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ASYMMETRIC SYNTHESIS OF 3'-CARBOMETHOXYMETHYL-3'-DEOXYTHYMIDINE VIA RADICAL CYCLIZATION

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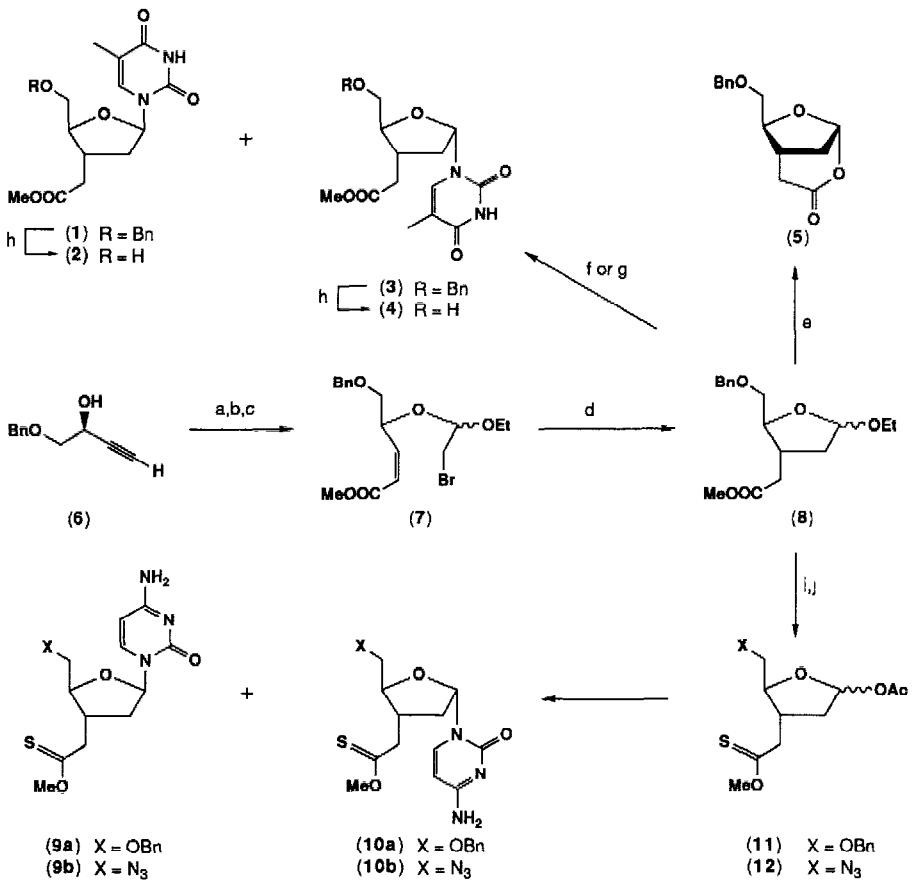
Abstract: An efficient asymmetric synthesis of 3'-C-carbomethoxymethyl- 3'-deoxythymidine **2**, using a highly stereocontrolled radical cyclization from bromoacetal **7** to furanose **8**, followed by a dimethylboron bromide mediated nucleoside formation, is described A 96 4 β-selectivity was observed for thionoester-controlled base attachment.

The discovery of 3'-azido-3'-deoxythymidine as a therapeutic agent against acquired immunodeficiency syndrome (AIDS)[1] has led to a renewed interest in the synthesis of nucleoside analogs[2] Recently, 3'-carbon-substituted-2',3'-dideoxynucleosides have been pointed out as attractive synthetic targets[3,4] These reports prompted us to publish our findings in this field

