ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

Full Paper

Total synthesis of entecavir: a robust route for pilot production

Hua Xu, Fang Wang, Weicai Xue, Yunjie Zheng, Qi Wang, Fayang Qiu, and Yehua Jin

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.8b00007 • Publication Date (Web): 12 Feb 2018

ACS Publications

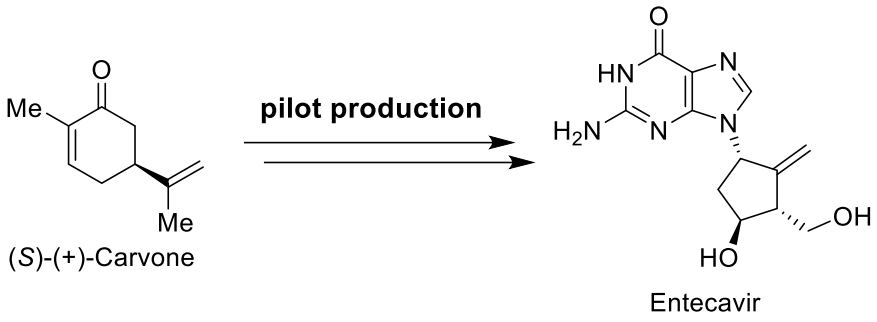
Organic Process Research & Development is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Total synthesis of entecavir: a robust route for pilot production

Hua Xu[‡], Fang Wang[‡], Weicai Xue, Yunjie Zheng, Qi Wang, Fayang G. Qiu, and Yehua Jin**

Launch-Pharma Technologies, Ltd., 188 Kaiyuan Boulevard, Building D, 5th Floor, the Science Park of Guangzhou, Guangzhou, 510530, China.

Table of Contents Graphic:



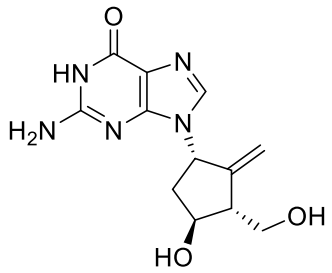
(*S*)-(+)-Carvone

Entecavir

ABSTRACT: A practical synthetic route for pilot production of entecavir is described. It is safe, robust and scalable to kilogram scale. Starting from (*S*)-(+)-carvone, this synthetic route consists of a series of highly efficient reactions including a Favorskii rearrangement-elimination-epimerization sequence to establish the cyclopentene skeleton; the Baeyer-Villiger oxidation/rearrangement to afford the correct configuration of the secondary alcohol and a directed homoallylic epoxidation followed by epoxide ring-opening to introduce the hydroxyl group suitable for the Mitsunobu reaction. In addition, the synthesis contains only 4 brief chromatographic purifications.

KEYWORDS: entecavir; hepatitis B virus; total synthesis; Favorskii rearrangement; Baeyer-Villiger oxidation.

Approved by the US FDA in 2005 for the treatment of hepatitis B virus (HBV) infected patients under the trade name of Baraclude ®, entecavir (**1**), (**Figure 1**), is a nucleoside analogue with potent activity and selectivity against HBV by inhibiting the replication process of the virus. It was first discovered and synthesized by the chemists from Bristol-Myers Squibb.[1]



Entecavir (**1**)

Figure 1: Entecavir.

Given its biological activities and novel molecular framework, several synthetic groups around the world have been attracted to study its total synthesis.[1(a), 2, 3] From a practical point of view, we have developed an efficient synthetic route that is suitable for the production of kilograms of high quality product with 100% ee. The summary of the total syntheses of entecavir is shown in **Figure 2**.

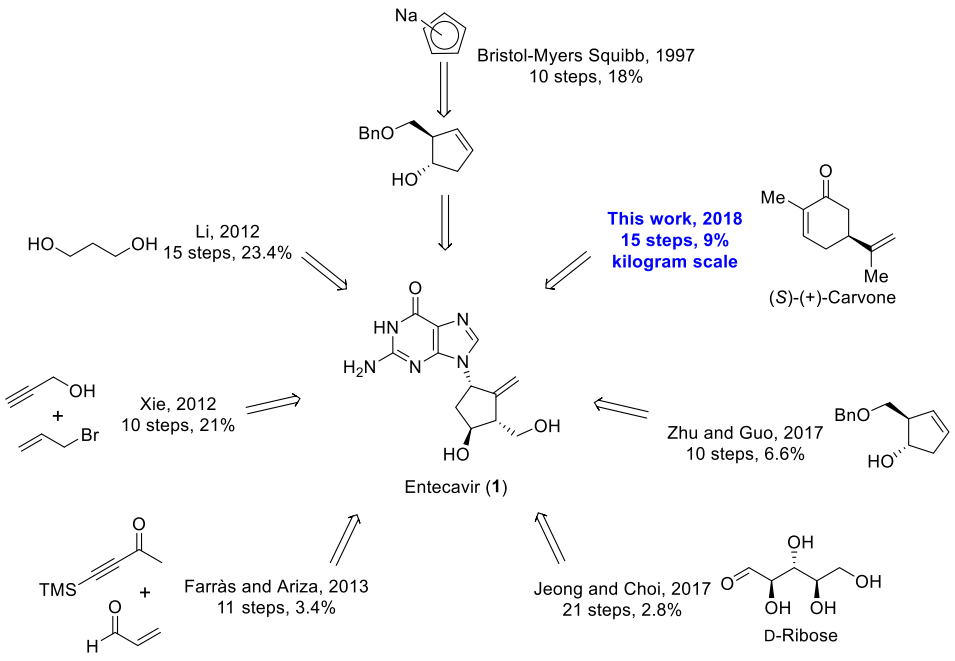
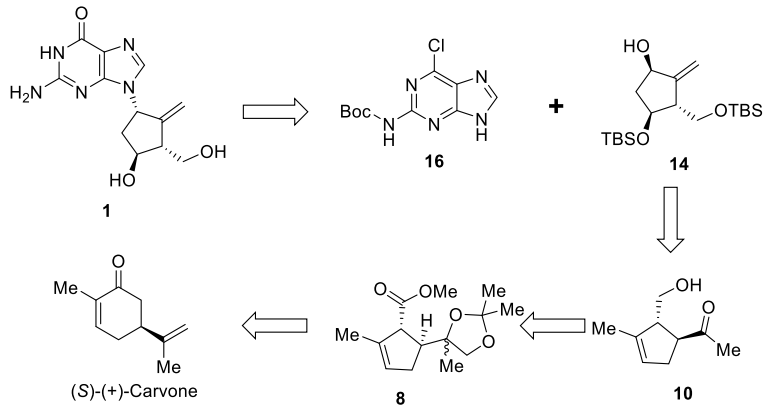


Figure 2: Schematic summary of the total syntheses of entecavir.

