Supporting Information

Total Syntheses of Securinega Alkaloids (-)-Norsecurinine, (-)-Niruroidine and (-)-Flueggine A

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Isolation and structure determination of (-)-niruroidine

(-)-niruroidine (**3**) was isolated as colorless oil, $[\alpha]_D^{20}$ -41.2° (c = 0.50, CH_3OH). The molecular formula of **3** was established as $C_{12}H_{15}NO_3$ by its HR-ESI-MS (*m/z* 222.1130 $[M + H]^+$, calcd for $C_{12}H_{16}NO_3$: 222.1125). The UV absorption maximum at 247 nm and IR bands at 3413 and 1751 cm^{-1} implied the presence of α,β-unsaturated γ-lactone ring and hydroxyl group. The NMR spectra revealed that **3** possessed twelve carbons including an α,β-unsaturated γ-lactone ring [δ_H 5.71 (1H, dd, J = 2.0, 2.0 Hz); δ_C 175.3, 173.9, 110.3 and 84.3]. The above spectral data were the same with niruroidine,[1] the absolute configuration of which had not been determined. In order to establish the absolute configuration of **3**, the theoretical optical rotation (OR) values of (2*R*,7*R*,8*R*,10*S*)-**3** and (2*S*,7*S*,8*S*,10*R*)-**3** were calculated at three different levels (B3LYP/6-311++g(2d,p), B3LYP/cc-pVDZ and B3LYP/aug-cc-pVDZ) in Gaussian 09 software.[2-5] The calculated specific optical rotation values of (2*R*,7*R*,8*R*,10*S*)-**3** and (2*S*,7*S*,8*S*,10*R*)-**3** and the experimental data for **3** were summarized in Table 2. Thus, the absolute configuration of **3** was assigned as 2*R*, 7*R*, 8*R* and 10*S*.

Table 1 ^{1}H and ^{13}C NMR data of 3 (in $CDCl_3$, δ, J in Hz)

	3	
no.	δ_H	δ_C
2	**3.00 t (6.8)**	**61.5**
3a	**1.95 m**	**27.3**
3b	**1.78 m**	
4a	**1.91 m**	**27.2**

[⊥] These authors contributed equally to the work.

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4b	**1.78 m**	
5a	**3.12 m**	**51.2**
5b	**2.89 m**	
7	**3.13 m**	**55.7**
8	**4.42 m**	**62.0**
9a	**2.79 dd (13.6, 9.6)**	**34.1**
9b	**1.34 ddd (13.6, 3.2, 1.2)**	
10	**-**	**84.3**
12	**-**	**175.3**
13	**5.71 dd (2.0, 2.0)**	**110.3**
14	**-**	**173.9**
15a	**3.25 m**	**25.6**
15b	**2.90 ddd (19.2, 2.0, 2.0)**	

Table 2 Calculated optical rotation values of (2*R*,7*R*,8*R*,10*S*)-3 and (2*S*,7*S*,8*S*,10*R*)-3 and experimental optical rotation values for 3 (in deg [dm g/cm^{-3}]$^{-1}$)

Calcd			**Exptl**
Methods	**(2*R*,7*R*,8*R*,10*S*)-3**	**(2*S*,7*S*,8*S*,10*R*)-3**	**3**
B3LYP/6-311++g(2d,p)	**-67.96**	**67.97**	
B3LYP/cc-pVDZ	**-48.29**	**48.30**	**-41.2**
B3LYP/aug-cc-pVDZ	**-65.28**	**65.28**	

[1] Babady-Bila; Gedris, T. E.; Herz, W. *Phytochemistry* **1996**, *41*, 1441-1443.
[2] Miao, F. P.; Liang, X. R.; Yin, X. L.; Wang, G.; Ji, N. Y. *Org. Lett.* **2012**, *14*, 3815.
[3] Wang, F.; Gao, Y.; Zhang, L.; Bai, B.; Hu, Y. N.; Dong, Z. J.; Zhai, Q. W.; Zhu, H. J.; Liu, J. K. *Org. Lett*. **2010**, *12*, 3196.
[4] Zuber, R.; Goldsmith, M. R.; Beratan, D. N.; Wipf, P. *Chirality* **2005**, *17*, 507.
[5] Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

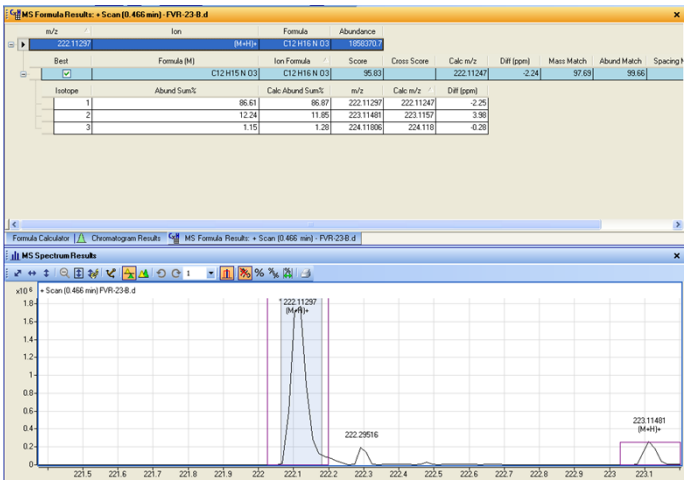


Figure 1. HR-ESI-MS spectrum of 3

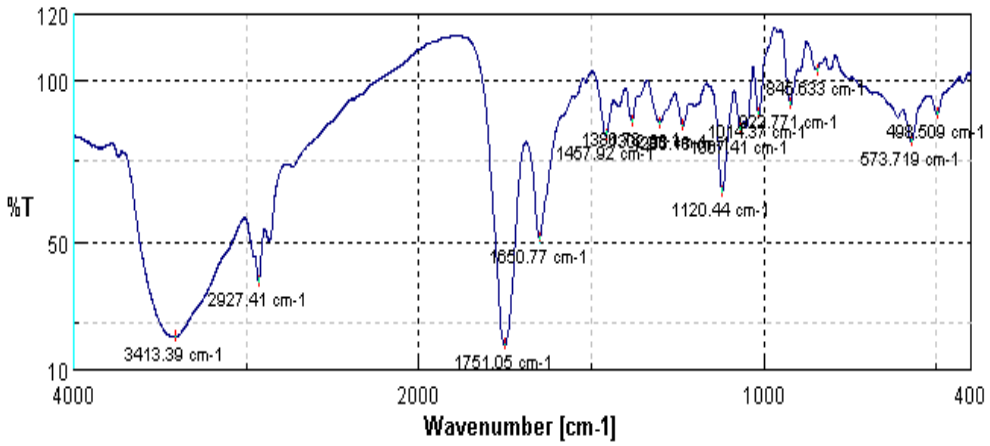


Figure 2. IR spectrum of 3 (KBr)

