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Formal Synthesis of (±)-Upial. Oxidative Free-Radical Cyclization of Unsaturated 1,3-Cyclohexanediones

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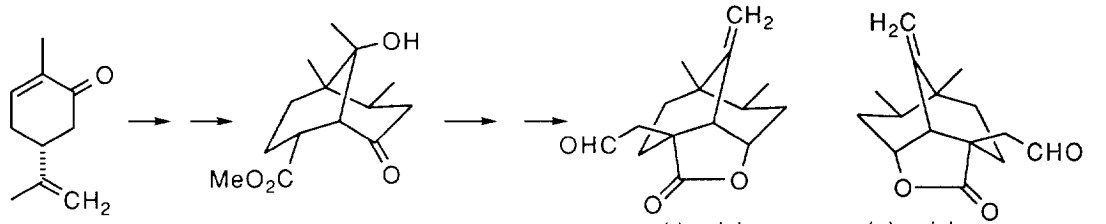
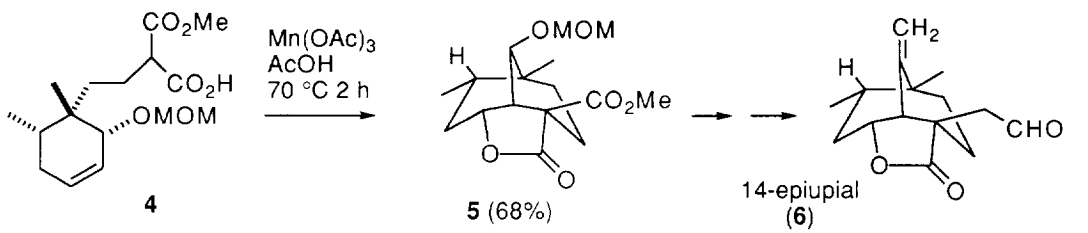
Abstract: Oxidative free-radical cyclization of 4-(3-hexenyl)-1,3-cyclohexanedione **8** affords 85% of a mixture of **7** and **29**. Short sequences were developed to convert this mixture to **2**, a late intermediate in Taschner's synthesis of upial.

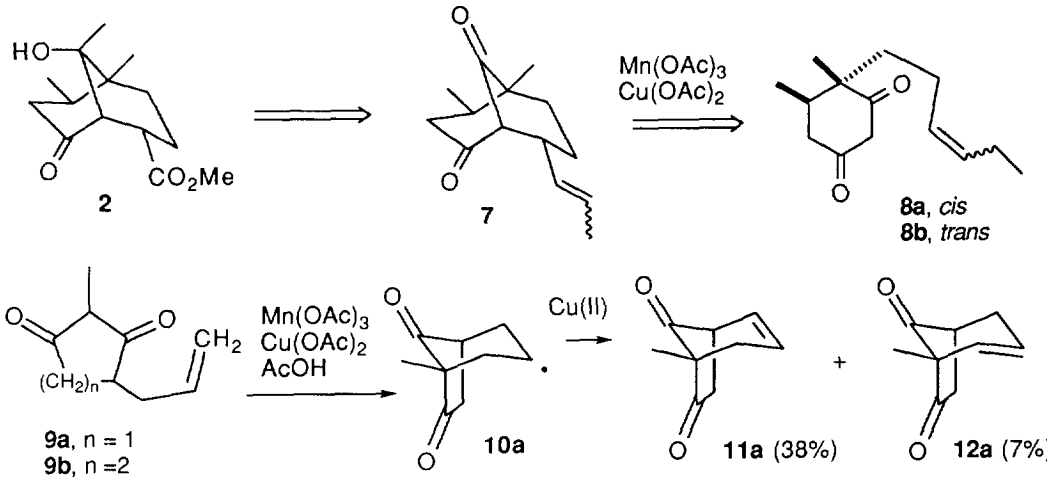
(+)-Upial (**3**) is an unusual bicyclo[3.3.1]nonane sesquiterpene isolated in 1979 by Scheuer and co-workers from the sponge *Dysidea fragilis* found in Kaneohe Bay, Oahu.[1] The absolute configuration was established by Taschner and Shahripour who synthesized (-)-upial (**3**) in 1985 from (-)-carvone (**1**) by a sequence proceeding through bicyclic hydroxy keto ester **2**.[2] Paquette reported a 23 step synthesis of 14-epiupial (**6**) using the Mn(III)-based oxidative cyclization of half malonate ester **4** to give 68% of tricyclic lactone **5** as the key step.[3] Unfortunately, none of the stereoisomers of **4** undergo this oxidative cyclization so that this approach cannot be used for the synthesis of upial itself. Nagaoka, Shibuya, and Yamada recently synthesized (+)-upial (**3**).[4]



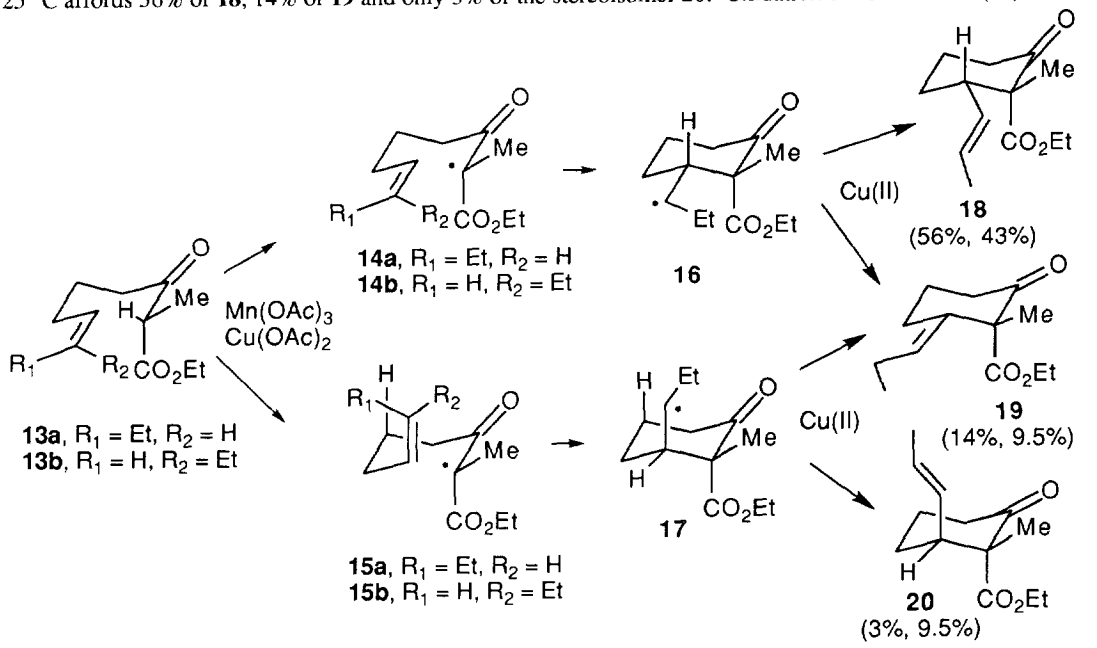


We thought that Taschner's intermediate **2** should be readily available from 4,5-dimethyl-8-(1-propenyl)bicyclo[3.3.1]nonane-2,9-dione (**7**), which should be easily formed by Mn(III)-based oxidative cyclization of 4-(3-hexenyl)-4,5-dimethyl-1,3-cyclohexanedione (**8**). We have successfully carried out oxidative cyclizations of 1,3-diketones such as the 6-*endo*-cyclization of cyclopentane-1,3-dione **9a** to give radical **10a**, which is

oxidized by Cu(II) to a mixture of **11a** (38%) and **12a** (7%).[5] However, oxidative cyclization of **9b** fails, indicating that the parameters controlling the oxidative cyclizations of 1,3-diketones are not fully understood. The need for additional experiments to determine the scope and limitations of oxidative cyclizations of 1,3-diones provided further impetus for our undertaking the synthesis of upial intermediate **2**.



