On Structural Determination of C-7-Substituted 6,8-Dioxabicyclo[3.2.1]octanes. A Reevaluation

Bradford P. Mundy,* Gary W. Dirks, Raima M. Larter, and Arnold C. Craig

Department of Chemistry, Montana State University, Bozeman, Montana 59717

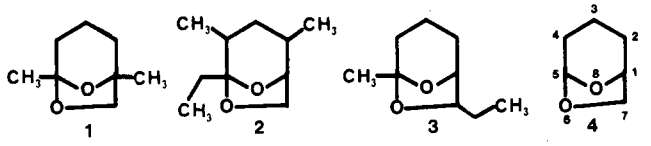
Kenneth B. Lipkowitz* and John Carter

Department of Chemistry, Indiana-Purdue University, Indianapolis, Indiana 46200

Received May 14, 1981

The use of mass spectral and lanthanide shift reagent NMR data for structural elucidation in the 6,8-dioxabicyclo[3.2.1]octane series is examined. Sufficient irregularities associated with 7-substituted members of this series are found to prompt a cautionary response to their unconditional use in determining structures of these bicyclic ketals. A molecular mechanics calculational analysis of various members of the series examines how substituents affect the conformation of these ketals. CNDO/2 calculations to evaluate the Lewis basicity of the two ketal oxygens lead to the conclusion that any preferential coordination will most likely find its origins in steric rather than electronic effects.

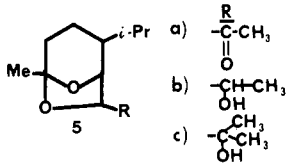
Frontalin (1), multistriatin (2), and brevicomin (3) are



the aggregating pheromones of several pernicious and as yet uncontrolled beetles.[1] The basic ring structure, a 6,8-dioxabicyclo[3.2.1]octane (4), has been found in plants and animals.[2] Typically, structural assignments of these and related molecules have been based on infrared, NMR, and mass spectral measurements although limited crystallographic studies have been performed to unambiguously confirm structural features of interest.[3] In this paper we reevaluate several experiments and present evidence to caution the use of spectral fragmentation patterns and NMR shift reagent studies to unambiguously assign the configuration of substituents at C-7 as previously assumed.

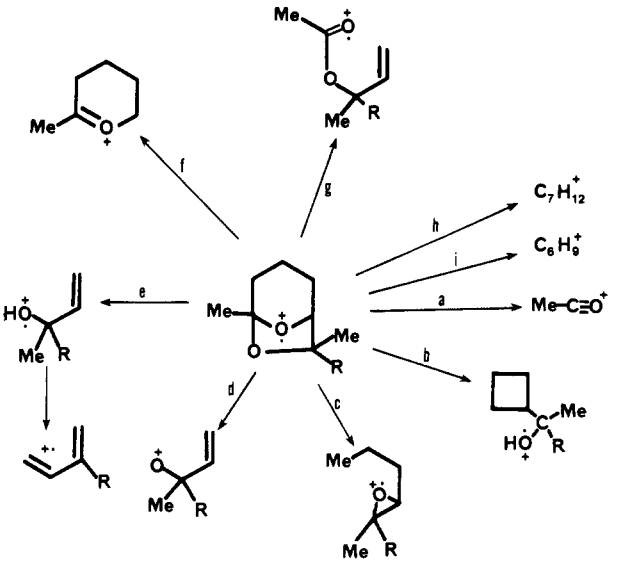
Mass Spectroscopy

A detailed mass spectral analysis of 1–3 has been reported in which these ketals were noted to give rise to characteristic fragmentation patterns[4] (see Scheme I). These modes of fragmentation, however, could not be correlated with the reported mass spectrum of 5 isolated



from tobacco,[5] which lead Gore and co-workers to the conclusion that "complex substituents may make a significant contribution to the mass spectra of substituted dioxabicyclo[3.2.1]octanes." Interestingly, substituents at C-7 have been observed to influence the structure of these ketals.[6] Here we further explore the consequences of C-7

Scheme I. Fragmentations of Members of the 6,8-Dioxabicyclo[3.2.1]octane Series[a]



	m/e				
	R = H	R = Me	R = Et	R = *i*-Pr	R = Ph
a = 43	*b*	*b*	*b*	*b*	*b*
b = 99 + R	100[b]	114	128[b]	142[b]	175[b]
c = 99 + R	100[b]	114	128[b]	142[b]	175[b]
d = 70 + R	71[b]	85[b]	99[b]	113[b]	147
e = 71 + R	72[b]	86[b]	100[b]	114	148
e′ = (71 + R) − 18	54[b]	55[b]	92[b]	96[b]	130[b]
f = 99	*b*	*b*	*b*	*b*	*b*
g = 113 + R	114[b]	128	142[b]	156	190
h = 96		*b*		*b*	
i = 81	*b*	*b*	*b*	*b*	

[a] This is a slightly modified scheme of fragmentations, as first presented by Gore et al.[4b] [b] Peak present.

(1) (a) Frontalin was isolated from the pine bark beetles *Dendroctonus frontalis*: G. W. Kinser, A. F. Fentiman, Jr., T. F. Page, Jr., R. L. Folta, J. P. Vite, and G. Pitman, *Nature (London)*, **221** 477 (1969). (b) Brevicomin was isolated from the pine bark beetle *Dendroctonus brevicomis*: R. M. Silverstein, R. G. Brownlee, T. E. Bellas, D. L. Wood, and L. B. Brown, *Sciences*, **159**, 889 (1968). (c) Multistriatin was isolated from the elm bark beetle *Scolytus multistriatus*: G. T. Pearce, W. E. Gore, R. M. Silverstein, J. W. Peacock, R. A. Cuthbert, G. N. Lanier, and J. B. Simone, *J. Chem. Ecol.*, 1, 115 (1975).

(2) Leading references can be found in reviews: (a) B. P. Mundy, K. B. Lipkowitz, and G. W. Dirks, *Heterocycles*, 6, 51 (1977); (b) J. M. Brand, J. C. Young, and R. M. Silverstein, *Fortschr. Chem. Org. Naturst.*, **37**, 1 (1979).

(3) (a) B. P. Mundy, G. W. Dirks, R. D. Larsen, and C. N. Caughlan, *J. Org. Chem.*, **43**, 2347 (1978); (b) J. H. Noordik and G. A. Jeffrey, *Acta Crystallogr., Sect B*, **B33**, 403 (1977).

