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Triazolyl Derivatives for Acidic Release of Alcohols

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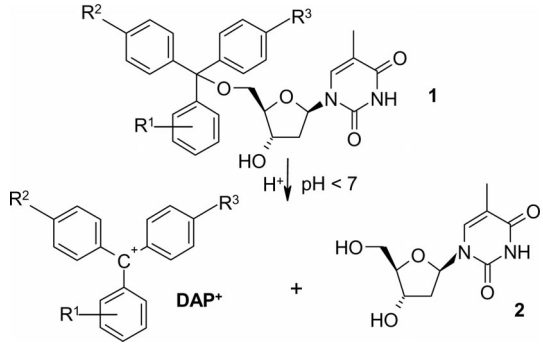
New triazolyl-based carbonates and ethers have been investigated as potential alcohol-releasing systems under mild acidic conditions. Triazolyl carbonates could not be prepared because of their apparent instability, whereas ethers were successfully obtained. The rate of hydrolysis of these ethers ramged from a few hours to several days. A theoretical investigation demonstrated that the acidic release of alcohols from triazole derivatives proceeds first by protonation of the triazole ring followed by proton transfer from the triazole ring to the carbonyl group of the carbonates or to the oxygen atom of the ether derivatives. The rate of the decomposition reaction was shown to depend on the length of the N3–H···O hydrogen bond in the intermediate **C-NH⁺/E-NH⁺** structures and on the stability of the triazole carbocation, which is closely related to the π-donating effect of its R^2 and R^3 substituents.

Introduction

Drug delivery based on nanoparticle vectors such as polymers,[1] liposomes or polyplexes is a well-known process in which the vectors are internalized by cellular endocytosis,[2] a natural process that allows cells to internalize bulky objects, such as nutriments, for their needs. The process starts with the encapsulation, by the membrane, of the object to be internalized, with subsequent generation of an intracellular vesicle called endosome at a mildly acidic internal pH (pH = 6). On maturation endosomes give more acidic lysosome vesicles (pH 4–5),[3] responsible for the degradation of the internalized objects. This mechanism has been exploited for the cellular internalization of various drug delivery systems prepared through two different approaches. The first approach relies on non-covalent assembly between the vectors and cargos, as in the case of the polyaminated polyplexes used for carrying DNA. The second approach is based on covalent objects into which acid-sensitive bonds are introduced. Many polymeric vectors have been designed in this way, for instance HPMA, as proposed by Kopececk and Duncan,[4] polyethylene oxides (PEO), polylactic acid (PLA) or polyglutamic acid (PGA). To exploit the increasing acidity of endocytosis, ortho esters,[5] acetals[6] or polyurethanes[7] have been proposed as acid-sensitive vectors designed to reach the lysosomal stage before being degraded. When covalent links between the bioactive molecules and vectors are involved, hydrazone,[8] benzaldehyde[9] and trityl[10,11] groups have been used for targeting biomolecules with amines or alcohols. These constructs must be rapidly cleaved at mild acidic pH values to exploit endosome maturation, a process that is completed in less than 1 hour.[12] This objective can be achieved by systems generating positive species on protonation such as carbocations. The more stabilized the species, the faster the acidic hydrolysis should be. For the trityl-like groups, and especially with *p*-methoxy-substituted phenyl rings,[13] the mesomeric effect gives a highly stabilized dianisylphenyl carbocation (Scheme 1, DAP⁺: R^1 = vector, R^2 = R^3 = OMe). Thus, dimethoxytrityl derivatives have been particu-



Scheme 1. Example and principle for the design of trityl-like sensitive groups.

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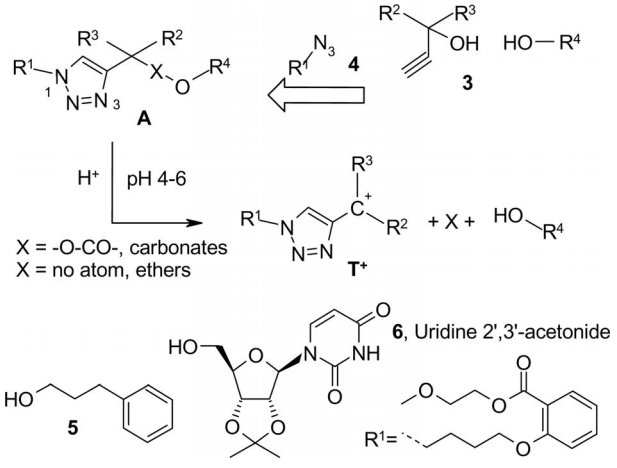
larly developed for the acidic pH release of nucleosides, as exemplified in Scheme 1 with the 5-*O*-trityl ether **1** of thymidine **2**.[11]

To achieve conjugation to the vectors, one of the phenyl groups was substituted with an electron-withdrawing amide (R^1) to link the trityl group to the vector via a spacer. This synthetic strategy can be improved by recently developed ligation methods. Cycloaddition reactions have been introduced for bioconjugation to several types of nanoparticles.[14] The Huisgen azide–alkyne cycloaddition[15] improved by Sharpless and co-workers[16] is now commonly used in the popular concept of click chemistry when applied to terminal alkynes and azides. It allows the selective synthesis of 1,4-disubstituted triazole rings under copper catalysis. When used for bioconjugation, the resulting aromatic triazole ring has rarely been exploited.[17–19]

