lactones where the trans lactone **8g** was the almost exclusive desired product.[29] **Cis-(*RS,SR*) lactone 7g**: ^{1}H NMR ($CDCl_3$) characteristic peaks δ 0.9 (d, J = 6 Hz, 3 H, β-CH_3), 5.65 (d, J = 6 Hz, 1 H, γ-H). **Trans-(*RR,SS*) lactone 8g**: mp 98-99 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 6 Hz, 3 H, β-CH_3), 2.35 (dd, J = 15, 6 Hz, 1 H), 2.82 (dd, J = 15, 6 Hz, 1 H), 2.8-3.0 (m, 1 H, β-H), 3.7 (s, 3 H), 5.08 (d, J = 6 Hz, 1 H, γ-H), 6.1 (t, J = 2 Hz, 1 H), 6.2 (s (br), 1 H), 6.7 (s (br), 1 H). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.16; H, 7.42; N, 8.12.

γ-Hydroxy-γ-(2-methoxyphenyl)-β-methylbutanoic Acid Lactone (7h and 8h). Cis-(*RS,SR*) lactone 7h: ^{1}H NMR ($CDCl_3$) δ 0.68 (d, J = 5 Hz, 3 H, β-CH_3), 2.35 (dd, J = 14, 3 Hz, 1 H), 2.85 (dd, J = 14, 6 Hz, 1 H), 2.95-3.1 (m, 1 H, β-H), 3.85 (s, 3 H), 5.82 (d, J = 5 Hz, 1 H, γ-H), 6.9 (d, J = 6 Hz, 1 H), 7.0 (t, J = 6 Hz, 1 H), 7.25-7.4 (m, 2 H). **Trans-(*RR,SS*) lactone 8h**: ^{1}H NMR ($CDCl_3$) δ 1.22 (d, J = 6 Hz, 3 H, β-CH_3), 2.28 (dd, J = 16, 8 Hz, 1 H), 2.45-2.65 (m, 1 H, β-H), 2.78 (dd, J = 16, 6 Hz, 1 H), 3.85 (s, 3 H), 5.38 (d, J = 6 Hz, 1 H, γ-H), 6.92 (d, J = 6 Hz, 1 H), 7.0 (t, J = 6 Hz, 1 H), 7.25-7.4 (m, 2 H). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.82; H, 6.75.

γ-Hydroxy-β-methyl-γ-[2-(methylthio)phenyl]butanoic Acid Lactone (7i and 8i). Cis-(*RS,SR*) lactone 7i: ^{1}H NMR ($CDCl_3$) δ 0.65 (d, J = 6 Hz, 3 H, β-CH_3), 2.35 (dd, J = 16, 2 Hz, 1 H), 2.5 (s, 3 H), 2.95 (dd, J = 16, 8 Hz, 1 H), 3.05-3.2 (m, 1 H, β-H), 5.9 (d, J = 6 Hz, 1 H, γ-H), 7.15-7.38 (m, 3 H), 7.42 (d, J = 6 Hz, 1 H). **Trans-(*RR,SS*) lactone 8i**: ^{1}H NMR ($CDCl_3$) δ 1.3 (d, J = 6 Hz, 3 H, β-CH_3), 2.28 (dd, J = 14, 6 Hz), 2.5 (s, 3 H), 3.75 (dd, J = 14, 6 Hz, 1 H), 2.7-3.0 (m, 1 H, β-H), 5.5 (d, J = 6 Hz, 1 H, γ-H), 7.15-7.25 (m, 1 H), 7.25-7.35 (m, 3 H). Anal. Calcd for $C_{12}H_{14}O_2S$: C, 64.84; H, 6.35. Found: C, 65.01; H, 6.42.

γ-Hydroxy-γ-[2-(methoxymethoxy)phenyl]-β-methylbutanoic Acid Lactone (7j and 8j). Cis-(*RS,SR*) lactone 7j: ^{1}H NMR ($CDCl_3$) δ 0.70 (d, J = 6 Hz, 3 H, β-CH_3), 2.35 (dd, J = 16, 3 Hz, 1 H), 2.88 (dd, J = 16, 7 Hz, 1 H), 3.0-3.12 (m, 1 H, β-H), 3.5 (s, 3 H), 5.22 (s, 2 H), 5.87 (d, J = 6 Hz, 1 H, γ-H), 7.03 (t, J = 6 Hz, 1 H), 7.12 (d, J = 6 Hz, 1 H), 7.3 (t, J = 6 Hz, 1 H), 7.38 (t, J = 6 Hz, 1 H). **Trans-(*RR,SS*) lactone 8j**: ^{1}H NMR ($CDCl_3$) characteristic peaks δ 1.2 (d, J = 6 Hz, 3 H, β-CH_3), 5.4 (d, J = 6 Hz, 1 H, γ-H). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.17; H, 6.89.

γ-Hydroxy-β-methyl-γ-[2-(methylsulfinyl)phenyl]butanoic Acid Lactone (7k and 8k). Cis-(*RS,SR*) lactone 7k: ^{1}H NMR ($CDCl_3$) δ 0.72 (d, J = 6 Hz, 1.5 H) and 0.76 (d, J = 6 Hz, 1.5 H), 2.38 (dd, J = 4.5, 1.5 Hz, 0.5 H) and 2.43 (dd, J = 4.5, 1.5 Hz, 0.5 H), 2.77 (s, 1.5 H) and 2.79 (s, 1.5 H), 2.8-3.1 (m, 2 H), 5.78 (d, J = 6 Hz, 0.5 H) and 6.02 (d, J = 6 Hz, 0.5 H), 7.4-7.7 (m, 3 H), 8.07 (dt, J = 4, 1.5 Hz, 1 H). **Trans-(*RR,SS*) lactone 8k**: characteristic peaks ^{1}H NMR ($CDCl_3$) δ 1.11 (d, J = 6 Hz, 0.5 H) and 1.15 (d, J = 6 Hz, 0.5 H), 5.45 (d, J = 5 Hz, 0.5 H) and 5.6 (d, J = 5 Hz, 0.5 H). Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92. Found: C, 60.73; H, 6.14.

γ-Hydroxy-β-methoxy-γ-phenylbutanoic Acid Lactones (10 and 11). In this case, the desired cis-(*RR,SS*) and trans-(*RS,SR*) lactones were easily separated in a column of flash silica gel (230-400 mesh), eluting with 3:7 ethyl acetate-hexane to give the less polar product as the trans lactone **11** and the most polar product as the cis lactone **10**,[30] total yield 78%. **Cis-(*RR,SS*) lactone 10**: ^{1}H NMR ($CDCl_3$) δ 2.78-2.88 (m, 2 H), 3.0 (s, 3 H), 4.18-4.25 (m, 1 H, β-H), 5.53 (d, J = 4 Hz, 1 H, γ-H), 7.4 (s, 5 H). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.75; H, 6.32. **Trans-(*RS,SR*) lactone 11**: ^{1}H NMR ($CDCl_3$) δ 2.6 (dd, J = 16, 3 Hz, 1 H), 2.82 (dd, J = 16, 5 Hz, 1 H), 3.42 (s, 3 H), 3.95-4.05 (m, 1 H, β-H), 5.5 (d, J = 3 Hz, γ-H), 7.3-7.5 (m, 5 H). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: 68.82; H, 6.27.

***cis*- and *trans*-Tetrahydro-3-methyl-5-oxo-2-furancarboxylic Acid Methyl Ester (14 and 15[4b]).** To a 99:1 mixture of lactones **12** and **13**[1] (or 10:90 mixture of **7d** and **8d**)[19] (1 mmol) in CCl_4 (4 mL) and CH_3CN (4 mL) were added H_2O (6 mL) followed by $NaIO_4$ (14.5 mmol). The solution was vigourously stirred, and $RuCl_3$ (5 mg) was added. The thick white suspension was stirred at room temperature for 18 h. The reaction mixture was poured onto a solution of 1 N HCl saturated with NaCl, extracted with ethyl acetate (2×), and dried over Na_2SO_4 to give the mixture of **14** and **15** acid derivatives. The mixture was then treated with CH_2N_2 in Et_2O to give after evaporation the crude mixture of **14** and **15**. A short chromatography in a plug of silica gel, eluting with CH_2Cl_2, afforded, as an oil, the desired products as a mixture of **14** and **15**. The cis lactone **14** was characterized as a 99:1 mixture of **14** and **15**, starting from **12** and **13** (ratio 99:1) (yield 82%). The trans lactone **15** was characterized as a 10:90 mixture of **14** and **15**, starting from **7d** and **8d** (ratio 10:90) (yield 71%). **Cis lactone 14**: ^{1}H NMR ($CDCl_3$) δ 1.1 (d, J = 7 Hz, 3 H), 2.35 (dd, J = 16, 5 Hz, 1 H), 2.65 (dd, J = 16, 5 Hz, 1 H), 2.8-3.0 (m, 1 H), 3.8 (s, 3 H), 4.95 (d, J = 7 Hz, 1 H); IR (thin film) 1785, 1750 cm^{-1}. **Trans lactone 15**: ^{1}H NMR ($CDCl_3$) δ 1.3 (d, J = 6 Hz, 3 H), 2.2 (dd, J = 14, 5 Hz, 1 H), 2.6-2.75 (m, 1 H), 2.8 (dd, J = 14, 5 Hz, 1 H), 3.8 (s, 3 H), 4.52 (d, J = 5 Hz, 1 H).

(29) Assignment of the trans lactone **8g** as the major lactone obtained was based on the strength of NOE experimental results.

(30) Identification of the cis lactone **10** and the trans lactone **11** was determined by NOE studies on both pure lactones isolated after silica gel chromatography.

Mn(III)-Mediated Tandem Oxidative Cyclizations of β-Diesters. Influence of Cu(II) upon the Chemoselectivity of the Reaction

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Mn(III)-mediated oxidative cyclization of esters derived from allylmalonic and benzylmalonic acids afforded through two consecutive cyclizations bislactones (**17, 5**) and bicyclic lactones (**19, 21**) or tricyclic lactones (**7, 9**). The ratio of these products is controlled by the stereoselectivity of the first step involving the intramolecular addition of a carbon-centered radical to a double bond. Oxidations conducted either in the presence of stoichiometric cupric ion or without added Cu(II) provide a comprehensive view of the respective influences of Mn(III) and Cu(II) upon the chemoselectivity of the reaction, which are related to their ability to oxidize radicals of different classes. For example, the primary and secondary radicals **3a** and **3b**, which are not efficiently oxidized by Mn(III), undergo cyclization leading to the trans fused tricyclic γ-lactones **9a** and **9b** exclusively in the absence of cupric ion.

