[4 + 3] Cycloaddition of a Trimethylenemethane Fragment. An Approach to Polyhydroazulenes

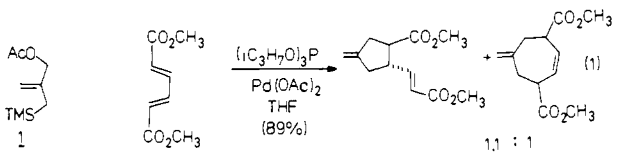
Barry M. Trost* and David T. MacPherson

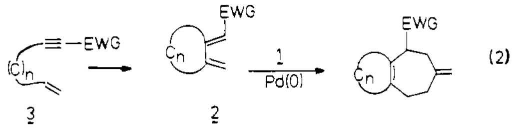
McElvain Laboratories, Department of Chemistry
University of Wisconsin, Madison, Wisconsin 53706

Received February 2, 1987

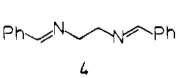
The benefits of cycloaddition reactions, which are so amply demonstrated in the Diels–Alder reaction, stimulate the search for such processes to rings other than six membered. In seeking to exploit the availability of a reactive trimethylenemethane metal complex,[1,2] we considered the possibility that such a fragment might be of general use as a building block for [2n + 3] cycloadditions. We have established the feasibility of the process for the case of $n = 1$.[3] Utilizing tropone as an acceptor creates nine-membered rings (i.e., $n = 3$).[4] In this paper we consider the case of $n = 2$ within the context of a polyhydroazulene synthesis.[5]

The possibility of a cycloaddition to create a seven-membered ring had been noticed in the reaction of dimethyl (*E*,*E*)-muconate which gave a 1:1 mixture of the five- and seven-membered rings (eq 1).[6] Geometrically restricting the diene to a cisoid conformation as in **2** should enhance the formation of the seven-membered ring (eq 2). The problem then became the availability of substrates such as **2**. Our recent discovery of the cyclization of enynes to 1,2-dimethylenecycloalkanes[7] suggested the overall sequence shown in eq 2 whereby construction of the bicyclic system occurs by two sequential palladium-catalyzed cyclizations. Considering the importance of polyhydroazulenes as a core ring system of so many natural products, we focused our efforts on the case of $n = 2$ which constructs an octahydroazulene.

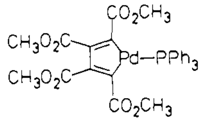




Our initial work on the enyne cyclization suggested that alkyl substituents at the acetylene terminus strongly inhibited the reaction.[7] For the present purposes, we explored the role electron-withdrawing groups have.[8] Cyclizations proceeded in modest to poor yields by using our standard conditions of 5 mol % Pd(OAc)$_2$ and 10 mol % of a triarylphosphine in benzene. Use of Pd(OAc)$_2$ alone proceeded satisfactorily in some cases as illustrated in entry 3 of Table I. Best results were obtained by using *N*,*N*′-dibenzylideneethylenediamine (**4**) as ligand.[9] For example, switching the ligand from triphenylphosphine to no ligand to **4** in the case of entry 1 increased the yield of the diene from less than 20% to 49% to 83%.



4



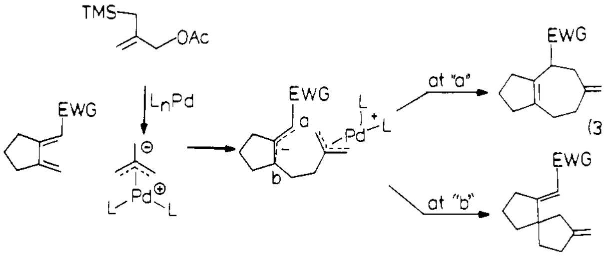
5

The sulfone substrate of entry 5 proved to be particularly troublesome, giving the desired diene in less than 20% yield over a broad array of conditions. Concomitant work in our laboratories[10] on the use of the palladiacyclopentadiene **5**[11] as a catalyst for enyne cyclizations induced us to examine its effect here. Subjecting the acetylenic sulfone (entry 5, Table I) to 5 mol % of **5** in 1,2-dichloroethane gave a 73% yield of the desired diene.

