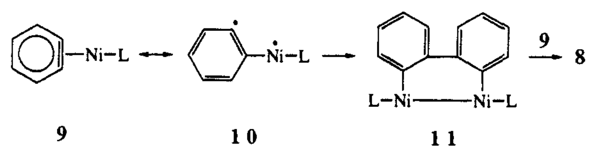
Scheme I



triangle of nickel atoms each bearing one triisopropylphosphine ligand [Ni(1)–Ni(2) = 2.405 (1) Å, Ni(2)–Ni(3) = 2.408 (1) Å, Ni(1)–Ni(2)–Ni(3) = 90.81 (2)°]. The triangle is bridged by a C_6H_4 unit on one face and a 2,2′-biphenylyl (C_6H_4–C_6H_4) unit on the other; the $Ni_3(\mu_3\text{-}C_6H_4)(\mu_3\text{-}C_6H_4\text{–}C_6H_4)$ core exhibits almost exact mirror symmetry. The four-electron-donor benzyne unit is σ-bonded to Ni(1) and Ni(3), and π-bonded to Ni(2), the geometry being like that found in complexes **2–5**. In contrast, the 2- and 2′-carbon atoms of the C_6H_4–C_6H_4 unit are σ-bonded to Ni(2) and bound orthogonally to Ni(1) and Ni(3), respectively. The four Ni–C distances to the C_6H_4–C_6H_4 unit are in the range 1.95–2.00 Å, which is similar to that observed for the compounds $\{Ni(C_6H_5)_2(CH_2 = CH_2)\}_2Na_4(THF)_5$[16] and $C_6H_5(Na{\cdot}OEt_2)_2\text{-}\{Ni(C_6H_5)_2\}_2(N_2)NaLi_6(OEt)_4{\cdot}OEt_2$,[17] in which the phenyl groups bridge nickel and sodium atoms, but greater than that found in the η^1-phenylnickel(II) complexes $Ni(\eta\text{-}C_5H_5)(C_6H_5)(PPh_3)$ [1.904 (7) Å][18] and $[Ni(C_6H_5)\{N(CH_2CH_2AsPh_2)_3\}]BPh_4$ [1.87 (2) Å].[19] Although the 2- and 2′-carbon atoms in **8** are each nearly equidistant from the bridged pair of nickel atoms, the σ-bonded nickel atom Ni(2) is within 0.1 Å of the C_6H_4–C_6H_4 ring plane, whereas nickel atoms Ni(1) and Ni(3) are 1.75 and 1.72 Å, respectively, below the plane. Thus, the interactions of the 2- and 2′-carbon atoms with the nickel atoms differ from the more usual three-center, two-electron bonds found in the 2,2′-biphenylyllithium compound $(C_6H_4\text{–}C_6H_4)Li_2(tmeda)_2$,[20] and in other μ-aryls and μ-alkyls of main group and transition elements, e.g., $Al_2(\mu\text{-}C_6H_5)_2(C_6H_5)_4$,[21] $Os_3(CO)_8(\mu_2\text{-}PPh_2)(\mu_2\text{-}PPhC_6H_4)(\mu_2\text{-}C_6H_5)$,[9a] $Pt_3(PPh_3)_2(\mu_2\text{-}PPh_2)_3(\mu_2\text{-}C_6H_5)$,[22] and $Ni_2(\mu_2\text{-}CH_3)_2(\eta^3\text{-}1,3\text{-dimethylallyl})_2$.[23]

Complex **8** can be classified as a 44e cluster if we assume that μ_3-C_6H_4 and μ_3-C_6H_4–C_6H_4 donate four electrons each to the three nickel atoms and if we exclude Ni–Ni bonding electrons. It is therefore related to the unsaturated clusters of the nickel triad such as $Pt_3(CN\text{-}t\text{-}Bu)_6$ (42e),[24] $Pt_3(CO)_3(PCy_3)_3$ (42e),[25] and $Pt_3(CO)_3(PCy_3)_4$ (44e),[26] which, however, differ from **8** in having equilateral triangles. The only other compound in which a μ_3-alkyne is attached to an isosceles triangle of nickel atoms is the electronically saturated 48e-complex $Ni_3(CO)_3(\mu_3\text{-}CF_3C_2CF_3)(\mu_3\text{-}\eta^8\text{-}C_8H_8)$.[27]

