amine–nitrile complex was obtained cleanly only for benzylamine.

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Electrostatic Facilitation of General Acid Catalyzed α-Oxonium Ion Formation in a Lysozyme-Like Environment: Synthesis of the Models

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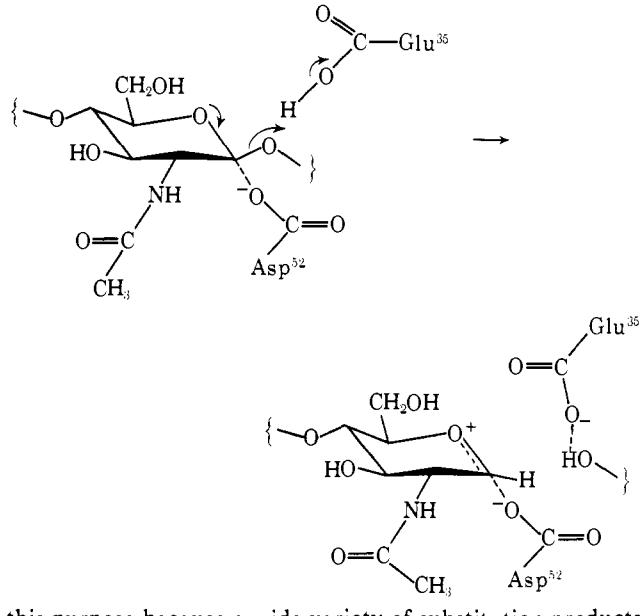
Abstract: The syntheses and structural correlations of *exo*-2,5-dimethyl-*endo*-2-(1-methoxyvinyl)bicyclo[2.2.1]heptyl-*endo*-5-carboxylic acid (**1**) and a reference compound, *exo*-2-methyl-*endo*-2-(1-methoxyvinyl)bicyclo[2.2.1]heptyl-*exo*-5-carboxylic acid (**2**) are described, and arguments are presented which suggest that the effect of ionization of the *endo*-carboxylic acid group on the hydrolysis of **1** should be a reasonable model for the effect of aspartic acid-52 of lysozyme on saccharide hydrolysis by the enzyme.

Crystallographic results have suggested several catalytic features which are believed to be of importance in the mechanism of action of hen lysozyme.[1] For example, "general acid catalysis" of saccharide substrates by glutamic acid-35 (Glu^{35}) of the enzyme has been postulated, and the reasonableness of such a mechanism has been amply verified in model studies.[2] Substrate distortion was implicated in the catalytic mechanism of the enzyme from the crystallographic results, and model studies have shown that this feature may indeed lead to substantial rate enhancements in acetal and ketal hydrolyses.[3-7] One aspect of lysozyme catalysis, however, which has not been satisfactorily reproduced with models is a postulated rate enhancement due to stabilization of the developing carbonium ion intermediate in the saccharide cleavage reaction by a second ionized carboxyl group, identified as aspartic acid-52 (Asp_{52}) from the crystallographic work (Scheme I). Despite a large number of attempts, no case of such a rate acceleration has been found which is at the same time kinetically unambiguous.

In previous work examining this question using both acetal[2] and vinyl ether[8,9] hydrolyses to generate the appropriate α-oxocarbonium ion, the rigid template to which the carboxylate ion and the proionic carbon have been attached, is a small, planar (or nearly planar) ring system, usually a benzene ring. Aromatic systems are generally excellent for

Scheme I

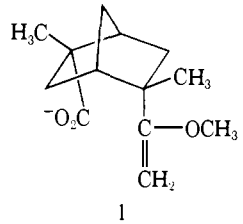


this purpose because a wide variety of substitution products are synthetically accessible,[10] aromatic chromophores ren-

der the appropriate reactions spectrophotometrically observable, and substituent effects in aromatic systems are so well characterized that through-ring effects can easily be calculated with a reasonable degree of accuracy. The consistent failure to observe a significant Asp[52]-like carbonium ion stabilizing effect in these systems has led to the suggestion[8,11,12] that the "microenvironment" of the carboxylate–carbonium ion interaction is perhaps crucial to the observation of a significant effect.[13] The pH–rate profile of lysozyme catalysis[14] shows a pK_a in one arm of 3.8, and a similar pK_a has been associated with Asp[52] The presence of other carboxyl groups in the active site makes direct titration results or pH dependencies difficult to interpret; nevertheless, the assigned pK_a of 3.8 for Asp[52] would be difficult (although not impossible) to reconcile with the above suggestion of a hydrophobic active site. The difference titration results of Parsons and Raftery[15] assign a somewhat higher pK_a to this residue, so that the hydrophobic environment around Asp[52] remains a possibility; further, in making an Asp[52] ethyl ester,[16] these investigators found that triethyloxonium fluoroborate was specifically reactive with primarily Asp[52]. This large hydrophobic ion could have been site directed toward Asp[52] by hydrophobic interactions.

None of the models hitherto studied, including our own, has incorporated an effort to build in a solvent-restricted environment for the carboxyl–carbonium ion interaction, although Bruice and Dunn[12] have shown that a change of solvent can have a dramatic effect on rate enhancements of ketal hydrolysis by proximal carboxyl groups. The planar benzene ring does not provide a simple way of creating such a solvent-restricted environment, so that other systems must be considered.

The large amount of both synthetic and mechanistic chemistry of the bicyclo[2.2.1]heptyl (norbornyl) skeleton of recent years[17] has suggested that this ring system might prove to be an exceptionally valuable "rigid template" with which to create a substantially solvent-free microenvironment for the investigation of the question of electrostatic facilitation of α-oxocarbonium ion formation in aqueous solution. There has been substantial interest by others in this and similar ring systems[18-24] because of the variety of stereochemically well-defined juxtapositions of reacting groups which it can provide. We thus conceived that compound **1** and a control compound **2** would represent reasonable models for the study of the interaction of a carboxylate ion with a developing α-oxocarbonium ion. The following observations led to the development of **1** as our model. (a) There is no ground-state resonance interaction between the carboxyl group and vinyl ether, unlike the situation in benzenoid[8] or unsaturated aliphatic[25] systems; such effects can lead to an apparent enhancement in rate over the rate observed when the carboxyl group is un-ionized. Compound **2** serves as a model or control for any (presumably modest[26]) σ-bond inductive effects. (b) The distance between the carboxylate and proacyl carbon in **1** is about 2.5–3.0 Å (from models), very similar to the appropriate interatomic distance deduced for the lysozyme-carbonium ion complex.[1] (c) Internal "general acid catalysis" (delivery of the catalyzing proton to the double bond by the carboxyl group) by the un-



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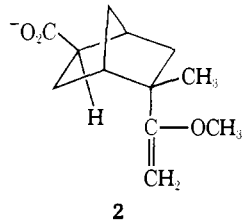

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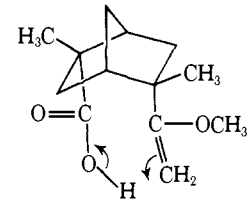
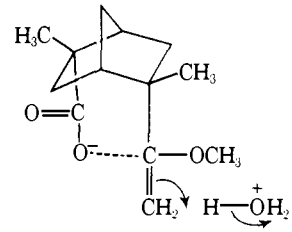
ionized form of **1** (**3a**) would be kinetically indistinguishable from an electrostatic effect of the ionized carboxyl of **1** on H_3O^+ catalysis (**3b**) and might be anticipated to veil the

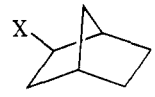


3a

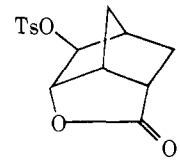


3b

latter mechanism (which we wish to observe) and perhaps even swamp out buffer catalysis; however, the internal "general acid catalysis" mechanism **3a** requires for maximum efficiency that the π-orbitals of the vinyl ether double bond and the entering proton be on-line; from models, such an arrangement results in severe nonbonded interactions of the vinyl and endo-ring protons. (d) The well-known "steric hindrance to ionization" hypothesis for solvolysis of 2-substituted norbornyl derivatives[27] and the preference of many additions to norbornenes for the exo face of the molecule[28] suggested that the crowded environment at the endo face of **1** would substantially exclude solvent. The enhancement of electrostatic interactions via solvent-free endo cavities was invoked to explain the relative rates of acetolysis of **4a** and **5** at 100°:[29] the relative rate of **4a** to **5** was found to be 10^8, whereas ethano-bridged **6** solvolyzed at a normal rate (relative to **4b**). Other evidence to support the idea of exclusion of solvent and nucleophiles from the endo face of **1** was gleaned from our synthetic operations and will be presented below. (e) Finally, the two exo-methyl groups in **1** would protect against epimerization and/or migration of the vinyl ether double bond, and would additionally enhance by a "buttressing" effect the crowding at the endo face of the ring.



4a, X = OTs
4b, X = OBs



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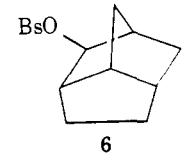


