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The Exocyclic Effect: Protecting Group Strategy to Enhance Stereoselectivity in Hydrogen Transfer Reactions of Acyclic Free Radicals

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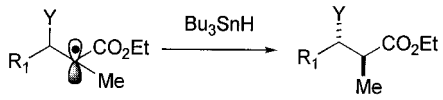
To enhance the diastereoselectivity of the hydrogen transfer reaction of acyclic substrates bearing 1,2- or 1,3-diols, the feasibility of a strategy employing bifunctional protecting groups has been demonstrated. This strategy is based upon the "exocyclic effect" or the significant improvement of *anti*-selectivity exhibited by the reductions of substrates in which the two substituents (R_1 and Y) at the stereogenic center α to the radical center are linked together. A rationale for the excellent facial discrimination of these *exocyclic* radicals is offered based on an analysis of transition state models, which considers both steric and electronic factors.

Introduction

The induction of chirality in radical-based processes involving acyclic substrates has attracted much attention in the past decade.[1−7] Our group has focused particularly on atom and group transfer reactions of radicals (eq 1) which are flanked by an ester and by a stereogenic center bearing an electron-withdrawing group Y (e.g. OMe, OBzl, or F).[8,9] Typical of kinetically controlled reactions, the hydrogen transfers demonstrate enhanced diastereoselectivity at lower reaction temperatures,[8] and ratios as high as 32:1 in favor of the *anti* products could be attained at −78 °C (Table 1, entry 1). However, as our understanding of the structural prerequisites for facial selectivity became clearer, our hope for the general use of this reaction in synthesis began to fade; good diastereoselectivity appeared be limited to substrates bearing an aromatic or a sterically demanding R_1 group (eq 1).[8] As shown by entries 2 and 3 (Table 1), the ratios are significantly decreased when R_1 is smaller, such as an ethyl or isopropyl group.



(1)

If this process had proven to be more general, it would complement the largely *syn*-selective aldol methodologies by providing access to *anti* aldol-like products. A possible means to broaden the scope of this radical-based methodology came to light from the observation that substrates, in which Y and R_1 (eq 1) were linked together, reduced with significantly greater diastereoselectivity than their acyclic counterparts. For example, the hydrogen transfer reactions of **10** and **13** (entries 5 and 6) demonstrate enhanced *anti*-selectivity compared to the

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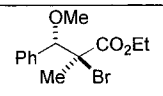
Table 1. Effect of Substituents on Diastereoselectivity of Radical Reduction[a]

Entry	Substrate	Product (*anti:syn*)	Ratio[b] (*anti:syn*)	Solvent	Temperature (°C)	Yield[c] (%)
1	 **1**	**2:3**	30:1	toluene	-78	90
2	**4**: R = H	**5:6**	1.5:1	CH_2Cl_2	-78	89
3	**7**: R = Me	**8:9**	8:1	toluene	-78	66
4	**10**: R = H	**11:12**	8:1	toluene	23	92
5	**10**: R = H	**11:12**	12:1	toluene	-30	90
6	**13**: R = Me	**14:15**	52:1	toluene	-30	93
7	**16**: n = 2	**17:18**	1.5:1	toluene		60
8	**19**: n = 1	**20:21**	2:1	toluene		62
9	**22a**: R_1=Ph, R_2=H	**23:24**	43:1	toluene	-78	69
10	**22a**: R_1=Ph, R_2=H	**23:24**	25:1	toluene	-30	79
11	**22a**: R_1=Ph, R_2=H	**23:24**	14:1	toluene	23	69
12	**22b**: R_1=Ph, R_2=H	**23:24**	40:1	toluene	-78	73
13	**22b**: R_1=Ph, R_2=H	**23:24**	25:1	toluene	-30	81
14	**22**: R_1=Ph, R_2=H	**23:24**	40:1	THF	-78	74
15	**22**: R_1=Ph, R_2=H	**23:24**	21:1	CH_2Cl_2	-78	68
16	**25**: R_1=R_2=Me	**26:27**	32:1	toluene	-78	66
17	**28**: R_1=R_2=H	**29:30**	9:1	toluene	-78	52
18	**31**: R_1=Me,R_2=H	**32:33**	>100:1	toluene	-78	54
19	**34**: R_1=H,R_2=Me	**35:36**	>100:1	toluene	-78	49

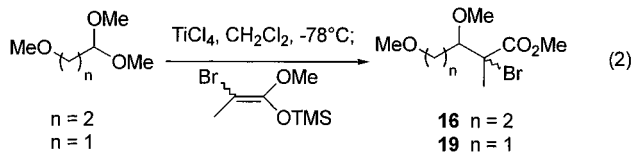
[a]All reactions were performed at a substrate concentration of 0.1 M using 2.0 equiv of Bu_3SnH. Initiation was accomplished using Et_3B. [b]Ratios were determined by ^1H nmr spectroscopy and/or GC. [c]Yields of isolated products.

reactions of their respective acyclic analogues **4** and **7** (entries 2 and 3), respectively. These intriguing observations have subsequently led us to examine the role of the ring in increasing facial selectivity of the radical,[10] as well as to consider various means by which this effect could be exploited synthetically to access molecules with an *anti*-aldol motif.

Opportunities to employ this strategy to good advantage are often presented by synthetic targets bearing functionalities such as 1,2 or 1,3-diols, -amino alcohols, and -diamines, which can be linked together by bifunctional protecting groups[11] prior to radical reduction. To demonstrate the practicality of this strategy, we subjected a series of cyclic and acyclic protected 1,3- and 1,2-diols to hydrogen transfer conditions, the results of which are reported herein.

Results and Discussion

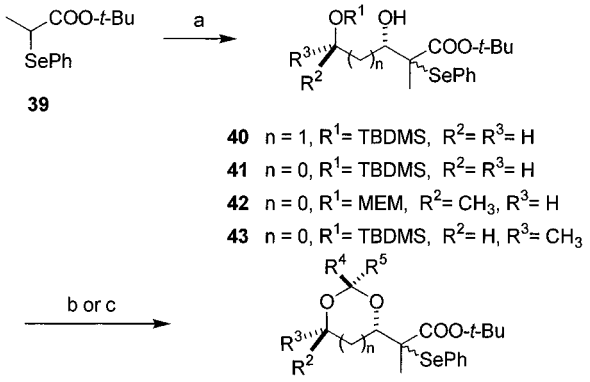
The radical reduction of acyclic protected 1,3- and 1,2-diols **16** and **19** would serve as controls for the reactions of their cyclic counterparts. These compounds were prepared from a Mukaiyama aldol condensation between the corresponding dimethyl acetal and 2-bromo-1-methoxy-1-[(trimethylsilyl)oxy]-1-propene in the presence of $TiCl_4$ (eq 2).



(2)

Scheme 1 shows the two-step synthesis of cyclic substrates **22**, **25**, **28**, **31**, and **34**. Aldol condensation between the α-phenylseleno ester **39** and the appropriate aldehyde (**40**, **41**, **42**, or **43**) gave a mixture of diastereomers, which were separated chromatographically. Each diastereomer was subsequently converted to a cyclic acetal (**22**, **25**, **28**, **31**, or **34**) under conditions that permitted in situ deprotection of either the *tert*-butyldimethylsilyl ether (for **40**, **41**, and **43**) or the methoxymethyl ether (for **42**).

