3-Methyl-γ-butyrolactones as Templates for the Synthesis of Polypropionates: The Basic Strategy[1]

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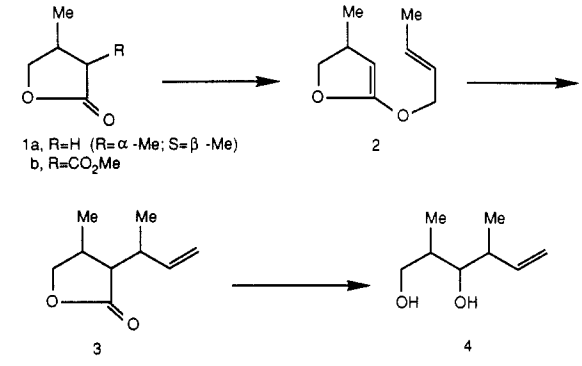
Abstract: The basic principles of the 3-methyl-γ-butyrolactone strategy for the synthesis of polypropionate starter units of high enantiomeric purity are discussed. Either enantiomer of lactones **16**, **26**, and **28** is available. The extrusion of the carbonyl carbon of these lactones and its replacement with a hydroxyl group with retention of stereochemistry is achieved with a Criegee rearrangement. For further chain extension, a palladium(0)-mediated alkylation is required. The amount of racemization during the alkylation is determined.

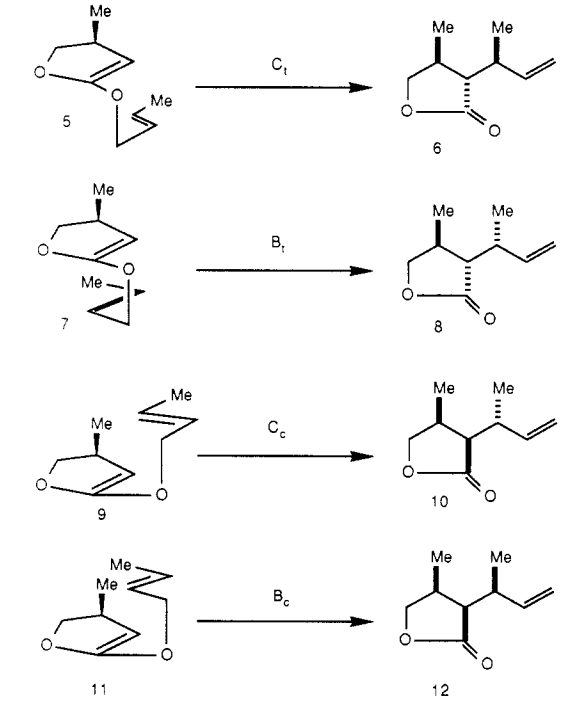
Natural products formally derived from the condensation of propionic acid units are ubiquitous. They are recognized by the alternation of methyl groups and oxygen functionality (alcohol, ketone, or carboxyl) along a carbon chain. The synthesis of stereochemically diverse polypropionates[2] has provided a rewarding challenge to the imagination and skill of synthetic organic chemists; the achievements in this area have been outstanding.[3] Of the generalized strategies for the synthesis of polypropionates, the aldol approach, as principally established by Heathcock,[4] Evans,[5] and Masamune;[6] Kishi's[7] use of allylic epoxy alcohols and their opening with cuprates; Danishefsky's[8] hetero Diels–Alder methodology; and the tested utility of carbohydrates[9] as a "chiral pool" have all met with marked success.

Several years ago, we initiated a program directed toward the stereocontrolled synthesis of polypropionates with the expectation that these substances could be prepared in a highly stereoselective fashion in high enantiomeric purity.[10] The prevailing concept was that 3-methyl-γ-butyrolactone **1a** could serve as a template for the iterative generation of propionate units by utilization of the Claisen rearrangement as illustrated in Scheme I.[11] The

Scheme I



Scheme II



success of the scheme would require a thorough understanding of the stereochemistry of the rearrangement (**2** → **3**), the realization of a formal Baeyer–Villiger oxidation of γ-butyrolactones (**3** → **4**), and the selective functionalization of either end of the growing chain to produce a new iterated butyrolactone.

Ketene–acetal **2**, which bears a single stereogenic center that renders the faces of the olefins uniquely diastereotopic, can produce four possible stereoisomers upon Claisen rearrangement. Conformations **5**, **7**, **9**, and **11** of Scheme II (transition states implied) illustrate the four possible permutations of olefin facial interaction, while structures **6**, **8**, **10**, and **12** represent their respective ste-

(1) Taken in part from the Ph.D. Theses of R.T.W. (Yale, 1986) and A.K. (Yale, 1987).

(2) Strictly speaking, these substances should be termed "oligopropionates", as they contain only several propionate residues; however, the alliterative "polypropionates" is in common usage among synthetic organic chemists.

(3) For a recent review, see: Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569.

(4) (a) Heathcock, C. H.; Young, S. D.; Hagan, J. P.; Pilli, R.; Badertscher, U. *J. Org. Chem.* **1985**, *50*, 2095. (b) Heathcock, C. H.; Pirrung, M. C.; Young, S. D.; Hagan, J. P.; Jarvi, E. T.; Badertscher, U. *J. Am. Chem. Soc.* **1984**, *106*, 8161.

(5) (a) Evans, D. A.; Polniaszek; R. P. *Tetrahedron Lett.* **1986**, *27*, 5683. (b) Evans, D. A.; Dow, R. L. *Tetrahedron Lett.* **1985**, *26*, 1007. (c) Evans, D. A.; Bender, S. L. *Tetrahedron Lett.* **1985**, *26*, 799. See earlier references cited herein.

(6) (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (b) Masamune, S. *Heterocycles* **1984**, *21*, 107. (c) Masamune, S.; Imperiali, B.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5528.

(7) (a) Kishi, Y. *Pure Appl. Chem.* **1981**, *53*, 1163. (b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (c) Lewis, M. D.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2343.

(8) (a) Danishefsky, S.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *99*, 15. (b) Danishefsky, S.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082. (c) Danishefsky, S.; Selnick, H. G.; DeNinno, M. P.; Zelle, R. E. *Ibid.* **1987**, *109*, 1572. (d) Danishefsky, S.; Myles, D.; Harvey, D. *Ibid.* **1987**, *109*, 862. (e) Danishefsky, S.; Harvey, D. *Ibid.* **1985**, *107*, 6647. (f) Danishefsky, S.; Barbachyn, M. *Ibid.* **1985**, *107*, 7761. See earlier references cited therein.

(9) (a) Hanessian, S. *Total Synthesis of Natural Products: The "Chiron" Approach*; Pergamon: Oxford, 1983. (b) Toshima, K.; Tatsuta, K.; Kinoshita, M. *Tetrahedron Lett.* **1986**, *27*, 4741. (c) Fraser-Reid, B. *Acc. Chem. Res.* **1985**, *18*, 347. (d) Hanessian, S.; Pougny, J.-R.; Boessenkool, I. K. *Tetrahedron* **1984**, *40*, 1289. (e) Oikawa, Y.; Nishi, T.; Itaya, H.; Yonemitsu, O. *Tetrahedron Lett.* **1983**, *24*, 1987. (f) Ireland, R. E.; Daub, J. P.; Mandel, G. S.; Mandel, N. S. *J. Org. Chem.* **1983**, *48*, 1312. (g) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1983**, *48*, 1303.

(10) Ziegler, F. E.; Thottathil, J. K. *Tetrahedron Lett.* **1982**, *23*, 3531.

(11) (a) Hanessian, S.; Murray, P. J.; Sahoo, S. P. *Tetrahedron Lett.* **1985**, *26*, 5623, 5627, 5631. (b) Stork, G.; Rychnovsky, S. D. *Pure Appl. Chem.* **1986**, *58*, 767. (c) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1564, 1565.

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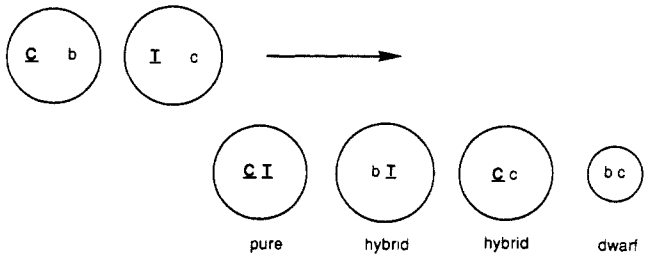
Scheme III

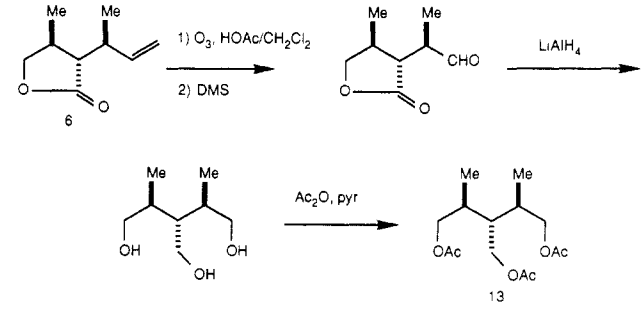


reoisomers.[12] Two pairs of descriptors define the stereochemical course of the rearrangement. The rearrangement can proceed through a chairlike (C) (**5** and **9**) or boatlike (B) (**7** and **11**) transition state. In each of these pairs, carbon–carbon bond formation can occur either trans (t) (**5** and **7**) or cis (c) (**9** and **11**) to the ring methyl group. Thus, the descriptors are defined as C_t, B_t, C_c, and B_c. A careful reading of Scheme II reveals that the chair–boat option within the trans and cis pairs controls the facial selectivity of the chain olefin and thereby the relative stereochemistry of the methyl groups in the products. In a similar fashion, the trans–cis option dictates the facial selectivity of the ring olefin and is translated into the stereochemistry of the substituents on the lactone ring (i.e., trans- or cis-substituted lactones). As the Claisen rearrangement of ketene–acetals is irreversible, the issue of the relative rates of rearrangement of the four transition state conformers of ketene–acetal **2** is significant in the synthetic sense, as the relative rates will control the product distribution. In general, the Claisen rearrangement of "simple" allyl vinyl ethers prefers the chairlike over the boatlike transition state.[13] Likewise, bond formation trans to the methyl group would be expected to be preferrable to cis addition. Accordingly, the C_t transition state can be considered the lowest, the B_t and C_c intermediate, and the B_c highest in energy. Alternatively viewed in a genetic sense, chairlike ("C" in Scheme III) is dominant over boatlike, and trans ("T" in Scheme III) is dominant over cis.[14]

