General Procedure for the Formation of Anhydrides. Palladium acetate (0.022 g, 0.10 mmol), triphenylphosphine (0.077 g, 0.30 mmol), and anhydrous sodium benzoate (0.216 g, 1.50 mmol) were placed in the reaction vessel. After the system was purged several times with carbon monoxide, a *N,N*-dimethylformamide (10 mL) solution containing the iodoarene (1.0 mmol) and biphenyl (internal standard) was added. The reaction vessel was then pressurized to 2.7 atm with carbon monoxide. The reaction mixture was heated to 95 °C for 18 h, during which time the color of the solution changed from yellow to deep violet (no precipitate was formed). The reaction mixture was cooled to room temperature, and the vessel was opened under a nitrogen atmosphere. Pure anhydride was obtained by rapid ether extraction of the DMF solution (the latter having been treated with ice-cold aqueous sodium chloride), followed by column chromatography through a short silica gel column.

In order to isolate the benzoylpiperidine, piperidine (0.25 g, 3.0 mmol) was added, followed by tetrahydrofuran (10 mL), and the reaction mixture was stirred overnight at room temperature. Dilute hydrochloric acid was added, and the mixture was extracted with ether. The ether extract was washed with a saturated solution of sodium carbonate, dried ($MgSO_4$), and concentrated to give the pure *N*-aroylpiperidine.

Acknowledgment. We are grateful to British Petroleum and to the Natural Sciences and Engineering Research Council for support of this research. Dr. Pri-Bar is indebted to NSERC for support on an International Scientific Exchange Award.

Registry No. PhI, 591-50-4; PhBr, 108-86-1; 4-$CH_3C_6H_4I$, 624-31-7; 4-$CH_3OC_6H_4I$, 696-62-8; 4-ClC_6H_4I, 637-87-6; 4-$O_2NC_6H_4I$, 636-98-6; 1-$C_{10}H_7I$, 90-14-2; $PhCO_2Na$, 532-32-1; $PhCO_2K$, 582-25-2; $(PhCO_2)_2C_9$, 2090-05-3; 4-$CH_3C_6H_4CO_2Na$, 17264-54-9; 4-$O_2NC_6H_4CO_2Na$, 3847-57-2; 4-$CH_3OC_6H_4CO_2Na$, 536-45-8; 4-$ClC_6H_4CO_2Na$, 3686-66-6; 1-$C_{10}H_7CO_2Na$, 17273-44-8; Ph_3P, 603-35-0; 4-$CH_3OC_6H_4CONC_5H_{10}$, 57700-94-4; $PhCONC_5H_{10}$, 776-75-0; $(C_4H_9)_4N^+I^-$, 311-28-4; benzoic anhydride, 93-97-0; 4-methylbenzoic anhydride, 13222-85-0, 4-methoxybenzoic anhydride, 794-94-5; 4-chlorobenzoic anhydride, 790-41-0; 4-nitrobenzoic anhydride, 902-47-6; 1-naphthalene carboxylic anhydride, 64985-86-0; 1,2-benzenedicarboxylic acid, 88-99-3; 1,4-benzenedicarboxylic acid, 100-21-0; palladium acetate, 3375-31-3; sodium 2-iodobenzoate, 2532-17-4; 1,2-diiodobenzene, 615-42-9; 1,4-diiodobenzene, 624-38-4; dibenzo-18-crown-6, 14098-24-9; tri-*o*-tolylphosphine, 1038-95-5; 1,2-bis[bis(diphenylphosphino)]ethane, 1663-45-2; phthalic anhydride, 85-44-9.

Manganese(III)-Based Oxidative Free-Radical Cyclizations.[1] Oxidative Cyclization and Aromatization of 3-Oxo-6-heptenoate Esters

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Treatment of 3-oxo-6-heptenoate esters **1**, **2**, **4–15** with 4 equiv of $Mn(OAc)_3{\cdot}2H_2O$ and 1 equiv of $Cu(OAc)_2{\cdot}H_2O$ gave salicylate esters **16–29** in yields of 17–78%. Similar treatment with 4 equiv of $Mn(OAc)_3{\cdot}2H_2O$ and excess LiCl gave mixtures of salicylate esters and chlorides such as **45** and **46**, which could be converted to the salicylate ester by heating at reflux in acetic acid containing excess LiCl in overall yields of 40–90%. Treatment of α-chloro β-keto ester **3** with 2 equiv of $Mn(OAc)_3{\cdot}2H_2O$ and 1 equiv of $Cu(OAc)_2{\cdot}H_2O$ gave a mixture of salicylate **17** and methylenecyclohexane **41**. Treatment of δ-hydroxy β-keto esters **51a** and **51b** with 2 equiv of $Mn(OAc)_3{\cdot}2H_2O$ gave epoxides **53a** and **53b** in 50% and 30% yield, respectively.

Introduction

We have recently reported that oxidative cyclization of β-keto ester **1** with 4 equiv of $Mn(OAc)_3{\cdot}2H_2O$[3] and 1 equiv of $Cu(OAc)_2{\cdot}H_2O$ gave methyl salicylate (**16**) in 77% yield as shown in Table I.[1c,4] Since β-keto esters such as **1** are readily available by alkylation of the dianion of methyl acetoacetate,[5] this procedure appeared to offer a novel and general method for the preparation of salicylate derivatives.[6] We report here studies indicating the scope and limitations of this oxidative cyclization procedure.

The detailed steps involved in the conversion of β-keto ester **1** to salicylate **16** can be surmised based on cyclizations of related β-keto esters that do not give aromatic products.[1] Presumably, the β-keto ester of **1** forms a manganese enolate, which interacts with the double bond to give the cyclic radical **30** as a reactive intermediate.[1d] The enol radical is not a plausible intermediate since we have shown that the double bond is involved in the rate-determining step of the oxidation of β-keto esters containing two hydrogens on the α-carbon. Secondary radicals react with cupric acetate to give copper(III) intermediates, which undergo oxidative β-hydride elimination to give alkenes and cuprous acetate.[7] The radical of **30** should react with cupric acetate to give **31** as a mixture of double-bond isomers. The cuprous acetate produced in this oxidation is reoxidized by a second equivalent of $Mn(OAc)_3{\cdot}2H_2O$; however, neither isomer of **31** can be isolated, even when a deficiency of $Mn(OAc)_3{\cdot}2H_2O$ is used. Presumably, β-keto ester **31** is converted to the manganese enolate, which is oxidized to the enol radical. Oxidative β-hydride elimination will give the cyclohexadienone,

(1) For previous papers in this series, see: (a) Snider, B. B.; Mohan, R. M.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659. (b) Snider, B. B.; Mohan, R. M.; Kates, S. A. *Tetrahedron Lett.* **1987**, *28*, 841. (c) Mohan, R.; Kates, S. A.; Dombroski, M.; Snider, B. B. *Ibid.* **1987**, *28*, 845. (d) Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *53*, 2137. (e) Snider, B. B.; Dombroski, M. A. *J. Org. Chem.* **1987**, *52*, 5487.

(2) Dreyfus Teacher–Scholar 1982–1987.

(3) For a review of $Mn(OAc)_3{\cdot}2H_2O$ as an oxidant, see: de Klein, W. J. In *Organic Synthesis by Oxidation with Metal Compounds*; Mijs, W. J., de Jonge, C. R. H., Eds.; Plenum: New York, 1986, pp 261–314.

(4) For a rediscovery of this reaction, see: Peterson, J. R.; Egler, R. S.; Horsley, D. B.; Winter, T. J. *Tetrahedron Lett.* **1987**, *28*, 6109.

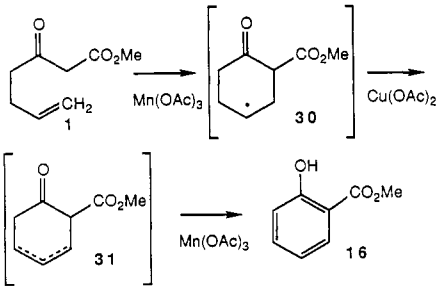
(5) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

(6) For a review on the synthesis of aromatic rings from acyclic precursors, see: Bamfield, P.; Gordon, P. F. *Chem. Soc. Rev.* **1984**, *13*, 441. Cf. Hormi, O. E. O. *J. Org. Chem.* **1988**, *53*, 880.

(7) Kochi, J. K.; Bemis, A.; Jenkins, C. L. *J. Am. Chem. Soc.* **1968**, *90*, 4616. Kochi, J. K.; Bacha, J. D. *J. Org. Chem.* **1968**, *33*, 2746. Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 843. Kochi, J. K. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Chapter 11. Nonhebel, D. C. In *Essays on Free-Radical Chemistry, Special Publication 24*, Chemical Society: London, 1970; p 409. Kochi, J. K. *Science (Washington, D.C.)* **1967**, *155*, 415.

0022-3263/89/1954-0038$01.50/0

which will tautomerize to salicylate **16**. This process requires 4 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and a catalytic amount of $Cu(OAc)_2 \cdot H_2O$.

