Clearly species 2 is the least "homoaromatic" or "anthracene-like" and the most "annulene-like".

The fact that carbon 7 is the thermodynamically favored protonation site in 3 but not in 2 follows the same pattern and agrees with simple frontier MO theory considerations. Most likely, in 2 the increased strain in the central ring caused by protonation at positions 7 or 14 is not compensated by transannular stabilization as it is in the case of cation 3. Thus in superacid media the most stable species from 2 is the unsymmetrical ion protonated at carbon 2.

Although these considerations are consistent with the observation that overall 3 is deuteriated somewhat faster than 2 in weaker acids (CF_3COOD) and that position 7 in 2 is more resistant to deuterium exchange than the corresponding position in 3, the fact that carbon 7 is kinetically the least reactive site for exchange in both 2 and 3 makes it clear that an interpretation of the exchange rates is impossible without a consideration of the relative kinetic acidities of the exo and the endo protons, in the protonated form.

(ii) Failure To Form a Dication. In the series of dianions generated from 2, 3, and 4, the paratropism is observed to decrease[4] as the annulene rings become less planar and the transannular interaction increases. As these 4N-electron species are gradually transformed from "annulene-like" to "homoaromatic", or "anthracene-like", their antiaromaticity decreases. In keeping with the preceding discussion, the more strongly antiaromatic dication of 2 would be expected to be less stable and more strongly paratropic than the dications of 3 and 4. It is tempting to attribute the failure of the ion **2B** to form to its more annulene-like nature, although the explanation may also simply be that a facile rearrangement route is available to the monocation **2A** but not to **1A**, **3A**, and **4A**, preempting the oxidation to the dication.

(iii) Broadening of the Aliphatic ^1H NMR Signals in CF_3COOH. Both 2 and 3 show exchange broadening in the aromatic region of the ^1H NMR spectrum in CF_3COOH, attributed to the reversible protonation of the ring. The mechanism of the protonation and the small effects it has on the line widths of the aromatic proton signals are not understood in detail.

The aliphatic protons of 3 are unaffected by this exchange process while the bridgehead protons of 2 broaden dramatically (compare Figures 5a and 6) in spite of the fact that the net exchange is proceeding at comparable rates for both. The ^{13}C NMR spectra show no change in either system. This rules out electron exchange of the type seen for octamethylbiphenylene in the same solvent system.[14] It is known[2a] that the hyperfine coupling of the bridgehead protons in the radical cation of 2 is much larger than in that of 3. This is understood in terms of the better overlap of the bridgehead π-p AO's with the aliphatic C-H bond in the former. A similar hyperconjugative interaction in our diamagnetic protonated cations **2A** and **3A** would account for a chemical shift perturbation of hydrogen 15 in 2, not seen in 3. An analogous change in chemical shift should result from the interruption of the ring current by protonation. This, however, would be expected to occur in both 2 and 3, and this is not observed.

In summary, the factors responsible for the differences in the spectral properties of 1, the bridged annulenes **1A**–**4A**, and dications **1B**, **3B**, and **4B**, primarily varying degrees of transannular interaction, can also be invoked to rationalize the thermodynamics of the protonation behavior of 1–4. However, additional factors, such as steric hindrance to deprotonation, dictate the deuterium exchange rates in these annulenes.

Acknowledgment. This work was supported by the National Institute of Health (GM 37929) and the National Science Foundation (CHE 8796257).

(14) Hart, H.; Teuerstein, A.; Babin, M. A. *J. Am. Chem. Soc.* **1981**, *103*, 903.

Synthesis of *exo*-Bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic Anhydrides by Thermal Isomerization of *trans*-Diacids

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Bicyclo[2.2.2]oct-5-ene-*trans*-1,2-dicarboxylic acid and substituted analogues afford mixtures of the corresponding *exo*- and *endo*-anhydrides upon heating at 250–300 °C. This isomerization provides a practical pathway to substituted and deuterium-labeled *exo*-anhydrides which are otherwise difficult to obtain. A mechanistic study shows that retro-diene fragmentation is not involved in the isomerization.

