Enantioselective Synthesis of Pyrrolydinonyl Thymine Nucleoside Analogues

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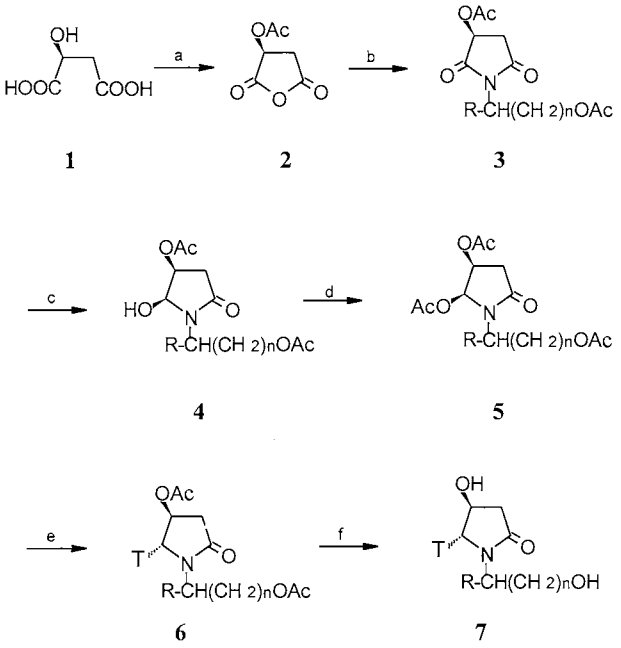
Enantioselective synthesis of a novel kind of optically active nucleoside analogues from natural malic acid is described. In the given nucleoside analogues the tetrahydrofuran ring is replaced by a pyrrolidinonyl ring bearing both a primary and a secondary hydroxy groups which could be useful for the preparation of novel oligonucleotides. Assay of the prepared nucleoside analogues showed non-activity against virus.

Naturally occurring nucleosides provide a structural insight for chemists to synthesize new nucleoside analogues for the development of potent antitumor and antiviral agents.[1] Of the synthesized nucleosides , apart from oxa-cyclic analogues, other heterocylic or carbocyclic analogues have also been investigated. Because of the presence of chiral carbons in the sugar ring, it seems more difficult to synthesize the optically active heterocylic or carbocyclic nucleoside analogues than the oxa-cyclic ones due to the limitation of resources. Herein we report the synthesis of a new kind of optically active aza-cyclic nucleoside analogues.

The synthetic route (Scheme 1) to the pyrrolidinonyl thymine nucleoside analogues **7** started from (*S*)-malic acid (**1**). Reflux of a suspension of (*S*)-malic acid in acetyl chloride gave (*S*)-4-acetoxysuccic anhydride (**2**). The anhydride **2** was then reacted with aminoalcohol (2 eq) in CH_2Cl_2 below 30 ℃ and successively in acetyl chloride at reflux to form (*S*)-4-acetoxysuccinimide (**3**) in 80% yield.[2] Regio- and diastereoselective reduction[3] of **3** with sodium borohydride in methanol afforded (4*S*, 5*S*)-4-acetoxy-1-acetoxyalkyl-5-hydroxy-2-pyrrolidinone (**4**), which was then acetylated with acetic anhydride/pyridine to give (4*S*,5*S*)-1-acetoxyethyl-4,5-diacetoxy-2-pyrrolidinone (**5**) in quantitative yield. The configurational assignment of **5** was made according to the observed vicinal coupling constants[4] ($J_{4\text{-}5}$=5.0~5.4Hz). Condensation[5] of **5** with bis(trimethylsilyl)thymine[6] in the presence of $TiCl_4$ at −15 ℃ afforded protected pyrrodinonyl thymine nucleoside analogue **6** in 70% yield. The configurations of **6** were assigned by ^{1}H NMR. The singlet at ~5.6 ppm attributed to the proton H-5 in pyrrolidinonyl ring indicated that the *trans*-diastereoisomer **6** was obtained in the condensation reaction. ^{1}H-^{1}H COSY spectra showed no correlation between H-4 and H-5. It should be noted that the ^{1}H NMR spectra measured at r. t. in $CDCl_3$ or DMSO-d6 showed a broad singlet at ~5.6 ppm attributed to H-5, however, a sharp singlet at ~5.6 ppm was shown in the spectra obtained in DMSO-d6 at higher temperature (95 ℃), although the explanation to the result has not been given. Deacetylation[7] of **6** with ammonia in methanol at 5 ℃ gave the final pyrrodinonyl thymine nucleoside analogues **7** in 90% yield. It was found that the acetyl group in pyrrodinonyl ring was removed prior to that in the side chain. As a result, a mono-deacylation product, which was easily separeted by silica gel chromatography (eluent, dichloromethane-methanol 95:5) from **6** and **7**, has been isolated in 40% yield and characterized.

