

Development of Molecular Mechanics Torsion Parameters for α,β -Cyclopropyl Ketones and Conformational Analysis of Bicyclo[*m*.1.0]alkan-2-ones

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Conformations of cyclopropyl methyl ketone have been studied using *ab initio* methods in an effort to quantify the effects of conjugative overlap between the cyclopropane ring and an adjacent ketone carbonyl. Results were comparable with previous experimental and theoretical studies. Cyclopropyl methyl ketone exhibits a global energy minimum in the *s*-cis conformer and a local energy minimum near 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]alkan-2-ones having larger ring sizes from five- to 16-membered. Similar conformations for the cyclopropyl ketone substructure are observed for all the medium and large ring systems examined. Possible synthetic ramifications of local conformational anchoring by this functional group array are discussed.

Introduction

The interplay between conformation and stereoselective manipulation of carbocyclic rings is an historically important and continually developing area of research. Observations on the reactivity of small and common¹ carbocycles has led to a deeper understanding of the conformations of these ring systems.² In turn, understanding the conformations of small and common rings has been useful in predicting reactivity.³ The conformational behaviors and reactivities of medium and large carbocycles are less well studied than their small and common homologues.⁴ The need to better understand the

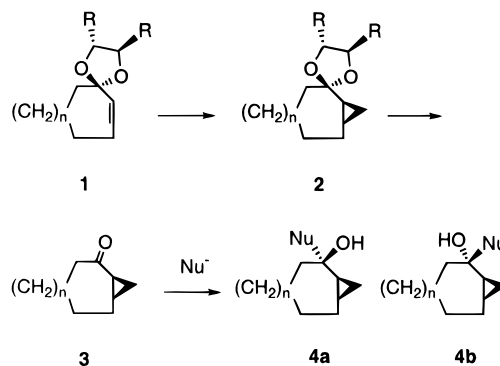


Figure 1. Synthesis of bicyclo[*m*.1.0]alkan-2-ones **3** and their reactivity toward additions of nucleophiles.

relation between conformation and chemical reactivity (and between conformation and biological function) has provided impetus for the development of tools for accurate conformational modeling. Development of software for automatic conformational searching⁵ has greatly facilitated the study of flexible rings, so that systematic correlations of the conformations and reactivities of medium and large carbocycles are now possible.^{4n,o}

Previously we developed a method for diastereoselective cyclopropanation of 2-cycloalken-1-one ketals **1** (Figure 1).⁶ Thus, bicyclo[*m*.1.0]alkan-2-ones **3** possessing *cis* ring fusion for *m* = 3–14 or *trans* ring fusion for *m* = 7–14 are available in either enantiomeric form via hydrolyses of the corresponding cyclopropane ketals **2**. In a preliminary study, additions of nucleophiles to the carbonyl carbons of several ketones **3** were found to be highly stereoselective, producing a predominant diaste-

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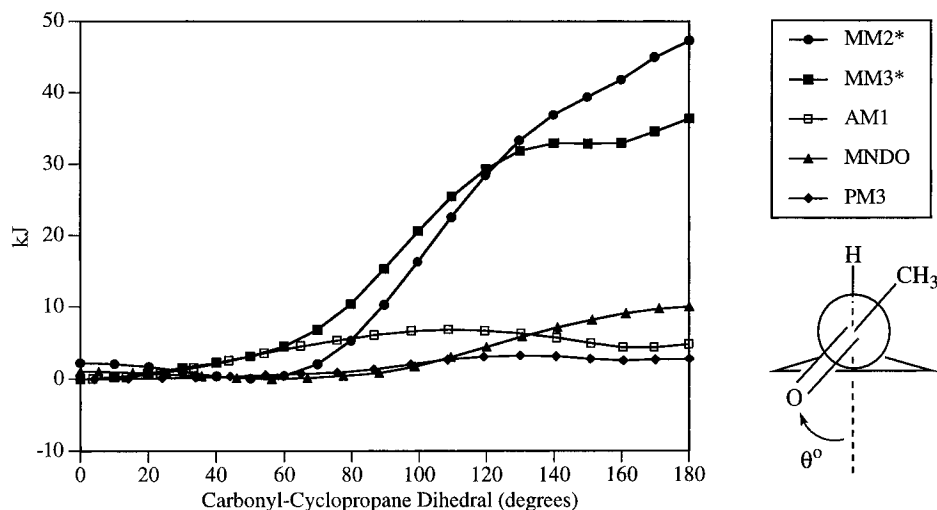


