Diastereoselective synthesis of α-substituted-γ-butyrolactones of nucleosides *via* [1,5]-C,H insertion reactions of α-diazomalonates of nucleosides†

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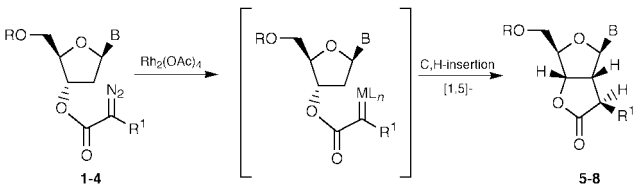
Diastereoselective and regioselective [1,5]-C,H insertion reactions of 2′-deoxy-3′-diazomalonate nucleosides afforded τ-butyrolactones of nucleosides as chiral synthons for the preparation of 2′-*C*-branched nucleosides.

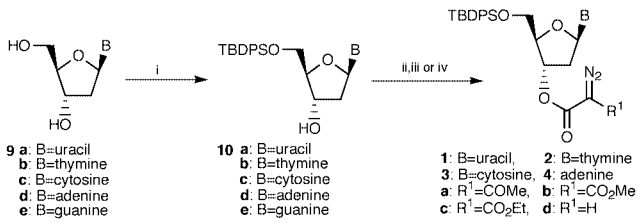
Since oxetanocin[1] was isolated and turned out to show potent antiviral activity such as inhibition of HIV-1 antigens and infectivity, *C*-branched nucleosides bearing carbon–carbon bonds at the furanose rings have attracted considerable attention as clinically useful chemotherapeutic agents.[2] Moreover, the discovery of a positive correlation between inhibitory activity against ribonucleotide reductase and antitumor activity,[3] has led to rational drug design to find potent antitumor agents having C–C bonds at the 2′-positions.[4] The key step in the synthesis of *C*-branched nucleosides is stereocontrolled C–C bond formation at the branching site of the ribofuranose ring. However, it is especially difficult to construct C–C bonds at the 2′-position of nucleosides. Intramolecular cyclization is a facile and useful strategy for stereo- and regio-controlled C–C bond formation to provide γ-butyrolactones of nucleosides as a useful chiral synthon for the synthesis of *C*-branched nucleosides.[5] The γ-butyrolactones of nucleosides are important key intermediates to manipulate various 2′-*C*-branched nucleoside analogues. Recently Camarasa and coworkers reported that γ-butyrolactones of nucleosides were prepared by intramolecular radical cyclization in good diastereoselectivities but low yields[6] which might result from reductive deoxygenation, which is a feature of free radical cyclizations. Intramolecular [1,5]-C,H insertion reactions of α-diazocarbonyl compounds have been among the most attractive and effective methods for the construction of functionalized five membered rings.[7] Substrates can be smoothly cyclized without difficulty by dirhodium(II)-catalyzed C,H-insertion reactions. However, surprisingly, no successful C,H-insertion reactions in the modification of ribofuranose ring of nucleosides have been reported. Efficient construction of a C–C bond at the branching point has been a difficult task especially at the 2′-position of nucleosides by currently available methods. Here, we describe diastereoselective intramolecular C,H-insertion of 2′-deoxy-3′-α-diazoacetates of nucleosides in the presence of a catalytic amount of dirhodium tetraacetate to [3.3.0] fused lactones (γ-butyrolactones) of a series of nucleosides having a new chiral center at an off-template site of the ribofuranose ring, in high yields, as shown in Scheme 1.

For the synthesis of the fused γ-butyrolactones of nucleosides we chose 2′-deoxy-3′-diazoacetates of nucleosides (R^1 = H, MeCO, MeO_2C, EtO_2C) as templates for [1,5]-C,H insertion reactions. The general strategy is shown in Scheme 2.

