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Synthesis of 2,3-Anti-3,4-anti and 2,3-Anti-3,4-syn Propionate Motifs: A Diastereoselective Tandem Sequence of Mukaiyama and Free-Radical-Based Hydrogen Transfer Reactions

Yvan Guindon,* Michel Prévost, Philippe Mochirian, and Brigitte Guérin

Institut de recherches cliniques de Montréal (IRCM), Bio-organic Chemistry Laboratory, 110 avenue des Pins Ouest, Montréal, Québec, Canada H2W 1R7, and Department of Chemistry and Department of Pharmacology, Université de Montréal, C.P. 6128, succursale Centre-ville, Montréal, Québec, Canada H3C 3J7

guindoy@ircm.qc.ca

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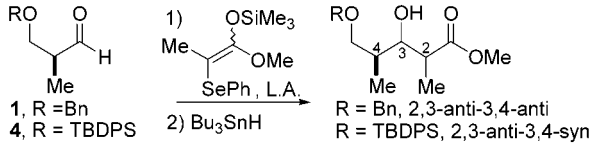
ABSTRACT



Reported herein is a strategy employing a Mukaiyama reaction in tandem with a hydrogen transfer reaction for the elaboration of 2,3-anti-3,4-anti and 2,3-anti-3,4-syn propionate motifs. The mode of complexation is controlled through monodentate or chelate pathways for the Mukaiyama reaction to give access to either syn or anti aldol products, precursors of the free-radical reduction reaction. Boron Lewis acid is used to control the free-radical reaction through the exocyclic pathway.

The synthesis of propionate motifs, subunits of biologically important polyketide products, has been a topic of intense research interest. Despite recent advances in the field,[1] the formation of the anti-anti propionate unit has remained a tactical challenge for organic chemists. In this paper, we present an efficient and diastereoselective approach to the synthesis of this "arduously accessible"[2] motif based on a tandem Mukaiyama/hydrogen transfer reaction sequence (Scheme 1). The latter step of this sequence involves free radical intermediates, which were recently shown to react with high diastereoselectivity and enantioselectivity.[3] Also shown herein is that the boron atom has a remarkable affinity for intramolecular coordination with the oxygen atoms of ethers, even when the ether bears a sterically encumbered silyl group[4] and competing carbonyl functionalities are present.

For the formation of the 2,3-anti-3,4-anti propionate motif, we looked to our previous studies, which showed that an anti isomer preference could be favored in free-radical-based hydrogen transfer reactions through the control of the *exocyclic effect*.[5] In this process, two of the substituents of the carbon bearing the heteroatom α to a carbon-centered free radical flanked by an ester are embedded in a permanent

(1) Selected examples: (a) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1998**, *63*, 4572. (b) Chemler, S. R.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 3800. (c) Hanessian, S.; Ma, J.; Wang, W. *Tetrahedron Lett.* **1999**, *40*, 4627 and 4631. (d) Breit, B.; Zahn, S. K. *J. Org. Chem.* **2001**, *66*, 4870. (e) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2001**, *66*, 7825.

(2) Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556.

(3) For general references on free-radical processes involving acyclic precursors, see: *Radicals in Organic Synthesis*, 1st ed.; Renaud, P., Sibi, M. P., Eds; Wiley-VCH: 2001; Vols. 1 and 2.

(4) 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.

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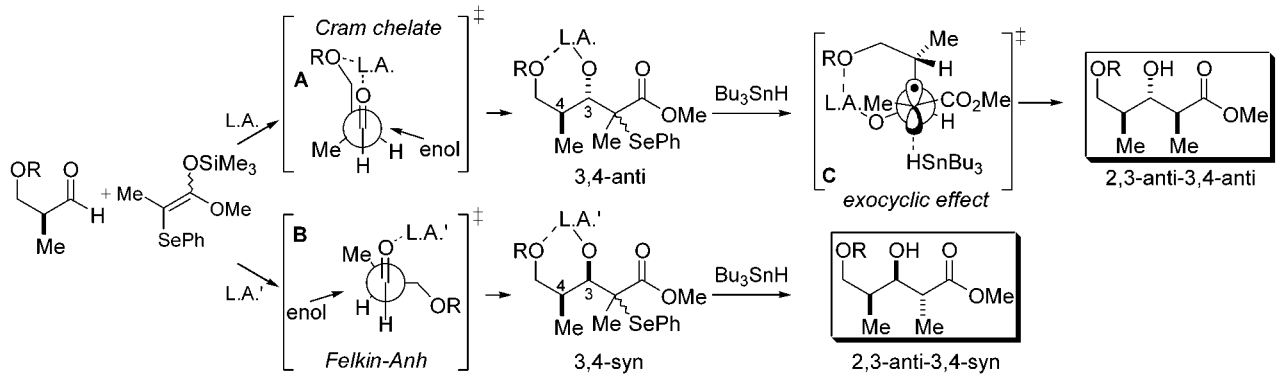
Scheme 1. Tandem Mukaiyama/Hydrogen Transfer Reaction, Exocyclic Effect



