Preparation of 1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (d4T)[1] and 2′,3′-Dideoxyadenosine (ddA): General Methods for the Synthesis of 2′,3′-Olefinic and 2′,3′-Dideoxy Nucleoside Analogues Active against HIV

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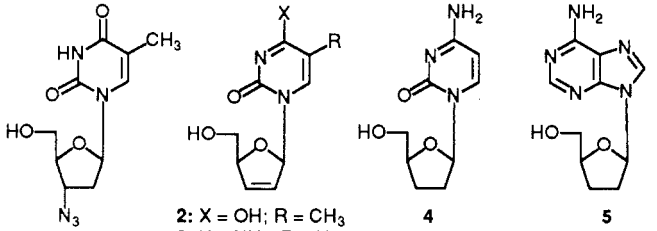
The 2′,3′-unsaturated thymidine and cytidine analogues **2** and **3**, respectively, 2′,3′-dideoxycytidine (**4**), and 2′,3′-dideoxyadenosine (**5**) have been shown to be active in vitro against HIV; therefore, methods for the preparation of these substances are of interest. The conversion of the vicinal diol functionality of ribonucleosides to the 2′,3′-olefinic 2′,3′-dideoxy analogues represents one of the most general routes for the preparation of these unsaturated nucleoside analogues. Here, we report on three methods for transforming ribonucleosides to the corresponding olefins. The methods used were the Corey–Winter reaction involving the fragmentation of a cyclic thionocarbonate **10**, olefin formation from 2′,3′-*O*-alkoxymethylidene cyclic ortho esters **15**, and the reductive elimination of the 2′,3′ halo acetates **20**, **23**, **26**, **27**, and **30**. Of these three, the last method was found to be the most versatile, since the intermediate *cis*-2′-bromo-3′-*O*-acetyl-2′-deoxyribosylpyrimidines **20**, **23**, and **30** or the *trans*-3′(2′)-bromo-2′(3′)-*O*-acetyl-3′(2′)-deoxyarabinosylpurines **26** and **27** are readily transformed to the corresponding olefins. As an example of the preparation of a saturated 2′,3′-dideoxy analogue, 2′,3′-dideoxyadenosine (**5**) was obtained by catalytic reduction of the corresponding olefinic nucleoside **29**.

Acquired immunodeficiency syndrome (AIDS) is a devastating disease that results from infection by human immunodeficiency virus (HIV).[2] HIV, as a retrovirus, has a unique viral specified enzyme, reverse transcriptase (RT), which transcribes the RNA of the virus into proviral DNA. This process is essential for virus replication. Many of the compounds found as anti-HIV agents have been targeted against RT.[3]

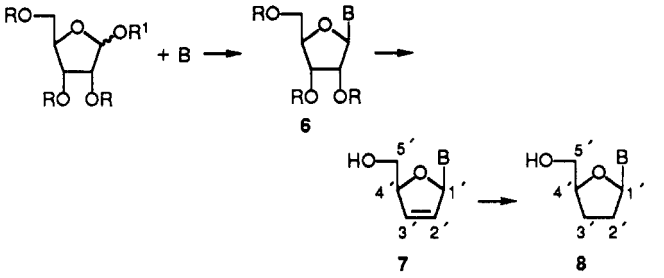
Nearly all of the compounds tested as potential RT inhibitors are nucleoside analogues, and one example, 3′-azido-3′-deoxythymidine (AZT, **1**), is the only drug approved for the treatment of AIDS.[4] The mode of action of these substances involves conversion to the nucleoside triphosphates, and it is the triphosphates that inhibit the enzyme, RT.[5] Because the phosphorylation of the parent nucleoside analogue to the biologically active triphosphate involves several kinases with different specificities, the structure–activity relationship (SAR) of this class of anti-HIV compounds is complex. Among the compounds that have shown comparable in vitro activity to AZT against HIV are the unsaturated nucleoside analogues 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (d4T, **2**) and 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)cytosine (d4C, **3**).[6,7] Several saturated or 2′,3′-dideoxy analogues such as 2′,3′-dideoxycytidine (ddC, **4**) and 2′,3′-dideoxyadenosine (ddA, **5**) have also exhibited promising in vitro activity.[8]



1 **2**: X = OH; R = CH_3 **3**: X = NH_2; R = H **4** **5**

Since multigram quantities of these unsaturated and saturated nucleoside analogues were required for advanced biological studies, methods that facilitate the synthesis of these substances in a more general and economical manner than the preparations previously described were explored. In this paper, we report on three approaches that allow

Scheme I[a]



6 **7** **8**

[a] R = Ac or Bz; R^1 = Ac; B = nucleoside base.

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(1) The abbreviation d4T used in this paper is derived from the non-IUPAC name 2′,3′-didehydro-2′,3′-dideoxythymidine. This compound has also been referred to as 2′,3′-dideoxythymidinene (ddThd).

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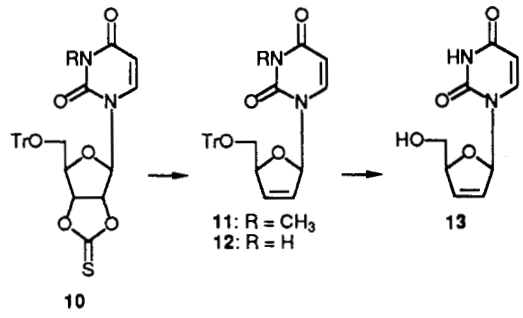
0022-3263/89/1954-4780$01.50/0

Scheme II



access to 2',3'-olefinic derivatives **7** and subsequently the 2',3'-dideoxy nucleosides **8** from the corresponding 2',3'-dihydroxy precursors (ribonucleosides). The general strategy is outlined in Scheme I.

