providing **20** (5:1, γ/α) in 60% overall yield from **19**.[21] Conversion of **20** (Scheme II) to (±)-mutilin (**2**) proceeded uneventfully by standard methods (80% overall from **20**). (±)-**2** (mp 186.5–188 °C; lit.[7] mp 187.5–189 °C) was spectroscopically identical with both natural (+)-**2** and synthetic (±)-**2**.[7] (±)-**2** was converted to (±)-pleuromutilin (**1**) by the two-step procedure of Gibbons.[7] (±)-**1** (mp 167–169.5 °C) was also spectroscopically identical with natural (+)-**1**.[22]

The synthetic route described above makes use of novel approaches to the construction of the tricyclic framework and for introduction of the stereogenic centers present on the eight-membered ring, and provides (±)-pleuromutilin (**1**) in 25 steps from readily available materials.

Acknowledgment. We are extremely grateful to the Institute of General Medical Sciences (NIGMS) of the National Institutes of Health for a grant (GM-29290) in support of these studies.

Supplementary Material Available: NMR spectroscopic data for compounds **1**, **2**, **4–8**, and **10–20**, combustion analytical data for compounds **5**, **6**, **8**, **11**, **15**, **17**, **19**, and **20**, and HRMS data for compounds **4**, **13**, and **14** (21 pages). Ordering information is given on any current masthead page.

(21) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 2318.

(22) The melting point reported for (±)-**1** is the first reported determination since the Gibbons conversion of (±)-**2** to (±)-**1** was effected on a sample that had been admixed with authentic (+)-**2** as a relay.[23]

(23) Gibbons, E. G. Ph.D. Dissertation, Harvard University, 1982.

A New, Highly Efficient, Selective Methodology for Formation of Medium-Ring and Macrocyclic Lactones via Intramolecular Ketene Trapping: An Application to a Convergent Synthesis of (−)-Kromycin

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Over the past decade, there has been intense interest in the development of methodology for formation of macrocyclic and medium-ring lactones, since a number of these substances possess important and useful biological properties.[1] A number of ingenious methods have been developed and applied to the synthesis of an array of naturally occurring systems.[2-4] However, limitations on most of the methods exist due particularly to the incompatibility of the activated carbonyl derivative that is the common intermediate in most methods with a number of functional groups and reaction conditions. Thus, the development of a method incorporating a masked activated carbonyl derivative that would be compatible with a variety of types of transformations and that would permit generation of the reactive species under mild neutral conditions in the presence of the nucleophilic hydroxyl group might serve to overcome many of the limitations. We describe in this communication the use of dioxolenones as precursors of β-acyl ketenes,[5] which can be thermally generated under mild neutral conditions in the absence of other nucleophiles to afford good yields of medium- and large-ring lactones[6-8]

(1) *Macrolides*; Omura, S., Ed.; Academic Press: New York, 1984.

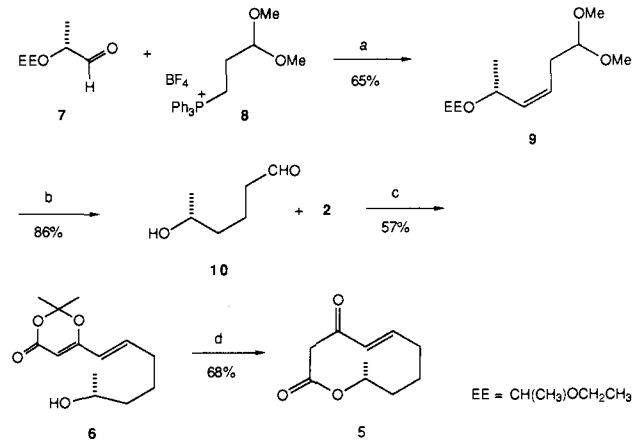
(2) Nicoloau, K. C. *Tetrahedron* **1977**, *33*, 683. Masamune, S.; Bates, G. S.; Corcoran, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. Back, T. G. *Tetrahedron* **1977**, *33*, 3041.

(3) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569.

