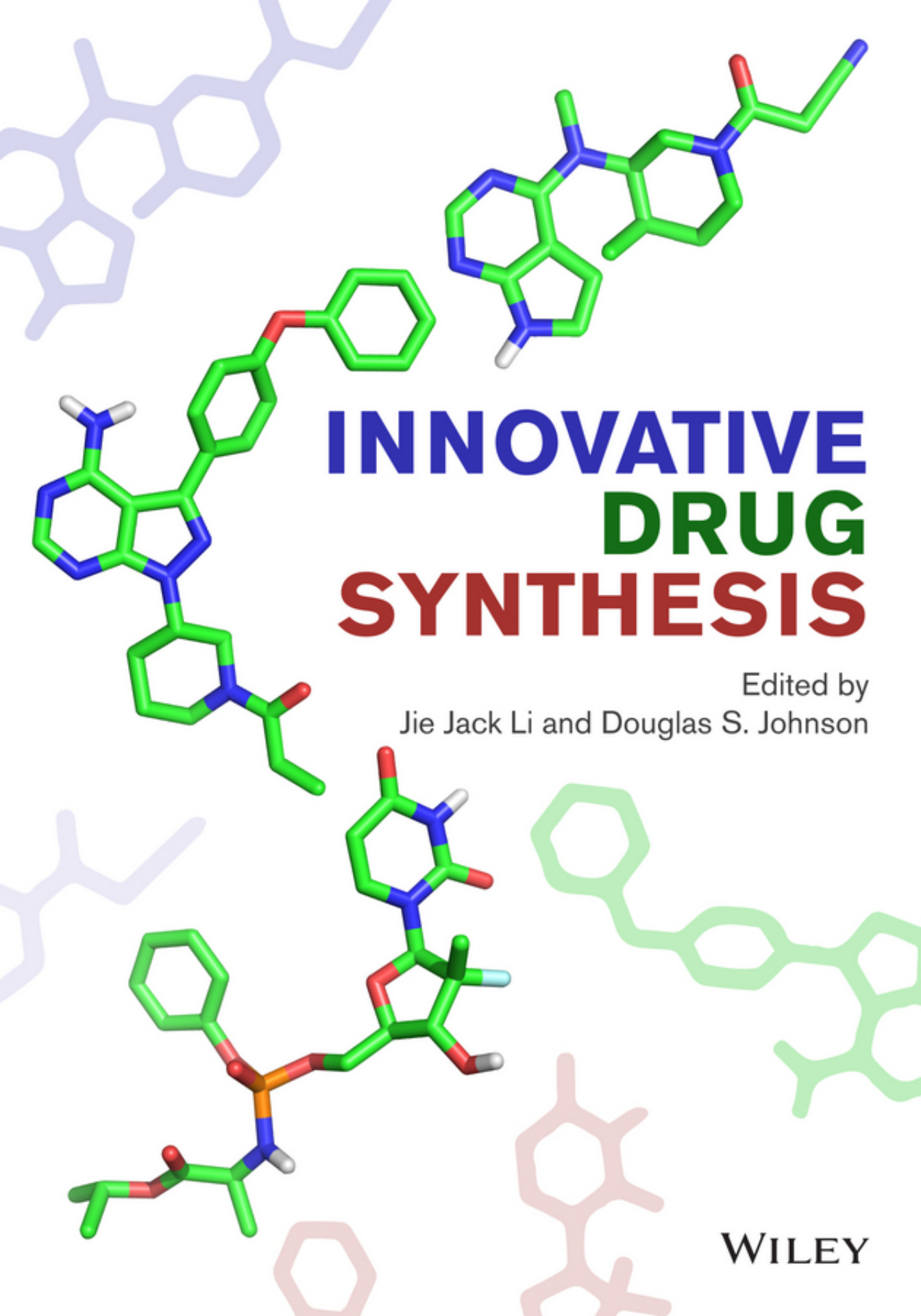

INNOVATIVE DRUG SYNTHESIS

Edited by
Jie Jack Li and Douglas S. Johnson

WILEY

Innovative Drug Synthesis

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Edited by:

Jie Jack Li
University of San Francisco

and

Douglas S. Johnson
Pfizer Worldwide Research and Development

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Preface

Our first three installments on drug synthesis, *Contemporary Drug Synthesis, The Art of Drug Synthesis,* and *Modern Drug Synthesis* were published in 2004, 2007, and 2010, respectively. They have been warmly received by the chemistry community. The current title, *Innovative Drug Synthesis*, is our fourth installment of Wiley's *Drug Synthesis Series*.