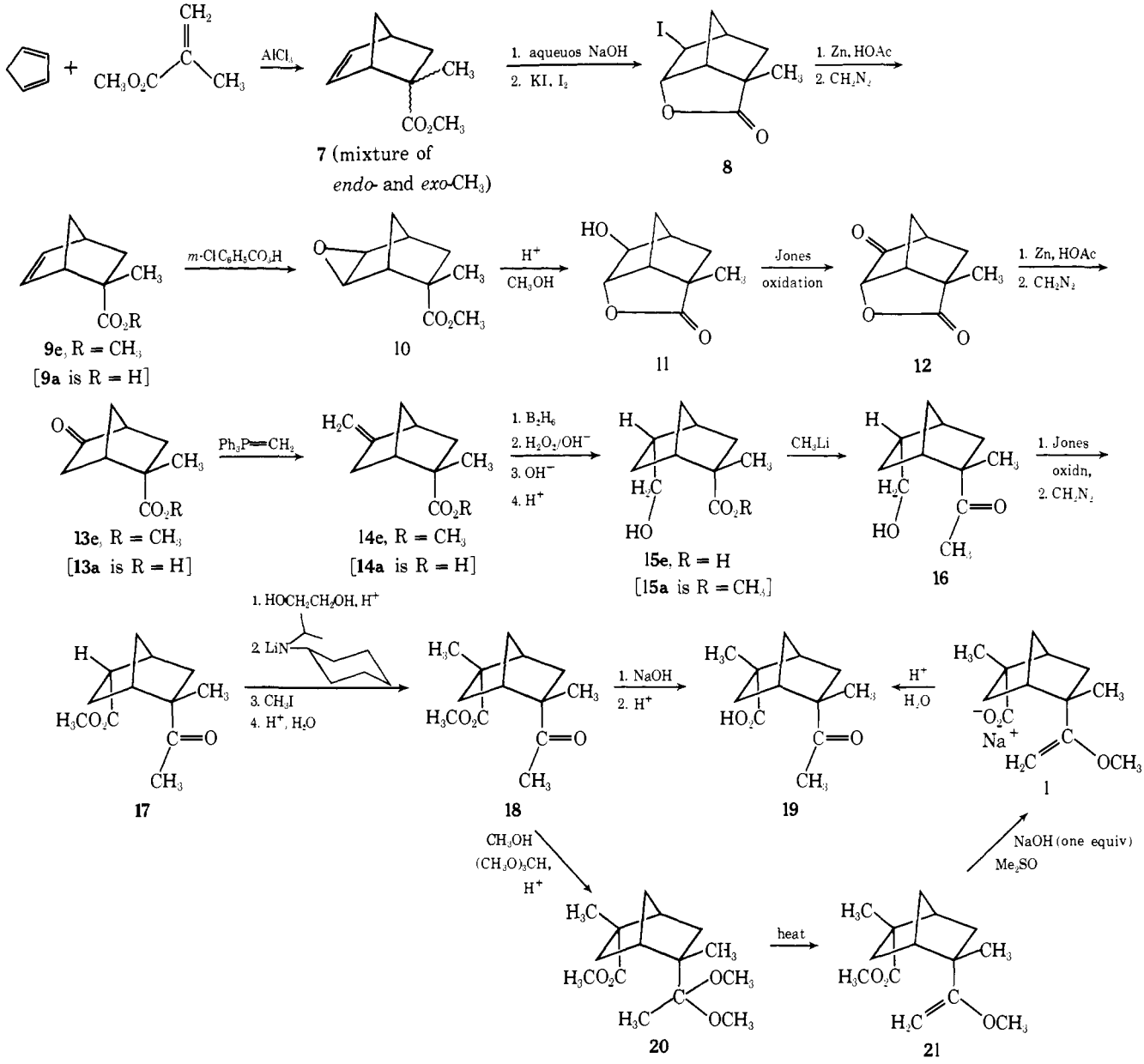
6

We here describe the synthesis and structural arguments for **1** and **2**; our kinetic studies on the hydrolytic reactions of these compounds are discussed in the accompanying paper.

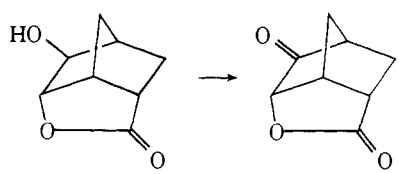
Results and Discussion

Synthesis of 1. The synthesis of compound **1** is summarized in Scheme II. The Diels–Alder reaction of cyclopentadiene and methyl methacrylate proceeded in good yield in the Inukai[30] modification with $AlCl_3$ to give the *exo*-CH_3 and *endo*-CH_3 components in 3:2 ratio.[31,32] Subsequent reactions through hydroxylactone **11** proceeded normally. The 2,6 (as opposed to 2,5) regioselectivity of the lactonization was assumed by analogy of this process to iodolactonization, for the product of which a rigorous structure proof exists,[33] the carbonyl ir stretching frequency of 1780 cm^{-1}, and the fact that the acidic conditions used to open the epoxide would be expected to equilibrate the 2,6- and highly strained 2,5-lactone. In addition, the alcohol **15** (Scheme II) could not be induced to lactonize, whereas a 2,5 relationship at the epoxide opening stage should lead to a lactonizable, 2,6 ester or acid at the stage of **15**. Nevertheless, conclusive proof of the regioselectivity and the lack of Wagner-Meerwein rearrangements will be offered below. Al-

Scheme II

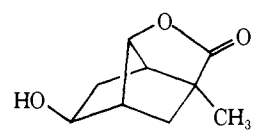


though there is no report of any attempted oxidation of **11** to **12**, the closely analogous reaction of **22** to **23** was studied by Crundwell and Templeton,[34] who reported failure of five modifications of CrO_3 oxidation, $KMnO_4$–acetic acid, and *N*-bromosuccinimide. In 1972, Moriarty et al.[35] discussed in a full paper their earlier observations[36] that RuO_4 oxidizes **22** to **23** in 80% yield; these authors mention the failure



22 **23**

of 20 standard oxidizing procedures in the face of their sole success with RuO_4. RuO_4 was evidently the reagent of choice for oxidation of **11**, but we discovered that certain forms of reduced ruthenium (specifically, anhydrous $RuCl_3$ and anhydrous RuO_2) totally fail in this reaction. This feature of the RuO_4 method is not well documented in the literature and to our knowledge is only mentioned in the review of Lee and Engh.[55] For the purpose of transforming **11** to **12** on a large scale, we found that, in spite of the aforementioned literature failures, the Jones oxidation method[40] conveniently afforded ketolactone **12** in 70% yield. The isolated product was identical with **12** obtained in lower yields from the neutral oxidation methods of Collins[39] and Corey[38] and from the mild procedure of Brown and Garg;[37] an attempt to oxidize **11** with DDQ gave back starting material. The spectral features of **12** were virtually identical with those of **23** with the obvious exceptions.[41] A Wagner–Meerwein rearrangement of **11** (to **24**) under the acidic



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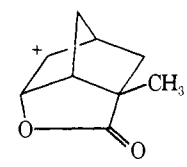


25

conditions used in the Jones oxidation is precluded by subsequent Zn reduction of the ketolactone **12**, which could not occur on the ketolactone corresponding to **24**, and is argued against on theoretical grounds by the difficulty of forming

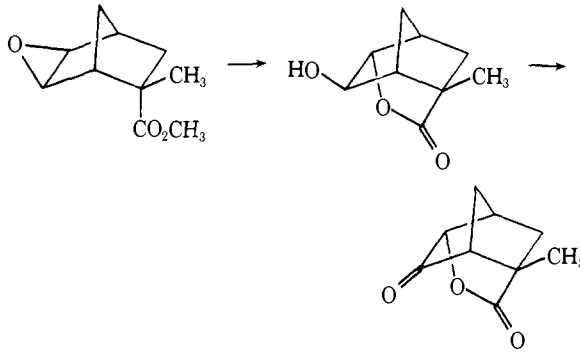
Table I. Comparison of Critical Spectral Characteristics of **13a** and **27**

Compd	Ir, cm^{-1}	NMR[a] δ Exchangeable-H	NMR[a] δ C(2)-methyl
	3800-2450 (br)		
13a	1750	11.0	1.48
	1705		
27	3400	4.7-5.0	1.20
	1760		

[a] For conditions of spectra, see Experimental Section.

carbonium ion **25** even at 100° due to extremely unfavorable charge-dipole interaction (see above discussion relating to **5** and **6**).

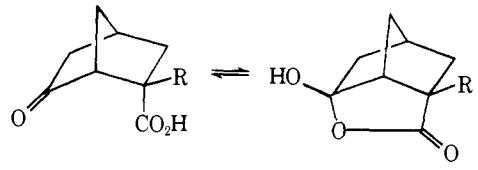
At this point we consider further the question of the possibility of 2,5 lactonization at the stage of epoxide ring opening (**10**). Although disputed previously, the formal possibility that the reaction sequence, which is shown in eq 1,



(1)

26

may have occurred must be granted. However, Zn reduction of **26** would yield **27,** for which we have an authentic sample; the latter was prepared in a manner identical with that used for the preparation of **28,** for which, in turn, a rigorous structure proof exists.[42] Further, the spectral characteristics (Table I) readily identified **28** as a pseudo-acid **30,**

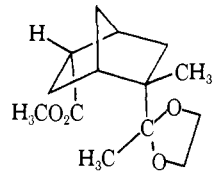


27, R = CH_3 **29**, R = H

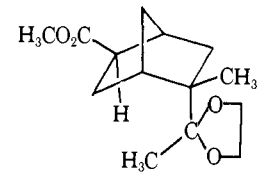
28, R = H **30**, R = CH_3

confirming the 2,6 relationship of the ketone and acid functions. Compound **27** and the compound which we have treated as **13a** (Scheme II) differ by spectra, melting point, and mixture melting point. Finally, Wagner-Meerwein rearrangement of **10** was ruled out by the facile Zn reduction of **12,** which could not occur with such rearrangement products.

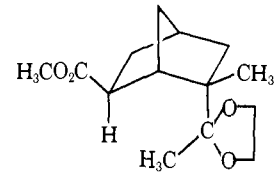
Following an uneventful Wittig reaction which proceeded equally well on the ester **13e** or its corresponding acid, the hydroboration-oxidation of **14e** gave predominantly one isomer of **15e,** reasonably assumed to result from attack at the exo face of **14e;** a minor impurity was noted by analytical GLC of the acetylated product and was assumed to be the isomer resulting from endo attack. Since the following saponification was expected to yield crystalline **15a,** the impurity was carried through this step; saponification followed by crystallization yielded a single pure isomer of **15a.** This material showed no tendency to lactonize. The steps to **18** proceeded in excellent yield as expected. As evidence that the alkylation of the enolate of **30** (in the **17** → **18** conversion) was exo, we note that the isomeric ketals **31** and **32** (to



30

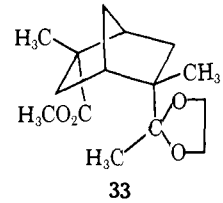


31



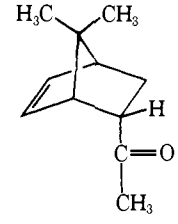
32

be described below) would not deprotonate with lithium isopropylcyclohexylamide (or a variety of other bases), presumably *because of endo hindrance.* The preparation of dimethyl ketal **20** under a variety of conditions, using large excesses of water-scavenging reagents, could never be driven to >90% completion, a result again consistent with the remarkable *steric hindrance in the endo pocket.* Final purification at the ketal step could be effected by GLC; preparative GLC at 210° on Carbowax yielded by thermal cracking pure **21,** easily separated from keto ester **18.** The saponification of **21** was both informative and frustrating. We wished to saponify with exactly 1 equiv of NaOH so that we could isolate the sodium salt of **1,** since the free acid was expected to be unstable. The use of 1.1 equiv of NaOH in water-methanol at reflux gave no saponification of **21.** Only a small amount of **1** was obtained on reflux with 5 equiv of NaOH for 10 h. LiI in dimethylformamide gave no reaction. Finally, 1.1 equiv of anhydrous NaOH was generated in dimethyl sulfoxide (Me_2SO) by addition of an equivalent of water to NaH; heating this solution containing **21** to 85° for 20-24 h yielded 66% of **1.** The difficulty in this saponification is attributed to the *extraordinary steric hindrance* at the ester carbonyl; parenthetically we note that the Me_2SO-NaOH conditions that were successful in saponifying **21** had no effect on **33.**