During the last decade, an impressive number of synthetic applications have demonstrated the efficiency of free-radical reactions in the elaboration of cyclic compounds.[1] Among the methods available to generate rad-

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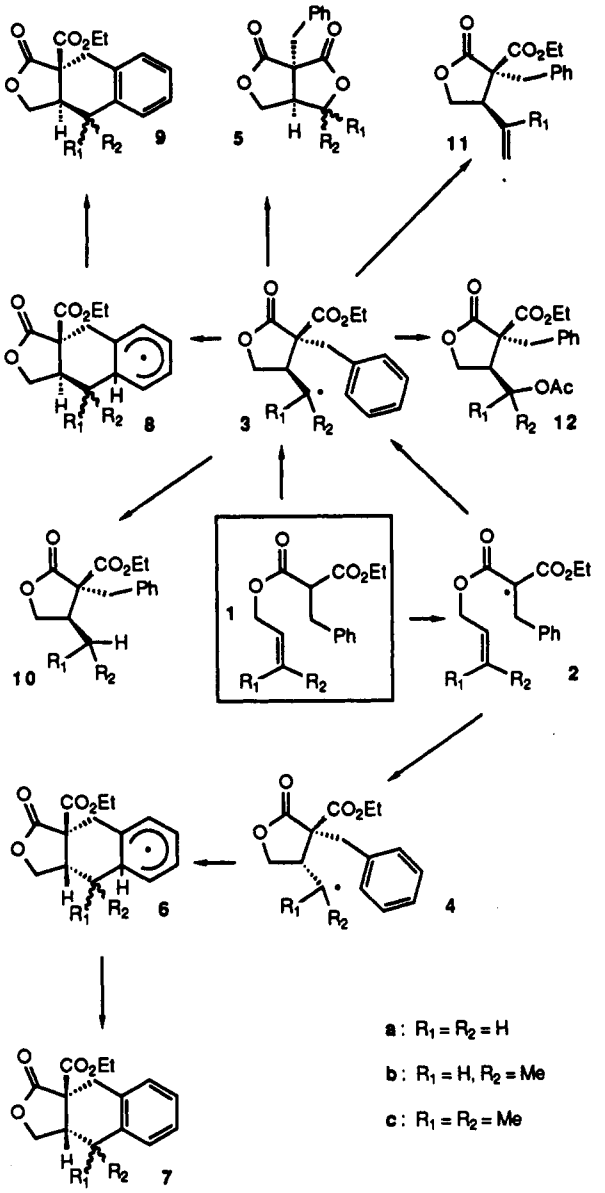
Table I. Oxidative Cyclizations of Esters 1a-c

reactant	cond	products[a] (%) 5	7	9	10	11	12	cis:trans cyclization ratio (3:4)
1a	A	40	19					2:1
	B		15	23	4			1.8:1
1b	A	10	24			56		2.7:1
	B	1	20	57	traces	traces		2.7:1
1c	A	8	17			28	9	2.6:1
	B	13	21	traces		20	14	2.2:1

[a] Yields refer to isolated products. They are corrected taking into account the amount of recovered substrate.

icals, the most widely used is certainly the so-called "tin method". The main criticism addressed to this protocol concerns the fact that the ring is constructed at the expense of two functional groups, whereas since the last step is a hydrogen atom transfer from Bu_3SnH, the product is not further functionalized. Variations allowing the introduction of a new function have been developed,[2] notably in the field of lactone synthesis, which is the theme of this paper.[3] Alternative methods such as iodine atom transfer[4] or initiation with reducing metallic salts[5] address this deficiency. Snider has recently emphasized the advantage of oxidative cyclizations over the tin method by applying Mn(III)-mediated oxidation to serial cyclizations of β-keto esters.[6a] Oxidative addition of carboxylic acids to olefins is a good method for the synthesis of γ-lactones.[3,7] Activated acids and esters have been shown to react in the same way under milder conditions.[8] In a previous paper,

Scheme I



we have described the ability of Mn(III) to induce the ring closure of β-diesters to γ-lactones.[9] This radical process, which was considered impossible for a long while[10] (some recent examples[11] have been published, however), could be facilitated through complexation of the α-dicarbonyl radical with the metallic cation.[6,8b,12] We report herein our results on $Mn(OAc)_3$-mediated lactonizations of allylmalonates. We have investigated the ability of this reaction to afford polycyclic lactones through tandem cy-

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clization and tried to delineate whether cupric ion is necessary or not to achieve this purpose. Substrates designed for the present study are esters of allylmalonic acid and benzylmalonic acid with various allylic alcohols.

Results and Discussion

Oxidative Cyclization of Benzylmalonic Acid Derivatives. Ethyl potassium benzylmalonate was esterified under phase-transfer catalysis conditions.[13] Reaction with allyl chloride affords β-diester **1a** in 85% yield; reaction with crotyl bromide provides ester **1b** in 95% yield, and reaction with prenyl bromide affords **1c** in 95% yield.

Oxidative cyclizations of **1a–c** were performed at 110 °C in acetic acid by treating an 0.012 M solution of ester with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ in the presence of 1 equiv of NaOAc (these experimental conditions will be further designated as conditions A, cf. Table I). For each of these substrates, comparative experiments were conducted in the absence of cupric salt (conditions B).

Oxidation of **1a** gives the radical **2a**, which might be complexed with manganese.[6,7a,f,8b] Cyclization of **2a** leads exclusively to the two diastereoisomeric five-membered ring primary radicals **3a** and **4a** (Scheme I). It should be noted that no six-membered ring product resulting from an endo cyclization mode was isolated, even in the absence of an efficient oxidative radical trap (cupric ion), in which case one might expect the intramolecular addition of such a radical to be reversible.[14]

Under conditions A, radical **3a** is quickly oxidized by $Cu(OAc)_2$ to give what is formally an alkylcopper(III) species.[15] Due to its proximity, the ester carbonyl participates[6a,8f] in this oxidation step, and bislactone **5a** is formed in 40% yield.

Owing to the cis relationship of the primary reactive center with the benzyl substituent on the lactone ring, radical **4a** is trapped by the neighboring aromatic ring. The resulting cyclohexadienyl radical **6a** is easily oxidized either by Mn(III) or by Cu(III) to the tricyclic lactone **7a** (19%). These results indicate that radicals **3a** and **4a** are formed in a ratio of 2:1. Therefore, even in the presence of 0.012 M cupric ion, the trapping of the primary radical **4a** by the aromatic ring is faster than oxidative elimination, which would lead, as previously shown, to a β-methylene lactone.[9] This implies that the rate of cyclization of **4a** is significantly greater than the rate of oxidation of **4a** by cupric ion. Kochi reported a ratio of 350 for k_{ox}/k_{cycl} for the 4-phenylbutyl radical at 0.025 M cupric ion in AcOH.[15d] Our result, at nearly half the cupric ion concentration, is not surprising, taking into account that radical **4a** contains an additional ring favoring cyclization by decreasing the degrees of rotational freedom.

Under experimental conditions B, the oxidation of primary radicals is too slow to be competitive and the formation of bislactone **5a** is completely suppressed. Under conditions B, radical **4a** gives lactone **7a**[16] in 15% yield, which demonstrates that Mn(III) is as efficient as Cu(II) in oxidizing dienyl radical **6a**. Two competitive pathways are available for **3a**. Although slower than in the case of **4a**, addition to the aromatic π system leading to a trans fused compound is now observed, and the tricyclic lactone **9a**[16] is formed in 23% yield after oxidation of cyclohexadienyl radical **8a**. In the second pathway, radical **3a** undergoes abstraction of a hydrogen atom to give the minor product **10a** in 4% yield. This is in agreement with the rate constant for hydrogen abstraction being higher than that for the oxidation of a primary radical; $k_{ox}/k_H = 0.3$ for the decarboxylation of *n*-butyric acid with Mn(III).[15b] The stereochemistry of **10a** is assigned on the basis of ^{13}C NMR; the chemical shift of the benzylic methylene carbon is consistent with a trans relationship between benzyl and methyl groups (the γ gauche effect contributes to a significant shielding of the corresponding methylene carbon nucleus in compounds presenting the opposite relative stereochemistry, cf. Table II). Furthermore, this proposal is in agreement with mechanistic considerations. The distribution of the products indicates a 1.8:1 ratio for reaction via **3a**/**4a**. This ratio is slightly lower than observed under conditions A; this may result from some telomerization since the overall yield is also lowered.

Table II. Benzylic CH_2 Chemical Shifts

compd	shift (δ)	compd	shift (δ)
7a	32.8	**10a**	35.8
7b	32.3	**11b**	35.9
7c	32.3	**11c**	37.4
9a	34.5	**12c**	38.0
9b	35.2		

Oxidation of **1b** in the presence of Cu(II) leads to vinyl lactone **11b** as the major product (56%). Bislactone **5b** is obtained in 10% yield as a mixture of isomers (nearly 1:1 endo/exo), and tricyclic lactone **7b** is formed in 24% yield. The latter is a mixture of isomers, but the minor one was only detected by ^1H NMR. Whereas radical **4b** undergoes intramolecular rearrangement leading to **7b** faster than any other competitive pathway, oxidative substitution and oxidative elimination constitute the preferred reactions of radical **3b**. As expected, oxidative elimination gives the major product **11b** (56%). However, we were surprised to find that a 10% yield of bislactone **5b** was obtained, since oxidative elimination is known to be favored over oxidative substitution by more than 100 times with cupric ion.[15] The stereochemistry of **11b** suggested on the basis of mechanistic considerations was established from the NMR data. The chemical shift of the benzylic carbon (35.9 ppm) is consistent with the lack of a γ gauche effect and is very similar to chemical shifts of the corresponding methylene carbon nuclei in lactones **9** (cf. Table II).

The distribution of the products is markedly different under conditions B. Oxidation of the secondary radical **3b** is suppressed; only traces of bislactone **5b** (1%) and olefin **11b** are detected together with traces of reduction product **10b**. Just as **4b** gives **7b** (20%), **3b** is efficiently converted to tricyclic lactone **9b** (57%) through a second

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(16) ^1H NMR studies of isomeric tricyclic lactones **7a** and **9a** provided characteristic features of cis- and trans-fused-γ-lactone rings that were further confirmed by the spectral data for **7b** and **9b** and **7c** and **9c**. The two protons of the lactone ring methylene exhibit very close chemical shifts in the trans isomers **9**; they are both deshielded with regard to the methylene group of the carbethoxy substituent (200-MHz ^1H NMR spectra of **9a–c** show the characteristic pattern of the AB part of an ABX spectrum between δ 4.50 and 4.75). In the cis isomers **7**, one of the two protons is shielded with regard to the ethoxy quartet while the other proton is deshielded with regard to the same reference.

Table III. Oxidative Cyclizations of Esters 13a–c

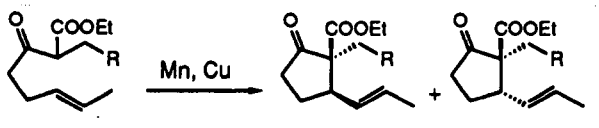
reactant	cond	products[a] (%) 17	19	21	22	23	24	25	26	cis:trans cyclization ratio (15:16)
13a	A	47	3.5	3.5						14:1
	B			11			7			
13b	A		18					43		2.5:1
	B			17	traces	traces	9			
13c	A	11	26					31	9	1.9:1
	B	9			9	traces		14	11	

[a] Yields refer to isolated products. They are corrected taking into account the amount of recovered substrate.

cyclization step. Lactone **9b** is a single crystalline isomer; J_{3a-4} = 11.7 Hz indicates that H_4 is axial and the methyl group equatorial. The overall ratio of reaction via **3b**/**4b** is 2.75:1 regardless of the experimental conditions.