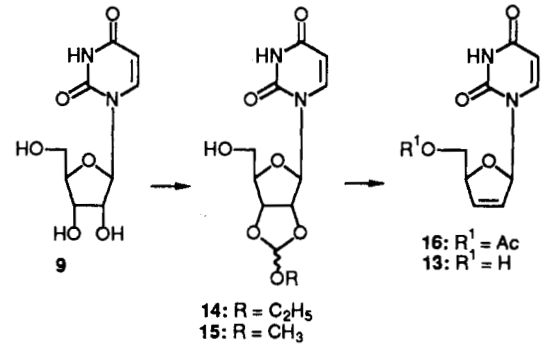
Results and Discussion

Few of the known methods[9] for conversion of vicinal diols to olefins have been applied to ribonucleosides. In part, this may be due to the lability of the derived allylic glycosidic bond to either acidic[10] or basic[7] conditions. Therefore, the conversion of the cis vicinal diol to the olefin should be carried out under mild, neutral conditions. In those cases where the 5'-OH is protected, the removal of the protecting group must also be conducted under mild conditions.

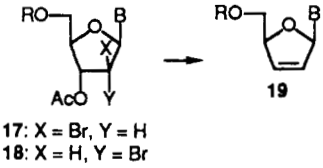
The first approach to the unsaturated nucleoside derivatives utilized the Corey-Winter reaction.[11-13] In this procedure, a 1,2-diol is converted to a 1,3-dioxolane-2-thione (cyclic thionocarbonate), which fragments under the appropriate conditions to furnish the corresponding olefin. In our initial studies, uridine was used as the starting ribonucleoside. Protection of uridine (**9**) as its 5'-*O*-trityl ether followed by reaction with 1,1'-thiocarbonyldiimidazole gave the desired cyclic thionocarbonate **10** in 67% yield for the two steps.[14,15] (See Scheme II.)

Patchett and co-workers found that when **10** was heated with trimethyl phosphite, olefination and methylation at N^3 occurred concomitantly to give **11** as the only isolated product.[15] (See Scheme II.) We have found that when **10** was heated with triethyl phosphite at 160 °C for 1 h, olefination occurred without N^3-alkylation to afford **12** as the major product in 45% yield after flash column chromatography. Deprotection of **12** to **13** with catalytic *p*-toluenesulfonic acid (*p*-TsOH) in 5:1 chloroform/methanol proceeded in 40% yield. The major byproduct of the deprotection step was uracil, which is formed as a result of cleavage of the glycosidic bond under the acidic conditions necessary to remove the trityl group. Since the yield from uridine (**9**) to **12** was only a modest 30%, no attempt was made to improve the final deprotection by using 5'-protecting groups other than the trityl moiety.[16] This sequence gave an overall yield of 12% for the four steps from uridine (**9**) to 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (d4U, **13**).[17]

Scheme III



Scheme IV



2-Alkoxy-1,3-dioxolanes were used as intermediates for our second approach for the conversion of ribonucleosides to unsaturated olefins. (See Scheme III.) Reaction of uridine (**9**) with triethyl orthoformate gave the 2-ethoxy-1,3-dioxolane **14** in good yield. Unfortunately, treatment of the nucleoside **14** with benzoic acid according to the Eastwood deoxygenation procedure failed to give the desired olefin.[18-21] (See Scheme III.)

The recent observation that 2-methoxy-1,3-dioxolanes can also be converted to the corresponding olefins on heating to reflux in acetic anhydride prompted us to investigate this as an alternative[22] to the Eastwood procedure. A solution of uridine (**9**) and trimethyl orthoformate in THF was heated at reflux with a catalytic amount of *p*-TsOH to provide ortho ester **15** in 68% yield after flash column chromatography.[23,24] The ortho ester **15** was heated at reflux in acetic anhydride for 3 h to give the protected nucleoside **16** in 40% yield along with N^1-acetyluracil after flash column chromatography. The acetate **16** was then heated in a saturated solution of ammonia in methanol at 60 °C overnight to provide the desired product, d4U (**13**), in 75% yield after recrystallization. With this modified method, the overall yield of the isolated product for the three-step sequence from uridine (**9**) to **13** was 22%.

The olefination reaction was also carried out in the presence of a base such as triethylamine or sodium bicarbonate to neutralize the acetic acid formed as a byproduct during the reaction; however, the yield of **16** did

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(17) Chu, C. K.; Bhadti, V. S.; Dobeszewski, B.; Gu, Z. P.; Kosugi, Y.; Pullaiah, K. C.; Van Roey, P. *J. Org. Chem.* **1989**, *54*, 2217. These authors reported on an alternative organosulfur approach to **13**.
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not improve. Also, the reaction proceeded more slowly in the presence of base. Conversely, the olefination reaction (**15** → **16**) proceeded faster on addition of a catalytic amount of *p*-TsOH. Despite the increase in the reaction rate, the yield of the isolated product **16** remained at 40%. This result suggests that the presence of acid accelerates the formation, but also promotes the decomposition of the product olefin.[10,25]

