A New Allenic Pauson-Khand Cycloaddition for the Preparation of α-Methylene Cyclopentenones

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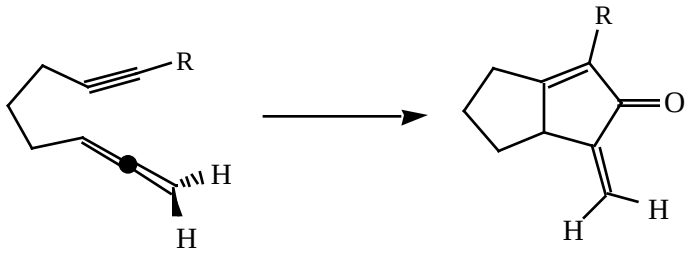
Abstract: Alkynyl allenes undergo an intramolecular molybdenum-mediated Pauson-Khand cycloaddition to provide functionalized α-methylene cyclopentenones in one step.

The chemistry of allenes has received an enormous amount of attention recently; this may in part be due to the versatility imparted by this moiety. For instance, allenes have been used successfully in a variety of reactions including cycloadditions,[1] electrocyclizations[2] and in the formation of π-allyl palladium complexes.[3] Curiously no examples of the use of allenes as the olefin component in the Pauson-Khand (P-K) reaction have been reported. The Pauson-Khand reaction, the three component cyclopentenone synthesis, has been used extensively in the synthesis of natural products.[4] We have recently discovered that alkynyl allenes are viable substrates for intramolecular P-K cycloadditions (Scheme 1). This cycloaddition directly affords substituted α-methylene cyclopentenones. This substructure is embodied in a number of biologically active compounds such as the triquinane sesquiterpene[5] and methylenomycin antitumor antibiotics.[6]

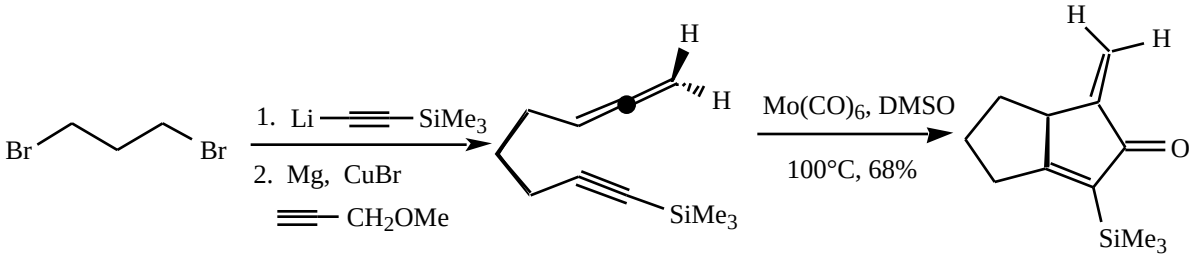
Scheme 1



1 **2**

In order to determine the feasibility of the allenic P-K cycloaddition we prepared compound **3** according to Scheme 2. Addition of lithium trimethylsilylacetylide to 1,3-dibromopropane followed by treatment of the resulting bromoalkyne with magnesium, catalytic copper bromide and propargyl methyl ether afforded the desired alkynyl allene **3**.[7,11] All attempts to effect a Pauson-Khand type cycloaddition of compound **3** using dicobalt octacarbonyl [$Co_2(CO)_8$] were unsuccessful.[8] However, use of conditions reported by Jeong and coworkers[9] proved to be quite successful in the formation of α-methylene cyclopentenone **4**. Treatment of alkynyl allene **3** with molybdenum hexacarbonyl [$Mo(CO)_6$] and dimethylsulfoxide at 100°C[10] gave compound **4** in a 68% yield.[11]