Introduction

The Diels-Alder addition shows normally a great preference for the formation of adducts with an endo configuration.[1] In numerous cases the endo adducts are the exclusive products of the reaction. Alternative routes have to be developed in order to prepare the exo isomers.[2-5]

In the case of the adducts of cyclopentadiene and maleic anhydride 1, the exo isomer is easily obtained by heating the original *endo*-anhydride at 190 °C.[6] Careful thermodynamic and isotope labeling studies[7,8] have shown that

(1) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 211; **1967**, *6*, 16. Herndon, W. G. *Chem. Rev.* **1972**, *72*, 157.
(2) Alder, K.; Stein, G. *Justus Liebigs Ann. Chem.* **1934**, *514*, 17.
(3) Ziegler, K.; Schenck, G.; Krockow, E. W.; Siebert, A.; Wenz, A.; Weber, H. *Justus Liebigs Ann. Chem.* **1942**, *551*, 1.
(4) Stork, G.; Van Tamelen, E. E.; Friedman, L. J.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1953**, *75*, 384.
(5) Christol, H.; Levy, M. *Bull. Soc. Chim. Fr.* **1964**, 3046.
(6) Craig, D. *J. Am. Chem. Soc.* **1951**, *73*, 4889.
(7) Rogers, F. E.; Quan, S. W. *J. Phys. Chem.* **1973**, *77*, 828.

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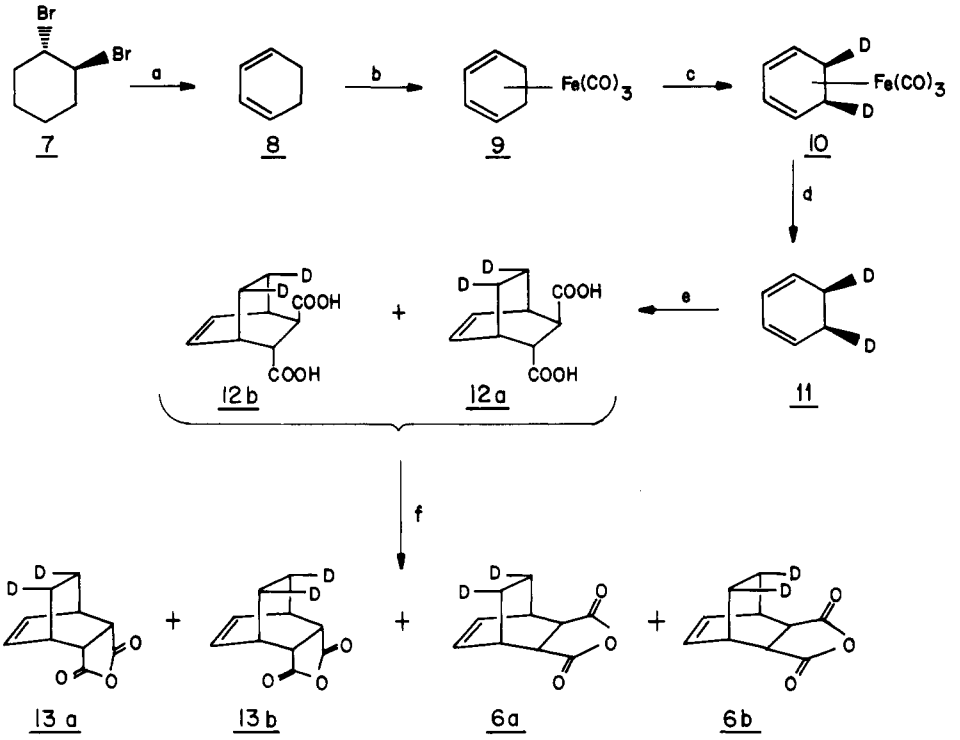
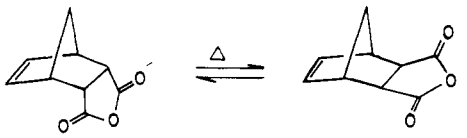
Scheme I[a]



[a] (a) LiCl, Li_2CO_3, HMPA, 160 °C;[16] (b) $Fe(CO)_5$, *hν* 450 W, 5 h, C_6H_6; (c) CF_3COOD; (d) $CuCl_2 \cdot 2H_2O$, CH_3OH; (e) fumaroyl dichloride, H_2O; (f) 250–280 °C, 10 min.

the isomerization of *endo*-**1** to *exo*-**1** takes place by a retro-diene mechanism, the thermodynamically more stable *exo*-**1** being preferred at higher temperatures.

