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Mn(III)-Based Oxidative Free-Radical Cyclizations of Substituted Allyl α-Methyl-β-ketoesters: Syntheses, DFT Calculations, and Mechanistic Studies

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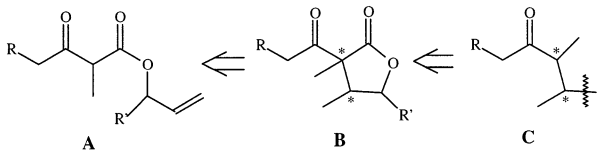
The cyclizations of the substituted allyl α-methyl-β-ketoester radicals **11**, **14**, and **18** were studied by the DFT method at the UB3LYP/6-31G* level; the results show that the cis cyclization is easier than the corresponding trans cyclization, but the generated cis radicals are not necessarily more stable than the corresponding generated trans radicals after the cyclizations. The free-radical cyclizations of **11**, **14**, and **18** in the presence of $Mn(OAc)_3$ in acetic acid or acetonitrile are all reversible and operate under thermodynamic control, and stereoselectivity of the cyclizations depends on relative stability of the cyclization-generated radicals. Therefore, the oxidative free-radical cyclization of allyl α-methyl-β-ketoester **5a** with $Mn(OAc)_3$ gives a cis product as a major product, while the same oxidative free-radical cyclizations of substituted allyl α-methyl-β-ketoesters **5b** and **5c** with $Mn(OAc)_3$ produce trans products as major products.

Introduction

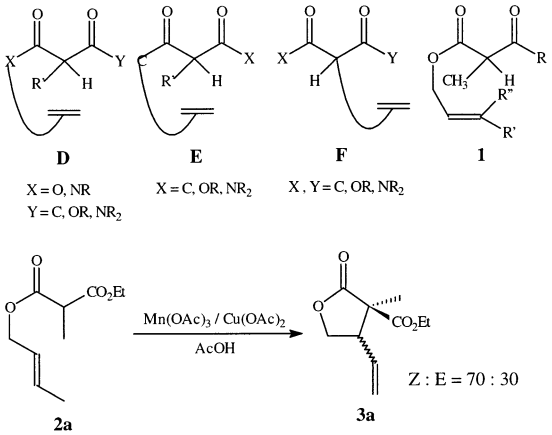
Because enantiomers of the same general compound may have different biological activities, syntheses of chiral compounds have been a hot topic in organic chemistry.[1] Stereoselective formation of C−C bonds is one strategy for synthesizing chiral compounds, and ionic Aldol condensation and pericyclic reactions are usual methodologies for such syntheses.[1] In this study, we investigated the possibility of the stereoselective formation of a C−C bond through a free-radical cyclization mechanism.



A **B** **C**

For the above retrosynthetic analysis, if one uses a chiral catalyst or a chiral auxiliary at R or R′ of **A** and **B**, it is possible to diastereoselectively make a ketone **C** with two adjacent chiral centers on C_α and C_β. In this study, a chiral catalyst or a chiral auxiliary was not used, but our major concern was whether the cyclization from **A** to **B** through the free-radical mechanism was stereoselective.

Heiba and Dessau reported in 1974 that β-ketoesters and related β-dicarbonyl compounds are oxidized to radicals at 25−70 °C in acetic acid with $Mn(OAc)_3$.[2] Later, the application of the oxidant to the oxidative free-radical cyclizations was investigated extensively.[3,4] There are at least three types of β-dicarbonyl compounds **D**−**F** that have been used to undergo the oxidative free-radical monocyclizations with $Mn(OAc)_3$.[4] To our knowledge, there is no known example for monocyclization of **1** with $Mn(OAc)_3$, and the advantage for this type of monocyclization is that it may stereoselectively form a C−C bond with two adjacent chiral centers after hydrolysis and decarboxylation and leave R intact, which is a main part of the original structure.



Bertrand et al. has performed the oxidative free-radical cyclization of allyl malonate **2a** with $Mn(OAc)_3/Cu(OAc)_2$ in acetic acid to produce vinyl lactone **3a** with an *Z*:*E* ratio of 70:30.[3j] However, there was no explanation of the stereoselectivity. The oxidative free-radical cyclization of the allyl malonates usually produces 5-exo cyclization products, and no 6-endo cyclization products have been

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observed.[3j,4,5] Structures of the substituted allyl β-ketoesters **1** are similar to that of allyl malonate **2a**, so the oxidative free-radical cyclization of **1** may give the 5-exo cyclization products only, which makes system **1** a good model for studying the stereoselectivity of the cyclization.

In this study, we investigated the mechanisms and stereoselectivity of the free-radical cyclizations of substituted allyl α-methyl-β-ketoester radicals, which were prepared from oxidation of **1** with $Mn(OAc)_3$, by means of syntheses and DFT calculations. Hopefully, the results in this study help chemists to control the stereoselectivity of the free-radical cyclization of this type of compound.

Computational Details

All calculations reported here were performed with Gaussian98 program.[6] Geometry optimizations of **11**, *cis*-**12(TS)**, *cis*-**13**, *cis*-**6**, *trans*-**12(TS)**, *trans*-**13**, *trans*-**6**, **14**, *cis*-**15(TS)**, *cis*-**16**, *cis*-**7**, *trans*-**15(TS)**, *trans*-**16**, *trans*-**7**, **17**, **18**, *cis*-**19(TS)**, *cis*-**20**, *cis*-**9**, *trans*-**19(TS)**, *trans*-**20**, *trans*-**9**, *cis*-**22a**, *cis*-**22b**, *trans*-**22a**, and *trans*-**22b** were carried out at the UB3LYP/6-31G*[7] level for radicals and the B3LYP/6-31G*[7] level for nonradicals without any symmetry restriction except for *cis*-**22a** and *cis*-**22b**, whose dihedral angle between propionyl C═O and the five-membered ring is fixed at −15.8° in order to avoid the attack of the carbonyl oxygen on the carbon cation. The optimized structures of *cis*-**22a**, *cis*-**22b**, *trans*-**22a**, and *trans*-**22b** are shown in Figure 1, and the others are shown in Figures 2−4 in Supporting Information. After all the geometry optimizations were performed, analytical vibration frequencies were calculated at the same level to determine the nature of the located stationary points. Thus, all the stationary points found were properly characterized by evaluation of the harmonic frequencies. The energies of all the stationary points were calculated at the same level with scaled zero-point vibration energies included. The scaled factor of 0.9804 for the zero-point vibration energies is used according to the literature.[7a] Many possible conformations have been optimized for each of the above configurations, and the conformation with the lowest energy was chosen for each configuration. Spin contamination from higher spin states is significant for both HF and MP2 methods, but it is much less for both UB3LYP and QCISD methods.[7a,b] Therefore, the reliability of the calculations on the radicals at the UB3LYP/6-31G* level in this study should be good.[7a,b]

