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Synthesis of polypropionate motifs containing the *anti–anti* unit

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Abstract—Reported herein is the iteration of a strategy employing a Mukaiyama reaction in tandem with a hydrogen transfer reaction for the elaboration of four polypropionate motifs containing the *anti–anti* unit. In this process, Lewis acid acts as the key element in controlling the diastereoselectivity of each step, the outcome of which is >20:1 for all of the reactions performed.

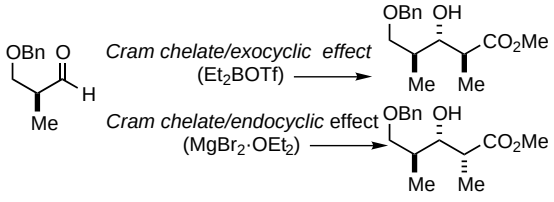
The synthesis of propionate and polypropionate motifs,[1] subunits of biologically important polyketide products, has been a topic of intense research interest. Many elegant approaches have been developed, yet the synthesis of propionate motifs remains a significant challenge. For this reason, the pursuit and study of alternative strategies continues. To this end, we have already developed an approach based on a tandem Mukaiyama/free radical based hydrogen transfer reaction sequence, where Lewis acid acts as the key element in controlling the stereochemical outcome of each step.[2]

In this approach, the Mukaiyama reaction[3] was performed with a β-benzyloxy α-methyl aldehyde (Scheme 1) to give 3,4-*anti* stereochemistry when $MgBr_2{\cdot}OEt_2$ or Et_2BOTf was used. In either case, the reaction favored a Cram chelate pathway.[2] Using a bulky silyloxy aldehyde (Scheme 2) with $BF_3{\cdot}OEt_2$ or Me_2AlCl led to a 3,4-*syn* motif and the reaction favored a Felkin–Anh pathway.[2]

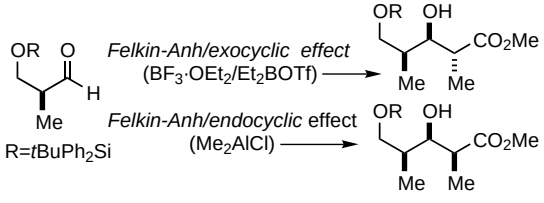
For the subsequent hydrogen transfer reaction, $MgBr_2{\cdot}OEt_2$ and Me_2AlCl were particularly efficient in favoring the endocyclic effect[4] and in giving access to the *syn* reduced product. Boron based Lewis acids, such as Bu_2BOTf or Et_2BOTf, effectively favored the exocyclic pathway[5] to give the *anti* reduced product.

One of the challenges in the above approach was the potential for competition between pathways in both steps of the reaction sequence. A judicious choice of Lewis acid proved critical in overcoming this problem. Our approach offered access to all four propionate motifs with excellent yield and diastereoselectivity in a convenient one-pot process.

Remaining to be determined was whether the sequence could be iterated. In other words, could the approach used to create these four stereotriads also be used to



Scheme 1. Tandem Mukaiyama (Cram chelate)/hydrogen transfer reaction sequences.



Scheme 2. Tandem Mukaiyama (Felkin–Anh)/hydrogen transfer reaction sequences.

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synthesize the corresponding sixteen stereopentads? Given the current interest within the field of organic chemistry to achieve the *anti–anti* motif, we decided for our first study on the synthesis of these stereopentads to concentrate on the four derived from aldehyde **1**,[2b,6] as depicted in Scheme 3.

