Total Syntheses of the Structures Assigned to the Marine Natural Products Orthoscuticellines A-E

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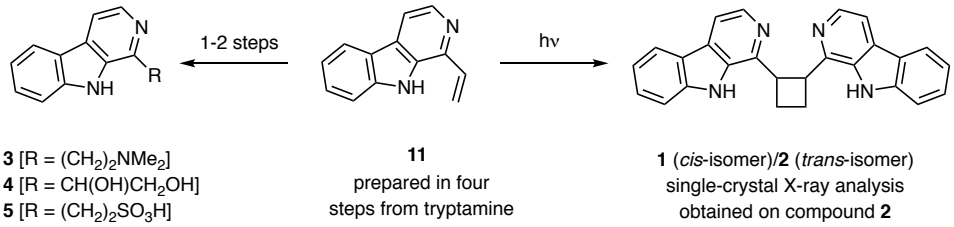


3 [R = $(CH_2)_2NMe_2$]
4 [R = $CH(OH)CH_2OH$]
5 [R = $(CH_2)_2SO_3H$]

11
prepared in four steps from tryptamine

1 (*cis*-isomer)/**2** (*trans*-isomer)
single-crystal X-ray analysis obtained on compound **2**

ABSTRACT: The readily prepared vinylated β-carboline **11** has been converted over one or two steps into compounds **1**-**5**, the structures assigned to the recently reported marine natural products orthoscuticellines A-E. The spectral data recorded on the synthetically-derived compounds are fully consistent with the assigned structures and, on making allowances for variations in the pH of the medium in which the spectra of the natural products were recorded, it is concluded that the structures assigned to orthoscuticellines A-E are most likely correct. Certainly, the calculated ^{13}C NMR spectra of the α-, γ- and δ-carboline isomers of compounds **1**-**5** suggest that orthoscuticellines A-E do incorporate the assigned β-carboline core.

INTRODUCTION

In 2020 Carroll and co-workers reported[1] the isolation and spectroscopic characterization of eleven alkaloids from the bryozoan *Orthoscuticella ventricosa* collected as storm debris on a beach in Northern New South Wales, Australia. The structures, **1**-**11**, assigned to these compounds are shown in Figure 1, the first five of which (*viz*. **1**-**5**) were named orthoscuticellines A-E, respectively. The remaining six compounds, two of which (**9** and **11**) were not isolated in pure form, were assigned on the basis that they were all known compounds and that the derived ^{1}H NMR spectral and positive ESIMS data (not provided) compared favorably with those reported[2,3,4] previously. Biological screening of these marine natural products[1] established that those assigned structures **1**, **4**, **5**, **6** and **7** exhibited some antiplasmodial activity against a chloroquine-sensitive strain of *P. falciparum*. Compound **1** also displayed some activity against the tumorigenic HEK293 cell line (IC_{50} = 10 □M).

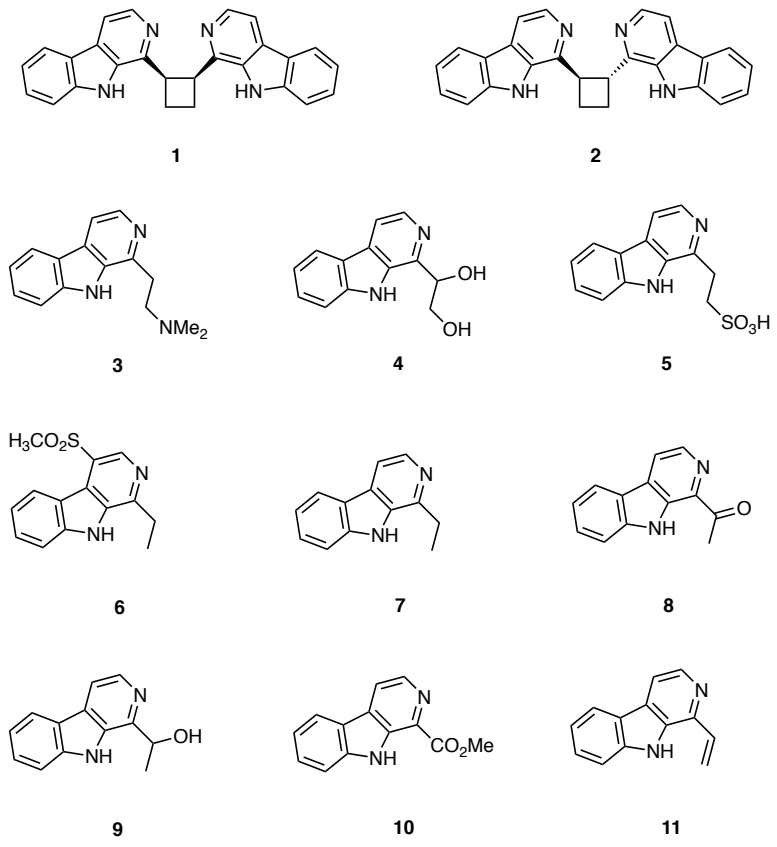


Figure 1: The structures **1**-**11** assigned to the first marine natural products isolated from the bryozoan *Orthoscuticella ventricosa*

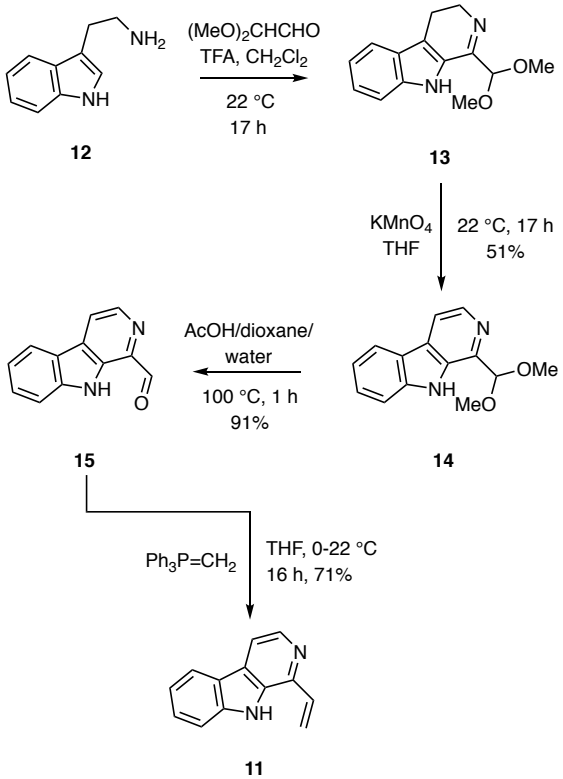
Diol **4** has also been isolated, by Liu and co-workers, from *Arenaria kansuensis* (Caryophyllaceae), a plant of significance in Chinese folk medicine and extracts of which have been used to treat inflammation of the lungs, jaundice, influenza and rheumatism.[5]

As a result of our ongoing interest in the chemistry of carbolines and their potential for development as medicinal agents,[6] we sought to establish syntheses of compounds **1**-**5** so as to eventually create sufficient supplies of them for further biological evaluation. Herein we report our efforts in this regard and that have led to the conclusion that the structures assigned to orthoscuticellines A-E are probably correct.

RESULTS AND DISCUSSION

The precursor to targets **1**-**5** selected for the present study was alkene **11**. The straightforward synthesis of compound **11** started from commercially available tryptamine (**12**) and followed, as shown in Scheme 1, the pathway reported[7] by Vaquero and co-workers.

