amino compound 13*. Cyclisation of 13* yields 3-(ethoxycarbonyl)pyridin-2(1*H*)-one (14*), which after hydrolysis gives the acid 15*, and subsequent decarboxylation yields pyridin-2(1*H*)-one (16*). Nitration of 16* to give 17* followed by treatment with phosphorus oxychloride yields 1*.

Experimental Section

Melting points are uncorrected. The ^{1}H NMR spectra were recorded on a Hitachi Perkin-Elmer R24B spectrometer and a Varian EM 390 spectrometer equipped with a Varian EM 3940 variable-temperature controller. Me_4Si was used as internal standard (δ = 0 ppm). The ^{13}C NMR spectra were recorded at 75.460 MHz on a Bruker CXP-300 spectrometer. Spectral parameters: spectral width 15000 Hz, pulse width 7 μs (30°), pulse delay 2 s.

Mass spectra were obtained on a AEI MS 902 spectrometer equipped with a VG ZAB console. Column chromatography was carried out over Merck silica gel 60 (70–230-mesh ASTM).

Preparation of Starting Materials and Reference Compounds. A. 2-Chloro-3,5-dinitropyridine (1),[7] 2-amino-3,5-dinitropyridine (6),[8] and 6-deuterio-2-chloro-3,5-dinitropyridine (8)[4] were all prepared according to known synthetic procedures.

B. [2-^{13}C]-2-Chloro-3,5-dinitropyridine (1*). This compound was synthesized following the route given in Scheme III. The ^{13}C-labeled compounds 11*–15* were all prepared according to the procedures described for the unlabeled compounds 11[9] and 12-15.[10] In the synthesis of ^{13}C-labeled diethyl malonate (11*), potassium cyanide enriched with about 10% ^{13}C was used. In our hands the best result in the synthesis of 3-ethoxyallylidene malonate (12*) was obtained after a reaction time of 72 h instead of the 1 h reaction time mentioned in the literature.[10]

The decarboxylation of [2-^{13}C]-3(1-^{13}C)-carboxypyridin-2-(1*H*)-one (15*) into [2-^{13}C]pyridin-2(1*H*)-one (16*) was achieved by heating 1 g of 15* to a temperature just above its melting point (about 260 °C) in an open Carius tube. After the evolution of carbon dioxide had ceased, the residue was extracted with dichloromethane. After filtration of the solution and evaporation of the solvent in vacuo, 16* was obtained in quantitative yield, mp 105–106 °C (lit.[11] mp 106–107 °C). The conversion of 16* into 1* via 17* was performed according to the procedures described for the unlabeled compound 16.[7] ^{13}C NMR data are given in Table I.

Amination of 1* in Liquid Ammonia. This reaction was carried out as described for unlabeled 1, to yield [2-^{13}C]-2-amino-3,5-dinitropyridine (6B*).[4]

Amination of 6-Deuterio-2-chloro-3,5-dinitropyridine (8). This reaction was carried out as described for 1 and gave 6-deuterio-2-amino-3,5-dinitropyridine.[4]

Amination of 1 in ^{15}N-Labeled Liquid Ammonia. This reaction was carried out as described before to yield ^{15}N-labeled 2-amino-3,5-dinitropyridine.[4] The conversion of the ^{15}N-labeled 2-amino-3,5-dinitropyridine thus obtained into 2-fluoro-3,5-dinitropyridine was performed by the procedure described for unlabeled 6.[12]

Acknowledgment. We are indebted to Drs. C. A. Landheer and Mr. C. J. Teunis for mass spectroscopic data and to Dr. H. A. J. Holterman and Mr. A. van Veldhuizen for measuring NMR spectra.

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An Improved Synthesis of 2′-Deoxy-5-azacytidine by Condensation of a 9-Fluorenylmethoxycarbonyl-Protected Sugar onto the Silylated Base

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Recent reports describing the role of 2′-deoxy-5-azacytidine (6β) in the regulation of gene expression through the inhibition of DNA methylation[1,2] have generated renewed interest in this nucleoside. 2′-Deoxy-5-azacytidine was first synthesized in 1964 by a multistep procedure described by Pliml and Sorm.[3] More recently, improved yields were obtained by a direct glycosylation procedure of silylated 5-azacytosine[4-6] or via a total synthesis using glycosyl isocyanates as intermediates.[7]

