

Synthesis of Novel Retinoid X Receptor-Selective Retinoids

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Supporting Information Available: Complete experimental information for the synthesis of **8**, **16**, **13**, **15**, **19**, **2**, **11**, **12** and **25** are provided. This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. TLC was performed on Kieselgel 60 F254 plates (Merck) using reagent grade solvents. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). ^1H NMR were performed at 300 MHz and ^{13}C NMR at 75 MHz in CDCl_3 , unless otherwise specified. Chemical shifts are in ppm downfield from internal tetramethylsilane. Mass spectral and combustion analysis were performed by the Eli Lilly and Co. Physical Chemistry Department.

1,1,4,4-Tetramethyl-1,2,3,4-tetrahydronaphthylene (8): 2,5-dimethyl-2,5-hexanediol (391 g, 2.67 mol) was combined with reagent grade conc. HCl (6 L) and stirred at ambient temperature for 3 hr. Water (4 L) and CH_2Cl_2 (4 L) were then added to dissolve the solids. The layers were separated and the aqueous layer back-extracted with additional CH_2Cl_2 (1 L). The combined organic layers were dried (MgSO_4) and filtered using CH_2Cl_2 (1 L) to rinse. Toluene (372 g, 430 mL, 4.04 mol) was added to the CH_2Cl_2 solution of **7** and

AlCl_3 (17.5 g, 0.131 mol) was added in portions over 25 min at ambient temperature while scrubbing vigorous HCl off-gassing. The reaction, which was complete upon addition of AlCl_3 , was quenched with deionized water (4 L) while keeping the reaction temperature $<25^\circ\text{C}$. Heptane (4 L) was added and organic layer removed. The aqueous layer was back-extracted with additional heptane (1 L). The combined organic layers were washed with water (4 L), brine (2 L) and dried (MgSO_4) and the solvent removed *in vacuo* to give 538 g (99%) of **8** as a colorless oil that crystallized upon cooling.

Pyridine 2,5-dicarboxylic acid 5-methyl ester (16): To a suspension of dimethyl 2,5-pyridinedicarboxylate (1.26 Kg, 6.45 mol) in MeOH (11.3 L) was added NaOH pellets (274 g, 6.85 mol) in one portion, and the mixture stirred and heated to reflux for 1-4 hr. Aqueous 2.0 N HCl (4.75 L, 10.7 mol) was then added dropwise at 60° to 75°C over 20-60 min and the resultant slurry allowed to stir and cool gradually to 15° to 20°C with an ice-water bath. The reaction was filtered, rinsed with 2:1 MeOH:water (1.5 L), then water (2 L). The wet cake was dried in a vacuum oven at 50° to 60°C to yield 803 g (69%) **16** as an off-white solid.

Methyl 6-[(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]nicotinate (13): To a suspension of **16** (750 g, 4.14 mol) in CH_2Cl_2 (5.3 L) under N_2 was added a catalytic amount of DMF (9.4 mL, 0.110 mol) followed by oxalyl chloride (380 mL, 4.35 mol) dropwise at 15° to 30°C over 10-60 min. The reaction mixture was stirred at 15° to 30°C for 1-4 hr. Nitromethane (115 mL, 2.12 mol) and **8** (922 g, 4.56 mol) were charged, and the resulting mixture stirred and cooled to 5° to 15°C using an ice water bath. AlCl_3 (1658 g, 12.4 mol) was added in portions at 5° to 30°C over 10-30 min. The dark reaction mixture was allowed to stir at 15° to 30°C for 12-24 hr. The reaction mixture was added dropwise over 45-90 min at 15° to 35°C to a separate flask containing deionized water (7.4 L) stirring in an ice water bath. The quenched reaction mixture was stirred at 15° to 35°C for 10-30 min, then the layers were separated. The upper aqueous layer was extracted with CH_2Cl_2 (1.4 L) and the combined organic layers dried (MgSO_4). The reaction was

