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Synthesis of racemic Entecavir

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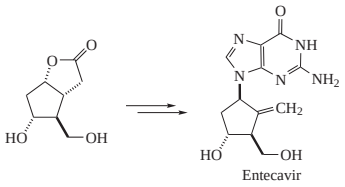
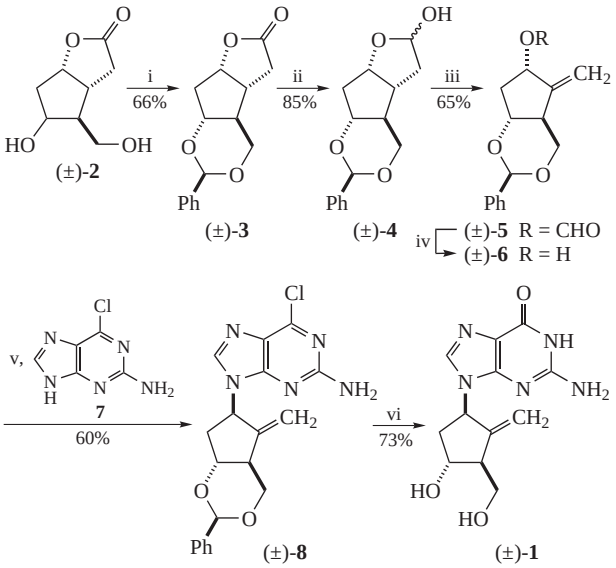
Racemic Entecavir was prepared from Corey lactone diol benzylidene acetal in four steps in 24% overall yield.



Hepatitis B is one of global problems of public health service. About a third of inhabitants of the planet are infected by a hepatitis B virus (HBV). According to the data of 2014, ~240 million of diseased persons are in dangerous phase of chronic hepatitis, and lethal complications in this category of people are higher than 0.8 million a year because of subsequent development of dangerous diseases such as cirrhosis and liver carcinoma.

Carbanucleoside Entecavir **1** (BMS-200475) is an acting substance of 'Baraclude' drug,[2] and it is the most effective in HBV therapy. Entecavir is the most selective against HBV, it suppresses HBV on a nanomolar level (ED_{50} = 3 nM), does not show marked side effects, and is convenient in the use.[3] The published syntheses of (+)-Entecavir **1** and intermediates are performed in an asymmetric version and aimed at preparation of more active enantiomerically pure product.[4] At the same time, evidence is absent on synthesis of racemic Entecavir, and the present article is devoted to this purpose.

(±)-Entecavir was prepared from racemic Corey lactone diol **2**.[5] Hydroxy groups of lactone **2** were protected with benzylidene acetal protecting group.† Lactone **3** was reduced with Bu^iAlH to lactol **4** which was converted by oxidative decarbonylation using $Pb(OAc)_4$–$Cu(OAc)_2$[6] to *exo*-methylidenecyclopentanone **5**. It is of note that short synthesis of new tris-TBS derivative of *exo*-methylidenecyclopentanetriol from Corey lactone diol was previously described by us.[7] A formate protecting group of **5** was removed by treatment with aqueous NH_4OH under mild conditions. Allylic alcohol **6** obtained was introduced into the key stage of the Mitzunobu coupling with chloropurine **7**. In the final step block **8** was exhaustively hydrolyzed by keeping in 80% HCOOH at 80 °C followed by aqueous treatment and purification on SiO_2. Thus, product (±)-**1** (mp 228–230 °C) was isolated as a white crystalline powder (Scheme 1).



Scheme 1 *Reagents and conditions*: i, $PhCH(OMe)_2$, C_6H_6, TsOH (cat.), Δ; ii, Bu^i_2AlH, –78 °C, CH_2Cl_2; iii, $Pb(OAc)_4$–$Cu(OAc)_2$, C_6H_6, Δ; iv, aq. NH_4OH; v, DIAD, PPh_3, THF; vi, 80% HCO_2H, 80 °C.

† IR spectra were recorded in a film or in Nujol using a Shimadzu IRPrestige-21 spectrophotometer. The ^1H and ^{13}C NMR spectra were measured on Bruker AM-300 (300.13 and 75.47 MHz, respectively) and Bruker Avance-500 instruments (500.13 and 125.77 MHz). The mass spectra (positive electrospray ionization) were obtained on a Shimadzu LCMS-2010EV instrument. The progress of the reactions was monitored by 'Sorbfil' TLC method. The final reaction mixtures were extracted with EtOAc. The extract was washed with brine and dried with Na_2SO_4, then evaporated and chromatographed on silica gel.