Scheme 1



39

40 n = 1, R^1= TBDMS, R^2= R^3= H
41 n = 0, R^1= TBDMS, R^2= R^3= H
42 n = 0, R^1= MEM, R^2= CH_3, R^3= H
43 n = 0, R^1= TBDMS, R^2= H, R^3= CH_3

22 n = 1, R^2= R^3= H, R^4= H, R^5= Ph
25 n = 1, R^2= R^3= H, R^4= R^5= CH_3
28 n = 0, R^2= R^3= H, R^4= R^5= CH_3
31 n = 0, R^2= CH_3, R^3= H, R^4= R^5= CH_3
34 n = 0, R^2= H, R^3= R^4= R^5= CH_3

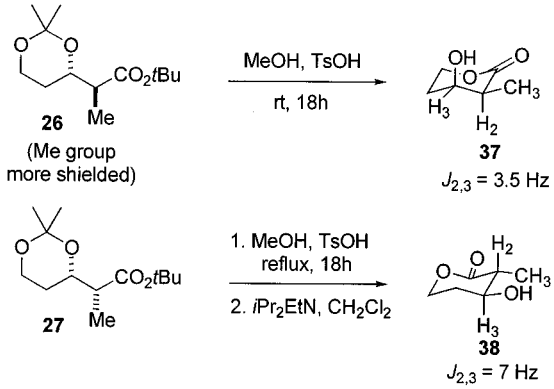
Key: (a) LDA, -78 °C, 1 h; then $(R^1O)R^2R^3C(CH_2)_nCHO$, -78 °C, 1-3 h. (b) When R^1= TBDMS: TsOH, 10 min, MeOH; then $R^4R^5C(OMe)_2$, 20- 30 min. (c) When R^1= MEM: TsOH, $MgBr_2{\cdot}Et_2O$, MeOH, 2,2-dimethoxypropane, 3 h.

Hydrogen Transfer Reactions. Compounds **16**, **19**, **22**, **25**, **28**, **31**, and **34** were subjected to hydrogen transfer with tributyltin hydride for 30 min. These reactions were initiated by the addition of catalytic amounts of Et_3B. As shown by entry 7, the 1,3-diol protected as the acyclic bis(methyl ether) **16** was predictably reduced with little selectivity. By contrast, the hydrogen transfer reactions of the cyclic analogues, such as benzylidene acetal **22** and isopropylidene acetal **25** proceeded with excellent diastereoselectivity (≥32:1; entries 9 and 16) in favor of the *anti* product. In these cases, the relative configuration of the substrate at C-2 had little influence on the stereochemical outcome since the reaction of epimeric selenides **22a** and **22b** (cf. entries 9 and 12; cf. entries 10 and 13) afforded essentially the same product distribution.

Similar results were obtained in the 1,2-diol series. Compared to the poorly selective hydrogen transfer reaction of the 1,2-diol protected as bis(methyl ether) **19** (2:1; entry 8), the reaction of the corresponding isopropylidene acetal **28** demonstrated greater facial differentiation, although the *anti*/*syn* ratio is modest (9:1; entry 17). It is interesting to note that the diastereoselectivity could be further enhanced by alkyl substitution at the γ-carbon (relative to the ester) in this series of cyclic substrates; subjection of the γ-substituted isopropylidene acetals **31** and **34** to radical reduction produced exclusively *anti* products (>100:1; entries 18 and 19). This effect is consistent with the trends observed for the hydrogen transfer reaction of other cyclic substrates studied in our laboratory.[12] In the case of acetal **31** in which the γ-substituent is *anti* to the radical-bearing appendage with respect to the ring, the excellent facial discrimination of the radical is attributed to an electronic control element (vide infra).

Other factors that influence the diastereoselectivity of the hydrogen transfer reaction include reaction temperature and solvent. In all cases shown in Table 1, the ratios favoring *anti* products were higher when the reduction was performed at −78 °C compared to ratios obtained at reaction temperatures of −30 °C or 23 °C (cf. entries 9−11; cf. entries 12 and 13). The solvent effect on the stereochemical outcome is shown by a comparison between entries 9, 14, and 15: greater selectivity was observed when the reaction was conducted in THF or toluene, while there was some erosion in the *anti*-selectivity when dichloromethane was employed as solvent.

Scheme 2



26
(Me group more shielded)

37
$J_{2,3}$ = 3.5 Hz

27

38
$J_{2,3}$ = 7 Hz

The relative configuration of reduced products was deduced by correlation of ^{1}H NMR spectral data. In all cases, the methyl group α to the ester in the *anti* diastereomer resonates slightly upfield to that of the *syn* diastereomer, in agreement with previously published results.[13] A more rigorous stereochemical assignment was performed for the *anti* and *syn* reduction products **26** and **27**, each of which was subjected to acidic methanolic conditions to afford the respective lactones **37** and **38** (Scheme 2). Lactone **37** which is derived from *anti* product **26** is characterized by a smaller H(2)−H(3) coupling constant (3.5 Hz) than that (7 Hz) of lactone **38** derived from *syn* product **27**.

Mechanistic Considerations. While the results described here clearly demonstrate the feasibility of a strategy employing bifunctional cyclic protecting groups to enhance the selectivity of the radical reduction, a rationale for the greater facial discrimination offered by an exocyclic[14] radical (the "exocyclic effect") would be insightful for the development of other strategies based on the same phenomenon. Because these radical-mediated processes are under kinetic control, the rationale for the stereochemical outcome is based on transition state analysis. To account for the predominant *anti*-product, we and others have favored transition state model **A** (Scheme 3),[15] which is stabilized by a balance of steric and electronic factors.[8] Minimization of 1,3- and 1,2-allylic strain, minimization of intramolecular dipole−dipole effects, as well as the beneficial hyperconjugative contribution[12] of R_1 (depicted in **A** to **D** as an ethyl group) have been cited as possible controlling elements that stabilize this transition state model.

We have proposed two transition state models (**B** and **C**) to account for the formation of the minor *syn*-product.

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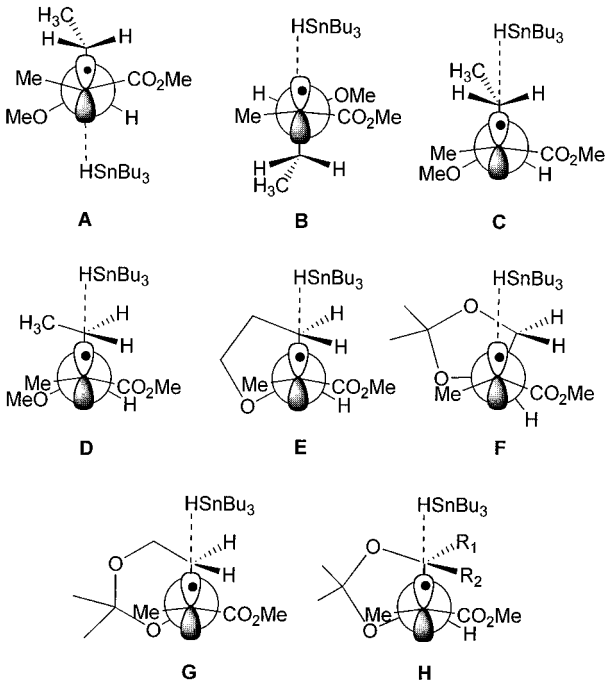
(10) Guindon, Y.; Yoakim, C.; Gorys, V.; Ogilvie, W. W.; Delorme, D.; Renaud, J.; Robinson, G.; Lavallée, J.-F.; Slassi, A.; Jung, G.; Rancourt, J.; Durkin, K.; Liotta, D. *J. Org. Chem.* **1994**, *59*, 1166.

