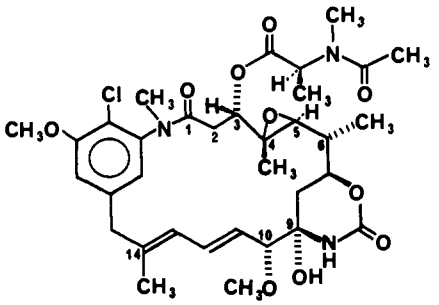
Total Synthesis of Maytansine

Sir:

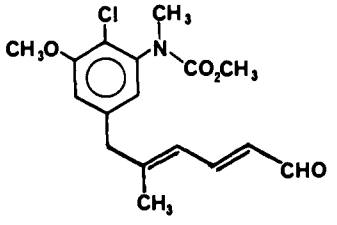
The extraordinary antitumor activity of maytansine (**1**), the key member of a new and rare class of natural products,[1] and its promise as a chemotherapeutic agent have combined to elicit



1

widespread interest in chemical synthesis.[2] We now report the first total synthesis of this important substance which has been used in clinical studies with some success in the treatment of acute lymphoblastic leukemia and malignant lymphoma.[3] The synthesis outlined herein, which procedes with uniformly good yields in the individual steps and with excellent stereochemical control, represents the denouement of the plan which earlier led to successful synthesis of the simpler maytansinoid *N*-methylmaysenine.[4]

We have previously described stereospecific and highly effective processes for production of the dienal **2** and the ketal thioacetal **3** (with absolute configuration as shown). These components were



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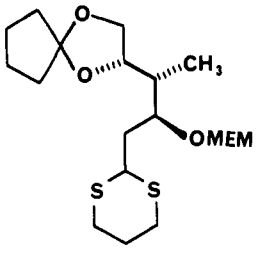

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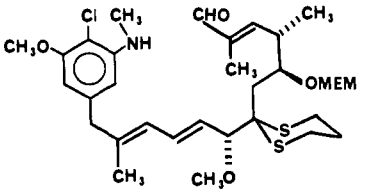
utilized for an efficient, stereocontrolled synthesis of the aldehyde **4** which served as a key intermediate in the previously described synthesis of *N*-methylmaysenine (natural, i.e., levo, form)[4a] and which also was utilized for the synthesis of maytansine recorded here.

The carbon skeleton of maytansine was completed, and the chiral center at C-3 was set in place, starting from the aldehyde **4** by a two-carbon chain extension by using as reagent (*R*)-(+)-*p*-tolyl phenoxycarbonylmethyl sulfoxide **7** which was prepared as follows. (*S*)-(−)-*p*-Toluenesulfinic acid (−)-menthyl ester (**5**)[5] in tetrahydrofuran (THF) at −30 °C[6] was allowed to react with



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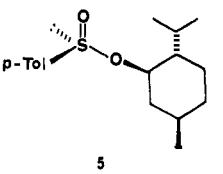

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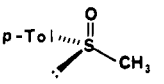

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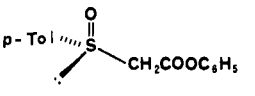
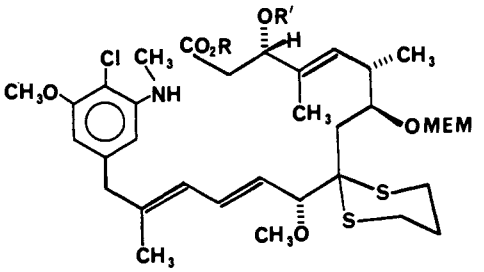