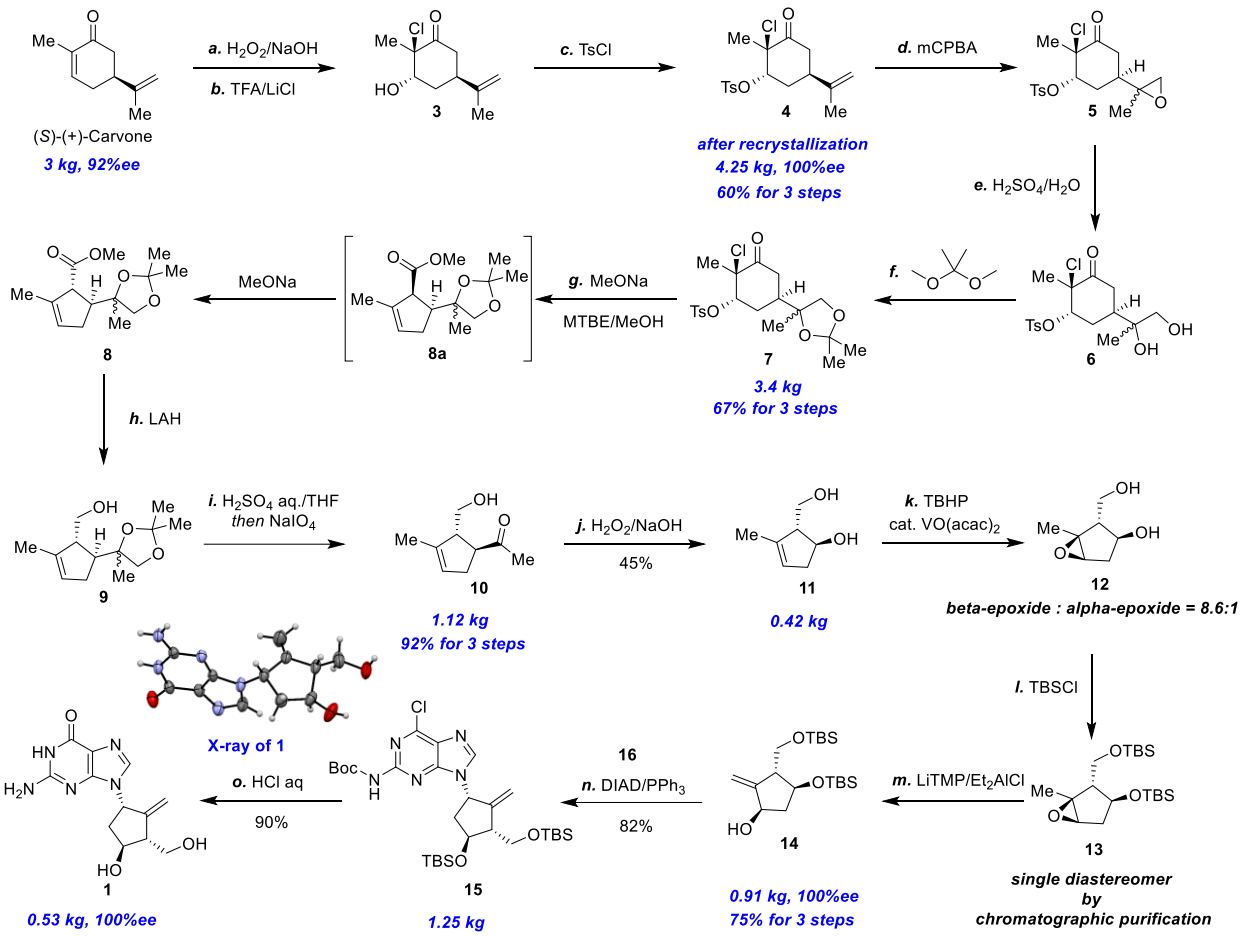
As shown in **Scheme 1**, entecavir may be assembled with cyclopentanol **14** and protected purine **16** via a Mitsunobu reaction.[2d] Compound **14** may be derived from the *trans*-substituted ketone **10** through a series of transformations, including the most challenging one, conversion of a methyl ketone into an alcohol in the presence of an alkene functionality. Compound **10** may be obtained through conventional methods from carboxylate **8**, an intermediate that may be derived from (*S*)-(+)-carvone.



Scheme 1: The retrosynthetic analysis of entecavir **1**.

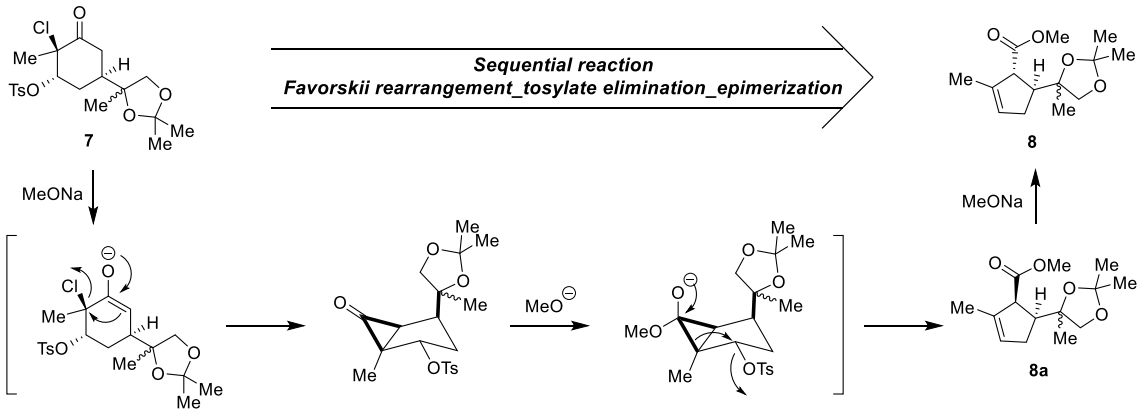
As shown in **Scheme 2**, compound **3** was prepared as a single diastereomer from 3 kg of 92% ee (*S*)-(+)-carvone via a two-step transformation including a stereoselective epoxidation and chlorohydrin formation from the newly formed epoxide.[4] Tosylation of the *sec*-hydroxyl group of compound **3** afforded 4.25 kg of product **4** (60% yield over 3 steps) in 100% ee after recrystallization from MeOH. This ultra-pure intermediate was then reacted with mCPBA to afford epoxide **5**, which was converted into diol **6** after treatment with dilute aqueous sulfuric acid. Protection of the diol with dimethoxypropane afforded 3.4 kg of intermediate **7** (67% over 3 steps). This product was treated with sodium methoxide in methanol to initially provide the *cis*-substituted Favorskii rearrangement product **8a**, which upon isomerization gave the thermodynamically more stable cyclopentanecarboxylate **8** under the reaction conditions, though the epimerization was incomplete even after being stirred for 24 hours (50 g scale) at room temperature. Fortunately, the problem was solved by using methyl *t*-butyl ether (MTBE)/methanol as the solvent and the reaction was complete in less than 17 hours (50 g scale). The postulated mechanism of this reaction is shown in **Scheme 3**.

Scheme 2: Synthesis of entecavir (**1**).



Reagents and conditions: (***a***). 30% $H_2O_{2(aq)}$, 4N $NaOH_{(aq)}$, MeOH, 0 °C; (***b***) TFA, LiCl, THF, 0-5 °C; (***c***) TsCl, DMAP, CH_2Cl_2, 25 °C (60% for 3 steps); (***d***) mCPBA, CH_2Cl_2, 25 °C; (***e***) H_2SO_4, H_2O, THF, 25 °C; (***f***) 2, 2-Dimethoxypropane, *cat.* PSA, CH_2Cl_2, 25 °C (67% for 3 steps); (***g***) MeONa, MTBE/MeOH, 0-25 °C; (***h***) LAH, THF, 5-10 °C; (***i***) 20% $H_2SO_{4(aq)}$, THF, 25 °C, *then* $NaIO_4$ 25 °C (92% for 3 steps); (***j***) 30% $H_2O_{2(aq)}$, 10% $NaOH_{(aq)}$, MeOH, 70 °C (45%); (***k***) *cat.* $VO(acac)_2$, TBHP, CH_2Cl_2, 0±5 °C; (***l***) TBSCl, imidazole, *cat.* DMAP, DMF, 25 °C; (***m***) LiTMP, Et_2AlCl, toluene, 0 °C (75% for 3 steps); (***n***) **16**, DIAD, PPh_3, THF, 0 °C (82%) (***o***) 3N $HCl_{(aq)}$, THF, 55 °C (90%).

