Total Synthesis of (-)-Pironetin

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Supporting Information

General Information: ^1H NMR spectra were recorded on either a Varian Gemini-300 (300 MHz) or a Varian Inova-500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl_3 at 7.26 ppm) unless otherwise indicated. Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, apt = apparent triplet, m = multiplet, brs = broad singlet, coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on either a Varian Gemini-300 (75 MHz), a Bruker AC 300/P (75 MHz) or a Varian Inova-500 (125 MHz) spectrometers and are recorded in ppm using solvent as an internal standard (CDCl_3 at 77.0 ppm) unless otherwise indicated.

Aldol (+)-8: $[\alpha]_{\text{D}}^{20} +51.5$ (*c* 1.15, CH_2Cl_2); IR (film) ν_{max} 3489, 3031, 2938, 2866, 1774, 1691, 1609, 1511, 1454, 1382, 1300, 1243, 1207, 1104, 1032, 970, 821, 750, 697cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.28 (m, 7H), 6.87 (d, *J* 8.5 Hz, 2H), 4.58 (ddd, *J* 12.8, 7.0 and 3.4 Hz), 4.44 (s, 2H), 4.18 (m, 3H), 3.80 (m, 1H), 3.80 (s, 3H), 3.68 (m, 1H), 3.63 (m, 1H), 3.34 (brs, 1H), 3.25 (dd, *J* 13.4 and 3.1 Hz, 1H), 2.78 (dd, *J* 13.4 and 9.5 Hz, 1H), 1.86 (m, 1H), 1.72 (m, 1H), 1.28 (d, *J* 6.9 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.6, 159.2, 153.1, 135.1, 130.2, 129.4, 129.3, 129.0, 127.4, 113.8, 72.9, 70.5, 68.1, 66.1, 55.3 (55.278), 55.3 (55.271), 42.5, 37.8, 33.7, 11.1; TLC (EtOAc/hexanes 50%) *R*_f 0.34.

Weinreb amide (+)-9: $[\alpha]_D^{20} +4.27$ (*c* 1.17, EtOH); IR (film)

$\nu_{\max}$ 3488, 2954, 2936, 2862, 1658, 1616, 1503, 1461, 1379, 1299, 1249, 1175, 1100, 1038, 996, 835, 773, 667 cm^{-1} ; ^1H

NMR (500 MHz, CDCl_3) δ 7.24 (d, 2H, *J* 8.8 Hz), 6.86 (d, *J* 8.5 Hz, 2H), 4.42 (d, *J* 11.7 Hz, 1H), 4.39 (d, *J* 11.7 Hz, 1H), 4.02 (dt, *J* 7.8 and 5.0 Hz, 1H), 3.80 (s, 3H), 3.60 (s, 3H), 3.56 (dt, *J* 9.0 and 7.1 Hz, 1H), 3.49 (dt, *J* 9.3 and 7.0 Hz, 1H), 3.14 (s, 3H), 3.01 (brs, 1H), 1.83 (m, 2H), 1.13 (d, *J* 7.1 Hz, 3H), 0.88 (s, 9H), 0.054 (s, 3H), 0.042 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 176.6, 159.0, 130.6, 129.3, 113.7, 72.5, 71.3, 66.2, 61.2, 55.2, 41.2, 35.4, 32.0, 25.9, 18.0, 14.5, -4.4, -4.5; TLC (EtOAc/hexanes 33%) *R*_f 0.39.

