NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 6 H, 2 CH_3 on $C_{4'}$), 1.70 (s, 3 H, CH_3 on C_7), 1.85 (t, 2 H, H_2 on $C_{3'}$, J = 5 Hz), 2.12, 2.16, 2.17, 2.32 (4 s, 4 × 3 H, CH_3 on C_3, $C_{5'}$, $C_{7'}$, and $C_{8'}$), 3.80 (s, 3 H, OCH_3), 4.15 (t, 2 H, H_2 on $C_{2'}$, J = 5 Hz), 5.61 (s, broad pic, 1 H, H_4), 5.65 (d, 1 H, H_8, J = 16 Hz), 6.51 (s, 1 H, H_2), 6.90 (d, 1 H, H_9, J = 16 Hz).

Ethyl 9-(4′,4′,5′,7′,8′-pentamethyl-6′-chromanyl)-3,7-dimethyl-(2*Z*,4*E*,6*E*,8*E*)-nona-2,4,6,8-tetraenoate (28b) was obtained by the same procedure as the ester **28a** from the ester **22b**, overall yield 60%, mp 110–112 °C dec. ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, 3 H, CH_2CH_3, J = 7 Hz), 1.32 (s, 6 H, CH_3 on $C_{4'}$), 1.81 (t, 2 H on $C_{3'}$, J = 5 Hz), 2.08, 2.10, 2.13, 2.17, 2.20 (5 s, 5 × 3 H, CH_3 on C_3, C_7, $C_{5'}$, $C_{7'}$, and $C_{8'}$), 4.12–4.23 (m, 4 H, CH_2CH_3 and H_2 on $C_{2'}$), 5.65 (s, 1 H, H_2), 6.20 (d, 1 H, H_8, J = 16 Hz), 6.28 (d, 1 H, H_6, J = 11.5 Hz), 6.71 (d, 1 H, H_9, J = 16 Hz), 7.01 (dd, 1 H, H_5, J = 15 Hz, J = 11.5 Hz), 7.80 (d, 1 H, H_4, J = 15 Hz). Anal. Calcd for $C_{27}H_{36}O_3$: C, 79.37; H, 8.88. Found: C, 79.59; H, 8.79.

9-(4′,4′,5′,7′,8′-Pentamethyl-6′-chromanyl)-3,7-dimethyl-(2*Z*,4*E*,6*E*,8*E*)-nona-2,4,6,8-tetraenoic acid (30b) was obtained by saponification of the ester **28b**, yield 60%, mp 195 °C dec. ^1H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 6 H, CH_3 on $C_{4'}$), 1.82–1.87 (m, 2 H, CH_2 on $C_{3'}$), 2.08, 2.13, 2.18, 2.22, 2.28 (5 s, 5 × 3 H, CH_3 on C_3, C_7, $C_{5'}$, $C_{7'}$, and $C_{8'}$), 4.13–4.18 (m, 2 H, CH_2 on $C_{2'}$), 5.65 (s, 1 H, H_2), 6.15 (d, 1 H, H_8, J = 16 Hz), 6.28 (d, 1 H, H_6, J = 10 Hz), 6.71 (d, 1 H, H_9, J = 16 Hz), 7.06 (dd, 1 H, H_5, J = 15 Hz, J = 10 Hz), 7.73 (d, 1 H, H_4, J = 15 Hz). Anal. Calcd for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48. Found: C, 78.77; H, 8.61.

Acknowledgment. Financial support by L'OREAL is gratefully acknowledged.

Registry No. 1*E*, 62054-49-3; 1*E* (dimethyl acetal), 65527-84-6; 1*Z* (dimethyl acetal), 70423-44-8; (±)-**2**, 94369-94-5; (±)-**3** (isomer 1), 118304-67-9; (±)-**3** (isomer 2), 118333-95-2; (±)-**3** (triol, isomer 1), 118304-71-5; (±)-**3** (triol, isomer 2), 118333-96-3; (±)-**4** (isomer 1), 118304-68-0; (±)-**4** (isomer 2), 118304-64-6; (±)-**4** (alkyne, isomer 1), 118304-70-4; (±)-**4** (alkyne, isomer 2), 118304-66-8; (±)-**5** (isomer 1), 118304-65-7; (±)-**5** (isomer 2), 118304-69-1; **6**, 118353-70-1; **6** (alcohol), 68-26-8; **6** (aldehyde), 116-31-4; **6** (acid), 302-79-4; (±)-**7**, 78646-59-0; **8**, 96928-85-7; **9**, 119947-50-2; **9** (triol), 119947-83-0; **10**, 62054-50-6; **11**, 119947-51-2; **12a**, 120306-88-9; **12b**, 119947-81-8; **12c**, 119947-82-9; **12** (triol), 119996-77-9; **13a**, 118304-54-4; **13b**, 118304-57-7; **13c**, 118304-60-2; **13** (alcohol), 2052-63-3; **13** (aldehyde), 472-86-6; **13** (acid), 59699-82-0; **13** (acid, ethyl ester), 4759-48-2; **14**, 697-82-5; **15**, 119947-52-3; (±)-**15** (epoxide), 119947-80-7; **16**, 119947-53-4; **17a**, 55646-01-0; **17b**, 40614-29-7; **18a**, 119947-54-5; **18b**, 119947-77-2; **19a**, 119947-55-6; **19b**, 119947-78-3; (±)-**20a**, 119947-56-7; (±)-**20b**, 119947-79-4; (±)-**21a** (isomer 1), 119947-57-8; (±)-**21a** (isomer 2), 119947-86-3; (±)-**21a** (triol, isomer 1), 119947-71-6; (±)-**21a** (triol, isomer 2), 119947-90-9; (±)-**21b** (isomer 1), 119947-63-6; (±)-**21b** (isomer 2), 119947-87-4; (±)-**21b** (triol, isomer 1), 119947-72-7; (±)-**21b** (triol, isomer 2), 119947-91-0; **22a**, 119947-58-9; **22a** (triol), 120306-91-4; **22b** (triol), 120306-92-5; **22b**, 119947-64-7; (±)-**23a** (isomer 1), 119947-59-0; (±)-**23a** (isomer 2), 119947-84-1; (±)-**23a** (alkyne isomer 1), 119947-69-2; (±)-**23a** (alkyne isomer 2), 119947-88-5; (±)-**23b** (isomer 1), 119947-65-8; (±)-**23b** (isomer 2), 119947-85-2; (±)-**23b** (alkyne isomer 1), 119947-70-5; (±)-**23b** (alkyne, isomer 2), 119947-89-6; **24a**, 120306-89-0; **24a** (5,6-didehydro), 120306-93-6; **24b**, 120306-90-3; **24b** (5,6-didehydro), 120306-94-7; **25a**, 119947-60-3; **25a** (alcohol), 119947-73-8; **25b**, 119947-66-9; **25b** (alcohol), 119947-74-9; **26a**, 120020-73-7; **26a** (alcohol), 120020-79-3; **26b**, 120020-76-0; **26b** (alcohol), 120020-80-6; **27a**, 119947-61-4; **27b**, 119947-67-0; **28a**, 120020-74-8; **28b**, 120020-77-1; **29a**, 119947-62-5; **29a** (aldehyde), 119947-75-0; **29b**, 119947-68-1; **29b** (aldehyde), 119947-76-1; **30a**, 120020-75-9; **30a** (aldehyde), 120020-81-7; **30b**, 120020-78-2; **30b** (aldehyde), 120020-82-8; $(MeO)_2CHCOCH_3$, 6342-56-9; β-ionone, 79-77-6.