With a facile synthesis of the requisite dialkylidenecyclopentanes in hand, we turned our attention to the [4 + 3] cycloaddition. Generally, the diene and approximately 1.5 equiv of the bifunctional conjunctive reagent **1** were subjected to approximately 5 mol % of a Pd(0) catalyst in refluxing THF. The catalyst was generated in situ by treating Pd(OAc)$_2$ with triisopropyl phosphite. More reproducible results occurred when 2 equiv of *n*-butyllithium (relative to Pd(OAc)$_2$) was added as the reducing agent.[12]

In all cases, the seven-membered ring products were the major to exclusive products as summarized in Table I. The major byproducts were the five-membered rings resulting from cycloaddition to the γ,δ double bond. The cycloheptene products have characteristic ^{1}H NMR signals at δ 4.60–4.90 for the exocyclic methylene group and at δ 3.1–3.4 for the proton α to the ester group (δ 3.7–3.8 for the proton α to the sulfone). The carbonyl frequencies for the saturated esters appear at 1729–1740 cm^{-1}. On the other hand, the five-membered ring byproducts exhibit ^{1}H NMR signals for the exocyclic methylene protons at 0.1–0.2 ppm downfield of the corresponding signals for the octahydroazulene and for the olefinic proton α to the ester or sulfone at around δ 5.70 and 5.30, respectively. The unsaturated nature of the ester group in the cyclopentane products also is confirmed by the infrared frequency at 1704–1717 cm^{-1}.

To the extent that the (trimethylenemethane)palladium complex may be viewed as a 2-substituted allyl cation derivative, a concerted cycloaddition is feasible. However, formation of five-membered ring products in addition to the seven-membered ring products is taken as evidence for a stepwise process as outlined in eq 3.



Seven-membered ring formation is favored by the propensity for

---

[1] Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315, 2326. Gordon, D. J.; Fenske, R. F.; Nanninga, T. N.; Trost, B. M. *J. Am. Chem. Soc.* **1981**, *103*, 5974. Albright, T. A. *Acc. Chem. Res.* **1982**, *15*, 149.

[2] For related work on cooligomerizations of methylenecyclopropanes with olefins, see: Binger, P.; Buch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77.

[3] Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1.

[4] Trost, B. M.; Seoane, P. R. *J. Am. Chem. Soc.* **1987**, *109*, 615.

[5] (a) For a review, see: Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; Apsimon, J. W., Ed.; Wiley: New York, 1982; Vol. 5. (b) For alternative [4 + 3] cycloaddltions, see: Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1; **1973**, *12*, 819. Noyori, R. *Acc. Chem. Res.* **1979**, *12*, 61. (c) For some recent cycloaddition approaches to perhydroazulene synthesis, see: Rigby, J. H.; Wilson, J. Z. *J. Am. Chem. Soc.* **1984**, *106*, 8217; *J. Org. Chem.* **1987**, *52*, 34. Bromidge, S. M.; Sammes, P. G.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1725. Kozikowski, A. P.; Mugrage, B. B.; Warn, B. C.; Xu, Z. *Tetrahedron Lett.* **1983**, 3705.

[6] Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *Organometallics* **1982**, *1*, 1543.

[7] Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781. Also see: Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 6422. Negishi, E.; Holmes, S. S.; Tour, J. M.; Miller, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 2568. Grigg, R.; Malone, J. F.; Mitchell, T. R. B.; Ramasubbu, A.; Scott, R. M. *J. Chem. Soc., Perkins Trans. 1* **1984**, 1745.

[8] A broad study of the effect of substituents on the intramolecular carbametalation was being pursued concomitant with these studies. Chan, C., unpublished work in these laboratories.

[9] The benefits of this ligand was developed by: Jebaratnam, D., unpublished work in these laboratories. Also see: Trost, B. M.; Chen, S. F. *J. Am. Chem. Soc.* **1986**, *108*, 6053.

