An Unusual Mechanism of a Palladium-Catalyzed Intramolecular Carbametalation. A Novel Palladium-Catalyzed Rearrangement

Barry M. Trost* and Gerald J. Tanoury

Department of Chemistry, Stanford University
Stanford, California 94305
McElvain Laboratories of Organic Chemistry
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706

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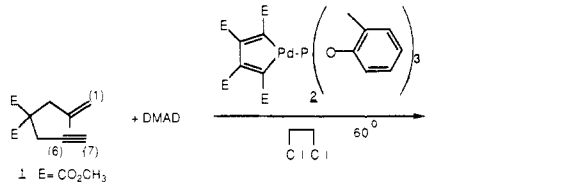
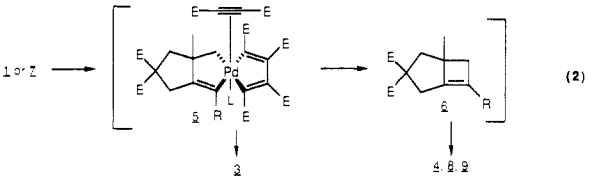
Intramolecular carbametalations offer an exciting opportunity to form rings under very mild conditions.[1-5] The catalytic reaction to 1,6-enynes has already led to a valuable approach to cyclic 1,3- and 1,4-dienes[3,4] as well as [2 + 2 + 2] cycloadditions.[5] In this communication, we report a novel metal-catalyzed skeletal rearrangement of 1,6-enynes that appears to proceed by at least two mechanisms as well as direct evidence for a 1,1-reductive elimination on Pd to form cyclobutenes.

Treatment of the 1,6-enyne **1** with tetracarbomethoxypalladacyclopentadiene (TCPC, **2**)[6] in the presence of tri-*o*-tolylphosphite and 1.1 equiv of dimethyl acetylenedicarboxylate (DMAD) leads to a 1:1.2 ratio (97% yield) of the expected[5] [2 + 2 + 2] cycloadduct **3** and the vinylcyclopentene **4** (eq. 1). The



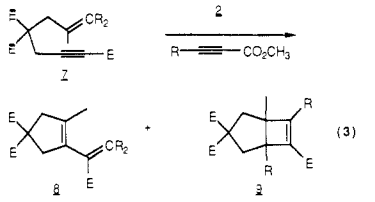
(1)



(2)

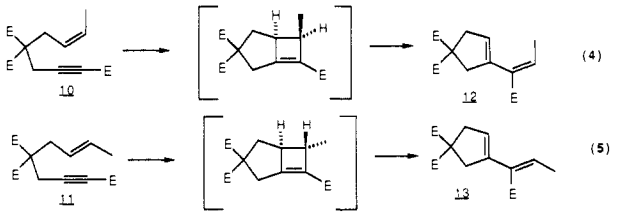
simplest explanation for the production of the unexpected skeletally rearranged product invokes the intermediacy of a cyclobutene **6** which could arise by 1,1-reductive elimination[7,8] from the proposed intermediate **5** for [2 + 2 + 2] cycloaddition (eq 2). Assignment of **4** was derived from its spectral data and comparison to an authentic sample prepared by our palladium acetate catalyzed intramolecular carbametalation followed by 1,5-hydrogen shift.[2,9,10]

Initial support for the pathway proposed in eq 1 arose by examining the reaction of enyne **7** (R = H) which bears a carbomethoxy group as a marker (eq 3). In this case, no [2 + 2 + 2] cycloadduct formed. Two isomeric cyclization products formed in an 81% yield and a 1:1.4 ratio to which structures **8**[9] (R = H) and **9**[9] (R = H) can be readily assigned based on spectroscopic data.[11] The formation of both **8** (R = H) and **9** (R = H) support the intervention of **6** (R = CO_2CH_3) in which a conrotatory ring opening produces the rearranged diene **8** (R = H), and a hydrogen rearrangement, presumably metal catalyzed, produces cyclobutene **9** (R = H). That the partitioning of **6** depends upon the catalyst derives from the observation that replacing DMAD with methyl 2-butynoate exclusively produces the diene **8** (R = H). Use of the deuteriated analogue **7** (R = D) produced **8** (R = D) and **9** (R = D) to reveal that the bridgehead hydrogen of **9** did arise by migration of one of the vinylic hydrogens.[12]