The synthesis of thymidine analog **2** starts with the known chiral acetylenic alcohol **6**, obtained in 4 steps from *cis*-2-butene-1,4-diol in good overall yield and ≥97% ee[5] After bromoacetalization[6] (90%), the acetylenic bromoacetal was converted to the corresponding acetylenic ester[7,8] in 85% yield, which upon partial hydrogenation, afforded **7** The subsequent tributyltin hydride mediated radical cyclization[9] was stereoselective (≥97% trans products) and produced dideoxyribofuranose **8** in high yield The *cis* double bond is crucial for good stereochemical control in this cyclization[10]. The stereochemistry at C-3 was confirmed by the ^{1}H NMR spectrum of the bicyclic compound **5**, readily obtained from **8** The coupling constant $J_{3,4}$ of ~0 Hz in **5** indicates a *trans* relationship between H-3 and H-4[11] Moreover, nOe experiments showed that irradiation of H-4 gives a significant enhancement of H-6 In an attempt to control the stereochemistry of nucleoside formation, lactone **5** was treated with silylated cytosine and trimethylsilyl triflate (TMSOTf) or $TiCl_4$[12] in methylene chloride at room temperature Only starting material or decomposition products were obtained When the corresponding acetate (**8**, OEt = OAc) was used as substrate under the same reaction conditions, α and β-anomers **1** and **3** (base = CYT) were obtained in a 45 55 ratio Submitting acetal **8** to the same conditions gave no nucleoside

However, activation of acetal **8** could be achieved by the use of dimethylboron bromide The use of dimethylboron bromide for the selective cleavage of acetals is well known[13] However, it was reported that the kinetic product for tetrahydropyranyl and tetrahydrofuranyl ethers[14] or glycopyranosides[15] was that resulting from selective cleavage of the ring carbon-oxygen bond Contrary to these results we have observed the selective cleavage of the exocyclic carbon-oxygen bond of dideoxyribofuranose **8** after a few minutes at -78°C with $(Me)_2BBr$. It seems that in our case, the participation of the ester group favors a rapid equilibration between the cyclic and the acyclic bromoacetals, leading to the thermodynamic product. The resulting unstable cyclic bromoacetal was treated with bis-(trimethylsilyl)thymine in dichloroethane at 0°C to produce a 3·1 diastereomeric mixture of **1** and **3** in 75% yield The coupling reaction is perhaps catalysed by residual $(Me)_2BBr$ or $(Me)_2BOEt$, since the bromoacetal could not be purified. Finally, hydrogenolysis over $Pd(OH)_2$ on carbon in ethanol[16] gave **2** and **4** (3·1 mixture) in 88% yield These compounds could also be obtained directly from **8**, in 70% overall yield and in the same ratio as above, by treatment with 3 0 eq of dimethylboron bromide from -78°C to 0°C in methylene chloride, followed by bis-(trimethylsilyl) thymine in dichloroethane at 0°C[17] The products were separated by flash



a Br_2, ethyl vinyl ether, CH_2Cl_2, -35°C, then **6** and Et_3N, -35°C to r.t. (90%) b. LDA, THF, -78°C; then methyl chloroformate (85%) c. H_2, Lindlar catalyst, AcOEt d. $(Bu)_3SnH$ 1.15 eq., AIBN, benzene (0.026 M), reflux (92% for c and d). e 1N KOH/THF, then PPTS, benzene, reflux (75%) f Me_2BBr 3.0 eq., CH_2Cl_2, -78°C to 0°C on **8**, then bis-(trimethylsilyl)thymine, $(CH_2)_2Cl_2$, 0°C (70%) g Me_2BBr 1.3 eq., CH_2Cl_2, -78°C, bis-(trimethylsilyl)thymine. h. H_2, Pd/C (10%), EtOH (88%) i LDA, THF, Me_3SiCl, -78°C; then H_2S (78%). j CSA, Ac_2O, AcOH, 75%.

chromatography on silica gel (4.3 methylene chloride. acetone) and the relative stereochemistries were assigned by nOe experiments[18]

