Synthesis of the debrominated analog of dihydroflustramine C utilizing a sulfur ylide- initiated thio-Claisen rearrangement

Amir Sabahi and Jon D. Rainier*

Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, UT 84112, USA
E-mail: rainier@chem.utah.edu

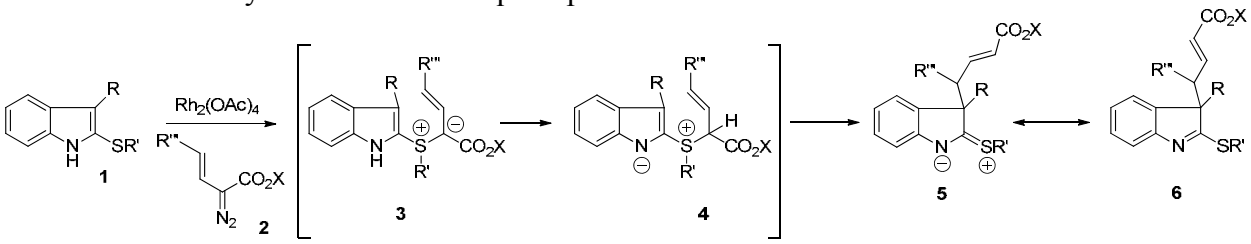
Dedicated to Bruce and Cynthia Maryanoff for their invaluable contributions to Organic Chemistry

Abstract
In investigating the scope and limitations of the sulfur ylide initiated thio-Claisen rearrangement developed in our laboratory, we have been able to efficiently synthesize highly functionalized pyrroloindoline ring systems. This functionality is present in a variety of natural and non-natural products and here we report our synthesis of the debrominated analog of dihydroflustramine C.

Keywords: Sulfur ylide, flustramine, rearrangement, synthesis

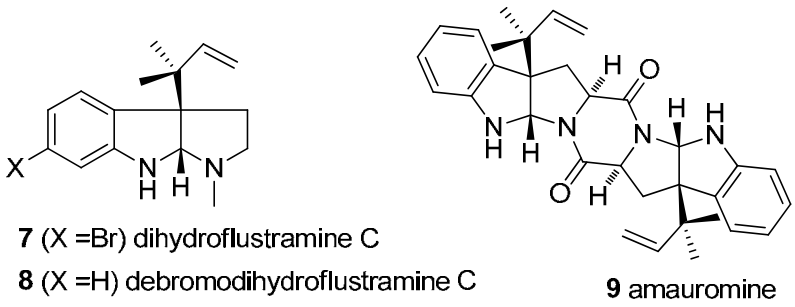
Introduction

The presence of vicinal C(3) quaternary substitution in a variety of indoline- containing natural and non-natural products has inspired a number of groups, including ours, to develop new and improved routes to their synthesis.[1,2,3,4] Our entry into this area is a result of our discovery that C(3) quaternary substituted indolines **6** can be generated from the coupling of 2-thioindoles **1** with vinyl diazoacetates **2** in the presence of Rh(II) catalysts (Scheme 1).[5] We have proposed that **6** results from a [3,3]-sigmatropic rearrangement of the charge separated ion pair **4** that comes from sulfur ylide **3** and a subsequent proton transfer.[6,7]



Scheme 1

Having a route to highly substituted indolines, we became intrigued with the possibility of applying it to the synthesis of indoline containing natural products.[8,9] Among the numerous possibilities, it occurred to us that pyrroloindolines of the dihydroflustramine C and amauromine class might come from relatively straightforward manipulations of the product from the sulfur ylide reaction. We now report our initial work in this area and the synthesis of the debrominated analog of dihydroflustamine C.

