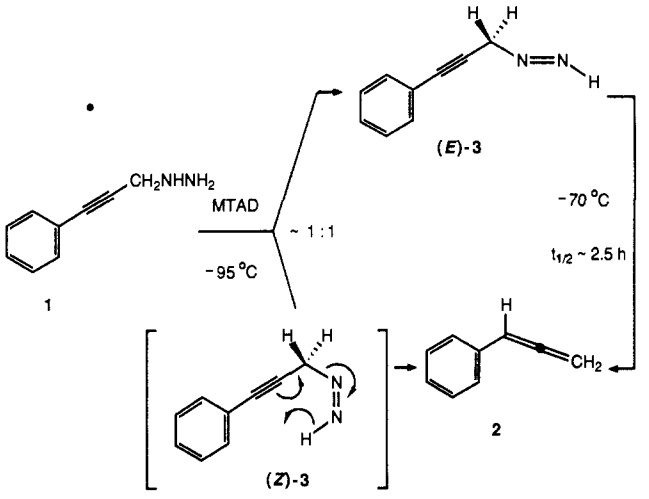
Scheme I



Given the proposed formation of (*Z*)-**3** in oxidation of **1** with MTAD and the modest yield of (*E*)-**4** in oxidation of phenylhydrazine, it is tempting to speculate that (*Z*)-**4** was produced in the latter reaction but is quite unstable in solution, even at −95 °C.[11] This must certainly be the case for (*Z*)-**3**, were it produced, where $\Delta G^{\ddagger}$ for the proposed sigmatropic elimination can be estimated to be <12 kcal/mol at −95 °C.

Acknowledgment. We are grateful to Professor John D. Roberts for discussions concerning ^{15}N NMR spectroscopy and to Dr. David R. Wheeler for assistance with high-vacuum techniques. This research was generously supported by the National Science Foundation, the David and Lucile Packard Foundation, and the following industrial sponsors: Monsanto Company, Rohm & Haas Company, Eli Lilly and Company, and Hoffman-La Roche Inc.

Supplementary Material Available: A low-temperature NMR spectrum of **2** and **3** and a plot of the first-order decomposition of **3** at −70 °C (1 page). Ordering information is given on any current masthead page.

Kinetics by High-Pressure Nuclear Magnetic Resonance: Reversible Hydrogen Binding in $(\eta^2\text{-}H_2)Cr(CO)_3[P(C_6H_{11})_3]_2$

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High-pressure NMR is a powerful technique for studying a variety of important systems.[1] Molecular hydrogen complexes are important intermediates for homogeneous catalytic hydrogenation reactions, and numerous examples have been prepared and characterized under ambient conditions.[2] Since several hydrogenation catalyst systems are used above atmospheric H_2 pressure,[3] studies of the behavior of molecular hydrogen complexes under pressure are of great interest. Although it has been shown by high-pressure IR that $Cr(CO)_3[P(C_6H_{11})_3]_2$ (**1**) reversibly binds H_2 under pressure (eq 1), the coordination mode of the added H_2

$$\underset{\mathbf{1}}{Cr(CO)_3[P(C_6H_{11})_3]_2} + H_2 \underset{K_a}{\overset{K_e}{\rightleftharpoons}} \underset{\mathbf{2}}{(\eta^2\text{-}H_2)Cr(CO)_3[P(C_6H_{11})_3]_2} \quad (1)$$

could not be established.[4] We report that the reversible reaction of **1** with H_2 results in the formation of $(\eta^2\text{-}H_2)Cr(CO)_3[P(C_6H_{11})_3]_2$ (**2**) (eq 1) and the elimination of the side-on coordinated hydrogen, $\eta^2\text{-}H_2$, from **2** has an activation energy of 12.7 ± 1.0 kcal/mol and is independent of the H_2 pressure.