(3)

The reactions of the *Z*- and *E*-enynes **10** and **11** probe the stereochemistry of formation of the skeletally rearranged products. Upon the basis of the intervention of the cyclobutenes as shown in eq 4 and 5, we expect the *Z* isomer **10** to produce the *E* product



(4)

(5)

12 and the *E* isomer **11** to produce the *Z* product **13**. By using our standard conditions, enyne **10** gave a 68% yield of the diene product which consisted of only the *E* isomer **12**.[9] Similarly, the *E* substrate **11** gave predominantly (>10:1) the *Z* product **13**.[9]

While the results are nicely accommodated by the pathway depicted in eq 2, we were concerned by the possibility of migration

* Address correspondence to this author at Stanford University.

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(3) Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 5268.

(4) For a reductive catalytic enyne cyclization, see: Trost, B. M.; Rise, F. *J. Am. Chem. Soc.* **1987**, *109*, 3161.

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(8) For a leading reference on the conversion of metallocyclopentadienes to cyclobutadienes, see: Ville, G. A.; Vollhardt, K. P. C.; Winter, M. J. *Organometallics* **1984**, *3*, 1177.

(9) New compounds have been fully characterized spectroscopically and elemental composition established by high resolution mass spectroscopy and/or combustion analysis.

(10) The thermodynamically more stable diene **4** arises by in situ isomerization of the kinetically formed diene, also catalyzed by Pd^{2+}.

(11) **8**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.26 (d, J = 1.7 Hz, 1 H), 5.54 (d, J = 1.7 Hz, 1 H), 3.76 (s, 3 H), 3.74 (s, 6 H), 3.22 (q, J = 1.9 Hz, 2 H), 3.07 (s, 2 H), 1.66 (t, J = 1.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.37 (2C), 166.93, 136.62, 135.12, 129.28, 127.05, 57.49, 52.79 (2C), 51.92, 46.08, 44.09, 14.64; IR ($CDCl_3$) 1740, 1440 cm^{-1}; calcd for $C_{13}H_{15}O_5$ (M - OCH_3) 251.0917, found 251.0919. **9**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.58 (s, 1 H), 3.73 (s, 3 H), 3.70 (s, 3 H), 3.62 (s, 3 H), 3.00 (d, J = 7.2 Hz, 1 H), 2.76 (d, J = 13.6 Hz, 1 H), 2.63 (dd, J = 13.4, 1.2 Hz, 1 H), 2.04 (dd, J = 13.6, 7.2 Hz, 1 H), 1.84 (d, J = 13.4 Hz, 1 H), 1.34 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.93, 171.85, 162.17, 151.65, 126.70, 61.33, 52.94, 52.36, 51.73 (2C), 51.23, 40.93, 33.77, 20.93; IR ($CDCl_3$) 1725, 1610, 1425 cm^{-1}; calcd for $C_{14}H_{18}O_6$ 282.1103, found 282.1100.

(12) In addition to the ^{13}C labeling, we also performed the reaction by using a deuterium label in the terminal methylene group. NMR analysis reveals that with use of **7** of >97% d_2 produces **8** of >97% d_2 and **9** pssessing >97% d at the vinylic position and 80% d at the bridgehead position. The small amount of exchange at the bridgehead position is consistent with formation of a π-allylpalladium hydride intermediate that suffers some exchange with the medium competing with reductive elimination.