33

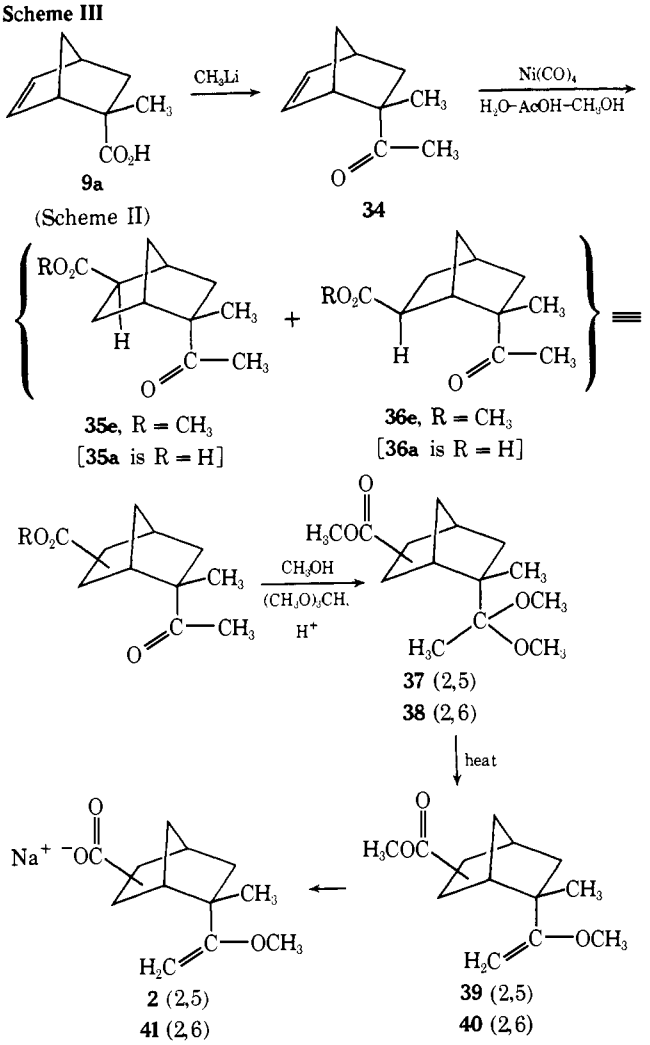
Synthesis of 2. The synthesis of the control compound **2** is shown in Scheme III. The $Ni(CO)_4$ reaction gave a clean, two-component mixture of **35** and **36.** We attempted to execute the same reaction on **43,**[44] in which exo attack should



43

be hindered; no reaction of **43** could be observed after 24 h (**34** reacts in about 10 min). Thus, we deduce that **35** and

Scheme III



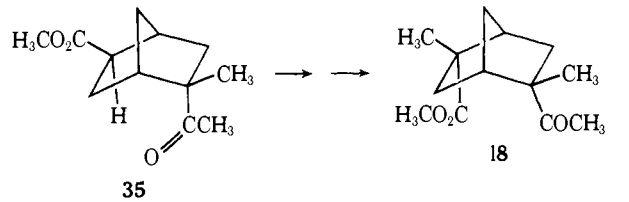
9a (Scheme II) **34**

35e, R = CH_3 [**35a** is R = H] **36e**, R = CH_3 [**36a** is R = H]

37 (2,5) **38** (2,6)

2 (2,5) **41** (2,6) **39** (2,5) **40** (2,6)

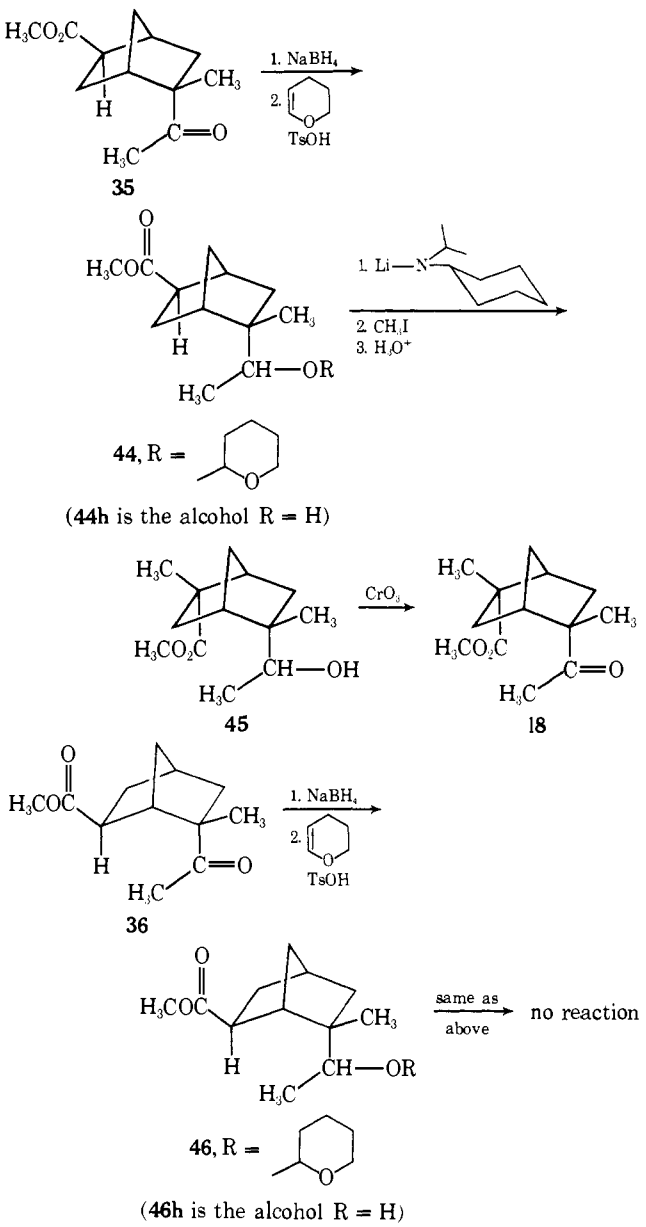
36 are a mixture of the two exo isomers. It remained to show which of the two exo addition products was opposite (2,5) and which was adjacent (2,6). We decided that the correlation **35** → **18** would establish the identity of the 2,5



35 **18**

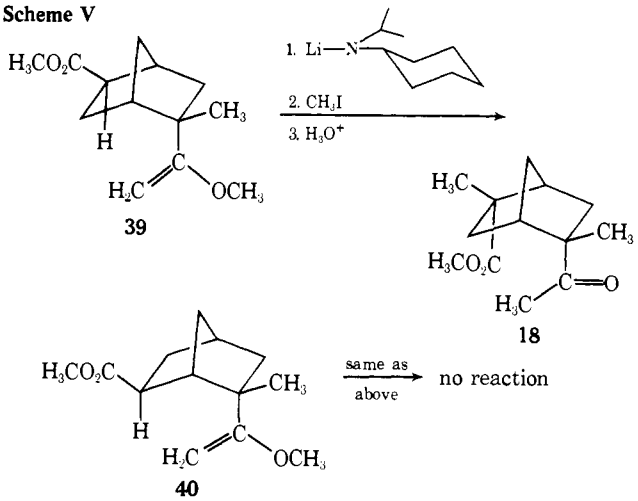
isomer and would further support the identity of **18.** In order to be rigorous, a successful **35** → **18** correlation should be accompanied by an equivalent demonstration that **36** does not give **18.** We have already cited the fact that neither **31** not **32** would deprotonate under a variety of conditions, so that these compounds could not be used in the correlations. However, compounds **31** and **32** provided a piece of spectral evidence which gave a working hypothesis concerning the identity of the two isomers. The NMR spectrum of one of these compounds contained a one-proton multiplet centered at δ 3.27, a full 0.8 ppm downfield from any corresponding peak in the NMR spectrum of the other, and 1.0 ppm downfield from any of the ring hydrogen signals in its own spectrum. Examination of a model of **32** showed that particularly severe steric compression of the C(6) endo H was to be expected from its interactions with the ketal and endo methyl (of the ketal function) at C(2); downfield shifts as a result of these effects are often observed.[46] We have already noted the inability to exchange with deuterium the C(6) endo H and C(5) endo H in **32** and **31,** respectively, so that the identity of the δ 3.27 resonance rests only on the fact that no other signal should be expected in this region. Correlation was, however, achieved in two ways, as shown in Schemes IV and V. Identity of the

Scheme IV



35 **44**, R = (**44h** is the alcohol R = H) **45** **18** **36** **46**, R = (**46h** is the alcohol R = H)

Scheme V



39 **18** **40**

material claimed to be **18** with the material prepared by the reactions of Scheme II was demonstrated by ir, NMR, MS, and GLC retention time. The inability to deprotonate either **46** or **40** leaves incomplete the desired demonstration that **40** does not correlate to **18;** on the other hand, this result is expected from the enhanced constriction expected in the 2,6 isomer.

Therefore, the complete synthesis of the desired models **1** and **2** has been executed. During this synthesis, a number of situations were encountered in which nucleophilic reactions at atoms α-endo to the norbornyl ring were made difficult or impossible by steric hindrance. In the difficulty of saponifying **21,** contrasted with the relative ease of the same reaction on **39,** the system is at least superficially similar to the resistance of lysozyme-Asp[52] ethyl ester to nucleophilic attack.

Experimental Section

General Synthetic Procedures. The ^1H nuclear magnetic resonance spectra (NMR) were obtained at 60 MHz with Varian A-60A and Perkin-Elmer R-24 instruments; the chemical shifts in carbon tetrachloride and deuteriochloroform are expressed as parts per million downfield from tetramethylsilane. The infrared (ir) spectra were recorded on a Perkin-Elmer grating instrument (Infracord) and were all calibrated with polystyrene film. Mass spectra were obtained on an Associated Electronics Industries MS 902 spectrometer; gas chromatography-mass spectra (GC-MS) were obtained on Perkin-Elmer Model 270 and Finnigan 3300 instruments.

