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# Synthesis of (±)-1,2,3-triazolo-3′-deoxy-4′-hydroxymethyl carbanucleosides via 'click' cycloaddition

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ABSTRACT

The synthesis of 1,2,3-triazolo-3′-deoxy-4′-hydroxymethyl carbanucleosides with different reaction conditions and diverse modulations on the heterocycle residues was developed. Heterocycle moieties were efficiently introduced on the pseudo-sugar either via nucleophilic substitution or via 1,3-dipolar Huisgen cycloaddition. With this latter approach, 1,4-disubstituted and 1,4,5-trisubstituted-(±)-[1,2,3]-triazolo-3′-deoxy-4′-hydroxymethyl carbanucleosides were prepared from the corresponding azido-carbocycle and various terminal or internal alkynes. Antiviral activities and cellular toxicities of the final compounds were evaluated as smallpox inhibitors. Unfortunately, at concentrations up to 100 mM, none of them inhibited production of vaccinia virus (Lister strain) or cowpox virus (Brighton strain) in vero cells.



## 1. Introduction

In the last decade, nucleosides and carbanucleosides have played a major role in the treatment of viral infectious disease such as AIDS and hepatitis.[1] Carbocyclic analogues of nucleosides are compounds in which the furan ring of a nucleoside has been replaced by mainly a cyclopentane system.[2] This modification makes these compounds more resistant to hydrolases but does not prevent their enzymatic conversion to nucleotide analogues. More recently, compounds as 5′-homoaristeromycin,[3] 3-deaza-carbaadenosine, and 3′-deoxy-3′-fluorocarbaadenosine[4] have displayed good in vitro activities against vaccinia virus, cowpox and monkeypox virus (Fig. 1).[5] We and others have reported the synthesis of diverse carbanucleosides bearing a 1,2,3-triazole moiety, presented as ribavirin analogues, with interesting antiviral activities against HIV-1,[6] varicella-zoster virus,[7] or vaccinia virus.[8]

Thus, the pharmaceutical importance of designing effective anti-smallpox agents and the biological interest of 1,2,3-triazoles[9] prompted us to replace the conventional heterocycle by 1,2,3-triazole derivatives and, taking inspiration of new insights in the literature,[10] to introduce a second 4′-hydroxymethyl group. As part of our smallpox drug discovery program, we herein report the efficient and simple syntheses of 1,4-disubstituted-1,2,3-triazolo-3′-deoxy-4′-hydroxymethyl carbanucleosides via the Huisgen alkyne–azide cycloaddition,[11] which catalyzed by copper(I) species offers an easy access to the 1,4-isomer.[12] We speculated that the hydroxyl group of the second 4′-hydroxymethyl moiety could mimic the 3′-hydroxyl group of a ribo-sugar and, therefore, it might

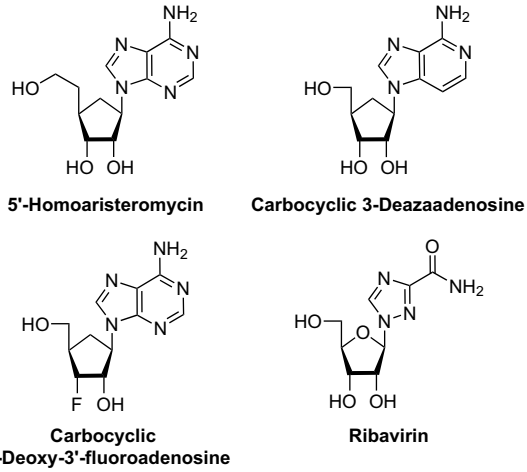


**Figure 1.** Nucleosides with in vitro anti-pox activity.

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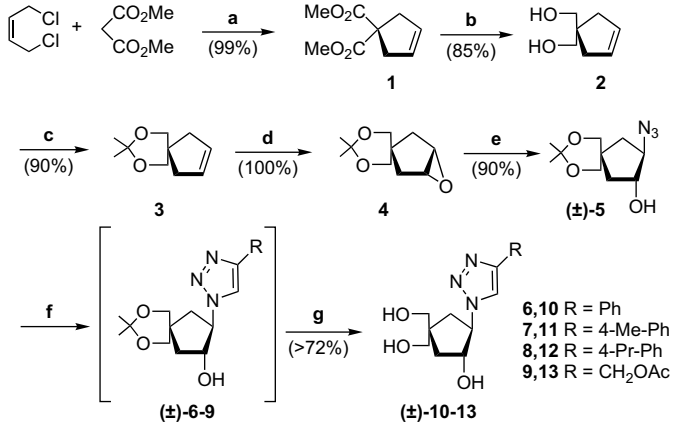
confer to the carbocycle a more pronounced South conformation, a enzyme preferred pseudo-sugar conformation.[10c] Different reaction conditions have been investigated starting from azido-sugar with or without protection on the diol moiety. Microwave heating and two different copper catalysts were also used in order to improve the reaction output. The resulting 1,4-disubstituted-carbanucleosides could also be further derivatized to other triazolo-compounds. Alternatively, the synthesis of 1,4,5-trisubstituted-triazolo-3′-deoxy-4′-hydroxymethyl carbanucleosides was also studied. The preparation of these compounds is of significant interest as little is known about the effect of copper(I) catalysts on the cycloaddition reaction between an azido-sugar moiety and internal alkynes. To date, the only reported examples of copper(I) catalyzed cycloaddition with internal alkynes involve benzyl azides as substrates.[13,14] The final compounds were evaluated against vaccinia and cowpox virus cells in order to determine their antiviral activities and cellular toxicities as smallpox inhibitors.

## 2. Results and discussion

### 2.1. Synthesis of 1,2,3-triazolo-3′-deoxy-4′-hydroxymethyl carbanucleosides from a protected azido-sugar moiety

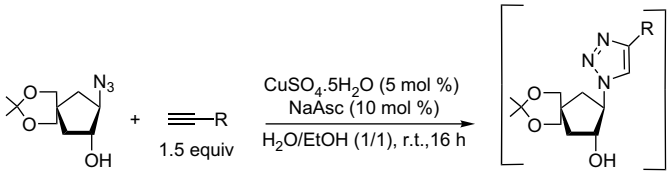
The synthetic strategy for the preparation of the starting azide (±)-**5** is depicted in Scheme 1. Cyclopent-3-ene diester **1** was obtained via malonic synthesis from methyl malonate and *cis*-1,4-dichloro-2-butene.[15,16] After reduction of the diester **1**, the dialcohol **2** was protected with an isopropylidene group. The volatile compound **3** was then stirred for 4 days in the presence of 3-chloroperoxybenzoic acid (*m*-CPBA) to yield the epoxide **4** quantitatively. Finally, the azido-carbocycle (±)-**5** was obtained after the nucleophilic ring opening of the strained epoxide function group **4** by sodium azide. This five-step procedure afforded azide (±)-**5** with a good overall yield of 68%. Moreover, column chromatography purification was only performed in the last stage of this efficient and multigram scale synthesis.

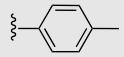
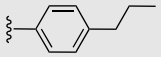
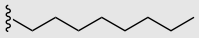



**Scheme 1.** Reagents and conditions: (a) LiH, DMF, rt, 3 days; (b) $LiAlH_4$, $Et_2O$, 0 °C, 1 h; (c) 2-methoxypropene, PTSA, DMF, 0 °C to rt, 16 h; (d) *m*-CPBA, $CH_2Cl_2$, 0 °C to rt, 4 days; (e) $NaN_3$, MeOH/$H_2O$ (8:2), reflux, 3 days; (f) see Table 1; (g) 80% AcOH in $H_2O$, rt, 16 h.

1,2,3-Triazolo-carbanucleosides (±)-**6**–**9** were synthesized in very good yields by reaction of (±)-**5** and various alkynes under standard cycloaddition conditions (Table 1). The copper(I) species was in situ generated by reduction of copper sulfate by sodium ascorbate (NaAsc). In each case, total consumption of (±)-**5** was observed. Compounds (±)-**10** and (±)-**11** were obtained in good yields after simple filtration over a silica gel pad of (±)-**6** and (±)-**7**

**Table 1**
Synthesis of carbanucleosides **6**–**9** via CuAAC

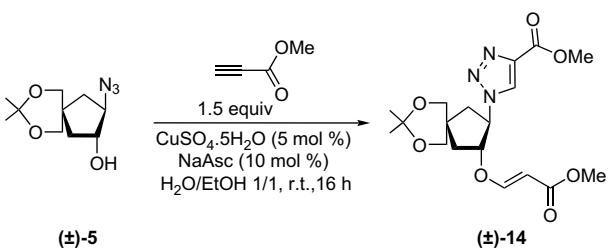



| Entry | R | Triazole | Conversion (%) |
|---|---|---|---|
| 1 |  | (±)-**6** | 98 |
| 2 |  | (±)-**7** | 85 |
| 3 |  | (±)-**8** | 76[a] |
| 4 |  | (±)-**9** | 85[a] |
| 5 |  | — | 0 |
| 6 |  | — | 0 |

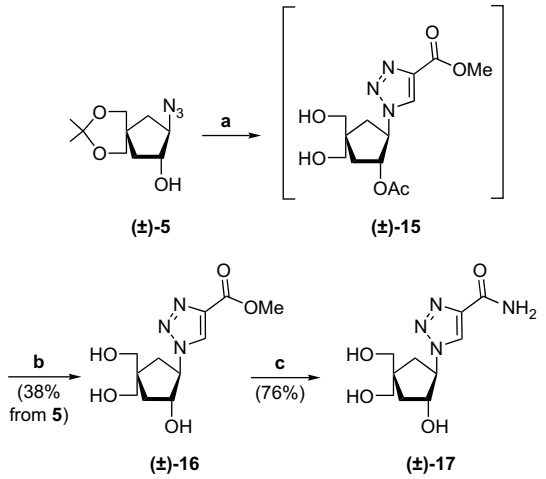
[a] Conversion accounting for the determination for the formation of (±)-**8** and (±)-**9** and the corresponding diols.

followed by subsequent deprotection. Partial deprotection of the hydroxyl groups occurred in the case of compounds (±)-**8** and (±)-**9**; thus the obtained mixture of 1,2,3-triazolo-carbanucleosides was directly deprotected in acetic acid to afford the corresponding diols (±)-**12** and **13**, respectively. Similar protecting group cleavages have already been observed in other copper(I)-mediated reactions.[17] Trimethylsilylacetylene (Table 1, entry 5) and 1-decyne (Table 1, entry 6) failed to react under these reaction conditions and only starting material (as an acetal or a diol) was recovered.