Figure 2. Energy barrier to rotation about the C(1)–C(4) σ bond of cyclopropyl methyl ketone (**5**) calculated using molecular mechanics and semiempirical force fields.

reomer, **4a** or **4b** (Figure 1).⁷ For such kinetically controlled, exothermic reactions, starting material-like transition states are anticipated in accordance with the Hammond Postulate.⁸ Thus, the sense of the stereoselection for 1,2-carbonyl additions might be predictable from the geometry of the starting ketone. These observations and considerations prompted the study of the conformations of bicyclo[*m*.1.0]alkan-2-ones **3a–t** presented herein.

Ab Initio Study of Cyclopropyl Methyl Ketone

The model compound, cyclopropyl methyl ketone (**5**), was studied to evaluate the performance of available computational methods. We observed that the energy barrier to rotation about the C(1)–C(4) σ bond calculated using the MM2* and MM3* force fields in BATCHMIN v4.0⁹ and the AM1, PM3, and MNDO semiempirical Hamiltonians in Spartan v4.0¹⁰ did not reflect the torsion-dependent stabilization expected from conjugative overlap of the cyclopropane with the ketone carbonyl (Figure 2).¹¹ From consideration of orbital overlap, energy minima are expected at $\theta = 0^\circ$ and 180° . In response, we have studied the energy profile of this torsion by *ab initio* methods and have developed MM2* parameters which reflect the cyclopropane–carbonyl conjugative interaction.

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Table 1. *Ab Initio* and Relative Energies for the C(1)–C(4) σ Bond Torsion of Cyclopropyl Methyl Ketone (**5**)

θ , deg	<i>ab initio</i> energies, Hartrees		relative energies, kJ/mol	
	RHF/3-21G	MP2/6-31G*	RHF/3-21G	MP2/6-31G*
0	-267.3263	-269.6809	0	0
10	-267.3260	-269.6806	0.75	0.79
20	-267.3252	-269.6798	2.93	3.10
30	-267.3239	-269.6785	6.11	6.44
40	-267.3224	-269.6770	10.0	10.4
50	-267.3207	-269.6753	14.5	14.6
60	-267.3190	-269.6738	19.2	18.8
70	-267.3172	-269.6723	23.9	22.6
80	-267.3154	-269.6710	28.4	25.9
90	-267.3139	-269.6700	32.3	28.6
100	-267.3128	-269.6694	35.3	30.2
110	-267.3123	-269.6693	36.5	30.5
120	-267.3127	-269.6698	35.7	29.2
130	-267.3138	-269.6709	32.8	26.2
140	-267.3153	-269.6725	28.8	22.2
150	-267.3168	-269.6740	24.8	18.2
160	-267.3179	-269.6752	21.8	15.1
170	-267.3184	-269.6758	20.6	13.5
180	-267.3175	-269.6758	23.1	13.6

Ketone **5** was previously studied by gas phase IR spectroscopy, where bands of only the *s*-cis conformer were observed.¹² From this it was inferred that the energy difference between the *s*-cis and *s*-trans conformers for **5** is greater than 11.3 kJ/mol. *Ab initio* calculations at the MP2 level using the 6-31G* basis set indicated an energy difference of 13.1 kJ/mol.^{11j} Observations in the UV spectrum gave a range of 13.4–33.1 kJ/mol.¹³ A computational study of the saddle point conformation which lies between the *s*-cis and *s*-trans conformers gave a barrier of 27.4 kJ/mol for the transition from *s*-cis to *s*-trans.^{11j}

In this work, an initial torsion driving study was performed on **5** by constraining the cyclopropyl–carbonyl bond at 10° intervals between the *s*-cis and the *s*-trans conformers. Each conformer was optimized using *Gaussian 92*¹⁴ at the RHF level with the 3-21G basis set. The resulting geometries were then reoptimized 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.

