SUPPLEMENTARY MATERIAL

TOTAL SYNTHESIS OF (–)-TUBEROSTEMONINE

Peter Wipf,* Stacey R. Rector and Hidenori Takahashi

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

pwipf+@pitt.edu

Experimental procedures, and characterization data for key transformations (preparation of **3**, **16**, and **1**, and copies of 1D and 2D NMR spectra for **1**).

General Methods. All moisture-sensitive reactions were performed under an atmosphere of N₂ and glassware was dried in an oven at 140 °C prior to use. THF and Et₂O were dried by distillation over Na/Benzophenone and dry CH₂Cl₂ and toluene were obtained by distillation from CaH₂. Unless otherwise stated, solvents or reagents were used as received without further purification. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F-254 plates (particle size 0.040-0.055 mm, 230-400 mesh) and visualization was accomplished with a 254 nm UV light and/or by staining with PMA (5g of phosphomolybdic acid in 100mL of EtOH), anisaldehyde (2.5 mL of p-anisaldehyde in 2 mL of HOAc, 3.5 mL of conc. H₂SO₄, and 92 mL of EtOH), or ninhydrin (0.3g of ninhydrin in 3 mL of conc. HOAc and 100 mL of n-butyl alcohol). NMR spectra were recorded at 300 MHz/75 MHz (¹H/¹³C NMR) in CDCl₃ using a Bruker AVANCE 300 MHz spectrometer at 21 °C unless stated otherwise. Chemical shifts (δ) are reported in parts per million and the residual solvent peak was used as an internal standard. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad), integration, and coupling constants. IR spectra were obtained on an IBM IR/32 FT-IR spectrometer or on a Nicolet AVATAR 360 FT-IR E.S.P. Spectrometer. Mass spectra were obtained on a VG-70-70-HF. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

(2*S*,3,3*aR*,6*S*,7,7*aR*)-Hexahydro-6-hydroxyindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (3). To a solution of **2** (34 g, 75 mmol) in THF (340 mL) was added Pd₂(dba)₃CHCl₃ (1.6 g, 1.5 mmol) and tribenzylphosphine (1.8 g, 6.0 mmol). The reaction mixture was stirred for one minute, and triethylamine (36 mL, 260 mmol) was added followed immediately by formic acid (9.8 mL, 260 mmol). The solution was then heated at reflux for 16 h. The color changed to a lighter clear-orange-brown color and CO₂ gas was evolved upon heating. After 16 h, the mixture was cooled to room temperature and the solvent removed *in vacuo*. The remaining residue was purified by chromatography on SiO₂ (Hexanes/EtOAc, 4:1 to 2:1 to 1:1) to give 23 g (93%) of **3**¹ as a yellow foam. ¹H NMR (DMSO-d₆, 373K) δ 7.39-7.27 (m, 5 H), 5.73 (bd, 1 H, *J* = 9.8 Hz), 5.61 (bd, 1 H, *J* = 9.3 Hz), 5.09, 5.02 (AB, 2 H, *J* = 12.4 Hz), 4.43-4.31 (m, 2 H), 3.55 (s, 3 H), 3.23-3.14 (m, 1 H), 2.50-2.37 (m, 2 H), 1.60-1.36 (m, 2 H).

