Stereoselective Reduction of γ-Oxobutanoic Acids Using DIBAL-H and $ZnCl_2$

R. Frenette,* M. Monette, M. A. Bernstein, R. N. Young, and T. R. Verhoeven†

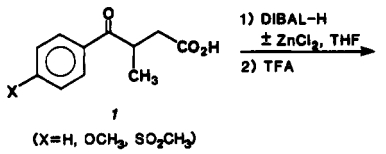
Merck Frosst Centre for Therapeutic Research, Pointe Claire-Dorval, Quebec, Canada H9R 4P8, and Merck & Co., Inc., Rahway, New Jersey 07065

Received September 6, 1990

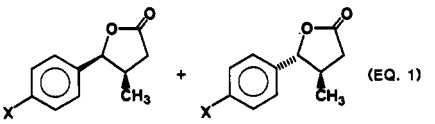
A variety of γ-aromatic γ-ketobutanoic acids can be reduced selectively, under optimized conditions, by the use of DIBAL-H and $ZnCl_2$ to provide the (*RS,SR*)-γ-aryl-γ-hydroxy-β-methylbutanoic acids. Further evidence has been gathered to support the hypothesis that the reaction proceeds by formation of a seven-membered ring complex with the aluminium or zinc atom bridging the ketone and carboxyl groups which preceeds the reduction step and that this templated reduction accounts for observed high diastereoselectivity. Also we have shown that some γ-aryl-γ-butyrolactones can be easily transformed via an oxidative cleavage of the aromatic ring to provide selective synthesis of either cis- or *trans*-tetrahydro-3-methyl-5-oxo-2-furancarboxylic acid derivatives.

Introduction

We have previously reported[1] that the reduction of γ-aryl-β-methyl-γ-oxobutanoic acids **1** with diisobutylaluminium hydride (DIBAL-H), in the presence or absence of zinc chloride ($ZnCl_2$), proceeds in a highly stereoselective manner, giving product ratios of 93:7 to 99:1 in favor of the syn-(*RS,SR*) products **2**. In that study various parameters (e.g. temperature of the reaction, nature of the solvent used) were studied and optimized conditions were found. The best diastereofacial selectivity was achieved when the γ-oxo acids **1** were treated first with $ZnCl_2$ (1.1 equiv) in tetrahydrofuran (THF) at room temperature followed by addition of DIBAL-H (2.4 equiv) in toluene at −78 °C (eq 1).



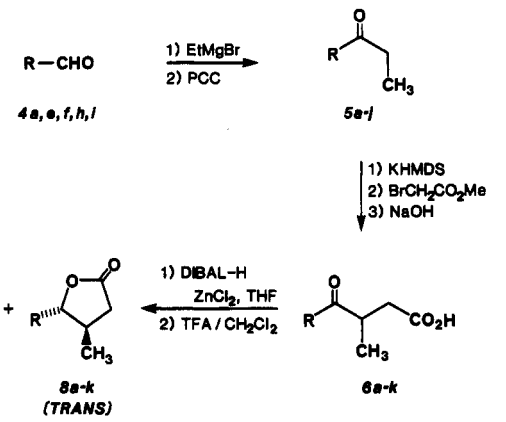
1
(X=H, OCH_3, SO_2CH_3)

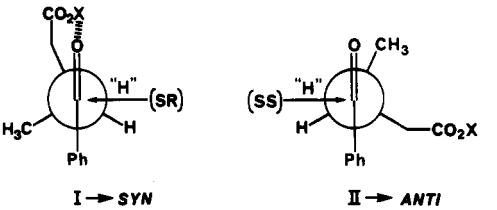


2 SYN CIS (RS, SR) **3** ANTI TRANS (RR, SS)

We proposed that the observed syn selectivity could result from the formation of a seven-membered ring complex with the aluminium or zinc atom bridging the ketone and the carboxyl groups. The aluminate salt of the acid formed with the first equivalent of DIBAL-H produced the cyclic complex and the second equivalent of reagent reduced the ketone. Under optimized conditions, $ZnCl_2$ probably exchanges with aluminium to form a zinc-based cyclic complex to produce an improved selectivity toward the (*RS,SR*) products **2** (I). If desired, the anti isomers ((*RR,SS*)-lactones **3**) could be derived from reduction under steric approach control[2] with reagents such as L-Selectride (Aldrich) which cannot form such a cyclic complex.[1] Here the Felkin-Anh model[3] would predict the approach of the hydride to be directed by bulky alkyl groups (II).

Scheme I





This paper provides further experimental details and discussion of the mechanism of this novel reaction. Also, in order to extend the scope and better define limitations of the syn-selective reduction mediated by DIBAL-H, we have focused our attention on the choice of the Lewis acid used and addressed its involvement in the formation of the putative cyclic seven-membered complex. The scope and the effect of the γ-substituent on the selectivity in the reduction of **6** has been explored. We also report herein the successful application of the present methodology to the synthesis of *cis*- and *trans*-tetrahydro-3-methyl-5-oxo-2-furancarboxylic acids, useful precursors in the synthesis of natural products.[4]

Discussion

The required keto acids **6** were prepared via the alkylation of the corresponding 1-propanone derivatives **5** with

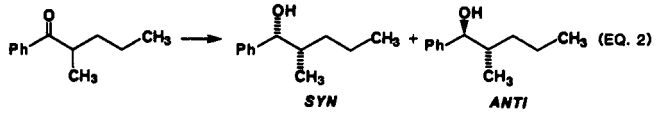
(1) Frenette, R.; Kakushima, M.; Zamboni, R.; Young, R. N.; Verhoeven, T. R. *J. Org. Chem.* **1987**, *52*, 304.
(2) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.
(3) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199, (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, 61. (c) Morrison, J. D.; Mosher, H. S. *Asymmetric organic reactions*; Prentice-Hall: New York, 1971, p 94.

(4) For examples, see: (a) Kunesch, G.; Zagatti, P.; Gallois, P. *Tetrahedron* **1984**, *40*, 3521. (b) Bassi, L.; Joos, B.; Gassman, P.; Kaiser, H.-P.; Leuenberger, H.; Keller-Schierlein, W. *Helv. Chim. Acta* **1983**, *66*, 92. (c) Tomioka, K.; Sato, F.; Koga, K. *Heterocycles* **1982**, *17*, 311.