Analytical gas-liquid partition chromatography (GLC) was performed on a Hewlett-Packard Model 700 gas chromatograph. Preparative GLC was carried out on the same instrument, as well as a Varian Aerograph Model 90-P. The following GLC columns were commonly used:

Column A: 10 ft × 0.375 in. 20% Carbowax 20M
Column B: 8 ft × 0.25 in. 20% Carbowax 20M
Column C: 6 ft × 0.125 in. 3% OV-1
Column D: 6 ft × 0.125 in. 20% Carbowax 20M

Preliminary drying of organic extracts was done with anhydrous $MgSO_4$. Dry THF (tetrahydrofuran) refers to the solvent used immediately after distillation from lithium aluminum hydride. Other dry solvents were used as obtained commercially unless otherwise specified. Solutions of alkyllithium reagents were purchased from Alfa Inorganics.

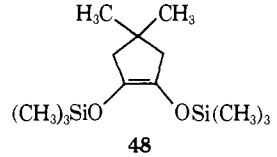
In order to obtain usable amounts of material at the end of the sequence, many of the following syntheses were carried out on a rather large scale and are so reported. In all cases, these reactions were scaled-up versions of our best efforts conducted at the millimole level.

Melting points are uncorrected and were determined on a Büchi melting point apparatus. Microanalyses were performed by Scandinavia Microanalytical Laboratory and Galbraith Laboratories, Inc.

The first two of the following procedures represent modifications of the Rouse and Tyler[45] procedures in the synthesis of 1,1-dimethylcyclopentadiene.

4,4-Dimethyl-2-hydroxycyclopentan-1-one (47). The acyloin was conveniently prepared following the modification of Schräpler and Ruhlmann[47] on methyl 3,3-dimethylglutarate (108 g, 0.576 mol). Distillation of the product afforded 137 g (88%) of the bis(silyl) ether **48:** bp 100-103 °C (10-12 Torr); NMR ($CDCl_3$, relative to $CHCl_3$ at 7.27) 0.14 (s, 18 H, Si-CH_3), 1.03 (s, 6 H, *gem*-CH_3), 2.02 (s, 4 H, CH_2); ir (CCl_4) 1710, 1320, 1250 cm^{-1}.

To a solution of 137 g (0.506 mol) of **48** in 170 ml of THF under nitrogen was added 30 g of 1 N aqueous HCl, dropwise over 30 min. After an initial exothermic period, the solution was refluxed for 1.5 h. The reaction mixture was then cooled to 0° and treated with 30 g of anhydrous $CaCO_3$, filtered, concentrated in vacuo, and distilled, affording 56.5 g (87%) or **47:** bp 84.5-87 °C (8-10 Torr) [lit.[45] 69-70 °C (2 Torr)]; NMR (CCl_4) 1.12 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.00-2.33 (m, 2 H, C(3) CH_2), 2.12 (s, 2 H, C(5) CH_3), 3.90 (br s, 1 H, OH), 4.20 (m, 1 H, CH); ir (CCl_4) 3500, 1750 cm^{-1}.



48

4,4-Dimethyl-2-cyclopenten-1-one (49). To 111 g of 10% by weight P_2O_5 in methanesulfonic acid (prepared by dissolving 11 g of P_2O_5 in 100 g of 98% methanesulfonic acid) at 0° under nitrogen was added slowly 16.5 g (0.128 mol) of **47.** The reaction was allowed to warm to room temperature and after 4 h the dark-brown solution was poured onto ice-water and extracted with ether. Concentration of the carbonate-washed, dried, ethereal extracts and distillation of the residue afforded 6.40 g (46%) of **49:** bp 64-67.5 °C (25-28 Torr) [lit.[51] 75 °C (45 Torr)]; NMR (CCl_4) 1.20 (s, 6 H, *gem*-CH_3), 2.14 (s, 2 H, CH_2), 5.90 (d, J = 5.5 Hz, 1 H, vinyl H), 7.41 (d, J = 5.5 Hz, 1 H, vinyl H); ir (CCl_4) 1710, 1590 cm^{-1}.

***endo*-2-Acetyl-7,7-dimethylbicyclo[2.2.1]hept-5-ene (43).** A mixture of 1.90 g (20.2 mmol) of 1,1-dimethylcyclopentadiene[45] and 1.70 g (24.1 mmol) methyl vinyl ketone was heated at 65-67 °C for 24 h. The reaction mixture was concentrated in vacuo. Sublimation of the crude product at 35 °C (20 Torr) afforded 2.40 g (73%) of **43:** mp 39-41°; NMR (CCl_4) 0.98 (s, 3 H, CH_3), 1.00 (s, 3 H, CH_3), 1.20-2.20 (m, 2 H, CH_2), 1.99 (s, 3 H, acetyl CH_3), 2.30 (br m, 1 H, C(4) bridgehead H), 2.65 (br m, 1 H, C(1) bridgehead H), 3.00 (m, 1 H, C(2) CH), 5.60-6.20 (m, 2 H, vinyl H); ir ($CHCl_3$) 1710 cm^{-1}; mass spectral molecular weight, 164 (electron impact).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.32; H, 9.78.

Aluminum Chloride Catalyzed Diels-Alder Reaction between Methyl Methacrylate and Cyclopentadiene. To a rapidly stirred suspension of 720 g (5.41 mol) of anhydrous $AlCl_3$ in 3 l. of dry benzene under nitrogen at 0 °C was added over a period of 1.5 h, 614 g (6.14 mol) of methyl methacrylate (Eastman Organic Chemicals). The mixture was stirred an additional 15 min, then filtered through Whatman No. 1 filter paper to afford a clear, light-amber colored solution. The filtrate was transferred to a dry flask under an atmosphere of nitrogen and, a solution of 482 g (7.30 mol) of freshly prepared cyclopentadiene in 1.5 l of dry benzene was added over a period of 1.5 h at 0°. After 4 h at 0°, the brownish reaction mixture was filtered free of polymeric material and separated into two 3-l. portions. Each portion was poured into a bucket containing 5 l. of ice and 500 ml of water, stirred vigorously, and worked up in the following manner. The resulting aqueous layer was extracted with two 900-ml portions of ether. The combined organic solutions were washed with three 900-ml portions of water, three 900-ml portions of saturated aqueous NaCl, dried, and concentrated in vacuo. Distillation afforded 820 g (81%) of adduct mixture **7:** bp 51-55 °C (3-4 Torr); NMR ($CDCl_3$, partial) 1.10 (s, *endo*-CH_3), 1.42 (s, *exo*-CH_3), 3.60 (s, *endo*-$COOCH_3$), 3.69 (s, *exo*-$COOCH_3$), 5.89-6.33 (m, vinyl H).

GLC analysis on a 8.5 ft × 0.125 in. 10% 1,2,3,-tris(2-cyanoethoxy)propane (TCEP) column at 85 °C indicated an approximate 60:40 ratio for *exo*- to *endo*-methyl isomers.[30] This ratio was confirmed by relative integration of the *endo*- and *exo*-$COOCH_3$ peaks in the NMR spectrum of the mixture.

***endo*-6-Hydroxy-*exo*-5-iodo-*exo*-2-methylbicyclo[2.2.1]heptane-*endo*-2-carboxylic Acid Lactone (8).** A mixture of 410 g (2.47 mol) of **7,** 417 g of 25% aqueous NaOH (2.60 mol of NaOH), and 100 ml of methanol was refluxed under argon for 15 h. The reaction mixture was cooled and washed with several portions of ether to remove unsaponified ester. To the aqueous solution at room temperature was added 55 g of $NaHCO_3$, followed by a solution of 440 g of iodine (1.73 mol, 1.2 equiv based on 60% *exo*-methyl isomer in the mixture **7** from the Diels-Alder reaction) dissolved in 350 ml of saturated aqueous potassium iodide. After stirring for 3 h at room temperature, the reaction mixture was extracted with 80:20 (v:v) ether:ethyl acetate in two 1.5-l. portions. The organic extract was washed with saturated aqueous sodium thiosulfate until decolorized, then with several portions of water and saturated aqueous NaCl, and then dried with $MgSO_4$ and a small amount of sodium bisulfite. Repeated concentration of the extract on the rotary evaporator, followed by filtration to collect the precipitated iodolactone yielded 376 g (54% based on total endo-exo mixture) of quite pure

white, crystalline **8**, *exo*-methyl isomer: mp 85-86.5 °C (lit.[41,49] 85-86 °C); NMR ($CDCl_3$) 1.17 (s, 3 H, CH_3), 1.41-2.93 (m, 6 H), 3.87 (d, J = 2.5 Hz, 1 H, C(5) endo H), 5.10 (d, J = 2.5 Hz, 1 H, C(6) exo H); ir ($CHCl_3$) 1780 cm^{-1}.

Methyl *exo*-2-Methylbicyclo[2.2.1]hept-5-ene-*endo*-2-carboxylate (9e). The corresponding acid was prepared by the method of Berson and Ben-Ephraim[50] in 87% yield: mp 104-107 °C (lit.[51] 108-110 °C); NMR ($CDCl_3$) 1.31-2.07 (m, 4 H, CH_2), 1.49 (s, 3 H, CH_3), 2.82 (br m, 2 H, bridgehead H), 6.15 (m, 2 H, vinyl H), 10.75 (br s, 1 H, COOH); ir ($CHCl_3$) 3800-2400 (br carboxyl-OH-str), 1695 cm^{-1}.

The methyl ester was synthesized by a conventional diazomethane procedure using the *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald) precursor on small batches of **9a.** Distillation of the combined products from 333 g (2.19 mol) of the acid **9a** afforded 314 g (81%) of **9e:** bp 42-43 °C (1.3 Torr) [lit.[52] 56 °C (3 Torr)]; NMR ($CDCl_3$) 1.27-2.11 (m, 4 H, CH_2), 1.43 (s, 3 H, CH_3), 2.80 (m, 2 H, bridgehead H), 3.61 (s, 3 H, $COOCH_3$), 6.09 (m, 2 H, vinyl H); ir (liquid film) 1740 cm^{-1}.

Methyl exo-5,6-Epoxy-*exo*-2-methylbicyclo[2.2.1]heptane-*endo*-2-carboxylate (10) was prepared by the method of Malinovskii et al.[53] Compound **10** was a colorless, viscous liquid that contained traces of hydroxylactone **11,** detectable by NMR and probably arising during work-up. This material, which may solidify upon standing, is of sufficient purity for conversion to **11** in the next step. A sample of **10** purified by "bulb-to-bulb" distillation at ca. 150 °C (0.1 Torr) gave material with the following characteristics: NMR ($CDCl_3$) 0.93-2.27 (m, 4 H, CH_2), 1.30 (s, 3 H, CH_3), 2.43 (br m, 2 H, bridgehead H), 3.06 (br s, 2H, C(5) and C(6) endo H), 3.69 (s, 3 H, $COOCH_3$); ir (liquid film) 1735 cm^{-1}; mass spectral molecular weight, 182 (electron impact).