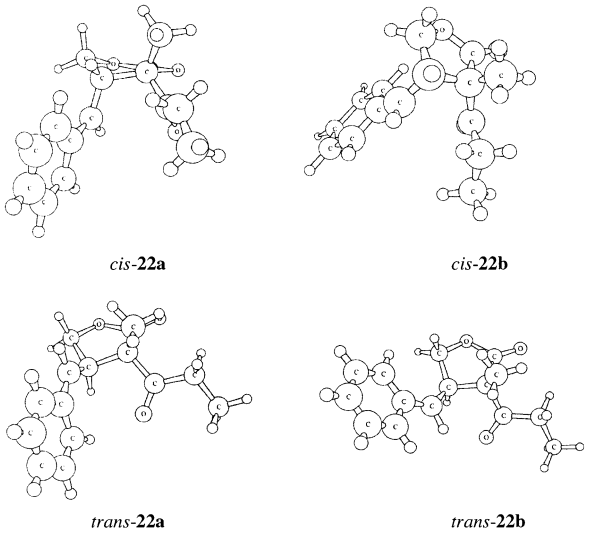

FIGURE 1. Optimized structures of *cis*-**22a**, *cis*-**22b**, *trans*-**22a**, and *trans*-**22b** at the B3LYP/6-31G* level.

Results

DFT Calculations. It is known that the reactions of the α-alkyl-β-ketoesters with $Mn(OAc)_3$ generate the α-alkyl-β-ketoester radicals with loss of Mn(II),[3e,k] so we monitored the free-radical cyclization reactions of the substituted allyl α-methyl-β-ketoester radicals by starting from the generated radicals **11**, **14**, and **18**. There are two possible routes through which each of the generated radicals could undergo the cyclization reactions; one forms a cis product through the cyclization, and the other produces a trans product. All of them are monitored by the density functional theory at the UB3LYP/6-31G* level for radicals and the B3LYP/6-31G* level for nonradicals, and the results are shown in Table 1. Regarding the α-methyl-β-ketoester radical **11**, activation energy to form *cis*-**13** is 2.22 kcal/mol smaller than that forming *trans*-**13**, and *cis*-**13** is 0.08 kcal/mol more stable than *trans*-**13** (Scheme 1). After hydrogen abstraction, *trans*-**6** is 0.62 kcal/mol more stable than *cis*-**6**. As far as the α-methyl-β-ketoester radical **14** is concerned, the activation energy to form *cis*-**16** is 2.86 kcal/mol smaller than that forming *trans*-**16**, while *trans*-**16** is 1.97 kcal/mol more stable than *cis*-**16** (Scheme 2). After

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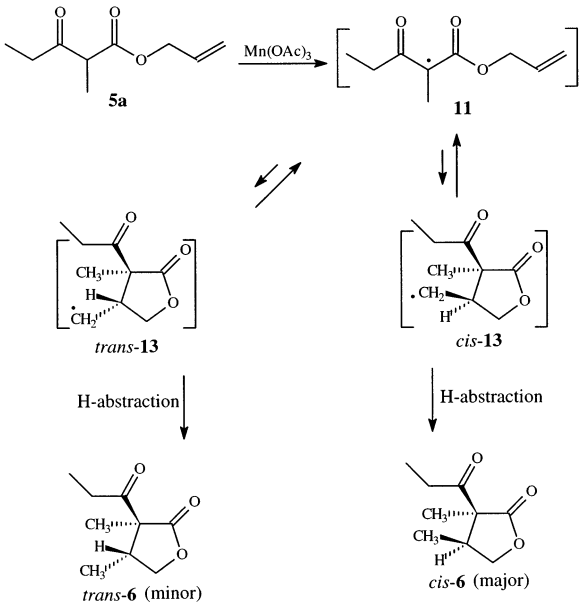
TABLE 1. Calculated Energies, Imaginary Frequencies, Relative Energies, Spin Density, and ⟨S²⟩ of the Stationary Points along the Cyclization Paths of the Radicals 11, 14, and 18 at the UB3LYP/6-31G* Level[a]

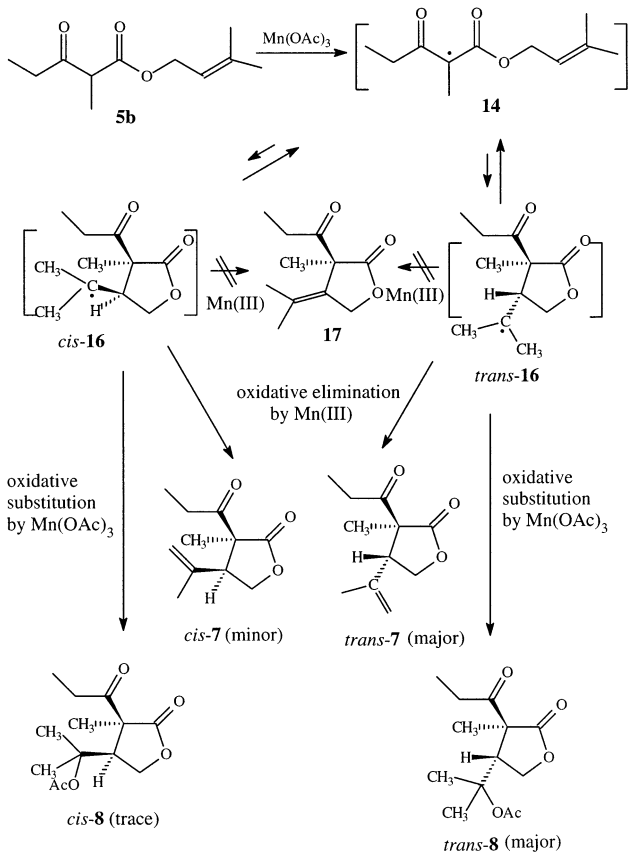
				spin density on			
stationary point	energy (hartree)	imaginary frequency cm^{-1}	relative energy (kcal/mol)	ketone oxygen	ester oxygen	carbon radical	⟨S²⟩
11	−576.20382		0.00	0.23	0.14	0.78	0.7501
cis-**12(TS)**	−576.17626	−459	17.29	0.13	0.05	0.58[b]/0.57[c]	0.7503
cis-**13**	−576.20055		2.05	0.00	0.00	1.07	0.7500
cis-**6**	−576.85709						
trans-**12(TS)**	−576.17273	−448	19.51	0.14	0.04	0.55[b]/0.59[c]	0.7504
trans-**13**	−576.20042		2.13	0.00	0.00	1.07	0.7500
trans-**6**	−576.85808						
14	−654.78545		0.00	0.23	0.14	0.78	0.7501
cis-**15(TS)**	−654.75971	−440	16.15	0.13	0.05	0.52[b]/0.53[c]	0.7503
cis-**16**	−654.77989		3.49	0.00	0.00	0.96	0.7500
cis-**7**	−654.21557						
trans-**15(TS)**	−654.75516	−424	19.01	0.13	0.04	0.49[b]/0.57[c]	0.7503
trans-**16**	−654.78303		1.52	0.00	0.00	0.96	0.7500
trans-**7**	−654.21882						
17	−654.22543						
18	−807.18464		6.56	0.23	0.14	0.78	0.7501
cis-**19(TS)**	−807.16300	−372	20.14	0.14	0.06	0.39[b]/0.58[c]	0.7507
cis-**20**	−807.19391		0.75	0.00	0.00	0.75	0.7506
cis-**9**	−1035.66227						
trans-**19(TS)**	−807.15993	−341	22.07	0.16	0.05	0.35[b]/0.61[c]	0.7506
trans-**20**	−807.19510		0.00	0.00	0.00	0.75	0.7506
trans-**9**	−1035.66238						

