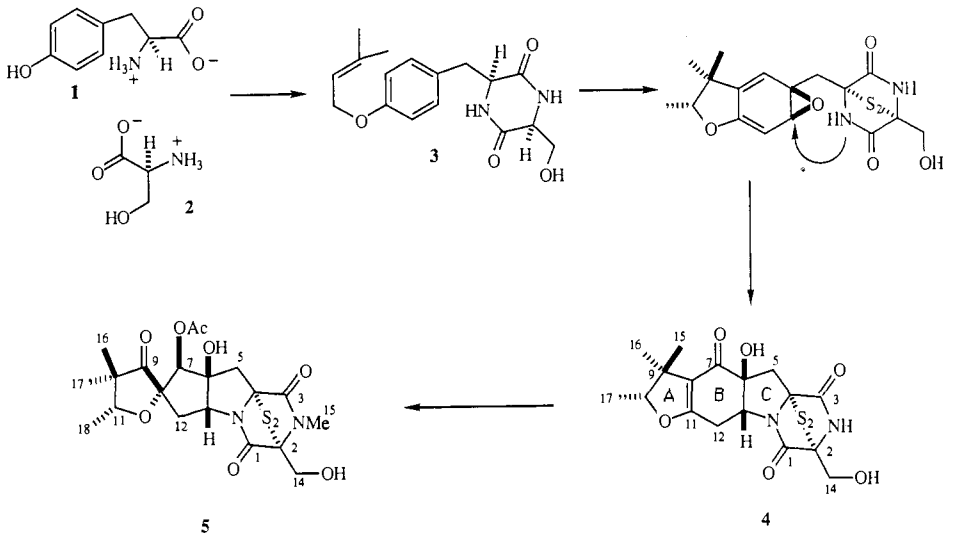
Scheme I



intermolecular hydrogen bond formed between O14 and O1.

Phomalirazine (**4**) possesses a new ring system, and its epidithiodioxopiperazine group is unusual because one of the nitrogen atoms is not alkylated.[13] The biosynthesis of polythiodioxopiperazines has been studied, and a general pathway is acknowledged.[14,15] Cyclic dipeptides act as precursors of epipolythiodioxopiperazines; however, there are very few intermediates which give any clues on the sequence of steps necessary to accomplish the transformation. In particular for "sirodesmins" a pathway was proposed[16] and later partly confirmed by the incorporation of L-tyrosine (**1**), L-serine (**2**), and the cyclic dipeptide **3** into sirodesmin PL (**5**).[17] The sequence of steps required to transform **3** into **5**, namely introduction of the disulfur bridge, N-methylation, and cyclization to form both the A and the C rings, is not known. Phomalirazine (**4**) is a likely intermediate between **3** and **5** (Scheme I). This proposal is consistent with the absolute configurations of compounds **4** and **5**. Carbons 2, 4, 6, 10, and 13 of **4** have absolute configurations identical with carbons 2, 4, 6, 11, and 13, respectively, of sirodesmin PL (**5**). The isolation of **4** indicates that, during the transformation of **3** into **5**, oxidative cyclization through a possible arene oxide intermediate[16] (to form the C ring) occurs prior to the N-methylation step. Oxidative ring contraction of the B ring of phomalirazine can then originate sirodesmin PL (**5**).

Recently there has been a renewed interest in the epipolythiodioxopiperazines due to their inhibitory effect on platelet aggregation and immunosuppressive properties.[18,19] Metabolites containing that group have been isolated from diverse fungal sources,[14] and their biological activity has been associated with the epipolythiodioxopiperazine group.[18,20,21]

Phomalirazine is active at 10^{-5} M in a cotyledon assay, whereas sirodesmin PL is active at 2×10^{-4} M. Further biological studies are under way.

Acknowledgment. A culture of *P. lingam* was provided by Dr. G. A. Petrie, Agriculture Canada Research Station, Saskatoon. M.S.C.P. thanks the Natural Sciences and Engineering Research Council (Canada) for financial support in the form of a Canadian Government Laboratory Visiting Fellowship. J.W.Q. and Z.J. thank Dr. L. T. J. Delbaere for use of facilities for collecting data and Dr. Prasad for valuable suggestions. Z.J. thanks the Department of Chemistry, University of Saskatchewan for financial support through a graduate scholarship (NRCC No. 29584).