The nucleoside analogues synthesized have been fully characterized using ^{1}H NMR, COSY at 500 MHz and MS(ESI).



Scheme 1. Reagents, conditions and yields. (a) CH_3COCl, reflux, 5 h. (b) aminoalcohol/CH_2Cl_2, then CH_3COCl, reflux, 5 h, 80%. (c) $NaBH_4/CH_3OH$, -5 ℃, 10 min, 88%. (d) Ac_2O/Py, 2 h, quantitatively. (e) bis(trimethylsilyl)thymine/ $TiCl_4$/ CH_3CN, -20~ -10℃, 3 h, 70%. (f) NH_3/CH_3OH, 5 ℃, 3 day, 90%.

In summary, an efficient and general synthetic route to a new kind of optically active pyrrolidinonyl nucleoside analogues has been developed. The compounds **7** with both a primary and a secondary hydroxy groups could be useful for the preparation of new oligonucleotides. Assay of the prepared nucleoside analogues showed non-activity against virus. Synthesis of the modified oligonucleotides from the nucleoside analogues above and comparison of the Tm's of the oligonucleotides with those of the corresponding natural oligonucleotides will be reported elsewhere.

Table 1. Selected spectroscopic data

Compds	R	n	$[\alpha]_D$	^{1}H NMR (500 MHz) δ:
6a	H	1	+5.66 (c 1.93, CH_2Cl_2)	($CDCl_3$): 1.95(s, 3H), 2.05(s, 3H), 2.15(s, 3H), 2.53(d, J=18.2Hz, 1H), 3.15(dd, J=7.2x18.2Hz, 1H), 3.2(m, 1H), 3.87(m, 1H), 4.15(m, 1H), 4.3(m, 1H), 5.2(d, J=7.2Hz, 1H), 5.6(bs, 1H), 6.95(s, 1H), 9.9(s, 1H)
6b	H	2	+4.98 (c 2.09, CH_2Cl_2)	($CDCl_3$): 1.6~1.8(m, 2H), 1.95(s, 3H), 2.06(s, 3H), 2.14(s, 3H,), 2.53(d, J=18Hz, 1H), 2.86(m, 1H), 3.16(dd, J=7.4x18Hz, 1H), 3.7(m, 1H), 4.1(m, 2H), 5.21(d, J=7.4Hz, 1H), 5.65(bs, 1H), 6.81(s, 1H), 9.0(s, 1H)
6c	H	3	-1.17 (c 2.32, CH_2Cl_2)	($CDCl_3$): 1.5~1.7(m, 4H), 1.95(s, 3H), 2.05(s, 3H), 2.14(s, 3H,), 2.53(d, J=18Hz, 1H), 2.85(m, 1H), 3.15(dd, J=7.2x18Hz, 1H), 3.7(m, 1H), 4.07(m, 2H), 5.2(d, J=7.2Hz, 1H), 5.64(bs, 1H), 6.81(s, 1H), 9.0(s, 1H)
