Rearrangement Approaches to Polycyclic Skeletons. 1. Bridgehead-Substituted Bicyclo[3.2.1]octene Derivatives from Bicyclo[2.2.2]octene Precursors[1]

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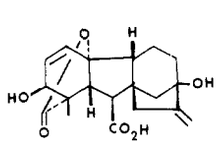
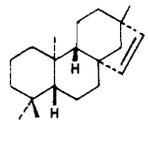
Preparation of a variety of 1-substituted bicyclo[3.2.1]oct-3- (and -6-) en-2-yl derivatives by acid-catalyzed rearrangement of 1-H and 1-methoxy-2-alkylbicyclo[2.2.2]oct-5-en-2-ols and of 1-methoxybicyclo[2.2.2]oct-5-en-2-alkylidene derivatives is described. In the 1-H series, both the exo and the endo tertiary alcohol precursors yield the more stable bicyclo[3.2.1]oct-3-en-2-yl product; in the 1-methoxy series, the exo tertiary alcohols and the α,β-unsaturated ester precursors furnish the nonconjugated bicyclo[3.2.1]oct-6-en-2-one products, while the endo tertiary alcohols and the unsaturated ketone starting materials give the conjugated bicyclo[3.2.1]oct-3-en-2-one products predominantly. A facile rearrangement of 1-ketoalkylbicyclo[3.2.1]oct-6-en-2-ones to 1-ketoalkylbicyclo[3.2.1]oct-3-en-2-ones is described. The observed regioselectivity of these rearrangements is discussed.

The structural complexities and diverse biological activities of several classes of tetracyclic natural products, such as the gibberellins (**1**), the beyeranes (**2**), and the grayanotoxins (**3**), among others,[2] make them important and challenging



1, Gibberellic Acid



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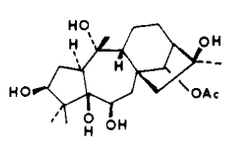
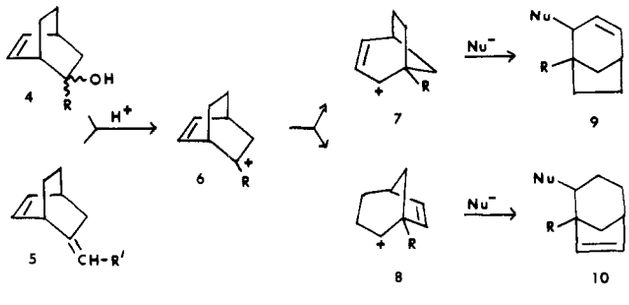


3, Grayanotoxin I

synthetic targets.[3] Structurally, each of these families contain a 1,2-disubstituted bicyclo[3.2.1]octane nucleus, and the presence of this common element provides the basis for an attractive convergent synthetic approach to these related materials. The synthetic strategy envisioned involves initial preparation of suitably functionalized, bridgehead-substituted bicyclo[3.2.1]octane derivatives, followed by subsequent elaboration of the fused-ring skeleton: a formal C/D → A-B-C/D route to these tetracyclic substances. The successful completion of the initial synthetic goal of this general approach, the development of an efficient procedure to prepare a variety of C/D ring synthons which contain functionality suitable for further conversion into the target natural products, is described herein.

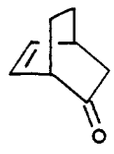
The overall route to the desired bridgehead-substituted bicyclo[3.2.1]octane derivatives is depicted in Scheme I. The key step involves the rearrangement of the bicyclo[2.2.2]octenyl cation **6** into the bicyclo[3.2.1]octenyl cations **7** and/or **8**.[4] Nucleophilic trapping of these cations then furnishes 1-alkylbicyclo[3.2.1]octene derivatives containing either functionality only in the three-carbon bridge (**9**) or differentiated functionality in the two- and the three-carbon bridges (**10**). As described below, the bicyclo[2.2.2]octene derivatives, the exo and/or endo tertiary alcohols **4**, as well as the dienes **5**, can serve as formal precursors to cation **6**; these bicyclo[2.2.2]-octene substrates are readily prepared by a convergent sequence which allows structural variation in both the bicyclic skeleton and in the R substituent; and the rearrangement regioselectivity exhibited by these substrates is such that controlled synthetic entry into either bicyclo[3.2.1]octene series, **9** or **10**, can be achieved.

Scheme I



Results

The starting materials for the preparation of the bicyclo[2.2.2]octene precursors **4** and **5** were the Diels–Alder derived bicyclo[2.2.2]octenones **11**,[5] **12**,[6] and **13**. Both the known



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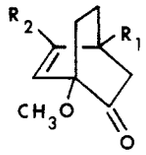
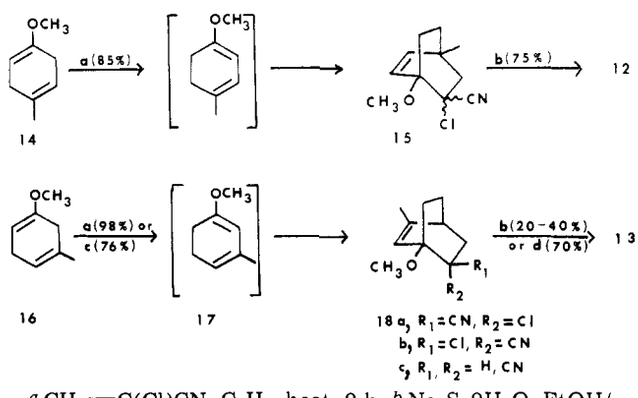


12, $R_1 = CH_3$, $R_2 = H$
13, $R_1 = H$, $R_2 = CH_3$

1-methoxy-4-methyl ketone **12** and the previously unreported 5-methyl derivative **13** were prepared from the Birch reduction products **14** and **16** as shown in Scheme II. Cycloaddition[6,7] of α-chloroacrylonitrile with the conjugated diene **17**, generated in situ from **16**, yielded a separable mixture of chloronitriles **18a,b** (2:1) in 90% yield in which the exo-nitrile **18a** predominated.[8] A third product was isolated in ca. 10%

Scheme II



[a] $CH_2{=}C(Cl)CN$, C_6H_6, heat, 9 h. [b] $Na_2S \cdot 9H_2O$, EtOH/H_2O, heat, 15 h. [c] $CH_2{=}CHCN$, 120 °C, 16 h. [d] (i) LDA/THF, −78 °C; (ii) O_2, −78 °C; (iii) Na_2SO_3, 0–25 °C.

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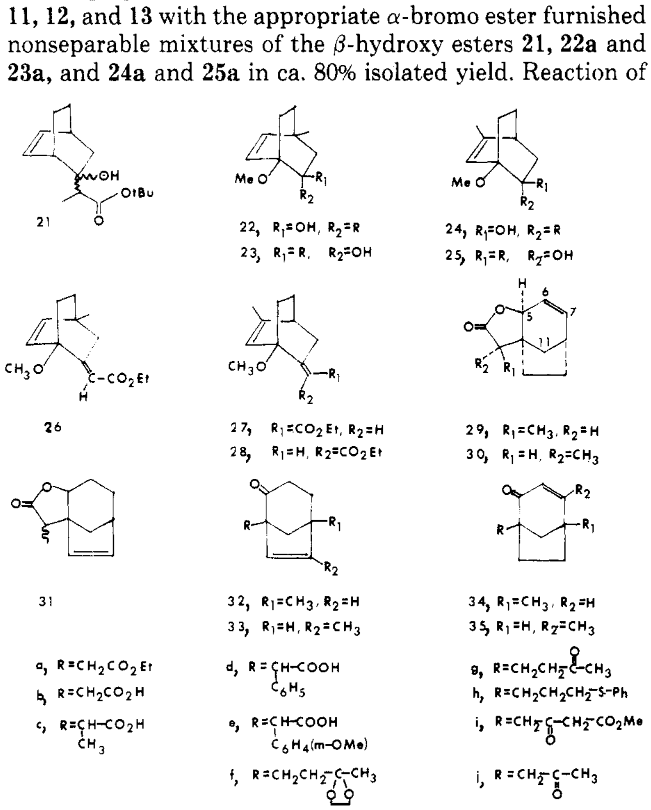
yield from this reaction, and after aqueous acid hydrolysis it was tentatively identified as the keto chloronitrile **19** on the

19 20

basis of spectral properties. Presumably, this minor product results from cycloaddition of the alternative conjugated endocyclic diene **20**. The conversion of chloronitriles **18a,b** to 5-methyl ketone **13** under a variety of conditions[5,6] gave reproducibly poor yields[9] (20–40%) and led to an examination of an alternative route to **13**. In practice, a more satisfactory preparation of ketone **13** was achieved by cycloaddition of acrylonitrile and diene **16** to give nitrile **18c**, which when treated sequentially with lithium diisopropylamide in THF, dry oxygen, and then sodium sulfite[10] yielded 5-methyl ketone **13** in 53% overall yield from diene **16**.

