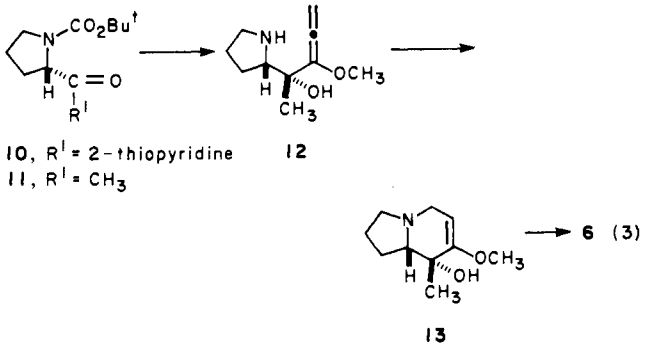
Indolizidinone **6** was successfully prepared in high enantiomeric purity by the sequence outlined in eq 3. Conversion of *N*-



10, R^1 = 2-thiopyridine **12**
11, $R^1 = CH_3$

13

BOC-L-Pro to thioester **10**[10] and subsequent reaction with $LiMe_2Cu$ provided methyl ketone **11**[10] (mp 38 °C; $[\alpha]_D$ −57.8°, *c* 4.3, $CHCl_3$) in 70% yield. Treatment of **11** with CF_3COOH (23 °C, anisole, CH_2Cl_2) followed by concentration and immediate reaction (−78 °C, THF) of the resulting trifluoroacetate salt with 5 equiv of 1-lithio-1-methoxyallene[14] afforded **12** as the only detectable product. This extremely labile adduct, which results from cyclic-Cram diastereoselectivity, could not be purified without extensive decomposition. However, treatment of crude **12** with slightly less than 1 equiv of dry *p*-toluenesulfonic acid (CH_3CN, 23 °C) gave the bicyclic enol ether **13**[10] (mp 76–77 °C) in 35–40% overall yield from **11**. Hydrolysis of **13** (5% HCl, 23 °C) provided indolizidinone **6**[10] ($[\alpha]^{25}_D$ −44.2°, *c* 4.7 $CHCl_3$; >95% ee[8b]) in 76% yield.

The alkylidene side chain was introduced in the following fashion (see Scheme I). Conversion of **6** to its lithium dianion (Ph_3CLi, Et_2O, 0 °C) followed by reaction with (*R*)-2-methylhexanal[15] (0 °C, 5 min) gave a ~1:1 mixture of two major aldol diastereomers **14**.[16] Direct dehydration [$(CF_3CO)_2O$, DBU, DMAP, 0 °C][17] of this mixture gave **15**[10] ($[\alpha]^{25}_D$ −6.5°, *c* 1.1, $CHCl_3$) as the major product in 41% overall yield from **6**.[18] Reduction of **15** with $NaBH_4$–$CeCl_3$[19] produced the equatorial alcohol **16**[10,20] in essentially quantitative yield. Similar stereoselectivity was seen with a variety of other hydride reducing agents. Reduction of **15** with $LiAlH_4$ (0 °C, THF) provided a 6:1 mixture of **16** and **1**, from which pure (+)-allopumiliotoxin 267A ($[\alpha]^{25}_D$ +12.8°, *c* 0.1, MeOH) could be isolated in low yield.[21]

The more complex allopumiliotoxin 339B (**3**) was prepared in a related fashion. An aldol-dehydration sequence identical with that described above provided enone **17**[10] ($[\alpha]_D$ −16.0°, *c* 4.2, MeOH) in 37% overall yield from **6** and (*R*)-4-(benzyloxy)-2-methylbutanal.[15] Reduction ($NaBH_4$–$CeCl_3$,[19] 58% yield) of **17** followed by selective protection (BuLi, HMPA, −78 °C; excess *t*-$BuMe_2SiCl$; 49% yield) of the resulting secondary alcohol provided **18**.[10] This intermediate was converted to aldehyde **19** (83% yield) and treated with the enantiomerically pure ylide **21**[6b] to provide the (*E*)-enone **20**[10] ($[\alpha]^{25}_D$ −1.8°, *c* 0.4, MeOH; 55% yield) by a sequence identical with the one we had previously employed[6b] to prepared **4**. Threo-selective reduction of **20** ($LiAlH_4$, −20 °C)[6b,24] followed by desilylation[6b] afforded (+)-allopumiliotoxin 339B (**3**) ($[\alpha]^{25}_D$ + 8.8°, *c* 1.0, MeOH) in 49% yield after chromatographic purification.[25]

