8-Methyl-1,4-diazabicyclo[4.2.0]octane-2,5-dione (16). Procedure A. Sodium hydride (0.2 g of a 60% dispersion in mineral oil, 2 equiv) was added to a solution of 1-(iodoacetyl)-6-methyl-1,4,5,6-tetrahydro-3(2*H*)-pyridazinone (**15**, 0.71 g, 2.5 mmol) in methylene chloride (40 mL), and the mixture was stirred for 1 h. The mixture was evaporated under reduced pressure and the residue purified by column chromatography on silica with 30/70 ether/petroleum ether to give 0.09 g (24%) of the product as an orange oil.

Procedure B. DCC (0.80 g, 1.1 equiv) was added to a solution of 2-(carboxymethyl)-6-methyl-1,4,5,6-tetrahydro-3(2*H*)-pyridazinone (**17**, 0.60 g, 3.5 mmol) in methylene chloride (45 mL), and the mixture was stirred for 2 h. The mixture was then filtered, and the filtrate was evaporated under reduced pressure. Column chromatography of the residue (as in procedure A) gave 0.22 g (40%) of the product: IR (neat) 1798, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.1 (s, 2 H), 3.5–2.5 (m, 5 H), 1.2 (d, J = 7.5 Hz, 3 H). LRMS (70 eV), m/z (relative intensity) 154 (M^+, 5), 141 (90), 139 (90), 127 (100), 101 (100); HRMS calcd for $C_7H_{10}N_2O_2$ m/z 154.0742, found m/z 154.0740 ± 0.0015.

2-(Carboxymethyl)-6-methyl-1,4,5,6-tetrahydro-3(2*H*)-pyridazinone (17). Sodium hydride (0.16 g, 1.1 equiv) was added to a solution of 6-methyl-1,4,5,6-tetrahydro-3(2*H*)-pyridazinone (0.45 g, 3.9 mmol) in THF (10 mL) at 0 °C. A solution of sodium iodoacetate [prepared from sodium hydride (0.16 g) and iodoacetic acid (0.75 g, 3.9 mmol) in THF (10 mL)] was added, and the mixture was stirred for 2 h at 0 °C. The mixture was warmed to room temperature and filtered, the filtrate evaporated under reduced pressure, and the residue taken up in methylene chloride. This material was used directly in subsequent reactions, since it decomposed upon attempted purification. The product was identified by spectral data and chemical conversion to **16**: IR (neat) 1720 (br), 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.0 (s, 2 H), 3.4–2.4 (m, 7 H), 1.1 (d, J = 7.5 Hz, 3 H).

Registry No. **5**, 108511-40-6; **6**, 14790-51-3; **7**, 108511-41-7; **8**, 108511-42-8; **9**, 108511-43-9; **10**, 108511-44-0; **11**, 114-83-0; **12**, 108511-45-1; **13**, 108511-46-2; **14**, 33018-73-4; **15**, 108511-47-3; **16**, 108511-48-4; **17**, 108511-49-5; DCC, 538-75-0; $ClCH_2C(O)Cl$, 79-04-9; PhNHNHPh, 122-66-7; ICH_2CO_2H, 64-69-7; PhNHNHAc·Na, 108511-50-8; ICH_2CO_2Na, 305-53-3; PhNHNHPh·2Na, 23458-78-8; sodium cyanoborohydride, 25895-60-7; 4,5-dihydro-6-methyl-3(2*H*)-pyridazinone, 5157-08-4.

General Approach to the Synthesis of Polyquinanes. Preparation of *trans,trans*-4,8-Diacetoxytetracyclo[9.3.0.0^{1,5}.0^{7,11}]-tetradecan-6-one[1]

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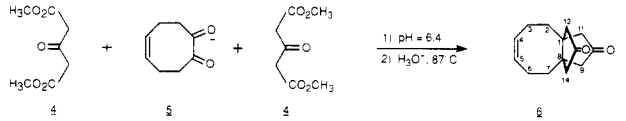
Received March 24, 1987

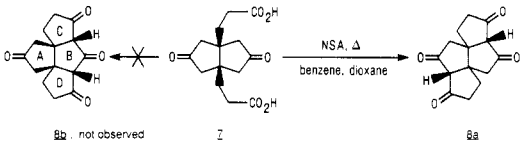
In 1971 Nozoe et al. reported the structure of a novel polyquinane 1,[2] the parent ring system of which is composed of four fused five-membered rings. This diketone **1** arose through cyclization of a transformation product of the sesterterpene ophioboline D.[2] Since we have been interested for some time in a general approach to polyquinanes via the reaction of 1,2-dicarbonyl compounds with dimethyl 3-oxoglutarate,[3] the unusual system of four fused five-membered rings attracted our attention. Outlined below is the synthesis of *trans,trans*-4,8-diacetoxytetracyclo[9.3.0.0^{1,5}.0^{7,11}]tetradecan-6-one (**2**), the first synthetic compound to contain four five-membered rings joined as in **1**. The importance of diacetate **2** goes far beyond the preparation of a new polyquinane ring system. Two of the five-membered rings in **2** are held in a disposition such that elimination of the two acetate groups (**2** → **3a**) would provide a diene in which through-space interactions of the olefinic π electrons can be anticipated. Furthermore, the p orbital of the carbonyl group of **3a** is orthogonal to those of the diene but would project into the diene system. Comparison of the photoelectron spectrum of **3a** with that of **3b** would, therefore, be interesting in regard to interaction of the electrons in these π orbitals.[4] This possibility provided additional stimulus for the synthesis of a molecule such as **2**.

Scheme I

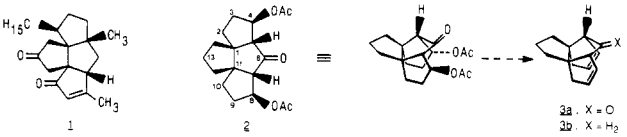


4 5 4 6

Scheme II



8b, not observed 7 8a



1 2

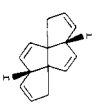
The condensation of 1,2-dicarbonyl compounds with dimethyl 3-oxoglutarate (Scheme I) has been shown to be a facile and general method for the preparation of polyquinanes.[3] The reaction in aqueous buffer of dimethyl 3-oxoglutarate (**4**) with the 1,2-dione **5**, prepared by the method of Yates,[5] results in an excellent yield of the [6.3.3]propellene, tetramethyl 10,13-dioxotricyclo-[6.3.3.0^{1,8}]tetradec-4-ene-9,11,12,14-tetracarboxylate.[3] Hydrolysis of the ester functions followed by decarboxylation gave tricyclo[6.3.3.0^{1,8}]tetradec-4-ene-10,13-dione **6** in 87% yield.[3] The [6.3.3]propellene **6** could be converted into the diacid **7**; however, the generation of four five-membered rings fused as in **2** would be expected to

(1) This work was presented in preliminary form: Venkatachalam, M.; Wehrli, S.; Kubiak, G.; Weiss, U.; Cook, J. M. *Tetrahedron Lett.* **1986**, *27*, 4111–4114.

