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TOTAL SYNTHESIS OF AMAUROMINE

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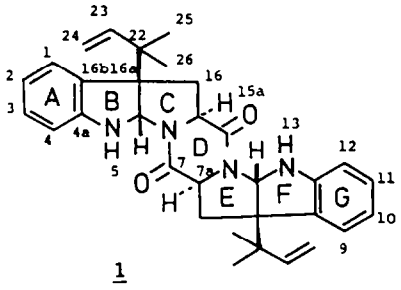
Abstract - A total synthesis of amauromine (1) is described. Starting with L-tryptophan, diketopiperazine 4 was synthesized in nine steps. Thio-Claisen rearrangement of the sulphonium cation derived from the key intermediate 4 proceeded at the two sites simultaneously to provide 3 along with 12. Reductive desulphurization on 3 using $TiCl_4$-$LiAlH_4$ (1:2) resulted in concurrent cyclization to lead to amauromine (1).

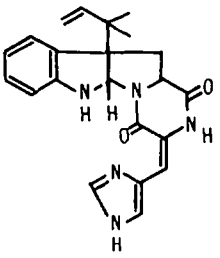
As described in the preceding paper[1], amauromine (1) is a dimeric alkaloid recently discovered from microbial origin. The new alkaloid 1 seems to attract considerable interest for synthetic chemists because of its structural uniqueness[2] and the biological activity[3] as a vasodilator. Preceding to the synthetic study of this natural product 1, we succeeded in synthesis[1] of a model compound, i.e. debromo-8,8a-dihydroflustramine C[4] utilizing thio-Claisen rearrangement through a sulphonium cation at the key stage. Essentially based on the methodology used in the model synthesis, we achieved the first total synthesis of amauromine, the synthetic course of which might be partly along the biosynthesis of the alkaloid 1. In this report, we describe a full account of this synthesis of 1, which is preliminarily communicated[5].



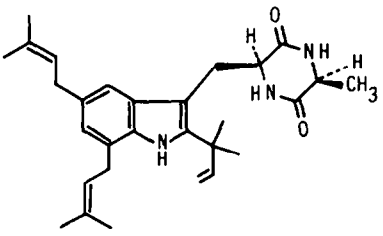
1

The group of the indole alkaloids possessing the reversed prenyl substituent at the position 3 and the position 2 of the indole nucleus has been rapidly expanding[6]. The mechanism of the introduction of the 1,1-dimethyl-2-propenyl group in vivo into those alkaloids seems to be still controversial, although several biosynthetic studies[7] on roquefortine and on echinulin have been reported recently.

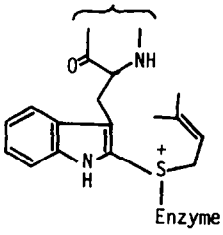
As remarked in the preceding paper[1], Bycroft and Landon[8] developed a new type of thio-Claisen rearrangement reaction of 2-indolyl sulphonium cation, which is parallel to the hypothetical enzyme-participated intermediate 2 in their biosynthetic consideration. The success of the synthesis of a model compound for amauromine, debromo-8,8a-dihydroflustramine C, by application of this new rearrangement reaction urged us to plan a synthesis of amauromine (1), by use of



