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Synthesis of 9-methyl-1*H*-[1,4]thiazino[3,2-*g*]quinoline-2,5,10(3*H*)-trione, the B,C,D ring core of the shermilamine alkaloids

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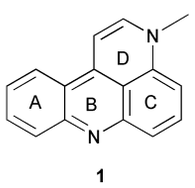
Synthesis of 9-methyl-1*H*-[1,4]thiazino[3,2-*g*]quinoline-2,5,10(3*H*)-trione (**4**), from *N*-(4-bromo-2,5-dimethoxyphenyl)acetamide (**23**) is described. Oxidative cyclisation of 2,2′-disulfanediylbis[*N*-(2,5-dimethoxyphenyl)acetamide] (**19**) to 5,8-dimethoxy-2*H*-1,4-benzothiazin-3(4*H*)-one (**7b**) is also reported.

Introduction

Pyridoacridine alkaloids of basic skeleton **1** are secondary metabolites of marine invertebrates, which show a wide range of biological activity.[1] They vary in structure by having different side chain appendages or different heterocyclic rings fused to ring C. Shermilamine A and B (**2** and **3**) have a 2*H*-1,4-thiazin-3(4*H*)-one ring fused to ring C.



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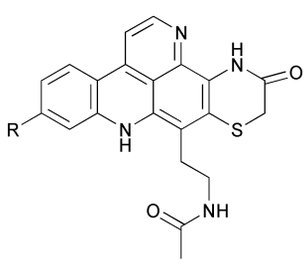
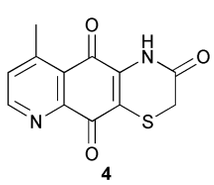


2 R = Br
3 R = H



4

Our interest in the synthesis of analogues of shermilamine B led us to investigate the synthesis of 9-methyl-1*H*-[1,4]thiazino-[3,2-*g*]quinoline-2,5,10(3*H*)-trione (**4**). Retrosynthetic analysis (Scheme 1) pointed us to two likely pathways:

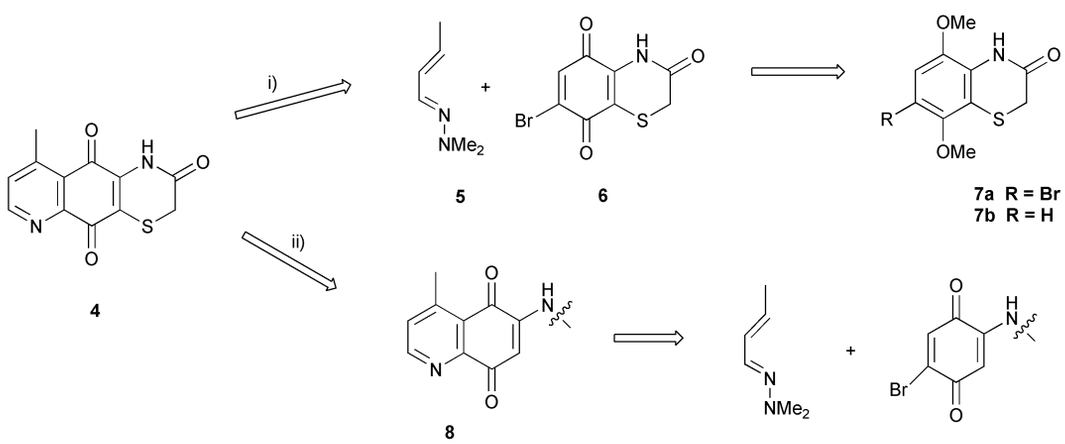
i) hetero-Diels–Alder reaction on a thiazinoquinone or
ii) building the thiazinone ring onto a quinolinequinone.
We set out to explore these pathways.

Results and discussion

Formation of **4** by the hetero-Diels–Alder reaction would require bromoquinone **6**, the bromo substituent set to direct the regiochemistry of the cycloaddition.[2] 7-Bromo-5,8-dimethoxy-2*H*-1,4-benzothiazin-3(4*H*)-one (**7a**) was therefore the target of this pathway, since it seemed that **6** could be obtained by oxidative demethylation of **7a**.

Popular methods for the synthesis of 2*H*-1,4-thiazin-3(4*H*)-ones include condensation of 2-aminothiophenols with glycidyl esters,[3] 2-haloacetic acids,[4] or α,β-unsaturated acids,[5] and reductive cyclization of 2-nitrobenzenethioglycolic acids[6] or esters.[7] More recently, other methods have been reported. These include ring expansion of benzothiazoles,[8] ring contraction of 1,5-benzothiazepin-4-ones,[9] reaction of bis(*o*-nitrophenyl)-disulfides with samarium iodide followed by 2-haloacids or esters,[10] and treatment of *N*,*N*-diphenylacetamides with thionyl chloride.[11]

We were drawn to a report which involved the synthesis of 2-carboxybenzothiophene by treatment of α-mercaptocinnamic acid with iodine in nitrobenzene.[12] Campaigne and Cline established that the reaction proceeded *via* the disulfide, that the reaction was acid-catalysed and that iodine proved very effective as it acted not only as a Lewis acid, but also as an oxidising agent, thus enabling the cyclisation. These workers showed that dihydronaphthothiophenes and -thiopyrans could also be formed in this way (Fig. 1).[13]



