Synthesis and Characterization of Nucleoside Peptides: Toward Chemical Ribonucleases. 1

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Site-selective cleavage of nucleic acids by chemical analogues of nuclease enzymes is an area of major interest. Since imidazole is known to catalyze the hydrolysis of RNA, we postulated that oligonucleotides with pendant imidazole groups could be used to hydrolyze RNA in a sequence specific manner, utilizing complementarity, the natural nucleic acid recognition mechanism. We report here the synthesis and complete characterization of a series of uridine–imidazole conjugates which are based on C-5 substituted deoxyuridine. The nucleoside is joined with a variable-length linker arm to histidine or related imidazole-containing moieties, and protecting groups were employed to allow the subsequent conversion of the nucleoside–peptides into phosphoramidites suitable for oligonucleotide synthesis. Extensive multidimensional NMR characterization of the novel nucleoside–peptides is reported.

The term "chemical nucleases" has been used to describe a series of molecules which result from an elegant juxtaposition of chemical reactivity and biochemical molecular recognition.[1] These nucleases cleave nucleic acids in a sequence-selective manner; they are comprised of a nucleic acid binding group, which can be a protein,[2] peptide,[3] or single-stranded oligonucleotide,[4] and a cleavage agent, which is usually[4] a redox-active metal complex such as Cu(II)–*o*-phenanthroline[6] or Fe(II)EDTA.[7] Cleavage is initiated by adding external reducing or oxidizing agents and is thought to be effected by metal-bound or free hydroxyl radicals. The products of redox-active nucleases cannot be religated enzymatically, because the necessary 3′-phosphate and 5′-hydroxyl groups are destroyed during cleavage.

The site-selective *hydrolysis* of nucleic acids would offer some advantages over oxidative cleavage in that the products could serve as substrates for subsequent enzymatic reactions, and hydrolytic probes might be less inclined to self-destruction than their oxidative counterparts. For example, Schultz and co-workers[8] have prepared site-selective, hydrolytic nucleases by covalently linking the enzyme staphylococcal nuclease to oligonucleotides.

Imidazole is known to hydrolyze RNA catalytically, although the details of this general acid/general base process have only recently been discovered through a series of elegant studies by Breslow and co-workers.[9] The first step of the reaction was found[9b] to be protonation of RNA by imidazolium ion (the general acid), followed by deprotonation of the 2′-hydroxyl group by imidazole (the general base) in a sequential manner. These studies have a direct bearing on the mechanism of RNA cleavage by bovine pancreatic ribonuclease A, which possesses two imidazole groups in the active site located on histidine residues 12 and 119.[9c,10] We proposed that *hydrolytic* ribonuclease mimics could be prepared by combining the RNA-hydrolysis activity of imidazole with the ability of oligonucleotides to bind to RNA in a site-specific manner.

In addition to the application of nucleoside–imidazole conjugates to RNA hydrolysis, these compounds are of inherent interest due to the established biological activity of the class of bioconjugates known as nucleoside peptides. Thus, a number of amino acid or peptide conjugates of purine and pyrimidine nucleosides have been reported which exhibit antitumor, antifungal, or antiviral activity in cell culture.[11–22] Nucleoside- and nucleotide–peptides, both synthetic or isolated from various sources, differ considerably in structure, nucleotide or peptide chain length, and the nature and position of peptide linkage.[23–32]

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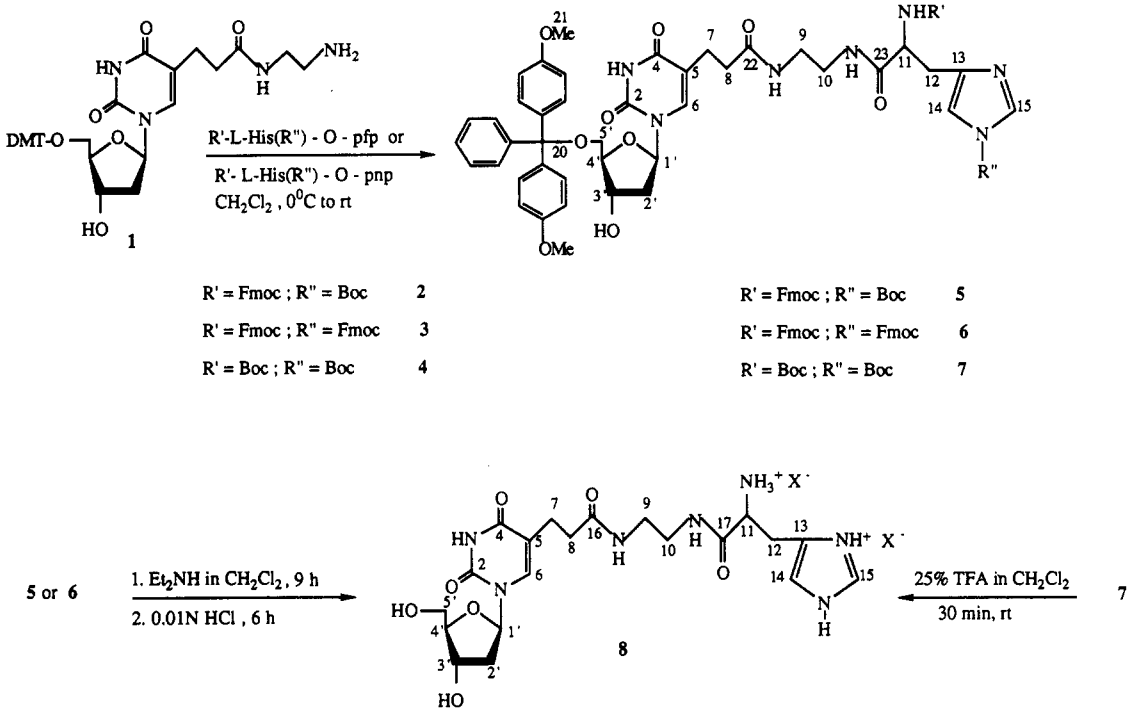
Scheme I



Pyrimidine nucleosides derivatized at the C-5 position constitute a class of biologically potent molecules serving as biochemical tools and diagnostic probes.[33-40] For example, L-Lys-5-aminouridine inhibited herpes simplex, parainfluenza, rhino, and adeno virus in cell culture.[12] Furthermore, amino acids have been found covalently linked to both RNA and DNA,[41-43] and certain proteins bind covalently to viral RNA.[44]

Therefore, because of our specific interest in ribonuclease mimics and the growing importance of nucleic acid–protein conjugates, we undertook the systematic preparation and characterization of a series of nucleoside amino acids, having an imidazole ring at the end of a linker arm of varying chain lengths, with the aim of using the conjugates as building blocks compatible with automated DNA synthesis. The versatile C-5 substituted pyrimidine nucleosides were employed as our synthetic substrates. We describe below a synthetic pathway for the preparation of these modified mononucleosides, and we provide extensive ^1H and ^{13}C NMR data from 1D and 2D experiments which allowed their complete characterization, in conjunction with FAB mass spectra. Conversion of the nucleoside amino acids to diisopropylamino β-cyanoethyl phosphoramidites, and the preparation of di- and oligonucleotide peptide conjugates, will be reported in a subsequent paper.

