Development of Molecular Mechanics Torsion Parameters for α,*β*-Cyclopropyl α′,*β*′-Enones and Conformational Analysis of Bicyclo[*m*.1.0]alk-3-en-2-ones

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Conformations of cyclopropyl vinyl ketone have been studied using *ab initio* methods in an effort to quantify the effects of conjugative overlap between the cyclopropane ring and adjacent enone carbonyl. With respect to the cyclopropyl carbonyl torsion, cyclopropyl vinyl ketone exhibits a global energy minimum in the *s*-cis conformer and a local energy minimum in the *s*-trans conformer. The potential energy curve obtained was used to derive torsion parameters which were employed in molecular mechanics studies of the conformations of the set of bicyclo[*m*.1.0]alk-3-en-2-ones having larger ring sizes from 5- to 16-membered.

Introduction

In an effort to develop a general synthetic approach to natural products that contain medium or large carbocyclic rings, we have undertaken studies of the conformations and reactivities of bicyclo[*m*.1.0]alkane derivatives. Previously we obtained molecular mechanics torsion parameters for the cyclopropyl-to-carbonyl *σ* bond of cyclopropyl methyl ketone (CMK) by means of an *ab initio* study of torsion about this bond.[1] The conformational ensembles for the family of bicyclo[*m*.1.0]alkan-2-ones **1** possessing cis ring fusion and $m = 3-14$ or trans ring fusion and $m = 7-14$ were then found by a stochastic search method. It was observed that the local conformation of the α,*β*-cyclopropyl ketone functional group array was similar in all bicyclo[*m*.1.0]alkan-2-ones when $m \geq 6$, independent of ring fusion geometry (Figure 1). It was also observed that, under kinetic control, 1,2-additions of nucleophiles to the carbonyl carbons of these ketones exhibited high diastereoselectivity.[2] This was attributed to the highly conserved local conformation for the α,*β*-cyclopropyl ketone functional group array, which results in hindered approach to one face of the carbonyl due to the transannular atoms of the medium or large ring.[2b]

Bicyclo[*m*.1.0]alk-3-en-2-ones **2** could be of particular value in the construction of natural products that incorporate common, medium, or large carbocyclic rings (Figure 2).[3] Such α,*β*-cyclopropyl α′,*β*′-enones should be derivable from ketones **1**[4] and may afford opportunities for stereocontrolled manipulation of reactive centers at multiple positions on the larger carbocyclic ring. For example, following a diastereoselective 1,2-addition, the resulting allylic alcohol **3** might be employed in a stereocontrolled functionalization of the alkene. Alternatively, a diastereoselective 1,4-addition might be followed by a stereocontrolled alkylation of the enolate **4**.

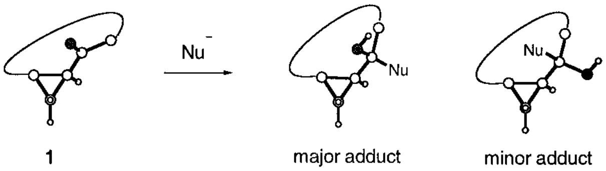

Figure 1. Diastereoselective 1,2-addition to bicyclo[*m*.1.0]-alkan-2-ones **1**.

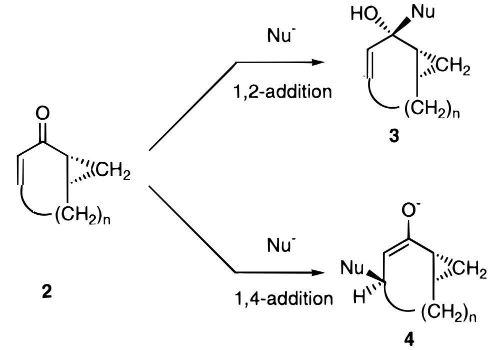

Figure 2. Hypothetical diastereoselective manipulations of bicyclo[*m*.1.0]alk-3-en-2-ones **2**.

Knowledge of the conformational ensembles for the various enones **2** would be useful for prediction of diastereoselectivities and in interpretation of results from synthetic studies. In accord with the Hammond postulate, major and minor product diastereomers should be predictable from knowledge of the conformational ensemble for highly exothermic reactions, such as 1,2-carbonyl addition reactions, where starting material-like transition states are anticipated.[5] A number of synthetic transformations for the alkene moiety are also possible, including 1,4-additions of soft nucleophiles.[6] Mechanisms for such reactions vary, but for those that involve early transition states, consideration of the conformational

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(1) Mash, E. A.; Gregg, T. M.; Stahl, M. T.; Walters, W. P. *J. Org. Chem.* **1996**, *61*, 2738−2742.

(2) (a) Mash, E. A.; Kaczynski, M. A.; Dolata, D. P. *Tetrahedron Lett.* **1990**, *31*, 4565−4568. (b) Mash, E. A.; Gregg, T. M.; Kaczynski, M. A. *J. Org. Chem.* **1996**, *61*, 2743−2752.

(3) For classification of rings by size, see: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994, pp 678.

(4) Enantiomerically enriched bicyclo[*m*.1.0]alkan-2-ones **1** are readily prepared from 2-cycloalken-1-one ketals, see: (a) Mash, E. A.; Nelson, K. A. *Tetrahedron* **1987**, *43*, 679−692. (b) Mash, E. A.; Torok, D. S. *J. Org. Chem.* **1989**, *54*, 250−253. (c) Mash, E. A.; Math, S. K.; Arterburn, J. A. *J. Org. Chem.* **1989**, *54*, 4951−4953.