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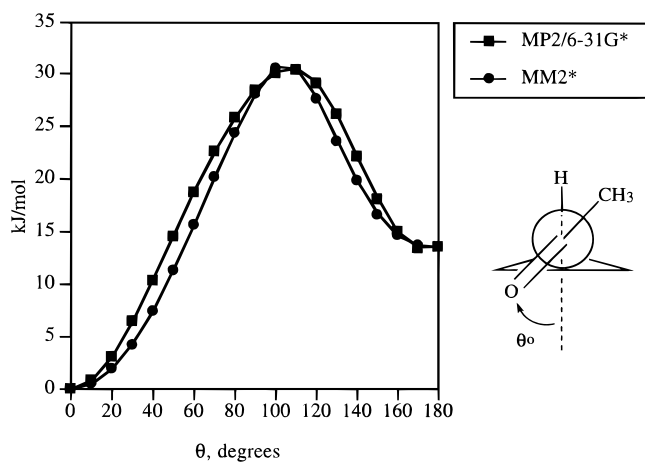


Figure 3. Energy barrier to rotation about the C(1)–C(4) σ bond of cyclopropyl methyl ketone (**5**) calculated using *ab initio* methods and a modified MM2* force field.

Table 2. MM2* Torsion Parameters for Cyclopropyl Alkyl Ketones

V_1	V_2	V_3
-1.6400	9.7600	-1.3000

Ketone **5** has two conformational energy minima, *s-cis* (Figure 3, $\theta = 0^\circ$, global minimum) and *s-trans* ($\theta \approx 180^\circ$, local minimum). The calculated energy difference between the *s-cis* and the *s-trans* conformers was 13.5 kJ/mol. Further refinement of the curve via torsion driving using a 0.5° resolution found the local energy minimum for the family of *s-trans* conformers at 172° , rather than 180° . The saddle point conformation which lies between the *s-cis* and *s-trans* conformers had a torsion angle of 105.5° . The energy of this structure was 30.6 kJ/mol higher than that of the *s-cis* conformer. These results are in close agreement with previous computations performed with a different gradient optimization method.^{14j}

Molecular Mechanics Parameterization

Conventional parameterization of torsion potentials involves dividing the total energy among all contributing dihedral angles. From *ab initio* calculations the potential energy function for **5** was found to be primarily 2-fold.

This complicated parameterization of the cyclopropyl ketone torsion since there were contributions from all three substituents on the α -carbon, each out of phase with the others. To simplify this process, only the dihedral angles between the two cyclopropyl α, β - σ bonds 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 $C_{\beta 1}-C_\alpha-C=O$ and $C_{\beta 2}-C_\alpha-C=O$ dihedrals).

A new "cyclopropylketone" 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 were not altered as 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 **5** 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 which closely fit that produced by *ab initio* calculations (see Figure 3). The new 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 in determination of the conformations of the bicyclo[*m*.1.0]alkan-2-ones **3a-t**.

Conformations of the Bicyclo[*m*.1.0]alkan-2-ones

The most appropriate method for automatic structure searching in conformationally flexible carbocyclic systems is the Monte Carlo method.^{5b,e} 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.

