

as the use of the main group heterocycles in materials and organic synthesis.

Registry No. 1, 84101-39-3; 2, 113132-34-6; 3, 53433-58-2; 4, 113132-35-7; 5, 113132-36-8; 6, 113132-37-9; 7a, 112549-07-2; 7b, 113111-17-4; 7c, 113111-18-5; 7d, 113111-19-6; 7e, 113111-26-5; 7f, 113111-27-6; 8, 113111-20-9; 9a, 113132-39-1; 9b, 113132-41-5; 10a, 26461-34-7; 10b, 113111-21-0; 11, 113111-22-1; 12, 113111-23-2; 13, 113111-24-3; 14, 14409-95-1; 15, 113111-25-4; Et₄N⁺InCl₄⁻, 20678-78-8; Cp₂ZrCl₂, 1291-32-3; PhPCl₂, 644-97-3; PhAsCl₂, 696-28-6; SbCl₃, 10025-91-9; BiCl₃, 7787-60-2; GeCl₄, 10038-98-9; GaCl₃, 13450-90-3; S₂Cl₂, 10025-67-9; Se₂Cl₂, 10025-68-0; Me₂SnBr₂, 2767-47-7; SOCl₂, 7719-09-7; SiCl₄, 10026-04-7; 2,8-decadiyne, 4116-93-2.

Supplementary Material Available: ¹H NMR, ¹³C NMR, ³¹P NMR, and mass spectral data for the compounds 7-15 (4 pages). Ordering information is given on any current masthead page.

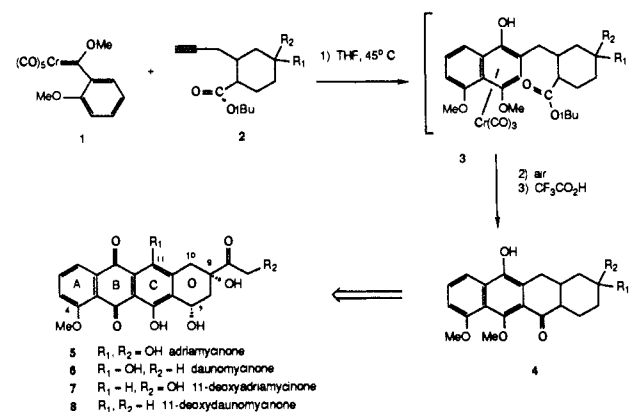
An Organochromium-Mediated Synthesis of 11-Deoxydaunomycinone via a Tandem Benzannulation/Friedel-Crafts Double Cyclization[†]

William D. Wulff*¹ and Yao-Chang Xu

Searle Chemistry Laboratory
Department of Chemistry, University of Chicago
Chicago, Illinois 60637
Received October 28, 1987

Members of the anthracycline family of antitumor antibiotics are well established clinically important agents in cancer chemotherapy² and have attracted the interest of synthetic organic chemists for the last 12 years.³ The clinically effective agents are members of the 11-oxy class of anthracyclines, and members of the 11-deoxy class are presently in human trials. The tetracyclic carbon skeleton of the anthracycline family has served as the anvil against which a large array of elegant and practical new synthetic methods in the chemistry of aromatic rings have been forged and is revealed, for example, in the reported syntheses of 11-deoxydaunomycinone.⁴ The reactions of chromium carbene complexes

Scheme I



with acetylenes produce substituted 4-alkoxyphenols with a high degree of control of regiochemistry under neutral conditions and at near ambient temperatures.⁵ Together with the fact that chromium carbene complexes are relatively inexpensive and easy to make and handle, the benzannulation reaction of chromium carbene complexes is one of the most powerful methods for the preparation of substituted 4-alkoxyphenols (and therefore quinones) and should thus be well suited for utilization in anthracycline synthesis. Three years ago we reported the first anthracycline synthesis^{6,7} utilizing the benzannulation reaction of a chromium carbene complex and an acetylene which in terms of efficiency fell short of state of the art. The synthesis of 11-deoxydaunomycinone described herein⁸ from the carbene complex 1 is comparable in overall efficiency to the best of the syntheses that have been reported to date⁴ and is highlighted by the first synthetic application of a one-pot double-cyclization incorporating a tandem benzannulation/Friedel-Crafts sequence.