The exo and endo tertiary alcohols **4** and the dienes **5**, which serve as precursors of the bicyclo[3.2.1]octenes **9** and **10** containing substituted acetic acid substituents at C-1 (see Table I), were prepared as follows. Reformatsky reaction[11] of ketones **11**, **12**, and **13** with the appropriate α-bromo ester furnished nonseparable mixtures of the β-hydroxy esters **21**, **22a** and **23a**, and **24a** and **25a** in ca. 80% isolated yield. Reaction of



ketone **13** with the appropriate carboxylic acid dianion[12] gave mixtures of the β-hydroxy acids **24,25 (b–e)** in 60–80% yield in which the exo alcohol **24** usually predominated. Crystallization of these mixtures normally furnished the pure exo alcohols, e.g., **24c,d,e**, although in one case the pure endo alcohol **25b** was obtained. The exo/endo structure assignments were based on the observation that the NMR chemical shift of the substituent methylene or methine group proton(s) in the exo alcohol **24** was shifted upfield due to the shielding effect of the adjacent C_5–C_6 double bond[13] (see Experimental Section for details). In addition, formation of the exo alcohols **24** as the major products is consistent with addition to the less hindered face of the bicyclo[2.2.2]octenone substrates.[4,14] When the 5-methyl ketone **13** was allowed to react with the lithium enolate of ethyl trimethylsilylacetate,[15] a mixture of α,β-unsaturated esters **27,28** was obtained which showed bridgehead

Table I. Rearrangement of Bicyclo[2.2.2]octenes to Bicyclo[3.2.1]octene-1-acetic Acid Derivatives

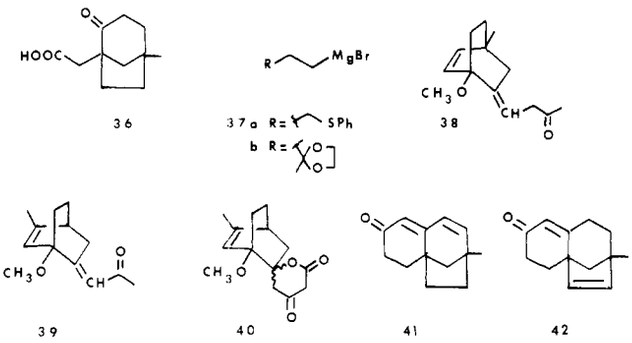
substrate	conditions	products (yield, %)
alcohols		
21	*a*	**29,30** (70)
22a,23a (1:1)	*a*	**32b** (59), **34b** (35)[c]
24c	*a*	**33c** (90)
24d	*a*	**33d** (93)
24e	*a*	**33e** (100)
25b	*a*	**33b** (33), **35b** (67)
dienes		
26	*b*	**32b** (80), **34b** (10)[c]
27,28	*b*	**33b** (80)[c]

[a] Catalytic amount of TsOH in acetic acid, Δ, 4h. [b] TsOH (1 equiv) in acetic acid, Δ, 4h. [c] Isolated initially as a mixture of ethyl esters and carboxylic acids.

methoxy group signals at δ 3.35 and 3.46 (1:2 ratio). The minor component (δ 3.35) is assigned as the Z isomer **28** on the basis of the expected shielding effect of the carbethoxy group on the methoxy substituent.[16] Dehydration of the β-hydroxy esters **22a,23a** and **24a,25a** with thionyl chloride/pyridine yielded *only* the 5-methylbicyclo[2.2.2]octene E isomer **27** and a single α,β-unsaturated ester **26** in the 4-methyl series, which by analogy is tentatively assigned the E configuration (i.e., formation of the more stable isomer).

As summarized in Table I, exposure of the 1-H and 1-methoxy series β-hydroxy acid and ester substrates to a catalytic amount of p-toluenesulfonic acid in acetic acid at reflux for ca. 4 h resulted in smooth rearrangement to give bridgehead-substituted bicyclo[3.2.1]octene derivatives in good to excellent yield. Under similar conditions, the 1-methoxy series diene precursers **26**, **27**, and **28** were recovered unchanged; however, when these dienes were treated at reflux with 1 equiv of TsOH in acetic acid, rearrangement to the 1-substituted bicyclo[3.2.1]octenone nucleus did occur in excellent yield. In each case, the isolated bicyclo[3.2.1]octenone-1-acetic acid products [**32–35 (a–e)**] were shown to be stable to the reaction conditions.

Rearrangement of the epimeric 1-H series β-hydroxy esters **21** yielded a mixture of two crystalline products which was assigned as the isomeric lactones **29,30**. The contiguous nature of the C-5 oxygen-substituted carbon atom of the lactone group and the C_6–C_7 double bond was established by the observed coupling, $J_{5,6} = 4$ Hz, in both isomers. The cis fusion of the γ-lactone moiety on the six-membered ring is consistent with the mode of formation (vide infra) and was confirmed in both lactones by an observed long-range (W) coupling of the C-5 hydrogen and the anti C-11 hydrogen in the one-carbon bridge of $J = 1$ Hz.[17] No evidence for the alternative rearrangement product, lactone **31**, was observed. In the rearrangement of the 1-methoxy series substrates, the exo alcohols **22,24** and the 5-methyl dienes **27,28** gave the *nonconjugated* bicyclo[3.2.1]octenones **32,33** as the exclusive products, while the endo alcohols **23,25** and the 4-methyl diene **26** yielded a mixture of both possible structural isomers, the nonconjugated enones **32,33** and the conjugated bicyclo[3.2.1]octenones **34,35**. The structures assigned to the two series of products are fully consistent with the observed spectral data. In the case of enones **34,35**, the presence of the bicyclo[3.2.1]octenone nucleus is established unambiguously since this carbon skeleton is required to accommodate the observed (IR) α,β-unsaturated carbonyl moiety in these materials. The nonconjugated enones **32,33** are also assigned as bicyclo[3.2.1]octenone derivatives, and in the case of acid **32b** this assignment was confirmed since catalytic hydrogenation of **32b** and the conjugated isomer **34b** yielded the same saturated bicyclic acid **36**.



Attention was next directed toward the preparation of tertiary alcohol **4** and diene **5** precursors containing other functional groups. Treatment of the 4-methyl ketone **12** with Grignard reagents[18] **37** yielded separable mixtures of *exo*-/*endo*-γ-phenylthio alcohols **22h,23h** (94%, 3.5:1) and *exo*-/*endo*-γ-hydroxy ketals **22f,23f** (95%, 2.5:1). Dehydration of the hydroxy ketal mixture **22f,23f** with thionyl chloride/pyridine yielded, after aqueous workup, a crude mixture of two isomers of the β,γ-unsaturated ketone **38** (80%). In the 5-methyl series, addition of the dianion[19] of methyl acetoacetate to ketone **13** gave an exo/endo mixture of γ-hydroxy-β-keto esters **24i,25i** (2:1) in 65% yield. When this mixture is heated (~200 °C), a facile dehydration–decarbethoxylation occurs to give the α,β-unsaturated ketone **39** as the only observed product (83%). This interesting transformation, which may involve the intermediary of lactone **40** and a Stobbe-like elimination, constitutes an attractive alternative to the Wittig–Emmons-type routes to α,β-unsaturated ketones.

Rearrangement of the isomerically pure exo and endo tertiary alcohols **22f** and **23f** and the exo/endo mixture **24i,25i** using a catalytic amount of TsOH in acetic acid, as well as the pure exo and endo alcohols **22h,23h** using 0.5 equiv of TsOH in acetic acid, proceeded analogously to that described above for the β-hydroxy acid/esters to give the bicyclo[3.2.1]octenes shown in Table II. In marked contrast to the α,β-unsaturated esters **26** and **27,28**, the conjugated dienone **39** underwent facile rearrangement when treated with catalytic TsOH in acetic acid to give a mixture of the nonconjugated and conjugated bicyclo[3.2.1]octenones **33j** and **35j** (Table II). When dienones **38** and **39** were treated with 1 equiv of TsOH in acetic acid, the *exclusive* products observed were the conjugated derivatives **41** and **35j**. Presumably, the conjugated tricyclic ketone **41** is formed by acid-catalyzed aldol cyclization of the corresponding conjugated bicyclic enone **34g**. Appropriate control experiments revealed that while the nonconjugated ketones **32g** and **33j** were moderately stable to catalytic TsOH in acetic acid, exposure of these substances to 1 equiv of TsOH in acetic acid resulted in rapid and essentially quantitative rearrangement to the conjugated species **41** and **35j**. Although no detailed kinetic studies were conducted, a qualitative estimate of the relative rates of initial rearrangement of dienone **39** and the nonconjugated product **33j** suggests that both **33j** and the conjugated product **35j** are primary rearrangement products. In separate experiments it was shown that the alternative aldol product **42**, prepared readily from **32g** by base treatment, was stable to exposure to 1 equiv of TsOH in acetic acid at reflux, as was the nonconjugated γ-phenylthiopropyl bridgehead-substituted derivative **32h**.

Discussion

The experimental results summarized in Tables I and II show that both tertiary alcohols **4** and dienes **5** function as efficient precursors of bridgehead-substituted bicyclo[3.2.1]-octene derivatives **9** and **10**. The qualitative differences in the rearrangement conditions required for these two substrates, catalytic TsOH for the tertiary alcohols **4** and, in general, 1

Table II. Rearrangement of Bicyclo[2.2.2]octenes to 1-Propyl and 1-Butylbicyclo[3.2.1]octene Derivatives

substrate	conditions	products (yield, %)
alcohols		
22f	*a*	**32g** (96)
23f	*a*	**32g** (28), **34g** (56)
22h	*c*	**32h** (90)
23h	*c*	**32h** (24), **34h** (64)
24i,25i (2:1)	*a*	**33j** (36), **35j** (36)
dienes		
38	*b*	**41** (96)
39	*a*	**33j** (19), **35j** (57)
39	*b*	**35j** (85)

[a,b] See footnotes *a* and *b* in Table I. [c] TsOH (0.5 equiv) in acetic acid, Δ, 20 h.

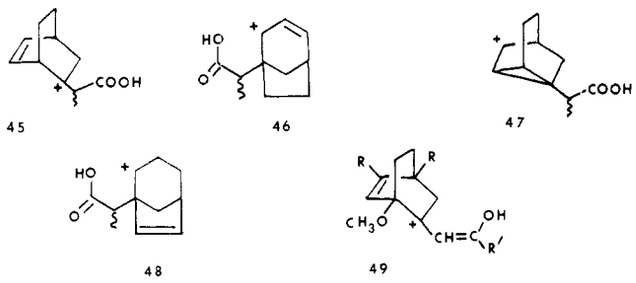
prepared as the major or exclusive products from the 1-methoxy series exo alcohols **22** and **24** as well as from the α,β-unsaturated esters **26** and **27,28**. Alternatively, the preparation of bicyclo[3.2.1]octene derivatives containing functionality only in the three-carbon bridge, e.g., **29, 30, 34,** and **35,** can be realized from the 1-H series exo/endo alcohols **21**, the 1-methoxy series endo alcohols **23** and **25,** and the diene precursors containing a ketone group substituent, e.g., **38** and **39**.

