result in Table 1.

The major product of a reaction that involves multiple pathways may not necessarily arise from the lowest energy intermediate, based on the Curtin–Hammet principle. Indeed, computational studies on related five-membered oxocarbenium ions have shown inconsistency between calculations and experimental results if the most stable conformation was the only argument considered.[28] The reaction outcome and the corresponding DFT calculations of glycosylations involving related bicyclic thioglycoside intermediates[29] further support the likelihood of reaction from a less stable intermediate. Unlike most glycosylations,[30] the transition states in our investigation bear a substituent on the C1 position. Thus, in the cases of 4,6-fused and 5,6-fused transition states (the ones with apparent anchimeric assistance), the nucleobase would have to attack a pseudotertiary carbon center (see Figure 7). In accordance with

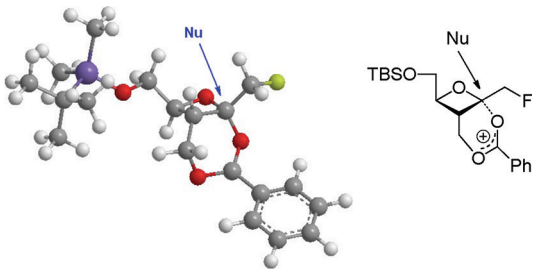


Figure 7. S_N2-like trajectory for nucleobase incorporation on fused carbocation from 2-methyleneoxetane **16b**.

the Curtin–Hammet principle, the transition barrier of this nucleophilic addition may be large enough to hamper anchimerically assisted product formation, although both the 4,6-fused and 5,6-fused cations are at least 10 kcal/mol more stable than their corresponding open oxocarbenium ions. It is entirely possible (and even likely) that the fused carbocation is forming, but if the reaction proceeds mostly by an S_N1 pathway, this will not be evident. On the other hand, when five-membered anchimeric assistance was utilized (Schemes 4 and 5), the formation of the open oxocarbenium ions is likely to be less favored because of the adjacent strong electron-withdrawing benzoyloxy group

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on C2.[31] Instead, products resulting from the 4,5-fused and 5,5-fused cations would be more readily formed. The formation of a single product for methylene-THF **39**, while methyleneoxetane **46** resulted in both N7 and N9 isomers (but on a single face), is interesting. As mentioned previously, the latter was the slowest F^+-mediated nucleobase incorporation conducted. This would be consistent with the pathway involving the open oxocarbenium ion being suitably high enough in energy that it does not compete with the congested S_N2-like reaction with the fused cation. The presence of the regioisomeric products is likely a reflection of migration of the TMS group between N7 and N9 over the course of the longer reaction period.

The high stereoselectivity in the nucleobase incorporation for 2-methylene-THF **25** is likely to be a result of conformational influences that affect the relative energies of the intermediates and the transition states. According to the proposal by Woerpel and co-workers and calculations by Rhoad et al.,[28] five-membered oxocarbenium ions are likely to adopt low energy conformations that place C3 substituents having oxygen attached to the ring in a pseudoaxial position. As a result, it would be likely that the *trans*-hydroxymethyl at C2 would be pseudoaxial, as well. It would not be unexpected that this could alter the relative energies of the intermediates or the barriers to the reactions from them.

CONCLUSION

A fluorine-containing *psico*-oxetanocin A analogue has been prepared in a straightforward manner. Key steps of the protocol, including carbonylation of readily accessible epoxides and fluorine-mediated nucleobase incorporation, will allow for rapid construction and, thus, evaluation of other novel *psico*-nucleosides containing an oxetane sugar. Although the protocol suffers from relatively low stereoselectivity in nucleobase incorporation, it should be noted at this stage, when we are trying to evaluate the potential of *psico*-oxetanocin-type frameworks, access to both facial diastereoisomers is a plus. There are biologically interesting L- and D-nucleosides that have the nucleobase and a C4 hydroxymethyl moiety in an *anti*-relationship.[32] In addition, neighboring group participation in F^+-mediated nucleobase incorporation with both 2-methyleneoxetanes and 2-methylenetetrahydrofurans has been studied. Anchimeric assistance has been seen with five-membered closed-ring transition states, but generally not with six- or seven-membered ones. Electronic structural calculations have been conducted, and they support the concept that intermediates having neighboring group participation are significantly lower in energy than the related open oxocarbenium ions. Our experimental results demonstrate that this greater stability may not be the only factor to influence the reaction outcome. The 4,6- and 5,6-fused cationic intermediates accessible from the 2-methyleneoxetanes and 2-methylene-THFs investigated are sterically congested, and reaction along this trajectory appears not to dominate. There would be similar congestion in the 4,5- and 5,5-fused cationic intermediates. However, the experimental outcomes suggest that the corresponding open oxocarbenium ions experience enough destabilization in comparison to the energy difference between the neighboring group-stabilized intermediates and the transition state leading to product that the predominant pathway involves anchimeric assistance.

EXPERIMENTAL SECTION

General Carbonylation Procedure.[11a] A 100 mL Parr high-pressure reactor with a mechanical stirrer was dried overnight under vacuum. In a N_2 drybox, the reactor was charged with $[(ClTPP)Al(THF)_2]^+[Co(CO)_4]^-$ (**9**) (0.01 equiv) and oxiranes (1 equiv, 1 M in THF), then closed and removed from the drybox. The reactor was pressurized with 800 psi CO, stirred at 60 °C for 26 h, then cooled and vented. The volatile materials were removed in vacuo. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 9:1) afforded the β-lactones as white solids.

General Methylenation Procedure.[12] A solution of dimethyltitanocene (0.5 M in toluene, 1.5 equiv) and β-lactone (1 equiv) was stirred at 80 °C under N_2 in the dark. The reaction was monitored over a period of 2 h by TLC. A second portion of dimethyltitanocene (0.5−1 equiv) was added if the starting material was still present, and the reaction was stirred at 80 °C until the starting material disappeared. The reaction mixture was allowed to cool to rt, and petroleum ether (20 × $PhCH_3$ volume) was added, followed by overnight stirring. The mixture was filtered through Celite, and the Celite cake was washed with petroleum ether until the filtrate was colorless. The filtrate was concentrated and purified by flash chromatography on silica gel to afford the corresponding 2-methyleneoxetanes or THFs as pale yellow oils.

6-Chloro-9-(trimethylsilyl)-9*H*-purine.[33] A mixture of 6-chloro-9*H*-purine (0.17 g, 1.1 mmol) and chlorotrimethylsilane (2.3 mL) in HMDS (12 mL) was refluxed at 120 °C for 1 h until a clear solution resulted. After cooling to rt, the reaction was concentrated in vacuo to provide 6-chloro-9-(trimethylsilyl)-9*H*-purine as a yellow solid (0.25 g, 1.1 mmol), which was used directly for the next reaction.

General Procedure for Fluorine-Mediated Nucleobase Incorporation. A solution of 2-methyleneoxetanes or THFs (1 equiv, 0.08 M in nitromethane) was added to a solution of 6-chloro-9-(trimethylsilyl)-9*H*-purine (1.5 equiv, 0.12 M in nitromethane), followed by the addition of Selectfluor (1.2 equiv) in one portion. The solution was stirred at rt for 2 h. The resulting solution was concentrated, and the diastereomeric ratio of the *psico*-nucleosides was determined by ^1H NMR of the crude product.

***cis*-1,4-Bis(*tert*-butyldimethylsilyloxy)but-2-ene.**[34] *cis*-1,4-Butenediol (2.12 g, 24 mmol) was dissolved in CH_2Cl_2 (60 mL). Imidazole (4.92 g, 72 mmol) and DMAP (59 mg, 0.48 mmol) were added to the solution. *tert*-Butyldimethylsilylchloride (7.3 g, 48 mmol) was added, and the solution was stirred for 12 h. The solvent was removed in vacuo. The residue was dissolved in diethyl ether (60 mL) and washed with 1 M HCl (60 mL) and brine (60 mL). The organic layer was dried ($MgSO_4$) and concentrated to afford *cis*-1,4-bis(*tert*-butyldimethylsilyloxy)but-2-ene as a colorless oil (6.84 g, 90%): ^1H NMR (400 MHz, $CDCl_3$) δ 5.56 (m, 2H), 4.25 (d, J = 3.2 Hz, 4H), 0.91 (s, 18H), 0.10 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.4, 59.8, 26.1, 18.6, −5.0.

***cis*-2,3-Bis(*tert*-butyldimethylsilyloxymethyl)oxirane (8).**[35] A solution of dimethyldioxirane (10.5 mL, 0.23 M, 2.43 mmol) in CH_2Cl_2 was added to a solution of *cis*-1,4-bis(*tert*-butyldimethylsilyloxy)-but-2-ene (0.4 g, 1.21 mmol) in CH_2Cl_2 (2 mL), and the resulting solution was stirred at rt for 4 h. The solution was concentrated in vacuo and purified by flash chromatography on silica gel (petroleum ether/EtOAc 95:5) to give **8** as a colorless oil (0.38 g, 94%): ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (dd, J = 11.8, 3.6 Hz, 2H), 3.73 (dd, J = 11.7, 5.6 Hz, 2H), 3.13 (m, 2H), 0.91 (s, 18H), 0.09 (s, 6H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.9, 57.1, 26.1, 18.5, −5.0, −5.0.

***trans*-3,4-Bis(*tert*-butyldimethylsilyloxymethyl)oxetan-2-one (10).** The general carbonylation procedure was applied to *cis*-2,3-bis(*tert*-butyldimethylsilyloxymethyl)oxirane (**8**) (5.1 g, 15 mmol). Purification afforded **10** as a white solid (3.5 g, 63%): mp 43−44 °C; IR (KBr) 2959, 2929, 2858, 1818, 1466, 1255, 1130, 1014, 863, 838, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.63 (ddd, J = 3.2, 3.2, 3.2 Hz, 1H), 4.02 (m, 2H), 3.83 (m, 2H), 3.74 (ddd, J = 3.7, 3.7, 3.7 Hz, 1H), 0.90 (s, 9H), 0.89 (s, 9H), 0.08 (s, 6H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 73.9, 62.4, 58.0, 54.7, 26.0, 25.9, 18.5, 18.4, −5.3, −5.3, −5.3, −5.4; MS (EI) m/z 345 ($M^+ - CH_3$), 303,

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273, 231, 189, 171, 147, 117 (100), 89, 73; HRMS (ESI) calcd for $C_{17}H_{37}O_4Si_2$ (M^+ + H) m/z 361.2225, found 361.2226.