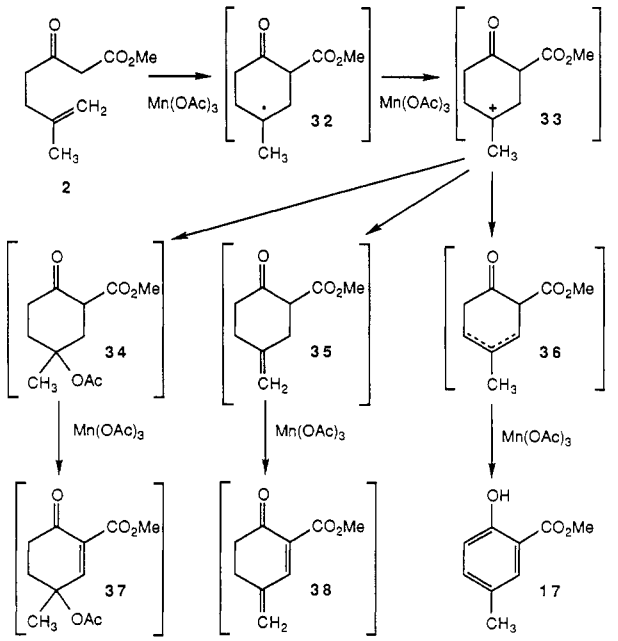


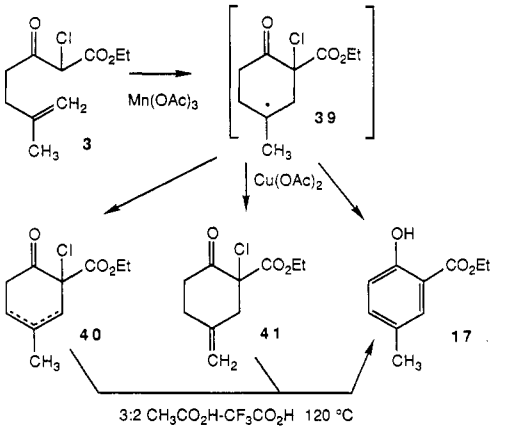
Results and Discussion

Our studies indicating the scope and limitations of salicylate synthesis by oxidative cyclization are shown in Table I. The β-keto esters were prepared in the yields shown by alkylation of the dianion[5] of methyl acetoacetate (procedure A), methyl 3-oxopentanoate (procedure B), ethyl 2-chloroacetoacetate (procedure C), methyl 3-oxo-4-phenylbutanoate (procedure E), or 1-phenyl-1,3-butanedione (procedure F). β-Keto esters **4**, **10**, and **13** were prepared from the methyl ketone by conversion to the enolate with LDA and reaction with methyl cyanoformate (procedure D).[8,9] Oxidative cyclization of **2**, **4**, and **5** under the standard reaction conditions (procedure A, 4 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ in acetic acid for 1–2 days at 25 °C) gave salicylates **17**, **18**, and **19** in yields of 17%, 38%, and 78%, respectively. These reaction conditions are therefore well-suited for the preparation of 3-alkylsalicylates such as **19**, marginally acceptable for the preparation of 4-alkylsalicylates such as **18**, and unsuitable for the preparation of 5-alkylsalicylates such as **17**.

The low yield of salicylate from the oxidative cyclization of **2** was discouraging, especially since the tertiary radical **32** should be formed from **2** more rapidly than the secondary radical **30** is formed from **1**. Examination of the pathway from radical **32** to salicylate **17** suggested the origin of the low yield. Secondary radicals such as **30** are not oxidized by $Mn(OAc)_3 \cdot 2H_2O$ but instead are oxidized to the alkene without the intermediacy of a cation by $Cu(OAc)_2 \cdot H_2O$.[7] On the other hand, tertiary radicals such as **32** are oxidized to cations such as **33** by either $Mn(OAc)_3 \cdot 2H_2O$ or $Cu(OAc)_2 \cdot H_2O$. Cation **33** can react with solvent to give acetate **34** or lose a proton to give either **35**, with an exocyclic double bond, or **36** as a mixture of endocyclic double bond isomers. Oxidation of **36** should lead to salicylate **17** analogously to the proposed oxidation of **31** to **16**. Oxidation of **34** should give **37**, which might lose acetic acid to give salicylate **17**. Oxidation of **35** should give diene **38**, which should polymerize rather than rearrange to salicylate **17**.

Oxidative Cyclization of α-Chloro β-Keto Esters. We therefore turned to alternative oxidative protocols to devise an effective method for the preparation of salicylate **17**. We have previously shown in related oxidative cyclizations that better yields are obtained with α-chloro β-keto esters than with α-unsubstituted β-keto esters since the presence of the chlorine prevents overoxidation of the initial cyclic product.[1d] We therefore decided to examine the oxidation of **3** since the presence of the chlorine should prevent the formation of diene **38**. Oxidative cyclization of **3** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ (procedure B) gave the desired salicylate **17** in 30% yield accompanied by 47% of **41** and 11% of **40** as a mixture of isomers. Initial cyclization gives a tertiary radical, which undergoes oxidative β-hydride elimination by $Cu(OAc)_2 \cdot H_2O$ to give a mixture of **40** and **41**. We have shown that the presence of the chlorine prevents oxidation of the tertiary radical to a cation by either Mn(III) or Cu(II) in closely related systems.[1d] Salicylate **17** is probably formed by elimination of hydrogen chloride from **40** and tautomerization.



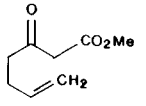
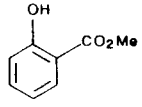
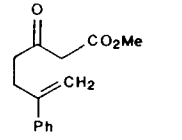
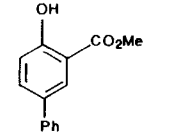
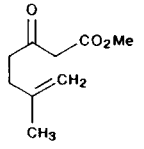
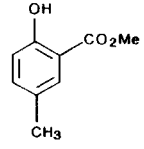
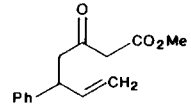
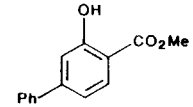
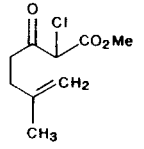
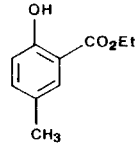
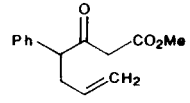
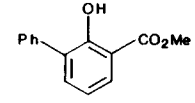
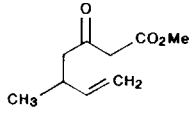
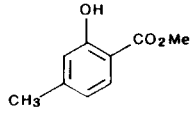
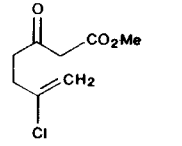
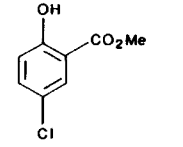
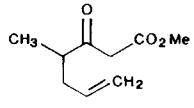
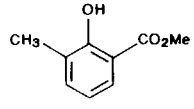
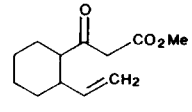
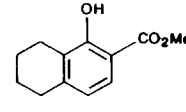
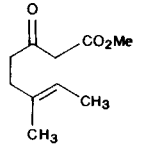
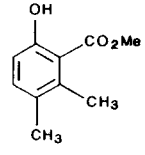
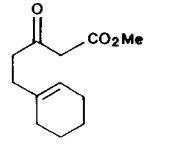
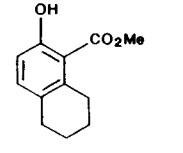
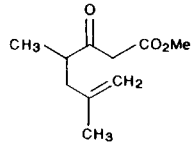
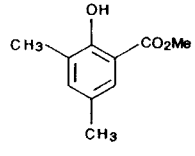
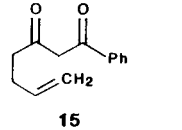
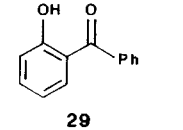


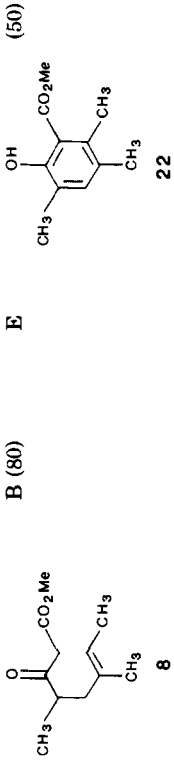
This reaction protocol is not directly suitable for the preparation of **17**, which is obtained in only 30% yield, even through an 88% overall yield of monomeric products is obtained from **3**. β-Keto esters **40** and **41**, formed in 58% yield, are at the salicylate oxidation state. Isomerization of the double bond of **41** into the ring to give either isomer of **40**, and loss of hydrogen chloride should give **17**. This transformation can be carried out by heating **41** or **40** in 3:2 acetic acid–trifluoroacetic acid at reflux for 10 h.[10] The overall transformation (procedure C) was carried out by reaction of **3** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ in acetic acid for 1–2 days at 25 °C followed by workup and heating the crude product in 3:2 acetic acid–trifluoroacetic acid to give a 71% yield of

(8) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.
(9) Childs, M. E.; Weber, W. P. *J. Org. Chem.* **1976**, *41*, 3486.

(10) Extensive decomposition occurred on attempted rearrangement of **40** and **41** to **17** in the presence of copper and manganese salts. Heating the crude product in acetic acid for 10 h at reflux gave **17** in 45% yield and recovered **41** in 24% yield, indicating that use of trifluoroacetic acid as a cosolvent is necessary.

