2f (R″ = C_4H_9), 113747-79-8; methyl α-methyltryptophan·HCl, 84120-83-2; nitroethane, 79-24-3; 2-nitropropanoic acid, 113747-80-1; allyl acetate, 591-87-7; methyl 2-methyl-2-nitropentanoate, 113747-81-2; methallyl acetate, 820-71-3; butyl acrylate, 141-32-2; methyl vinyl ketone, 78-94-4; gramine, 87-52-5; (–)-L-methyl 3-(3-indolyl)-2-methyl-2-nitropropanoate, 113829-15-5; α-chymotrypsin, 9004-07-3; (+)-L-methyl α-methyltryptophan·HCl, 84120-86-5.

General Approach to the Synthesis of Polyquinenes via the Weiss Reaction. 6. Progress toward the Synthesis of Dicyclopentapentalenes

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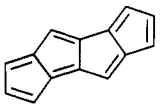
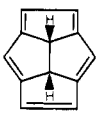
The synthesis of the three tetraquinanes tetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]dodecanetetraol (**27**), tetracyclo[6.6.0.$0^{2,6}$.$0^{9,13}$]tetradecanediol (**36**), and tetracyclo[6.6.0.$0^{2,6}$.$0^{10,14}$]tetradecanediol (**39**) has been achieved via the Weiss reaction. Reaction of glyoxal (**4a**) with di-*tert*-butyl 3-oxoglutarate (**5b**) gave tetra-*tert*-butyl 3,7-dioxo-*cis*-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate (**6b**) in excellent yield. This was converted, regiospecifically, into bisenol ether **20b** with diazomethane. The bisalkylation of **20b** was effected with allyl iodide/KH to provide a mixture of the 2,6-diallyl regioisomer **23b** (64%) and the corresponding 2,8-diallyl dione **24b** (36%); the former compound crystallized from the reaction mixture. Hydrolysis of tetraester **23b** furnished 2,6-diallyl dione **7**, which was oxidized and cyclized to diketo diol **26**, isolated as a mixture of diexo and diendo stereoisomers **26a** and **26b**, both of which were reduced with borane–tetrahydrofuran to provide the desired tetraol **27** in 80% yield. The HMPA-mediated dehydration of **27** gave the tetracyclotetradecadiene **28**. Furthermore, the 2,6-diallyl diones **7a** and **7b** were converted with HBr–peroxides into dibromides **35a,b**, and this mixture of epimers was cyclized to the tetracyclotetradecanediol **36** on stirring with samarium diiodide (80% yield). Analogous to the chemistry developed for preparation of **36**, the 2,8-diallyl tetra-*tert*-butyl ester **24b** was converted into the 2,8-bis(3-bromopropyl) dione **38**, which cyclized on treatment with SmI_2 to the desired tetracyclic tetradecanediol **39** in 68% yield.

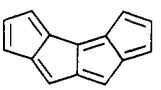
The preparation of highly strained polyunsaturated cyclopentanoid compounds (polyquinenes) has received a great deal of attention in recent years. Katz[1a] reported the formation of the dianion of pentalene in 1964. This was followed by studies on the synthesis of pentalene and its derivatives by Hafner[1b] and others.[1c] Moreover, de Meijere has detailed attempts to prepare acepentalene and has recently reported the preparation of dihydroacepentalenediide.[2] To date, the 14π-annulenes dicyclopenta[*a*,*e*]pentalene (**1**) and dicyclopenta[*a*,*d*]pentalene (**3**), as well as the 10π-annulene *cis*-tetracyclo-



1

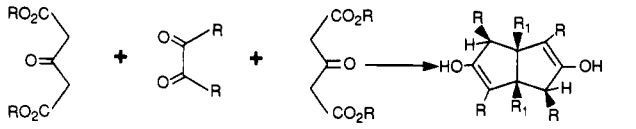


2



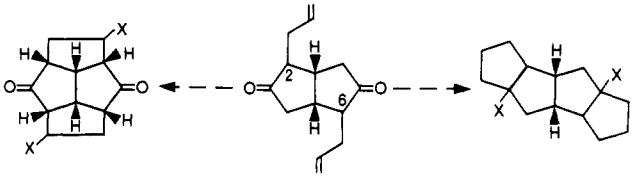
3

Scheme I



5a, R=CH_3 5b, R=t-Bu | 4a, R=H 4b, R=CH_3 | 5a, R=CH_3 5b, R=t-Bu | 6a, R_1=H, R=CO_2CH_3 6b, R_1=H, R=CO_2tBu; 84%

Scheme II



9 7 8

[7.2.1.$0^{4,11}$.$0^{6,10}$]dodeca-1,3,5,7,9(12)-pentaene (**2**) have been discussed only from a theoretical point of view despite the preparation of the carbon skeletons of these molecules by several groups.[3-5]

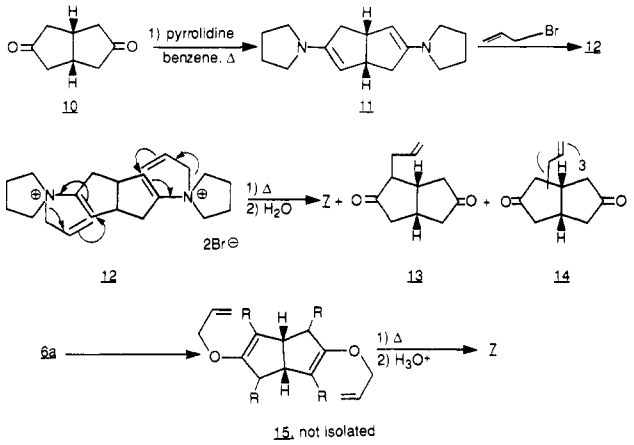
(1) (a) Katz, T.; Rosenberger, M.; O'Hara, R. K. *J. Am. Chem. Soc.* **1964**, *86*, 249–252. (b) Hafner, K.; Süss, H. U. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 575–577. Hafner, K.; Dönges, R.; Goedeck, E.; Kaiser, R. *Angew. Chem.* **1973**, *85*, 362–364. Dönges, R.; Hafner, K.; Lindner, H.-J. *Tetrahedron Lett.* **1976**, *17*, 1345–1348. (c) Jean, Y. *Nouv. J. Chim.* **1980**, *4*, 11–15. Bloch, R.; Marty, R. A.; de Mayo, P. *J. Am. Chem. Soc.* **1971**, *93*, 3071–3072; Baird, N. C.; West, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 3072–3073.

(2) Butenschön, H.; de Meijere, A. *Tetrahedron* **1986**, *42*, 1721–1729 and references cited therein. Lendvai, T.; Friedl, T.; Butenschön, H.; Clark, T.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 719–720.

(3) Uggeri, F.; Srikrishna, A.; Eaton, P. E. *J. Org. Chem.* **1984**, *49*, 1728–1732. McKervey, M. A.; Vibuljan, P.; Ferguson, G.; Siew, P. *J. Chem. Soc., Chem. Commun.* **1981**, 912–914.

0022-3263/88/1953-2327$01.50/0

Scheme III

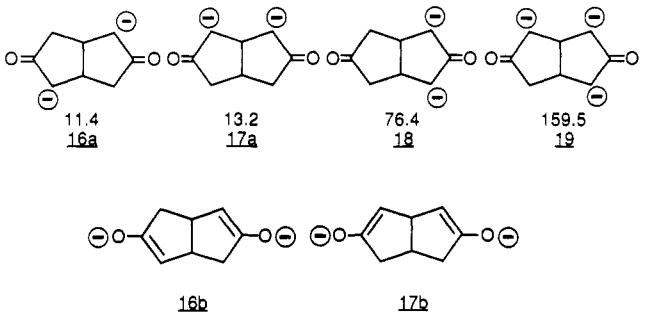


Recently, a general approach to the synthesis of polyquinenes has been developed in our laboratory[6] and has resulted in the preparation of a number of polyquinenes, including stauranetetraene[7] and triquinacene.[8] This method is based on the generation of 3,7-dioxo-substituted *cis*-bicyclo[3.3.0]octane derivatives from reaction of substituted glyoxals with dimethyl 3-oxoglutarate (Scheme I). This process has now been employed to provide simple entry into the requisite ring systems of the three annulenes, suitably functionalized (OH) for later conversion into **1–3**.

Controversy exists as to whether polyquinenes such as **1–3** are delocalized, exhibit aromatic Hückel "type" stability, or exist as alternate hydrocarbons that behave as highly reactive olefins.[9–16] This controversy provided the impetus for the present study.

Earlier, during the synthesis of triquinacene[8] the tetraester **6b**, which is readily available from glyoxal (**4a**) and di-*tert*-butyl 3-oxoglutarate (**5b**), was converted into the bisenol ether. This tetraester could be monoalkylated in >90% yield and converted into triquinacene.[8] This chemistry served as the foundation for the work that follows. It was felt that if a *cis*-bicyclo[3.3.0]octane-3,7-dione could be converted into the 2,6-diallyl derivative **7**, then this intermediate could be employed for synthetic entry into the perhydrodicyclopenta[*a*,*e*]pentalene system **8**, as well as for the construction of the tetrahydro-[7.2.1.$0^{4,11}$.$0^{6,10}$] skeleton present in **9**. Initial attempts to prepare **7**, regiospecifically, centered on the aza-Cope rearrangement, outlined in Scheme III. *cis*-Bicyclo[3.3.0]-octane-3,7-dione (**10**), available in high yield from hydrolysis and decarboxylation of tetraester **6a**,[17] was converted into the bisenamine **11** in quantitative yield,[18] according to the method of Stork.[19] This enamine existed with the two double bonds disposed anti to each other, as illustrated (Scheme III). The structure of **11** was confirmed by the presence of eight lines in its carbon-13 NMR spectrum; moreover, none of the syn isomer was detected. This serves to indicate that the anti isomer **11**, as expected, is the preferred compound on thermodynamic grounds. The bisenamine was treated with 2 equiv of allyl bromide at low temperature, followed by heating to effect the simultaneous [3.3]-sigmatropic rearrangement of the two allyl functions (see **12**, proposed intermediate). However, on hydrolysis and workup a mixture of **7**, 2-(3-propenyl)-*cis*-bicyclo[3.3.0]octane-3,7-dione (**13**), and the trialkylated derivatives represented by **14** was isolated.[18] In an attempt to employ the Claisen rearrangement for the regiospecific preparation of the 2,6-diallyl derivative **7**, we reacted **6a** with allyl iodide, followed by the steps depicted at the bottom of Scheme III. Unfortunately, again a mixture of mono-, di-, and trialkylated materials was obtained; consequently the approach toward **7** via a [3.3]-sigmatropic rearrangement was discontinued.

Table I. MNDO-Calculated Values for the Heat of Formation (kcal/mol)



Attempts to convert *cis*-bicyclo[3.3.0]octane-3,7-dione (**10**) into a dianion, followed by alkylation with allyl iodide, were considered. However, the relative energies of the anti dianion **16a** and the syn dianion **17a** derived from MNDO calculations[20] militated against this approach. As illustrated in Table I, the heats of formation of dianion **18** and trianion **19** are much greater than those of dianions **16a** (11.4 kcal/mol) and **17a** (13.2 kcal/mol), but the energy difference between **16a** and **17a** was not considered large enough to pursue this approach. Although electron–electron repulsion between the two negative charges of **17a**

(4) Fukunaga, T.; Clement, R. H. *J. Org. Chem.* **1977**, *42*, 270–275. Wyvratt, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1974**, *96*, 4671–4674. Mehta, G.; Nair, M. S. *J. Chem. Soc., Chem. Commun.* **1985**, 629–630. Sedelmeier, G.; Fessner, W.-D.; Pinkos, R.; Clemens, G.; Bulusu, A. R. C. Murty; Hunkler, D.; Rihs, G.; Fritz, H.; Kruger, C.; Prinzbach, H. *Chem. Ber.* **1986**, *119*, 3442–3472. Paquette, L. A.; Nakamura, K.; Engel, P. *Chem. Ber.* **1986**, *119*, 3782–3800. Lannoye, G.; Cook, J. M. *Tetrahedron Lett.* **1987**, *28*, 4821–4824.

(5) Eaton, P. E.; Mueller, R. H.; Carlson, G. R.; Cullison, D. A.; Cooper, G. F.; Chou, T.-C.; Krebs, E.-P. *J. Am. Chem. Soc.* **1977**, *99*, 2751–2767. Krishnamurthy, N.; Mehta, G. *J. Chem. Soc., Chem. Commun.* **1986**, 1319–1321. Mehta, G.; Sambasivarao, K. *J. Org. Chem.* **1985**, *50*, 5537–5543.

(6) Venkatachalam, M.; Deshpande, M. N.; Jawdosiuk, M.; Kubiak, G.; Wehrli, S.; Weiss, U.; Cook, J. M. *Tetrahedron* **1986**, *42*, 1597–1605.

(7) Deshpande, M. N.; Jawdos.uk, M.; Kubiak, G.; Venkatachalam, M.; Weiss, U.; Cook, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 4786–4788.

(8) Bertz, S. H.; Lannoye, G.; Cook, J. M. *Tetrahedron Lett.* **1985**, *26*, 4695–4698.

(9) Hess, B. A., Jr.; Schaad, L. J. *J. Org. Chem.* **1971**, *36*, 3418. Hess, B. A., Jr.; Schaad, L. J. *J. Am. Chem. Soc.* **1971**, *93*, 305–310.

(10) Toyota, A.; Nakajima, T. *Tetrahedron* **1981**, *37*, 2575. Nakajima, T.; Toyota, A.; Kataoka, M. *J. Am. Chem. Soc.* **1982**, *104*, 5610–5616.

(11) Gutman, I.; Trinajstic, N. *Can. J. Chem.* **1976**, *54*, 1789–1794.

(12) Stowasser, B.; Hafner, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 466–468.

(13) (a) Platt, J. R. *J. Chem. Phys.* **1954**, *22*, 1448–1455. (b) Garrat, P. J.; Sargent, M. V. "Nonbenzenoid Conjugated Cyclic Hydrocarbons". In *Adv. Org. Chem.* **1980**, *6*.

