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Total Synthesis of Putative Montamine and a Proposed Structural Reassignment

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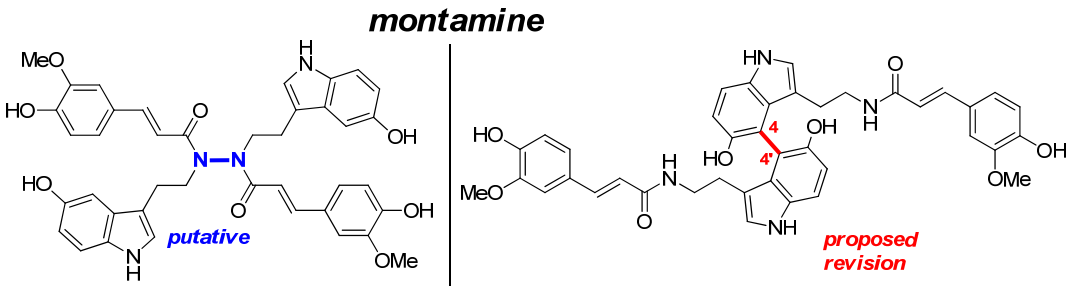
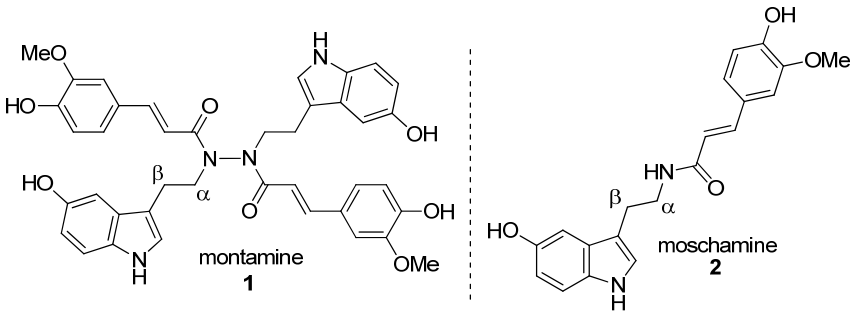


ABSTRACT: The natural product montamine was originally assigned as a homodimer of moschamine linked by a N–N′ bond at the serotonin side-chain. A total synthesis of the reported structure has shown this to be incorrect. Analysis of the spectroscopic data suggests that the dimerization site has been incorrectly assigned, and montamine is likely to be a 4,4′-bismoschamine natural product previously described in the literature.

Montamine (**1**) is an alkaloid isolated from seeds of the ornamental plant *Centaurea montana* in 2006,[1] the structure of which is proposed to be a homodimer of moschamine (**2**) linked by a N–N′ bond at the serotonin side-chain.[2] The homodimerization site was elucidated by comparing the chemical shifts of the α-CH_2 and β-CH_2 protons in the ^{1}H NMR spectrum of **1** to those of the known monomeric natural product moschamine (**2**) (Figure 1). The α-CH_2 and β-CH_2 protons are observed at δ_H 2.86–2.77 ppm (m) and δ_H 2.27–2.19 ppm (m) in montamine (**1**), significantly upfield relative to the corresponding protons in moschamine (**2**) [δ_H 3.58 ppm (t) and δ_H 2.94 ppm (t)]. This upfield shift was attributed to shielding of the methylenes due to their close proximity with the aromatic electron clouds upon formation of

the N–N′ dimer at the serotonin side chain. Intrigued by these NMR data and structural assignment, together with an ongoing interest in the synthesis of natural products that possess a N–N bond,[3] we set out to corroborate the structure of the natural product by completing its total synthesis.

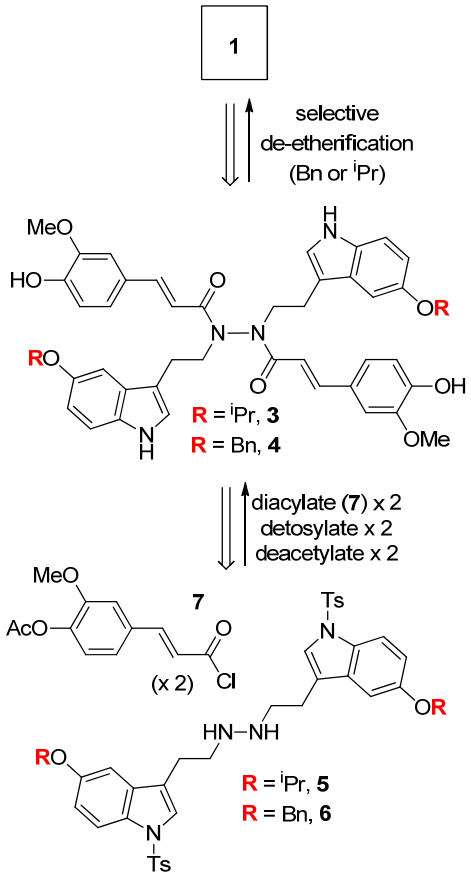
Both of our research groups have an ongoing interest in this natural product, separately reporting similar synthetic routes to the bis(indolyl)ethylhydrazine core[4] and montamine dimethyl ether,[5] respectively. Using the bidirectional approach in the latter example as a guide,[5] two planned syntheses of **1** are shown in Scheme 1. It was envisaged montamine (**1**) could be obtained by the selective deprotection of either its diisopropyl ether **3** or dibenzyl ether **4** which are both available from the hydrazines **5** and **6** by diacylation with the feruloyl chloride **7** followed by deacetylation-detosylation.



