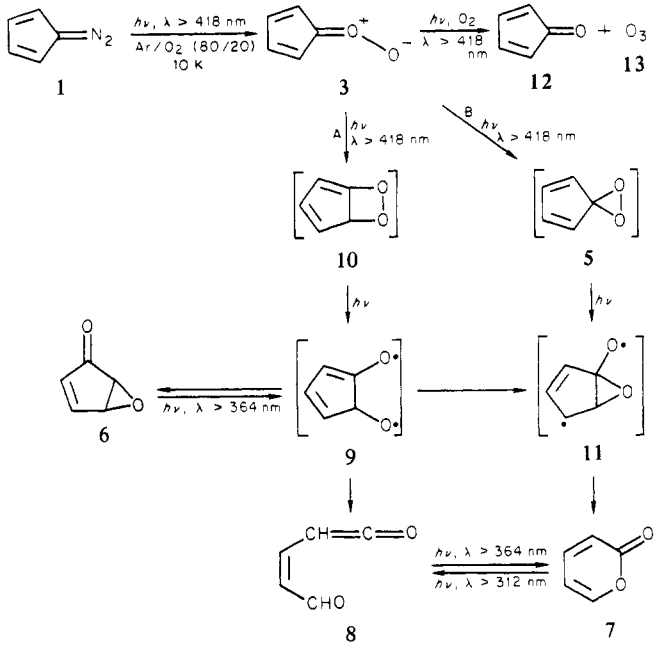
these bands to the O–O stretch in the carbonyl oxide **3**. It is significant that this stretching frequency comes approximately midway between carbon–oxygen double- (~1700 cm^{-1}) and single-bond (~1150 cm^{-1}) frequencies. The corresponding band in ozone comes at 1110 cm^{-1}.[13] When $^{18}O_2$ (99% double label) is used in the matrix, new bands at 1383 and 1373 cm^{-1} are observed. Both bands show intensity perturbations and are shifted. When a mixture of unlabeled oxygen and $^{18}O_2$ (99% double label) is used, four bands (1395, 1385, 1383, and 1373 cm^{-1}) are observed. These experiments show that both the 1395 and 1385 cm^{-1} bands are due to a carbon–oxygen bond.

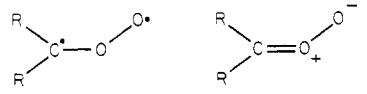
The photochemistry of the oxygen-trapped product is also explicable in terms of the carbonyl oxide **3**. Irradiation ($\lambda > 418$ nm) of the oxygen-trapped product partitions it between two reaction pathways. The first pathway involves reaction with oxygen giving cyclopentadienone (**12**)[14] and ozone (**13**).[15] The second pathway involves rearrangement to cyclopentadienone oxide (**6**), α-pyrone (**7**), and the aldehyde ene ketene **8**. It is probable



that this rearrangement proceeds via the diradical **9**, which partitions between the observed products **6**–**8**. Identification of α-pyrone (**7**) and the aldehyde ene ketene **8** was based on comparison of infrared spectra with the authentic materials matrix isolated in argon[16] and on the previously described photochemical interconversion of **7** and **8**.[16] Photoisomerization of α-pyrone to the Corey–Streith β-lactone[17] provided confirmation of the identification. The epoxide **6** was synthesized independently and identified by comparison of the infrared spectrum with that of the authentic substance matrix isolated in argon.[18] Irradiation ($\lambda > 364$ nm) of cyclopentadienone epoxide (**6**) matrix isolated in argon gave α-pyrone (**7**) and the aldehyde ene ketene **8**. The photoisomerization of substituted cyclopentadienone oxides to pyrones has been described previously.[19]

Several reaction paths leading from the carbonyl oxide **2** to the diradical **9** may be considered, and two (A and B) are shown. Path A involves an eight-electron electrocyclic process to the dioxetane **10**. Cleavage of the peroxide bond would then give **9**. Path B involves a four-electron electrocyclic reaction giving the dioxirane **5**, which on cleavage of the peroxide bond could rearrange to **9** via **11**. Two arguments can be made that favor path A over path B. First, evidence is available that substituted diradicals related to **9** rearrange to pyrones via substituted derivatives of **11**,[19] but no evidence of the reverse process has been reported. Second, in orbital-symmetry-controlled pericyclic reactions, the more delocalized transition state is usually preferred.[20]