Intramolecular addition of radical **2c** to the alkene leads to tertiary radicals. Radical **3c** undergoes oxidative substitution to **5c** and **12c** and oxidative elimination to **11c** under either conditions A or B. However, overall oxidative substitution predominates over oxidative elimination in the absence of cupric ion (17:28% under conditions A; 27:20% under conditions B). This is in agreement with Kochi's report,[15] but the differences are small and these results should be taken as evidence for an intermediate carbonium ion under both conditions, mainly because of the formation of an acetate. The stereochemistry of **11c** and **12c** is assigned on the basis of ^{13}C NMR data (cf. Table II); additional proof was secured by the chemical transformation of olefin **11c** into bislactone **5c** under acidic conditions (TsOH, H_2O/toluene at reflux). The tricyclic lactone **7c**, which results from the bicyclization of radical **4c**, was obtained in 17% yield (A) or 21% yield (B) depending on the experimental conditions. Again, the stereoselectivity of the first cyclization step does not depend much on the experimental conditions (**3c**:**4c** = 2.6:1 under conditions A and 2.2:1 under conditions B).

Comparison among the three different substrates shows that radical **3** is clearly favored over radical **4**. The overall cis/trans ratio is only slightly modified by changing the experimental conditions; the variations could be accounted for by some reversibility of the first cyclization step in the absence of Cu(II). Steric effects of the substituents on the double bond slightly enhance this preference. Snider reported that, whereas an α-methyl β-keto ester bearing a 1,2-disubstituted double bond gives a 2.5:1 mixture of cis and trans isomers, the α-benzyl homologue leads exclusively to a cis cyclopentanone[6g] (cf. eq 1). We have observed that the replacement of a methyl substituent by a benzyl group does not alter the stereoselectivity in the case of β-diesters.[9]



(1)

R = Ph	50%	100	0
R = H	40%	2.5	1

On the basis of steric effect in a chairlike transition state,[1a] one might have predicted the opposite stereoselectivity, assuming that an axial methyl group would be less stable than an axial carboxylate.[17] Two hypotheses can be considered to account for the observed trend. The first would invoke a secondary orbital interaction between the developing cyclized radical and the π system of the carboxylate, but this hypothesis does not fit well with the low stereoselectivity that has been reported for $(Bu_3Sn)_2$-based cyclizations of methyl and *tert*-butyl 2-iodo-6-heptenoate.[5,11a] Secondly, the observed selectivity could result from Mn-cation complexation of both the radical and the double bond during the cyclization process, as discussed previously.[6d,9b]

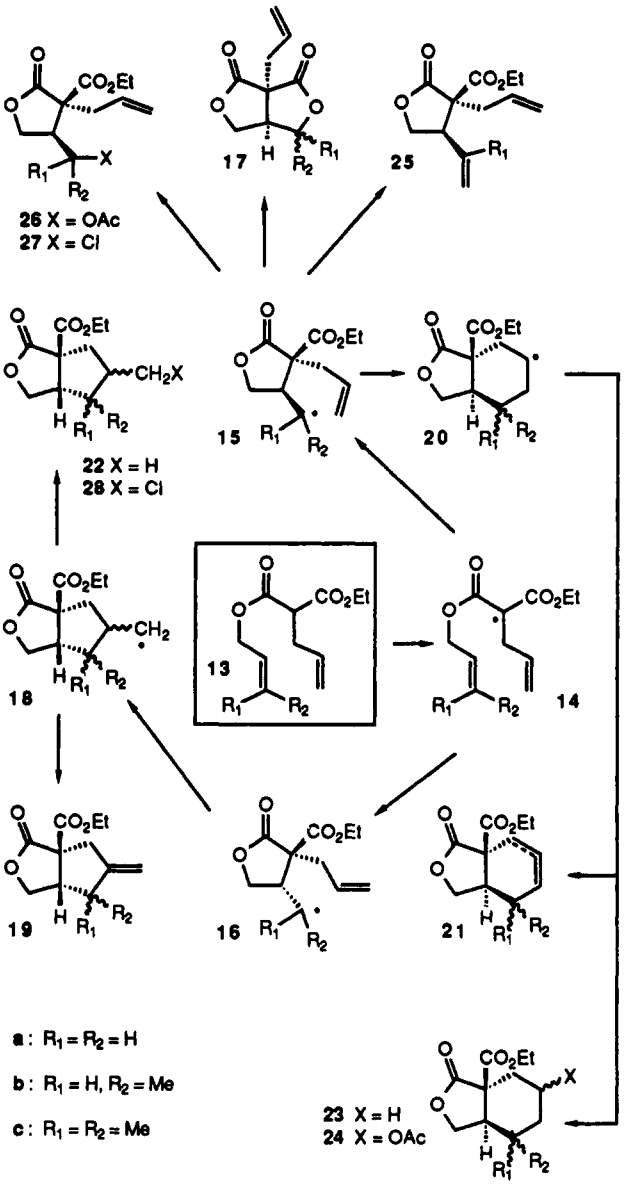
Oxidative Cyclization of Esters Derived from Allylmalonic Acid. Ethyl potassium malonate was alkylated under the experimental conditions mentioned for the synthesis of **1**. This protocol applied to allyl chloride, crotyl bromide, and prenyl bromide leads to esters **13a** (58%), **13b** (98%), and **13c** (95%), respectively. These substrates were submitted to $Mn(OAc_3)$-mediated cyclization under experimental conditions A and B in order to test the influence of Cu(II) on the fate of the delocalized radical **14**.

The stereoselectivity of the intramolecular addition step determines the **15**/**16** ratio. Oxidation of **13a** shows that **15a** largely predominates over **16a** under conditions A (cf Table III). The major product, bislactone **17a** (47%), results from oxidative substitution of **15a**. The radical **16a** gives rise to bicyclic product **19a** in 3.5% yield. Intramolecular addition to the double bond of the allyl substituent, cis with regard to the radical center, leads to **18a**, the oxidative elimination of which results in **19a**. Lactone **19a** was isolated as a mixture along with compound **21a**. Separation was not fully achieved (cf. Experimental Section), but the ratio **19a**/**21a** in the isolated mixture was determined by the relative intensities of ethylenic protons signals. The *exo*-methylene protons in **19a** are more shielded (δ 4.94) than those of the intracyclic double bond in 21a (δ 5.77). Oxidative elimination by Cu(II) appears to be regioselective since only one regioisomer of **21a** was observed. We did not investigate thoroughly the structure of this very minor product, but the close chemical shifts of both the two ethylenic protons and their linked carbon nuclei (δ 125.9 and 126.0) suggest the structure in which the unsaturation is γ with regard to the carboxylate rather than β. This was later confirmed by the oxidation of **13b** to **21b** under conditions A. The trans ring junction is corroborated by the ^1H NMR spectrum. Both protons of the γ lactone ring are more deshielded than the carbethoxy quartet. This characteristic pattern was previously observed for lactones **9**.[16] ^1H NMR data also confirm the cis ring junction in **19a**. Of the two protons of the methylene probe, one is shielded and the other deshielded with regard to the reference quartet.[16]

Oxidation of **13a** in the absence of cupric ion appears to be far less efficient and nonselective; this could be ascribed to a higher degree of oligomerization. Only three products were identified: an inseparable mixture of **21a** and **22a** in 11% yield and a higher molecular weight product identified as acetate **24a** in 7% yield. From these

(17) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 3rd ed.; Wiley-Interscience: New York, 1985; p 126.

Scheme II



results, it is obvious that Mn(III) alone is unable to oxidize the primary radical **18a** resulting from the cyclization of **16a**. Radical **18a** gives rise to the reduction product **22a** and possibly to telomers. The trans bicyclo[4.3.0] compounds **21a** and **24a** originate from the intramolecular addition of radical **15a** to the remaining double bond. Contrary to the reports of Beckwith,[18] Snider,[6h] and Kilburn,[19] who found minor to significant formation of trans-fused bicyclo[3.3.0] compounds, we did not detect any trans-fused bicyclic lactone resulting from the cyclization of **15a** by a 5-exo mode.

Two observations should be emphasized concerning the fate of radical **20a**. Unlike oxidative elimination with Cu(II), oxidative elimination with Mn(III) is not regioselective. Olefin **21a** is contaminated by a small amount of its regioisomer. This was later confirmed by oxidative cyclization of **13b** under conditions A and B. Doublets of triplets are detected at δ 5.89 (J = 9.8 and 3.7 Hz) and at δ 6.14 (J = 9.8 and 2.2 Hz) in the ^{1}H NMR spectrum of the mixture, indicating the presence of a CCH=CHCH$_2$ linkage. The second point of interest is that oxidative substitution of the secondary cyclic radical **20a** does compete with oxidative elimination by Mn(III). Oxidation is fast enough with respect to competitive nonoxidative pathways to be observed. However, **21a** and **24a** together do not account for the amount of **15a** expected on the basis of the 47% yield of **17a** obtained under conditions A.

Oxidation of **13b** under conditions A leads to **25b** in 43% yield and to **19b** in 18% yield. As expected, the major stereoisomer **15b**, resulting from cyclization of **14b**, undergoes oxidative elimination to give **25b** exclusively. Radical **16b**, through intramolecular addition and subsequent oxidative elimination, leads to **19b** as a mixture of isomers.

Under conditions B, oxidation of **13b** approximately duplicates that of **13a**. Radical **15b** does not undergo oxidative elimination; therefore, it is partially trapped by the double bond to give **20b**. Radical **20b** is transformed by hydrogen atom transfer into **23b** (detected in trace amounts) through oxidative elimination into **21b** (17% as a mixture of regioisomers) and into acetate **24b** (9%) through oxidative substitution. Rearrangement of radical **16b** affords the primary radical **18b**, which is neither efficiently oxidized nor reduced by hydrogen abstraction (only traces of **22b** (<2%) are recovered).

As expected from the results with **1c**, oxidation of **13c** in the presence of cupric ion leads to four products: **17c** (11%), **25c** (31%), and **26c** (9%) resulting from radical **15c** (the overall oxidative elimination versus oxidative substitution ratio is 20:31) and **19c** (26%) resulting from **16c**. However, the product balance is significantly different under conditions B. Yields of **17c** (9%) and **26c** (11%) are not altered, but oxidative elimination seems not to be as efficient, since **25c** is formed in only 14% yield along with a small amount of reduction product **23c** (2%). Furthermore, **19c** disappears since Mn(III) cannot oxidize the primary radical **18c** and only the reduction product **22c** is recovered in 9% yield.

It is clear from these results that oxidative cyclization leading to primary radicals needs both Mn(III) and Cu(II) to obtain optimal yields of oxidatively terminated products. For this reason, the overall cis/trans selectivity can only be taken as representative under these experimental conditions. The values of 2.5:1 and 1.9:1 observed with **13b** and **13c**, respectively, are in agreement with those discussed previously. However the 14:1 ratio of **15**:**16** observed for **13a** is somewhat unexpected[20] and appears to be the consequence of an unexplained low yield in **19a**.

