Table I. Isotopic Analysis of Anethole Samples from Different Origins[a]

origin	D/H, ppm	f(I)	f(II)	f(III)	f(IV)	f(V)	f(VI)	R(6)	R(2,3)	T_S
statistics		0.250	0.166	0.166	0.083	0.083	0.250	3	4	
fennel										
A	140.0	0.228	0.226	0.166	0.085	0.085	0.210	2.763	5.158	
B	143.0	0.231	0.230	0.163	0.079	0.081	0.216	2.805	5.104	2.650
mean	141.5	0.230	0.228	0.164	0.082	0.083	0.213	2.784	5.131	
CAT										
C	144.0	0.222	0.207	0.164	0.083	0.077	0.247	3.338	5.013	
D	141.5	0.227	0.212	0.156	0.079	0.073	0.253	3.343	4.863	
E	140.5	0.220	0.211	0.162	0.084	0.078	0.245	3.341	5.086	2.636
mean	142.0	0.223	0.210	0.161	0.082	0.076	0.248	3.340	4.962	
estragole F	151.5	0.223	0.186	0.148	0.115	0.075	0.254	3.417	4.493	3.058
synthesis G	136.0	0.250	0.176	0.170	0.053	0.081	0.270	3.240	4.152	2.495

[a] $f(i)$ are the molar fractions of the different deuterated molecules i and $R(i)$ the relative enrichment factors. Usually several spectra (three to eight) were recorded for each sample of anethole, and each spectrum was treated at least three times. The average values given for $f(i)$ and $R(i)$ are characterized by standard deviations of about 0.008 and 0.07, respectively. The D/H values have been obtained by mass spectrometry. They are referenced to the SLAP-SMOW scale.[6] The ^{2}H NMR spectra were obtained with a Bruker WM 250 spectrometer (5.87 T) using a 15-mm cell, an acquisition time of 6.8 s (sweep width 1200 Hz), and a 90° pulse (100 × 10^{-6} s); 2000–2500 scans were stored for each spectrum (T = 308 K). [b] SAT = star anise tree.

This external reference also enabled the relative overall ^{2}H contents of the various samples, $T_S = \sum_{i=0}^{6} S(i)/S(\text{ref})$, to be determined. The absolute values of these overall contents can be obtained by calibrating the results with respect to the international standard, SMOW.[6]

We investigated seven different samples of anetholes referenced A–G. Samples A and B were obtained from fennel (*Foeniculum vulgare* Miller) and samples C–E from star anise tree (*Illicium verum* Hooker). Anethole F was prepared by the isomerization of a sample of estragole extracted from turpentine, and anethole G was synthetized from anisole. Table I lists the values of the molar fractions $f(i)$ of the six monodeuterated species and those of the internal factors $R(i) = 3S(i)/S(CH_3O)$, which characterize the internal distribution referred to the CH_3O site.[1]

A statistical distribution of ^{2}H among the six molecular sites would correspond to probability factors, $R(i)$ statistics, equal to the number of hydrogens in each site. The values $f(i)$ statistics corresponding to the statistical distribution are also given in the table.

It may be emphasized first that a satisfactory agreement exists between the overall contents of ^{2}H as determined by mass and ^{2}H NMR spectrometry: D/H D/H = 68.4 + 27.2 T_S, with R = 0.99. In the present state of the experimental techniques, the NMR method is the less accurate but does not require tedious preparation of the samples, and the time consumption is reduced by a factor 1–5 for concentrated or liquid samples. The major interest of the NMR method, however, lies in its ability to provide information about the internal distribution. Indeed mass spectrometry is unable to make the distinction between anetholes obtained from fennel and those obtained from star anise tree since the D/H values are nearly equal for samples A–E. The quantitatively ^{2}H NMR method, on the contrary, succeeds in distinguishing these compounds. Thus we observe that methyl group 6 of the propenyl fragment is systematically enriched with respect to methoxy group 1 in the anetholes extracted from star anise tree, whereas the reverse situation is found in samples A and B obtained from fennel. This behavior is clearly shown by the $R(6)$ values. In fact a simple inspection of the spectra enables the immediate identification of each sample.[7] The synthetic anethole G is clearly distinguishable from the others, in particular by a strong ^{2}H depletion in the ethylenic site 4. Interestingly a noticeable enrichment of this ethylenic site 4 with respect to 5 is observed in the anethole F, which results from an isomerization of estragole, itself extracted from turpentine and characterized by a high deuterium content in the methylene group involved in the isomerization process. It is worth noting that the natural products exhibit a high aromatic ^{2}H enrichment, which is understandable if we bear in mind that the aromatic ring originates from photosynthesized carbohydrates having a high overall D/H content.[3c]

Registry No. *trans*-Anethole, 4180-23-8.

