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Intramolecular Ketene−Allene Cycloadditions

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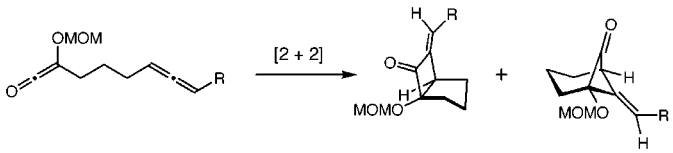
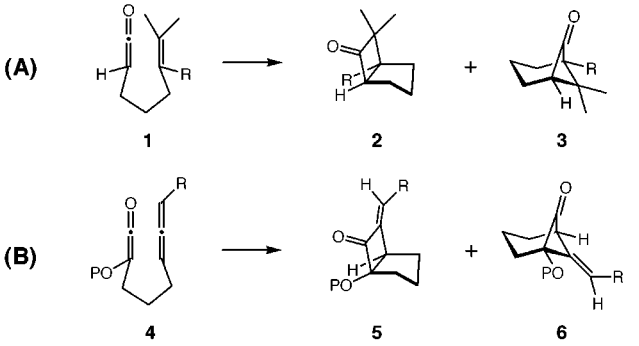
ABSTRACT



This report describes intramolecular thermal [2 + 2] cycloadditions between ketenes and allenes. The formation of ketenes and the subsequent cycloadditions occurred under a variety of conditions, affording 7-methylidinebicyclo[3.2.0]heptanones and 7-methylidinebicyclo[3.1.1]heptanones in 45−78% yields. The regioselectivity of the cycloaddition varied with the substitution of the allene, and the yield of cyclized products varied with reaction conditions.

Intramolecular [2 + 2] ketene−olefin cycloadditions have been successfully applied to the synthesis of several natural products.[1] A general cycloaddition is shown in Scheme 1A.[1g] Ketene−allene [2 + 2] cycloadditions have also been reported in the intermolecular mode, although they have not been as widely studied.[2] To the best of our knowledge, an intramolecular ketene−allene cycloaddition has not been reported.[3] This Letter describes the synthesis of compounds containing ketenes tethered to allenes and their thermal [2 + 2] cycloadditions to give 7-methylidinebicyclo[3.2.0]-heptanones and 7-methylidinebicyclo[3.1.1]heptanones (Scheme 1B).

Scheme 1



The system chosen for study was compound **4** (Scheme 1B), which has a three-atom tether between the ketene and the allene. The alkoxy group was built into the system to exploit the possibility that heteroatoms on the ketene might facilitate the cycloaddition.[1g] [2 + 2] cycloadditions with

(1) Selected examples of intramolecular ketene−olefin cycloadditions: (a) Paquette, L. A.; Sun, L. Q.; Watson, T. J. N.; Friedrich, D.; Freeman, B. T. *J. Org. Chem.* **1997**, *62*, 8155−8161. (b) Shishido, K.; Azuma, T.; Shibuya, M. *Tetrahedron Lett.* **1990**, *31*, 219−220. (c) Snider, B. B.; Allentoff, A. J.; Walner, M. B. *Tetrahedron* **1990**, *46*, 8031−8042. (d) Kher, S. M.; Kulkarni, G. H.; Mitra, R. B. *Synth. Commun.* **1989**, *19*, 597−604. (e) Corey, E. J.; Kang, M.; Desai, M. C.; Ghosh, A. K.; Houpis, J. N. *J. Am. Chem. Soc.* **1988**, *110*, 649−651. (f) Funk, R. L.; Novak, P. M.; Abelman, M. M. *Tetrahedron Lett.* **1988**, *29*, 1493−1496. (g) Snider, B. B. *Chem. Rev.* **1988**, *88*, 793−811. (h) Brady, W. T.; Marchand, A. P.; Giang, Y. F.; Wu, A. H. *Synthesis* **1987**, 395−396.

