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## Nucleosides, Nucleotides and Nucleic Acids

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### Simplified Analogues of Acyclonucleosides. Synthesis of 6-[N-Alkyl-N-(4-hydroxybutyl)amino]pyrimidine Derivatives

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**SIMPLIFIED ANALOGUES OF ACYCLONUCLEOSIDES.  
SYNTHESIS OF 6-[N-ALKYL-N-(4-  
HYDROXYBUTYL)AMINO]PYRIMIDINE DERIVATIVES<sup>§</sup>**

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**Abstract.** *The synthesis of some 6-alkylaminopyrimidine derivatives bearing a 4-hydroxybutyl chain as sugar mimic is described. These new compounds can be regarded as simplified, ring-opened analogues of purine acyclonucleosides.*

The finding that a retrovirus, known as the human immunodeficiency virus (HIV), is the causative agent of the acquired immune deficiency syndrome (AIDS) has been spurring a great deal of searches for new selective anti-HIV agents,<sup>1</sup> leading in particular to the discovery of a myriad of HIV reverse transcriptase (RT) inhibitors. These include a wide array of nucleoside and non-nucleoside compounds, antisense oligonucleotides, and both small and large anionic molecules.<sup>2</sup>

The most well-known and intensively studied HIV RT inhibitors are the nucleoside derivatives.<sup>3</sup> Three representatives of this group, 3'-azido-2',3'-dideoxythymidine (AZT), 2',3'-dideoxyinosine (DDI) and 2',3'-dideoxycytidine (DDC) are the only federally licensed antivirals in U.S.A. for the treatment of AIDS (FIG. 1). However, the demonstrated clinical toxicities of these agents and other members of this class, the emergence of resistance to these agents, and their inability to cure AIDS have propelled the search for different classes of RT inhibitors. Unique among these are 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) and its analogues.<sup>4</sup> Although structurally related to the nucleoside antivirals, HEPT agents exert their anti-HIV-1 activity by interacting with HIV-1 RT at a site that is distinct from the binding site of the anti-HIV-1 nucleosides.<sup>5</sup> In addition, it is remarkable that the RT inhibitory activity of HEPT analogues is associated to the presence of substituents in positions 5 and 6 of the uracil,

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<sup>§</sup>Dedicated to Professor Marino Artico on the occasion of his 60th birthday.