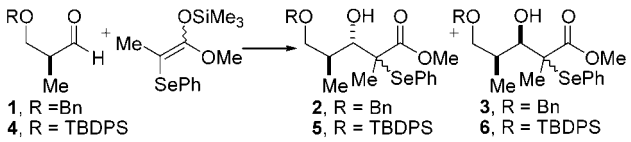
or temporary ring. For the tandem sequences to be reported herein, boron Lewis acid is used to form the temporary cycle that links together the oxygen atoms at C-3 and C-5 (Scheme 1) to induce the 2,3-anti relative stereochemistry in the free-radical step. The 3,4-anti relative stereochemistry results from a Cram chelate-based Mukaiyama[6] reaction performed as the first step of the tandem sequence leading to the anti-anti propionate motif. Alternatively, the formation of the 2,3-anti-3,4-syn propionate motif involves a Felkin−Anh based Mukaiyama reaction,[6] while the subsequent reduction again takes place under the control of the exocyclic effect. This sequence is conceptually interesting given that the sterically encumbered silyl ethers required for maximizing diastereoselectivity in the Mukaiyama reaction should generally impede the formation of the temporary cycle sought for the hydrogen transfer step.[4]

Table 1 shows the results obtained for the Mukaiyama reactions performed with various Lewis acids and alkoxy aldehydes. The addition of the tetrasubstituted seleno-enoxysilane to β-benzyloxy aldehyde **1**[7] in the presence of Et_2BOTf[8] led to good yields and high ratios of products with 3,4-anti relative stereochemistry (entry 1).[9] The reaction with Et_2BOTf was completed in less than 10 min. The order of addition proved to be essential in this latter reaction as precomplexation of **1** with Et_2BOTf led to a very rapid degradation of the aldehyde (entry 2).

The monodentate Lewis acid $BF_3{\cdot}OEt_2$ was then evaluated as seen in entries 3 and 4. A reversal in diastereoselectivity was noted, as expected, and a synthetically interesting ratio of 1:11 in favor of the 3,4-syn products **6a** and **6b** was obtained when the bulky β-silyloxy aldehyde **4**[10] was used (entry 4).[9] Surprisingly, poor diastereoselectivity was observed in favor of the Felkin−Anh products when either Bu_2BOTf or Et_2BOTf was used (entries 5 and 6).[11]

The products obtained from the Mukaiyama reactions were subsequently used for our study of the second chemical step of the planned sequence (Table 2). Excellent diastereoselectivity favoring the 2,3-anti relative stereochemistry was obtained from the reduction of the benzyloxy substrates **2a** and **2b** with either Bu_2BOTf or Et_2BOTf in the presence of

Table 1. Mukaiyama Reactions[a]



entry	aldehyde	Lewis acid (equiv)	3,4-(anti:syn) products	3,4-(anti:syn) ratio[b]	yield[c] (%)
1	**1**	Et_2BOTf (1.2)[d]	**2a**,**b**:**3a**,**b**	>20:1	86
2	**1**	Et_2BOTf (1.2)[e]	**2a**,**b**:**3a**,**b**		
3	**1**	$BF_3{\cdot}OEt_2$ (1.5)	**2a**,**b**:**3a**,**b**	1:4	64
4	**4**	$BF_3{\cdot}OEt_2$ (1.5)	**5a**,**b**:**6a**,**b**	1:11	84
5	**4**	Bu_2BOTf (1.5)	**5a**,**b**:**6a**,**b**	1:2	88[f]
6	**4**	Et_2BOTf (1.5)	**5a**,**b**:**6a**,**b**	1:4.6	81

[a] Aldehyde (0.1M) in CH_2Cl_2 was treated at −78 °C with enoxysilane (1.2 equiv when **1** was used or 2.0 equiv when **4** was used) and the appropriate Lewis acid. [b] Ratios were determined by ^1H NMR spectroscopy. [c] Yields of isolated products. [d] Reaction was completed in 10 min. [e] Et_2BOTf was precomplexed to aldehyde **1** 2 min prior to the addition of the enoxysilane. Degradation of the aldehyde was observed. [f] Reaction was performed at −40 °C, and the yield was evaluated on the basis of the one-pot process result.