(4) Boeckman, R. K., Jr.; Goldstein, S. W. *Total Synth. Nat. Prod.* **1988**, *7*, 1.

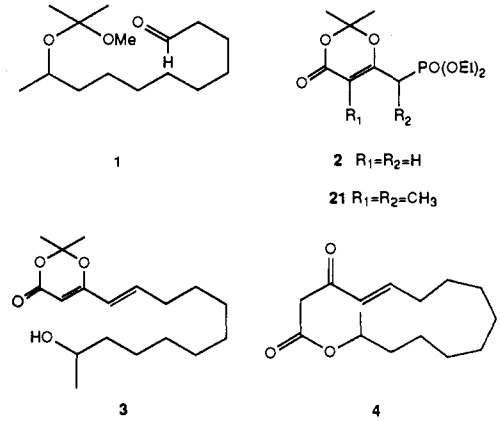
(5) Hyatt, J. A.; Feldman, P. L.; Clemens, R. J. *J. Org. Chem.* **1984**, *49*, 5105.

Scheme I[a]



[a] Reagents: (a) **8** (1.05 equiv), *t*-BuOK (1.05 equiv), THF, 0 °C, then **7** (1 equiv), −20 °C → 25 °C, 3 h; (b) H_2 (3 atm), PtO_2, EtOAc, 12 h, then Amberlyst-15 (catalytic), THF–H_2O (98:2, v/v); (c) **2** (2 equiv), *t*-BuOK (2 equiv), THF, −78 °C → 25 °C, 5 h; (d) **6** (~10^{-4} M), $PhCH_3$, Δ, 4 h.

We initiated our investigation by attempting formation of a 15-membered lactone. Treatment of the protected hydroxy aldehyde **1**[9] with dioxolenone phosphonate **2**[10] and *t*-BuOK in THF provided the required dioxolenone **3** after deprotection (Amberlyst-15/2% aqueous acetone) in ~80% overall yield.[11] Thermolysis of **3** in $PhCH_3$ at reflux (~10^{-4} M) for 2 h cleanly afforded the desired β-keto lactone **4** in 60% yield (unoptimized) after chromatographic purification.[12]



1 **2** $R_1=R_2=H$ **21** $R_1=R_2=CH_3$ **3** **4**

To investigate the limitations of the cyclization method and enable direct comparison of the efficiency with other known methods, we next chose to prepare (+)-diplodialide A (**5**) as shown in Scheme I.[13] The strained 10-membered ring in **5** bearing a

(6) For representative cases of bimolecular trapping, see: Sato, M.; Kanuma, N.; Sato, T. *Chem. Pharm. Bull.* **1984**, *32*, 106. Winkler, J. D.; Hershberger, P. M.; Springer, J. P. *Tetrahedron Lett.* **1986**, *27*, 5177. Yamamoto, Y.; Morita, Y. *Chem. Pharm. Bull.* **1984**, *32*, 2555. Sato, M.; Ogasawara, H.; Komatsu, S.; Kato, T. *Chem. Pharm. Bull.* **1984**, *32*, 3848. See also ref 7.

(7) Boeckman, R. K., Jr.; Potenza, J. C.; Enholm, E. J. *J. Org. Chem.* **1987**, *52*, 469.

(8) For cases of intramolecular trapping, see: Boeckman, R. K., Jr.; Perni, R. B. *J. Org. Chem.* **1986**, *51*, 5486 (by an amine). Quinkert, G.; Billhardt, U.-M.; Jakob, H.; Fischer, G.; Glenneberg, J.; Nagler, P.; Autze, V.; Heim, N.; Wacker, M.; Schwalbe, T.; Kurth, Y.; Bats, J. W.; Durner, G.; Zimmermann, G.; Kessler, H. *Helv. Chim. Acta* **1987**, *70*, 771 (by alcohols using photochemical ketene generation).

(9) Available in four steps from 10-undecenoic acid by standard methods.