(2) Nozoe, S.; Itai, A.; Iitaka, Y. *J. Chem. Soc. D* **1971**, 872–873.

(3) Mitschka, R.; Oehldrich, J.; Takahashi, K.; Weiss, U.; Silverton, J. V.; Cook, J. M. *Tetrahedron* **1981**, *37*, 4521–4542.

(4) (a) McMurry, J. E.; Haley, G. J.; Matz, J. R.; Clardy, J. C.; Duyne, G. V.; Gleiter, R.; Schäfer, W.; White, D. H. *J. Am. Chem. Soc.* **1984**, *106*, 5018–5019. (b) Gleiter, R.; Cook, J., M.; unpublished results. The photoelectron spectrum of polyquinene **28** does not show any evidence for interaction of the π bonds via homoconjugation. The peak at 9.0 eV is due to the ionization from all four π MO's. It is not split at all; it is therefore difficult to prove that the signal is composed of four bands. The disposition of the double bonds in **3a**, however, is much different from that in **28**.

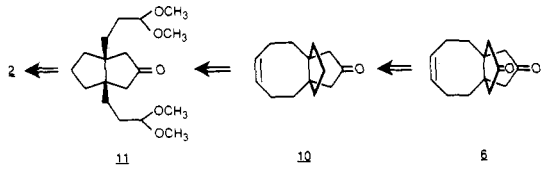


28

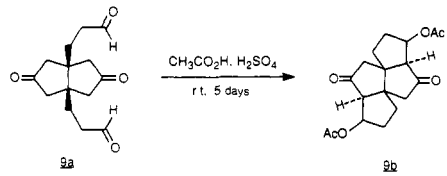
(5) Yates, P.; Lewars, E. G.; McCabe, P. H. *Can. J. Chem.* **1972**, *50*, 1548–1556.

0022-3263/87/1952-4110$01.50/0

Scheme III



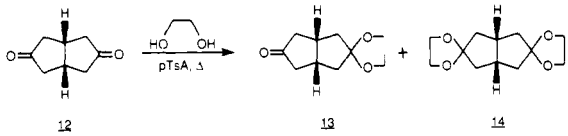
be difficult. This is due to the nonbonded interactions between the methylene hydrogens of rings C and D (see **8b**) and the relative strain that results from the three sp^2-hybridized carbon atoms in **8b** (Scheme II). In this regard, the acid-catalyzed cyclization of diketo diacid **7** gave tetrone **8a** to the complete exclusion of regioisomer **8b**.[3] To overcome these difficulties, it was decided to direct efforts toward construction of **2** via an aldol approach.[6] This method had proven successful in the conversion of dialdehyde **9a** into the tetraquinane **9b**.[6] In this sequence,



the acid-catalyzed aldol cyclization was carried out in acetic acid/H_2SO_4, which converted the resulting β-hydroxy ketone functionalities into β-acetoxycarbonyl groups. This prevented ring opening via retro-aldol reactions.[6]

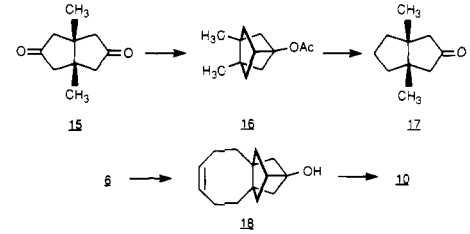
In order to direct cyclization toward **2** rather than to a derivative of **9b**, it is necessary to differentiate between the two carbonyl groups of propellenedione **6** (Scheme III). Once this had been accomplished, the eight-membered ring could be cleaved to provide the *cis*-1,5-disubstituted bicyclo[3.3.0]octanone **11** and the desired cyclization effected. The synthesis of **2** rested then on the preparation of the [6.3.3]propellene **10**, in which one of the carbonyl groups had been reduced to methylene.

Selective functionalization of one carbonyl group in a symmetrical *cis*-bicyclo[3.3.0]octane-3,7-dione is not a trivial problem. Lok et al. obtained an approximately statistical mixture of starting dione **12** (13), monoketal **13** (40), and bis(ethylene ketal) **14** (24) during attempts to differentiate between the carbonyl groups of *cis*-bicyclo-[3.3.0]octane-3,7-dione through selective ketalization.[7] Others[8] have been able to increase the amount of the monoketal **13** by formation of the bisketal **14**, followed by partial hydrolysis to the desired monoketal, but several recycle passes were necessary to obtain high yields of the monoketal **13**.



Our first attempt to convert dione **6** into monoketone **10** was therefore carried out following the work of Borden,[9]

Scheme IV



Scheme V

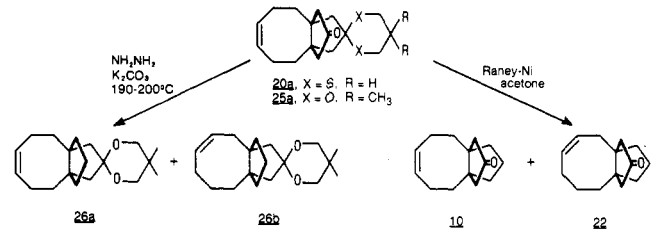
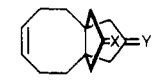
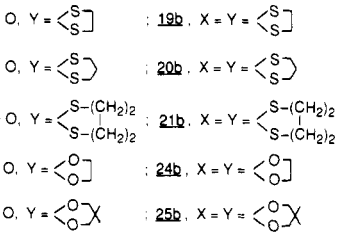


Chart I





who had demonstrated that 1,5-dimethyl-*cis*-bicyclo-[3.3.0]octane-3,7-dione (**15**) could be transformed into the corresponding bisnoradamantyl alcohol **16** via Clemmensen reduction (Scheme IV). On subsequent treatment with base, **16** opened up to provide monoketone **17**. This modified Clemmensen reduction reaction[9] has also been employed in our laboratory[10] to prepare the 4,5-dihydro derivative of **18**. When, however, the same procedure [Zn(Hg), HCl, $(CH_3CO)_2O$, 0 °C] was applied to **6**, the desired monol **18** (Scheme IV) was obtained, accompanied by several other compounds. Its separation from these byproducts proved to be difficult and this approach was abandoned.

