Supporting Information

for

A new formal synthetic route to Entecavir

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General Information

All air and water sensitive reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. All the chemicals were purchased commercially and used without further purification. Anhydrous THF was distilled from sodium-benzophenone, and dichloromethane was distilled from calcium hydride. Yields refer to chromatographically, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (60F-254) that were analyzed by staining with phosphomolybdic acid hydrate (100 mL 95% EtOH of 10 g H₃MoO₁₂O₄P). Silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. NMR spectra were recorded on a Bruker Avance 400 MHz instrument (¹H: 400 MHz, ¹³C: 100 MHz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, dd = doublet of doublets. High resolution mass spectra were obtained from a MALDI-TOF mass spectrometer.

2-Hydroxymethyl-2-cyclopenten-1-one (5)

To a solution of 2-cyclopenten-1-one 6 (10 g, 121.8 mmol) in CHCl₃ (60 mL) and MeOH (40 mL) was added 37% formaldehyde in water (11.9 mL, 146.2 mmol) at room temperature. A solution of tributyl phosphate (1.5 mL, 6.09 mmol) in CHCl₃ (5 mL) was then added to the reaction mixture and the resultant mixture was stirred at room temperature for 2 h. After that, the mixture was quenched by the addition of water (20 mL). The layers were separated and the aqueous phase was extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. Silica gel flash column chromatography (hexanes/ethyl acetate = 2:1) of the residue gave a white solid (5, 13.2 g, 118.1 mmol, 97%) as the product[1].

(1S,5S)-1-(Hydroxymethyl)-6-oxabicyclo[3.1.0]hexan-2-one (7)

To a stirred suspension of pulverized 4 Å molecular sieves (4.5 g) in anhydrous DCM (384 mL) at -25°C was added dropwise L-(p)-disopropyl tartrate (25.3 mL, 120.4 mmol) dissolved in anhydrous DCM (30 mL). Then Ti(Oi-Pr)₄ (35.6 mL, 120.4 mmol) was added. After 15 min later, a solution of 5 (9 g, 80.3 mmol) in anhydrous DCM (40 mL) was added to the mixture. Subsequently, a solution of TBHP (5.50 M in decane, 43.8 mL, 240.8 mmol) was added dropwise. The mixture was stirred for another 90 h and quenched by 10% aqueous tartaric acid (30 mL). The resultant mixture was filtered and the filtrate was extracted with DCM (3 × 200 mL). The extract was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by silica gel column chromatography (Petroleum ether/Ethyl acetate = 3:1) and compound 7 (8.9 g, 69.9 mmol, 87%, er = 8:1) was obtained as a yellowish oil[1].

¹H NMR (400 MHz, CDCl₃): δ 1.93-2.03 (m, 1H), 2.09 (dd, J = 17.8, 9.4 Hz, 1H), 2.17-2.31 (m, 2H), 2.30 (t, J = 5.6 Hz, 1H), 3.87-3.90 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 22.4, 32.2, 56.5, 62.6, 63.4, 211.1; HRMS (ESI): m/z calcd. for C₈H₁₄O₃Na [M+Na]⁺ 151.0366, found 151.0366.

Determination of the enantiomeric ratio of 7

The enantiomeric ratio of 7 was determined to be 8:1 by analyzing the $^1$H NMR spectra of the (R)-MTPA esters derived from 7. The hydroxyl-bearing methylene protons of the (R)-MTPA ester appeared at $\delta$ 3.86 ppm (s, 8H) as the major peaks and $\delta$ 3.89 ppm (s, 1H) as the minor peaks.

(1S,5S)-1-(((tert-butylidimethylsilyl)oxy)methyl)-6-oxabicyclo[3.1.0]hexan-2-one (4)

To a solution of (1S,5S)-1-(hydroxymethyl)-6-oxabicyclo[3.1.0]hexan-2-one 7 (8 g, 62.4 mmol) in DMF (50 mL) at 0°C was added 1,3-diazole (14.9 g, 218.6 mmol). 15 min later, TBSCI (11.3 g, 74.9 mmol) was added to the mixture and it was stirred at 0°C for another 2 h. Then the reaction was quenched by the addition of water (20 mL). The combined organic extracts were washed with brine (100 mL) and extracted with EtOAc (3 × 30 mL), dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Petroleum ether/Ethyl acetate = 10:1) and compound 4 (14.8 g, 61.1 mmol, 98%) was obtained as a colorless oil. 4: $[\alpha]_D^{20}$ = +1.65 (c 2.2, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$); $\delta$ 0.05 (s, 6H), 0.88 (s, 9H), 1.99-2.05 (m, 1H), 2.11-2.18 (m, 1H), 2.28 (dd, $J$ = 13.5, 9.5 Hz, 1H), 2.36-2.42 (m, 1H), 3.93-3.96 (m, 2H), 4.17 (d, $J$ = 12.6 Hz, 1H); $^1$C NMR (100 MHz, CDCl$_3$); $\delta$ 12.0, 18.8, 22.8, 26.3, 32.8, 57.0, 62.3, 64.4, 210.4; HRMS (ESI): m/z calcd. for C$_{12}$H$_{23}$O$_4$SiNa [M+Na]$^+$ 265.1230, found 265.1232.