Roquefortine



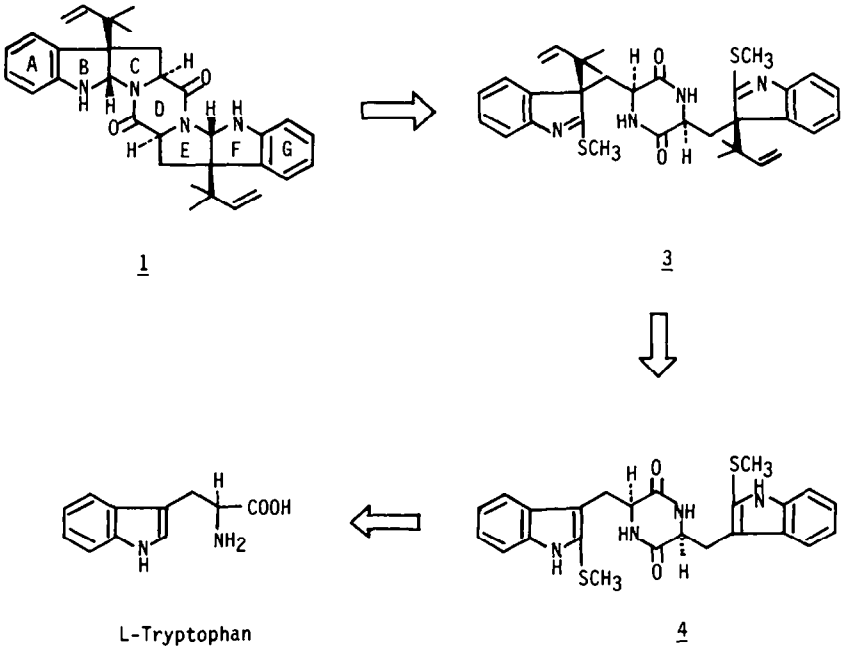
Echinulin



2

the thio-Claisen rearrangement reaction through a sulphonium salt for introduction of 1,1-dimethyl-2-propenyl group into 8a,16a-positions of 1 and by use of L-tryptophan, a probable biosynthetic origin, as the starting material. Under the consideration of the remarkable structural feature of 1 that a C_2 symmetry axis exists on the center of the diketopiperazine ring, a convergent synthetic route outlined retrosynthetically in Scheme 1 was designed. Thus, our approach is to effect the key rearrangement reaction on the C_2 symmetrical diketopiperazine 4 at the two sites simultaneously, followed by successive stepwise substitutive cyclization and reduction or by direct reductive cyclization on 3 toward construction of the seven rings 1.

N^{α}-Benzyloxycarbonyl-L-tryptophan was oxidized to oxindole 5 by DMSO-conc HCl[9] and subsequent treatment of 5 with 10% methanolic hydrogen chloride gave the methyl ester 6. The methylthio function at position 2 of indole skeleton was introduced by refluxing of 6 with phosphorus pentasulfide in pyridine, followed by methylation of the resulting 2-thione with methyl iodide in acetone in the



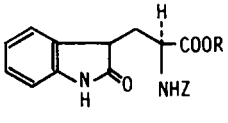
1 3

L-Tryptophan 4

Scheme - 1

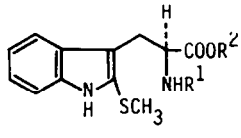
presence of potassium carbonate to lead to 7*. The methyl ester of 7 was hydrolized with NaOH in THF-MeOH-H_2O to the carboxylic acid 8, while the benzyloxycarbonyl (Z) group of 7 was cleaved by treatment with 30% HBr-AcOH to the amine 9, both quantitatively. From thus prepared 2-methylthio-L-tryptophan derivatives 8 and 9, synthesis of the key intermediate 4 was achieved as follows. The active ester derived from 8 by DCC-HOSu was coupled with amine 9 at room temperature to provide the dipeptide 10 in 52% yield, the Z-group of which was removed by treatment with 30% HBr-AcOH. The resulting amine 11 was dissolved in dry methanol and then saturated with dry ammonia gas at 0°C. Standing for 4 hour at room temperature resulted in formation of the diketopiperazine 4 bearing a C_2 symmetry axis, in the yield of 71%.

Two inverted prenyl groups could be introduced to 4 simultaneously by the thio-Claisen rearrangement reaction through the sulphonium salt. A mixture of 4, prenyl bromide and anhydrous potassium carbonate was stirred in dioxane at room temperature for 7 days under argon atmosphere. The reaction products, which revealed 3 spots on TLC, were purified by medium pressure liquid chromatography, eluted with chloroform-methanol (200:3) to give 3 fractions. Rf values on TLC (chloroform-methanol 20:1) of fraction I, II and III are 0.55, 0.40 and 0.35, respectively. Although fraction II was a inseparable mixture by further purification using preparative TLC or HPLC, repurification of fraction I and III by preparative TLC on silica gel developed with ethyl acetate afforded single compounds 3 (18%) and 12 (15%), respectively. At this stage, the stereochemistry of these products was not known, even though both compounds were shown to have C_2 symmetry from measurement of their specific rotations, ^1H NMR and mass spectra. Unequivocal determination of stereochemistry of 3 was achieved after the success of its transformation into tetrahydroamauromine (14)[2]. Thus, 3 was subjected to catalytic reduction over PtO_2 to convert to the tetrahydro derivative 13, which



