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Singlet Oxygen in Synthesis.
Formation of *d,l*- and *meso*-Isochrysohermidin from a 3,3'-Bipyrrole Precursor.

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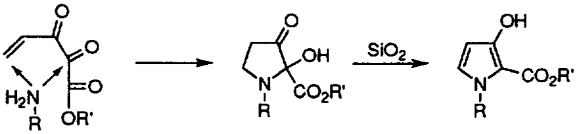
Abstract: A synthesis of the *d,l* and *meso* forms of isochrysohermidin **3** is outlined which employs the singlet oxygen oxidation of pyrroles as the key step. The bipyrrole precursor **8** was synthesized from a 3-hydroxy monopyrrole which, in turn, was prepared by addition of methylamine to a vinyl vicinal tricarbonyl.

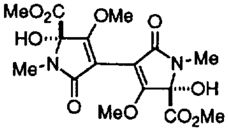
During studies on the chemistry of vicinal tricarbonyl systems we have explored the reactions of primary amines with the vinyl tricarbonyl reagent **1**, leading to substituted pyrroles **2**.[1] As shown in Scheme 1, the reaction appears to take place by tandem addition of the amine to the two electrophilic sites forming 2-hydroxy-3-pyrrolidone-2-carboxylic esters which then undergo dehydration on silica gel to form the pyrrole **2a**. 3-Hydroxypyrrole-2-carboxylates have previously been shown to be important intermediates in the synthesis of varied systems, including the natural products prodigiosin[2] and slaframine.[3] The ready availability of this heterocyclic system suggested a particularly advantageous application in the synthesis of the highly oxygenated pyrrolic plant product isochrysohermidin, isolated by Masui in *d,l* form **3a**, and later, in *meso* form **3b**, by methanolic extraction of *Mercurialis leiocarpa*.[4]

Scheme 1



1

2a, R = R' = CH_3

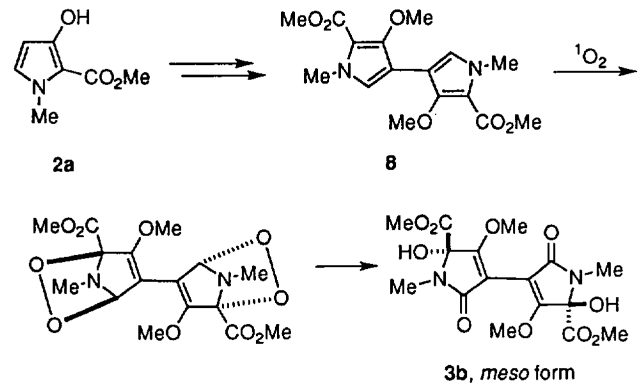


3a, *dl* form

Our synthetic strategy involved the formation of N-methyl-3-hydroxy-2-carbomethoxypyrrole (**2a**), methylation of the hydroxy group, oxidative coupling to form the 3,3'-bipyrrole **8** and then 2,5-addition of molecular oxygen in Diels-Alder fashion to form the product(s). We anticipated that both *d,l*- and *meso* products (**3a** and **3b**) would be formed depending on the facial selectivity of the oxygen uptake. Scheme 2 illustrates one such possibility, the conversion of the pyrrole **2a** by symmetrical addition of $^1O_2$ to the meso isomer **3b**. Our plan would thus make use of the well-known reactivity of electron-rich pyrroles with singlet oxygen to form 2,5-endoperoxide intermediates.[5,6]

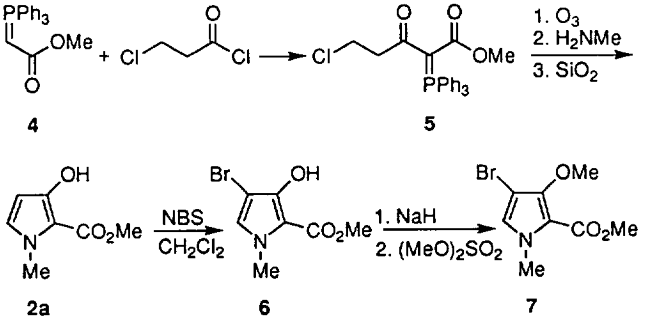
Dedicated to Professor Samuel Danishefsky on his award of the Tetrahedron Prize for Creativity in Organic Synthesis