*(2*R*,4a*S*,4b*R*,7a*S*,8a*R*)-2-Phenylhexahydrofuro[3',2':3,4]cyclopenta[1,2-*d*][1,3]dioxin-6(4*H*)-one* **3**. White crystals, mp 176–178 °C. IR (ν/cm^{-1}): 692, 740, 953, 1098, 1167, 1376, 1460, 1703, 2800–3000. ^1H NMR (300 MHz, CD_3OD) δ: 1.83–2.05 (m, 2H), 2.35–2.50 (m, 2H), 2.68–2.82 (m, 2H), 3.63 (dt, 1H, H^{8a}, *J* 7.1, 11.4 Hz), 3.80 (t, 1H, H^4, *J* 10.7 Hz), 4.45 (dd, 1H, H^4, *J* 4.3, 10.7 Hz), 4.93 (dt, 1H, H^{7a}, *J* 4.4, 7.2 Hz), 5.50 (s, 1H, H^2, *J* 2.1 Hz), 7.35 (m, 3H, Ph), 7.50 (m, 2H, Ph). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 32.28 (C^5), 36.44 (C^8), 36.81 (C^{4b}), 45.19 (C^{4a}), 70.80 (C^4), 80.06, 80.34 (C^{7a}, C^{8a}), 126.07, 128.19, 129.00, 137.39 (Ph), 175.91 (C^6). MS (ESI), *m*/*z* (%): 261 $[M+H]^+$ (100).

*(2*R*,4a*S*,4b*R*,7a*S*,8a*R*)-2-Phenyloctahydrofuro[3',2':3,4]cyclopenta[1,2-*d*][1,3]dioxin-6-ol* **4**. White crystals, mp 127–130 °C. IR (ν/cm^{-1}): 696, 985, 1360, 1440, 2800–3030, 3395. MS (ESI), *m*/*z* (%): 263 $[M+H]^+$ (13), 245 $[M+H-H_2O]^+$ (53), 115 (100).

*(2*R*,4a*S*,6*S*,7a*R*)-5-Methylidene-2-phenylhexahydrocyclopenta-[d][1,3]dioxin-6-yl formate* **5**.Viscous oil. ^1H NMR (300 MHz, CD_3OD) δ: 1.90 (dt, 1H, H^7, *J* 6.5, 11.9 Hz), 2.70–2.80 (m, 2H), 3.50 (dt, 1H, H^{7a}, *J* 6.6, 11.0 Hz), 3.86 (t, 1H, H^4, *J* 10.6 Hz), 4.60 (dd, 1H, H^4, *J* 4.2, 10.6 Hz), 4.95 (s, 1H, $=CH_2$), 5.30 (s, $=CH_2$), 6.50 (s, 1H, H^2), 5.70 (m, 1H, H^6), 7.30 (m, 3H, Ph), 7.50 (m, 2H, Ph), 8.10 (s, 1H, CHO). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 35.98 (C^7), 45.20 (C^{4a}), 70.14 (C^4), 71.62 (C^{7a}), 78.98 (C^6), 102.23 (C^1), 113.18 ($=CH_2$), 126.27, 128.39, 129.14, 137.71 (Ph), 144.51 (C^5), 160.70 (CHO).

Note that the synthetic routes to Entecavir from Corey lactone diol close to the aforementioned methods were described in the patent literature,[8] in particular, the formation of *exo*-methylidene double bond of lactone **3** fragment, *i.e.*, the **3** → **6** conversion, was carried out in 6 steps with moderate yields in every step.

According to published data,[4(c)] the melting point of (+)-Entecavir monohydrate recrystallized from water was 248 °C, whereas the substance that we obtained has mp 228–230 °C. According to the thermographic analysis data (differential scanning calorimetry) on the (+)-Entecavir samples recrystallized from water the loss of 6 wt% at 75–80 °C indicates Entecavir crystallized with water in 1 : 1 molar ratio.[9] The strong sharp-pointed endothermic peak at 244 °C without weight loss corresponds to the approximate melting point of anhydrous Entecavir.[9(a)] Evidently, the reported[4(c)] melting point of 248 °C refers to anhydrous sample. One could suppose that in our case the melting point of 228–230 °C corresponds to anhydrous form of racemic Entecavir. In the purification step a contact of the product with water is excluded because it is purified by column chromatography on SiO_2, recrystallized from anhydrous DMSO and dried in vacuum (20–30 °C at 2 Torr) for 5 h. It is known that physicochemical properties of racemic and enantiomerically pure compounds can differ in solubility, melting point, hygroscopicity and even spectral data.[10] Polymorphism or differences in crystal forms can affect the drug bioavailability.[9(b)] Differences in skin permeability of racemate and enantiomer of Ibuprofen are reported.[11] Unlike enantiomer, the racemate bioactivity is not the simple sum of activities of individual enantiomers (synergism or 'compensation' effects). These circumstances have stimulated synthesis of (±)-Entecavir, which we realized.

