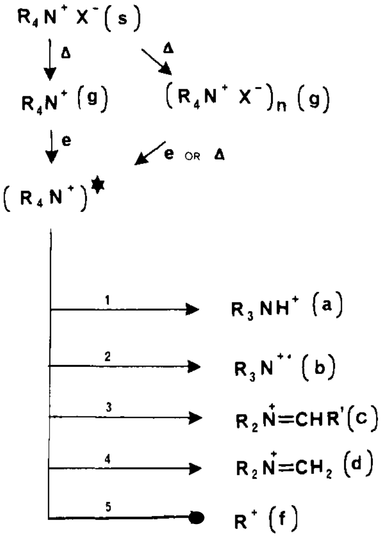

Since the parent ions ($R_4N^+$) have considerably long lifetimes (ca. $10^{-4}$–$10^{-5}$ s, metastable window region) they cannot be electronically excited but only vibrationally excited[13] and are closely related to active species obtained by laser desorption, secondary ion mass spectrometry,[14] plasma desorption, and field desorption (collision-induced dissociation) of these compounds. Although quaternary ammonium cations have hitherto been believed to decompose before evaporation, our results indicate clearly that they survive in a gas phase, are excited into higher vibrational states upon electron impact, and then decompose to give the fragment ions. We believe our results are the first reported examples of electron-impact-induced fragmentation of quaternary ammonium salts.

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(13) Williams, D. H.; Howe, I. "Principles of Organic Mass Spectrometry"; McGraw-Hill: London, 1972; Chapter 1.

(14) Day, R. J.; Unger, S. E.; Cooks, R. G. *J. Am. Chem. Soc.* **1979**, *101*, 501.

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# Nickel-Promoted Cyclization/Carbonylation in the Preparation of α-Methylene γ-Lactones: Stereospecific Synthesis of (±)-Frullanolide

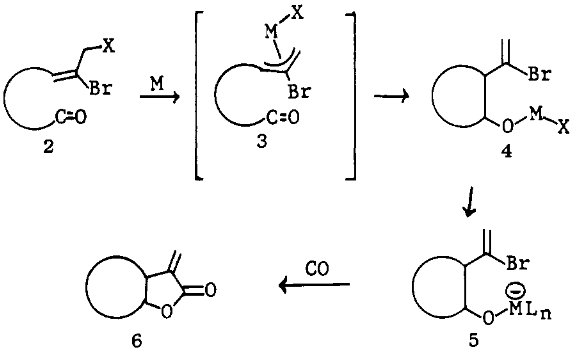
M. F. Semmelhack* and Steven J. Brickner

*Department of Chemistry, Princeton University*
*Princeton, New Jersey 08544*
*and Department of Chemistry, Cornell University*
*Ithaca New York 14853*

*Received December 1, 1980*

The biological activity of compounds containing the α-methylene lactone group has prompted vigorous development of appropriate methodology and many specific syntheses of natural examples.[1] The most common strategy relies on modification of a preformed lactone ring, usually by multistep procedures, for introduction of the α-methylene unit. We have been developing methods based on zero-valent metal reagents which promote crucial carbon–carbon coupling reactions and lactone formation and produce the α-methylene lactones directly.[2,3] We have recently reported[4] formation of α-methylene lactones using nickel carbonyl to promote intramolecular alkoxycarbonylation of vinyl halides, extending the method of Corey and Hegedus.[5] Here we report that these developments can be combined into a simple procedure for α-methylene lactone synthesis, where nickel carbonyl brings about two different carbon–carbon coupling steps. The method is sensitive to sterochemical features as evidenced by sterospecific synthesis of the natural α-methylene γ-lactone, frullanolide (**1**).[6]

Scheme I. General Pathway



(1)

The general procedure is summarized in Scheme I. The allylic system in **2** (X = halide or sulfonate ester) can be activated as an allyl–nickel complex (e.g., **3**, M = Ni)[7] and then cyclize with the aldehyde unit to produce **4** (potentially a cis/trans mixture). While the general method is well precedented,[7,8] no example of a (2-bromoallyl)nickel complex has been characterized or employed in additions to carbonyl units. The proposed intermediate **4** would be formed with M = Ni(II). If M = Ni(0) as in **5**, alkoxycarbonylation to give **6** can be expected;[4] however, exchange of Ni(II) and Ni(0) in species such as **4** has not been studied systematically.