compound	α–CH_2	β–CH_2
Montamine (**1**)	2.86-2.77, m	2.27-2.19, m
Moschamine (**2**)	3.58, t	2.94, t

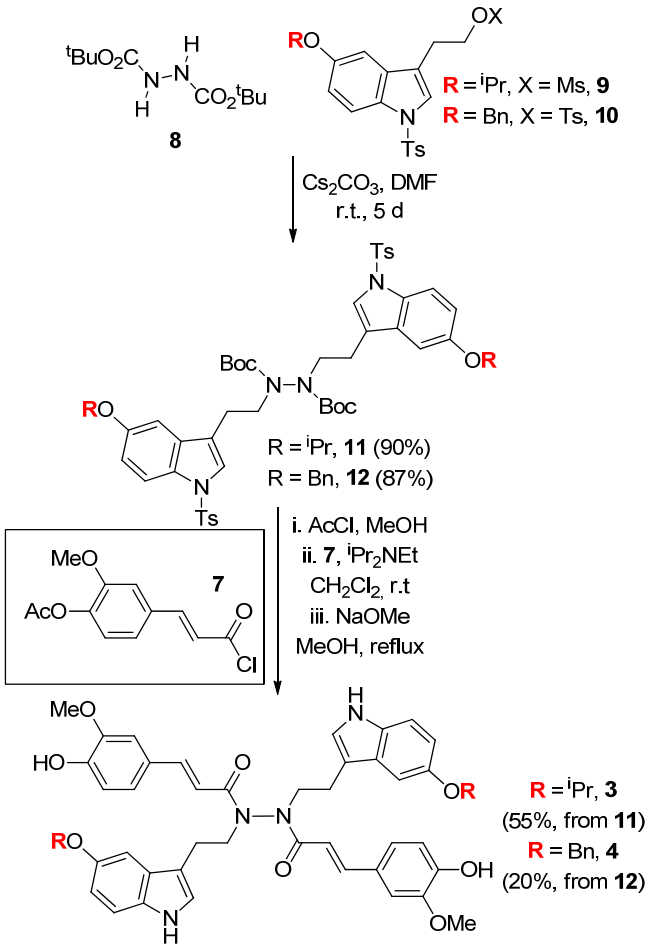
Figure 1. Natural products montamine (**1**), moschamine (**2**) and selected ^{1}H NMR data (CD_3OD)[1]

Scheme 1. Synthetic approaches to montamine (1)



Di-*tert*-butyl hydrazodicarboxylate **8** was subjected to dialkylation[6] with the appropriately protected 5-alkoxytryptophol derivatives **9** and **10** to give the carbazates **11** and **12**, respectively (Scheme 2). Boc-cleavage of **11** and **12** followed by immediate diacylation of the resulting hydrazines with the feruloyl chloride **7** and subsequent sodium methoxide-mediated one-pot detosylation-deacetylation gave montamine diisopropyl ether (**3**) and dibenzyl ether (**4**), respectively. The yields of **3** (55%) and **4** (20%) represent eight transformations (di-deBoc, diacylation, di-deactylation and di-detosylation) over four steps which when combined with the high yielding initial dialkylation step, makes this bidirectional synthetic route an efficient one.

Scheme 2. Synthesis of montamine diisopropyl and dibenzyl ethers (3) and (4)

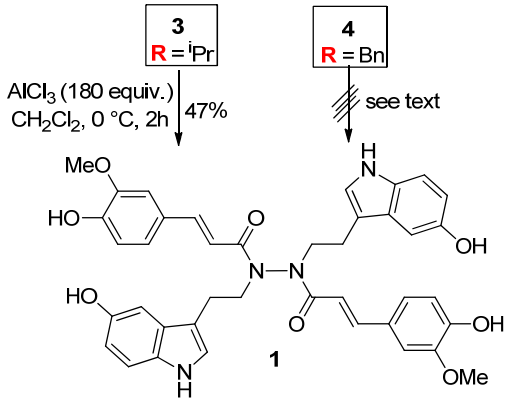


With montamine diisopropyl and dibenzyl ethers **3** and **4** in hand, selective deprotections could be attempted (Scheme 3). Attempted debenzylation of **4** using BCl_3, BBr_3, and triethylsilane/I_2 all gave some conversion as evidenced by NMR and MS, but the product could not be isolated in suitable quantities. Treating **4** with $AlCl_3$ led to complete conversion but the product could not be isolated in sufficient quantity or purity to allow full characterization. Fortunately, a better outcome was realized when conducting the selective de-etherification on montamine diisopropyl ether **3**. As aryl isopropyl ethers can be selectively cleaved in preference to their methyl counterparts using $AlCl_3$,[7] diisopropyl ether **3** was exposed to $AlCl_3$ in dichloromethane at room temperature; however, only degradation was observed. This could be avoided by conducting the reaction at 0 °C, but a significant excess of $AlCl_3$ had to be added to effect complete conversion of the starting material to give the desired product **1**.