5 R=H

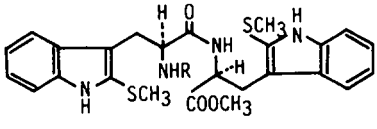
6 R=CH_3



7 R^1=$COOCH_2C_6H_5$, R^2=CH_3

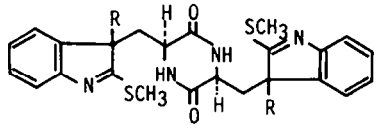
8 R^1=$COOCH_2C_6H_5$, R^2=H

9 R^1=H, R^2=CH_3



10 R=$COOCH_2C_6H_5$

11 R=H

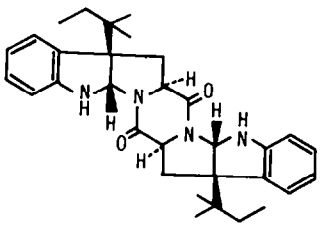


12 R=

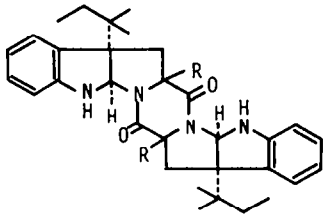
13 R=

*In contrast to the instability of the corresponding 2-methylthioindole derivative in the preceding synthesis of the model compound[1], the compound 7 was stable enough to isolate.

was treated with deactivated Ra-Ni in refluxing acetone for 70 min. This reductive desulfurization was accompanied by cyclization to give the compound all identical with 14 in 41% yield. Through the same reaction sequences as above, compound 12 was transformed to 15, a diastereomer of 14. On treatment with sodium carbonate in refluxing methanol, 15 was changed into 16, the antipode of tetrahydroamauromine (14). Accordingly, the stereochemistry of 12 was also established.



14



15 R= ···H

16 R= ◀ H

The stage was now set for the critical conversion of the key precursor 3 into amauromine 1 keeping the inverted prenyl groups intact. Abstraction of amide hydrogen of the diketopiperazine in 3 by sodium hydride, which is the method used for the synthesis[1] of model compound, debromo-8,8a-dihydroflustramine C, did not give any cyclized products. Although other attempts to activate the thio methyl function as leaving group were unsuccessful, the combined use of titanium tetrachloride and lithium aluminium hydride[10] on 3 effected reductive desulphurization concurrent with cyclization without destruction of the inverted prenyl function to afford compound 1 in 15% yield, which was identical with amauromine in all respects : synthetic: $[\alpha]_D^{23}$ -581° (c=0.65, $CHCl_3$); natural: $[\alpha]_D^{23}$ -583° (c=1.0, $CHCl_3$). Since the specific rotation value of the synthetic sample was in accord with that of the natural amauromine, it is understood that no epimerization occured during the present synthesis.

The fact that a total synthesis of amauromine has been achieved by way of the thio-Claisen rearrangement of sulphonium cation at a moderate reaction condition as descrived above, might promote the possibility of the earlier Bycroft's hypothesis on the mode of introduction of the inverted isoprene unit in vivo into related indole alkaloids.

EXPERIMENTAL

^1H NMR spectra were measured at 60 MHz (Jeol JNM-PMX 60), 100 MHz (Jeol MH-100) or 270 MHz (Jeol JNM FX270) and ^{13}C NMR spectra at 67.8 MHz (Jeol JNM FX270) as indicated. IR spectra were recorded on a JASCO A-102 infrared spectrometer. Optical rotations were measured with a JASCO DIP-140 polarimeter, using a 10 cm-microcell. Low-resolution and high-resolution electron impact mass spectra (HRMS) were obtained on a Jeol JMS-D300 mass spectrometer. Medium pressure LC was performed by using Lobar pre-packed column (Merck), F. M. I. pump and UV detector UVILOG-10V (Yamazen). Column chromatography was performed with Merck silica gel (Art 7734) and preparative TLC with pre-coated silica gel plates (Merck, Art 5744).