The total syntheses recorded here confirm the stereostructures and absolute configurations of allopumiliotoxins 267A and 339B, which had previously been assigned[2] on the basis of spectroscopic data alone. The synthetic sequence developed is concise, stereocontrolled, and potentially quite general. However, improvements in efficiency are required before useful amounts of the allopumiliotoxins could be secured in this manner for testing. Our investigations in this area are continuing.

Acknowledgment. We particularly thank Dr. J. W. Daly for comparison samples of **1** and **3** and Professor D. Evans for the complete experimental details for ref 15. This study was supported by PHS Grant HL-25854-02-06 and NSF instrumentation grants.

Supplementary Material Available: NMR spectra and spectroscopic and analytical data for **1, 3, 6, 13, 15,** and **18** (8 pages). Ordering information is given on any current masthead page.

(14) Brandsma, L.; Hoff, S.; Arens, J. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 916.
(15) Conveniently prepared by using the chiral enolate chemistry of Evans: Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(16) A variety of other aldol conditions (e.g., variations in base, solvent, temperature and counterion) were found to be inferior. The presence of a secondary amine was clearly deleterious.
(17) Stork, G.; Shiner, C. S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 310.
(18) None of the *Z* diastereomer of **15** was detected, although a trace amount (~5%) of the C-11 epimer of **15** was produced, and 27% of **6** was recovered unchanged. The C-11 epimer is believed to arise from the ~10% of enone formed directly in the aldol step. Identical condensation[11] of **6** with racemic 2-methylhexanal provided a 1:1 mixture of **15** and its C-11 epimer.
(19) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(20) An axial hydrogen at C-7 shows characteristic allylic coupling in the 250-MHz ^1H NMR spectrum: H-10 of **16** δ 5.47 (dt, $J_{10,11}$ = 9.9, $J_{5\beta,10}$ = $J_{7\beta,10}$ = 1.8 Hz), H-10 of **1** δ 5.34 (dd, $J_{10,11}$ = 9.7, $J_{5\beta,10}$ = 1.5 Hz).
(21) Synthetic **1** was identical with a natural sample[22] by TLC (three solvents), capillary GC, 250-MHz ^1H NMR, and 63-MHz ^{13}C NMR comparisons. A rotation at the sodium D line of +24.7° (*c* 0.17, MeOH) has been reported[2] for a very dilute sample of natural **1**.[23]
(22) Kindly supplied by Dr. J. Daly.
(23) Until more of this material is isolated from natural sources, the significance (if any) of the discrepancies observed in the rotations of the synthetic and natural allopumiliotoxins cannot be established.
(24) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 2355.
(25) Pumiliotoxin 339B is remarkably unstable to storage and only trace amounts of the natural alkaloid were available[22] for comparison. Synthetic **3** exhibited the same R_f by TLC analysis (three solvents) as a natural sample, and all ^1H NMR signals (250 MHz) observed for synthetic **3** were seen in an identical spectrum of impure natural **3**. A rotation at the sodium D line of +4.4° (*c* 0.5, MeOH) has been reported[2] for a very dilute sample of natural **3**.[23]

The C_3H_4 Surface

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Interconversions of the stable C_3H_4 isomers, methylacetylene, allene, cyclopropene, propenylidene, vinylmethylene, and cyclopropylidene are of considerable interest; these involve diradical formation, ring opening and closing, and various hydrogen shifts. In addition, they also serve as a model for much larger systems. Many experiments[1-3] and theoretical calculations[4-8] have been

