An Efficient Synthesis of a New Series of Acyclonucleosides Starting from β-Amino Alcohols

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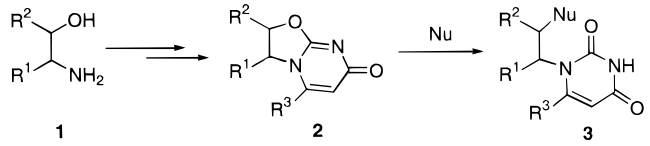
A series of new acyclonucleosides analogues **3** has been synthesized very efficiently in three steps starting from β-amino alcohols **1**. The key step of this process is a nucleophilic substitution with various nucleophiles on 2,2′-anhydronucleosides **2**. The chemo- and stereoselectivities of this reaction are discussed. AM1 calculations sustained the observed chemoselectivity.

Introduction

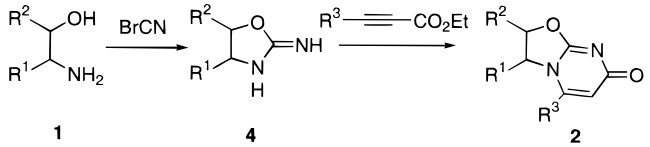
Considerable interest in the synthesis of nucleoside analogues stems from their antiviral and antitumoral activities.[1] Sugar-modified nucleosides have assumed a major role since the development of AZT in HIV chemotherapy. Removal of the furanose moiety leading to a simplification of the structures led to new therapeutic antiviral agents. Thus, the emergence of Acyclovir[2] as a successful agent has stimulated the synthesis of acyclic nucleosides,[3] and much effort has been devoted to broaden our knowledge of this new class of nucleosides. Majority of reactions concerning the synthesis of such acyclonucleosides had been made by regioselective *N*-alkylations of the purine ring system.[4] We have developed a more convergent method starting from β-amino alcohols[5] (Scheme 1) that allows the efficient synthesis of a great variety of nucleosides **3**.

Pyrimidinones **2** could be used as synthons to produce new classes of acyclonucleosides by reaction with the appropriate nucleophiles. Moreover, this synthesis allows the introduction of a substituent on C-6 of the uracil ring. An analogous method, involving an intermediate similar to **2**, had already been reported in the ribonucleoside series.[6]

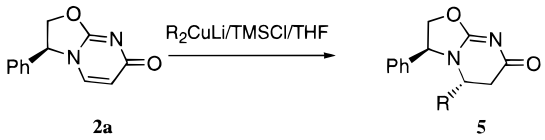
Scheme 1



Scheme 2



Scheme 3



Herein we report full details about the preparation of pyrimidinones **2** and about their reactions with various nucleophiles and the stereo- and chemoselective transformations into pyrimidines **3**.

Results

Synthesis of Pyrimidinones 2. Pyrimidinones **2** were synthesized by the following two-step sequence: (i) reaction between β-amino alcohols **1** and cyanogen bromide[7] affording compounds **4** in quantitative yields, (ii) condensation of these heterocycles with ethyl propiolate or ethyl butynoate to form bicyclic compounds **2** (Scheme 2).

Nucleophilic Opening of Pyrimidinones 2. We have already reported that synthons **2a** react stereoselectively at the C-6 site of the uracil ring with different organocuprate reagents (Scheme 3), leading to alkylated compounds **5**. These heterocycles eventually were transformed into pure β-amino acids.[8]