(2) Selected examples of intermolecular ketene−allene [2 + 2] cycloadditions: (a) Brady, W. T.; Giang, Y. S. F.; Marchand, A. P.; Wu, A. H. *J. Org. Chem.* **1987**, *52*, 3457−3461. (b) Bertrand, M.; Gil, G.; Junino, A.; Maurin, R. *Tetrahedron* **1985**, *41*, 2759−2764. (c) Bertrand, M.; Maurin, R.; Gras, J. L.; Gil, G. *Tetrahedron* **1975**, *31*, 849−855. (d) Bertrand, M.; Gras, J. L.; Gore, J. *Tetrahedron* **1975**, *31*, 857−862. (e) Bampfield, H. A.; Brook, P. R.; McDonald, W. S. *J. Chem. Soc., Chem. Commun.* **1975**, 132−133. (f) Brady, W. T.; Stockton, J. D.; Patel, A. D. *J. Org. Chem.* **1974**, *39*, 236−238. (g) Duncan, W. G.; Weyler, W., Jr.; Moore, H. W. *Tetrahedron Lett.* **1973**, *44*, 4391−4394. (h) Tidwell, T. T. *Ketenes*; Wiley: New York, 1995. (i) Brady, W. T. Stockton, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7447−7449. (j) Weyler, W. J.; Byrd, L. R.; Caserio, M. C.; Moore, H. W. *J. Am. Chem. Soc.* **1972**, *94*, 1027−1029. (k) England, D. C.; Krespan, C. G. *J. Org. Chem.* **1970**, *35*, 3322−3327. (l) Huang, W.; Tidwell, T. T. *Synthesis* **2000**, *3*, 457−470.

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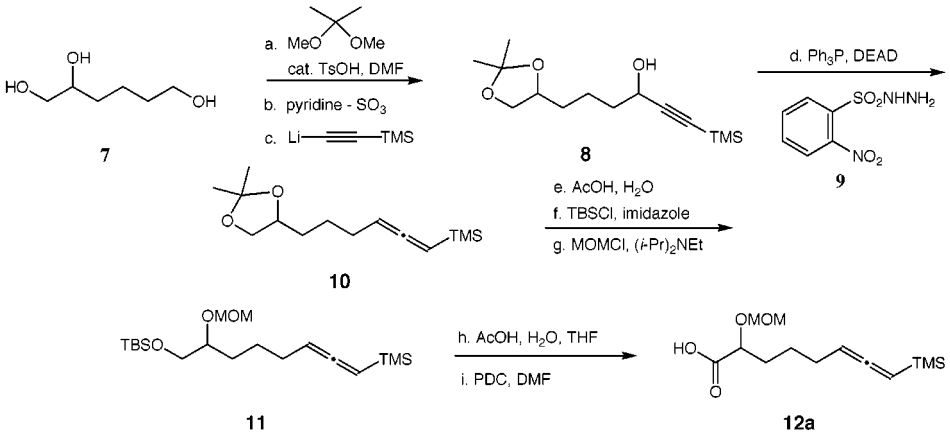
Scheme 2[a]



[a] Reagents and conditions: (a) 2,2-dimethoxypropane (1 equiv), TsOH (0.2 equiv), DMF, rt, 3 h (57%); (b) pyridine−SO_3 (2 equiv), DMSO (4 equiv), Et_3N (3 equiv), CH_2Cl_2, 0 °C, 4 h, (91%); (c) trimethylsilylacetylene (1.1 equiv), *n*-BuLi (1.1 equiv), 0 °C to rt, 10 h, (95%, 1:1 mixture of diastereomers); (d) Ph_3P (1.3 equiv), DEAD (1.3 equiv), NBSH (**9**) (1.5 equiv), −10 °C to rt, 12 h (95%, 1:1 mixture of diastereomers); (e) AcOH, H_2O (3:1), rt, 3.5 h, (67%); (f) Imidazole (1.5 equiv), TBSCl (1 equiv), DMF, rt, 1.5 h, (93%); (g) DIEA (10 equiv), MOM-Cl (5 equiv), CH_2Cl_2, rt, 16 h, (97%); (h) AcOH, H_2O, THF (3:1:1), rt, 36 h, (96%); (i) PDC (5 equiv), DMF, rt, 18 h, (65%).