(S)-2-Benzyloxycarbonylamino-3-((RS)-2-oxo-3-indolinyl)propanoic acid (5).

N $^{\alpha}$-Benzyloxycarbonyl-L-tryptophan (50 g, 0.15 mole) was dissolved in dimethylsulfoxide (105ml), and conc HCl (250ml) was added in one batch with stirring. The mixture was stirred for 30min at ambient temperature and then

diluted with water and extracted with ethyl acetate (x3). The combined organic solution was washed with water, brine, dried over magnesium sulfate and evaporated under reduced pressure to give 29 g (55%) of 5 as a colorless powder: IR (KBr) 3500-2800, 1720-1680, 1620, 1520, 1230, 1050 cm^{-1}; ^1H NMR (60MHz, DMSO-d_6-D_2O) δ 7.30 (5H,s), 7.33-6.50 (4H,m), 5.03 (2H,s), 4.25 (1H,m), 3.40 (1H,m), 2.20-1.80 (2H,m); MS m/z 354 (M^+).

Methyl (S)-2-benzyloxycarbonylamino-3-[(RS)-2-oxo-3-indolinyl]propanoate (6). Compound 5 (18 g, 0.05 mole) was dissolved in anhydrous 10% methanolic hydrogen chloride solution (200ml) and the solution was allowed to stand overnight at room temperature. The solution was evaporated to dryness under reduced pressure to give an oil which was dissolved in dry methanol and the solution was concentrated to dryness under reduced pressure to leave 18 g (96%) of 6 as an oil. The product 6 was proved to be a epimeric mixture at position 3 of oxindole moiety as judged from NMR analysis. IR ($CHCl_3$) 3450, 3250, 1720-1700, 1620, 1520, 1220, 1050 cm^{-1}; ^1H NMR (100MHz, $CDCl_3$) δ 9.20 (0.5H,s,exchangeable), 9.02 (0.5H,s,exchangeable), 7.34 (2.5H,s), 7.30 (2.5H,s), 7.40-6.70 (4H,m), 6.34 (0.5H,d,J=8Hz,exchangeable), 6.10 (0.5H,d,J=8Hz,exchangeable), 5.08 (1H,s), 5.00 (1H,s), 4.65 (1H,m), 3.70 (1.5H,s), 3.67 (1.5H,s), 3.50 (1H,m), 2.50-2.20 (2H,m); MS m/z 368 (M^+).

Methyl (S)-2-benzyloxycarbonylamino-3-(2-methylthio-3-indolyl)propanoate (7). Phosphorus pentasulfide (5.8g) was added to a solution of 6 (18g) in pyridine (116ml) and the mixture was refluxed for 3 hr with stirring under argon atmosphere. The solvent was removed under reduced pressure to leave a residue which was diluted with cold water. The mixture was acidified to pH 2 and extracted with ethyl acetate (x3). The combined organic solution was washed with water, brine, dried over magnesium sulfate and evaporated to dryness to give methyl 2-benzyloxycarbonylamino-3-(2-thioxo-3-indolinyl)propanoate as a pale yellow powder. This compound was used to the next reaction without purification. To a mixture of the 2-thione and potassium carbonate (13g) in acetone (50ml) was added methyl iodide (2.2ml) and the mixture was stirred for 5 min at room temperature. Removal of the solvent gave a residue which was diluted with water, extracted with chloroform. The organic solution was washed with water, brine, dried over magnesium sulfate and evaporated under reduced pressure to give 18 g of a red oil. The oil was purified by column chromatography on silica gel (n-hexane-ethyl acetate 5:2) to afford 6.2 g (32%) of 7 as an oil: $[\alpha]_D^{23}$ +31° (c=1.0, $CHCl_3$); UV (MeOH) nm (ε) 290 (10700) and 298 (9400); IR ($CHCl_3$) 3480, 3450, 2970, 1720, 1510, 1450, 1350, 1220, 1060 cm^{-1}; ^1H NMR (100MHz, $CDCl_3$) 8.32 (1H,s), 7.54-6.92 (4H,m), 7.30 (5H,s), 5.42 (1H,d,J=8Hz), 5.07 (2H,s), 4.70 (1H,m), 3.70 (3H,s), 3.38 (2H,d,J=6Hz), 2.32 (3H,s); MS m/z 176 (base peak), 398 (M^+); HRMS m/z 398.1327 ($C_{21}H_{22}N_2O_4S$ requires 398.1302).