Scheme 3: Proposed mechanism of the tandem reaction sequence from **7** to **8**.



Reduction of carboxylate **8** using lithium aluminum hydride (LAH) provided alcohol **9**, which was converted into ketone **10** through hydrolysis of the isopropylidene followed by oxidative cleavage of the newly formed diol. The Baeyer-Villiger oxidation (BV Oxidation) of ketone **10** was more challenging. Although peracids such as CF_3CO_3H, mCPBA or CH_3CO_3H are popular reagents for this purpose, all of them underwent the alkene epoxidation rather than the desired BV oxidation. In order to avoid the olefin epoxidation, nucleophilic oxidation conditions were applied. To our delight, hydrogen peroxide under basic conditions (H_2O_2/NaOH) was found to be an efficient oxidant and a kilogram scale reaction afforded compound **11**, after chromatographic separation, in 45% yield.[5]

Diol **11** was converted into the desired β-epoxide **12** (β-epoxide : α-epoxide = 8.6:1) through the vanadium-catalyzed stereoselective epoxidation of homoallylic alcohol.[2d, 6] In this case, the stereoselectivity of the epoxidation was mainly directed by the secondary alcohol instead of the primary alcohol, which was to our desire and surprise.

Protection of the hydroxyl groups of **12** with TBSCl/imidazole delivered TBS ether **13** as a single diastereomer after a brief chromatographic purification, the latter was converted into intermediate **14** in kilogram scale through a known method using LiTMP/Et_2AlCl to open the epoxide.[2d] Condensation of **14** with protected purine **16** via a Mitsunobu reaction afforded compound **15** as a single diastereomer,[2d, 7] hydrolysis of which with aqueous HCl provided the final product, i.e., entecavir **1** in 90% yield. The identity of the final product was confirmed by X-ray crystallography. Starting from 3 kg (*S*)-(+)-carvone (92% ee), 530 g of enantiomerically pure entecavir **1** was obtained, which corresponds to an overall yield of 9% over 15 steps.

In summary, we have accomplished a robust kilogram-scale total synthesis of entecavir with high purity which meets the API requirements. The starting (*S*)-(+)-carvone is inexpensive and

commercially available in bulk quantities. The reaction conditions are mild (mostly 0 ~ 25 °C; only two reactions require heating to 55 °C and 70 °C, respectively); and most of the reagents used in this synthesis are inexpensive commercial materials. The success of this approach is dependent on a series of key chemical transformations, including: 1) tandem reaction of Favorskii rearrangement-tosylate elimination-epimerization; 2) Baeyer-Villiger oxidation under basic conditions; 3) vanadium-catalyzed stereoselective epoxidation of a homoallylic alcohol directed by the secondary hydroxyl group (rather than the competing primary hydroxyl group); and 4) S_N2 Mitsunobu reaction.

EXPERIMENTAL SECTION

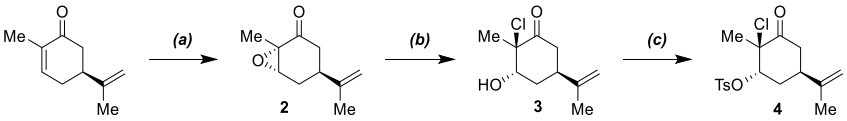
General Procedures:

All reactions were carried out under a nitrogen atmosphere unless otherwise stated. All the solvents and reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated.

Reactions were monitored by thin-layer chromatography (TLC) carried out on commercial silica gel plates (GF254) using UV light as visualizing agent and an acidic mixture of anisaldehyde, phosphomolybdic acid, or ceric ammonium molybdate, or basic aqueous potassium permanganate ($KMnO_4$), and heat as developing agents. Flash chromatography was performed on silica gel 60 (200–300 mesh). Concentration of organic solvents was performed on a rotary evaporator under reduced pressure followed by further evacuation using a two-stage mechanical pump. NMR spectra were recorded on 400 MHz or/and 500 MHz Bruker FT-NMR spectrometers and calibrated

using residual undeuterated solvent as an internal reference ($CHCl_3$ @ δ 7.26 ppm ^1H NMR, δ 77.16 ppm ^{13}C NMR; DMSO @ δ 2.50 ppm ^1H NMR, δ 39.52 ppm ^{13}C NMR). The following abbreviations (or combinations thereof) were used to explain ^1H NMR multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, br = broad. High Resolution Mass (MS) analysis was obtained using on an Agilent 6210 LC/MSD TOF spectrometer system with Electrospray Ionization (ESI). Optical rotation were obtained on a Perkin-Elmer 341 polarimeter at 20 °C, measured at 589 nm.

Experimental procedure:



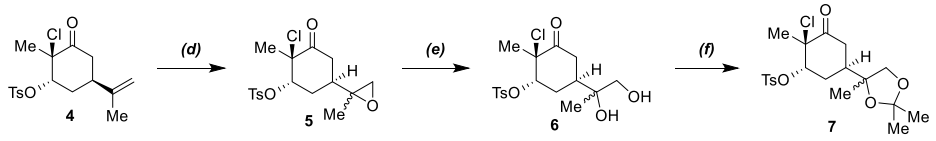
Synthesis of 2: (+)-Carvone (3.00 kg, 19.97 mol, 1.00 equiv) was charged to a 50 L glass reactor. MeOH (15 L) was added under vacuum, and the mixture was stirred for 10 min before being cooled to 0 ± 5 °C. Aqueous NaOH (4 M, 1.00 L, 3.99 mol, 0.20 equiv) and aqueous H_2O_2 (30%wt, 2.49 kg, 21.97 mol, 1.10 equiv) were added dropwise while keeping the temperature below 5°C. The reaction mixture was stirred at 0 °C for about 10 h at which time no (+)-carvone was detected (monitored by TLC). Anhydrous sodium sulfite (0.60 kg) was added to quench the reaction. After being stirred for 0.5 h, no more H_2O_2 was detected (monitored by KI-starch paper). The solvent was concentrated under reduced pressure at 55 °C and the residual slurry was diluted with H_2O (5 L) before DCM (15 L) was added. The mixture was stirred at room temperature for 20 min. After standing for a few minutes, the organic phase was separated and the aqueous phase was extracted with DCM (2 ×10 L). The combined organic layers were washed with brine (5 L). After separation, the organic phase was concentrated under reduced pressure to provide an orange red oil which was then dissolved in PE (16 L). The organic solution was filtered through a Buchner funnel loaded

with a pat of silica gel (0.5 kg). The gel was washed with PE/EA (20:1, 15 L). The combined organic solution was concentrated under reduced pressure to afford compound **2** (4.10 kg) as a pale yellow oil, which was used directly in the next step. Data for compound **2**: Physical state: pale yellow oil; R_f = 0.54 (PE/EA = 10:1; PMA); HRMS (*m/z*): calc. for $C_{10}H_{15}O_2$ $[M+H]^+$= 167.1072; found, 167.1071; $[\alpha]_D$= −60.7° (*c* = 1.03, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.78 (s, 1H), 4.71 (s, 1H), 3.43 (d, *J* = 2.6 Hz, 1H), 2.71 (td, *J* = 11.2, 5.3 Hz, 1H), 2.58 (dd, *J* = 17.6, 4.5 Hz, 1H), 2.36 (d, *J* = 14.8 Hz, 1H), 2.02 (dd, *J* = 17.6, 11.6 Hz, 1H), 1.93 – 1.84 (m, 1H), 1.70 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.5, 146.5, 110.6, 61.5, 58.9, 41.9, 35.2, 28.9, 20.7, 15.4.

