Synthesis of Propionate Motifs: Diastereoselective Tandem Reactions Involving Anionic and Free Radical Based Processes

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Abstract: Reported herein is a strategy employing a Mukaiyama reaction in tandem with a hydrogen transfer reaction for the elaboration of propionate motifs. The nature of the protecting groups on the chiral β-alkoxy aldehyde and the type of Lewis acid used are varied to modulate the stereochemical outcome of the tandem reactions. The mode of complexation is thus controlled (monodentate or chelate) for the Mukaiyama reaction to give access to either syn or anti aldol products, precursors of the free radical reduction reaction. The endocyclic effect is subsequently capitalized upon to control the hydrogen transfer step so that the syn-reduced product may be achieved. Proceeding with excellent yield and diastereoselectivity, the synthetic sequence proposed gives access to syn-syn and syn-anti propionate motifs. Also considered is a complementary approach using a chelation-controlled Mukaiyama reaction in tandem with a free radical allylation reaction under the control of the endocyclic effect that leads to the anti-anti product.

The synthesis of propionate motifs,[1] generally found in biologically important polyketide products, has been a topic of considerable interest for organic chemists. Many approaches have been developed for the elaboration of propionate motifs, but few[2] have offered all four motifs with good diastereocontrol. To this end, we have been intrigued by the prospect of an approach involving a free radical based hydrogen transfer reaction as a key element of a tandem reaction sequence. Such a strategy might have been considered a heresy just a decade ago, prior to the advent of free radical intermediates being used in reactions aimed at achieving the induction of stereogenic centers on acyclic molecules.[3]

Our group has worked extensively with reactions involving free radicals flanked by an ester moiety and a carbon center bearing a heteroatom such as an oxygen,[4] and we have recently demonstrated that it is possible to predetermine the outcome of a hydrogen transfer reaction by varying the type of Lewis acid (L.A.) used.[5] Indeed, some Lewis acids can coordinate with the oxygen of the stereogenic center α to the carbon-centered radical and another neighboring heteroatom to form a temporary ring adjacent to the radical center that contributes to an enhancement of anti selectivity (the *exocyclic effect*, Scheme 1a).[4b,c] Alternatively, and central to this present study, some Lewis acids chelate between the oxygen of the stereogenic center and the carbonyl of the ester, leading to the syn product with high stereocontrol (the *endocyclic effect*, Scheme 1b).[5a,c,d] Another approach we have developed employs the control of the endocyclic effect to arrive at the anti product in allylation reactions with secondary or tertiary halides (Scheme 1c).[5b,e]

The efficiency of Lewis acid in controlling not only radical reactions but also other types of reactions involving chelated intermediates inspired us to consider the possibility of a tandem process that would give access to propionate motifs. The Mukaiyama reaction,[6] a powerful variant of the classical aldol reaction, seemed a plausible candidate for the tandem sequence

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(1) Selected examples: (a) Iio, H.; Nagaoka, H.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7965 and preceding papers. (b) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487. (c) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem.* **1985**, *97*, 1; *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (d) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151. (e) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797. (f) Paterson, I.; Cumming, J. G. *Tetrahedron Lett.* **1992**, *33*, 2847. (g) Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233. (h) Harada, T.; Inoue, A.; Wada, I.; Uchimura, J.; Tanaka, S.; Oku, A. *J. Am. Chem. Soc.* **1993**, *115*, 7665. (i) Hoffmann, R. W.; Dahmann, G.; Anderson, M. W. *Synthesis* **1994**, 629. (j) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073. (k) Hanessian, S.; Gai, Y.; Wang, W. *Tetrahedron Lett.* **1996**, *37*, 7473. (l) Roush, W. R.; Chemler, S. R. *J. Org. Chem.* **1998**, *63*, 3800.

(2) (a) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 3701. (b) Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556. (c) Marshall, J. A.; Maxson, K. *J. Org. Chem.* **2000**, *65*, 630.

(3) (a) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (b) Liotta, D. C.; Durkin, K. A.; Soria, J. J. *Chemtracts* **1992**, *5*, 197. (c) Miracle, G. S.; Cannizzaro, S. M.; Porter, N. A. *Chemtracts* **1993**, *6*, 147. (d) Smadja, W. *Synlett* **1994**, 1. (e) Giese, B.; Damm, W.; Batra, R. *Chemtracts* **1994**, *7*, 355. (f) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions − Concepts, Guidelines and Synthetic Applications*; VCH: New York, 1996. (g) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562.

(4) (a) Guindon, Y.; Yoakim, C.; Lemieux, R.; Boisvert, L.; Delorme, D.; Lavallée, J.-F. *Tetrahedron Lett.* **1990**, *31*, 2845. (b) 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. (c) Guindon, Y.; Faucher, A.-M.; Bourque, É.; Caron, V.; Jung, G.; Landry, S. R. *J. Org. Chem.* **1997**, *62*, 9276 and references therein.

