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Oxetane Ring-Opening Reaction: a Key Step for the Preparation of Substituted (Fluoro)alkenyl as Acyclonucleoside Mimics

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Abstract: The ring-opening reaction of functionalized oxetanes opens a direct access to tri- and tetra-substituted alkenes, including fluoroalkenes. The introduction of adenosine nucleic base allows the preparation of alkenyl and fluoroalkenyl derivatives that were evaluated towards DItA enzyme as potential nucleoside mimics.

Introduction

The emergence of viral and bacterial diseases, illustrated by the recent viral pandemic and the apparition of bacterial resistance phenomena, needs to identify new biological targets and develop new drugs.^[1] Modified nucleosides and their analogues represent an important class of compounds to treat these diseases.^[2,3] The structural modification of naturally occurring nucleosides was essential to improve their *in vivo* stability and efficacy towards a viral target. The synthesis of acyclonucleosides was early explored leading to the discovery of Acyclovir, Cidofovir, and Tenofovir to fight viruses such as Herpes or HIV, and more recently Ebola.^[1-3] Since these pioneering works, acyclonucleosides synthesis are still an ongoing task in drug discovery to develop new drugs targeting specific enzymes related to diseases caused by bacteria or parasites.^[4-6] Alkylated nucleic bases by a β -hydroxy- or -amino-phosphonates alkyl chain were described as potent inhibitors of parasites growth,^[7-11] and antibacterial agents, controlling bacterial growth.^[12,13] To limit conformational change of acyclonucleosides the incorporation of a carbon-carbon double bond onto the backbone was benefit. Indeed, alkylated nucleic bases containing a functionalized butenyl alkyl chain, such as (*E*)-butenylphosphonates, were described as efficient substrate of kinases (TK) and polymerases (Figure 1).^[14-22] This successful backbone modification was also found in novel class of human deoxyuridine inhibitors and new generation of modified oligonucleotides (Figure 1).^[23] While the introduction of a fluorine atom onto nucleos(t)ides has been intensively studied to prepare new drugs for cancer therapy or antivirals,^[24] the synthesis of fluoroalkenyl acyclonucleosides related to (*E*)-butenyl, such as compounds **1** or **2**, was scarcely described (Figure 1).^[25-29] The introduction of a fluorine atom onto the carbon-carbon double bond was achieved to modify the polarity and the electronic distribution of the molecule. Except these works no other examples were reported due to limited access to diversely functionalized fluorobutenyl nucleosides. Indeed, diol **2** cannot be selectively functionalized.

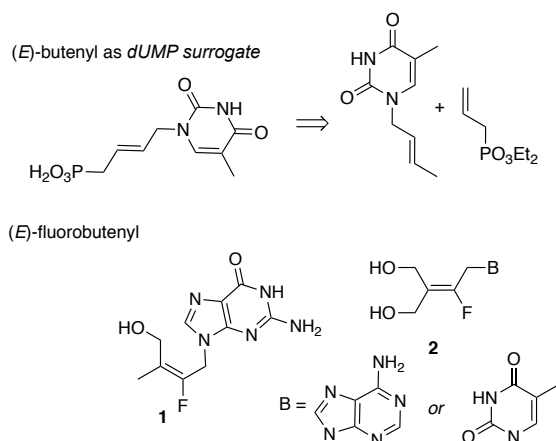
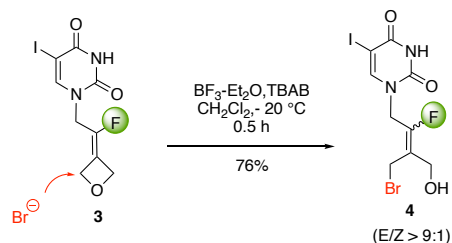


Figure 1. (Fluoro)-Alkenylacyclonucleosides.