Synthesis of 3: Compound **2** (4.10 kg) was charged to a 50 L glass reactor. THF (20 L) was added under vacuum, and the mixture was stirred for 10 min before being cooled down to 0-5 °C. After addition of LiCl (0.93 kg, 21.97 mol, 1.10 equiv), trifluoroacetic acid (2.51 kg, 21.97 mol, 1.10 equiv) was added dropwise to the reaction mixture at 0-5 °C. The reaction mixture was stirred at r.t. for 8 h at which point no compound **2** was detected (monitored by TLC). Saturated aqueous $NaHCO_3$ [preparation: $NaHCO_3$ (1.80 kg) dissolved in H_2O (10 L)] was added to neutralize the reaction mixture to pH 7-8. After being stirred for 0.5 h, the THF was removed under reduced pressure at 50 °C. The residual mixture was extracted with EA (3 × 13 L). The combined organic layers were washed with brine (2 × 10 L), dried over anhydrous Na_2SO_4 before being concentrated under reduced pressure to afford compound **3** (4.50 kg) as a pale yellow oil, which was used directly in the next step. Data for compound **3**: Physical state: pale yellow oil; R_f = 0.23 (PE/EA = 10:1; PMA); HRMS (*m/z*): calc. for $C_{10}H_{15}ClNaO_2$ $[M+Na]^+$= 225.0658; found, 225.0654; $[\alpha]_D$= −123.2° (*c* = 1.95, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.84 – 4.81 (m, 1H), 4.79 (s, 1H), 4.29 – 4.24 (m, 1H), 3.04 (t, *J* = 13.4 Hz, 1H), 2.83 (tt, *J* = 12.8, 3.7 Hz, 1H), 2.49 – 2.35 (m, 2H), 1.92

(ddd, J = 14.2, 5.5, 3.5 Hz, 1H), 1.76 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.8, 146.6, 110.8, 77.2, 68.2, 41.3, 39.2, 33.1, 22.2, 20.5.

Synthesis of **4**: Compound **3** (4.50 kg) was charged to a 50 L glass reactor. DCM (12 L) was added under vacuum, and the mixture was stirred for 10 min before being cooled to 10-25 °C. After addition of DMAP (4.39 kg, 35.97 mol, 1.80 equiv), TsCl (5.71 kg, 29.97 mol, 1.50 equiv) dissolved in DCM (12 L) was added dropwise to the reaction mixture at 10-25 °C. After the addition, the mixture was stirred at room temperature for about 12 h at which point no compound **2** was detected (monitored by TLC) and H_2O (15 L) was added to the reaction mixture. The organic layer was separated, washed respectively with aqueous HCl (2-3%, 15 L) and H_2O (15 L). The organic layer was then dried over anhydrous Na_2SO_4, filtered through a Buchner funnel before being concentrated under reduced pressure to provide an orange solid, which was dissolved in MeOH (20 L). The mixture was stirred at 0-5 °C for 8 h and compound **4** crystallized out of the solution. The crystals were then dried under vacuum (50 mmHg) for 5 h. The final product weighted 4.25 kg (59.6% for 3 steps) with 98% HPLC purity and 100%ee. Data for Compound **4**: Physical state: white solid; R_f = 0.54 (PE/EA = 10:1; PMA); HRMS (*m/z*): calc. for $C_{17}H_{22}ClO_4S$ $[M+H]^+$= 357.0927; found, 357.0931; $[\alpha]_D$= −75.2° (*c* = 0.83, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 5.03 (dd, J = 3.0, 2.1 Hz, 1H), 4.79 (s, 1H), 4.69 (s, 1H), 2.97 (t, J = 13.8 Hz, 1H), 2.66 (tt, J = 13.1, 3.4 Hz, 1H), 2.45 (s, 3H), 2.42 – 2.34 (m, 2H), 2.03 (ddd, J = 14.8, 5.5, 3.3 Hz, 1H), 1.65 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.8, 145.62, 145.58, 133.8, 130.2, 127.9, 111.1, 85.3, 65.7, 40.8, 38.8, 31.2, 22.2, 21.8, 20.3.

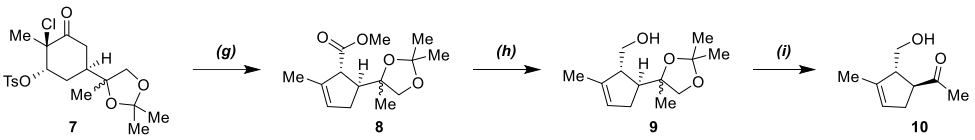


Synthesis of **5**: Compound **4** (4.20 kg, 11.77 mol, 1.00 equiv) was charged to a 50 L glass reactor. DCM (21 L) was added under vacuum, and the mixture was stirred for 10 min before being cooled to 10-25 °C. *m*-CPBA (purity ≥ 85 %, 2.63 kg, 12.95 mol, 1.10 equiv) was added in four equal portions in 30 min intervals. The reaction mixture was stirred at room temperature for 5 h before being cooled to 0 °C. The cold mixture was filtered through a Buchner funnel under reduced pressure, and the filter cake was washed with cold DCM (5 L). The combined filtrate was charged to a 50 L glass reactor. Saturated aqueous $NaHCO_3$ (5 L) was added. The mixture was stirred at room temperature for 30 min. After separation of the organic layer, the aqueous layer was washed with DCM (10 L). The combined organic layers were filtered through a Buchner funnel loaded with a pat of silica gel (0.5 kg) under reduced pressure. The gel was washed with DCM (10 L). The combined organic solution was concentrated under reduced pressure to afford compound **5** (4.60 kg) as a white solid, which was used directly in the next step. Data for compound **5**: Physical state: white solid; R_f = 0.14 (PE/EA = 10:1; PMA); HRMS (*m/z*): calc. for $C_{17}H_{22}ClO_5S$ $[M+H]^+$= 373.0876; found, 373.0867; $[\alpha]_D$= −56.9° (*c* = 0.68, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 7.9 Hz, 2H), 5.05 – 4.99 (m, 1H), 2.86 (td, *J* = 13.9, 9.9 Hz, 1H), 2.63 (d, *J* = 4.4 Hz, 0.5H), 2.54 (d, *J* = 4.4 Hz, 0.5H), 2.53 (s, 1H), 2.45 (s, 3H), 2.44 – 2.27 (m, 2H), 2.16 – 1.96 (m, 2H), 1.45 (s, 3H), 1.25 (s, 1.5H), 1.24 (s, 1.5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.1, 201.0, 145.70, 145.68, 133.6, 133.5, 130.2, 127.94, 127.89, 84.9, 84.8, 65.61, 65.55, 57.65, 57.60, 52.7, 52.6, 37.7, 37.6, 37.6, 37.5, 28.4, 28.0, 22.2, 21.8, 18.6, 18.3.