(14) For the synthesis of a related annulene, see: (a) Vogel, E.; Reeal, H. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 1013–1014. Vogel, E.; Wieland, H.; Schmalsteig, L.; Lex, J. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 717–719. (b) Trost, B. M.; Kinson, P. L. *J. Am. Chem. Soc.* **1975**, *97*, 2438–2449.

(15) McEwen, A. B.; von R. Schleyer, P. *J. Org. Chem.* **1986**, *51*, 4357–4368.

(16) Lannoye, G. Ph.D. Thesis, University of Wisconsin—Milwaukee, 1987.

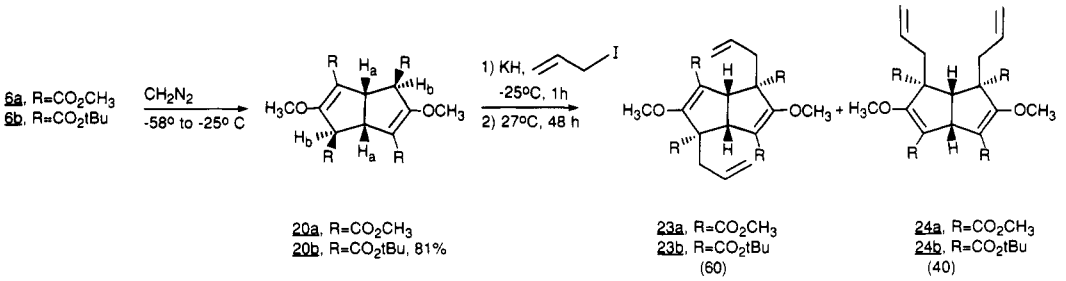
(17) Bertz, S.; Cook, J. M.; Gawish, A.; Weiss, U. *Org. Synth.* **1985**, *64*, 27–37.

(18) Gawish, A.; Cook, J. M., unpublished results.

(19) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207–222.

(20) The calculations were carried out on a VAX computer using the MNDO molecular orbital approximations. The program was obtained through the Quantum Chemistry Program Exchange, Indiana University, Bloomington, IN, and adapted to the Sperry 110 system by T. Sorensen (UWM). All geometric variables were allowed to optimize. (b) Dewar, M. J. S.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, *100*, 784–790.

Scheme IV

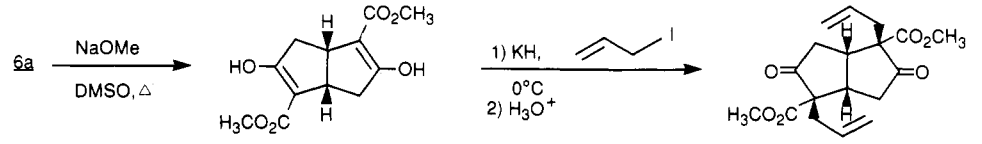


20a, R=CO_2CH_3
20b, R=CO_2tBu, 81%

23a, R=CO_2CH_3
23b, R=CO_2tBu
(60)

24a, R=CO_2CH_3
24b, R=CO_2tBu
(40)

Scheme V



21 22

would be expected to be greater than in **16a**, resonance delocalization to provide the oxy-stabilized dianions **16b** and **17b** (Table I), respectively, effectively separates the anionic charges. The relative energies of dianions **16a** and **17a** are too similar to permit regiospecific 2,6-dialkylation. The energies of dianions **16–19** are relative energies for comparison purposes and are not to be interpreted in an absolute sense.[20]

Attempts to dialkylate the disodium salt of **6a**, or **6a** itself, with allyl iodide to provide the 2,6-dialkylated derivative yielded mixtures of mono-, di-, and trialkylated materials, the last of which consisted of O-alkylated tetraester.[16] Initially, this was disappointing but eventually led to a solution of the problem. It was decided to prohibit both O-alkylation and trialkylation by conversion of the bisenolic tetramethyl ester **6a** into the corresponding bisenol ether **20a**. Since only two sites would remain available for alklation, this would greatly simplify the problem. Treatment of tetramethyl ester **6a** with diazomethane resulted in the formation of bisenol ether **20a** cleanly and in 90% yield. The structure and the disposition of the double bonds in **20a** were deduced from ^{13}C NMR spectroscopy; the reaction product was composed of a single diastereomer. The bisenol ether **20a** is characterized by a twofold axis of symmetry (C_{2v}), in agreement with the nine lines observed in the ^{13}C NMR spectrum of this compound. The stereochemistry of the two ester functions (positions 4 and 8) was confirmed (exo,exo) by ^1H NMR spectroscopy and by correlation to the spectral data reported for tetraethyl 3,7-dioxo-*cis*-bicyclo[3.3.0]-octane-2,4,6,8-tetracarboxylate by Camps.[21] The coupling constant between protons H_a and H_b of **20a** was found to be 1.8 Hz. In keeping with the Karplus variation of the three-bond coupling constant, the small value (<2 Hz) supports the trans configuration of H_a and H_b.[22] These two hydrogen atoms are located on opposite faces of the molecule; consequently, the two ester groups (C-4, C-8) are situated on the exo face of **20a**.[16] Treatment of bisenol tetramethyl ester **20a** with potassium hydride followed by allyl iodide gave the 2,6-diallyl derivative **23a** in 49% yield, accompanied by 44% of a second component felt to be the 2,8-regioisomer **24a** (Scheme IV). The ^{13}C NMR spectrum of **23a** consisted of 12 lines, which implies that the symmetry of the molecule has not been altered during bisalkylation. The exo,exo nature of the two diallyl substituents in **23a** has been proposed based on the symmetry of the molecule (C_{2v}) observed by ^{13}C NMR and the propensity of these systems to undergo attack from the convex faces of the molecule.

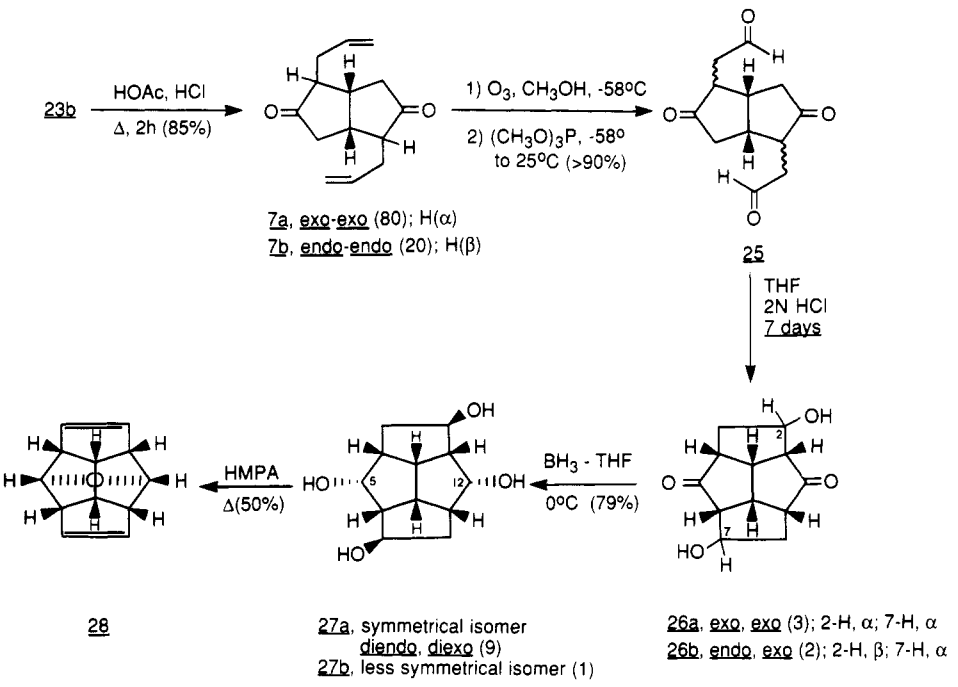
Hydrolysis of the tetramethyl ester functions in **23a**, under a variety of conditions, furnished the 2,6-diallyl 2,6-diester **22** as the major component; the desired 2,6-diallyl-*cis*-bicyclo[3.3.0]octane-3,7-dione (**7**) proved to be a minor constituent in this process. The parent tetramethyl ester **6a** usually underwent acid-catalyzed hydrolysis, followed by decarboxylation, with relative ease.[17] In contrast, the 2,6-diallyl tetramethyl ester **23a** resisted hydrolysis under the usual conditions. Presumably, alkylation from the convex face of **20a** provided **23a** with the ester functions positioned endo with respect to the remainder of the molecule. If this were the case, hydrolysis of the 2,6-diester functions in **23a** would be expected to be retarded based on steric arguments.

The structure of diallyl diester **22** was proposed based on NMR spectroscopy[16] and was verified by independent synthesis (Scheme V). Tetramethyl ester **6a** was hydrolyzed (NaOMe, DMSO, Δ) and decarboxylated via the method of Bhatnagar and Weiss[24] to provide 2,6-diester **21** (49% yield) of known structure. The yield of this sequence on a small scale is very good but decreases dramatically on scale up.[16] The diester was treated with potassium hydride and allyl iodide to provide 2,6-diallyl 2,6-diester **22** in 65% yield. This diester was identical in all respects with diester **22** described above. Consideration was given to use of the technology of Weiss (Scheme V)[24] for synthesis of 2,6-dialkylated *cis*-bicyclooctanediones but was rejectd due to the low yield in conversion of **6a** into **21** on scale up and the difficulty in removal of the 2,6-dimethyl diester functions in **22**. Attempts to hydrolyze the dimethyl diester functions of **22** and **23a** with LiI in collidine[25] as well as a number of other reagents, including trifluoroacetic acid, were not successful in a practical sense; consequently, a modification of the route to **7** was required.

To circumvent the difficulty of incomplete hydrolysis in the case of tetramethyl tetraester **23a**, advantage was taken of the versatility of the Weiss reaction. Dimethyl

(21) Camps, P. *Tetrahedron Lett.* **1974**, 4067–4068.
(22) Karplus, M.; Pople, J. A. *J. Chem. Phys.* **1963**, *38*, 2803–2807. Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11–15.
(23) Mitschka, R.; Oehldrich, J.; Takahashi, K.; Cook, J. M.; Weiss, U.; Silverton, J. V. *Tetrahedron* **1981**, *37*, 4521–4542.
(24) Bhatnagar, S.; Weiss, U. *J. Org. Chem.* **1977**, *42*, 3089–3091.
(25) McMurray, J. *Organic Reactions*; Wiley-Interscience: New York, 1976; Vol. 24, Chapter 2, p 187.

Scheme VI



3-oxoglutarate (**5a**) was replaced in this condensation with di-*tert*-butyl 3-oxoglutarate (**5b**). When **5b** was reacted with glyoxal (**4a**) in aqueous alkaline solution (room temperature), tetra-*tert*-butyl 3,7-dioxo-*cis*-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate (**6b**) was produced in yields ranging from 80 to 85%. The four *tert*-butyl ester functions in **6b** could be readily hydrolyzed (HCl/HOAc, Δ, 1 h) and decarboxylated to provide the parent dione **10** in excellent yield. The *tert*-butyl ester functions are labile, as expected, to both heat and acid.

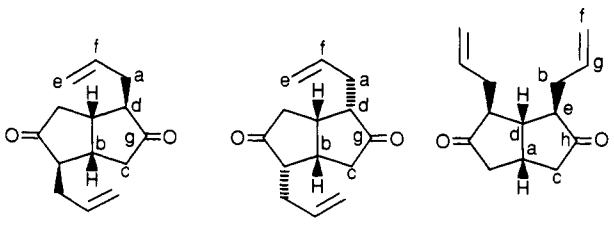
Tetraester **6b** exists in solution entirely as the bisenol (Scheme I) tautomer and can be converted into the desired bisenol ether **20b** in 81% yield on treatment with diazomethane. The anti disposition of the two double bonds in both **6b** and **20b** was deduced from ^{13}C NMR spectroscopy. On examination of the ^{13}C NMR spectrum of **6b**, 10 lines were observed, which corresponds to 20 carbon atoms, while 11 lines were found in the spectrum of bisenol ether **20b**. This is consistent with the symmetry (C_{2v}) of both tetraesters. The signals from the off-resonance decoupled spectra of **6b** and **20b**, respectively, were in complete agreement with this assignment.[16] The stereochemistry of the two methine hydrogen atoms geminal to the ester carbonyl functions in both **6b** and **20b** was assigned from ^1H NMR spectroscopy and correlation with the data on **6a** (see above). The coupling constants observed in the proton spectrum for H_a and H_b (Scheme IV) in **6b** (J_{ab} = 2.1 Hz) and in **20b** (J_{ab} = 1.8 Hz) are in agreement with the exo stereochemistry assigned to the two ester functions located at C-2 and C-6. The two methine protons must lie on opposite faces (trans coupling)[22] of the molecule; consequently, the two ester groups must be located on the exo faces of **6b** and **20b**, respectively.

Although tetra-*tert*-butyl ester **20b** could be readily monoalkylated (−60 to −40 °C) with potassium hydride/allyl iodide in >90% yield, the sequential alkylation at both position 2 and position 6 required more vigorous conditions. This is in contrast to bisalkylation of tetramethyl ester analogue **20a**, which occurs very readily at low temperature. Because of this, initially, a two-step bisalkylation procedure was devised wherein monoalkylation of **20b** to provide the monoallyl derivative was carried out at low temperature (−60 °C), followed by a second alkylation to furnish the dialkylated tetraesters **23b** and **24b**. A wide variety of reaction conditions were employed to assess the effect of temperature on the alkylation process.[16] If the second alkylation was carried out at low temperature (−25 °C), 2,6-diallyl tetraester **23b** formed in preference to 2,8-diallyl isomer **24b**; the two regioisomers were formed in yields >90% in an approximate ratio of 3:2. At higher temperatures (40–80 °C) the ratio approached a 1:1 mixture of the two regioisomers **23b** and **24b**, respectively. Variations of reaction time, stoichiometry, and temperature were investigated;[16] however, the regioselectivity of the process was never realized in a ratio higher than 64 (**23b**):36 (**24b**). Despite numerous attempts, conditions were never found wherein the 2,8-diallyl derivative predominated over **23b**.