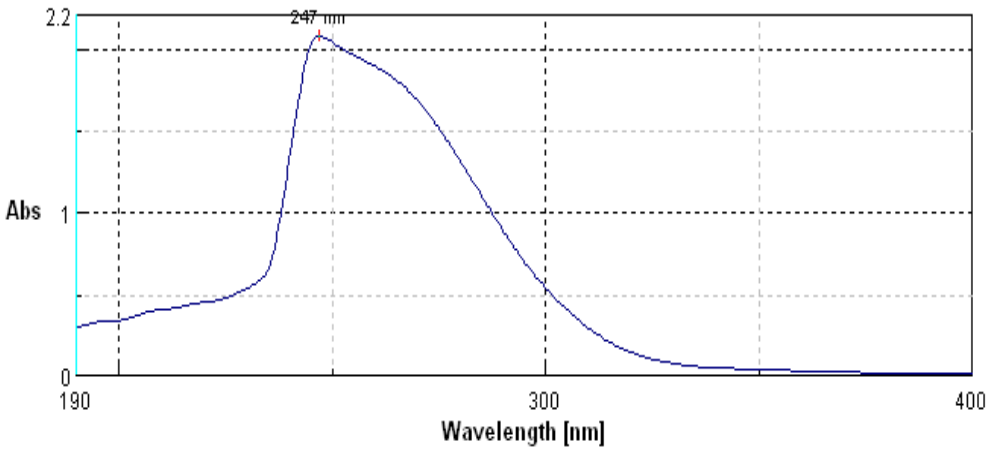


Figure 3. UV spectrum of 3 (CH_3OH)

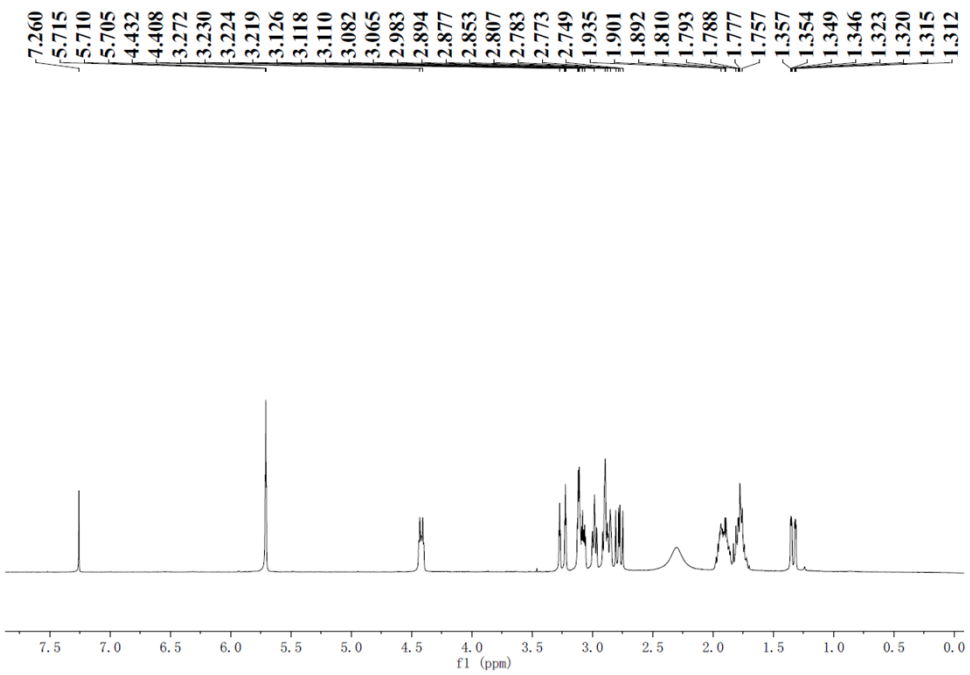


Figure 4. 1H NMR spectrum of 3 (CDCl3)

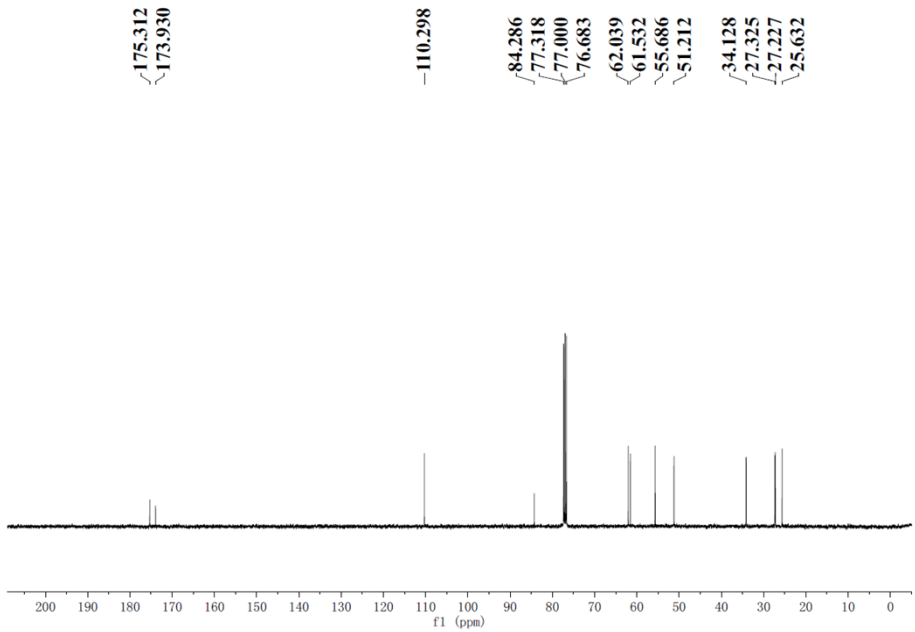
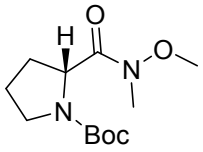


Figure 5. ^{13}C NMR spectrum of 3 ($CDCl_3$)

Chemistry

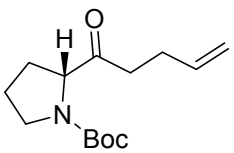
General Experimental Methods: ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance ARX- 400. Mass spectra were performed on Kompact Axima-CFR MALDI mass spectrometers. Optical rotations were recorded on a Perkin Elmer 341 polarimeter. Anhydrous solvents were obtained as follows: THF and diethyl ether by distillation from sodium and benzophenone; dichloromethane from CaH_2. All other solvents were reagent grade. All moisture sensitive reactions were carried out in flame dried flask under argon atmosphere.