Synthesis of **7**: Compound **5** (4.61 kg) was charged to a 50 L glass reactor. THF (23 L) was added under vacuum, and the mixture was stirred for 10 min before aqueous H_2SO_4 [98% H_2SO_4 (1.15 kg) dissolved in H_2O (4.6 L)] was added to the reaction mixture. After being stirred for 12 h at room temperature, $NaHCO_3$ (2.1 kg) was added to neutralize the reaction mixture to pH 7-8.

The reaction mixture was stirred at r.t. for 30 min before being filtered through a Buchner funnel under reduced pressure. The filter cake was washed with THF (1 L). The combined filtrates were concentrated under reduced pressure to remove THF. The residual slurry was diluted with EA (10 L) and H_2O (3 L). After being stirred for 10 min, the organic layer was separated, and the aqueous layer was extracted with EA (2 × 5 L). The combined organic layers were washed with brine (5 L), dried over anhydrous Na_2SO_4, and filtered through a Buchner funnel before being concentrated under reduced pressure to provide crude compound **6** (5.10 kg), which was used directly in the next step. The compound **6** (5.10 kg) was charged to a 50 L glass reactor. DCM (15 L) was added under vacuum, and the mixture was stirred for 10 min before p-toluenesulfonic acid monohydrate (0.10 kg, 0.53 mol, 0.044 equiv) and 2,2-Dimethoxypropane (1.49 kg, 14.36 mol, 1.22 equiv) were added. After being stirred for 1 h at room temperature, saturated aqueous $NaHCO_3$ (2 L) was added slowly. The mixture was stirred at room temperature for 30 min and the organic layer was separated, dried over anhydrous Na_2SO_4, filtered through a Buchner funnel before being concentrated under reduced pressure to provide the crude product **7**, which was mixed with MeOH (12 L), and stirred at 0-5 °C for 2 h. The cold mixture was filtered through a Buchner funnel under reduced pressure, and compound **7** was collected, washed with cold MeOH (5 L), and then dried under vacuum (50 mmHg) for 5 h. The final product weighted 3.40 kg (67.1% yield for 3 steps) as a white solid with 96.5% HPLC purity, which was used directly in the next step. Data for compound **7**: Physical state: white solid; R_f = 0.21 (PE/EA = 10:1; PMA); HRMS (*m/z*): calc. for $C_{20}H_{28}ClO_6S$ $[M+H]^+$= 431.1295; found, 431.1288; $[\alpha]_D$= −61.2° (*c* = 1.22, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.73 (m, 2H), 7.39 – 7.32 (m, 2H), 5.07 (s, 0.6H), 5.03 (s, 0.4H), 3.76 (d, *J* = 8.8 Hz, 0.6H), 3.64 (d, *J* = 8.4 Hz, 0.4H), 3.69 – 3.59 (m, 1H), 2.88 (t, *J* = 13.8 Hz, 0.4H), 2.87 (t, *J* = 13.7 Hz, 0.6H), 2.50 (d, *J* = 14.3 Hz, 0.4H), 2.45 (s, 3H), 2.39 – 2.09 (m, 3.2H), 1.87

(d, J = 14.4 Hz, 0.4H), 1.50 (s, 1.2H), 1.48 (s, 1.8H), 1.36 (s, 3H), 1.33 (s, 1.8H), 1.31 (s, 1.2H), 1.21 (s, 1.8), 1.19 (s, 1.2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.0, 201.7, 145.64, 145.56, 133.78, 133.76, 130.23, 130.18, 127.9, 109.89, 109.85, 85.2, 85.1, 81.6, 72.8, 72.6, 65.7, 65.6, 40.2, 40.1, 37.9, 37.2, 27.9, 27.3, 26.9, 26.83, 26.78, 22.5, 22.4, 22.21, 22.19, 21.8.

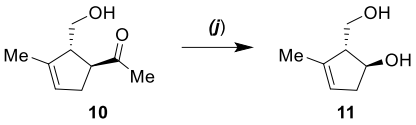


Synthesis of **8**: Compound **7** (3.40 kg, 7.88 mol, 1.00 equiv) was charged to a 100 L glass reactor. MTBE (34 L) and MeOH (6.8 L) were added under vacuum, and the mixture was stirred for 10 min before being cooled to 0-5 °C. MeONa (30% in methanol, 4.55 kg, 25.25 mol, 3.20 equiv) was added dropwise while keeping the temperature below 5°C. After being stirred for about 20 h at room temperature, the reaction temperature was cooled to 5-10 °C. Cold H_2O (17.5 L) was added dropwise to quench the reaction. After separation of the organic layer, the aqueous layer was extracted with MTBE (2 × 10 L). The combined organic layers were washed with brine (2 × 10 L), dried over anhydrous Na_2SO_4 before being concentrated under reduced pressure to afford a crude oil, which was dissolved in PE (8 L), filtered through a Buchner funnel loaded with a pat of silica gel (0.5 kg) under reduced pressure. The gel was washed with PE/EA (25:1, 12 L). The combined organic solution was concentrated under reduced pressure to afford compound **8** (2.08 kg) as a yellow oil, which was used directly in the next step. Data for compound **8**: Physical state: pale yellow oil; R_f = 0.41 (PE/EA = 10:1; PMA); HRMS (*m/z*): calc. for $C_{14}H_{23}O_4$ $[M+H]^+$= 255.1596; found, 255.1597; $[\alpha]_D$= +127.7° (c = 0.69, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 – 5.39 (m, 1H), 3.81 (t, J = 8.7 Hz, 1H), 3.705 (s, 1.8H), 3.700 (s, 1.2H), 3.70 – 3.66 (m, 1H), 3.43 – 3.36 (m, 0.4H), 3.36 – 3.29 (m, 0.6H), 3.00 – 2.88 (m, 1H), 2.60 – 2.44 (m, 1H), 2.22 – 2.06 (m, 1H), 1.67 (s, 1.2H), 1.65 (s, 1.8H), 1.38 (s, 1.8H), 1.37 (s, 1.8H), 1.36 (s, 1.2H), 1.35 (s, 1.2H),

1.26 (s, 1.8H), 1.22 (s, 1.2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 175.5, 137.5, 137.3, 127.5, 127.4, 109.54, 109.47, 82.9, 73.3, 72.3, 56.5, 56.1, 51.93, 51.91, 50.3, 50.2, 34.5, 34.3, 27.2, 27.1, 27.0, 26.9, 24.5, 22.4, 15.31, 15.27.