(5) (a) Kamernitzky, A. V.; Akhrem, A. A. *Tetrahedron* **1962**, *18*, 705−750 and references cited therein. (b) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108−1117. (c) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry;* 3rd ed.; Harper & Row: New York, 1987, pp 661−693 and references cited therein. (d) Wu, Y.-D.; Houk, K. N.; Florez, J.; Trost, B. M. *J. Org. Chem.* **1991**, *56*, 3656−3664. (e) Eksterowicz, J. E.; Houk, K. N. *Chem. Rev.* **1993**, *93*, 2439−2461.

(6) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*, Pergamon Press: Oxford, 1992, Chapters 1 and 3.

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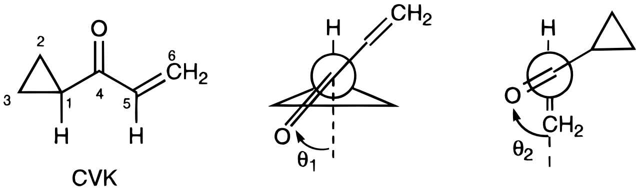
ensemble for an enone starting material may be useful in predicting diastereoselectivity. These considerations prompted the development of suitable molecular mechanics torsion parameters for α,β-cyclopropyl α′,β′-enones and the study of the conformations of bicyclo[*m*.1.0]alk-3-en-2-ones **2** described herein.

Ab Initio Study of Cyclopropyl Vinyl Ketone

Previously we found that the MM2* and MM3* force fields resident in BATCHMIN version 4.0[7] and the AM1, PM3, and MNDO semiempirical Hamiltonians in Spartan version 4.0[8] did not reflect the torsion-dependent stabilization expected from conjugative overlap of a cyclopropane with a ketone carbonyl.[1] In order to develop suitable molecular mechanics torsion parameters for α,β-cyclopropyl α′,β′-enones, an *ab inito* study of cyclopropyl vinyl ketone (CVK) was undertaken.[9] A major complication in the study of CVK is the simultaneous torsional freedom of both the vinyl and cyclopropyl groups. From consideration of orbital overlap, energy minima are expected at or near $\theta_1 = 0°$ (*s*-cis) and $\theta_1 = 180°$ (*s*-trans) for the cyclopropyl carbonyl functional group array and at or near $\theta_2 = 0°$ (*s*-cis) and $\theta_2 = 180°$ (*s*-trans) for the enone functional group array.[10] As a simplification in the present work, the enone geometry was initially set to *s*-cis ($\theta_2 = 0°$) but not constrained. A torsion driving study was performed on CVK by constraining the cyclopropyl−carbonyl bond at 10° intervals between the *s*-cis ($\theta_1 = 0°$) and *s*-trans ($\theta_1 = 180°$) conformers. Each conformer was optimized using Gaussian 92[11] at the RHF level with the 3-21G basis set. The resulting geometries were then re-optimized using the 6-31G* basis set with electron correlation at the MP2 level. Numerical results for these calculations are given in Table 1 and are presented graphically in Figure 3.



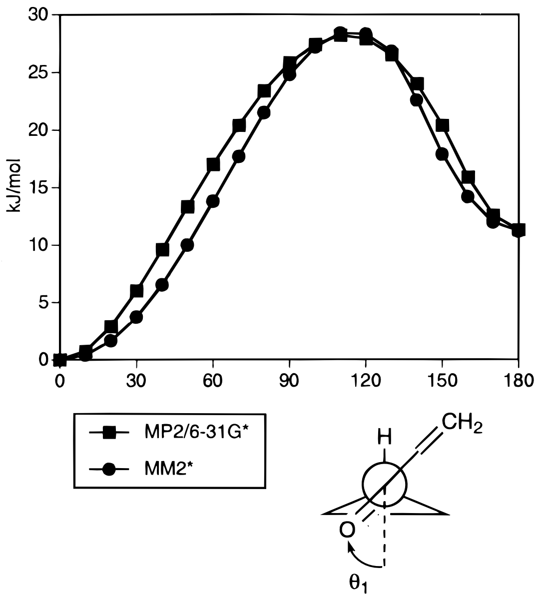


Figure 3. Energy barrier to rotation about the C(1)−C(4) σ bond of cyclopropyl vinyl ketone (CVK) calculated using *ab initio* methods and a modified MM2* force field.

Table 1. *Ab Initio* and Relative Energies for the C(1)−C(4) σ Bond Torsion of Cyclopropyl Vinyl Ketone (CVK)

	ab initio energies (hartrees)		relative energies (kJ/mol)	
θ_1, deg	RHF/ 3-21G	MP2/ 6-31G*	RHF/ 3-21G	MP2/ 6-31G*
0	−304.9606	−307.6484	0.00	0.00
10	−304.9603	−307.6481	0.75	0.75
20	−304.9595	−307.6473	2.89	2.89
30	−304.9583	−307.6461	5.94	5.98
40	−304.9569	−307.6448	9.54	9.58
50	−304.9554	−307.6434	13.5	13.3
60	−304.9539	−307.6420	17.6	17.0
70	−304.9523	−307.6407	21.8	20.4
80	−304.9507	−307.6395	25.8	23.4
90	−304.9494	−307.6386	29.4	25.8
100	−304.9482	−307.6380	32.4	27.4
110	−304.9474	−307.6377	34.4	28.2
120	−304.9471	−307.6378	35.2	27.9
130	−304.9475	−307.6383	34.3	26.5
140	−304.9485	−307.6393	31.6	24.1
150	−304.9501	−307.6407	27.5	20.4
160	−304.9517	−307.6424	23.2	15.9
170	−304.9530	−307.6436	20.0	12.6
180	−304.9534	−307.6441	18.7	11.3

