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Original article

Design and concise synthesis of *gem*-difluoromethylenated analogue of 7-*epi*-castanospermine

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ABSTRACT

A novel *gem*-difluoromethylenated castanospermine analogue **B** was designed and synthesized, starting from 3-bromo-3,3-difluoropropene and L-(−)-malic acid. The key steps involve substitution cyclization reaction and RCM reaction to construct the aza fused bicyclic framework.

1. Introduction

Polyhydroxylated indolizidine alkaloids are widely found in microorganisms, vertebrates, higher invertebrates, and plants [1]. Some of these aza fused bicyclic compounds, such as lentiginosine [2], swainsonine [3], and castanospermine [4], have been reported to exhibit good glycosidase inhibition activity, which makes them potential therapeutic agents (Fig. 1). Among them, castanospermine has attracted considerable attention. It is a strong inhibitor of α- and β-glucosidases [5] and has shown potential antitumor, antiviral, and immunomodulating activities [6]. Because of its unique biological activities, a lot of efforts have been devoted into the synthesis of castanospermine [7] as well as its analogues [8] to study their structure-activity relationship (SAR).

The major drawback for castanospermine in clinical applications is the low inhibition selectivity between α- and β-glucosidases. In 1997, Tyler and co-workers reported that 7-*epi*-castanospermine showed higher α/β glucosidase selectivity than castanospermine while retaining almost complete activity towards α-glucosidase (Scheme 1) [9]. To further improve the selectivity and the potency of the inhibition of glycosidases, it is highly desirable to develop new polyhydroxylated alkaloid analogues. In 2006, our group found that introduction of a *gem*-difluoromethylene group (CF_2) into 1-deoxymannonojirimycin (DMJ) could improve the inhibition selectivity of compound **A** [10]. As a part of our interest in the synthesis of fluorinated iminosugars [10,11], we designed a new *gem*-difluoromethylenated analogue **B** of 7-*epi*-castanospermine. The strongly electron-withdrawing *gem*-difluoromethylene group would reduce the pK_a value and might change the stereoconfiguration, thus affecting the inhibition activity and selectivity. In this paper, we present our results on the synthesis of this novel castanospermine analogue.

2. Experimental

2.1. (3S,4R)-Methyl 3-(benzyloxy)-5,5-difluoro-4-hydroxyhept-6-enoate (**3a**) and (4S,5S)-4-(benzyloxy)-5-(1,1-difluoroallyl)dihydrofuran-2(3H)-one (**3b**)

To a stirring solution of (*S*)-*O*-benzylmalic acid dimethyl ester **2** (0.90 g, 3.57 mmol) in CH_2Cl_2 (50 mL) was added magnesium bromide etherate (1.0 g, 4.0 mmol) at 0 °C. The solution was stirred for 1 h at 0 °C and cooled to −90 °C. To the solution was added a 1.5 mol/L solution of diisobutylaluminum hydride in toluene (3.0 mL, 4.5 mmol) *via* syringe pump over 90 min, then the reaction mixture was stirred at −90 °C for 2 h. Methanol (4 mL) was slowly added followed by saturated Rochelle salts (80 mL). The mixture was warmed to room temperature and stirred for 12 h. The layers were separated and the aqueous phase was

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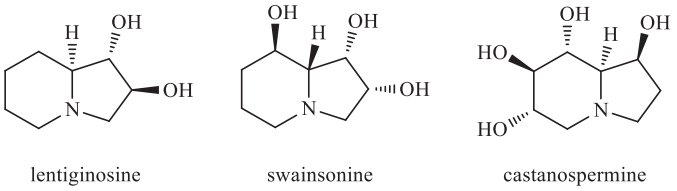


Fig. 1. Polyhydroxylated indolizidines.

extracted three times with methylene dichloride. The combined organic phase was dried with Na_2SO_4 and concentrated. The mixture was separated by flash column chromatography (petroleum ether/ethyl acetate = 8/1) to yield 0.61 g (77%) of a colourless oil. The colourless oil was dissolved in DMF (10 mL). After that, indium (474 mg, 4.12 mmol) and 3-bromo-3,3-difluoropropane (420 μL, 4.20 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then quenched with 1 mol/L HCl and extracted with CH_2Cl_2. The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 8/1) to give 255 mg (31% yield) of compound **3a** as a clear oil and 362 mg (44% yield) of compound **3b** as a clear oil.

3a: $[\alpha]_D^{20} = -6.93$ (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.31–7.30 (m, 5H), 6.08–5.95 (m, 1H), 5.76–5.68 (m, 1H), 5.54–5.47 (m, 1H), 4.67–4.60 (m, 2H), 4.28–4.25 (m, 1H), 3.76–3.64 (m, 4H), 2.73–2.71 (m, 2H), 2.42 (br, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −107.0 (dt, 1F, J = 253.0 Hz, 9.45 Hz), −111.5 (dt, 1F, J = 252.4 Hz, 11.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 137.4, 130.6 (t, J = 25.7 Hz), 128.5, 128.1, 120.7 (t, J = 9.5 Hz), 119.4 (t, J = 242.8 Hz), 74.1 (t, J = 29.6 Hz), 73.2, 72.9, 51.8, 37.3; IR (thin film, cm^{-1}): 3500, 3033, 2953, 1738, 1439; MS (ESI): *m*/*z* 301.3 ($M+H^+$), 318.3 ($M+NH_4^+$); 323.2 ($M+Na^+$); HRMS Calcd. for $C_{15}H_{18}O_4F_2Na$: 323.1065; Found: 323.1073.

