A Biomimetic Synthesis of Tangutorine following new biogenetic proposals

A contribution by

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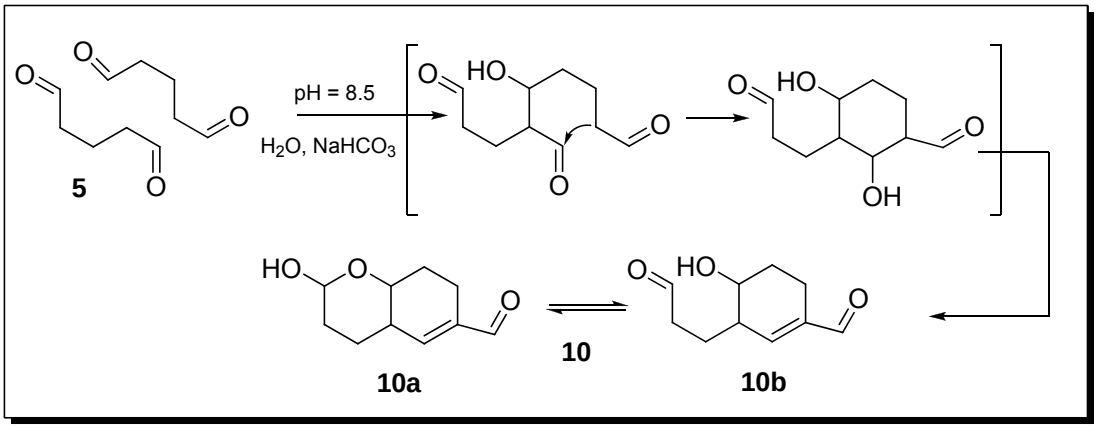
SUPPORTING INFORMATION - 1-

Experimental procedures and analytical data

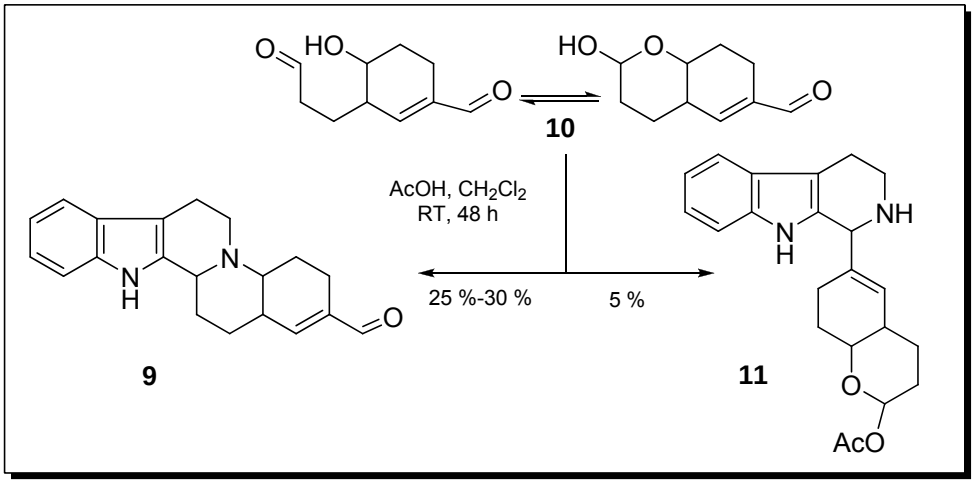
■ Synthesis of compound **10**:



An aqueous 50 % solution of 15 g of glutaraldehyde was diluted 5 times with water and alkalized to pH 8.5 with sodium bicarbonate. The alkalized solution was heated at 60 °C for 2 h, cooled to room temperature, and extracted three times with CH_2Cl_2. The concentration of the combined organic layers gave a crude product that was purified by silica gel flash column chromatography (CH_2Cl_2/ethyl acetate (8:2) to (7:3)) to afford **10** (3-4 g) as a white solid and as a mixture of four diastereomers.