Compound **1** exists as a mixture of rotamers[8] and the gross structure was confirmed by detailed spectroscopic analysis. Comparison of the NMR data for synthetic **1** and that of the natural product montamine (Table 1) revealed several key differences.[9] Notably, the chemical shifts of the α-CH_2 and β-CH_2 protons

in synthetic **1** are observed at δ_H 4.12–3.81 ppm (m) and δ_H 3.08–2.92 ppm (m), significantly downfield to those in the natural product montamine and inferring that these protons are not shielded by the aromatic electron clouds. The α-CH_2 signal in the synthetic material also appears further downfield in the ^{13}C NMR spectrum (δ_C 50.4 ppm vs δ_C 41.0 ppm). Other pronounced differences are evident around the feruloyl alkene region (C7′, C8′) and the indole (C4, C6) in both the ^1H and ^{13}C NMR data. Interestingly, the HMBC data for synthetic **1** and the natural product montamine are in good agreement,[10] suggesting that the homodimerization site may have been incorrectly assigned. A comparison of the NMR data for montamine to the known natural product 4,4′-bismoschamine (**13**), isolated in 1996 from *Carthamus tinctorius* L.,[11] reveals a good overall resemblance (Table 1). The ^1H NMR data shows that the α-CH_2, β-CH_2, and C7′-H protons display similarly upfield resonances in both montamine and **13** when compared to the monomer **2**. Indeed, the upfield resonances of the α-CH_2 and β-CH_2 protons are not unique to compound **13**, but appear to be a general characteristic exhibited by 4,4′-bis-serotonin derivatives such as the related compounds **14** and **15**,[11] as well as compound **16**[12] (Figure 2A).

Scheme 3. Selective de-etherification.



When considering the ^{13}C NMR data, the chemical shift of C4 appears further downfield in both montamine (δ_C 111.2 ppm) and **13** (δ_C 114.0 ppm) compared to the monomer moschamine **2** (δ_C 102.2)[13] and synthetic **1** (δ_C 103.6), consistent with the formation of a biaryl bond at the C4 site. The C4 in the related natural products **14** and **15** show similar downfield resonances (Figure 2A), but unfortunately no ^{13}C NMR data exists for compound **16**[12] or 4,4′-bis-serotonin.[14] However, a similar downfield shift of the C4 resonance is evident upon dimerization of 5,6-dihydroxyindole 2-carboxylic acid (**17**) at C4 (**18**, Figure 2B).[15]

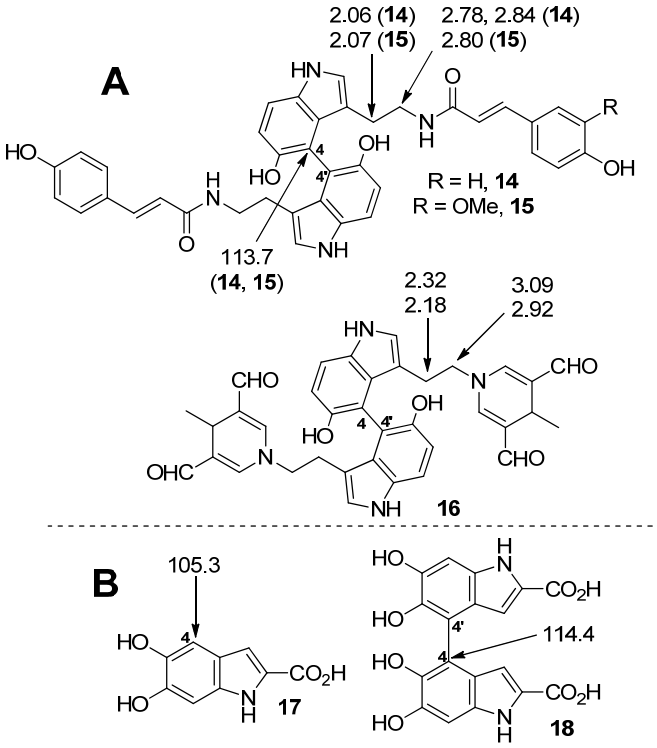
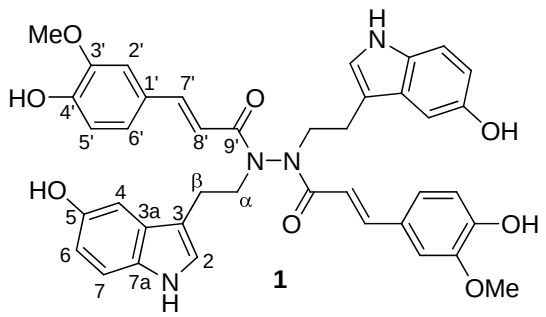
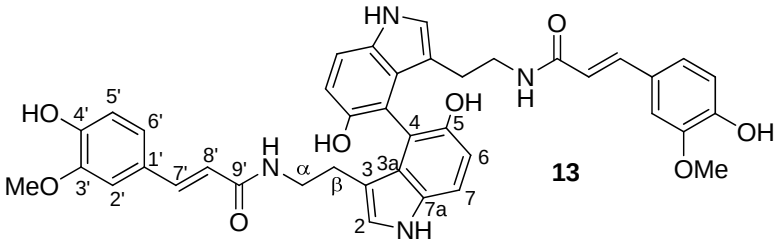