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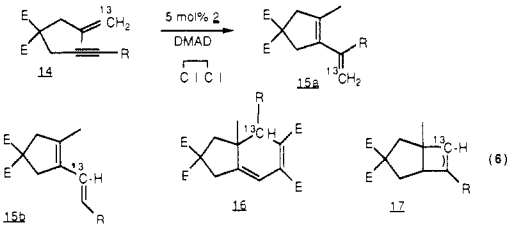
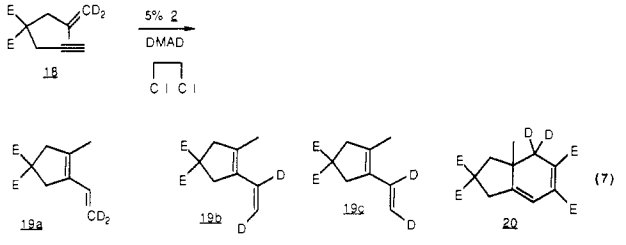
of substitutents. Therefore, we examined the rearrangement of the ^{13}C labeled substrate **14** (R = H)[13] which produced a 52% yield of the rearranged products **15a** (R = H) and **15b** (R = H) and a 12% yield of the [2 + 2 + 2] product **16** (R = H) (eq 6).



As expected, ^1H and ^{13}C NMR spectral analysis of **16** (R = H) revealed the position of the label as depicted (δ ^{13}C 37.35). On the other hand, analysis of the labeled diene **15** proved quite surprising. Mass spectral analysis indicated the diene was singly labeled—a fact that indicates no intermolecular scrambling occurs. The ^1H (δ 6.55, ddd, J = 151, 17.5, 10.8 Hz, 5.08, dd, J = 153, 10.8 Hz, 5.04, dd, J = 153, 17.5 Hz) and ^{13}C (δ ^{13}C 129.97 and 113.72) NMR spectral data reveal that 77% of the label appears at the methine vinyl carbon as shown in **15b** (R = H) and only 23% at the terminal carbon as in **15a** (R = H). While the formation of **15a** (R = H) is consistent with the mechanism depicted in eq 2, this pathway represents only a minor one. The preferential formation of **15b** (R = H) indicates a much more deep-seated rearrangement occurred.

Since reactions 3–5 correlated extremely well with the pathway of eq 2, we examined whether the carbomethoxy group affected the rearrangement by exploring the ^{13}C labeled version of **7**,[12] i.e., **14** (R = CO_2CH_3). This reaction produced a 76% yield of a 1:1 ratio of **15a** (R = CO_2CH_3) and **17** (R = CO_2CH_3) as verified by both ^1H (**15a**, R = CO_2CH_3, δ 6.27, dd, J = 157, 1.7 Hz, 5.55, dd, J = 155, 1.7 Hz, **17** R = CO_2CH_3, δ 6.58, d, J = 181 Hz) and ^{13}C (**15a**, R = CO_2CH_3, δ 151.66) NMR spectroscopy. The exclusive formation of **15a** (R = CO_2CH_3) reaffirms the mechanism of eq 2 for this case.

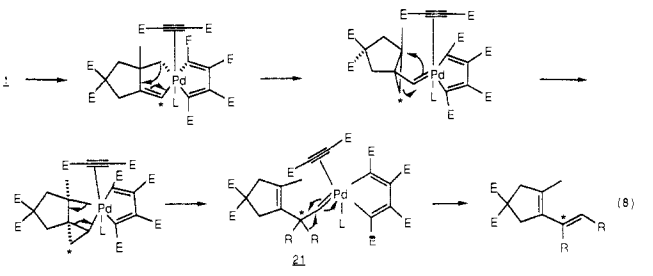
To further probe the nature of the rearrangement of **1**, we also examined the reaction of the dideutero analogue[14] **18**, which gave a 42% yield of the rearranged diene **19** and a 19% yield of the cycloadduct **20** (eq 7). Again, the labeling pattern of the cycloadduct was consistent with its formation as suggested in eq 2,[15] but the labeling pattern of the rearranged dienes **19** was not. The ratio of 1:3 for **19a**:**19b** + **19c** as determined by ^1H (**19a** δ 6.56, 0.17 H, **19b** 5.08, 0.18 H, **19c** 5.05, 0.65 H), ^2H (**19a** δ 6.56, **19b** + **19c** δ 5.07), and ^{13}C (**19a** δ 113.3, p, J = 24 Hz, **19b** + **19c**



