Enolate Additions to a Chiral 3-Hydroxypropionate 2,3-Dication Equivalent. Enantioselective Synthesis of *β,δ*-Dihydroxy Esters

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The use of optically active dicarbonyl cyclopentadienyliron(vinyl ether) BF_4 salts, **3** and **4**, as enantioselective 3-hydroxypropionate 2,3-dication equivalents is outlined. Complexes **3** and **4** are readily available by exchange etherification of **2**, and these have been transformed to enantiomeric dicarbonyl (η-cyclopentadienyliron)(η^2-1-methoxypropene) BF_4 **5** and *ent*-**5**. Complex **5** has been converted to the corresponding *p*-methoxybenzyloxy vinyl ether complex **7** by exchange etherification. Condensation of this salt with a number of terminal and nonterminal enolates yields adducts, which are then transformed by redox-promoted alkoxycarbonylation, followed by alcohol deprotection, to optically active 2-methyl-3-hydroxy-5 keto esters. 1,3-Reduction of these ketols can be effected to give either *syn*- or *anti*-1,3-diols and thence their related pentanolides.

Introduction

We have earlier reported the preparation of the Fp-(vinyl ether)BF_4 salts **1 a**−**d** (Fp = dicarbonyl-η-cyclopentadienyliron) and their use as vinyl, *trans*-propenyl, isopropenyl, and α-carbomethoxyvinyl cation equivalents in reactions with enolates to give β,γ-unsaturated ketones[1] and α-methylene-γ-lactones[2] (Figure 1).

The closely related 1,2-diethoxyethylene complex **2**, obtained by exchange complexation of the olefin with Fp-(isobutylene)BF_4, has been shown to function as either a *cis*- or *trans*-vinylene dication with stabilized and unstabilized carbon nucleophiles.[3]

These transformations, summarized in Figure 2, take advantage of the regio- and stereochemical control exercised by the Fp group in nucleophile addition and elimination reactions, and of the low-energy barrier associated with rotation about the putative double bond in Fp-(vinyl ether) salts, which enables ready conversion of a *trans*-alkenyl ligand to its thermodynamically preferred *cis* form. Salt **2** thus provides a synthetic sequence alternative to classical olefination reactions and, in particular, provides a convenient route to *cis*- or *trans*-β,γ-unsaturated carbonyl compounds.[4]

Complex **2** has been converted to the optically active dioxino complexes **3** and **4**, through exchange etherification with (*S*)-propane-1,2-diol and (*R,R*)-butane-2,3-diol, respectively (Figure 3), and these have been used in the preparation of complexes **1a,b** in optically active form.[5] We have also shown that the absolute configurations of Fp-(vinyl ether) and vinylene diether complexes may be assigned through application of a simple CD quadrant rule.[6]

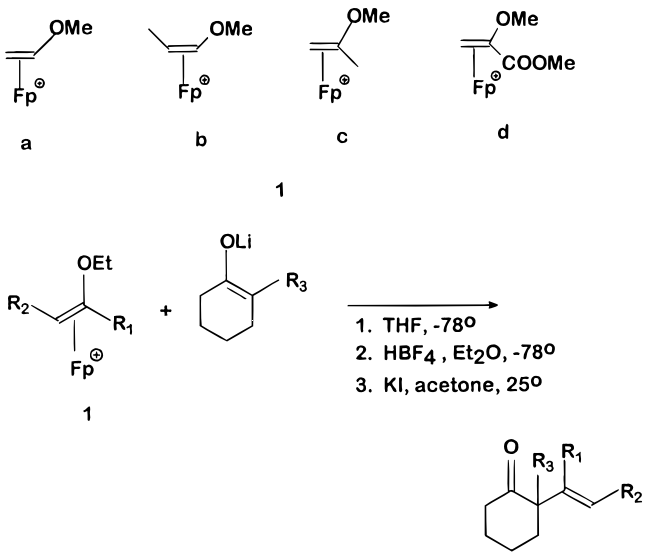

Figure 1.

Although the diastereomers **3a,b**, formed in the reaction of **2** and (*S*)-propane-1,2-diol, may be separated, this is not necessary, since each adds nucleophiles regioselectively (at C-3 for **3a** and at C-2 for **3b**) to give adducts with the same configuration at the newly created tetrahedral centers.[5b] As shown in Scheme 1 below, these adducts may be transformed, without isolation, through successive low temperature protonation, and exchange etherification, to enantiomeric vinyl ether complexes **5** and **6**.[5] A short paper reporting preliminary results in this area was recently published.[7] Structural assignments for diastereomers **3a,b** are based on proton and ^{13}C NMR analysis and on X-ray structure determination of the parent dioxin complex[5b] and are summarized in the Experimental Section.

The present paper describes the use of complexes **3a,b** as chiral 3-hydroxypropionate 2,3-dication equivalents (Figure 4) and especially their application in the synthesis of *syn*- and *anti*-β,δ-dihydroxy esters and their derived δ-lactones, which are important structural elements in

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(1) (a) Chang, T. C-T.; Rosenblum, Samuels, S. B. *J. Am. Chem. Soc.* **1980**, *102*, 5930 (b) Chang, T. C-T.; Rosenblum, M. *J. Org. Chem.* **1981**, *46*, 4103. (c) Chang, T. C-T.; Rosenblum, M. *Isr. J. Chem.* **1984**, *24*, 99. (d) Chang, T. C-T., Coolbaugh, T. S.; Foxman, B. M.; Rosenblum, M.; Simms, N.; Stockman, C. *Organometallics* **1987**, *6*, 2394.

(2) Chang, T. C-T.; Rosenblum, M. *J. Org. Chem.* **1981**, *46*, 4626. Chang, T-C. T.; Rosenblum, M. *Tetrahedron Lett.* **1983**, *24*, 695.

(3) Marsi, M.; Rosenblum, M. *J. Am. Chem. Soc.* **1984**, *106*, 7264.

(4) Hudrlik, P. F.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1981**, *103*, 6251 and references therein.

(5) (a) Rosenblum, M.; Turnbull, M. M.; Foxman, B. M. *Organometallics* **1986**, *5*, 1062. (b) Turnbull, M. M.; Foxman, B. M.; Rosenblum, M. *Organometallics* **1988**, *7*, 200.

(6) Begum, M. K.; Chu, K-H.; Coolbaugh, T. S.; Rosenblum, M. Zhu, X-Y. *J. Am. Chem. Soc.* **1989**, *111*, 5252.

(7) Chu, K-H.; Zhen, W.; Zhu, X-Y.; Rosenblum, M. *Tetrahedron Lett.* **1992**, *33*, 1173.

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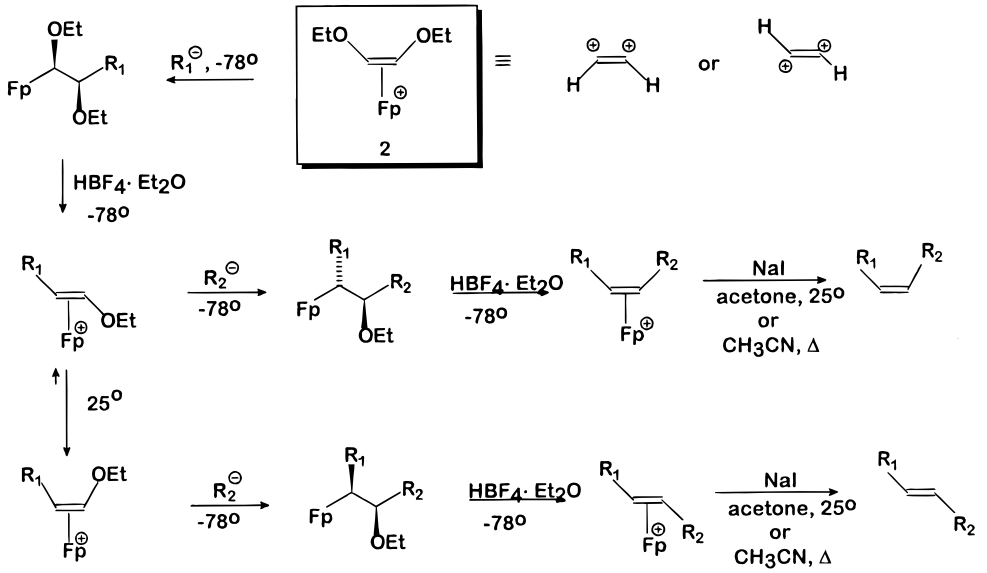


Figure 2.

a large number of biologically active natural products.[8] The retrosynthetic analysis shown in Figure 4 illustrates the very different disconnections associated with the synthesis of 2-alkyl-3-hydroxy esters following either the reaction path involving synthons **5** and **6**, derived from **3** or **4** or that involving a related aldol type reaction.[9]

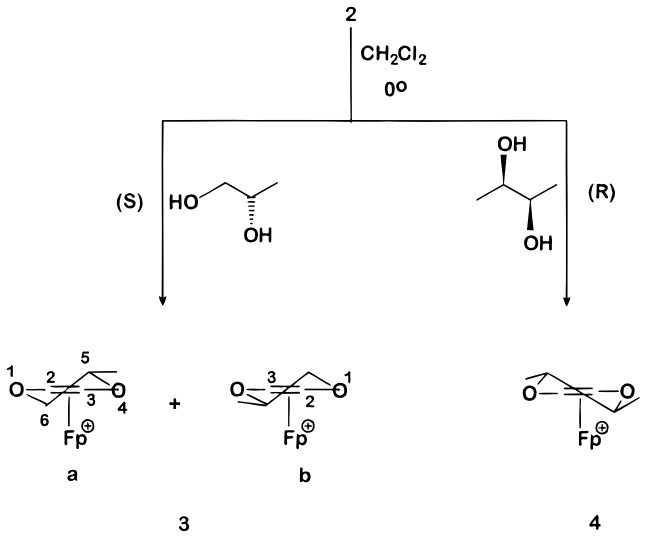
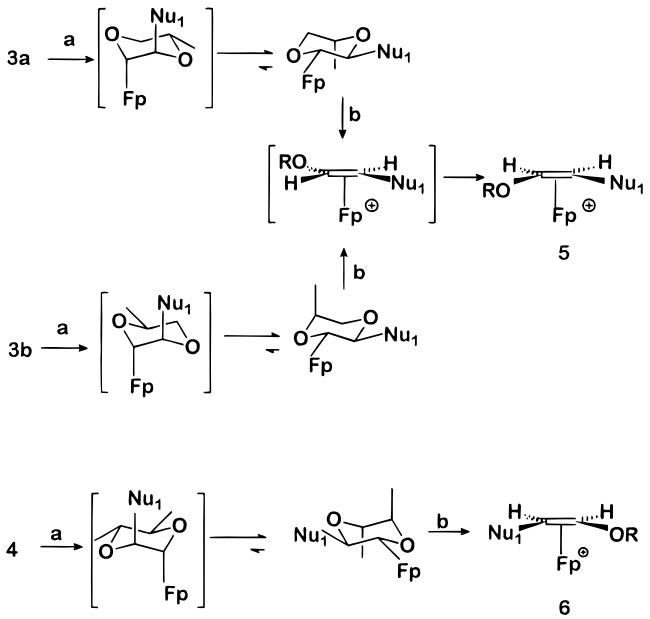


Figure 3.

Moreover, asymmetric induction and diastereoselection, which is generally achieved in the aldol reaction through control of the six-center cyclic transition state generally associated with these reactions, is derived instead, for **5** and **6**, from the planar chirality of the organometallic reagent and the stereochemically enforced mode by which it reacts with nucleophiles.

Scheme 1[a]



[a] Reaction conditions: (a) Nu_1^-, TEA, THF, −78 °C, 1h; (b) HBF_4, CH_2Cl_2, −78 °C; ROH, 25 °C.