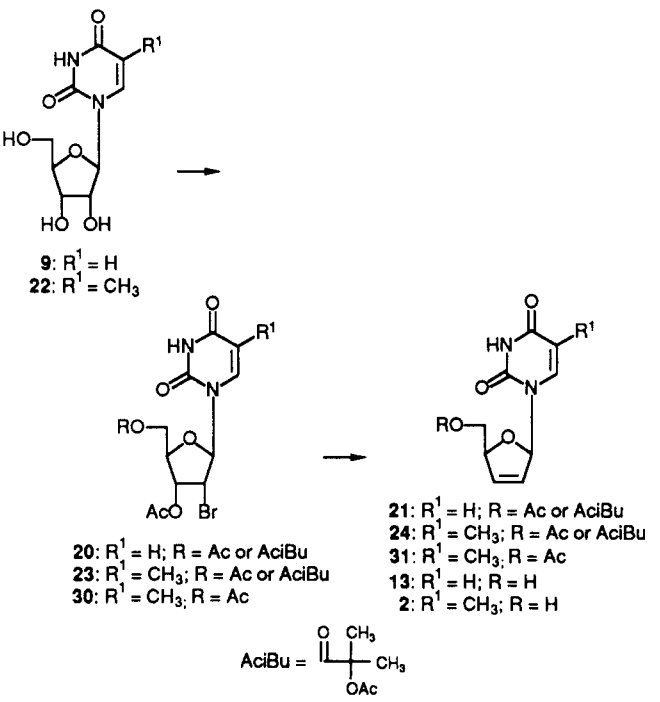
Verheyden and Moffatt had originally shown that both 2′,3′-trans halo acetate **17** or 2′,3′-cis halo acetate **18** could be converted to the olefinic nucleoside **19** on treatment with chromous acetate.[26,27] (See Scheme IV.) In a later improvement, Classon used zinc/acetic acid rather than chromous acetate for the same conversion,[28] and most recently, Robins has reported the use of a Zn/Cu couple for this transformation.[29] We investigated this chemistry as our third approach.

As before, we first applied this strategy to uridine (**9**). Reaction of uridine (**9**) with 2-acetoxyisobutyryl bromide (Mattocks's bromide)[30] gave 5′-*O*-protected bromo acetate **20** in 67% yield after flash column chromatography. The 5′-*O*-protecting group was a mixture of either the 5′-*O*-2-acetoxyisobutyrate or the 5′-*O*-acetate. The heterogeneous mixture of **20** was stirred in DMF with an activated Zn/Cu couple for 2.5 h, and the crude reaction mixture was treated with a saturated solution of ammonia in methanol to give the desired olefin **13** in 55% yield after column chromatography. Uracil was also formed as the major side product. In this sequence, uridine (**9**) was converted to the 2′,3′-olefinic 2′,3′-dideoxy compound **13** in a two-step procedure in 40% overall yield. These preliminary results encouraged us to extend this third method to additional analogues.

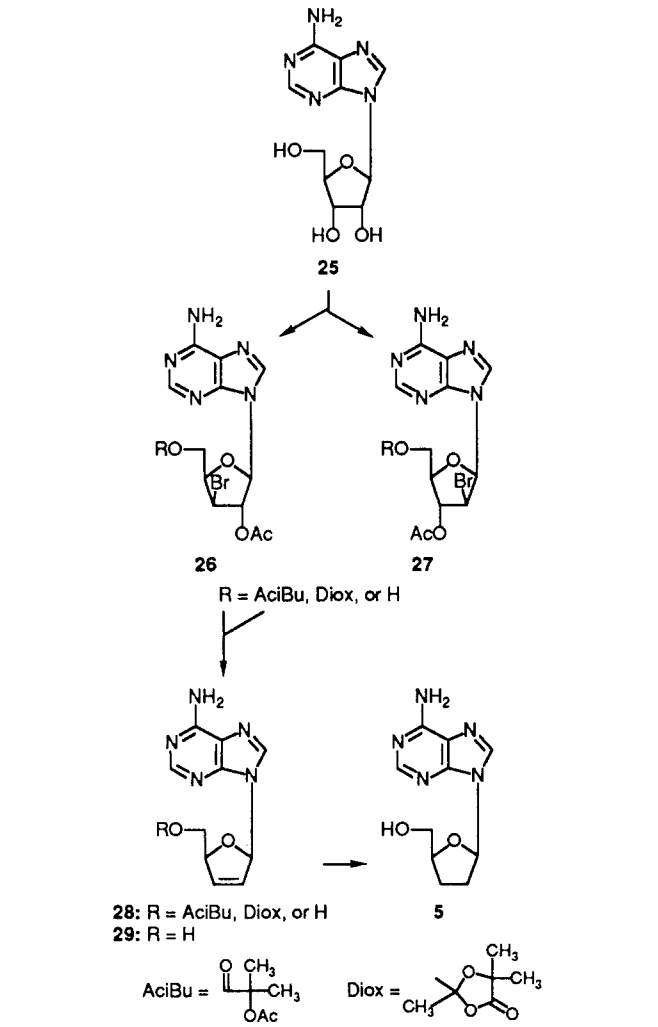
For the preparation of 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (d4T, **2**), 5-methyluridine (**22**) was synthesized by a coupling reaction between 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribose and silylated thymine.[31] The benzoate protecting groups were easily removed with sodium methoxide in methanol to give **22** as a crystalline solid in excellent overall yield (80–85%). This sequence was carried out on a multigram scale and required no chromatography. Reaction of **22** with Mattocks's bromide gave a mixture of esters **23**, which was directly reduced with the activated Zn/Cu couple (10 equiv). The desired olefinic product **24** was obtained in 38% overall yield from **22** after chromatography. Thymine was the major side product from the reduction reaction (40%). Several variations in reaction times and stoichiometry of the reagents were examined in an attempt to optimize the yield of **24** over that of thymine. However, these variations gave either incomplete consumption of starting material or an increase in the amount of thymine formed.

The desired final product d4T (**2**) was obtained in greater than 72% yield by stirring **24** with sodium methoxide in methanol for 16 h. The overall yield for the preparation of d4T (**2**) for this sequence was 27% from 5-methyluridine. (See Scheme V.)

