Designed Chiral Acyl Radical Equivalents. Preparation and Cyclizations of Disymmetrically Substituted 1,3-Dioxabicyclo[4.4.0]decan-2-yl Radicals

D. Stien,[†,‡] R. Samy,[‡] R. Nouguier,[‡] D. Crich,*[,‡] and M. P. Bertrand*[,†]

LCMO, Associé au CNRS, Faculté des Sciences Saint-Jérôme, Av. Normandie-Niemen, 13397 Marseille Cedex 20, France, and Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061

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The diastereoselectivity of 5-*exo-trigonal* cyclizations of 2-(4-penten-1-yl)-1,3-dioxolan-2-yl and 2-(4-penten-1-yl)-1,3-dioxan-2-yl radicals is investigated. When dioxolanes or dioxanes derived from C_2 symmetrically substituted diols are employed the diastereoselectivity is poor. In the dioxanyl series this is a consequence of the cyclization occurring through a twist-boat conformer. Disymmetrically substituted dioxanyl radicals, derived from the alcohols **21** and **41**, are, however, constrained to chairlike conformations and accordingly give rise to highly diastereoselective cyclizations. Conditions are described for the hydrolysis of the resulting spiroacetals and for determination of the ee of the resulting 2-methylcyclopentanones.

Introduction

Stereoselective radical reactions have been vigorously pursued over the last decade. Many successful enantioselective radical additions and cyclizations have now been performed *via* the temporary incorporation of a chiral auxiliary.[1,2] Recent demonstrations of the compatibility of Lewis acids with certain types of radical reactions suggest that further progress in radical stereoselectivity is to be anticipated; indeed, examples of the successful use of designed Lewis acids in the promotion of diastereoselective radical reactions have already been documented.[3] For a number of years we have been interested in the development of acyl radicals and their application in synthesis.[4] A logical extrapolation is the design of chiral acyl radical equivalents. In this context, we describe in detail here our studies of the cyclizations of chirally substituted 1,3-dioxolan-2-yl and 1,3-dioxan-2-yl radicals.[5]

Results and Discussion

The obvious starting point for this investigation was the examination of the 5-*exo-trig* cyclizations of C_2-symmetric 1,3-dioxan-2-yl radicals.[6] Such α,α-dialkoxy radicals may be generated for addition to CC multiple bonds by a variety of pathways.[7] Hydrogen atom abstraction from acetals by *t*-BuO• radicals,[7a] or by excited states of benzophenone,[7b] is reported to give preparatively useful yields in intermolecular additions but was less successful when applied to the cyclizations of dioxolanyl and dioxanyl radicals.[7c] However, the generation of 1,3-dioxolan-2-yl and dioxan-2-yl radicals bearing an appropriate ethylenic tether can readily be achieved via intramolecular hydrogen atom abstraction with vinyl radicals, as established by Curran,[7d,e] and this was the strategy adopted in this study. The various substrates (**3**) were readily obtained through standard malonate and acetalization techniques (Scheme 1).

5-*exo* Cyclizations of 1,3-Dioxolan-2-yl Radicals. Three substrates (**3a**−**c**) were prepared from readily available C_2-symmetric 1,2-diols. These (0.05 M) were then subjected to cyclization under a standard set of experimental conditions involving the *in situ* generation of Bu_3SnH by reduction of Bu_3SnCl (0.005 M) with $NaBH_3CN$ in 2-methyl-2-propanol,[8] at 80 °C in the presence of AIBN. After completion, the crude reaction mixtures were filtered on silica gel to remove stannyl residues. The spirocyclic products **4** and **5** were thus obtained in admixture with the comigrating reduction product **6**. After ozonolysis,[7e] or treatment with catalytic

[†] LCMO.
[‡] University of Illinois at Chicago.
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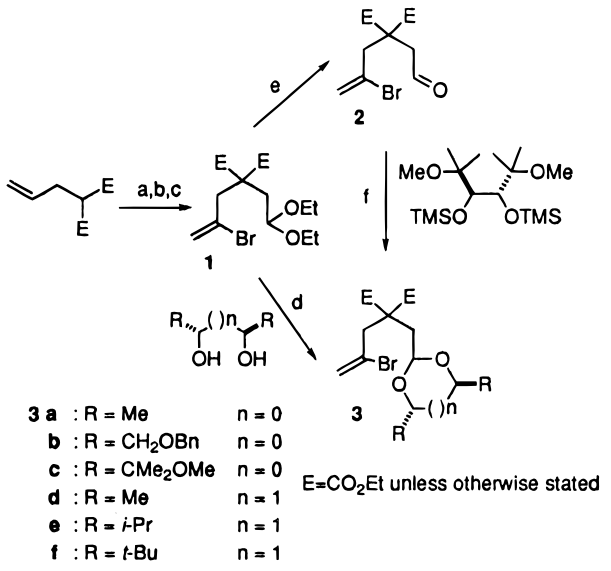
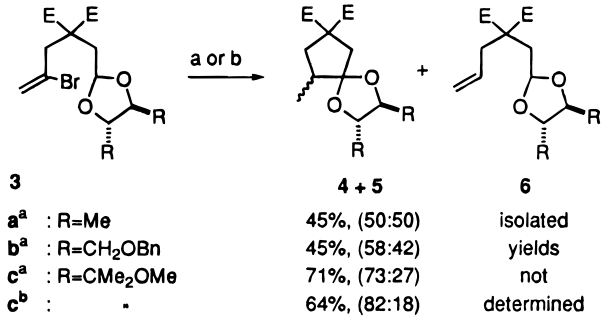
Scheme 1[a]



[a] Key: (a) O_3, Me_2S; (b) $HC(OEt)_3$, TsOH; (c) NaH, $CH_2{=}C(Br)$-CH_2Br; (d) CSA, toluene, Δ; (e) H_2SO_4, SiO_2; (f) TMSOTf, −80 → 40 °C.

Scheme 2[a]



[a] Key: (a) Bu_3SnCl, $NaBH_3CN$, AIBN, *t*-BuOH, 80 °C; (b) Bu_3SnH, AIBN, benzene, *hν*, 20 °C.

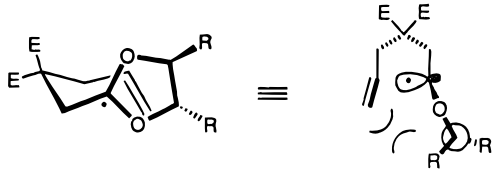


Figure 1.

$OsO_4/NaIO_4$, and subsequent chromatography, a mixture of **4** and **5** was obtained free of **6** and subjected to analysis by either capillary GC or ^{1}H NMR spectroscopy. As reported in Scheme 2, no stereoinduction was observed with either **3a** or **3b**, possibly because 1,3-dioxolanyl radicals are pyramidal,[9] which reduces steric interactions between the R group and the double bond in the assumed chairlike cyclization transition state (Figure 1).[10] Nevertheless, the use of a bulky, tertiary R group (**3c**) resulted in a 52% diastereomeric excess at 80 °C and 64% at 20 °C.

5-*exo* Cyclizations of 1,3-Dioxan-2-yl Radicals. The failure to induce high diastereoselectivity in the cyclization of 1,3-dioxolan-2-yl radicals led us to investigate C_2-symmetric 1,3-dioxan-2-yl radicals. Such sp^3-hybridized, σ-type species adopt a chairlike conformation with the unpaired spin axial.[11] In this they are closely analogous to the 1-alkoxy-1-glycopyranosyl radicals, which are trapped selectively from the axial direction.[12] On this basis we reasoned that 1,3-dioxan-2-yl radicals bearing an appropriate unsaturated chain at the radical center would react preferentially along the axial direction in 5-hexenyl cyclizations. Use of a C_2-symmetric system would result in only two diastereomeric transition states (Figure 2), one of which would be significantly disfavored on steric grounds. Racemic substrates **3d**−**f** were subjected to the standard cyclization, and workup, conditions leading to the results outlined in Scheme 3.

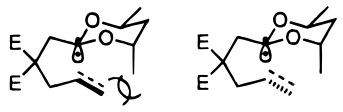
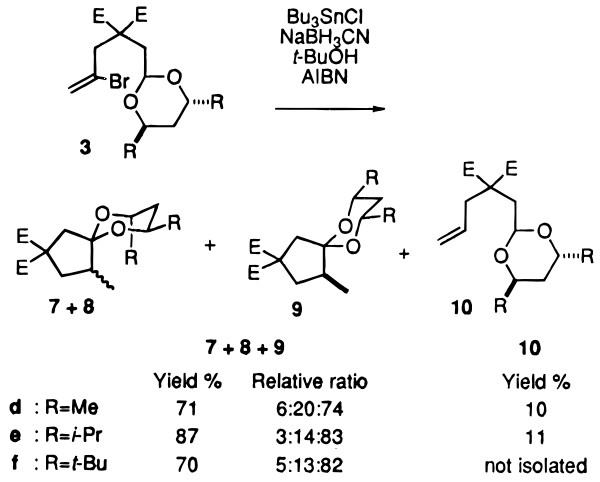


Figure 2.

Scheme 3



Apart from a few percent of the uncyclized reduction product **10**, these reactions each led to three spirocyclic diastereomers **7**−**9**. These could not be isolated separately; consequently, the ^{1}H NMR spectral and GC analyses were conducted on the mixture. From the NMR data it was clear that in each case the major component (**9**) of the mixture had undergone a structural modification in the acetal moiety. Thus, in the *trans*-dimethyldioxane series, as typified by **3d**, two distinct methyl doublets, reflecting their axial and equatorial nature, are present at δ 1.15 and 1.32. In contrast, in the *cis*-series, for example, **9d**, the equatorial nature of the two corresponding methyl groups is evident from the close similarities of their chemical shifts (δ 1.10 and 1.14). A parallel observation relates to the corresponding protons

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(10) Note, however, that boatlike transition structures lead to the same prediction for stereoinduction.

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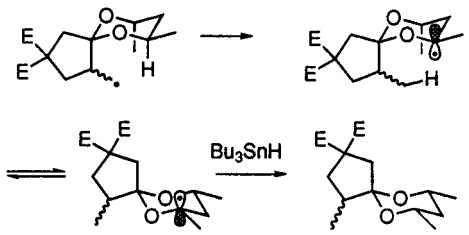
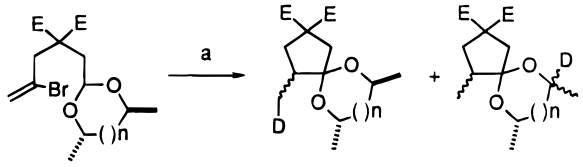
Scheme 4



Scheme 5[a]



3a : n=0	100	0
3d : n=1	20	80

[a] Key: (a) Bu_3SnCl, $NaBD_3CN$, AIBN, *t*-BuOH, 80 °C.

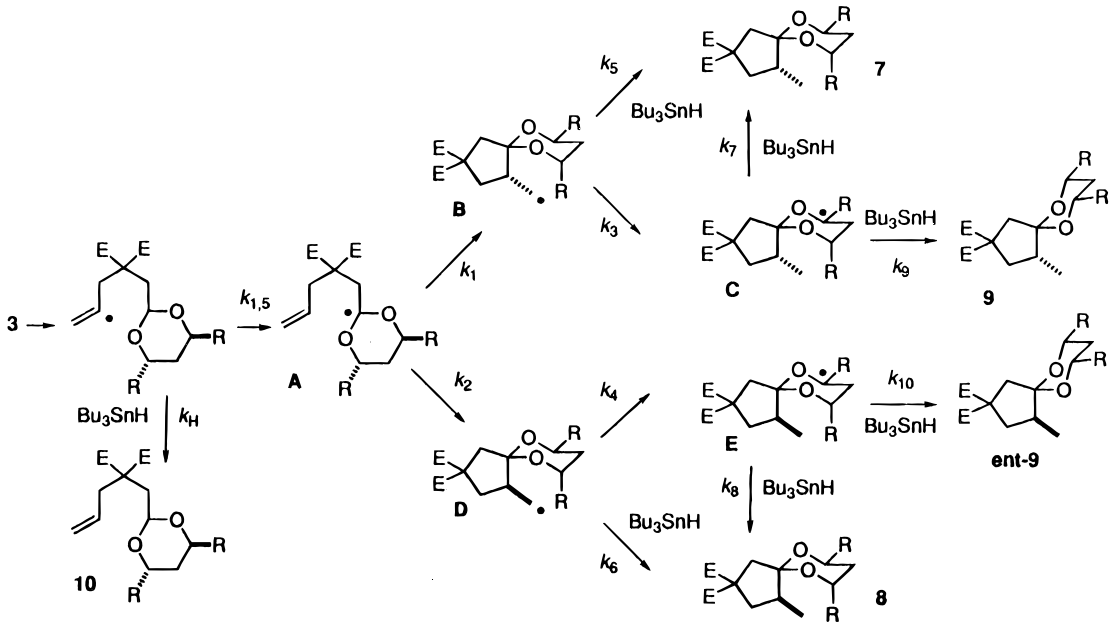
at positions 4 and 6 of the dioxanyl ring. In **3d** the axial proton is a doublet of doublet of quartet at δ 3.80 and the equatorial a multiplet at δ 4.08−4.27, whereas in **9d** the corresponding two protons are grouped in a single multiplet at δ 3.77−3.97. This result can only be explained by a radical translocation consecutive to the 5-*exo* cyclization (Scheme 4). To confirm this mechanism **3d** was cyclized with catalytic Bu_3SnCl and $NaBD_3CN$ as overall reductant. The ^2H NMR spectrum of the reduced products showed that 80% of the deuterium was attached to the carbon α to the oxygen and that only 20% of the product was deuterated at the cyclization terminus (Scheme 5).[13] Similar labeling experiments were conducted on the bromide **3a**, leading to the conclusion that no corresponding 1,5-hydrogen shift had occurred in the dioxolanyl series, once again bearing witness to the considerable susceptibility of 1,5-hydrogen atom abstractions to transition state geometry (Scheme 5).[12c,d]

These unanticipated results posed several new questions. As no separation of the diastereomeric products could be achieved, it was not possible to unambiguously identify **7** and **8**. Consequently, in a first-degree approach, for instance in the case of **3d**, the diastereoselectivity of the cyclization step could be either (6 + 74):20 = 80:20 or (20 + 74):6 = 94:6. Furthermore, in addition to this difficulty, it became obvious that a complete mechanistic scheme should take into account the possibility that both diastereoisomeric cyclopentylmethyl radicals (**B** and **D**) might rearrange according to Scheme 6. Indeed, there is evidence in the literature that radicals of types **B** and **D** can undergo 1,5-hydrogen shifts (Scheme 7).[14]

Although the rearrangement of **D** (Scheme 6) appeared less likely than that of **B** and, indeed, than that of the comparable, less strained [5.5]spirocyclic system in Scheme 7, it was necessary to check this hypothesis. If both **B** and **D** underwent 1,5-hydrogen transfer the chances of good stereoinduction in the optically pure series would be low since the ensuing radicals **C** and **E** would lead to enantiomeric forms of **9** (Scheme 6). Furthermore, since no separation of **9** and *ent*-**9** could be achieved on chiral phases,[15] a direct measure of the selectivity was impossible, even when starting from an enantiomerically pure substrate. To approach this problem a series of cyclizations were conducted at different concentrations of Bu_3SnH, based on the assumption that **B** but not **D** was subject to the second 1,5-hydrogen atom transfer. Thus, the cyclization selectivity (**7** + **9**):**8**, or (**8** + **9**):**7** in view of the uncertainty in the identity of **7** and **8**, should be independent of [Bu_3SnH] but the ratio of **7**:**9** (or **8**:**9**) should vary in a linear manner with [Bu_3SnH] so enabling a distinction to be made between **7** and **8**. In the event (Table 1), the data were ambiguous, suggesting that both **B** and **D** underwent intramolecular hydrogen atom abstractions. Nevertheless, examination of molecular models suggested that radical **B** should undergo 1,5-hydrogen transfer much more rapidly than **D**, even if the six-membered ring were to adopt a boat conformation.