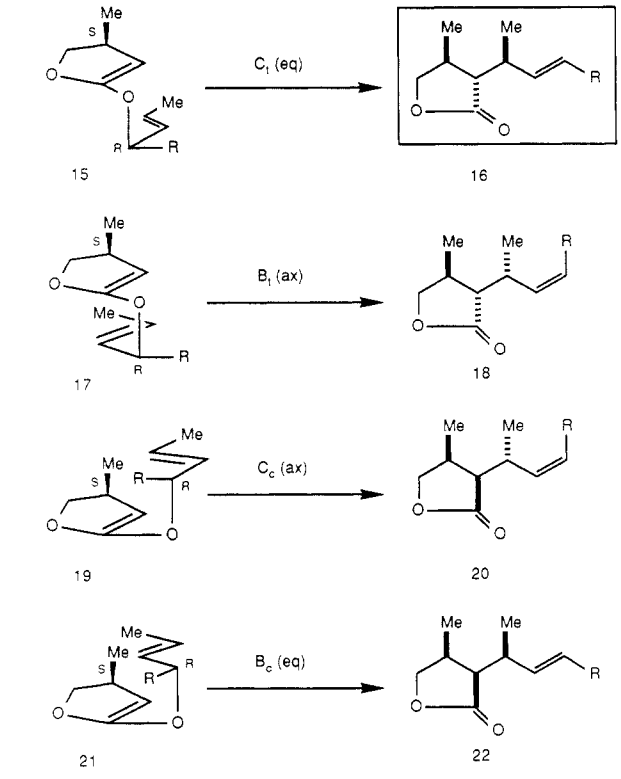
To test this argument, racemic 3-methyl-γ-butyrolactone was converted ($Et_3O^+BF_4^{\bullet-}$, EtONa/EtOH) into its ortholactone as described by Lythgoe.[15] Claisen rearrangement of the ortholactone with (*E*)-2-buten-1-ol in refluxing toluene containing propionic acid as a catalyst gave a mixture (capillary GC) of three stereoisomers: **6** (C_t, 74%), **8** (B_t, 14%), and **10** (C_c, 12%). The B_c isomer **12** was not detected. Two experiments defined the stereochemistry of the isomers. When compound **10**, which could be separated from the other two by flash chromatography, was subjected to equilibration with *t*-BuOK/*t*-BuOH at room temperature, a 98:2 mixture of **8**/**10**, respectively, was obtained, indicating that a cis stereoisomer had been epimerized to its more stable trans isomer. Secondly, an enriched sample of **6** was separated from **8** by preparative gas chromatography and subjected to the operations of Scheme IV. The ^{13}C NMR spectrum of triacetate **13** revealed nine signals, indicating a structure having a plane of symmetry. Only the triacetates derived from the C_t isomer **6** and the B_c isomer **12**, which are related by epimerization, are capable of meeting this requirement. Since the major component (**6**) of the mixture did not undergo epimerization, it must have been the C_t isomer. When the mixture of three isomers was exposed to epimerization conditions, an inseparable 2:1 mixture of **6** and **8** was formed. Clearly, this approach was an unworkable solution to the problem at hand.

To make the rearrangement more stereoselective, a new control element was introduced to restrain the chair–boat interconversion. The process required (*S*)-3-methyl-γ-butyrolactone and its *R* enantiomer, both readily available from commercial methyl (*R*)-3-hydroxy-2-methylpropionate and its *S* enantiomer, respectively.[16,17] In addition, both enantiomers of a secondary *E* allylic alcohol were required; the kinetic solution procedure of Sharpless[18] readily afforded alcohols **14a,b** and their enantiomers, *ent*-**14a,b**.

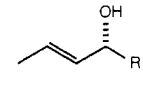
Scheme IV



Scheme V



Whereas the stereochemical analysis of Scheme II employing an achiral alcohol is tenable for both racemic and enantiomerically pure 3-methyl-γ-butyrolactone, the utilization of both a lactone and alcohol bearing stereogenic centers requires the use of the enantiomeric forms of both reactants. In Scheme V, which is identical with Scheme II except that the "R" substituent is now an *n*-butyl (from alcohol **14a**) or an isopropyl group (from alcohol **14b**) rather than hydrogen, the Claisen rearrangement of (*S*)-3-methyl-γ-butyrolactone with either *R* alcohol **14** is considered.



14a, R = n-Bu
b, R = i-Pr

(12) The stereochemistry of the carbonyl carbon–carbon bond is drawn to correspond to the eventual hydroxyl stereochemistry.

(13) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. See also ref 17, 19, 21 and 22.

(14) A similar experiment employing δ-valerolactone and (*E*)-3-penten-2-ol gave an 88:12 mixture of rearrangement products with the chair-derived product predominating.[15]

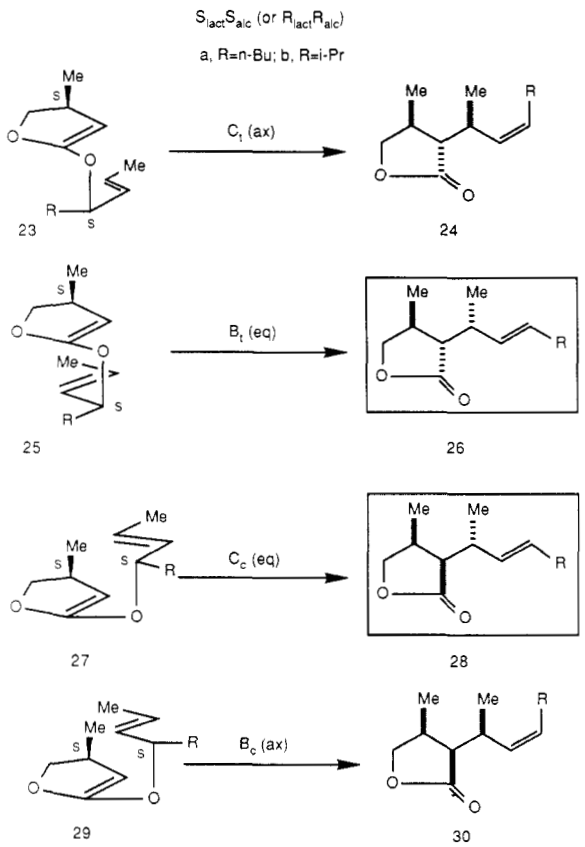
(15) Chapleo, C. B.; Hallett, P.; Lythgoe, B.; Waterhouse, I.; Wright, P. W. *J. Chem. Soc., Perkin Trans. I* **1977**, 1211.

(16) Mori, K. *Tetrahedron* **1983**, *39*, 3107.

(17) For a related study of Claisen rearrangements where both reacting partners bear stereogenic centers, see: Cave, P. J.; Lythgoe, B.; Metcalfe, D. A.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. I* **1977**, 1218.

(18) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

Scheme VI



The analysis is also valid for the isoenergetic enantiomer of $S_{lact}R_{alc}$, $R_{lact}S_{alc}$.

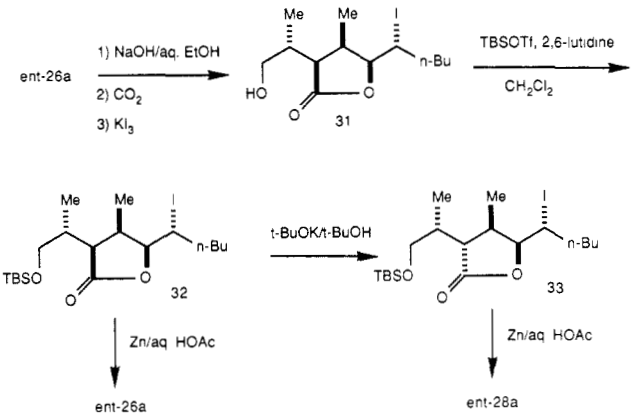
Consider the rearrangement of C_t conformation **15**. This transition state will provide an *E* olefin in **16**. However, if the chain of **15** is allowed to undergo conformational inversion to a boat, the alkyl substituent that was equatorial in **15** will now be axial in **17**, thereby providing B_t isomer **18** containing a *Z* olefin. However, the B_t transition state is forbidden as the Claisen rearrangement of secondary *E* allylic alcohol derived ketene–acetals has been demonstrated to afford *E* 1,2-disubstituted olefins[15,17,19] with transfer of stereogenicity.[20] The B_t isomer will not be formed. The C_c conformation **19** also suffers from an axial substituent in its transition state; *Z* olefin **20** will not be formed. While the B_c transition state **21** meets the requirement of an equatorial alkyl substituent, the expectation is that isomer **22** will not form because the B_c isomer did not arise when the substituent was hydrogen.

What will be the consequences of the diastereomeric reaction, $S_{lact}S_{alc}$ (or $R_{lact}R_{alc}$)? This issue is examined in Scheme VI. Transition states **23**, **25**, **27**, and **29** are in all respects identical with their diastereomeric counterparts **15**, **17**, **19**, and **21**, respectively, of Scheme V, except that the "R" substituent is now axial in **23** (C_t) and **29** (B_c) and equatorial in **25** (B_t) and **27** (C_c). Accordingly, the formation of **24** (C_t) and **30** (B_c) bearing *Z* olefins will be forbidden; *E* olefins **26** (B_t) and **28** (C_c) will be allowed.

By use of the genetic analogy of Scheme III, the pure C_t phenotype can be prepared independently of the hybrid B_t and C_c phenotypes. In chemical terms, it is an example of double diastereoselection wherein $S_{lact}R_{alc}$ ($R_{lact}S_{alc}$) represents the matched pair, and $S_{lact}S_{alc}$ ($R_{lact}R_{alc}$) is the mismatched pair.[6a]

When *S* lactone **1a** (as its ortholactone) was subjected to rearrangement with *R* alcohol **14a**, the sole product was the C_t isomer **16a** obtained in 88% yield. The failure of the lactone to undergo epimerization and the ^{13}C NMR of its triacetate degradation product (vide supra) secured its stereochemistry. In the limiting case, if the lactone and the alcohol are less than 100% enantiomerically pure, other diastereomers will arise. Indeed, the presence of diastereomers, as will be discussed later, can be used to assay the enantiomeric purity of one of the reactants if the percent is known for the other component; the percent ee of the reactants will also be discussed later.

Scheme VII



The diastereomeric rearrangements followed the predicted course. Thus, *S* lactone **1a** and *S* alcohol *ent*-**14a** afforded a 55:45 mixture of B_t isomer **26a** and C_c isomer **28a**, respectively. The enantiomeric pairing, *R* lactone and *R* alcohol **14a** provided the enantiomers *ent*-**26a** and *ent*-**28a** in the same ratio. The small excess of the B_t isomer over the C_c isomer requires the trans–cis control element to be marginally more important than the chair–boat. Equilibration of the mixture gave a 97:3 ratio of products wherein the B_t isomer predominated. Expectedly, when the ortholactone of *S* lactone **1a** was allowed to undergo rearrangement in the presence of 1 equiv of *rac*-**14a**, the C_t isomer **16a** constituted 50% of the products, being derived from the *R* alcohol, and the B_t (**26a**) and C_c (**28a**) isomers (55:45 ratio) comprised the other 50% of the products originating from the *S* alcohol. Under no circumstances could the B_c isomer **22** be detected. The same results were obtained when the enantiomers of alcohol **14b** were employed in the "isopropyl series".

