

Super Silyl Stereo-Directing Groups for Complete 1,5-Syn and -Anti Stereoselectivities in the Aldol Reactions of β -Siloxy Methyl Ketones with Aldehydes

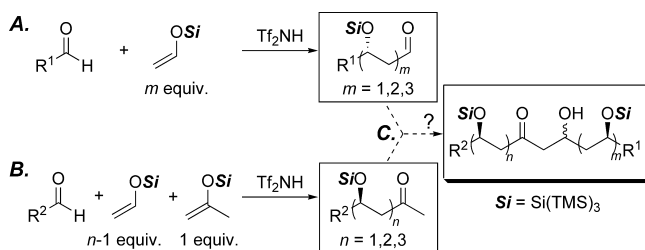
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Polyketides are an important class of natural products, and the 1,3-polyol motif is commonly found in these biologically significant compounds.¹ Undoubtedly, the asymmetric aldol reaction provides a straightforward route for the stereoselective construction of these required polyol subunits. We recently introduced a cascade Mukaiyama aldol reaction based on super silyl and super Brønsted acid chemistry that gave the required polyol-carbonyls stereoselectively in a single step (Scheme 1A,B).^{2,3} To upgrade the cascade process for even broader utility, such as rapid construction of polyketide frameworks, we here focused on 1,5-stereoselective aldol reactions that use our cascade products directly; these reactions represent a series of two consecutive aldol reactions of a central ketone with two polyol-aldehydes (Scheme 1C).^{4,5}

Scheme 1. Aldol Reactions Utilizing 1,3- and 1,5-Stereoinduction



General methodologies for high 1,5-stereoinduction in the aldol reactions of methyl ketones have not been established to date because the reaction site is far from the chiral center of the substrate in comparison with 1,2- or 1,3-inductions. Nonetheless, several methods for 1,5-anti asymmetric induction in aldol reactions have been disclosed.⁶ The most commonly used method of 1,5-anti induction is the boron-mediated aldol reaction of β -alkoxy methyl ketones with aldehydes. Unfortunately, switching the protecting group from a β -alkoxy group to a siloxy group leads to significantly lower diastereoselectivities, with a few exceptions.⁷ Thus, the method cannot be used directly on the product of Mukaiyama aldol reactions and requires extra deprotection and protection steps. To obtain 1,5-syn stereoselectivity in aldol reactions using methyl ketones is even more difficult.⁸ Synthetic methods for achieving 1,5-asymmetric induction in the context of asymmetric synthesis have been reported by both Denmark^{8a-c} and Dias.^{8d,e} However, a general diastereoselective approach to 1,5-syn induction is still challenging. Herein we report new methods for both high 1,5-syn and -anti induction in the aldol reaction of β -siloxy methyl ketones with aldehydes using substrate control.

To examine whether the use of bulky β -super siloxy groups could lead to high 1,5-stereoinduction in the aldol reaction, compounds **1a** and **2a** were prepared using our reported methodology.² Simple treatment of the lithium enolate of **1a** with pivalaldehyde in tetrahydrofuran (THF) at -78°C gave **4a** with low selectivity (Table 1, entry

1). The use of a noncoordinating solvent such as CH_2Cl_2 or toluene gave low selectivities (entries 2 and 3). Gratifyingly, the use of *N,N*-dimethylformamide (DMF) as the solvent gave *syn*-**4a** in 94% yield with good selectivity (entry 4). Finally, when the TMS-type super silyl [i.e., tris(trimethylsilyl)silyl] group was changed to a TES-type super silyl [i.e., tris(triethylsilyl)silyl] group,⁹ the diastereoselectivity increased to 96:4 (entry 5). As anticipated, the use of **3a** having a much smaller TBS protecting group gave **6a** with low selectivity (entry 6). Apparently, the super silyl group plays an important role in achieving high selectivity because of its extreme steric bulk in comparison with other silyl groups.^{2a}