Extensive work has been carried out over the last decade to synthesize pyrimidine nucleosides substituted at the C-5 position by carbon- or sulfur-linked side chains. Recently, Hobbs[45] reported the synthesis of alkynylamino C-5 nucleosides by the reaction of alkenylamines with iodonucleosides using tetrakis(triphenylphosphine)palladium-(0) and copper iodide. 2′-Deoxyuridine, on reaction with mercuric acetate and sodium chloride, yields 5-(chloromercuri)-2′-deoxyuridine which, on treatment with M_2PdCl_4 (M = K, Na) and olefins or disulfides,[46-48] results in C-5 substituted nucleosides. An alternate route to 5-substituted nucleosides utilizes a catalytic amount of $Pd(OAc)_2$, with 5-iodo-2′-deoxyuridine, triphenylphosphine, triethylamine, and methyl acrylate[40] as the other components. 5-(2-Carbomethoxyethenyl)-2′-deoxyuridine, on hydrogenation[40] with Pd/C, gave 5-(2-carbomethoxyethyl)-2′-deoxyuridine, which was protected by dimeth-

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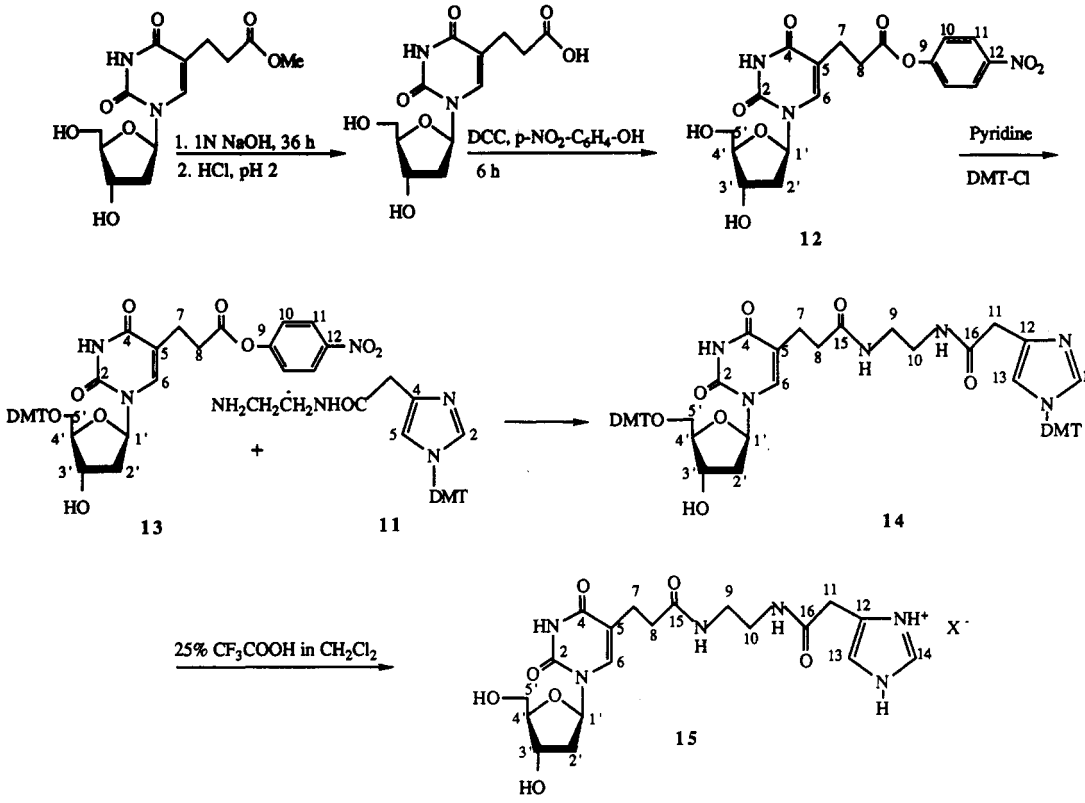
Scheme II



oxytrityl (DMT), a group compatible with the protocols of oligonucleotide synthesis on automated machines.[49,50] The reaction of ethylenediamine with 5′-*O*-DMT-5-(2-carbomethoxyethyl)-2′-deoxyuridine[40] gave an extension of the linker arom through an amide linkage to a terminal amino group to yield 5′-*O*-DMT-5-[3-[(2-aminoethyl)-amino]-3-oxopropyl]-2′-deoxyuridine, **1**. The terminal amino group can be derivatized with amino acids, peptides, and other groups of interest, as we describe below.

Results and Discussion

We found that coupling of Fmoc-L-His(Boc)-*O*-pfp ester **2**, Fmoc-L-His(Fmoc)-*O*-pfp ester **3**, and Boc-L-His-(Boc)-*O*-pnp ester[51] **4** with 5′-*O*-DMT-5-[3-[(2-amino-ethyl)amino]-3-oxopropyl]-2′-deoxyuridine (**1**) yields 5′-DMT-2′-deoxyuridine–His conjugates **5**, **6**, and **7** (Scheme I). Deprotection of these nucleoside–amino acids was investigated to determine conditions for later use on oligonucleotide–amino acid conjugates. Compounds **5** and **6**, on treatment with diethylamine and hydrochloric acid, and compound **7** on treatment with trifluoroacetic acid, gave the monomer His-2′-deoxyuridine **8** (Scheme I).

To eliminate the primary amine of histidine, which requires a protecting group, a procedure based on suitably protected 4-imidazoleacetic acid was investigated. Attempts to synthesize active pnp or pfp esters of 4-imidazoleacetic acid suitably N-protected to be compatible with DNA synthesis were unsuccessful. However, we found that the ethyl ester of 4-imidazoleacetic acid hydrochloride, after protection with DMT-Cl, reacted conveniently with ethylenediamine to give a terminal amino group, resulting in a product which could be linked to uridine. Thus, 4-imidazoleacetic acid hydrochloride, on esterification with ethanol/sulfuric acid, gave 4-imidazoleacetic acid ethyl ester **9**. Protection of N-1 in **9** was carried out by reaction with DMT-Cl to yield 1-DMT-4-imidazoleacetic acid ethyl ester, **10**. The reaction of ethylenediamine with **10** afforded a quantitative yield of 1-DMT-*N*-(2-aminoethyl)-1*H*-imidazole-4-acetamide, **11**. This procedure is shown in Scheme II. Nucleoside 5′-*O*-DMT-5-[3-(4-nitrophenoxy)-3-oxopropyl]-2′-deoxyuridine (**13**) was coupled with **11** to yield the conjugate **14**, which is suitable for conversion to a phosphoramidite, or which, on treatment with 20% CF_3COOH in CH_2Cl_2, gave the deprotected nucleoside **15**. As shown in Scheme III, the chain length and structure of the linker arm was varied using the route developed by Bergstrom,[46] which places a thioether bridge at the C-5 position of 2′-deoxyuridine. 5′-*O*-DMT-5-[[2-[(trifluoroacetyl)amino]ethyl]thio]-2′-deoxyuridine was treated with NH_3 to give 5′-*O*-DMT-5-[(2-aminoethyl)-thio]-2′-deoxyuridine, **16**, which, when coupled with Boc-L-His(Boc)-*O*-pnp ester **4**, yielded the desired product **17**. Treatment of **17** with 25% CF_3COOH in CH_2Cl_2 gave the deprotected nucleoside **18**.

NMR Characterization. We undertook the complete NMR assignment of the new compounds reported here in order to prove their structures and because such extensive characterization of modified nucleosides has not been widely reported. Detailed NMR assignments are given in the Experimental Section, and spectra are supplied as supplementary material with the appropriate NMR acquisition and processing parameters. Representative examples are discussed below.

Characterization by NMR was begun with survey ^1H, ^{13}C, and APT (attached proton test) spectra. For molecules such as **9** and **10**, this was adequate to allow complete

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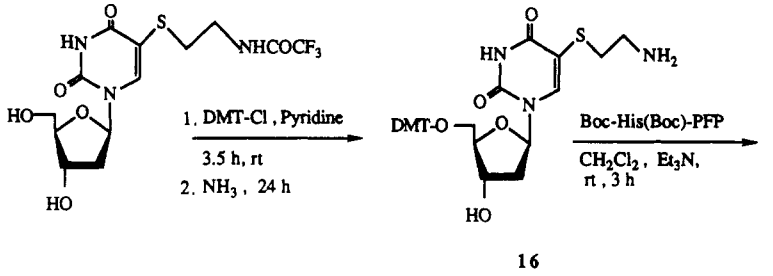
Scheme III