***trans*-3,4-Bis(*tert*-butyldimethylsilyloxymethyl)-2-methyleneoxetane (11).** The general methylenation procedure was applied to *trans*-3,4-bis(tert-butyldimethylsilyloxymethyl)oxetan-2-one (**10**) (0.20 g, 0.55 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc/Et_3N 97:2:1) afforded **11** as a pale yellow oil (0.162 g, 81%): IR (KBr) 2955, 2930, 2896, 2858, 1694, 1472, 1256, 1141, 1059, 838, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.63 (ddd, J = 4.2, 4.2, 4.2 Hz, 1H), 4.12 (m, 1H), 3.83 (m, 4H), 3.76 (m, 1H), 3.40 (m, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.09 (s, 6H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 83.2, 79.6, 64.8, 63.0, 45.5, 26.1, 26.1, 18.6, 18.5, −5.2, −5.2; MS (EI) m/z 301 (M^+ − C_4H_9), 271, 231, 211, 169, 147, 117, 89, 73 (100); HRMS (ESI) calcd for $C_{18}H_{39}O_3Si_2$ (M^+ + H) m/z 359.2432, found 359.2417.

3α,4β-Bis(*tert*-butyldimethylsilyloxymethyl)-2-(6-chloro-9*H*-purin-9-yl)-2-fluoromethyloxetane (12) and 3α,4β-Bis(*tert*-butyldimethylsilyloxymethyl)-2-(6-chloro-7*H*-purin-7-yl)-2-fluoromethyloxetane (13). The general procedure for fluorine-mediated nucleobase incorporation was applied to *trans*-3,4-bis(*tert*-butyldimethylsilyloxymethyl)-2-methyleneoxetane (**11**) (0.15 g, 0.42 mmol). A ^1H NMR of the crude product indicated the formation of four *psico*-nucleosides in a ratio of 1:1:0.6:0.3. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 70:30) afforded a mixture of four diastereomers as a clear wax (0.17 g, 76%). Further purification by flash chromatography on silica gel (petroleum ether/EtOAc 70:30) provided an **12** as inseparable 63:37 mixture, favoring the desired β-product as a clear oil (93 mg, 42%; β-product, 27%): ^1H NMR (400 MHz, $CDCl_3$) (peaks assigned for the β-product) δ 8.69 (s, 1H), 8.44 (s, 1H), 5.21 (dd, J = 47.3, 10.3 Hz, 1H), 5.01 (dd, J = 47.3, 10.4 Hz, 1H), 4.93 (m, 1H), 4.23 (dd, J = 11.2, 5.2 Hz, 1H), 4.01 (dd, J = 11.0, 5.1 Hz, 1H), 3.90 (dd, J = 12.2, 1.8 Hz, 1H), 3.63 (m, 2H), 0.93 (s, 9H), 0.67 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), −0.08 (s, 3H), −0.09 (s, 3H); (peaks assigned for the α-product) δ 8.67 (s, 1H), 8.52 (s, 1H), 5.23 (dd, J = 46.7, 10.0 Hz, 1H), 5.03 (dd, J = 46.7, 9.8 Hz, 1H), 5.00 (m, 1H), 3.99 (dd, J = 11.8, 3.4 Hz, 1H), 3.86 (dd, J = 12.1, 3.7 Hz, 1H), 3.63 (m, 1H), 3.54 (dd, J = 11.5, 4.6 Hz, 1H), 3.39 (m, 1H), 0.95 (s, 9H), 0.63 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), −0.25 (s, 3H), −0.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (peaks assigned for the β-product) δ 151.9, 151.2, 150.3, 143.9, 132.5, 93.0 (d, J_{CF} = 18 Hz), 82.6 (d, J_{CF} = 179 Hz), 81.4, 63.8, 59.0, 46.0, 26.0, 25.8, 18.4, −5.3, −5.3, −5.4, −5.5; (peaks assigned for the α-product) δ 151.6, 151.4, 150.9, 144.3, 133.2, 94.8 (d, J_{CF} = 20 Hz), 82.4 (d, J_{CF} = 181 Hz), 80.0, 64.2, 59.0, 42.1, 26.1, 25.8, 18.7, 18.1, −5.1, −5.2, −5.8, −5.9; MS (EI) m/z β-product 515 (M^+ − CH_3), 473, 357, 187, 147, 117, 89, 73 (100), 56; α-product 515 (M^+ − CH_3), 473, 357, 299, 187, 147, 117, 89, 73 (100), 56. Compound **13** was isolated as an inseparable 77:23 mixture, favoring the β-product as a clear oil (80 mg, 34%; β-product, 27%): ^1H NMR (300 MHz, $CDCl_3$) (peaks assigned for the β-product) δ 8.88 (s, 1H), 8.70 (s, 1H), 5.02 (dd, J = 46.7, 10.5 Hz, 1H), 4.92 (dd, J = 46.5, 10.5 Hz, 1H), 4.84 (m, 1H), 4.23 (dd, J = 10.7, 5.6 Hz, 1H), 4.11 (dd, J = 10.9, 5.8 Hz, 1H), 3.88 (dd, J = 12.5, 2.4 Hz, 1H), 3.69 (m, 1H), 3.63 (dd, J = 12.6, 2.7 Hz, 1H), 0.93 (s, 9H), 0.63 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H), −0.16 (s, 3H), −0.18 (s, 3H); (peaks assigned for the α-product) δ 8.90 (s, 1H), 8.80 (s, 1H), 5.27 (dd, J = 46.4, 10.4 Hz, 1H), 4.96 (m, 1H), 4.88 (dd, J = 46.4, 10.4 Hz, 1H), 4.02 (dd, J = 12.0, 3.5 Hz, 1H), 3.91 (dd, J = 12.0, 4.1 Hz, 1H), 3.79 (m, 2H), 3.38 (ddd, J = 5.0, 5.0, 5.0 Hz, 1H), 0.95 (s, 9H), 0.66 (s, 9H), 0.14 (s, 6H), −0.21 (s, 3H), −0.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) (peaks assigned for β-product) δ 163.7, 152.6, 148.5, 142.2, 121.8, 94.1 (d, J_{CF} = 19.6 Hz), 83.5 (d, J_{CF} = 181.1 Hz), 81.6, 63.8, 59.6 (d, J_{CF} = 2.9 Hz), 46.6, 26.0, 25.7, 18.3, −5.4, −5.4, −5.5, −5.6; (peaks assigned for the α-product) δ 164.2, 152.5, 148.1, 141.5, 121.8, 95.0 (d, J_{CF} = 19.7 Hz), 85.2 (d, J_{CF} = 181.8 Hz), 80.5, 64.4, 59.8, 42.1, 26.1, 25.8, 18.6, 18.1, −5.2, −5.2, −5.8, −5.9; MS (EI) m/z β-product 473 (M^+ − C_4H_9), 443, 379, 357, 341, 269, 229, 187, 117, 89, 73 (100); α-product 473 (M^+ − C_4H_9), 443, 357, 299, 245, 187, 117, 89, 73 (100).

2β-(6-Amino-9*H*-purin-9-yl)-2α-fluoromethyl-*trans*-3α,4β-bis(hydroxymethyl)oxetane (2). The 63:37 mixture of 3α,4β-bis(*tert*-butyldimethylsilyloxy)methyl)-2-(6-chloro-9*H*-purin-9-yl)-2-fluoromethyloxetane (**12**) (8.5 mg, 0.016 mmol) was dissolved in *i*-PrOH saturated with ammonia (4 mL). The solution was sealed in a reaction vessel and stirred at 100 °C overnight. The solution was allowed to cool to rt, and the solvent was removed in vacuo. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 95:5) provided a mixture of bis-TBDMS protected adenine containing nucleoside as a clear oil (7.6 mg, 93%): ^1H NMR (300 MHz, $CDCl_3$) (peaks assigned for the β-product) δ 8.28 (s, 1H), 8.12 (s, 1H), 6.09 (s, 2H), 5.21 (dd, J = 47.2, 10.3 Hz, 1H), 4.94 (dd, J = 47.2, 10.4 Hz, 1H), 4.88 (m, 1H), 4.23 (dd, J = 10.9, 5.9 Hz, 1H), 4.05 (dd, J = 11.0, 5.0 Hz, 1H), 3.88 (dd, J = 12.4, 3.1 Hz, 1H), 3.66 (dd, J = 12.3, 3.0 Hz, 1H), 3.61 (m, 1H), 0.92 (s, 9H), 0.73 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), −0.05 (s, 6H); (peaks assigned for the α-product) δ 8.27 (s, 1H), 8.22 (s, 1H), 6.14 (s, 2H), 5.23 (dd, J = 46.9, 10.1 Hz, 1H), 4.96 (m, 1H), 4.90 (dd, J = 46.8, 10.3 Hz, 1H), 3.97 (dd, J = 11.9, 3.2 Hz, 1H), 3.88 (m, 1H), 3.61 (m, 2H), 3.36 (ddd, J = 5.4, 5.4, 5.4 Hz, 1H), 0.95 (s, 9H), 0.69 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), −0.21 (s, 3H), −0.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) (peaks assigned for β-product) δ 155.8, 153.0, 148.8, 138.9, 120.3, 92.4 (d, J_{CF} = 19 Hz), 82.8 (d, J_{CF} = 178 Hz), 81.5, 64.3, 59.3 (d, J_{CF} = 2.3 Hz), 46.5, 26.0, 25.9, 18.4, 18.4, −5.3, −5.3, −5.4, −5.4; (peaks assigned for the α-product) δ 155.9, 152.7, 149.1, 139.3, 121.1, 94.3 (d, J_{CF} = 19 Hz), 82.7 (d, J_{CF} = 180 Hz), 80.6, 64.7, 59.3, 42.0, 26.1, 25.9, 18.7, 18.2, −5.1, −5.2, −5.8, −5.8; MS (EI) m/z β-product 496 (M^+ − CH_3), 454, 338, 196, 136, 117, 89, 73 (100), 56; α-product 496 (M^+ − CH_3), 454, 338, 281, 196, 136, 117, 89, 73 (100), 56. This mixture of bis-TBDMS-protected nucleosides (35 mg, 0.068 mmol) was dissolved in THF (2 mL), and a solution of TBAF in THF (1 M, 0.17 mL, 0.17 mmol) was added dropwise. The resulting solution was stirred at rt for 1 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (EtOAc/*i*-PrOH/acetone/H_2O 80:8:8:4) to afford **2** as a clear wax (12 mg, 96%): IR (KBr) 3386 (br), 2925, 2852, 1655, 1603, 1385 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 8.31 (s, 1H, H8), 8.20 (s, 1H, H2), 5.25 (dd, J = 46.9, 10.6 Hz, 1H), 5.05 (dd, J = 46.6, 10.6 Hz, 1H), 4.83 (m, 1H), 4.12 (dd, J = 11.6, 6.8 Hz, 1H), 4.05 (dd, J = 11.6, 6.2 Hz, 1H), 3.82 (dd, J = 13.3, 1.8 Hz, 1H), 3.63 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 157.5 (C6), 153.8 (C2), 149.3 (C4), 140.3 (C8), 120.8 (C5), 93.6 (d, J_{CF} = 19 Hz), 83.8 (d, J_{CF} = 177 Hz), 83.3, 64.1, 59.1 (d, J_{CF} = 3 Hz), 47.8; HRMS (ESI) calcd for $C_{11}H_{15}FN_5O_3$ (M^+ + H) m/z 284.1153, found 284.1154.