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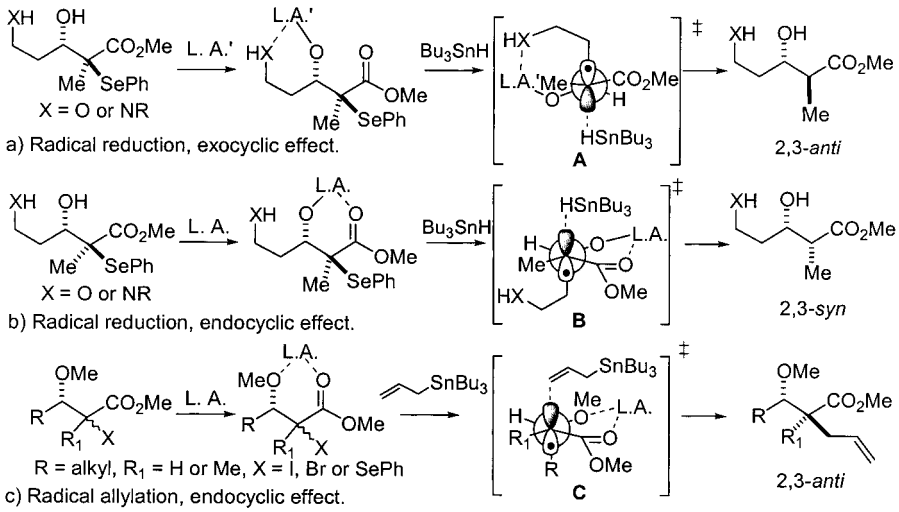
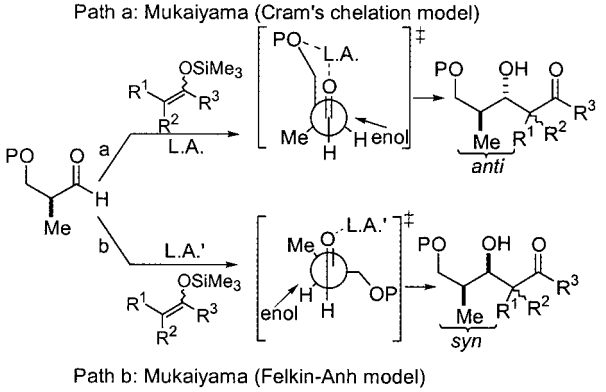
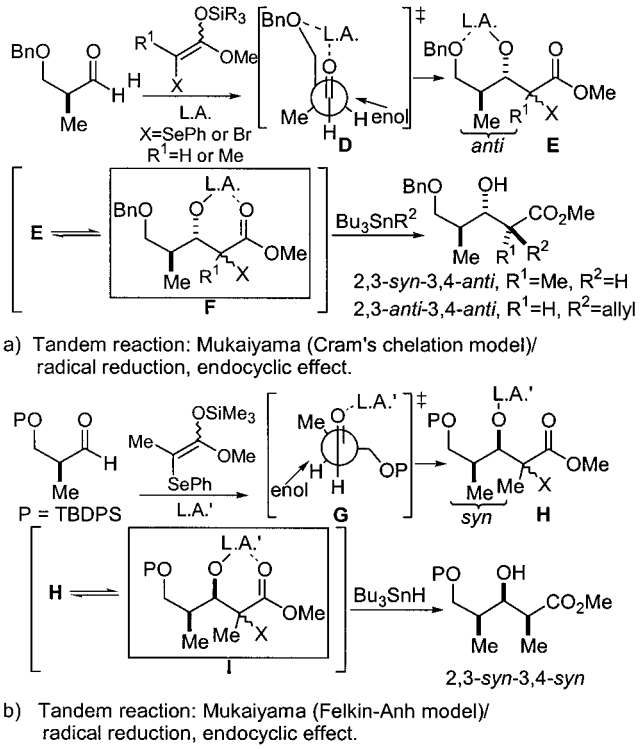
Scheme 1



Scheme 2



Scheme 3



in question for two reasons. First, the outcome of this carbon−carbon bond-forming reaction can be dictated by the type of Lewis acid used. With bidentate Lewis acid, the Mukaiyama reaction has been shown to lead to the anti product through Cram chelate control when an aldehyde with a stereogenic center at the α position is involved (Scheme 2, path a).[6] Alternatively, the use of a monodentate Lewis acid in this reaction has been shown to lead to the syn product, in which case an open Felkin−Anh transition state (Scheme 2, path b) is proposed.[6] Second, the Mukaiyama reaction should be able to give access to the chelated species illustrated in Scheme 1, which could then be used in a subsequent radical reaction. Given this, a tandem sequence that combines the Mukaiyama reaction, using either Cram chelation or a Felkin−Anh pathway, with a radical reduction proceeding through either the endocyclic or exocyclic pathway should allow access to all four propionate motifs.

