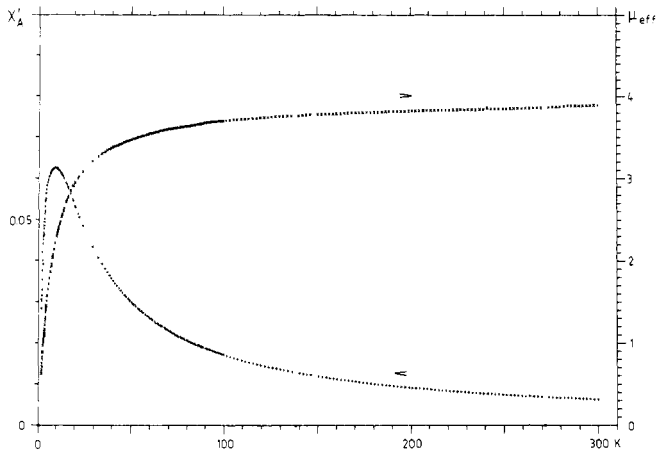

Figure 2. Magnetic susceptibilities in cgs units (left scale) and effective magnetic moments in Bohr magnetons (right scale) of **2**.

Table II. Results of Fitting Susceptibilities to Eq 1

	1	2	model
J, cm^{-1}	2.27 (1)	4.58 (1)	1
var/f	1.54	1.67	
f	237	227	
J, cm^{-1}	2.40 (2)	4.86 (3)	2
j, cm^{-1}	−0.036 (4)	−0.061 (5)	
var/f	1.13	1.01	
f	236	226	
E(1)	2.03 (3)	4.40 (3)	3
E(2)	6.86 (3)	13.84 (5)	
E(3)	13.6 (1)	28.3 (1)	
var/f	1.02	1.00	
f	235	225	

ferromagnetic coupling between the two nearest centers. The susceptibilities were fitted to the expression

$$\chi'_A(T) = -\frac{N}{2H}\frac{\sum_i \left[\frac{\partial E_i}{\partial H}\right]\exp(-E_i/kT)}{\sum_i \exp(-E_i/kT)} + K \qquad (1)$$

by minimization of

$$\sum_j \frac{[\chi^{obsd}(T_j) - \chi'_A(T_j)]^2}{\left[\sigma^2\{\chi(T_j)\} + \frac{\partial \chi^{obsd}}{\partial T}(T_j)\right]^2 \sigma^2(T_j)} \qquad (2)$$

In (1) E_i values are the energies of the sixteen components of the ground-state manifold obtained from an isotropic Zeeman term, $\beta g H \cdot S$, in the Hamiltonian by addition of exchange terms according to three different models. The Heisenberg-type Hamiltonian is

$$\hat{H} = J\hat{S}_1 \cdot \hat{S}_2 - j(\hat{S}_1 \cdot \hat{S}_2)^2 \qquad (3)$$

in which the triplet, quintet, and septet energies are $J + 6.5j$, $3J + 13.5j$, and $6J + 9j$, respectively. In the following (3) is referred to as model 2. If j is fixed to zero we call it model 1. A generalized Hamiltonian has the eigenvalues $E(S')$ at zero field where S' has the values 0–3 in this case with two spins of $^3/_2$. This is called model 3. The adjustable parameters in the fitting procedure are g, K, and J or J and j or $E(S')$ according to models 1–3, respectively. Other symbols in (1), (2), and (3) have their usual meaning.

The results of the data fittings are shown in Table II, apart from values of g and K which in both cases came out as slightly below 2.00 and as approximately zero, respectively. Also given in Table II, are the calculated variances per degree of freedom, var/f.

For both compounds models 2 and 3 fit the data well according to a V^2 test as seen from var/f and significantly better than model 1. But even model 1 with only one exchange parameter gives a fair description of the data.

