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Novel 3′-deoxy analogs of the anti-HBV agent entecavir: synthesis of enantiomers from a single chiral epoxide

Edward Ruediger,[a,*] Alain Martel,[a] Nicholas Meanwell,[b] Carola Solomon[a] and Brigitte Turmel[a]

[a]*Bristol-Myers Squibb Pharmaceutical Research Institute, 100 boul. de l'Industrie, Candiac, QC, Canada J5R 1J1*
[b]*Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA*

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Dedicated to Professor Edward Piers, a respected mentor and friend, on the occasion of his retirement

Abstract—A synthesis of novel 3′-deoxy analogs of the anti-HBV agent entecavir (BMS-200475) was devised using regioselective ring opening of suitable cyclopentene epoxides as the key step. This versatile approach afforded access to an enantiomeric pair of carbocyclic nucleosides from a single chiral intermediate.

With an estimated 400 million people being chronically infected, Hepatitis B virus (HBV) represents one of the most pervasive viral diseases in the world.[1] Chronic infection with HBV is a major cause of chronic liver disease and is associated with the development of hepatocellular carcinoma.[2] Current therapy for carriers chronically infected with HBV has focused on interferon, although results have been mixed and significant side effects have been observed.[3,4] Lamivudine (3TC, **4**) (Fig. 1) has been approved for the treatment of HBV infection, however the emergence of drug resistance has been noted.[5] More recently, the bis(pivaloyloxymethyl) ester of adefovir[6a] (**5**) (adefovir dipivoxil) was approved for the treatment of lamivudine-resistant HBV.[6b] Famciclovir (**6**), a pro-drug of penciclovir (**7**), showed good oral bioavailability, but was dropped from Phase III clinical trials due to a lack of efficacy.[7] There remains considerable ongoing effort to synthesize novel nucleoside analogs with antiviral activity and several examples of these have been reported to exhibit potent inhibition of HBV.[8]

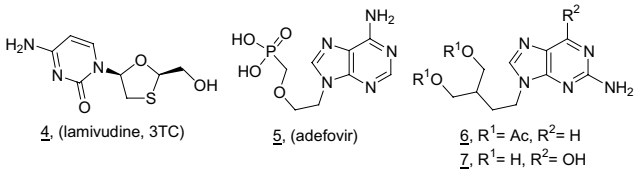

Figure 1.

Entecavir (BMS-200475, **8**) is a novel carbocyclic 2′-deoxyguanosine analog, which has shown potent and selective activity against HBV.[9,10] During the course of synthetic efforts to prepare novel analogs related to BMS-200475, we were particularly interested in devising methodology for the synthesis of 3′-deoxy analogs. In addition, we were interested in the possibility of exploiting the known chiral epoxide **1**,[11] that had been previously used to good advantage for the synthesis of BMS-200475 itself (Fig. 2).[10]

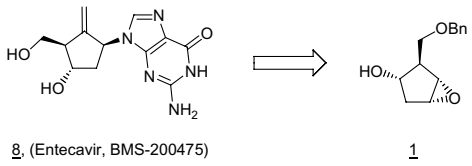

Figure 2.

Keywords: HBV; Entecavir; Carbacyclic nucleosides; Epoxide rearrangement.
* Corresponding author. Tel.: +1-450-444-4127; fax: +1-450-444-4166; e-mail: edward.ruediger@bms.com

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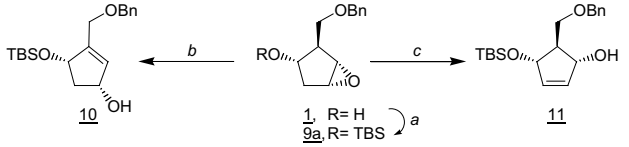
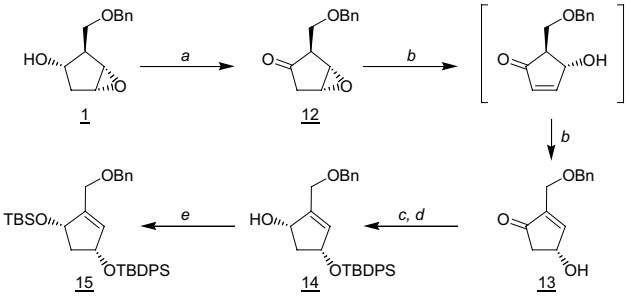
Since both nucleosides with the unnatural β-L-configuration, as well as the natural β-D-configuration have been shown to display potent antiviral activity,[8a] we felt that it was equally important to be able to access both enantiomers in a given series from a common intermediate. It seemed to us that generation and desymmetrization of a latent *meso*-diol was an overall strategy that would allow us to do just that.