3b: $[\alpha]_D^{20} = -15.17$ (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.30 (m, 5H), 6.04–5.87 (m, 1H), 5.80–5.74 (m, 1H), 5.63–5.60 (m, 1H), 4.65–4.51 (m, 3H), 4.46–4.44 (m, 1H), 2.87–2.78 (m, 1H), 2.65–2.59 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −109.8 (ddd, 1F, J = 258.6 Hz, 12.7 Hz, 4.5 Hz), −113.0 (ddd, 1F, J = 258.9 Hz, 18.6 Hz, 10.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 136.7, 128.8 (t, J = 25.8 Hz), 128.7, 128.3, 127.9, 122.9 (t, J = 9.5 Hz), 117.6 (t, J = 242.7 Hz), 84.3 (t, J = 31.4 Hz), 73.4, 71.4, 34.9; IR (thin film, cm^{-1}): 3033, 2932, 1691, 1455, 1208; MS (ESI): *m*/*z* 286.2 ($M+NH_4^+$); HRMS Calcd. for $C_{14}H_{14}O_3F_2Na$: 291.0803; Found: 291.0811.

2.2. (3S,4S)-3-(Benzyloxy)-5,5-difluorohept-6-ene-1,4-diol (*4*)

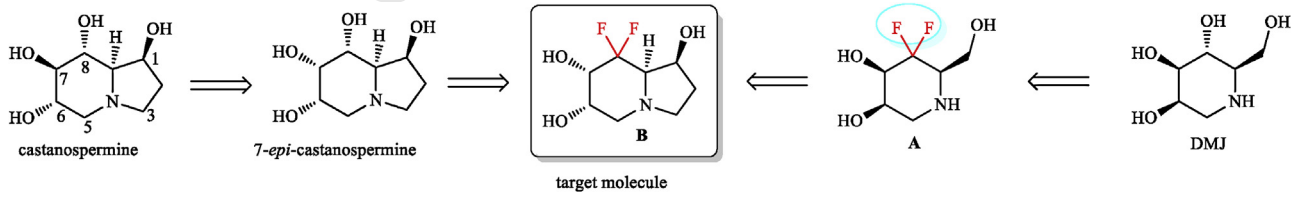
To a suspension of $LiAlH_4$ (91.2 mg, 2.4 mmol) in dry THF (5 mL) was added a solution of **3b** (0.36 g, 1.2 mmol) in dry THF at 0 °C. The mixture was stirred for 3 h at 0 °C and quenched by careful addition of water and then extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was quickly purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2/1) to afford compound **4** (0.28 g, 86%) as a clear oil. $[\alpha]_D^{20} = -17.01$ (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.25 (m, 5H), 6.10–5.93 (m, 1H), 5.73–5.68 (m, 1H), 5.50–5.47 (m, 1H), 4.52 (dd, 2H, J = 17.4 Hz, 11.4 Hz), 4.07–3.98 (m, 1H), 3.90–3.63 (m, 3H), 2.96 (br, 2H), 2.02–1.92 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −107.7 (dt, 1F, J = 251.5 Hz, 10.3 Hz), −109.3 (dt, 1F, J = 251.8 Hz, 12.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 130.9 (t, J = 25.4 Hz), 128.6, 128.1, 128.0, 120.4 (t, J = 9.5 Hz), 119.7 (t, J = 243.1 Hz), 76.3, 73.8 (t, J = 27.9 Hz), 71.8, 58.9, 31.7; IR (thin film, cm^{-1}): 3392, 3033, 2928, 1664, 1056; MS (ESI): *m*/*z* 295.2 ($M+Na^+$); HRMS Calcd. for $C_{14}H_{18}O_3F_2Na$: 295.1116; Found: 295.1120.

2.3. (2R,3S)-1-Allyl-3-(benzyloxy)-2-(1,1-difluoroallyl)pyrrolidine (*5*)