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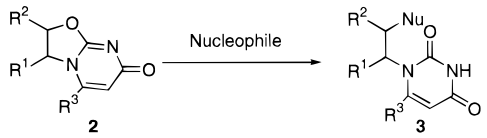
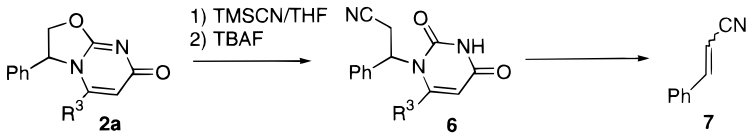
Table 1



entry	substrate	R^1	R^2	R^3	conditions	product	yield (%)	Nu
1	**2a**	Ph	H	H	TMSCl/THF	**3a**	80	Cl
2	**2a**	Ph	H	H	MeOH/PTSA	**3b**	87	OMe
3	**2a**	Ph	H	H	H_2O/THF/PTSA	**3c**	91	OH
4	**2a**	Ph	H	H	$TMSN_3$/TBAF	**3d**	95	N_3
5	**2a**	Ph	H	H	TMSCN/TBAF	/	/	/
6	**2b**	Ph	H	Me	TMSCl/THF	**3e**	78	Cl
7	**2c**	Me	Ph	H	TMSCl/THF	**3f**	79	Cl
8	**2c**	Me	Ph	H	H_2O/THF/PTSA	**3g**	78	OH
9	**2c**	Me	Ph	H	MeOH/PTSA	**3h**	95	OMe
10	**2d**	H	Me	H	TMSCl/THF	**3i**	85	Cl

Scheme 4



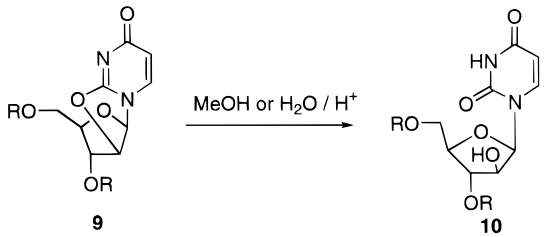
Perusal of the literature showed that 2,2′-anhydronucleosides, whose heterocyclic core corresponds to pyrimidinones **2**, can be substituted with nucleophiles such as azide[9] and halide ions.[10] To obtain functionalized pyrimidines **3**, we investigated the reactivity of compounds **2** with such nucleophiles. To this aim, H_2O, MeOH, and trimethylsilyl chloride, azide, and cyanide were reacted with pyrimidinones **2** (Table 1).

All nucleophiles, except cyanide ion from TMSCN, react in acidic conditions to afford functionalized pyrimidines **3** in good yields. These nucleophilic substitutions are chemo- and diastereoselective as well. Substrate **2c**, which possesses a stereocenter at the reaction site (C-2′), reacts with three different nucleophiles (entries 7−9) in a completely stereoselective way: each product was obtained as a unique diastereomer. The reactions with trimethylsilyl derivatives were completed in 2 h at room temperature (entries 1, 4, 6, 7, 10) but needed 12 h at reflux under solvolytic conditions (entries 2, 3, 8, 9). When trimethylsilyl cyanide was used as a nucleophile (entry 5), the substitution took place but the resulting product **6** was unstable and underwent a β-elimination to afford cinnamonitrile **7** (Scheme 4).

It is noteworthing that when trimethylsilyl cyanide and azide were used without addition of tetrabutylammonium fluoride (TBAF), no reaction occurs.[11]

Structure of Pyrimidines 3. The chemoselectivity of the reaction in acidic solvolysis was surprising. Hydrolysis and methanolysis of compound **2c** afforded, respectively, optically pure derivatives **3g** and **3h**, i.e., the nucleophile attack occurred exclusively at the C-2′ site (Scheme 6). In the ribonucleoside series, many authors reported that 2,2′anhydronucleosides **9** were cleaved with an inverse chemoselectivity (i.e., attack on C-2 leading to products **10**) (Scheme 5).[12]

Scheme 5



To further scrutinize the regiochemical outcome of these hydrolytic reactions, we performed similar nucleophilic substitutions in basic media. The chemoselectivity was inverted: in water ($NaOH/H_2O$) as well as in methanol (MeONa/MeOH) the same hydroxylic compound **3j** was obtained. This compound results from an addition of the nucleophile on the C-2 center followed by hydrolysis. Such addition−elimination reactions at C-2 of 2,2′-anhydronucleosides by a variety of basic nucleophiles (^-OH, NH_2, ^-SH, dithiane anions) are well-known.[13] Structures of compounds **3g** and **3j** were ascertained because they afford ethers **3h** and **3k** when they are methylated in THF by using sodium hydride as the base and methyl iodide as the methylating agent (Scheme 6). Compound **3h** was also obtained directly via an acidic methanolysis of **2c**.