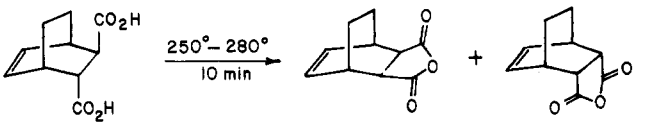


The *exo*-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride (*exo*-**2**) was prepared in a low yield from the endo isomer *endo*-**2** by a multistep synthesis including bromination, hydrolysis, isomerization, and debromination[2] steps. A direct endo-exo isomerization has not been reported in this system.

The need for *exo*-**2** and for substituted analogues in the course of our study of stereospecific hydrogen migrations occurring in gas-phase cations under electron impact[9] brought us to the search for a more convenient route to these compounds.

Results and Discussion

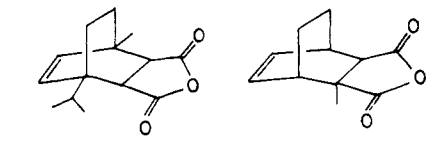
The adduct of 1,3-cyclohexadiene and maleic anhydride is stable under the condition for isomerization in the norbornene series (*endo*-**1**–*exo*-**1**). We were able to observe a partial isomerization to *exo*-**2** above 350 °C, but the isolated yields were very low due to a great extent of material decomposition (formation of tars). Heating of



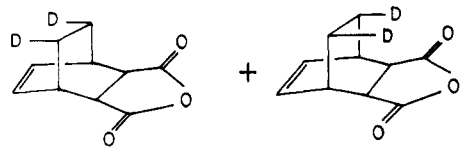
the *trans*-diacid **3** for a short period of time at 250–280 °C leads to a partial elimination of water, and the product of the dehydration is a mixture of *exo*-**2** and *endo*-**2** which can be easily separated by flash chromatography on a silica gel column.[10] Repetitive dehydration of **3** is a practical route to the preparation of the *exo*-anhydride on a laboratory scale. This method was successfully used in the preparation of 1-isopropyl-4-methyl-*exo*-bicyclo[2.2.2]-oct-5-ene-2,3-dicarboxylic anhydride (*exo*-**4**), 3-methyl-*exo*-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride (*exo*-**5**), and the deuterium-labeled analogues *cis-endo*- and *cis-exo*-7,8-dideuterio-*exo*-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic anhydrides (**6a** + **6b** respectively). The detailed procedure for preparation of the latter mixture of **6a** and **6b** is shown in Scheme I.

The introduction of two deuterium atoms in the cis configuration in cyclohexadiene–iron tricarbonyl **9** was achieved by equilibration with trifluoroacetic acid-*d*.[11] Attempts at liberation of *cis*-5,6-dideuterio-1,3-cyclohexadiene (**11**) from the deuterium-labeled iron tricarbonyl complex **10** with the usual reagents such as Ce^{IV} salts,[12] trimethylamine oxide,[13] and cuprous chloride in ethanol[14]

(8) Ganter, C.; Scheidegger, U.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 2771.
(9) Mandelbaum, A.; Weisz, A.; Karpati, A. *Int. J. Mass Spectrom. Ion Phys.* **1983**, *47*, 415.
(10) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(11) Whitesides, T. H.; Arhart, R. W. *J. Am. Chem. Soc.* **1971**, *93*, 5296.
(12) Birch, A. J.; Chamberlain, K. K.; Haas, M. A.; Thompson, D. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1882.



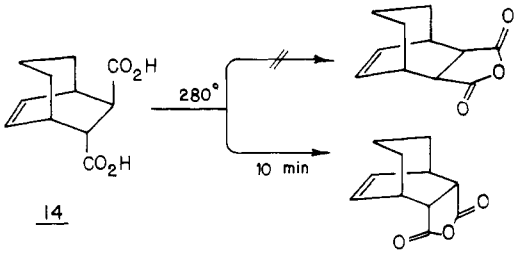
exo-4 exo-5



6a 6b

proved unsuccessful. Treatment of **10** with $CuCl_2 \cdot 2H_2O$ in methanol[15] afforded the stereospecifically deuterium labeled diene **11**, which upon reaction with fumaroyl dichloride followed by water hydrolysis and heating gave rise to a mixture of the two stereotopomeric *exo*-anhydrides **6a** and **6b**.