In addition, in contrast to (*E*)-butenyl derivatives that can be easily prepared by cross metathesis reactions, synthesis of tetrasubstituted fluoroalkenes are not possible directly by this way.^[30,31] To extend the scope of the preparation diversely substituted acyclonucleoside analogues from functionalized fluoroalkenyls we explored an alternative approach based on the ring-opening reaction of oxetanes.

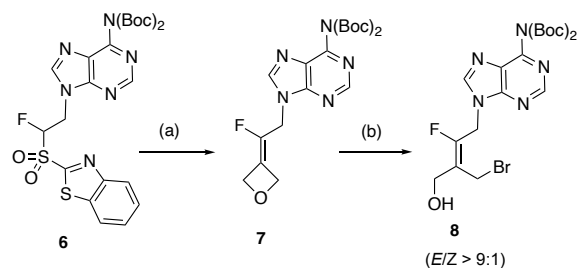
Results and Discussion

In our preliminary report we described a ring-opening reaction of functionalized fluoroalkylidene-oxetanes to access to tetrasubstituted fluoroalkenes instead of an olefination reaction of carbonyl compounds.^[32] This reaction was investigated to prepare fluoro-alkenyls substituted by a nucleic base to access to acyclonucleoside analogues related to (*E*)-butenyl derivatives. Alkylidene oxetanes **3** substituted by a 5-iodo-uracil was tested to study the ring-opening reaction (Scheme 1). Conducted in the presence of TBAB (Bu_4NBr) as bromide source and a Lewis acid ($\text{BF}_3\text{-Et}_2\text{O}$), the corresponding allylic derivatives **4** was obtained in high yields (76%) and excellent *E*-selectivity up to 9:1 (Scheme 1). Importantly, the oxetane ring-opening reaction with bromide ion was observed being highly selective. Based on this first result we were engaged in the preparation of functionalized analogues of butenyl acyclonucleosides.



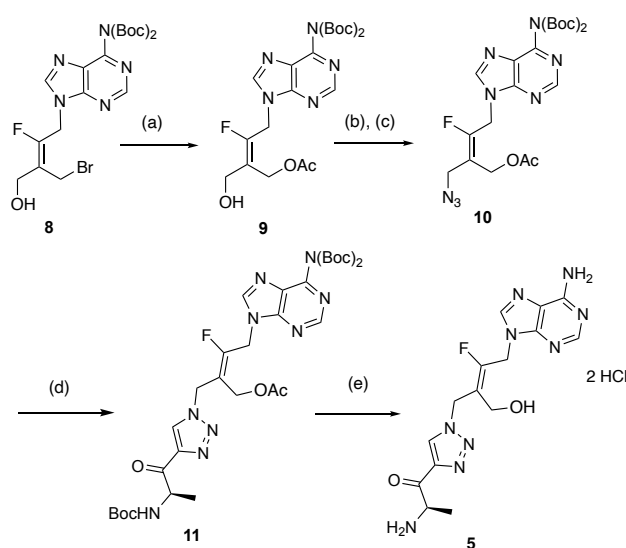
Scheme 1. Ring-opening reaction of an oxetane containing a nucleic base.

We focused this work on the synthesis of analogues of functionalized adenine derivatives as enzyme inhibitors. In connection with our recent work related to the preparation of inhibitors of a protein implicated in the antibioresistance,^[33-35] we wanted to know what would be the influence of the fluorinated derivative **5** containing an alkenyl chain in place of the ribosyl ring onto its biological activity (Scheme 3). Based on the preliminary work realized with iodo-uracil derivative **3** the ring-opening reaction of fluoroalkylidene **7** substituted with an adenine was explored to access to tetrasubstituted alkene **8** (Scheme 2). This latter was obtained from 3-oxetanone and an appropriate sulfone **6** engaged in the modified Julia reaction to afford oxetane **7** in 76% yield.^[28, 36] From compound **7** the reaction was conducted in the presence of TBAB (Bu_4NBr) as bromide source and a Lewis acid ($\text{BF}_3\text{-Et}_2\text{O}$). To our delight, the corresponding allylic derivatives **8** was obtained in high yield (72%) and with an excellent *E*-selectivity up to 9:1 (Scheme 2).^[37]