9

(*R*)-tert-butyl 2-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate (**9**)

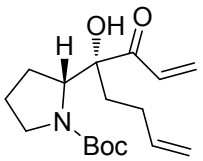
To a magnetically stirred solution of L-proline (12.0 g, 89.7 mmol) in sat. aq. $NaHCO_3$ (180 mL) was added $(Boc)_2O$ (21.6 g, 98.7 mmol) in THF (60 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 19 h. THF was removed through rotatory evaporation and the residue was cooled to 0 °C and acidified with 3N HCl to pH 2-3. The reaction mixture was extracted with ethyl acetate (4 x 400 mL). The combined organic layers was dried over Na_2SO_4 and concentrated under reduced pressure to yield a white solid which was directly used for further reaction without purification. The above mention solid in dry CH_2Cl_2 (200 mL) was added carbonyl diimidazole (17.5 g, 107.7 mmol) portion wise at room temperature and stirred for 30 min. To this *N*,*O*-dimethylhydroxylamine hydrochloride (10.5 g, 107.7 mmol) was added at once and stirred for 20 h. The reaction mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified through column chromatography to give the desired product **9** as a colourless viscous liquid (23.2 g, 100%). $[\alpha]^{20}_D$ + 50.0 (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 4.71 - 4.59 (dd, *J* = 7.0 Hz, 1H), 3.78 (s, 1.5 H), 3.72 (s, 1.5H), 3.62 - 3.56 (m, 1H), 3.50 - 3.37 (m, 1H), 3.19 (s, 3H), 2.23 - 2.13 (m, 1H), 2.03 - 1.82 (m, 1H), 1.45 (s, 4.5H), 1.41 (s, 4.5H) ppm.



10

(*R*)-tert-butyl 2-pent-4-enoylpyrrolidine-1-carboxylate (**10**)

Mg (1.5 g), 1,2-dibromoethane (0.1 mL), THF (20 mL) were added into a 250 mL round bottom flask and stirred for 10 min, to this 4-bromo-1-butene (10.46 g, 77.4 mmol) was added dropwise and stirred for 40 min at roomtemperature. The solution was cooled to 0 °C. To this compound **9** (6.46 g, 25 mmol) in THF (40 mL) was added dropwise. The reaction was slowly warmed to room temperature and stirred for 4 h. The reaction mixture was quenched with saturated aq.NH_4Cl (40 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified through column chromatography to give the **10** as a colorless liquid. (5.7 g, 90%). $[\alpha]^{20}_D$ + 60.6 (*c* 0.42, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 5.82 - 5.72 (m, 1H), 5.02 - 4.90 (m, 2H), 4.32 - 4.18 (m, 1H), 3.51 - 3.38 (m, 2H), 2.58 - 2.41 (m, 2H), 2.32 - 2.27 (m, 2H), 2.17 - 2.06 (m, 1H), 1.86 - 1.77 (m, 3H), 1.42 (s, 4.5 H), 1.36 (s, 4.5 H) ppm ^{13}C (125 MHz, $CDCl_3$) (mixture of rotamers) δ 209.13/209.09, 154.5/153.8, 137.1/136.9, 115.3/115.0, 80.0/79.7, 65.1/64.6, 46.8/46.6, 38.2/37.5, 29.8/28.6, 28.3/28.2, 27.2, 24.3, 23.6.

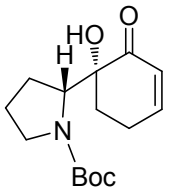


11

(*R*)-tert-butyl 2-((R)-4-hydroxy-3-oxoocta-1,7-dien-4-yl)pyrrolidine-1- carboxylate (**11**)

Potassium t-butoxide (300 mg, 2.67 mmol) was added to molecular sieve dried methyl propargyl ether (1.87 g, 26.7 mmol). The mixture was stirred at 50 °C for 2 h and filtered under reduced pressure at r.t.. To the filtrate was added 2.4 M nbutyllithium in n-hexane (9.2 mL, 22 mmol) at –78 °C under argon atmosphere, and the mixture was stirred at –78°C for 30 min. Then the mixture was added dropwise to a THF (40.0 mL) solution of **10** (2.8 g, 11 mmol) at –78 °C in a cannula manner. After being stirred at –78 °C for 30 min, the reaction mixture was acidified by 1 N HCl, homogenized with MeOH and then the reaction temperature was raised to room temperature. After being stirred at room temperature for 1 h, the reaction mixture was extracted with ethyl acetate. The ester extract was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to afford a crude product, which was purified by column chromatography to give **11** (2.4 g, 70 %) as a colorless liquid. $[\alpha]^{20}_D$ + 77.9 (*c* 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (dd, *J* = 10.8, 16.4 Hz, 1H), 6.30 (d, *J* = 17.2 Hz, 1H), 6.23 (s, 1H), 5.79 - 5.71 (m, 1H), 5.64 (d, *J* = 10.0 Hz, 1H), 4.97 (dd, *J* = 1.6, 17.2 Hz,

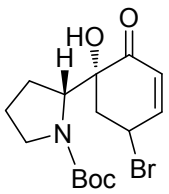
1H), 4.90 (d, J = 10.4 Hz, 1H), 4.11 (brs, 1H), 3.53 (brs, 1H), 3.01 (brs, 1H), 2.11(brs, 1H), 2.03 - 1.95 (m, 6H), 1.84 - 1.77 (m, 1H), 1.46 (s, 9H) ppm ^{13}C (125 MHz, $CDCl_3$) δ 204.2, 157.6, 138.4, 131.2, 128.6, 114.5, 84.00, 80.6, 64.6, 47.8, 35.3, 29.7, 28.3, 27.2, 24.1 ppm. HRMS(ESI) *m/z* calculated for $C_{17}H_{27}NO_4$ 309.1940, found 309.1939.



