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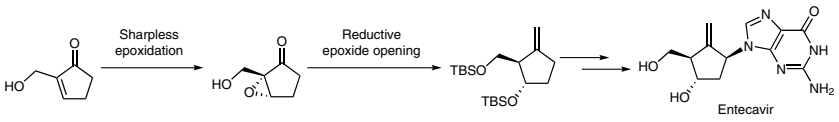
# A New Formal Synthetic Route to Entecavir

**Lixia Liu**[a]
**Yongli Sun**[a]
**Jiwu Wang**[b]
**Wentao Ou**[a]
**Xiaoji Wang**[*a]
**Shuangping Huang**[*b,c]

[a] School of Life Science, Jiangxi Science and Technology Normal University, 330013 Nanchang, Jiangxi, P. R. of China
[b] School of Pharmacy, Jiangxi Science and Technology Normal University, 330013 Nanchang, Jiangxi, P. R. of China
[c] College of Biomedical Engineering, Taiyuan University of Technology, 030024 Taiyuan, Shanxi, P. R. of China
2012207455@tju.edu.cn

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**Abstract** We describe a new and straightforward approach to the formal synthesis of the hepatitis B virus inhibitor entecavir, an important hepatitis B drug, in ten steps overall. Key features of the route are a Morita–Baylis–Hillman reaction, a Sharpless asymmetric epoxidation, a reductive epoxide opening of an α,β-epoxy ketone, and a Riley selenium dioxide oxidation.

**Key words** entecavir, formal synthesis, epoxy ketones, Sharpless epoxidation, ring cleavage, Riley oxidation

Hepatitis B, also known as serum hepatitis, is caused by hepatitis B virus (HBV) and is a serious and widespread disease that is particularly prevalent in Asia. According to a modeling study involving a Delphi process and a dynamic HBV transmission and progression model, it is possible that about 300 million people may have been infected with HBV.[1] In the absence of a response to chemotherapy, some patients are likely to contract such diseases as liver cirrhosis or liver cancer, ultimately resulting in many deaths. Currently, hepatitis B can be treated with interferon or with antiviral agents. Since its approval by the US Federal Drug Administration in 2005, entecavir (BMS-200475; Figure 1), a nucleoside analogue that inhibits the viral polymerase of HBV, has become one of the most frequently used HBV inhibitors for the treatment of hepatitis B . Entecavir is considered to be one of the most effective drugs against HBV because of its high efficacy and limited viral resistance.[2] It has therefore attracted considerable interest from the synthetic chemistry community since Bristol-Myers Squibb first accomplished a total synthesis of the drug in 1992.[2,3] Because of its long synthetic route involving many chiral reagents, entecavir is expensive, placing a heavy burden on carriers of HBV As part of our ongoing interest in research on bioactive natural products and pharmaceuticals,[4] we disclose a new, concise, and straightforward approach to entecavir.

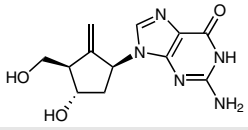
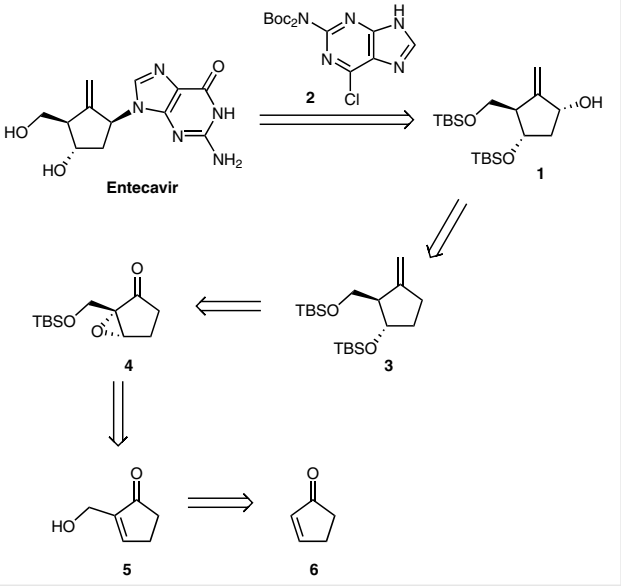



