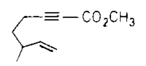
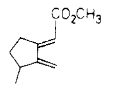
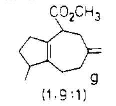
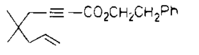
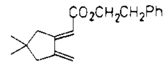
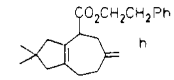
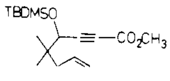
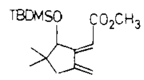
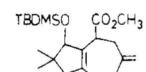
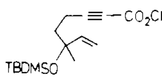
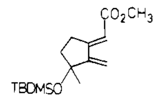
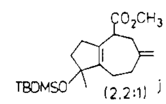
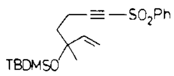
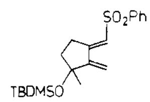
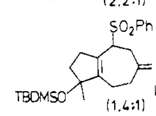
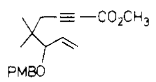
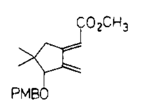
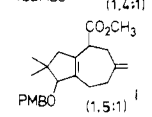
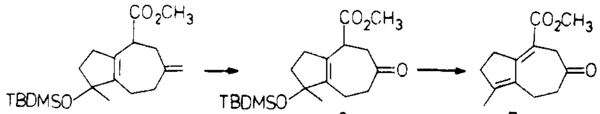
Table I. Synthesis of Octahydroazulenes

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	 g (1.9:1)	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_3P (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



6 7 (4)

intermediate toward procurcumenol[15] and diene **7** as an intermediate toward helispendiolide.[16]

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.

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(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]

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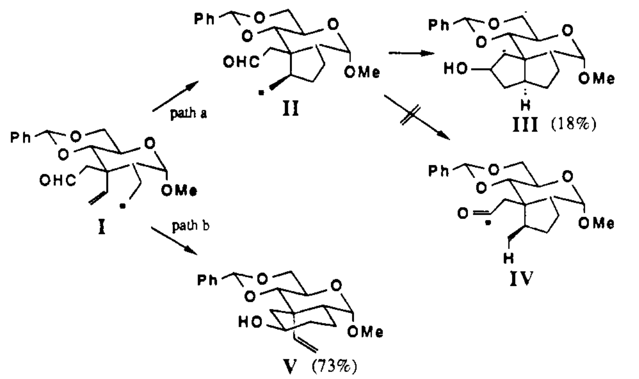
Received January 29, 1987

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.

Scheme I



relied very heavily on this precept, and some of the most dramatic developments in the realm of synthetic organic chemistry have apparently attested to its validity.[5-7] It was in this context that we had examined[8] the radical cyclization of I (Scheme I). The formation of the cyclopentylmethyl radical II being taken for granted, the troubling question, we thought, was whether the diquinane III would then ensue, or whether energy-favored hydrogen transfer to give the acyl radical IV would be the overwhelming alternative. In the event compound III was indeed obtained, but only to the extent of 18%. The predominant product was the cyclohexanol V (73%).

One implication of the foregoing results was that radical cyclization to aldehydes (i.e., path b) was an underappreciated route to cyclohexanols, and indeed, we have subsequently established this fact.[9] However, a second, probably more troubling implication was that radical cyclization to an aldehyde (path b) could overwhelm 5-hexenyl cyclization (path a)!! The carbohydrate backbone used in our studies is frequently maligned for its idiosyncrasies, and hence, we have examined the second implication with a variety of ordinary substrates, **1** → **6**, as shown in Chart I.