Results

In order to examine the use of **3a,b** as a chiral dication synthetic equivalent, the mixture of diastereomers was first converted to the optically active propenyl ether complex **7** (Scheme 2). Experiments were also carried out with the more accessible racemic salt *rac*-**7**, which is readily prepared in multigram quantities by metalation of bromopropionaldehyde diethyl acetal with FpNa, followed by acid-promoted elimination of ethanol and ether exchange[10] (Scheme 2).

Illustrative of the use of **7** as an optically active α-methyl-β-hydroxypropionate β-cation equivalent is its

(8) Pettit, G. R. *Pure Appl. Chem.* **1994**, *66*, 2271. Omura, S.; Tanaka, H. in *Macrolide Antibiotics: Chemistry, Biology and Practice*; Omura, S.; Ed.; Academic Press: New York, 1984. Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346. Harada, T.; Shintani, T.; Oku, A. *J. Am. Chem. Soc.* **1995**, *117*, 12346 and references therein. Martin, S.; Guinn, D. E. *Synthesis* **1991**, 245. De Mico, A.; Piancatelli, G.; Cacurri, S.; Sperandina, L. *Gazz. Chim. Ital.* **1992**, *122*, 415. Stokker, G. E.; Alberts, A. W.; Anderson, P. S.; Cragoe, E. J.; Deana, A. A.; Gilfillan, J. L.; Hirshfield, J.; Holtz, W. J.; Hoffman, W. F.; Huff, J. W.; Lee, T. J.; Novello, F. C.; Prugh, J. D.; Rooney, C. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 170 and references therein.

(9) Heathcock, C. H. *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.: Pergamon Press: New York, 1991; Vol. 2, p 181; Kim, B. M.; Williams, S. F., Masamune, S. *Ibid.* Vol. 2, p 239; Patterson, I. *Ibid.* Vol. 2, p 301.

(10) Cutler, A.; Raghu, S.; Rosenblum, M. *J. Organometal. Chem.* **1974**, *77*, 381.

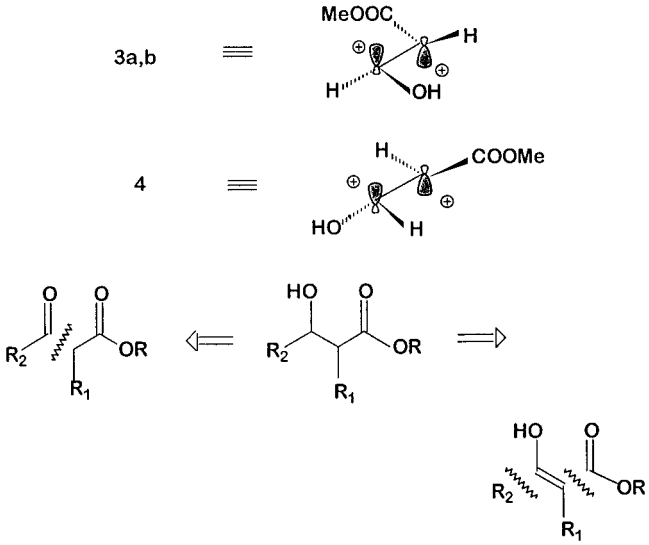
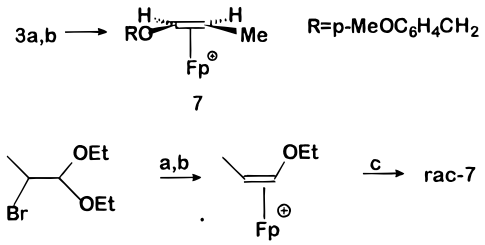


Figure 4.

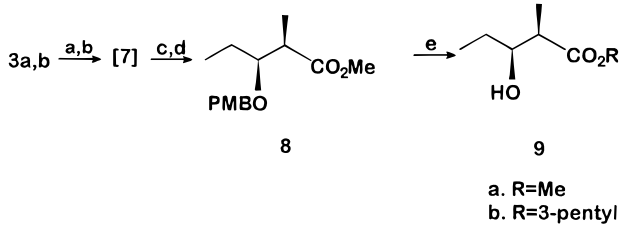
conversion to the protected hydroxy ester **8** through addition of ethyl Grignard, followed by *in situ* redox-promoted methoxycarbonylation of the adduct (Scheme 3). A number of oxidizing reagents were examined as

Scheme 2[a]



[a] Reaction conditions: (a) FpNa, THF, 25 °C, 3.5 h; (b) HBF_4–Et_2O, (c) *p*-$MeOC_6H_4CH_2OH$, 25 °C, 20 min.

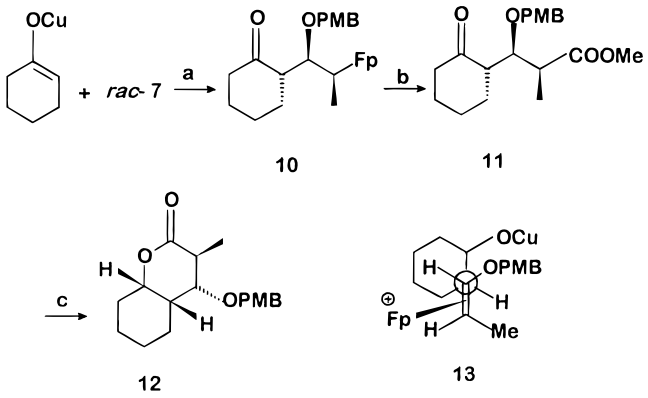
Scheme 3[a]



[a] Reaction conditions: (a) $LiMe_2Cu$, Et_3N. −78 °C, 4 h; (b) CH_2Cl_2, HBF_4–Et_2O, −78 °C, *p*-$MeOC_6H_4OH$; (c) EtMgBr, Et_3N, THF/Et_2O, −78 °C, 1 h; (d) $Ce(NH_4)_2(NO_3)_6$, NaOAc, MeOH, CO, −78 °C to 25 °C; (e) DDQ, CH_2Cl_2, H_2O, 25 °C, 2 h.

promoters of the carbonylation step, among them bromine, chlorine, NBS, $AgBF_4$, Ag_2O, O_2, and $Ce(NH_4)$-$(NO_3)_6$. Of these, the last proved the most effective. The reaction sequence shown in Scheme 3, can alternatively be carried through beginning with **3a,b**, without isolation and purification of intermediates, to give **8** in 61% overall yield. Deprotection of the hydroxyl group with DDQ gave (2*R*,3*S*)-hydroxy ester **9a**.[11] When redox-promoted alkoxycarbonylation is carried out in the presence of 3-pentanol, the sequence gives *ent*-sitophilate **9b**, the granary weevil

Scheme 4[a]



[a] Reaction conditions: (a) −78 °C, 1 h, THF; (b) NaOAc, MeOH, $Ce(NH_4)_2(NO_3)_6$, −78 °C to 25 °C, (c) THF, L-Selectride, −78 °C to 25 °C.

aggregation pheromone.[12] In order to examine the enantioselectivity of the overall sequence, *rac*-**7** was carried through to *rac*-**9a**. Examination of the proton NMR spectrum of this material in the presence of $Eu(hfc)_3$ showed that the optically active ester is formed with >98% ee.[13]

The reaction of **7** with a number of enolates was also examined. Although the lithium enolate of cyclohexanone had been used successfully with vinyl ether complexes **1**, it gave poor and irreproducible yields of adduct in reactions with *rac*-**7**. Since we had earlier observed that alkyl cuprates and higher order cyanocuprates gave better yields of addition product with a number of Fp(vinyl ether) salts,[3] lithium cyclohexanone enolate was converted to the cuprate salt by treatment with CuBr–Me_2S,[14] and this was added to **7**. Under these reaction conditions, the adduct **10** was obtained in 90% yield as a single diastereomer. The stereochemistry of the adduct was determined by redox-promoted methoxycarbonylation to give **11**, which was reduced with L-Selectride and cyclized to the lactone **12**. Examination of its proton NMR spectrum confirmed the structure of the lactone (Scheme 4). The *anti* diastereochemistry observed for **11** corresponds to that observed in the reactions of a number of cyclohexanone enolates with complex cation **1a**[1d] and is compatible with a preferred antiperiplanar transition state **13** for the reacting components.

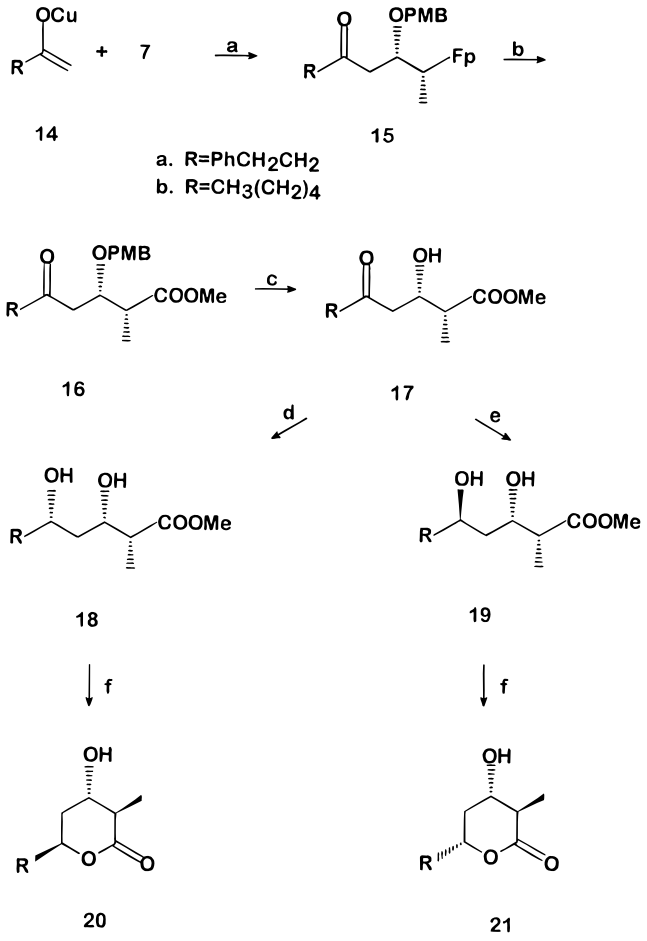
(11) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.

(12) Philips, J. K.; Miller, S. P. F.; Anderson, J. F.; Falles, H. M.; Burkholder, W. E. *Tetrahedron Lett.* **1987**, *28*, 6145. Chong, J. M. *Tetrahedron* **1989**, *45*, 623.

(13) In the racemic ester, the doublet proton resonance of the α-methyl group is split into a double doublet at δ 1.20 by the chiral shift reagent. This resonance remains unchanged in the optically active ester.

(14) Present experimental evidence suggests that metal enolates, formed by conjugate addition of cuprates to enones, are better represented as the lithium enolate: House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1978**, *43*, 2443; House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1976**, *41*, 4031. Nevertheless, the species formed by treatment of lithium enolates with copper(I) would appear to differ from these, and we have represented this salt tentatively here as a copper enolate. For example, while lithium dienolates derived from α,β-unsaturated acids underwent preferential α-alkylation, the corresponding "copper dienolates", formed by treatment of the lithium salts with CuI were observed to give selective γ-alkylation: Katzenellenbogen, J. A.; Crumrine, A. L. *J. Am. Chem. Soc.* **1976**, *98*, 4925. Similarly, while the lithium enolate of ethyl acetate was observed to react with propargyl bromide to give ethyl 4-pentynoate, the "copper enolate" gave the corresponding ethyl 3,4-pentadienoate: Amos, R. A.; Katzenellenbogen, J. A. *J. Org. Chem.* **1978**, *43*, 555. Finally, the course of alkylation of β-aryl and β-aralkylcyclopentanones and cyclohexanones in the presence or absence of copper(I) was found to be distinctly different: Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934.