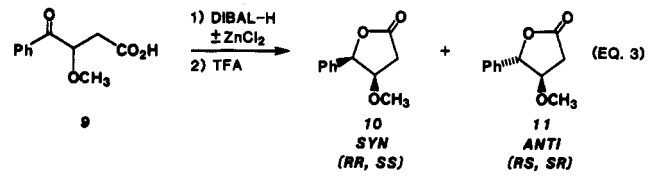
0022-3263/91/1956-3083$02.50/0

potassium hexamethyldisilazide (KHMDS) and methyl bromoacetate at −78 °C, followed by aqueous hydrolysis. If not available, the 1-propanone derivative was easily prepared from the corresponding aldehyde 4 as shown in Scheme I. The resulting γ-keto acids were subjected to the reduction conditions to provide the syn and anti products. To facilitate the isolation and isomer ratio characterization,[5] the reduction products were converted to the corresponding γ-butyrolactones 7 and 8 (lactonization catalyzed with trifluoroacetic acid (TFA)).[6]

Our hypothesis of the critical role of a seven-membered ring chelate for diastereoselective reduction of keto acids such as 1 implies an important role for the carboxyl group. Thus, if a carboxylic acid moiety were replaced by a moiety such as an ethyl group with no ability to participate to a cyclic complex, no such chelation control would be possible and selectivity should be reduced. To test this hypothesis, the reduction of 2-methyl-1-phenyl-1-pentanone[7] was studied. Under optimized conditions (DIBAL-H and $ZnCl_2$), the reduction favored the formation of the anti products in a 35:65 syn:anti ratio as predicted by Cram's rule or Felkin–Ahn model. The predominate rotomer which controls the reaction thus arrays the hydroxy and methyl groups in an anti relationship (eq 2).

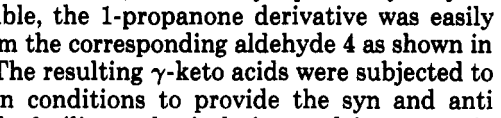


The nature of the β-substituent was found to exert a profound influence on the selectivity of the reduction especially if it has any coordinating ability. The reduction of the ketone 9, which bears a methoxy group at the β-position (eq 3), under the previously optimized conditions (with $ZnCl_2$) gave reversal of selectivity, i.e. a 15:85 ratio of products 10 and 11 in favor of the anti products (trans lactones).



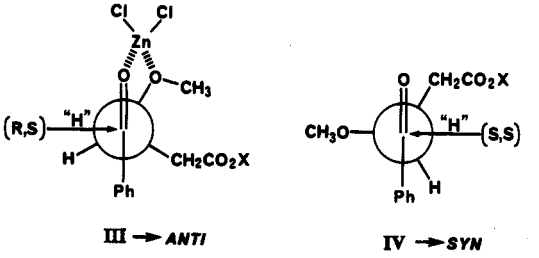
Presumably the methoxy group competes for complexation and thus overrides the control by the seven-membered chelate. This could produce a five-membered complex (α-coordination transition-state model[8]) which would be expected to mediate attack anti to the carboxymethyl group thus yielding anti products (III). However, the reduction of 9 with DIBAL-H in absence of $ZnCl_2$ produced a 25:75 ratio of 10:11, and more surprisingly a trialkylborohydride, such as lithium tri-sec-butylborohydride (L-Selectride), gave a similar ratio of 10:11. While in the case of DIBAL-H (2.4 equiv) alone, aluminium may play a role in forming a five-membered ring complex, the "bulky naked hydrides",[9] such as trialkylborohydrides, having *no* Lewis acidity,[10] are of low coordinating ability, and thus in this case the reaction mode via an acyclic complex is the likely process. It is clear that the classical Felkin–Ahn model cannot adequately explain these results. This model would predict the opposite stereochemical outcome via the transition state IV which is stabilized by the overlap between the low-lying antibonding σ^*_{C-O} orbital with the π^*_{C-O}.[3b] However, in the Felkin model, the difficulties inherent in the determination of the ordering of the substituents with respect to their polarity and "effective size" have been noted before.[3b,c] Making the stereochemical interpretation of the reduction of β-methoxy keto acid 9 much more difficult than with β-methyl keto acid 1 (X = H).

Table I. Reduction of Ketone 1 in the Presence of Various Lewis Acids



entry	Lewis acid	product ratio after lactonization[c,d] 2:3
1	–	95:5
2	$ZnCl_2$	99:1
3	ZnI_2	99:1
4	$ZnTf_2$	97:3
5	$BF_3{\cdot}OEt_2$	96:4
6	$TiCl_4$	94:6
7	$MgBr_2{\cdot}OEt_2$	86:14
8	$AlCl_3$	68:32

[a] The solution of ketone was stirred at room temperature for 5 min in the presence of the Lewis acid and then cooled to −78 °C for reduction. [b] Solution of 0.2% of TFA in CH_2Cl_2. [c] Total isolated yield of mixture of 2 and 3 after flash silica gel chromatography varied from 65% to 90%. [d] Diastereomeric ratios were determined from intensities of relevant ^1H NMR signals of the crude mixtures of lactones.



Effect of Lewis Acid. A variety of experiments were performed to better define the importance of the role of the Lewis acid in this reduction. Various Lewis acid were used in the reduction, and the results are presented in Table I.[11] Examination of Table I shows that while reduction of the keto acid 1 (X = H) with DIBAL-H alone exhibits high syn selectivity (entry 1), the reduction in the presence of zinc-based Lewis acid (entries 2–4) yields even higher selectivity (more particularly with $ZnCl_2$ and ZnI_2).

(5) The diastereomeric ratios were determined from intensities of relevant ^1H NMR signals and were performed on crude lactone mixture before any attempt was made at the separation and purification of individual lactones. No epimerization of the reduction products was observed during work up and lactonization, and only a small amount of lactones (less than 10%) was detected by NMR in the crude mixture prior to the lactonization step.

(6) Care had to be taken in the lactonization step of the reduced products to add the requisite amount of TFA in CH_2Cl_2 because excess reagent resulted in some cases in partial epimerization. Some lactones were showed to be epimerizable when excess TFA was used (see footnote *e*, Table II). Also when neutral conditions of lactonization such as carbodiimide in THF at room temperature were used, identical ratios to those obtained with 0.2% of TFA in CH_2Cl_2 were recorded.

(7) Prepared from alkylation of 1-propiophenone with KHMDS and 1-iodopropane at room temperature.

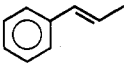
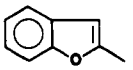
(8) Still, W. C.; Mcdonald, J. H. III *Tetrahedron Lett.* **1980**, *21*, 1031. Glass, R. S.; Deardorff, D. R.; Henegar, K. *Tetrahedron Lett.* **1980**, *21*, 2467.

(9) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 4629.

(10) Negishi, E. *Organometallics in Organic Synthetis*; Wiley-Interscience: New York, 1980; Vol. 1, Chapter 5.

(11) A solution of keto acid 1 (X = H) (1 mmol) and Lewis acid (1.1 mmol) in anhydrous THF (5 mL) was stirred at room temperature for 5 min and then cooled to −78 °C, a solution of 1.5 M DIBAL-H in toluene (2.4 mmol) was added, and the mixture was stirred at −78 °C for 3 h.