The regioselectivity observed in the rearrangement of the 1-methoxy series exo alcohols **22** and **24** can be rationalized satisfactorily by postulating solvolysis of the tertiary hydroxyl group with concomitant participation of the double bond to furnish a cyclopropylcarbinyl intermediate, e.g., structure **43.** equiv of TsOH for the dienes **5,** suggest that the dienes **5** are not intermediates in the rearrangement of the tertiary alcohols **4.** In terms of the actual synthetic goals, the nonconjugated bicyclo[3.2.1]octenone derivatives containing differentiated functionality in two bridges, e.g., **32** and **33,** can be readily

Assisted fragmentation of **43** (see arrows) yields intermediate **44,** which after hydrolysis gives the nonconjugated bicyclo[3.2.1]octenones **32,33.** The facile fragmentation of cation **43** thus accounts for the exclusive migration of the trans antiparallel vinyl carbon atom observed in the rearrangement of these *exo*-bicyclo[2.2.2]octenols.

The predominant formation of the conjugated bicyclo[3.2.1]octenones **34** and **35** from rearrangement of the 1-methoxy series endo alcohols **23** and **25** suggests that these products are formed via a concerted trans antiparallel migration (pinacol-type) in which some crossover occurs to give products formally derived from the cyclopropylcarbinyl intermediate **43.**

In contrast to the 1-methoxy series substrates, the regioselectivity observed in the 1-H series exo/endo alcohols **21** appears to involve acid-catalyzed solvolysis of **21** to give cation **45** with concomitant hydrolysis of the *tert*-butyl ester, rearrangement of **45** to the thermodynamically more stable allylic carbonium ion **46,** and finally intramolecular trapping of cation **46** by the carboxyl group via the less strained transition state to give the cis-fused cyclohexene γ-lactone moiety. Delocalization of the cation **45** by π-bond participation to give the cyclopropylcarbinyl species **47** may occur, but in the absence of the bridgehead methoxy group (e.g., **43**), formation



of the isolated secondary carbonium ion **48** (and/or lactone **31**) is apparently not competitive with the formation of the resonance-stabilized cation **46.**

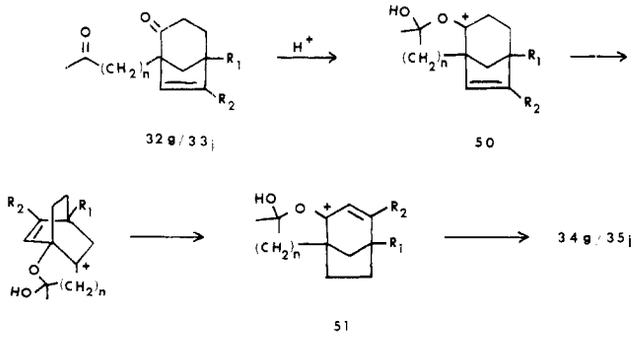
The rearrangement of the 1-methoxy series α,β-unsaturated diene precursors presumably is initiated by initial protonation on the oxygen atom of the carbonyl moiety to generate cation **49.**[20] The preferential formation of the nonconjugated products **32,33** from the α,β-unsaturated ester substrates **26** and **27,28** suggests the intermediacy of the cyclopropylcarbinyl cation **43** followed by fragmentation as described above. The greater regioselectivity shown by the 5-methyl precursors **27,28** as compared to the 4-methyl derivative **26** may be a reflection of the relative stabilities of the cyclopropylcarbinyl cations **43** ($R_2 = CH_3$ vs. $R_2 = H$). The decreased rearrangement regioselectivity exhibited by the α,β-unsaturated ketone **39,** as well as the relative ease with which enone **39** undergoes rearrangement as compared to the α,β-unsaturated esters **27,28,** apparently reflects the relative stability of the initial protonation species **49** ($R' = CH_3$ or $R' = OH$).

Lastly, the rearrangement of the nonconjugated 1-ketoalkylbicyclo[3.2.1]oct-6-en-2-ones **32g** and **33j** to furnish the conjugated derivatives **34g** and **35j** is a mechanistically interesting and a synthetically useful observation. Of the various bridgehead substituent functional groups examined, e.g., aryl, carboxyl, thioether, and keto, only those bicyclo[3.2.1]octenone substrates containing a C-1 keto alkyl substituent undergo further rearrangement when exposed to 1 equiv of TsOH in acetic acid. As shown in Scheme III, this rearrangement is postulated to involve intramolecular participation of the C-1 substituent ketone group to give the oxonium ion **50,** which then rearranges to the *more stable* allyl oxonium ion **51.** Thus, both structural series, **9** and **10,** can be conveniently obtained when a C-1 keto alkyl substituent is present.

Experimental Section

General. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 237B grating infrared spectrometer; nuclear magnetic resonance spectra were measured on Varian Associates Model A-60 and HA-100 or Perkin-Elmer Model R-12 spectrometers, and chemical shifts are reported in parts per million downfield (δ) from internal Me_4Si; and ultraviolet spectra were recorded on a Cary Model 14 spectrometer. Low-resolution mass spectra were obtained on a DuPont Model 21-491 mass spectrometer and high-resolution spectra on a CEC Model 21-100 mass spectrometer. Organic solutions were routinely dried over anhydrous $MgSO_4$. Combustion analyses were performed by Chemalytics Inc., Tempe, Ariz.

Scheme III



1-Methoxy-4-methylbicyclo[2.2.2]oct-5-en-2-one (12). Crude chloronitriles **15** (42.3 g, 0.2 mol) and $Na_2S{\cdot}9H_2O$ (144 g, 0.6 mol) were dissolved in 95% ethanol (400 mL) and water (200 mL). The mixture was heated at reflux under N_2 for 15 h, cooled, and extracted with benzene/ether (1:3). The combined organic extracts were washed with brine, the solvent was evaporated, and the residue was distilled to give 25 g (75%) of the known[6] 4-methyl ketone **12:** bp 79–81 °C (0.6 mm); IR ($CHCl_3$) 1730 cm^{-1}; NMR (CCl_4) δ 1.27 (s, 3), 1.35 (2.20 (m, 6), 3.45 (s, 3), 6.05 (d, 1, J = 8.6 Hz), and 6.22 (d, 1, J = 8.6 Hz); mass spectrum, *m/e* (relative intensity) 166 (5, M^+), 151 (5), 138 (10), 124 (100), 109 (60), 91 (20), and 67 (20).

1-Methoxy-5-methylbicyclo[2.2.2]oct-5-en-2-one (13). A. Using the procedure described above for the 4-methyl ketone **12,** reaction of chloronitrile mixture **18a,b** with $Na_2S{\cdot}9H_2O$ (0.1-mol scale) yielded pure 5-methyl ketone **13** in 20–40% yield: bp 68–72 °C (0.2 mm); IR ($CHCl_3$) 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.4–2.1 (m, 4), 1.87 (d, 3, J = 1.5 Hz), 2.0 (d, 2, J = 2.5 Hz), 2.67 (m, 1), 3.43 (s, 3), and 5.77 (m, 1); mass spectrum, *m/e* (relative intensity) 166 (6), 138 (38), 124 (50), 123 (100), 110 (54), 109 (53), and 91 (36).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.95; H, 8.49.

B. Nitrile **18c** (56.5 g, 0.32 mol) in THF (100 mL) was added dropwise at −78 °C to a stirred solution of lithium diisopropylamide (0.33 mol), prepared by the dropwise addition of *n*-butyllithium (2.23 M, 148 mL, 0.33 mol) to diisopropylamine (33.3 g, 0.33 mol) in THF (250 mL) at −78 °C under N_2. After stirring for 1 h, oxygen (dried by passing through a KOH tower) was bubbled into the lithionitrile solution at −78 °C for 5 h. The reaction was quenched with 1 M sodium sulfite (300 mL) and allowed to stir for 30 min at 0 °C and then for 12 h at 25 °C. The reaction mixture was extracted with ether, and the combined organic extracts were washed with 2 N sodium hydroxide and saturated brine solution and then dried. The solvent was evaporated and the residue distilled to give 37.7 g (70%) of ketone **73,** bp 80–85 °C (0.6 mm). This material was identical by NMR and IR with that prepared by method A.

1-Methoxy-4-methyl-1,4-cyclohexadiene (14). Lithium wire (11.2 g, 1.6 g-atom) was added in small pieces to a stirred solution of *p*-methylanisole (48.8 g, 0.4 mol), *tert*-butyl alcohol (200 mL), and THF (200 mL) in liquid ammonia (1000 mL). After stirring for 1 h, methanol (80 mL) was added dropwise and the ammonia was allowed to evaporate. Water and ether were added, the organic phase was separated, the aqueous phase was extracted with fresh ether, and the combined organic phases were washed with a saturated brine solution and then dried (K_2CO_3). The organic solvent was evaporated and the residue distilled to give 38.9 g (78%) of pure diene **14:** bp 71–73 °C (23 mm) [lit.[21] bp 74 °C (17 mm)]; NMR (CCl_4) δ 1.67 (broad s, 3), 2.63 (broad s, 4), 3.46 (s, 3), 4.46 (m, 1), and 5.28 (m, 1).

