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Mn(III)/Cu(II)-Mediated Oxidative Radical Cyclization of α-(Methylthio)acetamides Leading to Erythrinanes

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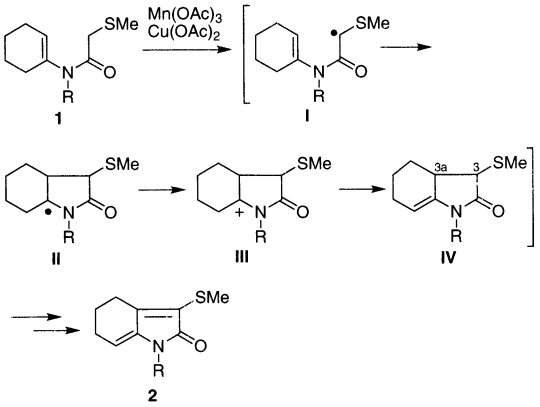
Treatment of *N*-[2-(3,4-dimethoxyphenyl)ethyl]-α-(methylthio)acetamide **3** with $Mn(OAc)_3$ in the presence of $Cu(OAc)_2$ gave tetrahydroindol-2-one **4**, which then cyclized with $Mn(OAc)_3$ to give 4-acetoxyerythrinane **5**. A similar reaction of the 3,4-methylenedioxyphenyl congener **8** also gave tetrahydroindol-2-one **9**, which, however, gave only a trace amount of the $Mn(OAc)_3$-mediated cyclization product **11** and afforded the oxidation product **10**. On the basis of these results, formation of **5** from **4** was thought to proceed via nucleophilic attack of the pyrrole ring on the cation-radical **lX**, generated by a single electron-transfer reaction of the acetoxy-substituted intermediate **V**. Treatment of compound **16** with $Mn(OAc)_3/Cu(OAc)_2$ gave no erythrinane derivative with recovery of the starting material, indicating that the presence of a methylthio group of **4** is essential for effecting the formation of erythrinane **5**. On the other hand, treatment of **3** with $Mn(OAc)_3$ using $Cu(OTf)_2$ as an additive in place of $Cu(OAc)_2$ gave another erythrinane **17**. This method was applied to a formal synthesis of 3-demethoxyerythratidinone (**20**), a naturally occurring *Erythrina* alkaloid.

Introduction

Oxidative radical cyclization using Mn(III) acetate has attracted considerable attention in recent years.[1,2] In a previous paper, we reported that *N*-(cyclohex-1-enyl)-α-(methylthio)acetamides **1** upon treatment with $Mn(OAc)_3$ in boiling CF_3CH_2OH in the presence of $Cu(OAc)_2$ gave tetrahydroindol-2-ones **2** in good yields (Scheme 1).[3] The acetamide bearing a methyl group (Me) in place of the methylthio group (SMe) of **1** gave no cyclization product and without the use of $Cu(OAc)_2$ acetamides **1** gave trace amounts of the cyclization products **2**. These results

SCHEME 1



indicate that both the presence of a methylthio group and the use of $Cu(OAc)_2$ as an additive are essential for effecting the cyclization of **1** with $Mn(OAc)_3$. Formation of **2** from **1** may be explained by assuming that the methylthio-substituted carbamoylmethyl radicals **I** are formed from **1** by action with $Mn(OAc)_3/Cu(OAc)_2$ through a single eletron transfer (SET) reaction, and radicals **I** undergo cyclization in a 5-*endo-trig* manner[4] to give new radicals **II**. This step is then followed by oxidation with $Mn(OAc)_3$ or with $Cu(OAc)_2$, deprotonation of the resulting carbocations **III**, and further oxidation at the C_3-C_{3a} bond of **IV** with $Mn(OAc)_3/Cu(OAc)_2$, to give **2**.

Subsequently, we found that treatment of *N*-(cyclohex-1-enyl)-α-(methylthio)acetamide **3**, having a 2-(3,4-

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(1) For reviews on the use of $Mn(OAc)_3$ in oxidative radical cyclizations, see: Melikyan, G. G. *Aldrichimica Acta* **1998**, *31*, 50. Melikyan, G. G. *Org. React.* **1997**, *49*, 427. Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519. Melikyan, G. G. *Synthesis* **1993**, 833.

(2) For recent works on oxidative radical reactions with $Mn(OAc)_3$, see: Méou, A.; Lamarque, L.; Brun, P. *Tetrahedron Lett.* **2002**, *43*, 5301. Garzino, F.; Méou, A.; Brun, P. *Tetrahedron Lett.* **2002**, *43*, 5049. Bar, G.; Parsons, A. F.; Thomas, C. B. *Synlett* **2002**, 1069. Hirase, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2002**, *67*, 970. Taylor, E. C.; Liu, B. *J. Org. Chem.* **2001**, *66*, 3726. Lavilla, R.; Spada, A.; Carranco, I.; Bosch, J. *J. Org. Chem.* **2001**, *66*, 1487. Calestani, G.; Capella, L.; Leardini, R.; Minozzi, M.; Nanni, D.; Papa, R.; Zanardi, G. *Tetrahedron* **2001**, *57*, 7221. Wu, Y.-L.; Chuang, C.-P.; Lin, P.-Y. *Tetrahedron* **2001**, *57*, 5543. Yang, D.; Xu, M. *Org. Lett.* **2001**, *3*, 1785. Yang, D.; Ye, X.-Y.; Xu, M.; Pang, K.-W.; Cheung, K.-K. *J. Am. Chem. Soc.* **2000**, *122*, 1658. D'Annibale, A.; Nanni, D.; Trogolo, C.; Umani, F. *Org. Lett.* **2000**, *2*, 401. Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron* **2000**, *56*, 3941. Wu, Y.-L.; Chuang, C.-P.; Lin, P.-Y. *Tetrahedron* **2000**, *56*, 6209. Chuang, C.-P.; Wu, Y.-L.; Jiang, M.-C. *Tetrahedron* **1999**, *55*, 11229. Chuang, C.-P.; Wang, S.-F. *Tetrahedron* **1998**, *54*, 10043. Chowdhury, F. A.; Nishino, H.; Kurosawa, K. *Tetrahedron Lett.* **1998,** *39*, 7931. See also references therein.

(3) Ishibashi, H.; Toyao, A.; Takeda, Y. *Synlett* **1999**, 1468.

(4) For a review on 5-*endo-trig* radical cyclizations, see: Ishibashi, H.; Sato, T.; Ikeda, M. *Synthesis* **2002**, 695.