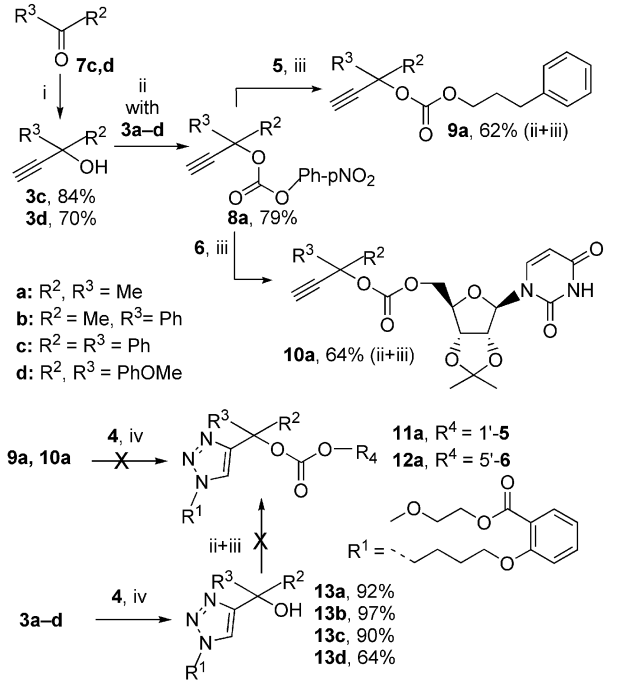
We have recently proposed this chemistry for a bioconjugation process leading at the same time to a new type of acid-sensitive group,[20] with the triazole group considered as a possible substituent for one of the phenyl groups in the trityl structure, as in generic compounds **A** (Scheme 2, $R^2 = R^3 = Ph$). In this way, cycloaddition with convenient 1,1-disubstituted propargyl alcohols **3** and alkyl azide **4** should lead to both ligation and the formation of a pH-sensitive system. On acidic hydrolysis, a dialkyltriazolylmethyl-stabilized carbocation ($\mathbf{T^+}$) should be formed. We have already successfully developed this concept with benzylamine, producing a carbamate cleaved at mildly acidic pH 4 with a half-life of 22 h.[20] We now propose to use this strategy to prepare "protected" alcohol derivatives for the release of bioactive molecules with hydroxy functional groups. Carbonates were investigated (Scheme 2) by analogy to our carbamates but ether versions were also considered, in accord with existing literature. In addition to the synthetic work and hydrolysis experiments, molecular modelling was performed to find the correlation between the stability of the resulting carbonates and ethers in acidic environments and the experimental half-lives of the protected molecules and to explore the possible participation of the triazole ring in such a hydrolysis.



Scheme 2. Dialkyltriazolylmethane as trityl analogues.

Results and Discussion

Alcohol **5** was selected as a standard aliphatic alcohol model and uridine 2′,3′-acetonide **6** for potential application with nucleoside derivatives. Azide **4** used in this work has already been described by us.[20] The carbonates were synthesized based on two possible routes from alcohols **3** (Scheme 3). Alcohols **3** could be converted into triazolyl carbonates **11/12** via propargyl carbonates **9/10** or via alcohols **13**. Non-commercial propargylic alcohols **3c**,**d** were prepared by a known procedure from ketones **7c**,**d**.[21] Alcohols **3** were then tentatively converted into the corresponding carbonates. Alcohol **3a** was successfully converted into the intermediate carbonate **8a** prior to nucleophilic substitution with alcohol **5** to afford **9a**. Initial attempts to directly use the unprotected uridine to prepare unprotected uridine carbonate **8a** failed due to its low solubility in organic solvent. The corresponding soluble 2′,3′-acetonide **6**[22] was finally prepared and allowed the synthesis of carbonate **10a** in good yields. Attempts to convert alcohols **3b**–**d** into the corresponding carbonates **9b**–**d** and **10b**–**d** failed. The two propargyl carbonates **9a** and **10a** were then submitted to the cycloaddition reaction with azide **4** under various copper catalysis conditions.

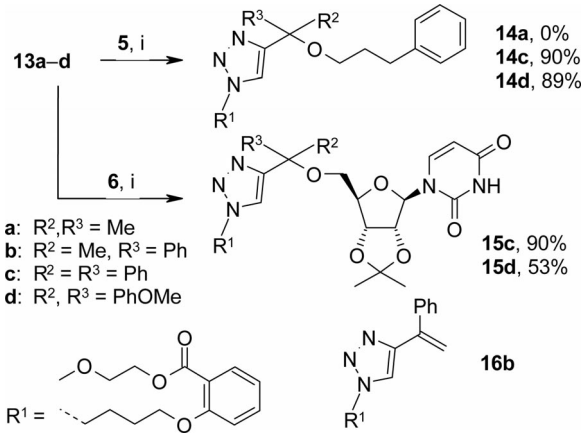


Scheme 3. Reagents and conditions: i) THF, Li–C≡C–TMS, –60 to 0 °C overnight; ii) *p*-NO_2PhCOCl, NEt_3, CH_2Cl_2; iii) CH_2Cl_2, pyridine, DMAP, 25 °C; iv) $CuSO_4 \cdot 5H_2O$ + NaAscorbate or CuI, THF/H_2O, 1:1, 25 °C.

Unfortunately, only the cycloadduct **11a** was detected in the crude and subsequent purification led to decomposition whereas none of the other carbonates were observed. The instability of the propargylic carbonates **9** and **10** during cycloaddition prompted us to investigate prior cycloaddition between alcohols **3** and azide **4** and subsequent functionalization. Alcohols **3** were treated with azide **4** using

$CuSO_4 \cdot 5H_2O$ in THF/H_2O. In our case, THF was found more convenient in relation to compound solubility and afforded the cycloadducts **13** in good-to-high yields. The various methods used to try and activate the alcohols **13** (nitrophenyl formate, prior deprotonation with bases) were unsuccessful and we were not able to prepare the desired triazolyl carbonates **11** or **12** from **13**.