The benzyne and 2,2′-biphenylyl ligands display well-defined intra-ring bond length (and bond angle) inequalities (Figure 1). The pattern in the benzyne ring resembles that observed in **4**. However, the distance between the metal-bound carbon atoms [1.434 (3) Å] and also the average length of the remaining C–C bonds (1.403 Å) in the μ_3-C_6H_4 ring each significantly exceed the corresponding values in **4** (1.40 and 1.38 Å, respectively). This agrees with the idea that the electronic unsaturation of **8** reduces the π-orbital population of its *o*-phenylene group relative to that in the 48e complex **4**.

Since **8** is not formed from **7** under the reaction conditions, we suggest that the first step is dissociation of one of the bulky P-*i*-Pr_3 ligands from **6**. Two-electron reduction of the resulting three-coordinate nickel(II) complex could give a 14e benzyne–nickel(0) fragment $Ni(C_6H_4)(P\text{-}i\text{-}Pr_3)$ (**9**), which could be regarded as the nickel(I) complex of a phenyl radical (**10**) (Scheme I). Such a compound could be expected to dimerize to the 2,2′-biphenylylnickel(I) species **11**, which could react with more **9** to give the trimeric compound **8**. A somewhat similar stepwise sequence in which free arynes react with organolithium compounds has been invoked to account for the formation of triphenylenes from the thermal decomposition of 2-halophenyl derivatives of lithium or magnesium,[28] and from the reaction of lithium metal with *o*-diiodobenzene or *o*-bromoiodobenzene.[29] Experiments to test the proposed sequence and to prepare related clusters containing other alkynes and metals are in progress.

Supplementary Material Available: Tables of crystal data, non-hydrogen atom position and thermal parameters, and bond lengths and angles (9 pages); listing of observed and calculated structure factors for **8** (30 pages). Ordering information is given on any current masthead page.

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(15) Crystallography: Philips PW1100/20 diffractometer, Mo K$\bar{\alpha}$ radiation (λ = 0.7107 Å, graphite crystal monochromator), 4 deg min^{-1} 2θ, 2 × 5 s backgrounds at extremes, T = 164 K. Black, metallic crystals from diethyl ether; $C_{45}H_{75}P_3Ni_3$; triclinic, space group $P\bar{1}$, a = 19.467 (3), b = 11.116 (2), c = 10.542 (2) Å; α = 78.22 (1), β = 84.78 (1), γ = 85.44 (1)°; M_r = 885.15; ρ_{calcd} = 1.32 g cm^{-3}; Z = 2; μ = 13.9 cm^{-1}. Specimen crystal dimensions 0.45 × 0.23 × 0.14 mm., maximum/minimum transmission = 0.84/0.76. A total of 12384 measured reflections ($\pm h \pm k \pm l$, $5 < 2\theta < 45°$), 5169 unique observed reflections ($I \geq 3\sigma$). Structure solution by direct methods (DIRDIF); refinement by full-matrix least-squares on F; non-hydrogen atoms anisotropic, hydrogen atoms located by calculation, reflection weights $(\sigma_s{}^2 + 0.0005F^2)^{-1}$; 460 refined parameters, R = 0.022, R_w = 0.033, GOF = 1.23; maximum shift/error = 0.16, maximum/minimum excursions in final difference map +0.27/–0.25 e $Å^{-3}$.

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A Heterogeneous "Ligand-Accelerated" Reaction: Enantioselective Hydrogenation of Ethyl Pyruvate Catalyzed by Cinchona-Modified Pt/Al_2O_3 Catalysts

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Enantioselective hydrogenation reactions are a topic current interest.[1] While there is a growing understanding of the mechanism of homogeneously catalyzed reactions,[2] less is known about chiral heterogeneous catalysts.[3] One such enantioselective catalytic system, Pt/Al_2O_3 modified with cinchona alkaloids, is able to hydrogenate α-keto esters with optical yields approaching 90%.[4-7] It was noted that modification leads to a marked increase in reaction rate,[6] suggesting a mode of action that has recently