On the other hand, first attempts of cycloaddition between azide (±)-**5** and methyl propiolate afforded the 4-methyl carboxylate triazole (±)-**14** (Scheme 2) in which a Michael addition of the 2′-hydroxyle on a second molecule of alkyne also occurred. To overcome this reactivity, the alcohol in position 2′ was protected as an acetate prior to the cycloaddition (Scheme 3). Despite efficient protection and deprotection steps, the obtained yield was surprisingly low for this type of electron-deficient alkyne cycloaddition (38%). Subsequent deprotections afforded the triol (±)-**16**. To introduce more pharmacomodulation, this latter was further easily transformed into amido-triazole (±)-**17** by treatment with a solution of ammonia (Scheme 3).

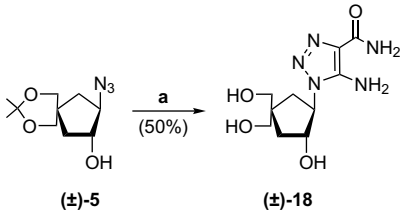



**Scheme 2.** Reaction of (±)-**5** with methyl propiolate.




**Scheme 3.** Reagents and conditions: (a) (i)$Ac_2O$, pyridine, rt, overnight; (ii) methyl propiolate, $CuSO_4{\cdot}5H_2O$ (5 mol %), NaAsc (10 mol %), $H_2O$/EtOH (1:1), rt, 16 h; (iii) 80% AcOH in $H_2O$, rt, overnight; (b) 0.1 N NaOMe in MeOH, rt, overnight; (c) $NH_3$/MeOH, rt, 24 h.

For our first effort to synthesize a 1,4,5-trisubstituted-triazolo-3′-deoxy-4′-hydroxymethyl carbanucleoside, we selected a reported 1,3-dipolar cycloaddition between an azide and the 2-cyanoacetamide.[18] Thus, azide (±)-**5** yielded after deprotection the trisubstituted 4-amido-5-amino-triazole (±)-**18** (Scheme 4). To achieve that addition, we applied our previous protocol optimized for 1,2,3-triazolo-3′-deoxy-4′-hydroxymethyl carbanucleosides.[19]

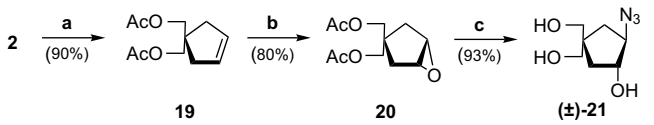



**Scheme 4.** Reagents and conditions: (a) i) 2-cyanoacetamide, Na, EtOH, reflux, 9 h; (ii) 80% AcOH in $H_2O$, rt, 16 h.

## 2.2. Improved synthesis of 1,2,3-triazolo-3′-deoxy-4′-hydroxymethyl carbanucleosides

In the previous preparation of triazoles (±)-**10**–**13**, (±)-**16**, (±)-**18**, at least one sequence protection/deprotection along with long reaction times (16 h) was required to yield the potentially active products. Even if the obtained overall yields were good, we decided to explore a more direct 'click' approach as reported by Sharpless et al.,[20] cutting down the number of steps. As the deprotection of (±)-**5** either by treatment with TFA or by acetic acid with an amberlite resin IR $120H^+$ was incomplete even after several days or formed an unknown byproduct, the synthesis of (±)-**21** was realized from **2** (Scheme 5). The acetylation of **2** afforded the protected cyclopentene **19** in high yields and subsequent oxidation with *m*-CPBA generated the epoxide **20**. Finally, the nucleophilic ring opening of **20** with $NaN_3$ was concomitant with its deacylation. Thus, the desired azido-carbocycle (±)-**21** was isolated in good overall yield after only five steps starting from commercial products. This pathway also appeared to be more convenient and efficient as the reaction times were considerably reduced (the azidation of **20** occurred in 4 h meanwhile the azidation of **4** required 3 days).

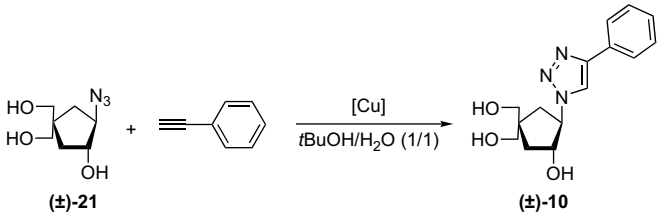
The mixture copper $Cu^0$/copper sulfate $Cu^{II}SO_4$, in situ comproportionated to form $Cu^I$, can also be used as a water soluble in




**Scheme 5.** Reagents and conditions: (a) $Ac_2O$, pyridine, 0 °C to rt, 3 h; (b) *m*-CPBA, $CH_2Cl_2$, 0 °C to rt, 3 days; (c) $NaN_3$, MeOH/$H_2O$ (8:2), reflux, 4 h.

situ generated catalyst in the Huisgen cycloaddition.[12a,21] Experiments showed that the reaction occurs on the surface of the copper particles, rather than via $Cu^0$ atoms or $Cu^I/Cu^{II}$ ions that are leached into the reaction mixture.[22] This option is particularly attractive, as copper metal and sulfate copper are inexpensive. Moreover, the reducing agent ascorbate and its oxidation products, which are sometimes not tolerated by the substrate, can thus be avoided.[23] Accordingly with our preliminary account on CuAAC,[24] when the phenylacetylene was reacted with (±)-**21** in the presence of copper(0)/copper sulfate in a mixture of water and *tert*-butanol, a complete conversion of (±)-**21** into the desired triazole (±)-**10** was obtained in short reaction times without formation of by-products (Table 2). Reaction times could be further shortened to only 2 min using microwave irradiation. Moreover, under the same conditions and with an equal proportion of $CuSO_4$, the reduction method in presence of NaAsc slowed the reaction compared to the comproportionated specie.

**Table 2**
Optimization studies[a]

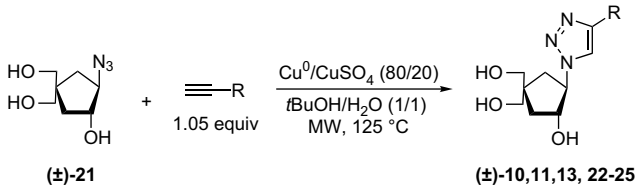


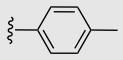
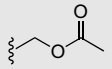
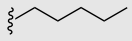
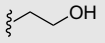

| Catalyst | Concentration (mol %) | Temperature | Time |
|---|---|---|---|
| $CuSO_4/Cu^0$ | 20:80 | rt. | 11 h |
| $CuSO_4/Cu^0$ | 20:80 | Δ, 75 °C | 40 min |
| $CuSO_4/Cu^0$ | 20:80 | MW, 125 °C | 2 min |
| $CuSO_4$/NaAsc | 5:10 | MW, 125 °C | 1.5 h |
| $CuSO_4$/NaAsc | 20:40 | MW, 125 °C | 15 min |

[a] Reaction conditions: azide (±)-**21** (0.27 mmol), phenylacetylene (1.05 equiv), *t*-BuOH/$H_2O$ (1:1) (2 mL).

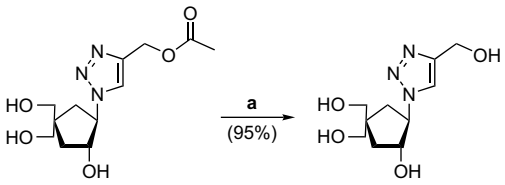
Thus, we applied these optimized conditions to the enlargement of our series of 1,4-disubstituted-1,2,3-triazolo-3′-deoxy-4′-hydroxymethyl carbanucleosides (Table 3). In all cases, complete conversion of (±)-**21** into the desired triazole was obtained in short reaction times with no observable formation of by-products. As expected,[11,25] electron-poor alkynes (Table 3, entries 3, 6, and 7) were more reactive than electron-rich ones (Table 3, entries 1, 2, 4, and 5). If we compare the cycloaddition yields in entries 1–3 with the ones obtained from azide (±)-**5** (Table 1, entries 1, 2, and 4), better results were generally observed for the same alkynes. In one step starting from the azide (±)-**21**, the cycloaddition reaction afforded (±)-**10**, (±)-**11**, and (±)-**13** in less than 10 min in better yields (≥94%). Depending on the nature of the 4-substituent, different treatments were required to isolate the formed triazoles. Compounds with electron-donating substituents, e.g., (±)-**10**, **11**, **22**, and **23**, were obtained with excellent yields after a simple extraction with ethyl acetate. Triazoles with electron-withdrawing substituents, e.g., (±)-**13**, **24**, and **25**, had to be filtrated on silica gel to eliminate the inorganic salts, since these products are water soluble.