Examination of the structure of the propellenedione **6** indicated, however, that the steric interactions between a suitably chosen protecting group and the blades of the propellane **6** should allow protection of one carbonyl group in the presence of the other. Treatment of the diketone **6** with 1 equiv of ethanedithiol gave the bis(ethylene thioketal) **19b** in 40% yield, accompanied by starting material and monothioketal **19a** (see Chart I). Selective monothioketalization of **6** to provide **20a** was achieved in 70% yield by stirring the diketone with 1.2 equiv of propane-1,3-dithiol at −10 °C in the presence of boron trifluoride etherate. The reaction medium was composed of ether and acetic acid in a ratio of 3:2. The lower temperature is critical to prevent formation of the bisthioketal **20b** of **6**. It is noteworthy that the 70% yield of crystalline **20a** required no recycling of **6**, although this process could be performed, if desired. Attempts to employ 1,4-butanedithiol (BF_3 etherate) in the thioketalization process

(6) Venkatachalam, M.; Jawdosiuk, M.; Deshpande, M.; Cook, J. M. *Tetrahedron Lett.* **1985**, *26*, 2275–2278. Venkatachalam, M.; Deshpande, M. N.; Jawdosiuk, M.; Kubiak, G.; Wehrli, S.; Weiss, U.; Cook, J. M. *Tetrahedron* **1986**, *42*, 1597–1605.

(7) Lok, R.; Coward, J. K. *J. Org. Chem.* **1974**, *39*, 2377–2382.

(8) Serratosa, F.; Moyano, E.; Carcellen, E. *Tetrahedron Lett.* **1984**, *25*, 2031–2034. Coates, R. M.; Shah, S. K.; Mason, R. W. *J. Am. Chem. Soc.* **1982**, *104*, 2198–2208. Paquette, L. A.; Han, Y. K. *J. Org. Chem.* **1979**, *44*, 4014–4016. Nicolau, K. C.; Sipio, W. J.; Magolda, R. L.; Seitz, S.; Barnette, W. E. *J. Chem. Soc., Chem. Commun.* **1978**, 1067–1068.

(9) Borden, W. T.; Ravindranathan, T. *J. Org. Chem.* **1971**, *36*, 4125–4127.

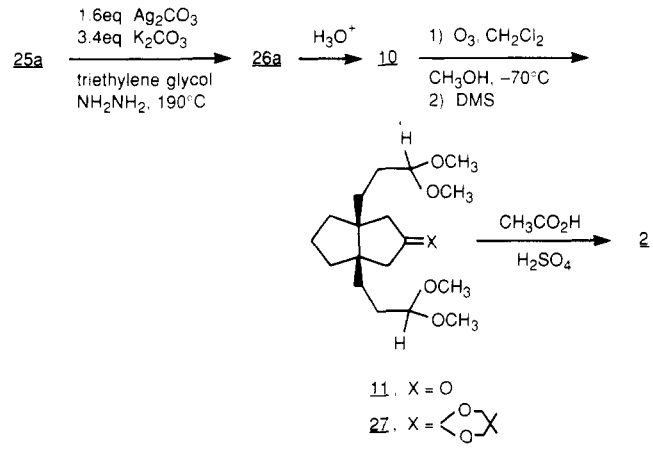
(10) Yang, S.; Cook, J. M. *J. Org. Chem.* **1976**, *41*, 1903–1907.

were unsatisfactory. At room temperature none of the desired thioketal **21a** was isolated; at reflux a mixture of monothioketal **21a** and bisthioketal **21b** was observed in a ratio of 2:1. These components were also accompanied by **6** (30%).

The Raney Ni mediated desulfurization of monothioketal **20a** proved troublesome. Although various experimental procedures were attempted, the highest yield of monoketone **10** was achieved when **20a** was stirred with a tenfold excess of deactivated Raney Ni in refluxing acetone.[11] However, this procedure always gave both the desired monoketone **10** and the Δ^3-olefinic isomer **22** (Scheme V), usually in a ratio of 5 to 1. More active catalysts reduced both the carbonyl group and the double bond of **20a**. The migration of the Δ^4-double bond in the eight-membered ring to provide the Δ^3-isomer **22** was clearly evident on examination of the GC/MS and ^{13}C NMR spectra of the material. Further evidence for the formation of **22** was obtained by oxidation; **22** was converted into the less symmetrical diacid, *cis*-5-(carboxymethyl)-3-oxobicyclo[3.3.0]octane-1-butanoic acid (**23**) (see ref 12). The separation of the two alkenes **10** and **22** proved to be difficult on a preparative scale and the thioketal approach to monoketone **10** was discontinued. Attempts to convert **6** into monoketal **24a** with ethylene glycol were unsuccessful, since significant amounts of bisacetal **24b** were isolated; 1,4-butanediol was similarly unsatisfactory. When, however, diketone **6** was heated with 2,2-dimethylpropane-1,3-diol in refluxing benzene in the presence of *p*-toluenesulfonic acid,[13] good yields of monoketal **25a** were realized. When the progress of the reaction was monitored by GLC, it indicated that the best yield of **25a** was realized if the reaction was terminated after 2 h (see Table I, Experimental Section, for details). The ratio of starting dione **6** to monoketal **25a** to bisketal **25b** was 24:76:0. Chromatography provided crystalline **25a** in 74% yield together with 20% recovered starting dione **6**. The selective protection of one of the two equivalent carbonyl groups of **6** had again been achieved; moreover, the starting dione **6** could be recycled, if desired.