It is noteworthy that the method suggested here for the preparation of *exo*-bicyclo[2.2.2]oct-5-ene anhydrides is not successful in the case of the bicyclo[3.2.2]non-5-ene homologue. Heating of bicyclo[3.2.2]non-5-ene-*trans*-2,3-dicarboxylic acid (**14**) afforded only the *endo*-anhydride **15**, which was identical with the product of the Diels–Alder addition of 1,3-cycloheptadiene and maleic anhydride.



14 15

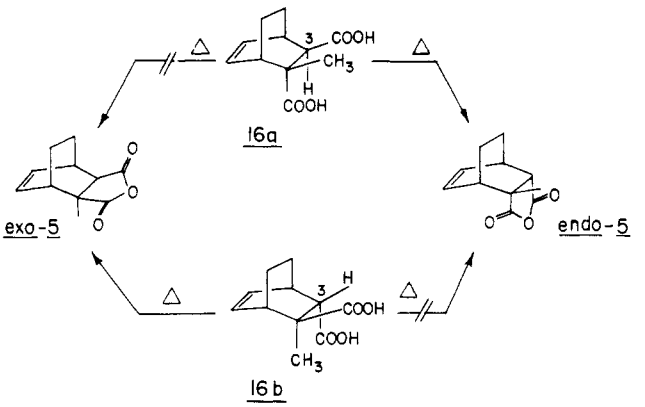
The endo to exo isomerization in the norbornene series takes place by a retro-diene mechanism. The reluctance of bicyclo[2.2.2]octene analogues to undergo a similar isomerization indicates that the conversion of the *trans*-diacids to the *exo*- and *endo*-anhydrides takes place by a different mechanism, which does not involve a fragmentation step. This conclusion is supported by the isomerization of the stereoisomeric 2-methylbicyclo[2.2.2]oct-5-ene-*trans*-2,3-dicarboxylic acids **16a** and **16b**, which differ

16a 16b

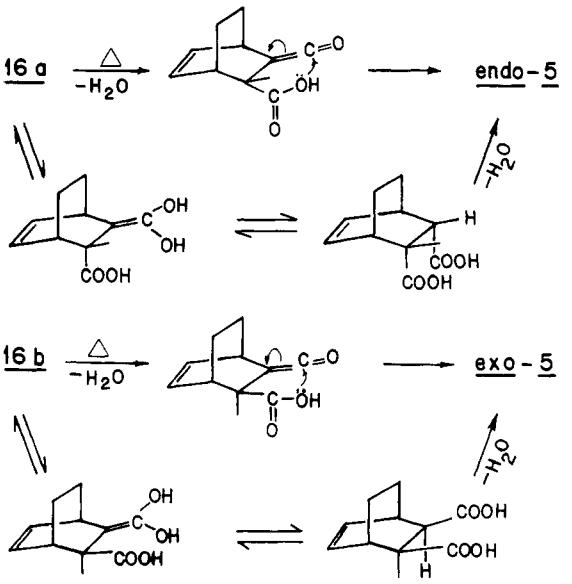
in the configuration of the methyl group. A retro-diene mechanism would lead to a mixture of *exo*- and *endo*-anhydrides from both **16a** and **16b**. However, **16a** yields only the *endo*-anhydride (*endo*-**5**), while **16b** is converted exclusively to the exo isomer (*exo*-**5**) on heating (Scheme II). This result clearly shows that the isomerization involves the inversion of configuration at C-3, which carries a hydrogen atom α to the carboxyl group.

(13) Shvo, Y.; Hazum, E. *J. Chem. Soc., Chem. Commun.* **1974**, 336.
(14) Thompson, D. J. *J. Organomet. Chem.* **1976**, *108*, 381.
(15) Taylor, G. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1716.

