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Study of the Factors that Control the Ratio of the Products between 5-Fluorouracil, Uracil, and Tetrahydrobenzoxazepine *O,O*-Acetals Bearing Electron-Withdrawing Groups on the Nitrogen Atom

Mónica Díaz-Gavilán, José A. Gómez-Vidal, Antonio Entrena, Miguel A. Gallo, Antonio Espinosa, and Joaquín M. Campos*

Departamento de Química Farmacéutica y Orgánica, Facultad de Farmacia, c/ Campus de Cartuja s/n, 18071 Granada, Spain

jmcampos@ugr.es

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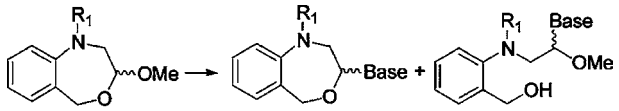
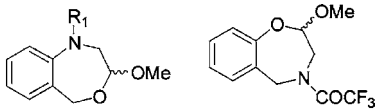


(*RS*)-1-(2-Nitrobenzenesulfonyl)- and (*RS*)-1-(4-nitrobenzenesulfonyl)-3-methoxy-1,2,3,5-tetrahydro-4,1-benzoxazepines are better substrates than 1-acyl-3-methoxy-1,2,3,5-tetrahydro-4,1-benzoxazepine derivatives for the Lewis acid mediated condensation reaction with pyrimidine bases to give *O,N*-acetals. Acetonitrile, stannic chloride, 50 °C, and a reaction time higher than 48 h are the optimum conditions for such condensation reactions. Under these conditions, 5-fluorouracil preferably links to the aminalic carbon through its *N*-1″ position, while the attachment of the uracil fragment is through *N*-3″ or *N*-1″ of the cyclic or acyclic products, respectively. The causes that influence the course of the reactions are analyzed and discussed. Examination of the ^{1}H NMR spectra revealed the presence of a single form for the secondary amine **11** and of two conformers for the tertiary sulfonamides **7a**,**b**, **9a**,**b**, and **10b** and for the amides **7d** and **13**, with the following distribution: **7a**, 59/41; **7b**, 53/47; **9a**, 52/48; **9b**, 59/41; **10b**, 56/44; **7d**, 50/50; **13**, 80/20. On increasing the temperature, the ^{1}H NMR spectrum (DMSO-d_6) of **7b** showed coalescence at 110 °C. The torsional barrier determined [$\Delta G_c^{\ddagger}$ value of 19.0 ± 0.2 kcal·mol^{-1} (79.1 ± 1.0 kJ·mol^{-1})] proved to be the highest ever observed for sulfonamide moieties.

Introduction

X,Y-Acetals are functional groups consisting of an sp^3-carbon atom attached to two heteroatom groups, where X and Y are heteroatoms such as oxygen, nitrogen, sulfur, phosphorus, and so on and are widely utilized as versatile intermediates in organic synthesis. The synthesis of the (*RS*)-*N*-containing-*O,O*-acetals with different electron-withdrawing groups on *N*-1 (**1a**−**e**) or *N*-4 (**2**) positions, respectively,[1] has been previously reported. These compounds were designed to serve as scaffolds for the preparation of 5-fluorouracil *O,N*-acetals.[1]

Under acidic conditions, an *O,O*-acetal can be activated to generate an α-heteroatom-substituted carbenium ion as a reactive intermediate, which reacts with a nucleophile to form a



1a R_1 = SO_2-C_6H_4-NO_2-(2)
b R_1 = SO_2-C_6H_4-NO_2-(4)
c R_1 = $CO(CH_2)_2CH_3$
d R_1 = COPh
e R_1 = $COCF_3$

2

substitution product. In this process, the acid coordinates to a lone pair of one of the heteroatoms to cleave the oxygen−carbon bond with the assistance of electron donation from a lone pair of the other oxygen atom. It is obvious that the reaction of unsymmetrical *O,O*-acetals involves a chemoselective problem, namely whether the endocyclic or the exocyclic oxygen atoms are activated by the acid. In this case, these compounds can undergo two types of reactions, i.e., substitution of the exocyclic oxygen atom by a nucleophile or ring-opening addition of a nucleophile. In this paper, we will describe the condensation

* To whom correspondence should be addressed. Phone: +34-958-243849. Fax: +34-958-243845.

(1) Díaz-Gavilán, M.; Rodríguez-Serrano, F.; Gómez-Vidal, J. A.; Marchal, J. A.; Aránega, A.; Gallo, M. A.; Espinosa, A.; Campos, J. M. *Tetrahedron* **2004**, *60*, 11547−11557.

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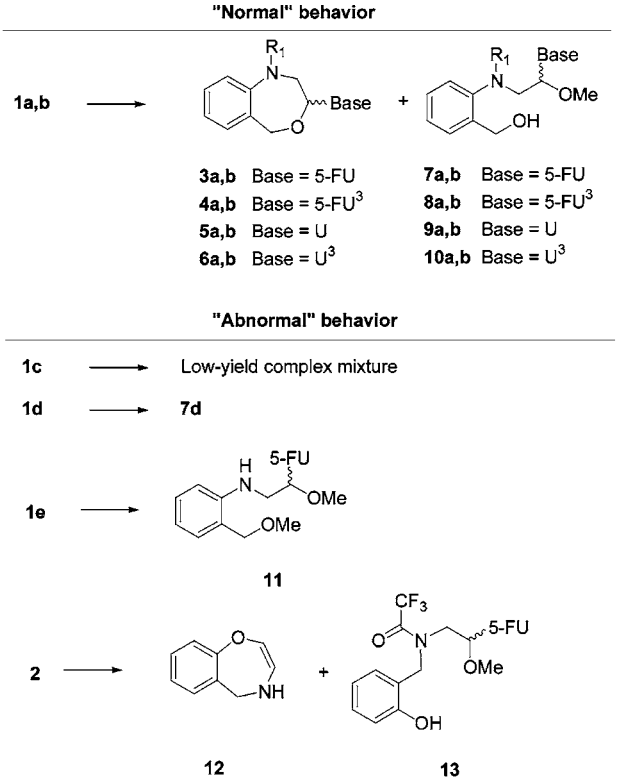
SCHEME 1. "Normal" and "Abnormal" Derivatives 3a,b−10a,b and 7d, 11−13, Respectively, Discussed in This Paper[a]



[a] The experimental conditions imply the use of 5-FU or U, HMDS, TMSCl, and an anhydrous solvent.

reactions between **1a** (and **1b**) and the pyrimidine bases 5-fluorouracil (5-FU) and uracil (U). Each reaction leads to four possible products such as the two cyclic *O*,*N*-acetals in which the two pyrimidines are linked to the C-3 atom through their *N*-1″ or *N*-3″ atoms (compounds **3a**,**b**−**6a**,**b**, Scheme 1) and the two corresponding acyclic *O*,*N*-acetals (**7a**,**b**−**10a**,**b**, Scheme 1).

In contrast to the "normal" behavior depicted by compounds **1a** and **1b**, the "abnormal" conduct is represented by acetals **1c**−**e** and **2** in their reactions with 5-FU (Scheme 1). We refer to "normal" behavior as that followed by alkoxyheteroxepanes[2] and according to it, a saturated seven-membered *O*,*O*-acetal in its reaction with 5-FU, after a reaction time of 24 h, gives rise to the corresponding cyclic and acyclic *O*,*N*-acetals; obviously, the "abnormal" one does not follow this pattern. Between the two (*RS*)-*O*,*O*-acetals **1c** and **1d**, the latter (with the benzoyl moiety) leads to the acyclic *O*,*N*-acetal **7d**, while **1c** (with the butanoyl fragment) does not react with the nucleophile 5-FU. Compound **1e** (with the trifluoromethylacetyl moiety) gives rise to the acyclic *O*,*N*-acetal **11** in which the benzylic oxygen atom is methylated and **2** gives rise to the acyclic 5-FU *O*,*N*-acetal **13**, in addition to the nonacetalic compound **12**. All of the 5-FU-containing *O*,*N*-acetals show in vitro antiproliferative activities against the MCF-7 human breast cancer cell line in the submicromolar range (data not shown). Nevertheless, the U-containing *O*,*N*-acetals present antiproliferative activities against the same cell line that are only 2-fold less active than their corresponding 5-FU analogs (data not shown). This is an outstanding fact that has not been previously reported in the literature, and these compounds may serve as prototypes for the development of even more potent structures, probably endowed with a new mechanism of action. Herein, we report the first systematic study on the reactions of the *N*-containing-*O*,*O*-acetals **1a**−**e** and **2** with uracils. Finally, some spectroscopic rules are found that permit by comparison the establishment of the type of aminalic bond (*N*-1″ or *N*-3″) occurring in *O*,*N*-acetalic regioisomers.[3]

Results and Discussion

Reactions between the (*RS*)-*N*-Containing *O*,*O*-Acetals 1b,a and the Pyrimidine Bases 5-FU and U. To start with, the *O*,*O*-acetal **1b** and 5-FU were used as substrate and nucleophile with the aim to establish the best reaction conditions that could be applied later to the rest of the transformations. Several variables have been changed such as the solvent, the ratio of the reagents, the temperature of addition of the reagents, reaction temperature, and the nature of the Lewis acid [$SnCl_4$ and $Sc(OTf)_3$]. The variation of the conditions has been oriented toward the increment in the yields of the cyclic *O*,*N*-acetals to the detriment of the acyclic ones, because of the increased biological activities of the former[4,5] in relation to the latter.[5,6] The results are shown in Table 1.

All the reactions were carried out applying the same general procedure: the silylating agents, 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and trimethylsilyl chloride (TMSCl), and the Lewis acid were added slowly in this order under an inert atmosphere of argon, over a suspension of **1b** (1.0 equiv) and 5-FU (see Table 1 for the equivalents used) in the corresponding solvent (5 mL/mmol of **1b**). Once the corresponding reaction temperature was reached, the stirring was maintained during the time indicated (Table 1). The more influential factors turned out to be the acid Lewis, the reaction temperature and the solvent. The use of $SnCl_4$, 50 °C, and MeCN as the solvent has led to the best results.

In recent years, scandium triflate has received considerable attention as a mild Lewis acid for an array of organic transformations[7] because the catalyst is stable in water and is reusable. Nevertheless, 1.04 equiv of $Sc(OTf)_3$ in CH_2Cl_2 or MeCN has not been enough to produce the *O*,*N*-acetals, predictably due to the acid consumption in the binding with the electron-rich groups that are in the substrates or in the acetonitrile (Table 1).

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(3) For the numbering of the compounds, the atoms of the benzoxazepine and those of the aminobenzene ring are tagged with numbers without primes, the atoms of the R_1 group are numbered with primes, while the pyrimidine bases are numbered with double primes.

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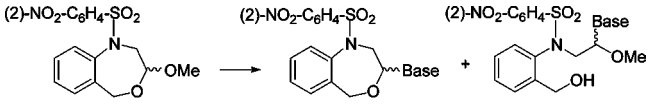
TABLE 1. Several Conditions Studied for the Optimization of the Reaction between 1b and 5-FU[a]



1b — **3b** Base = 5-FU; **4b** Base = 5-FU[3] — **7b** Base = 5-FU; **8b** Base = 5-FU[3]

reaction conditions and products obtained	Lewis acid				
	$SnCl_4$ (1 M in CH_2Cl_2) (4.0 equiv)[b]			$Sc(OTf)_3$ (1.04 equiv)[c]	
5-FU (equiv)	2.1	2.5		1.5	
HMDS (equiv)	3.6	4.0		2.0	
TMSCl (equiv)	3.6	4.0		2.0	
solvent	CH_2Cl_2	CH_2Cl_2	MeCN	CH_2Cl_2	MeCN
addition temp of reagents (°C)	rt	0	0	0	0
reaction temp (°C)	rt	40[d]	50[d]	40[d]	50[d]
reaction time (h)	72	47	91	24	24
3b (yield, %)		5	15	no reaction obsd	
4b (yield, %)		4	5		
7b (yield, %)	13	18	24		
8b (yield, %)					
total cyclic *O,N*-acetals/ total acyclic *O,N*-acetals	0	0.5	0.8		

[a] All the solvents were anhydrous, and the reactions were carried out under argon. [b] When the reaction was performed using 2.5 equiv of $SnCl_4$, 3.6 equiv of HMDS, and TMSCl and 2.1 equiv of 5-FU, at rt using CH_2Cl_2 as the solvent, no formation of the products was observed. [c] No reaction was detected when 1.04 equiv of $Sc(OTf)_3$ was used, although there is evidence of effective activation of acetals, bearing a nitro group, by catalytic metal triflates (see ref 8). [d] When the reaction temperature varies from 40 to 50 °C these conditions could be considered similar.

When the combination $SnCl_4/CH_2Cl_2$ was used at room temperature, the only product obtained was the acyclic *O,N*-acetal **7b** with a 13% yield. On raising the reaction temperature to 40 °C, the yield of this product was increased up to 18%, and moreover, the formation of the cyclic *O,N*-acetals through the *N*-1″ (**3b**) and *N*-3″ (**4b**) bonds was observed, although with low yields (5% and 4%, respectively, see Table 1). When the solvent was changed to MeCN, a general increase of the yields of all the products was noticed, especially in the case of **3b**. In general, the increase in the temperature of the reaction augments the yields of all the products obtained and in particular that of the formation of the cyclic *O,N*-acetals. This influence of the temperature could be expected for any nucleophilic reaction. On the other hand, basically there exist two reaction times: lesser and higher than 48 h, i.e., on increasing the reaction time up to 48 h, there is no variation on the yields of the several final products as can be stated by TLC. No reaction was detected when 1.04 equiv of $Sc(OTf)_3$ was used, although there is evidence of effective activation of acetals, bearing a nitro group, by catalytic metal triflates.[8] Those conditions that led to the best outcome (see Table 1) were used with the later reactions (the three remaining combinations between the *O,O*-acetals **1a**,**b** and the pyrimidine bases 5-FU and U). Table 2 shows a summary of all the results obtained.