This book has six sections. Section I, "Infectious Diseases" covers five drugs; Section II, "Cancer" reviews five drugs, three of which are kinase inhibitors; Section III covers one drug that targets cardiovascular and metabolic diseases; Section IV on central nervous system diseases concerns four classes of recent drugs; Section V summarizes a new anti-inflammatory drug; and Section VI covers two additional drugs.

In addition to a detailed account of the drug synthesis, each chapter also covers background material on the drug class and/or disease indication, as well as key aspects relevant to the discovery of the drug, including, structure-activity relationships, pharmacokinetics, drug metabolism, efficacy and safety.

We are indebted to the contributing authors from both industry and academia. Many of them are veterans and well-known experts in medicinal chemistry. Some of them discovered the drugs that they reviewed. As a consequence, their work tremendously elevated the quality of this book. One of us (JJL) would like to thank his students, Elizabeth N. Cruz, Taylor D. Krueger, Cho K. Lai, Amanda N. Moules, Emily S. Murzinski, Karla E. Rodriguez, and Theresa V. Song for taking part in this writing project.

Meanwhile, we welcome your critique and suggestions so we can make this *Drug Synthesis Series* even more useful to the medicinal/organic chemistry community.

Jack Li and Doug Johnson
May 1, 2015

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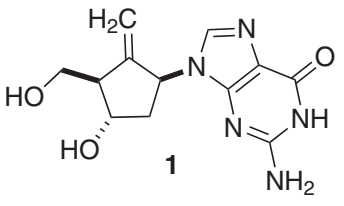
I

INFECTIOUS DISEASES

1

Entecavir (Baraclude): A Carbocyclic Nucleoside for the Treatment for Chronic Hepatitis B

Jie Jack Li



1

USAN: Entecavir
Trade name: Baraclude®
Bristol-Myers Squibb Co.
Launched: 2005

1 Background

Chronic hepatitis B virus (HBV) infection is a major global cause of morbidity and mortality. An estimated 400 million people worldwide have chronic HBV infection and more than half a million people die every year because of complications from HBV-related chronic liver disease such as liver failure and hepatocellular carcinoma (HCC). In the United States, 12 million people have been infected at some time in their lives with HBV. Of those individuals, more than 1 million people have subsequently developed chronic hepatitis B infection. These chronically infected persons are at highest risk of death from liver scarring (cirrhosis) and liver cancer. In fact, more than five thousand Americans die from hepatitis B-related liver complications each year. In many Asian and African countries where the HBV is endemic, up to 20% of the population may be carriers, and transmission occurs primarily through perinatal or early childhood infection. In some of these areas, the perinatal transmission rate may be as high as 90%![1–4]

During the last 10 years, hepatitis B treatment has made significant progresses. For example, two biologics have been approved by the FDA, namely, interferon-α (IFN-α) and Pegylated-interferon-α (PEG-IFN-α). Also on the market are five small molecule