(S)-2-Benzyloxycarbonylamino-3-(2-methylthio-3-indolyl)propanoic acid (8). To a solution of 7 (4g) in a mixture of methanol (10ml) and tetrahydrofuran (10ml) were added 1N sodium hydroxide solution (11ml) and water (6ml) and the mixture was stirred overnight at room temperature under argon atmosphere. After removal of the organic solvent under reduced pressure, the mixture was acidified with 5% citric acid and extracted with ethyl acetate (x2). The combined organic solution was washed with brine, dried over magnesium sulfate and evaporated to dryness to give 3.8 g (99%) of 8 as an oil: $[\alpha]_D^{23}$ +14° (c=1.0, $CHCl_3$); UV (MeOH) nm (ε) 290 (11000) and 298 (9500); IR ($CHCl_3$) 3460, 3000, 1720-1710, 1510, 1450, 1340, 1220, 1060 cm^{-1}; ^1H NMR (100MHz, $CDCl_3$) δ 8.84 (1H,s,exchangeable), 8.30 (1H,s, exchangeable), 7.48 (1H,d,J=8Hz), 7.30 (5H,s), 7.35-6.90 (3H,m), 5.50 (1H,d,J=8Hz, exchangeable), 5.00 (2H,s), 4.66 (1H,m), 3.35 (2H,d,J=5Hz), 2.25 (3H,s); MS m/z 176 (base peak), 384 (M^+); HRMS m/z 384.1128 ($C_{20}H_{20}N_2O_4S$ requires 384.1142).

Methyl (S)-2-amino-3-(2-methylthio-3-indolyl)propanoate (9). To a solution of 7 (6g) in acetic acid (10ml) was added 30% hydrogen bromide-acetic acid (23ml) at 0°C and the mixture was stirred for 60min at room temperature. The reaction mixture was poured to n-hexane (500ml) and the supernatant was decanted. The resulting residue was diluted with cold aqueous 5% sodium carbonate solution. The mixture was extracted with ethyl acetate (x2) and the combined organic solution was washed with brine, dried over potassium carbonate and evaporated to dryness under reduced pressure to give 3.9 g (98%) of 9 as an oil: $[\alpha]_D^{23}$ +17° (c=1.0, $CHCl_3$); UV (MeOH) nm (ε) 290 (10500) and 298 (9400); IR ($CHCl_3$) 3470, 3370, 3000, 2960, 1730, 1440, 1340, 1280, 1220 cm^{-1}; ^1H NMR (100MHz, $CDCl_3$) δ 8.86 (1H,s,exchangeable), 7.50 (1H,m), 7.24-6.96 (3H,m), 3.88 (1H,dd,J=8 and 5Hz), 3.68 (3H,s), 3.32 (1H,dd,J=14 and 5Hz), 3.16 (1H,dd,J=14 and 8Hz), 2.32 (3H,s), 1.72 (2H,s,exchangeable); MS m/z 176 (base peak), 264 (M^+); HRMS m/z 264.0950 ($C_{13}H_{16}N_2O_2S$ requires 264.0932).

