Figure 2. RR spectra of methoxycarbonyl-L-phenylalanylglycine dithioacyl papain in solution at room temperature (bottom); in ice matrix near 77 K (top). L = laser plasma line, S = peak due to CH_3CN used to carry substrate into solution. Inset: 450–750 cm^{-1} spectral regions of room temperature and 77 K traces compared, with intensities of the 588-cm^{-1} peaks equalized.

PheGly dithioacyl papain is a "good intermediate" possessing the correct Phe side chain-enzyme and several enzyme-substrate C=O⋯H–N H-bond linkages to ensure proper orientation in the active site[10] (where the substrate can be said to "zip-up" the two lobes of papain). Unlike the *N*-benzoylglycine intermediate freezing at 250 K causes no change in the Ψ' sensitive 1140-cm^{-1} band (data not shown; RR spectra from six experiments going from room temperature to 250 K are superimposable). This is a surprising result since it shows that the normal mode pattern of the dithioacyl group in the active site is not measurably perturbed by the phase change in the surrounding solvent. Thus the zippered-up structure seems "protected" from solvent freezing. However, upon lowering the temperature to 77 K[11] the 1140-cm^{-1} band decreases to 1136 cm^{-1} (Figure 2, identical results were obtained for four separate samples). The favored explanation is that removing thermal energy from the protein matrix allows Ψ' to relax by approximately 15° toward a nonstrained (smaller) value found in the corresponding PheGly ethyl dithio ester model compound.[12] The obverse of this inference is that the thermal energy available in the protein at room temperature drives Ψ' toward a value closer to that found in the transition state for deacylation.[13,14]

The PheGly dithioacylpapain, just as for the *N*-benzoylglycine derivative, shows an intriguing increase (3-fold, relative to other RR features) in the 669-cm^{-1} peak intensity at 77 K (Figure 2). The increase could simply correspond to a better mapping of the vibrational mode onto the excited electronic state at low temperature. However, it is remarkable that this feature is from a normal mode associated with an enzyme bond, S–C of cysteine-25,[6] and that the same effect is seen for both "good" (PheGly) and "poor" *N*-benzoylglycine) intermediates. This demonstrates that the vibrational and/or electronic properties of the cysteine-25 S–C bond vary markedly with temperature, and future studies should address the question of whether these properties are used by the enzyme to assist the catalytic process.

Work is in progress to measure the temperature dependence of the RR spectral changes between 77 and 250 K and to extend our observations to liquid helium temperatures.

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(14) Increasing Ψ' increases the N⋯S (thiol) distance and reduces the weak N⋯S bonding interaction (Varughese, K. I.; Storer, A. C.; Carey, P. R. *J. Am. Chem. Soc.* **1984**, *106*, 8252). For a series of *N*-benzoylglycine dithioacyl papains it was shown that the N⋯S contact was broken in the rate-determining step for deacylation (Carey, P. R.; Lee, H.; Ozaki, Y.; Storer, A. C. *J. Am. Chem. Soc.* **1984**, *106*, 8258).

(15) Issued as NRCC No. 29907.

Acid-Catalyzed Electron-Transfer Processes in Reduction of α-Haloketones by an NADH Model Compound and Ferrocene Derivatives

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Nonenzymatic reductions of substrates by reduced nicotinamide adenide dinucleotide (NADH) and NADH model compounds have been extensively studied in order to understand the mechanisms of enzymatic reductions of substrates by NADH.[1,2] However, model studies have hitherto revealed that NADH or NADH model compounds can reduce thermally only activated carbonyl compounds, which are rather strong oxidants, although the excited states of NADH and NADH model compounds can reduce a variety of substrates.[3] Since acid catalysis is known to play an essential role in the enzyme-catalyzed reduction of carbonyl compounds by NADH,[4] it is required to explore the acid-catalyzed reduction of nonactivated carbonyl compounds which would otherwise be reduced only by the presence of an appropriate enzyme.[5] We wish to report herein the first successful reduction of α-haloketones, which are weak oxidants, by an acid-stable NADH model compound, 10-methylacridan ($AcrH_2$),[6,7] in the

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(1) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1. Stout, D. M.; Meyer, A. I. *Chem. Rev.* **1982**, *82*, 223.