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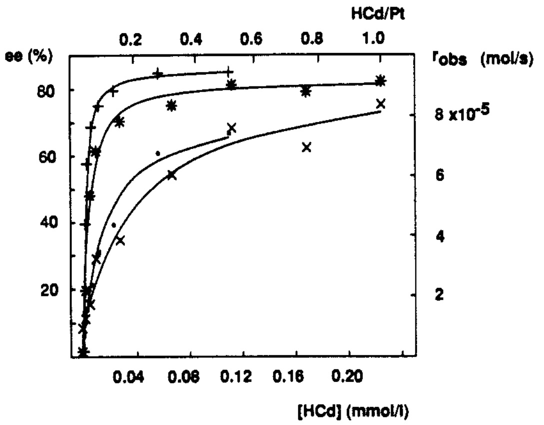
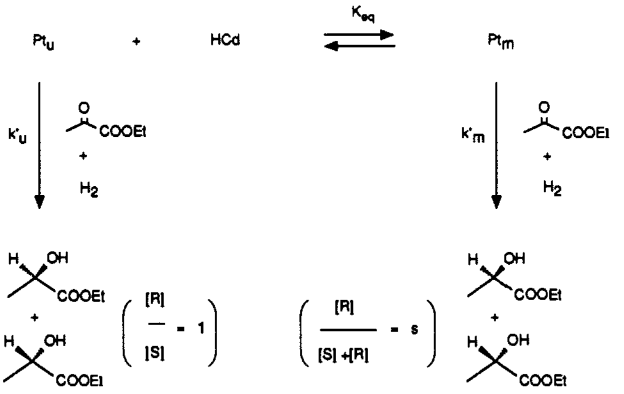


Figure 1. Plots of initial rate and optical yield versus total concentration of 10,11-dihydrocinchonidine (HCd). Toluene: (■) observed and (—) calculated rate; (+) observed and (—) calculated optical yield. Ethanol: (×) observed and (—) calculated rate; (*) observed and (—) calculated optical yield.

Scheme I



been called "ligand-accelerated" catalysis.[8] In order to test this concept for a modified hetereogenous system, the effect of low modifier concentrations on the rate and enantioselectivity (ee) of the ethyl pyruvate hydrogenation catalyzed by Pt/Al_2O_3 modified with 10,11-dihydrocinchonidine (HCd) was studied. The resulting data (rate and ee) were successfully analyzed in the context of a *general* two-cycle mechanistic scheme.

The modifier concentration was varied between 0 and 0.23 mmol/L, corresponding to 0–1 HCd molecule per exposed platinum atom.[9-11] We found that for experiments performed at *very* low modifier concentrations, the observed ee's decrease as a function of time, but in the first 5 min of reaction they never varied more than 10 relative %.[12] Initial rates and initial optical yields as a function of the HCd concentration were determined in toluene and ethanol (Figure 1). It is noteworthy that both rate and ee reach a maximum at extremely low concentrations of HCd, corresponding to an HCd/Pt_{surf} ratio of 0.5 (toluene) and 1 (EtOH).

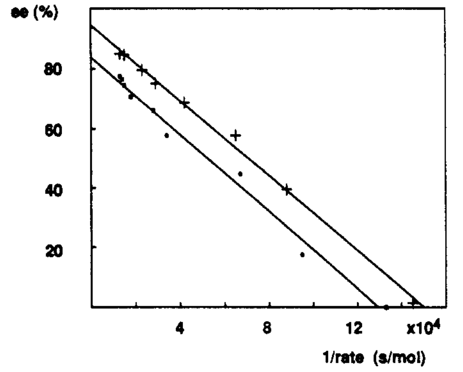


Figure 2. Plot of observed enantioselectivity versus the reciprocal of the observed rate. (+) toluene, (■) ethanol. Data from Figure 1.

Our kinetic analysis uses the following definitions: Pt, Pt_u, and Pt_m are the number of moles of total, unmodified, and modified *surface* platinum atoms, respectively; k'_u and k'_m are pseudo-first-order rate constants of the unmodified and modified cycle;[13] and s is the intrinsic selectivity for the modified sites.