Structures of compound **3h** and **3k** and thereby **3g** and **3j** shows clearly that the stereochemical outcome of the reaction in acidic mediums involves an inversion of configuration at C-2′. It seems likely that the same stereochemistry should be observed in the reaction with trimethylsilyl derivatives as nucleophiles.

Summing up our results in acidic conditions, the conversion of pyrimidinones **2** into pyrimidines **3** can be

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(11) When TBAF was added prior to trimethylsilylcyanide or azide, substrate **2a** led quickly to a compound which resulted from a β-elimination.

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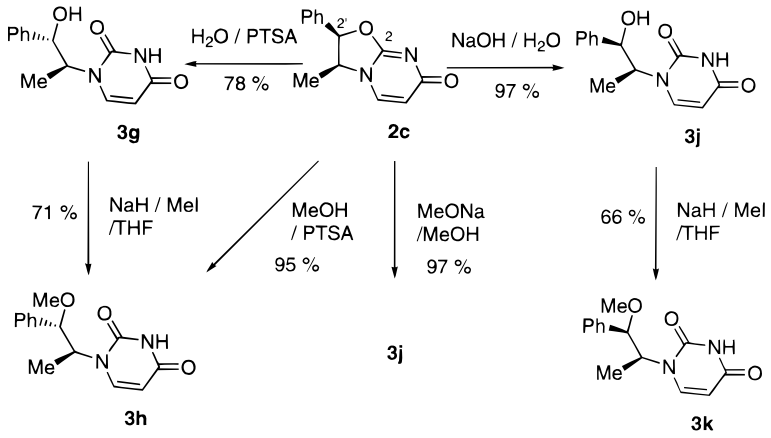
Scheme 6



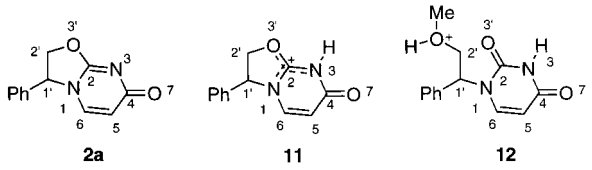


Figure 1.

interpreted as an N-3 protonation followed by a selective C-2′—O rather than C-2—O bond cleavage. This mechanism is sustained by AM1 calculations indicating that cation **11** (Figure 1) showing that N-3 protonation is favored over N-1, O-7, or O-3′ protonation since it leads to the more-stabilized cation. This cation could react with a nucleophile either at C-2 or C-2′. Calculations show that the former attack is the preferred one. Addition on C-2 would lead to a highly energetic intermediate (133 kcal mol^{-1}) whereas nucleophilic substitution at C-2′ affording intermediate **12** (Figure 1) needs an activation energy equal to only 26.2 kcal mol^{-1}. This transition state shows parameters that are characteristic of an S_N2 process (bond orders for Me—O—C-2′, for C—2′—OC-2 and for C—2′O—C-2 equal to 0.377, 0.212, 1.521, respectively).

On the other hand, the reaction of methoxy anion on substrate **2a** shows that, in basic medium, addition on C-2 is preferred to substitution on C-2′. AM1 calculations show that the addition—elimination process involves a transition state whose energy is lower compared to the substitution pathway $\Delta(E_a) = 2.2$ kcal mol^{-1}.

In summary, a concise and practical synthesis of pyrimidines **3** has been developed starting from *β*-amino-alcohols. This procedure has a wide scope and should allow for the synthesis of a large variety of acyclonucleosides.

From a mechanistic point of view, AM1 calculations are consistent with the observed results indicating that, in acidic conditions, S_N2 is operating on C-2′ and that, in basic medium, addition on C-2 is observed.