Finally, the cyclization stereoselectivity was deduced with the aid of a full kinetic analysis of the system. Assuming the concentrations of all the radical species in the medium to be stationary, the following equations giving the ratios [**7**] + [**8**] + [**9**]/[**7**] and [**7**] + [**8**] + [**9**]/[**8**] can be derived (Figure 3). Given the reasonable assump-

Scheme 6



Scheme 7

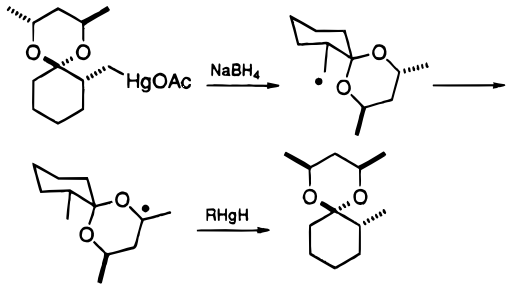


Table 1. Reduction of 3d at Different Tin Hydride Concentrations

$[Bu_3SnH] \times 10^3$ (M)	product ratio				(7d + 9d)/8d	(8d + 9d)/7d
	7d	8d	9d	10d		
5.4	5.8	18	61.7	14.5	3.75	13.74
13.0	9.9	21.1	40.1	28.9	2.37	6.18
15.6	10.7	20.9	35.7	32.7	2.22	5.29
19.4	11.3	20.2	30.8	37.7	2.08	4.51
38.9	12.8	16.2	16.2	54.8	1.79	2.53
45.4	11.8	14.9	14.7	58.6	1.78	2.51

tion that $k_7 \ll k_9$ and, symmetrically, that $k_8 \ll k_{10}$[14,16] the two ratios should depend linearly on $1/[Bu_3SnH]$.

In the event both relationships held, so justifying the above hypothesis and enabling the assignment of **7** and **8**. Graphical and mathematical resolution of the data (Supporting Information) led to the ratio $k_1/k_2 = 1.3$ for the cyclization of **3d**. This selectivity was even lower than that previously obtained with 1,3-dioxolan-2-yl radicals in the case of **3c**.

Attempts to slow down the rearrangements of radicals **B** and **D** by taking advantage of the primary kinetic isotopic effect were carried out with acetals derived from (±)-2,4-dideuterio-2,4-pentanediol and from (±)-3,5-dideuterio-2,2,6,6-tetramethyl-3,5-heptanediol.[17] Unfortunately, no significant modification in the distribution of the products was observed.

In a further series of experiments substrates **11**, designed with a view to eliminating the problematic 1,5-hydrogen transfer by benzylic stabilization of the cyclized radical, were prepared by standard methods. When these substrates were subjected to the standard cyclization conditions isomerization of the auxiliary was avoided, but the diastereoselectivities were disappointingly low (Scheme 8). Additional complications are introduced with the use of a nonterminal vinyl bromide as in **11a,b** owing to the uncertain nature of the alkene geometry in the crucial

$$[7]+[8]+[9]/[7] = \frac{k_1+k_2}{k_1} \times \frac{k_3 + k_5[Bu_3SnH]}{\frac{k_3k_7}{k_7+k_9} + k_5[Bu_3SnH]}$$

$$\text{if } k_7 \ll k_9 \Downarrow$$

$$[7]+[8]+[9]/[7] = \frac{k_1+k_2}{k_1} + \frac{(k_1+k_2)k_3}{k_1k_5} \times \frac{1}{[Bu_3SnH]}$$

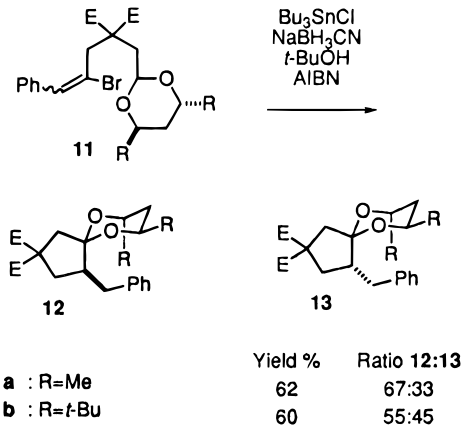
$$[7]+[8]+[9]/[8] = \frac{k_1+k_2}{k_2} \times \frac{k_4 + k_6[Bu_3SnH]}{\frac{k_4k_8}{k_8+k_{10}} + k_6[Bu_3SnH]}$$

$$\text{if } k_8 \ll k_{10} \Downarrow$$

$$[7]+[8]+[9]/[8] = \frac{k_1+k_2}{k_2} + \frac{(k_1+k_2)k_4}{k_2k_6} \times \frac{1}{[Bu_3SnH]}$$

Figure 3.

Scheme 8



cyclization reaction. Simple, unconjugated, vinyl radicals are sp^2-hybridized with the single electron in an sp^2-hybrid (σ-like) orbital. They exist as mixtures of two geometric isomers that interconvert via a low barrier.[18] If this inversion occurs more rapidly than the 1,5-hydrogen atom abstraction, the geometry of the alkene must arise from a balancing of steric interactions between the vinyl radical substituents and the chiral auxiliary. Examination of molecular models leads to the conclusion that for the vinyl radicals derived from **11a,b**, 1,5-hydrogen atom abstraction will lead preferentially to the *cis*-alkene (Scheme 9).[19,20] However, it is likely that this selectivity will not be complete and that mixtures of (*E*)- and (*Z*)-alkenes will be generated.

(13) (a) The deuteration is only partial under these experimental conditions since deuterium and hydrogen can exchange between *t*-BuOH and $NaBD_3CN$; see: Kreevoy, M. M.; Hutchins, J. E. C. *J. Am. Chem. Soc.* **1969**, *91*, 4329. (b) Two broad singlets were registered in the 2D spectrum at 3.69 and 0.98 ppm, respectively (4:1 relative integration).

(14) (a) Sugimura, T.; Goto, S.-I.; Koguro, K.; Futagawa, T.; Misaki, S.; Morimoto, Y.; Yasuoka, N.; Tai, A. *Tetrahedron Lett.* **1993**, *34*, 505. (b) Sugimura, T.; Tai, A.; Koguro, K. *Tetrahedron* **1994**, *50*, 11647.

(15) Attempts to achieve the separation of **9** and *ent*-**9** by GC on FS-hydrodex β-PM or FS-Lipodex A (Macherey Nagel) and by HPLC on Chiracel ODH (Daicel) were unsuccessful.

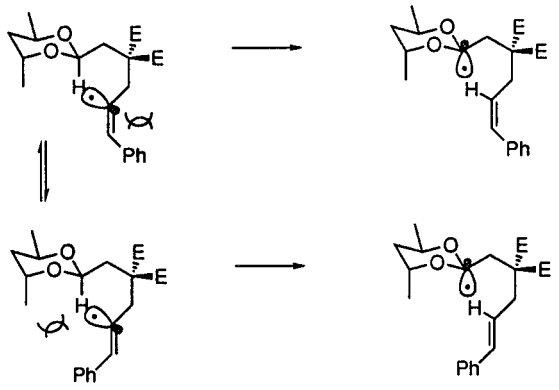
(16) For examples of selective axial trapping of closely related radicals see: (a) Rychnovsky, S. D.; Skalitzky, D. J. *Synlett* **1995**, 555. (b) Rychnovsky, S. D.; Plzak, K.; Pickering, D. *Tetrahedron Lett.* **1994**, *35*, 6799. (c) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969.

(17) For the use of primary isotope effects to retard 1,5- and even intermolecular hydrogen atom abstractions see: (a) Clive, D. L. J.; Cantin, M.; Khodabocus, A.; Kong, X.; Tao, Y. *Tetrahedron* **1993**, *49*, 7917. (b) Warth, J. L.; Frank, B. L.; Christner, D. F.; Absalon, M. J.; Stubbe, J.; Kozarich, J. W. *Biochemistry* **1993**, *32*, 2601. (c) Sugiyama, H.; Fujimoto, K.; Saito, I.; Kawashima, E.; Sekine, T.; Ishido, Y. *Tetrahedron Lett.* **1996**, *37*, 1805.

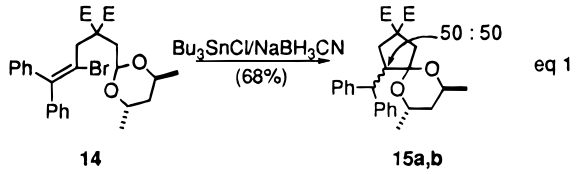
(18) For a compilation of ESR spectroscopic data for vinyl radicals see: Neugebauer, F. A. in *Lanholt−Bornstein New Series*; Fischer, H., Ed.; Springer-Verlag: Berlin, 1989; Vol. 17b, p 492. Also see: Simamura, O. *Top. Stereochem.* **1969**, *4*, 1.

(19) A kinetically equivalent scheme applies to more conjugated π-type vinyl radicals such as the α-phenylvinyl system, which adopts a linear geometry with the single electron in an sp-hybrid (π-like) orbital with maximum stabilization from overlap with the conjugated moiety. Stereoselectivity is again determined by steric factors at the transition state for quenching.

Scheme 9



A further cyclization was also conducted with a view to probing the effect of a trisubstituted alkenes on the selectivity of cyclization (eq 1), but no measureable selectivity was observed.



14 **15a,b**

Consideration of Schemes 8 and 9 and eq 1 reveals that cyclization onto *cis*-styrenes is somewhat less selective than that to terminal alkenes and that any *trans*-substituent on the alkene completely eliminates selectivity.[21] We were thus led to the conclusion that the lack of stereoselectivity in the entire dioxanyl series originates from the ability of the dioxane ring to adopt a twist-boat conformation of type **H** (Figure 4) in which 1,3-diaxial-type interactions between the developing bond and the axial R group in either of the chairs **F** and **G** are avoided.[22] We therefore focused our attention on imposing a chairlike conformation on the dioxanyl radical throughout the course of the cyclization. On the grounds that the rigid *trans*-fused bicyclic system would reduce the incidence of boat and/or twist-boat conformers, *trans*-1,3-dioxabicyclo[4.4.0]decan-2-yl transition states **I** were targeted (Figure 4).

In **I** the substituent R is the primary stereodirecting group and R″ a group intended to further disfavor boat and twist-boat conformers. The group R′ (= R) was originally intended simply to be an artifact of the synthesis enabling ready preparation of the tertiary alcohol by Grignard reaction with an ester. However, subsequent computational studies reveal it to play a major role in destabilizing twist boats. Thus, with the

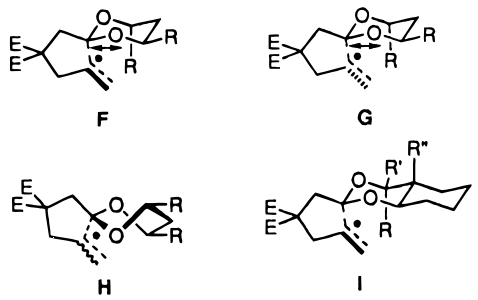


Figure 4.

