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Diastereoselective Mukaiyama and Free Radical Processes for the Synthesis of Polypropionate Units

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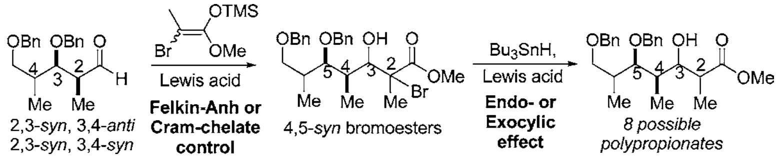
ABSTRACT



Reported herein is the synthesis of 8 out of 16 polypropionates derived from our propionate units. A new strategy involving a stereoselective Mukaiyama aldol reaction followed by a stereoselective free-radical-based hydrogen transfer, both under Lewis acid control, is used. Of particular interest is the remarkable reactivity of (*i*-PrO)TiCl$_3$ in this context to give only the 3,4-*anti* bromoesters.

Polypropionates are important subunits of numerous biologically active molecules, and the development of methods for their synthesis has driven the discovery of many new methodologies.[1] We became interested in this field of research as a result of our discovery that β-alkoxy-α-halo- or -selenoesters can undergo a kinetically stereocontrolled hydrogen transfer reaction.[2]

We recently embarked on a systematic study of what we hope will be a versatile substrate-controlled approach to polypropionates[3] by combining a Mukaiyama aldol reaction[4] with a diastereoselective free-radical-based hydrogen transfer reaction as illustrated in Scheme 1. The first step of our strategy involves a reaction between an aldehyde and a tetrasubstituted enoxysilane bearing a functionality (e.g., I, Br, or SePh) that could subsequently, through homolytic bond cleavage, be used as a free radical precursor. Bidentate Lewis acid mediated activation of β-alkoxy-α-methyl aldehyde **1** should favor the 3,4-*anti* adduct **3** via a Cram-chelate[5] transition state. Using monodentate Lewis acids or preventing the chelation with a bulky protecting group on the alcohol

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[1] Selected examples: (a) Chemler, S. R.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 3800. (b) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1998**, *63*, 4572 (c) Hanessian, S.; Ma, J.; Wang, W. *Tetrahedron Lett.* **1999**, *40*, 4627. (d) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2001**, *66*, 7825. (e) Evans, D. A.; Allison, B. D.; Yang, M. C.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840. (f) Yeung, K.-S.; Paterson, I. *Angew. Chem., Int. Ed.* **2002**, *41*, 4632.

[2] (a) Guindon, Y.; Yoakim, C.; Lemieux, R.; Boisvert L.; Delorme, D.; Lavallée, D. *Tetrahedron Lett.* **1990**, *31*, 2845. (b) Guindon, Y.; Lavallée, J.-F.; Boisvert, L.; Chabot, C.; Delorme, D.; Yoakim, C.; Hall, D.; Lemieux, R.; Simoneau, B. *Tetrahedron Lett.* **1991**, *32*, 27. (c) Durkin, K.; Liotta, D.; Rancourt, J.; Lavallée, J.-F.; Boisvert, L.; Guindon, Y. *J. Am. Chem. Soc.* **1992**, *114*, 4912. (d) Guindon, Y.; Slassi, A.; Rancourt, J.; Bantle, G.; Bencheqroun, M.; Murtagh, L.; Ghiro, E.; Jung, G. *J. Org. Chem.* **1995**, *60*, 288.

[3] Our first approach to the synthesis of polypropionates involved the combination of cyclofunctionalization reactions followed by hydrogen transfer reaction and opening of the heterocycles. See: Guindon, Y.; Murtagh, L.; Caron, V.; Landry, S. R.; Jung, G.; Bencheqroun, M.; Faucher, A.-M.; Guérin, B. *J. Org. Chem.* **2001**, *66*, 5427.

[4] (a) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. (b) Gennari, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1993; Vol. 2, Chapter 2.4, p 629.

[5] (a) Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Chapter 5, p 125. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (c) Reetz, M. T.; Hüllmann, M.; Seitz, T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 477.