Scheme 2



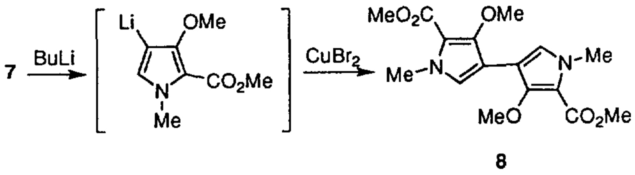
Pyrrole 2a was prepared both as a starting material for the formation of the bipyrrolic precursor and also as an intermediate for model singlet oxygen-pyrrole studies. Addition of methyl(triphenylphosphoranylidine) acetate (4) to 3-chloropropionyl chloride gave the keto-ylide carboxylate 5. Ozonolysis of 5 followed by treatment with methylamine and then dehydration with silica gel yielded hydroxypyrrole 2a. In order to form the desired bipyrrole precursor 8, we converted 2a to the 3-hydroxy-4-bromo derivative 6 with NBS in methylene chloride.[7] Treatment of 6 with sodium hydride and then dimethyl sulfate gave the bromomethoxy derivative 7 (Scheme 3).

Scheme 3



With the bromomethoxy pyrrole (7) in hand, studies of the reductive coupling of this system were undertaken. The Ullman reaction[8] of 7, using copper metal prepared in a variety of ways resulted in no observable change at temperatures up to 220 °C, with decomposition occurring above this temperature. Attempts to couple 7 using tetrakis(triphenylphosphine) nickel[9] were likewise unsuccessful, yielding only dehalogenated material. Metal/halogen exchange using butyllithium, followed by addition of copper (I) iodide gave the desired bipyrrole (8),[10] but under these conditions, large quantities of dehalogenated material were recovered. More favorably, the use of copper (II) bromide[11] along with butyllithium yielded bipyrrole 8 in 83% yield (Scheme 4).

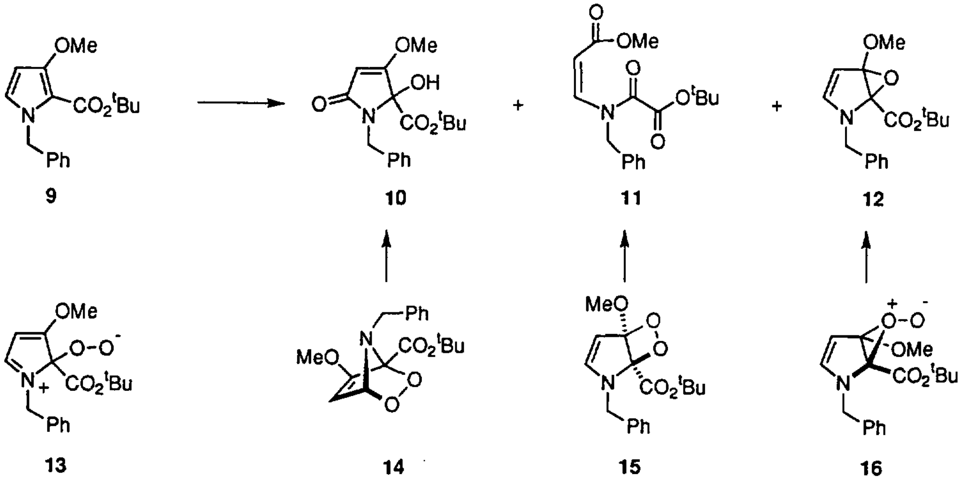
Scheme 4



The next phase of our work involved studies on the conversion of **8** to **3a** and **3b** by reaction with singlet oxygen. In order to explore the conditions for this oxidation we undertook model studies on the dye-sensitized photooxidation of the tert-butyl ester of 2-carboxy-3-methoxy-N-benzylpyrrole (**9**). In general, pyrroles bearing electron-withdrawing substituents at the 2-position react sluggishly with singlet oxygen. Alkyl substitution increases the reactivity, but the effect of a strongly electron-releasing 3-hydroxyl or 3-methoxyl substituent in the presence of a 2-carboalkoxy group was not well known.[12] We found that **9** reacts rapidly with singlet oxygen, to give a mixture of products. The photooxygenation, run in methanol at 15 °C with methylene blue as sensitizer, a 650 watt Sylvania projector lamp as the light source, and water-cooling, was complete in 4-5 minutes, yielding products (**10**) (45%), (**11**) (35%), and (**12**) (10%).[13]