Earlier studies have demonstrated that Mn(OAc)$_3$·2H$_2$O and LiCl can be used in oxidative additions[21] and oxidative cyclizations[6a,c,d] to trap the final radical by delivering a chloride. We examined these conditions on substrates **13** (cf. Scheme II). Monocyclic chlorides **27a** (27%) and **27b** (39% as a mixture of two diastereoisomers) are isolated in addition to bicyclic chlorides **28a** (14%) and **28b** (22%). Bislactone **17a** is isolated in 5% yield, probably deriving from **27a**, as indicated by the recovery of **17a** after prolonged heating of **27a** at reflux in acetic acid. These results indicate that, contrary to our expectations, the trapping of radicals **15a** and **15b** with chloride is faster than intramolecular addition leading to trans-fused bicyclic compounds. This process must be too fast for bicyclization leading to the trans-bicyclo[4.3.0] skeleton to occur. On

(18) Beckwith, A. L. J.; Phillipou, G.; Serelis, A. K. *Tetrahedron Lett.* **1981**, *22*, 2811.
(19) Kilburn, J. D. *Tetrahedron Lett.* **1990**, *31*, 2193.
(20) A previous experiment leading to **17a** (60%) and to **19a** + **21a** (10%) could not be reproduced. However, it already indicated a 13:1 cis/trans stereoselectivity.
(21) (a) Vinogradov, M. G.; Kovalev, I. P.; Nikishin, G. I. *Izv. Akad. Nauk SSR Ser. Khim.* **1984**, 375. (b) Vinogradov. M. G.; Dolinko, V.; Nikishin, G. I. *Ibid.* **1984**, 2065.

the contrary, radicals **16a** and **16b** cyclize rapidly and the trapping of the resulting radicals **18a** and **18b** results in **28a** and **28b**. The oxidation of **13c** afforded **25c** (11%), **17c** (37%), and **28c** (23%), but no acetate was isolated. The obtention of **28c** in 23% yield reflects the isolation of **19c** in 26% yield under conditions A. The intermediate radical **15c** is transformed through oxidative elimination and oxidative substitution into **25c** and **17c**; however, the relative amount of **17c** is increased compared to conditions A. This might be due to a complete conversion of the tertiary chloride **27c** into **17c**. It should be pointed out that cis/trans stereoselectivity is more or less in agreement with what would be expected on the basis of previous experiments: 2.2:1 for **13a**; 1.8:1 for **13b**, and 2.1:1 for **13c**.

Several conclusions may be drawn from this study. Our results confirm the high potential of Mn(III)-based oxidative cyclizations compared to classical free-radical methods. The first cyclization step leads predominantly (roughly in a 2:1 ratio) to radicals **3** or **15** bearing the carbethoxy group in a cis position. The stereoselectivity is little influenced by the nature of the substituent on the malonate (it remains quite unchanged with either methyl,[9] allyl **13** or benzyl **1** malonates) or by the experimental conditions (presence or absence of cupric ion). Taken together, these results provide a good understanding of the respective roles of Mn(III) and Cu(II). When the final radical is not easily oxidized with Mn(III), Cu(II) is necessary to obtain good yields of oxidatively terminated products. On the other hand, when Mn(III) is able to oxidize the final radical, such as the cyclohexadienyl radicals resulting from **1**, it is possible to control the nature of the products by modifying the experimental conditions. These reactions are of preparative value; we are currently investigating activating groups other than the carboxylate function that might induce better stereoselectivity.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ solution (unless otherwise stated) on Varian XL 200, Bruker AC 100, or Bruker AC 200 spectrometers (J is given in hertz). Column chromatography was performed on silica gel 60 (Merck 7734). $Mn(OAc)_3 \cdot 2H_2O$ was purchased from Aldrich Chemical Co. and used without purification.

General Procedure for the Preparation of β-Diesters. Saponification of diethyl allylmalonate or diethyl benzylmalonate afforded the corresponding monopotassium salts.[13] Alkylations were conducted as follows. To a suspension of ethyl potassium malonate (14 mmol) in CH_2Cl_2 (30 mL) in the presence of tetrabutylammonium bromide (450 mg; 10% molar) was added quickly the appropriate alkyl halide (14 mmol). The reaction mixture was stirred at room temperature up to the complete disappearance of the halide (the reaction was monitored by thin-layer chromatography (TLC)). After evaporation of CH_2Cl_2, the residue was diluted with Et_2O (40 mL) and then washed with water before drying over Na_2SO_4. The crude ester was estimated as satisfactorily pure on the basis of TLC, and the ^1H NMR was obtained without further purification.

Ethyl 2-propenyl 2-benzylpropanedioate (1a): IR 1748, 1731, 1643 cm^{-1}; ^1H NMR δ 1.21 (t, J = 7.1, 3 H), 3.23 (d, J = 7.8, 2 H), 3.70 (t, J = 7.8, 1 H), 4.20 (q, J = 7.1, 3 H), 3.23 (d, J = 7.1, 2 H), 4.61 (d, J = 5.5, 2 H), 5.18–5.31 (m, 2 H), 5.84 (ddt, J = 17.2, 10.4, 5.5), 7.25 (s, 5 H).

(*E*)-2-Butenyl ethyl 2-benzylpropanedioate (1b): IR 1748, 1731, 1677 cm^{-1}, ^1H NMR δ 1.25 (t, J = 7.1, 3 H), 1.72 (dd, J = 6.3, 1, 3 H), 3.20 (d, J = 7.9, 2 H), 3.70 (t, J = 7.9, 1 H), 4.20 (q, J = 7.1, 2 H), 4.55 (d, J = 6.3, 2 H), 5.49 (dt, J = 16.7, 6.3, 1 H), 5.71 (dq, J = 15.3, 6.3, 1 H), 7.25 (s, 5 H).

Ethyl 3-methyl-2-butenyl 2-benzylpropanedioate (1c): IR 1748, 1731, 1677 cm^{-1}; ^1H NMR δ 1.25 (t, J = 7.1, 3 H), 1.63 (s, 3 H), 1.70 (s, 3 H), 3.18 (d, J = 7.9, 2 H), 3.65 (t, J = 7.9, 1 H), 4.10 (q, J = 7.1, 2 H), 4.55 (d, J = 7.2, 2 H), 5.23 (t, J = 7.2, 1 H), 7.2 (m, 5 H).

Ethyl 2-propenyl 2-(2-propenyl)propanedioate (13a): IR 1751, 1735, 1644 cm^{-1}; ^1H NMR δ 1.26 (t, J = 7.1, 3 H), 2.66 (t, J = 7.6, 2 H), 3.47 (t, J = 7.6, 1 H), 4.25 (q, J = 7.1, 2 H), 4.63 (d, J = 5.6, 2 H), 5.03–5.37 (m, 4 H), 5.80 (m, 2 H).

(*E*)-2-Butenyl ethyl 2-(2-propenyl)propanedioate (13b): IR 1751, 1735, 1673, 1644 cm^{-1}; ^1H NMR δ 1.25 (t, J = 7.1, 3 H), 1.70 (dd, J = 6.3, 1, 3 H), 2.64 (t, J = 7.5, 2 H), 3.45 (t, J = 7.5, 1 H), 4.2 (q, J = 7.1, 2 H), 4.55 (d, J = 6.3, 2 H), 5.0–5.16 (m, 2 H), 5.5–5.86 (m, 3 H).

Ethyl 3-methyl-2-butenyl 2-(2-propenyl)propanedioate (13c): IR 1751, 1734, 1675, 1643 cm^{-1}; ^1H NMR δ 1.21 (t, J = 7.1, 3 H), 1.65 (s, 3 H), 1.70 (s, 3 H), 2.58 (t, J = 7.5, 2 H), 3.45 (t, J = 7.5, 1 H), 4.12 (q, J = 7.1, 2 H), 4.57 (d, J = 7.2, 2 H), 4.97–5.10 (m, 2 H), 5.27 (t, J = 7.2, 1 H), 5.73 (m, 1 H).

Oxidative Cyclization of 1a. This reaction and the following ones were strictly performed under the experimental conditions previously described in the presence of $Cu(OAc)_2 \cdot H_2O$ (conditions A).[9b] Experiments of type B were carried out in the same way, except that $Cu(OAc)_2 \cdot H_2O$ was omitted. Separation by column chromatography on silica gel (45 × 1.5 cm) was performed with EtOAc/pentane mixtures of gradually increased polarity.

Oxidation of **1a** (1 g, 3.81 mmol) in the presence of cupric ion afforded 0.95 g of a crude mixture, the separation of which led, in their order of elution, to 14 mg (rate of conversion (conv) 98.5%) of unreacted **1a**, 190 mg (19%) of **7a**, and 348 mg (40%) of **5a**. Under conditions B, separation of the crude reaction mixture afforded 43 mg (conv 96%) of **1a**, 43 mg (4%) of **10a**, 145 mg of **9a**, and 210 mg of a 1:2 mixture of **9a** and **7a**. This ratio, determined by ^1H NMR spectroscopy, was based on the relative integration of the signals at δ 3.86 and 3.60 corresponding to one specific proton of **7a** and **9a**, respectively.

1-Benzyl-3,7-dioxabicyclo[3.3.0]octane-2,8-dione (5a): mp 194 °C ($C_5H_{12}/CHCl_3$); IR 1783, 1746 cm^{-1}; ^1H NMR (DMSO) δ 3.21 (s, 2 H), 3.51 (m, 1 H), 3.95–4.30 (AB part of an ABX spectrum, J_{AB} = 9.7, 4 H), 7.4–7.8 (m, 5 H); ^{13}C NMR δ 37.9 (CH_2), 39.9 (CH), 56.3 (C), 70.1 (CH_2), 127.5 (=CH), 128.6 (=CH), 129.4 (=CH), 134.8 (=C), 171.8 (C=O). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.20; H, 5.15.

Ethyl *cis*-1,3,3a,4,9,9a-hexahydro-1-oxoisonaphthofuran-9a-carboxylate (7a): IR 1780, 1740 cm^{-1}; ^1H NMR δ 1.29 (t, J = 7.1, 3 H), 2.67 (dd, J = 14.8, 4.6, 1 H), 2.88 (dd, J = 14.8, 5.7, 1 H), 3.21 (AB spectrum, J_{AB} = 14.8, $\Delta\nu$ = 14.6, 2 H), 3.30 (superimposed m, 1 H), 3.86 (dd, J = 9, 3.9, 1 H), 4.22 (q, J = 7.1, 2 H), 4.57 (t, J = 9, 1 H), 7.00–7.30 (m, 5 H); ^{13}C NMR δ 14.0 (CH_3), 32.8 (CH_2), 32.9 (CH_2), 39.7 (CH), 55.9 (C), 62.4 (CH_2), 72.1 (CH_2), 127.3 (=CH), 127.4 (=CH), 127.8 (=CH), 128.4 (=CH), 134.8 (2×C), 170.1 (C=O), 175.4 (C=O). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.01; H, 6.34.

