A SHORTCUT AND STEREOSELECTIVE SYNTHESIS OF 1-β-ALKYL-2-DEOXY-D-RIBOSE DERIVATIVES *VIA* WITTIG-HORNER-EMMONS REACTION

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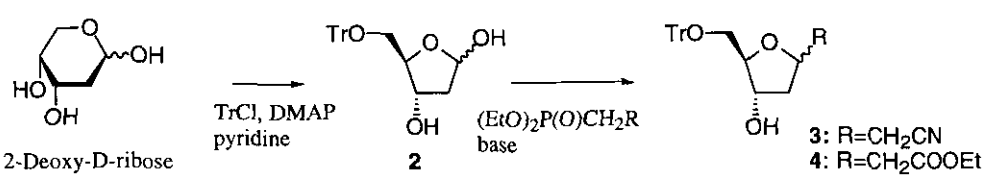
Abstract- A shortcut and stereoselective synthesis of 1-β-alkyl-2-deoxy-D-ribose derivatives has been achieved *via* Wittig-Horner-Emmons reaction followed by intramolecular 1,4-addition. After the systematic investigation of the effects of the base and the solvent, the best β-selectivity, as much as 12:1, was obtained with potassium *tert*-butoxide in THF.

The development of new nucleoside analogs has attracted considerable interest from the viewpoint of new therapeutic agents, biological tools, and so on.[1] *C*-Nucleosides have a C-C bond instead of a C-N bond at the anomeric carbon, and are no longer cleaved by hydrolysis; therefore, they are useful in metabolic studies. Recently, *C*-nucleosides are employed as non-natural components of nucleic acids in the structural studies.[2] Since most of the natural nucleosides exit in β-stereochemistry at the anomeric site, stereoselective preparation of β-*C*-nucleosides is desirable. There are several methods for β-selective alkylation at the anomeric carbon of ribose, in which stereo- and electrochemical participation of the 2-oxygen atom is included.[2] On the other hand, direct β-selective alkylation of 2-deoxy-D-ribose is rather difficult because of the lack of such neighboring effects, and β-alkyl 2-deoxy-D-ribose is usually obtained *via* multi-step transformation from β-*C*-ribose, including reductive deoxygenation of the 2-hydroxyl group. 1-β-Aryl derivatives of 2-deoxy-D-ribose were prepared by isomerization of the α-isomer under acidic conditions.[2d] An example has been reported of the utilization of the 3-*O*-methylsulfinylethyl group of 2-deoxy-D-ribose for direct β-selective alkylation in Lewis acid-catalyzed alkylation.[3] Here we wish to report a shortcut and stereoselective synthesis of 1-β-alkyl-2-deoxy-D-ribose derivatives through alkylation of the 2-deoxy-D-ribose derivative.

Scheme 1



1: 2-Deoxy-D-ribose

2

The Wittig reaction has been applied to the selective formation of β-*C*-riobfuranosides and β-*C*-glucopyranosides. However, when this method is applied to 5-*O*-tritylated 2-deoxy-D-ribose using a Horner-Emmons reagent (R=CN), only low selectivity was obtained.[2c] Therefore, we initiated systematic investigation of the base and solvent effects on the β-selectivity (Table 1).

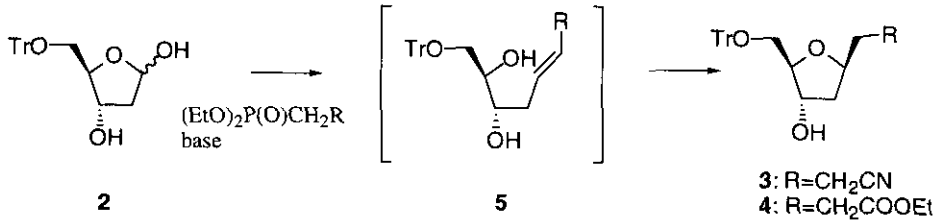


Table 1. The yield and α:β ratio of C1-alkylated 2-deoxy-D-riboses (**3** and **4**).