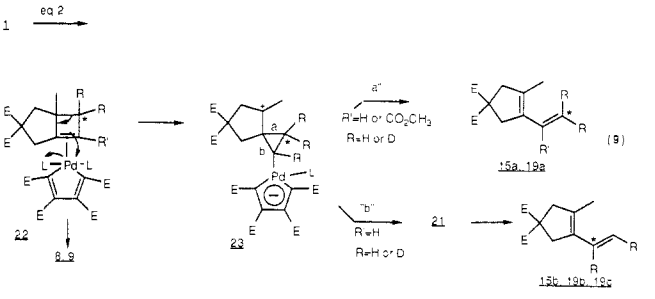
δ 129.75 and 129.57, t, J = 23 Hz) NMR spectroscopy corresponds, within experimental error, to the ratio obtained in the ^{13}C labeled study.

The above labeling studies clearly reveal two mechanistic pathways for the reactions of 1,6-enynes with **2**. The results strongly support the formation of a palladacyclopentene such as **5** and its fascinating 1,1-reductive elimination to form a cyclobutene.[7,8,15] The presence of the ester group apparently facilitates this reductive elimination such that this pathway becomes the exclusive one for the carboxylated acetylenes.[17]

In the absence of the acetylenic ester, the 1,1-reductive elimination may be slowed such that a number of other processes can compete. One of these competitive processes is the [2 + 2 + 2] cycloaddition. *The other involves a reaction whereby C(1) of* ***1*** *formally inserts between the acetylenic carbons C(6) and C(7)!* Any mechanism which invokes intermolecular scrambling of C(1) is precluded by the labeling results. Two plausible, albeit unprecedented, mechanisms are presented in eq **8** and **9**. The increase in strain associated with a palladacyclopentene to palladavinylcyclopropane rearrangement in eq 8 detracts from this



rationale. Invoking a palladacyclopentadiene as a Lewis acid type catalyst to initiate cyclobutyl to cyclopropyl carbinyl cationic rearrangements raises some questions about the validity of eq 9.



Nevertheless, this latter pathway provides a concise global explanation of the reactions of the substrates bearing a terminal acetylene and a carboxylated terminal acetylene.[18] In this regard, the cyclobutene **22** becomes the common intermediate. When R′ = CO_2CH_3, hydrogen shift to **9** and conrotatory ring opening to **8** (**12** and **13** in the case of substrates **10** and **11**) occur. When R′ = H, ring contraction to the stabilized cyclopropylcarbinyl and palladacyclopentadienyl anion **23** occurs. Cleavage of either bonds "a" or "b" account for the diene products **15a** and **19a** or **15b**, **19b**, and **19c**, respectively. The destablization of positive charge and the steric hindrance offered by the ester group accounts for the partitioning in the two series. Both eq 8 and 9 invoke a nonstabilized palladium carbene complex **21**, a type of reactive intermediate that has not previously been established.[19,20]

(13) Prepared from the corresponding ketone by using the Lombardi modification of the Nozaki olefination employing 92.1% ^{13}C enriched methylene iodide. In all reactions, the enriched sample was diluted with unlabeled substrate (1:3 ratio), and all analyses were corrected for this dilution, see: Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, *19*, 2417. Lombardi, L. *Tetrahedron Lett.* **1982**, *23*, 4293. For an improved procedure, see: Lombardi, L. *Org. Synth.* **1987**, *65*, 81. Also, see: Okazoe, T.; Hibino, J.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5581.