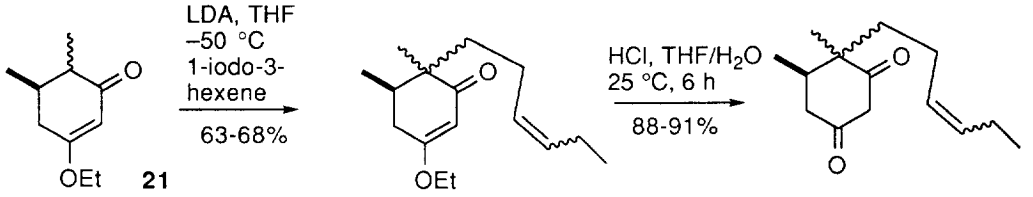
There was good precedent to suggest that **7**, with an equatorial propenyl group, would be formed selectively from **8a** with a cis double bond. Oxidative cyclization of **13a** with $Mn(OAc)_3$ and $Cu(OAc)_2$ in AcOH at 25 °C affords 56% of **18**, 14% of **19** and only 3% of the stereoisomer **20**. Oxidation of **13a** with Mn(III)



affords the radical, which undergoes a 6-*exo*-cyclization through chair transition state **14a** to give **16** selectively.[5] Cu(II) oxidation of **16** affords the less substituted alkene **18** selectively as the *trans*-isomer. Only 3% of **20** is formed by cyclization through chair transition state **15a** to give **17**, since this transition state is destabilized by steric hindrance between the axial ring hydrogen shown and R_1 (ethyl group). 6-*exo*-Cyclization of the radical formed from *trans*-alkene **13b** is much less selective, affording 43% of **18**, 9.5% of **19** and 9.5% of **20**.[5] Steric hindrance between the axial hydrogen and R_1 (hydrogen) in chair transition state **15b** is less severe with the trans double bond.

Results and Discussion

Oxidative Cyclization of 8 and 30. Alkylation of the lithium enolate of **21**[6] with 1-iodo-3*Z*-hexene[7] affords 63% of a 6:1 mixture of **22a** and **23a** analogous to that reported by Majetich for a related alkylation.[6] Hydrolysis of the mixture with HCl in aqueous THF yields 88% of a separable mixture of **8a** and **24a**.

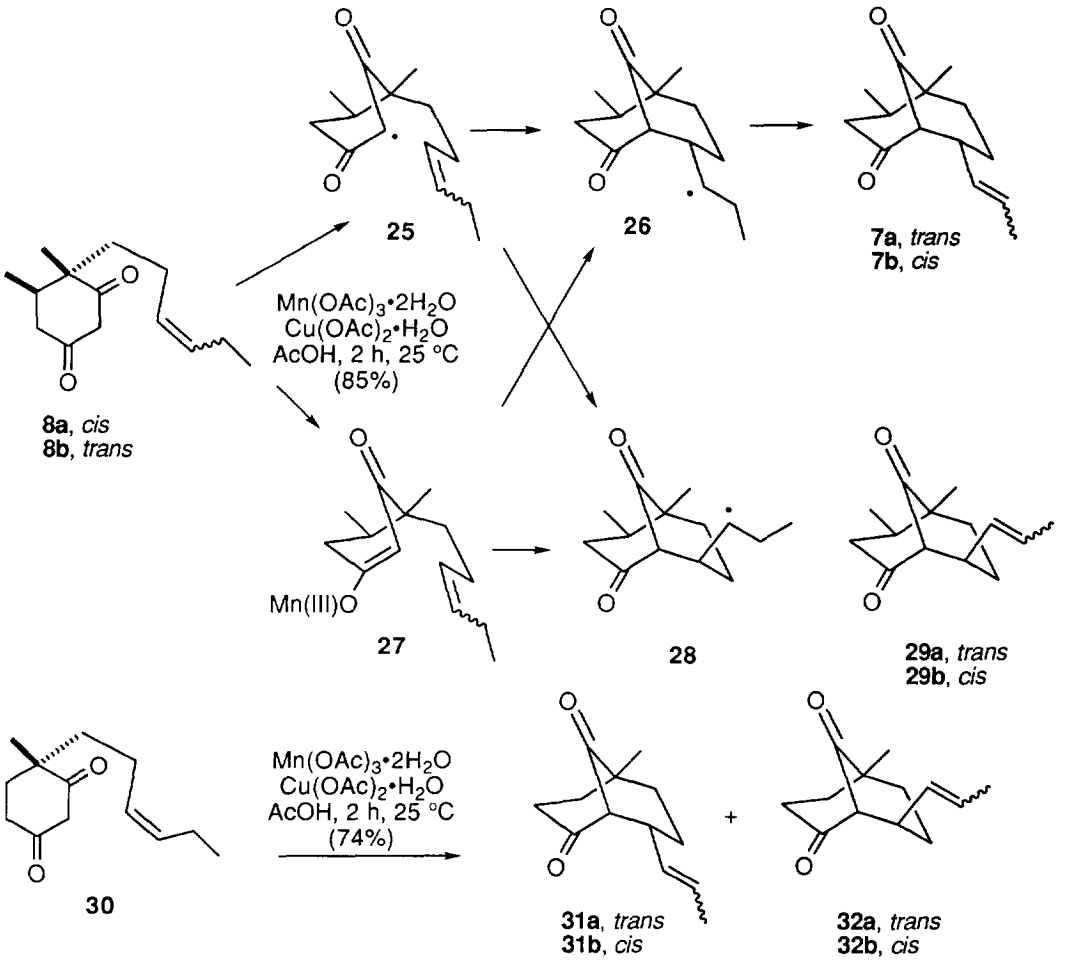


22a, β-Me, *cis*
23a, α-Me, *cis*
22b, β-Me, *trans*
23b, α-Me, *trans*

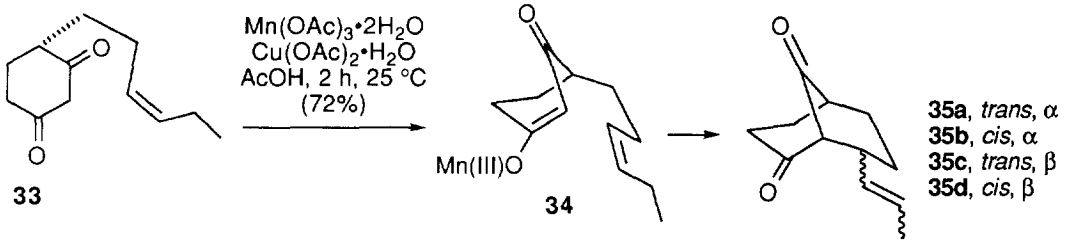
8a, β-Me, *cis*
24a, α-Me, *cis*
8b, β-Me, *trans*
24b, α-Me, *trans*