We then investigated the preparation of the ether versions (Scheme 2, X = no atom) using an analogous strategy. The ethers could also be obtained as a propargylic intermediate prior to cycloaddition or could be prepared after cycloaddition. According to our application and the difficulties encountered in the synthetic path with propargylic derivatives, we focused on the preparation of ethers **14** and **15** via alcohols **13** (Scheme 4). Several methods have been used to prepare trityl ethers. Patel et al.[10] proposed an initial conversion to the corresponding chloride (AcCl, reflux). In our hands, this procedure and others [$SOCl_2$/pyridine, THF, DMF, $(COCl)_2/CH_2Cl_2$ or toluene, PCl_3/Benzene] failed when applied to alcohols **13**. Recently, Lewis acid catalysis with $B(C_6F_5)_3$ as the catalyst has been described for the preparation of ethers from two alcohols, one of which is a good nucleophile and the other is able to generate a stable carbocation under Lewis acid catalysis.[23] This procedure was first investigated with alcohol **5** to prepare ethers **14** (Scheme 4). As expected, no reaction occurred with alcohol **13a**, the two methyl groups not being able to sufficiently stabilize the potential carbocation and alcohol **13a** being itself probably as nucleophilic as the other alcohol **5**. Alcohol **13b** gave a mixture of ether **14b** and alkene **16b**, which were difficult to separate. Alkene **16** was observed only starting from alcohol **13b** as a result of proton loss from the carbocation. This was facilitated by the resulting conjugation, not possible for the other alcohols **13**. Ethers **14c**,**d** were obtained in high yields, which confirms the importance of the aromatic effect for the cation stabilization in this type of reaction. This protocol was applied to the preparation of ethers **15c**,**d**, which were obtained in good-to-high yields. The lower yield found for ether **15d** was the result of an incomplete reaction, as unreacted materials were recovered. This has been attributed to a competitive reaction with the resulting water molecule as the dianisyltriazolyl carbocation may be more sensitive to less nucleophilic compounds.[24] This etherification procedure appeared to be very convenient and practical in such cases. It also appeared to be more efficient than previously reported methods in which trityl alcohols were first converted into halogen derivatives prior to substitution. The acetonide protecting group was found to be stable under these conditions.



Scheme 4. Reagents and conditions: i) $B(C_6F_5)_3$, CH_2Cl_2, reflux.

Having obtained four molecules **14c**,**d** and **15c**,**d** as potential acidic releasing systems, the rate of hydrolysis of these compounds was studied. Preliminary tests revealed that the solubility was not complete in aqueous buffered solutions (pH 1, HCl/KCl; pH 4, citrate buffer). The use of co-solvents was then investigated: acetonitrile, methanol and dimethoxydiethylene glycol [$(DME)_2O$]. The hydrolysis at pH = 1 of ethers **15c**,**d** was at this stage monitored by TLC to obtain indicative rates as a function of the co-solvent (Table 1). In all cases, compound **15d** was rapidly hydrolysed. Acetonitrile appeared to give increased solubility and faster hydrolysis for compound **15c**, confirming the correlation between rate of hydrolysis and solubility. An 80:20 mixture of buffer/CH_3CN was consequently selected to precisely determine the values of $t_{1/2}$ for the rate of hydrolysis of the ethers **14** and **15** in buffered solutions at pH 1 and 4. In the latter case, addition of CH_3CN gave a final pH of 4.3. This value is in agreement with the known lysosomal pH (range 4–5), the cellular vesicles where our compounds should be cleaved by an acidic reaction to release the alcohols. Reaction mixtures were neutralized at indicated times and the formation of released alcohols (**13** or **5**/**6**) from the initial ethers followed over time (see Hydrolysis Experiments in the Supporting Information).

Table 1. Rates of hydrolysis of ethers **15** in pH 1 buffered solutions.

Head 1[a]	Time	**15c**, R^2,R^3 = Ph [%]	**15d**, R^2,R^3 = $MeOC_6H_4$ [%]
$(DME)_2O$	20 min	–	100
	3 h	7	n.d.[a]
MeOH	3 h	9	n.d.[a]
CH_3CN	20 min	n.d.[a]	100
	3 h	53	n.d.[a]

[a] n.d.: not determined.

The observed half-lives are reported in Table 2. ^{1}H NMR signals of compounds **5**/**6**, **13** and **14**/**15** were selected to monitor the hydrolysis (Figure 1). Attempts to quantify more precisely the hydrolysis rates by HPLC were not successful due to co-elution of alcohols **13** and **14** or **15**. All ethers were rapidly hydrolysed at pH = 1, making such diaryltriazolylmethyl ether derivatives suitable protecting groups for alcohols. The nucleoside **6** was released at pH 4.3 without degradation of the acetonide group, as shown in the ^{1}H NMR spectrum of the crude. A comparison between the ethers **14c**/**15c** and **14d**/**15d** showed that, as expected, the **d** compounds are hydrolysed more rapidly, a result directly correlated to the stabilization effect of the two anisyl groups compared with the phenyl ones. At physiological pH (buffer TRISMA/CH_3CN, 80:20), ethers **15** were stable over

8 d. In the case of ether **14c**, the system used to evaluate the hydrolysis rate was not optimal with partial precipitation and this may explain the differences observed with the corresponding nucleoside **15c**, which is slowly hydrolysed. The opposite result was observed for compounds **14d** and **15d**, with the propanol ether more rapidly hydrolysed at pH = 1 and 4. These results are consistent with the moderate solubility of the **c** series compared with the **d** series and may also be explained by possible side-protonations on the nucleoside moiety in compounds **15**, whereas ethers **14** have only one protonation site. At pH = 1, the acidity could compensate this side-protonation for **15**, whereas at pH = 4, this is not possible. In our hands, the dianisyltriazolylmethyl ethers appeared to be suited to the preparation of acid pH-sensitive protecting groups that may be used for hydroxy-drug release.

Table 2. Determination of $t_{1/2}$ for the hydrolysis of ethers **14c**,**d** and **15c**,**d** in buffered solutions at pH 1 and 4 with acetonitrile as co-solvent.

pH	$t_{1/2}$			
	14c	**14d**	**15c**	**15d**
1	[a]	<20 min	3 h	<20 min
4.3	∞[b]	6–7 h	>60 h[c]	60 h
7.3	n.d.[d]	n.d.[d]	Stable[e]	Stable[e]

[a] Inadequate solubility. [b] Not hydrolysed. [c] 15% hydrolysed at 60 h. [d] n.d.: not determined. [e] After 8 d.