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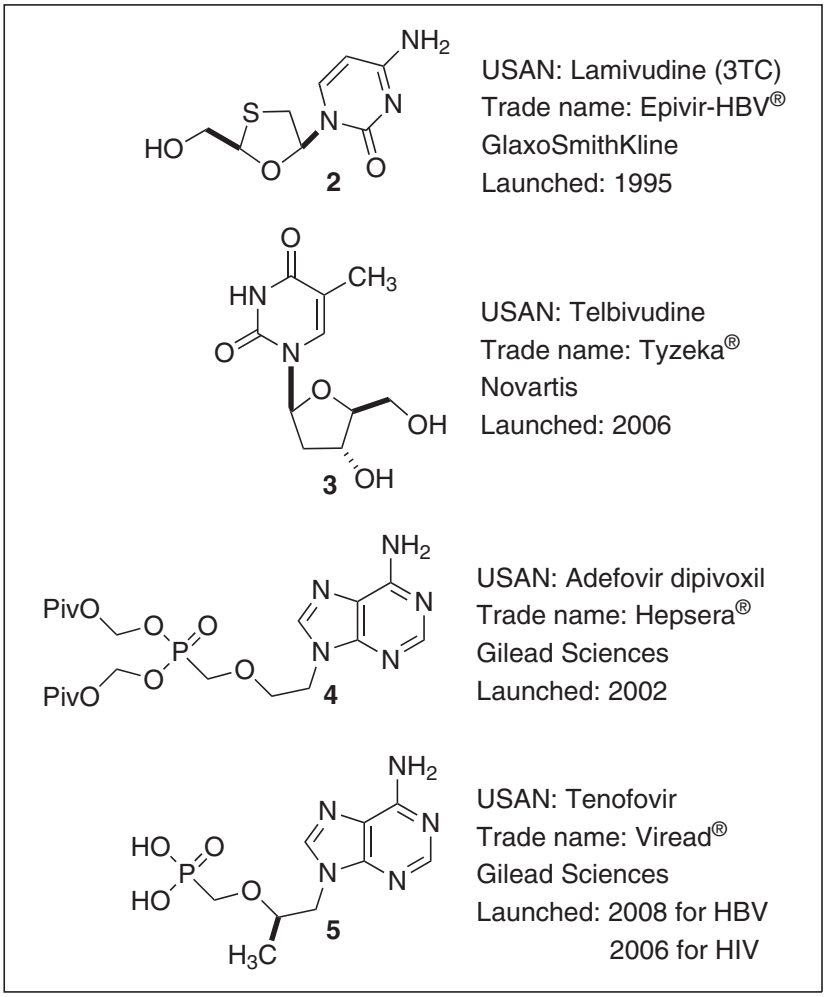
antiviral agents for the treatment of chronic HBV, namely, entecavir (**1**), lamivudine (**2**), telbivudine (**3**), adefovir dipivoxil (**4**), and tenofovir (**5**).



As a biologic, INF-α is effective only in a subset of patients, is often poorly tolerated, requires parenteral administration, and is expensive. Hence, there is a need for alternative therapies for chronic hepatitis B. The introduction of lamivudine (**2**) in 1995, the first oral treatment for chronic HBV, ushered in a new era in the treatment of chronic hepatitis B when safe, effective, and well-tolerated oral medications were made available. It is a nucleoside reverse transcriptase inhibitor (NRTI) with activity against both human immunodeficiency virus type 1 (HIV-1) and HBV. It has been used for the treatment of chronic hepatitis B at a lower dose than for the treatment of HIV, and it improves the

seroconversion of e-antigen-positive hepatitis B and also improves histology staging of the liver. Unfortunately, long-term use of lamivudine (**2**) leads to emergence of a resistant HBV mutant (Tyr-Met-Asp-Asp, YMDD). Despite this fact, lamivudine (**2**) is still used widely as it is well tolerated.[5]

Telbivudine (**3**), a synthetic thymidine nucleoside analog, is the unmodified L-enantiomer of the naturally occurring D-thymidine. It prevents HBV DNA synthesis by acting as an HBV polymerase inhibitor. Within hepatocytes, telbivudine (**3**) is phosphorylated by host cell kinase to telbivudine-5′-triphosphate which, once incorporated into HBV DNA, causes DNA chain termination, thus inhibiting HBV replication. In this sense, telbivudine (**3**), like most nucleotide antiviral drugs, is a prodrug. Clinical trials have shown telbivudine (**3**) to be significantly more effective than lamivudine (**2**) or adefovir dipivoxil (**4**) and less likely to cause resistance.[6]

Adefovir dipivoxil (**4**) was initially developed as a treatment for HIV, but the FDA in 1999 rejected the drug due to concerns about the severity and frequency of kidney toxicity when dosed at 60 or 120 mg, respectively. However, **4** was effective at a much lower dose of 10 mg for the treatment of chronic hepatitis B in adults with evidence of active viral replication and either evidence of persistent elevations in serum alanine aminotransferases (primarily ALT) or histologically active disease. It works by blocking reverse transcriptase, an enzyme that is crucial for the HBV to reproduce in the body. Overall, the efficacy of **4** against wild-type and lamivudine (**2**)-resistant HBV and the delayed emergence of **4**-resistance during monotherapy contribute to the durable safety and efficacy observed in a wide range of chronic hepatitis B patients.[7]

Tenofovir (**5**), a nucleotide analog closely related to adefovir dipivoxil (**4**) has been approved for the treatment of HBV in 2008, subsequent to its approval for the treatment of HIV infection in 2006. *In vitro* studies showed that it has activity against HBV with equimolar potency to **4**. Clinical studies confirmed the efficacy of **5** in suppressing HBV replication, and it appears to be equally effective against both wild-type and lamivudine (**2**)-resistant HBV. The role of **5** in the rapidly expanding armamentarium of hepatitis B treatments will depend on the demonstration of long-term safety (renal and skeletal) and efficacy against wild-type HBV and HBV mutants that involve substitution of methionine within the YMDD motif, as well as a very low rate of resistance in NA-naïve as well as NA-experienced patients.[8–10] NA stands for nucleos(t)ide analog.