A simple test case was examined. The compounds **11** and **13** were prepared in a direct way starting with a Wadsworth–Emmons procedure[9] (89% yield) using 6,6-dimethoxyhexanal (**8**)[10] and the anion from α-bromo-α-phosphonoacetate **7** in dimethoxyethane at 25 °C for 1.5 h to give the isomers **9**. The isomers **9***Z* and **9***E* were separated by medium pressure liquid chromatography[11] (MPLC), although for preliminary studies mixtures of *E* and *Z* isomers were employed. Reaction of **9** with 2.75 mol equiv of diisobutylaluminum hydride provided the allylic alcohols **10** (80–85%) yield. The double-bond geometries are assigned on the basis of an analysis [12] of the $^1$H NMR spectra of the acrylates **9**. Reaction with phosphorus tribromide and an aqueous isolation procedure converted the alcohols **10** to the allylic bromides **11***E* and **11***Z*. The corresponding methanesulfonate esters (**13***E* and **13***Z*) were obtained in good yield from the hydroxy aldehydes **12** ($Et_3N$, $CH_3SO_2Cl$, 0 °C, $CH_2Cl_2$). Most of the optimization experiments for the nickel-promoted cyclization were carried out

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*Address correspondence to this author at Princeton University.

(1) For recent examples in the pseudoguianolide series and leading references, see M. R. Roberts and R. H. Schlessinger, *J. Am. Chem. Soc.*, **101**, 7626 (1979).

(2) M. F. Semmelhack, E. S. C. Wu, *J. Am. Chem. Soc.*, **98**, 3384 (1976).

(3) M. F. Semmelhack, A. Yamashita, J. C. Tomesh, and K. Hirotsu, *J. Am. Chem. Soc.*, **100**, 5565 (1978).

(4) M. F. Semmelhack and S. J. Brickner, *J. Org. Chem.*, to be published.

(5) (a) E. J. Corey, L. S. Hegedus, *J. Am. Chem. Soc.*, **91**, 1233 n1969). (b) L. S. Hegedus, Ph.D. Thesis, Harvard University, 1969.

(6) (a) The isolation and properties have been described: G. W. Perold, J. C. Muller, and G. Ourisson, *Tetrahedron*, **28**, 5797 (1972). Several syntheses have been reported: (b) A. E. Greene, J. C. Muller, and G. Ourisson, *Tetrahedron Lett.*, 2489 (1972); (c) W. C. Still and M. J. Schneider, *J. Am. Chem. Soc.*, **99**, 948 (1977); (d) F. Kido, R. Maruta, K. Tsutsumi, and A. Yoshikoshi, *ibid*, **101**, 6420 (1979).

(7) See M. F. Semmelhack, *Org. React.* **19**, 119 (1972).

(8) L. S. Hegedus, S. D. Wagner, E. L. Waterman, and K. Siirala-Hansen, *J. Org. Chem.*, **40**, 593 (1975).

(9) W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 1961).

(10) R. K. Boeckman, D. M. Blum, and S. D. Arthur, *J. Am. Chem. Soc.*, **101**, 5060 (1979).

(11) A. I. Meyers, J. Slade, R. K. Smith, E. D. Mihelich, F. Hershenson, and C. D. Liang, *J. Org. Chem.*, **44**, 2247 (1979).

(12) The vinyl hydrogen in **9***Z* produced a signal at δ 7.22 with an apparent first-order coupling constant of 7.5 Hz, characteristic of the proton syn to the ester unit in acrylate derivatives. Similarly, **9***E* showed a signal at δ 6.60, *J* = 7.5 Hz, consistent with a proton at the β carbon in an anti relationship with the ester unit. For a discussion, see A. Loeffler, R. J. *Pratt*, H. P. Reusch, and A. S. Drieding, *Helv. Chim. Acta*, **53**, 383 (1970).