Scheme II



Scheme III



This mechanism of the isomerization may thus take place either by enolization of one of the carbonyl groups (that having an α-hydrogen in the case of **16**) or by an initial thermal dehydration to a ketene followed by a rearrangement to the *cis*-anhydride (Scheme III). No attempt has been made to determine which of the two pathways is operating in this isomerization. We are not aware of mechanistic studies of analogous processes under similar conditions.

The isolated yields of the *exo*-anhydrides are rather low (~20% before separation and purification, 5.5% of isolated pure *exo*-**2** under unoptimized conditions). However, the simplicity and low cost of the starting materials and the ease of the present procedure suggest it as a practical route for the synthesis of *exo*-anhydrides on a laboratory scale. It should be mentioned here that the only available literature procedure for the preparation of *exo*-**2** consists of about 10 steps and the overall yield was very low.[2]

Experimental Section

Preparative separations were accomplished through the use of flash chromatography.[10] Gas chromatographic analyses were performed on a Varian Aerograph 920 gas chromatograph using N_2 as the carrier gas at 120 °C and a 1.5-m column of 1% Se-30 on Chromosorb G A/W. Proton nuclear magnetic resonance (^1H NMR) spectra were obtained on a Bruker AM-400 spectrometer. Mass spectra were measured with Varian 711 mass spectrometer.

Bicyclo[2.2.2]oct-2-ene-*trans*-2,3-dicarboxylic Acid (*trans*-3). To a solution of 5 g (0.063 mol) of freshly prepared cyclohexadiene[16] in 6.5 mL of anhydrous ether contained in a

100-mL round-bottomed flask equipped with magnetic stirrer, thermometer, and dropping funnel was added a solution of 9.625 g (0.063 mol) of fumaroyl dichloride in 7 mL of anhydrous ether. The addition was effected dropwise with stirring and the temperature maintained at 15 °C. At the end, the mixture was left at room temperature for 1.5 h. Water (30 mL) was added to the reaction flask, and the mixture was left overnight with stirring. Bicyclo[2.2.2]oct-5-ene-*trans*-2,3-dicarboxylic acid (*trans*-**3**, 7.29 g, 59.5%) was obtained as a white powder after filtration and drying in vacuum.

***exo*-Bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic Anhydride (*exo*-2).** *trans*-**3** (1.58 g) was heated in a test tube in a metal bath at 250–280 °C for 10 min. Water was evolved during the heating. After the mixture was cooled to room temperature, it was dissolved in benzene. A gas chromatographic analysis showed that a 1:1.2 mixture of *exo*- and *endo*-anhydrides was obtained. (Heating the *trans*-diacid for a longer period of time (30 min) did not improve the yield of *exo*-anhydride.) The mixture (0.66 g) was separated by flash chromatography. The eluent used was a mixture of benzene and ether (27:1). The *exo*-anhydride [exo-**2**, 81 mg, mp 152–153 °C (lit.[2] mp 157–158 °C)] was eluted first and was followed by mixtures of *endo*-**2** and *exo*-**2**. No attempts have been made to optimize the synthetic and separation procedure.

Conversion of 16a to *endo*-5. *endo*-**5**, obtained[18] from cyclohexadiene[16] and citraconic anhydride, was methylated with dimethyl sulfate and sodium hydroxide, resulting in a mixture of 2-*exo*-methylbicyclo[2.2.2]oct-5-ene-*endo*- and -*trans*-2,3-dicarboxylic dimethyl esters.[19] This mixture was epimerized with a solution of 1 M sodium methoxide in methanol[5] and hydrolyzed by refluxing in a 95% ethanol solution of KOH. On heating of the resulting 2-*exo*-methylbicyclo[2.2.2]oct-5-ene-*trans*-2,3-dicarboxylic acid (**16a**) for 5 min at 300 °C, only *endo*-**5** was obtained, as demonstrated by gas chromatographic analysis.