(5*S*)-((1,2*S*,4,5,6,7,7*aS*,8*S*,10*aR*,10*bS*)-8-Hydroxydecahydroazepino[3,2,1-*hi*]indol-2-yl)-(3*S*)-methyldihydrofuran-2-one (16). To a solution of 4,4'-di-*tert*-butylbiphenyl (4.85 g, 18.2 mmol) in THF (35 mL) was added small pieces of lithium wire (106 mg, 15.2 mmol). The reaction mixture was cooled to -15 °C, and the blue-green solution was stirred at that temperature for 20 h, cooled to -78 °C, and treated with a solution of orthoester **14** (ca. 2.6 g, 10.4 mmol) in THF (5 mL) until it turned a deep red color. After stirring for 30 min at -78 °C, a solution of Weinreb amide **13** (1.00 g, 2.53 mmol) in THF (4 mL) was added. This mixture was stirred at -78 °C for an additional 15 min and quenched with wet Et₂O (50 mL). The organic layer was washed with water and brine, dried (MgSO₄), concentrated *in vacuo*, and purified *via* chromatography on SiO₂ prewashed with a solution of 0.5% NEt₃ in Hexanes/EtOAc (95:5) (Hexanes/EtOAc gradient elution from 95:5 to 4:1) to give 1.21 g (95%) of **15** as a light yellow oil. A solution of this oil in THF (50 mL) was treated at -78 °C dropwise with a 1.0 M solution of lithium tri-*sec*-butylborohydride in THF (4.78 mL, 4.78 mmol). The reaction mixture was stirred at -78 °C for 2 h, then warmed to -15 °C and stirred for 15 h. At that time, the

¹ Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106.

solution was quenched with 10% aqueous ethanolamine and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried (MgSO₄), concentrated *in vacuo*, and purified by chromatography on SiO₂ prewashed with a solution of 0.5% NEt₃ in Hexanes/EtOAc (9:1) (Hexanes/EtOAc gradient elution from 9:1 to 4:1, to EtOAc) to give 970 mg (80%) of a white foam that was dissolved in MeOH (80 mL) and treated with *p*-toluenesulfonic acid monohydrate (551 mg, 2.87 mmol) at room temperature for 20 h. The reaction mixture was concentrated *in vacuo*, diluted with a saturated NaHCO₃ solution and extracted into EtOAc (2 X 50 mL) and CH₂Cl₂ (1 x 50 mL). The combined organic layers were dried (MgSO₄) and purified *via* chromatography on SiO₂ (Hexanes/EtOAc, 4:1 to 1:1 to CH₂Cl₂/MeOH, 95:5 to 85:15) to give 388 mg (70%) of **16** as a white foam: [α]_D -52.8 (*c* 0.65, CHCl₃, 21 °C); IR (neat) 3378, 2931, 1758, 1457 cm⁻¹; ¹H NMR δ 5.75 (bd, 1 H, *J* = 9.9 Hz), 5.50 (bd, 1 H, *J* = 9.9 Hz), 4.53-4.51 (m, 1 H), 4.33 (ddd, 1 H, *J* = 13.2, 7.9, 5.5 Hz), 3.22 (dd, 1 H, *J* = 15.2, 6.5 Hz), 3.11 (dt, 2 H, *J* = 9.5, 7.8 Hz), 2.97 (dd, 1 H, *J* = 14.9, 9.5 Hz), 2.63 (ddd, 1 H, *J* = 12.2, 8.3, 7.7 Hz), 2.60-2.34 (m, 3 H), 2.13 (dt, 1 H, *J* = 11.7, 5.7 Hz), 2.05-2.01 (m, 1 H), 1.95-1.91 (m, 1 H), 1.58-1.45 (m, 3 H), 1.37-1.21 (m, 2 H), 1.25 (d, 3 H, *J* = 7.0 Hz), 1.15 (q, 1 H, *J* = 11.3 Hz); ¹³C NMR δ 179.2, 132.4, 127.0, 82.5, 71.2, 67.8, 67.6, 53.6, 41.1, 38.0, 35.2, 34.1, 31.7, 29.0, 25.6, 22.0, 14.8; MS (EI) *m/z* (rel. intensity) 291(M⁺, 2), 273 (5), 192 (100), 172 (7), 91 (6), 77 (8); HRMS *m/z* calculated for C₁₇H₂₅NO₃ 291.1834, found 291.1846.