From the reaction scheme and the assumption that chiral active sites are formed by reversible adsorption of cinchona molecules on the Pt surface, a mass balance over the surface platinum ($Pt = Pt_u + Pt_m$), expressions for the fraction x of modified Pt atoms ($x = Pt_m/Pt$) and the observed rate, $r_{obs} = (-dH_2/dt)$, eq 1 can

$$r_{obs} = r_m + r_u = k'_m Pt_m + k'_u Pt_u = (xk'_m + (1 - x)k'_u)Pt \quad (1)$$

$$ee_{obs} = 100(r_R - r_S)/(r_R + r_S) = 100(2s - 1)xk'_m Pt/r_{obs} \quad (2)$$

be written. Further, $sk'_m Pt_m$ is the rate of formation of the *R* enantiomer, while $(1 - s)k'_m Pt_m$ is the rate of formation of the *S* enantiomer on *modified* sites. The total rates r_R and r_S from both modified and unmodified sites follow and the observed enantiomeric excess, ee_{obs}, is calculated as eq 2.

We rearrange eq 1 for the fraction modification x and substitute this result into eq 2.

$$ee_{obs} = 100(2s - 1)k'_m/(k'_m - k'_u) + [-100(2s - 1)(k'_m k'_u Pt)/(k'_m - k'_u)]/r_{obs} \quad (3)$$

Equation 3 predicts that if the proposed simple mechanism is operative, then a *linear relationship should exist between the observed ee and the reciprocal observed rate.* Since no assumptions had to be made concerning the rate law or the adsorption equilibrium for the modifier, our mathematical treatment lends itself to the analysis of catalytic systems where only a limited number of parameters can be measured.

Figure 2 depicts a plot of ee_{obs} versus $1/r_{obs}$, showing a very good linear correlation, exactly as predicted for a ligand-accelerated reaction. A regression of the data gives the rate constants of the unmodified platinum as k'_u(ethanol) = 1.15 ± 0.07 s^{-1} and k'_u(toluene) = 1.03 ± 0.07 s^{-1}. Further, from the maximum r_{obs} (and the implicit assumption that $x_{max} = 1$), the rate constants for the modified platinum are calculated as k'_m(ethanol) = 11.8 ± 0.7 s^{-1}, k'_m(toluene) = 10.0 ± 0.7 s^{-1} and the intrinsic selectivities s are 0.89 ± 0.02 (ethanol) and 0.93 ± 0.02 (toluene).

For homogeneous systems this type of analysis is valid without qualification. For heterogeneous catalysts, however, the assumption that each surface platinum atom Pt_m and Pt_u is an active site is an oversimplification. It can be shown that the general implications of our analysis remain valid when we introduce concepts like ensembles and nonuniformity of surfaces.[14] In this

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(8) (a) Jacobsen, E. N.; Marko, I.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 737. (b) *J. Am. Chem. Soc.* **1988**, *110*, 1968. A reaction is considered ligand accelerated if there is a slower unmodified (unselective) cycle and a faster modified (selective) cycle.

(9) Experiments were conducted with 100 mg of 5% Pt/Al_2O_3,[10] 20 mL of solvent, 0.09 mol of ethyl pyruvate, and 0–2 mg of HCd at 20 °C, 20 bar, and 900 rpm in a 50-mL autoclave. $r_{obs}(= -dH_2/dt)$ were calculated from the pressure drop (1–5 min) in a reservoir. Conversion to ethyl lactate varied from 2.5 to 27%, ee's were determined by GLC.[6]

(10) With 5% Pt/Al_2O_3 Engelhard 4759 (platinum dispersion 0.28), pretreated for 2 h at 400 °C in H_2.[6]

(11) It was demonstrated that the reaction is first order in Pt/Al_2O_3 and that no mass transport limitations interfere: Garland, M.; Jalett, H. P.; Blaser, H. U. In ref 5.

(12) In these cases we also observed a strong decrease in rate as a function of time. ^{13}C NMR spectra of compounds isolated from the reaction solution show that hydrogenation of the quinoline part of HCd occurred.

(13) At low conversion, the concentrations of H_2, ethyl pyruvate, and modifier can be treated as constant and that of ethyl lactate as negligible. Therefore, k'_i's are pseudo-first-order rate constants (s^{-1}) according to the general Langmuir formalism. See, e.g.: Boudart, M.; Burwell, R., Jr. In *Techniques of Chemistry, Vol. VI, Part 1, Investigation of Rates and Mechanisms of Reactions*; Lewis, E. S.; Ed.; Wiley: New York, 1974.