We were delighted to find that oxidative cyclization of **8a** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ in acetic acid proceeds rapidly (2 h, 25 °C) and much more efficiently (85% of a 39:11:36:14 mixture of bicyclic products **7a**, **7b**, **29a** and **29b**) than in earlier studies with **9a** and **9b**. However, the reaction did not show either the expected selectivity for the formation of **7** with an equatorial propenyl group, or for the formation of the trans double bond as observed in the cyclization of **13a**. The product mixture obtained from **8b** was nearly identical, indicating that the geometry of the double bond has little effect on the stereochemistry of the cyclization of **8**, in marked contrast to the cyclization of β-keto ester **13**.[5] The secondary methyl group of **8** has a modest effect on the selectivity of the cyclization. Oxidative cyclization of **30** affords 74% of a 64:7:20:9 mixture of **31a**, **31b**, **32a** and **32b**, respectively, showing somewhat better selectively for **31a** with an equatorial, *trans*-propenyl side chain. The stereochemistry of the products was assigned based on the larger coupling constants for the trans double bond and the very broad peak ($W_{1/2}$ = 24 Hz) for the axial methine hydrogen in the major isomer **7a**.

We were puzzled as to why the oxidative cyclizations of **8a** (85%) and **30** (74%) proceed so much more efficiently than those of **9a** (45%) and **9b** (0%), and why the cyclizations of **8a** and **30** did not show the expected stereochemical control seen in the cyclization of **13a**. There are three differences between **30**, which cyclizes efficiently, and **9b**, which doesn't cyclize at all. First, the length of the tether and position of the double bond is different. Second, the 4-methyl group of **30** makes the conformation needed for cyclization with an axial alkenyl side chain energetically more accessible than in **9b**. We established that the 4-methyl group of **8**



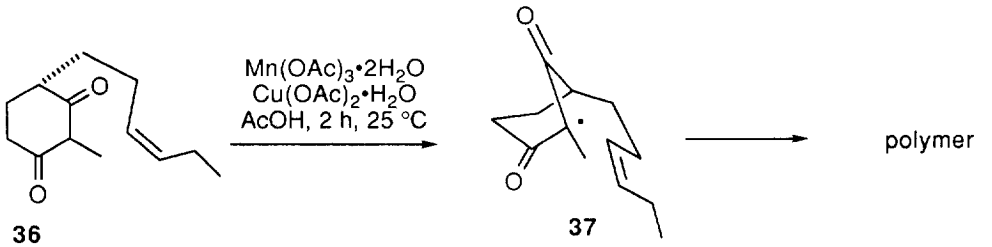
and **30** is not necessary for successful cyclization by oxidative cyclization of **33** to afford 72% of a 60:11:22:7 mixture of **35a-d**. Finally, and most importantly, there is a methyl group at C-2 in **9**, but not in **8a**, **30**, or **33**.



We have shown that oxidative cyclizations of α-alkyl β-keto esters such as **13** proceed through free-radicals while oxidative cyclizations of α-unsubstituted β-keto esters proceed by addition of the alkene to a manganese enolate.[10] This suggests that oxidative cyclization of **8** should proceed by direct cyclization of

manganese enolate **27** to give bicyclic radicals **26** and **28**. However, 1,3-cyclohexanediones are much more acidic than β-keto esters, and the oxidation potential of the enolates will be different. Therefore, we cannot exclude the possibility that **8** is oxidized to radical **25** which cyclizes to give **26** and **28**. We speculated that the improved yield of products from **8**, **30**, and **33** as compared to **9**, and the decreased stereoselectivity as compared to **13a**, results from **8**, **30**, and **33** cyclizing via a Mn(III) enolate, while **13** cyclizes through free-radicals **14** and **15**, and **9b** is oxidized to a free-radical that polymerizes.

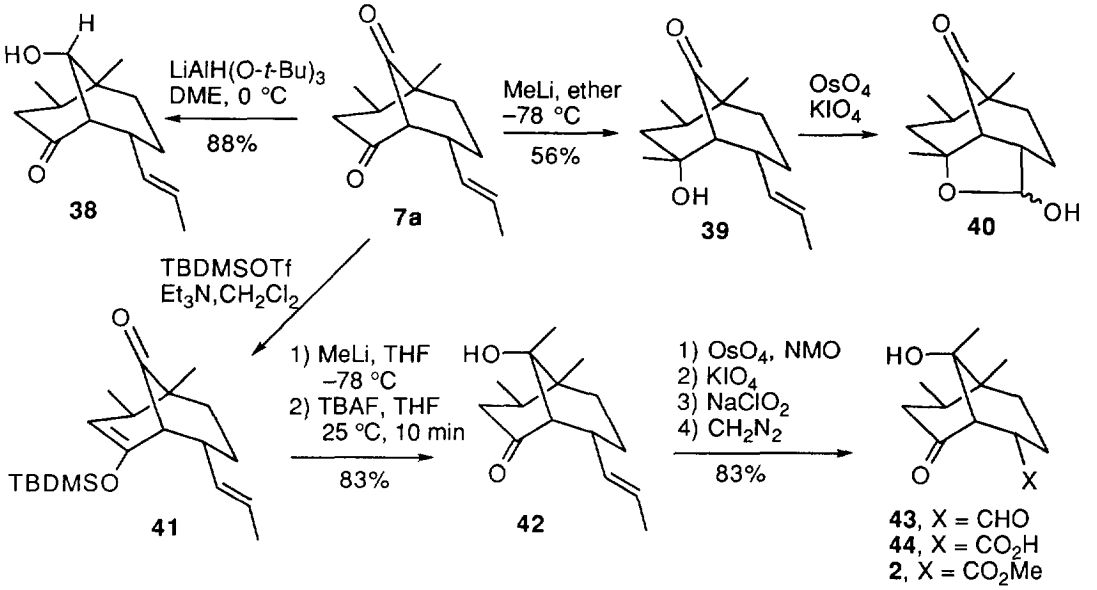
We tested this hypothesis by the attempted oxidative cyclization of **36**, which reacts rapidly with $Mn(OAc)_3$ and $Cu(OAc)_2$ in acetic acid to give a complex polymeric mixture. The remarkable difference in the reactivity of **33** and **36** suggests that the presence of the α-methyl group changes the rate determining step of the oxidative cyclization as we have previously shown for β-keto esters.[10] Dione **33** cyclizes through Mn(III) enolate **34**, while dione **36** is oxidized to radical **37**, which polymerizes. This change in mechanism may also be responsible for the differing stereoselectivity. Oxidative cyclization of 1,3-cyclohexanediones **8a**, **30**, and **33** proceeds through a Mn(III) enolate with little control of side chain stereochemistry, while **13a** cyclizes stereospecifically through free-radical **14a**.