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, interatomic distances, and interatomic and torsional angles for phomalirazine and an ORTEP drawing of **4** along with a packing diagram illustrating the hydrogen bonding (8 pages). Ordering information is given on any current masthead page.

(13) See, for example: Turner, W. B.; Aldridge, D. C. *Fungal Metabolites II*; Academic: New York, 1983; pp 417-422.

(14) Taylor, A. *Microbial Toxins Vol VII*; Kadis, S., Ciegler, A., Ajl, S. J., Eds.; Academic: New York, 1971; pp 337-376, and references therein.

(15) Kirby, G. W.; Robins, D. J. *The Biosynthesis of Mycotoxins*; Stein, P. S., Ed.; Academic: New York, 1980; pp 301-326.

(16) Curtis, P. J.; Greatbanks, D.; Hesp, B.; Cameron, A. F.; Freer, A. A. *J. Chem. Soc., Perkin Trans 1* **1977**, 180-189.

(17) Férézou, J. P.; Quesneau-Thierry, A.; Servy, C.; Zissmann, E.; Barbier, M. *J. Chem. Soc., Perkin Trans 1* **1980**, 1739-1746.

(18) Sakay, M.; Watanuki, M. *Agric. Biol. Chem.* **1987**, *51*, 2167-2170.

(19) Mullbacher, A.; Eichner, R. D. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 3835-3837.

(20) Brewer, D.; Hannah, D. E.; Taylor, A. *Can. J. Microbiol.* **1966**, *12*, 1187-1195.

(21) Murdock, K. C. *J. Med. Chem.* **1974**, *17*, 827-835.

The Ambiphilic Nature of *N*-Acyliminium Ion-Enamide Tautomers. A Novel Annulation to Enantiomerically Pure Polycyclic Frameworks

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The recently promoted synthetic utility of *N*-acyliminium ions has been reviewed by Speckamp and Hiemstra.[1] These authors and others have also contributed a vast amount of useful chemistry[2] to this subject by treating succinimides **1** with borohydride to afford the carbinol amides **2A** (R = H). These species are in facile acid-catalyzed equilibrium with the *N*-acyliminium ions **2B** (R = H) which are, in turn, capable of intramolecular capture of a wide variety of nucleophiles (Nuc:alkene, alkyne, aryl, enamine, etc.) producing polycyclic systems such as **3**. In spite of the impressive behavior of acyliminium ions, there is still one member of the family (**2C**) which has shown little, if any, synthetic importance.[3] Thus, deprotonation of **2B** or dehydration of **2A**

(1) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

(2) Klaver, W. J.; Moolenaar, M. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1988**, *44*, 3805 and earlier references cited.

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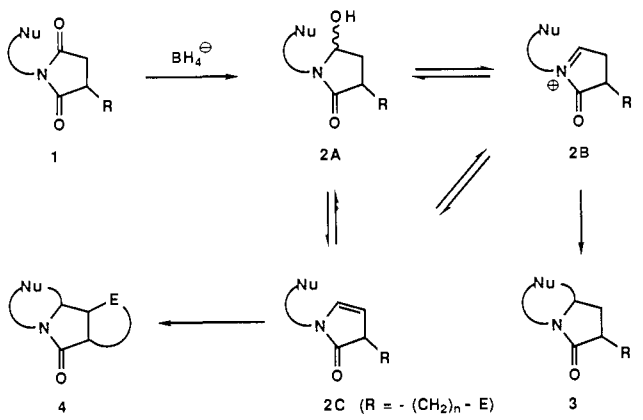
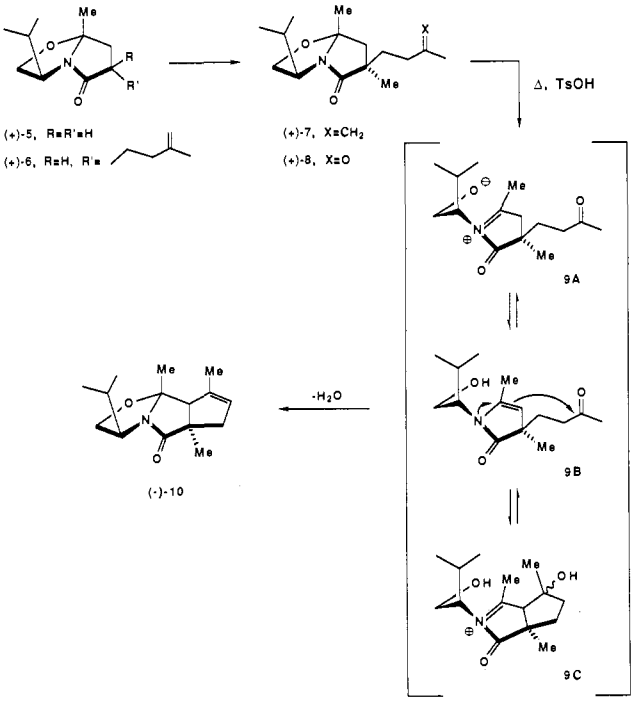