(2) Fukuzumi, S.; Koumitsu, S.; Hironaka, K.; Tanaka, T. *J. Am. Chem. Soc.* **1987**, *109*, 305 and references therein.
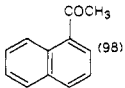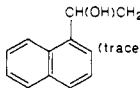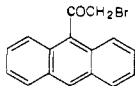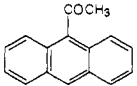
(3) Fukuzumi, S.; Tanaka, T. *Photoinduced Electron Transfer*; Fox, M. A., Chanon, M., Eds.; Elsevier: Amsterdam, 1988; Chapter 4-10.

(4) Eklund, H.; Brändén, C.-I. *Zinc Enzymes*; Spiro, T. G., Ed.; Wiley-Interscience: New York, 1983; Chapter 4.

(5) Although acid-catalyzed reduction of some substrates by NADH model compounds have been reported, the substrates which can be reduced efficiently have still been limited to relatively strong oxidants: van Eikeren, P.; Grier, D. L. *J. Am. Chem. Soc.* **1976**, *98*, 4655. Ohno, A.; Ishikawa, Y.; Ushida, S.; Oka, S. *Tetrahedron Lett.* **1982**, *23*, 3185. Shinkai, S.; Hamada, H.; Kusano, Y.; Manabe, O. *J. Chem. Soc., Perkin Trans. 2* **1979**, 699. Shinkai, S.; Hamada, H.; Manabe, O. *Tetrahedron Lett.* **1979**, 1397. Shinkai, S.; Hamada, H.; Kusano, Y.; Manabe, O. *Tetrahedron Lett.* **1979**, 3511. Awano, H.; Tagaki, W. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3117. Singh, S.; Gill, S.; Sharma, V. K.; Nagrath, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1273.

(6) 10-Methylacridan is stable in the presence of $HClO_4$ although the protonation equilibrium exists in MeCN, see: Fukuzumi, S.; Ishikawa, M.; Tanaka, T. *J. Chem. Soc., Chem. Commun.* **1985**, 1069. Fukuzumi, S.; Ishikawa, M.; Tanaka, T. *Tetrahedron* **1986**, *42*, 1021.

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(10) Reference 8 p 90.

(11) Under the experimental conditions employed, in which the sample is moved in the laser beam, we estimate that the maximum rise in temperature due to the laser beam (≈100 mW power) is 10 K.
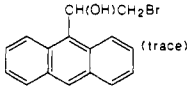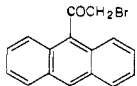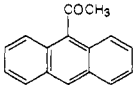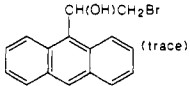
(12) Several lines of evidence suggest a relationship exists between Ψ' and the exact position of the 1140-cm^{-1} peak and this peak position has been discussed before in terms of conformational activation upon going from a substrate based on a single amino acid to a di-, tri-, and tetrapeptide: Angus, R. H.; Carey, P. R.; Lee, H.; Storer, A. C. *Biochemistry* **1986**, *25*, 3304. Recent RR and X-ray crystallographic analyses of *N*-(β-phenylpropionyl)-glycine (Huber, C. P. *Acta Crystallogr.* **1987**, *C43*, 902) and *N*-methoxycarbonyl-L-phenylalanylglycine- (Varughese, K. I.; Huber, C. P.; Storer, A. C.; Carey, P. R., manuscript in preparation) ethyl dithio esters show that a change in Ψ' from −19 to −30° changes the position of the intense band from 1134 to 1137 cm^{-1}.

(13) Storer, A. C.; Carey, P. R. *Biochemistry* **1985**, *24*, 6808.

Table I. Acid-Catalyzed Reduction of α-Haloketones by AcrH$_2$ (0.10 M), AcrD$_2$ (0.10 M), and Fe(MeC$_5$H$_4$)$_2$ (5.0 $\times$ 10^{-2} M) in the Presence of HClO$_4$ (0.30 M) in Acetonitrile at 335 K