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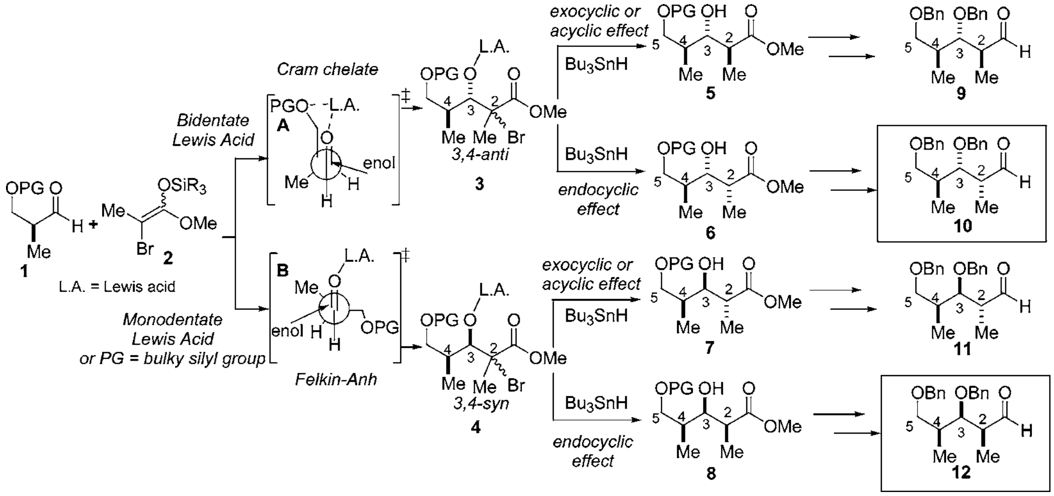
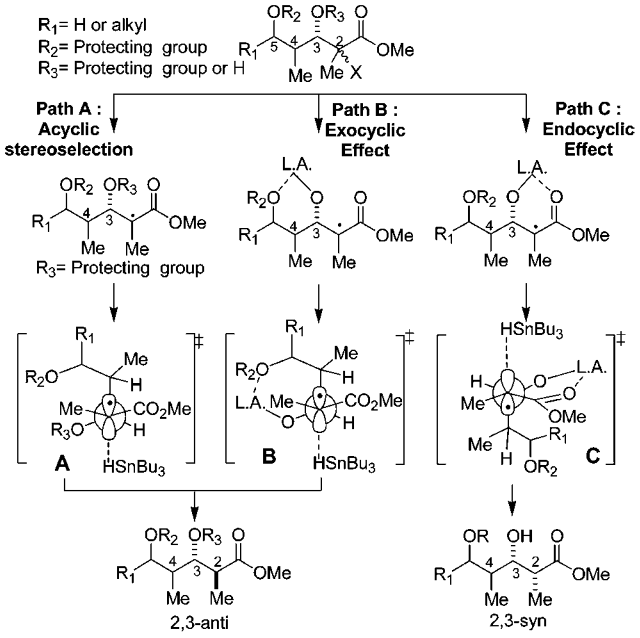
Scheme 1



functionality should lead to 3,4-*syn* product **4** through a Felkin−Anh[6] pathway. Contrary to other approaches to polypropionates based on the use of aldol-like reaction, the *E/Z* stereochemistry of the enoxysilane **2** does not need to be controlled in our strategy. Indeed, the C-2 stereochemistry of the Mukaiyama adducts is not important in our approach, this site being transformed into a carbon-centered free radical in the next step.