**Table 3**
Microwave assisted 1,3-dipolar cycloaddition of unprotected azido derivative (±)-**21**




| Entry | R | Triazole | Time | Yield (%) |
|---|---|---|---|---|
| 1 |  | (±)-**10** | 2 min | 98 |
| 2 |  | (±)-**11** | 10 min | 94 |
| 3 |  | (±)-**13** | <1 min | 95 |
| 4 |  | (±)-**22** | 1 h | 98 |
| 5 |  | (±)-**23** | 1.5 h | 95 |
| 6 |  | (±)-**24** | 2 min | 95 |
| 7 |  | (±)-**25** | 1 min | 78 |

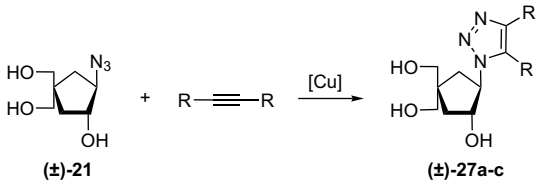
A final deacylation of (±)-**13** in a solution of ammonia afforded the corresponding hydroxymethyl (±)-**26** (Scheme 6).




**Scheme 6.** Reagents and conditions: (a) $NH_3$ 7 N in MeOH, 4 °C, overnight.

The literature only reports few examples of 1,4,5-trisubstituted-1,2,3-triazolo nucleosides. They have been prepared either via direct glycosylation of a suitable trimethylsilyl derivative of 4,5-disubstituted-1,2,3-triazole (convergent approach)[26] or in few steps using linear methodologies.[27,28] Few examples based on 1,3-dipolar cycloaddition with symmetric 1,4-dihalo or 1,4-dihydroxybutyne have been also reported.[29] Limitation of the substituents' scope underlines the need for a versatile and efficient methodology. The successful tool developed for the preparation of 1,4-disubstituted-1,2,3-triazolo-carbanucleosides prompted us to examine the reactivity of copper(I)-based catalytic systems in the synthesis of 1,4,5-trisubstituted-1,2,3-triazoles via Huisgen 1,3-dipolar cycloaddition. In our preceding studies, disubstituted alkynes were successfully used to afford 1,4,5-trisubstituted-1,2,3-triazoles via (*N*-heterocyclic carbene)/$Cu^I$ catalyzed cycloaddition.[13] Thus, we first tried to employ [1,2-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene]bromocopper [(IMes)CuBr] with the previously optimized conditions for (±)-**21**.[21] Unfortunately, no reaction of (±)-**21** with diphenylacetylene was observed (Table 4, entry 1). We then applied different conditions (catalyst, solvent, and heating method) with a more activated alkyne (entries 2–7). Two other NHC/copper(I) complexes were tested: [(IPr)CuCl][30] (IPr=*N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) and [(SIMes)CuBr][13] (SIMes=*N*,*N*′-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene). Once again no conversion was detected. Finally, the 1,4,5-trisubstituted (±)-**27c** was successfully obtained in good yield in only 1 h of microwave irradiation (entries 8 and 9). However, this reaction between the azide (±)-**21** and the strongly electron-deficient dimethyl acetylenedicarboxylate proceeded also under copper-free conditions. These results indicate that there is no copper(I) catalysts' effect on the cycloaddition reaction between non-activated azido-sugar moiety and internal alkynes. Completion could be reached by using 1.1 equiv of dimethyl acetylenedicarboxylate.

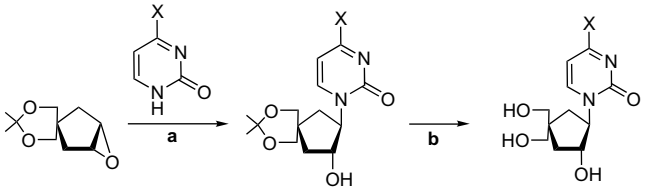
**Table 4**
1,3-Dipolar cycloaddition with internal alkynes




| Entry | (±)-**27** (R=) | Catalyst (5 mol %) | Solvent | Conditions | Conversion[a] (%) |
|---|---|---|---|---|---|
| 1 | **a** (–Ph) | [(IMes)CuBr] | *t*-BuOH/$H_2O$ (1:1) | 70 °C, 24 h | 0 |
| 2 | **b** (–$CH_2OH$) | — | *t*-BuOH/$H_2O$ (1:1) | 70 °C, 24 h | 0 |
| 3 | | [$Cu^0$/$CuSO_4$] | *t*-BuOH/$H_2O$ (1:1) | 70 °C, 24 h | 0 |
| 4 | | [(IPr)CuCl] | *t*-BuOH/$H_2O$ (1:1) | 70 °C, 24 h | 0 |
| 5 | | [(IPr)CuCl] | $CH_3CN$ | 70 °C, 24 h | 0 |
| 6 | | [(IPr)CuCl] | *t*-BuOH/$H_2O$ (1:1) | MW, 70 °C, 1 h | 0 |
| 7 | | [(IPr)CuCl] | *t*-BuOH/$H_2O$ (1:1) | MW, 125 °C, 1 h | 0 |
| 8 | **c** (–$CO_2Me$) | — | *t*-BuOH/$H_2O$ (1:1) | MW, 125 °C, 1 h | 88[b] |
| 9 | | [(SIMes)CuBr] | *t*-BuOH/$H_2O$ (1:1) | MW, 125 °C, 1 h | 80 |

[a] Conversions are an average of two runs and were determined by $^1H$ NMR of the crude product.
[b] 100% with alkyne (1.1 equiv).

In order to investigate the structure–activity relationships, carbocyclic analogues of the previously presented 1,2,3-triazolo-3′-deoxy-4′-hydroxymethyl carbanucleosides, bearing an uracil or a cytosine heterocycle as models were also synthesized for the biological essays (Scheme 7). A ring opening of epoxide **4** with the potassium salt of the nucleobase[31] afforded the $N^1$ carbanucleosides (±)-**28a**,**b** regioselectively, which after treatment with a solution of TFA gave the corresponding compounds (±)-**29a**,**b**.




**Scheme 7.** Reagents and conditions: (a) $K_2CO_3$, DMF, 130 °C, 24 h; (b) TFA 60%, rt, 24 h.

All $IC_{50}$ (minimum inhibitory concentration required to reduce virus-induced cytopathogenicity by 50%) and $CC_{50}$ (minimum cytotoxic concentration required to cause a microscopically detectable alteration of normal cell morphology) of the synthesized nucleosidic analogues were measured at concentrations up to 100 mM. Accordingly, none of them inhibited production of vaccinia virus (Lister strain) or cowpox virus (Brighton strain) in vero cells. The models bearing natural nucleosidic bases ((±)-**29a** and (±)-**29b**) were also found to be inactive. The lack of activity being independent of the nature of the base, the second 4′-hydroxymethyl group may impose unfavorable steric effects that decrease the biological results despite conferring a pseudo-sugar conformation.[10c]

## 3. Conclusion

In conclusion, the efficient synthesis of a variety of hitherto unknown 1,2,3-triazolo-3′-deoxy-4′-hydroxymethyl carbanucleosides have been accomplished using two different catalytic systems. The method with $Cu^0/CuSO_4$ as copper(I)-catalyst precursor appeared to be optimum for the formation of 1,4-disubstituted-1,2,3-triazolo-carbanucleosides by microwave assisted 1,3-dipolar Huisgen cycloaddition. 1,4,5-Trisubstituted-1,2,3-triazolo-3′-deoxy-4′-hydroxymethyl carbanucleosides and carbocyclic analogues with conventional base were also synthesized. None of the synthesized compounds inhibited production of vaccinia virus (Lister strain) or cowpox virus (Brighton strains) in vero cells.

## 4. Experimental section

### 4.1. General

Microwave reactions were carried out in a Biotage AB Initiator EXP EU with a maximum power of 300 W and 0.5–2 mL process vials. All reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel plates (Kieselgel 60 $F_{254}$). Column chromatography was performed on silica gel 60M (0.040–0.063 mm). $^1$H NMR spectra were recorded on 250 MHz or 400 MHz spectrometer, and $^{13}$C NMR on 62.9 MHz or 100 MHz spectrometer at room temperature, using deuterated solvents as the internal standard. Chemical shifts are given in parts per million and multiplicity is reported as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Assignments of NMR spectra follow standard nucleosides nomenclature: triazole bases are numbered from N-1 to C-5 and carbocycles are numbered from C-1′ to C-7′ with C-5′ and C-7′ for the two 4′-hydroxymethyl chains. Similar conventions apply for the corresponding hydrogen atoms. HRMS analyses were performed by the Mass Spectrometry Facility at the Institute of Chemical Research of Catalonia (ICIQ), Tarragona (Spain). Evidence of purity has been done from a proton-decoupled $^{13}$C NMR spectrum with a signal-to-noise ratio sufficient to permit seeing peak with 5% of the intensity of the strongest peak.

### 4.2. Dimethyl-cyclopent-3-ene-1,1-dicarboxylate (1)

To a stirred solution of dimethyl malonate (11.4 mL, 0.1 mol) in DMF (150 mL) at 0 °C, lithium hydride (2.00 g, 0.25 mol, 2.5 equiv) was added in one portion. The reaction mixture was stirred at 0 °C for 4 h. Then, *cis*-1,4-dichloro-2-butene (12.6 mL, 0.12 mol, 1.2 equiv) was added and the mixture was allowed to warm up to room temperature. After 3 days, the resulting solution was cooled at 0 °C, diluted with petroleum ether/$Et_2O$ 8:2 (100 mL), and poured into cold water (50 mL). The aqueous layer was extracted with petroleum ether/$Et_2O$ 8:2 (4×50 mL), the combined organic layers were washed with an aqueous solution saturated in $NaHCO_3$ (3×50 mL), and then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting solid was triturated with pentane and dried to give compound **1** as a white crystalline solid (18.20 g, 99%). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 5.57 (s, 2H, HC═), 3.70 (s, 6H, $CH_3O$), 2.98 (s, 4H, $CH_2$). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 172.7 (C═O), 127.8 (C═), 58.8 (C), 52.9 ($OCH_3$), 41.0 ($CH_2$). HRMS (ESI): *m*/*z* calcd for $C_9H_{12}O_4Na$ ($M^+$+Na) 207.0633, found 207.0633.