1-Methoxy-2-chloro-2-cyano-4-methylbicyclo[2.2.2]oct-5-ene (15). Diene **14** (6.2 g, 0.05 mol) was added dropwise to a solution of freshly distilled 2-chloroacrylonitrile (8.8 g, 0.1 mol) and phenothiazine (50 mg) in benzene (45 mL). The resulting mixture was treated at reflux for 9 h under N_2. The benzene and excess 2-chloroacrylonitrile were removed by distillation, and the residue solidified on standing at 0 °C to give 9.9 g (85%) of a mixture of known[6] bicyclic chloronitriles **15;** crystallization from hexane yielded a single epimer of **15:** mp 64–65 °C; IR ($CHCl_3$) 2240 cm^{-1}; NMR (CCl_4) δ 1.18 (s, 3), 1.35, 2.50 (m, 6), 3.48 (s, 3), 6.04 (d, 1, J = 8.6 Hz), and 6.23 (d, 1, J = 8.6 Hz); mass spectrum, *m/e* (relative intensity) 211 (very weak) 183 (5), 175 (2), 160 (2), 148 (30), 124 (100), 109 (35), 91 (6), and 77 (8).

1-Methoxy-5-methyl-1,4-cyclohexadiene (16) was prepared from *m*-methylanisole using the procedure described above in 80% yield: bp 77–79 °C (25–28 mm) [lit.[22] bp 75–77 °C (aspirator pressure)]; IR ($CHCl_3$) 1700 and 1670 cm^{-1}; NMR (CCl_4) δ 1.68 (s, 3), 2.59 (m, 4), 3.46 (s, 3), 4.50 (m, 1), and 5.31 (m, 1); mass spectrum, *m/e* (relative intensity) 124 (100), 123 (31), 122 (31), 109 (76), and 91 (28).

1-Methoxy-2-chloro-2-cyano-5-methylbicyclo[2.2.2]oct-5-ene (18a,b). Using the general procedure described above for **15** with the *crucial* modification that the benzene solvent was distilled from $LiAlH_4$ prior to use, diene **16** and 2-chloroacrylonitrile furnished a quantitative yield of crude cycloaddition products. VPC analysis (QF-1, 180 °C) revealed a 9:1 mixture of **18a,b** and the enol ether of **19.** This mixture was separated by chromatography on Al_2O_3 using hexane/ethyl acetate to give a 2:1 mixture of chloronitriles **18a,b** (90%): NMR (CCl_4) δ 1.33–2.75 (m, 7), 1.83 (d, 3, J = 1.5 Hz), 3.44 (s, 3), 5.8 (m, 0.67), and 5.95 (m, 0.33).

Crystallization of this mixture from hexane yield the pure exo nitrile–endo chloro derivative **18a:** mp 85–87 °C; IR (CCl_3) 2250 and

1650 cm^{-1}; NMR ($CDCl_3$) δ 1.33–2.75 (m, 7), 1.83 (d, 3, J = 1.5 Hz), 3.44 (s, 3), and 5.75 (m, 1); mass spectrum, m/e (relative intensity) 211 (1), 148 (33), 124 (100), and 109 (78).

Anal. Calcd for $C_{11}H_{14}ClNO$: C, 62.40; H, 6.67; Cl, 16.75; N, 6.62. Found: C, 62.44; H, 6.67; Cl, 16.92; N, 6.56.

Treatment of the minor chromatography fraction with dilute hydrochloric acid furnished, after crystallization from ether/hexane, a material tentatively assigned structure **19:** mp 160–162 °C; IR (CCl_4) 1745 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (s, 3) and 1.7–3.15 (m, 9); mass spectrum, m/e (relative intensity) 199 (5), 197 (14), 124 (80), 118 (57), 110 (100), 109 (47), 95 (75), 77 (50), 55 (80), 41 (62), 39 (67), and 27 (43).

Anal. ($C_{10}H_{12}NOCl$): calcd mol wt, 197.0607; found, 197.0615.

1-Methoxy-2-cyano-5-methylbicyclo[2.2.2]oct-5-ene (18c). A mixture of diene **16** (44.0 g, 0.36 mol), acrylonitrile (37.6 g, 0.71 mol), and hydroquinone (10 mg) was placed in a stainless steel bomb and heated at 120 °C for 16 h. After cooling, the reaction mixture was dissolved in ether and filtered through Al_2O_3. Distillation gave 49.1 g (76%) of a 1:1 mixture of nitriles **18c:** bp 107–110 °C (0.5 mm); IR ($CHCl_3$) 2225 cm^{-1}; NMR (CCl_4) δ 1.26–2.9 (m, 8), 1.80 (d, 1.5, J = 1.5 Hz), 1.85 (d, 1.5, J = 1.5 Hz), 3.35 (s, 3), and 5.9 (m, 1); mass spectrum, m/e (relative intensity) 177 (5), 130 (27), 124 (100), 123 (57), 109 (75), and 91 (22). VPC analysis (5% SE 30, 180 °C) indicated a 1:1 mixture of isomers.

Alternatively, reduction of chloronitrile **18a** with lithium in liquid ammonia furnished nitrile **18c** in 72% yield.

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.28; H, 8.34; N, 8.19.

***tert*-Butyl 2-(2-Hydroxybicyclo[2.2.2]oct-5-en-2-yl)propionate (21).** A solution of ketone **11**[5] (48.9 g, 0.44 mol) and *tert*-butyl 2-bromopropionate[23] (109.0 g, 0.52 mol) in THF (300 mL) was added gradually to a mixture of magnesium[24] (18.3 g, 0.8 g-atom), iodine (one crystal), and methyl iodide (3 drops) in THF (300 mL) heated at reflux under N_2. After the vigorous reaction subsided, the mixture was heated at reflux for an additional 12 h and then cooled and added to ice-cold 1 M sulfuric acid (1 L). This resulting mixture was extracted with ether. After drying, the ether was evaporated and the residue was distilled to give 90.8 g (81%) of product **21,** which contained two major components by TLC: bp 91–92 °C (0.1 mm); IR (CCl_4) 3479 and 1700 cm^{-1}; NMR (CCl_4) δ 1.0–2.7 (m, 12), 1.45 (d, 9, J = 3 Hz), 3.3–3.7 (m, 1), and 6.18 (m, 2).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 70.99; H, 9.59.

Ethyl (1-Methoxy-2-hydroxy-4-methylbicyclo[2.2.2]oct-5-en-2-yl)acetate (22a,23a). Using the general procedure of Rathke,[11b] 4-methyl ketone **12** (13.3 g, 0.08 mol), activated[25] zinc (8.8 g, 0.12 g-atom), and ethyl bromoacetate (13.3 g, 0.12 mol) in THF (25 mL) and trimethyl borate (25 mL) yielded, after 48 h at room temperature, 4.0 g of recovered 4-methyl ketone **12** and 11.0 g (80%) of a 1:1 mixture (by NMR) of hydroxy esters **22a** and **23a,** bp 117–125 °C (0.4 mm), which could not be separated by crystallization or chromatography: IR ($CHCl_3$) 3530, 1715, and 1600 cm^{-1}; NMR (CCl_4) δ 1.10 (s, 1.5), 1.13 (s, 1.5), 1.25 (t, 3, J = 7.0 Hz), 3.32 (s, 1.5), 3.37 (s, 1.5), 4.0 (q, 2, J = 7.0 Hz), and 6.0 (m, 2); mass spectrum, m/e (relative intensity) 254 (very weak, M^+), 237 (5), 209 (10), and 124 (100).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.85; H, 8.86.

2-(2-[1-Methoxy-2-hydroxy-4-methylbicyclo[2.2.2]oct-5-en-2-yl]ethyl)-2-methyl-1,3-dioxolane (22f,23f). A solution of the Grignard reagent **37b** prepared from 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (1.95 g, 10 mmol) using the procedure of Ponaras[18b] was added at 0 °C to a stirred solution of 4-methyl ketone **12** (1.40 g, 8.4 mmol) in THF (10 mL). After stirring for 5 h at room temperature, the reaction mixture was added to ammonium chloride (20%, 40 mL) and extracted with ether. The combined extracts were washed with water and then brine, dried, and evaporated to yield 2.1 g (87.5%) of crude product. Chromatography of a portion of this crude product (1.0 g) on silica gel using ether/pentane (1:1) yielded recovered 4-methyl ketone **12** (150 mg), pure liquid *endo*-hydroxy ketal **23f** (240 mg, 27% overall yield), and crystalline *exo*-hydroxy ketal **22f** (600 mg, 68% overall yield). Pure **22f** could also be obtained by crystallization of the crude product from ether/pentane. Pure **23f:** NMR (CCl_4) δ 1.12 (s, 3), 1.25 (s, 3), 1.30–2.00 (m, 10), 3.40 (s, 3), 3.86 (s, 4), 5.94 (d, 1, J = 9.0 Hz), and 6.26 (d, 1, J = 9.0 Hz); mass spectrum, m/e (relative intensity) 282 (very weak), 267 (1), 221 (3), 167 (1), 135 (5), 124 (100), 109 (20), and 87 (15).

Anal. ($C_{16}H_{26}O_4$); calcd mol wt, 282.1834; found, 282.1843.

Pure **22f:** mp 68.5–~69.5 °C; NMR (CCl_4) δ 1.10 (s, 3), 1.20 (s, 3), 1.25–2.00 (m, 10), 3.32 (s, 3), 3.81 (s, 4), 5.82 (d, 1, J = 9.0 Hz), and 6.20 (d, 1, J = 9.0 Hz); mass spectrum, m/e (relative intensity) 282 (very weak), 267 (1), 221 (1), 162 (1), 138 (9), 124 (100), 109 (22), and 87 (30).

Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.08; H, 9.22. Found: C, 68.02; H, 9.54.