(14) Prepared as in ref 12 by using 99.8% enriched dideuteriomethylene iodide or 99.6% dideuteriomethylene bromide.

(15) In the ^1H NMR spectrum, the AB pattern at δ 2.65 and 2.50 was absent; the ^2H NMR spectrum showed 1D each at δ 2.59 and 2.44. In the ^{13}C NMR spectrum, the signal at δ 37.26 for the nondeuteriated sample virtually disappears in the spectrum of the deuteriated sample.

(16) To our knowledge, this represents the first example of a 1,1-reductive elimination to form a cyclobutene.

(17) Electron-withdrawing ligands on the metal are known to accelerate 1,1-reductive eliminations, see: Kurosawa, H.; Emoto, M. *Chem. Lett.* **1985**, 1161. Kurosawa, H.; Emoto, M.; Urabe, A. *Chem. Commun.* **1984**, 968. Numata, S.; Kurosawa, H. *J. Organomet. Chem.* **1977**, *131*, 301. Temple, J. S.; Riediker, M.; Schwartz, J. *J. Am. Chem. soc.* **1982**, *104*, 1310.

(18) In this case, we do not need to invoke a differentiation between the noncarboxylated and carboxylated acetylenic substrates in terms of the rate of the 1,1-reductive elimination to form the cyclobutene although it could still be the case.

Acknowledgment. We thank the National Science Foundation for their generous support of our programs.

Registry No. 1, 109468-75-9; **2**, 112713-31-2; **3**, 109468-77-1; **4**, 109468-82-8; **7** (R = H), 112713-14-1; **7** (R = D), 112713-17-4; **8** (R = H), 112713-15-2; **8** (R = D), 112713-18-5; **9** (R = H), 112713-16-3; **9** (R = D), 112713-19-6; **10** (R′ = H), 112739-95-4; **11**, 112713-32-3; **12**, 112713-20-9; **13**, 112713-21-0; **14** (R = H), 109468-75-9; **14** (R = CO_2CH_3), 112713-33-4; **15a** (R = H), 112713-22-1; **15a** (R = CO_2CH_3), 112713-25-4; **15b** (R = H), 112713-23-2; **16** (R = H), 112713-24-3; **17** (R = CO_2CH_3), 112739-96-5; **18**, 112713-26-5; **19a**, 112713-27-6; **19b**, 112713-28-7; **19c**, 112713-29-8; **20**, 112713-30-1; DMAD, 762-42-5; methyl 2-butynoate, 23326-27-4.

(19) Crocianai, B.; Boschi, T.; Belluco, U. *Inorg. Chem.* **1970**, *9*, 2021. Bonati, F.; Minghetti, G.; Boschi, T.; Crociani, B. *J. organomet. Chem.* **1970**, *25*, 255. Miller, J. S.; Balch, A. L. *Inorg. Chem.* **1972**, *11*, 2069. Larkin, G. A.; Scott, R. P.; Wallbridge, M. G. H. *J. Organomet. Chem.* **1972**, *37*, C21. Busetto, L.; Pallazi, A.; Crociani, B.; Belluco, V.; Badley, E. M.; Kilby, B. J. L.; Richards, R. L. *J. Chem. Soc., Dalton Trans.* **1972**, *1800*. Davies, C. H.; Garne, C. H.; Green, M.; Stone, F. G. A. *J. Chem. Soc., Dalton Trans.* **1974**, 357. Bartel, K.; Fehlhammer, W. P. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 599. Cardin, D. J.; Cetinkaya, B.; Cetinkaya, E.; Lappert, M. F. *J. Chem. Soc., Dalton Trans.* **1973**, 514. Clark, H. C.; Jablonski, C. R. *Inorg. Chem.* **1974**, *13*, 2213. Clark, H. C.; Fiess, P. L.; Wong, C. S. *Can. J. Chem.* **1977**, *55*, 177. For Pd-catalyzed reactions of diazo compounds that may proceed via carbene intermediates, see: Hoffmann, K. L.; Regitz, M. *Tetrahedron Lett.* **1983**, *24*, 5355. Bien, S.; Segal, Y. *J. Org. Chem.* **1977**, *42*, 1685. Bien, S.; Ovadia, D. *J. Org. Chem.* **1970**, *35*, 1028. Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssie, P. *J. Org. Chem.* **1980**, *45*, 695. Mende, U.; Raduchel, B.; Skuballa, W.; Vorbruggen, H. *Tetrahedron Lett.* **1975**, 629. Also, see: Catellani, M.; Chiusoli, G. P. *Tetrahedron Lett.* **1983**, *24*, 4493.