[a] E_a for (**11**−*cis*-**12(TS)**−*cis*-**13**) = 17.29 kcal/mol; E_a for (**11**−*trans*-**12(TS)**−*trans*-**13**) = 19.51 kcal/mol); E_a for (**14**−*cis*-**15(TS)**−*cis*-**16**) = 16.15 kcal/mol; E_a for (**14**−*trans*-**15(TS)**−*trans*-**16**) = 19.01 kcal/mol; E_a for (**18**−*cis*-**19(TS)**−*cis*-**20**) = 13.58 kcal/mol; E_a for (**18**−*trans*-**19(TS)**−*trans*-**20**) = 15.51 kcal/mol. <S²> is the one after annihilation. [b] Forming carbon radical. [c] Disappearing carbon radical.

SCHEME 1



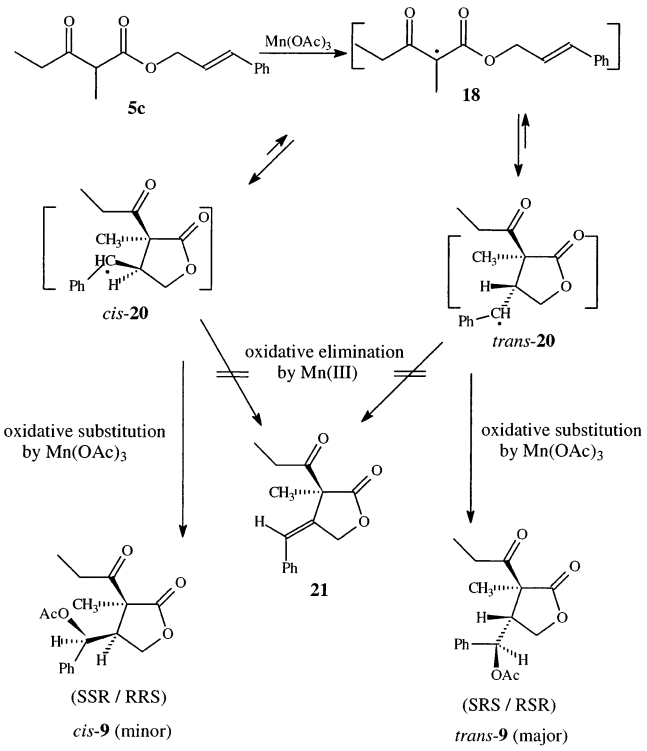
SCHEME 2



further oxidative elimination (Hofmann β-elimination), the generated *trans*-**7** is 2.04 kcal/mol more stable than the generated *cis*-**7**. On the other hand, the product **17** from Zaitsev β-elimination is 4.15 kcal/mol more stable than the product *trans*-**7** from Hofmann β-elimination. As for the α-methyl-β-ketoester radical **18**, the activation energy to form *cis*-**20** is 1.93 kcal/mol smaller than that forming *trans*-**20**, while *trans*-**20** is 0.75 kcal/mol more stable than *cis*-**20** (Scheme 3). After further oxidative substitution, both *cis*-**9** and *trans*-**9** were produced and *trans*-**9** is 0.07 kcal/mol more stable than *cis*-**9**.

Synthesis. Reactions of **4** with alcohols in the presence of catalytic sodium acetate produced the corresponding α-methyl-β-ketoesters **5** in good yields (Scheme 4). Product distribution, yields, and reaction conditions for the oxidative free-radical cyclizations of **5a**−**d** with 2 equiv

SCHEME 3



SCHEME 4

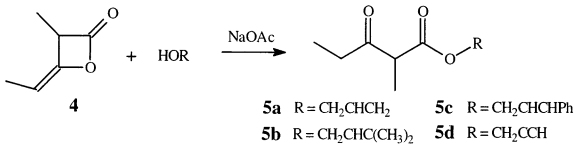
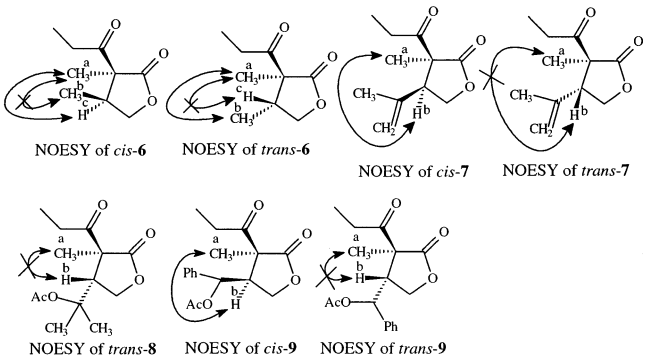