Scheme V



Scheme VI



(25) During the preparation of this manuscript, a similar dioxolane-based route to **12** was reported. The authors report observations similar to our own. See: Shiragami, H.; Irie, Y.; Shirae, H.; Yokozeki, K.; Yasuda, N. *J. Org. Chem.* **1988**, *53*, 5179.

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While Robins has successfully applied this chemistry to the preparation of ddA (5) from adenosine (25), the reaction sequence was conducted on a small scale and required two chromatographic purifications. For multigram preparations of ddA (5), our goal was to modify the sequence such that it was amenable to scale up and to avoid the use of any intermediate chromatographic purification.

Reaction of adenosine (25) with 2-acetoxyisobutyryl bromide provided the bromo acetates 26 and 27, in which the 5'-position was protected as a mixture of either the 2-acetoxyisobutyrate or the dioxolane. (See Scheme VI.) The bromo acetates (26/27) were treated with the Zn/Cu couple at room temperature in DMF for 5–10 min to afford protected olefins 28. Treatment of the crude mixture of olefins with a saturated solution of ammonia in methanol at 20 °C overnight gave d4A (29) in 55% yield. We have also found that the Zn/Cu reaction can be carried out in MeOH or THF rather than DMF.[32] This modification was especially useful on larger scale reactions since the larger volumes of solvent can be removed at lower temperatures; prolonged exposure to higher temperatures can lead to cleavage of the glycosidic bond.[7] None of the intermediates between adenosine (27) and d4A (29) were purified. The olefin 29 was hydrogenated to give ddA (5) in greater than 70% isolated yield. The overall yield for the conversion of adenosine (25) to ddA (5) was 36–39%.

The strategy of using the reductive elimination of the bromo acetates to give the olefinic nucleosides is very attractive; however, the use of Mattocks's bromide is not ideal. The reagent is expensive and gives a mixture of products. The earlier report that addition of acetyl bromide to a suspension of uridine in acetonitrile heated at reflux gave the 2'-bromo-3',5'-di-*O*-acetyl-2'-deoxyuridine[33] led us to substitute acetyl bromide for Mattocks's bromide in our d4T synthesis.

Acetyl bromide was added to a solution of 5-methyluridine (22) in acetonitrile heated at reflux to give 30 (R = $COCH_3$ only) in 97% yield. (See Scheme V.) The reaction is cleaner because the 5'-position is protected only as the acetate. Olefination of 30 (R = $COCH_3$ only) with the Zn/Cu reagent afforded 31 in 50–55% yield. The olefin was deprotected with methoxide in methanol to give 2 in 87% yield. This latter sequence, using acetyl bromide, gave d4T (2) in 40% overall yield for the five-step reaction sequence from 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribose as opposed to 27% overall yield using the Mattocks's bromide approach.

In their initial studies, Moffatt et al. noted that the reaction of pyrimidines with Mattocks's bromide gave only cis bromo acetates. This is due to the intramolecular participation of the *O*-2 oxygen to give the *O*-2,2'-anhydro compound. The anhydro can subsequently be opened with bromide ion to give the bromo acetates 20. With the purine analogues, this intramolecular participation is not possible; consequently, a mixture of trans bromo acetates are formed.

Of the three methods described for the preparation of 2',3'-olefinic nucleosides, the reductive elimination of bromo acetates was found to be the most efficient and versatile. The use of acetyl bromide, rather than 2-acetoxyisobutryl bromide, to prepare the intermediate bromo acetates makes this approach higher yielding and more economical. The utility of this chemistry has been illustrated with our synthesis of d4T (2). The use of ribonucleosides to prepare 2',3'-olefinic nucleosides also provides an efficient entry to 2',3'-dideoxy nucleosides.

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Experimental Section

The melting points were determined on an Electrotherm capillary apparatus and are uncorrected. TLC was performed on silica gel 60 F-254 plates purchased from E. Merck and Co., and flash column chromatography was performed on silica gel (40-μM particle size, Baker). The NMR spectra were recorded on Varian Gemini 300-MHz or Bruker 360-MHz instruments and are reported in parts per million from tetramethylsilane. The mass spectra were recorded on a Finnegan Model 4500 instrument, and the high-resolution mass spectra were measured on a Kratos MS 25 instrument. Microanalytical data were obtained through the Bristol-Myers Analytical Research Department, Wallingford, CT.

1-(2,3-*O*-Thiocarbonyl-5-*O*-tritylribofuranosyl)uracil (10). Dry tetrahydrofuran (110 mL) was added to 5'-*O*-trityluridine[14,15] (10.6 g, 22 mmol) under an argon atmosphere and stirred until the reaction mixture was homogeneous. 1,1'-Thiocarbonyldiimidazole (4.3 g, 27 mmol) was added to the solution in one portion, and the resulting yellow reaction mixture was stirred at room temperature for 72 h. The solvent was removed in vacuo and the resulting syrup purified by flash column chromatography on silica gel, ethyl acetate/hexane (3:1). The product was recrystallized from absolute ethanol to give a white powder (8.8 g, 77%): ^{1}H NMR (360 MHz, $CDCl_3$) 8.89 (br s, 1 H, NH), 7.34–7.19 (m, 16 H, 3 C_6H_5, H-6), 5.71 (d, 1 H, J = 8.0 Hz, H-5), 5.65 (m, 2 H, H-2', H-3'), 5.43 (m, 1 H, H-1'), 4.44 (m, 1 H, H-4'), 3.48 (dd, 1 H, J = 6.6 Hz, J = 10.3 Hz, H-5'a), and 3.37 (dd, 1 H, J = 4.9 Hz, J = 10.3 Hz, H-5'b).