(20) In acetylene trimerizations to benzenes, unusual regioselectivity that arises by formal insertion into an acetylenic bond has been observed as very minor pathways. Whitesides, G. M.; Ehmann, W. J. *J. Am. Chem. Soc.* **1969**, *91*, 3800. Dietl, H.; Reinheimer, H.; Moffat, J.; Maitlis, P. M. *J. Am. Chem. Soc.* **1970**, *92*, 2276. Maitlis, P. M. *Acc. Chem. Res.* **1976**, *9*, 93. Maitlis, P. M. *J. Organomet. Chem.* **1980**, *200*, 161.

Nonpeptide Mimetics of β-Turns: A Facile Oxidative Intramolecular Cycloaddition of an Azodicarbonyl System

Michael Kahn,*[1] Susanne Wilke, Barbara Chen, and Kagari Fujita

University of Illinois at Chicago
Department of Chemistry, P.O. Box 4348
Chicago, Illinois 60680

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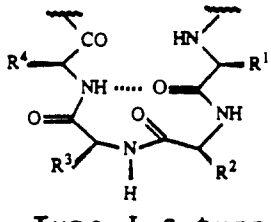
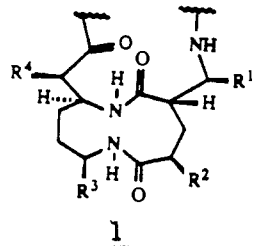
As part of our program to utilize conformationally restricted nonpeptide mimetics to investigate the relationship between peptide structure and function,[2] we have designed system **1**[3] as a mimetic of a type I beta turn.[4] An efficacious and versatile retrosynthetic strategy is outlined in Scheme I. The key transformation involves the previously unreported intramolecular Diels–Alder reaction of an azodicarbonyl system.[5,6] We wish to disclose the success of a model study of this key cycloaddition reaction (Scheme II), the facility with which this reaction proceeds, despite the unusual bridging between diene and dienophile, and the strained tricyclic system which is produced.[7] We envisioned that the requisite precursor **2** could be generated in situ via oxidation of the diacylhydrazide **3**, which would subsequently undergo cycloaddition through a less encumbered exo transition state. The synthesis of **4** commences with the readily available ethyl 5-phenyl-4-pentenoate (**5**) (Scheme III).[8] Cyclocondensation with *N*-chlorosulfonyl isocyanate (18 h, room temperature) proceeds smoothly providing trans β-lactam **6** in 72% yield.[9] Benzylation using the