Effect of the Isosteric Change *O* → *N*-EWG: Comparison between 1a and 1b and 15. The results obtained in the formation of the 5-FU and U *O,N*-acetals from the *O,O*-acetals

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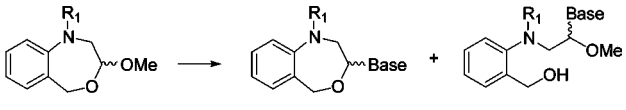
TABLE 2. Comparison in the Ratio of Products Obtained in the Condensation Reactions between 1a and 1b with 5-FU and U[a]



1a,b

a R_1 = SO_2-C_6H_4-NO_2-(2)
b R_1 = SO_2-C_6H_4-NO_2-(4)

3a,b Base = 5-FU; **4a,b** Base = 5-FU[3]; **5a,b** Base = U; **6a,b** Base = U[3]

7a,b Base = 5-FU; **8a,b** Base = 5-FU[3]; **9a,b** Base = U; **10a,b** Base = U[3]

		reaction conditions		yield (%)	
starting *O,O*-acetal	pyrimidine	*T* (°C)	time (h)	total cyclic *O,N*-acetals	total acyclic *O,N*-acetals
1a	5-FU	40	51	(23)	(30)
				3a (19) **4a** (4)	**7a** (30) **8a** (−)
	U	50	67	(59)	(12)
				5a (26) **6a** (33)	**9a** (12) **10a** (−)
1b	5-FU	50	91	(20)	(24)
				3b (15) **4b** (5)	**7b** (24) **8b** (−)
	U	50	69	(60)	(13)
				5b (11) **6b** (49)	**9b** (11) **10b** (2)

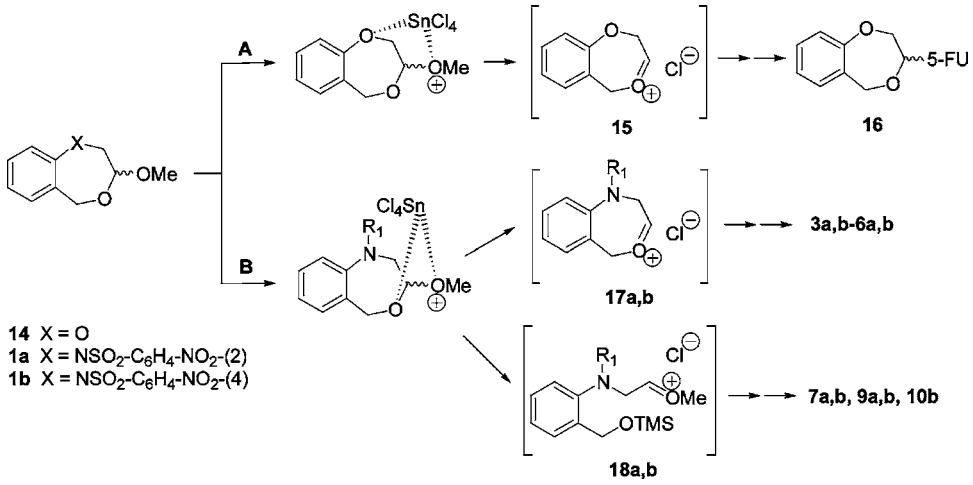
[a] All of the reactions were carried out in the presence of the pyrimidine base (2.5 equiv), $SnCl_4$ (4.0 equiv), TMSCl (4.0 equiv), and HMDS (4.0 equiv) in anhydrous MeCN.

1a and **1b** have served to determine the influence of the substituent on the *N*-1 atom of the benzoxazepine moiety (the 2-nitrobenzenesulfonyl group against the 4-nitrobenzenesulfonyl one) and the nucleophile used (5-FU against U) in the course of the reaction. Some comparative data and their corresponding to theoretical proposals are detailed as follows.

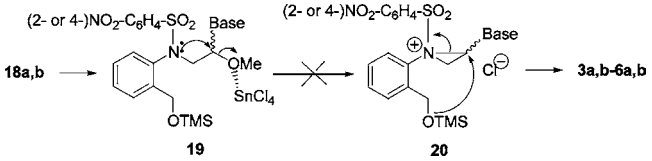
Several differences can be noticed on comparing the results obtained with those previously attained with the (*RS*)-*O,O*-acetal **14**[2] ($SnCl_4$/MeCN/rt): (a) the higher yields of (*RS*)-1-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-5-fluorouracil[4] in relation to its benzoxazepine counterparts, and (b) the formation of cyclic and acyclic *O,N*-acetals but with no formation of the corresponding acyclic *O,N*-acetal in the former. Because of the fact that both reaction conditions are comparable, such differences may be due to structural characteristics of the *O,O*-acetalic substrates. Scheme 2 shows the reaction mechanism for the formation of **17** (route **A**), **3a**,**b**−**6a**,**b** and **7a**,**b**, **8a**, **9a**,**b**, and **10b** (route **B**).

The most distinctive feature between both routes **A** and **B** is one of the sites of coordination between $SnCl_4$ (in the two cases, the second anchorage position is the exocyclic acetalic oxygen atom) and the seven-membered ring: i.e., when X = O the chelate is established with the ethereal *O*-1 atom, leading to **16** through cyclic oxocarbenium **15**; and when X = NSO_2-C_6H_4-NO_2-(2 or 4)- the other coordination location is the endocyclic acetalic oxygen atom (route **B**) and not the sulfonyl nitrogen atom because its basicity is very low. In this case, **3a**,**b**−**6a**,**b** are formed through cyclic oxocarbenium ions **17a**,**b** (route **A**), while acyclic oxocarbenium ions **18a**,**b** lead to **7a**,**b**, **9a**,**b**, and **10b** (route **B**). Moreover, the following features of **1a**,**b** modulate the reactivity of their acetalic functional group: The presence of bulky substituents close to the acetalic function in benzoxazepines, such as the nitrobenzenesulfonyl group, might hinder the approach of the Lewis acid (mainly to the exocyclic acetalic oxygen atom) and the pyrimidine base, causing a deceleration of the reaction and a decrease of the yields. On the other hand, the centers with high electronic density, such as the nitro or sulfonyl groups, are able to coordinate with the

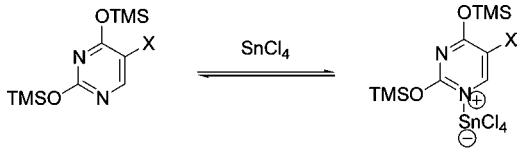
SCHEME 2. Differences in the Mechanistic Outcome between the *O,O*-Acetals 14, 1a, and 1b



SCHEME 3. Inability for the Formation of Benzoxazepines 3a,b−6a,b through Neighboring-Group Participation of the Sulfonylamino Group of 1a,b



SCHEME 4. Equilibrium between the *σ* Complex 22, Silylated Base 21, and $SnCl_4$



Lewis acid, consuming it. This could be the reason for the need of high quantities of acid, which affect the regioselectivity, the reaction rate and the yields. And finally, the electron-withdrawing nature of the nitrobenzenesulfonyl group would prevent the neighboring-group participation of the *N*-1 atom of **19** (Scheme 3) in the cyclization process through the aziridinium ion **20**, as has been stated for the formation of benzodioxepin 5-FU *O*,*N*-acetals, through an oxyranium ion.[6]

Effect of the Substituent on the *N*-1 Atom of the *O,O*-Acetals 1a and 1b and the Nucleophile in the Results. From Table 2 the following consequences are inferred:

(1) The total yields in the formation of the cyclic and acyclic *O*,*N*-acetals from **1a** are very similar to the ones obtained from **1b**.

(2) The reactivity of U is superior to that of 5-FU, the former giving rise to higher yields in the total formation of products (72% and 73%) than the latter (56% and 44%), from **1a** and **1b**, respectively.

(3) The ratio "cyclic *O*,*N*-acetals/acyclic *O*,*N*-acetals" obtained in the reactions with 5-FU and U presents very similar values for **1a** and **1b** (0.8 for both substrates in their reactions with 5-FU; 4.5 and 4.6, respectively, in their reaction with U). In the two benzoxazepines, the yield of the acyclic compounds is higher than that of the cyclic ones when 5-FU is used. The contrary holds true when U is used.

(4) In the formation of the cyclic *O*,*N*-acetals, 5-FU and U differ in the position through which they establish the bonding to the benzoxazepine rings. 5-FU mainly links through its *N*-1 atom, while U does so through its *N*-3 atom. The ratio of cyclic *N*-1″/*N*-3″ *O*,*N*-acetal derivatives presents similar values from **1a** and **1b** (4.8 and 3.0, respectively). Nevertheless, the cyclic derivatives of U present different *N*-1″/*N*-3″ ratios from **1a** and **1b** (0.8 and 0.2, respectively), this being the only difference observed in the behavior of both benzoxazepines. There is hardly any formation of acyclic 5-FU and U *O*,*N*-acetals with N-3″ aminalic bonds.

Formation of the *σ* complexes between Lewis acids and silylated bases is dependent on the acidity of the former as well as on the basicity of the silylated heterocyclic bases. Although the pK_a values for silylated heterocyclic bases have not been determined, the pK_a values of the closely related pyrimidine bases can be used for purposes of comparison: the increase in basicity from 5-FU (pK_a = 7.93)[10] to U (pK_a = 9.42)[10] explains why 2,4-bis(trimethylsilyloxy)uracil (**21a**, Scheme 4) forms stronger *σ* complexes than 2,4-bis(trimethylsilyloxy)-5-FU (**21b**, Scheme 4). Furthermore, in the equilibrium between the *σ* complex **22a**, silylated base **21a** and $SnCl_4$, the $SnCl_4$ will stay close to the electron-rich center at the *N*-1 atom. In this slightly dissociated form, the *N*-1 atom is still blocked and the *N*-3 atom is available. Then, the *N*-3 atom reacts with the oxocarbenium ion to form the "less common" cyclic *N*-3″ U *O*,*N*-acetals **6a** and **6b** in higher yields (33% and 49%, respectively) than the corresponding cyclic *N*-1″ U *O*,*N*-acetals **5a** and **5b** (26% and 11%, respectively). On the other hand, since the *N*-3 atom in **21b** is sterically more encumbered than the *N*-1 atom, higher yields are obtained in the formation of the cyclic *N*-1″ 5-FU *O*,*N*-acetals **3a** and **3b** (19% and 15%) than the corresponding cyclic *N*-3″ 5-FU *O*,*N*-acetals **4a** and **4b** (4% and 5%, respectively).

Acetonitrile also competes with the silylated 5-FU base for the Lewis acid $SnCl_4$ to form the corresponding *σ* complexes. Consequently, the most electron-rich *N*-1 atom of the silylated 5-FU is only partially blocked by complex formation with $SnCl_4$, so that the nucleophilic *N*-1 atom can react with the oxocarbe-

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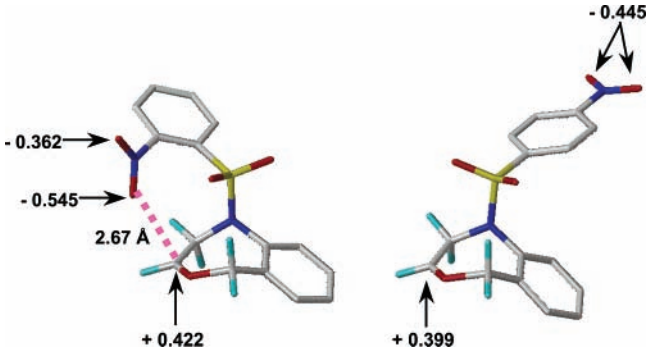


FIGURE 1. Cyclic carbenium ions **17a** (left) and **17b** (right). The distance between interacting groups and the charges on the positive carbon atom and the oxygen atoms of the nitro group are shown. Calculations have been carried out by means of HF 6-31G* optimized with Gaussian.[12]

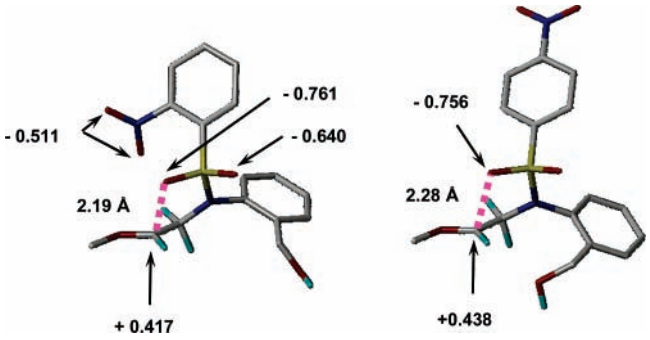


FIGURE 2. Acyclic carbenium ions **18a** (left) and **18b** (right). The distance between interacting groups and the charges on the positive carbon atom and the oxygen atoms of the nitro group are shown. Calculations have been carried out by means of HF 6-31G* optimized with Gaussian.[12]

nium ion to produce the *N*-1″ 5-FU *O*,*N*-acetal. If, however, $SnCl_4$ blocks most of the *N*-1 atom of 5-FU by σ-complex formation, only the less basic and reactive *N*-3 atom is available to condense with the oxocarbenium ion to give the "less common" *N*-3″ 5-FU *O*,*N*-acetal. Therefore, the ratio between the free and the complex form of the silylated base is dependent on the polarity of the solvent. The more nucleophilic solvent acetonitrile, which forms σ complexes with $SnCl_4$[11] competes with the silylated 5-FU base **21b** for the electrophile to form the σ complex **22b** and simultaneously favors the formation of the corresponding oxocarbenium ion. Consequently, more silylated base and more oxocarbenium are present in acetonitrile, and thus more of the *N*-1″ 5-FU *O*,*N*-acetals **3a**,**b** (or **7a**,**b**) are formed. In short, due to its polarity acetonitrile will stabilize the oxocarbenium ions and will improve both the solubility and nucleophilicity of the pyrimidine.

Keeping in mind the structures of the two substrates **1a** and **1b**, it is logical to think that any difference observed in behavior during their transformation into the *O*,*N*-acetals is due to the position of the nitro group on the benzenesulfonyl moiety. Figure 1 shows the optimized geometry (ab initio) and the partial atomic charges of the possible oxocarbenium ions intermediates in the formation of compounds **3a**,**b**−**6a**,**b**, calculated using the Hartree−Fock Hamiltonian at the 6-31G** level (Gaussian 98).[12] In the intermediate derivated from compound **1a**, an interesting attractive interaction occurs between one of the oxygen atoms of the 2-NO_2 group (negatively charged) and the electron-deficient carbon atom C-3. Such an attractive interaction would constitute a steric hindrance for the nucleophilic attack of the silylated pyrimidine, and it would specially affect the attack through the more sterically hindered *N*-3 position (left-hand oxocarbenium, Figure 1).