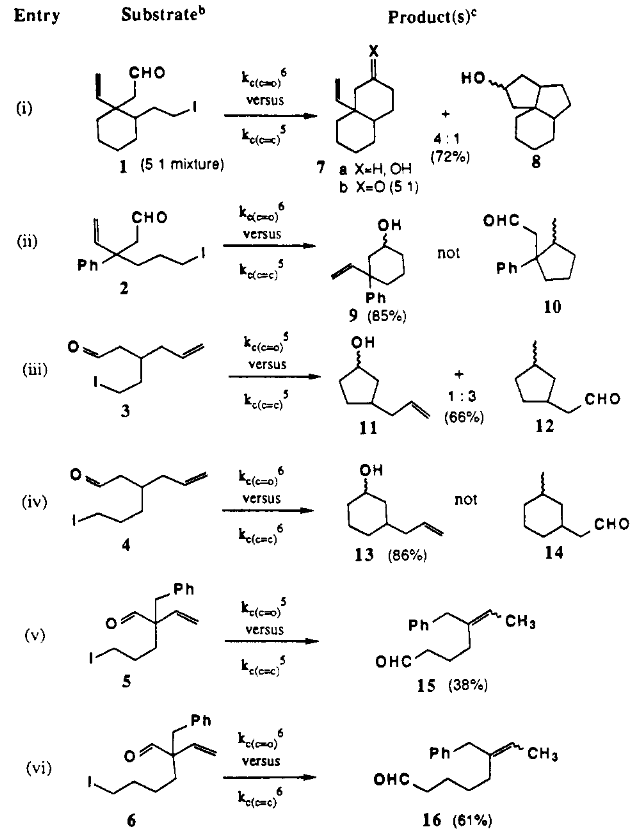
Compound **1**, chosen as a carbocyclic equivalent of I, was prepared as a 5:1 mixture of isomers from cyclohexanone. As indicated in entry i, the cyclohexanol **7a** was the major product of radical cyclization. *Indeed, the 4:1 ratio of **7a** and **8** was identical with that observed for V and III (Scheme I) in the previously reported "carbohydrate" example.*[8] Furthermore, the existence of ketone **7b**, also as a 5:1 mixture of isomers, indicated that the *aldehydo* group had triumphed over the alkene, irrespective of its cis or trans relationship to the radical-bearing appendage.

Perhaps the rigidity of the backbones of I and **1** was responsible for the cyclization giving cyclohexanol [$k_{c\,(C=O)}{}^6$] rather than the cyclopentane [$k_{c\,(C=C)}{}^5$]. However, this concern was dispelled by the exclusive formation of **9** in the case of the acyclic substrate **2** shown in entry ii.

The energetics behind the pathways in entries i and ii await further refinement; however, our recent studies have suggested that cyclohexanols are formed more readily than cyclopentanols,[9] and substrates **3** and **4** (entries iii and iv) were designed in light of these precedents. Given the results in entries i and ii, the preferential formation of **13** and the absence of **14** are "to be expected". Similarly, the result in entry iii is in keeping with the previously observed inferior status of cyclopentanol formation, so that the methylcyclopentane **12** is now formed in slight preference to the alcohol **11**.

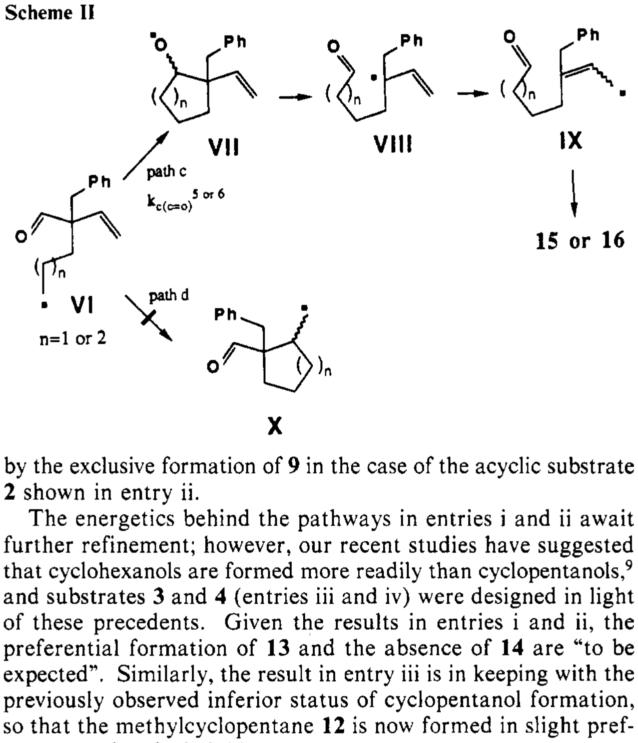
The results in entries v and vi give much food for thought. The products **15** and **16** arose by a series of rearrangements depicted