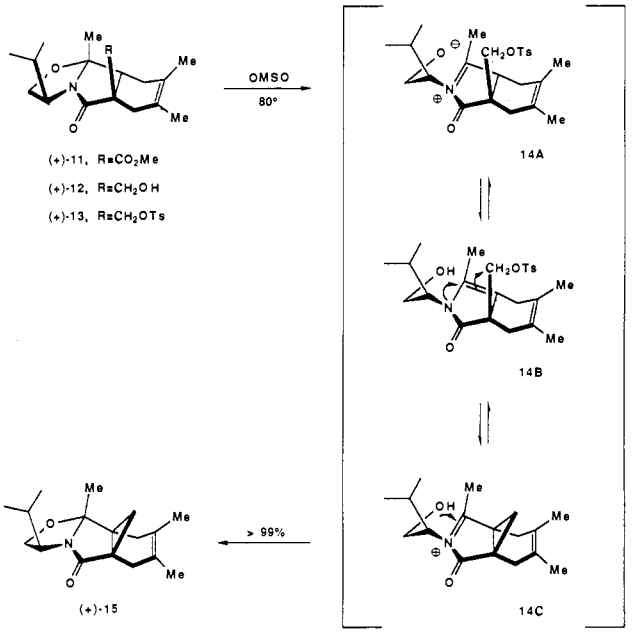
introduces the enamide **2C** as an active player in the potential intramolecular reaction with electrophiles and may cyclize to the 1-azabicyclo system **4** via the acyliminium ion, as described above. We wish to report some preliminary observations which hold great promise for the intermediate enamide **2C** in the trio depicted by **2A–C**. The potential of **2C** for intramolecular alkylation by an electrophile to give **4** is the purpose of this communication. Furthermore, the products of these enamide alkylations, as performed herein, are enantiomerically pure and represent some rather diverse carbon frameworks.

Treatment of **5**[4] with LDA followed by prenyl iodide gives high yields of **6** (endo-preferred alkylation), and a second metalation



followed by methyl iodide gives **7** (endo-preferred alkylation) as a 91:9 mixture of diastereomers. Pure (+)-**7** was isolated in 84% yield after flash chromatography. Ozonolysis of (+)-**7** gave the ketone (+)-**8** in 98% yield which now represents the precursor to this novel annulation. When **8** was heated in toluene at reflux for 30 min (*p*-TsOH, 3Å molecular sieves), a single product **10** ($[\alpha]_D$ −75.0°, *c* 1.3, $CHCl_3$) was obtained in 80% yield. It is assumed that the latter arose from the series of intermediates which incude the initially formed *N*-acyliminium ion **9A**, via thermal- or acid-catalyzed ring fracture of **8**. The cascade of **9A** to enamide **9B**, cyclization to **9C**, and ring closure may be viewed as a possible pathway for the formation of (−)-**10**.[5] Thus, we have evidence for the first time that these bicyclic lactams **5–8** are capable of ring fracture–ring repair while simultaneously giving rise to a nucleophilic species.[6]

We have observed another analogous annulation which implies that this interesting property may, in fact, be rather general in scope. The diastereomerically pure system **11** was generated in