Although regiospecific synthesis of the 2,6-diallyl isomer **23b** or the 2,8-isomer **24b** was not achieved, it was decided to prepare **23b** and **24b** via this procedure, since large quantities of material could be obtained readily. When the dialkylation was carried out on a large scale, the 2,6- and 2,8-regioisomers were obtained in near-quantitative yield in a ratio (percent) of 60:38. More importantly, it was found that the 2,6-diallyl isomer **23b** could be preferentially removed from the mixture by crystallization. The 2,8-isomer **24b** remained in the mother liquor and was easily purified by flash chromatography. Since both the 2,6- (**23b**) and the 2,8-diallyl isomers are required in the present study, this result was gratifying. The structures and stereochemistry of **23b** and **24b** were determined by spectroscopy (especially ^1H and ^{13}C NMR) and are as depicted in Scheme IV.

Hydrolysis of tetraester **23b**, followed by decarboxylation, was effected with remarkable ease to provide the pivotal 2,6-diallyl-*cis*-bicyclo[3.3.0]octane-3,7-dione (**7**) in 85% yield. Analogous to earlier results in the triquinacene area,[8] the diallyl dione **7** was obtained as a mixture of diastereomers, as illustrated in Scheme VI. This mixture was composed of the *exo,exo*-2,6-diallyl dione **7a** and the endo,endo diastereomer **7b** in a ratio of 4:1, accompanied by only trace amounts of the endo,exo diastereomer.[16] The structures of the two major components were confirmed

Table II. ^{13}C NMR Chemical Shifts ($CDCl_3$, ppm)



	7a, exo-exo	7b, endo,endo	37a, exo,exo
a	33.56	30.11	32.10
b	38.96	38.33	34.12
c	43.29	42.08	43.42
d	52.74	53.29	46.76
e	117.39	116.21	52.96
f	134.92	135.79	117.61
g	218.10	216.59	134.96
h	---	---	217.72

by spectroscopy. The ^{13}C NMR chemical shifts obtained for the two diastereomers are depicted in Table II. Both 2,6-diallyl diones **7a** and **7b** are characterized by a twofold axis of symmetry (C_{2v}); consequently the ^{13}C NMR spectrum would be expected to contain seven lines. This was observed. In contrast, the 2,8-disubstituted diallyl dione (available on hydrolysis of **24b**) possesses one symmetry plane (C_s) and would be expected to have an eight-line ^{13}C NMR spectrum, as illustrated in Table II. The seven-line carbon spectra for both **7a** and **7b** serve to confirm the disposition of the allyl groups as 2,6. The 2,6-endo,exo diastereomer was observed only by GC and GC–mass spectroscopy, for it was present in a quantity too small to characterize. Hydrolysis of **24b** will be addressed in a later section.

Since the 2,6-diallyl-*cis*-bicyclo[3.3.0]octane-3,7-dione (**7**) could now be synthesized on a preparative scale, efforts turned to the conversion of **7** into the desired tetracyclo-[7.2.1.$0^{4,10}$.$0^{6,10}$]dodecane derivative **9**. When the mixture of diastereomers represented by **7** was oxidized with OsO_4/$NaIO_4$ on a small scale, an 89% yield of a mixture of epimeric dialdehydes **25** was achieved. From the beginning it was felt that the relative stereochemistry of **7a** and **7b** was of no consequence in regard to the synthesis of **9**. This was based on the aldol chemistry developed during the synthesis of triquinacene in which the exo isomer epimerized to the endo diastereomer and underwent the desired cyclization in high yield (see ref 8). Examination of the mixture of epimeric aldehydes **25** by ^1H NMR spectroscopy indicated the presence of aldehydic functions (δ = 9.1, 2 H); however, analysis of **25** by TLC and mass spectroscopy indicated that appreciable amounts of material had cyclized in the desired fashion (see **26**). Because of the tendency of **25** to undergo the intramolecular aldol cyclization, it was decided to forego complete characterization of **25** at this juncture and convert it into the dihydroxytetraquinane **26** (Scheme VI). The scale up of the OsO_4-mediated oxidation proved troublesome, for yields decreased drastically. For this reason the 2,6-diallyl dione **7** was treated with ozone, followed by treatment with dimethyl sulfide (DMS).[26] Although dimethyl sulfide has

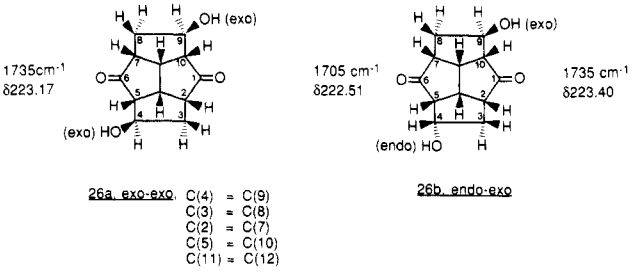


Figure 1.

been employed extensively in our laboratory[6,8] to reduce the oxidative intermediates obtained from ozonides, this ozonide from **7** was found to be exceptionally stable in the presence of DMS. Analysis of the reaction mixture indicated the presence of two epimeric aldehydes **25**, but moderate amounts of other materials felt to be peracetals or keto acetals were observed (see ref 16 for details). The bisozonide of **7**, however, underwent smooth reduction with trimethyl phosphite[27] to provide the mixture of epimeric aldehydes cleanly and in excellent yield. The presence of trimethyl phosphate [$(MeO)_3PO$] in the reaction product is of little consequence, since it is converted into phosphoric acid during the acid-catalyzed aldol cyclization (see below).

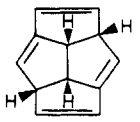
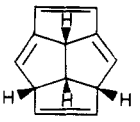
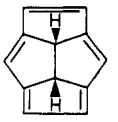
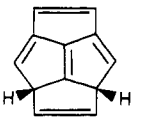
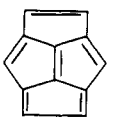
The bisaldolization of **25** was effected under acidic conditions (2 N HCl, THF).[8] A dilute solution of **25** was employed to facilitate the intramolecular aldol condensation in preference to the corresponding intermolecular process. Because dialdehyde **25** is composed of a mixture of the exo,exo isomer and the endo,endo diastereomer (based on **7**) in an approximate ratio of 3:1 (^{13}C NMR), the aldol condensation proceeds slowly. Analogous to the cyclization in the triquinacene series,[8] the 2,6-dialdehydic groups oriented exo epimerize to the endo stereochemistry and then undergo cyclization to furnish the desired five-membered rings. Although this process takes several days to go to completion at room temperature, bisaldehyde **25**, from the O_3/$(MeO)_3P$ method, cyclized in 60–80% yield to provide a mixture of the two epimeric 2,7-dihydroxytetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]dodecane-5,11-diones represented by **26a** and **26b**. The yield of conversion of **25** into **26** is lower when the bisaldehyde generated from the OsO_4/$NaIO_4$ or O_3/DMS oxidation is employed in the cyclization.

The structure and stereochemistry of **26a** and **26b** have been assigned as exo,exo (**26a**) and endo,exo (**26b**) based on NMR and IR spectroscopy. In brief, the ^{13}C NMR spectrum of the exo,exo stereoisomer **26a** contains six lines indicative of the symmetry (C_{2v}) of the molecule. Assignment of the stereochemistry to **26b** was a simple process, for the carbon spectrum of this diol exhibited 12 signals consonant with a structure (**26b**) of less symmetry, as compared to **26a**. Consequently, the diketo diol **26b**, by virtue of its 12-line ^{13}C NMR spectrum, must possess both an endo and an exo hydroxyl group. The stereochemistry of the hydroxyl functions in **26a** was deduced by high-resolution ^1H NMR spectroscopy. The chemical shifts and coupling constants for each proton were determined by 2D COSY NMR and proton–proton double-irradiation experiments (see Tables I and II, Supplementary Material, for individual assignments). In the endo,exo diastereomer **26b**, the chemical shift and coupling constants for the endo proton at C-9 (see Figure 1) are as follows: δ 4.495 [$J_{H(9)-H(10)} \simeq 3$ Hz; $J_{H(9)-CH_2(8)endo} \simeq 6$ Hz; $J_{H(9)-CH_2(8)exo} \simeq 4$ Hz; $J_{H(9)-H(7)}$ = very small], while the exo

(26) Gupta, D.; Soman, R.; Dev, S. *Tetrahedron* **1982**, *38*, 3013–3018. Lorenz, O. *Anal. Chem.* **1965**, *37*, 101–102. Odinokov, V. N.; Tolstikov, G. A. *Russ. Chem. Rev. (Engl. Transl.)* **1981**, *50*(7), 636–656.

(27) Knowles, W. S.; Thompson, Q. E. *J. Org. Chem.* **1960**, *25*, 1031–1033.

Table III. MNDO-Calculated Heats of Formation

	 29	 30	 2	 31	 32a planar representation	32b nonplanar representation
Hf (kcal/mole)	95.97	97.10	166.30	178.80	408.30	255.90
total energy -(eV)	1672.40	1672.40	1641.00	1640.50	1602.20	1698.80
I.P. (eV)	8.89	8.75	7.99	8.51	8.52	8.51
no. # μe	8.	8.	10.	10.	12.	12.
strain energy (kcal/mol)	56.70	56.70	108.20	•	•	•

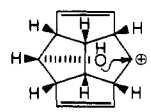
proton (C-4) was found at δ 4.313 [$J_{H(4)-H(5)} \simeq 6$ Hz; $J_{H(4)-CH_2(8)endo} \simeq 1.5$ Hz; $J_{H(4)-CH_2(3)exo} \sim 4$ Hz; $J_{H(4)-H(2)}$ = very small]. The endo proton at C-9 was found to experience an NOE (15%) effect only from the endo proton at C-8. Furthermore, the exo proton at C-4 experienced NOE effects from both the exo proton at C-5 (20%) and the exo proton located at C-3 (8%). These data are consistent with the stereochemistry of **26b** depicted in Figure 1. Comparison of the chemical shift and J values for the endo proton at C-4(9) in the symmetrical exo,exo alcohol **26a** [δ 4.325; $J_{H(4)-H(5)}$ = 2.0 Hz; $J_{H(4)-CH_2(3)endo}$ = 4.5 Hz; $J_{H(4)-CH_2(3)exo}$ = 2.7 Hz; $J_{H(4)-H(2)}$ = broadening] to that in the spectrum of **26b** supports the assignments as illustrated (Supplementary Material). NOE enhancement between the endo proton at C-9 and the endo proton at C-3 was also observed. Long-range coupling between the exo proton at C(5) and the exo proton at C(3) was employed to differentiate between the endo and exo protons that reside on carbon atom 3(8) of **26a**. Furthermore, evidence from IR spectroscopy supports the configurational assignment of both hydroxyl groups in **26a** as exo. Examination of molecular models indicates that there is little opportunity for intramolecular hydrogen bonding between the exo hydroxyl functions and a neighboring carbonyl group, whereas the endo hydroxyl groups are suitably disposed to interact with the carbonyl in a strong intramolecular hydrogen bond. Since the diketo diol **26b** must possess both an endo and an exo hydroxyl group, it serves as a standard for both types of interaction. In fact, in the infrared spectrum of **26b**, an absorption occurs at 1705 cm^{-1}, while a second carbonyl band was observed at 1735 cm^{-1} (see Figure 1). It is anticipated that the band at lower frequency[28a] results from interaction (H bond) of an endo hydroxyl group with the neighboring carbonyl function. A corresponding upfield shift (δ 222.51, **26b**) for this carbon atom (C=O) should be seen via ^{13}C NMR[28b] and this was observed (Figure 1). More importantly, in exo,exo isomer **26a** only one carbonyl absorption was observed (1735 cm^{-1}), and the frequency suggests it is not hydrogen bonded when compared to the spectrum of **26b**. The shifts in the IR spectrum of **26a** relative to **26b**, as well as the ^{13}C and ^{1}H NMR assignments are in agreement with the assignments depicted in Figure 1. The actual stereochemistry of the hydroxyl groups in **26** is of no practical consequence since they will be eliminated in the later stages of the route to **2**.

Reduction of diketo diol **26a** to provide tetracyclo-[7.2.1.$0^{4,11}$.$0^{6,10}$]dodecane-2,5,7,12-tetraol **27a** was accomplished with borane–THF in 80% yield. In the initial experiments the more symmetrical diol **26a** was employed to facilitate characterization of the tetraol **27a** that resulted. Two tetraols were isolated in a ratio of 9:1 from this process. The major isomer was the more symmetrical of the two as evidenced by its ^{13}C NMR spectrum (six lines) and was accompanied by small quantities of an isomer **27b** of lower symmetry (^{13}C NMR). The latter diastereomer is felt to be the product of hydride attack on the convex face of one carbonyl group and the concave face of the other. Regardless of which diketo dione **26** is employed, hydride attack will occur predominantly from the convex face of the molecule. The final configuration of the newly formed hydroxyl groups will be endo in the isomer that predominates. The reduction of the mixture of diastereomers **26a** and **26b** also proceeded smoothly to provide a mixture of diastereomeric tetraols including **27a** and **27b**. Examination of the tetraols **27a** and **27b** by mass spectroscopy confirmed the presence of four hydroxyl groups represented by a weak parent ion (P + 1, m/e 227), which rapidly lost three molecules of water to provide an ion at 173 amu (74%). Loss of a fourth molecule of water, which would have represented the parent ion for either of the tetraenes **29** or **30**, however, was not observed. In itself, this latter observation may be an indication of the instability of such tetraenes.