(11) Beattie, I. R.; Rule, L. *J. Chem. Soc.* **1964**, 3267−3273.

(12) Gaussian 98, Revision A.7. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, V.; Cammi, R.; Mennucci, V.; Pomelli, V.; Adamo, C.; Clifford, S.; Ochterski, V.; Petersson, V.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1998.

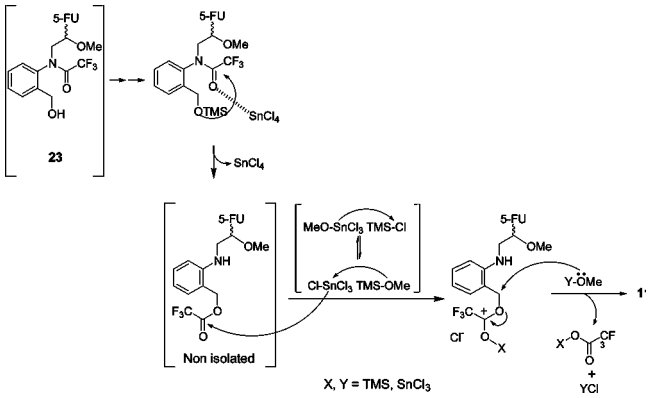
The experimental results obtained are in line with this hypothesis, and a lesser formation of products through the *N*-3 atom is noticed in the reaction between **1a** and U. 5-FU hardly reacts through its slightly nucleophilic *N*-3 atom. In short, the interactions due to the nitro group result in higher yields of products with an *N*-1″ aminalic bond and lesser ones with an aminalic *N*-3 one derived from **1a**. Nevertheless, there is no stabilization by the nitro group in the oxocarbenium ion derived from **1b**, thus leaving the C-3 electron-deficient atom free for the silylated pyrimidine approach and subsequent nucleophilic attack (right-hand oxocarbenium ion, Figure 1).

On the other hand, an interaction might exist between the cationic position and other electron-rich groups in the acyclic oxocarbenium ions, such as the oxygen atoms of the sulfonyl groups (Figure 2) that could approach each other due to the flexibility of the acyclic chains. This fact could explain the practically null formation of acyclic *O*,*N*-acetals with aminalic *N*-3″ bonds (see Table 2).

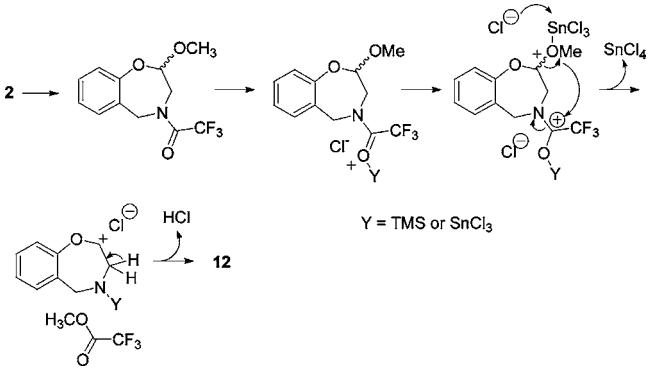
Lewis Acid Mediated Reactions of (*RS*)-1c−e with 5-FU. *N*-Acyl compounds **1c**, **1d,** and **1e** were subjected to the nucleophilic attack of 5-FU in the presence of $SnCl_4$ and Sc(OTf)$_3$. From the results of these three compounds, we can compare the behavior of carbonyl derivatives with α-hydrogens (**1c**) and without them (**1d**, **1e**), as also with a high electrophilic carbonyl group (**1d**). Such reactions have not led to the expected products, presumably due to the interferences caused by the carbonyl groups in the evolution of the reaction. There has been reported a great capacity of coordination for the $SnCl_4$ to the carbonyl groups of esters and amides.[9] Between the *N*-containing-*O*,*O*-acetals **1c**−**e**, only the *N*-benzoyl derivative (**1d**) afforded one of the expected compounds, though with a low yield (5% of **7d** using $SnCl_4$ and room temperature in MeCN). When Sc(OTf)$_3$ was used in MeCN at 40 °C the yield of the acyclic *O*,*N*-acetal **7d** increased slightly (11%) but no cyclic *O*,*N*-acetal was isolated. Compound **1c** led to a low-yield complex mixture of unidentified compounds.

Reactions were carried out at room temperature in order to avoid amide breakdown. The amount of Lewis acid needed for the reaction progress was lower than that for the nitrophenylsulfonyl derivatives [3.0 equiv of $SnCl_4$ for compounds **1c** and **1d** and 1.4 equiv of $SnCl_4$ or 0.6 equiv of Sc(OTf)$_3$ for **1d**, while in the case of the nitrobenzenesulfonamides **1a** and **1b**, 4.0 equiv of $SnCl_4$ were used (see Table 1)]. Compound **1e** led to the acyclic product (**11**) (yield 16%). The formation of the unexpected compound **11** might be explained by the initial

SCHEME 5. Proposed Mechanism for the Formation of 11



SCHEME 6. Proposed Mechanism for the Formation of 12

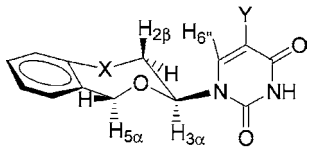


formation of the nonisolated compound **23**, whose most important characteristic is the presence of a very electrophilic carbonyl group (CF_3CO) and the nucleophilic OH group in the same molecule (Scheme 5). In the reaction medium, the electrophilicity of the carbonyl group might be increased by the coordination of the Lewis acid and the nucleophilicity of the benzylic OH group by silylation. Other nucleophiles in the reaction medium (stabilized methoxy ions) contribute to the formation of acyclic *O*,*N*-acetal **11**. The Lewis acid mediated nucleophilic attack to carbonyl groups has been reported.[13] The proposed mechanism is depicted in Scheme 5. The proposed structure of **11** will be discussed later on (vide infra).

Lewis Acid Mediated Reaction of (*RS*)-2 with 5-FU. The reaction was carried out with 5-FU (1.2 equiv), HMDS (1.2 equiv), TMSCl (1.2 equiv), $SnCl_4$ (1.2 equiv), and anhydrous MeCN under argon at room temperature and 70 h of reaction time (Scheme 6). Again, the quantities of the Lewis acid and the remaining reagents necessary for the reaction to take place were lower than in the case of the nitrobenzenesulfonamide derivatives. The acyclic product (**13**) was obtained with a moderate yield (33%) when stirring of the reaction was continued for 70 h (after 24 h, most of the initial product remained unchanged). It is worth comparing the stability of the acyclic *O*,*N*-acetals **23** (nonisolated, Scheme 5) and **13** (Scheme 1). The stability of **13** compared with the unstability of **23** might be explained by the lesser nucleophilicity of the phenolic OH group in relation with the benzylic OH one for the attack on the carbonyl group of the trifluoroacetyl moiety, whose electrophilicity, is increased in the case of **23** because of the aniline nature of the *N*-1 atom that bears it. The two following facts have to be pointed out: (a) no cyclic 5-FU *O*,*N*-acetal was detected, and (b) together with the acyclic *O*,*N*-acetal **13**, the apolar nonacetalic compound **12** was obtained in a 55% yield (Scheme 1).

The formation of **12** may be explained by silylation or $SnCl_4$ coordination to both the carbonyl oxygen and the acetalic methoxy group and the subsequent elimination of methyl trifluoroacetate and hydrochloric acid (Scheme 6).

Spectroscopic Analysis of Cyclic Pyrimidine *O*,*N*-Acetals 3a,b−6a,b. Conformational information was obtained by NOESY studies on **3b** and **4b** and NOEdiff studies on **5a** and **6a**. All these experiences have been carried out in acetone-d_6 (400 MHz). The face of the molecule containing the H-3 proton was denominated as α. Those protons that showed NOE interaction with H-3α were designated as α, while those that were located on the opposite face of the molecule were designated as *β*. The values of coupling constants between H-2 and H-3α confirm the *trans* disposition between H-2*β* and H-3α (ranging from 9.3 to 10.1 Hz) and the *cis* disposition for H-2α and H-3α (their coupling constants ranging from 1.8 to 2.2 Hz). Accordingly, the denominations H-2*β* and H-2α have been generalized to all the cyclic molecules for those H-2 atoms that showed the higher and lower coupling constants with H-3α, respectively. In compound **3b**, the interactions H-2*β*−H-6″ (characteristic of an *N*-1″ aminalic bond), H-3α−H-5α, H-5*β*−H-6 and H-3α−H-2′ have been detected by means of a NOESY experience. The interaction H-2*β*−H-6″ is compatible with our previous findings according to which, in compounds **24**[4] and **25**[14] the seven-membered rings have a chair conformation with the 5-FU fragments in equatorial positions, and the H-6″ atoms pointing out toward the heptagonal moiety.



24 X = O Y = F
25 X = S Y = H

Figure 3 depicts the NOESY interactions for compounds **3b**, **4b**, and the NOEdiff ones for compounds **5a** and **6a**.

On the other hand, resonance of H-3α in those compounds in which *N*-1″ was linked to the acetal moiety appeared as a double doublet of doublets (three coupling constants, with H-2α, H-2*β* and F). When pyrimidine was linked through its *N*-3″ atom, long distance coupling H−F was not transmitted through the carbonyl groups and H-3*β* appeared as a double doublet (from H-2α and H-2*β* coupling).[6]

Tables 3 and 4 show the ^1H and ^{13}C NMR data for compounds **3a**,**b**−**6a**,**b**. The unambiguous assignment of the proton and carbon atoms were confirmed by HMQC in **5a** (acetone-d_6, 300 MHz).

Some common spectroscopic characteristics have been found by comparing the ^1H and ^{13}C NMR spectra (acetone-d_6) of 5-FU and U cyclic *O*,*N*-acetals that present the same *N*-1″ or *N*-3″ aminalic bonding:

(1) The resonance signals corresponding to the H-2*β* and H-3α atoms always resonate at higher fields for the *N*-1″ aminalic compounds than for the *N*-3″ ones.

(13) Tsujimoto, T.; Murai, A. *Synlett* **2002**, *8*, 1283−1284.

(14) Núñez, M. C.; Entrena, A.; Rodríguez-Serrano, F.; Marchal, J. A.; Aránega, A.; Gallo, M. A.; Espinosa, A.; Campos, J. M. *Tetrahedron* **2005**, *61*, 10363−10369.

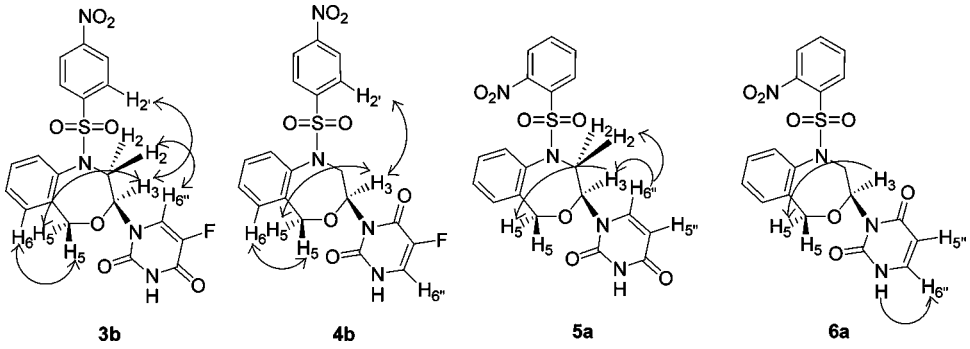


FIGURE 3. Representation of the NOESY interactions (with double-tipped arrows) for compounds **3b** and **4b** and NOEdiff interactions (with single-tipped arrows) for compounds **5a** and **6a**.

TABLE 3. ^{1}H NMR (rt) Data Obtained for the Cyclic *O,N*-Acetals 3a,b−6a,b

	H-2α		H-2β		H-3α		H-5α		H-5β		H-5″		H-6″	
compd[a]	δ	$J_{2\alpha-2\beta}$, $J_{2\alpha-3\alpha}$	δ	$J_{2\alpha-2\beta}$, $J_{2\beta-3\alpha}$	δ	$J_{3\alpha-2\beta}$, $J_{3\alpha-2\alpha}$, $J_{3\alpha-F}$	δ	$J_{5\alpha-5\beta}$	δ	$J_{5\alpha-5\beta}$	δ	$J_{5''-6''}$, $J_{5''-NH}$	δ	$J_{6''-5''}$, $J_{6''-NH}$
3a	4.53	14.9	3.64	14.9	5.94	10.0	4.84		4.84				7.80	6.8
	dd	2.1	dd	10.1	ddd	1.8	s		s				d	
						1.8								
4a	4.44	15.1	4.55	15.0	6.20	9.4	4.78		4.78				7.69	6.1
	dd	2.2	dd	9.3	dd	2.1	s		s				pt	5.4
3b	4.64	15.0	3.57	15.0	5.82	10.0	4.70	13.9	4.29	13.9			7.73	6.8
	dd	2.0	dd	10.1	ddd	1.7	d		d				d	
						1.7								
4b[b]	4.54	14.9	4.44	14.9	6.12	9.3	4.62	13.8	4.20	13.8			7.68	5.2
	dd	2.2	dd	9.3	dd	2.0	d		d				d	
5a	4.54	15.0	3.61	15.0	5.93	10.1	4.82		4.82		5.59	7.9	7.54	8.1
	dd	2.1	dd	10.1	ddd	2.1	s		s		dd	1.3	d	
6a	4.41	15.0	4.57	15.0	6.24	9.6	4.77		4.77		5.58	7.7	7.43	7.7
	dd	1.8	dd	9.6	dd	1.9	s		s		d	1.6	dd	6.0
5b[c]	4.42	15.1	3.60	14.9	5.74	8.5	4.75	13.8	4.35	13.8	5.51	8.1	7.53	8.1
	dd	ND[d]	dd	10.1	bd		d		d		d		d	
6b	4.41	15.0	4.26	15.0	6.03	7.8	4.69	13.7	4.25	13.3	5.56	7.6	7.43	
	dd	1.8	dd	9.4	dd	ND[d]	d		d		d		m	

[a] Chemical shifts are expressed in ppm and the coupling constants (*J*) in hertz (Hz). Unless otherwise stated, the spectra were run in acetone-d_6. [b] Some drops of CD_3OD were added to the acetone-d_6. [c] DMSO-d_6. [d] ND: Not determined.