The 5′-position of 2′-deoxynucleosides were protected with *tert*-butyldiphenylsilyl chloride in dried pyridine at room temperature. These 5′-*O*-protected-2′-deoxynucleoside derivatives **10a**–**e** undergo transesterification[8] by reaction with the corresponding methyl ester to give 3′-*O*-acetoacetyl-2′-deoxy-



Scheme 1



Scheme 2 *Reagents and conditions*: i, TBDPSCl, pyridine, rt; ii, $R^1C(N_2)CO_2Me$, DMAP, toluene, reflux; iii, (1) $EtO_2CCH_2CO_2H$, DCC, DMAP; (2) MsN_3, Et_3N, MeCN; iv, TsNHN=CHCOCl, Et_3N, MeCN.

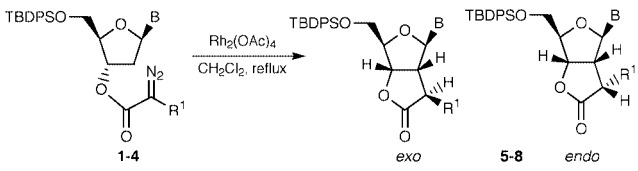
nucleosides and 2′-deoxy-3′-*O*-α-(methoxycarbonyl)acetylnucleosides in moderate yields. Diazo transfer of these esters with methanesulfonyl azide and triethylamine in acetonitrile[9] afforded the corresponding 3′-diazoester derivatives **1a**–**4a** and **1b**–**4b** in poor yields (*ca.* 50%). These low yields might be due to steric hindrance by furanose rings. It was found, however, that the satisfactory yields (84–96%) of **1a**–**4a** and **1b**–**4b** could be smoothly obtained using methyl α-diazoacetate derivatives instead of methylacetate ones, and α-ethoxycarbonylacetates of nucleosides **1c** and **2c** were not formed by this procedure. The desired products **1c** and **2c** could be obtained by a coupling reaction of 5′-*O*-protected-2′-deoxynucleosides **10a**,**b** with monoethyl malonate followed by diazo transfer in moderate yields (56–71%), while 2′-deoxy-3′-α-diazoacetates of nucleosides **1d** and **2d** could be obtained in good yields (78–90%) using the modified House–Blankey procedure.[11]

Our initial studies on stereocontrolled C,H-insertion of 2′-deoxy-3′-α-diazoacetates of nucleosides were performed in the presence of dirhodium tetraacetate (1.0 mol%) in dichloromethane at room temperature. However, only a trace amount of product was obtained and starting material was recovered. To improve the yields, when the reaction mixture was refluxed, high yields of γ-butyrolactones of nucleosides **5**–**8** were obtained and results obtained are summarized in Table 1.

Moreover, the C,H-insertion of 2′-deoxy-3′-α-diazoacetates of nucleosides **1**–**4** afforded the γ-butyrolactones of nucleosides **5**–**8** with high diastereoselectivities. Through the J_{H-H} coupling constant ($J_{1''-2'}$ 8.8 Hz) between 1″-hydrogen and 2′-hydrogen of **6b**, the stereochemistry of 1″-position of γ-butyrolactone of nucleoside **6b** was determined as *exo*. Irradiation of the anomeric proton of **6b** caused enhancement of the signal for H-1″ (8%), indicating that the configuration at C-1″ of **6b** was (*S*). A possible mechanism for the stereochemical outcomes of γ-

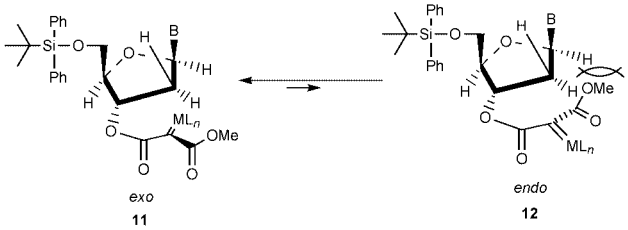
† Electronic supplementary information (ESI) available: NMR data for **2b** and **6b**. See http://www.rsc.org/suppdata/cc/b0/b000524j/