The hydrogen transfer step can give either 2,3-*syn* or -*anti* relative stereochemistry. Minimization of 1,3-allylic strain and intramolecular dipole−dipole interactions is at the origin of the *anti* selectivity in these π-delocalized radicals (Scheme 2, transition state **A**). This *anti* preference can be enhanced by taking advantage of the exocyclic effect.[7] In this case, a ring (permanent[7a−c] or temporary[7d]) is created adjacent to the carbon-centered radical. We showed that bidentate Lewis acids could generate such a temporary ring by chelating the C-3 and C-5 hydroxy groups (Scheme 2, transition state **B**). On the other hand, the 2,3-*syn* relative stereochemistry could be induced using the hydrogen transfer reaction by taking advantage of the endocyclic effect.[8] In this case, the carbon-centered free radical, now embedded within a Lewis acid induced ring (Scheme 2, transition state **C**), will give *syn* products. One should note that a free C-3 hydroxy group could, through hydrogen bonding with the oxygen of the carbonyl, follow a similar pathway (Scheme 2, transition state **C**, L.A. = H). Thus, as in the first step (the Mukaiyama reaction), through appropriate Lewis acid selection, one could choose between the different pathways to control the stereochemical outcome of the hydrogen transfer process. The validity of our strategy was first evaluated using primary β-benzyloxyaldehyde **1** as starting material, the four stereotriads **5**−**8** (Scheme 1) having been synthesized in high yield and stereocontrol.[9] We then turned our attention to secondary β-benzyloxyaldehydes to ascertain the importance of additional stereocenters and their steric effects in our substrate-controlled approach. Aldehydes **9**−**12** (Scheme 1) were selected for this study, to test, as well, the iterative potential

Scheme 2



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[6] (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (c) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

[7] (a) 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. (b) Guindon, Y.; Faucher, A.-M.; Bourque, E.; Caron, V.; Jung, G.; Landry, S. R. *J. Org. Chem.* **1997**, *62*, 9276. (c) Guindon, Y.; Liu, Z.; Jung, G. *J. Am. Chem. Soc.* **1997**, *119*, 9289. (d) Bouvier, J.-P.; Jung, G.; Liu, Z.; Guérin, B.; Guindon, Y. *Org. Lett.* **2001**, *3*, 1391.

[8] (a) Guindon, Y.; Lavallée, J.-F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 9701. (b) Guindon, Y.; Rancourt, J. *J. Org. Chem.* **1998**, *63*, 6566. (c) Guindon, Y.; Houde, K.; Prévost, M.; Cardinal-David, B.; Landry, S. R.; Daoust, B.; Bencheqroun, M.; Guérin, B. *J. Am. Chem. Soc.* **2001**, *123*, 8496.

[9] Guindon, Y.; Prévost, M.; Mochirian, P.; Guérin, B. *Org. Lett.* **2002**, *4*, 1019. (b) See ref 2c.

of our reaction sequence for the synthesis of polypropionate stereopentads.

In the case of the 2,3-*anti*-3,4-*anti* bis(benzyloxy)aldehyde **9**, this approach was successfully demonstrated.[10] Central to the present study are aldehydes **10** and **12**.[11] Indeed, their relative 2,3-*syn* stereochemistry could pose new problems in the Cram-chelated Mukaiyama reaction. As illustrated in Figure 1, the Lewis acid chelated intermediates (whether in boat or half-chair conformation) may not be thermodynamically favored because of unfavorable steric interactions between the 2,3-*syn* substituents. This may lead to an erosion of stereocontrol by allowing competing reaction pathways involving the less hindered monodentate species. Indeed, our first experiments aimed at probing the Cram-chelate pathway using the 2,3-*syn*-3,4-*anti* aldehyde **10** and the bromoenoxysilane **2** (4:1 *E*:*Z* mixture) with bidentate Lewis acids ($MgBr_2 \cdot OEt_2$, Et_2BOTf, $SnCl_4$, Me_2AlCl, etc.) were disappointing. Even $TiCl_4$, which proved to be effective in the Mukaiyama reaction involving aldehyde **9**,[10b] turned out to be ineffective in this case (Table 1, entry 1). Extensive decomposition of the aldehyde and cleavage of the primary benzyl ether were noted.