To a solution of compound **4** (1.0 g, 3.68 mmol) in anhydrous CH_2Cl_2 (12 mL), and NEt_3 (3.4 mL, 23.8 mmol), MsCl (1.3 mL, 16.7 mmol) was added slowly at 0 °C. The reaction mixture was then warmed to room temperature and stirred overnight. The reaction was quenched with water. The resulting mixture was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed *in vacuo*. The residue was dissolved in allylamine (6 mL). Then the reaction mixture was heated to 145 °C in the sealed tub for 10 h. The allylamine was removed *in vacuo* and then the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 15/1) to give 870 mg (81%, yield, two steps) of compound **5** as a clear oil. $[\alpha]_D^{20} = -16.86$ (*c* 1.10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.25 (m, 5H), 6.35–6.17 (m, 1H), 5.93–5.79 (m, 1H), 5.68–5.62 (m, 1H), 5.42–5.38 (m, 1H), 5.19–5.09 (m, 2H), 4.53 (s, 2H), 4.12 (q, 1H, J = 6.3 Hz), 3.57–3.51 (m, 1H), 3.18–3.00 (m, 3H), 3.17 (q, 1H, J = 8.7 Hz), 1.99–1.92 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.4 (d, 1F, J = 255.2 Hz), −97.3 (dt, 1F, J = 254.9 Hz, 13.25 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 134.8, 133.0 (t, J = 24.5 Hz), 128.3, 127.7, 127.6, 121.6 (t, J = 239.9 Hz), 119.3 (t, J = 9.65 Hz), 117.4, 79.1 (d, J = 7.0 Hz), 72.1, 68.7 (dd, J = 30.3 Hz, 25.6 Hz), 58.2, 50.0 (d, J = 6 Hz), 30.4; IR (thin film, cm^{-1}): 3066, 2924, 2359, 1419, 1354, 1121, 738; MS (ESI): *m*/*z* 298.4 ($M+H^+$); HRMS Calcd. for $C_{17}H_{22}OF_2N$: 294.1664; Found: 294.1657.

2.4. (1S,8aR)-1-(Benzyloxy)-8,8-difluoro-1,2,3,5,8,8a-hexahydroindolizine (*6*)

To a solution of compound **5** (520 mg, 1.77 mmol) in anhydrous toluene (50 mL) was added Grubbs' II catalyst (70 mg, 0.0824 mmol). The reaction mixture was then warmed to 80 °C and stirred for 10 h. After the solvent was evaporated, the crude product was purified by flash silica gel column chromatography (petroleum ether/ethyl acetate = 6/1) to give compound **6** (375 mg, 80%) as a clear oil. $[\alpha]_D^{20} = 98.66$ (*c* 1.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.23 (m, 5H), 6.15–6.11 (m, 1H), 5.92–5.86 (m, 1H), 4.66 (dd, 2H, J = 37.5 Hz, 12.3 Hz), 4.39–4.33 (m, 1H),



Scheme 1. Design of target molecule **B**.

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3.61–3.55 (m, 1H), 3.28 (t, 1H, J = 8.6 Hz), 3.00–2.93 (m, 1H), 2.73–2.64 (m, 1H), 2.36 (q, 1H, J = 8.4 Hz), 2.26–2.15 (m, 1H), 2.07–1.95 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −98.3 (d, 1F, J = 270.4 Hz), −100.5 (d, 1F, J = 269.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 133.8 (t, J = 9.8 Hz), 128.3, 127.4, 127.3, 123.7 (dd, J = 30.3 Hz, 26.4 Hz), 117.7 (dd, J = 244.8 Hz, 229.7 Hz), 78.2, 72.2, 65.9 (d, J = 20.7 Hz), 65.6 (d, J = 21.3 Hz), 51.6, 31.2; IR (thin film, cm^{-1}): 3033, 2987, 1620, 1237, 987; MS (ESI): m/z 266.3 ($M+H^+$); HRMS Calcd. for $C_{15}H_{17}OF_2NNa$: 288.1170; Found: 288.1164.

2.5. (3S,4S)-3-(Benzyloxy)-5,5-difluoro-4-hydroxyhept-6-enyl acetate (**7**)

To a solution of compound **4** (1.032 g, 3.79 mmol) in vinyl acetate (15 mL) was added lipase AK (0.52 g). The solution was stirred at room temperature. After 24 h, the solution was filtered and volatiles were removed by reduced pressure. The crude product was chromatographed (petroleum ether/ethyl acetate = 8/1) to afford **7** (1.037 g, 87%) as a clear oil. $[\alpha]_D^{20}$ = −35.71 35.71 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.25 (m, 5H), 6.05–5.92 (m, 1H), 5.69 (d, 1H, J = 17.2 Hz), 5.49 (d, 1H, J = 11.2 Hz), 4.51 (dd, 2H, J = 34.4 Hz, 11.2 Hz), 4.23–4.12 (m, 2H), 4.03 (td, 1H, J = 11.2 Hz, 3.2 Hz), 3.77–3.74 (m, 1H), 2.04–1.91 (m, 5H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −107.5 (dt, 1F, J = 251.5 Hz, 11.3 Hz), −109.4 (dt, 1F, J = 251.3 Hz, 11.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 137.4, 130.5 (t, J = 25.3 Hz), 128.5, 128.1, 128.0, 120.6 (t, J = 9.7 Hz), 119.4 (dd, J = 241.2 Hz, 243.3 Hz), 74.6 (t, J = 1.5 Hz), 73.6 (t, J = 28.3 Hz), 72.0, 61.1, 28.7, 20.9; IR (thin film, cm^{-1}): 3466, 3032, 2904, 1736, 819; MS (ESI): m/z 315.0 ($M+H^+$); HRMS Calcd. for $C_{16}H_{20}O_4F_2NNa$: 337.1222; Found: 337.1223.