10a (the two major diastereomers are described): R_f = 0.45 (silica gel, CH_2Cl_2/ethyl acetate 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.38 (dq, 2H, J = 3.2, 12.4 Hz), 1.93-1.46 (m, 7H), 1.69 (m, 3H), 2.15 (m, 4H), 2.42 (dd, 2H, J = 6.4, 17.6), 3.21 (ddd, 1H, J = 3.3, 8.9, 12.0), 3.82 (ddd, 1H, J = 3.2, 9.3, 12.3), 4.78 (d, 1H, J = 12), 5.27 (brs, 1H), 6.38 (s, 1H), 6.39 (s, 1H), 9.34 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 21.11, 21.29, 23.05, 27.10, 30.70, 33.13, 40.39, 41.21, 69.25, 76.17, 91.63, 95.68, 96.41, 140.17, 140.37, 150.05, 151.20, 193.41, 193.55; MS (TOF, ESI): *m/z* 181 (M–H); HRMS *m/z* calcd for $C_{10}H_{13}O_3$ 181.0861 (M–H), found 181.0873. Characterization matched with literature[1].

■ Synthesis of compounds **9** and **11**:



To a solution of **10** (2 g, 0.011 mol) in CH_2Cl_2 (10 mL) was added tryptamine (1.76 g, 0.011 mol, 1 eq.), the solution was diluted with acetic acid (15 mL) and stirred for 48 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and alkalized to pH 8 with a 4N solution of sodium hydroxide. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulted crude mixture was purified by silica gel flash column chromatography

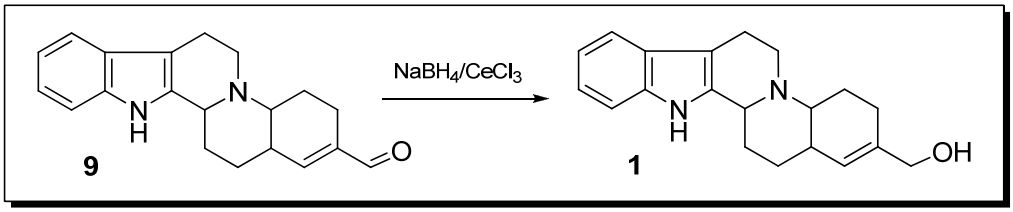
[1] Y. Kuroda, S.yagi, T. Nakagawa, *J. Org. Chem*. **1991**, *56*, 694–697

(CH_2Cl_2/ethyl acetate (8:2) then CH_2Cl_2/MeOH (95:5)) to afford **9-9'** (0.84 to 1 g, 25-30 %) as a mixture of diastereomers 75:25. and **11** (~200 mg, ~5 %).

9: was obtained as a single diastereomer after recrystallization of a trifluoroacetate salt precipitated from H_2O/CH_3CN (8:2): colorless solid; R_f = 0.28 (CH_2Cl_2/ethyl acetate (1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.47-1.58 (m, 2H), 1.85 (dddd, 1H, *J* = 3.2,12.4, 12.4, 12.4 Hz), 2.08 (brd, *J* = 10.4 1H), 2.19 (m, 2H), 2.27 (t, 1H, *J* = 10 Hz), 2.42-2.50 (m, 3H), 2.60 (dd, 1H, *J* = 4.8, 18.1 Hz), 2.80 (brd, 1H, *J* = 15.4 Hz), 2.92 (dddd, 1H, *J* = 2.0, 5.0, 9.5, 15.4 Hz), 3.52 (brd, 1H, *J* = 11.6 Hz), 3.60 (m, 1H), 6.47 (brs, 1H), 7.08 (ddd, 1H, *J* = 1.2, 7.2, 7.2 Hz), 7.013 (ddd ,1H, *J* = 1.2, 7.2, 7.2 Hz), 7.30 (d, 1H, *J* = 7.6 Hz), 7.46 (d, 1H, *J* = 8.0 Hz), 7.84 (brs, NH) 9.47 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm , 21.8, 21.9, 25.1, 29.7, 29.9, 41.0, 45.4, 60.3, 64.2, 108.1, 110.7, 118.1, 119.3, 121.3, 127.1, 134.8, 136.0, 139.9, 152.7, 193.7; IR (thin film) cm^{-1} 2917, 1674, 1454, 907, 732; MS (TOF MS ES+) : *m/z* (% relative intensity) 307 (100) ($M+H^+$), 290(10); HRMS *m/z* calcd for $C_{20}H_{23}N_2O$ 307.1805 ($M+H^+$), found 307.1809.