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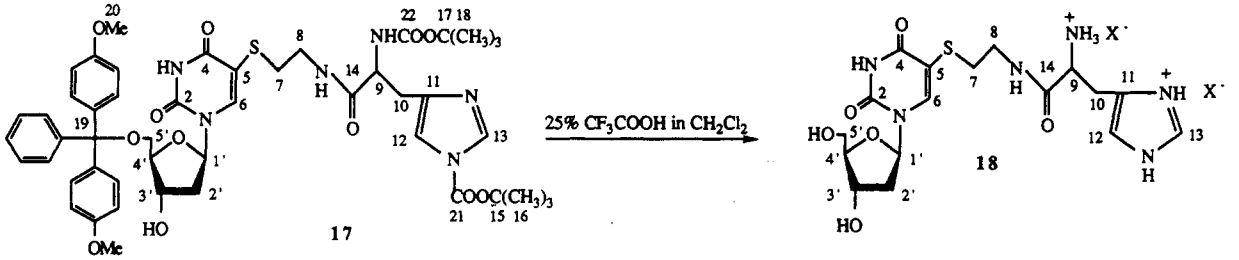

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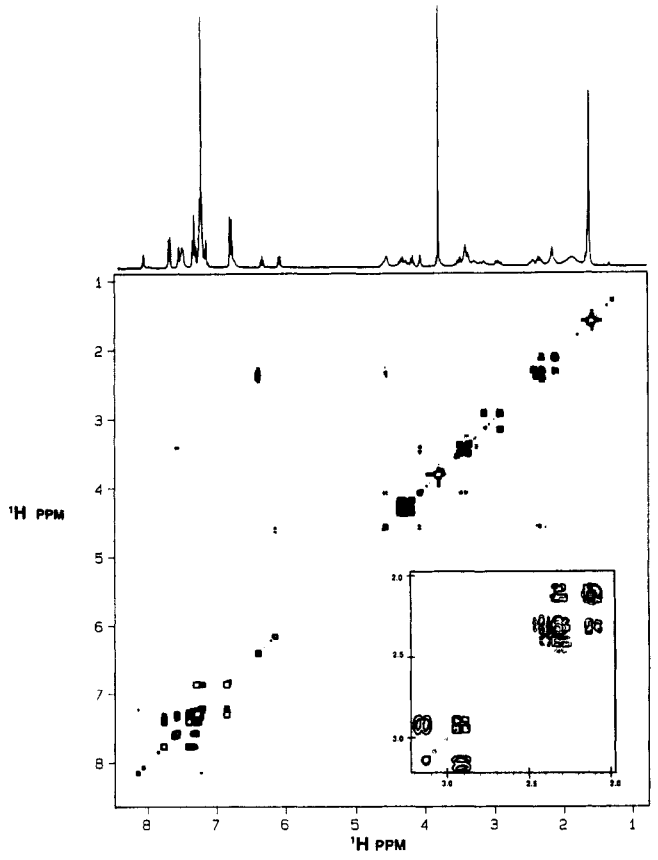


Figure 1. The COSY spectrum of **5** allowed resolution of overlapping peaks into two dimensions. This was particularly important for the methylene region (see inset), where the coupling is seen for the overlapping 2, 2', 7, and 8 resonances near 2 δ and the 9, 10, and 12 resonances near 3 δ. Both the 1D ^{1}H (shown across the top) and COSY spectra were run at 300 MHz. The 2D experiment was run in absolute value mode, with a 256 × 2K data matrix and 96 transients per increment. The spectrum was obtained after zero-filling to a 2K × 2K data matrix and application of a pseudo-echo weighting function in both dimensions.

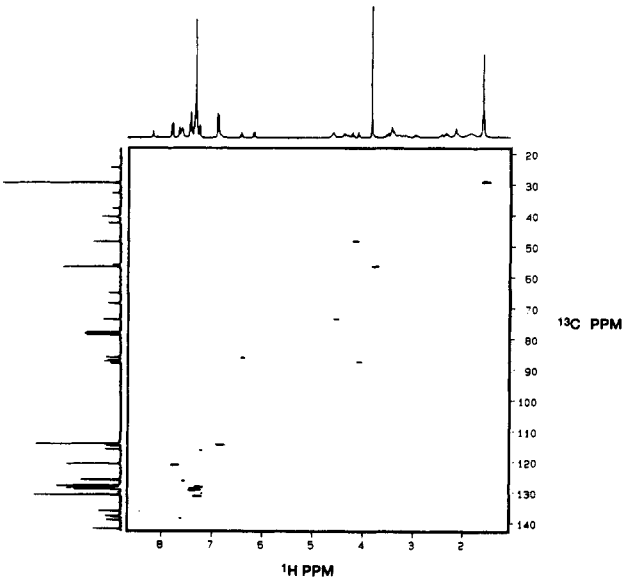


Figure 2. The combined use of ^{1}H and ^{13}C NMR spectroscopy on **5** is shown. The 1D ^{1}H spectrum is given at the top, with the 1D ^{13}C spectrum at the left. Attached proton test results (APT, not shown) yielded multiplicities of the carbons, which, in conjunction with the HETCOR spectrum, allowed individual proton-to-carbon assignments to be made. For example, the ^{13}C peak at 27.7 ppm was identified as a methyl group from the APT data; it is correlated with a ^{1}H peak at 1.6 δ, so this proton peak can be definitively assigned to a set of methyl protons. The HETCOR was run in absolute value mode, with a 256 × 4K data matrix and 192 transients per increment. The spectrum was obtained after zero-filling to a 512 × 4K data matrix and application of a pseudo-echo weighting function in both dimensions.

assignment of all resonances. In some cases, more extensive investigation was necessary, and a number of specialized experiments were performed, including both one- and two-dimensional NMR analysis. Due to the complexity of the fully protected nucleoside–amino acid conjugates **5**, **6**, **7**, and **8**, extensive overlapping of peaks was found, and unambiguous assignments were impossible from 1D NMR data. Where additional investigation was required, e.g. for **5**, homonuclear correlated spectra (COSY) were collected to correctly assign overlapping proton peaks. As shown in Figure 1, congestion of the 1D spectrum is a particular problem in the methylene region, but the off-diagonal COSY peaks allow the network of coupled resonances to be unraveled. An expansion of the methylene region is also displayed as an inset, showing the separation

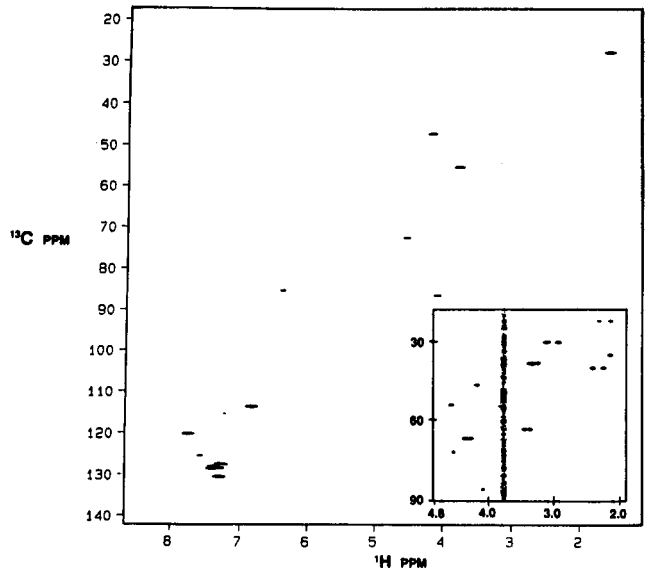
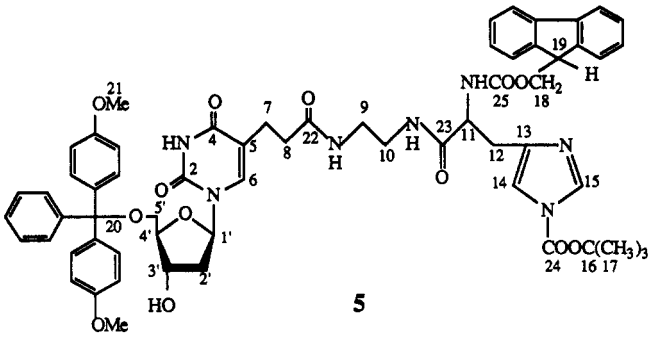


