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[3 + 2]-Annulation Reactions of Chiral Allylsilanes and Chiral Aldehydes. Studies on the Synthesis of Bis-tetrahydrofuran Substructures of Annonaceous Acetogenins

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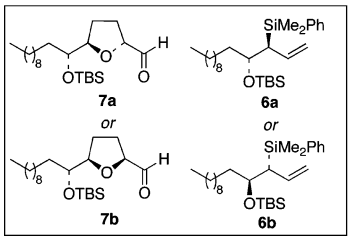


*[3+2]-Annulation reactions of **7a** and **7b** with **6a** and **6b** (all combinations) are examined using BF_3·OEt_2 and $SnCl_4$ as Lewis acid catalysts*

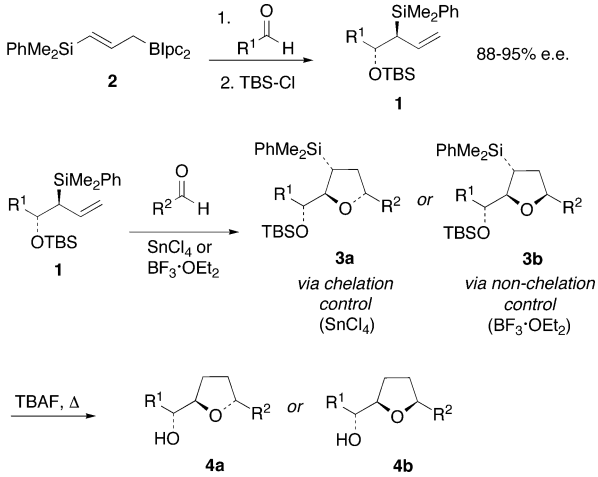
Double asymmetric [3 + 2]-annulation reactions of chiral β-silyloxyallylsilanes with chiral 2-tetrahydrofuranyl carboxaldehydes have been studied, leading to the stereocontrolled synthesis of six diastereomeric bis-tetrahydrofuran structures corresponding to the core subunits of members of the Annonaceous acetogenin family of natural products. Transition-state models are proposed to account for the stereoselectivity of the double-stereodifferentiating [3 + 2]-annulation reactions.

Introduction

Allylsilanes are versatile reagents that participate in a variety of synthetically important C−C bond-forming reactions.[1] Among these are allylation reactions of carbonyl compounds and [3 + 2]-annulation reactions of carbonyl compounds, imines, and activated double bonds to form substituted 5-membered ring carbocycles and heterocycles. Chiral allylsilanes have been utilized in [3 + 2]-annulation reactions in a number of natural product total syntheses in recent years.[2]

We have reported an efficient and enantioselective synthesis of chiral, nonracemic *anti* β-silyloxy allylsilanes **1** through the reaction of aldehydes with chiral (*E*)-γ-(dimethylphenylsilyl)allylborane reagent **2** (Scheme 1).[3] Subsequent treatment of **1** with a second aldehyde in the presence of $SnCl_4$ or BF_3·OEt_2 then provides tetrahydrofurans **3a** or **3b** with substitution at the 2, 3, and 5 positions.[4] Key to this process is the discovery that the [3 + 2]-annulation reaction of **1** in the presence of BF_3·OEt_2 provides the 2,5-*cis*-substituted tetrahydrofuran **3b** with excellent selectivity via a nonchelate-controlled transition state, whereas the reaction of **1** with α-alkoxy-

SCHEME 1



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(1) (a) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57. (b) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293. (c) Knölker, H.-J. *J. Prakt. Chem.* **1997**, *339,* 304. (d) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, 3173.

(2) Examples and lead references include: (a) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2001**, *3,* 675. (b) Roberson, C. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124,* 11342. (c) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2002**, *4,* 2945. (d) Angle, S. R.; El-Said, N. A. *J. Am. Chem. Soc.* **2002**, *124,* 3608. (e) Peng, Z.-H.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125,* 6018. (f) Hoye, T. R.; Wang, J. *J. Am. Chem. Soc.* **2005**, *127*, 6950.

(3) Roush, W. R.; Pinchuk, A. N.; Micalizio, G. C. *Tetrahedron Lett.* **2000**, *41,* 9413.

(4) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2000**, *2,* 461.

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SCHEME 2

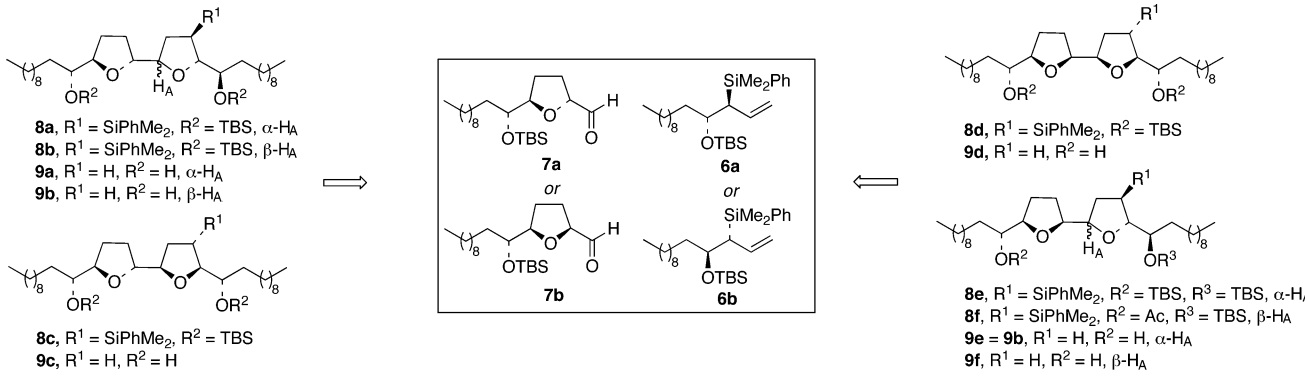
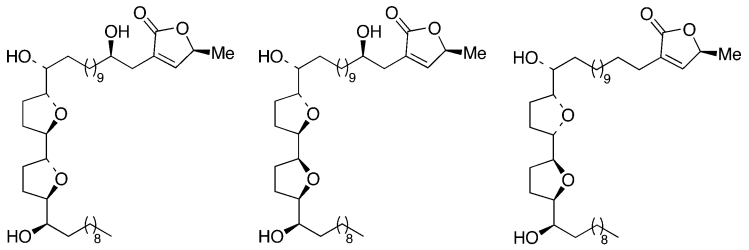


CHART 1



substituted aldehydes in the presence of $SnCl_4$ provides the isomeric 2,5-*trans*-tetrahydrofuran **3a** via a chelate-controlled transition state.[4] Removal of the 3-$PhMe_2Si$ substituent in **3a** or **3b** by protiodesilylation yields the 2,5-disubstituted tetrahydrofurans **4a** and **4b**.[5] Alternatively, transformation of the $PhMe_2Si$ group into a secondary alcohol can occur via the Tamao−Fleming oxidation.[6] Our laboratory has recently employed our [3 + 2]-annulation process toward the total synthesis of several tetrahydrofuran-containing natural products, including pectenotoxin II, amphidinolide F, and asimicin (**5**).[7]

