Highly diastereoselective synthesis of modified nucleosides *via* an asymmetric multicomponent reaction†

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We have developed a practical synthesis of unique nucleoside derivatives *via* $TiCl_4$ promoted multicomponent reaction of optically active dihydrofuran, ethyl pyruvate/glyoxylate, and a TMS protected nucleobase in a single-pot operation.

The design and synthesis of modified nucleosides are of significant interest because of their widespread applications as antiviral, antitumor, and antibacterial agents.[1] A variety of synthetic nucleosides are also utilized in gene-therapy, duplex stability and molecular probes for biological recognition. Acyclic, carbocyclic, c-nucleosides and other modified nucleosides have been used for treatment of AIDS, herpes, hepatitis, and cancers.[2] The well known modified nucleosides, AZT[3] and floxuridine[4] (Fig. 1), are used for HIV/AIDS and cancer respectively. Since the discovery of AZT, a number of more effective modified nucleosides that lack specific components inherent to natural counterparts have emerged for the treatment of HIV/AIDS.[5] When these modified nucleosides enter into the cell, they are phosphorylated at the 5′-position by kinases. Their subsequent incorporation into the DNA as triphosphate leads to the termination of synthesis of new strands of DNA or RNA. There is a considerable interest in the development of effective methods for the synthesis of modified nucleosides because of their significance in medicinal and nucleic acid research.[6,7]

The pioneering work of Niedballa and Vorbrüggen showed the utility of addition of trimethylsilyl protected purine and pyrimidine bases to oxocarbenium ions to form nucleosides and nucleoside analogs.[8] In these reactions, an appropriately protected sugar, usually ribose, is reacted with a strong Lewis acid to form an oxocarbenium ion, to which a silated nucleoside is added.[9] This reaction generally gives functionalized nucleosides in a single one-pot operation. Herein, we report $TiCl_4$ promoted multicomponent reactions of protected (2,3-dihydrofuran-2-yl)methanol with α-keto esters in the presence of silylated pyrimidines and purines provided rapid access to functionalized nucleosides containing three contiguous chiral centers in excellent diastereoselectivity and good to excellent isolated yields.

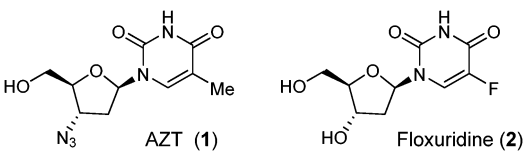
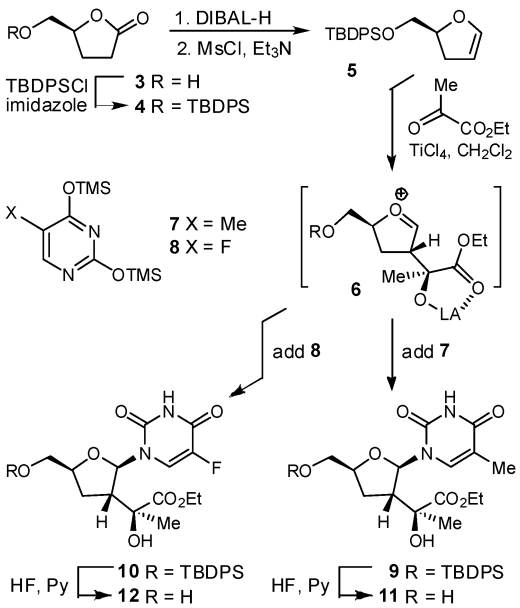


Fig. 1 Structure of AZT and floxuridine.

As shown in Scheme 1, (*S*)-5-hydroxymethyl-2,3-dihydrofuran (**3**) readily prepared[11] from glutamic acid was converted to its silyl ether **4**. Dibal-H reduction of **4** afforded the corresponding lactol. Treatment of the resulting lactol with mesyl chloride and Et_3N at 0 °C followed by heating the resulting mixture at 42 °C provided dihydrofuran **5** in 56% yield in two steps.‡ Our multicomponent strategy involved a Lewis acid activation of pyruvate followed by attack with the dihydrofuran derivative to form oxocarbenium ion (**6**), which can be attacked by an appropriate purine or pyrimidine base as a nucleophile to furnish the modified nucleoside. Accordingly, ethyl pyruvate (1 equiv.) and $TiCl_4$ (1.2 equiv.) in CH_2Cl_2 were reacted with optically active dihydrofuran **5** (1 equiv.) at −78 °C for 1 h. Bis(trimethylsilyl)thymine **7** (3 equiv.) was then added, and the resulting reaction mixture was kept at −78 °C for 1 h. The reaction was allowed to warm to 23 °C for 1 h. After this period, the mixture was quenched with $NaHCO_3$ followed by standard workup and flash chromatography over silica gel to provide nucleoside derivative **9** as a single



Scheme 1 Multicomponent nucleoside synthesis.