Figure 2. (**A**) Distinctive chemical shifts in compounds **14**, **15** and **16** (all in d_6-DMSO); (**B**) downfield shift of C4 upon homodimerization of 5,6-dihydroxyindole 2-carboxylic acid at C4 (d_6-DMSO)

Table 1. NMR spectroscopic data for the monomer moschamine (2),[13] synthetic 1 (this work), the natural product montamine[1] and the known natural product 13[11]





	^{1}H, mult., *J* (Hz)					^{13}C		
Carbon	moschamine[13] (**2**) (CD_3OD, 400 MHz)	synthetic **1** (CD_3OD, 400 MHz)	montamine[1] (CD_3OD, 400 MHz)	natural product **13**[11] (d_6-DMSO, 500 MHz)	moschamine (**2**) (CD_3OD, 100 MHz)	synthetic **1** (CD_3OD, 100 MHz)	montamine (CD_3OD, 100 MHz)	natural product **13**[11] (d_6-DMSO, 125 MHz)
2	7.02, d, 0.5	7.05, s	6.93, s	6.90, d, 1.8	122.9	124.4	126.0	123.9
3	-	-	-	-	111.1	112.1	111.0	113.2
3a	-	-	-	-	128.1	129.4	129.5	127.9
4	6.95, d, 2.3	6.95, s	6.83, d, 2.0	-	102.2	103.6	111.2	114.0
5	-	-	-	-	149.8	151.3	148.0	148.4
6	6.67, dd, 2.3, 8.6	6.66, m	6.82, dd, 2.0, 8.0	6.74, d, 8.5	111.0	116.6	111.1	111.6
7	7.16, dd, 0.5, 8.6	7.14, d, 8.6	7.26, d, 8.0	7.14, d, 8.5	111.2	112.8	111.5	111.0
7a	-	-	-	-	131.7	133.2	133.0	131.7
β-CH_2	2.94, t, 7.1	3.08, m 2.92, m	2.27, m 2.19, m	2.07, m	25.1	24.2	25.0	25.7
α-CH_2	3.58, t, 7.1	4.12, m 3.81, m	2.86, m 2.77, m	2.80, m	40.1	50.4	41.0	40.7
1′	-	-	-	-	126.9	127.8	129.0	125.0
2′	7.12, d, 1.9	6.88, s	6.99, d, 2.0	7.02, d, 1.8	110.2	112.4	110.0	111.3
3′	-	-	-	-	147.9	149.1	146.0	148.4
4′	-	-	-	-	148.4	150.4	149.0	148.8
5′	6.79, d, 8.2	6.66, m	6.70, d, 8.4	6.74, d, 7.9	115.0	112.6	115.0	116.2
6′	7.02, dd, 1.9, 8.2	6.66, m	6.91, dd, 2.0, 8.4	6.90, dd, 1.8, 7.9	121.8	123.3	121.0	122.0
7′	7.43, d, 15.7	7.60, d, 15.4	7.27, d, 15.6	7.21, d, 15.8	140.5	146.9	141.0	139.2
8′	6.42, d, 15.7	6.41, d, 15.4	6.31, d, 15.6	6.40, d, 15.8	117.5	113.5	117.5	119.8[a]
9′	-	-	-	-	167.8	171.4	172.0	165.8
OMe	3.88, s	3.78, s	3.78, s	3.72, s	55.0	56.4	55.5	56.1

[a]The peak at C8′ in **13** was quoted at δ_C 119.8 in the original report,[11a] but δ_C 129.8 in the subsequent full paper.[11b] We assume that the original report is correct.[17]

While the NMR data for montamine and **13** are remarkably consistent and point toward structural equivalency, an obvious issue remains: if montamine has the same structure as **13**, there would not be a resonance for C4-H in the ^{1}H NMR spectrum, yet a signal attributed to the C4-H of montamine was reported at δ_H 6.83 ppm (Table 1). Because this resonance overlaps with the C6-H resonance at δ_H 6.82 ppm, we posit the simple explanation that the ^{1}H NMR signals between δ_H 6.82-6.83 ppm could represent only a single proton, C6-H. Likewise, the resonances for C4 and C6 are very similar in the ^{13}C NMR spectrum (δ_C 111.2 ppm and δ_C 111.1 ppm, respectively). This pattern of overlapping peaks have complicated the NMR experiments which has resulted in an incorrect structural assignment.[10] For example, the HMBC correlations imparted by C6-H have also been assigned to 'C4-H' and the DEPT / ^{1}H-^{13}C HSQC experiments that should have identified C4 as a quaternary carbon have been misinterpreted as C4 overlaps with C6-H in the ^{13}C NMR spectrum. Unfortunately, unequivocal confirmation of the structural reassignment of montamine as structure **13** has been stymied by several factors: (1) unattainable copies of authentic spectra for montamine and **13**; (2) the tabulated NMR data for montamine and **13** are reported in different solvents (CD_3OD and d_6-DMSO); (3) the absence of authentic samples of both natural products, precluding a full spectroscopic comparison in the same NMR solvent.[16,17]