TABLE 2. Product Distribution, Yields, and Reaction Conditions for the Oxidative Free-Radical Cyclizations of 5a−d with $Mn(OAc)_3$

reactant	solvent	temp (°C)	time (h)	products (yield)
5a	CH_3CN	80	15	*cis*-**6** (37%), *trans*-**6** (19%)
5a	CH_3CO_2H	80	15	*cis*-**6** (26%), *trans*-**6** (14%)
5b	CH_3CN	80	15	*cis*-**7** (12%), *trans*-**7** (34%) *trans*-**8** (18%)
5b	CH_3CO_2H	80	15	*cis*-**7** (12%), *trans*-**7** (28%) *trans*-**8** (25%)
5c	CH_3CN	50	15	*cis*-**9** (11%), *trans*-**9** (20%)
5c	CH_3CO_2H	50	15	*cis*-**9** (9%), *trans*-**9** (24%)
5c	CH_3CN	80	15	*cis*-**9** (7%), *trans*-**9** (28%)
5c	CH_3CO_2H	80	15	*cis*-**9** (7%), *trans*-**9** (34%)
5d	CH_3CO_2H	50	10	**10** (38%)
5d	CH_3CN	80	10	**10** (42%)

of $Mn(OAc)_3$ are shown in Table 2. Reaction of **5a** with 2 equiv of $Mn(OAc)_3$ in acetonitrile or glacial acetic acid at 80 °C for 15 h produced both *cis*-**6** and *trans*-**6** with the cis isomer as a major product (Scheme 1). The cis/trans configurations were confirmed by their NOESY spectra (Scheme 5). The NOESY of *cis*-**6** shows a correlation between CH_3(a) and H(c), but there is no correlation between CH_3(a) and CH_3(b). The NOESY of *trans*-**6** shows a correlation between CH_3(a) and CH_3(b), but there is no correlation between CH_3(a) and H(c). Due to deshielding of propionyl moiety, H(c) in *trans*-**6** is ca. 0.5 ppm more downfield than H(c) in *cis*-**6**. Due to shielding of CH_3(b), CH_3(a) (1.35 ppm) in *trans*-**6** is 0.14 ppm more upfield than that (1.49 ppm) in *cis*-**6**.

SCHEME 5



Reaction of **5b** with 2 equiv of $Mn(OAc)_3$ in either acetonitrile or glacial acetic acid at 80 °C for 15 h produced *cis*-**7**, *trans*-**7**, and *trans*-**8** with the trans isomers as major products (Scheme 2). The amount of *cis*-**8** was too small to be detected, and the Zaitsev β-elimination product **17** was not found. The NOESY of *cis*-**7** shows a correlation between CH_3(a) and H(b), while there is no correlation between CH_3(a) and H(b) in both the NOESY of *trans*-**7** and the NOESY of *trans*-**8** (Scheme 5). Due to deshielding of propionyl moiety, H(b) in *trans*-**7** is ca. 0.6 ppm more downfield than H(b) in *cis*-**7**. Due to shielding of the *i*-propenyl group, CH_3(a) (1.29 ppm) in *trans*-**7** is 0.31 ppm more upfield than that (1.60 ppm) in *cis*-**7**. However, CH_3(a) (1.59 ppm) in *trans*-**8** is 0.30 ppm more downfield than that (1.29 ppm) in *trans*-**7**, and this is due to deshielding of the carbonyl group of AcO in *trans*-**8**.

Reaction of **5c** with 2 equiv of $Mn(OAc)_3$ in either acetonitrile or glacial acetic acid at 50 or 80 °C for 15 h produced both *cis*-**9** and *trans*-**9** with the trans isomer as a major product (Scheme 3). The Zaitsev β-elimination product **21** was not found. The NOESY of *cis*-**9** shows a correlation between CH_3(a) and H(b), while there is no correlation between CH_3(a) and H(b) in the NOESY of *trans*-**9** (Scheme 5). Due to deshielding of the propionyl moiety, H(b) in *trans*-**9** is ca. 0.6 ppm more downfield than H(b) in *cis*-**9**. Due to deshielding of carbonyl group of AcO in *trans*-**9**, CH_3(a) (1.48 ppm) in *trans*-**9** is 0.08 ppm more downfield than that (1.40 ppm) in *cis*-**9**.

The oxidative free-radical cyclization of **5c** with $Mn(OAc)_3$ may produce both radicals *cis*-**20** and *trans*-**20**, followed by oxidative substitution by $Mn(OAc)_3$ to give both *cis*-**9** and *trans*-**9**. During the oxidative substitution, another stereocenter was generated, and its configuration was assigned (Scheme 3) on the basis of ^{1}H NMR spectra and the computational results. The oxidative substitution may involve carbon cations,[8] so the carbon cations **22** were optimized at the B3LYP/6-31G* level (Figure 1). Conformer *cis*-**22a** is 1.64 kcal/mol more stable than conformer *cis*-**22b**, because the latter suffers more "butane-gauche" nonbonding interactions. Similarly, conformer *trans*-**22a** is also 4.67 kcal/mol more stable than conformer *trans*-**22b**. During the oxidative substitution, due to steric hindrance of both propionyl and methyl groups,

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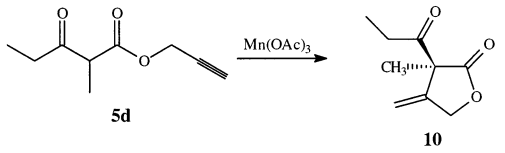
SCHEME 6



the facial selectivity of the carbon cations *cis*-**22a** and *trans*-**22a** is very high when they are attacked by acetate. In other words, the acetate prefers to attack the carbon cations *cis*-**22a** and *trans*-**22a** from the face opposite to both propionyl and methyl groups. Therefore, only one diastereomer resulted from each isomer of radicals **20**. On the basis of their ^{1}H NMR spectra, the other racemic diastereomers could not be found for *cis*-**9** or *trans*-**9**.

Reaction of **5d** with 2 equiv of $Mn(OAc)_3$ in either acetonitrile or glacial acetic acid at 50 or 80 °C for 10 h produced **10** in ca. 40% yield (Scheme 6). All the above oxidative free-radical cyclizations of **5a**−**d** with 2 equiv of $Mn(OAc)_3$ generated the 5-exo cyclization products, and no 6-endo cyclization products could be found.

The free-radical cyclizations of the α-methyl-*β*-ketoesters such as **5a**−**d** with $Mn(OAc)_3$ usually produce a significant amount of polar polymers as major byproducts.[3k] These polymeric byproducts are produced by some monomers that are generated from the α-methyl-*β*-ketoester radicals before the cyclizations,[3k] so the amount of the polymeric byproducts should have nothing to do with the stereoselectivity of the free-radical cyclizations. In addition to the polymeric byproducts, most of other products were collected for analysis of the stereoselectivity for the oxidative cyclization reactions, so the synthetic results in the study should be reliable.