(10) Boeckman, R. K., Jr.; Thomas, A. J. *J. Org. Chem.* **1982**, *47*, 2823. Boeckman, R. K., Jr.; Perni, R. B.; Macdonald, J. E.; Thomas, A. J. *Org. Synth.* **1988**, *66*, 194.

(11) All new substances exhibited satisfactory spectroscopic (NMR, IR, UV) and combustion or high resolution mass spectral analytical data.

(12) The cyclizations are conducted by addition of the substrate via syringe pump to refluxing $PhCH_3$ at such a rate as to maintain ~10^{-4} M in reacting substrate.

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trans double bond has been demonstrated to be difficult to close in high yield during previous successful synthetic work on **5**.[14]

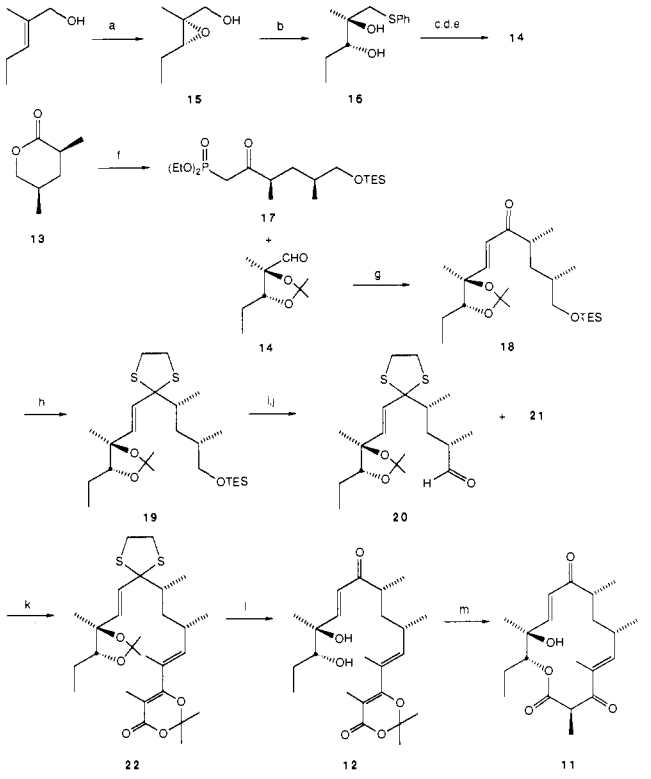
The required optically pure cyclization substrate, dioxolenone alcohol **6**, was obtained in a straightforward way beginning with the protected *R*-(+) aldehyde **7** (Scheme I).[7] Wittig reaction with the ylide derived from phosphonium fluoroborate **8**[15] afforded exclusively the *Z* olefin **9** (65%).[7] After catalytic reduction and deprotection, the resulting hydroxy aldehyde **10** was condensed with **2** (2 equiv) to afford **6** (57%). We were pleased to observe that upon thermolysis of **6** in $PhCH_3$ at reflux ($\sim 10^{-4}$ M) for 4 h we obtained (+)-diplodialide A (**5**) ($[\alpha]^{23}_D$ +128° (*c* 1.09, $CHCl_3$), lit.[13] $[\alpha]^{26}_D$ +142° (*c* 1.02, $CHCl_3$)) in 68% yield (optimized). In this case, polymeric byproducts are observed if the reaction is conducted at a substantially higher concentration. This process is thus significantly more efficient than previously reported cyclization methods (~15–20%) and affords **5** directly.[4,14]

We next selected the 16-membered macrolide (−)-kromycin (**11**),[16,17] due to the high density of functionality present in the projected precursor, dioxolenone diol **12**, and the requirement for regioselective closure on the secondary hydroxyl group of the diol. Successful cyclization of **12** to **11** would appear to provide convincing evidence for the applicability of the method to complex substrates bearing potentially interfering functionality. The newly created β-keto ester chiral center was expected to be under thermodynamic control.[17]