2β-(6-Amino-7*H*-purin-7-yl)-2α-fluoromethyl-*trans*-3α,4α-bis(hydroxymethyl)oxetane (14). The 3:1 mixture of 3α,4β-bis(*tert*-butyldimethylsilyloxy)methyl)-2-(6-chloro-7*H*-purin-7-yl)-2-fluoromethyloxetane (**13**) (70 mg, 0.098 mmol) was dissolved in MeOH saturated with ammonia (10 mL). The solution was sealed in a tube and stirred at 80 °C overnight. The solution was allowed to cool to rt, and the solvent was removed in vacuo. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 96:4) provided bis-TBDMS-protected analogue of **14** as a yellow solid (35 mg, 70%): mp 169−171 °C; IR (KBr) 3422, 2930, 2857, 1637, 1474, 1255, 1140, 1086, 838, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.18 (s, 1H), 6.06 (br, 2H), 4.79 (m, 1H), 4.75 (dd, J = 46.9, 10.2 Hz, 1H), 4.58 (dd, J = 46.0, 10.3 Hz, 1H), 4.27 (m, 1H), 3.93 (m, 2H), 3.84 (dd, J = 12.5, 2.8 Hz, 1H), 3.69 (dd, J = 12.4, 2.9 Hz, 1H), 0.94 (s, 9H), 0.67 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), −0.06 (s, 3H), −0.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 153.9, 151.1, 142.5, 111.0, 91.9 (d, J_{CF} = 22.1 Hz), 83.0 (d, J_{CF} = 183.3 Hz), 81.4, 63.7, 59.4 (d, J_{CF} = 4.7 Hz), 46.7, 26.1, 25.6, 18.4, 18.2, −5.4, −5.5, −5.6; MS (EI) m/z 379 (M^+ − H − OTBDMS), 357, 341, 229, 211, 187, 154, 117, 89, 73 (100); HRMS (ESI) calcd for $C_{23}H_{43}FN_5O_3Si_2$ (M^+ + H) m/z 512.2883, found 512.2873. This bis-TBDMS-protected nucleoside (23 mg, 0.045 mmol) was dissolved in THF (2 mL), and a solution of TBAF in THF (1 M, 0.11 mL, 0.11 mmol) was added dropwise. The resulting solution was stirred at rt for 1 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (EtOAc/EtOH/acetone/H_2O 6:1:1:0.5) to afford **14** as a clear wax (12 mg, 94%): IR (KBr) 3422, 2925, 2855, 1637, 1597, 1560, 1475, 1398, 1037 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 8.44 (s, 1H, H8), 8.28 (s, 1H, H2), 4.95 (dd, J = 46.7, 10.6 Hz, 1H), 4.84 (m, 1H), 4.76 (dd, J = 46.1, 10.6 Hz, 1H), 4.18 (dd, J = 9.9, 9.9 Hz, 1H), 3.99 (dd, J = 11.4, 5.4 Hz, 1H), 3.84 (m,

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1H), 3.80 (dd, J = 13.3, 2.6 Hz, 1H), 3.65 (dd, J = 13.3, 3.9 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 161.2 (C4), 154.1 (C2), 153.5 (C6), 144.7 (C8), 112.0 (C5), 93.6 (d, J_{CF} = 25 Hz), 84.2 (d, J_{CF} = 180 Hz), 83.8, 63.8, 58.8, 47.6; HRMS (ESI) calcd for $C_{11}H_{15}FN_5O_3$ (M^+ + H) m/z 284.1153, found 284.1148.

***cis*-1,4-Bis(benzoyloxy)but-2-ene.**[36] *cis*-1,4-Butenediol (10.0 g, 114 mmol) was dissolved in CH_2Cl_2 (150 mL). Pyridine (27.9 mL, 341 mmol) was added to the solution, which was cooled to 0 °C. Benzoyl chloride (39.6 mL, 341 mmol) was added dropwise to the solution, and it was warmed to rt after 15 min and stirred for 4 h. The solution was diluted with Et_2O (125 mL) and washed with 2 M HCl (125 mL), H_2O (125 mL), saturated $NaHCO_3$ (125 mL), and brine (125 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The resulting oil was purified by flash chromatography on silica gel (petroleum ether/EtOAc 95:5−85:15) to give 1,4-*cis*-bis(benzoyloxy)but-2-ene as a white solid (33.3 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (m, 4H), 7.43 (m, 6H), 5.93 (m, 2H), 5.03 (m, 4H).

***cis*-2,3-Bis(benzoyloxymethyl)oxirane.**[37] *cis*-1,4-Bis(benzoyloxy)but-2-ene (20.0 g, 67.5 mmol) was dissolved in CH_2Cl_2 (50 mL). The solution was cooled to 0 °C. *m*-CPBA (25.0 g (70% in *m*-CPBA), 101 mmol of *m*-CPBA) in CH_2Cl_2 (125 mL) was added dropwise to the solution, which was stirred for 48 h at rt. The solution was cooled to 0 °C, and the white solid (*m*-chlorobenzoic acid) was removed by rapid filtration. The solution was then washed with saturated $NaHCO_3$, saturated Na_2SO_3, and brine. The organic layer was dried ($MgSO_4$), concentrated in vacuo, and purified by flash chromatography on silica gel (petroleum ether/EtOAc 80:20) to give *cis*-2,3-bis(benzoyloxymethyl)oxirane as a white solid (12.3 g, 58%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (m, 4H), 7.55 (m, 6H), 4.66 (m, 2H), 4.52 (m, 2H), 3.53 (t, J = 3.0 Hz, 2H).

***trans*-3,4-Bis(benzoyloxymethyl)oxetan-2-one (15a).** The general carbonylation procedure (modified to 600 psi CO, 30 °C) was applied to *cis*-2,3-bis(benzoyloxymethyl)oxirane (810 mg, 2.6 mmol). Purification afforded **15a** as a white solid (429 mg, 48%): mp 102−103 °C; IR (KBr) 3071, 2966, 1826, 1721, 1602, 1451, 1275, 1123, 827, 710 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 4H), 7.58 (m, 2H), 7.41 (m, 4H), 4.94 (dd, J = 7.8, 3.9 Hz, 1H), 4.74 (dd, J = 13.1, 3.9 Hz, 1H), 4.68 (m, 2H), 4.61 (dd, J = 13.0, 4.4 Hz, 1H), 4.06 (dd, J = 8.8, 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.9, 166.2, 166.1, 133.9, 133.8, 130.0, 130.0, 129.1, 129.1, 128.7, 128.7, 72.3, 63.4, 59.5, 55.7; MS (ESI) m/z 341 (M^+ + H), 295, 219, 105 (100), 73. Anal. Calcd for $C_{19}H_{16}O_6$: C, 67.05; H, 4.74. Found: C, 67.45; H, 4.47.

***trans*-3,4-Bis(benzoyloxymethyl)-2-methyleneoxetane (16a).** The general methylenation procedure was applied to *trans*-3,4-bis(benzoyloxymethyl)oxetan-2-one (**15a**) (0.66 g, 2.0 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc/Et_3N 92.5:7:0.5) afforded **16a** as a yellow oil (0.32 g, 48%): IR (KBr) 3063, 2951, 1722, 1696, 1452, 1270, 1114, 709 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (m, 4H), 7.53 (m, 2H), 7.39 (m, 4H), 5.04 (dd, J = 8.6, 4.6 Hz, 1H), 4.63 (m, 2H), 4.53 (m, 2H), 4.27 (s, 1H), 4.08 (s, 1H), 3.78 (dd, J = 4.7, 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 166.4, 161.7, 133.5, 133.5, 130.0, 129.9, 129.7, 129.7, 128.7, 128.6, 81.8, 80.0, 65.3, 63.7, 43.8; MS (ESI) m/z 361 (M^+ + Na), 217, 118, 95 (100). Anal. Calcd for $C_{20}H_{18}O_5$: C, 70.99; H, 5.36. Found: C, 71.38; H, 4.96.