36 **37**

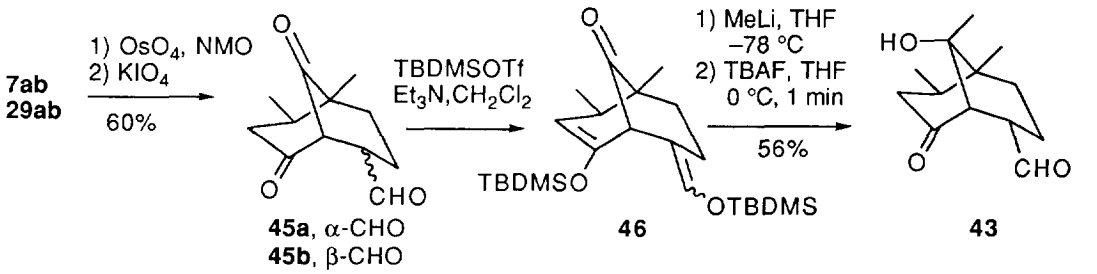
Synthesis of Upial Intermediate 2. While all four cyclization products **7a**, **7b**, **29a** and **29b** should be suitable for elaboration to **2**, it was not practical to develop the synthetic sequence with a mixture of four compounds. Fortunately, **7a** is easily isolated in pure form (29%) by fractional crystallization from hexane. Different approaches to upial were possible depending on the relative reactivity of the two carbonyl groups. Reduction with $LiAlH(O\text{-}t\text{-}Bu)_3$ gives exclusively hydroxy ketone **38** resulting from addition of hydride to the less hindered face of the C-9 carbonyl. The structure of the product was established by the absorption of the C*H*OH proton as a broad singlet and the upfield shift of quaternary C-5 from δ 48.8 in **7a** to δ 36.4 in **38**. However, MeLi reacts selectively at C-2, although competing enolization is a significant side reaction. The crude product was added twice more to MeLi giving 56% of **39**. The structure of the product was established by the absorption of the quaternary C-5 at δ 48.3, indicating that this carbon is still adjacent to a carbonyl group and by the smaller geminal coupling constant for the C-3 methylene group (-14.5 Hz) in **39** than in **7a** (-17.8 Hz) and **38** (-18.0 Hz), in which these hydrogens are adjacent to a carbonyl group rather than a tertiary alcohol. The structure and stereochemistry of **39** was confirmed by oxidative cleavage of the alkene with osmium tetroxide and potassium periodate to give lactol **40**.

The facile enolization of the C-2 carbonyl group suggested an efficient route to the desired C-9 tertiary alcohol **42** by protecting the C-2 carbonyl group as the silyl enol ether.[11] Treatment of **7a** with TBDMSOTf and Et_3N affords silyl enol ether **41**, which was added to MeLi at -78 °C. Brief treatment of the crude product with TBAF in THF provides the desired hydroxy ketone **42** in 83% yield for the three-step sequence. The preparation of **2** was completed in 83% yield by oxidation of the double bond to the diol with osmium tetroxide



and *N*-methylmorpholine *N*-oxide, cleavage of the diol with potassium periodate to give aldehyde **43**, oxidation of the aldehyde with sodium chlorite to give acid **44**, and esterification with diazomethane giving (±)-**2**. The ^{1}H and ^{13}C NMR and IR spectral data are identical to those kindly provided by Prof. Taschner for an authentic sample of (-)-**2**.

This sequence was readily adapted to the conversion of all four cyclization products **7a**, **7b**, **29a**, and **29b** to upial intermediate **2**. Treatment of the mother liquor remaining after recrystallization of **7a** with osmium tetroxide and *N*-methylmorpholine *N*-oxide, followed by cleavage of the diol with potassium periodate provides 60% of a 40:60 mixture of bis ketone aldehyde isomers **45a** and **45b**. Treatment of the mixture with TBDMSOTf and Et_3N affords bis silyl enol ether **46**, which is treated with MeLi at -78 °C and TBAF in THF to give 56% of aldehyde **43**, which is converted to ester **2** as described above.



An efficient 10-step route to the late upial intermediate **2** has been developed that proceeds in 30% overall yield from ethoxycyclohexenone **21** utilizing all stereoisomers produced in the oxidative cyclization of **8**. These studies also further define the scope and mechanism of oxidative cyclization of 1,3-cyclohexanediones, suggesting that the reaction will be general if there are no substituents at C-2.

Experimental

General. All NMR spectra were recorded at 300 MHz in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in δ and coupling constants are reported in Hz.

3-Ethoxy-6-(3*Z*-hexenyl)-5,6-dimethyl-2-cyclohexenone (22a). To a solution of 1.41 mL (10.8 mmol) of diisopropylamine in 8 mL of THF at 0 °C was added 4.26 mL of 2.5 M BuLi in hexanes. The LDA solution was stirred at 0 °C for 30 min and cooled to -78 °C. A solution containing 1.2 g (7.14 mmol) of ethoxy enone **21**[6] in 3 mL of THF was added dropwise over 40 min. The solution was stirred at -78 °C for an additional 30 min, warmed to -50 °C, and treated with 0.918 g (7.14 mmol) of DMPU in 3 mL of THF and then with 2.7 g (12.9 mmol) of 1-iodo-3*Z*-hexene.[7] The solution was gradually warmed to rt over 12 h. The dark solution was quenched with H_2O and diluted with 120 mL of ether. The ether solution was washed twice with H_2O and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 1.12 g (63%) of a 6:1 mixture of **22a** and **23a**, respectively, after flash chromatography on silica (10:1 hexane/EtOAc). The diastereomers were partially separated during the chromatography to give 700 mg of a 10:1 mixture of **22a** and **23a** in the latter fractions: ^{1}H NMR 5.35-5.30 (m, 2), 5.27 (s, 1 × 0.91), 5.25 (s, 1 × 0.09), 3.88 (q, 2, J = 7.0), 2.46-1.47 (m, 9), 1.36 (t, 3, J = 7.0), 1.14 (s, 3 × 0.09), 1.02 (d, 3 × 0.09, J = 6.9), 0.99 (d, 3 × 0.91, J = 6.5), 0.96 (s, 3 × 0.91), 0.95 (t, 3 × 0.91, J = 7.5), 0.93 (t, 3 × 0.09, J = 7.5); ^{13}C NMR (**22a**) 204.0, 174.5, 131.6, 128.9, 101.4, 63.9, 47.3, 35.3, 34.2, 32.7, 21.9, 20.4, 18.5, 15.0, 14.3, 14.1; (**23a**) 203.8, 174.2, 131.7, 128.9, 100.8, 63.9, 46.8, 37.2, 34.3, 31.1, 21.5, 20.4, 19.7, 15.2, 14.3, 14.0; IR (neat) 2964, 1652, 1610, 1379, 1198.