4 **5** **6** **7a** R = Br **7b** R = H **8**

Scheme 1

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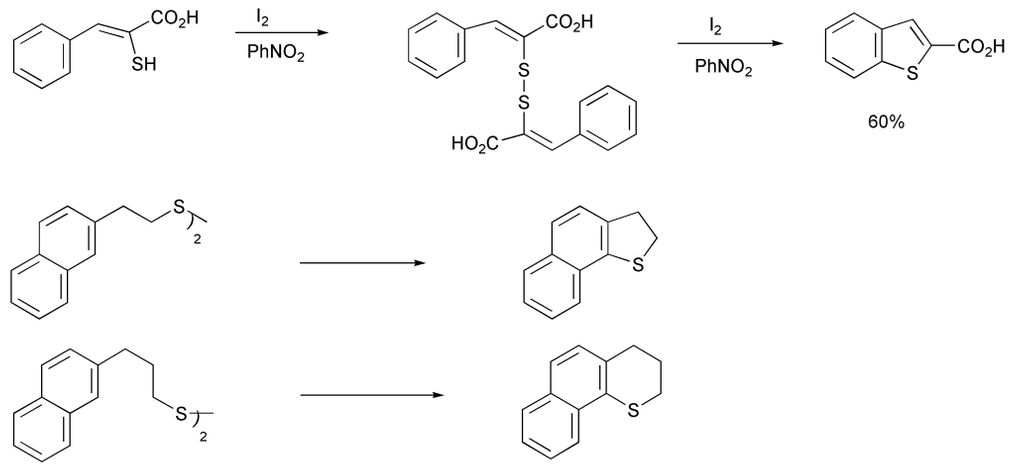
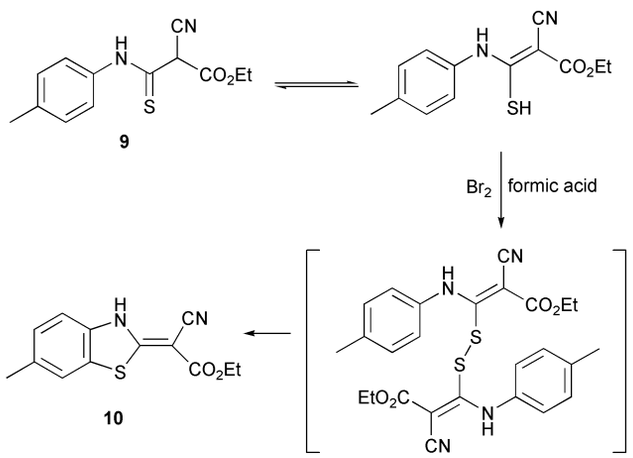


Fig. 1

Kunzek and Barnikow later formed benzothiazoline **10** by treatment of thioenol **9** with bromine in formic acid (Scheme 2).[14]



Scheme 2

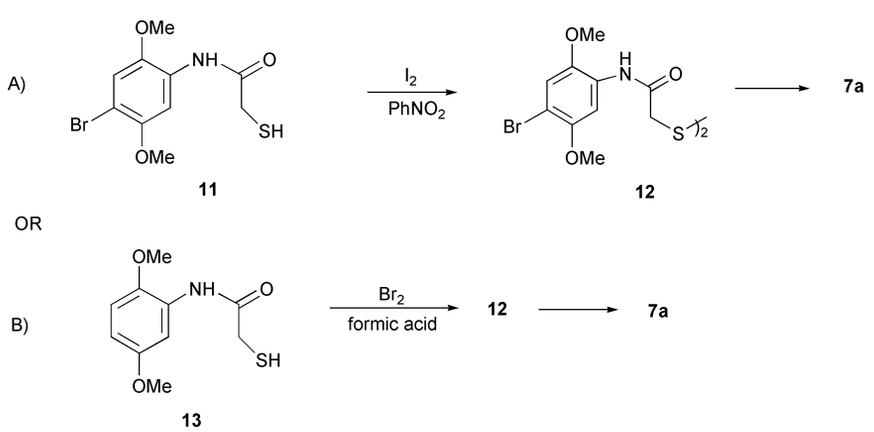
We thought it possible that the desired 7-bromo-5,8-dimethoxy-1,4-thiazin-3-one (**7a**) could be synthesised by similar oxidative cyclization (Scheme 3A), and saw this as a more direct route than *via* the highly substituted thiophenol required for formation of the thiazinone by more customary pathways. This route (Scheme 3A) would require α-mercapto-4-bromo-2,5-dimethoxyacetanilide (**11**) or the corresponding disulfide **12**. With 2,5-dimethoxyaniline and chloroacetyl chloride in hand, synthesis of **11** or **12** seemed to be straightforward.

It seemed also that Kunzek and Barnikow's approach could bring about bromination and cyclisation in one step (Scheme 3B), thus improving the efficiency of the process. Both these ideas were investigated.

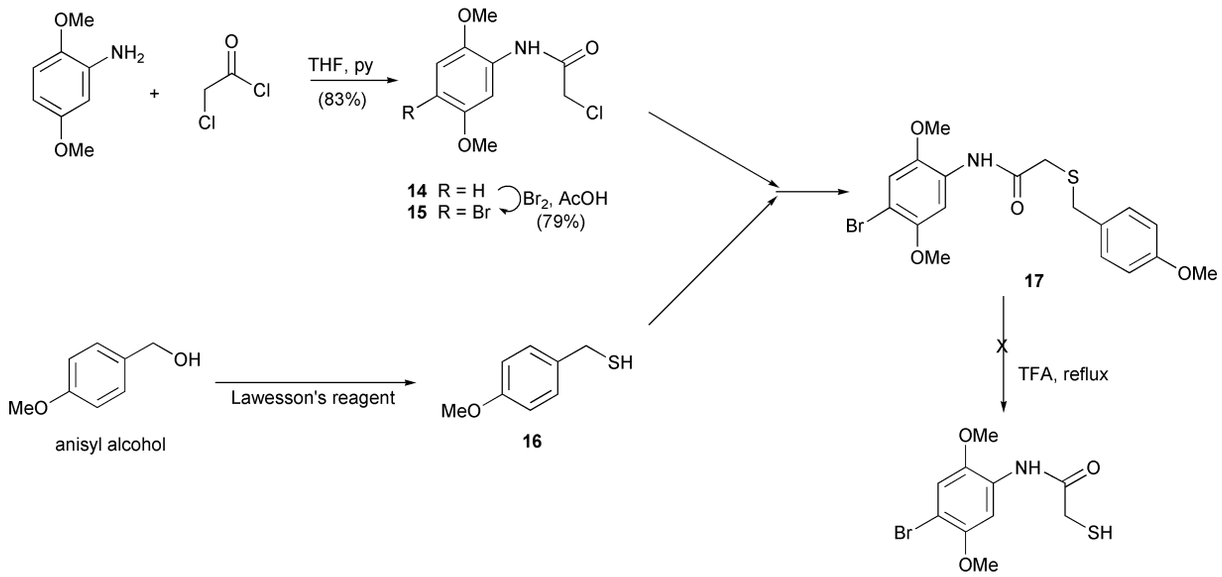
Reaction of 2,5-dimethoxyaniline with pyridine and chloroacetyl chloride in THF gave the α-chloroacetanilide **14** in reasonable yield. This was brominated regioselectively to produce **15**. Treatment of compound **15** with thiol **16** (obtained from reaction of anisyl alcohol with Lawesson's reagent), formed the *p*-methoxybenzyl sulfide **17** (63%), but this proved resistant to deprotection in refluxing TFA (Scheme 4).