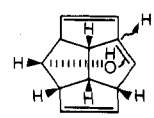
A variety of methods are available to convert the tetraol **27** into either of the desired tetraenes **29** or **30**. Secondary hydroxyl groups are smoothly eliminated on heating the corresponding polyhydroxyl compounds in HMPA;[6] consequently this process was considered for dehydration of the mixture of tetraols represented by **27**. Since this method[8] to dehydrate the hydroxyl groups of **27** might well lead to the formation of isomeric tetraenes, it was desirable to determine the relative energies of **29** and **30**, as well as to determine how much higher in energy the 10π-annulene **2** and the hexaene **32** lie relative to **29** and **30**. Therefore, MNDO calculations[29] with regard to the relative stabilities and strain energies of these polyquinenes were carried out. As illustrated in Table III calculations indicate that tetraene **29** with the two internal double bonds disposed in an anti relationship has a slightly lower heat of formation

(28) (a) Silverstein, R. M.; Clayton, G.; Bassler, I.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 4th ed.; Wiley-Interscience: New York, 1984; p 210. (b) *Ibid.*, p 118.

(29) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899–4907.



33



34

Figure 2.

than its syn counterpart **30**, although the difference is not significant. Because the two tetraenes **29** and **30** possess essentially the same H_f and strain energy, it suggests that experiments designed to prepare one of the tetraenes via dehydration of a suitable tetraol will provide a mixture of the olefinic isomers. Experimentally, this does not constitute a problem since both **29** and **30** can be employed for preparation of **2**.

Extreme care must be taken during the dehydration reaction, since the tetraenes may be air sensitive. It had been previously established in our laboratories[6] that some tetracyclic tetraenes react with oxygen to form insoluble polymers, although this has never been observed for triquinacene or isotriquinacene in our hands.[8] When tetraol **27** was heated in HMPA, a new tetraquinane was isolated in approximately 50% yield, accompanied by another material present in too small a quantity to characterize. The structure of the major component **28** was deduced from spectroscopy, with particular emphasis on ^{13}C NMR. Examination of the ^{13}C spectrum of the compound revealed the presence of four signals [δ 54.5 (d), 57.3 (d), 77.2 (d), 131.9 (d)] that are consistent only with the structure of the dione ether **28**.[30] Both tetraenes **29** and **30** are relatively high in energy, as evidenced by the MNDO calculations. It is this energy content as well as the endo disposition of the 5,12-hydroxyl groups in **27** that results in the formation of ether **28** in preference to tetraenes **29** and **30**.

The formation of diene ether **28** can be envisaged as follows. The 2- and 7-hydroxyl groups are eliminated via the E2 mechanisms earlier reported by Monson.[31a] The third hydroxyl group could then react with a molecule of HMPA to form an alkyl tetramethylphosphorodiimidate intermediate that on release provides a secondary carbocation **33** (Figure 2). The carbonium ion is then attacked by the oxygen atom of the remaining endo hydroxyl group to provide ether **28**. The formation of a secondary carbonium ion during the HMPA-mediated dehydration of **27** is contrary to the mechanism proposed by Monson. Secondary carbocations are not generally accepted as reactive intermediates in this process.[31a] However, it has been reported by some authors that these carbocations do exist during this dehydration sequence.[31b] An alternate pathway is illustrated in Figure 2. MNDO calculations confirm that tetraene **30** is relatively high in energy. Loss of the phosphoroimidate function via an E2 elimination would generate a bridgehead double bond (see **34**) that may react with the oxygen atom, as illustrated, to provide **28** and avoid **30**.

Since semiempirical methods such as MNDO are parameterized to fit experimental data,[32a] it was possible to determine a relative energy difference between the two different polyquinenes **2** and **29**; the difference in the heat of formation was found to be 70.33 kcal/mol (Table III). The strain energy can be defined as the difference between the H_f value and the summation of the strain free energy;[32b] therefore, it was possible to calculate the strain energy for some of the tetraquinenes. The value of most importance in regard to the present study is 51.5 kcal/mol. This is the increase in strain energy encountered in going from tetraene **29** to the desired 10π-annulene **2**. It represents a substantial increase in energy but is not necessarily prohibitive. From the heat of formation depicted in Table III, the desired 10π-annulene **2** should predominate over the isomeric pentaene **31**; moreover, our calculations indicate that hexaene **32** lies at an extremely high energy relative to **2**. The isolation of **32** would be expected to be difficult, if not impossible. Further studies are under way to convert **27** or **28** into pentaene **2**.

With gram quantities of 2,6-diallyl dione **7** in hand, attention now turned to synthetic entry into the perhydrodicyclopenta[*a*,*e*]pentalene system represented by **8** (Scheme II). 2,8-Diallyl dione **24b** could in turn be employed for construction of the other system of interest, dicyclopenta[*a*,*d*]pentalene (**3**) (see below). Originally, allyl groups had been chosen to functionalize the *cis*-bicyclo[3.3.0]octanedione system **6b**, for these groups are stable to hydrolysis and facilitate the synthesis of **7** from **23b** in high yield. Moreover, the π system serves as latent functionality to be released when required. It was now time to take full advantage of this strategy. A number of methods were available to functionalize the double bonds in **7**. It was felt that phenylsulfenyl chloride might add across the olefinic bond with a high degree of regioselectivity;[32] however, this goal was not realized (see ref 16 for details). Consequently, attention turned to the addition of hydrogen bromide to the double bonds in the presence of peroxides.[33] The anti-Markovnikov addition of HBr to **7** gave the desired 2,6-bis(3-bromopropyl)-*cis*-bicyclo[3.3.0]octane-3,7-dione (**35**), as a mixture of diastereomers, in yields ranging from 68 to 80%. Since **7** was present as a mixture of diastereomers **7a** and **7b**, in a ratio of 4:1, it was not surprising that exo,exo stereoisomer **35a** comprised approximately 90% of the material. It was accompanied by a second diastereomer (10%), which is, presumably, endo,endo diastereomer **35b**. The ^{13}C NMR spectrum of **35a** contained only seven lines, in agreement with the symmetry of the exo,exo diastereomer. Moreover, it appears that epimerization of **7a** to **7b** has not occurred under these conditions; the stereochemical integrity of **7a** is apparently maintained on conversion into **35a** based on comparison of their ^{13}C NMR spectra. The structure of the minor isomer could be inferred from gas chromatography and GC–mass spectroscopy, as well as chemical reactivity (see below).

Several approaches to effect the simultaneous cyclization of the bromopropyl substituents with the carbonyl units in **35** to provide **36** were envisaged. The simplest method rested on the treatment of bromo ketone **35** with activated magnesium;[34] however, in model systems this sequence gave extensive formation of pinacol products,[16] analogous to earlier reports by Crandall.[35] Cyclization mediated by lithium metal was also considered but yields in simpler systems were 40–50%[35] and militated against this approach. However, Kagen[36] had discovered a method, which

(30) Professor Mehta has observed the formation of this ether under similar conditions. Mehta, G., private communication.

(31) (a) Monson, R. S. *Tetrahedron Lett.* **1971**, 567–570. Monson, R. S.; Priest, D. N. *J. Org. Chem.* **1971**, *36*, 3826–3828. (b) Lomas, J. S.; Sagatys, D. S.; Dubois, J. E. *Tetrahedron Lett.* **1972**, 165–168.

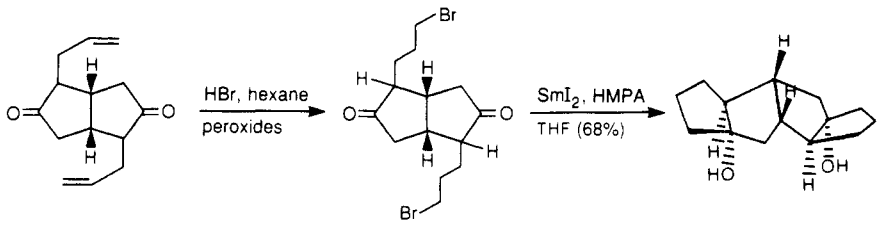
(32) (a) Mueller, W. H. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 482–492. Clark, T. *A Handbook of Computational Chemistry*; Wiley-Interscience: New York, 1985; p 97. (b) Benson, S. W., et al. *Chem. Rev.* **1969**, 69, 279–324.

(33) Skell, P. S.; Freeman, P. K. *J. Org. Chem.* **1964**, *29*, 2524–2526. Vogel, A. *Vogel's Practical Organic Chemistry*; Longman: New York, 1978; p 399.

(34) Rieke, R.; Hudnall, P. *J. Am. Chem. Soc.* **1972**, *94*, 7178–7179. Bales, S.; Hudnall, P.; Poindexter, G.; Rieke, R. *Org. Synth.* **1980**, *29*, 85–94.

(35) Magaha, H. S.; Crandall, J. K. *J. Org. Chem.* **1982**, *47*, 5368–5371.

Scheme VII



7

35a, exo, exo (-H, α)
35b, (-H, β)

36a, cis-cisoid-cis-cisoid (75)
36b, cis-transoid-cis-transoid (10)

was reduced to practice in the laboratories of Molander[37] and permitted the addition of an electrophilic alkyl halide to a carbonyl group under mild conditions. This was achieved by converting the carbonyl group into a ketyl radical with samarium diiodide, followed by attack on the reactive alkyl halide or its corresponding radical anion.[36,37a] Moreover, recent reports by Inanaga et al. indicate that HMPA is an effective catalyst in these electron-transfer processes.[37b] In agreement with this, the dibromo dione **35a,b** was reacted with samarium diiodide (HMPA–THF) via the conditions of Molander[37] to provide a mixture of the stereoisomeric tetracyclic diols **36a** and **36b** in an approximate ratio of 15:2. The overall yield of this process was 80%. The major cis–cisoid–cis–cisoid perhydrocyclopentapentalene, **36a**, derived from *exo,exo*-dibromide **35a**, obtained from this cyclization reaction is represented by structure **36a**, as illustrated in Scheme VII. The initial exo,exo stereochemistry of **35a** does not appear to be altered under the reaction conditions. Diol **36a** possesses a twofold axis of symmetry (C_{2v}), in agreement with the seven-line ^{13}C NMR spectrum (δ 25.6, 34.5, 42.0, 47.3, 51.3, 58.0, 92.8) obtained for this tetraquinane. Examination of the reaction mixture via GC–mass spectroscopy and ^{13}C NMR spectroscopy reflected the presence of the second stereoisomer **36b** (<8%). If the stereochemistry of **35b** is maintained during the cyclization, the product mixture should reflect this. In fact, the starting dibromide **35** contained small quantities (10%) of the symmetrical endo,endo epimer, which should result in formation of the cis–transoid–cis–transoid isomer **36b**. In this isomer, the two external five-membered rings possess the endo configuration with respect to the central cis-fused bicyclo[3.3.0]octanedione unit, rather than the exo configuration present in **36a**. The ^{13}C NMR spectrum of this diol should also contain signals for seven different carbon atoms. Although this isomer was present in quantities too small to be isolated in pure form, evidence from ^{13}C NMR and GC–mass spectroscopy on a sample enriched in **36b** suggests this stereoisomer was indeed present.[16] Neither the stereochemistry of the diol functions in **36** nor that of the cis-fused five-membered rings relative to one another is of any practical consequence since both will be destroyed on the pathway toward **1**.

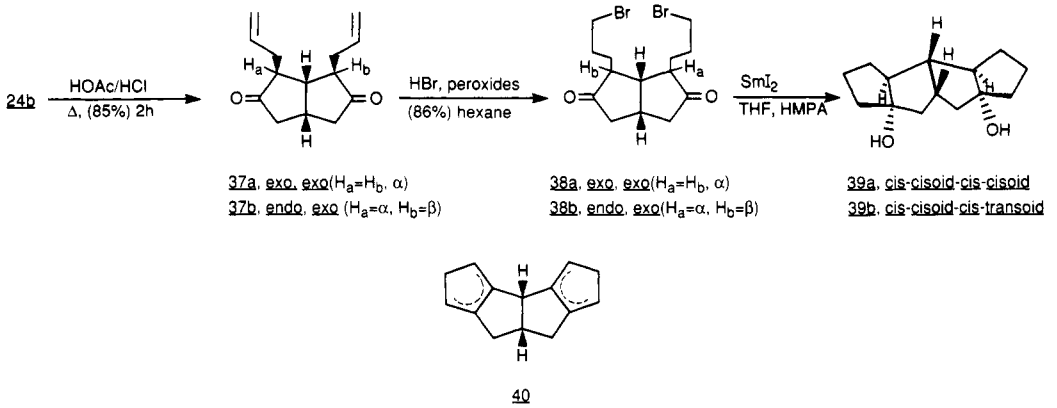
Based on the successful conversion of diallyl dione **7** into dicyclopentapentalene **36**, efforts were now begun to convert 2,8-diallyl isomer **24b** into perhydrodicyclopenta[*a*,*d*]pentalene **39** via a similar protocol. Hydrolysis of the *tert*-butyl ester groups of **24b** followed by decarboxylation furnished 2,8-diallyl regioisomer **37** in 85% yield. This mixture was composed of *exo,exo*-2,8-diallyl stereoisomer **37a** and endo,exo diastereomer **37b** in a ratio of 85:15, accompanied by a trace of a third epimer (GC–mass spectroscopy) felt to be the *endo,endo*-2,8-diallyl dione. The eight-line ^{13}C NMR spectrum of exo,exo isomer **37a** is in agreement with the C_s symmetry of the molecule; moreover, the stereochemistry of exo,endo stereoisomer **37b** was confirmed on examination of the 14-line ^{13}C NMR spectrum obtained for this molecule. Analogous to the sequence of events during the synthesis of **36**, the epimeric mixture of 2,8-diallyl diones **37** was reacted with HBr in the presence of peroxides. This process proceeded cleanly and in high yield (86%) to provide the two epimeric dibromides **38a** and **38b**. As expected, exo,exo stereoisomer **38a** predominated in the mixture in preference to the less stable endo,exo isomer **38b** (ratio ~9:1). The stereochemical integrity of the hydrobromination was maintained as evidenced on examination of the eight-line ^{13}C NMR spectrum of the major isomer **38a**. When this mixture of dibromides **38** was stirred with samarium diiodide at room temperature for several hours, the simultaneous cyclization of the two bromoalkyl substituents was effected to furnish the perhydrodicyclopenta[*a*,*d*]pentalene system **39** in 68% yield. The ratio of the two diastereomeric tetraquinanes **39a** to **39b** is at least 30:4 and is perhaps higher since this value is based on NMR spectroscopy. No attempts to maximize the yield of this process have been made to date. The cis–cisoid–cis–cisoid stereochemistry of the major isomer **39a** is based on the stereochemistry of the starting dibromide **38a** as well as the eight-line ^{13}C NMR spectrum observed for **39a**. Europium shift reagents and 2D COSY NMR spectroscopy were employed to assign the stereochemistry of **39a**. Despite this effort it was not possible to assign this stereochemistry unequivocally. However, based on the preferred cis geometry of bicyclo[3.3.0]octanes on thermodynamic grounds[38] as well as the preference for exo substituents in these systems,[8] the stereochemical assignment of the hydroxyl functions in **39a** rests on seemingly firm ground. Since the starting dibromide contained about 10% of endo,exo isomer **39b**, the isolation of the second, minor isomer **39b** is not surprising. The isomer of lower symmetry **38b** should cyclize to provide the cis–cisoid–cis–transoid diastereomer, which would be characterized by a 14-line ^{13}C NMR spectrum. Although **39b** was not isolated in pure form, the ^{13}C NMR chemical shifts and GC–mass spectroscopic data obtained on a fraction enriched in **39b** suggest that this assignment is correct. Again, in agreement with the original synthetic plan, the stereochemistry of the diols in **39** will be destroyed in later work on the route to dicyclopenta[*a*,*d*]pentalene (**3**).