Table II. Reduction of Ketones 6 in the Absence or Presence of $ZnCl_2$[a] (see Scheme I)

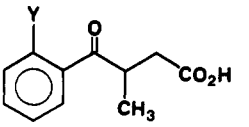
entry	ketone	R	product ratio after lactonization[b] lactones[c,d]	$-ZnCl_2$	$+ZnCl_2$
1	1		2:3	95:5	99:1
2	6a		7a:8a	60:40	70:30
3	6b		7b:8b	85:15	96:4
4	6c		7c:8c[e]	75:25	91:9
5	6d		7d:8d[e]	83:17	90:10
6	6e		7e:8e	92:8	98:2
7	6f		7f:8f[e]	92:8	94:6
8	6g		7g:8g[f]	1:99	1:99

[a] Reactions were run in THF at −78 °C and worked up after 3 h. [b] Ratios were determined by ^1H NMR of the crude mixture of lactones. [c] Lactones obtained after TFA treatment (0.2% TFA in CH_2Cl_2 at room temperature for 2 h) of the reduced products. [d] Total isolated yield of lactones after flash silica gel chromatography varied from 59% to 90%. [e] The lactone showed major epimerization if treated with a solution of 2% TFA in CH_2Cl_2 at room temperature for 4 h. [f] Complete lactonization occurred during the workup with 1 N HCl.

The normally monodentate Lewis acid BF_3·OEt_2 showed surprisingly high selectivity (ratio 96:4) (entry 5) when the keto acid was reduced with 2.4 equiv of DIBAL-H. When this experiment was repeated on the sodium salt of the carboxylate followed by the addition of BF_3·OEt_2 prior to the addition of 1.4 equiv of DIBAL-H, an only slightly less selective reduction was observed (ratio 92:8) (a similar experiment with DIBAL-H alone was previously shown to have greatly reduced selectivity[1]). In spite of the observed selectivity, the participation of boron in a cyclic complex would be quite surprising. Two other Lewis acids capable of producing bidentate complexes such as $TiCl_4$ and $MgBr_2$ showed somewhat reduced selectivity (entries 6 and 7) and stronger Lewis acid $AlCl_3$ produced lower syn selectivity probably due to its preference to complex only with the ketone group (entry 8).

Nature of γ-Substituent. The effect of the γ-substituent on selectivity was also explored, and the results listed in Tables II and III show that the DIBAL-H reduction with a variety of keto acid **6** proceeds with fair to excellent syn selectivity. Table II shows the highest selectivity was obtained when R was phenyl (entry 1, $+ZnCl_2$). When the phenyl group was replaced by the cyclohexyl group, the selectivity was surprisingly greatly diminished even in the presence of $ZnCl_2$ (entry 2). One possible explanation of the lower selectivity could derive from the reduced basicity and thus poorer coordinating ability of the carbonyl oxygen in this case.[12] However, we have shown previously[1] that the electronic effects do not seem to play an important role in the selectivity of the reduction. When the relatively flat cyclohexen-1-yl group

Table III. Reduction of Ortho-Substituted Phenyl Ketone in the Absence or Presence of $ZnCl_2$[a]



1, 6h - 6k

entry	ketone	Y	product ratio after lactonization lactones	$-ZnCl_2$	$+ZnCl_2$
1	1	H	2:3[c]	95:5	99:1
2	6h	OCH_3	7h:8h[d,e]	90:10	96:4
3	6i	SCH_3	7i:8i[d,e]	94:6	99:4
4	6j	OCH_2OCH_3	7j:8j[d,e]	94:6	96:4
5	6k		7k:8k[c]	60:40	75:25

[a] Reactions were run in THF at −78 °C and worked up after 3 h. [b] Ratios obtained from ^1H NMR analysis of the crude mixture of lactones. [c] Method A: 0.2% TFA in CH_2Cl_2, 2 h, rt. [d] Method B: carbodiimide (2.5 equiv) in a 1:1 mixture of THF and CH_2Cl_2, 18 h, rt. [e] The lactone showed major epimerization if treated with a solution of 2% of TFA in CH_2Cl_2 at room temperature for 4 h.

is used, selectivity was largely restored (entry 3), suggesting an important steric effect. However, the styryl ketone **6c** was less selectively reduced (entry 4). It is clear that no simple explanation can account for all these results and a combination of electronic and steric factors may be involved.

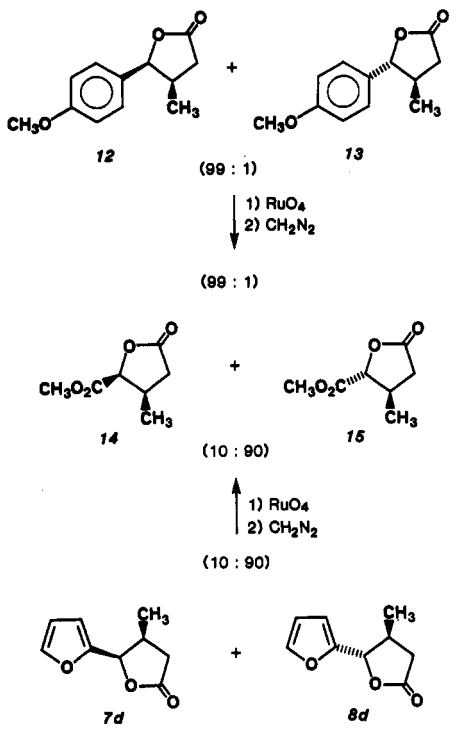
Four heterocyclic ketones (**6d–g**) were studied to examine the importance of a heteroatom adjacent in the γ-substituent. Among the first three examples (entries 5–7), the highest syn selectivity was observed for the 3-furanyl derivative in the presence of $ZnCl_2$ (entry 6), and thus it is clear that furan oxygen is not detrimental. In the case of the reduction of the *N*-methylpyrrol-2-yl ketone (**6g**), the direct reduction products could not be isolated (entry 8) and a high selectivity for anti lactone was observed. In contrast to all other cases the lactones **7g** and **8g** were isolated directly from the workup of the reduction and little acyclic hydroxy acid was found in the crude reaction mixture. In this case we propose that lactonization and probably full *epimerization* of the lactones occurs in the course of the reaction and workup yielding what is the thermodynamic mixture of products (i.e. almost exclusively of the anti product (trans lactone **8g**)). We postulate that initial reduction is likely to be syn selective, but the ability of the nitrogen to bear a positive charge leads to solvolysis at the γ-center and subsequent trapping of the intermediate pyrrylium ion by the carboxylate to provide the epimerized lactone.

We also studied the effect of an ortho substituent on the γ-aromatic ring on the selectivity of the reduction. This ortho substituent could participate or compete with the coordination of the ketone function with the metal ion. This would predict as a consequence a less syn-selective reduction. Brown has reported the reduction of β-aryl-β-keto esters by excess of complex metal hydrides in which variation of the ortho aromatic substituents led selectively to either syn and anti products.[13] He noted that in the case of $LiBH_4$, syn selectivity increased as the steric bulk of the ortho group increased, with the exception of the methoxy derivative, which was more selective than would have been expected from its size. It was postulated that

(12) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, 2653.