The approval of the nucleotide and nucleoside analogs **1**–**5** marked a significant advance in the treatment of chronic hepatitis B. In comparison to compounds **2**–**5**, entecavir (**1**) is a novel carbocyclic nucleoside analog with potent and highly selective activity against HBV, as well as a low rate of resistance. In this chapter, the pharmacological profile and syntheses of entecavir (**1**) will be profiled in detail.

2 Pharmacology

The hallmark of acute HBV infection is elevated alanine aminotransferase (ALT) levels. As a matter of fact, ALT levels are routinely screened during our annual physical exams where an elevated ALT level is a sign of a concern with regard to the liver function. For

instance, long-term consumption of too much alcohol would cause liver to become hardened along with elevated ALT levels. Other telltale signs of acute HBV infection also include the presence of hepatitis B surface antigen (HBsAg), IgM antibody to hepatitis B core antigen (anti-HBc), and hepatitis B e-antigen (HBeAg), although the latter serological test is not routinely used. Chronic hepatitis B is defined as the presence of HBsAg or other viral markers in serum for more than 2 months.

Entecavir (**1**) is converted in mammalian cells *in vitro* to the 5′-triphosphate, which then acts as an inhibitor of hepadnaviral polymerase with an IC_{50} value for inhibition of HBV of 0.2–0.3 nM. The *K*i value for binding of **1**-triphosphate to HBV polymerase is 3.2 nM. In the HepG2 stably transfected cell line 2.2.15, **1** had an EC_{50} (50% effective concentration) value of 3.5 nM against HBV and an CC_{50} (50% cytotoxic concentration) value of ~30 μM against HBV as determined by analysis of secreted HBV DNA.[11,12] This represents an excellent selectivity index of ~8,000 (toxicity dose is 8,000-fold greater than the concentration needed to inhibit HBV replication in the same cell line). Direct comparison with other nucleoside analogs in this cell line demonstrated that **1** is the most potent inhibitor of HBV replication, as shown in Table 1.[13]

Table 1. Potency of various nucleoside analogs for HBV inhibition based on the EC_{50} for inhibition of HBV replicase in HepG2.2.15 cell line.[13]

Analog	EC_{50} (μM)	Relative potency
Entecavir (**1**)	0.004	1
Lamivudine (**2**)	0.02	0.2
Adefovir dipivoxil (**4**)	0.11	0.04
Tenofovir (**5**)	0.14	0.03

Woodchucks (*Marmota monax*) infected with woodchuck hepatitis virus (WHV) were used as an *in vivo* model of HBV infection. During the first 4 weeks of study, **1** was administered at various doses and was found to suppress HBV DNA replication by approximately 3 log10 copies/mL regardless of the dose administered. After 12 weeks, most of the animals became HBV DNA-negative, reflecting greater than a 1,000-fold suppression in circulating HBV. Similar results were observed for **1** using ducks as the animal model.[13]

3 Structure–Activity Relationship (SAR)

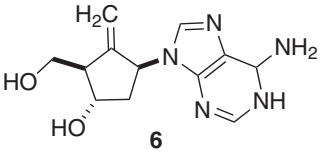
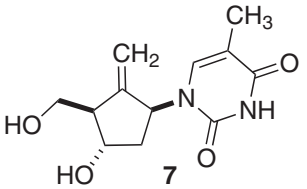
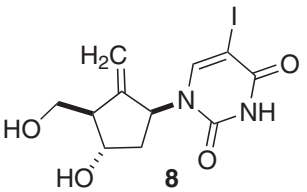
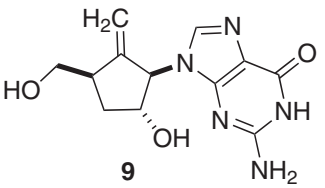
The structure–activity relationship (SAR) around entecavir (**1**) was exhaustively investigated, and **1** was found to be the most potent member in the series as tested against HBV in HepG2.2.15 cells. As shown in Table 2 (next page), the enantiomer of **1** (*ent*-**1**) was inactive, while **1** was 6.6-fold more potent than lamivudine (**2**, entry 3).[14] Similarly, the adenine analog **6** (entry 4) was 43-fold less potent than **1**, while the thymine analog **7** (entry 5) and the 5-iodouracil analog **8** (entry 6) were much less potent in HepG2.2.15 cell culture.