6-Substituted Bicyclo[2.2.1]hept-5-en-2-one Ketals

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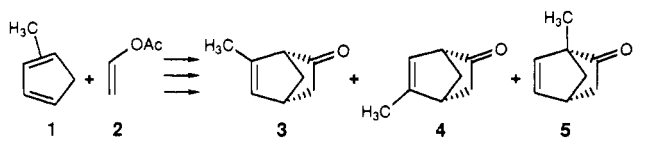
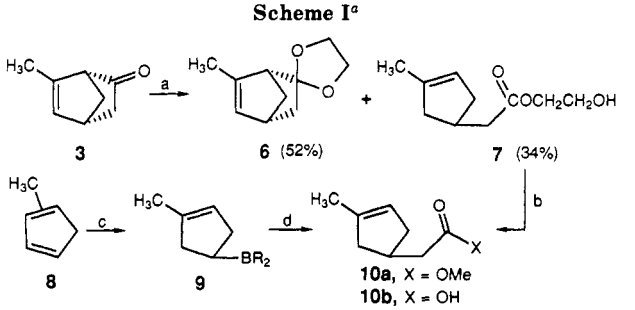
Structurally specific syntheses of isomerically pure 6-substituted bicyclo[2.2.1]hept-5-en-2-one ketals were explored. A conversion of the Diels–Alder adduct of itaconic anhydride with cyclopenta-1,3-diene into a ketal of 6-methylbicyclo[2.2.1]hept-5-en-2-one was accomplished, but the last step, an oxidative vicinal bisdecarboxylation, gave only a 35% yield. The ethylene ketal of 6-methylbicyclo[2.2.1]hept-5-en-2-one was prepared in 80% overall yield from bicyclo[2.2.1]hept-5-en-2-one by a regioselective replacement of hydrogen with a methyl group. Practical syntheses of the 6-bromo, 6-carbomethoxy, 6-phenylthio, and 6-trimethylsilyl analogues were accomplished similarly.

We recently demonstrated that carbonyl-masked derivatives of 6-methylbicyclo[2.2.1]hept-5-en-2-one (**3**) are valuable intermediates for the total synthesis of spatane diterpenes.[1] A Diels–Alder strategy provides a practical route to multimolar quantities of 6-methylbicyclo[2.2.1]-hept-5-en-2-one (**3**) from methyl-1,3-cyclopentadiene (**1**) and vinyl acetate (**2**)[2] since the isomeric coproducts **4** and **5** are separable by spinning-band distillation.[2d] However,



Scheme I[a]



[a] (a) Ethylene glycol/*p*-TsOH/benzene/Dean–Stark trap/boil 2.5 h; (b) *p*-TsOH/THF/H_2O/boil/48 h, then CH_2N_2/ether; (c) borane/THF; (d) t-BuOH/t-BuOK/$BrCH_2COOMe$, then 1 N $NaOH/H_2O_2$.

ethylene ketalization of **3** gave the ketal in disappointingly low yield (vide infra) under conditions that give an excellent yield of ketal from the 6-unsubstituted analogue bicyclo[2.2.1]hept-5-en-2-one.[3] To improve the availability

(1) Salomon, R. G.; Sachinvala, N. D.; Raychaudhuri, S. R.; Miller, D. B. *J. Am. Chem. Soc.* **1984**, *106*, 2211.

(2) (a) Krieger, H.; Mason, S.-E. *Suomen Kemistilehti B* **1970**, *43*, 318. (b) Mason, S.-E.; Krieger, H. *Ibid.* **1969**, *42*, 1. (c) Brown, H. C.; Peters, E. N.; Ravindranathan, M. *J. Am. Chem. Soc.* **1975**, *97*, 7449: the procedure is easily performed on a multikilogram scale, and the reported yield of **3** can be more than doubled by employing Swern rather than Jones oxidation of intermediate methylbicyclo[2.2.1]hept-5-enols. (d) Goering, H. L.; Chang, C.-S. *J. Org. Chem.* **1975**, *40*, 2565.