Synthesis of **10**: THF (18 L) was charged to a 50 L glass reactor. After being cooled to 0 °C, LAH (0.33 kg, 8.67 mol, 1.10 equiv) was added to the solvent under nitrogen. Compound **8** (2.08 kg) dissolved in THF (2 L) was added dropwise to the reaction mixture while keeping the temperature at 5-10 °C. After being stirred at the same temperature for 2 h, saturated aqueous Na_2SO_4 (1.32 L) was added slowly to quench the reaction. The reaction mixture was stirred at room temperature for 30 min, and filtered through a Buchner funnel under reduced pressure. The filter cake was washed with THF (3 × 6 L). The combined organic solution was concentrated under reduced pressure to ~ 18 L residual volume. The residual solution (of compound **9**) was charged to a 50 L glass reactor and $H_2SO_{4(aq)}$ (20%, 3.86 L, 7.88 mol, 1.00 equiv) was added to the reaction mixture, which was stirred at the room temperature for about 5 h at which time no compound **9** was detected (monitored by TLC). The reaction mixture was then diluted with H_2O (15 L). $NaHCO_3$ (1.3 – 1.5 kg) was slowly added to neutralize the reaction mixture to pH 7-8. Then $NaIO_4$ (1.68 kg, 7.88 mol, 1.00 equiv) was added in small portions. After the addition was complete, the mixture was stirred for 2 h before it was filtered through a Buchner funnel under reduced pressure. The filter cake was washed with THF (3 × 1 L). The combined filtrates were charge to a 50 L glass reactor. Anhydrous sodium sulfite (1.49 kg, 1.50 equiv) was added to the combined filtrates. After being stirred for 0.5 h, no more peroxide was detected (monitored by KI-starch paper). The mixture was concentrated under reduced pressure to remove THF. The residual mixture was extracted with EA (3 × 10 L). The combined organic layers were washed with brine (10 L), dried over anhydrous Na_2SO_4 for 4 h, and then filtered through a Buchner funnel loaded with a pat of silica gel (0.5 kg)

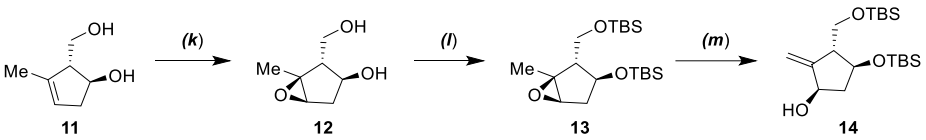
before being concentrated under reduced pressure to give compound **10** (1.12 kg, 92% yield for 3 steps) as a pale yellow oil. Data for compound **10**: Physical state: pale yellow oil; R_f = 0.57 (PE/EA = 1:1; PMA); HRMS (*m/z*): calc. for $C_9H_{15}O_2$ $[M+H]^+$ = 155.1072; found, 155.1078; $[\alpha]_D$ = +105.7° (*c* = 1.42, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (s, 1H), 3.80 – 3.71 (m, 1H), 3.65 – 3.57 (m, 1H), 3.18 (dt, *J* = 9.7, 6.2 Hz, 1H), 2.98 (s, 1H), 2.62 (ddd, *J* = 11.7, 10.8, 1.8 Hz, 1H), 2.50 – 2.39 (m, 1H), 2.19 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.4, 138.3, 124.8, 63.9, 54.4, 52.5, 34.3, 28.4, 14.7.



10 **11**

Synthesis of **11**: Compound **10** (1.12 kg, 7.26 mol, 1.00 equiv) and MeOH (40 L) were charged to a 100 L glass reactor fitted with a condenser. After being stirred for 5 min, H_2O_2 (30%wt, 1.86 kg, 16.41 mol, 2.26 equiv) was slowly added during 0.5 h. After being warmed to 60 °C, $NaOH_{(aq)}$ (2.50 mol/L, 2.53 L, 6.25 mol, 0.86 equiv) was added dropwise during 1.5 h. The reaction mixture was stirred at 65 to 70 °C for 0.5 h. The addition of H_2O_2 (30%wt) and $NaOH_{(aq)}$ was repeated for 3 times at which point no compound **10** was detected (monitored by TLC). The reaction mixture was stirred at 65 to 70 °C for 1 h before being cooled down to room temperature. The reaction mixture was extracted with EA (10 × 40 L). The combined organic layers were dried over anhydrous Na_2SO_4, and then filtered through a Buchner funnel. To the filtrate was added PPh_3 (0.70 kg) and it was stirred at room temperature for 2 h, before being concentrated under reduced pressure to give a crude oil. Purification of this crude product using flash column chromatography (silica gel, PE/EA = 10:1 to 1:2) afforded compound **11** (0.42 kg, 45% yield) as a pale yellow solid. Data for compound **11**: Physical state: pale yellow solid; R_f = 0.19 (PE/EA = 1:1; PMA); HRMS (*m/z*): calc. for $C_7H_{13}O_2$ $[M+H]^+$ = 129.0916; found, 129.0907; $[\alpha]_D$ = +98.1° (*c* = 2.63,

MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 – 5.32 (m, 1H), 4.38 (dt, *J* = 7.1, 3.7 Hz, 1H), 3.84 (dd, *J* = 10.7, 3.9 Hz, 1H), 3.50 (dd, *J* = 10.7, 7.6 Hz, 1H), 2.83 (brs, 2H), 2.69 – 2.59 (m, 1H), 2.59 – 2.51 (m, 1H), 2.26 – 2.14 (m, 1H), 1.69 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.6, 124.5, 76.6, 63.2, 59.8, 41.1, 15.3.



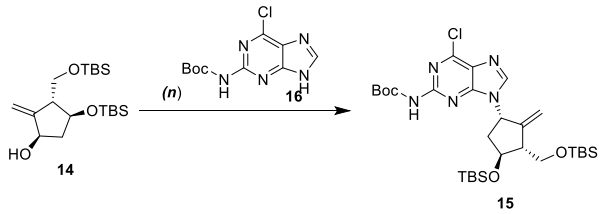
11 12 13 14

Synthesis of **12**: Compound **11** (0.42 kg, 3.28 mol, 1.00 equiv) was charged to a 10 L glass reactor. DCM (4.2 L) was added, and the mixture was stirred for 10 min before being cooled to 0 ± 5 °C. After addition of $VO(acac)_2$ (40g, 0.15 mol, 0.046 equiv), TBHP (in 0.8 L DCM) was added dropwise. [Preparation of TBHP solution (in DCM, 0.8 L): TBHP (70wt% in water, 0.52 kg, 4.00 mol, 1.22 equiv) was extracted with DCM (0.8 L), and the DCM layer was dried over anhydrous $MgSO_4$, filtered through a Buchner funnel]. The reaction mixture was stirred at 0 ± 5 °C for about 7 h at which point no compound **11** was detected (monitored by TLC). Na_2SO_3 (0.3 kg) was added to quench the excessive peroxide. After being stirred for about 3 h, the reaction mixture was filtered through a Buchner funnel loaded with a pat of silica gel (0.2 kg) under reduced pressure. The gel was washed with EA (5 L). The combined organic solution was concentrated under reduced pressure to afford compound **12** (0.45 kg) as a yellow oil, which was used directly in the next step. Data for compound **12**: Physical state: pale yellow oil; R_f = 0.11 (PE/EA = 1:1; PMA); HRMS (*m/z*): calc. for $C_7H_{13}O_3$ $[M+H]^+$= 145.0865; found, 145.0873; $[\alpha]_D$= +38.9° (*c* = 1.81, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00 (dd, *J* = 11.6, 6.0 Hz, 1H), 3.76 (d, *J* = 10.6 Hz, 1H), 3.58 – 3.51 (m, 1H), 3.45 (s, 1H), 2.57 (d, *J* = 11.8 Hz, 1H), 2.17 – 2.11 (m, 2H), 2.00 (d, *J* = 15.2 Hz, 1H), 1.48 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 74.0, 66.2, 64.3, 61.6, 54.8, 37.6, 15.6.