3-Ethoxy-6-(3*E*-hexenyl)-5,6-dimethyl-2-cyclohexenone (22b). Ethoxy enone **21**[6] (2.0 g, 11.9 mmol) was alkylated with 4.5 g (21.5 mmol) of 1-iodo-3*E*-hexene[7] by the procedure described above for the preparation of **22a** to give a 6:1 mixture of alkylated products **22b** and **23b**, respectively. Flash chromatography of the residue on silica gel (10:1 hexane/EtOAc) gave 700 mg of a 2.5:1 mixture of **22b** and **23b** followed by 1.35 g of a 10:1 mixture rich in **22b** (68% total): ^{1}H NMR 5.49-5.31 (m, 2), 5.26 (s, 1 × 0.91), 5.24 (s, 1 × 0.09), 3.87 (q, 2, J = 7.0), 2.45-1.50 (m, 9), 1.35 (t, 3, J = 7.0), 1.12 (s, 3 × 0.09), 1.01 (d, 3 × 0.09, J = 6.8), 0.98 (d, 3 × 0.91, J = 6.5), 0.95 (s, 3 × 0.91), 0.94 (t, 3 × 0.91, J = 7.5); ^{13}C NMR (**22b**) 204.1, 174.5, 131.8, 129.1, 101.5, 63.9, 47.3, 35.3, 34.2, 32.7, 27.3, 25.5, 18.5, 15.0, 14.1, 13.8; (**23b**) 203.9, 174.2, 131.9, 129.1, 100.9, 63.9, 46.7, 37.2, 34.3, 31.1, 26.8, 25.5, 19.9, 15.3, 14.1, 13.8; IR (neat) 2962, 1651, 1614, 1379, 1197 cm^{-1}. Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.42; H, 10.57.

4-(3Z-Hexenyl)-4,5-dimethyl-1,3-cyclohexanedione (8a). A solution containing 1.85 g of a 10:1 mixture of **22a** and **23a**, respectively, and 2 mL of 3 M HCl in 35 mL of THF was stirred at rt for 6 h. The solution was diluted with 200 mL of ether, washed with H_2O and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 1.66 g of crude **8a**. Flash chromatography on silica (5:1, followed by 2:1 hexane/EtOAc) gave 300 mg of a 3:2 mixture of **24a** and **8a**, respectively, followed by 1.09 g of pure **8a** as a 3:1 mixture of keto and enol tautomers (91% yield of dione mixture): ^{1}H NMR 5.43 (s, 1 × 0.25), 5.41-5.23 (m, 2), 3.52 (dd, 1 × 0.75, J = 17.6, 0.8), 3.32 (dd, 1 × 0.75, J = 17.6, 1.6), 2.81 (dd, 1 × 0.75, J = 16.6, 4.8), 2.42 (ddd, 1 × 0.75, J = 16.6, 7.8, 1.6), 2.39-1.58 (m, 7 × 0.75 + 9 × 0.25), 1.10 (s, 3 × 0.75), 1.01 (s, 3 × 0.25), 0.99 (d, 3 × 0.25, J = 6.4), 0.96 (t, 3 × 0.75, J = 7.4), 0.95 (d, 3 × 0.75, J = 7.0), 0.94 (t, 3 ×

0.25, J = 7.4); ^{13}C NMR (k) 208.1, 204.2, 132.7, 127.7, 56.1, 51.1, 44.6, 36.6, 32.4, 21.9, 20.5, 17.9, 15.6, 14.3; (e) 131.8, 128.7, 104.0, 45.6, 36.3, 35.3, 32.6, 22.0, 20.4, 18.8, 14.9, 14.4, the carbonyl carbon and enolic carbon were not found; IR 2964, 2646, 1703, 1600, 1233, 1200 cm^{-1}.

4-(3*E*-Hexenyl)-4,5-dimethyl-1,3-cyclohexanedione (8b). A 10:1 mixture of **22b** and **23b** (1.35 g) was hydrolyzed by the procedure described above to give 1.21 g of crude **8b**. Flash chromatography of the residue on silica gel (5:1 hexane/EtOAc) gave 113 mg of a 4:1 mixture of **24b** and **8b**, respectively, followed by 937 mg of pure **8b** as a 2:1 mixture of keto and enol tautomers (88% yield of dione mixture): ^{1}H NMR 5.53 (m, 2), 5.43 (s, 1 × 0.33), 3.53 (d, 1 × 0.67, J = 17.5), 3.31 (dd, 1 × 0.67, J = 17.5, 1.5), 2.82 (dd, 1 × 0.67, J = 16.7, 5.0), 2.41 (ddd, 1 × 0.67, J = 16.7, 7.6, 1.5), 2.39-1.36 (m, 7 × 0.67 + 9 × 0.33), 1.08 (s, 3 × 0.67), 1.00 (s, 3 × 0.33), 0.97 (d, 3 × 0.33, J = 6.2), 0.96 (t, 3 × 0.67, J = 7.5), 0.95 (t, 3 × 0.33, J = 7.4), 0.94 (d, 3 × 0.67, J = 7.1); ^{13}C NMR (k) 208.2, 204.3, 133.0, 127.9, 56.1, 51.0, 44.6, 36.6, 32.3, 27.2, 25.5, 17.9, 15.6, 13.7; (e) 200.3, 185.2, 132.0, 128.9, 103.9, 45.5, 36.3, 35.2, 32.6, 27.3, 25.5, 18.9, 14.9, 13.8; IR (neat) 2964, 2681, 1704, 1613, 1231 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.55; H, 9.83.

4,5-Dimethyl-8-(1-propenyl)bicyclo[3.3.1]nonan-2,9-dione (7a, 7b, 29a, and 29b). A solution containing 1.00 g (4.5 mmol) of dione **8a**, 2.50 g (9.3 mmol) of $Mn(OAc)_3 \cdot 2H_2O$, and 910 mg (4.5 mmol) of $Cu(OAc)_2 \cdot H_2O$ in 75 mL of degassed HOAc was stirred at rt under N_2 for 2 h. The solution was then diluted with 200 mL of CH_2Cl_2 and washed with H_2O, saturated $NaHCO_3$ solution, and brine. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure to give 930 mg of crude product. Flash chromatography of the residue on silica gel (5:1 hexane/EtOAc) yielded 852 mg (85%) of a crystalline 39:11:36:14 mixture of **7a**, **7b**, **29a**, and **29b**, respectively. Recrystallization of the mixture from hexane gave 290 mg of pure **7a**: mp 97.5-99.0 °C; ^{1}H NMR 5.48 (ddq, 1, J = 15.2, 1.0, 6.4), 5.28 (ddq, 1, J = 15.2, 7.3, 1.5), 3.27 (dd, 1, J = 4.0, 1.5), 3.03 (dd, 1, J = 17.6, 7.8), 2.81 (m, 1), 2.46 (br d, 1, J = 17.6), 2.25-2.10 (m, 2), 2.00-1.78 (m, 3), 1.65 (dd, 3, J = 6.4, 1.5), 1.13 (s, 3), 0.85 (d, 3, J = 7.3); ^{13}C NMR 210.6, 206.8, 130.2, 126.8, 71.9, 49.1, 48.83, 48.79, 41.7, 36.4, 27.6, 21.5, 19.9, 17.9; IR (KBr) 2942, 1720, 1690, 1244, 955 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.45; H, 9.41.

Partial data for **7b**, **29a**, and **29b**: ^{1}H NMR (**7b**) 1.15 (s, 3), 0.86 (d, 3, J = 7.1); (**29a**) 5.54 (ddq, 1, J = 15.2, 1.1, 6.4), 5.35 (ddq, 1, J = 15.2, 7.4, 1.4), 3.13 (br d, 1, J = 3.0), 1.65 (br d, 3, J = 6.4), 1.13 (s, 3), 0.91 (d, 3, J = 7.1); (**29b**) 3.19 (br s, 1), 1.14 (s, 3), 0.92 (d, 3, J = 7.1); ^{13}C NMR (**7b**) 129.9, 126.8; (**29a**) 210.7, 208.7, 130.3, 126.9, 69.5, 47.8, 47.7, 39.9, 35.0, 25.7, 20.6, 19.2, 17.9, the quaternary carbon was not observed; (**29b**) 211.0, 208.6, 129.0, 125.9.