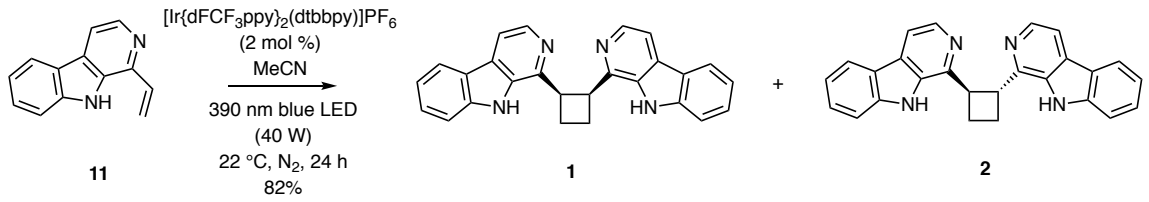
Scheme 1: Synthesis of alkene **11** from tryptamine (**12**)



Specifically, then, a dichloromethane solution of tryptamine (**12**) was treated with an aqueous solution of dimethoxyglyoxal then trifluoroacetic acid (TFA) and so resulting, after a basic work up, in the formation of the dihydrocarboline **13**. Reaction of crude samples of the last compound with potassium permanganate in THF at ambient temperatures then provided the fully aromatic heterocycle **14** (51% from **12**), the spectral data derived from which were in complete accord with those reported previously.[7] Hydrolysis of the acetal residue associated with compound **14** under conventional conditions then gave the corresponding aldehyde **15** (91%) that was itself subjected to a Wittig olefination reaction with the *in situ* generated ylide $Ph_3P{=}CH_2$ and so providing the required alkene **11** in 71% yield. All the spectral data obtained on this pivotal precursor to targets **1**-**5** were in complete accord with the assigned structure and consistent with those reported[7] earlier.

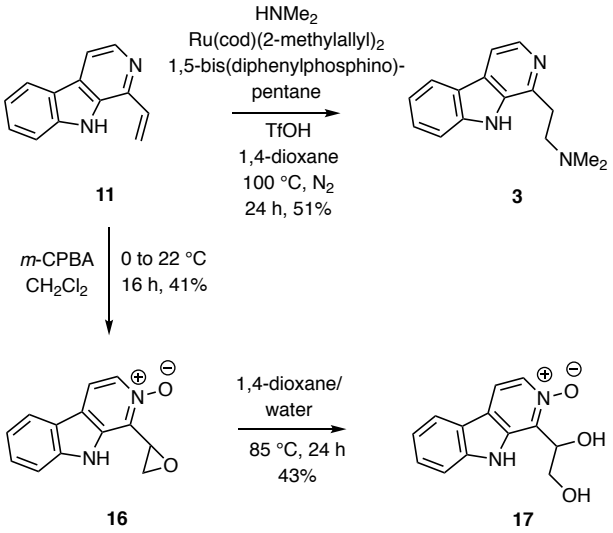
Syntheses of compounds **1** and **2**, the structures assigned to orthoscuticellines A and B respectively, were pursued by photochemical means using protocols related to those we have successfully applied in the synthesis of other cyclobutane-containing natural products.[8] In the first such attempt, an acetonitrile solution of the monomer **11** containing Hünig's base, $LiBF_4$ and 2% $Ru(bpy)_3Cl_2$[9] was irradiated, while being maintained under nitrogen at ambient temperatures, for 20 h with a blue LED (390 nm). As a result the reduction product **7** was obtained in 64% yield as the only isolable product of reaction. On the basis that the hydrogen-donor leading to this photoproduct is the Hünig's base, an acetonitrile solution of the substrate (viz. alkene **11**) now containing $[Ir\{dFCF_3ppy\}_2(dtbbpy)]PF_6$[9] alone was subjected to irradiation (again with a blue LED) and under such conditions, and as shown in Scheme 2, clean [2+2]-cycloaddition reactions took place to afford a ca. 1:3 mixture of the head-to-head dimers **1** and **2** (82% combined yield). Products **1** and **2** could be separated from one another by conventional chromatographic methods and a single-crystal X-ray analysis was conducted on the latter (details provided in the Experimental Section and the Supporting Information – SI) and so establishing the illustrated *trans*-disposition of the two β-carboline residues about the central cyclobutane ring.

Scheme 2: The [2+2]-photodimerization of alkene **11** leading to compounds **1** and **2**.



The initial approach used in efforts to convert olefin **11** into the structures assigned to orthoscuticellines C and D (viz. **3** and **4**, respectively) is shown in Scheme 3. Thus, following a protocol defined by Hartwig,[10] compound **11** was subjected to a ruthenium-catalyzed anti-Markovnikov hydroamination reaction using dimethylamine and so affording target **3** directly in 51% yield.

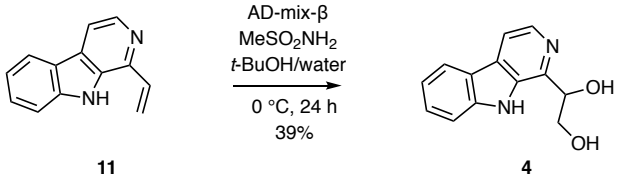
Scheme 3: The conversion of alkene **11** into compounds **3** and **17**



The obvious means for converting olefin **11** into the target diol **4** was not immediately available to us because of our inability to secure, from commercial sources, osmium tetroxide and so the illustrated (Scheme 3), two-step pathway was explored. Specifically, the alkene **11** was treated with *m*-chloroperbenzoic acid (*m*-CPBA) and so affording compound **16** (41%) embodying not just the required epoxide moiety but also the *N*-oxide residue. Upon subjecting this epoxide to acid-catalysed hydrolysis then the *N*-oxide, **17**, of target diol **4** was obtained in 43% yield. While a range of means is available for the reductive deoxygenation of pyridine and related *N*-oxides, the timely acquisition of AD-mix-α, one of the two key reagents used

in Sharpless asymmetric dihydroxylation reactions, enabled us to finally explore the more direct means of obtaining compound **4**. Specifically, then, and as shown in Scheme 4, treating alkene **11** with this oxidizing system in the presence of methanesulfonamide, and using a *t*-BuOH/water mixture as the reaction medium, gave the target diol **4** in 39% yield and as a crystalline solid. While such a conversion probably proceeds with some level of asymmetric induction, no effort was made to establish either the enantiomeric excess or the absolute configuration of this dihydroxylation product. This was because in neither the Carroll[1] nor Liu[5] studies was any evidence offered that the diol-containing natural product occurs in homochiral form.

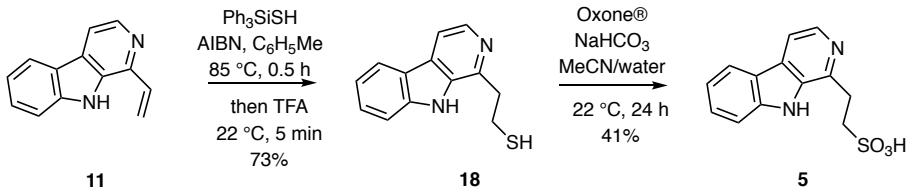
Scheme 4: The direct conversion of alkene **11** into diol **4**



11 **4**

The two-step synthesis of the final target, orthoscuticelline E (**5**), is shown in Scheme 5 and involved treating the starting alkene **11** with triphenylsilanolthiol (Ph_3SiSH)[11] in the presence of AIBN and after work-up of the reaction mixture with aqueous TFA the thiol **18** was obtained in 73% yield. Oxidation of this last compound with Oxone® in the presence of sodium bicarbonate[12] then gave the target sulfonic acid **5** in 41% yield.