In both **1** and **2** the exchange couplings are unexpectedly large in view of the Cr–Cr distances of 5.118 and 4.797 Å respectively, and the coupling constants are within the range observed for di-μ-hydroxo complexes of chromium.[6] There is no doubt that the O–H–O bridges act as exchange paths, although only weakly so. This is not surprising since for chromium(III) systems π-overlaps are known to be important for antiferromagnetic coupling, and hydrogen bonds are expected to be poor π-bond transmitters. To our knowledge these examples are the only ones known in which chromium(III) centers exhibit a fairly strong magnetic interaction via hydrogen bonds. Some related copper(II) systems having M–O–H–O–M structures[7] show fairly strong antiferromagnetic couplings due to σ-overlaps in which hydrogen bonds could be good σ-bond transmitters.

Structural and magnetic measurements will be conducted on other hydroxoaqua–chromium(III) complexes, in order to achieve a more precise location of the positions of the terminal hydrogen atoms of the $H_3O_2^-$ ligand. This will enable comparison of the coupling constants in terms of the Glerup–Hodgson–Pedersen model.[6]

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Supplementary Material Available: Tables of atomic positional and thermal positional and thermal parameters for **2** (3 pages). Ordering information is given on any current masthead page.

(5) (a) Michelsen, K. *Acta Chem. Scand.* **1977**, *A31*, 429–436. (b) Fischer, H. R.; Hodgson, D. J.; Michelsen, K.; Pedersen, E. *Inorg. Chim. Acta* **1984**, *88*, 143–150.

(6) Glerup, J.; Hodgson, D. J.; Pedersen, E. *Acta Chem. Scand.* **1983**, *A37*, 161.

(7) (a) Bertrand, J. A.; Black, T. S.; Eller, P. G.; Helm, F. T.; Mahmood, R. *Inorg. Chem.* **1976**, *15*, 2965–2970. (b) Muhonen, H. *Inorg. Chem.* **1986**, *25*, 4692–4698, and references therein.

Asymmetric Hydrogenation of β-Keto Carboxylic Esters. A Practical, Purely Chemical Access to β-Hydroxy Esters in High Enantiomeric Purity

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Optically active β-hydroxy carboxylic esters are an extremely important class of compounds for natural product synthesis. Access to such compounds has so far relied mainly on biological or biochemical transformations.[1] Asymmetric hydrogenation of the keto esters is an alternative complementary methodology, and the purely chemical means should allow even easier control of the chiral outcome at will, giving both antipodes with equal ease.

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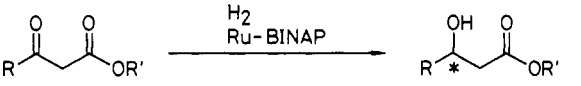
Table I. BINAP–Ru-Catalyzed Asymmetric Hydrogenation of β-Keto Esters[a]

	substrate			conditions			product 2		
	R	R′	catalyst	S/C	H_2, atm	time, h	% yield[b]	% ee[c]	config[d]
1a	CH_3	CH_3	$RuCl_2$[(*R*)-binap]	2000[e]	100	36	99, 96[f]	>99	*R*
1a	CH_3	CH_3	$RuCl_2$[(*S*)-binap]	1400	83	40	97	>99	*S*
1a	CH_3	CH_3	$RuBr_2$[(*R*)-binap]	2100[g]	100	43	99, 96[f]	>99	*R*
1a	CH_3	CH_3	RuI_2[(*S*)-binap]	1400	100	40	99	>99	*S*
1a	CH_3	CH_3	Ru_2Cl_4[(*R*)-binap]$_2(C_2H_5)_3N$	1400	100	40	95	>99	*R*
1b	CH_3	C_2H_5	$RuCl_2$[(*R*)-binap]	1000[h]	103	58	99	99	*R*
1c	CH_3	$(CH_3)_2CH$	$RuBr_2$[(*R*)-binap]	1100	73	34	93	98	*R*[i]
1d	CH_3	$(CH_3)_3C$	$RuCl_2$[(*R*)-binap]	1000	70	34	98	98	*R*[i]
1e	C_2H_5	CH_3	$RuBr_2$[(*R*)-binap]	1200	98	52	99	100[j]	*R*[k]
1f	n-C_4H_9	CH_3	$RuCl_2$[(*S*)-binap]	850	94	58	99	98[l]	*S*[m]
1g	$(CH_3)_2CH$	CH_3	$RuCl_2$[(*R*)-binap]	1100	100	61	99	>99	*S*[k]
1h	C_6H_5	C_2H_5	$RuBr_2$[(*R*)-binap]	760[h]	91	106	>99.5	85[l]	*S*[k]