(2R,3S)-2-(((tert-butylidimethylsilyl)oxy)methyl)-3-Hydroxycyclopentanone (8)

To a degassed solution of N-acetyl-cysteine (28.3 g, 173.3 mmol) and borax (66.1 g, 173.3 mmol) in phosphate buffer (pH = 4.5, 400 mL) at 15°C was added 5% H$_3$PO$_4$ to adjust the pH of system to 6.0, and diphenyl diselenide (0.9 g, 2.9 mmol) in methanol (20 mL) was then added dropwise. After stirred for 20 min, compound 4 (14 g, 57.8 mmol) dissolved in methanol (180 mL) was added dropwise. Three days later, the reaction mixture was saturated with NaCl and extracted with DCM (3 × 200 mL) and the extracts were dried over Na$_2$SO$_4$. The resulting mixture was purified by silica gel column chromatography (Petroleum ether/Ethyl acetate = 10:1→5:1) and compound 8 (6.07 g, 24.9 mmol, 56%, $\text{dr} = 1:3.4$) was as a colorless oil. 8: $[\alpha]_D^{20}$ = +0.055 (c 1.46, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$); $\delta$ 0.06 (d, $J$ = 3.4 Hz, 6H), 0.88 (s, 9H), 1.61 (m, 1H), 1.80-1.88 (m, 1H), 2.11-2.16 (m, 1H), 2.33-2.35 (m, 2H), 2.48 (dd, $J$ = 19.0, 9.0 Hz, 1H), 3.79-3.83 (m, 1H), 4.01 (dd, $J$ = 10.4, 4.3Hz, 1H), 4.41 (dd, $J$ = 14.8, 8.3Hz, 1H); $^1$C NMR (100 MHz, CDCl$_3$); $\delta$ -5.3, -5.2, 18.5, 26.1, 26.2, 30.3, 35.4, 37.7, 59.4, 61.2, 73.2, 216.6; HRMS (ESI): m/z calcd. for C$_{12}$H$_{23}$O$_4$SiNa [M+Na]$^+$ 267.1387, found 267.1385.

(2R,3S)-3-(((tert-butylidimethylsilyl)oxy)-2-(((tert-butylidimethylsilyl)oxy)methyl)cyclopentanone (10)

To a solution of compound 8 (5 g, 20.5 mmol) in DMF (40 mL) at 0°C was added 1,3-diazole (4.9 g, 71.6 mmol). 15 min later, TBSCI (4.6 g, 30.8 mmol) was added. The mixture was stirred at 0°C for 2 h, and then it was quenched by the addition of water (20 mL). The combined organic extracts were washed with brine (100 mL) and extracted with EtOAc (3 × 30 mL), dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Petroleum ether/Ethyl acetate = 20:1) and compound 10 (5.9 g, 16.4 mmol, 80%) was obtained as a colorless oil. 10: $[\alpha]_D^{20}$ = -10.10 (c 1.56, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$); $\delta$ 0.01 (t, $J$ = 7.0 Hz, 6H), 0.07 (t, $J$ = 3.4 Hz, 6H), 0.83 (d, $J$ = 8.4 Hz, 9H), 0.86 (d, $J$ = 7.9 Hz, 9H), 1.70-1.86 (m, 1H), 1.94-2.07 (m, 2H), 2.11-2.20 (m, 1H), 2.37-2.39 (m, 1H), 3.61-3.69 (m, 1H), 4.965-4969


3.93-3.96 (m, 1H), 4.47-4.53 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) -5.7,-5.6, -4.7, -4.5, 18.0, 18.2, 25.8, 31.1, 37.7, 58.6, 59.9, 71.2, 216.7; HRMS (ESI): m/z calcd. for C\(_{18}\)H\(_{38}\)O\(_3\)Si\(_2\)Na [M+Na]\(^+\) 381.2252, found 381.2249.

tert-butyl((1R,2S)-2-((tert-butylidimethylsilyl)oxy)-5-methylenecyclopentyl)methoxy)dimethylsilane (3)