7

1.1 equiv of methylmagnesium bromide in ether for 25 min to give in 80% yield (*R*)-(+)-*p*-tolyl methyl sulfoxide (**6**); mp 71–72 °C, $[\alpha]^{25}_D$ +223° (*c* 1.0, $CHCl_3$). Deprotonation of **6** with 1 equiv of lithium diisopropylamide in THF at −78 °C for 25 min followed by treatment of the resulting sulfinyl carbanion with 0.5 equiv of phenyl chloroformate in THF afforded the (*R*)-(+)-α-sulfinyl phenyl ester **7** [mp 90–91 °C, IR_{max} 1755 cm^{-1} ($CHCl_3$), $[\alpha]^{25}_D$ +87° (*c* 0.95, $CHCl_3$)] in 80% yield based on chloroformate. The (*R*)-(+)-α-sulfinyl phenyl ester **7** was converted to the magnesium derivative by reaction in THF with 1 equiv of *tert*-butylmagnesium chloride at −78 °C, and to this was added a solution of the conjugated aldehyde **4** in THF.[7] After 15 h at −78 °C, the formyl addition product was isolated by quenching at −78 °C with pH 7 phosphate buffer and extractive workup, and the crude product was subjected to reductive cleavage[8,9] of the α-sulfinyl group by reaction with 20 equiv of aluminum amalgam in 10% aqueous THF at 23 °C for 2 h to afford with high stereoselectivity the desired 4,5-unsaturated 3-(*S*)-hydroxy ester **8** as principal product



8, R = C_6H_5, R′ = H
9, R = C_6H_5, R′ = $SiMe_2tBu$
10, R = H, R′ = $SiMe_2tBu$

(>80% yield).[9] High-performance liquid chromatographic (high-performance LC) analysis revealed that the ratio of **8** to the C-3 epimer in this reaction product is ca. 93:7. In contrast the addition of α-lithioacetic acid tetrahydropyranyl (THP) ester to **4** was not stereoselective and furnished in high yield a 1:1 mixture of the THP ester corresponding to **8** and the 3-(*R*)-epimer,[10] in accord with expectations. Silylation of **8** with excess *tert*-butyldimethylsilyl chloride–imidazole in dimethylformamide (DMF) at 25 °C for 3 h afforded **9**, $[\alpha]^{25}_D$ +6.6° (*c* 0.15, CH_2Cl_2),

(1) (a) Kupchan, S. M.; Komoda, Y.; Court, W. A.; Thomas, G. J.; Smith, R. M.; Karim, A.; Gilmore, C. J.; Haltiwanger, R. C.; Bryan, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 1354. (b) Kupchan, S. M.; Komoda, Y.; Braufman, A. R.; Sneden, A. T.; Court, W. A.; Thomas, G. J.; Hintz, H. P. J.; Smith, R. M.; Karim, A.; Howie, G. A.; Verma, A. K.; Nagao, Y.; Dailey, R. G., Jr.; Zimmerly, V. A.; Sumner, W. C., Jr. *J. Org. Chem.* **1977**, *42*, 2349.

(2) See, for example: (a) Meyers, A. I.; Comins, D. L.; Roland, D. M.; Henning, R.; Shimizu, K. *J. Am. Chem. Soc.* **1980**, *101*, 7104. (b) Bonjoukalian, R.; Ganem, B. *Carbohydr. Res.* **1979**, *76*, 245. (c) Ho, P.-T. *Can. J. Chem.* **1980**, *58*, 858, 861. (d) Götschi, E.; Schneider, F.; Wagner, H.; Bernauer, K. *Helv. Chim. Acta* **1977**, *60*, 1416. (e) Back, T. G.; Edwards, O. E.; MacAlpine, G. A. *Tetrahedron Lett.* **1977**, 2651. (f) Elliot, W. J.; Fried, J. *J. Org. Chem.* **1976**, *41*, 2469.

(3) Issell, B. F.; Crooke, S. T. *Cancer Treat. Rev.* **1978**, *5*, 199.