(11) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons, Inc.: New York, 1991; pp 118−142.

(12) Guindon, Y.; Slassi, A.; Rancourt, J.; Bantle, G.; Bencheqroun, M.; Murtagh, L.; Ghiro, É.; Jung, G. *J. Org. Chem.* **1995**, *60*, 288.

Scheme 3



In conjunction with model **A**, they will be analyzed for their consistency with observed product distributions. Indirect support for **B** as the *syn* predictive model is found in the semiempirical calculations performed by Liotta[16] and Giese[17] which revealed a similarity between the second most stable ground state conformer of the radical and the radical depicted in transition state model **B**. Similar to **A**, **B** benefits from hyperconjugative stabilization of the electron-poor, low SOMO radical by the ethyl group. However, 1,3-allylic strain appears to be a key destabilizing factor in **B**; furthermore, intramolecular dipole−dipole interactions are not minimized in this model as they are in **A**. The major shortcoming of the **A**/**B** pair as a model to rationalize stereochemical outcomes is its inability to account for the enhancement of *anti* selectivity when bulkier alkyl groups are used in place of the ethyl group (entries 2 and 3). Since the tin reagent is approaching the radical from the face *opposite* to that shielded by the alkyl group, it is not clear why a size increase of the alkyl group should affect **B** (by diminishing attack by the tin reagent) more than **A**.

The model that best rationalizes our experimental observations to date (in conjunction with model **A**), is depicted as **C**. Clearly the contribution of **C** to the facial selectivity of the reaction would be influenced by (1) the spatial orientation of R_1 relative to the radical p orbital (i.e. extent of overlap between the C−R_1 bond and the radical p orbital), and (2) the steric shielding provided by the alkyl R_1 to top-face attack by the tin reagent. On the basis of the assumption that the radical reaction proceeds through an early transition state, both models **A** and **C** bear a marked similarity to the ground state conformer of the radical.[15,18] In effect, the two products would arise from attack by the tin reagent on either face (**A** or **C**) of the same radical conformer, and the ratio of *anti*- and *syn*-products would be dictated by the energy difference between transition states **A** and **C**.

In the case of the acyclic radical in which R_1 (eq 1) is an ethyl group, the poor diastereoselectivity (Table 1, entry 2) suggests little energy difference between **A** and **C**. Furthermore, the facility of top-face attack by the tin reagent to give *syn*-product suggests the rotamer depicted in **C** (rather than **D**), in which the methyl group (of the ethyl chain) is oriented the farthest from the radical reactive site to provide the least top-face shielding.

This scenario, however, changes considerably when the ethyl and OMe groups are linked to give the tetrahydrofuran **10**. While the structural changes (loss of two hydrogens, additional C−C bond) of cycle formation may seem subtle, they confer a significant enhancement in selectivity (≥8:1) in the hydrogen transfer reaction of **10** (entries 4 and 5). In the reduction of **10**, either the energy barrier to reach the *anti* transition state is decreased, or the energy barrier to reach the *syn* transition state is increased compared to the reaction of the acyclic substrate **4**. It is not clear how cycle formation would render the *anti* pathway more accessible.[10] On the other hand, the enhanced *anti* preference of the exocyclic radical could be more easily rationalized by the greater destabilization of its *syn* transition state relative to the acyclic case; that is, the conformational rigidity of the radical arising from tetrahydrofuran **10** permits greater steric hindrance by the hydrogen at C-4 (relative to ester C-1) to top-face approach of the incoming tin reagent in *syn* transition state **E**. In the reduction of acyclic substrate **4**, the rotamerically analogous *syn* transition state **D** that would provide similar steric encumbrance to top-face attack is destabilized by the steric compression between the methyl group of the R_1 ethyl substituent and the methyl group residing on the radical-bearing center. In essence, the steric contribution of R_1 is magnified in exocyclic radicals.

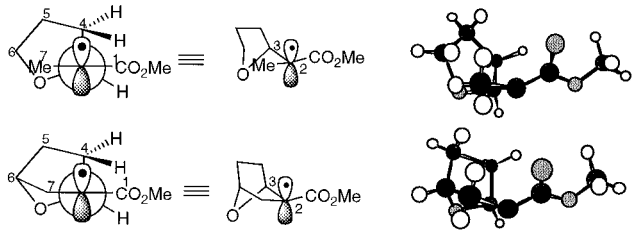
This exocyclic effect however is optimal to diminish top-face attack by the tin reagent only when the C−R_1 bond is orthogonal to the radical π system, permitting overlap between the σ_{C-R_1} bond and the radical p orbital. The extent of orbital overlap (and therefore orthogonality of the C−R_1 bond to the radical π system) is dependent on the σ-donating properties of R_1 in the stabilization of the electron-poor, low SOMO radical through hyperconjugation. We have shown that γ-heteroatom substitutions (relative to the ester) of cyclic substrates have a deleterious effect on the *anti*-selectivity of the hydrogen-transfer reaction, presumably by weakening the SOMO−(C−R_1) interaction and by producing a slight angular offset of this alignment.[12] The poorer diastereoselectivity (9:1; entry 17) exhibited in the reduction of acetonide **28**, as opposed to that of tetrahydrofuran **10** (12:1, entry 5), is attributed to such an offset of alignment (transition state **F**), which would consequently permit more *syn* product formation. When the heteroatom substitution is more remote (e.g. δ-carbon relative to ester) from the radical center (cf. acetonides **25** and **28**), the increased *anti*

(13) Gouzoules, F. H.; Whitney, R. A. *J. Org. Chem.* **1986**, *51*, 2024−2030.

(14) The term "exocyclic effect" refers to the increased diastereoselectivity demonstrated by the reactions of a radical adjacent or *exo* to a ring formed by tethering the β-heteroatom (Y) to the R_1 substituent in the radical shown in eq 1. In contrast to such *exocyclic* radicals, which undergo hydrogen transfer to give predominantly *anti*-products, *endocyclic* radicals derived from bidentate Lewis acid chelation between the ester carbonyl and β-heteroatom react with *syn*-selection.

(15) This model was first proposed by Hart: (a) Hart, D. J.; Huang, H.-C. *Tetrahedron Lett.* **1985**, *26*, 3749. (b) Hart, D. J.; Krishnamurthy, R. *J. Org. Chem.* **1992**, *57*, 4457. Ab initio calculations have been used to reveal the collinear arrangement of attacking and leaving radicals in the transition state of a hydrogen transfer reaction: Dakternieks, D.; Henry, D. J.; Schiesser, C. H. *J. Chem. Soc., Perkin Trans. 2*, **1997**, 1665.

Scheme 4



selectivity (32:1; entry 16) shown in the reaction of **25** is consistent with a stronger SOMO−(C−R_1) interaction (transition state **G**).