Type I β-turn



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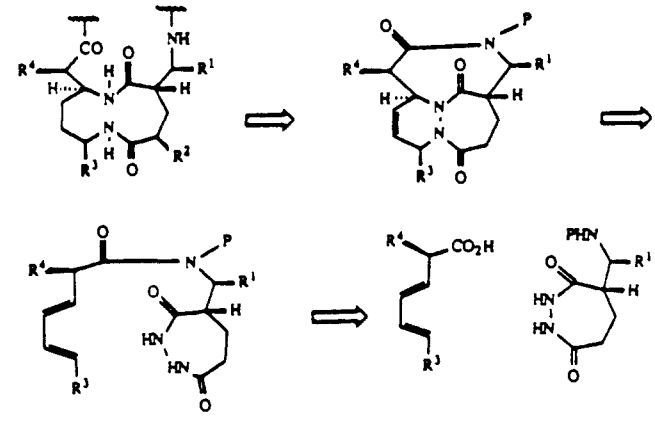
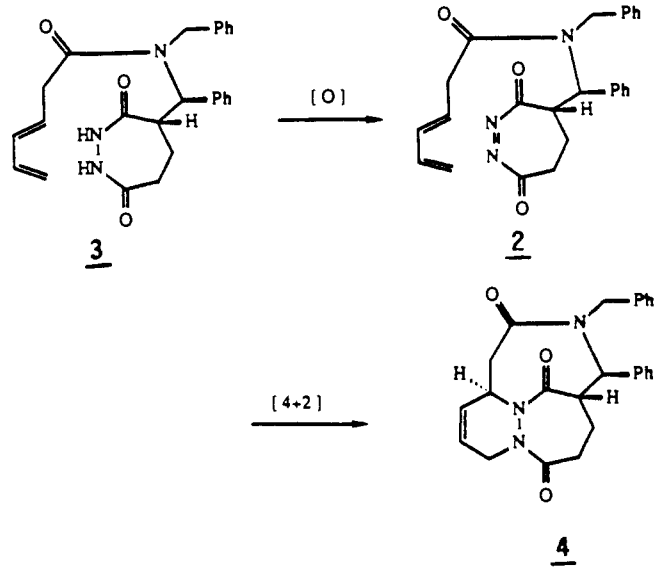
Scheme I



Scheme II



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(1) Recipient of a Dreyfus Young Faculty Grant (1985–1990), Searle Scholars Award (1986–1989), Presidential Young Investigators Award (1987–1992), and an American Cancer Society Junior Faculty Fellowship (1987–1990).

(2) Kahn, M.; Su, T. Proceedings of the Tenth American Peptide Symposium, St. Louis, MO, in press. Kahn, M.; Chen, B. *Tetrahedron Lett.* **1987**, 1623. Kahn, M.; Chen, B.; Zieske, P. *Heterocycles* **1987**, 29. Kahn, M.; Devens, B. *Tetrahedron Lett.* **1986**, 4861.

(3) Details of the design and modeling will be published separately: Kahn, M.; Johnson, M.; Lee, Y.; Wilke, S.; Chen, B. *J. Biomol. Recogn.*, in press.

(4) For an excellent review on turns, see; Rose, G. D.; Gierasch, L. M.; Smith, J. A. *Adv. Prot. Chem.* **1985**, *37*, 1–104.

(5) Despite the long history of azodienophiles (for a recent review, see: Adam, W.; DeLucchi, O. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 762 and references therein), until the recent report of Medina et al. (Medina, J. C.; Cadilla, R.; Kyler, K. S. *Tetrahedron Lett.* **1987**, 1059) which appeared during the course of our investigation, the intramolecular version of this reaction remained unprecedented.

(6) For a recent review on the intramolecular Diels–Alder reaction, see: Fallis, A. *Can. J. Chem.* **1985**, 4297.

(7) For examples of intramolecular Diels–Alder reactions leading to strained ring systems, see: Shea, K. J.; Gilman, J. W.; Huffner, C. D.; Dougherty, T. K. *J. Am. Chem. Soc.* **1986**, *108*, 4953 and references therein.

(8) Prepared by vinyl Grignard addition to benzaldehyde and subsequent ortho ester Claisen rearrangement.

(9) For recent reviews on the use of CSI, see: Rasmussen, J. K.; Hassner, A. *Chem. Rev.* **1975**, 389. Kamal, A.; Sutter, P. B.; *Heterocycles* **1987**, *26*, 1051.

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