(5) (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, É.; 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.

(6) (a) Gennari, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1993; Vol. 2, Chapter 2.4, pp 629−660. (b) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095.

(7) For the preparation of aldehyde **1**, see: Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035.

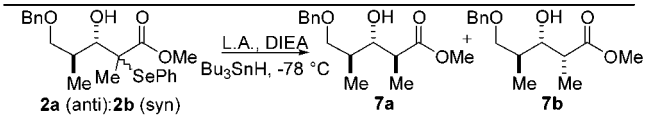
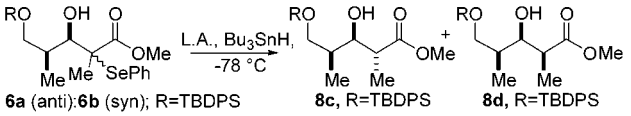
(8) Et_2BOTf was prepared following the procedure described by: Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

(9) The relative configuration for **2a** and **6b** was determined by the X-ray structure of the corresponding lactone; see ref 14.

(10) For the preparation of aldehyde **4**, see: Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.

(11) The erosion of syn preference noted for these reactions suggested that competitive reactions involving chelate intermediates might have taken place. Chelation-controlled addition was also observed with the TBS-protected aldehyde in the presence of either Me_2AlCl or $MeAlCl_2$; see: Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840.

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

entry	substrates (ratio)	L.A. (equiv)	product ratio[b] 2,3-(anti:syn)	yield[c] (%)
	 **2a** (anti):**2b** (syn)		**7a** / **7b**	
1	**2a**:**2b** (>20:1)	Bu_2BOTf (1.5)[d]	>>20 : 1	75
2	**2a**:**2b** (1:1.2)	Et_2BOTf (1.2)[e]	>>20 : 1	65
	 **6a** (anti):**6b** (syn); R=TBDPS		**8c**, R=TBDPS / **8d**, R=TBDPS	
3	**6a**:**6b** (1:2)[f]	Et_2BOTf (1.5)[d]	>20 : 1	77
4	**6a**:**6b** (1:2)[f]	Et_3B (3.0)	1 : 1	82
5	**6a**:**6b** (1:2)[f]	CH_3COOH/ Et_3B (3.0)[g]	>20 : 1	79

[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. With Et_3B, the reaction mixture was stirred under an air atmosphere 1 h prior to the addition of Bu_3SnH. [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. [e] $i Pr_2NEt$ (1.4 equiv) was added to the reaction mixture prior to the addition of Lewis acid. [f] 8% of **5a**,**b** was present for the radical reduction. [g] CH_3COOH (3.0 equiv) was added, and stirring under an air atmosphere was maintained for 1 h prior to the addition of Bu_3SnH.

DIEA (entries 1 and 2).[12] Very interestingly, when silyloxy substrates **6a** and **6b** were treated with Et_2BOTf in the presence of DIEA and Bu_3SnH, an excellent ratio was again obtained in favor of the 2,3-anti reduced product (entry 3).[12] These results were consistent with transition state **C**, wherein the boron atoms of the boronates formed on C-3 undergo intramolecular coordination with the oxygen at C-5, despite the presence of the bulky silyl group on the oxygen (Scheme 1).

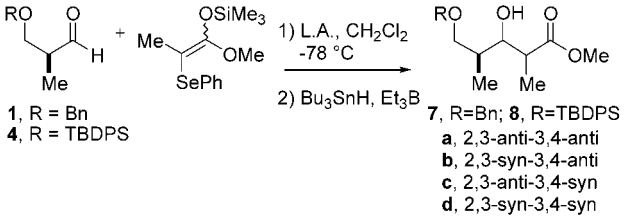
Et_3B, which is normally used as a radical initiator, was then considered for the formation of the borinates described above. Our first attempt using 3 equiv of Et_3B gave no diastereoselectivity (entry 4), but a combination of CH_3COOH[13] and Et_3B led easily to the desired anti reduced product, implying the formation of the borinate (entry 5).