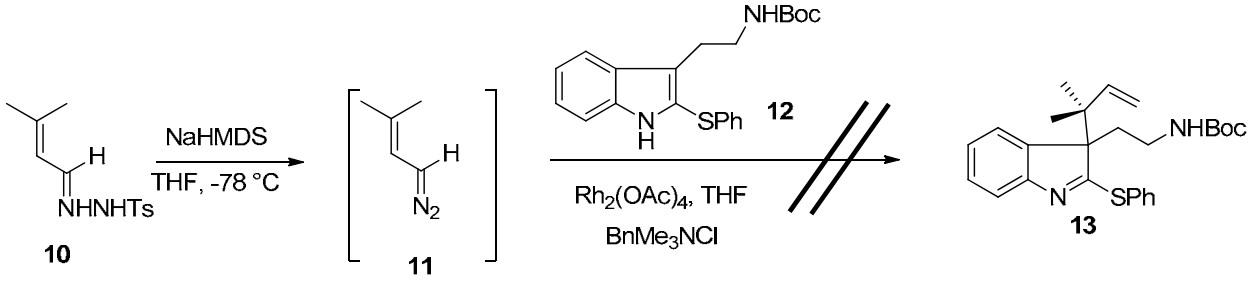


7 (X =Br) dihydroflustramine C
8 (X =H) debromodihydroflustramine C
9 amauromine

Figure 1

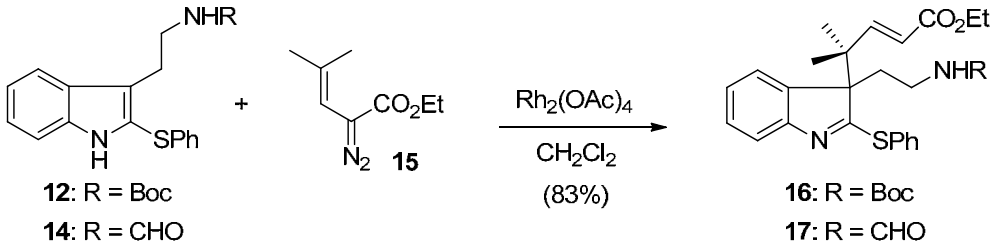
Results and Discussion

Our initial plan was to generate the indoline precursor to **8** directly from the coupling chemistry of unsubstituted vinyldiazo substrate **11** with 2-thiotryptamine (Scheme 2). Although Aggarwal had previously used **11** in the generation of sulfur ylides,[10] in our hands the coupling of 2-thiotryptamine **12** with **11** resulted only in the recovery of starting material.



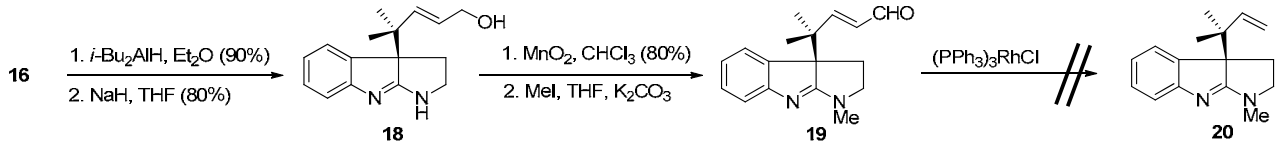
Scheme 2

Having failed in the direct coupling to the flustramines using **11**, we turned to a more circuitous path and vinyl diazoacetate **15** whose use would require the decarboxylation of the ester after coupling. To this goal, we utilized both Boc- and formamide- protected tryptamines **12** and **14**, respectively, in the reaction with **15** giving vicinal quaternary substituted indolines **16** and **17**, each in 83% yield.