11: colorless oil; R_f = 0.55 (CH_2Cl_2/MeOH (9:1)); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.71-1.47 (m, 3H), 1.92-1.86 (m, 3H), 2.10 (s, 1H), 2.16 (d, 1H, *J* = 6.4), 2.31-2.16 (m, 2H), 2.84-2.72 (m, 2H), 3.08 (m, 1H), 3.34 (m, 1H), 3.71(dt, 1H, *J* = 2.8, 11 Hz), 4.00 (brs, NH), 4.58 (s, 1H), 5.43 (s, 1H), 6.18 (s, 1H), 7.10 (t, 1H, *J* = 7.6 Hz), 7.16 (t, 1H, *J* = 7.6 Hz), 7.30 (d, 1H, *J* = 8 Hz), 7.48 (d, 1H, *J* = 8 Hz), 7.88 (brs, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm , 21.22, 21.96, 24.29, 25.02, 28.17, 29.58, 39.80, 42.28, 58.73, 72.79, 92.39, 109.65, 110.77, 118.08, 119.03, 121.65, 127.32, 128.44, 132.91, 135.64, 137.92, 169.75; IR (thin film) cm^{-1} 3644, 2930, 1737, 1568, 1371, 739; MS (TOF MS ES^+): *m/z* (% relative intensity) 367 (100) ($M+H^+$). HRMS *m/z* calcd for $C_{22}H_{27}N_2O_3$ 367.2022 ($M+H^+$), found 367.2021.

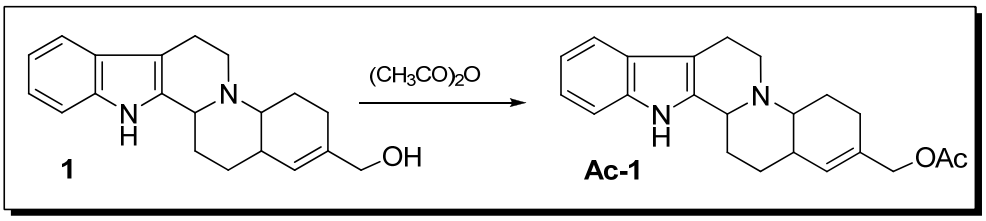
■ Synthesis of **1** (tangutorine):



To a stirred mixture of **9** (0.26 g, 0.849 mmol) and $CeCl_3$ (0.209 g, 0.849 mmol, 1eq.) in MeOH (8 mL) was added $NaBH_4$ (0.032 g, 0.849 mmol, 1eq.) over a few min. After 5 min the mixture was diluted with water (5 mL) and then CH_2Cl_2 (20 mL) was added. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried over $MgSO_4$, filtration and concentration gave the crude product that was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH (95:5)) to afford **1** (0.249 g, 95%),) as a mixture of diastereomers (75:25). (±)-tangutorine **1** was obtained by recrystallization of the major diastereomer from CH_2Cl_2/MeOH (95:5).