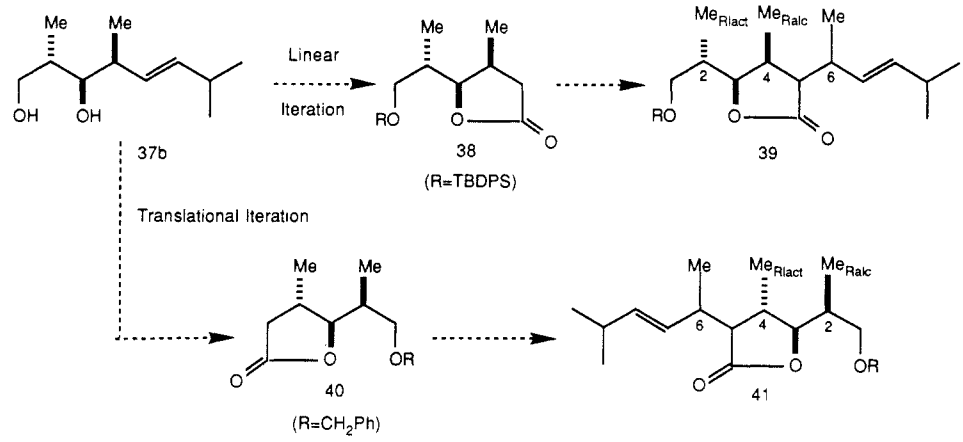
From the foregoing results, the expectation is that the activation energy for these favorable rearrangements, as well as for the earlier examples, is in the order $C_t < B_t \leq C_c < B_c$. If the exchange of the alcohol with the ortholactone were to be more rapid than rearrangement, and the reaction could be run at a low enough temperature to exclude the three higher activation energy processes, then kinetic resolution of racemic alcohol **14a** with a limited amount of enantiomerically pure lactone via the C_t transition state could be realized. In the event, no kinetic resolution could be detected, ostensibly indicating that rearrangement is more rapid than exchange. The lack of kinetic resolution requires the enantiomerically pure lactone to react statistically with the enantiomers of the alcohol.

Thus far, the methodology permits the synthesis of the C_t and B_t isomers and their enantiomers, the former under kinetic and the latter under thermodynamic control. But what of the C_c isomer? Can it be formed with the exclusion of the B_t isomer? The B_t and C_c isomers bear a pseudo-C_2-symmetry element formed by rotation about an axis passing through the carbonyl carbon and the adjacent carbon. This property can be utilized to convert the B_t into the C_c isomer. Saponification of B_t isomer *ent*-**26a** (Scheme VII) followed by buffered iodolactonization afforded iodolactone **31**, having all substituents cis-substituted on the lactone ring; the contiguous ring protons displayed NOE enhancements of 4–9%. Protection of the primary hydroxyl group of lactone **31** as its *tert*-butyldimethylsilyl ether was conducted to avoid the possibility of translactonization during subsequent epimerization. Reduction of iodolactone **32** with zinc in aqueous acetic acid not only accomplished the regeneration of the *E* olefin from the iodo lactone, but also effected desilylation and lactonization to give

(19) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. Johnson, W. S.; Werthermann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-t.; Faulkner, D. J.; Petersen, M. R.; *J. Am. Chem. Soc.* **1970**, *92*, 741. (b) Katzenellenbogen, J. A.; Christy, K. J. *J. Org. Chem.* **1974**, *39*, 3315.

(20) Hill, R. K.; Soman, R.; Sawada, S. *J. Org. Chem.* **1972**, *37*, 3737.

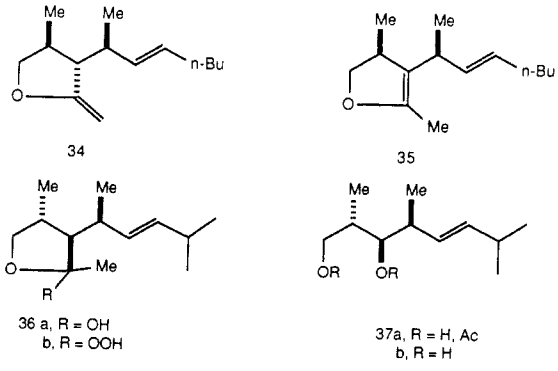
Scheme VIII



B_t isomer *ent*-**26a**. Having established the means for reversal of the iodolactonization procedure, cis lactone **32** was epimerized under dilute, basic conditions to a 97:3 mixture (**33**/**32**), wherein the trans lactone predominated. Reduction of iodo lactone **33** gave rise to the C_c isomer, *ent*-**28a**. With this technique at hand, three of the four possible stereoisomers of the prototypical lactones became available. Although the B_c isomer **22** could not be generated, it did become accessible in more complex cases.[21]

With the stereochemical issues addressed, our attention was turned to the establishment of a protocol that would accomplish a formal Baeyer–Villiger oxidation of these three lactones with the proviso that, as in the case of the Baeyer–Villiger oxidation itself, rearrangement must occur with retention to preserve the stereochemistry that was created in the lactones. Fortunately at this time, Schreiber and Liew in this Laboratory[22] were studying the Criegee rearrangement[23] of methoxy hydroperoxides (generated by ozonolysis of enol ethers) with anhydrides; a variant of this method proved amenable to the solution of the problem at hand.

Our initial attempts to add methylmagnesium bromide to C_t isomer **16a** proved unsuccessful in that the lactone was recovered unchanged, owing to apparent facile enolization. Although Tebbe's reagent provided the exocyclic vinyl ether **34**,[24] the product was often contaminated with endocyclic isomer **35**, and residual metal salts were difficult to remove. The acetic acid promoted addition of the elements of hydrogen peroxide to the double bond of either enol ether gave the same mixture of hydroperoxides. The kinetic protonation of **35** to regenerate the C_t stereochemistry, while acceptable in the present instance, would be untenable if the starting material had been the C_c isomer, as the B_t stereochemistry would be expected. Thus, hard-won stereochemistry would have been lost. A more manageable solution employed the monoaddition of methyllithium to the lactones.



To this end, treatment of lactone **26b** with methyllithium at 0 °C afforded a mixture of hemiacetals **36a** that, without purification, was converted to a mixture of hydroperoxy hemiketals **36b** upon exposure to 30% H_2O_2 in THF containing acetic acid. Acetylation of the crude hydroperoxides and rearrangement in refluxing CH_2Cl_2 gave a mixture of hydroxy acetates **37a** that were saponified to the diol **37b**. This operation provided the diol in 84% yield from lactone **26b**.

Diol **37b** represents a polypropionate building block that is differentially functionalized at the termini of the growing chain (i.e., primary alcohol and olefin). The developing chain can be constructed by two basic methods: linear and translational iteration. As illustrated in Scheme VIII, linear iteration involves the addition of methyl groups in a single direction, in this case to the "right". Thus, diol **37b** would be subjected to cleavage of the olefin and elaboration to the lactone **38**, a substrate that could undergo continued chain extension to the "right". The methyl groups at C_2 and C_4 of lactone **39** are derived from the original *R* lactone **1a** and *R* alcohol **14b**, while the configuration of the C_6 methyl is once again controlled by the appropriate choice of alcohol **14b**, *R* for the β-configuration (bold) and *S* for the α-configuration (dotted). The configuration at C_5 would be established kinetically (C_t) when the C_4 and C_6 methyls have the syn relationship or by equilibration (B_t) or iodolactonization (C_c) when the methyls are anti to one another.

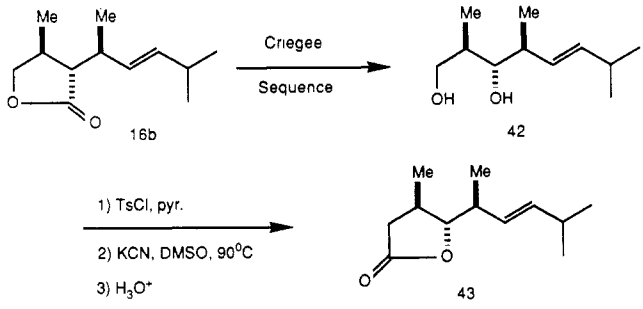
The second method of chain extension is the translational mode. In this scheme the olefin of diol **37b** must be cleaved oxidatively, reduced, and suitably protected prior to one carbon chain extension of the primary alcohol and lactonization to **40**. This operation has in effect changed the absolute *R* configuration at the ring methyl of B_t isomer **26b** (from which diol **37b** was derived) to the *S* configuration in lactone **40** by inversion of the element of "CO_2" present in the lactone. As the chain is constructed by iteration to the "left", an *R* alcohol would provide the α-configuration (dotted) and the *S* alcohol would afford the β-configuration (bold). That is to say, "bold–right" and "dotted–left" have the same absolute sense of chirality established by the *R* alcohol while "dotted–right" and "bold–left" have the opposite chirality and are *S* alcohol derived.

In the examples provided in Scheme VIII, the two modes of iteration necessarily provide diastereomers, independent of whether *R* or *S* alcohols are employed as lactone **39** bears a C_2,C_3-anti, C_3,C_4-syn relationship while lactone **41** has a C_2,C_3-syn, C_3,C_4-anti stereochemistry. If diol **37b** had been derived from a C_t isomer (**16b** → **42**, Scheme IX). then lactones **38** and **40** would be enantiomers; mirror image iterations would provide enantiomers; non mirror image interactions would give diastereomers.

Scheme IX outlines the method used in the transposition of lactone **16b** to lactone **43**. The Criegee sequence proceeded without complication in 81% yield. The primary monotosylate of **42** underwent one-carbon homologation to the γ-hydroxy nitrile **45b** in dimethyl sulfoxide (DMSO) and eventual hydrolysis to the lactone **43** (81% yield). Inferential evidence suggests that the displacement occurs through the intermediate oxetane. In an

(21) See the accompanying paper in this issue.
(22) Schreiber, S. L.; Liew, W.-F. *Tetrahedron Lett.* **1983**, *24*, 2363.
(23) (a) Criegee, R. *Chem. Ber.* **1944**, *77*, 722. (b) Criegee, R.; Kaspar, R. *Justus Liebigs Ann. Chem.* **1948**, *560*, 127.
(24) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270.

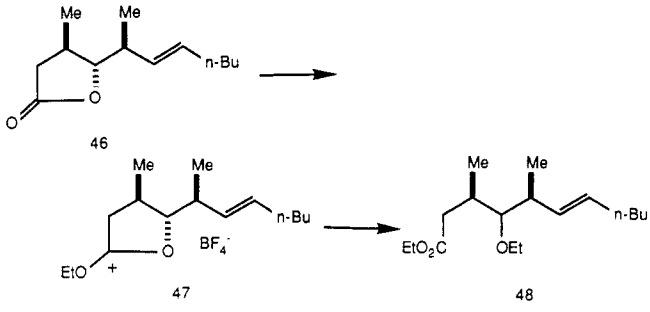
Scheme IX



earlier study with the diol derived from lactone **16a**, cyanide displacement of the monotosylate in ethanol afforded the oxetane **44a**, which then provided the nitrile **45a** upon treatment with KCN in DMSO. Indeed, small quantities of oxetane **44a** were found when the monotosylate was subjected to cyanide in DMSO for less than the required amount of time. While these experiments established that the oxetane was converted into the nitrile, they did not provide any evidence for direct displacement of tosylate by cyanide.