(1) (a) Hutton, R. S.; Manion, M. L.; Roth, H. D.; Wessermann, E. *J. Am. Chem. Soc.* **1974**, *96*, 4680. (b) Palmer, G. E.; Bolton, J. R.; Arnold, D. R. *Ibid.* **1974**, *96*, 3708. (c) Chapman, O. L.; Chedekel, M.; Pacansky, J.; Rosenquist, N.; Roth, R.; Sheridan, R. S., unpublished results.
(2) (a) York, E. J.; Dittmar, W.; Stevenson, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 5680. (b) Bradley, J. H.; West, K. O. *J. Chem. Soc., Faraday Trans. 1* **1975**, *71*, 967. (c) Lifshitz, A.; Frenklack, M.; Burcat, A. *J. Phys. Chem.* **1975**, *79*, 1148. (d) Walsh, R. *J. Chem. Soc., Faraday Trans.* **1976**, *72*, 2137. (e) Bailey, I. M.; Walsh, R. *J. Chem. Soc., Faraday Trans. 1* **1978**, *74*, 1146. (f) Hopf, H.; Priebe, H.; Walsh, R. *J. Am. Chem. Soc.* **1980**, *102*, 1210.
(3) (a) Chapman, O. L. *Pure Appl. Chem.* **1975**, 511. (b) Arnold, D. R.; Humphreys, R. W.; Leigh, W. J.; Palmer, G. E. *J. Am. Chem. Soc.* **1976**, *96*, 3708.
(4) (a) Hoffmann, R.; Zeiss, G. D.; Van Dine, G. W. *J. Am. Chem. Soc.* **1968**, *90*, 1485. (b) Davis, J. H.; Goddard, III, W. A.; Bergman, R. G. *Ibid.* **1976**, *98*, 4015; **1977**, *99*, 2424. (c) Feller, D.; Borden, W. T.; Davidison, E. R. *J. Phys. Chem.* **1983**, *87*, 4833.
(5) (a) Binkly, J. S.; Pople, J. A.; Hehre, W. J. *Chem. Phys. Lett.* **1975**, *36*, 1. (b) Nomura, O.; Iwata, S. *J. Chem. Phys.* **1981**, *74*, 6830.
(6) (a) Shaad, L. J.; Burnelle, L. A.; Dressler, K. P. *Theor. Chim. Acta* **1969**, *15*, 91. (b) Dykstra, C. E. *J. Am. Chem. Soc.* **1977**, *99*, 2060. (c) Staemmler, V. *Theor. Chim. Acta* **1977**, *45*, 89. (d) Rauk, A.; Drake, A. F.; Mason, S. F. *J. Am. Chem. Soc.* **1979**, *101*, 2284.

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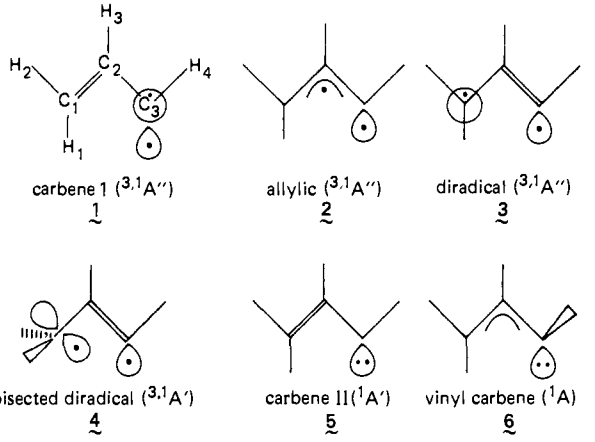

Figure 1. Possible structures for vinylmethylene. Only trans structures are shown. Each structure has a corresponding cis structure where H_4 is cis with respect to the C_1–C_2 bond.

Table I. MRSDCI Results for C–C Bond Lengths and Energies Relative to Methylacetylene (in kcal/mol) for the Low-Lying States of Vinylmethylene

state	bond lengths C_1–C_2	bond lengths C_2–C_3	rel energies
trans ^{3}A″	1.385	1.391	45.7
cis ^{3}A″	1.389	1.390	45.6
trans ^{1}A	1.397	1.405	58.0
cis ^{1}A	1.397	1.378	57.9

carried out to elucidate kinetics and mechanisms of these interconversions. The details of the mechanisms, however, have not been well established. Our extensive ab initio calculations[9] on the C_3H_4 isomers and their rearrangement paths revealed that the allene to methylacetylene thermal rearrangement should proceed via vinylmethylene, cyclopropene, and propenylidene. Other pathways proposed for this rearrangement[2b-f] are found to be high in energy.

