Pergamon

Tetrahedron 58 (2002) 25–34

TETRAHEDRON

Mn(III)-based oxidative free-radical cyclizations of alkenyl Meldrum's acids

Barry B. Snider* and Rachel B. Smith

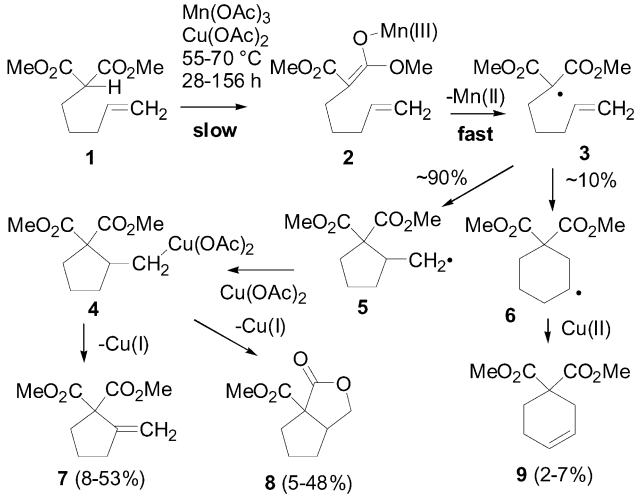
Department of Chemistry MS015, Brandeis University, Waltham, MA 02454-9110, USA

Received 24 September 2001; accepted 1 November 2001

Abstract—Oxidative cyclization of unsaturated Meldrum's acids can be carried out at temperatures as low as −30°C. The rate-determining step is cyclization of the enolate to the alkene (**11** to **14** and **15**) rather than enolization, which is the rate-determining step with dimethyl 4-pentenylmalonate (**1**). While cyclization of **1** gives mainly cyclopentanes, cyclization of Meldrum's acids provides a versatile route to cyclohexenes. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

We have extensively developed $Mn(OAc)_3$-based oxidative free-radical cyclizations of unsaturated carbonyl and dicarbonyl compounds as a versatile procedure for generating a radical that can cyclize by enolization and oxidation of the enolate. Oxidation of the cyclic radical by $Cu(OAc)_2$ generates the least substituted alkene regiospecifically.[1] Enolization of dimethyl 4-pentenylmalonate (**1**) to give manganese enolate **2** is the slow, rate-determining step in the oxidative cyclization with $Mn(OAc)_3$ (Scheme 1).[2–4] Rapid loss of Mn(II) from **2** generates radical **3**, which cyclizes to give a ~9:1 mixture of cyclopentanemethyl radical **5** and cyclohexyl radical **6**. Reaction of **5** with $Cu(OAc)_2$ gives Cu(III) intermediate **4** which undergoes oxidative elimination to give methylenecyclopentane **7** and ligand transfer to give lactone **8**. A similar oxidation converts **6** to cyclohexene **9**. Reaction in AcOH (55°C, 28 h) affords a 2.5:1 mixture of **8** and **7**. Reaction in EtOH (60°C, 156 h) is much slower, but yields a 2:3 mixture of **8** and **7**, while reaction in DMSO (75°C, 68 h) forms a 1:10 mixture of **8** and **7**.



Scheme 1. Oxidative cyclization of malonate **1**.

We thought the cyclization of alkenyl Meldrum's acid **10** might occur more rapidly and at lower temperatures since Meldrum's acid is more acidic than dimethyl malonate by ~8.5 pK_a units in either H_2O or DMSO.[5] Selective monoalkylation of Meldrum's acid is difficult; the dialkylated product usually predominates.[6,7] Fortunately, **10** can be easily prepared by a modification of the literature procedure.[8] Ethylenediammonium diacetate-catalyzed Knoevenagel condensation of Meldrum's acid and 4-pentenal for 1 h at 25°C followed by addition of $BH_3{\cdot}NHMe_2$ and stirring for 18 h affords 69% of **10**. This one-pot reaction was used with the appropriate aldehyde or ketone to prepare all the cyclization substrates in 50–70% yield.[9]

2. Results and discussion

Oxidative cyclization of **10** as a 0.1 M solution in EtOH with 2 equiv. of $Mn(OAc)_3{\cdot}2H_2O$ and 1 equiv. of $Cu(OAc)_2{\cdot}H_2O$ for 10 min at 25°C provides 8% of methylenecyclopentane **13**, 65% of cyclohexene **16**,[10] and 4% of cyclohexene **17** (Scheme 2). Oxidation of cyclohexyl radical **15** with Cu(II) selectively removes the least hindered proton to form mainly cyclohexene **16**.[1a] Similar results are obtained in AcOH, with 3 equiv. of KOAc added to minimize

Keywords: cyclisation; manganese; copper; radical reactions; cyclohexenes.

* Corresponding author. Tel.: +1-781-736-2550; fax: +1-781-736-2516; e-mail: snider@brandeis.edu

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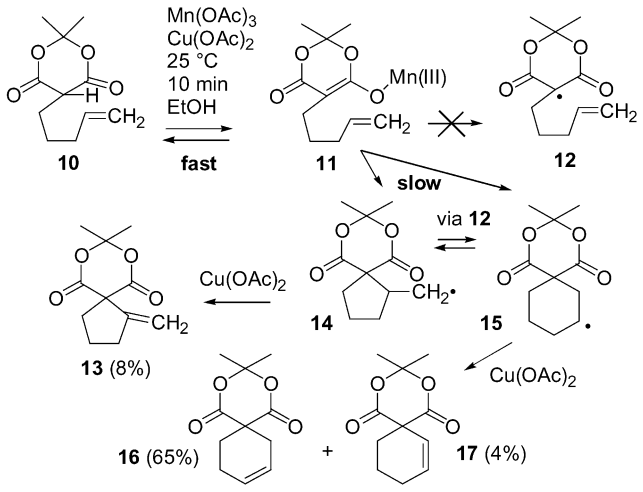
PII: S0040-4020(01)01054-7

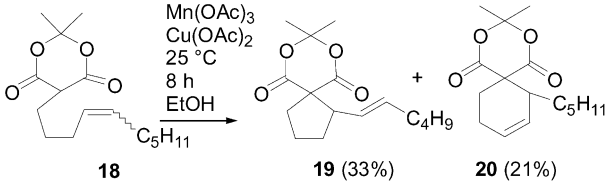
hydrolysis of the Meldrum's acid, except that 5–10% of the lactone analogous to **8** is obtained instead of **13**.



Scheme 2. Oxidative cyclization of Meldrum's acid **10**.

As expected, oxidative cyclization of **10**, with a half life in EtOH of <5 min at 25°C and 2 h at −30°C, is much faster than that of the less acidic dimethyl ester **1**, which requires 156 h at 60°C for complete reaction. More surprisingly, **10** gives predominantly products derived from cyclohexyl radical **15**, while **1** gives mainly products derived from cyclopentanemethyl radical **5** suggesting that these two reactions are mechanistically distinct.

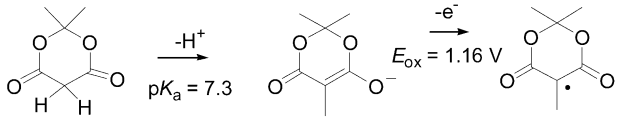
The oxidative cyclization of either the cis or trans isomer of **18** to provide 33% of hexenylcyclopentane **19** and 21% of cyclohexene **20** requires 8 h at 25°C with a half-life of 2 h. The change in half life from <5 min with **10** to 2 h with **18** clearly indicates that the double bond participates in the rate-determining step. Loss of a proton from **10** to give Mn(III) enolate **11** should be rapid and reversible. Loss of Mn(II) from enolate **11** to form radical **12** cannot be occurring because this reaction would proceed at the same rate with **11** and the enolate derived from **18** (Scheme 3).



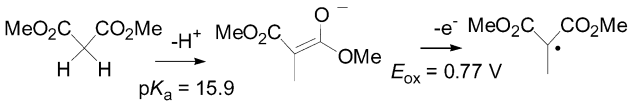
Scheme 3.

Direct cyclization of the alkene of **11** with the Mn(III) enolate to give cyclic radicals **14** and **15** is the slow, rate-determining step in the oxidative cyclization of these Meldrum's acid derivatives, while formation of enolate **2** is the slow, rate-determining step in the oxidative cyclization of **1**. We have previously observed analogous shifts in mechanism as a function of the acidity of the dicarbonyl compound and the oxidation potential of the enolate. Direct cyclization of the enolate is the rate-determining step with α-unsubstituted β-keto esters, which are relatively acidic and form enolates that have a large oxidation potential.[4a] Formation of the enolate is the rate-determining step with α-substituted β-keto esters, which are less acidic and form enolates that have a lower oxidation potential.