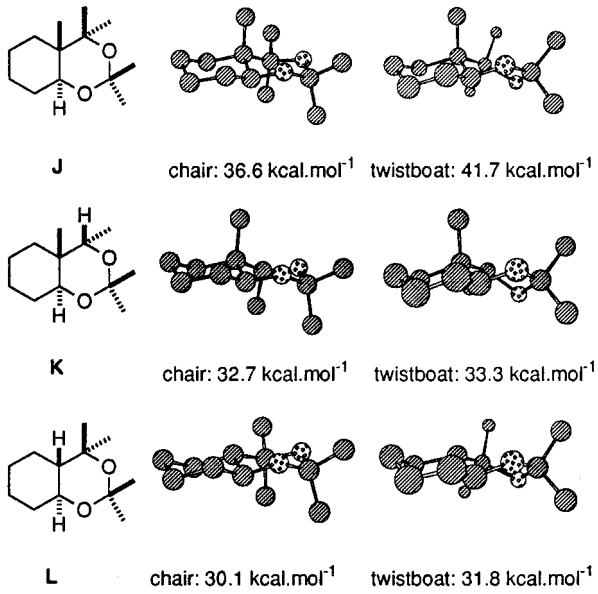


Figure 5.

aid of the MM2 force field within the Chem3D Pro program, we have modeled chair and twist-boat conformers for the series of dioxanes **J**−**L** (Figure 5). In the fully methylated series (**J**) the chair is found to be some 5 kcal·mol^{-1} lower in energy than the twist boat. Removal of the "equatorial" methyl group (**K**, ≡ **I**, R′ = H) puts the chair and twist-boat conformers within a 1 kcal·mol^{-1} range. In the absence of the angular methyl group (**L**, ≡ **I**, R″ = H) the chair conformation is only 1.7 kcal·mol^{-1} lower in energy than the twist boat. Thus, the combined importance of the "equatorial" and angular methyl groups in imposing the chair conformation on **J** is readily appreciated. Although we have not attempted to model transition states for the cyclizations, it seems reasonable to expect a similar influence of R′ and R″ on the conformation of the dioxanyl radical.

The racemic diol **21** was prepared as illustrated in Scheme 10. Thus, β-keto ester **16** was transformed through alkylation and subsequent reduction with LAH into diol **18**, the relative configuration of which had been determined by X-ray crystallography.[23] Two consecutive oxidation steps[24] led to ester **20**, which was converted into **21** by treatment with MeMgI (Scheme 10). Commercial[25] (−)-*trans*-*p*-menthane-3,8-diol (**22**)[26] was selected to probe the importance of the angular methyl group.

(20) In principle, this question may be addressed through the use of higher stannane concentrations such that, following 1,5-hydrogen atom abstraction, the dioxanyl radical is trapped by the stannane rather than by cyclization. In practice, such an approach is likely to result simply in the quenching of the vinyl radical by the stannane. Such experiments were therefore not attempted.

(21) For substrates **11a,b**, **14**, **21**, **39**, and **45** there is also the possibility that, due to benzylic stabilization of the cyclized radicals rendering the cyclization more exothermic, the earlier transition state with its longer developing bond results in a reduction in energy differential between chairs **F** and **G**. We thank Professor P. J. Garner, Case Western Reserve University, for this insight; see ref 2b,c.

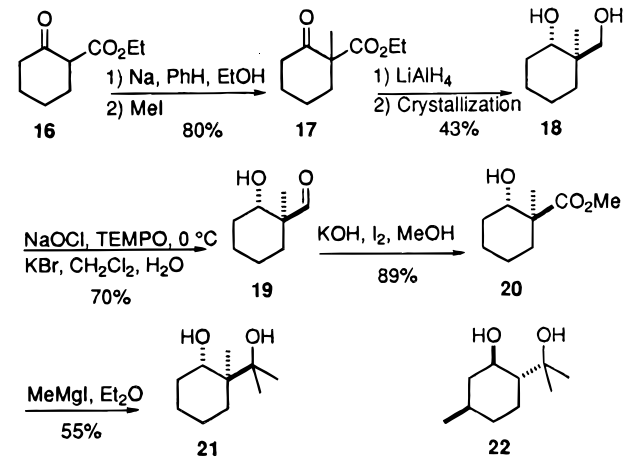
(22) *trans*-4,6-Disubstituted-2,2-dimethyl-1,3-dioxanes adopt twist-boat conformations: (a) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511. (b) Rychnovsky, S. D.; Yang, G.; Powers, J. P. *J. Org. Chem.* **1993**, *58*, 5251. (c) For conformational analysis of 1,3-dioxanes: Antenuis, M. J. O.; Tavernier, D.; Borremans, F. *Heterocycles* **1976**, *4*, 293.

(23) Smith, W. B. *J. Org. Chem.* **1979**, *44*, 1631.

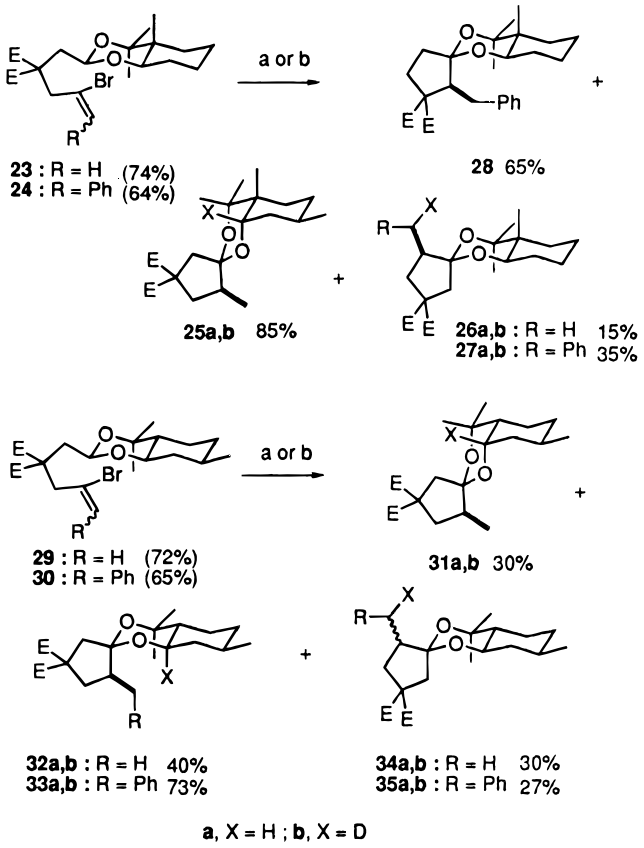
(24) (a) Anelli, P. L.; Biffi, C. Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559. (b) Inch, T. D.; Ley, R. V.; Rich, P. *J. Chem. Soc. C* **1968**, 1693.

(25) Aldrich Chemical Co., Milwaukee, WI.

Scheme 10



Scheme 11[a]



[a] Key: (a) Bu_3SnCl, $NaBH_3CN$, *t*-BuOH, AIBN, 80 °C; (b) Bu_3SnD, AIBN, PhH, syringe pump addition, 80 °C.

Transacetalization of bromide **1** with **21** and **22** led to substrates **23** and **29**, respectively, the cyclizations of which were performed under standard conditions at reflux in 2-methyl-2-propanol with the results reported in Scheme 11.

The major product **25** isolated from **23** arises from a fast 1,5-shift of the bridgehead hydrogen followed by trapping of the resulting radical **P** leading to a *cis*-dioxadecalin, according to the general mechanism in Scheme 12. The ^1H NMR spectrum provided clear evidence for the *cis*-fused nature of **25**. Thus, the bridgehead proton, a double doublet with $J = 11$ and 5 Hz at δ 3.68 for the precursor **23**, was a broad singlet at δ 3.85 in **25**. Further confirmation was obtained from experiments with Bu_3SnD. The minor product, which did not incorporate deuterium at the bridgehead position in the presence of Bu_3SnD, retained the *trans*-dioxadecaline configuration.[27] It was tentatively assigned structure **26** and results either from the "equatorial" trapping of the dioxolanyl radical by the double bond or, more likely, from a twist-boat conformation of the auxiliary in the transition structure **R** (Scheme 12). We note that the angular methyl group apparently induces a high stereoselectivity in this last process. A single diastereomer of **26** resulting from **R** was detected, the alternative twist-boat **S** being sterically disfavored.[28] This assignment was supported by reactions run at different [Bu_3SnCl] concentrations wherein the **25**/**26** ratio was not significantly modified. Therefore, the two products could not derive from a common intermediate radical of the type **O**. Since intermediate **Q** was precluded on grounds of prohibitive steric strain, **26** could only be formed *via* radical **T** (Scheme 12). Under the same conditions, **29** gave a mixture of four spirocyclic products. Two of them (**31** and **32**) resulted from the axial trapping of the dioxanyl radical by the double bond. The radical **O** rearranged, as in the previous case, to the bridgehead radical *via* hydrogen migration. However, in the absence of the angular methyl group the final hydrogen abstraction from tin hydride was no longer selective and led to a mixture of *cis*- and *trans*-dioxadecalins.[27] As previously shown, the ^1H NMR resonances of the bridgehead protons (td, $J = 10.6$, 4.2 Hz at δ 3.39 in **29**; broad s at δ 4.21 in **31**; td, $J = 10.6$, 4.4 Hz at δ 3.46 ppm in **32**) were diagnostic. Confirmation of the proposed mechanism was again obtained from experiments conducted with Bu_3SnD. Two other epimeric products **34** (1:1), resulting from equatorial trapping by the double bond (or from twist-boat conformers), accounted for 30% of the mixture (both incorporated label at the methyl group). Thus, as expected, appropriately substituted 1,3-dioxabicyclo[4.4.0]-decan-2-yl radicals improved the stereoinduction with respect to C_2-symmetric 1,3-dioxan-2-yl radicals. In the best case, however, a 70% ee could be expected after hydrolysis.

Diol **41** was designed as a readily available, optically pure equivalent of diol **21** that, furthermore, might improve stereoinduction due to more severe steric strain and to the replacement of the angular methyl group by a tertiary alkyl group.[29] It was prepared according to Scheme 13 from ketopinic acid **36**[30] and readily converted to the dioxane **44** by reaction of its bis-TMS ether with aldehyde **2** under the Noyori-type conditions.[31]

When **44** was cyclized under the standard conditions at 80 °C, a mixture of three products (**46**, **48**, **49**) was isolated in 74% yield (Scheme 14). The two major products resulted from the preferred cyclization followed by 1,5-hydrogen atom transfer and nonselective quench-

(26) For the configuration of **22** and its stereoisomers see: (a) Asakawa, Y.; Mutsuda, R.; Tori, M.; Hashimoto, T. *Phytochemistry* **1988**, *27*, 3861. (b) Shishibori, T. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1170.

(27) Greene, F. D.; Lowry, N. N. *J. Org. Chem.* **1967**, *32*, 882.

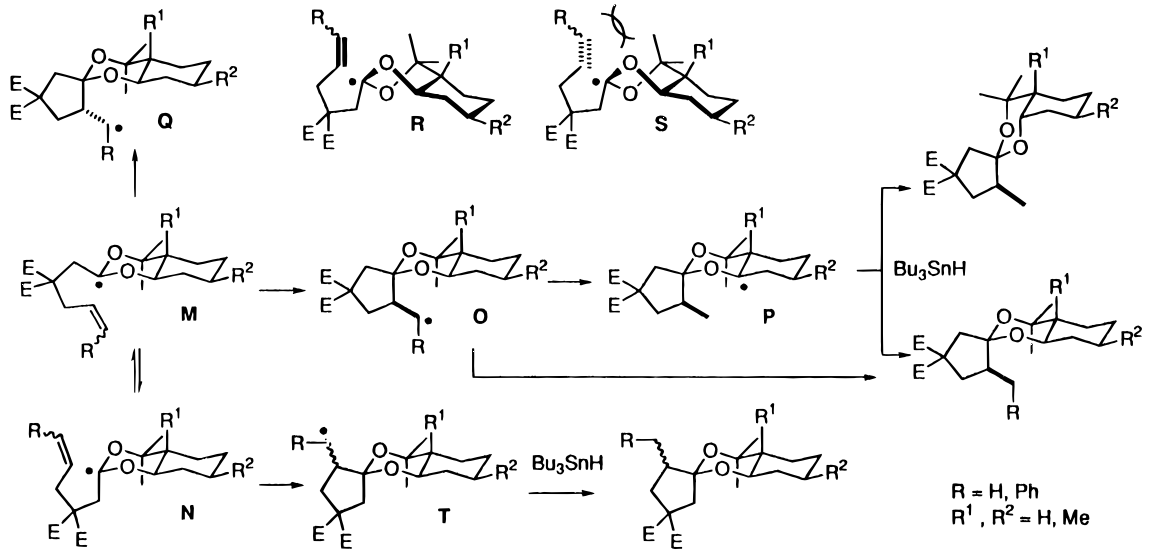
(28) Unfortunately, no supplementary information could be gained from NOESY spectra.

(29) More exact, optically pure analogs of **21** might be readily prepared from natural products such as hederagenin and aphidicolin, which incorporate the essential diol functionality in **18**; however, this was not pursued due to the relative inaccessibility of such terpenoids.

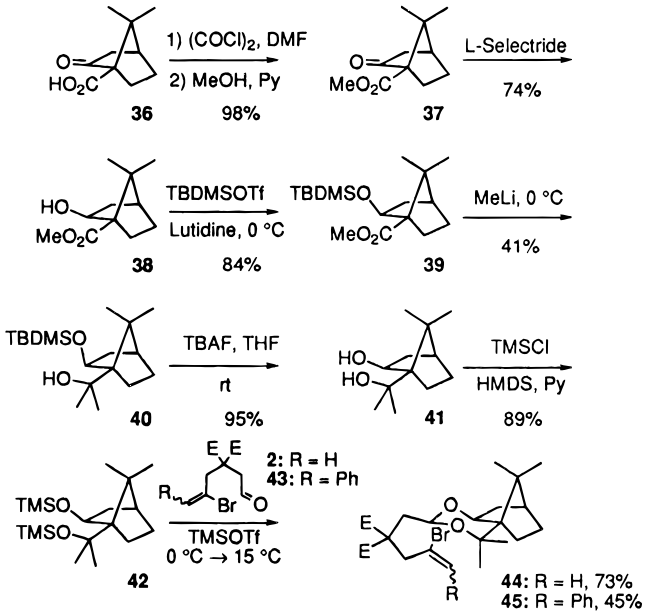
(30) Bartlett, P. D.; Knox, L. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 689.