We suggest that the uptake of singlet oxygen takes place through the zwitterion (**13**) which may break down through intermediates (**14**), (**15**), or (**16**) to yield the products as shown in Scheme 5. Formation of the hydroxy lactam (**10**) is in accord with the expected decomposition of an intermediate 2,5-transannular peroxide **14** by a β-elimination process. The intermediate (**15**) may be formed either by direct uptake of molecular oxygen in a 2+2 addition or by ring closure of **13**. The latter zwitterion, which may lead to **11** through the dioxetane (**15**), could also be a precursor of epoxide (**12**), through the perepoxide (**16**).

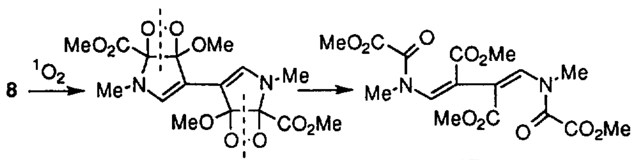
Scheme 5



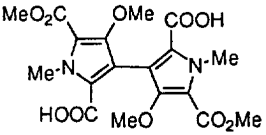
Support for the above reaction profile was found when a base was added to facilitate the β-elimination. In the presence of 10% pyridine (-20 °C, Rose Bengal), the unsaturated hydroxy lactam (**10**) was formed in greatly enhanced yield (80%). Only 10-15% of the epoxide (**12**) and trace amounts of the 2,3-cleavage product (**11**) were formed concurrently. On the other hand, in the presence of a large excess of diphenyl sulfide[14] capable of deoxygenating the peroxy intermediates (**13**), (**14**), or (**16**), the 2,3-epoxide (**12**) was generated as the main product (56%) along with **10** as the minor product (36%).

We then turned our attention to the reaction of **8** with singlet oxygen. We considered it likely that formation of the 2,5-transannular peroxide, followed by β-elimination in the presence of pyridine, would lead to both *d,l* and *meso* products (**3a** and **3b**). We found, however, that under the conditions used with the monopyrrole **9** (methanol/pyridine/Sensitox®), only 2,3-cleavage occurred. Single crystal X-ray analysis[13] established the structure of this product to be the bis-oxalamide (**17**), resulting from the formation of an intermediate dioxetane (Scheme 6). In other studies on the photooxidation of bipyrrole (**8**), we isolated the product of 2,3-cleavage in only one ring. This intermediate yielded **17** on further reaction with singlet oxygen. These results are particularly noteworthy in view of the parallel work of Boger and Baldino[15,17] where dye-sensitized photooxidation of the related bis-carboxylic acid derivative **18** in the presence of collidine yielded a *d,l/meso* mixture of the natural product.

Scheme 6



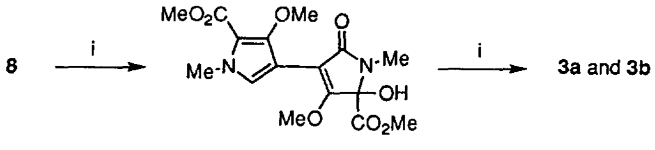
17



18

In our further work, we explored the reactions of the bipyrrole (**8**) with singlet oxygen generated under other conditions. Thus, treatment of **8** with one molar equivalent of triphenylphosphite ozonide[16] at -78 °C gave a sharp ^{1}H NMR signal at δ 2.8, characteristic of the N-CH_3 group in *d,l*-isochrysohermidin. The crude reaction mixture also contained the *meso* isomer.[21] However it was difficult to isolate pure **3a** or **3b** in the presence of the triphenylphosphate coproduct. In a more successful approach, we were able to convert the bipyrrole **8** to a mixture of *d,l* - and *meso* -isochrysohermidin (**3a** and **3b**) by an oxidation involving the reaction of dilute ozone with the bipyrrole substrate. By this procedure, in which singlet oxygen appears to be the oxidizing species (*vide infra*), a solution of methylene chloride at -78 °C was first saturated with ozone until the blue color persisted. The solution was then purged with nitrogen at -78 °C until the color was almost completely faded. The flask containing the pale blue ozone solution was then connected through a glass tube to a flask containing the bipyrrole, and nitrogen was swept for ten minutes through the dilute ozone solution into the reaction flask containing **8**. In this way, a low concentration of ozone was transferred to the bipyrrole. Removal of solvent and purification of the residue by flash chromatography yielded 42% of isochrysohermidin as a crude mixture containing both *d,l* and *meso* isomers. These products were separated by selective crystallization of the *d,l*-isomer and further purification on silica gel chromatography to isolate the *meso*-isomer. Both products were identical with the authentic compounds provided by Masui[18] and Boger.[17,18] If the introduction of the dilute ozone into the bipyrrole solution was discontinued after 5 min, one half of the bipyrrole was oxidized, yielding product **19**. Further treatment of **19** with dilute ozone gave a mixture of **3a** and **3b** (Scheme 7).