Mixture of 2-*exo*-Methyl- and 2-*endo*-Methylbicyclo-[2.2.2]oct-5-ene-*trans*-2,3-dicarboxylic Acids (16a and 16b). A solution of cyclohexadiene[16] (8 g) and mesaconoyl dichloride (8.3 g) in benzene (10 mL) was refluxed for 24 h. The solution was acidified (20 mL of H_2O and 15 mL of HCl, 1 N), and after 1 h at room temperature, a yellowish solid precipitated. Dissolution in 10% NaOH and reprecipitation with 20% HCl yielded a crude mixture of diacids **16a** and **16b** (5.05 g, 48%, yellow powder). The NMR analysis indicated the presence of the two methyl groups (1.24 and 1.01 ppm, corresponding to the endo and exo isomers respectively). Alder et al. reported isolation of **16a** by crystallization of the crude product.[18]

Conversion of a Mixture of 16a and 16b to a Mixture of *endo*-5 and *exo*-5. Heating of the mixture of diacids **16a** + **16b** for 5 min at 300 °C produced a mixture of anhydrides *endo*-**5** and *exo*-**5** in the ratio of 1:1, as demonstrated by gas chromatographic analysis and by the NMR spectrum (two CH_3 absorptions at 1.41 and 1.24 ppm, respectively).

Bicyclo[3.2.2]non-5-ene-*trans*-2,3-dicarboxylic Acid (14). A solution of 1,3-cycloheptadiene[16] (4.4 g) and fumaroyl dichloride (7.16 g) in *n*-hexane (10 mL) was refluxed for 24 h. After addition of water (20 mL), the mixture was magnetically stirred for 1 h at room temperature. The resulting precipitate was filtered and dissolved in NaOH, 5% (50 mL). Filtration and addition of HCl, 1 N, to pH ~2 yielded **14** [2.7 g, 27.7% mp 202–203 °C (lit.[20] mp 202–203 °C)], which was used for isomerization.

Isomerization of Bicyclo[3.2.2]non-5-ene-*trans*-2,3-dicarboxylic Acid (14). Heating of **14** for 10 min at 280 °C yielded only the *endo*-bicyclo[3.2.2]non-5-ene-2,3-dicarboxylic anhydride (**15**), which was identical with the product of Diels–Alder addition of 1,3-cycloheptadiene and maleic anhydride.

***cis*-5,6-Dideuterio-1,3-cyclohexadiene (11).** A solution of 1,3-cyclohexadiene[16] (23 g) and iron pentacarbonyl (18 g) in benzene (30 mL) was irradiated with a 450-W Hanovia lamp for 5 h. (A literature procedure[17] with a 125-W mercury lamp for 50 h gave a somewhat lower yield.) Filtration through Celite 545 to remove particles of iron and evaporation of the solvent afforded a reddish-violet oil. The oil was dissolved in hexane, and the solution was passed through a column of neutral alumina I. Solvent evaporation followed by distillation (0.7 Torr/55 °C) yielded the complex **9** (11.98 g, 59.3%, lit.[17] 56%) as a light yellow oil.

The exchange of two *cis*-hydrogen atoms at positions 5 and 6 by deuterium in **9** to obtain complex **10** was performed with trifluoroacetic acid-*d*.[11] Removal of the ligand to obtain the diene **11** was achieved by $CuCl_2 \cdot 2H_2O$ in methanol.[15]

CF_3COOD [35 mL, freshly prepared from $(CF_3CO)_2O$ (75.1 g, 0.3576 mol) and deuterium oxide (99.99% D_2O, 7.152 g, 0.3576 mol)] was added to cyclohexadiene–iron tricarbonyl **9** (3.33 g, 0.015 14 mol). After magnetic stirring (2 min), hexane (20 mL) was added and a red-violet-colored one-phase solution was obtained. The CF_3COOH and hexane were removed by distillation (50–60 °C/~680–700 mmHg), and a solution of $CuCl_2 \cdot 2H_2O$ in methanol (60 mL) (prepared immediately beforehand by dissolving 7.3 g of $CuCl_2 \cdot 2H_2O$ in 73 mL of CH_3OH) was added. Gas evolution was instantly observed. After 2 h of magnetic stirring at room temperature, gas evolution was no longer observed (in total, 550 cm^3 of gas evolved), and the greenish solution was transferred to a separation funnel. The solid remainder was washed with hexane (1 × 10 mL, 2 × 5 mL). The combined hexane solution was washed with water (50 mL) and dried with several pellets of KOH. The resulting hexane solution of diene **11** was directly used for the Diels–Alder addition.