Thiols are often obtained by acid hydrolysis of the corresponding Bunte salt.[15] Treatment of compound **14** with sodium thiosulfate in ethanol produced the Bunte salt **18** in 87% yield, verified by the known reaction with thiourea, to produce a disulfide[16]—in this case, compound **19**. All attempts at acid hydrolysis of the salt **18**, however, failed to give the α-mercaptoacetanilide. Reaction of 2,5-dimethoxyaniline with thioglycolic acid in the presence of DCC–DMAP also gave the disulfide **19** in 67% yield after 12 hours at room temperature (Scheme 5).

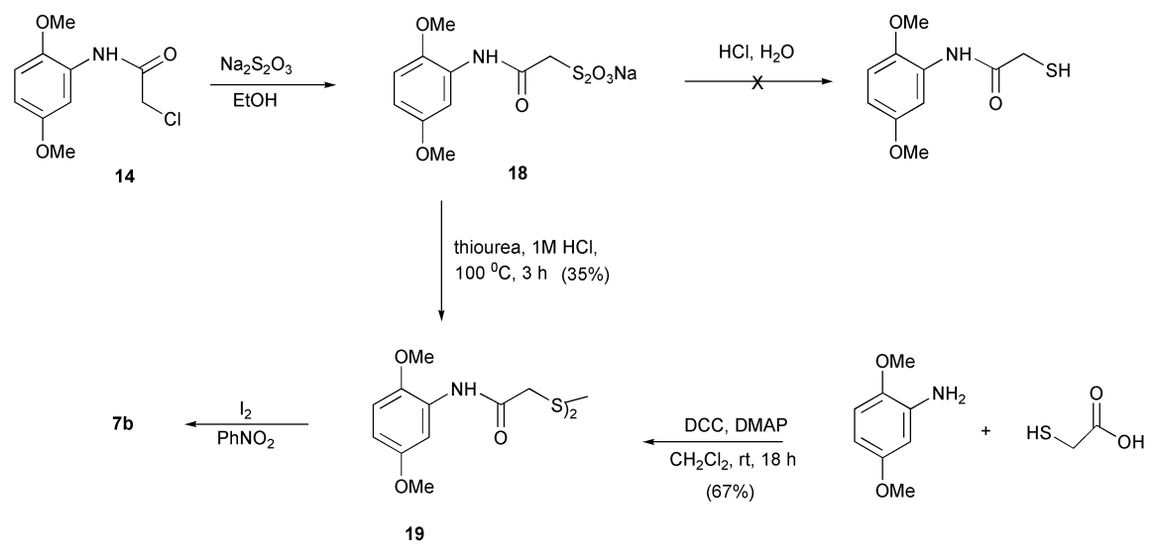
With disulfide **19** in hand we explored ring closure to thiazinone **7b** using 1.1 molar equivalents of bromine in acetic acid. After four hours at room temperature the ^{1}H-NMR spectrum of the major product showed two singlets in the aromatic region resonating at 7.06 and 8.14 ppm and the chemical shift of the methylene protons was not significantly different from that in the starting material. This suggested that the proton at position-4 had been substituted and that no cyclisation had occurred. The major product of the reaction was dibromodisulfide **20**, obtained in 40% yield. Tribromide **21** was also obtained in 14% yield. Another product, which we have identified from ^{1}H-NMR as tetrabromide **22**, was obtained in 8% yield. This compound, however, was always obtained as a mixture with the tribromide **21** (Scheme 6).