(3) Monti, S. A.; Yuan, S.-S. *J. Org. Chem.* **1971**, *36*, 3350.

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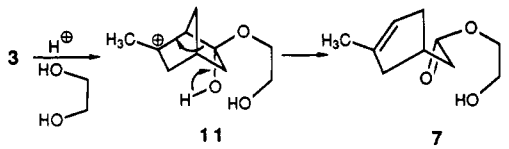
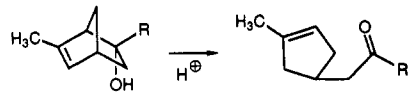
of such potentially useful intermediates and obviate the necessity for a tedious separation of undesired isomeric coproducts, structurally specific syntheses of isomerically pure 6-substituted bicyclo[2.2.1]hept-5-en-2-one ketals were explored.

Results and Discussion

Ethylene Ketalization of 3. Unfortunately, fragmentation producing **7** competes with ketalization of **3** (Scheme I). The structure of the byproduct **7** was confirmed by an unambiguous synthesis. Hydroboration of methylcyclopenta-1,3-diene (**8**) generates borane **9**, which gave ester **10a** in low yield upon reaction with methyl bromoacetate.[4] Both **7** and **10a** afford the same acid **10b** upon hydrolysis. The profound influence of the methyl group in **3** undoubtedly stems from its ability to stabilize a pivotal carbenium ion intermediate **11**. A similar mechanism accounts for the acid-catalyzed fragmentations of bicyclo[2.2.1]heptenols **12h** and **12m** to cyclopentenes **10h** and **10m**.[5]



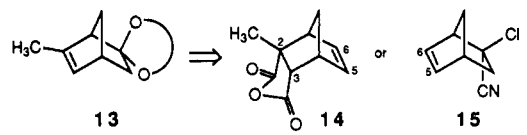
11 **7**



12h, R = H
12m, R = CH_3

10h, R = H (99%)
10m, R = CH3 (90%)

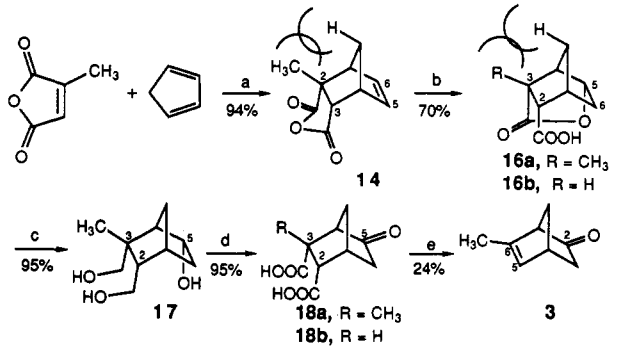
Two intriguing strategies for syntheses of ketals **13** of **3** depend on regioselective functionalization of readily available Diels–Alder adducts **14** and **15**. The starting material **14** contains the unsaturation of **13** in latent form as a vicinal dicarboxylic acid, and requires regioselective addition of oxygen functionality at the 6-position. The starting material **15** contains the oxygen functionality of **13** in latent form as an α-chloronitrile, and requires addition of a methyl substituent at the 6-position.



13 **14** **15**

A Synthesis from Citraconic Anhydride. Regioselective functionalization of the 5,6-C=C bond in **14** is readily achieved (see Scheme II) by acid-catalyzed addition of the *endo*-2-carboxyl group.[6] The preference for this cyclization over the alternative possibility involving the *endo*-3-carboxyl group may arise from a decrease in steric strain between the 2-methyl group and *syn*-7-H concomitant with the former but not the latter cyclization. The influence of the C(2) methyl substituent on the stability of the lactone in **16a** is evident from the contrasting behavior of the unsubstituted analogue **16b** upon saponification with KOH followed by oxidation with $NaIO_4$ and RuO_2. Under these conditions **16b** is transformed into **18b** in 68% yield,[7] but we recovered **16a** unchanged presumably because this lactone is refractory toward cleavage by base. Cleavage of the lactone was therefore achieved reductively. Oxidation of the intermediate triol **17** proceeded smoothly, delivering the keto diacid **18a** in excellent yield upon treatment with $KMnO_4$ in NaOH. The efficacy of this reagent was unexpected since it has been suggested that "oxidations of the type **19** → **20** using $KMnO_4/HO^-$ give poor yields".[7a]

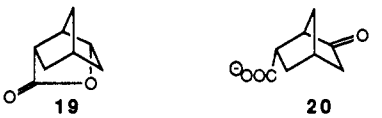
Scheme II[a]



14 **16a**, R = CH_3 **16b**, R = H

17 **18a**, R = CH_3 **18b**, R = H **3**

[a] (a) 60 °C/24 h; (b) 50% H_2SO_4/60 °C/2 h; (c) LAH/THF; (d) $KMnO_4$/NaOH; (e) Pt anode (300 mA)/Et_3N/pyridine–H_2O (9:1)/18–20 °C/32 h.

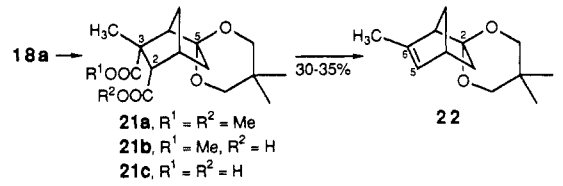


19 **20**

Thus, the penultimate product of Scheme I, the vicinal dicarboxylic acid **18a**, is readily available by a short and efficient synthesis from citraconic anhydride and 1,3-cyclopentadiene. Oxidative bisdecarboxylation providing alkenes in good yields from vicinal dicarboxylic acids has been accomplished in several cases. However, oxidative bisdecarboxylation of **18a** could not be achieved in satisfactory yield with any of the reagents or reaction conditions examined. Reaction with $Pb(OAc)_4$ under a variety of conditions[8] failed to deliver more than a few percent yield of the desired unsaturated ketone **3**. Reaction of keto diacid **18a** with Cu_2O and 2,2′-dipyridyl in quinoline[9] gave a 10% yield of **3**. The best yield of **3**, 24%, was obtained by electrochemical oxidative decarboxylation of **18a** in aqueous pyridine–triethylamine.[10]