Table 1 Dirhodium(II) tetraacetate catalyzed formation of **5**–**8**



Run	Reactant	Product	*t*/h	Yield(%)[a]	*exo*:*endo*[b]
1	**1a**	**5a**	1.5	69	96:4
2	**1b**	**5b**	2	72	>98:2
3	**1c**	**5c**	2	70	>98:2
4	**1d**	**5d**	1	75	
5	**2a**	**6a**	1.5	64	95:5
6	**2b**	**6b**	1	70	>98:2
7	**2c**	**6c**	1	65	>98:2
8	**2d**	**6d**	1	71	
9	**3a**	**7a**	2.5	58	95:5
10	**3b**	**7b**	3	71	>98:2
11	**4a**	**8a**	5	66	97:3
12	**4b**	**8b**	5	80	>98:2

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy.



Scheme 3

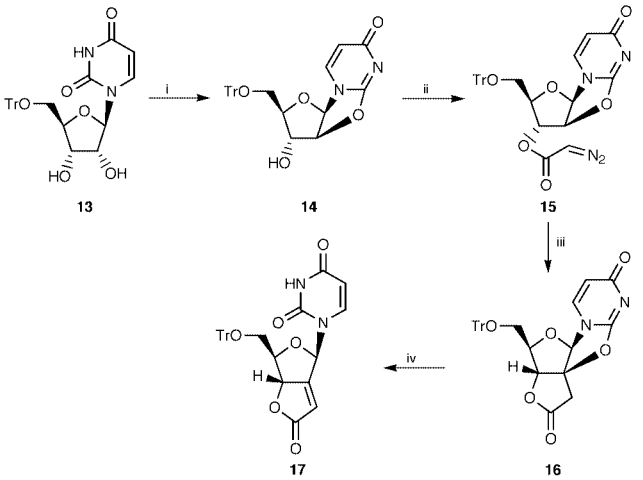
butyrolactones of nucleosides **5**–**8** is proposed as shown in Scheme 3.

The unfavorable steric hindrance between the anomeric proton and the methyl ester in *endo* transition state **12** drives the equilibrium to the left to the *exo* transition state **11**, which gives the (*S*) conformer (*exo* adduct, **5**–**8**) stereoselectively. When pure **6b** was refluxed in CH_2Cl_2 for 10 h, no epimerization occurred.

The γ-butyrolactones of the nucleosides described above can be considered as useful chiral synthons for the synthesis of *C*-branched nucleosides. In connection with biologically interesting nucleosides containing the 2′-methylene moiety, for instance (*E*)-FMC[3] and (*E*)-2′-deoxy-2′-(carboxymethylene)-5′-*O*-trityluridine-3′,2′-γ-lactone **17**,[12] the synthesis of **17** was attempted by employing C,H-insertion of the 2′,5′-cyclouridine derivative **14** as shown in Scheme 4.

Cyclization of 5′-*O*-trityluridine **13** by basic diphenylcarbonate gave the 2′,5′-cyclouridine **14** in 81% yield. Exposure of **14** to the House–Blankey protocol afforded the corresponding diazo compound **15**, which could be converted to the γ-butyrolactone of uridine **16** in 65% yield. Product **17** could be smoothly obtained by an elimination reaction with sodium hydride in 85% yield.

In conclusion, we have achieved the new stereoselective syntheses of α-substituted-γ-butyrolactones of nucleosides *via* [1,5]-C,H insertion reactions of α-diazo-γ-butyrolactones of nucleosides.



Scheme 4 *Reagents and conditions*: i, $(PhO)_2CO$, $NaHCO_3$, DMF; ii, TsHNN=CHCOCl, Et_3N, MeCN; iii, $Rh_2(OAc)_4$, CH_2Cl_2, reflux; iv, NaH, MeCN.

Furthermore, this reaction can be applied to the synthesis of (*E*)-2′-deoxy-2′-(carboxymethylene)-5′-*O*-trityluridine-3′,2′-γ-lactone **17**, a chiral synthon in the synthesis of 2′-*C*-branched nucleosides.

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