10.1021/jo020573p CCC: $25.00
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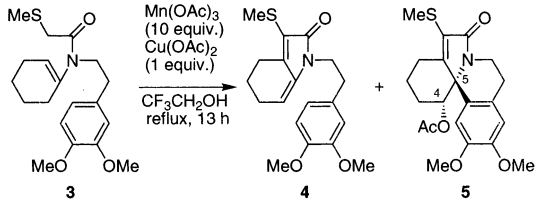
SCHEME 2



dimethoxyphenyl)ethyl group on the nitrogen atom, with $Mn(OAc)_3/Cu(OAc)_2$ provided a concise route to the synthesis of an erythrinane skeleton **5** (Scheme 2).[5] The expected primary product **4** from **3** with $Mn(OAc)_3/Cu(OAc)_2$ was thought to be an intermediate for the formation of erythrinane **5**. In this paper, we describe in detail works using this method for the synthesis of erythrinane derivatives, including studies on the mechanism for the formation of **5** from **4**. A formal synthesis of a naturally occurring *Erythrina* alkaloid, 3-demethoxyerythratidinone (**20**), using the method with $Cu(OTf)_2$ in place of $Cu(OAc)_2$ as an additive, is also described.

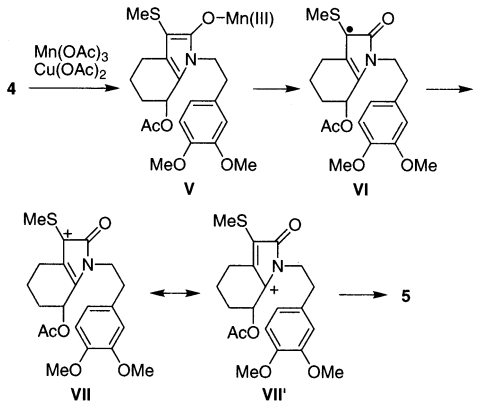
Results and Discussion

1. Synthesis of Erythrinanes with $Mn(OAc)_3/Cu(OAc)_2$. When amide **3**[6] was treated with 6 equiv of $Mn(OAc)_3 \cdot 2H_2O$ in boiling CF_3CH_2OH for 9 h in the presence of $Cu(OAc)_2$ (1 equiv) the erythrinane derivative **5** was obtained in 6% yield along with compound **4** (72%) with recovery of the starting material **3** (19%). On the other hand, treatment of amide **3** with a much larger amount (10 equiv) of $Mn(OAc)_3 \cdot 2H_2O$ in the presence of $Cu(OAc)_2$ (1 equiv) for a much longer period (13 h) of heating improved the yield of **5** to 52% with a decrease in the yield of **4** (39%).

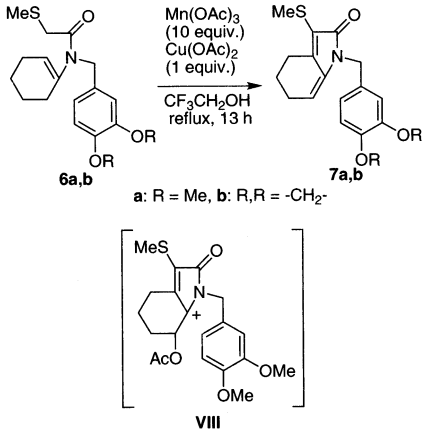
The structure of **5** was deduced from its spectral properties. The IR spectrum showed bands at 1735 and 1675 cm^{-1}, which were clearly indicative of an ester group and an unsaturated five-membered lactam, respectively. The ^1H NMR spectrum exhibited two singlets due to AcO and MeS groups at δ 2.00 and 2.49, respectively, and a doublet ($J = 2.6$ Hz) due to the methine proton on C-4 at δ 5.34, which indicated the axial nature of the AcO group on C-4. The ^{13}C NMR spectrum exhibited a signal due to the quaternary carbon atom on C-5 at δ 68.3. The structure of **5** was finally established by X-ray crystallographic analysis.

Treatment of compound **4** with $Mn(OAc)_3 \cdot 2H_2O$ (4 equiv) in boiling CF_3CH_2OH in the presence of $Cu(OAc)_2$ (1 equiv) for 2 days also gave erythrinane **5** in 37% yield with recovery of the starting material **4** (57%). $Mn(OAc)_3 \cdot 2H_2O$ alone also effected the cyclization of **4** to give **5** in 31% yield with recovery of **4** (51%) after 3 days of heating.[7] These results indicated that compound **4** might be an intermediate for the formation of **5**, although the reaction of **4** giving **5** required a longer period of heating than that (13 h) for the direct formation of **5** from **3**.

SCHEME 3



SCHEME 4



2. Studies on the Mechanism of the Formation of 5 from 4. The formation of **5** from **4** may involve a coordination of the lactam carbonyl oxygen atom of **4** to $Mn(OAc)_3$ with concomitant addition of AcOH to give manganese-enolate **V** (Scheme 3). The driving force for this reaction might be the formation of the aromatic pyrrole ring of **V**. A subsequent SET reaction of **V** gives radical **VI**, which is then oxidized with $Mn(OAc)_3$ [or with $Cu(OAc)_2$] to give the cationic intermediate **VII**. The cationic form **VII′** can also be described as a resonance structure of cation **VII**, and, hence, the 3,4-dimethoxyphenyl group attacks the cationic center of **VII′** from the face opposite that of the AcO group to give erythrinane **5**.

Several questions, however, have been raised concerning the proposed mechanism of the formation of **5** from **4** as shown in Scheme 3. Treatment of the *N*-benzyl congener **6a** with $Mn(OAc)_3$ (10 equiv) and $Cu(OAc)_2$ (1 equiv) gave tetrahydroindol-2-one **7a** in 96% yield (Scheme 4). If the proposed mechanism of the formation of **5** from **4** as shown in Scheme 3 is correct, compound **6a** would also give the cationic intermediate **VIII** (like **VII′**) via tetrahydroindol-2-one **7a**. Even if the dimethoxyphenyl group could not attack the cationic center of **VIII**, some products might result from **VIII**, since cation **VIII** could no longer return to tetrahydroindol-2-one **7a**. However, compound **7a** was obtained in high yield.

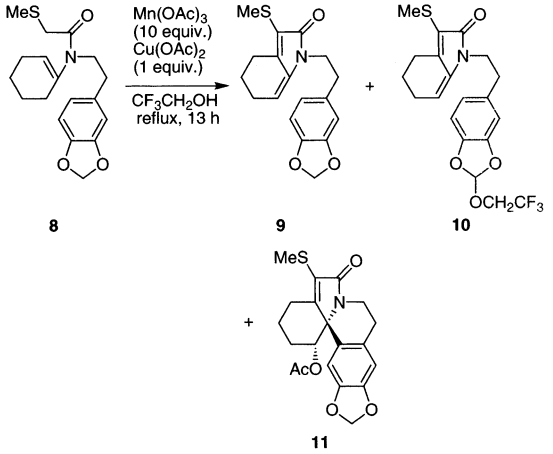
We therefore next examined the modes of reaction of **6b** and **8**, which have 3,4-methylenedioxy groups on their aromatic rings. When the benzyl derivative **6b** was treated with $Mn(OAc)_3 \cdot 2H_2O$ (10 equiv) and $Cu(OAc)_2$ (1

(5) Toyao, A.; Chikaoka, S.; Takeda, Y.; Tamura, O.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *Tetrahedron Lett.* **2001**, *42*, 1729.