Scheme 5[a]



[a] Reaction conditions: (a) THF, −78 °C, 30 min; (b) CAN, THF, NaOMe, CO, −60 °C; (c) DDQ, CH_2Cl_2/H_2O, 25 °C, 2 h; (d) Et_3B, THF/MeOH, −78 °C, 30 min; $NaBH_4$, 5 h; (e) $Me_4NBH(OAc)_3$, CH_3CN/HOAc, −40 °C, 18 h; (f) *p*-TsOH, C_6H_6, 25 °C, 18 h.

The reactions of **7** with two terminal enolates (**14a** and **14b**) were also examined (Scheme 5). While the lithium enolates yielded almost exclusively the product of O-alkylation, the copper enolates gave C-alkylation products **15a** and **15b**, respectively, in high yield. Redox-promoted methoxycarbonylation of these, using ceric ammonium nitrate (CAN) in methanol at −60 °C, afforded the keto esters **16a** and **16b**, and these were transformed to the deprotected hydroxy keto esters **17a** and **17b** with DDQ. In the presence of a sufficient excess of ceric reagent, both oxidative carbonylation of the alkylFp intermediates **15a** and **15b** as well as deprotection of the alcohol function can be achieved. Thus, using 3−4 equiv of CAN with **15a** and workup of the reaction at −30 °C gave **16a** and **17a** (95:5) in 70% yield, while the use of 6 equivs of CAN and workup at room temperature gave these products in an inverted ratio of 5:95 in 65% yield. It is important to note here as well that, whereas sodium acetate was used in the redox-promoted alkoxycarbonylation reactions of Schemes 3 and 4, sodium methoxide proved to give better yields of product in the transformation of **15** and was consequently used in all subsequent oxidation reactions.

Further elaboration of **17a,b** to either the *syn*- or *anti*-1,3-diols **18a,b** or **19a,b** was readily achieved by reduction of the ketol employing the methods of Prasad[15] and of Evans,[16] respectively. In our hands, these were found to give high yields of the requisite *syn*- or *anti*-diols with high stereoselectivity. The 1,3-diols were in turn transformed to the δ-lactones **20a,b** and **21a,b** and the stereochemistry of each of these was confirmed by comparison of ring proton coupling constants observed for these compounds with those calculated for the model compounds **20** and **21** (R = Me).[17] These data are summarized in Table 1. The proton NMR spectra of each of the diastereomeric lactones did not show the presence of the other diastereoisomer in the product. The synthesis of *cis*-diols **18a,b** and the derived lactones **20a,b** was carried out on optically active material, derived from use of (2*R*,3*S*)-**7**, while the synthesis of diols **19a,b** and their derived lactones **21a,b** was carried out with *rac*-**7**.

Table 1. Calculated and Observed Proton Coupling Constants for 20 and 21

	$J_{2,3}$	
lactone	obsd[a]	calcd[b]
20a	9.93	9.47
20b	9.90	9.47
21a	6.72	4.84
21b	6.60	4.84

[a] By decoupling experiments. [b] For **20** and **21**, R = Me.

The diastereoselectivity of reactions involving *rac*-**7** with nonterminal enolates was also of interest, and two such enolates were examined (Scheme 6). (*Z*)-2-(Trimethylsiloxy)-2-heptene was prepared from 2-heptanone and ethyl (trimethylsilyl)acetate, following the method of Kuwajima,[18] and converted to the copper enolate **22a**. Reaction of this with *rac*-**7** gave a 3.5:1 mixture of diastereoisomeric products, which were not separated but converted through redox-promoted methoxycarbonylation and alcohol deprotection to a mixture of keto esters **25a** and **26a** (50%), from which the major isomer could be separated and characterized. The mixture of keto esters was in turn reduced to the *anti*-1,3-diols **27a** and **28a** (95%) and cyclized to give lactones **30a** and **31a**. The structures of the major and minor isomers (**30a** and **31a**, respectively) were assigned from an analysis of their ring proton coupling constants and a comparison of these with coupling constants calculated for the model lactones **30** and **31** (R = Et). These results, summarized in table 2 support the assignment of the major condensation product as **23a**. Analogously, *syn*-reduction of the mixture of keto esters **25a** and **26a** resulted in the reduction of the major isomer **25a** alone (50%). The unreduced keto ester **26a** could not be separated from **29a**, but cyclization of this mixture led to the formation of lactone **32a**, from which **26a** could be recovered. An analysis of the ring proton coupling constants for this lactone (Table 2) confirms its structural assignment and thence the assignment of structure **23a** as the major product of the condensation reaction.

Similarly, (*Z*)-4-phenyl-2-(trimethylsiloxy)-2-butene was prepared following House's procedure,[19] purified by spinning band distillation, and converted to the copper

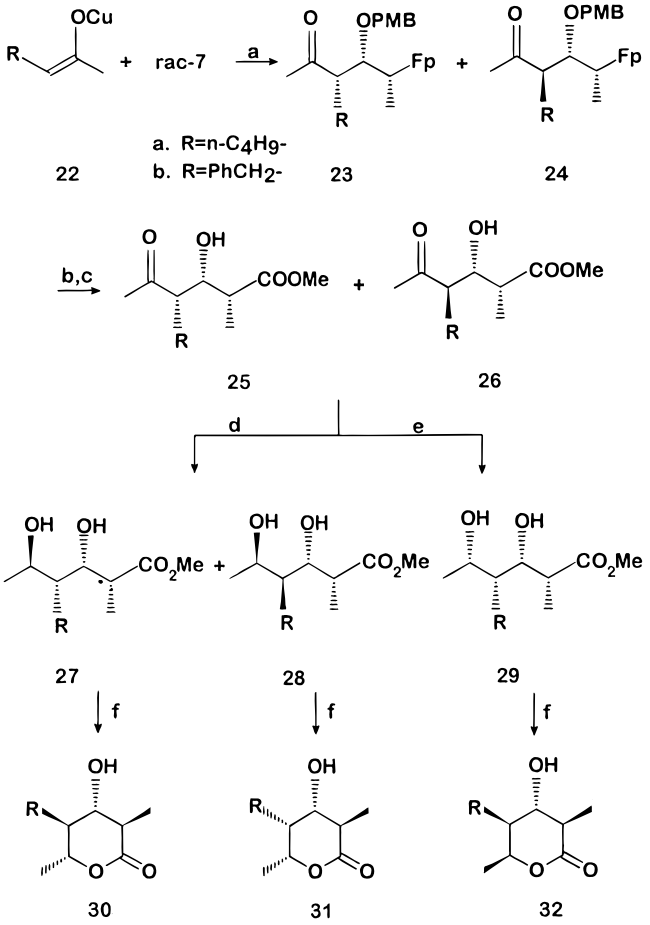
(15) Chen, K. M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, J. M. *Chemistry Lett.* **1987**, 1923. Kathawala, F. G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M. J.; Stabler, R. S.; Widler, L. *Helv. Chim. Acta* **1986**, *69*, 803.

(16) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(17) Model version KS 2.99, obtained from Prof. K. Steliou, Boston University, was used in the conformational search and MM2 calculations.

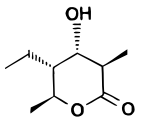
(18) Nakamura, E.; Hashimoto, K.; Kuwajima, I. *Tetrahedron Lett.* **1978**, *24*, 2079. Nakamura, E.; Murofushi, T. Shimizu; M.; Kuwajima, I. *J. Am. Chem. Soc.* **1976**, *98*, 2346.

Scheme 6[a]



[a] Reaction conditions: (a) THF, −78 °C, 30 min; (b) CAN, THF, NaOMe, CO, −60 °C to 25 °C; (c) DDQ, CH_2Cl_2/H_2O, 25 °C, 2 h; (d) $Me_4NBH(OAc)_3$, CH_3CN/HOAc, −40 °C, 18 h; (e) Et_3B, THF/MeOH, −78 °C, 30 min; $NaBH_4$, 5 h; (f) *p*-TsOH, C_6H_6, 25 °C, 18 h.

Table 2. Calculated and Observed Coupling Constants for Lactones 30−32

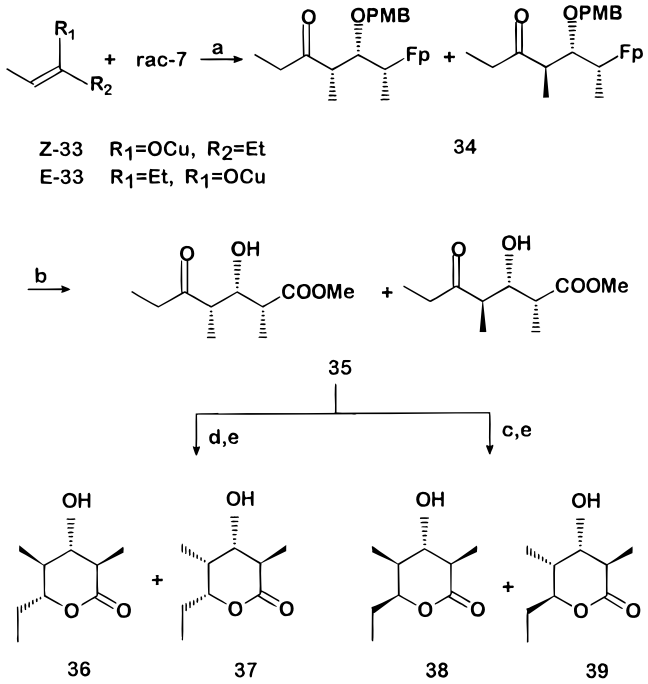


	$J_{2,3}$		$J_{3,4}$		$J_{4,5}$	
lactone	obsd[a]	calcd[b]	obsd[a]	calcd[b]	obsd[a]	calcd[b]
30a	9.8	8.3	9.6	8.4	7.7	8.3
31a	8.6	5.6	4.2	3.4	3.0	4.0
3a	7.9	7.6	4.1	2.1	3.2	1.9
A	–	4.1	–	2.6	–	9.8
30b	9.7	8.3	10.1	8.4	9.8	8.3
31b	8.3	5.6	4.2	3.4	3.0	4.0
32b	8.1	7.6	3.4	2.1	3.2	1.9

[a] By decoupling experiments. [b] For **30**−**32**, R = Et.

enolate. Reaction of this with *rac*-**7** gave a mixture of diastereoisomer condensation products **23b** and **24b** in a ratio of 2.5:1. The structure of these isomers was determined, as before, by their conversion, through redox-promoted methoxycarbonylation, to the esters **25b** and **26b**, which were in turn transformed to *anti*-1,3-diols and

Scheme 7[a]



[a] Reaction conditions: (a) THF, −78 °C, 2.5 h; (b) CAN, THF, −60 °C to −30 °C, NaOMe, CO; (c) Et_3B, THF/MeOH, −78 °C, 30 min; (d) $Me_4NBH(OAc)_3$, CH_3CN/HOAc, −40 °C, 5 h; (e) *p*-TsOH, C_6H_6, 25 °C, 18 h.

thence to the lactones **30b** and **31b** in a 2.5:1 ratio. As before, we observed that corresponding *syn*-reduction[14] of the mixture of keto esters **25b** and **26b** resulted in the selective reduction of the major isomer **25b** alone. The resulting mixture of **29b** and unchanged **26b** was lactonized, and **26b** was separated from the lactone, which was characterized by its PMR spectrum. As before, these experiments establish **23b** as the principal product resulting from the condensation of **22b** and **7**.