The plan in Scheme I was designed to include several members of the class of 11-deoxyanthracyclines, and has as its ultimate feature the construction of the anthracycline tetracyclic carbon skeleton in a single pot from the carbene complex 1 and an acetylene of the general structure 2. It has been demonstrated that naphthalenes can be prepared from the annulation of the *o*-methoxyphenyl complex 1^{5c,9,10c} and it has also previously been demonstrated that terminal acetylenes are regioselectively incorporated into the annulated products with the acetylene substituent adjacent to the hydroxyl group.¹⁰ With the preparation of the requisite acetylene of the type 2, the anticipated sequence of events begins with the formation of the naphthol chromium tricarbonyl complex 3 from the reaction of acetylene 2 with the carbene complex 1. It has been our experience that naphthol chromium tricarbonyl complexes are very rapidly oxi-

[†] Dedicated to Professor N. C. Yang on the occasion of his 60th birthday.

- (1) Eli Lilly Young Scholar, 1986-1987.
(2) For reviews of anthracyclines, see: (a) El Khadem, H. S., Ed.; Academic Press: New York, 1982. (b) Arcamone, F. *Med. Chem. (Academic)* **1981**, 17.
(3) For reviews on anthracycline synthesis, see: (a) Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1986**, 25, 790. (b) Kelly, T. R. *Tetrahedron* **1984**, 40, 4539-4793; *Tetrahedron Symposia-in-Print* no. 17.
(4) For formal and total syntheses of 11-deoxydaunomycinone, see: (a) Gesson, J. P.; Jacquesy, J. C.; Mondon, M. *Tetrahedron Lett.* **1980**, 21, 3351. (b) Bauman, J. G.; Barber, R. B.; Gless, R. D.; Rapoport, H. *Tetrahedron Lett.* **1980**, 21, 4777. (c) Alexander, J.; Flynn, D. L.; Mitscher, L. A.; Veysoglu, T. *Tetrahedron Lett.* **1981**, 22, 3711. (d) Kimball, S. D.; Walt, D. R.; Johnson, F. *J. Am. Chem. Soc.* **1981**, 103, 1561. (e) Yadav, J.; Corey, P.; Hsu, C. T.; Perlman, K.; Sih, C. J. *Tetrahedron Lett.* **1981**, 22, 811. (f) Rao, A. V. R.; Deshpande, V. H.; Reddy, N. L. *Tetrahedron Lett.* **1982**, 23, 775. (g) Gesson, J. P.; Mondon, M. *J. Chem. Soc., Chem. Commun.* **1982**, 421. (h) Rao, A. V. R.; Mehendale, A. R.; Reddy, K. B. *Tetrahedron Lett.* **1982**, 23, 2415. (i) Sekizaki, H.; Jung, M.; McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, 104, 7372. (j) Jung, M. E.; Node, M.; Pfluger, R. W.; Lyster, M. A.; Lowe, J. A., III. *J. Org. Chem.* **1982**, 47, 1150. (k) Rao, A. V. R.; Reddy, K. B.; Mehendale, A. R. *J. Chem. Soc., Chem. Commun.* **1983**, 564. (l) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1983**, 105, 5688. (m) Hauser, F. M.; Prasanna, S.; Combs, D. W. *J. Org. Chem.* **1983**, 48, 1328. (n) Tamura, Y.; Akai, S.; Sasho, M.; Kita, Y. *Tetrahedron Lett.* **1984**, 25, 1167. (o) Uemura, M.; Minami, T.; Hayashi, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1193. (p) Tamura, Y.; Sasho, M.; Akai, S.; Wada, A.; Kita, Y. *Tetrahedron* **1984**, 40, 4539. (q) Jung, M. E.; Lowe, J. A., III. Lyster, M. A.; Node, M.; Pfluger, R. W.; Brown, R. W. *Tetrahedron* **1984**, 40, 4751. (r) Parker, K. A.; Tallman, E. A. *Tetrahedron* **1984**, 40, 4781. (s) Rao, A. V. R.; Mehendale, A. R.; Reddy, K. B. *Ind. J. Chem.* **1984**, 23B, 1154. (t) Uemura, M.; Take, K.; Isobe, K.; Minami, T.; Hayashi, Y. *Tetrahedron* **1985**, 41, 5771. (u) Abdallah, A. A.; Gesson, J. P.; Jacquesy, J. C.; Mondon, M. *Bull. Soc. Chim. Fr.* **1986**, 93. (v) Naruta, Y.; Mishigaichi, Y.; Maruyama, K. *Chem. Lett.* **1986**, 1703. (w) Tamura, Y.; Akai, S.; Kishimoto, H.; Kiriwara, M.; Sasho, M.; Kita, Y. *Tetrahedron Lett.* **1987**, 28, 4583. For syntheses of the related 11-deoxydaunomycinone, see: (x) Kende, A. S.; Boettger, S. D. *J. Org. Chem.* **1981**, 46, 2799. (y) Vedejs, E.; Miller, W. H.; Pribish, J. R. *J. Org. Chem.* **1983**, 48, 3611. (z) Krohn, K.; Sarstedt, B. *Angew. Chem., Int. Ed. Engl.* **1983**, 22, 875. For syntheses of other 11-deoxyanthracyclines see ref 3.