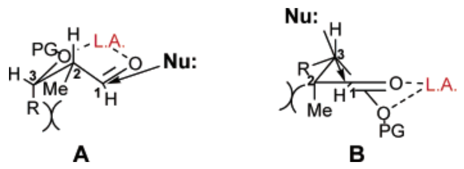
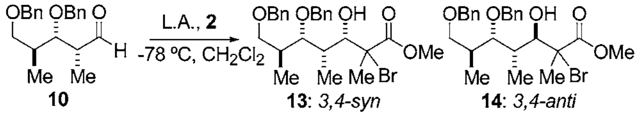
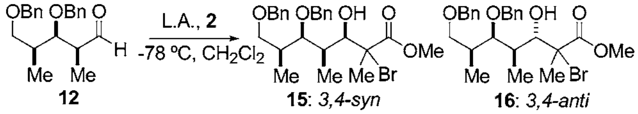


Figure 1. Possible Lewis acid chelated transition states in boat (**A**) or half-chair (**B**) conformations.

Table 1. Mukaiyama Reactions of **10** and **12**[a]

Entry	aldehyde	Lewis acid (equiv.)	3,4-*syn:anti*[b] products	ratio	yield[c] (%)
					
1	**10**	$TiCl_4$ (1.2)	**13:14**	-	-[d]
2	**10**	$(i\text{-PrO})_2TiCl_2$ (1.2)	**13:14**	-	-[e]
3	**10**	$(i\text{-PrO})TiCl_3$ (1.2)	**13:14**	1:3	67
4	**10**	$(i\text{-PrO})TiCl_3$ (2.0)	**13:14**	1:10	62
5	**10**	$(i\text{-PrO})TiCl_3$ (2.5)	**13:14**	1:>20	77
6	**10**	$BF_3 \cdot OEt_2$ (1.2)	**13:14**	>20:1	89[f]
					
7	**12**	$(i\text{-PrO})TiCl_3$ (2.5)	**15:16**	1:>20	87
8	**12**	$BF_3 \cdot OEt_2$ (1.2)	**15:16**	>20:1	88[f]

[a] Aldehyde **10** or **12** (0.1 M) in CH_2Cl_2 was precomplexed at −78 °C with the appropriate Lewis acid followed by addition of bromoenoxysilane **2** (1.3 equiv). [b] Ratios were determined by ^1H NMR spectroscopy. [c] Yields of isolated products. [d] Degradation of the aldehyde was observed. [e] Starting material was recovered. [f] Aldehyde **10** or **12** (0.1 M) in CH_2Cl_2 was treated at −78 °C with $BF_3 \cdot OEt_2$ and then with bromoenoxysilane **2** (1.3 equiv).

Obviously, changing the primary hydroxy-protecting group would have been a solution to circumvent the latter reaction. Instead, we decided to evaluate other Lewis acids. Since the cleavage of a benzyl ether requires activation of the benzylic oxygen by the Lewis acid, we focused on lowering the titanium Lewis acidity. This was done by considering $(i\text{-PrO})TiCl_3$[12] and $(i\text{-PrO})_2TiCl_2$,[13] which have been found to be useful in aldol reactions.[14] As seen in entry 2, no reaction (Mukaiyama aldol nor benzyl ether cleavage) was noted when $(i\text{-PrO})_2TiCl_2$ was used. Interestingly, the use of $(i\text{-PrO})TiCl_3$ provided our first positive result, the aldol products **13** and **14** being obtained (Table 1, entry 3) in good yield albeit with modest Cram-chelate selectivity. Even more interesting was our observation that this drawback could be overcome by increasing the Lewis acid:aldehyde stoichiometry, as indicated by the impressive 3,4-*anti* stereoselectivity favoring compound **14** (entries 4 and 5). The 3,4-*syn* product **13** was observed with excellent diastereomeric ratio using the monodentate Lewis acid $BF_3 \cdot OEt_2$ (entry 6). Similar results were achieved with aldehyde **12**. The Cram-chelate pathway was favored with 2.5 equiv of $(i\text{-PrO})TiCl_3$, exclusive formation of product **16** was observed (entry 7). Conversely, the Mukaiyama adduct **15** was the only observed product when $BF_3 \cdot OEt_2$ was used, indicative of a reaction under Felkin−Anh control (entry 8). Again, $TiCl_4$ was ineffective in this case.