Table 3. Monte Carlo Search Results for Conformers of Bicyclo[*m*.1.0]alkan-2-ones **3a-t**

bicyclo[<i>m</i> .1.0]alkan-2-one	conformers within 20 or 5 kJ of the Global Minimum ^a		first occurrence of an <i>s-trans</i> conformer, rank (%)	weighted average O=C(2)–C(1)–H(1) dihedral angles
	20	5		
3a <i>cis</i> -[3.1.0]hexan	1	1	1 (100)	338
3b <i>cis</i> -[4.1.0]heptan	2	2	1 (55)	343
3c <i>cis</i> -[5.1.0]octan	7	4	1 (59)	112
3d <i>cis</i> -[6.1.0]nonan	5	2	3 ($\ll 1$)	224
3e <i>cis</i> -[7.1.0]decan	12	1	13 ($\ll 1$)	214
3f <i>cis</i> -[8.1.0]undecan	9	3	none ^b	202
3g <i>cis</i> -[9.1.0]dodecan	47	7	none ^b	194
3h <i>cis</i> -[10.1.0]tridecan	73	4	none ^b	198
3i <i>cis</i> -[11.1.0]tetradecan	265	17	180 ($\ll 1$)	194
3j <i>cis</i> -[12.1.0]pentadecan	162	4	359 ($\ll 1$)	197
3k <i>cis</i> -[13.1.0]hexadecan	752	11	641 ($\ll 1$)	190
3l <i>cis</i> -[14.1.0]heptadecan	766	9	none ^b	197
3m <i>trans</i> -[7.1.0]decan	9	2	none ^b	205
3n <i>trans</i> -[8.1.0]undecan	12	2	none ^b	190
3o <i>trans</i> -[9.1.0]dodecan	34	3	43 ($\ll 1$)	186
3p <i>trans</i> -[10.1.0]tridecan	91	11	121 ($\ll 1$)	185
3q <i>trans</i> -[11.1.0]tetradecan	201	14	184 ($\ll 1$)	181
3r <i>trans</i> -[12.1.0]pentadecan	322	9	248 ($\ll 1$)	182
3s <i>trans</i> -[13.1.0]hexadecan	891	14	387 ($\ll 1$)	178
3t <i>trans</i> -[14.1.0]heptadecan	504	5	458 ($\ll 1$)	186

^a At 195 K. ^b Within 20 kJ/mol of the global minimum.

