Supplementary Information

Practical Synthesis of Fingolimod from Diethyl acetamidomalonate

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General Methods

Unless otherwise stated, all commercial reagents and solvents were used without additional purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light (254 nm) or iodine spray. Column chromatography was performed on silica gel (60-120 mesh) using a proper eluent. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ and DMSO solutions using Varian MR 400 (400 and 100 MHz) spectrometers respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.0) as internal standard and expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as br (broad). Coupling constants (J) are given in Hertz. Infrared spectra were recorded on a Jasco FTIR-4200 spectrometer. Melting points were determined by using a Buchi melting point B-540 apparatus. MS spectra were recorded using an Agilent 6430 triple quadrapole mass spectrometer. Reverse phase HPLC analysis was recorded on a Waters Alliance HPLC (e2695) using xBridge C18 (150 x 4.6 mm, 5μ) column [UV (230 nm), Mobile phase: A) 5mM NH_4OAc in H_2O B) Acetonitrile (gradient system)].

Experimental

Diethyl 2-acetamido-2-phenethylmalonate (3): To a stirred solution of Diethyl acetamidomalonate (235.8 g, 1.09 moles) in DMSO (2000 mL) was added Cs_2CO_3 (442.6 g, 1.4 moles) at 0 ^oC. The resulting reaction mixture was stirred at RT for 1 h. Phenylethyl bromide (100 g, 0.54 moles) was added to the reaction mixture at RT. The resulting reaction mixture was stirred at 65 ^oC for 5h. The progress of the reaction was monitored by TLC, after completion of the reaction by TLC. RM cooled to RT and poured into ice cold water (5L) and stirred for 1h. The obtained off white solid was filtered and dried under vacuum to give **3** (132.7 g, 75%) as an off white solid. The obtained crude compound was used for the next step without any further purification. mp: 110-113 °C (Literature mp: 116 °C); IR: **(**KBr**)** cm^{-1} 3486, 3238, 2982, 1750, 1649; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.86 (br s, 1H), 7.38 (m, 5H), 2.70 (t, 2H), 2.42 (t, 2H), 2.18 (m, 4H), 2.15 (s, 3H), 1.21 (t, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.05, 169.60, 167.86, 166.94, 141.23, 128.80, 128.65, 126.40, 66.30, 62.08, 62.03, 56.54, 35.00, 29.83, 22.55, 22.37, 14.24; Mass: *(m/z)* = 321.9 $[M+H]^+$; HPLC Purity: 98.0%.

N-(1-Hydroxy-2-(hydroxymethyl)-4-phenylbutan-2-yl)acetamide (4): To a stirred solution of Diethyl 2-acetamido-2-phenethylmalonate **(3)** (200 g, 0.62 moles) in MeOH (2 L) was cooled to 0 ^oC. $NaBH_4$ (184.4 g, 4.99 moles) was added to the reaction mixture portion wise over a period of 2h at 0 ^oC and stirred for 16h at RT. The progress of the reaction was monitored by TLC, after completion of the reaction by TLC the reaction mixture was concentrated under reduced pressure. The obtained crude material was quenched with water (500 mL) and extracted with EtOAc (3 x 500 mL). The combined organic extracts were washed with brine solution (2 x 500 mL) and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to give **4** (130 g, 88%) as a colorless thick syrup. The obtained crude compound was used for the next step without any further purification. IR: **(**KBr**)** cm^{-1} 3680, 3309, 2021, 1738, 1617; ^{1}H NMR (400 MHz, DMSO-d_6) : δ 7.11-7.27 (m, 5H), 4.84 (t, 1H), 3.57 (m, 2H), 3.47 (m, 2H), 2.49 (t, 1H), 2.39 (t, 2H), 1.83-1.88 (m, 2H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.10, 141.28, 128.47, 128.31, 126.06, 64.47, 58.13, 33.53, 29.61, 24.09; Mass: *(m/z)* = 237.9 $[M+H]^+$; HPLC Purity : 98.8%

2-Acetamido-2-phenethylpropane-1,3-diyl diacetate (5): To a stirred solution of **4** (130 g, 0.55 moles) in Pyridine (130 mL) was cooled to 0 ^oC. Acetic anhydride (130 mL) was added drop wise to the reaction mixture over a period of 1h at 0 ^oC and the resulting reaction mixture was stirred at RT for 14h. The progress of the reaction was monitored by TLC, after completion of the reaction by TLC, the RM cooled to 0 ^oC and diluted with water (200 mL) and stirred for 2h at 0 ^oC. The obtained solid was filtered and washed with water (2 x 130 mL), followed by hexane (2 x 260 mL). The solid material was dried under vacuum to furnish **5** (158.4 g, 90%) as a white crystalline solid. The obtained crude compound was used for the next step without any further purification. mp: 116-118 °C (literature mp: 116-117 °C); IR: **(**KBr**)** cm^{-1} 3463, 3313, 2955, 1737, 1649; ^1H NMR (400 MHz, $CDCl_3$) : δ 7.17-7.26 (m, 5H), 5.62 (br s, 1H), 4.38 (s, 4H), 2.61-2.59 (m, 2H), 2.22-2.20 (m, 2H), 2.09 (s, 6H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.79, 170.10, 141.28, 128.47, 128.31, 126.06, 64.47, 58.13, 33.53, 29.61, 24.09, 20.81; Mass: *(m/z)* = 322 $[M+H]^+$; HPLC Purity : 99.7%.

