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A FACILE SYNTHESIS OF AN (*E*)-4-METHYL-4-HEXENOIC ACID SUBSTITUTED PYRIDINE ANALOGUE OF MYCOPHENOLIC ACID

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ABSTRACT: An (E)-4-methyl-4-hexenoic acid substituted pyridine analogue, **2**, of mycophenolic acid has been synthesized from 6-methyl-2-pyridine-carboxaldehyde in 6 steps via a Claisen rearrangment.

Mycophenolic acid (MPA, **1**) is one of the most potent inhibitors of *inosine monophosphate dehydrogenase* (*IMPD*).[1] The enzyme is rate-limiting in guanine nucleotide biosynthesis and inhibitors have been shown to possess significant antineoplastic, antiparasitic, antiviral, and immunosuppressive activities.[2] MPA may bind in the NAD^+/NADH domain in the *IMPD* active site like the *IMPD* inhibitors tiazofurin and selenazofurin.[3] The major problem with MPA in humans is that conjugation of the phenolic hydroxyl group with glucuronic acid is so rapid that therapeutic levels of the drug cannot be achieved.[4]

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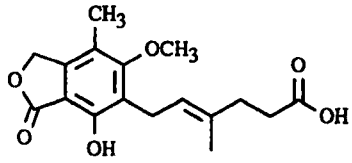

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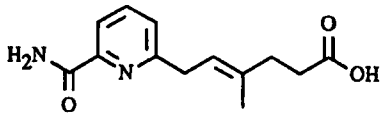


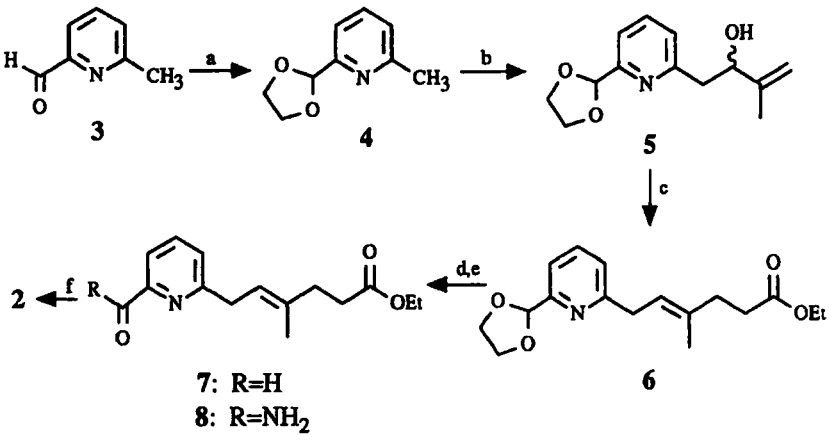
2

In our effort to develop potent, metabolically stable inhibitors of *IMPD* using MPA as a "lead" compound, we have designed and synthesized a number of heterocyclic analogues of MPA. Studies of the structure activity relationships of MPA have shown that any modifications of the (*E*)-4-methyl-4-hexenoic acid side chain markedly diminishes or obliterates activity.[2,5] Therefore, we required a versatile method for the incorporation of the MPA side chain in a variety of MPA analogues. This report describes one approach to the elaboration of the side chain on a pyridine.

The (*E*)-4-methyl-4-hexenoic acid side chain in MPA derivatives has been synthesized by direct incoporation of the (*E*)-4-methyl-4-hexenoic acid moiety (prepared from geraniol[6]) and a linear approach *via* a Wittig reaction.[7] The direct alkylation of α-lithiopyridines with (*E*)-1-bromo-6-(*tert*-butyldimethylsiloxy)-3-methyl-2-hexene was unsuccessful[8] and the linear multi-step Wittig route was not attractive because of very low yields in the late steps. We therefore developed a Claisen rearrangment route to the MPA side chain in **2**.

Commercially available 6-methyl-2-pyridinecarboxaldehyde (**3**) was protected as the cyclic acetal (1,2-ethanediol, TsOH, benzene, reflux, 24 h). The acetal **4** was lithiated (2 M phenyllithium, 1.1 equiv) at -20 °C in ether[9] and treated with methacrolein (1.2 equiv) to afford **5**, a key intermediate for the Claisen rearrangment. Rearrangment of **5** to **6** was accomplished using triethyl

orthoacetate (7 equiv) in the presence of catalytic amount (0.3 equiv) of propionic acid at 138 °C for 2 h.[10] Deprotection of cyclic acetal **6** under a variety of acidic conditions[11] was unsuccessful, however transketalization of **5** (cat. TsOH, acetone-H_2O)[11] gave the corresponding aldehyde **7**. The amide **8** was obtained from **7** using Gilman's procedure.[12] Alkaline hydrolysis of the methyl ester **8** produced the target compound **2** as white solid.