To be considered herein are tandem sequences that employ the control of the endocyclic effect for the free radical step. The Mukaiyama reaction is combined in tandem (i.e., one-pot reaction) with a hydrogen transfer reaction for the elaboration of 2,3-syn-3,4-anti and 2,3-syn-3,4-syn propionate motifs. This strategy is then extended to a tandem Mukaiyama/free radical based allylation reaction sequence to access a molecule bearing stereocenters with a 2,3-anti-3,4-anti relative stereochemistry, a motif that remains synthetically challenging despite recent contributions within this field.[7]

As depicted in Scheme 3, a high anti selectivity between the methyl group at the C-4 position and the newly formed alcohol at C-3 is expected from the addition of a tetrasubstituted enoxysilane bearing either a bromide or a phenylselenide on a chelated α-methyl *β*-benzyloxy aldehyde (transition state **D**).[8] On the resultant aldol product **E**, a Lewis acid that has been chosen judiciously should migrate from the alkoxy group to

(6) (a) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1993; Vol. 2, Chapter 2.4. (b) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095.

(7) Selected examples: (a) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489. (b) Hoffmann, R. W.; Dresely, S. *Chem. Ber.* **1989**, *122*, 903. (c) Tanimoto, N.; Gerritz, S. W.; Sawabe, A.; Noda, T.; Filla, S. A.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 673. (d) Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556. (e) Jain, N. F.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1996**, *111*, 6429. See ref 1b, e, f, h, i, and l.

(8) Open or extended transition state models have provided the best rationalization for the stereochemical results of the Mukaiyama reaction. (a) Nakamura, E.; Yamago, S.; Machii, D.; Kuwajima, I. *Tetrahedron Lett.* **1988**, *29*, 2207. (b) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1989**, *111*, 8032.

the more basic oxygen on the carbonyl of the ester, allowing for the formation of a new six-membered ring complex (chelate **F**). The hydrogen transfer reaction should then be able to take place via the endocyclic chelation mode and lead to a 2,3-syn-3,4-anti propionate motif. A similar anti selectivity between the methyl group at C-4 and the hydroxyl group at C-3 should be expected from the chelation-controlled addition of a trisubstituted enoxysilane bearing a phenylselenide. Under the control of the endocyclic effect, the addition of allyltributyltin should give a 2,3-anti-3,4-anti motif.[9]

Alternatively, we envision the use of a substrate that prevents chelation in order to reverse the facial selectivity of the Mukaiyama reaction and thus favor the 3,4-syn product (Scheme 3b). An open Felkin−Anh transition state such as **G**[5] is sought for access to this stereochemical result. If the Lewis acid used in the Mukaiyama step has the potential to form a chelate as illustrated in **I**, then the subsequent radical reduction of the phenylselenide should take place under endocyclic control leading to the 2,3-syn isomer (Scheme 3).

The main advantage of the proposed sequences is that two new stereogenic centers may be induced from a single chiral center. Furthermore, the tandem sequence may be conveniently carried out as a one-pot process, which offers an efficient new approach to the preparation of propionate motifs. Complementary to previous approaches, such as the classical aldol reaction[1j] and the crotylation reaction,[1l,2] our strategy may offer an alternative method for obtaining some of the more challenging motifs. Our preliminary results of these tandem Mukaiyama/free radical based reactions are described herein.

Results and Discussion

The Mukaiyama Reaction. The first part of the two-step process, the enoxysilane addition to the aldehyde, is reviewed in Table 1. Different Lewis acids were added to a CH_2Cl_2 solution of β-benzyloxy-α-methylpropionaldehyde **1**[10] and an *E:Z* mixture of seleno-enoxysilane (4:1, 1.5 equiv) at −60 °C. Attempts to achieve the 3,4-anti aldol product (Table 1, entries 1−5) using $TiCl_4$, $TiCl_2(i\text{OPr})_2$, Me_2AlCl, and $MeAlCl_2$ were unsuccessful; however, $MgBr_2{\cdot}OEt_2$ in excess amounts (>5 equiv)[11] gave excellent diastereoselectivity favoring the 3,4 anti isomers **2a** and **2b**[12] (Table 1, entries 6−10) in good yield. A remarkable level of stereocontrol favoring anti-aldol products (epimeric at C-2) was also obtained with bromo-enoxysilane under optimized conditions (Table 1, entry 11). These results were very encouraging for the planned tandem sequences considering that $MgBr_2{\cdot}OEt_2$ had already proven to be successful in chelation-controlled radical reduction reactions leading to the syn product.[5a,c,d]

The optimized Mukaiyama conditions were applied to the α-benzyloxy-aldehyde **6**[13] to achieve carbon−carbon bond formation with significant diastereoselectivity (Table 1, entries 12 and 13). For the selenide series, an additional 25% of aldol products bearing a trimethylsilyl ether group at C-3 was isolated in a >20:1 ratio favoring 3,4-anti selectivity (Table 1, entry 12).[14] Bromide compounds **9a** and **9b** were obtained in superior yield, and no silylated side products were observed for this series (Table 1, entry 13).

To obtain the syn aldol product, we used β-silyloxy aldehyde **11**[15] based on the presumption that a bulky silyl protecting group would prevent the formation of the chelate.[16] To this aldehyde was added seleno-enoxysilane, and the resultant mixture was tested with different Lewis acids at −78 °C. An excess of $MgBr_2{\cdot}OEt_2$ performed poorly, and aldehyde **11** was recovered even though the reaction mixture was warmed to −40 °C (Table 1, entry 14). The best results were achieved with $BF_3{\cdot}OEt_2$ and Me_2AlCl, a notable ratio of 1:11 having been obtained for both in favor of 3,4-syn relative stereochemistry (Table 1, entries 15 and 16). The latter Lewis acid was able to form a chelate between the hydroxyl and carbonyl groups of the Mukaiyama product and was therefore retained for use in the tandem process.