To a solution of Nysted reagent (20 wt. % in THF, 63.9 g, 27.9 mmol) in DCM (45 mL) at -78\(^\circ\)C, was added dropwise compound 10 (5 g, 13.9 mmol) dissolved in anhydrous DCM (15 mL). 15 min later, TiCl\(_4\) (2.9 mL, 26.4 mmol) was added dropwise, and the reaction mixture was allowed to stir at room temperature for another 2 hours. Then the reaction was quenched with saturated NaHCO\(_3\) solution, diluted with water, and was extracted with DCM (3 x 50 mL). The combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\) and concentrated. The residue was purified through silica gel column chromatography (Petroleum ether/Ethyl acetate = 50:1) and compound 3 (4.3 g, 12.1 mmol, 87%) was obtained as a clear oil. 3: [\(\alpha\)]\(^D\) = +7.85 (c 1.25, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.04-0.10 (m, 12H), 0.90 (s, 9H), 0.91 (s, 9H), 1.61-1.67 (m, 1H), 1.81-1.87 (m, 1H), 2.21-2.25 (m, 1H), 2.46-2.54 (m, 2H), 3.52-3.61 (m, 1H), 3.62-3.67 (m, 1H), 4.21 (q, \(J = 4.8\) Hz, 1H), 4.94-4.96 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) -5.3, -5.2, -5.1, -4.5, -4.4, 18.2, 18.5, 25.9, 26.0, 26.1, 30.6, 33.7, 55.7, 64.0, 75.1, 106.8, 151.4; HRMS (ESI): m/z calcd. for C\(_{19}\)H\(_{38}\)O\(_3\)Si\(_2\)Na [M+Na]\(^+\) 379.2459, found 379.2472.

(3R,4S)-4-((tert-butylidimethylsilyl)oxy)-3-(((tert-butylidimethylsilyl)oxy)methyl)-2-methylene cyclopentanone (11)

To a flame-dried round-bottom flask equipped with a stir bar was added activated 4 Å molecular sieves (1.12 g), SeO\(_2\) (1.2 g, 11.2 mmol), and anhydrous dichloromethane (60 mL) respectively. The resultant mixture was cooled down to 0 \(^\circ\)C, and TBHP (5.50 M in decane, 7.4 mL, 40.9 mmol) was added dropwise. 15 min later, compound 3 (4 g, 11.2 mmol) in anhydrous DCM (20 mL) was added. The reaction was allowed to stir at room temperature for 30 hours. Then it was quenched with saturated NaHCO\(_3\) solution, and was extracted with DCM (3 x 50 mL). The combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\) and concentrated. The residue was purified through silica gel column chromatography (Petroleum ether/Ethyl acetate = 30:1) and compound 11 (1.8 g, 4.8 mmol, 43%) was obtained as a clear oil. 11: [\(\alpha\)]\(^D\) = +2.05 (c 1.02, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.02 (d, \(J = 6.0\) Hz, 6H), 0.05 (d, \(J = 4.9\) Hz, 6H), 0.85 (s, 18H), 2.29-2.34 (m, 1H), 2.61-2.66 (m, 1H), 2.83 (s,1H), 3.71-3.73 (m, 2H), 4.33 (t, \(J = 4.4\) Hz, 1H), 5.40 (d, \(J = 2.1\) Hz, 1H), 6.11 (d, \(J = 2.1\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) -5.5, -5.3, -4.7, -4.5, 18.1, 18.4, 25.9, 26.0, 47.4, 53.8, 63.6, 69.3, 119.1, 145.2, 204.8; HRMS (ESI): m/z calcd. for C\(_{19}\)H\(_{38}\)O\(_3\)Si\(_2\)Na [M+Na]\(^+\) 393.2252, found 393.2251.
NMR Spectra

$^1$H and $^{13}$C NMR spectra of 5 in CDCl$_3$
$^1$H and $^{13}$C NMR spectra of 7 in CDCl$_3$
$^{1}$H and $^{13}$C NMR spectra of 4 in CDCl$_3$
$^1$H and $^{13}$C NMR spectra of 8 in CDCl$_3$
$^1$H and $^{13}$C NMR spectra of 10 in CDCl$_3$
$^1$H and $^{13}$C NMR spectra of 3 in CDCl$_3$
$^1$H and $^{13}$C NMR spectra of II in CDCl$_3$
$^1$H and $^{13}$C NMR spectra of 1 in CDCl$_3$
Determination of the enantiomeric ratio of 7
$^1$H NMR spectra of 9 in CDCl$_3$
HRMS spectra