Reagent (% yields): (a) ethylene glycol, TsOH, benzene, reflux (95%). (b) PhLi, ether, -20°C; methacrolein (56%). (c) $CH_3C(OEt)_3$, propionic acid, 138°C, 2hr (82%). (d) TsOH, aq. acetone, reflux (65%). (e) NaCN, MnO_2, NH_3, 2-PrOH (84%). (f) KOH, EtOH-H_2O (96%).

This facile two-step procedure involving benzylic alkylation and Claisen rearrangment will be of significant value in the synthesis of the (*E*)-4-methyl-4-hexenoic acid side chain in a variety of MPA analogues.

Experimental

Melting points (uncorrected) were determined in open capillary tubes on a Thomas-Hoover Unimelt apparatus. Infrared spectra were obtained on a Matteson

Polaris FT-IR interferometer. ^{1}H-NMR spectra ($CDCl_3$/TMS, unless noted otherwise) were obtained on a Varian EM390 spectrometer at 90 MHz. Elemental analysis were performed by Atlantic Microlab, Atlanta, GA. Flash column chromatography was performed with Kieselgel 60 (EM Science, 230-400 mesh).

2-(1,3-Dioxolan-2-yl)-6-methylpyridine (4). A solution of 6-methyl-2-pyridinecarboxaldehyde (**3**, 5 g, 41.3 mmol), 1,2-ethanediol (9 mL, 161 mmol), and *p*-toluenesulfonic acid monohydrate (0.2 g, 1 mmol) in benzene (250 mL) was placed in round-bottom flask fitted with Dean-Stark trap and a condenser and heated at reflux for 2 days. The reaction mixture was cooled to room temperature and excess benzene (200 mL) was added. The organic solution was washed [5 % sodium hydroxide solution (100 mL) then water (2 x 50 mL)], dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give **4** as an clear oil (6.48 g, 95 %) that was used in the next reaction without further purification: ^{1}H-NMR δ 7.70 (t, 1 H), 7.35 (d, 1 H), 7.10 (d, 1 H), 5.80 (s, 1 H), 4.3-3.9 (m, 4 H), 2.50 (s, 3 H); IR (neat) 2957, 2887, 1596, 1461, 1109 cm^{-1}. *Anal.* Calcd for $C_9H_{11}NO_2$: C, 65.43; H, 6.71; N, 8.48 Found: C, 65.26; H, 6.70; N, 8.43.

2-(2-Hydroxy-3-methyl-3-butenyl)-6-(1,3-dioxolan-2-yl)pyridine (5). A solution of phenyllithium (2 M, 18.2 mL, 36.4 mmol) was added dropwise to a solution of **4** (6 g, 36.32 mmol) in anhydrous ether (250 mL) at -20 °C and the mixture was stirred for 15 min. A solution of methacrolein (2.54 g, 3 mL, 36.25 mmol) in anhydrous ether (30 mL) was added and the mixture was warmed to room temperature. Water (50 mL) was added, the organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatograpy (ethyl acetate-hexane, 2:1) to afford **5** as an oil (4.78 g, 56 %): ^{1}H-NMR δ 7.1-7.8 (m, 3 H), 5.80 (s, 1 H), 5.00 (bs, 1 H), 4.83

(bs, 1 H), 4.50 (t, 1 H), 3.9-4.3 (m, 4 H), 3.00 (d, 2 H), 2.53 (bs, 1 H), 1.80 (s, 3 H); IR (neat) 3385, 3071, 2965, 2888, 1650, 1596, 1460, 1371 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.29; N, 5.95. Found: C, 66.38; H, 7.31; N, 5.93.

Ethyl (*E*)-4-methyl-6-[6-(1,3-dioxolan-2-yl)pyridin-2-yl]-4-hexenoate (6). A mixture of **5** (3.53 g, 15 mmol), propionic acid (0.37 g, 5 mmol) and triethyl orthoacetate (17 g, 19.25 mL, 105 mmol) was heated at 138 °C for 2 h with continuous removal of ethanol. The excess triethyl orthoacetate was removed *in vacuo* and the crude residue was purified by flash chromatography (ethyl acetate-hexane, 1:1) to afford **6** as an oil (3.75 g, 82 %): ^1H NMR δ 7.1-7.8 (m, 3 H), 5.80 (s, 1 H), 5.50 (t, 1 H), 4.0-4.3 (m, 6 H), 3.60 (d, 2 H), 2.2-2.6 (m, 4 H), 1.80 (s, 3 H), 1.25 (t, 3 H); IR (neat) 2979, 2888, 1731, 1594, 1458, 1370 cm^{-1}. *Anal.* Calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.93; H, 7.63; N, 4.60.