Figure 3. The ability of ^{1}H-detected (or reverse detection) HMQC to reveal weak correlations is clearly shown in this comparison with the direct detection HETCOR experiment for **5**. Although the majority of proton-coupled carbons are observed in the latter spectrum, the methylene region is unsatisfactory. A detail of the HMQC data for this region is shown as an inset. All methylenes were observed in the HMQC spectrum, in contrast to the HETCOR spectrum, which is relatively bare in this region. Details of the HMQC experiment are given in the supplementary data (spectrum 7). The dark line in the HMQC spectrum is t_1 noise from the intense OMe peak.

of the individual peaks. The COSY experiment was used in conjunction with heteronuclear correlated spectroscopy (HETCOR), which correlates coupled proton and carbon peaks, in most instances allowing full assignment of the protons and carbons of a molecule. The HETCOR spectrum of **5** is shown in Figure 2, with the 1D ^{1}H and ^{13}C spectra shown along the axes. For most of the compounds



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reported here, the survey 1D, COSY, and HETCOR spectra were sufficient for complete characterization. However, under some circumstances, proton-detected heteronuclear multiquantum coherence[54] (HMQC) was required. HMQC is preferred over HETCOR for investigation of the methylene region (δ 2–5), where artifacts have been observed[55] and occasionally broad lines and T_2 problems result in a loss of sensitivity, or when there is insufficient compound for a HETCOR experiment. These circumstances arose for **5**, where the methylenes gave very weak cross peaks in the HETCOR spectrum, but were easily detected by the reverse detection HMQC experiment, as shown in Figure 3. The inset shows the HMQC

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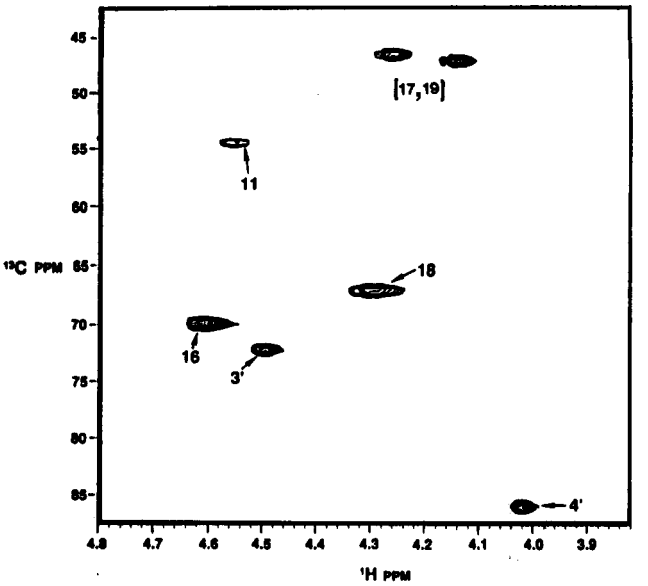
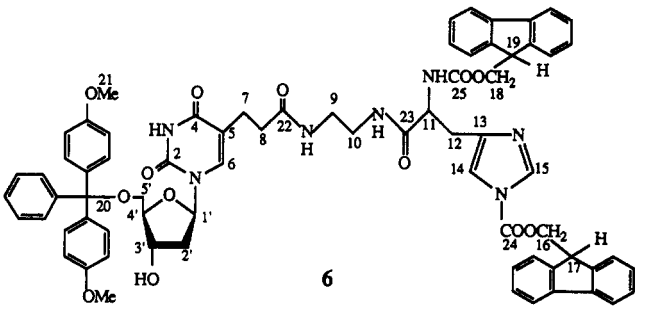


Figure 4. Detail of the HMQC NMR spectrum of **6** showing that the crowded methylene region, which is unresolved in the 1D ^{1}H spectrum, can be fully assigned from the 2D experiment. The spectrum was measured at 28 °C on a VXR-400 spectrometer; it results from a 2 × 256 × 3200 data matrix, with acquisition times of 15 and 500 ms in the t_1 and t_2 dimensions, respectively. The delay between scans (including the 500-ms t_2 acquisition period and the 650-ms period for the BIRD pulse and the start of the actual sequence) was 3.15 s. For each t_1 value, 4 steady-state scans were applied and 32 scans were recorded, yielding a total measuring time of 28.7 h. Prior to Fourier transformation, the data matrix was zero-filled to 4096 × 1024 and Gaussian weighting factors of 0.220 and 0.008 were applied to the t_2 and t_1 domains, respectively. All data processing was performed on a Sun Microsystems 3/110 computer.

results for these methylene signals, which allowed their assignment to be made in conjunction with the other proton and carbon NMR data. An HMQC experiment was also required for the crowded methylene region of **6**. Figure 4 is an expanded view of its HMQC spectrum. Resonances which overlap in the proton dimension are clearly separated and assigned based on their position along the carbon axis.



6

Preparation of Phosphoramidites for DNA Synthesis. The primary concern in developing highly functionalized nucleoside analogues to be used in oligonucleotide synthesis[49,50] is to ensure that phosphitylation occurs only at the desired site: the 5′-hydroxyl of the polymer-supported oligonucleotide chain. Ideally, any additional protecting groups would survive the conditions found in the detritylation step (3% dichloroacetic acid) and the capping step (acetic anhydride/DMAP) and would be removed by the ammonia cleavage procedure (which deblocks the exocyclic NH_2 groups and the phosphate linkages). As will be described in a forthcoming paper, the fully protected nucleoside amino acids **5**, **6**, and **7** were treated with diisopropylamino β-cyanoethyl phosphoro-

chloridite in the presence of diisopropylethylamine, according to the literature procedure[52] for synthesizing nucleoside phosphoramidites for solid-phase DNA synthesis. Although the Boc group is acid labile, its removal from primary amines requires strong acid (CF_3COOH or HCl(aq)) relative to nucleoside detritylation conditions, and we found R′ to survive DNA synthesis conditions (see Scheme I for labeling). The preparation of a phosphoramidite failed in the case of **6** because Fmoc (R″) was removed from the imidazole group by diisopropylethylamine, leading to partial N-phosphitylation. An alternative synthesis[54] for the phosphorylation of **6** using bis(diisopropylamino)(β-cyanoethyl)phosphine in the presence of tetrazole is under investigation, as is the conversion of **14** and **17** into phosphoramidites.

Conclusions

In order to prepare site-selective RNA hydrolysis catalysts comprised of imidazole groups and oligonucleotides, we have systematically prepared a series of 2′-deoxyuridine–imidazole conjugates. These compounds allow us to vary the chain length of the arom that links imidazole to nucleosides, and they provide protecting-group strategies which are compatible with solid-phase DNA synthesis protocols. For example, compounds **5**, **7**, **14**, and **17** are precursors to phosphoramidites which can be employed in oligonucleotide synthesis. Appropriate deprotection conditions were determined to allow convenient synthesis of oligonucleotide–amino acid conjugates. All compounds were fully characterized, and extensive NMR and FAB mass spectral data are presented. In addition to studying the properties of these mononucleoside derivatives, we are incorporating them into oligonucleotides, preparing oligonucleotides containing peptide side chains, and characterizing the interactions between these conjugates and their complementary nucleic acid sequences.

Experimental Section

General. Melting points were taken in Kimax soft glass capillary tubes on a Melt-Temp melting point apparatus equipped with a calibrated thermometer. Nuclear magnetic resonance spectra (^1H, ^{13}C) were recorded on Varian XL-200, VXR-300, VXR-400, or VXR-500 spectrometers. Details are given in the supplementary material. The significant chemical shifts are reported in ppm (δ units) downfield from TMS and the *J* values are given in hertz. All compounds are more than 98% pure by ^{13}C and ^1H NMR spectroscopy. Exchangeable protons are labeled (ex.). Elemental analyses were determined by Galbraith Laboratories, Knoxville, TN. The high-resolution mass spectra were recorded on a Finnegan/MAT90 spectrometer while the FAB^+ low-resolution spectra were run on a VG 40-250T spectrometer. The FAB matrix was a saturated solution of LiI in 3-nitrobenzyl alcohol, which is especially useful for acid-labile, protected nucleosides. Thin-layer chromatography was performed on Baker-Flex silica gel IB2-F plates, and spots were visualized by irradiation with UV light (254 nm). Column (flash) chromatography was performed on silica gel (Merck SG-60, 230–240 mesh). 2′-Deoxyuridine, *p*-nitrophenol (Sigma Chemicals), Fmoc-L-His(Boc)-*O*-pfp, Fmoc-L-His(Fmoc)-*O*-pfp (Pharmacia), *N*,*N*-di-Boc-L-histidine dicyclohexylammonium salt (Fluka), and dicyclohexylcarbodiimide (DCC, Aldrich) were used without any further purification.