Scheme 2. Preparation of tetra-substituted fluoroalkene derivative by ring-opening reaction. (a) LiHMDS, 3-oxetanone, THF, -78°C to 20°C , 4 h, 76%. (b) TBAB, $\text{BF}_3\text{-OEt}_2$, CH_2Cl_2 , -20°C , 3 h, 72%.

To access to the final target compound **5**, the preparation of fluorinated azide **10** was realized from tetrasubstituted (*E*)-alkene **8**. The substitution of the bromine atom was performed with KOAc to afford intermediate acetylated alcohol **9**, which was mesylated then treated with NaN_3 to give azide **10** in 74% overall yield. Finally, the expected fluorinated triazolyl **11** was obtained in 79% yield from **10** and *N*-Boc 4-amino-pentynone. Compound **11** was treated by an acidic methanolic solution to give **5** in 76% yield (Scheme 3).

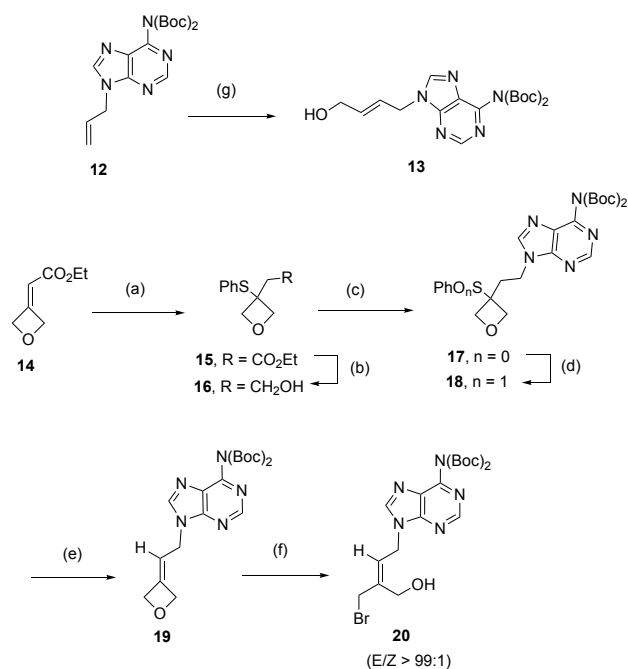


Scheme 3. Preparation of triazolyl derivatives in F-series. (a) KOAc, DMF, 20°C , 16 h, 86%. (b) MsCl, Et_3N , CH_2Cl_2 , 0°C , 2 h, (c) NaN_3 , DMF, 20°C , 12 h, 74% (2 steps). (d) *N*-Boc-amino-pentynone, $\text{CuSO}_4\cdot 5\text{H}_2\text{O}$, sodium ascorbate, *t*-BuOH, H_2O , 40°C , 24 h, 79%. (d) HCl_{aq} (3N), MeOH, 20°C , 20 h, 76%.

The preparation of non-fluorinated *trans*-butenyl series was investigated. The disubstituted (*E*)-butenyl derivative **13** was easily obtained in one step in 60% yield by an olefin cross-metathesis reaction from allylic alcohol and *N*-allyl *N*-Boc₂-adenine **12**, following previous reported methods (Scheme 4).^[38] However, the preparation of alkene **20** cannot be performed by an olefin cross-metathesis reaction due to a moderate control of the carbon-carbon double bond geometry. Thus, the ring-opening reaction of alkylidene oxetane **19** was tested. To access to **19** the olefination reaction of 3-oxetanone was not successful,^[39] and compound **19** was prepared from the known carboxylic ester **14** (Scheme 4). Ester **14** was transformed in sulfoxide **18** in four steps in 60% overall yield, including a thiol conjugate addition and the adenine introduction steps. The intermediate sulfoxide **18** was submitted to elimination of sulfenic acid to install the required carbon-carbon double bond. A fast elimination reaction was observed when this sulfoxide **18** was heated at 160°C under micro-wave irradiation (200 W) over 45 minutes to afford the expected alkylidene oxetane **19** in 74% yield.