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† Electronic supplementary information (ESI) available: Experimental procedures, ^1H and ^{13}C NMR spectra for all new compounds and X-ray crystallographic data for **9**. CCDC 757621. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b924807b

diastereomer (by ^{1}H NMR and HPLC analysis) in 70% yield. This multicomponent reaction with 5-fluorobis(trimethylsilyl)-pyrimidine **8** afforded functionalized nucleoside **10** in 65% yield. Desilylation with HF·pyridine furnished modified nucleosides **11** and **12**.[12] Stereochemical assignment of the newly generated asymmetric centers is based upon our previous observations,[10] extensive ^{1}H NMR studies, and X-ray structural analysis of **10** (Fig. 2, see ESI† for details). As shown in Table 1, the corresponding multicomponent reaction with ethyl glyoxylate provided a 50 : 50 mixture of diastereomers at the stereocenter bearing the hydroxyl group (entry 3). We have also examined the synthesis of modified nucleosides with a host of functionalized purine and pyrimidine bases. Reactions with N^6-benzoylcytosine and benzoyladenine provided nucleosides **14** and **15** respectively (entries 4 and 5). While, the reaction with N^2-acetylguanine at −78 °C for 1 h and then at 23 °C for 4 h resulted in a mixture (55 : 45) of natural (**17a**) and unnatural (**17b**) isomers (entry 6). The isomers were separated by HPLC and diastereoselectivity was determined by analytical HPLC.[13] Similar selectivity problems were reported in the literature.[14] The lack of regio-selectivity is due to the fact that the steric differentiation between the corresponding THM-derivative of N^2-acetylguanine, tautomers **16a** and **16b**, is marginal as shown in Scheme 2. To overcome the regioselectivity issue, we have converted guanine **18** to bulky N^2-acetyl-O^6-diphenylcarbamoylguanine **19** as shown.[15] Presumably, tautomer **19b** (R = TMS) is more stable over **19a** (R = TMS) because of the developing non-bonding interactions. Thus, multicomponent reaction with the corresponding *in situ* generated silyl derivative afforded the natural N^9 nucleoside **20** (entry 7) as a single product in 42% yield.

In conclusion, we have developed an effective multi-component reaction for the synthesis of modified nucleosides in a single step operation. The reaction formed three new stereogenic centers in excellent diastereoselectivity. The methodology provided convenient access to a variety of novel modified nucleosides. Design and synthesis of modified nucleosides for biological evaluation are in progress.