Wolff–Kishner or Huang-Minlon[14] reduction of **25a** produced, in 70% yield, a mixture of the desired alkene **26a** and the Δ^3-isomer **26b** (Scheme V). The ratio of **26a** to **26b** was generally 2:3, but did vary with temperature. Such migration of double bonds under Wolff–Kishner conditions has been observed before.[15] Similarly, reduction of dione **6**, under analogous conditions, furnished a mixture of the Δ^3 and Δ^4 isomers, tricyclo[6.3.3.$0^{1,8}$]tetradec-3-ene and tricyclo[6.3.3.$0^{1,8}$]tetradec-4-ene, respectively (see Experimental Section). Although it seemed that the isomerization of **25a** would force abandonment of this approach, an interesting report by Corey et al. offered a possible solution.[16] Silver(I) ion had been successfully employed by these workers to prevent isomerization of olefinic bonds in the oxidative (NBS) removal of 1,3-dithiane protecting groups. In agreement with this observation, Wolff–Kishner reduction of the monoketal **25a**, when carried out in the presence of 1.6 equiv of Ag_2CO_3, gave a 73% yield of the desired alkene **26a** together with less than 1% of the Δ^3-isomer **26b**. The use of silver(I) ion constitutes a significant improvement in the reduction process and may find applications in other organic reactions where olefin isomerization presents a problem. Deketalization of **26a** was then conducted in straightforward fashion to provide the desired [6.3.3]propellenone **10** in 80% yield.[12]

Scheme VI

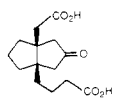


The monoketone **10**, available now in gram quantities, was oxidized with ozone followed by reductive workup (DMS, dimethyl sulfide) to provide the bisacetal **11** in 90% yield.[12] In an analogous manner, the monoketal **26a** was converted into the corresponding trisacetal **27** (>85%). When either the bisacetal **11** or the corresponding trisacetal **27**, was heated for 10 days (50 °C) in a mixture of acetic and sulfuric acids (cf. the conversion of **9a** → **9b**),[6] a 40% yield of *trans,trans*-4,8-diacetoxytetracyclo[9.3.0.$0^{1,5}$.$0^{7,11}$]tetradecan-6-one (**2**) was obtained (Scheme VI). The yields of diacetate **2** obtained from either **11** or **27**[12] were identical within experimental error, while the remainder of the material was composed of products of incomplete cyclization.[12] The yield of **2** is much lower than that encountered in the preparation of **9b**[6] under similar reaction conditions, presumably because of the nonbonded interactions between the five-membered rings in the cis,syn,cis molecule **2**, which are absent in diacetate **9b**.

A plane of symmetry passes through atoms C(6) and C(13) of the diacetate **2** and also through the midpoint of the C(1)–C(11) bond. This symmetry is reflected by the ten-line carbon-13 NMR spectrum [20.93 (q), 24.20 (t), 33.34 (t), 33.74 (t), 42.80 (t), 56.03 (s), 66.23 (d), 76.25 (d), 170.06 (s), 213.10 (s)]. The elemental analysis and spectroscopic data are in good agreement with structure **2**, and the stereochemistry of the acetate functions was assigned on the basis of coupling constants observed in the 250-MHz proton NMR spectrum. The proton attached to the carbon atom bearing the acetate function appears in the spectrum of **2** at δ 5.30, which is in excellent agreement with the chemical shift observed for protons in similar environments such as those in **9b**.[6] Although this signal, when expanded, appeared as a doublet of triplets, it was not resolved well enough to make a definitive assignment of the coupling

(11) Woodward, R. B.; Patchett, A. A.; Barton, D. H. R.; Ives, D. A. T.; Kelly, R. B. *J. Chem. Soc.* **1957**, 1131–1144. Hauptmann, H.; Walter, W. *Chem. Rev.* **1962**, *62*, 347–404. Augustine, R. L. In *Reduction*; Marcel Decker: New York, 1967.

(12) The structure of the less symmetrical diacid **23** is as represented here: Venkatachalam, M. Ph.D. Thesis; University of Wisconsin—Milwaukee, 1987.



23

(13) Clarke, R. L.; Martini, C. M. *J. Am. Chem. Soc.* **1959**, *81*, 5721–5725.

(14) Huang-Minlon, *J. Am. Chem. Soc.* **1946**, *68*, 2487–2488; **1949**, *71*, 3301–3303; Nagata, W.; Itazaki, H. *Chem. Ind. (London)* **1964**, 1194–1195.

(15) See, for example: Sisido, K.; Kawanisi, M. *J. Org. Chem.* **1962**, *27*, 3722–3724. Hünig, S.; Eckart, W. *Chem. Ber.* **1962**, *95*, 2493–2497.

(16) Corey, E. J.; Erickson, B. *J. Org. Chem.* **1971**, *36*, 3553–3560.

constants. However, on irradiation at δ 5.30 the signal for the junction proton at δ 2.70 became narrower by 1.5 Hz. On the other hand, when complete irradiation of the multiplet centered at δ 1.70 was effected, this same junction proton appeared as a doublet (J = 1.5 Hz). Consequently, the coupling constant of 1.5 Hz is due to the interaction of the junction proton with the proton attached to the acetate-bearing carbon. In keeping with the Karplus variation of the three-bond coupling constant, the small coupling constant (1.5 Hz instead of 9.5 Hz) supports the trans relationship of these vicinal protons.[17,18] This conclusion is in agreement with coupling constants observed earlier in related diacetates.[6,19] This stereochemistry places the two acetate groups on the convex faces of **2** rather than inside the sterically congested cleft formed by the cis,cisoid,cis fusion of the three rings. Attempts to convert **2** into **3a** and **3b** 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 Corporation 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 with an EM-360 NMR spectrometer, 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 and electron impact (EI) 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 Beckmann Acculab-1 spectrometer while FT-IR were taken on a Nicolet MX-1 instrument.

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 using 4–63-μm silica gel. The spray reagent was composed of 2,4-dinitrophenylhydrazine, ethanol, and sulfuric acid. The citrate–phosphate buffer (pH 5.6) was prepared by dissolving disodium hydrogen phosphate heptahydrate (11.67 g) and citric acid (3.68 g) in water (900 mL). The alkaline medium (pH 8.3) was prepared by adding $NaHCO_3$ (1.2 g) to water (100 mL). 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. Unless otherwise stated, all starting materials were purchased from Aldrich Chemical Co., Milwaukee, WI.

Analytical GLC was performed on a Hewlett-Packard Model 5880A capillary gas chromatograph, using helium as a carrier gas. The following columns were used: (A) high performance capillary column containing dimethyl silicone fluid, length 25 m, internal diameter 0.31 μm; (B) high performance capillary column containing cross-linked 5% phenyl methyl silicone, length 25 m, film thickness 0.52 μm.