(31) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

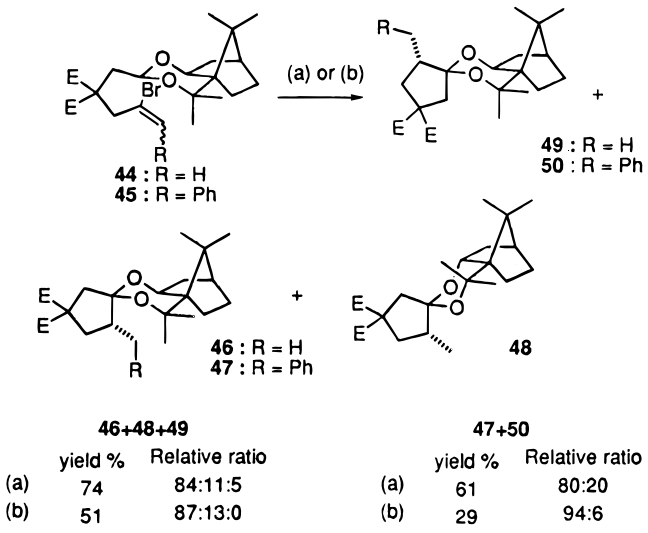
Scheme 12



Scheme 13



Scheme 14[a]



	46+48+49		47+50	
	yield %	Relative ratio	yield %	Relative ratio
(a)	74	84:11:5	61	80:20
(b)	51	87:13:0	29	94:6

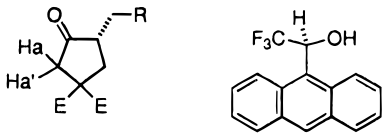
[a] Key: (a) Bu_3SnCl, $NaBH_3CN$, 80 °C, *t*-BuOH; (b) Bu_3SnH, *hν*, 20 °C, PhH.

ing. This was confirmed by an experiment with Bu_3SnD, when both incorporated the label at the ring junction. Compound **46** retained the *exo*-borneol structure as indicated by the doublet of doublet nature of the ring junction proton (δ 3.79). This assignment is further corroborated by a strong crosspeak in the NOESY spectrum between the Me doublet at δ 0.95 and the ring junction proton (δ 3.79). Compound **48** is clearly an *endo*-borneol derivative as evidenced by the downfield nature of the ring junction proton (δ 4.52) and its multiplicity (ddd) with the additional ^4J (W) coupling. The third, minor product (**49**) retains the *exo*-borneol structure (δ 3.80, dd) and does not incorporate deuterium at the ring junction in the presence of Bu_3SnD. This minor product must arise from "equatorial" quenching of a twist-boat conformer comparable to **R** in Scheme 12. When the cyclization was conducted photochemically at 20 °C, only **46** and **48** were formed (Scheme 14). As both **46** and **48** arise from the same cyclized radical the selectivity in the cyclization step for **44** at 20 °C is essentially total. Moreover, hydrolysis of the mixture of **46** and **48** should result in the optically pure ketone **51**.

A series of phenyl-substituted substrates **24**, **30**, and **45** were also prepared from bromide **43** and from diols **21**, **22**, and **41**, respectively, and subjected to the standard cyclization conditions in 2-methyl-2-propanol at reflux. In each case (Schemes 11 and 14), the second 1,5-hydrogen transfer was effectively suppressed but, as noted for **11** above, the cyclizations were somewhat less selective than in the corresponding simple, unsubstituted series presumably for the same reasons. Nevertheless, when **45** was subjected to cyclization with photochemical initiation at 20 °C a highly selective cyclization was observed in which the ratio of products was 94:6, representing a de of 88% (Scheme 14).

Finally, we turned to hydrolysis of the cyclized product mixtures and determination of the ee of the resulting ketones. Racemic samples of ketones **51** and **52** were prepared and used to devise appropriate techniques for the determination of ee's. Screening of numerous chiral lanthanide shift reagents failed to reveal conditions for base-line resolution of (±)-**51** in the ^{1}H NMR spectrum, and we eventually turned our attention to the Pirkle chiral solvating agent **53** (Chart 1). Although this reagent is most commonly applied to more polar species,

Chart 1



(*R*)-(+)-**51**: R = H
(*R*)-(+)-**52**: R = Ph

53

it has been successfully used for the NMR resolution of simple lactones.[32] In the event, successful base-line resolution of one wing of an AB quartet assigned to HaHa′ was readily achieved in the ^{1}H NMR spectrum of (±)-**51** in $CDCl_3$ solution in the presence of a slight excess of (*S*)-**53**. Numerous variations on standard hydrolysis conditions were then applied to the cyclization mixtures from **44** and the ee of the resulting ketone determined. Unfortunately, in most instances, **51** was found to be almost or completely racemic, suggesting considerable susceptibility to enolization under even very mild acidic conditions. However, the use of $PdCl_2(CH_3CN)_2$ in acetone[33] was found to minimize this problem. Application of these conditions to the mixture of **46**, **48**, and **49** derived from the cyclization of **44** at 80 °C gave an 89:11 enantiomeric ratio of ketones, while the mixture obtained by conducting the cyclization at 20 °C resulted in a 95:5 mixture of enantiomers. These enantiomeric ratios are marginally lower than those calculated according to the ratio of **46**:**48**:**49** in the mixtures employed indicating that, although racemization has been minimized, it has not been completely suppressed. Ketone **51** obtained in this manner from **46**:**48**:**49** was found to be dextrotatory and to have a negative Cotton effect in the CD spectrum consistent with it being enriched in the (*R*)-enantiomer. This in turn is fully consonant with the above rationale for diastereoselectivity in the cyclization of **44**. Predictably, therefore, hydrolysis of the cyclization mixture from **29** gave **51** moderately enriched in the (−)-enantiomer. The same hydrolysis protocol was applied to the mixtures of **47** and **50**, giving the benzylcyclopentanone **52** in excellent yield. Disappointingly, the benzylic methylene resonances of **52** obscured the HaHa′ AB quartet and so prevented application of the same convenient direct NMR determination of enantiomeric purity. Eventually, we had recourse to the reduction of **52** with $NaBH_4$ at 0 °C to the mixture of alcohols **54**, which was converted to the corresponding Mosher esters and analyzed by ^{1}H and ^{19}F NMR. In this manner, the ee of **52** obtained by cyclization of **45** at 80 and 20 °C followed by Pd(II)-catalyzed hydrolysis was found to be 38 and 62%, respectively. It will be noted that the liberation of ketone **52** from the various cyclization mixtures appears to have occurred with significantly greater racemization than was the case with **51**. We suspect that this is an artifact of the method used to measure ee and that significant racemization is taking place in the course of the borohydride reduction, meaning that the values reported for **52** are only lower limits.

In summary, this paper reports the progression of our concept of asymmetric acyl radical equivalents. The design of these reactive species led us to abandon successively C_2-symmetric 1,3-dioxolan-2-yl and 1,3-dioxan-2-yl radicals for disymmetrically substituted 1,3-dioxabicyclo[4.4.0]decan-2-yl radicals. We have demonstrated that it is necessary to maintain the 1,3-dioxane ring in a chair conformation in order to achieve a high stereoinduction in the cyclization reaction. Conformational rigidity of the masked acyl radical is of prime importance, as is further underlined by the recent related work of Nishida.[34] The 2-alkylcyclopentanone **51** was prepared with a very high enantiomeric excess. Further developments will be reported in due course.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded in $CDCl_3$ at 200, 300, or 400 MHz and ^{13}C NMR spectra in $CDCl_3$ at 50, 75, or 100 MHz as indicated. Chemical shifts (δ) are in ppm downfield from tetramethylsilane, and coupling constants (J) are in Hz. All solvents were dried and distilled by standard techniques. LC is column chromatography on silica gel.

Acetalization Procedures. Method A. A solution of **1** (0.14 mmol/mL of solvent), the appropriate diol (1.1 equiv), and camphorsulfonic acid (0.1 equiv) in toluene was heated at reflux for 2 h. After distillation of the toluene−ethanol azeotrope, the residue was diluted with Et_2O and washed successively with saturated aqueous $NaHCO_3$ and with water. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* and the residue purified by LC. **Method B**.[31] In a typical experiment, TMSOTf (21 μL, 0.11 mmol, 0.1 equiv) was added at −80 °C to a solution of **2** (340 mg, 1.06 mmol) and the bis(trimethylsilyl)-*O*-protected diol (1.06 mmol, 1 equiv) in dichloromethane (9 mL). The reaction mixture was allowed to warm slowly to the specified temperature, and then a few drops of pyridine were added immediately followed by saturated aqueous $NaHCO_3$. The aqueous phase was extracted with dichloromethane, and the combined organic layers were dried (Na_2SO_4). After removal of the solvent *in vacuo*, the residue was purified by LC.

(*S,*S**)-2-Bromo-4,4-bis(ethoxycarbonyl)-5-(4,5-dimethyl-1,3-dioxolan-2-yl)-1-pentene (3a).** Method A. The reaction of **1** (280 mg, 0.71 mmol) with (±)-2,3-butanediol led to **3a** (230 mg) in 83% yield: ^{1}H NMR (200 MHz) δ 1.16−1.20 (m, 3H), 1.23−1.27 (superimposed m, 3H), 1.27 (t, J = 7.1, 6H), 2.39 (d, J = 4.9, 2H), 3.29 (d, J = 0.5, 2H), 3.50−3.58 (m, 2H), 4.12−4.25 (m, 4H), 5.17 (t, J = 4.9, 1H), 5.61 (d, J = 1.5, 1H), 5.77 (m, 1H); ^{13}C NMR (50.3 MHz) δ 13.6, 16.3, 16.6, 35.6, 43.1, 54.0, 61.2, 61.3, 77.5, 79.5, 100.0, 122.2, 127.2, 169.8. Anal. Calcd for $C_{16}H_{25}BrO_6$: C, 48.97; H, 6.43. Found: C, 48.90; H, 6.38.

(*S*,*S*)-2-Bromo-4,4-bis(ethoxycarbonyl)-5-[4,5-bis-[(benzyloxy)methyl]-1,3-dioxolan-2-yl]-1-pentene (3b). Method A. The reaction of **1** (395 mg, 1.0 mmol) with (*S*,*S*)-dibenzylthreitol led after purification by LC (10−20% ethyl acetate/pentane) to **3b** (471 mg, 78%): ^{1}H NMR (200 MHz) δ 1.22 (t, J = 7.3, 6H), 2.43 (d, J = 4.6, 2H), 3.28 (m, 2H), 3.54−3.62 (m, 4H), 3.88−4.10 (m, 2H), 4.10−4.22 (m, 4H), 4.54 (s, 2H), 4.55 (s, 2H), 5.18 (t, J = 4.6, 1H), 5.57 (d, J = 1.5, 1H), 5.74 (m, 1H), 7.31 (m, 10H); ^{13}C NMR (50.3 MHz) δ 13.7, 35.2, 43.4, 54.1, 61.5, 70.1, 70.3, 73.2, 73.3, 77.1, 77.7, 101.9, 122.5, 127.1, 127.3, 127.5, 128.3, 137.7, 170.0. Anal. Calcd for $C_{30}H_{37}O_8Br$: C, 59.59; H, 6.17. Found: C, 59.57; H, 6.17.

(*R*,*R*)-2-Bromo-4,4-bis(ethoxycarbonyl)-5-[4,5-bis(1-methoxy-1-methylethyl)-1,3-dioxolan-2-yl]-1-pentene (3c). Method B: 40 °C, 30 min. TMS triflate (14 μL, 0.07 mmol) was added to a solution of the bis(trimethylsilyl) ether of (*R*,*R*)-2,5-dimethoxy-2,5-dimethylhexane-3,4-diol (226 mg, 0.64 mmol) and **2** (207 mg, 0.64 mmol) in CH_2Cl_2 (5 mL). After workup and LC (5−10% ethyl acetate/pentane), **3c** was isolated (260 mg, 80%): ^{1}H NMR (200 MHz): δ 1.07 (s, 3H), 1.08 (s, 3H), 1.18 (s, 3H), 1.20 (s, 3H), 1.25 (t, J = 7.2, 6H), 2.38 (d, J = 5.5, 2H), 3.17 (s, 3H), 3.20 (s, 3H), 3.27 (AB quartet, J_{AB} = 15.4, 2H), 3.76 (d, J = 3.6, 1H), 4.2 (d, J = 3.6, 1H), 4.08−4.27 (m,

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(33) Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705.

(34) Nishida, A.; Kawahara, N.; Nishida, M.; Yonemitsu, O. *Tetrahedron* **1996**, *52*, 9713.

4H), 5.27 (t, J = 5.5, 1H), 5.59 (d, J = 1.5, 1H), 5.72−5.75 (m, 1H); ^{13}C NMR (50.3 MHz) δ 13.7, 18.7, 21.1, 22.1, 35.7, 43.1, 49.0, 49.3, 54.4, 61.5, 75.6, 77.1, 81.3, 83.9, 102.2, 122.2, 127.4, 170.0. Anal. Calcd for $C_{22}H_{37}BrO_8$: C, 51.87; H, 7.32. Found: C, 51.84; H, 7.35.

(*S*,S)-2-Bromo-4,4-bis(ethoxycarbonyl)-5-(4,6-dimethyl-1,3-dioxan-2-yl)-1-pentene (3d).** Method A. The reaction of **1** (580 mg, 1.47 mmol) with (±)-2,4-pentanediol led to **3d** (543 mg, 91%): ^{1}H NMR (200 MHz) δ 1.15 (d, J = 6.1, 3H), 1.26 (t, J = 7.3, 6H), 1.32 (d, J = 7.1, 3H), 1.14−1.34 (superimposed m, 1H), 1.80 (ddd, J = 13.2, 11.6, 6.1, 1H), 2.32 (d, J = 5.1, 2H), 3.25 (broad s, 2H), 3.80−4.03 (m, 2H), 4.03−4.30 (m, 4H), 4.99 (t, J = 5.1, 1H), 5.59 (d, J = 1.5, 1H), 5.71 (m, 1H); ^{13}C NMR (50.3 MHz) δ 13.7, 16.8, 21.5, 36.3, 36.4, 43.5, 54.3, 61.3, 67.5, 67.9, 91.3, 122.0, 127.3, 170.0. Anal. Calcd for $C_{17}H_{27}BrO_6$: C, 50.13; H, 6.68. Found: C, 50.59; H, 6.83.