Relatively few double-stereodifferentiating[8] [3 + 2]-annulation reactions of chiral, nonracemic allylsilanes and chiral aldehydes have been reported. Panek reported examples of double asymmetric [3 + 2]-annulation reactions of (*S*)-2-(benzyloxy)propanal with two enantiomeric chiral crotylsilanes.[9] Woerpel has disclosed examples of kinetic resolution involving [3 + 2]-annulation reactions of chiral aldehydes and racemic allylsilanes.[2c,e] We report herein an investigation of double-stereodifferentiating [3 + 2]-annulation reactions of a pair of enantiomeric chiral allylsilanes **6a** and **6b** with chiral tetrahydrofuranyl aldehydes **7a** and **7b** (Scheme 2). This study was stimulated by our interest in developing a stereochemically general synthesis of bis-tetrahydrofurans **8a**−**f** and the derived desilylated bis-tetrahydrofurans **9a**−**f**, compounds whose structures are related to the core subunits of several highly potent antitumor compounds from the Annonaceous acetogenin family of natural products (Chart 1).[10] During the course of these studies, we developed a highly stereoselective synthesis of asimicin **5**, an Annonaceous acetogenin possessing a *trans-threo-trans* bis-tetrahydrofuran core.[7c] The stereochemical generality of the [3 + 2]-annulation reaction, and its potential to access a stereochemically diverse group of structures from common precursors, makes our approach a complementary alternative to existing modular syntheses of the Annonaceous acetogenins and small libraries of stereochemically diverse bis-tetrahydrofuran systems.[11,12]

Results

Chiral allylsilane **6a** was synthesized through the reaction of undecanal **12** with (*E*)-γ-[(dimethylphenylsi-

(5) (a) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1982**, *104,* 6809. (b) Hudrlik, P. F.; Holmes, P. E.; Hudrlik, A. M. *Tetrahedron Lett.* **1988**, *29*, 6395. (c) Heitzman, C.; Lambert, W. T.; Mertz, E.; Shotwell, J. B.; Tinsley, J. M.; Va, P.; Roush, W. R. *Org. Lett.* **2005**, *7*, 2405.

(6) Review on oxidation of C−Si bonds: Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599.

(7) (a) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949. (b) Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2004**, *6,* 3865. (c) Tinsley, J. M.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 10818.

(8) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

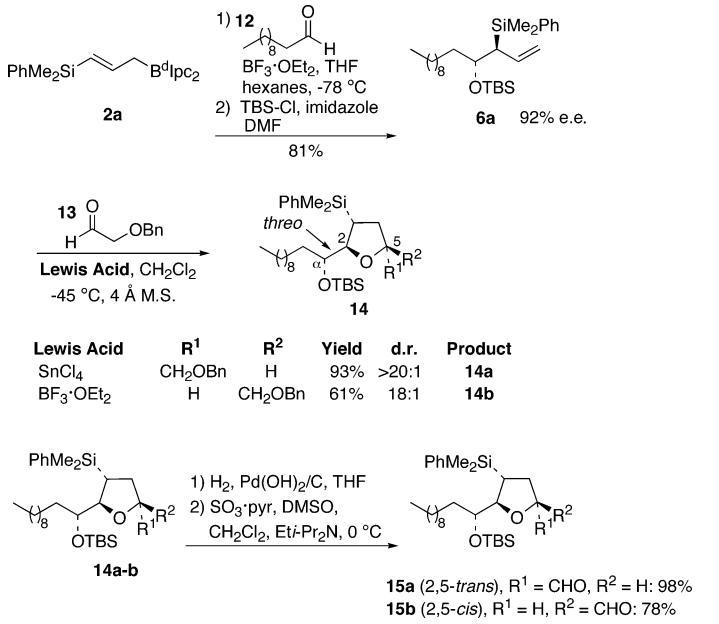
(9) Panek, J. S.; Beresis, R. *J. Org. Chem.* **1993**, *58*, 809.

(10) (a) Zafra-Polo, M. C.; Figadere, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48,* 1087. (b) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62,* 504. (c) Wang, X.-W.; Xie, H. *Drugs Future* **1999**, *24*, 159.

(11) (a) Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419. (b) Hoye, T. R.; Tan, L. *Tetrahedron Lett.* **1995**, *36,* 1981. (c) Sinha, S. C.; Sinha-Bagchi, A.; Yazbak, A.; Keinan, E. *Tetrahedron Lett.* **1995**, *36,* 9257. (d) Sinha, S. C.; Sinha, A.; Yazbak, A.; Keinan, E. *J. Org. Chem.* **1996**, *61*, 7640. (e) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1997**, *62,* 5989. (f) Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1999**, *64*, 971. (g) Emde, U.; Koert, U. *Eur. J. Org. Chem.* **2000**, 1889. (h) A modular approach to sixteen diastereomeric mono-tetrahydrofuran Annonaceous acetogenins has been recently disclosed in: Zhang, Q.; Lu, H.; Richard, C.; Curran, D. P. *J. Am. Chem. Soc.* **2004**, *126,* 36.

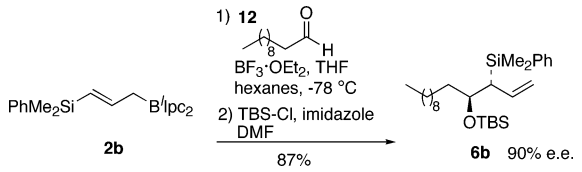
(12) (a) Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 5312. (b) Hoye, T. R.; Suhadolnik, J. C. *Tetrahedron* **1986**, *42,* 2855. (c) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996**, *61*, 4247. (d) Figadére, B.; Peyrat, J.-F.; Cavè, A. *J. Org. Chem.* **1997**, *62*, 3428. (e) Keinan, E.; Sinha, A.; Yazbak, A.; Sinha, S. C.; Sinha, S. C. *Pure Appl. Chem.* **1997**, *69,* 423. (f) Bruns, R.; Kopf, J.; Köll, P. *Chem. Eur. J.* **2000**, *6,* 1337. (g) Kojima, N.; Maezaki, N.; Tominaga, H.; Yanai, M.; Urabe, D.; Tanaka, T. *Chem. Eur. J.* **2004**, *10,* 672.