(14) If the modified active sites are not single platinum atoms but ensembles, then Pt_m has to be replaced by the number of ensembles Pt^*_m and the modified rate constants k'_m by k^*_m. For nonuniform surfaces the rate constants would represent average values.

case rate constants and selectivities of active sites can only be calculated if the fraction modification x can be determined independently. For a strongly adsorbed modifier a rough lower limit of k^*_m can be estimated from the initial dependence of r_{obs} on the amount of modifier added.[15] For the case of toluene, where these conditions may be met, we obtain $k^*_m \geq 130\ s^{-1}$, corresponding to the turnover frequency of a modified site.

We would like to make the following statements concerning the reaction mechanism: (1) our analysis is in complete agreement with a simple two-cycle mechanism (linear relationship between ee_{obs} and $1/r_{obs}$); (2) adsorption of HCd on the Pt surface must be reasonably strong and/or only a small fraction of the surface platinum is modifiable (full modification effect is reached at extremely low HCd concentrations); (3) simple geometric considerations indicate that a modified ensemble should consist of one adsorbed cinchona molecule and 10–20 platinum atoms, in good agreement with the ratio $k^*_m/k'_m \geq 13$ found in toluene.[16]

The implications of the present mechanistic picture will be examined further.

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(15) For large equilibrium constants we can substitute the approximation HCd = Pt_m into eq 1. Taking the derivative with respect to HCd gives an estimate of k^*_m.

(16) Ordered arrays of adsorbed cinchona alkaloids have been proposed as an alternative explanation for the observed enantioselection: (a) Thomas, J. *Angew. Chem. Adv. Mater.* **1989**, *101*, 1105. (b) Wells, P. B. *Faraday Discuss. Chem. Soc.* **1989**, *87*, 1.

Facile Reduction of Ethyl Thiol Esters to Aldehydes: Application to a Total Synthesis of (+)-Neothramycin A Methyl Ether

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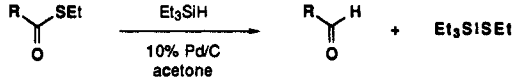
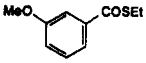
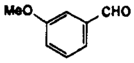
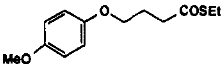
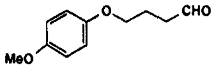
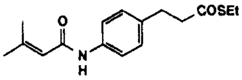
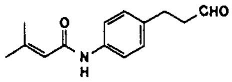
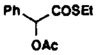
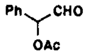
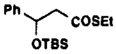
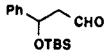
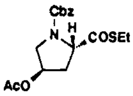
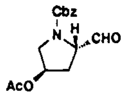
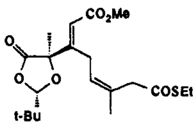
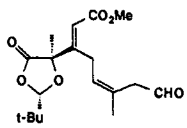
Transformation of carboxylic acids to aldehydes has been the subject of intensive investigation among synthetic organic chemists. With a few exceptions,[1] derivatives of acid such as acid chlorides, amides, and esters are usually converted to aldehydes by selective reduction. Although a number of synthetic methods have been reported to date, none seems to be generally applicable to multifunctional compounds. Hence the most frequently employed procedure at the present time is reduction of acid or its derivative followed by mild oxidation of the resultant alcohol. In this communication we report a highly efficient reduction of ethyl thiol esters to aldehydes with triethylsilane and a catalytic amount of palladium on carbon. Since acids can be readily converted to ethyl thiol esters under mild conditions,[2] this procedure provides a powerful alternative to the arsenal of synthetic chemists for transformation of acids to aldehydes. The versatility of our novel method is fully demonstrated in a total synthesis of (+)-neothramycin A methyl ether **11**.