Experimental Section

General Methods. ^{1}H NMR and ^{13}C NMR spectra ($CDCl_3$ solutions unless otherwise stated) were carried out at 250 and 62.9 MHz. Column chromatography was performed on silica gel 230—400 mesh with various mixtures of ethyl acetate (AcOEt) and methanol (MeOH). Tetrahydrofuran was distilled from benzophenone ketyl.

The geometries of the initial states were optimized by using the Davidson—Fletcher—Powell algorithm (FLEPO procedure), minimizing the energy with respect to all internal coordinates. Approximative transition states were obtained from the energy profiles in a reaction path (the reaction coordinates being the distance between the carbon atom of C2′-0 or C2—O and the reactive oxygen of MeO^- and MeOH; then the transition states were optimized by minimizing the energy gradient (NLLSQ procedure).

General Procedure for the Preparation of Pyrimidinones 2. To a stirred solution of *β*-amino alcohol **1** (13.2 mmol) in EtOH (50 mL) was added, over a period of 5 min, cyanogen bromide (2.8 g, 21.7 mmol). After 6 h at reflux, EtOH was removed under reduced pressure, replaced with a aqueous solution of NaOH (50 mL, 1 M), and extracted twice with CH_2Cl_2 (50 mL). The organic layer was washed with water, dried over $MgSO_4$, and evaporated under reduced pressure. To a stirred solution of the obtained intermediate **4** in EtOH (50 mL) was added ethyl propiolate or ethyl butynoate (14.5 mmol). After 12 h at reflux, the reaction mixture was concentrated under reduced pressure, and CH_2Cl_2 was added and washed with water, dried over $MgSO_4$, and removed under reduced pressure. The solid obtained was washed with 20 mL of hot EtOAc and filtered of to afford pyrimidinones **2** as white solids.

3-Phenyl-2,3-dihydrooxazolo[3,2-*a*]pyrimidin-7-one (2a): 70.5% yield, ^{1}H NMR ($CDCl_3$) δ 4.49 (dd, J = 7.8, 9.2 Hz, 1H), 5.01 (t, J = 9.2 Hz, 1H), 5.53 (dd, J = 7.8, 9.2 Hz, 1H), 5.95 (d, J = 7.5 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 7.27 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 61.8, 73.9, 109.8, 127.0, 129.7, 130.0, 135.0, 135.8, 160.9, 175.0. HRMS calcd for $C_{12}H_{10}O_2N_2 + H^+$ m/z 215.0821, obs m/z 215.0816.

9-Methyl-3-phenyl-2,3-dihydrooxazolo[3,2-*a*]pyrimidin-7-one (2b): 72% yield, ^{1}H NMR ($CDCl_3$) δ 1.85 (s, 3H), 4.40 (dd, J = 4.0, 8.9 Hz, 1H), 5.06 (t, J = 8.9 Hz, 1H), 5.62 (dd, J = 4.0, 8.9 Hz, 1H), 5.70 (s, 1H), 7.27 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 17.8, 60.5, 73.8, 108.2, 125.8, 128.9, 129.6, 137.5,147.6, 161.5, 172.7.

(3*S*)-Methyl-(2*R*)-phenyl-2,3-dihydrooxazolo[3,2-*a*]pyrimidin-7-one (2c): 76.% yield, ^{1}H NMR ($CDCl_3$) δ 1.01 (d, J = 6.5 Hz, 3H), 4.76 (m,1H), 6.04 (d, J = 8.2 Hz, 1H), 6.11 (d, J = 7.2 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 7.30 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 16.5, 58.0, 83.4, 110.5, 126.5, 129.3, 129.4, 133.0, 136.1, 162.0, 173.0. $[\alpha]^{25}_D$: −305 (*c* 0.85, $CHCl_3$). HRMS calcd for $C_{13}H_{12}O_2N_2 + H^+$ m/z, 229.0977obs m/z 229.0979.