(*S*,S)-2-Bromo-4,4-bis(ethoxycarbonyl)-5-(4,6-diisopropyl-1,3-dioxan-2-yl)-1-pentene (3e).** Method A. The reaction of **1** (1.186 g, 3.0 mmol) with (±)-2,6-dimethyl-3,5-heptanediol led, after purification by LC (5% ethyl acetate/pentane) to **3e** (770 mg, 55%): ^{1}H NMR (200 MHz) δ 0.84 (d, J = 6.3, 3H), 0.86 (d, J = 6.8, 3H), 0.91 (d, J = 6.8, 3H), 0.96 (d, J = 6.6, 3H), 1.24 (t, J = 7.3, 3H), 1.25 (t, J = 7.3, 3H), 1.49−1.79 (m, 3H), 2.14−2.30 (m, 1H), 2.38 (d, J = 5.1, 2H), 3.19 (dd, J = 15.1, 0.5, 1H), 3.35 (dd, J = 15.1, 0.5, 1H), 3.28−3.39 (m, 1H), 3.42−3.52 (m, 1H), 4.10−4.25 (m, 4H), 4.86 (t, J = 5.1, 1H), 5.60 (d, J = 1.7, 1H), 5.77 (m, 1H); ^{13}C NMR (50.3 MHz) δ 13.7, 17.7, 18.1, 19.3, 19.3, 26.9, 27.9, 32.6, 36.1, 43.1, 54.3, 61.3, 61.4, 77.0, 78.2, 92.7, 122.1, 127.4, 170.0. Anal. Calcd for $C_{21}H_{35}BrO_6$: C, 54.53; H, 7.63. Found: C, 54.41; H, 7.69.

(*S*,S)-2-Bromo-4,4-bis(ethoxycarbonyl)-5-(4,6-*tert*-butyl-1,3-dioxan-2-yl)-1-pentene (3f).** Method A. **1** (197.5 mg, 0.5 mmol) and (±)-2,2,6,6-tetramethyl-3,5-heptanediol (113 mg, 0.6 mmol) in benzene (25 mL) gave, after 2 h and LC (6/1 hexane/ethyl acetate), **3f** as an oil (203 mg, 83%): ^{1}H NMR (300 MHz) δ 0.82 (s, 18H), 1.23 (t, J = 5.1, 6H), 1.58 (m, 2H). 2.30 (dd, J = 3.9, 14.7, 1H), 2.44 (dd, J = 7.3, 14.8, 1H), 3.27 (m, 3H), 4.17 (m, 4H), 4.97 (dd, J = 3.8, 7.3, 1H), 5.59 (d, J = 1.51, 1H), 5.73 (s, 1H); ^{13}C NMR (75 MHz) δ 13.8, 13.9, 25.3, 25.8, 26.9, 33.8, 34.1, 35.6, 43.2, 54.4, 61.4, 61.5, 74.7, 80.5, 96.9, 121.9, 127.8, 170.0, 170.1; ν (CH_2Cl_2) 1734 cm^{-1}. Anal. Calcd for $C_{23}H_{39}BrO_6$: C, 56.21; H, 8.00. Found: C, 56.21; H, 7.76.

General Procedure for Radical Cyclizations. AIBN (0.2 equiv) was added in portions over 5 h to a refluxing solution of **3** (0.05 M) in degassed 2-methyl-2-propanol, containing Bu_3SnCl (0.1 equiv) and $NaBH_3CN$ (2 equiv). After evaporation of the solvent different workups were performed depending on the substrate: direct purification of the residue by LC; ozonolysis and then LC; oxidation with OsO_4/$NaIO_4$ in THF−H_2O (4:1) followed by extraction with dichloromethane and purification by LC. Deuteration experiments were conducted by slowly adding (3 h) with a syringe pump a solution of Bu_3SnD (1.5 equiv) and AIBN (0.15 equiv) in benzene (∼1 mL) to a refluxing solution of substrate (0.05 M) in benzene. The reaction mixture was heated 2 h more after the end of the addition and then concentrated.

Cyclization of 3a. Cyclization of **3a** (212 mg, 0.54 mmol) led, after purification of the crude product by LC (0 to 5% ethyl acetate/pentane), to a mixture of **4a**, **5a**, and **6a** (122 mg, 72%). After reductive ozonolysis and a second purification by LC (5% ethyl acetate/pentane) a 1:1 mixture of **4a** and **5a** (74 mg, 45%) was isolated.

Diethyl 1,7,8-trimethyl-6,9-dioxaspiro[4.4]nonane-3,3-dicarboxylate (4a, 5a): ^{1}H NMR (200 MHz) δ 0.94 (d, J = 6.6, 3H), 1.19−1.28 (m, 12H), 1.88 (dd, J = 12.4, 5.3, 0.5H), 1.94 (dd, J = 12.6, 4.0, 0.5H), 2.05−2.25 (m, 1H), 2.33 (d, J = 14.2, 0.5H), 2.47 (d, J = 14.2, 0.5H), 2.38−2.48 (m superimposed, 1H), 2.59 (d, J = 14.2, 0.5H), 2.61 (d, J = 14.2, 0.5H), 3.43−3.71 (m, 2H), 4.10−4.25 (m, 4H); ^{13}C NMR (50.3 MHz) δ 11.8, 13.9, 16.0, 16.2, 17.2, 38.1, 38.3, 40.4, 40.6, 43.5, 44.5, 55.5, 55.8, 61.2, 61.4, 77.6, 78.5, 79.1, 79.2, 115.0, 115.3, 171.5, 172.0, 172.2. Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.11; H, 8.34. Found: C, 61.09; H, 8.30.

Cyclization of 3b. Cyclization of **3b** (200 mg, 0.33 mmol) led, after purification of the crude product by LC (0−10% ethyl acetate/pentane), to a mixture of **4b**, **5b**, and **6b** (130 mg, 75%). After reductive ozonolysis and a second purification by LC (10% ethyl acetate/pentane) a 58:42 mixture of **4b** and **5b** (74 mg, 45%) was isolated.

Diethyl (2*S*,3*S*,9*S)-2,3-bis[(benzyloxy)methyl]-6-methyl-1,4-dioxaspiro[4.4]nonane-8,8-dicarboxylate (4b, 5b):** ^{1}H NMR (200 MHz) δ 0.93 (d, J = 6.6, 3H), 1.18−1.27 (m, 6H), 1.90 (dd, J = 12.7, 3.2, 0.42H), 1.96 (dd, J = 12.7, 2.9, 0.58H), 2.13−2.32 (m, 1H), 2.32−2.53 (m, 2H), 2.64 (d, J = 14.4, 0.42H), 2.67 (d, J = 14.4, 0.58H), 3.55−3.64 (m, 4H), 3.81−4.15 (m, 2H), 4.10−4.22 (m, 4H), 4.55−4.57 (m, 4H), 7.28−7.32 (m, 10H); ^{13}C NMR (50.3 MHz) δ 11.8, 11.82, 13.9, 38.0, 38.3, 40.0, 40.4, 43.2, 44.0, 55.6, 55.7, 61.3, 61.4, 69.7, 69.9, 70.1, 70.5, 70.7, 73.2, 73.3, 76.6, 78.0, 78.1, 78.3, 116.7, 117.1, 127.4, 127.5, 128.3, 137.8, 137.9, 171.5, 172.0, 172.1. Anal. Calcd for $C_{30}H_{38}O_8$: C, 68.41; H, 7.28. Found: C, 68.45; H, 7.31.

Cyclization of 3c. Cyclization of **3c** (102 mg, 0.2 mmol) led after purification by LC (0−10% ethyl acetate/pentane) to a mixture of **4c** and **5c** (70 mg, 81%) in a 73:27 ratio (GC), only traces of **6c** were detected. When a mixture of **3c** (20.4 mg, 0.04 mmol), Bu_3SnH (16 μL, 0.06 mmol), and AIBN (1.3 mg, 0.008 mmol) in solution in benzene (4 mL) was irradiated for 3 h at rt, **4c** and **5c** (82:18) were isolated (15.4 mg, 64%) after ozonolysis.

Diethyl (2*R*,3*R*,9*R)-2,3-bis(1-methoxy-1-methylethyl)-6-methyl-1,4-dioxaspiro[4.4]nonane-8,8-dicarboxylate (4c, 5c):** ^{1}H NMR (200 MHz) δ 0.93 (d, J = 6.8, 2.1H), 0.96 (d, J = 6.8, 0.9H), 1.10−1.29 (m, 18H), 1.77−1.98 (m, 1.3H), 2.10−2.30 (m, 0.7H), 2.35-2.70 (m, 2.3H), 2.77 (d, J = 14.2, 0.7H), 3.17, 3.18, 3.20 (3 x s, 6H), 3.84 (d, J = 5.9, 0.7H), 3.89 (d, J = 5.1, 0.3H), 3.98 (d, J = 5.9, 0.7H), 4.01 (d, J = 5.1, 0.3H), 4.02−4.27 (m, 4H). Anal. Calcd for $C_{22}H_{38}O_8$: C, 61.37; H, 8.90. Found: C, 61.72; H, 9.06.

Cyclization of 3d. Cyclization of **3d** (244 mg, 0.6 mmol) led, after purification of the crude product by LC (10% ethyl acetate/pentane) to a mixture of **7d**, **8d**, and **9d** (140 mg, 71%) in a 6/20/74 relative ratio and to **10** (20 mg, 10%).

Diethyl 1,7,9-trimethyl-6,10-dioxaspiro[4.5]decane-3,3-dicarboxylate (major isomer 9d): ^{1}H NMR (200 MHz) δ 0.95 (d, J = 6.6, 3H), 1.10 (d, J = 5.9, 3H), 1.14 (d, J = 6.1, 3H), 1.24 (t, J = 7.1, 3H), 1.25 (t, J = 7.1, 3H), 1.30−1.40 (superimposed m, 1H), 1.49 (dt, J = 12.9, 2.4, 1H), 1.91 (dd, J = 12.5, 11.5, 1H), 1.98−2.13 (m, 1H), 2.22 (d, J = 13.7, 1H), 2.48 (dd, J = 12.7, 7.3, 1H), 3.05 (d, J = 13.7, 1H), 3.77−3.97 (m, 2H), 4.17 (q, J = 7.1, 4H); ^{13}C NMR (50.3 MHz) δ 11.9, 13.9 (2), 21.6 (2), 37.4, 37.6, 40.3, 42.8, 56.4, 61.3, 61.4, 65.6, 67.6, 106.2, 171.7, 172.3. Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.16; H, 8.60. Found: C, 62.01; H, 8.62.

(*S*,S)-4,4-Bis(ethoxycarbonyl)-5-(4,6-dimethyl-1,3-dioxan-2-yl)-1-pentene (10d):** ^{1}H NMR (200 MHz) δ 1.15 (d, J = 6.1, 3H), 1.24 (t, J = 7.1, 6H), 1.31 (d, J = 7.1, 3H), 1.10−1.30 (superimposed m, 1H), 1.80 (ddd, J = 13.2, 11.5, 6.1, 1H), 2.20 (AB part of an ABX pattern, 2H), 2.71 (dt, J = 7.3, 0.9, 2H), 3.81−3.97 (m, 1H), 4.08−4.27 (m, 5H), 4.96 (t, J = 5.2, 1H), 5.06 (m, 1H), 5.13 (m, 1H), 5.58−5.79 (m, 1H). Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.18; H, 8.59. Found: C, 62.19; H, 8.57.

Cyclization of 3e. Cyclization of **3e** (185 mg, 0.4 mmol) led, after purification of the crude product by LC (0−3% ethyl acetate/pentane), to a mixture of **7e**, **8e**, and **9e** (134 mg (34 mg of a pure sample of **9e** were separated), 87%) in a 3/14/83 relative ratio and to **10e** (17 mg, 11%).

Diethyl 7,9-diisopropyl-1-methyl-6,10-dioxaspiro[4.5]-decane-3,3-dicarboxylate (major isomer 9e): ^{1}H NMR (200 MHz) δ 0.88 (d, J = 6.5, 3H), 0.89 (d, J = 6.5, 6H), 0.91 (d, J = 6.5, 3H), 0.98 (d, J = 6.6, 3H), 1.27 (t, J = 7.1, 6H), 1.27 (superimposed m, 1H), 1.46 (dt, J = 12.4, 2.4, 1H), 1.52−1.72 (m, 2H), 1.92 (dd, J = 12.5, 10.0, 1H), 2.02−2.20 (m, 1H), 2.20 (d, J = 14.6, 1H), 2.47 (dd, J = 12.5, 7.3, 1H), 3.05 (d, J = 14.6, 1H), 3.33−3.53 (m, 2H), 4.19 (q, J = 7.1, 2H), 4.14−4.26 (superimposed m, 2H); ^{13}C NMR (50.3 MHz) δ 11.7, 13.9, 17.5, 17.8, 17.9, 18.1, 30.3, 32.9, 33.1, 37.7, 43.0, 56.4, 61.2, 61.4,

74.1, 76.3, 105.9, 171.7, 172.5. Anal. Calcd for $C_{21}H_{36}O_6$: C, 65.58; H, 9.44. Found: C, 65.54; H, 9.34.

(*S,*S**)-4,4-Bis(ethoxycarbonyl)-5-(4,6-diisopropyl-1,3-dioxan-2-yl)-1-pentene (10e):** ^{1}H NMR (200 MHz) δ 0.83 (d, J = 6.6, 3H), 0.86 (d, J = 6.8, 3H), 0.91 (d, J = 6.8, 3H), 0.96 (d, J = 6.6, 3H), 1.23 (t, J = 7.2, 3H), 1.24 (t, J = 7.2, 3H), 1.50−1.80 (m, 3H), 2.12−2.36 (m, 3H), 2.62−2.85 (m, 2H), 3.33 (ddd, J = 11.2, 6.1, 2.9, 1H), 3.47 (ddd, J = 12.0, 8.8, 1.5, 1H), 4.02−4.25 (m, 4H), 4.81 (dd, J = 5.9, 3.9, 1H), 5.02−5.16 (m, 2H), 5.61−5.82 (m, 1H). Anal. Calcd for $C_{21}H_{36}O_6$: C, 65.60; H, 9.44. Found: C, 65.63; H, 9.46.