SCHEME 3

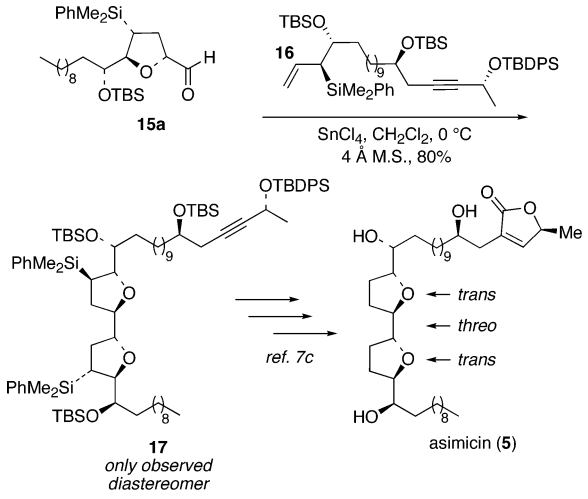


Lewis Acid	R^1	R^2	Yield	d.r.	Product
$SnCl_4$	CH_2OBn	H	93%	>20:1	**14a**
$BF_3{\cdot}OEt_2$	H	CH_2OBn	61%	18:1	**14b**

SCHEME 4



SCHEME 5



lyl)allyl]diisopinocampheylborane (derived from (−)-Ipc$_2$-BOMe and allyldimethylphenylsilane, Scheme 3).[3,7c] The absolute configurations and enantiopurity of **6a** and its enantiomer **6b** (derived from (+)-Ipc$_2$BOMe and allyldimethylphenylsilane, Scheme 4) were determined through Mosher ester analysis of the corresponding secondary alcohols.[13,14] Treatment of **6a** with α-(benzyloxy)acetaldehyde **13** in the presence of either $SnCl_4$ or $BF_3{\cdot}OEt_2$ gave the 2,5-*trans*-tetrahydrofuran **14a** and the 2,5-*cis*-tetrahydrofuran **14b**, respectively (Scheme 3). The relative stereochemistry at the C2 and C5 positions in **14a** and **14b** were assigned using ^{1}H NOE analysis, consistent with our previously reported synthesis of 2,3,5-trisubstituted tetrahydrofuran rings.[4,13] The relative configuration about the C2−Cα bond in **14a** and **14b** was assigned as *threo* on the basis of our previous findings that the *threo* relationship at this position results from [3 + 2]-annulation reactions of *β*-silyloxyallylsilanes with *anti* relative stereochemistry (e.g., allylsilanes **6a** and **6b**).[4]

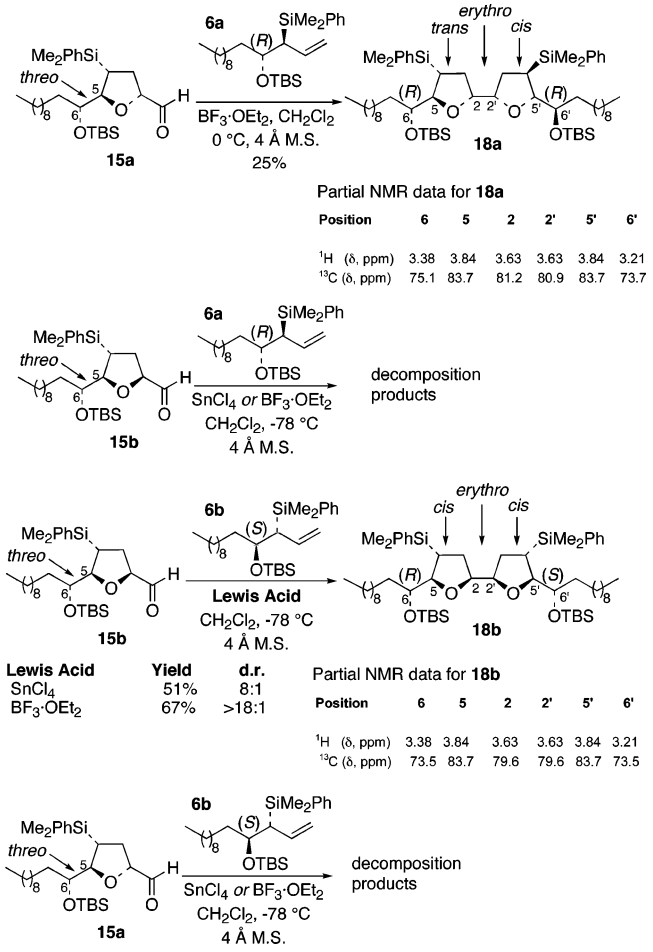
In our total synthesis of asimicin **5**, the 2,5-*trans*-tetrahydrofuryl aldehyde **15a**, which was synthesized from **14a** (Scheme 3), underwent a $SnCl_4$-catalyzed [3 + 2]-annulation reaction with the chiral allylsilane **16** to form the *trans-threo-trans* core **17** in 80% yield with excellent diastereoselectivity (Scheme 5).[7c] To explore extensions of this iterative [3 + 2]-annulation strategy in the synthesis of additional bis-tetrahydrofuran stereoisomers, allylsilane **6a** was employed as a simplified analogue of **16**. The $BF_3{\cdot}OEt_2$-catalyzed [3 + 2] annulation reaction of **6a** with **15a** afforded the *trans-erythro-cis* bis-tetrahydrofuran structure **18a** in 25% yield as the only bis-tetrahydrofuran product (Scheme 6).

The stereochemistry of **18a** was assigned through inspection of its ^{1}H and ^{13}C NMR spectra. Six separate methine resonances were observed consistent with an unsymmetric structure. The absolute configurations of the two stereogenic centers flanking the bis-tetrahydrofuran moiety (C6 and C6′) are known to be *R* from Mosher ester analysis of the parent allylsilane **6a**. It is also known from the stereochemistry of the parent aldehyde **15a** that one of the tetrahydrofuran rings in **18a** is a 2,5-*trans*-substituted ring and that a *threo* relationship exists between the C5 and C6 substituents. Given this information, there is no unsymmetric structure other than the *trans-erythro-cis* structure **18a,** which could result from the $BF_3{\cdot}OEt_2$-catalyzed [3 + 2]-annulation between **6a** and **15a**.

The [3 + 2]-annulation reactions of the 2,5-*cis*-tetrahydrofuryl aldehyde **15b** with allylsilane **6a** were also attempted; however, neither the $BF_3{\cdot}OEt_2$-catalyzed

(13) See the Supporting Information.
(14) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

SCHEME 6



reaction nor the $SnCl_4$-catalyzed reaction reliably gave bis-tetrahydrofuran products. Instead, a complex mixture of unidentified decomposition products was obtained. However, [3 + 2]-annulation reactions of **15b** and the enantiomeric allylsilane **6b** furnished [3 + 2]-annulation products under both chelation- and nonchelation-controlled conditions (Scheme 6). Surprisingly, both the BF_3·OEt_2- and $SnCl_4$-catalyzed reactions gave the *cis-erythro-cis* stereoisomer **18b** as the major product. Particularly striking was the fact that the $SnCl_4$-mediated annulation produced a 2,5-*cis*-substituted tetrahydrofuran ring, contrary to our previous results of chelation controlled [3 + 2]-annulations involving achiral aldehydes.[4] Reaction of **6b** and the 2,5-*trans*-aldehyde **15a** in the presence of either BF_3·OEt_2 or $SnCl_4$ gave largely decomposition products and trace (<5%) amounts of [3 + 2]-annulation products.