During the synthesis of deoxynucleosides by the glycosylation procedure, the sugar protecting groups play an important role in the regulation of the relative amounts of the two anomeric forms, α and β, in the final product mixture. The contributing factors in this regulation seem to be the steric and the electronic effects exerted by these groups on the C-1 position of the sugar ring.[8] Aroyl groups such as benzoyl,[9] nitrobenzoyl, chlorobenzoyl, and especially toluoyl[10] have been sucessfully used to date. The latter was found to be the protecting group of choice in the synthesis of 2′-deoxy-5-azacytidine,[6] although the strongly basic conditions (sodium methoxide in methanol) necessary for deprotection led to a significant hydrolysis of the product.[11,12] The difficulties associated with the removal of the sugar protecting groups are not confined to 2′-deoxy-5-azacytidine; the synthesis of any base-labile nucleoside analogue would meet with the same problems.

The benzyl group, removable under the neutral conditions of hydrogenolysis, was also employed in nucleoside synthesis,[9] although the 3,5-di-*O*-benzyl-2-deoxypentofuranosyl chloride is not a suitable intermediate for this purpose.[8,9] Moreover, some reduction of the aromatic ring of the nucleoside during the hydrogenolytic removal of this protecting group has been observed.[13]

Our attempts at the synthesis of 2′-deoxy-5-azacytidine via the glycosylation procedure described by Piskala,[5] using the toluoyl group for protection of the sugar moiety, were largely unsuccessful, due to the hydrolysis of the product during the final deprotection procedure. We therefore decided to investigate other protecting groups that would eliminate this problem.

In choosing a sugar protecting group suitable for the synthesis of labile nucleosides by the glycosylation pro-

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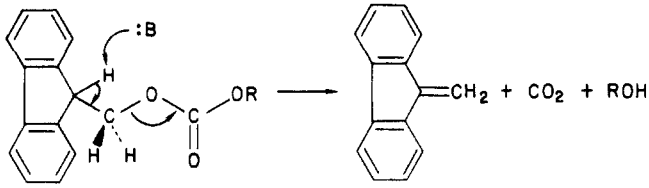
Scheme I



cedure, the following three requirements should be fulfilled: (1) It should be stable under strongly acidic conditions to enable facile synthesis of the 3,5-diprotected 1-chloro-2-deoxyribofuranose building block. (2) It should be bulky in order to exert sufficient steric effect at the C-1 position of the sugar, which apparently helps to determine the relative yield of the two anomeric products. (3) It should be removable under neutral or mildly basic conditions.

The 9-fluorenylmethoxycarbonyl group (Fmoc) satisfies all the above requirements. Although its use to date has been almost exclusively limited to peptide synthesis,[14] Chattopadhyaya et al. have recently demonstrated its usefulness in oligonucleotide synthesis both as an amino[15] and a hydroxy protecting group.[16] Its removal, via a β-elimination reaction (Scheme I), may be facilitated by the action of aqueous ammonia, piperidine, morpholine, ethanolamine,[17] or even triethylamine.[18] When used for the protection of hydroxyl groups, it may be conveniently removed by the action of triethylamine in dry pyridine.