2.6. (3S,4R)-4-Azido-3-(benzyloxy)-5,5-difluorohept-6-enyl acetate (**8**)

Compound **7** (2.62 g, 8.34 mmol) was dissolved in dry CH_2Cl_2 (50 mL). After that, DMAP (2.03 g, 16.68 mmol) was added. The resulting mixture was cooled to −35 °C. Then, Tf_2O (2.10 mL, 12.52 mmol) was added dropwise to the solution with stirring. After that, the reaction mixture was stirred for about 3 h at 0 °C. Water and $NaHCO_3$ solution were added successively after the mixture was warmed to room temperature. Then the mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4. The mixture was separated by flash column (petroleum ether/ethyl acetate = 8/1) to yield a colourless oil. The colourless oil was dissolved in DMF (20 mL). Then, sodium azide (2.7 g, 41.7 mmol) was added carefully with stirring at 0 °C in an ice bath. The reaction mixture was stirred overnight at room temperature. Water was added to quench the reaction. The aqueous phase was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was quickly purified by silica gel column chromatography (petroleum ether/ethyl acetate = 8/1) to afford compound **8** (1.95 g, 69% yield) as a clear oil. $[\alpha]_D^{20}$ = −45.97 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.25 (m, 5H), 6.08–5.95 (m, 1H), 5.78 (dt, 1H, J = 17.4 Hz, 2.1 Hz), 5.49 (d, 1H, J = 11.1 Hz), 4.59 (dd, 2H, J = 39.3 Hz, 11.1 Hz), 4.24–4.08 (m, 2H), 3.92–3.86 (m, 1H), 3.58–3.49 (m, 1H), 2.03–1.97 (m, 5H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −97.98 (d, 1F, J = 253.2 Hz), −104.70 (d, 1F, J = 251.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 136.9, 129.8 (t, J = 25.1 Hz), 128.0, 127.6, 127.5, 120.7 (t, J = 9.6 Hz), 119.0 (dd, J = 244.7 Hz, 243.6 Hz), 73.8 (d, J = 2.7 Hz), 72.8, 66.7 (t, J = 28.3 Hz), 60.1, 31.0, 20.4; IR (thin film, cm^{-1}): 3032, 2962, 2114, 1740, 1240, 989; MS (ESI): m/z 357.1 ($M+NH_4^+$); HRMS Calcd. for $C_{16}H_{19}O_3F_2N_3Na$: 362.1287; Found: 362.1287.

2.7. (3S,4R)-4-Azido-3-(benzyloxy)-5,5-difluorohept-6-en-1-ol (**9**)

Compound **8** (0.87 g, 4.06 mmol) was dissolved in MeOH (15 mL). After that, KOH (0.12 g) was added. The resulting mixture was stirred for about 1 h. Water was added and the aqueous phase was extracted with CH_2Cl_2. Then, the combined organic layers were washed with brine. After the resultant solution was dried over anhydrous Na_2SO_4 and filtered, the solvent was removed *in vacuo*. The residue was purified by flash silica gel column chromatography (petroleum ether/ethyl acetate = 6/1) to give **9** (713 mg, 96%) as a clear oil. $[\alpha]_D^{20}$ = −49.66 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.27 (m, 5H), 6.09–5.96 (m, 1H), 5.77 (d, 1H, J = 17.2 Hz), 5.54 (d, 1H, J = 11.1 Hz), 4.62 (dd, 2H, J = 36.8 Hz, 26.0 Hz), 4.02–3.98 (m, 1H), 3.73 (t, 2H, J = 5.6 Hz), 3.62–3.56 (m, 1H), 1.92 (q, 2H, J = 6.0 Hz), 1.73 (br, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −98.6 (dt, 1F, J = 253.5 Hz, 9.9 Hz), −105.24 (dt, 1F, J = 251.5 Hz, 11.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 130.3 (t, J = 25.3 Hz), 128.5, 128.0, 127.9, 121.1 (t, J = 9.7 Hz), 119.5 (t, J = 244.2 Hz), 75.0 (d, J = 3.7 Hz), 73.2, 67.3 (t, J = 28.3 Hz), 59.1, 34.8 (d, J = 1.5 Hz); IR (thin film, cm^{-1}): 3387, 2929, 2883, 2113, 989; MS (ESI): m/z 268.0 ($[M-N_2-H]^+$); HRMS Calcd. for $C_{14}H_{16}O_2F_2N$: 268.1149; Found: 268.1152.