To rationalize our experimental kinetic data and to elucidate the hydrolysis mechanism, we performed molecular DFT B3LYP/6-31G(d,p) gas-phase calculations. This theoretical level[25] of calculation is widely used and has been proven to give reliable results in a number of mechanistic studies.[26] Acidic protonation of triazoles has also been extensively studied[27] by this method for various substituted

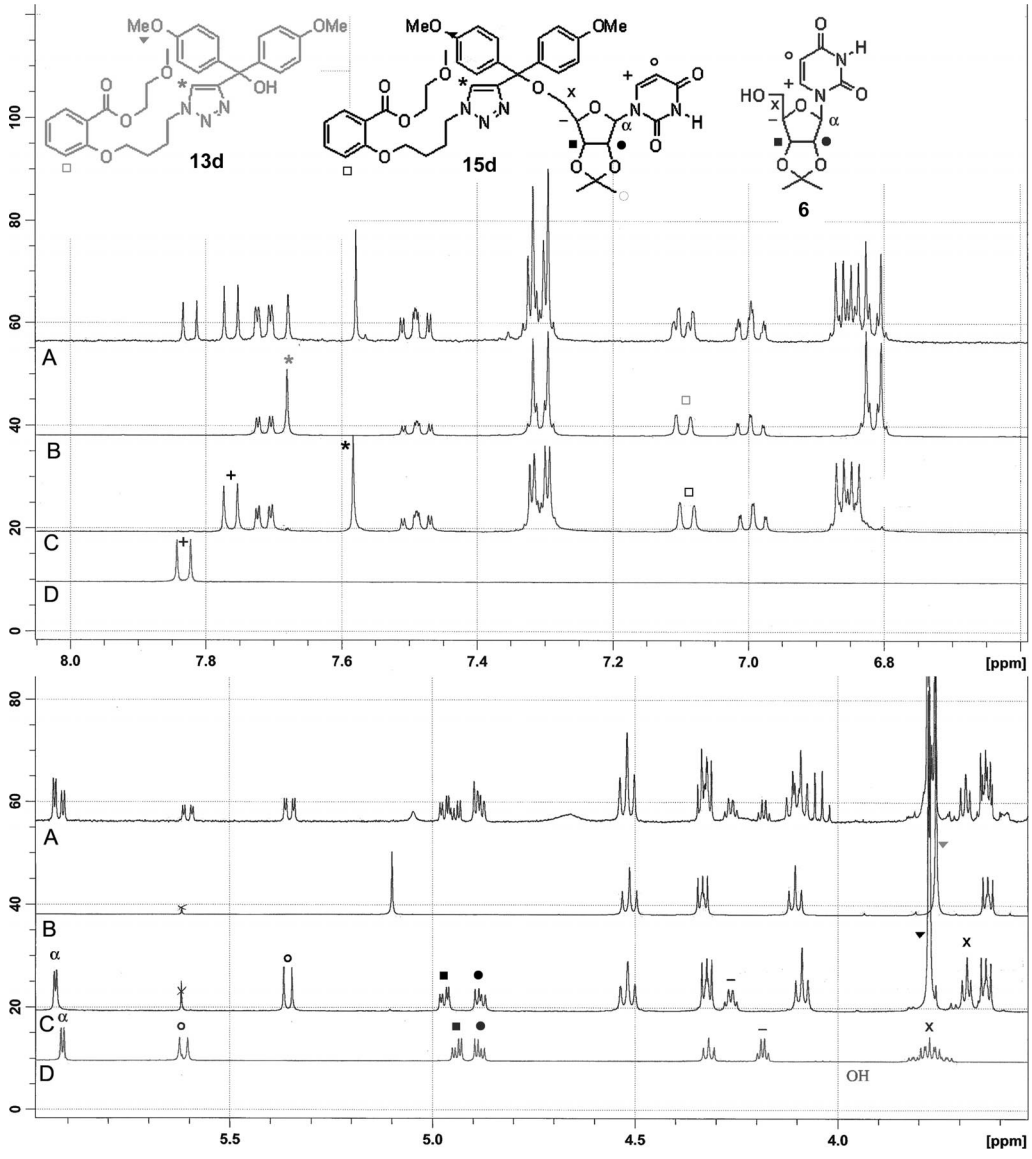


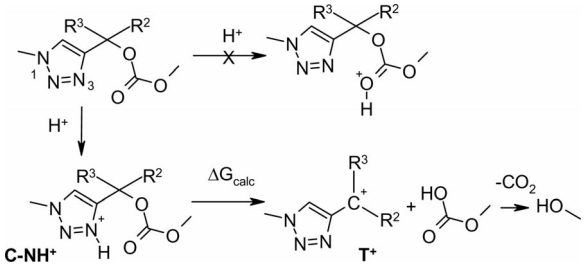
Figure 1. ^{1}H NMR monitoring of the hydrolysis of ether **15d** with citrate buffer/CH_3CN 4:1 (pH = 4.3). A) Crude reaction mixture from hydrolysis with pH = 4.3 citrate buffer. B) Alcohol **13d**. C) Ether **15d**. D) Uridine acetonide **6**.

triazoles and 1,4-disubstituted triazoles. Preferential protonation sites were shown to be the N3 nitrogen atom and then N2 (Scheme 2, see compound A). To account for the medium sensitivity of these reactions, solvent effects were included in the energy calculations using the SMD continuum model.[28] B3LYP/6-31G(d,p) geometries and SMD-B3LYP/6-31G(d)//B3LYP/6-31G(d,p) aqueous free energies can be found in the Supporting Information. We have chosen to discuss the aqueous solution Gibbs' free energies. Several pairs of substituents R^2 and R^3 were investigated for both the triazolyl carbonates and triazolyl ethers series, although some of the compounds calculated were not obtained (Table 3). R^1 = R^4 = methyl substituents were used to reduce calculation times. All calculations were performed with the Gaussian 09 package[29] and computational details are described in the Exp. Section. Let us first start our discussion with carbonate derivatives even if half-live measurements could not be achieved for these compounds. We performed theoretical calculations on these systems to gain a better understanding of their apparent instability. First, the protonation step was studied (Scheme 5). In Scheme 6, the stability of the protonated species are given relative to N1 in model a. In agreement with previous calculations,[27] the protonation of the triazole N2 atom is less favoured by about 18 kcal/mol than the N3 site (water phase free energy).

Table 3. Computed aqueous free energies (ΔG_{calc} in) for protonated triazolyl carbonates **C-NH$^+$** and triazolyl ethers **E-NH$^+$** decomposition reactions.

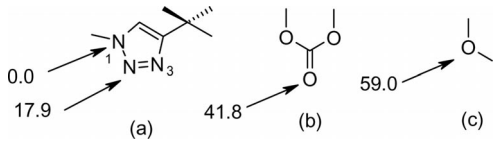
R^2	R^3	$\Delta G_{calcd.}$ [kcal/mol]	
		C-NH$^+$	**E-NH$^+$**
Me	Me	+1.1	+5.8
Me	Ph	–4.0	+2.3
Ph	Ph	–10.6	–5.7
Tol[a]	Tol[a]	–13.8	–8.9
An[a]	An[a]	–17.4	–12.5

[a] An = Anisyl = 4-MeOPh; Tol = 4-MePh.