To conclude, a total synthesis of the putative structure of montamine reveals it to be incorrect. Analysis of the NMR spectroscopic data for montamine shows that the dimerization site has been incorrectly assigned, and that the data bears a striking resemblance to a 4,4′-bismoschamine natural product previously reported in the literature.[11]

Experimental

General

All reactions were carried out in oven-dried or flame-dried glassware under a nitrogen atmosphere unless otherwise stated. Anhydrous dichloromethane, THF, DMF and dimethylacetamide (DMA) were purchased from Sigma-Aldrich and used as received; methanol was purchased from VWR and used without purification. Sodium hydride (NaH, 95%), *p*-toluenesulfonyl chloride, cesium carbonate (Cs_2CO_3), acetyl chloride, and 25% sodium methoxide in methanol were purchased from Sigma-Aldrich and used as received. Di-*tert*-butyl hydrazine-1,2-dicarboxylate was purchased from Alfa Aesar and used without purification. Analytical thin layer chromatography was performed using 0.2 mm Kieselgel F254 (Merck) silica plates and compounds were visualized under 365 nm ultraviolet irradiation followed by staining with either alkaline permanganate, ethanolic vanillin or 12-molybdophosphoric acid (PMA stain) solutions. Flash chromatography was performed using silica gel 60 (40-63 μm) from BDH. Infra-

red spectra were obtained using a Perkin Elmer spectrum One Fourier Transform Infrared spectrometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}). Optical rotations were measured using a Perkin-Elmer 341 polarimeter at λ = 598 nm and are given in 10^{-1} deg cm^2 g^{-1}. Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded as indicated on either a Bruker DRX-400 spectrometer operating at 400 MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei or on a Bruker Avance 300 spectrometer operating at 300 MHz and 75 MHz for ^1H and ^{13}C nuclei at the University of Auckland, or on a Varian 400 MHz spectrometer at the University of Massachusetts Medical School. Chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak recorded as δ 0.00 ppm in $CDCl_3$/ TMS solvent, or the residual chloroform (δ 7.26 ppm), DMSO (δ 2.50 ppm) or methanol (δ 3.31 ppm) peaks. The ^{13}C NMR values were referenced to the residual chloroform (δ 77.1 ppm), DMSO (δ 39.5 ppm) or methanol (δ 49.0 ppm) peaks. ^{13}C NMR values are reported as chemical shift δ, multiplicity and assignment. ^1H NMR shift values are reported as chemical shift δ, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (*J* in Hz) and assignment. Assignments are made with the aid of DEPT 135, COSY, NOESY and HSQC experiments. High resolution mass spectra were recorded on a VG-70SE mass spectrometer at a nominal accelerating voltage of 70 eV at the University of Auckland, or on a Waters Q-TOF Premier Mass Spectrometer at the University of Massachusetts Medical School Proteomics and Mass Spectrometry Laboratory.

2-(5-benzyloxy-1-tosyl-indol-3-yl)ethyl 4-methylbenzenesulfonate (10)

A solution of 5-benzyloxytryptophol in THF (0.824 g, 3.08 mmol, in 21 mL) was cooled to 0 °C in an ice bath. Sodium hydride (1.00 g, 41.7 mmol) was added carefully in one portion and the reaction mixture was stirred at 0 °C for 1.25 h. *p*-Toluenesulfonyl chloride (2.35 g, 12.3 mmol) was added carefully in one portion, the reaction was stirred at 0 °C for 10 min then allowed to warm to ambient temperature and stirred for 40 h. The reaction mixture was diluted with 50 mL ethyl acetate and carefully quenched with water (50 mL). The aqueous phase was extracted with ethyl acetate (2 x 30 mL). The combined organic phase was washed with brine (2 x 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was recrystallized from 25 mL ethyl acetate. The filtrate was concentrated and recrystallized from ethyl acetate (15 mL) for a second crop of off-white crystals; (Total: 1.104 g, 1.92 mmol, 62%); Mp: 143-146 ˚C; IR (thin film): 3107, 3058, 3028, 2956, 2920, 2853, 1595 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.86 (1 H, d, *J* = 9.0 Hz, ArH), 7.74 (2 H, d, *J* = 7.8 Hz, ArH), 7.53 (2 H, d, *J* = 7.8 Hz, ArH), 7.45 (2 H, m, ArH), 7.40 (2 H, t, *J* = 7.4 Hz, ArH), 7.34 (1H, d, *J* = 7.0 Hz, ArH), 7.31 (1 H, s, ArH), 7.20 (2 H, d, *J* = 8.6 Hz, ArH), 7.11 (2 H, d, *J* = 8.2 Hz, ArH), 7.00 (1 H, dd, *J* = 2.0, 9.0 Hz,

ArH), 6.83 (1 H, d, J = 2.0 Hz, ArH), 5.00 (2 H, s, OCH_2Ph), 4.24 (2 H, t, J = 6.3 Hz, CH_2), 2.96 (2 H, t, J = 6.3 Hz, CH_2), 2.35 (3 H, s, Ts Me), 2.29 (3 H, s, Me); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.5, 145.0, 144.8, 136.9, 135.0, 132.3, 131.2, 129.9, 129.8, 129.7, 128.6, 128.0, 127.6, 126.7, 125.0, 117.4, 114.6, 114.3, 102.8, 70.4, 68.7, 24.9, 21.6, 21.5; HRMS (ESI-TOF): *m/z* calcd for $C_{31}H_{32}N_2O_6S_2$ ($[M+NH_3]^+$) 593.1780 found 593.1752.