### 4.3. Cyclopent-3-ene-1,1-diyldimethanol (2)

To a suspension of $LiAlH_4$ (2.04 g, 54 mmol, 3.4 equiv) in 50 mL of diethyl ether stirred at 0 °C under argon atmosphere, a solution of **1** (2.90 g, 15.7 mmol) in 20 mL of diethyl ether was added dropwise. The mixture was stirred for 1 h at room temperature. Then, at 0 °C, water (2 mL), an aqueous solution 3 N in NaOH (2 mL) and water (6 mL) were successively added dropwise and stirring was continued for 15 min more. The resulting mixture was then filtered over Celite and rinsed several times with diethyl ether. The organic layer was separated, dried on $MgSO_4$, filtered, and concentrated under reduced pressure. Compound **2** was obtained as a white solid (1.72 g, 85%). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 5.61 (s, 2H, HC═), 3.68 (s, 2H, C$H_2$OH), 3.67 (s, 2H, C$H_2$OH), 2.81 (br s, 2H, OH), 2.22 (s, 4H, $CH_2$). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 128.6 (C═), 68.0 ($CH_2OH$), 47.6 (C), 38.5 ($CH_2$). HRMS (ESI): *m*/*z* calcd for $C_7H_{12}O_2Na$ ($M^+$+Na) 151.0735, found 151.0735.

### 4.4. 8,8-Dimethyl-7,9-dioxa-spiro[4.5]dec-2-ene (3)

To a solution of **2** (1.72 g, 13 mmol) in DMF (10 mL), maintained at 0 °C under argon atmosphere, 2-methoxypropene (2.6 mL, 27 mmol, 2 equiv) and a small amount of *p*-toluenesulfonic acid were added. After 16 h of stirring at room temperature, a small amount of $NaHCO_3$, water (60 mL), and AcOEt (50 mL) were added to the reaction mixture. The aqueous layer was extracted with AcOEt (3×30 mL), the combined organic layers were washed with water (50 mL) and then with brine (50 mL). The organic layer was finally dried over $MgSO_4$, filtered, and concentrated under reduced pressure (caution: product **3** is volatile). The product **3** was obtained as a yellow oil (2.03 g, 90%). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 5.61 (s, 2H, HC═), 3.67 (s, 4H, $CH_2O$), 2.25 (s, 4H, $CH_2$), 1.43 (s, 6H, $CH_3$). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 128.8 (C═), 97.8 (*C*$(CH_3)_2$), 69.5 ($CH_2O$), 40.9 (C), 40.3 ($CH_2$), 24.0 ($CH_3$).

### 4.5. 2-Methoxy-8,8-dimethyl-7,9-dioxa-spiro[4.5]decane (4)

To a solution of **3** (2.03 g, 12 mmol) in $CH_2Cl_2$ (40 mL) under argon atmosphere, 3-chloroperoxybenzoic acid 77% (4.06 g, 18 mmol, 1.5 equiv) was added at 0 °C. The reaction mixture was stirred at room temperature for 4 days before pouring $CH_2Cl_2$ (50 mL). The resulting solution was washed with a saturated aqueous solution of $Na_2S_2O_3$ (50 mL) and the aqueous layer was then extracted with $CH_2Cl_2$ (4×50 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (3×50 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (50 mL). Finally, the combined organic layers were dried on $MgSO_4$, filtered, and concentrated under reduced pressure to obtain compound **4** as a yellow solid (2.22 g, 100%). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 3.45 (s, 2H, $CH_2O$), 3.39 (s, 2H, $CH_2O$), 3.32 (s, 2H, CH), 1.92 (d, 2H, *J*=14.8 Hz, C$H_a$H$_b$), 1.36 (d, 2H, *J*=14.8 Hz, CH$_a$*H*$_b$), 1.22 (s, 6H, $CH_3$). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 96.8 (*C*$(CH_3)_2$), 70.0 ($CH_2O$), 69.0 ($CH_2O$), 57.0 (CH), 39.1 (C), 34.6 ($CH_2$), 23.3 ($CH_3$). HRMS (ESI): *m*/*z* calcd for $C_{10}H_{17}O_3$ ($M^+$+H) 185.1178, found 185.1173.

### 4.6. (±)-3-Azido-8,8-dimethyl-7,9-dioxa-spiro[4.5]decan-2-ol (5)

To a solution of **4** (1.34 g, 7.3 mmol) in a mixture 8:2 of MeOH/$H_2O$ (80 mL), sodium azide (0.95 g, 14 mmol, 2 equiv) was added. The reaction mixture was refluxed for 3 days and solvents were evaporated under reduced pressure. The oily residue was purified by silica gel column chromatography (petroleum ether/EtOAc 5:5 to 2:8) to yield (±)-**5** as a yellow oil (1.49 g, 90%). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 4.08 (q, 1H, *J*=6.0 Hz, H$^{1'}$), 3.76 (q, 1H, *J*=6.0 Hz, H$^{2'}$), 3.68–3.55 (m, 4H, H$^{5'}$+H$^{7'}$), 2.10 (dd, 1H, *J*=14.2, 6.0 Hz, H$^{3'}$), 1.94 (dd, 1H, *J*=14.2, 6.0 Hz, H$^{6'}$), 1.60–1.49 (m, 2H, H$^{3'}$+H$^{6'}$), 1.40 (s, 6H, $CH_3$). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 98.0 (*C*$(CH_3)_2$), 76.4 (CH, C$^{1'}$), 70.1 ($CH_2$, C$^{5'}$), 70.0 ($CH_2$, C$^{7'}$), 67.5 (CH, C$^{2'}$), 39.2 ($CH_2$, C$^{6'}$), 38.7 (C, C$^{4'}$), 36.1 ($CH_2$, C$^{3'}$), 24.4 ($CH_3$), 23.3 ($CH_3$). HRMS (ESI): *m*/*z* calcd for $C_{10}H_{18}N_3O_3$ ($M^+$+H) 228.1348, found 228.1351.

### 4.7. General procedure for the copper(I) alkyne–azide cycloaddition

Procedure A. To a solution of azide (±)-**5** (50 mg, 0.22 mmol) in a 1:1 mixture of water and ethanol (4 mL), copper(II) sulfate pentahydrate (2.8 mg, 5 mol %), sodium ascorbate (4.4 mg, 10 mol %), and the alkyne (0.33 mmol, 1.5 equiv) was added. The reaction mixture was stirred at room temperature for 16 h and then filtered over a silica gel pad (~5 cm) with EtOAc. The resulting product was dissolved in an 80% acetic acid solution in water (2 mL) and stirred at room temperature for 16 h. The desired triazoles were obtained after evaporation under reduced pressure.

Procedure B. To a solution of azide (±)-**21** (50 mg, 0.27 mmol) in a 1:1 mixture of water and *t*-BuOH (2 mL) in a glass vial equipped with a magnetic stirring bar, copper powder (13.5 mg, 80 mol %), a solution 1 M of copper sulfate in water (54 μL, 20 mol %), and finally the alkyne (0.28 mmol, 1.05 equiv) was added. The vial was sealed with an aluminum/Teflon crimp top and the reaction mixture was then irradiated at 125 °C. Upon completion of the reaction, the vial was cooled to 50 °C by air jet cooling before opening.

#### *4.7.1. (±)-4,4-Bis(hydroxymethyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)cyclopentanol (**10**)*

Procedure A. The title compound was obtained from phenylacetylene (36 μL) as a white resin (56 mg, 88%). Procedure B. The title compound was prepared from phenylacetylene (31 μL) after 2 min of microwave irradiation. The reaction mixture was filtered over a plug of Celite (MeOH) and the filtrate was evaporated under reduced pressure. The oily residue was then dissolved in EtOAc (20 mL) and washed with an aqueous saturated $NaHCO_3$ solution (2×5 mL) and brine (5 mL). The aqueous phases were extracted with EtOAc (2×20 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield compound (±)-**10** as a white resin (76 mg, 98%). $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 8.38 (s, 1H, $H^5$), 7.81 (d, 2H, $J$=7.5 Hz, $H^{Ar}$), 7.42 (t, 2H, $J$=7.5 Hz, $H^{Ar}$), 7.33 (t, 1H, $J$=7.5 Hz, $H^{Ar}$), 4.82–4.71 (m, 1H, $H^{1'}$), 4.53 (q, 1H, $J$=9.0 Hz, $H^{2'}$), 3.54 (s, 2H, $H^{5'}$), 3.53 (s, 2H, $H^{7'}$), 2.27 (dd, 1H, $J$=13.5, 8.3 Hz, $H^{6'}$), 2.15–2.10 (m, 2H, $H^{3'}$+$H^{6'}$), 1.66 (dd, 1H, $J$=13.4, 9.0 Hz, $H^{3'}$). $^{13}$C NMR (62.9 MHz, $CD_3OD$) $\delta$ 148.6 (C, $C^4$), 131.8 (C, $C^{Ar}$), 130.0 (CH, $C^{Ar}$), 129.3 (CH, $C^{Ar}$), 126.6 (CH, $C^{Ar}$), 121.4 (CH, $C^5$), 77.0 (CH, $C^{2'}$), 68.8 (CH, $C^{1'}$), 67.9 ($CH_2$, $C^{5'}$), 67.8 ($CH_2$, $C^{7'}$), 45.5 (C, $C^{4'}$), 38.3 ($CH_2$, $C^{3'}$), 35.8 ($CH_2$, $C^{6'}$). HRMS (ESI): *m*/*z* calcd for $C_{15}H_{19}N_3O_3Na$ ($M^+$+Na) 312.1324, found 312.1320.