1-Methoxy-2-hydroxy-2-(γ-phenylthiopropyl)-4-methylbicyclo[2.2.2]oct-5-ene (22h,23h). The Grignard reagent[18a] generated from 3-bromopropyl phenyl sulfide (1.62 g, 7 mmol) and magnesium (170 mg, 7 mmol) in ether (10 mL) was added dropwise to the 4-methyl ketone **12** (500 mg, 3 mmol) in ether (10 mL) in an ice–water bath. After stirring for 6 h at room temperature, the reaction mixture was added to ammonium chloride (30 mL) and extracted with ether. The combined extracts were washed with water and then brine, dried, and evaporated to yield 950 mg (≈100%) of crude product. Chromatography of this crude product on silica gel using ether/pentane (2:1) yielded pure liquid *endo*-γ-phenylthio alcohol **23h** (200 mg, 21% overall yield) and crystalline *exo*-γ-phenylthio alcohol **22h** (700 mg, 74% overall yield). Pure **22h** could also be obtained by crystallization of the crude product from ether/pentane. Pure **23h:** NMR (CCl_4) δ 1.09 (s, 3), 1.20–~2.00 (m, 10), 2.93 (t, 2, J = 6.0 Hz), 3.37 (s, 3), 5.91 (d, 1, J = 8 Hz), 6.21 (d, 1, J = 8 Hz), and 7.23 (broad s, 5). Pure **22h:** mp 72–~73 °C; NMR (CCl_4) δ 1.07 (s, 3), 1.15–~2.0 (m, 10), 2.83 (t, 2, J = 6 Hz), 3.31 (s, 3), 5.80 (d, 1, J = 9 Hz), 6.17 (d, 1, J = 9 Hz), 7.22 (broad s, 5); mass spectrum (low temperature), m/e (relative intensity) 318 (30, M^+), 286 (5), 261 (3), 205 (10), 191 (12), 152 (10), 136 (10), 124 (100), and 109 (50).

Anal. Calcd for $C_{19}H_{26}O_2S$: C, 71.70; H, 8.18; S, 10.06. Found: C, 71.88; H, 8.05; S, 9.97.

(1-Methoxy-2-hydroxy-5-methylbicyclo[2.2.2]oct-5-en-2-yl)acetic Acid (24b,25b). To a stirred solution of lithium diisopropylamide at −20 °C, prepared by the dropwise addition of *n*-butyllithium in ether (2.23 M, 60 mL, 0.14 mol) to diisopropylamine (14.2 g, 0.14 mol) in THF (100 mL) at −20 °C, was added a solution of acetic acid (4.2 g, 0.07 mol) in THF (10 mL) dropwise. The reaction mixture was stirred for 30 min at −20 °C and then at 40–50 °C for 1 h. This mixture was cooled to 0 °C, the 5-methyl ketone **13** (10.0 g, 0.06 mol) in THF (20 mL) was added dropwise, and the resulting mixture was stirred at 0 °C for 1 h and then at 25 °C for 12 h. After acidification with dilute HCl, the reaction mixture was extracted with ether. The combined organic extracts were extracted with 0.3 N NaOH, and the basic aqueous phase was acidified with cold 10% HCl and then extracted with ether to yield 5.5 g (81% based on 48% conversion) of a 1:1 mixture (by NMR) of hydroxy acids **24b** and **25b:** IR ($CHCl_3$) 3350–2850, 1700, and 1645 cm^{-1}. Crystallization of this mixture from ether yielded pure endo isomer **25b:** mp 105–107 °C; NMR ($CDCl_3$) δ 1.37–1.90 (m, 6), 1.85 (d, 3, J = 1.5 Hz), 2.35 (m, 1), 2.49 (d, 1, J = 15 Hz), 2.92 (d, 1, J = 15 Hz), 3.39 (s, 3), and 5.9 (m, 1); mass spectrum, m/e (relative intensity) 180 (13), 138 (29), 124 (100), 123 (67), 109 (52), and 91 (41). The mother liquors contained a 2:1 mixture of **24b** and **25b.** The characteristic NMR signals of **24b** were ($CDCl_3$) δ 2.44 (d, 1, J = 15 Hz) and 2.77 (d, 1, J = 15 Hz).

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.78; H, 7.75.

2-(1-Methoxy-2-hydroxy-5-methylbicyclo[2.2.2]oct-5-en-2-yl)propionic Acid (24c,25c). Using the general procedure described above, 5-methyl ketone **13** (4.5 g, 27 mmol) and propionic acid (2.0 g, 27 mmol) furnished 2.3 g (64% based on 56% conversion) of a 2:1 mixture (by NMR) of **24c** and **25c.** The major component was obtained by crystallization from acetonitrile and was assigned structure **24c:** mp 134–135 °C; IR ($CHCl_3$) 3500–2500 and 1695 cm^{-1}; NMR ($CDCl_3$) δ 1.05–2.6 (m, 8), 1.18 (d, 3, J = 7 Hz), 1.77 (d, 3, J = 1.5 Hz), 3.29 (s, 3), and 5.92 (m, 1); mass spectrum, m/e (relative intensity) 194 (2), 124 (100), and 109 (41). The mother liquors contained a 1:1 mixture of **24c** and **25c.** The characteristic NMR methyl signal for **25c** was ($CDCl_3$) δ 1.22 (d, 3, J = 7 Hz).

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.26; H, 8.39.

(1-Methoxy-2-hydroxy-5-methylbicyclo[2.2.2]oct-5-en-2-yl)phenylacetic Acid (24d,25d). Using the general procedure described above, 5-methyl ketone **13** (2.0 g, 12 mmol) and phenylacetic acid (1.63 g, 12 mmol) furnished 1.7 g (60% based on 78% conversion) of a 2:1 mixture (by NMR) of **24d** and **25d.** The major component was obtained by crystallization from acetonitrile and was assigned structure **24d:** mp 189–191 °C; IR ($CHCl_3$) 3450, 3300–2800, and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.14–2.34 (m, 7), 1.77 (d, 3, J = 1.5 Hz), 3.20 (s, 3), 3.48 (s, 1), 5.95 (m, 1), and 7.18–7.62 (m, 5); mass spectrum, m/e (relative intensity) 256 (4), 138 (78), 136 (48), 124 (100), 123 (95), 118 (50), 110 (85), 109 (73), 91 (71), and 65 (60). The mother liquors contained a 1:1 mixture of **24d** and **25d.** The characteristic NMR methine signal for **25d** was ($CDCl_3$) δ 3.50 (s, 1).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.63; H, 7.32.

(1-Methoxy-2-hydroxy-5-methylbicyclo[2.2.2]oct-5-en-2-

yl)-*m*-methoxyphenylacetic Acid (24e,25e). Using the general procedure described above, 5-methyl ketone **13** (4.0 g, 24 mmol) and *m*-methoxy phenylacetic acid (4.32 g, 26 mmol) furnished 4.97 g (83% based on 75% conversion) of a 4:1 mixture (by NMR) of **24e** and **25e**. The major component was obtained by crystallization from acetonitrile and was assigned structure **24e**: mp 186–187 °C; IR ($CHCl_3$) 3400, 3300–2800, and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.17–2.33 (m, 7), 1.75 (d, 3, J = 1.5 Hz), 3.22 (s, 3), 3.45 (s, 1), 3.77 (s, 3), 5.95 (m, 1), and 6.7–7.3 (m, 4); mass spectrum, *m/e* (relative intensity) 286 (5), 166 (75), 148 (76), 138 (52), 124 (100), 123 (87), 121 (78), 110 (36), 109 (30), and 91 (52). The mother liquors contained a 1:1 mixture of **24e** and **25e**. The characteristic NMR methine signal for **25e** was ($CDCl_3$) δ 3.49 (s, 1).

Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.67; H, 7.48.

Methyl 4-(1-Methoxy-2-hydroxy-5-methylbicyclo[2.2.2]oct-5-en-2-yl)-3-oxobutanoate (24i,25i). Methyl acetoacetate (0.70 g, 6 mmol) was added dropwise to the cooled slurry of sodium hydride (0.30 g, 7 mmol) in THF (25 mL) at 0 °C. After stirring for 10 min at 0 °C, *n*-butyllithium (4.5 mL, 1.6 M, 7 mmol) was added dropwise, and the reaction was allowed to stir at 0 °C for 10 min. The 5-methyl ketone **13** (1.00 g, 6 mmol) was added in one portion, and the reaction mixture was stirred at 0 °C for 30 min and then at 25 °C for 2 h. Concentrated hydrochloric acid (2 mL), water (100 mL), and ether (35 mL) were added, the reaction mixture was extracted with ether, and the combined organic extracts were washed with brine, dried, and then evaporated to give a residue which was purified by chromatography on Al_2O_3 with hexane/ethyl acetate to give 1.12 g (65%) of a 2:1 mixture (by NMR) of **24i** and **25i** which was not separated: IR (CCl_4) 3500, 1750, 1705, and 1625 cm^{-1}; NMR ($CDCl_3$) δ 1.3–3.05 (m, 10), 1.75 (d, 2, J = 1.5 Hz), 1.81 (d, 1, J = 1.5 Hz), 3.34 (s, 2), 3.39 (s, 1), 3.54 (s, 1.33), 3.64 (s, 0.67), 3.73 (s, 3), and 5.7–5.93 (m, 1); mass spectrum, *m/e* (relative intensity) 264 (2), 124 (100), 123 (50), 109 (45), and 91 (23).

Anal. ($C_{15}H_{22}O_5$): calcd mol wt for $M^+ - 18$, *m/e* 264.1362; found, *m/e* 264.1361.