2.8. 1-((2R,3S)-3-(Benzyloxy)-2-(1,1-difluoroallyl)pyrrolidin-1-yl)prop-2-en-1-one (**10**)

A solution of compound **9** (3.897 g, 13.12 mmol) in dry CH_2Cl_2 (30 mL) was cooled to 0 °C. Et_3N (3.975 g, 39.36 mmol), DMAP (80 mg, 0.656 mmol), and MsCl (5 mL, 65.6 mmol) were added. The mixture was stirred at room temperature for 12 h and then quenched with water. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 6/1) to give methanesulfonate (4.543 g, 12.08 mmol) as a clear oil. To a solution of methanesulfonate in THF (50 mL) was added Ph_3P (4.75 g, 18.12 mmol) and water (4 mL). The reaction mixture was warmed to 80 °C and stirred for 4 h and then the reaction mixture was monitored by TLC. When the starting material was consumed, 10% NaOH (aq., 15 mL) was added and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture extracted with ethyl acetate. The combined organic layer was washed with water and dried over Na_2SO_4. The residue was dissolved in CH_2Cl_2 (20 mL). Then, K_2CO_3 (3.33 g, 24.16 mmol) and acryloyl chloride (2.18 g, 24.16 mmol) was added. The mixture was stirred at room temperature for 12 h and then quenched with water. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give compound **10** (2.54 g, 63%) as a clear oil. $[\alpha]_D^{20}$ = −56.83 (*c* 2.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.26 (m, 5H), 6.57–6.51 (m, 0.5H), 6.41–6.37 (m, 1.5H), 6.23–6.07 (m, 1H), 5.74–5.66 (m, 2H), 5.44 (dd, 1H, J = 21.2, 11.2 Hz), 4.95–4.87 (m, 0.5H), 4.70–4.63 (m, 1H), 4.55–4.49 (m, 1H), 4.45–4.38 (m, 0.5H), 4.25–4.08 (m, 1H), 3.74–3.64 (m, 1H), 3.57–3.46 (m, 1H), 2.37–2.12 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −96.2 (dd, 0.48F, J = 252.3 Hz, 10.9 Hz), −102.7 (dt, 0.52F, J = 249.3 Hz, 13.9 Hz), −102.8 (dt, 0.48F, J = 250.8 Hz, 10.9 Hz), −103.4 (dt, 0.52F, J = 249.3 Hz, 12.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 137.5, 137.3, 132.4 (t, J = 24.6 Hz), 131.9 (t, J = 24.6 Hz), 129.1, 128.5, 128.4, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 120.7 (t, J = 11.1 Hz), 119.5 (t, J = 9.6 Hz), 118.3 (t, J = 245.3 Hz), 117.4 (t, J = 244.9 Hz), 77.8, 76.5, 72.7, 61.4 (t, J = 23.1 Hz), 58.1 (t, J = 26.8 Hz), 44.0, 43.1, 29.5, 27.5; IR (thin film, cm^{-1}): 3030, 2896, 1655, 1614, 1421; MS

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(ESI): *m*/*z* 308 ($M+H^+$); HRMS Calcd. for $C_{17}H_{19}O_2F_2NNa$: 330.1276; Found: 330.1270.

2.9. (1S,8aR)-1-(Benzyloxy)-8,8-difluoro-2,3,8,8a-tetrahydroindolizin-5(1H)-one (**11**)

Compound **10** (643 mg, 0.31 mmol) and titanium isopropoxide (180 mg, 0.643 mmol) in dry toluene (20 mL) was refluxed for 3 h under an argon atmosphere. Then Grubbs' II catalyst dissolved in toluene (5 mL) was added dropwise to the mixture. The reaction mixture was stirred at reflux for 10 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 8/1) to give compound **11** (450 mg, 78% yield) as a yellow oil. $[\alpha]_D^{20} = -716.00$ (*c* 0.51, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.24 (m, 5H), 6.52–6.47 (m, 1H), 6.20 (d, 1H, *J* = 7.8 Hz), 4.63 (dd, 2H, *J* = 19.5 Hz, 9.0 Hz), 4.48 (d, 1H, *J* = 1.8 Hz), 3.97–3.88 (m, 1H), 3.77–3.65 (m, 2H), 2.21–2.15 (m, 1H), 1.93–1.84 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −101.4 (dd, 1F, *J* = 254.9 Hz, 25.6 Hz), −106.4 (dt, 1F, *J* = 273.7 Hz, 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0 (d, *J* = 3.3 Hz), 131.7, 133.7 (dd, *J* = 32.6 Hz, 24.3 Hz), 131.0 (dd, *J* = 11.3 Hz, 8.3 Hz), 128.4, 127.8, 127.5, 116.2 (dd, *J* = 251.3 Hz, 231.5 Hz), 77.85, 72.2 (d, *J* = 1.5 Hz), 62.8 (dd, *J* = 35.7 Hz, 24.3 Hz), 43.0, 29.9; IR (thin film, cm^{-1}): 2952, 1675, 1616, 1445, 1206; MS (ESI): *m*/*z* 302.0 ($M+Na^+$), 280.0 ($M+H^+$); HRMS Calcd. for $C_{15}H_{16}O_2F_2N$: 280.1144; Found: 280.1154.