(4) (a) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Lipshutz, B. *J. Am. Chem. Soc.* **1980**, *102*, 1439. (b) Corey, E. J.; Weigel, L. O.; Floyd, D.; Bock, M. G. *Ibid.* **1978**, *100*, 2916. (c) Corey, E. J.; Wetter, H. F.; Kozikowski, A.; Rama Rao, A. V. *Tetrahedron Lett.* **1977**, 777. (d) Corey, E. J.; Bock, M. G. *Ibid.* **1975**, 2643.

(5) Phillips, H. *J. Chem. Soc.* **1925**, 2552.

(6) Satisfactory infrared, ultraviolet, proton magnetic resonance and mass spectral data were obtained for each isolated synthetic intermediate by using a purified, chromatographically homogeneous sample. All reactions were conducted under an argon atmosphere.

(7) A ca. 5-fold excess of the anion of **7** over the conjugated aldehyde **4** was used for small-scale experiments (<500 mg of **4**); at larger scale and higher concentrations, a smaller amount of **7** can be used.

(8) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1964**, *86*, 1639.

(9) Mioskowski, C.; Solladie, G. *Tetrahedron* **1980**, *36*, 227, and previous papers cited therein. The degree of stereoselectivity and the absolute chirality observed in the present work are fully consonant with the observations of Mioskowski and Solladie by using the *tert*-butyl ester corresponding to **7** and simple aldehydes as substrates. We have also observed high stereoselectivity with tigaldehyde as a model for **4** with **7** and other esters such as *tert*-butyl.

(10) Although this mixture can be (and has been) carried through the subsequent steps of the scheme outlined here, it is less satisfactory than the approach with **7** since stereochemistry at C-3 is not controlled.

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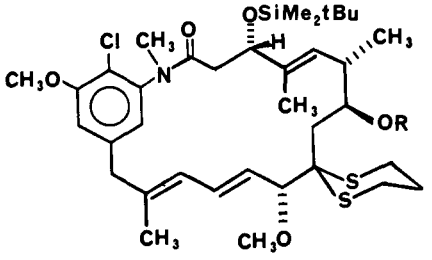
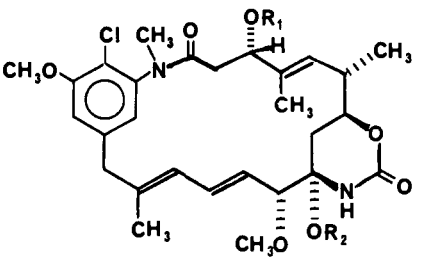
in 70% overall yield after chromatography on silica gel.[11] Hydrolysis of the phenyl ester **9** with 3 equiv of lithium hydroxide in dimethoxyethane (DME)–water at 27 °C for 5 h provided the acid **10** in 81% yield and >99% purity (high-performance LC analysis)[12] after preparative thin-layer chromatography on silica gel (p-TLC-sg). Cyclization of **10** was effected smoothly by using the general method utilized previously for *N*-methylmaysenine.[4a] A solution of the tetra-*n*-butylammonium salt of **10** (rigorously dried by azeotropic distillation of toluene at 25 °C) in benzene was slowly added by motor-driven syringe to an excess of 10^{-2} M mesitylenesulfonyl chloride–10^{-2} M diisopropylethylamine in benzene at 40 °C over 28 h, the reaction mixture was treated with aqueous pyridine to hydrolyze excess sulfonyl chloride, and the product was obtained by concentration in vacuo, extractive isolation, and chromatography on silica gel. The analytical yield (high-performance LC)[12] of macrocyclic lactam **11** was 78–83%;



11, R = MEM
12, R = H
13, R = $CONH_2$

corrected for 10% recovery of starting acid **10**, the isolated yield of **11** was 71%.[13,14] With this transformation, the most crucial elements of the maytansine structure had been established.