Tricyclo[6.3.3.0^{1,8}]tetradec-4-ene-10,13-dione (6). The dione **6** was synthesized via a four-step sequence, according to the procedure of Gawish et al.[3] The melting point and IR and NMR spectra of the dione were identical with those reported for **6**.[3]

Tricyclo[6.3.3.0^{1,8}]tetradec-4-ene-10,13-dione Bis(ethylene dithioketal) (19b). The dione (**6**, 1.0 g, 4.6 mmol) was dissolved in glacial acetic acid (50 mL) and ether (25 mL). Ethanedithiol (0.47 g, 5 mmol) and boron trifluoride etherate (1.3 mL, 10 mmol) were added. The reaction was stirred at room temperature for 1 h. A white solid (dithioketal **19b**) precipitated, was filtered off, was washed with acetic acid, followed by ether, and dried: mp 124–125 °C; IR (FT, KBr) 3177, 3099, 2937, 2854, 1461, 1377 cm^{-1}; mass spectrum (CI, CH_4), m/e (relative intensity) 371 (M + 1, 100.0), 277 (24.4), 237 (17.6); ^{1}H NMR ($CDCl_3$) δ 1.95–1.99 (m, 8 H), 2.15–2.66 (m, 10 H, $J_{9a,9b}$ = 14.6 Hz), 3.32–3.21 (m, 6 H), 5.64 (t, 2 H); ^{13}C NMR ($CDCl_3$) δ 23.72 (t), 37.27 (t), 39.30 (t), 39.88 (t), 57.25 (s), 58.90 (t), 66.90 (s), 130.33 (d). Anal. Calcd for $C_{18}H_{26}S_4$: C, 58.38; H, 7.02. Found: C, 58.30; H, 6.98. The filtrate contained small amounts of the starting dione **6** and the desired monothioketal (**19a**).

Attempted Monoketalization of 6 with 1,4-Butanethiol. Tricyclo[6.3.3.0^{1,8}]tetradec-4-ene-10,13-dione (**6**, 0.5 g, 2.4 mmol) was dissolved in a solution of glacial acetic acid (distilled, 50 mL) and anhydrous ether (50 mL). The mixture was stirred in an ice bath, after which butane-1,4-dithiol (0.3 g, 2.5 mmol) and freshly distilled boron trifluoride etherate (5 mL) were added. The mixture was stirred at 0 °C under nitrogen for 24 h. Analysis by GLC and mass spectroscopy indicated the presence of the starting dione **6** and none of the desired monothioketal **21a**. Even after the mixture had been stirred at room temperature, the formation of monothioketal **21a** was not observed. The solution was then held at reflux under nitrogen for 24 h. The mass spectrum and GLC of the product indicated the presence of both the desired monothioketal **21a** and the bisthioketal **21b** in a ratio of 2:1, together with 30% of **6**.

Attempted Preparation of Tetracyclo[6.3.3.0.0^{10,13}]tetradec-4-en-10-ol (18).[9,10] Acetic anhydride (20 mL) was saturated with HCl gas at −5 °C to −10 °C, after which diketone (**6**, 500 mg, 2.2 mmol) was added. Activated zinc dust[9] (5 g) was added slowly in portions over 3 h with vigorous stirring, keeping the temperature below −5 °C. On completion of the addition, the mixture was stirred for an additional 2 h at −5 °C and then filtered quickly through a funnel prechilled with cold acetic anhydride. The filtrate was added to cold methanol (50 mL) and left to stand overnight. The solvents were removed under reduced pressure and the oily residue was taken up in dichloromethane and washed consecutively with water (2 × 25 mL), $NaHCO_3$ (2 × 25 mL, 10%), and water (25 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. Examination of the crude mixture by TLC, mass spectroscopy (CI, CH_4) and IR revealed a number of components including the monoketone **10**, the monol **18**, and its corresponding acetate. It proved too difficult to separate the mixture and this approach[9] was abandoned.

10,10-(1,3-Propylenedithio)tricyclo[6.3.3.0^{1,8}]tetradec-4-en-13-one (20a). The dione (**6**, 5.0 g, 23 mmol) was dissolved in a solution of anhydrous ether (100 mL) and acetic acid (distilled, 150 mL). The mixture was stirred in an ice bath under an atmosphere of nitrogen. Propane-1,3-dithiol (2.5 g, 23 mmol) and boron trifluoride etherate (10 mL, distilled) were added, and the solution was stirred at −5 °C to −10 °C for 48 h. The reaction was monitored by TLC (R_f 0.85, silica gel, CH_2Cl_2). The mixture was poured into ice water (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were washed with saturated aqueous Na_2CO_3 solution (2 × 200 mL), water (100 mL), and brine (100 mL). The organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure to provide a thick oil. This material was separated by column chromatography (alumina, CH_2Cl_2) to yield 5.0 g (71%) of monothioketal (**20a**), accompanied by the starting dione (**6**, 1.2 g, 24%) and a trace of bisthioketal (**20b**). **20a**: white solid; mp 84.5–85.5 °C; IR (FT, KBr) 2943.6, 2869.3, 1730.3, 602.7 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.78–1.67 (m, 2 H), 2.00–2.07 (m, 2 H), 2.41–2.48 (m, 4 H, $J_{9a,9b}$ = 14.6 Hz), 2.57 (s, 4 H), 2.65–2.89 (m, 8 H), 2.91–2.97 (m, 4 H), 5.54 (t, 2 H); ^{13}C NMR ($CDCl_3$) 24.86 (t), 24.91 (t), 29.29 (t), 29.57 (t), 35.51 (t) 50.98 (s), 51.53 (t), 53.18 (s), 58.15 (t), 129.23 (d), 218.48 (s); mass spectrum (CI, CH_4), m/e (relative intensity) 309 (M + 1, 100.0), 291 (12.1), 201 (7.2). Anal. Calcd for $C_{17}H_{24}OS_2$: C, 66.23; H, 7.79. Found: C, 66.10; H, 7.75.