The stereochemistry of the bis-tetrahydrofuran **18b** was again assigned through inspection of its ^1H and ^{13}C NMR spectral data. Only three separate methine resonances exist for **18b**, consistent with a *meso* or C_2-symmetric structure. The *R* absolute configuration of C6 in **18b** is known from the stereochemistry of **6a**, the parent allylsilane employed in the synthesis of aldehyde **15b**. Likewise, the *S* configuration of C6′ is known from Mosher ester analysis of the *β*-hydroxyallylsilane precursor to **6b**. We also know that one of the tetrahydrofuran rings in **18b** possesses the 2,5-*cis* stereochemistry present in aldehyde **15b**, and a *threo* relationship is known

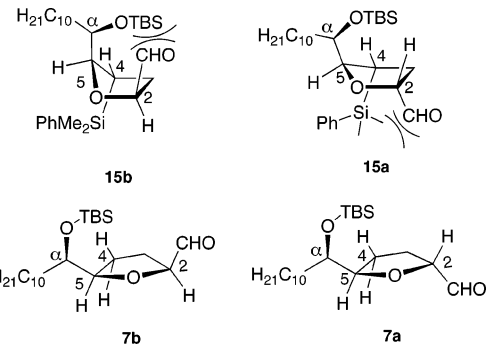
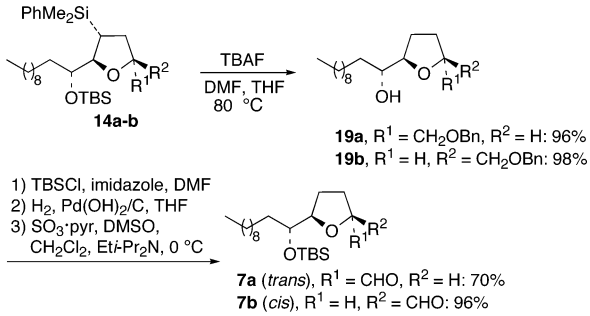


FIGURE 1. Comparison of proposed conformations of the trisubstituted tetrahydrofuryl aldehydes **15a/15b** with conformations for **7a/7b**.

SCHEME 7

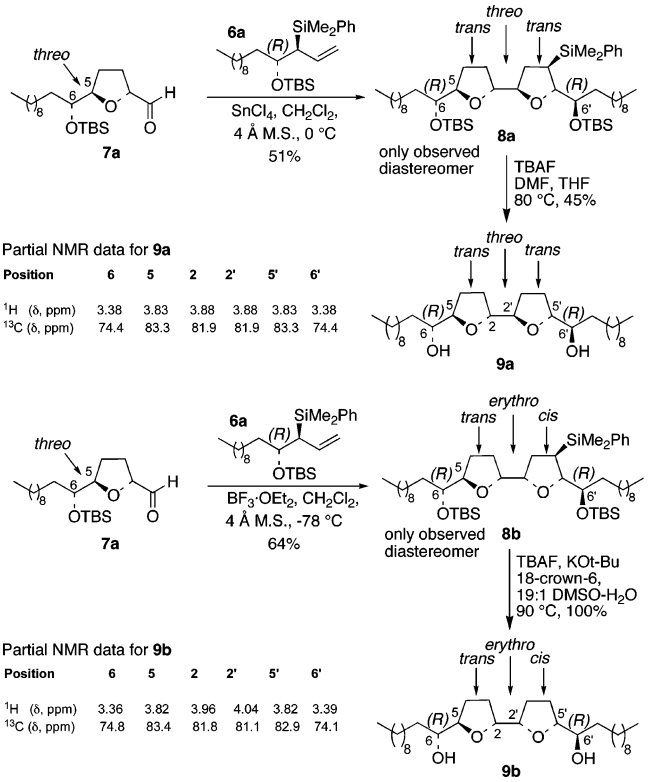


between the C5 and C6 substituents. Thus, there is no symmetric structure other than the *cis-erythro-cis* structure **18b** which could result from a [3 + 2]-annulation between **15b** and **6b**.

MM2 energy minimization calculations suggested that the carbonyl group in the 2,5-*cis*-tetrahydrofuryl aldehyde **15b** is quite sterically encumbered due to its close proximity to the Cα substituent (Figure 1). Nonbonded interactions between the aldehyde and the Cα substituent result from a puckered conformation of the tetrahydrofuran ring; this conformation presumably is adopted in order to minimize gauche interactions between the C5-alkyl substituent and the large C4-phenyldimethylsilyl group. The aldehyde carbonyl group in the 2,5-*trans*-tetrahydrofuryl aldehyde **15a** is also thought to be sterically hindered, although less severely. In the case of **15a**, nonbonded interactions arise between the carbonyl group and the C4-phenyldimethylsilyl substituent. It was proposed that the tetrahydrofuran ring in the disubstituted aldehydes **7a** and **7b** would exist in a more planar conformation, relieving steric hindrance of the aldehyde carbonyl groups and thus increasing their reactivity in the [3 + 2]-annulation reaction. Accordingly, **7a** and **7b** were synthesized by first subjecting **14a** and **14b** to protiodesilylation mediated by tetrabutylammonium fluoride (TBAF) in a THF−DMF mixture to give **19a** and **19b** (Scheme 7).[5] Removal of the benzyl ether protecting group by catalytic hydrogenolysis, followed by oxidation of the resulting primary alcohol provided the 2,5-*trans*- and 2,5-*cis*-disubstituted tetrahydrofuryl aldehydes **7a** and **7b**.