(13) Brown, G. R.; Foubister, A. J. *J. Chem. Soc., Chem. Commun.* **1985**, 455.

Scheme II



this increased selectivity might be due to chelation of the methoxy group oxygen atom to the reducing lithium species.

Our results are reported in Table III. We observed that inclusion of an ortho substituent did not significantly affect the syn and anti product ratios (entries 2–4) except for ketone **6k** (entry 5). In all cases, the addition of $ZnCl_2$ produced a higher syn selectivity. Even the use of the methoxymethyl ether group (entry 4) did not adversely affect selectivity.[14] Only the methylsulfinyl group (entry 5) seemed to influence the selectivity of the reduction to give only fair syn-selective reduction.[15] Clearly the latter group is the most potent chelating group of the series, and it would appear that only in this case can the substituent compete with the metal ion in coordination.

From the results presented in Tables II and III, it is clear that, except in the case of ketones **6a** and **6k**, excellent syn-selective reduction of γ-substituted γ-keto acids **6** can be achieved under optimized conditions (DIBAL-H and $ZnCl_2$) and a variety of "R" groups is tolerated.

Application. The utility of the substituted γ-butyrolactone moiety as a structural subunit for synthesis of natural products has been demonstrated in the past.[4] Consequently, we considered that aromatic rings such as 4-methoxyphenyl and 2-furanyl, which are known to serve as masked carboxyl group, could be used in conjunction with the γ-butyrolactone moiety to prepare some potentially useful tetrahydro-3-methyl-5-oxo-2-furancarboxylic acid derivatives. Our methodology gives efficient access to *cis*-γ-aryl-γ-butyrolactone (**7**) under optimized conditions. For example, the reduction of **1** (X = OCH_3) with DIBAL-H and $ZnCl_2$ produced the lactones **12** and **13** (ratio 99:1) (Scheme II). Also the *trans*-γ-aryl-γ-butyrolactone (**8**) can be obtained in majority, in some cases, under thermodynamic control. For example, the trans lactone **8d** could be obtained as the major component from a mixture of **7d** and **8d** (ratio 10:90) by epimerization[17] of the initial mixture of lactones (ratio 90:10) with excess TFA. Ruthenium tetroxide oxidation[18] of either mixture (**12**:**13** or **7d**:**8d**) afforded, after diazomethane treatment, a mixture of lactone esters **14** and **15** (Scheme II). ^1H NMR comparison of the obtained mixture with the NMR data[4b] reported for pure **14** and **15** confirmed that the ratio of lactones obtained after oxidation was the same as that of the initial mixture.[19] Thus, the lactones **14** and **15** were obtained in a 99:1 ratio from **12** and **13** (ratio 99:1) and a 10:90 ratio from the mixture of **7d** and **8d** (ratio 10:90). The selective synthesis of **14** and **15** in racemic form demonstrates the potential of *cis*- and *trans*-γ-aryl-γ-butyrolactones **7** and **8** for the preparation of precursors useful in the synthesis of natural products.

Conclusions

We have shown that DIBAL-H and $ZnCl_2$, used under optimized conditions, reduce a variety of γ-aromatic γ-ketobutanoic acids **6** with high syn selectivity. Further evidence has been gathered to support the hypothesis that the reaction proceeds by formation of a seven-membered ring complex with the aluminium or zinc atom bridging the ketone and carboxyl groups which precedes the reduction step and that this templated reduction accounts for observed high diastereoselectivity. Also we have shown that some γ-aryl-γ-butyrolactones can be easily transformed via an oxidative cleavage of the aromatic ring to provide selective synthesis of either *cis*- or *trans*-tetrahydro-3-methyl-5-oxo-2-furancarboxylic acid derivatives (**14** or **15**).

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. All reactions were conducted under N_2. Flash chromatographies were done on column of silica gel, 230–400 mesh. Melting points are uncorrected. ^1H NMR spectra were determined at 250 MHz. Elemental analyses were done on mixtures of cis and trans lactones unless mentioned otherwise.

General Preparation of 1-Propanone Derivatives (5a,e-j). A solution of aldehyde (10 mmol) **4** in dry THF (25 mL) was cooled to −20 °C. To this solution was slowly added a solution of 3.0 M ethylmagnesium bromide in Et_2O (12 mmol). The mixture was stirred at −20 °C for 2 h, quenched in 1 N HCl, and extracted with ether, and the organic layer was dried over Na_2SO_4 and evaporated at reduced pressure. The crude alcohol derivatives were oxidized as follows: To a solution of crude 1-propanol derivative in CH_2Cl_2 (40 mL) was added a mixture of pyridinium chlorochromate (PCC) (20 mmol) and Celite (4.3 g). This mixture was stirred at room temperature for 4–18 h. The reaction mixture was diluted with ether (150 mL), stirred for 30 min, filtered on pad of silica gel (70–230 mesh), and washed with ether. The ether was evaporated at reduced pressure to afford the crude propanone,

(14) For selective reduction of α,β-bis(methoxymethyl)oxy ketones, see: Yamazaki, N.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1396.

(15) In this case, the presence of the stereogenic center (i.e. the methylsulfinyl group) makes the ^1H NMR analysis of the crude mixture of lactones formed more complex because of the duplication of some groups of proton. To simplify the NMR analysis, these crude mixtures of lactones could be oxidized with *m*-CPBA in CH_2Cl_2[16] to their corresponding methyl sulfone derivative. They were analyzed by NMR, and determination of the product ratio of the initial mixture of lactones was then made simpler.

(16) The methylsulfinyl derivative was treated with 1.5 equiv of *m*-CPBA in CH_2Cl_2 for 1.5 h at room temperature. Then solid $Ca(OH)_2$ (3 equiv) was added, and the mixture was stirred at room temperature for 15 min and filtered through Celite. Evaporation of liquors produced the methyl sulfone derivative.

(17) Obtained after treatment of a mixture of lactones **7d** and **8d** (90:10 ratio) with 2% TFA in CH_2Cl_2 for 4 h at room temperature.

(18) Carlson, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(19) Similar strategy has been used by Woodard to prepare (*R*)- and (*S*)-[^2H]glycine of high chiral purity, see: Ramalingan, K.; Nanjappan, P.; Kalvin, D. M.; Woodard, R. W. *Tetrahedron* **1988**, *44*, 5597.

which was chromatographed in a column of flash silica gel, eluting with ethyl acetate–hexane (range from 5:95 to 15:85), to afford the desired 1-propanone derivatives **5**: IR (thin layer) $\nu_{C=O}$ 1680 cm^{-1}.