44 a, R = n-Bu b, R = i-Pr 45

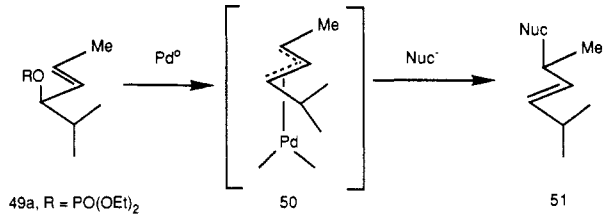
Efforts to prepare the ortholactone of lactone **46** were unsuccessful. When the Lythgoe conditions[15] employed with 3-methyl-γ-butyrolactone **1a** were utilized, the starting lactone was consumed and the ^1H NMR spectrum of the crude material showed ethyl patterns. Hydrolysis of this material with mineral acid, in an attempt to destroy any ortholactone, did not remove the ethyl patterns in the NMR spectrum. Although 4-substituted γ-butyrolactones have been reported to undergo ortholactone formation with Meerwein's reagent,[25] it is not unreasonable to suspect that fragmentation of the intermediate dioxenium ion **47** to a secondary carbocation with subsequent capture by diethyl ether (**48**) had occurred. Efforts at realizing an intramolecular Pinner reaction,[26] the process by which nitriles are transformed into orthoesters, were also found to be unsuccessful.



The inability to apply the Claisen rearrangement strategy required an operationally equivalent process. As the Claisen rearrangement can be described as a suprafacial, intramolecular S_N2' alkylation, these conditions are met in the palladium(0)-mediated alkylation of allylic esters with malonic ester derivatives, a reaction known to proceed by a double inversion mechanism.[27]

Phosphate **49a** and acetate **49b** (Scheme X) represent activated esters of *R* alcohol **14a** that would undergo initial backside displacement to give chiral complex **50** and then a second displacement with inversion to afford alkylation product **51**. Keinan[28] has investigated the alkylation of palladium π-allyl complexes bearing 1,3-methyl alkyl substituents and has found that when the alkyl substituent is isopropyl, the regioselectivity of alkylation with sodio dimethyl malonate is 99:1 in favor of the terminus bearing the methyl group. While π-σ-π isomerization of complex **50** at the methyl terminus followed by alkylation at this site would also produce **51**, π-σ-π isomerization at the isopropyl end and alkylation at the methyl terminus to provide a *Z* olefin bearing the opposite chirality present at the sp^3 center of **51** is unlikely on steric grounds.

Scheme X



49a, R = $PO(OEt)_2$ b, R = Ac 50 51

A second concern associated with this alkylation procedure is the possibility of racemization of complex **50**. Tsuji,[29] Bosnich,[30] and Hayashi[31] have presented ample evidence that chiral π-allyl palladium complexes such as **50** can undergo racemization by backside displacement on the complex by palladium(0), the bimolecular racemization process being more acute at higher (i.e., stoichiometric palladium) concentrations.

Before turning to the issue of racemization, the enantiomeric purity of the *R* and *S* lactones **1**, the alcohols **14**, and ***ent*-14** and their products of Claisen rearrangement, **16**, **26**, and **28**, needed to be determined.[32] In this reaction scheme, which displays no kinetic resolution, consider a sample of lactone **1a** wherein the mole fraction of the major *R* enantiomer is x ($0.5 < x \leq 1$); then, the minor *S* enantiomer is $1 - x$. Similarly, if the mole fraction of the major *R* enantiomer of the alcohol is y ($0.5 < y \leq 1$), then the minor *S* enantiomer is given by $1 - y$. By the definition of enantiomeric excess (ee = A − B/A + B), the fractional enantiomeric excess[33] p is given by

$$p_{lact} = 2x - 1, \text{ or } x = (p_{lact} + 1)/2 \quad (1)$$

where $ee_{lact} = 100(p_{lact})$ and

$$p_{alc} = 2y - 1, \text{ or } y = (p_{alc} + 1)/2 \quad (2)$$

where $ee_{alc} = 100(p_{alc})$. Since two diastereomers (*RR*;*SS* and *RS*;*SR*)[34] can be formed in the statistical union of the lactones and alcohols, then

$$p_{RR} = \frac{xy - (1-x)(1-y)}{xy + (1-x)(1-y)} = \frac{p_{lact} + p_{alc}}{(p_{lact})(p_{alc}) + 1} \quad (3)$$

where $ee_{RR} = 100(p_{RR})$ and

$$p_{RS} = \frac{x(1-y) - y(1-x)}{x(1-y) + y(1-x)} = \frac{p_{lact} - p_{alc}}{1 - (p_{lact})(p_{alc})} \quad (4)$$

where $ee_{RS} = 100(p_{RS})$.

When $p_{lact} = p_{alc} = 0$, the lactone and alcohol are both racemic, $p_{RR} = p_{RS} = 0$ (eq 3 and 4). In addition, when the purity of both reactants is unity, $p_{RR} = 1$ and the *RS* diastereomer does not exist. When the purity of one of the reactants is unity and the other

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(27) (a) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615. (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730. (c) Trost, B. M.; Klun, T. P. *Ibid.* **1981**, *103*, 1864. (d) Tsuji, J. *Fortschr. Chem. (Moscow)* **1980**, *91*, 29. (e) Tsuji, J. *Pure Appl. Chem.* **1982**, *54*, 197.
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(29) Takahashi, T.; Jinbo, Y.; Kitamura, K.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 5921.
(30) (a) Bosnich, B. *Pure Appl. Chem.* **1982**, *54*, 189. (b) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033.
(31) (a) Hayashi, T.; Konishi, M.; Kumada, M. *J. Chem. Soc., Chem. Commun.* **1984**, 107. (b) Hayashi, T.; Hagihara, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1983**, *105*, 7767.
(32) Ziegler, F. E.; Kneisley, A. K.; Wester, R. T. *Tetrahedron Lett.* **1986**, *27*, 1221.
(33) For a related treatment with *d,l* and meso compounds, see: Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055.
(34) In this treatment, *RR* designates one diastereomer, *RS* the other.

Table I[a]

entry	lactone	alcohol or der[b]	% cat.	temp, °C	time, h	$C_t/B_t/C_c/B_c$[c]	major diast[c]	major/minor	%de	% rac
1	(*R*)-**1a**	**14a**		110	48	1.3/53.6/45.1/0	B_t, C_c	98.7/1.3	97.4	
2	(*R*)-**1b**[d]	**49a**	5	25	2	3.4/79.3/16.4/0.9	B_t, C_c	95.7/4.3	91.4	6.2
3	(*R*)-**1b**[d]	**49a**	10	25	2	3.0/78.8/17.3/0.9	B_t, C_c	96.1/3.9	92.2	5.4
4	(*R*)-**1b**[d]	**49b**	10[e]	65	18	5.8/79.4/13.7/1.1	B_t, C_c	93.1/6.9	86.2	11.4
5	(*S*)-**1b**[d]	**49a**	5	25	2	94.8/3.9/0/1.3[f]	C_t, B_c	96.1/3.9	92.2	4.4[g]

[a] All entries are the average of three runs. [b] 2.0–2.5 equiv of ester was used. [c] $C_t/B_t/C_c/B_c$ = *ent*-**16**, *ent*-**26**, *ent*-**28**, and *ent*-**22**, respectively. Major diastereomers have high ee; the minor diastereomers are partially racemized. [d] The chirality is based upon the C_3-methyl configuration. [e] 10 mol % 18-crown-6 employed. [f] After *t*-BuOK/*t*-BuOH equilibration. [g] % ee (*S*)-**1b** = % ee lactone (*S*)-**1a** = 96.4.

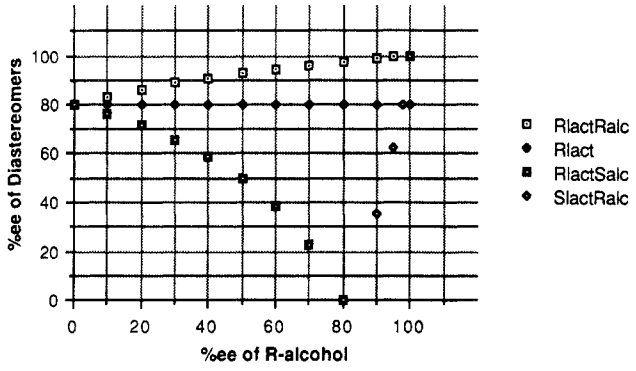

Figure 1. Percent ee of diastereomers vs percent ee of *R* alcohol.

is nonunity, $p_{RR} = p_{RS} = 1$. When the purity of both reactants is nonzero, equal and nonunity, $p_{RS} = 0$ and $p_{RR} > p_{lact}$ or p_{alc}. The last set of conditions, and that in which both purities are nonzero, nonequal, and nonunity is illustrated in Figure 1. The plot shows the influence of reactant purity (i.e., percent ee) on product purity with *R* lactone of 80% ee reacting with *R* alcohol ranging from 0 to 100% ee. With racemic alcohol both diastereomers, *RR* and *RS*, are formed with 80% ee. As the percent ee of the *R* alcohol increases, the *RR* diastereomer increases in purity, always being purer (or equal at percent ee $R_{alc} = 0$ or 100) than either reactant.[35] At the same time, the *RS* diastereomer's percent ee drops rapidly until the percent ee is zero at 80% ee of the *R* alcohol. The percent ee of the *RS* diastereomer is always less than that of the *R* lactone between 0 and 80% ee of the *R* alcohol, greater than that of the *R* alcohol at values less than 50% ee, and less between 50 and 80% ee. At values of percent ee *R* alcohol >80 and <100, eq 4 provides negative values for the *RS* diastereomer, which means that the opposite enantiomer, $S_{lact}R_{alc}$, is now dominant. In this range the percent ee of this diastereomer never exceeds the percent ee of the *R* alcohol but is greater than the percent ee of the *R* lactone when the percent ee of the *R* alcohol is in the range 97.6–100.

The diastereomeric excess (de, or diastereomeric selectivity, ds[36]) of the *RR* isomer over the *RS* is given by

$$\text{de} = \frac{[xy + (1-x)(1-y)] - [x(1-y) + y(1-x)]}{[xy + (1-x)(1-y)] + [x(1-y) + y(1-x)]} \quad (5)$$

which reduces to

$$\text{de} = (2x-1)(2y-1) = (p_{lact})(p_{alc}) \qquad \%\text{de} = 100(\text{de}) \quad (6)$$

Thus, if the purity of either reactant is known, the purity of the other can be determined if the diastereoselectivity of the reaction is known.

The purity of *R* and *S* lactone **1a** could not be determined readily by NMR techniques with chiral shift reagents. The method of Helmchen[37] was employed, which involves the aminolysis of a lactone with an enantiomerically pure amine in the presence of 2-hydroxypyridine. The enantiomeric excess of the amine, (*R*)-(+)-ethylbenzylamine, was shown to be 98.6% by ^{1}NMR integration (C_6D_6, Eu(thc)$_3$) of the methyl doublet of the *S* enantiomer vs the upfield ^{13}C satellite of the *R* enantiomer. The area of the satellite was multiplied by 182 (half of the ^{13}C natural abundance correction factor, 1/0.0055) to give the amount of the *R* amine.[38] The aminolysis of racemic lactone **1a** showed no kinetic resolution. Aminolysis of *R* lactone **1a** gave a 98.0:2.0 ratio (%de = 96.0) of hydroxy amides, which, by using eq 6, showed that the *R* lactone **1a** had a %ee = 97.4 (98.7:1.3); *S* lactone **1a** was shown to have a %ee = 96.4 (98.2:1.8).

