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

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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  $\alpha$ - and  $\beta$ -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.<sup>5</sup> And the number of drug resistance mutations is reported to increase quickly.<sup>6</sup> 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.<sup>7–9</sup> 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.<sup>13</sup> Sommadossi et al. has found that long-term treatment of AIDS patients using AZT would arouse the defect of d4T phosphate.<sup>14</sup> 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 antiretroviral 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

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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<sub>2</sub>Cl<sub>2</sub>, 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<sub>2</sub>, 10% Pd–C, in CH<sub>3</sub>OH–THF–NH<sub>4</sub>OH, 50 Psi, rt, 4 h; (g) BCl<sub>3</sub>, 12 equiv, in CH<sub>2</sub>Cl<sub>2</sub>, -72 °C, 4 h.

form 1-chloro-2,3,5-triphenylmethoxyl-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 2amino-6-chloro-purine to form 2-amino-6-chloro-9-(2,3,5-triphenylmethoxyl-β-D-arabianofuranosyl)purine (4).<sup>17</sup> The reaction yield was obviously improved (78.5%) and only the aim product  $\beta$ -isomer was formed, effectively solving the problem of separating  $\beta$ -isomers from  $\alpha$ - 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<sup>19</sup> when intermediate 4 reacted with 2-mercaptoethanol using sodium methoxide as catalyst. 9- $\beta$ -D-Arabianofuranosyl guanine (6)<sup>20</sup> 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)<sup>21</sup> 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-( $\beta$ -D-arabianofuranosyl)purine (8)<sup>22</sup> can be obtained in 58.6% yield by removing the benzyl group of 7 with BCl<sub>3</sub> 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  $\beta$ -isomer was formed. 9- $\beta$ -D-arabianofuranosyl guanine (6) and 2-amino-9-( $\beta$ -D-arabianofuranosyl)purine (8) were then conveniently prepared from this key intermediate. The experiments on biological activity are in progress.

## References and notes

- 1. Cohen, J. Science 1997, 276, 520.
- Katlama, C.; Clotet, B.; Plettenberg, A.; Jost, J.; Arasteh, K.; Bernasconi, E.; Jeantils, V.; Cutrell, A.; Stone, C.; Ait-Khaled, M.; Purdon, S. AIDS 2000, 14, 781.
- Chang, C.-N.; Dong, S.-L.; Zhou, J. H.; Beach, J. W.; Jeong, L. S.; Chu, C. K.; Tsai, C. H.; Cheng, Y. C.; Liotta, D.; Schinazi, R. J. Biol. Chem. 1992, 267, 13938.
- Schooley, R. T.; Ruane, P.; Myers, R. A.; Beall, G.; Lampiris, H.; Berger, D.; Chen, S. S.; Miller, M. D.; Isaacson, E.; Cheng, A. K. AIDS 2002, 16, 1257.
- Schinaz, R. F.; Larder, B. A.; Mellors, J. W. Int. Antivir. News 1994, 2, 72.
- Schinazi, R. F.; Larder, B. A.; Mellors, J. W. Int. Antivir. News 1996, 4, 95.
- 7. Ho, D. D.; Newmann, A. U.; Perelson, A. S.; Chen, W.; Leonard, J. M.; Markowitz, M. *Nature* **1995**, *373*, 123.
- Wei, X.; Ghosh, S. K.; Taylor, M. E.; Johnson, V. A.; Emini, E. A.; Deutsch, P.; Lifson, J. D.; Bonhoeffer, S.; Novak, M. A.; Hahn, B. H.; Saag, M. S.; Shaw, G. M. Nature 1995, 373, 117.
- 9. Coffin, J. M. Science 1995, 267, 483.
- Hahn, B. H.; Shaw, G. M.; Taylor, M. E.; Redfield, R. R.; Markham, P. D.; Salahuddin, S. Z.; Wong-Staal, F.; Gallo, R. C.; Parks, E. S.; Parks, W. P. Science 1986, 232, 1548.
- 11. Larder, B. A.; Kemp, S. D. Science 1989, 246, 1155.