#### *4.7.2. (±)-4,4-Bis(hydroxymethyl)-2-(4-p-tolyl-1H-1,2,3-triazol-1-yl)cyclopentanol (**11**)*

Procedure A. The title compound was obtained from 4-ethynyltoluene (42 μL) as a white solid (48 mg, 72%). Procedure B. The title compound was prepared from 4-ethynyltoluene (36 μL) after 10 min of microwave irradiation. The reaction mixture was filtered over a plug of Celite (MeOH) and the filtrate was evaporated under reduced pressure. The oily residue was then dissolved in EtOAc (20 mL) and washed with an aqueous saturated $NaHCO_3$ solution (2×5 mL) and brine (5 mL). The aqueous phases were extracted with EtOAc (2×20 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield compound (±)-**11** as a white solid (76 mg, 94%). $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 8.33 (s, 1H, $H^5$), 7.69 (d, 2H, $J$=8.0 Hz, $H^{Ar}$), 7.24 (d, 2H, $J$=8.0 Hz, $H^{Ar}$), 4.85–4.72 (m, 1H, $H^{1'}$), 4.52 (q, 1H, $J$=9.0 Hz, $H^{2'}$), 3.54 (s, 2H, $H^{5'}$), 3.53 (s, 2H, $H^{7'}$), 2.36 (s, 3H, $CH_3$), 2.26 (dd, 1H, $J$=13.5, 8.1 Hz, $H^{6'}$), 2.14–2.08 (m, 2H, $H^{3'}$+$H^{6'}$), 1.65 (dd, 1H, $J$=13.5, 9.0 Hz, $H^{3'}$). $^{13}$C NMR (62.9 MHz, $CD_3OD$) $\delta$ 156.5 (C, $C^4$), 139.4 (C, $C^{Ar}$), 130.6 (CH, $C^{Ar}$), 129.0 (C, $C^{Ar}$), 126.6 (CH, $C^{Ar}$), 121.1 (CH, $C^5$), 77.0 (CH, $C^{2'}$), 68.8 (CH, $C^{1'}$), 67.9 ($CH_2$, $C^{5'}$), 67.8 ($CH_2$, $C^{7'}$), 45.6 (C, $C^{4'}$), 38.3 ($CH_2$, $C^{3'}$), 35.8 ($CH_2$, $C^{6'}$), 21.3 ($CH_3$). HRMS (ESI): *m*/*z* calcd for $C_{16}H_{21}N_3O_3Na$ ($M^+$+Na) 326.1481, found 326.1490.

#### *4.7.3. (±)-4,4-Bis(hydroxymethyl)-2-[4-(4-propylphenyl)-1H-1,2,3-triazol-1-yl]cyclopentanol (**12**)*

Procedure A. The title compound was obtained from 1-ethynyl-4-propylbenzene (48 mg) as colorless oil (54 mg, 74%). $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 8.34 (s, 1H, $H^5$), 7.72 (d, 2H, $J$=8.0 Hz, $H^{Ar}$), 7.25 (d, 2H, $J$=8.0 Hz, $H^{Ar}$), 4.79–4.72 (m, 1H, $H^{1'}$), 4.52 (q, 1H, $J$=8.8 Hz, $H^{2'}$), 3.54 (s, 2H, $H^{5'}$), 3.53 (s, 2H, $H^{7'}$), 2.62 (t, 2H, $J$=8.0 Hz, =C–$CH_2$), 2.27 (dd, 1H, $J$=13.6, 8.0 Hz, $H^{6'}$), 2.15–2.08 (m, 2H, $H^{3'}$+$H^{6'}$), 1.72–1.62 (m, 3H, $H^{3'}$+–$CH_2CH_3$), 0.96 (t, 3H, $J$=7.2 Hz, $CH_3$). $^{13}$C NMR (62.9 MHz, $CD_3OD$) $\delta$ 148.7 (C, $C^4$), 144.1 (C, $C^{Ar}$), 130.0 (CH, $C^{Ar}$), 129.2 (C, $C^{Ar}$), 126.6 (CH, $C^{Ar}$), 121.1 (CH, $C^5$), 77.0 (CH, $C^{2'}$), 68.7 (CH, $C^{1'}$), 67.9 ($CH_2$, $C^{5'}$), 67.8 ($CH_2$, $C^{7'}$), 45.5 (C, $C^{4'}$), 38.8 ($CH_2$, =C–$CH_2$–), 38.3 ($CH_2$, $C^{3'}$), 35.8 ($CH_2$, $C^{6'}$), 25.6 ($CH_2$, –$CH_2$–$CH_3$), 14.0 ($CH_3$). HRMS (ESI): *m*/*z* calcd for $C_{18}H_{26}N_3O_3$ ($M^+$+H) 332.1974, found 332.1982.

#### *4.7.4. (±)-Acetic acid 1-(2-hydroxy-4,4-bis(hydroxymethyl)-cyclopentyl)-1H-1,2,3-triazol-4-ylmethyl ester (**13**)*

Procedure A. The title compound was obtained from propargyl acetate (33 μL) as a transparent oil (49 mg, 78%).

Procedure B. The title compound was prepared from propargyl acetate (28 μL) after 1 min of microwave irradiation. The reaction mixture was evaporated under reduced pressure and the residue was purified by a silica gel column chromatography (EtOAc/MeOH 1:0 to 95:5). Compound (±)-**13** was isolated as colorless oil (73 mg, 95%). $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 8.08 (s, 1H, $H^5$), 5.18 (s, 2H, $CH_2$), 4.76–4.65 (m, 1H, $H^{1'}$), 4.45 (q, 1H, $J$=9.0 Hz, $H^{2'}$), 3.52 (s, 2H, $H^{5'}$), 3.50 (s, 2H, $H^{7'}$), 2.22 (dd, 1H, $J$=13.5, 8.2 Hz, $H^{6'}$), 2.10–2.04 (m, 2H, $H^{3'}$+$H^{6'}$), 2.05 (s, 3H, $CH_3$), 1.62 (dd, 1H, $J$=13.4, 9.0 Hz, $H^{3'}$). $^{13}$C NMR (62.9 MHz, $CD_3OD$) $\delta$ 172.4 (C, C=O), 143.8 (C, $C^4$), 125.0 (CH, $C^5$), 76.9 (CH, $C^{2'}$), 68.8 (CH, $C^{1'}$), 67.84 ($CH_2$, $C^{5'}$), 67.78 ($CH_2$, $C^{7'}$), 58.4 ($CH_2$), 45.5 (C, $C^{4'}$), 38.3 ($CH_2$, $C^{3'}$), 35.7 ($CH_2$, $C^{6'}$), 20.7 ($CH_3$). HRMS (ESI): *m*/*z* calcd for $C_{12}H_{19}N_3O_5Na$ ($M^+$+Na) 308.1222, found 308.1229.

#### *4.7.5. (±)-Methyl-1-(2-hydroxy-4,4-bis(hydroxymethyl)cyclopentyl)-1H-1,2,3-triazol-4-ylcarboxylate (**16**)*

Acetic anhydride (1 mL, 10.6 mmol) was added to a solution of (±)-**5** (90 mg, 0.4 mmol) in pyridine (2 mL) at 0 °C under argon atmosphere. After stirring overnight at room temperature, the solvent was coevaporated with toluene. The protected azido-intermediate was obtained quantitatively as a yellow oil (0.1 g, 100%). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 5.02–4.96 (m, 1H, $H^{1'}$), 3.95 (q, 1H, $J$=6.0 Hz, $H^{2'}$), 3.70–3.60 (m, 4H, $H^{5'}$+$H^{7'}$), 2.11–2.02 (m, 2H, $H^{3'}$+$H^{6'}$), 2.05 (s, 3H, $CH_3$), 1.69–1.55 (m, 2H, $H^{3'}$+$H^{6'}$), 1.41 (s, 6H, $CH_3$).

The azido-intermediate was dissolved in a 1:1 mixture of water and ethanol (6 mL) and then copper(II) sulfate pentahydrate (5 mg, 5 mol %), sodium ascorbate (7.9 mg, 10 mol %), and methyl propiolate (54 μL, 0.6 mmol, 1.5 equiv) were added. The reaction mixture was stirred 16 h at room temperature and then filtered over a silica gel pad (~5 cm) with EtOAc. The isolated crude was directly deprotected by stirring in acetic acid (80%) (2 mL) overnight. After evaporation, the triazole intermediate (±)-**15** was obtained as a colorless oil (47 mg, 38%). $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 8.66 (s, 1H, $H^5$), 5.48 (q, 1H, $J$=8.5 Hz, $H^{1'}$), 5.18–5.07 (m, 1H, $H^{2'}$), 3.91 (s, 3H, $OCH_3$), 3.54 (s, 4H, $H^{5'}$+$H^{7'}$), 3.36–2.05 (m, 3H, $H^{3'}$+2$H^{6'}$), 1.98 (s, 3H, $CH_3$), 1.73 (dd, 1H, $J$=13.6, 8.7 Hz, $H^{3'}$).

Subsequent overnight deacylation of (±)-**15** with a methanol solution of 0.1 N NaOMe (1.3 mL) followed by column chromatography on silica gel (EtOAc to EtOAc/MeOH 8:2) afforded (±)-**16** as a white solid (23 mg, 57%). $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 8.61 (s, 1H, $H^5$), 4.65–4.85 (m, 1H, $H^{1'}$), 4.47 (q, 1H, $J$=9.2 Hz, $H^{2'}$), 3.92 (s, 3H, $OCH_3$), 3.52 (s, 2H, $H^{5'}$), 3.50 (s, 2H, $H^{7'}$), 2.25 (m, 1H, $H^{6'}$), 2.16–2.04 (m, 2H, $H^{3'}$+$H^{6'}$), 1.63 (dd, 1H, $J$=13.2, 9.7 Hz, $H^{3'}$). $^{13}$C NMR (62.9 MHz, $CD_3OD$) $\delta$ 162.5 (C=O), 128.9 (C, $C^4$), 127.3 (CH, $C^5$), 77.0

(CH, $C^{2'}$), 69.0 (CH, $C^{1'}$), 67.8 ($CH_2$, $C^{5'}$), 67.8 ($CH_2$, $C^{7'}$), 52.5 ($OCH_3$), 45.6 (C, $C^{4'}$), 38.2 ($CH_2$, $C^{3'}$), 35.6 ($CH_2$, $C^{6'}$). HRMS (ESI): *m*/*z* calcd for $C_{11}H_{17}N_3O_5Na$ ($M^+$+Na) 294.2621, found 294.2619.