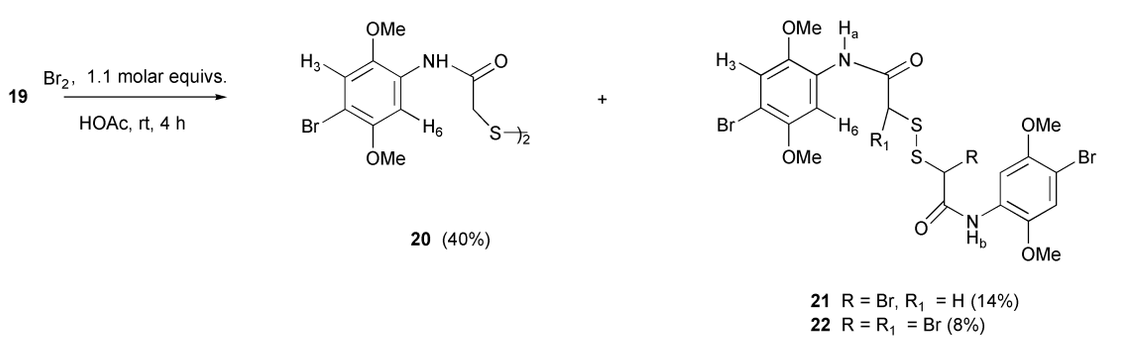
Scheme 3



Scheme 4



Scheme 5



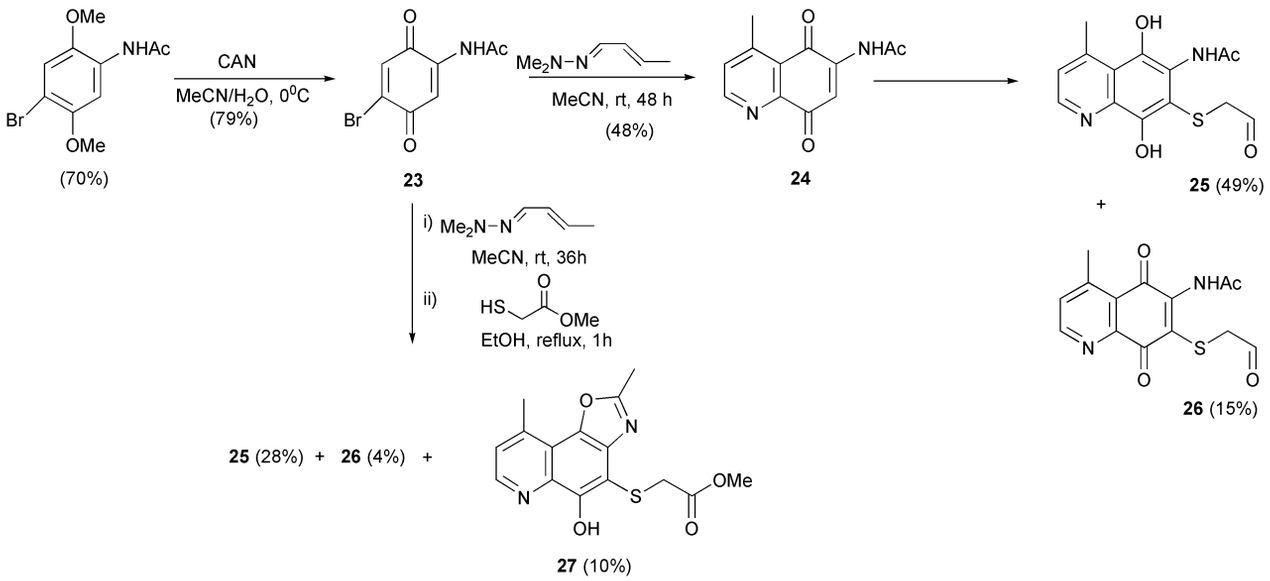
Scheme 6

Table 1 ^{1}H-NMR data of compound **19**–**22**

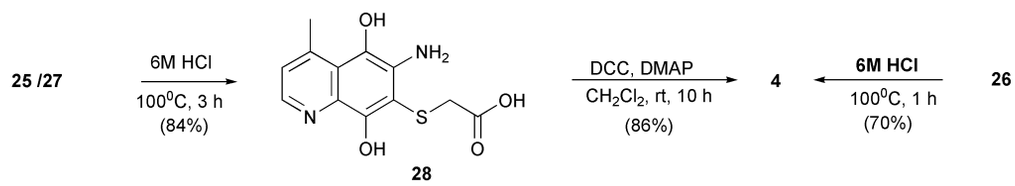
	Chemical shifts of protons (ppm)						
Compound	CH_2	CH–Br	H-3	H-4	H-6	NH_a	NH_b
19	3.69	—	6.78	6.58	8.07	8.57	—
20	3.63	—	6.96	—	8.09	8.42	
21	3.70	5.53	6.97	—	8.06	8.29	8.73
22[a]	—	5.56	6.97	—	8.07	—	8.76

[a] Obtained as a mixture with **21**.

The ^{1}H-NMR data of compounds **19**–**22** are given in Table 1. Note that bromination of the methylene group leads to a methine proton resonating at about 5.5 ppm (the methylene peak resonates at 3.6–3.7 ppm) and results in the peak corresponding to the amido proton which is closer to the CHBr group being shifted downfield by about 0.4 ppm. The ^{1}H-NMR spectrum of compound **21** is, as would be expected, a composite of the spectra of **20** and **22**. Repeating the reaction in the dark made no difference to the product composition. Bromination to form **21** and **22** may have occurred *via* a Pummerer-type mechanism.[17]



Scheme 7



Scheme 8

Table 2 Formation of thiazinone **7b** from disulfide **19** using iodine in various solvents

Entry	I_2 (mol. equiv.)	Solvent	Catalyst	*T*/°C	Time	Thiazinone **7b** (%)
1	2	$PhNO_2$	—	160	4 h	15
2	3	$PhNO_2$	—	200	4 h	18
3	2	$PhNO_2$	$AlCl_3$	120	4 h	15
4	2	1,2-Ethanediol	—	200	2 h	16
5	2	1,2-Ethanediol	—	200	15 min	10
6	2	1,2-Ethanediol	—	30	24 h	12
7	1	EtOH	—	30	24 h	0
8	2	EtOH	—	30	24 h	0
9	2	EtOH	—	Reflux	24 h	0
10	2	CCl_4	$AlCl_3$	Reflux	4 h	15
11	4	$PhNO_2$	—	202	5 min	53

Treatment of disulfide **19** with iodine–nitrobenzene did produce the thiazinone **7b** in 53% yield after five minutes at 202 °C. Other reaction conditions tried are reported in Table 2. With solvents such as ethylene glycol and carbon tetrachloride (entries 4–6 and 10), yields were very low and under the conditions used there was much charring of the material. When the reaction was carried out in ethanol (entries 7–9), only starting material was obtained (Table 2).

Treatment of the dibromodisulfide **20** under conditions which brought about thiazinone formation in **19** failed to give the desired **7a**. Oxidative demethylation was therefore attempted on thiazinone **7b** using CAN. This yielded a product which was insoluble in most organic solvents and in water. ^{1}H-NMR of the crude material suggested that no demethylation had occurred and that the thiazinone ring had been oxidised (S to SO) since the peak corresponding to the methylene protons resonated at about 5.2 ppm, and the methoxy peaks were still quite prominent.