Table I. Oxidative Cyclization of Unsaturated β-Keto Esters to Salicylate Esters

β-keto ester	method of preparation[a] (% yield)	cyclization procedure[b]	product (% yield)	β-keto ester	method of preparation[a] (% yield)	cyclization procedure[b]	product (% yield)
 1	A (55)	A	 16 (78)	 9	A (59)	A D E	 23 (0) (24) (44)
 2	A (70)	A D E	 17 (17) (6)[c] (70)	 10	D (71)	A	 24 (11)
 3	C (44)	B C	 17 (30)[d] (71)	 11	E (66)	A	 25 (20)
 4	D (60)	A	 18 (38)	 12	A (77)	A D E	 26 (10) (14)[e] (14)[e]
 5	B (84)	A	 19 (78)	 13	D (54)	A	 27 (46)
 6	A (79)	A E	 20 (0) (40)	 14	A (65)	E	 28 (37)
 7	B (85)	E	 21 (91)	 15	F (66)	A	 29 (47)

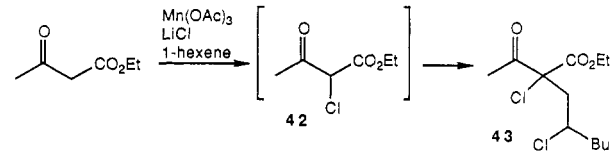


8 B (80) 22 E (50)

[a] Procedures used for preparation of β-keto esters: Alkylation of the dianion of (A) methyl acetoacetate, (B) methyl 3-oxopentanoate, (C) methyl chloroacetoacetate, (E) methyl 4-phenyl-3-oxobutanoate, or (F) 1-phenylpentane-2,4-dione with the appropriate allylic halide; (D) carbomethoxylation of the kinetic lithium enolate of the methylketone with methylcyanoformate.[8,9] [b] Procedures for oxidative cyclization: (A) oxidation with 4 equiv of Mn and 1 equiv of Cu; (B) oxidation of the α-chloro β-keto ester with 2 equiv of Mn and 1 equiv of Cu; (C) procedure B followed by heating the crude product in 3:2 HOAc–TFA at 120 °C for 10 h; (D) oxidation with 4 equiv of Mn and 4–10 equiv of LiCl; (E) procedure D followed by heating the crude product in HOAc containing 6 equiv of LiCl at 100 °C for 1 day. (c) 47.6% of **45** and 25.6% of **46** were also obtained. (d) 11% of **40** and 47% of **41** were also obtained. (e) 44% of **47** was also obtained.

17. Although this procedure produces **17** in good yield from **3**, alkylation of the dianion of ethyl 2-chloroacetoacetate produces **3** in only 44% yield. We therefore examined alternate methods for production of salicylate **17** from **2**, which can be prepared in 70% yield by alkylation of the dianion of methyl acetoacetate.

Oxidative Cyclization with $Mn(OAc)_3 \cdot 2H_2O$ and LiCl. The use of $Mn(OAc)_3 \cdot 2H_2O$ and LiCl as reported by Vinogradov and Nikishin provided a solution to this problem.[11] They explored the oxidation of ethyl acetoacetate by $Mn(OAc)_3 \cdot 2H_2O$ in the presence of LiCl and 1-hexene. They found that ethyl 2-chloroacetoacetate (**42**) was initially formed. Further oxidation led to a radical, which added to 1-hexene to give a radical, which was trapped by chloride to give dichloride **43** in 67% yield. We have shown that addition of LiCl to oxidative cyclization reactions produces similar results.[1d]



Reaction of β-keto ester **2** with 4 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 10 equiv of LiCl in acetic acid for 16 h (procedure D) gave a 48% yield of a single unassigned isomer of the expected dichloride **45**, a 6% yield of **17**, and a 26% yield of **46**. Dichloride **45** and monochloride **46** are at the salicylate oxidation level. Loss of two molecules of hydrogen chloride from **45** and one molecule of hydrogen chloride from **46** will give salicylate **17**. This transformation can be carried out by an E2C elimination[12] in acetic acid with excess LiCl at 100 °C.[13] Reaction of β-keto ester **2** with 4 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 4 equiv of LiCl in acetic acid for 1 day followed by workup and heating the crude product with 5 equiv of LiCl in acetic acid at 100 °C for 1 day (procedure E) gave a 71% yield of salicylate **17**. Similar results were obtained with LiBr in place of LiCl in the oxidative cyclization step.

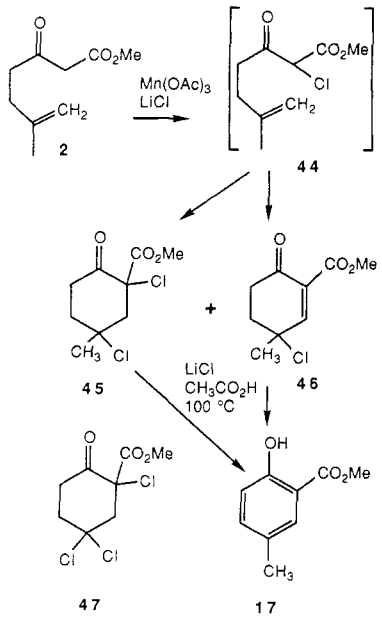
Table I shows the range of salicylates that can be prepared by this oxidative cyclization. Polymethyl salicylates **20**, **21**, and **22** were prepared using procedure E in 40%, 91%, and 51% yield, respectively. Complex mixtures of dichlorides were produced as expected from procedure D. The following conclusions can be drawn from examination of entries 1–8. 3-Methylsalicylates can be prepared in the highest yield. Introduction of methyl groups in the other positions results in decreased yields of salicylate.

We examined the use of this procedure to prepare biphenyls **23–25** (entries 9–11). Procedure E gives biphenyl **23** in a satisfactory yield of 44%. Biphenyls **24** and **25** are prepared in low yield by procedure A. Unfortunately, procedure E is not applicable since elimination of secondary chlorides is problematic. Similar problems occur in the attempted preparation of chlorosalicylate **26** since elimination of hydrogen chloride from a geminal dichloride is difficult. The major product from either procedure D or E is the trichloride **47**, which is formed in 44% yield.

(11) (a) Vinogradov, M. G.; Dolinko, V. I.; Nikishin, G. I. *Bull. Nat. Acad. Sci. USSR, Ser. Chem.* **1984**, 1884; *Izv. Akad. Nauk SSSR., Ser. Khim.* **1984**, 2065. (b) Vinogradov, M. G.; Dolinko, V. I.; Nikishin, G. I. *Ibid.* **1984**, 334; **1984**, 375.

(12) McLennan, D. J. *Tetrahedron* **1975**, *31*, 2999. Ford, W. T. *Acc. Chem. Res.* **1973**, *6*, 410.

(13) Heating the mixture obtained from **2** by procedure D in acetic acid at 100 °C without added LiCl gave **17** (41%) and recovered **45** (42.5%). This result suggests that **46** is easily converted to **17** in hot acetic acid, but that efficient conversion of **45** to **17** requires the presence of LiCl.



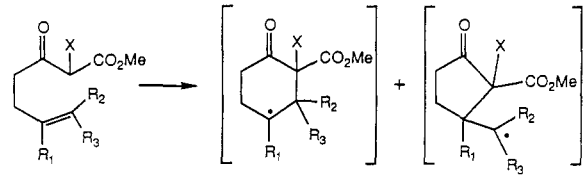
Tetralins **27** and **28** are formed in acceptable yields.

Oxidation of 1,3-diketone **15** results in the formation of 2-hydroxybenzophenone (**29**) in 47% yield. This yield contrasts with a 96% yield (apparently based on 50% conversion with use of 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$) for the conversion of 7-octene-2,4-dione to 2-hydroxyacetophenone reported by Peterson et al.[4] We obtained a ≈25% yield of **29** by using 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ either as described above or by Peterson's modification of our procedure.[4]

These oxidative cyclizations produce phenols, which are themselves easily oxidized.[3] Even though the presence of the ester will deactivate the phenol, overoxidation is a potentially serious problem. Treatment of methoxy-substituted 2-hydroxybenzophenones with $Mn(OAc)_3 \cdot 2H_2O$ in acetic acid at reflux has been developed as a xanthone synthesis.[14] No reaction occurred, however, on treatment of **29** with $Mn(OAc)_3 \cdot 2H_2O$ in acetic acid for 1 day at 25 °C. We did find that treatment of **20** with 1 equiv of $Mn(OAc)_3 \cdot 2H_2O$ in acetic acid for 10 h at 25 °C led to ≈85% decomposition. The low yields in many cases are probably due to competitive oxidation of the salicylate product. The effect of substituents on the yield may therefore be due to either decreasing the rate of oxidative cyclization or increasing the rate of oxidative destruction of the salicylate product.

Cyclization Regiochemistry. Cyclizations of unstabilized 5-hexenyl radicals typically give the cyclopentane methyl radical in a kinetically controlled process.[15] Cyclizations of stabilized 5-hexenyl radicals give mixtures rich in the more stable cyclohexyl radical since the cyclization of stabilized radicals is reversible.[15] These $Mn(OAc)_3 \cdot 2H_2O$-based oxidative cyclizations involve stabilized free radicals, so that cyclohexyl radicals should be major products in most cases.

From our studies of $Mn(OAc)_3 \cdot 2H_2O$-initiated cyclizations of a variety of ϵ,ζ-unsaturated β-keto esters **48**, the following conclusions can be drawn about the regiochemistry of cyclization. A tertiary radical will be formed exclusively in competition with a primary or secondary radical regardless of the ring size. Formation of **49**, R_1 = alkyl, will occur exclusively if R_2 = H and R_3 = H or alkyl.