Cyclization of 3f. Cyclization of **3f** (166 mg, 0.34 mmol) gave after treatment with catalytic OsO_4 and $NaIO_4$ (364 mg, 1.7 mmol) and purification by LC (95/5 hexane/ethyl acetate) **7f**, **8f**, and **9f** as an inseparable mixture of diastereomers (90 mg, 65%).

Diethyl 7,9-di-*tert*-butyl-1-methyl-6,10-dioxaspiro[4.5]-decane-3,3-dicarboxylate (7f, 8f, and 9f): ^{1}H NMR (300 MHz) δ 0.82 (s, 9H), 0.85 (s, 9H), 0.93 (d, J = 6.6, 3H), 1.23 (m, 6H), 1.29 (t, J = 2.6, 2H), 1.91 (d, J = 12.5, 1H), 2.07 (m, 2H), 2.38 (dd, J = 12.8, 7.1, 1H), 3.06 (d, J = 13.9, 1H), 3.23 (dd, J = 11.3, 2.3, 1H), 3.34 (dd, J = 11.3, 2.6, 1H), 4.16 (m, 4H); ^{13}C NMR (75 MHz) δ 11.4, 13.9, 25.1, 25.4, 25.6, 33.8, 34.1, 37.9, 38.0, 43.3, 56.3, 61.2, 61.4, 75.5, 79.0, 105.8, 171.6, 172.8; ν (CH_2Cl_2) 1731 cm^{-1}. Anal. Calcd for $C_{23}H_{40}O_6$: C, 66.96; H, 9.77. Found: C, 66.73; H, 9.69.

(*S,*S**)-2-Bromo-4,4-bis(ethoxycarbonyl)-5-(4,6-dimethyl-1,3-dioxan-2-yl)-1-phenyl-1-pentene (11a).** Method A. 2-Bromo-4,4-bis(ethoxycarbonyl)-6,6-diethoxy-1-phenyl-1-hexene (236 mg, 0.5 mmol) and (±)-2,4-pentanediol (63 mg, 0.6 mmol) gave **11a** (205 mg, 85%) as an inseparable mixture of *E*- and *Z*-isomers: ^{1}H NMR (300 MHz) δ 0.76 (d, J = 7.6, 3H), 1.03 (d, J = 6.1, 3H), 1.22 (m, 15H), 1.33 (d, J = 6.8, 3H), 1.62 (m, 2H), 1.81 (dd, J = 12.7, 6.2, 2H), 2.18 (dd, J = 14.4, 3.6, 1H), 2.31 (m, 1H), 2.37 (d, J = 5.1, 2H), 3.25 (m, 2H), 3.44 (s, 2H), 3.49 (d, J = 15.5, 1H), 3.76 (d, J = 15.4, 1H), 3.92 (m, 2H), 4.17 (m, 9H), 5.06 (t, J = 5.5, 1H), 6.89 (s, 1H), 7.15 (s, 1H), 7.35 (m, 8H), 7.50 (d, J = 7.3, 2H); ^{13}C NMR (75 MHz) δ 13.7, 13.9, 16.2, 16.9, 21.5, 21.6, 36.2, 36.3, 36.4, 36.6, 37.0, 45.4, 54.5, 54.9, 61.4, 67.1, 67.6, 67.0, 90.5, 91.5, 120.2, 123.9, 127.6, 127.8, 128.0, 128.5, 128.7, 128.8, 133.0,135.7, 136.6, 170.1, 170.3, 170.4. Anal. Calcd for $C_{23}H_{31}BrO_6$: C, 57.15; H, 6.46. Found: C, 56.99; H, 6.40.

Cyclization of 11a. Cyclization of **11a** (106 mg, 0.22 mmol) in 2-methyl-2-propanol (4.4 mL, 0.05 M), followed by treatment with catalytic OsO_4 and $NaIO_4$ (235 mg, 1.1 mmol) and purification by LC (95/5 hexane/ethyl acetate), gave **12a** and **13a** as an inseparable mixture of diastereomers (55 mg, 62%).

Diethyl 1-benzyl-7,9-dimethyl-6,10-dioxaspiro[4.5]-decane-3,3-dicarboxylate (12a and 13a): ^{1}H NMR (300 MHz) δ 1.21 (m, 24H), 1.48 (m, 1H), 1.62 (t, J = 6.9, 4H), 1.99 (m, 1H), 2.13 (d, J = 13.9, 2H), 2.39 (m, 7H), 2.78 (d, J = 13.8, 1H), 2.97 (m, 1H), 3.10 (d, J = 13.8, 1H), 3.99 (m, 3H), 4.14 (m, 9H), 7.22 (m, 10H); ^{13}C NMR (75 MHz) δ 14.0, 21.2, 21.4, 21.7, 21.9, 33.8, 35.1, 37.8, 40.1, 41.0, 41.8, 47.9, 50.0, 56.1, 61.4, 61.5, 61.8, 63.4, 65.3, 66.2, 105.7, 108.5, 125.5, 125.7, 128.1, 128.2, 128.9, 140.7, 141.2, 171.8, 172.3; ν (CH_2Cl_2) 1726 cm^{-1}. Anal. Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.16; H, 7.81.

(*S,*S**)-2-Bromo-4,4-bis(ethoxycarbonyl)-5-(4,6-di-*tert*-butyl-1,3-dioxan-2-yl)-1-phenyl-1-pentene (11b).** Method A. **72** (236 mg, 0.5 mmol) and (±)-2,2,6,6-tetramethyl-3,5-heptanediol (113 mg, 0.6 mmol) gave **11b** (255 mg, 90%) as an inseparable mixture of *E*- and *Z*-isomers: ^{1}H NMR (300 MHz) δ 0.67 (s, 9H), 0.78 (s, 9H), 0.86 (s, 9H), 0.88 (s, 9H), 1.19 (t, J = 7.2, 6H), 1.28 (t, J = 7.3, 6H), 1.62 (t, J = 5.3, 2H), 2.21 (dd, J = 4.3, 14.7, 1H), 2.50 (m, 3H), 3.42 (m, 6H), 4.07 (m, 4H), 4.20 (m, 8H), 4.43 (dd, J = 4.3, 7.6, 1H), 5.05 (dd, J = 4.0, 7.2, 1H), 6.96 (s, 1H), 7.14 (s, 1H), 7.31 (m, 8H), 7.50 (d, J = 8.4, 2H); ^{13}C NMR (75 MHz) δ 13.8, 13.9, 22.6, 25.1, 25.4, 25.7, 25.9, 26.7, 26.9, 31.6, 33.5, 33.8, 33.9, 34.1, 35.7, 35.9, 36.8, 41.5, 45.1, 54.7, 54.9, 61.3, 61.6, 62.9, 74.3, 74.8, 79.9, 80.7, 96.0, 97.2, 120.6, 124.2, 127.6, 127.8, 18.0, 128.5, 128.7, 130.0, 135.8, 136.0, 136.6, 169.9, 170.2, 170.3, 170.6; ν (CH_2Cl_2) 1739 cm^{-1}. Anal. Calcd for $C_{29}H_{43}BrO_6$: C, 61.37; H, 7.64. Found: C, 61.06; H, 7.79.

Cyclization of 11b. Cyclization of **11b** (84 mg, 0.15 mmol) followed by treatment with catalytic OsO_4 and $NaIO_4$ (160 mg, 0.75 mmol) and purification by LC (95/5 hexane/ethyl acetate) gave **12b** and **13b** as an inseparable mixture of diastereomers (44 mg, 60%).

Diethyl 1-Benzyl-7,9-di-*tert*-butyl-6,10-dioxaspiro[4.5]-decane-3,3-dicarboxylate (12b and 13b): ^{1}H NMR (300 MHz) δ 0.84 (s, 9H), 0.86 (s, 9H), 0.90 (s, 9H), 0.92 (s, 9H), 1.21 (m, 12H), 1.57 (m, 4H), 2.10 (m, 3H), 2.44 (m, 4H), 2.51 (m, 3H), 2.65 (d, J = 13.8, 2H), 3.06 (t, J = 10.0, 2H), 3.44 (m, 4H), 4.14 (m, 8H), 7.14 (m, 6H), 7.28 (m, 4H); ^{13}C NMR (75 MHz) δ 13.8, 13.9, 25.0, 25.2, 25.3, 25.5, 27.3, 27.5, 33.4, 33.9, 34.1, 34.5, 35.2, 35.6, 41.2, 41.9, 48.5, 55.4, 55.8, 61.2, 61.4, 75.1, 75.3, 75.5, 75.8, 108.2, 108.4, 125.6, 128.1, 128.9, 140.9, 141.1, 171.7, 172.2; ν (CH_2Cl_2) 1731 cm^{-1}. Anal. Calcd for $C_{29}H_{44}O_6$: C, 71.28; H, 9.08. Found: C, 71.12; H, 9.11.

(*S,*S**)-2-Bromo-4,4-bis(ethoxycarbonyl)-5-(4,6-dimethyl-1,3-dioxan-2-yl)-1,1-diphenyl-1-pentene (14).** Method A. 2-Bromo-4,4-bis(ethoxycarbonyl)-6,6-diethoxy-1,1-diphenyl-1-hexene (99 mg, 0.18 mmol) and (±)-2,4-pentanediol (23 mg, 0.22 mmol) gave **14** (90 mg, 90%): ^{1}H NMR (300 MHz) δ 0.87 (d, J = 7.0, 3H), 1.08 (d, J = 6.1, 3H), 1.20 (m, 6H), 1.35 (m, 1H), 1.67 (dd, J = 12.2, 6.1, 1H), 2.28 (dd, J = 14.5, 3.8, 1H), 2.41 (dd, J = 14.5, 6.9, 1H), 3.50 (d, J = 15.3, 1H), 3.52 (m, 1H), 3.82 (d, J = 15.3, 1H), 4.09 (m, 5H), 4.37 (dd, J = 6.9, 3.9, 1H), 7.26 (m, 10H); ^{13}C NMR (75 MHz) δ 13.7, 16.4, 21.6, 36.4, 36.6, 39.6, 55.1, 61.3, 61.4, 67.1, 67.8, 90.7, 121.5, 127.3, 127.7, 128.0, 128.3, 128.5, 129.2, 129.7, 140.0, 143.8, 146.4, 170.2, 170.7. Anal. Calcd for $C_{29}H_{35}BrO_6$: C, 62.26; H, 6.31. Found: C, 62.15; H, 6.22.

Cyclization of 14. Cyclization of **14** (67 mg, 0.12 mmol) followed by treatment with catalytic OsO_4 and $NaIO_4$ (130 mg, 0.60 mmol) and purification by LC (95/5 hexane/ethyl acetate) gave **15a** and **15b** as an inseparable mixture of diastereomers (32 mg, 62%).

Diethyl 1-benzhydryl-7,9-dimethyl-6,10-dioxaspiro-[4.5]decane-3,3-dicarboxylate (15a and 15b): ^{1}H NMR (300 MHz) δ 0.81 (d, J = 6.4, 6H), 0.90 (d, J = 6.2, 6H), 1.21 (m, 12H), 1.36 (m, 4H), 1.86 (m, 1H), 1.95 (d, J = 13.7, 1H), 2.17 (d, J = 14.1, 1H), 2.29 (dd, J = 13.8, 8.4, 1H), 2.42 (dd, J = 13.7, 7.9, 1H), 2.62 (d, J = 13.9, 1H), 2.74 (d, J = 13.9, 1H), 2.90 (m, 1H), 3.05 (d, J = 14.0, 1H), 3.16 (m, 2H), 3.33 (m, 1H), 3.86 (m, 1H), 4.11 (m, 11H), 7.11 (m, 4H), 7.29 (m, 16H); ^{13}C NMR (75 MHz) δ 14.0, 20.8, 21.1, 21.8, 22.0, 36.3, 37.0, 37.4, 38.2, 42.7, 43.0, 50.6, 51.2, 53.0, 55.4, 56.0, 61.4, 62.4, 63.2, 64.0, 106.2, 107.6, 125.5, 126.0, 127.8, 128.0, 128.1, 128.2, 128.5, 129.0, 144.5, 144.7, 145.1, 171.6, 171.7, 172.2, 172.4. Anal. Calcd for $C_{29}H_{36}O_6$: C, 72.48; H, 7.54. Found: C, 72.44; H, 7.32.

(2*R,4a*R**,8a*R**)-2-[4-Bromo-2,2-bis(ethoxycarbonyl)-4-penten-1-yl]-4,4,4a-trimethylhexahydrobenzo-1,3-dioxin (23).** Method A. The reaction of **1** (255 mg, 0.644 mmol) with **21** led to **23** as a single epimer (270 mg, 88%), after the crude product was purified by LC (3% ethyl acetate−pentane): ^{1}H NMR (300 MHz) δ 1.00−1.10 (m, 1H), 1.05 (s, 3H), 1.06 (s, 3H), 1.25 (t, J = 7.2, 6H), 1.30 (s, 3H), 1.34−1.64 (m, 6H), 1.70−1.78 (m, 1H), 2.34 (d, J = 5.4, 2H), 3.21 (dd, J = 15.2, 0.7, 1H), 3.30 (dd, J = 15.2, 0.7, 1H), 3.68 (dd, J = 11.0, 5.0, 1H), 4.16 (q, J = 7.2, 2H), 4.16 (q, J = 7.2, 2H), 5.00 (t, J = 5.4, 1H), 5.59 (d, J = 1.5, 1H), 5.74 (m, 1H); ^{13}C NMR (75 MHz) δ 13.5, 13.8, 19.7, 20.8, 24.0, 24.5, 26.7, 30.8, 35.8, 39.2, 43.3, 54.3, 61.2, 76.74, 78.1, 93.2, 122.0, 127.6, 170.1. Anal. Calcd for $C_{22}H_{35}BrO_6$: C, 55.58; H, 7.42. Found: C, 55.59; H, 7.48.