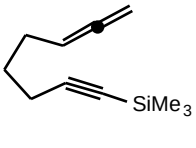
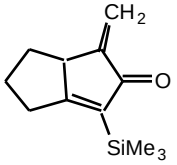
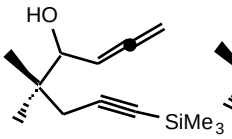
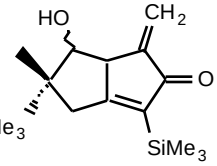
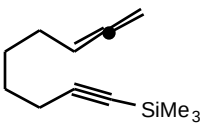
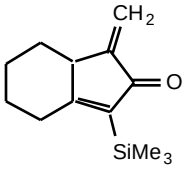
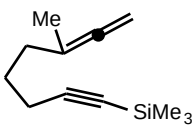
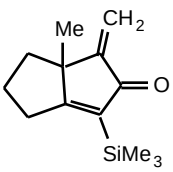
Scheme 2



3 **4**

The scope of this new method is currently under investigation. The various examples that have been examined thus far are collected in Table I. We have prepared a system that contains C-4 and C-5 substitution on the tether (entry 2). This cycloaddition was effected to give the highly-functionalized bicyclic α-methylene cyclopentenone as a mixture of diastereomers (3:1) in 47% yield.[11] Based on this result, the allenic P-K reaction appears to be more facile and higher yielding than a normal P-K reaction.[12] Increasing the length of the tether by one methylene unit (entry 3) gave the corresponding bicyclo[4.3.0]nonane ring system. The cycloaddition went in a much lower yield in comparison to entry 1, in accordance with a typical enyne P-K reaction.[13] We also examined a variation of substituents on the allene moieties (entry 4). In this case the additional substituent prevented the cycloaddition from occurring. Decomposition of starting material was observed after heating for 16h at 100°C.

TABLE I

Entry	Alkynyl Allene	α-Methylene Cyclopentenone	Reaction Conditions	Yield
1			$Mo(CO)_6$, DMSO 100°C, toluene	68%
2			$Mo(CO)_6$, DMSO 100°C, toluene	47%[a]
3			$Mo(CO)_6$, DMSO 80°C, benzene	30%
4			$Mo(CO)_6$, DMSO 100°C, toluene	0%

[a] Product was isolated as a mixture of diastereomers (3 : 1). For spectroscopic data of the alkynyl allene and the two diastereomeric α-methylene cyclopentenones see ref. 11.

In summary, the first examples of allenes used in the Pauson-Khand cycloaddition are reported herein. We are currently investigating other aspects of this reaction. How does allenic strain affect the allenic P-K cycloaddition and how complete is the transfer of chirality in the cycloaddition if the starting allene is chiral? This method is also being applied to the total synthesis of the antitumor antibiotic hypnophilin.

Typical Procedure: To a 0.1M solution of alkynyl allene in toluene or benzene was added dimethyl sulfoxide (10 equiv) followed by molybdenum hexacarbonyl (1.2 equiv). The mixture was heated to 80°-100°C and maintained at this temperature for 3h under argon atmosphere. The mixture turned from clear to yellow to dark brown/blue, after which time TLC analysis indicated consumption of the starting alkynyl allene. The reaction mixture was cooled to room temperature and the solids were removed by filtration through Celite. The filtrate was concentrated and the product was purified by flash chromatography on silica gel (ethyl acetate-hexanes).

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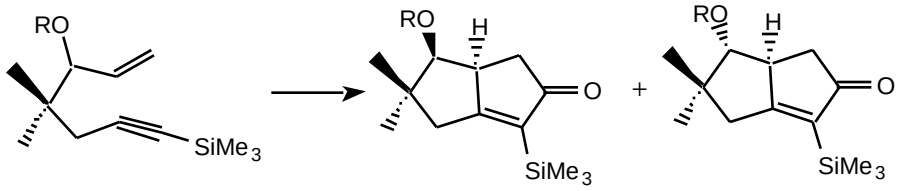
10. Cycloadditions were performed at the lowest effective temperature in order to minimize decomposition of the somewhat labile α-methylene cyclopentenones.