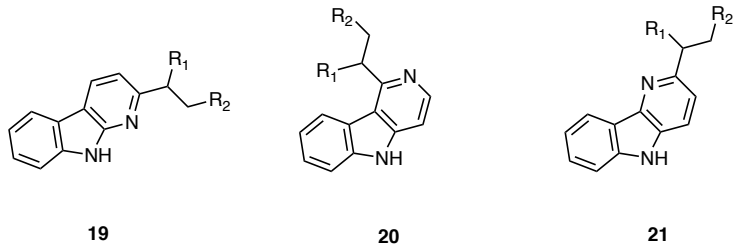
Scheme 5: The synthesis of sulfonic acid **5**



11 **18** **5**

The NMR, IR and mass spectral data acquired on compounds **1-5** obtained by the pathways detailed above were in complete accord with their assigned structures. However, comparisons of the ^{1}H and ^{13}C NMR spectral data sets with those reported[1] for orthoscuticellines A-E (see Tables S1-S13 in the SI) revealed generally less than ideal matches and to some extent this

remained the case even as the pH of the medium [$(CD_3)_2SO$ in all cases)] used in recording the spectra of the synthetic materials was lowered by adding defined quantities of TFA. As a consequence, we considered the possibility that the heterocyclic cores of the title alkaloids could have been assigned incorrectly. Such misassignments are not uncommon[13] and more likely when the ratio of the number of hydrogens to carbons is less than 1 (Crews' rule),[13] (as is the case for the molecular formulae established for orthoscuticellines A, B, D and E) – a consequence of NMR spectroscopic methods being critically dependant on detection through protons. While β-carboline-containing marine natural products are most common,[2,3,4,14] others containing the isomeric α- and γ-frameworks are known.[15,16] Furthermore, plant-derived natural products containing δ-carboline substructures have been reported.[17] As such, we thought it prudent to consider the possibility that the title alkaloids could be of the general form **19**, **20** or **21** as shown in Figure 2. While no such compounds have been reported previously, to a first approximation the 1D ^1H and $^{13}C\{^1H\}$ NMR spectra of these would be expected to be similar to those reported[1] for orthoscuticellines A-E.



19 **20** **21**

R_1,R_2 = part of cyclobutane dimer; R_1=H, R_2=NMe_2; R_1=R_2=OH; R_1=H, R_2=SO_3H

Figure 2: Possible alternative structures, **19**-**20**, considered for orthoscuticellines A-E

In an effort to explore such possibilities, computational methods (see Experimental Section and SI for details) were employed to predict the ^{13}C NMR chemical shifts of the α-, γ- and δ-carboline analogues of compounds **1**-**5** and tabular comparisons then made with those calculated for the assigned β-carboline structures as well as those reported for the natural products and those acquired on the synthetic materials (recorded under both neutral conditions and after treatment with TFA – the comparisons made after TFA treatments are provided in the SI). The resulting and tabulated data sets associated with compound **1** are presented in Table 1 and illustrative of our approach (although in this instance the compound proved unstable and so we were unable to acquire a ^{13}C NMR spectrum on the TFA-treated material).

The *cis*-1,3-disubstituted β-carboline cyclobutane structure entertained by Carroll and co-workers as a possible structure for orthoscuticelline A was also subjected to computational study. Amongst all of those studied, the computed data set with the lowest mean absolute error (MAE) (of 6.97) relative to that reported for orthoscuticelline A was the one associated with the originally assigned structure **1** (by comparison, the MAE for the ^{13}C NMR data set acquired on synthetically-derived compound **1** was of 1.69).

Table 1: Comparison of the ^{13}C NMR chemical shift data reported for orthoscuticelline A (o-A) with those obtained from synthetically-derived compound **1**, with those calculated for the possible isomeric forms **1** and **19-21** as well as with those calculated for the isomeric 1,3-β-dicarboline *cis*-dimer

δ_C for o-A[a]	δ_C alpha[b,c]	δ_C beta (1,2)[c,d]	δ_C gamma[c,e]	δ_C delta[c,f]	δ_C beta (1,3)[c,g]	δ_C for **1**[h]
142.8	170.0	155.2	165.8	163.1	158.4	144.7
141.5	158.6	147.1	152.0	148.0	148.4	139.9
133.1	145.8	146.0	151.0	147.9	145.7	136.9
132.5	136.4	139.9	146.2	137.9	140.2	133.8
129.5	133.7	136.0	133.4	135.2	136.7	127.2
129.3	128.3	134.0	132.6	128.7	136.3	126.0
122.3	127.8	129.4	128.1	128.2	130.0	121.2
120.2	126.0	127.5	125.6	127.2	128.4	120.5
119.9	121.5	125.5	123.7	125.6	125.9	118.6
114.1	118.7	118.9	116.6	124.6	120.1	112.1
112.1	117.3	118.1	109.6	117.6	118.5	111.5
40.3	53.8	47.4	51.2	53.5	38.8	41.7
22.8	25.6	26.0	24.4	26.7	37.4	21.7
MAE[i]	**8.09**	**6.97**	**8.06**	**8.08**	**8.26**	**1.69**

[a]data from ref. 1, recorded at 200 MHz in $(CD_3)_2SO$; [b]computationally-generated δ_C values for alpha-carboline-containing isomer, **19**, of structure **1**; [c]calculations conducted assuming $(CD_3)_2SO$ is solvent; [d]computationally-generated δ_C values for beta-carboline structure **1**; [e]computationally-generated δ_C values for gamma-carboline-containing isomer, **20**, of structure **1**; [f]computationally-generated δ_C values for delta-carboline-containing isomer, **21**, of structure **1**; [g]computationally-generated δ_C values for 1,3-substituted beta-carboline-containing isomer of structure **1**; [h]experimentally-determined δ_C values for synthetically-derived compound **1** recorded at 75 MHz in $(CD_3)_2SO$; [i]MAE = mean absolute error (relative to δ_C values for o-A listed in first column).

An analogous computational study was conducted on compound **2** and the corresponding suite of isomeric forms of this structure (see Figure 2). The outcomes of such efforts are presented in Table 2. Once again, the lowest MAE amongst the calculated structures corresponded to the β-carboline form assigned to orthoscuticelline B (and not, for example, the corresponding 1,3-disubstituted isomer also considered by Carroll and co-workers).

Table 2: Comparison of the ^{13}C NMR chemical shift data reported for orthoscuticelline B (o-B) with those obtained from synthetically-derived compound **2**, with those calculated for the possible isomeric forms **2** and **19-21** as well as with those calculated for the isomeric 1,3-β-dicarboline *trans*-dimer

δ_C for o-B[a]	δ_C alpha[b,c]	δ_C beta (1,2)[c,d]	δ_C gamma[c,e]	δ_C delta[c,f]	δ_C beta (1,3)[c,g]	δ_C for **2**[h]
143.4	170.6	156.7	167.7	164.7	157.7	146.7
142.5	159.6	148.3	153.4	148.8	147.8	140.4
133.6	146.2	144.9	151.4	148.3	146.6	137.3
132.4	137.2	140.7	146.0	138.7	140.0	133.4
130.1	134.0	136.3	132.8	135.6	136.3	127.9
129.6	128.7	135.3	129.9	128.5	134.9	127.2
122.4	127.9	129.9	128.1	127.7	129.9	121.7
120.9	126.2	128.5	125.8	126.9	128.4	121.0
120.2	121.0	126.0	124.4	125.9	126.0	119.3
114.2	120.0	120.3	116.4	125.4	119.6	113.2
112.3	117.5	118.4	110.9	117.9	118.1	112.2
40.0	55.8	49.0	55.6	56.2	37.7	41.1
23.9	28.2	25.8	22.0	28.6	34.9	24.2
MAE[i]	**8.40**	**7.28**	**8.12**	**8.45**	**7.46**	**1.45**

[a]data from ref. 1, recorded at 200 MHz in $(CD_3)_2SO$; [b]computationally-generated δ_C values for alpha-carboline-containing isomer, **19**, of structure **2**; [c]calculations conducted assuming $(CD_3)_2SO$ is solvent; [d]computationally-generated δ_C values for beta-carboline structure **2**; [e]computationally-generated δ_C values for gamma-carboline-containing isomer, **20**, of structure **2**; [f]computationally-generated δ_C values for delta-carboline-containing isomer, **21**, of structure **2**; [g]computationally-generated δ_C values for 1,3-substituted beta-carboline-containing isomer of structure **2**; [h]experimentally-determined δ_C values for synthetically-derived compound **2** recorded at 75 MHz in $(CD_3)_2SO$; [i]MAE = mean absolute error (relative to δ_C values for o-B listed in first column).