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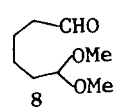
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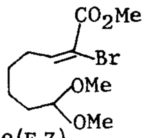
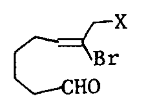
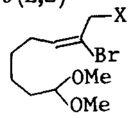
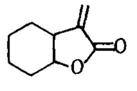
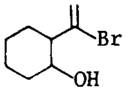
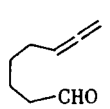

9(E,Z)


11: X=Br(E,Z)
12: X=OH(E,Z)
13: X=OSO$_2$Me (E,Z)


10: X=OH (E,Z)


14: cis, trans


15: cis, trans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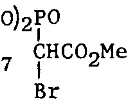
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$(EtO)_2PO$–$CH(Br)CO_2Me$

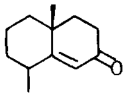
with isomeric mixtures **11** and **13**, but tests of the influence of double-bond geometry on stereoselectivity required pure isomers.

On the basis of the accelerating effect of polar solvents on reactions of allyl-nickel complexes,[7] initial experiments were carried out in tetrahydrofuran. Typical of a series of experiments is the reaction of **13** (0.61 mmol, $E/Z = 1/4$) with nickel carbonyl (6 mmol) in tetrahydrofuran (35 ml) under argon at 65 °C for 38.5 h, which gave the desired lactones[13] (**14** cis/trans = 1/2, 2% yield), the vinyl bromide–alcohols **15**[4] (cis/trans = 1/2, 30% yield), and a product tentatively identified as a coupling product[14] (50% yield). Under similar conditions, but using bis(triphenylphosphine)nickel dicarbonyl (2.4 mol equiv), the major product (61% yield) was allene **16**, suggesting that the 2-bromoallyl ligand can undergo elimination of bromide.[15] Under similar conditions, but using bis(1,5-cyclooctadiene)nickel (3.0 mol equiv), the reaction with **11** was over within a few hours at 25 °C, but only the coupling product was obtained (75% yield).

The intermolecular coupling was largely inhibited by using benzene as the reaction medium.[7] With the bromide **11** ($E/Z = 3/1$), and ca. 10 mol equiv of nickel carbonyl in benzene at 65 °C, a red solid was deposited within minutes.[16] More than 95% conversion of **11** was observed after 28 h, and the lactone **14** was isolated (9% yield, cis/trans = 1/3), but the major product was the vinyl bromide–alcohol **15** (49% yield, cis/trans = 1/2). The failure of **15** to go on to **14** is at first surprising, since it had been established that simply mixing **15** with nickel carbonyl in hot benzene gave **14** in good yield.[4] The corresponding allylic methanesulfonate ester **13** with excess nickel carbonyl in benzene at 65 °C gave a pale yellow intermediate and led, after 28 h, to the α-methylene γ-lactone **14** (5% yield) and **15** (37%). More complete conversion to **14** was observed upon long heating and addition of nickel carbonyl periodically; 45 h at 65 °C gave **15** (25% yield) and **14** (39%), while after 95 h at 65 °C, only **14** was isolated (58%).[17] One interpretation of these results is that initial complex formation (e.g., to form **3**) and ring closure (to **4**) are fast, but carbonylation is slow. The rate-determining step might be the exchange of Ni(0) for Ni(II) after the ring closure, as a prelude to carbonylation. Attempts to facilitate a nickel exchange through hydrolysis of the presumed nickel alkoxide **4** by means of added water and through addition of triethylamine were unsuccessful.

High sterospecificity for the cis product had been observed in closely related nickel-promoted cyclizations of 2-(carboalkoxy)allylic halides,[2,3] and it was of interest to see if similar selectivity could be obtained with the 2-bromoallyl species. A sample of pure **11***E* reacted with excess nickel carbonyl in benzene to give a mixture of **14** and **15**, with the cis/trans ratio = 1/2 in both products. With **11***Z* under identical conditions, the ratios of cis/trans for **14** was 1/1 and for **15** was 2/3. A sample of pure **13***E* gave **14** with cis/trans = 1/2. There was no significant dependence of yield on double-bond geometry, but clearly the process is only moderately specific, tending toward the trans product.