11. All new compounds reported herein exhibit satisfactory spectral (IR, NMR, MS) characteristics. **Alkynyl Allene 3**: R_f 0.68 (1:19, ethyl acetate-hexanes); IR (neat) 2958, 2175, 1957, 1250, 842, 760 cm^{-1}; ^1H NMR (270MHz, $CDCl_3$) δ5.10 (dt, J=13.1, 5.9Hz, 1H), 4.68 (m, 2H), 2.28 (t, J=8.1Hz, 2H), 2.11 (m, 2H), 1.65 (t, J=6.5Hz, 2H), 0.14 (s, 9H); MS m/e 163 (M-15), 147, 135, 118, 109. **α-Methylene cyclopentenone 4**: R_f 0.30 (1:19, ethyl acetate-hexanes); IR (neat) 2935, 1692, 1597, 1249 cm^{-1}; ^1H NMR (270MHz, $CDCl_3$) δ5.92 (dd, J=2.1, 1.2Hz, 1H), 5.27 (br dd, J=1.6, 1.1Hz, 1H), 3.32 (m, 1H), 2.65 (m, 1H), 2.56 (m, 1H), 2.29-2.18 (m, 1H), 2.14-2.05 (m, 2H), 1.22-1.09 (m, 1H), 0.27 (s, 9H); MS m/e 206 (M^+), 191, 163, 135, 117. **Entry 2, Alkynyl Allene**: R_f 0.43 (1:4, ethyl acetate-hexanes); IR (neat) 3449, 2174, 1956, 1250, 1037, 842, 760 cm^{-1}; ^1H NMR (270MHz, $CDCl_3$) δ5.28 (q, J=6.6, 1H), 4.87 (dd, J=2.4, 6.6, 2H), 4.04 (m, 1H), 2.30 (d, J=16.9Hz, 1H), 2.18 (d, J=16.7Hz, 1H), 1.96 (d, J=5.1Hz, 1H), 0.99 (s, 3H), 0.98 (s, 3H), 0.15 (s, 9H); ^{13}C NMR (67.9MHz, $CDCl_3$) δ207.6, 105.0, 91.4, 87.0, 77.4, 75.6, 38.6, 29.9, 23.1, 22.2, 0.1; MS m/e 222 (M^+), 207, 183, 139, 111, 73. **Entry 2, α-Methylene cyclopentenone**: IR (neat) 3431, 2957, 1682, 1647, 1591, 1248, 841 cm^{-1}; Major isomer: R_f 0.13 (1:5, ethyl acetate-hexanes); ^1H NMR (270MHz, $CDCl_3$) δ5.93 (dd, J=2.0, 1.1Hz, 1H), 5.50 (t, J=1.3Hz, 1H), 3.58 (d, J=10.1Hz, 1H), 3.41 (d, J=10.1Hz, 1H), 2.72 (d, J=18.7Hz, 1H), 2.47 (d, J=18.7Hz, 1H), 1.19 (s, 3H), 1.11 (s, 3H), 0.20 (s, 9H); ^{13}C NMR (67.9MHz, $CDCl_3$) δ185.8, 146.0, 139.2, 114.0, 82.0, 55.4, 43.4, 43.0, 28.2, 25.8, 23.7, -1.2; MS m/e 250 (M^+), 235, 217, 207, 180, 160, 117, 75, 73. Minor isomer: R_f 0.13 (1:5, ethyl acetate-hexanes); ^1H NMR (270MHz, $CDCl_3$) δ6.08 (br s, 1H), 5.34 (br s, 1H), 3.88 (s, 2H), 2.58 (d, J=17.8Hz, 1H), 2.50 (d, J=17.4Hz, 1H), 1.21 (s, 6H), 0.21 (s, 9H); ^{13}C NMR (67.9MHz, $CDCl_3$) δ191.3, 143.0, 139.0, 114.7, 77.2, 56.5, 45.9, 41.5, 41.4, 29.2, 23.7, -1.2; MS m/e 250 (M^+), 235, 207, 180, 117, 75, 73.

12. The toleration of the substitution at C-5 appears to be higher in the allenic P-K reaction when one compares the example below with entry 2 in Table I. See Ref. 4, pp. 1053-1054.



R=H, 25% yield 28 : 72

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