The enantiomers of *R* alcohol **14b** and *S* alcohol *ent*-**14b** were prepared by the method of Sharpless[18] from the racemate;[39] their percent ee's were determined by the Claisen rearrangement of *R* lactone **1a** with the alcohols (eq 6). Thus, the percent de for the *R* lactone and *R* alcohol reaction is simply $(C_t + B_c) - (B_t + C_c)$, while for the *S* alcohol it is $(B_t + C_c) - (C_t + B_c)$.[40] When the rearrangement with a sample of *R* alcohol was conducted, the percent de was 97.4 (98.7:1.3), indicating that the percent ee of the alcohol was, within the limitation of the measurement, 100% enantiomerically pure. This result requires the products formed by the Claisen rearrangement to be virtually 100% enantiomerically pure.

Finally, if the palladium(0)-catalyzed alkylation proceeds to give a $\%\text{de}_{Pd} = 97.4$, then no racemization will have taken place. If the $\%\text{de}_{Pd} = 0$, then complete racemization will have occurred. In more general terms

$$\%_{rac} = \frac{100(\%\text{de}_{Claisen} - \%\text{de}_{Pd})}{\%\text{de}_{Claisen}} \quad (7)$$

The alkylation of palladium π-allyl complexes requires sufficiently soft nucleophiles such as malonates. Accordingly, the *R* and *S* lactones **1a** were converted into their malonate derivatives **1b** by carbomethoxylation with LDA/methyl cyanoformate, with the proviso that 2 equiv of base were employed.[41] Murahashi has demonstrated that allylic diethyl phosphates are an order of magnitude more reactive than allylic acetates in palladium(0)-mediated alkylations.[42] The phosphate esters **49a** and *ent*-**49a** were prepared by treatment of the respective alcohols **14b** with *n*-butyllithium followed by reaction with diethyl phosphorochloridate. The phosphates were generally used as soon as they were prepared, although they could be stored in a freezer without deterioration of stereoselectivity. The malonates were converted to their partially soluble (THF) sodium salts with NaH. The acetates **49b** required elevated temperature to obtain an adequate reaction rate, and frequently additional catalyst had to be added to the reaction mixture. The alkylated malonates were subjected to decarboxylation under standard Krapcho[43] conditions (LiCl, aqueous DMSO, 190 °C); epimerizations were accomplished with *t*-BuOK/*t*-BuOH.

The results of the study are summarized in Table I. Entries 2 and 3 indicate that catalyst stoichiometry in the range 5–10 mol

(35) (a) Mori, K.; Watanabe, H. *Tetrahedron* **1986**, *42*, 295. (b) Midland, M. M.; Gabriel, J. J. *J. Org. Chem.* **1985**, *50*, 1143. (c) Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 5312. (d) Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1984**, *49*, 576.

(36) Thaisrivongs, S.; Seebach, D. *J. Am. Chem. Soc.* **1983**, *24*, 5425.

(37) Helmchen, G.; Nill, G. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 65.

(38) HPLC analysis: hydroxy amide ($R_{lact}R_{amine}$) 4.4 min, hydroxy amide ($S_{lact}R_{amine}$) 5.6 min. See the introduction to the Experimental Section for instrumentation.

(39) Stevens, P. G. *J. Am. Chem. Soc.* **1935**, *57*, 1112.

(40) Although no B_c isomer is formed in these reaction, it does appear in the subsequent palladium(0)-mediated alkylations.

(41) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425. For a study on the mechanism of this reaction, see: Ziegler, F. E.; Wang, T.-F. *Tetrahedron Lett.* **1985**, *26*, 2291.

(42) Tanigawa, Y.; Nishimura, K.; Kawasaki, A.; Murahashi, S. *Tetrahedron Lett.* **1982**, *23*, 5549.

(43) Krapcho, A. P. *Synthesis* **1982**, 805.

% does not appreciably affect the amount of racemization. Additionally, use of the *S* lactone (entry 5) does not alter the amount of racemization and predictably provides different diastereomers from entry 2. Entry 4 reveals a greater degree of racemization under conditions necessary to achieve an appreciable rate of reaction.

As the diastereoselection is always higher for the preparation of lactones **16**, **26**, and **28** via the Claisen rearrangement than the palladium(0)-mediated alkylation, the former process is employed in the formation of these lactones; the latter method is used in the further iteration of these lactones and their higher homologues. Also, as iteration proceeds, the enantiomeric excess of each desired diastereomer will be higher than its predecessor. Synthetic applications of the palladium(0)-mediated alkylation are detailed in the following paper.

Experimental Section

All reactions were performed in flame-dried glassware under N_2 unless otherwise noted. Diethyl ether and THF were distilled from sodium benzophenone ketyl under N_2. Diisopropylamine, pyridine, toluene, hexane, CH_2Cl_2, Et_3N, *t*-BuOH, and dimethyl sulfoxide (DMSO) were distilled from CaH_2. Acetic anhydride, diethyl phosphorochloridate, and hexamethylphosphoramide (HMPA) were distilled prior to use. All other reagents were used as received. Workup means drying organic extracts over anhydrous $MgSO_4$, filtration, and concentration.

Melting points: uncorrected. NMR: $CDCl_3$ unless otherwise specified, proton assignments are numbered by using the IUPAC name. Gas chromatography: flame, 6 ft × $^1/_8$ in. 5% Carbowax/Anakrom AS 100/120 column (80–200 °C, 8 °C/min, method A); capillary, 25 m bonded Carbowax 20 M, 0.25 μm (140 °C, 0.5 mL/min, method B). HPLC: Waters Radical Pak B SiO_2 cartridge (100% EtOAc, 3 mL/min). Optical rotations: 25 °C in indicated solvent. Elemental analyses: analyses were within 0.4%.

3(*r*)-(Acetoxymethyl)-1,5-diacetoxy-2(*R*),4(*S*)-dimethylpentane (13). A solution of racemic 2,2-diethoxy-3-methyltetrahydrofuran (1.0 g, 5.7 mmol), (*E*)-2-buten-1-ol (329 mg, 4.56 mmol), and propionic acid (42.7 mg, 0.57 mmol) in 35 mL of toluene was heated at reflux for 42 h with periodic removal of ethanol. The cooled solution was diluted with ether, washed with 5% aqueous HCl and water, dried over Na_2CO_3, filtered, and concentrated. Distillation (Kugelrohr, 65 °C, 0.25 Torr) gave 75 mg (89%) of lactones **6**, **8**, and **10**. Capillary GC showed **6** (74%, t_R 9.4 min), **8** (14%, t_R 9.6 min), and **10** (12%, t_R 13.3 min). Chromatography (10% ether/hexane) gave 183 mg of **6** (%ds = 97.6), a 355 mg fraction of **6** (80%) and **8** (20%), and 83 mg of **10**. Lactone **6**: ^{1}H NMR (250 MHz) δ 1.13 (3 H, d, *J* = 6.6 Hz), 1.18 (3 H, d, *J* = 7.0 Hz), 2.24 (1 H, dd, *J* = 9.3, 3.5 Hz), 2.41 (1 H, m), 2.74 (1 H, m), 3.72 (1 H, t, *J* = 8.7 Hz), 4.33 (1 H, dd, *J* = 8.7, 7.8 Hz), 5.10 (2 H, m), 5.84 (1 H, m). A solution of lactone **6** (41 mg, 0.27 mmol) in 20 mL of CH_2Cl_2 containing 200 μL of acetic acid was ozonized at 0 °C until the effluent turned aqueous KI brown. The solution was purged with N_2, dimethyl sulfide (2 mL) was added, and the mixture was warmed to 25 °C followed by stirring for 2 h. The solution was diluted with ether, washed with water, dried over Na_2SO_4, filtered, and concentrated to give 43 mg of crude aldehyde: ^{1}H NMR (250 MHz, partial) δ 1.14 (3 H, d, *J* = 6.6 Hz), 1.25 (3 H, d, *J* = 7.5 Hz), 3.00 (1 H, dd, *J* = 7.4, 3.2 Hz), 3.77 (1 H, m), 4.40 (1 H, m), 9.74 (1 H, s). The crude aldehyde in THF (2.8 mL) was reduced with $LiAlH_4$ (76 mg, 2.0 mmol) at 0 °C. The mixture was warmed to 25 °C; stirred for 16 h; decomposed with 200 μL of saturated, aqueous sodium potassium tartrate; diluted with 20 mL of MeOH; filtered; and concentrated to give crude triol. The residue was dissolved in pyridine (2 mL) at 0 °C, acetic anhydride (225 mg, 2.2 mmol) was added, and the mixture was warmed to 25 °C and allowed to stir for 21 h. The mixture was diluted with ether, washed with 1% HCl and aqueous $NaHCO_3$, and worked up. Chromatography (25% ethyl acetate/hexane) gave the anti,anti triacetate **13** (44%): ^{1}H NMR (250 MHz) δ 1.06 (6 H, d, *J* = 6.9 Hz), 2.04 (3 H, s), 2.05 (6 H, s), 2.10 (3 H, m), 3.89 (2 H, dd, *J* = 11.1, 7.2 Hz), 4.13 (2 H, dd, *J* = 11.0, 4.7 Hz), 4.14 (2 H, d, *J* = 4.8 Hz); ^{13}C NMR (62.9 MHz) δ 16.3, 20.7, 20.8, 32.2, 43.6, 62.3, 66.9, 170.8, 171.0.

4(*S*)-Methyl-3(*S*)-(1(*S*)-Methyl-2(*E*)-heptenyl)dihydro-2(3*H*)-furanone (C_t, 16a). A solution of 0.20 g (1.2 mmol) of 2,2-diethoxy-3-(*S*)-methyltetrahydrofuran,[15,16] 0.35 g (2.7 mmol) of (*R*)-2(*E*)-octen-4-ol[20] (**14a**), and 20 mg of pivalic acid was heated at reflux in 25 mL of toluene for 12 h. The solution was concentrated in vacuo and washed successively with 10% aqueous HCl and saturated aqueous $NaHCO_3$. Workup and vacuum distillation (Kugelrohr) gave lactone **16a** in 88% yield: IR (neat) 1777 cm^{-1}; ^{1}H NMR (90 MHz, partial) δ 0.85 (3 H, t), 1.07 (3 H, d, *J* = 6.4 Hz), 1.11 (3 H, d, *J* = 7.0 Hz), 3.66 (3 H, t, *J* = 8.4 Hz), 4.26 (1 H, t, *J* = 7.6 Hz), 4.26 (1 H, t, *J* = 7.7 Hz), 5.47 (2 H, m); ^{13}C NMR 13.8, 17.0, 17.6, 22.5, 31.5, 32.0, 32.6, 36.1, 52.1, 72.7, 131.4, 131.7, 177.9; $[\alpha]_D$ −44.8° (*c* 10.2, $CHCl_3$). Anal. ($C_{13}H_{22}O_2$) C, H.