7

(*R*)-*tert*-butyl 2-((R)-1-hydroxy-2-oxocyclohex-3-enyl)pyrrolidine-1-carboxylate (**7**)

To a solution of **11** (1.17 g, 3.8 mmol) in dry DCM (80 mL) was added Grubbs II catalyst (80 mg, 0.095 mmol). The mixture was then stirred for 1h. Evaporation of the solvent and purified by column chromatography of the residue over silica gel, gave **7** (1.1 g, 96%) as a white solid. [α] $^{20}_{D}$ -16.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 - 6.99 (m, 1H), 6.06 (d, J = 9.6 Hz, 1H), 4.26 (s, 1H), 4.00 (s, 1H), 3.60 (brs, 1H), 3.37 - 3.32 (m, 2H), 2.45 - 2.34 (m, 2H), 1.98 - 1.96 (m, 1H), 1.87 - 1.83 (m, 1H), 1.70 (brs, 3H), 1.46 (s, 9H) ppm ^{13}C (125 MHz, CD_3OD) δ 201.3, 156.2, 152.1, 126.7, 79.4, 78.9, 58.9, 47.7, 32.5, 27.3, 25.3, 24.9, 24.0. ppm. HRMS(ESI) *m/z* calculated for $C_{15}H_{23}NO_4$ 281.1627, found 281.1625.



13

(*R*)-*tert*-butyl 2-((R)-5-bromo-1-hydroxy-2-oxocyclohex-3-enyl)pyrrolidine-1- carboxylate (**13**)

A solution of compound **7** (186 mg, 0.66 mmol), *N*-bromosuccinamide (129 mg, 0.73 mmol) and AIBN (5.4 mg, 0.03 mmol) in CCl_4 (5 mL) was refluxed for 1 h. The reaction mixture was filtered and the filterate was washed saturated aq.$NaHCO_3$ (5 mL) solution. Organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude was purified by column chromatography to afford **13** as a diastereomeric mixture (140 mg, 59%) as yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 7.02 (d, J = 10.0 Hz, 1H), 6.01(d, J = 10.0 Hz, 1H), 5.89 (s, 1H), 4.10 (s, 1H), 3.78 (s, 1H), 3.55 (s, 1H), 3.34 - 3.28 (m, 1H), 2.94 - 2.91 (m, 1H), 2.28 (t, J = 12.0 Hz, 1H), 1.99 - 1.93 (m, 1H), 1.74 - 1.64 (m, 3H), 1.46 (s, 9H) ppm ^{13}C (125 MHz, $CDCl_3$) (mixture of rotamers) δ 200.5, 156.3, 151.8, 125.8, 80.5, 80.0, 59.4, 47.7, 44.4, 42.2, 28.3, 25.1, 24.6 ppm. HRMS(ESI) *m/z* calculated for $C_{15}H_{22}BrNO_4$ 360.1979, found 360.1979.

CHIRALPAK® AD-H column (ADH0CE-OJ007, 4.6 mm × 250 mm) with the solvent system (elution conditions: hexane : isopropanol = 95 : 5), with monitoring between 200 and 300 nm.

Data Report

Sample Information

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Method File	: 10%,25MIN.lcm
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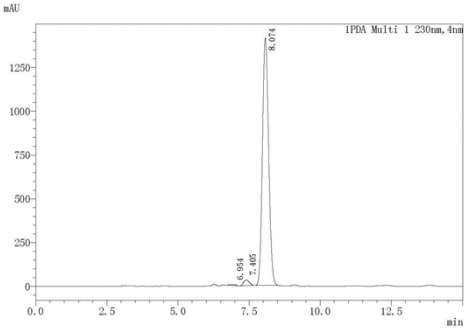
Date Processed	: 2014/5/27 10:34:54



PDA Ch1 230nm

NO.	Ret.Time	Height(uAU)	Area(uAU*min)	Rel.Area %	Resolution(USP)
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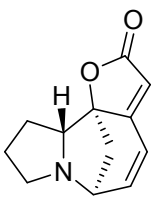
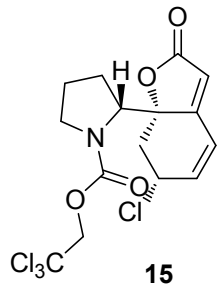


(-)-norsecurinine (**2**)

(-)-Norsecurinine (**2**)

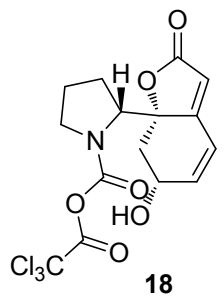
To a solution of **13** (338 mg, 0.94 mmol) in dry DCM (5 mL) was added trifluoroacetic acid (0.7 ml, 9.4 mmol). The reaction was refluxed for 2 h before removing the solvent and TFA in vacuo and redissolving the brown residue in dry DCM (5 mL). To this solution was added dry Et_3N and the reaction was stirred at room temperature for 10 mins and the solvent was removed in vacuo and the residue was taken up in ethyl acetate and filtered to remove the majority of the TFA•Et_3N salt. The crude was dissolved in DCM (5 mL), then dicyclohexylcarbodiimide (386 mg, 1.88 mmol) and diethylphosphonoacetic acid (368 mg, 1.88 mmol) was added. The reaction was refluxed for 2 h. The mixture was filtered and concentrated in vacuo and redissolving in dry THF (5 ml), to the mixture NaH (60%) (45 mg, 1.1 mmol) was added at 0 ºC. The reaction was stirred for 1 h before quenching with sat. aq. NH_4Cl (5 mL), extracted with EtOAc (4 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated and purified by column chromatography to yield (-)-norsecurinine (**2**) as a yellow oil (74 mg, 39% yield). [α] $^{20}_D$ -256 (*c* 0.1, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (dd, *J* = 9.0, 6.5 Hz, 1H), 6.50 (d, *J* = 9.0 Hz, 1H), 5.67 (s, 1H), 3.64 (dd, *J* = 6.5, 4.8 Hz, 1H), 3.32 (t, *J* = 7.8 Hz, 1H), 3.22 (t, *J* = 7.7 Hz, 1H), 2.61 - 2.52 (m, 2H), 2.01 - 1.97 (m, 2H), 1.84 - 1.78 (m, 2H), 1.74 (d, *J* = 10.8 Hz, 1H). ppm. ^{13}C (125 MHz, $CDCl_3$) δ 172.7, 168.4, 143.7, 120.4, 107.8, 91.8, 65.1, 59.8, 55.3, 35.8, 29.3, 26.8 ppm. HRMS(ESI) *m/z* calculated for $C_{12}H_{13}NO_2$ 203.0946, found 203.0947.



