Singlet Oxygen Oxidation of Bipyrroles: Total Synthesis of *d,l*- and *meso*-Isochrysohermidin

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Received April 20, 1993

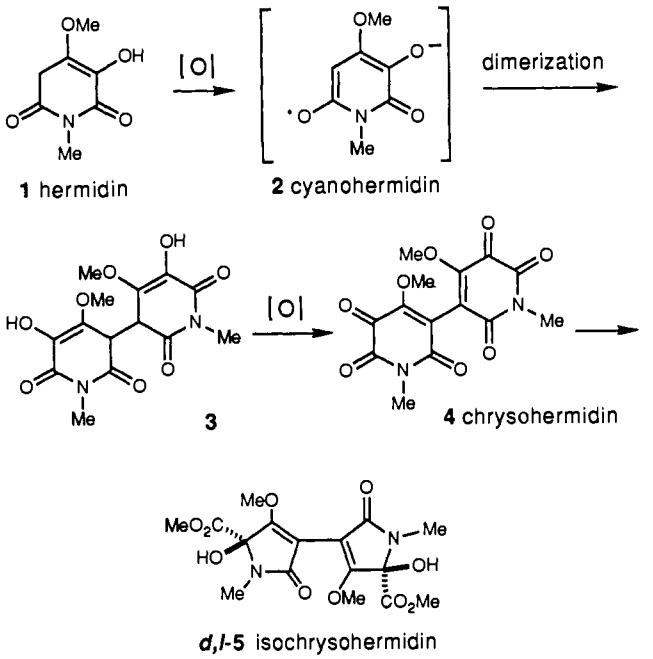
Autoxidation of the colorless chromogen hermidin (**1**),[1] isolated from *Mercurialis perennis L.*,[2] sequentially provides the transient blue radical-anion cyanohermidin (**2**),[3] the dehydrohermidin dimer (**3**),[1] and chrysohermidin (**4**)[1,4] and may precede conversion to isochrysohermidin (**5**),[5] a bis(2-oxo-3-pyrroline) derivative first isolated from *Mercurialis leiocarpa* and recently shown to be related to **4** through a sodium methoxide-promoted rearrangement (Scheme I).[6] This plant product was first characterized by Masui,[5,6] who demonstrated that both *d,l*-**5**[5a] and *meso*-**5**[5b] are present in the samples derived from natural sources. The structure of the *d,l* diastereomer was unambiguously established by X-ray crystallography.[5a]

In examining the unique, highly oxygenated framework of **5**, we were intrigued by the possibility that this system could be generated in one straightforward oxidative process by a well-precedented addition–elimination sequence involving the uptake of singlet oxygen by a suitable bipyrrole precursor.[7,8,14] As shown in Scheme II, this sequence could yield both the *d,l* and the *meso* forms, depending on the facial selectivity of the singlet oxygen addition. In the laboratories at Yale, the chosen precursor was the bipyrrole **6a**;[8] at Scripps, the corresponding dicarboxylic acid derivative **6b** was used for the oxidation. In this report, we describe recent studies on the reactions of bipyrroles **6a** and **6b** with singlet oxygen under different conditions. We have now found that both precursors can be converted by $^1O_2$ to the *d,l* and *meso* forms of the Masui product. Formation of both diastereomers could result from a two-stage addition of $^1O_2$ to the pyrrole rings without selectivity in the second-stage addition or, possibly, from the interconversion of *meso* and *d,l* forms.[15]