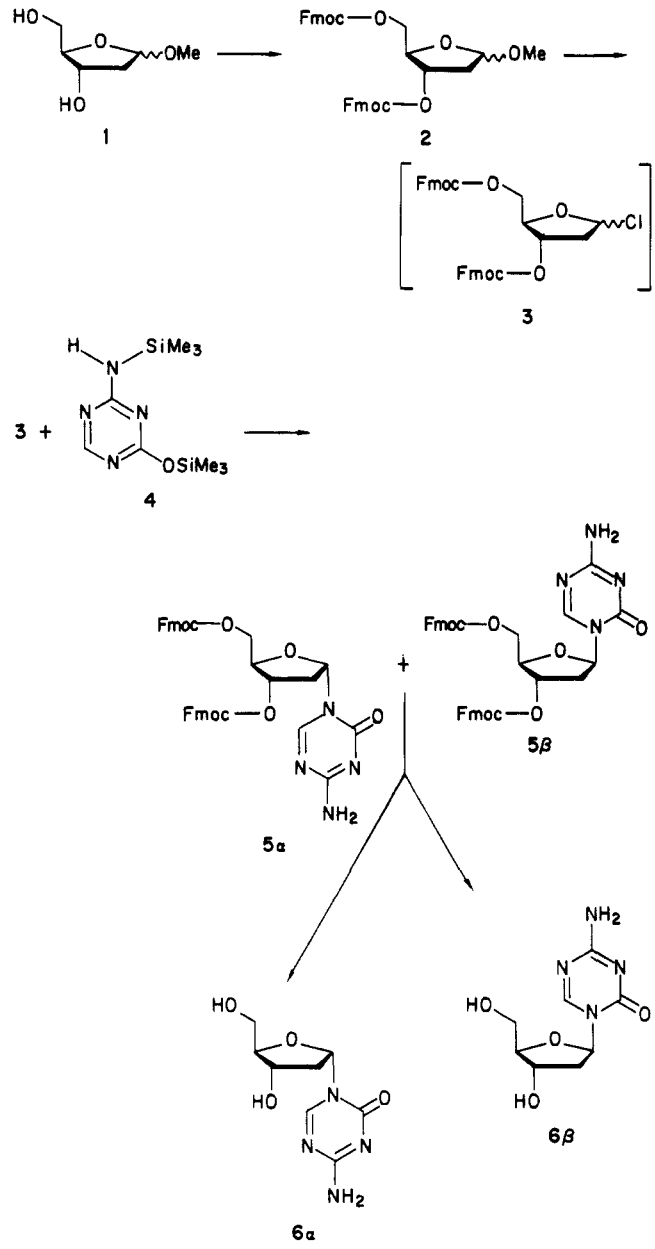
The reaction of methyl 2-deoxy-α,β-D-ribofuranoside (**1**)[19] with 9-fluorenylmethoxycarbonyl chloride in anhydrous pyridine at 0–5 °C gave 1-methoxy-3,5-bis(*O*-Fmoc)-2-deoxyribofuranose (**2**) in 93% isolated yield. The 1-chloro derivative **3**, prepared from **2** in situ, was reacted with the disilylated 5-azacytosine **4** at room temperature in 1,2-dichloroethane, in the presence of a catalytic amount of $SnCl_4$.[6,20] The resulting product mixture contained the two anomers (**5**α and **5**β) in approximately equimolar amounts. The overall yield of the reaction (45%) was comparable to the two best methods.[6,7]

The fully deprotected crystalline product **6**β was obtained from **5**α,β by the reaction of 15 equiv of triethylamine in dry pyridine after 1 h at room temperature in a 36% yield.

The use of the Fmoc group in nucleoside synthesis represents a significant improvement of the existing methodology. Our procedure should be applicable to the synthesis of numerous other nucleoside analogues, unobtainable by the standard route.

Experimental Section

1-Methoxy-2-deoxy-3,5-bis(*O*-Fmoc)-D-ribofuranose (2). Crystalline Fmoc chloride (11.3 g, 43.7 mmol, Fluka) was added cautiously to a cooled (0 °C), magnetically stirred solution of methyl-2-deoxy-α,β-D-ribofuranoside (**1**) (2.83 g, 19 mmol)[19] in anhydrous pyridine (20 mL). The reaction was allowed to proceed for 3 h at room temperature. It was then cooled (0 °C), and 60 mL of water followed by 60 mL of ether was added. The organic layer was separated, and the aqueous phase was extracted with



ether (2 × 60 mL). The combined organic extracts were evaporated to dryness under reduced pressure and traces of water were removed by coevaporation with toluene. Following chromatography (silica gel column eluted with a linear gradient of 30–65% dichloromethane in hexane), **2** was obtained as colorless glass in a 93% yield (10.46 g, 17.7 mmol): ^{1}H NMR (Me_2SO-d_6) δ 7.3–7.9 (m, 12, Ar), 5.05 (t, 0.35, H-1′β), 4.95 (dd, 0.65, H-1′α), 4.6 (m, 4, CH_2-Fmoc), 4–4.35 (m, 5, H-4′,5′, CH-Fmoc), 3.15 (s, 1.05, $OCH_3\beta$), 3.25 (s, 1.95, $OCH_3\alpha$), 2.2 (m, 2, H-2′).