Scheme 7

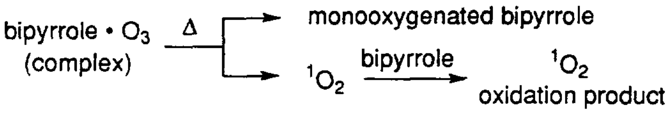


19

i = dilute O_3, CH_2Cl_2, 0 °C, 5 min

In our earlier report,[17] we suggested that singlet oxygen was swept over by nitrogen from an ozone solution containing Ph_3P or $(PhO)_3P$. This possibility, which is unlikely due to the expected rapid collisional deactivation of the $^1O_2$ in the glass tube[19] has now been ruled out by experiments in which neither triphenyl phosphine nor triphenyl phosphite were present in the dilute ozone solution. It thus appears most likely that the bipyrrole reacts with dilute ozone to form a complex (similar to the $(PhO)_3P{\bullet}O_3$ complex) capable of delivering singlet oxygen to uncomplexed bipyrrole (Scheme 8). This idea has been substantiated in recent work, to be reported separately,[20] in which we have shown that dilute ozone, generated as described above, is capable of bringing about typical singlet oxygen reactions with other heterocyclic systems such as pyrroles, oxazoles and imidazoles. With higher concentrations of ozone, the reactions with these heterocyclic systems take other oxidative pathways including extensive decomposition.

Scheme 8



We are continuing studies on the reaction of oxygen with the bipyrrole **8** in order to explain the variation of oxidation products with different reaction conditions of light, temperature, solvent, and solutes.

Experimental

General. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Bruker WM-250 or GE QE-300 spectrometer. The infrared spectra were recorded on a Perkin-Elmer 1420 or Midac M1200 (FT) spectrometer. Low resolution mass spectra were obtained on a Hewlett-Packard GC 5890II/MS 5971A system or Hewlett-Packard 5989A instrument. High resolution mass spectra were obtained on a Kratos MS-80 RFA system. All reactions were performed under an atmosphere of nitrogen unless otherwise noted.

Methyl, 5-chloro-3-oxo-2-(triphenylphosphoranylidene)pentano- ate (5). To a cold (5 °C) solution of methyl, triphenylphosphoranylidene acetate **4** (37.5 g, 0.11 mole) in benzene (500 mL) was added bis(trimethylsilyl)acetamide (47.6 mL, 0.19 mole) followed by 3-chloropropionyl chloride (10.5 mL, 0.11 mole). The reaction mixture was stirred at 5 °C for 10 min, then at rt for 30 min. The solution was washed with H_2O (200 mL x 2) and the aqueous layer was extracted with Et_2O (200 mL x 2). The combined organic layer was washed with brine (200 mL x 1), dried over $MgSO_4$, then evaporated to give a pale orange solid, which was washed with hexane (300 mL) to produce **5** (41 g, 88%) as a pale yellow solid. mp 114-115 °C (hexane/EtOAc); IR (CCl_4) 3060, 2940, 1668, 1432, 1380, 1300, 1110, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.72-7.61 (m, 6H), 7.58-7.40 (m, 9H), 3.81 (t, J = 7.9 Hz, 2H), 3.39 (t, J = 7.9 Hz, 2H), 3.16 (s, 3H); Anal. Calcd for $C_{24}H_{22}ClO_3P$: C, 67.85; H, 5.22. Found: C, 67.73; H, 5.23.