A final comment on the structure of the carbonyl oxide **3** is in order. Calculations on the simplest carbonyl oxide suggest that it is best described as the singlet diradical structure **14a** (R = H).[21]



14a 14b

Addition of methyl groups stabilizes the carbonyl oxide relative to the singlet diradical structure, so that in the dimethyl compound **14** ($R = CH_3$) the singlet diradical structure **14a** ($R = CH_3$) is degenerate with the carbonyl oxide structure **14b** ($R = CH_3$).[21] The carbonyl oxide derived from cyclopentadienylidene is further stabilized by resonance (**3a,b**) and hence is properly described by the zwitterionic structure.

Acknowledgment. This research was supported by Grant CHE81-11196 from the National Science Foundation and Grant GM24427 from the National Institute of General Medical Science, National Institutes of Health.

Registry No. 1, 1192-27-4; **3**, 88766-67-0; **4**, 4727-22-4; **6**, 68781-88-4; **7**, 504-31-4; **8**, 39763-18-3; **12**, 13177-38-3; 1,3-cyclopentadiene, 542-92-7; 5,5-dimethyl-1,3-cyclopentadiene, 4125-18-2.

(13) Wilson, M. K.; Badger, R. M. *J. Chem. Phys.* **1948**, *16*, 741–742.
(14) Chapman, O. L.; McIntosh, C. L. *J. Chem. Soc. D* **1971**, 770–771. Abelt, C. J.; Chapman, O. L. unpublished observations. The argon matrix IR spectrum is identical with that of authentic cyclopentadienone in argon.
(15) Identified by comparison of the infrared spectrum with that of an authentic sample matrix isolated in an argon/oxygen matrix.
(16) Pong, R. G. S.; Shirk, J. S. *J. Am. Chem. Soc.* **1973**, *95*, 248–249. Chapman, O. L.; McIntosh, C. L.; Pacansky, J. *Ibid.* **1973**, *95*, 244–246.
(17) Corey, E. J.; Streith, J. *J. Am. Chem. Soc.* **1964**, *86*, 950–951. Chapman, O. L.; McIntosh, C. L.; Pacansky, J. *Ibid.* **1973**, *95*, 614–617.
(18) Chapman, O. L.; Hess, T. C. *J. Org. Chem.* **1979**, *44*, 962–964.
(19) For example, see: Padwa, A.; Hartman, R. *J. Am. Chem. Soc.* **1966**, *88*, 1518–1524. Ishibe, N.; Sunami, M.; Odani, H. *Ibid.* **1975**, *95*, 463–468.
(20) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie: Weinheim/Bergstr., 1970.
(21) Harding, L. B.; Goddard, W. A., III. *J. Am. Chem. Soc.* **1978**, *100*, 7180–7188. Wadt, W. R.; Goddard, W. A., III. *Ibid.* **1975**, *97*, 3004–3021.

On the Mechanism of the Triphenylphosphine–Azodicarboxylate (Mitsunobu Reaction) Esterification

Waldemar Adam,* Nozomu Narita, and Yoshinori Nishizawa†

Institute of Organic Chemistry, University of Würzburg D-8700 Würzburg, West Germany