15

(*R*)-2,2,2-trichloroethyl 2-((6*R*, 7a*S*)-6-chloro-2-oxo-2,6,7,7a- tetrahydrobenzofuran-7a-yl)pyrrolidine-1- carboxylate (**15**)

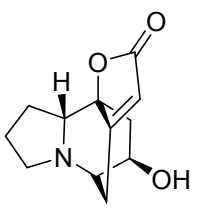
To a stirred solution of **2** (1.3755 g, 6.776 mmol) in CH_2Cl_2 (20 mL) at 0 °C, $ClCO_2CH_2CCl_3$ (1.399 mL, 10.164 mmol) was added drop-wise followed by the addition of K_2CO_3 (2.8 g). The resulting mixture was stirred at 0°C for 1.5h. The reaction was diluted with CH_2Cl_2 (10 mL) and quenched with saturated aqueous NH_4Cl (20 mL) solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), rotary evaporated and chromatographed (silica gel, Petroleum ether: ethyl acetate = 6: 1) to give **15** (2.7 g, 96%) as a white crystal. R_f 0.45 (Petroleum ether : ethyl acetate = 2 : 1); $[\alpha]^{20}_D$ + 108 (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (dd, *J* = 9.9, 2.4 Hz, 1H), 6.31 (dd, *J* = 9.9, 2.4 Hz, 1H), 5.95 (s, 1H), 5.63-5.58 (m, 1H), 4.87(d, *J* = 12.0 Hz, 1H), 4.76(d, *J* = 12.0 Hz, 1H), 4.23(dd, *J* = 8.4, 2.4 Hz, 1H), 3.85-3.78(m, 1H), 3.62-3.56 (m, 1H), 3.11 (dd, *J* = 12.8, 6.4 Hz, 1H), 2.08-1.96 (m, 2H), 1.89-1.83 (m, 1H), 1.75-1.69 (m, 1H), 1.54-1.49 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 163.5, 155.3, 140.1, 120.0, 113.8, 95.6, 88.8, 59.7, 75.1, 52.2, 47.2, 41.7, 24.9, 24.6 ppm. HRMS-ESI calcd for $C_{15}H_{16}Cl_4NO_4$ [M + H$^+$]: 413.9828; Found: 413.9828.



18

(*R*)-2,2,2-trichloroethyl 2-((6*R*, 7a*S*)-6-hydroxy-2-oxo-2,6,7,7a- tetrahydrobenzofuran-7a-yl)pyrrolidine-1-carboxylate (**18**)

To a solution of **15** (100 mg, 0.2427 mmol) in acetone (8 mL) at room temperature, $AgBF_4$ (56.7 mg, 0.2913 mmol) in H_2O (5 mL) was added, the resulting mixture was stirred at 60°C for 12h. The reaction was filtered and the filtrate was washed by saturated aqueous NaCl and extracted with ethyl acetate (2× 20 mL), the combined organic layers were dried (Na_2SO_4), rotary evaporated and chromatographed (CH_2Cl_2, Petroleum ether : ethyl acetate = 1 : 1, ethyl acetate) to give **18** (72 mg, 75% , yellow oil). R_f 0.45 (silica gel, petroleum ether: ethyl acetate= 1 : 1); $[\alpha]^{20}_D$ + 47.8 (*c* 0.1, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.55 (dd, *J* = 10, 1.6 Hz, 1H), 6.32 (dd, *J* = 10, 1.6 Hz, 1H), 5.89 (s, 1H), 5.34-5.30 (m, 1H), 4.84 (d, *J* = 12.0 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.19 (dd, *J* = 8.4, 2.2 Hz, 1H), 3.85-3.78 (m, 1H), 3.63-3.57 (m, 1H), 2.95 (d, *J* = 12.2, 5.6,Hz, 1H), 2.42 (s, 1H), 2.03-1.93 (m, 1H), 1.88-1.80 (m, 1H), 1.75-1.55 (m, 1H), 1.68-1.62 (m, 1H), 1.53 (m, 1H) ppm. ^{13}C NMR (125MHz, $CDCl_3$) δ 172.1, 164.9, 155.2, 143.0, 119.8, 112.9, 99.6, 89.7, 75.1, 66.1, 60.0, 47.3, 41.6, 25.0, 24.5 ppm. HRMS-ESI calcd for $C_{15}H_{17}Cl_3NO_5$ [M + H$^+$]: 396.0167; Found: 396.0167.

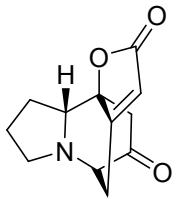


(-)-niruroidine (**3**)

(-)-Niruroidine (**3**)

To a stirred solution of **18** (24.4 mg, 0.4616 mmol) in AcOH/H_2O (4:1, 3 mL) at 15°C, Zn powder (1.823 g, 28 mmol) was added, the resulting mixture was stirred at 15°C for 30min. The reaction was filtered and the filtrate rotary evaporated, then $NH_3{\cdot}H_2O$ in $CHCl_3$ was added (pH 9-10), stire for 2h, extracted with $CHCl_3$, rotary evaporated and chromatographed (silica gel, CH_2Cl_2: MeOH = 20: 1) to give **3** (52.1 mg, 0.2354 mmol, 51%) as yellow oil. R_f 0.3 (silica gel, CH_2Cl_2: MeOH= 10: 1). $[\alpha]^{20}_D$ -38.2° (*c* 0.1 $CHCl_3$). ^{1}H NMR (400MHz, $CDCl_3$) δ 5.73 (s, 1H), 4.43 (m, 1H), 3.26 (dt, *J* = 19.2,

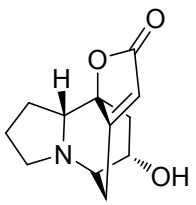
2.3 Hz, 1H), 3.17-3.13 (m, 1H), 3.13-3.10 (m, 1H), 3.03-2.98 (m, 1H), 2.95-2.94 (m, 1H), 2.93-2.90(m, 1H), 2.83-2.78 (m, 1H), 2.74 (s, 1H), 1.99-1.93 (m, 1H), 1.93-1.87 (m, 1H), 1.83-1.74 (m, 2H), 1.35 (ddd, J = 13.8, 3.4, 1.6 Hz, 1H) ppm. ^{13}C NMR (125MHz, $CDCl_3$) δ 175.3, 173.9, 110.3, 84.3, 62.0, 61.6, 55.7, 51.2, 34.2, 27.4, 27.3, 25.7 ppm. HRMS-ESI calcd for $C_{12}H_{16}NO_3$ [M + H$^+$]: 222.1125; Found: 222.1124.