Ethyl (1-Methoxy-4-methylbicyclo[2.2.2]oct-5-en-2-ylidine)acetate (26). Thionyl chloride (0.57 g, 4.8 mmol) was added dropwise to a stirred solution of β-hydroxy esters **22a/23a** (1.00 g, 4 mmol) in pyridine (10 mL) at 0 °C. After the addition was completed, the mixture was allowed to warm to 25 °C. It was stirred for 1 h, poured into ice water, and, after acidification with 20% HCl, extracted with ether. After drying, evaporation of the ether yielded 700 mg (74%) of crude liquid diene **26**, which could be purified by chromatography on alumina with pentane/ether (2:1). Diene 26: IR ($CHCl_3$) 1705 and 1650 cm^{-1}; NMR (CCl_4) δ 1.23 (t, 3, J = 8 Hz), 1.25 (s, 3), 1.40–~3.00 (m, 6), 3.41 (s, 3), 4.07 (q, 2, J = 8.0 Hz), 5.81 (t, 1, J = 2.0 Hz), 6.00 (d, 1, J = 8.0 Hz), 6.21 (d, 1, J = 8.0 Hz); mass spectrum, *m/e* (relative intensity) 236 (5, M^+), 208 (100), 179 (18), 162 (50), 147 (25), 135 (20), 121 (15), and 91 (14).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.19; H, 8.47. Found: C, 70.27; H, 8.19.

Ethyl (1-Methoxy-5-methylbicyclo[2.2.2]oct-5-en-2-ylidene)acetate (27,28). Method A. Thionyl chloride was added dropwise to a solution of β-hydroxy esters **24a/25a** (5.1 g, 0.02 mol) in pyridine (25 mL) at 0 °C. The reaction mixture was stirred for 8 h as it warmed to room temperature and then poured into ice. The mixture was acidified with 10% HCl and extracted with ether. The ether solution was washed with H_2O and dried. The solvent was evaporated at reduced pressure, and the residue was distilled to give 1.7 g (36%) of diene **27**: bp 125–130 °C (0.7 mm); IR (CCl_4) 1710 and 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (t, 3, J = 7 Hz), 1.83 (d, 3, J = 1.5 Hz), 1.43–2.75 (m, 7), 3.46 (s, 3), 4.06 (q, 2, J = 7 Hz), and 5.82 (m, 2); mass spectrum, *m/e* (relative intensity) 236 (17, M^+), 208 (100), 179 (53), 135 (40), 124 (33), and 91 (28).

Method B. *n*-Butyllithium (1.33 M, 15 mL, 20 mmol) was added dropwise to a solution of diisopropylamine (2.02 g, 20 mmol) in tetrahydrofuran (100 mL) at −70 °C. After 15 min, ethyl trimethylsilylacetate (3.2 g, 20 mmol) was added dropwise over a 10-min period and the mixture was stirred for 10 min at −70 °C. Ketone **13** (1.66 g, 10 mmol) in tetrahydrofuran (20 mL) was added dropwise, and the resulting solution was stirred at −70 °C for 1 h, at −25 °C for 1 h, and at 25 °C for 6 h. The mixture was acidified with 10% HCl and extracted with ether. The ether solution was washed with H_2O and dried. The solvent was evaporated in vacuo, and the residue was chromatographed (Al_2O_3, hexane/ethyl acetate) to give 1.40 g (60%) of a 2:1 mixture (NMR) of dienes **27** and **28**. The distinguishing NMR signals ($CDCl_3$) for **28** were δ 1.31 (t, 3, J = 7 Hz), 3.35 (s, 3), 4.20 (q, 2, J = 7 Hz), 5.56 (t, 1, J = 2 Hz), and 5.89 (m, 1).

Anal. ($C_{14}H_{20}O_3$): calcd mol wt, 236.1421; found, 236.1419.

Rearrangement of 2-Hydroxybicyclo[2.2.2]oct-5-en-2-yl Derivatives: General Procedures. A. A mixture in the approximate ratio of bicyclic alcohol or diene (1 mmol), acetic acid (10 mL), and *p*-toluenesulfonic acid (ca. 10 mg) was heated at reflux for 4 h, and then the acetic acid was evaporated at reduced pressure and the product was isolated by normal workup.

B. This was identical with procedure A, except that 1 mmol of *p*-toluenesulfonic acid was used per 1 mmol of bicyclic substrate.

Rearrangement of hydroxy esters 21 (90.8 g, 0.38 mol) using procedure A yielded 48.2 g (70%) of 2-methyl-4-oxatricyclo[6.2.1.$0^{1,5}$]undec-6-en-3-one (**29/30**). Fractional crystallization from ethyl acetate/ether yielded one pure epimer: mp 105–105.5 °C; IR (CCl_4) 1775 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (d, 3, J = 8 Hz), 1.3–2.0 (m, 6), 2.42 (q, 1, J = 7 Hz), 2.6 (m, 1), 4.45 (dd, 1, J = 4 and 1 Hz), 5.7 (dd, 1, J = 10 and 4 Hz), and 6.4 (dd, 1, J = 10 and 6 Hz). Fractional crystallization from *n*-hexane yielded the other epimer: mp 57–58 °C; IR (CCl_4) 1775 cm^{-1}; NMR ($CDCl_3$) δ 1.1 (d, 3, J = 8 Hz), 1.2–2.0 (m, 6), 2.6 (m, 1), 2.75 (q, 1, J = 7 Hz), 4.25 (dd, 1, J = 4 and 1 Hz), 5.7 (dd, 1, J = 10 and 4 Hz), and 6.4 (dd, 1, J = 10 and 6 Hz). When treated with sodium methoxide, the two epimers were interconverted and the mp 105 °C epimer predominated at apparent equilibrium. Mass spectrum, *m/e* (relative intensity) 178 (9), 176 (49), 161 (36), 148 (70), 123 (43), 106 (47), 105 (100), 91 (73), 79 (51), and 69 (45).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.01; H, 7.56.

Rearrangement of hydroxy esters 22a,23a (1:1, 2.0 g, 8.0 mmol) using procedure A yielded 1.30 g (73%) of a 2:1 mixture (by NMR) of esters **32a** and **34a** and 325 mg (21%) of a 1:1 mixture (by NMR) of acids **32b** and **34b**. Hydrolysis of esters **32a,34a** with aqueous methanolic KOH gave, in 80% yield, acids **32b** and **34b**. This mixture of acids was separated by fractional crystallization from ether/pentane to give (5-methylbicyclo[3.2.1]oct-6-en-2-on-1-yl)acetic acid (**32b**) [mp 60–61 °C; IR ($CHCl_3$) 3600, 3400–2800, and ≈1710 (broad) cm^{-1}; NMR ($CDCl_3$) δ 1.25 (s, 3), 1.3–2.0 (m, 4), 2.05 (m, 2), 2.60 (s, 2), and 5.95 (s, 2); mass spectrum, *m/e* (relative intensity) 194 (10, M^+), 176 (20), and 93 (100). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22. Found: C, 67.73; H, 7.44.] and (5-methylbicyclo[3.2.1]oct-3-en-2-on-1-yl)acetic acid (**34b**) [mp 121–123 °C; IR ($CHCl_3$) 3400–2800, 1710, and 1675 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (s, 3), 1.5–2.3 (m, 6), 2.50 (d, 1, J = 17 Hz), 2.95 (d, 1, J = 17 Hz), 5.93 (d, 1, J = 9.0 Hz), and 7.07 (dd, 1, J = 9 and 2 Hz); mass spectrum, *m/e* (relative intensity) 194 (60, M^+), 176 (60), 166 (30), 148 (50), 138 (40), 134 (20), 120 (15), 105 (30), and 95 (100). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22. Found: C, 67.87; H, 7.52.].

Rearrangement of *exo*-hydroxy acid 24c (0.24 g, 1 mmol) using procedure A yielded 0.18 g (90%) of 2-(6-methylbicyclo[3.2.1]oct-6-en-2-on-1-yl)propionic acid (**33c**): mp 123–125 °C; IR ($CHCl_3$) 3400–2800 and 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.14 (d, 3, J = 7 Hz), 1.83 (d, 3, J = 1.5 Hz), 1.75–2.8 (m, 7), 3.03 (q, 1, J = 7 Hz), 5.3 (m, 1), and 10.83 (s, 1); mass spectrum, *m/e* (relative intensity) 208 (23), 152 (57), 107 (100), and 91 (20).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.03; H, 8.00.

Rearrangement of *exo*-hydroxy acid 24d (296 mg, 1 mmol) using procedure A gave 247 mg (93%) of (6-methylbicyclo[3.2.1]oct-6-en-2-on-1-yl)phenylacetic acid (**33d**): mp 196–198 °C; IR ($CHCl_3$) 3300–2800 and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.7 (m, 7), 1.68 (d, 3, J = 1.5 Hz), 4.30 (s, 1), 5.24 (m, 1), and 7.28 (s, 5); mass spectrum, *m/e* (relative intensity) 270 (6), 214 (21), 170 (30), 169 (100), 118 (38), and 91 (60).

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.41; H, 6.80.

Rearrangement of *exo*-hydroxy acid 24e (420 mg, 1.3 mmol) using procedure A furnished 380 mg (100%) of (6-methylbicyclo[3.2.1]oct-6-en-2-on-1-yl)-*m*-methoxyphenylacetic acid (**33e**): mp 194–195 °C; IR ($CHCl_3$) 3500–2800 and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.8 (m, 7), 1.68 (d, 3, J = 1.5 Hz), 3.75 (s, 3), 4.25 (m, 1), 6.7–7.25 (m, 4), and 8.4–8.75 (m, 1); mass spectrum, *m/e* (relative intensity) 300 (27), 244 (33), 199 (64), 166 (92), 148 (31), 124 (45), 121 (100), and 91 (37).

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.69; H, 6.90.

Rearrangement of *endo*-hydroxy acid 25b (440 mg, 1.9 mmol) using procedure A gave 370 mg (100%) of a 2:1 mixture (by NMR) of keto acids **35b** and **33b**. Crystallization of this mixture from ether gave the major isomer, (4-methylbicyclo[3.2.1]oct-3-en-2-on-1-yl)acetic acid (**35b**): mp 145–146.5 °C, IR ($CHCl_3$) 3500–2600, 1710, 1670, and 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.4–2.9 (m, 6), 2.04 (d, 3, J = 1.5 Hz), 2.50 (d, 1, J = 16 Hz), 2.86 (d, 1, J = 16 Hz), 2.79 (m, 1), 5.69 (m, 1), and 8.58–9.16 (m, 1); mass spectrum, *m/e* (relative intensity) 194 (57), 148 (28), 138 (39), 95 (100), 93 (50), and 67 (37).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.73; H,

7.08.