(2*R,4a*R**,8a*R**)-2-[4-Bromo-2,2-bis(ethoxycarbonyl)-5-phenyl-4-penten-1-yl]-4,4,4a-trimethylhexahydrobenzo-1,3-dioxin (24).** Method A. 2-Bromo-4,4-bis(ethoxycarbonyl)-6,6-diethoxy-1-phenyl-1-hexene (236 mg, 0.5 mmol) and (±)-**21** (104 mg, 0.6 mmol) gave **24** (215 mg, 78%) as an inseparable mixture of *E*- and *Z*-isomers: ^{1}H NMR (300 MHz) δ 0.66 (3H, s), 0.84 (s, 3H), 0.91 (s, 3H), 1.07 (s, 6H), 1.22 (m, 12H), 1.32 (s, 3H), 1.36−1.76 (m, 16H), 2.16 (dd, J = 14.4, 3.5, 1H), 2.37 (m, 4H),3.45 (m, 4H), 3.70 (dd, J = 10.9, 4.9, 1H), 3.78 (d, J = 15.5, 1H), 4.00 (m, 1H), 4.14 (m, 8H), 5.06 (t, J = 5.2, 1H), 6.95 (s, 1H), 7.14 (s, 1H), 7.33 (m, 8H), 7.50 (d, J = 7.2, 2H); ^{13}C NMR (75 MHz) δ 13.3, 13.6, 13.8, 13.8, 19.2, 19.8, 20.8,

23.9, 24.2, 24.6, 26.6, 26.8, 30.6, 35.9, 36.1, 36.8, 39.2, 39.3, 45.2, 54.5, 54.9, 61.1, 61.3, 76.2, 76.8, 77.4, 78.2, 92.3, 93.4, 120.5, 124.2, 127.6, 127.8, 128.0, 128.6, 128.7, 128.9, 133.1, 135.9, 136.0, 136.7, 170.0, 170.4, 170.6; ν (CH_2Cl_2) 1732 cm^{-1}; HRMS calcd for $C_{28}H_{39}BrO_6$ 551.1832, found 551.1838 ($M^{\bullet+}$).

Cyclization of 23. Cyclization of **23** (100 mg, 0.21 mmol) led, after workup, subsequent treatment with $NaIO_4$ (5 equiv) and OsO_4 (cat.), and purification by LC (0−3% ethyl acetate/pentane) to **25** (47 mg, 56%) and to a mixture of **25** and **26** (15 mg, 18%). The relative ratio of **25**/**26** was determined on the crude mixture from ^{1}H NMR. When the reaction was performed in the presence of 0.2 and 0.4 equiv of Bu_3SnCl, this ratio became, respectively, 82/18 and 81/19.

Acetal 25: ^{1}H NMR (300 MHz) δ 0.79 (s, 3H), 1.03 (d, J = 6.7, 3H), 1.04 (s, 3H), 1.23 (t, J = 7.1, 3H), 1.25 (t, J = 7.1, 3H), 1.30 (s, 3H), 1.15−1.63 (m, 8H), 1.87 (t, J = 12.5, 1H), 1.95 (d, J = 13.6, 1H), 1.92−2.12 (m, 1H), 2.34 (dd, J = 12.8, 7.8, 1H), 3.18 (d, J = 13.6, 1H), 3.84 (broad s, 1H), 4.12−4.20 (m, 2H), 4.16 (q, J = 7.1, 2H); ^{13}C NMR (75 MHz) δ 11.4, 13.9, 16.5, 19.3, 21.2, 24.2, 24.6, 25.9, 27.2, 36.0, 36.1, 41.3, 44.2, 56.5, 61.1, 61.3, 67.7, 77.2, 103.9, 171.8, 172.8. Anal. Calcd for $C_{22}H_{36}O_6$: C, 66.64; H, 9.15. Found: C, 66.50; H, 9.09. The essential characteristics of **26** taken from a mixture are as follows: ^{1}H NMR (300 MHz) δ 0.98 (d, J = 7.1, 3H), 1.03 (s, 3H), 1.10 (s, 3H), 2.41 (dd, J = 13.4, 2.1, 1H), 2.46 (m, 1H), 2.66 (d, J = 13.4, 1H), 2.88 (dd, J = 13.4, 7.9, 1H), 3.74 (dd, J = 10.9, 4.9, 1H).

Cyclization of 24. Cyclization of **24** (55 mg, 0.10 mmol) followed by treatment with catalytic OsO_4 and $NaIO_4$ (107 mg, 0.50 mmol) and purification by LC (95/5 hexane/ethyl acetate) gave **27a** and **28** as an inseparable mixture of diastereomers (30 mg, 64%).

Acetals 27a and 28: ^{1}H NMR δ 0.90 (m, 4H), 0.98 (s, 6H), 1.05 (s, 6H), 1.15 (s, 3H), 1.22 (m, 12H), 1.37 (s, 3H), 1.47 (m, 12H), 1.87 (m, 6H), 2.70 (m, 8H), 3.70 (dd, J = 10.4, 5.3, 0.35H), 3.83 (dd, J = 10.3, 5.2, 0.65H), 4.15 (m, 8H), 7.18 (m, 6H), 7.28 (m, 4H); ^{13}C NMR δ 13.5, 13.7, 14.0, 20.9, 21.1, 23.5, 24.5, 24.7, 25.2, 25.5, 26.9, 27.0, 30.9, 31.2, 35.0, 35.5, 35.9, 37.2, 38.5, 38.8, 44.9, 45.1, 45.3, 55.4, 61.2, 61.5, 61.8, 69.5, 71.7, 78.3, 79.2, 107.5, 108.5, 125.8, 128.4, 129.0, 140.8, 141.2, 171.5, 171.6, 172.9, 173.2; ν (CH_2Cl_2) 1734 cm^{-1}. HRMS calcd for $C_{28}H_{40}O_6$ 478.2824, found 478.2824 ($M^{\bullet+}$).

(2*R*,4a*R*,7*R*,8a*R*)-2-[4-Bromo-2,2-bis(ethoxycarbonyl)-4-penten-1-yl]-4,4,7-trimethylhexahydrobenzo-1,3-dioxin (29, E = CO_2Et). Method A. The reaction of **1** (588 mg, 2.5 mmol) with (−)-*trans*-*p*-menthane-3,8-diol (**22**) led after purification by LC (2% ethyl acetate−pentane) to **29** as a mixture of epimers (>95:5; 1 g, 84%): ^{1}H NMR (300 MHz) major isomer δ 0.91 (d, J = 6.5, 3H), 0.80−1.09 (m, 3H), 1.63−1.71 (m, 1H), 1.15 (s, 3H); 1.17 (s, 3H), 1.25 (t, J = 7.1, 6H), 1.25−1.59 (m, 3H), 1.63−1.71 (m, 1H), 1.83−1.92 (m, 1H), 2.33 (m, 2H), 3.15−3.37 (m, 2H), 3.39 (td, J = 10.6, 4.2, 1H), 4.09−4.24 (m, 4H), 4.93 (t, J = 5.2, 1H), 5.59 (d, J = 1.6, 1H), 5.73 (m, 1H); ^{13}C NMR (75 MHz) δ 13.67, 18.2, 22.0, 24.9, 28.45, 30.9, 34.3, 35.8, 40.3, 43.2, 49.3, 54.2, 61.1, 61.2, 74.7, 74.9, 92.1, 122.0, 127.3, 169.9, 170.0. Anal. Calcd for $C_{22}H_{35}BrO_6$: C, 55.58; H, 7.42. Found: C, 55.37; H, 7.36. Due to the complexity of the spectra of the cyclization products, the homologous dimethyl ester was prepared.

(2*R*,4a*R*,7*R*,8a*R*)-2-[4-Bromo-2,2-bis(methoxycarbonyl)-4-penten-1-yl]-4,4,7-trimethylhexahydrobenzo-1,3-dioxin (29, E = CO_2Me). Method A. The reaction of **1a** (E = CO_2Me) dimethyl acetal (0.984 g, 2.9 mmol) with (−)-*trans*-*p*-menthane-3,8-diol (**22**) led after purification by LC (4% ethyl acetate−pentane) to **29** as a mixture of epimers (>95:5; 1.032 g, 80%): ^{1}H NMR (300 MHz) δ 0.92 (d, J = 6.5, 3H), 0.81−1.09 (m, 3H), 1.15 (s, 3H), 1.18 (s, 3H), 1.26−1.59 (m, 3H), 1.64−1.73 (m, 1H), 1.84−1.92 (m, 1H), 2.33 (m, 2H), 3.22 (dd, J = 15.2, 0.7, 1H), 3.30 (dd,J = 15.2, 0.7, 1H), 3.39 (td, J = 10.6, 4.2, 1H), 3.71 (s, 6H), 4.95 (t, J = 5.3, 1H), 5.60 (d, J = 1.6, 1H), 5.72 (m, 1H); ^{13}C NMR (75 MHz) δ 18.2, 22.0, 24.9, 28.6, 31.0, 34.8, 36.1, 40.4, 43.5, 49.3, 52.3, 52.3, 54.2, 74.8, 74.9, 92.0, 122.1,127.2, 170.4, 170.5. Anal. Calcd for $C_{20}H_{31}BrO_6$: C, 53.70; H, 6.98. Found: C, 54.03; H, 6.98.

(2*R*,4a*R*,7*R*,8a*R*)-2-[4-Bromo-2,2-bis(ethoxycarbonyl)-5-phenyl-4-penten-1-yl]-4,4,7-trimethylhexahydrobenzo-1,3-dioxin (30). Method A. Reaction of 2-bromo-4,4-bis(ethoxycarbonyl)-6,6-diethoxy-1-phenyl-1-hexene (471 mg, 1.0 mmol) and **22** (207 mg, 1.2 mmol) gave **30** (507 mg, 92%) as an inseparable mixture of *E*- and *Z*-isomers: ^{1}H NMR δ 0.98 (m, 15H), 1.22 (m, 23H), 1.68 (m, 4H), 1.88 (m, 2H), 2.24 (m, 2H), 2.38 (dd, J = 5.1, 2.0, 3H), 2.73 (dd, J = 10.7, 4.0, 1H), 3.44 (m, 5H), 3.79 (d, J = 15.5, 1H), 3.98 (m, 1H), 4.16 (m, 8H), 5.00 (t, J = 5.1, 1H), 6.93 (s, 1H), 7.15 (s, 1H), 7.39 (m, 8H), 7.50 (d, J = 6.9, 2H); ^{13}C NMR δ 13.7, 13.8, 13.9, 17.7, 18.5, 22.2, 24.9, 24.1, 28.5, 28.7, 31.8, 31.2, 34.4, 34.6, 36.1, 36.2, 36.9, 40.4, 40.6, 49.3, 49.5, 55.1, 61.2, 61.4, 61.5, 74.5, 74.7, 75.0, 75.2, 91.6, 92.5, 120.4, 124.1, 127.7, 127.8, 128.1, 128.6, 128.7, 128.9, 133.1, 135.9, 136.0, 136.6, 170.1, 170.4, 170.6; ν (CH_2Cl_2) 1731 cm^{-1}. Anal. Calcd for $C_{28}H_{39}BrO_6$: C, 60.98; H, 7.13. Found: C, 60.73; H, 7.15.

Cyclization of 29. Cyclization of **29** (E = CO_2Me) (1.03 g, 2.3 mmol) led, after purification of the crude product by LC (0−2% ethyl acetate/pentane) to a complex mixture of products. After treatment with $NaIO_4$ (5 equiv) and OsO_4 (cat.) in THF/H_2O (4/1) and workup, the crude product was purified by LC (1−4% ethyl acetate/pentane). A mixture of **31**, **32**, and **34** (two epimers) in 30/40/15/15 relative proportions was isolated (606 mg, 72%). Anal. Calcd for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75. Found: C, 64.70; H, 8.68. The ^{1}H NMR spectrum was too complex to be fully assigned: ^{1}H NMR (300 MHz) of the mixture δ 0.82−2.08 (m, 22H), 2.33−2.41 (m, 1.5H), 2.65−2.79 (m, 1H), 3.18−3.23 (m, 0.3H), 3.46 (td, J = 10.6, 4.4, 0.4H, **31**), 3.49−3.57 (m, 0.3H, **32** + **34**), 3.69−3.74 (m, 6H), 4.21 (m, 0.3H, **32**).

Cyclization of 30. Cyclization of **30** (500 mg, 0.91 mmol) and treatment with catalytic OsO_4 and $NaIO_4$ (973 mg, 4.55 mmol) followed by purification by LC (95/5 hexane/ethyl acetate) gave **33** and **35** as an inseparable mixture of diastereomers (279 mg, 65%).

Acetals 33a and 35: ^{1}H NMR δ 0.98 (m, 13H), 1.23 (m, 24H), 1.53 (m, 10H), 1.96 (m, 2H), 2.50 (m, 7H), 2.99 (m, 4H), 3.55 (m, 2H), 4.14 (m, 4H), 7.21 (m, 10H); ^{13}C NMR δ 13.9, 14.0, 14.1, 22.0, 22.2, 22.6, 23.2, 23.8, 25.5, 25.6, 29.5, 29.8, 31.0, 31.2, 31.5, 33.6, 34.4, 34.5, 34.9, 35.0, 35.2, 35.4, 40.7, 40.9, 41.2, 41.3, 45.8, 46.6, 46.7, 47.7, 48.2, 48.9, 49.2, 50.3, 51.2, 54.7, 55.9, 61.2, 61.4, 66.8, 68.0, 69.1, 70.3, 74.1, 74.6, 75.2, 104.6, 105.6, 125.6, 125.7, 128.0, 128.2, 129.9, 141.1, 141.2, 171.8, 172.0, 172.4; ν (CH_2Cl_2) 1735 cm^{-1}. Anal. Calcd for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53. Found: C, 70.82; H, 8.55.