Table 1. Optimization of the Aldol Reactions of **1a–3a** with Pivalaldehyde

1a : Si = Si(TMS) ₃		<i>syn</i> - 4a : Si = Si(TMS) ₃		<i>anti</i> - 4a : Si = Si(TMS) ₃		
2a : Si = Si(TES) ₃		<i>syn</i> - 5a : Si = Si(TES) ₃		<i>anti</i> - 5a : Si = Si(TES) ₃		
3a : Si = TBS		<i>syn</i> - 6a : Si = TBS		<i>anti</i> - 6a : Si = TBS		
entry	substrate	enolization reagent	<i>T</i> (°C)	solvent	% yield ^a	syn/anti ^b
1	1a	LiHMDS	−78	THF	89	40:60
2	1a	LiHMDS	−60	CH ₂ Cl ₂	50	60:40
3	1a	LiHMDS	−60	toluene	70	60:40
4	1a	LiHMDS	−60	DMF	94	87:13
5	2a	LiHMDS	−60	DMF	82	96:4
6	3a	LiHMDS	−60	DMF	69	66:34
7	1a	TMSOTf/Et ₃ N ^c	−78	CH ₂ Cl ₂	82	5:95
8	1a	TESOTf/Et ₃ N ^c	−78	CH ₂ Cl ₂	65	15:85
9	1a	TMSOTf/Et ₃ N ^c	−78	hexane	72	15:85
10	1a	TMSOTf/Et ₃ N ^c	−78	toluene	82	3:97
11	2a	TMSOTf/Et ₃ N ^c	−78	toluene	79	2:98
12	3a	TMSOTf/Et ₃ N ^c	−78	toluene	78	45:55

between the R¹ group and the olefin of the enolate that is present in conformation **B**. In the case of the lithium-mediated aldol reaction, the syn selectivity can be attributed to the unfavorable 1,3-diaxial interactions found in transition state **D**, which are absent in transition state **C**. A bulkier coordinating solvent such as THF destabilizes conformation **A** as a result of the repulsion between R¹ and the coordinated solvent molecules, leading to lower syn selectivity. In the case of the acid-catalyzed aldol reaction, anti selectivity is observed because transition state **E** has less interaction between the R² group and the methylene group than exists in transition state **F**. Switching to a bulkier silyl group in the silyl enol ether destabilizes conformation **A** as a result of the repulsion between the R¹ group and the siloxy group, leading to lower anti selectivity.

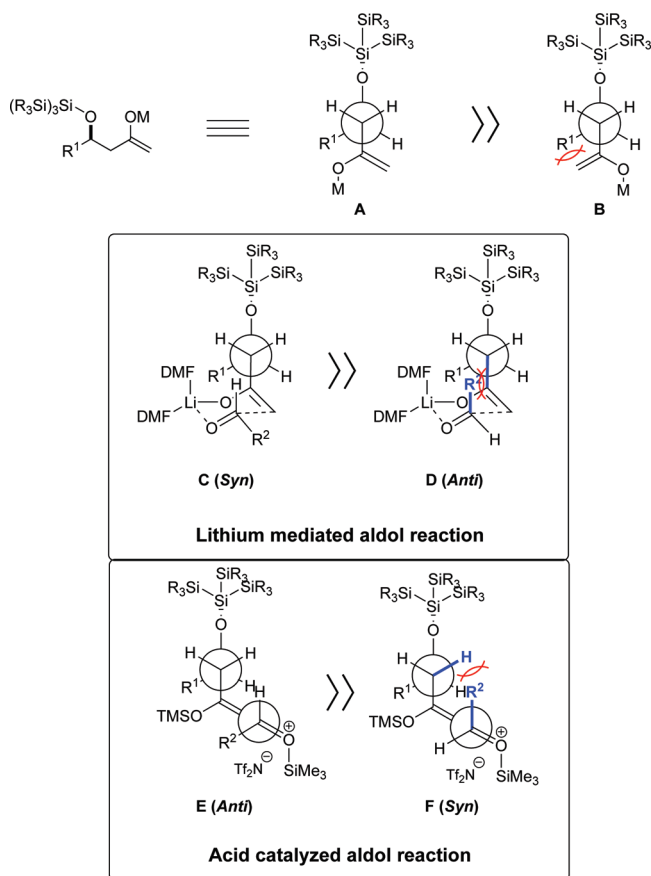


Figure 1. Plausible transition states for 1,5-syn and 1,5-anti inductions.

Under the optimized reaction conditions, the 1,5-syn-selective aldol reaction was achieved using various aldehydes and methyl ketones, and the results are summarized in Table 2. The reactions of **2a** with various aliphatic aldehydes gave **syn-5a–d** with high diastereoselectivities (entries 1–4). The aldol reactions of **2a** with aromatic and conjugated aldehydes gave **syn-5e–g** with slightly lower diastereoselectivities (entries 5–7). Methyl ketones bearing various β -alkyl substituents (**2b–d**) produced **syn-5h–m** with high diastereoselectivities (entries 8–13). Thus, the 1,5-syn aldol reaction using the TES-type super silyl group proved to be rather general in scope.

