Stereoselective synthesis of 1′β-2′,3′-dideoxy-2′-bis(ethoxycarbonyl)methyluridine nucleosides by ring opening of cyclopropanated glycals

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Cyclopropanations of glycals followed by Lewis acid-mediated glycosylations with 5-substituted uracils afforded 1′β-2′,3′-dideoxy-2′-bis(ethoxycarbonyl)methyluridine nucleosides in a highly regiospecific and stereoselective manner in good yields.

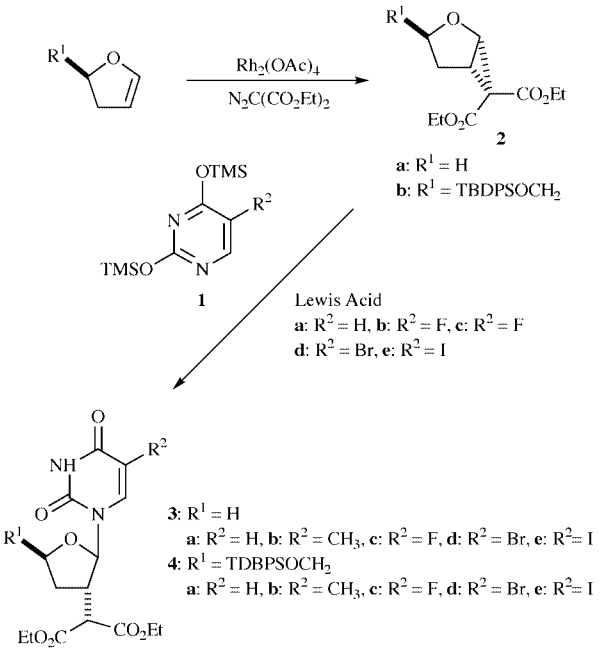
A number of 2′-C-branched nucleosides bearing 2′-deoxy-2′-carbon–carbon bonds have displayed clinically useful chemotherapeutic activities[1] as well as interesting biochemical properties such as ribonucleotide reductase inactivation.[2] Moreover, the discovery of a positive correlation between inhibitory activity against ribonucleotide reductase and antitumor activity[3] has led to mechanism-based molecular design to find potent antitumor agents.[4] On the basis of these findings, a lot of 2′-C-branched nucleosides have been synthesized by the use of modified nucleosides and carbohydrates as well. Although there are numerous examples of syntheses from intact nucleosides,[5] there are surprisingly few reports on the stereocontrolled synthesis of nucleosides using 2′-ketoribose requiring multi-step reactions.[6] This may be attributed to the fact that both stereochemically controlled C–C bond formations and glycosylations cannot be attained concurrently. Quite recently, there have been reported stereoselective cyclopropanations of glycals,[7] which could serve key intermediates to synthesize 2′-C-branched nucleosides stereoselectively.

Danishefsky and co-workers reported the highly stereocontrolled synthesis of pyrimidine nucleosides by an opening of strained glycal epoxides though the chemical yields are low.[8]

On the supposition that Lewis acid-mediated direct glycosylations between nucleobases and cyclopropanated sugars might be one promising operation to couple nucleobases with sugars, cyclopropanated sugars containing electron-withdrawing groups were reacted with pyrimidine bases in the presence of Lewis acid.

In this paper, we describe stereocontrolled cyclopropanations of glycals with diethoxycarbonyl metallocarbenoids with high stereoselectivity and regiospecific glycosylations of nucleobases to cyclopropanated sugars with extremely high stereoselectivity for β-formation of uridines (β : α = > 99 : 1) as shown in Scheme 1.

Our initial studies on stereocontrolled cyclopropanations of glycals sought to improve both high diastereoselectivities and chemical yields. In the hope of attaining these goals, the reaction conditions were controlled by minimizing the concentration of metallocarbenoid. Decreasing the molar ratios of diazomalonate and dirhodium tetraacetate ($N_2C(CO_2Et)_2$: $Rh_2(OAc)_4$: glycal = 2 : 0.01 : 1) afforded high stereoselectivities and good yields.[9] Accelerated addition of the diazomalonate resulted in dimerization of diethoxycarbonylcarbene and lowered the yield. The stereochemistry of the major isomer **2b** was confirmed using ^{1}H-NOE experiments and the ratio of β to α (<1 : 99) was determined by HPLC (chiral Daicel OD column, i-PrOH : *n*-hexane = 1 : 9, retention time; β 10.76 min, α 10.81 min). Irradiation of H-4 gave no NOE effect at H-1 and H-2, which supports the *trans* conformation of **2b**. If the product had a *cis* conformation a NOE effect would be observed upon irradiation of H-4.