Di-*tert*-butyl 1,2-bis(2-(5-isopropoxy-1-tosyl-indol-3-yl)ethyl)hydrazine-1,2-dicarboxylate (11)

To a solution of mesylate **9**[4] (300 mg, 0.66 mmol) in dimethylformamide (1.2 mL) was added di-*tert*-butyl hydrazine-1,2-dicarboxylate (38.6 mg, 0.17 mmol), followed by cesium carbonate (162 mg, 0.50 mmol) and the reaction mixture was stirred vigorously for five days at room temperature. The reaction mixture was then poured onto diethyl ether (100 mL) and washed with water (2 x 25 mL), followed by brine (2 x 25 mL). The organic extract was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes-ethyl acetate (4:1 → 7:3) gave the *title compound* as a colourless solid; (141 mg, 0.15 mmol, 90%); Mp: 135-140 °C; IR (thin film): 2980, 2930, 1716, 1368, 1168, 1115, 662, 574, 536, 514, 506 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz,): δ = 7.95-7.83 (2 H, m, 2 x ArH), 7.72-7.66 (4 H, m, 4 x ArH), 7.12-6.79 (10 H, m, 10 x ArH), 4.57-4.46 (2 H, m, 2 x CH), 3.77-3.22 (4 H, m, 2 x CH_2), 2.91-2.70 (4 H, m, 2 x CH_2), 2.24-2.11 (6 H, m, 2 x Me), 1.55-1.47 (18 H, m, 6 x Me), 1.31-1.26 (12 H, m, 4 x Me); ^{13}C NMR ($CDCl_3$, 100MHz): δ = 155.0 (2 x C), 154.7 (2 x C), 144.9 $_{[min]}$ + 144.8 $_{[maj]}$ + 144.7 $_{[min]}$ (2 x C), 135.4 $_{[maj]}$ + 135.1 $_{[min]}$ (2 x C), 132.1 (2 x C), 130.2 $_{[min]}$ + 129.9 $_{[maj]}$ (4 x CH), 126.9 $_{[maj]}$ + 126.8 $_{[min]}$ (4 x CH), 124.1 $_{[min]}$ + 124.0 $_{[maj]}$ + 123.7 $_{[min]}$ (2 x CH), 120.2 $_{[min]}$ + 119.9 $_{[maj]}$ (2 x C), 115.5 $_{[min]}$ + 115.4 $_{[maj]}$ (2 x CH), 115.1 $_{[min]}$ + 114.8 $_{[maj]}$ (2 x CH), 105.4 $_{[min]}$ + 105.1 $_{[maj]}$ (2 x CH), 81.9 $_{[min]}$ + 81.4 $_{[maj]}$ + 81.3 $_{[min]}$ (2 x C), 71.1 $_{[min]}$ + 70.8 $_{[maj]}$ (2 x CH), 51.2 $_{[min]}$ + 50.6 $_{[min]}$ + 50.4 $_{[maj]}$ (2 x CH_2), 28.5 $_{[min]}$ + 28.42 $_{[maj]}$ + 28.36 $_{[min]}$ (6 x Me), 23.7 (2 x CH_2), 22.3 $_{[maj]}$ + 22.2 $_{[min]}$ + 22.1 $_{[maj]}$ (4 x Me), 21.6 (2 x Me), 2 x C not observed; ESI-HRMS: *m/z* calcd for $C_{50}H_{62}N_4NaO_{10}S_2$ ($[M + Na]^+$) 965.3800 found 965.3822.

Di-*tert*-butyl 1,2-bis(2-(5-benzyloxy-1-tosyl-indol-3-yl)ethyl)hydrazine-1,2-dicarboxylate (12)

To a solution of ditosylate **10** (1.07 g, 1.86 mmol) in dimethylformamide (4.4 mL) was added di-*tert*-butyl hydrazine-1,2-dicarboxylate (0.108 g, 0.465 mmol), followed by cesium carbonate (0.454 g, 1.39 mmol) and the reaction mixture was stirred at ambient temperature for 5 days, then partitioned between ethyl acetate (70 mL) and water (40 mL). The aqueous phase was extracted with 70 mL dichloromethane which dissolved residual solids. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by gradient flash column chromatography;