(4) (a) *exo*- and *endo*-brevicomin were first compared by Silverstein: R. M. Silverstein, *J. Chem. Educ.*, **45**, 794 (1968). In this report, differences in relative abundance of some of the fragments could be noted. Also, some metastable peaks in the exo isomer were observed. (b) W. E. Gore, G. T. Pearce, and R. M. Silverstein, *J. Org. Chem.*, **41**, 607 (1976).

(5) These products, isolated from tobacco, have been examined: (a) E. Demole, C. Demole and D. Berthet, *Helv. Chem. Acta*, **57**, 192 (1974); (b) E. Demole and C. Demole, *ibid.*, **58**, 1867 (1975).

(6) The steric effects of *endo*-alkyl groups on the coupling constant for the C-7 and C-1 protons has been observed: J. Colonge, J. Buendia, and H. Guignard, *Bull. Soc. Chim. Fr.*, 956 (1969). The changes in dihedral angle as the size of the *endo*-alkyl group increased can be suggestive of skeletal deformation.

0022-3263/81/1946-4005$01.25/0

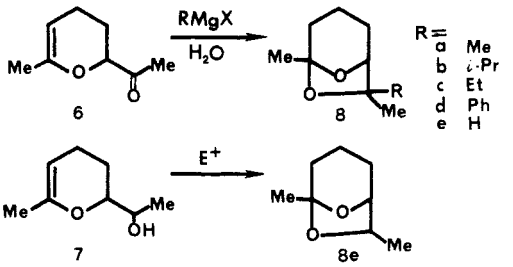
Table I. Mass Spectral Fragmentation Patterns[a]

8a		8b		8c		8d		8e	8e intens	
peak	intens	peak	intens	peak	peak	peak	intens	peak	exo	endo
43	100	43	100	43	100	32	100	43	100	100
44	4	44	7	44	6	39	6	44	5	5
53	6	45	8	45	4	40	34	45	5	5
54	3	53	7	53	6	41	8	53	6	6
55	15	55	17	54	4	43	67	54	13	7
57	9	69	22	55	26	51	7	55	21	20
58	7	70	8	56	6	55	7	56	4	3
59	7	71	24	57	20	77	13	57	8	9
67	13	81	17	58	7	78	6	58	10	6
68	55	83	14	67	26	79	6	67	11	12
69	21	84	10	68	5	83	6	69	4	4
70	7	87	55	69	9	91	16	71	33	20
71	42	95	10	70	4	97	4	72	21	28
72	13	96	10	71	30	98	36	81	5	4
81	32	97	24	72	16	99	4	83	7	9
82	7	98	83	73	4	103	7	85	5	8
83	13	99	17	79	4	104	6	97	4	5
85	19	141	45	81	26	105	21	98	17	18
86	39	184	21	82	44	115	6	99	5	6
95	21			83	12	129	10	100	33	12
96	73			85	25	130	6	101	3	
97	17			86	8	131	22	114	3	6
98	64			95	20	134	6	142	9	10
99	13			97	14	143	10			
113	13			98	51	157	31			
141	9			99	13	158	34			
156	13			100	7	159	6			
				110	25	175	4			
				113	15	218	4			
				127	4					
				128	31					
				140	3					
				141	49					
				142	6					
				170	13					

[a] Peaks are m/e values, and intens is the relative intensity.

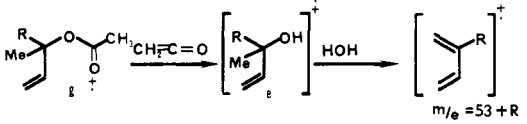
substitution on the electron-impact (EI) fragmentation pattern, with focus on the 7,7-disubstituted systems.

All new 7,7-disubstituted bicyclic ketals were prepared by the addition of **6** to the corresponding Grignard reagents



in typical fashion.[7] The propensity for alcohols like **7** to ketalize in the presence of the mildest of electrophilic reagents has been studied, and even with great care to avoid any reagent more acidic than water in the workup of the anticipated tertiary alcohol **7**, **8** was frequently the only product isolated. All new ketals were formed in high yield and were purified as a mixture of exo/endo isomers with the exception of **8b**. When a deuterium-labeled methyl Grignard was used, it was observed that 60% of the deuterium was located in the *exo*-methyl group of **8a**. The origin of this stereoselectivity is not fully understood; however, a similar selectivity is found in borohydride reduction of **6**. The expectation that exo and endo isomers can be differentiated by their cracking pattern[8] is not borne out experimentally. Fragmentation patterns of the exo and endo isomers of 7-methyl (**8e**) and 7-ethyl (**3**) groups are indistinct, and little stereochemical information about the seven position can be ascertained (Table I). When subjected to 70-eV EI, **8** produced many of the fragments recognized from published work (Scheme I).[9]

In most of the examples the fragmentations predicted are found, and exceptions can be rationalized by other transformations. The absence of **g** and **e** in several spectra deserve comment since these can be related by the transformation shown in eq 1. We observe ions at m/e



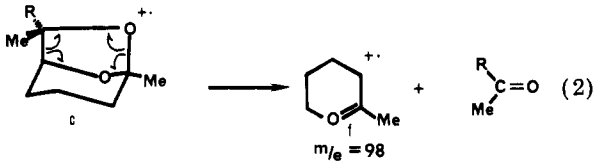
(1)

53 + R for all the 7,7-disubstituted ketals as expected for the tertiary alcohol fragment. Facile dehydration of **b** might also be anticipated, resulting in m/e 81 + R which likewise is found for each molecule. Examination of the fragmentation for each bicyclic ketal indicates an ion at m/e 98 derived from bond rupture as shown in eq 2. The complementary ketone may serve as progenitor to fragment **a**, a $[CH_3C{=}O]^{+\cdot}$ (m/e 28 + R), which was also observed for each ketal. We must stress that 7,7-disubstitution significantly enhances this mode of fragmentation.

(7) The dimer of methyl vinyl ketone has been well characterized: K. B. Lipkowitz, B. P. Mundy, and D. Geeseman, *Synth. Commun.*, **3**, 453 (1973).

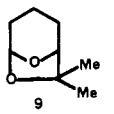
(8) For leading references see M. M. Green *Top. Sterochem.*, **9**, 35 (1976).

(9) This scheme is adapted and modified from ref 4b.



