it to be ethylidene fragments (Pt_n=$CHCH_3$),[11] but our present results argue for the formation of chemisorbed ethylene instead. More research is needed to clarify this point.

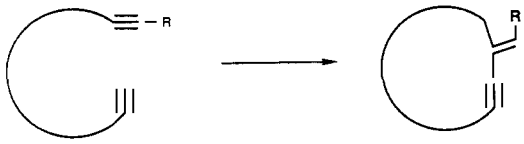
Registry No. Pt, 7440-06-4; CH_3CH_2I, 75-03-6; ethyl, 2025-56-1.

Cycloisomerization of α,ω-Diynes to Macrocycles

Barry M. Trost,* Seijiro Matsubara, and Joseph J. Caringi

Department of Chemistry, Stanford University
Stanford, California 94305
Received June 19, 1989

Cyclic acetylenes have attracted considerable interest recently with the discovery of the potent antitumor properties of neocarzinostatin and calichemicin/esperamicin.[2] In exploring new synthetic strategies, we have attempted to develop reactions in which the sum of the reactants corresponds precisely to the desired product to enhance chemical efficiency. In terms of a cyclization, such a process is an isomerization.[3,4] We record a successful realization of this goal directed toward cycloalkynes as outlined in eq 1 in which remarkable chemoselectivity is observed.[5]

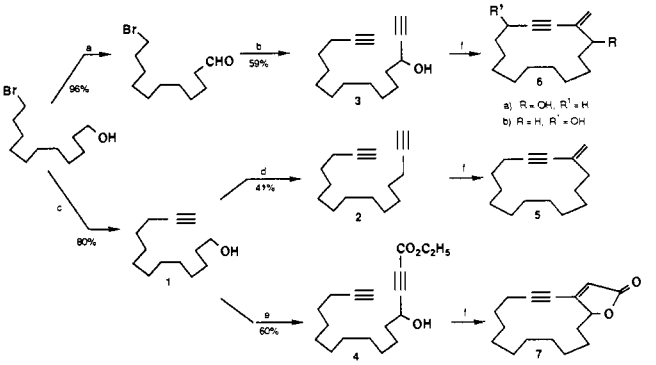


(1)

Scheme I exemplifies the ease with which suitable substrates **2**–**4** can be synthesized. Displacements of alkyl halides with acetylide anion require the use of a dipolar aprotic solvent admixed with THF. HMPA or DMPU (1,3-dimethylhexahydro-2-pyrimidone) proved efficacious.[6] In the synthesis of **3**, both acetylenes were introduced in a single operation, wherein addition of the first equivalent of the acetylide in THF at −78 °C occurred at the carbonyl group and subsequent addition of HMPA and a second equivalent of the acetylide effected displacement of the bromide.

If both acetylenes are terminal, the issue of chemoselectivity arises. To evade this issue initially, a benzene solution of the symmetrical diyne **2** was added slowly to 10 mol % of palladium acetate and 20 mol % of TDMPP [tris(2,6-dimethoxyphenyl)-phosphine] in benzene at reflux. This reaction produced a 41% yield[7] of the monocyclic 14-membered-ring compound **5**.[8] The

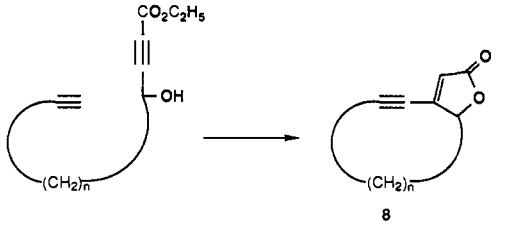
Scheme I. Synthesis and Cyclization of Diyne Substrates Exemplified[a]