Route ii) as shown in Scheme 1 was thus investigated. 2-Acetamido-5-bromo-1,4-benzoquinone (**23**) was easily prepared from the corresponding 4-bromo-*N*-(2,5-dimethoxyphenyl)acetamide[18] by oxidative demethylation using CAN.[19] Reaction of **23** with azadiene **5**[20] gave the adduct **24** as the sole product in 50% yield. When quinone **24** was treated with equimolar amounts of methyl thioglycolate in refluxing ethanol, dihydroxyquinoline **25** and the corresponding quinone **26** were obtained in 49 and 15% yield, respectively (Scheme 7).

We found that when the Diels–Alder adduct was not isolated, *i.e.* when bromoquinone **23** was treated with crotonaldehyde dimethylhydrazone **5** in acetonitrile at room temperature for 24 hours, and then the solvent removed, methyl thioglycolate added in ethanol and this mixture heated at reflux for one hour, compounds **25** and **26** were obtained in 28% and 4% yield, respectively, and benzoxazole **27** was also formed in 10% yield. Both compounds **25** and **27**, when heated in 6 M HCl, produce the amino acid **28**, which cyclizes on treatment with DCC–DMAP to give the target thiazinone **4** (56%) (Scheme 8). Amino acid **28** is also gradually converted to the thiazinone **4** on standing in air. Compound **26** on the other hand, produces the desired thiazinone **4** directly, and in 70% yield, on treatment with 6 M HCl.

We have thus prepared the BCD ring core of the shermilamine alkaloids in four steps and 18% overall yield from the known *N*-(4-bromo-2,5-dimethoxyphenyl)acetamide.

Experimental

General

All melting points are uncorrected. IR spectra were obtained on a Perkin Elmer 735B model or a Perkin Elmer 1600 FT-IR spectrometer and are for KBr discs. Unless otherwise stated, NMR spectra were run on a Bruker 200 MHz or 500 MHz spectrometer and were determined in $CDCl_3$ solution. Resonances are reported in δ units downfield from TMS; J values are given in Hz. Elemental analyses were carried out by MEDAC Ltd., Egham, Surrey, UK.

2-Chloro-*N*-(2,5-dimethoxyphenyl)acetamide 14

Dimethoxyaniline (2.01 g, 13.1 mmol) was dissolved in a solution of THF (20 mL) and pyridine (1 mL) and the resulting solution cooled in an ice–water bath. Chloroacetyl chloride (3 mL, 4.25 g, 37.6 mmol) was added dropwise to the cold solution with vigorous stirring. After the addition was complete the reaction was allowed to come to room temperature and was then stirred for 2 h. The solvent was removed *in vacuo* and the crude product recrystallized from ethanol to give **14** as a grey crystalline solid (2.50 g, 83%): mp 76–78 °C (ethanol) (Found C, 52.51; H, 5.30; N, 6.08. Calc. for $C_{10}H_{12}NO_3Cl$: C, 52.30; H, 5.27; N, 6.10%); IR ν_{max}/cm^{-1} 3396, 1682, 1491; ^{1}H-NMR δ_H 3.81 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.20 (s, 2H, CH_2Cl), 6.63 (dd, 1H, J 3.4 and J 8, 4-H), 6.85 (d, 1H, J 8, 3-H), 8.08 (d, 1H, J 3.4, 6-H), 8.97 (br s, 1H, NH); ^{13}C-NMR δ_C 43.1, 55.8, 56.4, 106.0, 109.3, 110.9, 127.3, 142.5, 153.8, 165.6.

N-(4-Bromo-2,5-dimethoxyphenyl)-2-chloroacetamide 15

2-Chloro-*N*-(2,5-dimethoxyphenyl)acetamide (**14**) (5.20 g, 22.6 mmol) was dissolved in glacial acetic acid (26 mL) and the resulting solution cooled in an ice–water bath. A solution of bromine (1.5 mL, 4.65 g, 29.1 mmol) in glacial acetic acid (10 mL) was then added dropwise and the temperature of this mixture allowed to rise to room temperature. Stirring was continued at room temperature for 5 h after which the reaction mixture was poured into water (150 mL) containing sodium bisulfite (10% aqueous, 5 mL). The precipitate formed was collected by filtration, washed with water (3 × 50 mL) and then air dried. The crude product was recrystallized from methanol to give **15** as a grey crystalline solid (5.51 g, 79%): mp 117–120 °C (methanol) (Found C, 39.33; H, 3.67; N, 4.44. Calc. for $C_{10}H_{11}NO_3BrCl$: C, 38.93; H, 3.59; N, 4.54%) IR ν_{max}/cm^{-1} 3392, 1678, 1588; ^{1}H-NMR δ_H 3.87 (s, 6H, 2 × OCH_3), 4.19 (s, 2H, CH_2Cl), 7.07 (s, 1H, 3-H), 8.18 (s, 1H, 6-H), 8.90 (br s, 1H, NH); ^{13}C-NMR δ_C 43.1, 56.6, 56.8, 104.4, 105.2, 110.9, 126.5, 142.5, 150.1, 163.7.

