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A New Five-Membered Ring Annulation Method Based on Pd(0)-Catalyzed Intramolecular Coupling of Vinyl Iodide and Enolate Anion Functions

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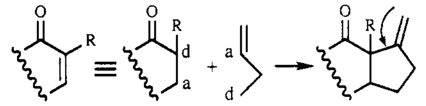
Summary: Conjugate addition of the cuprate reagent **6** to the enones **7**, **11**, and **15a–c**, followed by treatment of the resultant products with I_2 in CH_2Cl_2, provides the keto iodides **9**, **13**, and **17a–c**, respectively. Cyclization of the latter substances via a novel Pd(0)-catalyzed coupling process affords the annulation products **10**, **14**, and **19a–c**.

The discovery of new methods for the construction of usefully functionalized five-membered rings continues to be a current research objective. In connection with a continuing interest in developing five-membered ring annulations that would be useful in natural product syntheses, we were intrigued by the possibility of effecting conversion of an enone (see **1**) into a methylenecyclopentane annulation product of general structure **4**. This transformation would require the (theoretical) combination of synthon **2** (equivalent to **1**) with the 1-butene a^2,d^4 synthon[1] **3**. Thus, a reagent equivalent to **3** would have to be developed and a method for forming the carbon-carbon bond designated by the arrow in **4** would have to be devised. We report here preliminary results of a study that brings this idea to fruition.

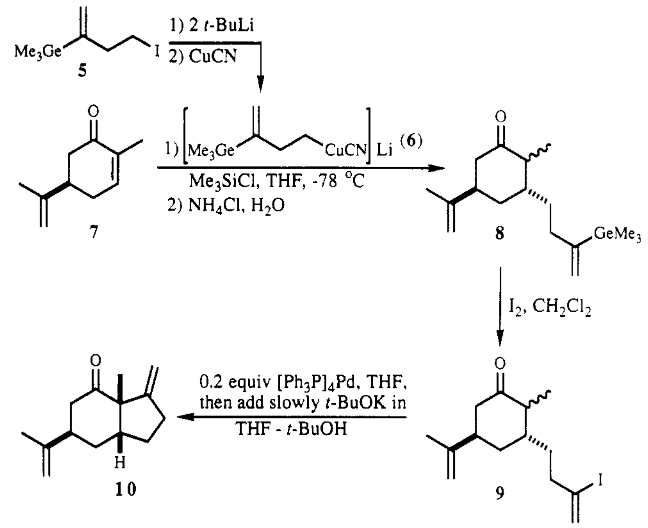


1 2 3 4

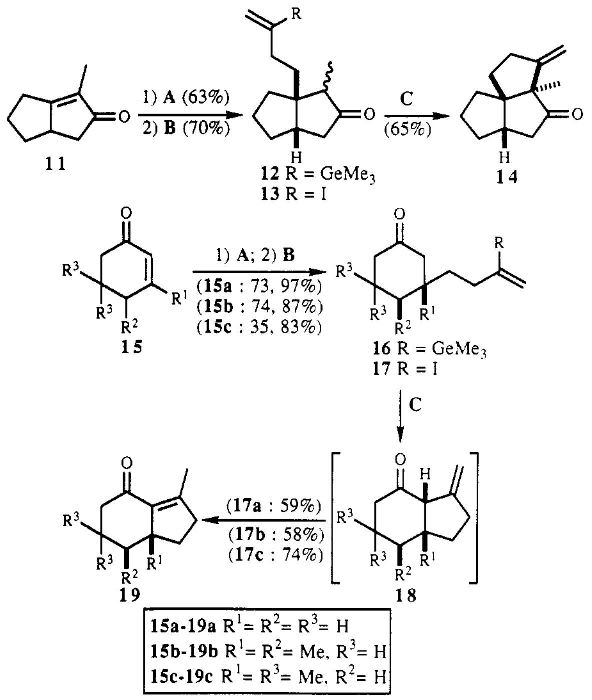
Rapid addition of *t*-BuLi (2 equiv, pentane solution) to a cold (−95 °C) solution of 4-iodo-2-(trimethylgermyl)-1-butene (**5**)[2] in dry tetrahydrofuran (THF), followed by addition of CuCN (~1.1 equiv) and brief warming of the mixture to −35 °C, provided a solution of the lower order cuprate **6** (see Scheme I). Reaction (−78 °C) of the latter species with (*R*)-(−)-carvone (**7**) in the presence of Me_3SiCl gave, after hydrolysis of the resultant enol silyl ether, the conjugate addition product **8**[3] (88%, mixture of epimers at C-2). Transformation[4] of the vinylgermane **8** into the corresponding iodide **9** proceeded smoothly (80%).