The necessity of having to use 2.5 equiv of $(i\text{-PrO})TiCl_3$ to achieve high stereocontrol may suggest the existence of reactive complexes different from the simple chelates illustrated in Figure 1. Our preliminary NMR studies are consistent with the presence of an *ate* complex in solution.[15] Further investigations will be required to fully characterize the structure of the reacting complex.[16]

The first step of our planned consecutive process having been completed, we then turned our attention to the free-

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[10] In this case, one should have expected 1,2- and 1,3-inductions to oppose each other, thus potentially eroding stereocontrol in the Cram-chelate Mukaiyama reaction. However, we and Evans et al. showed 1,2-induction to be dominant when using hindered enoxysilanes: (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 4322. (b) Mochirian, P.; Cardinal-David, B.; Guérin, B.; Prévost, M.; Guindon, Y. *Tetrahedron Lett.* **2002**, *43*, 7067.

[11] For preparation of aldehydes **10** and **12**, see Supporting Information.

[12] Solsona, J. G.; Romea, P. D.; Urpý, F.; Vilarrasa, J. *Org. Lett.* **2003**, *5*, 519.

[13] Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949.

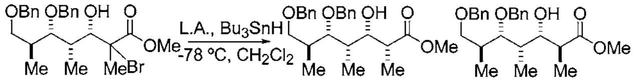
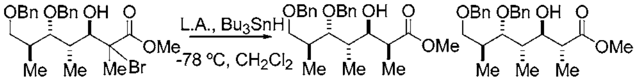
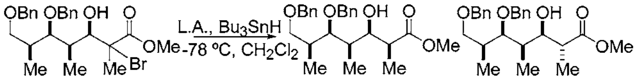
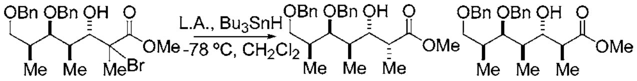
[14] Selected examples: (a) Ishimura, K.; Monda, K.; Yamamoto, Y.; Akiba, K. *Tetrahedron* **1998**, *54*, 727. (b) See ref 12.

[15] Evans et al. noticed a similar preference for the Cram-chelate controlled aldol reaction as a result of an increase of the Lewis acid (Me_2AlCl) stoichiometry. An *ate* complex was invoked; see ref 1e.

[16] Suggestions on the structure of the complexes could be derived from the work of Gau, who suggested the prevalence of six-coordinate complexes in which the relative bonding ability of various ligands can be established as $i\text{-PrO}^- > Cl^- >$ THF $> Et_2O >$ PhCHO. (a) Lee, C.-H.; Kuo, C.-C.; Shao, M.-Y.; Gau, H.-M. *Inorg. Chim. Acta* **1999**, *285*, 254. (b) Wu, Y.-T.; Ho, Y.-C.; Lin, C.-C.; Gau, H.-M. *Inorg. Chem.* **1996**, *35*, 5948. (c) Gau, H.-M.; Lee, C.-S.; Lin, C.-C.; Jiang, M.-K.; Ho, Y.-C.; Kuo, C.-N. *J. Am. Chem. Soc.* **1996**, *118*, 2936.

radical-mediated hydrogen transfer reaction. The reductions are normally performed, after the precomplexation of the α-bromo-β-hydroxy ester with the appropriate Lewis acid, by adding Bu_3SnH in the presence of Et_3B as an initiator. The use of bidendate aluminum-derived Lewis acids was first considered. As seen in Table 2, excellent yields and ratios in favor of the 2,3-*syn* products were obtained when $AlMe_3$ was used (entries 1, 3, 5, and 7). Regardless of the substrate relative stereochemistry, the reduction under the endocyclic effect (Scheme 2, transition state **C**) was highly efficient.