***cis*-*endo*- and *cis*-*exo*-7,8-Dideuteriobicyclo[2.2.2]oct-5-ene-*trans*-2,3-dicarboxylic Acids (12a + 12b).** A solution of fumaroyl dichloride (5 g) in hexane (3 mL) was added to the above hexane solution of diene **11** (two batches). The reaction was slightly exothermic. After 12 h at room temperature and subsequent hydrolysis of the chloride (by adding 10 mL of water), a white-yellowish precipitate was obtained. Filtration and washing with a small amount of water afforded the *trans*-diacid mixture **12a** + **12b** and a small amount of fumaric acid (5.8 g).

***cis*-*endo*- and *cis*-*exo*-7,8-Dideuterio-*exo*-bicyclo[2.2.2]-oct-5-ene-2,3-dicarboxylic Anhydrides (6a + 6b).** The mixture of the *trans*-diacids **12a** and **12b** (0.86 g) was heated for 10 min at 250 °C and treated with benzene, resulting in a mixture of *exo*- and *endo*-anhydrides (0.24 g) in the ratio of 1:1.3 (by gas chromatographic analysis). After separation of the isomers by flash chromatography, 36 mg of pure endo isomers **13a** and **13b** and 5 mg of pure exo isomers **6a** and **6b** were obtained.

1-Isopropyl-4-methyl-*exo*-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic Anhydride (*exo*-4). The corresponding *trans*-diacid was obtained from α-terpinene and fumaroyl dichloride in benzene by the method described for *trans*-**3**. Heating of the diacid for 10 min at 250 °C afforded a mixture of *endo*- and *exo*-anhydrides in the ratio of 4:1 respectively. Separation by flash chromatography (as described for *exo*-**2**) yielded *exo*-**4**. NMR: 0.96 (d, J = 6.5) and 1.08 ppm (d, J = 6.5), isopropyl methyls; 1.44 ppm (s), 4-methyl; 2.80 (d, J = 10.3) and 3.16 ppm (d, J = 10.2), 5-H and 6-H; 6.08 (d, J = 8) and 6.20 ppm (d, J = 8), 2-H and 3-H. Molecular weight ($M^{\cdot+}$, high-resolution mass spectrometry): 234.1248. Calcd for $C_{14}H_{18}O_3$: 234.1256.

Acknowledgment. We thank the Lady Davis Foundation for a postdoctoral fellowship to A.W. This research was supported by the Fund for Promotion of Research at the Technion.

Registry No. *exo*-**2**, 3769-13-9; *endo*-**2**, 24327-08-0; *trans*-**3**, 28871-80-9; *exo*-**4**, 117305-74-5; *exo*-**5**, 6303-67-9; *endo*-**5**, 67504-35-2; **6a**, 117305-72-3; **6b**, 117305-73-4; **8**, 592-57-4; **9**, 12152-72-6; **11**, 26005-40-3; **12a**, 117203-65-3; **12b**, 117305-71-2; **13a**, 85081-17-0; **13b**, 85015-28-7; **14**, 117305-70-1; **15**, 29577-71-7; **16a**, 117203-63-1; **16b**, 117305-69-8; fumaroyl chloride, 627-63-4; dimethyl 2-*exo*-methylbicyclo[2.2.2]oct-5-ene-*endo*-2,3-dicarboxylate, 117203-64-2; dimethyl 2-*exo*-methylbicyclo[2.2.2]oct-5-ene-*trans*-2,3-dicarboxylate, 117305-68-7; mesaconoyl dichloride, 20537-97-7; 1,3-cycloheptadiene, 4054-38-0; α-terpinene, 99-86-5.

(16) Weisz, A.; Mandelbaum, A. *J. Org. Chem.* **1984**, *49*, 2648.
(17) Birch, A. J.; Cross, P. E.; Lewis, J.; White, D. A.; Wild, S. B. *J. Chem. Soc. A* **1968**, 332.
(18) Alder, K.; Brochhagen, F.; Kaiser, C.; Roth, W. *Justus Liebigs Ann. Chem.* **1955**, *593*, 1.
(19) Grundy, J.; James, B. G.; Pattenden, G. *Tetrahedron Lett.* **1972**, 757.
(20) Alder, K.; Molls, H. H. *Chem. Ber.* **1956**, *89*, 1960.