(5) For reviews on the chemistry of carbene complexes, see: (a) Dötz, K. H.; Fischer, H.; Hofmann, P.; Kreissel, F. R.; Schubert, U.; Weiss, K. *Transition Metal Carbene Complexes*; Verlag Chemie: Deerfield Beach, FL, 1984. (b) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, 23, 587. (c) Wulff, W. D.; Tang, P. C.; Chan, K. S.; McCallum, J. S.; Yang, D. C.; Gilbertson, S. R. *Tetrahedron* **1985**, 41, 5813. (d) Dötz, K. H.; Popall, M.; Müller, G. *J. Organomet. Chem.* **1987**, 334, 57. (e) Wulff, W. D. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press Inc.: Greenwich, CN, 1988; Vol. 1.

(6) Wulff, W. D.; Tang, P. C. *J. Am. Chem. Soc.* **1984**, 106, 434.

(7) For other studies concerning the applications of chromium carbene complexes in anthracycline synthesis see ref 5c,d,e and the following: (a) Dötz, K. H.; Popall, M. *J. Organomet. Chem.* **1985**, 291, C1. (b) Dötz, K. H.; Popall, M. *Tetrahedron* **1985**, 41, 5797. (c) Subsequent to the reviewing process, related work involving the synthesis of an 11-deoxydaunomycinone intermediate from complex 1 was reported: Dötz, K. H.; Popall, M. *Angew. Chem., Int. Ed. Engl.* **1987**, 26, 1158.

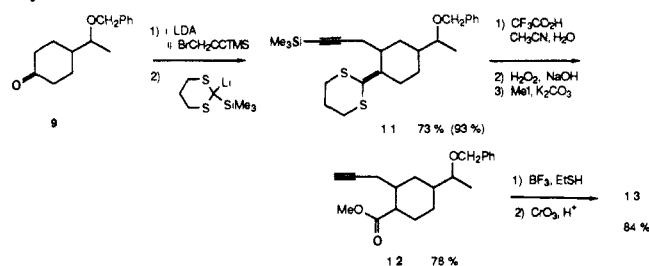
(8) This work was presented at the 194th National Meeting of the American Chemical Society, August 3-September 4, 1987, New Orleans, LA, Abstract 251.

(9) Chan, K. S.; Peterson, G. A.; Brandvold, T. A.; Faron, K. L.; Challener, C. A.; Hyldahl, C.; Wulff, W. D. *J. Organomet. Chem.* **1987**, 334, 9.