Energy minima for the cyclopropyl−carbonyl torsion of CVK were found at $\theta_1 = 0°$ (*s*-cis, global minimum) and $\theta_1 = 180°$ (*s*-trans, local minimum). The energy difference between the *s*-cis and *s*-trans conformers was 11.3 kJ/mol, similar to that observed for CMK.[1] The barrier to interconversion for these conformers was 28.2 kJ/mol, 2.4 kJ/mol lower than that observed for CMK.[1] The optimized geometries showed a lengthening by 1.4% of the C(1)−C(4) σ bond and a shortening by 0.3% of the carbonyl π bond as the cyclopropyl−carbonyl torsion is moved from the conjugated *s*-cis configuration ($\theta_1 = 0°$) to a nonconjugated configuration ($\theta_1 \sim 90°$). This observation is consistent with effects on bond order due to the expected σ−π* overlap in this system. For the unconstrained enone, the largest observed torsional deviation of θ_2 from the initial *s*-cis geometry was 13°. This distortion was observed when the cyclopropyl−carbonyl torsion was at its energy maximum and can be attributed to a repulsive interaction between the vinylic α-hydrogen and a β-hydrogen on the cyclopropane.

Molecular Mechanics Parameterization

Conventional parameterization of a torsion potential involves dividing the total energy among all contributing dihedral angles. From *ab initio* calculations the potential energy function for CVK was found to be primarily 2-fold. This complicated parameterization of the cyclopropyl ketone torsion since there were contributions from all

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[7] (a) *BATCHMIN, 4.0*; Columbia University: New York, 1993. (b) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

[8] *Spartan, 4.0*; Wavefunction, Inc.: Irvine, CA, 1995.

[9] To the best of our knowledge, no experimental or theoretical data pertaining to the torsional barriers in cyclopropyl vinyl ketone (**5**) has appeared in the literature.

[10] The cyclopropyl ketone and enone functional group arrays cannot simultaneously be near the *s*-trans conformation ($\theta_1 = \theta_2 = 180°$) due to severe steric interactions.

[11] Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *Gaussian 92, Revision G.2*; Gaussian, Inc.: Pittsburgh, 1992.

Table 2. MM2* Torsion Parameters for Cyclopropyl Vinyl Ketones

v_1	v_2	v_3
−1.2700	9.1600	−1.4000

three substituents on the α-carbon, each out of phase with the others. To simplify this process, only the dihedral angles between cyclopropyl σ bonds C(1)−C(2) and C(1)−C(3) and the carbonyl were used to calculate the total potential. Thus, the mechanics calculation of the total torsion potential involves two simultaneous functions out of phase with each other by 72° (the difference between the C(2)−C(1)−C(4)═O and C(3)−C(1)−C(4)═O dihedrals).

A new "cyclopropyl vinyl ketone" substructure was defined and inserted into the BATCHMIN parameter list. The substructure matching facilities in BATCHMIN allow mechanics parameters to be preferentially assigned on the basis of atom type within the defined molecular fragment. Parameters defined from hybridization alone are not altered, because identical parameters, placed in the substructure list, are employed. Torsion parameters contributing to the energy for rotation about the cyclopropyl−carbonyl bond were initially set to zero, and optimized energies for CVK were calculated at the same torsion increments used in the *ab initio* studies. The resulting energies were subtracted from the corresponding *ab initio* energies to give a difference curve representing the needed changes in the mechanics calculation. This difference curve was used to make an initial approximation of the necessary torsion parameters. Small iterative adjustments then gave a mechanics potential curve that closely fit the potential curve produced by *ab initio* calculations (see Figure 3). The new MM2* torsion parameter set derived in this manner is given in Table 2. The conformational search and molecular mechanics facilities resident in BATCHMIN were then used to determine the conformations of bicyclo[*m*.1.0]alk-3-en-2-ones **2**.

Conformations of the Bicyclo[*m*.1.0]alk-3-en-2-ones 2[12]

The most appropriate method for automatic structure searching in conformationally flexible carbocyclic systems is the Monte Carlo method.[13] This approach to conformational searching involves random alteration of molecular coordinates to produce new conformations. Each structure generated is subjected to geometry optimization using molecular mechanics, and unique structures are added to the ensemble of conformations.

Presented in Table 3 is a summary of the results of the Monte Carlo searches for the populated conformers of the family of bicyclo[*m*.1.0]alk-3-en-2-ones possessing cis ring fusion and *m* = 3−14 or trans ring fusion and *m* = 7−14.[12] Depicted in Figures 4−7 are the global minima observed for each of these bicycles, as well as the percentage of the population and the O═C(4)−C(1)−H(1) and O═C(4)−C(5)−H(5) dihedral angles, θ_1 and θ_2, for each global minimum.[14] Accommodation of trans stereochemistry in either the cyclopropane or alkene functional group requires the bicyclo[7.1.0]dec-3-en-2-one ring system or larger, while simultaneous accommodation of trans stereochemistry in both functional groups requires the bicyclo[8.1.0]undec-3-en-2-one ring system or larger.