To that end, the key step in our approach to the synthesis of 3′-deoxycarbacyclic nucleoside analogs involved the regioselective ring opening of the cyclopentene epoxide **1**.[12] Literature precedent suggested that treatment with lithium dialkylamides (especially lithium diethylamide or lithium di-*n*-propylamide) would favor the epoxide/allylic alcohol rearrangement[13a] and that deprotonation should occur at the least hindered carbon.[13b] We were surprised to find that treatment of the suitably protected epoxide **9a** (R = TBS) with lithium di-*n*-propylamide in ether at 0 °C cleanly afforded the unexpected allylic alcohol **10**[14] (Scheme 1). Interestingly, when **9a** was treated with lithium bistrimethylsilylamide in THF at reflux temperature for several hours, the desired allylic alcohol **11**[15] was formed exclusively. The reason for this reversal in regioselectivity remains unclear.

Corroboration of the structure of **10** was accomplished using the regioselective ring opening of the epoxycyclopentanone **12**[16a] (Scheme 2). Treatment of **12** with basic alumina (Brockmann Activity I) in ether[16b] led to ring opening of the epoxide, followed by based-induced equilibration to give cyclopentenone **13** almost exclusively (>92:<8 mixture of regioisomers by ^{1}H NMR). Subsequent protection and stereoselective reduction of the enone gave predominantly the *cis*-diol **14**. The latter was conveniently protected as its TBS-ether to afford the fully protected triol **15**. The ^{1}H NMR of **15**[17] was found to be identical with that of the TBDPS-ether of **10**.



Scheme 1. Reagents and conditions: (a) *t*-BuMe$_2$SiCl, imidazole, DMF, 90%; (b) LiN(*n*-Pr)$_2$, Et$_2$O, 0 °C, 80%; (c) LiN(SiMe$_3$)$_2$, THF, reflux, 60%.

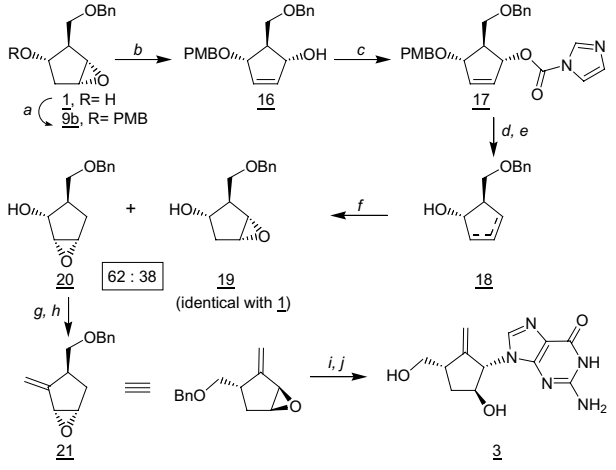


Scheme 2. Reagents and conditions: (a) Jones' reagent, acetone, 95%; (b) Al_2O_3 (basic), Et_2O, 92%; (c) *t*-BuPh$_2$SiCl, imidazole, DMF, 90%; (d) $NaBH_4$–$CeCl_3$, EtOH, −50 °C, 70%; (e) *t*-BuMe$_2$SiCl, imidazole, DMF, 98%.

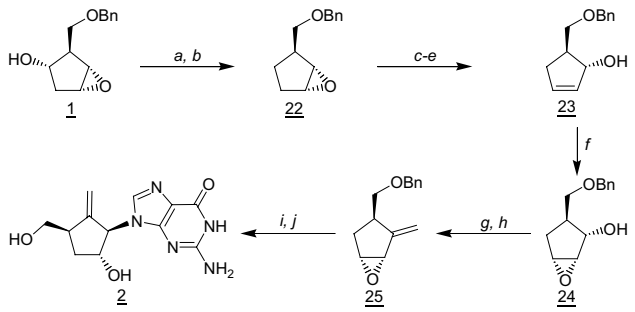
With the selectivity of the epoxide/allylic alcohol rearrangement established, it was felt that **1** could serve to generate both L- and the D-enantiomeric intermediates by using a radical deoxygenation sequence either after or before epoxide opening, respectively. As an approach to the L-series, epoxide **9b** (R = PMB) was rearranged at room temperature to give the allylic alcohol **16**, which was then submitted to radical deoxygenation conditions[18] to give, after cleavage of the PMB-ether, a mixture of the allylic and homoallylic alcohols **18** (Scheme 3). This mixture of olefins was then stereoselectively epoxidized[19] to give a separable mixture of epoxides **19** and **20**, with the latter predominating. Dess–Martin oxidation[20] of **20**, followed by a Wittig-type methylenation,[21] gave the key intermediate **21**. The latter was then coupled with *O*-benzylguanine and debenzylated to give carbocyclic nucleoside **3**.