TABLE 4. ^{13}C NMR (rt) Data Obtained for the Cyclic *O,N*-Acetals 3a,b−6a,b

	C-2	C-3	C-5	C-2″	C-4″		C-5″		C-6″	
compd[a]	δ	δ	δ	δ	δ	$J_{4''-F}$	δ	$J_{5''-F}$	δ	$J_{6''-F}$
3a	53.8	84.2	71.1	148.6	156.7	26.5	140.8	231.4	124.7	34.7
	s	s	s	s	d		d		d	
4a[b]	53.8	ND	72.8	150.5	157.0	24.8	139.8	331.6	123.5	31.8
	s		s	s	d		d		d	
3b	53.5	83.4	71.0	150.7	156.5	33.2	140.7	231.3	124.4	34.8
	s	s	s	s	d		d		d	
4b[c]	54.2	84.7	72.5	150.2	158.2	25.0	140.6	226.6	125.7	32.5
	s	s	s	s	d		d		d	
5a	54.0	84.1	71.1	150.0	162.6		102.2		140.2	
	s	s	s	s	s		s		s	
6a	54.3	84.4	71.8	151.0	162.8		100.5		140.8	
	s	s	s	s	s		s		s	
5b[d]	53.6	83.8	70.8	150.7	163.4		102.5		141.4	
	s	s	s	s	s		s		s	
6b[d]	53.8	83.6	71.5	151.4	163.2		100.5		142.3	
	s	s	s	s	s		s		s	

[a] Chemical shifts are expressed in ppm and the coupling constants (*J*) in hertz (Hz). Unless otherwise stated, the spectra were run in acetone-d_6. [b] Spectrum registered in $CDCl_3$ with some drops of acetone-d_6. [c] Some drops of CD_3OD were added to the acetone-d_6. [d] DMSO-d_6.

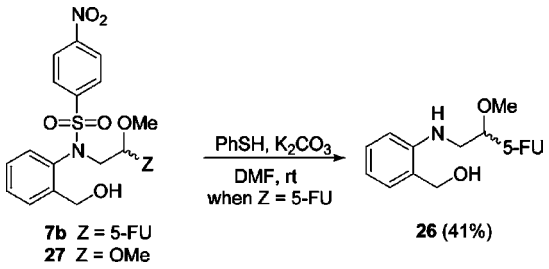
(2) The resonance signals corresponding to the H-2α and H-6″ atoms always resonate at lower fields for the *N*-1″ aminalic compounds than for the *N*-3″ ones.

(3) The coupling constant H-2β-H-3α always presents a higher value in *O,N*-acetals with the aminalic *N*-1″ bond than in compounds with the aminalic *N*-3″ one.

(4) The resonance signal corresponding to the C-5 atom always appears at higher fields for *O,N*-acetals with the aminalic *N*-1″ bond than in compounds with the aminalic *N*-3″ one.

(5) The coupling constants C-4″−F and C-6″−F always present higher values in *O,N*-acetals with the aminalic *N*-1″ bond than in compounds with the aminalic *N*-3″ one.

SCHEME 7. Synthesis of 26



Spectroscopic Analysis of Acyclic Pyrimidine *O,N*-Acetals. The ^{1}H and ^{13}C NMR spectra of acyclic *N*-1-sulfonyl and *N*-1-acyl[15] *O,N*-acetals at room temperature show the existence of two structures for each of the sulfonamides **7a**,**b**, **9a**,**b**, and **10b** and for each of the amides **7d** and **13**, with the following distribution: **7a**, 59/41; **7b**, 53/47; **9a**, 52/48; **9b**, 59/41; **10b**, 56/44; **7d**, 50/50; **13**, 80/20. This fact does not occur in the secondary amine **26** (Scheme 7), which appears as a single structure. Compound **26** was obtained by the elimination of the 4-nitrobenzenesulfonyl group under the conditions reported by Fukuyama et al.[16] with a yield of 41% (Scheme 7).

The *N*-1-tertiary sulfonamide adopts certain orientations, nonconvertible between each other, in such a way that two conformers may be observed. Next we decided to study ^{1}H NMR high-temperature experiments in order to determine the coalescence temperature of such a dynamic process in **7d**. From the H-6″, the aminalic and the benzylic protons, we have calculated an $\Delta G_c^{\ddagger}$ value of 19.0 ± 0.2 kcal·mol^{-1} (79.1 ± 1.0 kJ·mol^{-1}) using the Eyring equation[17,18] at a coalescence temperature (T_c) of 110 °C for **7b**. Slow rotation about the S−N bond in *N*,*N*-disubstituted nonafluorobutane-1-sulfonamides have been detected by NMR measurements.[19] The torsional barriers determined (62−71 kJ·mol^{-1}) proved to be the highest ever observed up to now for sulfonamide moieties; nevertheless, the $\Delta G_c^{\ddagger}$ value found for **7b** is considerable higher and is comparable to those calculated for carboxylic acid amides.[20] This is worth pointing out because the S atom of the sulfonamido moiety normally exhibits a much lower tendency to π-bond, and in consequence the barriers to rotation in sulfonamides are expected to be much lower than those of carboxylic acid amides. Probably, the highly electron-withdrawing effect of the (4)-NO_2 group favors the dipolar resonance with S═N, in which the positive charge is maximally transferred from the sulfur atom of the sulfonamido group to the N atom. An important fact is that the acyclic *O,O*-acetalic compound **27**[1] does not show the presence of two conformers at room temperature. As the only difference between **7b** and **27** is the presence of the 5-FU moiety in the former, instead of the methoxy group in the latter, the existence of two conformers in **7b** can be inferred. The presence of both sulfonamido and pyrimidine fragments is necessary. Moreover, as the diastereotopic character of the hydrogen atoms of the NCH_2 moiety is shown in both compounds **7d** and **27**, this peculiarity is independent from the *O,N*-acetalic nature of **7d**.

5-FU *O,N*-acetals with an *N*-1″ aminalic bond were identified from the coupling pattern of the aminalic proton as a ddd, due to the H-3−H-2α, H-3−H-2β and H-3−F couplings. In the case of U *O,N*-acetals the identification of the *N*-1″ aminalic bond was carried out from the coupling pattern of H-6″ as a d, as a consequence of its coupling with H-5″.

The structure proposed for **11** is based on the analysis of its ^{1}H and ^{13}C NMR. The existence of only one structure at room temperature for this compound and the chemical shift of C-2 (δ 46.46 ppm), not affected by the -M effect of the amide moiety, suggest that *N*-1″ is unsubstituted. In **26** with a secondary amino group, C-2 appears at δ 46.50 ppm, while in compounds substituted with electron-withdrawing groupings on *N*-1, it appears between δ 54.11 ppm and δ 51.47 ppm. On the other hand, in **11** the benzylic carbon atom appears at lower fields (δ 74.06 ppm) than in the remaining of the acyclic *O,N*-acetals (between δ 60.59 ppm and δ 59.51 ppm in sulfonamides, δ 64.19 ppm in the amine **26** and δ 60.31 ppm in the benzamide **7d**). This supports the linkage between the benzylic oxygen atom to a group of a higher electron-releasing ability than the hydrogen atom, as the methyl group. The MS and elemental analysis finally confirm the proposed structure.

Conclusions

The 1-(2- or 4-nitrobenzenesulfonyl)substituted *O,O*-acetals **1a** and **1b** are better substrates for the Lewis acid mediated condensation reaction with pyrimidine bases than the corresponding 1-acyl-*O,O*-acetals derivatives. Cyclic and acyclic *O,N*-acetalic products are obtained in the condensation reaction of **1a** and **1b** with 5-FU or U, in the presence of $SnCl_4$ and MeCN. Proportions differ according to the pyrimidine base used. 5-FU lead to the formation of a higher proportion of acyclic products than the cyclic ones, the opposite situation taking place from U. 5-FU links preferably to the acetalic position through its *N*-1″ atom, while U does so through *N*-3″ or *N*-1″ of the corresponding cyclic and acyclic products, respectively. The determination of which nitrogen atom of the pyrimidine bases is involved in the aminalic bond can be deduced from the multiplicities observed for certain signals in the ^{1}H NMR spectra or by means of NOESY or NOEdiff experiments. Moreover, spectroscopic characteristics exist (chemical shifts and coupling constants of certain hydrogen and carbon atoms) that permit by comparison the establishment of the type of bonding occurring in each of the members of a pair of the 5-FU or U *O,N*-acetalic regioisomers.

Experimental Section

The general methods were the same as those previously described.[1,21] One-dimensional NOE-difference experiments were performed by irradiation for 4 s in a series of eight scans with

(15) The study of the two isomers of the acyclic *N*-acyl derivatives is complicated as there is the possibility of rotamers through the *N*−CO bond.

(16) Fukuyama, T.; Jow, C. K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373−6374.

(17) Kemp, W. *NMR in Chemistry. A Multinuclear Introduction*; The MacMillan Press Ltd.: London, 1986; pp 158−168.

(18) The rate constant (k_c) and the free energy of activation ($\Delta G_c^{\ddagger}$) at the coalescence temperature (T_c) were calculated using Gutowsky (1) and Eyring (2) equations, respectively. $\Delta\upsilon$ is the limiting frequency separation. For equations (1) and (2), see ref 17.

$$k_c = \pi(\Delta\upsilon)/\sqrt{2}\ \text{Gutowsky eq 1}$$

$$\Delta G_c^{\ddagger} = 19.12T_c(10.32 + \log T_c - \log k_c)\ \text{Eyring eq 2}$$

(19) Lyapkalo, I. M.; Reising, H.-U.; Schäffer, A.; Wagner, A. *Helv. Chim. Acta*, **2002**, *85*, 4206−4215.

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alternating on- and off-resonance. The irradiating power was set low to achieve selectivity. The NOESY spectra[22a,b] were recorded using a 256 × 1024 data matrix and 256 time increments of each 16 scans (mixing time 0.5 s), in a phase-sensitive mode, and processed with a Gauss apodization function. The HMQC spectra (inv4gs in the standard Bruker software) resulted from a 256 × 1024 data matrix size with 16−64 scans per t_1 depending on the sample concentration and inter-pulse delay of 3.2 ms and a 5:3:4 gradient combination.[23]

General Procedure for the Reaction between (*RS*)-3-Methoxy-1-(nitrophenylsulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepines and Pyrimidine Bases. Method A. Synthesis of (*RS*)-1-{2-[*N*-(2-Hydroxymethylphenyl)-4-nitrobenzenesulfonamido]-1-methoxyethyl}-5-fluorouracil 7b. A 1.0 M solution of $SnCl_4/CH_2Cl_2$ (4.0 equiv) was added dropwise with stirring under argon at room temperature to a suspension of **1b**[1] (1 equiv) and 5-FU (2.1 equiv), which contains TMSCl (3.6 equiv) and HMDS (3.6 equiv) in anhydrous MeCN (5 mL/mmol of **1b**[1]). After 72 h of stirring, the reaction was quenched by the addition of H_2O and neutralization with a 10% aqueous solution of $NaHCO_3$ and extracted with EtOAc (3 × 20 mL). The organic layers were pooled, dried (Na_2SO_4), and filtered, and the solvent was removed under vacuum. The residue was purified by flash chromatography under gradient elution conditions using mixtures of CH_2Cl_2/MeOH or EtOAc/hexane, and **7b** was obtained (13% yield).

Method B. **Synthesis of (*RS*)-1-[1-(4-Nitrophenylsulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-yl]-5-fluorouracil 3b, (*RS*)-3-[1-(4-Nitrophenylsulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-yl]-5-fluorouracil 4b, and (*RS*)-1-{2-[*N*-(2-Hydroxymethylphenyl)-4-nitrobenzenesulfonamido]-1-methoxyethyl}-5-fluorouracil 7b.** The differences in relation to method A are the following: 5-FU (2.5 equiv), TCS (4.0 equiv), HMDS (3.6 equiv), temperature of addition of the reagents was 0 °C, the reaction temperature was 40 °C, and the reaction time 47 h. After the usual workup, **3b** (5%), **4b** (4%), and **7b** (18%) were obtained.

Method C. The differences in relation to method B are the following: the solvent was anhydrous MeCN and the reaction temperature 50 °C. After the usual workup, **3b** (15%), **4b** (5%), and **7b** (24%) were obtained. **3b:** elution by flash chromatography EtOAc/hexane 1/1, or CH_2Cl_2/MeOH 0.2/10; R_f (1/1, EtOAc/hexane) 0.33; white solid; mp 174−175 °C; ^{1}H NMR [$(CD_3)_2CO$, 300 MHz] δ (ppm) 10.60 (bs, 1H, N*H*), 8.47 (d, $J_{3'-2'} = J_{5'-6'} =$ 8.9 Hz, 2H, H-3′, 5′), 8.12 (d, $J_{2'-3'} = J_{6'-5'} =$ 8.9 Hz, 2H, H-2′, 6′), 7.45−7.40 (m, 4H, H-6, 7, 8, 9), 5.82 (ddd, $J_{3\beta-2\alpha} =$ 10.0 Hz, $J_{3\beta-2\beta} =$ 1.7 Hz, $J_{3\beta-F} =$ 1.7 Hz, 1H, H-3β), 4.70 (d, $J_{\text{gem } 5\alpha-5\beta} =$ 13.9 Hz, 1H, H-5α), 4.64 (dd, $J_{\text{gem } 2\beta-2\alpha} =$ 15.0 Hz, $J_{2\beta-3\beta} =$ 2.0 Hz, 1H, H-2β), 4.29 (d, $J_{\text{gem } 5\beta-5\alpha} =$ 13.8 Hz, 1H, H-5β), 3.57 (dd, $J_{\text{gem } 2\beta-2\alpha} =$ 15.0 Hz, $J_{2\alpha-3\beta} =$ 10.1 Hz, 1H, H-2α); ^{13}C NMR [$(CD_3)_2CO$, 75 MHz] δ (ppm) 156.5 (d, $J_{C-F} =$ 33.2 Hz, C-4″), 140.7 (d, $J_{C-F} =$ 231.3 Hz, C-5″), 150.7, 148.5, 146.6, 139.0 and 137.4 (C-5a, C-9a, C-1′, C-4′, C-2″), 130.1, 129.6 and 129.1 (CH-6, CH-7, CH-8, CH-9), 128.8 and 125.0 (CH-2′, CH-3′, CH-5′, CH-6′), 124,4 (d, $J_{C-F} =$ 34.8 Hz, CH-6″), 84.7 (CH-3), 72.5 (CH-5), 54,2 (CH_2-2); HR LSIMS calcd for $C_{19}H_{15}N_4O_7FSNa$ $(M+Na)^+$ 485.0543, found 485.0543. Anal. Calcd for $C_{19}H_{15}N4O_7FS\cdot 0.15H_2O$: C, 49.07; H, 3.32; N, 12.05. Found: C, 49.46; H, 3.05; N, 12.00.