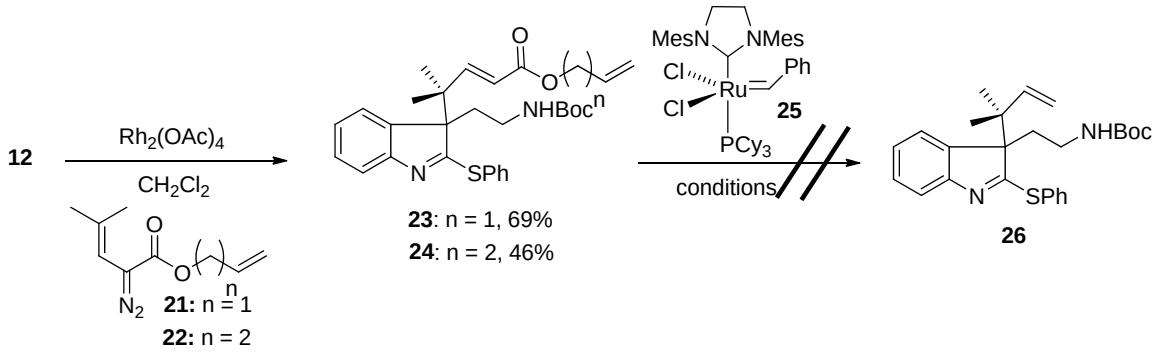
Scheme 3

With **16** and **17** in hand, we opted to initially examine the use of a decarbonylation strategy to convert them into the requisite terminal alkene needed for the synthesis of dehydroflustramine C.[11] Reduction of **16** using *i*-Bu_2AlH gave the corresponding allylic alcohol in 90% yield. While generally stable to a variety of conditions such as the *i*-Bu_2AlH reduction and hydrolysis, we have found thio-imides such as **16** and **17** to be susceptible to reactions with internal nucleophiles. For example, pyrrole **18** was formed in 80% yield when the amine from **16** was treated with NaH. Interestingly, these conditions also resulted in the removal of the Boc group. Oxidation of the allylic alcohol and methyl amine formation gave decarbonylation precursor **19**. Unfortunately, the attempted decarbonylation of **19** using Wilkinson's catalyst was unsuccessful in our hands.



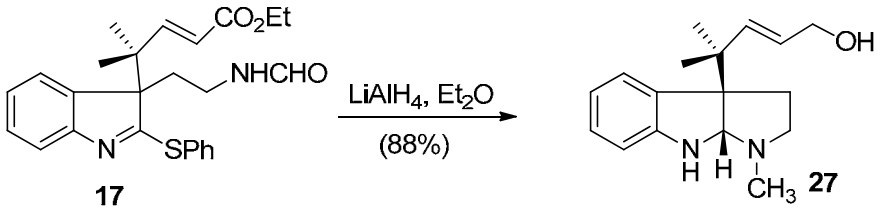
Scheme 4

We next explored a metathesis strategy to the requisite alkene (Scheme 5). We envisioned that the incorporation of an olefin into the vinyldiazoester coupling precursor would give the desired product after ring-closing metathesis (RCM).[12] With this as a goal, the $Rh_2(OAc)_4$ catalyzed coupling of **12** with vinyl diazoacetates **21** and **22** gave indolines **24** and **25**, respectively. Unfortunately, all attempts at RCM using the 2nd generation Grubbs catalyst **26** were completely unsuccessful here.