Similarly, ^{13}C NMR chemical shift calculations performed on the TFA salt of orthoscuticelline C (which was characterised by Carroll et al as this salt and not as the free base) and the corresponding alternative α-, γ- and δ-carboline structures (Table 3) also revealed the originally assigned one (viz. **3**) gave the best MAE value.

Table 3: Comparison of the ^{13}C NMR chemical shift data reported for the TFA salt of orthoscuticelline C (o-C) with those obtained from the TFA salt of synthetically-derived compound **3** and with those calculated for the possible isomeric forms **3** and **19-21**

δ_C for o-C[a]	δ_C alpha[b,c]	δ_C beta[c,d]	δ_C gamma[c,e]	δ_C delta[c,f]	δ_C for **3**[g]
141.3	170.8	157.1	167.2	163.9	142.7
139.7	159.1	148.5	153.1	148.4	137.5
133.9	145.9	145.8	151.7	148.0	134.1
–	137.0	142.6	147.1	138.3	131.7
132.8	133.8	135.9	133.9	135.4	131.6
129.1	128.3	134.9	131.1	128.5	130.7
122.0	128.2	129.9	128.6	128.1	123.1
120.6	126.2	128.6	126.8	127.4	120.9
119.9	122.1	125.5	123.6	125.8	120.1
114.1	119.4	119.6	117.4	125.3	115.6
112.0	117.3	118.4	110.2	117.7	112.7
54.5	66.1	64.1	62.9	66.7	54.3
42.2	48.0	47.4	48.1	48.1	42.4
26.6	41.7	39.6	41.0	41.5	25.6
MAE[h]	**8.56**	**7.61**	**7.89**	**8.38**	**0.84**

[a]data from ref. 1, recorded at 200 MHz in $(CD_3)_2SO$ **on TFA salt**; [b]computationally-generated δ_C values for alpha-carboline-containing isomer, **19**, of structure **3**; [c]calculations conducted assuming $(CD_3)_2SO$ is solvent; [d]computationally-generated δ_C values for beta-carboline structure **3**; [e]computationally-generated δ_C values for gamma-carboline-containing isomer, **20**, of structure **3**; [f]computationally-generated δ_C values for delta-carboline-containing isomer, **21**, of structure **3**; [g]experimentally-determined δ_C values for synthetically-derived compound **3** recorded at 100 MHz in $(CD_3)_2SO$ **on TFA salt**; [h]MAE = mean absolute error (relative to δ_C values for o-C listed in first column).

A comparison of the ^1H and ^{13}C NMR data set acquired (in its free-base form) on the synthetically-derived sample of diol **4** with those reported[5] for the natural product isolated by Liu and co-workers from the Chinese medical plant *Arenaria kansuensis* revealed an excellent agreement (see Table S6 of the SI) between the two and so confirming the structure assigned to this metabolite. However, the agreement between these data sets and those reported[5] for orthoscuticelline D was less convincing and so prompting, once again, the computation of the carbon chemical shifts for the relevant suite of α-, β-, γ- and δ-carboline structures (Table 4). As was the case with the preceding computational work, the best MAE corresponded to the assigned β-carboline structure **4**.

Table 4: Comparison of the ^{13}C NMR chemical shift data reported for orthoscuticelline D (o-D) with those obtained from synthetically-derived compound **4** and with those calculated for the possible isomeric forms **4** and **19-21**

δ_C for o-D[a]	δ_C alpha[b,c]	δ_C beta[c,d]	δ_C gamma[c,e]	δ_C delta[c,f]	δ_C for **4**[g]
143.3	168.0	151.5	163.1	160.2	145.8
141.8	157.5	148.3	152.0	148.3	140.5
133.7	146.2	144.9	151.5	147.0	136.7
132.7	138.3	138.9	147.5	139.5	133.4
131.4	134.4	137.0	134.6	136.0	128.1
128.4	128.8	136.4	131.5	127.9	127.9
123.2	128.0	130.0	127.9	127.7	121.4
121.2	126.7	128.2	127.4	126.6	120.4
119.1	121.4	126.5	122.2	126.3	119.1
115.9	119.3	121.3	117.7	125.6	113.6
112.8	117.6	118.2	111.8	118.0	112.3
69.3	80.4	77.4	79.2	80.9	74.5
64.1	74.5	73.0	72.9	76.0	65.3
MAE[h]	**8.02**	**7.29**	**8.03**	**8.01**	**1.78**

[a]data from ref. 1, recorded at 200 MHz in $(CD_3)_2SO$; [b]computationally-generated δ_C values for alpha-carboline-containing isomer, **19**, of structure **4**; [c]calculations conducted assuming $(CD_3)_2SO$ is solvent; [d]computationally-generated δ_C values for beta-carboline structure **4**; [e]computationally-generated δ_C values for gamma-carboline-containing isomer, **20**, of structure **4**; [f]computationally-generated δ_C values for delta-carboline-containing isomer, **21**, of structure **4**; [g]experimentally-determined δ_C values for synthetically-derived compound **4** recorded at 100 MHz in $(CD_3)_2SO$; [h]MAE = mean absolute error (relative to δ_C values for o-D listed in first column).

The ^1H and ^{13}C NMR data acquired on sulfonic acid **5** did bear a closer resemblance to those reported for orthoscuticelline E (see Table S7 of the SI) but given the discrepancies, as noted immediately above, between the other data sets and the presumably common biosynthetic origins of all of the title natural products, it was deemed appropriate to undertake computational studies on this system and its analogues as well. Such studies were conducted on the zwitterionic forms, **22-25** (Figure 3), of compound **5** and its possible isomers and these revealed, as shown in Table 5, that, yet again, the β-carboline structure assigned to this natural product is the most plausible.

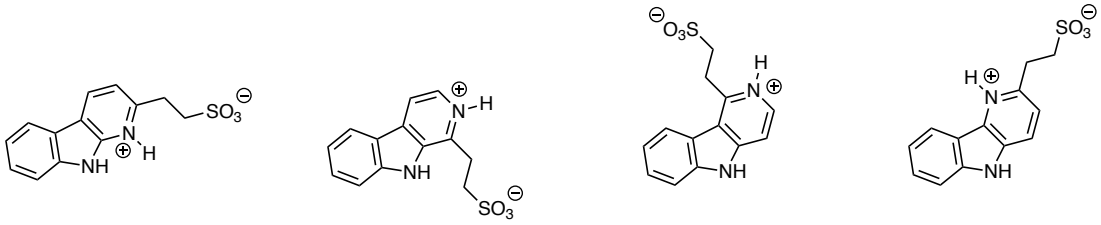


Figure 3: The zwitterions **22-25** subjected to ^{13}C NMR chemical shift calculations in seeking to evaluate the structure, **5**, assigned to orthoscuticelline E

Table 5: Comparison of the ^{13}C NMR chemical shift data reported for orthoscuticelline E (o-E) with those obtained from synthetically-derived compound **5** and with those calculated for the possible isomeric forms **5** and **19**-**21**