(-)-Tuberostemonine (1). To a solution of **20** (53.1 mg, 0.137 mmol) in CH₂Cl₂ (2.5 mL) was added allyltritylamine (82.0 mg, 0.274 mmol), ruthenium catalyst **9**² (25.0 mg, 0.0274 mmol), and N,N-diisopropylethylamine (23.9 μ L, 0.137 mmol). The reaction mixture was heated at reflux for 16 h, concentrated *in vacuo*, and purified *via* chromatography on SiO₂ prewashed with a solution of 0.5% NEt₃ in Hexanes/EtOAc (9:1) (Hexanes/EtOAc gradient elution from 9:1 to 2:1 to 1:1, to EtOAc) to give 45.3 mg (85%) of an (*E*),(*Z*)-mixture (ca. 2:1) of **21** as a yellow oil. A solution of this mixture of double bond isomers (47.1 mg, 0.122 mmol) in CH₂Cl₂ (5.2 mL) was treated with *p*-toluenesulfonic acid monohydrate (23.2 mg, 0.122 mmol) and heated at reflux for 30 min. After addition of catalyst **23**³ (3.6 mg, 0.0058 mmol), the solution was heated at reflux while ethylene gas was bubbled through it with additional portions of catalyst **23** (3.81 mg, 0.0061 mmol) added approximately every 12 h. After 60 h, the mixture was diluted with EtOAc and washed with saturated NaHCO₃ and brine, dried (MgSO₄), concentrated *in vacuo* and purified *via* chromatography on SiO₂ prewashed with a solution of 0.5% NEt₃ in Hexanes/EtOAc (9:1) (Hexanes/EtOAc gradient elution from 9:1 to 2:1 to 1:1 to 1:2) to give 37.1 mg (81%) of **22** as a white foam. A solution of **22** in methanol (4.6 mL) was hydrogenated for 17h at room temperature in the presence of 10% Pd/C (37.1 mg), filtered through a plug of Celite and concentrated *in vacuo* to give 36.0 mg (97%) of **1** as a white foam: [α]_D -29.4 (*c* 0.10, acetone, 21 °C) [Lit.⁴ [α]_D -25.4 (*c* 0.06, acetone, 21 °C)]; IR (neat) 2925, 1772, 1451, 1163 cm⁻¹; ¹H NMR (CD₂Cl₂) δ 4.41 (t, 1 H, *J* = 7.8 Hz), 4.25 (ddd, 1 H, *J* = 10.7, 7.8, 5.4 Hz), 3.42-3.37 (m, 2 H), 3.02 (dd, 1 H, *J* = 11.2, 6.5 Hz), 2.68-2.51 (m, 2 H), 2.39-2.29 (m, 2 H), 2.15 (dt, 1 H, *J* = 12.1, 6.7 Hz), 2.00 (dt, 1 H, 10.2, 7.6 Hz), 1.83-1.74 (m, 4 H), 1.59-1.39 (m, 8 H), 1.22 (d, 3 H, *J* = 7.3 Hz), 1.19 (d, 3 H, *J* = 6.9 Hz), 1.12-1.01 (m, 1 H), 0.94 (t, 3 H, *J* = 7.3Hz); ¹³C NMR (CD₂Cl₂)

² (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312.

³ (a) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

⁴ Lin, W.-H.; Ye, Y.; Xu, R.-S. *J. Nat. Prod.* **1992**, *55*, 571.

δ 179.7 (s), 179.5 (s), 82.0 (d), 80.6 (d), 65.2 (d), 63.8 (d), 48.1 (t), 47.5 (d), 45.2 (d), 42.2 (d), 41.2 (d), 41.1 (d), 35.1 (d), 34.8 (t), 32.4 (t), 30.5 (t), 30.3 (t), 28.8 (t), 24.7 (t), 15.0 (q), 14.9 (q), 11.2 (q); MS (EI) m/z (rel. intensity) 375 (M^+ , 1), 374 (4), 373 (5), 344 (14), 304 (15), 290 (26), 276 (100), 260 (11), 200 (6), 134 (6); HRMS m/z calculated for $C_{22}H_{32}NO_4$ (M-H) 374.2331, found 374.2317.