***exo*-5-*endo*-6-Dihydroxy-*exo*-2-methylbicyclo[2.2.1]heptane-*endo*-2-carboxylic Acid *endo*-6-Lactone (11).** A mixture of 330 g (1.81 mol) of **10,** 1.5 l. of methanol, 165 ml of water, and 10 ml of 6 N aqueous HCl was heated to reflux for 5 h, then stirred at room temperature overnight. The reaction mixture was then concentrated in vacuo to a slurry of white solid which was dissolved in 500 ml of chloroform. The organic solution was separated from the aqueous layer which was further extracted with two portions of 250 ml of chloroform. The combined organic extract was washed with 300 ml of saturated aqueous NaCl, dried, and concentrated in vacuo to afford 290 g (96%) of **11:** after sublimation 79 °C (0.1 Torr) and recrystallization from ethyl acetate-hexanes, mp 107.5-109° (lit.[53] 109 °C); NMR ($CHCl_3$) 1.20 (s, 3 H, CH_3), 1.25-2.50 (m, 5 H), 2.75 (m, J = 5 Hz, 1 H, C(1) H), 2.98 (br s, 1 H, OH), 3.73 (br s, 1 H, C(5) endo H), 4.40 (d of d, J = 5 Hz, J' = 2 Hz, 1 H, C(6) exo H); ir ($CHCl_3$) 3750, 3550, 1780 cm^{-1}.

5-Keto-*endo*-6-hydroxy-*exo*-2-methylbicyclo[2.2.1]heptane-*endo*-2-carboxylic Acid Lactone (12). Unsuccessful attempts, listed in the text, to prepare this compound are fully described in the dissertation describing this work.[63]

To a well-stirred solution of 100 g (0.596 mol) of **11** in 3 l. of acetone cooled in an ice-water bath was added 400 ml of Jones reagent[40] over a period of 2 h. During this time the temperature of the reaction was maintained between 4 and 7.5 °C. The cold bath was allowed to warm to room temperature overnight, and the excess oxidizing agent was then quenched with isopropyl alcohol ca. 12 h after the addition of the Jones reagent was completed. The reaction mixture was filtered over Celite, then concentrated in vacuo to remove the acetone. The residue remaining was extracted with six 200-ml portions of chloroform. The combined extracts were then washed with saturated aqueous NaCl, dried, and concentrated in vacuo to afford 69.0 g (70% crude yield) of **12** as a slightly yellow oil. Ketolactone **12** obtained in this manner, although difficult to purify with good recovery, was of sufficient purity to carry on to the next reaction. Purified material was obtained by repeated recrystallization from ethyl acetate-hexanes: mp 130-131 °C; NMR ($CDCl_3$) 1.37 (s, 3 H, CH_3), 1.63-2.35 (m, 4 H, CH_2), 2.75 (br m, 1 H, bridgehead H), 3.16 (br m, 1 H, bridgehead H), 4.31 (d of d, J = 5.5 Hz, J' = 1 Hz, 1 H, C(6) exo H); ir ($CHCl_3$) 1790 cm^{-1} (unresolved); mass spectral molecular weight, 166 (electron impact).

Methyl 5-Keto-*exo*-2-methylbicyclo[2.2.1]heptane-*endo*-2-carboxylate (13e). A mixture of 69.0 g (0.416 mol) of crude ketolactone **12** and 150 g (2.30 g-atoms) of zinc dust in 750 ml of glacial acetic acid was refluxed for 12 h. The cooled reaction mixture was filtered, and the solid residue was washed with further portions of acetic acid. The combined solutions were concentrated in vacuo, and the residue was partitioned between 300 ml of ether and an aqueous solution made up of 50 ml of water and 150 ml of saturated aqueous NaCl solution. The aqueous layer was extracted with three 150-ml portions of ether, and the combined ethereal extracts were washed with 150 ml of saturated aqueous NaCl, dried, and concentrated in vacuo to a viscous oil. The hot oil was triturated with 500 ml of pentane and 51.5 g (73%) of crude **13a** was obtained. Two recrystallizations from ethyl acetate-hexanes afforded white crystalline **13a:** mp 146.5-147.5 °C; NMR ($CDCl_3$) 1.48 (s, 3 H, CH_3), 1.60-2.75 (m, 8 H), 11.0 (s, 1 H, COOH); ir ($CHCl_3$) 3800-2450 (br carboxyl-OH str), 1750, 1705 cm^{-1}; mass spectral molecular weight, 169 (chemical ionization, isobutane).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.19; H, 7.35.

The methyl ester **13e** was prepared from 51.5 g (0.306 mol) of crude **13a** by reaction with diazomethane generated from the decomposition of "Diazald" as previously described. Distillation afforded 42.7 g of **13e** in 77% yield (13.5 g of purified **13a** afforded a 90% yield of methyl ester **13e**): bp 70-74.5 °C (0.25 Torr); NMR ($CDCl_3$) 1.44 (s, 3 H, CH_3), 1.50-2.70 (m, 8 H), 3.71 (s, 3 H, $COOCH_3$); ir ($CHCl_3$) 1745, 1725 cm^{-1} (shoulder); mass spectral molecular weight, 182 (GC-MS, 130 °C, column C, chemical ionization using methane).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.94; H, 7.73.

Methyl 5-Methylene-*exo*-2-methylbicyclo[2.2.1]heptane-*endo*-2-carboxylate (14e). To a suspension of 83.8 g (0.234 mol) of methyltriphenylphosphonium bromide in 710 ml of dry THF under argon at room temperature was added 123 ml (0.1246 mol) of 2 M phenyllithium in hexane-ether. After 4 h, a solution of 42.7 g (0.234 mol) of **13e** in 50 ml of dry THF was added over a period of 20 min. The reaction was then stirred an additional 26 h. At the end of this time, the solution was concentrated in vacuo, and the resulting concentrate was treated with 300 ml of pentane. The precipitated triphenylphosphine oxide was removed by filtration, the filtrate was reconcentrated and again treated with pentane. Several repetitions of this cycle afforded upon final concentration ca. 60 g of a crude, dark red oil, which upon distillation gave 29.0 g (69%) of **14e:** bp 69.5-72 °C (4.2 Torr); NMR ($CDCl_3$) 1.31 (s, 3 H, CH_3), 1.20-2.80 (m, 8 H), 3.69 (s, 3 H, $COOCH_3$), 4.61 (br m, 1 H, vinyl H), 4.90 (br m, 1 H, vinyl H); ir ($CHCl_3$) 1725, 1660 (weak), 885 cm^{-1} (terminal methylene, out-of-plane deformation); mass spectral molecular weight, 180 (GC-MS, 130°, column C, chemical ionization using methane).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.94; H, 8.92.

A Wittig reaction could be executed on the corresponding acid **13a** with 2 equiv of Wittig reagent. The corresponding acid product **14a** was obtained in 62% yield and had satisfactory spectral and analytical properties.

Methyl *endo*-5-Hydroxymethyl-*exo*-2-methylbicyclo[2.2.1]heptane-*endo*-2-carboxylate (15e). To a solution of 44.0 g (0.244 mol) of **14e** in 750 ml of dry THF under argon at room temperature was added over a period of 40 min 100 ml (0.100 mol) of 1 M BH_3·THF complex in THF. After 1 h at room temperature, the reaction was cooled to 0 °C and quenched by careful addition of 25 ml of water, 50 ml of 4 N aqueous NaOH, and finally 50 ml of 30% aqueous H_2O_2. The resulting solution was then heated at 40-45 °C for 45 min, cooled, and added to a mixture of 200 ml of water and 200 ml of saturated aqueous NaCl. The organic layer was then separated and the aqueous layer extracted with three 200-ml portions of ether. The combined organic solutions were washed with saturated aqueous NaCl, dried, and concentrated in vacuo. Distillation afforded 39.3 g (81%) of **15e:** bp 98-100 °C (0.2 Torr); NMR ($CDCl_3$) 0.40-2.55 (m, 9 H), 1.23 (s, 3 H, CH_3), 3.41 (s, 1 H, OH), 3.40-3175 (m, 2 H, $-CH_2OH$), 3.69 (s, 3 H, $COOCH_3$); ir ($CHCl_3$) 3500, 1725 cm^{-1}.

The corresponding acetate of **15e** was prepared for analysis using acetic anhydride-pyridine.[56] The product isolated by "bulb-to-bulb" distillation [90 °C (0.03 Torr)] was characterized by: NMR ($CDCl_3$) 0.50-2.60 (m, 9 H), 1.26 (s, 3 H, CH_3), 2.02 (s, 3 H, acetoxy CH_3), 3.71 (s, 3 H, $COOCH_3$), 4.10 (m, J = 7 Hz, J' = 2 Hz, 2 H, $-CH_2$-OAc); ir ($CHCl_3$) 1725 cm^{-1} (unresolved); mass spectral molecular weight, 240 (GC-MS, 130°, column C,

chemical ionization using methane gave a weak P + 1 ion).

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.97; H, 8.40.

***endo*-5-Hydroxymethyl-*exo*-2-methylbicyclo[2.2.1]heptane-*endo*-2-carboxylic Acid (15a).** A solution of 39.3 g (0.199 mol) of **15e** in 200 ml of methanol and 700 ml of 10% aqueous NaOH was refluxed under argon for 14 h to yield, after work-up, 31.1 g (85%) of **15a** with a mp 186–191.5 °C. Recrystallization from ethyl acetate–hexanes afforded a white powder: mp 191–192.5 °C; NMR (dimethyl-d_6 sulfoxide) 0.50–2.40 (m, 9 H), 1.18 (s, 3 H, CH_3), 3.35 (d, J = 7 Hz, 2 H, $-CH_2$-OH); ir (KBr pellet) 3600–2200 (br carboxyl-OH str), 1690 cm^{-1}; mass spectral molecular weight, 184 (weak P + 1 by chemical ionization using methane).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.09; H, 8.74.

***endo*-2-Acetyl-*endo*-5-hydroxymethyl-*exo*-2-methylbicyclo[2.2.1]heptane (16).** The methyl ketone was prepared by a procedure similar to that of House and Bare.[57] To a solution of 30.0 g (0.163 mol) of **15a** in 1 l. of dry THF under argon at room temperature was added 1.50 g (0.188 mol) of lithium hydride. After evolution of hydrogen had ceased, excess methyllithium solution (260 ml, 0.494 mol, 1.9 M in ether) was added dropwise. The reaction was inversely quenched into slightly less than an equivalent amount of HCl in 1 l. of water cooled to 0°. Conventional work-up afforded a crude product, distillation of which gave 26.0 g (88%) of **16:** bp 99–103 °C (0.15 Torr); NMR ($CDCl_3$) 0.40–2.60 (m, 9 H), 1.17 (s, 3 H, CH_3), 2.11 (s, 3 H, acetyl CH_3), 2.70 (br s, 1 H, OH), 3.52 (d, J = 7 Hz, 2 H, CH_2OH); ir ($CHCl_3$) 3690, 3500, 1700 cm^{-1}; mass spectral molecular weight, 182 (GC–MS, 130 °C, column C, chemical ionization using methane).