δ_C for o-E[a]	δ_C alpha[b,c]	δ_C beta[c,d]	δ_C gamma[c,e]	δ_C delta[c,f]	δ_C for **5**[g]
143.0	162.2	150.7	161.8	158.2	142.5
141.1	150.1	149.9	153.6	149.4	142.2
133.4	146.3	140.3	148.7	140.6	133.7
131.9	145.1	140.3	142.9	139.8	131.2
130.7	137.0	139.7	136.8	139.0	130.7
127.9	129.5	136.7	131.8	134.7	130.3
126.2	129.4	131.7	129.4	130.3	122.8
122.8	127.3	128.4	128.8	129.0	120.6
120.6	126.5	127.5	124.7	128.3	120.2
114.7	122.6	122.4	119.0	121.8	114.7
112.4	119.0	118.9	112.8	119.0	112.6
48.3	59.6	59.0	59.2	60.1	48.8
26.5	34.4	29.8	32.4	34.2	27.4
MAE[h]	**8.42**	**7.37**	**7.88**	**8.07**	**0.97**

[a]data from ref. 1, recorded at 200 MHz in $(CD_3)_2SO$; [b]computationally-generated δ_C values for alpha-carboline-containing isomer, **19**, of structure **5**; [c]calculations conducted assuming $(CD_3)_2SO$ is solvent; [d]computationally-generated δ_C values for beta-carboline structure **5**; [e]computationally-generated δ_C values for gamma-carboline-containing isomer, **20**, of structure **5**; [f]computationally-generated δ_C values for delta-carboline-containing isomer, **21**, of structure **5**; [g]experimentally-determined δ_C values for synthetically-derived compound **5** recorded at 100 MHz in $(CD_3)_2SO$; [h]MAE = mean absolute error (relative to δ_C values for o-E listed in first column).

CONCLUSION

On balance, we conclude that the structures **1**-**5** assigned to orthoscuticellines A-E, respectively, are most likely correct. What can be stated with greater confidence is that structure **4** corresponds to one of the (unnamed) natural products isolated by Liu and co-workers[5] from *Arenaria kansuensis* (Caryophyllaceae). The ready preparation of compounds **1**-**5** from the synthetically accessible alkene **11** and the occurrence of this last compound as a co-metabolite (pavettine)[2] of orthoscuticellines A-E in the producing organism, viz. bryozoan *Orthoscuticella ventricosa*, suggests that compound **11** could be the common biogenetic precursor to all the others. Furthermore, the straightforward nature of the synthetic sequences detailed above will allow for the accumulation of compounds **1**-**5** and various precursors in sufficient quantity for their comprehensive biological evaluation. Work directed toward such ends is now underway and results will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Protocols

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C{^{1}H}) NMR spectra were recorded at room temperature in $CDCl_3$ or $(CD_3)_2SO$ on spectrometers operating at 300 or 400 MHz for proton and 75, 100 and 125 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from the residual protioforms of the solvent were used as the internal standards. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. In the case of those spectra recorded in $(CD_3)_2SO$, the ^{1}H and ^{13}C chemical shifts were referenced to the residual solvent peaks appearing at δ_H 2.50 and δ_C 39.5, respectively. Infrared spectra were recorded, as thin films or solids, on a Nicolet iS50 FT-IR spectrometer fitted with a Smart iTX sampling module. High-resolution ESI mass spectra were recorded on a time-of-flight instrument. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on glass-backed silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid: ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g: 5 mL : 300 mL). Flash chromatographic separations were

carried out following protocols defined by Still et al.[18] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Petroleum ether refers to the fraction boiling between 40 and 60 °C. Starting materials, reagents and drying agents as well as other inorganic salts were generally available from commercial sources and used as supplied. Where necessary, reactions were performed under a nitrogen atmosphere. In those instances were reaction mixtures required heating then the specified temperatures refer those of the oil bath used for such purposes.

Specific Chemical Transformations

1-(Dimethoxymethyl)-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole (13) and 1-(Dimethoxymethyl)-9*H*-pyrido[3,4-*b*]indole (14). A magnetically stirred solution of tryptamine (**12**) (1.50 g, 9.36 mmol) in dichloromethane (90 mL) maintained at ambient temperatures was treated with glyoxal dimethylacetal (1.95 mL of a 60% aqueous solution) and trifluoroacetic acid (36 □L). The resulting mixture was stirred for 17 h then poured into sodium bicarbonate (15 mL of a 10% w/v aqueous solution) and the organic phase separated then dried (Na_2SO_4) before being filtered and concentrated under reduced pressure. The residue thus obtained, and which was assumed to contain compound **13**, was dissolved in THF (20 mL) and the resulting solution treated with $KMnO_4$ (4.44 g, 28.1 mmol) then stirred at ambient temperatures for 17 h. The ensuing mixture was filtered through a short pad of Celite® contained in a sintered glass funnel and the filtrate concentrated under reduced pressure. The yellow-brown oil so-obtained was subjected to flash chromatography (silica, 5:1 v/v petroleum ether/ethyl acetate gradient elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.6 in 1:1 v/v petroleum ether/ethyl acetate) afforded compound **14**[7] (1.15 g, 51%) as clear, brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.24 (s, 1H), 8.43 (d, J = 5.3 Hz, 1H), 8.11 (m, 1H), 7.93 (d, J = 5.3 Hz, 1H), 7.57–7.49 (complex m, 2H), 7.26 (ddd, J = 10.0, 6.1 and 2.0 Hz, 1H), 5.75 (s, 1H), 3.50 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 140.3, 140.0, 137.9, 133.4, 130.2, 128.6, 121.6, 121.0, 119.9, 114.9, 111.6, 106.3, 54.2; IR ν_{max} 2929, 2830, 1626, 1493, 1428, 1357, 1321, 1110, 1052, 977, 906, 829, 734 cm^{-1}; LRMS (ESI, +ve) 243 {100%, $(M+H)^+$}, 211 (95).

Concentration of fraction B (R_f = 0.4 in 1:1 v/v petroleum ether/ethyl acetate) afforded compound **13**[7] (370 mg, 16%) as clear, red but rather unstable oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.92 (broad s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.39 (m, 1H), 7.29 (m, 1H), 7.13 (ddd, J = 8.1, 6.9 and 1.1 Hz, 1H), 5.03 (s, 1H), 3.97 (m, 2H), 3.53 (s, 6H), 2.93 (m, 2H).

9*H*-Pyrido[3,4-*b*]indole-1-carbaldehyde (15). A magnetically stirred solution of compound **14** (1.15 g, 4.75 mmol) in acetic acid/dioxane/water (21 mL of a 2:1:0.5 v/v/v mixture) was heated at 100 ºC for 1 h then cooled and concentrated under reduced pressure. The oily residue thus obtained was poured onto $NaHCO_3$ (20 mL of a saturated aqueous solution) then extracted with ethyl acetate (3 × 30 mL). The combined organic phases were then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a clear brown oil that was subjected to flash chromatography (silica, 5:1 v/v petroleum ether/ethyl acetate elution) to afford, after concentration of the relevant fractions (R_f = 0.6 in 3:1 v/v petroleum ether/ethyl acetate) aldehyde **15**[7] (850 mg, 91%) as a light-red solid, m.p. = 202–204 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.35 (s, 1H), 10.10 (broad s, 1H), 8.64 (d, *J* = 5.0 Hz, 1H), 8.17–8.15 (complex m, 2H), 7.66–7.57 (complex m, 2H), 7.36 (ddd, *J* = 8.1, 6.5 and 1.7 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 195.6, 141.2, 139.5, 135.8, 135.2, 131.6, 129.6, 121.9, 121.1, 120.4, 119.3, 112.0; IR ν_{max} 3381, 2920, 1684, 1451, 1204, 1122, 741, 725, 649, 602 cm^{-1}; LRMS (ESI, +ve) 197 {90%, $(M+H)^+$}, 229 (100).