1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl-5-*O*-trityl)uracil (12). Triethyl phosphite was heated to 160 °C, and 1-(2,3-*O*-thiocarbonyl-5-*O*-tritylribofuranosyl)uracil (10) (6 g, 11.4 mmol) was then added in one portion. The reaction mixture was heated at 160 °C for a further 1 h. The solvent was removed in vacuo and the resultant glassy solid purified by flash column chromatography on silica gel, ethyl acetate/hexane (3:1). The desired product was isolated, recrystallized from ethyl acetate/hexane, and collected as a white solid (2.3 g, 45%): mp 188–191 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.95 (br s, 1 H, NH), 7.97 (d, 1 H, J = 8.1 Hz, H-6), 7.53–7.40 (m, 15 H, 3 C_6H_5), 7.19 (m, 1 H, H-1'), 6.51 (m, 1 H, H-3'), 6.05 (m, 1 H, H-2'), 5.21 (dd, 1 H, J = 1.6 Hz, J = 8.1 Hz, H-5), 5.13 (br s, 1 H, H-4'), 3.66 (dd, 1 H, J = 3.3 Hz, J = 10.8 Hz, H-5'a), and 3.59 (dd, 1 H, J = 2.6 Hz, J = 10.8 Hz, H-5'b); ^{13}C NMR (75.5 MHz, $CDCl_3$) 163.05 (C-4), 150.50 (C-2), 142.96 (aromatic), 141.18 (C-6), 134.36 (C-3'), 128.65, 127.90, 127.37 (aromatic), 126.26 (C-2'), 102.18 (C-5), 89.97 (C-1'), 87.35 (C-4'), 85.87 (CPh_3), and 64.34 (C-5'). Anal. Calcd for $C_{28}H_{24}N_2O_4$: C, 74.33; H, 5.31; N, 6.19. Found: C, 74.23; H, 5.29; N, 6.13.

1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (d4U) (13). 1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl-5-*O*-trityl)uracil (12) (0.5 g, 1.1 mmol) was dissolved in a chloroform (10 mL) and methanol (2 mL) mixture containing *p*-toluenesulfonic acid (45 mg, 0.24 mmol). The solution was stirred at room temperature for 0.75 h and then neutralized with 2 N NaOH (0.5 mL). The solvents were removed in vacuo and the residue purified by flash column chromatography on silica gel, chloroform/acetone (2:1). The desired product was isolated as a white crystalline solid (93 mg, 40%): mp 154–157 °C (lit.[26] mp 154–155 °C); ^{1}H NMR (200 MHz, D_2O/DMSO-d_6) 11.22 (m, 1 H, NH), 7.75 (d, 1 H, J = 8.2 Hz, H-6), 6.81 (m, 1 H, H-1'), 6.39 (d, 1 H, J = 6.0 Hz, H-3'), 5.91 (d, 1 H, J = 5.8 Hz, H-2'), 5.59 (d, 1 H, J = 8.2 Hz, H-5), 4.98 (m, 1 H, H-4'), and 3.58 (m, 2 H, H-5'); ^{13}C NMR (75.5 MHz, D_2O/DMSO-d_6) 165.66 (C-4), 155.37 (C-2), 141.63 (C-6), 134.00 (C-3'), 126.81 (C-2'), 101.64 (C-5), 89.16 (C-1'), 87.51 (C-4'), and 62.39 (C-5').

2',3'-*O*-(Methoxymethylidene)uridine (15). Uridine (9) (50 g, 205 mmol) and pyridinium *p*-toluenesulfonate (5 g, 20 mmol) were added to freshly distilled tetrahydrofuran (500 mL) under nitrogen to give a heterogeneous mixture. Trimethyl orthoformate (109 g, 1.03 mmol) was added dropwise and the reaction mixture stirred for 18 h at ambient temperature. The resulting solution was treated with water (18 g, 1 mol) and stirred for a further 0.5 h, pyridine (20 mL) was added, and the reaction was stirred at room temperature for 18 h. The solvents were removed in vacuo, and the resultant white solid was purified by flash column

chromatography on silica gel, chloroform/acetone (4:1), to give the desired product as a white solid (40 g, 68%): mp 188–190 °C. (lit.[23,24] mp 189–190 °C).

1-(5-*O*-Acetyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (16). *p*-Toluenesulfonic acid (20 mg) was added to a solution of the methoxymethylidene compound **15** (10 g, 35 mmol) in acetic anhydride (100 mL) and the solution heated at 140 °C for 6 h. The solution was allowed to cool to room temperature, and triethylamine (1 mL) was added. The solvents were removed in vacuo, and the product was purified by flash column chromatography on silica gel, chloroform/acetone (4:1), to give the desired product **16** as a clear oil, which converted to a white foam under vacuum (4.0 g, 45%): mp 127–129 °C (lit.[26] mp 127–128 °C); ^{1}H NMR (360 MHz, $CDCl_3$) 8.53 (br s, 1 H, NH), 7.47 (d, 1 H, J = 8.6 Hz, H-6), 7.00 (m, 1 H, H-1′), 6.51 (m, 1 H, H-3′), 5.93 (m, 1 H, H-2′), 5.72 (dd, 1 H, J = 2.2 Hz, J = 8.7 Hz, H-5), 5.08 (m, 1 H, H-4′), 4.38 (dd, 1 H, J = 3.2 Hz, J = 13.2 Hz, H-5′a), 4.25 (dd, 1 H, J = 2.2 Hz, J = 13.6 Hz, H-5′b), and 2.01 (s, 3 H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 171.11 (C=O), 164.18 (C-4), 151.48 (C-2), 140.55 (C-3′), 134.09 (C-2′), 127.61 (C-6), 103.08 (C-5), 90.47 (C-1′), 84.79 (C-4′), 64.94 (C-5′), and 20.92 (CH_3).