4b: elution by flash chromatography EtOAc/hexane 1.5/1, or CH_2Cl_2/MeOH 0.2/10; R_f (2/1, EtOAc/hexane) 0.25; white solid; mp 185.4−186.2 °C; ^{1}H NMR [$(CD_3)_2CO$/drops of CD_3OD, 400 MHz] δ (ppm) 9.90 (bs, N*H*), 8.46 (d, $J_{3'-2'} = J_{5'-6'} =$ 8.9 Hz, 2H, H-3′, 5′), 8.08 (d, $J_{2'-3'} = J_{6'-5'} =$ 8.9 Hz, 2H, H-2′, 6′), 7.40−7.35 (m, 4H, H-6,7,8,9), 6.12 (ddd, $J_{3\beta-2\alpha} =$ 9.3 Hz, $J_{3\beta-2\beta} =$ 2.0 Hz, 1H, H-3β), 4.62 (d, $J_{\text{gem } 5\alpha-5\beta} =$ 13.7 Hz, 1H, H-5α), 4.54 (dd, $J_{\text{gem } 2\beta-2\alpha} =$ 14.9 Hz, $J_{2\beta-3\beta} =$ 2.2 Hz, 1H, H-2β), 4.44 (dd, $J_{\text{gem } 2\beta-2\alpha} =$ 14.9 Hz, $J_{2\alpha-3\beta} =$ 9.3 Hz, 1H, H-2α), 4.20 (d, $J_{\text{gem } 5\beta-5\alpha} =$ 13.8 Hz, 1H, H-5β); ^{13}C NMR [$(CD_3)_2CO$/drops CD_3OD, 100 MHz] δ (ppm) 158.2 (d, $J_{C-F} =$ 25.0 Hz, C-4″), 140.6 (d, $J_{C-F} =$ 226.6 Hz, C-5″), 151.4, 150.2, 147.6, 140.2 and 138.7 (C-5a, C-9a, C-1′, C-4′, C-2″), 130.9, 130.2, 129.5, 129.4 and 125.7 (CH-6, CH-7, CH-8, CH-9), 125.7 (d, $J_{C-F} =$ 32.5 Hz, C-6″), 84.7 (CH-3), 72.5 (CH_2-5), 54.2 (CH_2-2); HR LSIMS calcd for $C_{19}H_{15}N_4O_7FSNa$ $(M + Na)^+$ 485.0543, found 485.0545. Anal. Calcd for $C_{19}H_{15}N4O_7FS\cdot 0.65H_2O$: C, 48.14; H, 3.46; N, 11.82. Found: C, 47.84; H, 3.48; N, 12.01.

7b: elution by flash chromatography EtOAc/hexane:1.5/1, or CH_2Cl_2/MeOH 0.2/10; R_f (2/1, EtOAc/hexane) 0.20; white solid; mp 142−143 °C; ($CDCl_3$, rt isomer A (59%), *isomer B* (41%)) ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 9.18 (bd, $J_{NH-F} =$ 4.6 Hz, 1H, N*H*), 8.88 (bd, $J_{NH-F} =$ 4.3 Hz, 1H, *NH*), 8.34 (d, $J_{3'-2'} = J_{5'-6'} =$ 8.8 Hz, 2H, H-3′, 5′), 8.33 (d, $J_{3'-2'} = J_{5'-6'} =$ 8.8 Hz, 2H, *H-3′*, *5′*), 7.80 (d, $J_{2'-3'} = J_{6'-5'} =$ 8.8 Hz, 2H, H-2′, 6′), 7.76 (d, $J_{2'-3'} = J_{6'-5'} =$ 8.8 Hz, 2H, *H-2′*, *6′*), 7.72−7.68 (m, 1H, *1H*), 7.47−7.40 (m, 1H, *1H*), 7.35 (d, $J_{6''-F} =$ 5.5 Hz, 1H, H-6″), 7.22−7.18 (m, 1H, *2H*), 6.49 (d, $J =$ 7.8 Hz, *1H*), 6.44 (d, $J =$ 7.8 Hz, 1H), 5.70 (ddd, $J_{CHCH2N} =$ 6.3 Hz, $J_{\text{aminalic CH}-F} =$ 1.5 Hz, 1H, aminalic H), 5.55 (ddd, $J_{CHCH2N} =$ 5.9 Hz, $J_{\text{aminalic CH}-F} =$ 1.6 Hz, 1H, *aminalic H*), 4.82−4.63 (m, 4H, benzylic H, *benzylic H*), 4.15 (dd, $J_{\text{gem NCH2}} =$ 14.0 Hz, $J_{8-9} =$ 5.8 Hz, 1H, *NCH*$_2$), 3.98 (dd, $J_{\text{gem NCH2}} =$ 14.5 Hz, $J_{8-9} =$ 6.4 Hz, 1H, NCH$_2$), 3.60 (dd, $J_{\text{gem NCH2}} =$ 14.5 Hz, $J_{8-9} =$ 6.2 Hz, 1H, NCH$_2$), 3.51 (dd, $J_{\text{gem NCH2}} =$ 13.9 Hz, $J_{8-9} =$ 5.8 Hz, 1H, *NCH*$_2$), 3.32 (s, 3H, OMe), 3.29 (s, 3H, *OMe*), 3.10 (bs, 1H, O*H*), 2.85 (bb, 1H, *OH*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 156.8 (d, $J_{C-F} =$ 26.4 Hz, C-4″), 156.6 (d, $J_{C-F} =$ 26.5 Hz, *C-4″*), 150.5, 150.3 and 149.7 (C-2″, *C-2″*, C-4′, *C-4′*), 142.5, 142.4, 142.4, 142.3, 136.4 and 135.4 (C-1, *C-1*, C-1′, *C-1′*, C-2, *C-2*), 141.5 (d, $J_{C-F} =$ 239.0 Hz, C-5″), 141.3 (d, $J_{C-F} =$ 238.4 Hz, *C-5″*), 131.5, 131.3, 130.0, 129.6, 129.4, 128.8, 128.7, 126.8, 126.6, 124.4 and 124.3, (CH-aromatics), 122.4 (d, $J_{C-F} =$ 33.7 Hz, CH-6″ or *CH-6″*), 122.1 (d, $J_{C-F} =$ 33.9 Hz, *CH-6″*or CH-6″), 84.8 and 84.8 (aminalic CH, *aminalic CH*), 60.6 and 60.5 (benzylic CH_2, *benzylic CH*$_2$), 57.2 and 57.0 (OMe, *OMe*), 54.1 and 53.4 (NCH$_2$, *NCH*$_2$); (DMSO-d_6, rt, isomer A (slightly predominant), *isomer B*) ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 11.80 (bs, N*H*), 8.38 (d, $J_{3'-2'} = J_{5'-6'} =$ 8.9 Hz, H-3′, 5′ or *H-3′*, *5′*), 8.37 (d, $J_{3'-2'} = J_{5'-6'} =$ 8.9 Hz, H-3′, 5′ or *H-3′*, *5′*), 7.90−7.82 (m), 7.58−7.56 (m), 7.40−7.35 (m), 7.19−7.13 (m), 6.72 (d, $J =$ 7.9 Hz), 6.60 (d, $J =$ 7.65 Hz), 5.52 (pt, $J_1 =$ 5.0 Hz, $J_2 =$ 6.3 Hz, aminalic H or *aminalic H*), 5.31 (t, $J =$ 5.3 Hz, *aminalic H* or aminalic H), 5.14 (t, $J_{CH2OH} =$ 5.4 Hz, O*H* or *OH*), 4.56−4.38 (m, benzylic H, *benzylic H*), 4.01 (dd, $J_{\text{gem NCH2}} =$ 14.4 Hz, $J_{8-9} =$ 7.0 Hz, NCH$_2$ or *NCH*$_2$), 3.87 (d, $J =$ 6.1 Hz, *NCH*$_2$ or NCH$_2$), 3.74 (dd, $J_{\text{gem NCH2}} =$ 14.3 Hz, $J_{8-9} =$ 4.9 Hz, NCH$_2$ or *NCH*$_2$), 3.14 (s, OMe or *OMe*), 3.08 (s, *OMe* or OMe); (DMSO-d_6, 110 °C) ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 11.40 (bs, N*H*), 8.34 (d, $J =$ 8.8 Hz), 7.88 (d, $J =$ 8.2 Hz), 7.66 (d, $J =$ 6.3 Hz), 7.58 (d, $J =$ 7.7 Hz), 7.36 (t, $J =$ 7.5 Hz), 7.17 (t, $J =$ 7.6 Hz), 6.78 (bs), 5.47 (bs, 1H, aminalic H), 4.68 (bs, 1H, O*H*), 4.46 (bs, 2H, benzylic H), 3.97 (dd, $J_{\text{gem NCH2}} =$ 14.8 Hz, $J_{8-9} =$ 6.7 Hz, NCH$_2$), 3.86 (ddd, $J_{\text{gem NCH2}} =$ 14.8 Hz, $J_{8-9} =$ 5.2 Hz, NCH$_2$), 3.15 (s, OMe); HR LSIMS calcd for $C_{20}H_{19}N_4O_8FSNa$ $(M+Na)^+$ 517.0805, found 517.0805. Anal. Calcd for $C_{20}H_{19}N4O_8FS$: C, 48.58; H, 3.87; N, 11.33. Found: C, 48.60; H, 3.75; N, 11.38.

Method D. According to the general procedure, but using Sc(OTf)$_3$ (1.04 equiv), 5-FU (1.5 equiv), TCS (2.0 equiv), HMDS (2.0 equiv), the temperature of addition of the reagents was 0 °C, the reaction temperature 40 °C, and the reaction time 24 h, no reaction was observed.

Method E. According to method D, but using anhydrous MeCN as the solvent, and the reaction temperature 50 °C, no reaction was observed.

Method C. Synthesis of (*RS*)-1-[1-(2-Nitrophenylsulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-yl]-5-fluorouracil 3a,

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(23) Hurd, R. E.; John, B. K. *J. Magn. Reson.* **1991**, *91*, 648−653.

***(RS)*-3-[1-(2-Nitrophenylsulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-yl]-5-fluorouracil 4a, and (*RS*)-1-{2-[*N*-(2-Hydroxymethylphenyl)-2-nitrobenzenesulfonamido}-1-methoxyethyl)-5-fluorouracil 7a.** Following method C with a reaction time of 51 h, the reaction between **1a**[1] and 5-FU gave the following results. **3a:** elution by flash chromatography EtOAc/hexane 2/1, or CH_2Cl_2; R_f (2/1, EtOAc/hexane) 0.33; R_f (10/0.25, CH_2Cl_2/MeOH) 0.38; white solid; mp 178.1−179.1 °C; yield 19%; ^{1}H NMR [$(CD_3)_2$CO, 300 MHz] δ (ppm) 10.60 (bs, 1H, N*H*), 8.12−7.96 (m, 3H, H-PhSO$_2$), 7.90 (ddd, $J_1 = 7.8$ Hz, $J_2 = 6.4$ Hz, $J_3 = 2.4$ Hz, 1H, H-PhSO$_2$), 7.51 (dd, $J_1 = 7.4$ Hz, $J_2 = 1.8$ Hz, 1H), 7.40 (ddd, $J_1 = J_2 = 7.4$ Hz, $J_3 = 1.4$ Hz, 1H), 7.33 (ddd, $J_1 = J_2 = 7.7$ Hz, $J_3 = 1.8$ Hz, 1H), 7.09 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.4$ Hz, 1H), 5.94 (ddd, $J_{3\beta-2\alpha} = 10.0$ Hz, $J_{3\beta-2\beta} = 1.8$ Hz, $J_{3\beta-F} = 1.8$ Hz, 1H, H-3β), 4.84 (s, 2H, H-5), 4.53 (dd, $J_{\text{gem } 2\beta-2\alpha} = 14.9$ Hz, $J_{2\beta-3\beta} = 2.1$ Hz, 1H, H-2β), 3.64 (dd, $J_{\text{gem } 2\beta-2\alpha} = 14.9$ Hz, $J_{2\alpha-3\beta} = 10.1$ Hz, 1H, H-2α); ^{13}C NMR [$(CD_3)_2$CO, 75 MHz] δ (ppm) 156.7 (d, $J_{C-F} = 26.5$ Hz, C-4″), 148.6 and 147.9 (C-2′ and C-2″), 140.8 (d, $J_{C-F} = 231.4$ Hz, C-5″), 139.2, 138.3, and 133.2 (C-5a, C-9a and C-1′), 135.3, 132.8, 131.5, 130.2, 129.5, 128.9, 128.5 and 125.0 (CH-6, CH-7, CH-8, CH-9, CH-3′, CH-4′, CH-5′, CH-6′), 124.7 (d, $J_{C-F} = 34.7$ Hz, C-6″), 84.2 (CH-3), 71.1 (CH_2-5), 53.8 (CH_2-2); HR LSIMS calcd for $C_{19}H_{15}N_4O_7FSNa$ (M + Na)$^+$ 485.0543, found 485.0543. Anal. Calcd for $C_{19}H_{15}N4O_7FS\cdot1.76H_2O$: C, 46.19; H, 3.78; N, 11.34; S, 6.49. Found: C, 46.59; H, 3.49; N, 11.51; S, 6.51.