It has been shown that equilibrium 1 is shifted to **2** above 300 psi of H_2 pressure at 25 °C.[4] Accordingly, when a purple solution of **1** in d_8-toluene is charged with 400 psi of H_2 at room temperature, the color immediately changes to bright yellow.[5] ^{31}P NMR shows nearly quantitative reaction, as the resonance of **1** at 63.6 ppm is replaced with a new singlet at 73.5 ppm for **2**.[6] ^1H NMR at room temperature shows the resonances of the $P(C_6H_{11})_3$ ligands and a broad peak at 4.5 ppm for the dissolved H_2. The latter indicates exchange between dissolved and coordinated H_2, and this resonance sharpens upon cooling to −60 °C as expected. Below −10 °C a new broad singlet appears at −7.2 ppm, which broadens further upon cooling to −60 °C, suggesting the presence of an $\eta^2\text{-}H_2$ in **2**.[7] This assignment is also supported by the short T_1 minimum (≤10 ms) of the $\eta^2\text{-}H_2$.[7] No evidence was found for the formation of a classical dihydride species from **2**.

The rate of $\eta^2\text{-}H_2$ elimination from **2** was determined by analysis of ^1H inversion recovery experiments performed in which both the bound and dissolved H_2 were inverted (Figure 1). This is not a generally applicable method for obtaining rate information but works in this case since the recovery from inversion is quite

Table I[a]

pressure, psi	temp, °C	R_{BF}	T_{1F}, ms	T_{1B}, ms	T_{1F^e}, ms	T_{1B^e}, ms	K_e, s^{-1}
150 H_2	−33	0.49	121	10.8	1450	9	23.0 ± 2.0
150 H_2	−41	0.56	330	10.0	1450	11	5.0 ± 0.5
150 H_2	−52	0.58	780	16.0	1450	13.5	1.1 ± 0.1
150 H_2	−61	0.60	1080	16.9	1450	18	0.6 ± 0.15
413 H_2	−42	0.14	806	9.8	1450	10	4.0 ± 0.5
800 H_2	−24	0.16	139	17.3	1450	9	62.5 ± 2.5
800 H_2	−35	0.15	465	9.5	1450	9.8	10.0 ± 1.0
800 H_2	−43	0.15	711	9.9	1450	9.8	5.0 ± 0.5
800 H_2	−50	0.26	895	10.1	1450	11	1.9 ± 0.2
800 H_2	−59	0.19	1146	16.0	1450	16	1.0 ± 0.1

[a] R_{BF} is the ratio of concentrations of bound hydrogen to dissolved hydrogen. T_{1F} and T_{1B} are the "apparent" T_1's, i.e., the time constants obtained by fitting the inversion recovery data to a single exponential. T_{1F^e} and T_{1B^e} are the T_1's calculated in the hypothetical absence of exchange. Error limits for K_e's were estimated by determining the range for which the variance between calculated and experimental inversion recovery data differed by ≤1%.

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(4) Gonzalez, A. A.; Mukerjee, S. L.; Chou, S.-J.; Kai, Z.; Hoff, C. D. *J. Am. Chem. Soc.* **1988**, *110*, 4419.

(5) (a) Measurements were made on a 7.05-T commercial instrument using d_8-toluene solutions of **1** (6 mmol/L) in high-pressure NMR tubes described previously,[1c] and all temperatures were measured by using a methanol standard.[5b] (b) Van Geet, A. L. *Anal. Chem.* **1968**, *40*, 2227.

(6) In addition, a small ^{31}P resonance at 67.1 ppm was found in nearly all cases due to $Cr(CO)_4[P(C_6H_{11})_3]_2$, which does not coordinate H_2 under pressure. In separate experiments we have found that its presence has no effect on the T_1 of dissolved and/or coordinated hydrogen and, therefore, does not interfere with T_1 measurements in any way.

(7) Hamilton, D. G.; Crabtree, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 4126.