2.10. (1S,6R,7S,8aR)-1-(Benzyloxy)-8,8-difluoro-6,7-dihydroxyhexahydroindolizin-5(1H)-one (**12**)

To a solution of compound **11** (450 mg, 1.61 mmol) in acetone (5 mL) was added NMNO (438 mg, 3.23 mmol), followed by addition of water (10 mL) at room temperature with stirring. Then a catalytic amount of OsO_4 (5 mol %) solution in water (4% solution) was added. After the reaction mixture was stirred at room temperature for 48 h, it was quenched with saturated $NaHSO_3$ solution and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2/1) to give 402 mg (80% yield) of compound **12** as a yellow oil. $[\alpha]_D^{20} = 93.56$ (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.27 (m, 5H), 4.63 (dd, 2H, *J* = 14.7 Hz, 9.0 Hz), 4.40–4.32 (m, 2H), 4.32 (s, 1H), 4.15 (d, 1H, *J* = 19.5 Hz), 3.69–3.65 (m, 2H), 2.21–2.15 (m, 1H), 1.97–1.92 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −113.6 (dd, 1F, *J* = 256.0 Hz, 8.3 Hz), −117.7 (dd, 1F, *J* = 256.0 Hz, 25.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 137.7, 128.4, 127.8, 127.5, 118.6 (t, *J* = 248.6 Hz), 76.9, 71.9 (d, *J* = 1.5 Hz), 70.3 (dd, *J* = 32.8, 21.6 Hz), 69.1 (d, *J* = 8.2 Hz), 59.9 (dd, *J* = 37.2, 19.4 Hz), 43.4, 29.6; IR (thin film, cm^{-1}): 3372, 2896, 1644, 1117, 1068; MS (ESI): *m*/*z* 314.0 ($M+H^+$); HRMS Calcd. for $C_{15}H_{18}O_4F_2N$: 314.1198; Found: 314.1212.

2.11. (1S,6S,7S,8aR)-1-(Benzyloxy)-8,8-difluorooctahydroindolizine-6,7-diol (**13**)

To a stirred, cooled (0 °C, ice bath) solution of **12** (185 mg, 0.585 mmol) in THF (3 mL) was added borane dimethylsulfide complex (2.0 mol/L in THF, 3.0 mL, 6.0 mmol). After 30 min, the cold bath was removed, and the reaction was heated to reflux and then stirred for 20 h. The reaction was then quenched with MeOH (1 mL) and concentrated under reduced pressure. The residue was dissolved in MeOH (5 mL). Then, the reaction was heated to reflux and stirred for 12 h. The mixture was concentrated under reduced pressure and the residue purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$ = 1/50) to afford **13** (147 mg, 85%) as a white solid. $[\alpha]_D^{20} = 18.06$ (*c* 1.00, CD_3OD); ^1H NMR (400 MHz, CD_3OD): δ 7.34–7.20 (m, 5H), 4.85 (s, 2H), 4.53 (dd, 2H, *J* = 11.1 Hz, 9.3 Hz), 4.28–4.25 (m, 1H), 3.93–3.84 (m, 2H), 3.14–3.10 (m, 1H), 2.93–2.90 (m, 1H), 2.66 (dd, 1H, *J* = 19.2 Hz, 3.3 Hz), 2.33 (t, 1H, *J* = 8.4 Hz), 2.26–2.15 (m, 2H), 1.93–1.89 (m, 1H); ^{19}F NMR (376 MHz, CD_3OD): δ −114.5 (d, 1F, *J* = 253.5 Hz), −117.1 (dd, 1F, *J* = 254.5 Hz, 26.0 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ 138.5, 127.6, 127.2, 127.0, 120.0 (t, *J* = 243.8 Hz), 76.9, 71.3, 70.9 (dd, *J* = 32.6 Hz, 20.5 Hz), 66.6 (d, *J* = 6.8 Hz), 63.2 (dd, *J* = 30.4 Hz, 19.0 Hz), 51.9, 51.3, 30.8; IR (thin film, cm^{-1}): 3531, 2952, 1116, 1049, 740; MS (ESI): *m*/*z* 300.0 ($M+H^+$); HRMS Calcd. for $C_{15}H_{19}O_3F_2NNa$: 322.1225; Found: 322.1212.

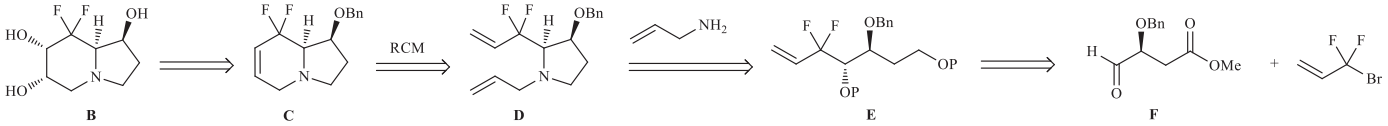
2.12. 7-epi-8,8-Difluorocastanospermine (***B***)