4(*S*)-Methyl-3(*S*)-(1(*S*),4-dimethyl-2(*E*)-pentenyl)dihydro-2(3*H*)-furanone (C_t, 16b). A solution of 18.5 g (0.11 mol) of 2,2-diethoxy-3-(*S*)-methyltetrahydrofuran, 9.7 g (0.085 mol) of (*R*)-2-methyl-4(*E*)-hexen-2-ol (**14b**), and 300 mg of pivalic acid in 650 mL of toluene was heated at reflux for 48 h in a flask equipped with a solvent take-off head. Ethanol was removed by occasionally draining the solvent collected in the head. The reaction mixture was processed as described above and chromatographed (15% Et_2O/hexane) to afford 13.8 g (83%) of lactone **16b**: IR ($CHCl_3$) 1763 cm^{-1}; ^{1}H NMR (250 MHz) δ 0.98 (6 H, d, *J* = 6.7 Hz), 1.12 (3 H, d, *J* = 6.7 Hz), 1.14 (3 H, d, *J* = 7.1 Hz), 2.19 (1 H, dd, *J* = 9.1, 3.6 Hz), 2.26 (1 H, m), 2.44 (1 H, m), 2.64 (1 H, m), 3.71 (1 H, t, *J* = 8.6 Hz), 4.31 (1 H, dd, *J* = 8.8, 8.1 Hz), 5.43 (2 H, m)); $[\alpha]_D$ −37.8° (*c* 11.9, $CHCl_3$). Anal. ($C_{12}H_{20}O_2$) C, H.

4(*R*)-Methyl-3(*R*)-(1(*S*)-methyl-2(*E*)-heptenyl)dihydro-2(3*H*)-furanone (B_t, *ent*-26a) and 4(*R*)-Methyl-3(*S*)-(1(*S*)-methyl-2(*E*)-heptenyl)dihydro-2(3*H*)-furanone (C_c, *ent*-28a). A solution of 314 mg (1.8 mmol) of 2,2-diethoxy-3(*R*)-methyltetrahydrofuran, 232 mg (1.8 mmol) of (*R*)-2(*E*)-octen-4-ol, and 20 mg of pivalic acid in 30 mL of toluene was added at reflux for 64 h, periodically removing ethanol. Workup (vide supra) and Kugelrohr distillation (140–150 °C, 1 mm) gave 354 mg (94%) of lactones *ent*-**26a** and *ent*-**28a** in a 55:45 ratio (GC analysis, method A). Chromatography (5% EtOAc/hexane) gave separated samples. Lactone *ent*-**26a**: IR (CCl_4) 1782 cm^{-1}; ^{1}H NMR (250 MHz) δ 0.91 (3 H, t, $C_{7'}$-H), 1.16 (3 H, d, *J* = 6.3 Hz), 1.17 (3 H, d, *J* = 6.8 Hz), 1.23–1.40 (4 H, m), 2.02 (2 H, m), 2.13 (1 H, dd, *J* = 7.8, 5.5 Hz, C_3-H), 2.44 (1 H, m, C_1-H), 2.69 (1 H, m, C_4-H), 3.73 (1 H, dd, *J* = 8.8, 7.0 Hz, C_5-H) 4.30 (1 H, dd, *J* = 8.8, 7.5 Hz, C_5-H), 5.36 (1 H, dd, *J* = 13.8, 7.0 Hz, $C_{2'}$-H), 5.42 (1 H, m, $C_{3'}$-H); $[\alpha]_D$ −18.9° (*c* 0.37, $CHCl_3$). Anal. ($C_{13}H_{22}O_2$) C, H. Lactone *ent*-**28a**: IR (CCl_4) 1783 cm^{-1}; ^{1}H NMR (250 MHz) δ 0.87 (3 H, t, $C_{10'}$-H), 1.11 (3 H, d, *J* = 5.0 Hz), 1.18 (3 H, d, *J* = 7.5 Hz), 1.25–1.45 (4 H, m), 2.05 (2 H, m), 2.44 (1 H, dd, *J* = 7.8, 5.0 Hz, C_3-H), 2.57 (1 H, m, C_1-H), 2.70 (1 H, m, C_4-H), 3.88 (1 H, dd, *J* = 7.8, 5.3 Hz, C_5-H), 4.24 (1 H, dd, *J* = 7.8, 6.3 Hz, C_5-H), 5.54 (2 H, m, $C_{2'}$-H, $C_{3'}$-H); $[\alpha]_D$ −4.48° (*c* 0.34, $CHCl_3$). Anal. ($C_{13}H_{22}O_2$) C, H.

Equilibration of Lactones *ent*-26a and *ent*-28a. A solution of 262 mg (1.25 mmol) of a 55:45 mixture of lactones *ent*-**26a** and *ent*-**28a** in 30 mL of Et_2O was treated with 3.0 mL of a 1.2 M solution of *t*-BuOK/*t*-BuOH. The solution was stirred for 1 h at 25 °C, poured into 5% aqueous HCl, extracted with Et_2O, dried with anhydrous Na_2CO_3, filtered, and concentrated. Kugelrohr distillation (150 °C, 4 mm) gave a 100% yield of a 97:3 mixture of lactones *ent*-**26a** and *ent*-**28a**, respectively.

4(*R*)-Methyl-3(*R*)-(1(*S*),4-dimethyl-2(*E*)-pentenyl)dihydro-2-(3*H*)-furanone (B_t, *ent*-26b) and 4(*R*)-Methyl-3(*S*)-(1(*S*),4-dimethyl-2(*E*)-pentenyl)dihydro-2(3*H*)-furanone (C_c, *ent*-28b). A solution of 826 mg (4.7 mmol) of 2,2-diethoxy-3(*R*)-methyltetrahydrofuran, 544 mg (4.7 mmol) of (*R*)-2-methyl-4(*E*)-hexen-2-ol (**14b**), and 25 mg of pivalic acid in 50 mL of toluene was heated at reflux for 48 h with periodic removal of ethanol. Workup (vide supra) and Kugelrohr distillation (130 °C, 3 mm) gave 865 mg (93%) of a 55:45 mixture (GC analysis, method A) of lactones *ent*-**26b** and *ent*-**28b**. Chromatography (10% EtOAc/hexane) gave partial separation of diastereomers. Less polar lactone, *ent*-**26b**: IR (CCl_4) 1786 cm^{-1}; ^{1}H NMR (250 MHz) δ 0.96 (6 H, d, *J* = 6.4 Hz), 1.16 (3 H, d, *J* = 6.4 Hz), 1.17 (3 H, d, *J* = 6.4 Hz), 2.13 (1 H, dd, *J* = 7.5, 5.0 Hz, C_3-H), 2.26 (1 H, m, C_4-H), 2.43 (1 H, m, C_1-H), 2.68 (1 H, m, C_1-H), 3.75 (1 H, dd, *J* = 9.0, 7.2 Hz, C_1-H), 4.31 (1 H, t, *J* = 9.0 Hz, C_1-H), 5.32 (1 H, dd, *J* = 15.0, 7.5 Hz, vinyl H), 5.49 (1 H, dd, *J* = 15.0, 7.5 Hz, vinyl H); $[\alpha]_D$ −16.1° (*c* 1.43, $CHCl_3$). Anal. ($C_{12}H_{20}C_2$) C, H. More polar lactone, *ent*-**28b**: IR (CCl_4) 1782 cm^{-1}; ^{1}H NMR (250 MHz) δ 0.97 (3 H, d, *J* = 6.8 Hz), 0.98 (3 H, d, *J* = 6.8 Hz), 1.13 (3 H , d, *J* = 6.8 Hz), 1.89 (3 H, d, *J* = 6.8 Hz), 2.28 (1 H, m, C_4-H), 2.44 (1 H, dd, *J* = 7.5, 7.0 Hz, C_3-H), 2.56 (1 H, m, C_1-H), 2.69 (1 H, m, C_4-H), 3.86 (1 H, dd, *J* = 8.8, 6.3 Hz, C_1-H), 4.24 (1 H, dd, *J* = 8.8, 6.3 Hz, C_1-H), 5.47 (2 H, m, $C_{2'}$-H, $C_{3'}$-H); $[\alpha]_D$ −15.5° (*c* 1.5, $CHCl_3$); HRMS (EI) calcd for $C_{12}H_{20}O_2$ 196.1464, found 196.1470. Anal. ($C_{12}H_{20}O_2$) C, H.

Equilibration of Lactones *ent*-26b and *ent*-28b. A solution of a mixture (55:45) of 6.0 g (30.6 mmol) of lactones *ent*-**26b** and *ent*-**28b** in 120 mL of Et_2O and 13 mL of *t*-BuOH containing 1.55 g (13.8 mmol) of *t*-BuOK was stirred at 25 °C for 18 h. Workup and Kugelrohr distillation (130 °C, 1 mm) provided a 97:3 (GC analysis, method A) mixture of *ent*-**26b**/*ent*-**28b** in 97% yield.

4(*R*)-Methyl-3(*S*)-(1(*R*)-methyl-2-hydroxyethyl)-5(*S*)-(1(*R*)-iodopentyl)dihydro-2(3*H*)-furanone (31). A solution of 10 mg (0.048 mmol) of lactone *ent*-**26a** in 1% aqueous NaOH (2 mL) and ethanol (2 mL) was heated at 80 °C for 2 h and then cooled to room temperature followed

by removal of ethanol in vacuo. The aqueous solution was buffered to pH 8 by passing CO_2 (from the sublimation of dry ice) through the solution. The flask was protected from light (Al foil) as an aqueous KI_3 solution (25.4 mg (0.01 mmol) of I_2 and 48.1 mg (0.29 mmol) of KI in 0.2 mL of H_2O) was added dropwise followed by an additional 0.4 mL of H_2O. The reaction mixture was stirred for 24 h and was then extracted with Et_2O, washed with 25% aqueous $Na_2S_2O_3$, and worked up. Chromatography (20% EtOAc/hexane) gave 14.8 mg of iodo lactone **31** as a white, crystalline solid in 87% yield: mp 73 °C dec; IR (CCl_4) 3476, 1755, 1181, 1044 cm^{-1}; ^1H NMR (250 MHz) δ 0.95 (3 H, d, J = 6.1 Hz), 0.96 (3 H, t), 1.03 (3 H, d, J = 7.3 Hz), 1.1–2.2 (7 H, m), 2.66 (1 H, dd, J = 10.0, 6.1 Hz, C_3-H), 2.84 (1 H, m, C_4-H), 3.35 (1 H, m, OH), 3.76 (2 H, m, HOC*H*H), 3.90 (1 H, m, CHI), 4.48 (1 H, dd, J = 10.0, 3.0 Hz, C_5-H); $[\alpha]_D$ −12.8° (c 0.24, $CHCl_3$). Anal. ($C_{13}H_{23}O_3I$) C, H, I.