Discussion

According to the DFT calculations, the cis cyclization is easier than the trans cyclization for radicals **11**, **14**, and **18**, but the generated cis radicals (*cis*-**13**, *cis*-**16**, and *cis*-**20**) are not necessarily more stable than the corresponding generated trans radicals (*trans*-**13**, *trans*-**16**, and *trans*-**20**) after the cyclizations. Common features of both cis and trans transition structures during the cyclizations of radicals **11**, **14**, and **18** are (1) the spin on α-carbon prefer to have resonance with the propionyl carbonyl group, (2) the forming five-membered ring has the shape of an envelope, and (3) the substituted vinyl group, which sits on the out-of-plane carbon of the envelope five-membered ring, is located at an equatorial position. A major difference between the cis and trans transition structures is that the substituted vinyl group is closer to the propionyl group (dihedral angle = 44.1° for *cis*-**12(TS)**, 48.7° for *cis*-**15(TS)**, 43.1° for *cis*-**19(TS)**) than to the methyl group (dihedral angle = 83.8° for *cis*-**12(TS)**, 80.0° for *cis*-**15(TS)**, 84.3° for *cis*-**19(TS)**) in the cis transition structures, while the substituted vinyl group is closer to the methyl group (dihedral angle = 38.9° for *trans*-**12(TS)**, 46.0° for *trans*-**15(TS)**, 41.2° for *trans*-**19(TS)**) than to the propionyl group (dihedral angle = 89.1° for *trans*-**12(TS)**, 82.6° for *trans*-**15(TS)**, 86.6° for *trans*-**19(TS)**) in the trans transition structures. The steric repulsive interaction between the vinyl group and the propionyl group is less than that between the vinyl group and the methyl group, because the former has a parallel planar sp^2/planar sp^2 interaction, while the latter has a planar sp^2/ball-shape sp^3 interaction. That is why the cis transition structures are more stable than the corresponding trans transition structures in this study. After the cyclization, the vinyl group is close to both the propionyl group and methyl group for the generated cis radicals (*cis*-**13**, *cis*-**16**, and *cis*-**20**), generating two steric repulsive interactions, while in the generated trans radicals (*trans*-**13**, *trans*-**16**, and *trans*-**20**), the vinyl group is close to the methyl group but distant from the propionyl group. When the substituents on the vinyl group are hydrogen, the two steric repulsive interactions of the cis radical are milder than that of the trans radical, so *cis*-**13** is more stable than *trans*-**13**. As the vinyl group has bulky substituents, the two steric repulsive interactions of the cis radicals are more significant than those of the corresponding trans radicals, so *trans*-**16** and *trans*-**20** are more stable than *cis*-**16** and *cis*-**20**, respectively.

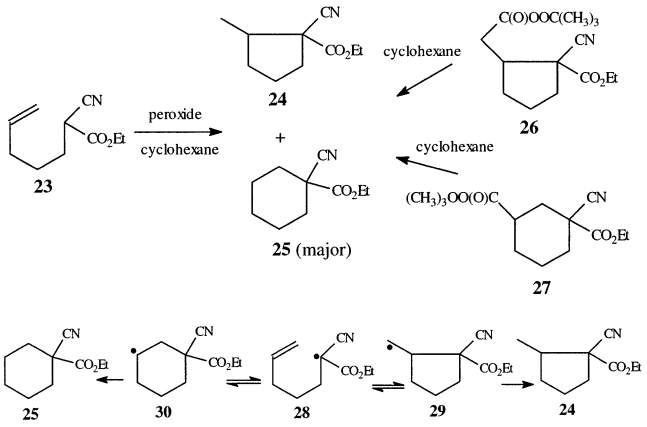
Curran et al.[3e] demonstrated that the nature of the α-alkyl-*β*-ketoester radicals generated by either Mn(III)-mediated oxidation or Me_6Sn_2-induced atom transfer is the same, indicating the existence of free radicals **11**, **14**, and **18** with loss of Mn(II) during the oxidation of the α-alkyl-*β*-ketoesters with $Mn(OAc)_3$. In addition, the oxidation of 2-butanone with $Mn(OAc)_3$ in the absence of olefins produces 1- and 3-acetoxybutan-2-ones in a ratio of 2.5:1,[9a] as opposed to the 1:3 ratio of addition of the generated isomeric radicals to an alkene,[9b] implying that the oxidative radical generation rate with $Mn(OAc)_3$ has very little influence on either the regioselectivity or the stereoselectivity of the cyclizations of the substituted allyl α-methyl-*β*-ketoester radicals.

The cyclization of hex-5-en-1-yl radical generated by 1-bromohex-5-ene with tributyltin hydride in benzene produces a 5-exo cyclization product.[10] Because the cyclization generated radical is trapped very fast by hydrogen abstraction from tributyltin hydride at the rate constant of ca. 10^6 M^{-1} s^{-1},[10] the cyclization process is irreversible and operates under kinetic control. On the other hand, as the free-radical carbon atom is substituted with resonance-stabilized substituents, it is more possible that the cyclization becomes reversible.[11] When cyano esters **23**/peroxide, **26**, or **27** were heated in boiling cyclohexane, cyclization products **24** and **25** were produced with **25** as a major product,[11] indicating that the resonance-stabilized radical **28** undergoes the cyclization reversibly and the cyclization operates under thermodynamic control. The poor hydrogen-donating solvent, cyclohexane, makes **29** and **30** prefer ring opening to hydrogen abstraction. Therefore, the relative stability of **29** and **30** plays an important role on the proportion of final products. However, addition of good hydrogen-donating solvents such as cumene increased the proportion of **24**, indicating that faster hydrogen abstraction may trap the rapidly formed **29** before the ring opening.[11]

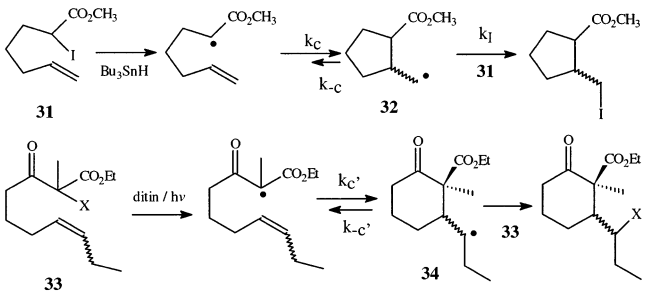
(9) (a) Okano, M.; Aratani, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2811. (b) Vinogradov, M. G.; Verenchikov, S. P.; Fedorova, T. M.; Nikishin, G. I. *J. Org. Chem. USSR* **1975**, *11*, 937.