- 12. Arts, E. J.; Wainberg, M. A. Antimicrob. Agents Chemother. 1996, 40, 527.
- 13. Schinazi, R. F.; Lloyd, R. M., Jr.; Nguyen, M.-H.; Cannon, D. L.; McMillan, A.; Ilksoy, N.; Chu, C. K.; Liotta, D. C.; Bazmi, H. Z.; Mellors, J. W. *Antimicrob. Agents Chemother.* **1993**, *37*, 875.
- Sommadossi, J. P.; Zhou, X. J.; Moore, J.; Havlir, D. V.; Friedland, G.; Tierney, C.; Smeaton, L.; Fox, L.; Richman, D.; Pollard, R. Abstracts of the 5th Conference on Retrovirues and Opportunistic Infections, Chicago, IL 1998; Session 5, Poster #3, Feb. 1–5.
- Weiser, B.; Burger, H.; Camphell, P.; Donelan, S.; Mladenovic, J. AIDS Res. Hum. Retroviruses 1996, 12, 1551
- Finzi, D.; Hermankova, M.; Pierson, T.; Carruth, L. M.; Buck, C.; Chaisson, R. E.; Quinn, T. C.; Chadwick, K.; Margolick, J.; Brookmeter, R.; Gallant, J.; Markowitz, M.; Ho, D. D.; Richman, D. D.; Siliciano, R. F. Science 1997, 278, 1295.
- 17. Compound 4: UV (CH<sub>3</sub>OH)  $\lambda_{\text{max}}$ : 248.0, 310.0 nm; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  3.65 (2H, d, OCH<sub>2</sub>), 4.22 (3H, m, 3CH), 4.57 (6H, d, 3ArCH<sub>2</sub>), 5.03 (2H, br s, D<sub>2</sub>O exchangeable, NH<sub>2</sub>), 6.30 (1H, d, CH), 6.93–7.31 (15H, m, Ar-H), 8.12 (1H, s, purine CH).
- Lee, W. W.; Martinez, A. P.; Goodman, L.; Henry, D. W. J. Org. Chem. 1972, 37, 2923.
- Compound 5: UV (CH<sub>3</sub>OH) λ<sub>max</sub>: 253.0, 274.0 nm; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.64 (2H, d, OCH<sub>2</sub>), 4.21 (3H, m, 3CH), 4.51 (6H, d, 3ArCH<sub>2</sub>), 6.28 (1H, d, CH), 6.41

- (2H, br s, D<sub>2</sub>O exchangeable, NH<sub>2</sub>), 7.10–7.25 (15H, m, Ar-*H*), 7.82 (1H, s, purine CH).
- 20. Compound **6**: UV ( $\dot{H}_2O$ )  $\lambda_{max}$ : 252.0, 270.0 nm;  $^1H$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  3.61 (2H, m, OCH<sub>2</sub>), 3.75 (1H, m, CH), 4.02 (2H, m, 2CH), 5.05 (1H, br s, CH<sub>2</sub>OH), 5.55 (1H, br s, CHOH), 5.65 (1H, br s, CHOH), 6.00 (1H, d, CH), 6.55 (2H, br s, D<sub>2</sub>O exchangeable, NH<sub>2</sub>), 7.75 (1H, s, purine CH); HRMS: found 284.0998 [M+H]<sup>+</sup> (calcd for  $C_{10}H_{13}N_5O_5$  [M+H]<sup>+</sup> 284.0995).
- 21. Compound 7: UV (CH<sub>3</sub>OH)  $\lambda_{\text{max}}$ : 211.5, 245.5, 308.5 nm; <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  3.69 (2H, m, OCH<sub>2</sub>), 4.13 (1H, m, CH), 4.51 (6H, d, 3ArCH<sub>2</sub>), 4.68 (2H, m, 2CH), 6.33 (1H, d, CH), 6.60 (2H, br s, NH<sub>2</sub>), 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 C<sub>31</sub>H<sub>31</sub>N<sub>5</sub>O<sub>4</sub>·0.3H<sub>2</sub>O: C, 68.55; H, 6.14; N, 12.75
- 22. Compound **8**: mp: 228–230 °C;  $[\alpha]_D^{25}$  +64.8° (c 0.075, CH<sub>3</sub>OH); UV (H<sub>2</sub>O)  $\lambda_{max}$ : 305.5 nm ( $\epsilon$  6095, pH 7), 312.5 nm ( $\epsilon$  3950, pH 2), 305.0 nm ( $\epsilon$ 529, pH 11); <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  3.64 (2H, q, OCH<sub>2</sub>), 3.77 (1H, m, CH), 4.09 (2H, d, 2CH), 5.06 (1H, s, D<sub>2</sub>O exchangeable, OH), 5.51 (1H, s, D<sub>2</sub>O exchangeable, OH), 5.64 (1H, s, D<sub>2</sub>O exchangeable, OH), 6.16 (1H, d, CH), 6.52 (2H, br s, D<sub>2</sub>O exchangeable, NH<sub>2</sub>), 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 C<sub>10</sub>H<sub>13</sub>N<sub>5</sub>O<sub>4</sub>·0.5H<sub>2</sub>O: C, 43.78; H, 5.11; N, 25.35; HRMS: found 268.1040 [M+H]<sup>+</sup> (calcd for C<sub>10</sub>H<sub>13</sub>N<sub>5</sub>O<sub>4</sub> [M+H]<sup>+</sup>, 268.1046).