Ethyl (*E*)-6-(6-formylpyridin-2-yl)-4-methyl-4-hexenoate (7). A solution of **6** (3.05 g, 10 mmol) and *p*-toluenesulfonic acid (0.2 g, 1 mmol) in water-acetone (120 mL, 1:5) was heated at reflux for 24 h. The mixture was allowed to cool to room temperature, the acetone was removed *in vacuo* and ethyl acetate (200 mL) was added. The organic layer was washed [saturated sodium carbonate solution (50 mL) then water (2 x 50 mL)], dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate-hexane, 1:3) to afford **7** as an oil (1.71 g, 65 %): ^1H NMR δ 10.1 (s, 1 H), 7.3-7.9 (m, 3 H), 5.55 (t, 1 H), 4.10 (q, 2 H), 3.65 (d, 2 H), 2.2-2.6 (m, 4 H), 1.80 (s, 3 H), 1.25 (t, 3 H); IR (neat) 2979, 2941, 2826, 1731, 1712, 1590, 1455, 1370 cm^{-1}. *Anal.* Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.05; H, 7.35; N, 5.32.

Ethyl (*E*)-6-(6-carboxamidopyridin-2-yl)-4-methyl-4-hexenoate (8). Sodium cyanide (1.225 g, 25 mmol) was added to a solution of 2-propanol (50 mL) saturated with ammonia at 0 °C and, after 5 min, a solution of **7** (1.3 g, 5 mmol) in 2-propanol (20 mL) was added followed by maganese oxide (8.69 g, 100 mmol, added in 2 portions 10 min apart). The mixture was stirred for 4 h at 0 ^{0}C, diluted with dichloromethane (150 mL) and filtered through Celite. The filtrate was concentrated *in vacuo* and the crude residue was purified by flash chromatography (ethyl acetate-hexane, 2:1) to afford **8** as an oil (1.16 g, 84 %): ^{1}H NMR δ 7.7-8.1 (m, 3 H, including deutrium exchangable 1 H), 7.40 (m, 1 H), 6.8 (bs, 1 H, NH), 5.50 (t, 1 H), 4.10 (q, 2 H), 3.60 (d, 2 H), 2.2-2.6 (m, 4 H), 1.80 (s, 3 H), 1.20 (t, 3 H); IR (neat) 3451, 3318, 2979, 1731, 1690, 1590, 1459, 1385 cm^{-1}. *Anal.* Calcd. for $C_{15}H_{20}N_2O_3$: C, 65.19; H, 7.30; N, 10.14. Found: C, 65.03; H, 7.34; N, 10.10.

(*E*)-6-(6-carboxamidopyridin-2-yl)-4-methyl-4-hexenoic acid (2). Potassium hydroxide solution (0.5 M, 40 mL) was added to a solution of **8** (0.83 g, 3 mmol) in ethanol (5 mL) at 0 ^{0}C and the mixture was stirred at room temperature for 2 h. The mixture was washed with ether (40 mL) and acidified to pH 3 with cold 5 % HCl solution. The aqueous solution was extracted with ethyl acetate (3 x 100 mL) and the combined organic layer was washed with water (2 x 100 mL), dried ($MgSO_4$) and concentrated. The crude residue was purified by flash chromatography (chloroform-ethyl acetate-formic acid, 50:50:1) to give **2** as a white solid (0.71 g, 96 %): mp 115-116 ^{0}C; ^{1}H NMR (DMSO-d_6/TMS) δ 7.7-8.1 (m, 3 H, including deutrium exchangable 1 H), 7.60 (bs, 1 H, NH_2), 7.43 (m, 1 H), 5.53 (t, 1 H), 3.55 (d, 2 H), 2.1-2.6 (m, 4 H) 1.73 (s, 3 H); IR (KBr)

3443, 3236, 2915, 2531, 1717, 1650, 1588, 1395, 1300, 1201 cm^{-1}. *Anal.* Cacld. for $C_{13}H_{16}N_2O_3$: C, 62.88; H, 6.50; N, 11.29. Found: C, 62.80; H, 6.52; N, 11.19.

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