1-Cyclohexyl-1-propanone (5a):[20] from commercial cyclohexanecarboxaldehyde (Aldrich); yield 3.5 g (54%); bp 78–80 °C (20 mmHg) (lit.[21] bp 65–67 °C (7 mmHg)); ^1H NMR ($CDCl_3$) δ 1.05 (t, J = 7 Hz, 3 H), 1.2–1.45 (m, 5 H), 1.65–1.75 (m, 1 H), 1.75–1.9 (m, 4 H), 2.3–2.4 (m, 1 H), 2.48 (q, J = 7 Hz, 2 H).

1-(3-Furanyl)-1-propanone (5e): from commercial 3-furaldehyde (Aldrich); yield 4.8 g (42%); ^1H NMR ($CDCl_3$) δ 1.2 (t, J = 6 Hz, 3 H), 2.8 (q, J = 6 Hz, 2 H), 6.78 (s, 1 H), 7.43 (t, J = 1 Hz, 1 H), 8.03 (s, 1 H). Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.87; H, 6.32.

1-(2-Benzofuranyl)-1-propanone (5f): from commercial benzofuran-2-carboxaldehyde (Alfa); yield 0.77 g (46%); ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 6 Hz, 3 H), 3.0 (q, J = 6 Hz, 2 H), 7.2 (t, J = 6 Hz, 1 H), 7.48 (t, J = 6 Hz, 1 H), 7.5 (s, 1 H), 7.6 (d, J = 6 Hz, 1 H), 7.7 (d, J = 6 Hz, 1 H). Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.88; H, 5.67.

1-(1-Methyl-1*H*-pyrrol-2-yl)-1-propanone (5g). A solution of 0.65 M of potassium hexamethyldisilazide (KHMDS) in toluene (22 mmol) was diluted in THF (20 mL) and cooled to −78 °C. To this mixture was added dropwise a solution of 1-(1*H*-pyrrol-2-yl)-1-propanone[22] (20 mmol) in THF (20 mL), and the solution was stirred at −78 °C for 15 min. Then iodomethane (30 mmol) was added and finally stirred at room temperature for 1 h. The mixture was quenched in 1 N HCl and extracted with ether, and the organic layer was dried over Na_2SO_4, and evaporated at reduced pressure. The crude pyrrole was chromatographed in a column of flash silica gel, eluting with 1:9 ethyl acetate–hexane to afford the title product, identical with that reported by Cuvigny:[23] yield 2.6 g (88%); ^1H NMR ($CDCl_3$) δ 1.2 (t, J = 6 Hz, 3 H), 2.83 (q, J = 6 Hz, 2 H), 3.95 (s, 3 H), 6.1 ("t", J = 3 Hz, 1 H), 6.78 ("s", 1 H), 6.95 (dd, J = 4, 2 Hz, 1 H).

1-(2-Methoxyphenyl)-1-propanone (5h):[24] from commercial *o*-anisaldehyde (Aldrich); yield 3.5 g (96%); ^1H NMR ($CDCl_3$) δ 1.15 (t, J = 6 Hz, 3 H), 3.0 (q, J = 6 Hz, 2 H), 3.9 (s, 3 H), 6.9–7.05 (m, 2 H), 7.45 (dt, J = 7, 2 Hz, 1 H), 7.7 (dd, J = 7, 2 Hz, 1 H). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.25; H, 7.40.

1-[2-(Methylthio)phenyl]-1-propanone (5i): from 2-(methylthio)benzaldehyde;[25] yield 1.4 g (52%); mp 58–59 °C; ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 6 Hz, 3 H), 2.45 (s, 3 H), 3.0 (q, J = 6 Hz, 2 H), 7.2 (t, J = 6 Hz, 1 H), 7.35 (d, J = 6 Hz, 1 H), 7.48 (t, J = 6 Hz, 1 H), 7.85 (d, J = 6 Hz, 1 H). Anal. Calcd for $C_{10}H_{12}OS$: C, 66.63; H, 6.71. Found: C, 66.75; H, 6.76.

1-[2-(Methoxymethoxy)phenyl]-1-propanone (5j). The title product was prepared according to the method described by Townsend and Bloom.[26] To a solution of (methoxymethyl)phenol (20 mmol) in dry ether (120 mL) was added under an inert atmosphere a solution of 1.6 M of *n*-butyllithium in hexane (24 mmol), and the mixture was stirred 2 h at room temperature to give a cloudy yellow suspension. The mixture was then cooled to 0 °C, freshly distilled propionic anhydride was added, and the resulting mixture was stirred at this temperature for 3 h. The reaction mixture was poured into 25% aqueous NH_4OAc, extracted with ether, dried over Na_2SO_4, and evaporated to dryness to give crude product. The mixture was chromatographed in a column of flash silica gel, eluting with 1:9 ethyl acetate–hexane to afford the desired product **5j** as an oil: yield 0.73 g (25%); ^1H NMR ($CDCl_3$) δ 1.2 (t, J = 6 Hz, 3 H), 3.02 (q, J = 6 Hz, 2 H), 3.5 (s, 3 H), 5.28 (s, 2 H), 7.05 (t, J = 7 Hz, 1 H), 7.18 (d, J = 7 Hz, 1 H), 7.42 (dt, J = 7, 1.5 Hz, 1 H), 7.65 (dd, J = 1.5 Hz, 1 H). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.15; H, 7.23.

(20) Morris, H. H.; Lusth, M. L. *J. Am. Chem. Soc.* **1954**, *76*, 1237.
(21) Kugatova-Shemyakima, G. P.; Andreev, V. M.; Anarkubova, L. Sh. *Zh. Org. Chim.* **1967**, *3*, 1220; *Chem. Abstr.* **1967**, *67*, 90430a.
(22) Prepared as described by Alonso Garido, D. O.; Buldain, G.; Frydman, B. *J. Org. Chem.* **1984**, *49*, 2619.
(23) Cuvigny, T.; Normant, H. *Bull. Soc. Chim. Fr.* **1968**, *12*, 4990.
(24) Carter, R. H.; Garson, M. J.; Hill, R. A.; Staunton, J.; Sunter, D. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 471.
(25) Traynelis, V. J.; Borgnaes, D. M. *J. Org. Chem.* **1972**, *37*, 3824.
(26) Townsend, C. A.; Bloom, L. M. *Tetrahedron Lett.* **1981**, *22*, 3923.