Scheme 1

In the absence of Lewis acid no coupling product was attained and starting material was recovered (Table 1, run 1). Treatment of cyclopropanated sugar **2a**–**b** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) produced the desired coupling product in low yield (run 2), with accompaning byproducts.[10] Controlling the temperature and dropwise addition of TMSOTf did not improve the yield. Lower yields were obtained using $BF_3{\cdot}OEt_2$ (run 3) or ZnI_2 (run 4). Glycosylation with methanesulfonic acid (MSA), however, afforded the desired product exclusively in low yield (run 5), but starting material (the free pyrimidine base) remained. We attributed this low yield to decomposition of the reactive silylated nucleobase to non-reactive naked nucleobase by MSA. Thus, the reactions were attempted with more than 1 equivalent of nucleobase to sugar to improve the yields. Through a series of examinations, the yields have been optimized with 1 equivalent of MSA and 2 equivalents of nucleobases in acetonitrile at 20 °C.[11] The results obtained are summarized in Table 1 (run 6–10, 11–15).

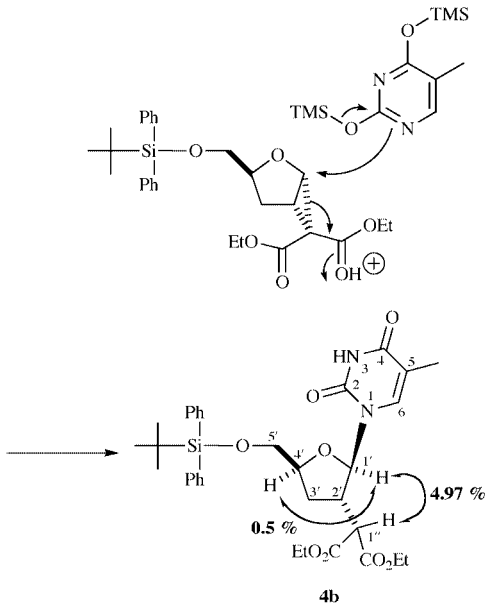
The stereochemistry of the products was defined using ^{1}H-NOE experiments and the ratio of β to α by HPLC (chiral Daicel OD column, i-PrOH : *n*-hexane = 1 : 9, retention time; β 5.51 min, α 5.42 min). There are good correlations between 1′-H and 1″-H (4.97%) as well as between 1′-H and 4′-H (0.5%) of 2′-C-branched nucleosides. The coupling reaction appears to undergo a nucleophilic attack by nucleobase to the *anti* face of cyclopropane ring exclusively as shown in Scheme 2.

A limitation of the reaction is seen with cytosine and purine bases (run 16). The glycosylations did not arise with these nucleobases. The reason is uncertain, however, basic amino groups might bind with Lewis acid preferentially, which would

Table 1 Stereoselective glycosylation with **1** and **2**

Run	Base	Sugar[a]	1:2	Lewis acid	Product	Yield (%)[b]	β:α (%)[c]
1	**1a**	**2a**	1:1	None		0	
2	**1a**	**2a**	1:1	TMSOTf	**3a**	44	>99:1
3	**1a**	**2a**	1:1	BF_3OEt_2	**3a**	36	>99:1
4	**1a**	**2a**	1:1	ZnI_2	**3a**	15	>99:1
5	**1a**	**2a**	1:1	MSA[d]	**3a**	54 (95)	>99:1
6	**1a**	**2a**	2:1	MSA[d]	**3a**	81 (98)	>99:1
7	**1b**	**2a**	2:1	MSA[d]	**3b**	75 (99)	>99:1
8	**1c**	**2a**	2:1	MSA[d]	**3c**	77 (98)	>99:1
9	**1d**	**2a**	2:1	MSA[d]	**3d**	66 (97)	>99:1
10	**1e**	**2a**	2:1	MSA[d]	**3e**	64 (97)	>99:1
11	**1a**	**2b**	2:1	MSA[d]	**4a**	75 (99)	>99:1
12	**1b**	**2b**	2:1	MSA[d]	**4b**	71 (98)	>99:1
13	**1c**	**2b**	2:1	MSA[d]	**4c**	65 (97)	>99:1
14	**1d**	**2b**	2:1	MSA[d]	**4d**	55 (96)	>99:1
15	**1e**	**2b**	2:1	MSA[d]	**4e**	53 (95)	>99:1
16	Cytosine	**2b**	2:1	MSA[d]		0	

[a] **2a**: R^1 = H, **2b**: R^2 = $TBDPSOCH_2$. [b] Isolated yields (conversion yields). [c] Determined by HPLC (chiral Daicel OD column, iPrOH : *n*-hexane = 1 : 9) and ^{1}H-NOE data. [d] MSA = methanesulfonic acid.



Scheme 2 Determination of stereochemistry.

inhibit the activation of the cyclopropane diester, and give rise to no reaction.