HCOOH (1.045 mL) was added to a mixture of compound **13** (25 mg, 0.084 mmol) and 10% Pd/C (334 mg) in MeOH (5 mL) under an argon atmosphere. The suspension was stirred for 4 h and then filtered through a short pad of celite. The filtrate was concentrated under reduced pressure and the residue was dissolved in water and passed through a column of ion-exchange resin (Dowex 1 × 8, OH-form) eluting with MeOH. The eluent was concentrated under reduced pressure to give 7-*epi*-8,8-difluorocastanospermine (**B**) (16 mg, 92%) as a colourless solid. $[\alpha]_D^{20} = 20.52$ (*c* 0.50, CD_3OD); ^1H NMR (400 MHz, CD_3OD): δ 4.47 (s, 1H), 3.91–3.89 (m, 1H), 3.82 (s, 1H), 3.13 (t, 1H, *J* = 3.3 Hz), 2.93–2.91 (m, 1H), 2.51 (d, 1H, *J* = 12.0 Hz), 2.33–2.22 (m, 2H), 2.15 (q, 1H, *J* = 8.8 Hz), 1.77–1.69 (m, 1H); ^{19}F NMR (376 MHz, CD_3OD): δ −112.6 (d, 1F, *J* = 251.9 Hz), −113.8 (dd, 1F, *J* = 250.3 Hz, 22.9 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ 120.2 (t, *J* = 247.5 Hz), 70.8 (dd, *J* = 32.6 Hz, 21.3 Hz), 69.3, 66.9 (d, *J* = 6.8 Hz), 63.8 (dd, *J* = 28.8 Hz, 19.0 Hz), 51.9, 51.1, 33.1; IR (thin film, cm^{-1}): 3401, 3321, 2938, 1079, 1057; MS (ESI): *m*/*z* 209.9 ($M+H^+$); HRMS Calcd. for $C_8H_{14}O_3F_2N$: 210.0936; Found: 210.0946.

3. Results and discussion

The retrosynthetic analysis of target molecule **B** is shown in Scheme 2. Compound **B** could be prepared by substrate-controlled *cis*-dihydroxylation of cycloalkene **C**. The six-member ring in compound **C** could be constructed by ring-closing metathesis (RCM) reaction from diene **D**, in which the pyrrolidine ring is easily accessible by intermolecular cyclization of allylamine and compound **E**. Compound **E** is expected to be obtained by coupling of 3-bromo-3,3-difluoropropene and aldehyde **F**.

Our initial route towards compound **B** commenced from the cheap and commercially available L-(−)-malic acid **1** (Scheme 3). Esterfication of compound **1** with SO_2Cl_2/MeOH and then protection of the hydroxyl group under the condition of Ag_2O/BnBr gave compound **2** in high yield. Lewis acid mediated selective reduction of compound **2** produced the desired aldehyde [12],



Scheme 2. Retrosynthetic analysis of target molecule **B**.

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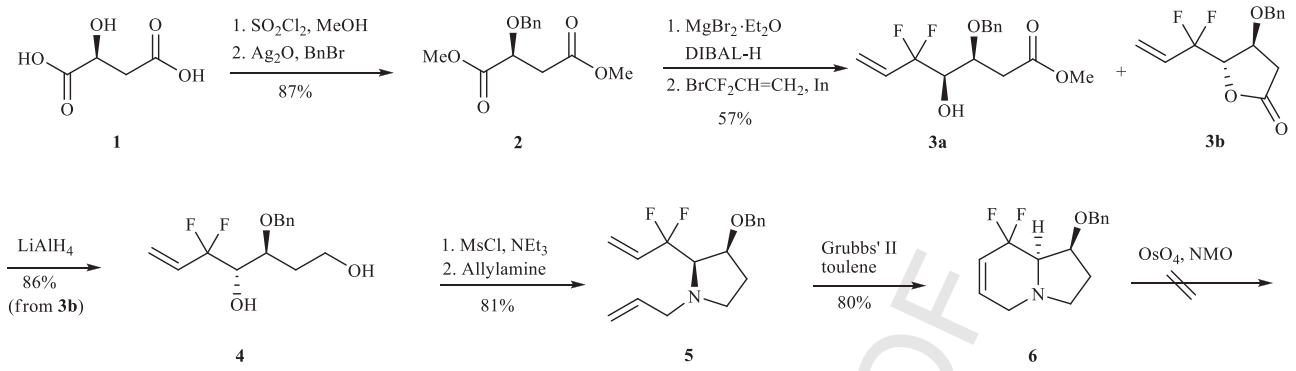
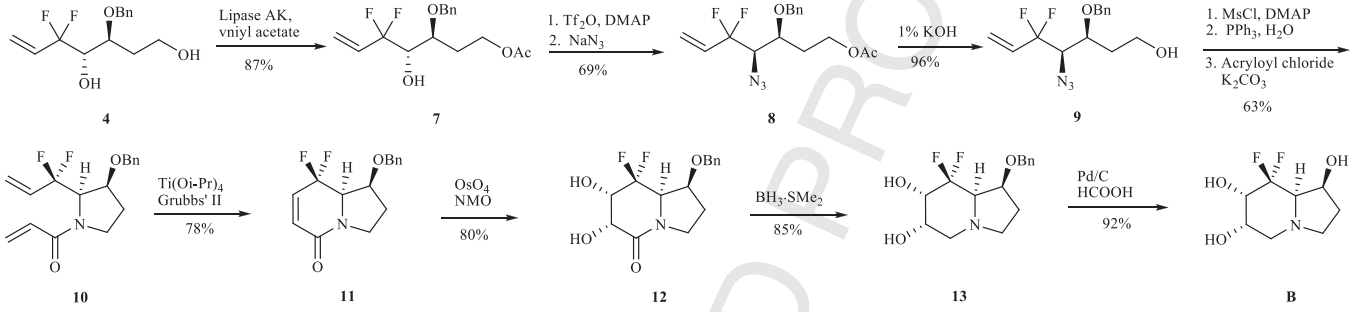


