Synthetic Study towards Entecavir

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Abstract. A synthetic design of Entecavir was described, and the intermediate, (S)-N-methoxy -3-((4-methoxybenzyl)oxy)-N-methylpent-4-enamide, was synthesized using acrylaldehyde as the starting material, which was obtained via an Evans Aldol reaction, Weinreb amide formation, and a PMB protection.

Introduction

Hepatitis B virus (HBV) represents one of the most prevalent viral diseases in the world[1] and is known to be a cause of serious liver disorders. It is reported that more than 400 million people have been chronically infected and there is a continuing need for new therapies for individuals infected with HBV. Entecavir (BMS-200475, **1**) **(Fig. 1)** is a carbocyclic guanosine nucleoside analog with potent selectivity against hepatitis B virus[2] which was approved under the trade name Baraclude in March 2005 by the US Food and Drug Administration for the treatment of chronic HBV infection in adults. Entecavir inhibits DNA synthesis in HBV infected cells in three steps: the priming of the polymerase, the reverse transcription of the pregenomic messenger RNA and the synthesis of the positive strand of HBV DNA. Entecavir is also effected to lamivudine- and adefovir-resistant HBV strains[3].

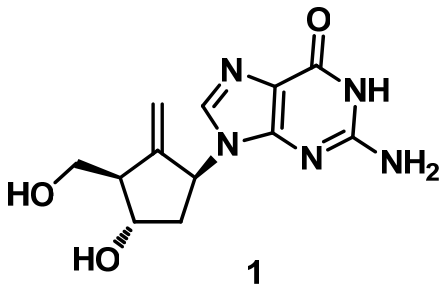

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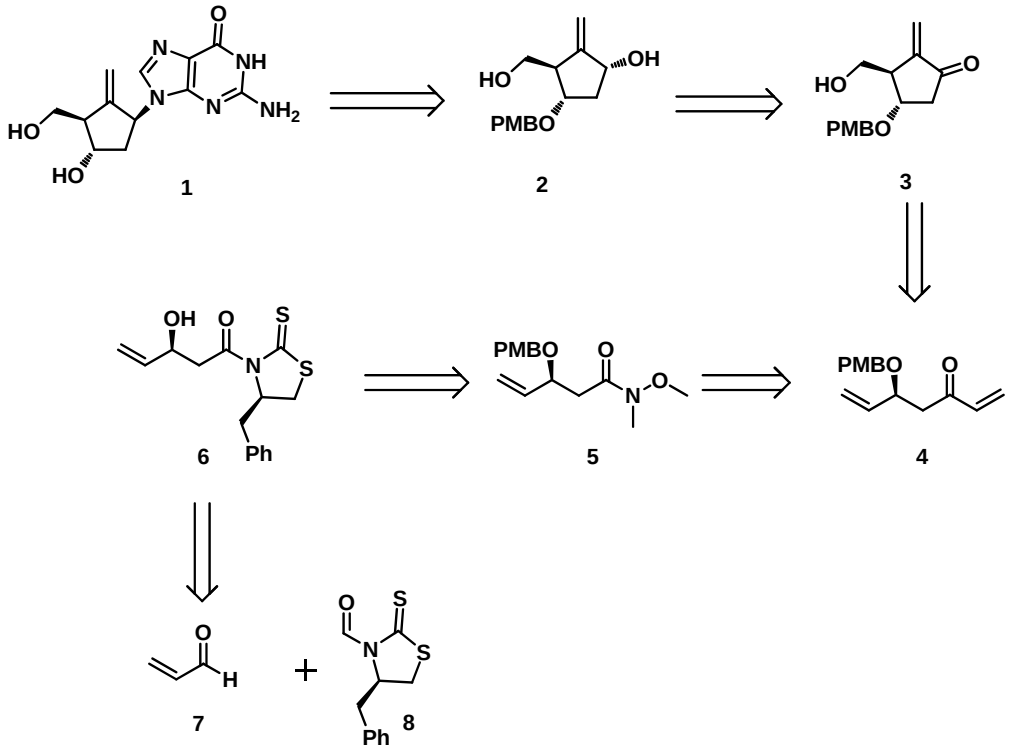
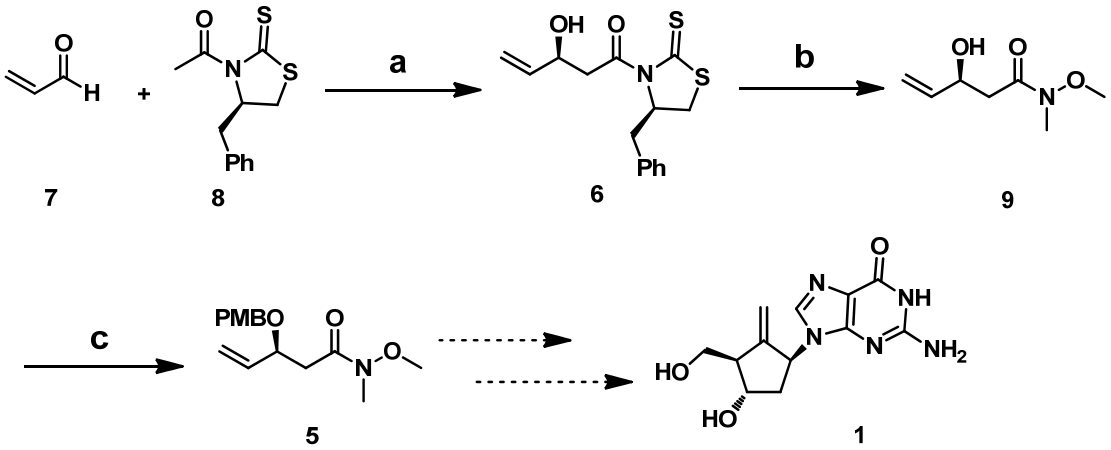
Figure 1. The structure of Entecavir

