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Asymmetric Synthesis of Polyhydroxy Pyrrolidinonyl Nucleoside Analogues from Tartaric acid

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Abstract: Asymmetric synthesis of novel optically active nucleoside analogues **7** from natural tartaric acid is described. In the given nucleoside analogues an optically active polyhydroxy pyrrolidinonyl ring is in place of the tetrahydrofuran ring.

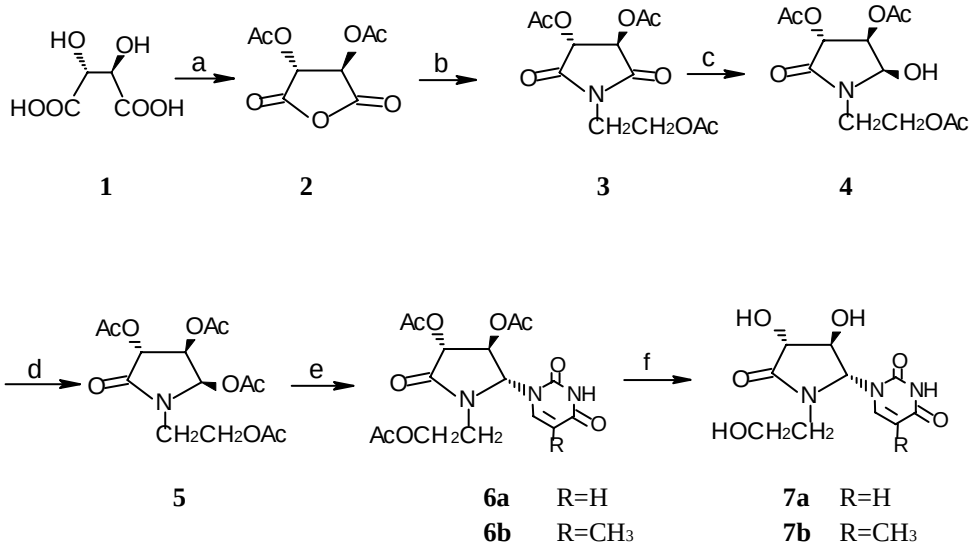
Keywords: Nucleoside: pyrrolidinone, asymmetric synthesis.

Modification of nucleoside is an efficient procedure to develop new potent agents against human tumor or viruses[1]. More challenging is to synthesize new optically active polyhydroxy nucleoside analogues. Because of the limitation of resources, it seems a rather arduous work to synthesize optically active carbocyclic or other heterocyclic nucleoside analogues with more than two chiral carbons, though natural sugars are available starting materials to oxa-cyclic nucleosides, such as furanosyl or pyranosyl ones. In this paper, we report an efficient and general synthetic route to optically active polyhydroxy aza-nucleosides from natural tartaric acid.

The synthesis of the pyrrolidinonyl nucleoside analogues **7** is shown in **scheme 1**. Reflux of a suspension of L-tartaric acid in acetyl anhydride gave diacetoxysuccinic anhydride **2**[2]. The anhydride **2** was treated with 2-aminoethanol (2 eq) in CH_2Cl_2 at room temperature and successively in acetyl chloride at reflux to form (3*R*, 4*R*)-3, 4-diacetoxysuccinimide **3** in 80% yield[3]. The excess of free amino group was kept to avoid the possible acylation of the hydroxy group by addition of the anhydride **2** to the solution of aminoethanol in dichloromethane. One mole excess of aminoethanol was used as a base which could be replaced by triethylamine. In the presence of excessive aminoethanol, 2-diacetylaminoethyl acetate was formed which could be separated from the desired product by chromatography on silica gel. Diastereoselective reduction of **3** with sodium borohydride[4] in methanol afforded (3*R*, 4*R*, 5*R*)-3,4-diacetoxy-1-(2-acetoxyethyl)-5-hydroxy-2-pyrrolidinone **4**; the result obtained seems different from that given by Yuda[5]. The diastereoselectivity (about 95%) of the reduction was determined based on the ^{1}H NMR data of **5**, which was derived from **4** *via* acylation of **4** with acetic anhydride/pyridine in quantitative yield. The configurational assignment of **5** was made by the observed vicinal coupling constants ($J_{3\text{-}4}$=4.3Hz,