***N*,*N*-Bis[(2,2-dimethylethoxy)carbonyl]histidine *p*-Nitrophenyl Ester (4).** The dicyclohexylammonium salt of di-Boc-L-His (25 g, 0.046 mol) was dissolved in water (150 mL) and treated with a solution of $KHSO_4$ (6.35 g) in water (50 mL). The free acid was then extracted in EtOAc (200 mL). The organic layer was washed with water (50 mL), dried over $MgSO_4$, and concentrated to yield di-Boc-L-His (12.36 g, 0.036 mol, 80%). The free acid and *p*-nitrophenol (10.1 g, 0.072 mol) were dissolved in EtOAc, and the mixture was cooled to 0 °C in an ice bath. DCC (7.78 g, 0.038 mol) was added to this mixture in small portions, and the mixture was stirred at 0 °C for 30 min. The ice bath was removed, and the mixture was allowed to stir at room temperature for 2 h. DCC urea which precipitated out was filtered off, and the filtrate was concentrated to dryness. The residue was dissolved in CH_2Cl_2 (300 mL) and washed with aqueous Na_2CO_3 (2 × 200 mL) to remove excess *p*-nitrophenol. The dried organic extract was concentrated, and the product was crystallized from CH_2Cl_2 and petroleum ether to yield **4** (13.6 g, 0.026 mol, 73%); mp 150 °C. Anal. Found: C, 55.80; H, 6.02; N, 11.46. Calcd for $C_{22}H_{28}N_4O_8$: C, 55.45; H, 5.92; N, 11.75. ^{13}C NMR ($CDCl_3$, ppm): 138.4 (1 C), 125.7 (2 C), 123.0 (3 C), 146.0 (4 C), 170.4 (5 C), 53.8 (6 C), 30.4 (7 C), 138.4 (8 C), 115.5 (9 C), 137.6 (10 C), 156.0 (12 C), 86.6 (12 C), 28.4 (13 C), 147.2 (14 C), 80.8 (15 C), 28.8 (16 C); ^1H NMR ($CDCl_3$) δ 8.3 (d, 2 H, H2), 7.4 (d, 2 H, H3), 4.85 (m, 1 H, H6), 3.25 (m, 2 H, H7), 7.25 (s, 1 H, H9), 8.05 (s, 1 H, H10), 1.6 (s, 9 H, H13), 1.4 (s, 9 H, H16), 5.8 (d, 1 H, NH ex.). Mass: 483^+ (M + Li), 427^+ (M + Li − C_4H_8), 327^+ (427 − Boc). Exact mass found 483.2079, calculated for $C_{22}H_{28}N_4O_8Li$ 483.2067.

5′-*O*-[Bis(4-methoxyphenyl)phenylmethyl]-5-[3-[[2-[[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino]-3-[1-[(2,2-dimethylethoxy)carbonyl]-1*H*-imidazol-4-yl]-1-oxopropyl]amino]ethyl]amino]-3-oxopropyl]-2′-deoxyuridine (5). A solution of nucleoside **1** (0.644 g, 1 mmol) and Et_3N (0.3 mL, 2 mmol) in CH_2Cl_2 (10 mL) and acetonitrile (10 mL) was cooled to 0 °C in an ice bath, and Fmoc-L-His(Boc)-*O*-pfp **2** (0.965 g, 1.5 mmol) was added to the stirred reaction mixture. After 15 min the ice bath was removed, and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated and purified by flash chromatography on a silica gel column, eluting with a gradient of 0–12% EtOH in CH_2Cl_2. The desired product **5** (0.695 g, 0.63 mmol, 63%) eluted with 10% EtOH in CH_2Cl_2 (R_f ~0.45). Mp: 146–8 °C. ^{13}C NMR ($CDCl_3$, ppm): 84.8 (1′ C), 40.8 (2′ C), 72.3 (3′ C), 86.2 (4′ C), 63.7 (5′ C), 164.6 (4 CO), 150.5 (2 CO), 113.9, (5 C), 137.3 (6 C), 22.8 (7 C), 36.0 (8 C), 38.8 and 38.9 (9 C and 10 C), 54.5 (11 C), 31.1 (12 C), 135.4 (13 C), 115.0 (14 C), 137.1 (15 C), 86.7 (16 C), 27.7 (17 C), 67.0 (18 C), 47.0 (19 C), 85.8 (20 C), 55.2 (21 C), 172.8 (22 C), 171.5 (23 C), 156.2 (24 C), 146.6 (25 C). ^1H NMR ($CDCl_3$): δ 6.4 (t, 1 H, H1′, *J* = 7.0 Hz), 2.2–2.4 (m, 2 H, H2′), 4.6 (m, 1 H, H3′), 4.2 (m, 1 H, H4′), 3.4 (m, 2 H, H5′), 7.6 (s, 1 H, H6), 2–2.2 (m, 4 H, H7 and H8), 3.0 (m, 4 H, H9 and H10), 4.6 (m, 1 H, H11), 3–3.2 (m, 2 H, H12), 7.2 (s, 1 H, H14), 8.2 (s, 1 H, H15), 1.6 (s, 9 H, H17), 4.2 (t, 1 H, H19), 3.8 (s, 6 H, H21). FABMS *m*/*z* 1110^+ (M + Li), 1082^+ (M + Li − CO), 808^+ (M + Li − DMT), 751^+ (808^+ − C_4H_8), 592^+ (M + Li − 5′-DMT-D-U). Exact mass found 1110.4860, calculated for $C_{61}H_{65}N_7O_{13}Li$ 1110.4800.

5′-*O*-[Bis(4-methoxyphenyl)phenylmethyl]-5-[3-[[2-[[2-[[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino]-3-[1-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-1*H*-imidazol-4-yl]-1-oxopropyl]amino]ethyl]amino]-3-oxopropyl]-2′-deoxyuridine (6). A solution of nucleoside **1** (0.644 g, 1 mol) in CH_2Cl_2 (10 mL) and acetonitrile (10 mL) was cooled to 0 °C in an ice bath, and Fmoc-L-His(Fmoc)-*O*-pfp **3** (1.148 g, 1.5 mmol) was added to the stirred reaction mixture. After 15 min the ice bath was removed, and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated and chromatographed on a silica gel column, eluting with a gradient of 0–12% EtOH in CH_2Cl_2. The desired product **6** (0.834 g, 0.68 mmol, 68%) eluted with 10% EtOH in CH_2Cl_2 (R_f ~0.42). Mp: 148–150 °C. ^{13}C NMR ($CDCl_3$, ppm): 85.0 (1′ C), 40.9 (2′ C), 72.4 (3′ C), 86.3 (4′ C), 63.8 (5′ C), 164.7 (4 CO), 150.6 (2 CO), 113.9 (5 C), 137.4 (6 C), 23.0 (7 C), 36.1 (8 C), 39.0 (9 C and 10 C), 54.6 (11 C), 31.2 (12 C), 135.5 (13 C), 114.9 (14 C), 137.4 (15 C), 70.1 (16 C), 46.6 and 47.1 (17 C and 19 C), 67.2 (18 C), 86.8 (20 C), 55.3 (21 C), 172.9 (22 C), 171.6 (23 C), 156.3 (24 C), 148.3 (25 C). ^1H NMR ($CDCl_3$): δ 6.4 (t, 1 H, H1′, *J* = 7.0 Hz), 2.2–2.4 (m, 2 H, H2′), 4.45 (m, 1 H, H3′), 4.05 (m, 1 H, H4′), 3.4 (m, 2 H, H5′), 2.2–2.4 (m, 2 H, H7), 2.2 (m, 2 H, H8), 3.2–3.4 (m, 4 H, H9 and H10), 4.6 (m, 1 H, H11), 2.9–3.1 (m, 2 H, H12), 8.2 (s, 1 H, H15), 4.6 (m, 2 H, H16), 4.3 (m, 2 H, H18), 4.2 and 4.3 (m, 2 H, H17 and H19), 3.8 (s, 6 H, H21). FABMS *m*/*z* 1232^+ (M + Li), 928^+ (M + Li − DMT), 814^+ (M + Li − 5′-DMT-sugar), 746^+ (M + Li − 5′-DMT-D-U). Exact mass found 1232.4827, calculated for $C_{71}H_{67}N_7O_{13}Li$ 1232.4957.