[a] Reaction was carried out at 23–30 °C in 0.7–2.9 M methanol solution of the substrate (2.6–8.6 mmol) unless otherwise specified. The conversion was 100%. In some cases, the dimethyl acetal was obtained in 0.5–5% yield. [b] Determined by GC or 270-MHz ^1H NMR analysis. [c] HPLC analysis of the (*R*)-MTPA ester unless otherwise specified. The value is consistent with the rotation value. [d] Determined by sign of the rotation. [e] The substrate (0.862 mol) was used with 50% concentration. [f] Isolated yield after distillation. [g] The substrate (0.172 mol) was used with 50% concentration. [h] Ethanol was used as the solvent. [i] Based on the rotation value of the corresponding diol obtained by $LiAlH_4$ reduction: (*S*)-(+)-1,3-butanediol, $[\alpha]_D^{21}$ +25° (*c* 1, ethanol) (Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta* **1976**, *59*, 755). [j] The minor isomer was not detectable by HPLC analysis of the MTPA ester. [k] Based on the rotation values of the corresponding acids obtained by alkaline hydrolysis. For (*R*)-(−)-3-hydroxypentanoic acid, (*S*)-(−)-3-hydroxy-4-methylpentanoic acid, and (*S*)-(−)-3-hydroxy-3-phenylpropanoic acid, see: Klyne, W.; Buckingham, J. *Atlas of Stereochemistry*; Chapman and Hall: London, 1974; Volume 1, p 10, 12, and 27. [l] ^1H NMR analysis (270 MHz) of the (*R*)-MTPA ester. [m] Based on the rotation value of 3-heptanol obtained by $LiAlH_4$ reduction, monotosylation, and $LiAlH_4$ reduction. For (*S*)-(+)-3-heptanol, see: p 62 in the reference of footnote *k*.

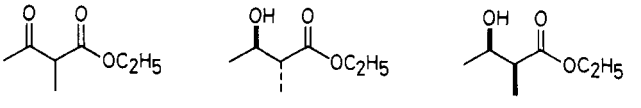
However, the practical chemical processes have not sufficiently been exploited.[2,3] We disclose here the first efficient transition-metal catalysis that effects highly enantioselective hydrogenation of β-keto esters in homogeneous phase.

In view of the excellent chiral recognition ability of the BINAP-coordinated Ru(II) complexes[4-7] and in hopes of exploring wider utility of such complexes, we screened a variety of related catalysts in the hydrogenation of methyl 3-oxobutanoate which gives methyl 3-hydroxybutanoate. As a result the selectivity profile appeared to be different from that observed with olefinic substrates. The BINAP–Ru dicarboxylate complexes, which proved to be the best for enantioselective hydrogenation of various olefins,[5-7] were totally ineffective.[8] However, the halogen-containing complexes having an empirical formula RuX_2(binap) (X = Cl, Br, or I; molecular weight unknown), prepared by mixing Ru-$(OCOCH_3)_2$[(*R*)- or (*S*)-binap] and HX or $(CH_3)_3SiI$ in 1:2 ratio, or Ru_2Cl_4(binap)$_2(C_2H_5)_3N$[9] served as excellent catalyst precursors. The enantioselective hydrogenation using a substrate to catalyst mole ratio (S/C) of >1000 proceeded smoothly in methanol under an initial hydrogen pressure of 50–100 atm. At 4 atm, the reaction was very slow although the stereoselectivity was slightly affected. Thus, as exemplified in Table I, a variety of prochiral β-keto esters **1** were hydrogenated in nearly quantitative yields and with extremely high (up to 100%) enantioselectivities. Esters of methyl, primary, secondary, and tertiary alcohols were equally employable.