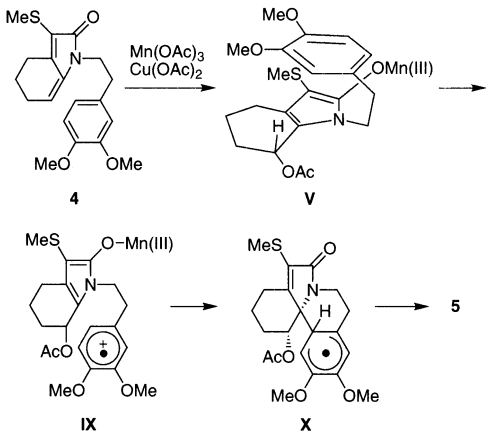
(6) Ishibashi, H.; Sato, K.; Ikeda, M.; Maeda, H.; Akai, S.; Tamura, Y. *J. Chem. Soc., Perkin Trans. 1* **1985**, 605.

(7) The use of $Mn(OAc)_2$ in place of $Mn(OAc)_3$ in the presence of $Cu(OAc)_2$ gave no erythrinane **5**. This was also the case for the use of $Cu(OAc)_2$ alone, which resulted in recovery of the starting material **4**.

SCHEME 5



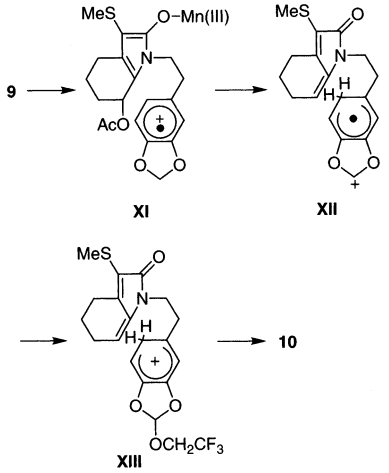
SCHEME 6



equiv) in boiling CF_3CH_3OH, compound **7b** was obtained in good yield (74%) (Scheme 4). A similar treatment of the 2-phenylethyl derivative **8** with $Mn(OAc)_3/Cu(OAc)_2$ gave tetrahydroindol-2-one **9** and trifluoroethoxy-substituted compound **10** in 28% and 21% yields, respectively (Scheme 5). Surprisingly, in this case, only a trace amount of the expected erythrinane derivative **11** was obtained. The structure of **10** was deduced from its ^1H NMR spectrum, which exhibited a signal due to the methylene protons of OCH_2CF_3 at δ 3.96 as a quartet (J = 8.4 Hz) and a signal due to the methine proton of $OCH(OCH_2CF_3)O$ at δ 6.76 as a singlet.

If the proposed mechanism of the formation of **5** from **4**, as shown in Scheme 3, is correct, formation of the erythrinane derivative **11** might result from the intermediate **9** in a manner similar to that in the case of **4**. We therefore decided to consider an alternative mechanism of the formation of the erythrinane derivative **5** from **4**. When the 3,4-dimethoxyphenyl and pyrrole rings of acetoxy-substituted intermediate **V** are brought very close together, as depicted in Scheme 6, a mutual $\pi-\pi$ interaction[8] between the two aromatic rings becomes evident. If the HOMO level of this system is enhanced, either the 3,4-dimethoxyphenyl or pyrrole ring would be readily oxidized. More rapid oxidation of the electron-rich 3,4-dimethoxyphenyl ring than that of the pyrrole ring might result in the formation of the cation-radical **IX**. This step would then be followed by a nucleophilic attack of the pyrrole ring on the cation-radical **IX** to give radical **X**. A further oxidation of **X** and deprotonation of the resulting cation would give **5**. In the case of the *N*-benzyl derivative **7a** formed from **6a**, a mutual $\pi-\pi$ interaction, as shown in Scheme 6, might not occur due to the shortness of the side chain.

SCHEME 7



This speculation might be supported by the results obtained using 3,4-methylenedioxyphenyl congener **9**. The electron-rich 3,4-methylenedioxyphenyl ring would be readily oxidized to give **XI** (Scheme 7), in a manner similar to that in the case of the 3,4-dimethoxyphenyl ring of **4** (Scheme 6). This step would then be followed by a rapid hydride shift with concomitant elimination of acetic acid to give very stable oxonium ion **XII**. Subsequently, CF_3CH_2OH used as a solvent would attack the cationic center of **XII** to give **10**, through oxidation of the phenyl ring and deprotonation of the resulting cation **XIII**. The formation of **10** from **9** cannot be explained by the mechanism shown in Scheme 3.

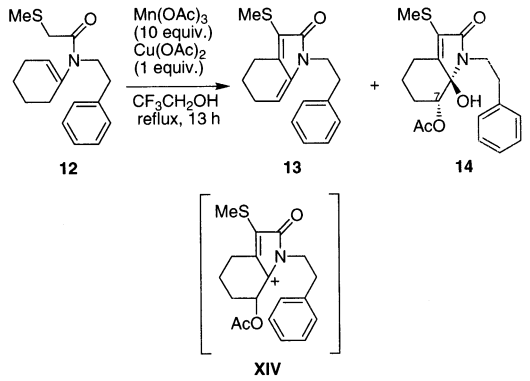
A remarkable difference between the mechanisms shown in Schemes 3 and 6 is in the outcome of the reactions of **V**. In the former process (Scheme 3), the nucleophilic 3,4-dimethoxyphenyl ring attacks the cationic center of **VII′** to give **5**, whereas in the latter process (Scheme 6), the nucleophilic pyrrole ring attacks the cationic 3,4-dimethoxyphenyl ring of **IX** to give **5**.

If the mechanism shown in Scheme 6 is correct, what happens in the case of compound **12** having no electron-donating group on the phenyl ring? When compound **12** was treated with $Mn(OAc)_3/Cu(OAc)_2$, the normal unsaturated lactam, tetrahydroindol-2-one **13**, was obtained in good yield (88%) together with compound **14** (11%) (Scheme 8).

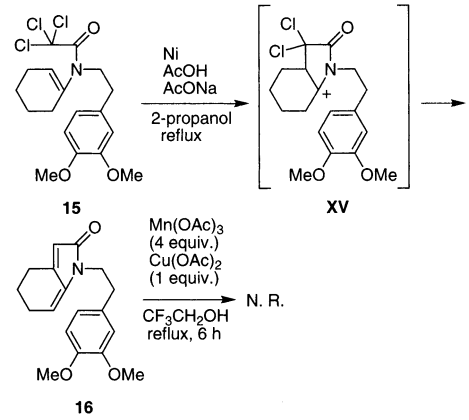
The structure of **14** was deduced from its spectral properties. The high-resolution mass spectrum (HRMS) of **14** indicated it to be a product having AcO and OH groups. The IR spectrum showed bands at 1740 and 1695 cm^{-1}, which were indicative of an ester and an unsaturated five-membered lactam, respectively. The ^1H NMR spectrum exhibited a broad singlet due to H-7 at δ 5.23, indicating an axial nature of the AcO group on C-7.