ketenes are consistent with a Woodward−Hoffmann allowed [$_\pi 2_s + _\pi 2_a$] process. Presumably, the oxygen, perhaps due to its electronegative nature, lowers the energy of the ketene LUMO, resulting in a better energy match with the allene HOMO.[1g] Three different substituted allenes (**12a**−**c**) were chosen for the initial studies (Scheme 3). These allenes, one with a large electron-donating group (**12a**, R = TMS), one with a dialkyl intermediate (**12b**, R = *n*-Bu), and one with an unsubstituted allene terminus (**12c**, R = H), should provide some preliminary data on the effects of substituents on this reaction. In addition, it was anticipated that generation of the ketene would be immediately followed by a rapid cyclization, so attempts were not made to isolate the intermediate ketenes.[1f,2i,4]

The ketene cyclization precursors were synthesized from 1,2,6-trihydroxyhexane, **7** (Scheme 2). The 1,2-diol was protected as an acetonide; then the primary alcohol was oxidized with pyridine−SO_3, to give the corresponding aldehyde.[5] Deprotonation of trimethylsilylacetylene with *n*-butyllithium and addition of the aldehyde afforded the propargyl alcohol adduct **8** as a 1:1 mixture of diastereomers. Reduction with triphenylphosphine, diethyl azodicarboxylate, and *o*-nitrobenzenesulfonylhydrazide, **9**, according to the method of Myers,[6] provided **10** in 95% yield. The product allene was isolated as a 1:1 mixture of diastereomers. Hydrolysis of the acetonide with 3:1 acetic acid:H_2O, selective protection of the primary alcohol as a *tert*-butyldimethylsilyl ether, and protection of the secondary alcohol as a methoxymethyl ether gave **11**. Removal of the *tert*-butyldimethylsilyl group with 3:1:1 AcOH:H_2O:THF gave an intermediate alcohol that was converted to the carboxylic acid **12a** by oxidation with pyridinium dichromate in DMF.[7] Allenes **12b** (R = *n*-Bu) and **12c** (R = H) were synthesized by an analogous sequence of reactions (full details are available in the Supporting Information).

Two different methods for the generation of ketenes from **12a**−**c** and subsequent cycloadditions were studied. Method A employed the conditions developed by Funk and co-workers, in which a carboxylic acid is added to a solution of triethylamine and 2-chloro-*N*-methylpyridinium iodide in acetonitrile heated at reflux.[1f,4] Method B is the classical method for generating ketenes by treating the corresponding acyl chloride with an amine base in benzene heated at reflux.[2i] The products of the intramolecular [2 + 2] cycloaddition are shown in Scheme 3.

Two major products, **15** and **16**, were obtained from the [2 + 2] process. Compound **15** arose from formation of a bond between the central ketene carbon and the central allene carbon to afford the [3.2.0] fused bicyclic system. The [3.1.1] bridged bicyclic system **16** resulted from bond formation between the alkoxy-substituted carbon of the ketene with the central allene carbon and the central ketene carbon with

(3) Selected examples of intramolecular cycloadditions with allenes: (a) Villar, F.; Equey, O.; Renaud, P. *Org. Lett.* **2000**, *2*, 1061−1064. (b) Brummond, K. M.; Lu, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 5087−5088. (c) Wender, P. A.; Fuji, M.; Husfeld, C. O.; Love, J. A. *Org. Lett.* **1999**, *1*, 137−139. (d) Wei, L. L.; Hsung, R. P.; Xiong, H.; Mulder, J. A.; Nkansah, N. T. *Org. Lett.* **1999**, *1*, 2145−2148. (e) Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139−11143. (f) van Henegouwen, W. G. B.; Fieseler, R. M.; Rutjes, F.; Hiemstra, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2214−2217. (g) Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012−10020. (h) Arredondo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 3633−3639. (i) Carreira, E. M.; Hastings, C. A.; Shepard, M. S.; Yerkey, L. A.; Millward, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 6622−6630. (j) Yoshida, M.; Hidaka, Y.; Nawata, Y.; Rudzinski, J. M.; Osawa, E.; Kanematsu, K. *J. Am. Chem. Soc.* **1988**, *110*, 1232−1238. (k) Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453−1473. (l) *Allenes in Organic Synthesis*; Schuster, H. F., Coppola, G. M., Eds.; Wiley-Interscience: New York, 1984. (m) Landor, S. R. *The Chemistry of the Allenes*; Academic Press: New York, 1982.