(10) (a) Beckwith, A. L. J.; Blair, I.; Phillipou, G. *J. Am. Chem. Soc.* **1974**, *96*, 1613. (b) Beckwith, A. L. J.; Lawrence, T.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 484. (c) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.

(11) (a) Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386. (b) Julia, M.; Maumy, M. *Bull. Soc. Chim. Fr.* **1969**, 2415. (c) Julia, M.; Maumy, M. *Bull. Soc. Chim. Fr.* **1969**, 2427. (d) Ruechardt, C. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 830.



Curran[12] performed atom transfer cyclization of α-iodo ester **31** and found that the ring-opening rate constant k_{-c} of **32** is smaller than 4×10^3 s^{-1}, which is much smaller than the iodine-transfer rate constant k_I (ca. 3×10^8 M^{-1} s^{-1}) of **32**, indicating that the cyclization operates under kinetic control. Later, he performed the atom transfer cyclization of α-halo-*β*-ketoester **33** and found that **34** has a much faster ring-opening rate ($k_{-c'} = 10^5-10^8$ s^{-1}), because the iodine transfer sufficiently traps **34** but the bromine transfer does not.[3e] Radicals **13**, **16**, **20** in this study, like radical **34**, have the moiety of *β*-ketoester to stabilize the ring-opening-generated radicals, but the ring-opening rates of the cyclopentylcarbinyl radicals are usually more rapid than those of the corresponding cyclohexylcarbinyl radicals because the former has a higher ring strain.[13] Therefore, the ring-opening rates of the radicals **13**, **16**, and **20** should be much more rapid than that of the radical **34**.



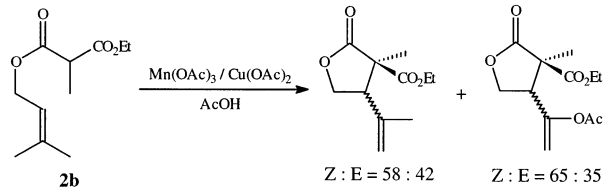
Radicals **13** are primary radicals, which are not readily oxidized by $Mn(OAc)_3$,[4] so they abstract a hydrogen atom from the solvents. It is known that the methyl radical abstracts a hydrogen atom slowly from acetic acid ($k = 2 \times 10^2$ M^{-1} s^{-1}) and acetonitrile ($k < 3 \times 10^2$ M^{-1} s^{-1}) in the liquid phase.[14] Therefore, the second-order rate constants for the primary radicals to abstract a hydrogen atom from either acetic acid or acetonitrile are expected to be smaller than 2×10^2 M^{-1} s^{-1}, whose pseudo-first-order rate constants with 10 M acetic acid or acetonitrile are smaller than 2×10^3 s^{-1}, which are much smaller than the ring-opening rate constants of the radicals **13**; this indicates that the intramolecular free-radical cyclization of **11** is reversible and operates under thermodynamic control. It is reasonable to assume that the hydrogen-abstraction rates of the primary radicals *trans*-**13** and *cis*-**13** are almost the same, so the stereoselectivity of the reversible and thermodynamic-control cyclization of **11** depends on the relative stability of *trans*-**13** and *cis*-**13**. According to the DFT calculations, *cis*-**13** is 0.08 kcal/mol more stable than *trans*-**13**. On the basis of the experimental results, the cyclization of **11** gives products of both *cis*-**6** and *trans*-**6** in a ratio of 2:1, which indicates that the proposed mechanism in Scheme 1 is very likely.

What is the result if the oxidative free-radical cyclization of **5a** is carried out under kinetic control? The oxidative free-radical cyclization of allyl malonate **2a**, whose structure is very similar to that of **5a**, has been carried out under kinetic control by $Mn(OAc)_3/Cu(OAc)_2$ in acetic acid, and vinyl lactone **3a** was produced with the cis isomer as a major product.[3j] The oxidative free-radical cyclization of **2a** with $Mn(OAc)_3$ generates a secondary lactone radical, which is trapped quickly by further oxidation with $Cu(OAc)_2$, instead of the ring opening, because $Cu(OAc)_2$ oxidizes radicals 350 times faster than $Mn(OAc)_3$;[15] this makes the further oxidation rate of the generated secondary lactone radical faster than its ring-opening rate. The reaction result under kinetic control is consistent with our computation results.

Radicals **16** are tertiary radicals, which are oxidized by $Mn(OAc)_3$ more easily than a hydrogen atom can be abstracted from the solvents for of the following reason. It is known that $Cu(OAc)_2$ oxidizes the tertiary radicals 350 times faster than $Mn(OAc)_3$[15] and $Cu(OAc)_2$ oxidizes the tertiary radicals with the second-order rate constants of ca. 10^7 M^{-1} s^{-1}.[16] Therefore, the second-order rate constants for $Mn(OAc)_3$ to oxidize the tertiary radicals are expected to be ca. 2.9×10^5 M^{-1} s^{-1}, whose pseudo-first-order rate constant with 0.1 M $Mn(OAc)_3$ is ca. 2.9×10^4 s^{-1}, which is much bigger than the hydrogen abstraction rate constants from the solvents but smaller than the ring-opening rate constants of radicals **16**, causing the intramolecular free-radical cyclization of **14** to be reversible and to operate under thermodynamic control. It is reasonable to assume that the further oxidation rates of the tertiary radicals *trans*-**16** and *cis*-**16** by $Mn(OAc)_3$ are almost the same. Therefore, the stereoselectivity of the reversible and thermodynamic-control cyclization of **14** depends on the relative stability of *trans*-**16** and *cis*-**16**. The DFT calculations show that *trans*-**16** is 1.97 kcal/mol more stable than *cis*-**16**. According to the experimental results, the cyclization of **14** gives both cis and trans products in a ratio of 1:4.4, which indicates that the proposed mechanism in Scheme 2 is very likely.

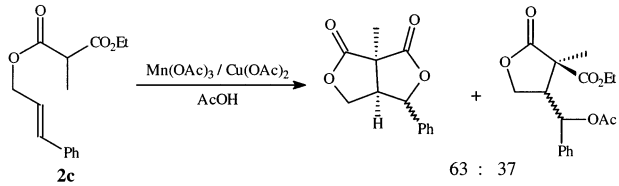
What is the result if the oxidative free-radical cyclization of **5b** is carried out under kinetic control? The oxidative free-radical cyclization of allyl malonates **2b**, whose structure is very similar to that of **5b**, has been carried out under kinetic control by $Mn(OAc)_3/Cu(OAc)_2$ in acetic acid, and the major products are cis isomers.[3j] The reaction result under kinetic control is consistent with our computation results.