In 2004, Ruediger et al. at Bristol-Myers Squibb (BMS) prepared the 3′-deoxy analog (**9**) of entecavir (**1**), which is the carbocyclic 2′-deoxyguanosine.[15] Unfortunately, both the 3′-deoxy analog **9** and its enantiomer (*ent*-**9**) were found to be inactive against HBV in HepG2.2.15 cell culture.

4 Pharmacokinetics and Drug Metabolism

The plasma half-life of entecavir (**1**) in rats and dogs was 4–9 h. It was metabolized by HepG2 cells to the corresponding mono-, di-, and triphosphates. The uptake of **1** was linear between 1–25 μM, and intracellular triphosphate accumulated most efficiently in the micro-molar range, with an intracellular half-life for **1**-triphosphate determined to be 15 h.[11]

Table 2. Activity of nucleoside analogs against HBV in HepG2.2.15 cells.

Entry	Compound	EC_{50}(μM)
1	1	0.03
2	*ent*-1	100
3	**2** (3TC)	0.2
4	 **6**	0.128
5	 **7**	>100
6	 **8**	10.5
7	 **9**	>100
8	*ent*-**9**	>100

In humans, peak plasma concentration occurred between 0.5 and 1.5 h following oral administration of **1** in healthy males. Steady-state concentration was achieved in 6–10 days, with a twofold accumulation and an effective accumulation half-time of about 24 h. Compound **1** is not a substrate, inducer, or inhibitor of the cytochrome P450 enzyme system; therefore, it has limited potential for drug–drug interactions (DDIs).[13]

5 Efficacy and Safety

Entecavir (**1**) is a potent inhibitor of HBV replication. It is active against lamivudine (**2**)-resistant HBV and also offers the convenience of once daily dosing and a favorable safety profile.

In phase III clinical trials, more than 1,500 patients participated in three major studies: AI463-022, which compared the investigational agent **1** to treatment with **2** in nucleoside-naïve, HBeAg-positive chronic hepatitis B patients; AI463-027 which compared **1** to **2** in nucleoside-naïve patients with HBeAg-negative chronic hepatitis B; and AI463-026, which evaluated patients with **2**-refractory HBeAg-positive chronic hepatitis B who were either switched directly to **1** or continued to receive **2**. Entecavir (**1**) demonstrated significant histological improvement and significantly reduced viral load versus **2**, with a similar safety profile at 48 weeks in these three studies. The most common adverse events of moderate to severe intensity that occurred in >1% of patients treated with **1** were headache, fatigue, diarrhea, and dyspepsia.[13]