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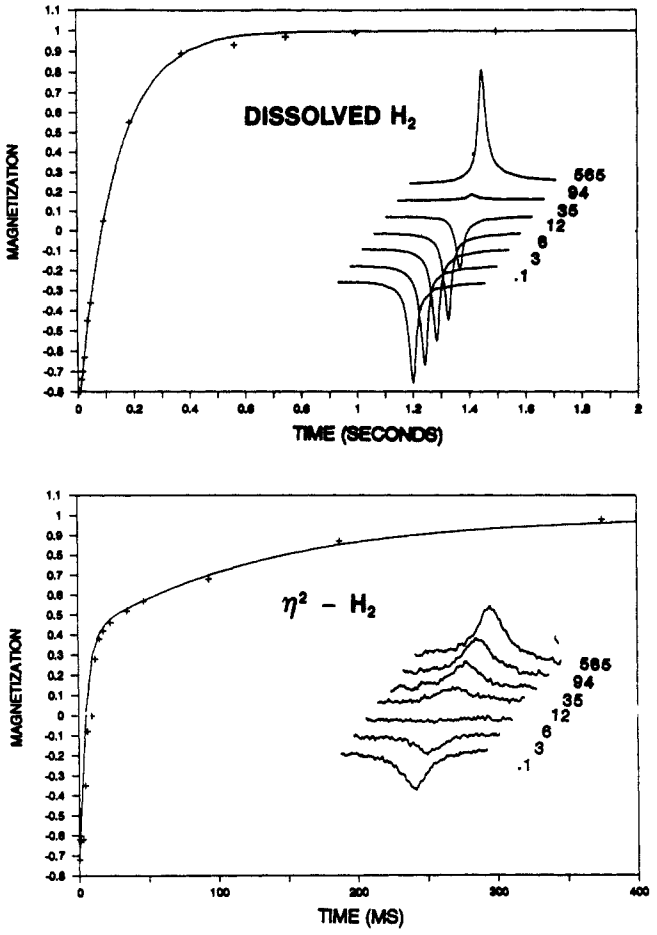


Figure 1. Inversion recovery ^1H NMR spectra of dissolved H_2 and η^2-H_2 of **1** in d_8-toluene under 800 psi of H_2 recorded at −24 °C. Experimental inversion recovery data (+) and calculated fits (solid lines) are shown. Numbers in the insets are the delays of the inversion recovery sequence given in milliseconds.

sensitive to the effects of this chemical exchange process owing to the large difference in the intrinsic relaxation rates of the two species. Rate constants for hydrogen elimination from **2** (K_e, see Table I) were calculated by fitting the observed recovery data to biexponential solutions of the coupled Bloch equations which govern the process.[8] The fitting procedure is documented in detail in the supplementary material, and results are summarized in Table I. Arrhenius plots for the elimination of hydrogen from $(\eta^2\text{-}H_2)Cr(CO)_3[P(C_6H_{11})_3]_2$ (**2**) under 150, 413, and 800 psi of H_2 pressures fall on a single line (Figure 2), indicating clearly that the elimination is a unimolecular process. These data give the calculated activation parameters[9] E_a = 12.7 ± 1.0 kcal/mol, $\Delta H^\ddagger$ = 12.1 ± 1.0 kcal/mol, $\Delta S^\ddagger$ = −2.1 ± 4.5 cal/(deg mol), and $\Delta G^\ddagger$ (298 K) = 12.7 ± 1.7 kcal/mol.

The enthalpy of activation for binding H_2 in eq 1 is calculated to be 4.8 ± 2.3 kcal/mol.[10] This value is smaller than the