(6) R. Gonfiantini, *Nature (London)*, **271**, 534 (1978).
(7) It should be noted that due to the limited number of samples investigated the quantitative conclusions given here may not necessarily extend to the whole population of anethole samples.

Total Synthesis of (±)-Mycorrhizin A and (±)-Dechloromycorrhizin A

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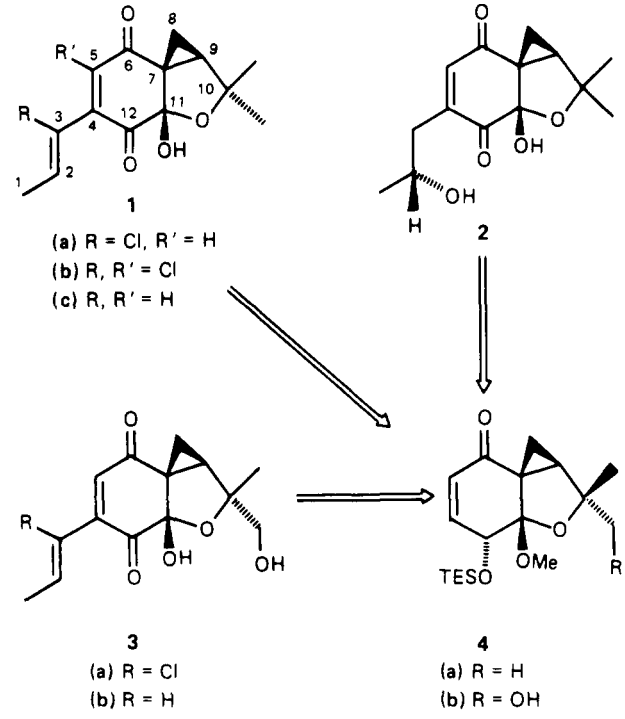
Mycorrhizin A (**1a**), an antibiotic first isolated by Wickberg



and Trofast[2] in 1977 from a sterile mycelium (ATCC No. 36554)

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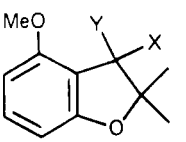
of an endomycorrhizinal fungus found to associate with the roots of the Norway spruce (*Picea abies*) and pinesap (*Monotropa hypopytis*, L.), belongs to a group of architecturally related fungal metabolites that include chloromycorrhizin A (**1b**),[2] gilmicolin (**2**),[3,5] mikrolin (**3a**),[4,5] and dechloromikrolin (**3b**).[4,5] The structural similarity of these metabolites, along with their coocurrence in culture filtrates of *Gilmaniela humicola*, suggests a common biosynthetic pathway; indeed, in 1979 Tamm and co-workers[3,6] postulated that dechloromycorrhizin A (**1c**), a compound yet to be isolated, may play a pivotal role in the biogenesis of these substances.

Despite both the novel structural features[5] of this family of mold metabolites and their potential economical importance in the control of root-rot pathogens (cf. *Fomes annosus*) of the major softwood forests of the world,[2,7] efforts directed toward the synthesis of the basic tricyclic skeleton have been few.[7,8] In this communication we wish to record the *first* total synthesis of mycorrhizin A (**1a**) and dechloromycorrhizin A (**1c**) via a route potentially adaptable to the other members of this class.

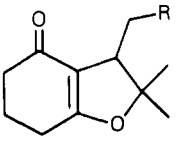
From the retrosynthetic perspective enone **4** appeared to be an ideal advanced intermediate for elaboration of this family of mold metabolites. Conjugate addition of a propenyl unit to **4a**, followed by deprotection and oxidation, was envisioned to lead to dechloromycorrhizin A (**1c**). Alternatively, introduction of chlorine at C(3) or oxygen at C(2), with the added possibility of stereocontrol via the latent C(12) hydroxyl, was in turn seen to be a viable route to mycorrhizin A (**1a**) and gilmicolin (**2**). In our approach to **4a**, we thought it desirable to include the option of constructing this material with the proper absolute configuration.