Bausch's studies of the oxidation potential of the enolates of dimethyl malonate and Meldrum's acid in DMSO support this interpretation.[11] The pK_as of Meldrum's acid and dimethyl malonate in DMSO are 7.3 and 15.9, respectively, indicating that enolization of Meldrum's acid is favored by 11.8 kcal mol^{-1} (Eqs. (1) and (2)). On the other hand the oxidation potentials of the enolates are 1.16 and 0.77 V, respectively, indicating that it is 9 kcal mol^{-1} easier to oxidize the enolate of dimethyl malonate. Combining these two reactions establishes that formation of the radical from Meldrum's acid should be favored by 2.8 kcal mol^{-1}.



(1)



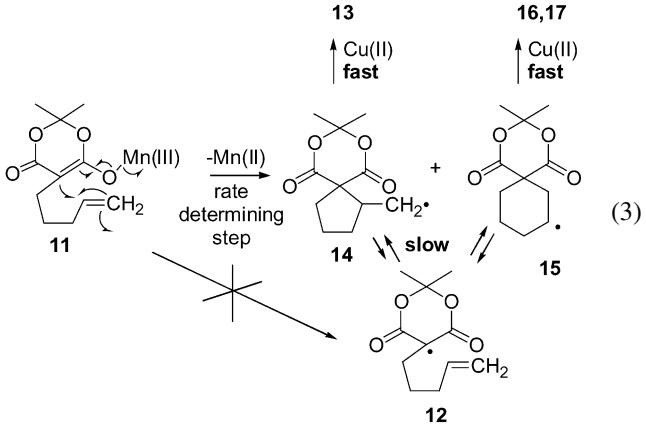
(2)

Loss of a proton from **1** to give enolate **2** should be slow, with rapid loss of Mn(II) to give acyclic radical **3**. On the other hand, loss of a proton from **10** to give enolate **11** should be fast. However, loss of Mn(II) to give acyclic radical **12** will be slow because the oxidation potential of **11** is large, so that cyclization of **11** to **14** and **15** is the rate-determining step. Since these two cyclizations are mechanistically distinct, there is no contradiction in the preferential formation of cyclopentanemethyl radical **5** from **1** and cyclohexyl radical **15** from **10**.

Selectivity for cyclohexene **16** can be increased by carrying out the cyclization with only 0.05 equiv. of $Cu(OAc)_2 \cdot H_2O$. Under these conditions we obtain only 0.5% of methylenecyclopentane **13**, 74% of cyclohexene **16** and 3% of cyclohexene **17**. At low Cu(II) concentration, radicals **14** and **15** have longer life times and equilibrate prior to oxidation, presumably by opening to acyclic radical **12**. Under thermodynamic control, the cyclohexyl radical **15** should be strongly preferred. Even though radical **12** is not formed from enolate **11**, Bausch's studies indicate that **12** is more stable than **3**, so that equilibration of **14** and **15** via **12** should occur if trapping of the radical is slow.[12]

To summarize, these mechanistic studies clearly indicate that the oxidative cyclization of very acidic alkenyl Meldrum's acids **10** and **18** is quite different from that of 4-pentenylmalonate diester **1**. Formation of enolate **11** is rapid while formation of enolate **2** is slow. Since the half life for oxidative cyclization of **18** is >25 times slower than for the cyclization of **10**, the double bond must be involved in the rate determining step, which is probably the cyclization of **11** to give cyclic radicals **14** and **15** with loss of Mn(II) without the intermediacy of acyclic radical **12**

(Eq. (3)). Although this cyclization does not fit into standard mechanistic schemes, the kinetic data clearly indicate that radical **12** is not an intermediate. It is tempting to suggest that the alkene coordinates to Mn(III) or Cu(II) prior to cyclization. However, coordination of alkenes to these metals in high oxidation states is unlikely.

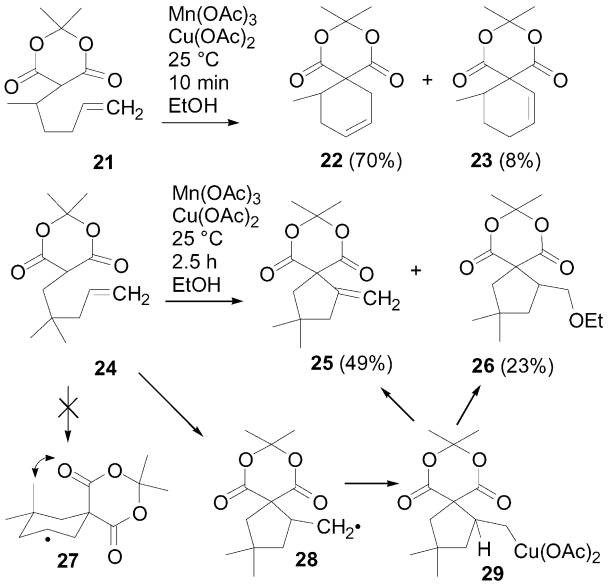


(3)

Oxidation of radicals **14** and **15** proceeds by formation of Cu(III) intermediates with a second order rate constant of approximately $10^6\ M^{-1}\ s^{-1}$. If 1.0 equiv. of $Cu(OAc)_2$ is used the radicals are trapped rapidly so that the ratio of products reflects the ratio of radicals formed in the cyclization. If only 0.05 equiv. of $Cu(OAc)_2$ is used the radicals have a longer lifetime and can equilibrate by reversible ring opening to acyclic radical **12**.[12] This process will lead to higher concentrations of the more stable cyclohexyl radical **15**, which will lead to increased yields of **16** and **17** at the expense of methylenecyclopentane **13**.

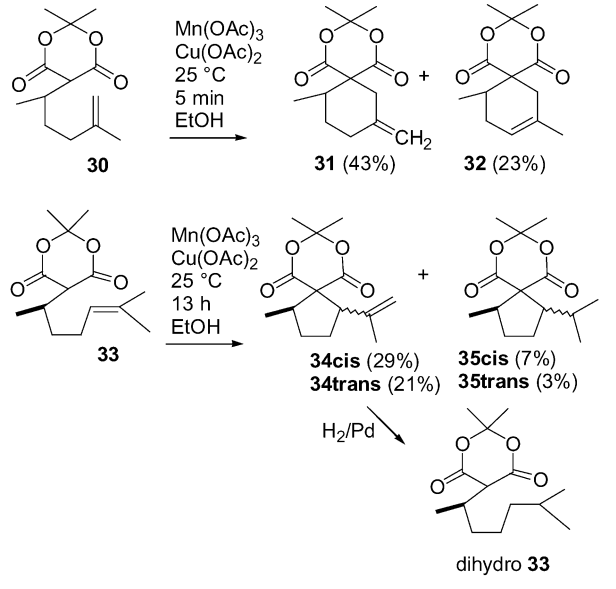
Oxidative cyclization of **21** with 2 equiv. of $Mn(OAc)_3 \cdot 2H_2O$ and only 0.05 equiv. of $Cu(OAc)_2 \cdot H_2O$ for 10 min at 25°C proceeds analogously to give 70% of cyclohexene **22**, 8% of cyclohexene **23**, and 1% of the methylenecyclopentane analogous to **13**. However, oxidative cyclization of **24**[8c] with 2 equiv. of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv. of $Cu(OAc)_2 \cdot H_2O$ requires 2.5 h at 25°C and gives 49% of methylenecyclopentane **25** and 23% of ethoxymethylcyclopentane **26**. No cyclohexene was observed; <4% of the cyclohexene was obtained with only 0.05 equiv. of $Cu(OAc)_2 \cdot H_2O$, which should favor equilibration of the radicals. Severe 1,3-diaxial interactions between the geminal dimethyl group and the carbonyl groups of the Meldrum's acid make the formation of cyclohexyl radical **27** kinetically and thermodynamically disfavored. The hydrogen in Cu(III) intermediate **29** is very hindered. Therefore, ligand transfer with solvent to give **26** competes with oxidative elimination to give the expected methylenecyclopentane **25**[13] (Scheme 4).