Desulfurization of 10,10-(1,3-Propylenedithio)tricyclo[6.3.3.0^{1,8}]tetradec-4-en-13-one (20a) with Raney Ni. A mixture of monothioketal (**20a**, 1.0 g, 3.3 mmol), Raney nickel (W_2, 45 g), and acetone was shaken mechanically for 12 h under nitrogen. Analysis of the mixture by GC and TLC indicated the presence only of starting material. The mixture was then held at reflux for 8 h. The Raney nickel was removed by filtration through Celite and the Celite pad was washed with several portions of acetone. The solvent was removed under reduced pressure to afford a

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mixture (0.55 g) of at least three components including **10** and **22**. GC/mass spectroscopy indicated the presence of a compound whose parent ion (CI, P + 1) occurred at m/e 203. This corresponds to the molecular weight of a keto diene which would arise from a side reaction during the desulfurization process.[12] This material was not isolated.

The reaction was repeated with Raney nickel that had been deactivated by heating in ethyl acetate for 3 h,[11] followed by heating in acetone for at least 3 h. The desulfurization of **20a** was also attempted in solvents such as methanol, acetone, and dioxane. In all cases, a mixture of products was obtained that was very difficult to separate and this route was not pursued further.

Evidence for the Migration of the Double Bond during the Raney Ni Desulfurization of 20a. Tricyclo[6.3.3.0^{1,8}]tetradec-3-en-10-one (**22**) (500 mg, 2.5 mmol) obtained from the Raney Ni desulfurization of **20a** was dissolved in dry acetone (40 mL). The solution was cooled to −70 °C in a dry ice–acetone bath and ozone was passed through the mixture until a deep blue color was observed. The solution was stirred for 5 min and the excess ozone was purged from the medium with a stream of nitrogen (10 min). The reaction mixture then became colorless. To this solution was added Jones' reagent (1.23 M, 20 mL) over a period of 30 min.[2] The orange solution that resulted was stirred for 30 min at −78 °C. The reaction mixture was allowed to warm to room temperature (1 h) after which water (25 mL) and ethyl acetate (25 mL) were added. To this mixture was added solid sodium bisulfite slowly until the ethyl acetate became clear. The aqueous layer was extracted with ethyl acetate (5 × 50 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to yield diacid **23**[12] (0.6 g, 87%) as a white solid. It was crystallized from ethyl acetate to provide the crystalline *cis*-5-(carboxymethyl)-3-oxobicyclo[3.3.0]octane-1-butanoic acid (**23**):[12] mp 165 °C; IR (KBr) 3200–2900, 1745, 1710 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.17–1.84 (m, 8 H), 2.13–2.59 (m, 6 H), 3.37 (s, 4 H), 12.11 (broad singlet, 2 H); carbon-13 NMR (Me_2SO-d_6) 20.86, 21.15, 34.16, 34.23, 35.45, 36.62, 48.26, 49.14, 50.17, 52.23, 173.51, 174.18, 217.18; mass spectrum, m/e (relative intensity) 268 (43.1), 250 (100.0), 232 (55). Anal. Calcd for $C_{14}H_{20}O_5$: C, 59.57; H, 6.38. Found: C, 59.80; H, 6.20.

Attempted Monoketalization of 6 with Ethylene Glycol. A mixture of tricyclo[6.3.3.0^{1,8}]tetradec-4-ene-10,13-dione (**6**, 1.0 g, 4.6 mmol), anhydrous benzene (100 mL), *p*-toluenesulfonic acid monohydrate (50 mg), and distilled ethylene glycol (0.28 g, 4.6 mmol) was heated to reflux for 24 h in a flask equipped with a condenser and Dean–Stark trap. Analysis of the mixture by TLC and GC indicated that the solution contained dione **6**, monoketal **24a**, and predominantly bisketal **24b**. After the mixture was held at reflux for 24 h, it was cooled and washed with dilute aqueous $NaHCO_3$ solution, followed by brine. After removing a portion of the solvent and cooling, a white precipitate of tricyclo-[6.3.3.0^{1,8}]tetradec-4-ene-10,13-dione bis(ethylene ketal) (**24b**) formed: mp 88.5 °C; IR (FT, KBr) 2949, 515, 482 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 18.60, 27.76, 31.96, 34.91, 42.89, 43.24, 47.03, 48.24, 62.01, 69.56, 81.58, 115.64; mass spectrum (CI, CH_4), m/e (relative intensity) 307 (M + 1, 100.0), 308 (20.0), 245 (10.4). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.60; H, 8.50. Found: C, 70.10; H, 8.40.

Selective Monoketalization of 6 with 2,2-Dimethylpropane-1,3-diol. A mixture of dione **6** (1.0 g, 4.6 mmol), 2,2-dimethylpropane-1,3-diol (0.48 g, 4.6 mmol), and *p*-toluenesulfonic acid monohydrate (50 mg) was dissolved in dry benzene (100 mL). The solution was heated to reflux under nitrogen with a condenser and a Dean–Stark trap attached to the flask. The reaction was monitored by TLC (silica gel; ethyl acetate/hexane 30:70). By withdrawing small volumes (5 mL) from the reaction, followed by workup and GLC analysis (column B, oven temperature 200 °C, injection temperature 250 °C, detection temperature 300 °C), the ratio of products (with retention time) present at different intervals was observed (see Table I).

After 12 h, the mixture was cooled and washed consecutively with saturated aqueous $NaHCO_3$ solution (2 × 75 mL) and water (2 × 50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield an oil, which was chromatographed on activated basic alumina (20:80 ethyl acetate/hexane; gradient elution). This workup gave tricyclo[6.3.3.0^{1,8}]tetradec-4-ene-10,13-dione bis(2,2-dimethyltrimethylene ketal) (**25b**, 220 mg, 12%) followed by the desired monoketal (**25a**, 6.92 g, 65%) and the starting dione **6** (100 mg, 10%). Tricyclo[6.3.3.0^{1,8}]tetradec-4-ene-10,13-dione bis(2,2-dimethyltrimethylene ketal) (**25b**): IR (FT, neat) 2957, 2865 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (s, 12 H), 1.77–2.17 (m, 16 H), 3.39 (d, 8 H), 5.49 (t, 2 H); ^{13}C NMR ($CDCl_3$) δ 22.41 (q), 24.17 (t), 29.81 (s), 36.22 (t), 49.74 (t), 51.95 (s), 71.80 (t), 71.92 (t), 107.90 (s), 121.67 (d); mass spectrum (CI, CH_4), m/e (relative intensity) 391 (M + 1, 100.0) 389 (21.0), 390 (9.7), 375 (3.5).