Chart I. CHO vs. CH=CH$_2$ Radical Cyclizations[a]



[a] In a typical reaction the radical was generated by treating a 0.032 M solution of the iodide in benzene with 1 equiv of n-Bu$_3$SnH and a catalytic amount of AIBN under reflux in an argon atmosphere. The yields quoted are after chromatographic isolation. [b] Substrates **1**–**6** were prepared by standard procedures which will be described in the full paper. [c] All products were identified by ^{1}H NMR (300 MHz), IR, and elemental analysis and/or by comparison with known materials.

Scheme II



(5) (a) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321. (b) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 3720. (c) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. (d) Stork, G. In *Selectivity—A Goal for Synthetic Efficiency*; Bartman, W., Trost, B. M., Eds.; Verlag Chemie: Weinheim, Deerfield Beach, FL, Basel, 1984; p 296. (e) Stork, G.; Baine, N. H. *Tetrahedron Lett.* **1985**, *26*, 5927. (f) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. (g) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303. (h) Stork, G.; Sofia, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 6826. (i) Stork, G.; Mook, R., Jr. *Tetrahedron Lett.* **1986**, *27*, 4529.

(6) (a) Curran, D. P.; Chen, M. H. *Tetrahedron Lett.* **1985**, *26*, 4991. (b) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. (c) Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943. (d) Curran, D. P.; Kim, D. *Tetrahedron Lett.* **1986**, *27*, 5821. (e) Curran, D. P.; Kuo, S. C. *J. Am. Chem. Soc.* **1986**, *108*, 1106. (f) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489.

(7) (a) Beckwith, A. L. J.; Roberts, D. H.; Schiesser, C. H.; Wallner, A. *Tetrahedron Lett.* **1985**, *26*, 3349. (b) Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Lett.* **1986**, *27*, 4525. Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 5893.

(8) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116.

(9) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 8102.

(10) Korcek, S.; Chernier, J. H. B.; Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1972**, *50*, 2285.

(11) Relative to stabilization energy for $CH_3CH_2{}^\bullet$ = 0 kcal/mol, the value for $CH_2{=}CH{-}CH_2{}^\bullet$ = 10^{10}.

in Scheme II which require *that cyclization to the aldehyde occurs in preference to cyclization to the alkene irrespective of ring size.* As observed in our recent work,[9] aldehyde transposition frequently occurs quantitatively if a more stable radical can be formed thereby. The rearrangement VII → VIII is therefore understandable in view of the stability of the allylic radical.[10,11]

The absence of an *aldehydo* methyl cyclopentane implies that path c is kinetically preferred to path d. This follows because the retrocyclization, X → VI, is not in keeping with the ample literature precedents.[2,3,5]

Furthermore, since the competing sites in VI for radical attack are both neopentyl, do the results imply that an aldehyde may be less susceptible to steric hindrance in radical attack than an alkene?

Answers to questions such as the foregoing and a full exposition of the kinetic implications of the case histories in Chart I must await further study. However, for the present it seems beyond question that radical cyclization of a 5-formyl-*n*-pentyl radical to give a cyclohexanol seems to be preferred to cyclization of a 5-hexenyl radical. Further examination of this surprising departure from conventional wisdom is under way and will be reported in due course.

Acknowledgment. We are deeply indebted to our colleague, Professor Ned Porter, for his sustained interest and several helpful discussions.

Metal-Mediated Approach to Enynes

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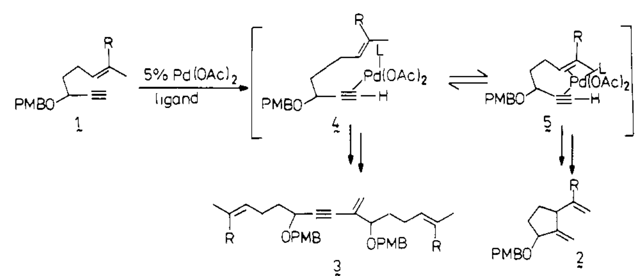
The presence of enynes in natural products and their utility as building blocks for further structural elaboration stimulate the interest in seeking simple synthetic routes to them. One of the more attractive is the coupling of terminal acetylenes with vinyl halides or triflates.[1] The direct coupling of two acetylenes, while highly attractive since economy of mass is optimized (i.e., the product corresponds to the exact sum of the two reactants) has failed to be synthetically useful[2–4] due to lack of control and the preference for trimerization. We wish to report that the homocoupling and cross-coupling of acetylenes can be achieved in high yield by using a palladium template.