(2)

This is exemplified by 7,7-dimethyl-6,8-dioxabicyclo-[3.2.1]octane (**9**), which produced ion **f** as the most



9

abundant species. Introduction of a methyl group at C-5 reduces this to 64% relative abundance (Scheme I). The relative abundances of ion *m/e* 98 are 64%, 83%, 51%, and 36% for disubstituted ketals **8a–d**, respectively, and only 17% and 18% for the two isomeric 7-monosubstituted ketals **8e**. Mass spectra of other unsubstituted and monosubstituted 6,8-dioxabicyclo[3.2.1]octanes follow this pattern.

It was suggested[4] that the presence of alkyl groups at C-1 can be determined on the basis of the relative abundance of **d** and **e** (see Scheme I). We must express concern over this statement by noting that of the 6,8-dioxabicyclic ketals studied here, *none* possess an alkyl group at C-1, yet most produce ions **d** and **e**. Furthermore, the ratios of **d**/**e** are 19:39 for **8a**, 13:7 for **8c**, 33:21 for *exo*-**8e** and 20:28 for *endo*-**8e**, which demonstrates that the **d**/**e** ratio of <1 is not necessarily attributable to an alkyl substituent at C-1, as suggested.

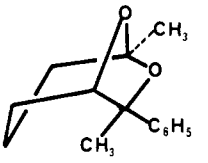
We conclude from the above discussion that gross structural information about 6,8-dioxabicyclic ketals can be obtained by mass spectrometry. Stereochemical information, however, generally cannot be ascertained by electron-impact studies at 70 eV. When used as a definitive tool for structural work, it must be emphasized that bicyclic ketals with substituents at C-7 favor certain modes of fragmentation when compared to unsubstituted ketals. One must therefore exercise caution in spectral interpretation with regards to the stereochemistry at C-7 and the position of substituents on the ketal substructure.

NMR Shift Reagent Studies

The use of lanthanide shift reagents (LSRs) to determine the structure of organic molecules has been widespread.[10] A detailed LSR analysis of several bicyclic ketals has been published.[11] In that study, the problems addressed included (1) the existence of multiple binding sites and (2) the fact that precise geometries for the shift reagent study were unavailable because the crystal structures of these systems were not known at that time. Here we reassess the LSR analysis of bicyclic ketals using improved geometries. It will be seen that the shift reagent method cannot always be used to unambiguously determine the stereochemistry at C-7.

Most of the simple bicyclic ketals are liquids, but the *exo*-7-phenyl-*endo*-7-methyl derivative, **8d**, is a solid. The crystal structure of this dioxabicyclic ketal has been completed and published elsewhere.[3a]

With this precise set of atomic coordinates available, we were able to pursue a more thorough analysis of the LSR experiment. To a weighed sample of **8d** was added aliquots



8d

of a stock solution of $Eu(fod)_3$. After each addition, the spectrum was recorded. The calculated slopes of a plot of induced chemical shift vs. $[Eu(fod)_3]/[substrate]$ are presented in Table II. It can be noted that only the protons associated with the C-5 and C-7 methyl groups, the C-7 phenyl group, and C-1 give distinguishable signals. The C-2 and C-4 protons shifted as an unresolved multiplet.

With these slopes as input data, along with the crystallographic coordinates for **8d**, we utilized the calculational approach, PDIGM.[12] This program calculates, using the McConnell–Robertson equation, an induced chemical shift for each proton measured and compares the calculated to the observed value. PDIGM searches, for each incremental distance the lanthanide is moved from the coordinating atom, a sphere around the coordinating atom. The position, reported in polar coordinates, at which the calculated induced shift most closely agrees with the experimental value is printed as output, along with the agreement factor (*R*), which measures how closely the calculated and experimental induced chemical shifts match. A plot of the agreement factor vs. europium distance for the experiment with **8d** is reported in Figure 1.

Two commonly held notions about use of these data are (1) that "meaningful" agreement factors must be <0.10 and (2) that the distance of the lanthanide from the coordinating side should not be over 3.5 Å. Using these as guides for data interpretation, one sees a clear preference for *O*-6 coordination. That we should find such good agreement is not surprising. Hinckley has reported that better agreement is found when accurate coordinate systems are utilized.[13]

A second test system to analyze the utility of the LSR experiments to bicyclic ketals was **8a**. The LSR experiment for **8a** whose coordinate system was generated by modification of that for **8d**, was performed in the same manner as with **8d**; the data and agreement factor plots are found in Table III and Figure 2, respectively.

Of particular interest from this plot is the observation, again, that O-6 coordination is much preferred over O-8.

At this juncture, we decided to examine one of the natural products. A study has been performed on frontalin by Gore,[11] with the conclusion that preferential coordination occurred at O-6. This is consistent with our observations with model systems; however, we were concerned that the agreement factor of 6% was reported at unusually long distances (between 3.5 and 3.9 Å). We have noted, for many systems, that there is a tendency for agreement factors to appear to minimize at longer distances; but are these real values? A second concern was that the ad hoc coordinate system for frontalin might not be as good as one generated from an established ketal structure.

Accordingly, the coordinate system of **1** was generated from **8d**. The LSR data and a plot of the agreement factor are reported in Table IV and Figure 3, respectively.

(10) For reviews see: (a) R. E. Sievers, Ed., "Nuclear Magnetic Resonance Shift Reagents", Academic Press, New York, 1973; (b) O. Hofer, *Top. Stereochem.*, **9**, 111 (1976).
(11) W. E. Gore and I. M. Armitage, *J. Org. Chem.*, **41**, 1926 (1976).
(12) R. E. R. Davis and M. R. Willcott, III, in "Nuclear Magnetic Resonance Shift Reagents", Academic Press, New York, 1973, pp 143–158.
(13) C. C. Hinckley and W. C. Brunley, *J. Am. Chem. Soc.*, **98**, 1331 (1976).

Table II. LSR Data for 5,7-Dimethyl-7-phenyl-6,8-dioxabicyclo[3.2.1]octane

protons	slope	cor coeff
C-5 methyl	0.49	0.994
C-7 methyl	0.34	0.991
C-1	0.30	0.989
C-7 phenyl	0.84	0.988

Table III. LSR Data for 5,7,7-Trimethyl-6,8-dioxabicyclo[3.2.1]octane

protons	slope	cor coeff
C-5 methyl	0.659	0.999
C-7 methyl (exo)	0.406	0.998
C-7 methyl (endo)	0.353	0.998
C-1	0.989	0.999

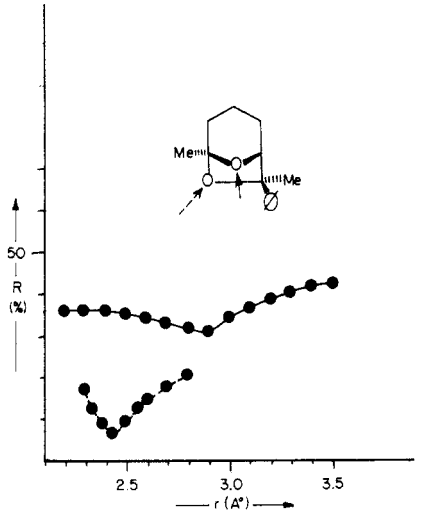


Figure 1. LSR study of *exo*-7-phenyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane.

