

Stereoselective synthesis of 9- β -D-arabianofuranosyl guanine and 2-amino-9-(β -D-arabianofuranosyl)purine

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Received 12 September 2004; revised 10 November 2004; accepted 11 November 2004

Available online 8 December 2004

Abstract—9- β -D-Arabianofuranosyl guanine (**6**) and 2-amino-9-(β -D-arabianofuranosyl)purine (**8**) were prepared from 2-amino-6-chloro-9-(2,3,5-triphenylmethoxyl- β -D-arabianofuranosyl)purine (**4**), a key intermediate which was stereoselectively prepared from 2,3,5-triphenylmethoxyl-D-arabianofuranose and 2-amino-6-chloro-purine. The yield of the intermediate was obviously improved and only β -isomer was formed by using the activated molecular sieve as environmental friendly catalyst, overcoming the defect that a 1:1 mixture of α - and β -isomers was formed, which was difficult to separate, when toxic mercury cyanide was previously used as catalyst.

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In the past 10 years, remarkable progress has been made for the treatment of AIDS due to the development of new anti-AIDS drugs and improved treatment, leading to longer life for AIDS patients.^{1–4} The serious problem facing us today, however, is that these drugs will soon produce resistance in the human body. In 1994, Schinazt et al. reported 42 different mutations of HIV-RT and its relative protease.⁵ And the number of drug resistance mutations is reported to increase quickly.⁶ It was found from the latest pathology research that HIV virus breeds very fast. The composite lifespan of plasma virus and virus-producing cells is remarkably short (half-life period $\sim$ 2 days). Almost complete replacement of wild-type virus in plasma by drug-resistant variants occurs after two weeks of antiretroviral drug therapy, therefore production of resistance to the drugs concerned is unavoidable.^{7–9} So far HIV-1 has developed resistance to all approved nucleotide drugs in clinical application.^{10–12} Resistance to AZT is particularly pronounced due to its longer clinical application.¹³ Sommadossi et al. has found that long-term treatment of AIDS patients using AZT would arouse the defect of d4T phosphate.¹⁴ It

was also found that HIV virus would develop resistance to nonnucleotide inhibition of reverse transcriptase.

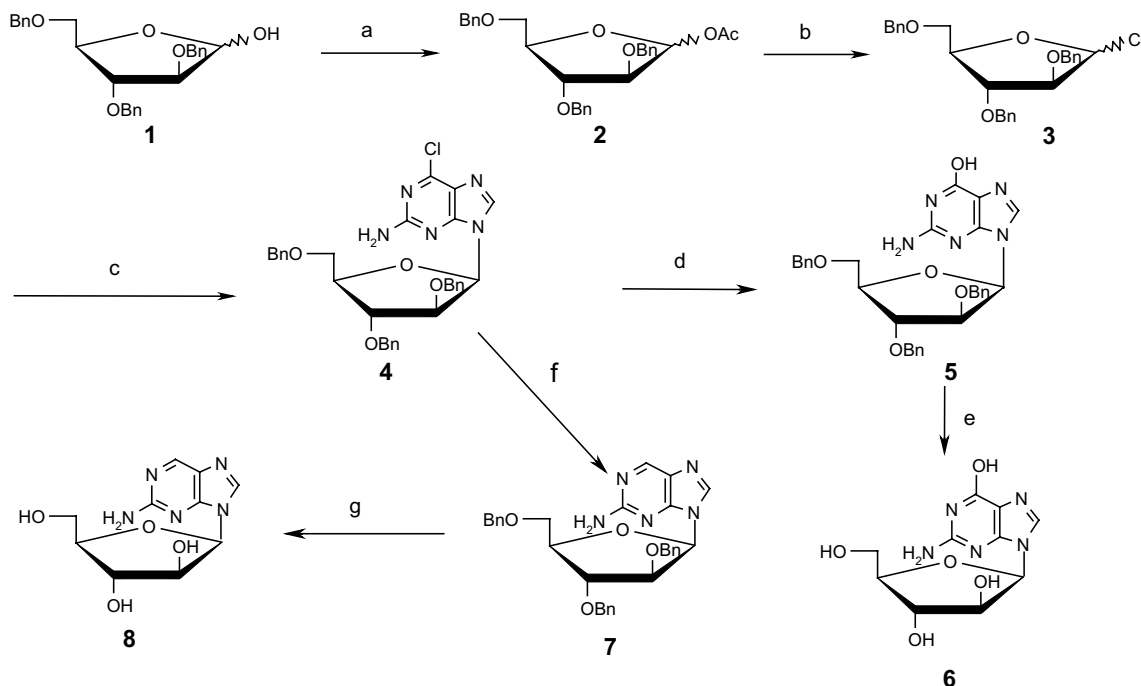
Another serious problem comes from the existence of HIV virus reservoir.¹⁵ Although the combination anti-retroviral therapy has been used for AIDS patients, HIV virus, which may be undetectable, would still exist in the plasma. HIV virus may hide in the quiescent CD4 + cell T-lymphocyte, macrophage, lymphatic and central nervous system. These harbor latent HIV viruses which can be reactivated or reinfect the peripheral sites.¹⁶