The diastereofacial discrimination attributed to the extent of the SOMO−(C−R_1) interaction can be furthermore controlled by alkyl substitution (γ to the ester) on the ring. In comparison with the modestly selective reaction of the unsubstituted acetonide **28**, the radical reduction of the acetonides (entries 18 and 19) substituted with a γ-methyl group afforded exclusively *anti* products (>100:1). By enhancing the hyperconjugative ability of the C−R_1 bond, the methyl substituent *anti* to the radical-bearing appendage on the ring in **31** may confer better top-face shielding through optimal realignment of the C−R_1 bond with the radical p orbital as shown in **H**. Both hyperconjugative and steric shielding effects are probably contributing to the excellent selectivity shown in the reduction of **34**, in which the methyl substituent is *syn* to the radical-bearing appendage on the ring.

Approach of the tin reagent *syn* to the alkyl group may seem highly improbable chiefly because of steric compression between the incoming tin reagent and alkyl substituent. Another argument disfavoring this model could be derived from Houk's "staggered model" describing the trajectory and allylic conformation for attack of radicals on double bonds:[19] *Syn*-attack (with respect to the R_1 alkyl group) would not be favored since rehybridization of the radical center would afford a transition state in which the substituents on the radical center and on the chiral center are eclipsed. While these arguments may be used more often in the rationalization of *major* product formation, *syn* attack may nevertheless contribute to a *minor* reaction pathway, its role becoming more prevalent in the cases where the orientation of the C−R_1 bond deviates from overlap with the radical p orbital.

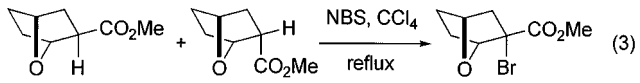
Does the *syn* product arise from transition state **C**? While this question may be very difficult or impossible to address, the *likelihood* of its contribution to the stereochemical outcome could be evaluated however by means such as calculation. To ascertain the *possibility* of *syn* attack, we devised a strategy based on the following line of reasoning: any *syn* product formation from the hydrogen transfer reaction of a radical that is locked in the conformation depicted in a transition state (eg. **C** or **E**) would have to arise from *syn* attack. To minimize the steric perturbation introduced by conformational rigidification, we chose as control a substrate which was already somewhat conformationally limited, such as the tetrahydrofuran **10** (Scheme 4). A conformational lock could be achieved by linking the methyl group (C-7) residing on the radical center to the carbon (C-6) adjacent to the tetrahydrofuran ring oxygen, to approximate the radical rotamer depicted in **E**. A study of a conformationally locked mimic of the radical depicted in transition state **E** under hydrogen transfer conditions thus necessitated the synthesis of 2-bromo-2-*exo*-carbomethoxy-7-oxabicyclo[2.2.1]heptane (**44**). A mixture of bicyclic precursors **45** and **46**, prepared as described by Brion,[20] was smoothly brominated to afford **44** (eq 3).

Table 2. Synperiplanar versus Antiperiplanar Attack in the Radical Reduction[a]

44 **45** **46**

entry	ratio[b] (*anti*:*syn*)	temperature (°C)	yield[c] (%)
1	43:1	−30	62
2	20:1	23	77

[a] All reactions were performed at a substrate concentration of 0.1 M in toluene using 2.0 equiv of Bu_3SnH and Et_3B for initiation. [b] Ratios were determined by ^1H NMR spectroscopy and/or GC. [c] Yields of isolated products.



45 **46** **44**

Predictably, subjection of the bicyclic bromide **44** to hydrogen transfer afforded chiefly the *endo* product (**45**) resultant from *anti* attack (43:1, entry 1, Table 2).[21] To obtain sufficient quantities of the minor product for characterization, the reaction was conducted at a higher temperature (20:1, entry 2). The formation of minor product **46** which can arise only through *syn*-attack thus attests to the plausibility of transition state **E**. Interestingly, the *anti*-selectivity of the reduction of **44** is 3-fold higher than that for the tetrahydrofuran case (cf. entry 1, Table 2 and entry 5, Table 1). This observation suggests that the transition states leading to the *syn* product in these two reactions are not identical; indeed, a slight offset of the C−R_1 bond from overlap with the radical orbital in the tetrahydrofuran case may facilitate the *syn* trajectory of the tin reagent to account for the discrepancy in diastereoselectivities.

Conclusions. We have shown that a bifunctional cyclic protecting group strategy may be employed to significantly increase the selectivity of free-radical based processes involving acyclic substrates. Furthermore, this strategy may be used to best advantage for acyclic substrates bearing a γ-alkyl substituent (i.e. 1,2-diol, in which the γ-alcohol is secondary), as well as for acyclic substrates with 1,3-heteroatom disubstitution. While benzylidene and isopropylidene ketals have been employed successfully in this study, other types of cyclic protecting groups would have to be studied to ascertain the generality of this approach. Based on the *exocyclic effect*, this and other strategies that we are currently developing should broaden the applicability of radical processes in organic synthesis.

Experimental Section

General Methods. All reactions requiring anhydrous conditions were conducted under a positive nitrogen atmosphere in oven-dried glassware and by using standard syringe techniques. The anhydrous solvents were purchased from Aldrich and were used as received. *i*-Pr_2NH and Et_3N were freshly distilled from CaH_2 under N_2 atmosphere. *n*-Butyllithium (1.6 M solution in hexanes) was purchased from Aldrich and titrated prior to use (diphenylacetic acid end-point

in dry THF). Tributyltin hydride, triethylborane (1 M solution in hexanes), *tert*-butyl 2-bromoacetate, and 2,2-dimethoxypropane were also purchased from Aldrich and used as received. 1,1,2-trimethoxyethane and 1,1,3-trimethoxypropane were purchased from Aldrich and distilled prior to use. Flash chromatography was performed on Merck silica gel 60 (0.040−0.063 mm) using nitrogen pressure. Analytical thin-layer chromatography (TLC) was carried out on precoated (0.25 mm) Merck silica gel F-254 plates. Melting points were determined on an electrothermal melting point apparatus and are uncorrected.

The preparation and characterization data of **1**−**15** have been previously reported.[10]

Methyl (±)-2-Bromo-3,5-dimethoxy-2-methylpentanoate (16). To a stirred, cold (−78 °C) solution of 1,1,3-trimethoxypropane (595 μL, 4.17 mmol) in CH_2Cl_2 (20 mL) was added $TiCl_4$ (457 μL, 4.17 mmol). After this solution was stirred for 5 min, 2-bromo-1-methoxy-1-(trimethylsiloxy)-1-propene (2 g, 8.34 mmol) was added dropwise. When the reaction was complete (20 min; TLC), the reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude isolate was purified by flash column chromatography (hexanes−EtOAc, 5:1) and afforded the two diastereomers **16a** (least polar, 409 mg, 37%) and **16b** (most polar, 576 mg, 51%).

Compound **16a**: white solid, mp 31−2 °C; R_f 0.4 (hexanes−EtOAc, 5:1); IR (neat) ν_{max} 1740 cm^{-1}; MS (CI, isobutane) *m/e* 270 (57%, MH^+, ^{81}Br), 268 (55%, MH^+, ^{79}Br), 238 (100%, $M^+ - 34$, ^{81}Br), 236 (97%, $M^+ - 34$, ^{79}Br); ^1H NMR (400 MHz, $CDCl_3$) δ 1.64−1.70 (m, 1H), 1.80 (s, 3H), 2.27−2.31 (m, 1H), 3.36 (s, 3H), 3.41 (s, 3H), 3.50−3.58 (m, 2H), 3.80 (s, 3H), 4.02 (dd, J = 9.9, 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 30.9, 52.8, 58.3, 60.5, 60.9, 69.3, 81.6, 171.2; HRMS (CI, isobutane) calcd for $C_9H_{18}BrO_4$: 269.0388, found: 269.0399 (+4 ppm). Anal. Calcd for $C_9H_{17}BrO_4$: C 40.16%, H 6.37%; found: C 39.76%, H 6.33%.