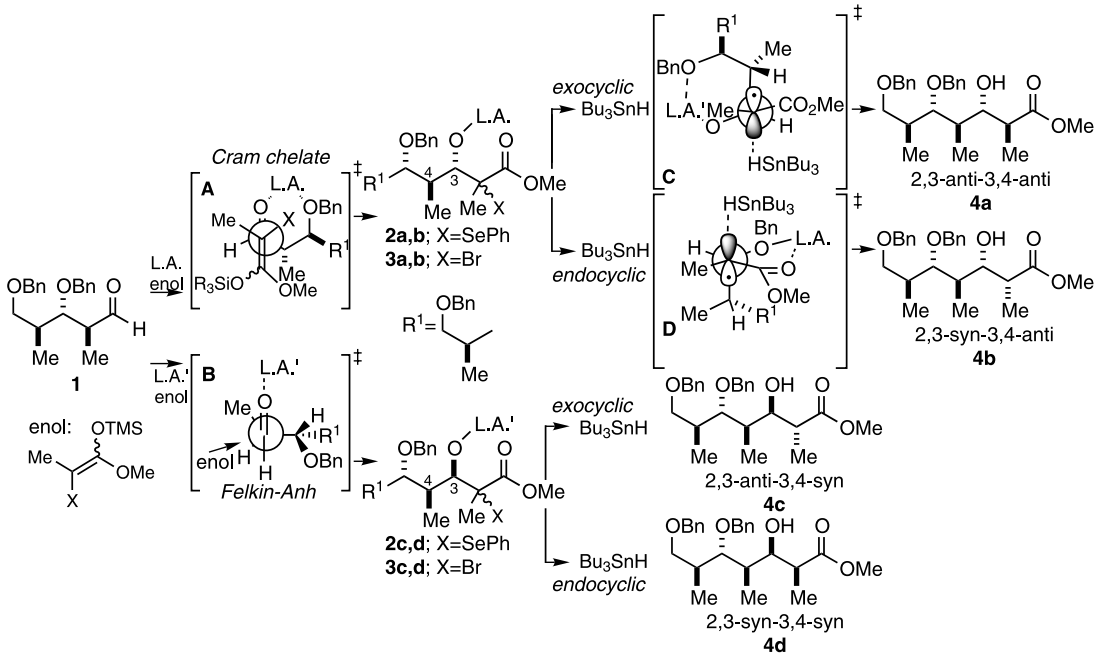
The proposed iterative sequence presented several potential challenges. First, would the Mukaiyama reaction favor a significant *anti* preference when the Cram chelate pathway was involved? As seen in Scheme 3, both substituents on the aldehyde (**1**) are disposed on opposite faces of the chelate (transition state **A**), suggesting the possibility of reduced stereocontrol.[7] Alternatively, good diastereoselectivity should be achieved in the case of a Felkin–Anh pathway, as 1,2-induction and 1,3-induction are thought to favor the same face of attack on the carbonyl (transition state **B**).[8] Second, a chelate would have to form between the oxygen atoms at C-3 and C-5 in order to drive the reaction through the exocyclic pathway (transition state **C**) in the second step of the reaction sequence. Could a putative cyclic intermediate such as this, encumbered now by three substituents in the iterative sequence, be formed preferentially and still compete with the endocyclic pathway (transition state **D**)?

The 2,3-*anti*-3,4-*anti* aldehyde **1** was prepared from the corresponding β-hydroxy ester[2b] obtained from the original reaction sequence (Scheme 1). As illustrated in Table 1, the results from our first attempts at iterating the Mukaiyama reaction were disappointing. The Et_2BOTf proved inefficient for the initiation of the Mukaiyama reaction regardless of the enoxysilane used (entries 1 and 2). We propose that the presence of polyethers on the molecule could be at the heart of the problem. Indeed, the boron based Lewis acid may prefer to chelate with the oxygen atoms at C-3 and C-5[2b] instead of with the carbonyl of the aldehyde and the hydroxy at C-3.[9]

We then turned our attention to $TiCl_4$, a stronger Lewis acid known to coordinate well with carbonyl functions. As seen in entry 3, an excellent ratio favoring 3,4-*anti* products **3a** and **3b** was noted when bromo-enoxysilane was used. This suggested that the formation of the desired bidentate intermediate had occurred, which answered our first question as to whether such an intermediate could give appropriate diastereoselectivity despite the unfavorable positioning of the two substituents (vide supra).

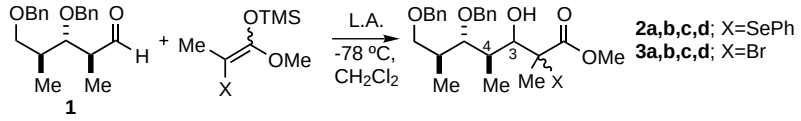
Surprisingly, a ratio of >20:1 in favor of one 3,4-*syn* product and a long reaction time were noted when a phenylselanyl-enoxysilane was used (entry 4). A number of scenarios may account for the reversed, yet excellent, diastereoselectivity obtained with phenylselanyl-enoxysilane. First, the selenium on the enoxysilane may interfere with and destroy the preformed chelate, forcing the reaction to occur through a Felkin–Anh pathway.[10] Second, the sterically encumbered nucleophile may prefer to attack the chelate-controlled carbonyl opposite the bulky R^1 substituent as opposed to the methyl as is the case when bromo-enoxysilane is used.[11] Third, transmetalation may occur between Si and Ti, leading to an alternative Zimmerman–Traxler type transition state and a 3,4-*syn* product. The latter two scenarios may also account for the longer reaction time experienced for entry 4. We are in the process of verifying and validating these possibilities.