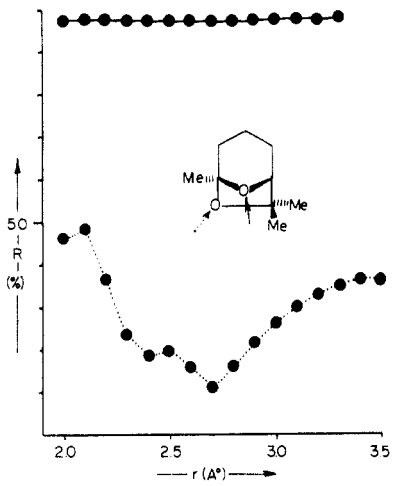


Figure 2. LSR study of 5,7,7-trimethyl-6,8-dioxabicyclo-[3.2.1]octane.

From the plot in Figure 3, we find minimum R values at distances greater than 3.5 Å, in agreement with the previously published work.[11] However, there appears also to be a well in the region of 2.2 Å. Is this significant? In the general use of PDIGM, distance calculations are carried out for 0.1-Å increments. We changed this to calculate at 0.01 Å increments and examined the valley (shown in Figure 4 by a "box") at these intervals. This plot is reported in Figure 4. One observes from this plot that the agreement factor is improved and that there is a genuine, well-defined region for the minimum. We suggest that this

Table IV. LSR Data for Frontalin

protons	slope	cor coeff
C-1 methyl	5.67	0.97
C-5 methyl	12.95	0.98
C-7 H (exo)	16.90	0.98
C-7 H (endo)	17.65	0.98

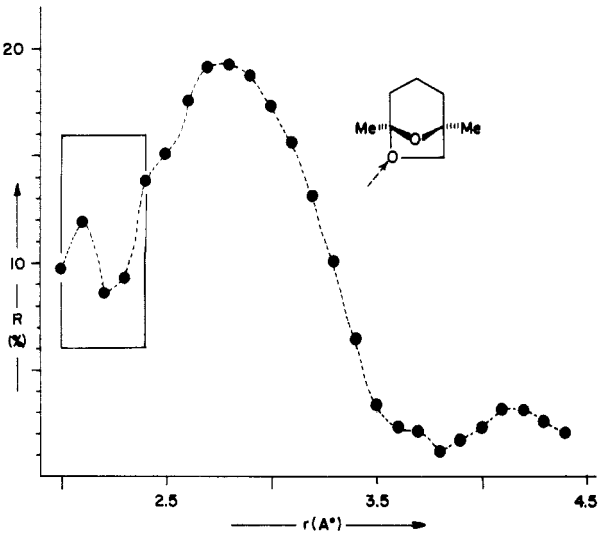


Figure 3. LSR study of frontalin.

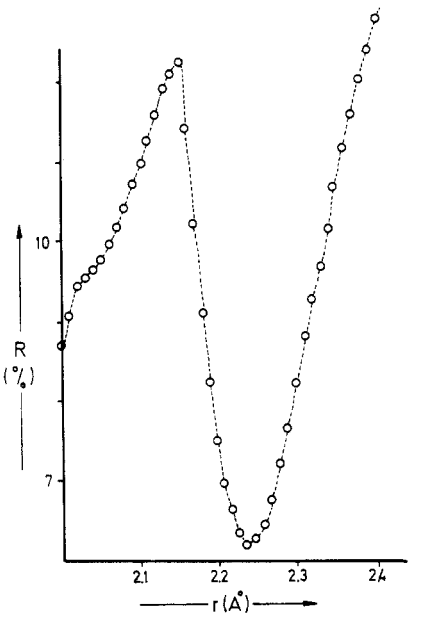


Figure 4. Detailed LSR study of frontalin.

is quantitatively a more realistic appraisal of the LSR interaction with 1; however, the qualitative interpretation remains unchanged. This analysis also demonstrates that it is necessary to examine apparent minima with care.

At this point, there appears to be a well-characterized utility in examining compounds in this ketal series by the LSR method. However, can this method be applied to determining isomer composition? Gore has utilized the technique to examine structures of the multistriatin diastereomers and has found agreement with analyses performed by other methods.[11] Again there is no doubt that the conclusions are correct; but, if the answers had not been unambiguously available by other methods, one must question the reliability of the LSR experiment. In fact, by examining the long Eu–O distances used by Gore along with the small differences in agreement factors, an R ratio factor for one degree of freedom *in the best case* gives only

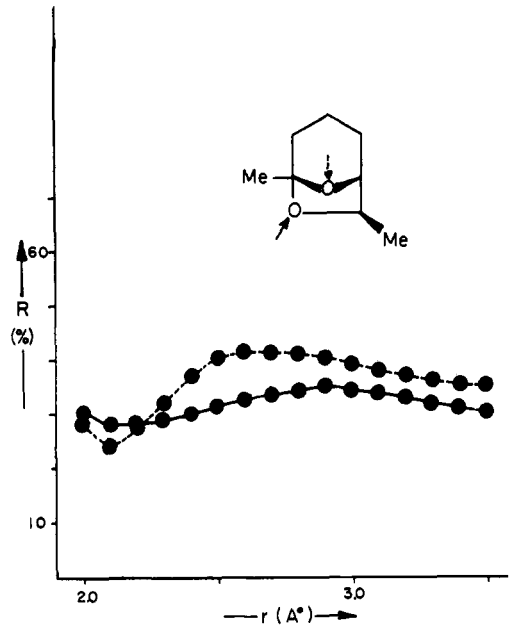


Figure 5. LSR study of *exo*-5,7-dimethyl-6,8-dioxabicyclo-[3.2.1]octane.