Fewer conformers were found within 20 kJ of the global minima for bicyclic enones **5**−**16** than were found for the corresponding bicyclo[*m*.1.0]alkan-2-ones,[1] which have more degrees of freedom. As expected, more low-energy conformers were found for rings of greater size. For example, three conformers were found for *cis,cis*-bicyclo[6.1.0]non-3-en-2-one (**8cc**), 18 conformers for *cis,cis*-bicyclo[10.1.0]tridec-3-en-2-one (**12cc**), and 502 conformers for *cis,cis*-bicyclo[14.1.0]heptadec-3-en-2-one (**16cc**) within 20 kJ of their respective global minima. Six or fewer conformers were found within 5 kJ of the global minimum in 26 out of the 35 bicycles studied.[15]

Bicyclo[*m*.1.0]alk-3-en-2-ones with common rings have little or no conformational freedom. Cis ring fusion and cis alkene geometry are obligatory. One low-energy conformer was found for each of the enones **5cc** and **6cc**, and three conformers were found within 20 kJ of the global minimum for enone **7cc** (Figure 8). For **5cc-1**, **6cc-1**, and **7cc-1**, the cyclopropane adopts a pseudoaxial orientation, sharply angled with respect to the mean plane of the common ring, while the carbonyl is pseudoequatorially disposed. Considerable stabilization due to conjugative overlap of the carbonyl with the cyclopropane and the alkene exists for each of these conformers since θ_1 and θ_2 are both within ~30° of an ideal *s*-trans geometry. One or both of the torsion angles, θ_1 and θ_2, in conformers **7cc-2** and **7cc-3** are less favorable to conjugative overlap.

A transition in conformational behavior was noted within the series of *cis,cis*-bicyclo[*m*.1.0]alk-3-en-2-ones containing medium rings. For **8cc**, **9cc**, and **10cc**, simultaneous conjugative overlap of the carbonyl with the cyclopropane and the alkene functional groups is disfavored due to transannular interactions and ring size limitations. Some conformers exhibit substantial conjugative overlap of the carbonyl with the alkene functional group, but most exhibit overlap of the carbonyl with the cyclopropane. As the ring size increases from 8 to 11 and beyond, the weighted average cyclopropyl ketone dihedral approaches 180°, an ideal *s*-cis geometry. The weighted average enone dihedral increases with increased ring size and for **11cc** comes within 30° of an ideal *s*-cis geometry. The situation for **12cc** is similar, and the trend toward more ideal *s*-cis geometries and simultaneous conjugative overlap of the carbonyl with the cyclopropane and alkene functional groups is carried through **13cc**−**16cc**, which contain large rings.

Simultaneous conjugative overlap of the carbonyl with the cyclopropane and alkene functional groups is prohibited for cis-fused bicyclo[*m*.1.0]alk-3-en-2-ones that

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[12] Each of the bicyclo[*m*.1.0]alk-3-en-2-ones is hereafter given a number and a two-letter designation for purposes of rapid identification. The number refers to the larger ring size, the first letter to the relative stereochemistry about the cyclopropane, and the second letter to the relative stereochemistry about the alkene. Thus, **12ct** refers to a bicyclo[10.1.0]tridec-3-en-2-one in which the relative stereochemistry about the cyclopropane is cis and the relative stereochemistry about the alkene is trans.

[13] (a) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982. (b) Saunders, M. *J. Am. Chem. Soc.* **1987**, *109*, 3150−3152. (c) Howard, A. E.; Kollman, P. A. *J. Med. Chem.* **1988**, *31*, 1669−1675. (d) Saunders, M. *J. Comput. Chem.* **1989**, *10*, 203−208. (e) Leach, A. R. In *Rev. Comput. Chem.*; K. B. Lipkowitz and D. B. Boyd, Eds.; VCH Publishers, Inc.: New York, 1991; Vol. 2; pp 1−55.

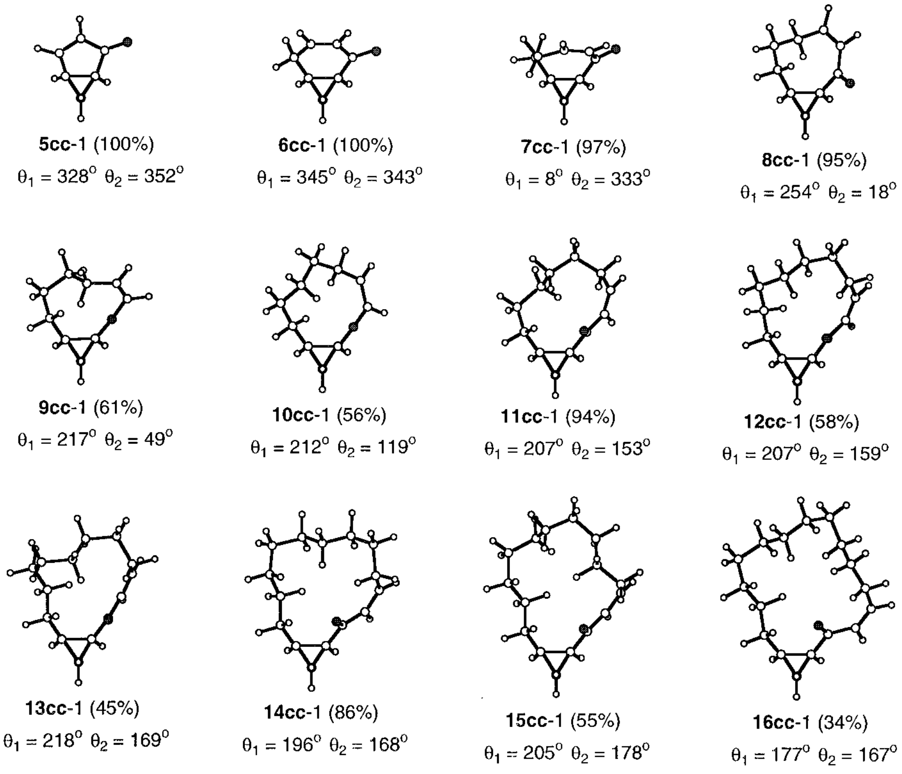
[14] This numbering scheme is consistent with the numbering of CVK depicted earlier in this article. For the bicyclo[*m*.1.0]alk-3-en-2-ones **5**−**16**, the cyclopropyl ketone and enone are near the *s*-trans conformation when θ_1 and θ_2, respectively, are near 0°.