Figure. Structure and Observed NOESY Correlations for Tuberostemonine (600 MHz in CD_2Cl_2 ; mixing time 350 msec).

Table. ^1H NMR/ ^{13}C NMR Assignments for Tuberostemonine (300/75 MHz in CD_2Cl_2).

C #	^1H δ [ppm], mult (J)	^{13}C δ [ppm], mult
1	1.83-1.74, m	41.2, d
2	α 2.15, dt (12.1, 6.7 Hz) β 1.12-1.01, m	32.4, t
3	3.42-3.37, m	65.2, d
5	α 2.68-2.51, m β 3.42-3.37, m	48.1, t
6	α 1.59-1.39, m β 1.59-1.39, m	30.5, t
7	α 1.59-1.39, m β 1.59-1.39, m	28.8, t
8	α 1.83-1.74, m β 1.83-1.74, m	30.3, t
9	1.83-1.74, m	42.2, d
9a	3.02, dd (11.2, 6.5 Hz)	63.8, d
10	1.59-1.39, m	45.2, d
11	4.41, t (7.8 Hz)	80.6, d
12	2.00, dt (10.2, 7.6 Hz)	47.5, d
13	2.39-2.29, m	41.1, d
14	-----	179.7, s
15	1.22, d (7.3 Hz)	15.0, q
16	α 1.59-1.39, m β 1.59-1.39, m	24.7, t
17	0.94, t (7.3 Hz)	11.2, q
18	4.25, ddd (10.7, 7.8, 5.4 Hz)	82.0, d
19	α 1.59-1.39, m β 2.39-2.29, m	34.8, t
20	2.68-2.51, m	35.1, d
21	-----	179.5, s
22	1.19, d (6.9 Hz)	14.9, q

sr7-122 cd2c12 rt 600MHz/151mhz hc2d co1oc (HNBC) 9/10/02

Current Data Parameters

NAME sr7-122
EXPNO 1122
PROCNO 1

F2 - Acquisition Parameters

Date_ 20020910
Time 18.43
INSTRUM spect
PROBHD 5 mm TBI 1H/
PULPROG invgprnd
TD 4096
SOLVENT CDCl3
NS 36
DS 4
SWH 8692.806 Hz
FIDRES 2.156509 Hz
AQ 0.2277876 sec
RG 16384
RW 81.890 umsec
DE 8.00 umsec
TE 310.0 K
D1 0.00003200 sec
D11 1.00000000 sec
D12 0.00000000 sec
D13 0.00000000 sec
D18 0.00000000 sec
D19 0.00013263 sec

CHANNEL f1

NUC1 1H
P1 9.00 umsec
PL1 19.20 umsec
PL2 0.00 dB
RF1 800.633000 MHz

CHANNEL f2

NUC2 13C
P2 13.50 umsec
PL2 0.00 dB
RF2 151.0533627 MHz

SHOULDER CHANNEL

PL8 1000.00 umsec

F1 - Acquisition parameters

NO 2
TD 256
SFO1 151.0534 MHz
FIDRES 147.40565 Hz
SW 249.749 ppm
SI 1024
SF 600.830105 MHz
WDW SINC
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