1: colorless crystals; R_f = 0.1 (MeOH/$CHCl_3$ (9:1)); ^{1}H NMR (600 MHz, $CDCl_3$/DMSO-d_6 (1:1)): δ ppm 1.43 (dddd, 1H, *J* = 3.6, 12.6, 12.6, 12.6 Hz), 1.58 (m, 1H), 1.72 (dddd, 1H, *J* = 3, 12.6, 12.6, 12.6), 2.02 (dd, 1H, *J* = 12.8 Hz), 2.23-2.25 (m, 3H), 2.31 (dd, 1H, *J* = 4.9, 16.6, Hz), 2.40-2.46 (m, 3H), 2.81 (brd, 1H, *J* = 15.2 Hz), 2.92 (dddd,1H, *J* = 2.1, 5.2, 10.6, 15.2 Hz), 3.51 (brd, 1H, *J* = 11.2 Hz), 3.67 (m, 1H), 3.99 (brs, 2H), 4.55 (t, OH, *J* = 5.3 Hz), 5.46 (br s, 1H), 7.04 (dd, 1H, *J* = 7.2 Hz), 7.10 (dd, 1H, *J* = 7.2 Hz), 7.38 (d, 1H, *J* = 7.9 Hz), 7.46 (d, 1H, *J* = 7.7 Hz), 10.38 (bds, 1H, NH); ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$ (93:7)): δ ppm 1.37 (dddd, 1H, *J* = 3.6, 12.8, 12.8, 12.8 Hz), 1.57 (dddd, 1H, *J* = 6, 11.6.11.6, 11.6 Hz,), 1.76 (ddt, 1H, *J* = 3, 12.6, 12.6, 12.6), 1.96 (brd, 1H, *J* = 12.8 Hz), 2.18-2.27 (m, 5H), 2.34 (dd, 1H, *J* = 5.4, 17 Hz), 2.46 (dt, 1H, *J* = 4.5, 10.5 Hz), 2.82 (brd, 1H, *J* = 15.2 Hz), 2.93 (dddd,1H, *J* = 2.1, 5.1, 9.6, 15.2 Hz), 3.56 (brd, 1H, *J* = 11.26 Hz), 3.61 (m, 1H), 3.99 (brs, 2H),5.40 (brs, 1H), 7.05 (ddd, 1H, *J* = 1.2, 7.2, 7.2 Hz), 7.11 (ddd, 1H, *J* = 1.2, 7.2, 7.2 Hz), 7.35 (d, 1H, *J* = 7.5 Hz), 7.46 (d, 1H, *J* = 7.5 Hz; ^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6 (1:1)): δ ppm 22.5, 26.4, 30.1, 31.5, 45.8, 61.1, 65.0, 65.4, 107.0, 111.3, 117.9, 118.6, 120.6, 124.6, 127.1, 136.4, 136.7, 137.5; ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$ (93:7)) δ ppm 22.0, 26.2, 26.5, 29.4, 31.4, 39.3, 45.8, 61.4, 65.6, 66,0 107.3, 111.4, 118.1, 119.1, 121.3, 125.9, 127.3, 135.6, 135.8, 137.0;IR (thin film) cm^{-1} 3749, 3242, 2918, 2847, 2367, 1456, 1320, 1020, 731 ; MS (TOF ES^+): *m/z* (% relative intensity) 309 (100) ($M+H^+$); HRMS: *m/z* calcd for $C_{20}H_{25}N_2O$ 309.1961 ($M+H^+$), found 309.1957.

■ Synthesis of **Ac-1**: acetylation of tangutorine for analytical purposes



To a stirred mixture of **1** (50 mg, 0.162 mmol) in acetic anhydride (5 mL) at rt was added dimethylaminopyridine (DMAP) (4 mg, 0.032 mmol, 0.2 eq.). The solution was stirred for 12h and the reaction mixture was diluted with (10 mL) of CH_2Cl_2. Acetic anhydride was neutralized by adding an aqueous solution of $NaHCO_3$ (10%), the organic layer was dried over $MgSO_4$, filtration and concentration gave the crude product which was purified by silica gel flash column chromatography (eluent: CH_2Cl_2/ ethylacetate (7:3)) to afford **Ac-1** (51 mg, 0.146 mmol, 90%) as a mixture of diastereomers (1/3).