$J_{4\text{-}5}$=2.2Hz). Additional support on the conclusion of the *cis*-diastereoseletive reduction of **3** with sodium borohydride comes from the evidence of the reduction of the compounds from L-malic acid[6]. Condensation[7] of **5** with *bis*-(trimethylsilyl)uracil or *bis*-(trimethylsilyl)thymine[8] in the presence of $TiCl_4$ at -15℃ afforded protected pyrrolidinonyl nucleoside analogues **6** in 60% yield. The vicinal coupling constants ($J_{3\text{-}4}$=4.3Hz, $J_{4\text{-}5}$=6Hz) of **6** indicated the *trans*-diastereoselectivity of the condensation. The conclusion of the configurational assignment is in accord with that given by Langlois[9], although a different result was reported by Yuda[5]. Deacylation[10] of **6** with ammonia in methanol at 5℃ gave the final pyrrolidinonyl nucleoside analogues **7** in 90% yield. It was detected that the acetyl group in pyrrolidinonyl ring was removed prior to that in the side chain. Completion of the deacylation was monitored by TLC (eluent: dichloromethane/methanol, 95/5).

Scheme 1. The synthetic route of the compounds **7**



Reagents, conditions and yields:

(a) acetic anhydride, reflux, 2 hrs, 90%;

(b) 2-aminoethanol/CH_2Cl_2, then CH_3COCl, reflux, 5 hrs, 80%;

(c) $NaBH_4$/CH_3OH, -15℃~ -5℃, 10 mins, 88%;

(d) Ac_2O/Py, 2 hrs, quantitatively;

(e) *bis*-(trimethylsilyl)uracil or *bis*-(trimethylsilyl)thymine/ $TiCl_4$/ CH_3CN, -20~ -10℃, 3 hrs, 60%;

(f) NH_3/CH_3OH, 5℃, 3 days, 90%.

Table 1. ^{1}H and ^{13}C NMR spectral data of the compounds

Compds	^{1}H , ^{13}C NMR spectral data
3	δ ($CDCl_3$): 2.0(s, 3H, CH_3), 2.19(s, 6H, 2 CH_3), 3.84(m, 2H, CH_2OCO), 4.21(m, 1H, NCHH), 4.32(m, 1H, NCHH), 5.52(s, 2H, CH in cycle)
4	δ ($CDCl_3$): 2.06(s, 3H, CH_3), 2.15(s, 3H, CH_3), 2.16(s, 3H, CH_3), 3.59(ddd, J=4.6x6.6x14.6Hz, 1H, H in chain), 3.74(ddd, J=4.6x6.5x14.6Hz, 1H, H in chain), 4.23(ddd, 4.6x6.6x11.6Hz, 1H, H in chain), 4.3(ddd, J=4.6x6.5x11.6Hz, 1H, H in chain), 5.08(d, J=2.6Hz, 1H, H-3), 5.11(dd, J=2.6x4.8Hz, 1H, H-4), 5.14(d, J=4.8Hz, 1H, H-5)
5	δ ($CDCl_3$): 2.06(s, 3H, CH_3), 2.12(s, 3H, CH_3), 2.16(s, 3H, CH_3), 2.17(s, 3H, CH_3), 3.26(ddd, J=4.1x6.8x14.8Hz, 1H, H in chain), 3.88(ddd, J=4.3x6.6x14.8Hz,1H, H in chain), 4.12(ddd, J=4.3x6.8x11.8Hz, 1H, H in chain), 4.36(ddd, J=4.1x6.6x11.8Hz, 1H, H in chain), 5.22(dd, J=2.2x4.3Hz, 1H, H-4), 5.34(d, J=4.3Hz, 1H, H-3), 6.23(d, J=2.2Hz, 1H, H-5)
6a	δ ($CDCl_3$): 2.07(s, 3H, CH_3), 2.17(s, 3H, CH_3), 2.20(s, 3H, CH_3), 2.96(ddd, J=2.8x6.3x14.8Hz, 1H, H in chain), 3.98 (ddd, J=3.1x6.8x14.8Hz, 1H, H in chain), 4.12(ddd, J=3.1x6.3x11.8Hz,1H, H in chain), 4.32(ddd, J=2.8x6.8x11.8Hz, 1H, H in chain), 5.06(d, J=4.3, 1H, H-3), 5.43(dd, J=4.3x5.9Hz, 1H, H-4), 5.9(d, J=8.0Hz, 1H, H in uracil), 6.24(d, J=5.9Hz, 1H, H-5), 7.5(d, J=8.0Hz, 1H, H in uracil), 9.6(bs, 1H, NH).
6b	δ ($CDCl_3$): 2.05(d, J=1.2Hz, 3H, CH_3), 2.15(s, 3H, CH_3), 2.25(s, 3H, CH_3), 2.29(s, 3H, CH_3), 3.0(ddd, J=3.1x6.8x15.1Hz, 1H, H in chain), 4.08(ddd, J=3.2x7.0x15.1Hz, 1H, H in chain), 4.21(ddd, J=3.2x6.7x12.1Hz,1H, H in chain), 4.41(ddd, J=3.1x7.0x12.1Hz, 1H, H in chain), 5.15(d, J=4.3Hz, 1H, H-3), 5.53(dd, J=4.3x6.0Hz, 1H, H-4), 6.34(d, J=6Hz, 1H, H-5), 7.35(s, 1H, H in thymine), 8.9(bs, 1H, NH).
7a	δ (DMSO-d6+D_2O): 2.51(m, 1H, H in chain), 3.3~3.44(m, 3H, H in chain), 3.9(bs, 1H, H-4), 4.01(d, J=6.2Hz, 1H, H-3), 5.71(d, J=8.0Hz, 1H, H in uracil), 5.8(bs, 1H, H-5), 7.53(d, J=8.0Hz, 1H, H in uracil).
7b	δ (DMSO-d6+D_2O): 1.80(s, 3H, CH3), 2.63(m, 1H, H in chain), 3.3~3.5(m, 3H, H in chain), 3.92(bs, 1H, H-4), 4.1(d, J=6.1Hz, 1H, H-3), 5.8(bs, 1H, H-5), 7.3(s, 1H, H in thymine). ^{13}C NMR (DMSO-d6, 500MHz) δ: 16.92, 46.79, 62.08, 74.83, 78.88, 81.57, 116.38, 140.06, 156.16, 169.22, 178.86.