Compound **16b**: colorless oil; R_f 0.3 (hexanes−EtOAc, 5:1); IR (neat) ν_{max} 1740 cm^{-1}; MS (EI) *m/e* 210 (3%, $MeOCHC^{81}Br(Me)CCO_2Me$), 208 (3%, $MeOCHC^{79}Br(Me)CCO_2Me$), 103 (100%, $M^+ - 166$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.59−1.76 (m, 2H), 1.82 (s, 3H), 3.32 (s, 3H), 3.43−3.55 (m, 2H), 3.58 (s, 3H), 3.78 (s, 3H), 3.87 (dd, J = 9.5, 2.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 32.4, 53.0, 58.3, 61.7, 64.9, 68.9, 82.4, 170.8. Anal. Calcd for $C_9H_{17}BrO_4$: C 40.16%, H 6.37%; found: C 40.15%, H 6.42%.

Methyl (±)-2-Bromo-3,4-dimethoxy-2-methylbutyrate (19). Compounds **19a** (least polar, 243 mg, 15%) and **19b** (most polar, 305 mg, 19%) were prepared using 1,1,2-trimethoxyethane (808 μL, 6.271 mmol) by following the procedure described above for **16**.

***tert*-Butyl (±)-2-(phenylselenenyl)propionate (39).** To a solution of diphenyl diselenide (7.53 g, 24.11 mmol) in MeOH (127 mL) was added in small portions $NaBH_4$ (1.84 g, 48.65 mmol). After the resultant solution was stirred at rt for 10 min, *tert*-butyl (±)-2-bromopropionate (9.0 g, 43.05 mmol) was added. When the reaction was complete (2 h; TLC), the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (100 mL), extracted with CH_2Cl_2, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes−EtOAc, 1:0 to 10:1) afforded **39** (11.5 g, 93%) as a pale yellow oil: R_f 0.6 (hexanes−EtOAc, 9:1); IR (neat) ν_{max} 1725, 1580 cm^{-1}; MS (EI) *m/e* 286 (75%, M^+), 230 (100%, M^+ − isobutylene), 185 (97%, $M^+ - 128$), 157 (85%, PhSeH); ^1H NMR (200 MHz, $CDCl_3$) δ 1.35 (s, 9H), 1.5 (d, J = 7.3 Hz, 3H), 3.7 (q, J = 7.3 Hz, 1H), 7.21−7.68 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.6, 27.8, 38.6, 81.0, 128.1, 128.5, 128.9, 135.3, 172.7; HRMS (EI) calcd for $C_{13}H_{18}O_2Se$: 286.0472, found: 286.0469 (−0.8 ppm).

General Procedure for the Aldol Condensation of the α-Selenenyl Esters with the Corresponding Aldehydes. To a cold (0 °C), stirred solution of *i*-Pr_2NH (1.2 equiv) in THF (anhydrous, 0.2 M solution) under a N_2 atmosphere was added a hexane solution of *n*-butyllithium (1.1 equiv), and the resultant mixture was stirred for 30 min. When the resultant LDA solution was cooled to −78 °C, the α-selenenyl ester was added. After the reaction mixture was stirred at −78 °C for 1 h, the appropriate aldehyde was added, and the resultant solution was stirred at −78 °C until the reaction was complete (1−3 h; TLC). Subsequently, the cold bath was removed, and the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The mixture was then extracted once with Et_2O and twice with CH_2Cl_2, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude mixture by flash column chromatography afforded two diastereomers **a** (least polar) and **b** (most polar).

***tert*-Butyl (±)-5-(*tert*-Butyldimethylsiloxy)-3-hydroxy-2-methyl-2-(phenylselenenyl)pentanoate (40).** Compound **40a** was isolated as a colorless oil (50%): R_f 0.45 (hexanes−EtOAc, 5:1); IR (neat) ν_{max} 3540, 1730 cm^{-1}; MS (EI) *m/e* 474 (3%, M^+), 361 (17%, $M^+ - CO_2tBu$), 241 (100%, $M^+ - 233$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.95 (s, 9H), 1.40 (s, 9H), 1.45 (s, 3H), 1.5−1.9 (m, 2H), 3.62 (s, 1H, OH), 3.75−3.95 (m, 2H), 4.08−4.18 (m, 1H), 7.28−7.5 (m, 3H), 7.68−7.75 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.5, 17.1, 18.2, 25.9, 27.7, 34.2, 56.7, 61.8, 71.7, 81.3, 127.0, 128.6, 129.1, 138.1, 172.0; HRMS (EI) calcd for $C_{22}H_{38}O_4SeSi$: 474.1705, found: 474.1693 (−2.5 ppm). Anal. Calcd: C 55.80%, H 8.09%; found: C 55.44%, H 8.22%.

Compound **40b** was isolated as a colorless oil (25%): R_f 0.4 (hexanes−EtOAc, 5:1); IR (neat), ν_{max} 3500, 1740 cm^{-1}; MS (EI) *m/e* 474 (0.8%, M^+), 361 (33%, $M^+ - CO_2tBu$), 241 (100%, $M^+ - 233$). ^1H NMR (200 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.94 (s, 9H), 1.38 (s, 3H), 1.46 (s, 9H), 1.55−1.75 (m, 1H), 2.10−2.25 (m, 1H), 3.24 (d, J = 5.5 Hz, 1H, OH), 3.8−3.95 (m, 2H), 4.05−4.17 (m, 1H), 7.25−7.48 (m, 3H), 7.6−7.7 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.4, 18.3, 18.5, 25.9, 27.9, 34.4, 54.9, 61.2, 73.3, 81.7, 126.9, 128.6, 129.1, 138.1, 172.9; HRMS (EI) calcd for $C_{22}H_{38}O_4SeSi$: 474.1705, found: 474.1721 (+3.3 ppm). Anal. Calcd: C 55.80%, H 8.09%; found: C 55.57%, H 8.24%.

Aldol Condensation of *tert*-Butyl (±)-2-(Phenylselenenyl)propionate (39) with (±)-2-[(2-Methoxyethoxy)-methoxy]propionaldehyde. The use of THF as solvent produced a mixture of the (3*S**,4*S**) diastereomers (epimeric at C-2). To also access the desired (3*R**,4*S**) diastereomers, toluene was used as a solvent; four diastereomers were obtained as a 1:1:2:2 mixture in 60% yield. Purification by dry-packed flash column chromatography (CH_2Cl_2−acetone, 20:1) afforded the (3*R**,4*S**) **42a** and **42b** diastereomers as an unseparable mixture (minor), and the (3*S**,4*S**) **42c** and **42d** diastereomers as an unseparable mixture (major).