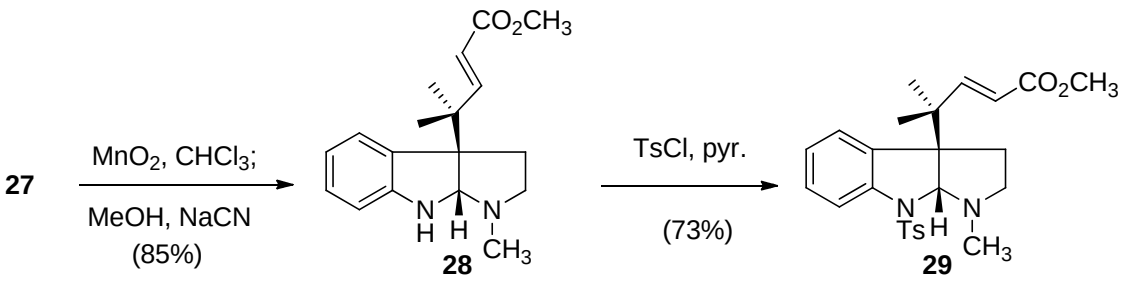
Scheme 5

Our lack of success in the decarbonylation and metathesis approaches to the terminal olefin directed our attention to an oxidative fragmentation strategy. If this were successful, a subsequent Wittig reaction would deliver the desired material. Of note was that a similar sequence had been employed by Crich during his syntheses of debromoflustramine B and pseudophyryaminol.[12] With the Crich precedent in mind, we became interested in carrying out the oxidative fragmentation chemistry on pyrrolo-indoline **27** whose synthesis in a single step from the reaction of **17** with $LiAlH_4$ is illustrated in Scheme 6. This highly efficient reaction involved the reduction of the ester and formamide, along with a subsequent cyclization and reduction of the resulting amidine.



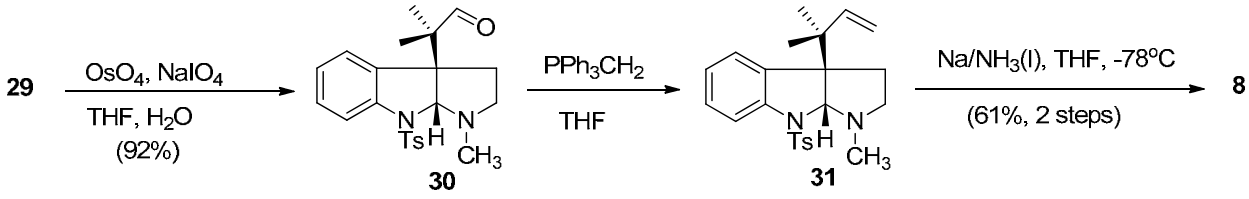
Scheme 6

As with the decarbonylation and RCM chemistry, our attempts to cleave the alkene directly from **27** (or the corresponding *N*-tosyl derivative of **27**) using oxidative conditions (OsO_4, $NaIO_4$ or O_3) were unsuccessful. We next turned to α,β-unsaturated ester **29**. The conversion of **27** into ester **28** was accomplished in a two step, single flask operation by first oxidizing **27** using MnO_2 in $CHCl_3$, concentrating the reaction mixture, dissolving the resulting residue containing the aldehyde corresponding to **27** in MeOH, and adding NaCN and additional MnO_2 (Scheme 7). In our hands this was superior to the direct oxidation of **27** using the Corey procedure (MnO_2, NaCN, MeOH).[13] Subsequent to oxidation, the free aminal nitrogen was converted into the corresponding N-tosyl amine derivative **29** in 73% yield.



Scheme 7

While **30** proved to be amenable to oxidative cleavage using OsO_4 and $NaIO_4$, long reaction times and stoichiometric amounts of OsO_4 were required. Aldehyde **31** was converted into (±)-debromodihydroflustramine C in 61% overall yield following Wittig olefination and removal of the N-tosyl group (Scheme 8).



Scheme 8

Conclusions

In summary, when coupled with reductive cyclization reactions, sulfur ylide rearrangements lead to the efficient generation of pyrroloindolines. We have shown that these reactions can be used to synthesize debromodihydroflustamine C. Further studies to utilize sulfur ylide rearrangements are ongoing.

Experimental Section

General. Di-ethyl ether (ether), THF, benzene, and toluene were distilled from sodium/benzophenone, and CH_2Cl_2, NEt_3, DMSO, MeOH, and CH_3CN were distilled from CaH_2. All other reagents were used without purification unless otherwise stated. All reactions were run under an atmosphere of nitrogen. NMR spectra were recorded on the VXL-300, Unity-300, VXR-500 or Inova-500 spectrometers. Chemical shifts were reported in δ, part per million (ppm), relative to chloroform (δ = 7.24 ppm) or CH_2Cl_2 (δ = 5.26 ppm) as an internal standard unless otherwise stated. Mass Spectra were recorded at the Mass Spectrometry facility in the

Department of Chemistry at the University of Utah. IR spectra were recorded on a Nicolet Impact 400.