Ac-1: colorless solid, R_f = 0.3 (50% CH_2Cl_2/ethyl acetate), ^{1}H NMR (400 MHz, $CDCl_3$); δ ppm 1.37 (ddd, *J* = 1H, 3.6, 12.4, 12.4, 1.4 Hz),1.59 (m, 1H), 1.79 (ddd, 1H, *J* = 3.6, 12.4, 12.4, 12.4 Hz), 1.95 (dd, 1H, *J* = 2.8, 13 Hz),2.09 (s, 3H), 2.13-2.59 (m, 5H), 2.33-2.44 (m, 2H), 2.78 (brd, 1H, *J* = 15.6)), 2.93 (m, 1H), 3.48 (d, 1H, *J* = 11.12 Hz), 3.60 (m, 1H), 4.49 (brs, 1H), 5.45 (brs, 1H), 7.07 (dd, 1H, *J* = 7.2, 7.2 Hz), 7.14 (dd, 1H, *J* = 7.2, 7.2 Hz), 7.29 (d, 1H, *J* = 8 Hz), 7.47 (d, 1H, *J* = 7.6 Hz), 7.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 21.0, 22.1, 26.1, 26.6, 29.8, 30.8, 39.8, 45.6, 60.6, 64.7, 67.8, 108.3110.6, 118.1, 119.3, 121.3, 127.3, 129.3, 132.1, 135.3, 136.0, 170.9; MS (APCI): *m/z* 351 ($M+H^+$). HPLC chromatogram is provided (see other file), it is the only case where two peaks were clearly separated and permitted the determination of diastereomeric ratio.

Spectroscopic Comparisons for the synthetic (±)-tangutorine (tables 1, 2, and 3).

■ **TABLE 1: ^{13}C NMR**

Reported in this work ($CDCl_3$/MeOD 91:9 *v/v*)	Literature[2] ($CDCl_3$/MeOD 4.8%)	Δδ
22.0	21.8	+ 0.2
26.2	25.9	+ 0.3
26.5	26.2	+ 0.3
29.4	29.2	+ 0.2
31.4	31.0	+ 0.4
39.3	39.0	+ 0.3
45.9	45.9	0.0
61.4	60.9	+ 0.5
65.6	65.2	+ 0.4
66.0	65.9	+ 0.1
107.3	107.3	0.0
111.3	110.9	+ 0.4
118.1	118.0	+ 0.1
119.1	119.0	+ 0.1
121.3	121.1	+ 0.2
125.9	125.6	+ 0.3
127.3	127.0	+ 0.3
135.6	135.2	+ 0.4
137.0	136.6	+ 0.4
137.0	136.7	+ 0.3

■ **TABLE 2: ^{13}C NMR**

Reported in this work ($CDCl_3$/MeOD 91:9 *v/v*)	Literature[3] ($CDCl_3$/MeOD no precision given)	Δδ
22.0	22.2	– 0.2
26.2	26.4	– 0.2
26.5	26.6	– 0.1
29.4	29.5	– 0.1
31.4	31.5	– 0.1
39.3	39.6	– 0.3
45.9	46.1	– 0.2
61.4	61.6	– 0.2
65.6	65.8	– 0.2
66.0	66.1	– 0.1
107.3	107.4	– 0.1
111.3	111.5	– 0.2
118.1	118.2	– 0.1
119.1	119.2	– 0.1
121.3	121.4	– 0.1
125.9	125.9	0.0
127.3	127.4	– 0.1
135.6	135.8	– 0.2
137.0	137.1	– 0.1
137.0	137.2	– 0.2

[2] *Org. Lett*. **2003**, *5*, 4709–4712.
[3] *Tetrahedron Lett*. **1999**, *40*, 2593–2596.