The general success of the model led us to devise a plan for the simple sesquiterpene lactone, frullanolide (**1**), which is somewhat more elaborate than the model, with one additional element of stereochemistry. Through a series of four conventional steps, dimethyloctalone **17**[18] was converted to aldehyde **18** in 30% yield overall.[19] When the procedure for preparation of **13** was used, allylic alcohols **19** were obtained, separated, and converted to the sensitive methanesulfonate esters **20** which were used without purification. The yield overall for four steps from **18** to **20** is about 60% for both series, *E* and *Z*.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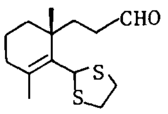
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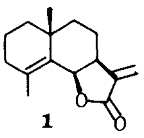
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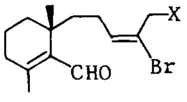
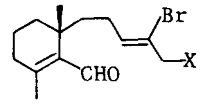
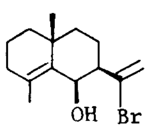

19E: X = OH
20E: X = OSO$_2$Me


19Z: X = OH
20Z: X = OSO$_2$Me


21

Reaction of **20***E* (0.30 mmol) with nickel carbonyl (7.8 mmol) in 100 mL of benzene at 65 °C for 27 h led to complete conversion and two major products. MPLC allowed isolation of colorless crystals with mp 94.2–95.2 °C (from pentane: and a colorless oil. From the $^1$H NMR spectrum of the crude product, it was evident that the two products were formed in equimolar amounts, about 50–60% yield together. The crystals were identified as frullanolide (**1**) by comparison with samples obtained from other sources,[20] while the oil was assigned structure **21** based on consistent spectral data[21] and efficient conversion to frullanolide (**1**) upon treatment

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[13] Lactones **14** were characterized in earlier work[2] and are well-known in the literature. For example, see J. A. Marshall and N. Cohen, *J. Org. Chem.*, **30**, 3475 (1965).

[14] The byproduct was not fully characterized or purified. It was nonvolatile and showed spectral features similar to a coupling product observed earlier in a similar reaction.[2]

[15] The allene was fully characterized by $^1$H NMR, $^{13}$C NMR, IR, and mass spectral analysis. Expecially useful were the signals at δ 5.10 (quintet, $J$ = 6.5 and 1.0 Hz, 1 H) and 4.73–4.55 (m, 2.0 H) in the $^1$H NMR spectrum and 1960 (s), 1630 (w), and 850 (vs) cm$^{-1}$ for the $C{=}C{=}CH_2$ unit in the IR spectrum.

[16] The appearance of a red precipitate and light red-colored solution is taken as evidence for initial formation of a π-allylnickel bromide complex.

[17] The yield is based on pure **14** after short path distillation. The isolated yield instead of spectroscopic yield or GC yield is particularly significant in α-methylene γ-lactone syntheses, since losses during purification can be subsantial. In general, weight recovery in the crude product is high.

[18] (a) W. C. Still and F. L. van Middlesworth, *J. Org. Chem.*, **42**, 1258 (1977); (b) D. Caine and F. N. Tuller, **34**, 222 (1969); (c) J. A. Marshall and D. J. Sachaeffer, *ibid.*, **30**, 3642 (1965).

[19] The key step is oxidative cleavage of a dienol ether according to a published method: D. N. Kirk and J. M. Wiles, *Chem. Commun.* 1015 (1970).

[20] We are grateful to Professor W. Clark Still, Columbia University, for a sample of racemic frullanolide obtained by synthesis and Professor Claude Benezra, University Louis Pasteur (Strasbourg), for a sample of natural (–)-frullanolide.

with excess nickel carbonyl and triethylamine (2 mol equiv) in benzene at 65 °C for 10 min.[4]

Attempts to obtain complete conversion of **21** to **1** directly during reaction of **20*E*** were not successful. Higher reaction temperatures, longer times, and the use of polar solvents led to decomposition of **1** and lower overall yields. The most efficient procedure is a two-step process. The methanesulfonate ester **20*E*** (0.30 mmol) was cyclized with excess nickel carbonyl in benzene at 65 °C for 25 h as before, and most of the solvent and excess nickel carbonyl were removed into a cold trap at aspirator vacuum to leave about 30 mL. This residual suspension was filtered through Celite and concentrated at oil pump vacuum to leave a yellow oil. The residue was dissolved in a mixture of triethylamine (0.35 mmol), nickel carbonyl (7.8 mmol), and benzene (50 mL) under argon and heated at 65–68 °C for 10 min. Then the solvent and excess nickel carbonyl were removed under vacuum, and the residue was examined by **1H** NMR spectroscopy. Frullanolide (**1**) was present (45% yield) along with a high molecular weight compound tentatively identified as a coupling product of **20*E*** (about 10%), but the intermediate **21** was absent. Isolation of **1** by MPLC gave 28 mg of colorless crystals, 40% yield.