Ethyl *trans*-1,3,3a,4,9,9a-hexahydro-1-oxoisonaphthofuran-9a-carboxylate (9a): mp 104–105 °C ($C_5H_{12}/CHCl_3$); IR 1774, 1730 cm^{-1}; ^1H NMR δ 1.14 (t, J = 7.1, 3 H), 2.72–3.00 (m, 4 H), 3.60 (d, J = 16, 1 H), 4.13 (q, J = 7.1, 2 H), 4.49–4.69 (m, 2 H), 7.00–7.20 (m, 5 H); ^{13}C NMR δ 13.9 (CH_3), 28.4 (CH_2), 34.5 (CH_2), 44.0 (CH), 53.0 (C), 62.1 (CH_2), 71.3 (CH_2), 126.3 (=CH), 126.7 (=CH), 129.5 (=CH), 130.0 (=CH), 133.6 (=C), 134.2 (=C), 167.6 (C=O), 173.9 (C=O). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.16; H, 6.16.

Ethyl 3-benzyl-4-methyl-2-oxotetrahydrofuran-3-carboxylate (10a): IR 1776, 1738 cm^{-1}; ^1H NMR δ 1.00 (d, J = 6.9, 3 H), 1.32 (t, J = 7.1, 3 H), 2.51 (m, 1 H), 3.21 (d, J = 14.2, 1 H), 3.43 (d, J = 14.2, 1 H), 3.91 (dd, J = 10.6, 8.3, 1 H), 4.14 (t, J = 8.3, 1 H), 4.0–4.2 (m, 2 H), 7.26 (m, 5 H); ^{13}C NMR δ 11.4 (CH_3), 14.1 (CH_3), 35.4 (CH), 35.8 (CH_2), 59.2 (C), 62.0 (CH_2), 71.6 (CH_2), 127.1 (=CH), 128.5 (=CH), 130.6 (=CH), 135.2 (=C), 168.5 (C=O), 175.8 (C=O). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.63; H, 7.19.

Oxidative Cyclization of 1b. Under conditions A, oxidation of **1b** (1 g, 3.62 mmol) led to 20 mg (conv 98%) of recovered **1b**, 550 mg (56%) of **11b**, 230 mg of **7b** (24%), and 89 mg (10%) of **5b**. Under conditions B, the reaction led to 10 mg (conv 90%) of unreacted **1b**, 14 mg of a mixture of **10b** and **11b** (spectroscopic ^1H NMR data of **10b** was deduced from the spectrum of the mixture), 510 mg (57%) of **9b**, 171 mg (20%) of **7b**, and 11 mg (1%) of **5b**.

1-Benzyl-3,7-dioxa-4-methylbicyclo[3.3.0]heptane-2,8-dione (5b). The product is a mixture (ratio ≈ 52:48); after recrystallization a single isomer was isolated, the NMR data of which correspond to the chemical shifts indicated without asterisk (vide infra): mp 127–128 °C ($CHCl_3/C_5H_{12}$); IR 1789, 1753 cm^{-1}; 1H NMR (the peaks marked with an asterisk were used to differentiate the two isomers) δ 1.31 and 1.33* (two superimposed d, J = 6.3, 6.6, 3 H), 2.84* (td, J = 6.3, 1.6, 0.5 H), 3.4 (two superimposed AB spectra; J^*_{AB} = 13.8 − Δν = 50.4, J_{AB} = 13.9 − Δν = 16.4 plus a hidden m, total areas 2.5H), 3.67* (dd, J = 9.8, 6.4, 0.5 H), 4.00–4.27 (m, 2 H), 4.36* (quintuplet, J = 6.3, 0.5 H), 7.3 (m, 5 H); ^{13}C NMR δ 15.7, 20.7* (CH_3), 38.3, 38.8* (CH_2), 44.1, 48.0* (CH), 58.2, 58.3* (C), 65.1, 69.3* (CH_2O), 75.3, 79.4* (CHO), 128.1 (=CH), 129.2 (=CH), 129.5 (=CH), 134.3 (=C), 170.9 (C=O), 171.6 (C=O). Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.72. Found: C, 68.15; H, 5.85.

Ethyl *cis*-1,3,3a,4,9,9a-hexahydro-4-methyl-1-oxoisonaphthofuran-9a-carboxylate (7b): IR 1780, 1740 cm^{-1}; 1H NMR δ (major isomer) 1.25 (t, J = 7.1, 3 H), 1.36 (d, J = 6.8, 3 H), 2.68–2.69 (m, 2 H), 2.98 (d, J = 15.3, 1 H), 3.58 (d, J = 15.3, 1 H), 4.07 (dd, J = 9.1, 4.3, 1 H), 4.2 (q, J = 7.1, 2 H), 4.64 (t, J = 9.1, 1 H), 7.22 (m, 5 H) (traces of the minor isomer show absorptions at 1.11 (t, J = 7.1) and at 1.48 (d, J = 6.4)); ^{13}C NMR (major isomer) δ 13.7 (CH_3), 18.1 (CH_3), 32.3 (CH_2), 37.3 (CH), 46.6 (CH), 55.7 (C), 62.3 (CH_2), 67.8 (CH_2), 125.9 (=CH), 127.4 (=CH), 128.2 (=CH), 129.6 (=CH), 134.0 (=C), 139.4 (=C), 170.1 (C=O), 175.9 (C=O). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.93; H, 6.72.

Ethyl *trans*-1,3,3a,4,9,9a-hexahydro-4-methyl-1-oxoisonaphthofuran-9a-carboxylate (9b): mp 120–121 °C ($C_5H_{12}/CHCl_3$); IR 1775, 1729 cm^{-1}; 1H NMR ($CDCl_3$) δ 1.11 (t, J = 7.1, 3 H), 1.37 (d, J = 6.7, 3 H), 2.51 (td, J = 11.7, 7.5, 1 H), 2.99 (d, J = 15.8, 1 H), 3.09 (m, 1 H), 3.58 (d, J = 15.9, 1 H), 4.10 (q, J = 7.1, 2 H), 4.70–5.52 (AB part of an ABX, J_{AB} = 8, 2 H), 7.13–7.32 (m, 5 H); ^{13}C NMR δ 13.8 (CH_3), 18.6 (CH_3), 32.7 (CH), 35.2 (CH_2), 50.7 (CH), 53.0 (C), 61.9 (CH_2), 70.9 (CH_2), 126.6 (=CH), 126.8 (2×=CH), 129.8 (=CH), 134.1 (=C), 139.1 (=C), 167.7 (C=O), 174.0 (C=O). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.05; H, 6.57.

Ethyl 3-benzyl-4-ethyl-2-oxotetrahydrofuran-3-carboxylate (10b): 1H NMR δ 0.92 (t, J = 7.4, 3 H), 1.32 (t, J = 7.1, 3 H), 1.40–1.60 (m, 2 H), 2.08 (m, 1 H), 3.22 (d, J = 14.2, 1 H), 3.48 (d, J = 14.2, 1 H), 3.9 (dd, J = 11, 9, 1 H), 4.1–4.4 (m, 3 H).

Ethyl 3-benzyl-2-oxo-4-vinyltetrahydrofuran-3-carboxylate (11b): IR 1780, 1740, 1640 cm^{-1}; 1H NMR δ 1.30 (t, J = 7.1, 3 H), 3.16 (m, 1 H), 3.18 (superimposed d, J = 14.2, 1 H), 3.46 (d, J = 14.2, 1 H), 4.0–4.4 (m, 4 H), 5.17–5.30 (m, 2 H), 5.60 (ddd, J = 16.9, 10.3, 7.9, 1 H), 7.25 (m, 5 H); ^{13}C NMR δ 14.2 (CH_3), 35.9 (CH_2), 44.8 (CH), 59.5 (C), 62.2 (CH_2), 69.3 (CH_2), 120.9 (=CH_2), 127.3 (=CH), 128.7 (2×=CH), 130.9 (3×=CH), 135.2 (=C), 168.1 (C=O), 174.6 (C=O). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.08; H, 6.55.

Oxidative Cyclization of 1c. Oxidation of **1c** (1 g, 3.47 mmol) in the presence of cupric salt led to 32 mg (conv 97%) of unreacted **1c**, 280 mg of **11c**, 151 mg of **7c**, 105 mg of **12c**, and 71 mg of **5c**. In the absence of copper(II), 69 mg (conv 93%) of **1c** was recovered and 183 mg of **11c**, 192 mg of **7c**, 154 mg of **12c**, and 110 mg of **5c** were eluted successively.

1-Benzyl-4,4-dimethyl-3,7-dioxabicyclo[3.3.0]octane-2,8-dione (5c): mp 127–128 °C ($C_5H_{12}/CHCl_3$); IR 1786, 1747 cm^{-1}; 1H NMR δ 1.32 (s, 3 H), 1.41 (S, 3 H), 2.94 (dd, J = 7.1, 1.7, 1 H), 3.27 (d, J = 13.8, 1 H), 3.41 (d, J = 13.8, 1 H), 3.67 (dd, J = 10.5, 7.1, 1 H), 4.27 (dd, J = 10.5, 1.7, 1 H), 7.21–7.37 (m, 5 H); ^{13}C NMR δ 23.9 (CH_3), 30.4 (CH_3), 39.4 (CH_2), 49.5 (CH), 58.8 (C), 66.7 (CH_2), 83.9 (C), 128.1 (=CH), 129.2 (=CH), 129.5 (=CH), 134.5 (=C), 170.0 (C=O), 172.0 (C=O). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.19. Found: C, 69.20; H, 6.27.

Ethyl *cis*-4,4-dimethyl-1,3,3a,4,9,9a-hexahydro-1-oxoisonaphthofuran-9a-carboxylate (7c): mp 64 °C ($C_5H_{12}/CHCl_3$); IR 1774, 1667 cm^{-1}; 1H NMR δ 1.24 (s, 3 H), 1.32 (t, J = 7.1, 3 H), 1.33 (superimposed s, 3 H), 3.17 (dd, J = 9.8, 1 H), 3.19 (d, J = 16.9, 1 H), 3.57 (dd, J = 8, 9, 1 H), 3.79 (d, J = 16.9, 1 H), 4.29 (q, J = 7.1, 2 H), 4.42 (t, J = 9, 1 H); ^{13}C NMR δ 14.0 (CH_3), 25.0 (CH_3), 27.6 (CH_3), 32.3 (CH_2), 37.0 (C), 51.1 (CH), 54.3 (C), 62.6 (CH_2), 69.6 (CH_2), 124.7 (=CH), 126.9 (=CH), 127.4 (=CH), 129.1 (=CH), 132.8 (=C), 141.7 (=C), 170.9 (C=O), 177.1 (C=O). Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.83; H, 6.89.