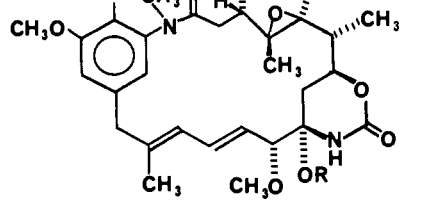
The 7-*O*-β-(methoxyethyl)methyl (MEM) protecting group was then cleaved cleanly from **11** by a novel and very mild two-step process. Reaction of a mixture of **11** and 2-propanethiol in methylene chloride at −78 °C with 5 equiv of boron trifluoride etherate for 5 min followed by rapid addition to a quenching mixture of 8:8:1 0.4 M tetra-*n*-butylammonium hydroxide in water–benzene–2-propanethiol at 27 °C followed by extractive isolation provided the 7-*O*-isopropylthio methyl ether which was then cleaved to the desired 7-alcohol **12** by stirring with 5 equiv of silver nitrate and 3 equiv of 2,6-lutidine in 4:1 THF–water at 25 °C for 1.75 h. Reaction of **12** (without purification) with 4 equiv of *p*-nitrophenyl chloroformate in pyridine at 27 °C for 20 min followed by treatment of the whole with 15 N ammonium hydroxide–water–*tert*-butyl alcohol (1:2.3:5) at 27 °C for 2 h led to the carbamate ester **13** [IR_{max} 1735, 1665, 1600, 1585 cm^{-1} ($CDCl_3$)] with no significant byproducts by TLC analysis. Exposure of **13** to 3 equiv of mercuric chloride and 8 equiv of powdered calcium carbonate in 5:1 acetonitrile–water at 25 °C for 12 h followed by addition of 4.5 equiv of diisopropylethylamine, concentration in vacuo, dilution with ethyl acetate–water, addition of sodium sulfide (to remove mercury), and filtration through Celite gave after isolation and column chromatographic purification (silica gel) the desired cyclic urethane **14** in 60% overall



14, R_1 = $SiMe_2tBu$, R_2 = H
15, R_1 = H, R_2 = H
16, R_1 = H, R_2 = CH_3

yield from **11**: IR_{max} 1718, 1568, 1600, 1588 cm^{-1} ($CDCl_3$); UV_{max} (in ethanol) 204 (ϵ 39 600), 223 (38 500), 233 (37 200), 251 (35 000), 279 (4650), and 288 (5200) nm.[15] Desilylation of **14** was accomplished smoothly by using 23:1:1 acetonitrile–hydrogen fluoride–water at 0 °C for 45 min and gave **15** in 83% yield after chromatography on silica gel, further converted to the 9-methyl ether **16** (>90% yield) by exposure to 0.1% *p*-toluenesulfonic acid in methanol at 25 °C for 30 min. This synthetic product was identical in all respects with a sample of 4,5-deoxymaytansinol 9-*O*-methyl ether synthesized by deoxygenation[16] of naturally derived maytansinol 9-*O*-methyl ether.[17,18]

Reaction of synthetic **16** with 3 equiv of *tert*-butyl hydroperoxide, 0.03 equiv of oxyvanadium(IV) bis(acetylacetonate), and 1 equiv of 2,6-lutidine in 10:7 toluene–benzene at 25 °C for 3.5 h followed by workup, including (1) stirring with added dimethyl sulfide at 25 °C for 30 min, (2) dilution with ethanol–water–pH 7 buffer, (3) cooling to −5 °C and treatment with sodium borohydride, (4) concentration in vacuo, (5) extractive isolation, and (6) p-TLC-sg (1% isopropyl alcohol in ethyl acetate for development) afforded in pure form the desired 4,5-epoxide, maytansinol 9-*O*-methyl ether (**17**), in 87% yield. The reaction was highly



17, R = Me
18, R = H

stereoselective as indicated by high-performance LC analysis of the crude reaction mixture which allowed determination of the ratio of epoxide **17** to its 4,5-epimer as >200:1.[19] The only other detectable byproduct was the enone produced by oxidation of the

(11) The small amount of C-3 epimer (ca. 7%) was not separated from **8** or **9** at this stage, but at the next step instead.