***trans*-3-Benzyloxymethyl-4-(*tert*-butyldimethylsilyloxymethyl)-oxetan-2-one and *trans*-4-Benzyloxymethyl-3-(*tert*-butyldimethylsilyloxymethyl)oxetan-2-one (21).** The general carbonylation procedure was applied to *cis*-2-benzoyloxymethyl-3-*tert*-butyldimethylsilyloxymethyloxirane (**20**)[20] (5 g, 16 mmol). Purification afforded **21a** and **21b** as an inseparable 3:2 mixture (4.34 g, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 10H), 4.75 (m, 1H), 4.62 (m, 5H), 4.03 (m, 2H), 3.86 (m, 6H), 3.72 (m, 2H), 0.91 (s, 9H), 0.91 (s, 9H), −0.05 (s, 12H).

***trans*-3-Benzoyloxymethyl-4-(*tert*-butyldimethylsilyloxymethyl)-oxetan-2-one (15b) and *trans*-4-Benzoyloxymethyl-3-(*tert*-butyldimethylsilyloxymethyl)oxetan-2-one (15c).** *trans*-Benzyloxymethyl-(*tert*-butyldimethylsilyloxymethyl)oxetan-2-ones (**21**) (3.3 g, 9.7 mmol) were dissolved in EtOH/CH_2Cl_2 (v/v 4:1, 80 mL) and $Pd(OH)_2$/C (0.44 g) was added. The mixture was stirred at rt overnight under H_2. It was then filtered through Celite and concentrated to give a mixture of the corresponding alcohols as a pale yellow oil (2.1 g, 89%). Benzoyl chloride (1.3 g, 1.1 mL, 9.5 mmol) was added dropwise into a solution of the alcohols (1.2 g, 4.8 mmol) and pyridine (0.75 g, 0.78 mL, 9.5 mmol) in CH_2Cl_2 (20 mL). The solution was stirred at rt overnight. It was then diluted with Et_2O (100 mL), washed with 2 M HCl (50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 92:8) provided **15b** as a white solid (0.54 g, 33%): mp 44−46 °C; IR (KBr) 2952, 2929, 2885, 1826, 1724, 1279, 1120, 839, 706 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (m, 2H), 7.59 (tt, J = 7.4, 1.2 Hz, 1H), 7.45 (m, 2H), 4.67 (m, 1H), 4.65 (d, J = 4.4 Hz, 2H), 4.09 (ddd, J = 4.3, 4.3, 4.3 Hz, 1H), 4.06 (dd, J = 12.5, 2.5 Hz, 1H), 3.89 (dd, J = 12.5, 2.8 Hz, 1H), 0.90 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 166.2, 133.7, 129.9, 129.4, 128.7, 74.9, 61.9, 59.6, 51.5, 25.9, 18.5, −5.3, −5.4; MS (EI) m/z 293 (M^+ − $C(CH_3)_3$), 179, 171, 135, 117, 105 (100), 77; HRMS (ESI) calcd for $C_{18}H_{26}NaO_5Si$ (M^+ + Na) m/z 373.1442, found 373.1419. **15c** (white solid, 0.62 g, 37%): mp 60−62 °C; IR (KBr) 2956, 2929, 2858, 1832, 1724, 1273, 1120, 839, 714 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (m, 2H), 7.61 (m, 1H), 7.47 (m, 2H), 4.93 (m, 1H), 4.75 (dd, J = 12.9, 2.9 Hz, 1H), 4.59 (dd, J = 12.8, 4.5 Hz, 1H), 4.06 (dd, J = 11.0, 3.5 Hz, 1H), 3.87 (dd, J = 11.1, 2.9 Hz, 1H), 3.75 (m, 1H), 0.91 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 166.3, 133.8, 130.0, 129.4, 128.8, 71.0, 63.8, 57.8, 56.4, 25.9, 18.4, −5.3, −5.4; MS (EI) m/z 293 (M^+ − $C(CH_3)_3$), 213, 171 (100), 127, 105, 77; HRMS (ESI) calcd for $C_{18}H_{26}NaO_5Si$ (M^+ + Na) m/z 373.1442, found 373.1429.

***trans*-3-Benzoyloxymethyl-4-*tert*-butyldimethylsilyloxymethyl-2-methyleneoxetane (16b).** The general methylenation procedure was applied to *trans*-3-benzoyloxymethyl-4-(*tert*-butyldimethylsilyloxymethyl)oxetan-2-one (**15b**) (0.35 g, 1 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc/Et_3N 95:4:1) afforded **16b** as a pale yellow oil (0.26 g, 75%): IR (KBr) 2954, 2929, 2858, 1720, 1275, 1120, 839, 714 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (m, 2H), 7.58 (m, 1H), 7.45 (m, 2H), 4.75 (m, 1H), 4.60 (dd, J = 11.4, 7.3 Hz, 1H), 4.50 (dd, J = 11.4, 5.5 Hz, 1H), 4.23 (m, 1H), 3.91 (m, 2H), 3.84 (dd, J = 11.9, 4.1 Hz, 1H), 3.74 (m, 1H), 0.91 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 162.8, 133.4, 130.0, 129.9, 128.6, 82.7, 80.6, 64.3, 63.9, 42.6, 26.0, 18.5, −5.2; HRMS (ESI) calcd for $C_{19}H_{28}NaO_4Si$ (M^+ + Na) m/z 371.1649, found 371.1631.

***trans*-4-Benzoyloxymethyl-3-*tert*-butyldimethylsilyloxymethyl-2-methyleneoxetane (16c).** The general methylenation procedure was applied to *trans*-4-benzoyloxymethyl-3-(*tert*-butyldimethylsilyloxymethyl)oxetan-2-one (**15c**) (90 mg, 0.26 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc/Et_3N 96:3:1) afforded **16c** as a pale yellow oil (54 mg, 60%): IR (KBr) 2954, 2929, 2858, 1726, 1695, 1273, 1124, 837, 712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (m, 2H), 7.58 (tt, J = 7.4, 1.3 Hz, 1H), 7.45 (m, 2H), 4.93 (m, 1H), 4.62 (dd, J = 12.5, 3.2 Hz, 1H), 4.51 (dd, J = 12.5, 5.5 Hz, 1H), 4.23 (dd, J = 3.7, 2.2 Hz, 1H), 3.85 (m, 3H), 3.49 (m, 1H), 0.90 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 163.3, 133.4, 130.0, 129.9, 128.6, 80.7, 80.0, 65.7, 62.8, 46.5, 26.0, 18.5, −5.2, −5.2; MS (EI) m/z 291 (M^+ − $C(CH_3)_3$), 179, 169, 105 (100), 95, 77; HRMS (ESI) calcd for $C_{19}H_{28}NaO_4Si$ (M^+ + Na) m/z 371.1649, found 371.1640.

3-(Benzoyloxymethyl)dihydrofuran-2(3*H*)-one (26). Pd(OH)$_2$/C (180 mg) was added to a solution of 3-(benzyloxymethyl)-dihydrofuran-2(3*H*)-one (**30**)[21] (0.72 g, 3.5 mmol) in EtOH (18 mL). The mixture was stirred at rt overnight under H_2. It was then filtered through Celite and concentrated to give the corresponding alcohol as a pale yellow oil (0.46 g, 99%). The resulting alcohol was mixed with CH_2Cl_2 (20 mL) and pyridine (0.55 g, 0.57 mL, 7.0 mmol). Benzoyl chloride (0.98 g, 0.81 mL, 7.0 mmol) was added dropwise, and the resulting mixture was stirred at rt overnight. It was then diluted with CH_2Cl_2 (100 mL), washed with 2 M HCl (50 mL), saturated

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$NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 70:30) provided **26** as a white solid (0.60 g, 78%): mp 72−73 °C; IR (KBr) 2922, 1765, 1712, 1283, 1178, 1116, 1017, 716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 4.65 (dd, J = 11.3, 4.0 Hz, 1H), 4.51 (dd, J = 11.3, 5.5 Hz, 1H), 4.39 (ddd, J = 8.9, 8.9, 3.3 Hz, 1H), 4.25 (m, 1H), 3.02 (m, 1H), 2.47 (m, 1H), 2.26 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 166.2, 133.4, 129.6, 129.6, 128.5, 66.8, 63.1, 39.4, 25.9; MS (EI) m/z 220 (M^+), 122, 105 (100), 99, 77; HRMS (ESI) calcd for $C_{12}H_{12}NaO_4$ (M^+ + Na) m/z 243.0628, found 243.0624.

4-Benzoyloxydihydrofuran-2(3*H*)-one (27). 4-Hydroxydihydrofuran-2(3*H*)-one (**31**)[22] (0.21 g, 2.1 mmol) was mixed with CH_2Cl_2 (8 mL) and pyridine (0.33 g, 0.34 mL, 4.2 mmol). Benzoyl chloride (0.58 g, 0.48 mL, 4.2 mmol) was added dropwise, and the resulting mixture was stirred at rt overnight. It was then diluted with Et_2O (20 mL), washed with 2 M HCl (20 mL), H_2O (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 80:20) provided **27** as a white solid (0.32 g, 74%): mp 98−99 °C; IR (KBr) 2925, 1774, 1718, 1281, 1176, 715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 7.3 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 5.67 (m, 1H), 4.61 (dd, J = 11.1, 4.7 Hz, 1H), 4.50 (d, J = 11.0 Hz, 1H), 2.97 (dd, J = 18.5, 6.7 Hz, 1H), 2.75 (d, J = 18.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 165.9, 133.8, 129.8, 129.0, 128.7, 73.2, 70.5, 34.7; MS (EI) m/z 206 (M^+), 123, 105 (100), 77, 51; HRMS (ESI) calcd for $C_{11}H_{10}NaO_4$ (M^+ + Na) m/z 229.0471, found 229.0495.