Cyclohexyl radical **49** should also be the major product with an unsubstituted double bond (**48**, $R_1 = R_2 = R_3$ = H). Cyclization of **48** with an unsubstituted double bond and X = alkyl, benzyl, or allyl gives a 3:1 mixture of **49** and **50**.[1] As indicated in Table I, cyclization of **48** with an unsubstituted double bond and X = H appears to lead exclusively to products derived from **49** (X = H, $R_1 = R_2 = R_3$ = H). There are several possible explanations for this observation. The most likely one is that products derived from **50** are converted to uncharacterizable oligomers by overoxidation. Alternatively, formation of **50** might be reversible, with cyclopentane products obtained only when the primary radical can be trapped by addition to X = benzyl, etc. Finally, we have shown that the rate-determining step in the oxidation is alkene dependent if X = H and alkene independent if X ≠ H.[1d] Since the mechanism differs depending on the nature of X, it is possible that **50** is not formed, even as a kinetic product with X = H.

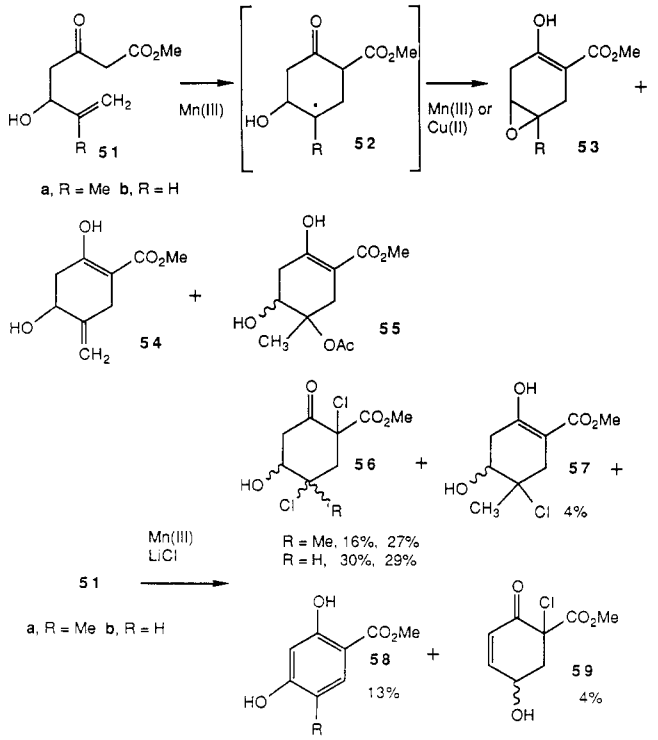
If the radicals of both **49** and **50** are secondary, **50** will be the major product. Cyclization of **48** ($R_1 = R_2$ = H, R_3 = alkyl) gives a 4:1 mixture of **50** and **49**.[1a,d] The natural preference for the cyclopentane methyl radical predominates since a secondary radical is formed in both products. This oxidative cyclization–aromatization procedure is therefore not applicable to the synthesis of 6-alkylsalicylates.[1a]

Cyclization of ϵ,ζ-Unsaturated δ-Hydroxy β-Keto Esters. We also examined the oxidative cyclization of δ-hydroxy β-keto esters **51a** and **51b** in an attempt to prepare resorcinols **58a** and **58b**. Although these attempts have met with limited success, we have found that oxidative cyclization of **51a** and **51b** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ in acetic acid for 3 h at 25 °C gave **53a** and **53b** in 50% and 30% yield, respectively. Use of $Cu(OAc)_2 \cdot H_2O$ as a cooxidant is not necessary for the formation of epoxide. Lower yields of **53** are obtained in the presence of $Cu(OAc)_2 \cdot H_2O$ (vide infra). Presumably radical **52** is formed initially. The hydroxyl group then interacts with the radical to give a complex, which is oxidized by $Mn(OAc)_3 \cdot 2H_2O$ with loss of a proton to give an epoxide directly.[16] The cation is not a likely intermediate since secondary radical **52b** should not be oxidized to a cation by $Mn(OAc)_3 \cdot 2H_2O$. The formation of an epoxide from oxidation of a β-hydroxy radical by $Mn(OAc)_3 \cdot 2H_2O$ is an unexpected reaction. We are currently exploring the scope and utility of this unusual epoxide synthesis.

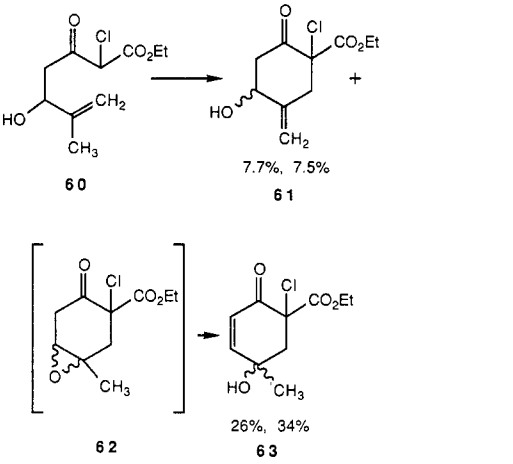
Alternate methods of cyclization also failed to convert **51** efficiently to **58**. Oxidation of **51a** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ gave **53a** in 21% yield, **54** in 12% yield, and **55** in 11% yield. Treatment of **51a** by procedure D gave two diastereomers of **56a** in 16% and 27% yield, **57** in 4% yield, and **58a** in 13% yield. Treatment of **51b** by procedure D gave two diastereomers of **56b** in 30% and 29% yield and 4% of **59**.

(14) Ueda, S.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 193.
(15) (a) Surzur, J-M. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum: New York, 1982; Vol. 2, pp 121–295 and references cited therein. (b) Beckwith, A. L. *J. Tetrahedron* **1981**, *37*, 3073. (c) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.

(16) For the preparation of epoxides by the oxidation of β-hydroxyalkyl radicals, see: Corey, E. J.; Casanova, J., Jr. *J. Am. Chem. Soc.* **1963**, *85*, 165. Corey, E. J.; Casanova, J., Jr.; Vatakencherry, P. A.; Winter, R. *Ibid.* **1963**, *85*, 169.

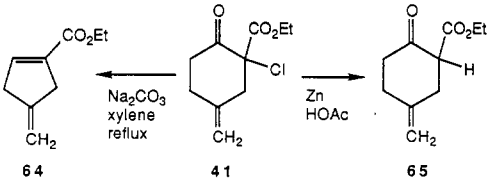


Unfortunately, dichloride **56** could not be converted to resorcinol **58** by heating in acetic acid with LiCl. Treatment of **60** by procedure B gave **61** as a 1:1 mixture of diastereomers in 15% yield and **63** as a 4:3 mixture of diastereomers in 60% yield. Cyclohexenone **63** is probably formed by opening of epoxide **62**. The presence of the chlorine prevents enolization of the ketone toward the ester so that elimination of the β,γ-unsaturated epoxide occurs during the course of the oxidative cyclization.



Since methylenecyclohexane **41** is readily available from **3** we decided to explore its reactivity. Dehydrochlorination–decarbonylation carried out with sodium carbonate in xylene at reflux by the procedure of Büchi[17] gave ester **64**[18] in 91% yield. Reduction of **41** with zinc in acetic acid gave ester **65**[19] in 95% yield.

We have shown that oxidative cyclization and aromatization of 3-oxo-6-heptenoate esters provides a general route to a variety of salicylate derivatives, cyclohexanone



derivatives such as **41** and **45**, and epoxides such as **53a** and **53b**. We are continuing to explore the utility of $Mn(OAc)_3 \cdot 2H_2O$-based oxidative cyclizations.

Experimental Section

Materials and Methods. NMR spectra were recorded on Varian EM-390 and XL-300 spectrometers in $CDCl_3$. Chemical shifts are reported in δ, and coupling constants are reported in hertz. IR spectra were obtained on a Perkin-Elmer 683 spectrometer. All air-sensitive reactions were run under nitrogen in flame-dried glassware with magnetic stirring. Reagents were added via oven-dried syringes through septa. All solvents for air- or moisture-sensitive reactions were dried by standard procedures.

Preparation of Unsaturated β-Keto Esters 1–3, 5–9, 11, 12, 14, and 15 (Procedures A–C, E, F). The following general procedure is a modification of that described by Huckin and Weiler.[5] All operations were carried out at 0 °C under a nitrogen atmosphere. One equivalent of the appropriate acetoacetate (typically 15.0–25.0 mmol) was added neat over ≈10 min to a stirred suspension of 1.1 equiv of sodium hydride (60% dispersion in mineral oil) in sufficient THF to result in a 0.4–0.5 M solution of the starting ester. The light yellow solution was stirred for 20 min before the addition of 1.1 equiv of *n*-BuLi (≈2.5 M solution in hexanes) over a 15–25-min period. After being stirred for an additional 20 min, the dark yellow to red mixture of dianion was treated with 1.1 equiv of the appropriate allylic halide or α,β-unsaturated aldehyde (added rapidly via syringe). The immediate formation of a thick precipitate usually followed the addition of halide. The reaction mixture was then stirred for 10–25 min before the ice bath was removed. Careful hydrolysis with a solution of 5 mL of concentrated HCl in 10 mL of H_2O was performed after 1 h at room temperature. The product mixture was diluted with H_2O and extracted three times with diethyl ether. The organic layers were combined, washed with H_2O, dried ($MgSO_4$), and concentrated under reduced pressure. Purification procedures and spectral and analytical data are given in the supplementary material.