(36) Namy, J. L.; Souppe, J.; Collin, J.; Kagen, H. B. *J. Org. Chem.* **1984**, *49*, 2045–2049. Imamoto, T.; Takeyama, T.; Yokoyama, M. *Tetrahedron Lett.* **1984**, 3225–3226.

(37) (a) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1986**, *51*, 1778–1786 and references cited therein. (b) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485–1487. Otsubo, K.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 1487–1490 and references cited therein.

(38) Linstead, R. P.; Meade, E. M. *J. Chem. Soc.* **1934**, 935–946.

Scheme VIII



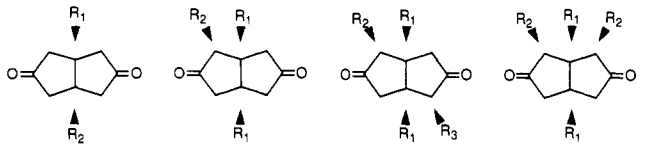


Figure 3.

Preliminary experiments have been carried out with regard to the removal of the hydroxyl groups from **39** to provide diene **40**. Although six possible isomeric dienes are possible, on treatment of **39a** with (1,1,1,3,3,3-hexafluoro-2-phenyl-2-propoxy)diphenylsulfurane,[39] four isomeric dienes were observed by gas chromatography and GC–mass spectroscopy. Since all four dienes are useful for the preparation of **3**, they were not separated. Studies are currently under way to convert **36** and **40** into the 14π-annulenes dicyclopenta[*a*,*e*]pentalene (**1**) and dicyclopenta[*a*,*d*]pentalene (**3**) respectively.

In summary, synthetic entry into the tetracyclo[6.6.0.0^{2,6}.0^{9,13}]tetradecane, tetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane, and tetracyclo[6.6.0.0^{2,6}.0^{10,14}]tetradecane ring systems has been achieved via the Weiss reaction. The preparation of 2,5,7,12-tetrahydroxytetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane (**27**) was accomplished from glyoxal (**4a**) and di-*tert*-butyl 3-oxoglutarate (**5b**) in six steps, while perhydrodicyclopentapentalenes **36** and **39** have been synthesized from **4a** and **5b** in an analogous number of transformations. The ease with which tetraquinanes **27**, **37**, and **39** have been synthesized attests to the versatility of this condensation for the construction of polycyclopentanoid compounds.[6]

Although substitution at positions 1 and 5 of *cis*-bicyclo[3.3.0]octane-3,7-diones can be achieved via the Weiss reaction by judicious choice of starting 1,2-dicarbonyl compound (e.g., see **4b**, Scheme I), the ability to monoalkylate (C-2) or to dialkylate bisenol ether **20b** at positions 2,6 or 2,8 expands significantly the scope of the reaction of **4** with **5**. Substitution can now be introduced at the 1, 1,5, 1,2,5, 1,2,5,6, and 1,2,5,8 positions; moreover, functionalization of the carbonyl groups at positions 3 and 7 has been reported previously. A schematic of these observations is outlined in Figure 3.

With regard to the synthesis of tetraquinanes **37** and **39**, the SmI_2-mediated cyclization to provide fused five-membered rings has been reported.[37a] In the present case two cyclizations to provide *cis*-bicyclo[3.3.0]octanes were carried out simultaneously and in good yield to provide tetracyclic diols **36** and **39**, respectively. This one-pot biscyclization further demonstrates the synthetic potential of this reductive cyclization, especially in the field of fused five-membered rings. Further studies with regard to the synthesis of annulenes **1–3** will be reported in due course.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus; they are uncorrected. Microanalyses were performed on an F and M Scientific Corp. carbon, hydrogen, nitrogen analyzer Model 185; some analyses were also carried out at the National Institutes of Health, Bethesda, MD. Low-resolution nuclear magnetic resonance spectra were recorded on Varian T-60 (^{1}H), EM-360A (^{1}H), and CFT-20 (^{13}C) NMR spectrometers, while the high-resolution nuclear magnetic resonance spectra were run on a Bruker 250-MHz multiple-probe instrument. The low-resolution chemical ionization (CI) mass spectra were obtained on a Hewlett-Packard 5985 gas chromatograph–mass spectrometer, while high-resolution spectra were recorded on an AEI MS-902 mass spectrometer. The infrared spectra were recorded on a Beckman Acculab-1 spectrometer, while FT-IR spectra were taken on a Mattson Instruments Polaris FT-IR spectrometer. Ozone was generated with a Welsbach laboratory ozonator Model T-408.

Analytical TLC plates used were E. Merck Brinkmann UV-active silica gel or alumina on plastic. Flash chromatography was performed according to the method of Still[40] using 4–63-μm silica gel. The spray reagent was composed of a solution of 2,4-dinitrophenylhydrazine, ethanol, and sulfuric acid. High-pressure liquid chromatography was performed with the Waters HP-500 preparatory system. A typical eluent consisted of distilled hexane and ethyl acetate (75:25). The pump rate was 1.5 L/min. Analytical GLC was performed on a Hewlett-Packard Model 5880A capillary gas chromatograph, using helium as a carrier gas.

Benzene, THF, and ether were distilled from sodium–benzophenone as needed. Methanol was dried by distillation over active magnesium metal, while dichloromethane was distilled from calcium hydride. Hexane was dried with phosphorus pentoxide. DMF was dried overnight with KOH pellets, decanted, distilled from magnesium sulfate, and stored over activated molecular sieves.

Samarium metal powder was purchased from Research Chemicals, Phoenix, AZ. Unless otherwise stated, all other starting materials were purchased from Aldrich Chemical Co., Milwaukee, WI.

Tetra-*tert*-butyl *cis*-3,7-Dihydroxy-*cis*-bicyclo[3.3.0]-octa-2,6-diene-2,4,6,8-tetracarboxylate (6b). Di-*tert*-butyl ester **5b** (49.7 g, 185.6 mmol) was dissolved in methanol (180 mL). Anhydrous K_2CO_3 (27.4 g, 198.5 mmol) was dissolved in water (80.0 mL) and then added to the solution of diester **5b**. Aqueous sodium bicarbonate (65 mL, 10% (w/w)) was also added to this mixture. After a few minutes the solution became turbid. The solution was then permitted to cool to about 35 °C. At this point, aqueous glyoxal **4a** (5.588 g, 96.3 mmol) was added very slowly with a disposable pipet into the well-stirred solution. It was very

(39) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 5003–5010.

(40) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

important to use an overhead stirrer to keep the mixture homogeneous. The reaction mixture was allowed to stir for 16 h, after which the solution was cooled and filtered. The precipitate that formed was filtered from the medium; however, the filtrate was not discarded, since it still contained appreciable amounts of **6b**. The solid was placed in a large Erlenmeyer flask that contained water (300 mL) and $CHCl_3$ (300 mL). Ice was added to the mixture to maintain a temperature of 0 °C. Cold aqueous HCl (200 mL, 1.0 N) was added to the well-stirred solution, and stirring was continued for 15 min. The organic layer was then separated from the aqueous layer, and the water layer was extracted with fresh $CHCl_3$ (2 × 100 mL). The organic layers were combined and the solvent was removed under reduced pressure. The solid that resulted was dried at 50 °C in a heated vacuum oven. This material was recrystallized from a mixture of ethyl acetate–hexane to provide a light yellow solid **6b** (38.7 g, 71.9 mmol, 77.5%). Additional quantities of **6b** could be obtained from the filtrate. For example, when a cold solution of dilute aqueous HCl was added to the mother liquor, additional tetraester precipitated from the solution. It was filtered from the medium and recrystallized. **6b**: mp 140–141 °C; IR (KBr) 1730, 1720, 1660 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.45, 1.49 (two s, 36 H), 3.47 (t, J = 2.1 Hz, 2 H), 3.71 (t, J = 2.1 Hz, 2 H), 10.59 (broad, 2 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 27.9 (q), 28.2 (q), 43.5 (d, bridgehead carbons), 56.7 (d) 81.5 (s), 81.0 (s), 104.0 (s), 168.9 (s), 170.3 (s), 171.0 (s); mass spectrum (EI, 15 eV) m/e (relative intensity) 538 (P^+, trace), 482 (1.9), 465 (trace), 425 (8.5). Anal. Calcd for $C_{28}H_{42}O_{10}$: C, 62.43; H, 7.86. Found: C, 62.24;, H, 8.04. The highest combined yield of **6b** via this process was 84%.

Tetra-*tert*-butyl 3,7-Dimethoxy-*cis*-bicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate (20b). Tetra-*tert*-butyl ester **6b** (24.71 g, 45.7 mmol) was dissolved in ether (200 mL). Freshly generated diazomethane (0.3 mol) was added to the cooled solution of tetraester **6b** at −58 °C (hexane/dry ice bath). The reaction was allowed to stir overnight at room temperature. Excess diazomethane was removed with a water aspirator in a well-ventillated fume hood. The solvent was removed under reduced pressure, and the yellowish crystalline material that remained was recrystallized from an ethyl acetate–hexane mixture. The solid **20b** (21.24 g, 37.5 mmol, 81.8%) was dried under reduced pressure (drying oven). **20b**: mp 128–129 °C; IR (KBr) 1710, 1690, 1620 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.44, 1.47 (two s, 36 H), 3.67 (m, J = 1.8 Hz, 4 H), 3.80 (s, 6 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 25.7 (q), 27.9 (q), 45.7 (d), 55.6 (d), 58.2 (q, OCH_3), 79.7 (s), 81.2 (s), 109.7 (s), 162.8 (s), 164.4 (s), 170.1 (s); mass spectrum (CI, CH_4) m/e (relative intensity) 567 (P + 1, 29.7), 511 (32.1), 493 (37.8), 455 (100). Anal. Calcd for $C_{30}H_{46}O_{10}$: C, 63.58; H, 8.18. Found: C, 63.28; H, 8.43.

Decarboxylation of Tetra-*tert*-butyl 3,7-Dimethoxy-*cis*-bicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate (20b). Tetra-*tert*-butyl ester **20b** (4.983 g, 8.8 mmol) was suspended in a mixture of glacial acetic acid (20 mL) and aqueous HCl (2.0 N, 50 mL). The reaction mixture was heated to reflux and maintained at this temperature for 1.0 h. The reaction was then cooled to 0 °C and extracted with $CHCl_3$ (2 × 100 mL). The solvent was removed under reduced pressure. The residue was dissolved in fresh $CHCl_3$ (100 mL) and was washed with aqueous sodium bicarbonate solution (50 mL, 10% (w/w)). The organic layer was washed with brine and dried ($MgSO_4$), and the solvent was removed under reduced pressure to provide bicyclo[3.3.0]octane-3,7-dione (**10**) (1.075 g, 7.8 mmol, 89%): mp 83–85 °C (lit.[17] mp 84–85 °C).

2-(3-Propenyl)-*cis*-bicyclo[3.3.0]octane-3,7-dione (13). Tetra-*tert*-butyl ester **20b** (31.8 g, 56.2 mmol) was dissolved in dry DMF (200.0 mL). This solution was slowly added to a three-neck round-bottom flask that contained KH (7.3 g, 182.5 mmol). The reaction mixture was maintained under a dry, inert atmosphere (Ar) and kept at −25 °C (CCl_4/dry ice bath). After tetraester **20b** was added to the slurry of KH, the temperature was lowered to −58 °C (hexane/dry ice bath) for 1.0 h. An overhead stirrer was necessary to keep the solution from solidifying. A large excess of allyl iodide (17.0 mL, 185.9 mmol) was added to the reaction mixture with a syringe and the temperature was maintained at −58 °C for 5.0 h. The reaction was quenched by adding an excess of aqueous HCl (250.0 mL, 1.0 N) to the mixture at −58 °C. The solution was permitted to warm to room temperature. Water (2.0 L) was added and the reaction mixture was extracted with ether (3 × 150 mL). The organic layers were combined, and the solvent was removed under reduced pressure. The oil that resulted was suitable for decarboxylation. Decarboxylation was accomplished by heating the tetraester in a mixture of glacial acetic acid and aqueous HCl (1.0 N) at reflux for 1.5 h. The solution was then cooled to room temperature, diluted with water, and washed with $CHCl_3$ (3 × 75 mL). The organic layers were combined, washed with aqueous sodium bicarbonate (10% (w/w)), and then dried ($MgSO_4$). The solvent was removed under reduced pressure to provide a light orange oil (9.86 g). Analysis of the crude material by gas chromatography indicated the oil was composed of the following components: **13** (91.0%, 8.97 g, 50.4 mmol) and *cis*-bicyclo[3.3.0]octane-3,7-dione (**10**) (8.0%, 0.79 g, 5.7 mmol). A small amount of material composed of a mixture of several diallyl diones was also isolated. The spectral properties of the purified material were identical with those of monoallyl dione **13**, which had been prepared previously by another method.[8] The retention times of the two epimeric monoallyl derivatives analyzed by capillary gas chromatography were 12.45 (exo) and 14.30 min (endo). The oven temperature was 130 °C (isotherm).