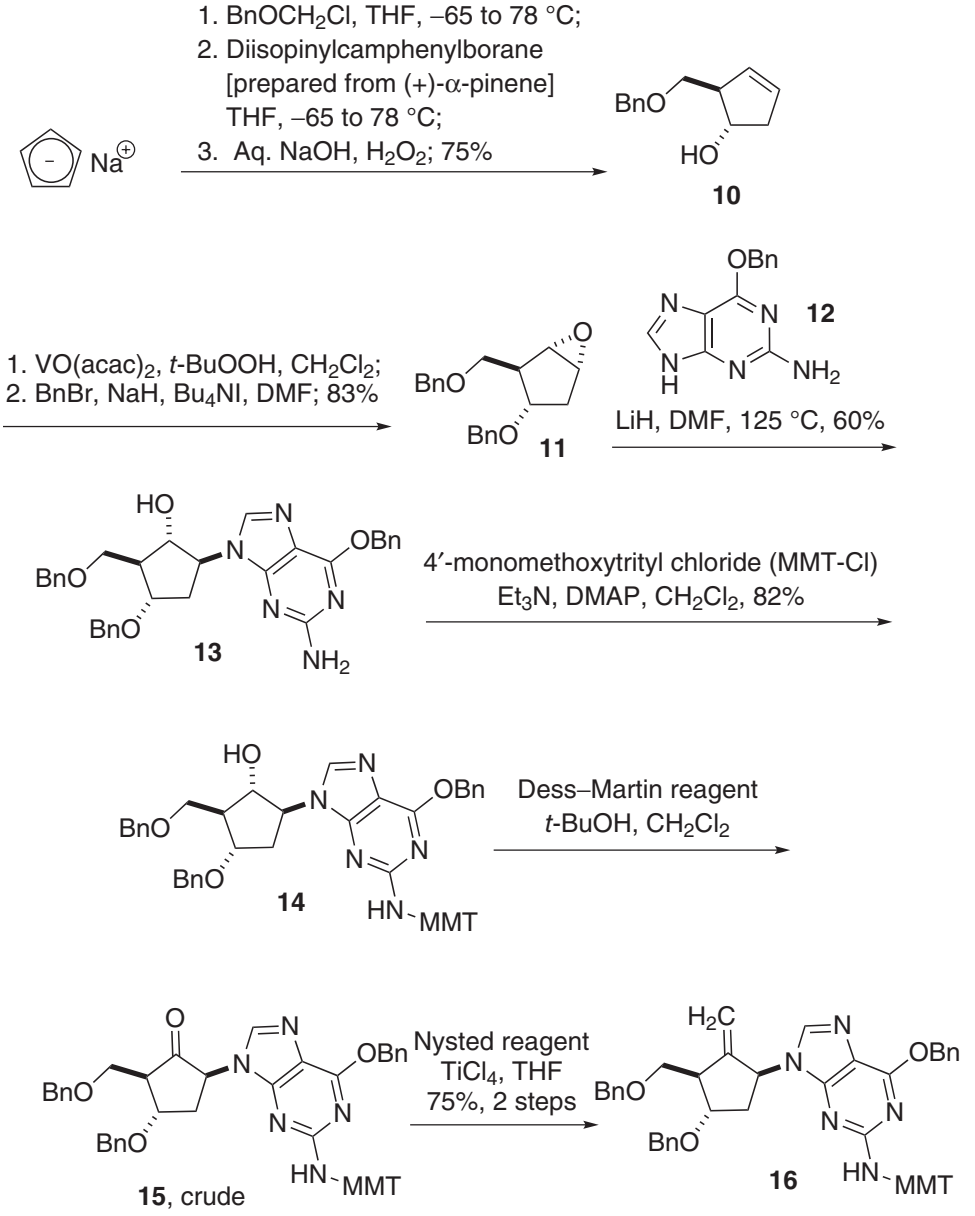
6 Syntheses

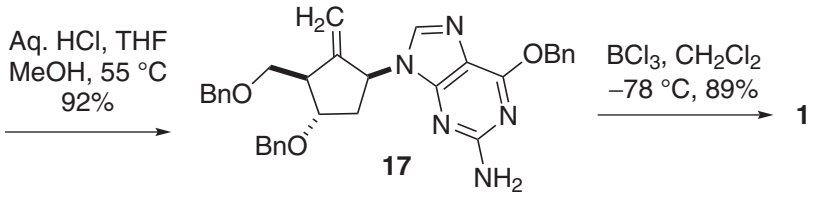
6.1 Discovery Synthesis

The BMS discovery synthesis of entecavir (**1**) was patented by Zahler and Slusarchyk,[16,17] whereas Bisacchi and Zahler et al.[14,17,18] of BMS reported the process synthesis of **1**. Although the synthetic route of the process synthesis of **1** is similar to the discovery approach, the process synthesis was superior with regard to yields and ease of operation on large scales.

The process synthesis of **1**, as reported by Bisacchi and Zahler et al.,[14] commenced with the known chiral synthon **11**. Thus, cyclopentene **10** was prepared in 75% yield and 96.6–98.8% *ee* using commercially available sodium cyclopentadienide.[19] Cyclopentyl epoxide **11** was easily assembled by epoxidation of **10** with $VO(acac)_2$ and *t*-butyl peroxide, followed by O-benzylation. Lithiation of 6-(benzyloxy)-9*H*-purin-2-amine (**12**) with LiH was followed by reaction with epoxide **11** to afford the *N*-9 adduct **13**. Protection of the purine amine was found to be necessary for the subsequent oxidation of the cyclopentyl alcohol, and this was done using 4′-monomethoxytrityl chloride (MMT-Cl). Subsequent oxidation was achieved using the Dess–Martin reagent to give ketone **15**, while other oxidation methods such as Moffatt and TPAP–NMMO oxidation did not work as well. Several methods for the methylenation of ketone **15** were successfully employed, with the Nysted reagent working better on large scales in comparison to the Tebbe reagent, the Simmons–Smith reagent, and the Lombardo reagent, to afford olefin **16**. Acid-mediated deprotection then provided **17** and a final