The 2,5-*trans*-tetrahydrofuryl aldehyde **7a** underwent a [3 + 2]-annulation with **6a** in the presence of $SnCl_4$ at 0 °C to give the bis-tetrahydrofuran diastereomer **8a** with high stereoselectivity (Scheme 8). The *trans-threo-trans*

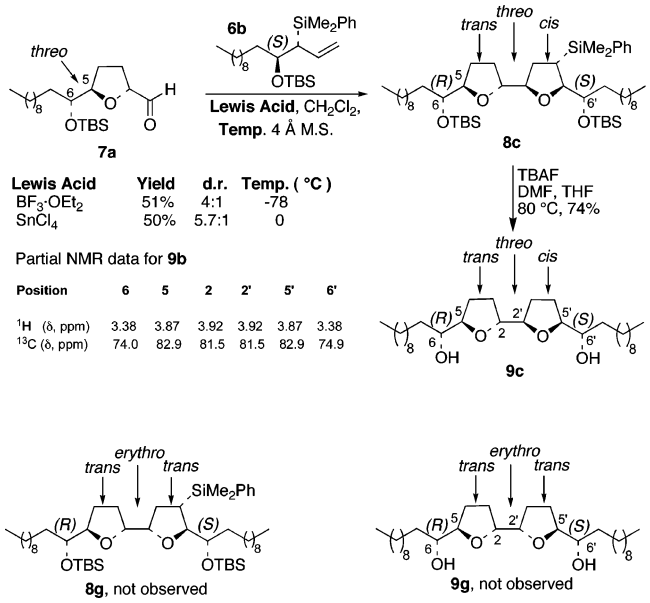
SCHEME 8



stereochemistry of **8a** was determined through protiodesilylation to afford the bis-tetrahydrofuran **9a**. This compound exhibited only three methine resonances in its ^{13}C and ^{1}H NMR spectra, indicative of a symmetric structure. Because both the C6 and C6′ are known to have the *R* configuration, and one 2,5-*trans*-disubstituted ring with a *threo* relationship between the C5 and C6 positions is present in **9a,** its structure was assigned as the symmetric *trans-threo-trans* stereochemistry.[15] The $BF_3{\cdot}OEt_2$-catalyzed reaction of **7a** and **6a** afforded a different bis-tetrahydrofuran product **8b**. Protiodesilylation of **8b** provided **9b**, a bis-tetrahydrofuran with six separate methine resonances in its ^{1}H and ^{13}C spectra. The unsymmetric *trans-erythro-cis* stereochemical relationship was thus assigned to **8b** and **9b**.

Reactions of the 2,5-*trans*-aldehyde **7a** with the enantiomeric allylsilane **6b** illustrate the improvement in reactivity which was obtained by removal of the $PhMe_2Si-$ group from the tetrahydrofuryl aldehyde substrates (Scheme 9). In this case, the same diastereomer **8c** was obtained when either $SnCl_4$ or $BF_3{\cdot}OEt_2$ was used as the Lewis acid catalyst.[16] Also noteworthy is the diminished selectivity for formation of **8c** compared to annulations giving **8a** and **8b** (Scheme 8). Protiodesilylation of **8c** yielded bis-tetrahydrofuran **9c**, which possessed three separate methine resonances in its ^{1}H NMR spectrum.

SCHEME 9



The *R* configuration at C6 and the *S* configuration at C6′ were known from the allylsilane precursors to **8c**, and the stereochemistry of aldehyde **7a** established one ring in **9c** to have 2,5-*trans* stereochemistry with a *threo* relationship between the C5 and C6 substituents. All of this evidence initially pointed to the *trans-erythro-trans* stereochemistry shown in **8g** and **9g**. However, the ^{13}C NMR data for **9c** did not unambiguously indicate a symmetric compound, and further stereochemical correlation studies, to be discussed in a subsequent section, confirmed the *trans-threo-cis* stereochemistry for **8c** and **9c**.

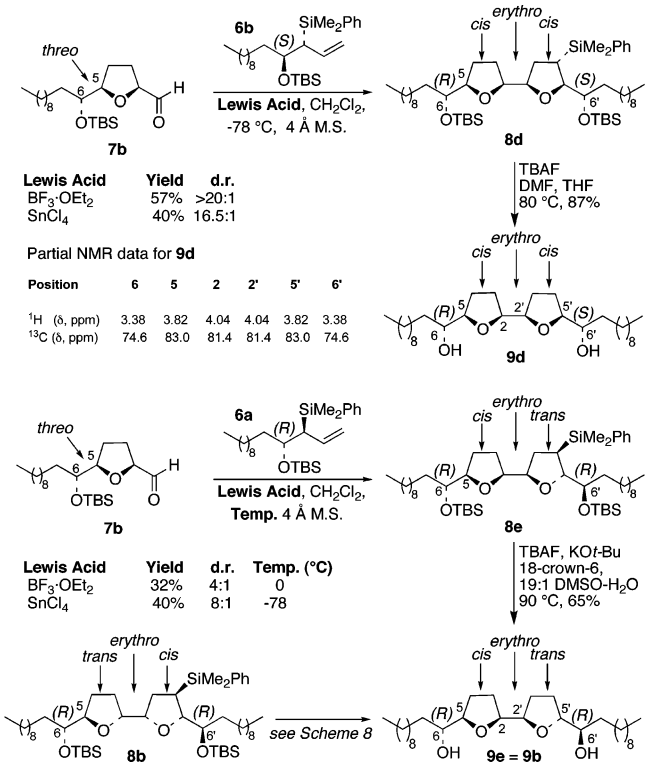
Reactions of the 2,5-*cis*-tetrahydrofuryl aldehyde **7b** with both enantiomeric allylsilanes **6a** and **6b** were also stereoconvergent under chelation-controlled and nonchelation-controlled [3 + 2]-annulation conditions (Scheme 10). The [3 + 2]-annulation of **7b** with **6b** gave the *cis-erythro-cis* isomer **8d** preferentially in the presence of either $SnCl_4$ or $BF_3{\cdot}OEt_2$. Protiodesilylation of **8d** revealed the symmetric bis-tetrahydrofuran **9d**, which exhibits only three nonequivalent methine resonances in its ^{1}H and ^{13}C NMR spectra. The *R* absolute configuration of C6 in **9d** is known from the stereochemistry of the parent allylsilane employed in the synthesis of aldehyde **7b**. Likewise, the *S* configuration of C6′ is known from allylsilane **6b**. We also know that one tetrahydrofuran ring in **9d** possesses the 2,5-*cis* stereochemistry present in aldehyde **7b**, and a *threo* relationship is known between the C5 and C6 substituents. Thus, there is no symmetric structure other than the *cis-erythro-cis* structure that can be assigned for **9d**.

While a [3 + 2]-annulation reaction of the 4-$PhMe_2Si$-substituted 2,5-*cis*-disubstituted aldehyde **15b** with **6a** was not observed, reaction of **7b** with **6b** resulted in the *cis-erythro-trans* bis-tetrahydrofuran **8e** using either Lewis acid catalyst. Protiodesilylation of **8e** gave the unsymmetric bis-tetrahydrofuran **9e** which is identical to **9b**, the product obtained from protiodesilylation of **8b**. The fact that both **8b** and **8e** converge to a single bis-tetrahydrofuran product upon protiodesilylation provides additional support for the *trans-erythro-cis* stereochemis-

(15) ^{1}H and ^{13}C NMR data for compound **9a** matched data reported from previous syntheses of this compound: (a) Rieser, M. J.; Hui, Y.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10203. (b) Naito, H. Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419. (c) Hamada, T.; Naoya, I.; Abe, M.; Fujita, D.; Kenmochi, A.; Nishioka, T.; Zwicker, K.; Brandt, U.; Miyoshi, H. *Biochemisry* **2004**, *43*, 3651.