Oxidative cyclization of **30** is rapid, giving 43% of methylenecyclohexane **31** and 23% of methylcyclohexene **32**, both of which are derived from the tertiary cyclohexyl radical. Oxidative cyclization of **33** with 2 equiv. of $Mn(OAc)_3 \cdot 2H_2O$ and 2 equiv. of $Cu(OAc)_2 \cdot H_2O$ affords exclusively the tertiary cyclopentanemethyl radical, which is oxidized by $Cu(OAc)_2$ to give 29% of ***34cis*** and 21% of ***34trans***. Saturated products ***35cis*** (7%) and ***35trans*** (3%)



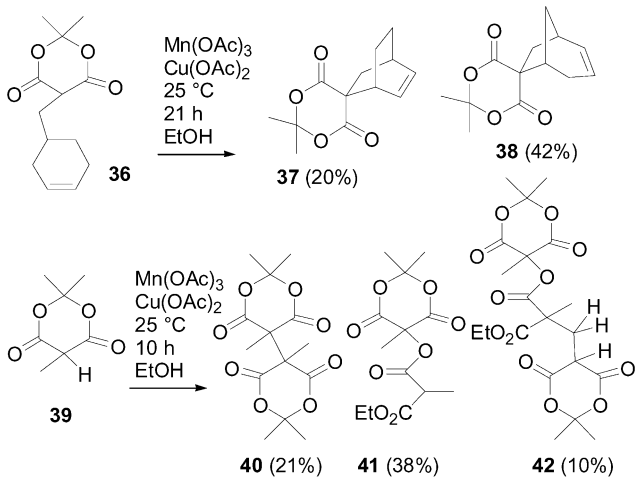
Scheme 4.

are also obtained indicating that the hindered tertiary radical reacts with Cu(II) slowly so that hydrogen abstraction from EtOH is competitive. With only 0.05 equiv. of $Cu(OAc)_2 \cdot H_2O$, ***35cis*** (28%) and ***35trans*** (14%) are the major products, with only traces of ***34cis*** and ***34trans***. No saturated products are formed in AcOH, but the overall yields are lower. Hydrogenation of **34** over Pd/C or Rh/Al_2O_3 gives predominantly dihydro **33**, indicating that cleavage to the Meldrum's acid anion and an allylic organometallic, which is hydrogenated, is faster than hydrogenation of the double bond[14] (Scheme 5).



Scheme 5.

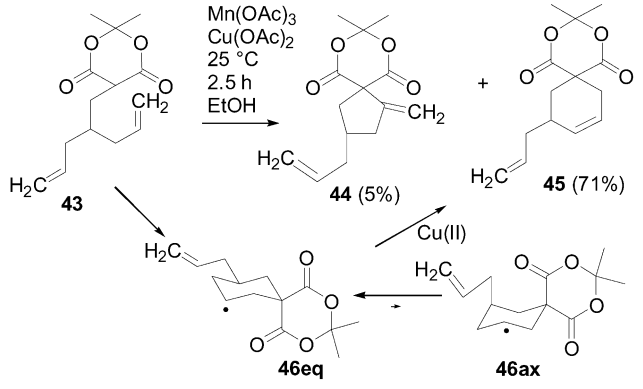
Cyclization of cyclohexene **36** affords a mixture of **37** and **38** and compounds that appear to be dimers. The cyclization should be slow since the cyclohexene must adopt an unfavorable conformation with a pseudoaxial side chain. To prevent dimerization, we added **36** over 12 h to the



Scheme 6.

oxidants. Under these conditions we obtain 20% of **37**,[10] 42% of **38**, and no dimers. The dimerization was investigated in detail with methyl Meldrum's acid (**39**), which gives 21% of C–C dimer **40**,[15a] 38% of C–O dimer **41**, and 10% of **42**, resulting from addition of **41** to methylene Meldrum's acid formed by oxidation of **39**[15] (Scheme 6).

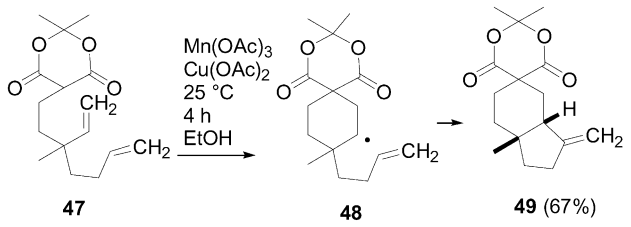
Attempted tandem cyclization of **43** yields 5% of methylenecyclopentane **44** and 71% of cyclohexene **45**. Cyclohexyl radical **46eq** must flip to **46ax** with an axial allyl side chain for tandem cyclization to occur. 1,3-Diaxial interactions make this energetically unfavorable, so that it is slower than oxidation of **46eq** to **45**, even if only 0.05 equiv. of $Cu(OAc)_2 \cdot H_2O$ is used (Scheme 7).



Scheme 7.

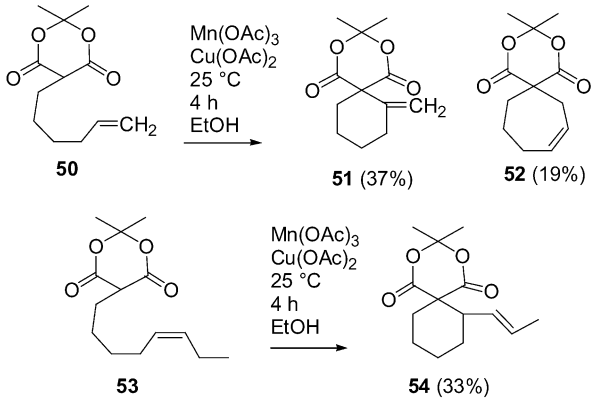
Tandem oxidative cyclization of **47** provides 67% of perhydroindane **49** as the only product. The second cyclization of cyclohexyl radical **48** is fast since a fused, rather than a bridged, ring system is formed and cyclization can therefore occur from either chair conformer of **48** (Scheme 8).

Cyclizations of 5-alkenyl Meldrum's acids can also be successfully carried out to give cycloheptenes and unsaturated cyclohexanes. Oxidative cyclization of **50** affords 37% of methylenecyclohexane **51** and 19% of cycloheptene **52**. Oxidative cyclization of **53** provides 33% of propenylcyclohexane **54**. As expected, the yields of these cyclizations are



Scheme 8.

somewhat lower than those of the comparable 4-alkenyl Meldrum's acids. Cyclizations of 5-alkenyl Meldrum's acids will be slower since they have a more negative entropy of cyclization, while dimerization and other side reactions will occur at the same rate (Scheme 9).



Scheme 9.

In conclusion, we have developed a facile oxidative cyclization of unsaturated Meldrum's acid derivatives that can be carried out at temperatures as low as −30°C. The rate-determining step is cyclization of the enolate to the alkene (**11** to **14** and **15**) rather than enolization, which is the rate-determining step with dimethyl 4-pentenylmalonate (**1**). While cyclization of **1** gives mainly cyclopentanes, cyclization of Meldrum's acid derivatives provides a versatile route to cyclohexenes that should be broadly applicable in organic synthesis.

3. Experimental

3.1. General

NMR spectra were recorded at 400 MHz in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in δ and coupling constants in Hz. IR spectra are reported in cm^{-1}. Most of these compounds did not give parents by CI mass spectroscopy. The highest mass peak was usually M-58 (acetone) resulting from the facile fragmentation of the Meldrum's acid.[16]

3.2. Preparation of alkenyl Meldrum's acids

3.2.1. 2,2-Dimethyl-5-(4-pentenyl)-1,3-dioxane-4,6-dione (10). Ethylene diammonium diacetate (EDDA) (248 mg, 1.4 mmol) was added to a solution of Meldrum's acid

(1.188 g, 8.5 mmol) and 4-pentenal (460 mg, 5.5 mmol) in absolute EtOH (6.6 mL) at rt and the resulting solution was stirred for 1 h. $BH_3{\cdot}NH(CH_3)_2$ (326 mg, 5.5 mmol) was added to the reaction, which was stirred for 17.5 h. Water (35 mL) and 5% aqueous HCl solution (3 mL) were added to the reaction, which was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give 1.47 g of crude product. Flash chromatography (9:1 hexanes/EtOAc containing 0.5% HOAc) gave 805 mg (69%) of pure **10** as a white solid: mp 48–50°C; ^{1}H NMR 5.80 (ddt, 1, J=17.1, 10.4, 6.1 Hz), 5.04 (d, 1, J=17.1 Hz), 4.99 (d, 1, J=10.4 Hz), 3.52 (t, 1, J=4.9 Hz), 2.17–2.10 (m, 4), 1.79 (s, 3), 1.76 (s, 3), 1.61–1.53 (m, 2); ^{13}C NMR 165.5 (2C), 137.7, 115.2, 104.8, 46.1, 33.5, 28.4, 26.9, 26.1, 25.6. This compound has previously been synthesized by reaction of allyltrimethylsilane with 6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione.[17]

3.2.2. 5-(*cis*-4-Decenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (18*cis*). Reaction of EDDA (88 mg, 0.49 mmol), Meldrum's acid (421 mg, 2.9 mmol), and *cis*-4-decenal (301 mg, 1.96 mmol) in absolute EtOH (4.0 mL) followed by reduction with $BH_3{\cdot}NH(CH_3)_2$ (127 mg, 2.1 mmol) and workup and chromatography as described earlier gave 160 mg (54%) of pure **18*cis*** as an oil: ^{1}H NMR 5.44–5.31 (m, 2), 3.51 (t, 1, J=5.2 Hz), 2.15–1.95 (m, 6), 1.79 (s, 3), 1.76 (s, 3), 1.57–1.49 (m, 2), 1.37–1.26 (m, 6), 0.89 (t, 3, J=7.0 Hz); ^{13}C NMR 165.6 (2C), 131.0, 128.4, 104.8, 46.1, 31.5, 29.3, 28.5, 27.2, 27.0, 26.9, 26.5, 26.3, 22.6, 14.1.