[a] (a) $(COCl)_2$, DMSO, $(C_2H_5)_3N$, CH_2Cl_2. (b) (i) TMSC≡CLi, THF, −78 °C, then add HMPA, −78 °C to room temperature; (ii) TBAF, THF, H_2O, room temperature. (c) (i) TMSC≡CLi, THF, DMPU, −78 °C to room temperature (see text), then H_2SO_4, H_2O, THF; (ii) TBAF, THF, H_2O, room temperature. (d) (i) Br_2, dppe, CH_2Cl_2, 0 °C to room temperature; (ii) TMSC≡CLi, THF, DMPU, −78 °C to room temperature; (iii) TBAF, THF, H_2O, room temperature. (e) (i) $(COCl)_2$, DMSO, $(C_2H_5)_3N$, CH_2Cl_2; (ii) $LiC{\equiv}CCO_2C_2H_5$, THF, −78 °C. (f) See text.

enyne moiety is characterized by both the ^1H (δ 5.16, d, J = 2.3 Hz, 1 H and 5.11, t, J = 1.1 Hz, 1 H for =CH_2; 2.34, t, J = 6.2 Hz, 2 H for =CCH_2; 2.12, t, J = 7.3 Hz, 2 H for =CCH_2) and ^{13}C (δ 132.5 and 119.4 for C=CH_2; 90.7 and 81.3 for C=C) NMR spectra. *Repeating this protocol with the unsymmetrical diyne 3 remarkably led to a single macrocycle in 46% yield.* Assignment as **6a**[8] rather than **6b** arises from the ^1H NMR spectrum, in which the signal for the propargylic methylene group remains (δ 2.38, ddd, J = 16.3, 6.9, 4.1 Hz and 2.33, ddd, J = 16.3, 7.0, 4.0 Hz) and the single allylic hydrogen appears at δ 4.08 (q, J = 6.0 Hz)[9] with small couplings to the terminal methylene hydrogens (J = 1.2 and 0.8 Hz) established by spin-decoupling experiments. This remarkably chemoselective cyclization appears to generate the thermodynamically more stable product, as predicted by MM2 calculations, which indicate that **6a** is about 1.9 kcal/mol more stable than **6b**.

Replacing the terminal hydrogen of the acceptor acetylene with an electron-withdrawing group enhances the efficiency of the cyclization. The tetrolic ester substrate **4** constitutes a particularly intriguing case to examine compatibility with functional groups since a tandem annulation can result in direct formation of a bicyclic lactone. Indeed, subjecting diyne **4** to the above cyclization conditions produced macrocycle **7**[8] in 66% yield. Utilizing 5 mol % of $[(o\text{-tol})_3P]_2Pd(OAc)_2$ as an alternative catalyst, and approximately an amount of 5 Å molecular sieves equivalent in weight to substrate at 0.02 M in substrate in refluxing benzene, gave a 59% yield of the macrocycle **7**[8]. This novel bicycloannulation was extended to the 13-membered (**8**, n = 9, 58%)[8] and 16-membered (**8**, n = 12, 38%)[8] macrocycles (eq 2) by em-



8

(2)

ploying the latter conditions. The power of this strategy is revealed by the fact that even a 10-membered ring (**8**, n = 6)[8] can be produced, albeit in only 16% yield.[10]

(1) Hensens, O. D.; Dewey, R. S.; Liesch, J. M.; Napier, M. A.; Reamer, R. A.; Smith, J. L.; Albers-Schonberg, G.; Goldberg, I. H. *Biochem. Biophys. Res. Commun.* **1983**, *113*, 538. Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331. Meyers, A. G.; Proteau, P. J.; Handed, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7212.

(2) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466. Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saithoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, J.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saithoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462.

(3) The intramolecular Diels–Alder and Alder ene reactions are excellent illustrations. See: Taber, D. F. *Intramolecular Diels–Alder and Alder Ene Reactions*; Springer-Verlag: Berlin, 1984.

(4) (a) For metal-catalyzed examples, see: Trost, B. M.; Lee, D. C. *J. Org. Chem.* **1989**, *54*, 2271 and earlier references therein. Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 5231 and earlier references therein. Trost, B. M.; Hane, J. T.; Metz, P. *Tetrahedron Lett.* **1986**, *27*, 5695 and earlier references therein. (b) For cyclizations involving palladium-catalyzed carbametalations of acetylenes as the ring-forming step, see: Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454. Burns, B.; Grigg, R.; Sridharan, V.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 4325. Chatani, N.; Takeyasu, T.; Horiuchi, N.; Hanafusa, T. *J. Org. Chem.* **1988**, *53*, 3539. Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 7255. (c) For an example of a simple base-catalyzed cycloisomerization to produce a cycloalkyne, see: Deslongchamps, P.; Roy, B. L. *Can. J. Chem.* **1986**, *64*, 2068.