***tert*-Butyl (±)-(3*R**,4*S**)-4-[(2-methoxyethoxy)methoxy]-3-hydroxy-2-methyl-2-(phenylselenenyl)pentanoates (42a and 42b)**: colorless oil; R_f 0.42 (CH_2Cl_2−acetone, 20:1); IR (neat) ν_{max} 3520, 1715, 1575 cm^{-1}; MS (CI, isobutane) *m/e* 449 (6%, MH^+), 393 (27%, MH^+ − isobutylene), 373 (28%, $M^+ - OCH_2CH_2OCH_3$), 317 (100%, $M^+ - 131$); ^1H NMR (400 MHz, $CDCl_3$, mixture of diastereomers; major italic) δ 1.22 (d, J = 6.4 Hz, 3H), *1.31* (s, 3H), *1.32* (d, J = 7.3 Hz, 3H), *1.36* (s, 3H), *1.47* (s, 9H), *3.19* (d, 1H), *3.36* (s, 3H), 3.38 (s, 3H), *3.51* (t, J = 4.7 Hz, 1H), 3.55 (t, J = 4.5 Hz, 1H), 3.65−3.78 (m), 3.91 (qd, J = 6.7, 3.5 Hz, 1H), *3.95* (d, J = 10.5 Hz, 1H), *4.11* (qd, J = 6.0, 1.5 Hz, 1H), 4.63 (d, J = 7.3 Hz, 1H), 4.75−4.83 (m), 7.26−7.4 (m), 7.58−7.68 (m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 20.4, 27.8, 53.2, 58.9, 67.6, 71.7, 71.9, 80.2, 81.9, 93.6, 126.9, 128.7, 129.1, 138.2, 172.8. Anal. Calcd for $C_{20}H_{32}O_6Se$: C 53.69%, H 7.21%; found: C 53.54%, H 7.39%.

***tert*-Butyl (±)-(3*S**,4*S**)-4-[(2-methoxyethoxy)methoxy]-3-hydroxy-2-methyl-2-(phenylselenenyl)pentanoates (42c and 42d)**: colorless oil; R_f 0.35 (CH_2Cl_2−acetone, 20:1); IR (neat) 3520, 1715, 1575 cm^{-1}; MS (CI, isobutane) *m/e* 449 (5%, MH^+), 431 (7%, $MH^+ - H_2O$), 373 (50%, $M^+ - OCH_2CH_2OCH_3$), 317 (100%, $M^+ - 131$); ^1H NMR (400 MHz, $CDCl_3$, mixture of diastereomers, major italic) δ 1.27 (d, J = 6.4 Hz, 3H) 1.32 (s, 9H), *1.33* (s, 3H), *1.34* (d, J = 6.0 Hz, 3H), 1.39 (s, 3H), 1.43 (s, 9H), *2.98* (d, J = 2.2 Hz, 1H), *3.36* (s, 3H), 3.38 (s, 3H), *3.50* (t, J = 4.5 Hz, 1H), 3.54 (t, J = 4.8 Hz, 1H), 3.62−3.75 (m), 3.91 (quint, J = 5.7 Hz, 1H), *4.58* (d, J = 7.3 Hz, 1H), *4.71* (d, J = 7.3 Hz, 1H), 4.74 (d, J = 7.0 Hz, 1H), 4.78 (d, J = 7.0 Hz, 1H), 7.16−7.40 (m), 7.60−7.64 (m); ^{13}C NMR (100

MHz, $CDCl_3$) δ 16.0, 16.7, 17.1, 18.4, 27.7, 27.9, 58.0, 59.0, 66.6, 71.7, 74.5, 75.4, 80.7, 94.0, 94.22, 127.1, 128.7, 128.9, 129.3, 137.8, 138.4, 171.1. Anal. Calcd for $C_{20}H_{32}O_6Se$: C 53.69%, H 7.21%; found: C 53.53%, H 7.35%.

General Procedure for the *in Situ* Deprotection of the *tert*-Butyldimethylsilyl Ethers 40 (a and b) and Formation of the Benzylidene Acetals 22 (a and b). To a 0.1 M solution of the alcohol **40a** or **40b** in MeOH was added *p*-toluenesulfonic acid monohydrate (0.3 equiv). The deprotection was monitored by TLC (10 min), and when the reaction was complete, benzaldehyde dimethylacetal (1/10 v/v) was added. After the resultant mixture was stirred for 20 min, the solvent was evaporated under reduced pressure and replaced with an equal volume of CH_2Cl_2. When the reaction was completed (5 min; TLC), the reaction mixture was diluted with more CH_2Cl_2, washed with a saturated aqueous solution of $NaHCO_3$, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude benzylidene acetals were then purified by flash column chromatography (hexanes−EtOAc, 20:1).

***tert*-Butyl (±)-2(2*R**,4*R**)-2-[2-Phenyl-1,3-dioxan-4-yl]-2-(phenylselenenyl)propionate (22).** Compound **22a**, prepared from **40a**, was isolated as a colorless oil (88%); R_f 0.35 (hexanes−EtOAc, 9:1); IR (neat) ν_{max} 1710, 1580 cm^{-1}; MS (EI) *m/e* 448 (39%, M^+), 241 (13%, $M^+ - 207$), 163 (100%, $M^+ - CH_3(PhSe)CHCO_2tBu$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.56 (s, 3H), 1.94 (qd, J = 12, 5 Hz, 1H), 3.88 (qd, J = 12, 2.6 Hz, 1H), 4.03 (dd, J = 11, 1.8 Hz, 1H), 4.24 (dd, J = 11, 4.4 Hz, 1H), 5.42 (s, 1H), 7.2−7.7 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.8, 26.1, 27.8, 53.6, 66.6, 78.5, 81.4, 101.3, 126.0, 127.1, 128.2, 128.5, 128.7, 129.2, 138.4, 138.5, 171.0; HRMS (EI) calcd for $C_{23}H_{28}O_4Se$: 448.1153, found: 448.1148 (−1.0 ppm). Anal. Calcd: C 61.74%, H 6.31%; found: C 61.80%, H 6.29%.

General Procedure for the *in Situ* Deprotection of the *tert*-Butyldimethylsilyl Ethers 40, 41, and 43, and Formation of the Isopropylidene Acetals 25, 28, and 34. To a 0.1 M solution of the alcohol **a** or **b** of **40**, **41**, or **43** in MeOH was added *p*-toluenesulfonic acid monohydrate. The deprotection was monitored by TLC (10 min) and when it was complete, 2,2-dimethoxypropane (1/1 v/v) was added. After the resultant mixture was stirred for 20 min, the solvents were evaporated under reduced pressure and replaced with 2,2-dimethoxypropane. When acetal formation was complete (5 min; TLC), the reaction mixture was diluted with CH_2Cl_2, washed with a saturated aqueous solution of $NaHCO_3$, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude acetals were then purified by flash column chromatography (hexanes−EtOAc, 20:1).