4a: elution by flash chromatography EtOAc, or CH_2Cl_2/MeOH 6/0.1; R_f (10/0.5, CH_2Cl_2/MeOH) 0.46; white solid; mp 171.6−172.6 °C; yield 4%; ^{1}H NMR [$(CD_3)_2$CO, 300 MHz] δ (ppm) 9.80 (bs, 1H, N*H*), 8.06−7.97 (m, 3H), 7.90 (ddd, $J_1 = 7.9$ Hz, $J_2 = 6.3$ Hz, $J_3 = 2.6$ Hz, 1H), 7.47 (dd, $J_1 = 7.4$ Hz, $J_2 = 1.8$ Hz, 1H), 7.37 (ddd, $J_1 = J_2 = 7.4$ Hz, $J_3 = 1.4$ Hz, 1H), 7.30 (ddd, $J_1 = J_2 = 7.6$ Hz, $J_3 = 1.8$ Hz, 1H), 7.05 (dd, $J_1 = 7.7$ Hz, $J_2 = 1.3$ Hz, 1H),), 6.20 (dd, $J_{3\beta-2\alpha} = 9.4$ Hz, $J_{3\beta-2\beta} = 2.1$ Hz, 1H, H-3β), 4.78 (s, 2H, H-5), 4.55 (dd, $J_{\text{gem } 2\beta-2\alpha} = 15.0$ Hz, $J_{2\alpha-3\beta} = 9.3$ Hz, 1H, H-2α), 4.44 (dd, $J_{\text{gem } 2\beta-2\alpha} = 15.1$ Hz, $J_{2\beta-3\beta} = 2.2$ Hz, 1H, H-2β); ^{13}C NMR [$CDCl_3$/drops of $(CD_3)_2$CO, 75 MHz] δ (ppm) 157.0 (d, $J_{C-F} = 24.8$ Hz, C-4″), 150.5 and 147.9 (C-2′ and C-2″), 139.8 (d, $J_{C-F} = 331.6$ Hz, C-5″), 139.1, 134.2 and 128.6 (C-5a, C-9a and C-1′), 134.4, 132.2, 131.8, 130.5, 129.4, 129.0 and 124.7 (CH-6, CH-7, CH-8, CH-9, CH-3′, CH-4′, CH-5′, CH-6′), 123.5 (d, $J_{C-F} = 31.8$ Hz, CH-6″), 72.8 (CH_2-5), 53.8 (CH_2-2); HR LSIMS calcd for $C_{19}H_{15}N_4O_7FSNa$ (M + Na)$^+$ 485.0543, found 485.0542. Anal. Calcd for $C_{19}H_{15}N4O_7FS$: C, 49.35; H, 3.27; N, 12.12; S, 6.93. Found: C, 49.40; H, 3.40; N, 12.41; S, 6.92.

7a: elution by flash chromatography EtOAc, or CH_2Cl_2/MeOH 6/0.1; R_f (10/0.5, CH_2Cl_2/MeOH) 0.36; white solid; mp 179−180 °C; yield 30%; ($CDCl_3$/drops of $(CD_3)_2$CO, rt, isomer A (53%), *isomer B* (47%)) ^{1}H NMR [$CDCl_3$/drops of $(CD_3)_2$CO, 300 MHz] δ (ppm) 9.75 (bs, 1H, N*H*), 9.58 (bs, 1H, *NH*), 7.67−7.53 (m, 3H, *3H*), 7.44−7.10 (m, 4H, *4H*), 7.31 (d, $J_{6''-F} = 6.0$ Hz, 1H, H-6″or *H-6*″), 7.28 (d, $J_{6''-F} = 5.8$ Hz, 1H, *H-6*″or H-6″), 6.93−6.89 (m, 1H, *1H*), 5.55 (ddd, $J_{NCH2CH} = 5.7$ Hz, $J_{\text{aminalic H}-F}$ = nondetermined, 1H, aminalic H or *aminalic H*), 5.49 (ddd, $J_{NCH2CH} = 6.1$ Hz, $J_{\text{aminalic H}-F} = 1.8$ Hz, 1H, aminalic H or *aminalic H*), 4.57 (d, $J_{\text{gem benzylic H}} = 13.0$ Hz, 1H, benzylic H or *benzylic H*), 4.49 (d, $J_{\text{gem benzylic H}} = 13.0$ Hz, 1H, benzylic H or *benzylic H*), 4.47 (d, $J_{\text{gem benzylic H}} = 13.0$ Hz, 1H, benzylic H or *benzylic H*), 4.30 (d, $J_{\text{gem benzylic H}} = 13.0$ Hz, 1H, benzylic H or *benzylic H*), 4.13 (dd, $J_{\text{gem NCH2}} = 14.6$ Hz, $J_{NCH2CH} = 6.3$ Hz, 1H, *NCH$_2$*), 4.11 (dd, $J_{\text{gem NCH2}} = 15.2$ Hz, $J_{NCH2CH} = 6.8$ Hz, 1H, NCH$_2$), 3.92 (dd, $J_{\text{gem NCH2}} = 15.1$ Hz, $J_{NCH2CH} = 5.9$ Hz, 1H, NCH$_2$), 3.79 (dd, $J_{\text{gem NCH2}} = 14.7$ Hz, $J_{NCH2CH} = 5.9$ Hz, 1H, *NCH$_2$*), 3.24 (s, 3H, *OMe*), 3.20 (s, 3H, OMe); [$(CD_3)_2$CO, rt, major isomer (51%), *minor isomer* (49%)] ^{13}C NMR [$(CD_3)_2$CO, 75 MHz] δ (ppm) 156.6 (d, $J_{C-F} = 26.9$ Hz, C-4″), 150.0, 150.0 and 148.2 (C-2″, *C-2*″, C-2′, *C-2*′), 142.8, 142.2, 135.6, 131.1 and 130.5 (C-1, *C-1*, C-1′, *C-1*′, C-2, *C-2*), 141.2 (d, $J_{C-F} = 225.0$ Hz, C-5″ or *C-5*″), 141.0 (d, $J_{C-F} = 225.0$ Hz, C-5″ or *C-5*″), 135.0, 135.0, 131.8, 131.8, 131.6, 131.4, 130.2, 130.1, 130.0, 129.6, 129.4, 129.4, 128.0, 127.9, 124.2 and 124.2 (CH-aromatics), 123.3 (d, $J_{C-F} = 33.9$ Hz, CH-6″ or *CH-6*″), 123.0 (d, $J_{C-F} = 34.0$ Hz, *CH-6*″or CH-6″), 84.7 and 84.1 (aminalic C, *aminalic C*), 59.5 (benzylic C, *benzylic C*), 56.0 and 55.9 (OMe, O*Me*), 54.0 and 53.3 (NCH$_2$, N*CH$_2$*); HR LSIMS calcd for $C_{20}H_{19}N_4O_8FSNa$ (M + Na)$^+$ 517.0805, found 517.0805. Anal. Calcd for $C_{20}H_{19}N4O_8FS$: C, 48.58; H, 3.87; N, 11.33; S, 6.48. Found: C, 48.88; H, 3.75; N, 11.37; S, 6.20.

Method C: Synthesis of (*RS*)-1-[1-(2-Nitrophenylsulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-yl]uracil 5a, (*RS*)-3-[1-(2-Nitrophenylsulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-yl]uracil 6a, and (*RS*)-1-{2-[*N*-2-Hydroxymethylphenyl)-2-nitrobenzenesulfonamido]-1-methoxyethyl)uracil 9a. Following method C with a reaction time of 67 h, the reaction between **1a** and U gave the following results:

5a: elution by flash chromatography EtOAc; R_f (10/0.3, CH_2Cl_2/MeOH) 0.25; pale yellow solid; mp 179−180 °C; yield 27%; ^{1}H NMR [$(CD_3)_2$CO, 300 MHz] δ (ppm) 10.20 (bs, 1H, N*H*), 8.13 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.2$ Hz, 1H, H-PhSO$_2$), 8.03−7.89 (m, 3H, H-PhSO$_2$), 7.50 (dd, $J_1 = 7.3$ Hz, $J_2 = 1.8$ Hz, 1H), 7.40 (ddd, $J_1 = J_2 = 7.4$ Hz, $J_3 = 1.4$ Hz, 1H), 7.33 (ddd, $J_1 = J_2 = 7.6$ Hz, $J_3 = 1.8$ Hz, 1H), 7.11 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.4$ Hz, 1H), 5.93 (dd, $J_{3\beta-2\alpha} = 10.1$ Hz, $J_{3\beta-2\beta} = 2.1$ Hz, 1H, H-3β), 5.59 (dd, $J_{5''-6''} = 7.9$ Hz, $J_{5''-NH} = 1.3$ Hz, 1H, H-5″), 4.82 (s, 2H, H-5), 4.54 (dd, $J_{\text{gem } 2\beta-2\alpha} = 15.0$ Hz, $J_{2\beta-3\beta} = 2.1$ Hz, 1H, H-2β), 3.61 (dd, $J_{\text{gem } 2\beta-2\alpha} = 15.0$ Hz, $J_{2\alpha-3\beta} = 10.1$ Hz, 1H, H-2α); ^{13}C NMR [$(CD_3)_2$CO, 75 MHz] δ (ppm) 162.6 (C-4″), 150.0 and 148.0 (C-2′, C-2″), 140.2 (CH-6″), 139.2 and 138.2 (C-9a, C-1′), 133.3 (C-5a), 135.2, 132.8 and 131.5 (CH−PhSO$_2$), 130.1, 129.4, 128.9 and 128.6 (CH-6, CH-7, CH-8, CH-9), 124.9 (CH−PhSO$_2$), 102.2 (CH-5″), 84.1 (CH-3), 71.1 (CH_2-5), 54.0 (CH_2-2); proton and carbon atom shifts are confirmed by a HMQC study; HR LSIMS calcd for $C_{19}H_{16}N_4O_7SNa$ (M + Na)$^+$ 467.0637, found 467.0637. Anal. Calcd for $C_{19}H_{16}N4O_7S\cdot0.78H20$: C, 49.78; H, 3.86; N, 12.22; S, 6.99. Found: C, 50.18; H, 4.13; N, 12.59; S, 6.80.

6a: Elution by flash chromatography with EtOAc, or with CH_2Cl_2/MeOH 10/0.2; R_f (10/0.4, CH_2Cl_2/MeOH) 0.47; pale yellow solid; mp 158−159 °C; yield 33%; ^{1}H NMR [$(CD_3)_2$CO, 300 MHz] δ (ppm) 9.90 (bs, 1H, N*H*), 8.06−7.94 (m, 3H, H−PhSO$_2$), 7.88 (ddd, $J_1 = 7.8$ Hz, $J_2 = 6.1$ Hz, $J_3 = 2.8$ Hz, 1H, H−PhSO$_2$), 7.45 (dd, $J_1 = 7.3$ Hz, $J_2 = 1.8$ Hz, 1H), 7.35 (ddd, $J_1 = J_2 = 7.4$ Hz, $J_3 = 1.5$ Hz, 1H), 7.29 (ddd, $J_1 = J_2 = 7.6$ Hz, $J_3 = 1.9$ Hz, 1H), 7.05 (dd, $J_1 = 7.7$ Hz, $J_2 = 1.4$ Hz, 1H), 6.24 (dd, $J_{3\beta-2\alpha} = 9.6$ Hz, $J_{3\beta-2\beta} = 1.9$ Hz, 1H, H-3β), 5.58 (dd, $J_{5''-6''} = 7.7$ Hz, $J_{5''-NH} = 1.6$ Hz, 1H, H-5″), 4.77 (s, 2H, H-5), 4.57 (dd, $J_{\text{gem } 2\beta-2\alpha} = 15.0$ Hz, $J_{2\alpha-3\beta} = 9.6$ Hz, 1H, H-2α), 4.41 (dd, $J_{\text{gem } 2\beta-2\alpha} = 15.0$ Hz, $J_{2\beta-3\beta} = 1.8$ Hz, 1H, H-2β); ^{13}C NMR [$(CD_3)_2$CO, 75 MHz] δ (ppm) 162.8 (C-4″), 148.0 (C-2′), 151.0 and 148.0 (C-2′, C-2″), 140.8 (CH-6″), 139.8 and 138.8 (C-9a, C-1′), 133.7 (C-5a), 135.0, 132.7, 131.2, 130.2, 129.2, 128.7, 128.3 and 124.9 (CH-6, CH-7, CH-8, CH-9, CH-3′, CH-4′, CH-5′, CH-6′), 100.5 (CH-5″), 84.4 (CH-3), 71.8 (CH_2-5), 54.3 (CH_2-2); HR LSIMS calcd for $C_{19}H_{16}N_4O_7SNa$ (M + Na)$^+$ 467.0637, found 467.063. Anal. Calcd for $C_{19}H_{16}N4O_7S\cdot2.24H_2O$: C, 47.08; H, 4.23; N, 11.57; S, 6.61. Found: C, 47.47; H, 4.00; N, 11.85; S, 6.55.