**Figure 1** Structure of entecavir

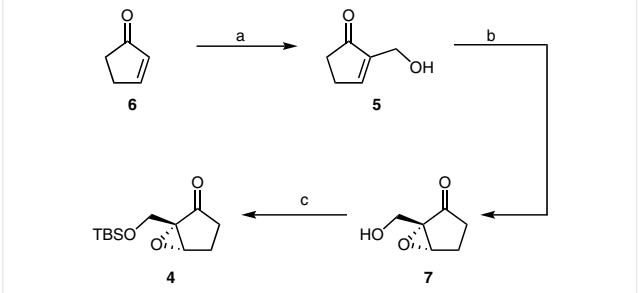
Our retrosynthetic analysis of entecavir is depicted in Scheme 1.




**Scheme 1** Retrosynthetic analysis of entecavir.

Entecavir might be readily prepared from compound **1** through modified Mitsunobu coupling with purine **2** by following the reported procedure.[3h] We hypothesized that the allylic hydroxy group in **1** might be constructed from the protected diol **3** by allylic oxidation. We assumed that the exocyclic double bond and the 1,3-diol moiety of compound **3** could be established through olefination and reductive epoxide opening of the α,β-epoxy ketone **4**. The key chiral center in compound **4** might be introduced by Sharpless epoxidation of the unsaturated α,β-ketone **5**, which might be obtained from cyclopent-2-en-1-one (**6**) by a Morita–Baylis–Hillman reaction.

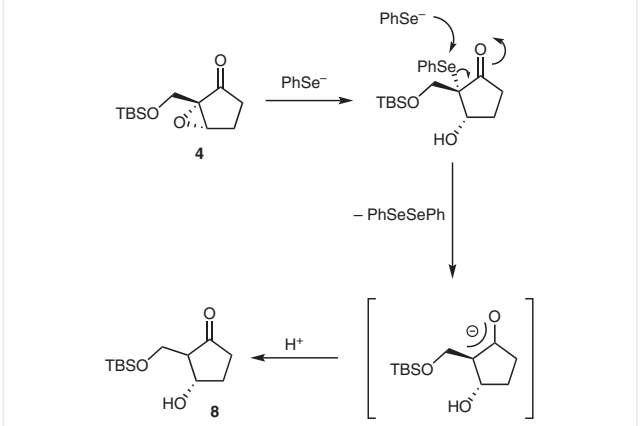
On the basis of this retrosynthetic analysis, commercially available cyclopent-2-en-1-one (**6**) was subjected to a Morita–Baylis–Hillman reaction. In the presence of tributylphosphine, cyclopent-2-en-1-one (**6**) was added to a 37% w/w aqueous solution of formaldehyde, stabilized with 7–8% MeOH, in a mixed MeOH–$CHCl_3$ solvent, to give adduct **5** in 97% yield.[5] Subsequently, Sharpless asymmetric epoxidation was employed to introduce the chiral center.[6] Next, the effects were examined of changing the weight of 4 Å molecular sieves, the temperature, the number of equivalents of ligand, and the Lewis acid. Eventually, epoxide **7** was obtained in a maximum yield of 87% and 8:1 er by using dipropyl L-(+)-tartrate [L-(+)-DIPT, 1.5 equiv], $Ti(OiPr)_4$ (1.5 equiv), and *tert*-butyl hydroperoxide (TBHP; 3.0 equiv) in the presence of 4 Å MS (0.4 g/mol) in $CH_2Cl_2$ at −25 °C for 90 hours. To avoid the potential for free hydroxy group opening of the epoxide, TBS-protection was conducted in the presence of imidazole in DMF at 0 °C to generate intermediate **4** in almost quantitative yield (Scheme 2).




**Scheme 2** *Reagents and conditions*: (a) HCHO, $PBu_3$, MeOH–$CHCl_3$ (1:1.5), r.t., 2 h, 97%; (b) L-(+)-DIPT, $Ti(OiPr)_4$, TBHP, 4Å MS, $CH_2Cl_2$, −25 ℃, 90 h, 87%, er = 8:1; (c) TBSCl, imidazole, DMF, 0 ℃, 2 h, 98%.