(8) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525. Hunter, C. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1584.

SCHEME 8



SCHEME 9

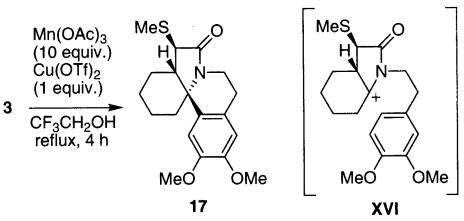


The fact that compound **13** was obtained in high yield (88%) from **12** might indicate that the oxidation of the phenyl ring of **13** did not occur due to the absence of an electron-donating group on the phenyl ring, and the formation of a detectable amount of **14** may be explained by assuming that the pyrrole ring is partially oxidized more rapidly than is a phenyl ring, thereby affording the cationic intermediate **XIV**. Water derived from $Mn(OAc)_3 \cdot 2H_2O$ is then added to the cation **XIV** to give **14**.

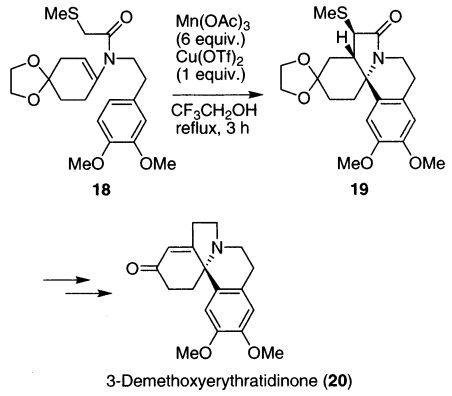
The presence of the methylthio group of **4** has been proven to be essential for effecting the formation of erythrinane **5**. Treatment of **16**, prepared by Ni/AcOH-mediated reductive radical cyclization of trichloro acetamide **15**,[9] with $Mn(OAc)_3/Cu(OAc)_2$ resulted in recovery of the starting material **16** (Scheme 9). Although the exact role of the methylthio group of **4** is not clear at present, one possible explanation for the result is derived from consideration that Michael-type addition of acetic acid for the formation of the acetoxy-substituted intermediate **V** (Scheme 3) is promoted by the presence of a methylthio group.[10]

3. Synthesis of Erythrinanes with $Mn(OAc)_3/Cu(OTf)_2$: A Formal Synthesis of 3-Demethoxyerythratidinone. When amide **3** was treated with $Mn(OAc)_3$ (6 equiv) in the presence of $Cu(OTf)_2$ (1 equiv) in place of

SCHEME 10



SCHEME 11



$Cu(OAc)_2$ as an additive, another erythrinane derivative **17**[6] was obtained in 54% yield as a sole product (Scheme 10). Formation of **17** from **3** can be simply rationalized by assuming that an aromatic ring attacks the cationic intermediate **XVI** corresponding to **III** in Scheme 1.

One possible explanation for the difference between the modes of reaction of **3** with $Cu(OAc)_2$ and with $Cu(OTf)_2$ as an additive is the difference in the acidities of the reaction systems. When $Cu(OTf)_2$ was used, enamide **IV** [R = $CH_2CH_2C_6H_3(OMe)_2$] (Scheme 1) was readily protonated with a strong acid, TfOH, formed during the course of the reaction with $Cu(OTf)_2$, to give **III** (i.e., **XVI**). On the other hand, when $Cu(OAc)_2$ was used, less acidic AcOH could not protonate toward **IV** [R = CH_2-$CH_2C_6H_3(OMe)_2$] (Scheme 1), which then underwent further oxidation to give **4**.

The one-step formation of **17** from **3** through the intermediate **XVI** is of great interest, since the analogous cationic intermediate **XV** for the formation of **16** from **15** (Scheme 9) gave no erythrinane derivative under the conditions employed (Ni/AcOH/NaOAc in boiling 2-propanol).

Treatment of **18**[11] with $Mn(OAc)_3$ in the presence of $Cu(OTf)_2$ in boiling CF_3CH_2OH gave erythrinane derivative **19**[11] in 31% yield (Scheme 11). The transformation of **19** into a naturally occurring *Erythrina* alkaloid,[12] (±)-3-demethoxyerythratidinone (**20**), has already been accomplished,[11] and, hence, the present method means, in a formal sense, a total synthesis of the alkaloid **20**.

4. Attempted Synthesis of Homoerythrinane. Finally, we attempted to apply the method with $Cu(OAc)_2$ as an additive to the synthesis of a homoerythrinane derivative from compound **21** bearing three methylene

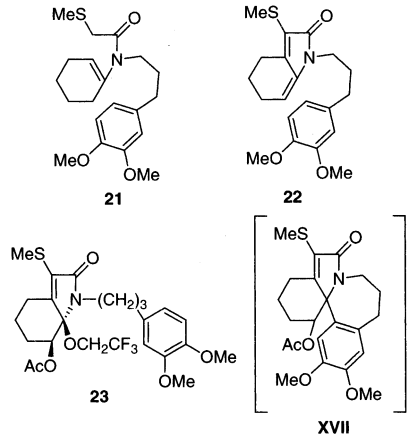
(9) Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 8995.

(10) The introduction of a thio group α into the α,β-unsaturated carbonyl compounds greatly enhanced the nature of the Michael acceptor of the parent compounds. See: Cregge, R. J.; Herrmann, J. L.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2603. Kato, M.; Ouchi, A.; Yoshikoshi, A. *Chem. Lett.* **1983**, 1511.

(11) Ishibashi, H.; Sato, T.; Takahashi, M.; Hayashi, M.; Ishikawa, K.; Ikeda, M. *Chem. Pharm. Bull.* **1990**, *38*, 907.

(12) For a review of *Erythrina* alkaloids, see: Tsuda, Y.; Sano, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA,-1996; Vol. 48, p 249.

groups between the nitrogen atom and the 3,4-dimethoxyphenyl group.



Treatment of **21**[11] with $Mn(OAc)_3 \cdot 2H_2O$ (10 equiv) and $Cu(OAc)_2$ (1 equiv) in boiling CF_3CH_2OH for 5 h, however, gave the normal cyclization product, tetrahydroindol-2-one **22**, in good yield (80%), along with a trace amount of **23** and the starting material **21** (18%): no homoerythrinane derivative was obtained.

The ^1H NMR spectrum of **23** exhibited a signal due to H-7 as a double doublet having $J = 11.6$ and 4.3 Hz at δ 4.61, indicating an equatorial nature of the OAc group on C-7.