4-(3*Z*-Hexenyl)-4-methyl-1,3-cyclohexanedione (30). A solution containing 0.65 mL (4.9 mmol) of diisopropylamine and 2 mL of 2.5 M BuLi in 5 mL of THF was stirred at 0 °C for 30 min and cooled to -78 °C. Alkylation of 500 mg (3.2 mmol) of 4-methyl-3-ethoxy-2-cyclohexenone[12] with 3.0 g of 1-iodo-3*Z*-hexene[7] as described above for the preparation of **22a** followed by flash chromatography of the residue on silica gel (10:1 hexane/EtOAc) yielded 360 mg (47%) of pure 3-Ethoxy-6-(3*Z*-hexenyl)-6-methyl-2-cyclohexenone: ^{1}H NMR 5.32 (m, 2), 5.25 (s, 1), 3.88 (q, 2, J = 7.0), 2.51-2.34 (m, 2), 2.07-1.90 (m, 5), 1.75 (ddd, 1, J = 13.4, 7.5, 5.8), 1.64-1.43 (m, 2), 1.36 (t, 3, J = 7.0), 1.10 (s, 3), 0.95 (d, 3, J = 7.5); ^{13}C NMR 203.9, 175.5, 131.8, 128.8, 101.3, 64.1, 43.3, 36.9, 32.1, 26.0, 22.2, 21.9, 20.4, 14.3, 14.1; IR (neat) 2933, 1654, 1610, 1378, 1190 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C,

76.13; H, 9.98.

A solution containing 277 mg (1.17 mmol) of 3-Ethoxy-6-(3Z-hexenyl)-6-methyl-2-cyclohexenone and 1 mL of 3 M HCl in 10 mL of THF was stirred at rt overnight. The solution was diluted with ether, washed with H_2O and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 230 mg of crude **30**. Flash chromatography of the residue on silica gel (5:1 hexane/EtOAc) gave 218 mg (89%) of pure **30** as a 2.5:1 mixture of keto and enol tautomers, respectively: ^{1}H NMR 5.41 (s, 1 × 0.29), 5.41-5.26 (m, 2), 3.50 (d, 1 × 0.71, J = 17.3), 3.38 (dd, 1 × 0.71, J = 17.3, 1.1), 2.73-1.46 (m, 10), 1.19 (s, 3 × 0.71), 1.15 (s, 3 × 0.29), 0.96 (t, 3 × 0.71, J = 7.5), 0.95 (t, 3 × 0.29, J = 7.5); ^{13}C NMR (keto) 207.7, 204.5, 132.7, 127.6, 56.1, 47.3, 36.9, 36.4, 30.4, 22.7, 21.6, 20.5, 14.2; (enol) 186.0, 131.9, 128.6, 103.6, 41.5, 37.4, 36.5, 32.1, 28.2, 21.9, 20.4, 14.3, the carbonyl carbon was not observed; IR (neat) 2962, 2683, 1573, 1462, 1405, 1197 cm^{-1}.

Oxidative cyclization of 30. A solution containing 60 mg (0.29 mmol) of **30**, 164 mg (0.61 mmol) of $Mn(OAc)_3$•$2H_2O$, and 58 mg (0.29 mmol) of $Cu(OAc)_2$•H_2O in 6 mL of degassed HOAc was stirred at rt under N_2 for 1 h. Workup as described above for the cyclization of **8a** gave 56 mg of crude product. Flash chromatography of the residue on silica gel (10:1 hexane/EtOAc) gave 44 mg (74%) of an inseparable 64:7:20:9 mixture of bicyclic diones **31a**, **31b**, **32a**, and **32b**: ^{1}H NMR 5.52 (ddq, 1 × 0.64, J = 15.3, 1.0, 6.3), 5.31 (ddq, 1 × 0.64, J = 15.3, 7.2, 1.5), 5.19 (ddd, 1 × 0.07 or 0.09, J = 11.1, 9.3, 1.8), 3.32 (br d, 1 × 0.64, J = 4.2), 3.25 (br d, 1 × 0.07, J = 4.3), 3.17 (br s, 1 × 0.20), 3.04 (br d, 1 × 0.09, J = 3.0), 3.50-1.60 (m, 9), 1.65 (br d, 3, J = 6.3), 1.17 (s, 3 × 0.09), 1.16 (s, 3 × 0.20), 1.15 (s, 3 × 0.07), 1.13 (s, 3 × 0.64); ^{13}C NMR (**31a**) 210.4, 207.0, 130.1, 126.8, 71.9, 48.8, 41.3, 39.9, 31.7, 27.0, 23.6, 17.8, quaternary carbon was not identified; (**32a**) 129.9, 127.2, 68.9, 45.5, 39.5, 39.1, 30.7, 25.4, 24.0, 17.9, all carbons could not be identified; (**31b**) 128.3, 126.1; (**32b**) 128.9, 126.3; IR (neat) 2930, 1727, 1704, 1454, 1380, 1242 cm^{-1}.

4-(3Z-Hexenyl)-1,3-cyclohexanedione (33). 3-Ethoxy-2-cyclohexenone (1.0 g, 7.1 mmol) was alkylated with 2.0 g (9.5 mmol) of 1-iodo-3Z-hexene[7] as described above for **22a** to give 883 mg (56%) of 3-ethoxy-6-(3Z-hexenyl)-2-cyclohexenone after chromatography on silica gel (5:1 hexane/EtOAc): ^{1}H NMR 5.35 (m, 2), 5.31 (s, 1), 3.89 (q, 2, J = 7.0), 2.43 (apparent dd, 2, J = 7.1, 5.4), 2.25-1.87 (m, 7), 1.73 (dddd, 1, J = 13.3, 9.9, 7.1, 7.1), 1.40 (m, 1), 1.36 (t, 3, J = 7.0), 0.96 (t, 3, J = 7.5); ^{13}C NMR 201.5, 176.5, 132.1, 128.4, 102.2, 64.1, 44.5, 29.4, 27.9, 26.2, 24.5, 20.5, 14.3, 14.1; IR (neat) 2935, 1657, 1609, 1379, 1191.

Hydrolysis of 3-ethoxy-6-(3Z-hexenyl)-2-cyclohexenone (650 mg, 2.9 mmol) as described above for the preparation of **8a** gave 503 mg (89%) of **33** after chromatography on silica gel (1:1 hexane/EtOAc) as a 1:1 mixture of keto and enol tautomers: ^{1}H NMR 8.92 (br s, 1 × 0.5, OH), 5.44 (s, 1 × 0.5), 5.47-5.27 (m, 2), 3.46 (d, 1 × 0.5, J = 16.9), 3.40 (d, 1 × 0.5, J = 16.9), 2.73-1.4 (m, 11), 0.96 (t, 3 × 0.5, J = 7.5), 0.95 (t, 3 × 0.5, J = 7.5); ^{13}C NMR 204.7, 204.1, 196.7, 188.9, 132.9, 132.4, 128.0, 127.6, 103.9, 58.2, 48.5, 41.3, 39.6, 29.9, 29.8, 28.9, 25.7, 24.6, 24.4, 24.3, 20.5, 14.3, all carbons could not be identified; IR (neat) 2933, 2658, 1577, 1196.