19

Compound **19**

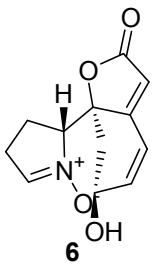
To a stirred solution of **3** (65 mg, 0.294 mmol) in anhydrous CH_2Cl_2, DMP (249.39 mg, 0.588 mmol) was added, the resulting mixture was stirred for 0.5h. The reaction was quenched with saturated aqueous Na_2SO_3 solution and extracted with CH_2Cl_2, the combined organic layers were dried (Na_2SO_4), rotary evaporated and chromatographed (Petroleum ether: ethyl acetate = 2: 1) to give **19** (47 mg, 0.2147 mmol, 73%) as yellow oil. R_f 0.35(silica gel, ethyl acetate); $[\alpha]^{20}_D$ 418.5(c 0.1, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 5.86 (s, 1H), 3.33-3.32 (m, 1H), 3.29-3.27(m, 1H), 3.26-3.19 (m, 1H), 3.14-3.06 (m, 1H), 3.05-3.01 (m, 1H), 2.98-2.93(m, 1H), 2.50-2.44 (m, 1H), 2.26-2.21 (m, 1H), 2.11-2.03 (m, 1H), 1.92-1.89 (m, 1H), 1.88-1.76 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4, 172.6, 170.8, 112.1, 83.9, 62.3, 61.9, 52.2, 40.3, 27.8, 26.4, 24.7 ppm. HRMS-ESI calcd for $C_{12}H_{14}NO_3$ [M + H$^+$]: 220.0968; Found: 220.0968.



20

Compound **20**

To stirred solution of **19** (35.4 mg, 0.1616 mmol) in anhydrous MeOH (2 mL) at 0^{o}C, $NaBH_4$ (18.34 mg, 0.4848 mmol) was added and the resulting mixture was stirred for 40min. The reaction was quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with $CHCl_3$, the combined organic layers were dried (Na_2SO_4), rotary evaporated and chromatographed (ethyl acetate) to give **20** (28.59 mg, 0.129 mmol, 80%) as a colourless crystal. R_f 0.2 (silica gel, ethyl acetate: MeOH = 20:1); $[\alpha]^{20}_D$ -30.25 (c 0.1 $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 5.75 (s, 1H), 4.24 (dd, J = 10.5, 4.7 Hz, 1H), 3.71-3.64 (m, 1H), 3.29 (s, 1H), 3.12-3.07 (m, 2H), 2.98 (dd, J = 19.2, 3.4 Hz, 1H), 2.66 (d, J =19.0Hz, 1H), 2.37 (dd, J = 13.7, 4.7 Hz, 1H), 2.2-2.08 (m, 2H), 1.97-1.87 (m, 3H), 1.75-1.69 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 173.7, 111.6, 84.6, 72.4, 63.3, 56.3, 52.7, 34.0, 31.3, 27.0, 25.6 ppm. HRMS-ESI calcd for $C_{12}H_{16}NO_3$ [M + H$^+$]: 222.1125; Found: 222.1123.

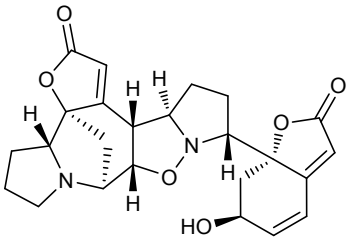


6

Compound **6**

To a solution of **20** (17 mg, 0.07688 mmol) in MeOH (1 mL) was added to Na_2WO_4 (12.68 mg, 0.0384 mmol), then H_2O_2 (3.92 mg, 0.1153 mmol) was added at 0^{o}C，the temperature was immediately rise to 15^{o}C, stirred for 5min, rise to 20^{o}C and stirred for 15min. The reaction was quenched with saturated aqueous NH_4Cl solution (6 mL), extracted with ethyl acetate (3× 6 mL), the combined organic layers were dried (Na_2SO_4), rotary evaporated and chromatographed (ethyl acetate) to give **6** (9.95 mg, 0.0423 mmol, 55%). R_f 0.45(silica gel, ethyl acetate: MeOH = 10: 1); $[\alpha]^{20}_D$ -480 (c 0.1,

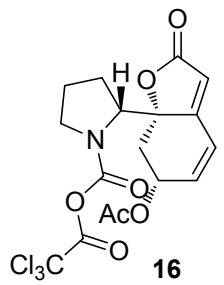
$CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, J = 2.8 Hz, 1H), 6.50 – 6.41 (m, 2H), 5.91 (s, 1H), 4.73-4.70 (m, 1H), 4.66-4.64 (m, 1H), 3.54 (dd, J = 14.1, 1.7 Hz, 1H), 2.88-2.8 (m, 1H), 2.57 (dd, J = 18.7, 9.7 Hz,1H), 2.23 – 2.16 (m, 1H), 2.05 – 2.00 (m, 1H), 1.76 – 1.70 (m, 1H), 1.30-1.24 (m, 1H).^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 163.8, 141.5, 139.4, 118.2, 113.1, 84.8, 73.7, 63.3, 36.1, 28.2, 21.6 ppm. HRMS-ESI calcd for $C_{12}H_{14}NO_4$ [M + H^+]: 236.0917; Found: 236.0918.



(-)-flueggine A (**4**)

(-)-Flueggine A (**4**)

Compound **6** (10 mg, 0.043 mmol) and (-)-norsecurinine **2** (17.5 mg, 0.086 mmol) were dissolved in toluene (3 mL), and the mixture was stirred at reflux for 12h. Then, the reaction was rotary evaporated and chromatographed (CH_2Cl_2: MeOH = 15:1) to give **4:** (-)-flueggine A (12.31 mg, 0.0281 mmol, 66%) as white solid. R_f = 0.45 (silica gel, ethyl acetate: MeOH = 10: 1); $[\alpha]^{20}_D$ -31.6 (*c* 0.1, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 6.50 (d, J = 9.9, 1H), 6.21 (dd, J = 9.9, 4.5Hz, 1H), 5.77 (br s, 1H), 5.78 (br s, 1H), 5.19 (s, 1H), 4.44 (m, 1H), 4.32 (t, J = 4.8 Hz, 1H), 4.02 (t, J = 8.0 Hz, 1H), 3.39-3.35 (m, 2H), 3.30 – 3.22 (m, 1H), 3.18 (dd, J = 10.0, 6.0 Hz, 2H), 2.71(d, J = 14.6 Hz, 1H), 2.67-2.61 (m, 1H), 2.33 (dd, J = 11.8, 5.5 Hz, 2H), 2.13-2.07 (m, 1H), 2.08-2.04 (m, 1H), 2.00 – 1.93 (m, 2H), 1.76-1.68 (m, 5H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 172.0, 171.4, 166.7, 138.1, 120.4, 112.5, 112.0, 91.5, 85.0, 76.2, 73.8, 68.9, 65.5, 63.7, 60.8, 57.2, 49.0, 36.5, 30.0, 29.6, 29.1, 26.6, 25.9 ppm. HRMS-ESI calcd for $C_{24}H_{27}N_2O_6$ [M + H^+]: 439.1869; Found: 439.1866.