3.2.3. 2,2-Dimethyl-5-(1-methyl-4-pentenyl)-1,3-dioxane-4,6-dione (21). Reaction of EDDA (203 mg, 1.1 mmol), Meldrum's acid (844 mg, 5.9 mmol) and 5-hexen-2-one (548 mg, 5.6 mmol) in absolute EtOH (7.0 mL) followed by reduction with $BH_3{\cdot}NH(CH_3)_2$ (342 mg, 5.8 mmol) and workup and chromatography as described earlier gave 490 mg (39%) of pure **21** as a white solid, followed by 230 mg of 73% pure **21** contaminated with the product of condensation of Meldrum's acid with acetone derived from hydrolysis of Meldrum's acid. The overall yield of **21** was 52%: mp 64–65°C; ^{1}H NMR 5.78 (ddt, 1, J=10.4, 17.1, 6.7 Hz), 5.02 (dd, 1, J=1.8, 17.1 Hz), 4.97 (dd, 1, J=1.8, 10.4 Hz), 3.44 (d, 1, J=2.4 Hz), 2.63–2.57 (m, 1), 2.21–2.12 (m, 1), 2.09–2.00 (m, 1), 1.78–1.61 (m, 2), 1.74 (s, 3), 1.73 (s, 3), 1.10 (d, 3, J=6.7 Hz); ^{13}C NMR 165.5, 164.7, 138.0, 115.1, 104.7, 50.5, 33.4, 32.7, 31.9, 28.2, 27.4, 16.3. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.68; H, 8.10.

3.2.4. 2,2-Dimethyl-5-(2,2-dimethyl-4-pentenyl)-1,3-dioxane-4,6-dione (24). Reaction of EDDA (154 mg, 0.85 mmol), Meldrum's acid (737 mg, 5.1 mmol), and 2,2-dimethyl-4-pentenal (90%, 425 mg, 3.4 mmol) in absolute EtOH (13.6 mL) followed by reduction with $BH_3{\cdot}NH(CH_3)_2$ (221 mg, 3.7 mmol) and workup and chromatography as described earlier gave 555 mg (68%) of pure **24**[8c] as a waxy solid: mp 38–40°C; ^{1}H NMR 5.88 (ddt, 1, J=10.3, 17.7, 7.5 Hz), 5.07 (br d, 1, J=10.3 Hz), 5.05 (br d, 1, J=17.7 Hz), 3.42 (t, 1, J=4.1 Hz), 2.16 (d, 2, J=4.1 Hz), 2.04 (d, 2, J=7.5 Hz), 1.84 (s, 3), 1.77 (s, 3), 0.95 (s, 6); ^{13}C NMR 166.1 (2C), 134.7, 117.7, 104.5, 46.7, 43.1, 36.5, 33.2, 28.8, 26.5 (2C), 26.4. The ^{1}H NMR spectrum is identical to that previously reported.[8c]

3.2.5. 2,2-Dimethyl-5-(1,4-dimethyl-4-pentenyl)-1,3-dioxane-4,6-dione (30). Reaction of EDDA (217.2, 1.2 mmol), Meldrum's acid (691 mg, 4.8 mmol) and 5-methyl-5-hexen-2-one (539 mg, 4.8 mmol) in absolute EtOH (6 mL) followed by reduction with $BH_3{\cdot}NH(CH_3)_2$ (295 mg, 5.0 mmol) and workup and chromatography as described earlier gave 634 mg (55%) of pure **30** as a colorless oil which solidified upon standing: mp 52–53°C; ^{1}H NMR 4.73 (br s, 1), 4.70 (br s, 1), 3.50 (d, 1, J=3.1 Hz), 2.62–2.59 (dtq, 1, J=3.1, 7.0, 6.7 Hz), 2.17–1.99 (m, 2), 1.78–1.72 (m, 2), 1.76 (s, 3), 1.75 (s, 3), 1.73 (s, 3), 1.13 (d, 3, J=6.7 Hz); ^{13}C NMR 165.4, 164.7, 145.2, 110.5, 104.6, 50.5, 35.9, 33.5, 31.3, 28.2, 27.3, 22.2, 16.3. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.74; H, 8.43.

3.2.6. 2,2-Dimethyl-5-(1,5-dimethyl-4-hexenyl)-1,3-dioxane-4,6-dione (33). Reaction of EDDA (144 mg, 0.8 mmol), Meldrum's acid (571 mg, 4.0 mmol) and 6-methyl-5-hepten-2-one (496 mg, 3.9 mmol) in absolute EtOH (5.1 mL) followed by reduction with $BH_3{\cdot}NH(CH_3)_2$ (246 mg, 4.2 mmol) and workup and chromatography as described earlier gave 534 mg (53%) of pure **33** as a colorless oil: ^{1}H NMR 5.11 (t, 1, J=7.3 Hz), 3.47 (d, 1, J=3.1 Hz), 2.64–2.58 (m, 1), 2.11–1.96 (m, 2), 1.75 (s, 3), 1.74 (s, 3), 1.71–1.57 (m, 2), 1.68 (s, 3), 1.61 (s, 3), 1.11 (d, 3, J=7.3 Hz); ^{13}C NMR 165.6, 164.8, 132.2, 123.7, 104.6, 50.4, 33.6 (2C), 28.2, 27.4, 26.2, 25.7, 17.7, 16.4.

3.2.7. 5-(3-Cyclohexenylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (36). Reaction of EDDA (72 mg, 0.4 mmol), Meldrum's acid (251 mg, 1.7 mmol), and 3-cyclohexenecarboxaldehyde (179 mg, 1.6 mmol) in absolute EtOH (2 mL) followed by reduction with $BH_3{\cdot}NH(CH_3)_2$ (101 mg, 1.7 mmol) and workup and chromatography as described earlier gave 226 mg (56%) of pure **36** as a white solid: mp 113–114°C; ^{1}H NMR 5.70–5.62 (m, 2), 3.51 (t, 1, J=6.1 Hz), 2.18–1.69 (m, 8), 1.81 (s, 3), 1.77 (s, 3), 1.36–1.26 (m, 1); ^{13}C NMR 165.9 (2C), 127.0, 125.5, 104.8, 43.6, 33.0, 31.3, 31.2, 28.5, 28.4, 26.7, 24.8. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.07; H, 7.65.

3.2.8. 2-(2-Propenyl)-4-pentenal (43a). Pyridine (5.2 mL, 64 mmol) was added to a solution of CrO_3 (3.19 g, 31.9 mmol) in CH_2Cl_2 (25 mL) at 0°C. The mixture was stirred for 5 min at this temperature and allowed to warm to 25°C over 15 min. 2-(2-Propenyl)-4-penten-1-ol[18] (574 mg, 4.6 mmol) in CH_2Cl_2 (2 mL) was added by cannula. The reaction was stirred at 25°C for 8 h and decanted. The flask was washed with three portions of ether. The combined organic layers were washed sequentially with 5% aqueous NaOH, 5% aqueous HCl, satd $CuSO_4$, water, and satd $NaHCO_3$, dried ($MgSO_4$) and concentrated to give 469 mg (83%) of crude aldehyde **43a** which was used without purification.

3.2.9. 2,2-Dimethyl 5-(2-propenyl-4-pentenyl)-1,3-dioxane-4,6-dione (43). Reaction of EDDA (165 mg, 0.91 mmol), Meldrum's acid (985 mg, 6.84 mmol) and crude aldehyde **43a** (469 mg, 3.79 mmol) in absolute

EtOH (45 mL) followed by reduction with $BH_3{\cdot}NH(CH_3)_2$ (272 mg, 4.6 mmol) and workup and chromatography as described earlier gave 432 mg (38% for 2 steps) of pure **43** as a colorless oil: ^{1}H NMR 5.77 (ddt, 2, J=17.1, 10.4, 6.7 Hz), 5.03 (d, 2, J=17.1 Hz), 5.02 (d, 2, J=10.4 Hz), 3.68 (t, 1, J=6.1 Hz), 2.15–2.02 (m, 7), 1.75 (s, 3), 1.71 (s, 3); ^{13}C NMR 165.7 (2C), 136.5 (2C), 116.8 (2C), 104.8, 44.3, 38.3 (2C), 34.5, 30.9, 28.6, 26.5.