With isomer **20*Z***, reaction with nickel carbonyl in benzene at 58–63 °C for 20 h produced a single lactone (**1**, 10% yield) and a single isomer of the intermediate (**21**, 40%). The crude mixture of **1** and **21** was carried on with nickel carbonyl and triethylamine as above, producing **1** in 31% yield after chromatography. The formation of the same ring fusion isomer (**1**, **21**) from both **20*E*** and **20*Z*** may be accounted for simply by rapid isomerization of the allylic double bond during formation of the (presumed) common allyl–nickel intermediate. The origin of the very high selectivity for the cis ring fusion and the syn orientation of the lactone ring with respect to the angular methyl group is not clear and will be the subject of future study.

**Acknowledgment.** We are grateful fo the National Institutes of Health (CA 26727) for generous support of this work.

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(21) $^1$,h NMR ($CDCl_3$) δ 5.75 (t, *J* = 1.5 Hz, 1 H, HC=CBr anti), 5.67 (m, 1 H, HC=CBr syn), 5.10 (br s, 1H, CHO), 2.5–1.9 (7, 8 H, $CH_2$), 1.22 (s, 3H, $CH_3$). $^{13}C$ NMR ($CDCl_3$) δ 136.4, 134.5, 132.6, 117.5, 66.5, 54.2, 41.5, 40.9 33.5, 27.1, 21.2, 19.1, 18.6 (one carbon not observed); IR ($CHCl_3$) 3560(w, OH), 625 (m C=C), 1600 (w, C=C), 1460(m), 1373 (m), 955 (m), 900(m) $cm^{-1}$; mass spectrum, *M*, 284.0781; clacd for $C_{14}H_{21}O^{79}Br$: 284.0776.

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# Dioxygenase Model Studies: Reaction of Oxygen with Iron Catecholates

Randall B. Lauffer, Robert H. Heistand II,[†] and Lawrence Que, Jr.*

*Department of Chemistry, Cornell University*
*Ithaca, New York 14853*

*Received January 30, 1981*

Protocatechuate 3,4-dioxygenase and catechol 1,2-dioxygenase are high-spin ferric enzymes[1,2] which catalyze the oxidative cleavage of catechols to *cis,cis*-muconic acids. One proposed role for the iron in these enzymes is the binding and activation of molecular oxygen after substrate reduction of the ferric center to the ferrous oxidation state.[1] However, Mössbauer studies[3,4] of the enzyme–substrate complexes and an oxygenated intermediate show the active-site iron to remain high-spin ferric in these states. On the basis of these observations, we have proposed an alternative mechanism[5] which does not involve the ferrous oxidation state; instead, we suggest that coordination of the catechol to the ferric center activates the catechol to attack by oxygen, resulting in the formation of semiquinone and superoxide (or the hydroperoxy radical). We have explored the reaction of oxygen with model catecholate complexes and report our results in this communication.