The secondary phenylselenide required for the completion of the anti-anti allylated motif was achieved through the addition of a trisubstituted enoxysilane to aldehyde **1**. The use of the *tert*-butyldimethylsilyl enolate in the presence of $MgBr_2{\cdot}OEt_2$ led to an excellent anti ratio between the hydroxy group at C-3 and the methyl group at C-4.[17] The yield of this reaction (53%, see Table 1, entry 17) was increased significantly by using the triethyl silyloxy (TES) analogue to give in excellent yield (90%) selenides **14a** and **14b** (Table 1, entry 18) while maintaining superior diastereoselectivity.[18]

The Free Radical Step. The second chemical step involving the free radical reactions was then evaluated. As seen in Table 2 (entry 1), anti selenide **2a** in the presence of a large excess of $MgBr_2{\cdot}OEt_2$ was reduced at −78 °C with Bu_3SnH and Et_3B, as the initiator, to give in good yield an excellent syn:anti ratio >100:1.[19] In the bromide series, the radical reduction of anti isomer **4a** gave higher selectivity than that noted for the reduction of the syn counterpart **4b** (Table 2, entries 2 and 3).[20] Ratios of reduced products >30:1 were observed for selenides **7a** and **7b** as well as for bromides **9a** and **9b** (Table 2, entries 4 and 5). In each case, the major syn product **17a** was obtained, corroborating that chelate formation between the hydroxyl and carbonyl groups of the substrate had taken place. Me_2AlCl, which had been efficient in the Mukaiyama reaction involving a Felkin−Anh pathway, facilitated the formation of the chelate with the β-hydroxy-α-seleno ester **13a**, giving a ratio >20:1 in favor of the 2,3-syn reduced product **18c** (Table 2, entry 6).

The free radical based allylation reactions are summarized in Table 3. As seen in entry 1, an excess of $MgBr_2{\cdot}OEt_2$ in the presence of allyltributyltin was added to the solution of phenylselenide **14a**, which had been cooled to −40 °C. The reaction was then allowed to warm to 0 °C. These conditions

(9) It has already been shown that α-phenylseleno-β-hydroxy esters can give the anti allylated product under chelation-controlled conditions; see Gerster, M.; Audergon, L.; Moufid, N.; Renaud, P. *Tetrahedron Lett.* **1996**, *37*, 6335.

(10) The preparation and characterization of aldehyde **1** have been reported previously in Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035.

(11) A similar observation has been made in chelation-controlled radical reduction and allylation reactions (see ref 4b−e).

(12) The optimized Mukaiyama conditions offered a >20:1 (**2a**:**2b**) ratio.

(13) The preparation and characterization of aldehyde **6** have been reported previously in Varelis, P.; Johnson, B. L. *Austr. J. Chem.* **1995**, *48*, 1775.

(14) These aldol products could be easily converted into products **7a** and **7b** by modifying the workup procedure.

(15) The preparation of aldehyde **11** has been reported previously in Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.

(16) Oxygen atoms of hindered silyl ethers are known to be less efficient in complexation with Lewis acids; see Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778 and references therein.

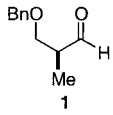
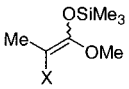
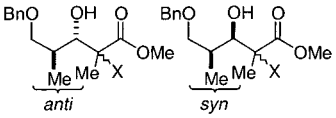
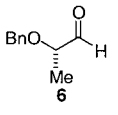
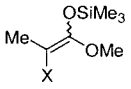
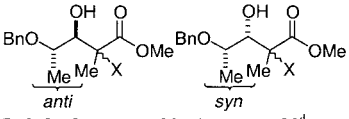
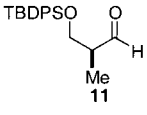
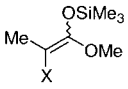
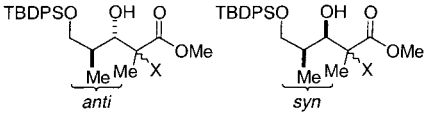
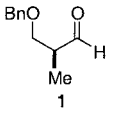
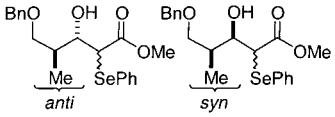
(17) The optimized Mukaiyama conditions offered a 7:1 (**14a**:**14b**) ratio.

(18) Me_2AlCl, which had already performed poorly in our chelation-controlled Mukaiyama reaction involving the quaternary enoxysilane (Table 1, entry 5), gave only a weak 1.1:1 ratio in favor of the 3,4-anti product when used in combination with TES enolate.

(19) Compound **16b** was derivatized in lactone, and the relative configuration of the resultant product was established by NOE NMR analysis.