Based on results obtained from a number of exploratory reactions, it was found that the annulative conversion of **9** into the bicyclic keto alkene **10** could be effected conveniently via the following procedure. To a solution (dry THF, room temperature, argon atmosphere) of **9** containing ~0.2 equiv of $[Ph_3P]_4Pd$ was added, *slowly*,[5] a solution of *t*-BuOK in *t*-BuOH–THF. Workup, followed by flash chromatography[6] of the crude product on silica gel, produced the annulation product **10** in 65% yield.

Scheme I



Scheme II^a



^{a}(A) reagent **6**, THF, Me_3SiCl, −78 °C; NH_4Cl, H_2O; (B) I_2, CH_2Cl_2, overnight; (C) $[Ph_3P]_4Pd$, THF, then add, dropwise, *t*-BuOK, *t*-BuOH–THF, and stir for an additional 1 h.

The overall annulation method shown in Scheme I was applied to a number of other enones, and the results are summarized in Scheme II.

A number of comments regarding the annulation sequences shown in Schemes I and II should be made. Based on ample literature precedents,[7–9] the stereochemistry of

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[1] Cf. Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.

[2] Piers, E.; Marais, P. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1222.

[3] All compounds reported herein exhibited spectra in full accord with structural assignments. New compounds were carefully purified and gave satisfactory elemental (C, H) analyses and/or molecular mass determinations (high-resolution mass spectrometry).

[4] Oda, H.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 3221.

[5] It was important to add the solution of base slowly (dropwise, over a period of ~3 h). Higher concentrations of base in the reaction mixture resulted in a competition between the desired cyclization and elimination of the elements of HI from the substrate, to form the corresponding keto alkyne. Even under the "optimized" conditions, the annulation product was usually accompanied by minor amounts of the alkyne.

[6] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[7] Allinger, N. L.; Riew, C. K. *Tetrahedron Lett.* **1966**, 1269. House, H. O.; Fischer, W. F., Jr. *J. Org. Chem.* **1968**, *33*, 949.

[8] Paquette, L. A.; Roberts, R. A.; Drtina, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 6690, and citations therein.

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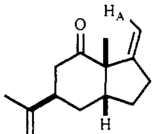
the conjugate addition products **8**, **12**, and **16b** derived from the enones **7**, **11**,[10] and **15b**, respectively, could be assigned with confidence. The Pd(0)-catalyzed ring closures of **9** and **13** were expected to produce the corresponding cis-fused products (**10**, **14**, respectively), and these predictions were confirmed by ^{1}H NMR spectroscopy. Thus, in a NOE difference experiment, irradiation at δ 1.25 (angular Me signal) in the ^{1}H NMR spectrum of **10**, caused enhancement of the signal (δ 4.84) due to H_A. Similarly, saturation of the signal (δ 1.08) due to the angular Me group in the ^{1}H NMR spectrum of **14** increased the intensity of the resonance (δ 4.93) due to H_B. Molecular models show clearly that these signal enhancements are possible only if the substances **10** and **14** have the stereochemistry indicated. In the corresponding trans-fused isomers, the angular methyl protons and the designated olefinic protons (H_A, H_B) are spatially remote and nuclear Overhauser enhancements would be very unlikely.



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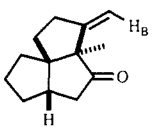

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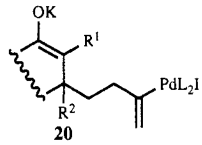
The initially formed annulation products (e.g. **18a–c**) derived from keto iodides (e.g. **17a–c**) that do not contain an α-substituent at C-2 are unstable under the reaction conditions necessary for ring closure. Not surprisingly, the presence of base (t-BuOK) causes isomerization of these substances to the more stable conjugated ketones (e.g. **19a–c**).