2,2′-Disulfanediylbis[*N*-(2,5-dimethoxyphenyl)acetamide] 19

Method 1. Thioglycolic acid (1.6 g, 17.4 mmol) and dimethoxyaniline (2.63 g, 17.2 mmol) were stirred together in dry dichloromethane (30 mL). DCC (3.64 g, 17.6 mmol) and DMAP (100 mg, 0.8 mmol) were then added to the solution and the resulting mixture stirred at room temperature for 18 h. After evaporation of the solvent, the crude product was purified by column chromatography, eluting first with dichloromethane to remove impurities higher in R_f than the product. Subsequent elution with ethanol then yielded **19** as a white solid (2.60 g, 67%): mp 129–131 °C (ethanol); IR ν_{max}/cm^{-1} 3370, 3306, 2938, 2837, 1656 cm^{-1}; ^{1}H-NMR δ_H 3.69 (s, 4H, 2 × SCH_2), 3.78 (s, 6H, 2 × OCH_3), 3.82 (s, 6H, 2 × OCH_3), 6.58 (dd, 2H, J 3.4 and J 8, 2 × 4-H), 6.84 (d, 2H, J 8, 2 × 3-H), 8.07 (d, 2H, J 3.4, 2 × 6-H), 8.57 (br s, 2H, 2 × NH); ^{13}C-NMR δ_C 44.1, 55.8, 56.3, 106.2, 108.9, 110.9, 127.8, 142.3, 153.7, 165.9; HRMS calcd. for $C_{20}H_{24}N_2O_6S_2$: 452.1076; found: 452.1085.

Method 2. 2-Chloro-*N*-(2,5-dimethoxyphenyl)acetamide (**14**) (220 mg, 0.96 mmol) was dissolved in 20% aqueous ethanol (13 mL) then sodium thiosulfate pentahydrate (250 mg, 1.00 mmol) was added to the solution which was then heated at reflux for 3 h under nitrogen. The reaction mixture was cooled to room temperature, diluted with water (5 mL) and filtered to remove any organic impurities. The filtrate was evaporated to dryness *in vacuo* and the residue extracted exhaustively with boiling ethanol. The salt (**18**) crystallized out on cooling. A second crop was obtained by concentrating the mother liquor. Combined yield—308 mg (97%).

Without further purification the thiosulfate (308 mg, 0.93 mmol) was added to 1 M HCl (20 mL). Thiourea (73 mg, 0.96 mmol) was added to the mixture which was heated at 100 °C for 3 h. The mixture was cooled to room temperature and then extracted with dichloromethane (3 × 15 mL). The combined extract was washed with water (3 × 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by column chromatography (CH_2Cl_2 : EtOAc 1 : 10) to give **19** as a white solid (76 mg, 35% overall yield from **14**).

Bromination of disulfide 19

A solution of bromine (0.51 mL, 1.58 g, 9.88 mmol) in glacial acetic acid (5 mL) was added dropwise to a cold suspension of 2,2′-disulfanediylbis[*N*-(2,5-dimethoxyphenyl)acetamide] (**19**) (1.51 g, 3.34 mmol) in acetic acid (50 mL). When the addition of bromine was complete, the mixture was stirred at room temperature for 4 h then poured into water (200 mL) and the resultant precipitate was collected by filtration, washed with water (5 × 25 mL) and then air-dried. The crude product was purified by column chromatography (dichloromethane) to give three products.

i) 2,2′-Disulfanediylbis[*N*-(4-bromo-2,5-dimethoxyphenyl)-acetamide] (20). Off-white solid (804 mg, 40%): mp 170–171 °C (ethanol) (Found: C, 39.62; H, 3.74; N, 4.46. Calc. for $C_{20}H_{22}N_2O_6S_2Br_2$: C, 39.36; H, 3.63; N, 4.59%); IR ν_{max}/cm^{-1} 3422, 3336, 2935, 2837, 1690; ^{1}H-NMR δ_H 3.63 (s, 4H, 2 × SCH_2), 3.75 (s, 6H, 2 × OCH_3), 3.78 (s, 6H, 2 × OCH_3), 6.96 (s, 2H, 2 × 3-H), 8.09 (s, 2H, 2 × 6-H), 8.42 (br s, 2H, 2 × NH); ^{13}C-NMR δ_C 44.7, 56.9, 57.2, 105.1, 105.2, 115.6, 127.4, 142.7, 150.5, 166.3.

ii) 2-Bromo-*N*-(4-bromo-2,5-dimethoxyphenyl)-2-({2-[(4-bromo-2,5-dimethoxyphenyl)amino]-2-oxoethyl}disulfanyl)-acetamide 21. Light brown solid (320 mg, 14%): mp 168–170 °C (ethanol) (Found: C, 35.29; H, 3.07; N, 3.98. Calc. for $C_{20}H_{21}N_2O_6S_2Br_3$: C, 34.85; H, 3.07; N, 4.06%); IR ν_{max}/cm^{-1} 3287, 2942, 2833, 1656; ^{1}H-NMR δ_H 3.70 (s, 2H, SCH_2), 3.76 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 5.53 (s, 1H, SCHBr), 6.97 (s, 2H, 2 × 3-H), 8.06 (s, 2H, 2 × 6-H), 8.29 (br s, 1H, NH), 8.73 (br s, 1H, NH); ^{13}C-NMR δ_C 44.6, 54.1, 56.9, 57.0, 57.2, 104.9, 105.2, 106.1, 115.6, 115.7, 126.8, 143.0, 150.5, 163.2, 165.8.

iii) 2,2′-Disulfanediylbis[*N*-(4-bromo-2,5-dimethoxyphenyl)-2-bromoacetamide] 22. (8%), obtained as a mixture with **21**.