***endo*-2-Acetyl-*exo*-2-methylbicyclo[2.2.1]heptane-*endo*-5-carboxylic Acid (19).** To a solution of 26.0 g (0.143 mol) of **16** in a solution of 1 l. of acetone and 100 ml of water at 0° was added dropwise over a period of 30 min a total of 2.5 ml of Jones reagent. After 23 h at room temperature, the reaction was quenched with isopropyl alcohol, filtered through Celite, and concentrated in vacuo to remove acetone. The resulting aqueous solution was extracted with five 100-ml portions of ether. Concentration of the dried ethereal extract gave a white solid which was triturated with pentane to afford 25.5 g (91%) of crude **19** with mp 101–111 °C. Recrystallization from ethyl acetate–hexanes gave 20.0 g (71%) of **19:** mp 114.8–115.8 °C; NMR ($CDCl_3$) 0.90–3.00 (m, 9 H), 1.17 (s, 3 H, CH_3), 2.16 (s, 3 H, acetyl CH_3), 11.13 (s, 1 H, COOH); ir ($CHCl_3$) 3600–2400 (br carboxyl-OH str), 1700 cm^{-1}; mass spectral molecular weight, 196 (weak P + 1 by chemical ionization using methane).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.42; H, 8.20.

Methyl *endo*-2-Acetyl-*exo*-2-methylbicyclo[2.2.1]heptane-*endo*-5-carboxylate (17). The methyl ester was prepared from 19.8 g (0.101 mol) of recrystallized **19** by reaction with diazomethane as described previously. Work-up afforded 20.4 g (96%) of crude **17** that was pure by analytical GLC (160 °C, column D): bp 78–80 °C (0.07 Torr); NMR ($CDCl_3$) 0.95–2.90 (m, 9 H), 1.17 (s, 3 H, CH_3), 2.18 (s, 3 H, acetyl CH_3), 3.70 (s, 3 H, $COOCH_3$); ir ($CHCl_3$) 1730, 1705 cm^{-1}; mass spectral molecular weight, 210 (GC–MS, 130 °C, column C, chemical ionization using methane).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.72; H, 8.66.

Methyl *endo*-2-(1,1-Ethylenedioxy)ethyl-*exo*-2-methylbicyclo[2.2.1]heptane-*endo*-5-carboxylate (33). A mixture of 4.02 g (19.1 mmol) of **17**, 20 ml of ethylene glycol, 36 ml of triethyl orthoformate, and 600 mg of *p*-toluenesulfonic acid monohydrate was refluxed under argon for 28 h. At the end of this time, the volatile products were removed by distillation at 1 atm. The residue was dissolved in 125 ml of pentane. The organic solution was then washed with two 40-ml portions of 10% aqueous NaOH and 40 ml of saturated aqueous NaCl, dried with anhydrous K_2CO_3, and concentrated in vacuo. Distillation afforded 4.26 g (88%) of **33:** bp 97–100 °C (0.12 Torr); NMR ($CDCl_3$) 0.82–2.60 (m, 9 H), 1.11 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 3.68 (s, 3 H, $COOCH_3$), 3.75–4.00 (m, 4 H, OCH_2CH_2O); ir ($CHCl_3$) 1720 cm^{-1}; mass spectral molecular weight, 254 (GC–MS, 130°, column C, chemical ionization using methane).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.31; H, 8.76.

Methyl *endo*-2-Acetyl-*exo,exo*-2,5-dimethylbicyclo[2.2.1]heptane-*endo*-5-carboxylate (18). Lithium *N*-isopropylcyclohexylamide[58] was prepared in THF by the addition of 12.8 ml (26.8 mmol) of 2.1 M *n*-butyllithium in hexane to a solution of 5.11 ml (28.2 mmol) of *N*-isopropylcyclohexylamine in 170 ml of dry THF under argon at room temperature. After 30 min, the solution was cooled to −78° and 4.26 g (16.8 mmol) of **33** in 20 ml of dry THF was added over a period of 30 min. After an additional 15 min at −78°, 17.1 ml (0.274 mol) of methyl iodide was added in one portion. After stirring overnight at room temperature, the reaction was quenched by the addition of 80 ml of water. The aqueous layer was further extracted with four 80-ml portions of ether. All organic solutions were then combined and washed twice with 0.1 N aqueous HCl. At this point the alkylated ketal could be isolated by appropriate work-up followed by distillation. In this manner methyl *endo*-2-(1,1-ethylenedioxy)ethyl-*exo,exo*-2,5-dimethylbicyclo[2.2.1]heptane-*endo*-5-carboxylate was obtained: bp 84 °C (0.11 Torr); NMR ($CDCl_3$) 0.80–2.80 (m, 8 H), 1.11 (s, 3 H, CH_3), 1.22 (s, 6 H, unresolved CH_3 singlets), 3.67 (s, 3 H, $COOCH_3$), 3.71–4.00 (m, 4 H, OCH_2CH_2O). However, in this experiment the ethereal extract was next washed with saturated aqueous NaCl and concentrated in vacuo. The crude ketal obtained was hydrolyzed at room temperature for 23 h with a mixture of 70 ml of THF, 25 ml of water, and 40 drops of 6 N aqueous HCl. At the end of this time, the aqueous THF solution was saturated with NaCl, and the layers were separated. The aqueous portion was further extracted with three 25-ml portions of ether. The combined organic solutions were washed with saturated aqueous NaCl, dried, and concentrated in vacuo. Distillation afforded 3.24 g (86%) of **18:** bp 72–74 °C (0.06 Torr); NMR ($CDCl_3$) 0.80–2.60 (m, 8 H), 1.15 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3), 2.11 (s, 3 H, acetyl CH_3), 3.69 (s, 3 H, $COOCH_3$); ir ($CHCl_3$) 1730, 1705 cm^{-1}; mass spectral molecular weight, 224 (electron impact).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.40; H, 8.98.

Methyl *endo*-2-(1-Methoxy)vinyl-*exo,exo*-2,5-dimethylbicyclo[2.2.1]heptane-*endo*-5-carboxylate (21). To a solution of 35 ml of anhydrous methanol and 15 ml of trimethyl orthoformate was added 505 mg (2.25 mmol) of **18** and 93 mg of *p*-toluenesulfonic acid monohydrate. The reaction mixture was then blanketed with argon, stoppered, and left at room temperature for 3 days. At the end of this time, the reaction was quenched by the addition of 30 mg of sodium methoxide and concentrated in vacuo to remove methanol, methyl formate, and trimethyl orthoformate. The residue was taken up in portions of pentane, which were filtered to separate the insoluble salts. The pentane extracts were then concentrated in vacuo to an oil which was immediately distilled "bulb-to-bulb" [130 °C (0.1 Torr)] to afford 591 mg of crude **21** containing a small amount of unreacted starting ketone **18** and a trace of the isomeric *exo*-5-carbomethoxy enol ether **50.** Preparative GLC (210°, column A, flow rate of 150 ml per min) afforded **50** which was characterized by its NMR spectrum ($CDCl_3$): 1.16 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3), 1.00–2.55 (m, 8 H), 3.54 (s, 3 H, ether OCH_3), 3.68 (s, 3 H, $COOCH_3$), 4.04 (AB quartet, 2 H, vinyl H). Under the same preparative GLC conditions was obtained 363 mg (68%) of pure *endo*-carbomethoxy enol **21.** The product thus obtained was homogeneous under analytical GLC conditions (130°, column D) and was characterized as follows: NMR ($CDCl_3$) 1.16 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3), 1.00–2.32 (m, 8 H), 3.51 (s, 3 H, ether OCH_3), 3.64 (s, 3 H, $COOCH_3$), 3.90 (collapsed AB-quartet, 2 H, vinyl H); ir ($CHCl_3$) 1725, 1650, 1605 cm^{-1}; mass spectral molecular weight, 238 (GC–MS, 130 °C, column C, chemical ionization using methane).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.84; H, 9.35.

Sodium Salt of *endo*-2-(1-Methoxy)vinyl-*exo,exo*-2,5-dimethylbicyclo[2.2.1]heptane-*endo*-5-carboxylic Acid (1). Saponification of *endo*-carbomethoxy enol ether **21** was successfully carried out by a modification of a procedure of Roberts and Whiting.[59] To 38.0 mg (1.60 mmol) of pentane-washed, oil-free NaH under argon was added 5 ml of freshly dried, distilled Me_2SO, followed by the careful addition of 29 μl (1.60 mmol) of water. The solution was then heated moderately (50 °C) for a few minutes, after which time 363 mg (1.52 mmol) of **21** was added with the aid of ca. 1 ml of Me_2SO. After heating the reaction mixture at 85° for 20.5 h, the Me_2SO was largely removed in vacuo (0.03 Torr) at room temper-

ature overnight, then at ca. 60-80° for a few hours the next day. Lyophilization of the residue obtained afforded 374 mg of crude sodium salt as a pale brown solid. By dissolving the crude product in a minimal amount of ethanol, then adding ether to the cloud point and allowing recrystallization to proceed at room temperature, the sodium salt of **1** could be obtained in sufficient purity for kinetics. In this manner, two crops of the sodium salt of *endo*-carboxy enol ether **1** displayed the following NMR spectrum in D_2O (shifts are ppm downfield, δ, from the singlet of internal DSS): 1.13, 1.16 (partially resolved singlets, 3 H each, CH_3), 1.00-2.15 (m, 8 H), 3.54 (s, 3 H, OCH_3), 4.11 (collapsed AB-quartet, 2H, vinyl H); these NMR spectra invariably contained an extraneous singlet due to some contamination by Me_2SO. Because of the extreme sensitivity of this compound, and since the Me_2SO did not interfere with the kinetics, no further attempt was made to remove this contaminant.

6-Keto-*exo*-2-methylbicyclo[2.2.1]heptane-*endo*-2-carboxylic acid (27) was prepared following the procedure of Beckmann and Geiger[60] on 60 g (0.214 mol) of iodolactone **8** to yield **27,** mp 127.5-129 °C (lit.[60] 129-130 °C), in 50% crude yield, which displayed the following spectral features: NMR ($CDCl_3$) 1.22 (s, 3 H, CH_3), 1.10-2.70 (m, 8 H), 5.10 (slightly br s, 1 H, OH of pseudo-acid structure); ir ($CHCl_3$) 3400, 1760 cm^{-1}.