In this study structures and paths were determined by self-consistent-field wavefunctions with a double-ζ plus polarization function basis[10] (SCF(DZP)) or, when necessary, multiconfiguration SCF wavefunctions with the 4-31G basis[11] (MCSCF-(431G)). For evaluation of quantitatively accurate energy profile of paths, either one-reference single- and double-excitation configuration-interaction wavefunctions with the DZP basis (SDCI(DZP)) or multi-reference SDCI wavefunctions (MRSDCI(DZP)) were employed. The results are estimated to be accurate to within 2 kcal/mol.

The intermediates that are suspected to play a central role on the C_3H_4 surface are vinylmethylenes (Figure 1), therefore it was imperative to determine if their structures represent minima. MCSCF and MRSDCI calculations (Table I) show that the ^{3}A″ states of *trans*- and *cis*-vinylmethylene have the allylic structure **2** and are isoenergetic lying 46 kcal/mol above the ground $^1A_1$ state of methylacetylene with a potential energy barrier of 6.5 kcal/mol between them. These findings are in accord with the ESR results[1a] and confirmed by the recent work of Feller and co-workers.[4c] For the singlet states of vinylmethylene which are most likely involved in the interconversions, similar calculations yielded rather unexpected results that allylic-like structures with the terminal hydrogen above or below the plane of the three carbon atoms (structures **6** in Figure 1) represent local minima for both *trans*- and *cis*-vinylmethylenes. These four minima are isoenergetic lying 12 kcal/mol above the triplet states, but the barriers to ring closure differ considerably; 4.8 kcal/mol for the trans and less than 1.2 kcal/mol for the cis system are our best estimates. No planar and bisected structures are found to be stable points on the singlet surface.

The pertinent results for the total energy of the isomers and reaction paths on the singlet C_3H_4 electronic state calculated relative to methylacetylene are summarized in Figures 2 and 3. Figure 2 shows the lowest energy path for the allene (**7**), cyclopropene (**8**), methylacetylene (**10**) rearrangement. The barrier heights in kcal/mol with the experimental activation energies[2e] in parentheses are summarized:

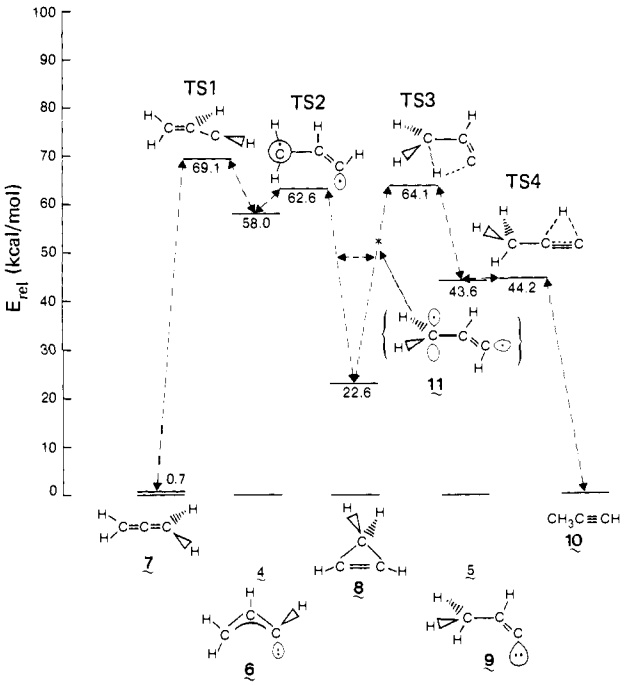

Figure 2. Lowest energy reaction path for the interconversion of allene, cyclopropene, and methylacetylene on the C_3H_4 singlet surface.