Finally, the effect of enolate geometry on the diastereoselectivity of the condensation reaction was examined (Scheme 7). Both the *Z*-[18] and *E*-enolates[20] of 3-pentanone gave mixtures of *syn*- and *anti*-**34**, in which the *syn*-isomer predominated (1.5:1). As before, these mixtures were transformed through redox-promoted methoxycarbonylation, reduction, and lactonization to the lactones **36**−**39**, which were characterized by their ring coupling constants (Table 3). The possibility that *E*- and *Z*-copper enolates of 3-pentanone equilibrate under conditions of their formation was examined, by conversion of (*Z*)-(trimethylsiloxy)-2-pentene (99% *Z*) to the copper enolate and quenching this with TMSCl. The product was observed to be the (Z)-silyl ether free of detectable amounts of the *E*-isomer.

Discussion

The predominance of *syn*-product in the condensation of nonterminal acyclic enolates with cationic vinyl ether complex **7** forms a close parallel with the *syn*-selectivity observed in reactions of tris(dialkylamino)sulfonium enolates with aldehydes[21] and in the reactions of *cis*- and *trans*-allylic silanes and stannanes with aldehydes.[22] Here, too, *syn*-selectivity in the product is largely inde-

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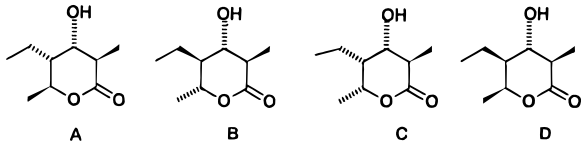
Table 3. Calculated and Observed Coupling Constants for Lactones 36−38



	$J_{2,3}$		$J_{3,4}$		$J_{4,5}$	
lactone	obsd[a]	calcd	obsd[a]	calcd	obsd[a]	calcd
36	10.5	8.3 (B)	8.5	8.4 (B)	7.3	8.3 (B)
37	9.8	5.6 (C)	3.9	3.4 (C)	3.3	4.0 (C)
38	7.6	7.5 (D)	2.1	2.1 (D)	2.7	1.9 (D)
39	4.0	4.1 (A)	2.6	2.6 (A)	9.9	9.8 (A)

[a] By decoupling experiments.

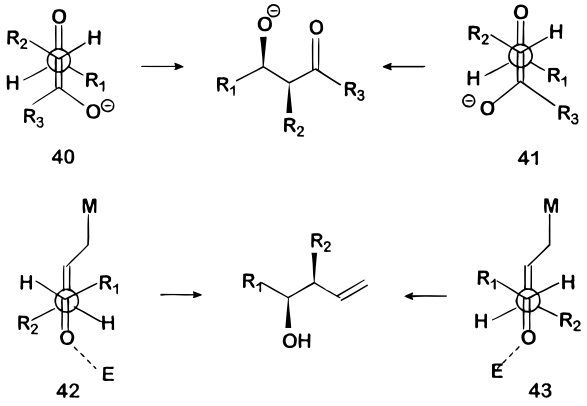


Figure 5.

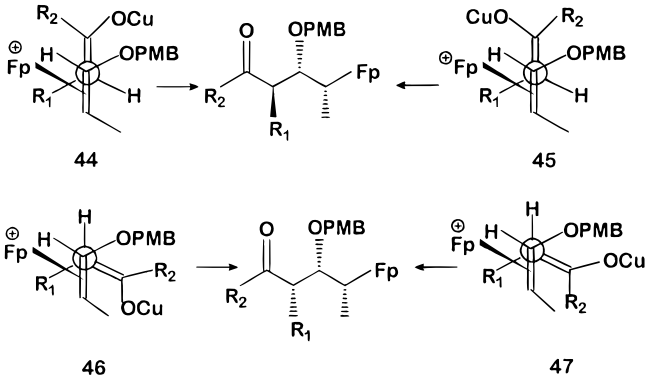


Figure 6.

pendent of enolate or allylmetal geometry. These results have been accounted for in terms of open or non-chelated antiperiplanar transition states **40**−**43**, in which steric interactions of substituent groups (R_1 and R_2) at the reaction center control the diastereofacial selectivity of the reaction[22] (Figure 5).

This construct cannot apply to the reactions of **7** with enolates, since antiperiplanar transition states **44** and **45** should then lead to preferential formation of *anti*-product from both *Z*- and *E*-enolates (Figure 6). A synclinal transition state for the reacting components gives a better account of the experimental results for both *E*- and *Z*-enolates, and such an orientation of reactants has also been proposed for intramolecular reactions of allylsilanes and allylstannanes and aldehydes.[23] Whatever the precise orientational preference of reacting components in these reactions, it seems that only small energy differences separate idealized antiperiplanar and synclinal transition states from one another. Indeed, recent calculations indicate that the energies of such open transition states for the condensation of acetaldehyde enolate and formaldehyde are computationally indistinguishable.[24] It has also been suggested that stereoelectronic factors may favor a synclinal orientation of donor and acceptor components in Michael reactions of nitroolefines with enamines.[25] While the modest *syn*-diastereoselectivity observed in the reactions of **7** with acyclic *Z*- and *E*-enolates is in accord with a small difference in energy between antiperiplanar and synclinal transition states, the contrasting high *anti*-diastereoselectivity observed in the reaction of cyclohexanone enolate with **7** suggests a clear preference for the antiperiplanar transition state **13**. For the cyclic enolate, this conformation is free of steric interactions involving the benzyloxy group with either adjacent or across ring protons of the cyclohexane ring, while none of the related synclinal conformations are free of such interactions.

Conclusion

In this and earlier publications,[1d,5,8] the organometallic salts **3a,b** and **4** have been shown to behave as stabilized, enantioselective carbocations toward carbon nucleophiles. The transformation of the resulting neutral complexes, through ring opening and alcohol exchange, sets the stage for addition of a second nucleophile. The present paper has examined the diastereoselective addition of cyclic as well as terminal and nonterminal acyclic enolates to the vinyl ether complex **7**, derived from **3a,b**. These reactions, combined with chain functionalization through stereospecific redox-promoted methoxycarbonylation, provide facile entry to optically active *syn*- and *anti*-β,δ-dihydroxypropionates.

Experimental Section

Materials and Methods. Solvents were freshly distilled by standard procedures, maintained under a nitrogen atmosphere, and degassed by passing through a stream of nitrogen prior to use. All reactions and subsequent manipulations were handled under either a nitrogen or argon atmosphere. Elemental analyses were determined by Desert Analytics, Tucson, AZ. Several of the products which were too unstable to submit for elemental analyses were characterized by their ^{1}H and ^{13}C NMR spectra. All chemicals were purchased from Aldrich Chemical Co. unless otherwise specified.

***cis*-1,2-Dimethoxyethylene.** This was prepared by pyrolysis of 2-methoxyacetaldehyde dimethyl acetal, following the procedure of McElvain and Stammer,[26] except that commercial 12−32 mesh alumina, purchased from EM Science, was used. Separation of the *cis*- and *trans*-products was achieved by spinning band distillation (*cis*-1,2-dimethoxyethylene, bp 92−94 °C, *trans*-isomer bp 90−92 °C). *cis*-Isomer ^{1}H NMR ($CDCl_3$) δ 5.30 (s, 1H), 3.62 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 130.0, 60.2. *trans*-Isomer ^{1}H NMR ($CDCl_3$) δ 6.30 (s, 1H), 3.48 (s, 3H), ^{13}C NMR ($CDCl_3$) δ 134.5, 58.2. Dicarbonyl-η-cyclopentadienyliron η^2-*cis*-1,2-dimethoxyethylene tetrafluoroborate (**11**) was pre-

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pared from the *cis*-isomer in 90% yield, following the procedure of Turnbull et al.[5b]

(5*R*)-(Dicarbonyl-η-cyclopentadienyl iron)-5,6-dihydro-5-methyl-1,4-dioxin Tetrafluoroborate (3a) and (6*R*)-(Dicarbonyl-η-cyclopentadienyl)-5,6-dihydro-6-methyl-1,4-dioxin Tetrafluoroborate (3b). The following procedure represents an improvement of that given earlier[5b] for the preparation of these complexes. To a 100 mL Schlenk reaction flask containing Fp-dimethoxyethylene tetrafluoroborate **2** (5.28 g, 15 mmol) were added 10 mL of CH_2Cl_2 and 5.53 mL of (*S*)-(+)-1,2-propanediol (5.70 g, 75 mmol) consecutively at 0 °C. The reaction changed from a dark orange suspension to a dark brown solution quickly. A constant flow of argon was applied to entrain the methanol side product. In 15 min, a solid precipitated, and the stirred reaction suspension was maintained at 0 °C for another hour. Over 20 mL of ether was introduced and stirring was continued. The yellow solid was then collected on a sintered glass funnel, washed repeatedly with ether, and dried to give the product as a bright yellow solid, (5g, 92%) which was composed of two diastereomers, **3a** and **3b**, in a ratio of 3:1. If the reaction is run using 30 mL of solvent for the same scale of reactants, a 1:1 ratio of the same two diastereomers is formed. A single diastereomer, **3a**, can be obtained in 50% yield from the mixture by simply washing it (isomer ratio 3:1) with a small amount of cold methylene chloride several times, which removes the more soluble isomer **3b**.

The structural assignments for **3a** and **3b** were made as follows. It is known from the X-ray diffraction study of the parent Fp-(dioxin) BF_4[5b] that the Fp group is moved laterally along the C=C bond axis in order to reduce steric interactions between the syn-axial proton across the dioxine ring and an Fp carbonyl ligand. This interaction is also relieved in part by deflection of the carbon center bonded to the syn-axial proton into the O−C=C−O plane, partly by bending of the Fp group away and out from under the dioxin ring, and most importantly for the present analysis by the lateral displacement cited above. This displacement has the effect of increasing positive charge density on the distal oxygen atom of the complexed vinylene diether function (O_1 in **3**) and consequently to the saturated carbon center (C_6, Figure 3) bonded to this oxygen center. Hence, the methylene carbon signals in **3a** and **3b** are at δ 69.5 and 68.7 respectively, while the corresponding methine carbon resonances in **3a** and **3b** are at δ 70.4 and 71.7 respectively. Furthermore, the syn axial proton across the heterocyclic ring, which interacts sterically with the Fp group, lies in the shielding cone of the Fp group. In conformity with this, the axial proton in **3a**, the methylene proton, is observed at δ 3.35 while that of **3b** is at δ 3.64, while the axial methine proton in **3b** is more highly shielded than is the axial methine proton in **3a** (δ 3.91 vs 4.05). These same effects are seen in **4**.[5b]

***rac*-(Dicarbonyl-(η-cyclopentadienyliron)(η^2-1-ethoxypropene) Tetrafluoroborate (*rac*-5 R = Et, Nu = Me).** This was prepared following the procedure for the preparation of the corresponding hexafluorophosphate[10] from bromopropionaldehyde diethyl acetal: ^{1}H NMR (CD_3NO_2/TMS) δ 7.73 (d, 1H, J = 4.5 Hz), 5.52 (s, 5H), 4.48 (dq, 1H, J = 7.1, J = 10.0 Hz), 4.42 (dq, 1H, J = 7.1, J = 10.0 Hz), 3.60 (dq, 1H, J = 4.5 Hz, 6.2 Hz), 1.65 (d, 3H, J = 6.2 Hz), 1.41 (dd, 3H, J = 7.1, 7.1 Hz); ^{13}C NMR (CD_3NO_2/TMS) δ 214.0, 212.5, 136.2, 88.8, 73.3, 46.7, 15.0, 14.4. Anal. Calcd for $C_{12}H_{15}FeO_3BF_4$: C, 41.19; H, 4.32. Found: C, 40.92; H, 4.52.