In order to synthesize the enantiomeric D-series, compound **1** itself was deoxygenated to cleanly give epoxide **22** (Scheme 4). Unfortunately, efforts to convert **22** to the allylic alcohol **23**, as done previously with epoxides **9**, were unsuccessful. However, **22** could be readily opened with phenylselenide anion[22] and subsequent oxidation and warming to room temperature did in fact afford **23**. The latter was then converted to the key epoxide intermediate **25** as done in the L-series, which ultimately afforded the enantiomeric carbocyclic nucleoside **2**.

Contrary to the potent anti-HBV activity shown by BMS-200475 (**8**) and similar to *ent*-**8**, both of the



Scheme 3. Reagents and conditions: (a) *p*-MeOPhCH$_2$Cl, NaH, DMF, 85%; (b) LiN(SiMe$_3$)$_2$, THF, rt, 80%; (c) 1,1′-thiocarbonyldiimidazole, THF, 72%; (d) *n*-Bu$_3$SnH, AIBN (cat), toluene, reflux, 83%; (e) DDQ, CH$_2$Cl$_2$–H$_2$O, 84%; (f) *t*-BuOOH, VO(acac)$_2$, CH$_2$Cl$_2$, 68%; (g) Dess–Martin periodinane, *t*-BuOH, CH$_2$Cl$_2$, 61%; (h) Ph$_3$PCH$_3^+$Br$^-$, MeLi, THF, 53%; (i) *O*-Benzylguanine, LiH, DMF, 120 °C, 55%; (j) BCl$_3$, CH$_2$Cl$_2$, −78 °C, 72%.



Scheme 4. Reagents and conditions: (a) 1,1′-thiocarbonyldiimidazole, THF, 96%; (b) *n*-Bu_3SnH, AIBN (cat), toluene, reflux, 83%; (c) $(PhSe)_2$, $NaBH_4$, EtOH; (d) 35% H_2O_2, THF; (e) rt, 49% for steps c–e; (f) *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, 93%; (g) Dess–Martin periodinane, *t*-BuOH, CH_2Cl_2, 89%; (h) $Ph_3PCH_3^+Br^-$, MeLi, THF, 71%; (i) *O*-Benzylguanine, LiH, DMF, 120 °C, 41%; (j) BCl_3, CH_2Cl_2, −78 °C, 88%.

Table 1. Anti-HBV activity of nucleoside analogs in HepG2.215 cells[23]

Compound	EC_{50} (μM)
8, BMS-200475	0.003
ent-**8**	100
2	>100
3	>100
4, 3TC	0.2

3′-deoxy analogs **2** and **3** proved to be inactive against HBV (Table 1).

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14. Compound **10**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5H), 5.92 (s, 1H), 4.64 (m, 1H), 4.61 (m, 1H), 4.55 (s, 2H), 4.15 (s, 2H), 2.74 (dt, $J = 7.1$, 13.6 Hz, 1H), 2.09 (br s, 1H), 1.61 (dt, $J = 4.7$, 13.6 Hz, 1H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H).
15. Compound **11**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5H), 5.90 (d, $J = 5.5$ Hz, 1H), 5.83 (d, $J = 5.5$ Hz, 1H), 4.62 (ab d, $J = 12.2$ Hz, 1H), 4.56 (ab d, $J = 12.2$ Hz, 1H), 4.56–4.51 (m, 2H), 3.79 (dd, $J = 4.7$, 9.0 Hz, 1H), 3.63 (dd, $J = 7.1$, 9.0 Hz, 1H), 2.13 (quintet, $J = 5.5$ Hz, 1H), 1.99 (br s, 1H), 0.90 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).
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17. Compound **15**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.74–7.70 (m, 5H), 7.48–7.30 (m, 10H), 5.76 (s, 1H), 4.63 (t, $J = 7.1$ Hz, 1H), 4.54 (t, $J = 4.5$ Hz, 1H), 4.51 (s, 2H), 4.12 (s, 2H), 2.56 (dt, $J = 7.1$, 13.3 Hz, 1H), 1.76 (dt, $J = 5.9$, 12.9 Hz, 1H), 1.10 (s, 9H), 0.93 (s, 9H), 0.08 (s, 6H).
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23. HepG2.2.15 human liver cells, which harbor integrated HBV genomes, secrete substantial amounts of infectious HBV particles bearing viral DNA genomes into the medium. Antiviral effects were scored as reductions in

the amount of HBV DNA present in the media after treatment of the cells with drug for 9 days. HBV DNA was released from secreted virus particles by alkali treatment, after which it was immobilized onto membranes and quantified by hybridization with a radiolabelled HBV DNA probe.