### 4.8. (±)-1-(2-Hydroxy-4,4-bis(hydroxymethyl)-cyclopentyl)-1*H*-1,2,3-triazol-4-ylcarboxamide (17)

Compound (±)-**16** (50 mg, 0.18 mmol) was stirred in an ammonia 7 N solution in methanol (2 mL) during 24 h. After evaporation, compound (±)-**17** was obtained as a colorless oil (36 mg, 76%). $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 8.44 (s, 1H, $H^5$), 4.85–4.65 (m, 1H, $H^{1'}$), 4.47 (q, 1H, *J*=9.0 Hz, $H^{2'}$), 3.52 (s, 2H, $H^{5'}$), 3.50 (s, 2H, $H^{7'}$), 2.27 (dd, 1H, *J*=13.3, 8.3 Hz, $H^{6'}$), 2.13–2.04 (m, 2H, $H^{3'}$+$H^{6'}$), 1.63 (dd, 1H, *J*=13.3, 9.6 Hz, $H^{3'}$). $^{13}$C NMR (62.9 MHz, $CD_3OD$) $\delta$ 164.9 (C=O), 143.5 (C, $C^4$), 126.8 (CH, $C^5$), 77.0 (CH, $C^{2'}$), 68.8 (CH, $C^{1'}$), 67.8 ($CH_2$, $C^{5'}$), 67.8 ($CH_2$, $C^{7'}$), 45.6 (C, $C^{4'}$), 38.2 ($CH_2$, $C^{3'}$), 35.7 ($CH_2$, $C^{6'}$). HRMS (ESI): *m*/*z* calcd for $C_{10}H_{16}N_4O_4Na$ ($M^+$+Na) 279.2505, found 279.2504.

### 4.9. (±)-5-Amino-1-(2-hydroxy-4,4-bis(hydroxymethyl)-cyclopentyl)-1*H*-1,2,3-triazol-4-ylcarboxamide (18)

To a solution of azide (±)-**5** (50 mg, 0.22 mmol) in ethanol (2 mL) under argon atmosphere, a freshly prepared solution of sodium (10 mg, 0.44 mmol, 2 equiv) in ethanol (1 mL) and then 2-cyanoacetamide (28 mg, 0.33 mmol, 1.5 equiv) were added. The reaction mixture was refluxed for 9 h. After evaporation of the solvent, the resulting residue was purified by silica gel column chromatography ($CH_2Cl_2$/MeOH 19:1) to yield the protected triazole as a colorless oil (41 mg, 60%). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 4.59–4.39 (m, 2H, $H^{1'}$+$H^{2'}$), 3.77 (s, 2H, $H^{5'}$), 3.74 (s, 2H, $H^{7'}$), 2.31 (dd, 1H, *J*=14, 8 Hz, $H^{6'}$), 2.18–2.05 (m, 2H, $H^{3'}$+$H^{6'}$), 1.55 (dd, 1H, *J*=13.5, 8 Hz, $H^{3'}$), 1.41 (s, 3H, $CH_3$), 1.38 (s, 3H, $CH_3$).

Deprotection of the intermediate was performed in an 80% acetic acid solution (2 mL) with overnight stirring. After evaporation, compound (±)-**18** was obtained as a white solid (30 mg, 84%). $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 4.60 (q, 1H, *J*=8.8 Hz, $H^{1'}$), 4.43 (q, 1H, *J*=8.8 Hz, $H^{2'}$), 3.54 (s, 2H, $H^{5'}$), 3.51 (s, 2H, $H^{7'}$), 2.14 (m, 1H, $H^{6'}$), 2.11–2.03 (m, 2H, $H^{3'}$+$H^{6'}$), 1.62 (dd, 1H, *J*=13.5, 9.4 Hz, $H^{3'}$). $^{13}$C NMR (62.9 MHz, $CD_3OD$) $\delta$ 167.1 (C=O), 147.2 (C, $C^4$), 123.2 (C, $C^5$), 76.4 (CH, $C^{2'}$), 68.0 ($CH_2$, $C^{5'}$), 67.8 ($CH_2$, $C^{7'}$), 64.7 (CH, $C^{1'}$), 45.7 (C, $C^{4'}$), 38.4 ($CH_2$, $C^{3'}$), 34.1 ($CH_2$, $C^{6'}$). HRMS (ESI): *m*/*z* calcd for $C_{10}H_{17}N_5O_4Na$ ($M^+$+Na) 294.2651, found 294.2650.

### 4.10. Cyclopent-3-ene-1,1-diylbis(methylene) diacetate (19)

To a solution of **2** (0.5 g, 3.9 mmol) in pyridine (5 mL), under argon atmosphere acetic anhydride (0.74 mL, 7.8 mmol, 2 equiv) was added at 0 °C. The reaction mixture was stirred for 3 h at room temperature and then the solvent was coevaporated with toluene to obtain compound **19** as a yellow oil (0.75 g, 90%). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 5.61 (s, 2H, HC=), 4.04 (s, 4H, $CH_2O$), 2.25 (s, 4H, $CH_2$), 2.06 (s, 6H, $CH_3$). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 171.4 (C=O), 128.7 (C=), 67.3 ($CH_2O$), 44.9 (C), 39.2 ($CH_2$), 21.0 ($CH_3$). HRMS (ESI): *m*/*z* calcd for $C_{11}H_{16}O_4Na$ ($M^+$+Na) 235.0946, found 235.0939.

### 4.11. 6-Oxabicyclo[3.1.0]hexane-3,3-diylbis(methylene) diacetate (20)

To a solution of **19** (0.75 g, 3.5 mmol) in $CH_2Cl_2$ (8 mL), 3-chloroperoxybenzoic acid 77% (1.19 g, 5.3 mmol, 1.5 equiv) was added at 0 °C under argon atmosphere. The mixture was stirred at room temperature. After 72 h of reaction, $CH_2Cl_2$ (20 mL) was poured and the resulting solution was washed with an aqueous saturated $Na_2S_2O_3$ solution (2×20 mL). The aqueous layer was then extracted with $CH_2Cl_2$ (4×20 mL). The combined organic layers were washed with an aqueous saturated $NaHCO_3$ solution (3×20 mL) and an aqueous saturated $Na_2S_2O_3$ solution (30 mL). Finally, the combined organic layers were dried on $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc 8:2 to 5:5) to give **20** as a colorless oil (0.65 g, 80%). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 3.95 (s, 2H, $CH_2O$), 3.89 (s, 2H, $CH_2O$), 3.49 (s, 2H, CH), 2.07 (s, 3H, $CH_3$), 2.05 (s, 3H, $CH_3$), 1.96 (d, 2H, *J*=14.8 Hz, $CH_aH_b$), 1.64 (d, 2H, *J*=14.8 Hz, $CH_aH_b$). $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 171.1 (C=O), 170.9 (C=O), 68.5 ($CH_2O$), 67.8 ($CH_2O$), 58.1 (CH), 43.9 (C), 33.7 ($CH_2$), 20.9 ($CH_3$). HRMS (ESI): *m*/*z* calcd for $C_{11}H_{16}O_5Na$ ($M^+$+Na) 251.0895, found 251.0900.

### 4.12. (±)-2-Azido-4,4-bis(hydroxymethyl)cyclopentanol (21)

To a solution of **20** (0.65 g, 2.9 mmol) in a MeOH/$H_2O$ 8:2 mixture (20 mL), sodium azide (0.37 g, 5.8 mmol, 2 equiv) was added. The reaction mixture was refluxed for 4 h. Then, solvents were evaporated under reduced pressure and the oily residue was purified by silica gel column chromatography (petroleum ether/EtOAc 5:5 to 2:8) to yield (±)-**21** as a colorless oil (0.50 g, 93%). $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 3.94 (q, 1H, *J*=7.2 Hz, $H^{1'}$), 3.67 (q, 1H, *J*=7.2 Hz, $H^{2'}$), 3.44 (s, 2H, $H^{5'}$), 3.40 (s, 2H, $H^{7'}$), 1.92 (dd, 1H, *J*=13.7, 7.2 Hz, $H^{3'}$), 1.87 (dd, 1H, *J*=13.5, 7.2 Hz, $H^{6'}$), 1.49–1.40 (m, 2H, $H^{6'}$+ $H^{3'}$). $^{13}$C NMR (62.9 MHz, $CD_3OD$) $\delta$ 77.2 (CH, $C^{1'}$), 68.9 (CH, $C^{2'}$), 68.0 ($CH_2$, $C^{5'}$), 67.9 ($CH_2$, $C^{7'}$), 46.1 (C, $C^{4'}$), 38.3 ($CH_2$, $C^{6'}$), 34.4 ($CH_2$, $C^{3'}$). HRMS (ESI): *m*/*z* calcd for $C_7H_{13}N_3O_3Na$ ($M^+$+Na) 210.0855, found 210.0854.