2-Methyl-2,3-dihydrooxazolo[3,2-*a*]pyrimidin-7-one (2d): 38.% yield, ^{1}H NMR ($CDCl_3$) δ 1.54 (d, J = 8.5 Hz, 3H), 3.74 (dd, J = 7.7, 9.5 Hz, 1H), 4.28 (dd, J = 8.5, 9.5 Hz, 1H,), 5.05 (m,1H), 5.95 (d, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 20.4, 53.1, 76.2, 110.3, 136.4, 171.1, 175.2. HRMS calcd for $C_7H_8O_2N_2 + H^+$ m/z 153.0664, obs m/z 153.0664.

General Procedure for the Acidic Hydrolysis: Preparation of Pyrimidine 3c and 3g. To a stirred solution of pyrimidinones **2a** or **2c** (0.438 mmol) in a 1:1 mixture of THF and H_2O (4 mL) was added *p*-toluenesulfonic acid (100 mg, 0.581 mmol). After 12h at reflux, CH_2Cl_2 was added, and the

organic layer was washed with an aqueous saturated solution of $NaHCO_3$, dried over $MgSO_4$, and evaporated under reduced pressure. Flash chromatography (MeOH/ethyl acetate 1/99) of the residue afforded pyrimidines **3c** and **3g** as white solids.

1-(2-Hydroxy-1-phenylethyl)-1*H*-pyrimidine-2,4-dione (3c): 91% yield, ^{1}H NMR ($CDCl_3$) δ 4.21 (m, 2H), 5.54 (d, J = 8 Hz, 1H), 5.85 (m, 1H), 7.15 (d, J = 8 Hz, 1H), 7.30 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 59.5, 62.0, 102.1, 128.0, 128.7, 129.2, 135.7, 142.9, 152.0, 163.7. HRMS calcd for $C_{12}H_{12}O_3N_2 + H^+$ m/z 233.0926, obs m/z 233.0920.

1-((2*S*)-Hydroxy-(1*S*)-methyl-2-phenylethyl)-1*H*-pyrimidine-2,4-dione (3g): 78% yield, ^{1}H NMR ($CDCl_3$) δ 0.9 (d, J = 7.2 Hz, 3H), 2.74 (brs,1H), 4.86 (m, 2H), 5.02 (m, 1H), 5.66 (d, J = 5.0 Hz,1H), 7.33 (m,6H), 8.75 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 15.8, 60.9, 78.3, 104.9, 130.0, 131.7, 132.4, 145.7, 147.8, 155.0, 168.0. $[\alpha]^{25}_D$: +13 (*c* 0.3, MeOH). HRMS calcd for $C_{13}H_{14}O_3N_2 + H^+$ m/z 247.1083, obs m/z 247.1078.

General Procedure for the Basic Hydrolysis: Preparation of Pyrimidine 3j. To a stirred solution of pyrimidinones **2c** (100 mg, 0.438 mmol) in a 1:1 mixture of THF and H_2O (4 mL) was added NaOH as solid (26 mg, 0.650 mmol). After 1 h at room temperature, CH_2Cl_2 was added, and the organic layer was washed with an aqueous saturated solution of NH_4Cl, dried over $MgSO_4$, and evaporated under reduced pressure. Flash chromatography (MeOH/ethyl acetate 1/99) of the residue afforded pyrimidines **3j** as white solids (105 mg).

1-((2*R*)-Hydroxy-(1*S*)-methyl-2-phenylethyl)-1*H*-pyrimidine-2,4-dione (3j): 97% yield, ^{1}H NMR ($CDCl_3$) δ 0.9 (d, J = 7.2 Hz, 3H), 2.74 (brs,1H), 4.86 (m, 2H), 5.66 (d, J = 5 Hz,1H), 7.33 (m,5H), 8.75 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 15.8, 60.9, 78.3, 104.9, 130.0, 131.7, 132.4, 145.7, 147.8, 155.0, 168.0. $[\alpha]^{25}_D$: −25 (*c* 0.7, $CHCl_3$).