Received August 4, 1983
Revised Manuscript Received January 12, 1984

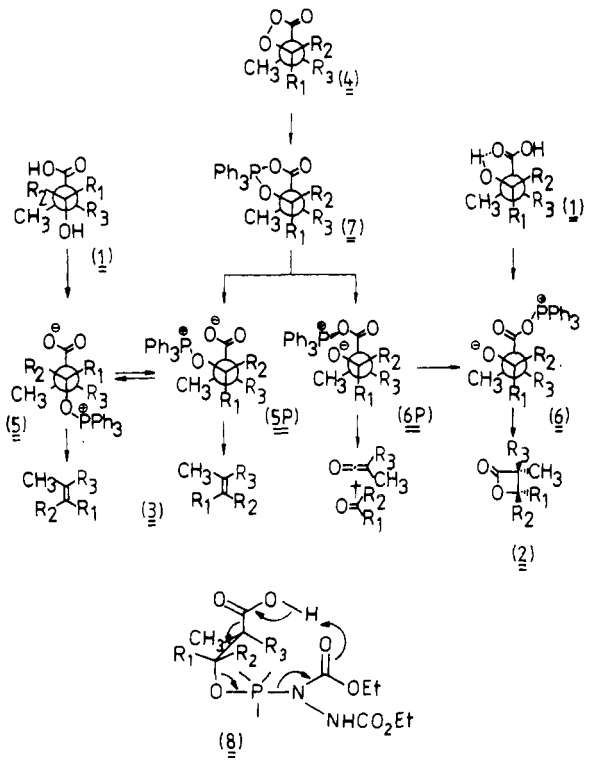
In the Mitsunobu reaction[1] of β-hydroxy acids **1** β-lactones **2** and/or alkenes **3** are formed, depending on the activation of hydroxy (HGA) vs. carboxy (CGA) groups.[2] These products are also obtained in the reaction of β-peroxy lactones **4** with phosphines (Scheme I).[3] The dipolar ions **5** and **6** are postulated as intermediates in the HGA and CGA routes of the acids **1**. Such intermediates presumably also intervene in the β-peroxy lactone–phosphine reaction, except that here biphilic insertion leads first to phosphorane **7**, which fragments to give **5** and **6**. However, in view of recent evidence,[4] the phosphorane **8** has been suggested[5] as precursor to the alkene products in the Mitsunobu reaction.

The latter interpretation cannot account for alkene formation from the β-peroxy lactones **4**. Thus, the β-peroxy lactone–

† Alexander von Humboldt postdoctoral fellowship, 1981–1983.
(1) Mitsunobu, O. *Synthesis* **1981**, 1.
(2) (a) Mulzer, J.; Pointner, A.; Chucholowski, A.; Brüntrup, G. *J. Chem. Soc., Chem. Commun.* **1979**, 52. (b) Mulzer, J.; Brüntrup, G.; Chucholowski, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 622.
(3) Adam, W.; Ramirez, R. J.; Tsai, S.-C. *J. Am. Chem. Soc.* **1969**, *91*, 1254.
(4) Grochowski, E.; Hilton, B. D.; Kupper, R. J.; Michejda, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 6876.
(5) Mulzer, J.; Lammer, D. O. *Angew. Chem. Suppl.* **1983**, 887.

0002-7863/84/1506-1843$01.50/0

Scheme I



a, $R_1 = R_2 = R_3 = CH_3$
b, $R_1 = PhCH_2$; $R_2 = Ph$; $R_3 = H$
c, $R_1 = Ph$; $R_2 = PhCH_2$; $R_3 = H$

phosphine reaction provides a potential tool to probe whether the dipolar intermediates **5** and **6** (a) intervene, (b) undergo characteristic transformations, and (c) interconvert through phosphorane **7** by comparing product distributions and stereochemistry. To this end we investigated the Mitsunobu reaction of **1a–c**, respectively 3-hydroxy-2,2,3-trimethylbutyric acid and *erythro*- and threo-3,4-diphenyl-3-hydroxy-2-methylbutyric acid, and the triphenylphosphine deoxygenation of the corresponding **4a–c**.[6] In view of the established stereochemistry of the Mitsunobu reaction of α,β-disubstituted β-hydroxy acids,[2,5] it is most unfortunate that stereomeric pairs of α,β-disubstituted β-peroxy lactones (as contrasted to trisubstituted pairs) could so far not be prepared.

The results for **1a** and **4a** are summarized in Table I. Clearly, in acetonitrile the product distributions are quite distinct. In the Mitsunobu process of **1a** cyclization takes place predominantly to **2a**, while in the deoxygenation **4a** fragments mainly to **3a**. Since solvent polarity influences appreciably the degree of HGA vs. CGA (Table I), the possibility had to be excluded that the different reaction conditions could be responsible for the distinct product distributions. For this purpose the Mitsunobu reaction of **1a** was run in the spent solution of the **4a** deoxygenation and vice versa. Such medium effects cause only minor changes in the product distributions (Table I).