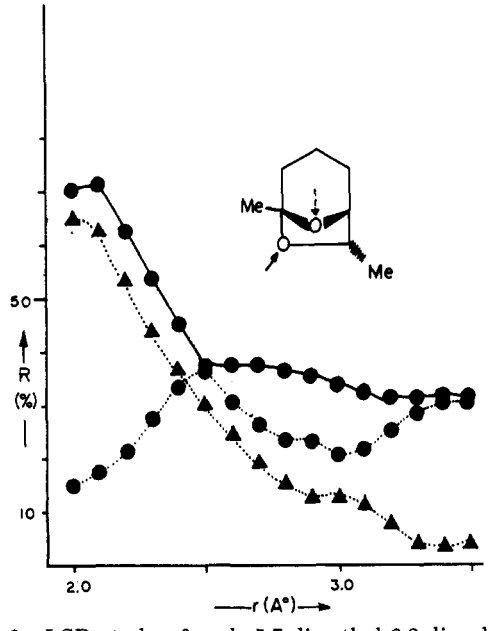
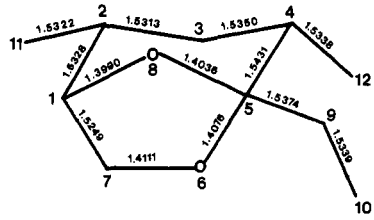


Figure 6. LSR study of *endo*-5,7-dimethyl-6,8-dioxabicyclo-[3.2.1]octane.

a 50% confidence level. Accordingly, we decided to examine the isomers, *exo*-**8e** and *endo*-**8e**. These have been previously prepared and their constitution well-established.[14]

By use of procedures identical with those reported above, the analyses for structures of *exo*-**8e** and *endo*-**8e** are summarized in Figures 5 and 6, respectively.

It was a surprise to note that in neither case, whether calculating by O-6 or O-8 coordination, reasonable agreement was found. For the endo isomer, we attempted a calculation approximating a 50:50 attachment to both oxygens by europium (Δ line). This was performed by computer generating a false oxygen atom between O-6 and O-8 and directing the lanthanide to this atom. Better agreement was found here, in support of the report by Gore



Bond Angles	Theta
C(2) - C(1) - O(8)	109.318
C(2) - C(1) - C(7)	116.404
O(8) - C(1) - C(7)	99.519
C(1) - C(2) - C(3)	109.511
C(1) - C(2) - C(11)	113.256
C(3) - C(2) - C(11)	112.926
C(2) - C(3) - C(4)	110.841
C(3) - C(4) - C(5)	109.049
C(3) - C(4) - C(12)	111.215
C(5) - C(4) - C(12)	114.341
C(4) - C(5) - O(8)	109.520
C(4) - C(5) - O(6)	110.259
C(4) - C(5) - C(9)	113.321
O(8) - C(5) - O(6)	106.875
O(8) - C(5) - C(9)	107.862
O(6) - C(5) - C(9)	108.776
C(1) - O(8) - C(5)	101.460
C(1) - C(7) - O(6)	104.274
C(5) - O(6) - C(7)	105.133
C(5) - C(9) - C(10)	113.253

Figure 7. α-Multistriatin.

that steric effects might play an important role in directing the lanthanide. For our case, however, we have to reject this notion because of the very good results obtained on **8a** which should have steric effects characteristic of both *exo*-**8e** and *endo*-**8e**. Another possible explanation presented itself, that of an earlier misassignment of structures for these isomers. We thus applied the exo shift data to the coordinate system for the endo isomer and vice versa. There was no improvement of the calculated agreements.

At this writing we cannot rationalize the source of our inability to evaluate the structures for *exo*-**8e** and *endo*-**8e** by the LSR technique. Davis[12] has described the existence of homometric sets, two or more structures that give the same set of lanthanide-induced shifts. We may be experiencing this. Another possibility may be that the lack of a larger number of observable and assignable proton shifts is resulting in statistically nondistinguishable data. This problem, not unique in structure work in organic chemistry because of symmetry, methyl proton equivalences, and nonresolvable proton signals with low frequency instrumentation, will continue to face chemists using the LSR technique.

Yet another alternative is that the calculated induced chemical shifts critically depend upon the input geometry. Throughout the course of this work, we have assumed that the basic ring structure is the same from compound to compound. This assumption may not be valid. As a check, we present the results of empirical force field calculations on several representative ketals to see if the basic ring structure remains invariant to substituents.

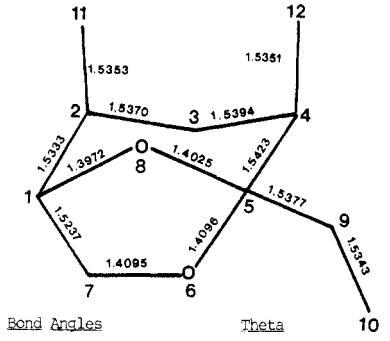
Empirical Force Field Results

Geometry optimization of large organic molecules can be approached two ways: quantum mechanically or by molecular mechanics.[15] Because we have no interest in the electronic properties of these ketals and because molecular mechanics can give structural results that rival experiment at a fraction of the cost of the simplest all-valence-electron quantum methods, we decided to compute the structures with an empirical force field. Specifically, we used Allinger's force field[16] method because it is sufficiently parameterized to treat these systems.

(14) (a) K. B. Lipkowitz and B. P. Mundy, *J. Org. Chem.*, 41, 371 (1976); (b) K. B. Lipkowitz, B. P. Mundy and T. H. Matsko, *ibid.*, 41, 373 (1976).

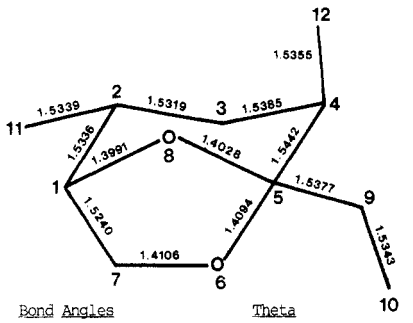
(15) A review of the philosophy and underlying principles of empirical force fields can be found: D. B. Boyd and K. B. Lipkowitz, *J. Chem. Educ.*, in press.

(16) N. L. Allinger, *Adv. Phys. Org. Chem.*, 13, 1, (1977).