1-Vinyl-9*H*-pyrido[3,4-*b*]indole (11). A magnetically stirred solution of H_3CPPh_3Br (3.55 g, 4.32 mmol) in dry THF (80 mL) maintained under nitrogen atmosphere was cooled to 0 °C then treated with NaH (430 mg, 10.8 mmol), The ensuing mixture was warmed to and then stirred at ambient temperatures for 2 h before being re-cooled to 0 °C. Thereafter a solution of aldehyde **15** (850 mg, 4.32 mmol) in THF/dioxane (10 mL of a 4:1 v/v mixture) was added to the reaction mixture that was then stirred at ambient temperatures overnight before being quenched with NH_4Cl (10 ml of a saturated aqueous solution) (CAUTION: possibility of hydrogen gas evolution). The mixture thus obtained was extracted with dichloromethane (3 × 100 mL) and the combined organic extracts was then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography (silica, 45:1 v/v dichloromethane/methanol elution) and concentration of the relevant fractions (R_f = 0.4 in 45:1 v/v dichloromethane/methanol) gave alkene **11**[7,19] (600 mg, 71%) as a yellow, crystalline solid, m.p. = 164–166 °C (lit.[19] m.p. = 167 °C). ^{1}H NMR {$(CD_3)_2SO$, 300 MHz} δ 11.77 (s, 1H), 8.35 (d, *J* = 5.1 Hz, 1H), 8.22 (d, *J* = 7.9 Hz, 1H), 8.03 (d, *J* = 5.1 Hz, 1H), 7.62 (m, 1H), 7.56 (ddd, *J* = 8.1, 6.9 and 1.2 Hz, 1H), 7.45 (dd, *J* = 17.1 and 10.8 Hz, 1H), 7.25 (ddd, *J* = 8.1, 6.9 and 1.2 Hz, 1H), 6.49 (dd, *J* = 17.1 and 2.2, 1H), 5.62 (dd, *J* = 10.8 and 2.2 Hz, 1H); ^{13}C{^{1}H} NMR {$(CD_3)_2SO$, 75 MHz} δ 140.7, 138.9, 138.1, 133.6, 132.2, 128.7, 128.3, 121.8, 120.8, 119.5, 118.1, 114.2, 112.0; IR ν_{max} 3142, 3058,

2918, 1621, 1591, 1564, 1501, 1424, 1322, 1235, 1173, 1118, 721, 538 cm^{-1}; LRMS (ESI, +ve) 195 {100%, $(M+H)^+$}, 389 (66).

1-Ethyl-9*H*-pyrido[3,4-*b*]indole (7). An oven-dried reaction tube equipped with a magnetic stirring bar was charged with the vinylated *β*-carboline **11** (38.8 mg, 0.2 mmol), $LiBF_4$ (38 mg, 0.4 mmol) and $Ru(ppy)_3Cl_2•6H_2O$ (6.4 mg, 5 mol %). The tube was then evacuated and backfilled with nitrogen three times. Thereafter, acetonitrile (2.0 mL) and *N,N*-diisopropylethylamine (65 μL, 0.4 mmol) were added into the reaction vessel via syringe and the ensuing magnetically stirred solution, maintained at ambient temperatures, was irradiated with a Kessil blue LED (390 nm, 40 W) for 20 h. After removal of the solvent the residue thus obtained was subjected to flash-column chromatography (silica, 30:1 → 20:1 v/v dichloromethane/methanol gradient elution). Concentration of the relevant fractions (R_f = 0.2 in 40:1 v/v dichloromethane/methanol) compound **7**[20] (25 mg, 64%) as a light-yellow solid, m.p. = 143–144 °C (lit.[20] m.p. = 198–201 °C). ^{1}H NMR {$(CD_3)_2SO$, 400 MHz} δ 11.58 (s, 1H), 8.23 (d, *J* = 5.3 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.93 (d, *J* = 5.3 Hz, 1H), 7.59 (m, 1H), 7.52 (ddd, *J* = 8.2, 6.9 and 1.2 Hz, 1H), 7.22 (ddd, *J* = 7.9, 6.9 and 1.2 Hz, 1H), 3.11 (q, *J* = 7.5 Hz, 2H), 1.36 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR {$(CD_3)_2SO$, 125 MHz} δ 146.8, 140.3, 137.4, 133.7, 127.8, 127.1, 121.6, 121.1, 119.1, 112.6, 111.9, 26.6, 12.7; IR ν_{max} 3143, 2923, 2852, 1626, 1456, 1242, 1024, 743 cm^{-1}; HRMS (ESI, +ve) $(M+H)^+$ calcd for $C_{13}H_{13}N_2$ 197.1073, found 197.1071.

(1*r*,2*s*)-1,2-bis(9*H*-Pyrido[3,4-*b*]indol-1-yl)cyclobutane (1) and (1*r*,2*r*)-1,2-bis(9*H*-Pyrido[3,4-*b*]indol-1-yl)cyclobutane (2). An oven-dried soda glass tube was charged with the vinylated *β*–carboline **11** (38.8 mg, 0.2 mmol) and $[Ir\{dFCF_3ppy\}_2(dtbbpy)]PF_6$ (2.0 mg, 2 mmol %). The tube was evacuated and backfilled with nitrogen with this process being repeated three times. Acetonitrile (2.0 mL) was then added into the reaction vessel via syringe and the ensuing magnetically stirred solution, maintained at ambient temperatures, was irradiated with a Kessil blue LED (390 nm, 40 W) for 24 h. The ensuing precipitate was collected by filtration and washed with ethyl acetate (3 x 5 mL) and so affording a ca. 1:3 mixture of compounds **1** and **2** (31.9 mg, 82% combined yield). This mixture was subjected to flash-column chromatography (silica, 40:1 → 20:1 v/v dichloromethane/methanol gradient elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.3 in 20:1 v/v dichloromethane/methanol) afforded compound **1** as a light-yellow solid, m.p. = 213–214 °C; ^{1}H NMR {$(CD_3)_2SO$, 300 MHz} δ 11.50 (s, 2H), 7.97 (d, *J* = 5.3 Hz, 2H), 7.86 (d, *J* = 7.8 Hz, 2H), 7.51 (d, *J* = 5.3 Hz, 2H), 7.46

(d, J = 8.2 Hz, 2H), 7.32 (m, 2H), 6.99 (t, J = 7.3 Hz, 2H), 4.97 (broad s, 2H), 3.32–3.21 (complex m, 4H); $^{13}C\{^{1}H\}$ NMR {$(CD_3)_2SO$, 75 MHz} δ 144.7, 139.9, 136.9, 133.8, 127.2, 126.0, 121.2, 120.5, 118.6, 112.1, 111.5, 41.7, 21.7; IR ν_{max} 3228, 1626, 1566, 1501, 1455, 1427, 1323, 1239, 742 cm^{-1}; HRMS (ESI, +ve) $(M+H)^+$ calcd for $C_{26}H_{21}N_4$ 389.1766, found 389.1774.