(1*R*,2*R*)-(Dicarbonyl-(η-cyclopentadienyliron)(η^2-1-methoxypropene) Tetrafluoroborate (5, R = Me, Nu = Me). This was prepared following the procedure Turnbull et al.[5b] used in the preparation of the enantiomeric (*S*,*S*)-triflate salt. Lithium dimethyl cuprate was generated *in situ* from 123 mg (0.6 mmol) of CuBr−SMe_2 and 0.86 mL (1.4 M, 1.2 mmol) of methyllithium in ether and 5 mL of THF at −78 °C for 0.5 h. This was transferred via cannula to a suspension of **3a,b** (72.8 mg, 0.2 mmol) in 10 mL of THF and 0.17 mL (1.2 mmol) of triethylamine. The reaction was stirred at −78 °C for 1 h and then allowed to warm up to room temperature and quenched with water. The solution was extracted with ether, dried over magnesium sulfate, and concentrated to give an oily crude product quantitatively (61−84%). This crude product was redissolved in 5 mL of methylene chloride and cooled to −78 °C. HBF_4−Et_2O (0.35 mL, 0.22 mmol) was added and the formation of an orange solid was observed. After an additional 15 min, 0.24 mL (6 mmol) of methanol was added to dissolve the solid, and the solution was stirred at −40 °C for 1 h and then allowed to warm to 0 °C. Ether was slowly added to precipitate an orange solid (45.3 mg, 67%): ^{1}H NMR (acetone-d_6/TMS) δ 7.95 (d, 1H, J_{cis} = 4.0 Hz), 5.76 (s, 5H), 4.18 (s, 3H), 3.70−3.95(dq, 1H, J = 4.0, 6.1 Hz), 1.61 (d, 3H, J = 6.1 Hz); CD (CH_2Cl_2, −30 °C) $\Delta\epsilon_{455}$ = −1.85 M^{-1} cm^{-1}, $\Delta\epsilon_{345}$ = 3.41 M^{-1} cm^{-1}.

(1*R*,2*R*)-(Dicarbonyl-η-cyclopentadienyliron)(η^2-1-[(*p*-methoxybenzyl)oxy]propene) Tetrafluoroborate (7). To a 100 mL Schlenk reaction flask were added 260 mg (0.773 mmol) of (*R*,*R*)-Fp-(η^2-1-methoxypropene) BF_4 complex **5**, 10 mL of methylene chloride, and 0.96 mL (7.73 mmol) of *p*-methoxybenzyl alcohol at 0 °C. A constant flow of nitrogen was applied during the reaction to entrain the methanol byproduct. The system was flushed to dryness and the product was redissolved in methylene chloride. This was repeated five times over the course of 5 h. Finally, ether was added slowly to precipitate a solid. The compound was filtered, washed with ether, and dried in *vacuo* to give 282 mg of **7** (82%) as a yellow powder. This compound could also be prepared and used without isolation by adding *p*-methoxybenzyl alcohol to the dioxin ring opening intermediate, as described in the synthesis of ester **8**: ^{1}H NMR (CD_3NO_2/TMS) δ 7.81 (d, 1H, J = 4.4 Hz), 7.46 (d, 2H, J = 8.6 Hz), 7.02 (d, 2H, J = 8.6 Hz), 5.51 (s, 5H), 5.37 (d, 1H, J = 11.3 Hz), 5.31 (d, 1H, J = 11.3 Hz), 3.84 (s, 3H), 3.65 (dq, 1H, J = 4.4 Hz, J = 6.2 Hz), 1.65 (d, 3H, J = 6.3 Hz); ^{13}C NMR (CD_3NO_2/TMS) δ 213.1, 209.4, 162.0, 134.2, 132.0, 127.9, 115.5, 88.8, 78.2, 56.2, 47.5, 14.4; IR (CH_2Cl_2) 2060, 2020 cm^{-1}; CD (CH_2Cl_2, −30 °C) $\Delta\epsilon_{455}$ = −1.17 M^{-1} cm^{-1}, $\Delta\epsilon_{365}$ = 1.96 M^{-1} cm^{-1}. Anal. Calcd for $C_{18}H_{19}O_4FeBF_4$: C, 48.91; H, 4.33. Found: C, 48.76; H, 4.12. The corresponding *rac*-**7** was prepared similarly by treating 3.50 g (10.0 mmol) of *rac*-Fp-(η^2-1-ethoxypropene) BF_4 (*rac*-**5**) in 20 mL of methylene chloride with 12.5 mL (100 mmol) of *p*-methoxybenzyl alcohol. After reacting for 12 h at 0 °C, *rac*-**7** was precipitated, filtered, washed with ether, and dried in *vacuo* to give 3.57 g of product (81%) as a yellow powder.

(2*R*,3*S*)-Methyl 2-Methyl-3-[(*p*-methoxybenzyl)oxy]pentanoate (8). Lithium dimethylcuprate, generated *in situ* from 0.411 g (2 mmol) of CuBr−SMe_2 and 2.86 mL (4 mmol) of 1.4 M methyllithium in ether solution was added at −78 °C to a solution of **3a,b** (0.728 g, 2 mmol) in 10 mL of THF containing 0.835 mL (606 mg, 6 mmol) of triethylamine. After 4 h at −78 °C, the reaction solution was transferred *via* cannula to a short plug of alumina (Brockmann, Basic IV). The red filtrate was concentrated in *vacuo* to give a dark oil. Column chromatography of this oil on alumina, (Brockmann, Basic IV, 250 g), eluting with ether:hexane, 1:1, afforded 518 mg (88.7%) of adduct (Scheme 1, Nu = Me), preceded by a small amount of Fp-methyl. The product was redissolved in 10 mL of methylene chloride and cooled to −78 °C, and HBF_4−Et_2O (0.35 mL, 2.2 mmol) was added to give a light yellow precipitate of **5** (R = OCH(Me)CH_2OH, Nu = Me). After 0.5 h, ether was slowly added to precipitate additional product. Solvent was removed by cannula filtration and was replaced by methylene chloride (10 mL), followed by a solution of *p*-methoxybenzyl alcohol in methylene chloride (2.76 g, in 5 mL) at −5 °C. After stirring at 0 °C for 10 h, ether was added to precipitate the yellow gummy product **7** (784 mg, 81%). This was taken up in 10 mL of THF and cooled to −78 °C, and a solution of ethylmagnesium bromide in THF/ether (2.0 mmol) containing 0.83 mL of triethylamine was added dropwise. After stirring at −78 °C for 1 h, a solution of sodium acetate in methanol (492 mg, in 5 mL of methanol) and a solution of ceric ammonium nitrate in methanol (5.48 g, in 10 mL of methanol) were added sequentially under a CO atmosphere. A color change from orange to green was observed and the reaction was allowed to warm up slowly. Water was added to quench the reaction, and the organic layer was separated and concentrated to give a gummy residue. Exhaustive extraction of this with ether and hexane, followed by removal of solvent in

vacuo, gave 227 mg (61%) of **8** as a brown oil: ^{1}H NMR ($CDCl_3$/TMS) δ 7.25 (d, 2H, J = 8.7 Hz), 6.87 (d, 2H, J = 8.7 Hz), 4.45 (bs, 1H), 4.46 (bs, 1H), 3.79 (s, 3H), 3.66 (s, 3H), 3.58−3.72 (m, 1H), 2.66 (dq, 1H, J = 5.7, 7.1 Hz), 1.42−1.72 (m, 2H), 1.20 (d, 3H, J = 7.2 Hz), 0.93 (t, 3H, J = 7.4); ^{13}C NMR ($CDCl_3$/TMS) δ 175.6, 159.1, 130.7, 129.4, 113.7, 81.0, 71.8, 55.3, 51.6, 43.0, 24.9, 11.9, 9.8; $[\alpha]^{25}_D$ = −5.46° (0.90, $CHCl_3$).

(2*R*,3*S*)-Methyl 2-Methyl-3-hydroxypentanoate (9a). To a solution of (2*R*, 3*S*)-methyl 2-methyl-3-(*p*-methoxybenzyloxy)pentanonate (**8**) (44 mg, 0.155 mmol) in 5 mL of methylene chloride was added 39 mg (0.17 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone at room temperature. After stirring for 10 min, 2 mL of water was added and the reaction was stirred for an additional 2 h. Ether was added to extract the methylene chloride solution and the solvent was removed *in vacuo* to give 15.2 mg (70%) of product **9a**: ^{1}H NMR ($CDCl_3$/TMS) δ 3.76−3.88 (m, 1H), 3.71 (s, 3H), 2.55 (dq, 1H, J = 3.6, 7.2 Hz), 2.47 (d, 1H, J = 4.8 Hz), 1.42−1.56 (m, 2H), 1.18 (d, 3H, J = 7.2 Hz), 0.97 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 176.6, 73.2, 51.8, 43.8, 26.7, 10.5, 10.4; $[\alpha]^{25}_D$ = −2.70° (0.65, $CHCl_3$). Both the ^{1}H and ^{13}C NMR spectrum data are identical with the data reported in the literature.[11]

(2*S,3*S**,4*S**)-Methyl 2-Methyl-3-[4-(methoxylbenzyl)-oxy]-3-(2-oxocyclohexyl)propionate (*rac*-11).** Lithium cyclohexanone enolate (2.0 mmol) was prepared by slow addition of *n*-butyllithium (0.8 mL, 2.5 M in hexane, 2.0 mmol) to a solution of 1-cyclohexenyl-trimethylsilyl ether (0.340 g, 2.0 mmol) in THF. After stirring for 0.5 h the mixture was transferred to a suspension of $CuBr-SMe_2$ (0.205 g, 1.0 mmol), cooled to −78 °C. The resulting mixture was stirred for an additional 0.5 h and transferred by cannula to a suspension of *rac*-Fp-(1-[(*p*-methoxybenzyl)oxy]propene) BF_4 (**7**) (0.442 g, 1.0 mmol) in 20 mL of THF, cooled to −78 °C. After stirring for 1 h, a solution of sodium acetate in methanol (0.984 g in 10 mL) was added, followed by dropwise addition of a methanol solution of ceric ammonium nitrate (2.74 g, 5 mmol), under a CO atmosphere. The reaction was then allowed to warm up to room temperature without removing the cold bath. During this period, the color of the solution, which had turned green after one-third of the oxidizing reagent had been added, changed to brown at −50 °C. Solvent was removed in *vacuo* and the resulting gum was taken up in ether solution, which was washed with a solution of sodium bicarbonate and dried. Removal of solvent left an oil which was purified by preparative TLC (1500 μm silica plate, eluted with ether:hexane, 1:1) to give 0.152 g (46%) of *rac*-**11** as a clear oil: ^{1}H NMR ($CDCl_3$/TMS) δ 7.21 (d, 2H, J = 8.6 Hz), 6.83 (d, 2H, J = 8.6 Hz), 4.59 (d, 1H, J = 10.3 Hz), 4.38 (d, 1H, J = 10.3 Hz), 4.34 (dd, 1H, J = 3.9, 7.8 Hz), 3.77 (s, 3H), 3.69 (s, 3H), 2.63 (dq, 1H, J = 4.0, 7.1 Hz), 2.52−2.70 (m, 1H), 2.28−2.42 (m, 2H), 1.44−2.08 (m, 6H), 1.20 (d, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 211.2, 175.6, 159.1, 130.7, 129.5, 113.7, 78.0, 73.3, 55.2, 54.4, 51.7, 42.5, 40.8, 30.1, 28.0, 24.8, 10.5. Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.26; H, 7.78. Found: C, 68.36; H, 8.06.

rac-Lactone (*rac*-12). To a solution of *rac*-keto ester **11** (0.100 g, 0.3 mmol) in 5 mL of THF was added 0.33 mL of L-Selectride (1.1 mmol, 1.0 M in THF) dropwise at −78 °C. The reaction was stirred at −78 °C for 1 h, allowed to warm up to room temperature, and then quenched with aqueous sodium bicarbonate. Workup gave the crude product as a brown oil. This was purified by preparative TLC (1500 μm silica plate, ether:hexane, 3:7) to give 0.064 g (70%) of *rac*-**12** as a clear oil. A minor impurity which was separated by preparative TLC (1000 μm silica plate, acetate:hexane, 2:8) was determined not to be a diastereomer. ^{1}H NMR ($CDCl_3$/TMS) δ 7.26 (d, 2H, 8.7 Hz), 6.89 (d, 2H, J = 8.7 Hz), 4.60 (d, 1H, J = 11.1 Hz), 4.37 (d, 1H, J = 11.1 Hz), 4.26−4.42 (m, 1H), 3.81 (s, 3H), 3.46 (dd, 1H, J = 4.6, 10.3 Hz), 2.56 (dq, 1H, J = 7.02, 10.25 Hz), 2.07−2.22 (m, 1H), 1.86−1.18 (m, 8H), 1.36 (d, 3H, J = 7.02 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 174.3, 159.4, 129.8, 129.4, 113.9, 80.1, 75.2, 70.4, 55.3, 38.7, 36.7, 30.7, 24.5, 19.9, 19.1, 14.8.