N-(4-Bromo-2,5-dimethoxyphenyl)-2-(4′-methoxybenzyl-sulfanyl)acetamide 17

4-Methoxybenzyl alcohol (2.0 mL, 2.34 g, 16.9 mmol) and Lawesson's reagent (4.80 g, 11.9 mmol) were added to dry toluene (30 mL) and the mixture heated at reflux under nitrogen for 3 h. The reaction was cooled to 0 °C and filtered. The filtrate was evaporated *in vacuo* and the crude product added to ethanol (35 mL). Potassium carbonate (1.01 g, 7.31 mmol) and *N*-(4-bromo-2,5-dimethoxyphenyl)-2-chloroacetamide (**15**) (1.52 g, 4.92 mmol) were added to the solution and the resulting mixture heated at reflux for 6 h. The reaction mixture was cooled to room temperature, filtered to remove the K_2CO_3 and the ethanol evaporated *in vacuo*. The product was purified by column chromatography (dichloromethane : hexane 2 : 1) to

give a brownish grey solid (1.32 g, 63%): mp 87–89 °C (ethanol); IR ν_{max}/cm^{-1} 3298, 2998, 2935, 2833, 1667; ^{1}H-NMR δ_H 3.29 (s, 2H, SCH_2), 3.75 (s, 3H, OCH_3), 3.77 (s, 2H, SCH_2), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.81 (d, 2H, *J* 9, 3′-, 5-H), 7.08 (s, 1H, 3-H), 7.22 (d, 2H, *J* 9, 2′-, 6′-H), 8.19 (s, 1H, 6-H), 9.12 (br s, 1H, NH); ^{13}C-NMR δ_C 36.9, 37.0, 55.6, 56.9, 57.3, 104.8, 104.9, 114.5, 115.4, 127.7, 128.9, 130.6, 142.9, 150.5, 159.4, 167.1 (HRMS calcd. for $C_{18}H_{20}NO_4SBr$: 425.0296; found: 425.0289.

5,8-Dimethoxy-2*H*-1,4-benzothiazin-3(4*H*)-one 7b

2,2′-Disulfanediylbis[*N*-(2,5-dimethoxyphenyl)acetamide] (**19**) (1.02 g, 2.21 mmol) was dissolved in nitrobenzene (30 mL). Iodine (2.25 g, 8.86 mmol) was added to the solution and the mixture stirred vigorously to dissolve the iodine. The resulting solution was heated at 202 °C for 5–10 min. The reaction mixture was cooled rapidly under tap water then adsorbed on to a column of silica (40 : 1, SiO_2 : compound) and eluted with hexane to remove the nitrobenzene. The product was obtained by eluting with dichloromethane. Recrystallization from methanol yielded 5,8-dimethoxy-2*H*-1,4-benzothiazin-3(4*H*)-one (**7b**) as a light brown crystalline solid (525 mg, 53%): mp 148–150 °C (methanol) (Found: C, 53.11; H, 4.94; N, 6.12. Calc. for $C_{10}H_{11}NO_3S$: C, 53.32; H, 4.92; N, 6.22%); IR ν_{max}/cm^{-1} 3220, 2998, 2935, 2841, 1671; ^{1}H-NMR δ_H 3.32 (s, 2H, SCH_2), 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.43 (d, 1H, *J* 9, 7-H), 6.60 (d, 1H, *J* 9, 6-H), 7.95 (br s, 1H, NH); ^{13}C-NMR δ_C 29.4, 56.6, 56.7, 104.8, 108.4, 109.7, 126.9, 141.7, 50.5, 164.6.

N-(4-Methyl-5,8-dioxo-5,8-dihydroquinolin-6-yl)acetamide 24

2-Acetamido-5-bromo-1,4-benzoquinone (**23**) (0.761 g, 3.12 mmol) was stirred in acetonitrile (50 mL), and to this suspension was added crotonaldehyde *N*,*N*-dimethylhydrazone (450 mg, 3.98 mmol) in acetonitrile (10 mL). The reaction was stirred at room temperature for 48 h. The acetonitrile was then removed *in vacuo* and the crude product purified by column chromatography (dichloromethane) to give **24** as a green solid (346 mg, 48%): mp 232–234 °C (methanol) (Found: C, 62.49; H, 4.38; N, 12.11. Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17%); IR ν_{max}/cm^{-1} 3223, 1670, 1504; ^{1}H-NMR δ_H 2.30 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 7.44 (d, 2H, *J* 5, 3-H), 7.98 (s, 1H, 7-H), 8.34 (br s, 1H, NH), 8.86 (d, 2H, *J* 5, 2-H); ^{13}C-NMR δ_C 22.4, 25.1, 116.5, 125.7, 130.5, 140.2, 148.8, 151.0, 153.4, 169.3, 182.3, 183.7.

Reaction of methyl thioglycolate with *N*-(4-methyl-5,8-dioxo-5,8-dihydroquinolin-6-yl)acetamide 24

Method 1. *N*-(4-Methyl-5,8-dioxo-5,8-dihydroquinolin-6-yl)-acetamide (**24**) (1.25 g, 5.43 mmol) was stirred in ethanol (20 mL) at 60 °C in a round bottom flask fitted with a condenser. Methyl thioglycolate (0.49 mL, 573 mg, 5.39 mmol) was then carefully added to the warm suspension. The resulting mixture was heated at reflux for 1 h after which the heat source was removed and the reaction stirred for a further 3 h. The solvent was evaporated *in vacuo* with special care being taken to keep the temperature below 80 °C. The crude product was then purified by column chromatography (CH_2Cl_2 : EtOAc 10 : 1) to give two products.

i) Methyl {[6-(acetylamino)-5,8-dihydroxy-4-methylquinolin-7-yl]sulfanyl}acetate ***25***. Obtained as an off-white crystalline solid (0.894, 49%): mp 155–157 °C (Found: C, 53.57; H, 4.82; N, 8.27. Calcd. for $C_{15}H_{16}N_2O_5S$: C, 53.56; H, 4.79; N, 8.33%); IR ν_{max}/cm^{-1} 3340, 2991, 2927, 1735, 1637; ^{1}H-NMR δ_H 2.42 (s, 3H, CH_3), 2.95 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 3.78 (s, 2H, SCH_2), 7.16 (d, 1H, *J* 5, 3-H), 8.77 (d, 1H, *J* 5, 2-H), 9.92 (s, 1H, NH); ^{13}C-NMR δ_C 23.5, 24.1, 37.0, 53.0, 107.6, 122.9, 123.1, 125.1, 136.9, 139.7, 147.3, 148.2, 148.9, 170.8, 172.2.