(12) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.
(13) (a) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 2674. (b) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 230.
(14) Gilbert, B. C.; Norman, R. O. C.; Placucci, G.; Sealy, R. C. *J. Chem. Soc., Perkin Trans. 2* **1975**, 885.
(15) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 524.
(16) (a) Kochi, J. K.; Subramanian, R. V. *J. Am. Chem. Soc.* **1965**, *87*, 4855. (b) Kochi, J. K.; Subramanian, R. V. *Inorg. Chem.* **1965**, *4*, 1527. (c) Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 843.



According to the DFT calculations, the cis cyclization of **18** is 1.93 kcal/mol lower in energy than the corresponding trans cyclization, but the resulting radical *trans*-**20** is 0.75 kcal/mol more stable than *cis*-**20**. On the basis of the experimental results, the cyclization of **18** produces both *cis*-**9** and *trans*-**9** in ratios of 1:2 at 50 °C and 1:4 at 80 °C, and the amount of *trans*-**9** increases as the reaction temperature increases, indicating that the intramolecular free-radical cyclization of **18** is reversible and operates under thermodynamic control. Radicals **20** are secondary benzyl radicals, which were reported to be oxidized by $Mn(OAc)_3$ more easily than a hydrogen atom could be abstracted from the solvents.[4b] On the other hand, the benzyl radicals **20** are stabilized by the phenyl group significantly, and that makes the ring-opening barriers of **20** higher, implying that the ring opening of **20** is getting more difficult. The knowledge of the oxidative solvolysis rates of the secondary radicals by Mn(III) might help to give an understanding of why a thermodynamic control would operate in this case.

What is the result if the oxidative free-radical cyclization of **5c** is carried out under kinetic control? The oxidative free-radical cyclization of allyl malonates **2c**, whose structure is very similar to that of **5c**, has been carried out under kinetic control by $Mn(OAc)_3/Cu(OAc)_2$ in acetic acid, and the major products are cis isomers.[3j] The reaction result under kinetic control is consistent with our computation results.



According to the experimental results, the oxidative free-radical cyclization of **5b** with $Mn(OAc)_3$ produced *cis*-**7**, *trans*-**7**, and *trans*-**8**, but **17** could not be found, indicating that both *cis*-**16** and *trans*-**16** undergo both oxidative elimination and substitution. Because the oxidative elimination does not go through carbon cations[8] and because a β-H with less steric hindrance more easily undergoes β-elimination, the Hofmann β-elimination products were produced, but the Zaitsev β-elimination **17** was not, even though the latter is much more stable than the former. Similar results were observed for the oxidative free-radical cyclization of **5c** with $Mn(OAc)_3$, which produced both *cis*-**9** and *trans*-**9** but did not generate the Zaitsev β-elimination product **21**, indicating that both *cis*-**20** and *trans*-**20** undergo the oxidative substitution rather than the oxidative elimination.

Conclusion

The oxidative free-radical cyclizations of the substituted allyl α-methyl-β- ketoesters **5a**−**d** with 2 equiv of $Mn(OAc)_3$ generated the 5-exo cyclization products, instead of the 6-endo cyclization products. The ring-opening rates of radicals **13** are much faster than their hydrogen abstraction rates from the solvents, causing the free-radical cyclization of the radical **11** to be reversible and to operate under thermodynamic control, and the stereoselectivity of the cyclization depends on the relative stability of the cyclization-generated radicals *trans*-**13** and *cis*-**13**. Since *cis*-**13** is 0.08 kcal/mol more stable than *trans*-**13**, the oxidative free-radical cyclization of **5a** with $Mn(OAc)_3$ gives products of both *cis*-**6** and *trans*-**6** in a ratio of 2:1. The ring-opening rates of radicals **16** and **20** are faster than their further oxidation rates by Mn(III), causing the free-radical cyclizations of the radicals **14** and **18** to be reversible and to operate under thermodynamic control, and the stereoselectivity of the cyclizations depends on the relative stability of the cyclization-generated radicals *trans*-**16**/*cis*-**16** and *trans*-**20**/*cis*-**20**, respectively. Since *trans*-**16** is 1.97 kcal/mol more stable than *cis*-**16** and *trans*-**20** is 0.75 kcal/mol more stable than *cis*-**20**, the oxidative free-radical cyclizations of **5b** and **5c** with $Mn(OAc)_3$ give the trans products as major products.

Experimental Section

General. Unless otherwise stated, reagents were obtained from commercial suppliers and used as received. The β-lactone **4** was prepared according to a literature method.[17] Preparation and spectroscopic data of **5a**−**d** are shown in Supporting Information.

General Method for Oxidative Cyclization of 5 with $Mn(OAc)_3$. A solution of **5** (2 mmol) and $Mn(OAc)_3$ (4 mmol) in 10 mL of degassed acetonitrile or glacial acetic acid was heated at 50 or 80 °C under nitrogen for 15 or 10 h. After reaction, the reaction mixture was poured through a short silica gel column and eluted with ether. The collected solution was washed with saturated $NaHCO_3$ aqueous solution, dried over anhydrous $MgSO_4$, and evaporated in a vacuum to give crude products, which were purified by column chromatography on silica gel with an eluent of 7:3 hexane/ethyl acetate.

***cis*-3,4-Dimethyl-3-propionyl-dihydrofuran-2-one (*cis*-6):** colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.03 (6H, m, CH_3), 1.49 (3H, s, CH_3), 2.55 (3H, m, CH and CH_2), 3.95 (1H, d of d, J = 9.5, 8.5 Hz, CH), 4.37 (1H, d of d, J = 8.5, 8.2 Hz, CH); ^{13}C NMR ($CDCl_3$) δ 6.92, 11.81, 19.00, 34.56, 42.62, 58.99, 71.53, 177.56, 207.70; IR (thin film) 1768, 1708 (C=O) cm^{-1}; MS (EI) *m*/*z* 170 (35, M$^+$), 114 (95), 99 (100), 84 (30), 71 (30), 57 (60); HRMS (EI) *m*/*z* calcd for $C_9H_{14}O_3$ 170.0943, found 170.0946.