1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (d4U) (13). 1-(5-*O*-Acetyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (**16**) (3.2 g, 9.5 mmol) was added in one portion to a saturated solution of ammonia in methanol (20 mL). The solution was stirred at ambient temperature overnight and concentrated, and the crude material was purified by flash column chromatography on silica gel, methylene chloride/methanol (20:1 decreasing to 10:1). The desired product **13** was isolated as a white solid (1.8 g, 75%): mp 152–154 °C (lit.[26] mp 154–155 °C). The ^{1}H and ^{13}C NMR and TLC of the substance were identical with those described above for **13**.

1-(5-*O*-(Acetoxyisobutyryl)-3-*O*-acetyl-2-bromo-2-deoxyribosyl)uracil (20). 2-Acetoxyisobutyryl bromide (12.85 g, 63 mmol) was added over 0.25 h to a suspension of uridine (**9**) (5.0 g, 21 mmol) in acetonitrile (90 mL) and the solution heated at 80 °C for 3 h. The solution was cooled to room temperature and the solvent removed in vacuo. The resulting syrup was dissolved in ethyl acetate (200 mL) and washed with saturated sodium bicarbonate (3 × 100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated and the residue purified by flash column chromatography on silica gel, ethyl acetate/hexane (3:1), to give 6.7 g (67%) of a white foam. The crude reaction product was used in the next step without further purification: mp 68–70 °C; mass spectrum MH^+ = 477.

1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (d4U) (13). The crude bromouridine **20** (2 g, 4.2 mmol) was dissolved in DMF (3 mL) and added dropwise to a slurry of freshly prepared Zn/Cu couple (0.70 g, 10.5 mmol)[34] in dry DMF (25 mL). The mixture was stirred at room temperature until no starting material remained. The mixture was filtered through Celite and the filtrate concentrated in vacuo. The resulting white solid (1.1 g, 85%) was dissolved in methanol and cooled to 0 °C in an ice/water bath. Anhydrous ammonia gas was bubbled into the solution for 0.3 h, and the solution was then warmed at 60 °C for 18 h. The solvents were removed, and the resulting white solid was purified by flash column chromatography on silica gel, methanol/chloroform (1:9), to give 0.5 g (55%) of the desired product from the bromouridine: mp 154–156 °C (lit.[26] mp 154–155 °C). The ^{1}H and ^{13}C NMR and TLC of d4U (**13**) prepared by this method were identical with those of samples of d4U prepared by the alternative methods described above.

5-Methyluridine (22). Thymine (3.80 g, 30.23 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribose (12.7 g, 25.4 mmol) were suspended in dry acetonitrile (350 mL). Trimethylsilyl chloride (3.2 mL, 25.9 mmol), hexamethyldisilazane (5.3 mL, 25.4 mmol), and trifluoromethanesulfonic acid (2.7 mL, 30.23 mmol) were added, and the suspension was heated to reflux for 1 h. The solution was concentrated in vacuo and then diluted with methylene chloride (100 mL). The organic solution was washed with water (20 mL), saturated sodium bicarbonate (2 × 20 mL), and brine (20 mL) and then dried ($MgSO_4$). The organic solution was filtered and concentrated to give 2′,3′,5′-tri-*O*-benzoyl-5-methyluridine as a white solid (14.36 g). The solid (14.36 g, 25.2 mmol) was dissolved in methanol (350 mL), sodium methoxide (8.16 g, 151.2 mmol) was added, and the reaction mixture was stirred at room temperature overnight. The solution was neutralized with Dowex 50 × 8-200 ion-exchange resin. The reaction mixture was concentrated, dissolved in water (100 mL), washed with ether (2 × 150 mL), and then lyophilized. The dried sample was recrystallized from absolute ethanol to give **22** as a white solid (5.76 g, 88%): mp 178–180 °C (lit.[31] mp 178–179 °C).

1-(5-*O*-(Acetoxyisobutyryl)-3-*O*-acetyl-2-bromo-2-deoxyribosyl)thymine (23). 2-Acetoxyisobutyryl bromide (2.09 g, 9.88 mmol) was added to a suspension of 5-methyluridine (**22**) (0.85 g, 3.29 mmol) in acetonitrile (50 mL). The mixture was heated at reflux for 2 h and then allowed to cool. The solvent was removed in vacuo, and the residue was dissolved in ethyl acetate, washed with saturated sodium bicarbonate (30 mL) and water (30 mL), and dried ($MgSO_4$). The dried solution was filtered and concentrated to afford a crude product (1.6 g), which was used in the next step without purification.

1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (d4T) (2). A freshly prepared Zn/Cu couple (1.5 g)[34] was added to a solution of the crude reaction product from the previous reaction (1.6 g) in DMF (5 mL). The mixture was stirred at room temperature for 20 h, excess solid sodium bicarbonate was added, and the solvent was removed in vacuo. The residue was purified by flash column chromatography, methylene chloride/methanol (20:1), to give the desired olefinic product **24** (0.48 g, 30% from **22**).

Sodium methoxide (0.22 g, 4.08 mmol) was added to a solution of **24** (0.48 g, 1.4 mmol) in methanol (40 mL), and the mixture was stirred for 16 h. The mixture was neutralized with Dowex 50 × 8-200 acidic resin (which had previously been washed with methanol). The resin was filtered and washed with methanol. The combined filtrates were concentrated, and the residue was purified by flash column chromatography, methylene chloride/methanol/ammonium hydroxide (90:10:1). d4T was collected as a white solid (0.20 g, 27% from **22**): mp 163–166 °C (lit.[7,35] mp 164–166).