Keto diacid **18a** was converted into the corresponding ketal diacid **21c** through an intermediate diester **21a**. Interestingly, bissaponification of **21a** could only be achieved under harsh conditions (KO-t-Bu/DMSO/70 °C/12 h). Under milder conditions only monosaponification producing **21b** occurred, presumably owing to steric congestion around the carbomethoxyl at position 6. Yields for oxidative decarboxylation of **21c** were somewhat improved in comparison with those from the keto diacid **18a**, perhaps because the unsaturated ketal product **22** is less volatile than the unsaturated ketone product **3**. Reaction

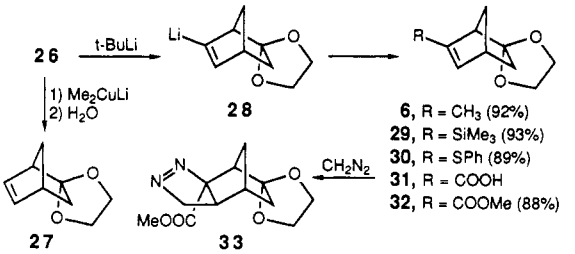
(4) Brown, H. C.; Rogic, M. M.; Rathke, M. W.; Kabalka, G. W. *J. Am. Chem. Soc.* **1968**, *90*, 818.
(5) Lajunen, M.; Lyytikainen, H. *Acta Chem. Scand.* **1981**, *A35*, 139.
(6) Nazerov, I. N.; Kucherov, V. F.; Bukharov, V. G. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1957**, 95.
(7) (a) Moriarty, R. M.; Gopal, H.; Adams, T. *Tetrahedron Lett.* **1970**, 4003. (b) Gopal, H.; Adams, T.; Moriarty, R. M. *Tetrahedron* **1972**, *28*, 4259.
(8) (a) Chapman, N. B.; Sotheeswaran, S.; Toyne, K. J. *J. Chem. Soc., Chem. Commun.* **1965**, 214. (b) Cimarsti, C. M.; Wolinski, J. *J. Am. Chem. Soc.* **1968**, *90*, 113. (c) Wagner, H. P. *Org. React.* **1972**, *19*, 362. (d) Thummel, R. P.; Natukul, W. *J. Org. Chem.* **1977**, *42*, 300.
(9) Snow, R. A.; Degenhardt, C. R.; Paquette, L. A. *Tetrahedron Lett.* **1976**, 4447.
(10) (a) Westberg, H. H.; Dauben, H. J., Jr. *Tetrahedron Lett.* **1968**, 5123. (b) Ebberson, L.; Utley, J. H. P. In *Organic Electrochemistry*, 2nd ed.; Baizer, M. M., Lund, H., Eds.; Marcel Dekker: New York, 1983; p 457 and references cited therein.



of **21c** with $Pb(OAc)_4$ in pyridine[8b] provided unsaturated ketal **22** in 7% yield, while reaction with Cu_2O and 2,2′-dipyridyl in pyridine or quinoline[9] delivered **22** in 20% yield. Again, the best yields of oxidative vicinal decarboxylation were achieved elctrochemically. With a homogeneous reaction mixture in aqueous pyridine–triethylamine[10] the desired unsaturated ketal **22** was obtained in 20–25% yields. Some improvement was realized by using a two-phase reaction mixture. Thus, electrochemical oxidative vicinal bisdecarboxylation of **21c** in aqueous pyridine–triethylamine overlayered with *n*-heptane reproducibly delivered unsaturated ketal **22** in 30–35% yields.

Synthesis from α-Chloroacrylonitrile. Particularly attractive as a starting material is the unsubstituted bicyclo[2.2.1]heptenone **23**, which is readily available in multimolar quantities from inexpensive starting materials.[11,12] Thus, Diels–Alder reaction of 1,3-cyclopentadiene with α-chloroacrylonitrile provides an α-chloronitrile **15**, which is readily hydrolyzed in basic aqueous DMSO to afford **23** in 70% yield overall. A remarkably regioselective functionalization of the 5,6-C=C bond in **23** can be accomplished through bromoselenation-deselenation as outlined in Scheme III. Homoconjugative electron donation by the carbonyl group favoring electronic deficiency at the 6-position in an intermediate selenonium ion may account for the regioselectivity of the electrophilic addition.[13] Alternatively, steric hindrance by the 3-endo hydrogen of endo attack at the 5-position may orient the addition. Whatever the reason, the selenide **24** is obtained quantitatively as a crystalline solid (mp 75–7 °C) upon reaction of **23** with phenylselenyl bromide. Subsequent oxidative deselenation under carefully controlled conditions (see Experimental Section) provides 6-bromobicyclo[2.2.1]hept-5-en-2-one (**25**) in 91% yield overall from the hydrocarbon **23**. Moreover, diphenyl diselenide can be recovered by reduction of $PhSeO_2H$ with $NaHSO_3$. Since a vinyl bromide is less reactive than the corresponding methylalkene toward protonation, a fragmentation of vinyl bromide–ketone **25** analogous to that observed during ketalization of 6-methylbicyclo[2.2.1]hept-5-en-2-one (**3**) does not occur. Rather, ketal **26** is obtained quantitatively from ketone **25**.