Although a detailed mechanistic discussion is beyond the scope of this paper, it may be proposed that the novel Pd(0)-catalyzed cyclization[11] of **9**, **13**, and **17a–c** occurs, in each case, via an intermediate of general structure **20**. The latter species would be formed from the substrate keto iodide by a combination of oxidative addition of the Pd(0) catalyst to the carbon–iodide bond and the formation of an enolate anion by proton abstraction by base (t-BuOK). Intramolecular "transmetalation" of **20** would afford the six-membered palladocycle **21**, which, upon reductive elimination of Pd(0) would provide the cyclized product **22**.



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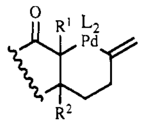

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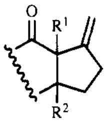

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It is interesting to note explicitly that the new methylenecyclopentane annulation method described herein (see **1** → **4**) is regiochemically opposite (and therefore complementary) to that developed earlier in our laboratory.[12] Extensions to this work, including the application of the newly developed annulation sequence to natural product synthesis, are in progress.

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Supplementary Material Available: Experimental procedures for the preparation of, and spectral data for, compounds **8–10**; ^{1}H NMR spectra of compounds **8–10**; ^{13}C NMR spectrum of compound **10**; spectral data for compounds **12–14**, **16a–c**, **17a–c**, and **19a–c** (9 pages). Ordering information is given on any current masthead page.

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(9) Ziegler, F. E.; Reid, G. R.; Studt, W. L.; Wender, P. L. *J. Org. Chem.* **1977**, *42*, 1991.

(10) The enone **11** was prepared from the *N,N*-dimethylhydrazone of cyclopentanone via the following four-step sequence (see: Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1362): LDA, THF, 0 °C, then 1,2-epoxybutane; $NaIO_4$, THF, H_2O; pyridinium chlorochromate, CH_2Cl_2; KOH, EtOH. For an alternative preparation, see: Begley, M. J.; Cooper, K.; Pattenden, G. *Tetrahedron* **1981**, *37*, 4503.

(11) For examples of Pd(0)-catalyzed intramolecular coupling of *aryl* iodides with soft enolate anions, see: Ciufolini, M. A.; Qi, H.-B.; Browne, M. E. *J. Org. Chem.* **1988**, *53*, 4149 and citations therein. For examples of transition metal catalyzed intramolecular carbonylative coupling of aryl and vinyl iodides with soft enolate anions, see: Negishi, E.; Zhang, Y.; Shimoyama, I.; Wu, G. *J. Am. Chem. Soc.* **1989**, *111*, 8018.

(12) Piers, E.; Karunaratne, V. *J. Chem. Soc., Chem. Commun.* **1983**, 935; *Tetrahedron* **1989**, *45*, 1089.

Acceleration of Cope Rearrangement by a Remote Carbenium Ion Center: Theoretical Elucidation of the Electronic Origin

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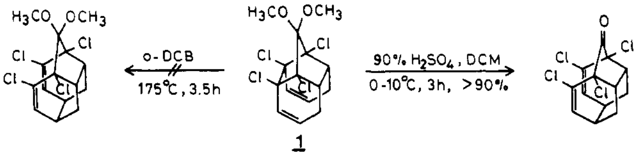
Summary: MNDO calculations on model systems reveal a stepwise process via classical carbocation intermediates as well as a pathway involving a pyramidal, bis-olefin π-complex of CH^+ as being responsible for the acid catalysis of Cope rearrangement found recently in a rigid tetracyclic system.

Recently a remarkable acceleration of Cope rearrangement by a remote carbenium ion center was found in a rigid tetracyclic molecule, **1** (Scheme I).[2] Direct conjugation at the transition state cannot be the driving force in this system, unlike in the previously known acid-catalyzed Cope rearrangements (Scheme II).[3] However, there

Scheme I



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(1) (a) Indian Institute of Science. (b) University of Hyderabad.

(2) Mehta, G.; Padma, S. *J. Org. Chem.* **1988**, *53*, 4892.

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