Entry	Substrate (R=)	Base	Solvent	Temperature (°C)	Time (h)	Yiled (%)[a]		
						3 or **4**	α:β ratio[b]	**5**
1	CN	NaH	THF	0	6	64	40:60	0
2	COOEt	NaH	THF	0	0.5	79	10:90	7
3	COOEt	NaH	Acetonitrile	0	0.5	83	11:89	0
4	COOEt	NaH	DME	0	0.5	50	20:80	18
5	COOEt	NaH	Toluene	0	0.5	28	25:75	38
6	COOEt	NaH	DMF	0	0.5	84	33:64	0
7	COOEt	*t*-BuOK	THF	0	0.5	90	8:92	0
8	COOEt	*t*-BuOK	THF	-48~-40	0.5	32	9:91	58
9	COOEt	*t*-BuOK	Acetonitrile	0	0.5	80	11:89	0
10	COOEt	LDA	THF	-70~0	0.5	89	50:50	1

a) Isolated yield for the mixture of the isomers, b) The α:β ratios were obtained by HPLC analysis and ^{1}H-NMR measurements. Retention time: **5** (R=COOEt): 26 min, α-**4** (R=COOEt): 28.6 min, β-**4** (R=COOEt): 29.8 min. HPLC conditions; column: nacalai tesque 5C18-MS 4.6x250 mm, MeOH- H_2O 70% to 80%/30 min linear gradient, then 80% MeOH- H_2O 10 min, flow rate: 1 mL/min, monitored at 254 nm.

A typical procedure (Entry 7 in Table 1) in a preparative scale is as follows: a solution of triethyl phosphonoacetate (5.5 mL, 27.7 mmol) was treated with *tert*-BuOK (3.34 g, 29.8 mmol) in THF (50 mL) under argon atmosphere at 0 ℃ for 20 min. A solution of **2**[2c] (8.0 g, 21.3 mmol) in THF (70 mL) was added into the above solution at 0 ℃, and the reaction mixture was stirred for 30 min at the same temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted with AcOEt. The isomers were separated by medium-pressure liquid chromatography on a silica gel column

(hexane/acetone=6/1) to give α-**4** (0.58 g, 1.3 mmol) in 6 % and β-**4** (6.93 g, 15.5 mmol) in 73 %.[6] The non-cyclized compound, *E*-olefin (**5**), was isolated under some conditions (Entries 2, 4, 5, 8). The stereochemistry of the isomer was unambiguously determined by comparison of their ^{1}H-COSY and NOESY spectra (Figure 1), and the chemical correlation of the β-isomer to the known compound (3,5-*O*-bismethoxymethyl derivative of **4** (R=CH_2COOEt) derived from D-ribose.[4, 5a] The reaction was performed under different conditions, and the α:β ratio of the crude product was analyzed by HPLC and ^{1}H-NMR (Table 1).

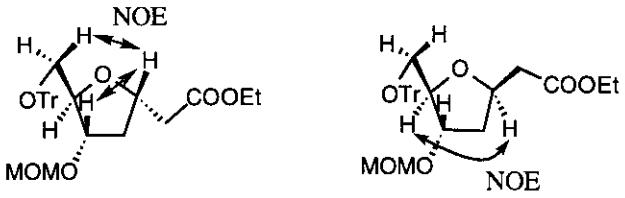


Figure 1

The reaction of diethyl cyanomethylphophonate proceeded slowly and gave low β-selectivity.[2c] When triethyl phosphonoacetate was used as the Horner-Emmons reagent, the reaction proceeded faster and better β-selectivity was obtained (Entry 2). The reactions in DME, toluene or DMF were less efficient (Entries 4-6). Utilization of *tert*-BuOK produced the highest yield as well as the highest β-selectivity in THF or in acetonitrile (Entries 7 and 9). Selectivity was not improved in the reaction under lower temperature (Entry 8). On the other hand, the reaction proceeded smoothly with LDA, but only an equimolar mixture of the α- and β-isomers was obtained (Entry 10).

It is apparent that the reaction occurs through the open intermediate (**5**), because the cyclized product (**4**) was also obtained from **5** by treatment with *tert*-BuOK in ethanol in 5:1 β-to-α ratio. But neither isomerization nor ring-opening was found with *tert*-BuOK in THF. These results suggested that the stereochemistry is determined kinetically in the reaction with *tert*-BuOK in THF. However, neither the origin of the β-selectivity nor the effect of the counter cation has been clearly explained at present.