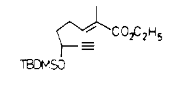
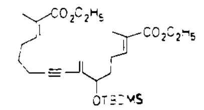
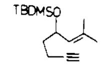
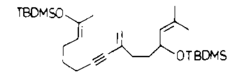
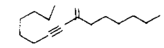
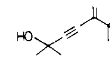
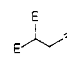
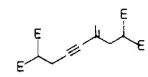
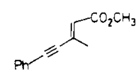
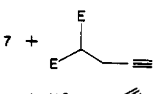
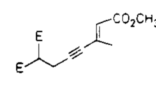
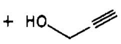
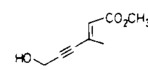
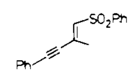
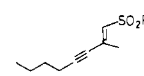
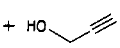
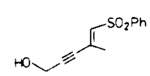
During the course of our studies of the enyne cyclization[5] of **1** (R = CH_3) using Ph_3P and $Pd(OAc)_2$, we noted that in competition with the anticipated cyclization to cyclopentane **2** (R = CH_3), we obtained a dimeric product whose spectral data identified it as enyne **3** (R = CH_3).[6] Anticipating that formation of the



cyclopentane required bidentate coordination as illustrated in **5** (R = CH_3), the unexpected formation of the dimer may arise from the steric hindrance associated with a trisubstituted double bond serving as a ligand. By favoring the monodentate coordination as in **4** (R = CH_3), insertion in the acetylene hydrogen may compete with cyclization and ultimately produce the enyne **3** (R = CH_3). This explanation suggests that increasing the steric bulk of the ligand should disfavor formation of **5** (R = CH_3) and thus disfavor formation of the cyclization product **2** (R = CH_3). By use of tri-*o*-tolylphosphine in lieu of triphenylphosphine, the isolated yield of enyne jumps from between 9% and 22% to 66.5%.

In seeking to generalize this useful coupling with substrates possessing less substituted olefins such as **1** (R = H), we antic-

Table I. Additional Homo- and Codimerization of Acetylenes[a]

entry	acetylene(s)	time, h	enyne[e]	yield
1[b]		16		83%
2		14		89%
3		64		63%
4[c]		24		64%
5		19		81%
6[d]	$CH_3C{\equiv}CCO_2CH_3$ (**7**) + $PhC{\equiv}CH$	0.5		92%
7[d]	**7** + 	15		87%
8[d]	**7** + 	7		67%
9[d]	$CH_3C{\equiv}CSO_2Ph$ (**8**) + $PhC{\equiv}CH$	2		91%
10[d]	**8** + $nC_4H_9C{\equiv}CH$	24		54%
11[d]	**8** + 	18		50%

[a] All reactions were done at room temperature either in PhH or PhH-d_6 using 2–5 mol % palladium acetate and 2–5 mol % phosphine **6** unless stated otherwise. [b] In this case, tri-*o*-tolylphosphine was employed. [c] The dimeric product has a mp 77–78 °C (lit.[2a] mp 77.5–79°). In addition, we obtained 21% of a trimeric product. [d] CH_3 group and vinyl H shifts at δ 2.38 and 6.14 (entry 6), δ 2.20 and 5.95 (entry 7), δ 2.29 and 6.06 (entry 8), δ 2.38 and 6.63 (entry 9), δ 2.22 and 6.43 (entry 10), and δ 2.23 and 6.50 (entry 11). [e] See ref 6.

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(6) All new compounds have been fully characterized spectrally and elemental composition has been established by combustion analysis and/or high-resolution mass spectroscopy.

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