Aldehyde (+)-6: $[\alpha]_D^{20} +44.7$ (*c* 1.00, CH_2Cl_2); IR (film) $\nu_{\max}$ 2953,

2850, 2711, 1773, 1614, 1583, 1511, 1459, 1366, 1299, 1248, 1171, 1093, 1037, 836, 774 cm^{-1} ; ^1H NMR (300 MHz, C_6D_6) δ 9.61 (s, 1H),

7.20 (d, 2H, *J* 8.4 Hz), 6.81 (d, *J* 8.0 Hz, 2H), 4.28 (m, 1H), 4.30 (d, *J* 11.7 Hz, 1H), 4.24 (d, *J* 11.7 Hz, 1H), 3.33 (dt, *J* 9.5 e 6.4 Hz), 3.29 (s, 3H), 3.24 (dt, *J* 9.5 and 5.7 Hz, 1H), 2.15 (ddd, *J* 14.1, 7.0 and 3.5 Hz), 1.67 (q, *J* 6.2 Hz, 2H), 0.97 (d, *J* 7.0 Hz, 3H), 0.90 (s, 9H), 0.036 (s, 3H), 0.008 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 203.9, 160.3, 131.4, 129.9, 114.6, 73.2, 69.7, 66.6, 55.1, 51.9, 35.4, 26.3, 18.5, 8.0, -4.1, -4.3; TLC (EtOAc/hexanes 20%) *R*_f 0.47.

Aldol 10: IR (film) $\nu_{\max}$ 3463, 3036, 2928, 2856, 1784,

1701, 1608, 1511, 1454, 1387, 1294, 1243, 1212, 1078, 836, 696 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.27 (m, 7H),

6.87 (d, *J* 8.8 Hz, 2H), 4.67 (m, 1H), 4.44 (d, *J* 11.7 Hz,

1H), 4.38 (d, *J* 11.7 Hz, 1H), 4.27 (brs, 1H), 4.17 (m, 2H), 4.05 (dt, *J* 9.1 and 3.2 Hz, 1H), 4.01 (dt, *J* 10.2 and 1.7 Hz, 1H), 3.86 (qd, *J* 6.8 and 1.6 Hz, 1H), 3.80 (s, 3H), 3.49 (m, 2H), 3.35 (dd, *J* 13.2 and 3.3 Hz, 1H), 2.74 (dd, *J* 13.4 and 9.7 Hz, 1H), 1.83 (m, 3H), 1.20 (d, *J* 7.0 Hz, 3H), 0.88 (s, 9H), 0.86 (d, *J* 7.0 Hz, 3H), 0.12 (s, 3H), 0.065 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.0, 159.2, 153.3, 135.6, 130.5, 129.5, 129.3, 129.0, 127.3, 113.8, 73.4, 73.0, 72.5, 66.6, 66.1, 55.8, 55.2, 40.6, 39.7, 37.6, 31.9, 25.7, 17.8, 12.1, 8.2, -4.6, -5.1; TLC (EtOAc/hexanes 30%) *R*_f 0.44.

Lactone (+)-14: $[\alpha]_D^{20} +66.6$ (*c* 1.05, CH₂Cl₂); IR (film) $\nu_{\max}$ 3432, 2916, 2848, 1716, 1612, 1516, 1464, 1361, 1299, 1253, 1099, 1031, 979, 818, 732 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 7.19 (d, *J* 8.5 Hz, 2H), 6.80 (d, *J* 8.5 Hz, 2H), 4.28 (d, *J* 11.7 Hz, 1H), 4.23 (d, *J* 11.5 Hz, 1H), 4.08 (ddd, *J* 2.4, 3.9 and 9.3 Hz), 3.47 (dt, *J* 4.5 and 9.1 Hz, 1H), 3.31 (m, 1H), 3.28 (s, 3H), 2.99 (dd, *J* 3.8 and 10.4 Hz, 1H), 2.15 (dq, *J* 7.1 and 10.3 Hz, 1H), 1.73 (m, 1H), 1.46 (m, 1H), 1.39 (m, 1H), 1.34 (brs, 1H), 1.23 (d, *J* 6.8 Hz, 3H), 0.59 (d, *J* 7.1 Hz, 3H); ¹³C NMR (75 MHz, C₆D₆) δ 172.1, 159.9, 131.0, 129.5, 114.1, 75.8, 73.5, 72.9, 65.8, 54.6, 39.8, 33.4, 33.1, 14.1, 4.3; TLC (EtOAc/hexanes 50%) *R*_f 0.21.