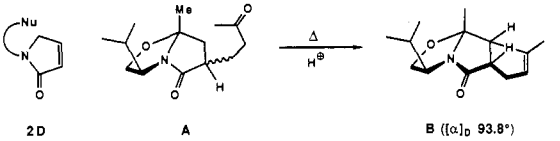
a (4 + 2) cycloaddition of 2,3-dimethylbutadiene and the α-carbomethoxy-α,β-unsaturated lactam.[7] Reduction to the primary alcohol **12** was accomplished in 94% yield with $NaBH_4$, and transformation to the tosylate **13** was performed under usual conditions (TsCl, DMAP, CH_2Cl_2, 25 °C, 99% yield). When this tosylate was heated in dimethyl sulfoxide (80 °C, 9 h), the cyclopropane derivative **15** was produced in quantitative yield. This product may also be considered to arise via the thermal- or acid-catalyzed ring fracture of **13** to the *N*-acyliminium ion **14A** which, after proton transfer, furnishes **14B**. The latter is then in a primed position for tosylate displacement producing the

(3) (a) Tamura, Y.; Maeda, H.; Akai, S.; Ishibashi, H. *Tetrahedron Lett.* **1982**, 2209. (b) Lenz, G. R.; Woo, C.-M.; Hawkins, B. L. *J. Org. Chem.* **1982**, *47*, 3049. (c) Meth-Cohn, O.; Westwood, K. T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1173. (d) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697. (e) Brossi, A.; Dolan, L. A.; Teitel, S. *Org. Synth.* **1977**, *56*, 3.

(4) Preparation and alkylation of **5** has been reported in the context of preparing a number of chiral, quaternary-substituted compounds, e.g.: Meyers, A. I.; Lefker, B. A. *Tetrahedron* **1987**, *43*, 5663 and earlier references cited.

(5) A referee has astutely pointed out that the scheme **9A–C** may be alternatively reviewed by the intervention of an intermediate derived from **9B**. Thus, hydroxyl addition to the amide carbonyl would produce a hemiamino ortho ester which would behave more like a traditional enamine. After C-alkylation, the hydroxyl could return to its original position and reclose the bicyclic system, via **9C**. This would require several extra steps, but it is not an unreasonable pathway, and proof of either process must await further study.

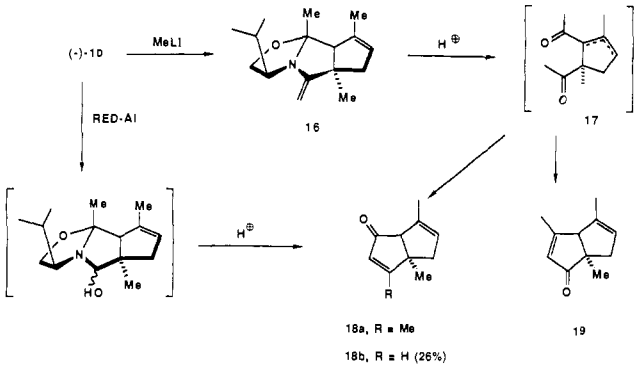
(6) The possibility exists that the α,β-unsaturated lactam **2D** is also a component in the equilibrium of **2A–2C** and if true would appear when a proton is present in the α-position to the carbonyl in **9B**. Thus, **A**, as a mixture of endo/exo epimers, was heated in toluene and gave a single annulated product **B** in 57% yield. This result strongly implies that this process will not be limited to quaternary substituted lactams such as **8** and **13**.



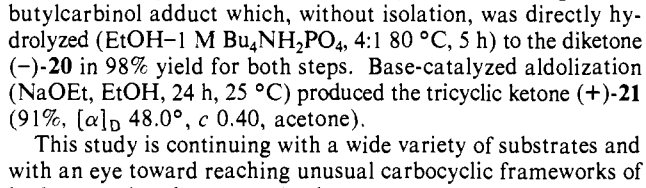
(7) The preparation of this compound is analogous to that prepared in earlier reports from our laboratory: Meyers, A. I.; Fleming, S. A. *J. Am. Chem. Soc.* **1986**, *108*, 306. Further details for the synthesis of **11** may be found in the Supplementary Material section. A more complete account of this cycloaddition will be forthcoming (Busacca, C., research in progress.)

acylium ion **14C** which rapidly recyclizes to the product (+)-**15**. The facility with which this process occurs both in the cyclopentano annulation **10** and the cyclopropano annulation **15** bodes well for its synthetic utility.