Ethyl 3-benzyl-4-isopropenyl-2-oxotetrahydrofuran-3-carboxylate (11c): mp 84 °C ($C_5H_{12}/CHCl_3$); IR 1769, 1739, 1649 cm^{-1}; 1H NMR δ 1.28 (t, J = 7.1, 3 H), 1.88 (s, 3 H), 3.08 (dd, J = 10.8, 8.5, 1 H), 3.35 (d, J = 14.4, 1 H), 3.60 (d, J = 14.4, 1 H), 4.12 (t, J = 8.5, 1 H), 4.20 (q, J = 7.1, 2 H), 4.38 (dd, J = 10.8, 8.5, 1 H), 4.78 (s, 1 H), 5.01 (s, 1 H), 7.28 (m, 5 H); ^{13}C NMR δ 14.1 (CH_3), 23.4 (CH_3), 37.4 (CH_2), 45.5 (CH), 59.8 (C), 62.1 (CH_2), 68.5 (CH_2) 113.8 (=CH_2), 127.4 (=CH), 128.8 (=CH), 130.8 (=CH), 135.2 (=C), 139.4 (=C), 168.4 (C=O), 175.0 (C=O). Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.79; H, 7.02.

Ethyl 4-(1-acetoxyisopropyl)-3-benzyl-2-oxotetrahydrofuran-3-carboxylate (12c): mp 94 °C ($C_5H_{12}/CHCl_3$); IR 1771, 1737 cm^{-1}; 1H NMR δ 1.33 (t, J = 7.1, 3 H), 1.46 (s, 3 H), 1.76 (s, 3 H), 1.98 (s, 3 H), 2.55 (dd, J = 11.1, 8.2, 1 H), 3.44 (d, J = 14.6, 1 H), 3.59 (d, J = 14.6, 1 H), 4.12–4.20 (m, 2 H), 4.20–4.55 (m, 2 H), 7.26 (m, 5 H); ^{13}C NMR δ 13.9 (CH_3), 22.2 (CH_3), 24.2 (CH_3), 24.7 (CH_3), 38.1 (CH_2), 50.4 (CH), 57.4 (C), 62.1 (CH_2), 66.4 (CH_2), 80.5 (C), 127.4 (=CH), 128.8 (=CH), 130.8 (=CH), 135.1 (=C), 169.0 (C=O), 169.4 (C=O), 175.4 (C=O). Anal. Calcd for $C_{19}H_{14}O_6$: C, 65.50; H, 6.94. Found: C, 65.48; H, 7.19.

Oxidative Cyclization of 13a. Oxidation of **13a** (1 g, 4.71 mmol), under conditions A, afforded after recovery of 22 mg (conv 98%) of **13a** 23 mg of **21a**; 33 mg of a 1:2.4 mixture of **21a** and **19a** (determined by the NMR peaks for the ethylenic protons signals); 13 mg of **19a**, and 395 mg of **17a**. Under conditions B, the reaction led 52 mg of a 18:1 mixture of **21a** (a single regioisomer) and **22a**; 58 mg of a 2.2:1 mixture of **21a** (two regioisomers) and **22a**, and 89 mg of **24a** (conv 100%). According to 1H NMR analysis of the isolated mixtures, the following signals were assigned to **22a**: 1.02 (d, J = 5.8, 3 H), 3.18 (tt, J = 8.6, 2.8, 1 H), 4.05 (dd, J = 8.6, 2.8, 1 H), 4.55 (t, J = 8.6, 1 H). The respective chemical shifts of the two protons of the lactone ring methylene, one shielded, the other deshielded with regard to the ethyl quartet, confirm the cis ring junction. The **21a**/**22a** ratio was determined on the basis of the relative intensity of the doublet at δ 1.02 specific to **22a**.

1-(2-Propenyl)-3,7-dioxabicyclo[3.3.0]octane-2,8-dione (17a): mp 104–105 °C ($C_5H_{12}/CHCl_3$); IR 1786, 1744, 1641 cm^{-1}; 1H NMR 2.76 (d, J = 7.3, 2 H), 3.42 (tt, J = 7.8, 4.4, 1 H), 4.21 (dd, J = 9.8, 4.4, 2 H), 4.54 (dd, J = 9.8, 7.8, 2 H), 5.26–5.34 (m, 2 H), 5.70 (ddt, J = 17.1, 10.0, 7.3, 1 H); ^{13}C NMR (acetone-d_6) δ 37.3 (CH_2), 41.4 (CH), 55.6 (C), 71.1 (CH_2), 121.3 (=CH_2), 132.1 (=CH), 172.3 (C=O). Anal. Calcd for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.33; H, 5.66.

Ethyl 7-methylene-3-oxa-2-oxobicyclo[3.3.0]octane-1-carboxylate (19a): IR 1778, 1734, 1666 cm^{-1}; 1H NMR 1.29 δ (t, J = 7.1, 3 H), 2.25 (m, 1 H), 2.7–2.95 (m, 2 H), 3.1–3.2 (m, 2 H), 3.99 (dd, J = 9.2, 2.7, 1 H), 4.24 (q, J = 7.1, 2 H), 4.52 (dd, J = 9.2, 7, 1 H), 4.94 (m, 2 H); ^{13}C NMR δ 14.0 (CH_3), 39.1 (CH_2), 39.4 (CH_2), 45.0 (CH), 60.6 (C), 62.3 (CH_2), 72.5 (CH_2), 108.5 (=CH_2), 146.3 (=C), 169.2 (C=O), 175.8 (C=O). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.88; H, 6.83.

Ethyl 3,4-didehydro-8-oxa-9-oxobicyclo[4.3.0]nonane-1-carboxylate (21a): IR 1782, 1734, 1633 cm^{-1}; 1H NMR δ 1.26 (t, J = 7.1, 3 H), 2.20–2.50 (m, 3 H), 2.70 (m, 1 H), 2.95 (m, 1 H), 4.20 (q, J = 7.1, 2 H), 4.43 (t, J = 8, 1 H), 4.60 (dd, J = 11.5, 8, 1 H), 5.77 (m, 2 H); ^{13}C NMR δ 14.0 (CH_3), 24.9 (CH_2), 30.7 (CH_2), 43.2 (CH), 52.3 (C), 62.0 (CH_2), 71.7 (CH_2), 125.9 (=CH), 126.0 (=CH), 167.8 (C=O), 173.9 (C=O). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.00; H, 6.75.

Ethyl 3-acetoxy-8-oxa-9-oxobicyclo[4.3.0]nonane-1-carboxylate (24a): IR 1784, 1732, 1367, 1233 cm^{-1}; 1H NMR δ 1.28 (t, J = 7.1, 3 H), 1.4 (m, 1 H), 1.47 (t, J = 11.7, 1 H), 1.70–2.20 (m, 3 H), 2.01 (superimposed s, 3 H), 2.4 (m, 1 H), 2.88 (dd, J = 12.3, 4.6, 1 H), 4.1–4.28 (m, 3 H), 4.61 (dd, J = 11.2, 7.6, 1 H), 5.01 (tt, J = 12.3, 5, 1 H); ^{13}C NMR δ 13.9 (CH_3), 20.2 (CH_2), 21.2 (CH_3), 30.6 (CH_2), 35.3 (CH_2), 47.0 (CH), 54.0 (C), 62.4 (CH_2), 69.6 (CH), 71.2 (CH_2), 170.1 (C=O), 170.3 (C=O), 172.5 (C=O). Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.74; H, 6.77.

Oxidative Cyclization of 13b. Under conditions A, oxidation of **13b** (1 g, 4.42 mmol) led to 73 mg (conv 92%) of unreacted **13b**,

392 mg (43%) of **25b**, and 165 mg (18%) of **19b**. Under conditions B, 22 mg (conv 98%) of **13b** was recovered, and then traces of **23b**, 168 mg (17%) of **21b** as a mixture of isomers, traces of **22b**, and 108 mg (9%) of **24b** were eluted successively. **22b** and **23b** were identified on the basis of ^{1}H NMR exclusively.

Ethyl 7-Methylene-6-methyl-3-oxa-2-oxobicyclo[3.3.0]octane-1-carboxylate (19b). Major isomer: IR 1785, 1745, 1670 cm^{-1}; ^{1}H NMR δ 1.18 (d, J = 6.6, 3 H), 1.28 (t, J = 7.1, 3 H), 2.4 (m, 1 H), 2.69 (m, 1 H), 2.93 (d br, J = 17.5 1 H), 3.24 (d br, J = 17.5, 1 H), 4.18–4.30 (m, 3 H), 4.56 (dd, J = 9.2, 5.9, 1 H), 4.86 (q, J = 2.1, 1 H), 4.94 (q, J = 2.1, 1 H); ^{13}C NMR δ 14.0 (CH_3), 16.6 (CH_3), 38.4 (CH_2), 44.5 (CH), 53.6 (CH), 59.1 (C), 62.4 (CH_2), 70.9 (CH_2), 106.9 (=CH_2), 151.5 (=C), 169.3 (C=O), 176.1 (C=O). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.24; H, 7.06. The minor isomer is characterized by ^{1}H NMR spectroscopy by the following signals: δ 1.09 (d, J = 6.9, 3 H), 1.29 (t, J = 7.1, 3 H), 4.06 (dd, J = 9.5, 5.9, 1 H), 4.39 (dd, J = 9.5, 8.4, 1 H).

Ethyl 3,4-Didehydro-5-methyl-8-oxa-9-oxobicyclo[4.3.0]nonane-1-carboxylate (21b). Major isomer: IR 1785, 1735, 1640 cm^{-1}; ^{1}H NMR 1.05 (d, J = 6.7, 3 H), 1.26 (t, J = 7.1, 3 H), 2.4 (m, 2 H), 2.53 (m, 1 H), 2.92 (m, 1 H), 4.2 (q, J = 7.1, 2 H), 4.47 (t, J = 8, 1 H), 4.59 (dd, J = 11.5, 8, 1 H), 5.53 (d br, J = 9.5, 1 H), 5.74 (dtd, J = 9.5, 5, 2, 1 H). The minor isomer is detected at 5.88 (dt, J = 9.7, 3.7, 1 H), 6.10 (dt, J = 9.7, 2.2, 1 H); ^{13}C NMR (major isomer) δ 14.0 (CH_3), 16.7 (CH_3), 30.5 (CH_2), 31.1 (CH), 50.3 (CH), 52.8 (C), 62.1 (CH_2), 71.0 (CH_2), 125.0 (=CH), 133.1 (=CH), 167.8 (C=O), 174.1 (C=O); (minor isomer) δ 14.0 (CH_3), 19.2 (CH_3), 26.2 (CH_2), 35.3 (CH), 51.2 (CH), 53.6 (C), 62.3 (CH_2), 70.3 (CH_2), 122.9 (=CH), 132.4 (=CH), 167.5 (C=O), 172.7 (C=O).

Ethyl 6,7-dimethyl-3-oxa-2-oxobicyclo[3.3.0]octane-1-carboxylate (22b): ^{1}H NMR δ 0.93 (d, J = 6.7, 3 H), 0.95 (d, J = 7, 3 H), 1.28 (t, J = 7.1, 3 H), 1.95 (dd, J = 12.7, 6.1, 1 H), 2.20 (m, 1 H), 2.20–2.40 (m, 2 H), 2.78 (m, 1 H), 4.09 (dd, J = 9.3, 2.4, 1 H), 4.22 (q, J = 7.1, 2 H), 4.56 (dd, J = 9.3, 7.6, 1 H).