The product distribution and stereochemical course, employing **1b,c** and the corresponding **4b,c**, provide mechanistic fingerprints (Table I). Thus, in both processes retained **2** are formed, which implies that the same dipole **6** serves as precursor. However, in the Mitsunobu reaction of **1b,c**, **2b,c** are formed exclusively, while in the deoxygenation of **4b,c** benzyl phenyl ketone is the main product. Steric encumbrance and internal hydrogen bonding in **1** presumably oblige attachment of the Ph_3P moiety at the carboxylate group anti to the hydroxy group. This charge-remote dipole **6** is optimally alligned for the formation of retained **2**. On biphilic insertion of Ph_3P into **4** necessarily a charge-proximate dipole **6P** is produced by ring opening of the phosphorane **7**. Most of **6P** fragments into ketone and ketene, but an appreciable fraction cyclizes into retained **2** via **6**. Rotation of **6P** into its conformer **6** is essential because β-lactonization is encumbered by the large Ph_3P group.

Table I. Product Distribution of the Mitsunobu Reaction[a] of β-Hydroxy Acids **1** and Deoxygenation Reaction[b] of β-Peroxy Lactones **4**

substrate	conditions	product yields, %[c,d] β-lactones (**2**)	alkenes (**3**)	ketone
1a[d]	CH_3CN	91	9	
	m-xylene	44	56	
	m-xylene[f]	38	62	
4a[d]	CH_3CN	12	88	
	m-xylene	3	97	
	m-xylene[g]	3	97	
1b[e]	CD_3CN	trace (c), 100 (b)		
	CD_3CN/C_6D_6[h]	2 (c), 98 (b)		
1c[e]	CD_3CN	100 (c), trace (b)		
	CD_3CN/C_6D_6[h]	100 (c), trace (b)		
4b[e]	CD_3CN	25 (b)	20 (c), 8 (b)	47
	CD_3CN/C_6D_6[h]	27 (b)	10 (c), 8 (b)	55
	C_6D_6	28 (b)	3 (c), 10 (b)	59
4c[e]	CD_3CN	22 (c)	1 (c), 21 (b)	56
	CD_3CN/C_6D_6[h]	16 (c)	6 (c), 18 (b)	60
	C_6D_6	18 (c)	9 (c), 8 (b)	65

[a] Run with ethyl or methyl azocarboxylate at 20 °C. [b] Run with triphenylphosphine at 20 °C. [c] Relative yields; product balance in the case of β-lactones **2**, alkenes **3**, and ketones greater than 80% and for triphenylphosphine oxide over 95%. [d] Quantitative yields of products were determined by GC using a 4-m glass column packed with 5% FFAP; ca. ±2% error of listed values; averaged over at least three independent determinations. [e] Quantitative yields of products were determined by 400-MHz ^1H NMR; ca. 2% error of listed value; averaged over at least two independent determinations. [f] Run in the reaction mixture after deoxygenation of **4a**. [g] Run in the reaction mixture after Mitsunobu reaction of **1a**. [h] Solvent mixture consisting of 17% CD_3CN and 83% C_6D_6.

An additional competing process in the deoxygenation of **4b,c** is formation of alkene **3**. Unfortunately, in the Mitsunobu reaction of the corresponding β-hydroxy acids **1b,c** no alkenes **3** are produced. Presumably sterically demanding β-substituents promote the CGA over the HGA course.[2] While such alkenes are formed in the Mitsunobu reaction of the tetrasubstituted **1a**, in fact as major product (Table I), the lack of stereochemical information precludes detailed mechanistic analysis with this substrate, although clearly HGA must be involved.

For the present purposes, the formation of alkenes **3b,c** from β-peroxy lactones **4b,c** reveals some important mechanistic features. In acetonitrile predominantly inverted **3** is produced (Table I). Thus, the HGA-type dipole **5P** is the logical precursor to **3b,c**. Decarboxylation of the initially formed dipole **5P** leads to retained **3**, i.e., **4b** → **3b** and **4c** → **4c**, while the dipole **5** affords inverted **3**, i.e., **4b** → **3c** and **4c** → **3b**. The polar acetonitrile promotes charge separation and thereby enhances formation of inverted **3** via the preferred conformer **5**.

With respect to partitioning of the phosphorane **7** into HGA-type dipole **5P** (precursor to **3**) vs. CGA-type dipole **6P** (precursor to **2** and ketone), it is surprising that the latter path predominates. Clearly, dipole **5P** is energetically more stable than **6P** and alkene **3** formation should be preferred. Furthermore, in the trigonal-bipyramidal phosphorane **7** the more electronegative carboxy moiety should occupy an apical and the alkoxy moiety then necessarily an equatorial position.[7] Since departure of the leaving

(6) For the preparation of the β-peroxy lactones **4b,c**, cf.: Adam. W.; Rojas, C. I. *Synthesis* **1972**, 616. **4a** cf.: Adam, W.; Cueto, O.; Guedes, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 2106.