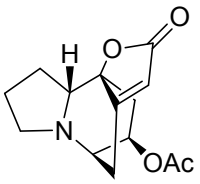


16

(*R*)-2,2,2-trichloroethyl 2-((6*R*,7a*S*)-6-acetoxy-2-oxo-2,6,7,7a- tetrahydrobenzofuran-7a-yl)pyrrolidine-1-carboxylate (**16**)

Compound **15** (151 mg, 0.3639 mmol) and NaI (272.69mg, 1.819mmol) were dissolved in acetone 3 mL, and the mixture was stirred at 60°C for 6 days. Then the reaction was diluted with H_2O (5mL) and extracted with $CHCl_3$ (5 mL×3), the combined organic layers were dried (Na_2SO_4), rotary evaporated, this crude material was used in the following step without further purification.

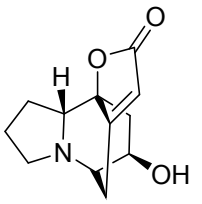
The crude material and AgOAc (272.69 mg, 1.819 mmol) were dissolved in AcOH 3 mL, and the mixture was stirred at 60°C for 6 days. Then the reaction was filtered and the filtrate was diluted with H_2O (5 mL) and extracted with $CHCl_3$ (5 mL×3), the combined organic layers were dried (Na_2SO_4)， rotary evaporated and chromatographed （silica gel, petroleum ether: ethyl acetate = 5: 1）to give compound **16** (127.22 mg，0.2911 mmol, percent conversion：60% over 2 steps) as yellow oil. R_f 0.7(silica gel, petroleum ether: ethyl acetate= 1:1). $[\alpha]^{20}_D$ +35.8 (*c* 0.1 $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ 6.62 (d, J = 9.7 Hz, 1H), 6.20 (s, 1H), 5.90 (s, 1H), 4.84 (d, J = 11.9 Hz, 1H), 4.70 (d, J = 11.9 Hz, 1H), 4.21 (d, J = 8.3 Hz, 1H), 3.78 (q, J = 8.3,Hz, 1H), 3.55 (td, J = 10.5, 5.0 Hz, 1H), 2.96 (dd, J= 12.0, 4.0 Hz, 1H), 2.05 (s, 3H), 1.97 (d, J = 7.5 Hz, 1H), 1.87 – 1.81 (m, 1H), 1.79 (d, J = 10.0 Hz, 1H), 1.76 – 1.68 (m, 2H), 1.59 – 1.50 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 169.8, 164.3, 154.9, 138.1, 121.5, 113.1, 95.5, 89.0, 76.7, 75.1, 68.3, 60.4, 47.3, 25.2, 24.5, 20. 9 ppm. HRMS-ESI calcd for $C_{17}H_{19}Cl_3NO_6$ [M + H^+]: 438.0273; Found: 438.0275.



17

Compound **17**

Zn powder (149.6 g, 2.288 mmol) in AcOH/H_2O (4: 1, 2 mL) was added to a stirred solution of **16** (100 mg, 0.2288 mmol) in AcOH (1 mL) at 15°C, the resulting mixture was stirred at 15°C for 2h. The reaction was filtered and the filtrate rotary evaporated, then $NH_3{\cdot}H_2O$ in $CHCl_3$ was added (pH 9-10), stire for 2h, extracted with $CHCl_3$, rotary evaporated and chromatographed (silica gel, petroleum ether: ethyl acetate= 1: 10) to give **17** (46.94 mg, 0.1785 mmol, 78%) as yellow oil. R_f 0.3(silica gel, ethyl acetate). $[\alpha]^{20}_D$-30.67 (*c* 0.1 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (t, *J* = 2.0 Hz, 1H), 5.35 – 5.15 (m, 1H), 3.22 (q, *J* = 3.1 Hz, 1H), 3.12-3.04 (m, 2H), 3.03-2.99 (m, 1H), 2.97- 2.95 (m, 1H), 2.93-2.91 (m, 1H), 2.89 – 2.83 (m, 1H), 2.03 (s, 3H), 1.98-1.91 (m, 2H), 1.83 – 1.75 (m, 2H), 1.37 (ddd, *J* = 14.2, 3.7, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 173.4, 170.1, 110.7, 83.6, 64.2, 62.2, 52.9, 51.2, 31.6, 28.2, 27.2, 25.6, 21.0. HRMS-ESI calcd for $C_{14}H_{18}NO_4$ [M + H^+]: 264.1230; Found: 246.1231.

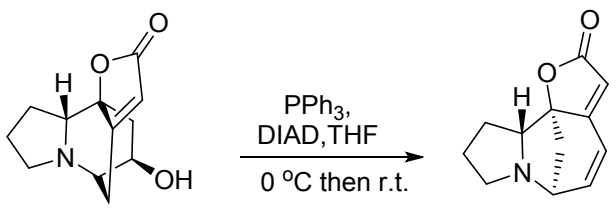


(-)-niruroidine (**3**)

(-)-Niruroidine (**3)**

NaOH (30.72 mg, 0.768 mmol) was added dropwise to a stirred solution of compound **17** (101 mg, 0.384 mmol) in THF/H_2O (2.5 mL, 3:2), stirred at room temperature for 0.5h. The reaction was rotary evaporated and chromatographed (silica gel, CH_2Cl_2: MeOH= 20: 1) to give **3** (69.62 mg, 0.3149 mmol, 82%) as yellow oil. R_f 0.3 (silica gel, CH_2Cl_2: MeOH = 10: 1). $[\alpha]^{20}_D$ -12.0 (*c* 0.1 $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$) δ 5.73 (s, 1H), 4.43 (m, 1H), 3.26 (dt, *J* = 19.2, 2.3 Hz, 1H), 3.17-3.15 (m, 1H), 3.14-3.10 (m, 1H), 3.05-2.98 (m, 1H), 2.95-2.94 (m, 1H), 2.93-2.90(m, 1H), 2.83-2.78 (m, 1H), 2.74 (s, 1H), 1.99-1.93 (m, 1H), 1.93-1.87 (m, 1H), 1.83-1.76 (m, 2H), 1.38-1.33 (m, 1H) ppm.