One possible explanation for the failure to obtain a homoerythrinane derivative from **21** is derived from consideration that a $\pi-\pi$ complex such as **V** shown in Scheme 6 is not formed from compound **22** because of the entropy effect due to the long side chain. Even when a cation-radical like **IX** was formed, the formation of a homoerythrinane skeleton seemed to be difficult,[12] and the oxidation level was therefore shifted to the pyrrole system giving **23**.

Conclusion

We found that 1-[2-(3,4-dimethoxypheyl)ethyl]-3-(methylthio)tetrahydroindol-2-one **4** formed by the Mn(III)/Cu(II)-mediated oxidative radical reaction of α-(methylthio)acetamide **3** cyclized with Mn(III) to give the erythrinane derivative **5**. It was thought that oxidation of the phenyl ring via a $\pi-\pi$ interaction between the phenyl and pyrrole rings as depicted in Scheme 6 was involved in the formation of **5** from **4**. The *N*-benzyl **7a** and *N*-3-phenylpropyl congeners **22** were rather stable under conditions similar to those in which **5** was obtained from **4**, and it was therefore thought that the presence of two methylene groups between the nitrogen atom and the phenyl rings of tetrahydroindol-2-one **4** played an important role in elicitation of the $\pi-\pi$ interaction.

Experimental Section

Melting points are uncorrected. IR spectra were recorded in $CHCl_3$. ^1H (270 MHz) and ^{13}C (67.8 MHz) NMR spectra were measured for solutions in $CDCl_3$. δ values quoted are relative to tetramethylsilane. Column chromatography was performed on Silica gel 60 PF_{254} under pressure.

***N*-(Cyclohex-1-enyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-(methylthio)acetamide (3).** According to the reported procedure,[6] the imine prepared from homoveratrylamine (1.02 g, 5.62 mmol) and cyclohexanone (1.11 g, 11.3 mmol) was treated with 2-(methylthio)acetic anhydride (2.18 g, 11.3 mmol) in the presence of pyridine (888 mg, 11.3 mmol) to give **3**[6] (901 mg, 46%): IR ν 1635 cm^{-1}; ^1H NMR δ 1.58−1.80 (m, 4H), 1.95−2.21 (m, 4H), 2.23 (s, 3H), 2.80 (t, $J = 7.9$ Hz, 2H), 3.25 (s, 2H), 3.60 (br t, $J = 7.9$ Hz, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 5.62 (br s, 1H), 6.76−6.81 (m, 3H).

1,4,5,6-Tetrahydro-1-[2-(3,4-dimethoxyphenyl)ethyl]-3-methylthio-2*H*-indol-2-one (4) and (4*R,5*S**)-4-Acetoxy-15,16-dimethoxy-7-(methylthio)erythrin-6-en-8-one (5): General Procedure for $Mn(OAc)_3$-Mediated Cyclization.** To a mixture of $Mn(OAc)_3 \cdot 2H_2O$ (391 mg, 1.43 mmol) and $Cu(OAc)_2$ (25.9 mg, 0.143 mmol) in boiling CF_3CH_2OH (5 mL) was added dropwise a solution of **3** (50.0 mg, 0.143 mmol) in CF_3CH_2OH (2 mL) and the mixture was heated under reflux for 13 h. Et_2O (5 mL) was added to the reaction mixture and the precipitated salts were removed by filtration with Celite. A saturated aqueous solution of hydroxylamine hydrochloride was added to the filtrate until the brown color of the solution faded. A 10% w/w aqueous solution of ethylenediaminetetraacetic acid disodium salt (5 mL) was added to the mixture to remove Cu(II). The organic phase was separated and an aqueous phase was further extracted with AcOEt. The combined organic phase was washed successively with a saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 10:1 to 5:1). The first fraction gave **4** (19.1 mg, 39%): IR ν 1680 cm^{-1}; ^1H NMR δ 1.81 (quint, $J = 6.3$ Hz, 2H), 2.30 (q, $J = 5.5$ Hz, 2H), 2.50 (s, 3H), 2.60 (t, $J = 6.6$ Hz, 2H), 2.81 (t, $J = 7.6$ Hz, 2H), 3.74 (t, $J = 7.6$ Hz, 2H), 3.85 (s, 6H), 5.50 (t, $J = 4.8$ Hz, 1H), 6.69−6.80 (m, 3H); ^{13}C NMR δ 15.4, 23.1, 23.3, 24.3, 34.6, 41.2, 55.8, 55.9, 109.8, 111.3, 112.1, 120.7, 122.3, 131.2, 138.2, 144.0, 147.6, 148.9, 168.0; HRMS calcd for $C_{19}H_{23}NO_3S$ (M^+) 345.1398, found 345.1393. The second fraction gave **5** (29.8 mg, 52%): mp 156−157 °C (EtOH); IR ν 1735, 1675 cm^{-1}; ^1H NMR δ 1.76−1.96 (m, 4H), 2.00 (s, 3H), 2.49 (s, 3H), 2.74−2.82 (m, 1H), 2.88 (ddd, $J = 15.8$, 6.3, 4.0 Hz, 1H), 3.30 (ddd, $J = 15.8$, 9.8, 6.5 Hz, 1H), 3.38−3.57 (m, 2H), 3.64 (ddd, $J = 12.2$, 10.2, 7.0 Hz, 1H), 3.88 (s, 6H), 5.34 (d, $J = 2.6$ Hz, 1H), 6.76 (s, 1H), 7.01 (s, 1H); ^{13}C NMR δ 15.7, 20.3, 21.0, 25.8. 27.3, 27.9, 38.7, 55.9, 56.5, 68.3, 73.5, 110.6, 112.3, 127.2, 129.0, 129.9, 147.0, 148.8, 156.4, 169.9. Anal. Calcd for $C_{21}H_{25}NO_5S$: C, 62.51; H, 6.25; N, 3.47. Found: C, 62.36; H, 6.29; N, 3.37. The structure of **5** was established by X-ray crystallographic analysis.

Transformation of 4 to 5: (a) With $Mn(OAc)_3$ and $Cu(OAc)_2$. Following the general procedure, compound **4** (49.1 mg, 0.142 mmol) was treated with $Mn(OAc)_3 \cdot 2H_2O$ (157 mg, 0.569 mmol) and $Cu(OAc)_2$ (25.8 mg, 0.142 mmol) in boiling CF_3CH_2OH (10 mL) for 48 h. After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 10:1 to 5:1). The first fraction gave **4** (28.0 mg, 57%). The second fraction gave **5** (21.0 mg, 37%). **(b) With $Mn(OAc)_3$ Alone.** Following the genenal procedure, compound **4** (70.6 mg, 0.205 mmol) was treated with $Mn(OAc)_3 \cdot 2H_2O$ (224 mg, 0.818 mmol) in boiling CF_3CH_2OH (13 mL) for 72 h. After workup, the crude material was chromatographed on silice gel (hexane/AcOEt, 10:1 to 5:1). The first fraction gave **4** (35.8 mg, 51%). The second fraction gave **5** (25.3 mg, 31%).