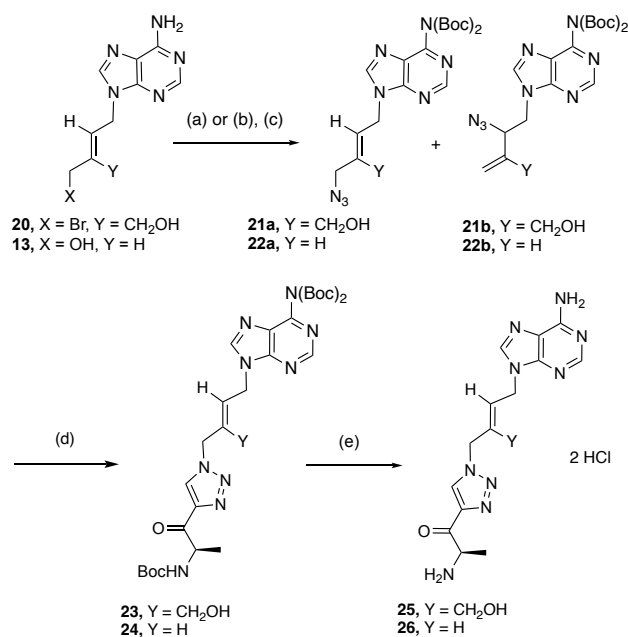
The oxetane ring-opening reaction was studied from **19** and conducted following our reported procedure (HBr 33% in AcOH, TBAB).^[32] In this case, the reaction was selective and when

performed with **19** the (*E*)-bromoalcohol **20** was obtained exclusively in good yield (77%), the *Z* isomer was not detected in the crude.



Scheme 4. Preparation of alkenes by ring-opening reaction and metathesis. ^aConditions: (a) PhSH, TBAF cat, THF, 20 °C, 12 h, 89%. (b) LiAlH₄, THF, 20 °C, 2 h, 88%. (c) *N*⁶-(Boc)₂-Adenine, DIAD, PPh₃, THF, 20 °C, 12 h, 90%. (d) NaIO₄, MeOH/H₂O (5:1), 40 °C, 12 h, 85%. (e) 160 °C, 45 min, toluene, MW, 200 W, 74%. (f) HBr, AcOH, TBAB, CH₂Cl₂, Et₂O, -20 °C, 1 h, 77%. (g) Allylic alcohol, Grubb's II (10 mol%), CH₂Cl₂, 40 °C, 16 h, 60%.

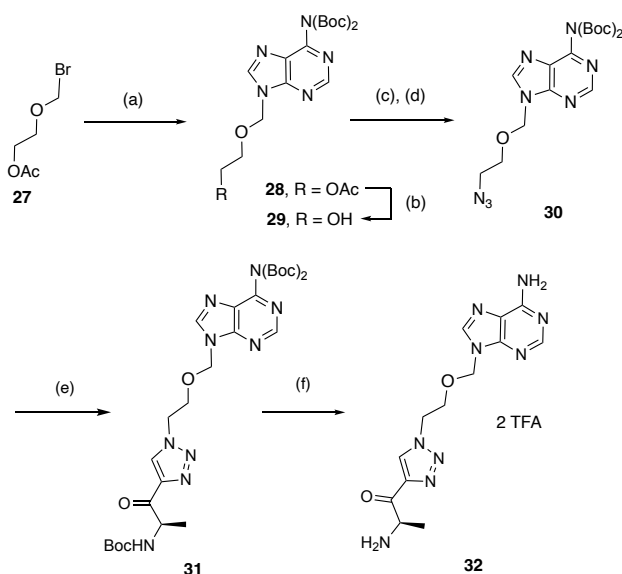
The incorporation of the triazolyl linker was investigated from these alkenyl derivatives **20** and **13** (Scheme 5). From bromide **20** the direct introduction of the azide function with NaN₃ led to a mixture of primary and secondary azides **21a** and **21b** in 92% yield (64/36 ratio) due to a competitive azide-sigmatropic rearrangement.^[40]