Furthermore, the substrate scope for the 1,5-anti-selective aldol reaction was also investigated (Table 3). The aldol reactions of **1a'** with various aldehydes gave **anti-4a–g** with high diastereoselectivities (entries 1–7), and methyl ketones bearing various β -alkyl substituents (**1b'–d'**) also gave **anti-4h–m** without exception (entries 8–13). Thus, the anti-selective acidic aldol process also proved to be very general.

Table 2. Substrate Scope of 1,5-Syn Aldol Reactions with **2a–d**

entry	R ¹ (2)	R ²	product (% yield ^a)	syn/anti ^b
1	<i>t</i> -Bu (2a)	<i>t</i> -Bu	5a (82)	96:4
2	<i>t</i> -Bu (2a)	<i>i</i> -Pr	5b (82)	95:5
3	<i>t</i> -Bu (2a)	<i>c</i> -Hex	5c (77)	96:4
4	<i>t</i> -Bu (2a)	<i>n</i> -Hept	5d (70)	93:7
5	<i>t</i> -Bu (2a)	4-MeO-Ph	5e (72)	89:11
6	<i>t</i> -Bu (2a)	4-NO ₂ -Ph	5f (70)	88:12
7	<i>t</i> -Bu (2a)	PhCH=CH (E)	5g (83)	85:15
8	<i>i</i> -Pr (2b)	<i>t</i> -Bu	5h (84)	96:4
9	<i>i</i> -Pr (2b)	<i>c</i> -Hex	5i (80)	95:5
10	<i>c</i> -Hex (2c)	<i>t</i> -Bu	5j (84)	97:3
11	<i>c</i> -Hex (2c)	<i>c</i> -Hex	5k (82)	97:3
12	<i>n</i> -Hept (2d)	<i>t</i> -Bu	5l (85)	93:7
13	<i>n</i> -Hept (2d)	<i>c</i> -Hex	5m (80)	92:8

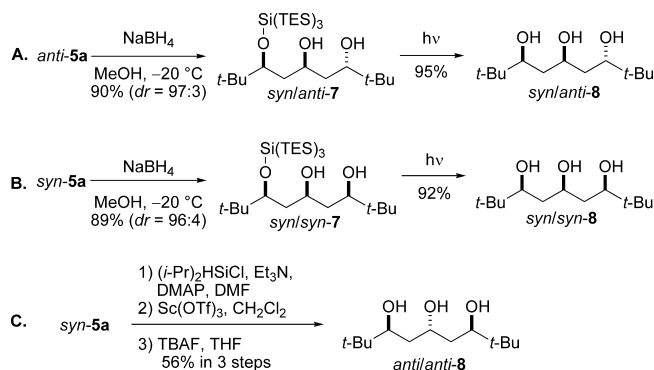
^a Isolated yield. ^b Determined by ¹H NMR analysis of the crude product.

Table 3. Substrate Scope of 1,5-Anti Aldol Reactions with **1a'–d'**

entry	R ¹ (1')	R ²	product (% yield ^a)	anti/syn ^b
1	<i>t</i> -Bu (1a')	<i>t</i> -Bu	4a (82)	97:3
2	<i>t</i> -Bu (1a')	<i>i</i> -Pr	4b (87)	95:5
3	<i>t</i> -Bu (1a')	<i>c</i> -Hex	4c (80)	97:3
4	<i>t</i> -Bu (1a')	<i>n</i> -Hept	4d (91)	95:5
5	<i>t</i> -Bu (1a')	4-MeO-Ph	4e (85)	97:3
6	<i>t</i> -Bu (1a')	4-NO ₂ -Ph	4f (92)	95:5
7	<i>t</i> -Bu (1a')	PhCH=CH (E)	4g (83)	98:2
8	<i>i</i> -Pr (1b')	<i>t</i> -Bu	4h (90)	98:2
9	<i>i</i> -Pr (1b')	<i>c</i> -Hex	4i (87)	97:3
10	<i>c</i> -Hex (1c')	<i>t</i> -Bu	4j (77)	95:5
11	<i>c</i> -Hex (1c')	<i>c</i> -Hex	4k (74)	97:3
12	<i>n</i> -Hept (1d')	<i>t</i> -Bu	4l (71)	94:6
13	<i>n</i> -Hept (1d')	<i>c</i> -Hex	4m (78)	97:3