Diethyl *erythro*-2-benzyloxymethyl-3-hydroxysuccinate (33).[38] *n*-BuLi (2.5 M in hexane, 9.5 mL, 23.8 mmol) was added dropwise to a solution of diisopropylamine (4.3 mL, 26.2 mmol) in THF (40 mL) at 0 °C. The resulting pale yellow solution was stirred at 0 °C for 10 min and cooled to −78 °C. A solution of diethyl 2-hydroxysuccinate (**32**)[23] (2.06 g, 10.8 mmol) in THF (2 mL) was added dropwise. The solution was stirred at −78 °C for 30 min and at −20 °C for 1 h. After cooling to −78 °C, a solution of benzyloxymethyl chloride (1.86 g, 1.65 mL, 11.9 mmol) in HMPA (8 mL) was added dropwise. The reaction was stirred at −78 °C for 5 h. After the addition of glacial acetic acid (3 mL) and Et_2O (4 mL), the mixture was poured into H_2O (50 mL) and extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with 1 M HCl (2 × 25 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 80:20) afforded **33** as a pale yellow oil (1.34 g, 40%): IR (KBr) 3348 (br), 2981, 2927, 1736, 1228, 1097, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.58 (m, 3H), 4.26 (m, 2H), 4.15 (m, 2H), 3.92 (dd, J = 9.5, 5.6 Hz, 1H), 3.83 (dd, J = 9.2, 9.2 Hz, 1H), 3.29 (m, 1H), 3.26 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 170.4, 138.1, 128.6, 128.0, 127.9, 73.7, 69.0, 67.1, 62.1, 61.2, 49.1, 14.3, 14.3; HRMS (ESI) calcd for $C_{16}H_{23}O_6$ (M^+ + H) m/z 311.1489, found 311.1488.

Ethyl *erythro*-2-benzyloxymethyl-3,4-dihydroxybutanoate (34). $BH_3{\cdot}SMe_2$ (2 M in THF, 0.39 mL, 0.78 mmol) was added dropwise to a solution of diethyl *erythro*-2-benzyloxymethyl-3-hydroxysuccinate (**33**) (0.24 g, 0.78 mmol) in THF (1.5 mL) as gas released. The solution was stirred at rt for 30 min, and $NaBH_4$ (3 mg, 0.078 mmol) was added. The resulting mixture was stirred at rt overnight. CH_3OH (1 mL) was added, and the solution was concentrated in vacuo to give a yellow oil. Purification by flash chromatography on silica gel (CH_2Cl_2/CH_3OH 96:4) afforded **34** as a colorless oil (0.11 g, 51%; 64% based on recovered starting material): IR (KBr) 3423 (br), 2924, 2854, 1720, 1458, 1186, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.53 (s, 2H), 4.21 (q, J = 7.1 Hz, 2H), 4.08 (m, 1H), 3.78 (m, 2H), 3.73 (m, 1H), 3.66 (m, 1H), 3.18 (d, J = 6.6 Hz, 1H), 2.89 (dt, J = 5.8, 5.8 Hz, 1H), 2.17 (t, J = 6.3 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 137.8, 128.7, 128.1, 127.9, 73.7, 70.9, 68.3, 64.8, 61.4, 48.6, 14.4; HRMS (ESI) calcd for $C_{14}H_{21}O_5$ (M^+ + H) m/z 269.1384, found 269.1384.

***cis*-3-Benzyloxymethyl-4-hydroxydihydrofuran-2(3*H*)-one (35).** CSA (11 mg, 0.047 mmol) was added to a solution of ethyl *erythro*-2-benzyloxymethyl-3,4-dihydroxybutanoate (**34**) (0.11 g, 0.4 mmol) in $CHCl_3$ (40 mL). The solution was refluxed for 24 h. Concentration and purification by flash chromatography on silica gel (petroleum ether/EtOAc 60:40) afforded **35** as a clear oil (71 mg, 81%): IR (KBr) 3435 (br), 2922, 1772, 1456, 1369, 1213, 1167, 1093, 1032, 972, 742, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.69 (m, 1H), 4.57 (s, 2H), 4.31 (dd, J = 10.2, 4.0 Hz, 1H), 4.27 (dd, J = 10.2, 1.4 Hz, 1H), 3.96 (d, J = 5.7 Hz, 2H), 3.33 (d, J = 4.2 Hz, 1H), 2.86 (ddd, J = 5.7, 5.7, 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 137.2, 128.8, 128.4, 128.0, 74.9, 74.0, 69.4, 65.3, 45.2; MS (EI) m/z 121 ($BnOCH_2$), 116 (M^+ − BnOH), 107, 91 (100), 79, 73; HRMS (ESI) calcd for $C_{12}H_{14}NaO_4$ (M^+ + Na) m/z 245.0784, found 245.0776.

***cis*-4-Benzoyloxy-3-(benzoyloxymethyl)dihydrofuran-2(3*H*)-one (28).** $Pd(OH)_2/C$ (80 mg) was added to a mixture of *cis*-3-benzyloxymethyl-4-hydroxydihydrofuran-2(3*H*)-one (**35**) (0.28 g, 1.3 mmol) and EtOH (15 mL). The mixture was stirred at rt under H_2 for 2 h. It was then filtered through Celite and concentrated to give the corresponding diol as a clear oil (0.17 g, 99%): IR (KBr) 3421 (br), 2925, 1763, 1211, 1165, 1041, 912 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 4.65 (m, 1H), 4.39 (dd, J = 10.0, 3.5 Hz, 1H), 4.22 (d, J = 10.0 Hz, 1H), 3.93 (d, J = 6.3 Hz, 2H), 2.88 (ddd, J = 6.0, 6.0, 6.0 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 177.2, 75.1, 68.2, 56.4, 47.4; HRMS (ESI) calcd for $C_5H_8NaO_4$ (M^+ + Na) m/z 155.0315, found 155.0315. This diol was then mixed with CH_2Cl_2 (15 mL) and pyridine (0.99 g, 1.03 mL, 12.6 mmol). Benzoyl chloride (1.77 g, 1.46 mL, 12.6 mmol) was added dropwise, and the resulting mixture was stirred at rt overnight. The reaction mixture was then diluted with Et_2O (50 mL), washed with 2 M HCl (20 mL), H_2O (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 70:30) provided **28** as a white solid, which was contaminated with a single, unidentified byproduct (~15 mol %). Prior attempts at repeated purification had led to decomposition; consequently, this material was used directly in the preparation of *cis*-4-benzoyloxy-3-benzoyloxymethyl-2-methylenetetrahydrofuran (**24**). Characterization of **28**: IR (KBr) 3063, 2966, 1784, 1722, 1277, 1115, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (t, J = 8.1 Hz, 4H), 7.58 (m, 2H), 7.42 (m, 4H), 5.94 (m, 1H), 4.92 (dd, J = 11.5, 4.3 Hz, 1H), 4.69 (dd, J = 11.4, 8.7 Hz, 1H), 4.61 (dd, J = 11.1, 3.7 Hz, 1H), 4.53 (d, J = 11.2 Hz, 1H), 3.43 (m, 1H); MS (EI) m/z 218 (M^+ − BzOH), 122, 105 (100), 77, 51; HRMS (ESI) calcd for $C_{19}H_{16}NaO_6$ (M^+ + Na) m/z 363.0839, found 363.0825.

***trans*-3-Benzyloxymethyl-4-hydroxydihydrofuran-2(3*H*)-one (36).** *n*-BuLi (2.5 M in hexane, 10.8 mL, 27 mmol) was added dropwise to a solution of diisopropylamine (4.46 mL, 27 mmol) in THF (20 mL) at 0 °C. The resulting pale yellow solution was stirred at 0 °C for 10 min and cooled to −78 °C. A solution of β-hydroxy-γ-butyrolactone (**31**)[22] (1.1 g, 10.8 mmol) in THF (5 mL) was added dropwise. After stirring at −78 °C for 10 min, a solution of benzyloxymethyl chloride (1.86 g, 1.65 mL, 11.9 mmol) in HMPA (7 mL) was added dropwise. The reaction was stirred at −78 °C for 2 h. After the addition of 1 M HCl (50 mL), the mixture was extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with H_2O (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 1:1) afforded **35** (0.12 g, 5%) and **36** as clear oils (0.24 g, 10%). Characterization of **36**: IR (KBr) 3433 (br), 2868, 1772, 1458, 1363, 1178, 1109, 1026, 739, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.59 (m, 1H), 4.52 (m, 2H), 4.44 (m, 1H), 4.08 (dd, J = 9.4, 4.3 Hz, 1H), 3.79 (m, 2H), 3.01 (s, 1H), 2.72 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 137.6, 128.7, 128.1, 127.8, 74.1, 73.7,

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71.0, 67.6, 49.9; MS (EI) m/z 121 ($BnOCH_2$), 116 ($M^+ - BnOH$), 107, 91 (100), 79, 73; HRMS (ESI) calcd for $C_{12}H_{14}NaO_4$ ($M^+ + Na$) m/z 245.0784, found 245.0777.

***trans*-4-Benzoyloxy-3-(benzoyloxymethyl)dihydrofuran-2(3*H*)-one (29).** $Pd(OH)_2/C$ (50 mg) was added to a solution of *trans*-3-benzyloxymethyl-4-hydroxydihydrofuran-2(3*H*)-one (**36**) (0.19 g, 0.86 mmol) and EtOH (10 mL). The mixture was stirred at rt under H_2 for 2 h. It was then filtered through Celite and concentrated to give the corresponding diol as a clear oil (0.11 g, 99%): IR (KBr) 3406 (br), 2935, 1765, 1178, 1093, 1024 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 4.57 (m, 1H), 4.47 (dd, J = 9.4, 5.8 Hz, 1H), 4.10 (dd, J = 9.4, 3.5 Hz, 1H), 3.88 (m, 2H), 2.57 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 178.0, 74.4, 69.3, 58.6, 51.8; HRMS (ESI) calcd for $C_5H_8NaO_4$ ($M^+ + Na$) m/z 155.0315, found 155.0315. This diol was then mixed with CH_2Cl_2 (10 mL) and pyridine (0.67 g, 0.7 mL, 8.5 mmol). Benzoyl chloride (1.19 g, 1.0 mL, 8.5 mmol) was added dropwise, and the resulting mixture was stirred at rt overnight. It was then diluted with Et_2O (50 mL), washed with 2 M HCl (30 mL), H_2O (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 70:30) provided **29** as a white solid (0.22 g, 75%): mp 111−113 °C; IR (KBr) 3060, 2935, 1774, 1714, 1273, 1113, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (t, J = 8.4 Hz, 4H), 7.60 (m, 2H), 7.46 (m, 4H), 5.70 (m, 1H), 4.88 (dd, J = 11.4, 3.6 Hz, 1H), 4.80 (dd, J = 10.7, 6.2 Hz, 1H), 4.71 (dd, J = 11.4, 5.0 Hz, 1H), 4.45 (dd, J = 10.7, 3.4 Hz, 1H), 3.29 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 166.1, 134.1, 133.7, 130.0, 129.9, 128.8, 128.8, 73.1, 71.9, 62.2, 46.2; MS (EI) m/z 218 ($M^+ - BzOH$), 122, 105 (100), 77, 51; HRMS (ESI) calcd for $C_{19}H_{16}NaO_6$ ($M^+ + Na$) m/z 363.0839, found 363.0833.