1-[3,5-Bis(Fmoc)-2′-deoxyribofuranosyl]-5-azacytidine (5). Anhydrous HCl gas was passed through an ice-cold solution of **2** (4.75 g, 8 mmol) in dry ether (40 mL). The reaction was discontinued after 30 min, and the solvent was removed under reduced pressure. The oily residue (**3**) was dissolved in 100 mL of anhydrous 1,2-dichloroethane and 2-[(trimethylsilyl)amino]-4-[(trimethylsilyl)oxy]-*s*-triazine (**4**) (2.06 g, 8 mmol),[7] followed by a solution of $SnCl_4$ (0.59 mL, 5 mmol) in dry 1,2-dichloroethane (15 mL) were slowly added at room temperature. The reaction was allowed to proceed for 2 h. It was then diluted with 60 mL of dichloromethane and extracted with a saturated ice-cold solution of $NaHCO_3$. The organic layer was filtered through Celite and dried (Na_2SO_4), and the solvents were removed under reduced pressure. The residue was dissolved in a small amount of chloroform and applied onto a silica gel column eluted with a linear gradient of 0–4% ethanol in chloroform (v/v). The products **5**α,β (2.4 g, 45% yield) were obtained in an anomeric ratio α/β = 1:0.9, as determined by HPTLC (three elutions with chloroform con-

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taining 2% v/v ethanol). The α anomer is the faster moving spot. ^{1}H NMR (Me_2SO-d_6) δ 8.28 (s, 1, H-6), 5.95 (m, 1, H-1′), 5.05–5.15 (m, 1, H-3′), 4.6 (m, 1, H-4′), 4.1–4.5 (m, 5, H-5′, CH_2-Fmoc, CH-Fmoc), 2.3–2.75 (m, 2 H-2′).

5-Aza-2′-deoxycytidine (6). Triethylamine (5.6 mL, 40 mmol) was added to a solution of **5** (1.8 g, 2.67 mmol) in anhydrous pyridine (25 mL). After 1 h at room temperature, the solvents were removed under reduced pressure, and the residue was dissolved in a small volume of dry methanol. The pure β anomer (**6**β) crystallized from this solution in a 36% yield (215 mg): mp 191 °C dec (lit. mp 191–196 °C);[4] ^{1}H NMR (Me_2SO-d_6) δ 8.45 (s, 1, H-6), 7.5 (d, 2, NH_2), 6.05 (dd, 1, H-1′), 5.2 (d, 1, OH-3′), 5.05 (t, 1, OH-5′), 4.25 (m, 1, H-3′), 3.80 (m, 1, H-4′), 3.6 (m, 2, H-5′), 2.15 (m, 2, H-2′). The filtrate was evaporated to an oil, dissolved in 5 mL of methanol, and the pure α anomer (**6**α) (280 mg, 46%) was obtained by the addition of 50 mL of ether: ^{1}H NMR (Me_2SO-d_6) δ 8.27 (s, 1, H-6), 7.4 (s, 2, NH_2), 5.95 (d, 1, H-1′), 5.2 (d, 1, OH-3′), 4.85 (t, 1, OH-5′), 4.25 (m, 2, H-3′,4′), 3.4 (m, 2, H-5′), 2.3 (m, 2, H-2′); mp (methanol) 181 °C dec (lit. mp 181–182 °C).[7]

Registry No. 1α, 51255-17-5; 1β, 51255-18-6; 2α, 102831-61-8; 2β, 102831-62-9; **4**, 52523-35-0; 5α, 102831-63-0; 5β, 102851-36-5; 6α, 22432-95-7; 6β, 2353-33-5; Fmoc Cl, 28920-43-6.

A Novel Procedure for the Cleavage of Olefin Derivatives to Aldehydes Using Potassium Permanganate

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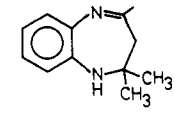
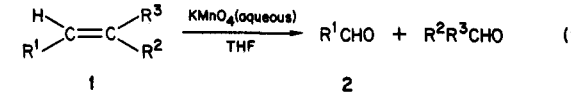
Oxidation of olefin-type substrates with $KMnO_4$ yields mostly dihydroxylated or hydroxy oxo products in alkaline or neutral media, and the double bond is cleaved to the corresponding acids in acidic solutions.[1-9] A series of studies on the mechanism and intermediates of such oxidations in aqueous solution have revealed the transient formation of aldehydes, which, however, undergo further oxidation by manganese(III) and/or manganese(IV) intermediates.[8] No attempt was made at utilizing the cleavage reaction on a preparative scale, although the possibility of quenching the manganese intermediates for saving the aldehydes had been pointed out.[8b-e] Under phase-transfer conditions, isolated examples of olefin to aldehyde conversion have been reported.[2,7] There is, however, no convenient procedure for double bond cleavage to aldehydes in aqueous organic mixtures which would not require special additivies (phase-transfer agent) or techniques (chemical quenching). We now report a simple method in THF/water, in which the solvent plays the role of a quenching reagent, permitting good yields of the aldehydes.