Oxidative cyclization of 33. A solution containing 140 mg (0.72 mmol) of **33**, 387 mg (1.44 mmol) of $Mn(OAc)_3$•$2H_2O$, and 144 mg (0.72 mmol) of $Cu(OAc)_2$•H_2O in 17 mL of degassed HOAc was stirred at rt under N_2 for 2 hrs. Workup as described above for the cyclization of **8a** followed by chromatography on silica gel (5:1 hexane/EtOAc) gave 100 mg (72%) of an inseparable 60:22:11:7 mixture of bicyclic diones **35a-d** (the

product ratio was determined from the relative ^{13}C peak intensities of C-1 and the olefin carbons): ^1H NMR (partial data for **35a**) 5.52 (ddq, 1 × 0.60, J = 15.2, 1.0, 6.4), 5.31 (ddq, 1 × 0.60, J = 15.2, 7.2, 1.5), 3.26 (dd, 1 × 0.60, J = 4.2, 1.8), 1.67 (br d, 3 × 0.60, J = 6.4); (partial data for **35c**) 5.58 (ddq, 1 × 0.22, J = 15.3, 1.3, 6.4), 3.11 (br s, 1 × 0.22); ^{13}C NMR (**35a**) 210.0, 206.8, 130.2, 126.7, 72.1, 48.9, 44.1, 39.7, 33.4, 26.4, 23.6, 17.8; (partial data for **35c**) 129.8, 127.2, 168.9, 47.9, 44.2, 38.9, 31.6, 23.9, 22.4, 17.9; (partial data for **35b** and **35d**) 128.9, 128.2, 126.3, 125.9, 71.2, 68.9; IR (neat) 2939, 2863, 1729, 1699, 1454, 1250.

9-Hydroxy-4,5-dimethyl-8-(1*E*-propenyl)bicyclo[3.3.1]nonan-2-one (38). To a solution containing 255 mg (6.7 mmol) of LAH in 5 mL of DME was added 1.9 mL (20 mmol) of *t*-BuOH dropwise over 1 h at 0 °C. The $LiAlH(O\text{-}t\text{-}Bu)_3$ solution was added dropwise to a solution containing 8 mg (0.04 mmol) of dione **7a** in 1 mL of DME at 0 °C until **7a** disappeared by TLC analysis. The solution was quenched with water and extracted with ether. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (10:1 hexane/EtOAc) yielded 7 mg (88%) of **38**: ^1H NMR 5.48-5.33 (m, 2), 3.72 (br s, 1), 2.59 (br d, 1, J = 3.9), 2.58 (dd, 1, J = 18.0, 8.9), 2.44-2.36 (m, 1), 2.35 (ddd, 1, J = 18.0, 5.0, 1.1), 2.01-1.89 (m, 1), 1.68-1.41 (m, 4), 1.65 (dd, 3, J = 4.8, 1.0), 1.15 (s, 3), 1.13 (d, 3, J = 7.4); ^{13}C NMR 213.4, 132.3, 125.0, 80.9, 58.5, 48.1, 43.1, 41.9, 36.4, 35.4, 26.4, 24.1, 21.9, 18.0.

2-Hydroxy-8-(1*E*-propenyl)-2,4,5-trimethylbicyclo[3.3.1]nonan-9-one (39). A 1.4 M MeLi solution was added slowly at -78 °C to a solution containing 43 mg (0.20 mmol) of dione **7a** in 4 mL of ether while monitoring reaction progress by TLC. Despite the addition of a large excess of MeLi (1 mL of 1.4 M), the reaction did not proceed to completion. The reaction was quenched with water and extracted three times with ether. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give a mixture containing about 50% of starting dione **7a**. This was taken up in ether and treated with MeLi as before. After repeating this twice more followed by the usual ether workup, 40 mg of crude **39** was obtained. Flash chromatography of the residue on silica gel (10:1 hexane/EtOAc) yielded 26 mg (56%) of pure **39**, followed by 8 mg of dione **7a**: ^1H NMR 5.81 (br d, 1, J = 15.7), 5.58 (ddq, 1, J = 15.7, 1.8, 6.4), 2.68-2.50 (m, 1), 2.60 (br s, 1), 2.39 (dd, 1, J = 14.5, 7.0), 2.33 (s, 1, OH), 2.31-2.25 (m, 1), 2.21 (qdd, 1, J = 7.4, 7.0, 6.0), 2.08-2.00 (m, 1), 1.78-1.62 (m, 2), 1.70 (br d, 3, J = 6.4), 1.51 (dd, 1, J = 14.5, 6.0), 1.21 (s, 3), 0.97 (s, 3), 0.92 (d, 3, J = 7.4); ^{13}C NMR 134.6, 125.2, 77.5, 63.5, 48.3, 46.7, 45.7, 42.7, 38.2, 33.7, 25.3, 20.9, 20.0, 18.1, carbonyl carbon was not observed; IR (CCl_4) 3547, 3398, 2973, 2932, 1714 cm^{-1}.

9-Hydroxy-4,5,9-trimethyl-8-(1*E*-propenyl)bicyclo[3.3.1]nonan-2-one (42). To a solution of 100 mg (0.45 mmol) of dione **7a** in 4 mL of CH_2Cl_2 was added 0.25 mL (1.8 mmol) of Et_3N and 0.45 mL (1.9 mmol) of TBSOTf at 0 °C. The solution was warmed to rt slowly over a 3 h period, diluted with CH_2Cl_2, and washed twice with H_2O. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure to give crude silyl enol ether **41**.

Crude **41** in 7 mL of THF was treated with 2.5 mL of 1.4 M MeLi solution at -78 °C. The solution was stirred at -78 °C for 1 h, quenched with H_2O, and extracted four times with ether. The combined ether extracts were washed with water and brine and concentrated under reduced pressure.

The crude residue remaining was dissolved in 7 mL of THF and treated with 0.75 mL of 1.0 M TBAF.

After 10 min, the solution was diluted with ether, washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (5:1 hexane/EtOAc) gave 88.5 mg (83%) of ketol **42** as a white solid. Further purification was accomplished by recrystallization from hexane: mp 111-112 °C; ^{1}H NMR 5.43 (ddq, 1, *J* = 15.3, 1.1, 6.3), 5.27 (ddq, 1, *J* = 15.3, 6.8, 1.4), 2.66 (dd, 1, *J* = 18.7, 9.7), 2.47 (m, 1), 2.34 (br d, 1, *J* = 18.7), 2.30 (br s, 1), 2.03-1.91 (m, 1), 1.63 (br d, 3, *J* = 6.3), 1.68-1.43 (m, 4), 1.31 (s, 3), 1.16 (d, 3, *J* = 7.4), 1.03 (s, 3); ^{13}C NMR 213.4, 132.4, 125.0, 77.9, 64.5, 48.8, 40.6, 40.4, 38.5, 38.4, 26.4, 24.6, 22.7, 21.2, 17.9; IR (CCl_4) 3605, 3434, 2936, 1706 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.13; H, 9.97.