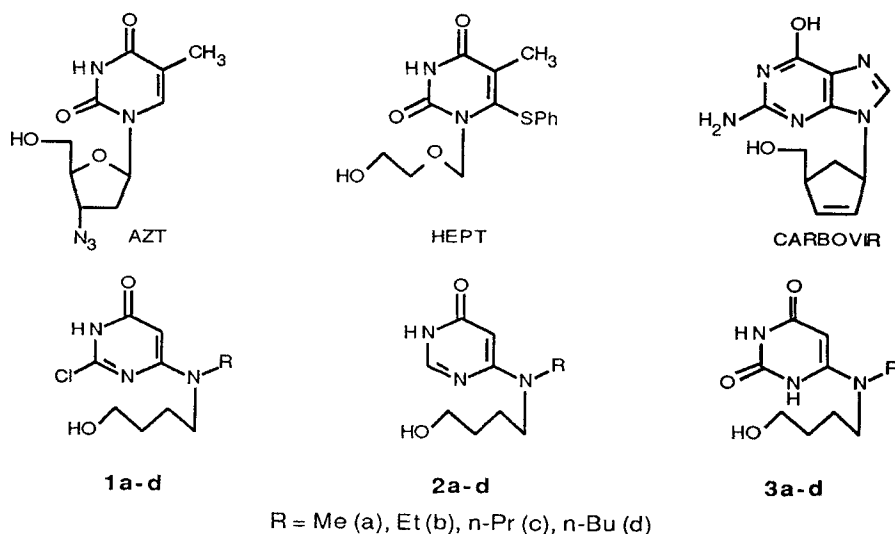


FIG. 1

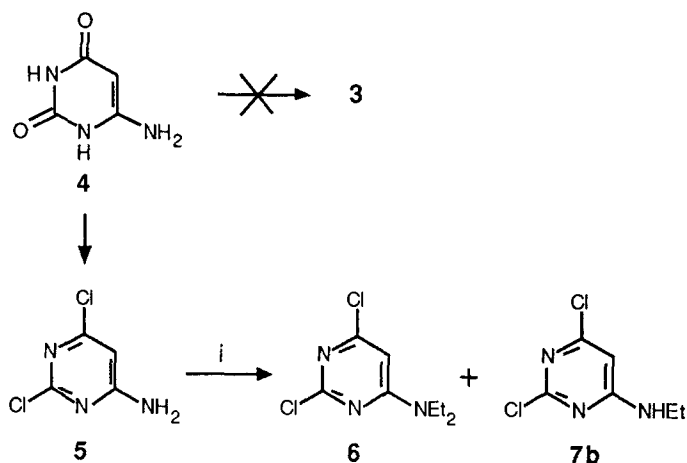
while in position 1 they can also bear chains unable to undergo phosphorylation by thymidine kinase.

Apart from HEPT compounds, little information is available concerning the antiviral properties of 6-substituted pyrimidine derivatives, presumably because the preparation of such compounds is not a trivial task.<sup>6,7</sup>

For several years we have been engaged in the synthesis and biological evaluation of new, usually 6-substituted, pyrimidine derivatives.<sup>8</sup> Here we wish to report the synthesis of some 6-alkylaminopyrimidine derivatives of general formulas **1**, **2**, and **3**, bearing a 4-hydroxybutyl chain as sugar mimic, which can be regarded as simplified, conformationally less rigid analogs of purine acyclonucleosides.

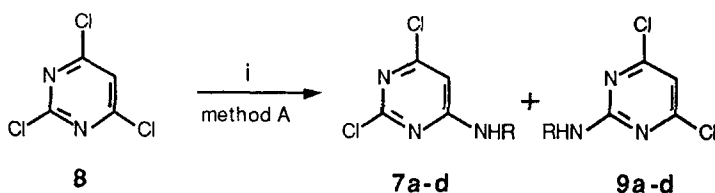
Early attempts to synthesize compounds **3** by direct alkylation of commercially available 6-aminouracil **4** failed, probably because of the poor nucleophilic reactivity and the scarce solubility in the most common solvents of this substrate (Scheme 1). Subsequently we transformed **4** into the dichloro derivative **5**,<sup>9</sup> which was subjected to nitrogen alkylation with ethyl iodide (NaH, DMF) to afford a mixture of compounds **6** and **7b** in the ratio of 2:1. Attempts to obtain the monoalkylated compound **7b** as the main reaction product under different experimental conditions were unsuccessful.

Next we chose as starting material 2,4,6-trichloropyrimidine (**8**) since a patent report claimed the formation of **7** as a single reaction product when **8** was treated with



