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Synthesis of the Four Possible Stereoisomeric 5'-Nor Carbocyclic Nucleosides from One Common Enantiomerically Pure Starting Material

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Abstract: A flexible synthesis of the four stereoisomeric enantiomerically pure 5'-nor carbocyclic nucleosides **2b**, *ent*-**2b**, **3b**, and *ent*-**3b** starting from the common enantiomerically pure allylic monoacetate **1** has been developed.

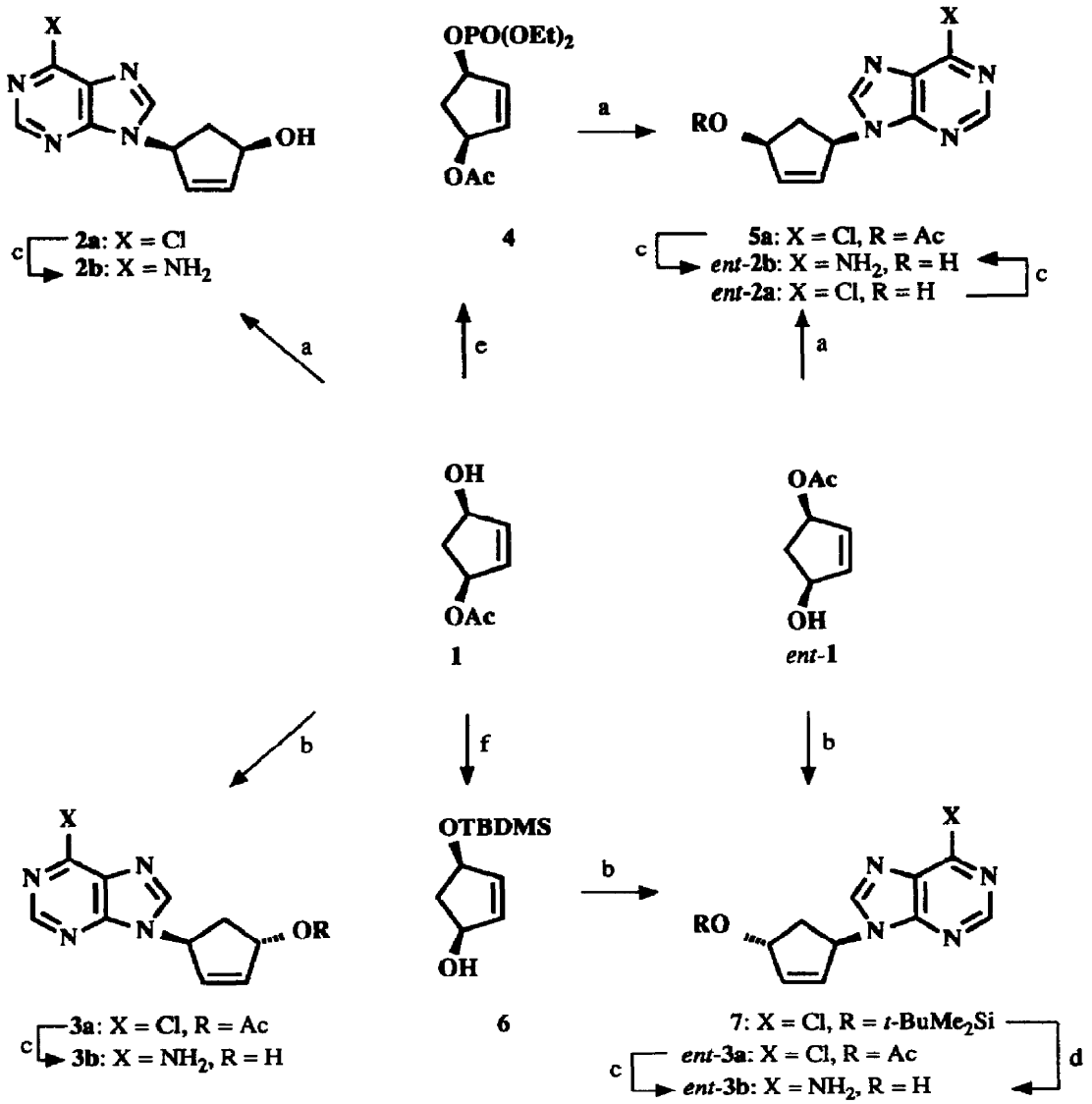
There is intense current interest in the synthesis of carbocyclic nucleoside analogues due to their metabolic stability and especially their anti-tumor and anti-viral properties.[1] Yet, only a few synthetic compounds of this type have been obtained enantiomerically pure by chemical approach.[2] As a part of an ongoing program to expand the structural versatility of nucleoside phosphonates,[3] we wanted to unterstand better the reactivity of carbocyclic versions of the ring system.