The methyl ester of **27** was obtained by treatment with diazomethane: NMR ($CDCl_3$) 1.36 (s, 3 H, CH_3), 1.20-2.84 (m, 8 H), 3.66 (s, 3 H, $COOCH_3$); ir ($CHCl_3$) 1750, 1725 cm^{-1}. Mass spectral molecular weight: 182 (GC-MS, 125°, column C, chemical ionization using methane).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 66.03; H, 7.71.

***endo*-2-Acetyl-*exo*-2-methylbicyclo[2.2.1]hept-5-ene (34).** The methyl ketone was prepared by a procedure similar to that used for hydroxy ketone **16**[57] on a 35.0-g (0.230 mol) scale to give 30.2 g (87%) of **55:** bp 71-72 °C (8 Torr); NMR ($CDCl_3$) 1.20-2.17 (m, 4 H, CH_2), 1.36 (s, 3 H, CH_3), 2.08 (s, 3 H, acetyl CH_3), 2.80 (br m, 2 H, bridgehead H), 6.06 (m, 2 H, vinyl H); ir (liquid film) 1710 cm^{-1} (no evidence of tertiary alcohol).

Reaction of 34 with $Ni(CO)_4$. Synthesis of Isomeric Keto Esters 35e and 36e. The mixture of isomeric keto esters was prepared by the reaction of strained bicyclic olefins with $Ni(CO)_4$ developed by Bird et al.[48] A mixture of 18.9 g (0.126 mol) of **34,** 12.5 ml of $Ni(CO)_4$, and 80 ml of a solvent mixture that was 30:1.5:1 (v:v:v) methanol:acetic acid:water was heated at 50-70 °C under argon overnight. The reaction was then cooled to 0° and treated with 80 ml of 2 N aqueous H_2SO_4 for 15 min. The reaction mixture was filtered through Celite with 2 N aqueous H_2SO_4 (80 ml) and, 60-70 °C petroleum ether (100 ml) rinses were used to achieve complete transfer of the reaction mixture. The aqueous layer was separated and further extracted with three 75-ml portions of 60-70 °C petroleum ether. The combined organic solutions were washed with saturated aqueous NaCl and concentrated in vacuo. The residue obtained was dissolved in 200 ml of CH_2Cl_2, washed with two 30-ml portions of 2 N aq H_2SO_4, once with water, saturated aqueous NaCl, then dried, and concentrated in vacuo. Distillation (8-in. Vigreux) of the residue afforded 20.6 g (78%) of **35e, 36e:** bp 65-85 °C (0.06-0.08 Torr) [1st fraction, 65-75 °C, 14.6 g, ca. 50:50 mixture by analytical GLC (180 °C, column D); 2d fraction, 75-85 °C, 4.0 g, ca. 25:75 enriched in the greater retained component by GLC]; NMR ($CDCl_3$, partial) 1.23 (s, CH_3, both isomers), 2.14, 2.19 (s, acetyl CH_3), 3.63, 3.66 (s, $COOCH_3$).

The mixture of isomers could not be separated by distillation [66-76° (0.08-0.15 Torr)] on a 50-cm Nester Faust Teflon spinning band column. However, several enriched fractions were obtained.

Separation was achieved by preparative GLC (210 °C, column A, flow rate of 150 ml per min). Later studies identified the less retained component as **methyl *endo*-2-acetyl-*exo*-2-methylbicyclo[2.2.1]heptane-*exo*-6-carboxylate (36e):** NMR ($CDCl_3$) 1.23 (s, 3 H, CH_3), 0.90-2.60 (m, 9 H), 2.20 (s, 3 H, acetyl CH_3), 3.66 (s, 3 H, $COOCH_3$); ir ($CHCl_3$) 1730, 1705 cm^{-1}; mass spectral molecular weight, 210 (electron impact).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.62; H, 8.62.

The greater retained component of the mixture was identified as **methyl *endo*-2-acetyl-*exo*-2-methylbicyclo[2.2.1]heptane-*exo*-5-carboxylate (35e):** NMR ($CDCl_3$) 1.23 (s, 3 H, CH_3), 0.94-2.61 (m, 9 H), 2.14 (s, 3 H, acetyl CH_3), 3.63 (s, 3 H, $COOCH_3$); ir ($CHCl_3$) 1730, 1705 cm^{-1}; mass spectral molecular weight, 210 (electron impact).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.18; H, 8.88.

Methyl *endo*-2-(Methoxy)vinyl-*exo*-2-methylbicyclo[2.2.1]heptane-*exo*-5-carboxylate (39). By the same procedure used for the preparation of **21,** *exo*-carbomethoxy enol ether **39** was obtained in 60% yield after preparative GLC (210 °C, column A, flow rate of 150 ml per min). Enol ether **39,** which was homogeneous by analytical GLC (130 °C, column D), was characterized by the following spectral data: NMR ($CDCl_3$) 1.13 (s, 3 H, CH_3), 1.00-2.35 (m, 9 H), 3.35 (s, 3 H, ether OCH_3), 3.50 (s, 3 H, $COOCH_3$), 3.70 (AB quartet, 2 H, vinyl H); ir ($CHCl_3$) 1730, 1650, 1605 cm^{-1}; mass spectral molecular weight, 224 (GC-MS, 130°, column C, chemical ionization using methane).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.45; H, 9.09.

Sodium Salt of *endo*-2-(1-Methoxy)vinyl-*exo*-2-methylbicyclo[2.2.1]heptane-*exo*-5-carboxylic Acid (2). A. Aqueous Saponification of *exo*-Carbomethoxy Enol Ether (39). To a solution of 10 ml of water and 0.312 ml of 2.05 N aqueous KOH (0.639 mmol, 1.1 equiv) was added 130 mg (0.581 mmol) of **39.** The reaction mixture was refluxed for 1.5 h; thin-layer chromatography (TLC) analysis (silica gel, ether) then showed no evidence of starting material. The solution was cooled and washed with one portion of 5 ml of ether, then lyophilized to yield 154 mg (crude recovery was quantitative) of a white solid. NMR analysis of this product in basic D_2O indicated the presence of some hydrolysis product (keto acid), as well as the desired enol ether. This was inferred by the presence of two sharp C-CH_3 singlets in the δ 1.2 region (downfield from DSS).

B. Saponification with NaOH in Anhydrous Dimethyl Sulfoxide. By the same procedure described in the synthesis of the sodium salt of **1,** anhydrous sodium hydroxide was prepared in Me_2SO. Ester **39,** 283 mg (1.26 mmol), was added with the aid of ca. 1 ml of Me_2SO with the solution of NaOH in Me_2SO at 50-55 °C. After 20 min at this temperature, the solution had become a thick suspension of white solid material. The heating bath was removed and the reaction left at room temperature overnight. The solution was then diluted with 15 ml of ether and filtered to yield 186 mg of white sodium salt of **2** contaminated with a trace of Me_2SO as indicated by NMR analysis. The filtrate was concentrated at high vacuum (0.04 Torr) to afford an additional 90 mg of crude product. The material isolated in this manner (94% crude yield) was of sufficient purity for kinetics. The NMR spectrum (D_2O, shifts relative to HDO as δ 4.65) of the sodium salt of **2** contained the following peaks: 1.10 (s, 3 H, CH_3), 1.10-2.50 (m, 9 H), 3.53 (s, 3 H, ether OCH_3), 4.19 (AB quartet, 2 H, vinyl H).

Methyl *endo*-2-(1,1-Ethylenedioxy)ethyl-*exo*-2-methylbicyclo[2.2.1]heptane-*exo*-5-carboxylate (31). The ethylene ketal was prepared by a procedure similar to that of Marquet et al.[61] A mixture of 1.65 g (7.87 mmol) of **35e,** 12 ml of triethyl orthoformate, 6 ml of ethylene glycol, and 250 mg of *p*-toluenesulfonic acid monohydrate was refluxed under argon for 19 h to afford after work-up and short-path distillation 1.90 g (95%) of **31:** bp 90-92 °C (0.11 Torr); NMR ($CDCl_3$) 1.13 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 0.86-2.61 (m, 9 H), 3.63 (s, 3 H, $COOCH_3$), 3.70-4.20 (m, 4 H, OCH_2CH_2O).

Methyl *endo*-2-(1,1-Ethylenedioxy)ethyl-*exo*-2-methylbicyclo[2.2.1]heptane-*exo*-6-carboxylate (32). In the same manner above was obtained from **36e** by "bulb-to-bulb" distillation [ca. 160 °C (0.07 Torr)] 1.71 g (99%) of **32:** NMR ($CDCl_3$) 1.13 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 0.83-1.90 (m, 6 H, CH_2), 2.24 (broad m, 2 H, bridgehead H), 3.14-3.41 (br m, 1 H, C(6) endo H), 3.65 (s, 3 H, $COOCH_3$), 3.68-4.18 (m, 4 H, OCH_2CH_2O).

Attempts to alkylate methyl *endo*-2-(1,1-ethylenedioxy)ethyl-*exo*-2-methylbicyclo[2.2.1]heptane-*exo*-5-carboxylate (31) using lithium *N*-isopropylcyclohexylamide or potassium amide are described in detail elsewhere[63] and were uniformly unsuccessful.

Methyl *endo*-2-(1-Hydroxy)ethyl-*exo*-2-methylbicyclo[2.2.1]heptane-*exo*-5-carboxylate (44h). To a solution of 500 mg (2.38 mmol) of **35** in 20 ml of methanol cooled to 0 °C was added in small portions 800 mg of sodium borohydride. After 90 min at 0 °C, the reaction mixture was poured onto 50 ml of ice-water and extracted with four 20-ml portions of ether. The ethereal extract was washed

with saturated aqueous NaCl, dried, and concentrated in vacuo. "Bulb-to-bulb" distillation afforded 450 mg (89%) of **44h** as an oil which solidified upon standing: NMR ($CDCl_3$) 0.92 (s, 3 H, CH_3), 1.10 (d, J = 6.5 Hz, 3 H, CHOH-CH_3), 0.70-2.50 (m, 9 H), 3.00 (br s, 1 H, OH), 3.63 (m, 1 H, CHOH-CH_3), 3.65 (s, 3 H, $COOCH_3$); ir ($CHCl_3$), 3780, 3650, 1730 cm^{-1}.