(10) (a) Yamashita, A.; Toy, A. *Tetrahedron Lett.* **1986**, 27, 3471. (b) Dötz, K. H.; Muhlemeister, J.; Schubert, U.; Orama, O. *J. Organomet. Chem.* **1983**, 247, 187. (c) Wulff, W. D.; Tang, P. C.; McCallum, J. S. *J. Am. Chem. Soc.* **1981**, 103, 7677.

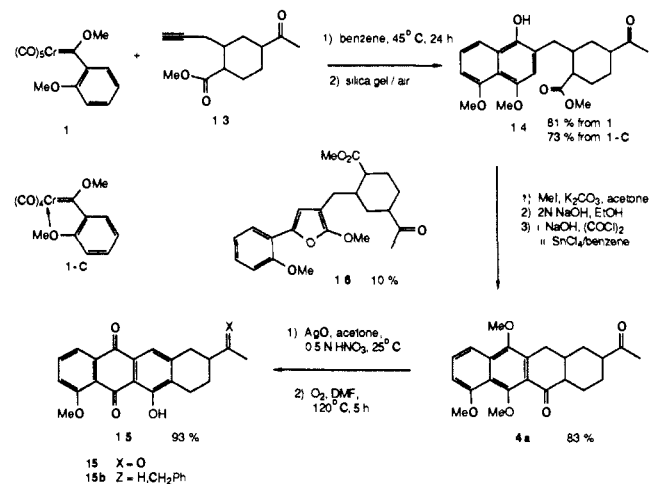
dized in air to the free naphthol with concomitant formation of a flocculent green precipitate presumably due to Cr^{III}. The plan is to expose the solution of the crude reaction mixture containing **3** to air for a few minutes, and then treating the resulting uncomplexed naphthol with trifluoroacetic acid to initiate the Friedel–Crafts cyclization leading to the tetracyclic intermediate **4**.

The preparation of the acetylenes necessary for the synthesis of 11-deoxydaunomycinone was achieved from the cyclohexanone derivative **9** which can be obtained from 2-methoxybutadiene and methyl vinyl ketone in 84% yield.^{11a} The propargyl group can be introduced in 81% yield by alkylation with trimethylsilyl-propargyl bromide,¹² and the resulting ketone **9d** homologated in the Peterson reaction with 1-lithio-1-trimethylsilyl-1,3-dithiane¹³ in 90% yield. The ketene thioacetal **11** is available in 73% yield from **9** and in 93% yield from **9** based on unrecovered starting material for each step. Ketene thioacetals have been hydrolyzed with mercuric oxide;¹⁴ however, the alkyne functionality in **11** was incompatible with this method. It was found that after initial acid hydrolysis of the ketene thioacetal,¹⁵ the base hydrolysis of the crude mixture containing the *S*-thioester¹⁶ could be facilitated by oxidation with hydrogen peroxide¹⁷ and that the resulting acid could be esterified to give the methyl ester **12** in 76% overall yield from **11**. This procedure liberated the unprotected terminal acetylene, and the final steps in the synthesis include cleavage of the benzyl ether¹⁸ and oxidation of the resultant secondary alcohol to give acetylene **13** in 49% overall yield from methyl vinyl ketone. The carbene complex **1** can be prepared in a single step from chromium hexacarbonyl in 80% yield and can be obtained in an open-ended scale since this complex is most easily purified by crystallization.^{5c,19}



The synthesis of 11-deoxydaunomycinone was first attempted with the construction of the tetracyclic carbon skeleton in two steps. Initial attempts at the one-pot double cyclization failed in a model system^{5c,9} which was attributed to the incompatibility of THF to the Friedel–Crafts reaction. The benzannulation of chromium carbene complexes had been reported to be effective only in ethereal solvents; however, these initial failures in the one-pot double cyclization prompted us to become involved in the examination of the effect of solvent on the benzannulation reaction, initially to find solvents that would be compatible with both the