Nucleophilic methylation of vinyl bromide–ketal **26** with lithium dimethylcuprate[14] was plagued by metal–halogen exchange followed by protonation during aqueous workup of the organocopper derivative from **26**. The resulting net reductive debromination[14,15] produces the ethylene ketal **27** of the starting ketone **23** instead of the desired methylation product **6**. Addition of methyl iodide to the reaction mixture prior to aqueous workup improved the **6** to **27** ratio only slightly. Apparently the vinylcopper intermediate produced by metal–halogen exchange is only poorly reactive toward methylation. We therefore prepared the more reactive vinyllithium derivative **28** from vinyl bromide **26** by lithium–bromine exchange. Electrophilic methylation of **28** with methyl iodide delivered the target methylalkene **6** in excellent yield. Other 6-substituted bicyclo[2.2.1]hept-5-en-2-one ketals **29–31** were also readily available from **28** by silylation, phenylsulfenylation, or carboxylation, respectively. Not surprisingly, methylation of the carboxylic acid **31** with diazomethane was accompanied by 1,3-dipolar cycloaddition affording pyrazoline **33**. However, the methyl ester **32** was easily obtained in 88% overall yield from vinyl bromide **26** by methylation of the intermediate acid **31** with methanol and dicyclohexylcarbodiimide.



Experimental Section

General Procedures. Reaction conditions, solvent purification, and chromatographic and spectroscopic methods were described previously.[16] ^1H NMR spectra were recorded at 200 MHz in $CDCl_3$ unless stated otherwise. ^{13}C NMR spectra were recorded at 50.31 MHz. Hydrogen substitution on C atoms was determined as described previously.[16] The (+) and (–) signs refer to peaks above (singlet and triplet) and below (doublet and quartet) the base line, respectively.

5-*endo*-Hydroxy-3-*exo*-methylbicyclo[2.2.1]heptane-2-*endo*,3-*endo*-dimethanol (17). Lactone acid **16a** (9.81 g, 0.05 mol) was added in portions (~0.5 g) to a stirring suspension of $LiAlH_4$ (6.83 g, 0.18 mol) in anhydrous THF (150 mL) at 0 °C under argon over 30 min. The reaction mixture was allowed to come to room temperature and then boiled 12 h under reflux with mechanical stirring. It was cooled to 0 °C and then successively treated with water (7 mL), 15% aqueous NaOH (7 mL), and water (20 mL). The organic layer was filtered off, and the white residue was washed with THF (4 × 100 mL). The combined organic filtrates were concentrated under reduced pressure, and the residue thus obtained was crystallized from ethyl acetate to give triol **17** (8.80 g, 94.5%): mp 215–6 °C; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 4.60 (d, J = 4.2 Hz, H, OH, D_2O exchanged), 4.20 (t, J = 4.2 Hz, H, OH, D_2O exchanged), 4.07 (m, H), 3.40–3.78 (m, 5 H, 1 H, D_2O exchanged), 2.11 (m, H), 1.84 (m, H), 1.61–1.78 (m, 2 H), 1.39 (m, H), 1.06–1.26 (m, 2 H), 0.93 (s, 3 H); HRMS calcd for $C_{10}H_{18}O_3$ 186.1256, found 186.1266; MS *m/z* (relative intensity) 186 (3.7, M^+), 170 (4.7), 169 (9.7), 138 (100), 122 (11.7), 120 (23.2), 107 (74.2), 91 (45.6), 79 (85.9).

3-*exo*-Methyl-5-oxobicyclo[2.2.1]heptane-2-*endo*,3-*endo*-dicarboxylic Acid (18a). A solution of $KMnO_4$ (19.76 g, 125 mmol) in water (300 mL) was added to a mechanically stirred solution of triol **17** (4.66 g, 25 mmol) in 1 N NaOH (30 mL) at 0 °C over 30 min. The reaction mixture was stirred 16 h at 8–10 °C. Excess $KMnO_4$ was decomposed with aqueous sodium sulfite solution. The precipitate thus formed was filtered off, and the filtrate was acidified to pH 3 with dilute aqueous HCl. Water was evaporated under reduced pressure. The dried residue thus obtained was extracted with hot ethyl acetate (3 × 75 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give crystals of keto dicarboxylic acid **18a**: yield 5.05 g (95%); mp 185–6 °C; ^1H NMR

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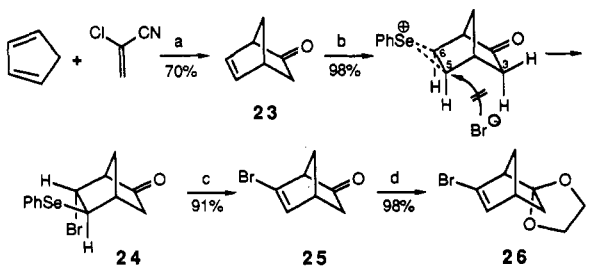
Scheme III[a]



[a] (a) Benzene/50 °C/3 h, then KOH/DMSO/H_2O; (b) PhSeBr/THF/−78 °C/3 h; (c) H_2O_2/THF/AcOH; (d) $HOCH_2CH_2OH$/*p*-TsOH/benzene.

($CDCl_3$ + DMSO-d_6) δ 2.26–2.53 (m, 4 H), 1.38–1.78 (m, 3 H), 1.14 (s, 3 H); HRMS calcd for $C_{10}H_{12}O_5$ 212.0684, found 212.0687; MS *m/z* (relative intensity) 212 (0.2, M^+), 195 (9.4), 168 (10.9), 138 (27.8), 120 (10.3), 93 (11.2), 80 (14.8).