Attempted Preparation of Tetramethyl 2,6-Di(3-propenyl)-3,7-dioxo-*cis*-bicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate from Tetramethyl Ester 6a. Tetramethyl ester **6a** (3.0 g, 8.11 mmol) was dissolved in dry DMF (150 mL). This mixture was slowly injected into a cooled mixture (0 °C) of NaH (0.61 g, 25.4 mmol) and dry DMF (10 mL) with a double-ended needle. The reaction mixture was maintained under an inert atmosphere (dry nitrogen gas), and allyl bromide (3.5 mL, 40.4 mmol) was added. After stirring for 1 h, the solution was quenched with aqueous HCl (100 mL, 1.0 N). The reaction mixture was diluted with water (600 mL) and then extracted with ether (3 × 100 mL). The ether layers were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure to provide an orange oil (3.00 g). Peaks in the mass spectrum corresponding to P − 32 (MeOH)[41] were used for estimating the ratios of the products. Analysis of the material by mass spectroscopy indicated the presence of mono- (M^+, 410), di- (M^+, 450), and trialkylated (M^+, 490) products. The crude products in this mixture proved too difficult to separate from each other and were not characterized further. Mass spectrum (CI, CH_4) m/e (relative intensity) 411 (P + 1, 2.5), 379 (P + 1 − 32, 4.2); 451 (P + 1, 48.4), 419 (P + 1 − 32, 100); 491 (P + 1, 14.9), 459 (P + 1 − 32, 29.6).

Preparation of the Disodium Salt of Tetramethyl 3,7-Dioxo-*cis*-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate (6a). Tetramethyl ester **6a** (3.0 g, 8.11 mmol) was dissolved in dry CH_3OH (50.0 mL). This mixture was slowly added to a solution of NaOH (0.64 g, 16 mmol) in methanol (50 mL). The reaction mixture was permitted to stir for 30 min, after which a white solid precipitated from the solution. This material was filtered from the medium and dried in a vaccum oven. The salt of **6a** (3.31 g, 8.00 mmol, 98%) obtained by this procedure was suitable for the alkylation work.[17]

Attempted Preparation of Tetramethyl 2,6-Di(3-propenyl)-3,7-dioxo-*cis*-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate via Alkylation of the Disodium Salt of Tetramethyl Ester 6a. Dry DMF (200 mL) was added with a double-ended needle to a 500-mL round-bottom flask that contained the disodium salt of **6a** (3.05 g, 7.37 mmol). Allyl bromide (0.8 mL, 9.0 mmol) was injected with a syringe into the reaction mixture. The reaction was maintained under an atmosphere of dry nitrogen. The reaction mixture was stirred at room temperature for 1.5 h and then treated with aqueous HCl (100 mL, 1.0 N). The solution was diluted with water (600 mL) and extracted with ether (2 × 150 mL). The ether layers were combined and dried (Na_2SO_4). The solvent was removed under reduced pressure to provide a light orange oil (2.44 g). The mass spectrum of the crude reaction material indicated that the mixture consisted of mono- (M^+, 410), di- (M^+, 450), and trialkylated (M^+, 490) products. The approximate ratio of the materials was estimated from mass spectroscopy. The peaks in the spectrum (EI) that corresponded to P − 32 (MeOH) were used to estimate the ratios

(41) Yang, S.; Cook, J. M. *J. Org. Chem.* **1976**, *41*, 1903–1907.

of the products. The products in this crude mixture were too difficult to separate and were not characterized further. Mass spectrum: (EI, 15 eV) m/e (relative intensity) 490 (P^+, 3.0), 458 (P - 32, 40); 450 (P^+, 17.0), 418 (P - 32, 63); 410 (P^+, 9.0); 378 (P - 32, 46).

Tetramethyl 2,6-Di(3-propenyl)-3,7-dimethoxy-*cis*-bicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate (23a). Bisenol ether **20a** (16.9 g, 42.4 mmol) was dissolved in dry DMF (350 mL). This solution was slowly injected with a double-ended needle into a cooled slurry (-25 °C) of NaH (3.05 g, 127 mmol) in dry DMF (30 mL). The reaction mixture was allowed to stir at room temperature for 30 min, after which the solution was again cooled to -25 °C and allyl bromide (10.0 mL, 115 mmol) was added. After 2 h, the reaction mixture was treated with aqueous HCl (200 mL, 1.0 N), and water (700 mL) was added to the solution, after which the mixture was treated as above and dried ($MgSO_4$). The solvent was removed under reduced pressure to provide an oil that was purified by high-pressure liquid chromatography (SiO_2; 40:60 ethyl acetate–hexane). 2,6-Diallyl tetramethyl ester **23a** was isolated as a clear oil. The rest of the material balance consisted of starting material **20a** and another dialkylated product. Analysis of the residual dialkylated material via ^{13}C spectroscopy suggests that it is 2,8-diallyl tetramethyl ester **24a** but did not unequivocally rule out the possibility of other isomers. Since the route via the tetramethyl ester was later discontinued, the second component was not characterized further. **23a** (9.94 g, 20.8 mmol, 49.0%): IR (neat) 1728, 1710, 1635 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 2.80–3.00 (m, 4 H), 3.65 (two s, 12 H), 3.85–4.00 (m, 8 H), 4.80–5.60 (m, 6 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) 39.58 (t, carbon α to alkene), 47.77 (d, bridgehead carbons), 50.96, 51.75 (q, OCH_3 ester), 62.68 (q, OCH_3, ether), 63.94 (s), 109.45 (s), 119.53 (t), 133.07 (d), 164.00 (s), 168.15 (s), 172.20 (s); mass spectrum (EI, 15 eV) m/e (relative intensity) 478 (P^+, 27), 436 (100), 405 (26), 395 (60). Anal. Calcd for $C_{24}H_{30}O_{10}$: C, 60.24; H, 6.32. Found: C, 60.27; H, 6.35.

Attempted Preparation of 2,6-Di(3-propenyl)-*cis*-bicyclo[3.3.0]octane-3,7-dione 7 via Acid Hydrolysis and Decarboxylation of Tetramethyl Ester 23a. Diallyl tetramethyl ester **23a** (7.90 g, 16.5 mmol) was dissolved in glacial acetic acid (150 mL). The solution was heated to reflux for 1 day, during which time aqueous HCl (1.0 N, total 400 mL) was added over a 5-h period. The reaction mixture was cooled and then diluted with water (350 mL). The mixture was then washed with $CHCl_3$ (3 × 150 mL), after which the organic layers were combined and dried ($MgSO_4$). The solvent was removed under reduced pressure to provide a light orange oil (**22**, 3.126 g). The oil, when analyzed by TLC, was found to react with 2,4-dinitrophenylhydrazine; however, the R_f of the oil did not correspond to that of diallyl dione **7**. Examination of the material by ^1H NMR and mass spectroscopy indicated that this material was diallyl diester **22**. Since this diester was fully characterized, when prepared by a different route, this particular sample was not further characterized (see below). **22**: ^1H NMR (60 MHz, $CDCl_3$) δ 1.80–3.20 (m, 8 H), 3.65 (two s, 6 H), 3.90 (s, 2 H), 4.80–5.60 (m, 6 H).

Dimethyl 3,7-Dioxo-*cis*-bicyclo[3.3.0]octane-2,6-dicarboxylate (21).[24] Sodium metal (21.85 g, 0.95 mol) was slowly added to dry CH_3OH (150 mL). After the addition of sodium metal was completed, the mixture was refluxed for 30 min. The solvent was removed under reduced pressure to provide sodium methoxide. The sodium methoxide was dissolved in a solution of dry dimethyl sulfoxide (1.5 L) and dry CH_3OH (125 mL). Tetramethyl ester **6a** (35.0 g, 94.6 mmol) was added to the solution, and the solution was heated to 58–80 °C. The reaction was permitted to run for 2 days, after which the volume of the solvent was reduced to 1.0 L via Kugelrohr distillation under vacuum. The solution that remained was diluted with water (1.0 L) and washed with $CHCl_3$ (3 × 200 mL). The organic layers were combined and dried ($MgSO_4$), and the solvent was removed under reduced pressure to provide a dark oil. The oil was purified by column chromatography (SiO_2, 40:60 ethyl acetate–hexane) to provide solid diester **21**. The diester was recrystallized from an ethyl acetate–hexane mixture. The final weight of diester **21** was 10.16 g (40 mmol, 42.3%). **21**: mp 99 °C (lit.[24] mp 110 °C); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 38.23 (t), 38.57 (d), 50.95 (q), 102.5 (s), 169.75 (s), 175.72 (s); mass spectrum (EI, 15 eV) m/e (relative intensity) 254 (P^+, 73), 222 (85), 190 (100).

Dimethyl 3,7-Dioxo-2,6-di(3-propenyl)-*cis*-bicyclo[3.3.0]-octane-2,6-dicarboxylate (22). Dimethyl ester **21** (0.212 g, 0.834 mmol) was dissolved in dry DMF (75 mL). The solution of the dimethyl ester was slowly injected into a mixture of KH (0.114 g, 2.84 mmol) in dry DMF (10 mL) that was cooled to -25 °C (CCl_4/dry ice bath). The reaction was maintained under argon gas. The mixture was allowed to come to room temperature over a period of 25 min, whereupon the reaction mixture was cooled to 0 °C. Allyl iodide (0.3 mL, 3.3 mmol) was added and the solution was permitted to stir for 30 min, followed by cooling to 0 °C. The reaction mixture was then quenched with aqueous HCl (50 mL, 1.0 N) and then diluted with water (900 mL). The solution was extracted with ether (3 × 100 mL), the ether layers were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The resulting oil was purified by column chromatography (Al_2O_3, 30:70 ethyl acetate–hexane). **22**: mp 91–92 °C; IR (KBr) 1730, 1710 (s), 1630 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.70–1.90 (t, 4 H), 2.50–3.30 (m, 6 H), 4.10 (s, 6 H), 4.50–4.90 (m, 2 H), 5.20–5.80 (m, 4 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 39.12 (t), 40.30 (t), 42.11 (d), 52.43 (q), 62.92 (s), 120.27 (t), 131.80 (d), 170.33 (s), 210.44 (s). Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.81; H, 6.73. The spectroscopic data for this sample **22** were identical with those of the material prepared by hydrolysis of tetraester **21** (see above).

2,6- and 2,8-Di(3-propenyl)-*cis*-bicyclo[3.3.0]octane-3,7-diones (7 and 37). Tetra-*tert*-butyl ester **20b** was converted into the monoallyl derivative via the procedure described above.[8] The mixture of monoallyl tetraesters (78.2 g, 129.0 mmol) was then dissolved in dry DMF (300 mL) and slowly injected with a double-ended needle into a slurry of KH (7.49 g, 0.187 mmol) in DMF (25 mL) that had been maintained at a temperature of -25 °C (CCl_4/dry ice bath). The reaction was carried out under argon. The mixture was stirred for 30 min, after which allyl iodide (18.3 mL, 200 mmol) was injected via a syringe into the cooled solution. The mixture was stirred for an additional 4.5 h at -25 °C and then slowly diluted with water (800 mL) and extracted with ether (4 × 150 mL). The organic layers were combined, and the solvent was removed under reduced pressure to provide a light orange oil. This material was hydrolyzed and decarboxylated analogously to the conditions described in a previous experiment. The crude oil, which contained diallyl-*cis*-bicyclo[3.3.0]octane-3,7-dione, was percolated through a short wash column (SiO_2) and then purified by HPLC (SiO_2, 30:70 ethyl acetate–hexane). Both 2,6- and 2,8-diallyl dione isomers **7** (10.75 g, 49.3 mmol, 47.4%) and **37** (7.98 g, 36.6 mmol, 35.2%), respectively, were cleanly separated. **7** (2,6-diallyl dione): **7a**:**7b** = 80:20; mp 42–44 °C; IR (neat) 1725, 1635 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 2.20–2.35 (m, 4 H), 2.50–2.70 (m, 8 H), 5.15 (m, 4 H), 5.40–5.60 (m, 2 H); (isomer **7a**) ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 33.56 (t, carbon α to the alkene group), 39.86 (d, bridgehead carbon), 43.29 (t, carbon α to the ketone), 52.74 (d), 117.39 (t), 134.92 (d), 218 (s); (isomer **7b**) ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 30.61 (t, carbon α to the alkene group), 38.33 (d), 42.08 (t), 53.29 (d), 116.21 (t), 135.79 (d), 216.59 (s); mass spectrum (CI, CH_4) m/e (relative intensity) 219 (P + 1, 100.0), 177 (3.4). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.13; H, 8.36. **37** (2,8-diallyl dione): **37a**:**37b** = 75:25; bp 136 °C (1 mmHg); ^1H NMR spectrum was indistinguishable for all practical purposes from the ^1H NMR spectrum of 2,6-diallyl dione **7** described above. **37a**: ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 32.10 (d), 34.12 (t), 43.42 (t), 46.76 (d), 52.96 (d), 117.6 (t), 134.96 (d), 217.72 (s). **37b**: ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 29.69 (t), 32.34 (d), 33.05 (t), 41.90 (t), 43.42 (d), 44.53 (t), 48.01 (d), 54.31 (d), 115.87 (t), 118.25 (t), 135.98 (d), 136.97 (d), 216.90 (s), 218.76 (s). The mixture of diallyl diones **37a** and **37b** was hygroscopic. Anal. Calcd for $C_{14}H_{18}O_2 \cdot {}^1/_4H_2O$: C, 75.48; H, 8.37. Found: C, 75.77; H, 8.15.