Table 2. Free-Radical-Mediated Hydrogen Transfer[a]

Entry	substrate	Lewis acid	2,3-(*syn:anti*)[b]		yield[c]
		(equiv.)	products	ratio	(%)
	**13**		**17**: 2,3-*syn*, 3,4-*syn* **18**: 2,3-*anti*, 3,4-*syn*		
1	**13**	$AlMe_3$ (3.0)	**17:18**	>20:1	81
2	**13**	Bu_2BOTf (1.2)	**17:18**	1:>20	90[d]
	**14**		**19**: 2,3-*syn*, 3,4-*anti* **20**: 2,3-*anti*, 3,4-*anti*		
3	**14**	$AlMe_3$ (3.0)	**19:20**	>20:1	83
4	**14**	Bu_2BOTf (1.2)	**19:20**	1:>20	89[d]
	**15**		**21**: 2,3-*syn*, 3,4-*syn* **22**: 2,3-*anti*, 3,4-*syn*		
5	**15**	$AlMe_3$ (3.0)	**21:22**	>20:1	83
6	**15**	Bu_2BOTf (1.2)	**21:22**	1:>20	81[d]
	**16**		**23**: 2,3-*syn*, 3,4-*anti* **24**: 2,3-*anti*, 3,4-*anti*		
7	**16**	$AlMe_3$ (3.0)	**23:24**	>20:1	82
8	**16**	Bu_2BOTf (1.2)	**23:24**	1:>20	84[d]

[a] Substrates (0.1 M) were pretreated with the appropriate Lewis acid followed by Bu_3SnH (1.5 or 1.8 equiv) in CH_2Cl_2 at −78°C. Addition of air and Et_3B (0.2 equiv) every 30 min was done until the reaction was complete by TLC. [b] Determined by ^1H NMR spectroscopy of crude reaction isolates. [c] Isolated yields. [d] $i$$Pr_2NEt$ (1.5 equiv) was added to the reaction mixture prior to the addition of Lewis acid.

Boron-based Lewis acids were then evaluated. Previous studies indicated that borinate[7d] derivatives of 3,5-dihydroxyesters give rise to excellent diastereocontrol through the assistance of the exocyclic effect. We were anxious to verify if good diastereoselectivity could be achieved in the present series. Indeed, it is very unlikely, particularly in the case of the bromoesters **15**, that such bidentate complex (Scheme 2, transition state **B**, R_1 = alkyl chain) be formed because of steric effects. Fortunately, impressive results were obtained. As illustrated in entries 2, 4, 6, and 8, very high 2,3-*anti* selectivity (>20:1) was observed, answering our concerns associated with highly substituted esters and suggesting that the acyclic stereocontrol (Scheme 2, transition state **A**) was sufficient in those cases. The Bu_2BOTf probably reacted with the C-3 hydroxy group to create a borinate, thus preventing a competing *syn* reduction under the control of the endocyclic effect induced by a hydrogen bond between this hydroxy and the ester (Scheme 2, transition state **C**, L.A. = H).

In conclusion, we showed that, through judicious selection between BF_3·OEt_2 and (i-PrO)$TiCl_3$ in the Mukaiyama aldol step and then between Bu_2BOTf and $AlMe_3$ in the hydrogen transfer step, one can generate polypropionate motifs with high stereocontrol.[17] By the choice of aldehydes tested in this study, we have also shown the potential of our sequence for iterative processes.[18] Indeed, this study suggests that our substrate-controlled approach could be useful in the synthesis of complex polypropionates. Further studies are planned to better define the nature of the "chelated" intermediates, particularly as it relates to the stoichiometry of the Lewis acid in the case of (i-PrO)$TiCl_3$.

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Supporting Information Available: Experimental procedures, characterization data, ^1H NMR spectra for compounds **10** and **12**−**24**, and proof of structure for **17**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] The polypropionates stereopentads **17**−**24** were transformed to their corresponding six-membered lactones by hydrogenolysis of the benzyl ethers. NMR analysis confirmed the indicated relative stereochemistry. See Supporting Information.

[18] An interesting complement to our approach has been reported by Kiyooka whereby an aldehyde lacking substituant at C-2 is reacted in an enantioselective aldolisation. However, this methodology is limited by the use of a stoichiometric amount of chiral oxazaborolidinone to give *syn*-α-bromo-β-hydroxy-α-methylpropionate esters. Also, the iterative aldol sequence under chelation control ($TiCl_4$-mediated reaction) has only been realized with aldehydes bearing a methyl protecting group on the secondary alcohol. See: Kiyooka, S.-I. *Tetrahedron: Asymmetry* **2003**, *14*, 2897 and reference therein.