General Procedure for the Formation of β-Methyl-γ-oxobutanoic Acids (1 (X = H), 6a–k). A solution of 0.65 M of KHMDS in toluene (11 mmol) was diluted in THF (15 mL) and cooled to −78 °C. To this mixture was added dropwise a solution of 1-propanone derivative **5** (10 mmol) in THF (5 mL), and the solution was stirred at −78 °C for 1 h. Then a solution of methyl bromoacetate (12 mmol) in THF (5 mL) was added dropwise, and the solution was stirred at −78 °C for 1 h. The mixture was quenched in 1 N HCl and extracted with ether, and the organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude ester was chromatographed in a column of flash silica gel, eluting with ethyl acetate–hexane (range from 10:90 to 40:60) to afford the desired γ-oxo ester as oil. It was hydrolyzed as follows: to a solution of γ-keto ester (1 equiv) in THF (3 mL per mmol) and MeOH (0.3 mL per mmol) was added 2 N NaOH (1.5 equiv), and the solution was stirred at room temperature for 2 h. Then the mixture was diluted with H_2O, acidified with 1 N HCl, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated under vacuum to afford the γ-keto acid **6** as a solid: IR (KBr) ν_{CO} 1665–1690, ν_{CO_2H} 1710–1735 cm^{-1}.

β-Methyl-γ-oxo-γ-phenylbutanoic Acid (1 (X = H)).[1]

γ-Cyclohexyl-β-methyl-γ-oxobutanoic acid (6a): from **5a**; yield 2.0 g (63%); mp 63–65 °C; ^1H NMR ($CDCl_3$) δ 1.15 (d, J = 6 Hz, 3 H), 1.18–1.35 (m, 4 H), 1.6–1.7 (m, 1 H), 1.7–1.88 (m, 4 H), 1.88–2.0 (m, 1 H), 2.32 (dd, J = 16, 4 Hz, 1 H), 2.5–2.65 (m, 1 H), 2.82 (dd, J = 16, 9 Hz, 1 H), 3.05–3.22 (m, 1 H, β-H). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.69; H, 9.29.

γ-(1-Cyclohexen-1-yl)-β-methyl-γ-oxobutanoic acid (6b): from 1-(1-cyclohexen-1-yl)-1-propanone;[27] oil; yield 3.6 g (89%); ^1H NMR ($CDCl_3$) δ 1.15 (d, J = 6 Hz, 3 H), 1.55–1.8 (m, 4 H), 2.15–2.3 (m, 4 H), 2.3 (dd, J = 16, 4 Hz, 1 H), 2.85 (dd, J = 16, 9 Hz, 1 H), 2.55–2.7 (m, 1 H, β-H), 5.98 (t, J = 2 Hz, 1 H). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.29; H, 8.36.

(*E*)-3-Methyl-4-oxo-6-phenyl-5-hexenoic acid (6c): from commercial 1-phenyl-1-penten-3-one (Frinton); yield 0.52 g (21%); mp 98–102 °C; ^1H NMR ($CDCl_3$) δ 1.25 (d, J = 6 Hz, 3 H), 2.4 (dd, J = 16, 4 Hz, 1 H), 2.9 (dd, J = 16, 9 Hz, 1 H), 3.3–3.45 (m, 1 H, β-H), 3.68 (s, 3 H), 6.85 (d, J = 12 Hz, 1 H), 7.35–7.45 (m, 3 H), 7.5–7.6 (m, 2 H), 7.68 (d, J = 12 Hz, 1 H). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.62; H, 6.51.

γ-(2-Furanyl)-β-methyl-γ-oxobutanoic acid (6d): from commercial 1-(2-furanyl)-propanoic (P&B); yield 5.9 g (87%); mp 87–89 °C; ^1H NMR ($CDCl_3$) δ 1.25 (d, J = 6 Hz, 3 H), 2.45 (dd, J = 16, 4 Hz, 1 H), 2.98 (dd, J = 16, 9 Hz, 1 H), 3.6–3.8 (m, 1 H, β-H), 6.55 (dd, J = 4, 2 Hz, 1 H), 7.25 (d, J = 4 Hz, 1 H), 7.6 (d, J = 2 Hz, 1 H); IR (neat) 1735, 1675 cm^{-1}. Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.51; H, 5.61.

γ-(3-Furanyl)-β-methyl-γ-oxobutanoic acid (6e): from **5e**; yield 0.56 g (76%); mp 93–95 °C; ^1H NMR ($CDCl_3$) δ 1.28 (d, J = 6 Hz, 3 H), 2.45 (dd, J = 16, 4 Hz, 1 H), 2.95 (dd, J = 16, 9 Hz, 1 H), 3.4–3.55 (m, 1 H, β-H), 6.8 (d, J = 2 Hz, 1 H), 7.48 (d, J = 2 Hz, 1 H), 8.1 (s, 1 H). Anal. Calcd for $C_9H_{10}O_6$: C, 59.34; H, 5.53. Found: C, 59.41; H, 5.57.

γ-(2-Benzofuranyl)-β-methyl-γ-oxobutanoic acid (6f): from **5f**; yield 0.69 g (90%); mp 138–140 °C; ^1H NMR (acetone-d_6) δ 1.3 (d, J = 6 Hz, 3 H), 2.55 (dd, J = 16, 4 Hz, 1 H), 2.95 (dd, J = 16, 9 Hz, 1 H), 3.8–4.0 (m, 1 H, β-H), 7.38 (t, J = 6 Hz, 1 H), 7.55 (dt, J = 6, 2 Hz, 1 H), 7.68 (d, J = 6 Hz, 1 H), 7.8 (s, 1 H), 7.85 (d, J = 6 Hz, 1 H). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.32; H, 5.24.

β-Methyl-γ-(1-methyl-1*H*-pyrrol-2-yl)-γ-oxobutanoic acid (6g): from **5g**; yield 1.3 g (96%); mp 106–108 °C; ^1H NMR ($CDCl_3$) δ 1.28 (d, J = 6 Hz, 3 H), 2.45 (dd, J = 16, 4 Hz, 1 H), 2.9 (dd, J = 16, 9 Hz, 1 H), 3.6–3.75 (m, 1 H, β-H), 3.92 (s, 3 H), 6.15 (dd, J = 4, 2 Hz, 1 H), 6.85 (d, J = 2 Hz, 1 H), 7.05 (dd, J = 4, 2 Hz, 1 H). Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.43; H, 6.82; N, 7.10.

γ-(2-Methoxyphenyl)-β-methyl-γ-oxobutanoic acid (6h): from **5h**; yield 0.89 g (80%); mp 68–70 °C; ^1H NMR ($CDCl_3$) δ 1.2 (d, J = 6 Hz, 3 H), 2.42 (dd, J = 16, 4 Hz, 1 H), 2.92 (dd, J = 16, 9 Hz, 1 H), 3.85–4.0 (m, 4 H, including β-H), 6.95–7.05 (m, 2 H), 7.45 (dt, J = 6, 2 Hz, 1 H), 7.65 (dd, J = 6, 2 Hz, 1 H). Anal.

(27) Shono, T.; Nishiguchi, I.; Sasaki, M.; Ikeda, H.; Kurita, M. *J. Org. Chem.* **1983**, *48*, 2503.

Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.01; H, 6.42.