It is therefore urgent to develop new anti-HIV drugs with higher activity to terminate the revival of the HIV virus hidden in the CD4 + cells, etc. and overcome other deficiencies of the present drugs. For this reason, we designed and developed some new compounds with anti-HIV activity.

9- β -D-Arabianofuranosyl guanine and 2-amino-9-(β -D-arabianofuranosyl)purine were prepared as in **Scheme 1**. Firstly, the key intermediate, 2-amino-6-chloro-9-(2,3,5-triphenylmethoxyl- β -D-arabianofuranosyl)purine (**4**), was prepared using 2,3,5-triphenylmethoxyl-D-arabianofuranose (**1**) as the raw material. Compound **1** reacted with acetic anhydride to form 1-*O*-acetyl-2,3,5-triphenylmethoxyl-D-arabianofuranose (**2**) in 98.5% yield, which was directly reacted with HCl at 0 °C to

Keywords: Stereoselective synthesis; β -D-Arabianofuranosyl guanine; 2-Amino-9-(β -D-arabianofuranosyl)purine.

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Scheme 1. Reagents and conditions: (a) acetic anhydride, 4.56 equiv, in pyridine, rt, 4 h; (b) HCl gas, in CH_2Cl_2 , 0 °C, 3 h; (c) trimethylsilyl protected 2-amino-6-chloro-purine, 1.0 equiv, 4 Å molecular sieve, in 1,2-dichloroethane, rt, 6 days; (d) 4.9 equiv 2-mercaptoethanol, 5.9 equiv sodium methoxide, in methanol, reflux, 24 h; (e) sodium particles, in THF–liquid ammonia, –65 °C, 20 min; (f) H_2 , 10% Pd–C, in CH_3OH –THF– NH_4OH , 50 Psi, rt, 4 h; (g) BCl_3 , 12 equiv, in CH_2Cl_2 , –72 °C, 4 h.

form 1-chloro-2,3,5-triphenylmethoxyl- β -D-arabianofuranose (**3**) in 87.1% yield. In the presence of activated molecular sieve (4 Å), **3** underwent a stereoselective condensation reaction with trimethylsilyl protected 2-amino-6-chloro-purine to form 2-amino-6-chloro-9-(2,3,5-triphenylmethoxyl- β -D-arabianofuranosyl)purine (**4**).¹⁷ The reaction yield was obviously improved (78.5%) and only the aim product β -isomer was formed, effectively solving the problem of separating β -isomers from α - in the reaction mixture prepared by the previous process using mercury cyanide as a catalyst.¹⁸ The chlorine at position 6 of purine was transferred to hydroxyl to get compound **5**¹⁹ when intermediate **4** reacted with 2-mercaptoethanol using sodium methoxide as catalyst. 9- β -D-Arabianofuranosyl guanine (**6**)²⁰ was then obtained with high yield (67.1%) by deleting the benzyl group of compound **5** in sodium–liquid ammonia. 2-Amino-9-(2,3,5-triphenylmethoxyl- β -D-arabianofuranosyl)purine (**7**)²¹ was obtained when intermediate **4** was hydrogenated using 10% Pd–C as catalyst. It was found that solvents have a great effect on the yield. When CH_3OH –THF– NH_4OH = 450/15/15 (v/v), the yield reaches 92.4%. The aim product 2-amino-9-(β -D-arabianofuranosyl)purine (**8**)²² can be obtained in 58.6% yield by removing the benzyl group of **7** with BCl_3 at low temperature.