In conclusion, we have achieved the new syntheses of 1′β-2′,3′-dideoxy-2′-bis(ethoxycarbonyl)methyluridine nucleosides, which may be used in biochemical studies on ribonucleotide reductase related to ribozyme[12] from carbohydrates in a stereoselective fashion. Furthermore, these 2′-C-branched nucleoside derivatives might display promising chemotherapeutic activities and we are currently exploring their biological activities.

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9 To a mixture of glycal **7e** (1.5 mmol) and dirhodium tetraacetate (15 μmol) in 5 ml of methylene chloride at 25 °C under argon atmosphere was added dropwise a solution of diethyl diazomalonate (3.0 mmol) in 9 ml of methylene chloride for 10 h *via* syringe pump. The reaction mixture was concentrated and separated by column chromatography on silica gel (230–400 mesh, 3 cm × 20 cm, solvent: EtOAc–*n*-hexane = 1 : 5) to give the cyclopropanated glycal **2b** (595.2 mg, 80%, >98% de) as a pale yellow oil; $[\alpha]_D^{20}$ +3.85 (*c* 1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3017, 2951, 2860, 1756, 1725, 1368, 1130 and 841; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.03 (9H, s, Me_3CSi), 1.30 (6H, tt, 2 × $CO_2CH_2CH_3$), 1.62 (1H, m, H-2), 1.93 (2H, m, H-3), 3.77 (3H, m, H-4,5), 4.13 (1H, d, *J* 4.2, H-1), 4.95 (4H, qq, 2 × $CO_2CH_3CH_3$) and 7.33–7.67 (10H, m, $(C_6H_5)_2Si$); δ_C(75 MHz; $CDCl_3$; Me_4Si) 14.0 (s), 14.5 (q), 14.6 (q), 19.6 (3 × q), 26.7 (d), 33.6 (t), 53.3 (s), 58.9 (t), 61.6 (t), 62.3 (d), 66.3 (t), 71.1 (d), 127.5–135.6 (Ph_2Si), 170.6 (s) and 170.7 (s); HRMS *m*/*z* (EI) calc'd. for $C_{28}H_{36}O_6Si$ (M^+): 496.2281; found: 496.2269.

10 Major byproduct was identified as 1,3-bis(2′-diethoxycarbonyl)-methyluridine nucleosides by ^{1}H NMR spectroscopy.

11 To a mixture of nucleobase (0.4 mmol) and cyclopropanated glycal (0.2 mmol) in 2 ml of acetonitrile was added *N*,*O*-bis(trimethylsilyl)acetamide (0.88 mmol) at 25 °C under argon atmosphere. After stirring for 1 h, the clear solution was treated with methanesulfonic acid (0.2 mmol) at this temperature and stirred until the reaction was

completed (1 h). The reaction mixture was quenched with saturated aqueous Na_2CO_3 solution (3 ml) and extracted with ethyl acetate (3 × 3ml). The combined organic layer was washed with brine (5 ml) and dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel (230–400 mesh, 3 cm × 20 cm, solvent: EtOAc–*n*-hexane = 1 : 2) to give the product.

All compounds exhibited satisfactory spectral and analytical properties, including proton and carbon NMR, and FTIR.

Representative spectral data for 1′β-2′,3′-dideoxy-2-bis(ethoxycarbonyl)-5′-*O*-(*tert*-butyldiphenylsilyl)thymidine **4b**: ν_{max}(film)/cm^{-1} 3493, 3063, 2983, 1732, 1709, 1695, 1461 and 1273; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.09 (9H, s, Me_2Si), 1.23 (6H, tt, 2 × $CO_2CH_2CH_3$), 1.60 (3H, s, 5-CH_3), 1.94–2.35 (2H, m, 3′-CH_2), 3.34 (1H, m, H-2′), 3.54 (1H, d, *J* 8.92, $CH(CO_2Et)_2$), 3.64 and 3.97 (2H, dd, 5′-CH_2), 4.11 (1H, m, H-4′), 4.20 (4H, qq, 2 × $CO_2CH_2CH_3$), 6.01 (1H, d, *J* 7.8, H-1′), 7.42 (1H, s, H-6), 7.34–7.68 (10H, m, $(C_6H_5)_2Si$) and 9.50 (1H, br s, NH); δ_C (75 MHz; $CDCl_3$; Me_4Si) 12.0 (2 × q), 13.9 (s), 19.3 (q), 27.0 (3 × q), 29.7 (t), 30.2 (d), 42.8 (d), 61.9 (2 × t), 65.7 (t), 77.8 (d), 87.3 (d), 111.2 (s), 127.9 (d), 129.9 (d), 130.0 (d), 132.5 (d), 133.1 (d), 135.3 (d), 135.6 (d), 150.6 (s) and 167.4 (3 × s); HRMS *m*/*z* (FAB) calc'd. for $C_{33}H_{41}N_2O_8Si$ (M^+): 622.2710; found: 622.2739.

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