ii) Methyl {[6-(acetylamino)-4-methyl-5,8-dioxo-5,8-dihydroxyquinolin-7-yl]sulfanyl}acetate ***26***. Obtained as a deep yellow solid (0.280, 15%): mp 160–163 °C (MeOH) (Found: C, 54.01; H, 4.27; N, 8.07. Calcd. for $C_{15}H_{14}N_2O_5S$: C, 53.89; H, 4.22; N, 8.38%); IR ν_{max}/cm^{-1} 3331, 3211, 1734, 1681, 1658; ^{1}H-NMR δ_H 2.29 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 3.59 (s, 3H, CH_3), 3.87 (s, 2H, SCH_2), 7.42 (d, 1H, *J* 5, 3-H), 8.19 (s, 1H, NH), 8.77 (d, 1H, *J* 5, 2-H); ^{13}C-NMR δ_C 22.3, 24.3,35.4, 52.9, 126.7, 131.1, 134.9, 141.3, 150.0, 151.2, 153.7, 168.3, 170.5, 179.8, 180.6.

One-pot Diels–Alder sulfenylation reaction

2-Acetamido-5-bromo-1,4-benzoquinone (**23**) (4.20 g, 17.2 mmol) was stirred in acetonitrile (250 mL) and crotonaldehyde *N*,*N*-dimethylhydrazone (**20**) (2.50 g, 22.1 mmol) in acetonitrile (20 mL) was added dropwise to the suspension. The mixture was stirred at room temperature for 36 h then the acetonitrile evaporated *in vacuo* to give an amorphous solid. Ethanol (100 mL) was added to the crude product followed by the careful addition of methyl thioglycolate (2.2 mL, 2.55 g, 24.1 mmol). The resulting mixture was heated at reflux for 1 hour after which it was cooled to room temperature and stirred at that temperature for a further 12 h. The solvent was removed *in vacuo* and the crude product purified by column chromatography (EtOAc : CH_2Cl_2 5 : 1) to give compound **25** (1.59 g, 27.5%), compound **26** (218 mg, 4%) and methyl [(5-hydroxy-2,9-dimethyl[1,3]oxazolo[5,4-*f*]quinolin-4-yl)sulfanyl]acetate (**27**) (520 mg, 9.5%) as a white crystalline solid (122 mg, 17.5%): mp 180 °C (Found: C, 56.53; H, 4.43; N, 8.71. Calcd. for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.80%); IR ν_{max}/cm^{-1} 3332, 3021, 2953, 1742; ^{1}H-NMR δ_H 2.74 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 3.94 (s, 2H, SCH_2), 7.35 (d, 1H, *J* 5, 3-H), 8.62 (d, 1H, *J* 5, 2-H); ^{13}C-NMR δ_C 14.8, 21.0, 35.3, 52.4, 106.4, 116.0, 123.7, 135.5, 138.8, 139.8, 142.9, 146.4, 150.6, 164.0, 170.2.

Preparation of 9-methyl-1*H*-[1,4]thiazino[3,2-*g*]quinoline-2,5,10(3*H*)-trione 4

From compound 25. Methyl {[6-(acetylamino)-5,8-dihydroxy-4-methylquinolin-7-yl]sulfanyl}acetate (**25**) (2.40 g, 7.23 mmol) was dissolved in 6 M HCl (20 mL) and the solution heated at reflux for 3 h. The heat was removed and the mixture allowed to cool to room temperature. Upon standing for 2 h at room temperature a solid precipitated out of solution. This was collected by filtration, washed with small amounts of cold water, followed by ethanol (3 × 5 mL) and then air dried to give compound **28** as the hydrochloride salt—confirmed by ^{13}C-NMR data (1.93 g, 84%): mp >250 °C; ^{1}H-NMR δ_H (CD_3OD) 3.10 (s, 3H, CH_3), 3.50 (s, 2H, SCH_2), 7.57 (d, 1H, *J* 5, 3-H), 8.54 (d, 1H, *J* 5, 2-H); ^{13}C-NMR δ_C 25.8, 30.4, 120.8, 123.5, 124.4, 130.2, 136.2, 139.2, 142.1, 161.5, 168.1.

Without further purification the salt (1.93 g, 6.09 mmol) was added to chloroform (40 mL). DCC (1.50 g, 7.27 mmol) and DMAP (1.0 g, 8.18 mmol) were then added to the suspension and the reaction mixture stirred at room temperature for 10 h. The chloroform was removed and the crude product purified by column chromatography (dichloromethane) to give **4** as a red solid (1.37 g, 86%): mp 252 °C (decomp.) (Found: C, 55.51; H, 3.31; N, 10.76. Calcd. for $C_{12}H_8N_2O_3S$: C, 55.38; H, 3.10; N, 10.76%); IR ν_{max}/cm^{-1} 3220, 2998, 1693, 1656; ^{1}H-NMR δ_H 2.75 (s, 3H, CH_3), 3.50 (s, 2H, SCH_2), 7.38 (d, 1H, *J* 5, 3-H), 8.37 (s, 1H, NH), 8.76 (d, 1H, *J* 5, 2-H); ^{13}C-NMR δ_C 22.6, 28.8, 123.2, 126.3, 131.3, 136.2, 149.2, 151.7, 153.8, 161.4, 177.3, 178.8.

(Using the above procedure, compound **27** produced thiazinone **4** in similar yield.)

From compound 26. Quinolinedione **26** (71 mg, 0.23 mmol) was dissolved in 6 M HCl (2 mL) and the solution was heated at

100 °C for 1 h. The mixture was cooled to room temperature, neutralized with solid sodium bicarbonate, then extracted with dichloromethane (3 × 5 mL). The combined organic layer was washed with water (2 × 5 mL), dried (Na_2SO_4), then evaporated *in vacuo*. Recrystallization from ethanol gave thiazinone **4** (42 mg, 70%).

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