Synthesis of **13**: A 10 L glass reactor was charged with compound **12** (0.45 kg), DMF (4 L), imidazole (0.49 kg, 7.21 mol, 2.20 equiv), and DMAP (40 g, 0.33 mol, 0.10 equiv). After being cooled to 10-15 °C, TBSCl (1.04 kg, 6.88mol, 2.10 equiv) was added in equal four portions in 20 min intervals. The reaction mixture was stirred at room temperature for about 12 h at which time no compound **12** was detected (monitored by TLC). The reaction mixture was transferred into a 50 L glass reactor and then MTBE (8 L) and H_2O (8 L) were added. After being stirred for 5 min, the two phases were separated. The organic layers were washed with brine (3 × 5 L), dried over anhydrous Na_2SO_4, and filtered through a Buchner funnel before being concentrated under reduced pressure to give a crude oil which was then dissolved in PE (4 L). The organic solution was filtered through a Buchner funnel loaded with a pat of silica gel (1.0 kg). The gel was washed with PE/EA (150:1, 4 L). The combined organic solution was concentrated under reduced pressure to afford crude oil **13**. Purification of this crude product using flash column chromatography (silica gel, PE/EA = 100%PE to 100:1) afforded pure compound **13** (0.98 kg) as a pale yellow oil. Data for compound **13**: Physical state: pale yellow oil; R_f = 0.69 (PE/EA = 10:1; PMA); HRMS (*m/z*): calc. for $C_{19}H_{41}O_3Si_2$ $[M+H]^+$= 373.2594; found, 373.2585; $[\alpha]_D$= +31.5° (*c* = 1.31, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27 (d, *J* = 7.6 Hz, 1H), 3.68 (d, *J* = 3.6 Hz, 2H), 3.25 (s, 1H), 2.10 (ddd, *J* = 14.6, 7.6, 1.4 Hz, 1H), 2.02 (s, 1H), 1.83 (d, *J* = 14.6 Hz, 1H), 1.41 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.050 (s, 3H), 0.054 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 76.5, 66.0, 64.8, 62.6, 55.3, 39.0, 26.0, 25.8, 18.2, 18.1, 16.1, -4.4, -4.5, -5.6, -5.7.

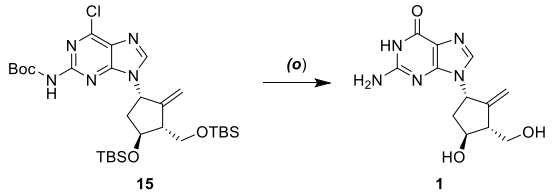
Synthesis of **14**: 2,2,6,6-Tetramethylpiperidine (0.48 kg, 3.42 mol, 1.30 equiv) was charged to a 20 L glass reactor. Toluene (8 L) was added, and the mixture was stirred for 10 min before being cooled to −10 to −5 °C. *n*-BuLi (2.5 mol/L in hexane, 1.37 L, 3.42 mol, 1.30 equiv) was added dropwise while the temperature was maintained below 0 °C. After the addition of n-BuLi, the

reaction mixture was stirred at the same temperature for 1 h before Et_2AlCl (2.0 mol/L in hexane, 1.71 L, 3.42 mol, 1.30 equiv) was added dropwise at the same temperature. After the addition of Et_2AlCl solution, the reaction mixture was stirred at the same temperature for 1.5 h. Compound **13** (0.98 kg, 2.63 mol, 1.00 equiv) dissolved in toluene (2 L) was added dropwise in about 2 h. The reaction mixture was then stirred at −5 to 0 °C for about 3 h at which time no compound **12** was detected (monitored by TLC). The reaction was quenched by slow addition of saturated Rochelle salt (600 mL). The reaction mixture was stirred at room temperature for 1 h before being filtered through a Buchner funnel. The filter cake was washed with EA (5 L), and the combined filtrates were washed with H_2O (3 × 3 L). The combined organic solution was concentrated under reduced pressure to afford a crude oil. Purification of this crude product using flash column chromatography (silica gel, PE/EA = 100%PE to 25:1) afforded a pale yellow solid compound **14** (0.91 kg, 74.5% for 3 steps) with 100%ee. Data for compound **14**: Physical state: pale yellow solid; R_f = 0.43 (PE/EA = 10:1; PMA); HRMS (*m/z*): calc. for $C_{19}H_{41}O_3Si_2$ $[M+H]^+$= 373.2594; found, 373.2585; $[\alpha]_D$= −51.9° (*c* = 1.07, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (s, 1H), 5.13 (s, 1H), 4.38 – 4.30 (m, 2H), 3.57 (dd, *J* = 10.2, 5.1 Hz, 1H), 3.32 (t, *J* = 9.3 Hz, 1H), 2.88 (d, *J* = 10.5 Hz, 1H), 2.80 – 2.71 (m, 1H), 1.99 (dt, *J* = 13.5, 4.9 Hz, 1H), 1.82 (d, *J* = 13.6 Hz, 1H), 0.89 (s, 18H), 0.09 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.6, 111.8, 75.7, 75.5, 64.9, 55.2, 42.3, 26.1, 26.0, 18.5, 18.1, -4.6, -4.7, -5.3, -5.4.



Synthesis of **15**: A 20 L glass reactor was charged with compound **14** (0.91 kg, 2.44 mol, 1.00 equiv), compound **16** (0.69 kg, 2.56 mol, 1.05 equiv), PPh_3 (0.96 kg, 3.66 mol, 1.50 equiv), and

dry THF (9 L). The mixture was stirred for 10 min before being cooled to 0 to 5 °C. DIAD (0.72 kg, 3.59 mol, 1.47 equiv) was added dropwise while keeping the temperature below 5 °C. The reaction mixture was stirred at 0 to 5 °C for about 3 h at which point no compound **14** was detected (monitored by TLC). The reaction mixture was concentrated under reduced pressure. The residual slurry was dissolved in EA (0.5 L) and PE (5 L). The mixture was stirred at r.t. for about 5 h to remove the solid impurities. After filtration through a Buchner funnel, the filter cake was washed with PE/EA (10:1, 2 L). The combined filtrates were concentrated under reduced pressure to afford a crude slurry. Purification of this crude slurry using flash column chromatography (silica gel, PE/EA = 10:1) afforded compound **15** (1.25kg, 82% yield) as a yellow solid. Data for compound **15**: Physical state: pale yellow solid; R_f = 0.1 (PE/EA = 10:1; PMA); HRMS (*m/z*): calc. for C29H50ClN5NaO4Si2 $[M+Na]^+$= 646.2988; found, 646.2988; $[\alpha]_D$= +26.3° (*c* = 1.07, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.41 (s, 1H), 5.65 (t, *J* = 8.1 Hz, 1H), 5.23 (s, 1H), 4.83 (s, 1H), 4.46 (d, *J* = 3.4 Hz, 1H), 3.83 (s, 1H), 3.82 (s, 1H), 2.67 (s, 1H), 2.40 – 2.31 (m, 1H), 2.28 – 2.19 (m, 1H), 2.04 (brs, 1H)1.54 (s, 9H), 0.93 (s, 9H), 0.91 (s, 9H), 0.11 (s, 6H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9, 152.2, 151.1, 150.1, 148.8, 143.8, 127.7, 111.8, 81.6, 72.3, 63.9, 56.9, 54.8, 40.6, 28.2, 26.0, 25.8, 18.5, 18.0, -4.60, -4.7, -5.35, -5.42.