Scheme 5. Preparation of triazolyl derivatives in H-series. (a) for **20**: NaN₃, DMF 20 °C, 12 h, 92%. (b) for **13**: (b) MsCl, Et₃N, CH₂Cl₂, 0 °C, 2 h. (c) NaN₃, DMF 20 °C, 12 h, 90% (2 steps). (d) *N*-Boc-amino-pentynone, CuSO₄·5H₂O, sodium ascorbate, *t*-BuOH, H₂O, 40 °C, 24 h, 52-69%. (e) HCl_{aq} (3N), MeOH, 20 °C, 20 h, 70-82%.

From alcohol **13**, the preparation of the intermediate mesylate was achieved prior to the azide substitution reaction. Again, during the treatment of the intermediate mesylate with NaN₃ an azide-sigmatropic rearrangement occurred to give a mixture of **22a** and **22b** (74/26 ratio) in 90% yield. In these two cases, the separation of the azides was difficult and the mixture of isomers was submitted to the next step without further purification. The mixtures of azides **21a,b** and **22a,b** were engaged in the cycloaddition reaction with *N*-Boc 4-amino-pentynone to give a mixture of corresponding triazolyl derivatives, which were easily separated by flash chromatography. Finally, triazolyl derivatives **23** and **24** were isolated in 52% and 69% yields, respectively. Triazolyl derivatives **23**, **24** were fully deprotected with HCl (3N) in MeOH to afford compounds **25** and **26** in 70-82% yields.

Finally, a last series was prepared containing the alkyl chain of the acyclovir. The triazolyl acyclonucleoside **32** containing an alkylether chain was prepared following a similar approach (Scheme 6). Alcohol **27** was transformed into the corresponding azide **30** after formation of the intermediate mesylate. This latter involved in the 1,3-cycloaddition reaction gave the triazolyl derivative **31**, and the expected acyclonucleoside analogue **32** after cleavage of the protecting groups. Having in hand the acyclonucleosides **5**, **25**, **26**, **32** their inhibitory activity towards DltA enzyme was evaluated and compared to the corresponding nucleosides.

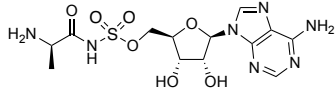
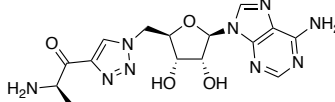
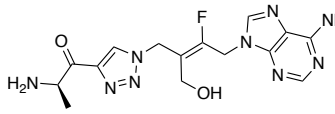
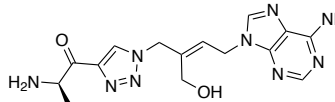
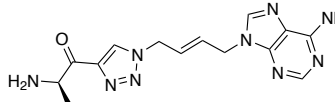
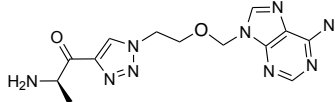


Scheme 6. Preparation of triazolyl derivative. (a) *N*⁶-(Boc)₂-Adenine, NaH, THF, 20 °C, 6 h, 62%. (b) K₂CO₃, MeOH, 20 °C, 0.5 h, 67%. (c) MsCl, Et₃N, CH₂Cl₂, 20 °C, 2 h. (d) NaN₃, DMF, 85 °C, 4 h, 80% (2 steps). (e) *N*-Boc-amino-pentynone, CuSO₄·5H₂O, sodium ascorbate, *t*-BuOH, H₂O, 40 °C, 24 h, 75%. (f) TFA, H₂O, CH₂Cl₂, 20 °C, 5 h, 84%.