Bond Angles	Theta
C(2) - C(1) - O(8)	110.137
C(2) - C(1) - C(7)	115.264
O(8) - C(1) - C(7)	99.900
C(1) - C(2) - C(3)	109.469
C(1) - C(2) - C(11)	111.698
C(3) - C(2) - C(11)	114.078
C(2) - C(3) - C(4)	113.393
C(3) - C(4) - C(5)	108.103
C(3) - C(4) - C(12)	113.933
C(5) - C(4) - C(12)	114.142
C(4) - C(5) - O(8)	109.421
C(4) - C(5) - O(6)	109.377
C(4) - C(5) - C(9)	113.618
O(8) - C(5) - O(6)	107.541
O(8) - C(5) - C(9)	108.136
O(6) - C(5) - C(9)	108.567
C(1) - O(8) - C(5)	101.658
C(1) - C(7) - O(6)	103.905
C(5) - O(6) - C(7)	105.263
C(5) - C(9) - C(10)	113.552

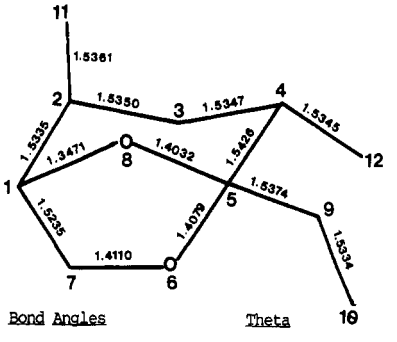
Figure 8. β-Multistriatin.



Bond Angles	Theta
C(2) - C(1) - O(8)	109.498
C(2) - C(1) - C(7)	116.170
O(8) - C(1) - C(7)	99.360
C(1) - C(2) - C(3)	109.607
C(1) - C(2) - C(11)	113.164
C(3) - C(3) - C(4)	110.794
C(3) - C(4) - C(5)	108.238
C(3) - C(4) - C(12)	112.053
C(5) - C(4) - C(12)	113.900
C(4) - C(5) - O(8)	109.730
C(4) - C(5) - O(6)	109.541
C(4) - C(5) - C(9)	113.599
O(8) - C(5) - O(6)	107.121
O(8) - C(5) - C(9)	107.979
O(6) - C(5) - C(9)	108.657
C(1) - O(8) - C(5)	101.431
C(1) - C(7) - O(6)	103.976
C(5) - O(6) - C(7)	105.133
C(5) - C(9) - C(10)	113.587

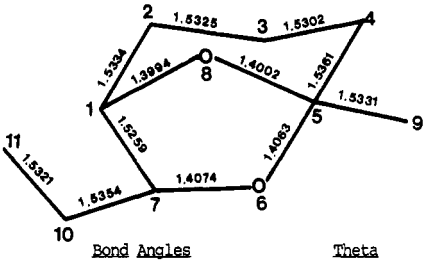
Figure 9. γ-Multistriatin.

The force field results for multistriatin and brevicomin are presented in Figures 7–12. Figure 13 lists pertinent bond lengths and bond angles of **8d** for comparison. The crystal structure of 3-amino-1,6-anhydro-3-deoxy-D-glucopyranose by neutron diffraction[3b] gives overall skeletal data in remarkably close agreement to that found for **8d** (Figure 14). The molecular mechanics results are in reasonably good agreement with the experimentally determined geometry. Major differences are found in the skeleton making up the dioxalane moiety of the compounds. Calculations are routinely found to shorten all the bonds by about 2%. However, we will point out that while the extraordinarily acute O8–C1–C7 bond angle has been successfully reproduced by the force field, the small C1–C7–O6 angle is not as satisfactory, with deviations of two to four degrees between experiment and theory.



Bond Angles	Theta
C(2) - C(1) - O(8)	109.925
C(2) - C(1) - C(7)	115.611
O(8) - C(1) - C(7)	99.848
C(1) - C(2) - C(3)	109.229
C(1) - C(2) - C(11)	111.360
C(3) - C(2) - C(11)	112.575
C(2) - C(3) - C(4)	111.624
C(3) - C(4) - C(5)	108.886
C(3) - C(4) - C(12)	111.397
C(5) - C(4) - C(12)	114.288
C(4) - C(5) - O(8)	109.597
C(4) - C(5) - O(6)	110.267
C(4) - C(5) - C(9)	113.354
O(8) - C(5) - O(6)	106.995
O(8) - C(5) - C(9)	107.827
O(6) - C(5) - C(9)	108.779
C(1) - O(8) - C(5)	101.499
C(1) - C(7) - O(6)	104.199
C(5) - O(6) - C(7)	105.192
C(5) - C(9) - C(10)	113.265

Figure 10. δ-Multistriatin.



Bond Angles	Theta
C(2) - C(1) - O(8)	109.379
C(2) - C(1) - C(7)	114.981
O(8) - C(1) - C(7)	100.947
C(1) - C(2) - C(3)	110.750
C(2) - C(3) - C(4)	109.058
C(3) - C(4) - C(5)	110.910
C(4) - C(5) - O(8)	110.013
C(4) - C(5) - O(6)	111.877
C(4) - C(5) - C(9)	110.782
O(8) - C(5) - O(6)	106.223
O(8) - C(5) - C(9)	108.608
O(6) - C(5) - C(9)	109.192
C(1) - O(8) - C(5)	100.502
C(1) - C(7) - O(6)	103.638
C(1) - C(7) - C(10)	115.825
O(6) - C(7) - C(10)	110.262
C(5) - O(6) - C(7)	105.663
C(7) - C(10) - C(11)	115.535

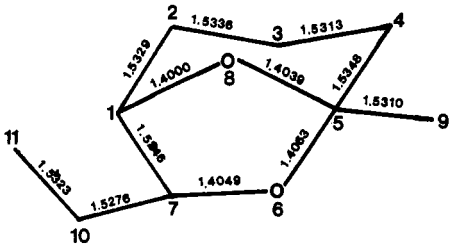
Figure 11. *exo*-Brevicomin.

Table V. MMI Computed Total Steric Energies of Multistriatin and Brevicomin

pheromone	kcal mol^{-1}	pheromone	kcal mol^{-1}
endo-brevicomin	23.20	β-multistriatin	27.77
exo-brevicomin	22.59[a]	γ-multistraitin	25.91
α-multistriatin	24.87[a]	δ-multistriatin	25.38

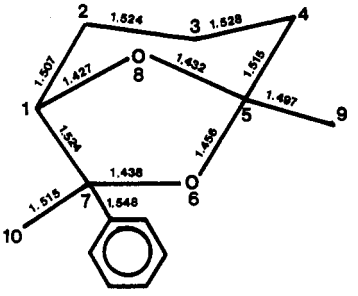
[a] Active form.