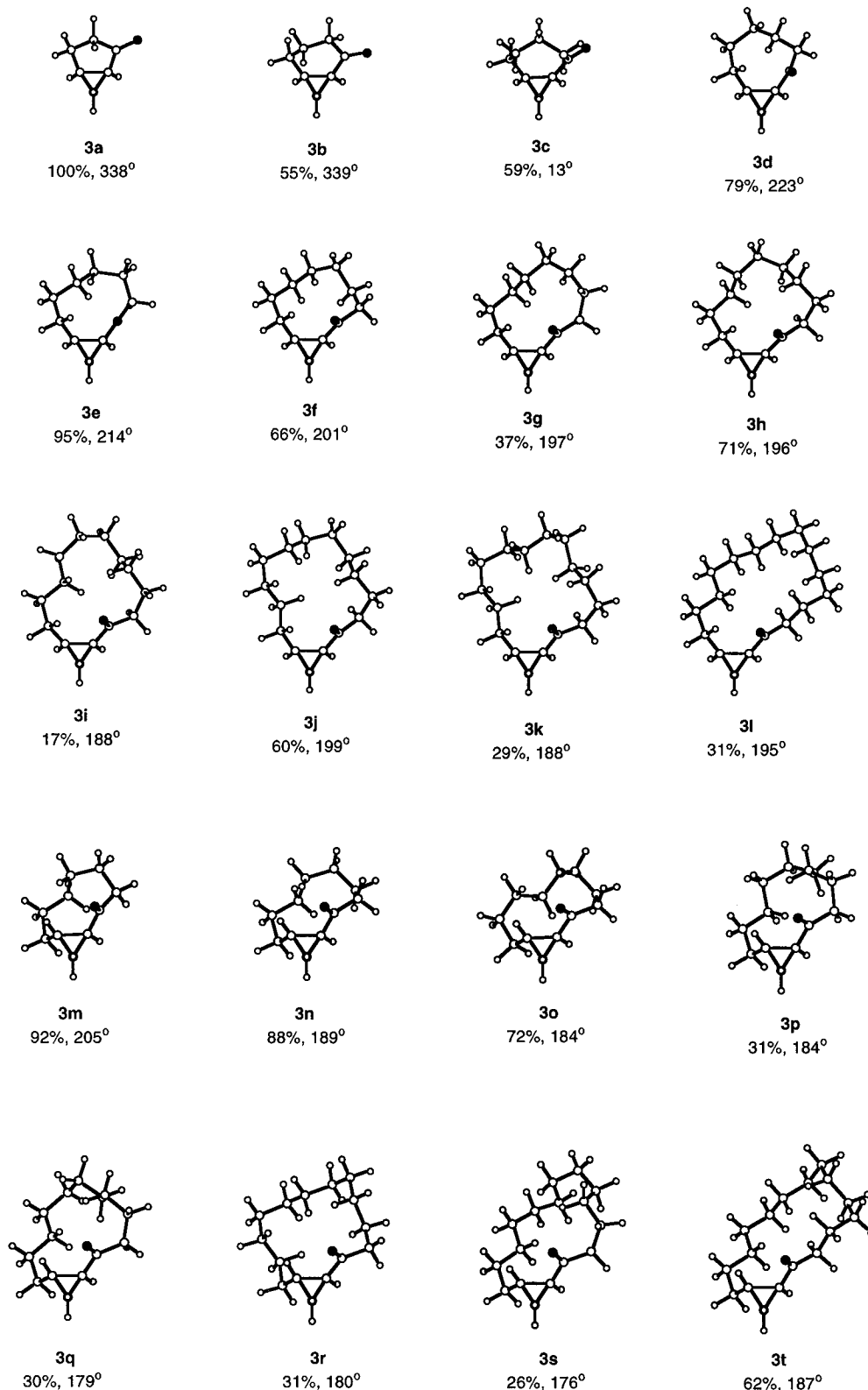


Figure 4. Conformational global minima for ketones **3a–t**.

Presented in Table 3 is a summary of the results of the Monte Carlo searches for the populated conformers of the bicyclo[*m*.1.0]alkan-2-ones **3a–t**. Depicted in Figure 4 are the global minima observed for each of these ketones, as well as the percentage of the population and the O=C(2)–C(1)–H(1) dihedral angle¹⁵ for each global minimum. As expected, there are generally more low-energy conformers for rings of greater size. For example, five conformers were found for *cis*-bicyclo[6.1.0]nonan-2-one (**3d**), 73 conformers were found for *cis*-bicyclo-

[10.1.0]tridecan-2-one (**3h**), and 766 conformers were found for *cis*-bicyclo[14.1.0]heptadecan-2-one (**3l**) within 20 kJ of the respective global minima.

For bicycles **3a** and **3b**, which contain five- and six-membered larger rings, there is little conformational diversity. The cyclopropane adopts a pseudoaxial orientation, sharply angled with respect to the mean plane of the larger ring, while the carbonyl is pseudoequatorially disposed. Geometries which are optimal for conjugative overlap of the cyclopropane and carbonyl atomic orbitals

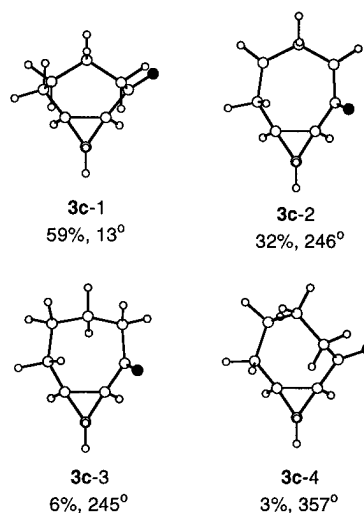


Figure 5. Low-energy conformers of *cis*-bicyclo[5.1.0]octan-2-one (**3c**).