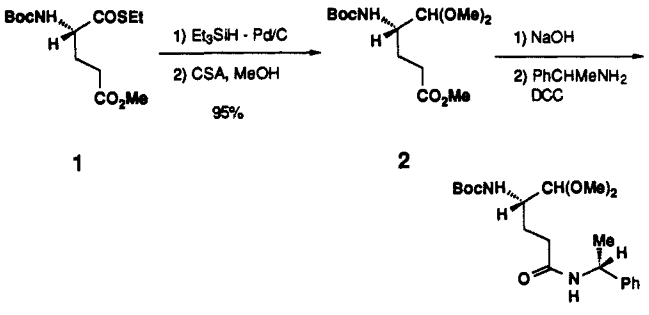
$$\mathrm{RC(O)SEt} \xrightarrow[\text{10\% Pd/C, acetone}]{\mathrm{Et_3SiH}} \mathrm{RC(O)H} + \mathrm{Et_3SiSEt}$$

As shown in Table I, a variety of functional groups survive the essentially neutral reduction conditions.[3,4] Our method is suited for the conversion of optically active amino acids to amino aldehyde derivatives that are known to racemize even under mild conditions. For example, the optically pure thiol ester **1** was converted to the dimethyl acetal **2** in 95% yield in a 40-g-scale experiment. The optical purity of **2** was virtually 100% based on the ^{1}H NMR studies of the corresponding (R)-(+)-α-methylbenzylamide derivative **3**.[5]

Table I. Reduction of Ethyl Thiol Esters with Triethylsilane and Palladium on Carbon

Entry	Substrate	Product	Yield (%)^a
1			91^b
2			94
3			97
4			84
5			88
6			75^b
7			88^c
8			92

^{a}Isolated yields after chromatographic purification. ^{b}Isolated as tosylhydrazone. ^{c}Formation of the cis isomer was not observed.



1 **2** **3**

To further demonstrate the usefulness of our procedure, neothramycins A and B (**4**)[6] were chosen as the target molecules for

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(1) For representative examples, see: (a) Cha, J. S.; Kim, J. E.; Yoon, M. S.; Kim, Y. S. *Tetrahedron Lett.* **1987**, *28*, 6231. (b) Corriu, R. J. P.; Lanneau, G. F.; Perrot, M. *Tetrahedron Lett.* **1987**, *28*, 3941. (c) Brown, H. C.; Cha, J. S.; Nazer, B.; Yoon, N. M. *J. Am. Chem. Soc.* **1984**, *106*, 8001 and references cited therein.

(2) Ethyl thiol esters can be conveniently made in 60–85% yield from the corresponding acids via mixed anhydride in a one-pot procedure (EtOCOCl (1.2 equiv), Et_3N (2.4 equiv), CH_2Cl_2, 0 °C, 10 min; EtSH (2.3 equiv), then DMAP (0.1 equiv), 0 °C, 10 min). For conversion of protected amino acids and precious acids, Steglich's method was employed: Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

(3) A general experimental procedure is as follows: To a stirred mixture of ethyl thiol ester (0.5–1 M solution) and 10% Pd on carbon (2–5 mol %) in acetone was added Et_3SiH (2–3 equiv) at room temperature under an argon atmosphere. Stirring was continued at room temperature until the reduction was completed (30–60 min). The catalyst was filtered off through Celite and washed with acetone. Evaporation and separation on a silica gel column gave the desired aldehyde in 80–97% yield. Methylene chloride can also be used as a solvent.

(4) The following functional groups are reduced under the reaction conditions and are incompatible: azide, nitro, and mono-substituted olefin.

(5) While the 300-MHz ^{1}H NMR spectrum of the amides derived from racemic glutamic acid 5-methyl ester exhibited two singlets at 3.33 and 3.41 ppm for the dimethyl acetal, the amide **3** derived from L-glutamic acid 5-methyl ester showed only a singlet at 3.33 ppm, and no trace of a peak at 3.41 ppm was observed.

(6) Isolation and structure determination: Takeuchi, T.; Miyamoto, M.; Ishizuka, M.; Naganawa, H. *J. Antibiot.* **1976**, *29*, 93. Synthesis: (a) Mori, M.; Uozumi, Y.; Ban, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 841. (b) Andriamialisoa, R. Z.; Langlois, N. *Tetrahedron Lett.* **1986**, *27*, 1149. (c) Miyamoto, M.; Kondo, S; Naganawa, H.; Maeda, K.; Ohno, M.; Umezawa, H. *J. Antibiot.* **1977**, *30*, 340.

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