1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)adenine (d4A) (29). Acetonitrile (20 mL), water (0.4 mL, 22.2 mmol), and 2-acetoxyisobutyryl bromide (12 mL, 80 mmol) were added to a slurry of adenosine (**25**) (5.34 g, 20 mmol) in acetonitrile (80 mL). The mixture was stirred for 1.5 h, then quenched with saturated $NaHCO_3$ (200 mL),[36] and stirred for a further 5 min. The resulting solution was extracted with methylene chloride (3 × 100 mL) and then concentrated to 50 mL. Methanol (100 mL) was added and the solution concentrated once more to 50 mL. Methanol (100 mL) was again added and the solution concentrated to 50 mL; this solution of **26** and **27** was used directly in the next step.

The solution of **26** and **27** obtained above was added to the freshly prepared Zn/Cu couple[34] and the heterogeneous reaction mixture stirred for 5 min. The reaction mixture was filtered through Celite and the Celite pad washed further with methanol (50 mL). The filtrate was collected and Amberlyst 27 exchange resin (OH form) added portionwise until a gradual increase in the pH was observed.[37] A white precipitate formed. The mixture was filtered through Celite and the pad washed with methanol (50 mL). The filtrate, which contained **28**, was concentrated to 50 mL and then added, at 0 °C, to a saturated solution of ammonia in methanol (50 mL). The solution was allowed to warm to 20 °C and stirred for 24 h. The reaction mixture was concentrated in vacuo and the residue triturated with ethanol at 0 °C for 1 h. The resultant solid was collected, washed with ethanol, and dried

(34) The Zn/Cu couple was prepared immediately before use. Glacial acetic acid (65 mL) was heated to ca. 110 °C. Copper(II) acetate monohydrate (2.2 g, 200 mmol) was added, followed by zinc powder (13.07 g, 200 mmol). The suspension was stirred for 1 min and then filtered onto a fritted-glass funnel. The couple was washed with acetic acid (2 × 25 mL) and methanol (2 × 25 mL), scraped into a clean reaction flask, and covered with methanol (25 mL).

(35) Horwitz, J.; Chua, J. In *Synthetic Procedures in Nucleic Acid Chemistry*; Zorbach, W. W., Tipson, R. S., Eds. Interscience: New York; Vol. 1, p 344.

(36) The solution should be slightly basic; if this is not the case, solid $NaHCO_3$ should be added to adjust to pH 8.

(37) A pH meter should be used. Normally 50–75 mL of resin is added.

to give the desired d4A (**29**) as a white crystalline solid (2.6 g, 56% from adenosine): mp 191–192 °C (lit.[28] mp 194–195 °C); ^{1}H NMR (360 MHz, DMSO-d_6) 8.18 (s, 1 H, H-2), 8.17 (s, 1 H, H-8), 7.34 (s, 2 H, NH_2), 6.95 (s, 1 H, H-1′), 6.46 (d, 1 H, J = 6.0 Hz, H-3′), 6.14 (d, 1 H, J = 6.0 Hz, H-2′), 5.07 (t, 1 H, J = 5.5 Hz, OH), 4.89 (m, 1 H, H-4′), and 3.57 (m, 2 H, H-5′); ^{13}C NMR (75.5 MHz, DMSO-d_6) 156.07 (C-2), 152.67 (C-6), 149.18 (C-4), 139.22 (C-8), 134.39 (C-2′), 125.54 (C-3′), 118.81 (C-5), 88.07 (C-1′), 87.89 (C-4′), and 62.81 (C-5′).

2′,3′-Dideoxyadenosine (ddA) (5). Palladium on carbon (5%) (2.3 g) was added to a slurry of d4A (**29**) (4.48 g, 19.3 mmol) in 90% aqueous ethanol (240 mL). The reaction mixture was exposed to hydrogen (pressure is not necessary) and stirred for 4 h. The mixture was filtered through Celite, and the Celite was washed with ethanol (100 mL). The combined filtrate was concentrated in vacuo to ca. 20 mL. The resulting slurry was dissolved in boiling ethanol (total volume 80 mL) and filtered hot through a dicalite pad. The filtrate was allowed to cool slowly to 20 °C and then stored at 0–5 °C for 18 h. The solid was collected, washed with ethanol (2 × 10 mL), and dried to give 3.23 g (72%) of ddA (**5**) as a white solid. This sample contained 96.8% of ddA by HPLC and 1.31% adenine. The amount of adenine could be reduced to 0.67% by a recrystallization from ethanol: mp 185–186 °C (lit.[29] mp 185–187 °C); ^{1}H NMR (360 MHz, DMSO-d_6) 8.35 (s, 1 H, H-2), 8.13 (s, 1 H, H-8), 7.27 (s, 2 H, NH_2), 6.21 (t, 1 H, J = 5.2, J = 5.5 Hz, H-1′), 5.06 (br s, 1 H, OH), 4.17 (m, 1 H, H-4′), 3.61 (m, 1 H, H-5′a), 3.50 (m, 1 H, H-5′b), 2.39 (m, 2 H, H-3′), and 2.04 (m, 2 H, H-2′); ^{13}C NMR (75.5 MHz, DMSO-d_6) 155.93 (C-2), 152.33 (C-6), 148.72 (C-4), 138.97 (C-8), 119.03 (C-5), 84.39 (C-1′), 81.67 (C-4′), 62.91 (C-5′), 31.77 (C-3′), and 25.70 (C-2′).