***N*-[2-[(2-Phenylthio)-(1*H*-indol-3-yl)]ethyl)]-formamide 14.** To a solution of Ac_2O (0.59 mL) and HCO_2H (0.63 mL) at RT, was added tryptamine (0.60 g, 3.1 mmol). The reaction mixture was stirred for 24 h and then the reaction was quenched by diluting it with H_2O (100 mL). K_2CO_3 was added until the mixture had a pH of 10. The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL) and dried (Na_2SO_4). Concentration gave a crude mixture which was used in the next experiment without additional purification.

To a solution of the formamide from above in CH_2Cl_2 (4.5 mL) at 0 ºC was added a solution of PhSCl (430 mg, 2.9 mmol) in CH_2Cl_2 (2 mL) dropwise via a syringe pump over 1 h. The reaction mixture was stirred for an additional 12 h. Concentration and purification by flash column chromatography (1:2 hexanes: ethyl acetate) afforded 0.87g (95%) of thioindole **15** as a colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.85 (s, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.25-7.06 (m, 7H), 5.63 (bs, 1H), 3.51 (t, *J* = 6.4 Hz, 2H), 3.08 (t, *J* =6.8 Hz, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 161.6, 137.8, 137.7, 129.7, 127.4, 127.3, 126.6, 124.1, 124.0, 120.5, 120.4, 119.7, 111.8, 38.9, 25.4. LRMS Calc. for $C_{17}H_{16}N_2OS$ (MH^+) 297.1. Found 297.1.

(±)-4-[3-[2-Formyl-amino]ethyl]-2-[phenylthio)-3*H*-indol-3-yl]-4-methyl-, ethyl ester 17. To a stirring solution of **14** (270 mg, 0.90 mmol) and $Rh_2(OAc)_4$ (40 mg, 0.09 mmol) in CH_2Cl_2 (60 mL) at RT, was added a solution of **15** (450 mg, 2.7 mmol) in CH_2Cl_2 (6 mL) dropwise over 3 h via syringe pump. After the addition was complete, the reaction was stirred for an additional 12 h. Concentration and purification by flash column chromatography (1:2 hexanes: ethyl acetate) afforded a green oil. The green oil was washed with water (25 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were dried (Na_2SO_4) and concentrated to give 0.32 g (83%) of the indoline **17** as a colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.91 (s, 1H), 7.67-7.63 (m, 2H), 7.42 (m, 2H), 7.32-7.12 (m, 5H), 5.83 (d, *J* = 16.1 Hz, 1H), 5.38 (bs, 1H), 4.21 (q, *J* = 7.3 Hz, 2H), 2.82-2.76 (m, 1H), 2.52-2.46 (m, 1H), 2.37-2.23 (m, 2H), 1.3 (t, *J* =7.3 Hz, 3H), 1.20 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 183.2, 166.7, 161.1, 155.2, 153.4, 139.1, 134.8, 129.6, 129.5, 128.7, 128.5, 124.4, 124.2, 121.1, 119.8, 68.5, 60.7, 41.1, 34.3, 32.1, 22.9, 22.6, 14.4; IR 3295, 3062, 2977, 2873, 2246, 1673, 1512, 1458 cm^{-1}; LRMS Calc. for $C_{25}H_{28}N_2O_3S$ (MH^+) 437.2. Found 437.2.