***trans*-3,4-Dimethyl-3-propionyl-dihydrofuran-2-one (*trans*-6):** colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.03 (6H, m, CH_3), 1.35 (3H, s, CH_3), 2.71 (2H, m, CH_2), 3.05 (1H, m, CH), 3.83 (1H, d of d, J = 8.5, 7.8 Hz, CH), 4.38 (1H, d of d, J = 8.5, 10.1 Hz, CH); ^{13}C NMR ($CDCl_3$) δ 7.81, 12.34, 14.36, 31.49, 36.00, 58.74, 72.01, 177.06, 205.75; IR (thin film) 1770, 1712 (C=O) cm^{-1}; MS (EI) *m*/*z* 170 (35, M$^+$), 114 (95), 99 (100), 84 (30), 71 (30), 57 (60); HRMS (EI) *m*/*z* calcd for $C_9H_{14}O_3$ 170.0943, found 170.0943.

***cis*-4-Isopropenyl-3-methyl-3-propionyl-dihydrofuran-2-one (*cis*-7):** colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.03 (3H, t, J = 7.1 Hz, CH_3), 1.60 (3H, s, CH_3), 1.75 (3H, s, CH_3), 2.63 (2H, q, J = 7.1 Hz, CH_2), 3.01 (1H, t, J = 9.1 Hz, CH), 4.36 (2H, d, J = 9.1 Hz, CH_2), 4.79 (1H, s, CH), 5.01 (1H, s, CH); ^{13}C NMR ($CDCl_3$) δ 7.05, 20.95, 23.10, 34.11, 53.52, 60.01, 68.24, 114.62, 139.04, 176.71, 206.93; IR (thin film) 1770, 1712 (C=O) cm^{-1}; MS (EI) *m*/*z* 196 (30, M$^+$), 140 (45), 99 (100), 84 (25), 57 (70); HRMS (EI) *m*/*z* calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1103.

(17) Sung, K.; Wu, S.-Y. *Synth. Commun.* **2001**, *31*, 3069.

***trans*-4-Isopropenyl-3-methyl-3-propionyl-dihydrofuran-2-one (*trans*-7):** colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.05 (3H, t, J = 7.2 Hz, CH_3), 1.29 (3H, s, CH_3), 1.71 (3H, s, CH_3), 2.63 (2H, m, CH_2), 3.64 (1H, m, CH), 4.36 (2H, m, CH_2), 4.77 (1H, s, CH), 4.97 (1H, s, CH); ^{13}C NMR ($CDCl_3$) δ 7.88, 14.91, 21.86, 31.37, 47.81, 58.91, 69.10, 114.92, 140.33, 176.32, 206.26; IR (thin film) 1770, 1714 (C═O) cm^{-1}; MS (EI) *m*/*z* 196 (30, M^+), 140 (45), 99 (100), 84 (25), 57 (70); HRMS (EI) *m*/*z* calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1101.

***trans*-Acetic Acid 1-Methyl-1-(4-methyl-5-oxo-4-propionyl-trtrahydrofuran- 3-yl)-ethyl Ester (*trans*-8):** colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.08 (3H, t, J = 7.2 Hz, CH_3), 1.46 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.97 (3H, s, CH_3), 2.73 (2H, m, CH_2), 3.43 (1H, m, CH), 4.37 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$) δ 7.97, 15.87, 22.33, 24.86, 24.89, 31.72, 50.52, 58.33, 66.57, 80.70, 169.49, 176.43, 206.70; IR (thin film) 1773, 1740, 1718 (C═O) cm^{-1}; MS (EI) *m*/*z* 256 (3, M^+), 239 (20), 197 (20), 140 (40), 99 (100); HRMS (EI) *m*/*z* calcd for $C_{13}H_{20}O_5$ 256.1311, found 256.1310.

***cis*-Acetic Acid (4-Methyl-5-oxo-4-propionyl-tetrahydrofuran-3-yl)-phenyl- methyl Ester (*cis*-9):** colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, t, J = 7.2 Hz, CH_3), 1.40 (3H, s, CH_3), 2.02 (3H, s, CH_3), 2.55 (2H, m, CH_2), 2.93 (1H, m, CH), 4.46 (2H, m, CH_2), 5.17 (1H, d, J = 4.7 Hz, CH), 7.35 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 7.03, 14.78, 19.99, 27.97, 57.29, 58.43, 70.99, 84.59,125.68, 128.61, 128.81, 140.53, 175.00, 177.07, 209.04; IR (thin film) 1778, 1714 (C═O) cm^{-1}; MS (EI) *m*/*z* 304 (1, M^+), 245 (M^+ − AcO, 100), 189 (20), 57 (50); HRMS (EI) *m*/*z* calcd for $C_{15}H_{17}O_3$ (M^+ − AcO) 245.1178, found 245.1181.

***trans*-Acetic Acid (4-Methyl-5-oxo-4-propionyl-trtrahydrofuran-3-yl)-phenyl-methyl Ester (*trans*-9):** colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, t, J = 7.2 Hz, CH_3), 1.48 (3H, s, CH_3), 2.13 (3H, s, CH_3), 2.55 (2H, m, CH_2), 3.60 (1H, m, CH), 4.30 (2H, m, CH_2), 5.88 (1H, d, J = 5.7 Hz, CH), 7.35 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 7.67, 14.80, 20.87, 31.27, 46.28, 58.21, 66.98, 73.51, 126.32, 128.62, 128.82, 137.24, 169.58, 176.04, 205.70; IR (thin film) 1778, 1714 (C═O) cm^{-1}; MS (EI) *m*/*z* 304 (1, M^+), 245 (M^+ − AcO, 100), 189 (20), 57 (50); HRMS (EI) *m*/*z* calcd for $C_{15}H_{17}O_3$ (M^+ − AcO) 245.1178, found 245.1179.

3-Methyl-4-methylene-3-propionyl-dihydrofuran-2-one (10): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.03 (3H, t, J = 7.2 Hz, CH_3), 1.55 (3H, s, CH_3), 2.55 (2H, m, CH_2), 4.84 (2H, s, CH_2), 5.12 (1H, s, CH), 5.22 (1H, s, CH); ^{13}C NMR ($CDCl_3$) δ 7.71, 19.44, 31.45, 59.85, 70.43, 110.22, 143.65, 176.17, 202.68; IR (thin film) 1778, 1724 (C═O) cm^{-1}; MS (EI) *m*/*z* 168 (3, M^+), 112 (90), 84 (50), 57 (100); HRMS (EI) *m*/*z* calcd for $C_9H_{12}O_3$ 168.0786, found 168.0786.

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Supporting Information Available: Total energies; Cartesian or *Z*-matrix coordinates; optimized structures (Figure 2−4) of the reactants, intermediates, transition states, and products discussed in this paper; and preparation and spectroscopic data of **5a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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