To demonstrate that these in situ enamide alkylations to **10** and **15** are only part of the inherent interest in these systems, we were able to transform them into chiral, nonracemic carbocycles. Thus, treatment of **10** with methyllithium (−78 °C to −40 °C,



THF) gave the dehydrated addition product **16** and then directly hydrolyzed (EtOH–1 M $Bu_4NH_2PO_4$, 1:1, 80 °C, 24 h), via the diketone **17**, to a 5:1 mixture of the novel chiral cyclopentenones **18a** ($[\alpha]^{22}_D$ 62.2°, *c* 0.6, $CHCl_3$) and **19** which were readily separated (SiO_2, Et_2O–Hex, 1:10). If (−)-**10** is reduced with RED-Al, the resulting carbinol amine is formed, which was hydrolyzed as above to the chiral cyclopentenone **18b**, along with 52% of the keto aldehyde precursor.[8] In a related manner, the cyclopropane derivative (+)-**15** could also be transformed into



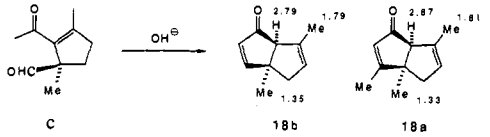
a novel carbocycle. Addition of *n*-butyllithium to **15** gave the butylcarbinol adduct which, without isolation, was directly hydrolyzed (EtOH–1 M $Bu_4NH_2PO_4$, 4:1 80 °C, 5 h) to the diketone (−)-**20** in 98% yield for both steps. Base-catalyzed aldolization (NaOEt, EtOH, 24 h, 25 °C) produced the tricyclic ketone (+)-**21** (91%, $[\alpha]_D$ 48.0°, *c* 0.40, acetone).

This study is continuing with a wide variety of substrates and with an eye toward reaching unusual carbocyclic frameworks of both natural and unnatural substances.

Acknowledgment. We are grateful to the National Institutes of Health and the National Science Foundation for financial support of this work. A fellowship (to St.B.) from the Schweizerische Nationalfonds zur Förderung der Wissenschaftlichen Forschung is also gratefully acknowledged.

Supplementary Material Available: Synthesis, analytical data, and spectral data (^1H NMR; ^{13}C NMR, IR, and MS) for all compounds (17 pages). Ordering information is given on any current masthead page.

(8) Support for the structural assignment of **18a** and **19** is gained from the spectral properties of **18b**. The latter shows proton chemical shifts very similar to **18a**. Since the precursor to **18b** is the keto-aldehyde **C**, it can only cyclize in the manner shown. The isomer **19** is quite different showing angular H at 3.15, angular methyl 1.25, and vinyl methyl at 1.86.



Structural and Electronic Consequences of Protonation in $\{Mn_4O_6\}^{4+}$ Cores: pH Dependent Properties of Oxo-Bridged Manganese Complexes

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Recognition that the oxygen-evolving complex of photosystem II (PSII) employs two to four manganese atoms to carry out catalytic water oxidation[1] has engendered interest in preparing synthetic models for this active site.[2] It is generally thought that ligands derived from water (O^{2-} or OH^-) are present as bridges between manganese atoms in the catalytic site. While a variety of oxo-bridged polynuclear manganese complexes has been characterized,[2] very few hydroxo-bridged species have been reported.[3] In the course of recent studies[2a] aimed at preparing polynuclear manganese complexes, we have discovered a synthetic route which affords the novel mixed oxo/hydroxo-bridged tetranuclear Mn(IV) complex, $[Mn_4O_5(OH)(tame)_4](CF_3SO_3)_5$,[4] $\mathbf{1}(CF_3SO_3)_5$. This compound contains a protonated form of the $\{Mn_4O_6\}^{4+}$ core, also found in $[Mn_4O_6(tacn)_4]^{4+}$.[5] The adamantane-shaped $\{Mn_4O_6\}^{4+}$ core has been proposed as a reaction intermediate in photosynthetic water oxidation.[6] As magnetic measurements have been used extensively to characterize the oxygen-evolving complex, structural and magnetic properties due to protonation of this tetranuclear core are of particular interest.