Table V lists the total steric energy of the six molecules considered. These numbers have no absolute meaning, so comparison of brevicomin and multistriatin energies is not possible. A comparison of the total steric energies between isomers does have a physical interpretation though, and it is clear that the most stable multistriatin is the α diastereomer and that the more stable brevicomin is the exo isomer. Perhaps fortuitously, these isomers are the active forms of the multistriatin and brevicomin pheromones.



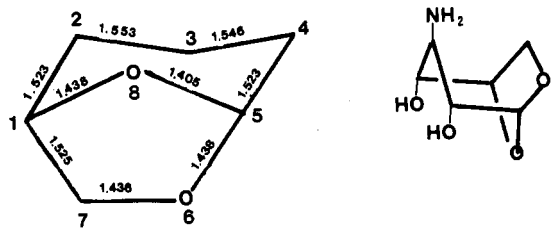
Bond Angles	Theta
C(2) - C(1) - O(8)	108.773
C(2) - C(1) - C(7)	117.891
O(8) - C(1) - C(7)	98.802
C(1) - C(2) - C(3)	112.552
C(2) - C(3) - C(4)	109.884
C(3) - C(4) - C(5)	109.009
C(4) - C(5) - O(8)	108.760
C(4) - C(5) - O(6)	110.301
C(4) - C(5) - C(9)	111.999
O(8) - C(5) - O(6)	107.736
O(8) - C(5) - C(9)	108.526
O(6) - C(5) - C(9)	109.406
C(1) - O(8) - C(5)	100.504
C(1) - C(7) - O(6)	102.441
C(1) - C(7) - C(10)	118.336
O(8) - C(7) - C(10)	111.932
C(5) - O(6) - C(7)	105.147
C(7) - C(10) - C(11)	113.026

Figure 12. *endo*-Brevicomin.



Bond Angles	Theta
C(2) - C(1) - O(8)	109.1
C(2) - C(1) - C(7)	116.9
O(8) - C(1) - C(7)	100.3
C(1) - C(2) - C(3)	112.2
C(2) - C(3) - C(4)	112.8
C(3) - C(4) - C(5)	111.3
C(4) - C(5) - O(8)	109.7
C(4) - C(5) - O(6)	108.0
C(4) - C(5) - C(9)	115.5
O(8) - C(5) - O(6)	104.1
O(8) - C(5) - C(9)	109.0
C(1) - O(8) - C(5)	102.5
C(1) - C(7) - O(6)	100.7
C(5) - O(6) - C(7)	107.9

Figure 13. *exo*-7-Phenyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]-octane.



Bond Angles	Theta
C(2) - C(1) - O(8)	108.3
C(2) - C(1) - C(7)	115.0
O(8) - C(1) - C(7)	100.8
C(1) - C(2) - C(3)	112.5
C(2) - C(3) - C(4)	113.0
C(3) - C(4) - C(5)	110.8
C(4) - C(5) - O(8)	110.4
C(4) - C(9) - O(6)	109.2
O(8) - C(5) - O(6)	106.3
C(1) - O(8) - C(5)	102.1
C(1) - C(7) - O(6)	102.9
C(5) - O(6) - C(7)	107.1

Figure 14. 3-Amino-1,6-anhydro-3-deoxy-β-D-glucopyranose

The gross geometric structures we calculate are similar to the experimental structure of Mundy et al.[3a] There are, however, substantial differences in the degree of pucker of the flexible portion of the ring in several cases. A hand-held mechanical model of β-multistriatin indicates a 1,3-diaxial interaction between the C-2 methyl and C-4 methyl groups. Our force field results indicate that the chair pyran has in fact been substantially flattened for this isomeric form of multistriatin. The two methyls have rotated out of their axial positions toward a pseudoaxial form. To a lesser extent of γ- and δ-multistriatins also show this behavior.

Table VI. CNDO/2 Oxygen Electron Densities of Brevicomin and Multistriatin

	brevicomin		multistriatin			
	exo	endo	α	β	γ	δ
O-6	6.263	6.266	6.267	6.264	6.266	6.265
O-8	6.266	6.271	6.258	1.260	6.260	1.258

The LSR studies we have presented above do not have substituents on the flexible portion of the ring and are not expected to deviate from the experimental geometry we used in the LSR calculations. In contrast, the LSR results of Gore et al. involved substituents on the flexible portion of the ring and may not have taken this into account. Hence, by not using experimental or force field optimized geometries, they may have constructed models that biased their results to give the answers they anticipated since they knew, a priori, which isomer was which. Real multistriatin geometries may result in an inability of PDIGM to distinguish (in a statistically valid sense) one diastereoisomer from the other.

A final theoretical aspect that has a bearing on the problem of binding sites concerns the Lewis basicity of the two oxygens. Table VI lists the total charge densities on the two oxygens for the ketals studied. The computational scheme employed is the well-established CNDO/2 approximate molecular orbital method.[17] MMI-optimized geometries were used as input. Clearly, there is little difference between oxygens, leading us to the conclusion that the binding site of the shift reagent, and perhaps the biological receptor, critically depends upon the steric interaction with substituents near the ketal oxygen.

Conclusion

The mass spectral fragmentation patterns of several C-7-substituted dioxabicyclic ketals were measured and compared with earlier experiments. We conclude that substituents at C-7 substantially alter the fragmentation pathways when compared to unsubstituted ketals and that only gross structural features may be evaluated. We also conclude that no useful stereochemical information at C-7 can be obtained by 70-eV electon-impact mass spectrometry.

A reevaluation of the LSR study of Gore et al. demonstrated that most of their work was correct, but a new and more reliable minimum R value was found for frontalin. The inability of the LSR technique to distinguish exo and endo isomers of a C-7-substituted pheromone analogue suggests that the method not be used as a definitive tool in structural assignment. The origin of the inability to differentiate exo and endo isomers may be that we are dealing with a homometric set of chemically induced shifts. Alternatively, we suggested that the computed R values critically depend upon input coordinates. The assumption that the same basic geometry can be used for all of our ketal LSR calculations may not be valid. To test whether

(17) J. A. Pople and D. A. Beveridge, "Approximate Molecular Orbital Theory", McGraw-Hill, New York, 1970.

or not the ring structure is invariant to substituents, we carried out empirical force field calculations. For all practical purposes, the ring structures of all bicyclic ketals studied in this paper were the same.

In contrast, axial substituents on the flexible portion of the pyran ring tend to distort the system toward a flattened chair structure. By not taking this into account, Gore et al. may have biased their results. It may be that real or force field optimized geometries will not allow PDIGM to differentiate between the four multistriatin isomers in a statistically meaningful way. We suggest that without a priori knowledge of detailed structural information, LSR studies may give misleading results and should be used with caution in the structural analyses of dioxabicyclic ketals.