Biological evaluation.^[35] The inhibition activities of all new compounds towards DltA enzyme (*Enterococcus faecalis*) were investigated and the values were compared to nucleoside **33** and triazolyl **34** (Table 1). The inhibition activity of compound **34** was evaluated and it appeared that the introduction of a triazolyl ring did not perturb the activity. Indeed, compound **34** appeared as potent inhibitor as acylsulfamate **33** with an IC₅₀ value of 3.4 μM. The replacement of the ribosyl ring by a fluoro *trans*-butenyl moiety was also well tolerated and compound **5** was recognized by the DltA enzyme. In the case of triazolyl **5** an IC₅₀ value of 7.4 μM was obtained, slightly higher to the value observed with adenosine derivative **34**. This first example of the use of fluorinated acyclonucleoside shows clearly that the fluorobutenyl moiety can be considered as a surrogate of the ribosyl moiety of nucleoside in view of the observed IC₅₀. The IC₅₀ values observed for triazolyl

derivatives **25** and **26** (10.5 μM and 13.8 μM , respectively), confirmed the mimicry between a butenyl moiety and a ribosyl ring of a nucleoside. In the present case the carbon-carbon double bond is crucial to improve the activity of acyclonucleosides, as reported for thymidylate kinase *trans*-butenyl substrates.^[20-21] Indeed, the acyclic analogue **32** containing an alkylether chain (2-oxa-butyl) instead of a (fluoro)alkenyl chain was the less efficient inhibitor of DltA enzyme with an inhibition constant of 20.1 μM . This lost in activity was probably related to the high flexibility of the alkyl chain allowing conformational changes. Importantly, the presence of the hydroxymethyl function onto the carbon-carbon double bond is also essential to improve the activity of butenyl derivatives (**25** vs **26**), and the presence of a fluorine atom appeared to be benefit. The (*E*)-fluorobutenyl moiety appeared as the best nucleoside mimic in the butenyl series (**25** vs **5**).

Table 1. Measured IC₅₀ values of compounds 3-8 towards DltA of *E. faecalis*.

Compound ^[a]	IC ₅₀ (μM)
33 	2.5 \pm 0.37
34 	3.4 \pm 1.80
5 	7.4 \pm 1.29
25 	10.4 \pm 0.50
26 	13.8 \pm 0.40
32 	20.1 \pm 0.6

[a] Determined with the HCl salts for compounds **5**, **25**, **26** and CF₃COOH salts for compounds **33**, **34**, **32**.

Conclusion

The selective ring-opening reaction of oxetane opened a direct access to tri- and tetrasubstituted allylic bromoalcohol in high *E* selectivity. These were involved in the synthesis of modified nucleosides in few steps. Some representative compounds revealed an inhibitory activity towards DltA enzyme close to the original nucleosides used in this study. In particular an acyclonucleoside containing an undescribed (fluoro)-alkenyl backbone instead of a ribose ring appears as efficient as a triazolyl nucleoside. This fluorinated backbone would be considered as a new nucleoside surrogate.

Experimental Section

General procedure for Oxetane Ring Opening Reaction of compounds (7) and (19).

(Method A): To a solution of alkylidene-oxetane (1 equiv.) in CH₂Cl₂/Et₂O (0.05 M, 4:10, v/v) was added *n*Bu₄Br (2.5 equiv.). A solution of 33% HBr in AcOH (1 equiv.) was added dropwise to the previous solution at –20 °C. The mixture was stirred for 1 h then the mixture was quenched with an aqueous solution of saturated NaHCO₃. The aqueous layer was extracted three times with EtOAc then combined organic layers was washed with brine/H₂O (1:1), dried over MgSO₄, filtered and concentrated under reduced pressure.