3.2.10. 3-Ethenyl-3-methyl-6-heptenal (47a). 3-Methyl-2-hepten-1-ol[19] (1.726 g, 13.7 mmol) in THF (17 mL) was added by cannula to a slurry of NaH (60%, 658 mg, 16.5 mmol) in THF (9 mL) and the resulting solution was stirred for 30 min. (*E*)-(Carboxyvinyl)trimethylammonium betaine[20] (2.3 g, 17.8 mmol) was added and the reaction was heated at reflux for 15.5 h. The reaction was allowed to cool and water (60 mL) and ether (20 mL) were added. The layers were separated and the aqueous layer was washed with ether (2×25 mL), acidified to pH 1 and extracted with ether (3×75 mL). The organic layers were dried and concentrated to give 1.02 g (38%) of 3-(3-methyl-2,6-heptadienyloxy)-propenoic acid. Bulb to bulb distillation (160–180°C, 4 mm Hg) gave 748 mg (78%) of **47a**, which was used without further purification: ^{1}H NMR 9.74 (t, 1, J=3.4 Hz), 5.85 (dd, 1, J=17.7, 11.0 Hz), 5.78 (ddt, 1, J=17.7, 9.8, 6.7 Hz), 5.13 (d, 1, J=11.0 Hz), 5.02 (d, 1, J=17.7 Hz), 5.01 (dd, 1, J=17.7, 1.5 Hz), 4.95 (d, 1, J=9.8 Hz), 2.41 (dd, 1, J=3.4, 15.0 Hz), 2.33 (dd, 1, J=3.4, 15.0 Hz), 2.03–1.97 (m, 2), 1.53–1.48 (m, 2), 1.16 (s, 3).

3.2.11. 5-(3-Ethenyl-3-methyl-6-heptenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (47). Reaction of EDDA (118 mg, 0.65 mmol), Meldrum's acid (750 mg, 5.2 mmol) and crude aldehyde **47a** (660 mg, 4.3 mmol) in absolute EtOH (10 mL) followed by reduction with $BH_3{\cdot}NH(CH_3)_2$ (269 mg, 4.6 mmol) and workup and chromatography as described earlier gave 585 mg (49%) of pure **47** as an oil: ^{1}H NMR 5.80 (ddt, 1, J=10.4, 17.1, 6.7 Hz), 5.70 (dd, 1, J=17.7, 11.0 Hz), 5.05 (dd, 1, J=11.0, 1.2 Hz), 5.00 (dd, 1, J=17.7, 1.2 Hz), 4.96 (dd, 1, J=17.1, 1.2 Hz), 4.91 (dd, 1, J=10.4, 1.2 Hz), 3.52 (d, 1, J=4.9 Hz), 2.07–1.95 (m, 4), 1.78 (s, 3), 1.76 (s, 3), 1.46–1.37 (m, 4), 1.01 (s, 3); ^{13}C NMR 165.4 (2C), 146.0, 139.2, 114.0, 112.6, 104.7, 46.2, 39.9, 39.3, 36.6, 28.4, 28.3, 26.8, 22.1, 21.5.

3.2.12. 5-(5-Hexenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (50). Reaction of EDDA (86 mg, 0.48 mmol), Meldrum's acid (455 mg, 3.2 mmol) and 5-hexenal (310 mg, 3.2 mmol), prepared by Collins' oxidation of 5-hexen-1-ol, in absolute EtOH (4 mL) followed by reduction with $BH_3{\cdot}NH(CH_3)_2$ (196 mg, 3.3 mmol) and workup and chromatography as described earlier gave 407 mg (57%) of pure **55** as a white solid: mp 44°C; ^{1}H NMR 5.80 (ddt, 1, J=10.4, 17.1, 6.7 Hz), 5.00 (dd, 1, J=17.1, 1.2 Hz), 4.95 (dd, 1, J=10.4, 1.2 Hz), 3.50 (t, 1, J=5.0 Hz), 2.14–2.07 (m, 4), 1.79 (s, 3), 1.76 (s, 3), 1.53–1.39 (m, 4); ^{13}C NMR 165.5 (2C), 138.4, 114.6, 104.8, 46.1, 33.3, 28.7, 28.4, 26.9, 26.5, 26.0. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.64; H, 8.13.

3.2.13. 2,2-Dimethyl-5-(*cis*-5-octenyl)-1,3-dioxane-4,6-dione (53). Reaction of EDDA (25 mg, 0.14 mmol), Meldrum's acid (100 mg, 0.69 mmol), and *cis*-5-octenal (115 μL, 0.69 mmol) in absolute EtOH (1.6 mL), followed by reduction with $BH_3{\cdot}NH(CH_3)_2$ (41 mg, 0.69 mmol) and workup and chromatography as described above gave 110 mg (60%) of pure **53** as an oil: ^{1}H NMR 5.39–5.27 (m, 2), 3.49 (t, 1, J=5.2 Hz), 2.14–1.97 (m, 6), 1.79 (s, 3), 1.76 (s, 3), 1.49–1.39 (m, 4), 0.95 (t, 3, J=7.6 Hz); ^{13}C NMR 165.6 (2C), 132.0, 128.6, 104.8, 46.1, 29.6, 28.4, 27.0, 26.7, 26.6, 26.2, 20.5, 14.3.

3.3. Oxidative cyclization of alkenyl meldrum's acids

3.3.1. Oxidative cyclization of 10. A solution of $Cu(OAc)_2{\cdot}H_2O$ (23 mg, 0.11 mmol) in EtOH (0.8 mL) was heated to reflux to ensure complete dissolution and cooled to 25°C. $Mn(OAc)_3{\cdot}2H_2O$ (61 mg, 0.22 mmol) was added and N_2 was bubbled through the resulting solution for 15 min. Meldrum's acid **10** (24 mg, 0.11 mmol) in 0.2 mL of EtOH was added by cannula and the addition flask was rinsed with EtOH (0.1 mL) which was also added to the reaction. The reaction was stirred for 10 min and quenched with several drops of 10% aqueous $NaHSO_3$ solution and 3 mL of H_2O. The reaction was extracted with CH_2Cl_2 (3×10 mL), dried ($MgSO_4$) and concentrated to give 21 mg of a crude mixture of **13**, **16**, and **17**. Purification by flash chromatography (9:1 hexanes/EtOAc) gave 0.5 mg of **13**, followed by 3.5 mg of a 1:7 mixture of **13** and **16**, 11 mg of a 2:20:1 mixture of **13, 16**, and **17** and 3 mg of a 3:1 mixture of **16** and **17**. The overall yield of **13** was 8%, of **16** was 63% and of **17** was 5%.

Data for 8,8-dimethyl-1-methylene-7,9-dioxaspiro[4.5]decane-6,10-dione (**13**): ^{1}H NMR 5.20 (s, 1), 5.06 (d, 1, J=1.2 Hz), 2.65 (tt, 2, J=1.2, 7.3 Hz), 2.47 (t, 2, J=6.7 Hz), 2.11 (tt, 2, J=7.3, 6.7 Hz), 1.81 (s, 3), 1.72 (s, 3); ^{13}C NMR (partial) 170.0, 154.5, 110.1, 104.9, 37.5, 34.1, 25.6.

Data for 3,3-dimethyl-2,4-dioxaspiro[5.5]undec-8-ene-1,5-dione (**16**): ^{1}H NMR 5.90–5.83 (m, 1), 5.77–5.71 (m, 1), 2.66–2.63 (m, 2), 2.27–2.22 (m, 2), 2.17 (br t, 2, J=6.1 Hz), 1.77 (s, 3), 1.74 (s, 3); ^{13}C NMR 169.6 (2C), 125.7, 122.3, 104.8, 47.3, 30.7, 30.5, 29.6, 28.4, 21.6. This compound has been previously made by a Diels–Alder reaction between methylene Meldrum's acid and butadiene.[10]

Partial data for 3,3-dimethyl-2,4-dioxaspiro[5.5]undec-7-ene-1,5-dione (**17**) was obtained from the mixture: ^{1}H NMR 6.26 (dt, 1, J=9.8, 3.7 Hz), 5.55 (br d, 1, J=9.8 Hz), 1.97 (tt, 2, J=6.1, 3.3 Hz), 1.77 (s, 3).

3.3.2. Oxidative cyclization of 18*cis*. Oxidative cyclization of **18*cis*** (99 mg, 0.35 mmol) with $Mn(OAc)_3{\cdot}2H_2O$ (188 mg, 0.7 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (71 mg, 0.35 mmol) in EtOH (3.5 mL) for 8 h followed by workup and chromatography as described above gave 33% (33 mg) of **19** followed by 22% (21 mg) of **20**.

Data for 1-(1*E*-hexenyl)-8,8-dimethyl-7,9-dioxaspiro[4.5]-decane-6,10-dione (**19**): ^{1}H NMR 5.56 (dt, 1, J=15.6, 6.7 Hz), 5.28 (dd, 1, J=15.6, 9.2 Hz), 3.28–3.22 (m, 1), 2.38–2.24 (m, 2), 2.05–1.82 (m, 6), 1.66 (s, 6), 1.32–1.19 (m, 4), 0.83 (t, 3, J=6.7 Hz); ^{13}C NMR 172.4, 169.5, 135.5, 126.9, 104.6, 59.0, 58.1, 38.5, 33.3, 32.0, 31.2, 29.7, 28.5, 25.5, 22.0, 13.8.