Tetra-*tert*-butyl 2,6-Di(3-propenyl)-3,7-dimethoxybicyclo[3.3.0]octa-3,7-diene-2,4,6,8-tetracarboxylate (23b) on a 100-g Scale. Tetra-*tert*-butyl ester **20a** (78.037 g, 138 mmol) was dissolved in dry DMF (800 mL), and the solution was injected with a double-ended needle into a cooled solution of KH (20.74 g, 517 mmol in 30 mL of dry DMF) at -25 °C. The reaction temperature was allowed to rise to 27 °C and the mixture was stirred for 1.0 h. The solution was then cooled to -25 °C (CCl_4/dry ice bath), after which the mixture was quenched with allyl bromide (52 mL, 601 mmol). The reaction temperature was allowed to rise to 27 °C and the mixture was stirred for 48 h. The reaction

mixture was slowly quenched with water (500 mL). The solution was then acidified with dilute HCl (1.0 N) and diluted with more water (500 mL). The aqueous solution was then extracted with ether (4 × 300 mL), and the ether was removed under reduced pressure to provide a dark semisolid. This material was triturated with cold methanol. The solid residue was recrystallized from a hexane–ethyl acetate mixture to provide solid 2,6-diallyl tetraester **23b** (53.584 g, 82.9 mmol, 60%) as a single stereoisomer. The mother liquor was retained, since it contained the 2,8-diallyl tetraester (38%). 2,8-Diallyl tetraester **24b** was purified by column chromatography (SiO_2, 40:60 ethyl acetate–hexane). Again, only 2,8-diallyl tetraester **24b** was present. **23b** (2,6-diallyl isomer): mp 115–118 °C; IR (KBr) 1735, 1705, 1640 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.40–1.50 (two s, 36 H), 3.32 (s, 2 H), 3.97 (s, 6 H), 5.00–5.10 (m, 4 H), 5.50–5.60 (m, 2 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 28.2 (q, 6 C), 28.4 (q, 6 C), 40.3 (t), 47.7 (d), 63.3 (q), 64.6 (s), 80.3 (s), 81.0 (s), 112.5 (s), 118.6 (d), 134.1 (t), 163.2 (s), 169.6 (s), 170.7 (s); mass spectrum (CI, CH_4) m/e (relative intensity) 647 (P + 1, 40), 591 (18), 573 (10), 535 (60). Anal. Calcd for $C_{36}H_{54}O_{10}$: C, 66.85; H, 8.42. Found: C, 66.58; H, 8.49. **24b** (2,8-diallyl isomer): IR (neat) 1735, 1710, 1695, 1625 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.30–1.50 (m, 36 H), 2.60–2.70 (m 4 H), 3.30–4.00 (m, 2 H), 3.80 (two s, 6 H), 4.90–5.10 (m, 4 H), 5.60–5.80 (m, 2 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 27.8 (q, 12 C), 42.0 (t), 46.8 (d), 49.2 (d), 60.8 (q), 61.0 (s), 80.3 (s), 81.5 (s), 111.1 (s), 118.2 (t), 133.9 (d), 162.5 (s), 165.1 (s), 169.6 (s). Mass spectrum (EI) m/e (relative intensity) 646 (30), 644 (30).

Preparation of 2,6-Di(3-propenyl)-*cis*-bicyclo[3.3.0]octane-3,7-dione (7) from the Tetra-*tert*-butyl (Diallyl) Ester 23b. Diallyl tetraester **23b** (43.266 g, 67.0 mmol) was dissolved in glacial acetic acid (100 mL). An aqueous solution of HCl (100 mL, 1.0 N) was added to the well-stirred solution of **23b**, and the mixture was heated to reflux. The reaction mixture was held at reflux for 2 h, after which it was cooled to 0 °C. The solution was diluted with water (400 mL) and extracted with $CHCl_3$ (3 × 150 mL). The organic layers were combined and dried ($MgSO_4$), the solvent was removed under reduced pressure. Fresh $CHCl_3$ was added to the residue and removed, with heating, under reduced pressure (repeated several times) to remove impurities by flash evporation. The residue was dissolved in $CHCl_3$ and washed with an aqueous solution of $NaHCO_3$ (10% (w/w)). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure to provide an oil that crystallized on standing. The solid was recrystallized from a hexane–ethyl acetate mixture to provide diallyl dione **7** (12.375 g, 56.8 mmol, 85%) as a water white solid. All spectroscopic data for this solid were identical with those of **7** reported above.

Preparation of 2,6-Bis(1-oxo-2-ethyl)-*cis*-bicyclo[3.3.0]octane-3,7-diones 25a and 25b via Oxidation with OsO_4/$NaIO_4$. The epimeric mixture of 2,6-diallyl diones **7a** and **7b** (3.965 g, 13.6 mmol) was dissolved in dioxane and water (55 mL:38 mL). The flask was wrapped with aluminum foil, and a catalytic amount of OsO_4 (50 mg) was added to the reaction mixture. The mixture was permitted to stir for 20 min, after which $NaIO_4$ (total weight 15.0 g, 61.1 mmol) was added in small quantities to the reaction mixture over a period of 3.5 h. The slurry was then filtered to remove inorganic salts, and the filtrate was extracted with EtOAc (8 × 100 mL). The organic layers were combined and then eluted through a small column of alumina. The fractions were combined and the solvent was removed under reduced pressure to provide dialdehydes **25a** and **25b** (2.176 g, 9.8 mmol, 72%). Dialdehyde **25** was then characterized by ^1H NMR (δ 9.1, 2 H) and mass spectroscopy (M^+ = 222). Since some of the dialdehyde had already cyclized to tetracyclic alcohol **26**, it was decided to execute cyclization and to characterize the diketo alcohol **26**. The dialdehyde was characterized later in greater detail (see below).

Preparation of 2,6-Bis(1-oxo-2-ethyl)-*cis*-bicyclo[3.3.0]octane-3,7-diones 25a and 25b via Ozonolysis Followed by Reduction of the Ozonide with Trimethyl Phosphite. Solid diallyl dione **7** (0.153 g, 0.7 mmol) was dissolved in dry MeOH (50 mL). The solution was cooled to −58 °C and degassed with argon (20 min). Ozone was then passed through the solution until it became light blue. Excess ozone was purged from the reaction mixture by passing argon through the solution. With the reaction maintained at a temperature of −58 °C, trimethyl phosphite (0.2 mL, 1.5 mmol) was injected into the solution with a syringe. The cold temperature was maintained for 2.0 h, after which time the temperature of the reaction mixture was permitted to rise to room temperature. After 10 h the solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure to provide a nonviscous oil. Excess trimethyl phosphite was removed from the crude product via Kugelrohr distillation. Analysis of the crude product by ^1H NMR and mass spectroscopy indicated the presence of two compounds. The first compound was dialdehyde **25**. Integration of the proton spectrum indicated that dialdehyde **25**, present as a mixture of endo and exo diastereomers **25a** and **25b**, was prepared in a yield exceeding 90% (weight of the crude oil, 0.378 g). **25**: ^1H NMR (60 MHz, $CDCl_3$) δ 2.10–2.70 (m, 12 H), 3.60 (two s, 9 H), 9.10 (two s, 2 H); mass spectrum (CI, CH_4) m/e (relative intensity) 223 (P + 1, 24), 205 (100), 141 (99). High-resolution mass spectrum calcd for $C_{12}H_{14}O_4$: 222.0892. Found: 222.0901. This reaction has also been recently conducted on a multigram scale in good yield.

Preparation of 2,6-Bis(1-oxo-2-ethyl)-*cis*-bicyclo[3.3.0]octane-3,7-diones 25a and 25b via Ozonolysis and Reduction of the Ozonide with Dimethyl Sulfide. The 2,6-diallyl dione (5.683 g, 26.07 mmol) was dissolved in dry ethyl acetate (600 mL). The well-stirred solution was degassed with argon, and the mixture was cooled to −60 °C (hexane/dry ice bath). Ozone was then bubbled into the solution until a light blue color was observed. The excess O_3 was purged from the medium with argon. Dry MeOH (50 mL) and dimethyl sulfide (11.3 mL) were added to the reaction mixture and the temperature was allowed to rise to room temperature. After the reaction was stirred for 48 h, the solvent was removed under reduced pressure to provide an oil. Toluene was added to the oil and was removed with heat under vacuum in order to remove DMSO. This process (flash evaporation) was repeated several times. The residue was taken up in fresh ethyl acetate and dried ($MgSO_4$). The solvent was removed under reduced pressure to provide dialdehydes **25a** and **25b** (5.328 g, 24.0 mmol, 92.0%). **25**: IR (neat) 1725, 1395 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.10–2.70 (m, 12 H), 9.10 (two s, 2 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) (exo,exo diastereomer) δ 38.78 (t), 41.48 (d), 42.18 (t), 47.16 (d), 200.49 (s), 217.84 (s); mass spectrum (EI, 15 eV) m/e (relative intensity) 222 (P^+, 13), 204 (64), 176 (100).

2β,7β-Dihydroxy-*all*-*cis*-tetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane-5,11-dione (26). The dialdehyde **25** (2.17 g, 9.8 mmol) was dissolved in THF (1.0 L). An aqueous solution of HCl (9.5 mL of a 2.0 N solution) was added to the reaction mixture, and it was stirred for 7 days. The reaction was monitored (via workup) by ^1H NMR spectroscopy. The solution was neutralized with solid $NaHCO_3$, and the inorganic material was filtered from the medium. The THF was removed under reduced pressure to provide the aqueous layer that contained the product. This aqueous layer was diluted with water (10 mL) and extracted with EtOAc (continuous extractor) for 4 days. The solvent was dried ($MgSO_4$) and then removed under reduced pressure to provide a brown oil (2.892 g, 8.5 mmol, 86.7%). This oily mixture was then purified by flash column chromatography (SiO_2, 10:90 MeOH–$CHCl_3$) to provide **26a** (0.452 g, 2.03 mmol, 20.7%) and **26b** (0.312 g, 1.40 mmol, 14.3%). The rest of the mass balance contained the desired diketo diol **26**, keto acid impurities, and cyclized keto acid derivatives. **26a** (exo,exo): IR (neat) 3400 (v br), 1735 cm^{-1}; ^1H NMR (250 MHz, CD_3OD) δ 1.68 (m, 2 H), 1.95 (m, 2 H), 3.02 (m, 2 H), 3.19 (m, 2 H), 3.70 (m, 2 H), 4.32 (m, 2 H); ^{13}C NMR (62.8 MHz, CD_3CN/DMSO-d_6) δ 39.94 (t), 44.01 (d), 53.81 (d), 65.62 (d), 78.54 (d), 223.17 (s). **26b** (endo,exo): mp 189–193 °C; IR (KBr) 3350 (v br), 2920, 1730, 1705, 1310, 1180, 1035 cm^{-1}; ^1H NMR (250 MHz, CD_3OD) δ 1.83 (m, 1 H), 1.97 (m, 1 H), 2.23 (m, 1 H), 2.43 (m, 1 H), 2.95 (m, 1 H), 2.98 (m, 1 H), 3.05 (m, 2 H), 3.54 (m, 1 H), 3.75 (m, 1 H), 4.31 (m, 1 H), 4.49 (m, 1 H); ^{13}C NMR (62.8 MHz, CD_3CN/DMSO-d_6) δ 39.75 (t), 40.23 (t), 42.62 (t), 44.76 (d), 45.54 (d), 55.22 (d), 56.17 (d), 61.38, 65.75 (d), 75.73, 79.04 (d), 223.40, 222.51 (s); mass spectrum (EI, 15 eV) m/e (relative intensity) 222 (P^+, 60), 204 (100), 185 (5). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.34. Found: C, 64.25; H, 6.31. High-resolution mass spectroscopy calcd for $C_{12}H_{14}O_4$: 222.0892. Found: 222.0890.

2β,7β,5α,12α-Tetrahydroxy-*all*-*cis*-tetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecane (27). Dry diketo diol **26a** (0.352 g, 1.58 mmol) was dissolved in dry THF (30 mL). The solution was cooled

to 0 °C and excess borane (25 mL of a 1.0 N solution of borane–THF, 25 mmol) was added. The reaction mixture was allowed to stir for 2 days at room temperature under an inert atmosphere (Ar). After 2 days methanol was added to the reaction mixture to quench the excess borane. The solvent was removed under reduced pressure. The oily residue was repeatedly heated with dry methanol, and the methanol was removed under reduced pressure until all the boric acid had been removed in the form of trimethoxyborane. The oily residue was composed of two isomeric tetraols in an approximate ratio of 9:1 (0.282 mg, 1.25 mmol, 79%). The residue was crystallized from a mixture of THF and hexane to provide solid **27a**. **27a**: mp 231–233 °C; IR (neat) 3300 (v br), 2920 cm^{-1}; ^1H NMR (60 MHz, MeOH-d_4) δ 1.50–1.80 (m, 4 H), 2.10–2.20 (two s, 4 H), 2.70–4.10 (m, 6 H), 4.60 (m, 4 H); ^{13}C NMR (60 MHz, DMSO-d_6) δ 36.7 (d), 48.3 (t), 49.9 (d), 59.5 (d), 74.0 (d), 74.1 (d); mass spectrum (CI, CH_4) m/e (relative intensity) 227 (P + 1, 0.7), 209 (20.9), 191 (100), 173 (74), 155 (1.4). High-resolution mass spectroscopy calcd for $C_{12}H_{16}O_3$ (loss of one molecule of water): 208.1099. Found: 208.1109. The carbon NMR spectrum of the minor isomer contained 12 lines consonant with a tetraol of lower symmetry than **27a**.

Attempted Preparation of Tetracyclo[7.2.1.0^{4,11}.0^{6,10}]-dodeca-2,4,7,12(1)-tetraene (29) or -2,4,7,12(9)-tetraene (30) via the HMPA-Mediated Dehydration of Tetraol 27. The dry tetraol **27** (80 mg, 0.35 mmol) was dissolved in HMPA (10 mL), and the mixture was heated to reflux and stirred for 10 h. A coil condenser (6 ft) was employed to trap the volatiles. The reaction mixture was cooled and then diluted with water (100 mL). The solution was extracted with pentane (4 × 50 mL). The pentane was dried ($MgSO_4$) and the solvent was removed via evaporation at room temperature in a fume hood to furnish oil **28** (32 mg). The solvent was placed in a beaker and covered with a watch glass that contained dry ice and hexane. **28**: IR (neat) 1659 cm^{-1}; (major isomer) ^{13}C NMR (60 MHz, $CDCl_3$) δ 54.5 (d), 57.3 (d), 77.2 (d), 131.9 (d); mass spectrum (EI, 15 eV) m/e (relative intensity) 172 (P^+, 50), 179 (P^+, HMPA, 70), 135 (fragment of HMPA, 100); mass spectrum (CI, CH_4) m/e (relative intensity) 173 (P + 1, 62), 180 (HMPA + 1, 100).