Methyl (S)-2-((S)-2-benzyloxycarbonylamino-3-(2-methylthio-3-indolyl)propanamido)-3-(2-methylthio-3-indolyl)propanoate (10). To a solution of 7 (5.3g), 8 (3.9g), N-hydroxysuccinimide (1.75g) in a mixture of ethyl acetate (100ml) and dioxane (100ml) was added dropwise at 5°C a solution of dicyclohexylcarbodiimide (2.85g) in ethyl acetate (20ml) and the mixture was stirred at room temperature overnight. Removal of the solvent gave a residue which was diluted with ethyl acetate and filtered. The filtrate was washed with 1N HCl, 5% sodium carbonate, brine, dried over magnesium sulfate and evaporated to dryness to give 11g of an oil. The oil was chromatographed on silica gel column (benzene-ethyl acetate 5:1) to give 4.5 g (52%) of 10 as an oil: $[\alpha]_D^{23}$ -10° (c=1.0, $CHCl_3$); UV (MeOH) nm (ε) 290 (20500) and 298 (17800); IR ($CHCl_3$) 3460, 3410, 3000, 1720, 1670, 1500, 1450, 1440, 1340, 1220 cm^{-1}; ^1H NMR (100MHz, $CDCl_3$) δ 8.34 (2H,s), 7.56-6.92 (8H,m), 7.34 (5H,s), 6.40 (1H,d,J=8Hz), 5.54 (1H,d,J=7Hz), 5.00 (2H,s), 4.80 (1H,m), 4.48 (1H,m), 3.52 (3H,S), 3.30-3.16 (4H,m), 2.22 (6H,s); MS m/z 176 (base peak), 630 (M^+); HRMS m/z 630.1949 ($C_{33}H_{34}N_4O_5S_2$ requires 630.1969).

Methyl (S)-2-((S)-2-amino-3-(2-methylthio-3-indolyl)propanamido)-3-(2-methylthio-3-indolyl)propanoate (11). To a solution of 10 (4.5g) in acetic acid (9ml) was added 30% hydrogen bromide-acetic acid (11ml) at 0°C and the mixture was stirred for 50min at room temperature. The mixture was poured to n-hexane (500ml) and the supernatant was decanted. The obtained gummy residue was diluted with cold 5% sodium carbonate and extracted with ethyl acetate (x2). The combined organic solution was washed with brine and dried over potassium carbonate. Removal of the solvent gave 3.3 g (93%) of 11 as an oil: $[\alpha]_D^{23}$ -16° (c=0.9, $CHCl_3$); UV (MeOH) nm (ε) 290 (19200) and 295 (17000); IR ($CHCl_3$) 3470, 3350, 3000, 1730, 1660, 1510, 1450, 1340, 1230 cm^{-1}; ^1H NMR (100MHz, $CDCl_3$) δ 8.47 (2H,s,exchangeable), 7.84 (1H,d,J=8Hz), 7.58-6.92 (8H,m), 4.94 (1H,m), 3.63 (3H,s), 3.70 (1H,m), 3.50-3.24 (3H,m), 2.86 (1H,dd,J=14 and 10Hz), 2.34 (3H,S), 2.28 (3H,s), 1.60 (2H,s, exchangeable); MS m/z 176 (base peak), 496 (M^+).

(3S,6S)-3,6-Bis((2-methylthio-3-indolyl)methyl)-2,5-piperazinedione (4). Compound 11 (3.3g) was dissolved in anhydrous methanol (100ml) and the solution was saturated with dry ammonia gas at 0°C and stored in a tightly glass-stoppered flask. After standing for 4hr at room temperature, the solution was evaporated to dryness under reduced pressure. Purification of the residue by column chromatography on silica gel (chloroform-methanol 20:1) afforded 2.2 g (71%) of 4 as a colorless powder: $[\alpha]_D^{23}$ +5° (c=0.5, AcOH); UV (MeOH) nm (ε) 290 (23600) and 298 (20400); IR (KBr) 3350, 2950, 1670, 1440, 1330, 750 cm^{-1}; ^1H NMR (270MHz, DMSO-d_6) δ 11.32 (2H,s,exchangeable), 7.86 (2H,d,J=3Hz,exchangeable), 7.33 (2H,d,J=8Hz), 7.30 (2H,d,J=8Hz), 7.14 (2H,t,J=8Hz), 7.02 (2H,t,J=8Hz), 3.99

(2H,m), 3.22 (2H,dd,J=14 and 3Hz), 2.98 (2H,dd,J=14 and 8Hz), 2.40 (6H,s); ^{13}C NMR (67.8MHz, DMSO-d_6) δ 166.5 (x2), 136.7 (x2), 129.0 (x2), 127.6 (x2), 121.6 (x2), 118.8 (x2), 118.6 (x2), 112.9 (x2), 110.6 (x2), 56.0 (x2), 30.8 (x2), 18.7 (x2); MS m/z 176 (base peak), 464 (M^+); HRMS m/z 464.1355 ($C_{24}H_{24}N_4O_2S_2$ requires 464.1342); Anal. Found: C, 61.50; H, 5.25; N, 11.87; S, 13.56. $C_{24}H_{24}N_4O_2S_2$ requires: C, 62.04; H, 5.21; N, 12.06; S, 13.80.