F2 - Processing parameters

SI 2048
SF 151.078757 MHz
WDW SINC
SSB 0
LB 0.00 Hz
GB 0

F1 - Processing parameters

SI 2048
SF 600.830105 MHz
WDW SINC
SSB 0
LB 0.00 Hz
GB 0
C2 16.00 cm
C3 16.00 cm
F2H0 5.222 ppm
F2L0 3137.50 Hz
F2H1 0.165 ppm
F2L1 99.02 Hz
F3H0 50.870 ppm
F3L0 13726.50 Hz
F4H1 -0.113 ppm
F4L1 -17.06 Hz
F5H0 0.20083 ppm/cm
F5L0 199.81027 Hz/cm
F6H0 8.06992 ppm/cm
F6L0 818.37189 Hz/cm

sr7-122 cd2c12 rt 600MHz hh2d noesy 9/11/02

Current Data Parameters
 NMR 1111
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20020910
 Time 22.03
 INSTRUM spect
 PROBHD 5 mm TBI 4H/
 PULPROG noesy1p
 TD 1024
 SOLVENT D2O
 NS 100
 DS 16
 SNR 2693.965 Hz
 FIDRES 2.630628 Hz
 AQ 0.1901044 sec
 RG 400
 DE 188.600 usec
 TE 300.2 K
 D1 0.0000000 sec
 D11 1.0000000 sec
 DB 0.3459599 sec
 INO 0.00018560 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 9.60 usec
 PL1 0.00 dB
 SF01 600.831823 MHz

F1 - Acquisition parameters
 NDO 2
 TD 233
 SF01 600.8317 MHz
 FIDRES 11.562084 Hz
 SN 4.484 ppm

F2 - Processing parameters
 SI 1024
 SF 600.8300228 MHz
 NON SINE
 SS 0
 LB 0.00 Hz
 GB 0
 PC 1.00

F1 - Processing parameters
 SI 1024
 SF 600.8300227 MHz
 NON SINE
 SS 0
 LB 0.00 Hz
 GB 0

2D NMR plot parameters
 CX2 15.00 ca
 CX1 15.00 ca
 F2P10 4.584 ppm
 F2L0 2976.46 Hz
 F2PHI 0.470 ppm
 F2H1 262.48 Hz
 F1P10 4.584 ppm
 F1L0 2976.35 Hz
 F1PHI 0.470 ppm
 F1H1 262.52 Hz
 F2PPOH 0.25852 ppm/ca
 F2LCA 179.58776 Hz/ca
 F1PPOH 0.25852 ppm/ca
 F1LCA 179.58776 Hz/ca

sr7-122 cd2c12 rt 600MHz hh2d cosy 9/10/02

Current Data Parameters
NAME sr7-122
EXPNO 11
PROCNO 1

F2 - Acquisition Parameters
Date_ 20020910
Time 15.28
INSTRUM spect
PROBHD 5 mm TBI 1H/
PULPROG noesy1p
TD 1024
SOLVENT CDCl3
NS 12
DS 16
SWH 7507.507 Hz
FIDRES 7.531850 Hz
AQ 0.0822484 sec
RG 200
CW 66.600 usec
DE 6.00 usec
TE 299.0 K
D0 0.00000000 sec
D1 1.00000000 sec
D8 0.34959595 sec
TM0 0.0006560 sec

CHANNEL f1
NUC1 1H
P1 13.50 usec
PL1 0.00 dB
SFO1 600.636050 MHz

F1 - Acquisition parameters
NUC0 1H
P0 256
SFO0 600.6336 MHz
FIDRES 29.326200 Hz
SN 12.495 ppm

F2 - Processing parameters
SI 1024
SF 600.6300221 MHz
WDW SINE
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

F1 - Processing parameters
SI 1024
IC2 1024
SF 600.6300220 MHz
WDW SINE
SSB 0
LB 0.00 Hz
GB 0

2D NMR plot parameters
CX2 16.00 cm
CY1 16.00 cm
F2DLO 8.067 ppm
F2DLO 3062.39 Hz
F2PHI 0.643 ppm
F2PHI 527.73 Hz
F1DLO 4.926 ppm
F1DLO 2959.77 Hz
F1PHI 0.631 ppm
F1PHI 379.06 Hz
F2PPMCH 0.30343 ppm/cm
F2PPMCH 182.31122 Hz/cm
F1PPMCH 0.26639 ppm/cm
F1PPMCH 172.04704 Hz/cm