(12) Waters Associates cyanopropyl column with hexane–methylene chloride–isopropyl alcohol as solvent.

(13) The following summary of reversed-phase (RP) high-performance LC analytical data is presented. RP-high-performance analysis was performed on a Waters Associates C_{18} μ-Bondapak column (3.9 mm × 30 cm) by using methanol–water–acetic acid (650:350:1) buffered to pH 5.6 with 2 N ammonium hydroxide, using a flow rate of 1 mL/min at 25 °C; with detection at 254 and 284 nm, the following retention times (in min) were observed: maytansine (11.5), **10** (21.6), **11** (104), **14** (54.6), **15** (11.4), **16** (16.3), **17** (15.6), **18** (13.0), maytansine 9-methyl ether (18.9).

(14) The following summarizes salient TLC R_f data for various synthetic intermediates by using E. Merck silica gel F-254 0.25-mm plates developed with ethyl acetate–methylene chloride–isopropyl alcohol (80:20:5): maytansine (0.19), **9** (0.70), **10** (0.63), **11** (0.62), **12** (0.60), **13** (0.55), **14** (0.36), **15** (0.28), **16** (0.40), **17** (0.29), **18** (0.10), maytansine 9-methyl ether (0.30).

(15) Also found for **14** were the following circular dichroism (CD) data (in ethanol): $\Delta\epsilon_{206}$ +29.5°, $\Delta\epsilon_{216}$ 0°, $\Delta\epsilon_{235}$ −7.8°, $\Delta\epsilon_{241}$ −7.4°, $\Delta\epsilon_{350}$ −8.7°, $\Delta\epsilon_{268}$ −0.9°, $\Delta\epsilon_{285}$ −2.8°. ^1H NMR ($CDCl_3$) δ 6.51 (1 H, br s, exchanges with D_2O), 3.20 and 3.08 (2, ratio 3:1, NCH_3, due to 3:1 rotomer mixture), 2.30 (s, 1 H, exchanges with D_2O), 0.91 and 0.79 (s, ratio, 3:1, *t*-BuSi, rotomer mixture), 0.12, 0.08, −0.18, −0.32 [s, $(CH_3)_2Si$, due to rotomer mixture]. Similarly, ^1H NMR spectral data indicated rotomer mixtures for intermediates **11**–**14**. Rotomers of the carbamate **13** could be separated by high-performance LC[12] and shown to revert to the original equilibrium mixture on storage at 25 °C.

(16) Details of this process will be described in a separate publication.

(17) We are indebted to Drs. Masao Nishikawa and Sueo Tatsuoka of Takeda Chemical Industries Ltd. for generously providing samples of maytansinol and ansamitocins; see: (a) Tanida, S.; Hasegawa, T.; Hatano, K.; Higashide, E.; Yoneda, M. *J. Antibiot.* **1980**, *33*, 192. (b) Asai, M.; Mizuta, E.; Izawa, M.; Haibara, K.; Kishi, T. *Tetrahedron* **1979**, *35*, 1079.

(18) Comparison was made by ^1H NMR (in $CDCl_3$, C_6D_6, and CD_3CO-CD_3 as solvent), high-performance LC[12] and RP-high-performance LC, TLC (several solvent systems), IR, UV, CD, and mass spectra.

(19) Retention times of **17** and the 4,5-epimer were 15.6 and 11.2 by RP-high-performance LC. For a recent review of selective epoxidation, see: Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.

3-hydroxyl group. Synthetic **17** was identical with a sample of naturally derived maytansinol 9-*O*-methyl ether (**17**).[18] 4,5-Epoxidation of **16** with *m*-chloroperbenzoic acid forms **17** with complete stereoselectivity, although the yield is diminished by side reactions involving the other double bonds. That the oxidation of the 4,5-double bond of **16** would be highly stereoselective was predicted in advance from a knowledge of the conformation of maytansinoids,[1a] and the directing effect of the 3α-hydroxyl function.[20] Hydrolysis of **17** affords maytansinol (**18**) in >90% yield.