(16) The structure of the minor diastereomer product in reactions of **7a** and **6b** was not unambiguously determined.

SCHEME 10

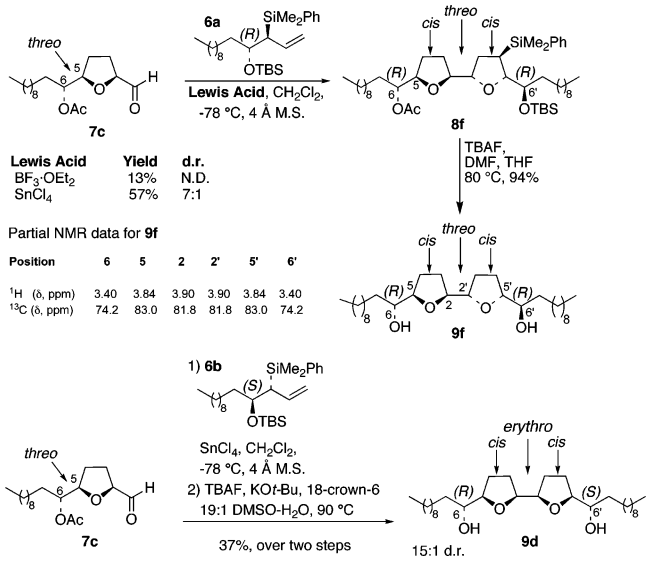


try of **9b**. We know that **9b** contains one 2,5-*trans*-disubstituted tetrahydrofuran and one 2,5-*cis*-disubstituted tetrahydrofuran ring. Both of the flanking OH groups in **9b** have the *R* absolute configuration, and these groups possess *threo* relationships with their adjacent stereogenic centers. Consequently, there are no bis-tetrahydrofuran structures other than **9b** that are possible.

Due to our inability to obtain different stereoisomers by changing the Lewis acid catalyst in [3 + 2]-annulations reactions of **7b** with either allylsilane enantiomer, we began to explore alternative tactics for achieving Lewis acid dependent stereodivergence with this substrate. The *cis*-tetrahydrofuryl aldehyde **7c**, which bears an acetate protecting group adjacent to the tetrahydrofuran ring rather than a TBS group, was synthesized to examine the effect of subtle structural modifications on the stereoselectivity of the annulation reaction (Scheme 11).[13] Remarkably, the $SnCl_4$-catalyzed reaction between **7c** and **6a** resulted in a complete reversal in stereoselectivity compared to **7b**, giving a 7:1 ratio of bis-tetrahydrofurans **8f** and **8e** in 57% yield. The $BF_3{\cdot}OEt_2$ catalyzed reaction of **7c** with **6a** was not successful, affording only a low yield of [3 + 2]-annulation products with poor diastereoselectivity. The *cis-threo-cis* stereochemistry of **8f** was established upon protiodesilylation to afford **9f**, a bis-tetrahydrofuran with ^1H and ^{13}C NMR data indicating a symmetric product. The *R* configuration at the 6 and 6′ positions in **9f** are known, and one 2,5-*cis*-tetrahydrofuran ring must be present in the structure. There are no other possible symmetric stereochemical assignments for **9f** other than the *cis-threo-cis* structure shown.

No reversal in diastereoselectivity was observed in the $SnCl_4$-catalyzed [3 + 2]-annulation reaction between **7c**

SCHEME 11

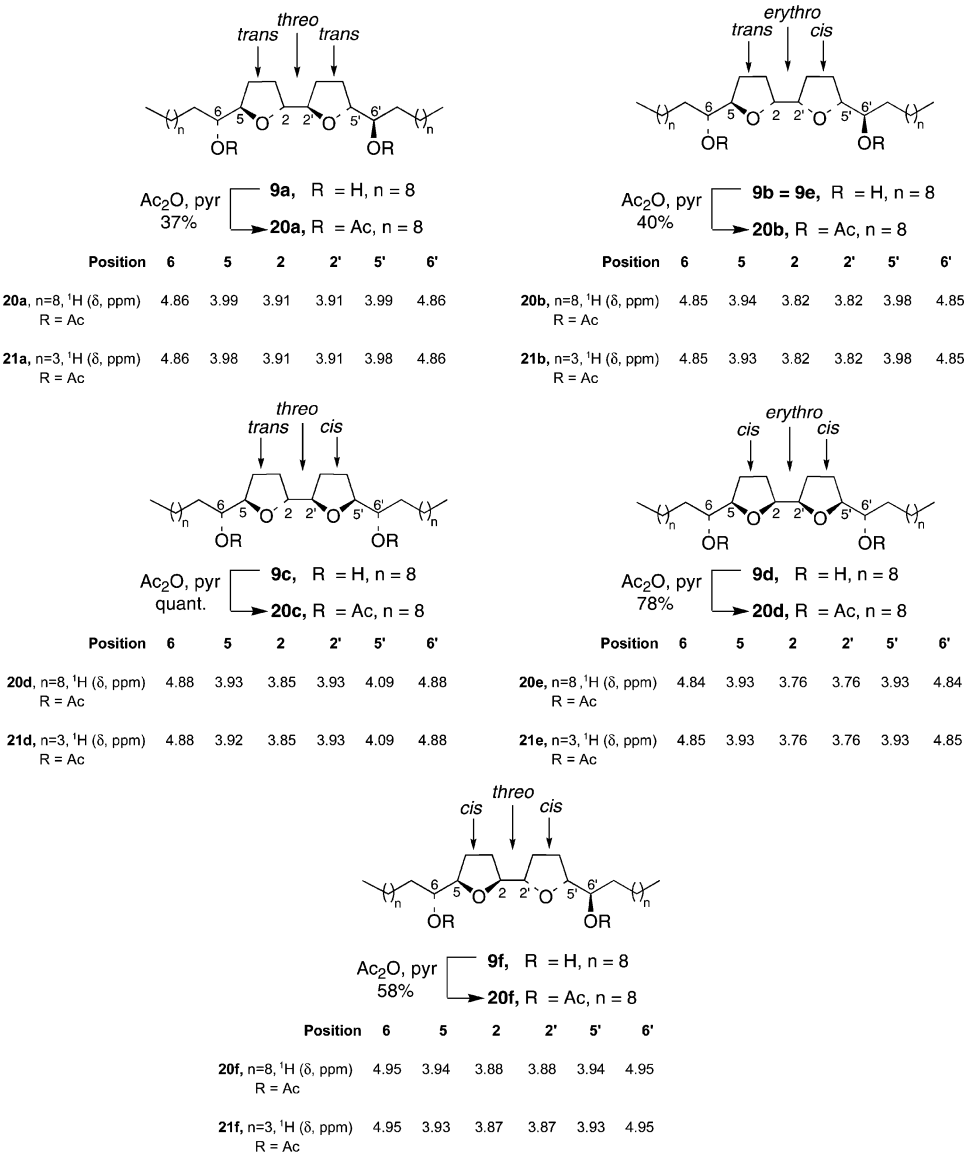


and allylsilane **6b** compared to the reaction of **7c** with **6a**. In this case, the [3 + 2]-annulation product was taken directly onto protiodesilylation to form the *cis-erythro-cis* bis-tetrahydrofuran product **9d** that was also obtained through the $SnCl_4$-catalyzed reaction of the TBS-protected tetrahydrofuryl aldehyde **7b** and allylsilane **6b** (Scheme 10).