filtered and rinsed with CH_2Cl_2 (1.5 L). The filtrate was concentrated *in vacuo* to a solid residue (1.54 Kg). MeOH (6.2 L) was added, and the mixture heated until all solids went into solution. The solution was allowed to stir and gradually cool to ambient temperature over 12-24 hr to crystallize the product. After stirring in an ice water bath at 0° to 10 °C for 1-2 hr, the product was isolated by vacuum filtration and rinsed with cold MeOH (3.0 L). The wet cake was dried in a vacuum oven at 50° to 60 °C to yield 1033 g (68%) **13** as an off-white solid.

Methyl 6-[(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethenyl]nicotinate (15): To a solution of **13** (3.40 kg, 9.3 mol) in toluene (34 L) at -10° to -5 °C under N_2 was added a 3.0 M solution of MeMgCl in THF (3.95 kg) over 15-120 min. Toluene (5.7 L) was used to rinse the MeMgCl solution. The reaction mixture was warmed to 20° to 25 °C, then quenched by addition to 1.0 N HCl (23 L) with stirring at 15° to 25 °C over 15-30 min. The reaction mixture was rinsed into the quench solution with more toluene (10 L). The layers were separated, and the organic layer washed with deionized water (24 L). The combined aqueous layers were back extracted with toluene (10 L). The combined organic layers were filtered over MgSO_4 (5 kg) and rinsed with toluene (10 L). The filtrate was stirred at 20° to 25 °C as *p*-TsOH· H_2O (1.77 kg) was added. The solution was heated to reflux for 3-15 hr to azeotrope water. The reaction solution was concentrated by atmospheric distillation to a total volume of ~30 L. A solution of Na_2CO_3 (2.6 kg) in deionized water (48 L) was added to the concentrated reaction solution at 20° to 25 °C over 1-60 min, and the layers were separated. The lower aqueous layer was back extracted with toluene (10 L). The combined organic layers were concentrated by atmospheric distillation to a total volume of ~14 L. MeOH (60 L) was added, and the mixture was again concentrated by atmospheric distillation to a total volume of ~35 L. MeOH (15 L) was added, and the mixture was again concentrated by atmospheric distillation to a total volume of 14-20 L. The resulting slurry of product was stirred at 22° to 28 °C for 1-3 hr, then filtered by nitrogen pressure and rinsed with MeOH (10 L). After drying in a vacuum oven at 40° to 50 °C, 2.07 kg (61%) **15** was obtained.

Methyl 6-[(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]nicotinate (19): To a stirred suspension of trimethylsulfoxonium iodide (726 g, 3.30 mol) in dry DMSO (2.4 L) was added potassium *tert*-butoxide, 20 % wt. in THF (1876 g, 3.34 mol). A solution of **15** (800 g, 2.20 mol) in dry THF (9.6 L) was prepared separately, then added to the above suspension over 20-60 min at 20° to 30 °C. The reaction was stirred at 20° to 30 °C for 30-60 min then quenched by addition of aqueous 2.0 N HCl (1.7 L, 3.5 mol HCl, 1.54 eq.) over 5-30 min. The two phase mixture was stirred at 20° to 35 °C for 15-60 min and deionized water (1.5 L) was added. The aqueous layer was back-extracted with EtOAc (2.0 L) and the combined organic layers concentrated *in vacuo* to a solid residue (1491 g). MeOH (6.2 L) was added, and the resulting slurry was stirred at 40° to 50 °C for 30-60 min, then cooled to 15° to 25 °C. After stirring at 15° to 25 °C for 1-2 hr, the product was isolated by vacuum filtration and rinsed with MeOH (3 L). The wet cake was dried in a vacuum oven at 50° to 60 °C to yield 681 g (82%) **19** as a white to off-white solid.