(5) For intermolecular Pd-catalyzed acetylene coupling, see: Trost, B. M.; Chan, C.; Ruhter, G. *J. Am. Chem. Soc.* **1987**, *109*, 3486.

(6) Cf.: Smith, W. N.; Beumet, O. F., Jr. *Synthesis* **1974**, 441.

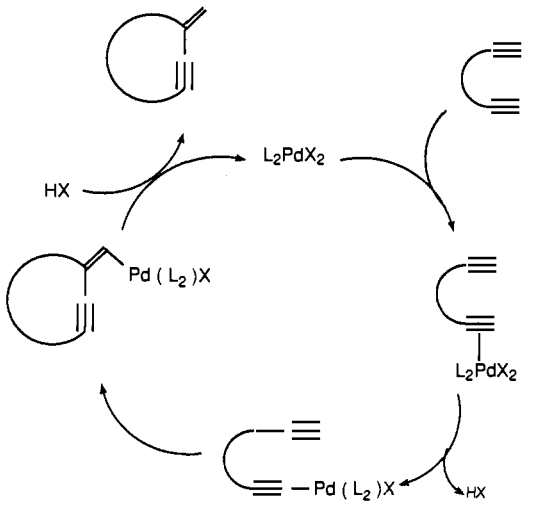
(7) We believe the yield reflects mechanical losses upon workup due to the volatility of the compound.

(8) Satisfactory characterization was obtained.

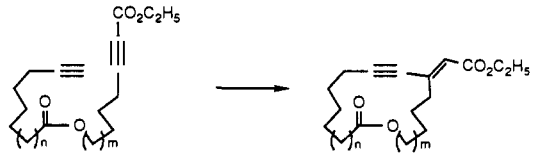
(9) Coupling to the hydroxyl proton with coupling equal to that with the adjacent methylene group. A broad triplet results when OH exchange is rapid.

0002-7863/89/1511-8745$01.50/0

Scheme II. A Catalytic Cycle



To test the chemoselectivity in terms of the synthesis of macrolides, the simple esters **9a–d** were prepared and cyclized (eq 3). The sluggishness of the cyclization of diyne **9a** under the above



(3)

9 **10**

a) m=1, n=2 b) m=1, n=1 c) m=1, n=6 d) m=8, n=6

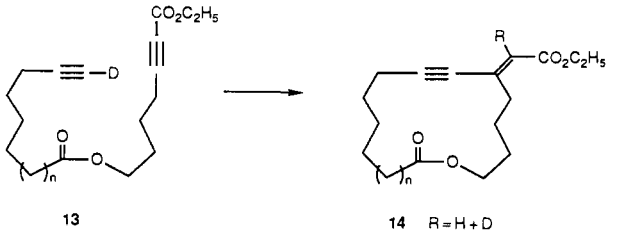
conditions led to an in-depth ligand study in which **9a** was added over 40 min to a refluxing mixture of 5 mol % of palladium acetate, 10 mol % of ligand, and 5 Å molecular sieves, with a 0.02 M final substrate concentration. The effectiveness of the ligands for palladium decreased in the order TDMPP > tris(*o*-methoxyphenyl)phosphine ~ triphenylphosphine ~ tris(2,4,6-trimethoxyphenyl)phosphine > tris(*o*-tolyl)phosphine > tris(2-furyl)phosphine > tris[3-(trifluoromethyl)phenyl]phosphine (see table in supplementary material). A combination of both steric and electronic effects appears important.