The preparation of diol **12** commenced from the known (−)-δ-valerolcatone **13** ($[\alpha]^{23}_D$ −41.1° (*c* 1.20, $CHCl_3$), ~95% ee) and aldehyde acetonide **14** (Scheme II).[18] Aldehyde **14** was prepared from (*E*)-2-methyl-2-penten-1-ol[19] by asymmetric epoxidation with (−)-dimethyl tartrate ((−)-DMT) affording **15** (78% yield, ≥98% ee),[20] followed by Payne rearrangement of **15** with trapping of the terminal epoxide by phenyl thiolate to provide diol thioether in **16** in 88% yield (Scheme II).[21,22] After acetonide formation, oxidation of the thioether, Pummerer rearrangement, and hydrolysis afforded the required optically pure aldehyde **14** ($[\alpha]^{25}_D$ −10.3° (*c* 3.00, $CHCl_3$) in 70% overall yield from **16**.[22]

Lactone **13** was condensed with the lithium anion of diethyl methylphosphonate and the resulting alkoxide trapped with TESCl to afford the protected β-keto phosphonate **17**. Wadsworth–Emmons olefination of aldehyde **14** proceeded smoothly with the potassium anion derived from **17** to provide exclusively the *E* enone **18** (96%). Due to difficulties encountered in attempts to olefinate the keto aldehyde derived from **18**, enone **18** was transformed to the thioketal alcohol **19** by exposure to 1,2-bis[(trimethylsilyl)-thio]ethane (ZnI_2 catalyst) and desilylation with fluoride (87% overall from **18**).[23] Swern oxidation of **19** then provided aldehyde **20**, suitable for olefination.[24] Wadsworth–Emmons reaction of

Scheme II[a]



[a] Reagents: (a) (−)-DMT, $Ti(OiPr)_4$, 3-Å molecular sieves, CH_2Cl_2, −20 °C, 24 h; (b) PhS^-K^+, KOH, H_2O, 25 °C, 8 h; (c) $(CH_3)_2C(OCH_3)_2$ (5 equiv), Amberlyst-15 (catalytic), 25 °C, 12 h; (d) MCPBA (1 equiv), CH_2Cl_2, 0 °C, 3 h; (e) $(CF_3CO)_2O$ (1 equiv), 2,6-lutidine (1 equiv), CH_3CN, 0 °C, 1 h, then $HgCl_2$ (excess), $CaCO_3$ (excess), aqueous THF, 25 °C, 4 h; (f) $CH_3P(O)(OEt)_2$ (1.5 equiv), nBuLi (1.5 equiv, 1.6 M in hexanes), THF, 0 °C, 2 h, then **13** (1 equiv), −78 °C, 1 h, followed by TESCl (3 equiv), −78 °C → 25 °C, 6 h; (g) *t*-BuOK (1.05 equiv), THF, 0 °C, 1 h, then **14** (1 equiv), −78 °C → 25 °C, 3h; (h) $(CH_2SSi(CH_3)_3)_2$ (1 equiv), ZnI_2 (catalytic) 0 °C → 25 °C, 12 h; (i) TBAF, THF, 0 °C, 10 min; (j) $(COCl)_2$ (1.5 equiv), DMSO (1.5 equiv), Et_3N (3 equiv), −78 °C, 1 h; (k) **21** (1.3 equiv), *t*-BuOK (1.3 equiv), THF, −78 °C → 25 °C, 5 h; (l) $TlNO_3$, CH_3OH, 25 °C, 5 min, then CH_3OH–H_2O (98:2, v/v), 25 °C, 1 h; (m) **12** (10^{-4} M), $PhCH_3$, Δ, 4.5 h.

20 with dioxolenone phosphonate **21**[25] then proceeded smoothly under standard conditions to afford exclusively the required *E* α,β-unsaturated dioxolenone **22** (by NOE) in 70% yield, which after deblocking gave the required cyclization substrate, diol **12** (82% overall from **22**).

We were exceedingly pleased to find that thermolysis of **12** in $PhCH_3$ ($\sim 10^{-4}$ M) for 4.5 h afforded (−)-kromycin (**11**) (mp 170–171 °C, $[\alpha]^{23}_D$ −25.2° (*c* 1.47, $CHCl_3$), lit.[17] $[\alpha]^{20}_D$ −23.3° (*c*, 1.74, $CHCl_3$)), identical in all respects with an authentic sample of (−)-kromycin (**11**), in 70% yield after chromatography.[26] No isolable amounts of byproducts were observed on a small scale.