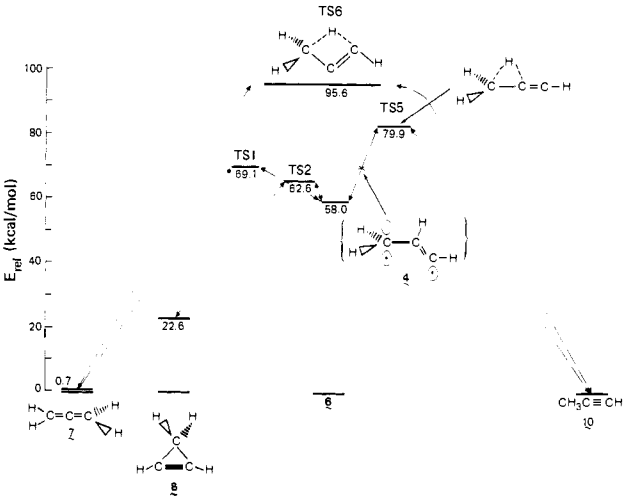

Figure 3. Energy path for the conversion of methylacetylene to allene via direct 1,2- and 1,3-hydrogen shifts, respectively.

(7) (a) Kao, J.; Radom, L. *J. Am. Chem. Soc.* **1978**, *100*, 379. (b) Wiberg, K. B.; Wendoloski, J. J. *Ibid.* **1978**, *100*, 723. (c) Gordon, M. S. *Ibid.* **1980**, *102*, 7419.

(8) (a) Dillon, P. W.; Underwood, G. R. *J. Am. Chem. Soc.* **1974**, *96*, 779; **1977**, *99*, 2435. (b) Baird, N. C.; Taylor, K. F. *Ibid.* **1978**, *100*, 1333. (c) Pasto, D. J.; Haley, M.; Chipman, D. M. *Ibid.* **1978**, *100*, 5272. (d) Minato, T.; Osamura, Y.; Yamabe, S.; Fukui, K. *Ibid.* **1980**, *102*, 581.

(9) The following computer programs are used: (a) HONDO (Dupuis, M.; Rys, J.; King H. F. *J. Chem. Phys.* **1976**, *65*, 111. Dupuis, M.; King, H. F. *Ibid.* **1978**, *68*, 3998). (b) GAMESS (Dupuis, M.; Wendoloski, J. J.; Spangler, D. *Nat. Res. Comput. Chem. Software Cat.* **1980**, *1*, QG01). (c) GENERIZED DIRECT CI (Siegbahn, P. E. M. *J. Chem. Phys.* **1979**, *70*, 5391; **1980**, *72*, 1647). (d) ALCHEMY MCSCF (Lengsfield, III, B. H. *J. Chem. Phys.* **1980**, *73*, 382. Lengsfield, B. H.; Liu, B. *Ibid.* **1981**, *75*, 478). (e) ALCHEMY II (Liu, B.; Yoshimine, M. *J. Chem. Phys.* **1981**, *74*, 612).

(10) For types and exponents used, see: Tanaka, K.; Yoshimine, M. *J. Am. Chem. Soc.* **1980**, *102*, 7655.

(11) Ditchfield, R.; Hehre, W. J.; Pople, J. *J. Chem. Phys.* **1971**, *54*, 724.

$$\text{allene} \underset{46.5\ (43.3)}{\overset{68.4\ (64.0)}{\rightleftharpoons}} \text{cyclopropene} \underset{64.1\ (59.8)}{\overset{41.5\ (37.5)}{\rightleftharpoons}} \text{methylacetylene} \quad (1)$$

These are in excellent agreement with the thermal experiments performed by Walsh and co-workers,[2e] and the involvement of cyclopropene in the allene to methylacetylene rearrangement is confirmed. Note that the reaction paths in Figure 2 require the vinylcarbene structure (**6**) and propenylidene (**9**). When they are not invoked the direct 1,2- or 1,3-hydrogen shifts to form cyclopropene and allene from methylacetylene, respectively, much larger barriers are calculated. The results shown in Figure 3 reveal that the transition states for the 1,3 and 1,2 shift are respectively 95.6 and 79.9 kcal/mol above methylacetylene. This latter transition state transforms to vinylmethylene and subsequently to either cyclopropene or allene.