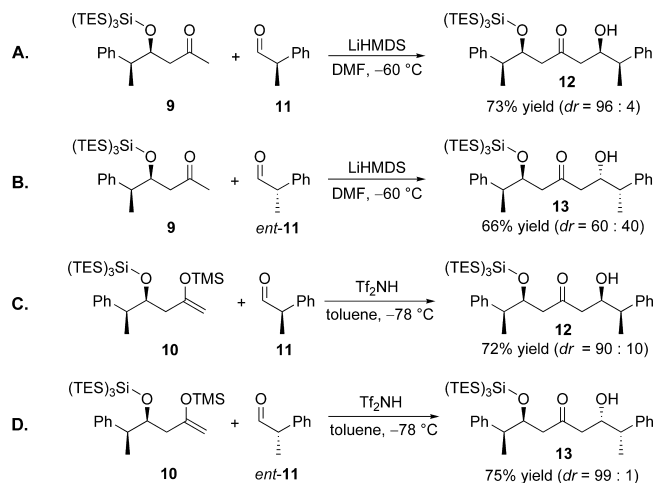
^a Isolated yield. ^b Determined by ¹H NMR analysis of the crude product.

Scheme 2. Syntheses of 1,3,5-Triols



Next, we investigated the conversion of *anti*- and *syn*-**5a** to 1,3,5-triol motifs (Scheme 2). 1,3,5-Triol *syn/anti*-**7** was obtained by the simple NaBH₄ reduction of *anti*-**5a** with excellent selectivity (Scheme 2A).¹² 1,3,5-Triol *syn/syn*-**7** was also obtained by the NaBH₄ reduction of *syn*-**5a** with high selectivity (Scheme 2B). These selectivities depended heavily on the tris(triethylsilyl)siloxy group because of its overwhelming steric hindrance. It should be noted that the TES-type super silyl group was also cleanly cleaved in MeOH/CH₂Cl₂ upon irradiation with UV light.¹³ 1,3,5-Triol *anti/anti*-**8** was obtained from *syn*-**5a** by an intramolecular hydrosilylation/scandium triflate-catalyzed reduction/desilylation sequence (Scheme 2C).^{14–16}

Scheme 3. Doubly Stereodifferentiating Aldol Reactions



Finally, the doubly stereodifferentiating aldol reactions of these enolates were examined, giving us a unique opportunity to study the absolute stereocontrol of the 1,5- versus 1,2-inductions (Scheme 3). The aldol reaction of the lithium enolate of **9**¹⁷ with aldehyde **11**¹⁷ in DMF gave **12** with high selectivity (Scheme 3A). However, the reaction of the lithium enolate of **9** with *ent*-**11** gave **13** with low selectivity (Scheme 3B). On the other hand, the aldol reactions of **10** with **11** and *ent*-**11** gave **12** and **13**, respectively, both with high selectivity (Scheme 3C,D). Thus, under acidic conditions, 1,2-induction predominates in both cases, while metalloenolate conditions give 1,5-induction in competition with the 1,2-process (Scheme 3B).

In summary, we have developed (1) 1,5-syn-selective aldol reactions of lithium enolates of β -super siloxy methyl ketones and aldehydes in DMF; (2) 1,5-anti-selective aldol reactions of the trimethylsilyl enol ethers of methyl ketones with aldehydes catalyzed by TiF_2NH in toluene; (3) a stereoselective synthesis of 1,3,5-triols *syn/syn*- and *anti/anti*-**7** from *syn*-**5a**; and (4) a stereoselective synthesis of 1,3,5-triol *syn/anti*-**7** from *anti*-**5a**. These methods are advantageous in 1,5-stereoinduction, which can be achieved from the same starting material, and all of the 1,3,5-triol stereoisomers can easily be prepared. Applications of this methodology in the synthesis of long-chain complex polyketides (Scheme 1) are currently under investigation.