Conversion of Iodo Lactone 31 to C_c Lactone 26a. To a solution of 21.5 mg (0.046 mmol) of iodo lactone **31** in 4 mL of CH_2Cl_2 at 0 °C was added dropwise 28.5 mg (0.27 mmol) of 2,6-lutidine and 32.4 mg (0.12 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. After the solution was stirred for 20 min, it was diluted with Et_2O, washed with 5% aqueous HCl, and worked up. Chromatography (5% EtOAc/hexane) gave 26.2 mg of silyl ether **32**: IR (CCl_4) 1786 cm^{-1}; ^1H NMR (250 MHz) δ 0.05 (3 H, s), 0.07 (3 H, s), 0.90 (9 H, s), 0.94 (6 H, m), 1.04 (3 H, d, J = 6.8 Hz), 1.2–2.2 (7 H, m), 2.86 (2 H, m), 3.81 (1 H, dd, J = 10.0, 3.0 Hz), 3.91 (1 H, td, J = 10.0, 2.5 Hz), 4.14 (1 H, dd, J = 9.6, 4.6 Hz), 4.41 (1 H, dd, J = 11.2, 3.3 Hz, C_5-H)). To a solution of 6.2 mg (0.01 mmol) of iodo lactone **32** in 1 mL of *t*-BuOH was added 0.02 mL of a 0.93 M solution of *t*-BuOK in *t*-BuOH. The solution was stirred at 25 °C for 36 h, diluted with 1% aqueous HCl, extracted with Et_2O, worked up, and filtered through SiO_2 with 5% EtOAc/hexane to give crude iodo lactone **33**: ^1H NMR (250 MHz, partial) δ 0.08 (6 H, s), 0.92 (9 H, s), 1.03 (3 H, d, J = 7.0 Hz), 1.09 (3 H, d, J = 7.0 Hz), 3.59 (2 H, m), 3.94 (1 H, m), 4.70 (1 H, dd). Without further purification, the residue was dissolved in 1 mL of AcOH containing 0.05 mL of H_2O and 30 mg (0.4 mmol) of Zn dust and was stirred at 25 °C for 36 h. The reaction mixture was diluted with Et_2O and then passed through a pad of Celite, and the filtrate was concentrated. The residue was partitioned between $CHCl_3$ and H_2O, and the organic phase was subjected to workup. Chromatography (10% EtOAc/hexane) gave 2.4 mg of a 3:97 (GC analysis, method A) mixture of lactones *ent*-**28a** (NMR comparison) and *ent*-**26a** in 85% yield from iodo lactone **32**.

2(*S*),4(*S*),7-Trimethyl-5(*E*)-octene-1,3(*R*)-diol (37b). A solution of 2.5 g (12.8 mmol) of lactone *ent*-**26b** in 83 mL of Et_2O was added dropwise to a solution of methyllithium (15.5 mL, 1.4M in Et_2O, 21.7 mmol) in 166 mL of Et_2O at 0 °C. After the solution was stirred for 2 h, it was poured into 100 mL of saturated aqueous $NaHCO_3$, and the layers were separated. The aqueous phase was extracted with Et_2O, and the combined layers were worked up (dried over anhydrous Na_2CO_3) to give 2.6 g of crude hemiacetals **36a**: ^1H NMR (250 MHz, partial) δ 3.34 (1 H, dd, J = 7.5, 5.0 Hz), 4.07 (1 H, t, J = 7.5 Hz). The hemiacetals were dissolved in 125 mL of THF and cooled to 0 °C. A solution of 4.5 mL (79 mmol) of HOAc in 78 mL (0.69 mol) of 30% H_2O_2 was added dropwise, and then the solution was allowed to warm to 25 °C and to stir for 16 h. The solution was poured into saturated aqueous $NaHCO_3$ and was successively extracted with hexanes and worked up to provide 2.75 g of crude hydroperoxides. The hydroperoxides were dissolved in 97 mL of CH_2Cl_2 and 3.49 g (34.5 mmol) of Et_3N followed by the addition of 187 mg (1.53 mmol) of 4-(dimethylamino)pyridine (DMAP). The solution was cooled to 0 °C, and 3.49 g (34.2 mmol) of acetic anhydride was added dropwise. After the addition the mixture was warmed to 25 °C and stirred for 40 min. The solution was poured onto ice water and was successively extracted with Et_2O, washed with 5% aqueous HCl and 5% aqueous $NaHCO_3$, and worked up. The residue was dissolved in 400 mL of CH_2Cl_2 and was heated at reflux for 18 h. The cooled solution was washed with water and worked up to give 2.96 g of crude acetates. The acetates were dissolved in 20 mL of Et_2O and added dropwise at 0 °C to 1.21 g (31.9 mmol) of $LiAlH_4$ in 140 mL of Et_2O followed by warming to 25 °C and stirring for 18 h. Successive dropwise addition of 1.2 mL of H_2O, 1.2 mL of 15% NaOH, and 1.2 mL of H_2O and workup gave 2.68 g of oil. Chromatography (50% Et_2O/hexane) and Kugelrohr distillation (140 °C, 0.25 mm) afforded 2.00 g (84%) of diol **37b**: IR (CCl_4) 3400 cm^{-1}; ^1H NMR (250 MHz) δ 0.91 (3 H, d, J = 7.0 Hz), 1.00 (6 H, d, J = 6.7 Hz), 1.02 (3 H, d, J = 6.9 Hz), 1.88 (1 H, m, C_2-H), 2.17 (1 H, OH), 2.99 (1 H, m, C_4-H), 2.41 (1 H, m, C_7-H), 2.92 (1 H, OH), 3.46 (1 H, m, C_3-H), 3.70 (2 H, m, C_1-H), 5.38 (1 H, dd, J = 16.1, 5.8 Hz), 5.52 (1 H, dd, J = 16.1, 9.3 Hz); $[\alpha]_D$ +1.38° (c 6.7, $CHCl_3$). Anal. ($C_{11}H_{22}O_2$) C, H.

2(*R*),4(*S*),7-Trimethyl-5(*E*)-octene-1,3(*S*)-diol (42). Via the above procedure, 750 mg of lactone **16b** was converted into diol **42** in 81% yield: IR ($CHCl_3$) 3500, 3620 cm^{-1}; ^1H NMR (250 MHz) δ 0.96 (3 H, d, J = 7.1 Hz), 1.01 (6 H, d, J = 8.0 Hz), 1.04 (3 H, d, J = 6.9 Hz), 1.80 (1 H, m), 2.34 (2 H, m), 3.33 (1 H, t, J = 6.0 Hz), 3.62 (1 H, dd, J = 9.8, 6.7 Hz), 3.78 (1 H, dd, J = 9.7, 3.2 Hz), 5.33 (1 H, dd, J = 15.0, 8.2 Hz), 5.50 (1 H, dd, J = 9.0, 5.7 Hz); $[\alpha]_D$ −27.0° (c 1.6, $CHCl_3$); MS (LRMS, CI), m/e $(M + 1)^+$ 187, $(M + NH_4^+)$ 204.

4(*R*)-(1(*S*),4-Dimethyl-2(*E*)-pentenyl)-2,2,5(*S*)-trimethyl-1,3-dioxane. Acetonide of Diol 37b. A solution of 120 mg (0.64 mmol) of diol **37b**, 3 mL of 2,2-dimethoxypropane, and 2 mg of *p*-TsOH·H_2O was stirred at 25 °C for 18 h. The solution was diluted with Et_2O, washed with aqueous $NaHCO_3$, and worked up. Chromatography (10% Et_2O/hexane) gave 131 mg (90%) of the acetonide: ^1H NMR (250 MHz) δ 0.75 (3 H, d, J = 6.7 Hz), 0.97 (9 H, d, J = 6.8 Hz), 1.37 (3 H, s), 1.39 (3 H, s), 1.82 (1 H, m), 2.28 (2 H, m), 3.39 (1 H, dd, J = 10.1, 3.2 Hz), 3.47 (1 H, t), 3.69 (1 H, dd, J = 11.4, 5.1 Hz), 5.41 (2 H, m); $[\alpha]_D$ +41.9° (c 1.3, $CHCl_3$). Anal. ($C_{14}H_{26}O_2$) C, H.

4(*S*)-Methyl-5(*R*)-[1(*S*)-methyl-2-[(*tert*-butyldiphenylsilyl)oxy]-ethyl]-dihydro-2(3*H*)-furanone (38). A solution of the acetonide of diol **37b** (3.0 g, 13.3 mmol) in 100 mL of MeOH was ozonized at −78 °C until the blue color persisted for 3 min. After concentration, the residue was dissolved in 20 mL of Et_2O at 0 °C and was cannulated into a 0 °C solution of 714 mg (19 mmol) of $LiAlH_4$ in 45 mL of Et_2O. After the mixture had been stirred for 6 h at 25 °C, it was decomposed (vide supra), dried over anhydrous $MgSO_4$, filtered through Celite, and concentrated to give 3.23 g of crude hydroxy acetonide (contaminated with isobutyl alcohol): ^1H NMR (250 MHz, partial) δ 0.73 (3 H, d, J = 6.7 Hz), 1.01 (3 H, d, J = 7.1 Hz), 1.38 (3 H, s), 1.46 (3 H, s). The crude alcohol in 66 mL of pyridine was treated at 0 °C with 6.55 g (34.4 mmol) of *p*-toluenesulfonyl chloride. The solution was stirred for 18 h at 25 °C, diluted with Et_2O, washed to acidity with ice-cold 1% aqueous HCl, backwashed with aqueous $NaHCO_3$, and worked up to give 5.2 g of crude tosylate: ^1H NMR (250 MHz, partial) δ 0.65 (3 H, d, J = 6.7 Hz), 0.82 (3 H, d, J = 7.0 Hz), 1.25 (3 H, s), 1.30 (3 H, s), 2.43 (3 H, s). The crude tosylate in 50 mL of DMSO containing 2.6 g (53.2 mmol) of NaCN was heated at 90 °C for 4.5 h. The cooled solution was diluted with water, extracted with Et_2O, and worked up to provide 2.6 g of crude nitrile: IR (CCl_4) 2253 cm^{-1}; ^1H NMR (250 MHz) δ 0.75 (3 H, d, J = 6.7 Hz), 1.01 (3 H, d, J = 6.5 Hz), 1.37 (3 H, s), 1.45 (3 H, s), 1.86 (1 H, m), 2.17 (1 H, m), 2.38 (2 H, m), 3.53 (1 H, t, J = 11.3 Hz), 3.62 (1 H, dd, J = 10.2, 2.3 Hz), 3.72 (1 H, dd, J = 11.5, 5.1 Hz). The crude nitrile in 60 mL of MeOH containing 3.6 mL of concentrated HCl was heated for 18 h at 65 °C. The cooled solution was diluted with water, extracted with Et_2O, and worked up to give 1.9 g of crude hydroxy lactone: ^1H NMR (250 MHz) δ 0.95 (3 H, d, J = 6.9 Hz), 1.02 (3 H, d, J = 7.0 Hz), 2.22 (1 H, d, J = 17.0 Hz), 2.75 (1 H, dd, J = 17.0, 7.3 Hz), 3.73 (2 H, m) 4.23 (1 H, dd, J = 10.8, 4.6 Hz). To a solution of the hydroxy lactone and 1.79 g (26.4 mmol) of imidazole in 58 mL of DMF was added 3.63 g (13.3 mmol) of *tert*-butyldiphenylsilyl chloride. The mixture was stirred at 25 °C for 18 h, diluted with Et_2O, washed to acidity with 5% aqueous HCl, back-washed with aqueous $NaHCO_3$, and worked up. Chromatography (25% Et_2O/hexane) gave 3.3 g (63% from **37b**) of lactone **38**: IR (CCl_4) 1786 cm^{-1}; ^1H NMR (250 MHz) δ 0.98 (3 H, d, J = 7.5 Hz), 1.03 (3 H, d, J = 7.5 Hz), 1.07 (s, 9 H), 1.90 (1 H, m, C_4-H), 2.21 (1 H, d, J = 16.8 Hz, C_3-H), 2.56 (1 H, m, C_1-H), 2.76 (1 H, dd, J = 16.8 Hz, C_3-H), 3.80 (2 H, m, C_1), 4.30 (1 H, dd, J = 10.0, 4.5 Hz, C_5-H), 7.41 (6 H, m), 7.67 (4 H, m); $[\alpha]_D$ −34.3° (c 1.0, $CHCl_3$). Anal. ($C_{24}H_{32}O_3Si$) C, H.