(−)-2-Bromo-4,4-bis(ethoxycarbonyl)-6,6-(10,10-dimethyl-2-*exo*,10-bornanedioxy)-1-hexene (44). Method B: 0 °C. TMS triflate (21 μL, 0.11 mmol) was added to a solution of the bis(trimethylsilyl) diether **42** (3.63 mg, 1.06 mmol) and **2** (340 mg, 1.06 mmol). After workup and purification by LC (3% ethyl acetate/pentane), **44** (390 mg, 73%) was isolated: mp = 97 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82−1.08 (m, 2H), 1.04 (s, 3H), 1.21 (s, 6H), 1.25 (t, J = 7.1, 6H), 1.27 (s, 3H), 1.50−1.78 (m, 5H), 2.33 (d, J = 5.7, 2H), 3.16 (broad d, J = 15.3, 1H), 3.29 (broad d, J = 15.3, 1H), 3.78 (dd, J = 7.8, 2.9, 1H), 4.11−4.21 (m, 4H), 4.96 (t, J = 5.7, 1H), 5.59 (d, J = 1.6, 1H), 5.71−5.72 (m, 1H); ^{13}C NMR (75 MHz) δ 13.8 21.6, 23.6, 24.0, 25.6, 27.0 27.9, 35.7, 36.6, 43.1, 47.0, 47.2, 50.3, 54.35, 61.2, 61.3, 76.2, 79.9, 90.6 , 121.9, 127.6, 170.0, 170.1. Anal. Calcd for $C_{24}H_{37}BrO_6$: C, 57.49; H, 7.41. Found: C, 57.43; H, 7.50.

(−)-2-Bromo-4,4-bis(ethoxycarbonyl)-6,6-(10,10-dimethyl-2-*exo*,10-bornanedioxy)-1-phenyl-1-hexene (45). Method B. To a solution containing **43** (87 mg, 0.22 mmol) and **42** (226 mg, 0.66 mmol) in dichloromethane (5 mL) at −78 °C was added TMSOTf (4.2 μL, 0.022 mmol) and allowed to warm to room temperature over a period of 10 h. After workup and purification by LC (95/5 hexane/ethyl acetate), **45** (60 mg, 49%) was isolated as an inseparable mixture of *E*- and *Z*-isomers: ^{1}H NMR δ 0.49 (s, 3H), 0.95 (m, 11H), 1.23 (m, 22H), 1.56 (m, 10H), 2.23 (m, 1H), 2.39 (d, J = 5.5, 2H), 3.36 (m, 4H), 3.76 (m, 2H), 3.99 (m, 1H), 4.17 (m, 9H), 5.03 (t, J = 5.5, 1H), 6.91 (s, 1H), 7.13 (s, 1H), 7.32 (m, 8H), 7.49 (d, J = 7.1, 2H); ^{13}C NMR δ 13.8, 13.9, 21.8, 22.0, 22.8, 23.8, 24.1, 24.2, 25.5, 25.6, 27.0, 27.1, 27.8, 28.1, 35.9, 36.0, 36.7, 45.0, 46.9, 47.1, 47.2, 47.3, 50.2, 50.4, 54.6, 55.1, 61.1, 61.3, 61.4, 61.5, 75.7, 76.3, 79.5, 80.1, 89.8, 90.9, 120.6, 124.1, 127.6, 127.8,

128.0, 128.6, 128.7, 128.9, 132.9, 135.8, 136.0, 136.6, 170.0, 170.3, 170.4; ν (CH_2Cl_2) 1735 cm^{-1}; HRMS calcd for $C_{30}H_{41}BrO_6$ $(M - H)^+$ 575.2008, found 575.2007.

Cyclization of 44. (a) Cyclization of **44** (138 mg, 0.275 mmol) was conducted at 80 °C according to the standard procedure. After treatment with $NaIO_4$ (5 equiv) and OsO_4 (cat.) and then workup, the crude product was purified by LC (1−3% ethyl acetate/pentane). A 84/11/5 mixture of **46**, **48**, and **49** was isolated (86 mg, 74%).

(b) A solution containing **44** (75 mg, 0.15 mmol), Bu_3SnH (48 μL, 0.18 mmol), and AIBN (5 mg, 0.03 mmol) in benzene (15 mL) was irradiated for 3 h at 18 °C. After concentration, a first purification by LC (0 to 3% ethyl acetate/pentane) yielded a mixture of **46** and **48** (in a 87/13 ratio) together with the uncyclized reduction product and traces of starting material to be isolated. Reductive ozonolysis of the mixture at −80 °C in CH_2Cl_2/MeOH (15 mL/4 mL) led after workup and a second purification by LC (0−3% ethyl acetate/pentane) to a mixture of **46** and **48** (32 mg, 51%). Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.06. Found: C, 67.81; H, 9.20. No traces of **49** were detected.

Acetal 46: ^{1}H NMR (400 MHz) δ 0.87−1.05 (m, 2H), 0.95 (superimposed d, J = 7.2, 3H), 1.03 (s, 3H), 1.17 (s, 3H), 1.22 (s, 3H), 1.25 (t, J = 7.2, 3H), 1.26 (t, J = 7.2, 3H), 1.28 (s, 3H), 1.49−1.69 (m, 4H), 1.68 (superimposed dd, J = 13.7, 3.3, 1H), 1.70−1.80 (m, 1H), 2.40 (d, J = 13.6, 2H), 2.58 (d, J = 13.6, 1H), 2.60−2.69 (m, 1H), 2.91 (dd, J = 13.7, 3.3, 1H), 3.79 (dd, J = 7.8, 2.6, 1H), 4.08−4.22 (m, 4H); ^{13}C NMR (75 MHz) δ 13.9, 13.9, 17.4, 21.8, 23.9, 27.0, 27.1, 28.2, 28.3, 37.2, 37.8, 39.3 45.2, 47.0, 47.2, 55.5, 61.0, 61.3, 75.4, 75.5, 107.3, 171.5, 172.6.

Acetal 48. Characteristic data deduced from spectra of the mixture: ^{1}H NMR (400 MHz) δ 2.85 (dd, J = 13.7, 7.4, 1H), 3.19 (d, J = 13.7, 1H), 4.10−4.21 (m, 4H), 4.50−4.55 (ddd, J = 10.5, 7.5, 2.2, 1H).

Acetal 49. Characteristic data deduced from spectra of the mixture: ^{1}H NMR (400 MHz) δ 2.99 (d, 1H, J = 13.6), 3.80 (partially masked dd, with the smallest of the two couplings J = 2.5, 1H).

Cyclization of 45. (a) Cyclization of **45** (115 mg, 0.20 mmol) according to the standard procedure followed by treatment and purification by LC (95/5 hexane/ethyl acetate) gave **47** and **50** as an inseparable 4/1 mixture of diastereomers (60 mg, 61%). (b) When the experiment was conducted at room temperature the yield of **47**+**50** (94/6) was 29%.

Acetals 47 and 50: ^{1}H NMR δ 0.95 (m, 4H), 1.04 (s, 3H), 1.06 (s, 3H), 1.18 (s, 6H), 1.20 (s, 6H), 1.24 (m, 12H), 1.32 (s, 3H), 1.34 (s, 3H), 1.54 (m, 1H), 1.66 (m, 5H), 1.82 (m, 4H), 2.52 (m, 9H), 2.96 (m, 3H), 3.75 (dd, J = 7.6, 2.6, 1H), 3.86 (dd, J = 7.6, 2.4, 1H), 4.17 (m, 8H), 7.17 (m, 6H), 7.27 (m, 4H); ^{13}C NMR δ 14.1, 21.9, 24.0, 27.1, 28.4, 28.6, 35.8, 37.3, 37.4, 45.2, 45.6, 47.1, 47.3, 50.1, 55.4, 61.1, 61.6, 75.7, 76.3, 107.2, 125.7, 128.2, 129.0, 141.2, 170.1, 170.4; HRMS calcd for $C_{30}H_{42}O_6$ 498.2981, found 498.2974.

Hydrolysis of 46 + 48. A mixture of **46/48/49** (84/11/5) (60 mg, 142 μmol), in solution in acetone (1.4 mL), was stirred with $PdCl_2(CH_3CN)_2$ (1.8 mg, 7 μmol). After 24 h at room temperature, $NaHCO_3$ was added and the solvent was evaporated. Purification by LC (5−10% ethyl acetate/pentane) led to **51** (30 mg, 87%). The 72% ee was determined by ^{1}H NMR in solution in $CDCl_3$ in the presence of the Pirkle alcohol (**53**). The enantiomeric ratio 86/14 indicated that some racemization had occurred concomitantly with the hydrolysis. The CD spectrum showed a negative CE with two minima (λ = 302.5, ϵ = −2.03; λ = 295, ϵ = −2.04; $[\alpha]_{mixture} = +56.6° \rightarrow [\alpha]_D = +78.6°$).

When the **46/48** mixture (12 mg, 0.028 mmol; isolated from the radical reaction at 18 °C according to the above procedure) was treated as above, LC purification led to **51** (6 mg, 87%; 90% ee based on 400 MHz ^{1}H NMR in the presence of **53**).

Hydrolysis was also performed on the mixture of **31**/**32**/**34** (30/40/30) (8.2 mg, 22 μmol), isolated from **29** in acetone-d_6 (0.5 mL). The reaction was monitored by NMR. After workup, the solvent was evaporated and the residue dissolved in $CDCl_3$. The two enantiomers were obtained in a 76/24 ratio (52% ee). NMR data demonstrated that the major enantiomer was reversed with respect to that from the hydrolysis of **46** + **48**.

4,4-Bis(ethoxycarbonyl)-2-methylcyclopentan-1-one (51): ^{1}H NMR δ 1.12 (d, J = 7.0, 3H), 1.25 (t, J = 7.2, 6H), 1.96 (t, J = 12.9, 1H), 2.40 (m, 1H), 2.74 (d, J = 19.1, 1H), 2.86 (m, 1H), 2.98 (d, J = 19.1, 1H), 4.22 (m, 4H). Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.12; H, 7.44.

Hydrolysis of 47 and 50. To a 94/6 mixture of **47** and **50** (25 mg, 0.05 mmol) in acetone (2 mL) was added $Pd(Cl)_2(CH_3CN)_2$ (0.65 mg, 0.0025 mmol) and the reaction mixture allowed to stir at room temperature for 48 h. The reaction mixture was concentrated and purified by LC (95/5 hexane/ethyl acetate) to yield **52** (13 mg, 82%). This ketone (13 mg, 0.04 mmol) was dissolved in methanol (2 mL) and stirred at room temperature with sodium borohydride (1.6 mg, 0.04 mmol) for 2 h. The reaction mixture was concentrated and purified by LC (1/1 hexane/ethyl acetate) to give an 85/15 trans/cis mixture[35] of two diastereomeric alcohols (13 mg, 99%): ^{1}H NMR (major isomer) δ 1.23 (m, 6H), 1.90 (dd, J = 8.7, 13.7, 1H), 2.25 (m, 2H), 2.52 (m, 3H), 2.82 (dd, J = 6.4, 13.7, 1H), 3.99 (q, J = 6.0, 1H), 4.18 (m, 4H), 7.21 (m, 3H), 7.30 (m, 2H); ^{13}C NMR δ 13.9, 34.8, 37.4, 39.2, 41.6, 43.2, 47.8, 49.1, 57.4, 61.2, 61.7, 73.8, 125.9, 126.2, 128.4, 128.5, 128.8, 140.1, 172.1, 172.9. To these alcohols (13 mg, 0.04 mmol) in CCl_4 (200 μL) and pyridine (200 μL) was added (+)-Mosher's acid chloride (20.6 mg, 0.08 mmol) and the reaction mixture allowed to stir overnight, after which time TLC indicated complete conversion. The reaction mixture was diluted with ether (15 mL) and washed with dilute HCl (5 mL), saturated sodium carbonate (5 mL), and brine (5 mL). The organic extracts were dried ($MgSO_4$) and concentrated under vacuum. The ^{19}F NMR spectrum of the extracts consisted of two major resonances (19/81) at δ 195.9 and 249.1 as well as a number of minor signals. Purification by LC (4/1 hexane/ethyl acetate) gave a clean mixture of two Mosher esters (14 mg, 64%) assigned as the diastereomers arising from esterification of the scalemic *trans*-alcohol: ^{1}H NMR δ 1.18 (m), 1.82 (m), 2.29 (dd, J = 4.9 and 14.8, 1H), 2.51 (m), 2.86 (m), 3.46 (s, 3H), 3.49 (s, 3H), 3.55 (s, 3H), 3.57 (s, 3H), 4.09 (m), 5.16 (1H, m), 7.19 (m), 7.43 (m); ^{19}F-NMR δ 195.9 and 249.1 in a ratio of 19/81 (ee 62%). Application of the same protocol to **52** derived from hydrolysis of a 80/20 mixture of **47** and **50** gave the same two ^{19}F NMR signals in a ratio of 31/69 (ee 39%).

2-Benzyl-4,4-bis(ethoxycarbonyl)cyclopentan-1-one (52): ^{1}H NMR δ 1.23 (m, 6H), 2.05 (br.s, 1H), 2.59 (m, 2H), 2.68 (s, 1H), 2.75 (s, 1H), 2.99 (d, J = 18.9, 1H), 3.19 (dd, J = 13.9, 3.4, 1H), 4.19 (m, 4H), 7.15 (d, J = 8.2, 2H), 7.22 (d, J = 7.1, 1H), 7.29 (m, 2H); ^{13}C NMR δ 13.9, 35.5, 35.7, 44.9, 54.7, 62.0, 126.4, 128.5, 128.8, 138.8, 170.6, 170.9, 214.4; ν (CH_2Cl_2) 1744, 1729 cm^{-1}. Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.96. Found: C, 67.60; H, 6.91.

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Supporting Information Available: Details of the preparation and characterization of all the substrates, their precursors, and diols **21** and **41**; derivation of the rate laws in the kinetic analysis (15 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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(35) This tentative assignment of a poorly resolved (^{1}H and ^{13}C NMR) mixture, not essential to the argument, is based on typical reductions of model 2-alkylcyclopentanones: Boone, J. R.; Ashby, E. C. *Top. Stereochem.* **1979**, *11*, 53.