(7) (a) Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70. (b) Ramirez, F. *Ibid.* **1968**, *1*, 168. (c) Hudson, R. F.; Brown, C. *Ibid.* **1972**, *5*, 204. (d) Bentrude, W. G. *Ibid.* **1982**, *15*, 117. (e) Corriu, R. J. P.; Lanneau, G. F.; Leclercq, D. *Tetrahedron Lett.* **1983**, *24*, 4323.

group is preferred from the apical site, we postulate that formation of dipole **5P** should also be kinetically preferred.

The mechanistic significance of the present study is that (a) the HGA-type and CGA-type dipoles **5** and **6** do lead to characteristic chemical transformations and (b) such intermediates do not interconvert via phosphorane **7**.

Acknowledgments are made to the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and the Humboldt Foundation for financial support.

Registry No. 1a, 594-88-7; **1b**, 40157-11-7; **1c**, 40157-10-6; **2a**, 10008-69-2; **2b**, 35947-72-9; **2c**, 35947-73-0; **3a**, 563-79-1; **3b**, 24274-73-5; **3c**, 35947-82-1; **4a**, 23438-10-0; **4b**, 35394-04-8; **4c**, 35394-03-7; ethyl azocarboxylate, 1972-28-7; methyl azocarboxylate, 2446-84-6; triphenylphosphine, 603-35-0; acetone, 67-64-1; 1,2-diphenylethanone, 451-40-1.

[(4 + 2) + (3 + 2)] Route to Multiply Fused Ring Systems: A New Notion in Polycycle Construction

Alan P. Kozikowski,*† Kunikazu Hiraga,†
James P. Springer,‡ B. C. Wang,§ and Zhang-Bao Xu§

Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260
Merck Institute
Rahway, New Jersey 07065
Veterans Administration Medical Center
Pittsburgh, Pennsylvania 15260

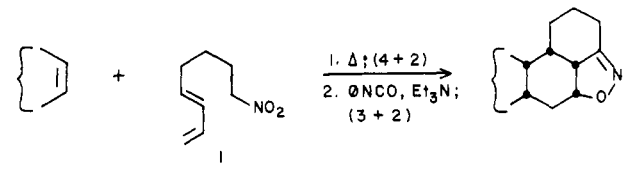
Received October 11, 1983

The construction of multiply fused carbocyclic systems has long commanded the attention of synthetic organic chemists. One need only trace the lengthy history associated with the production of steroids and steroid-like compounds to realize the veracity of such a statement. The primary ring-forming methodologies that have emerged as a consequence of the steroid efforts consist of (a) Friedel–Crafts type acylation reactions, (b) the Dieckmann condensation, (c) the Robinson annelation process, and (d) the Diels–Alder reaction.[1] Of course, these same methods have been used in generating the ring skeleton of non-steroid products as well.

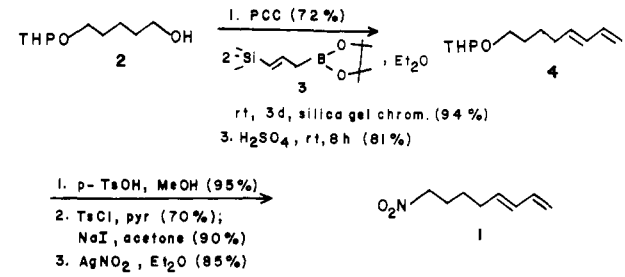
We would now like to introduce a new notion into the area of carbocycle synthesis, a notion that as diagrammed in Scheme I provides the chemist with a method for annealing three new rings (one being a heterocycle) to an existing ring structure so as to produce a tetracycle possessing five new precisely defined centers of asymmetry. The stereochemistry of the (4 + 2) cycloaddition process is controlled, of course, by secondary orbital interactions (Alder endo rule)[2] while that of the (3 + 2) reaction would seemingly be guided by the tendency to minimize nonbonded interactions in the transition state; i.e., the nitro group derived nitrile oxide would add to that face of the olefin that bears the nitrobutyl chain.[3] The isoxazoline ring generated in this process does further provide a versatile and easily manipulable functional array.[4]