(20) A similar observation has been made in chelation-controlled radical reduction and allylation reactions of secondary α-iodoesters. See refs 4a, b, and e.

Table 1. Mukaiyama Reactions[a]

entry	aldehyde	enoxysilane	L.A.(equiv)	products	ratio[b]	yield[c]
				3,4-(*anti*:*syn*)	3,4-(*anti*:*syn*)	(%)
	 **1**			 *anti* *syn*		
1	**1**	X=SePh	$TiCl_4$ (1.5)	**2a,b**:**3a,b**	1.3 : 1	75
2	**1**	X=SePh	$TiCl_2(iOPr)_2$ (1.2)	**2a,b**:**3a,b**	1.5 : 1	40
3	**1**	X=SePh	$SnCl_4$ (1.0)	**2a,b**:**3a,b**	1 : 2.3	61
4	**1**	X=SePh	$MeAlCl_2$ (2.5)	**2a,b**:**3a,b**	1 : 1	36
5	**1**	X=SePh	Me_2AlCl (2.5)	**2a,b**:**3a,b**	1 : 1.1	41
6	**1**	X=SePh	$MgBr_2{\cdot}OEt_2$ (1.5)	**2a,b**:**3a,b**	8 : 1	7
7	**1**	X=SePh	$MgBr_2{\cdot}OEt_2$ (2)	**2a,b**:**3a,b**	18 : 1	30
8	**1**	X=SePh	$MgBr_2{\cdot}OEt_2$ (3)	**2a,b**:**3a,b**	>20 : 1	49
9	**1**	X=SePh	$MgBr_2{\cdot}OEt_2$ (5)	**2a,b**:**3a,b**	>20 : 1	60
10	**1**	X=SePh	$MgBr_2{\cdot}OEt_2$ (7)	**2a,b**:**3a,b**	>20 : 1	62
11	**1**	X=Br	$MgBr_2{\cdot}OEt_2$ (7)	**4a,b**:**5a,b**	>20 : 1	65
	 **6**			 *anti* *syn*		
12	**6**	X=SePh	$MgBr_2{\cdot}OEt_2$ (7)	**7a,b**:**8 a,b**	>20 : 1	38[d]
13	**6**	X=Br	$MgBr_2{\cdot}OEt_2$ (7)	**9a,b**:**10a,b**	>20 : 1	71
	 **11**			 *anti* *syn*		
14	**11**	X=SePh	$MgBr_2{\cdot}OEt_2$ (5)	---	---	---[e]
15	**11**	X=SePh	$BF_3{\cdot}OEt_2$ (1.5)	**12a,b**:**13a,b**	1 : 11	85
16	**11**	X=SePh	Me_2AlCl (2)	**12a,b**:**13a,b**	1 : 11	78
	 **1**			 *anti* *syn*		
17	**1**	R=TBS[f]	$MgBr_2{\cdot}OEt_2$ (5)	**14a,b**:**15a,b**	>20 : 1	53
18	**1**	R=TES[f]	$MgBr_2{\cdot}OEt_2$ (5)	**14a,b**:**15a,b**	>20 : 1	90[g]

[a] When P = Bn: aldehydes (0.05 M) in CH_2Cl_2 were treated at −60 °C with 1.5 equiv of enoxysilane and the appropriate L.A; when P = TBDMS: the reaction was performed at −78 °C using a 0.1 M solution of aldehyde. [b] Ratios were determined by ^1H NMR spectroscopy and/or GC or HPLC. [c] Yields of isolated products. [d] 25% of isolated trimethylsilyl ether products were also obtained in a >20:1 anti:syn ratio. [e] At −40 °C, aldehyde **11** was recovered. [f] 1.75 equiv of enoxysilane was used. [g] The reaction was performed at −78 °C.

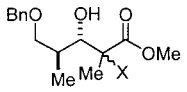
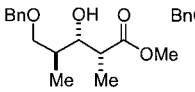
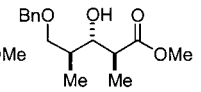
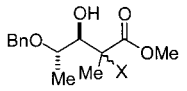
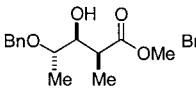
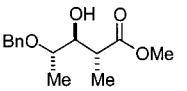
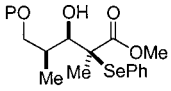
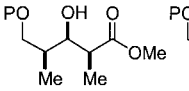
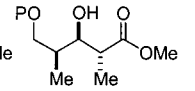
led to a ratio of >20:1 in favor of the anti allylated product and to an intermediate yield (62%). The use of aluminum based Lewis acids such as Me_2AlCl (Table 3, entry 2) and $AlMe_3$ (Table 3, entry 3) at −78 °C led to an improvement in yield, gave high diastereoselectivity, and were the most efficient in terms of reaction time. In these reactions, the stronger Lewis acids rendered the carbonyl of the ester more electronegative and in turn lowered the SOMO energy of the radical. Thus, the free radical became even more electrophilic, and the rate of addition to the electron rich double bond of the allylstannane was increased.