As seen in entries 5 and 6, excellent ratios favoring 3,4-*syn* products were obtained with both enoxysilanes in the presence of $BF_3{\cdot}OEt_2$, a secondary β-benzyloxy



Scheme 3. Tandem Mukaiyama/free radical hydrogen transfer reaction sequences, iterative process.

Table 1. Mukaiyama reactions[a]



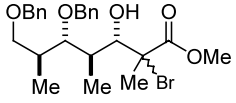
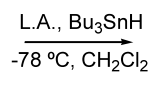
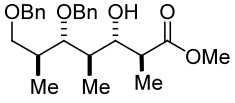
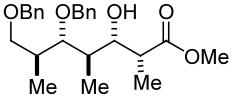
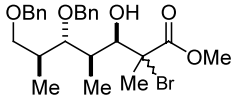
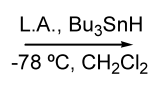
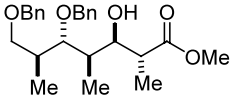
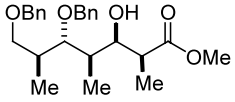
Entry	X	Lewis acid	Products[b]			
			Cram chelate 3,4-*anti* (**a**,**b**)		Felkin–Anh 3,4-syn (**c**,**d**)	Yield (%)
1	SePh	Et_2BOTf	–		–	–
2	Br	Et_2BOTf	–		–	–
3	Br	$TiCl_4$	100	:	1	77
4	SePh	$TiCl_4$	1	:	>20	75[c]
5	SePh	$BF_3{\cdot}OEt_2$[d]	1	:	>20	90
6	Br	$BF_3{\cdot}OEt_2$[d]	1	:	100	86
7	SePh	Me_2AlCl[e]	1	:	>20	84

[a] The aldehyde (0.1 M) in CH_2Cl_2 was treated at −78°C with enoxysilane (1.3 equiv.) and the appropriate LA (1.1 equiv.).
[b] Ratios were determined by ^1H NMR and HPLC spectroscopy, and yields were calculated from isolated products.
[c] Reaction time for this entry was 10 h.
[d] 2.0 equiv. was used.
[e] 2.5 equiv. was used.

aldehyde proving sufficient in this case for the induction of high *syn* diastereoselectivity. This contrasts results from our previous studies where a more bulky silyloxy aldehyde was required (Scheme 2).[2b] Finally, Me_2AlCl also led to Felkin–Anh like products with good yield and ratios when used in combination with phenylselanyl-enoxysilane. The high 3,4-*syn* diastereoselectivity achieved was not expected with the use of a bidentate Lewis acid in the presence of a benzyl ether but may be accounted for by scenarios similar to those proposed for the results with $TiCl_4$ (vide infra).

The first step of our planned tandem process having been completed successfully, we turned our attention to the hydrogen transfer step, results of which are depicted in Table 2. Treatment of a mixture of quaternary bromides (**3a**,**b**) with 1.4 equiv. of DIEA followed by 1.2 equiv. of Et_2BOTf led, after the addition of 1.8

Table 2. Free radical hydrogen transfer reactions[a]

Entry	Substrates (ratio)	Lewis acid	2,3-(anti:syn)[b]		Yield[c] (%)
			Products	Ratio[b]	
			 4a	 4b	
1	**3a**:**3b** (1.3:1)	Et_2BOTf[d]	**4a:4b**	>20 : 1	85
2	**3a**:**3b** (1.3:1)	Me_3Al	**4a:4b**	1 : >20	76
			 4c	 4d	
3	**3c**:**3d** (4:1)	Et_2BOTf[d]	**4c:4d**	>20 : 1	70
4	**3c**:**3d** (4:1)	Me_3Al	**4c:4d**	1 : >20	77

[a]Substrates (0.1 M) were pretreated with Lewis acid (1.2 equiv), Bu_3SnH (2 equiv), and Et_3B (0.2 equiv) in CH_2Cl_2 at −78 °C.
[b]Determined by ^1H NMR spectroscopy of crude reaction isolates. [c]Isolated yields. [d]iPr_2NEt (1.5 equiv) was added to the reaction mixture prior to the addition of L.A.

equiv. of Bu_3SnH and Et_3B at −78°C, to an excellent >20:1 ratio in favor of the 2,3-*anti*-3,4-*anti*-4,5-*anti*-5,6-*anti* stereopentad **4a** in good yield (entry 1).[12,13] A reversal of diastereoselectivity was noted with Me_3Al (entry 2), and a ratio of reduced products >20:1 favoring stereopentad **4b** was observed for bromides **3a** and **3b**.