β-Methyl-γ-[2-(methylthio)phenyl]-γ-oxobutanoic acid (6i): from **5i**; yield 0.62 g (55%); mp 103–105 °C; ^{1}H NMR ($CDCl_3$) δ 1.22 (d, J = 6 Hz, 3 H), 2.43 (s, 3 H), 2.48 (dd, J = 16, 4 Hz, 1 H), 3.0 (dd, J = 16, 9 Hz, 1 H), 3.85–4.0 (m, 1 H, β-H), 7.22 (dt, J = 6, 1.5 Hz, 1 H), 7.35 (d, J = 6 Hz, 1 H), 7.48 (dt, J = 6, 2 Hz, 1 H), 7.9 (d, J = 6 Hz, 1 H). Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92. Found: C, 60.62; H, 5.99.

γ-[2-(Methoxymethoxy)phenyl]-β-methyl-γ-oxobutanoic acid (6j): from **5j**; oil; yield 0.38 g (66%); ^{1}H NMR ($CDCl_3$) δ 1.2 (d, J = 7 Hz, 3 H), 2.45 (dd, J = 16, 6 Hz, 1 H), 2.95 (dd, J = 16, 7 Hz, 1 H), 3.5 (s, 3 H), 3.85–4.0 (m, 1 H, β-H), 5.26 (s, 2 H), 7.05 (t, J = 6 Hz, 1 H), 7.18 (d, J = 6 Hz, 1 H), 7.45 (dt, J = 6, 1.5 Hz, 1 H), 7.62 (dd, J = 6, 1.5 Hz, 1 H). Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 62.06; H, 6.31.

γ-[2-(Methylsulfinyl)phenyl]-β-methyl-γ-oxobutanoic Acid (6k). To a solution of **6i**, methyl ester (2 mmol) in CH_2Cl_2 (5 mL) kept at 0 °C was added a solution of m-chloroperoxybenzoic acid (*m*-CPBA, 2 mmol) in CH_2Cl_2 (5 mL), and the solution was stirred at this temperature for 2 h. Residual *m*-chlorobenzoic acid was removed as its calcium salt by adding solid $Ca(OH)_2$ (3 mmol) to the reaction mixture and stirring at room temperature for 30 min. The white solid formed was removed by filtration through a pad of Celite and rinsed with CH_2Cl_2, and the liquors were evaporated to dryness. The crude methylsulfinyl derivative was chromatographed on a column of flash silica gel, eluting with pure ethyl acetate to give the title product methyl ester which was hydrolyzed as described above to give the γ-oxo acid **6k** as a white solid: mp 165–166 °C; yield 0.53 g (84%); ^{1}H NMR (methanol-d_4) δ 1.15 (d, J = 6 Hz, 1.5 H) and 1.28 (d, J = 6 Hz, 1.5 H), 2.55 (dd, J = 15, 3 Hz, 1 H), 2.82 (s, 3 H), 2.92 (dd, J = 15, 7 Hz, 1 H), 3.9–4.1 (m, 1 H, β-H), 7.75 (dt, J = 6, 2 Hz, 1 H), 7.92 (dt, J = 6, 2 Hz, 1 H), 8.2–8.35 (m, 2 H). Anal. Calcd for $C_{12}H_{14}O_4S$: C, 56.68; H, 5.55. Found: C, 56.75; H, 5.67.

β-Methoxy-γ-oxo-γ-phenylbutanoic acid (9): from commercial 2-methoxyacetophenone (Aldrich); yield 3.4 g (85%); mp 86–88 °C; ^{1}H NMR ($CDCl_3$) δ 2.82 (dd, J = 16, 6 Hz, 1 H), 2.95 (dd, J = 16, 4 Hz, 1 H), 3.45 (s, 3 H), 5.08 (dd, J = 6, 3 Hz, 1 H, β-H), 7.5 (t, J = 6 Hz, 2 H), 7.6 (t, J = 6 Hz, 1 H), 8.05 (d, J = 6 Hz, 2 H). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.52; H, 5.92.

General Preparation of the Lactones 7 and 8. γ-Oxobutanoic acid **6** (1 mmol) and $ZnCl_2$ (1 mmol, as 1 M solution in THF) in anhydrous THF (5 mL) was cooled to −78 °C, and a solution of 1.5 M DIBAL-H in toluene (2.4 mmol) was added slowly and stirred at −78 °C for 3 h. The reaction was quenched in 1 N HCl, and the reaction products were extracted with ethyl acetate, dried over Na_2SO_4, and evaporated to give the crude γ-hydroxy acid, which was treated using preferred method of lactonization as reported in the tables.

Method A. Acidic Condition. The crude γ-hydroxy acid was dissolved in a solution of 0.2% trifluoroacetic acid (TFA) in CH_2Cl_2 (2 mL) and stirred at room temperature until the reaction was complete (usually 2 h). The mixture was evaporated to dryness and analyzed by NMR to give the crude mixture of the desired cis **7** and trans **8** lactones.

Method B. Neutral Condition. The crude γ-hydroxy acid was dissolved in a mixture of THF (5 mL) and CH_2Cl_2 (5 mL), and to this solution was added 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide methyl *p*-toluenesulfonate (2.5 mmol) and 4-(dimethylamino)pyridine (0.05 mmol). The mixture was stirred at room temperature for 18 h, diluted with H_2O, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, evaporated to dryness, and analyzed by NMR to give the crude mixture of the desired cis **7** and trans **8** lactones.

The crude mixtures of lactones were purified by flash chromatography, eluting with ethyl acetate–hexane (range from 10:90 to 30:70) to afford the mixture of the desired cis (*RS,SR* isomers) and trans (*RR,SS* isomers) lactones where the product ratio was determined by ^{1}H NMR.[28] Because the mixtures of cis and trans lactones were not normally separable in pure form by flash chromatography (except in the case of **7h** and **8h**, and **10** and **11**), cis lactones **7** were characterized as a mixture of **7** and **8** in a ratio largely favoring the cis isomer. Also the trans lactones **8** detected by NMR in smaller amounts were identified by their characteristic peaks (except in the case of **7g** and **8g**). When the mixture of lactones was epimerizable under TFA conditions to give the thermodynamic mixture favoring the trans lactone **8**, its full ^{1}H NMR analysis was reported: IR (thin layer) ν_{CO} 1780–1785 cm^{-1}.

γ-Hydroxy-β-methyl-γ-phenylbutanoic Acid Lactone 2 (X = H) and 3 (X = H).[1]

γ-Cyclohexyl-γ-hydroxy-β-methylbutanoic Acid Lactone (7a and 8a). Cis-(*RS,SR*) lactone 7a: ^{1}H NMR ($CDCl_3$) δ 1.0 (d, J = 6 Hz, 3 H), 1.15–1.4 (m, 4 H), 1.5–1.9 (m, 7 H), 2.2 (dd, J = 15, 2 Hz, 1 H), 2.5–2.65 (m, 1 H, β-H), 2.75 (dd, J = 12, 7 Hz, 1 H), 4.05 (dd, J = 7, 4 Hz, 1 H, γ-H). **Trans-(*RR,SS*) lactone 8a**: ^{1}H NMR ($CDCl_3$) δ (1.15 (d, J = 6 Hz, 3 H), 1.15–1.4 (m, 4 H), 1.5–1.9 (m, 7 H), 2.05 (d (br), J = 10 Hz, 1 H), 2.35–2.5 (m, 1 H, β-H), 2.7 ("t", J = 7 Hz), 3.88 ("t", J = 5 Hz, 1 H, γ-H). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.26; H, 8.97.