In summary, we have found an efficient method to stereoselectively synthesize the key intermediate, 2-amino-6-chloro-9-(2,3,5-triphenylmethoxyl- β -D-arabianofuranosyl)purine (**4**), by using activated molecular sieve instead of toxic mercury cyanide as environmental friendly catalyst. The reaction yield was markedly improved and

only the aim product β -isomer was formed. 9- β -D-arabianofuranosyl guanine (**6**) and 2-amino-9-(β -D-arabianofuranosyl)purine (**8**) were then conveniently prepared from this key intermediate. The experiments on biological activity are in progress.

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17. Compound **4**: UV (CH₃OH) λ_{max} : 248.0, 310.0 nm; ¹H NMR (400 MHz, CDCl₃): δ 3.65 (2H, d, OCH₂), 4.22 (3H, m, 3CH), 4.57 (6H, d, 3ArCH₂), 5.03 (2H, br s, D₂O exchangeable, NH₂), 6.30 (1H, d, CH), 6.93–7.31 (15H, m, Ar-H), 8.12 (1H, s, purine CH).
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19. Compound **5**: UV (CH₃OH) λ_{max} : 253.0, 274.0 nm; ¹H NMR (400 MHz, CDCl₃): δ 3.64 (2H, d, OCH₂), 4.21 (3H, m, 3CH), 4.51 (6H, d, 3ArCH₂), 6.28 (1H, d, CH), 6.41 (2H, br s, D₂O exchangeable, NH₂), 7.10–7.25 (15H, m, Ar-H), 7.82 (1H, s, purine CH).
20. Compound **6**: UV (H₂O) λ_{max} : 252.0, 270.0 nm; ¹H NMR (400 MHz, DMSO-*d*₆): δ 3.61 (2H, m, OCH₂), 3.75 (1H, m, CH), 4.02 (2H, m, 2CH), 5.05 (1H, br s, CH₂OH), 5.55 (1H, br s, CHOH), 5.65 (1H, br s, CHOH), 6.00 (1H, d, CH), 6.55 (2H, br s, D₂O exchangeable, NH₂), 7.75 (1H, s, purine CH); HRMS: found 284.0998 [M+H]⁺ (calcd for C₁₀H₁₃N₅O₅ [M+H]⁺ 284.0995).
21. Compound **7**: UV (CH₃OH) λ_{max} : 211.5, 245.5, 308.5 nm; ¹H NMR (400 MHz, DMSO-*d*₆): δ 3.69 (2H, m, OCH₂), 4.13 (1H, m, CH), 4.51 (6H, d, 3ArCH₂), 4.68 (2H, m, 2CH), 6.33 (1H, d, CH), 6.60 (2H, br s, NH₂), 6.96–7.30 (15H, m, Ar-H), 8.05 (1H, s, purine CH), 8.60 (1H, s, purine CH); Elem. Anal. found: C, 68.84; H, 5.87; N, 12.37 calcd for C₃₁H₃₁N₅O₄·0.3H₂O: C, 68.55; H, 6.14; N, 12.75.
22. Compound **8**: mp: 228–230 °C; [α]_D²⁵ +64.8° (*c* 0.075, CH₃OH); UV (H₂O) λ_{max} : 305.5 nm (ϵ 6095, pH 7), 312.5 nm (ϵ 3950, pH 2), 305.0 nm (6529, pH 11); ¹H NMR (400 MHz, DMSO-*d*₆): δ 3.64 (2H, q, OCH₂), 3.77 (1H, m, CH), 4.09 (2H, d, 2CH), 5.06 (1H, s, D₂O exchangeable, OH), 5.51 (1H, s, D₂O exchangeable, OH), 5.64 (1H, s, D₂O exchangeable, OH), 6.16 (1H, d, CH), 6.52 (2H, br s, D₂O exchangeable, NH₂), 8.10 (1H, s, purine CH), 8.56 (1H, s, purine CH); Elem. Anal. found: C, 43.79; H, 4.79; N, 25.54; calcd for C₁₀H₁₃N₅O₄·0.5H₂O: C, 43.78; H, 5.11; N, 25.35; HRMS: found 268.1040 [M+H]⁺ (calcd for C₁₀H₁₃N₅O₄ [M+H]⁺, 268.1046).