no.	substrate[a]	reductant	k_H/k_D[b]	product yields (%)[c]
1	C$_6$H$_5$COCH$_2$Cl	AcrH$_2$	5.0	C$_6$H$_5$COCH$_3$ (36), C$_6$H$_5$CH(OH)CH$_2$Cl (49)
	C$_6$H$_5$COCH$_2$Cl	AcrD$_2$		C$_6$H$_5$COCH$_3$ (57), C$_6$H$_5$CD(OH)CH$_2$Cl (27)
	C$_6$H$_5$COCH$_2$Cl[d]	Fe(MeC$_5$H$_4$)$_2$		C$_6$H$_5$COCH$_3$ (100)
2	C$_6$H$_5$COCH$_2$Br	AcrH$_2$	3.0	C$_6$H$_5$COCH$_3$ (82), C$_6$H$_5$CH(OH)CH$_2$Br (14)
	C$_6$H$_5$COCH$_2$Br	AcrD$_2$		C$_6$H$_5$COCH$_3$ (90), C$_6$H$_5$CD(OH)CH$_2$Br (7)
	C$_6$H$_5$COCH$_2$Br[d]	Fe(MeC$_5$H$_4$)$_2$		C$_6$H$_5$COCH$_3$ (100)
3	4-MeOC$_6$H$_4$COCH$_2$Br	AcrH$_2$	2.7	4-MeOC$_6$H$_4$COCH$_3$ (48), 4-MeOC$_6$H$_4$CH(OH)CH$_2$Br (46)
	4-MeOC$_6$H$_4$COCH$_2$Br	AcrD$_2$		4-MeOC$_6$H$_4$COCH$_3$ (72), 4-MeOC$_6$H$_4$CD(OH)CH$_2$Br (24)
	4-MeOC$_6$H$_4$COCH$_2$Br[d]	Fe(MeC$_5$H$_4$)$_2$		4-MeOC$_6$H$_4$COCH$_3$ (100)
4	4-MeC$_6$H$_4$COCH$_2$Br	AcrH$_2$	1.9	4-MeC$_6$H$_4$COCH$_3$ (82), 4-MeC$_6$H$_4$CH(OH)CH$_2$Br (14)
	4-MeC$_6$H$_4$COCH$_4$Br	AcrD$_2$		4-MeC$_6$H$_4$COCH$_3$ (91), 4-MeC$_6$H$_4$CD(OH)CH$_2$Br (4)
5	2,4-Cl$_2$C$_6$H$_3$COCH$_2$Br	AcrH$_2$		2,4-Cl$_2$C$_6$H$_3$COCH$_3$ (84), 2,4-Cl$_2$C$_6$H$_3$CH(OH)CH$_2$Br (9)
6	4-BrC$_6$H$_4$COCH$_2$Br	AcrH$_2$		4-BrC$_6$H$_4$COCH$_3$ (87), 4-BrC$_6$H$_4$CH(OH)CH$_2$Br (9)
7	4-(CN)C$_6$H$_4$COCH$_2$Br	AcrH$_2$		4-(CN)C$_6$H$_4$COCH$_3$ (95), 4-(CN)C$_6$H$_4$CH(OH)CH$_2$Br (trace)
8	C$_6$H$_5$CH(Br)C$_2$H$_5$	AcrH$_2$		C$_6$H$_5$COC$_3$H$_7$ (92), C$_6$H$_5$CH(OH)CH(Br)C$_2$H$_5$ (6)
9	C$_6$H$_5$COCH(Br)C$_8$H$_{17}$	AcrH$_2$		C$_6$H$_5$COC$_9$H$_{19}$ (55), C$_6$H$_5$CH(OH)CH(Br)C$_8$H$_{17}$ (45)
10		AcrH$_2$		
11	[d]	AcrH$_2$	1.4	

[a]The substrate concentration is 0.30 M unless otherwise noted. [b]Determined from the ratio of the rate constants of AcrH$_2$ to AcrD$_2$. [c]The alcohol produced by further reduction of each ketone is not included. [d]0.10 M.

presence of HClO$_4$ in acetonitrile (MeCN). The importance of acid-catalyzed electron-transfer process in the two-electron reduction of α-haloketones by AcrH$_2$ in the presence of HClO$_4$ will be demonstrated by the comparison with acid-catalyzed electron-transfer reactions from one-electron reductants, ferrocene derivatives, and the excited states of [Ru(bpy)$_3$]$^{2+}$ (bpy = 2,2'-bipyridine) to the same series of α-haloketones.

An NADH model compound (AcrH$_2$) shows no reactivity toward α-haloacetophenone (PhCOCH$_2$X; X = Br, Cl) in MeCN at 335 K in the dark.[8] When HClO$_4$ is added to the AcrH$_2$–PhCOCH$_2$X system, however, PhCOCH$_2$X is readily reduced by AcrH$_2$ to yield 10-methylacridinium ion (AcrH$^+$) and acetophenone (eq 1) as well as the corresponding halohydrin, α-(halomethyl)benzenemethanol (eq 2). Yields of ketones and

$$\text{AcrH}_2 + \text{PhCOCH}_2\text{X} \xrightarrow{\text{H}^+} \text{AcrH}^+ + \text{X}^- + \text{PhCOCH}_3 \quad (1)$$