γ-(1-Cyclohexen-1-yl)-γ-hydroxy-β-methylbutanoic Acid Lactone (7b and 8b). Cis-(*RS,SR*) lactone 7b: ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J = 5 Hz, 3 H, β-CH_3), 1.55–1.75 (m, 4 H), 1.8–1.95 (m, 2 H), 2.0–2.15 (m, 2 H), 2.25 (dd, J = 16, 4 Hz, 1 H), 2.6–2.75 (m, 1 H, β-H), 2.72 (dd, J = 16, 5 Hz, 1 H), 4.8 (d, J = 5 Hz, 1 H, γ-H), 5.8 (s (br), 1 H). **Trans-(*RR,SS*) lactone 8b**: ^{1}H NMR ($CDCl_3$) characteristic peaks δ 1.12 (d, J = 6 Hz, 3 H, β-CH_3), 4.32 (d, J = 6 Hz, 1 H, γ-H). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.32; H, 9.89.

(*E*)-4-Hydroxy-3-methyl-6-phenyl-5-hexenoic Acid Lactone (7c and 8c). Cis-(*RS,SR*) lactone 7c: ^{1}H NMR ($CDCl_3$) δ 1.1 (d, J = 6 Hz, 3 H, β-CH_3), 2.3 (dd, J = 16, 6 Hz, 1 H), 2.75 (dd, J = 16, 6 Hz, 1 H), 2.75–2.85 (m, 1 H, β-H), 5.15 (t, J = 6 Hz, γ-H), 6.18 (dd, J = 14, 5 Hz, 1 H), 6.7 (d, J = 14 Hz, 1 H), 7.25–7.5 (m, 5 H). **Trans-(*RR,SS*) lactone 8c**: ^{1}H NMR ($CDCl_3$) characteristic peaks δ 1.2 (d, J = 6 Hz, 3 H, β-CH_3), 4.58 (t, J = 6 Hz, 1 H, γ-H). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.32; H, 6.87.

γ-(2-Furanyl)-γ-hydroxy-β-methylbutanoic Acid Lactone (7d and 8d). Cis-(*RS,SR*) lactone 7d: ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 6 Hz, 3 H, β-CH_3), 2.55–2.65 ("dd", 2 H), 2.85–3.0 (m, 1 H, β-H), 5.48 (d, J = 6 Hz, 1 H, γ-H), 6.35 (s, 2 H), 7.42 (s, 1 H); IR (thin film) 1780 cm^{-1}. **Trans-(*RR,SS*) lactone 8d**: ^{1}H NMR ($CDCl_3$) δ 1.22 (d, J = 6 Hz, 3 H, β-CH_3), 2.32 (dd, J = 16, 9 Hz, 1 H), 2.8–2.95 (m, 2 H, including β-H), 5.0 (d, J = 6 Hz, 1 H, γ-H), 6.38 (s (br), 1 H), 6.47 (d, J = 3 Hz, 1 H), 7.47 (s, 1 H). Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.12; H, 6.01.

γ-(3-Furanyl)-γ-hydroxy-β-methylbutanoic Acid Lactone (7e and 8e). Cis-(*RS,SR*) lactone 7e: ^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 6 Hz, 3 H, β-CH_3), 2.35 (dd, J = 15, 4 Hz, 1 H), 2.75 (dd, J = 15, 6 Hz, 1 H), 2.75–2.9 (m, 1 H, β-H), 5.55 (d, J = 6 Hz, 1 H, γ-H), 6.32 (d, J = 2 Hz, 1 H), 7.4–7.5 (m, 2 H). **Trans-(*RR,SS*) lactone 8e**: ^{1}H NMR ($CDCl_3$) characteristic peaks δ 1.2 (d, J = 6 Hz, 3 H, β-CH_3), 4.95 (d, J = 6 Hz, 1 H, γ-H). Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.07; H, 6.14.

γ-(2-Benzofuranyl)-γ-hydroxy-β-methylbutanoic Acid Lactone (7f and 8f). Cis-(*RS,SR*) lactone 7f: ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J = 6 Hz, 3 H, β-CH_3), 2.6–2.8 (m, 2 H), 2.95–3.10 (m, 1 H, β-H), 5.6 (d, J = 6 Hz, 1 H, γ-H), 6.75 (s, 1 H), 7.2–7.35 (m, 2 H), 7.48 (d, J = 6 Hz, 1 H), 7.58 (dd, J = 6, 1.5 Hz, 1 H). **Trans-(*RR,SS*) lactone 8f**: ^{1}H NMR ($CDCl_3$) δ 1.28 (d, J = 6 Hz, 3 H, β-CH_3), 2.32 (dd, J = 16, 9 Hz, 1 H), 2.9 (dd, J = 16, 7 Hz, 1 H), 2.9–3.1 (m, 1 H, β-H), 5.12 (d, J = 6 Hz, 1 H, γ-H), 6.8 (s, 1 H), 7.2–7.4 (m, 2 H), 7.48 (d, J = 6 Hz, 1 H), 7.58 (dd, J = 6, 1.5 Hz, 1 H). Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.32; H, 5.49.

γ-Hydroxy-β-methyl-γ-(1-methyl-1*H*-pyrrol-2-yl)butanoic Acid Lactone (7g and 8g). The reaction was run as described above except for the workup which was done as follows: The reaction mixture was quenched with 1 N HCl and vigourously stirred for 30 min in the presence of ether. The aqueous layer was reextracted with ether, and the organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the liquors to dryness gave immediately the crude mixture of lactones, which was chromatographed in a column of flash silica gel, eluting with 3:7 ethyl acetate–hexane, to give the mixture of cis and trans

(28) Characteristic signals for cis γ-lactones (*RS,SR* isomers) **7** and trans γ-lactones (*RR,SS* isomers) **8** were determined by simple nuclear Overhauser effect (NOE) studies on both pure typical lactones isolated as described in ref 1, footnote 10.

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

M. P. Bertrand,* J.-M. Surzur, H. Oumar-Mahamat, and C. Moustrou

Laboratoire de Chimie Organique B-Associé au CNRS (URA 1412), Faculté des Sciences-St. Jérôme, 13397 Marseille Cedex 13, France

Received August 2, 1990

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-

0022-3263/91/1956-3089$02.50/0