The conversion of maytansinol to maytansine has already been described by the Takeda group.[21] The conversion of maytansinol 9-*O*-methyl ether to maytansine 9-*O*-methyl ether has also been carried out in the present study by using the imidazolide of *N*-acetyl-*N*-methyl-L-alanine in DMF–DME in the presence of imidazole at 45–47 °C for 75 h. Finally, hydrolysis of maytansine 9-*O*-methyl ether by using a 1% solution of pyridinium chloride in 1:1 THF–water at 25 °C for 14 h provides maytansine in 95% yield to complete our synthetic sequence.

The realization of the total synthesis of maytansine depended on the successful solution of a large number of critical problems including (1) control of stereochemistry, (2) introduction, protection, utilization, and manipulation of a formidable collection of functional groups, (3) carbon chain elaboration, and (4) macrocyclization. A number of new strategies and synthetic methods were crucial as were the availability of micro-scale physical measurements (notably ^{1}H NMR and mass spectral) and separations (high-performance LC). To our knowledge, no other stereocontrolled routes to maytansinoids or routes to chiral maytansinoids have been accomplished to date.[22]

(20) Interestingly, reduction of the 3-keto function of maytansin-3-one can be easily controlled to afford the 3β-alcohol stereospecifically, but does not seem to lead to the 3α-alcohol as the major product with the gamut of applicable reagents (unpublished work in these laboratories). This fact played a major role in dictating the successful stereochemical strategy outlined herein.

(21) Hashimoto, N.; Matsumura, K.; Motohashi, M.; Ootsu, K.; Kozai, Y.; Kishi, T. 177th National Meeting of the American Chemical Society, Honolulu, HI, 1979; Abstr. Medicinal Section No. 26.

(22) We are indebted to the National Institutes of Health and the Chas. Pfizer Co. for financial assistance and to the National Science Foundation for grants allowing the purchase of ^{1}H NMR and mass spectrometers. Finally, it is a pleasure to acknowledge valuable experimental contributions from several members of this research group including Drs. Mark G. Bock, A. V. Rama Rao, Jagabandhu Das, Geza Galambos, Marc Tius, Homer Pearce, Alan Barton, Bruce Lipshutz, and David Floyd. Dr. John Douros of the National Institutes of Health provided assistance and advice on a number of occasions.

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An Equilibrium between Carbene and a Metal–Carbene Complex. Homogeneous Catalysis by Mercury(II)

Sir:

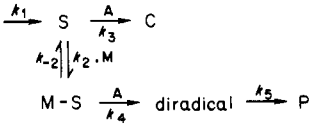
Metal–carbene complexes have usually been prepared by modification of noncarbene carbon ligands.[1,2] Preparation by direct reaction of the metal with a neutral carbene has seldom been observed.[1,3] We report herein that mercury(II) reacts directly with dibromocarbene to form a metal–carbene complex.

(1) For a complete compilation of methods, see: Cardin, D. J.; Çetinkaya, B.; Lappert, M. F. *Chem. Rev.* **1972**, *72*, 545–574.

(2) For other reviews, see: Kochi, J. K. "Organometallic Mechanisms and Catalysts", Academic Press: New York, 1978; pp 285f. Katz, T. J. *Adv. Organomet. Chem.* **1977**, *16*, 283–317. Farona, M. F. *CHEMTECH.* **1978**, *8*, 40–42.

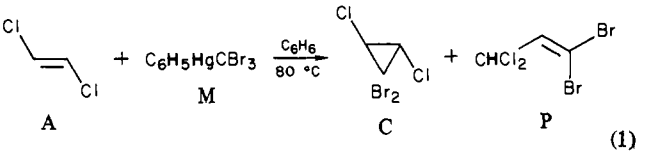
(3) Some difficulties are described for an Ir complex by Cooke, J.; Cullen, W. R.; Green, M.; Stone, F. G. A. *J. Chem. Soc. A* **1969**, 1872–1874.