The nucleoside analogues synthesized have been characterized using IR, ^{1}H NMR, at 500MHz and MS(ESI) as well as elemental analysis. The results of biological activity of the compounds prepared will be reported elsewhere.

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References

1. C. L. Propst, T. J. Perum. *Nucleic Targeted Drug Design*, Marcel Dekler Inc., New York, **1992**; D. M. Huryn, M. Okabe. *Chem. Rev*., **1992**, *92*, 1745.
2. R. L. Sheriner, C. L. Furrow Jr.. *Organic Synthesis*, Coll. Vol. IV, John Wiley & Sons, New York, **1963**, p242.
3. J. M. Dener, D. J. Hart, S. Ramesh. *J. Org. Chem*., **1988**, *53*, 6025.

4. J. C. Hubert, J. B. Wijnberg, W. N. Speckamp. *Tetrahedron*, **1975**, *31*, 1437; J. B.Wijinberg, H. E. Schoemaker, W. N.Speckamp. *Tetrahedron*, **1978**, *34*, 179.
5. H. Yuda, H. Kitayama, W. Yamada, T. Katagiri, K. Takabe. *Tetrahedron:Asymmetry*, **1993**, *4*, 1451;
   H. Yuda, H. Kitayama, T. Katagiri, K. Takabe. *Tetrahedron:Asymmetry*, **1993**, *4*, 1455.
6. A. R. Chamberlin, J. Y. L. Chung. *J. Amer. Chem. Soc*., **1983**, *105*, 3653.
7. T. Nishitani, H. Horikalva, T. Iwasaki, K. Matsumoto, I. Inoue, M. Miyoshi. *J. Org. Chem*., **1982**, *47*, 1706.
8. E. Wittenburg. *Chem. Ber*., **1966**, *99*, 2380.
9. D. Griffart-Brunet, N. Langlois. *Tetrahedron Lett.*, **1994**, *35*, 2889.
10. T. L. Su, B. Bennua, H. Vorbruggen, H. J. Lindner. *Chem. Ber*., **1981**, *114*, 1269.

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