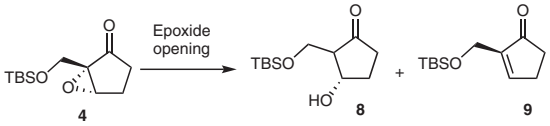
With epoxide **4** in hand, we focused our efforts on the subsequent epoxide opening. As shown in Table 1, a series of conditions reported in the literature for opening the α,β-epoxy ketone were examined. No product was obtained when the reaction was conducted in a Zn–HOAc[7] or a Zn–$NH_4Cl$[8] system (Table 1, entries 1 and 2). An attempt to open the α,β-epoxy ketone by hydrazine hydrate-induced reductive cleavage failed,[9] and only the starting material was recovered (entry 3). Finally, we carried out epoxide opening by treatment with diphenyldiselane and *N*-acetylcysteine (3.0 equiv) in an aqueous methanolic solution.[10] On following the reported procedure, numerous spots on the TLC plate were observed in the presence of sodium hydroxide (entry 4). Treatment in methanol/aqueous borax buffer without sodium hydroxide gave the epoxide-opening product **8** together with the elimination product **9** in yields of 16 and 44%, respectively (entry 5). Next, we considered the alkalinity of the methanolic aqueous borax buffer solution, as we expected that **9** would be more-readily produced under basic conditions. When the epoxide opening was conducted in phosphate buffers of pH = 4.5 and 6.5 at room temperature, neither **8** nor **9** was observed on the TLC (entries 6 and 7). Fortunately, however, in the presence of borax, the desired products **8** and **9** were obtained in similar yields in methanolic phosphate buffers with nominal pH values of 4.5 and 5.5 (entries 8 and 9). Because we found that the actual pH of the system was 6.6 under the conditions of entry 9, we added acid to decrease the pH and to decrease the amount of **9** that was formed. To our surprise, no reaction occurred when we used 5% HCl (entries 10 and 11), but changing to 5% $H_3PO_4$ gave **8** (35%) and **9** (35%) when the system pH was adjusted to 6.0 or 6.2 (entries 12 and 13). We were pleased to find that at a lower temperature of (15 °C), the yield of the epoxide-opened product **8** increased to 56% and the yield of **9** fell to 20% (entry 14). Attempts to reduce the amount of **9** formed by further decreasing the pH value failed, and no obvious changes in the yields of **8** and **9** were observed when the pH of the system was adjusted to 5.5 by using $H_3PO_4$ (entry 15).

Inspired by Engman's proposal, we suggest a reasonable mechanism for the epoxide opening of the α,β-epoxy ketone **4** to give **8**, as shown in Scheme 3. First, epoxide opening by the attack of a benzeneselenolate ion at the α-position relative to the carbonyl group gives an α-(phenylselenenyl) β-hydroxy ketone, which is then attacked by another benzeneselenolate ion. The resultant β-hydroxy ke-