$$\text{AcrH}_2 + \text{PhCOCH}_2\text{X} + \text{H}^+ \rightarrow \text{AcrH}^+ + \text{PhCH(OH)CH}_2\text{X} \quad (2)$$
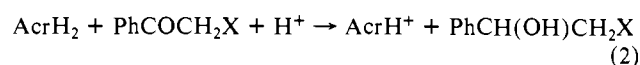
α-halohydrins in acid-catalyzed reduction of various α-haloketones in the presence of HClO$_4$ in MeCN are listed in Table I.[9] The product ratios between ketones (eq 1) and α-halohydrins (eq 2) vary depending on α-haloketones (Table I). When AcrH$_2$ was replaced by the 9,9'-dideuterated analogue (AcrD$_2$), no deuterium was incorporated into acetophenone, but it introduced to each halohydrin (Table I). The primary kinetic isotope effects have also been determined from the ratios of the rate constants of AcrH$_2$ to AcrD$_2$, and the k_H/k_D values are also listed in Table I.[10,11]

Figure 1. Plots of the rate constants (log k_{obsd}) for the acid-catalyzed reduction of α-haloketones by AcrH$_2$ in the presence of HClO$_4$ (0.30 M) in MeCN at 335 K vs the rate constants (log k_{et}) for the acid-catalyzed electron-transfer reactions from Fe(Me$_5$C$_5$)$_2$ (O) and [Ru(bpy)$_3$]$^{2+*}$ ($\bullet$) to α-haloketones in the presence of HClO$_4$ (0.30 M) at 298 K. Numbers refer to α-haloketones in Table I.

A mild one-electron reductant, 1,1'-dimethylferrocene [Fe(MeC$_5$H$_4$)$_2$], has no ability to reduce PhCOCH$_2$X in MeCN at

(7) NADH and ordinary NADH model compounds are known to be subjected to the acid-catalyzed hydration, see: Johnston, C. C.; Gardner, J. L.; Suelter, C. H.; Metzler, D. E. *Biochemistry* **1963**, *2*, 689. van Eikeren, P.; Grier, D. L.; Eliason, J. *J. Am. Chem. Soc.* **1979**, *101*, 7406. Skibo, E. B.; Bruice, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 3316.

(8) It has recently been reported that bromoacetophenone can be reduced by 1-alkyldihydronicotinamides to yield only acetonphenone by radical chain reactions initiated with light or radical initiators but that chloro- or fluoroacetophenone can be reduced only by the presence of an enzyme, horse liver alcohol dehydrogenase, to yield the corresponding halohydrins exclusively: Tanner, D. D.; Singh, H. K.; Kharrat, A.; Stein, A. R. *J. Org. Chem.* **1987**, *52*, 2142. Tanner, D. D.; Stein, A. R. *J. Org. Chem.* **1988**, *53*, 1642.

(9) The product yields were determined by ^{1}H NMR comparison with authentic materials independently obtained. Bromohydrin was prepared by the reaction of styrene with N-bromosuccinimide in water: Guss, C. O.; Rosenthal, R. *J. Am. Chem. Soc.* **1955**, *77*, 2549.
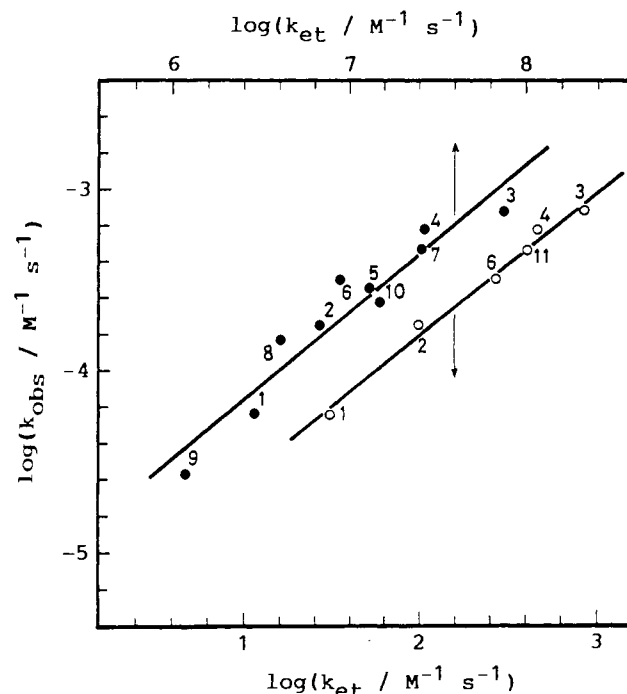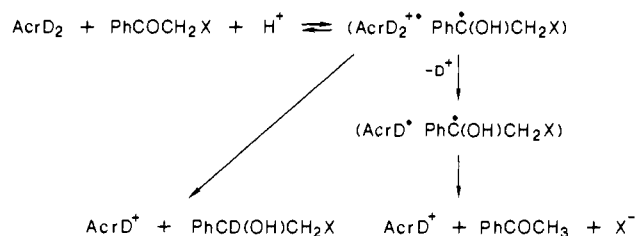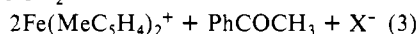
(10) No primary kinetic isotope effect has been observed when AcrH$_2$ is replaced by the 10-methyl-d_3 analogue (AcrH$_2$–CD$_3$), although, in the case of photoreduction of benzophenone by AcrH$_2$, the hydrogen of the 10-methyl position of AcrH$_2$ has been reported to be transferred to the ketone, see: Manring, L. E.; Peters, K. S. *J. Am. Chem. Soc.* **1985**, *107*, 6452.