1 **2**

When a chiral α-substituted β-keto ester was subjected to the hydrogenation, the corresponding *threo*- and *erythro*-hydroxy esters were produced in nearly equal amounts. Both diastereomers possessed the same absolute configuration at the newly created stereogenic centers and had equally high enantiomeric purity. For example, hydrogenation of racemic **3** in ethanol containing $RuBr_2$[(*R*)-binap] (S/C 1200, 100 atm, 25 °C, 40 h) gave a mixture of **4** (97% ee, 49%) and **5** (96% ee, 51%) having the 3*R* configuration.[10]



(±)-**3** **4** **5**

Thus, synthetic organic chemists no longer must envy bakers' yeast to effect stereoselective reduction of β-keto esters. The hydrogenation method is clean, operationally simple, economical, and hence is capable of conducting large-scale production of optically active β-hydroxy esters. A wide range of hydroxy esters of either chirality sense is available in high enantiomeric purity. Notably, transition-metal catalysis, unlike the biological version,[11] allows a high degree of enantioselective transformation with high (up to 50%) substrate concentration.

(1) Reviews: (a) Sih, C. J.; Chen, C.-S. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 570. (b) Oishi, T.; Akita, H. *J. Synth. Org. Chem. Jpn.* **1983**, *41*, 1031. (c) Fujisawa, T.; Sato, T.; Ito, T. *Ibid.* **1986**, *44*, 519. Depolymerization of poly-(*R*)-3-hydroxybutanoate, an intracellular storage product of *Alcaligenes eutrophus H 16*, gives homochiral (*R*)-3-hydroxybutanoates. See: (d) Seebach, D.; Züger, M. *Helv. Chim. Acta* **1982**, *65*, 495. (e) Seebach, D.; Züger, M. F. *Tetrahedron Lett.* **1984**, *25*, 2747.

(2) Heterogeneous hydrogenation of methyl 3-oxobutanoate over Raney nickel modified by tartaric acid and sodium bromide gave the hydroxybutanoate in up to 86% ee and in 98% yield. See: Tai, A.; Harada, T.; Hiraki, Y.; Murakami, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1414. Izumi, Y.; Imaida, M.; Fukawa, H.; Akabori, S. *Bull. Chem. Soc. Jpn.* **1963**, *36*, 21. The corresponding homogeneous hydrogenation was accomplished with a chiral phosphine–rhodium complex in 71% optical yield. See: Solodar, J. *Chem. Tech.* **1975**, 421.

(3) For stoichiometric asymmetric synthesis of β-hydroxy esters, see: Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Org. Chem.* **1986**, *51*, 3394. Soai, K.; Yamanoi, T.; Hikima, H.; Oyamada, H. *J. Chem. Soc., Chem. Commun.* **1985**, 138. Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 4643. Solladié, G. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Chapter 6. Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 2. Silverman, I. R.; Edington, C.; Elliott, J. D.; Johnson, W. S. *J. Org. Chem.* **1987**, *52*, 180.

(4) BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

(5) Noyori, R.; Ohta, M.; Hsiao, Yi.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc.* **1986**, *108*, 7117.

(6) Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596.

(7) Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3174.

(8) Hydrogenation of ethyl 3-oxobutanoate using 0.5 mol % of Ru-$(OCOCH_3)_2$[(*R*)-binap] (methanol, 100 atm, 25 °C, 48 h) proceeded slowly, and, at 41% conversion, the (*S*)-hydroxy ester was obtained in only 4% ee.

(9) Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun.* **1985**, 922.

(10) The enantiomeric excess and the absolute configuration of the products were determined by HPLC analysis of the corresponding (*R*)-1-(1-naphthyl)ethylcarbamate. See: Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269.