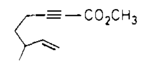
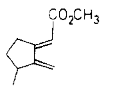
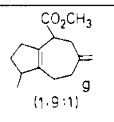
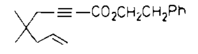
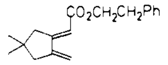
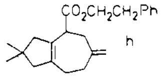
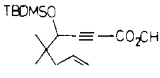
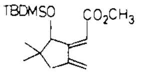
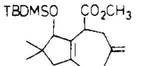
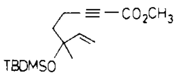
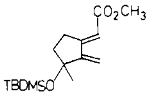
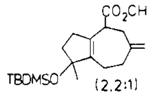
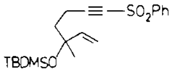
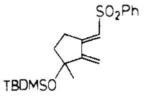
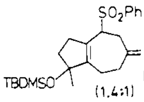
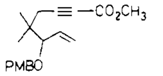
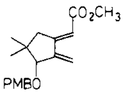
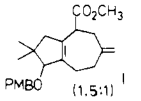
[10] Tanoury, G., unpublished work in these laboratories.

[11] Suzuki, H.; Itoh, K.; Ishii, Y.; Simon, K.; Ibers, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 8494. Mosely, K.; Maitlis, P. M. *J. Chem. Soc., Dalton Trans.* **1974**, 169.

[12] Trost, B. M.; Nanninga, T. N. *J. Am. Chem. Soc.* **1985**, *107*, 1293.

0002-7863/87/1509-3483$01.50/0 © 1987 American Chemical Society

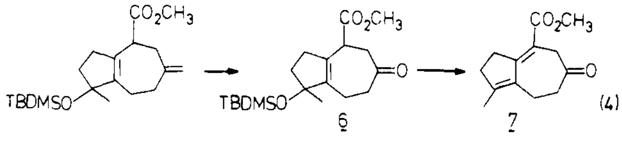
Table I. Synthesis of Octahydroazulenes

entry	enyne	catalyst[a]	cyclopentane	isolated yield[d]	cycloaddition time, h[e]	octahydroazulene (diastereomeric ratio)	isolated yield[d]
1		5 mol % Pd(OAc)$_2$, 6 mol % **4** (1 h)		83%	8.5	 (1.9:1)[g]	76%
2		5 mol % Pd(OAc)$_2$, 6 mol % **4** (1 h)		86%	8	 [h]	88%
3		5 mol % Pd(OAc)$_2$ (5 h)		71%	4[f]	 (2.4:1)[i]	87%
4		5 mol % Pd(OAc)$_2$, 6 mol % **4** (1.3 h)		75%	3[f]	 (2.2:1)[j]	65%
5		5 mol % **5**, 6 mol % Ph$_3$P (6 h)[b]		73%	2.5	 (1.4:1)[k]	73%
6		5 mol % Pd(OAc)$_2$, 6 mol % **4** (1.2 h)[c]		85%	22	 (1.5:1)[l]	80%

[a] Unless otherwise stated, reaction performed at 0.5 M in benzene or benzene-d_6 at 45–50 °C. [b] Reaction performed at 65–70 °C in 1,2-dichloroethane. [c] Reaction performed at 40 °C for 1 h and then 60 °C for 0.2 h. [d] Yield of product after chromatographic purification. All new compounds have been fully characterized spectrally and elemental composition established by high-resolution mass spectroscopy or combustion analysis. [e] Pd(0) catalyst prepared in situ from approximately 5 mol % Pd(OAc)$_2$, 35 mol % triisopropyl phosphite, and 10 mol % *n*-butyllithium in THF at room temperature. Reaction performed at about 0.2 M using a ratio of diene to TMM precursor of about 1:5.5. [f] No *n*-butyllithium was employed to generate catalyst. [g] A 2.4:1 ratio of the seven- to five-membered ring products. [h] A 5.7:1 ratio of seven- to five-membered ring products. [i] Only seven-membered ring products. [j] A 8.2:1 ratio of seven- to five-membered ring products. [k] A 36:1 ratio of seven- to five-membered ring products. [l] A 19:1 ratio of seven- to five-membered ring products.

polyenolates to alkylate at the α rather than δ position (presumably a reflection of higher negative charge at the α compared to the δ position). On the other hand, entropy of activation favors five- over seven-membered ring formation. The predominance of octahydroazulene formation suggests the charge distribution effect dominates. Increasing steric hindrance by increasing substitution on the five-membered ring of the diene acceptor generally enhances the selectivity for [4 + 3]- over [3 + 2]-type products.