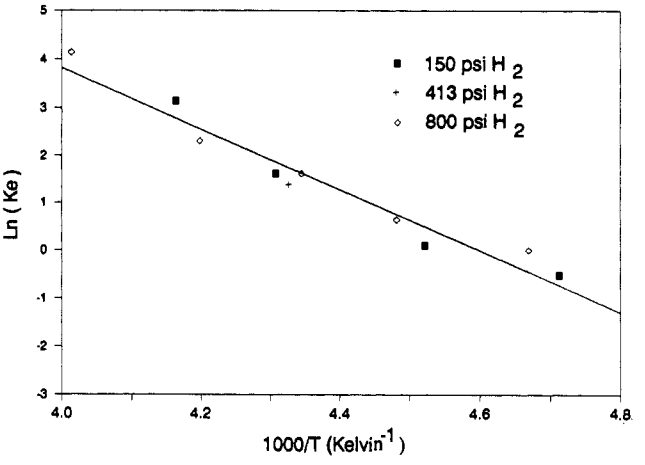


Figure 2. Arrhenius plot for the elimination of η^2-H_2 from $(\eta^2\text{-}H_2)Cr(CO)_3[P(C_6H_{11})_3]_2$ (**2**). The solid line was calculated by using the equation $\ln K_e = \ln A - E_a/RT$ and the parameters E_a = 12.7 kcal/mol and $\ln A$ = 29.40, which were determined by least-squares fitting of the experimental data.

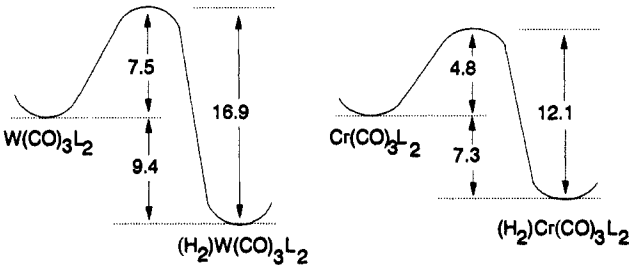


Figure 3. Reaction profile for the addition of H_2 to $M(CO)_3L_2$, L = $P(C_6H_{11})_3$; M = W[10] and M = Cr.

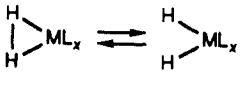
corresponding value for $W(CO)_3[P(C_6H_{11})_3]_2$, 7.5 ± 3.2 kcal/mol.[11] These values can be compared to enthalpies of activation for binding pyridine as shown in eq 2. Stopped-flow kinetic studies

$$M(CO)_3[P(C_6H_{11})_3]_2 + py \rightleftarrows M(py)(CO)_3[P(C_6H_{11})_3]_2 \quad (2)$$

have shown that $\Delta H^\ddagger$ = 4.7 kcal/mol for M = Cr and 4.5 kcal/mol for M = W.[12]

The crystal structures of $M(CO)_3[P(C_6H_{11})_3]_2$ (M = W,[13] Cr[14]) show three-center agostic M···H–C bonds between the cyclohexyl groups and the metal center. The transition states for ligand addition in these systems are likely to involve varying degrees of breaking the agostic bond, which is probably stronger for the tungsten complex. Time-resolved gas-phase infrared studies have shown that the $W(CO)_5(C_6H_{12})$ agostic bond strength is 11.6 ± 3 kcal/mol.[15] Photoacoustic calorimetry has shown that the $Cr(CO)_5(C_7H_{16})$ agostic bond strength is 9.8 kcal/mol.[16] Since the activation energies for ligand addition are smaller than these numbers, associative character of varying degree is indicated. The generally greater bond strengths to the third-row metal are reflected in the reaction profile in Figure 3.

Finally, it should be emphasized that there are a number of systems where exchange between two species of different intrinsic T_1 occurs, significantly affecting the observed T_1 values. For example, exchange between η^2-H_2 complexes and dihydride species are well documented.[2] Dihydride protons normally have a long