(3S,6S)-3,6-Bis(((R)-3-(1,1-dimethyl-2-propenyl)-2-methylthio-3H-indol-3-yl)-methyl)-2,5-piperazinedione (3) and (3S,6S)-3,6-bis(((S)-3-(1,1-dimethyl-2-propenyl)-2-methylthio-3H-indol-3-yl)methyl)-2,5-piperazinedione (12). To a solution of 4 (510 mg, 1.1 mmole) in dioxane (2ml) were added potassium carbonate (1200 mg, 8.7 mmole) and prenyl bromide (1-bromo-3-methyl-2-butene, 2.1 ml, 17.9 mmole) and the mixture was stirred for 7 days at room temperature under argon atmosphere. The reaction mixture was diluted with ethyl acetate, washed with 5% sodium hydrogen carbonate, brine and dried over magnesium sulfate. Removal of the solvent gave an oil which was purified by medium pressure LC (Lobar size C, chloroform-methanol 200:3) to give three fractions of I (Rf (chloroform-methanol 20:1) 0.55, 130mg), II (Rf 0.40, 102mg) and III (Rf 0.35, 110mg). Fraction II was a mixture inseparable by chromatographical technique. Purification of the fraction I by preparative TLC (ethyl acetate) yielded 119 mg (18%) of pure 3 as an oil: $[\alpha]_D^{23}$ -198° (c=1.0, $CHCl_3$); IR ($CHCl_3$) 3380, 2960, 1675, 1500, 1380, 1360, 920 cm^{-1}; ^1H NMR (100MHz, $CDCl_3$) δ 7.56-7.02 (8H,m), 6.06 (2H,dd,J=10.5 and 17Hz), 5.20 (2H,dd,J=10.5 and 1Hz), 5.08 (2H,dd,J=17 and 1Hz), 4.88 (2H,d,J=3Hz), 3.14 (2H,m), 2.72 (6H,s), 2.80-2.70 (4H,m), 1.08 (6H,s), 1.04 (6H,s); MS m/z 176 (base peak), 600 (M^+). The fraction III was purified by preparative TLC (ethyl acetate) to give 99 mg (15%) of pure 12 as an oil: $[\alpha]_D^{23}$ +32° (c=1.0, $CHCl_3$); IR ($CHCl_3$) 3380, 2960,1670, 1500, 1380, 1360, 920 cm^{-1}; ^1H NMR (100MHz, $CDCl_3$) δ 7.48-7.04 (8H,m), 5.96 (2H,dd,J=16 and 11Hz), 5.12 (2H,dd,J=11 and 1Hz), 5.00 (2H,dd,J=16 and 1Hz), 4.52 (2H,d,J=3Hz), 3.15 (2H,m), 2.72 (2H,d,J=16Hz), 2.60 (6H,s), 2.16 (2H,dd,J=16 and 8Hz), 1.08 (6H,s), 0.92 (6H,s); MS m/z 176 (base peak), 600 (M^+).

(3S,6S)-3,6-Bis(((R)-3-(1,1-dimethylpropyl)-2-methylthio-3H-indol-3-yl)methyl)-2,5-piperazinedione (13). Compound 3 (90mg) was dissolved in ethyl acetate (7ml) and the solution was hydrogenated over PtO_2 at 1 atm for 50min at room temperature. The mixture was filtered and the filtrate was concentrated to dryness under reduced pressure. The residual oil was purified by preparative TLC (chloroform-methanol 20:1) to give 78 mg (86%) of 13 as an oil: IR ($CHCl_3$) 3400, 2960, 1680, 1500, 1450, 1250 cm^{-1}; ^1H NMR (100MHz, $CDCl_3$) δ 7.57-7.06 (8H,m), 4.95 (2H,d,J=3Hz), 3.10 (2H,m), 2.82-2.70 (4H,m), 2.73 (6H,s), 1.43-1.13 (4H,m), 1.07 (6H,s), 1.03 (6H,s), 0.77 (6H,t,J=7Hz); MS m/z 176 (base peak), 604 (M^+).