In a mechanistic study on 1,5-benzodiazepines, we needed compound R^4CHO for identifying a reaction intermediate. Attempts at converting the 4-methyl of R^4CH_3 to a formyl group via oxidation or dihalogenation/hydrolysis were unsuccessful. We have found however that



(R^4)

treatment of a dilute THF solution of 1 (with $R^1 = R^4$, $R^2 = H$, and $R^3 = Ph$) by a concentrated aqueous solution of $KMnO_4$ afforded the desired aldehyde R^4CHO and benzaldehyde in 80% yield. The lack of extensive overoxidation is surprising since in the overwhelming majority of reported cases cleavage leads to the corresponding acids.



1 2 (1)

The testing of this procedure on some other olefinic compounds indicates that it may be useful in the synthesis of a variety of aldehydes. Examples are listed in Table I. Apparently, activation of the double bond by conjugation increases, whereas adjacent bulky groups decrease the yield.

Table I. Yield of Aldehyde R^1CHO in Reaction 1

R^1	R^2	R^3	yield, %
R^4	H	Ph	78.7
Ph	CO_2Et	CO_2Et	37.5
Ph	H	Ph	70.5
i-Pr	CO_2Et	CO_2Et	14.2
CO_2Et	H	CO_2Et	50.5
CO_2Et	CO_2Et	H	47.9
1,4-butylene		H	10.2[a]

[a] Product: 1,6-Hexadial.

Experimental Section

4-Formyl-2,2-dimethyl-1*H*-1,5-benzodiazepine (2, $R^1 = R^4$). To a solution of 10 g (0.036 mol) of 1 in 300 cm^3 of THF was added 10 g (0.063 mol) of $KMnO_4$ dissolved in 100 cm^3 of water, over a period of 3.5 h in small portions. The reaction mixture was allowed to warm up to 40 °C. After the addition was finished, the brown precipitate was filtered, and the filtrate was concentrated and extracted with diethyl ether. After drying, the organic phase was concentrated and the resulting oil crystallized from diisopropyl ether: 7 g (78.7%); mp 102–104 °C; ^{1}H NMR δ 1.30 (s, 6 H), 2.70 (s, 2 H), 4.15 (s, 1 H, NH), 6.5–7.7 (m, 4 H), 9.60 (s, 1 H); IR (KBr) ν_{NH} 3325; $\nu_{as\ gem\ CH_3}$ and $\nu_{s\ gem\ CH_3}$ 2960, 2870, ν_{CH_2} 2930, $\nu_{aldehyde\ CH}$ 2838, 2705, ν_{CO} 1692, γ_{C_ArH} 768 cm^{-1}; mass spectrum, M$^+$ for $C_{12}H_{14}N_2O$ 202.1102.

The above procedure can be used to synthesize all of the other aldehydes listed in Table I. Solubility of the starting material determines the THF/H_2O ratio. In case of low solubility, a few preliminary tests should be made to determine the minimum amount of THF. *Attention*: Usage of neat THF or addition of solid $KMnO_4$ may lead to an explosion and therefore must be avoided. Yields were determined by GC analysis (5% QF-1 column) of the Et_2O phase after suitable dilution.

4-(2-Phenylvinyl)-2,2-dimethyl-1*H*-1,5-benzodiazepine (1, $R^1 = R^4$, $R^2 = H$, $R^3 = Ph$). A solution of 10 g (0.053 mol) of 2,2,4-trimethyl-1*H*-1,5-benzodiazepine, 5.63 g (0.053 mol) of benzaldehyde, and 0.5 g of ammonium acetate in 100 cm^3 benzene was refluxed for 4 h and then concentrated. The resulting oil is crystallized from diisopropyl ether: 12.1 g (82.4%); mp 134–136 °C; ^{1}H NMR δ 1.35 (s, 6 H), 2.53 (s, 2 H), 2.90 (s, 1 H, NH), 6.6–7.6

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