To further support our stereochemical assignment of the bis-tetrahydrofuran stereoisomers, **9a**–**f** were treated with acetic anhydride in pyridine to obtain five bis-acetate derivatives **20a**–**f** (Figure 2). Hoye and co-workers have synthesized acetate derivatives of twelve diastereomers of related dihexyl-substituted bis-tetrahydrofurans with well-defined stereochemistry (i.e., **21a**–**f**).[12a] Since the disclosure of Hoye's study, the stereochemistry of the bis-tetrahydrofuran subunits of several Annonaceous acetogenins has been assigned by comparison of ^1H NMR chemical shifts of the peracetylated natural products with Hoye's prototype compounds. As shown in Figure 2, our synthetic bis-acetate derivatives **20a**–**f** match closely with the literature data for **21a**–**f**. Thus, the stereochemical assignments of **8a**–**f** and **9a**–**f** were confirmed. In the case of bis-tetrahydrofuran **9c**, conversion to the bis-acetate **20c** clearly gave an unsymmetric compound with six separate methine resonances, supporting the *trans-threo-cis* stereochemistry for **9c** as shown in Scheme 9.

Discussion

The results described above demonstrate that the paradigm governing stereoselectivity for [3 + 2]-annulation reactions of chiral allylsilanes with achiral aldehydes (i.e., that $SnCl_4$ provides 2,5-*trans*-substituted tetrahydrofurans via chelation controlled and $BF_3{\cdot}OEt_2$ gives 2,5-*cis*-substituted tetrahydrofurans via nonchelate controlled pathways) does not always predict the outcome of double-stereodifferentiating [3 + 2]-annulation reactions involving chiral tetrahydrofuryl aldehydes and chiral allylsilanes. Examination of possible transition states of each annulation process provides insight into the factors that may govern the stereochemical outcome of these reactions.



Position	6	5	2	2'	5'	6'
20a, n=8, ^{1}H (δ, ppm) R = Ac	4.86	3.99	3.91	3.91	3.99	4.86
21a, n=3, ^{1}H (δ, ppm) R = Ac	4.86	3.98	3.91	3.91	3.98	4.86
20b, n=8, ^{1}H (δ, ppm) R = Ac	4.85	3.94	3.82	3.82	3.98	4.85
21b, n=3, ^{1}H (δ, ppm) R = Ac	4.85	3.93	3.82	3.82	3.98	4.85
20d, n=8, ^{1}H (δ, ppm) R = Ac	4.88	3.93	3.85	3.93	4.09	4.88
21d, n=3, ^{1}H (δ, ppm) R = Ac	4.88	3.92	3.85	3.93	4.09	4.88
20e, n=8, ^{1}H (δ, ppm) R = Ac	4.84	3.93	3.76	3.76	3.93	4.84
21e, n=3, ^{1}H (δ, ppm) R = Ac	4.85	3.93	3.76	3.76	3.93	4.85
20f, n=8, ^{1}H (δ, ppm) R = Ac	4.95	3.94	3.88	3.88	3.94	4.95
21f, n=3, ^{1}H (δ, ppm) R = Ac	4.95	3.93	3.87	3.87	3.93	4.95

FIGURE 2. Synthesis of bis-acetate derivatives **20a**−**f** and comparison of ^{1}H NMR data for **20a**−**f** with literature data[12a] for related bis-tetrahydrofuran acetate derivatives **21a**−**f**.

We have previously proposed that the [3 + 2]-annulation of chiral allylsilanes with aldehydes proceeds through *syn*-synclinal transition states (shown as **I** and **II** for reaction of **6a** with **13**) in order for favorable electronic interactions between the two coupling partners to be optimized (Figure 3).[4,17,18] We suggest that the most sterically demanding quadrant of these structures is that occupied by the Lewis acid. Accordingly, $SnCl_4$ and BF_3•OEt_2 give rise to different *syn*-synclinal transition states based on the different geometry of the Lewis acid−aldehyde complex in the two transition states.

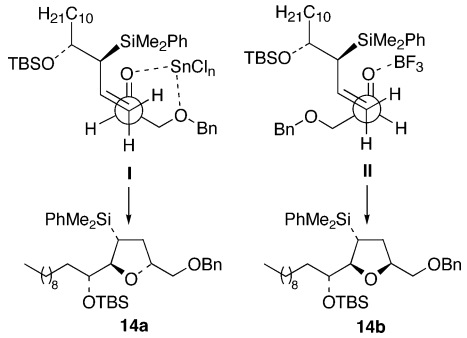


FIGURE 3. Proposed *syn*-synclinal transition states for the [3 + 2]-annulation of **6a** with an achiral aldehyde. Shown are transition states for reaction of **6a** with **13** to form monotetrahydrofurans **14a** and **14b**.

For [3 + 2]-annulation reactions involving chiral α-tetrahydrofuryl aldehydes **7a** and **7b**, the inherent diastereofacial preference of nucleophilic attack under che-

(17) The importance of *syn*-synclinal transition states for additions of type II allylmetal reagents to aldehydes has been supported by experimental and theoretical studies in: (a) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889. (b) Denmark, S. E.; Weber, E. J.; Wilson, T. M.; Willson, T. M. *Tetrahedron* **1989**, *45*, 1053.

(18) Other transition-state models have been proposed. Panek has proposed several [3 + 2]-annulation reactions to proceed through antiperiplanar transition states: Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868. Our laboratory has previously proposed the possibility of a synclinal addition mode.[4]

lation and nonchelation control must also be considered; the Cram chelate and Felkin models for carbonyl addition can be used to predict the facial bias of aldehydes **7a** and **7b**.[19] The stereoselectivity of substrate-controlled additions of achiral organometallic reagents to α-tetrahydrofuryl aldehydes under chelating and nonchelating conditions has been reported by several groups.[20] In general, 2,5-*trans*-disubstituted tetrahydrofuryl aldehydes analogous to **7a** exhibit the expected reversal of π-facial selectivity depending on chelation- or nonchelation-controlled conditions. These substrates achieve excellent induction via chelation control and moderate Felkin selectivity via nonchelation control. Conversely, 2,5-*cis*-disubstituted tetrahydrofuryl aldehydes similar to **7b** achieve excellent Felkin selectivity in the presence of nonchelating Lewis acids, but they have not furnished the complementary Cram chelate addition products expected in the presence of $SnCl_4$.[20d,i]