With these goals in mind, the synthesis of **4a** was initiated via bromination ($Br_2/CH_2Cl_2/0$ °C) of 2,6-dimethoxyisobutyrophenone[9a,b] followed by treatment with 2.2 equiv of $AlCl_3$ (CH_3Cl_2, 25 °C) to afford 4-hydroxy-2,2-dimethylbenzo-3(2*H*)-furanone. Without purification the latter was treated with excess methyl iodide (K_2CO_3/acetone, at reflux) to afford **5a**[10] (mp 93–94 °C), the overall yield[10c] after crystallization from ethyl acetate/hexane being 58%. Methenylation ($Ph_3P{=}CH_2$/THF, 25 °C) then afforded **5b**,[10a] which was hydroborated and oxidized (BH_3/THF; H_2O_2/NaOH) to yield alcohol **5c**.[10] Alternatively, this intermediate could be obtained from **5a** in comparable overall yield (~75%)[10c] enriched in either enantiomer (60% ee)[11] when the hydroboration step was carried out with (+)- or (−)-diisopinocamphenylborane.[12]



5

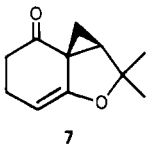
(a) X, Y = O
(b) X, Y = CH_2
(c) X = H, Y = CH_2OH



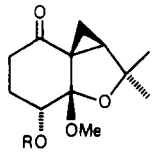
6

(a) R = OH
(b) R = OSO_2Me

In preparation for construction of the cyclopropane ring, Birch reduction of racemic **5c** ($Li/NH_3/t$-BuOH) followed by hydrolysis [$H_2O/(COOH)_2/CH_2Cl_2$] led to enone **6a**,[10a] which in turn was converted to mesylate **6b**[10] ($MsCl/Et_3N/CH_2Cl_2$, 0 °C). The overall yield from **5c** was 40%. Exposure of **6b** to lithium *tert*-butoxide (*t*-BuOH/THF, 25 °C) then resulted in the formation of the somewhat unstable cyclopropyl ketone **7**, which was oxidized



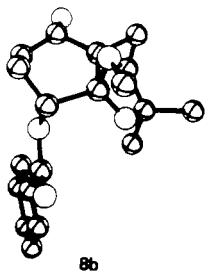
7



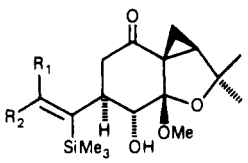
8

(a) R = H
(b) R = Bz

≡

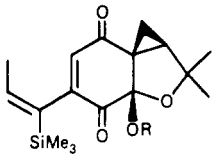


8b



9

(a) R_1 = Me, R_2 = H
(b) R_1 = H, R_2 = Me



10

(a) R = Me
(b) R = H

without purification with *m*-CPBA (CH_3OH, 0 °C) to afford a single keto alcohol (**8a**).[10a] The stereochemistry of **8a** was predicted by examination of Drieding models. In particular, it was

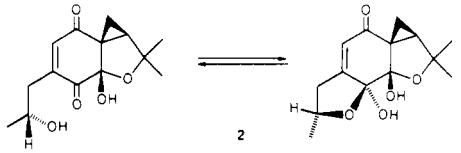
(1) Camille and Henry Dreyfus Teacher–Scholar Awardee, 1978–1983; National Institute of Health (National Cancer Institute) Career Awardee, 1980–1985.

(2) J. Trofast and B. Wickberg, *Tetrahedron*, **33**, 875 (1977).

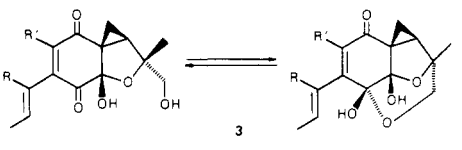
(3) K. K. Chexal, C. Tamm, J. Clardy, and K. Hirotsu, *Helv. Chim. Acta*, **62**, 1129 (1979).

(4) (a) P. Bollinger and T. Zardin-Tartaglia, *Helv. Chim. Acta*, **59**, 1809 (1976). (b) H. P. Weber and T. J. Pechter, *ibid.*, **59**, 1821 (1976).

(5) The structure given for the mikrolins and gilmicolin were drawn to emphasize the similarity of their enedione functionality to that of mycorrhizin. In fact, these compounds exist in solution as equilibrating tautomers with the tetracyclic forms predominating (see ref 3, 4, and 6):



2



3

(6) K. K. Chexal and C. Tamm, *Helv. Chim. Acta*, **61**, 2002 (1978).