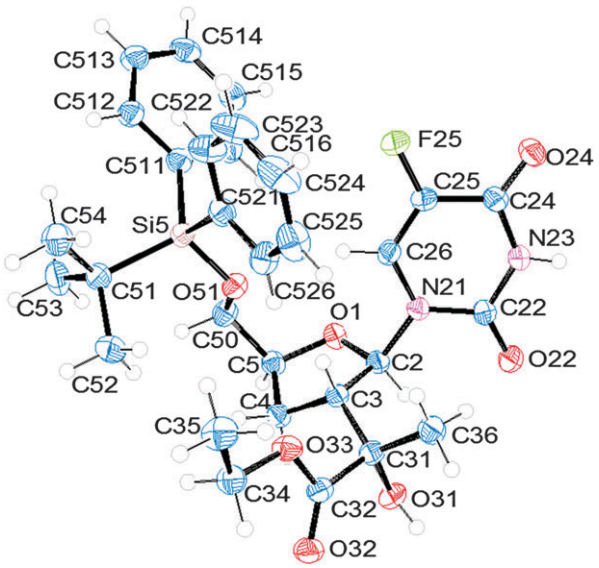
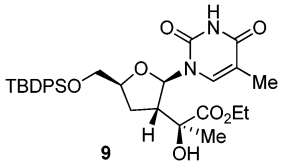
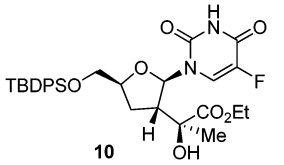
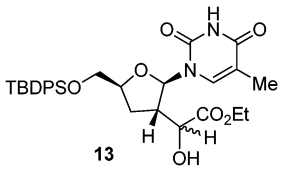
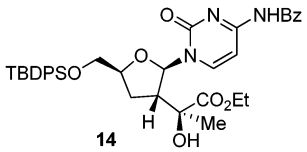
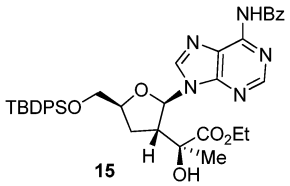
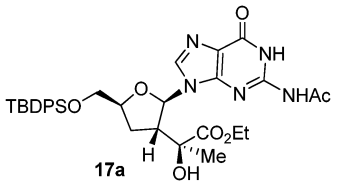
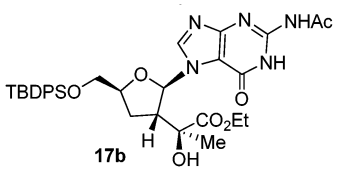
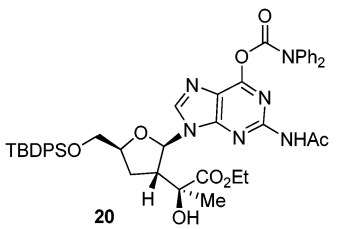


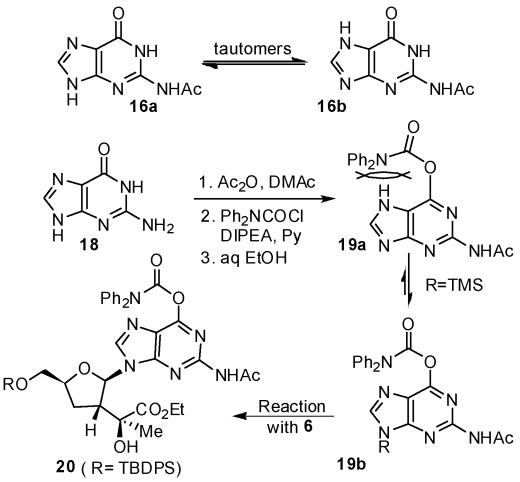
Fig. 2 X-Ray structure of compound **10**.

Table 1 Synthesis of modified nucleosides

Entry	Nucleoside structure	dr[a] (Yield (%))[b]
1	 **9**	99 : 1 (70)
2	 **10**	99 : 1 (65)
3	 **13**	50 : 50 (45)
4	 **14**	99 : 1 (53)
5	 **15**	99 : 1 (60)
6	 **17a**	99 : 1 (44)[c]
	 **17b**	99 : 1
7	 **20**	99 : 1 (42)

[a] Ratio was determined by ^{1}H NMR and HPLC analysis. [b] Isolated yield after chromatography. [c] Ratio of **17a** : **17b** = 55 : 45.

Financial support of this work was provided by the National Institutes of Health (GM 53386). We also thank Sarang Kulkarni (Purdue University) for his preliminary investigation.



Scheme 2 Nucleoside synthesis with N^2-acetylguanine.