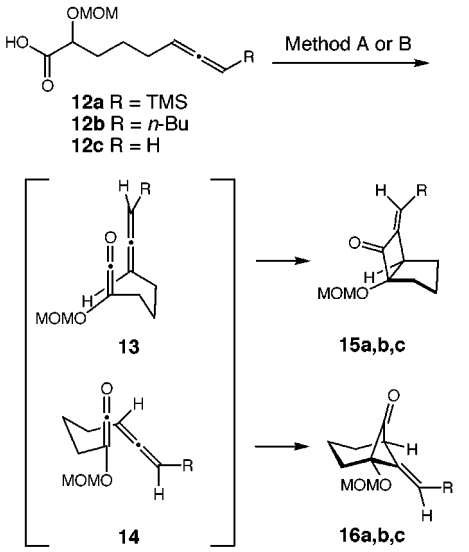
(4) Brady, W. T.; Giang, Y. S. F.; Marchand, A. P.; Wu, A. H. *J. Org. Chem.* **1987**, *52*, 3457−3461.

(5) Doering, W. V. E.; Parihk, J. R. *J. Am. Chem. Soc.* **1967**, *89*, 5507.

(6) Myers, A. G.; Zheng, B. *Org. Synth.* **1998**, *76*, 178−186.

(7) Vedejs, E. D.; Dent, W. H.; Gapinski, D. M.; McClure, C. K. *J. Am. Chem. Soc.* **1987**, *109*, 5437−5446.

Scheme 3[a]



[a] Method A: 2-chloro-*N*-methylpyridinium iodide (4 equiv), Et_3N (8 equiv), CH_3CN, 65 °C, 18h (57−60%). Method B: oxalyl chloride (3 equiv), benzene, rt, 4−10 h (79−99%); Et_3N (2.5 equiv), benzene, reflux, 12h (45−78%).

the internal allene carbon. The ratios of the products observed from these reactions are shown in Table 1.

Table 1. Product Ratios Resulting from the Intramolecular Cycloaddition

	products		
	15	**16**	yield (%)
a: R = TMS	1 (*E*:*Z* = 2.2:1)	3.5 (*E*:*Z* = 4:1)	59,[a] 70[b]
b: R = *n*-Bu	3 (*E*:*Z* = 2:1)	1 (*E*:*Z* = 1:1.2)	60,[a] 78[b]
c: R = H	5	1	57,[a] 45[b]

[a] Method A. [b] Method B.

Both methods used to generate the ketene gave cycloaddition products in approximately the same ratios and yields. The [3.2.0] bicyclic adduct was the major isomer formed from the reaction of **12c** (R = H) and **12b** (R = *n*-Bu). The selectivity of the cycloaddition was different with **12a** (R = TMS); the [3.1.1]bicycloheptanone **16a** was the major product. The *E* olefin isomer was generally the major geometric isomer observed. Interestingly, no products derived from cycloaddition of the ketene with the distal olefin were observed.

The structural characterization of the [3.1.1] and [3.2.0]-7-methyleneheptanones relied on distinguishing between the conjugated and nonconjugated cyclobutanones. The cyclic compounds were separated by flash chromatography on silica gel and HPLC and then analyzed by IR, UV, and NMR spectroscopy (Table 2). The IR spectra of the [3.1.1]-heptanones (**16a**−**c**) displayed the characteristic bands of

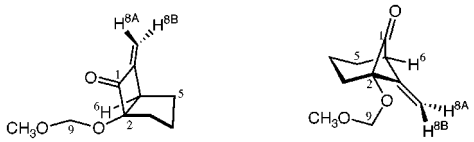
Table 2. Characteristic Absorptions of Conjugated and Nonconjugated Cyclobutanones

	15b	**16b**
IR C=O stretch	1741 cm^{-1}	1790 cm^{-1}
UV (CH_3CN) λ_{max}, nm (log ϵ)	272 (3.03) 374 (1.44)	230 (2.17)

ketones in four-membered rings at 1790 cm^{-1}.[8] Assignment of the structures of **15a**−**c** was supported by the presence of carbonyl stretches of the [3.2.0]heptanones at 1741 cm^{-1} in the IR, which is a 30−45 cm^{-1} shift to lower wavenumber that is generally associated with α,β-unsaturated carbonyls in four-membered rings.[8] Absorptions in the UV region supported the assignments of the conjugated (**15a**−**c**) and nonconjugated (**16a**−**c**) carbonyls. For example, the conjugated ketone **15b** has a λ_{max} at 374 nm in CH_3CN, while the nonconjugated ketone **16b** displayed a shorter λ_{max} at 230 nm in CH_3CN.