[15] The six lowest energy conformers for each bicycle studied are depicted in the supporting information which accompanies this article.

Table 3. Monte Carlo Search Results for Conformers of Bicyclo[*m*.1.0]alk-3-en-2-ones 5–16

		conformers within *x* kJ of the global minimum[a]		cyclopropyl ketone conformation		enone conformation		
	bicyclo[*m*.1.0]alk-3-en-2-one	20 kJ	5 kJ	weighted average O═C(4)–C(1)–H(1) dihedral angles,[b] θ_1, deg	first occurrence of an *s*-trans conformer,[c] rank (percent)	weighted average O═C(4)–C(5)–H(5) dihedral angles,[b] θ_2, deg	% *s*-trans[d]	% *s*-cis[e]
5cc	*cis*,*cis*-[3.1.0]hexenone	1	1	328	1 (100)	352	100	0
6cc	*cis*,*cis*-[4.1.0]heptenone	1	1	345	1 (100)	343	100	0
7cc	*cis*,*cis*-[5.1.0]octenone	3	1	5	1 (97)	335	97	0
8cc	*cis*,*cis*-[6.1.0]nonenone	3	1	256	2 (3)	17	95	0
9cc	*cis*,*cis*-[7.1.0]decenone	6	4	217	5 (0.4)	71	4	0
10cc	*cis*,*cis*-[8.1.0]undecenone	14	3	209	12 (0.003)	117	0	0
11cc	*cis*,*cis*-[9.1.0]dodecenone	15	2	206	4 (0.04)	152	0	94
12cc	*cis*,*cis*-[10.1.0]tridecenone	18	2	202	16 (0.0009)	154	0	58
13cc	*cis*,*cis*-[11.1.0]tetradecenone	60	3	215	19 (0.02)	174	0	>99
14cc	*cis*,*cis*-[12.1.0]pentadecenone	71	2	196	none[f]	166	0	94
15cc	*cis*,*cis*-[13.1.0]hexadecenone	181	4	204	none[f]	179	0	>99
16cc	*cis*,*cis*-[14.1.0]heptadecenone	502	9	189	258 (0.002)	175	0	98
9ct	*cis*,*trans*-[7.1.0]decenone	5	1	278	4 (0.03)	335	96	0
10ct	*cis*,*trans*-[8.1.0]undecenone	12	6	313	1 (36)	275	42	0
11ct	*cis*,*trans*-[9.1.0]dodecenone	22	8	244	11 (0.6)	na	82	17
12ct	*cis*,*trans*-[10.1.0]tridecenone	27	4	226	10 (0.07)	na	27	73
13ct	*cis*,*trans*-[11.1.0]tetradecenone	66	1	226	14 (0.1)	182	1	99
14ct	*cis*,*trans*-[12.1.0]pentadecenone	113	3	209	none[f]	180	4	96
15ct	*cis*,*trans*-[13.1.0]hexadecenone	546	15	208	125 (0.03)	177	4	96
16ct	*cis*,*trans*-[14.1.0]heptadecenone	505	13	200	none[f]	na	11	89
9tc	*trans*,*cis*-[7.1.0]decenone	4	2	212	none[f]	59	5	0
10tc	*trans*,*cis*-[8.1.0]undecenone	24	2	209	13 (0.00001)	58	2	0
11tc	*trans*,*cis*-[9.1.0]dodecenone	24	1	182	14 (0.008)	109	0	0
12tc	*trans*,*cis*-[10.1.0]tridecenone	23	1	180	10 (0.008)	126	0	0
13tc	*trans*,*cis*-[11.1.0]tetradecenone	102	8	179	22 (0.3)	139	0	11
14tc	*trans*,*cis*-[12.1.0]pentadecenone	86	3	181	31 (0.008)	144	0	1
15tc	*trans*,*cis*-[13.1.0]hexadecenone	416	17	178	80 (0.04)	158	0	77
16tc	*trans*,*cis*-[14.1.0]heptadecenone	368	10	174	58 (0.03)	161	0	95
10tt	*trans*,*trans*-[8.1.0]undecenone	9	1	249	none[f]	323	1	0
11tt	*trans*,*trans*-[9.1.0]dodecenone	14	1	236	none[f]	333	98	0
12tt	*trans*,*trans*-[10.1.0]tridecenone	33	8	215	31 (≪1)	na	81	18
13tt	*trans*,*trans*-[11.1.0]tetradecenone	88	2	208	60 (0.002)	na	7	92
14tt	*trans*,*trans*-[12.1.0]pentadecenone	77	1	196	none[f]	164	1	99
15tt	*trans*,*trans*-[13.1.0]hexadecenone	365	5	201	266 (0.0008)	185	4	96
16tt	*trans*,*trans*-[14.1.0]heptadecenone	367	8	181	249 (0.0007)	171	2	98

[a] At 195 K. [b] Numbering as for CVK (vide supra). [c] *s*-trans includes conformers where the O═C(4)–C(1)–H(1) dihedral = 0 ± 30°. [d] *s*-trans includes conformers where the O═C(4)–C(5)–H(5) dihedral = 0 ± 30°. [e] *s*-cis includes conformers where the O═C(4)–C(5)–H(5) dihedral = 180 ± 30°. [f] Within 20 kJ/mol of the global minimum.