***tert*-Butyl (±)-2-(2,2-Dimethyl-1,3-dioxan-4-yl)-2-(phenylselenenyl)propionate (25).** Compound **25a**, prepared from **40a**, was isolated as a colorless oil (86%); R_f 0.3 (hexanes−EtOAc, 9:1); IR (neat) ν_{max} 1710, 1580 cm^{-1}; MS (EI) *m/e* 400 (29%, M^+), 385 (10%, $M^+ - 15$), 286 (16%, $M^+ - 114$), 115 (100%, $M^+ - CH_3(PhSe)CHCO_2tBu$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.35 (s, 9H), 1.40 (s, 3H), 1.42 (s, 3H), 1.48 (s, 3H), 1.75 (qd, J = 12, 5 Hz, 1H), 3.81 (ddd, J = 12, 6, 2 Hz, 1H), 3.92 (td, J = 12, 3 Hz, 1H), 4.28 (dd, J = 11, 3 Hz, 1H), 7.22−7.41 (m, 3H), 7.62−7.68 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.9, 19.1, 26.1, 27.7, 29.7, 54.2, 59.6, 71.8, 81.3, 98.9, 127.4, 128.4, 128.9, 138.1, 171.1; HRMS calcd for $C_{19}H_{28}O_4Se$: 400.1153; found: 400.1157 (+1.1 ppm). Anal. Calcd (mixture of diastereomers **25a** and **25b**): C 57.14%, H 7.07%; found: C 56.92%, 7.20%.

Compound **25b**, prepared from **40b**, was isolated as a white solid (71%); mp 82−3 °C; R_f 0.4 (hexanes−EtOAc, 9:1); IR (neat) ν_{max} 1710, 1570 cm^{-1}; MS (EI) *m/e* 400 (32%, M^+), 385 (19%, $M^+ - 15$), 286 (28%, $M^+ - 114$), 115 (100%, $M^+ - CH_3(PhSe)CHCO_2tBu$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.36 (s, 9H), 1.37 (s, 3H), 1.40 (s, 3H), 1.75 (qd, J = 12, 5.4 Hz, 1H), 1.89 (qd, J = 2.5, 13 Hz, 1H), 3.92 (ddd, J = 12, 5.4, 2 Hz, 1H), 3.98 (td, J = 12, 3 Hz, 1H), 4.38 (dd, J = 12, 2.5 Hz, 1H), 7.26−7.41 (m, 3H), 7.58−7.62 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.9, 19.1, 25.8, 27.8, 29.7, 52.9, 60.3, 72.2, 80.7, 98.8, 126.6, 128.7, 129.2, 138.0, 171.7; HRMS calcd for $C_{19}H_{28}O_4Se$: 400.1153, found: 400.1157 (+1.1 ppm). Anal. Calcd (mixture of diastereomers **25a** and **25b**): C 57.14%, H 7.07%; found: C 56.92%, H 7.20%.

***tert*-Butyl (±)-[2*RS*,2(4*R**,5*S**)]-2-(2,2-Dimethyl-5-methyl-1,3-dioxolan-4-yl)-2-(phenylselenenyl)propionate (31).** To a stirred solution of the diastereomeric mixture of alcohols **42a** and **42b** (317 mg, 0.709 mmol) in 2,2-dimethoxypropane (7 mL) and MeOH (2.3 mL) were successively added $MgBr_2 \cdot Et_2O$ (183 mg, 0.709 mmol) and *p*-toluenesulfonic acid monohydrate (141 mg, 0.709 mmol). When acetal formation was complete (3 h; TLC), the reaction mixture was diluted with CH_2Cl_2, washed with a saturated aqueous solution of $NaHCO_3$, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude acetals were then purified by flash column chromatography (hexanes−EtOAc, 3:1) and afforded an unseparable diastereomeric mixture of the desired products **31** as a colorless oil (208 mg, 73%): R_f 0.64 (hexanes−EtOAc, 3:1); IR (neat) ν_{max} 1720, 1575 cm^{-1}; MS (CI, isobutane) *m/e* 400 (4%, MH^+), 287 (27%, $M^+ - 113$), 285 (13%, $CH_3(PhSe)CHCO_2tBu$), 230 (22%, $M^+ - 170$), 115 (100%, $M^+ - 285$); ^1H NMR (200 MHz, $CDCl_3$, 2 diastereomers, major italic) δ *1.27* (d, J = 6.0 Hz, 3H), 1.37 (s, 9H), 1.38 (s, 3H), 1.39 (s, 3H), *1.40* (s, 9H), *1.43* (s, 3H), *1.44* (s, 6H), *1.46* (s, 3H), 1.52 (d, J = 6.0 Hz, 3H), *4.01* (d, J = 7.6 Hz, 1H), *4.05* (qd, J = 6.0, 7.3 Hz, 1H), 4.19 (qd, J = 5.7, 7.3 Hz, 1H), 4.22 (d, J = 7.3 Hz, 1H), 7.26−7.32 (m, 3H), 7.35−7.40 (m, 3H), 7.60−7.63 (m, 2H), 7.68−7.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 18.3, 19.8, 21.5, 26.9, 27.4, 27.5, 27.8, 50.5, 73.2, 73.9, 81.3, 81.6, 84.0, 84.8, 107.9, 108.2, 126.5, 127.1, 128.5, 128.7, 129.2, 137.9, 138.2, 170.9, 171.0. Anal. Calcd for $C_{19}H_{28}O_4Se$: C 57.14%, H 7.07%; found: C 56.84%, H 7.16%.

(±)-*exo*-2-Bromo-2-carbomethoxy-7-oxabicyclo[2.2.1]-heptane (44). To a solution of a 1:2 mixture[20] of **45** and **46** (2.19 g, 14.0 mmol) in CCl_4 (50 mL) was added *N*-bromosuccinimide (12.5 g, 72.2 mml), and the resultant solution was then refluxed for 17 h. After the reaction mixture was allowed to cool to room temperature, it was filtered through Celite, and the filtrate was concentrated under vacuum. ^1H NMR analysis of the crude reaction isolate indicated a 2.5:1 mixture of **46** and the desired bromide **44**, respectively. Flash column chromatography (CH_2Cl_2) afforded **46** R_f 0.75 (CH_2Cl_2−acetone, 10:1) and **44** as a white solid (817 mg, 52% based on recovered starting material): R_f 0.95 (CH_2Cl_2−acetone, 10:1); IR (neat) ν_{max} 1730 cm^{-1}; MS (CI, isobutane) *m/e* 236 (9%, MH^+), 208 (81%), 206 (82%), 95 (100%); ^1H NMR (400 MHz, $CDCl_3$) δ 1.37−1.49 (m, 2H), 1.70−1.85 (m, 2H), 2.51 (ddd, J = 1.7, 6.2, 14.6 Hz, 1H), 2.68 (d, J = 14.6 Hz, 1H), 3.81 (s, 3H), 4.72 (t, J = 4.5 Hz, 1H), 4.73 (d, J = 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 28.6, 46.2, 53.2, 62.8, 78.0, 84.1, 169.9; HRMS calcd for $C_8H_{11}BrO_3$: 233.9891; found: 233.9888 (−1.8 ppm). Anal. Calcd for $C_8H_{11}BrO_3$: C 40.87%, H 4.72%; found: C 40.91%, H 4.76%.

General Procedure for Radical Reduction. A 0.1 M solution of substrate in solvent was brought to the desired temperature. Bu_3SnH (1.2 equiv for **16**, **19**, **22**, **25**, **28**, **31**, and **34**; or 2.0 equiv for **1**, **4**, **7**, **10**, and **13**) and Et_3B (1 M solution in hexane, 0.1−0.2 equiv) were then successively added. When the reduction was completed (TLC), the reaction mixture was concentrated under reduced pressure, and the crude isolate was partitioned between hexane and MeCN. The two phases were concentrated. The crude oil obtained from the hexane phase was analyzed by ^1H NMR to verify that no product other than Bu_3SnX was in the hexane layer. The ratios were determined by ^1H NMR or GC on the crude mixture obtained from the MeCN layer. This crude mixture was then purified by flash chromatography to afford the reduced product(s) with isolated yields ranging from 49 to 90%.