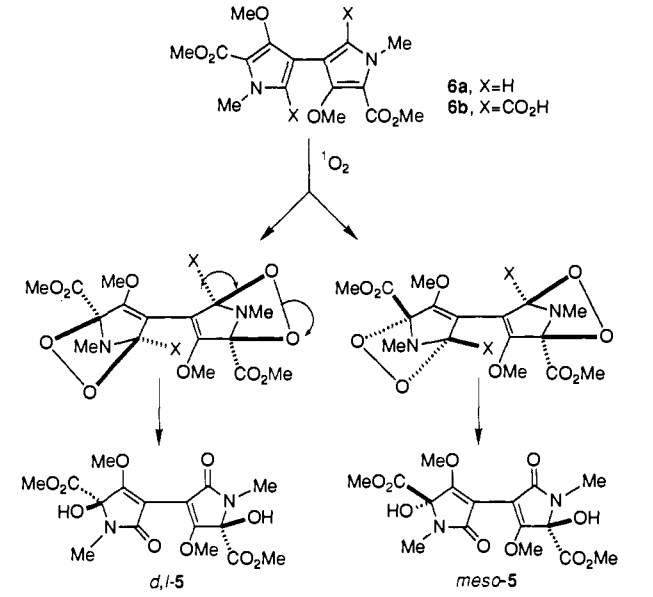
The preparation of **6a**, starting with the pyrrole-forming addition of methylamine to the vinyl tricarbonyl reagent **7** to form **8**, was previously outlined in an earlier communication and is summarized in Scheme III.[8]

The bipyrrole **6b** was prepared at Scripps by the sequence outlined in Scheme IV. The details of this approach, including

Scheme I



Scheme II



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(1) Swan, G. A. *Experientia* **1984**, *40*, 687.
(2) Haas, P.; Hill, T. G. *Biochem. J.* **1925**, *19*, 233 and 236.
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(5) (a) Masui, Y.; Kawabe, C.; Mastumoto, K.; Abe, K.; Miwa, T. *Phytochemistry* **1986**, *25*, 1470. (b) Abe, K.; Okada, T.; Masui, Y.; Miwa, T. *Chem. Express* **1990**, *5*, 13.
(6) Abe, K.; Okada, T.; Masui, Y.; Miwa, T. *Phytochemistry* **1989**, *28*, 960.
(7) (a) Foote, C. S.; Wexler, S.; Ando, W.; Higgins, R. *J. Am. Chem. Soc.* **1968**, *90*, 975. (b) Foote, C. S.; Wexter, S.; Ando, W. *Tetrahedron Lett.* **1965**, 4111. (c) Lightner, D. A.; Bisacchi, G. S.; Norris, R. D. *J. Am. Chem. Soc.* **1976**, *98*, 802. (d) Lightner, D. A.; Quistad, G. B. *J. Heterocycl. Chem.* **1973**, *10*, 273. (e) Lightner, D. A.; Crandall, D. C. *Experientia* **1973**, *29*, 262.
(8) (a) Wasserman, H. H.; Frechette, R.; Rotello, V. M.; Schulte, G. *Tetrahedron Lett.* **1991**, *32*, 7571. (b) The full details of the formation of **6a** from **7** are described in the Ph.D. dissertation of V. M. Rotello, Yale University, 1989.
(9) In the absence of pyridine, 2,5-addition was accompanied by 2,3-cleavage and 2,3-epoxide formation.
(10) Murray, R. W.; Kaplan, M. L. *J. Am. Chem. Soc.* **1969**, *91*, 5358.
(11) The following are standard experimental conditions. A solution of PPh_3 in CH_2Cl_2 at −78 °C was treated with O_3 (to generate $PPh_3{\cdot}O_3$) until a light blue color persisted. The solution was then purged with N_2 (until the light blue color faded) to remove the excess O_3. The reaction flask was connected through a glass tube to another flask containing bipyrrole **6a** in CH_2Cl_2 at 0 °C. N_2 was bubbled through the $PPh_3{\cdot}O_3$ solution while the mixture was allowed to warm to room temperature, thus generating singlet oxygen, which was bubbled through the bipyrrole/CH_2Cl_2 solution for 30 min. The solvent was then removed from the bipyrrole/CH_2Cl_2 solution under reduced pressure. The residue was chromatographed (silica gel, ethyl acetate) and the fractions with R_f 0.2–0.5 were collected to afford a 1:1 mixture of *d,l*-**5** and *meso*-**5** diastereomers of isochrysohermidin. Purification of the *d,l*-**5** isomer was accomplished by selective recrystallization from ethyl acetate to afford 18% of pure *d,l*-**5** as a white solid, mp 264–267 °C (lit.[5,6,12] 265–268 °C).
(12) We thank Prof. Y. Masui for sending an authentic sample of *d,l*-isochrysohermidin.
(13) Wasserman, H. H.; Scheffer, J. R.; Cooper, J. L. *J. Am. Chem. Soc.* **1972**, *94*, 4991.
(14) Boger, D. L.; Baldino, C. M. *J. Org. Chem.* **1991**, *56*, 6942.
(15) It has been shown both at Yale and at Scripps that under acidic conditions, pure *d,l*- or pure *meso*-**5** undergoes slow conversion to a 1:1 equilibrium mixture containing both diastereomers.