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Supporting Information Available: Experimental procedures, characterization of compounds **1a–d**, **1a'–d'**, **2a–d**, *syn*-**4a**, *anti*-**4a–m**, *anti*-**5a**, *syn*-**5a–m**, and **7–13**, including their ^1H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) For reviews of polyketides, see: (a) Rychnovsky, S. D. *Chem. Rev.* 1995, 95, 2021. (b) Koskinen, A. M. P.; Karisalmi, K. *Chem. Soc. Rev.* 2005, 34, 677.
- (2) (a) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* 2006, 128, 48. (b) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* 2007, 129, 2762. (c) Boxer, M. B.; Yamamoto, H. *Org. Lett.* 2008, 10, 453. (d) Boxer, M. B.; Akakura, M.; Yamamoto, H. *J. Am. Chem. Soc.* 2008, 130, 1580. (e) Albert, B. J.; Yamamoto, H. *Angew. Chem., Int. Ed.* 2010, 49, in press.
- (3) Akakura, M.; Boxer, M. B.; Yamamoto, H. *ARKIVOC* 2007, (x), 337.
- (4) For reviews of 1,5-asymmetric induction in the aldol reaction, see: (a) Yeung, K.; Paterson, I. *Chem. Rev.* 2005, 105, 4237. (b) Dias, L. C.; Aguilar, A. M. *Chem. Soc. Rev.* 2008, 37, 451.
- (5) Selected papers utilizing 1,5-induction in the aldol reaction for total synthesis: (a) Blanchette, M. A.; Malamas, M. S.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S.; Kageyama, M.; Tamura, T. *J. Org. Chem.* 1989, 54, 2817. (b) Claffey, M. M.; Heathcock, C. H. *J. Org. Chem.* 1996, 61, 7646. (c) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* 1996, 37, 8581. (d) Paterson, I.; Wallace, D. J.; Gibson, K. R. *Tetrahedron Lett.* 1997, 38, 8911. (e) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* 1999, 55, 8671. (f) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* 2000, 122, 10033. (g) Paterson, I.; Collett, L. A. *Tetrahedron Lett.* 2001, 42, 1187. (h) Kulkarni, B. A.; Roth, G. P.; Lobkovsky, E.; Porco, J. A., Jr. *J. Comb. Chem.* 2002, 4, 56. (i) Paterson, I.; Coster, M. J. *Tetrahedron Lett.* 2002, 43, 3285. (j) Sinz, C. J.; Rychnovsky, S. D. *Tetrahedron* 2002, 58, 6561. (k) Schneider, C.; Tolksdorf, F.; Rehfeuter, M. *Synlett* 2002, 2098. (l) Paterson, I.; Di Francesco, M. E.; Kühn, T. *Org. Lett.* 2003, 5, 599. (m) Hubbs, J.; Heathcock, C. H. *J. Am. Chem. Soc.* 2003, 125, 12836. (n) Zhang, D.-H.; Zhou, W.-S. *Synlett* 2003, 1817. (o) Paterson, I.; Britton, R.; Ashton, K.; Knust, H.; Stafford, J. *Proc. Natl. Acad. Sci. U.S.A.* 2004, 101, 11986. (p) Keck, G. E.; McLaws, M. D. *Tetrahedron Lett.* 2005, 46, 4911. (q) Paterson, I.; Coster, M. J.; Chen, D. Y.-K.; Oballa, R. M.; Wallace, D. J.; Norcross, R. D. *Org. Biomol. Chem.* 2005, 3, 2399. (r) Paterson, I.; Coster, M. J.; Chen, D. Y.-K.; Gibson, K. R.; Wallace, D. J. *Org. Biomol. Chem.* 2005, 3, 2410. (s) Paterson, I.; Anderson, E. A.; Dalby, S. M. *Synthesis* 2005, 3225. (t) Son, J. B.; Kim, S. N.; Kim, N. Y.; Lee, D. H. *Org. Lett.* 2006, 8, 611. (u) Park, P. K.; O'Malley, S. J.; Schmidt, D. R.; Leighton, J. M. *J. Am. Chem. Soc.* 2006, 128, 2796. (v) Alvarez-Bercedo, P.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* 2006, 62, 9641. (w) Li, D.-R.; Zhang, D.-H.; Sun, C.-Y.; Zhang, J.-W.; Yang, L.; Chen, J.; Liu, B.; Su, C.; Zhou, W.-S.; Lin, G.-Q. *Chem.-Eur. J.* 2006, 12, 1185. (x) Evans, D. A.; Nagorny, P.; McRae, K. J.; Sonntag, L.-S.; Reynolds, D. J.; Vounatsos, F. *Angew. Chem., Int. Ed.