Experimental Section

A preliminary report of the preparation of the bicyclic ketals has appeared,[7] and a typical preparation will be reported here. Satisfactory combustion analysis for new compounds in this study include the following. Calcd for **8a**: C, 69.2; H, 10.2. Found: C, 69.0; H, 9.9. Calcd for **8c**: C, 70.6; H, 10.6. Found: C, 70.6; H, 10.4. Calcd for **8d**: C, 77.0; H, 8.3. Found: C, 76.9; H, 8.4. The chemistry of **8e** has been well-documented.[14] The NMR spectrum for each compound is in accord with the assigned structure.

The procedure for **8c** was as follows. Methyl vinyl ketone dimer (0.007 mol) was slowly added to 1 equiv of ethyl Grignard in ether. After the addition was complete, the reaction mixture was stirred for an additional hour. Wet ether was added to the reaction mixture to hydrolyze the magnesium complex. The reaction mixture was extracted with dichloromethane. The extracts were dried and reduced in volume to 0.98 g of yellow liquid, composed of product and starting methyl vinyl ketone dimer in the ratio of 1:6.6. This constitutes a 72% yield of **8c**.

Acknowledgment. The Indiana University Computer Network is acknowledged for generously providing funds for the computational aspects of this work. Partial support of this work by the USDA Forest Service and the NSF-(ISP-8011449) is acknowledged.

Registry No. **1**, 28401-39-0; **α-2**, 59014-03-8; **β-2**, 59014-05-0; **γ-2**, 54832-21-2; **δ-2**, 54832-22-3; ***endo*-3**, 22625-19-0; ***exo*-3**, 20290-99-7; **8a**, 16566-96-4; ***exo*-8b**, 68378-84-7; ***endo*-8b**, 68378-85-8; ***exo*-8c**, 68378-86-9; ***endo*-8c**, 68378-87-0; ***exo*-8d**, 65899-46-9; ***endo*-8d**, 65899-47-0; ***exo*-8e**, 56057-15-9; ***endo*-8e**, 56057-16-0.

Preparation of 8-Alkyl-14-hydroxydihydrocodeinones[1]

David L. Leland, Joseph O. Polazzi, and Michael P. Kotick*

Chemistry Department, Corporate Research Division, Miles Laboratories, Inc., Elkhart, Indiana 46515

Received May 4, 1981

Reaction of 14-[(trimethylsilyl)oxy]codeinone (**1b**) with lithium dimethylcuprate gave a 2:1 isomeric mixture of the corresponding 8α-methyl (**2**) and 8β-methyl (**3**) 14-(trimethylsilyl)oxydihydro derivatives. Selective removal of the silyl group from α isomer **2** to give **4**, by use of silica gel, allowed resolution of the mixture. 8β-Methyl-14-hydroxydihydrocodeinone (**5**) was prepared from **3** by cleavage of the silyl ether with *n*-Bu_4NF. Treatment of 14-hydroxycodeinone with Me_2CuLi gave a 4:1 mixture of alkylated products **4** and **5**. The (*tert*-butyldimethylsilyl)oxy ether **1c** under similar conditions gave exclusively the stable 8α isomer **6**. Reaction of trimethylsilyl compound **1b** with Et_2CuLi or *n*-Bu_2CuLi gave approximately equal amounts of the corresponding 8-alkyl 14-O-silylated isomers. These results are in contrast to previous work with codeinone which demonstrated that lithium organocopper reagents add almost exclusively to the β face of "T-shaped" morphinone derivatives.

We have previously reported reaction of codeinone with lithium dialkylcuprates yields mainly 8β-alkylated dihydrocodeinones.[2] A minor product of some of these reactions was the corresponding 8α-alkyl isomer. As part of a program aimed at preparing morphine compounds modified in the C ring, a similar reaction of 14-hydroxycodeinone and some 14-*O*-silyl derivatives was investigated. We now report that such reactions yield a substantially higher proportion of the 8α-alkylated product.

Difficulty was experienced in the conversion of thebaine to 14-hydroxycodeinone (**1a**) with use of *m*-chloroperbenzoic acid as reported.[3] Iijima and co-workers[4] have found that this reaction is sensitive to changes in reaction conditions. In our hands, this reaction at first gave mixtures containing polar products. We found that **1a** could smoothly be obtained from thebaine, in the reported yield, by the inclusion of 10% water during this reaction.[5]

To increase the solubility of **1a** in ethereal solvents, the 14-*O*-trimethylsilyl ether **1b** was prepared by refluxing **1a** in hexamethyldisilizane. Efforts to purify **1b** by chromatography resulted only in recovery of starting material **1a**. Addition of an ethereal solution of crude **1b** to 1.25 equiv of Me_2CuLi in Et_2O gave an approximately 2:1 mixture of alkylated products **2** and **3** as indicated by NMR. Attempted concurrent removal of the silyl group and resolution of this mixture by chromatography unexpectedly yielded the silylated 8β-methyl product **3** and the deprotected 14-hydroxy-8α-methyl compound **4**. Improved resolution of these products was obtained by stirring the crude alkylation products with silica gel in $CHCl_3$ prior to chromatography. The silyl group in 8β-methyl compound **3** could then be easily removed, to give **5**, by treatment with *n*-Bu_4NF in THF (Scheme I).

The NMR spectrum of the crude reaction mixture obtained above indicated that the α isomer was the major product in contrast to previous results in the codeinone series. The structure of the C-8 methylated products are easily assigned based on the observation that the NMR signal for the 8-methyl group in the α isomer is observed

(1) Analgesic Narcotic Antagonists. 10. For paper 9, see Kotick, M. P.; Leland, D. L.; Polazzi, J. O.; Howes, J. F.; Bousquet, A. R. *J. Med. Chem.* **1981**, in press.
(2) Kotick, M. P.; Leland, D. L.; Polazzi, J. O.; Schut, R. N. *J. Med. Chem.* **1980**, *23*, 166.
(3) Hauser, F. M.; Chen, T. K.; Carroll, F. I. *J. Med. Chem.* **1974**, *17*, 1117.
(4) Iijima, I.; Rice, K. C.; Brossi, A. *Helv. Chim. Acta* **1977**, *60*, 2135.
(5) Kirk, D. N.; Wiles, J. M. *J. Chem. Soc. D* **1970**, 1015.

0022-3263/81/1946-4012$01.25/0