polarity started with 75:25 dichloromethane/hexanes for 500 mL, then increased to 80:20 dichloromethane/hexanes for 500 mL, then 90:10 dichloromethane/hexanes (200 mL) at which time the ditosylate had completely eluted. The polarity was increased to 100% dichloromethane, then the solvent system was changed to 98:2 dichloromethane/ethyl acetate which fully eluted the *title compound* as a white foam (0.421 g, 0.405 mmol, 87%); IR (thin film): 3028, 2969, 2924, 2853, 1738, 1724, 1595 cm^{-1}; As expected, ^{1}H NMR analysis revealed significant evidence of restricted rotation complicating several signals. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12-7.85 (2 H, m, 2 x ArH), 7.78-7.65 (4 H, m, 4 x ArH), 7.47-6.75 (20 H, m, 20 x ArH), 5.12-4.95 (4 H, m, 2 x OCH_2Ph), 3.88-2.91 (4 H, m, 2 x CH_2), 2.90-2.61 (4 H, m, 2 x CH_2), 2.36-1.94 (6 H, s, 2 x Me), 1.61-1.42 (18 H, m, 6 x Me); ^{13}C NMR ($CDCl_3$, 100 MHz): major rotamer**:** 155.8, 155.1, 145.0, 137.3, 135.4, 132.1, 130.0, 128.8, 128.1, 127.9, 127.6, 127.0, 124.2, 120.1, 103.5, 81.5, 70.7, 50.5, 28.6, 23.8, 21.6; HRMS (ESI-TOF): *m/z* calcd for $C_{58}H_{65}N_5O_{10}S_2$ ($[M+NH_3]^+$) 1056.4252 found 1056.4297.

Montamine diisopropyl ether (**3**)

To a suspension of carbazate **11** (40 mg, 42.4 μmol) in methanol (0.42 mL) at 0 °C was slowly added acetyl chloride (0.30 mL, 4.20 mmol), and the mixture was warmed to room temperature over 18h. The reaction mixture was then concentrated *in vacuo*, affording the crude hydrazine which was used immediately in the next step.

To a suspension of the crude hydrazine dichloride and acid chloride **7** (65 mg, 0.26 mmol) in dichloromethane (0.42 mL) at 0 °C was added *N*,*N*-diisopropylethylamine (44 μL, 0.26 mmol), and the mixture was warmed to room temperature over 42h. The reaction mixture was then diluted with dichloromethane (10 mL) and washed with water (10 mL), then 1.2M aqueous hydrochloric acid (10 mL), followed by 1M aqueous sodium hydroxide (10 mL), and finally brine (10 mL). The organic extract was dried (Na_2SO_4), filtered, and concentrated *in vacuo.*

To the crude mixture from the acylation procedure was taken up in methanol (0.4 mL) was slowly added a freshly prepared solution of 25% sodium methoxide in methanol (0.8 mL), and the reaction mixture was heated under reflux for 1.5 h. The reaction mixture was then cooled to 0 °C and acidified to pH <2 using 10% aqueous sulfuric acid. The mixture was then partitioned between water (20 mL) and dichloromethane (20 mL). The aqueous layer was further extracted with dichloromethane (2 x 20 mL), and the combined organic extracts were washed with a saturated solution of sodium hydrogen carbonate (20 mL), then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography

eluting with hexanes-ethyl acetate (1:3) gave the *title compound* as a yellow solid (18.5 mg, 24 μmol, 55%); Mp: 107 – 113 °C; IR (thin film): = 3356, 2973, 2932, 1642, 1587, 1512, 1450, 1429, 1370, 1266, 1186, 1170, 1114, 1031, 967, 911, 839, 813, 796, 704, 666; ^{1}H NMR ($CDCl_3$, 400MHz,): δ = 7.92 (2 H, br s, 2 x NH), 7.73 (2 H, d, *J* = 15.4 Hz, 2 x CH), 7.19 (2 H, d, *J* = 8.8 Hz, 2 x ArH), 7.09 (2 H, d, *J* = 1.9 Hz, 2 x ArH), 7.02 (2 H, d, *J* = 1.6 Hz, 2 x ArH), 6.82 (8 H, m, 8 x ArH), 6.52 (2 H, d, *J* = 15.4 Hz, 2 x CH), 5.88 (2 H, br s, 2 x OH), 4.46 (2 H, sep, *J* = 6.1 Hz, 2 x CHMe$_2$), 3.86 (4 H, m, 2 x CH_2), 3.83 (6 H, s, 2 x OMe), 3.14 (4 H, m, 2 x CH_2), 1.28 (12 H, m, 2 x CHMe$_2$); ^{13}C NMR ($CDCl_3$, 100MHz): δ = 169.2 (2 x C), 152.2 (2 x C), 148.0 (2 x C), 146.7 (2 x C), 145.7 (2 x CH), 131.8 (2 x C), 128.0 (2 x C), 127.3 (2 x C), 122.9 (2 x CH), 122.7 (2 x CH), 114.9 (2 x CH), 114.7 (2 x CH), 113.0 (2 x CH), 112.5 (2 x C), 111.9 (2 x CH), 110.3 (2 x CH), 104.6 (2 x CH), 71.4 (2 x CHMe$_2$), 56.2 (2 x OMe), 50.1 (2 x CH_2), 23.6 (2 x CH_2), 22.4 and 22.3 (2 x CHMe$_2$); ESI-HRMS: *m/z* calcd for $C_{46}H_{50}N_4NaO_8$ ($[M + Na]^+$) 809.3521 found 809.3503.