(7) J. Trofast, Ph.D. Thesis, Lund Institute of Technology, Lund, Sweden, 1978.

(8) R. F. C. Brown, B. R. Matthews, and I. D. Rae, *Tetrahedron Lett.*, 2915 (1981).

(9) (a) R. Levine and J. R. Sommers, *J. Org. Chem.*, **39**, 3559 (1974). (b) Prepared in 78% yield on a 0.5 mol scale via metalation of 1,3-dimethoxybenzene (*n*-BuLi/Et_2O, 35 °C, 4 h) followed by addition of isobutyryl chloride in ether at −78 °C.

(10) (a) The structure assigned to each new compound was in accord with its infrared and 60- and/or 250-MHz NMR spectra as well as appropriate parent ion identification by high-resolution mass spectrometry. (b) In addition, analytical samples of new compounds, obtained by recrystallization or chromatography (LC or TLC) gave satisfactory C and H combustion analyses within 0.4%. (c) All yields recorded here are based upon isolated material that was >97% pure. IR and 250-MHz NMR spectra data of representative intermediates are recorded. **6a**: IR (CCl_4) 3550 (br), 1600 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.26 (s, 3 H), 1.50 (s, 3 H), 2.05 (m, 2 H), 2.40 (m, 4 H), 3.10 (br t, J = 7 Hz, 1 H), 3.68 (m, 2 H), 5.35 (br d, 1 H, exchangeable). **8**: IR (CCl_4) 3450 (br), 1695 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.44 (s, 3 H), 1.70 (dd, J = 4, 9 Hz, 1 H), 1.82 (dd, J = 4, 6, Hz, 1 H), 2.24 (m, 5 H), 2.70 (m, 1 H), 3.30 (s, 3 H), 4.12 (m, 1 H). 10b: IR (CCl_4) 3350 (br), 1675 (s) cm^{-1}; NMR ($CDCl_3$) δ 0.18 (s, 9 H), 1.30 (s, 3 H), 1.40 (s, 3 H), 1.62–1.74, 1.70 (m, 1 H d, J = 6 Hz, 3 H), 2.00 (dd, J = 5, 8 Hz, 1 H), 2.24 (dd, J = 6, 8 Hz), 3.2 (s, 1 H), 6.18 (q, J = 6 Hz, 1 H), 6.5 (s, 1 H).

(11) Determined by chiral-shift NMR experiments using the shift reagent tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III).

(12) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Am. Chem. Soc.*, **86**, 397 (1964).

anticipated that approach of the peracid would occur from the less hindered α face of **7**; the resultant highly strained intermediate epoxide would then suffer in situ acid-catalyzed trans diaxial ring opening to yield **8a**. That our structural assignment for this compound was correct was confirmed by a single-crystal X-ray analysis of the derived benzoate ester (**8b**).[10,13] Final conversion of **8a** to **4a**[10] proceeded in 60% overall yield via protection of the hydroxyl group as the TES derivative (Et_3SiCl, Et_3N, DMAP, CH_2Cl_2, 25 °C) and execution of the Reich–Sharpless[14] phenyl selenation–oxidative elimination sequence.

With **4a** in hand, our plan for elaboration of dechloromycorrhizin A (**1c**) called for the addition of *trans*-bis(1-propenyl)copper lithium,[15] followed by desilylation (Bu_4NF), oxidation (Swern oxidation,[21] followed by SeO_2/pyridine/*t*-BuOH), and hydrolysis (aq HBF_4/dioxane) of the mixed methyl ketal of **1c**. It was anticipated (hoped) that the chlorine at C(3) could then be introduced via a chlorination–dehydrochlorination sequence to afford mycorrhizin A (**1a**). We were, in fact, successful in preparing dechloromycorrhizin A (**1c**) via this strategy in 12.6% overall yield from **4a**. Unfortunately, introduction of chlorine at C(3) proved problematic. We were, however, encouraged by the observations of Miller and McGarvey,[16] who demonstrated that vinylsilanes could be cleanly converted to vinyl chlorides of inverted configuration via a halogenation–desilylation protocol.