Scheme 5. Proposed mechanism for acidic release of alcohol from carbonates.

Thus, only two protonation sites were considered for these systems: the N3 atom of the triazolyl and the oxygen atom of the carbonyl. Protonation of the most basic nitrogen atom of the triazole ring gave the **C-NH$^+$** carbocation intermediate (local minimum on the potential energy surface). The attempt to protonate the oxygen atom of the carbonyl group resulted in C–O bond dissociation and the release of carbocation **T$^+$**. To determine which protonation site was the most reactive, additive calculations were performed on model compounds MeO–CO–OMe and 1,4-dimethyltriazolyl (Scheme 6). The results showed that protonation of the carbonyl oxygen atom of MeO–CO–OMe was not as favoured as the protonation of the N3 atom of the 1,4-dimethyltriazolyl model compound by as much as 42 kcal/mol. Even though these model compounds differ from the carbonates studied, such a high energy separation allowed us to conclude that the first protonation occurs at the N3 atom of the triazolyl (**C-NH$^+$** in Scheme 5) and revealed the particular role of the triazolyl ring acting as a protonated vector in this hydrolysis reaction. Thus, in an acidic medium (pH = 4), the protonated carbonates have structures analogous to the one displayed in Figure 2a (structural parameters are given in the Supporting Information). An interesting common feature can be reported for **C-NH$^+$** intermediates: the distance between the proton fixed on the N3 atom and the oxygen atom of the carbonyl group is ranked between 1.65 and 1.70 Å due to the non-planar seven-membered H–N3–C–C–O–C=O ring and the nucleophilic lone-pair on the carbonyl oxygen atom. This very short distance allows a smooth intramolecular proton shift, leading to the formation of the carbocation **T$^+$** and the MeO–CO–OH species.[30]



Scheme 6. Relative free energies [kcal/mol] determined at the B3LYP/6-31G(d,p) level of theory for protonation of the (a) triazole, (b) carbonate and (c) ether models.

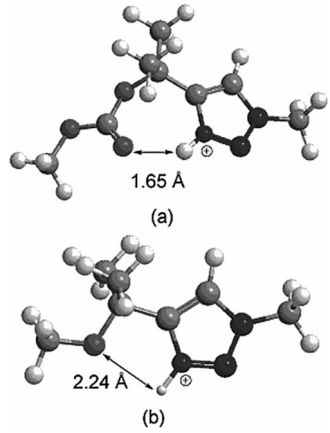
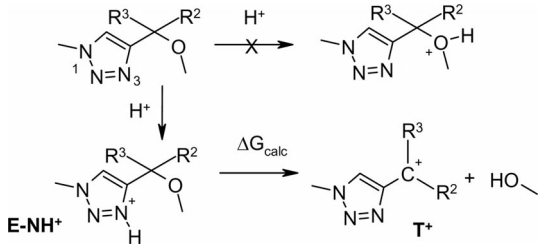


Figure 2. Selected distances [Å] for (a) protonated carbonate **C-NH$^+$** and (b) ether **E-N$_3$H$^+$** (R^1 = R^2 = Me) optimized structures at the B3LYP/6-31G(d,p) level of theory.

This decomposition process is the next step of our proposed hydrolysis mechanism (Scheme 5). The free energies of these decomposition steps, $\Delta G_{calcd.}$, are reported in Table 3. As expected, $\Delta G_{calcd.}$ correlates to the π-donating effect of the R^2 and R^3 substituents. Thus, the more π-do-

nating the R^2 and R^3 substituents, the more stable is the carbocation $\mathbf{T^+}$. In our experiments, the carbonates could not be observed, except for propargylic derivatives with $R^2 = R^3 = Me$, which decomposed when we tried to conduct the cycloaddition reaction. The instability of the carbonate compounds could originate from an easy intramolecular proton shift from the N3 atom to the oxygen atom of the carbonyl, facilitated by the short distance noted above.

Turning now to the ether compounds, two protonation sites were also considered: the N3 atom of the triazolyl and the oxygen atom of the ether. The attempt to protonate this oxygen atom leads to C–O bond dissociation and the formation of the carbocation $\mathbf{T^+}$ as well as MeOH. However, an additional calculation performed for the protonation of the oxygen atom of the dimethyl ether model showed that this is not as favoured as the protonation of the N3 atom of the 1,4-dimethyltriazolyl compound by about 59 kcal/mol (Scheme 6). Once again, despite these model compounds differing from the ethers investigated here, the protonation energies are so different that we can postulate that the N3 atom is protonated first ($\mathbf{E\text{-}NH^+}$ in Scheme 7). For these ether compounds, the R^2 and R^3 substituents were the same as for the carbonate series (Table 3). Five protonated species ($\mathbf{E\text{-}NH^+}$) were fully optimized and, in contrast to the carbonate species, the calculated distance between the proton fixed on the N3 atom and the ether oxygen atom appears to be significantly longer (2.20–2.40 Å, see Figure 2, b) due to the presence of a shorter –C(R^2R^3)–O– chain in the ethers compared with –C(R^2R^3)–O–C=O in the carbonates. This observation could explain the relative stability of the ether compounds relative to the carbonate compounds. The intramolecular proton shift from the N3 atom to the ether oxygen atom then leads to the formation of the carbocation $\mathbf{T^+}$ and MeOH species. The free energies of these decomposition reactions, $\Delta G_{calcd.}$, were calculated using the same procedure as for the carbonate species and are reported in Table 3. Similar trends are observed concerning the π-donating effect of the R^2 and R^3 substituents. The negative values of $\Delta G_{calcd.}$ for $R^2 = R^3$ = Ph, C_6H_4Me (tolyl) and C_6H_4OMe (anisyl) are consistent with our experimental observations as compounds **14c**, **14d**, **15c** and **15d** are all hydrolysed under mild acidic conditions. Moreover, the half-lives of these compounds at pH 1 and 4 (Table 2) correlate to $\Delta G_{calcd.}$: compounds **14d** and **15d** ($R^2 = R^3$ = anisyl, $\Delta G_{calcd.}$ = –12.5 kcal/mol) have shorter half-lives than compounds **14c** and **15c** ($\Delta G_{calcd.}$ = –5.7 kcal/mol). For reactions following the same mechanism, the most exergonic is likely to be the fastest, that is, the one with the lowest barrier and therefore the shortest half-life. These theoretical investigations demonstrated that the acidic release of alcohols from triazole derivatives proceeds first by the protonation of the triazole ring followed by a proton transfer from the triazole ring to the carbonyl group of the carbonates or the oxygen atom of the ether derivatives. The rate of the decomposition reaction has been shown to depend on the length of the N3–H···O hydrogen bond in the $\mathbf{C\text{-}NH^+/E\text{-}NH^+}$ intermediate structures. As the carbonate groups are longer and more flexible than the ether groups, the carbonyl nucleophilic site could be much closer to the triazolyl protonated site than the oxygen of the ether group. The shorter the hydrogen bond, the faster the proton transfer leading to the release of alcohols. It can be postulated from our results that a six- or seven-membered hydrogen-bond-containing ring can be used to design a cleavable system linked to a triazolyl ring. Such work is one of our forthcoming goals.