General Procedure for the Preparation of 4, 10, and 13. Methyl 5-methyl-3-oxo-6-heptenoate (**4**) was prepared from 4-methyl-5-hexen-2-one[20] by the procedure of Mander and Sethi.[8] A solution of lithium diisopropylamide (10.8 mmol) in 25 mL of THF was prepared at 0 °C under an atmosphere of nitrogen. This mixture was cooled to −78 °C, and a solution of 1.011 g (9.01 mmol) of 4-methyl-5-hexen-2-one[20] in 5 mL of THF was added rapidly with a dropping funnel. The solution was warmed to 0 °C, stirred for 1 h, and again brought to −78 °C. HMPA (1.57 mL, 1.62 g, 9.04 mmol) was added via syringe. Ten minutes later, a solution of 0.922 g (10.8 mmol) of methyl cyanoformate[9] in 3 mL of THF was added via syringe. The solution was stirred for 15 min at −78 °C, and the reaction mixture was hydrolyzed by pouring into 50 mL of rapidly stirring ice-cold water. The aqueous layer was extracted twice with diethyl ether, and the organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. Evaporative distillation (95–100 °C; 18 Torr) of the resulting light yellow oil gave 0.960 g (62.6%) of **4** containing ≈7% of its enolic form [characteristic ^1H NMR peaks of enol: δ 12.02 (s), 3.73 (s)]: ^1H NMR δ 5.75 (ddd, 1, J = 17.2, 10.4, 6.8), 5.04–4.94 (m, 2), 3.74 (s, 3), 3.44 (s, 2), 2.80–2.67 (m, 1), 2.60 (dd, 1, J = 16.6, 6.6), 2.49 (dd, 1, J = 16.6, 7.2), 1.04 (d, 3 J = 6.7); ^{13}C NMR δ 201.5, 167.4, 142.2, 113.4, 52.2, 49.4 (2), 33.0, 19.6; IR (neat) 3090, 3071, 1767, 1733, 1658 cm^{-1}. Anal. Calcd for $C_9H_{14}O_3$: 170.0943. Found: 170.0936.

General Procedure for the Preparation of 51a, 51b, and 60. Methyl 5-hydroxy-6-methyl-3-oxo-6-heptenoate (**51a**) was prepared via the general procedure outlined above for dianion alkylation by using methyl acetoacetate (2.090 g, 18.0 mmol), 60%

(17) (a) Büchi, G.; Hochstrasser, U.; Pawlak, W. *J. Org. Chem* **1973**, *38*, 4348. (b) Takeda, A.; Shinhama, K.; Tsuboi, S. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1831.

(18) Trost, B. M.; Balkovec, J. M.; Angle, S. R. *Tetrahedron Lett.* **1986**, *27*, 1445.

(19) Eaton, P. E.; Temme, G. H. *J. Am. Chem. Soc.* **1973**, *95*, 7508.

(20) Kimel, W.; Cope, A. C. *J. Am. Chem. Soc.* **1943**, *65*, 1992.

sodium hydride dispersion in mineral oil (0.7965 g, 19.9 mmol), 2.54 M *n*-BuLi (7.80 mL, 19.8 mmol), and methacrolein (1.64 mL, 19.8 mmol) in THF (40 mL). After being stirred for 25 min at 0 °C, the bright blue-green reaction mixture was hydrolyzed and worked up under normal conditions to give 3.727 g of crude product. Flash chromatography of 1.548 g on silica gel (60:40 hexane–EtOAc) afforded 1.049 g (75.4%) of **51a** containing ≈8% of its enolic form [characteristic ^{1}H NMR peaks of enol: δ 12.10 (s), 5.08 (s), 3.74 (s)]: ^{1}H NMR δ 5.02 (m, 1), 4.87 (m, 1), 4.53 (br dd, 1, *J* = 7.4, 4.9), 3.75 (s, 3), 3.54 (s,2), 2.96 (br s, 1), 2.78 (d, 1 *J* = 7.4), 2.78 (d, 1, *J* = 4.9), 1.75 (br s, 3); ^{13}C NMR δ 202.8, 167.4, 145.5, 111.3, 70.9, 52.3, 49.6, 48.1, 18.1; IR (neat) 3490, 3080, 1747, 1725, 1652, 1634 cm^{-1}. Anal. Calcd for $C_9H_{12}O_3$ (M – H_2O): 168.0787. Found: 168.0789.

General Procedures for Oxidative Cyclization of Unsaturated β-Keto Esters or β-Diketones. A. Use of 4 Equiv of $Mn(OAc)_3·2H_2O$ and 1 Equiv of $Cu(OAc)_2·H_2O$. A 25-mL flask was flame-dried under vacuum and allowed to cool under an atmosphere of nitrogen. The flask was charged with the appropriate amount of the unsaturated β-keto ester (typically 1 mmol), 4 equiv of $Mn(OAc)_3·2H_2O$, 1 equiv of $Cu(OAc)_2·H_2O$, and sufficient glacial acetic acid to result in a 0.1 M solution of the starting material. The mixture was then stirred at room temperature until the reddish-brown color of the manganese had dissipated (this coincides with the reaction becoming a bright blue-turquoise color from dissolved copper salts). Reactions were normally complete in 24–48 h. At this point the reaction mixture was diluted with H_2O and extracted successively with three portions of methylene chloride. Small amounts of unreacted Mn(III) salts were reduced to water-soluble Mn(II) salts during work up by the addition of a few drops of a 10% aqueous sodium bisulfite solution. The combined organic layers were then carefully neutralized by the addition of adequate amounts of a saturated aqueous solution of sodium bicarbonate. The methylene chloride layer was dried ($MgSO_4$) and concentrated via rotary evaporation to give crude product.

B. Use of 2 Equiv of $Mn(OAc)_3·2H_2O$ and 1 Equiv of $Cu(OAc)_2·H_2O$. This procedure was carried out as described above for A except that only 2 equiv of $Mn(OAc)_3·2H_2O$ were used.

C. Use of 2 Equiv of $Mn(OAc)_3·2H_2O$ and 1 Equiv of $Cu(OAc)_2·H_2O$. Subsequent Heating of the Crude Product in a Mixture of Glacial Acetic Acid and Trifluoroacetic Acid. The appropriate unsaturated α-chloro β-keto ester, 2 equiv of $Mn(OAc)_3·2H_2O$, and 1 equiv of $Cu(OAc)_2·H_2O$ were reacted as described above in procedure A. The usual work up gave crude product, which was dissolved in a 60:40 mixture of glacial acetic acid and trifluoroacetic acid, respectively (enough solvent was used to make an ≈0.1 M solution of the intermediate). This solution was then heated to 120 °C for 9–10 h under a nitrogen atmosphere. The dark brown mixture was cooled to room temperature, diluted with H_2O, and worked up as described in procedure A.

D. Use of 4 Equiv of $Mn(OAc)_3·2H_2O$ and an Excess of Lithium Chloride. A mixture of the β-keto ester (usually 1 mmol), 4 equiv of $Mn(OAc)_3·2H_2O$, and 4–10 equiv of LiCl in glacial acetic acid (a quantity of solvent was employed such that an ≈0.1 M solution of the starting material resulted) was prepared under nitrogen in a flame-dried 25-mL flask. These reagents were stirred at room temperature until the $Mn(OAc)_3·2H_2O$ had been completely consumed. This was evidenced by the disappearance of its characteristic brick-red color and typically occurred after 12–36 h of reaction time. Workup was performed as outlined above in procedure A.

E. Use of 4 Equiv of $Mn(OAc)_3·2H_2O$ and an Excess of Lithium Halide (Chloride or Bromide). Subsequent Heating of the Crude Product with Lithium Chloride in Glacial Acetic Acid. Approximately 1 mmol of the starting unsaturated β-keto ester was treated with $Mn(OAc)_3·2H_2O$ and LiX exactly as described above in procedure D. The crude product from this reaction was then heated under nitrogen with 5–6 equiv of LiCl in glacial acetic acid (enough solvent was used to produce an ≈0.2 M solution of the intermediate) at 100 °C (oil bath temperature) for 16–28 h. The reaction mixture was allowed to cool to room temperature and was worked up as usual (see procedure A).

Preparation of Methyl Salicylate (16). Reaction of **1** (0.076 g, 0.49 mmol) by procedure A followed by filtration through silica gel (80:20 hexane–EtOAc) afforded 0.057 g (78%) of **16**: ^{1}H NMR δ 10.76 (s, 1), 7.83 (dd, 1, *J* = 8.1, 2.7), 7.45 (ddd, 1, *J* = 9.7, 7.8, 2.3), 6.98 (dd, 1, *J* = 8.8, 1.2), 6.88 (ddd, 1 *J* = 9.7, 7.5, 1.2), 3.95 (s, 3); ^{13}C NMR δ 170.5, 161.5, 135.6, 129.8, 119.1, 117.5, 112.3, 52.2; IR (neat) 3200, 2970, 1750, 1745, 1690, 1685, 1620, 1590, 1490, 1445, 1380, 1335, 1310, 1260, 1220, 1160, 1095 cm^{-1}.

Preparation of Methyl (or Ethyl) 5-Methylsalicylate (17). Reaction of **2** (0.1705 g, 1.00 mmol) by procedure A followed by purification by filtering through silica gel with CH_2Cl_2 as eluent gave 0.0278 g (16.7%) of **17**.[21] ^{1}H NMR δ 10.56 (s, 1), 7.62 (d, 1, *J* = 2.0), 7.27 (dd, 1, *J* = 8.4, 2.0), 6.88 (d, 1, *J* = 8.4), 3.93 (s, 3), 2.27 (s, 3); ^{13}C NMR δ 170.5, 159.4, 136.6, 129.5, 128.2, 117.2, 111.8, 52.1, 20.3; IR (neat) 3320, 3024, 3000, 1678, 1615, 1596 cm^{-1}.