Toward this end addition of **4a** to a solution of the cuprate derived from (*E*)-(1-lithio-1-propenyl)trimethylsilane[17] resulted in the formation of **9a**[10] in 75% yield after selective O-desilylation (1.5 equiv of Bu_4NF/THF/0 °C). Also present, in 10% yield, was the corresponding *Z* isomer (**9b**), which could be separated chromatographically from **9a**.[19]

Swern oxidation[21] of **9a** [$(COCl)_2/Me_2SO/Et_3N$] gave the corresponding dione[10a] (mp 98–100 °C) in 65% yield. Further oxidation with SeO_2 (*t*-BuOH/pyridine, at reflux, 5 h) then afforded a 2:1 mixture of **10a**[10a] and **10b**,[10] respectively, in a combined yield of 55%. As anticipated, treatment of **10b** with chlorine at −75 °C, followed by brief exposure to KF in Me_2SO[16] at 25 °C gave racemic mycorrhizin A in 73% yield identical in all respects (IR, 250-MHz NMR, and TLC) with an authentic sample kindly provided by Wickberg and Trofast. Alternatively, exposure of **10a** to the same conditions produced the mixed methyl ketal of mycorrhizin A in 60% yield. The latter was then hydrolyzed [50% HBF_4/dioxane (1:6)/80 °C, 15 min, 60%] to mycorrhizin A via the Wickberg–Trofast protocol.[22]

In summation, the first total synthesis of (±)-mycorrhizin A and dechloromycorrhizin A has been achieved. Studies to improve this sequence, including a chiral synthesis of mycorrhizin A (**1a**), and to effect the total synthesis of gilmicolin by exploiting the α-hydroxyl functionality at C(12) to introduce oxygen at C(2) in a stereocontrolled fashion will be reported in due course.

Acknowledgment. It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health (Institute of General Medical Sciences) through Grant No. GM-24680. In addition, we thank S. T. Bella of the Rockefeller University for the microanalyses and Drs. G. Furst and T. Terwilliger of the University of Pennsylvania for aid in recording and interpretation of the high-field NMR and mass spectra.

(13) Unpublished results of P. Carroll and J. Safaryn of our laboratory.
(14) H. J. Reich, I. C. Reich, and J. M. Renga, *J. Am. Chem. Soc.*, **95**, 5813 (1973); K. B. Sharpless and R. F. Lauer, *ibid.*, 2697.
(15) G. Linstrumelle, J. K. Krieger, and G. M. Whitesides, *Org. Synth.*, **55**, 103 (1976).
(16) R. B. Miller and G. McGarvey, *J. Org. Chem.*, **43**, 4424 (1978).
(17) Prepared from (*Z*)-(1-bromo-1-propenyl)trimethylsilane[18] by halogen–metal exchange with *tert*-butyllithium.
(18) D. Seyferth, J. Lefferts, and R. L. Lambert, Jr., *J. Organomet. Chem.*, **142**, 39 (1977).
(19) The small amount of **9b** formed in the cuprate addition is due to the configurational instability of (1-lithio-1-alkenyl)trimethylsilanes at temperatures above −70 °C.[20]
(20) G. Zweifel, R. E. Murray, and H. P. On, *J. Org. Chem.*, **46**, 1292 (1981).
(21) A. J. Mancuso, S.-L. Huang, and D. Swern, *J. Org. Chem.*, **43**, 2480 (1978).
(22) Hydrolysis of the mixed methyl ketal of mycrorrhizin had been carried out by Trofast and Wickberg during their isolation studies; see ref 2 and 7.

A Dinuclear Rhodium Complex with an Octahedral Rhodium(III) and a Square-Planar Rhodium(I) Center

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A family of polynuclear rhodium hydrides of the form $\{HRh(PY_3)_2\}_n$[1] has been prepared, and we describe here the chemistry of $(\mu\text{-H})_2Rh_2\{P[N(CH_3)_2]_3\}_4$. Seminal are the structural features of an intermediate in the olefin hydrogenation cycle catalyzed by the dimer. This intermediate is distinguished by an octahedral rhodium(III) center and a square-planar rhodium(I) center joined through a common edge defined by the two bridging hydride ligands. This unique structure is the paradigm for the intermediate preceding olefin complexation in olefin hydrogenation cycles catalyzed by these polynuclear rhodium hydrides.