Similar results were obtained when the 3,4-*syn* bromides (**3c**,**d**) were used as substrates. With Et_2BOTf, bromides **3c** and **3d** led to stereopentad **4c**. Alternatively, stereopentad **4d** was obtained when **3c** and **3d** were reduced in the presence of Me_3Al. Of particular interest are the results of entries 1 and 3, which suggest that a borinate was formed and that an intramolecular complex with the oxygen atoms at C-3 and C-5 occurred. A study aimed at formally proving the presence of these intermediates is underway.

In conclusion, this study provides an approach to the synthesis of otherwise challenging polypropionate motifs containing the *anti–anti* unit. It provides support for our hypothesis that an iterative Mukaiyama/hydrogen transfer reaction sequence may offer a complementary general approach to the synthesis of polypropionate motifs. Future work is planned to verify the scope and limitations of this process and to provide access to one-pot procedures. Of particular importance will be the consideration of diverse protecting groups commonly used in synthesis.

Supplementary material

Experimental procedures and characterization data for compounds **1**–**4** and **6**–**8**. Determination of relative configuration for compounds **4a**–**d**. Experimental procedures and characterization data for lactones **5a**–**d**.

Acknowledgements

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4. Endocyclic effect: the chelation of Lewis acids between the oxygen of the stereogenic center and the carbonyl of the ester leading to the *syn* product with high stereocontrol. See (a) Guindon, Y.; Lavallée, J.-F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 9701; (b) Guindon, Y.; Guérin, B.; Chabot, C.; Ogilvie, W. W. *J. Am. Chem. Soc.* **1996**, *118*, 12528; (c) Guindon, Y.; Liu, Z.; Jung, G. *J. Am. Chem. Soc.* **1997**, *119*, 9289; (d) Guindon, Y.; Rancourt, J. *J. Org. Chem.* **1998**, *63*, 6554; (e) Guérin, B.; Chabot, C.; Mackintosh, N.; Ogilvie, W. W.; Guindon, Y. *Can. J. Chem.* **2000**, *78*, 852. See also Ref. 2a.
5. Exocyclic effect: the chelation of Lewis acids 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. See: Guindon, Y.; Liu, Z.; Jung, G. *J. Am. Chem. Soc.* **1997**, *119*, 9289. See also Ref. 2b.
6. Aldehyde **1** was prepared by transforming β-hydroxy ester **6** into benzyloxy ester **7**, which was then reduced to benzyloxy alcohol **8** before undergoing oxidation (see Supplementary material).
7. Variable and unpredictable selectivity is observed for chelate-controlled carbonyl additions of *anti* aldehydes containing opposing stereocontrol elements at α- and β-positions. See: Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840.
8. The *anti* relationship between the α and β substituents should contribute toward mutually reinforcing π-facial selectivity in carbonyl nucleophilic addition, see: Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.
9. There was no change in the ^{13}C chemical shift of the carbonyl in the presence of Et_2BOTf, indicating that chelation did not occur at this site. See: Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778.
10. Present studies on bidendate complexes are aimed at evaluating both the importance of steric effects and the nature of heteroatoms in the presence of metal (saturated: e.g. Ti, Sn; or unsatured: e.g. Mg, Zn).
11. Ratios of 9:1 (−78°C) and >20:1 (−100°C) in favor of 3,4-*anti* products were obtained for the β-benzyloxy aldehyde (Scheme 1) when treated with $TiCl_4$ and phenylselanyl-enoxysilane, indicating that the Mukaiyama reaction can take place under chelation control using these reagents.
12. Relative configuration for **4a**–**d** was determined by ^1H NMR analysis of the coupling constants of corresponding lactones **5a**–**d** that were obtained by removal of the benzyl groups via catalytic hydrogenolysis. X-Ray structure was obtained for **5a**.

13. A direct reduction could be achieved with the free hydroxy group in the absence of Lewis acid, but the results are more difficult to predict. This is due to intermolecular hydrogen bonding between the alcohol and the carbonyl and a subsequent competing endocyclic pathway. Alternatively, protection of the secondary alcohols by methyl ether should provide a 1:8 ratio (0°C) favoring the *anti* product as seen when an isopropyl is the substituent α to the alcohol. See Ref. 4d.