6d	Et	1	-4.20 (c 1.24, CH_2Cl_2)	($CDCl_3$): 0.94(t, J=7Hz, 3H), 1.5(m, 2H), 1.96(s, 3H), 2.02(s, 3H), 2.13(s, 3H,), 2.5(d, J=18Hz, 1H), 3.23(dd, J=7.2x18Hz, 1H), 4.0(m, 1H), 4.14(m, 1H), 4.46(m, 1H), 5.16(d, J=7.2Hz, 1H), 5.65(bs, 1H), 6.9(s, 1H), 8.7(s, 1H); (DMSO-d6, measured at 95℃): 0.85(t, J=7Hz, 3H), 1.48(m, 2H), 1.86(s, 3H), 1.95(s, 3H), 2.10(s, 3H,), 2.3(d, J=18Hz, 1H), 3.24(dd, J=7.4x18Hz, 1H), 3.78(m, 1H), 4.12(dd, J=4.7x11.7Hz, 1H), 4.31(dd, J=9.3x11.2Hz, 1H), 5.19(d, J=7.4Hz, 1H), 5.63(s, 1H), 7.5(s, 1H), 11.2(s, 1H)
7a	H	1	+64.03 (c 1.9, CH_3OH)	(DMSO-d6+D_2O): 1.91(s, 3H), 2.12(d, J=17.4Hz, 1H), 2.8(m, 1H), 2.92(dd, J=17.4x7.4Hz, 1H), 3.3~3.5(m, 3H), 4.25(d, J=7.2Hz, 1H), 5.64(s, 1H), 7 .36(s, 1H)
7b	H	2	+63.05 (c 2.0, CH_3OH)	(DMSO-d6+D_2O): 1.5(m, 1H), 1.6(m, 1H), 1.8(s, 3H), 2.15(d, J=18Hz, 1H), 2.75(m, 1H), 2.94(dd, J=7.4x18Hz, 1H), 3.3~3.5(m, 3H), 4.22(d, J=7.4Hz, 1H), 5.6(s, 1H), 7.28(s, 1H)
7c	H	3	+52.50 (c 1.2, CH_3OH)	(DMSO-d6+D_2O): 1.3~1.5(m, 4H), 1.8(s, 3H), 2.16(d, J=18Hz, 1H), 2.74(m 1H), 2.98(dd, J=7.4x18Hz, 1H), 3.37(t, J=6.2Hz, 2H), 3.42(m, 1H), 4.25(d, J=7.4Hz, 1H), 5.6(bs, 1H), 7.28(s, 1H)
7d	Et	1	+50.70 (c 2.0, CH_3OH)	(CD_3OD+D_2O): 0.89(t, J=7.4Hz, 3H), 1.4~1.5(m, 2H), 1.85(s, 3H), 2.25(d, J=18Hz, 1H), 3.12(dd, J=7.2x17.6Hz, 1H), 3.62(d, J=8.4Hz, 2H), 3.8(m, 1H), 4.33(d, J=7.2, 1H), 5.7(bs, 1H), 7.32(s, 1H)

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References

1 C. L. Propst and T. J. Perum, "Nucleic Targeted Drug Design", Marcel Dekler Inc., New York (1992); D. M. Huryn and M. Okabe, *Chem. Rev.*, **92**, 1745 (1992).
2 A. R. Chamberlin and J. Y. L. Chung, *J. Amer. Chem. Soc.*, **105**, 3653 (1983).
3 J. C. Hubert, J. B. Wijnberg, and W. N. Speckamp, *Tetrahedron*, **31**, 1437 (1975); J. B. Wijinberg, H. E. Schoemaker, and W. N. Speckamp, *Tetrahedron*, **34**, 179 (1978).
4 P. Q. Huang, S. L. Wang, H. Zheng, and X. S. Fei, *Tetrahedron Lett.*, **38**, 271 (1997); P. Jouin, B. Castro, and D. Nisato, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 1177.
5 T. Nishitani, H. Horikalva, and T. Iwasaki, *J. Org. Chem.*, **47**, 1706 (1982).
6 E. Wittenburg, *Chem. Ber.*, **99**, 2380 (1966).
7 T. L. Su, B. Bennua, H. Vorbruggen, and H. J. Lindner, *Chem. Ber.*, **114**, 1278 (1981).