The Tandem Reactions. With the significant results obtained from the independent Mukaiyama and free radical reactions, we were poised well to study the two-step sequences. First attempts to realize the tandem reactions using aldehyde **1** and $MgBr_2{\cdot}OEt_2$ proved to be difficult to reproduce. It was determined that the length of the reaction in the first step, having been performed under a N_2 atmosphere, had resulted in a dissipation of the oxygen that was needed to initiate and maintain the chain of the free radical reaction. The process was modified accordingly by exposing the reaction mixture to air (O_2) prior to initiation of the radical reduction step.

As seen in Table 4, two new stereogenic centers were introduced with high diastereoselectivity in favor of the 2,3-syn-3,4-anti propionate motif for both benzyloxy aldehydes **1** and **6** in the presence of $MgBr_2{\cdot}OEt_2$ (entries 1−4). A higher ratio was achieved with aldehyde **1** when seleno-enoxysilane was used in the one-pot process (Table 4, entry 1). Both seleno-enoxysilane and bromo-enoxysilane reacted well with aldehyde **6** under chelation control, leading to the desired syn-anti motif with excellent selectivity and in good yield (Table 4, entries 3−4).[21] The hydrogen transfer study was completed with the tandem reaction involving silyloxy aldehyde **11** in the presence

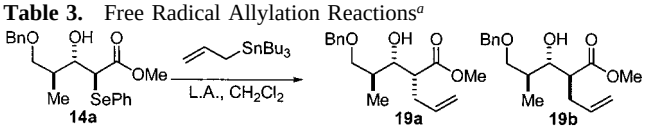
(21) For the selenide series, the crude mixture was subjected to flash chromatography before being treated with TBAF in THF for the cleavage of the trimethylsilyl ether group at C-3.

Table 2. Free Radical Hydrogen Transfer Reactions[a]

entry	substrate	L.A. (equiv)	ratio[b] 2,3-(*syn*:*anti*)	yield[c] (%)[c]
			 **16a**  **16b**	
1	**2a**,X=SePh *anti*	$MgBr_2{\cdot}OEt_2$ (7)	>100 : 1	75
2	**4a**,X=Br *anti*	$MgBr_2{\cdot}OEt_2$ (5)	>50 : 1	83
3	**4b**,X=Br *syn*	$MgBr_2{\cdot}OEt_2$ (5)	10 : 1	76
			 **17a**  **17b**	
4	**7a,b**,X=SePh	$MgBr_2{\cdot}OEt_2$ (5)	>30 : 1	73
5	**9a,b**,X=Br	$MgBr_2{\cdot}OEt_2$ (5)	>30 : 1	82
			 **18c**  **18d**	
6	**13a**,P=TBDPS[d]	Me_2AlCl[e] (2)	>20 : 1[f]	75

[a] Substrates (0.1 M) were pretreated with Lewis acid, 2 equiv of Bu_3SnH, and 0.2 equiv of Et_3B in CH_2Cl_2 at −78 °C. [b] Determined by GC analysis of crude reaction isolates. [c] Isolated yields. [d] An inseparable mixture of **13a** and **12a** (11%) was used for the radical reduction reaction. [e] 2.0 equiv of *i*Pr_2NEt was added. [f] Determined by ^1H NMR spectroscopy of crude reaction isolates.

Table 3. Free Radical Allylation Reactions[a]



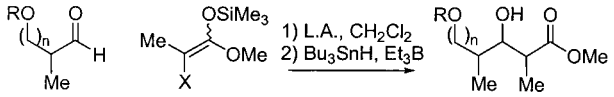
entry	L.A. (equiv)	reaction time (h)	temp (°C)	ratio[b] 2,3-(syn:anti)	yield[c] (%)
1	$MgBr_2{\cdot}OEt_2$ (5)	9	−40 to 0	1:>20	62
2	Me_2AlCl (2.5)	3.5	−78	1:>20	90
3	Me_3Al (2.5)	3.5	−78	1:>20	80

[a] Substrates (0.1 M) were pretreated with Lewis acid, 2 equiv of $allylSnBu_3$, and 0.2 equiv of Et_3B in CH_2Cl_2 at −78 °C. [b] Determined by ^1H NMR spectroscopy of crude reaction isolates. [c] Isolated yields.

of Me_2AlCl, which gave as the major constituent the desired compound **18c** with a 2,3-syn-3,4-syn propionate motif (Table 4, entry 5).

Carrying out the Mukaiyama/radical allylation tandem sequence was more complicated considering that different Lewis acids had given the best results for the reactions performed on an individual basis: $MgBr_2{\cdot}OEt_2$ having worked well in the Mukaiyama reaction,[18] and Me_2AlCl having provided the best yield for the allylation. When $MgBr_2{\cdot}OEt_2$ was used for both steps of the sequence, an excellent ratio of allylated products was obtained in a 35% yield (Table 5, entry 1). Performing the first step in the presence of $MgBr_2{\cdot}OEt_2$ followed by the addition of Me_2AlCl in the allylation reaction also led to high diastereoselectivity of >20:1, but the yield was still low (Table 5, entry 2). This suggested that the chelate formed by the magnesium did not equilibrate with the Me_2AlCl, which was surprising given that the latter was stronger than the $MgBr_2{\cdot}OEt_2$. The addition of an equimolar amount of acetic acid (CH_3COOH) prior to the addition of Me_2AlCl allowed for cleavage of the O−Mg bond so that the aluminum could replace the magnesium to form a chelate, resulting overall in a much improved 85% yield of allylated products (Table 5, entry 3).