***N*-(Cyclohex-1-enyl)-*N*-(3,4-dimethoxybenzyl)-2-(methylthio)acetamide (6a).** A solution of cyclohexanone (196 mg, 2 mmol) and veratrylamine (334 mg, 2 mmol) in toluene (20 mL) was heated under reflux for 5 h with azeotropic removal of water. After the mixture was cooled, a solution of chloroacetyl chloride (271 mg, 2.4 mmol) in toluene (10 mL) was added at 0 °C and the mixture was stirred at room temperature for 2 h. Et_3N (0.836 mL, 6 mmol) was added to this mixture at 0 °C and the mixture was further stirred at room temparature for 2 h. The reaction mixture was washed successively with a saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. The crude *N*-(cyclohex-

1-enyl)-*N*-(3,4-dimethoxybenzyl)-2-chloroacetamide thus obtained was dissolved in EtOH (5 mL) and the solution was added dropwise to a solution of NaSMe (295 mg, 4 mmol) in EtOH (10 mL) at 0 °C. The mixture was stirred at room temperature overnight and the solvent was evaporated off. The residue was dissolved in water (10 mL) and the mixture was extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 10:1) to give **6a** (254 mg, 38%): IR ν 1635 cm^{-1}; ^1H NMR δ 1.53−1.74 (m, 4H), 2.03 (m, 4H), 2.26 (s, 3H), 3.28 (s, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.56 (br s, 2H), 5.47 (s, 1H), 6.79 (s, 2H), 7.26 (s, 1H); ^{13}C NMR δ 16.3, 21.3, 22.6, 24.6, 28.1, 35.1, 49.1, 55.7, 110.5, 111.7, 120.8, 128.7, 130.4, 138.0, 148.1, 148.6, 168.7; HRMS calcd for $C_{18}H_{25}NO_3S$ (M^+) 335.1555, found 335.1559.

***N*-(1,3-Benzodioxol-5-ylmethyl)-*N*-(cyclohex-1-enyl)-2-(methylthio)acetamide (6b).** Using a procedure similar to that described above for **6a**, compound **6b** (543 mg, 34%) was obtained from cyclohexanone (491 mg, 5.00 mmol), piperonylamine (756 mg, 5.00 mmol), chloroacetyl chloride (678 mg, 6.00 mmol), and NaSMe (738 mg, 10.0 mmol): IR ν 1635 cm^{-1}; ^1H NMR δ 1.25−1.70 (m, 4H), 2.03 (br s, 4H), 2.25 (s, 3H), 3.28 (s, 3H), 4.52 (s, 2H), 5.48 (br s, 1H), 5.92 (s, 2H), 6.71 (s, 2H), 6.81 (s, 1H); ^{13}C NMR δ 16.3, 21.3, 22.6, 24.6, 28.1, 35.1, 49.2, 100.8, 107.7, 109.1, 121.9, 128.8, 131.7, 138.0, 146.6, 147.4, 168.8; HRMS (FAB) calcd for $C_{17}H_{22}NO_3S$ (MH^+) 320.1321, found 320.1327.

1,4,5,6-Tetrahydro-1-(3,4-dimethoxybenzyl)-3-methylthio-2*H*-indol-2-one (7a). Following the general procedure, compound **6a** (61.5 mg, 0.183 mmol) was treated with $Mn(OAc)_3{\cdot}2H_2O$ (502 mg, 1.83 mmol) and $Cu(OAc)_2$ (33.2 mg, 0.183 mmol) in CF_3CH_2OH. After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 10:1) to give **7a** (58.1 mg, 96%): IR ν 1685 cm^{-1}; ^1H NMR δ 1.80 (quint, J = 6.2 Hz, 2H), 2.28 (q, J = 5.5 Hz, 2H), 2.53 (s, 3H), 2.62 (t, J = 6.4 Hz, 2H), 3.85 (s, 6H), 4.70 (s, 2H), 5.54 (t, J = 4.6 Hz, 1H), 6.74−6.87 (m, 3H); ^{13}C NMR δ 15.5, 23.0, 23.3, 24.3, 43.0, 55.8, 55.9, 110.6, 110.7, 111.0, 119.5, 122.1, 129.9, 138.2, 144.5, 148.3, 149.1, 168.1; HRMS calcd for $C_{18}H_{21}NOS$ (M^+) 331.1242, found 331.1244.

1-(1,3-Benzodioxol-5-ylmethyl)-1,4,5,6-tetrahydro-3-methylthio-2*H*-indol-2-one (**7b**). Following the general procedure, compound **6b** (90.6 mg, 0.284 mmol) was treated with $Mn(OAc)_3{\cdot}2H_2O$ (777 mg, 2.84 mmol) and $Cu(OAc)_2$ (51.6 mg, 0.284 mmol) in CF_3CH_2OH. After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 10:1). The first fraction gave **7b** (66.0 mg, 74%): IR ν 1685 cm^{-1}; ^1H NMR δ 1.80 (quint, J = 6.1 Hz, 2H), 2.28 (q, J = 5.5 Hz, 2H), 2.53 (s, 3H), 2.62 (t, J = 6.4 Hz, 2H), 4.66 (s, 2H), 5.50 (t, J = 4.8 Hz, 1H), 5.92 (s, 2H), 6.71−6.81 (m, 3H); ^{13}C NMR δ 15.3, 23.0, 23.2, 24.2, 42.8, 101.0, 107.9, 108.1, 109.9, 118.0, 120.4, 131.3, 138.1, 144.0, 146.8, 147.9, 167.8; HRMS (FAB) calcd for $C_{17}H_{18}NO_3S$ (MH^+) 316.1008, found 316.1001. The second fraction gave the starting meterial **6b** (10.0 mg, 11%).

***N*-[2-(1,3-Benzodioxol-5-yl)ethyl]-*N*-(cyclohex-1-enyl)-2-(methylthio)acetamide (8)**. Using a procedure similar to that described above for **6a**, compound **8** (807 mg, 41%) was prepared from cyclohexanone (580 mg, 5.91 mmol), 3,4-(methylenedioxyphenyl)ethylamine (977 mg, 5.91 mmol), chloroacetyl chloride (801 mg, 7.09 mmol), and NaSMe (431 mg, 5.84 mmol): IR ν 1635 cm^{-1}; ^1H NMR δ 1.55−1.77 (m, 4H), 2.04−2.13 (m, 4H), 2.23 (s, 3H), 2.77 (t, J = 7.9 Hz, 2H), 3.24 (s, 2H), 3.55 (br t, J = 7.9 Hz, 2H), 5.63 (br s, 1H), 5.91 (s, 2H), 6.66−6.74 (m, 3H); ^{13}C NMR δ 16.3, 21.4, 22.7, 24.7, 27.9, 33.9, 35.2, 47.6, 100.7, 108.1, 109.2, 121.6, 128.0, 132.8, 130.6, 145.9, 147.5, 168.7; HRMS (FAB) calcd for $C_{18}H_{24}NO_3S$ (MH^+) 334.1477, found 334.1474.