**Scheme 3** Proposed mechanism for the benzeneselenolate-induced reductive epoxide opening of α,β-epoxy ketone **4**

**Table 1** Examination of the Epoxide-Opening Reaction




4 8 9

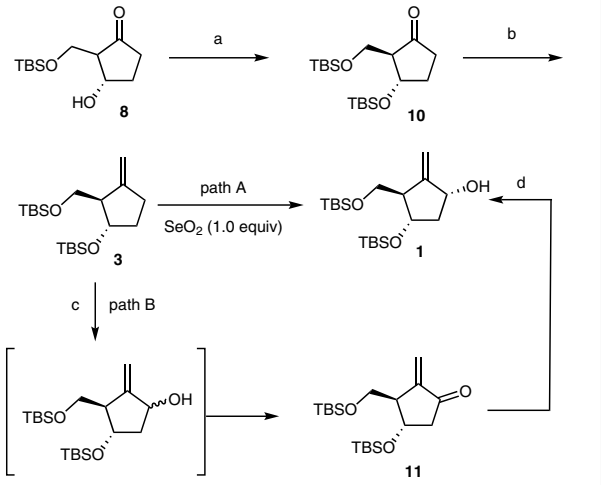
| Entry | Conditions | Result[a] |
|---|---|---|
| 1 | Zn, AcOH, THF, 50 °C | no reaction |
| 2 | Zn, $NH_4Cl$, MeOH, 75 °C | no reaction |
| 3 | $NH_2NH_2{\cdot}H_2O$, EtOH, r.t. | no reaction |
| 4 | *N*-acetylcysteine, PhSeSePh, NaOH, MeOH–$H_2O$, r.t. | decomposed |
| 5 | *N*-acetylcysteine, PhSeSePh, borax, MeOH–$H_2O$, r.t. | **8** (16%)[b], **9** (44%) |
| 6 | *N*-acetylcysteine, PhSeSePh, MeOH–phosphate buffer (pH = 4.5), system pH = 2.3, r.t. | –[c] |
| 7 | *N*-acetylcysteine, PhSeSePh, MeOH–phosphate buffer (pH = 6.5), system pH= 2.9, r.t. | –[c] |
| 8 | *N*-acetylcysteine, PhSeSePh, borax, MeOH–phosphate buffer (pH = 5.5), r.t. | **8** (30%, *trans*/*cis* = 2.8:1), **9** (40%) |
| 9 | *N*-acetylcysteine, PhSeSePh, borax, MeOH–phosphate buffer (pH = 4.5), system pH = 6.6, r.t. | **8** (31%, *trans*/*cis* = 2.8:1), **9** (40%) |
| 10 | *N*-acetylcysteine, PhSeSePh, borax, MeOH–phosphate buffer (pH = 4.5), addition of 5% HCl to adjust system pH to 5.5, r.t. | no reaction |
| 11 | *N*-acetylcysteine, PhSeSePh, borax, MeOH–phosphate buffer (pH = 4.5), addition of 5% HCl to adjust the system pH to 5.9, r.t. | no reaction |
| 12 | *N*-acetylcysteine, PhSeSePh, borax, MeOH–phosphate buffer (pH = 4.5), addition of 5% $H_3PO_4$ to adjust the system pH to 6.0, r.t. | **8** (35%, *trans*/*cis* = 3:1), **9** (35%) |
| 13 | *N*-acetylcysteine, PhSeSePh, borax, MeOH–phosphate buffer (pH = 4.5), addition of 5% $H_3PO_4$ to adjust the system pH to 6.2, r.t. | **8** (35%, *trans*/*cis* = 3:1), **9** (35%) |
| 14 | N-acetylcysteine, PhSeSePh, borax, MeOH–phosphate buffer (pH = 4.5), addition of 5% $H_3PO_4$ to adjust the system pH to 6.0, 15 °C | **8** (56%, *trans*/*cis* = 3.4:1), **9** (20%) |
| 15 | N-acetylcysteine, PhSeSePh, borax, MeOH–phosphate buffer (pH = 4.5), addition of 5% $H_3PO_4$ to adjust the system pH to 5.5, 15 °C | **8** (52%, *trans*/*cis* = 3.3:1), **9** (23%) |

[a] Yield of product isolated by chromatography on silica gel.
[b] The *trans*/*cis* ratio was not determined because of the low yield.
[c] No **8** or **9** was observed by TLC.

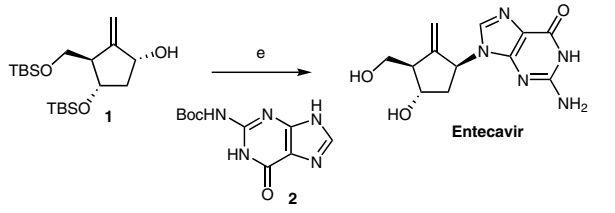
tone enolate is subsequently protonated, with formation of diphenyldiselane, to generate the desired β-hydroxy ketone product **8**. According to this proposed mechanism, it is reasonable that the reaction does not proceed under more-acidic conditions, because fewer benzeneselenolate ions would be available.

Because, it was not possible to separate the desired *trans*-isomer **8** from the corresponding *cis*-isomer, we used a mixture of *trans*- and *cis*-**8** in the next step. At this stage, the hydroxy group in intermediate **8** was protected with a TBS group under the same conditions as described previously to provide the *trans*-compound **10** in 80% yield. We originally thought that the subsequent conversion of the carbonyl group into a double bond would be achieved by a Wittig reaction, but no reaction was observed and only the starting material was recovered. We then attempted an olefination by using the Nysted reagent.[11] Treatment of ketone **10** with the Nysted reagent, by following the procedure developed by Ogan et al.,[12] produced the exocyclic olefin **3** in 87% yield when the reaction was conducted in the presence of $TiCl_4$ in $CH_2Cl_2$ at −78 °C with subsequent stirring at room temperature for two hours. We originally attempted to prepare the allylic alcohol from **3** by a Riley allylic oxidation with 1.0 equivalents of $SeO_2$ (Scheme 4).[13] However, allylic alcohol isomers, an enone produced by further oxidation of the allylic alcohols, and unreacted starting material were all present, which resulted in numerous spots on the TLC plate. We therefore explored alternative oxidation/reduction strategies for preparing the desired alcohol **1**. Treatment with excess $SeO_2$ and TBHP in the presence of 4 Å MS at $CH_2Cl_2$ at room temperature, followed by reduction with lithium triethylborohydride in THF at −78 °C gave the key intermediate **9** in 37% yield over two steps.[3g,14]