Diol (+)-11: $[\alpha]_D^{20} +31.4$ (*c* 1.11, CH₂Cl₂); IR (film) $\nu_{\max}$ 3421, 2956, 2929, 2858, 1721, 1612, 1514, 1465, 1382, 1361, 1300, 1250, 1175, 1087, 1032, 836, 780, 738 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.25 (d, *J* 8.8 Hz, 2H), 6.88 (d, *J* 8.5 Hz, 2H), 4.56 (brs, 1H), 4.45 (d, *J* 11.5 Hz, 1H), 4.39 (d, *J* 11.5 Hz), 3.97 (dt, *J* 9.0 and 3.2 Hz, 1H), 3.93 (dd, *J* 10.3 and 1.7 Hz), 3.81 (s, 3H), 3.79 (dd, *J* 10.5 and 3.6 Hz, 1H), 3.67 (dd, *J* 10.6 and 5.5 Hz, 1H), 3.53 (m, 2H), 2.81 (brs, 1H), 1.91 (m, 1H), 1.85 (m, 2H), 1.65 (m, 1H), 0.95 (d, *J* 6.8 Hz, 3H), 0.89 (s, 9H), 0.73 (d, *J* 7.1 Hz, 3H), 0.12 (s, 3H), 0.066 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 159.2, 130.5, 129.3, 113.8, 76.3, 75.1, 72.6, 68.0, 66.6, 55.3, 39.7, 36.2, 31.0, 25.7, 17.8, 13.5, 8.3, -4.4, -5.1; TLC (EtOAc/hexanes 50%) *R*_f 0.50.

Tosylate (+)-12: $[\alpha]_D^{20} +19.9$ (*c* 1.00, EtOH); IR (film) $\nu_{\max}$ 3465, 2956, 2929, 2858, 1721, 1612, 1514, 1465, 1361, 1300, 1246, 1175, 1099, 1033, 962, 835, 781, 737, 667 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.79 (d, *J* 8.4 Hz, 2H), 7.32 (d, *J* 7.7 Hz, 2H), 7.25 (d, *J* 8.8 Hz, 2H), 6.88 (d, *J* 8.8 Hz, 2H), 4.44 (d, *J* 11.3 Hz, 1H), 4.38 (d, *J* 11.3 Hz, 1H), 4.14 (brs, 1H), 4.09 (dd, *J* 9.5 and 7.3 Hz, 1H), 3.93 (m, 2H), 3.81 (s, 3H), 3.68 (dd, *J* 10.1 and 1.3 Hz, 2H), 3.50 (m, 2H), 2.43 (s, 3H), 1.81 (m, 4H), 0.86 (s, 9H), 0.83 (d, *J* 6.6 Hz, 3H), 0.68 (d, *J* 7.0 Hz, 3H), 0.084 (s, 3H), 0.046 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 159.2, 144.5, 133.3, 130.5, 129.7, 129.3, 127.9, 113.7, 74.8, 73.7, 72.5, 72.0, 66.5, 55.3,

39.4, 35.4, 31.1, 25.7, 21.6, 17.8, 13.3, 8.23, -4.46, -5.12; TLC (EtOAc/hexanes 50%) *R_f* 0.69.

