Enantioselective Total Synthesis of Ustiloxin D

Hiroko Tanaka, Andrew M. Sawayama, and Thomas J. Wandless

Department of Chemistry, Stanford University, Stanford, CA 94305

Supporting Information

Proton magnetic resonance spectra (^1H NMR) were recorded on Varian UI-500 (500 MHz) spectrometer using D_2O as solvent. Chemical shifts are reported in ppm from tetramethylsilane using the water resonance as an internal standard (4.67 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broadened, mult = multiplet), coupling constants (Hz). ^{13}C NMR spectra were recorded with complete proton decoupling on a Varian UI-500 (125.5 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane using a trace of 1,4-dioxane (66.5 ppm) as an internal standard.

HPLC traces were obtained using a Beckman System Gold 508 Autosampler, 125S Solvent Module and 166NM Single Wavelength Detector with a Waters Xterra M8 phenyl $5\mu\text{m}$ column (4.6 x 100 mm). 98% water and 2% acetonitrile was used as eluent, the water containing 0.05% trifluoroacetic acid. The Pd-mediated etherification formed two diastereomers (major is desired) that were carried through subsequent steps. Thus, the final synthetic step produced a 2:1 mixture of ustiloxin D and C2-epi-ustiloxin D. The 2:1 mixture of ustiloxin isomers were separated by preparative HPLC using a Waters Delta 600 Controller and 2996 Photodiode Array Detector with a Waters Xterra M8 phenyl $5\mu\text{m}$ (19 x 100 mm). 95% water and 5% acetonitrile was used as eluent, the water containing 0.05% trifluoroacetic acid. Products were detected at 220 nm. The specific rotation of Ustiloxin D was determined using a Jasco DIP-1000 digital polarimeter.

Comparison of synthetic and natural ustiloxin D using ^1H and ^{13}C NMR

^1H NMR δ (ppm)			^{13}C NMR δ (ppm)		
Position	Synthetic	Natural	Position	Synthetic	Natural ¹
3 ²			2	86.0	85.8
6	3.90 (d, J = 10)	3.89 (d, J = 10)	3	59.5	59.3
9*	3.74 (d, J = 9)	3.67 (d, J = 9)	5	171.2	171.5
10	4.60 (d, J = 9.5)	4.57 (d, J = 9.5)	6	60.2	60.2
12	7.01 (dd, J = 2, 8.5)	7.01 (dd, J = 2, 8.5)	8	166.3	166.3
13	6.90 (d, J = 8)	6.90 (d, J = 8)	9	69.0	68.9
16	6.84 (br, s)	6.84 (br, s)	10	73.1	73.0
19 [#]	3.67 (s)	3.59 (s)	11	130.7	130.7
21	1.53 (s)	1.53 (s)	12	122.7	122.7
22	1.52 (dq, J = 7.3, 21)	1.52 (dq, J = 7.5, 21)	13	119.1	119.1
	1.97 (dq, J = 7, 21)	1.97 (dq, J = 7, 21)	14	151.0	151.0
23	0.91 (t, J = 7.5)	0.91 (t, J = 7.5)	15	142.7	142.7
24	1.69 (m)	1.69 (m)	16	124.0	124.0
25	0.67 (d, J = 7)	0.67 (d, J = 7)	17	171.1	171.2
26	0.59 (d, J = 7)	0.59 (d, J = 6.5)	19	43.2	41.9
27 [#]	2.57 (s)	2.52 (s)	20	175.3	173.5
			21	21.3	21.4
			22	32.4	32.3
			23	8.1	8.0
			24	29.1	29.1
			25	18.5	18.4
			26	18.1	18.0
			27	32.4	32.4

HRMS calculated for $\text{C}_{23}\text{H}_{34}\text{N}_4\text{O}_8$ (M+H): 495.2449, found (MALDI): 495.2455.

Specific rotation of synthetic ustiloxin D: $[\alpha]_D^{27.5} = -49.7^\circ$ (c 0.35, H_2O).

Specific rotation of natural ustiloxin D: $[\alpha]_D^{20} = -48.8^\circ$ (c 0.5, H_2O).

¹ Cao, B.; Park, H.; Joullie, M. M.; *J. Am. Chem. Soc.* **2002**, 124, 520-521.

² Known resonance at δ 4.77 ppm hidden by H_2O resonance (δ 4.67 ppm).

[#] C-H protons adjacent to pH-sensitive functional groups.

Proton NMR of synthetic Ustiloxin D

Carbon 13 NMR of Synthetic Ustiloxin D

Proton NMR of natural Ustiloxin D

Natural sample

Synthetic sample

Natural sample
(0.3 to 2.3 ppm)

Synthetic sample
(0.3 to 2.3 ppm)

Natural sample
(6.5 to 7.2 ppm)

Synthetic sample
(6.5 to 7.2 ppm)

HPLC Trace of Synthetic Ustiloxin D

HPLC Trace of Natural Ustiloxin D

HPLC Trace of 1:2 Mixture of epi-Ustiloxin D and Synthetic Ustiloxin D

Overlay of Mixture, Synthetic
Ustiloxin D and Natural Ustiloxin D

HPLC Trace of Co-injection of
Natural and Synthetic Ustiloxin D