Scheme II



benzannulation and Friedel–Crafts reaction and later in the role of solvent on the product distribution.^{5c,9} It was found that nonpolar solvents such as hexane and benzene gave the highest selectivity for the benzannulated product from the reaction of carbene complexes and acetylenes.⁹ The benzannulation of the carbene complex **1** with the fully functionalized acetylene **13** proceeded in benzene to give, after purification on silica gel in the presence of air, the naphthol **14** as a single regioisomer in 81% yield along with a small amount of the furan **16**.²⁰ The efficiency of the annulation is not significantly different whether the pentacarbonyl complex **1** or the internally chelated tetracarbonyl complex **1-c**^{5c,21} is employed in the reaction. The closure of the C-ring was affected by a Friedel–Crafts cyclization of the acid chloride induced by tin tetrachloride after the phenol functionality was protected to give the tetracyclic intermediate **4a** in 83% yield. Oxidative demethylation with silver oxide and oxidation of the C-ring with molecular oxygen⁴¹ afforded a 93% yield of the anthracyclinone intermediate **15** (31% from MVK) which was found to have ¹H NMR, mass and infrared spectra, and melting point (mixed) identical with those of an authentic sample kindly provided by Professor F. Hauser. This completes a formal synthesis of 11-deoxydaunomycinone which has been prepared from **15** in four steps in 45% yield by Professor F. Johnson.^{4d}

The one-pot synthesis of **15b** via the benzyl-protected derivative **4b** could only be optimized to an overall 14% yield from the *tert*-butyl ester **17b**. After this initial discouraging result, it was therefore satisfying to find that the one-pot synthesis with the acetylene **17c** bearing the unprotected aceto group was successful. The acetylene **17c**^{11b} (1.3 equiv) and the complex **1** were heated under an inert atmosphere as a 0.2 M solution in benzene at 75°C for 12 h and then cooled to room temperature and opened to air for 10 min. The reaction mixture was diluted twofold with trifluoroacetic anhydride, treated with a catalytic amount of sodium acetate, stirred for 15 min, and then diluted with an equal volume of trifluoroacetic acid to induce cleavage of the *tert*-butyl ester and initiate the electrophilic ring closure which was complete in 90 min, and finally this was followed with a basic workup to provide a 56% yield of the unprotected naphthol **4c** which was directly oxidized in a manner similar to **4a** to the 11-deoxydaunomycinone intermediate **15** in 42% overall yield from **17c**. More efficiently, if intermediate **4c** is not purified by SGC, but rather oxidized directly, **15** can be obtained in 61% overall yield from **17c**.

Applications of this one-pot benzannulation/Friedel–Crafts double cyclization to the syntheses of other 11-deoxyanthracyclinones and to other polycyclic aromatic antitumor antibiotics will be reported in due course.

(11) (a) The Diels–Alder reaction of methyl vinyl ketone and 2-methoxybutadiene was carried out at 150°C for 5 h to give adduct **9a**. The crude mixture containing **9a** was reduced with sodium borohydride to the corresponding alcohol **9b**, and upon hydrolysis the keto alcohol **9c** was isolated in an overall 95% yield. The benzyl group is put on with sodium hydride and benzyl bromide after the ketone is first protected with ethylene glycol. Final cleavage of the acetal gives **9** in 84% yield from methyl vinyl ketone. (b) The *tert*-butyl ester **17c** was prepared from the methyl ester **13** in 56% overall yield by first base hydrolysis to the acid and then treatment with thionyl chloride/*tert*-butyl alcohol.

(12) Miller, R. B. *Synth. Commun.* **1972**, *2*, 267.

(13) (a) Jones, P. F.; Lappert, M. F. *J. Chem. Soc., Chem. Commun.* **1972**, 526. (b) Carey, F. A.; Court, A. S. *J. Org. Chem.* **1972**, *37*, 1926. (c) Seebach, D.; Gröbel, B. T.; Beck, A. K.; Braun, M.; Geiss, K. H. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 443. (d) Seebach, D.; Kolb, M.; Gröbel, B. T. *Chem. Ber.* **1973**, *106*, 2277.