Scheme 7. Proposed mechanism for the acidic release of alcohol from ethers.

Conclusions

The design of new pH-sensitive protecting groups based on diaryltriazolylmethyl ethers and carbonates has been investigated. The synthesis of such derivatives exploited the elegant regioselective cycloaddition of alkynes and azides, resulting in a short and modular synthesis for further development. This synthetic strategy was expected to allow the preparation of pH-sensitive vector linkers during the conjugation to the vector. Ethers were found particularly useful for an expected application as acid-sensitive protecting groups. These ethers were prepared by direct association of two alcohols, one nucleophilic and the other obtained by cycloaddition and generating a stable carbocation easily by Lewis acid catalysis. This overall synthesis for the preparation of ethers as acid-sensitive systems represents an improvement over known literature procedures and has been successfully applied to an advanced model of the nucleoside. The determination of the rate of hydrolysis of these ethers in acidic environments has shown that a more acidic pH can be used for fast hydrolysis, ranging from under 20 min to several hours. At a milder pH, the hydrolysis still required several hours for the most sensitive compound and days for our nucleoside model, a result that must be improved for biological applications. For both carbonates and ethers, theoretical investigations demonstrated that a proton transfer from the triazole ring to the carbonyl of the carbamate group or to the oxygen atom of the ether group was the initial step towards hydrolysis. The kinetics of the reaction may be related to the distance between the leaving proton and the accepting nucleophilic site in the $\mathbf{C\text{-}NH^+/E\text{-}NH^+}$ carbocation intermediate. The shorter the intermolecular hydrogen bond, the faster was the hydrolysis reaction. This structural effect is under investigation for the design of more efficient acid pH-sensitive protecting groups based on diaryltriazolylmethyl ethers. Moreover, molecular modelling revealed the importance of the π-donating effect

of the substituents on the stability of the carbocation intermediate: the more π-donating the R^3/R^4 substituents, the more stable is the carbocation. A subtle balance between carbocation stability/reactivity and the nucleophilic character of the carbonates/ethers explains the results observed during hydrolysis.

Experimental Section

Abbreviations used: EA = ethyl acetate, PE = petroleum ether, DMAP = 4-(dimethylamino)pyridine.

1,1-Dimethylprop-2-ynyl 3-Phenylpropyl Carbonate (9a): A solution of carbonate **8a** (700 mg, 2.81 mmol) in CH_2Cl_2 (8 mL) was treated with alcohol **5** (383 mg, 2.81 mmol) in the presence of pyridine (0.25 mL, 3.09 mmol) and of a catalytic amount of DMAP. After stirring 48 h at room temperature, the mixture was extracted with CH_2Cl_2 and washed with water. The organic phase was dried with $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography of the residue (EA/PE, 5:95 to 20:80) gave compound **9a** (430 mg, 62%) as an oil with the presence of starting material (73 mg, 9.6%). TLC (PE/EA): 90:10, R_f = 0.34. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.31 (m, 5 H, Ar), 4.15 (t, J = 6.6 Hz, 2 H, CH_2), 2.71 (dd, J = 8.0, 7.5 Hz, 2 H, CH_2), 2.57 (s, 1 H, H-C≡), 2.00 (m, 2 H, CH_2), 1.72 (s, 6 H, $2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1 (CO), 141.1 (C), 128.5 (CH), 128.4 (CH), 126.1 (CH), 84.2 (C≡), 73.8 (C), 72.8 (HC≡), 67.0 (CH_2), 32.0 (CH_2), 30.3 (CH_2), 28.8 ($2CH_3$) ppm. HRMS (TOF-MS ES+): calcd. for $C_{15}H_{18}O_3Na$ $[M + Na]^+$ 269.11536; found 269.1148.

1,1-Dimethylprop-2-ynyl 2′,3′-*O*-Isopropylideneuridin-5′-yl Carbonate (10a): A solution of carbonate **8a** (117.5 mg, 0.471 mmol) in CH_2Cl_2 (2 mL) was treated with uridine acetonide **6** (134 mg, 0.471 mmol) in the presence of pyridine (42 μL, 0.52 mmol) and of a catalytic amount of DMAP. After stirring overnight at room temperature the mixture was extracted with CH_2Cl_2 and washed with water. The organic phase was dried with $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography of the residue (EA/PE, 10:90 to MeOH/CH_2Cl_2, 2:98) gave compound **10a** as a white solid (120 mg, 64.5%, m.p. 80–82 °C). TLC (MeOH/CH_2Cl_2): 5:95, R_f = 0.46. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (br. s, 1 H, NH), 7.34 (d, J = 8.2 Hz, 1 H, CH=), 5.77 (d, J = 2.3 Hz, 1 H, 1′-H), 5.72 (dd, J = 8.2, 2.3 Hz, 1 H, -CH=), 4.94 (dd, J = 6.3, 2.3 Hz, 1 H, 2′-H′), 4.83 (dd, J = 6.3, 3.5 Hz, 1 H, 3′-H), 4.11–4.44 (m, 3 H, 2 × 5′-H and 4′-H), 2.58 (s, 1 H, H-C≡), 1.70 (s, 6 H, 2 CH_3), 1.57 (s, 3 H, CH_3), 1.36 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7 (CO), 152.4 (C), 142.0 (C-6), 114.6 (C), 102.6 (C-5), 94.1 (C-1′), 84.8 (C-4′), 84.6 (C-2′), 83.7 (C≡), 80.9 (C-3′), 74.5 (C), 73.3 (H-C≡), 66.9 (C-5′), 28.7 (CH_3), 28.6 (CH_3), 27.1 (CH_3), 25.3 (CH_3) ppm. HRMS (TOF-MS ES+): calcd. for $C_{18}H_{22}N_2O_8Na$ $[M + Na]^+$ 417.12739; found 417.1277.