Reaction of **3** (0.2191 g, 1.00 mmol) by procedure C followed by flash chromatography on silica gel (90:10 hexane–EtOAc) gave 53.4 mg (29.6%) of the ethyl ester of **17**, 101.9 mg (47.0%) of **41**, and 24.5 mg (11.3%) of **40** as a mixture of isomers.

The data for the ethyl ester of **17**.[22] ^{1}H NMR δ 10.65 (s, 1), 7.62 (br d, 1, *J* = 2.4), 7.25 (dd, 1, *J* = 8.5, 2.4), 6.87 (d, 1, *J* = 8.5), 4.39 (q, 2, *J* = 7.1), 2.28 (s, 3), 1.41 (t, 3, *J* = 7.1); ^{13}C NMR δ 170.1, 159.5, 136.5, 129.5, 128.1, 117.2, 112.1, 61.2, 20.3, 14.2; IR (neat) 3180, 1675, 1616, 1594 cm^{-1}.

The data for ethyl 1-chloro-5-methylene-2-oxocyclohexane-1-carboxylate (**41**): ^{1}H NMR δ 5.07 (br s, 1), 5.03 (br s, 1), 4.29 (q, 2, *J* = 7.0), 3.44 (d, 1, *J* = 14.2), 2.99–2.86 (m, 1), 2.77 (d, 1, *J* = 14.2), 2.62–2.50 (m, 3), 1.31 (t, 3, *J* = 7.0); ^{13}C NMR δ 198.7, 166.7, 139.1, 115.2, 72.4, 62.9, 46.2, 38.6, 33.3, 13.8; IR (neat) 3102, 3000, 1760, 1748, 1668 cm^{-1}. Anal. Calcd for $C_{10}H_{13}ClO_3$: 216.0554. Found: 216.0564.

Reaction of **3** (0.2202 g, 1.01 mmol) by procedure C gave crude dark brown product, which was passed through a small column of silica gel (90:10 hexane–EtOAc) to give 0.1293 g (71.3%) of the ethyl ester of **17**.

Reaction of **2** (0.1705 g, 1.00 mmol) by procedure D with 10 equiv of LiCl for 16 h followed by flash chromatography on silica gel (80:20 hexane–EtOAc) gave 9.3 mg (5.6%) of **17**, 114.0 mg (47.6%) of **45**, and 52.0 mg (25.6%) of **46**.

The data for methyl 1,5-dichloro-5-methyl-2-oxocyclohexane-1-carboxylate (**45**): ^{1}H NMR δ 3.85 (s, 3), 3.39 (dd, 1, *J* = 14.9, 3.8), 3.27 (ddd, 1, *J* = 14.9, 14.2, 5.8), 2.68 (ddd, 1, *J* = 14.9, 4.1, 2.8), 2.41 (d, 1, *J* = 14.9), 2.34 (dddd, 1, *J* = 14.4, 5.8, 3.8, 2.8), 2.10 (ddd, 1, *J* = 14.4, 14.2, 4.1), 1.73 (s, 3); ^{13}C NMR δ 197.4, 168.1, 70.9, 67.7, 53.8, 53.7, 41.6, 36.8, 32.7; IR (neat) 1753, 1743 cm^{-1}. Anal. Calcd for $C_9H_{12}Cl_2O_3$: 238.0165. Found: 238.0171.

The data for methyl 3-chloro-3-methyl-6-oxo-1-cyclohexene-1-carboxylate (**46**): ^{1}H NMR δ 7.35 (d, 1, *J* = 1.7), 3.83 (s, 3), 2.91 (ddd, 1, *J* = 16.6, 11.9, 4.5), 2.58 (ddd, 1, *J* = 16.6, 4.5, 4.1), 2.50 (dddd, 1, *J* = 14.3, 4.5, 4.5, 1.7), 2.32 (ddd, 1, *J* = 14.3, 11.9, 4.1), 1.86 (s, 3); ^{13}C NMR δ 193.0, 164.3, 154.1, 129.9, 63.4, 52.5, 38.1, 35.5, 31.4; IR (neat) 1747, 1725, 1695 cm^{-1}.

Reaction of **2** (0.1739 g, 1.02 mmol) by procedure E followed by chromatography on silica gel (90:10 hexane/EtOAc) gave 0.1196 g (70.4%) of compound **17**.

Preparation of Methyl 5-Chlorosalicylate (26). Reaction of **12** (0.1885 g, 0.989 mmol) by procedure A followed by filtration of the crude product through silica gel (80:20 hexane/EtOAc) gave 19.8 mg (10.7%) of **26**:[23] ^{1}H NMR δ 10.68 (s, 1), 7.80 (d, 1, *J* = 2.7), 7.40 (dd, 1, *J* = 8.9, 2.7), 6.93 (d, 1, *J* = 8.9), 3.96 (s, 3); ^{13}C NMR δ 169.5, 160.1, 135.6, 129.1, 127.8, 119.1, 113.2, 52.6; IR (neat) 1684, 1614 cm^{-1}.

Reaction of **12** (0.1906 g, 1.00 mmol) by procedure E followed by chromatography of the crude product on silica gel (85:15 hexane/EtOAc) gave 26.6 mg (14.3%) of **26** followed by 0.1152 g (44.4%) of methyl 1,5,5-trichloro-2-oxocyclohexane-1-carboxylate (**47**): ^{1}H NMR δ 3.88 (dd, 1, *J* = 14.8, 3.6), 3.87 (s, 3), 3.22–3.08 (m, 1), 3.01 (d, 1, *J* = 14.8), 2.92–2.64 (m, 3); ^{13}C NMR δ 194.9, 167.3, 84.0, 69.7, 56.3, 54.0, 45.7, 36.9; IR (neat) 1755, 1745, 1680 cm^{-1}. Anal. Calcd for $C_8H_9Cl_3O_3$: 257.9619. Found: 257.9610. Virtually identical results were obtained from procedure D.

Cyclization of Methyl 5-Hydroxy-6-methyl-3-oxo-6-heptenoate (51a) with 2 Equiv of $Mn(OAc)_3·2H_2O$. A mixture

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(22) McCulloch, A. W.; McInnes, A. G. *Can. J. Chem.* **1971**, *49*, 3152.
(23) Baker, W.; Downing, D. F.; Hewitt-Symonds, A. E.; McOmie, J. F. W. *J. Chem. Soc.* **1952**, 3796.

of 0.1730 g (0.9291 mmol) of **51a** and 0.5405 g (2.016 mmol) of $Mn(OAc)_3 \cdot 2H_2O$ in 10 mL of HOAc was stirred under nitrogen at room temperature for 3 h. Normal workup furnished 0.1707 g of crude material, which was purified by flash chromatography on silica gel (70:30 hexane/EtOAc) to give 85.3 mg (49.9%) of **53a** followed by 10.3 mg (4.5%) of **55**.

Data for 4-carbomethoxy-3-hydroxy-6-methyl-7-oxabicyclo-[4.1.0]hept-3-ene (**53a**): ^{1}H NMR δ 12.19 (s, 1), 3.75 (s, 3), 3.13 (br s, 1), 2.87 (dddd, 1, J = 17.7, 1.7, 1.7, 1.7), 2.81 (br d, 1, J = 19.1), 2.75 (br d, 1, J = 19.1), 2.51 (ddd, 1, J = 17.7, 1.7, 1.7), 1.43 (s, 3); ^{13}C NMR δ 172.4, 167.2, 93.4, 57.7, 56.7, 51.6, 30.3, 28.0, 22.7; IR (neat) 1747, 1720, 1667, 1626 cm^{-1}. Anal. Calcd for $C_9H_{12}O_4$: 184.0736. Found: 184.0735.

Data for methyl 5-acetoxy-2,4-dihydroxy-5-methyl-1-cyclohexene-1-carboxylate (**55**): ^{1}H NMR δ 12.10 (s, 1), 4.18 (br dd, 1, J = 6.6, 6.3), 3.76 (s, 3), 2.93 (br d, 1, J = 16.3), 2.76–2.29 (m, 3), 2.03 (s, 3), 1.54 (s, 3); IR (neat) 3460, 1725, 1660, 1620 cm^{-1}.

Cyclization of Methyl 5-Hydroxy-6-methyl-3-oxo-6-heptenoate (51a) by Procedure B. Reaction of **51a** (0.1842 g, 0.989 mmol) by procedure B followed by flash chromatography on silica gel (70:30 hexane/EtOAc) gave 34.3 mg (20.9%; 24.6% corrected for unreacted **51a**) of **17**, 38.9 mg (21.3%; 25.2% corrected) of **53a**, 22.8 mg (12.5%; 14.7% corrected) of **54**, 25.6 mg (10.6%; 12.5% corrected) of **55**, and 27.9 mg (0.150 mmol) of recovered **51a**.

Data for methyl 2,4-dihydroxy-5-methylene-1-cyclohexene-1-carboxylate (**54**): ^{1}H NMR δ 12.08 (s, 1), 5.07 (dddd, 1, J = 1.3, 1.3, 1.3, 1.3), 4.96 (dddd, 1, J = 1.4, 1.3, 1.3, 1.1), 4.61 (br dd, 1, J = 6.3, 5.4), 3.78 (s, 3), 3.17 (br d, 1, J = 17.6), 3.00 (ddd, 1, J = 17.6, 1.3, 1.3), 2.76–2.68 (m, 1), 2.46 (dddd, 1, J = 17.8, 6.3, 1.4, 0.9); IR (neat) 3450, 3076, 1739, 1717, 1660, 1620 cm^{-1}.