9-Hydroxy-4,5,9-trimethyl-8-oxobicyclo[3.3.1]nonane-2-carboxaldehyde (43) from 42. A solution containing 50 mg (0.21 mmol) of ketol **42** in 3 mL of acetone and 2.5 mL of water was treated with 33 mg (0.29 mmol) of *N*-methylmorpholine *N*-oxide and 0.15 mL of 2.5% OsO_4 solution in *t*-BuOH. The solution was stirred for 50 min and treated with 75 mg (0.33 mmol) of KIO_4. The solution was stirred for another 15 min, diluted with ether, washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 42 mg (89%) of pure **43** that was recrystallized from hexane/CH_2Cl_2: mp 117.5-118.5 °C; ^{1}H NMR 9.74 (s, 1), 2.80 (d, 1, *J* = 3.6), 2.60 (dd, 1, *J* = 18.5, 8.8), 2.61-2.54 (m, 1), 2.43 (dd, 1, *J* = 18.5, 6.6), 1.93 (ddq, 1, *J* = 8.8, 6.6, 7.2), 1.82-1.72 (m, 1), 1.64-1.42 (m, 3), 1.36 (s, 3), 1.15 (d, 3, *J* = 7.2), 1.08 (s, 3); ^{13}C NMR 201.5, 76.8, 57.8, 51.0, 48.1, 39.7, 39.0, 36.4, 24.2, 21.9, 20.5, 19.1, carbonyl carbon not observed; IR (CCl_4) 3603, 2970, 1729, 1700 cm^{-1}.

Methyl 9-Hydroxy-5,6,9-trimethyl-8-oxobicyclo[3.3.1]nonane-2-carboxylate (2). A solution containing 17 mg (0.08 mmol) of aldehyde **43** and 0.45 mL of 2-methyl-2-butene in 1.5 mL of *t*-BuOH was treated with 60 mg (0.44mmol) of $NaClO_2$ and 72 mg (0.52 mmol) of NaH_2PO_4•H_2O in 0.75 mL of H_2O dropwise at 0 °C. The solution was stirred for 5 min and treated with 0.5 mL of HOAc and then saturated with NaCl. The solution was extracted with EtOAc (5 × 3 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was taken up in heptane and concentrated again to remove HOAc. Crude **44** was dissolved in 6 mL of ether and treated with an ether solution of CH_2N_2. The excess CH_2N_2 was quenched with HOAc and the solution was diluted with 20 mL of ether. The organic solution was washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield 18 mg (93%) of pure **2** which was recrystallized from hexane/CH_2Cl_2: mp 133-134 °C; ^{1}H NMR 3.69 (s, 3), 2.77 (dd, 1, *J* = 18.5, 9.7), 2.75 (m, 1), 2.64 (dd, 1, *J* = 4.2, 1.0), 2.41 (ddd, 1, *J* = 18.5, 4.4, 1.0), 1.97 (ddq, 1, *J* = 4.4, 9.7, 7.3), 1.85-1.50 (m, 4), 1.33 (s, 3), 1.16 (d, 3, *J* = 7.3), 1.05 (s, 3); ^{13}C NMR 212.7, 173.2, 77.2, 60.0, 51.9, 48.2, 43.7, 39.7, 38.5, 37.6, 24.3, 22.3, 21.7, 20.9; IR (CCl_4) 3452, 2950, 1742, 1711 cm^{-1}. The spectral data are identical to those kindly provided by Prof. Taschner.

5,6-Dimethyl-8,9-dioxobicyclo[3.3.1]nonane-2-carboxaldehyde (45a and 45b). To a solution of the 14:10:49:27 mixture of **7a**, **7b**, **29a** and **29b** (285 mg, 1.3 mmol) remaining after recrystallization of **7a** in 30 mL of 1:1 acetone/H_2O was added 0.5 ml of 2.5% OsO_4 in *t*-BuOH and 220 mg (1.9 mmol) of *N*-methylmorpholine *N*-oxide. The solution was stirred for 2 h at rt, diluted with 100 ml of EtOAc, and washed twice with 50 mL of H_2O. The aqueous layers were saturated with NaCl and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give 284 mg of diols. This was dissolved in 30 mL of 1:1 acetone/H_2O and KIO_4 (1.20 g, 5.2 mmol) was added.

Cleavage of the diols proceeded rapidly at first (as monitored by TLC) and then slowed drastically presumably due to varying reactivities of the different isomers. The solution was stirred for 18 h to effect complete conversion to **45** and was worked up as described above for the preparation of **43**, giving 190 mg of a crude **45**. Flash chromatography on silica gel (1:1 hexane/EtOAc) gave 159 mg (60%) of a 40:60 mixture of **45a** and **45b**, respectively: ^{1}H NMR 9.68 (s, 1 × 0.40), 9.65 (s, 1 × 0.60), 3.72 (d, 1 × 0.40, J = 3.6), 3.60 (d, 1 × 0.60, J = 2.2), 3.20 (m, 1 × 0.60), 3.02 (dd, 1 × 0.60, J = 16.6, 6.6), 2.95 (m, 1 × 0.40), 2.89 (dd, 1 × 0.40, J = 17.0, 6.9), 2.40-1.72 (m, 6), 1.17 (s, 3 × 0.40), 1.10 (s, 3 × 0.60), 0.95 (d, 3 × 0.60, J = 7.1), 0.94 (d, 3 × 0.40, J = 7.1); ^{13}C NMR (mixture) 209.3, 209.1, 207.2, 206.7, 199.0, 198.5, 63.7, 62.4, 55.9, 55.7, 49.4, 49.2, 49.1, 48.3, 41.1, 40.2, 35.2, 34.7, 20.5, 20.1, 19.9, 19.5, 19.1, 19.0; IR (neat) 2935, 1698, 1455, 1389, 1241 cm^{-1}.

9-Hydroxy-5,6,9-trimethyl-8-oxobicyclo[3.3.1]nonane-2-carboxaldehyde (43) From 45. To a solution containing 25 mg (0.12 mmol) of a 1:1.5 mixture of **45a** and **45b** in 1.5 mL of CH_2Cl_2 was added 0.1 mL (0.72 mmol) of Et_3N and TBDMSOTf dropwise (≈ 15 drops) until TLC analysis indicated **45** had reacted completely and only one fairly nonpolar spot had formed. The reaction solution was diluted with 2 mL of hexane and passed through a short silica column. The solution was concentrated under reduced pressure and the residue was dissolved in 2 mL of THF. The solution was cooled to -78 °C and treated with 0.3 mL of 1.4 M MeLi solution and stirred at -78 °C for 40 min. The reaction was quenched with 2 mL of H_2O and extracted with Et_2O (4 × 5 mL). The solvent was removed under reduced pressure and the residue was dissolved in 2 mL of THF and cooled to 0 °C. Five drops of a 1 M solution of TBAF were added and the solution was immediately diluted with 30 mL of EtOAc and washed with 3 M HCl and brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give 40 mg of crude **43** and a trace of a minor aldehyde believed to be the axial isomer. Flash chromatography of the residue on silica (2:1 Hexane/EtOAc) gave 15 mg (56%) of pure crystalline **43**.

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