Tosylate 4: ^1H NMR (500 MHz, CDCl_3) δ 7.80 (d, *J* 8.3 Hz, 2H), 7.34 (d, *J* 8.0 Hz, 2H), 7.24 (d, *J* 8.6 Hz), 6.86 (d, *J* 8.8 Hz, 2H), 4.43 (d, *J* 11.5 Hz, 1H), 4.38 (d, *J* 11.5 Hz, 1H), 4.06 (m, 1H), 4.04 (apd, *J* 8.6 Hz, 1H), 3.96 (dd, *J* 9.3 and 6.4 Hz, 1H), 3.80 (s, 3H), 3.40 (m, 2H), 3.32 (s, 3H), 3.25 (dd, *J* 9.5 and 1.7 Hz, 1H), 2.45 (s, 3H), 2.00 (m, 1H), 1.81 (m, 2H), 1.51 (m, 1H), 0.87 (s, 9H), 0.76 (d, *J* 6.9 Hz, 3H), 0.67 (d, *J* 6.9 Hz, 3H), 0.061 (s, 3H), 0.054 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.0, 144.7, 133.2, 130.5, 129.8, 129.1, 127.9, 113.7, 80.4, 72.7, 72.6, 69.2, 67.0, 60.8, 55.2, 40.2, 35.6, 35.1, 26.0, 21.6, 18.3, 9.3, 9.1, -3.35 - 4.2; TLC (EtOAc/hexanes 33%) *R_f* 0.56.

Acetylene 15: ^1H NMR (300 MHz, CDCl_3) δ 7.26 (d, *J* 8.8 Hz, 2H), 6.87 (d, *J* 8.8 Hz, 2H), 4.44 (d, *J* 11.7 Hz, 1H), 4.39 (d, *J* 11.7 Hz, 1H), 4.13 (m, 1H), 3.80 (s, 3H), 3.51 (s, 3H), 3.39-3.60 (m, 3H), 2.19 (ddd, *J* 16.7, 6.6 and 2.5 Hz, 1H), 2.29 (ddd, *J* 16.7, 8.8 and 2.5 Hz, 1H), 1.98 (t, *J* 2.5 Hz, 1H), 1.78-1.94 (m, 3H), 1.56 (m, 1H), 0.88 (s, 9H), 0.86 (d, *J* 6.9 Hz, 3H), 0.74 (d, *J* 7.0 Hz, 3H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.1, 130.6, 129.1, 113.7, 83.9, 82.7, 72.6, 69.4, 67.2, 61.3, 55.2, 40.8, 35.9, 35.3, 26.0, 24.1, 18.3, 12.8, 9.3, -3.25, -4.25; TLC (EtOAc/hexanes 10%) *R_f* 0.56.

Primary alcohol 16: ^1H NMR (500 MHz, CDCl_3) δ 5.30-5.49 (m, 2H), 4.11 (ddd, *J* 7.75, 5.64 and 2.13 Hz, 1H), 3.66-3.71 (m, 2H), 3.48 (s, 3H), 3.16 (dd, *J* 9.15 and 1.85 Hz, 1H), 2.13 (m, 1H), 2.01 (m, 1H), 1.78 (m, 2H), 1.66 (dd, *J* 5.8 and 0.5 Hz, 3H), 1.58-1.71 (m, 2H), 0.88 (s, 9H), 0.82 (d, *J* 6.71 Hz, 3H), 0.76 (d, *J* 7.02 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 130.4, 126.4, 84.4, 69.6, 60.8, 60.0, 40.6, 38.5, 38.4, 35.5, 25.9, 18.2, 17.9, 12.8, 10.0, -3.5, -4.0; TLC (EtOAc/hexanes 20%) *R_f* 0.18.

Table 1. ^1H NMR data comparison of synthetic (-)-Pironetin (**1**) [recorded on a INOVA 500 (500 MHz in CDCl_3)] and authentic (-)-Pironetin.¹

¹ Taken from ref **1b**. Kobayashi, S.; Tsuchiya, K.; Kurokawa, T.; Nakagawa, T.; Shimada, N.; Iitaka, Y. *J. Antibiot.* **1994**, 47(6), 703.