Thus, intramolecular cyclization of β-acyl ketenes has been demonstrated to be an apparently general and high-yielding method to form medium-ring and macrocyclic lactones with ex-

(13) Ishida, T.; Wada, K. *J. Chem. Soc., Chem. Commun.* **1975**, 209. Wada, K.; Ishida, T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1154.

(14) Ishida, T.; Wada, K. *J. Chem. Soc., Chem. Commun.* **1977**, 337. Ishida, T.; Wada, K. *J. Chem. Soc., Perkin Trans. 1* **1979**, 323. Tsuji, J.; Mandai, T. *Tetrahedron Lett.* **1978**, 1817. Ireland, R. E.; Brown, F. R., Jr. *J. Org. Chem.* **1980**, *45*, 1868. Wakamatsu, T.; Akasaka, T.; Ban, Y. *J. Org. Chem.* **1979**, *44*, 2008. Shenvi, A. B.; Gerlach, H. *Helv. Chim. Acta* **1980**, *63*, 2426.

(15) Phosphonium fluoroborate **8** was prepared from acrolein by addition of $Ph_3PH^+BF_4^-$ in the presence of Ph_3P (catalytic) followed by treatment with $(CH_3O)_3CH$ (~100% overall). Fluoroborates offer significant advantages in rate and yield during ylide formation in some cases: Boeckman, R. K., Jr.; Pruitt, J. R.; MaGee, D. I. Unpublished results 1989.

(16) Hughes, R. E.; Muxfeldt, H.; Tsai, C.; Stezowski, J. J. *J. Am. Chem. Soc.* **1970**, *92*, 5267. Tsai, C.; Stezowski, J. J.; Hughes, R. E. *J. Am. Chem. Soc.* **1971**, *93*, 7286.

(17) Anliker, R.; Gubler, K. *Helv. Chim. Acta* **1957**, *40*, 119. Brockmann, H.; Oster, R. *Chem. Ber.* **1957**, *90*, 605.

(18) Hoffmann, R. W.; Zeiss, H.-J.; Ladner, W.; Tabche, S. *Chem. Ber.* **1982**, *115*, 2357.

(19) Chan, K. C.; Jewell, R. A.; Nutting, W. H.; Rapoport, H. *J. Org. Chem.* **1968**, *33*, 3382.

(20) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464. Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

(21) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819. Wrobel, J. E.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 3761.

(22) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, S. V.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373.

(23) Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009.

(24) Swern, D. A.; Omura, K. *Tetrahedron* **1978**, *34*, 1651.

(25) Dioxolenone phosphonate **21** was prepared from 3-pentanone via a three-step sequence: (1) CO_2(g) (excess), anhydrous NaI (4 equiv), anhydrous $MgCl_2$ (2 equiv), Et_3N (8 equiv), CH_3CN, 25 °C, 3 h (81%),[27] (2) $CH_2{=}C(OAc)CH_3$, concentrated H_2SO_4 (catalytic), 0 °C, 24 h (58%);[28] (3) LDA, −78 °C, then $ClP(OEt)_2$, −78 °C → 25 °C, followed by oxidation with H_2O_2, PhH, 5 °C (66%).

(26) An authentic sample of (−)-kromycin (**11**) was prepared from authentic (−)-pikromycin according to the literature procedure.[17] We thank Dr. Günter Benz and Bayer AG for a generous sample of natural (−)-pikromycin.

(27) Tirpak, R. E.; Olsen, R. S.; Rathke, M. W. *J. Org. Chem.* **1985**, *50*, 4877.

(28) Sato, M.; Ogasawara, H.; Oi, K.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 1896.

cellent selectivity and compatibility with other potentially interfering functionalities in complex substrates.