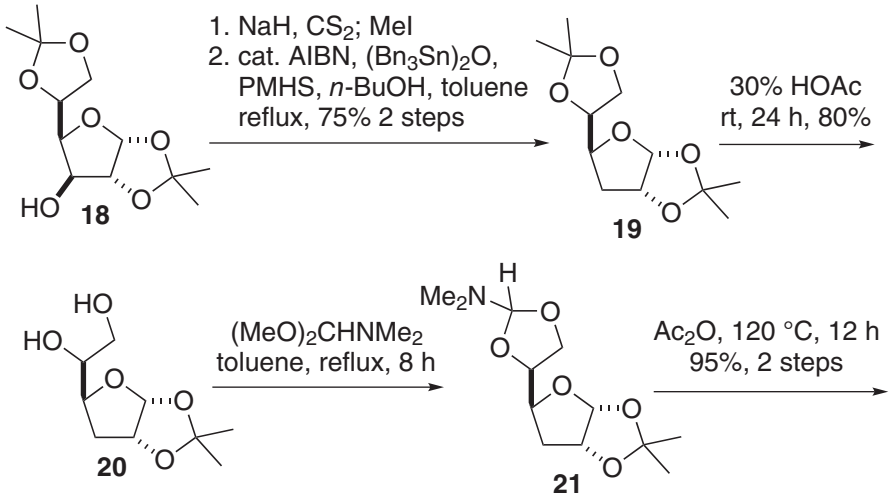
global de-benzylation step afforded **1** in 11 total steps and an overall yield of 18%. This route was used to make up to 20 g of **1**.