6-[1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]nicotinic acid (2): To a stirred suspension of **19** (1.09 kg, 2.89 mol) in MeOH (10.9 L) was added aqueous 50% sodium hydroxide (460 mL, 8.79 mol), and the slurry was heated to 60° to 70 °C for 0.5-2 hr until all solids went into solution and the reaction was complete. The hot solution was filtered and the filtrate solution with aqueous 6.0 N HCl (1.5 L, 9.00 mol), added over 45-90 min at 50° to 70 °C, to precipitate the product. Deionized water (3.5 L) was added in one portion to dissolve the sodium chloride and the resultant slurry was stirred at 50° to 70 °C for 20-60 min, then cooled to 20° to 25 °C using an ice-water bath. After stirring at 20° to 25 °C for 0.5-2 hr, the product was isolated by vacuum filtration, rinsed with 1:1 MeOH:water (1.2 L) and deionized water (3 L). The wet cake was dried in a vacuum oven at 50° to 60 °C to yield 1.04 kg (99%) **2** as a white to off-white solid.

Methyl 4-[(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)carbonyl]benzoate (11): To a solution of **8** (20.0 g, 98.8 mmol) and **9** (20.7 g, 98.8 mmol) in dichloroethane (20 mL) was added FeCl₃ (0.80 g, 4.93 mmol) and the reaction heated to 75 °C for 16 hr. The reaction was cooled and MeOH (60 mL) was

added. The resultant light green slurry was stirred overnight at ambient temperature, then filtered and rinsed with cold MeOH (60 mL) to give 29.3 g (81%) of **11**.

4-[(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)carbonyl]benzoic acid (12): A suspension of **11** (29.3 g, 80.3 mmol) in MeOH (290 mL) was treated with 50 wt. % NaOH (19.3 g, 12.7 mL, 0.24 mol) and the reaction heated to reflux for 1-2 hr. The reaction was then cooled to 55 °C and conc. HCl (20.1 mL, 0.24 mol) added dropwise at < 60 °C. The resultant slurry was cooled in an ice bath for 1 hr and filtered to give 30.1 g (100%) **12**.

1,1,4,4,6-Pentamethyl-1,3,4-trihydronaphthalene-2-one (25): A solution of 2-methyl-2-(*p*-tolyl)propanoic acid (10.0 g, 56.1 mmol) in CH₂Cl₂ and DMF (0.15 mL) was treated dropwise with oxalyl chloride (7.48 g, 5.14 mL, 58.9 mmol) and stirred at room temperature under N₂ for 2 h. The reaction was then cooled to -30 °C and catalytic SnCl₄ (2.23 g, 1.00 mL, 8.55 mmol) added. After stirring at <-30 °C for 15 min, isobutylene (12.6 g, 0.224 mol) was condensed into the reaction at -78 °C *via* cannula. The reaction was allowed to warm to room temperature over 1.5 h and then heated to reflux for 2.5 h. The reaction was cooled, quenched with water (50 mL), and then the organic layer washed with aqueous 1 N NaOH (50 mL) and dried (MgSO₄). The solvent removed *in vacuo* to give 13.6 g of an oil that was crystallized from MeOH (30 mL) to afford 7.36 g (61%) of **25**. ¹H NMR (500 MHz, CDCl₃) δ 7.25 (d, 1H, *J* = 8.05 Hz), 7.21 (s, 1H), 7.11 (d, 1H, *J* = 8.19 Hz), 2.69 (s, 2H), 2.39 (s, 3H), 1.52 (s, 6H), 1.34 (s, 6H); ¹³C (125 MHz, CDCl₃) 214.8, 143.9, 140.7, 136.4, 128.2, 127.6, 125.4, 52.0, 48.1, 38.3, 31.0, 28.9, 21.5; IR (KBr) ν 2965, 2928, 2870, 1711, 1499, 1462, 1380, 1366, 1313, 1237, 822 cm⁻¹. HRMS (FAB⁺) *m/z* exact mass calc'd for C₁₅H₂₁O 217.1592, found 217.1589.