Notes and references

‡ General experimental procedure for multicomponent nucleoside synthesis: dihydrofuran **5** (85 mg, 0.25 mmol) and ethyl pyruvate (34 μL, 0.3 mmol, 1.2 equiv.) were dissolved in DCM (3 mL) under argon. This was then cooled to −78 °C followed by the addition of $TiCl_4$ (0.3 mL, 1 M, 0.3 mmol, 1.2 equiv.). This was allowed to stir for 1 h. The TMS protected nucleoside (prepared according to either method A or B) was then added. The reaction was then stirred at 1 h at −78 °C followed by warming to 23 °C and stirring for 1 h. The reaction was then cooled back to −78 °C and quenched with aq. $NaHCO_3$. The reaction mixture was then allowed to warm to 23 °C then filtered through celite. The filtrate was then extracted with DCM (3 × 10 mL). The organics were then washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was then purified *via* flash chromatography. Method A: commercially available, *O*,*O*′-bis(trimethylsilyl)thymine **7** (405 mg, 1.5 mmol, Sigma-Aldrich) was added as a solid to the reaction mixture. Method B: silylated nucleoside was prepared as follows. To a suspension of nucleoside (0.75 mmol, 3 equiv.) in dichloromethane (4 mL) were added triethylamine (209 μL, 1.5 mmol, 6 equiv.), followed by trimethylsilyl triflate (271 μL, 6 equiv.). The resulting reaction mixture was stirred until clear, for about 30 min. The mixture was typically transferred *via* cannula to the multicomponent reaction. Ethyl 2-((2*R*,3*S*,5*S*)-5-((*tert*-butyldiphenylsilyloxy)methyl)-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-2-hydroxypropanoate (**9**): prepared *via* method A, purified with 60% EtOAc in hexanes. (70%) $[\alpha]_D^{23}$ +37.7 (*c* 1.12, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.08 (s, 1H), 7.66 (d, J = 6.5 Hz, 4H), 7.43–7.35 (m, 7H), 6.33 (d, J = 6.5 Hz, 1H), 4.38–4.18 (m, 4H), 3.98 (dd, J = 9.1, 2.4 Hz, 1H), 3.68 (dd, J = 8.6, 2.9 Hz, 1H), 2.76–2.70 (m, 1H), 2.25–2.18 (m, 1H), 2.20–1.86 (m, 1H), 1.58 (s, 3H), 1.42 (s, 3H), 1.32 (t, J = 7.1, 3H), 1.11 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.7, 163.7, 150.2, 135.8, 135.4, 135.2, 133.2, 132.6, 129.9, 129.8, 127.8, 127.7, 111.7, 85.1, 78.7, 77.2, 74.1, 65.1, 62.4, 51.3, 28.3, 27.0, 24.7, 19.4, 14.1, 11.9. FTIR (NaCl) ν_{max} = 2955, 2929, 1698, 1684, 1472, 1457, 1258, 1112, 703. ESI (+) LRMS *m*/*z* (relative intensity): $[M + Na]^+$ 603.14 (100%). ESI (+) HRMS (*m*/*z*): $[M]^+$ calcd for $C_{31}H_{40}N_2O_7Si$ 603.2503; found, 603.2506. Ethyl 2-((2*R*,3*S*,5*S*)-5-((*tert*-butyldiphenylsilyloxy)methyl)-2-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-2-hydroxypropanoate (**10**): prepared *via* method B, purified with 60% EtOAc in hexanes. (65%) $[\alpha]_D^{23}$ +50.3 (*c* 0.72, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.79 (d, J_{H-F} = 4.2 Hz, 1H), 7.91 (d, J = 5.7 Hz, 1H), 7.67–7.64 (m, 4H), 7.45–7.39 (m, 6H), 6.32 (dd, J = 3.9, 1.4 Hz, 1H), 4.40–4.23 (m, 3H), 4.00 (dd, J = 9.8, 2.0 Hz, 1H), 3.63 (s, 1H), 3.62 (dd, J = 9.1, 2.5 Hz, 1H), 2.74–2.68 (m, 1H), 2.24–2.16 (m, 1H), 1.91–1.85 (m, 1H), 1.48 (s, 3H), 1.32 (t, J = 7.1, 3H), 1.11 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.7, 157.2, 156.9, 148.9, 141.9, 139.5, 135.5, 135.4, 132.6, 132.5, 130.0, 129.9, 127.8, 127.6, 124.5, 124.2, 86.0, 79.9, 74.5, 64.8, 62.5, 60.4, 52.3, 28.0, 26.9, 26.8, 25.0, 19.2, 14.1. ^{19}F NMR ($CDCl_3$, 376 MHz) δ −164. FTIR (NaCl) ν_{max} = 3446, 3197, 3027, 2931, 2858, 1720, 1708, 1669, 1471, 1428, 1393, 1363, 1252, 1113, 1068, 758, 702. ESI (+) LRMS *m*/*z* (relative intensity): 606.99 (100%), 607.99 (35%). ESI (+) HRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{30}H_{37}N_2O_7FSi$ 607.2252; found, 607.2262.

1 P. Herdewijn, *Modified Nucleosides*, *Biochemistry Biotechnology and Medicine*, Wiley-VCH Verlag Gmbh & Co, Weinheim, 2008.