Cyclization of Methyl 5-Hydroxy-6-methyl-3-oxo-6-heptenoate (51a) by Procedure D. Reaction of **51a** (0.1882 g, 1.01 mmol) by procedure D followed by flash chromatography on silica gel (70:30 hexane/EtOAc) gave 2.0 mg (1.2%) of **17**, 23.7 mg (12.9%) of **58a**, 8.6 mg (3.9%) of **57**, 41.1 mg (15.9%) of one diastereomer of **56a**, and 70.1 mg (27.2%) of a second diastereomer of **56a**.

Data for methyl 4-hydroxy-5-methylsalicylate (**58a**):[24] ^{1}H NMR δ 10.78 (s, 1), 7.59 (s, 1), 6.37 (s, 1), 5.59 (s, 1), 3.91 (s, 3), 2.17 (s, 3); ^{13}C NMR δ 170.4, 161.7, 160.3, 131.9, 116.0, 105.2, 102.6, 51.9, 14.9; IR (neat) 3320, 3230, 1737, 1663, 1617 cm^{-1}.

Data for methyl 5-chloro-2,4-dihydroxy-5-methyl-1-cyclohexene-1-carboxylate (**57**): ^{1}H NMR δ 12.11 (s, 1), 4.01 (br dd, 1, J = 7.2, 5.9), 3.78 (s, 3), 2.88 (dddd, 1, J = 18.8, 5.9, 1.1, 1.1), 2.84 (br ddd, 1, J = 16.1, 1.1, 1.1), 2.73 (br d, 1, J = 16.1), 2.35 (dddd, 1, J = 18.8, 7.2, 1.7, 1.1), 1.59 (s, 3); IR (neat) 3480, 1743 (s), 1660 (vs), 1620 (s) cm^{-1}.

Data for the less polar diastereomer of methyl 1,5-dichloro-4-hydroxy-5-methyl-2-oxocyclohexane-1-carboxylate (**56a**): ^{1}H NMR δ 4.26 (m, 1), 3.84 (s, 3), 3.59 (dd, 1, J = 15.1, 2.9), 3.23 (dd, 1, J = 14.8, 2.0), 2.85 (d, 1, J = 14.8), 2.77 (dd, 1, J = 15.1, 3.6), 1.73 (s, 3); ^{13}C NMR δ 196.6, 168.2, 77.0, 70.7, 68.3, 53.8, 47.9, 44.6, 28.5; IR (neat) 3390, 1740 (vs), 1667 (w), 1623 (w) cm^{-1}.

Data for the more polar diastereomer of methyl 1,5-dichloro-4-hydroxy-5-methyl-2-oxocyclohexane-1-carboxylate (**56a**): ^{1}H NMR δ 3.85 (s, 3), 3.77 (m, 1), 3.46 (d, 1, J = 15.4), 3.12 (dd, 1, J = 14.2, 11.3), 3.00 (dd, 1, J = 14.2, 4.7), 2.46 (br s, 1), 2.32 (d, 1, J = 15.4), 1.77 (s, 3); ^{13}C NMR δ 194.5, 167.6, 74.7, 73.1, 70.6, 53.9, 48.9, 45.5, 28.8; IR (neat) 3420, 1736 (vs), 1624 (w) cm^{-1}.

Cyclization of Methyl 5-Hydroxy-3-oxo-6-heptenoate (51b) with 2 Equiv of $Mn(OAc)_3 \cdot 2H_2O$. The following reagents were stirred at room temperature under nitrogen for 3 h: **51b** (0.1708 g, 0.9920 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (0.5401 g, 2.015 mmol), HOAc (10 mL). The usual workup resulted in 0.1608 g of a crude product mixture that was purified by bulb-to-bulb distillation (60–80 °C; 0.10 Torr) to give 50.7 mg (30.0%) of 4-carbomethoxy-3-hydroxy-7-oxabicyclo[4.1.0]hept-3-ene (**53b**): ^{1}H NMR δ 12.22 (s, 1), 3.76 (s, 3), 3.34 (m, 2), 2.98 (br d, 1, J = 18.0), 2.84 (br d, 1, J = 19.8), 2.71 (br d, 1, J = 19.8), 2.60 (br d, 1, J = 18.0); ^{13}C NMR δ 172.5, 167.0, 92.6, 51.6, 50.9, 50.7, 29.4, 22.9; IR (neat) 3004, 1747, 1717, 1664, 1620 cm^{-1}. Anal. Calcd for $C_8H_{10}O_4$: 170.0579. Found: 170.0587.

(24) Whalley, W. B. *J. Chem. Soc.* **1957**, 1833.

Cyclization of Methyl 5-Hydroxy-3-oxo-6-heptenoate (51b) by Procedure B. Reaction of **51b** (0.1743 g, 1.01 mmol) by procedure B followed by flash chromatography on silica gel (70:30 hexane–EtOAc) gave 38.3 mg (22.2%; 26.3% when adjusted for 26.9 mg of recovered **51b**) of **53b**.

Cyclization of Methyl 5-Hydroxy-3-oxo-6-heptenoate (51b) by Procedure D. Reaction of **51b** (0.1754 g, 1.02 mmol) by procedure D followed by flash chromatography on silica gel (70:30 hexane–EtOAc) gave 8.5 mg (4.1%) of **59**, 73.9 mg (30.1%) of one diastereomer of **56b**, and 70.7 mg (28.8%) of a second diastereomer of **56b**.

Data for methyl 1-chloro-5-hydroxy-2-oxo-3-cyclohexene-1-carboxylate (**59**): ^{1}H NMR δ 6.97 (ddd, 1, J = 10.4, 2.2, 1.9), 6.10 (dd, 1, J = 10.4, 2.2), 4.98 (dddd, 1, J = 9.4, 5.1, 2.2, 2.2), 3.88 (s, 3), 3.17 (dd, 1, J = 14.4, 9.4), 2.93 (ddd, 1, J = 14.4, 5.1, 1.9); ^{13}C NMR δ 166.4, 149.4, 126.2, 67.9, 54.1, 49.9, 43.9 (ketone carbon not seen); IR (neat) 3450, 3066, 3008, 1769, 1744, 1699 cm^{-1}.

Data for the less polar diastereomer of methyl 1,5-dichloro-4-hydroxy-2-oxocyclohexane-1-carboxylate (**56b**): ^{1}H NMR δ 4.73 (ddd, 1, J = 11.7, 4.2, 2.1), 4.40 (br s, 1), 3.87 (s, 3), 3.42 (dd, 1, J = 14.5, 11.7), 3.32 (dd, 1, J = 15.2, 2.8), 2.74 (dd, 1, J = 15.2, 4.0), 2.68 (br s, 1), 2.55 (ddd, 1, J = 14.5, 4.2, 1.9); ^{13}C NMR δ 195.7, 166.1, 71.4, 70.7, 57.5, 54.0, 41.9, 39.7; IR (neat) 3400, 3006, 1740, 1662, 1620 cm^{-1}.

Data for the more polar diastereomer of methyl 1,5-dichloro-4-hydroxy-2-oxocyclohexane-1-carboxylate (**56b**): ^{1}H NMR δ 4.35 (ddd, 1, J = 10.2, 8.6, 4.4), 3.99 (ddd, 1, J = 10.3, 8.6, 5.1), 3.87 (s, 3), 3.14 (dd, 1, J = 14.7, 10.3), 2.97 (dd, 1, J = 14.7, 5.1), 2.92 (dd, 1, J = 15.1, 10.2), 2.79 (dd, 1, J = 15.1, 4.4); ^{13}C NMR δ 195.9, 166.5, 73.0, 70.3, 58.9, 54.0, 42.8, 41.0; IR (neat) 3380, 3057, 1755, 1741 cm^{-1}.

Cyclization of Ethyl 2-Chloro-5-hydroxy-6-methyl-3-oxo-6-heptenoate (60) by Procedure B. Reaction of **60** (0.1408 g, 0.600 mmol) by procedure B followed by flash chromatography on silica gel (70:30 hexane–EtOAc) gave 10.7 mg (7.7%) of one diastereomer of **61**, 10.4 mg (7.5%) of a second diastereomer of **61**, 35.8 mg (25.7%) of one diastereomer of **63**, and 47.2 mg (33.8%) of a second diastereomer of **63**.

Data for the less polar diastereomer of ethyl 1-chloro-4-hydroxy-5-methylene-2-oxocyclohexane-1-carboxylate (**61**): ^{1}H NMR δ 5.34 (br s, 1), 5.16 (br s, 1), 4.58 (br dd, 1, J = 6.4, 4.6), 4.31 (q, 2, J = 7.1), 3.72 (d, 1, J = 14.4), 3.25 (dd, 1, J = 14.3, 4.6), 2.66 (d, 1, J = 14.4), 2.63 (dd, 1, J = 14.3, 6.4), 1.32 (t, 3, J = 7.1); IR (neat) 3480, 1785, 1738 cm^{-1}. Anal. Calcd for $C_{10}H_{11}ClO_3$ (M – H_2O): 214.0397. Found: 214.0403.