The dimer, $(\mu\text{-H})_2Rh_2\{P[N(CH_3)_2]_3\}_4$, has in the solution state a near coplanar set of framework atoms, $P_2RhH_2RhP_2$, as judged by the NMR data[2] and is isostructural with $(\mu\text{-H})_2Rh_2[P(O\text{-}i\text{-}C_3H_7)_3]_4$. Both these dimers are active catalyst precursors for olefin hydrogenation. In this catalytic cycle, the first step is hydrogen addition,[1a] which is reversible for both dimers (see eq 1). However, the reverse step, hydrogen elimination, is slower

$$H_4Rh_2(PY_3)_4 \rightleftharpoons (\mu\text{-H})_2Rh_2(PY_3)_4 + H_2 \qquad (1)$$

for the phosphine derivative, a feature that facilitated isolation of the tetrahydride in single-crystal form (from toluene at −40 °C).[3]

Single crystals of $H_4Rh_2\{P[N(CH_3)_2]_3\}_4 \cdot 0.5CH_3C_6H_5$ (**1**) were triclinic, space group $P\bar{1}\text{-}C_i^1$ (No. 2), with a = 10.851 (3) Å, b = 13.326 (4) Å, c = 17.098 (5) Å, α = 85.93 (2)°, β = 95.02 (2)°, γ = 114.87 (2)°, and Z = 2 (ρ_{calcd} = 1.689 g cm^{-3}; μ_a (Mo K$\bar{\alpha}$) = 0.89 mm^{-1}). Three-dimensional X-ray diffraction data were collected (20 ± 1 °C) for 15 304 independent reflections

(1) Sivak, A. J.; Muetterties, E. L. *J. Am. Chem. Soc.* **1979**, *101*, 4878. (b) Burch, R. R.; Muetterties, E. L.; Day, V. W. *Organometallics* **1982**, *1*, 188.
(2) ^1H NMR (toluene-d_8, +28 °C, 180 MHz) δ + 2.2 (m, NCH_3), −9.2 (q of t, J_{Rh-H} = 33.3 Hz, J_{P-H} = 30.7 Hz); $^1H\{^{31}P\}$ NMR (toluene-d_8, +20 °C, 180 MHz) δ +2.2 (m, NCH_3), −9.2 (t, J_{Rh-H} = 33.3 Hz); $^1H\{^{31}P\}$ NMR (toluene-d_8, −70 °C, 180 MHz) δ +2.2 (m, NCH_3), −9.2 (t, J_{Rh-H} = 33.3 Hz); $^{31}P\{^1H\}$ NMR (toluene-d_8, +20 °C, 72.9 MHz) δ +132.2 (relative to 85% H_3PO_4) AA′A″A‴XX′ pattern characteristic of $(HRhP_2)_2$ compounds, but poorly resolved presumably due to the nitrogen quadrupolar nuclei; $^{31}P\{^1H\}$ NMR (toluene-d_8, −50 °C, 72.9 MHz) δ +132.5 (br d) (relative to 85% H_3PO_4).
(3) ^1H NMR (toluene-d_8, 20 °C, 250 MHz) δ +2.79 (t, J = 5.2 Hz, NCH_3), +2.62 (d, J = 8.8 Hz, NCH_3), −10.5 (m, H_b), −16.8 (approximate quin. of m, H_t, $J \simeq$ 18 Hz). When the sample was cooled to −70 °C, the chemical shifts were temperature independent but there was substantial line broadening. $^1H\{^{31}P\}$ NMR (toluene-d_8, 20 °C, 180 MHz) δ +2.79, +2.62 −10.5 (t, J_{Rh-H} = 52.5 Hz), −16.8 (d, J_{Rh-H} = 17.5 Hz); $^1H\{^{31}P\}$ NMR (toluene-d_8, −70 °C, 180 MHz) δ +2.79, +2.62, −10.5 (t of m, J_{Rh-H} = 26.6 Hz), −16.8 (br s); $^{31}P\{^1H\}$ NMR (toluene-d_8, 72.9 MHz) δ +147.3 (d, J_{Rh-P} = 142.5 Hz), +146.5 (d of d, J_{Rh-P} = 217 Hz, J_{Rh-P} = 3.3 Hz) (relative to 85% H_3PO_4); $^{31}P\{^1H\}$ NMR (toluene-d_8, −77 °C, 72.9 MHz) δ +147.8 (d, J_{Rh-P} = 142.5 Hz), +148.3 (d, J_{Rh-P} = 217 Hz) (relative to 85% H_3PO_4) (the temperature dependence of the $^{31}P\{^1H\}$ NMR spectra we attribute to excited-state contributions); ν(Rh–H) = 1995 cm^{-1} (pentane).

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