3-Benzoyloxymethyl-2-methylenetetrahydrofuran (22). The general methylenation procedure was applied to 3-(benzoyloxymethyl)-dihydrofuran-2(3*H*)-one (**26**) (147 mg, 0.67 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc/Et_3N 95:4:1) afforded **22** as a pale yellow oil (76 mg, 54%): IR (KBr) 2957, 2893, 1720, 1276, 1113, 713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (m, 2H), 7.58 (m, 1H), 7.45 (t, J = 7.7 Hz, 2H), 4.47 (dd, J = 11.0, 5.8 Hz, 1H), 4.36 (m, 1H), 4.33 (dd, J = 11.0, 7.8 Hz, 1H), 4.20 (m, 1H), 4.09 (m, 1H), 3.97 (m, 1H), 3.21 (m, 1H), 2.28 (m, 1H), 1.97 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 162.8, 133.3, 130.2, 129.8, 128.6, 80.8, 69.2, 66.2, 40.6, 29.2; MS (EI) m/z 218 (M^+), 122, 105, 96 (100), 77; HRMS (ESI) calcd for $C_{13}H_{15}O_3$ ($M^+ + H$) m/z 219.1016, found 219.1003.

4-Benzoyloxy-2-methylenetetrahydrofuran (23). The general methylenation procedure was applied to 4-benzoyloxydihydrofuran-2(3*H*)-one (**27**) (148 mg, 0.72 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc/Et_3N 97:2:1) afforded **23** as a pale yellow oil (71 mg, 48%): IR (KBr) 2918, 1718, 1277, 1113, 712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (m, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 5.57 (m, 1H), 4.37 (s, 1H), 4.33 (m, 2H), 3.97 (s, 1H), 2.98 (m, 1H), 2.83 (d, J = 17.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 160.5, 133.5, 129.9, 129.9, 128.6, 81.4, 75.2, 73.7, 35.7; MS (EI) m/z 204 (M^+), 105 (100), 77, 51; HRMS (ESI) calcd for $C_{12}H_{13}O_3$ ($M^+ + H$) m/z 205.0859, found 205.0852.

***cis*-4-Benzoyloxy-3-benzoyloxymethyl-2-methylenetetrahydrofuran (24).** The general methylenation procedure was applied to *cis*-4-benzoyloxy-3-(benzoyloxymethyl)dihydrofuran-2(3*H*)-one (**28**) (90 mg, 0.26 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc/Et_3N 89:10:1) afforded **24** as a pale yellow oil (33 mg, 22% from **35** over 3 steps): IR (KBr) 2924, 1720, 1277, 1111, 1065, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (t, J = 8.4 Hz, 4H), 7.56 (m, 2H), 7.42 (m, 4H), 5.82 (m, 1H), 4.73 (dd, J = 11.1, 5.8 Hz, 1H), 4.59 (m, 1H), 4.51 (s, 1H), 4.34 (m, 2H), 4.10 (s, 1H), 3.51 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 166.0, 160.6, 133.7, 133.4, 129.9, 129.8, 129.6, 128.7, 128.6, 82.0, 74.2, 73.4, 61.6, 44.0; MS (EI) m/z 216 ($M^+ - BzOH$), 122, 105, 94 (100), 77, 51; HRMS (ESI) calcd for $C_{20}H_{18}NaO_5$ ($M^+ + Na$) m/z 361.1046, found 361.1040.

***trans*-4-Benzoyloxy-3-benzoyloxymethyl-2-methylenetetrahydrofuran (25).** The general methylenation procedure was applied to *trans*-4-benzoyloxy-3-(benzoyloxymethyl)dihydrofuran-2(3*H*)-one (**29**) (193 mg, 0.57 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc/Et_3N 89:10:1) afforded **25** as a pale yellow oil (111 mg, 58%): IR (KBr) 2924, 1718, 1275, 1111, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (m, 4H), 7.56 (m, 2H), 7.43 (m, 4H), 5.59 (m, 1H), 4.59 (dd, J = 11.4, 5.2 Hz, 1H), 4.52 (m, 2H), 4.42 (dd, J = 11.3, 8.1 Hz, 1H), 4.31 (dd, J = 10.5, 2.2 Hz, 1H), 4.12 (m, 1H), 3.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 166.2, 160.6, 133.6, 133.4, 129.9, 129.9, 129.8, 129.5, 128.7, 128.6, 83.4, 76.1, 73.7, 64.6, 47.3; MS (EI) m/z 216 ($M^+ - BzOH$), 122, 105, 94 (100), 77, 51; HRMS (ESI) calcd for $C_{20}H_{18}NaO_5$ ($M^+ + Na$) m/z 361.1046, found 361.1038.

4β-Benzoyloxy-3α-benzoyloxymethyl-β-2β-(6-chloro-9*H*-purin-9-yl)-2α-fluoromethyltetrahydrofuran (37). The general procedure for fluorine mediated nucleobase incorporation was applied to *trans*-4-benzoyloxy-3-benzoyloxymethyl-2-methylenetetrahydrofuran (**25**) (41 mg, 0.12 mmol). An ^1H NMR of the crude nucleosides showed >20:1 dr. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 65:35) afforded **37** as a white solid (44 mg, 72%): mp 141−143 °C; IR (KBr) 2922, 1720, 1589, 1560, 1271, 1115, 712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.53 (s, 1H), 8.11 (d, J = 7.5 Hz, 2H), 7.63 (m, 1H), 7.50 (m, 3H), 7.23 (m, 4H), 5.72 (m, 1H), 5.04 (dd, J = 46.1, 10.2 Hz, 1H), 4.97 (dd, J = 46.4, 9.9 Hz, 1H), 4.83 (m, 2H), 4.68 (m, 2H), 4.40 (d, J = 11.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 165.2, 151.9, 151.5, 151.0, 143.9, 133.9, 133.8, 133.0, 129.9, 129.3, 129.0, 128.9, 128.5, 128.2, 97.7 (d, J_{CF} = 19 Hz), 82.5 (d, J_{CF} = 182 Hz), 76.3, 74.6, 60.9, 50.7; HRMS (ESI) calcd for $C_{25}H_{20}ClFN_4NaO_5$ ($M^+ + Na$) m/z 533.0998, found 533.0987.

3-Benzoyloxydihydrofuran-2(3*H*)-one (38). 3-Hydroxydihydrofuran-2(3*H*)-one[39] (0.20 g, 2.0 mmol) was mixed with CH_2Cl_2 (8 mL) and pyridine (0.23 g, 0.24 mL, 2.94 mmol). Benzoyl chloride (0.41 g, 0.34 mL, 2.94 mmol) was added dropwise, and the resulting mixture was stirred at rt for 8 h. It was then diluted with Et_2O (20 mL), washed with 2 M HCl (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 70:30) provided **38** as a pale yellow oil (0.14 g, 35%): IR (KBr) 3064, 3003, 2924, 1788, 1726, 1269, 1176, 1111, 1016, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (m, 2H), 7.57 (m, 1H), 7.43 (m, 2H), 5.65 (dd, J = 9.5, 8.7 Hz, 1H), 4.50 (ddd, J = 9.1, 9.1, 2.5 Hz, 1H), 4.34 (ddd, J = 9.6, 9.6, 6.5 Hz, 1H), 2.79 (dddd, J = 12.9, 9.0, 6.5, 2.5 Hz, 1H), 4.41 (dddd, J = 12.9, 9.6, 9.6, 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 165.5, 133.8, 130.0, 128.8, 128.6, 68.3, 65.3, 29.0; MS (EI) m/z 206 (M^+), 122, 105 (100), 77, 51; HRMS (ESI) calcd for $C_{11}H_{10}NaO_4$ ($M^+ + Na$) m/z 229.0471, found 229.0461.

3-Benzoyloxy-2-methylenetetrahydrofuran (39). The general methylenation procedure was applied to 3-benzoyloxydihydrofuran-2(3*H*)-one (**38**) (0.127 g, 0.62 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc/Et_3N 89:10:1) afforded **39** as a pale yellow oil (88 mg, 70%): IR (KBr) 2924, 1718, 1655, 1275, 1176, 1115, 714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 7.7 Hz, 2H), 7.57 (m, 1H), 7.45 (m, 2H), 5.86 (m, 1H), 4.48 (s, 1H), 4.30 (m, 3H), 2.40 (m, 1H), 2.23 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 160.8, 133.4, 130.1, 129.9, 128.6, 84.8, 73.3, 68.9, 32.3; MS (EI) m/z 204 (M^+), 122, 105 (100), 77, 51; HRMS (ESI) calcd for $C_{12}H_{13}O_3$ ($M^+ + H$) m/z 205.0859, found 205.0839.