<sup>a</sup>Key: (i) NaH, EtI, DMF

**SCHEME 1<sup>a</sup>**

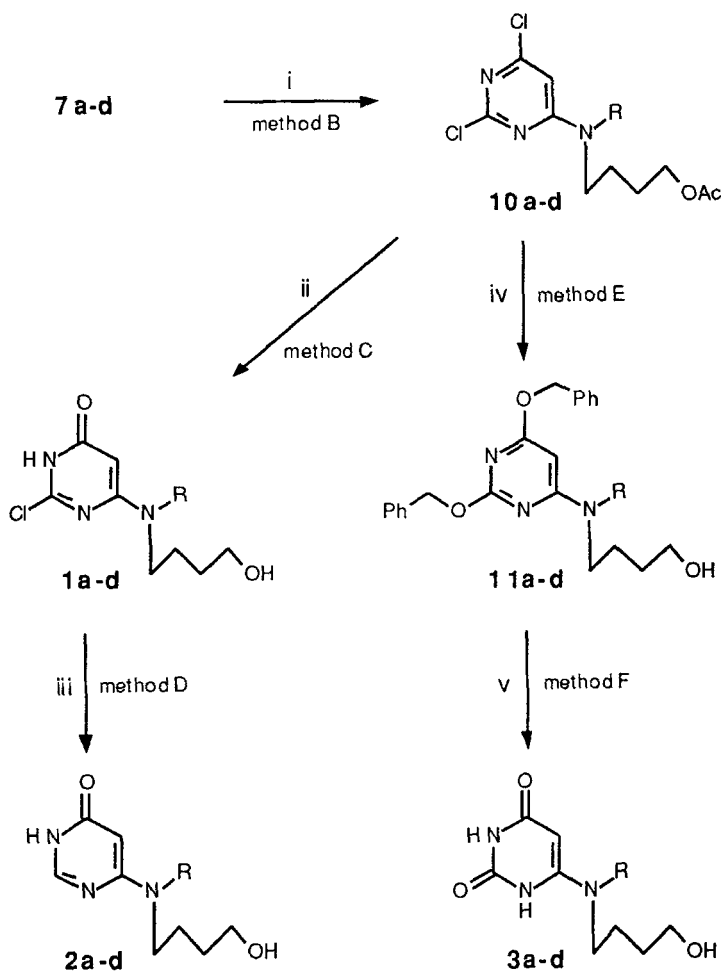


R = Me (a), Et (b), n-Pr (c), n-Bu (d)

<sup>a</sup>Key: (i) RNH<sub>2</sub>, EtOH

**SCHEME 2<sup>a</sup>**

alkyl amines<sup>10</sup> (Scheme 2). In contrast to this result, we always obtained in good yield a mixture of isomers 7 and 9 in about 2.5:1 ratio. The isomers could be separated by column chromatography on silica gel. The first eluted compound 9 showed a <sup>1</sup>H-NMR spectrum very similar to that of the isomer 7, the sole difference being the multiplicity of the signal relative to the protons on the side chain carbon atom linked to the NH group. In the case of 9b-d, in fact, this signal appears as a very broad singlet, whereas in compounds 7b-d it appears as a well defined quartet. The structure of 9b was also chemically confirmed by simply alkylating 2-amino-4,6-dichloropyrimidine with ethyl iodide.



<sup>a</sup> (i)  $\text{AcO}(\text{CH}_2)_4\text{I}$ , NaH, DMF; (ii) 2N HCl, AcOH; (iii) Raney-Ni,  $\text{H}_2\text{O}$ ; (iv) BnOH, NaH, dioxane; (v)  $\text{HCO}_2\text{NH}_4$ , Pd/C, MeOH

### SCHEME 3<sup>a</sup>

Treatment of derivatives **7a-d** (Scheme 3) with 4-acetoxypentyl iodide (NaH, DMF) gave the intermediates **10a-d**, which were subjected to hydrolysis with 2N hydrochloric acid in refluxing acetic acid to afford the chloropyrimidinones **1a-d**. These compounds could not be transformed into the corresponding uracil derivatives **3a-d** either in acidic or

basic conditions, but were easily dehalogenated to **2a-d** by the action of Raney-Ni in water (120°, 2 h). Compounds **3a-d** were prepared in very good yield via transfer catalytic hydrogenation (ammonium formate, Pd-C) of **11a-d**, that in turn were obtained by substitution of the chlorine atoms of **10a-d** with the sodium salt of benzylic alcohol in refluxing 1,4-dioxane. Under these conditions derivatives **10a-d** underwent concurrent deacetylation.

Chemical and physical data for the new compounds **1-3**, **7**, and **9-11** are reported in TABLE 1.