2-Acetamido-2-(4-octanoylphenethyl)propane-1,3-diyl diacetate (6): To a stirred solution of $AlCl_3$ (627.8 g, 4.71 moles) in EDC[1] (1890 mL) was cooled to 0 ^oC. Octanoyl chloride (509.1 mL, 2.94 moles) was added in one portion under N_2 atmosphere at 0 ^oC. The resulting reaction mixture was stirred at RT for 1h. The reaction mixture was again cooled to 0 ^oC, the solution of **5** (189 g, 0.59 moles) dissolved in EDC (567 mL) was added to the reaction mixture drop wise over a period of 1.5h at 0 ^oC. The resulting reaction mixture was stirred at RT for 16 h. The progress of the reaction was monitored by TLC, after completion of the reaction by TLC the reaction mixture poured into ice cold water (2L). Separate the organic layer from aqueous layer and washed with brine solution (2 x 1L) and dried over Na_2SO_4 (150 g). The organic layer was concentrated under reduced pressure to give a crude compound. The obtained crude material was triturated with hexane (3.5L) at RT for 2h, the obtained free flow solid was filtered and washed with hexane (300 mL) and dried under vacuum at RT for 6h to give **6** (213.2 g, 81%) as an off white solid. mp: 105-107 °C; IR: **(**KBr**)** cm^{-1} 3465, 3310, 2921, 2856, 1736, 1552 ; ^1H NMR

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[1] EDC can be replaced by Dichloromethane with similar yields.

(400 MHz, $CDCl_3$) : δ 7.87 (d, 2H, *J* = 8.4 Hz), 7.26 (d, 2H, *J* = 8.4 Hz), 5.69 (brs, 1H), 4.33 (s, 4H), 2.91 (t, 1H), 2.23-2.21 (m, 2H), 2.09 (s, 6H), 1.97 (s, 3H), 1.70-1.68 (m, 2H), 1.34-1.32 (m, 8H), 0.87 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.28, 170.76, 170.29, 146.86, 135.11, 128.54, 128.34, 64.39, 58.12, 38.52, 33.13, 31.64, 29.67, 29.27, 29.08, 24.41, 24.05, 22.55, 20.78, 14.03; Mass: *(m/z)* = 448 $[M+H]^+$; HPLC Purity : 99.0%

2-Acetamido-2-(4-octylphenethyl)propane-1,3-diyl diacetate (7): In a 2L steel hydrogenation vessel was charged with 10% Pd-C (20 g), EtOH (950 mL) and **6** (95 g, 0.212 moles) under N_2 atmosphere. The reaction mixture was hydrogenated (60 Psi H_2 pressure) using Parr hydrogenator at RT for 2h. The progress of the reaction was monitored by TLC, after completion of the reaction; the reaction mixture was filtered through celite bed and washed with EtOH (100 mL). The filtrate was concentrated under reduced pressure to give **7** (87.2 g, 95% yield) as a white solid. The obtained solid was used for the next step without any further purification. mp: 110-112 °C (literature mp: 111.8 °C); IR: **(**KBr**)** cm^{-1} 3460, 3309, 2921, 1738, 1650, 1238; ^1H NMR (400 MHz, $CDCl_3$) : δ 7.08 (s, 4H), 5.62 (br s, 1H), 4.34 (s, 4H), 2.56-2.54 (m, 4H), 2.20-2.18 (m, 2H), 2.08 (s, 6H), 1.94 (s, 3H), 1.57-1.56 (m, 2H), 1.27-1.26 (m, 10H), 0.87 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.80, 170.13, 140.71, 138.33, 128.48, 128.15, 64.49, 58.16, 35.49, 33.59, 31.84, 31.56, 29.43, 29.30, 29.22, 29.16, 24.07, 22.62, 20.81, 14.07; Mass: *(m/z)* = 434 $[M+H]^+$; HPLC Purity : 92.2%

Fingolimod*HCl (1*HCl): The mixture of **7** (87 g, 0.20 moles) and 6N aq. HCl (870 mL) was heated at 100 ^oC and stirred for 1h. The progress of the reaction was monitored by TLC, after completion of the reaction by TLC the reaction mixture was cooled to 0 ^oC. The reaction mixture was concentrated under reduced pressure to give a crude compound. The obtained solid was triturated with diethyl ether and filtered, dried under vacuum for 4h and then recrystallized using ethanol to furnish **1*HCl** (48.7g, 79% yield) as a white solid. mp: 107-110 °C (literature mp: 107-110 °C); IR: **(**K Br**)** cm^{-1} 3680, 3470, 3404, 2021, 1617; ^1H NMR (400 MHz, DMSO-d_6) : δ 7.88 (br s, 3H), 7.09 (s, 4H), 5.38 (t, 2H), 3.53-3.51 (m, 4H), 2.56-2.54 (m, 4H), 1.78-1.75 (m, 2H), 1.53-1.51 (m, 2H), 1.27-1.25 (m, 10H), 0.85 (t, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) : δ: 139.74, 138.79, 128.20, 127.99, 60.95, 60.20, 38.87, 34.70, 33.21, 31.23, 31.01, 28.79, 28.62, 27.90, 22.03, 13.91; Mass: *(m/z)* = 308 $[M+H]^+$; HPLC Purity : 99.1%

Overall Atom Economy of the Route: 35.8%

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