Acknowledgment. We are extremely grafteful to the National Cancer Institute (NCI) of the National Institutes of Health for a grant (CA-29108) in support of these studies. We also thank the National Institutes of General Medical Sciences for the award of an NRSA fellowship (GM-11760) to J.R.P.

Supplementary Material Available: ^{1}H NMR spectra for compounds **3–6**, **11** (natural and synthetic), and **12–22**, combustion analytical data for compounds **6**, **14**, **16–18**, and **21**, and HRMS data for compounds **3**, **4**, **8–10**, **12**, **19**, **20**, and **22** (18 pages). Ordering information is given on any current masthead page.

Time-Resolved IR Spectroscopy in Liquid Rare Gases: Direct Rate Measurement of an Intermolecular Alkane C–H Oxidative Addition Reaction

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Since the first demonstration of the intermolecular oxidative addition of alkane C–H bonds to transition-metal centers[1,2] illustrated in eq 1, there have been many studies of the mechanism of this reaction.[3] While these studies have illuminated many

$$\eta^5\text{-}C_5R_5M(L)X + RH \xrightarrow{h\nu} \eta^5\text{-}C_5R_5M(L)(R)(H) + X \quad (1)$$

R = H, CH_3; M = Rh or Ir, L = CO or PMe_3, X = CO or H_2

aspects of the C–H activation process, they do not provide direct information about the reactive intermediates or the potential energy surface for the elementary insertion reaction. Flash photolysis studies have been thwarted by extremely fast insertion rates in neat alkane solution[4] and by the lack of a suitable inert and transparent solvent for dilution of the alkane. We have overcome these difficulties with the use of liquid rare gases as solvents. Using a novel combination of low-temperature and IR laser flash kinetic techniques, we are able to detect the C–H activating transient intermediate formed from $Cp^*Rh(CO)_2$ ($Cp^* = (\eta^5\text{-}C_5Me_5)$) and measure its rate of reaction with cyclohexane over a wide range of concentrations and temperatures.[5]

The experimental apparatus is an IR laser flash kinetic spectrometer that incorporates a pulsed UV laser (XeCl, 308 nm) for excitation and a continuous-wave IR laser (CO, 2100–1800 cm^{-1}) for monitoring the CO stretching frequencies of transient species.[6]

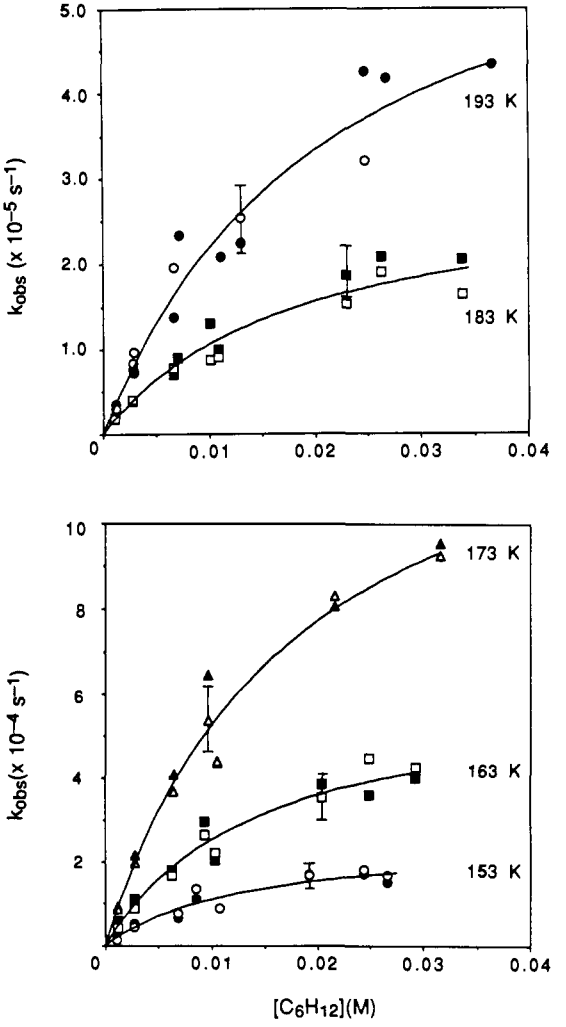

Figure 1. The observed rate constants (k_{obsd}) for the decay of the transient at 1947 cm^{-1} (filled symbols) and for the formation of the product at 2003 cm^{-1} (open symbols) as a function of cyclohexane concentration and temperature. For clarity, only representative error bars are indicated explicitly.