(2*R*,3*S*)-Methyl 2-Methyl-3-[(4-methoxybenzyl)oxy]-5-keto-7-phenylheptanoate (16a). A solution of 2-[(trimethylsilyl)oxy]-4-phenyl-1-butene (**14a**) (484 mg, 2.2 mmol) in 20 mL of THF, prepared from benzyl acetone,[19] was cooled to 0 °C, and *n*-butyllithium (0.90 mL, 2.5 M in hexane, 2.2 mmol) was added dropwise to this solution. The solution was stirred for 30 min and then cooled to −78 °C and transferred by cannula to a slurry of $CuBr-SMe_2$ (226 mg, 1.1 mmol) in 20 mL of THF at −78 °C. This solution was kept at −78 °C for 30 min and then transferred by cannula to a slurry of **7** (446 mg, 1.0 mmol) in 20 mL of THF at −78 °C. The reaction was continued for 2 h at −78 °C and then was allowed to warmed up to room temperature. The reaction solution was passed through a short plug of alumina (Brockmann, Basic IV) to remove excess enolate. The resulting clear olive-green solution was cooled again to −78 °C and CO gas was bubbled in to saturate the solution. NaOMe (0.54 g, 10 mmol) in 10 mL of methanol was syringed in, followed by the slow addition of CAN (2.74 g, 5 mmol) in 15 mL of methanol, while the solution temperature was maintained at −60 °C. The solution turned from light-green to dark-green when one-third of the CAN solution had been added and remained that color until the solution was allowed to warm up to −30 °C, at which point it turned to clear brown. Solvent was removed *in vacuo* at this temperature, and the product was extracted with a mixture of hexane and water. Workup followed by flash chromatography of the product on silica gel (Aldrich, 60-200 mesh, eluted with ether:hexane, 1:1) gave 163 mg of **16a** (43%) containing 5−10% of **17a** and p-methoxybenzaldehyde: ^{1}H NMR ($CDCl_3$/TMS) δ 7.18−7.35 (m, 5H), 7.25 (d, 2H, J = 8.7 Hz), 6.83 (d, 2H, J = 8.7 Hz), 4.45 (bs, 1H), 4.38 (bs, 1H), 4.24 (m, 1H), 3.77 (s, 3H), 3.66 (s, 3H), 2.7−2.9 (m, 7H), 1.15 (d, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 208.0, 174.6, 159.1, 140.8, 129.4, 128.4, 128.3, 128.2, 114.2, 113.6, 76.1, 72.2, 55.12, 51.6, 45.5, 45.3, 43.0, 29.4, 12.1.

(2*R*,3*S*)-Methyl 2-Methyl-3-hydroxy-5-keto-7-phenylheptanoate (17a). Deprotection of **16a**, obtained above (163 mg, 0.43 mmol), was carried out with $DDQ/H_2O/CH_2Cl_2$ as described in detail for the preparation of **9**. The product was purified by flash column chromatography on silica gel (ether/hexane, 1:1) to afford 74 mg of **17a** (60%): ^{1}H NMR ($CDCl_3$/TMS) δ 7.15−7.35 (m, 5H), 4.25−4.35 (m, 1H), 3.69 (s, 3H), 3.28 (bs, 1H), 2.48−2.93 (m, 7H), 1.05 (d, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 209.9, 175.4, 140.6, 128.5, 128.2, 126.1, 68.1, 51.8, 46.3, 45.0, 44.1, 29.4, 12.0; $[\alpha]^{27}_D$ = −3.40° (3.20, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.18; H, 7.63. Found: C, 67.72; H, 7.69.

(2*R*,3*S*,5*S*)-Methyl 2-Methyl-3,5-dihydroxy-7-phenylheptanoate (18a). A 1 M THF solution of Et_3B (1.1 mL) was added to a mixture of THF (8 mL) and methanol (2 mL) at room temperature under argon. After stirring for 1 h, the mixture was cooled to −78 °C and **17a** (265 mg, 1.0 mmol) was added. Reaction was continued for 30 min and sodium borohydride (1.1 mmol) was then added. After 5 h, the reaction mixture was diluted with ethyl acetate (20 mL) and quenched with aqueous ammonium chloride solution, and the organic phase was separated. Methanol (5 mL) and saturated aqueous ammonium chloride solution (5 mL) were added, and the solution was stirred at room temperature overnight. Workup gave an oil, which was purified by column chromatography on silica gel. Elution with 100% ether followed by ethyl acetate gave 172 mg (65%) of **18a**. The first fraction, about 40 mg was the boron dihydroxy intermediate, which could be recycled to the desired product by stirring overnight in methanol/THF/saturated aqueous ammonium): ^{1}H NMR ($CDCl_3$/TMS) δ 7.15−7.35 (m, 5H), 4.10−4.20 (m, 1H), 3.85−3.95 (m, 1H), 3.69 (s, 3H), 3.55 (d, 1H, J = 3.4 Hz), 3.45 (d, 1H, J = 1.9 Hz), 2.6−2.85 (m, 2 H), 2.40−2.50 (m, 1H), 1.40−1.80 (m, 4H), 1.19 (d, 3H, J = 7.23 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 176.6, 142.3, 128.8, 128.7, 126.2, 73.2, 72.0, 52.3, 45.0, 39.9, 39.8, 32.0, 11.1. $[\alpha]^{27}_D$ = −3.40° (1.30, $CHCl_3$).

(2*R*,3*S*,5*S*)-3-Hydroxy-2-methyl-5-(2-phenylethyl)-5-pentanolide (20a). To a solution of **18a** (80 mg, 0.30 mmol) in 5 mL of dry benzene was added *p*-TsOH (6 mg, 0.03 mmol), and the reaction was allowed to continue at room temperature for 8 h. Solvent was removed in *vacuo* and the product was purified by flash column chromatography on silica gel (Aldrich, 60-200 mesh, ethyl acetate:hexane, 1:1 (R_f = 0.25 on TLC plate), to give 62 mg (88%) of **20a**: ^{1}H NMR ($CDCl_3$/TMS) δ

7.17−7.32 (m, 5H), 4.51−4.62 (m, 1H), 3.84−3.94 (m, 1H), 2.82−2.92 (m, 2H), 2.53−2.62 (m, 1H), 1.80−2.10 (m, 4H), 1.32 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 174.4, 140.9, 128.5, 128.4, 126.1, 74.3, 69.2, 42.8, 37.1, 36.7, 31.1, 14.1; $[\alpha]^{27}_D$ = −7.06° (1.0, $CHCl_3$). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.72; H, 7.74. Found: C, 71.77; H, 7.74.

(2*R,3*S**,5*R**)-Methyl 2-Methyl-3,5-dihydroxy-7-(2-phenylethyl)heptanoate (*rac*-19a).** To a solution of 716 mg (2.72 mmol) of tetramethylammonium triacetoxyborohydride in 1.5 mL of anhydrous acetonitrile was added 1.5 mL of anhydrous acetic acid. The solution was stirred at ambient temperature for 30 min and then cooled to −40 °C, and a solution of 90 mg (0.34 mmol) of *rac*-methyl 2-methyl-3-hydroxy-5-keto-7-phenylheptanoate (*rac*-**17a**) in 1 mL of anhydrous acetonitrile was added via cannula. The mixture was stirred at −40 °C for 18 h. The reaction was quenched with 4.0 mL of 0.5 N aqueous sodium potassium tartrate, and the mixture was allowed to warm slowly to ambient temperature and was then diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. Further workup gave 90 mg (99%) of the product diol as a colorless oil: (The NMR spectrum of this product did not show any detectable amount of the *syn* isomer.) ^{1}H NMR ($CDCl_3$/TMS) δ 7.15−7.35 (m, 5H), 4.15−4.25 (m, 1H), 3.90−4.00 (m, 1H), 3.70 (s, 3H), 3.10 (bs, 1H), 2.45 (bs, 1H), 2.5−2.85 (m, 3H), 1.40−1.90 (m, 4H), 1.21 (d, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 176.3, 141.9, 128.4, 128.4, 125.8, 68.9, 68.7, 51.8, 44.6, 39.8, 39.0, 32.0, 11.5. This compound cyclized rapidly to the lactone **21a** in the NMR tube in $CDCl_3$ solution.

(2*R,3*S**,5*R**)-3-Hydroxy-2-methyl-6-(2-phenylethyl)-5-pentanolide (*rac*-21a).** To a solution of *rac*-**19a** (80 mg, 0.30 mmol) in 5 mL of dry benzene was added *p*-TsOH (6 mg, 0.03 mmol). The reaction was continued for 8 h at room temperature. Solvent was removed in *vacuo* and the product was purified by flash column chromatography on silica gel (60−200 mesh, ethyl acetate:hexane 1:1), to give 62 mg (88%) of *rac*-**21a**: ^{1}H NMR ($CDCl_3$/TMS) δ 7.15−7.35 (m, 5H), 4.17−4.25 (m, 1H), 3.68−3.71 (m, 1H), 2.70−2.90 (m, 2H), 2.35−2.43 (m, 1H, J = 7.1, 9.9, 1.4 Hz), 2.15−2.24 (m, 1H), 1.86−2.13 (m, 2H), 1.69−1.80 (m, 1H), 1.40 (d, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 176.3, 140.7, 128.5, 128.4, 126.1, 75.5, 70.0, 45.0, 38.2, 37.5, 30.9, 13.5. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.72; H, 7.74. Found: C, 71.45; H, 7.54.