5cc-1 (100%) $\theta_1 = 328^\circ$ $\theta_2 = 352^\circ$

6cc-1 (100%) $\theta_1 = 345^\circ$ $\theta_2 = 343^\circ$

7cc-1 (97%) $\theta_1 = 8^\circ$ $\theta_2 = 333^\circ$

8cc-1 (95%) $\theta_1 = 254^\circ$ $\theta_2 = 18^\circ$

9cc-1 (61%) $\theta_1 = 217^\circ$ $\theta_2 = 49^\circ$

10cc-1 (56%) $\theta_1 = 212^\circ$ $\theta_2 = 119^\circ$

11cc-1 (94%) $\theta_1 = 207^\circ$ $\theta_2 = 153^\circ$

12cc-1 (58%) $\theta_1 = 207^\circ$ $\theta_2 = 159^\circ$

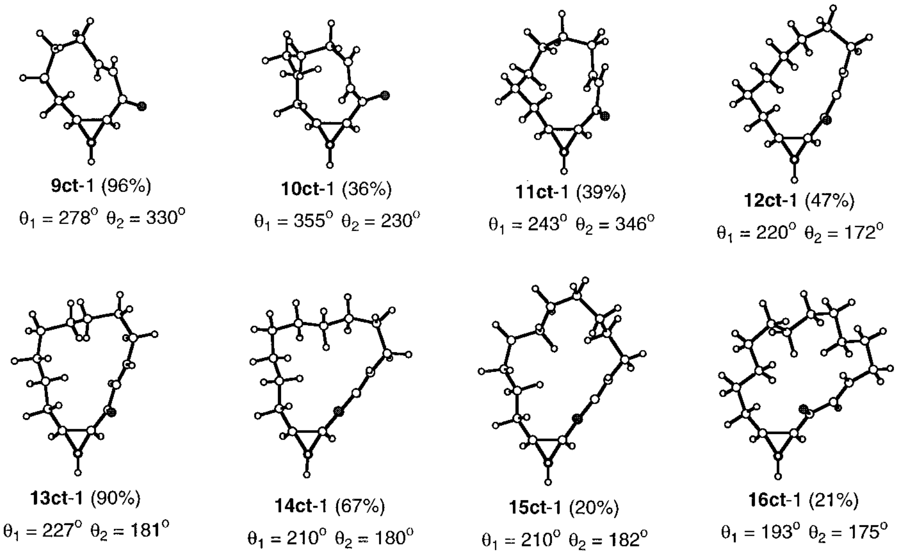
13cc-1 (45%) $\theta_1 = 218^\circ$ $\theta_2 = 169^\circ$

14cc-1 (86%) $\theta_1 = 196^\circ$ $\theta_2 = 168^\circ$

15cc-1 (55%) $\theta_1 = 205^\circ$ $\theta_2 = 178^\circ$

16cc-1 (34%) $\theta_1 = 177^\circ$ $\theta_2 = 167^\circ$

Figure 4. Conformational global minima for *cis*,*cis*-bicyclo[*m*.1.0]alk-3-en-2-ones **5cc**-**16cc**.


9ct-1 (96%) $\theta_1 = 278^\circ$ $\theta_2 = 330^\circ$

10ct-1 (36%) $\theta_1 = 355^\circ$ $\theta_2 = 230^\circ$

11ct-1 (39%) $\theta_1 = 243^\circ$ $\theta_2 = 346^\circ$

12ct-1 (47%) $\theta_1 = 220^\circ$ $\theta_2 = 172^\circ$

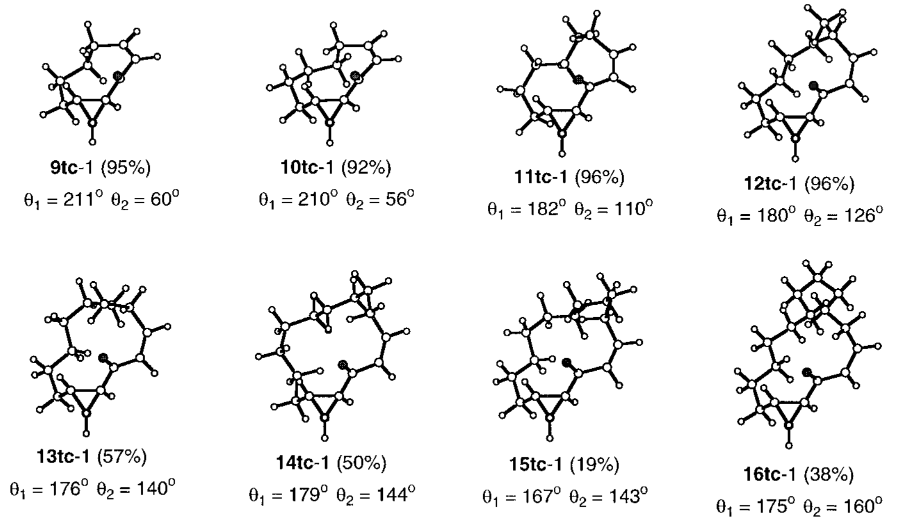
13ct-1 (90%) $\theta_1 = 227^\circ$ $\theta_2 = 181^\circ$

14ct-1 (67%) $\theta_1 = 210^\circ$ $\theta_2 = 180^\circ$

15ct-1 (20%) $\theta_1 = 210^\circ$ $\theta_2 = 182^\circ$

16ct-1 (21%) $\theta_1 = 193^\circ$ $\theta_2 = 175^\circ$

Figure 5. Conformational global minima for *cis,trans*-bicyclo[*m*.1.0]alk-3-en-2-ones **9ct-16ct**.