The corresponding acetate of **44h** was prepared for analysis using acetic anhydride-pyridine.[56] Recrystallization from pentane afforded white crystals of methyl *endo*-2-(α-acetoxy)ethyl-*exo*-2-methylbicyclo[2.2.1]heptane-*exo*-5-carboxylate: mp 56.5-59 °C; NMR ($CDCl_3$) 1.02 (s, 3 H, CH_3), 1.19 (d, J = 6 Hz, 3 H, CHOAc-CH_3), 0.87-2.56 (m, 9 H), 2.04 (s, 3 H, acetoxy CH_3), 3.66 (s, 3 H, $COOCH_3$), 4.73 (q, J = 6 Hz, 1 H, CHOAc-CH_3); ir ($CHCl_3$) 1730 cm^{-1} (unresolved); mass spectral molecular weight, 254 (chemical ionization using methane).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.91; H, 8.77.

Methyl *endo*-2-(1-hydroxyethyl)-*exo*-2-methylbicyclo[2.2.1]heptane-*exo*-6-carboxylate (46h) was obtained in the same manner as above in 91% yield: bp 92-93 °C (0.07 Torr); NMR ($CDCl_3$) 0.95 (s, 3 H, CH_3), 1.14 (d, J = 6.5 Hz, 3 H, CHOH-CH_3), 0.75-2.40 (m, 8 H), 2.60 (br s, 1 H, OH), 2.93 (m, 1 H), 3.70 (m, 1 H, CHOH-CH_3), 3.70 (s, 3 H, $COOCH_3$); ir ($CHCl_3$) 3780, 3600, 1730 cm^{-1}.

The corresponding acetate of **46h** was prepared for analysis using acetic anhydride-pyridine.[56] Preparative GLC (160 °C, column B) afforded, as an oil, methyl *endo*-2-(1-acetoxy)ethyl-*exo*-2-methylbicyclo[2.2.1]heptane-*exo*-6-carboxylate: NMR ($CDCl_3$) 1.02 (s, 3 H, CH_3), 1.19 (d, J = 6.5 Hz, 3 H, CHOAc-CH_3), 0.96-2.50 (m, 8 H), 2.06 (s, 3 H, acetoxy CH_3), 2.64 (m, 1 H), 3.65 (s, 3 H, $COOCH_3$), 4.76 (q, J = 6.5 Hz, 1 H, CHOAc-CH_3).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.08; H, 8.70.

Methyl *endo*-2-[1-(2-Tetrahydropyranyloxy)ethyl]-*exo*-2-methylbicyclo[2.2.1]heptane-*exo*-5-carboxylate (44). A solution of 415 mg (1.96 mmol) of **44h** and a few crystals of *p*-toluenesulfonic acid monohydrate in 4 ml of dihydropyran was stoppered and stirred for 16 h at room temperature. At the end of this time the reaction was quenched with a few milligrams of sodium methoxide, then concentrated in vacuo to a yellow oil which was "bulb-to-bulb" distilled [ca. 160 °C (0.1 Torr)] to afford 496 mg (86%) of **44:** NMR ($CDCl_3$) 0.93, 0.95 (partially resolved singlets, 3 H, C(2) CH_3 of each diastereomer), 0.70-2.50 (m, 18 H), 3.20-4.18 (m, 3 H, 6′-CH_2 of the tetrahydropyranyl group and $CHCH_3$-OTHP), 3.60 (s, 3 H, $COOCH_3$), 4.66 (br m, 1 H, 2′-CH of the tetrahydropyranyl group); ir ($CHCl_3$) 1730 cm^{-1}; mass spectral molecular weight, 296 (chemical ionization using methane). A purified sample was obtained for analysis by preparative GLC (170 °C, column B).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.62; H, 9.50.

Methyl *endo*-2-[1-(2-Tetrahydropyranyloxy)ethyl]-*exo*-2-methylbicyclo[2.2.1]heptane-*exo*-6-carboxylate (46). In a similar manner as above was isolated, by preparative TLC on 1-mm thick silica gel plates eluted with 25:75 (v:v) ethyl acetate-hexanes, 204 mg (63%) of **46:** NMR ($CDCl_3$) 0.94 (unresolved singlets, 3 H, C(2) CH_3 of each diastereomer), 0.80-2.50 (m, 17 H), 2.66-3.20 (m, 1 H, C(6) H), 3.20-4.20 (m, 3 H, 6′-CH_2 of the tetrahydropyranyl group and $CHCH_3$-OTHP), 3.67 (2, 3 H, $COOCH_3$), 4.71 (br m, 1 H, 2′-CH of the tetrahydropyranyl group). A purified sample was obtained for analysis by preparative GLC (170 °C, column B).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 69.09; H, 9.33.

Methyl *endo*-2-(1-hydroxyethyl)-*exo,exo*-2,5-dimethylbicyclo[2.2.1]heptane-*endo*-5-carboxylate (45) was prepared by the lithium *N*-isopropylcyclohexylamide-methyl iodide procedure used for **18.** The oil obtained upon concentration after the usual work-up was subjected to preparative TLC on 1-mm thick silica gel plates eluted with 10:90 (v:v) ethyl acetate-hexanes. A band (R_f 0.30) isolated after double elution afforded 55.6 mg (48%) of **45:** NMR ($CDCl_3$) 0.94 (s, 3 H, CH_3), 1.07 (d, J = 6 Hz, 3 H, CHOH-CH_3), 1.27 (s, 3 H, CH_3), 0.77-2.75 (m, 9 H, OH in this region), 3.64 (s, 3 H, $COOCH_3$), 3.82 (q, J = 6 Hz, 1 H, CHOH-CH_3); ir ($CHCl_3$) 3740, 3590, 1730 cm^{-1}; mass spectral molecular weight, 226 (GC-MS, temperature programmed at 150-220 °C, column C, chemical ionization using methane).

Oxidation of Methyl *endo*-2-(1-Hydroxyethyl)-*exo,exo*-2,5-dimethylbicyclo[2.2.1]heptane-*endo*-5-carboxylate (45). To a solution of 55.6 mg (0.246 mmol) of **45** in 3 ml of acetone at 0 °C was added dropwise 0.25 ml of Brown and Garg solution.[37] Oxidation appeared to proceed rapidly and after 1 h at 0 °C the reaction was quenched with isopropyl alcohol, filtered over Celite, and concentrated in vacuo. The residue was dissolved in pentane, washed with two 4-ml portions of saturated aqueous $NaHCO_3$ and 5 ml of saturated aqueous NaCl, dried, and concentrated in vacuo to afford 49.6 mg (90% crude yield) of methyl *endo*-2-acetyl-*exo,exo*-2,5-dimethylbicyclo[2.2.1]heptane-*endo*-5-carboxylate (**18**) which was identified by NMR, ir, mass spectral molecular weight (P + 1 = 225, P + 29 = 253 by chemical ionization using methane; GC-MS, temperature programmed at 130-220°, column C), and by GLC retention time (column D) to be keto ester **18** prepared by the alternate route.

Attempts to alkylate **46,** as well as **40** (see below), were unsuccessful and are described elsewhere.[63]

Alkylation of Methyl *endo*-2-(1-Methoxy)vinyl-*exo*-2-methylbicyclo[2.2.1]heptane-*exo*-5-carboxylate (39). In a modification of previous alkylation procedures used in the synthesis of **18** and **45,** lithium *N*-diisopropylamide was used as a base rather than lithium *N*-isopropylcyclohexylamide. The resulting oil was "bulb-to-bulb" distilled [130 °C (0.1 Torr)], yielding 75.8 mg (86%) of keto ester **18.** Material isolated in this manner, of course, contained minor impurities as was the case in the alkylation of ketal ester **33.** However, the major product was undoubtedly keto ester **18** by matching NMR and ir spectra, mass spectral molecular weight, and GLC retention (column D).

Methyl *endo*-2-(1-Methoxy)vinyl-*exo*-2-methylbicyclo[2.2.1]heptane-*exo*-6-carboxylate (40). Enol ether **40** was prepared in exactly the same manner as used for the synthesis of enol ethers **21** and **39.** The intermediate dimethyl ketal was characterized by its NMR spectrum ($CDCl_3$, partial): 1.04 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 3.10 (s, 3 H, ether OCH_3), 3.24 (s, 3 H, ether OCH_3), 3.65 (s, 3 H, $COOCH_3$). Preparative GLC (same conditions as before) afforded 434 mg (76%) of **40:** NMR ($CDCl_3$) 1.15 (s, 3 H, CH_3), 1.00-2.67 (m, 9 H), 3.53 (s, 3 H, ether OCH_3), 3.64 (s, 3 H, $COOCH_3$), 4.02 (AB-quartet, 2 H, vinyl H); ir ($CHCl_3$) 1730, 1650, 1610 cm^{-1}; mass spectral molecular weight, 224 (chemical ionization using methane).

***endo*-2-Acetyl-*exo,exo*-2,5-dimethylbicyclo[2.2.1]heptane-*endo*-5-carboxylic Acid (19).** A solution of 150 mg (0.670 mmol) of keto ester **18** in 3 ml of 10% aqueous NaOH and 1 ml of methanol was refluxed for 4 h. At the end of this time, the solution was cooled, washed with portions of ether, and acidified with concentrated aqueous HCl. The resulting solution was extracted with ether. The ethereal extract was washed with saturated aqueous NaCl, dried, and concentrated in vacuo to 142 mg of crude **19** as an oil (quantitative crude yield): crystals obtained from ethyl acetate-hexanes had mp 108-109.5 °C; NMR ($CDCl_3$) 1.17 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 0.90-2.50 (m, 8 H), 2.10 (s, 3 H, acetyl CH_3), 8.02 (br s, 1 H, COOH); ir ($CHCl_3$) 3700-2400 (br carboxyl-OH str), 1730 (shoulder), 1700 cm^{-1}; mass spectral molecular weight, 210 (weak P + 1, chemical ionization using methane).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.41; H, 8.67.

***endo*-2-Acetyl-*exo*-2-methylbicyclo[2.2.1]heptane-*exo*-5-carboxylic Acid (35a).** In the same manner as above was obtained, after recrystallization from ethyl acetate-hexanes, 337 mg (76%) of **35a** as a white solid: mp 115-116.2 °C; NMR ($CDCl_3$) 1.21 (s, 3 H, CH_3), 0.95-2.68 (m, 9 H), 2.16 (s, 3 H, acetyl CH_3), 10.8 (br s, 1 H, COOH); ir ($CHCl_3$) 3500-2400 (br carboxyl-OH str), 1730 (shoulder), 1700 cm^{-1}; mass spectral molecular weight, 196 (weak P + 1, chemical ionization using methane).

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References and Notes

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