5′-*O*-[Bis(4-methoxyphenyl)phenylmethyl]-5-[3-[[2-[[2-[[(2,2-dimethylethoxy)carbonyl]amino]-3-[1-[(2,2-dimethylethoxy)carbonyl]-1*H*-imidazol-4-yl]-1-oxopropyl]-

amino]ethyl]amino]-3-oxopropyl]-2′-deoxyuridine (7). A solution of nucleoside 1 (0.644 g, 1 mmol) and Et_3N (0.3 mL, 2 mmol) in CH_2Cl_2 (10 mL) and acetonitrile (10 mL) was cooled to 0 °C in an ice bath, and Boc-L-His(Boc)-*O*-pfp 4 (1.148 g, 1.5 mmol) was added to the stirred reaction mixture. After 15 min the ice bath was removed, and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated and chromatographed on a silica gel column eluting with a gradient of 0–12% EtOH in CH_2Cl_2. The desired product 7 (0.834 g, 0.68 mmol, 68%) eluted with 10% EtOH in CH_2Cl_2 (R_f –0.42). Mp: 142 °C. ^{13}C NMR ($CDCl_3$, ppm): 85.3 (1′ C), 41.1 (2′ C), 72.3 (3′ C), 86.6 (4′ C), 64.3 (5′ C), 164.9 (4 CO), 151.1 (2 CO), 114.2 (5 C), 137.6 (6 C), 23.4 (7 C), 36.1 (8 C), 39.4 (9 C and 10 C), 54.6 (11 C), 31.7 (12 C), 137.6 (13 C), 115.4 (14 C), 137.5 (15 C), 86.1 (16 C), 28.4 (17 C), 79.9 (18 C), 28.0 (19 C), 87.1 (20 C), 55.6 (21 C), 173.1 (22 C), 172.2 (23 C), 155.9 (24 C), 147.2 (25 C). ^1H NMR ($CDCl_3$): δ 6.3 (t, 1 H, H1′, J = 7.0 Hz), 2.2 (m, 2 H, H2′), 4.4 (m, 1 H, H3′), 4.0 (m, 1 H, H4′), 3.4 (m, 2 H, H5′), 7.5 (s, 1 H, H6), 2–2.2 (m, 4 H, H7 and H8), 3.3 (m, 4 H, H9 and H10), 4.5 (m, 1 H, H11), 2.8–3.0 (m, 2 H, H12), 7.15 (s, 1 H, H14), 8.05 (s, 1 H, H15), 1.55 (s, 9 H, H17), 1.35 (s, 9 H, H19), 3.75 (s, 6 H, H21). FABMS m/z 988^+ (M + Li). Exact mass found 988.4694, calculated for $C_{51}H_{63}N_7O_{13}Li$ 988.4644.

5-[3-[[2-[[2-Amino-3-(1*H*-imidazol-4-yl)-1-oxopropyl]amino]ethyl]amino]-3-oxopropyl]-2′-deoxyuridine (8). A solution of 5 (0.552 g, 0.5 mmol) in CH_2Cl_2 (5 mL) was treated with diethylamine (3 mL) and left stirring for 9 h. The reaction mixture was then concentrated and lyophilized three times to remove all traces of diethylamine. The solid was triturated with diethyl ether (3 × 20 mL) and decanted to yield a white solid. The solid was then dissolved in methanol (5 mL) and treated with 0.01 N HCl, pH 2 (5 mL), for 6 h. The aqueous mixture was washed with CH_2Cl_2 (2 × 20 mL) and then lyophilized twice to yield the final product 8 (0.224 g, 0.468 mmol, 93%). ^{13}C NMR (D_2O, ppm): 88.5 (1′ C), 42.3 (2′ C), 73.8 (3′ C), 89.9 (4′ C), 64.5 (5′ C), 168.8 (4 CO), 154.8 (2 CO), 116.6 (5 C), 141.6 (6 C), 26.2 (7 C), 37.8 (8 C), 42.0 and 41.6 (9 C and 10 C), 55.6 (11 C), 29.5 (12 C), 129.5 (13 C), 121.6 (14 C), 137.8 (15 C), 178.8 (16 C), 171.4 (17 C). ^1H NMR (D_2O): δ 6.3 (t, 1 H, H1′, J = 7.0 Hz), 2.3–2.4 (m, 2 H, H2′), 4.5 (m, 1 H, H3′), 4.05 (m, 1 H, H4′), 3.85 (m, 2 H, H5′), 7.7 (s, 1 H, H6), 2.4–2.6 (m, 4 H, H7 and H8), 3.25–3.35 (m, 4 H, H9 and H10), 4.25 (t, 1 H, H11), 3.35 (m, 2 H, H12), 7.4 (s, 1 H, H14), 8.7 (s, 1 H, H15). FABMS m/z 480^+ (M + H). Exact mass found 486.2294, calculated for $C_{20}H_{29}N_7O_7Li$ 486.2289.

1*H*-Imidazole-4-acetic Acid Ethyl Ester (9). 4-Imidazoleacetic acid hydrochloride (1 g, 6.1 mmol) was suspended in EtOH (25 mL), and concentrated sulfuric acid (1 mL) was added to this mixture. The mixture was then refluxed for 12 h until a homogeneous mixture was formed. The solution was then neutralized with 5 N NaOH to pH 8 and extracted with EtOAc (2 × 100 mL). The dried ($MgSO_4$) organic layer was concentrated to yield the ester 9 as a colorless oil (0.87 g, 5.66 mmol, 92%). ^{13}C NMR (CD_3OD, ppm): 14.5 ($COOCH_2CH_3$), 62.0 ($COOCH_2CH_3$), 33.8 ($COCH_2$), 172.7 (CO), 136.3 (2 C), 132.1 (4 C), 118.4 (5 C). ^1H NMR (CD_3OD): δ 1.2 (t, 3 H, $COOCH_2CH_3$), 4.15 (q, 2 H, $COOCH_2CH_3$), 3.6 (s, 2 H, $COCH_2$), 6.0 (br s, 1 H, NH ex.), 7.6 (s, 1 H, H2), 6.95 (s, 1 H, H5).

1-[Bis(4-methoxyphenyl)phenylmethyl]-1*H*-imidazole-4-acetic Acid Ethyl Ester (10). Ethyl ester 9 (0.770 g, 5 mmol) was dissolved in CH_2Cl_2 (10 mL), and DMT-Cl (1.863 g, 5.5 mmol) was added to the solution at room temperature. After 5 min of stirring Et_3N (0.766 mL, 5.5 mmol) was added to the reaction mixture and left to stir overnight. The reaction was quenched with MeOH (5 mL) and concentrated to dryness. The residue was taken up in CH_2Cl_2 (100 mL) and washed with $NaHCO_3$ (2 × 25 mL). The dried ($MgSO_4$) organic extracts were concentrated, and the residue was chromatographed over silica gel using a gradient of 0–5% EtOH in CH_2Cl_2 to yield 10 (1.732 g, 3.8 mmol, 76%). ^{13}C NMR (CD_2Cl_2, ppm): 14.5 ($COOCH_2CH_3$), 60.9 ($COOCH_2CH_3$), 35.1 ($COCH_2$), 171.5 (CO), 138.5 (2 C), 134.7 (4 C), 119.9 (5 C), 55.7 (OMe). ^1H NMR (CD_2Cl_2): δ 1.2 (t, 3 H, $COOCH_2CH_3$), 4.15 (q, 2 H, $COOCH_2CH_3$), 3.6 (s, 2 H, $COCH_2$), 6.0 (br s, 1 H, NH ex.), 7.3 (s, 1 H, H2), 6.75 (s, 1 H, H5).