Another viable but high-energy route for conversion of allene to cyclopropene is through cyclopropylidene, which lies 63.3 kcal/mol above methylacetylene. For the reaction to proceed two barriers must be surmounted, which collectively require 79.6 kcal/mol. The first barrier requires 74.2 kcal/mol to form cyclopropylidene via the bent, twisted allene transition state; the second requires 16.7 kcal/mol for the 1,2-hydrogen shift to produce cyclopropene.

Registry No. Methylacetylene, 74-99-7; allene, 463-49-0; cyclopropene, 2781-85-3; propenylidene, 70277-78-0; vinylmethylene, 19527-08-3; cyclopropylidene, 2143-70-6.

Reaction of Alkynes with (Ethoxyalkylidene)tetracarbonyliron(0) Complexes

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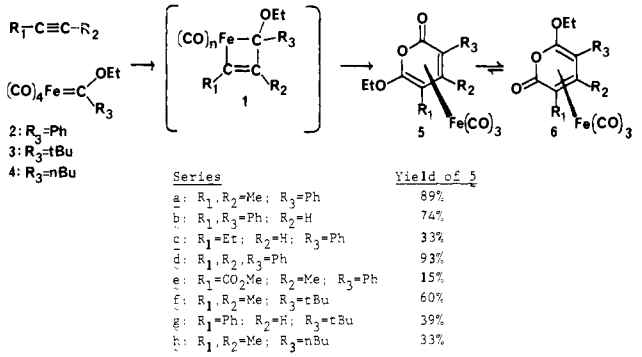
The reaction of alkynes with alkylidene–metal complexes appear in important organic processes such as alkyne polymerization[3] and naphthoquinone synthesis.[4] Initial formation of metallacyclobutenes (e.g., **1**) during these processes is suggested,[5] but has not been established. We have been interested[6] in the naphthoquinone synthesis with complexes such as $(CO)_5Cr{=}C(OMe)Ph$ and recently developed a general preparation of the analogous iron–alkylidene complexes (e.g., **2–4**).[7] Here we report the reaction of complexes **2–4** with alkynes which leads to 6-ethoxy-α-pyrone complexes (e.g., **5**). The reaction is highly regioselective with unsymmetrical alkynes, although a slow rearrangement process introduces a second isomer, of general structure **6**. Spectroscopic evidence has been obtained for a transient intermediate, for which the ferracyclobutene structure **1** is suggested.

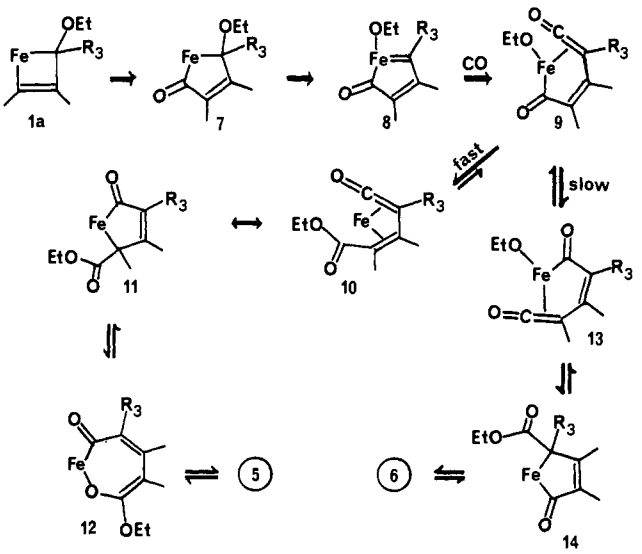
The prototype reaction is carried out as follows. A mixture of **2** and 2-butyne (10-fold molar excess) in dichloromethane at