are expected for O=C(2)–C(1)–H(1) dihedrals near 180° (cyclopropane and carbonyl *s*-cis) and 0/360° (cyclopropane and carbonyl *s*-trans). The weighted average O=C(2)–C(1)–H(1) dihedral angles for **3a** and **3b** are 338° and 343°, respectively, near to the *s*-trans geometry. Assuming the Bürgi–Dunitz trajectory for nucleophilic attack,¹⁶ impedance to approach at the *re* face of **3a** is expected from the endo hydrogen at C(6), while in **3b** both faces of the carbonyl appear to be comparably exposed.¹⁷

Bicyclic ketone **3c** contains a seven-membered larger ring and, in contrast to **3a** and **3b**, cannot be regarded as rigid. There are four conformers within 5 kJ of the global minimum (Figure 5). In conformers **3c-1** and **3c-4**, the cyclopropane is pseudoaxially oriented with respect to the mean plane of the larger ring and the cyclopropane–carbonyl torsion approaches an *s*-trans conformation. Approach of nucleophiles to the *si* face of the carbonyl is partially obstructed by one or more transannular hydrogen atoms of the larger ring. In conformers **3c-2** and **3c-3**, the cyclopropane adopts a pseudoequatorial orientation and the carbonyl is pseudoaxially disposed. Approach to the *re* face of the carbonyl is severely obstructed by the transannular carbon and hydrogen atoms of the larger ring. From the Hammond Postulate, a mixture of diastereomers might be expected for a

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kinetically controlled nucleophilic attack at the carbonyl of **3c**.¹⁷ However, since rapid equilibration of the conformers of **3c** is expected at or above 195 K, the Curtin–Hammett Principle applies, and the relative energies of the competing transition states will determine the diastereomer ratio.¹⁸ Work is in progress to ascertain the transition state geometries and energies for addition of nucleophiles to **3c**.¹⁹

In *cis*-fused bicycles **3d–l**, which incorporate an eight-membered or larger ring, as well as in *trans*-fused bicycles **3m–t**, the cyclopropane generally adopts a pseudoequatorial orientation with respect to the mean plane of the larger ring. As the length of the polymethylene chain connecting the ends of the cyclopropyl carbonyl functional group array increases, the cyclopropane–carbonyl torsion approaches a more ideal *s*-cis conformation (compare weighted average O=C(2)–C(1)–H(1) dihedral angles for **3d–l** and **3m–t**, Table 3). Remarkably, conformers possessing the *s*-trans substructure comprise a negligible fraction of the conformational populations for these ketones. While there is substantial variation in the conformation of the polymethylene chain,²⁰ the local conformation^{4p} of the cyclopropyl–carbonyl functional group array for the populated conformers of each of the ketones **3d–t** are similar and are well represented by the respective global minima depicted in Figure 4.²¹

From inspection of Figure 4 it is also apparent that the local conformation of the cyclopropyl–carbonyl functional group array is conserved in all bicyclo[*m*.1.0]alkan-2-ones possessing medium and large rings, independent even of ring fusion geometry. Approach to the *re* face of the carbonyl in ketones **3d–t** is severely obstructed by the transannular carbon and hydrogen atoms of the polymethylene chain. The conformational equilibria which operate do not alter this reality. Thus, nucleophilic attack which involves an early transition state would be expected to proceed with a high degree of 1,2-asymmetric induction for all bicyclo[*m*.1.0]alkan-2-ones which possess medium and large rings. Experimental testing of this hypothesis is the subject of the accompanying article.²²

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Supporting Information Available: MM2* special substructure parameter list employed in this study (1 page). 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.

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