With the results obtained from the independent Mukaiyama and free-radical-based hydrogen transfer reactions, we were then poised to study the tandem sequence. As described in Table 3, two new stereogenic centers were introduced with remarkable diastereoselectivity in favor of the 2,3-anti-3,4-anti product **7b** when β-benzyloxy aldehyde **1**, in the presence of Et_2BOTf (entry 1), was reacted sequentially with enoxysilane and Bu_3SnH. Of particular significance in this portion of the study was the ease with which the one-pot process provided the challenging motif.

For the formation of the 2,3-anti-3,4-syn product **8c**, the Mukaiyama reaction was performed with the silyloxy aldehyde **4** in the presence of $BF_3{\cdot}OEt_2$. The resultant products from this first step were then immediately treated to different sets of experimental conditions for the formation of the borinates. The combination of Et_3N and Et_2BOTf led to low diastereoselectivity following the reduction (entry 2). The next set of conditions to be tested was the combination of CH_3COOH and Et_3B, which were added at room temperature following the Mukaiyama reaction. The subsequent reduction gave a remarkable ratio in favor of **8c** (entry 3).

The tandem sequences depicted above offer an effective and convenient one-pot process for the synthesis of 2,3-anti-3,4-anti and 2,3-anti-3,4-syn propionate motifs. Boron Lewis acid is used advantageously to control the free-radical reaction through the exocyclic effect, and chelation occurs

Table 3. Tandem Mukaiyama and Free-Radical Hydrogen Transfer Reactions[a]



1, R = Bn
4, R = TBDPS

7, R=Bn; **8**, R=TBDPS
a, 2,3-anti-3,4-anti
b, 2,3-syn-3,4-anti
c, 2,3-anti-3,4-syn
d, 2,3-syn-3,4-syn

entry	aldehyde	Lewis acid (equiv)	products	ratio[b]	yield[c] (%)
1	**1**	Et_2BOTf (1.2)	**7a**:**7b**:**7c**:**7d**	>20:0:1:0	81
2	**4**	$BF_3{\cdot}OEt_2$ (1.5)/Et_2BOTf (1.5)	**8a**:**8b**:**8c**:**8d**	1:1.3:10:5	
3	**4**	$BF_3{\cdot}OEt_2$ (1.5)/CH_3COOH-Et_3B (3.0)[d]	**8a**:**8b**:**8c**:**8d**	1.5:0:20:1	64

[a] Mukaiyama: The aldehyde (0.1 M) was treated in CH_2Cl_2 at −78 °C with enoxysilane (1.2 equiv when **1** was used or 2.0 equiv when **4** was used) and Lewis acid (10 min); Reduction: For benzyloxy derivatives, Bu_3SnH (2 equiv) and Et_3B (0.2 equiv) were added to the reaction mixture at −78 °C. For silyloxy derivatives, Et_3N (1.5 equiv) and Et_2BOTf (1.5 equiv) were added to the reaction mixture, which was exposed to air for 1 h and cooled to −40 °C before the addition of Bu_3SnH (3 equiv) and Et_3B (0.2 equiv). [b] Ratios were determined by ^1H NMR spectroscopy of crude reaction isolates. [c] Yields of isolated products. [d] CH_3COOH (3.0 equiv) and Et_3B (3 equiv) were added to the reaction mixture, which was warmed to 20 °C, exposed to air for 2 h, and cooled to −78 °C prior to the addition of Bu_3SnH (3 equiv) and Et_3B (3 h).

even when a bulky silyloxy group is involved. These reaction sequences can be combined with previously delineated sequences, based on the endocyclic effect,[14] to allow for the synthesis of all four propionate motifs. The scope and limitations of these reactions will be examined further and their potential tested and explored in iterative processes.

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Supporting Information Available: Experimental procedures and characterization data for compound **8c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Compounds **7a** and **8d** were lactonized, and the relative configuration for the resultant products was established by NOE NMR analysis; see ref 14.

(13) Acidic activating agent, used in conjunction with Et_3B, has proven to be effective in boronate formation. See: Koester, R.; Fenzl, W.; Seidel, G. *Liebigs Ann. Chem.* **1975**, 352.

(14) 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.