When the above conditions were used with TDMPP as ligand, in addition to the 15-membered-ring lactone **10a**[8] (57% yield) were also obtained 14-membered-ring lactone **10b**,[8] 19-membered-ring lactone **10c**,[8] and 26-membered-ring lactone **10d**,[8] in 67%, 57%, and 70% yields, respectively. The *E* geometry of the exocyclic double bond derives from the strong deshielding of the allylic methylene group (e.g., δ 2.81 for **10a**), consistent with this group being cis to the ester group. Having the acceptor acetylene endocyclic with respect to the forming ring, as in diyne **11**, still permits cyclization to the cycloalkenyne **12** (eq 4, 38% yield).

(4)

11 **12**

Scheme II outlines a reasonable proposal for the catalytic cycle. Insertion into the acetylenic hydrogen appears to be fast and reversible relative to cyclization, as evidenced by H–D exchange in terminal alkynes being competitive with alkyne dimerization. Further, cyclization of the deuterated substrate **13** led to the cyclization product **14**, retaining only 39% of the deuterium. The



13 **14** R = H + D

remarkable chemoselectivity associated with cyclization of **3** then arises from a kinetic preference for the palladium acetylide to add to the alkyne of a propargyl alcohol compared to a simple terminal alkyne. Since electron-withdrawing groups clearly activate the acceptor acetylene, the inductive effect of the propargyl hydroxyl group may account for part of its activation. The fact that the *p*-methoxybenzyl and *tert*-butyldimethylsilyl ethers of **3** produce complex mixtures whereas the acetate cyclizes even more efficiently supports this contention. The geometry of cyclization products supports the clean cis addition. An alternative catalytic cycle in which the acetic acid moiety remains bonded to palladium throughout the cycle (i.e., invoking a Pd^{4+} species) cannot be discounted. Clearly, much work needs yet to be done to define the mechanism more fully, but the scheme serves as a convenient working hypothesis for predictive purposes. The ability to form macrocycles with such versatile functionality by a simple isomerization, however, should prove to be a useful new strategy. Further, the prospects for developing alternative tandem annulations may provide opportunities for new types of polycyclizations.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. We are grateful for mass spectra provided by the Mass Spectrometry Facility, University of California—San Francisco, supported by the NIH Division of Research Resources.

Supplementary Material Available: General experimental procedure, table of ligand effects on macrocyclization of diyne **9a**, and characterization for **2–8** and **10a–d** (4 pages). Ordering information is given on any current masthead page.

(10) Cyclodecyne has been calculated to have about 10 kcal/mol of strain energy. See: Allinger, N. L.; Meyer, A. Y. *Tetrahedron* **1975**, *31*, 1807. However, see: Turner, R. B.; Jarrett, A. D.; Goebel, P.; Mallon, B. J. *J. Am. Chem. Soc.* **1973**, *95*, 790. Oxidative dimerization of a diacetylene produced the 10-membered ring in only 6–9% yield; see: Wolovsky, R.; Sondheimer, F. *J. Am. Chem. Soc.* **1966**, *88*, 1525. For a cycloalkylation approach, see: Deslongchamps, P.; Lamothe, S.; Lin, H. J.; Ho, S. *Can. J. Chem.* **1987**, *65*, 1298.

Orbital Symmetry Control of Epimeric Rates of Generation of an Allylic Cation from Sterically Unbiased Precursors

Man-hua Lin,[1a] Mary K. Boyd,[1b] and W. J. le Noble*

Department of Chemistry, State University of New York Stony Brook, New York 11794

Received March 22, 1989
. Revised Manuscript Received September 21, 1989

The concept of orbital symmetry control of stereochemistry[2] has proved to be one of the most fruitful ideas to emerge in physical organic chemistry in recent decades. Its use to date has been restricted to the several groups of reactions collectively described as pericyclic; however, it is in principle applicable not merely to reactions involving cyclic arrays of p orbitals but to all processes featuring the interconversion of trigonal and tetragonal carbon. The question that occurred to us is whether the face selection that characterizes these reactions depends on orbital symmetry.

(1) (a) Present address: Plastics Research Department, Rohm and Haas Company, Box 219, Bristol, PA 19007. (b) Natural Sciences and Engineering Research Council of Canada Postdoctoral Fellow.

(2) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie/Academic Press: New York, 1971.

0002-7863/89/1511-8746$01.50/0