Data for 3,3-dimethyl-7-pentyl-2,4-dioxaspiro[5.5]undec-8-ene-1,5-dione (**20**): ^{1}H NMR 5.83–5.78 (m, 1), 5.65 (dd, 1, J=10.4, 1.8 Hz), 3.00 (m, 1), 2.31–2.09 (m, 4), 1.73 (s, 3), 1.72 (s, 3), 1.48–1.19 (m, 8), 0.84 (t, 3, J=7.3 Hz); ^{13}C NMR 171.1, 165.7, 126.6, 125.3, 104.8, 52.3, 42.2, 31.6, 31.25, 31.20, 29.6, 28.9, 26.8, 22.4, 22.3, 13.9.

3.3.3. Oxidative cyclization of 21. Oxidative cyclization of **21** (116 mg, 0.5 mmol) with $Mn(OAc)_3{\cdot}2H_2O$ (275 mg, 1.0 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (5 mg, 0.03 mmol) in EtOH (5 mL) for 10 min followed by workup and chromatography as described above gave 1 mg (1%) of the methylenecyclopentane, followed by 89 mg of a 9:1 mixture of **22** and **23**, respectively, giving an overall yield of 1 mg (1%) of the methylenecyclopentane, 80 mg (70%) of **22** and 8.6 mg (8%) of **23**.

Partial data for 4,8,8-trimethyl-1-methylene-7,9-dioxaspiro[4.5]decane-6,10-dione: ^{1}H NMR 5.18 (s, 1), 5.02 (s, 1), 1.13 (d, 3, J=6.7 Hz).

Data for 3,3,11-trimethyl-2,4-dioxaspiro[5.5]undec-8-ene-1,5-dione (**22**): ^{1}H NMR 5.87 (dt, 1, J=7.3, 2.4 Hz), 5.67 (ddt, 1, J=7.3, 4.9, 2.4 Hz), 2.81 (ddt, 1, J=17.7, 5.5, 2.4 Hz), 2.50–2.41 (m, 2), 2.19–2.12 (m, 2), 1.75 (s, 3), 1.74 (s, 3), 0.99 (d, 3, J=6.7 Hz).

Partial data for 3,3,11-trimethyl-2,4-dioxaspiro[5.5]undec-7-ene-1,5-dione (**23**): ^{1}H NMR 6.23 (dt, 1, J=3.7, 9.8 Hz), 5.51 (dt, 1, J=2.3, 9.8 Hz), 2.30–2.24 (m, 2).

3.3.4. Oxidative cyclization of 24. Oxidative cyclization of **24** (87 mg, 0.36 mmol) with $Mn(OAc)_3{\cdot}2H_2O$ (250 mg, 0.94 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (93 mg, 0.47 mmol) in EtOH (4.7 mL) for 2.5 h followed by workup as described above gave 75 mg of crude product. Purification by flash chromatography (15:1 hexanes/EtOAc) gave 43 mg (49%) of **25** as a white solid followed by 20 mg (23%) of **26** as an oil.

Data for 3,3,8,8-tetramethyl-1-methylene-7,9-dioxaspiro-[4.5]decane-6,10-dione (**25**): mp 59.6–60.3°C; ^{1}H NMR 5.16 (s, 1), 5.00 (s, 1), 2.49 (s, 2), 2.31 (s, 2), 1.80 (s, 3), 1.69 (s, 3), 1.20 (s, 6); ^{13}C NMR 169.9 (2C), 153.7, 110.8, 104.7, 59.4, 49.7, 49.4, 38.7, 30.1, 28.5 (2C), 27.6. Anal. Calcd for $C_{13}H_{18}O_4$ C, 65.53; H, 7.61. Found: C, 65.17; H, 7.60.

Data for 1-(ethoxymethyl)-3,3,8,8-tetramethyl-7,9-dioxaspiro[4.5]decane-6,10-dione (**26**): ^{1}H NMR 3.62 (dddd, 1 J=12.8, 11.0, 6.1, 6.1 Hz), 3.53 (dd, 1, J=9.1, 6.1 Hz), 3.40 (dq, 1, J=9.2, 7.3 Hz), 3.38 (dq, 1, J=9.2, 7.3 Hz), 3.36 (dd, 1, J=11.0, 9.1 Hz), 2.11 (d, 1, J=13.4 Hz), 2.07 (d, 1, J=13.4 Hz), 1.94 (dd, 1, J=12.8, 12.8 Hz), 1.73 (s, 3), 1.68 (s, 3), 1.59 (dd, 1, J=12.8, 6.1 Hz), 1.25 (s, 3), 1.17 (s, 3), 1.11 (t, 3, J=7.3 Hz); ^{13}C NMR 172.3, 170.2, 104.3, 69.6, 66.5, 55.8, 52.8, 52.1, 43.8, 40.6, 30.0, 29.93, 29.88, 28.0, 14.9.

3.3.5. Oxidative cyclization of 30. Oxidative cyclization of **30** (74 mg, 0.29 mmol) with $Mn(OAc)_3{\cdot}2H_2O$ (161 mg, 0.6 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (59 mg, 0.3 mmol) in EtOH (3 mL) for 5 min followed by workup as described previously gave 71 mg of crude product. Purification by flash chromatography (14:1 hexanes/EtOAc) gave 4.6 mg (6%) of pure **31** followed by 43 mg of a 3:2 mixture of **31** and **32** (an overall yield of 43% of **31** and 23% of **32**).

Data for 3,3,7-trimethyl-10-methylene-2,4-dioxaspiro[5.5]-undecane-1,5-dione (**31**): mp 85.1–86.1°C; ^{1}H NMR 4.87 (d, 1, J=1.8 Hz), 4.71 (d, 1, J=1.2 Hz), 2.79 (dd, 1, J=14.0, 1.8 Hz), 2.54 (dd, 1, J=14.0, 1.2 Hz), 2.48–2.39 (m, 2), 2.21–2.15 (m, 1), 1.93 (dddd, 1, J=13.4, 12.8, 12.8, 4.3 Hz), 1.74 (s, 3), 1.73 (s, 3), 1.72–1.63 (m, 1), 0.95 (d, 3, J=6.7 Hz); ^{13}C NMR 171.1, 166.0, 141.7, 111.5, 104.7, 55.8, 41.5, 39.3, 33.1, 30.3, 30.0, 28.7, 17.7. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.03; H, 7.54.

Partial data for 3,3,8,11-tetramethyl-2,4-dioxaspiro[5.5]-undec-8-ene-1,5-dione (**32**) were determined from the mixture: ^{1}H NMR 5.54 (br s, 1), 2.80-2.71 (m, 1), 2.45–2.34 (m, 1), 2.26–2.15 (m, 2), 0.98 (d, 3, J=6.7 Hz).

3.3.6. Oxidative cyclization of 33. Oxidative cyclization of **33** (102 mg, 0.40 mmol) with $Mn(OAc)_3{\cdot}2H_2O$ (214 mg, 0.8 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (160 mg, 0.8 mmol) in EtOH (4 mL) for 13 h followed by workup as described above and purification by chromatography (12:1 hexanes/EtOAc) gave 4 mg of pure ***34cis***, followed by 25 mg of a 83:17 mixture of ***34cis*** and ***35cis***, 21 mg of a 2:4:1:1 mixture of ***34cis***, ***34trans***, ***35cis*** and ***35trans***, 10 mg of a 1:9 mixture of ***35trans*** and ***34trans***, and 2 mg of pure ***34trans***, (an overall yield of 29% of ***34cis***, 21% of ***34trans***, 7% of ***35cis***, and 3% of ***35trans***.

Data for *cis*-4,8,8-trimethyl-1-(1-methylethenyl)-7,9-dioxaspiro[4.5]decane-6,10-dione (***34cis***): ^{1}H NMR; 4.98 (s, 1), 4.94 (s, 1), 3.48 (dd, 1, J=11.6, 8.5 Hz), 2.91 (ddq, 1, J=11.0, 9.2, 6.7 Hz), 2.33 (dddd, 1, J=12.9, 12.2, 11.6, 4.8 Hz), 2.08 (dddd, 1, J=14.9, 9.2, 7.9, 4.8 Hz), 1.96 (dddd, 1, J=12.9, 8.5, 7.9, 4.3 Hz), 1.81 (dddd, 1, J=14.9, 12.2, 11.0, 4.3 Hz), 1.73 (s, 3), 1.70 (s, 3), 1.67 (s, 3), 1.04 (d, 3, J=6.7 Hz); ^{13}C NMR 171.2, 141.9, 115.5, 105.1, 63.9, 58.4, 48.8, 31.2, 29.9, 29.6, 28.3, 22.0, 15.3, (one carbonyl carbon not observed).