(±)-3-(1,1-Dimethyl-4-hydroxy-butenyl)-8,8a-dihydro-pyrroloindoline 27. To a solution of the indoline (**17)** (280 mg, 0.64 mmol) in Et_2O (58 mL) at 0 ºC was added $LiAlH_4$ (490 mg, 12 mmol) in two portions over 0.5 h. The reaction mixture was warmed to RT over 24-48 h, then cooled to 0 ºC and the reaction was quenched by treating the mixture sequentially with H_2O, 1*M* NaOH, and H_2O (0.231 mL H_2O, 0.231 mL 1*M* NaOH, 0.693 mL H_2O). Filtration and concentration gave 150 mg of crude **27** as a clear oil which was used without further purification. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.12 (d, *J* = 8.3 Hz, 1H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 5.85 (d, *J* = 15.5 Hz, 1H), 5.61 (dt, *J* = 16.1 and 7.3 Hz, 1H), 5.34 (s, 1H), 4.43 (s, 1H), 4.00 (d, *J* =10.0 Hz, 2H), 2.62-2.58 (m, 1H), 2.45-2.38 (m, 1H), 2.35

(s, 3H), 2.31-2.26 (m, 1H), 1.85-1.81 (m, 1H), 1.12 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ 151.8, 138.3, 134.0, 128.9, 128.2, 125.7, 118.5, 109.1, 84.1, 65.2, 63.8, 53.6, 40.9, 36.8, 35.3, 23.9, 23.3. LRMS Calc. for $C_{17}H_{24}N_2O$ (MH^+) 273.2. Found 273.2.

(±)-3-(1,1-Dimethyl-4-methylcarboxy-butenyl)-8,8a-dihydro-pyrroloindoline 28. To a solution of **27** (130 mg, 0.50 mmol) in $CHCl_3$ (58 mL) at RT was added MnO_2 (1.3 g, 15 mmol). After 12 h, the reaction mixture was concentrated and diluted with MeOH (58 mL). To this mixture was added MnO_2 (1.3 g, 15 mmol) and NaCN (36 mg, 0.74 mmol). The resulting mixture was stirred for an additional 12 h, concentrated, diluted with CH_2Cl_2 (10 mL), filtered through Celite, and concentrated. Purification by flash column chromatography (6:1 CH_2Cl_2:MeOH) afforded 130 mg (87%) of ester **28** as a clear oil. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.14 (d, *J* = 8.3 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 7.03 (t, *J* = 7.3 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 6.57 (d, *J* = 15.5 Hz, 1H), 5.80 (dt, *J* = 16.1 and 7.3 Hz, 1H), 4.35 (s, 1H), 3.73 (s, 3H), 2.57-2.51 (m, 2H), 2.37 (s, 3H), 2.28 (dt, *J* = Hz, 1H), 1.86 (dt, *J* = Hz, 1H), 1.11 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ 167.3, 155.7, 151.3, 133.2, 128.1, 125.4, 119.5, 118.3, 108.9, 84.5, 64.3, 54.1, 51.5, 41.9, 36.9, 35.2, 22.9, 22.6. LRMS Calc. for $C_{18}H_{24}N_2O_2$ (MH^+) 301.2. Found 301.2.

(±)-3-(1,1-Dimethyl-4-methylcarboxy-butenyl)-8-tosyl-8a-hydro-pyrroloindoline 29. To a solution of ester **28** (11 mg, 0.038 mmol) in pyridine (2 mL) at RT was added tosyl chloride (72 mg, 0.38 mmol). The reaction mixture was stirred for 12 h and then concentrated. Purification by flash column chromatography (2:1 hexanes: ethyl acetate) afforded 13 mg (73%) of tosyl aminal **29** as clear oil. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 3H), 7.12 (d, *J* = 16.1 Hz, 1H), 7.08 (d, *J* = 6.8 Hz, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 5.69 (d, *J* = 14.6 Hz, 1H), 5.18 (s, 1H), 3.73 (s, 3H), 2.75-2.71 (m, 1H), 2.62 (s, 3H), 2.36-2.31 (m, 1H), 2.34 (s, 3H), 2.28-2.22 (m, 1H), 1.73 (dd, *J* = 4.9 and 8.8 Hz, 1H), 0.63 (s, 6H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 167.4, 154.7, 144.9, 143.3, 137.0, 135.6, 130.1, 128.8, 128.0, 126.0, 124.2, 120.6, 115.2, 88.8, 64.5, 53.0, 52.0, 41.7, 37.6, 36.1, 23.4, 22.8, 21.8; LRMS Calc. for $C_{25}H_{30}N_2O_4S$ (MH^+) 455.2. Found 455.4.