6-*endo*-Bromo-5-*exo*-(phenylseleno)bicyclo[2.2.1]heptan-2-one (24). Benzeneselenyl bromide (23.4 g, 0.1 mol), prepared from diphenyl diselenide (15.4 g, 49.5 mmol) and bromine (2.5 mL, 7.9 g, 49.6 mmol) in THF (75 mL), was added over 30 min to a stirring solution of bicyclo[2.2.1]hept-5-en-2-one **23**[12] (10.8 g, 0.1 mol) in THF (75 mL) at −78 °C under argon. The resulting yellow solution was stirred 2 h at −78 °C and was allowed to come to room temperature. The solvent was removed under reduced pressure, and the residue thus obtained was dissolved in ethyl acetate (200 mL) and decolorized with Darco G-60 activated carbon (5 g) and filtered. The solvent was removed under reduced pressure, and the residue thus obtained was crystallized from ethyl acetate–hexanes to give selenide **24** (33.5 g, 97.4%): mp 75–7 °C; ^1H NMR δ 7.56–7.70 (m, 2 H), 7.25–7.43 (m, 3 H), 4.24 (t, *J* = 3.8 Hz, H), 3.55 (t, *J* = 3 Hz, H), 2.86 (d, *J* = 4.4 Hz, H), 2.74 (d, *J* = 4 Hz, H), 0.79–1.40 (m, 4 H); ^{13}C NMR δ 35.69 (+, t), 42.64 (−, d), 44.40 (+, t), 48.72 (−, d), 52.63 (−, d), 57.57 (−, d), 128.21 (−, d), 128.38 (+, s), 129.32 (−, d, 2 C), 134.55 (−, d, 2 C), 209.89 (+, s). Anal. Calcd for $C_{13}H_{13}BrOSe$: C, 45.37; H, 3.81. Found: C, 45.37; H, 3.70.

6-Bromobicyclo[2.2.1]hept-5-en-2-one (25). Hydrogen peroxide[17] (2.27 mL, 30% wt solution in water, 0.68 g, 20 mmol) was added, dropwise, to a stirring solution of selenide **24** (3.4 g, 10 mmol) and acetic acid (0.7 mL, 0.74 g, 12.2 mmol) in anhydrous THF (25 mL) at −20 °C. *The oxidation is exothermic, and it is necessary to add H_2O_2 slowly.* The resulting mixture was allowed to come to 20–22 °C over 30 min (bubbling starts at ~18 °C) and stirred for an additional 90 min below 25 °C. The reaction mixture was poured into ether (350 mL), extracted with water (3 × 10 mL), saturated aqueous Na_2CO_3 solution (3 × 5 mL), and again with water (3 × 10 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The product thus obtained was purified by flash chromatography (10% ethyl acetate in hexanes) to give **25** (1.70 g, 91%): ^1H NMR δ 6.56 (d, *J* = 3 Hz, H), 3.23 (m, H), 3.01 (m, H), 2.47 (m, H), 1.95–2.05 (m, 3 H); HRMS calcd for $C_7H_7{}^{81}BrO$ 187.9658, found 187.9657 (for $C_7H_7{}^{79}BrO$ 185.9678, found 185.9676); MS *m/z* (relative intensity) 188 (3.3, M^{2+}), 186 (3.0, M^+), 146 (20.6), 144 (20.6), 123 (19.1), 94 (21.7), 80 (100), 71 (16.8), 65 (40.8), 57 (37.5). *Note: When this reaction was done in the absence of acetic acid, a complex mixture was formed. Moreover, it is important to note that the reaction mixture should be poured into ether and then extracted with aqueous Na_2CO_3 solution during workup to remove acetic acid and phenylselenic acid.* Alternative oxidative deselenation methods using $NaIO_4$–MeOH/H_2O[18] or pyridine/CH_2Cl_2/30% H_2O_2[19] gave only 37–40% yield of olefin **25**. The selenide **25** is light sensitive and was therefore oxidatively deselenated immediately.

Recovery of Diphenyl Diselenide.[20] The alkaline aqueous extracts containing $PhSeO_2^-Na^+$ were neutralized with acetic acid followed by reduction with excess $NaHSO_3$ to give yellow powdery PhSeSePh, which was collected by filtration and dried in the air (~65% recovery).

6-Bromobicyclo[2.2.1]hept-5-en-2-one Ethylene Ketal (26). A mixture of ketone **25** (1.5 g, 8.0 mmol), ethylene glycol (1.0 mL, 1.1 g, 17.9 mmol), and *p*-toluenesulfonic acid (10 mg, 0.05 mmol) in benzene (10 mL) was boiled 2 h under reflux with continuous separation of water using a Dean–Stark trap. The reaction mixture was cooled to room temperature, and then diluted with ether (40 mL), washed with saturated aqueous $NaHCO_3$ solution (2 × 1 mL) and water (3 × 2 mL), dried ($MgSO_4$), and filtered, and the solvent was removed with a rotary evaporator at ~30 °C to give ethylene ketal **26** (1.8 g, 98%): ^1H NMR δ 6.32 (d, *J* = 3.2 Hz, H), 3.84–4.17 (m, 4 H), 2.85 (m, H), 2.71 (m, H), 1.84–2.03 (m, 2 H), 1.58–1.82 (m, 2 H). Anal. Calcd for $C_9H_{11}BrO_2$: C, 46.77; H, 4.80. Found: C, 46.67; H, 4.86.