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(9) (a) Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley: New York, 1979. (b) The slope and slope intercept of plots of ln K_e vs $1/T$ were obtained by least-squares fitting using the subroutine LINFIT.[9c] Activation parameters were then calculated by using the formula[9a] $K_e = (kT/h)\exp(-\Delta G^\ddagger/RT)$. Standard deviations for E_a, $\Delta H^\ddagger$, $\Delta S^\ddagger$, and $\Delta G^\ddagger$ were obtained by standard methods for analysis of error propagation[9d] using the standard deviations calculated by LINFIT for the slope and slope intercepts of the ln K_e vs $1/T$ plots. The error limits quoted are 95% confidence limits obtained by using[9e] λ (95% confidence) = $t\sigma$. (c) Bevington, P. R. *Data Reduction and Error Analysis for the Physical Sciences*; Wiley: New York, 1969. (d) Shoemaker, D. P.; Garland, C. W.; Steinfeld, J. L. *Experiments in Physical Chemistry*, 3rd ed.; McGraw-Hill: New York, 1962. (e) Mandel, J. *The Statistical Analysis of Experimental Data*; Interscience: New York, 1964.

(10) (a) The enthalpy of activation of H_2 addition to **1** is calculated from the enthalpy of addition of H_2, −7.3 kcal/mol,[10b] and the enthalpy of activation for H_2 elimination of 12.1 kcal/mol. (b) Gonzalez, A. A.; Hoff, C. D. *Inorg. Chem.* **1989**, *28*, 4295.

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T_1; however, fast exchange with an η^2-H_2 having a short T_1 could certainly decrease the observed average value. One can imagine a system possessing a T_1 borderline between those of η^2-H_2 and dihydride protons consisting of an equilibrium between a dihydride and an unobserved dihydrogen.

Supplementary Material Available: Solutions to the Bloch equations in the presence of exchange and a description of the fitting procedure (3 pages). Ordering information is given on any current masthead page.

Total Synthesis of Natural Ambruticin

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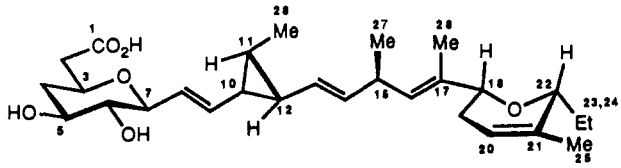
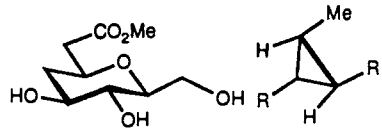
Received August 27, 1990

The structurally unique $C_{28}H_{42}O_6$ antifungal antibiotic ambruticin (**1**)[1] is systemically active against the diseases histoplasmosis and coccidiomycosis.[2,3] Its absolute configuration was established by synthesis of ozonolysis fragments **2** and **3a,b** from arabinose and resolved Feist's acid, respectively,[4] and confirmed by preparation of **3b** from citronellal.[5] Ambruticin has elicited



1



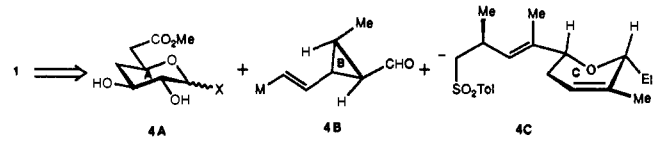
2

3a R = CH_2OH

3b R = CO_2H

considerable synthetic interest,[6] notably by Sinaÿ.[7] We now report the first total synthesis of (+)-ambruticin by a convergent strategy retrosynthetically represented in Figure 1, where X is a leaving group and M an appropriate metal.

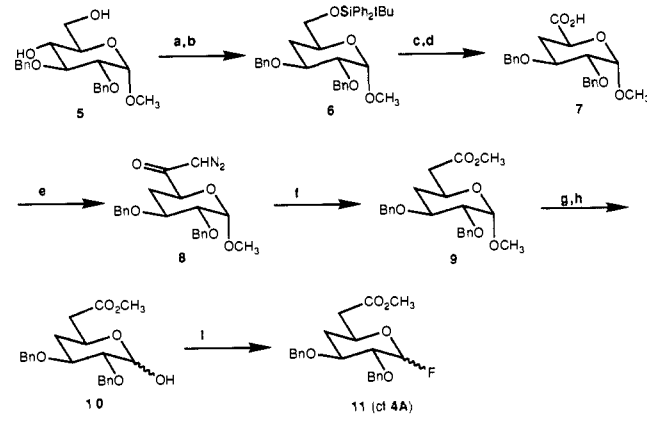
The C_7 deoxypyranose synthon **4A** was prepared in 10 steps (26% overall yield) from the methyl α-glucopyranoside **5**[8] of