9a: elution by flash chromatography CH_2Cl_2/MeOH 10/0.3; R_f (10/0.4, CH_2Cl_2/MeOH) 0.40; pale yellow solid; mp 97−98 °C; yield 12%; ($(CD_3)_2$CO, rt, isomer A (52%), *isomer B* (48%)) ^{1}H NMR [$(CD_3)_2$CO, 300 MHz] δ (ppm) 10.10 and 10.05 (2bs, 2H, N*H*, *NH*), 7.94−7.14 (m, 8H, *8H*), 7.50 (d, $J_{6''-5''} = 8.2$ Hz, 1H, H-6″or *H-6*″), 7.41 (d, $J_{6''-5''} = 8.0$ Hz, 1H, *H-6*″or H-6″), 5.69 (t, $J_{9-8} = 6.3$ Hz, 1H, aminalic H or *aminalic H*), 5.65 (dd, $J_{5''-6''} = 8.0$ Hz, $J_{5''-NH} = 1.8$ Hz, 1H, H-5″ or *H-5*″), 5.60 (t, $J_{NCH2CH} = 6.2$ Hz, 1H, aminalic H or *aminalic H*), 5.56 (dd, $J_{5''-6''} = 8.2$ Hz, $J_{5''-NH} = 1.8$ Hz, 1H, H-5″ or *H-5*″), 4.69 (dd, $J_{\text{gem benzylic H}} = 13.6$ Hz, $J_{CH2OH} = 4.2$ Hz, 1H, benzylic H or *benzylic H*), 4.55 (dd, $J_{\text{gem benzylic H}} = 13.4$ Hz, $J_{7-OH} = 4.3$ Hz, 1H, benzylic H or *benzylic H*), 4.39 (dd, $J_{\text{gem benzylic H}} = 13.7$ Hz, $J_{CH2OH} = 4.1$ Hz, 1H, benzylic H or *benzylic H*), 4.29 (dd, $J_{\text{gem benzylic H}} = 13.5$ Hz, $J_{CH2OH} = 4.0$

Hz, 1H, benzylic H or *benzylic H*), 4.24−3.99 (m, 6H, NCH_2, *NCH_2*, O*H*, *OH*), 3.29 (s, 3H, *OMe*), 3.26 (s, 3H, OMe); ^{13}C NMR [$(CD_3)_2CO$, 75 MHz] δ (ppm) 162.5 (C-4″, *C-4″*), 151.4, 151.2 and 148.2 (C-2″, *C-2″*, C-2′, *C-2′*), 142.9, 142.3, 135.5, 131.1 and 130.6 (C-1, *C-1*, C-1′, *C-1′*, C-2, *C-2*), 139.1 and 138.9 (CH-6″, *CH-6″*), 135.0, 134.9, 131.8, 131.7, 131.6, 131.4, 130.1, 129.8, 129.5, 129.4, 129.3, 128.0, 124.2 and 124.2 (CH-aromatics), 102.9 (CH-5″, *CH-5″*), 84.1 and 83.6 (aminalic C, *aminalic C*), 59.5 (benzylic C, *benzylic C*), 55.8 and 55.8 (OMe, *OMe*), 54.3 and 53.5 (NCH_2, N*CH_2*); HR LSIMS calcd for $C_{20}H_{20}N_4O_8SNa$ $(M + Na)^+$ 499.0900, found 499.0899. Anal. Calcd for $C_{20}H_{20}N4O_8S\cdot 0.27H_2O$: C, 49.91; H, 4.30; N, 11.64; S, 6.66. Found: C, 50.31; H, 4.63; N, 11.46; S, 6.99.

Method C: Synthesis of (*RS*)-1-[1-(4-Nitrophenylsulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-yl]uracil 5b, (*RS*)-3-[1-(4-Nitrophenylsulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-yl]uracil 6b, (*RS*)-1-{2-(*N*-(2-Hydroxymethylphenyl)-4-nitrobenzenesulfonamido]-1-methoxyethyl}uracil 9b, and (*RS*)-3-{2-[*N*-(2-Hydroxymethylphenyl)-4-nitrobenzenesulfonamido]-1-methoxyethyl}uracil 10b. Following method C with a reaction time of 69 h, the reaction between **1b**[1] and U gave the following results. **5b:** elution by flash chromatography EtOAc/hexane 1.5/1, or CH_2Cl_2/MeOH 10/0.1; R_f (10/0.3, CH_2Cl_2/MeOH) 0.30; white solid; mp 255−257 °C; yield 11%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm) 11.45 (bs, 1H, N*H*), 8.43 (d, $J_{3'-2'} = J_{5'-6'} = 8.8$ Hz, 2H, H-3′, 5′), 8.12 (d, $J_{2'-3'} = J_{6'-5'} = 8.8$ Hz, 2H, H-2′, 6′), 7.48−7.45 (m, 1H), 7.41−7.34 (m, 2H), 7.19−7.16 (m, 1H), 5.74 (bd, $J = 8.5$ Hz, 1H, H-3β), 5.51 (d, $J_{5''-6''} = 8.1$ Hz, 1H, H-5″), 4.75 (d, $J_{\text{gem } 5\alpha-5\beta} = 13.8$ Hz, 1H, H-5), 4.42 (dd, $J_{\text{gem } 2\beta-2\alpha} = 15.1$ Hz, $J_{2\beta-3\beta}$ = not det., 1H, H-2β), 4.35 (d, $J_{\text{gem } 5\beta-5\alpha} = 13.7$ Hz, 1H, H-5), 3.60 (dd, $J_{\text{gem } 2\beta-2\alpha} = 14.9$ Hz, $J_{2\alpha-3\beta} = 10.1$ Hz, 1H, H-2α); ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 163.4 (C-4″), 150.7 and 150.4 (C-4′ and C-2″), 146.2, 139.4 and 137.7 (C-5a, C-9a, C-1′), 130.7, 130.1, 129.1 and 128.3 (CH-6, CH-7, CH-8, CH-9), 129.2 and 125.7 (CH-2′, CH-3′, CH-5′, CH-6′), 102.5 (CH-5″), 83.8 (CH-3), 70.8 (CH_2-5), 53.6 (CH_2-2); HR LSIMS calcd for $C_{19}H_{16}N_4O_7SNa$ $(M + Na)^+$ 467.0637, found 467.0637. Anal. Calcd for $C_{19}H_{16}N4O_7S\cdot 0.89H_2O$: C, 49.56; H, 3.89; N, 12.17; S, 6.96. Found: C, 49.17; H, 3.76; N, 12.02; S, 6.81.

6b: elution by flash chromatography EtOAc/hexane 1.5/1, or CH_2Cl_2/MeOH 10/0.3; R_f (10/0.4, CH_2Cl_2/MeOH) 0.30; white solid; mp 276.9−277.9 °C dec; yield 49%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm) 11.20 (bs, 1H, N*H*), 8.41 (d, $J_{3'-2'} = J_{5'-6'} = 8.9$ Hz, 2H, H-3′, 5′), 8.09 (d, $J_{2'-3'} = J_{6'-5'} = 8.9$ Hz, 2H, H-2′, 6′), 7.44−7.33 (m, 4H), 7.15−7.12 (m, 1H), 6.03 (dd, $J_1 = 7.8$ Hz, J_2 = not det., 1H, H-3β), 5.56 (d, $J_{5''-6''} = 7.6$ Hz, 1H, H-5″), 4.69 (d, $J_{\text{gem } 5\alpha-5\beta} = 13.7$ Hz, 1H, H-5), 4.41 (dd, $J_{\text{gem } 2\beta-2\alpha} = 15.0$ Hz, $J_{2\beta-3\beta} = 1.8$ Hz, 1H, H-2β), 4.26 (dd, $J_{\text{gem } 2\beta-2\alpha} = 15.0$ Hz, $J_{2\alpha-3\beta} = 9.4$ Hz, 1H, H-2α), 4.25 (d, $J_{\text{gem } 5\beta-5\alpha} = 13.3$ Hz, 1H, H-5); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm) 163.2 (C-4″), 151.4 and 150.6 (C-4′, C-2″), 146.5, 139.8 and 138.1 (C-5a, C-9a, C-1′), 130.7, 130.0, 129.0 and 128.2 (CH-6, CH-7, CH-8, CH-9), 129.1 and 125.6 (CH-2′, CH-3′, CH-5′, CH-6′), 100.5 (CH-5″), 83.6 (CH-3), 71.5 (CH_2-5), 53.8 (CH_2-2); HR LSIMS calcd for $C_{19}H_{16}N_4O_7SNa$ $(M + Na)^+$ 467.0637, found 467.0637. Anal. Calcd for $C_{19}H_{16}N4O_7S\cdot 0.30H_2O$: C, 50.55; H, 3.75; N, 12.41; S, 7.10. Found: C, 50.95; H, 4.12; N, 12.51; S, 7.26.

9b: elution by flash chromatography EtOAc/hexane 2/1, or CH_2Cl_2/MeOH 10/0.3; R_f (10/0.4, CH_2Cl_2/MeOH) 0.43; white solid; mp 110.9−111 °C; yield 11%; ($CDCl_3$, rt isomer A (59%), *isomer B* (41%)) ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 9.50 (bs, 1H, N*H*), 9.30 (bs, 1H, *NH*), 8.34 (d, $J_{3'-2'} = J_{5'-6'} = 8.8$ Hz, 2H, H-3′, 5′), 8.32 (d, $J_{3'-2'} = J_{5'-6'} = 8.7$ Hz, 2H, *H-3′*, *5′*), 7.81 (d, $J_{2'-3'} = J_{6'-5'} = 8.8$ Hz, 2H, H-2′, 6′), 7.75 (d, $J_{2'-3'} = J_{6'-5'} = 8.8$ Hz, 2H, *H-2′*, *6′*), 7.71−7.67 (m, 1H, *1H*), 7.45−7.39 (m, 1H, *1H*), 7.32 (d, $J_{6''-5''} = 8.1$ Hz, 1H, H-6″), 7.25−7.16 (m, 1H, *2H*), 7.23 (d, $J_{6''-5''} = 8.0$ Hz, 1H, *H-6″*), 6.52 (d, $J = 7.4$ Hz, *1H*), 6.45 (d, $J = 7.4$ Hz, 1H), 5.84 (d, $J_{5''-6''} = 8.1$ Hz, 1H, H-5″), 5.74−5.68 (m, 2H, *H-5″*, aminalic H), 5.51 (t, $J_{9-8} = 5.9$ Hz, 1H, *aminalic H*), 4.82 (d, $J_{\text{gem NCH2}} = 12.8$ Hz, 1H, *benzylic H*), 4.73−4.61 (m, 3H, H-7, *benzylic H*), 4.11 (dd, $J_{\text{gem NCH2}} = 14.0$ Hz, $J_{8-9} = 6.2$ Hz, 1H, *NCH_2*), 3.99 (dd, $J_{\text{gem NCH2}} = 14.5$ Hz, $J_{\text{NCH2CH}} = 6.2$ Hz, 1H, NCH_2), 3.62 (dd, $J_{\text{gem NCH2}} = 14.5$ Hz, $J_{\text{NCH2CH}} = 6.6$ Hz, 1H, NCH_2), 3.58 (dd, $J_{\text{gem NCH2}} = 13.9$ Hz, $J_{\text{NCH2CH}} = 5.6$ Hz, 1H, *NCH_2*), 3.29 (s, 3H, OMe), 3.25 (s, 3H, *OMe*); ^{13}C NMR [$(CD_3)_2$-CO, 75 MHz] δ (ppm) 162.5 (C-4″), 151.3, 151.1 and 150.6 (C-2″, *C-2″*, C-4′, *C-4′*), 143.8, 143.6, 143.4 and 143.1 (C-1, *C-1*, C-1′, *C-1′*), 139.1 (CH-6″), 138.9 (*CH-6″*), 136.6 and 135.8 (C-2, *C-2*), 129.7, 129.4, 129.3, 129.1, 128.2, 127.9, 127.8, 124.5 and 124.3 (CH-aromatics), 102.9 (*CH-5″*), 102.8 (CH-5″), 84.3 (aminalic C), 83.8 (*aminalic C*), 59.9 (benzylic C, *benzylic C*), 55.9 (*OMe*), 55.8 (OMe), 53.9 (NCH_2), 53.8 (N*CH_2*); HR LSIMS calcd for $C_{20}H_{20}N_4O_8SNa$ $(M + Na)^+$ 499.0900, found 499.0900. Anal. Calcd for $C_{20}H_{20}N4O_8S\cdot 0.43H_2O$: C, 49.61; H, 4.34; N, 11.57; S, 6.62. Found: C, 50.02; H, 4.33; N, 11.33; S, 6.40.

10b: elution by flash chromatography EtOAc, or CH_2Cl_2/MeOH 10/0.4; R_f (10/0.5, CH_2Cl_2/MeOH) 0.13; white solid; mp 214−218 °C dec; yield 2%; (($CD_3)_2CO$/drops of CD_3OD, rt, isomer A (56%), *isomer B* (44%)) ^{1}H NMR ($CDCl_3$/drops of CD_3OD, 300 MHz) δ (ppm) 8.43 (d, $J_{3'-2'} = J_{5'-6'} = 8.8$ Hz, 4H, H-3′, 5′, *H-3′*, *5′*), 7.93 (d, $J_{2'-3'} = J_{6'-5'} = 8.9$ Hz, 2H, H-2′, 6′), 7.89 (d, $J_{2'-3'} = J_{6'-5'} = 8.8$ Hz, 2H, *H-2′*, *6′*), 7.69−7.65 (m, 1H, *1H*), 7.44−7.30 (m, 2H, *2H*), 7.19 (ddd, $J_1 = J_2 = 7.7$ Hz, $J_3 = 1.6$ Hz, 1H or *1H*), 7.15 (ddd, $J_1 = J_2 = 7.7$ Hz, $J_3 = 1.6$ Hz, 1H or *1H*), 6.74 (m, 1H, *1H*), 6.02 (bt, 1H), 5.92 (bt, *1H*), 5.56 (bd, $J = 7.6$ Hz, 1H), 5.43 (bd, $J = 7.6$ Hz, *1H*), 4.79−4.63 (m, 4H, benzylic H, *benzylic H*), 4.52 (dd, $J_{\text{gem NCH2}} = 14.3$ Hz, $J_{\text{NCH2CH}} = 6.3$ Hz, 1H, NCH_2), 4.41 (dd, $J_{\text{gem NCH2}} = 14.9$ Hz, $J_{\text{NCH2CH}} = 6.5$ Hz, 1H, *NCH_2*), 4.33 (dd, $J_{\text{gem NCH2}} = 14.8$ Hz, $J_{\text{NCH2CH}} = 5.2$ Hz, 1H, *NCH_2*), 4.23 (dd, $J_{\text{gem CH2}} = 14.2$ Hz, $J_{\text{NCH2CH}} = 5.4$ Hz, 1H, NCH_2), 3.17 (s, 3H, *OMe*), 3.12 (s, 3H, OMe); HR LSIM calcd for $C_{20}H_{20}N_4O_8SNa$ $(M + Na)^+$ 499.0900, found 499.0899. Anal. Calcd for $C_{20}H_{20}$-$N4O_8S$: C, 50.42; H, 4.23; N, 11.76; S, 6.73. Found: C, 50.32; H, 4.33; N, 11.48; S, 6.49.