6-Methylbicyclo[2.2.1]hept-5-en-2-one Ethylene Ketal (6). *tert*-Butyllithium (3.9 mL, 1.6 M solution in pentane, 6.3 mmol) was added to a stirring solution of bromide **26** (0.58 g, 2.5 mmol) in anhydrous THF (10 mL) at −78 °C under argon over 15 min. After the mixture was stirred for an additional 15 min, anhydrous methyl iodide (0.39 mL, 0.89 g, 6.3 mmol) was added. The resulting pale yellow solution was stirred for 1 h, warmed to −20 °C, and then saturated aqueous NH_4Cl solution (2 mL) was added. The reaction mixture was allowed to come to room temperature and was then diluted with ether (50 mL). The organic layer was washed with brine (3 × 5 mL), dried ($MgSO_4$), and filtered, and the solvent was removed with a rotary evaporator at ~30 °C to give ethylene ketal **6** (0.38 g, 92%): ^1H NMR δ 5.78 (br s), 3.80–4.02 (m, 4 H), 2.67 (br s, H), 2.38 (br s, H), 1.84 (d, *J* = 3.8 Hz, H), 1.78 (d, *J* = 1.6 Hz, 3 H), 1.65 (br s, 2 H), 1.48 (m, H); ^{13}C NMR δ 17.06 (−, q), 40.21 (+, t), 40.38 (−, d), 48.71 (+, t), 53.29 (−, d), 63.94 (+, t), 64.58 (+, t), 118.46 (+, s), 131.06 (−, d), 143.84 (+, s); HRMS calcd for $C_{10}H_{14}O_2$ 166.0990, found 166.0995; MS *m/z* (relative intensity) 166 (7.5, M^+), 151 (1.3), 138 (1.0), 121 (0.8), 105 (1.50), 86 (100), 80 (24.4), 65 (3.5), 57 (4.5).

6-(Trimethylsilyl)bicyclo[2.2.1]hept-5-en-2-one Ethylene Ketal (29). *tert*-Butyllithium (1.80 mL, 1.5 M in pentane, 2.70 mmol) was added to a stirring solution of bromide **26** (250 mg, 1.08 mmol) in anhydrous THF (5 mL) at −78 °C under argon over 15 min. After the mixture was stirred for an additional 15 min, freshly distilled trimethylsilyl chloride (275 mL, 235 mg, 2.16 mmol) was added. The resulting pale yellow solution was stirred 1 h and then warmed to −20 °C, and saturated aqueous NH_4Cl (0.5 mL) was added. The reaction mixture was allowed to come to room temperature and was then diluted with ether (20 mL). The organic layer was separated, and the aqueous layer was extracted with ether (2 × 3 mL). The combined organic extracts were warmed with brine (3 × 1 mL), dried ($MgSO_4$), and filtered, and the solvent was removed with a rotary evaporator to give **29** (225 mg, 93%): ^1H NMR δ 6.52 (d, *J* = 2.8 Hz, H), 3.71–3.96 (m, 4 H), 2.75 (br s, H) 2.65 (br s, H), 1.79 (dd, *J* = 3.4 and 12.2 Hz, H), 1.70 (m, H), 1.52 (m, H), 1.37 (dd, *J* = 3.4 and 12.2 Hz, H), −0.03 (s, 9 H); ^{13}C NMR δ −1.43 (−, q, 3 C), 40.12 (+, t), 41.89 (−, d), 50.00 (+, t), 52.01 (−, d), 64.10 (+, t), 64.70 (+, t), 118.16 (+, s), 147.34 (+, s), 149.12 (−, d); HRMS calcd for $C_{12}H_{20}O_2Si$ 224.1233, found 224.1237; MS *m/z* (relative intensity) 224 (3.0, M^+), 218 (6.2), 168 (6.0), 143 (22.4), 99 (12.1), 86 (83.7), 73 (46.6), 60 (36.8), 45 (100).

6-(Phenylthio)bicyclo[2.2.1]hept-5-en-2-one Ethylene Ketal (30). Bromide **26** (250 mg, 1.08 mmol) was lithiated with *tert*-butyllithium (1.80 mL, 1.5 M in pentane, 2.70 mL) in THF (5.0 mL) according to the procedure described for **29** and then sulfenated with diphenyl disulfide (472 mg, 2.16 mmol). The crude product was purified by flash chromatography (5% ethyl acetate in hexanes) to give **30** (250 mg, 89%): ^1H NMR δ 7.17–7.44 (m, 5 H), 6.27 (d, *J* = 2.8 Hz, H), 3.75–4.04 (m, 4 H), 2.91 (br s, H), 2.65 (br s, H), 1.95 (dd, *J* = 3.8 and 12.4 Hz, H), 1.86 (m, 2 H), 1.62 (dd, *J* = 3.4 and 12.4 Hz, H); ^{13}C NMR δ 39.57 (+, t), 41.78 (−, d), 48.17 (+, t), 52.35 (−, d), 128.91 (−, d, 2 C), 130.13 (−, d, 2 c), 135.00 (+, s), 138.43 (−, d), 139.16 (+, s); HRMS calcd for

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$C_{15}H_{16}O_2S$ 260.0872, found 260.0876; MS m/z (relative intensity) 260 (28.1, M^+), 173 (100), 129 (19.1), 109 (54.1), 86 (56.0), 77 (69.4), 65 (58.2), 53 (29.2), 42 (40.2).

Methyl 6-Oxobicyclo[2.2.1]hept-2-ene-2-carboxylate Ethylene Ketal (32). *tert*-Butyllithium (1.80 mL, 1.5 M in pentane, 2.70 mmol) was added to a stirring solution of bromide **26** (250 mg, 1.80 mmol) in anhydrous THF (5 mL) at -78 °C under argon over 15 min. After the mixture was stirred for an additional 15 min, bone-dry CO_2 gas was bubbled through the reaction mixture, which was then allowed to come to room temperature. Then the solvent was removed with a rotary evaporator. The crude carboxylic acid thus obtained was dissolved in water (5 mL), acidified with aqueous citric acid (2 mL), and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine (3 × 1 mL), dried ($MgSO_4$), and filtered, and the solvent was removed with a rotary evaporator. The carboxylic acid **31** thus obtained was dissolved in CH_2Cl_2 (5 mL). (Dimethylamino)pyridine (25 mg, 0.2 mmol) and methanol (125 μL, 99 mg, 3.09 mmol) were added, and the mixture was cooled to 0 °C. Dicyclohexylcarbodiimide (300 mg, 1.45 mmol) was added. The mixture was warmed to room temperature and stirred for 8 h. Dicyclohexylurea which formed was filtered off, and the filtrate was concentrated on the rotavapor. The residue thus obtained was purified by flash chromatography (30% ethyl acetate in hexanes) to give **32**, which was crystallized from hexanes: yield 200 mg (88%); mp 75-70 °C; ^1H NMR δ 7.16 (d, J = 3.2 Hz, H), 3.87-4.08 (m, 4 H), 3.74 (s, 3 H), 3.12 (br s, H), 2.98 (br s, H), 2.02 (dd, J = 4.0 and 14.0 Hz, H), 1.82 (br s, 2 H), 1.60 (m, H); ^{13}C NMR δ 38.20 (+, t), 41.84 (-, d), 48.39 (-, d), 48.57 (+, t), 51.36 (-, q), 64.18 (+, t), 64.70 (+, t), 117.15 (+, s), 139.19 (+, s), 149.32 (-, d), 165.05 (+, s); HRMS calcd for $C_{11}H_{14}O_4$ 210.0892, found 210.0897; MS m/z (relative intensity) 210 (10.2, M^+), 135 (3.5), 119 (2.6), 86 (100), 65 (17.7), 42 (52.7).