The minor isomer was assigned as (6-methylbicyclo[3.2.1]oct-6-en-2-on-1-yl)acetic acid (**33b**) on the basis of the following data for the methyl ester (CH_2N_2) of **33b:** IR (CCl_4) 1740 and 1710 cm^{-1}; NMR (CCl_4) δ 1.6–2.7 (m, 9), 1.82 (d, 3, J = 1.5 Hz), 3.55 (s, 3), and 5.47 (m, 1).

Anal. ($C_{12}H_{16}O_3$): calcd mol wt, 208.1099; found, 208.1099.

Rearrangement of α,β-Unsaturated Ester 26. Using procedure B, ester **26** (260 g, 11 mmol) gave 730 mg (30%) of neutral products, which were shown by NMR to be a 2:1 mixture of esters **32a** and **34a,** and 1.28 g (60%) of acid **32b.** The ester mixture was hydrolyzed with 5% methanolic KOH (70% yield), and after separation of the mixture by crystallization the individual acids from the product ester, as well as the initial acid product, were identified by spectral comparison (IR and NMR) with authentic material.

Rearrangement of α,β-Unsaturated Esters 27,28. Using procedure B, ester **27,** a mixture of esters **27,28,** and a sample of α,β-unsaturated acids obtained by base hydrolysis of **27,28** gave an ca. 80% yield of product. In the case of the ester substrates, the initial product contained 50% neutral material, assigned as ester **33a** on the basis of spectral data [IR (CCl_4) 1730 and 1710 cm^{-1}; NMR (CCl_4) δ 1.22 (t, 3, J = 7 Hz), 1.85 (d, 3, J = 1.5 Hz), 1.50–2.75 (m, 9), 4.03 (q, 2, J = 7 Hz), and 5.50 (m, 1)], and 30% of an acidic material, identified as acid **33b** by a comparison of IR and NMR data with authentic material. Rearrangement of the precursor unsaturated acids gave acid **33b** as the only observed product.

(5-Methylbicyclo[3.2.1]octan-2-on-1-yl)acetic Acid (36). A stirred ca. 2:1 mixture of unsaturated keto acids **32b** and **34b** (120 mg, 0.62 mmol) and a catalytic amount of PtO_2 in glacial acetic acid (10 mL) was allowed to react with hydrogen gas at 25 °C and atmospheric pressure until the uptake of hydrogen ceased (30 min). The reaction mixture was filtered, concentrated, dissolved in ether, and extracted with sodium bicarbonate. The aqueous extracts were acidified with 10% HCl and extracted with ether, and after drying the organic phase was evaporated to give 120 mg (100%) of crude acid **36** [NMR ($CDCl_3$) δ 1.15 (s, 3), 1.50–2.10 (m, 8), and 2.30–2.70 (m, 4)], which was characterized as its methyl ester (CH_2N_2, 100%): IR ($CHCl_3$) 1735 and 1705 cm^{-1}; NMR (CCl_4) δ 1.16 (s, 3), 1.50–2.0 (m, 8), 2.2–2.5 (m, 4), and 3.59 (s, 3); mass spectrum, m/e (relative intensity) 210 (25, M^+), 195 (10), 179 (30), 153 (100), 135 (8), 121 (30), 107 (15), 93 (100), and 81 (65). VPC analysis (10% SE 30) of this ester showed a single component; the sharp quaternary methyl group signal in the NMR spectrum of both the acid **36** and its methyl ester confirms the presence of a single hydrogenation product from both unsaturated keto acids.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.66; H, 8.59.

1-(1-Methoxy-4-methylbicyclo[2.2.2]oct-5-en-2-ylidene)-3-butanone (38). A 1:2 mixture of hydroxy ketal **22f,23f** (1.00 g, 3.5 mmol) was dissolved in pyridine (20 mL). The solution was cooled in an ice bath, and thionyl chloride (520 mg, 4.3 mmol) was added dropwise to the stirred solution. The mixture was then stirred at room temperature for an additional hour. The resulting suspension was poured onto cracked ice, and the mixture was acidified with cold 20% hydrochloric acid and then extracted with ether. The organic phase was dried and evaporated to give 620 mg (80%) of crude dienone **38** which by NMR was a 1:1 mixture of the two geometrical isomers. The crude product **38,** which was used without further purification, showed the following: IR ($CHCl_3$) 1715 and 1710 cm^{-1}; NMR (CCl_4) δ 1.22 (s, 1.5), 1.25 (s, 5), 2.06 (s, 1.5), 2.08 (s, 1.5), 3.42 (s, 1.5), 3.51 (s, 1.5), and 5.30–≈6.50 (m, 1). All attempts to prepare an analytical sample were unsuccessful.

1-(1-Methoxy-5-methylbicyclo[2.2.2]oct-5-en-2-ylidene)-2-propanone (39). The γ-hydroxy-β-keto esters **24i,25i** (2:1 mixture) (4.42 g, 15.6 mmol) were distilled (pot temperature, 190–220 °C) to furnish 2.70 g (83%) of **39:** bp 130–137 °C (1 mm); IR (CCl_4) 1680 and 1610 cm^{-1}; NMR (CCl_4) δ 1.30–1.70 (m, 4), 1.84 (d, 3, J = 1.5 Hz), 2.11 (s, 3), 2.45–2.70 (m, 3), 3.40 (s, 3), 5.83 (m, 1), and 6.62 (t, 1, J = 2 Hz); mass spectrum, m/e (relative intensity) 206 (11, M^+), 178 (68), 135 (100), 124 (85), 109 (60), and 91 (35).

Anal. ($C_{13}H_{18}O_2$): calcd mol wt, 206.1307; found, 206.1300.

Conjugated Tricyclic Dienone 41. A mixture of bicyclic dione **32g** (103 mg, 0.5 mmol) and TsOH (95 mg, 0.5 mmol) in acetic acid (5 mL) was heated at reflux for 10 h, the acetic acid was then evaporated at reduced pressure, and, after normal workup, 90 mg (95%) of a 9:1 (by NMR) mixture of products was isolated. After separation by chromatography on silica gel, the minor component was identified as the nonconjugated tricyclic dienone **42** by spectral comparison (IR and NMR) with authentic material. The major component was assigned as the conjugated tricyclic dienone **41** on the basis of the following data: UV (MeOH) λ_{max} 290 nm (log ϵ 4.38); IR ($CHCl_3$) 1650 and 1610 cm^{-1}; NMR (CCl_4) δ 1.24 (s, 3), 1.40–≈2.50 (m, 10), 5.46 (s, 1), 6.02 (d, 1, J = 9 Hz), and 6.25 (d, 1, J = 9 Hz); mass spectrum, m/e (relative intensity) 188 (66, M^+), 160 (40), 146 (21), 132 (60), 118 (100), 104 (26), and 91 (35).

Anal. ($C_{13}H_{16}O$): calcd mol wt, 188.1201; found, 188.1208.

Conjugated Tricyclic Dienone 42. Bicyclic dione **32g** (688 mg, 3.34 mmol) in benzene (10 mL) was added to a suspension of potassium *tert*-butoxide (561 mg, 5 mmol) in benzene (90 mL). The dark colored solution was heated at reflux for 5 h and then acidified with 5% hydrochloric acid until the color turned yellow. The organic layer was separated, and the aqueous layer was then extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate, water, and then brine. After drying, evaporation yielded 600 mg (95%) of crude product. Chromatography of this crude product on silica gel with ether/pentane (1:1) yielded 490 mg (78%) of pure liquid tricyclic dienone **42:** UV (MeOH) λ_{max} 242 nm (log ϵ 4.3); IR ($CHCl_3$) 1670 and 1615 cm^{-1}; NMR (CCl_4) δ 1.17 (s, 3), 1.30–≈2.70 (m, 10), 5.64 (m, 1), and 5.73 (s, 2); mass spectrum, m/e (relative intensity) 188 (54, M^+), 160 (100), 145 (30), 132 (70), 118 (80), 105 (20), 91 (40), and 77 (30).

Anal. ($C_{13}H_{16}O$): calcd mol wt, 188.1201; found, 188.1207.

Rearrangement of *exo*-hydroxy ketal 22f (980 mg, 3.5 mmol) using procedure A yielded a mixture of ethylene glycol diacetal and a bicyclo[3.2.1]octenone product which was separated by treatment with excess sodium methoxide in methanol (25 °C, 1 h) followed by chromatography on silica gel using ether/pentane to give 688 mg (96%) of liquid 4-(5-methylbicyclo[3.2.1]oct-6-en-2-on-1-yl)butan-2-one (**32g**): IR ($CHCl_3$) 1705 cm^{-1}; NMR (CCl_4) δ 1.24 (s, 3), 1.5–2.0 (m, 6), 2.08 (s, 3), 2.2–2.7 (m, 4), 5.66 (d, 1, J = 6.0 Hz), and 5.89 (d, 1, J = 6.0 Hz); mass spectrum, m/e (relative intensity) 206 (25, M^+), 163 (12), 150 (18), 107 (100), 92 (78), and 77 (25).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.73; H, 8.74. Found: C, 75.44; H, 9.00.

Rearrangement of *endo*-hydroxy ketal 23f (120 mg, 0.4 mmol) using procedure A yielded, after treatment with sodium methoxide in methanol, 100 mg (84%) of a 2:1 mixture of **34g** and **32g** as judged by NMR. No attempt was made to separate this mixture. The major product, **34g,** showed the following spectral properties: IR ($CHCl_3$) 1670 cm^{-1}; NMR (CCl_4) δ 1.31 (s, 3), 1.5–≈2.0 (m, 8), 2.08 (s, 3), 2.2–≈2.5 (m, 2), 5.90 (d, 1, J = 6 Hz), and 6.90 (m, 1).