N-Methyl-2-methoxycarbonyl-3-hydroxypyrrole (2a). A solution of **5** (9 g, 21 mmol) in (2:1) CH_2Cl_2:MeOH (150 mL) was treated with O_3 at -78 °C until a light blue color persisted and then warmed to rt. After the solvent was evaporated, the residue was dissolved in THF (100 mL) and treated with saturated $NaHCO_3$ (70 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min, then at rt for 3 h. The solution was diluted with H_2O (100 mL) then extracted with EtOAc (150 mL x 3). The combined organic layer was washed with brine (100 ml x 1), dried over $MgSO_4$, and evaporated to give a crude product **1** (3.0 g) as a light yellow oil, which was not stable at rt. This crude compound was then dissolved in CH_2Cl_2 (400 mL) at 0 °C and treated with 40% $MeNH_2$ in H_2O (1.6 mL, 19 mmol). The reaction mixture was stirred at rt for 15 min and then treated with SiO_2 (25 g). The resulting mixture was stirred for 1 h, filtered through a Celite pad, and washed with EtOAc (200 mL). The filtrate was evaporated and the residue was purified by flash chromatography (SiO_2, 1:1 hexane:EtOAc) to give pure **2a** (1.0 g, 32% isolated yield) as a light brown solid. mp 43-44 °C; R_f 0.46 (3:1 hexane:EtOAc); IR ($CHCl_3$) 3500, 2300, 1720, 1660, 1470, 1450, 1390, 1335, 1120, 1090, 1075 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98 (bs, 1H), 6.53 (d, J = 2.8 Hz, 1H), 5.72 (d, J = 2.8 Hz, 1H), 3.89 (s, 3H), 3.74 (s, 3H); MS (EI, 20 eV) 155 (M^+), 124, 123, 95, 86, 84; HRMS calcd for $C_7H_9NO_3$: 155.0583, found 155.0587; Anal. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.35; H, 5.92; N, 9.10.

N-Methyl-4-bromo-2-methoxycarbonyl-3-hydroxypyrrole (6). To a cold (-78 °C) solution of **2a** (0.57g, 3.67 mmol) in CH_2Cl_2 (40 mL) was added NBS (0.58 g, 3.30 mmol). The reaction mixture was stirred at -78 °C for 2 h, then quenched with 10% aqueous Na_2SO_3 (15 mL). The solution was warmed to rt and extracted with CH_2Cl_2 (150 mL x 2). The combined organic layer was dried over $MgSO_4$, and evaporated to give a crude product. This was purified by flash chromatography (SiO_2, 4:1 hexane:EtOAc) to give **6** (0.64 g, 83% isolated yield) as a white solid. mp 85-87 °C; R_f 0.38 (4:1 hexane:EtOAc); IR (CCl_4) 3495, 2950, 1715, 1664, 1485, 1470, 1450, 1405, 1370, 1335, 1290, 1160, 1110, 1100, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (bs, 1H), 6.59 (s, 1H), 3.91 (s, 3H), 3.75 (s, 3H); MS (EI, 20 eV) 235 (M^+), 233, 203, 201; HRMS calcd for $C_7H_8BrNO_3$: 234.9667, found 234.9668; Anal. Calcd for $C_7H_8BrNO_3$: C, 35.92; H, 3.45; N, 5.98. Found: C, 36.17; H, 3.50; N, 6.08.

N-Methyl-4-bromo-2-methoxycarbonyl-3-methoxypyrrole (7). To a cold (0 °C) solution of **6** (0.42 g, 1.79 mmol) in THF (10 mL) was added NaH (48 mg, 1.96 mmol) and the resulting reaction mixture stirred at 0 °C for 5 min. At this point, dimethylsulfate (0.2 mL, 1.96 mmol) was added and stirring continued at rt for 16 h. The reaction mixture was quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (100 mL x 2). The combined organic layer was dried over $MgSO_4$, and evaporated. The resulting product was purified by flash chromatography (SiO_2, 4:1 hexane:EtOAc) to give **7** (0.43 g, 99%) as a light yellow solid. mp 55-56 °C; R_f 0.51 (4:1 hexane:EtOAc); IR (CCl_4) 3000, 2945, 2920, 1700, 1440, 1405, 1360, 1275, 1170, 1105, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.65 (s, 1H), 3.87 (s, 6H), 3.82 (s, 3H); MS (EI, 20 eV) 249 (M^+), 247, 216, 214, 202, 200; HRMS calcd for $C_8H_{10}BrNO_3$: 248.9824, found 248.9829; Anal. Calcd for $C_8H_{10}BrNO_3$: C, 38.73; H, 4.06; N, 5.65. Found: C, 38.83; H, 4.07; N, 5.60.