1-[2-(1,3-Benzodioxol-5-yl)ethyl]-1,4,5,6-tetrahydro-3-methylthio-2*H*-indol-2-one (9), 1-{2-[2-(2,2,2-Trifluoroethoxy)-1,3-benzodioxol-5-yl]ethyl}-1,4,5,6-tetrahydro-3-methylthio-2*H*-indol-2-one (10), and (4*R,5*S**)-4-Acetoxy-15,16-methylenedioxy-7-(methylthio)erythrin-6-en-8-one (11)**. Following the general procedure, compound **8** (94.1 mg, 0.282 mmol) was treated with $Mn(OAc)_3{\cdot}2H_2O$ (772 mg, 2.82 mmol) and $Cu(OAc)_2$ (51.2 mg, 0.282 mmol) in CF_3CH_2OH. After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 20:1 to 10:1 to 5:1 to 3:1). The first fraction gave **9** (26.4 mg, 28%): IR ν 1715 cm^{-1}; ^1H NMR δ 1.81 (quint, J = 6.3 Hz, 2H), 2.31 (q, J = 5.5 Hz, 2H), 2.49 (s, 3H), 2.61 (t, J = 6.3 Hz, 2H), 2.77 (t, J = 7.6 Hz, 2H), 3.70 (t, J = 7.6 Hz, 2H), 5.46 (t, J = 4.8 Hz, 1H), 5.92 (s, 2H), 6.63 (dd, J = 7.8, 1.8 Hz, 1H), 6.68 (d, J = 1.3 Hz, 1H), 6.72 (d, J = 7.9 Hz, 1H); ^{13}C NMR δ 15.3, 23.2, 23.3, 24.3, 34.9, 41.2, 100.8, 108.3, 108.9, 109.3, 121.7, 122.4, 132.5, 138.3, 143.6, 146.1, 147.7, 167.7; HRMS calcd for $C_{18}H_{19}NO_3S$ (M^+) 329.1085, found 329.1093. The second fraction gave **10** (25.2 mg, 21%): IR ν 1715 cm^{-1}; ^1H NMR δ 1.81 (quint, J = 6.3 Hz, 2H), 2.30 (q, J = 5.4 Hz, 2H), 2.48 (s, 3H), 2.61 (t, J = 6.6 Hz, 2H), 2.80 (t, J = 7.6 Hz, 2H), 3.72 (t, J = 7.6 Hz, 2H), 3.96 (q, J = 8.4 Hz, 2H), 5.46 (t, J = 4.6 Hz, 1H), 6.73 (dd, J = 7.9, 1.7 Hz, 1H), 6.76 (d, J = 1.3 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 6.93 (s, 1H); ^{13}C NMR δ 15.3, 23.2, 23.3, 24.3, 34.9, 41.1, 60.2 (q, J = 36.6 Hz), 77.2, 108.4, 108.7, 109.3, 117.8, 122.5, 133.4, 138.3, 143.5, 144.0, 145.5, 167.7; HRMS calcd for $C_{20}H_{20}F_3NO_4S$ (M^+) 427.1065, found 427.1077. The third fraction gave the starting material **8** (5.4 mg, 6%). The fourth fraction gave **11** (trace): IR ν 1680, 1735 cm^{-1}; ^1H NMR δ 1.74−1.97 (m, 4H), 1.99 (s, 3H), 2.47 (s, 3H), 2.76−2.89 (m, 2H), 3.27−3.56 (m, 4H), 5.33 (d, J = 3.0 Hz, 1H), 5.94 (d, J = 1.3 Hz, 1H), 5.97 (d, J = 1.3 Hz, 1H), 6.74 (s, 1H), 6.97 (s, 1H).

***N*-(Cyclohex-1-enyl)-*N*-(2-phenylethyl)-2-(methylthio)-acetamide (12).** Using a procedure similar to that described above for **6a**, compound **12** (1.21 g, 61%) was obtained from cyclohexanone (687 mg, 7.00 mmol), 2-phenylethylamine (848 mg, 7.00 mmol), chloroacetyl chloride (949 mg, 8.40 mmol), and NaSMe (1.03 g, 16.8 mmol): IR ν 1635 cm^{-1}; ^1H NMR δ 1.56−1.73 (m, 4H), 2.08−2.09 (m, 4H), 2.22 (s, 3H), 2.85 (t, J = 7.9 Hz, 2H), 3.24 (s, 2H), 3.60 (br t, J = 7.9 Hz, 2H), 5.60 (br s, 1H), 7.18−7.30 (m, 5H); ^{13}C NMR δ 16.2, 21.3, 22.6, 24.5, 27.8, 34.0, 35.1, 47.2, 126.0, 127.9, 128.2, 128.6, 138.5, 138.9, 168.6; HRMS calcd for $C_{17}H_{23}NOS$ (M^+) 289.1500, found 289.1494.

1,4,5,6-Tetrahydro-3-methylthio-1-(2-phenylethyl)-2*H*-indol-2-one (13) and (7*R,7a*R**)-7-Acetoxy-1,4,5,6-tetrahydro-7a-hydroxy-3-methylthio-1-(2-phenylethyl)-2*H*-indol-2-one (14).** Following the general procedure, compound **12** (55.9 mg, 0.194 mmol) was treated with $Mn(OAc)_3{\cdot}2H_2O$ (531 mg, 1.94 mmol) and $Cu(OAc)_2$ (35.2 mg, 0.194 mmol) in CF_3CH_2OH. After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 10:1). The first fraction gave **13** (48.5 mg, 88%): IR ν 1690 cm^{-1}; ^1H NMR δ 1.80 (quint, J = 6.7 Hz, 2H), 2.28 (q, J = 5.9 Hz, 2H), 2.50 (s, 3H), 2.57−2.63 (m, 2H), 2.86 (t, J = 7.8 Hz, 2H), 3.77 (t, J = 7.8 Hz, 2H), 5.43 (t, J = 4.6 Hz, 1H), 7.18−7.31 (m, 5H); ^{13}C NMR δ 15.2, 23.1, 23.2, 24.3, 35.1, 41.0, 108.8, 126.4, 128.4, 128.8, 128.9, 138.2, 138.7, 143.4, 167.6; HRMS calcd for $C_{17}H_{19}NOS$ (M^+) 285.1188, found 285.1181. The second fraction gave **14** (8.0 mg, 11%): IR ν 1740, 1695 cm^{-1}; ^1H NMR δ 1.43−1.61 (m, 2H), 1.75−1.90 (m, 2H), 1.93 (s, 3H), 2.24 (td, J = 13.4, 5.6 Hz, 1H), 2.52 (s, 3H), 2.74−2.88 (m, 2H), 3.03−3.28 (m, 2H), 3.58 (ddd, J = 13.9, 8.5, 4.7 Hz, 1H), 5.23 (br s, 1H), 7.17−7.32 (m, 5H); ^{13}C NMR δ 15.8, 20.9, 21.2, 24.3, 26.1, 34.4, 41.2, 71.3, 77.2, 87.5, 126.6, 128.7, 129.0, 139.4, 155.6, 168.5, 169.5; HRMS calcd for $C_{19}H_{23}NO_4S$ (M^+) 361.1348, found 361.1353.