(2*R*,3*S*)-Methyl 2-Methyl-3-hydroxy-5-ketodecanoate (17b). Concurrent Carbomethoxylation−Deprotection of 15b. 2-[(Trimethylsilyl)oxy]-1-heptene was prepared according to House's procedure and purified by distillation (bp 40 °C/0.2 mm). A solution of the silyl ether (1.025 g, 5.5 mmol) in 30 mL of THF was cooled to 0 °C, and *n*-butyllithium (2.25 mL, 2.5 M in hexane, 5.5 mmol) was added dropwise to this solution. The solution was stirred for 30 min and then cooled to −78 °C and transferred by cannula to a slurry of CuBr−SMe_2 (0.56 g, 2.75 mmol) in 30 mL of THF at −78 °C. This solution was kept at −78 °C for 30 min and then transferred by cannula to a slurry of **7** (1.12 g, 2.50 mmol) in 30 mL of THF at −78 °C. The reaction was continued for 2 h at −78 °C and then was allowed to warm up to room temperature. The reaction solution was passed through a short plug of alumina (Brockmann, Basic IV) to remove excess of enolate. An NMR spectrum of an aliquot of the addition product **15b** showed it to be 85−90% pure (80−85% yield): ^{1}H NMR (acetone-d_6/TMS) δ 7.30 (d, 2H, J = 8.8 Hz), 6.87 (d, 2H, J = 8.8 Hz), 4.93 (s, 5H), 4.40 (bs, 1H), 4.41 (bs, 1H), 3.90−4.05 (m, 1H), 3.77 (s, 3H), 2.40−2.85 (m, 4H), 1.15−1.60 (m, 4H), 1.26 (d, 3H, J = 7.2 Hz), 0.87 (t, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 206.0, 160.1, 132.0, 130.2, 114.2, 86.9, 85.9, 71.4, 55.4, 47.5, 44.5, 32.1, 24.3, 24.0, 22.5, 14.2, 14.2. The clear olive-green solution of the adduct **15b** was cooled again to −78 °C and CO gas was bubbled in to saturate the solution. $NaOCH_3$ (0.540 g, 10 mmol) in 30 mL of methanol was added by syringe, followed by the slow addition of CAN (8.16 g, 15 mmol) in 40 mL of methanol, while the solution was kept at −60 °C. The solution color turned from light-green to dark-green when one-third of the CAN solution had been added and remained that color until the solution was allowed to warm up to room temperature, at which point it turned to clear brown. Solvent was removed *in vacuo* and the product was extracted with hexane and water. Workup followed by flash column chromatography of the crude product on silica gel (Aldrich, 60−200 mesh, eluted with ether:hexane, 1:1) afforded 161 mg of **17b** (35% based on **7**) and 25 mg of **16b**. **17b**: ^{1}H NMR ($CDCl_3$/TMS) δ 4.30 (m, 1H), 3.71 (s, 3H), 2.40−2,70 (m, 5H), 1.22−1.65 (m, 6H), 1.21 (d, 3H, J = 7.2 Hz), 0.89 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 211.4, 175.4, 68.38, 51.82, 45.9, 44.2, 43.6, 31.3, 23.2, 22.4, 13.8, 12.2.

(2*R,3*S**,5*R**)-3-Hydroxy-2-methyl-5-pentyl-5-pentanolide (*rac*-21b).** To a solution of 716 mg (2.72 mmol) of tetramethylammonium triacetoxyborohydride in 1.5 mL of anhydrous acetonitrile was added 1.5 mL of anhydrous acetic acid. The solution was stirred at ambient temperature for 30 min and then cooled to −40 °C, and a solution of 78.2 mg (0.34 mmol) of (2*R**,3*S**)-methyl 2-methyl-3-hydroxy-5-keto decanonate (*rac*-**17b**) in 1 mL of anhydrous acetonitrile was added *via* cannula. The mixture was stirred at −40 °C for 18 h. The reaction was quenched with 4.0 mL of 0.5 N aqueous sodium potassium tatrate, and the mixture was allowed to warm slowly to ambient temperature. The mixture was then diluted with dichloromethane and the organic solution was washed with aqueous saturated sodium bicarbonate. Workup gave 78 mg (99%) of the diol *rac*-**19b** as a colorless oil. The NMR spectrum of this product did not show any detectable amount of the syn isomers. To a solution of *rac*-**19b** (70 mg, 0.30 mmol) in 5 mL dry benzene was added *p*-TsOH (6 mg, 0.03 mmol). The reaction was continued for 8 h at room temperature. Solvent was removed *in vacuo* and the product was purified by flash column chromatography on silica gel (60−200 mesh, ethyl acetate:hexane, 1:1), to give 54 mg (90%) of *rac*-**21b**: ^{1}H NMR ($CDCl_3$/TMS) δ 4.17−4.29 (m, 1H), 3.70−3.81 (m, 1H), 2.35 (dq, 1H, J = 7.1, 9.7 Hz), 2.16−2.24 (m, 1H, J_{gem} = 13.3, 3.8, 3.2 Hz), 1.95 (d, 1H, J = 4.9 Hz), 1.27−1.75 (m, 9H), 1.41 (d, 3H, J = 7.1 Hz), 0.89 (t, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 173.3, 76.6, 70.3, 45.1, 38.2, 35.8, 22.5, 24.4, 31.5, 13.5, 13.9. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.96; H, 10.06. Found: C, 65.62; H, 9.85.

(2*R*,3*S*)-Methyl 2-Methyl-3-hydroxy-5-ketodecanoate (17b). Stepwise Oxidation of 15b. The condensation of copper enolate **14b** with 112 g (2.50 mmol) of **7** was carried as described earlier for the preparation of **17b**. After passing the solution of the crude product through a short plug of alumina (Brockmann, Basic IV) to remove excess enolate, the clear olive-green solution was cooled to −78 °C and CO gas was bubbled in to saturate the solution. $NaOCH_3$ (0.675 g, 12.5 mmol) in 30 mL of methanol was syringed in, followed by the slow addition of CAN (6.8 g, 12.5 mmol) in 40 mL of methanol, while the solution was kept at −60 °C. The solution was allowed to warm slowly to −30 °C. Solvent was removed *in vacuo* at this temperature, and the product was taken up in a mixture of 50 mL of hexane and 20 mL of water. Further workup, followed by flash column chromatography of the crude product on silica gel (Aldrich, 60−200 mesh, eluted with 1:1 ether:hexane) afforded 350 mg of **16b** (39% yield). Deprotection of **16b** was carried out with DDQ/H_2O/CH_2Cl_2 as described in detail for the preparation of **9a**. The product was purified by flash column chromatography on silica gel (Aldrich, 60−200 mesh, ether:hexane, 1:1) to afford 161 mg of **17b** (70%).

(2*R*,3*S*,5*S*)-3-Hydroxy-2-methyl-5-pentyl-5-pentanolide (20b). A 1.0 M THF solution of Et_3B (0.55 mL) was added to a mixture of dry THF (4 mL) and methanol (1 mL) at room temperature under argon. After stirring for 1 h, the mixture was cooled to −78 °C and **17b** (115 mg, 0.50 mmol) in 1 mL THF was added. Reaction was continued for 30 min and sodium borohydride (0.55 mmol) was then added. After 5 h, the reaction mixture was diluted with ethyl acetate (10 mL and quenched with aqueous ammonium chloride solution, and the organic phase was separated. Methanol (3 mL) and saturated aqueous ammonium chloride solution (3 mL) were added, and the solution was stirred at room temperature overnight. Workup gave an oil, which was purified by column chromatography on silica gel, first eluted with 100% ether and followed by ethyl acetate to give 75 mg of **18b** (65%). To a solution of **18b** (69 mg, 0.30 mmol) in 5 mL of dry benzene was added *p*-TsOH (6 mg, 0.03 mmol) and the reaction was

allowed to continue at room temperature for 8 h. Solvent was removed *in vacuo* and the product was purified by flash column chromatography on silica gel to give 53 mg (88%) of **20b**: ^{1}H NMR ($CDCl_3$/TMS) δ 4.48−4.62 (m, 1H), 3.82−3.94 (m, 1H), 2.58−2.68 (m, 1H), 1.84−2.04 (m, 2H), 1.40−1.75 (m, 8H), 1.32 (d, 3H, J = 6.9 Hz), 0.89 (t, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 174.2, 75.3, 69.5, 42.9, 37.2, 31.5, 26.6, 22.5, 14.1, 14.00; $[\alpha]^{27}_D$ = −2.0° (0.42, $CHCl_3$). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.96; H, 10.06. Found: 65.62; H,10.18.

(2*R,3*S**,4*S**,5*S**)-4-Benzyl-3-hydroxy-2,5-dimethyl-5-pentanolide (32b).** 3-[(Trimethylsilyl)oxy]-1-phenyl-2-butene was prepared by refluxing benzylacetone, triethylamine, trimethylsilyl chloride in DMF for 48 h.[19] This afforded a product with *Z*:*E*:T(terminal) isomers in a ratio of 5:3:4. The *Z*-isomer was further separated and concentrated by spinning band distillation *in vacuo* to give a product with *Z*:*E*:T = 10:1:0.4. This silyl enol ether (484 mg, 2.2 mmol) was converted to the lithium enolate with *n*-butyllithium and then to the cuprous enolate by treatment with CuBr−SMe_2 as described earlier in the preparation of **11**. Addition to *rac*-**7**, followed by redox-promoted carboxymethylation and deprotection of the p-methoxybenzyloxy function, afforded a mixture of diastereomeric ester products **25b** and **26b** in a ratio of 2.5:1, respectively. These could be distinguished by a pair of doublets at δ 1.83 and 1.93. The diastereomers could not be separated, but *cis* reduction of this mixture as for **17a** with Et_3B, MeOH, $NaBH_4$ resulted in the reduction of the major isomer (δ 1.83) alone. Cyclization of the mixture, and purification by flash chromatography afforded the titled compound **32b** (50 mg, 21%) and **26b**. ^{1}H NMR **32b**: ($CDCl_3$/TMS) δ 7.15−7.35 (m, 5H), 4.77 (dq, 1H, J = 6.6, 3.2 Hz), 3.45−3.55 (m, 1H, J = 3.4, 8.1 Hz, (coupling constants derived from spectra taken in D_2O)), 2.92 (dd, 1H, J = 14.0, 5.4 Hz), 2,52−2.62 (m, 1H, J = 6.7, 3.4 Hz, (coupling constants derived from spectra taken in D_2O)), 2.42 (dd, 1H, J = 14.0, 11.2 Hz), 2.16−2.28 (m, 1H), 1.79 (d, 1H, J = 4.2 Hz), 1.45 (d, 3H, J = 6.6 Hz), 1.33 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 174.0, 138.4, 129.0, 128.9, 126.7, 73.4, 73.6, 48.7, 42.2, 32.1, 17.2, 13.8. **26b**: ^{1}H NMR ($CDCl_3$/TMS) δ 7.14−7.35 (m, 5H), 3.82−3.94 (m, 1H), 3.69 (s, 3H), 3.38 (d, 1H, J = 7.5 Hz), 2.75−2.95 (m, 3H), 2.52−2.68 (m, 1H), 1.94 (s, 3H), 1.26 (d, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 207.0, 175.7, 138.1, 128.9, 128.4, 126.7, 73.6, 55.2, 51.9, 45.5, 42.2, 35.8, 12.3.

(2*R,3*S**,4*R**(*S**),5*R**)-4-Benzyl-3-hydroxy-2,5-dimethyl-5-pentanolide (30b and 31b).** The mixture of 120 mg of diastereomeric hydroxy keto esters **25b** and **26b**, prepared as described above in the preparation of **32**, from 484 mg (2.2 mmol) of silyl enol ether **22b**, was reduced to give a mixture of *trans*-1,3-diols **27b** and **28b**, following the procedure of Evans, employed in the preparation of **19a**. Purification and cyclization of these esters, as for **19a**, gave a mixture of lactones in a ratio of 2.5:1. These were purified and separated from other impurities by flash column chromatography and cyclized in dry benzene with a trace amount of *p*-TsOH to afford 90 mg (77%, two steps) of **30b** and **31b**. These products were assigned the relative configurations on the basis of their PMR. The major isomer is assigned as **(2*R**,3*S**,4*R**,5*R**)-4-benzyl-3-hydroxy-2,5-dimethyl-5-pentanolide (30b)**: ^{1}H NMR ($CDCl_3$/TMS) δ 7.15−7.35 (m, 5H), 4.15 (dq, 1H, J = 6.4, 9.8 Hz), 3.42−3.54 (m, 1H, J = 10.1, 9.7 Hz, (coupling constants derived from spectra taken in D_2O)), 2.86−3.04 (m, 2H), 2,38−2.50 (m, 1H, J = 7.1, 9.7 Hz, (coupling constants derived from spectra taken in D_2O)), 1.92−2.04 (m, 1H), 1.44 (d, 3H, J = 6.4 Hz), 1.36 (d, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 172.8, 137.8, 129.4, 128.9, 126.8, 76.8, 72.6, 48.7, 44.2, 34.5, 20.9, 13.5. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.72; H, 7.74. Found: C, 72.02; H, 7.79. The minor isomer was not isolated in pure form, and its structure as (**2*R**,3*S**,4*S**,5*R**)-4-benzyl-3-hydroxy-2,5-dimethyl-5-pentanolide (31b)** was assigned from its NMR spectrum, obtained by subtraction of the spectrum of purified **30b** from that of the mixture of the two isomers: ^{1}H NMR ($CDCl_3$/TMS) δ 7.15−7.35 (m, 5H), 4.51 (dq, 1H, J = 7.0, 3.1 Hz), 3.78−3.86 (m, 1H, J = 4.2, 8.3 Hz (coupling constants derived from spectrum taken in D_2O)), 2.86−3.04 (m, 1H), 2.74 (dd, 1H, J = 14.3, 7.0 Hz, (coupling constants derived from spectrum taken in D_2O)), 2.62 (dd, 1H J = 6.5, 8.3 Hz), 1.85−1.96 (m, 1H), 1.36 (d, 3H, J = 7.0 Hz), 1.30 (d, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 173.5, 140.1, 129.3, 128.7, 126.4, 76.9, 73.7, 48.7, 44.4, 41.4, 18.4, 14.9.