Lewis Acid Mediated Reaction between (*RS*)-*N*-Acyl-3-methoxy-1,2,3,5-tetrahydro-4,1-benzoxazepines with 5-FU. Method F: Synthesis of (*RS*)-1-{2-[*N*-(2-Hydroxymethylphenyl)-benzamido]-1-methoxyethyl}-5-fluorouracil 7d. A suspension of **1d** (1 equiv) and 5-FU (1.2 equiv) in anhydrous MeCN (5 mL/mmol of **1d**) was prepared under argon. The mixture was cooled to 0 °C, and TMSCl (1.2 equiv) and HMDS (1.2 equiv) were then added dropwise. Still at 0 °C, $SnCl_4$ (a 1 M solution in CH_2Cl_2, 1.4 equiv) was slowly added. After removing the cooling bath, the temperature was allowed to reach rt and was maintained for 48 h. The reaction mixture was then cooled and diluted (H_2O), and solid $NaHCO_3$ was added until neutralization. The aqueous layer was then extracted, first with EtOAc, and second with CH_2Cl_2, and the organic layers were pooled, dried (Na_2SO_4), filtered, and evaporated under vacuum. The residue was purified by flash chromatography, EtOAc, or CH_2Cl_2/MeOH 10/0.4; R_f (10/0.3, CH_2Cl_2/MeOH) 0.25; light yellow solid; mp 137−138 °C; yield of **7d** 5%.

Method G: **Synthesis of 7d.** According to method F, the following conditions have been changed: $Sc(OTf)_3$ (0.6 equiv), 5-FU (1 equiv), TMSCl (1.0 equiv), HMDS (1.0 equiv), the temperature of addition of the reagents 0 °C, reaction temperature 40 °C, and reaction time 26 h. Yield of **7d**: 11%; ($CDCl_3$/drops of CD_3OD, rt, isomer A (50%), *isomer B* (50%)) ^{1}H NMR ($CDCl_3$/drops of CD_3OD, 300 MHz) δ (ppm) 7.48−6.94 (m, 19H, CH-aromatics), 6.70 (d, $J = 7.8$ Hz, 1H, CH-aromatic), 5.84 (pt, 2H, aminalic H, *aminalic H*), 4.57−4.47 (m, 3H, benzylic 1H or *benzylic 1H*, 1H of NCH_2, *1H of NCH_2*), 4.43 (d, $J_{\text{gem benzylic H}} = 13.2$ Hz, 1H, benzylic H or *benzylic H*), 4.35 (d, $J_{\text{gem benzylic H}} = 12.8$ Hz, 1H, benzylic H or *benzylic H*), 4.18 (d, $J_{\text{gem benzylic H}} = 13.2$ Hz, 1H, benzylic H or *benzylic H*), 3.77 (dd, $J_{\text{gem NCH2}} = 14.2$ Hz, $J_{8-9} = 7.1$ Hz, 1H, NCH_2 or *NCH_2*), 3.57 (dd, $J_{\text{gem NCH2}} = 14.2$ Hz, $J_{\text{NCH2CH}} = 4.7$ Hz, 1H, NCH_2 or *NCH_2*), 3.25 (s, 6H, OMe, *OMe*); ^{13}C NMR ($CDCl_3$/drops of CD_3OD, 75 MHz) δ (ppm) 171.8 and 171.5 (C-1′, *C-1′*), 157.6 (d, $J_{C-F} = 35.0$ Hz, C-4″ or *C-4″*), 157.4

(d, J_{C-F} = 35.3 Hz, C-4″ or *C-4″*), 150.4 and 150.3 (C-2″, *C-2″*), 141.2 (d, J_{C-F} = 315.4 Hz, C-5″ or *C-5″*), 140.9 (d, J_{C-F} = 316.2 Hz, C-5″ or *C-5″*), 140.4, 140.2, 137.7, 137.3 and 134.7 (C-1, *C-1*, C-2, *C-2*, C-2′, *C-2′*), 130.3, 130.2, 130.1, 129.4, 128.8, 128.7, 128.5, 128.4, 128.2, 128.1, 127.8 and 127.7 (CH-aromatics), 123.6 (d, J_{C-F} = 44.7 Hz, CH-6″ or *CH-6″*), 123.0 (d, J_{C-F} = 44.2 Hz, CH-6″ or *CH-6″*), 84.3 and 83.8 (OMe, *OMe*), 60.3 (benzylic C, *benzylic C*), 56.6 and 56.5 (OMe, *OMe*), 51.9 and 51.5 (NCH_2, *NCH_2*); HR LSIMS calcd for $C_{21}H_{20}N_3O_5FNa$ $(M + Na)^+$ 436.1285, found 436.1285. Anal. Calcd for $C_{21}H_{20}N3O_5F$: C, 61.01; H, 4.88; N, 10.16. Found: C, 61.27; H, 4.85; N, 10.35.

Method H: Synthesis of (*RS*)-1-{1-Methoxy-2-[2-(methoxymethyl)phenylamino]ethyl}-5-fluorouracil 11. According to method F, the following conditions have been changed: $SnCl_4$ (3.0 equiv), TMSCl (3.0 equiv), HMDS (3.0 equiv), addition temperature of the reagents 0 °C, reaction temperature rt, and reaction time 54 h. **11**: 16% yield; elution by flash chromatography EtOAc/hexane 1/1.5, or CH_2Cl_2/MeOH 10/0.5; R_f (1/1, EtOAc/hexane) 0.29; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.40 (bs, 1H, NH-3″), 7.46 (d, $J_{6''-F}$ = 5.9 Hz, 1H, H-6″), 7.21 (ddd, $J_1 = J_2$ = 7.8 Hz, J_3 = 1.6 Hz, 1H), 7.05 (bs, J = 7.1 Hz, 1H), 6.73−6.67 (m, 2H), 5.74 (dt, J_{NCH2CH} = 5.0 Hz, $J_{aminalic\ CH-F}$ = 1.7 Hz, 1H, aminalic H), 5.10 (bs, 1H, N*H*), 4.44 (s, 2H, benzylic H), 3.48 (dd, J_{NCH2CH} = 4.9 Hz, J_{CH2-NH} = 2.1 Hz, 2H, NCH_2), 3.42 and 3.30 [2s, 6H, aminalic and benzylic OMe groups]; ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 156.5 (d, J_{C-F} = 27.3 Hz, C-4″), 149.3 and 146.6 (C-2″, C-1), 140.8 (d, J_{C-F} = 237.6 Hz, C-5″), 130.4, 129.8, 117.6 and 110.5 (CH-3, CH-4, CH-5, CH-6), 123.4 (d, J_{C-F} = 33.3 Hz, CH-6″), 122.1 (C-2), 86.0 (aminalic C), 74.1 (benzylic C), 57.6 and 57.3 (aminalic OMe, benzylic MeO), 46.5 (NCH_2); ^{19}F NMR ($CDCl_3$, 280 MHz, ref $CFCl_3$) δ (ppm) −164.5 (pt); HR LSIMS calcd for $C_{15}H_{18}N_3O_4FNa$ $(M + Na)^+$ 346.1179, found 346.1179. Anal. Calcd for $C_{15}H_{18}N_3O_4F$: C, 55.72; H, 5.61; N, 13.00. Found: C, 56.02; H, 5.73; N, 13.12.

Elimination of the 4-Nitrobenzenesulfonamide Moiety: Synthesis of (*RS*)-1-[2-(2-Hydroxymethylphenylamino)-1-methoxyethyl]-5-fluorouracil 26. A solution of **7b** (1 equiv) was prepared in DMF (5 mL/mmol of **7b**), and then K_2CO_3 (3 equiv) and thiophenol (1.1 equiv) were added. The reaction was stirred at room temperature for 2.5 h. The reaction mixture was then diluted with water and the aqueous layer extracted with CH_2Cl_2 and EtOAc. The organic layers were pooled, dried (Na_2SO_4), filtered, and evaporated under vacuum. The residue was purified by flash chromatography using mixtures of using EtOAc as eluant or mixtures of CH_2Cl_2/MeOH 10/0.14: R_f (10/0.2, CH_2Cl_2/MeOH) 0.13; white solid; mp 87−87.4; yield of **27** 41%; ^{1}H NMR ($CDCl_3$/drops CD_3OD, 300 MHz) δ (ppm) 10.00 (bs, 1H, NH-3″), 7.44 (d, $J_{6''-F}$ = 5.8 Hz, 1H, H-6″), 7.19 (ddd, $J_1 = J_2$ = 7.7 Hz, J_3 = 1.3 Hz, 1H), 7.03 (dd, J_1 = 7.3 Hz, J_2 = 1.5 Hz, 1H), 6.70−6.64 (m, 2H), 5.73 (m, 1H, aminalic H), 5.20 (bs, 1H, N*H*), 4.61 (d, $J_{gem\ benzylic\ H}$ = 12.8 Hz, 1H, benzylic H), 4.55 (d, $J_{gem\ benzylic\ H}$ = 12.3 Hz, 1H, benzylic H), 3.54−3.42 (m, 2H, NCH_2), 3.40 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$/drops CD_3OD, 100 MHz) δ (ppm) 150.1 and 146.4 (C-2″, C-1), 141.1 (d, J_{C-F} = 236.9 Hz, C-5″), 129.6, 117.6 and 110.6 (CH-3, CH-4, CH-5, CH-6), 124.8 (C-2), 123.3 (d, J_{C-F} = 33.4 Hz, CH-6″), 85.9 (CH-9), 64.2 (benzylic C), 57.4 (OMe), 46.5 (NCH_2); HR LSIM calcd for $C_{14}H_{17}N_3O_4F$ $(M + H)^+$ 310.1203, found 310.1203. Anal. Calcd for $C_{14}H_{16}N_3O_4F \cdot 0.07H_2O$: C, 54.14; H, 5.24; N, 13.53. Found: C, 54.54; H, 5.20; N, 13.57.

Method I: Synthesis of 4,5-Dihydro-1,4-benzoxazepine 12 and (*RS*)-1-{2-[*N*-(2-Hydroxyphenylmethyl)-*N*-trifluoroacetylamino]-1-methoxyethyl}-5-fluorouracil 13. The procedure was similar to method A, but changing the quantities of the reagents: the starting *O*,*O*-acetal was **2**, TMSCl (1.2 equiv), HMDS (1.2 equiv), 5-FU (1.2 equiv). The suspension was cooled to 0 °C before the addition of $SnCl_4$ (1.4 equiv, 1 M in CH_2Cl_2). The temperature reached rt, and the reaction time was 70 h. The residue was purified by flash chromatography under gradient elution conditions using mixtures of CH_2Cl_2/MeOH from 125/1 to 150/1, and the isolation of two compounds was achieved: **12** (55% yield, elution with CH_2Cl_2/MeOH 125/1; white solid; mp 170.3−172.3 °C; R_f (EtOAc/hexane 1/1 = 0.52) and **13** (33% yield, elution with MeOH/CH_2Cl_2 1/150; white solid; mp 202−203 °C; R_f (EtOAc/hexane 1/1 = 0.26). **12:** ^{1}H NMR [$(CD_3)_2CO$, 400 MHz] δ (ppm) 8.98 (s, 1H, N*H*), 7.32 (d, J = 0.7 Hz, 1H), 7.22 (ddd, $J_1 = J_2$ = 9.0 Hz, J_3 = 1.6 Hz, 1H), 7.08 (s, 1H), 6.97 (m, 2H), 6.87 (t, J = 7.4 Hz, 1H), 5.40 (s, 2H, H-5); ^{13}C NMR [$(CD_3)_2CO$, 100 MHz] δ (ppm) 155.74 (C-9a), 130.51, 129.75, 129.04, 125.42, 120.69 and 116.14 (CH-2, CH-3, CH-6, CH-7, CH-8, CH-9), 123.20 (C-5a), 46.57 (CH_2-5); HR LSIMS calcd for C_9H_9NO 147.0684, found 147.0684.

13: (CD_3OD, rt, isomer A (80%), *isomer B* (20%)) ^{1}H NMR (CD_3OD, 400 MHz) δ (ppm) 7.73 (d, $J_{6''-F}$ = 6.2 Hz, 1H, H-6″), 7.67 (d, $J_{6''-F}$ = 6.3 Hz, 1H, *H-6″*), 7.21−7.14, 7.09−7.07, 6.88−6.81 (m, *4H*, 4H), 5.90−5.87 (ddd, 2H, *aminalic H*, aminalic H), 4.79−4.67 (m, 3H, *2 benzylic Hs*, 1H, benzylic H), 3.79−3.74 (m, 3H, *NCH_2*, benzylic H, NCH_2), 3.61 (dd, $J_{gem\ NCH2}$ = 14.2 Hz, J_{NCH2CH} = 4.4 Hz, 2H, *NCH_2*, NCH_2), 3.35 (s, 6H, *OMe*, OMe); ^{13}C NMR (CD_3OD, 100 MHz) δ (ppm) 160.2 (*C-1′*), 159.3 (d, J_{C-F} = 35.8 Hz, *C-4″*, C-4″), 156.9, 151.6 and 151.3 (*C-2″*, C-2″, *C-1*, C-1), 142.6 (d, J_{C-F} = 233.4 Hz, C-5″), 142.3 (d, J_{C-F} = 233.4 Hz, *C-5″*), 131.2, 130.4, 120.7 and 116.2 (CH-2, CH-3, CH-4, CH-5), 130.7, 129.9, 121.0 and 116.4 (*CH-2*, *CH-3*, *CH-4*, *CH-5*), 124.6 (d, J_{C-F} = 33.0 Hz, *CH-6″*), 124.3 (d, CH-6″), 121.9 (*C-6*), 117.9 (q, J_{C-F} = 285.1 Hz, *C-2′*) 86.2 (aminalic C), 84.8 (*aminalic C*), 57.4 (OMe), 57.4 (*OMe*), 50.3, 47.8 and 47.8 (*CH_2*); HR LSIMS calcd. for $C_{16}H_{15}N_3O_5F_4Na$ $(M + Na)^+$ 428.0846, found 428.0846. Anal. Calcd for $C_{17}H_{17}F_4N_3O_5$: C, 48.69; H, 4.09; N, 10.02. Found: C, 48.71; H, 4.13; N, 10.06.

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