2-Methoxyethyl 2-(4-{4-[(3-Phenylpropoxy)diphenylmethyl]-1*H*-1,2,3-triazol-1-yl}butoxy)benzoate (14c): $B(C_6F_5)_3$ (6 mol-%) was added to a solution of azide alcohol **13c** (424 mg, 0.846 mmol) and 3-phenyl-1-propanol (115 mg, 0.846 mmol) in CH_2Cl_2 (10 mL). After being stirring overnight at reflux, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic phase was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on a silica gel column (5–30% gradient EA in PE, m.p. 66–66.5 °C) to afford the corresponding ether **14c** as a white solid (475 mg, 90%) after recrystallization in diethyl ether. TLC (PE/EA): 50:50, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (dd, J = 7.6,1.8 Hz, 1 H), 7.14–7.47 (m, 17 H), 6.97 (td, J = 7.6, 0.9 Hz, 1 H), 6.90 (d, J = 8.2 Hz, 1 H), 4.42 (t, J = 7.2 Hz, 2 H, CH_2), 4.34 (m, 2 H, CH_2), 4.03 (t, J = 5.8 Hz, 2 H, CH_2), 3.64 (m, 2 H), 3.44 (t, J = 6.3 Hz, 2 H, CH_2), 3.36 (s, 3 H, OMe), 2.69 (m, 2 H, CH_2), 2.16 (m, J = 7.2 Hz, 2 H, CH_2), 1.90 (m, 4 H, 2 CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9 (CO), 158.4 (C), 151.3 (C), 144.5 (C), 142.3 (C), 133.6 (CH), 131.9 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 127.92 (CH), 127.87 (CH), 127.2 (CH), 127.1 (CH), 125.6 (CH), 124.2 (CH), 120.3 and 120.1 (CH or C), 113.0 (CH), 81.1 (C), 70.5 (CH_2), 67.8 (CH_2), 63.7 (CH_2), 63.4 (CH_2), 58.9 (OCH_3), 49.8 (CH_2), 32.6 (CH_2), 31.8 (CH_2), 27.1 (CH_2), 26.0 (CH_2) ppm. HRMS (TOF-MS ES+): calcd. for $C_{38}H_{41}N_3O_5Na$ $[M + Na]^+$ 642.2944; found 642.2944.

2-Methoxyethyl 2-(4-{4-[(3-Phenylpropoxy)bis(4-methoxyphenyl)-methyl]-1*H*-1,2,3-triazol-1-yl}butoxy)benzoate (14d): $B(C_6F_5)_3$ (6 mol-%) was added to a solution of alcohol **13d** (326 mg, 0.581 mmol) and 3-phenyl-1-propanol (79 mg, 0.581 mmol) in CH_2Cl_2 (8 mL). After stirring overnight at reflux, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic phase was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on a silica gel column (20–30% gradient EA in PE) to afford the corresponding ether **14d** as an oil (352 mg, 89%). TLC (PE/EA): 50:50, R_f = 0.37. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79–7.45 (m, 17 H, 16 Ar-H and 1-H, triazole), 4.34–4.40 (m, 4 H, 2 CH_2), 4.02 (t, J = 6.0 Hz, 2 H, CH_2), 3.78 (s, 6 H, 2 OMe), 3.64 (m, 2 H, CH_2), 3.39 (m, 5 H, CH_2 and OMe), 2.69 (m, 2 H, CH_2), 2.15 (m, 2 H, CH_2), 1.86 (m, 4 H, $2CH_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9 (CO), 158.6 (C), 158.4 (C), 152.0 (C), 142.3 (C), 136.8 (C), 133.6 (CH), 131.9 (CH), 129.2 (CH), 128.5 (CH), 128.43 (CH), 128.4 (CH), 128.2 (CH), 125.6 (CH), 123.8 (CH), 120.2 (CH), 113.2 and 113.1 (2 CH and 1 C), 113.0, 80.7 (C), 70.6 (CH_2), 67.9 (CH_2), 63.7 (CH_2), 63.2 (CH_2), 58.9 (OMe), 55.2 (OMe), 49.7 (CH_2), 32.6 (CH_2), 31.9 (CH_2), 27.1 (CH_2), 26.1 (CH_2) ppm. HRMS (TOF-MS ES+): calcd. for $C_{40}H_{45}N_3O_7Na$ $[M + Na]^+$ 702.3155; found 702.3135.