Data for the more polar diastereomer of ethyl 1-chloro-4-hydroxy-5-methylene-2-oxocyclohexane-1-carboxylate (**61**): ^{1}H NMR δ 5.30 (br s, 1), 5.16 (br s, 1), 4.59 (br dd, 1, J = 5.5, 4.4), 4.28 (q, 2, J = 7.0), 3.33 (d, 1, J = 14.0), 3.10 (ddd, 1, J = 14.0, 1.1, 1.1), 2.97 (dd, 1, J = 14.5, 5.5), 2.84 (dd, 1, J = 14.5, 4.4), 1.30 (t, 3, J = 7.0); ^{13}C NMR δ 186.7, 141.9, 115.3, 67.6, 63.1, 47.4, 41.7, 13.9 (2 carbons not seen).

Data for the less polar diastereomer of ethyl 1-chloro-5-hydroxy-5-methyl-2-oxo-3-cyclohexene-1-carboxylate (**63**): ^{1}H NMR δ 6.77 (dd, 1, J = 10.3, 1.6), 6.05 (d, 1, J = 10.3), 4.32 (q, 2, J = 7.0), 3.08 (d, 1, J = 15.3), 2.65 (dd, 1, J = 15.3, 1.6), 1.44 (s, 3), 1.33 (t, 3, J = 7.0); ^{13}C NMR δ 187.5, 166.7, 152.8, 124.4, 72.2, 66.4, 63.5, 45.7, 28.9, 13.9; IR (neat) 3500, 1734, 1703 cm^{-1}.

Data for the more polar diastereomer of ethyl 1-chloro-5-hydroxy-5-methyl-2-oxo-3-cyclohexene-1-carboxylate (**63**): ^{1}H NMR δ 6.73 (dd, 1, J = 10.1, 1.8), 6.09 (d, 1, J = 10.1), 4.28 (q, 2, J = 7.0), 3.09 (dd, 1, J = 14.6, 1.8), 2.54 (d, 1, J = 14.6), 1.49 (s, 3), 1.29 (t, 3, J = 7.0); ^{13}C NMR δ 187.7, 168.9, 152.7, 125.4, 69.0, 67.5, 63.8, 48.2, 29.9, 13.6; IR (neat) 3500, 1798, 1733, 1705 cm^{-1}. Anal. Calcd for $C_{10}H_{13}ClO_4$: 232.0503. Found: 232.0502.

Ethyl 4-Methylene-1-cyclopentene-1-carboxylate (64). A mixture of 53.8 mg (0.248 mmol) of **41**, 0.2154 g (2.032 mmol) of sodium carbonate, and 0.5067 g of crushed glass in 2 mL of dry xylenes was stirred rapidly and heated to reflux under nitrogen for 36 h.[17] Solvent was removed by placing the crude reaction mixture on a 1.5 cm × 15.0 cm column of silica gel and eluting with 150 mL of hexane. Elution with 100 mL of CH_2Cl_2, followed by removal of solvent under reduced pressure, gave 34.4 mg (91.0%) of **64**:[18] ^{1}H NMR δ 6.79–6.75 (m, 1), 5.06–5.03 (m, 1), 5.03–5.00 (m, 1), 4.21 (q, 2, J = 7.2), 3.33–3.31 (m, 2), 3.27–3.24 (m, 2), 1.30 (t, 3, J = 7.2); ^{13}C NMR δ 164.8, 146.8, 141.8, 135.6,

108.4, 60.2, 39.8, 38.0, 14.2; IR (neat) 3080, 1719, 1672 cm^{-1}.

Ethyl 5-Methylene-2-oxocyclohexane-1-carboxylate (65). A solution of 54.2 mg (0.250 mmol) of **41** in 2 mL of HOAc was stirred with 0.1665 g (2.55 mmol) of zinc dust for 4.5 h under nitrogen at room temperature. Excess zinc was removed by filtration, and the residue was washed with CH_2Cl_2. Water (50 mL) was added to the filtrate, the organic layer was removed, and the aqueous layer was extracted twice with 20-mL portions of CH_2Cl_2. The organic layers were combined, neutralized with 25 mL of saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated under reduced pressure to give 43.5 mg (95.4%) of **65**[19] as a 4:1 mixture of enol and keto forms, respectively.

Data for the enol form of **65**: ^1H NMR δ 12.21 (s, 1), 4.85 (d, 1, J = 1.3), 4.80 (d, 1, J = 1.3), 4.23 (q, 2, J = 7.1), 2.97 (br d, 2, J = 1.3), 2.44–2.33 (m, 4), 1.32 (t, 3, J = 7.1); ^{13}C NMR δ 172.2, 171.5, 143.3, 109.5, 96.8, 60.3, 30.8, 30.4 (2), 14.3; IR (neat) 3074 (w), 1747 (m), 1720 (m), 1656 (s), 1619 (s) cm^{-1}.

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Registry No. **1**, 30414-57-4; **2**, 59529-68-9; **3**, 117369-82-1; **4**, 117369-83-2; **5**, 117369-84-3; **6**, 117369-85-4; **7**, 117369-86-5; **8**, 117369-87-6; **9**, 117369-88-7; **10**, 88681-86-1; **11**, 117369-89-8; **12**, 117369-90-1; **13**, 117369-91-2; **14**, 56028-92-3; **15**, 13163-77-4; **16**, 119-36-8; **17**, 22717-57-3; **17** (ethyl ester), 34265-58-2; **18**, 4670-56-8; **19**, 23287-26-5; **20**, 5628-60-4; **21**, 117369-92-3; **22**, 117369-93-4; **23**, 17504-13-1; **24**, 117369-94-5; **25**, 4906-69-8; **26**, 4068-78-4; **27**, 54815-88-2; **28**, 59604-96-5; **29**, 117-99-7; **40** (isomer 1), 117369-98-9; **40** (isomer 2), 117370-14-6; **41**, 117369-99-0; **45**, 117370-00-0; **46**, 117370-01-1; **47**, 117370-02-2; **51a**, 117369-96-7; **51b**, 62343-95-7; **53a**, 117370-03-3; **53b**, 117370-06-6; **55**, 117370-04-4; **56a**, 117370-05-5; **56b**, 117370-08-8; **58a**, 46174-31-6; **59**, 117370-07-7; **60**, 117369-97-8; **61** (isomer 1), 117370-09-9; **61** (isomer 2), 117370-10-2; **63** (isomer 1), 117370-11-3; **63** (isomer 2), 117370-12-4; **64**, 117370-13-5; **65**, 50635-46-6; $H_2C{=}CHCH_2Br$, 106-95-6; $H_2C{=}C(CH_3)CH_2Br$, 3017-69-4; (E)-$H_3CCH{=}C(CH_3)CH_2Br$, 57253-30-2; $H_2C{=}C(Ph)CH_2Br$, 3360-53-0; $H_2C{=}C(Cl)CH_2Br$, 4860-96-2; 1-bromomethylcyclohexene, 37677-17-1; methyl acetoacetate, 105-45-3; methyl 3-oxopentanoate, 30414-53-0; methyl chloroacetoacetate, 4755-81-1; methyl 4-phenyl-3-oxobutanoate, 37779-49-0; 1-phenylpentane-2,4-dione, 3318-61-4; 4-methyl-5-hexen-2-one, 61675-14-7; 4-phenyl-5-hexen-2-one, 50552-30-2; 1-acetyl-2-vinylcyclohexane, 117369-95-6; acrolein, 107-02-8; methacrolein, 78-85-3.

Supplementary Material Available: Experimental procedures and spectroscopic data for all compounds not described in the Experimental Section (8 pages). Ordering information is given on any current masthead page.

A Concise Synthesis of *d,l*-Methylenomycin A and *d,l-epi*-Methylenomycin A

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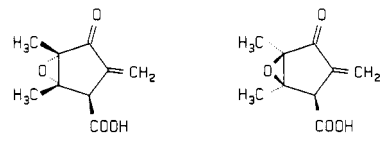
A cationic cyclopentaannelation reaction that was developed in our laboratories has been applied to the synthesis of *d,l*-methylenomycin A, a fungal metabolite that has been isolated from a strain of *Streptomyces violaceoruber*. The efficiency of the key reaction makes a very short total synthesis possible. A synthesis of *d,l-epi*-methylenomycin A has also been accomplished.

The synthesis of cyclopentanoids continues to be the focus of much research.[2] The isolation and structure elucidation of unusual cyclopentanoid natural products and the continuing interest in polyquinane chemistry accounts for this research activity. The family of methylenomycin antibiotics were isolated by Haneishi and coworkers from a *Streptomyces* strain.[3] Methylenomycin A is effective against Lewis lung carcinoma in mice.[4] Methylenomycin A and methylenomycin B are active against Gram-positive and Gram-negative bacteria and are cytotoxic in the KB assay.[3,5] The unprecedented structure of these fungal metabolites led to a flurry of synthetic activity that culminated in several successful total syntheses.[6] A cationic cyclopentaannelation reaction that was discovered in our laboratories offers an extremely straightforward and direct entry to these compounds.[7] We have reported the synthesis of some of the simpler members of this class of compounds, methylenomycin B, *d,l*-desepoxy-4,5-didehydromethylenomycin A, and *d,l*-desdihydroxy-4,5-didehydroxanthocidin.[8] We now report the total synthesis of *d,l*-methylenomycin A (**1**) and *d,l-epi*-methylenomycin A (**2**).



1 2

The retrosynthesis for **1** and **2** leads to tertiary alcohol **4** via *d,l*-desepoxy-4,5-didehydromethylenomycin A (**3**).

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