1-(2-Bromo-2-deoxy-3,5-di-*O*-acetylribosyl)thymine (30). Acetyl bromide (13.8 mL, 113 mmol) was added dropwise over 0.5 h to a suspension of 5-methyluridine (**22**) (5 g, 19.38 mmol) in acetonitrile (250 mL) heated at reflux. On completion of addition, the solution was allowed to cool and then concentrated. The residue was dissolved in methylene chloride (50 mL) and washed with water (50 mL). The organic phase was concentrated to leave **30** as a beige solid (7.8 g, 97%): mp 55–57 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 11.51 (s, 1 H, NH), 7.51 (s, 1 H, H-6), 6.12 (d, 1 H, J = 7.9 Hz, H-1′), 5.25 (dd, 1 H, J = 2.9 Hz, J = 6.0 Hz, H-3′), 4.97 (dd, 1 H, J = 6.0 Hz, J = 7.8 Hz, H-2′), 4.3 (m, 1 H, H-4′), 4.27 (m, 2 H, H-5′), 2.12 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3), and 1.79 (s, 3 H, CH_3);[37] ^{13}C NMR (75.5 MHz, DMSO-d_6) 170.23 (C=O), 169.36 (C=O), 163.52 (C-4), 150.67 (C-2), 135.46 (C-6), 110.65 (C-5), 88.38 (C-1′), 79.74 (C-4′), 71.35 (C-3′), 62.98 (C-5′), 47.25 (C-2′), 20.63 (2 CH_3), and 12.22 (CH_3).

1-(5-*O*-Acetyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (31). A Zn/Cu couple (3 g, Fairfield chemicals) was heated at reflux in acetic acid (20 mL) for 0.5 h. The suspension was filtered and washed with methanol. The couple was suspended in methanol (70 mL), and 1-(2-bromo-2-deoxy-3,5-di-*O*-acetylribosyl)thymine (**30**) (1 g, 2.4 mmol) was added, and the mixture was stirred for 0.5 h. The mixture was filtered and concentrated, to leave an oil, which was purified by flash column chromatography, methanol/methylene chloride (1:9). The desired product **31** was isolated as a white solid (0.64 g, 53%): mp 179–181 °C (lit.[39] mp 179–181 °C); ^{1}H NMR (300 MHz, DMSO-d_6) 11.37 (s, 1 H, NH), 7.25 (s, 1 H, H-6), 6.78 (s, 1 H, H-1′), 6.38 (d, 1 H, J = 6 Hz, H-3′), 5.98 (d, 1 H, J = 6 Hz, H-2′), 4.95 (s, 1 H, H-4′), 4.18 (m, 2 H, H-5′), 2.00 (s, 3 H, CH_3), and 1.75 (s, 3 H, CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6) 170.44 (C-4), 164.04 (C=O), 151.02 (C-2), 136.14 (C-6), 133.91 (C-3′), 126.75 (C-2′), 109.75 (C-5), 89.99 (C-1′), 83.90 (C-4′), 64.76 (C-5′), 20.83 (CH_3), and 12.35 (CH_3).

1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (d4T) (2). Sodium methoxide (0.12 g, 2.35 mmol) was added to a suspension of 1-(5-*O*-acetyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (**31**) (0.5 g, 1.88 mmol) in methanol (20 mL) and the solution stirred at ambient temperature for 2 h. The solution was neutralized with strongly acidic ion-exchange resin (Dowex 50 × 8-200), which had been washed with methanol. The resin was filtered and then washed with methanol (2 × 20 mL). The filtrate was concentrated and purified by flash column chromatography on silica gel, methylene chloride/methanol/ammonium hydroxide (90:10:1) to give a white solid (0.36 g, 87%): mp 165–166 °C (lit.[7,35] mp 164–166 °C); ^{1}H NMR (360 MHz, DMSO-d_6) 11.29 (s, 1 H, NH), 7.63 (s, 1 H, H-6), 6.80 (dt, 1 H, J = 1.3 Hz, J = 0.4 Hz, H-1′), 6.36 (dt, 1 H, J = 6.1 Hz, J = 1.7 Hz, H-3′), 5.90 (dt, 1 H, J = 6.1 Hz, J = 1.4 Hz, H-2′), 5.01 (m, 1 H, OH), 4.76 (s, 1 H, H-4′), 3.60 (m, 2 H, H-5′), and 1.71 (s, 3 H, CH_3).

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Registry No. **2**, 3056-17-5; **5**, 4097-22-7; **9**, 58-96-8; **10**, 6195-94-4; **12**, 6038-55-7; **13**, 5974-93-6; **15**, 16628-81-2; **16**, 42867-74-3; **20** R = AciBu, 42867-75-4; **22**, 1463-10-1; **22** (2′,3′,5′-tri-*O*-benzoyl deriv), 3180-76-5; **23** R = AciBu, 122383-24-8; **24** R = AciBu, 122383-25-9; **25**, 58-61-7; **26** R = AciBu, 122383-26-0; **27** R = AciBu, 122383-27-1; **28** R = AciBu, 122383-28-2; **29**, 7057-48-9; **30**, 110483-43-7; **31**, 77421-68-2; AciBuBr, 40635-67-4; 5′-*O*-trityluridine, 6554-10-5; thymine, 65-71-4; 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribose, 14215-97-5.

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Synthesis of Pyrano[4,3-*b*]indoles as Conformationally Restricted Analogues of the Serotonin Antagonist ICS 205-930 and as Precursors to 2-Vinylindoles

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A useful synthesis of some pyrano[4,3-*b*]indoles is described that allows access to conformationally restricted analogues of the serotonin ($5HT_3$) antagonist, ICS 205-930. These pyrano[4,3-*b*]indoles can be converted in one step to 2-vinylindole derivatives.

Introduction

Recently, in conjunction with attempts to discover the active conformation of the extremely novel and potent serotonin ($5HT_3$) antagonist ICS 205-930, there was a desire to synthesize the spiropyrano[4,3-*b*]indole **1** as a conformationally restricted analogue of the drug. A survey of the literature revealed that while the generic pyranoindole heterocycle has received some attention, pyrano-

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