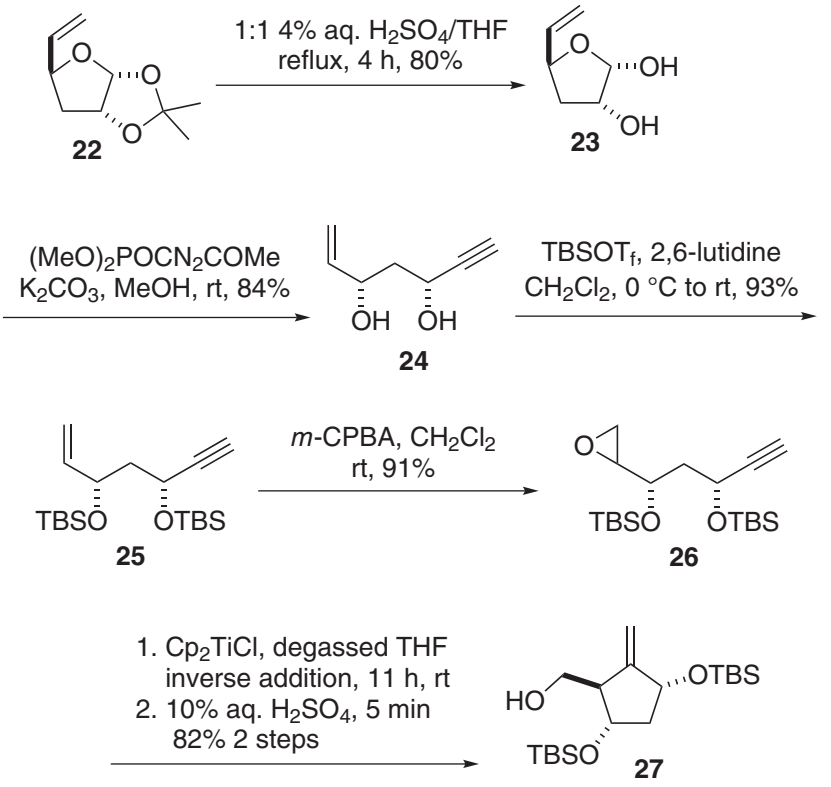




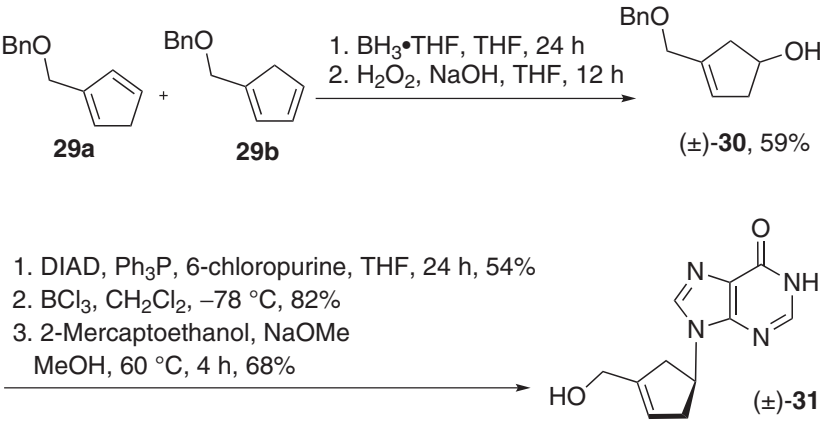
6.2 Alternative Syntheses

Ziegler reported a strategy, involving radical cyclization, which offered an alternative approach to the carbocyclic core of **1**.[20] The approach is intellectually interesting but less practical due to the lengthy synthesis. Ziegler began his endeavor using D-diacetone glucose (**18**) as the starting material. A Barton–McCombie deoxygenation of **18**, using Fu's catalytic *n*-Bu_3SnH protocol with polymethylhydrosiloxane (PMHS), removed the free hydroxyl group to give **19**. After chemo-selective removal of the pendant acetonide, the resulting diol **20** was converted to amide acetal **21** using the Eastwood procedure. Treatment of **21** with acetic anhydride at 120 °C then provided olefin **22**. Acetonide hydrolysis of **22** afforded **23**, which was treated with $(MeO)_2POCN_2COMe$ under Ohira's mild alkaline conditions to give acetylenic diol **24** in excellent yield. Bis-silyation of **24** gave **25**, which was non-selectively epoxidized using *m*-CPBA to give **26**. The stereochemical outcome is inconsequential here because the chirality would be obliterated later. With epoxy-acetylene **26** in hand, a Ti(III)-mediated generation of β-alkoxy carbon radical and subsequent cyclization delivered the desired methylene cyclopentane **27** after a quick acidic workup. Again, Ziegler's approach proved that the radical cyclization of epoxy-acetylene **26** would indeed produce the desired carbocyclic core of **1**, but this did not ultimately contribute to the manufacture of entecavir (**1**, Baraclude) or hasten its path to the market.





More recently, Reichardt and Meier[21] reported an efficient synthesis for racemic cyclopent-3-en-1-yl nucleoside analogs, which could, in principle, be applicable to the synthesis of entecavir (**1**). Their synthesis started from inexpensive cyclopentadiene, which was deprotonated with NaH and then quenched with benzyloxymethyl chloride to give diene **28**, which isomerized to give a mixture of two thermodynamically more stable alkylated cyclopentadienes **29**a,b. Regioselective hydroboration of **29**a,b was followed by oxidative alkaline workup to give rise to the key intermediate cyclopentenol (±)-**30**. Condensation of (±)-**30** with 6-chloropurine was then achieved using a modified Mitsunobu reaction. The adduct was debenzylated and the resulting chloropurine derivative was treated with sodium methoxide and 2-mercaptoethanol to produce the inosine nucleoside (±)-**31**. It is conceivable that this interesting approach could be adapted to the synthesis of (±)-entecavir (**1**).



During the development of entecavir (**1**), Ogan et al.[22] at BMS described the synthesis of [^{14}C]-radiolabeled entecavir, which was required for clinical studies of absorption, distribution, metabolism, and elimination (ADME). As a key step in their synthesis, they chose to elaborate the pyrimidine **46** to purine **47**, a known strategy in the literature for the synthesis of labeled nucleosides. To that end, chiral expoxide **11** was treated with sodium azide, and Staudinger reduction of the resulting azido-alcohol gave amino-alcohol **32**. Heating **32** with 4,6-dichloropyrimidin-2-amine then furnished 6-chloro-diaminopyrimidine **33**. Pyrimidine **33** was subsequently treated with the diazonium salt generated from *p*-chloroaniline to afford a bright yellow 5-diazopyrimidine, which was treated with potassium methoxide to provide the 4-methoxy-5-diazopyrimidine **34**. Cleavage of the diazo linkage of **34** with zinc in acetic acid gave the triaminopyrimidine **35**, which was treated with triethyl [^{14}C]-orthoformate to effect a ring annulation, and subsequent protection with the 4-methoxytrityl group provided the guanine **36**. Oxidation of **36** with Dess–Martin periodinane was followed by Nysted methylenation to afford the exocyclic methylenic compound **37**. Global de-protection of **37** then completed the synthesis of [^{14}C]-radiolabeled entecavir (**1**).