General Procedure for the Acidic Methanolysis: Preparation of Pyrimidine 3b and 3h. To a stirred solution of pyrimidinones **2a** and **2c** (0.438 mmol) in MeOH (4 mL) was added *p*-toluenesulfonic acid (100 mg, 0.581 mmol). After 12 h at reflux, MeOH was evaporated under reduced pressure, CH_2Cl_2 was added, and the organic layer was washed with an aqueous saturated solution of $NaHCO_3$, dried over $MgSO_4$, and evaporated under reduced pressure. Flash chromatography (MeOH/ethyl acetate 1/99) of the residue afforded pyrimidines **3b** and **3h** as white solids.

1-(2-Methoxy-1-phenylethyl)-1*H*-pyrimidine-2,4-dione (3b): 87.% yield, ^{1}H NMR ($CDCl_3$) δ 3.35 (s, 3H), 3.85 (dd, J = 5.2, 10.7 Hz, 1H), 3.96 (dd, J = 5.2, 10.7 Hz, 1H), 5.56 (d, J = 8.1 Hz, 1H), 5.88 (t, J = 5.2 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H), 7.28 (m, 5H), 8.9 (brs, 1H).^{13}C NMR ($CDCl_3$) δ 57.0, 59.2, 71.7 101.7, 127.9, 128.6, 129.1, 136.5, 142.9, 150.5, 163.5.

1-((2*S*)-Methoxy-(1*S*)-methyl-2-phenylethyl)-1*H*-pyrimidine-2,4-dione (3h): 95% yield, ^{1}H NMR ($CDCl_3$) δ 1.18 (d, J = 5.0 Hz, 3H), 3.21 (s, 3H), 4.33 (d, J = 2.5 Hz,1H), 4.72 (m,1H,), 5.62 (d, J = 7.5 Hz,1H), 7.25 (m, 5H), 7.40 (d, J = 7.5 Hz,1H), 9.2 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 12.2, 56.3, 57.9, 84.9, 101.7, 126.9, 128.5, 129.0, 138.1, 142.9, 151.5, 163.8. Anal. Calcd for $C_{14}H_{16}O_3N_2$ C, 64.60; H, 6.20; N, 10.76. Found C, 64.70; H, 6.20; N, 10.59.

1-((2*R*)-Methoxy-(1*S*)-methyl-2-phenylethyl)-1*H*-pyrimidine-2,4-dione (3k). To a stirred solution of pyrimidinones **3j** (100 mg, 0.438 mmol) in THF (4 mL) were added NaH (32 mg, 0.880 mmol) and methyl iodide (0.038 mL, 0.600 mmol). After 12 h at room temperature, CH_2Cl_2 was added, and the organic layer was washed with an aqueous saturated solution of NH_4Cl, dried over $MgSO_4$, and evaporated under reduced pressure. Flash chromatography (MeOH/ethyl acetate 1/99) of the residue afforded pyrimidines **3k** (71 mg, 66% yield) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.27 (d, J = 6.2 Hz, 3H), 3.29 (s,3H), 4.41 (d, 1H), 4.79 (m, 1H), 5.70 (d, J = 8.2 Hz, 1H), 7.32 (m, 5H), 7.48 (d, J = 8 Hz, 1H), 9.2 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 16.3, 57.7, 60.8, 85.2, 101.9, 127.3, 128.8, 129.0, 137.8, 143.1, 151.4, 163.8. $[\alpha]^{25}_D$: −31 (*c* 0.32, MeOH).

General Procedure for the Reaction of Pyrimidinones 2 with TMSCl. To a stirred solution of pyrimidinones **2** (0.703 mmol) in THF (8 mL) was added TMSCl (0.178 mL, 1.408 mmol). After 2 h at room temperature, CH_2Cl_2 was added, and the organic layer was washed with an aqueous saturated solution of $NaHCO_3$, dried over $MgSO_4$, and evaporated under reduced pressure. Flash chromatography (MeOH/ethyl acetate 1/99) of the residue afforded pyrimidines **3a, 3e, 3f, 3i** as white solids

1-(2-Chloro-1-phenylethyl)-1*H*-pyrimidine-2,4-dione (3a): 80% yield, ^{1}H NMR ($CDCl_3$) δ 4.10 (m, 2H), 5.63 (d, J = 8.2 Hz,1H), 5.93 (t, J = 7.2 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 7.30 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 43.2, 59.1, 102.5, 127.5, 129.2, 129.4, 134.7, 141.7, 151.2, 163.1. Anal. Calcd for $C_{12}H_{11}ClO_2N_2$ C, 57.49; H, 4.42; N, 11.17. Found C, 57.20; H, 4.71; N, 10.43.