### 4.13. (±)-4,4-Bis(hydroxymethyl)-2-(4-pentyl-1*H*-1,2,3-triazol-1-yl)cyclopentanol (22)

Procedure B. The title compound was prepared from 1-heptyne (37 μL) after 1 h of microwave irradiation. The reaction mixture was filtered over a plug of Celite (MeOH) and the filtrate was evaporated under reduced pressure. The oily residue was then dissolved in EtOAc (20 mL) and washed with an aqueous saturated $NaHCO_3$ solution (2×5 mL) and brine (5 mL). The aqueous phases were extracted with EtOAc (2×20 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield compound (±)-**22** as colorless oil (74 mg, 98%). $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 7.80 (s, 1H, $H^5$), 4.72–4.61 (m, 1H, $H^{1'}$), 4.45 (q, 1H, *J*=9.0 Hz, $H^{2'}$), 3.51 (s, 2H, $H^{5'}$), 3.50 (s, 2H, $H^{7'}$), 2.68 (t, 2H, *J*=7.7 Hz, =C–$CH_2$), 2.21 (dd, 1H, *J*=13.5, 8.2 Hz, $H^{6'}$), 2.10–2.01 (m, 2H, $H^{3'}$+$H^{6'}$), 1.74–1.64 (m, 2H, =C–$CH_2CH_2$), 1.61 (dd, 1H, *J*=13.4, 9.0 Hz, $H^{3'}$), 1.39–1.32 (m, 4H, $CH_2CH_2CH_3$), 0.92 (t, 3H, *J*=7.0 Hz, $CH_3$). $^{13}$C NMR (62.9 MHz, $CD_3OD$) $\delta$ 150.0 (C, $C^4$), 122.3 (CH, $C^5$), 76.9 (CH, $C^{2'}$), 68.5 (CH, $C^{1'}$), 67.9 ($CH_2$, $C^{5'}$), 67.8 ($CH_2$, $C^{7'}$), 45.5 (C, $C^{4'}$), 38.3 ($CH_2$, $C^{3'}$), 35.8 ($CH_2$, $C^{6'}$), 32.5 ($CH_2CH_2CH_3$), 30.3 (=C–$CH_2CH_2$), 26.3 (=C–$CH_2$), 23.4 ($CH_2CH_3$), 14.3 ($CH_3$). HRMS (ESI): *m*/*z* calcd for $C_{14}H_{25}N_3O_3Na$ ($M^+$+Na) 306.1794, found 306.1793.

### 4.14. (±)-4,4-Bis(hydroxymethyl)-2-(4-butyl-1*H*-1,2,3-triazol-1-yl)cyclopentanol (23)

Procedure B. The title compound was prepared from 1-hexyne (32 μL) and 1.5 h of microwave irradiation. The reaction mixture was filtered over a plug of Celite (MeOH) and the filtrate was evaporated under reduced pressure. The oily residue was then dissolved in EtOAc (20 mL) and washed with an aqueous saturated $NaHCO_3$ solution (2×5 mL) and brine (5 mL). The aqueous phases were extracted with EtOAc (2×20 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield compound (±)-**23** as colorless oil (68 mg, 95%). $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 7.77 (s, 1H, $H^5$), 4.82–4.57 (m, 1H, $H^{1'}$), 4.41 (q, 1H, *J*=8.0 Hz, $H^{2'}$), 3.48 (s, 2H, $H^{5'}$), 3.46 (s, 2H, $H^{7'}$), 2.65 (t, 2H, *J*=7.5 Hz, =C–$CH_2$), 2.17 (dd, 1H, *J*=13.5, 8.5 Hz, $H^{6'}$),

2.06–1.96 (m, 2H, $H^{3'}$+$H^{6'}$), 1.67–1.53 (m, 3H, $H^{3'}$+=C–$CH_2CH_2$), 1.43–1.25 (m, 2H, $CH_2CH_3$), 0.91 (t, 3H, $J$=7.5 Hz, $CH_3$). $^{13}$C NMR (62.9 MHz, $CD_3OD$) $\delta$ 150.0 (C, $C^4$), 122.3 (CH, $C^5$), 76.9 (CH, $C^{2'}$), 68.5 (CH, $C^{1'}$), 67.9 ($CH_2$, $C^{5'}$), 67.8 ($CH_2$, $C^{7'}$), 45.5 (C, $C^{4'}$), 38.3 ($CH_2$, $C^{3'}$), 35.8 ($CH_2$, $C^{6'}$), 32.7 (=C–$CH_2CH_2$), 26.0 (=C–$CH_2$), 23.3 ($CH_2CH_3$), 14.1 ($CH_3$). HRMS (ESI): $m/z$ calcd for $C_{13}H_{24}N_3O_3$ ($M^+$+H) 270.1818, found 270.1824.

### 4.15. (±)-4,4-Bis(hydroxymethyl)-2-[4-(2-hydroxyethyl)-1*H*-1,2,3-triazol-1-yl]cyclopentanol (24)

Procedure B. The title compound was prepared from 3-butyn-1-ol (21 μL) after 2 min of microwave irradiation. The reaction mixture was evaporated under reduced pressure and the residue was purified by a silica gel column chromatography (EtOAc/MeOH 1:0 to 95:5). Compound (±)-**24** was isolated as a colorless oil (65 mg, 95%). $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 7.86 (s, 1H, $H^5$), 4.69–4.65 (m, 1H, $H^{1'}$), 4.44 (q, 1H, $J$=9.0 Hz, $H^{2'}$), 3.81 (t, 2H, $J$=6.5 Hz, $CH_2OH$), 3.51 (s, 2H, $H^{5'}$), 3.50 (s, 2H, $H^{7'}$), 2.91 (t, 2H, $J$=6.5 Hz, =C–$CH_2$), 2.21 (dd, 1H, $J$=13.5, 8.3 Hz, $H^{6'}$), 2.10–2.03 (m, 2H, $H^{3'}$+$H^{6'}$), 1.61 (dd, 1H, $J$=13.4, 9.0 Hz, $H^{3'}$). $^{13}$C NMR (62.9 MHz, $CD_3OD$) $\delta$ 145.9 (C, $C^4$), 123.2 (CH, $C^5$), 77.0 (CH, $C^{2'}$), 68.5 (CH, $C^{1'}$), 67.9 ($CH_2$, $C^{5'}$), 67.8 ($CH_2$, $C^{7'}$), 62.1 ($CH_2OH$), 45.5 (C, $C^{4'}$), 38.2 ($CH_2$, $C^{3'}$), 35.7 ($CH_2$, $C^{6'}$), 29.9 (=C–$CH_2$). HRMS (ESI): $m/z$ calcd for $C_{11}H_{19}N_3O_4Na$ ($M^+$+Na) 280.1273, found 280.1269.

### 4.16. (±)-4,4-Bis(hydroxymethyl)-2-(4-pyridin-2-yl-1*H*-1,2,3-triazol-1-yl)cyclopentanol (25)

Procedure B. The title compound was prepared from 2-ethynylpyridine (28 μL) after 1 min of microwave irradiation. The reaction mixture was evaporated under reduced pressure and the residue was purified by a silica gel column chromatography (EtOAc/MeOH 1:0 to 95:5). Compound (±)-**25** was obtained as a colorless oil (61 mg, 78%). $^1$H NMR (250 MHz, DMSO) $\delta$ 8.66 (s, 1H, $H^5$), 8.59 (d, 1H, $J$=3.8 Hz, $H^{Ar}$), 8.03 (d, 1H, $J$=7.8 Hz, $H^{Ar}$), 7.90 (t, 1H, $J$=7.8 Hz, $H^{Ar}$), 7.34 (t, 1H, $J$=5.8 Hz, $H^{Ar}$), 4.73–4.61 (m, 1H, $H^{1'}$), 4.33 (q, 1H, $J$=9.0 Hz, $H^{2'}$), 3.32 (s, 2H, $H^{5'}$), 3.31 (s, 2H, $H^{7'}$), 2.09 (dd, 1H, $J$=13.2, 8.2 Hz, $H^{6'}$), 1.97–1.85 (m, 2H, $H^{3'}$+$H^{6'}$), 1.48 (dd, 1H, $J$=12.9, 9.0 Hz, $H^{3'}$). $^{13}$C NMR (62.9 MHz, DMSO) $\delta$ 150.1 (C, $C^{Ar}$), 149.5 (CH, $C^{Ar}$), 147.0 (C, $C^4$), 137.3 (CH, $C^{Ar}$), 122.9 (CH, $C^{Ar}$), 122.0 (CH, $C^5$), 119.4 (CH, $C^{Ar}$), 75.1 (CH, $C^{2'}$), 66.8 (CH, $C^{1'}$), 66.1 ($CH_2$, $C^{5'}$), 65.9 ($CH_2$, $C^{7'}$), 44.0 (C, $C^{4'}$), 37.3 ($CH_2$, $C^{3'}$), 34.5 ($CH_2$, $C^{6'}$). HRMS (ESI): $m/z$ calcd for $C_{14}H_{19}N_4O_3$ ($M^+$+H) 291.1457, found 291.1465.

### 4.17. (±)-4,4-Bis(hydroxymethyl)-2-[4-(2-hydroxymethyl)-1*H*-1,2,3-triazol-1-yl]cyclopentanol (26)

The deacetylation of compound (±)-**13** (73 mg, 0.25 mmol) was carried out at 4 °C overnight without stirring in an ammoniac solution 7 N in methanol (2 mL). Compound (±)-**26** was obtained after solvent evaporation as a transparent oil (59 mg, 95%). $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 7.98 (s, 1H, $H^5$), 4.75–4.59 (m, 1H, $H^{1'}$), 4.68 (s, 2H, $CH_2OH$), 4.46 (q, 1H, $J$=9.0 Hz, $H^{2'}$), 3.52 (s, 2H, $H^{5'}$), 3.50 (s, 2H, $H^{7'}$), 2.22 (dd, 1H, $J$=13.5, 8.2 Hz, $H^{6'}$), 2.12–2.00 (m, 2H, $H^{3'}$+$H^{6'}$), 1.62 (dd, 1H, $J$=13.5, 9.0 Hz, $H^{3'}$). $^{13}$C NMR (62.9 MHz, $CD_3OD$) $\delta$ 148.7 (C, $C^4$), 123.3 (CH, $C^5$), 76.9 (CH, $C^{2'}$), 68.5 (CH, $C^{1'}$), 67.9 ($CH_2$, $C^{5'}$), 67.8 ($CH_2$, $C^{7'}$), 56.5 ($CH_2OH$), 45.5 (C, $C^{4'}$), 38.3 ($CH_2$, $C^{3'}$), 35.7 ($CH_2$, $C^{6'}$). HRMS (ESI): $m/z$ calcd for $C_{10}H_{17}N_3O_4Na$ ($M^+$+Na) 266.1117, found 266.1119.