A typical laboratory-scale hydrogenation is illustrated as follows. To a vivid reddish yellow solution of $Ru(OCOCH_3)_2[(R)\text{-binap}]$[5] (806 mg, 0.957 mmol) in degassed dichloromethane (20 mL) was added 1.42 N HCl in 90% methanol (1.41 mL, 2.00 mmol). After the resulting dark red solution was stirred at 23 °C for 2.5 h, the solvent was removed under reduced pressure to give $RuCl_2$-[(*R*)-binap] (722 mg) as a reddish brown solid, which was used as the hydrogenation catalyst.[12] A solution of methyl 3-oxobutanoate (**1a**) (100 g, 0.862 mol) in degassed anhydrous methanol (100 mL) was placed in a 300-mL Schlenk vessel and degassed by 3 freeze–thaw cycles. With use of a cannula this was then mixed with the solid Ru–BINAP catalyst (341 mg, 0.429 mmol) in another 300-mL Schlenk tube under argon, and the resulting light yellow solution was transferred to a glass vessel placed in a 500-mL stainless steel autoclave. Hydrogen was pressurized to 100 atm, and the solution was stirred at 30 °C for 36 h. The solvent was removed under reduced pressure, and the residue was distilled to give methyl (*R*)-3-hydroxybutanoate (**2a**) (97.5 g, 96% yield), bp 40 °C/2 mmHg, $[\alpha]_D^{25}$ −24.2° (neat) (lit.[1d] $[\alpha]_D^{22}$ −23.5° (neat)). The enantiomeric excess was determined to be 99.4% by HPLC analysis after converting an aliquot of the product to the (*R*)-MTPA ester[13] (1.4 equiv of (*R*)-MTPACl, 9 equiv of pyridine, CH_2Cl_2, 20 °C, 12 h, 94% yield). HPLC analysis of this ester (column, YMC 003-3 SIL and 002-3 SIL; eluent, 1:3 ether–hexane mixture; flow rate, 1 mL/min; detection, 254-nm light) showed two signals with t_R = 15.2 and 16.0 min in 99.7:0.3 ratio assignable to the *R,R*- and *R,S*-diastereomers, respectively.

(11) Bakers' yeast with the aid of sucrose reduces ethyl 3-oxobutanoate to ethyl (*S*)-3-hydroxybutanoate in 88–97% ee in 70–80% yield. In order to obtain high (95–97%) enantioselectivity, the substrate concentration should be kept below 1 g/L. Wipf, B.; Kupfer, E.; Bertazzi, R.; Leuenberger, H. G. W. *Helv. Chim. Acta* **1983**, *66*, 485. Seebach, D.; Sutter, M. A.; Weber, R. H.; Züger, M. F. *Org. Synth.* **1985**, *63*, 1. Ehrler, J.; Giovannini, F.; Lamatsch, B.; Seebach, D. *Chimia* **1986**, *40*, 172.

(12) The complex can be stored under argon without loss of catalytic activity.

(13) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Characterization of an Endogenous Factor Controlling the Cell Cycle of Complex Tissues

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The study and characterization of factors called chalones which are capable of regulating specific cellular arrest in complex tissues has been ongoing since their discovery in 1960.[1] Their obvious potential chemotherapeutic use and more recently their potential involvement in circadian rhythms[2,3] has stimulated continual interest in these factors. Trigonelline, *N*-methylnicotinic acid, became the first structurally defined substance capable of promoting specific G2 cellular arrest.[4,5] It was subsequently found that the activity of trigonelline was regulated by the age of the organism.[6] We now describe the isolation and characterization

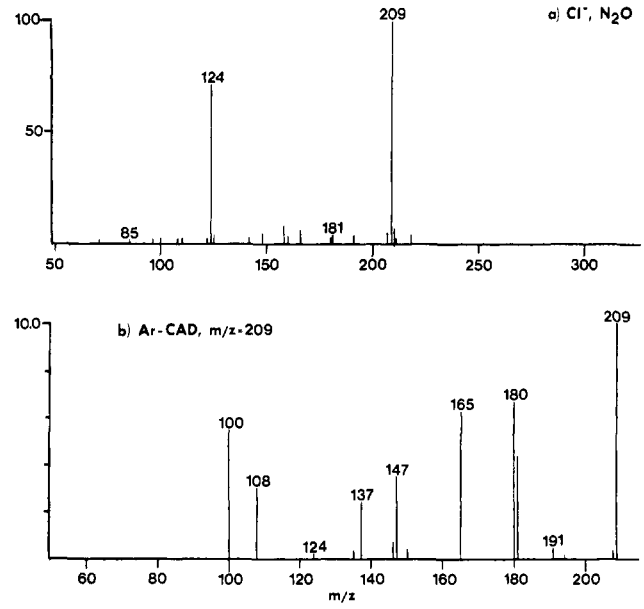

Figure 1. Negative ion chemical ionization (CI, N_2O) spectrum of **1** (a) and Cl^- spectrum (b). Selected *m/z* 209 ion collisionally decomposed with argon gas.

of an unusually substituted pyrrole **1** produced by older seedlings of *Pisum sativum* (Leguminasae) which functions as a specific endogenous regulator of trigonelline-induced G2 arrest.