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Methyl (±)-3,5-Dimethoxy-2-methylpentanoates (17 and 18). Compounds **17** and **18** were isolated prior to purification as a 1.5:1 mixture (ratio determined by ^{1}H NMR): colorless oil; R_f 0.3 (hexanes−EtOAc, 5:1); IR (neat), ν_{max} 1735 cm^{-1}; MS (CI, isobutane) *m/e* 191 (59%, MH$^+$), 159 (100%, MH$^+$ − MeOH), 127 (100%, MH$^+$ − 2MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, 1.5:1 mixture of diastereomers, major *anti* product italic) δ *1.09* (d, J = 7 Hz, 3H), 1.15 (d, J = 7 Hz, 3H), 1.60−1.82 (m, 2H), 2.61 (qd, J = 7.0, 5.1 Hz, 1H), *2.72* (quint, J = 7 Hz, 1H), *3.30* (s, 3H), 3.31 (s, 3H), *3.32*, (s, 3H), 3.34 (s, 3H), 3.40−3.50 (m, 2H), 3.52−3.62 (m, 1H), 3.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.71, *11.91*, *30.75*, 32.14, *42.96*, 43.18, 51.54, *57.84*, 58.17, 58.44, 58.50, *68.79*, 69.09, 79.19, *79.37*, 175.13.

***tert*-Butyl (±)-(2*R**,4*R**)-2-(2-Phenyl-1,3-dioxan-4-yl)-propionates (23 and 24).** Compounds **23** (*anti*) and **24** (*syn*) were isolated prior to purification as a mixture, the ratio of which was determined by GC.[22]

***t*-Butyl (±)-2-(2,2-Dimethyl-1,3-dioxan-4-yl)propionates (26 and 27).** Compounds **26** (*anti*) and **27** (*syn*) were isolated prior to purification as a mixture, the ratio (32:1) of which was determined by GC.[22]

(±)-(2*R,3*R**)-3-Hydroxy-2-methyl-δ-valerolactone (37).** A methanolic (3.5 mL) solution containing acetal **26** (103 mg, 0.351 mmol) and *p*-toluenesulfonic acid monohydrate (21 mg, 0.262 mmol) was refluxed overnight. The reaction mixture was concentrated under reduced pressure, diluted with CH_2Cl_2 (3.5 mL), and treated for 6 h with *i*Pr$_2$EtN (61 mL, 0.351 mmol). The reaction mixture was then concentrated under reduced pressure, and the product was purified by flash chromatography (CH_2Cl_2−acetone, 5:1) which afforded **37** (32 mg, 70%) as a colorless oil: R_f 0.28 (CH_2Cl_2−acetone, 10:1). IR (neat) ν_{max} 3450, 1720 cm^{-1}; MS (CI, isobutane) *m/e* 131 (100%, MH$^+$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32 (d, J = 7.1 Hz, 3H), 2.00 (dddd, J = 15.0, 5.9, 5.1, 4.0 Hz, 1H), 2.14−2.20 (m, 1H), 2.24 (dddd, J = 14.6, 10.1, 5.5, 4.6 Hz, 1H), 2.64 (qd, J = 7.13, 3.65 Hz, 1H), 4.22−4.29 (m, 1H), 4.30 (td, J = 5.7, 11.5 Hz, 1H), 4.58 (ddd, J = 11.5, 8.2, 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 31.0, 41.3, 65.0, 67.2, 173.9.

(±)-(2*S,3*R**)-3-Hydroxy-2-methyl-δ-valerolactone (38).** A methanolic solution containing acetal **27** (255 mg, 0.872 mmol) and *p*-toluenesulfonic acid monohydrate (52 mg, 0.262 mmol) was stirred at rt for 12 h. The reaction mixture was concentrated under reduced pressure, and the product was purified by flash chromatography (CH_2Cl_2−acetone, 5:1) which afforded **38** (71 mg, 62%) as a colorless oil: R_f 0.3 (CH_2Cl_2−acetone, 10:1); IR (neat) ν_{max} 3400, 1720 cm^{-1}; MS (CI, isobutane) *m/e* 131 (100%, MH$^+$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (d, J = 7.0 Hz, 3H), 1.92 (tdd, J = 6.4, 16.4, 4.2 Hz, 1H), 2.13−2.29 (m, 1H), 2.55 (quint, J = 7.3 Hz, 1H), 3.23 (d, J = 4.4 Hz, 1H, exch. D_2O), 3.78−3.92 (m, J = 7.0 Hz, 1H, q after exch D_2O), 4.26 (ddd, J = 13.3, 6.6, 4.6 Hz, 1H), 4.50 (ddd, J = 12.2, 8.2, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 31.0, 44.0, 65.0, 69.2, 174.5. Anal. Calcd for $C_6H_{10}O_3$: C 55.37%, H 7.75%; found: C 54.95%, H 7.89%.

***tert*-Butyl (±)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)propionates (29 and 30).** Compounds **29** and **30** were isolated prior to purification as a mixture, the ratio (9:1) of which was determined by GC.[22]

***tert*-Butyl (±)-2-(2,2-Dimethyl-5-methyl-1,3-dioxolan-4-yl)propionates (32 and 33).** Compounds **32** and **33** were isolated prior to purification as a mixture, the ratio of which was determined by GC.[23]

***tert*-Butyl (±)-2-(2,2-Dimethyl-5-methyl-1,3-dioxolan-4-yl)propionates (35 and 36).** Compounds **35** and **36** were isolated prior to purification as a mixture, the ratio (>100:1) of which was determined by GC.[23]

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Supporting Information Available: Characterization data for compounds **19**−**24**, **26**, **27**−**30**, **32**−**36**, **41**, **43**, **45**, **46**; ^{13}C NMR spectra for compounds **17**, **18**, **20**, **21**, **32**, **33**, **36**, **37**, and **39** (15 pages). This material is available on microfiche in libraries, immediately follows this article in the microfilm version of the journal, can be ordered from ACS, and can be downloaded through the Internet; see any current masthead page for ordering information and Internet access instructions.

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(21) The similarity in *anti*:*syn* ratios when tributyl deuteride was used showed that the role of intramolecular hydrogen transfer was negligible.

(22) The minor (*syn*) radical reduction product was synthesized via a different sequence for characterization purposes: Aldol condensation of the appropriate aldehyde with *tert*-butyl propionate instead of *tert*-butyl 2-(phenylselenenyl)propionate, followed by in situ deprotection of the *tert*-butyldimethylsilyl ether and formation of the acetal. This sequence afforded the same products as the radical reduction but where the *syn* diastereomer is favored.

(23) This minor *syn* radical reduction product was obtained via a different procedure for characterization purposes. The radical reduction was performed in CH_2Cl_2 at −78 °C in the presence of $MgBr_2 \cdot Et_2O$ (5 equiv). This modification gave an *anti*:*syn* ratio of 1.4:1 and 3.5:1 for **34** and **31**, respectively.