### 4.18. (±)-Dimethyl-1-(2-hydroxy-4,4-bis(hydroxymethyl)-cyclopentyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (27c)

To a solution of azide (±)-**21** (50 mg, 0.27 mmol) in a 1:1 mixture of water and *t*-BuOH (2 mL) in a glass vial equipped with a magnetic stirring bar, dimethyl acetylenedicarboxylate (36 μL, 0.30 mmol, 1.1 equiv) was added. The vial was sealed with an aluminum/Teflon crimp top and then irradiated at 125 °C for 1 h. After cooling to 50 °C by air jet, the resulting mixture was purified by silica gel column chromatography (EtOAc/MeOH 98:2). Compound (±)-**27c** was obtained as a transparent oil (79 mg, 89%). $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 4.98 (q, 1H, $J$=8.8 Hz, $H^{1'}$), 4.59 (q, 1H, $J$=8.8 Hz, $H^{2'}$), 3.99 (s, 3H, $OCH_3$), 3.93 (s, 3H, $OCH_3$), 3.52–3.50 (m, 4H, $H^{5'}$+$H^{7'}$), 2.23 (m, 2H, $H^{6'}$), 2.07 (dd, 1H, $J$=13.3, 8.8 Hz, $H^{3'}$), 1.61 (dd, 1H, $J$=13.3, 8.8 Hz, $H^{3'}$). $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 161.8 (C=O), 160.5 (C=O), 140.0 (C, $C^4$), 133.2 (C, $C^5$), 76.8 (CH, $C^{2'}$), 68.4 (CH, $C^{1'}$), 67.7 ($CH_2$, $C^{5'}$+$C^{7'}$), 54.0 ($OCH_3$), 53.0 ($OCH_3$), 45.7 (C, $C^{4'}$), 37.9 ($CH_2$, $C^{3'}$), 35.3 ($CH_2$, $C^{6'}$). HRMS (ESI): $m/z$ calcd for $C_{13}H_{19}N_3O_7Na$ ($M^+$+Na) 352.1121, found 352.1127.

### 4.19. (±)-1-(3-Hydroxy-8,8-dimethyl-7,9-dioxa-spiro[4.5]-decan-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (28a)

Epoxide **4** (0.22 g, 1.22 mmol, 1.05 equiv), uracil (0.13 g, 1.16 mmol, 1 equiv), and a small amount of $K_2CO_3$ were dissolved in dry DMF (4 mL). The mixture was heated at 136 °C for 20 h. After evaporation, the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 5:5 to 0:1) to yield (±)-**28a** as a white solid (0.1 g, 32%). $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 7.67 (d, 1H, $J$=8.0 Hz, $H^6$), 5.69 (d, 1H, $J$=8.0 Hz, $H^5$), 4.55–4.36 (m, 2H, $H^{1'}$+$H^{2'}$), 3.70 (s, 4H, $H^{5'}$+$H^{7'}$), 2.16–2.01 (m, 2H, $H^{3'}$+$H^{6'}$), 1.69 (dd, 1H, $J$=13.5, 10.8 Hz, $H^{6'}$), 1.45–1.37 (m, 1H, $H^{3'}$), 1.39 (s, 3H, $CH_3$), 1.37 (s, 3H, $CH_3$). $^{13}$C NMR (62.9 MHz, $CD_3OD$) $\delta$ 166.3 (C, $C^4$), 153.0 (C, $C^2$), 144.8 (CH, $C^6$), 102.5 (CH, $C^5$), 99.1 (C), 73.0 (CH, $C^{2'}$), 70.5 ($CH_2$, $C^{5'}$+$C^{7'}$), 65.0 (CH, $C^{1'}$), 39.2 ($CH_2$, $C^{3'}$), 37.4 (C, $C^{4'}$), 35.0 ($CH_2$, $C^{6'}$), 24.7 ($CH_3$), 23.5 ($CH_3$). HRMS (ESI): $m/z$ calcd for $C_{14}H_{20}N_2O_5Na$ ($M^+$+Na) 319.1270, found 319.1284.

### 4.20. (±)-4-Amino-1-(3-hydroxy-8,8-dimethyl-7,9-dioxa-spiro[4.5]decan-2-yl)pyrimidin-2(1*H*)-one (28b)

Epoxide **4** (0.23 g, 1.23 mmol, 1.05 equiv), cytosine (0.13 g, 1.17 mmol, 1 equiv), and a small amount of $K_2CO_3$ were dissolved in dry DMF (4 mL). The mixture was heated at 136 °C for 20 h. After evaporation, the residue was purified by silica gel column chromatography (EtOAc/MeOH 5:1) to yield (±)-**28b** as a white solid (0.2 g, 57%). $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 7.64 (d, 1H, $J$=7.5 Hz, $H^6$), 5.88 (d, 1H, $J$=7.5 Hz, $H^5$), 4.54–4.41 (m, 2H, $H^{1'}$+$H^{2'}$), 3.71 (s, 2H, $H^{5'}$), 3.70 (s, 2H, $H^{7'}$), 2.16–2.06 (m, 2H, $H^{3'}$+$H^{6'}$), 1.71–1.61 (m, 1H, $H^{6'}$), 1.47–1.37 (m, 1H, $H^{3'}$), 1.39 (s, 3H, $CH_3$), 1.37 (s, 3H, $CH_3$). $^{13}$C NMR (62.9 MHz, $CD_3OD$) $\delta$ 167.3 (C, $C^4$), 159.3 (C, $C^2$), 145.1 (CH, $C^6$), 99.1 (CH, $C^5$), 96.0 (C), 73.2 (CH, $C^{2'}$), 70.6 ($CH_2$, $C^{5'}$+$C^{7'}$), 66.3 (CH, $C^{1'}$), 39.8 ($CH_2$, $C^{3'}$), 37.6 (C, $C^{4'}$), 35.5 ($CH_2$, $C^{6'}$), 24.3 ($CH_3$), 23.9 ($CH_3$). HRMS (ESI): $m/z$ calcd for $C_{14}H_{22}N_3O_4$ ($M^+$+H) 296.1610, found 296.1607.

### 4.21. (±)-1-(2-Hydroxy-4,4-bis(hydroxymethyl)cyclopentyl)pyrimidine-2,4(1*H*,3*H*)-dione (29a)

Compound (±)-**28a** (0.1 g, 0.34 mmol) was dissolved in a 60% TFA solution in water (4 mL). After 24 h of stirring at room temperature and evaporation of the solvent, (±)-**29a** was obtained as a white solid (85 mg, 98%). $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 7.68 (d, 1H, $J$=8.0 Hz, $H^6$), 5.71 (d, 1H, $J$=8.0 Hz, $H^5$), 4.67–4.55 (m, 1H, $H^{1'}$), 4.44–4.34 (m, 1H, $H^{2'}$), 3.47 (s, 4H, $H^{5'}$+$H^{7'}$), 2.04–1.92 (m, 2H, $H^{3'}$+$H^{6'}$), 1.70–1.46 (m, 2H, $H^{3'}$+$H^{6'}$). $^{13}$C NMR (62.9 MHz, $CD_3OD$) $\delta$ 166.3 (C, $C^4$), 153.2 (C, $C^2$), 144.2 (CH, $C^6$), 102.6 (CH, $C^5$), 74.0 (CH, $C^{2'}$), 68.1 ($CH_2$, $C^{5'}$), 67.9 ($CH_2$, $C^{7'}$), 64.3 (CH, $C^{1'}$), 44.9 (C, $C^{4'}$), 37.9 ($CH_2$, $C^{3'}$), 33.3 ($CH_2$, $C^{6'}$). HRMS (ESI): $m/z$ calcd for $C_{11}H_{16}N_2O_5Na$ ($M^+$+Na) 279.0957, found 279.0969.

### 4.22. (±)-4-Amino-1-(2-hydroxy-4,4-bis(hydroxymethyl)-cyclopentyl)pyrimidin-2(1*H*)-one (29b)

Compound (±)-**28b** (0.1 g, 0.34 mmol) was dissolved in a 60% TFA solution in water (4 mL). After 24 h of stirring at room temperature and evaporation of the solvent, the resulting yellow precipitate was washed with EtOAc (5 mL) and then with diethyl ether. Compound (±)-**29b** was obtained as a white solid (54 mg, 62%). $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 7.88 (d, 1H, $J$=7.5 Hz, $H^6$), 6.04 (d, 1H, $J$=7.5 Hz, $H^5$), 4.65 (q, 1H, $J$=9.4 Hz, $H^{1'}$), 4.42 (q, 1H, $J$=9.4 Hz, $H^{2'}$), 3.47 (s, 4H, $H^{5'}$+$H^{7'}$), 2.06–1.97 (m, 2H, $H^{3'}$+$H^{6'}$), 1.71–1.48 (m, 2H, $H^{3'}$+$H^{6'}$). $^{13}$C NMR (62.9 MHz, $CD_3OD$) $\delta$ 161.1 (C, $C^4$), 149.6 (C, $C^2$), 148.2 (CH, $C^6$), 94.9 (CH, $C^5$), 74.1 (CH, $C^{2'}$), 68.0 ($CH_2$, $C^{5'}$), 67.8 ($CH_2$, $C^{7'}$), 65.8 (CH, $C^{1'}$), 45.0 (C, $C^{4'}$), 37.7 ($CH_2$, $C^{3'}$), 33.3 ($CH_2$, $C^{6'}$). HRMS (ESI): $m/z$ calcd for $C_{11}H_{18}N_3O_4$ ($M^+$+H) 256.1297, found 256.1285.

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