1-(2-Chloro-1-phenylethyl)-6-methyl-1*H*-pyrimidine-2,4-dione (3e): 78% yield, ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H), 4.18 (dd, J = 5,0, 11.2 Hz, 1H), 4.75 (dd, J = 8.9, 11.2 Hz, 1H), 5.30 (brs, 1H), 5.55 (s, 1H), 7.29 (m, 5H), 8.8 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 20.7, 43.0, 61.1, 102.3, 126.0, 127.9, 128.2, 135.3, 150.1, 153.6, 161.9.

1-((2*R*)-Chloro-(1*S*)-methyl-2-phenylethyl)-1*H*-pyrimidine-2,4-dione (3f): 79% yield, ^{1}H NMR ($CDCl_3$) δ 1.20 (d, J = 8 Hz, 3H), 5.10 (brs, 1H), 5.20 (m, 1H), 5.65 (d, J = 7.5 Hz, 1H), 7.07 (d, J = 7.5 Hz, 1H), 7.28 (m, 5H), 9.0 (brs, 1H). ^{13}C NMR ($CDCl_3$). δ 16.8, 53.5, 64.6, 102.7, 128.1, 129.4, 129.7, 137.3, 163.4, 166.6. $[\alpha]^{25}_D$: +432 (*c* 0.48, MeOH). HRMS calcd for $C_{13}H_{13}ClO_2N_2 + H^+$ m/z 265.0744, obs m/z 265.0753.

1-(2-Chloropropyl)-1*H*-pyrimidine-2,4-dione (3i): 85% yield, ^{1}H NMR ($CDCl_3$) δ 1.52 (d, J = 6.8 Hz, 3H), 3.44 (dd, J = 9.2, 14.2 Hz, 1H), 4.21 (dd, J = 3.2, 14.2 Hz, 1H), 4.32 (m, 1H), 5.64 (d, J = 7.5 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 22.7, 55.7, 56.9, 102.2, 145.9, 151.4, 164.2.

1-(2-Azido-1-phenylethyl)-9-methyl-1*H*-pyrimidine-2,4-dione (3d). To a stirred solution of pyrimidinones **2a** (0.703 mmol) in THF (4 mL) was added $TMSN_3$ (0.123 mL, 0.934 mmol) and TBAF (0.70 mL of a 1 M solution in THF, 0.700 mmol). After 24 h at room temperature, CH_2Cl_2 was added, and the organic layer was washed with an aqueous saturated solution of $NaHCO_3$, dried over $MgSO_4$, and evaporated under reduced pressure. Flash chromatography (MeOH/ethyl acetate 1/99) of the residue afforded pyrimidines **3d** (103 mg, 95% yield) as white solids: ^{1}H NMR ($CDCl_3$) δ 4.05 (m, 2H), 5.70 (d, J = 7.5 Hz, 1H), 5.92 (t, J = 5.0 Hz, 1H), 7.07 (d, J = 7.5 Hz, 1H), 7.35 (m, 5H), 9.18 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 52.0, 57.5, 103.1, 128.2, 129.6, 129.8, 135.2, 142.1, 151.5, 163.3. HRMS calc. For $C_{12}H_{11}O_2N_5 + H^+$ m/z 258.0991, obs m/z 258.0987.

Supporting Information Available: Spectrometric information (^{1}H NMR) for compounds **2a**,**b**, **3a**−**d**, **3e**−**k** and ^{13}C NMR for compounds **2a**−**d**, **3c**−**e**, **3g**−**k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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