Table 4. Tandem Mukaiyama and Free Radical Hydrogen Transfer Reactions[a]



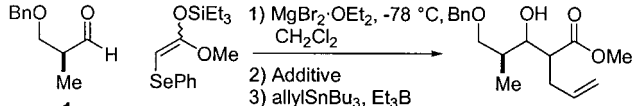
1, R = Bn, n = 1
6, R = Bn, n = 0
11, R = TBDPS, n = 1

a, 2,3-*syn*-3,4-*anti*
b, 2,3-*anti*-3,4-*anti*
c, 2,3-*syn*-3,4-*syn*
d, 2,3-*anti*-3,4-*syn*

entry	aldehyde	enoxysilane	products	ratio[b]	yield[c] (%)
1	**1**	X = SePh	**16a:16b:16c:16d**	>30:1:0:0	70
2	**1**	X = Br	**16a:16b:16c:16d**	10:1:0:0	68
3	**6**	X = SePh	**17a:17b:17c:17d**	50:1:0:0	65[d]
4	**6**	X = Br	**17a:17b:17c:17d**	100:1:0:0	69
5	**11**	X = SePh	**18a:18b:18c:18d**	1:0:11:0.1	66

[a] Mukaiyama: aldehydes **1** and **6** (0.05 M) were treated in CH_2Cl_2 at −60 °C with enoxysilane (1.5 equiv) and $MgBr_2{\cdot}OEt_2$ (4 h); for **11**: the reaction was performed at −78 °C using a 0.1 M solution of aldehyde and 2 equiv of Me_2AlCl (1 h). Reduction: the reaction mixture was exposed to air 1 h before the addition of 4 equiv of Bu_3SnH and 0.2 equiv of Et_3B at −78 °C. [b] Ratios were determined by GC or HPLC. [c] Yields of isolated products. [d] After flash chromatography, the mixture was treated with TBAF in THF to cleave the trimethylsilyl ether group at C-3.

Table 5. Tandem Mukaiyama and Allylation Reactions[a]



a, 2,3-*syn*-3,4-*anti*
b, 2,3-*anti*-3,4-*anti*
c, 2,3-*syn*-3,4-*syn*
d, 2,3-*anti*-3,4-*syn*

entry	additive (equiv)	products	ratio[b]	yield[c] (%)
1	none	**19a:19b:19c:19d**	1:>20:0:0	35
2	Me_2AlCl (3.5)	**19a:19b:19c:19d**	1:>20:0:0	52
3	CH_3COOH (1.2) Me_2AlCl (3.5)	**19a:19b:19c:19d**	1:>20:0:0	85

[a] Mukaiyama: aldehyde **1** (0.05 M) was treated in CH_2Cl_2 at −78 °C with enoxysilane (1.75 equiv) and $MgBr_2{\cdot}OEt_2$ (5 equiv, 1 h). Allylation: the reaction mixture was warmed to −40 °C before the addition of the *additive* with 4 equiv of $allylSnBu_3$ and 0.2 equiv of Et_3B. [b] Ratios were determined by ^1H NMR spectroscopy. [c] Yields of isolated products.

Conclusion

The two-step sequences offer an efficient and complementary approach to the synthesis of propionate motifs and are conceptually exciting from the viewpoint that anionic and radical processes are combined in the same reaction mixture. Furthermore, Lewis acid is used advantageously to activate and/or control both the Mukaiyama reaction and the free radical reaction. The endocyclic effect is capitalized upon for the free radical step to give the 2,3-syn product in the case of the hydrogen transfer reaction and the 2,3-anti product for the allylation reaction. The formation of chelates α to the radical center mimicking the exocyclic effect is a study that is presently underway to gain access, using the hydrogen transfer reaction, to other stereoisomers bearing a 2,3-anti relative diastereoselectivity. Through this work, we hope to establish a general and versatile approach to the synthesis of all propionate motifs. The scope and limitations of the two-step synthetic sequences will be evaluated further, while Lewis acids will continue to be explored and their potential tested in iterative processes.