The realization of the concept displayed in Scheme I requires only that we be able to prepare the nitro diene **1** in some reasonable manner. We have at present been able to generate the stereochemically pure (>97% by ^{1}H NMR analysis) (*E*)-diene **4** by reaction of Matteson's allyl boronate reagent **3**[5] with the aldehyde

Scheme I



Scheme II



prepared by oxidation of the mono-THP ether **2** of 1,5-pentanediol. The THP group of **4** is then cleaved and the hydroxyl group transformed to nitro by the three-step sequence shown (Scheme II).

To test the capability of this new diene for effecting the triannelation sequence, we studied its chemistry using first *p*-benzoquinone as the dienophile. The Diels–Alder reaction proceeded at 110 °C in toluene to provide **5** as an unstable oil. Since this intermediate was found to tautomerize on silica gel chromatography giving rise to **6a**, **5** was directly acetylated, and the dipolar cycloaddition reaction was then carried out. The crystalline tetracycle **7** (mp 109–110 °C, ethyl acetate–hexanes) was formed in high yield. In order to prevent the foregoing tautomerization process, the reaction of **1** with carbomethoxy-*p*-benzoquinone[6] was studied next. The primary Diels–Alder product formed in this case was found to undergo epimerization at C-5 during silica gel chromatography (trans/cis isomer ratio 95:5). Intermediate **8** provides an interesting substrate for the intramolecular nitrile oxide cycloaddition (INOC) reaction since it offers two very different sites for capture of the nitrile oxide. In the event, exposure of **8** to *p*-chlorophenyl isocyanate provided solely the bridged structure **9** (mp 147–148.5 °C, ethyl acetate–hexanes). The formation of an eight-membered ring in preference to a less strained six-membered ring presumably reflects the heightened reactivity of the C_2–C_3 double bond (i.e., the increased π-electron polarizability of the multiple bond).[7] The unexpected course of this cycloaddition reaction is not without some interest, especially if one recognizes the skeletal relationship of **9** to the taxanes.[8]

To steer the INOC reaction in the direction of the angularly fused system, removal of the more reactive double bond was required. Compound **8** was exposed to L-Selectride (Aldrich) and then the dipolar cycloaddition process carried out. The tetracycle **10** (mp 234–236 °C, ethyl acetate–hexanes) was thus formed in good overall yield. This particular synthesis of an angularly fused ring system holds considerable potential for the development of a unique route to the antileukemic principles, the quassinoids,[9] for the isoxazoline ring could be turned into the required δ-lactone subunit present in these natural products in a fairly straightforward fashion (Scheme III).

The assignment of stereochemistry to all of the products described in this paper was made on the basis of extensive ^{1}H NMR spin–spin decoupling experiments. Since some of the coupling constants observed were slightly larger than one normally finds in related six-membered ring fused compounds[10] (see ref 11), a

† University of Pittsburgh.
‡ Merck Institute.
§ Veterans Administration Medical Center.

(1) Akhrem, A. A.; Titov, Yu. A. "Total Steroid Synthesis"; Plenum Press: New York, 1970.
(2) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 16.
(3) For an example of such stereocontrol in the formation of a seven-membered ring, see: Kozikowski, A. P.; Mugrage, B. B. *Tetrahedron Lett.* **1983**, *24*, 3705.
(4) Kozikowski, A. P. *Acc. Chem. Res.*, submitted for publication.
(5) Tsai, D. J. S.; Matteson, D. S. *Tetrahedron Lett.* **1981**, *22*, 2751.
(6) Goldsmith, D. J.; Srouji, G.; Kwong, C. *J. Org. Chem.* **1978**, *43*, 3182. The reaction of carbomethoxy-*p*-benzoquinone with 1-vinylcyclohexene provides a less functionalized analogue of **10**: Orsini, F.; Pelizzoni, F.; Pitea, D.; Abbondanti, E; Mugnoli, A. *J. Org. Chem.* **1983**, **48**, 2866.
(7) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633.
(8) Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425.
(9) Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1973**, *30*, 101.

0002-7863/84/1506-1845$01.50/0