15 1

Synthesis of **1**: Compound **15** (1.25 kg, 2.00 mol, 1.00 equiv) and THF (7 L) were charged to a 20 L glass reactor. The $HCl_{(aq)}$ (3 mol/L, 7 L, 21.02 mol, 10.50 equiv) was slowly added at room temperature. The reaction mixture was stirred at room temperature for 1 h before being warmed to 55 °C. After being stirred at the same temperature for 10 h, the mixture was concentrated under

reduced pressure to remove THF. The residual aqueous layer was extracted with EA (2 × 3.5 L). After being cooled to 5-10 °C, the aqueous layer was neutralized with $NaOH_{(aq)}$ (6 mol/L) to pH 7-7.5. The product crystallized out from the stirred solution at 5 to 10 °C after 5 h. After filtration, the solid was washed with cold H_2O (1.5 L) follow by cold 95% EtOH (0.5 L). The combined filtrates were concentrated under reduced pressure to a residual volume of ~4 L, and more product (compound **1**) crystallized out from the stirred solution at 5 to 10 °C after 10 h. After filtration, the crop was washed with cold H_2O (0.8 L) followed by cold 95% EtOH (0.2 L). The combined solid (compound **1**) was dried under vacuum (50 mmHg) at 45 °C for 5 h. The final weight of **1** was 0.53 kg (90%yield, 98 % HPLC purity). This product was recrystallized from deionized water to furnish entecavir **1** (monohydrate) [total impurities (HPLC) < 0.3%, any single impurity (HPLC) < 0.1%, optical purity (HPLC) 100% ee, 73% yield]. Data for compound **1**: Physical state: white crystalline solid; HRMS (*m/z*): calc. for $C_{12}H_{16}N_5O_3$ $[M+H]^+$= 278.1253; found, 278.1255; $[\alpha]_D$= +27.2° [*c* = 1.07, DMF/H_2O (1:1)]; ^{1}H NMR (500 MHz, DMSO) δ 10.55 (s, 1H), 7.65 (s, 1H), 6.40 (s, 2H), 5.36 (dd, *J* = 10.3, 8.0 Hz, 1H), 5.10 (s, 1H), 4.85 (d, *J* = 3.1 Hz, 1H), 4.81 (t, *J* = 5.3 Hz, 1H), 4.56 (s, 1H), 4.23 (s, 1H), 3.54 (t, *J* = 6.1 Hz, 2H), 2.55 – 2.50 (m, 1H), 2.26 – 2.17 (m, 1H), 2.04 (dd, *J* = 12.5, 7.8 Hz, 1H); ^{13}C NMR (126 MHz, DMSO) δ 156.8, 153.4, 151.4, 151.3, 135.9, 116.2, 109.2, 70.4, 63.0, 55.1, 54.1, 39.2.

ASSOCIATED CONTENT

Supporting Information

^{1}H NMR, ^{13}C NMR, HPLC analysis, X-ray

AUTHOR INFORMATION

Corresponding Author

*jinyehua@launch-pharma.com

*qiufayang@launch-pharma.com

Author Contributions

‡These authors contributed equally.

Funding Sources

This work was supported by Launch-Pharma Technologies, Ltd.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

The authors thank Prof. Zhi Li (ShanghaiTech University, China) for helpful discussions and assistance in the preparation of the manuscript.

REFERENCES

(1) (a) 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*, 127−132 .(b) Innaimo, S. F.; Seifer, M.; Bisacchi, G. S.; Standring, D. N.; Zahler, R.; Colonno, R. J. *Antimicrob. Agents Chemother*. **1997**, *41*, 1444−1448. (c) Zahler, R.; Slusarchyk, W. A. Eur. Pat. EP0481754 B1, August 20, 1997. (d) Bisacchi, G. S.; Sundeen, J. E. WO 9809964 A1, August 26, 1997.

(2) (a) Pendri, Y. R.; Chen, C. H.; Patel, S. S.; Evans, J. M.; Liang, J.; Kronenthal, D. R.; Powers, G. L.; Prasad, S. J.; Bien, J. T.; Shi, Z.; Patel, R. N.; Chan, Y. Y.; Rijhwani, S. K.; Singh, A. K.; Wang, S.; Stojanovic, M.; Polniaszek, R.; Lewis, C.; Thottathil, J.; Krishnamurty, D.; Zhou, M. X.; Vemishetti, P. WO2004052310, A3, December 10, 2003. (b) Zhou, M. X.; Reiff, E. A.; Vemishetti, P.; Pendri, Y. R.; Singh, A. K.; Prasad, S. J.; Dhokte, U. P.; Qian, X.; Mountford, P.; Hartung, K. B.; Sailes, H. WO2005118585, A1, December 15, 2005. (c) Zhou, B.; Li, Y.; *Tetrahedron Lett*. **2012**, *53*, 502–504. (d) Liu, X.; Jiao, X.; Wu, Q.; Tian, C.; Li, R.; Xie, P. *Tetrahedron Lett*. **2012**, *53*, 3805–3807; (e) Velasco, J.; Ariza, X.; Badía, L.; Bartra, M.; Berenguer, R.; Farràs, J.; Gallardo, J.; Garcia, J.; Gasanz, Y. *J. Org. Chem*. **2013**, *78*, 5482–5491. (f) Hyun, Y. E.; Kim, H.-R.; Choi, Y.; Jeong, L. S.; *Asian J. Org. Chem*. **2017**, *6*, 1213–1218.

(3) During the final stage of manuscript preparation and submission, a scale-up route of entecavir is published: Wang, S.-C.; Zhang, X.-Q.; Gu, H.-M.; Zhu, X.-Y.; Guo, Y.-J. *Org. Prep. Proc. Int.*, **2017**, *49*, 568–574.

(4) (a) Lee, E.; Yoon, C. H. *J. Chem. Soc. Chem. Commun*. **1994**, 479–481. (b) Oliver, S. F.; Hçgenauer, K.; Simic, O.; Antonello, A.; Smith, M. D.; Ley, S. V. *Angew. Chem*. **2003**, *115*, 6178–6182; *Angew. Chem. Int. Ed*. **2003**, *42*, 5996–6000. (c) Andrews, S. P.; Ball, M.; Wierschem, F.; Cleator, E.; Oliver, S.; Hegenauer, K.; Simic, O.; Antonello, A.; Hinger, U.; Smith, M. D.; Ley, S. V. *Chem. Eur. J*. **2007**, *13*, 5688–5712. (d) Jin, Y.; Qiu, F. G. *Org. Biomol. Chem*. **2012**, *10*, 5452–5455. (e) Liu, Y.; Zhao, G. *Chin. J. Chem.* **2013**, *31*, 18–22.

(5) Grieco, P. A.; Vedananda, T. R. *J. Org. Chem*. **1983**, *48*, 3497–3502.

(6) (a) Chong, A. O.; Sharpless, K. B. *J. Org. Chem.* **1977**, *42*, 1587–1590. (b) Li, Z.; Yamamoto, H. *Acc. Chem. Res.*, **2013**, *46*, 506–518. (c) Yuan, C.; Jin, Y.; Wilde, N. C.; Baran, P. S. *Angew. Chem. Int. Ed.*, **2016**, *55*, 8280–8284.

(7) Preparation of **16**: Dey, S., Garner, P. *J. Org. Chem.* **2000**, *65*, 7697–7699.