***exo,exo*-2,6-Bis(3-bromopropyl)-*cis*-bicyclo[3.3.0]octane-3,7-dione (35).** 2,6-Diallyl dione **7** (2.51 g, 11.4 mmol) was dissolved in dry hexane (450 mL). Benzoyl peroxide (50 mg) was added to the reaction mixture, and the solution was degassed with argon for 25 min. Hydrogen bromide was bubbled through the well-stirred reaction mixture for 40 min at room temperature. During this period additional benzoyl peroxide (total 120 mg) was added to the mixture in small (30 mg) portions. At the end of the reaction period, argon was bubbled through the solution to remove residual HBr(g). The reaction mixture was cooled to 0 °C and an aqueous solution of $NaHCO_3$ (50 mL, 10% (w/w)) was added. The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure to provide a red oil. This oil was purified by column chromatography (SiO_2, 30:70 ethyl acetate–hexane). Solid biphenyl (a byproduct) eluted from the column first, followed by the dibromo dione **35** (2.77 g, 7.8 mmol, 68%). Since the dibromo dione decomposed upon vacuum distillation, an analytical sample was obtained by HPLC. **35a**: IR (neat) 2910, 1740, 1260 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.40–2.00 (m, 12 H), 2.20–2.80 (m, 4 H), 3.10–3.60 (two t, 4 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 27.6 (t), 29.3 (t), 33.2 (t), 40.0 (d), 42.7 (t), 50.7 (d), 217.8 (s); mass spectrum (CI, CH_4) m/e (relative intensity) 379 (P + 1, 52.2), 381 (P + 3, 100), 383 (P + 5, 51.9), 301 (77.1), 299 (74.2), 218 (11.4). Anal. Calcd for $C_{14}H_{20}O_2Br_2$: C, 44.23; H, 5.30. Found: C, 44.10; H, 5.31.

6α,13α-Dihydroxytetracyclo[6.6.0.0^{2,6}.0^{9,13}]tetradecane (36). Dry dibromo dione **35** (0.33 g, 0.87 mmol) was dissolved in dry distilled THF (60 mL). This solution was added dropwise to an anhydrous solution (60 mL) of samarium diiodide in THF. A catalytic amount of anhydrous, freshly distilled HMPA (1.2 mL) was added to the reaction mixture. This entire process was carried out under argon.

The solution of SmI_2 was prepared by injecting diiodoethane (2.3 g, 8.18 mmol), which had been dissolved in THF (30 mL), into a suspension of samarium powder (1.6 g, 10.6 mmol) that had been previously slurried in THF (30 mL). After the solution of SmI_2 took on a dark blue coloration, dibromide **35** in THF was added slowly via a double-ended needle. The mixture was allowed to stir at room temperature for 2 days under Ar. The reaction mixture was then quenched by addition of aqueous HCl (10 mL, 1 N), and the inorganic material was removed by filtration (Celite) under aspirator pressure. The volume of THF was reduced under vacuum and water (50 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 50 mL), after which the organic layer was washed successively with aqueous $Na_2S_2O_3$ (50 mL), aqueous HCl (1 H, 50 mL), and brine and subsequently dried ($MgSO_4$). The solvent was removed under reduced pressure to provide an oil (450 mg). The major isomer **36a** (40–50%) was isolated by column chromatography on silica gel (50 g), with 1:1 ethyl acetate–hexane serving as the eluent. Diol **36a** crystallized from CH_2Cl_2–hexane: mp 142–143 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.10–2.30 (m, 22 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 25.5 (t), 34.4 (t), 42.0 (t), 47.3 (t), 51.3 (d), 58.1 (d), 92.8 (s); mass spectrum (EI, 15 eV) m/e (relative intensity) 222 (P + 1, 5), 204 (32), 186 (60), 120 (100); mass spectrum (CI, CH_4) m/e (relative intensity) 205 (7.6), 203 (9.3), 187 (100), 131 (14.4). High-resolution mass spectrum calcd for $C_{14}H_{22}O_2$: 222.1619. Found: 222.1623. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.67; H, 9.90. Found: C, 75.91; H, 9.98.

When this reaction was repeated on larger scale, yields (0.5 g) varied from 50 to 80% with and without the addition of HMPA, especially if high-dilution conditions were employed (~350 mL of THF). In these cases dry $FeCl_3$ (30 mg) served as the catalyst.[16,37a]

***exo,exo*-2,8-Bis(3-bromopropyl)-*cis*-bicyclo[3.3.0]octane-3,7-dione (38).** Dibromo dione **38** was prepared by the same procedure as that described for dibromo dione **35** (see experiment immediately above). The conversion of diallyl dione **37** (6.678 g, 30.6 mmol) into dibromo dione **38** (10.103 g, 26.6 mmol) was achieved in 86% yield. **38a** (exo,exo): IR (neat) 1740, 1250 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.40–1.90 (m, 10 H), 2.00–2.40 (m, 4 H), 2.50–2.80 (m, 2 H), 3.10–3.60 (two t, 4 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 28.54 (t), 30.06 (t), 32.22 (d), 33.41 (t), 43.32 (t), 48.92 (d), 52.39 (d), 218.77 (s). High-resolution mass spectrum calcd for $C_{14}H_{20}O_2Br_2$: 379.9809. Found: 379.9804.

6α,10α-Dihydroxytetracyclo[6.6.0.0^{2,6}.0^{10,14}]tetradecane (39). Dry dibromo dione **38** (450 mg, 1.18 mmol) was dissolved in dry, distilled THF (60 mL). This solution was slowly injected with a double-ended needle into an anhydrous solution (60 mL) of SmI_2, which contained a catalytic amount (1.6 mL) of dry, distilled HMPA. The entire sequence was carried out under Ar.

The solution of samarium diiodide was prepared by injecting diiodoethane (2.3 g, 8.18 mmol), which had been dissolved in THF (30 mL), into a suspension of samarium powder (1.6 g, 10.6 mmol) in THF (30 mL). After the solution of SmI_2 had taken on a dark blue coloration, the dibromide **38**/THF solution was injected slowly with a double-ended needle into the solution of SmI_2 that contained the HMPA. The reaction mixture was allowed to stir for 2 days under an inert atmosphere. The reaction was quenched and worked up as detailed above for diol **36** to provide an oily product (246 mg). This material was purified by column chromatography (SiO_2, ethyl acetate–hexane) to furnish diol **39a** as the major product (140 mg, 53% yield): **39a** (mp 122–123 °C, from acetone); IR (KBr) 3300 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.19–1.27 (m, 2 H), 1.53–2.00 (m, 14 H), 2.17–2.24 (m, 2 H), 2.50–2.70 (m, 2 H), 3.38 (br s, 2 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 24.9 (t), 33.3 (t), 41.7 (t), 44.7 (d), 46.9 (t), 59.3 (d), 59.5 (d), 93.0 (s); mass spectrum (CI, CH_4) m/e (relative intensity) 223 (2.4), 205 (7.7), 203 (9.3), 187 (100), 131 (9.8). High-resolution mass spectrum calcd for $C_{14}H_{22}O_2$: 222.1620. Found: 222.1609. Anal. Calcd for $C_{14}H_{22}O_2 \cdot {}^1/_4H_2O$: C, 74.13; H, 10.00. Found: C, 74.06; H, 9.89.

When this reactin (891 mg) was carried out at high dilution (350 mL of THF)[16] with an $FeCl_3$ catalyst in place of HMPA, a 60% yield of **39a** was obtained by crystallization (308 mg), while the mother liquor contained additional diol, which was found to be a mixture of **39a** and **39b** (49 mg, 0.2 mmol, 8%).[16]

Dehydration of 6α,10α-Dihydroxytetracyclo-[6.6.0.0^{2,6}.0^{10,14}]tetradecane (39a) via Martin's Sulfurane Reagent.[39] Tetracyclic diol **39a** (0.033 g, 0.15 mmol) was dissolved in anhydrous methylene chloride (1.0 mL). The sulfurane reagent, (1,1,1,3,3,3-hexafluoro-2-phenyl-2-propoxy)diphenylsulfurane (0.25

g, 0.37 mmol), was dissolved in anhydrous methylene chloride (1.0 mL) and was added via a syringe to the solution of diol **39a**, which was held at −25 °C. The reaction mixture was permitted to stir for 2.5 h and was diluted with $CHCl_3$ (50 mL). This solution was extracted with an aqueous solution of Na_2CO_3 (20 mL, 10% (w/w)) and water (2 × 20 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure to provide a light yellow oil. The crude product was analyzed by gas chromatography and GC–mass spectroscopy. The analysis indicated that the product was a mixture of four dienes and four unsaturated alcohols. Retention times: dienes (MW = 186), 9.75, 9.99, 10.56, and 10.86 min; unsaturated alcohols (MW = 204), 16.03, 17.72, 18.22, and 18.51 min (GC column, 5% phenylmethylsilicone; carrier gas, He, at 18 psi; flow rate, 50 mL/min; initial oven temperature, 130 °C; hold initial oven temperature, 2 min; final oven temperature, 200 °C; oven temperature rate, 0.5 °C/min).

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Supplementary Material Available: Chemical shifts and coupling constants for **26a** and **26b** (2 pages). Ordering information is given on any current masthead page.

Modification of Macrolide Antibiotics. Synthesis of 11-Deoxy-11-(carboxyamino)-6-*O*-methylerythromycin A 11,12-(Cyclic esters) via an Intramolecular Michael Reaction of *O*-Carbamates with an α,β-Unsaturated Ketone[1]

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The synthesis of 11-deoxy-11-(carboxyamino)-6-*O*-methylerythromycin A 11,12-(cyclic esters) **13** was accomplished in five steps from 6-*O*-methylerythromycin A in 40% overall yield. The process featured a mild and stereoselective intramolecular Michael addition of C-12 *O*-carbamates to an α,β-unsaturated ketone. The Michael reaction required base catalysis and the rate of addition was fastest in polar solvents such as 10% aqueous acetonitrile or dimethylformamide. Reaction of the key intermediate acyl imidazole **11a** with primary amines produced in one operation the cyclic 11,12-carbamates. The stereochemistry of the product carbamates was determined by minimum energy calculations, two-dimensional NMR spectroscopic techniques, and ^{13}C NMR correlations.

Erythromycin A (**1**) commands a premier position in the market place as a safe and effective antibiotic for the treatment of gram-positive pathogens.[2] In particular, erythromycin A is the drug of choice for the treatment of Legionnaires' disease, an infection produced by *Legionella pneumophila*. However, one major limitation to erythromycin A therapy is its short in vivo half-life in humans (2 h).[3] Erythromycin A undergoes in vivo dehydration to anhydroerythromycin A, an inactive C-6/C-12 spiroketal metabolite.[4] Methods for inhibiting spirocyclization by ketone modification include (1) C-9 oxime;[5] (2) C-9 amino;[6] and (3) C-9 ketone replacement with ring expansion.[7] Two erythromycin A derivatives have been developed which stabilize the macrolide from spiroketalization while maintaining the C-9 carbonyl.

The first compound, 6-*O*-methylerythromycin A (**2**), prevents the formation of the spiroketal by blocking the C-6 hydroxyl group.[8] This antibiotic has shown excellent pharmacokinetic parameters and is undergoing clinical evaluation. Another approach to stabilizing the macrolide toward acid is masking the C-12 hydroxyl group. Erythromycin A 11,12-carbonate (**3**) fulfills this requirement.[9] The carbonate exhibits increased in vivo potency with a fourfold increase in in vivo half-life.[10] However, a major disadvantage of the carbonate is its liver toxicity. Both 6-*O*-methylerythromycin A 11,12-carbonate and erythromycin A 11,12-carbonate (**3**) were fivefold more hepatotoxic than erythromycin A (**1**) in the in vitro rat liver hepatotoxicity screen.[11] In connection with our efforts

(1) Dedicated to the memory of F.Q.B.
(2) For a comprehensive review of macrolide antibiotics, see: Omura, S.; Tanaka, H. *Macrolide Antibiotics, Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: New York, 1984.
(3) Welling, P. G.; Craig, W. A. *J. Pharm. Sci.* **1978**, *67*, 1057.
(4) Kurath, P.; Jones, P. H.; Egan, R. S.; Perun, T. J. *Experientia* **1971**, *27*, 362.
(5) Djokic, S.; Tamburasev, Z. *Tetrahedron Lett.* **1966**, 1645. Chantot, J. F.; Bryskier, A.; Gasc, J. C. *J. Antibiot.* **1986**, 660.
(6) Egan, R. S.; Freiberg, L. A.; Washburn, W. H. *J. Org. Chem.* **1974**, *39*, 2492.
(7) Djokic, S.; Kobrehel, G.; Lazarevski, G.; Lopotar, N.; Tamburasev, Z.; Kamenar, B.; Nagl, A.; Vickovic, I. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1881.
(8) 6-*O*-Methylerythromycin A (TE-031) is an in-licensed drug from the Taisho Pharmaceutical Co., Ltd., Tokyo, Japan: Watanabe, Y.; Morimoto, S.; Omura, S. U.S. Pat. 4 331 803, 1982.
(9) Neszmelyi, A.; Bojanska-Dahlig, H. *J. Antibiotic.* **1978**, *31*, 487.
(10) Mannisot, P. T.; Vuorela, A.; Mantyla, R.; Hanhijarvi, H.; Rauramaa, V. *Int. Congr. of Chemother.* **1983**, *5*, 107/5.
(11) Kingsley, E.; Gray, P.; Tolman, K. G.; Tweedale, R. *J. Clin. Pharmacol.* **1983**, *23*, 178.

0022-3263/88/1953-2340$01.50/0