In conclusion, we have established a very simple and practical procedure for the synthesis of 1-β-alkyl-2-deoxyribose derivatives. This procedure contains only two steps from 2-deoxy-D-ribose; furthermore, high total yield as well as high β-selectivity were achieved. We have already synthesized several non-natural nucleotide analogs from **4**,[5] which functions as a oligonucleotide component will be reported in due course.

ACKNOWLEDGMENTS

This study was partially supported by Grant-in-Aid for Scientific Research (C) from the Ministry of Education, Science, Sports and Culture of Japan.

REFERENCES AND NOTES

1. Reviews: a) M. H. D. Postema, *Tetrahedron,* 1992, **48**, 8545; b) K. Watanabe, *J. Syn. Org. Chem.*, 1987, **45**, 212, and reference cited therein.

2. a) N. C. Chaudhuri, R. X.-F. Ren, and E. T. Kool, *Synlett*, 1997, 341, and references cited therein; b) J. H. Boal, A. Wilk, C. L. Scremin, G. N. Gray, L. R. Phlips, and S. L. Beaucage, *J. Org. Chem.*, 1996, **61**, 8617; c) R. X.-F. Ren, N. C. Chaudhuri, P. L. Paris, S. Rummney IV, and E. T. Kool, *J. Am. Chem. Soc.*, 1996, **118**, 7671; d) C. L. Scremin, J. H. Boal, A. Wilk, L. R. Phlips, L. Zhou, and S. L. Beaucage, *Tetrahedron Lett.*, 1995, **36**, 8953.

3. K. Narasaka, Y. Ichikawa, and H. Kubota, *Chem. Lett.*, 1987, 2139.

4. G. S. Wilcox and R. M. Otoski, *Tetrahedron Lett.*, 1986, **27**, 1011.

5. a) S. Sasaki, S. Nakashima, F. Nagatsugi, Y. Tanaka, M. Hisatome, and M. Maeda, *Tetrahedron Lett.*, 1995, **36**, 9521; b) S. Nakashima, N. Matsuura, F. Nagatsugi, M. Maeda, and S. Sasaki, *Nucleic Acids, Symp. Ser.*, 1996, **35**, 105; c) S. Nakashima, N. Matsuura, F. Nagatsugi, M. Maeda, and S. Sasaki, *Nucleic Acids, Symp. Ser.*, 1997, **37**, 33.

6. **2**[2c]: mp 110-111 ℃ (hexane-AcOEt). α-**4**: a colorless oil, $[\alpha]_D^{20}$ +29.0° (c 1.15 EtOH), ^{1}H-NMR δ: 7.49-7.11 (15H, m), 4.48 (1H, dt, *J*=13.9, 6.4 Hz), 4.34-4.28 (1H, m), 4.15 (2H, q, *J*=7.1 Hz), 4.05 (1H, ddd, *J*=8.3, 4.6, 1.7 Hz), 3.24 (1H, dd, *J*=9.6, 4.6 Hz), 3.09 (1H, dd, *J*=9.6, 6.3 Hz), 2.73 (1H, dd, *J*=15.8, 6.6 Hz), 2.65 (1H, dd, *J*=15.8, 5.9 Hz), 2.47-2.40 (1H, m), 1.78 (1H, ddd, *J*=13.2, 6.3, 4.7 Hz), 1.24 (3H, t, *J*=7.1 Hz), IR (neat) cm^{-1}: 3400, 1720, 1590, FABMS (m/z): 447 $(M+H)^+$. β-**4**: a colorless oil, $[\alpha]_D^{20}$ +18.4° (c 1.0, EtOH), ^{1}H-NMR δ: 7.62-7.20 (15H, m), 4.59-4.47 (1H, m), 4.33-4.27 (1H, m), 4.15 (2H, q, *J*=6.9 Hz), 3.93 (1H, ddd, *J*=8.6, 3.0, 1.3 Hz), 3.24 (1H, dd, *J*=9.6, 4.3Hz), 3.09 (1H, dd, *J*=9.9, 5.9 Hz), 2.66 (1H, dd, *J*=15.2, 7.1 Hz), 2.51 (1H, dd, *J*=15.2, 6.1 Hz), 2.05-2.02 (1H, m), 1.89-1.81 (1H, m), 1.24 (3H, t, *J*=7.1 Hz), IR (neat) cm^{-1}: 3400, 1720, 1590, FABMS (m/z): 447 $(M+H)^+$.

Received, 28th January, 1999