Concentration of fraction B (R_f = 0.4 in 20:1 v/v dichloromethane/methanol) afforded compound **2** as a light-yellow crystalline solid, m.p. = 284 °C (decomp.). ^{1}H NMR {$(CD_3)_2SO$, 300 MHz} δ 11.92 (s, 2H), 8.40 (d, J = 5.3 Hz, 2H), 8.19 (d, J = 7.9 Hz, 2H), 7.99 (d, J = 5.3 Hz, 2H), 7.66 (m, 2H), 7.52 (ddd, J = 8.3, 7.0 and 1.2 Hz, 2H), 7.21 (m, 2H), 4.89 (m, 2H), 2.67–2.61 (complex m, 2H), 2.44–2.39 (complex m, 2H); $^{13}C\{^{1}H\}$ NMR {$(CD_3)_2SO$, 75 MHz} δ 146.7, 140.4, 137.3, 133.4, 127.9, 127.2, 121.7, 121.0, 119.3, 113.2, 112.2, 41.1, 24.2; IR ν_{max} 3339, 2947, 2835, 1651, 1409, 1112, 1017, 737 cm^{-1}; HRMS (ESI, +ve) $(M+H)^+$ calcd for $C_{26}H_{21}N_4$ 389.1766, found 389.1751.

***N*,*N*-Dimethyl-2-(9*H*-pyrido[3,4-*b*]indol-1-yl)ethan-1-amine (3)**. A magnetically stirred solution of alkene **11** (102 mg, 0.52 mmol) in 1,4-dioxane (500 □L) and maintained at ambient temperatures under nitrogen was treated with Ru(cod)(2-methylallyl)$_2$ (4 mg, 0.013 mmol), 1,5-bis(diphenylphosphino)pentane (8 mg, 0.018 mmol), TfOH (4 □L) then dimethylamine (130 □L, 0.26 mmol). The ensuing mixture was stirred at 100 ºC for 24 h then cooled and the entire reaction mixture subjected to flash column chromatography (silica, 30:1 v/v dichloromethane/methanol elution). Concentration of the relevant fractions (R_f = 0.2 in 30:1 v/v dichloromethane/methanol) afforded amine **3** (63 mg, 51%) as a brown solid m.p. = 92–96 °C. ^{1}H NMR {$(CD_3)_2SO$, 400 MHz} δ (free base) 11.66 (s, 1H), 8.23 (d, J = 7.0 Hz, 1H), 8.18 (d, J = 10.5 Hz, 1H), 7.92 (d, J = 7.0 Hz, 1H), 7.60 (m, 1H), 7.52 (ddd, J = 10.8, 9.2 and 1.5 Hz, 1H), 7.22 (ddd, J = 10.8, 9.2 and 1.5 Hz, 1H), 3.25 (t, J = 10.8 Hz, 2H), 2.77 (t, J = 10.8 Hz, 2H), 2.25 (s, 6H); $^{13}C\{^{1}H\}$ NMR {$(CD_3)_2SO$, 100 MHz} δ (for free base) 144.4, 140.4, 137.6, 134.3, 127.9, 127.3, 121.7, 121.1, 119.2, 112.7, 112.0, 57.8, 45.2, 31.6; IR ν_{max} 3370, 2924, 2363, 1649, 1024, 991, 826, 764 cm^{-1}; LRMS (ESI, +ve) 240 {100%, $(M+H)^+$}; HRMS (ESI, +ve) $(M+H)^+$ calcd for $C_{15}H_{18}N_3$ 240.1495, found 240.1485.

(±)-1-(Oxiran-2-yl)-9H-pyrido[3,4-b]indole 2-oxide (16). A magnetically stirred solution of alkene **11** (204 mg, 1.04 mmol) in dichloromethane (3.0 mL) maintained at 0 °C was treated with *m*-CPBA (312 mg of 70% material, 1.35 mmol) and the resulting mixture allowed to slowly warm to ambient temperatures then stirred for a further 16 h. Thereafter the reaction mixture was quenched with $Na_2S_2O_3$, (30 mL of a saturated aqueous solution) then extracted

with dichloromethane (3 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered and then concentrated under reduced pressure and the residue so-obtained subjected to flash chromatography (silica, 20:1 v/v ethyl acetate/methanol elution) to afford, after concentration of the appropriate fractions (R_f = 0.4 in 30:1 v/v dichloromethane/methanol), epoxide **16** (89 mg, 41%) as a light-orange solid, m.p. = 131 °C (decomp.). ^{1}H NMR {$(CD_3)_2SO$, 400 MHz} δ 11.15 (s, 1H), 8.14–8.08 (complex m, 3H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 4.70 (m, 1H), 3.43 (t, *J* = 5.1 Hz, 1H), 3.17 (m, 1H); ^{13}C{^{1}H} NMR {$(CD_3)_2SO$, 100 MHz} δ 141.5, 133.5, 131.8, 130.9, 127.1, 120.6, 120.3, 120.0, 119.9, 115.6, 112.5, 48.8, 47.6; IR ν_{max} 3300, 2922, 2839, 1649, 1458, 1437, 1408, 1194, 1175, 1016, 743 cm^{-1}; LRMS (ESI, +ve) 227 {40%, $(M+H)^+$, 211 (100); HRMS (ESI, +ve) $(M+H)^+$ calcd for $C_{13}H_{11}N_2O_2$ 227.0815, found 227.0813.

(±)-1-(1,2-Dihydroxyethyl)-9H-pyrido[3,4-b]indole 2-oxide (17). A magnetically stirred solution of epoxide **16** (58 mg, 0.26 mmol) in acetonitrile (2.7 mL) was treated with HCl (4 mL of a 1 M aqueous solution) then stirred at ambient temperatures for 16 h before being concentrated under reduced pressure. The residue thus obtained was extracted with ethyl acetate (3 × 15 mL) and the combined organic phases then dried (Na_2SO_4) filtered and concentrated under reduced pressure. The solid thus obtained was subjected to flash chromatography (silica, 20:1 v/v dichloromethane/methanol elution) to afford, after concentration of the relevant fractions (R_f = 0.3 in 20:1 v/v dichloromethane/methanol) diol **17** (27 mg, 43%) as a yellow solid, m.p. = 166 °C (decomp.). ^{1}H NMR {$(CD_3)_2SO$, 400 MHz} δ 11.28 (s, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.05 (s, 2H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.46 (broad t, *J* = 7.6 Hz, 1H), 7.22 (broad t, *J* = 7.6 Hz, 1H), 6.50 (m, 1H), 5.55 (broad s, 1H), 4.95 (m, 1H), 3.84 (m, 1H), 3.77 (m, 1H); ^{13}C{^{1}H} NMR {$(CD_3)_2SO$, 100 MHz} δ 141.4, 136.2, 135.3, 130.9, 127.1, 120.8, 120.3, 119.8, 119.8, 115.1, 112.3, 69.8, 62.8; IR ν_{max} 3319, 2953, 2843, 1649, 1454, 1112, 1014 cm^{-1}; LRMS (ESI, +ve) 489 (36%), 245 {100, $(M+H)^+$}, 185 (48); HRMS (ESI, +ve) $(M+H)^+$ calcd for $C_{13}H_{13}N_2O_3$ 245.0921, found 245.0910.