2 (*a*) C. K. Chu, *Antiviral Nucleosides: Chiral Synthesis and Chemotherapy*, Elsevier, New York, 2003; (*b*) C. K. Chu and D. C. Baker, *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*, Plenum Press, New York, 1993.

3 M. A. Richman Fischl, D. D. Grieco, M. H. Gottlieb, M. S. Volberding, P. A. Laskin, O. L. Leedom, J. M. Groopman, J. E. Mildvan, D. Schooley, R. T. Jackson, G. G. Durack and D. T. King, *New Engl. J. Med.*, 1987, **317**, 185–191.

4 D. B. Longley, D. P. Harkin and P. G. Johnston, *Nat. Rev. Cancer*, 2003, **3**, 330–338.

5 S. Broder, H. Mitsuya and R. Yarochoan, *Science*, 1990, **249**, 1533–1544.

6 *Handbook of Nucleoside Synthesis*, ed. H. Vorbruggen and C. Ruh-Pohlenz, Wiley Inter Science, New York, 2001.

7 For recent synthetic methods, see: (*a*) S. Son and G. C. Fu, *J. Am. Chem. Soc.*, 2007, **129**, 1046–1047; (*b*) M. K. Lakshman, J. C. Keeler, F. N. Ngassa, J. H. Hilmer, P. Pradhan, B. Zajc and K. A. Thomasson, *J. Am. Chem. Soc.*, 2007, **129**, 68–76; (*c*) A. K. Ogawa, Y. Q. Wu, D. L. McMinn, J. Q. Liu, P. G. Schultz and F. E. Romesberg, *J. Am. Chem. Soc.*, 2000, **122**, 3274–3287; (*d*) B. M. Trost and Z. Shi, *J. Am. Chem. Soc.*, 1996, **118**, 3037–3038; (*e*) W.-B. Choi, L. J. Wilson, S. Yeola and D. C. Liotta, *J. Am. Chem. Soc.*, 1991, **113**, 9377–9379; (*f*) L. J. Wilson and D. Liotta, *Tetrahedron Lett.*, 1990, **31**, 1815–1818; (*g*) L. J. Wilson and D. Liotta, *J. Org. Chem.*, 1992, **57**, 1948–1952 and references cited therein.

8 (*a*) U. Niedballa and H. Vorbrüggen, *J. Org. Chem.*, 1974, **39**, 3654–3660; (*b*) U. Niedballa and H. Vorbrüggen, *J. Org. Chem.*, 1974, **39**, 3672–3674 and references cited therein.

9 H. Vorbrüggen, K. Krolikiewicz and B. Bennua, *Chem. Ber.*, 1981, **114**, 1234–1255.

10 (*a*) A. K. Ghosh, S. S. Kulkarni, C.-X. Xu and P. E. Fanwich, *Org. Lett.*, 2006, **8**, 4509–4511; (*b*) A. K. Ghosh, C.-X. Xu, S. S. Kulkarni and D. Wink, *Org. Lett.*, 2005, **7**, 7–10; (*c*) A. K. Ghosh, R. Kawahama and D. Wink, *Tetrahedron Lett.*, 2000, **41**, 8425–8429; (*d*) A. K. Ghosh and R. Kawahama, *Tetrahedron Lett.*, 1999, **40**, 1083–1086.

11 (*a*) C. Herdeis, *Synthesis*, 1986, 232–233; (*b*) J. A. Walker, J. J. Chen, D. S. Wise and L. B. Townsend, *J. Org. Chem.*, 1996, **61**, 2219–2221.

12 Preliminary antiviral evaluation of compounds **11** and **12** was carried out by Dr Hiroaki Mitsuya and Dr Kenji Maeda (National Cancer Institute). These two compounds did not exhibit any appreciable antiviral activity. Evaluation of other analogs is ongoing.

13 Analytical HPLC conditions: column, Sunfire C_{18}, 30 × 100 mm, 5 micron, flow rate = 40 mL min^{-1}, λ = 215 nm,isocratic 75 : 25 MeOH–H_2O; R_t **17a**, 14.6 min; R_t **17b**, 14.3 min.

14 P. Garner and S. Ramakanth, *J. Org. Chem.*, 1988, **53**, 1294–1298.

15 R. Zou and M. J. Robins, *Can. J. Chem.*, 1987, **65**, 1436–1437.