Photooxidation of pyrrole 9. A solution of **9** (50 mg, 0.10 mmol) in MeOH (33 mL, 0.005 M) was oxygenated in the presence of methylene blue (1 mg) during irradiation with a tungsten-halogen light source (650 W) for 10 min. The solvent was evaporated and the residue was purified by flash chromatography (SiO_2, 2:1 hexane:EtOAc) to give **10**, **11**, and **12**. **Hydroxy Lactam 10:** (45%) as a white solid, mp 129-130 °C; R_f 0.09 (2:1 hexane:EtOAc); IR ($CHCl_3$) 3450, 2970, 1730, 1690, 1640, 1370, 1340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33-7.22 (m, 5H), 5.15 (s, 1H), 4.73 (d, J = 15.6 Hz, 1H), 4.61 (s, 1H), 4.18 (d, J = 15.5 Hz, 1H), 3.84 (s, 3H), 1,14 (s, 9H); MS (CI) 320 ($M+H^+$), 304, 292, 264, 246, 218, 140, 91; HRMS calcd for $C_{17}H_{22}NO_5$ ($M+H^+$): 320.1498, found 320.1503. **Enamide Diester 11:** 35% yield as a pale yellow oil, R_f 0.51 (2:1 hexane:EtOAc); IR ($CHCl_3$) 2970, 1740, 1675, 1630, 1390, 1370, 1280, 1145 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35-7.25 (m, 5H), 6.61 (d, J = 9.4 Hz, 1H), 5.51 (d, J = 9.4 Hz, 1H), 4.96 (s, 2H), 3.66 (s, 3H), 1.50 (s, 9H); MS (CI) 320 ($M+H^+$), 304, 292, 264, 232, 190, 175, 143, 119, 91; HRMS calcd for $C_{17}H_{22}NO_5$ ($M+H^+$): 320.1498, found 320.1502. **Pyrrole Epoxide 12:** 10% yield as a white solid, m.p. 93-94 °C; R_f 0.27 (2:1 hexane:EtOAc); IR ($CHCl_3$) 2970, 2920, 1740, 1720, 1635, 1600, 1445, 1430, 1385, 1365, 1220, 1150, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37-7.26 (m, 5H), 6.61 (d, J = 5.1 Hz, 1H), 5.30 (d, J = 5.1 Hz, 1H), 4.84 (d, J = 15.3 Hz, 1H), 4.45 (d, J = 15.3 Hz, 1H), 3.92 (s, 3H), 1.46 (s, 9H); MS (CI) 302 (M^+-H), 288, 272, 248, 232, 216, 204, 172, 140, 91; HRMS calcd for $C_{17}H_{22}NO_4$ ($M+H^+$): 304.1548, found 304.1543. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.06; H, 6.90; N, 4.61.

4,4'-Dimethoxy-5,5'-dimethoxycarbonyl-1,1'-dimethyl-3,3'-bipyrrole (8). To a cold (-78 °C) solution of **7** (66 mg, 0.27 mmol) and $CuBr_2$ (78 mg, 0.33 mmol) in THF (1 mL) was added n-BuLi (1.51 M in pentane, 0.23 mL, 0.35 mmol). Stirring was continued at -78 °C for 30 min, at 0 °C for 1 h, and then, at rt for 1 h. The reaction mixture was quenched with aqueous NH_4OH (2 mL of NH_4OH in 8 mL of H_2O) then extracted with CH_2Cl_2 (20 mL x 3). The combined organic layer was dried over $MgSO_4$, then evaporated to give a crude product. This was purified by flash chromatography (SiO_2, 4:1 hexane:EtOAc) to give **8** (37 mg, 83%) as a white solid. mp 172-173 °C; R_f 0.25 (4:1 hexane:EtOAc); IR (CCl_4) 3000, 2945, 1695, 1440, 1400, 1360, 1350, 1270, 1160, 1100, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.06 (s, 2H), 3.89 (s, 6H), 3.86 (s, 6H), 3.80 (s, 6H); HRMS calcd for $C_{16}H_{20}NO_6$: 336.1321, found 336.1325.