(11) Rates of the acid-catalyzed reduction of α-haloketones by AcrH$_2$ and AcrD$_2$ were followed by measuring the ^{1}H NMR spectra in CD$_3$CN at 335 K. The rates in the dark obeyed strictly the second-order kinetics showing the first-order dependence on each reactant concentration and thus no apparent contribution of radical chain reactions[8] has been observed in the present case.

Scheme I

AcrD$_2$ + PhCOCH$_2$X + H$^+$ $\rightleftharpoons$ (AcrD$_2$$^{\bullet+}$ PhĊ(OH)CH$_2$X)

-D$^+$ |

(AcrD$^\bullet$ PhĊ(OH)CH$_2$X)

AcrD$^+$ + PhCD(OH)CH$_2$X   AcrD$^+$ + PhCOCH$_3$ + X$^-$

335 K. In the presence of HClO$_4$, however, PhCOCH$_2$X can be readily reduced by two equivalent amounts of Fe(MeC$_5$H$_4$)$_2$ in MeCN to yield only acetophenone (eq 3, Table I). When Fe-

$$2\text{Fe}(\text{Me}_5\text{H}_4)_2 + \text{PhCOCH}_2\text{X} + \text{H}^+ \rightarrow$$
$$2\text{Fe}(\text{MeC}_5\text{H}_4)_2{}^+ + \text{PhCOCH}_3 + \text{X}^- \quad (3)$$

(MeC$_5$H$_4$)$_2$ was replaced by decamethylferrocene [Fe(Me$_5$C$_5$)$_2$], which is a much stronger one-electron reductant than Fe-(MeC$_5$H$_4$)$_2$,[12] the rates of the acid-catalyzed reduction of α-haloketones were much faster than those by Fe(MeC$_5$H$_4$)$_2$, and thus the rates were determined by using a stopped-flow technique at 298 K.[13] The second-order rate constant (k_{et}) increased linearly with an increase in the HClO$_4$ concentration. Such acid catalysis of electron-transfer reactions of α-haloketones is also observed for photoinduced electron transfer from the excited state of [Ru(bpy)$_3$]$^{2+}$ to α-haloketones.[14,15]

Comparison of the observed and second-order rate constants (k_{obsd} for the acid-catalyzed reduction of various α-haloketones by AcrH$_2$ with the rate constants (k_{et}) for the acid-catalyzed electron-transfer reactions from ferrocene derivatives and [Ru-(bpy)$_3$]$^{2+*}$ (* denotes the excited state) to the same series of α-ketones is shown in Figure 1. There are linear correlations between the k_{obsd} values and the k_{et} values, despite the apparent difference in the products between the reduction by a two-electron reductant (AcrH$_2$) and one-electron reductants (ferrocene derivatives) as shown in Table I. Such correlations strongly suggest that the acid-catalyzed reduction of α-haloketones by AcrH$_2$ to yield the corresponding ketones (eq 1) and halohydrins (eq 2) involves a common activation process, i.e., the acid-catalyzed single electron-transfer from AcrH$_2$ to α-haloketones as shown in Scheme I for the AcrD$_2$–PhCOCH$_2$X system. Since the one-electron reduction potentials of carbonyl compounds are known to be shifted in the positive direction significantly in the presence of HClO$_4$ in MeCN,[14] the acid-catalyzed electron transfer from AcrD$_2$ to PhCOCH$_2$X may occur to generate the radical pair (AcrD$_2$$^{\bullet+}$-PhĊ(OH)CH$_2$X), which disappears either by deuterium (or hydrogen) transfer from AcrD$_2$$^{\bullet+}$ to PhĊ(OH)CH$_2$X or second electron transfer from AcrD$^\bullet$, which is formed by the deprotonation of AcrD$_2$$^{\bullet+}$, to PhĊ(OH)CH$_2$X (Scheme I). The deuterium transfer yields PhCD(OH)CH$_2$X, while the second electron transfer yields PhCOCH$_3$, accompanied by the reductive dehalogenation (Scheme I). This may be the reason why the deuterium is incorporated into α-halohydrin but not into acetophenone. The observed primary kinetic isotope effects may be ascribed to the hydrogen-transfer process as well as the deprotonation process (Scheme I). In the case of one-electron reductants (ferrocene derivatives), no hydrogen-transfer process is involved, and thus the second electron transfer yields only PhCOCH$_3$.