Experimental Section

General Procedure for Radical Reduction or Allylation under Chelation-Controlled Conditions. To a stirred solution of α-selenoester or α-bromoester (1 equiv) in dry CH_2Cl_2 (0.1 M) at −78 °C was added the appropriate Lewis acid (with Me_2AlCl, 2.0 equiv of iPr_2Net was added to the reaction mixture). The mixture was stirred for 15 min at the same temperature before either Bu_3SnH or allyl$SnBu_3$ (2 equiv) and Et_3B (0.2 equiv of a 1.0 M solution in hexanes) was added. The resulting suspension was stirred at −78 °C, and 0.2 equiv of Et_3B was added each 30 min until the reaction was judged complete by TLC. 1,3-Dinitrobenzene (0.2 equiv) was then added to the solution, and the mixture was stirred an additional 15 min at −78 °C. The reaction mixture was poured into a saturated $NaHCO_3$ solution and extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

5-Benzyloxy-3-hydroxy-2,4-dimethylpentanoic Acid Methyl Ester (16a and 16b). The ratios for **16a** and **16b** were determined by GC analysis of the crude isolate arising from the radical reductions of **2a** and **4a**. The compounds were purified by flash chromatography on silica gel using 100% hexane to 10% EtOAc−hexane (82%). **Compound 16a (2*R*,3*S*,4*S*):** colorless oil; R_{xa6} 0.17 (hexane:EtOAc, 4:1); $[\alpha]^{25}_D = -1.3°$ (*c* 2.87, MeOH); IR (neat) υ_{max} 3500, 2950, 2880, 1740, 1455, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23−7.39 (m, 5H), 4.51 (s, 2H), 3.87−3.93 (m, 1H), 3.69 (s, 3H), 3.61−3.69 (m, 2H), 3.55 (dd, J = 6.6, 2.4 Hz, 1H), 2.58−2.66 (m, 1H), 1.85−1.95 (m, 1H), 1.19 (d, J = 7.1 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.1, 137.7, 128.5, 127.8, 127.7, 76.0, 74.8, 73.6, 51.9, 42.5, 35.8, 13.9, 9.8; MS (FAB) *m*/*z* 267 (MH^+, 49), 181 (7), 159 (12), 91 (100), 71 (8); HRMS calcd for $C_{15}H_{23}O_4$ (MH): 267.1596, found: 267.1592 (1.6 ppm).

Compounds **16a** and **16b** (inseparable 1:1 mixture; ratio determined by ^1H NMR analysis) resulted from the radical reduction of **2a** performed at 0 °C in the absence of Lewis acid. **Compound 16b (2*S*,3*S*,4*S*):** colorless oil; R_{xa6} 0.17 (hexane:EtOAc, 4:1); IR (neat) υ_{max} 3500, 2950, 2880, 1740, 1510, 1100, 740, 700 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 7.23−7.39 (m, 5H), 4.52 (s, 2H), 3.70 (s, 3H), 3.61−3.68 (m, 2H), 3.52−3.61 (m, 1H), 3.41 (d, J = 7.0 Hz, 1H), 2.70−2.79 (m, 1H), 1.84−2.00 (m, 1H), 1.22 (d, J = 7.5 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_176.1, 138.0, 128.5, 128.4, 127.6, 73.6, 73.5, 73.3, 51.7, 43.1, 36.2, 14.9, 14.6.

General Procedure for the Preparation of Benzyloxy Esters 16, 17, and 19 via in Situ Mukaiyama and Radical Reduction or Allylation Reactions. To a cold (−60 °C) solution of aldehyde **1** or **6** (1 equiv) in dry CH_2Cl_2 (0.05 M) were added the appropriate silylketene acetal (1.5 equiv of tetrasubstituted enoxysilane or 1.75 equiv of trisubstituted enoxysilane) and the appropriate Lewis acid. The resulting solution was stirred for 4 h at −60 °C (until the aldehyde was completely consumed, as determined by TLC). The reaction mixture was exposed to air (O_2) for 1h at 0 °C before the addition of either Bu_3SnH or allyl$SnBu_3$ (4 equiv) and Et_3B (0.2 equiv of a 1.0 M solution in hexanes) at −78 °C. Et_3B (0.2 equiv) was added each 30 min until the reaction was judged complete by TLC. 1,3-Dinitrobenzene (0.2 equiv) was then added to the solution, and the mixture was stirred an additional 15 min at −78 °C. The reaction mixture was poured into a saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

Preparation of Silyloxy Esters 18a−d via in Situ Mukaiyama and Radical Reduction Reactions. To a cold (−78 °C) solution of aldehyde **11** (100 mg, 0.31 mmol) in dry CH_2Cl_2 (0.1 M) were added the silylketene acetal (193 mg, 0.61 mmol) and Me_2AlCl (1.0 M in hexane, 600 μL). The resulting solution was stirred for 10 min at −78 °C (until the aldehyde was completely consumed, as determined by TLC). The reaction mixture was exposed to air (O_2) for 5 min, and the radical reduction reaction step was initiated as described above in the general procedure for the preparation of benzyloxy esters **16** and **17**.

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Supporting Information Available: Experimental procedures and characterization data for compounds *E*,*Z*-silylketenes, **2**−**15**, **17**−**19**; determination of relative configuration for compounds **2a**, **4b**, **7b**, **9b**, **13a**, **13b**, **14a**, **16b**, **17b**, **18a**, and **19b**; experimental procedures and characterization data for lactones **20**−**26**; NMR spectra for compounds *E*,*Z*-silylketenes, **2b**, **3a**, **3b**, **5a**, **5b**, **8b**, **10b**, **15a**, **15b**, **16b**, **18b**, **18d**, **19a**, **21**, **23**, and **25** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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