Table I

reactn time	product composition (%): dione **6** (7.13 min)	monoketal **25a** (20.94 min)	diketal **25b** (48.68 min)
60 min	80	20	0
120 min	24	76	0
240 min	20.5	77.0	2.5
360 min	16.5	78.7	4.8
480 min	14.2	76.3	9.5
12 h	12.5	72.5	15.0

Tricyclo[6.3.3.0^{1,8}]tetradec-4-ene-10,13-dione 2,2-Dimethyltrimethylene Monoketal (25a). A mixture of *p*-toluenesulfonic acid monohydrate (200 mg) and dry benzene (250 mL) was held at reflux for 6 h (Dean–Stark trap). After cooling the mixture to room temperature, tricyclo[6.3.3.0^{1,8}]tetradec-4-ene-10,13-dione (**6**, 5.0 g, 23.1 mmol) and 2,2-dimethylpropane-1,3-diol (2.4 g, 23.1 mmol) were added, and the mixture was heated at reflux under nitrogen for 2 h. The solution was cooled and washed successively with saturated aqueous $NaHCO_3$ solution (2 × 100 mL), water (2 × 100 mL), and saturated NaCl solution (2 × 75 mL). The organic layer was then dried ($MgSO_4$) and the solvent was removed under reduced pressure to yield an oil, which was chromatographed as described above to give only trace amounts of bisketal **25b**, followed by the desired monoketal (**25a**, 5.16 g, 74%); dione **6** (1.0 g, 20%) was also recovered. The monoketal, when pure, crystallized and was recrystallized from hexane–ethyl acetate to yield **25a**: mp 64.5-65 °C (white crystals); IR (FT, KBr) 2950, 2868, 1739, 1472, 1120 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (s, 6 H), 1.74–2.42 (m, 16 H), 3.38 (d, 4 H), 5.52 (t, 2 H); according to DEPT experiments, the ^{13}C NMR ($CDCl_3$) signals were composed of the following groups, δ 22.24 (q), 24.60 (t), 29.80 (s), 35.51 (d), 50.45 (s), 50.76 (d), 51.73 (t), 71.56 (t), 72.15 (t), 106.82 (s), 129.46 (d), 218.57 (s); mass spectrum (CI, CH_4), m/e (relative intensity) 305 (M + 1, 100.0), 219 (30.6), 201 (5.3). Anal. Calcd for $C_{19}H_{28}O_3$: C, 75.00; H, 9.20. Found: C, 74.98; H, 9.22.

Wolff–Kishner Reduction of Monoketal (25a). A mixture of monoketal (**25a**, 1.0 g, 3.3 mmol), potassium carbonate (1.5 g), hydrazine hydrate (3 mL), and triethylene glycol (50 mL) was heated at reflux for 2 h under a blanket of nitrogen. A small, short-path distillation head was placed on top of the reaction flask instead of the condenser and the pot temperature was then increased to 200 °C. The mixture was heated at 200 °C for 3 h. It was then cooled, diluted with water (200 mL), and extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed consecutively with water and brine (2 × 50 mL) and then dried. The crude product was passed through a short column of alumina (basic). GLC analysis of the mixture indicated two components in the ratio of 39.5 to 60.5 with retention times of 8.79 and 9.09 min, respectively (column B, oven temperature, 200 °C). The mass spectrum (GC/MS) indicated that the two components had the same molecular weight m/e 305 (M + 1, 100.0). Moreover, the ^{1}H NMR ($CDCl_3$, 250 MHz) as well as the ^{13}C NMR (62.9 MHz, $CDCl_3$) spectra indicated that the two components **26a** and **26b** were olefinic isomers. The signals for the double bond in the major isomer were located at δ 131.78, while the vinylic carbons in the spectrum of the minor isomer **26b** were found at δ 130.63 and 131.32, respectively; the former therefore has the symmetrical structure **26a**.[12]

Wolff–Kishner Reduction of Dione 6. Tricyclo[6.3.3.0^{1,8}]-tetradec-4-ene-10,13-dione (**6**, 500 mg, 2.2 mmol), 85% hydrazine hydrate (2 mL, 34 mmol), potassium carbonate (1.5 g, 11 mmol), and triethylene glycol (20 mL) were heated at 130 °C for 3 h under nitrogen. The pot temperature was raised to 200 °C and excess hydrazine was distilled off. The residue was treated in similar

fashion to that described above, to provide a hydrocarbon (0.32 g, 73%). On GLC analysis the mixture was found to contain two components with retention times of 18.91 and 19.55 min in the ratio 21.2:78.8 (column A; oven temperature 100 °C, 10 min–5°/min–250 °C), respectively. From GC/MS data and the ^{13}C NMR ($CDCl_3$) spectrum, the oil was found to contain the less symmetrical alkene as the minor component (15–20%) and the more symmetrical alkene as the major isomer. Tricyclo-[6.3.3.0^{1,8}]tetradec-4-ene: IR (FT, neat) 3016, 2901, 1467, 731, 639 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37–1.95 (m, 16 H), 2.11–2.21 (q, 4 H), 5.75 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 22.97, 24.21, 40.55, 43.60, 54.30, 131.88; mass spectrum (CI, CH_4) *m/e* (relative intensity) 191 (M + 1, 100), 190 (26), 189 (83), 149 (17), 135 (28), 109 (46). Anal. Calcd for $C_{14}H_{22}$: C, 88.42; H, 11.58. Found: C, 88.30; H, 11.68. Tricyclo[6.3.3.0^{1,8}]tetradec-3-ene: ^{13}C NMR ($CDCl_3$) δ 23.27 (t), 24.34 (t), 26.15 (s), 27.92 (s), 29.72 (t), 35.49 (t), 39.60 (t), 40.47 (t), 42.36 (t), 43.24 (t), 55.50 (t), 55.70 (t), 130.63 (d), 131.32 (d); mass spectrum (CI, CH_4), *m/e* (relative intensity) 191 (M + 1, 100).