***N*-(2-Aminoethyl)-1-[bis(4-methoxyphenyl)phenylmethyl]-1*H*-imidazole-4-acetamide (11).** Ethyl ester 10 (1.595 g, 3.5 mmol) was dissolved in ethylenediamine (10 mL) and left to stir at room temperature for 48 h. The excess ethylenediamine was removed by azeotroping with toluene, EtOH, and CH_2Cl_2 to yield 11 (1.505 g, 3.2 mmol, 91%). ^{13}C NMR (CD_2Cl_2, ppm): 36.5 ($COCH_2$), 170.9 (CO), 55.7 (OMe), 42.7 ($NHCH_2$), 41.9 (CH_2NH_2), 139.0 (2 C), 135.9 (4 C), 119.8 (5 C). ^1H NMR (CD_2Cl_2): δ 3.4 (s, 2 H, $COCH_2$), 3.75 (s, 3 H, OMe), 3.2 (q, 2 H, $NHCH_2$), 2.7 (t, 3 H, CH_2NH_2), 7.6 (t, 1 H, NH ex.), 1.95 (br s, 2 H, NH_2 ex.), 7.4 (s, 1 H, H2), 6.7 (s, 1 H, H5). FABMS m/z 447^+ (M + Li)$^+$.

2′-Deoxyuridine-5-propionic Acid *p*-Nitrophenyl Ester (12). 5-(2-Carboxyethyl)-2′-deoxyuridine (1.0 g, 3.33 mmol) and *p*-nitrophenol (0.555 g, 4 mmol) were dissolved in DMF (10 mL), and the mixture was cooled to 0 °C in an ice bath. DCC (0.721 g, 3.49 mmol) was added to this mixture in small portions, and the mixture was stirred at 0 °C for 30 min. The ice bath was removed, and the mixture was allowed to stir at room temperature for 6 h. The urea which precipitated out was filtered off, and the filtrate was concentrated to dryness. The residue was dissolved in CH_2Cl_2 and MeOH and chromatographed on a silica gel column. The desired compound 12 (1.1 g, 2.6 mmol, 79%) was eluted off the column with 15% EtOH in CH_2Cl_2. ^{13}C NMR (DMSO-d_6, ppm): 84.1 (1′ C), 39.4 (2′ C), 70.8 (3′ C), 87.7 (4′ C), 61.7 (5′ C), 163.5 (4 CO), 150.2 (2 CO), 111.9 (5 C), 137.1 (6 C), 22.0 (7 C), 32.0 (8 C), 170.0 (COOpnp). ^1H NMR (DMSO-d_6): δ 6.2 (t, 1 H, H1′, J = 7.0 Hz), 2.15 (m, 2 H, H2′), 4.3 (m, 1 H, H3′), 3.8 (m, 1 H, H4′), 3.6 (m, 2 H, H5′), 7.8 (s, 1 H, H6), 2.6 (t, 2 H, H7), 2.8 (t, 2 H, H8), 2.45 (m, 1 H, 5′OH ex.), 2.5 (m, 1 H, 3′OH ex.), 7.35 and 8.25 (2 d's, 4 H, pnp). FABMS m/z 428^+ (M + Li).

5′-*O*-[Bis(4-methoxyphenyl)phenylmethyl]-2′-deoxyuridine-5-propionic Acid *p*-Nitrophenyl Ester (13). Nucleoside 12 (0.8 g, 1.9 mmol) was dissolved in pyridine (10 mL), and pyridine was removed twice to remove traces of water or alcoholic solvents. The foam was redissolved in pyridine (10 mL). To this solution was added DMT-Cl (0.708 g, 2.09 mmol) in pyridine (5 mL), and the mixture was stirred under the exclusion of moisture for 3–4 h. MeOH (5 mL) was added to quench the reaction and stirred for 10 min. The mixture was concentrated to dryness, and the residue was dissolved in CH_2Cl_2 (100 mL). The CH_2Cl_2 solution was washed with water (2 × 25 mL), and the organic layer was dried over anhydrous $MgSO_4$ and concentrated to yield a glass. The glass was chromatographed on a silica gel column, and the final product 13 (0.962 g, 1.33 mmol, 70%) eluted with 3–5% EtOH in CH_2Cl_2. ^{13}C NMR (CD_3CN, ppm): 86.3 (1′ C), 41.6 (2′ C), 72.7 (3′ C), 87.6 (4′ C), 65.2 (5′ C), 165.0 (4 CO), 152.0 (2 CO), 113.8 (5 C), 23.9 (7 C), 34.3 (8 C), 172.0 (COOpnp), 87.9 (Ph_3C), 56.6 (OMe). ^1H NMR (CD_3CN): δ 6.2 (t, 1 H, H1′, J = 7.0 Hz), 2.15 (m, 2 H, H2′), 4.4 (m, 1 H, H3′), 3.9 (m, 1 H, H4′), 3.3 (m, 2 H, H5′), 7.6 (s, 1 H, H6), 2.4 (t, 2 H, H7), 2.6 (t, 2 H, H8), 3.7 (s, 3 H, OMe), 7.35 and 8.25 (2 d's, 4 H, pnp). FABMS m/z 730^+ (M + Li).

5′-*O*-[Bis(4-methoxyphenyl)phenylmethyl]-5-[3-[[2-[[[1-[bis(4-methoxyphenyl)phenylmethyl]-1*H*-imidazol-4-yl]acetyl]amino]ethyl]amino]-3-oxopropyl]-2′-deoxyuridine (14). Active ester 13 (0.940 g, 1.3 mmol) dissolved in dry CH_2Cl_2 (10 mL) was cooled to 0 °C in an ice bath, and imidazole derivative 11 (0.733 g, 1.56 mmol) was added to the stirred reaction mixture. Triethylamine (0.36 mL, 2.6 mmol) was added to the solution and the mixture was stirred at room temperature for 8 h. The reaction mixture was concentrated and chromatographed on a silica gel column eluting with a gradient of 0–12% EtOH in CH_2Cl_2. The desired product 14 (0.865 g, 0.82 mmol, 63%) eluted with 10–12% EtOH in CH_2Cl_2. ^{13}C NMR (CD_3CN, ppm): 85.4 (1′ C), 40.8 (2′ C), 71.9 (3′ C), 86.7 (4′ C), 64.8 (5′ C), 164.8 (4 CO), 151.4 (2 CO), 114.4 (5 C), 137.9 (6 C), 23.9 (7 C), 36.7 (8 C), 39.8 and 40.2 (9 C and 10 C), 36.3 (11 C), 120.5 (13 C), 139.5 (14 C), 173.0 (15 C), 171.7 (16 C), 87.3 (Ph_3C(5′-O-DMT)), 75.5 (Ph_3C(N-DMT)), 56.1 and 56.0 (OMe(DMT)). ^1H NMR (CD_3CN): δ 6.2 (t, 1 H, H1′, J = 7.0 Hz), 2.2 (m, 2 H, H2′), 4.4 (m, 1 H, H3′), 3.9 (m, 1 H, H4′), 3.2 (m, 2 H, H5′), 2.2 (m, 4 H, H7 and H8), 3.2 (m, 4 H, H9 and H10), 3.3 (m, 2 H, H11), 3.75 (s, 6 H, OMe), 3.8 (s, 6 H, OMe), 6.55 (t, 1 H, NH ex.). FABMS m/z 1067^+ (M + 2Li – H), 1061^+ (M + Li), 765^+ (M + 2 Li – H – DMT), 759^+ (M + Li – DMT). Exact mass found 1061.4626, calculated for $C_{61}H_{62}N_6O_{11}Li$ 1061.4637.