Compounds **1-3a-d** were tested against conventional DNA (Herpes Simplex type 1, Vaccinia, Polio type 1, Coxsackie B1) and RNA (Vesicular Stomatitis) viruses in plaque-reduction assays in Vero cells according to the procedure of Collins and Bauer,<sup>11</sup> but no activity was found at compound concentration less than 100 µM. Nevertheless, the majority of the test compounds showed cytotoxic effects only at a concentration higher than 1,000 µM. It is interesting to note that derivative **2a** exhibited a selective inhibition of HIV-1 replication in vitro with an ED<sub>50</sub> of 25 µM.<sup>12</sup>

## EXPERIMENTAL

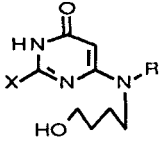
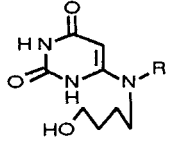
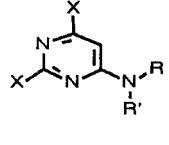
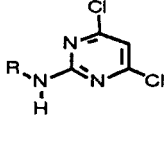
**Chemistry.** Melting points were determined with a Gallenkamp apparatus and are uncorrected. IR spectra (neat or KBr) were taken on a Perkin-Elmer 398 spectrophotometer. <sup>1</sup>H-NMR spectra were recorded at 200 MHz on a Varian XL 200 instrument using tetramethylsilane as the internal standard; chemical shifts are recorded in parts per million (ppm). Mass spectra were measured on a VG 70/250S spectrometer with an electron beam of 70 eV. Column chromatography was carried out on Merck silica gel 60. TLC was performed on silica gel (precoated silica gel plate 60 F254, Merck). Elemental analyses (within ±0.4% of the calculated values) were performed on a Perkin-Elmer 240-C elemental analyzer. Anhydrous sodium sulfate was used to dry organic solutions.

**Synthesis.** Specific examples presented below illustrate general synthetic methods A-F. In general, samples prepared for physical and biological studies were dried in high vacuum over P<sub>2</sub>O<sub>5</sub> for 20 h at temperatures ranging from 25 to 110°, depending on the sample melting point.

### **2,6-Dichloro-4-diethylaminopyrimidine 6 and 2,6-dichloro-4-ethylaminopyrimidine 7b.**

To a solution of 4-amino-2,6-dichloropyrimidine (1.00 g, 6 mmol) in dry N,N-dimethylformamide (40 ml) 97% sodium hydride (0.26 g, 6.6 mmol) was added. When