In this paper we wish to report our approach for the synthesis of stereoisomeric carbocyclic (2',3'-dideoxy-2',3'-didehydro)-5'-nor adenosine derivatives in enantiomerically pure form starting from one common chiral starting material. The aim of this investigation was to demonstrate the use of the enantiomerically pure allylic acetate **1** as a starting material for the synthesis of carbocyclic nucleoside analogues.

1 can be prepared by lipase-catalyzed transesterification of *cis*-cyclopent-2-en-1,4-diol[4] or by hydrolysis of the corresponding diacetate with porcine liver esterase.[5] By using **1** as the starting material it should be possible by switching the functional groups and by using two different types of nucleophilic substitution reactions to prepare the four possible stereoisomeric carbocyclic nucleoside analogues (two enantiomeric pairs of diastereomers). Having these isomers in the hand, it would allow to study the biological properties regarding chiral recognition in biological systems.

Reaction of **1** with the sodium salt of 6-chloropurine under Pd(0)-catalysis[6] gave **2a** under retention of configuration at the stereocenter adjacent to the acetate group. **2a** yielded the adenine derivative **2b**[7] by reaction with ammonia. On the contrary, reaction of **1** under Mitsunobu conditions[8] afforded **3a** under inversion of the configuration at the carbon atom attached to the hydroxy group.

Amination of **3a** gave the adenine derivative **3b**[9] which is diastereomeric to **2b**.



a: 6-chloropurine, NaH, $Pd(PPh_3)_4$, PPh_3
b: 6-chloropurine, PPh_3, DEAD
c: NH_3/MeOH
d: 1. TBAF, 2. NH_3/MeOH
e: $(EtO)_2POCl$, imidazole, MeCN
f: 1. *t*-$BuMe_2SiCl$, imidazole, 2. NaOMe/MeOH

Scheme 1

Transformation of **1** into the corresponding phosphate **4** switches the reactivity in the subsequent Pd(0)-catalyzed nucleophilic substitution with the sodium salt of 6-chloropurine to give **5** due to the higher reactivity of an allylic phosphate compared with the corresponding acetate.[10,11] **5** afforded after subsequent amination *ent*-**2b**.[12] Silylation of **1** followed by deacetylation gave **6** which yielded **7** under Mitsunobu conditions with inversion of the configuration at the reacting stereocentre. Finally, desilylation and subsequent reaction with ammonia gave *ent*-**3b**[13] (Scheme 1).

Due to the symmetry properties of **1**/*ent*-**1** the enantiomeric monoacetate *ent*-**1**[14] can serve as the starting material in an analogous manner. This was demonstrated by the synthesis of *ent*-**2b** and *ent*-**3b**. Reaction of *ent*-**1** under Pd(0)-catalysis with the sodium salt of 6-chloropurine gave *ent*-**2a** which afforded by amination *ent*-**2b**.[15] Mitsunobu reaction of *ent*-**1** with 6-chloropurine yielded *ent*-**3a** which was converted into *ent*-**3b**[16] by reaction with ammonia. By the latter sequences the structures of *ent*-**2b** and *ent*-**3b** prepared from **1** could be confirmed. The yields of all reactions have not been optimized.