The endgame for the synthesis of entecavir was the introduction of the purine moiety through nucleophilic substitution of the hydroxy group with compound **2**, with subsequent removal of the Boc and TBS groups with treatment with HCl according to the reported procedure (Scheme 5).[3h]




**Scheme 4** *Reagents and conditions*: (a) TBSCl, imidazole, DMF, 0 ℃, 2 h, 80%; (b) Nysted's reagent, $TiCl_4$, $CH_2Cl_2$, –78 ℃ to r.t., 2 h, 87%; (c) $SeO_2$, TBHP, 4Å MS, $CH_2Cl_2$, r.t., 30 h; (d) $LiBHEt_3$, THF, –78 ℃, 37% from **3**




**Scheme 5** *Reagents and conditions*: (e) See Ref. 3(h).

In conclusion, we have accomplished a formal synthesis of entecavir by a new and straightforward approach, in which the chiral center is introduced by a Sharpless asymmetric epoxidation. The use of a catalytic chiral reagent should decrease production costs in comparison with those of other synthetic routes. The other key features of the route include a Morita–Baylis–Hillman reaction, a reductive epoxide opening of an α,β-epoxy ketone, and a Riley selenium dioxide oxidation. We made a thorough study of the benzeneselenolate-induced reductive epoxide opening of an α,β-epoxy ketone to generate a β-hydroxy ketone, and we obtained a moderate yield of the epoxide-opened product in a mixture of buffer solvents. The present strategy provides an alternative approach to the synthesis of similar compounds. Further studies on the application of this approach to natural products and pharmaceuticals are in progress and will be reported in due course.

## Funding Information

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1612215.

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(14) **{[(1*R*,3*S*,4*S*)-4-methyl-5-methylenecyclopentane-1,3-diyl]bis(oxy)}bis[*tert*-butyl(dimethyl)silane] (1)**
A solution of the protected diol **11** (1.2 g, 3.2 mmol) in THF (14 mL) was treated by dropwise addition of a 1.0 M solution of

$LiBHEt_3$ in THF (6.5 mL, 6.4 mmol) at –78 °C, and the mixture was stirred for 15 min. The reaction was then quenched by addition of sat. aq $NH_4Cl$, and the resultant mixture was stirred at r.t. for another 20 min. The mixture was then poured into sat. aq potassium sodium tartrate (Rochelle salt), and the aqueous phase was extracted with $Et_2O$ (3 × 20 mL). The organic layers were combined, washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by column chromatography [silica gel, PE–EtOAc (10:1)] to give a clear solid; yield: 1.04 g (2.8 mmol, 87%); mp 63–65 °C, $[\alpha]_D^{20}$ –8.18 (*c* 1.25, $CHCl_3$).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 0.03 (d, *J* = 4.9 Hz, 6 H), 0.08 (s, 6 H), 0.88 (s, 18 H), 1.82 (d, *J* = 13.6 Hz, 1 H), 1.93–2.04 (m, 1 H), 2.74 (m, 1 H), 3.30 (dd, *J* = 10.2, 9.0 Hz, 1 H), 3.56 (dd, *J* = 10.3, 5.1 Hz, 1 H), 4.35 (d, *J* = 9.6 Hz, 2 H), 5.12 (s, 1 H), 5.38 (s, 1 H).$^{13}C$ NMR (100 MHz, $CDCl_3$) = –5.4, –5.3, –4.7, 18.0, 18.4, 25.9, 26.0, 42.2, 55.1, 64.8, 75.4, 111.7, 154.4. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{40}NaO_3Si_2$: 395.2408; found: 395.2406.