4A **4B** **4C**

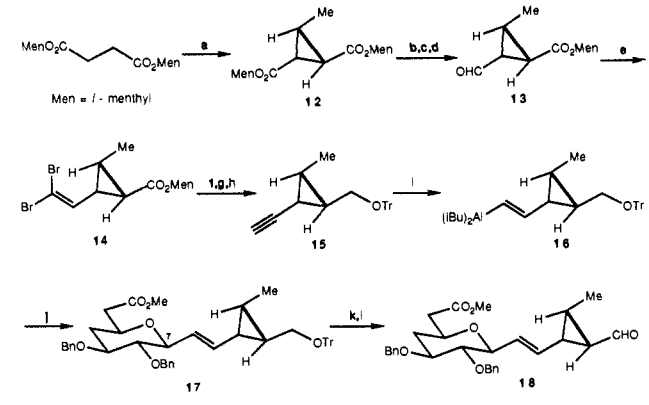
Figure 1.

Scheme I[a]



[a] (a) *t*-$BuPh_2SiCl$, imidazole, DMF, room temperature, 2 h, 99%; (b) Im_2CS, toluene, reflux, 8 h; Bu_3SnH, toluene, reflux, 16 h, 77%; (c) Bu_4NF, THF, room temperature, 18 h, 95%; (d) PDC, DMF, room temperature, 20 h, 88%; (e) $(COCl)_2$, DMF (cat.), CH_2Cl_2, room temperature, 2 h; CH_2N_2, Et_2O, 0 °C, 30 min, 78%; (f) *hν*, MeOH, 30 °C, 48 h, 68%; (g) Ac_2O, H_2SO_4 (cat.), -20 °C, 10 min, 88%; (h) MeONa, MeOH, 0 °C, 10 min, 97%; (i) Et_2NSF_3, CH_2Cl_2, -30 °C, 10 min, 92%.

Scheme II[a]



[a] (a) Lithium 2,2,6,6-tetramethylpiperidide, THF, 0 °C, then 1-bromo-1-chloroethane, -78 °C, 3 h, 45%; (b) 10% KOH (EtOH/H_2O, 9:1), room temperature, 83%; (c) B_2H_6/THF, 0 °C → room temperature, 8 h, 100%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78 °C → -30 °C, 96%; (e) Ph_3P, CBr_4, CH_2Cl_2, 0 °C, 30 min, 98%; (f) DIBAL, toluene, 0 °C, 30 min, 90%; (g) TrCl, DMAP, Et_3N, CH_2Cl_2, room temperature, 72 h, 90%; (h) nBuLi, THF, -78 °C, 10 min, 92%; (i) DIBAL, hexane, 50 °C, 2 h; (j) **11**, toluene, -20 °C → room temperature, 30 min, 49%; (k) pTSA (cat.), MeOH/CH_2Cl_2 (1:1), room temperature, 2 h, 92%; (l) Dess-Martin's periodinane, CH_2Cl_2, room temperature, 30 min, 90%.

Scheme I. Key steps included Barton deoxygenation[9] of the C-4 hydroxyl, photochemical Arndt-Eistert homologation[10] of **7**, and finally Et_2NSF_3 generation of a 73:27 β:α ratio of the glycosyl fluorides **11**.[11]

The cyclopropane precursor to synthon **4B** was synthesized (Scheme II) by an intriguing extension of Yamamoto's dianion chemistry,[12] whereby $CH_3CHBrCl$ as electrophile condenses with

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