Reaction of 31 with Diazomethane. The carboxylic acid **31** was methylated with an ether solution of CH_2N_2. After the usual workup the residue thus obtained was purified by flash chromatography (30% ethyl acetate, in hexane) to give pyrazoline **33**, which was crystallized from ethyl acetate-hexanes: yield 218 mg (80%); mp 101-3 °C; ^1H NMR δ 4.78 (m, H), 4.31 (m, H), 3.83-4.07 (m, 4 H), 3.78 (s, 3 H), 3.10 (br s, H), 2.49 (d, J = 9.0 Hz, H), 2.02 (br s, H), 0.70 (d, J = 11.6 Hz, H); ^{13}C NMR δ 32.91 (+, t), 38.94 (-, d), 40.90 (-, d), 42.50 (+, t), 85.32 (+, t), 107.71 (+, s), 114.50 (+, s), 168.44 (+, s); HRMS calcd for $C_{12}H_{16}N_2O_4$ 252.1111, found 252.1114; MS m/z (relative intensity) 252 (0.3, M^+), 218 (0.3), 149 (3.4), 112 (4.3), 91 (6.5), 86 (100), 77 (9.5), 42 (11.2).

6-Methylbicyclo[2.2.1]hept-5-en-2-one (3). A solution of ethylene ketal **6** (83 mg, 0.5 mmol), *p*-toluenesulfonic acid (0.5 mg), and water (0.1 mL) in THF (5 mL) was boiled 8 h under reflux with stirring. The reaction mixture was diluted with *n*-pentane (15 mL), extracted with aqueous $NaHCO_3$ solution (1 × 0.5 mL) and brine (2 × 1 mL), dried ($MgSO_4$), and filtered, and the solvent was removed with a rotary evaporator at ~20 °C to give **3** (58 mg, 95%).

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Registry No. **3**, 19740-15-9; **6**, 119595-31-2; **7**, 119619-05-5; **10a**, 119595-33-4; **10b**, 119595-30-1; **14**, 18310-60-6; **16a**, 119678-61-4; 3-epi-**16a**, 119677-59-7; 3-epi-**16a** methyl ester, 119677-60-0; **17**, 119595-36-7; **18a**, 119595-37-8; **18a** dimethyl ester, 119595-32-3; **21a**, 119595-38-9; **21b**, 119595-34-5; **21c**, 119595-35-6; **22**, 119595-39-0; **23**, 694-98-4; **24**, 83205-20-3; **25**, 119677-61-1; **26**, 119595-40-3; **27**, 31444-18-5; **29**, 119595-41-4; **30**, 119595-42-5; **31**, 119595-43-6; **32**, 119595-44-7; **33**, 119595-45-8; PhSeSePh, 1666-13-3; diphenyl disulfide, 882-33-7; methylcyclopentadiene, 26519-91-5; methyl bromoacetate, 96-32-2; benzeneselenyl bromide, 34837-55-3.

Supplementary Material Available: Experimental details for ethylene ketalization of **3**, as well as preparation of **7**, **10a**, **10b**, **16a**, **21a**, **21b**, **21c**, and **22** and oxidative decarboxylation of **18a** and **21c** (8 pages). Ordering information is given on any current masthead page.

Metacyclophanes and Related Compounds. 24. Preparation and Reaction of Trimethyl[2.2.2]- and Tetramethyl[2.2.2.2]metacyclophane[1]

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8,16,24,32-Tetramethyl[2.2.2.2]- and 8,16,24-trimethyl[2.2.2]metacyclophane (**9** and **10**) were prepared by using the *tert*-butyl group as a positional protective group. Friedel-Crafts acylation of **9** and **10** afforded the corresponding ketones, **12** and **13**, respectively. ^1H NMR spectra indicate that, to avoid the unfavorable steric repulsion among three internal methyl groups, [2.2.2]metacyclophane **10** and its derivatives take a folded form rather than a stepped one.

Host-guest chemistry has been developing in the last two decades.[2] Many macrocyclic compounds were employed as host molecules, especially cyclodextrins and calixarenes, which have attracted major interest, since they form inclusion complexes with various hydrophobic guests in aqueous solution. Also, up to now, there has been much work on the syntheses and inclusion properties of macrocyclic cyclophanes[3] in which, the designing of artificial cavities of various sizes is possible; thus, insight into the relationship between the size of a guest molecule and that of the cavities of a host molecule may be obtained. In this context, it is of interest to modify the cyclophane cavities by introducing functional group(s) into macrocyclophanes. Such chemical modification has been limited, however, because the preparation of large quantities of macrocyclophanes is not easy.

Previously, we developed convenient preparative routes for a series of [2.2]metacyclophanes using the *tert*-butyl

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