(5aS,7aS,8aR,13aS,15aS,16aR)-8a,16a-Bis(1,1-dimethylpropyl)-5a,8,8a,13,13a,15a,16,16a-octahydropyrazino[1",2":1,5;4",5":1',5']dipyrrolo[2,3-b:2',3'-b']diindole-7,15(5H,7aH)-dione (14). To a solution of 13 (60mg) in acetone (5ml) was added Raney-Nickel (W-2, dispersed in ethanol) and the mixture was refluxed for 70min with stirring. The reaction mixture was filtered and the filtrate was concentrated to dryness to leave an oil which was purified by preparative TLC (benzene-ethyl acetate 10:1). The objective material was recrystallized from ethanol to give 21 mg (41%) of 14 which is identical with tetrahydroamauromine[2] in all respects.

(5aR,7aS,8aS,13aR,15aS,16aS)-8a,16a-Bis(1,1-dimethylpropyl)-5a,8,8a,13,13a,15a,16,16a-octahydropyrazino[1",2":1,5;4",5":1',5']dipyrrolo[2,3-b:2',3'-b']diindole-7,15(5H,7aH)-dione (15). Compound 12 (90mg) was transformed to 15 (25 mg, overall yield 33%) by the substantially similar method to that of the preparation

of 14 from 3. Compound 15: $[\alpha]_D^{23}$ +310° (c=1.0, $CHCl_3$); IR ($CHCl_3$) 3430, 2960, 1660, 1600, 1420 cm^{-1}; ^1H NMR (100MHz, $CDCl_3$) δ 7.10 (2H,d,J=8Hz), 7.00 (2H,t,J=8Hz), 6.70 (2H,t,J=8Hz), 6.28 (2H,d,J=8Hz), 5.30 (2H,s), 5.08 (2H,s,exchangeable), 4.14 (2H,t,J=8Hz), 2.72 (2H,dd,J=14 and 8Hz), 2.68 (2H,dd,J=14 and 8Hz), 1.68-1.12 (4H,m), 0.92 (6H,s), 0.88 (6H,s), 0.80 (6H,t,J=8Hz); MS m/z 512 (M^+).

(5aR,7aR,8aS,13aR,15aR,16aS)-8a,16a-Bis(1,1-dimethylpropyl)-5a,8,8a,13,13a,15a,16,16a-octahydropyrazino[1",2":1,5;4",5":1',5']dipyrrolo[2,3-b:2',3'-b']diindole-7,15(5H,7aH)-dione (16). To a solution of 15 (14mg) in methanol (2ml) was added sodium carbonate (20mg) and the mixture was refluxed for 6hr with stirring. The reaction mixture was directly applied to preparative TLC (benzene-ethyl acetate 10:1) to give 10 mg (71%) of 16 as a colorless powder: $[\alpha]_D^{23}$ +552° (c=0.5, $CHCl_3$). IR, ^1H NMR and mass spectra are superimposable on those of tetrahydroamauromine[2].

(5aS,7aS,8aR,13aS,15aS,16aR)-8a,16a-Bis(1,1-dimethyl-2-propenyl)-5a,8,8a,13,13a,15a,16,16a-octahydropyrazino[1",2":1,5;4",5":1',5']dipyrrolo[2,3-b:2',3'-b']-diindole-7,15(5H,7aH)-dione (1). Lithium aluminium hydride (51mg) was added to a mixture of titanium tetrachloride (0.08ml) and anhydrous tetrahydrofuran (20ml) and the mixture was heated under reflux for 1hr under argon atmosphere. To this mixture, a solution of 3 (100mg) in anhydrous tetrahydrofuran (5ml) was added dropwise under refluxing and the reaction mixture was further refluxed for 40min. Removal of the solvent left a residue which was purified by preparative TLC (benzene-ethyl acetate 10:1) to give 13 mg (15%) of 1 as a colorless powder: $[\alpha]_D^{23}$ -581° (c=0.65, $CHCl_3$). The IR, ^1H NMR and mass spectra of 1 are identical with those of amauromine[2,3].

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