Attempted Cyclization of 16. Following the general procedure, compound **16**[9] (86.9 mg, 0.290 mmol) was treated with $Mn(OAc)_3{\cdot}2H_2O$ (318 mg, 1.16 mmol) and $Cu(OAc)_2$ (52.7 mg, 0.290 mmol) in CF_3CH_2OH for 6 h. After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 2:1) to give recovered **16** (69.0 mg, 79%): ^1H NMR δ 1.74−1.84 (m, 2H), 2.24−2.31 (m, 2H), 2.57−2.63 (m, 2H), 2.77−2.84 (m, 2H), 3.70−3.76 (m, 2H), 3.85 (s, 6H), 5.47 (br t, J = 4.6 Hz, 1H), 5.74 (s, 1H), 6.70−6.81 (m, 3H).

(±)-(15,16-Dimethoxy-7*β*-methylthio-*cis*-erythrinan-8-one (17). To a mixture of $Mn(OAc)_3 \cdot 2H_2O$ (234 mg, 0.858 mmol) and $Cu(OTf)_2$ (51.7 mg, 0.143 mmol) in boiling CF_3CH_2OH (7 mL) was added dropwise a solution of **3** (50.0 mg, 0.143 mmol) in CF_3CH_2OH (3 mL), and the mixture was heated under reflux for 4 h. After the usual workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 1:1) to give **17** (27.0 mg, 54%): mp 169−170 °C ($CHCl_3$/AcOEt) [lit.[6] mp 169.5−170.5 °C ($CHCl_3$/AcOEt)]; IR ν 1678 cm^{-1}; ^1H NMR δ 1.51−2.37 (m, 7H), 2.11 (s, 3H), 2.73−2.99 (m, 3H), 3.23−3.34 (m, 2H), 3.35 (d, J = 9.6 Hz, 1H), 3.87 (s, 3H), 3.90 (s, 3H), 4.05−4.14 (m, 1H), 6.62 (s, 1H), 6.94 (s, 1H).

(±)-2,2-Ethylenedioxy-15,16-dimethoxy-7*β*-methylthio-*cis*-erythrinan-8-one (19). Using a procedure similar to that discribed above for **17**, compound **18**[11] (50.0 mg, 0.123 mmol) was treated with $Mn(OAc)_3 \cdot 2H_2O$ (202 mg, 0.738 mmol) and $Cu(OTf)_2$ (44.5 mg, 0.123 mmol) in boiling CF_3CH_2OH (8 mL) for 9 h. After the usual workup, the crude material was chromatographed on silice gel (hexane/AcOEt, 1:3) to give **19** (27.0 mg, 54%): mp 169.5−170.5 °C (hexane/AcOEt) [lit.[11] mp 170−171 °C (hexane/AcOEt)]; IR ν 1680 cm^{-1}; ^1H NMR δ 1.65−2.01 (m, 4H), 2.09 (s, 3H), 2.26−2.28 (m, 2H), 2.47 (ddd, J = 9.5, 5.6, 3.9 Hz, 1H), 2.76 (ddd, J = 16.1, 5.6, 3.6 Hz, 1H), 2.94 (ddd, J = 16.1, 9.6, 6.6 Hz, 1H), 3.20−3.31 (m, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 3.90−3.92 (m, 5H), 4.14 (ddd, J = 13.2, 6.6, 3.6 Hz, 1H), 6.61 (s, 1H), 6.83 (s, 1H).

1,4,5,6-Tetrahydro-1-[3-(3,4-dimethoxyphenyl)propyl]-3-methylthio-2*H*-indol-2-one (22) and (7*S,7a*R**)-7-Acetoxy-7a-(2,2,2-trifluoroethoxy)-1,4,5,6-tetrahydro-1-[3-(3,4-dimethoxyphenyl)propyl]-3-methylthio-2*H*-indol-2-one (23).** Following the general procedure, compound **21**[11] (76.0 mg, 0.209 mmol) was treated with $Mn(OAc)_3 \cdot 2H_2O$ (572 mg, 2.09 mmol) and $Cu(OAc)_2$ (38.0 mg, 0.209 mmol) in boiling CF_3CH_2OH (10 mL) for 7 h. After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 10:1 to 2:1 to 1:1). The first fraction gave **22** (60.4 mg, 80%): IR ν 1685 cm^{-1}; ^1H NMR δ 1.80−1.95 (m, 4H), 2.28 (q, J = 5.9 Hz, 2H), 2.50 (s, 3H), 2.54−2.63 (m, 4H), 3.58 (t, J = 7.3 Hz, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 5.48 (t, J = 4.8 Hz, 1H), 6.71−6.80 (m, 3H); ^{13}C NMR δ 15.3, 23.2, 23.3, 24.3, 30.4, 32.7, 39.0, 55.9, 56.0, 108.8, 111.3, 111.8, 120.1, 122.4, 134.1, 138.5, 143.5, 147.3, 148.9, 167.9; HRMS calcd for $C_{20}H_{25}NO_3S$ (M^+) 359.1556, found 359.1548. The second fraction gave the starting material **21** (14.0 mg, 18%). The third fraction gave **23** (trace) as an oil: IR ν 1730, 1695 cm^{-1}; ^1H NMR δ 1.67−2.26 (m, 5H), 2.02 (s, 3H), 3.31−3.50 (m, 2H), 3.84 (s, 3H), 3.84−3.87 (m, 4H), 3.87 (s, 3H), 4.61 (dd, J = 11.6, 4.3 Hz, 1H), 6.69−6.80 (m, 3H); HRMS calcd for $C_{24}H_{30}F_3NO_6S$ (M^+) 517.1746, found 517.1743.

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Supporting Information Available: ^1H NMR spectra for **4**, **5**, **6a**,**b**, **7a**,**b**, **8**−**14**, **22**, and **23**; ^{13}C NMR spectra for **4**, **5**, **6a**,**b**, **7a**,**b**, **8**−**10**, **12**−**14**, and **22**; and X-ray crystal structure data for **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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