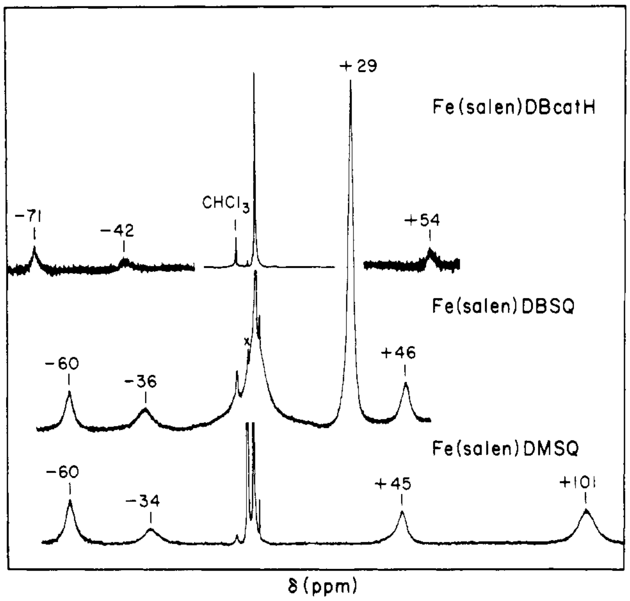

**Figure 1.** 80-MHz $^1H$ NMR spectra of (A) Fe(salen)DBcatH, (B) Fe(salen)DBSQ, and (C) Fe(salen)DMSQ in $CDCl_3$ solution. These spectra exhibit resonances in the diamagnetic region due to (A) bound and free $DBcatH_2$. (A one-fold excess of $DBcatH_2$ was added to ensure complete formation of Fe(salen)$DB_{cat}$H.[14]) (B) 3,5-Di-*tert*-butyl-*o*-benzoquinone from slight decomposition of Fe(salen)DBSQ, and (C) THF of crystallization. Spectra were obtained at ambient temperature on a Varian CFT-20 spectrometer operating at 80 MHz in the FT mode.

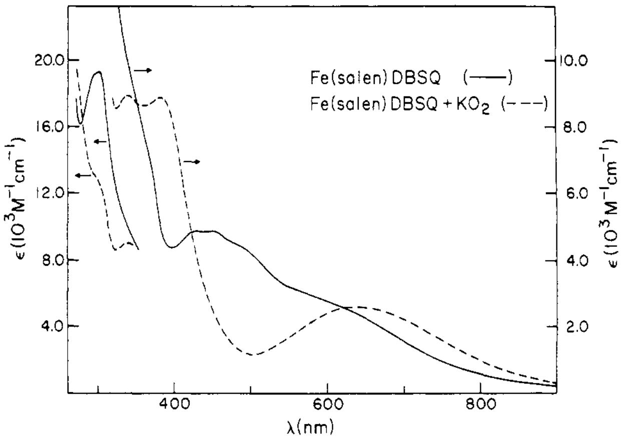

**Figure 2.** Electronic spectra of Fe(salen)DBSQ in THF solution before and after addition of 1 equiv of K(18-crown-6)$O_2$. The latter spectrum is identical with that of $[Fe(salen)DBcat]^-$. Spectra were obtained in 0.1-mm cells on a Cary 219 spectrophotometer.

Fe(salen)DBcatH,[6] a high-spin ferric complex synthesized from the ligand exchange reaction of Fe(salen)OAc with excess 3,5-di-*tert*-butylcatechol,[7] yields an NMR spectrum with paramagnetically shifted resonances (Figure 1). Upon introduction of oxygen, these resonances are replaced by features identified as

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[†] National Institutes of Health predoctoral trainee, 1978–1981.

(1) Nozaki, M. In "Molecular Mechanisms of Oxygen Activation", Hayaishi, O., Ed.; Academic Press: New York, 1974; Chapter 4.

(2) Que, L., Jr. *Struct. Bonding* (Berlin) **1980**, *40*, 39–72.

(3) Que, L., Jr.; Lipscomb, J. D.; Zimmerman, R.; Munck, E.; Orme-Johnson, W. H.; Orme-Johnson, N. R. *Biochim. Biophys. Acta* **1976**, *452*, 320–334.

(4) Kent, T.; Munck, E.; Widom, J.; Que, L., Jr., unpublished observations.

(5) Que, L., Jr.; Lipscomb, J. D.; Munck, E.; Wood, J. M. *Biochim. Biophys. Acta* **1977**, *485*, 60–74.

(6) Abbreviations used: salen, ethylenebis(salicylaldimine); $DBcatH_2$, 3,5-di-*tert*-butylcatechol: OAc, acetate; DBSQ, 3,5-di-*tert*-butyl-*o*-semiquinone anion; THF, tetrahydrofuran; PhOH, phenol; $catH_2$, catechol; saloph, *o*-phenylenebis(salicylaldimine); DMSQ, 4,5-dimethoxy-*o*-semiquinone anion.

(7) Que, L., Jr.; Heistand, R. H., II *J. Am. Chem. Soc.* **1979**, *101*, 2219–2221. Anal. Calcd for Fe(salen)DBcatH ($C_{30}H_{35}FeN_2O_4$): C, 66.30; H, 6.49; N, 5.15. Found: C, 66.04; H, 6.73; N, 5.22.

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