**TABLE 1.** Chemical and Physical Data for the New Compounds.

							
<b>1, 2</b>		<b>3</b>		<b>7, 10, 11</b>		<b>9</b>	
Compd	R	R'	X	% yield	mp, °C	formula	MS <i>m/z</i> ( <i>M</i> <sup>+</sup> )
<b>1a</b>	Me	-	Cl	65	oil	C <sub>9</sub> H <sub>14</sub> ClN <sub>3</sub> O <sub>2</sub>	231
<b>1b</b>	Et	-	Cl	50	109-11	C <sub>10</sub> H <sub>16</sub> ClN <sub>3</sub> O <sub>2</sub>	245
<b>1c</b>	<i>n</i> -Pr	-	Cl	62	151-3	C <sub>11</sub> H <sub>18</sub> ClN <sub>3</sub> O <sub>2</sub>	259
<b>1d</b>	<i>n</i> -Bu	-	Cl	60	oil	C <sub>12</sub> H <sub>20</sub> ClN <sub>3</sub> O <sub>2</sub>	273
<b>2a</b>	Me	-	H	85	oil	C <sub>9</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub>	197
<b>2b</b>	Et	-	H	89	oil	C <sub>10</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub>	211
<b>2c</b>	<i>n</i> -Pr	-	H	91	oil	C <sub>11</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub>	225
<b>2d</b>	<i>n</i> -Bu	-	H	86	oil	C <sub>12</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub>	239
<b>3a</b>	Me	-	-	93	184-6	C <sub>9</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub>	213
<b>3b</b>	Et	-	-	95	162-4	C <sub>10</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub>	227
<b>3c</b>	<i>n</i> -Pr	-	-	98	138-40	C <sub>11</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub>	241
<b>3d</b>	<i>n</i> -Bu	-	-	94	92-4	C <sub>12</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub>	255
<b>7a</b>	Me	H	Cl	60	175-7	C <sub>5</sub> H <sub>5</sub> Cl <sub>2</sub> N <sub>3</sub>	177
<b>7b</b>	Et	H	Cl	68	80-3	C <sub>6</sub> H <sub>7</sub> Cl <sub>2</sub> N <sub>3</sub>	191
<b>7c</b>	<i>n</i> -Pr	H	Cl	70	68-70	C <sub>7</sub> H <sub>9</sub> Cl <sub>2</sub> N <sub>3</sub>	205
<b>7d</b>	<i>n</i> -Bu	H	Cl	64	40-42	C <sub>8</sub> H <sub>11</sub> Cl <sub>2</sub> N <sub>3</sub>	219
<b>9a</b>	Me	-	-	25	85-7	C <sub>5</sub> H <sub>5</sub> Cl <sub>2</sub> N <sub>3</sub>	177
<b>9b</b>	Et	-	-	28	65-7	C <sub>6</sub> H <sub>7</sub> Cl <sub>2</sub> N <sub>3</sub>	191
<b>9c</b>	<i>n</i> -Pr	-	-	27	38-40	C <sub>7</sub> H <sub>9</sub> Cl <sub>2</sub> N <sub>3</sub>	205
<b>9d</b>	<i>n</i> -Bu	-	-	26	oil	C <sub>8</sub> H <sub>11</sub> Cl <sub>2</sub> N <sub>3</sub>	219
<b>10a</b>	Me	(CH <sub>2</sub> ) <sub>4</sub> OAc	Cl	87	oil	C <sub>11</sub> H <sub>15</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub>	291
<b>10b</b>	Et	(CH <sub>2</sub> ) <sub>4</sub> OAc	Cl	77	oil	C <sub>12</sub> H <sub>17</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub>	305
<b>10c</b>	<i>n</i> -Pr	(CH <sub>2</sub> ) <sub>4</sub> OAc	Cl	82	oil	C <sub>13</sub> H <sub>19</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub>	319
<b>10d</b>	<i>n</i> -Bu	(CH <sub>2</sub> ) <sub>4</sub> OAc	Cl	75	oil	C <sub>14</sub> H <sub>21</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub>	333
<b>11a</b>	Me	(CH <sub>2</sub> ) <sub>4</sub> OH	OBn	42	oil	C <sub>23</sub> H <sub>27</sub> N <sub>3</sub> O <sub>3</sub>	393
<b>11b</b>	Et	(CH <sub>2</sub> ) <sub>4</sub> OH	OBn	35	oil	C <sub>24</sub> H <sub>29</sub> N <sub>3</sub> O <sub>3</sub>	407
<b>11c</b>	<i>n</i> -Pr	(CH <sub>2</sub> ) <sub>4</sub> OH	OBn	53	oil	C <sub>25</sub> H <sub>31</sub> N <sub>3</sub> O <sub>3</sub>	421
<b>11d</b>	<i>n</i> -Bu	(CH <sub>2</sub> ) <sub>4</sub> OH	OBn	62	oil	C <sub>26</sub> H <sub>33</sub> N <sub>3</sub> O <sub>3</sub>	435

gas evolution ceased, ethyl iodide (0.5 ml, 6 mmol) was rapidly added to the reaction mixture. After stirring at room temperature for 20 min, the reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated. The residue was treated with chloroform-ethyl acetate (20:1) and filtered. The clear solution was applied to the top of a silica gel column. Elution with the same solvent afforded **6** (0.50 g, 38%) and subsequently **7b** (0.31 g, 26%).

**Method A Example. 4,6-Dichloro-2-propylaminopyrimidine 9c and 2,6-dichloro-4-propylaminopyrimidine 7c.**

A solution of 2,4,6-trichloropyrimidine (3.66 g, 20 mmol) and propylamine (1.48 g, 25 mmol) in dry ethanol (30 ml) was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was redissolved in dichloromethane. The solution was washed with saturated sodium carbonate solution, then with brine, and dried. After evaporation of the solvent, the residue was purified by column chromatography (chloroform as eluent) to give **9c** (1.11 g, 27%);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  0.99 (t, 3H); 1.62 (m, 2H); 3.35 (m, 2H); 5.65 (br s, 1H); 6.56 (s, 1H). Further elution with chloroform-ethyl acetate (20:1) afforded **7c** (2.88 g, 70%);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.01 (t, 3H); 1.62 (m, 2H); 3.25 (q, 2H); 5.85 (br s, 1H); 6.25 (s, 1H).