(Method B): To a solution of alkylidene-oxetane (1 equiv.) in CH₂Cl₂ (0.03 M) was added *n*Bu₄Br (2.5 equiv.) followed by addition of BF₃.OEt₂ (1.2 equiv.) to the previous solution at –20 °C. The mixture was stirred for 3 h then the mixture was quenched with an aqueous solution of saturated NaHCO₃. The aqueous layer was extracted three times with Et₂O then combined organic layers was washed with brine/H₂O (1:1), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to give bromo-alcohol.

N⁶,N⁶-Bis(tert-butoxycarbonyl)-(E)-(9-(4-bromo-2-fluoro-3-(hydroxymethyl)but-2-en-1-yl)-9H-purin-6-amine (8). The general procedure for Oxetane Ring Opening Reaction (Method B) was followed with (fluoro)alkenyl-oxetane **7** (128 mg, 0.29 mmol), *n*Bu₄Br (242 mg, 0.73 mmol) and BF₃.Et₂O (45 μL, 0.35 mmol) in CH₂Cl₂ (10.8 mL). The crude product was purified by column chromatography on silica gel (Eluent Pentane/EtOAc 4:6) to give (*E*)-**8** (110 mg, 0.21 mmol, 72%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 1.44 (s, 18H), 4.36 (d, *J* = 3.2 Hz, 2H), 4.44 (d, *J* = 1.1 Hz, 2H), 5.11 (d, *J* = 21.6 Hz, 2H), 8.17 (s, 1H), 8.85 (s, 1H); ¹⁹F NMR (470 MHz, CDCl₃) δ –107.8 (t, *J* = 21.6 Hz, 1F); ¹³C NMR (125 MHz, CDCl₃) δ 153.2, 152.6, 151.8 (d, *J* = 258.9 Hz), 150.7, 150.6, 144.3, 128.5, 121.1 (d, *J* = 15.2 Hz), 84.1, 56.4 (d, *J* = 8.1 Hz), 41.0 (d, *J* = 30.1 Hz), 28.0, 26.8 (d, *J* = 9.1 Hz); HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₀H₂₈BrFN₅O₅, 516.1258; found 516.1255.

N⁶,N⁶-Bis(tert-butoxycarbonyl)-(E)-(9-(4-bromo-3-(hydroxymethyl) but-2-en-1-yl)-9H-purin-6-amine (20). The general procedure for Oxetane Ring Opening Reaction (Method A) was followed with alkenyl-oxetane **19** (325 mg, 0.78 mmol), tetra-*n*-butylammonium bromide (628 mg, 1.95 mmol) and HBr (33% wt) in AcOH (0.13 mL, 0.78 mmol) in CH₂Cl₂/Et₂O (4:12 mL). The crude product was purified by column chromatography on silica gel (Eluent EtOAc/Pentane 8:2) to give (*E*)-**20** (300 mg, 0.60 mmol, 77%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 8.82 (s, 1H), 8.11 (s, 1H), 5.79 (t, *J* = 7.8 Hz, 1H), 5.06 (d, *J* = 7.8 Hz, 2H), 4.54 (s, 2H), 4.04 (s, 2H), 1.47 (s, 18H); ¹³C NMR (125 MHz, CDCl₃) δ 152.8, 151.9, 150.9, 150.6, 144.7, 142.8, 129.4, 124.1, 84.2, 58.7, 41.8, 35.2, 27.9; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₀H₂₉N₅O₅Br, 498.1352; found 498.1349.

All experimental details are provided in the Supporting Information, including details on a) reaction condition; b) analytical data, ¹H, ¹³C and ¹⁹F NMR spectroscopy, high-resolution mass spectrometry; and c) NMR spectra for all compounds.

Acknowledgements

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