■ **TABLE 3: ^{13}C NMR**

Reported in this work ($CDCl_3$/MeOD 91:9 *v/v*)	Literature[4] ($CDCl_3$/MeOD 95:5)	Δδ
22.0	21.4	+ 0.6
26.2	25.6	+ 0.6
26.5	25.9	+ 0.6
29.4	28.9	+ 0.5
31.4	30.7	+ 0.7
39.3	38.6	+ 0.7
45.9	45.1	+ 0.8
61.4	60.6	+ 0.8
65.6	65.0	+ 0.6
66.0	65.6	+ 0.4
107.3	106.9	+ 0.4
111.3	110.7	+ 0.6
118.1	117.7	+ 0.4
119.1	118.8	+ 0.3
121.3	120.9	+ 0.4
125.9	125.3	+ 0.6
127.3	126.7	+ 0.6
135.6	134.8	+ 0.8
137.0	136.1	+ 0.9
137.0	136.5	+ 0.5

■ **TABLE 4: ^{1}H NMR**

Reported in this work ($CDCl_3$/MeOD 91:9)	Literature[5] ($CDCl_3$/MeOD no precision given)	Δδ
1.37	1.39	– 0.02
1.57	1.55	+ 0.02
1.76	1.77	– 0.01
1.96	1.97	– 0.01
2.18-2.27	2.21	– 0.03 to – 0.05
	2.23	
	2.29	
	2.32	
2.34	2.37	– 0.03
2.46	2.45	+ 0.01
2.82	2.84	– 0.02
2.93	2.94	– 0.01
3.56	3.54	+0.02
3.61	3.61	0.00
3.99	3.97	+ 0.02
5.40	5.41	– 0.01
7.05	7.03	+ 0.02
7.11	7.10	+ 0.01
7.35	7.33	+ 0.02
7.46	7.14	+ 0.32

We totally agree with Richard P. Hsung and coll. modifications of assignments of ^{1}H NMR data (see Supporting Information in *Org. Lett*. **2003**, *5*, 4709–4712).

[4] *Helv. Chim. Acta* **2006**, *89*, 122–126.
[5] *Tetrahedron Lett*. **1999**, *40*, 2593–2596.

■ **TABLE 5: ^{1}H NMR**

Reported in this work ($CDCl_3$/MeOD 91:9)	Literature[6] ($CDCl_3$/MeOD 4.8%)	Δδ
1.37	1.35	+ 0.02
1.57	1.56	+ 0.01
1.76	1.77	– 0.01
1.96	1.94	+ 0.02
2.18-2.27	2.16-2.29	+ 0.02-0.02
2.34	2.35	– 0.01
2.46	2.41	+ 0.05
2.82	2.79	+ 0.03
2.93	2.92	+ 0.01
3.56	3.51	+ 0.04
3.61	3.59	+ 0.02
3.99	3.97-4.00	
5.40	5.38	+ 0.02
7.05	7.05	0.00
7.11	7.10	+ 0.01
7.35	7.29	+ 0.06
7.46	7.45	+ 0.01

■ **TABLE 6: ^{1}H NMR**

Reported in this work ($CDCl_3$/MeOD 91:9)	Literature[7] ($CDCl_3$/MeOD 95:5)	Δδ
1.37	1.20-1.29	
1.57	1.40-1.49	
1.76	1.60-1.68	
1.96	1.81.1.84	
2.18-2.27 [5 H]	2.05-2.22 [6 H]	
2.34 [1 H]		
2.46	2.35-2.38	
2.82	2.71	+ 0.11
2.93	2.79-2.85	
3.56	3.46	+ 0.1
3.61	3.55	+ 0.06
3.99	3.83-3.87	
5.40	5.26	+ 0.14
7.05	6.93	+ 0.12
7.11	6.99	+ 0.12
7.35	7.20	+ 0.15
7.46	7.34	+ 0.12

[6] *Org. Lett.* **2003**, *5*, 4709–4712.
[7] *Helv. Chim. Acta* **2006**, *89*, 122–126.