(14) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 5829.

(15) Seebach, D.; Bürstinghaus, R. *Synthesis* **1975**, 461.

(16) Marshall, J. A.; Belletire, J. L. *Tetrahedron Lett.* **1971**, 871.

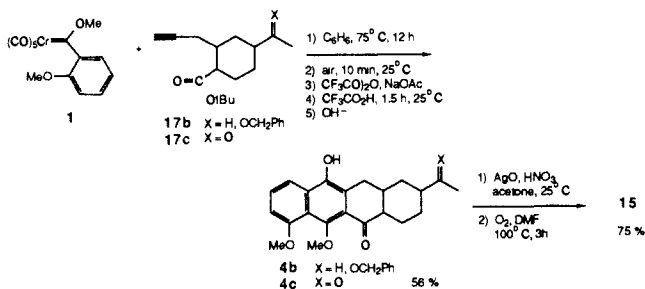
(17) Wulff, W. D.; Tang, P. C., unpublished results.

(18) Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E. *J. Org. Chem.* **1979**, *44*, 1661.

(19) Fischer, E. O.; Kreiter, C. G.; Kollmeier, H. J.; Müller, J.; Fischer, R. D. *J. Organomet. Chem.* **1971**, *28*, 237.

(20) (a) Wulff, W. D.; Gilbertson, S. R.; Springer, J. P. *J. Am. Chem. Soc.* **1986**, *108*, 520. (b) Dötz, K. H. *J. Organomet. Chem.* **1977**, *140*, 177.

(21) Dötz, K. H.; Sturm, W.; Popall, M.; Riede, J. *J. Organomet. Chem.* **1984**, *277*, 267.



Acknowledgment. This work was supported by the National Cancer Institute (CA-32974). Pressure Chemical Company is acknowledged for material support. The NMR instruments used were funded in part by the NSF Chemical Instrumentation Program and by the NCI via the University of Chicago Cancer Research Center (CA-14599).

Supplementary Material Available: Spectral and physical data for 4a, 9, 9a-d, 12-14, 14a, 15, 15a,b, 16, and 17b,c (5 pages). Ordering information is given on any current masthead page.

Transition Structures for the Claisen Rearrangement

Robert L. Vance* and Nelson G. Rondan*

Central Research Department, Dow Chemical Company, Midland, Michigan 48640

K. N. Houk* and Frank Jensen

Department of Chemistry and Biochemistry
University of California, Los Angeles
Los Angeles, California 90024

Weston Thatcher Borden*

Department of Chemistry, University of Washington
Seattle, Washington 98195

Andrew Komornicki

Polyatomics Research Institute, 1101 San Antonio Road, Suite 420, Mountain View, California 94043

Erich Wimmer

Cray Research Inc., 1333 Northland Drive
Mendota Heights, Minnesota 55120

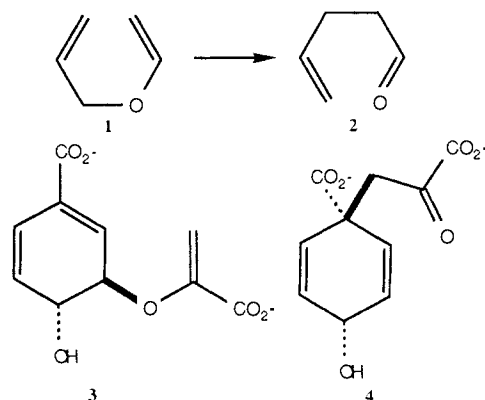
Received August 13, 1987

The Claisen rearrangement of allyl enol ethers (**1** → **2**) is a [3,3]-sigmatropic shift that is extremely valuable in synthesis.¹ The enzyme-catalyzed rearrangement of chorismate, **3** to prephenate, **4**, has caused this reaction also to be of considerable interest in bioorganic circles.² Much effort has been invested in the creation of chorismate mutase inhibitors designed to be transition state analogues for the [3,3]-sigmatropic shift.³

(1) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1. Bennett, G. B. *Synthesis* **1977**, 589. Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. Bartlett, P. A. *Tetrahedron* **1980**, *36*, 1.