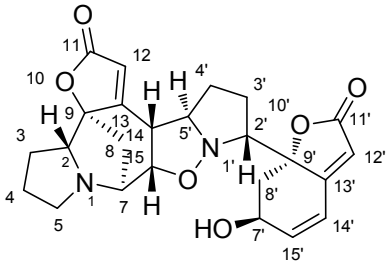
One step synthesis of (-)-norsecurinine (**2**):



(-)-niruroidine (**3**) (-)-norsecurinine (**2**)

To a stirred solution of PPh_3 (59.4 mg, 0.2265 mmol) in anhydrous THF (2 mL), DIAD (0.0491 mL, 0.2492 mmol) was added, then **3** (10 mg, 0.0453 mmol) was added drop-wise to the mixture solution at 0°C. The temperature was then rise to r.t. and stirred for 6h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (3 mL) and extracted with ethyl acetate (3×5 mL), the combined organic layers were dried (Na_2SO_4), rotary evaporated and chromatographed (ethyl acetate) to give **2** (8 mg, 0.0394 mmol, 87%) as a yellow oil. $[\alpha]^{20}_D$ -256 (*c* 0.1, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (dd, *J* = 9.0, 6.5 Hz, 1H), 6.50 (d, *J* = 9.0 Hz, 1H), 5.67 (s, 1H), 3.64 (dd, *J* = 6.5, 4.8 Hz, 1H), 3.32 (t, *J* = 7.8 Hz, 1H), 3.22 (t, *J* = 7.7 Hz, 1H), 2.61 - 2.52 (m, 2H), 2.01 - 1.97 (m, 2H), 1.84 - 1.78 (m, 2H), 1.74 (d, *J* = 10.8 Hz, 1H) ppm.

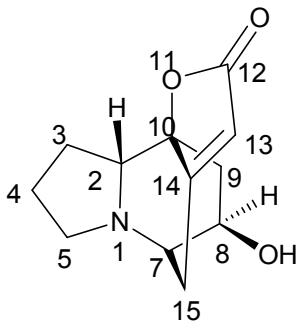
Comparison of the NMR spectroscopic data of natural and synthetic (-)-flueggine A.



NO.	δH Natural ^{1}H 600MHz	δH Synthetic ^{1}H 400HMz	Error (ppm)	δC Natural ^{13}C 150MHz	δC Synthetic ^{13}C 125MHz	Error (ppm)
2	3.15 (dd, 8.4, 6.6)	3.18 (dd,10.0, 6.0)	0.03	65.5	65.5	0
3	α1.75 (m)	1.75 (m)		29.1	29.1	0
	β 1.94 (m)	1.94 (m)				
4	α 1.98 (m)	1.98 (m)		26.6	26.6	0
	β 1.68 (m)	1.68 (m)				
5	α 2.63 (m)	2.63 (m)		57.2	57.2	0
	β 3.35 (m)	3.35 (m)				
7	3.24 (m)	3.24 (m)		60.7	60.8	0.1
8	a 2.32 (dd, 11.2, 4.8)	2.33 (dd,11.8, 5.5)	0.01	29.5	29.6	0.1
	b 1.80 (d, 11.2)	1.80 (m)	0			
9				91.7	91.5	0.2
11				171.5	171.4	0.1
12	5.78 (br s)	5.78 (br s)		112	112	0
13				172.9	172.8	-0.1
14	3.33 (dd, 8.8, 4.8)	3.33 (m)	0	49.1	49	-0.1
15	4.30 (t, 4.8)	4.32 (t, 4.8)	0.02	76.3	76.2	-0.1
2’	3.17 (dd, 10.0, 6.0)	3.18 (dd, 10.0, 6.0)	0.01	73.9	73.8	-0.1
3’	α 2.12 (m)	2.12 (m)		25.9	25.9	0
	β 1.77 (m)					
4’	α 2.34 (m)	2.33 (dd,11.8, 5.5)		30.1	30	-0.1
	β 1.72 (m)	1.72 (m)				
5’	4.01 (t, 8.0)	4.02 (t, 8.0)	0.01	68.9	68.9	0
7’	4.44 (m)	4.44 (m)		63.7	63.7	0

8'	**a 2.71 (d, 14.4)**	**2.71 (d, 14.6)**	**0**	**36.5**	**36.5**	**0**
	b 2.06 (dd, 14.4, 6.4)	**2.06 (m)**	**0**			
9'				**85**	**85**	**0**
11'				**172**	**172**	**0**
12'	**5.77 (br s)**	**5.77 (br s)**	**0**	**112.5**	**112.5**	**0**
13'				**166.8**	**166.7**	**-0.1**
14'	**6.50 (d, 9.6)**	**6.50 (d, 9.9)**	**0**	**120.4**	**120.4**	**0**
15'	**6.21 (dd, 9.6, 4.8)**	**6.21 (dd, 9.9,4.5)**	**0**	**138.1**	**138.1**	**0**

Comparison of the NMR spectroscopic data of natural and synthetic (-)-niruroidine.



NO.	δH Natural ^{1}H 600MHz	δH Synthetic ^{1}H 400HMz	Error (ppm)	δC Natural ^{13}C 150MHz	δC Synthetic ^{13}C 125MHz	Error (ppm)
2	**3.00 (t, 6.8)**	**3.01 (m)**	**0.1**	**61.5**	**61.6**	**0.1**
3a	**1.95 (m)**	**1.95 (m)**		**27.3**	**27.4**	**0.1**
3b	**1.78 (m)**	**1.78 (m)**				
4a	**1.91 (m)**	**1.91 (m)**		**27.2**	**27.3**	**0.1**
4b	**1.78 (m)**	**1.78 (m)**				
5a	**3.12 (m)**	**3.12 (m)**		**51.2**	**51.2**	**0**
5b	**2.89 (m)**	**2.88 (m)**				
7	**3.13 (m)**	**3.15 (m)**		**55.7**	**55.7**	**0**
8	**4.42 (m)**	**4.43 (m)**		**62.0**	**62.0**	**0**
9a	**2.79 (dd, 13.6, 9.6)**	**2.79 (m)**		**34.1**	**34.2**	**0.1**
9b	**1.34 (ddd, 13.6, 3.2, 1.2)**	**1.35 (ddd,13.8,3.4,1.6)**				
10				**84.3**	**84.3**	**0**

12				**175.3**	**175.3**	**0**
13	**5.71 (dd, 2.0, 2.0)**	**5.73 (s)**	**0.02**	**110.3**	**110.3**	**0**
14				**173.9**	**173.9**	**0**
15a	**3.25 m**	**3.26 (dt, 19.2, 2.3)**	**0.1**	**25.6**	**25.7**	**0.1**
15b	**2.90 (ddd, 19.2, 2.0, 2.0)**	**2.91 (m)**	**0.1**			