1-(9*H*-Pyrido[3,4-*b*]indol-1-yl)ethane-1,2-diol (4). A magnetically stirred solution of AD-mix-β (1.40 g) in *t*-butanol/water (10 mL of a 1:1 v/v mixture) maintained at ambient temperatures was treated with $MeSO_2NH_2$ (285 mg, 3.00 mmol) and stirred continued until the initially-formed suspension had completely dissolved. The resulting clear orange solution was then cooled to 0 ºC and treated with alkene **11** (194 mg, 1.00 mmol). After stirring for a further 24 h at 0 °C the reaction mixture was quenched with Na_2SO_3 (50 mL of a saturated aqueous solution). After stirring the ensuing mixture at ambient temperatures for a further 1 h

it was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered and then concentrated under reduced pressure and the clear brown residue so-obtained subjected to flash chromatography (silica, 20:1 v/v dichloromethane/methanol elution) to afford, after concentration of the appropriate fractions (R_f = 0.3 in 20:1 v/v dichloromethane/methanol), diol **4** (89 mg, 39%) as a brown solid, m.p. = 160–167 °C. ^{1}H NMR {$(CD_3)_2SO$, 400 MHz} δ 11.23 (s, 1H), 8.25 (d, *J* = 4.8 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 4.8 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.52 (broad t, *J* = 7.6 Hz, 1H), 7.21 (broad t, *J* = 7.6 Hz, 1H), 5.71 (broad s, 1H), 5.07 (m, 1H), 4.77 (broad s, 1H), 3.86 (m, 1H), 3.79 (m, 1H); ^{13}C{^{1}H} NMR {$(CD_3)_2SO$, 100 MHz} δ 145.8, 140.5, 136.7, 133.4, 128.1, 127.9, 121.4, 120.4, 119.0, 113.6, 112.3, 74.5, 65.3; IR ν_{max} 3267, 2922, 2852, 1627, 1568, 1548, 1494, 1479, 1454, 1429, 1371, 1323, 1278, 1236, 1151, 1124, 1070, 937, 879, 823, 785, 740, 707 cm^{-1}; LRMS (ESI, +ve) 229 {100%, $(M+H)^+$}; HRMS (ESI, +ve) $(M+H)^+$ calcd for $C_{13}H_{13}N_2O_2$ 229.0972, found 229.0972.

2-(9*H*-Pyrido[3,4-*b*]indol-1-yl)ethane-1-thiol (18). A magnetically stirred solution of alkene **11** (543 mg, 2.8 mmol) in toluene (6.0 mL) was treated with Ph_3SiSH (932 mg, 3.2 mmol) and AIBN (133 mg, 0.81 mmol). The ensuing mixture was maintained at 85 ºC for 0.5 h then cooled to ambient temperatures and quenched with TFA (1.10 mL, 14.0 mmol) before being concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:8 v/v petroleum ether/ethyl acetate elution) to afford, after concentration of the relevant fractions (R_f = 0.5 in 1:8 v/v petroleum ether/ethyl acetate), thiol **18** (466 mg, 73%) as a brown solid, m.p. = 90–93 °C. ^{1}H NMR {$(CD_3)_2SO$, 400 MHz} δ 12.76 (s, 1H), 8.48 (m, 2H), 8.41 (d, *J* = 8.0 Hz, 1H), 7.73 (m, 2H), 7.39 (m, 1H), 3.71 (t, *J* = 7.6 Hz, 2H), 3.32 (t, *J* = 7.6 Hz, 2H), 1.98 (s, 1H); ^{13}C{^{1}H} NMR {$(CD_3)_2SO$, 100 MHz} δ 142.8, 140.0, 133.9, 131.6, 130.8, 130.7, 123.1, 121.0, 120.0, 115.4, 112.7, 35.6, 30.4; IR ν_{max} 3369, 2924, 2853, 2257, 1672, 1634, 1200, 1130, 1024, 997, 823, 760 cm^{-1}; LRMS (ESI, +ve) 229 {100%, $(M+H)^+$}; HRMS (ESI, +ve) $(M+H)^+$ calcd for $C_{13}H_{13}N_2S$ 229.0794, found 229.0795.

2-(9*H*-Pyrido[3,4-*b*]indol-1-yl)ethane-1-sulfonic acid (5). A magnetically stirred solution of thiol **17** (102 mg, 0.45 mmol) in acetonitrile/water (5 mL of a 3:2 v/v mixture) maintained at ambient temperatures was treated with Oxone® (693 mg, 1.13 mmol) and $NaHCO_3$ (219 mg, 2.61 mmol). The resulting mixture was stirred for 24 h then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 8:1 v/v dichloromethane/methanol elution) to afford, after concentration of the relevant fractions (R_f

= 0.2 in 8:1 v/v dichloromethane/methanol) a crude mixture of sulfonic acid **5**. This material was then subjected to further purification using HPLC (Gemini® 5 μM C18-110A-LC 250× 212 mm column, 1:1 v/v methanol/water elution, flow rate = 10.0 mL/min) to afford a single fraction (R_t = 12 min) containing pure sulfonic acid **5** (51 mg, 41%) as a yellow solid, m.p. >280 °C; ^{1}H NMR {$(CD_3)_2SO$, 400 MHz} δ 12.54 (s, 1H), 8.39 (m, 3H), 7.73–7.67 (complex m, 2H), 7.36 (broad t, J = 7.4 Hz, 1H), 3.64 (broad t, J = 7.6 Hz, 2H), 3.11 (broad t, J = 7.6 Hz, 2H) (signal due to SO_3H group proton not observed); ^{13}C{^{1}H} NMR {$(CD_3)_2SO$, 100 MHz} δ 142.5, 142.2, 133.7, 131.2, 130.7, 130.3, 122.8, 120.6, 120.2, 114.7, 112.6, 48.8, 27.4; IR ν_{max} 3358, 2839, 1645, 1412, 1115, 1017 cm^{-1}; LRMS (ESI, +ve) 277 {100%, $(M+H)^+$}, 299 (28), 553 (18); HRMS (ESI, +ve) $(M+H)^+$ calcd for $C_{13}H_{13}N_2O_3S$ 277.0641, found 277.0633.

Crystallographic Study

Crystallographic Data

Compound **2**. $C_{26}H_{20}N_4$, M = 388.46, T = 150 K, triclinic, space group P-1, Z = 2, a = 7.8859(11) Å, b = 10.2778(17) Å, c = 12.6715(16) Å; α = 89.832(12) °, β = 85.721(5) °, γ = 68.268(14) °; V = 951.0(3) Å^3, D_x = 1.357 Mg m^{-3}, 3274 unique data ($2\theta_{max}$ = 133.194°), R = 0.0696 [for 2310 reflections with $I > 2.0\sigma(I)$]; Rw = 0.1847 (all data), S = 0.994.

Structure Determination

Data for compound **2** were collected on Rigaku Super Nova X-ray diffractometer employing CuKα radiation and a graphite monochromator (λ = 1.54184 Å). Using OLEX2,[21] the structure was solved by Intrinsic Phasing with the ShelXT[22] program and refined, using least squares minimization, with the ShelXL[23] package. Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC no. 2145585). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Theoretical Procedures

The NMR shifts (δ) were calculated relative to tetramethylsilane (TMS) as follows:

$$\delta = \sigma_{isotropic,TMS} - \sigma_{isotropic,XXX}$$

where σ are the respective isotropic shielding values. The NMR calculations were performed using Commandline Energetic SOrting (CENSO)[24] version 1.2.0 with the interface with ORCA 5.0.1.[25] The initial generation of conformers was obtained via Conformer–Rotamer Ensemble Sampling Tool (CREST)[26] version 2.11.1 at GFN2[27]//GFN-FF[28] with ALPB(DMSO)[29] to model the solvation effect. The CENSO workflow, which is outlined in detail in the supporting information, not only automatically considers the contribution of conformers toward the calculated ^{13}C NMR shifts but also incorporates the influence of the equivalent carbon centers caused by bond rotations. For the CENSO module, the default setting was adopted, except that the solvent was changed to dimethyl sulfoxide (DMSO) to match the experiments.

ASSOCIATED CONTENT

Supporting Information

Part A: Plot, X-ray data and cif for compound **2**; ^{1}H and ^{13}C NMR spectra of compounds **1**-**3**, **3**•TFA, **4**, **5**, **7**, **11, 13** (^{1}H NMR spectrum only) and **14**-**18**; ***Part B***: Computational details, NMR calculation details, references, structures of conformers and energetic information. This material is available free-of-charge via the Internet at http://pubs.acs.org.

Accession Codes

CCDC 2145585 contains the supplementary crystallographic data for compound **2**.

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Notes

The authors declare no competing financial interest.

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