5-[3-[[2-[[(1*H*-Imidazol-4-yl)acetyl]amino]ethyl]amino]-3-oxopropyl]-2′-deoxyuridine (15). The nucleoside 14 (0.4 g, 0.38 mmol) was dissolved in CH_2Cl_2 (5 mL), and a solution

of 20% CF_3COOH in CH_2Cl_2 (5 mL) was added to the stirred reaction mixture. After 30 min, the mixture was concentrated to dryness and the resulting solid was dissolved in water (10 mL). The aqueous solution was washed with CH_2Cl_2 (2 × 5 mL) and ether (2 × 5 mL) and then concentrated to give the desired product **15** (0.16 g, 0.33 mmol, 87%). ^{13}C NMR (D_2O, ppm): 88.5 (1′ C), 42.3 (2′ C), 73.8 (3′ C), 89.9 (4′ C), 64.5 (5′ C), 168.7 (4 CO), 154.8 (2 CO), 116.6 (5 C), 141.5 (6 C), 26.2 (7 C), 37.7 (8 C), 41.7 and 42.1 (9 C and 10 C), 34.4 (11 C), 130.0 (12 C), 120.8 (13 C), 136.9 (14 C), 178.7 (15 C), 173.9 (16 C). ^1H NMR (D_2O): δ 6.25 (t, 1 H, H1′, J = 7.0 Hz), 2.35 (m, 2 H, H2′), 4.45 (m, 1 H, H3′), 4.05 (m, 1 H, H4′), 3.8 (m, 2 H, H5′), 7.7 (s, 1 H, H6), 2.5 (m, 4 H, H7 and H8), 3.3 (br s, 4 H, H9 and H10), 3.8 (s, 2 H, H11), 7.4 (s, 1 H, H13), 8.7 (s, 1 H, H14). FABMS m/z 463^+ (M + 2 Li − H), 457^+ (M + Li), 341^+ (M + Li − sugar). Exact mass found 457.2094, calculated for $C_{19}H_{26}N_6O_7Li$ 547.2022.

5′-*O*-[Bis(4-methoxyphenyl)phenylmethyl]-5-[[2-[[2-[[(2,2-dimethylethoxy)carbonyl]amino]-3-[1-[(2,2-dimethylethoxy)carbonyl]-1*H*-imidazol-4-yl]-1-oxopropyl]amino]ethyl]thio]-2′-deoxyuridine (17). 5′-*O*-[Bis(4-methoxyphenyl)phenylmethyl]-5-[(2-aminoethyl)thio]-2′-deoxyuridine (**16**) (1.25 g, 2.07 mmol), Et_3N (0.3 mL, 2 mmol, and Boc-L-his(Boc)-*O*-pfp **4** (1.19 g, 2.5) mmol) were dissolved in CH_2Cl_2 (10 mL) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated and chromatographed on a silica gel column eluting with a gradient of 0 to 10% EtOH in CH_2Cl_2. The desired product **17** (1.5 g, 1.59 mmol, 77%) eluted with 8% EtOH in CH_2Cl_2 (R_f −0.52). Mp: 142 °C. ^{13}C NMR ($CDCl_3$, ppm): 85.8, (1′ C), 41.3 (2′ C), 72.3 (3′ C), 86.6 (4′ C), 63.8 (5′ C), 163.4 (4 CO), 150.3 (2 CO), 107.3 (5 C), 145.0 (6 C), 34.9 (7 C), 38.6 (8 C), 54.3 (9 C), 31.3 (10 C), 139.2 (11 C), 114.8 (12 C), 136.9 (13 C), 171.6 (14 C), 87.0 (15 C), 27.9 (16 C), 79.8 (17 C), 28.4 (18 C), 85.7 (19 C), 55.3 (20 C), 155.6, (21 C), 147.0 (22 C). ^1H NMR ($CDCl_3$): δ 6.35 (t, 1 H, H1′, J = 7.0 Hz), 2.4 (m, 2 H, H2′), 4.6 (m, 1 H, H3′), 4.15 (m, 1 H, H4′), 3.45 (m, 2 H, H5′), 3.0 (m, 4 H, H7 and H8), 4.45 (m, 1 H, H9), 3.3 (m, 2 H, H10), 1.6 (s, 9 H, H16), 1.4 (s, 9 H, H18), 3.8 (s, 6 H, H20). FABMS m/z 988^+, (M + Li). Exact mass found 949.3960, calculated for $C_{51}H_{63}N_7O_{13}Li$ 949.3933.

5-[[2-[[2-Amino-3-(1*H*-imidazol-4-yl)-1-oxopropyl]amino]ethyl]thio]-2′-deoxyuridine (18). The nucleoside **17** (0.2 g, 0.212 mmol) was dissolved in CH_2Cl_2 (5 mL), and a solution of 25% CF_3COOH in CH_2Cl_2 (5 mL) was added to the stirred reaction mixture. After 10 min, the mixture was concentrated to dryness. The solid was dissolved in water (10 mL), washed with CH_2Cl_2 (2 × 5 mL) and ether (2 × 5 mL), and concentrated to give the desired product **18** (0.086 g, 0.184 mmol, 87%). ^{13}C NMR (D_2O, ppm): 89.3 (1′ C), 42.4 (2′ C), 73.5 (3′ C), 90.2 (4′ C), 64.3 (5′ C), 167.9 (4 CO), 154.5 (2 CO), 109.5 (5 C), 149.2 (6 C), 36.2 (7 C), 41.6 (8 C), 55.6 (9 C), 29.4 (10 C), 129.3 (11 C), 121.7 (12 C), 137.7 (13 C), 171.1 (14 C). ^1H NMR (D_2O): δ 6.25 (t, 1 H, H1′, J = 7.0 Hz), 2.45 (m, 2 H, H2′), 4.5 (m, 1 H, H3′), 4.05 (m, 1 H, H4′), 3.85 (m, 2 H, H5′), 8.2 (s, 1 H, H6), 2.75 (m, 2 H, H7), 3.35 (m, 2 H, H8), 4.3 (t, 1 H, H9), 3.4 (m, 2 H, H10), 7.45 (s, 1 H, H12), 8.75 (s, 1 H, H13). FABMS m/z 447^+ (M + Li). Exact mass found 447.4694, calculated for $C_{20}H_{29}N_7O_7Li$ 447.4644.

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Supplementary Material Available: NMR spectra of representative compounds and the experimental conditions are given in supplementary material (29 pages). Ordering information is given on any current masthead page.

Organotin-Mediated Monoacylation of Diols with Reversed Chemoselectivity: A Convenient Synthetic Method[1]

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The organotin-mediated monoesterification of unsymmetrical diols with reversed chemoselectivity has been explored to ascertain scope and limits of the method and to provide an easy and convenient synthetic procedure. The reaction has been performed on a set of substituted diols with some acylating agents usually employed as protecting groups. Two different procedures have been devised to obtain either the desired diol monoesters directly or the corresponding trialkylsilyl ethers as protected derivatives. The latter provides a convenient approach to the preparation of easily interconvertible diol monoesters. Also, the reaction has been optimized as a one-pot procedure, avoiding the isolation and purification of the stannylated intermediates. The reversed monoesterification method has been successfully applied to 1,2-, 1,3-, and 1,4-diols of primary–secondary, primary–tertiary, and secondary–tertiary types and to ether functions containing 1,2-diols. Within its limits, the described method represents the first direct one-pot monoesterification of diols at the most substituted site, allowing some remarkable achievements as (a) an almost regiospecific reversed monobenzoylation of some 1,2-diols, (b) the selective acylation of the tertiary hydroxyl of a primary–tertiary diol, and (c) a highly selective preparation of the secondary pivalate of primary–secondary diols.

In a previous paper,[2] we reported experimental evidence that the reactivity order of hydroxyl groups toward acylating agents can be reversed by activation through their stannyl derivatives. In particular, unsymmetrically substituted ethylene glycols could be efficiently esterified at the most substituted site. Such observation was unprecedented in the chemical literature: while chemoselective esterification reactions of diols and polyols,[3] including regioselective manipulation of hydroxyl groups via organotin derivatives,[4] were reported to enhance the natural

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