Scheme 3. Initial synthetic route.



Scheme 4. Modified synthetic route.

which reacted with 3-bromo-3,3-difluoropropene in the presence of indium affording two diastereoisomers **3a** and **3b**. Interestingly, compound **3b** was obtained in the form of lactone. It was converted into diol **4** in high yield by reduction with $LiAlH_4$. Reaction of both of the hydroxyl groups in diol **4** with MsCl and subsequent intramolecular cyclization with allylamine afforded the RCM reaction precursor **5**. The RCM reaction of compound **5** with Grubbs' II catalyst proceeded smoothly to afford alkene **6** in 80% yield. To our disappointment, the dihydroxylation of alkene **6** could not be achieved, despite trying many different reaction systems [13]. The failure of the dihydroxylation reaction might be ascribed to the coordination of nitrogen atom to the catalyst OsO_4 [14].

To reduce the coordination ability of nitrogen to osmium, we decided to connect an electron-withdrawing group to the nitrogen atom. The modified synthetic route is shown in Scheme 4. Selective protection of the primary hydroxyl group in compound **4** with vinyl acetate and *Pseudomonas* (AK) [15] gave the secondary alcohol **7** in 87% yield. Reaction of alcohol **7** with Tf_2O in presence of DMAP afforded the corresponding triflate, which then reacted with NaN_3 to give azide **8**. Cleavage of the O-Ac group in a methanolic solution of 1% KOH afforded the desired alcohol **9**. Mesylation of the hydroxyl group in compound **9** gave the corresponding methanesulfonate. Reduction of azide group with triphenylphosphine and subsequent intramolecular substitution cyclization afforded the pyrrolidine intermediate, which then was directly treated with acryloyl chloride to give diene **10** in 63% overall yield. Considering the high electron-deficient properties of diene **10**, we performed the ring-closing metathesis (RCM) reaction under the reaction conditions developed by our group [16], with Grubbs' II catalyst and co-catalyst Ti(*i*-PrO)$_4$, affording the desired α,β-unsaturated lactam **11** in 78% yield. Dihydroxylation of lactam **11** catalyzed by OsO_4 proceeded well giving diol **12** as a single isomer. The high diastereoselectivity can be explained by the steric hindrance of benzyl ether. Subsequent reduction of lactam **12** with borane dimethyl sulfide complex gave indolizidine **13** in 85% yield. The absolute configuration of **13** was confirmed by single-crystal X-ray diffraction analysis (Fig. 2). Finally, removal of the benzyl group, *via* hydrogenolysis in the presence of 10% Pd/C, provided the target molecule 7-*epi*-8,8-difluorocastanospermine **B**.

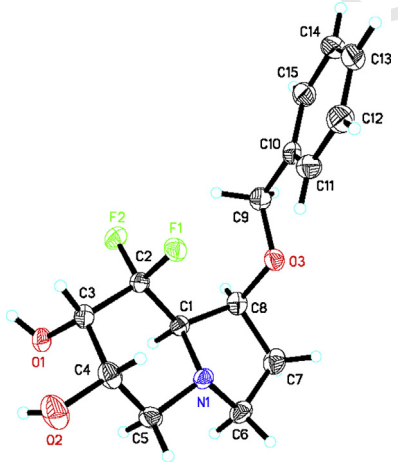


Fig. 2. X-ray crystallographic structures of compound **13**.

The synthesized 7-*epi*-8,8-difluorocastanospermine **B** was evaluated for its inhibitory activities against α-glucosidase from baker's yeast and β-glucosidase from almonds. Unfortunately no significant inhibitory activity was observed.

4. Conclusion

In conclusion, we have designed and prepared a novel *gem*-difluoromethylenated castanospermine analogue **B**. Intramolecular cyclization reaction was applied to construct pyrrolidine ring, while RCM reaction was used to achieve the desired bicyclic

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framework. Comparing the two synthetic routes, it was found that amide **11** showed much better reactivity than amine **6** in the dihydroxylation reaction. Thus, the introduction of an electron-withdrawing group to the nitrogen atom was the highlight of the modified route. The synthesis of other difluoromethylenated castanospermine isomers as well as evaluation of their biological activity are currently on progress.

Acknowledgments

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