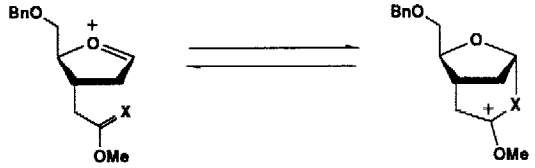
In order to improve the β-selectivity, the coupling reactions of thionoester **11** were studied. The latter was prepared from **8** by treatment with lithium diisopropylamide in THF in the presence of chlorotrimethylsilane[19] at -78°C, followed by hydrogen sulfide from 0°C to room temperature[20] The resulting thionoester, obtained in 78% yield, was treated with camphorsulfonic acid in acetic anhydride and acetic acid to produce the thionoester acyloxy acetal **11** in 75% yield. The results for the glycosylation reaction, using persilylated cytosine as the base, are reported in the Table

Starting Material	Conditions	Product ratio*, **9:10**
11	TMSOTf, $(CH_2)_2Cl_2$, 40-50°	77 23
11	TMSOTf, CH_3CN, r t.	76 24
11	$SnCl_4$, CH_3CN, r t	67 33
11	$SnCl_4$, $(CH_2)_2Cl_2$, r t	91 9
11	#$SnCl_4$, $(CH_2)_2Cl_2$, r t	96.4
12	#$SnCl_4$, $(CH_2)_2Cl_2$, r t.	96 4

*Ratios were estimated by NMR. # Silylated base and $SnCl_4$ were precomplexed at 25°C for 1h

The last two entries show that precomplexation of the silylated base with $SnCl_4$ for one hour[21], using 1,2-dichloroethane as solvent, gave **9a** with very high β-selectivity. A similar sequence, starting from azide **12**, gave the corresponding azido nucleoside **9b** with similar β-selectivity. Using persilylated thymine as the base, thionoester derivatives of **1** and **3** (COOME= CSOMe) were obtained in a 95:5 ratio.

The stereochemical control of these glycosylation reactions depends upon the equilibrium between oxonium ion **A** and bicyclic ion **B**. The former can, in principle, produce both isomers, whereas the latter leads only to the β-isomer. With



(A) **(B)**

X = O, the form **A** should predominate. On the other hand, when X is a sulfur atom, the bicyclic intermediate should predominate because the carbon sulfur double bond (1.6 Å) is much longer than the carbon oxygen double bond (1.2 Å).

In conclusion, we report on a new method for coupling 1-alkoxyfuranoses with silylated bases using dimethylboron bromide as an activating agent, and a rational method for controlling the β-selectivity when coupling a 2-deoxyribose derivative with silylated bases.

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17. To a stirred solution of **8** (100 mg, 0 32 mmol) in CH_2Cl_2 (3 6 ml) at -78°C under N_2 was added $(Me)_2BBr$ (100 µl, 1 02 mmol), after 15 min the solution was warmed up to 0°C After 1 h, CH_2Cl_2 was evaporated at low temperature The crude bromoacetal was then dissolved in $(CH_2)_2Cl_2$ (3 5 ml) and at 0°C bis-(trimethylsilyl) thymine (110 mg, 0 43 mmol) was added The reaction was worked up after 30 min **2**. ^1H NMR (200 MHz, $CDCl_3$) δ 1 87 (s, 3H, CH_3 at C-5), 2 10-2 90 (m, 6H, OH, H-2', H-3', H-6'), 3 68 (s, 3H, OCH_3), 3 67-3 80 (m, 2H, H-4', H-5'), 4 01 (m, 1H, H-5'), 6 08 (dd, J = 3 4 Hz, 6 9 Hz, 1H, H-1'), 7.70 (s, 1H, H-6), 9.31 (br s, 1H, NH-3); ^{13}C NMR (50 3 MHz, CD_3OD) δ 12 5 (Me at C-5), 34 9 (C-3'), 36 8 (C-2') 39.9 (C-6'), 52 4 (C-8'), 62 1 (C-5'), 86 4 (C-4'), 87 4 (C-1'), 111.2 (C-5), 138.8 (C-6), 152 7 (C-2), 167 0 (C-4), 174 6 (C-7')

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