The adducts can be selectively elaborated. For example, the adduct of entry 4 may be chemoselectively oxidized to ketone **6** (56% yield) by portionwise addition of benzyltriethylammonium permanganate[13] to a methylene chloride solution of the octahydroazulene and tetra-*n*-butylammonium periodate.[14] The ketone **6** corresponds to the equivalent of the cycloaddition of the 2-oxyallyl zwitterion in a [4 + 3] mode. Exposure of **6** to tetra-*n*-butylammonium fluoride at 0 °C in THF effects elimination to the diene **7** (65% yield). Ketone **6** can be envisioned as an intermediate toward procurcumenol[15] and diene **7** as an intermediate toward helispendiolide.[16]



(4)

Sequential palladium-catalyzed reactions provide a facile two-step synthesis of octahydroazulenes from acyclic precursors. Condensations involving a (trimethylenemethane)palladium intermediate now permit cycloaddition strategies to extend beyond five-membered ring formation to seven- and nine-membered rings as well.

Acknowledgment. We thank the National Science Foundation and the General Medical Sciences Institute for their generous support of our programs.

---

(13) Ogino, T.; Mochizuki, K. *Chem. Lett.* **1979**, 449.

(14) Inomata, K.; Nakayama, Y.; Kotake, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 565.

(15) Hikino, H.; Konno, K.; Nagashima, T.; Kohama, T.; Tsunematsu, T. *Chem. Pharm. Bull.* **1977**, *25*, 6. Hikino, H.; Sakurai, Y.; Takemoto, T. *Chem. Pham. Bull.* **1968**, *16*, 1605.

(16) Bohlmann, F.; Suwita, A. *Phytochemistry* **1979**, *18*, 885.

CHO vs. CH═CH$_2$ Competition in Radical Cyclizations: Is the 5-Hexenyl Radical Really Supreme?[1]

Ray Tsang,* John K. Dickson, Jr., Helen Pak,
Richard Walton, and Bert Fraser-Reid*

Department of Chemistry, Paul M. Gross
Chemical Laboratory, Duke University
Durham, North Carolina 27706

Received January 29, 1987

In the current renaissance of free radical chemistry,[2] one of the most highly cherished canons arises from the conviction that "the cyclization of (a) 5-hexenyl radical (can) be used as a kinetic yardstick against which the rates of competing processes can be measured".[3] Mechanistic studies of single electron transfer[4] have

---

(1) This work is supported by grants from NIH (GM 37380 and 32569).

(2) See, for example: (a) Giese, B. In *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Baldwin, J. E., Ed.; Pergamon: New York, 1986; (b) *Selectivity and Synthetic Applications of Radical Reaction*, Tetrahedron Symposia in Print 22; *Tetrahedron*, **1985**, *41*, 3887–4302. (c) Hart, D. J. *Science* (*Washington, D.C.*) **1984**, *223*, 883. (d) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.

(3) Beckwidth, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, p 188.

(4) See, for example: (a) Ashby, E. C.; Argyropoulos, J. N. *J. Org. Chem.* **1985**, *50*, 3274. (b) Alnajjar, M. S.; Kuivila, H. G. *J. Am. Chem. Soc.* **1985**, *107*, 416. (c) Ashby, E. C.; Wenderoth, B.; Pham, T. N.; Park, W.-S. *J. Org. Chem.* **1984**, *49*, 4505.

0002-7863/87/1509-3484$01.50/0 © 1987 American Chemical Society