As Entecavir's remarkable potency, resistance, and safety profile, a great deal of synthetic effort[4] has been devoted to the enantiospecific syntheses of Entecavir, among which most reported syntheses employ five-membered carbocyclic compounds as the starting material. In our study, we would describe our synthetic analysis towards Entecavir using acrylaldehyde as the starting material to construct the protected five member ring Entecavir **1** and our present work of the synthesis towards Entecavir. Our retrosynthetic route is outlined in **Scheme 2**.



Scheme 2. Our retrosynthetic analysis of Entecavir

As shown above, for the stereoselective introduction of the purine base, we planned to perform a Mitsunobu reaction between a substituted purine and allylic hydroxyl group of compound **2**, which could be easily obtained after a diastereoselective reduction from ketone **3**. The intermediate **3** was designed to be got from alkene **4**, and compound **4** could in turn be got from amide **5** via a Weinreb reaction with a Grignard reagent. The amide **5** could be smoothly obtained from compound **6** via a nucleophilic substitution. For the compound **6**, it would be readily got through an Evans Aldol reaction between acrylaldehyde **7** and Evans chiral auxiliary **8**. In this paper, we just reported the synthesis of intermediate **5.** The detailed route of compound **5** was shown in **Scheme 3**.



a) $TiCl_4$, DIPEA, DCM, 0ºC to -78ºC, 2h; b) MeONHMe•HCl, imidazole, CH_2Cl_2, rt, overnight; c) NaH, PMBBr, DMF, -10ºC, 30 min

Scheme 3. Synthetic route of compound **5**

Experimental

NMR spectra were recorded on Bruker AV-400MHz spectrometers. The solvents and reagents were purified and dried according to standard procedures: CH_2Cl_2, THF, DMF were distilled from CaH_2 prior to use.

(S)-1-((R)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxypent-4-en-1-one 6

(R)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone **8** (3.5 g, 14.08 mmol) was dissolved in CH_2Cl_2 (72 mL) and was cooled to 0 ^oC. Titanium tetrachloride (1.68 ml) was added dropwise. The thick suspension was stirred for 10 minutes, upon which diisopropylethylamine (2.68 mL) was added dropwise at 0 ^oC. After stirring for 10 min, the solution was cooled to - 78^oC and to the reaction mixture was added the solution of acrylaldehyde **7** (0.85 mL, 12.8 mmol) in CH_2Cl_2 (22 mL). The reaction was stirred for another 1 h and was then quenched with saturated ammonium chloride solution. The solution was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography to provide the product **6** (3.1 g, 79%).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.24 (m, 5H), 5.95 (ddd, *J* = 17.3, 10.5, 5.2 Hz, 1H), 5.44–5.30 (m, 2H), 5.17 (dt, *J* = 10.5, 1.4 Hz, 1H), 4.72–4.66 (m, 1H), 3.66 (dd, *J* = 17.3, 3.0 Hz, 1H), 3.41 (dd, *J* = 12.0, 7.5 Hz, 1H), 3.32 (dd, *J* = 17.3, 8.6 Hz, 1H), 3.23 (dd, *J* = 13.2, 3.7 Hz, 1H), 3.05 (dd, *J* = 13.2, 10.5 Hz, 1H), 2.90 (d, *J* = 12.0 Hz, 1H), 2.88–2.77 (br s, –OH, 1H).