Position	Carbon	δ (ppm), mult., J [Hz] 500 MHz, CDCl_3 Synthetic Pironetin	δ (ppm), mult., J [Hz] 400 MHz, CDCl_3 ^(a) Authentic Pironetin
1	C=O	---	---
2	CH=	6.03 (d, 1H, J 9.8 Hz)	6.03 (d, 1H, J 9.9 Hz)
3	CH=	7.02 (dd, 1H, J 9.8, 6.1 Hz)	7.02 (dd, 1H, J 9.9, 6.2 Hz)
4	CH	2.30 (m, 1H)	2.29 (m, 1H)
5	CH-O	4.75 (m, 1H)	4.74 (m, 1H)
6	CH ₂	1.71 (m, 2H)	1.71 (m, 2H)
7	CH-O	4.20 (brd, 1H)	4.21 (brd, 1H)
8	CH	1.77 (m, 1H)	1.77 (m, 1H)
9	CH-O	2.98 (dd, 1H, J 6.2, 4.4 Hz)	2.99 (dd, 1H, J 6.2, 4.4 Hz)
10	CH	1.83 (m, 1H)	1.85 (m, 1H)
11	CH ₂	1.84 (m, 1H), 2.09 (m, 1H)	1.85 (m, 1H), 2.10 (m, 1H)
12	CH=	5.35 (dt, 1H, J 15.2, 5.7 Hz)	5.37 (dt, 1H, J 15.4, 5.9 Hz)
13	CH=	5.44 (dq, 1H, J 15.2, 5.7 Hz)	5.45 (dq, 1H, J 15.4, 5.9 Hz)
14	CH ₃	1.67 (d, 3H, J 5.9 Hz)	1.67 (d, 3H, J 5.9 Hz)
15	CH ₂	1.53 (m 1H), 1.72 (m, 1H)	1.51 (m 1H), 1.71 (m, 1H)
16	CH ₃	0.97 (t, 3H, J 7.3 Hz)	0.97 (t, 3H, J 7.3 Hz)
17	CH ₃	1.00 (d, 3H, J 7.3 Hz)	1.00 (d, 3H, J 7.3 Hz)
18	CH ₃	0.97 (d, 3H, J 7.3 Hz)	0.97 (d, 3H, J 7.3 Hz)
19	CH ₃ -O	3.47 (s, 3H)	3.47 (s, 3H)
-OH	---	3.46 (d, 1H, J 2.5 Hz)	3.45 (d, 1H, J 2.6 Hz)

(a) Recorded on JEOL GX-400 NMR spectrometer

Table 2. ^{13}C NMR data comparison of synthetic (-)-Pironetin (**1**) [recorded on a INOVA 500 (125 MHz in CDCl_3)] and authentic (-)-Pironetin.¹

¹ Taken from ref **1b**. Kobayashi, S.; Tsuchiya, K.; Kurokawa, T.; Nakagawa, T.; Shimada, N.; Iitaka, Y. *J. Antibiot.* **1994**, 47(6), 703.

Position	Carbon ^(a)	δ (ppm) 125 MHz, CDCl_3 Synthetic Pironetin	δ (ppm) 100 MHz, CDCl_3 ^(b) Authentic Pironetin
1	C=O	164.5	164.7
2	CH=	120.8	120.7
3	CH=	150.4	150.7
4	CH	39.1	39.0
5	CH-O	77.6	77.7
6	CH ₂	36.7	36.7
7	CH-O	67.35	67.3
8	CH	38.8	38.9
9	CH-O	91.0	91.0
10	CH	36.0	36.1
11	CH ₂	37.0	37.2
12	CH=	128.5	128.7
13	CH=	126.9	126.9
14	CH ₃	17.9	17.9
15	CH ₂	20.6	20.7
16	CH ₃	11.1	11.0
17	CH ₃	12.0	12.1
18	CH ₃	15.2	15.2
19	CH ₃ -O	61.6	61.6

(a) Based on ^{13}C DEPT NMR experiments

(b) Recorded on JEOL GX-400 NMR spectrometer