3α-Benzoyloxymethyl-2β-(6-chloro-9*H*-purin-9-yl)-2α-fluoromethyltetrahydrofuran (40). The general procedure for fluorine-mediated nucleobase incorporation was applied to 3-benzoyloxy-2-methylenetetrahydrofuran (**39**) (74 mg, 0.36 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc 60:40) afforded **40** as a white solid (99 mg, 73%, >16:1 dr). Characterization for the major isomer: mp 167−169 °C; IR (KBr) 3128, 3062, 2912, 1726, 1589, 1560, 1271, 1136, 1111, 933, 712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.40 (s, 1H), 8.07 (d, J = 7.6 Hz, 2H), 7.64 (t, J = 7.3 Hz, 1H), 7.51 (t, J = 7.5 Hz, 2H), 6.69 (s, 1H), 5.18

(dd, J = 46.1, 10.1 Hz, 1H), 5.00 (dd, J = 47.0, 10.1 Hz, 1H), 4.52 (ddd, J = 8.2, 8.2, 8.2 Hz, 1H), 4.41 (m, 1H), 2.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 152.1, 151.5, 150.5, 143.8, 134.0, 129.9, 129.0, 128.9, 97.8 (d, J_{CF} = 17 Hz), 82.0 (d, J_{CF} = 179 Hz), 77.3, 69.2, 31.5; HRMS (ESI) calcd for $C_{17}H_{14}ClFN_4NaO_3$ (M^+ + Na) m/z 399.0631, found 399.0650.

***S*-*tert*-Butyl *erythro*-2-benzyloxy-3-hydroxy-4-methylpentanethioate (42).**[26] $TiCl_4$ (1 M in CH_2Cl_2, 13.4 mL, 13.4 mmol) was added dropwise to a solution of *S*-*tert*-butyl 2-(benzyloxy)ethanethioate (**41**)[40] (2.13 g, 8.94 mmol) in CH_2Cl_2 (100 mL) at −78 °C. After 2 min, triethyl amine (1.9 mL, 13.4 mmol) was added dropwise. After 30 min stirring at −78 °C, isobutyraldehyde (1.22 mL, 13.4 mmol) was added, and the resulting solution was left at −78 °C for 3 h. The reaction was quenched with saturated $NaHCO_3$ (50 mL), and the resulting slurry was filtered through Celite. The organic layer was separated and washed with saturated $NaHCO_3$ (50 mL) and H_2O (50 mL), dried ($MgSO_4$), and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 92:8) afforded **42** as a pale yellow oil (2.5 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 5H), 4.83 (d, J = 11.3 Hz, 1H), 4.46 (d, J = 11.3 Hz, 1H), 3.83 (d, J = 6.4 Hz, 1H), 3.64 (ddd, J = 5.5, 5.2, 5.1 Hz, 1H), 2.24 (d, J = 4.6 Hz, 1H), 1.97 (m, 1H), 1.51 (s, 9H), 0.97 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.4, 137.2, 128.7, 128.4, 128.3, 86.3, 77.2, 73.7, 47.9, 30.0, 29.5, 19.9, 16.5.

***trans*-3-Benzyloxy-4-isopropyloxetan-2-one (43).** *S*-*tert*-Butyl *erythro*-2-benzyloxy-3-hydroxy-4-methylpentanethioate (**42**) (2.5 g, 8.1 mmol) was dissolved in CH_3CN (250 mL), and $Hg(OCOCF_3)_2$ (5.2 g, 12 mmol) was added. The resulting solution was immediately immersed in a preheated 50 °C oil bath and heated for 5 min. A white precipitate was formed, and the slurry was filtered through Celite and washed with CH_2Cl_2 and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 92:8) afforded **43** as a pale yellow oil (0.80 g, 45%): IR (KBr) 3033, 2964, 2877, 1834, 1142, 876, 744, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 5H), 4.85 (d, J = 11.7 Hz, 1H), 4.69 (d, J = 11.7 Hz, 1H), 4.61 (d, J = 3.6 Hz, 1H), 4.22 (dd, J = 8.4, 3.6 Hz, 1H), 1.89 (m, 1H), 1.04 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 136.4, 128.8, 128.6, 128.3, 84.5, 83.7, 72.7, 31.1, 18.1, 17.1; HRMS (ESI) calcd for $C_{13}H_{16}NaO_3$ (M^+ + Na) m/z 243.0992, found 243.0983.

***trans*-3-Hydroxy-4-isopropyloxetan-2-one (44).** $Pd(OH)_2/C$ (7 mg, 0.05 mmol) was added to a solution of *trans*-3-benzyloxy-4-isopropyloxetan-2-one (**43**) (56 mg, 0.25 mmol) in THF (5 mL). The mixture was stirred at rt under H_2 for 2 h. It was then filtered through Celite and concentrated to give **44** as a clear oil (33 mg, 100%): IR (KBr) 3437 (br), 2966, 2879, 1832, 1146, 874, 849 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83 (m, 1H), 4.19 (dd, J = 8.2, 3.2 Hz, 1H), 3.29 (br, 1H), 1.96 (m, 1H), 1.08 (d, J = 6.6 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 86.7, 78.5, 31.2, 18.2, 17.0; HRMS (ESI) calcd for $C_6H_{10}NaO_3$ (M^+ + Na) m/z 153.0522, found 153.0492.

***trans*-3-Benzoyloxy-4-isopropyloxetan-2-one (45).** *trans*-3-Hydroxy-4-isopropyloxetan-2-one (**44**) (30 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (2 mL), and pyridine (27 mg, 0.03 mL, 0.35 mmol) was added. Benzoyl chloride (49 mg, 0.04 mL, 0.35 mmol) was added dropwise, and the resulting mixture was stirred at rt for 2 h. The reaction mixture was then concentrated and purified by flash chromatography on silica gel (petroleum ether/EtOAc 90:10) to provide **45** as a clear oil (48 mg, 88%): IR (KBr) 2968, 2879, 1842, 1735, 1271, 1130, 710 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.5 Hz, 2H), 7.63 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 5.88 (d, J = 3.7 Hz, 1H), 4.41 (dd, J = 7.9, 3.7 Hz, 1H), 2.13 (m, 1H), 1.12 (d, J = 6.7 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 164.7, 134.3, 130.3, 128.8, 128.2, 84.4, 77.0, 31.0, 17.8, 17.1; HRMS (ESI) calcd for $C_{13}H_{15}O_4$ (M^+ + H) m/z 235.0965, found 235.0956.

***trans*-3-Benzoyloxy-4-isopropyl-2-methyleneoxetane (46).** The general methylenation procedure was applied to *trans*-3-benzoyloxy-4-isopropyloxetan-2-one (**45**) (48 mg, 0.21 mmol). Purification by flash chromatography on silica gel (petroleum ether/EtOAc/Et_3N 96:3:1) afforded **46** as a pale yellow oil (31 mg, 65%): IR (KBr) 2962, 2925, 2853, 1729, 1700, 1274, 1119, 711 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 7.5 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.48 (d, J = 7.8 Hz, 2H), 5.80 (m, 1H), 4.56 (dd, J = 7.7, 3.9 Hz, 1H), 4.36 (dd, J = 3.7, 2.0 Hz, 1H), 4.21 (dd, J = 3.7, 1.2 Hz, 1H), 2.21 (m, 1H), 1.06 (d, J = 6.7 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 161.7, 133.7, 130.1, 129.5, 128.7, 91.1, 83.4, 71.9, 31.5, 17.3, 16.7; HRMS (ESI) calcd for $C_{14}H_{16}NaO_3$ (M^+ + Na) m/z 255.0992, found 255.0988.

3α-Benzoyloxy-2β-(6-chloro-9*H*-purin-9-yl)-2α-fluoromethyl-4β-isopropyloxetane (47) and 3α-Benzoyloxy-2β-(6-chloro-7*H*-purin-7-yl)-2α-fluoromethyl-4-isopropyloxetane (48). The general procedure for fluorine-mediated nucleobase incorporation was applied to *trans*-3-benzoyloxy-4-isopropyl-2-methyleneoxetane (**46**) (45 mg, 0.19 mmol). ^{1}H NMR of the crude mixture showed a 1:1 ratio of two fluorinated nucleosides. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 70:30−60:40) afforded **47** as a clear wax (27 mg, 34%) and **48** as a clear wax (26 mg, 34%). Characterization of **47**: IR (KBr) 2963, 2924, 2852, 1737, 1732, 1590, 1562, 1266, 1123, 711 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H, H2), 8.59 (s, 1H, H8), 8.12 (d, J = 7.4 Hz, 2H), 7.68 (t, J = 7.4 Hz, 1H), 7.54 (t, J = 7.6 Hz, 2H), 6.10 (d, J = 5.6 Hz, 1H), 5.32 (dd, J = 46.4, 10.6 Hz, 1H), 5.19 (dd, J = 46.3, 10.6 Hz, 1H), 4.65 (dd, J = 7.9, 5.6 Hz, 1H), 2.15 (m, 1H), 1.04 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 152.5 (C2), 151.9 (C4), 150.8 (C6), 143.0 (C8), 134.3, 132.7, 130.2, 129.0, 128.6 (C5), 92.7 (d, J_{CF} = 19 Hz), 90.1, 80.8 (d, J_{CF} = 182 Hz), 73.1, 32.6, 17.3, 16.4; HRMS (ESI) calcd for $C_{19}H_{19}ClFN_4O_3$ (M^+ + H) m/z 405.1124, found 405.1128. Characterization of **48**: IR (KBr) 2964, 2924, 1734, 1268, 1119, 711 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.94 (s, 1H), 8.12 (dd, J = 7.2, 1.3 Hz, 2H), 7.69 (tt, J = 7.5, 1.2 Hz, 1H), 7.55 (tt, J = 7.9, 1.6 Hz, 2H), 5.96 (d, J = 4.7 Hz, 1H), 5.22 (dd, J = 46.4, 10.5 Hz, 1H), 5.13 (dd, J = 46.4, 10.6 Hz, 1H), 4.62 (dd, J = 8.0, 4.8 Hz, 1H), 2.03 (m, 1H), 1.03 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 163.7 (C4), 153.2 (C2), 147.8 (C8), 142.7 (C6), 134.6, 130.2, 129.2, 128.4, 121.8 (C5), 93.8 (d, J_{CF} = 19 Hz), 90.6, 82.6 (d, J_{CF} = 183 Hz), 74.0, 32.6, 17.2, 16.5; HRMS (ESI) calcd for $C_{19}H_{19}ClFN_4O_3$ (M^+ + H) m/z 405.1124, found 405.1124.