Tricyclo[6.3.3.0^{1,8}]tetradec-4-en-10-one (10). A mixture of monoketal (**25a**, 2.0 g, 6.5 mmol), potassium carbonate (3.0 g, 22 mmol), silver carbonate (1.5 g, 10 mmol), hydrazine hydrate (6 mL), and triethylene glycol (50 mL) was heated at reflux for 2 h under nitrogen. A small short-path distillation head was then placed on top of the flask in place of the condenser. The pot temperature was increased to 200 °C and the material was held at this temperature for 5 h, after which it was cooled and diluted with water. The mixture was heated with 100 mL of 2 N sulfuric acid for 6 h, cooled, and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were washed consecutively with saturated $NaHCO_3$ solution and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to provide **10** (1.1 g, 84%), which was further purified by column chromatography on activated alumina (basic) with ethyl acetate–hexane (20:80). The 4-ene (**10**) is a viscous oil: IR (FT, neat) 2957, 2929, 1734, 1286, 594 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 21.16, 24.60, 35.77, 42.21, 51.79, 52.21, 129.82, 219.39; mass spectrum (CI, CH_4), *m/e* (relative intensity) 205 (M + 1, 100), 187 (43), 149 (11), 135 (3). Anal. Calcd for $C_{14}H_{20}O$: C, 82.35; H, 9.80. Found: C, 82.15; H, 9.70.

***cis*-3-Oxobicyclo[3.3.0]octane-1,5-dipropanal Dimethyl Acetal (11).** Tricyclo[6.3.3.0^{1,8}]tetradec-4-en-10-one (**10**, 1.0 g, 4.8 mmol) was dissolved in a mixture of dry CH_3OH (40 mL) and CH_2Cl_2 (80 mL). The solution was cooled to −70 °C in a dry ice–acetone bath and ozone was passed through the mixture until a deep blue coloration developed. The solution was stirred for 5 min and the excess ozone was purged from the medium with a stream of nitrogen (15 min), after which the reaction mixture became colorless. The solution was allowed to warm to −10 °C, and dimethyl sulfide (6.2 g, 0.1 mmol) was added slowly. The solution was stirred first at −10 °C for 1 h and then at room temperature overnight. The solvent was removed under reduced pressure and the residue was dissolved in water (50 mL) and subsequently extracted with chloroform (3 × 50 mL). The dimethyl sulfoxide remained in the water layer. The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to provide the bisacetal **11** (90%), accompanied by the corresponding dialdehyde. The bisacetal **11** was employed in the next step, although the same yield of **2** was obtained from the mixture of bisacetal **11** and dialdehyde as well as from the trisacetal **27**.[12]

Preparation of *trans,trans*-4,8-Diacetoxytetracyclo-[9.3.0.0.^{1,5}0^{7,11}]tetradecan-6-one (2). The *cis*-3-oxobicyclo-[3.3.0]octane-1,5-dipropanal dimethyl acetal (**11**) [or its hemiacetal (0.5 g)][12] was dissolved in glacial acetic acid (50 mL) and 3 drops of concentrated H_2SO_4 were added. The mixture was stirred under nitrogen for 10 days at 50 °C. The solution was cooled and brought to pH 4 with solid sodium carbonate, and the acetic acid was removed under reduced pressure. To the residue was added water (50 mL), and the solution was extracted with $CHCl_3$ (3 × 25 mL). The combined $CHCl_3$ extracts were washed consecutively with cold water, cold aqueous $NaHCO_3$ solution (5%, 30 mL), and brine. After drying ($MgSO_4$) the solvent was removed under reduced pressure to provide an oil (150 mg, 40% overall yield from the monoketone **10**). The crude **2** obtained in this fashion was purified by flash chromatography (2 times, ethyl acetate–hexane, 20:80) to provide white crystals of **2**: mp 98–99 °C; IR (FT, KBr) 2974, 2954, 1738, 1724, 1376, 1236, 1017 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.71 (m, 14 H), 2.05 (s, 6 H), 2.67 (m, 2 H), 5.28 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.93 (q), 24.20 (t), 33.34 (t), 33.74 (t), 42.80 (t), 56.03 (s), 66.23 (d), 76.25 (d), 170.06 (s), 213.10 (s); mass spectrum (EI, 15 ev), *m/e* (relative intensity) 320 (M$^+$, 3.4), 279 (23.8), 260 (22.3), 248 (14.1), 230 (15.3), 217 (32.7), 200 (100.0), 188 (31.1), 172 (55.7), 160 (18.5), 149 (34.3); high resolution mass spectrum calcd for $C_{18}H_{24}O_5$ − 60 (M$^+$ − CH_3COOH) 260.1412, found 260.1428; calcd for (M$^+$ − 2 × CH_3COOH) 200.1201, found 200.1230. Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.50; H, 7.50. Found: C, 67.25; H, 7.45.

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Registry No. **2**, 107784-79-2; **6**, 78046-17-0; **10**, 107784-85-0; **11**, 107802-95-9; **11**-(dialdehyde), 109307-54-2; **18**, 109307-55-3; **19a**, 109307-56-4; **19b**, 109307-57-5; **20a**, 107784-84-9; **21a**, 109307-58-6; **21b**, 109307-59-7; **22**, 107784-82-7; **23**, 109307-60-0; **24a**, 109307-61-1; **24b**, 109307-62-2; **25a**, 107784-81-6; **25b**, 107784-80-5; **26a**, 107784-83-8; **26b**, 107784-86-1; ethanedithiol, 540-63-6; butane-1,4-dithiol, 1191-08-8; propane-1,3-dithiol, 109-80-8; ethylene glycol, 107-21-1; 2,2-dimethylpropane-1,3-diol, 126-30-7; tricyclo[6.3.3.0^{1,8}]tetradec-4-ene, 109307-63-3; tricyclo-[6.3.3.0^{1,8}]tetradec-3-ene, 109307-64-4.

Polyvalent Iodine in Synthesis. 1. An Efficient Route to Isopropylidene Arylmalonates (5-Aryl-Substituted Meldrum's Acid)

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Meldrum's acid (**1**, isopropylidene malonate, 2,2-dimethyl-1,3-dioxane-4,6-dione) and its 5-substituted derivates are versatile reagents in organic synthesis[2] as well as valuable precursors in thermal decompositions.[3]

Several new methods have recently been reported[4–7] for the direct preparation of 5-alkyl-substituted derivatives from Meldrum's acid itself. However, few methods are available for the ready preparation of 5-aryl derivatives from **1** itself, as direct substitution with aryl halides by various salts of **1** via an S_NAr process requires highly activated aromatic substrates. The only known method of direct arylation employs aryllead triacetate as the arylating reagent to afford isopropylidene arylmalonates.[8] However, lead compounds are clearly toxic, and Meldrum's acid itself gave only a poor yield of the diarylated product.

Our recent interest[9] in tricoordinate iodine species and their renaissance in organic synthesis,[10] coupled with the ready availability and high reactivity[11] of diaryliodonium

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