(S)-3-hydroxy-N-methoxy-N-methylpent-4-enamide 9

To a soltion of alcohol **6** (781 mg, 2.54 mmol) in CH_2Cl_2 (12.7 mL) were added MeONHMe·HCl (496 mg, 5.08 mmol) and imidazole (865 mg, 12.7 mmol), and the resultant mixture was stirred at room temperature overnight. The reaction was then quenched with saturated aqueous NH_4Cl solution, and the resultant mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography gave Weinreb amide **9** (363.7 mg, 90%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92 (ddd, *J* = 17.3, 10.5, 5.5 Hz, 1H), 5.32 (dt, *J* = 17.3, 1.4 Hz, 1H), 5.16 (dt, *J* = 10.5, 1.4 Hz, 1H), 4.60–4.54 (m, 1H), 3.79 (br s, –OH, 1H), 3.69 (s, 3H), 3.20 (s, 3H), 2.72 (d, *J* = 16.1 Hz, 1H), 2.60 (dd, *J* = 16.1, 9.1 Hz, 1H).

(S)-N-methoxy-3-((4-methoxybenzyl)oxy)-N-methylpent-4-enamide 5

Under a nitrogen atmosphere, to a solution of compound **9** (282 mg, 1.77 mmol) in anhydrous DMF (5.5 mL) was added NaH (120mg of 60% wt suspension, 3.0 mmol) at -10°C. Then, 1-(bromomethyl)-4-methoxybenzene (0.45 mL, 3.0 mmol) was added dropwise. The suspension was stirred at the same temperature for 30 minutes then poured into H_2O (3 mL) and pentane/Ether (6 mL each). The layers were separated and the organic layer was sequentially washed with H_2O and brine. Then it was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography to provide PMB ether **5** (296 mg, 60%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.86-5.78 (m, 1H), 5.33 (dt, *J* = 17.3, 1.4 Hz, 1H), 5.25 (dt, *J* = 10.5, 1.4 Hz, 1H), 4.51 (d, *J* = 10.8 Hz, 1H), 4.39-4.34 (m, 2H), 3.79 (s, 3H), 3.65 (s, 3H), 3.19 (s, 3H), 2.95-2.89 (m, 1H), 2.57-2.51 (m, 1H)

Acknowledgement

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References

[1] Regev, A.; Schiff, E. R. *Adv. Inter. Med.* **2001**, *46*, 107.

[2] a) Innaimo, S. F.; Sieffer, M.; Bisacchi, G. S.; Standring, N.; Zahler, R.; Colonno, R. J. *Antimicrob. Agents Chemother.* **1997**, *41*, 1444; b) Lai, C.; Rosmawati, M.; Lao, J.; Vlierberghe, H.; Anderson, F.; Thomas, N.; De Hertogh, D. J. *Hepatology* **2001**, *34*, 24; c) Bisacchi, G. S.; Chao, S. T.; Bachand, C.; Daris, J. P.; Innaimo, S. F.; Jacobs, G. A.; Kocy, O.; Lapointe, P.; Martel, A.; Merchant, Z.; Slusarchyk, W. A.; Sundeen, J. E.; Young, M. G.; Colonno, R. J.; Zahler, R. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 127.

[3] a) Kwak, M. S.; Choi, J. W.; Lee, J. S.; Kim, K. A.; Suh, J. H.; Cho, Y. S.; Won, S. Y.; Park, B. K.; Lee, C. K. *J. Viral Hepat.* **2011**, *18*, 432; b) Chang, T. T.; Lai, C. L.; Yoon, S. K.; Lee, S. S.;

Coelho, H. S. M.; Carrilho, F. J.; Poordad, F.; Halota, W.; Horsmans, Y.; Tsai, N.; Zhang, H.; Tenney, D. J.; Tamez, R.; Iloeje, U. *Hepatology*. **2010**, *51*, 422.

[4] a) Ziegler, F. E.; Sarpong, M. A. *Tetrahedron* **2003**, *59*, 9013; b) Zhou, B.; Li, Y. C. *Tetrahedron Lett.* **2012**, *53*, 502; c) Bisacchi, G. S.; Chao, S. T.; Bachard, C.; Daris, J. P.; Innaimo, S.; Jacobs, G. A.; Kocy, O.; Lapointe, P.; Martel, A.; Merchant, Z.; Slusarchyk, W. A.; Sundeen, J. E.; Young, M. G.; Colonno, R.; Zahler, R. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 127; d) Bisacchi, G. S.; Sundeen, J. E. W.O. Patent 9809964, 1998.; e) Pendri, Y. R.; Chen, C. P. H.; Patel, S. S. et al. U. S. Patent 0192912, 2004.; f) Guo, L. W.; Xiao, Y. J.; Yang, L. P. *Chin. Chem. Lett.* **2006**, *17*, 907; g) Zhou, M. X.; Reiff, E. A. et al. U. S. Patent 7786300, 2010.