Formation of 17 by Photooxidation of Bipyrrole 8. A solution of **8** (35 mg, 0.10 mmol) in MeOH (60 mL) was oxygenated in the presence of methylene blue (1 mg) during irradiation with a tungsten-halogen light source (650 W) for 3.5 min. The solvent was evaporated and the residue was purified by flash chromatography (SiO_2, 1:1 hexane:EtOAc) to give the bisenamide **17** (13 mg, 30%) as a colorless foam. mp 123-124 °C (MeOH); ^1H NMR ($CDCl_3$) δ 6.76 (bs, 2H), 3.86 (s, 6H). 3.74 (s, 6H), 3.20 (s, 6H); MS (EI, 20eV) 400, 341, 281, 253.

Half-oxidized Bipyrrole 19. Methylene chloride (200 mL) at -78 °C was saturated with O_3 until a dark blue color persisted. The solution was then purged with N_2 at -78 °C until the blue color faded. The reaction flask was then connected through a glass tube to another flask containing **8** (20 mg, 0.059 mmol) in CH_2Cl_2 (20 mL) at 0 °C. N_2 was bubbled through the dilute O_3 solution to transfer a low concentration of O_3 to the bipyrrole **8** in CH_2Cl_2 for 5 min. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, EtOAc) to afford 11 mg (50%) of half oxidized bipyrrole **19**: R_f 0.50 (EtOAc); IR (CH_2Cl_2) 3478, 3407, 3186, 1760, 1740, 1695, 1644, 1393, 1363, 1253, 1147, 1052 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.75 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.71 (s, 3H), 2.77 (s, 3H); MS (EI) 368 (M^+), 352, 309, 293, 277, 236, 196, 172, 131; HRMS calcd for $C_{16}H_{20}N_2O_8$: 368.1220, found 368.1228.

Isochrysohermidin (3a, 3b). Compound **8** (14 mg, 0.042 mmole) was treated with dilute O_3 under identical oxidation conditions as stated above except that reaction with dilute O_3 was continued for a total of 10 min. The solvent was then removed under reduced pressure and the residue was passed through a short SiO_2 (2 cm) column with EtOAc. The fractions with R_f 0.2 to 0.5 were collected to afford 7 mg (42%) of a mixture containing the *d,l* and *meso* diastereomers of isochrysohermidin **3** in a 1:1 ratio. Purification of the *d,l* form **3a** was accomplished by selective recrystallization from EtOAc to afford 2.9 mg (18%) of pure **3a**. Purification of the *meso* form **3b** was accomplished by column chromatography (SiO_2, EtOAc) of the mother liquor to afford 1.0 mg (6%) of pure **3b**. The spectroscopic properties of the synthetic *d,l* and *meso* compounds were identical in all respects with the corresponding spectra of natural products supplied by Masui.[4b] We also compared our products with the corresponding synthetic *meso* and *d,l* products prepared by Boger and Baldino.[15] **3a**: mp 264-267 °C (EtOAc), lit. mp 265-268 °C (EtOAc); R_f 0.31 (EtOAc); IR (CH_2Cl_2) 3478, 3407, 3186, 1760, 1740, 1700, 1684, 1644, 1393, 1363, 1253, 1147, 1052 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.97 (s, 6H), 3.82 (s, 6H), 2.81 (s, 6H);

MS (EI, 20 eV) 400 (M^+), 368, 341, 323, 277, 236, 196, 129, 83; HRMS (M^+) calcd for $C_{16}H_{20}N_2O_{10}$: 400.1118, found 400.1117. **3b**: mp 207-210 °C (EtOAc), lit. mp 207-209 °C (1:1, EtOAc-Et_2O); R_f 0.21 (EtOAc); IR (CH_2Cl_2) 3478, 1750, 1700, 1684, 1644, 1363, 1300, 1253, 1147, 1052 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.97 (s, 6H), 3.88 (s, 6H), 2.79 (s, 6H); MS (EI, 20 eV) 400 (M^+), 355, 341, 323, 309, 295, 277, 265, 236, 208, 201; HRMS (CI, $M+H^+$) calcd for $C_{16}H_{21}N_2O_{10}$: 401.1196, found 401.1174.

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