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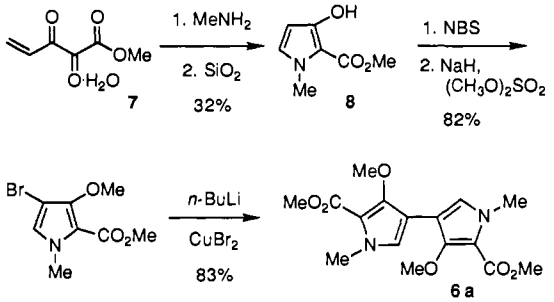
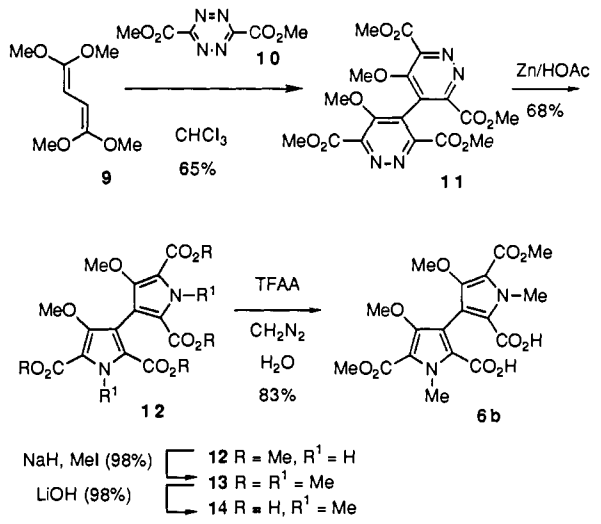
Scheme III



Scheme IV



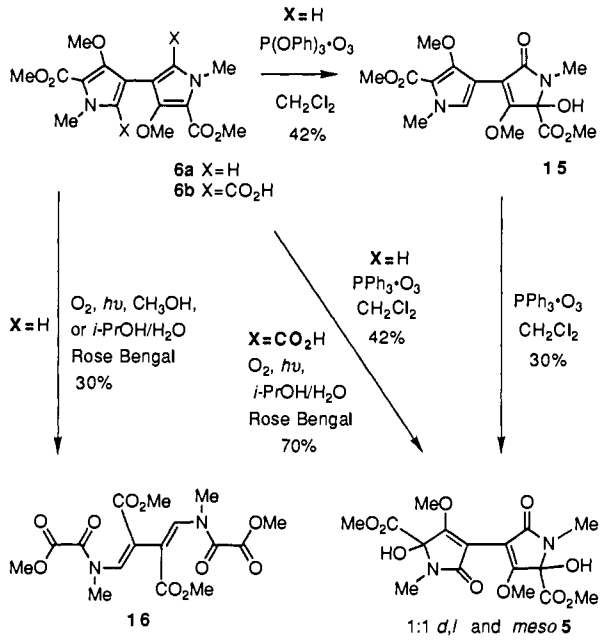
the method of forming the tetracarboxylic acid **14** and the selective methylation to generate **6b** through the intermediate cyclic anhydride, will be reported in a full account of the studies. Notably, two consecutive inverse electron demand Diels–Alder reactions of **9** with **10** followed by double reductive ring contraction of the 4,4′-bi-1,2-diazine **11** provided **12** in a two-step reaction sequence that constitutes an effective, new synthetic approach to functionalized 3,3′-bipyrroles.