Rearrangement of *exo*-Phenylthio Alcohol 22h. A mixture of *exo*-phenylthio alcohol **22h** (1.0 g, 3.14 mmol) and TsOH (300 mg, 1.57 mmol) in acetic acid (100 mL) was heated at reflux for 20 h, the acetic acid was evaporated at reduced pressure, and 850 mg (94%) of crude product was isolated by normal workup. Chromatography of this crude product on silica gel using pentane/ether (2:1) yielded 810 mg (90%) of pure liquid bicyclic [3.2.1] phenylthioenone **32h:** IR (CCl_4) 1705, 1580, 1455, and 685 cm^{-1}; NMR (CCl_4) δ 1.20 (s, 3), 1.40–≈2.00 (m, 8), 2.00–≈2.50 (m, 2), 2.88 (m, 2), 5.61 (d, 1, J = 5 Hz), 5.84 (d, 1, J = 5 Hz), and 7.22 (broad s, 5); mass spectrum, m/e (relative intensity) 286 (90, M^+), 230 (30), 177 (40), 149 (22), 136 (100), 120 (90), 105 (44), and 91 (33).

Anal. Calcd for $C_{18}H_{22}OS$: C, 75.52; H, 7.69; S, 11.19. Found: C, 75.77; H, 7.89; S, 11.00.

Rearrangement of *endo*-Phenylthio Alcohol 23h. Following the procedure described for the rearrangement of **22h,** *endo*-phenylthio alcohol **23h** (160 mg, 0.5 mmol) yield 34 mg (24%) of a liquid product, which was assigned as **32h** by comparison of the spectral data (IR and NMR) with authentic material, and 91 mg (64%) of a second liquid product, which was assigned as **34h** on the basis of the following data: IR (CCl_4) 1675, 1580, 1450, and 690 cm^{-1}; NMR (CCl_4) δ 1.26 (s, 3), 1.40–≈2.20 (m, 10), 2.88 (m, 2), 5.72 (d, 1, J = 10 Hz), 6.81 (dd, 1, J = 11 and 2 Hz), and 7.22 (broad s, 5); mass spectrum, m/e (relative intensity) 286 (25, M^+), 210 (4), 177 (100), 149 (67), 135 (15), 121 (18), 110 (14), and 91 (15).

Anal. ($C_{18}H_{22}OS$): calcd mol wt, 286.1391; found, 286.1397.

Rearrangement of hydroxy keto esters 24i,25i (2:1, 1.0 g, 3.5 mmol) using procedure A gave 500 mg (73%) of a 1:1 mixture (by NMR) of diketones **33j** and **35j,** which was separated by chromatography on Al_2O_3 using pentane/$CHCl_3$. Liquid 1-(6-methylbicyclo[3.2.1]oct-6-en-2-on-1-yl)propan-2-one (**33j**): IR ($CHCl_3$) 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.7–2.95 (m, 9), 1.84 (d, 3, J = 1.5 Hz), 2.10 (s, 3), and 5.50 (m, 1); mass spectrum, m/e (relative intensity) 192 (17), 149 (23), 136 (30), 124 (23), 107 (22), 93 (100), 91 (30), 77 (26), and 43 (67).

Anal. ($C_{12}H_{16}O_2$): calcd mol wt, 192.1150; found, 192.1151.

1-(4-Methylbicyclo[3.2.1]oct-3-en-2-on-1-yl)propan-2-one (**35j**): mp 62–63.5 °C (from hexane); IR ($CHCl_3$) 1715 and 1665 cm^{-1}; NMR ($CDCl_3$) δ 1.47–2.79 (m, 7), 2.01 (d, 3, J = 1.5 Hz), 2.21 (s, 3), 2.45 (d, 1, J = 17 Hz), 3.22 (d, 1, J = 17 Hz), and 5.7 (m, 1); mass spectrum, m/e (relative intensity) 192 (11), 177 (17), 149 (39), 134 (21), 122 (65),

121 (23), 95 (100), 67 (36), and 43 (66).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.77; H, 8.15.

Rearrangement of Dienone 38. Using procedure B, crude dienone **38** (220 mg, 1.0 mmol) furnished 180 mg (96%) of conjugated tricyclic dienone **41**, which was identified by comparison of spectral data (IR and NMR) with authentic material.

Rearrangement of α,β-Unsaturated Ketone 39. Using the general conditions described in procedure A and a reaction time of 2 h, ketone **39** (200 mg, 1.0 mmol) yielded 150 mg (78%) of a mixture which was shown by VPC (10% SE 30) to contain nonconjugated enone **33j** and conjugated enone **35j** in a ratio of 1:3. Exposure of product **33j** to identical conditions and reaction time resulted in a 1:1 mixture of **33j** and **35j**, thus suggesting that **33j** is a primary rearrangement product of **39**. Using procedure B, ketone **39** (1.1 g, 5.3 mmol) yielded 850 mg (85%) of conjugated enone **35j**.

Stability of Bicyclo[3.2.1]octene Products. Exposure of the nonconjugated enones **32g** and **33j** to procedure B conditions resulted in complete rearrangement to the conjugated products **41** and **35j**, respectively, as judged by IR and NMR. The nonconjugated bicyclo[3.2.1]octenones **32b, 32h, 33c–e,** and **42** did not rearrange to the corresponding conjugated analogues under these conditions.

Registry No.—**11**, 2220-40-8; **12**, 38258-84-3; **13**, 67316-12-5; **14**, 20023-36-3; **15** (isomer 1), 67337-34-2; **15** (isomer 2), 67337-35-3; **16**, 13697-84-2; **18a**, 64918-89-4; **18b**, 67337-36-4; **18c** (isomer 1), 67316-13-6; **18c** (isomer 2), 67337-37-5; **19**, 67316-14-7; **21**, 67316-15-8; **22a**, 67315-86-0; **22f**, 67316-02-3; **22h**, 67316-03-4; **23a**, 67337-29-5; **23f**, 67337-31-9; **23h**, 67337-32-0; **24a**, 67375-28-4; **24b**, 67337-38-6; **24c**, 67315-87-1; **24d**, 67315-88-2; **24e**, 67315-89-3; **24i**, 67316-04-5; **25a**, 67316-16-9; **25b**, 67315-90-6; **25i**, 67337-33-1; **26**, 67315-91-7; **27**, 67315-92-8; **28**, 67315-93-9; **29**, 67315-94-0; **30**, 67337-30-8; **32a**, 67316-17-0; **32b**, 67315-95-1; **32g**, 67316-07-8; **32h**, 67316-08-9; **33a**, 67316-18-1; **33b**, 67315-99-5; **33c**, 67315-96-2; **33d**, 67315-97-3; **33e**, 67315-98-4; **33j**, 67316-09-0; **34a**, 67316-19-2; **34b**, 67316-01-2; **34g**, 67316-20-5; **34h**, 67316-21-6; **35b**, 67316-00-1; **35j**, 67316-11-4; **36**, 67316-22-7; **36**, methyl ester, 67316-24-9; **38**, 67316-05-6; **39**, 67316-06-7; **41**, 67316-10-3; **42**, 67316-23-8; *p*-methylanisole, 104-93-8; 2-chloroacrylonitrile, 920-37-6; *m*-methylanisole, 100-84-5; acrylonitrile, 107-13-1; *tert*-butyl 2-bromopropionate, 39149-80-9; 2-(2-bromoethyl)-2-methyl-1,3-dioxolane, 37865-96-6; 3-bromopropyl phenyl sulfide, 3238-98-0; acetic acid, 64-19-7; propionic acid, 79-09-4; phenylacetic acid, 103-82-2; *m*-methoxyphenylacetic acid, 1798-09-0; methyl acetoacetate, 105-45-3.

References and Notes

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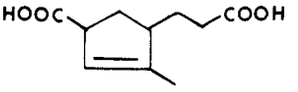

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Association Phenomena. 5. Synthesis and Properties of 1,4-Dipolar Substituted Cyclohexenes

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To study the intramolecular association between oppositely charged centers, several cyclohexenes substituted at the 1 and 4 positions with groups capable of carrying positive and negative charges have been synthesized. Included among these are the cis and trans isomers of 3-(methylamino)bicyclo[4.4.0]dec-1-ene-6-carboxylic acid (**7** and **9**), 6-carboxy-3-(trimethylammonio)bicyclo[4.4.0]dec-1-ene iodide (**8** and **10**), 2,3-dimethyl-6-(methylamino)cyclohexenecarboxylic acid (**17a** and **19**), and 3-carboxy-2,3-dimethyl-6-(trimethylammonio)cyclohexene chloride (**18a** and **20**) and the cis isomers of 3-methyl-6-(methylamino)cyclohexenecarboxylic acid (**17b**) and 3-carboxy-3-methyl-6-(trimethylammonio)cyclohexene chloride (**18b**). However, the expectation that the zwitterions of these compounds should, to a greater extent than the anionic or cationic species, exist in the boat conformation failed to be clearly demonstrable by ^1H and ^{13}C NMR measurements. It is postulated that the apparent lack of conformational response to changing pH is due to the rather large nonbonded interactions arising from the groups at C-2 (i.e., CH_2 in **7–10**, CH_3 in **17a–20**, and H in **17b** and **18b**) and at C-4 (i.e., $NHCH_3$ or $N(CH_3)_3^+$), which favor the half-chair conformation, and the rather small coulombic interaction of the carboxylate and ammonium centers in the zwitterion (calculated to be 3–5 kcal/mol), which favors the boat conformation.

Papers 1–4 of this series[1] deal with intermolecular association phenomena involving interactions between positively and negatively charged moieties. The present paper represents an intramolecular counterpart of these systems and involves an attempt to measure the extent of intramolecular association in cyclohexenes substituted at the 1 and 4 positions with

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