2-Methoxyethyl 2-(4-{4-[(2′,3′-*O*-Isopropylideneuridin-5′-yloxy)diphenylmethyl]-1*H*-1,2,3-triazol-1-yl}butoxy)benzoate (15c): $B(C_6F_5)_3$ (6 mol-%) was added to a solution of alcohol **13c** (403.7 mg, 0.805 mmol) and acetonide **6** (229 mg, 0.805 mmol) in CH_2Cl_2 (10 mL). After stirring overnight at reflux, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic phase was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on a silica gel column (1% gradient MeOH in CH_2Cl_2) to afford the corresponding ether **15c** as a white solid which precipitated in Et_2O (m.p. 72–75 °C, 558 mg, 90%). TLC (PE/EA): 50:50, R_f = 0.05; TLC (CH_2Cl_2/MeOH): 95:5, R_f = 0.36. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (s, 1 H, NH), 7.82 (dd, J = 7.6, 2.0 Hz, 1 H, CH), 7.65 (d, J = 8.1 Hz, 1 H, CH), 7.43 (ddd, J = 8.4, 7.6, 1.6 Hz, 1 H, CH), 7.29 (m, 10 H, Ar-H), 7.13 (s, 1 H, NCH=C), 6.96 (td, J = 7.6, 0.8 Hz, 1 H, CH), 6.91 (d, J = 8.4 Hz, 1 H, CH), 5.95 (d, J = 1.6 Hz, 1 H, CH), 5.25 (dd, J = 8.1, 2.4 Hz, 1 H, =CH), 4.81 (m, 2 H, 2 CH), 4.44 (t, J = 7.2 Hz, 2 H, CH_2), 4.37 (m, 1 H), 4.33 (m, 2 H, CH_2), 4.05 (m, 2 H, CH_2), 3.83 (m, 2 H, CH_2), 3.65 (m, 2 H, CH_2), 3.37 (s, 3 H, OMe), 2.16 (m, 2 H, CH_2),1.84 (m, 2 H, CH_2), 1.56 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9 (CO), 162.8 (CO), 158.4 (C), 150.5 (C), 149.9 (C), 143.5, 142.6, 141.1 (CH), 133.6 (CH), 131.9 (CH), 128.14 (CH), 128.11 (CH), 127.9 (CH), 127.8 (CH), 124.7 (N*C*H), 120.4 (CH), 120.0 (C), 114.1 (C), 113.0 (CH), 101.5 (CH), 92.1 (CH), 85.9 (CH), 85.1 (CH), 82.0 (C), 80.8 (CH), 70.5 (CH_2), 67.9 (CH_2), 64.5 (CH_2), 63.7 (CH_2), 58.9 (OMe), 49.9 (CH_2), 27.3 (CH_3), 27.2 (CH_2), 26.0 (CH_3), 25.4 (CH_2) ppm. HRMS (TOF-MS ES+): calcd. for $C_{41}H_{46}N_5O_{10}$ $[M + H]^+$ 768.3245; found 768.3237.

2-Methoxyethyl 2-(4-{4-[(2′,3′-*O*-Isopropylideneuridin-5′-yloxy)bis-(4-methoxyphenyl)methyl]-1*H*-1,2,3-triazol-1-yl}butoxy)benzoate (15d): $B(C_6F_5)_3$ (6 mol-%) was added to a solution of alcohol **13d** (283 mg, 0.50 mmol) and acetonide **6** (143 mg, 0.50 mmol) in CH_2Cl_2 (10 mL). After stirring overnight at reflux, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic phase was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on a silica gel column (1% gradient MeOH in CH_2Cl_2) to afford the corresponding ether **15d** as a white solid which precipitated in Et_2O (222 mg, 53.2%). TLC (CH_2Cl_2/MeOH): 95:5, R_f = 0.31. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (br. s, 1 H, NH), 7.82 (dd, J = 7.4, 1.7 Hz, 1 H, Ar-H), 7.70 (d, J = 8.1 Hz, 1 H, =CH), 7.44 (ddd, J = 8.3, 7.4, 1.7 Hz, 1 H, Ar-H), 7.20 (m, 4 H, 4 Ar-H), 7.11 (s, 1 H, NCH=C), 6.97 (t, J = 8 Hz, 1 H, Ar-H), 6.92 (d, J = 8 Hz, 1 H, Ar-H), 6.82 (m, 4 H, Ar-H), 5.97 (s, 1 H, CH), 5.28 (d, J = 8.1 Hz, 1 H, CH), 4.81 (m, 2 H, 2 CH), 4.43 (t, J = 7.2 Hz, 2 H, CH_2), 4.37 (m, 1 H, CH), 4.34 (m, 2 H, CH_2), 4.05 (t, J = 5.8 Hz, 2 H, CH_2), 3.78 (m, 8 H, CH_2 and 2 OMe), 3.66 (m, 2 H, CH_2), 3.38 (s, 3 H, OMe), 2.16 (m, 2 H, CH_2), 1.86 (m, 2 H, CH_2), 1.56 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9 (CO), 163.4 (CO), 158.9 (C), 158.4 (C), 151.1 (C), 150.2 (C), 141.1 (CH), 135.9 (C), 134.9 (C), 133.6 (CH), 131.9 (CH), 129.5 (CH), 129.3 (CH), 124.4 (N*C*H=C), 120.3 (CH), 120.0 (C), 114.1 (C), 113.4 (CH), 113.3 (CH), 113.0 (CH), 101.9 (CH), 92.1 (CH), 85.8 (CH), 85.1 (CH), 81.5 (C), 80.1 (CH), 70.5 (CH_2), 67.9 (CH_2), 64.3 (CH_2), 63.7 (CH_2), 58.9 (OMe), 55.2 (OMe), 49.9 (CH_2), 27.3 (CH_3), 27.1 (CH_2), 26.0 (CH_2), 25.4 (CH_3) ppm. HRMS (TOF-MS ES+): calcd. for $C_{43}H_{50}N_5O_{12}$ $[M + H]^+$ 828.3456; found 828.3430.

Computational Methods: All structures were studied by using the B3LYP method. The structures were fully optimized using the 6-31G(d,p) basis set [B3LYP/6-31G(d,p)]. In the gas phase, free energies were computed at 298.15 K without scaling vibrational frequencies. Solvent effects were calculated at the B3LYP/6-31G(d) level using the polarizable continuum SMD model (solvent = water) as single-point energy calculations on gas-phase optimized structures [SMD-B3LYP/6-31G(d)//B3LYP/6-31G(d,p)]. In all models, terminal groups R^1 = R^4 = CH_3 were used to limit the calculation time. All calculations were performed with the Gaussian 09 package[29] (see Molecular Modelling in the Supporting Information).

Supporting Information (see footnote on the first page of this article): Experimental procedure for alcohols **3** and **13**, analytical data for all compounds, acidic hydrolysis measurements and details for DFT calculations (energies, Cartesian coordinates).

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[30] The MeO–CO–OH compound is expected to be unstable. Its decomposition to $MeOH + CO_2$ is exergonic by –10.2 kcal/mol at the B3LYP/6-31G(d,p) level of calculation (gas-phase free energy).

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