Reactions with Singlet Oxygen. As reported earlier,[8] standard photooxygenation (–20 °C, Rose Bengal, methanol, 10% pyridine) of the model system 2-(carboxy-*tert*-butyl)-3-methoxy-*N*-benzylpyrrole gave 2,5-addition of $^1O_2$ in excellent yields (80%).[9] In striking contrast, the same reaction conditions applied to bipyrrole **6a** gave **16** (30%) as the only identifiable product by 2,3-cleavage (Scheme V).[8] Changing solvent, dye sensitizer, and base similarly led only to **16**.[8] On the other hand, the present studies show that when **6a** is allowed to react with triphenylphosphine and ozone in CH_2Cl_2 according to the Murray procedure,[10] a completely different result is obtained. Under these conditions, the reaction with $^1O_2$ takes place exclusively by 2,5-addition, leading to a 1:1 mixture of *meso* and *d,l* product (42%).[11] Our *d,l* material was identified by NMR, IR, and mass spectrometric comparison with data obtained from an authentic sample provided by Prof. Masui.[12]

When $P(OPh)_3$ was used instead of $P(Ph)_3$ in the reaction of **6a**, a half-oxidized product (**15**) was formed (42%). This material could be converted to **5** by the action of $^1O_2$ generated from triphenylphosphine with ozone (Scheme V). Under the conditions for generating $^1O_2$ by heating 9,10-diphenylanthracene peroxide in refluxing benzene,[13] only products of decomposition were found.

In the laboratories at Scripps, according to protocols introduced in a study of 4-methoxy-5-(methoxycarbonyl)-*N*-methylpyrrole-2-carboxylic acid, which provided the expected product of $^1O_2$ 2,5-addition and subsequent oxidative decarboxylation (93%),[14] the reaction of precursor **6b** with singlet oxygen yielded **5** as the same mixture of diastereomers. Recrystallization (EtOAc) of

Scheme V



the 1:1 mixture of *d,l*- and *meso*-**5** (*ca.* 70%) selectively provided pure *d,l*-**5** (37–40%, mp 266–268 °C). Repeated chromatography of the mother liquors provided a pure sample of the remaining *meso*-**5** (8%, mp 207–209 °C). The diastereomers do not readily interconvert under the conditions of recrystallization or chromatography.[15] In contrast to the findings with bipyrrole **6a**, the $^1O_2$ oxidation of **6b** to provide **5** took place smoothly under conditions of photooxygenation in 2-propanol/water in the presence of collidine or pyridine, using Rose Bengal as sensitizer and a 450-W Hanovia high-pressure mercury lamp as the light source. The triphenylphosphite–ozonide route[10] to singlet oxygen gave **5** but in lower yields.

Use of singlet oxygen for the direct conversion of the bipyrrole derivatives **6a** and **6b** to the *d,l*- and *meso*- forms of isochrysohermidin **5** represents a striking application of $^1O_2$ methodology in synthesis. These results have also raised a number of intriguing questions. The possibility that the singlet oxgyen reaction may mimic an in vitro enzymatic oxidation process lends biogenetic significance to the laboratory transformations. This work also highlights the importance of the reaction environment in determining the course of $^1O_2$ oxidations.[16] The initial peroxidic adduct of singlet oxygen and the substrate undergoes further reaction or rearrangement, with the outcome depending strongly on the nature of reactant substituents, the presence of other species in the reaction mixture, and the reaction conditions. Further studies on these fascinating findings are currently in progress in both laboratories.

Acknowledgment. The authors acknowledge the financial support of the National Institutes of Health (Grants CA-42056, GM-13854, and GM-07874). H.H.W. thanks Professor A. I. Scott for helpful discussions.

Supplementary Material Available: Experimental descriptions and spectroscopic data for compounds **7**, **8**, **8a**, **8b**, **6a**, **11**, **12**, **13**, **14**, **6b**, and **5** (*meso* and *d,l*) (11 pages). Ordering information is given on any current masthead page.

(16) *Singlet Oxygen*; Wasserman, H. H.; Murray, R. W., Eds.; Academic Press: New York, 1979.