Ethyl 5-methyl-8-oxa-9-oxobicyclo[4.3.0]nonane-1-carboxylate (23b): ^{1}H NMR 0.94 (d, J = 6.3, 3 H), 1.28 (t, J = 7.1, 3 H), 1.35–2.0 (m, 6 H), 2.15 (m, 1 H), 2.57 (m, 1 H), 4.1–4.25 (m, 2 H), 4.35 (t, J = 7.6, 1 H), 4.57 (dd, J = 11.5, 7.6, 1 H).

Ethyl 3-acetoxy-5-methyl-8-oxa-9-oxobicyclo[4.3.0]nonane-1-carboxylate (24b): IR 1785, 1734, 1240 cm^{-1}; ^{1}H NMR δ 0.98 (d, J = 6.1, 3 H), 1.31 (t, J = 7.1, 3 H), 1.35 (superimposed m, 1 H), 1.46 (t, J = 12, 1 H), 1.95–2.22 (m, 3 H), 2.04 (superimposed s, 3 H), 2.80 (dd, J = 12, 5, 1 H), 4.16–4.31 (m, 2 H), 4.37 (t, J = 8, 1 H), 4.57 (dd, J = 11.5, 8, 1 H), 5.07 (tt, J = 12, 5, 1 H); ^{13}C NMR δ 13.8 (CH_3), 18.6 (CH_3), 21.0 (CH_3), 27.1 (CH), 34.7 (CH_2), 39.7 (CH_2), 52.9 (CH), 54.0 (C), 62.2 (CH_2), 69.4 (CH), 70.3 (CH_2), 167.2 (C=O), 169.9 (C=O), 172.4 (C=O). Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.12; H, 7.25.

Ethyl 3-(2-propenyl)-2-oxo-4-vinyltetrahydrofuran-3-carboxylate (25b): IR 1785, 1745, 1650 cm^{-1}; ^{1}H NMR δ 1.29 (t, J = 7.1, 3 H), 2.60 (dd, J = 14.4, 8.9, 1 H), 2.76 (dd, J = 14.4, 5.8, 1 H), 3.34 (dt, J = 10.3, 8.2, 1 H), 4.1–4.5 (m, 4 H), 5.1–5.3 (m, 4 H), 5.5–5.9 (m, 2 H); ^{13}C NMR δ 14.2 (CH_3), 35.4 (CH_2), 46.3 (CH), 57.5 (C), 62.1 (CH_2), 69.5 (CH_2), 121.0 (=CH_2), 121.1 (=CH_2), 130.9 (=CH), 132.0 (=CH), 167.9 (C=O), 174.3 (C=O). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.14; H, 7.33.

Oxidative Cyclization of 13c. Under conditions A, **13c** (1 g, 4.16 mmol) afforded successively 88 mg (conv 91%) of unreacted **13c**; 150 mg of **25c**; 292 mg of a 1:1.26 mixture of **25c** and **19c** (the ratio was deduced from the ^{1}H NMR spectrum from the relative intensities of signals at 4.98 and 4.90 ppm, corresponding to 1 H of **25c** and **19c**, respectively); 61 mg of **19c** (the compound is contaminated with traces of an isomer that could be **21c**, owing to signals corresponding to ethylenic protons at δ 5.45 and 5.80 in the ^{1}H NMR spectrum to two monosubstituted ethylenic carbons at δ 123.3 and 136.8 in the ^{13}C NMR spectrum); 97 mg of **26c**, and 85 mg of **17c**. Under conditions B, the reaction led to the recovery of 22 mg (conv 98%) of **13c**, 135 mg of **25c**, traces of **23c** (identified exclusively by ^{1}H NMR spectroscopy), 97 mg of **22c**, 135 mg of **26c**, and 80 mg of **17c**.

4,4-Dimethyl-1-(2-propenyl)-3,7-dioxabicyclo[3.3.0]octane-2,8-dione (17c): mp 80–81 °C (C_5H_{12}/$CHCl_3$); IR 1780, 1747, 1644 cm^{-1}; ^{1}H NMR δ 1.46 (s, 3 H), 1.51 (s, 3 H), 2.74–2.98 (AB part of an ABX, J_{AB} = 14, 2 H), 2.99 (dd, J = 7, 2.3, 1 H), 4.3 (dd, J = 10.5, 7, 1 H), 4.45 (dd, J = 10.5, 2.3, 1 H), 5.24–5.32 (m, 2 H), 5.68 (ddt, J = 17.1, 9.6, 7.3, 1 H); ^{13}C NMR δ 23.9 (CH_3), 30.4 (CH_3), 38.0 (CH_2), 49.6 (CH), 57.0 (C), 66.7 (CH_2), 83.7 (C), 121.7 (=CH_2), 130.7 (=C), 169.7 (C=O), 171.7 (C=O). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.89; H, 6.80.

6,6-Dimethyl-7-methylene-3-oxa-2-oxobicyclo[3.3.0]octane-1-carboxylate (19c): IR 1775, 1735, 1660 cm^{-1}; ^{1}H NMR δ 1.06 (s, 3 H), 1.09 (s, 3 H), 1.29 (t, J = 7.1, 3 H), 2.85 (d, br, J = 17.3, 1 H), 2.96 (dd, J = 7.9, 5.1, 1 H), 3.48 (dt, J = 17.3, 2.3, 1 H), 4.09 (dd, J = 9.6, 5.1, 1 H), 4.30 (q, J = 7.1, 2 H), 4.45 (dd, J = 9.6, 7.9, 1 H), 4.84 (br s, 1 H), 4.91 (br s, 1 H); ^{13}C NMR δ 14.0 (CH_3), 21.8 (CH_3), 28.6 (CH_3), 37.7 (CH_2), 45.0 (C), 56.5 (CH), 57.9 (C), 62.4 (CH_2), 68.3 (CH_2), 106.2 (=CH_2), 155.0 (=C), 170.0 (C=O), 176.3 (C=O). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.52; H, 7.61. Found: C, 65.53; H, 7.64.

Ethyl 3-oxa-2-oxo-6,7,7-trimethylbicyclo[3.3.0]octane-1-carboxylate (22c): IR 1777, 1740 cm^{-1}; ^{1}H NMR δ 0.98 (s, 3 H), 0.98 (d, J = 6.2, 3 H), 1.6 (s, 3 H), 1.34 (t, J = 7.1, 3 H), 1.80 (m, 1 H), 2.33 (m, 2 H), 2.86 (dd, J = 8.1, 3.7, 1 H), 4.28 (q, J = 7.1, 2 H), 4.34 (superimposed m, 1 H), 4.44 (t, J = 8.1, 1 H); ^{13}C NMR δ 12.9 (CH_3), 13.9 (CH_3), 22.8 (CH_3), 23.3 (CH_3), 39.5 (CH_2), 42.4 (CH), 43.7 (C), 56.3 (CH), 59.5 (C), 62.0 (CH_2), 68.3 (CH_2), 170.1 (C=O), 176.3 (C=O). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.97; H, 8.38. Found: C, 64.96; H, 8.28.

Ethyl 5,5-dimethyl-8-oxa-9-oxobicyclo[4.3.0]nonane-1-carboxylate (23c): ^{1}H NMR δ 0.93 (s, 3 H), 1.07 (s, 3 H), 1.37 (t, J = 7.3, 3 H), 1.4–2.1 (m, 5 H), 2.31 (dd, J = 12.3, 7.5, 2 H), 2.63 (dt, J = 13.1, 3.4, 1 H), 4.30 (q, J = 7.3, 2 H), 4.39 (t, J = 7.5, 1 H), 4.80 (dd, J = 12.3, 7.5, 1 H).

Ethyl 4-isopropenyl-3-(2-propenyl)-2-oxotetrahydrofuran-3-carboxylate (25c): IR 1770, 1735, 1640 cm^{-1}; ^{1}H NMR δ 1.24 (t, J = 7.1, 3 H), 1.80 (s, 3 H), 2.76 (dd, J = 14.5, 9.5, 1 H), 2.96 (dd, J = 14.5, 5.1, 1 H), 3.28 (dd, J = 11, 8.5, 1 H), 4.16 (q, J = 7.1, 2 H), 4.33 (t, J = 8.5, 1 H), 4.45 (dd, J = 11, 8.5, 1 H), 4.75 (s, 1 H), 4.98 (s, 1 H), 5.19–5.28 (m, 2 H), 5.64 (m, 1 H); ^{13}C NMR δ 14.1 (CH_3), 23.0 (CH_3), 36.3 (CH_2), 46.7 (CH), 58.2 (C), 62.0 (CH_2), 68.3 (CH_2), 113.8 (=CH_2), 121.3 (=CH_2), 132.1 (=CH), 139.2 (=C), 168.1 (C=O), 174.4 (C=O). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.52; H, 7.61. Found: C, 65.54; H, 7.71.

Ethyl 4-(1-acetoxyisopropyl)-3-(2-propenyl)-2-oxotetrahydrofuran-3-carboxylate (26c): mp 78–79 °C ($C_5H_{12}CHCl_3$); IR 1770, 1740, 1644 cm^{-1}; ^{1}H NMR δ 1.30 (t, J = 7.1, 3 H), 1.53 (s, 3 H), 1.69 (s, 3 H), 1.95 (s, 3 H), 2.75 (dd, J = 11.1, 8.3, 1 H), 2.87–3.05 (AB part of an ABX, 2 H), 4.09–4.46 (m 4 H), 5.19–5.28 (m, 2 H), 5.47–5.54 (m, 1 H); ^{13}C NMR δ 13.9 (CH_3), 22.1 (CH_3), 23.7 (CH_3), 25.0 (CH_3), 37.0 (CH_2), 51.4 (CH), 55.6 (C), 61.9 (CH_2), 66.4 (CH_2), 80.3 (C), 121.4 (=CH_2), 132.1 (=C), 168.7 (C=O), 169.3 (C=O), 174.7 (C=O). Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.43; H, 7.49.

Oxidation of 13a with Mn(OAc)$_3$LiCl. The oxidation of **13a** (1 g, 4.71 mmol) in the presence of 2 equiv of LiCl led to 1.12 g of crude product. Separation by column chromatography afforded 146 mg of a mixture containing unreacted **13a**, 313 mg of **27a**, 165 mg of a fraction containing mainly the two stereoisomers of **28a** (from ^{1}H and ^{13}C NMR analysis, the presence of an unidentified third component, in traces amount, was suspected. The incorrect elemental analysis suggests that the third component might be the unstable isomeric chloride with a [4.3.0]bicyclononane skeleton, readily eliminated when heated. The ^{1}H NMR spectrum of *endo*- and *exo*-**28a** were deduced from the mixture spectrum), and 46 mg of **17a**.