4(*S*)-Methyl-5(*S*)-[1(*S*)-methyl-2-(benzyloxy)ethyl]dihydro-2-(3*H*)-furanone (40). Ozonolysis and $LiAlH_4$ reduction of 947 mg (4.2 mmol) (vide supra) of the acetonide of diol **37b** provided 909 mg of crude hydroxy acetonide contaminated with isobutyl alcohol. The crude alcohols in 75 mL of THF containing 426 mg (10.7 mmol, 60% dispersion) of NaH was heated at reflux for 4 h. The solution was cooled to 25 °C, 2.10 g (12.3 mmol) of benzyl bromide was added dropwise, and the mixture was stirred for 40 h. The mixture was poured into water, extracted with Et_2O, and worked up. Chromatography (10% Et_2O/hexane) gave 1.19 g of the benzyl ethers of both alcohols. The mixture was dissolved in 25 mL of THF containing 1 mL of water and 30 mg of *p*-TsOH·H_2O and was stirred at 25 °C for 45 h, during which time two additional portions of acid were added. The solution was diluted with Et_2O, washed with aqueous $NaHCO_3$ to neutrality, and worked up. Chromatography (50% Et_2O/hexane) gave 805 mg of diol in addition to 130 mg of recovered acetonide. The crude diol was dissolved in 15 mL of pyridine and cooled to 0 °C as 972 mg (5.1 mmol) of *p*-toluenesulfonyl chloride was added. The mixture was stirred at 25 °C for 18 h followed by dilution with Et_2O. The organic phase was washed successively with 1% aqueous HCl and saturated aqueous $NaHCO_3$ and worked up to give 1.30 g of crude tosylate. The tosylate (3.3 mmol) was dissolved in 50 mL of DMSO containing 820 mg (16.6 mmol) of NaCN and heated at 90 °C for 20 h. The mixture was diluted with water, extracted with pentane and worked up to afford 800 mg of crude nitrile. The crude

nitrile in 25 mL of MeOH containing 1 mL of concentrated hydrochloric acid was heated at reflux for 48 h. The cooled solution was diluted with water, thoroughly extracted with Et_2O, and worked up. Chromatography (15% Et_2O/hexane) and distillation (Kugelrohr, 145 °C, 0.1 mm) gave 510 mg (49%) of lactone **40**: IR ($CHCl_3$) 1783 cm^{-1}; ^1H NMR (250 MHz) δ 0.96 (3 H, d, J = 7.0 Hz), 1.14 (3 H, d, J = 6.6 Hz), 2.06 (1 H, m), 2.20 (1 H, dd, J = 17.0, 9.1 Hz, C_2-H), 2.44 (1 H, m), 2.69 (1 H, dd, J = 17.0, 8.3 Hz, C_2-H), 3.47 (2 H, m, $C_{2'}$-H), 4.27 (1 H, dd, J = 7.6, 3.4 Hz, C_5-H), 4.50 (1 H, d, J = 12.0 Hz, $PhCH_2$), 4.55 (1 H, d, J = 12.0 Hz, $PhCH_2$), 7.40 (5 H, m); $[\alpha]_D$ +46.9° (c 1.7, $CHCl_3$). Anal. ($C_{15}H_{20}O_3$) C, H.

4(*R*)-Methyl-5(*R*)-(1(*S*),4-dimethyl-2(*E*)-pentenyl)dihydro-2(3*H*)-furanone (43). Via the homologation technique described above, 990 mg (4.8 mmol) of diol **42** was converted into lactone **43** in 81% yield: IR ($CHCl_3$) 1765 cm^{-1}; ^1H NMR (250 MHz) δ 0.97 (6 H, d, J = 6.7 Hz), 1.11 (3 H, d, J = 6.6 Hz), 1.12 (3 H, d, J = 7.0 Hz), 2.14 (1 H, dd, J = 17.2, 8.2 Hz), 2.35 (3 H, m), 2.64 (1 H, dd, J = 17.2, 8.5 Hz), 3.98 (1 H, dd, J = 6.9, 3.4 Hz), 5.26 (1 H, dd, J = 15.5, 8.3 Hz), 5.48 (1 H, dd, J = 15.5, 6.5 Hz); $[\alpha]_D$ -20.4° (c 2.4, $CHCl_3$). Anal. ($C_{12}H_{20}O_2$) C, H.

3(*R*)-Carbomethoxy-4(*R*)-methyldihydro-2(3*H*)-furanone (1b). To a solution of 1.22 g (12.0 mmol) of diisopropylamine in 25 mL of THF at -10 °C was added 7.8 mL (1.54 M in hexane, 12.0 mmol) of n-butyllithium by using syringe techniques. After the solution had been stirred for 45 min, it was cooled to -78 °C. A solution of 600 mg (6.0 mmol) of R lactone **1** in 3 mL of THF was added dropwise followed by stirring of the reaction mixture for 1.5 h. The mixture was treated with 1.96 g (12.0 mmol) of HMPA followed by 1.02 g (12.0 mmol) of methyl cyanoformate and then stirred at -78 °C for 3 h. Dilution of the reaction mixture with brine, extraction with $CHCl_3$, workup, chromatography (50% Et_2O/hexane), and crystallization (Et_2O/pentane) gave 868 mg (91%) of lactonic ester **1b**: mp 46 °C; IR ($CHCl_3$) 1739, 1780 cm^{-1}; ^1H NMR (250 MHz) δ 1.21 (3 H, d, J = 6.6 Hz), 3.05 (1 H, m), 3.21 (1 H, d, J = 9.0 Hz), 3.83 (3 H, s), 3.86 (1 H, m), 4.52 (1 H, dd, J = 8.5, 7.0 Hz). The enantiomer provided the following data: $[\alpha]_D$ -44.1° (c 2.6, $CHCl_3$). Anal. ($C_7H_{10}O_4$) C, H.

Diethyl 2-Methyl-4(*E*)-hexen-3(*R*)-yl Phosphate (49a). To a 0 °C solution of 500 mg (4.4 mmol) of (*R*)-2-methyl-4-hexen-3-ol (**14b**) in 10 mL of Et_2O was added dropwise via syringe 1.77 mL (2.6 M/hexane, 4.6 mmol) of n-butyllithium. After the solution had been stirred for 1 h, 794 mg (4.6 mmol) of diethyl phosphorochloridate was added dropwise. The solution was stirred for 45 min at 0 °C and for 3 h at 25 °C, poured into water, and worked up. Distillation (Kugelrohr, 100 °C, 0.5 mm) provided the phosphate in quantitative yield: IR (CCl_4) 1260, 1034 cm^{-1}; ^1H NMR (250 MHz) δ 0.91 (3 H, d, J = 7.3 Hz), 0.93 (3 H, d, J = 7.7 Hz), 1.31 (6 H, m), 1.72 (3 H, dd, J = 6.3, 1.0 Hz), 1.88 (1 H, m), 4.07 (4 H, m), 4.46 (1 H, q, J = 7.2 Hz), 5.46 (1 H, dd, J = 15.3, 8.3 Hz), 5.76 (1 H, m).

Alkylation of Lactonic Ester 1b with Allylic Phosphate 49a. To a solution of 40 mg (0.26 mmol) of lactonic ester **1b** in 2 mL of THF was added 10.4 mg (0.26 mmol, 60% suspension) of NaH at 25 °C. After the mixture had been stirred for 1.5 h, 30.4 mg (0.026 mmol) of $(Ph_3P)_4Pd(0)$ and 7 mg (0.026 mmol) of Ph_3P were added followed by 128 mg (0.52 mmol) of phosphate **49a** in 0.5 mL of THF. After the mixture had been stirred for 2 h, it was diluted with water, extracted with ether, and worked up to give the crude alkylation product: ^1H NMR (250 MHz, partial for the major diastereomer) δ 0.97 (6 H, d, J = 7.0 Hz), 1.05 (3 H, d, J = 7.0 Hz), 1.24 (3 H, d, J = 7.0 Hz), 3.75 (3 H, s), 5.48 (1 H, dd, J = 15.0, 6.3 Hz), 5.59 (1 H, dd, J = 15.0, 6.3 Hz). The crude material was dissolved in 0.7 mL of DMSO containing 5 μL of water and 22.0 mg (0.52 mmol) of LiCl. The mixture was heated to 190 °C for 3 h followed by cooling to room temperature, dilution with water, extraction with ether, and workup. Distillation (Kugelrohr, 1 mm) of all material boiling below 200 °C gave 75 mg of distillate. Capillary GC analysis (method B) showed lactone *ent*-**16b** (C_t, t_R 16.8 min, 3.4%), *ent*-**26b** (B_t, t_R 17.2 min, 79.3%), *ent*-**22b** (B_c, t_R 16.4 min, 0.9%), and *ent*-**28b** (C_c, t_R 22.8 min, 16.4%).

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Applications of the 3-Methyl-γ-butyrolactone Strategy to the Synthesis of Polypropionates: The Prelog–Djerassi Lactonic Ester, *ent*-Invictolide, and the C_{19}–C_{27} Fragment of Rifamycin S[1]

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Abstract: Applications of the 3-methyl-γ-butyrolactone strategy for the synthesis of polypropionates are discussed. The preferred mode of hemiacetalization upon ozonolysis of bis(olefin) **8c** was determined by conversion of the products to the methyl ester of the Prelog–Djerassi lactone acid **1**. Similarly, lactone **2**, the enantiomer of invictolide, was prepared as a proof of the absolute stereochemistry of the pheromone. The bis(acetonide) **3**, an intermediate in the synthesis of the antibiotic rifamycin S, was synthesized. The transformation of lactones into β-hydroxy ketones and the thermodynamic stability of lactone intermediates are discussed.

In the preceding paper,[2] the basic strategy for the synthesis of enantiomerically pure polypropionate starter units from 3-methyl-γ-butyrolactone was discussed. In this paper, the details of the applicability of this approach to the synthesis of the Prelog–Djerassi lactonic ester **1**; lactone **2**, the enantiomer of the pheromone invictolide; and the C_{19}–C_{27} fragment **3** of the macrolide antibiotic rifamycin S, are discussed.

Our first task was to investigate the palladium-mediated alkylation of transposed lactone **4a**.[3,4] Carbomethoxylation of

(1) Taken in part from the Ph.D. theses of R.T.W. (Yale, 1986) and A.K. (Yale, 1987).

(2) Ziegler, F. E.; Kneisley, A.; Thottathil, J. K.; Wester, R. T. *J. Am. Chem. Soc.*, preceding paper in this issue.

(3) All structures are the enantiomers shown, unless designated otherwise.

(4) For a preliminary account, see: Ziegler, F. E.; Wester, R. T. *Tetrahedron Lett.* **1986**, *27*, 1225.

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