Scheme I



The free and the complexed carbenes lead to separate products whose ratio demonstrates the presence of the two distinct intermediates.

Reaction of *trans*-dichloroethene (A) with phenyl(tribromomethyl)mercury (M) gives two products in comparable amounts, the stereospecifically formed cyclopropane (C) and the rearranged propene (P) (eq 1).[4] A similar reaction is observed with the *cis*-



(1)

and *trans*-dibromoethenes, and the cyclopropane in each case is formed stereospecifically. This stereochemical result has traditionally been accepted as prima facie evidence for a singlet carbene.[5] The propene P is reasonably derived from a diradical of the structure ·CHCl–CHCl–CBr_2· (D), via a 1,2 shift of the chlorine atom. Chlorine has a high migratory aptitude toward a radical site.[6]

It is very unlikely that this open diradical, if produced by reaction of the singlet dibromocarbene (S) with dichloroethene, could be a common precursor of both C and P, because of the stereospecific formation of the cyclopropane product. Moreover, a stepwise reaction of the singlet carbene would contradict the Skell hypothesis.[5] Consequently, we sought to prove separate pathways for production of the propene and the cyclopropane.

Proof that the two products derive from distinct intermediates can come from the dependence of their ratio on the concentration of the alkene.[7] If the singlet carbene reacted directly with the alkene to produce both C and P via a common pathway, then their ratio would be independent of alkene concentration. If, however, the carbene either gives C directly by a concerted reaction with alkene or is competitively converted to a second intermediate that in turn reacts with alkene to give P via D, then the ratio [P]/[C] will show the following dependence

$$\frac{[P]}{[A]} = \frac{k_2}{k_3}\frac{1}{[A]}$$

in which k_2 is the rate of interconversion of the carbene to the second intermediate and k_3 is the rate of direct reaction of carbene with alkene.[8] *We observed a very clean, linear dependence of this ratio on 1/[A].* Consequently, we can conclude that there are two intermediates. Furthermore, the 1/[A] dependence requires that C come from the first-formed intermediate (free singlet carbene) and that P come from the second-formed intermediate

(4) Lambert, J. B.; Kobayashi, K.; Mueller, P. H. *Tetrahedron Lett.* **1978**, 4253–4256.

(5) Skell, P. S.; Valenty, S. J.; Humer, P. W. *J. Am. Chem. Soc.* **1973**, *95*, 5041–5042.

(6) Friedlina, R. K. *Adv. Free-Radical Chem.* **1965**, *1*, 231f.

(7) McConaghy, J. S., Jr.; Lwowski, W. *J. Am. Chem. Soc.* **1967**, *89*, 2357–2364. A kinetically equivalent study has been carried out on a noncarbene system: Corwin, L. R.; McDaniel, D. M.; Bushby, E. J.; Berson, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 276–287. It should be noted that their product ratio plot, Figure 7, uses the ratio of the second product to the first product, analogous to our [C]/[P].

(8) The steady-state approximation in the second intermediate gives a ratio (second intermediate to first intermediate) of $k_2/(k_4[A] + k_{-2})$. Substitution into the expression for the ratio of products gives $[P]/[C] = (k_4/k_3)(k_2/(k_4[A] + k_{-2}))$. The right-hand side of this equation reduces to $(k_2/k_3)(1/[A])$ if $k_4[A] \gg k_{-2}$. In our kinetic runs, we kept [A] extremely high in order that its concentration remain essentially constant throughout the reaction. This experimental requirement may have assisted the maintenance of the inequality. The validity of the inequality, however, is confirmed by the fact that the plots both of [P]/[C] vs. 1/[A] and of [C]/[P] vs. [A] are linear.

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