Montamine dibenzyl ether (4)

Carbazate **12** (119 mg, 0.115 mmol) was taken up in a 2:1 mixture of methanol and dichloromethane (2.25 mL). The heterogeneous mixture was cooled to 0 °C in an ice bath, then acetyl chloride was added dropwise (0.83 mL, 11.6 mmol). The mixture was stirred 18 h, coming to ambient temperature naturally. Volatile components were removed by concentration *in vacuo* and the crude hydrazine was used without purification.

Acid chloride **7** (198 mg, 0.777 mmol) was added to the flask containing the crude material and the vessel was purged with argon. Dichloromethane was added (1.4 mL) and the mixture was cooled to 0 °C in an ice bath. *N*,*N*-Diisopropylethylamine was added dropwise (0.13 mL, 0.746 mmol). After 5 min, the ice bath was removed and the reaction was stirred for 1.5 h at ambient temperature. The reaction mixture was then partitioned between dichloromethane (10 mL) and water (10 mL). The aqueous phase was extracted with dichloromethane (2 x 10 mL). The combined organic phase was washed with 1 M HCl (1 x 15 mL) and brine (20 mL), then dried (Na_2SO_4), filtered, and concentrated *in vacuo*.

The crude residue from the acylation procedure was taken up in a 1:1 mixture of THF and methanol (3 mL). 25% Sodium methoxide in methanol (1 mL) was added, and the mixture was heated to reflux for 1.5 h. After this time, ethyl acetate (10 mL) and water (10 mL) were added and the mixture was acidified to pH < 2 with 10% aq. sulfuric acid (2 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic phase was washed with brine (25 mL), dried (Na_2SO_4), filtered, and

concentrated *in vacuo*. Crude NMR analysis showed incomplete removal of the tosyl groups, so the material was taken up in a 1:1 mixture of THF and methanol (4 mL) and 25% sodium methoxide in methanol (1.5 mL) was added, and the mixture was heated under reflux for 1.5 h. Work-up was conducted as previously described. The crude residue was purified by flash column chromatography, 98:2 dichloromethane/methanol to give the *title compound* as a pale yellow oil (0.021 g, 0.024 mmol, 20% yield); IR (thin film): 3349, 2960, 2929, 2844, 1729, 1645, 1587 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (2 H, s, 2 x NH), 7.75 (2 H, d, *J* = 15.2 Hz, 2 x CH), 7.35-7.25 (10 H, m, 10 x ArH), 7.18 (2 H, d, *J* = 8.6 Hz, 2 x ArH), 7.15 (2 H, d, *J* = 2.0 Hz, 2 x ArH), 7.01 (2H, s, 2 x ArH), 6.88 (2 H, dd, *J* = 8.6, 2.0 Hz, 2 x ArH), 6.80-6.75 (6 H, m, 6 x ArH), 6.52 (2 H, d, *J* = 15.2 Hz, 2 x CH), 6.00 (2 H, s, 2 x OH), 5.00 (2 H, d, *J* = 11.5, OCH_2Ph), 4.96 (2 H, d, *J* = 11.5, OCH_2Ph), 4.12-4.05 (2 H, m, CH_2), 3.87-3.79 (2 H, m, CH_2), 3.75 (6 H, s, 2 x OMe) 3.21-3.13 (2 H, m, CH_2), 3.05-2.98 (2 H, m, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.5, 153.5, 148.2, 146.8, 145.9, 137.7, 131.8, 128.7, 128.1, 128.0, 127.9, 127.2, 123.1, 122.5, 115.0, 113.5, 112.9, 112.7, 112.2, 110.7, 102.0, 71.0, 56.2, 50.4, 23.5; HRMS (ESI-TOF): *m/z* calcd for $C_{54}H_{51}N_4O_8$ $([M+H]^+)$ 883.3707 found 883.3676.

Putative Montamine (1)

To a mixture of montamine diisopropyl ether **3** (13 mg, 16.5 μmol) in dichloromethane (12 mL) at 0 °C was added an excess of aluminium trichloride (400 mg, 3.0 mmol) in portions over a period of 2 h. The reaction mixture was then quenched by the addition of a saturated solution of ammonium chloride (12 mL) at 0 °C, and the mixture was warmed to room temperature and stirred vigorously for 30 min. The mixture was then extracted with dichloromethane (3 x 50 mL), and the organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes-ethyl acetate (1:4) gave the *title compound* as a pale yellow solid (5.5 mg, 7.83 μmol, 47%); Mp: 136 – 140 °C; IR (thin film) = 3347, 2923, 2852, 1638, 1584, 1513, 1452, 1429, 1393, 1363, 1263, 1208, 1183, 1123, 1029, 979, 936, 795, 839; ^{1}H NMR: See **Table 1**; ^{13}C NMR: See **Table 1**; ESI-HRMS: *m/z* calcd for $C_{40}H_{38}N_4NaO_8$ $([M + Na]^+)$: 725.2582 $[M + Na]^+$; found: 725.2590.

Supporting Information

Experimental procedures, 1D and 2D NMR spectra along with tabulated spectroscopic data.

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