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*(2*R**,4a*S**,6*S**,7a*R**)-5-Methylidene-2-phenylhexahydrocyclopenta-[*d*][1,3]dioxin-6-ol* **6**. White crystals, mp 122–126 °C. IR (ν/cm^{-1}): 697, 751, 1026, 1118, 1452, 1463, 1664, 2900–3000, 3301, 3373. ^{1}H NMR (CD_3OD) δ: 1.70 (dt, 1H, H^7, *J* 7.3, 10.6 Hz), 2.55 (dt, 1H, H^7, *J* 6.7, 10.6 Hz), 2.65 (m, 1H, H^{4a}), 3.50 (dt, 1H, H^{7a}, *J* 7.3, 10.6 Hz), 3.87 (t, 1H, H^4, *J* 10.4 Hz), 4.43 (dt, 1H, H^{7a}, *J* 2.0, 7.3 Hz), 4.53 (dd, 1H, H^4, *J* 4.2, 10.6 Hz), 4.95 (t, 1H, =CH_2, *J* 2.0 Hz), 5.20 (t, 1H, =CH_2, *J* 2.0 Hz), 7.30 (m, 3H, Ph), 7.50 (m, 2H, Ph). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 38.91 (C^7), 45.12 (C^{4a}), 70.38 (C^4), 70.95 (C^6), 79.01 (C^{7a}), 102.25 (C^2), 110.16 (=CH_2), 126.28, 128.37, 129.80, 137.60 (Ph), 149.36 (C^5). ^{13}C NMR (300 MHz, CD_3OD) δ: 39.70 (C^7), 46.80 (C^{4a}), 71.45 (C^4, C^6), 80.20 (C^{7a}), 103.39 (C^2), 110.27 (=CH_2), 127.51, 129.12, 129.90, 139.73 (Ph), 150.84 (C^5). MS (ESI), *m*/*z* (%): 233 $[M+H]^+$ (25), 129 (100).

*6-Chloro-9-[(2*R**,4a*S**,6*R**,7a*R**)-5-methylidene-2-phenylhexahydro-cyclopenta[*d*][1,3]dioxin-6-yl]-9*H*-purin-2-amine* **8**. White crystals, mp 203–205 °C. IR (ν/cm^{-1}): 786, 907, 968, 1091, 1176, 1211, 1377, 1479, 1522, 1560, 1616, 1644, 2854, 2924, 3201, 3317. ^{1}H NMR ($CDCl_3$) δ: 2.25 (ddd, 1H, H^7, *J* 1.5, 7.2, 12.8 Hz), 2.37 (td, 1H, H^7, *J* 11.0, 12.8 Hz), 2.56 (td, 1H, H^{4a}, *J* 1.5, 10.5 Hz), 4.00 (t, 1H, H^4, *J* 10.5 Hz), 4.50 (t, 1H, =CH_2, *J* 2.5 Hz), 4.50–4.58 (m, 2H, H^4, H^{7a}), 4.88 (t, 1H, =CH_2, *J* 2.5 Hz), 5.48 (d, 1H, H^6, *J* 10.4 Hz), 5.73 (s, 1H, H^2), 6.93 (s, 2H, NH_2), 7.35 (m, 3H, Ph), 7.43 (m, 2H, Ph), 8.15 (s, 1H, H^7_{purine}). ^{13}C NMR ($CDCl_3$) δ: 35.77 (C^7), 45.94 (C^{4a}), 53.02 (C^6), 69.81 (C^4), 79.70 (C^{7a}), 101.53 (C^2), 108.63 (=CH_2), 123.85 (C^5_{purine}), 126.69, 128.54, 129.93, 138.60 (Ph), 143.13 (C^6_{purine}), 146.72 (C^4_{purine}) 149.92 (C^5), 154.11 (C^8_{purine}), 160.02 (C^2_{purine}). MS (ESI), *m*/*z* (%): 384 $[M+H]^+$ (50), 425 $[M+H+MeCN]^+$ (50), 129 (100).

*2-Amino-9-[(1*R**,3*S**,4*R**)-4-hydroxy-3-hydroxymethyl-2-methylidene-cyclopentyl]-1,9-dihydro-6*H*-purin-6-one* **1**. White crystals, mp 228–230 °C. IR (ν/cm^{-1}): 3311, 3116, 1687, 1683. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.05 (dd, 1H, H^7, *J* 7.7, 12.1 Hz), 2.25 (td, 1H, H^7, *J* 4.2, 12.1 Hz), 2.50 (br. s, 1H, H^3), 3.52 (m, 2H, CH_2OH), 4.23 (s, 1H, H^4), 4.50 (s, 1H, =CH_2), 4.90 (br., 2H, 2OH), 5.10 (s, 1H, =CH_2), 5.35 (t, 1H, H^1, *J* 8.7 Hz), 6.60 (br. s, 2H, NH_2), 7.65 (s, 1H, H^8_{purine}), 10.80 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 500 MHz) δ: 39.22, 54.10, 55.31, 63.09, 70.52, 109.49, 116.17, 136.32, 151.32, 151.90, 153.78, 157.06. MS (ESI), *m*/*z* (%): 278 $[M+H]^+$ (100).