**Method B Example. 4-[N-(Acetoxybutyl)-N-methylamino]-2,6-dichloropyrimidine 10a.**

To a mixture of 97% sodium hydride (0.29 g, 12 mmol) and **7a** (1.78 g, 10 mmol) in dry *N,N*-dimethylformamide (50 ml) a solution of 85% 4-iodobutyl acetate (2.85 g, 10 mmol) in the same solvent (5 ml) was added dropwise. After stirring at room temperature for 1 h, the mixture was diluted with water and ethyl acetate. The organic layer was washed with brine, dried and evaporated. The residue was chromatographed (dichloromethane as eluent) to give **10a** (2.58 g, 87%);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.65 (m, 4H); 2.04 (s, 3H); 3.05 (m, 2H); 3.65 (br m, 3H); 4.25 (m, 2H); 6.30 (s, 1H).

**Method C Example. 2-Chloro-6-[N-ethyl-N-(4-hydroxybutyl)amino]-4(3H)-pyrimidinone 1b.**

A solution of **10b** (0.31 g, 1 mmol), 2N hydrochloric acid (2 ml), and glacial acetic acid (2 ml) was stirred at 120° for 20 h. The mixture was concentrated, diluted with water and neutralized with 25% ammonia solution. Water was removed and the residue was



purified by TLC (chloroform-methanol 7:1) to afford pure **1b** (0.12 g, 50%); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 1.05 (t, 3H); 1.45 (m, 4H); 3.45 (m, 6H); 6.09 (s, 1H); 8.30 (br s, 1H).

**Method D Example. 6-[N-Ethyl-N-(4-hydroxybutyl)amino]-4(3H)-pyrimidinone 2b.**

A mixture of **1b** (0.25 g, 1 mmol), water (10 ml) and one drop of methanol was treated with Raney-Ni at 120° for 2 h. The mixture was filtered and evaporated to give pure **2b** (0.19 g, 89%); <sup>1</sup>H-NMR (CD<sub>3</sub>OD): δ 1.50 (m, 4H); 3.00 (s, 3H); 3.30-4.10 (m, 7H); 5.80 (d, 1H); 7.45 (d, 1H). MS *m/z* 211 (M<sup>+</sup>).

**Method E Example. 2,6-Dibenzyloxy-4-[N-(hydroxybutyl)-N-methylamino]pyrimidine 11a.**

A mixture of **10a** (0.29 g, 1 mmol), benzyl alcohol (0.97 g, 9 mmol), 97% sodium hydride (0.16 g, 6.5 mmol), and dry 1,4-dioxane (10 ml) was refluxed for 3 h. After cooling, the reaction was quenched by adding water and ethyl acetate. The organic layer was washed with brine, dried, and evaporated. The residue was purified by column chromatography (hexanes-ethyl acetate 9:1 to 3:2) to give **11a** (0.16 g, 42%); <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.60 (m, 4H); 2.95 (s, 3H); 3.45 (m, 2H); 3.65 (m, 2H); 5.35-5.45 (m, 4H), 7.30 (m, 10H).

**Method F Example. 6-[N-Butyl-N-(4-hydroxybutyl)amino]uracil 3d.**

To a solution of **11d** (0.87 g, 2 mmol) in dry methanol (10 ml) ammonium formate (1.26 g, 20 mmol) and 10% palladium on charcoal (0.25 g) were added. After stirring for 3 h at reflux temperature the mixture was filtered and the solution was evaporated to afford pure **3d** (0.48 g, 94%); <sup>1</sup>H-NMR (CD<sub>3</sub>OD): δ 0.95 (t, 3H); 1.28 (m, 2H); 1.65 (m, 6H); 3.30 (m, 4H); 3.60 (t, 2H).

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