Ethyl 4-(chloromethyl)-3-(2-propenyl)-2-oxotetrahydrofuran-3-carboxylate (27a): IR 1781, 1740, 1642 cm^{-1}; ^{1}H NMR δ 1.37 (t, J = 7.1, 3 H), 2.80 (d, J = 7.3, 2 H), 3.12 (m, 1 H), 3.46 (t, J = 11, 1 H), 3.73 (dd, J = 11, 5.2, 1 H), 4.19 (dd, J = 10, 9, 1 H), 4.31 (q, J = 7.1, 2 H), 4.60 (t, J = 9, 1 H), 5.26–5.29 (m, 2 H), 5.72 (m, 1 H); ^{13}C NMR δ 14.1 (CH_3), 36.6 (CH_2), 41.4 (CH_2), 44.2 (CH), 56.8 (C), 62.5 (CH_2), 69.7 (CH_2), 121.5 (=CH_2), 131.5 (=CH), 167.6 (C=O), 173.7 (C=O). Anal. Calcd for $C_{11}H_{15}O_4Cl$: C, 53.55; H, 6.12; Cl, 14.37. Found: C, 53.59; H, 6.42; Cl, 14.6.

Ethyl 7-(chloromethyl)-6,6-dimethyl-3-oxa-2-oxobicyclo-[3.3.0]octane-1-carboxylate (28a): IR 1775, 1731 cm^{-1}; ^{1}H NMR δ 1.16 (t, J = 7.1, 0.5 × 3 H), 1.21 (t, J = 7.1, 0.5 × 3 H), 1.87 (m, 1 H), 1.94–2.60 (m, 3 H), 2.72 (two superimposed dd, J = 13.8, 7.9, 1 H), 2.97–3.16 (m, 1 H), 3.37–3.55 (m, 2 h), 4.04 (dd, J = 9.4,

2.3, 0.5 × 1 H), 4.16 (q, J = 7.1, 2 H), 4.0–4.26 (m, 0.5 × 1 H), 4.45 (dd, J = 9.2, 6.5, 0.5 × 1 H), 4.49 (dd, J = 9.4, 7.7, 0.5 × 1 H); ^{13}C NMR δ 14.0 (2 × CH_3), 36.8 (CH_2), 37.4 (CH_2), 37.8 (CH_2), 38.0 (CH_2), 41.2 (CH), 43.5 (CH), 44.2 (CH), 46.7 (2 × CH_2), 47.1 (CH), 61.3 (C), 61.7 (C), 62.3 (CH_2), 62.4 (CH_2), 71.2 (CH_2), 73.3 (CH_2), 169.2 (C=O), 169.5 (C=O), 175.8 (C=O), 176.1 (C=O). Anal. Calcd for $C_{11}H_{15}O_4Cl$: C, 53.55; H, 6.12; Cl, 14.37. Found: C, 53.51; H, 6.16; Cl, 12.1.

Oxidation of 13b with Mn(OAc)$_3$LiCl. Treating **13b** (1 g, 4.42 mmol) under the preceding conditions afforded 1.11 g of a crude product, the separation of which gave 98 mg (conv 90%) of unreacted **13b**; 269 mg of one diastereoisomer of **27b**; 137 mg of the other diastereomer of **27b**, and 226 mg of **28b** as a mixture of isomers.

Ethyl 4-(1-Chloromethyl)-3-(2-propenyl)-2-oxotetrahydrofuran-3-carboxylate (27b). First diastereoisomer: IR 1782 1739, 1643 cm^{-1}; ^{1}H NMR δ 1.24 (t, J = 7.1, 3 H), 1.54 (d, J = 6.5, 3 H), 2.56 (dd, J = 14.6, 5.0, 1 H), 2.63–2.97 (m, 2 H), 3.90 (dq, J = 10.4, 6.5, 1 H), 4.11 (dd, J = 10.6, 8.6, 1 H), 4.20 (q, J = 7.1, 2 H), 4.45 (t, J = 8.6, 1 H), 5.11–5.24 (m, 2 H), 5.55 (m, 1 H); ^{13}C NMR δ 14.1 (CH_3), 24.1 (CH_3), 36.5 (CH_2), 48.4 (CH), 56.6 (CH), 57.2 (C), 62.6 (CH_2), 69.9 (CH_2), 121.8 (=CH_2), 131.5 (=CH), 167.7 (C=O), 174.0 (C=O). Anal. Calcd for $C_{12}H_{17}O_4Cl$: C, 55.28; H, 6.57; Cl, 13.59. Found: C, 55.25; H, 6.44; Cl, 13.53. Second diastereoisomer: IR 1780, 1742, 1642 cm^{-1}; ^{1}H NMR δ 1.12 (t, J = 7.1, 3 H), 1.29 (d, J = 6.5, 3 H), 2.78–2.91 (m, 3 H), 3.87 (dd, J = 10.4, 8.6, 1 H), 3.91 (superimposed m, 1 H), 4.08 (q, J = 7.1, 2 H), 4.14 (t, J = 8.6, 1 H), 5.04–5.11 (m, 2 H), 5.41 (ddt, J = 16.2, 9.4, 6.6, 1 H); ^{13}C NMR δ 14.0 (CH_3), 23.6 (CH_3), 36.5 (CH_2), 48.4 (CH), 54.4 (CH), 57.6 (C), 62.4 (CH_2), 68.4 (CH_2), 121.8 (CH_2), 131.8 (CH), 167.8 (C=O), 173.9 (C=O). Anal. Calcd for $C_{12}H_{17}O_4Cl$: C, 55.28, H, 6.57; Cl, 13.59. Found: C, 55.28; H, 6.60; Cl, 13.50.

Ethyl 7-(chloromethyl)-6-methyl-3-oxa-2-oxobicyclo[3.3.0]octane-1-carboxylate (28b): IR 1774, 1738 cm^{-1}; ^{1}H NMR δ 0.95 (d, J = 7.1, 0.65 × 3 H), 1.01 (d, J = 7.3, 0.35 × 3 H), 1.21 (t, J = 7.1, 3 H), 1.6–2.8 (m, 5 H), 3.3–3.6 (m, 2 H), 4.04 (dd, J = 9.4, 2.8, 0.65 × 1 H), 4.16 (q, J = 7.1, 2 H), 4.24–4.45 (m, 0.35 × 2 H), 4.52 (dd, J = 9.4, 8.0, 0.65 × 1 H); ^{13}C NMR (major isomer) δ 13.6 (CH_3), 15.6 (CH_3), 35.5 (CH_2), 42.6 (CH), 52.3 (CH), 60.1 (C), 61.9 (CH_2), 71.79 (CH_2), 169.2 (C=O), 175.9 (C=O); (minor isomer) 12.8 (CH_3), 13.6 (CH_3), 35.8 (CH_2), 43.9 (CH), 44.4 (CH_2), 45.1 (CH), 54.4 (CH), 58.6 (C), 61.9 (CH_2), 69.7 (CH_2), 169.2 (C=O), the second C=O is not detected. Anal. Calcd for $C_{12}H_{17}O_4Cl$: C, 55.28; H, 6.57; Cl, 13.59. Found: C, 55.13; H, 6.60; Cl, 13.50.

Oxidation of 13c with Mn(OAc)$_3$LiCl. Treating **13c** (1 g, 4.16 mmol) led to 1.05 g of crude product. After column chromatography, 210 mg (conv 79%) of starting material, 82 mg of **28c** (as a 1:1 mixture of diastereoisomers), and 255 mg (37%) of **17c** were isolated successively.

Ethyl 7-(chloromethyl)-6,6-dimethyl-3-oxa-2-oxotetrahydrofuran-1-carboxylate (28c): IR 1776, 1738 cm^{-1}; ^{1}H NMR δ 0.81 (s, 0.5 × 3 H), 0.97 (s, 0.5 × 3 H), 1.14 (s, 0.5 × 3 H), 1.15 (s, 0.5 × 3 H), 1.32 (t, J = 7.1, 0.5 × 3 H), 1.33 (t, J = 7.1, 0.5 × 3 H), 1.95 (dd, J = 13.9, 12, 0.5 × 1 H), 2.05–2.38 (m, 2 H), 2.55 (AB part of a ABX, J_{AB} = 14, 0.5 × 2 H), 2.78 (d, J = 6.2, 0.5 × 1 H), 2.90 (dd, J = 8.3, 4, 0.5 × 1 H), 2.99 (dd, J = 13.9, 7.4, 0.5 × 2 H), 2.78 (d, J = 6.2, 0.5 × 1 H), 2.90 (dd, J = 8.3, 4, 0.5 × 1 H), 2.99 (dd, J = 13.9, 7.4, 0.5 × 1 H), 3.40 (dd, J = 10.8, 8.9, 0.5 × 1 H), 3.45 (t, J = 9, 0.5 × 1 H), 3.62 (dd, J = 9.5, 0.5 × 1 H), 3.64 (dd, J = 10.8, 4.9, 0.5 × 1 h), 4.27 (q, J = 7.1, 2 H), 4.27 (hidden m, 0.5 × 1 H), 4.33 (dd, J = 9.6, 4, 0.5 × 1 H), 4.50 (m, 1 H); ^{13}C NMR δ 14.0 (2 × CH_3), 15.7 (CH_3), 23.4 (CH_3), 23.7 (CH_3), 26.7 (CH_3), 35.7 (CH_2), 36.7 (CH_2), 43.8 (CH_2), 43.9 (2 × C), 44.1 (CH_2), 50.4 (CH), 53.2 (CH), 57.1 (CH), 58.0 (C), 58.3 (CH), 58.9 (C), 62.3 (CH_2), 62.4 (CH_2), 66.6 (CH_2), 68.0 (CH_2), 169.7 (C=O), 176.3 (C=O). Anal. Calcd for $C_{13}H_{19}O_4Cl$: C, 56.83; H, 6.97; Cl, 12.90. Found: C, 56.85; H, 6.88; Cl, 13.0.

Supplementary Material Available: ^{1}H NMR spectra of compounds **1a–c**, **13a–c**, **10b + 11b**, **11b**, **21b**, **22b**, **23b**, and **23c** and ^{13}C NMR spectrum of **21b** (13 pages). Ordering information is given on any current masterhead page.

Vinyl Radical Cyclizations: Synthesis of Substituted Bicyclooctanols

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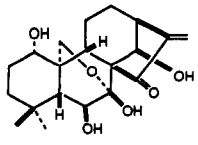
The preparation and free-radical bicyclic ring closure of 4-(2-bromo-2-propen-1-yl)cyclohexene **7** is described. The bicyclo[3.2.1] and -[2.2.2] alcohols **9** and **10** arising, respectively, from 5-*exo* and 6-*endo* (or 6-*exo*) modes of cyclization of a vinyl radical were isolated in a 1:1 ratio. Factors affecting the regiochemical outcome were investigated.

Introduction

Oridonin **1** is a member of a class of diterpenoids that have been isolated from various Rabdosia (Labiatae) species growing in China and Japan.[1] The *ent*-kaurane



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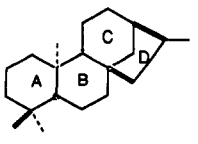

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structure **2** is a common feature of the majority of these diterpenoids. Its highly oxidized framework and its antitumor activity[1,2] make oridonin an attractive synthetic target. Our approach involves free-radical cyclization of a vinyl bromide for construction of the bicyclo[3.2.1]octanol derivative of the C/D subunit. This approach relies on precedent for intramolecular addition of vinyl radicals to carbon–carbion double bonds.[3-5]

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