A 1D NOESY experiment with irradiation of H_1 at δ 3.48 showed NOEs to H_4 at δ 2.91 establishing the *cis* stereochemistry, the two H_2 protons at δ 2.33 and 1.96, a vinyl proton at δ 4.94 and the methyl group at δ 1.70. A 1D NOESY experiment with irradiation of H_4 at δ 2.91 showed NOEs to H_1 at δ 3.48 and the two H_3 protons at δ 2.08 and 1.81.

Data for *trans*-4,8,8-trimethyl-1-(1-methylethenyl)-7,9-dioxaspiro[4.5]decane-6,10-dione (***34trans***): ^{1}H NMR 4.93 (d, 1, J=1.2 Hz), 4.83 (s, 1), 3.52 (dd, 1, J=12.2, 6.1 Hz), 2.83 (ddq, 1, J=9.8, 6.4, 7.3 Hz), 2.32–2.13 (m, 2), 1.92 (br ddd, 1, J=12.2, 6.4, 6.1 Hz), 1.74 (s, 3), 1.72 (s, 3), 1.71 (s, 3), 1.67–1.54 (m, 1), 1.13 (d, 3, J=7.3 Hz).

A 1D NOESY experiment with irradiation of H_1 at δ 3.52 showed an NOE to Me_4 at δ 1.13, but no NOE to H_4 at δ 2.83 indicating that this is the trans isomer, and to the two H_2 protons at δ 1.92 and 2.32–2.13, a vinyl proton at δ 4.83 and the methyl group at δ 1.72.

A similar cyclization of **33** (80.5 mg, 0.32 mmol) with $Mn(OAc)_3{\cdot}2H_2O$ (170 mg, 0.64 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (3 mg, 0.02 mmol) in EtOH (3.2 mL) for 9 h followed by workup as described above gave 44.3 mg of crude cyclized products containing mainly **35*cis*** and **35*trans***. The crude mixture was hydrogenated over 10% Pd on carbon (44.5 mg, 0.18 mmol) in EtOH (1.5 mL) to remove any **34**. The reaction was filtered through Celite, concentrated and purified by chromatography (15:1 hexanes/EtOAc) giving 5 mg of pure **35*cis***, followed by 29 mg of a 3:2 mixture of **35*cis*** and **35*trans***, and finally <1 mg of pure **35*trans***, (an overall yield of 28% of **35*cis*** and 14% of **35*trans***).

Data for *cis*-4,8,8-trimethyl-1-(1-methylethyl)-7,9-dioxaspiro[4.5]decane-6,10-dione (**35*cis***): mp 74.7–75.4°C; ^{1}H NMR 2.84 (ddq, 1, *J*=11.6, 8.3, 6.7 Hz), 2.67 (ddd, 1, *J*=9.8, 9.8, 9.8 Hz), 2.12–1.97 (m, 2), 1.90–1.62 (m, 3), 1.76 (s, 3), 1.75 (s, 3), 1.07 (d, 3, *J*=7.3 Hz), 0.90 (d, 3, *J*=6.7 Hz), 0.89 (d, 3, *J*=6.7 Hz); ^{13}C NMR 171.3, 165.8, 105.6, 61.7, 61.1, 48.6, 31.7, 30.6, 30.4, 29.3, 29.1, 22.1, 21.7, 16.2.

A 1D NOESY experiment with irradiation of H_1 at δ 2.67 shows NOEs to H_4 at δ 2.84 establishing the *cis* stereochemistry, one of the protons at δ 2.12–1.97, protons at δ 1.86, δ 1.83-1.62, and the methyl groups at δ 0.90 and δ 0.89.

Data for *trans*-4,8,8-trimethyl-1-(1-methylethyl)-7,9-dioxaspiro[4.5]decane-6,10-dione (**35*trans***): ^{1}H NMR 2.73–2.65 (m, 2), 2.17 (dddd, 1, *J*=12.6, 7.6, 7.6, 2.2 Hz), 2.04 (dddd, 1, *J*=12.3, 7.2, 7.2, 2.1 Hz), 1.88–1.75 (m, 2), 1.74 (s, 6), 1.60–1.51 (m, 1), 1.11 (d, 3, *J*=6.7 Hz), 0.93 (d, 3, *J*=6.7 Hz), 0.84 (d, 3, *J*=6.7 Hz).

3.3.7. Oxidative cyclization of 36. Oxidative cyclization of **36** (126 mg, 0.53 mmol in 20 mL of EtOH) by slow addition by syringe pump to $Mn(OAc)_3{\cdot}2H_2O$ (285 mg, 1.1 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (106 mg, 0.53 mmol) in EtOH (5.3 mL) over 12 h and stirring of the resulting solution for 9 h followed by workup as described above and purification by chromatography (16:1 hexanes/EtOAc) gave 6.9 mg of pure **37**, followed by a 35:65 mixture of **37** and **38** (50.4 mg), and 19.8 mg of pure **38** (an overall yield of 20% of **37** and 42% of **38**).

Data for 2′,2′-dimethylspiro[bicyclo[2.2.2]oct-5-ene-2,5′-[1,3]dioxane]-4′,6′-dione (**37**): mp 78.5–79.0°C (lit.[10] 78.7–79.1°C); ^{1}H NMR 6.48 (t, 1, *J*=7.3 Hz), 6.12 (t, 1, *J*=7.3 Hz), 3.02–2.98 (m, 1), 2.83–2.78 (m, 1), 2.22 (dd, 1, *J*=12.8, 2.4 Hz), 2.01 (dt, 1, *J*=12.8, 2.9 Hz), 1.85–1.74 (m, 2), 1.82 (s, 3), 1.68 (s, 3), 1.33–1.17 (m, 2); ^{13}C NMR 168.90, 168.88, 136.3, 128.8, 105.1, 54.4, 39.7, 32.5, 30.4, 29.2, 28.0, 22.3, 22.0. The ^{1}H NMR spectrum is identical to that previously reported.[10]

Data for 2′,2′-dimethylspiro[bicyclo[3.2.1]oct-2-ene-7,5′-[1,3]dioxane]-4′,6′-dione (**38**): ^{1}H NMR 5.81–5.77 (m, 1), 5.64 (t, 1, *J*=7.3 Hz), 2.95 (t, 1, *J*=5.5 Hz), 2.68 (dd, 1, *J*=12.8, 7.3 Hz), 2.58–2.42 (m, 2), 2.36 (dd, 1, *J*=13.8, 1.5 Hz), 2.28–2.23 (m, 1), 2.16 (br d, 1, *J*=18.3 Hz), 1.88–1.67 (m, 1), 1.84 (s, 3), 1.72 (s, 3); ^{13}C NMR 168.8, 167.1, 130.6, 125.9, 104.7, 63.8, 47.9, 39.3, 36.1, 34.3, 33.6, 29.9, 28.2; HRMS (DCI/NH_3) calcd for $C_{13}H_{16}O_4{\cdot}NH_4$ (MNH_4^+) 254.1404, found 254.1392.

3.3.8. Dimerization of 2,2,5-trimethyl-1,3-dioxane-4,6-dione (39). $Mn(OAc)_3{\cdot}2H_2O$ (340 mg, 1.27 mmol) was added to a solution of $Cu(OAc)_2{\cdot}H_2O$ (127 mg, 0.64 mmol) in EtOH (4.3 mL). Methyl Meldrum's acid (**39**) (200 mg, 1.27 mmol) in EtOH (2 mL) was added by cannula. The reaction was stirred for 10 h followed by workup as previously described to give 157 mg of crude material. Purification by flash chromatography (15:1–5:1 hexane/EtOAc) gave 73 mg (38%) of **41**, followed by 42 mg (21%) of **40**, and 29 mg (10%) of **42**.

Data for 5-(3-ethoxy-2-methyl-1,3-dioxopropoxy)-2,2,5-trimethyl-1,3-dioxan-2,4-dione (**41**): ^{1}H NMR 4.25 (dq, 1, *J*=11.0, 7.0 Hz), 4.23 (dq, 1, *J*=11.0, 7.0 Hz), 3.59 (q, 1, *J*=7.3 Hz), 1.92 (s, 3), 1.87 (s, 3), 1.82 (s, 3), 1.48 (d, 3, *J*=6.7 Hz), 1.31 (t, 3, *J*=7.0 Hz); ^{13}C NMR 169.5, 168.5, 164.6, 164.3, 107.9, 73.0, 61.9, 45.1, 28.7, 28.5, 23.5, 13.9, 13.2; IR 1758, 1736, 1647, 1265; HRMS (DCI/NH_3) calcd for $C_{13}H_{18}O_8{\cdot}NH_4$ (MNH_4^+) 320.1346, found 320.1345.