(2*R,3*S**,4*R**,5*S**)-3-*n*-Butyl-3-hydroxy-2,5-dimethyl-5-pentanolide (32a).** (*Z*)-[(Trimethylsilyl)oxy]-2-heptene was prepared from 2-heptanone (5 mL, 35.2 mmol) by treatment with ethyl (trimethylsilyl)acetate (1.1 equiv 7.2 mL, 39 mmol) in the presence of a catalytic amount of tetra-*n*-butylammonium fluoride (1.06 mmol).[18] The product was further purified by spinning band distillation to give a product with 98% purity. This (2.2 mmol) was converted to the copper enolate as described earlier and added to 1.0 mmol of *rac*-**51**. A PMR spectrum of this adduct showed two singlet resonances at δ 2.19 and 2.22, assigned to the acetyl function of **23a** and **24a**, respectively, formed in a ratio of 3.5:1. This mixture of adducts was converted to a mixture of diastereomeric esters **25a** and **26a**, (115 mg, 50%) through redox-promoted migratory insertion and deprotection. Some of the major isomer **25a** was isolated and purified by flash column chromatography on silica gel from the diastereomeric mixture: ^{1}H NMR ($CDCl_3$/TMS) δ 4.05−415 (m, 1H), 3.71 (s, 3H), 2.98 (d, 1H, J = 3.2 Hz), 2.5−2.7 (m, 2H), 2.19 (s, 3H), 1.20−1.80 (m, 6H), 1.23 (d, 3H, J = 7.2 Hz), 0.89 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 215.0, 176.2, 71.1, 55.0, 51.9, 42.3, 30.5, 29.6, 27.2, 22.9, 13.8, 11.80. *cis*-Reduction of the mixture of **25a** and **26a**[14] and then lactonization, following the procedure given earlier for the preparation of **20** and **21**, gave 42 mg (51%) of **32a** and 20 mg of unchanged **26a**. The lactone **32a**: ^{1}H NMR ($CDCl_3$/TMS) δ 4.74 (dq, 1H, J = 3.2, J = 7.0 Hz), 3.48−3.56 (m, 1H, J = 4.1, 7.9 Hz), 2.49−2.61 (m, 1H), 1.90 (d, 1H, J = 4.1 Hz),1.70−1.80 (m, 1H), 1.2−1.5 (m, 6H), 1.33−1.37 (t, J = 6.4 Hz, 6H), 0.91 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 174, 74.8, 73.9, 47.0, 42.8, 29.2, 25.7, 22.8, 17.1, 13.9 (2). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.96; H, 10.06. Found: C, 65.92; H, 9.91. The hydroxy ketone **26a, (2*R**,3*S**,4*R**)-methyl 2-methyl-3-hydroxy-4-*n*-butyl-5-ketohexanaote**: ^{1}H NMR ($CDCl_3$/TMS) δ 3.91−4.03 (m, 1H), 3.71 (s, 3H), 3.22 (d, 1H, J = 6.81 Hz), 2.54−2.67 (m, 2H), 2.22 (s, 3H), 1.25−1.60 (m, 6H), 1.24 (d, 3H, J = 7.1 Hz), 0.894 (t, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 214.2, 176.0, 73.1, 53.6, 51.9, 42.9, 31.5, 29.3, 28.8, 22.7, 13.8, 11.7.

(2*R,3*S**,4*S**(*R**),5*R**)-*n*-Butyl-3-hydroxy-2,5-dimethyl-5-pentanolide (30a and 31a).** The mixture of 115 mg of adducts **25a** and **26a**, prepared as described above, was reduced to a mixture of 110 mg (95%) of *trans*-1,3-diols **27a** and **28a** by the method of Evans. Lactonization of these diols with benzenesulfonic acid in benzene gave 99 mg (85%) of **30a** and **31a**. Separation of these two lactones was achieved by flash column chromatography on silica gel. These products were assigned the (2*R**,3*S**,4*S**(*R**),5*R**) configuration from their PMR spectrum. **(2*R**,3*S**,4*S**,5*R**)-*n*-Butyl-3-hydroxy-2,5-dimethyl-5-pentanolide (31a)**: ^{1}H NMR ($CDCl_3$/TMS) δ 4.48 (dq, 1H, J = 3.0, 6.7 Hz), 3.84 (q, 1H, J = 4.2, 8.6 Hz), 2.52 (q, 1H, J = 7.1 Hz, 8.6 Hz), 1.86−1.94 (m, 1H), 1.80 (d, 1H, J = 4.14 Hz), 1.2−1.5 (m, 6H), 1.41 (d, 3H, J = 6.7), 1.39 (d,3H, J = 7.1 Hz), 0.92 (t, 3H, J = 6.8 Hz); ^{13}NMR ($CDCl_3$/TMS) δ 173.6, 76.9, 74.1, 43.1, 40.9, 32.1, 23.0, 22.2, 18.3, 14.8, 13.9. **(2*R**,3*S**,4*R**,5*R**)-*n*-Butyl-3-hydroxy-2,5-dimethyl-5-pentanolide (30a)**: ^{1}H NMR ($CDCl_3$/TMS) δ 4.20 (dq, 1H, J = 6.4, 7.7 Hz), 3.46−3.58 (m, 1H, J = 9.6, 9.8 Hz), 2.38−2.48 (m, 1H, J = 6.9, 9.8 Hz), 1.85 (d, 1H, J = 4.1 Hz), 1.50−1.68 (m, 1H), 1.42 (d, 3H, J = 6.4 Hz), 1.40 (d, 3H, J = 6.9 Hz), 1.2−1.5 (m, 6H), 0.91 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$/TMS) δ 173.1, 76.9, 73.0, 47.3, 44.7, 27.6, 27.4, 25.7, 23.2, 20.3,-13.9, 13.7.

(2*R,3*S**,4*R**,5*S**)-5-Ethyl-3-hydroxy-2,4-dimethyl-5-pentanolide (38) and (2*R**,3*S**,4*S**,5*S**)-5-Ethyl-3-hydroxy-2,4-dimethyl-5-pentanolide (39).** *n*-Butyllithium (0.90 mL, 2.5 M in hexane, 2.2 mmol) was added dropwise to (*Z*)-3-[(trimethylsilyl)oxy]-2-pentene[18] (347.9 mg, 2.2 mmol) in 20 mL of THF, cooled to 0 °C. The solution was stirred for 30 min, cooled to −78 °C, and then transferred by cannula to a slurry of CuBr−SMe_2 (226 mg, 1.1 mmol) in 20 mL of THF cooled to −78 °C. This solution was kept at −78 °C for 30 min and then transferred by cannula to a slurry of *rac*-**7** (446 mg, 1.0 mmol) in 20 mL of THF at −78 °C. After 30 min, an

aliquot of the reaction mixture was taken for ^{1}H NMR analysis. The presence of two isomers (**34**) is evidenced by two pairs of singlets, one at δ 4.95 and 4.90, assigned to Cp ring protons, and another at δ 3.72 and 3.75, assigned to the *p*-methoxyphenyl protons. Both pairs show a relative intensity of 1.5:1.0. After an additional 2 h at −78 °C, the solution was allowed to come to room temperature and was passed through a short plug of alumina (Brockmann, Basic IV), to remove excess enolate. The resulting clear olive-green solution was cooled again to −78 °C and CO was bubbled in until the solution was saturated. Sodium methoxide (270 mg, 5 mmol) in 10 mL of methanol was added by syringe, followed by the slow addition of CAN (3.28 g, 6 mmol) in 15 mL of methanol, keeping the solution temperature at −60 °C. During this period, the solution turned from light green to dark-green when one-half of the CAN solution had been added and remained that color until the solution was allowed to warm up to −30 °C, at which point it turned to a clear brown color. Solvent was removed *in vacuo* and the product was extracted with hexane and water. Workup and removal of solvent left a residue, which after flash chromatography on silica gel (Aldrich, 60−200 mesh, eluted with ether:hexane, 1:1), gave 130 mg of hydroxy keto esters **35** (40% yield). This was reduced to the mixture of *cis*-1,3 diols[14] and then cyclized (*p*-TsOH, benzene) to give the titled compounds in 50% yield. These two stereoisomeric lactones (**38** and **39**) could not be separated. ^{1}H NMR ($CDCl_3$/TMS) δ 4.38−4.46 and 4.28−4.36 (m, 1H), 3.72−3.78 and 3.38−3.46 (m, 1H), 2.66−2.74 and 2.52−2.60 (m, 1H), 1.6−2.4 (m, 3H), 1.35 (pseudo triplet, 3H), 0.90−1.15 (m, 6H); ^{13}C NMR δ 174.3, 174.4, 81.1, 79.3, 73.4, 73.4, 42.3, 42.3, 40.7, 34.3, 25.7, 24.5, 15.8, 15.7, 14.2, 13.9, 12.7, 12.5, 12.0, 10.2, 8.7. Anal. Calcd for $C_9H_{16}O_3$: C, 62.91; H, 9.30. Found: C, 63.30; H, 9.27.

(2*R,3*S**,4*S**(*R**),5*R**)-5-Ethyl-3-hydroxy-2,4-dimethyl-5-pentanolide (36 and 37).** The mixture of hydroxy keto esters (76.4 mg, 0.40 mmol) **35**, prepared as above, was reduced to the corresponding *trans*-1,3-diols[16] following the procedure given for the preparation of **19a**. This was then cyclized (*p*-TsOH, benzene) to give the titled products in 85% yield. These two stereoisomers are very difficult to separate and NMR analysis was carried out on the mixture: ^{1}H NMR ($CDCl_3$/TMS) δ 4.10−418 and 3.88−3.94 (m, 1H), 3.76−3.84 and 3.32−3.38 (m, 1H), 2.36−2.50 (m, 2H), 1.6−2.2 (m, 3H), 1.41 (d, 3H, J = 7.1 Hz), 1.41 (d, 3H, J = 7.1 Hz), 0.9−1.12 (m, 6H); ^{13}C NMR δ 173.6, 173.3, 82.8, 81.8, 75.3, 73.9, 44.5, 39.9, 39.8, 36.7, 25.7, 25.2, 14.3, 14.1, 13.8, 13.1, 9.9, 8.5.

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Supporting Information Available: ^{1}H NMR spectra of compounds **8**, **11**, **16a**, **18a**, **18b**, **25a**, **26a**, **26b**, **30a**, **31a**, **32b**, **36**, and **37** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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