(12) The one-electron oxidation potential of Fe(Me$_5$C$_5$)$_2$, determined by the cyclic voltammetry in MeCN (–0.08 V vs SCE) is much more negative than that of Fe(MeC$_5$H$_4$)$_2$ (0.26 V vs SCE).

(13) Rates of the acid-catalyzed electron transfer from ferrocene derivatives to α-haloketones were determined by the increase in the absorbance due to the corresponding ferricenium ions in the long-wavelength region (650–750 nm).

(14) Fukuzumi, S.; Ishikawa, K.; Hironaka, K.; Tanaka, T. *J. Chem. Soc., Perkin Trans. 2* **1987,** 751.

(15) The rate constants (k_{et}) of photoinduced acid-catalyzed electron transfer from [Ru(bpy)$_3$]$^{2+*}$ to α-haloketones were determined by quenching experiments of the [Ru(bpy)$_3$]$^{2+*}$ luminescence by α-haloketones in the presence of HClO$_4$ in MeCN.[14] It was confirmed that the luminescence intensity in the absence of α-haloketones was unaffected by the presence of HClO$_4$ up to 2.0 M.

A Total Synthesis of (±)-Trichodermol

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Trichothecenes, exemplified by the simpler members trichodermol (**1**) and verrucarol (**2**), have attracted considerable interest for total synthesis,[2] owing to their diverse biological activity,[3] which ranges from antifungal to cytotoxic. They serve as useful, moderately complex, target molecules to illustrate the application of new synthesis technology. The fact that trichodermin (**1** acetate)[2a] and trichodermol[2b] have already succumbed to total synthesis introduces special challenges: any new approach must employ fewer synthetic steps, all of which should be high yielding; the synthesis must not involve difficult transformations, and it should not utilize functional groups that become redundant in the later stages.[4] This paper describes a short highly stereocontrolled route to (±)-trichodermol that was designed to achieve such objectives. The synthesis utilizes the newly discovered regiocontrolled addition of tin enolates[5] to cyclohexadienyl–iron complexes, it does not require protecting groups and it also illustrates the usefulness of the dimethylphenylsilyl group as a hydroxyl equivalent.[6]

1 X = H
2 X = OH

3 (a) R = SiMe$_3$
    (b) R = SnBu$_3$

4
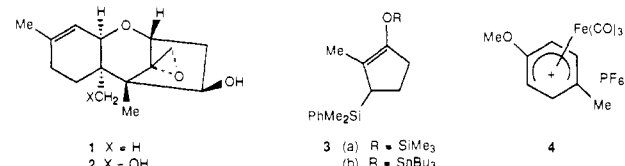
Dimethylphenylsilyl-substituted silyl enol ether **3a** was generated in 80–90% yield from 2-methylcyclopentanone in two synthetic operations (1) sulfuryl chloride, CCl$_4$, followed by distillation;[7] (2) 2Me$_2$PhSiLi, CuCN, THF, –23 °C then 0 °C, 2 h, followed by enolate trapping with Me$_3$SiCl, Et$_3$N, room temperature, 3 h). Conversion of **3a** to the corresponding tin enolate **3b** (1.2 equiv of MeLi, DME, room temperature, 45 min; 1.2 equiv of Bu$_3$SnCl, –78 °C, 1 h) followed by in situ reaction with complex **4**[8] afforded

(1) (a) Case Western Reserve University. (b) University of Toledo.

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