(2) Ganem, B. *Tetrahedron* **1978**, *34*, 3353. Haslam, E. *The Shikimic Acid Pathway*; Halstead Press: Wiley: New York, NY, 1974. Andrews, P. R.; Cain, E. N.; Rizzardo, E.; Smith, G. D. *Biochemistry* **1977**, *16*, 4848. Chao, H. S. I.; Berchtold, G. A. *Biochemistry* **1982**, *21*, 2778. Christopherson, R. I.; Heyde, E.; Morrison, J. F. *Biochemistry* **1983**, *22*, 1650. Sogo, S.; Widlanski, T. S.; Hoare, J. H.; Grimshaw, C. E.; Berchtold, G. A.; Knowles, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 2701 and references cited therein.

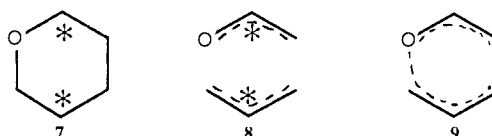
(3) Bartlett, P. A.; Johnson, C. R. *J. Am. Chem. Soc.* **1985**, *107*, 7792 and references therein.



The stereoselectivities observed for reactions of substituted molecules have led to the deduction that the transition structure for this transformation is chairlike, **5**, rather than boatlike, **6**.⁴



The same chair stereochemistry has been deduced for the enzymatic process.⁵ The extent of bond making and bond breaking has been controversial. At one extreme, the reaction might occur in two stages, via diradical or zwitterionic species, **7** or **8** (* denotes charge or an unpaired electron). Intermediate **7** is the result of CC bond making before CO bond breaking. This sequence of events is predicted by semiempirical quantum mechanical calculations.⁶ On the other hand, greater balance between CC bond making and CO bond breaking, to give the "aromatic transition state", **9**, has been deduced from secondary isotope effects⁷ and substituent effects on rates.⁸ Substituent effects also suggest that there is some charge separation in the transition states of reactions of substituted derivatives.⁸



We have performed ab initio quantum mechanical calculations to define the geometries and electronic characteristics of the chair and boat transition structures for the parent reaction. Our initial studies used the 3-21G, 4-31G, and 6-31G* basis sets.^{9,10} Geometries were optimized at the RHF level, and energies, including electron correlation, were calculated at the MP2/6-31G* level.¹⁰ MCSCF studies of the related Cope rearrangement have shown that RHF/3-21G geometries are similar to those obtained at adequate MCSCF levels.¹¹ Of course, a stable true diradical will

(4) Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67. Vittorelli, P.; Winkler, T.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 1457. Hansen, H.-J.; Schmid, H. *Tetrahedron* **1974**, *30*, 1959.

(5) Addadi, L.; Jaffe, E. K.; Knowles, J. R. *Biochemistry* **1983**, *22*, 4494.

(6) Dewar, M. J. S.; Healy, E. F. *J. Am. Chem. Soc.* **1984**, *106*, 7127.

(7) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**, *101*, 2727 and references cited therein.

(8) (a) Wilcox, C. S.; Babston, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 6636. (b) Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 1160. (c) Gajewski, J. J.; Jurayi, J.; Kimbrough, D. R.; Gande, M. E.; Ganem, B.; Carpenter, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 1170.

(9) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley and Sons: New York, NY, 1986; pp 466-504.

(10) Programs used were GAUSSIAN 82 (Binkley, J. S.; Whiteside, R.; Krishnan, R.; Seeger, R.; DeFrees, D. J.; Schlegel, H. B.; Topiol, S.; Kahn, L. R.; Pople, J. A. GAUSSIAN 82, Carnegie-Mellon University, Pittsburgh, PA) and GRADSCF (Komornicki, A. Polyatomics Research Institute, Mountain View, CA).