Calculational Details. Calculations were carried out on the three model structures shown in Figure 4 (starting material, open carbocation, and cyclic oxonium ion) and on the corresponding system with a five-membered ring. Trial conformations were generated by setting the three dihedral angles a, b, and d to initial values of ±60 and 180°, and the dihedral angle c to initial values of 0 (*Z*) and 180° (E). This approach yielded 54 (3 × 3 × 3 × 2) starting structures for each of the two starting materials, 18 (3 × 3 × 2) starting structures for each of the two open carbocations and three starting structures for each of the two cyclic oxonium ion.

For each trial structure, initial geometry optimization was carried out at HF/6-31G*. In some cases, more than one starting structure yielded a single optimized structure; that is, the total number of unique conformations was less than the number of starting conformations. Subsequent CBS-QB3 calculations were carried out each unique structure.[41] All structures were of C1 symmetry and were verified as minima via calculation of analytical second derivatives.

All calculations were performed using the Gaussian 09 package.[42] Energies as well as key dihedral angles and distances are provided with the Supporting Information.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data, as well as copies of high-resolution ^{1}H and ^{13}C NMR spectra for new compounds. A file of energies of intermediates, as well as key dihedral angles and distances. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) (a) Shimada, N.; Hasegawa, S.; Harada, T.; Tomisawa, T.; Fujii, A.; Takita, T. *J. Antibiot.* **1986**, *39*, 1623. (b) Nakamura, H.; Hasegawa, S.; Shimada, N.; Fujii, A.; Takita, T.; Iitaka, Y. *J. Antibiot.* **1986**, *39*, 1626.

(2) Hoshino, H.; Shimizu, N. *J. Antibiot.* **1987**, *40*, 1077.

(3) Ichikawa, E.; Kato, K. *Synthesis* **2002**, 1.

(4) Alder, J.; Mitten, M.; Norbeck, D.; Marsh, K.; Kern, E. R.; Clement, J. *Antiviral Res.* **1994**, *23*, 93.

(5) Nagahata, T.; Kitagawa, M.; Matsubari, K. *Antimicrob. Agents Chemother.* **1994**, *38*, 707.

(6) Nishiyama, Y.; Yamamoto, N.; Takahash, K.; Shimada, N. *Antimicrob. Agents Chemother.* **1988**, *32*, 1053.

(7) Richardson, S. K.; Howell, A. R.; Taboada, R. *Org. Prep. Proced. Int.* **2006**, *38*, 101.

(8) Howell, A. R.; Ndakala, A. J. *Org. Lett.* **1999**, *1*, 825.

(9) Taboada, R.; Ordonio, G. G.; Ndakala, A. J.; Howell, A. R.; Rablen, P. R. *J. Org. Chem.* **2003**, *68*, 1480.

(10) Molas, P.; Diaz, Y.; Matheu, M. I.; Castillon, S. *Synlett* **2003**, 207.

(11) (a) Schmidt, J. A. R.; Viswanath, M.; Getzler, Y. D. Y. L.; Coates, G. W. *Org. Lett.* **2004**, *6*, 373. (b) Rowley, J. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2007**, *129*, 4948. (c) Schmidt, J. A. R.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2005**, *127*, 11426.

(12) Dollinger, L. M.; Ndakala, A. J.; Hashemzadeh, M.; Wang, G.; Wang, Y.; Martinez, I.; Arcari, J. T.; Galluzzo, D. J.; Howell, A. R.; Rheingold, A. L.; Figuero, J. S. *J. Org. Chem.* **1999**, *64*, 7074.

(13) For examples, see: (a) Haraguchi, K.; Matsui, H.; Takami, S.; Tanaka, H. *J. Org. Chem.* **2009**, *74*, 2616. (b) Choudhury, A.; Jin, F.; Wang, D.; Wang, Z.; Xu, G.; Nguyen, D.; Castoro, J.; Pierce, M. E.; Confalone, P. N. *Tetrahedron Lett.* **2003**, *44*, 247.

(14) (a) Framski, G.; Gdaniec, Z.; Gdaniec, M.; Boryski, J. *Tetrahedron* **2006**, *62*, 10123. (b) Boryski, J. *Nucleosides, Nucleotides* **1996**, *15*, 771. (c) Sugimura, H.; Osumi, K.; Kodaka, Y.; Sujino, K. *J. Org. Chem.* **1994**, *59*, 7653.

(15) Seckarova, P.; Marek, R.; Malinakova, K.; Kolehmainen, E.; Hockova, D.; Hocek, M.; Sklenar, V. *Tetrahedron Lett.* **2004**, *45*, 6259.

(16) It should be noted that 10−15% of 6-methoxypurine byproduct has been isolated in both cases, indicating methanol may be a competing nucleophile. The yield was improved using 2-propanol as the solvent.

(17) See Supporting Information.

(18) Nishiyama, S.; Yamamura, S.; Kato, K.; Takita, T. *Tetrahedron Lett.* **1988**, *29*, 4743.

(19) Nishizono, N.; Akama, Y.; Agata, M.; Sugo, M.; Yamaguchi, Y.; Oda, K. *Tetrahedron* **2011**, *67*, 358.

(20) (a) Azzena, F.; Calvani, F.; Crotti, P.; Gardelli, C.; Macchia, F.; Pineschi, M. *Tetrahedron* **1995**, *51*, 10601. (b) Nobutaka, F.; Kazuo, N.; Hiromu, H.; Yuka, H.; Hirokazu, T.; Akira, O.; Toshiro, I. *Chem. Pharm. Bull.* **1994**, *42*, 2241.

(21) Sime, J. T.; Barnes, R. D.; Elson, S. W.; Jarvest, R. L.; O'Toole, K. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1653.

(22) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208.

(23) Motozaki, T.; Sawamura, K.; Suzuki, A.; Yoshida, K.; Ueki, T.; Ohara, A.; Munakata, R.; Takao, K.-i.; Tadano, K.-i. *Org. Lett.* **2005**, *7*, 2261.

(24) *cis*-γ-Lactone **28** was contaminated with a minor byproduct due to partial decomposition on silica gel during column chromatography. The mixture, however, was carried forward to the methylenation step to give **24** as a pure compound. The yield of **24** was calculated from **35** over three steps.

(25) Crich, D.; Hu, T.; Cai, F. *J. Org. Chem.* **2008**, *73*, 8942.

(26) Annumziata, R.; Cinquini, M.; Cozzi, F.; Lombardi Borgia, A. *J. Org. Chem.* **1992**, *57*, 6339.

(27) It is noteworthy that lactone **44** obtained in this hydrogenolysis step reacted with alcoholic solvents to give ring-opened products under these conditions. Consequently, THF was used as the solvent.

(28) (a) Rhoad, J. S.; Cagg, B. A.; Carver, P. W. *J. Phys. Chem. A* **2010**, *114*, 5180. (b) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879.

(29) Stalford, S. A; Kilner, C. A.; Leach, A. G.; Turnbull, W. B. *Org. Biomol. Chem.* **2009**, *7*, 4842.

(30) In a synthesis of a "ring-enlarged" OXT-A analogue, a furan with a benzoate in the same relative position as the benzoate in **24** underwent preferential β-face nucleobase incorporation. Anchimeric assistance was invoked, although it was said to be "less efficient" than when a system related to **39** was used. Our argument for the reason **24** gives multiple products is provided in this paragraph: Tseng, C. K.-H.; Marquez, V. E.; Milne, G. W. A.; Wysocki, R. J. Jr.; Mitsuya, H.; Shirasaki, T.; Driscoll, J. S. *J. Med. Chem.* **1991**, *34*, 343.

(31) Namchuk, M. N.; McCarter, J. D.; Becalski, A.; Andrews, T.; Withers, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 1270.

(32) (a) Luo, M.-Z.; Liu, M. C.; Mozdziesz, D. E.; Lin, T.-S.; Dutschman, G. E.; Gullen, E. A.; Cheng, Y.-C.; Sartorelli, A. C. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2145. (b) Lee, K.; Choi, Y.; Gullen, E.; Schlueter-Wirtz, S.; Schinazu, R. F.; Cheng, Y.-C.; Chu, C. K. *J. Med. Chem.* **1999**, *42*, 1320.

(33) Chu, C. K.; Ullas, G. V.; Jeong, L. S.; Ahn, S. I.; Doboszewski, B.; Lin, Z. X.; Beach, J. W.; Schinazi, R. F. *J. Med. Chem.* **1990**, *33*, 1553.

(34) Abraham, E.; Davis, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655.

(35) Righi, G.; Pescatore, G.; Bonadies, F.; Bonini, C. *Tetrahedron* **2001**, *57*, 5649.

(36) Nishizono, N.; Baba, R.; Nakamura, C.; Oda, K.; Machida, M. *Org. Biomol. Chem.* **2003**, *1*, 3692.

(37) Moseley, J.; Staunton, J. *Tetrahedron: Asymmetry* **2000**, *11*, 3197.

(38) Ueki, T.; Kinoshita, T. *Org. Biomol. Chem.* **2004**, *2*, 2777.

(39) Shiuey, S-J; Partridge, J. J.; Uskokovic, M. R. *J. Org. Chem.* **1988**, *53*, 1040.

(40) Gennari, C.; Vulpetti, A.; Pain, G. *Tetrahedron* **1997**, *53*, 5909.

(41) (a) Montgomery, J. A. Jr.; Frisch, M. J.; Ochterski, J. W.; Petersson, G. A. *J. Chem. Phys.* **1999**, *110*, 2822. (b) Montgomery, J. A. Jr.; Frisch, M. J.; Ochterski, J. W.; Petersson, G. A. *J. Chem. Phys.* **2000**, *112*, 6532.

(42) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, revision A.02; Gaussian, Inc.: Wallingford, CT, 2009.