Recently, **2a**, **2b**, *ent*-**2a**, and *ent*-**2b** have been prepared by lipase-catalyzed resolution of the corresponding racemic nucleoside analogues.[17]

The synthesis of the carbocyclic nucleoside analogues **2b** and **3b** as well as their corresponding enantiomers *ent*-**2b** and *ent*-**3b** from one common enantiomerically pure starting material demonstrates the flexibility of our synthetic scheme which allows to prepare the two enantiomeric pairs of diastereomers by using two different kinds of nucleophilic substitution reactions and switching the reactivity of **1** by functional group interconversion.

Synthesis and biological investigation of the corresponding phosphonate analogues of **2b**, *ent*-**2b**, **3b**, and *ent*-**3b** are under progress and will be published elsewhere together with full experimental details.

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7. **2b**: Yield 42% related to **1**; m.p. 196-197°C (acetone); uv (λ_{max}; MeOH) 261.4, 212.2 nm; $[\alpha]_D^{20}$ − 110.0 (c = 0.56, MeOH); ^{1}H-NMR (400 MHz; DMSO-d_6) 1.68 (1H, dtr, *J* = 14, 4,

5'-H), 2.84 (1H, dtr, J = 14, 8, 5'-H), 4.66 (1H, br s, 4'-H), 5.39 (1H, m, 1'-H), 5.52 (1H, d, J = 7, OH), 5.92 (1H, d, J = 4, 2'-H), 6.13 (1H, m, 3'-H), 7.24 (2H, s, NH_2), 8.02 (1H, s, H-8), 8.09 ppm (1H, s, H-2); ^{13}C-NMR (50 MHz, DMSO-d_6) 38.15 (C5'), 58.58 (C1'), 74.45 (C4'), 118.99 (C5), 131.02 (C2'), 138.80 (C3'), 140.14 (C8), 149.11 (C4), 152.25 (C2), 155.87 ppm (C6); MS 217 (M^+), 200, 135.

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9. **3b**: Yield 41% related to **1**; m.p. 208-209°C (EtOH); uv (λ_{max}; MeOH): 260.4, 212.6 nm; $[\alpha]_D^{20}$ − 208.8 (c = 0.85, MeOH); ^{1}H-NMR (400 MHz, DMSO-d_6): 2.19 (2H, m, 5'-H), 5.03 (2H, 2 s, overlapping, OH, 4'-H), 5.66 (1H, m, 1'-H), 5.96 (1H, dd, J = 5.5, 1.8, 2'-H or 3'-H), 6.13 (1H, dd, J = 5.5, 1.8, 2'-H or 3'-H), 7.18 (2H, s, NH_2), 7.94 (1H, s, (8-H), 8.09 ppm (1H, s, 2-H); ^{13}C-NMR (50 MHz, DMSO-d_6): 38.35 (C5'), 58.80 (C1'), 74.67 (C4'), 119.20 (C5), 131.24 (C2'), 139.00 (C3'), 140.36 (C8), 149.33 (C4), 152.47 (C2), 156.09 ppm (C6); MS 218 (M^+ + 1), 217 (M^+), 200, 136.

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12. *ent*-**2b**: Yield 25% related to **1**; 192-193°C (acetone); $[\alpha]_D^{20}$ + 122.0 (c = 0.56, MeOH). Uv-, ^{1}H-NMR-, ^{13}C-NMR-, and MS-spectra are identical with those of **2b**.

13. *ent*-**3b**: Yield 25% related to **1**; m.p. 207-209°C (EtOH); $[\alpha]_D^{20}$ + 222.1 (c = 0.59, MeOH). Uv-, ^{1}H-NMR-, ^{13}C-NMR-, and MS-spectra are identical with those of **3b**.

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15. *ent*-**2b** from *ent*-**1**: Yield 45% related to *ent*-**1**.

16. *ent*-**3b** from *ent*-**1**: Yield 43% related to *ent*-**1**.

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