The roots of 10-day-old etiolated *P. sativum* seedlings from ~1500 seeds were excised and blended (3×) at low speed for 45 min with sufficient methanol to cover the tissue. The extract was filtered through Celite, concentrated to 70 mL, applied to an open bed reverse phase filter, and step gradient washed with 150-mL portions of 0%, 25%, 50%, 75%, and 100% aqueous MeOH. The biologically active[5] 25% and 50% MeOH fractions were dried in vacuo onto a minimum amount of silica gel and washed with $MeOH/CHCl_3$, 1:1. The eluent was concentrated and chromatographed (SiO_2, 1–10% $CH_3CN/CHCl_3$) and preparatively purified on reverse phase HPLC (Zorbax C-8, 10% CH_3CN/H_2O, 2 mL/min, R_t = 4.2 min, 254-nm detection). Final purification was afforded on C-18 HPLC (Zorbax, 10% CH_3CN/H_2O, 2 mL/min, R_t = 4.2 min) yielding 20 μg of a clear oil. This procedure was repeated several times through the course of the characterization.

The UV spectrum (MeOH) of the purified material showed absorption maxima at 292 (9200) and 258 (3800) nm characteristic of a pyrrole bearing an α-carbonyl substituent.[7] IR bands at 1707 and 2840 cm^{-1} indicated an aldehyde, and stretching frequencies at 3300 and 1770 cm^{-1} suggested hydroxyl and γ-lactone functionality.

Negative ion chemical ionization (CI, N_2O),[8] Figure 1, and electron impact (EI, 70 eV) mass spectrometry gave an intense M^- ion at *m/z* 209 (EI 209.0691, calcd 209.0688) indicating a composition of $C_{10}H_{11}NO_4$. The CI spectra showed clean fragmentation to a single even mass ion at *m/z* 124. The mass of this ion, together with its subsequent fragmentation, led to the assignment of a formyl, hydroxymethyl pyrrole. Such intense C–N cleavage has proven to be characteristic of the *N*-alkyl-2-carbonyl pyrroles analyzed under $Cl(N_2O)$ negative ion conditions (unpublished).

Collision-activated decomposition[8] greatly accentuated the fragmentation of the molecular ion showing losses of H_2O (*m/z* 191), CO (*m/z* 181), CHO (*m/z* 180), and CO_2 (*m/z* 165). This induced fragmentation confirmed the functional groups suggested

† The University of Chicago.
‡ Manhattan College.

(1) Bullough, W. S.; Lacrum, E. B. *Proc. Royal Soc. London, Ser. B* **1960**, *151*, 517–536.

(2) Aardal, N. D.; Lacrum, O. D.; Paukovits, W. R. *Virchows Archiv B.* **1983**, *44*, 247–55.

(3) Vesely, D. L.; Cannella, N. K. *Res. Comm. Chem. Pathol. Pharm.* **1984**, *45*, 207–217.

(4) Lynn, D. G.; Nakanishi, K.; Patt, S. L.; Occolowitz, J. L.; Almeida, M. S.; Evans, L. S. *J. Am. Chem. Soc.* **1978**, *100*, 7759–7760.

(5) Evans, L. S.; Almeida, M. S.; Lynn, D. G.; Nakanishi, K. *Science* (Washington, D.C.) **1979**, *203*, 1122–1123.

(6) Evans, L. S.; Tramontano, W. *Am. J. Bot.* **1981**, *68*, 1282–1289.

(7) Jaffe, H. H.; Orchin, M. *Theory and Applications of Ultraviolet Spectroscopy*; Wiley: New York, 1962; pp 345–383. Cookson, G. H. *J. Chem. Soc.* **1953**, 2789–2795.

(8) CAD spectra were obtained on a Finnegan 3200 modified for tandem spectrometry or a VG 7070BEQQ. High resolution spectra were obtained on a VG 70-250.

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