* 2007, 46, 545. (y) Mitton-Fry, M. J.; Cullen, A.; Sammakia, T. *Angew. Chem., Int. Ed.* 2007, 46, 1066. (z) Paterson, I.; Ashton, K.; Britton, R.; Cecere, G.; Chourauqui, G.; Florence, G. J.; Stafford, J. *Angew. Chem., Int. Ed.* 2007, 46, 6167. (aa) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Genovino, J.; Maltas, P.; Moessner, C. *Angew. Chem., Int. Ed.* 2008, 47, 3016. (ab) Evans, D. A.; Burch, J. D.; Hu, E.; Jaeschke, G. *Tetrahedron* 2008, 64, 4671. (ac) Paterson, I.; Mühlthau, F.; Cordier, C. J.; Housden, M. P.; Burton, P. M.; Loiseleur, O. *Org. Lett.* 2009, 11, 353. (ad) Evans, D. A.; Welch, D. S.; Speed, A. W. H.; Moniz, G. A.; Reichelt, A.; Ho, S. J. *J. Am. Chem. Soc.* 2009, 131, 3840.
- (6) (a) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* 1996, 37, 8585. (b) Evans, A. D.; Coleman, P. J.; Côté, B. *J. Org. Chem.* 1997, 62, 788. (c) Evans, A. D.; Côté, B.; Coleman, P. J.; Connell, B. T. *J. Am. Chem. Soc.* 2003, 125, 10893. (d) Stocker, B. L.; Teesdale-Spittle, P.; Hoberg, J. O. *Eur. J. Org. Chem.* 2004, 330.
- (7) Computational studies: (a) Paton, R. S.; Goodman, J. M. *Org. Lett.* 2006, 8, 4299. (b) Paton, R. S.; Goodman, J. M. *J. Org. Chem.* 2008, 73, 1253. (c) Dias, L. C.; Pinheiro, S. M.; de Oliveira, V. M.; Ferreira, M. A. B.; Tormena, C. F.; Aguilar, A. M.; Zukerman-Schpector, J.; Tiekink, E. R. T. *Tetrahedron* 2009, 65, 8714.
- (8) (a) Denmark, S. E.; Fujimori, S. *Synlett* 2001, 1024. (b) Denmark, S. E.; Fujimori, S. *Org. Lett.* 2002, 4, 3477. (c) Denmark, S. E.; Fujimori, S.; Pham, S. M. *J. Org. Chem.* 2005, 70, 10823. (d) Dias, L. C.; de Marchi, A. A.; Ferreira, M. A. B.; Aguilar, A. M. *Org. Lett.* 2007, 9, 4869. (e) Dias, L. C.; de Marchi, A. A.; Ferreira, M. A. B.; Aguilar, A. M. *J. Org. Chem.* 2008, 73, 6299.
- (9) Tris(trimethylsilyl)silane can easily be prepared from chlorotriethylsilane and trichlorosilane. See: Bürger, H.; Kilian, W. *J. Organomet. Chem.* 1971, 26, 47.
- (10) (a) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* 1990, 55, 481. (b) Denmark, S. E.; Lee, W. *Chem.-Asian J.* 2008, 3, 327.
- (11) The use of the dicyclohexylboron enolate of substrate **1a** with pivalaldehyde gave a slightly lower anti selectivity (85:15).
- (12) The reduction of *anti*-**4a** also gave a *syn/anti* product mixture in 89% yield with high selectivity (91:9).
- (13) Using the same procedure as reported to remove the Si(TMS)₃ group. See: (a) Brook, M. A.; Gottardo, C.; Balduzzi, S.; Mohamed, M. *Tetrahedron Lett.* 1997, 38, 6997. (b) Brook, M. A.; Balduzzi, S.; Mohamed, M.; Gottardo, C. *Tetrahedron* 1999, 55, 10027.
- (14) Anwar, S.; Davis, A. P. *Tetrahedron* 1988, 44, 3761.
- (15) The use of Me₄NHB(OAc)₃, SmI₂/i-PrCHO, and DIBAL-H gave low yields or low selectivities for *anti/anti*-**8**.
- (16) The use of B(C₆F₅)₃ as the Lewis acid instead of Sc(OTf)₃ gave the 1,3,5-*syn/syn* product as a single isomer. The relative configurations of products **5a**, **7**, and **8** were determined on the basis of the NMR spectra of these related compounds (see the Supporting Information for full details).
- (17) For the synthesis of aldehyde **11**, see: Botuha, C.; Haddad, M.; Larchevêque, M. *Tetrahedron: Asymmetry* 1998, 9, 1929. For the synthesis of ketone **9**, see ref 2b.

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