Compound $\mathbf{1}(CF_3SO_3)_5$ was isolated in approximately 30% yield from a 1:1:3 acetonitrile solution of tame·$3CF_3SO_3H$, $Mn(CF_3SO_3)_2$·MeCN, and Et_3N after exposure to atmospheric O_2 for 36 h. Material suitable for elemental analysis[7] and X-ray diffraction experiments[8] was obtained directly from the reaction mixture. The cluster can be deprotonated by treatment with Et_3N in CH_3CN to give $[Mn_4O_6(tame)_4]^{4+}$ (**2**), which has a visible spectrum[9] very similar to that of $[Mn_4O_6(tacn)_4]^{4+}$ (**3**). For

(1) (a) Brudvig, G. W. In *Metal Clusters in Proteins*; Que, L., Jr., Ed.; ACS Symposium Series 372; American Chemical Society: Washington, DC, 1988; pp 221-237. (b) Pecoraro, V. L. *Photochem. Photobiol.* **1988**, *48*, 249-264. (c) Babcock, G. T. In *New Comprehensive Biochemistry: Photosynthesis*; Amesz, T., Ed.; Elsevier: Amsterdam, 1987; pp 125-158. (d) Dismukes, G. *Photochem. Photobiol.* **1986**, *43*, 89-115. (e) Govindjee; Karmbara, T.; Coleman, W. *Photochem. Photobiol.* **1985**, *42*, 187-210.

(2) Selected examples: (a) Hagen, K. S.; Armstrong, W. H.; Hope, H. *Inorg. Chem.* **1988**, *27*, 967-969. (b) Hagen, K. S.; Armstrong, W. H.; Olmstead, M. M. *J. Am. Chem. Soc.* **1989**, *111*, 774-775. (c) Christou, G.; Vincent, J. B. In *Metal Clusters in Proteins*; Que, L., Jr., Ed.; ACS Symposium Series 372; American Chemical Society: Washington, DC, 1988; pp 238-255. (d) Towle, D. K.; Botsford, C. A.; Hodgson, D. J. *Inorg. Chim. Acta* **1988**, *141*, 167-168. (e) Stebler, M.; Ludi, A.; Bürgi, H.-B. *Inorg. Chem.* **1986**, *25*, 4743-4750. (f) Ménage, S.; Girerd, J.-J.; Gleizes, A. *J. Chem. Soc., Chem. Commun.* **1988**, 431-432. (g) Suzuki, M.; Tokura, S.; Suhara, M.; Uehara, A. *Chem. Lett.* **1988**, 477-480.

(3) (a) Maslen, H. S.; Waters, T. N. *J. Chem. Soc., Chem. Commun.* **1973**, 760-761. (b) Boucher, L. J.; Coe, C. G. *Inorg. Chem.* **1976**, *15*, 1334-1340.

(4) Abbreviations used: tacn = 1,4,7-triazacyclononane, $HNCH_2CH_2NHCH_2CH_2NHCH_2CH_2$; tame = 1,1,1-tris(aminomethyl)ethane, $H_3CC(CH_2NH_2)_3$; PSII = photosystem II.

(5) (a) Wieghardt, K.; Bossek, U.; Gebert, W. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 328-329. (b) Wieghardt, K.; Bossek, U.; Nuber, B.; Weiss, J.; Bonvoisin, J.; Corbella, M.; Vitolis, S. E.; Girerd, J.-J. *J. Am. Chem. Soc.* **1988**, *110*, 7398-7411.

(6) Brudvig, G. W.; Crabtree, R. H. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4586-4588.

(7) Anal. Calcd for $C_{25}H_{61}F_{15}Mn_4N_{12}O_{21}S_5$: C, 19.61; H, 4.02; N, 10.98; S, 10.47. Found: C, 19.68; H, 3.95; N, 10.86; S, 10.56.

(8) X-ray analysis of $\mathbf{1}(CF_3SO_3)_5$. This complex crystallizes in the tetragonal space group $I4_1/a$, with a = 20.935 (3) Å, c = 13.084 (2) Å, V = 5735 Å^3, ρ_{calcd} = 1.773 g cm^{-3}, Z = 4. Data collection at 295 K out to 2θ = 45° afforded 1394 reflections with $I > 3\sigma(I)$. The structure was solved by direct methods and refined by using 200 parameters to final R (R_w) values of 5.47% (7.48%).

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