9tc-1 (95%) $\theta_1 = 211^\circ$ $\theta_2 = 60^\circ$

10tc-1 (92%) $\theta_1 = 210^\circ$ $\theta_2 = 56^\circ$

11tc-1 (96%) $\theta_1 = 182^\circ$ $\theta_2 = 110^\circ$

12tc-1 (96%) $\theta_1 = 180^\circ$ $\theta_2 = 126^\circ$

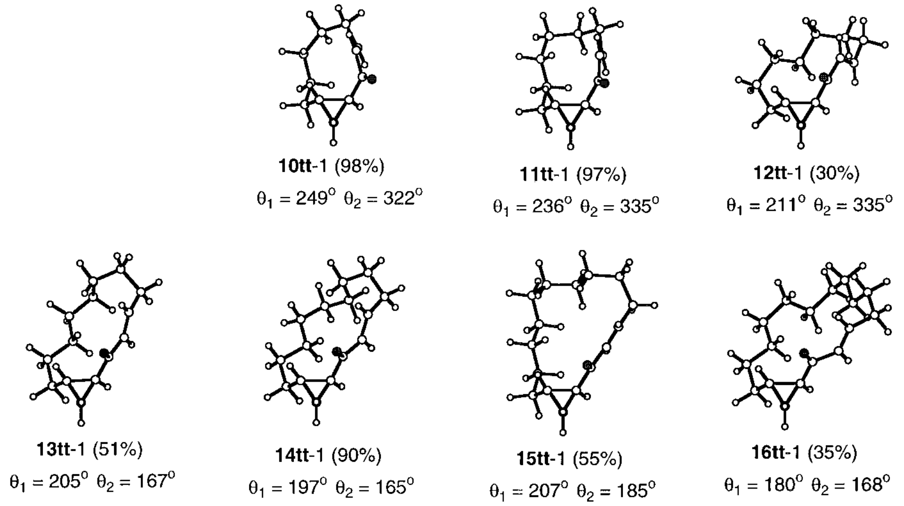
13tc-1 (57%) $\theta_1 = 176^\circ$ $\theta_2 = 140^\circ$

14tc-1 (50%) $\theta_1 = 179^\circ$ $\theta_2 = 144^\circ$

15tc-1 (19%) $\theta_1 = 167^\circ$ $\theta_2 = 143^\circ$

16tc-1 (38%) $\theta_1 = 175^\circ$ $\theta_2 = 160^\circ$

Figure 6. Conformational global minima for *trans,cis*-bicyclo[*m*.1.0]alk-3-en-2-ones **9tc-16tc**.


10tt-1 (98%) $\theta_1 = 249^\circ$ $\theta_2 = 322^\circ$

11tt-1 (97%) $\theta_1 = 236^\circ$ $\theta_2 = 335^\circ$

12tt-1 (30%) $\theta_1 = 211^\circ$ $\theta_2 = 335^\circ$

13tt-1 (51%) $\theta_1 = 205^\circ$ $\theta_2 = 167^\circ$

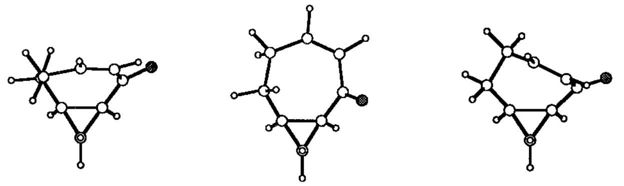
14tt-1 (90%) $\theta_1 = 197^\circ$ $\theta_2 = 165^\circ$

15tt-1 (55%) $\theta_1 = 207^\circ$ $\theta_2 = 185^\circ$

16tt-1 (35%) $\theta_1 = 180^\circ$ $\theta_2 = 168^\circ$

Figure 7. Conformational global minima for *trans,trans*-bicyclo[*m*.1.0]alk-3-en-2-ones **10tt-16tt**.

incorporate trans alkene geometry in a medium ring. For **9ct** one principal conformer was found in which overlap of the carbonyl with the alkene occurs in a near *s*-trans geometry ($\theta_2 = 330°$). A number of populated conformers were found for **10ct**, **11ct**, and **12ct.** Conformers of **10ct** exhibit overlap of the carbonyl with either the cyclopropane or alkene in near *s*-trans geometries. For **11ct** and **12ct** most conformers exhibit nonoptimal geometries for cyclopropyl ketone overlap ($\bar{\theta}_1 = 244°$ for **11ct**, $\bar{\theta}_1 = 226°$ for **12ct**) but nearly optimal geometries for enone con-



7cc-1 (96.8%) $\theta_1 = 8^\circ$ $\theta_2 = 333^\circ$

7cc-2 (2.8%) $\theta_1 = 259^\circ$ $\theta_2 = 45^\circ$

7cc-3 (0.4%) $\theta_1 = 3^\circ$ $\theta_2 = 310^\circ$

Figure 8. Low-energy conformers of *cis,cis*-bicyclo[5.1.0]oct-3-en-2-one (**7cc**).

jugation (82% *s*-trans and 17% *s*-cis for **11ct**, 27% *s*-trans and 73% *s*-cis for **12ct**). For **13ct**–**16ct**, which contain large rings, the trend again is toward greater uniformity and more ideal *s*-cis geometries for both components of the α,β-cyclopropyl α',β'-enone functional group array among populated conformers.

Near *s*-cis geometries were observed for the cyclopropyl ketone functional group array in most trans-fused bicyclo-[*m*.1.0]alk-3-en-2-one conformers that incorporate a cis alkene. The weighted average cyclopropyl ketone dihedrals $\bar{\theta}_1$ were 212° for **9tc**, 209° for **10tc**, and very near 180° for **11tc**–**16tc**. The weighted average enone dihedral increased gradually with ring size, and for **15tc** finally came within 30° of an ideal *s*-cis geometry. Effective conjugative overlap of the carbonyl with the alkene functional group was not observed in most conformers of **9tc**–**14tc**. Minor conformers **9tc-2** (5%, $\theta_2 = 28°$) and **10tc-3** (2%, $\theta_2 = 29°$) exhibit near *s*-trans enone geometry. No conformers of **11tc** or **12tc** exhibit *s*-trans or *s*-cis enone geometry. For **13tc** and **14tc** only a small percentage of conformers exhibit near *s*-cis enone geometry, while for **15tc** and **16tc** a large percentage of conformers exhibit this geometry. Thus, simultaneous conjugative overlap of the carbonyl with the cyclopropane and alkene functional groups is achieved for most conformers of **15tc** and **16tc**.