NOE difference NMR spectroscopy was also used extensively in assigning both the connectivity of the bicyclic adducts (Table 3) and the olefin stereochemistry of ***E***- and

Table 3. Assignment of Bicyclic Framework Using NOE



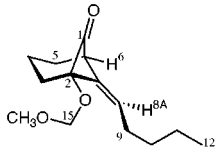
15c		**16c**	
NOE	% enhance.	NOE	% enhance.
$H^6 \rightarrow H^5$	11.8	$H^6 \rightarrow H^5$	2.0
$H^6 \rightarrow H^9$	2.6	$H^6 \rightarrow H^{8A}$	3.9
$H^6 \rightarrow H^{8B}$	<1	$H^{8A} \rightarrow H^{8B}$	5.8
$H^{8A} \rightarrow H^{8B}$	23.0	$H^{8B} \rightarrow H^9$	<1

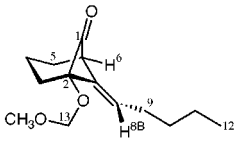
Z*-15** and ***E- and ***Z*-16** (Table 4). Comparing the [3.1.1]-bicycloheptanone **15c** to the [3.2.0]bicycloheptanone **16c**, as shown in Table 3, shows that the major diagnostic NOE is the 2.6% enhancement between H^6 and H^9 in **15c**, which is not observed in **16c**. This observation indicates that the methine proton in **15c** is in close proximity to the methylene of the acetal, a feature allowed only by the [3.2.0]bicycloheptanone.

In the assignment of *Z* versus *E* olefin geometry of **16b**, the observation of an NOE enhancement between H^6 and H^{8A} in ***Z*-16b** supports the assignment as the *Z* isomer, as shown in Table 4. Alternatively, the *E* isomers were assigned on the basis of the observation of an NOE between H^6 and H.[9] The structures of ***E***- and ***Z*-15a** and ***E***- and ***Z*-16a** were assigned by analogous NOE difference experiments.

(8) Lin-Vein, D.; Colthup, N. B.; Fateley, W. G.; Grasselli, J. G. *The Handbook of Infrared and Raman Characteristic Frequencies of Organic Molecules*; Academic Press: San Diego, CA, 1991.

Table 4. Assignment of Olefin Geometry Using NOE





***Z*-16c**		***E*-16c**	
NOE	% enhance.	NOE	% enhance.
$H^6 \rightarrow H^{8A}$	3.2	$H^6 \rightarrow H^5$	<1
$H^6 \rightarrow H5$	2.1	$H^6 \rightarrow H^9$	3.9
$H^6 \rightarrow H^9$	0	$H^6 \rightarrow H^{8B}$	0

The selectivity of these [2 + 2] reactions is worthy of comment. One possible hypothesis to explain the preference for *E* olefin isomers rests on the assumption that, due to steric demands, the ketene will prefer to approach the internal π-bond of the allene from the face which is not blocked by the substituent on the distal carbon of the external π-bond. Based on this assumption, the preference for *E* olefin isomers should increase with larger functional groups on the allene terminus.

The factors governing which bicycle is formed as the major product (Table 1) are less easily rationalized. On the basis of analogy to ketene−olefin cycloadditions,[1g] the bridged system **15** was expected; the silyl-substituted example **12a** gave an anomalous outcome in producing **16a** as the major product. In this case, one must distinguish between the electronic perturbation introduced by the electron-donating silicon and the steric bulk of the trimethylsilyl group. It is not unreasonable to assume that the carbon γ to the silicon is the most nucleophilic of the allene carbons and that this carbon may have a propensity to engage in a bonding interaction with the electrophilic central ketene carbon, which would lead to **16a**. Additional support for this hypothesis awaits future experiments.

In summary, a method for the intramolecular [2 + 2] thermal cycloaddition between an in situ generated ketene and an allene has been developed. This reaction generates bicyclic products containing di- or trisubstituted olefins, depending on the substitution pattern of the allene precursor. Different conditions have been used to generate the ketenes and facilitate the subsequent cycloaddition.

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Supporting Information Available: Full experimental procedures and spectral data for all reported compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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