In this study we use a high-pressure, low-temperature cell similar to those described by others[7a,b] with some improvements.[7c] The UV and IR beams pass colinearly through a long path (5 cm) while a perpendicular short path (1.4 cm) is used to monitor the overall changes in the sample with an FTIR spectrometer. The initial concentration of $Cp^*Rh(CO)_2$ is held constant at $\approx 5 \times 10^{-6}$ M, and the concentration of cyclohexane[8] or CO[9] is determined from the FTIR spectrum.[10]

Upon UV irradiation of $Cp^*Rh(CO)_2$ in liquid xenon at 242 K, a new monocarbonyl species is detected that exhibits an absorption at 1943 cm^{-1}.[11] In the presence of 0.017 M CO, this species decays surprisingly slowly at this temperature ($k = 4 \times 10^4$ s^{-1}) to reform starting material. In liquid Kr at lower temperatures (193–153 K), irradiation once again produces a single transient absorption with a similar band at 1947 cm^{-1}. However, this species appears to be substantially more reactive. It decays slowly ($k = 5 \times 10^3$ s^{-1}) in the absence of added reagents[12] and

† Deceased June 18, 1989. This paper is dedicated to the memory of Professor G. C. Pimentel.

(1) Hoyano, J. K.; Graham, W. A. G. *J. Am. Chem. Soc.* **1982**, *104*, 3723–3725.
(2) Janowicz, A. H.; Bergman, R. G. *J. Am. Chem. Soc.* **1982**, *104*, 352–354.
(3) (a) Janowicz, A. H.; Bergman, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 3929–3939. (b) Jones, W. D.; Feher, F. J. *J. Am. Chem. Soc.* **1984**, *106*, 1650–1663. (c) Bergman, R. G. *Science* **1984**, *223*, 902–908. (d) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245–269. (e) Buchanan, J. M.; Stryker, J. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 1537–1550. (f) Periana, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 7332–7346. (g) Ephritikhine, M. *New J. Chem.* **1986**, *10*, 9–15. (h) Nolan, S. P.; Hoff, C. D.; Stoutland, P. O.; Newman, L. J.; Buchanan, J. M.; Bergman, R. G.; Yang, G. K.; Peters, K. S. *J. Am. Chem. Soc.* **1987**, *109*, 3143–3145.
(4) Wasserman, E. P.; Moore, C. B.; Bergman, R. G., unpublished results.
(5) For a recent study involving the use of liquid xenon as a solvent for preparative alkane C–H oxidative addition reactions, see: Sponsler, M. B.; Weiller, B. H.; Stoutland, P. O.; Bergman, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 6841–6843.
(6) Wasserman, E. P.; Moore, C. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 6076–6084.
(7) (a) Beattie, W. H.; Maier, W. B., II; Holland, R. F.; Freund, S. M.; Stewart, B. *Laser Spectroscopy*; SPIE: New York, 1978; Vol. 158, p 113–121. (b) Maier, W. B.; Poliakoff, M.; Simpson, M. B.; Turner, J. J. *J. Mol. Struct.* **1982**, *80*, 83–86. (c) Weiller, B. H.; Gadd, G. E.; Pimentel, G. C., to be published.
(8) Hogan, T. R.; Steele, D. *J. Mol. Struct.* **1986**, *141*, 315–323.
(9) Pugh, L. A.; Rao, K. N. Intensities from Infrared Spectra. In *Molecular Spectroscopy: Modern Research*; Academic: New York, 1976; Vol. II, pp 165–227.
(10) Bulanin, M. O. *J. Mol. Struct.* **1973**, *19*, 59–79.
(11) Resolution = ±4 cm^{-1}.

0002-7863/89/1511-8288$01.50/0