Trans-fused bicyclo[*m*.1.0]alk-3-en-2-ones that incorporate a trans alkene in a medium ring exhibit nonoptimal geometries for cyclopropyl ketone overlap ($\bar{\theta}_1 = 249°$ for **10tt**, $\bar{\theta}_1 = 236°$ for **11tt**) and nearer to optimal *s*-trans geometries for enone conjugation ($\bar{\theta}_2 = 323°$ for **10tt**, $\bar{\theta}_2 = 333°$ for **11tt**) as the predominant conformational motif. A transition in conformational behavior was observed in the series **12tt**–**16tt**, which incorporate a trans alkene in a large ring. Cyclopropyl ketone overlap becomes more ideally *s*-cis, while the predominant enone geometry switches from *s*-trans to *s*-cis (81% *s*-trans and 18% *s*-cis for **12tt**, 7% *s*-trans and 92% *s*-cis for **13tt**, 1% *s*-trans and 99% *s*-cis for **14tt**). As before, simultaneous conjugative overlap of the carbonyl with the cyclopropane and alkene functional groups occurs in near *s*-cis geometries for sufficiently large rings.

Conformation and Chemical Reactivity

As nucleophilic 1,2-additions to ketones are synthetically useful, the ability to reliably predict the sense and degree of diastereoselection for specific bicyclo[*m*.1.0]alk-3-en-2-ones would be valuable. A single conformer or local conformational motif for the α,β-cyclopropyl ketone functional group array was predominant in the conformational ensemble for most bicyclic enones studied. Prediction of diastereoselection based on starting material geometry is appropriate for nucleophilic 1,2-additions that involve early transition states. Assuming the Bürgi–Dunitz trajectory for nucleophilic attack,[16] impedance to approach at the *Re* face of the carbonyl for **5cc** and **6cc** will be substantial due largely to the pseudoaxially disposed cyclopropane ring and the associated endo hydrogen. The situation for **7cc** is less clear, as both carbonyl faces appear susceptible to attack in the predominant conformer, **7cc-1**. For **8cc** and **9cc**, attack at the *Si* face of the carbonyl seems most likely, as the *Re* face is partially obstructed by transannular C and H atoms in the predominant conformers. For **9ct**, attack at the *Si* face is expected to predominate, while attack at the *Re* face should be favored for **10ct**. However, alternative low-energy conformers which exhibit very different α,β-cyclopropyl α',β'-enone conformational motifs exist for **7cc**, **8cc**, **9cc**, **9ct**, and **10ct**. Since rapid equilibration of the conformers of these molecules is expected at or above 195 K, the Curtin–Hammett principle applies, and the relative energies of the competing transition states must be considered.[17] For **10cc**–**16cc**, **11ct**–**16ct**, **9tc**–**16tc**, and **10tt**–**16tt**, the *Si* face of the carbonyl is exposed and the *Re* face obstructed by transannular C and H atoms in nearly all of the populated conformers, and high levels of 1,2-asymmetric induction would be expected in these cases.

Alkene-functionalizing reactions, including nucleophilic 1,4-additions to enones, are widely employed in synthesis. Reliable prediction of the sense and degree of diastereoselection for such reactions for specific bicyclo[*m*.1.0]alk-3-en-2-ones would be extremely valuable. For many of the bicyclic enones studied, a single conformer or local conformational motif for the α,β-enone functional group array was predominant in the conformational ensemble. In some cases (but not in all cases) this resulted in one face of the alkene being more exposed. In these cases, the conformational ensemble of the starting material should be useful for predicting diastereoselectivity when alkene-functionalizing reactions involve early transition states. For computational modeling of reactions known to involve late transition states, the conformational ensembles for the bicyclo[*m*.1.0]alk-3-en-2-ones can serve as a logical point of departure.

Studies in our laboratory with several bicyclo[*m*.1.0]-alk-3-en-2-ones have demonstrated high levels of 1,2-asymmetric induction and variable levels of 1,4-asymmetric induction.[18] These results will be disclosed shortly.

Acknowledgment. Partial support of this work from DuPont, Research Corporation, and from the University of Arizona through the Office of the Vice President for Research are gratefully acknowledged.

Supporting Information Available: The MM2* special substructure parameter list employed in this study and the structures of the six lowest energy conformers for each of the bicycles studied (33 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Note Added in Proof: At the suggestion of a reviewer, we examined the propriety of the enone torsion parameters employed in this study. The MM2* potential

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[16] (a) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563–1572. (b) Bürgi, H.-B. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 460–473.

[17] See ref 3, p 654 and accompanying discussion.

[18] Gregg, T. M. Ph.D. Dissertation, The University of Arizona, 1995.

in use underestimated the *s*-cis to *s*-trans energy barrier for cyclopropyl vinyl ketone by about 4 kJ when compared to *ab initio* calculations at the mp2/6-31G* level. Following re-parameterization to correct for this difference, we re-minimized the structures for **c7cc**, **c9tc**, and **c10cc** and found no significant change in the geometries of any of the low-energy conformers. The energies of the conformers possessing more twisted enones were raised somewhat, relative to conformers with less twisted enones, but remained within the limits of certainty of molecular mechanics techiques. We elected to retain the more general torsion parameters for enones which reside in the Batchmin v4.0 parameter list.

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