Scheme I



Series	Yield of 5
a: R_1,R_2=Me; R_3=Ph	89%
b: R_1,R_3=Ph; R_2=H	74%
c: R_1=Et; R_2=H; R_3=Ph	33%
d: R_1,R_2,R_3=Ph	93%
e: R_1=CO_2Me; R_2=Me; R_3=Ph	15%
f: R_1,R_2=Me; R_3=tBu	60%
g: R_1=Ph; R_2=H; R_3=tBu	39%
h: R_1,R_2=Me; R_3=nBu	33%

Scheme II



70 °C in a simple pressure vessel[8] at 55 psi of carbon monoxide for 1 h gave as the major product a yellow crystalline, air-stable compound which was isolated by chromatography. Reproducible yields of 92–98% have been obtained.[9,10] The structure **5a** was established by X-ray crystallography[11] and reveals the incorporation of two carbon monoxide molecules with apparent migration of the ethoxy group from the carbene carbon to a carbon monoxide unit.

Scheme I displays a series of examples with three alkylidene complexes and five alkynes leading to eight pyrone complexes.[9] In each case, the major product was isolated by simple chromatography and only one isomer of each product was detected. The structures of the pyrone products are not easily established by spectroscopy, but X-ray crystallography verified the structures assigned to **5a** and **5c**.[11] The regioselectivity of addition of alkynes to alkylidene–chromium complexes has been defined,[5,12] and

(1) Princeton University.
(2) Merck Institute for Theraputic Research.
(3) For examples, see: (a) Katz, T. J.; Lee, S. J. *J. Am. Chem. Soc.* **1980**, *102*, 422. Katz, T. J.; Savage, E. B.; Lee, S. J.; Nair, M. *Ibid.* **1980**, *102*, 7942.
(4) (a) Fischer, H.; Schubert, U.; Hofmann, P.; Kreissl, F. R.; Weiss, K.; Dötz, K. H. "Carbene Complexes"; Verlag Chemie: Weinheim, 1983. (b) Dötz, K. H.; Pruskil, I.; Muhlemeier, J. *Chem. Ber.* **1982**, *115*, 1278 and references therein.
(5) Dötz, K. H.; Fügen-Köster, B. *Chem. Ber.* **1980**, *113*, 1449–1457.
(6) (a) Semmelhack, M. F.; Bozell, J. J. *Tetrahedron Lett.* **1982**, 2931–2934. (b) Semmelhack, M. F.; Bozell, J. J.; Sato, T.; Spiess, E.; Zask, A. *J. Am. Chem. Soc.* **1982**, *104*, 5850–5852.
(7) Semmelhack, M. F.; Tamura, R. *J. Am. Chem. Soc.* **1983**, *105*, 4099–4100.
(8) A heavy-walled glass tube with a cap fitted with a pressure gauge and CO inlet was employed ("Griffin-Worden" vessel, Kontes No. K-767100, borosilicate). The iron–carbene complex and the alkyne were dissolved in degassed dichloromethane and transferred to the pressure vessel which was previously flushed with CO. The vessel was pressurized with CO. After the reaction period, the vessel was cooled to 25 °C and the CO was released. The volatile material was removed by rotary evaporation, and the residue was purified by column chromatography on silica gel, with mixtures of ether and hexane. The complexes **5** were obtained as yellow solids and could be recrystallized from hexane–ether at −20 °C.
(9) Satisfactory characterization data have been obtained; refer to supplementary material.
(10) A number of pyrone–$Fe(CO)_3$ complexes have been prepared by other routes. (a) Rosenblum, M.; Gatsonis, C. *J. Am. Chem. Soc.* **1967**, *89*, 5074. (b) Holland, J. M.; Jones, D. W. *Chem. Commun.* **1967**, 946. (c) Mitsudo, T.; Wantanabe, H.; Sasaki, T.; Wantanabe, Y.; Takegami, Y.; Kafuku, K.; Kinoshita, K.; Nakatzu, K. *J. Chem. Soc., Chem. Commun.* **1981**, 22. (d) Mitsudo, T.; Ogino, Y.; Komiya, Y.; Watanabe, H.; Watanabe, Y. *Organometallics* **1983**, *2*, 1202–1207.
(11) Refer to supplementary material.

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