Data for 2,2,2′,2′,5,5′-hexamethyl-[5,5′-di-1,3-dioxane]-4,4′,6,6′-tetrone (**40**): mp 196–197°C (lit.[15a] mp 197–198°C); ^{1}H NMR 2.08 (s, 6), 1.82 (s, 6), 1.79 (s, 6); ^{13}C NMR 167.8 (4 C), 107.2 (2C), 53.1 (2C), 29.2 (2C), 28.7 (2C), 22.2 (2C). Dimerization of **39** with $PhI(OAc)_2$ gave 45% of **41** with an identical ^{1}H NMR spectrum.[15a]

Data for **42**: ^{1}H NMR 4.25–4.15 (m, 2), 3.94 (dd, 1, *J*=4.6, 3.7 Hz), 2.94 (dd, 1, *J*=14.7, 3.7 Hz), 2.77 (dd, 1, *J*=14.7, 4.6 Hz), 1.91 (s, 3), 1.90 (s, 3), 1.85 (s, 3), 1.82 (s, 3), 1.76 (s, 3), 1.59 (s, 3), 1.29 (t, 3, *J*=7.0 Hz); ^{13}C NMR 171.1, 169.9, 165.1, 164.9, 164.5 (2C), 108.2, 105.2, 73.2, 62.4, 52.9, 44.8, 29.9, 28.9, 28.7, 28.6, 25.5, 23.3, 21.3, 13.7; IR 1756, 1637, 1265; HRMS (DCI/NH_3) calcd for $C_{20}H_{26}O_{12}{\cdot}NH_4$ (MNH_4^+) 476.1792, found 476.1768.

3.3.9. Oxidative cyclization of 43. Oxidative cyclization of **43** (113 mg, 0.45 mmol) with $Mn(OAc)_3{\cdot}2H_2O$ (241 mg, 0.90 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (180 mg, 0.90 mmol) in EtOH (4.5 mL) for 2.5 h followed by workup as described above gave 111 mg of crude cyclized product. Purification by flash chromatography (15:1 hexanes/EtOAc) gave 6 mg (5%) of pure **44** followed by 80 mg (71%) of **45**.

Data for 8,8-dimethyl-1-methylene-3-(2-propenyl)-7,9-dioxaspiro[4.5]decane-6,10-dione (**44**): ^{1}H NMR 5.81 (ddt, 1, *J*=17.7, 9.8, 6.7 Hz), 5.17 (s, 1), 5.05 (dd, 1, *J*=17.7, 1.9 Hz), 5.03 (s, 1), 5.02 (br d, 1, *J*=9.8 Hz), 2.72 (dd, 1, *J*=15.2, 7.3 Hz), 2.62 (ttt, 1, *J*=7.3, 7.3, 6.7 Hz), 2.45 (dd, 1, *J*=12.8, 7.3 Hz), 2.33 (ddt, 1, *J*=15.2, 11.0, 3.1 Hz), 2.27–2.16 (m, 3), 1.81 (s, 3), 1.70 (s, 3); ^{13}C NMR 170.3, 169.7, 153.6, 136.5, 116.2, 110.3, 104.9, 58.2, 42.4, 40.3, 38.9, 38.7, 30.2, 27.8.

Data for 3,3-dimethyl-8-(2-propenyl)-2,4-dioxaspiro[5.5]-undec-8-ene-1,5-dione (**45**): 5.80–5.70 (m, 3), 5.10–5.02 (m, 2), 2.84 (br d, 1, *J*=17.5 Hz), 2.50–2.36 (m, 2), 2.22–2.05 (m, 3), 1.84 (dd, 1, *J*=13.4, 11.6 Hz), 1.77 (s, 3), 1.73 (s, 3).

3.3.10. Oxidative cyclization of 47. Oxidative cyclization of **47** (75 mg, 0.27 mmol) with $Mn(OAc)_3 \cdot 2H_2O$ (145 mg, 0.54 mmol) and $Cu(OAc)_2 \cdot H_2O$ (5 mg, 0.03 mmol) in EtOH (2.7 mL) for 4 h followed by workup as described previously gave 63 mg of crude product. Purification by flash chromatography (13:1 hexanes/EtOAc) gave 50 mg (67%) of pure *cis*-octahydro-2,2,7a′-trimethyl-3′-methylene-spiro[1,3-dioxane-5,5′-[5*H*]indene]-4,6-dione (**49**): mp 105.0–105.7°C; ^{1}H NMR 4.87 (br s, 1), 4.85 (br s, 1), 2.50–2.41 (m, 3), 2.20 (ddd, 1, J=14.0, 12.8, 4.9 Hz), 1.99–1.81 (m, 4), 1.97 (ddd, 1, J=11.9, 11.6, 9.5 Hz), 1.73 (s, 6), 1.66 (ddd, 1, J=14.0, 4.9, 4.3 Hz), 1.32 (ddd, 1, J=11.9, 7.9, 3.1 Hz), 0.99 (s, 3); ^{13}C NMR 171.6, 168.4, 155.5, 107.2, 104.6, 48.6, 47.3, 39.3, 35.6, 33.3, 30.2, 29.2, 29.0, 28.9, 28.5, 28.0. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.28; H, 7.97.

A 1D NOESY experiment with irradiation of the $=CH_2$ group at δ 4.85–4.90 showed NOEs to H_3 and H_{3a} at δ 2.5–2.4, H_4 at δ 2.0–1.8 and the methyl group at δ 0.99. A 1D NOESY experiment with irradiation of the methyl group at δ 0.99 showed NOEs to H_{3a} at δ 2.5–2.4, and hydrogens at δ 2.0–1.8, 1.66 and 1.32. The intense NOE between the methyl group and H_{3a} establishes that the ring fusion is *cis*.

3.3.11. Oxidative cyclization of 50. Oxidative cyclization of **50** (94 mg, 0.42 mmol) with $Mn(OAc)_3 \cdot 2H_2O$ (223 mg, 0.84 mmol) and $Cu(OAc)_2 \cdot H_2O$ (168 mg, 0.84 mmol) in EtOH (4.2 mL) for 4 h followed by workup as described previously gave 78 mg of crude product containing some dimer. Purification by flash chromatography (16:1 hexanes/EtOAc) gave 22 mg of pure **51**, followed by 5 mg of a 83:16 mixture of **51** and **52**, and 17 mg of 80–90% pure **52** (an overall yield of 37% of **51** and 19% of **52**).

Data for 3,3-dimethyl-7-methylene-2,4-dioxaspiro[5.5]undecane-1,5-dione (**51**): ^{1}H NMR 5.16 (s, 1), 4.85 (s, 1), 2.46 (t, 2, J=5.8 Hz), 2.23 (t, 2, J=6.5 Hz), 2.00 (tt, 2, J=6.5, 6.2 Hz), 1.78 (s, 3), 1.75–1.68 (m, 2), 1.73 (s, 3), ^{13}C NMR 167.8 (2C), 144.1, 114.3, 105.1, 56.4, 35.3, 32.3, 29.2, 28.1, 26.8, 21.2.

Data for 3,3-dimethyl-2,4-dioxaspiro[5.6]dodec-8-ene (**52**): ^{1}H NMR 5.87 (dt, 1, J=11.0, 5.5 Hz), 5.64–5.58 (m, 1), 2.76 (d, 2, J=8.0 Hz), 2.35 (dt, 2, J=5.5, 6.1 Hz), 2.25 (m, 2), 1.94–1.87 (m, 2), 1.74 (s, 3), 1.73 (s, 3); ^{13}C NMR 170.6 (2C), 132.8, 123.6, 104.7, 51.2, 35.7, 33.1, 29.1, 28.9, 28.7, 19.8.

3.3.12. Oxidative cyclization of 53. Oxidative cyclization of **53** (36 mg, 0.14 mmol) with $Mn(OAc)_3 \cdot 2H_2O$ (76 mg, 0.28 mmol) and $Cu(OAc)_2 \cdot H_2O$ (1.2 mL of 0.12 M solution in EtOH, 0.14 mmol) for 8 h followed by workup as described previously gave 25 mg of crude product. Purification by flash chromatography (9:1 hexanes/EtOAc) gave 12 mg (33%) of 90% pure 3,3-dimethyl-1*E*-propenyl-2,4-dioxaspiro[5.5]undecane-1,5-dione (**54**): ^{1}H NMR 5.57 (dq, 1, J=15.0, 6.7 Hz), 5.23 (ddd, 1, J=15.0, 9.2, 1.5 Hz), 2.81 (ddd, 1, J=12.1, 9.2, 4.3 Hz), 2.09–1.61 (m, 7), 1.70 (s, 3), 1.66 (s, 3), 1.62 (d, 3, J=6.1 Hz), 1.39 (ddddd, 1, J=12.1, 12.1, 12.1, 3.8, 3.8 Hz); ^{13}C NMR 171.7, 167.3, 130.4, 129.2, 104.7, 54.0, 46.7, 34.1, 29.5, 29.1, 27.2, 24.4, 20.2, 17.8.

Acknowledgements

We are grateful to the NIH for generous financial support (GM-50151).

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