(±)-3-(1,1-Dimethyl-2-propenyl)-8-tosyl-8a-hydro-pyrroloindoline 31. To a stirring solution of **29** (4.7 mg, 0.010 mmol) in THF (1 mL) and H_2O (1 mL) at RT was added OsO_4 (0.13 μL, 0.16 *M* in THF) and $NaIO_4$ (22 mg, 0.10 mmol). The reaction mixture was stirred for one week before being diluted with H_2O (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), the extracts were dried (Na_2SO_4), and concentrated. Purification by flash column chromatography (2:1 hexanes: ethyl acetate) afforded 3.6 mg (92%) of the aldehyde **30** as a clear oil.

To a solution of the aldehyde **30** in THF (1 mL) was added Ph_3PCH_2 until no starting material was present by TLC. The reaction mixture was quenched with H_2O (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The extracts were dried (Na_2SO_4) and concentrated. Purification by flash column chromatography (2:1 hexanes: ethyl acetate) afforded 2.6 mg (72%) of terminal alkene **31** as clear oil. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 7.3 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 6.98 (t, *J* =

8.3 Hz, 1H), 5.83 (dd, *J* = 6.4, 8.7 Hz, 1H), 5.18 (s, 1H), 4.91 (d, *J* = 10.2 Hz, 1H), 4.83 (d, *J* = 16.1 Hz, 1H), 2.71 (t, *J* = 6.8 Hz, 1H), 2.62 (s, 3H), 2.36-2.31 (m, 1H), 2.35 (s, 3H), 2.28-2.24 (m, 1H), 1.85 (dd, *J* = 4.9, 8.8 Hz, 1H), 0.71 (s, 3H), 0.61 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 144.9, 144.7, 143.2, 137.1, 136.5, 130.0, 128.5, 128.1, 126.2, 123.9, 115.0, 113.7, 89.1, 64.6, 53.1, 41.4, 37.6, 35.9, 23.6, 23.1, 21.7; LRMS Calc. for $C_{23}H_{28}N_2O_2S$ (MH^+) 397.2. Found 397.2.

Synthesis of (±)-debromo-dihydroflustramine C 8

To a stirring solution of **31** (2.8 mg, 0.0070 mmol) in THF (0.5 mL) and NH_3 (5 mL) at -78 ºC was added Na metal until the mixture turned dark blue. At this point the reaction mixture was allowed to stir for an additional 10 min. Solid NH_4Cl was added to the reaction mixture, and it was warmed to RT and diluted with H_2O (5 mL). The aqueous phase was extracted with ethyl acetate (3x10 mL), the extracts were dried (Na_2SO_4) and concentrated. Purification by flash column chromatography (6:1 CH_2Cl_2:MeOH) afforded 1.5 mg (85%) of **8** as a clear oil. ^{1}H-NMR spectra and LRMS data were in good agreement with Aiko and Wright's data.[8] ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 7.3 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.70 (t, *J* = 7.6 Hz, 1H), 6.59 (d, *J* = 7.8 Hz, 1H), 6.00 (dd, *J* = 10.7, 17.6 Hz, 1H), 5.08 (d, *J* = 10.7, 1H), 5.03 (d, *J* = 17.6 Hz, 1H), 4.38 (s, 1H), 2.61-2.54 (m, 2H), 2.41 (s, 3H), 2.31 (dt, *J* = 6.8 and 12.2 Hz, 1H), 1.87 (dt, *J* = 5.4 and 12.2 Hz, 1H), 1.08 (s, 3H), 1.00 (s, 3H). LRMS Calc. for $C_{16}H_{22}N_2$ (MH^+) 243.2, Found 243.3.

Acknowledgements

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