For the $SnCl_4$-catalyzed reaction of **7a** with **6a**, approach of the allylsilane to the *re* face of the Lewis acid complexed aldehyde (transition state $\mathbf{III}_{\mathrm{Cram}}$) is preferred by the Cram chelate model (Figure 4). Transition state $\mathbf{III}_{\mathrm{Cram}}$ also minimizes steric interactions between **6a** and $SnCl_4$. This reaction can be considered a case of matched double stereodifferentiation, a conclusion consistent with the high level of stereoselectivity observed for the formation of the product **8a**. For the $BF_3{\cdot}OEt_2$-catalyzed [3 + 2]-annulation reaction of **7a** with **6a**, approach of the allylsilane to the *si* face of **7a** is predicted by the Felkin model, as illustrated by structure $\mathbf{IV}_{\mathrm{Felkin}}$. Because the Felkin transition state also minimizes steric interactions between the sterically large side chain of **6a** and BF_3, this reaction can also be viewed as a case of matched double stereodifferentiation. As a result, the bis-tetrahydrofuran product **8b** is formed with very high diastereoselectivity.

In the $SnCl_4$-catalyzed reaction of **7a** with the enantiomeric allylsilane **6b**, *syn*-synclinal approach of the least hindered face of the allylsilane to the Cram chelate predicted *re* face of **7a** results in transition state $\mathbf{V}_{\mathrm{syn-synclinal}}$, which would experience unfavorable steric interactions in the quadrant containing the Lewis acid (Figure 5). Consequently, this reaction is viewed as a mismatched double-asymmetric reaction, and transition state $\mathbf{V}_{\mathrm{syn-synclinal}}$ is likely a disfavored structure. The synclinal transition state $\mathbf{V}_{\mathrm{synclinal}}$, which leads to the observed product **8c**, should be a favorable reaction pathway due to reduced nonbonded interactions and attack of the allylsilane to the Cram chelate face of **7a**. Two alternative transition states, the anti-Cram *syn*-synclinal structure $\mathbf{VI}_{\mathrm{syn-synclinal}}$ and the antiperiplanar structure $\mathbf{VI}_{\mathrm{anti-periplanar}}$ both lead to the unobserved bis-tetrahydrofuran product **8g.** These transition-state structures are highly disfavored due to attack at the more hindered face of the $SnCl_4$-chelated aldehyde.

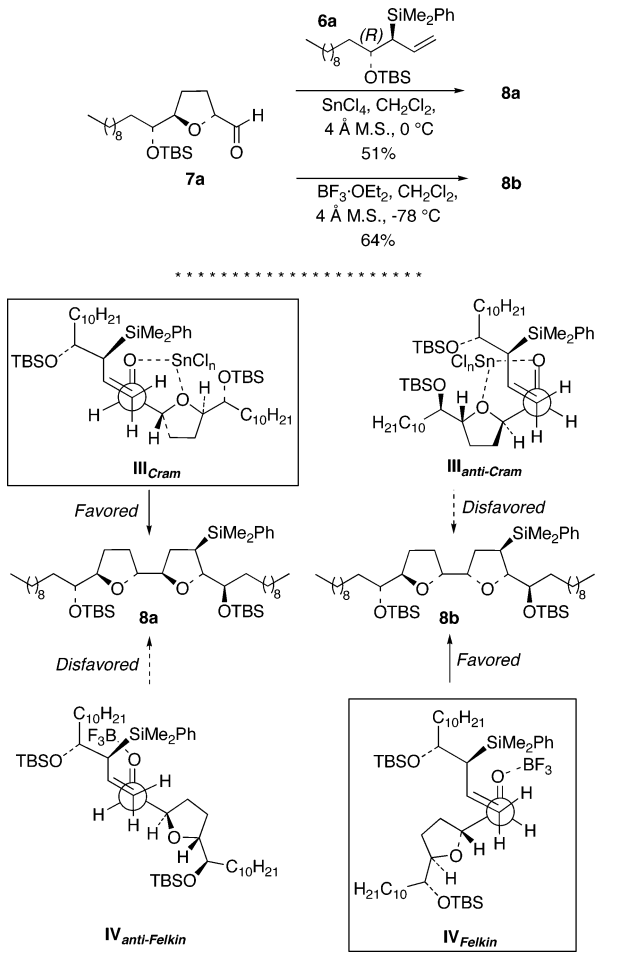


FIGURE 4. Proposed transition states for the chelation and nonchelation controlled [3 + 2]-annulations of **6a** and the 2,5-*trans*-disubstituted tetrahydrofuryl aldehyde **7a**.

The $BF_3{\cdot}OEt_2$-catalyzed reaction of **7a** with **6b** is also considered to be a mismatched double-asymmetric reaction (Figure 6). As illustrated by $\mathbf{VIII}_{\mathrm{Felkin}}$, *syn*-synclinal attack of **6b** at the Felkin-predicted *si* face of **7a** is sterically disfavored, and product **8g** is thus not isolated. Instead, **8c**, the product of addition of **6b** to the anti-Felkin face of **7a,** is obtained. Transition states $\mathbf{VII}_{\mathrm{syn-synclinal}}$ or $\mathbf{VII}_{\mathrm{synclinal}}$ must be operative in order to form **8c** in this reaction. The stereochemical mismatch of **7a** and **6b** is evident in the reduced levels of stereoselectivity in the reactions of these two substrates, and reduced product yields, a consequence of more side products of allylation and other minor reaction pathways. The magnitude in the difference in energy between transition states $\mathbf{VII}_{\mathrm{syn-synclinal}}$ and $\mathbf{VII}_{\mathrm{synclinal}}$ and competing pathways is likely not as great as in the matched double-stereodifferentiating reactions.

The stereoconvergent nature of the $SnCl_4$ and $BF_3{\cdot}OEt_2$-catalyzed reactions of **7a** with **6b** was puzzling, but not without precedent. In Panek's study of double-stereodifferentiation in the [3 + 2]-annulation reaction, an apparently mismatched reaction of a chiral crotylsilane with (*S*)-benzyloxypropanal afforded the same tetrahydrofuran stereoisomer in the presence of either $SnCl_4$ or $BF_3{\cdot}OEt_2$.[20d,i] Similar to our results, Panek

(19) (a) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. (b) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1967**, 2199. (c) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.

(20) (a) Williams, D. R.; Harigaya, Y. L.; Moore, J. L.; D'Sa, A. *J. Am. Chem. Soc.* **1984**, *106*, 2641. (b) Koert, U.; Stein, M.; Harms, K. *Tetrahedron Lett.* **1993**, *34,* 2299. (c) Koert, U. *Tetrahedron Lett.* **1994**, *35,* 2517. (d) Bradley, G. W.; Thomas, E. J. *Synlett* **1997**, 629. (e) Mori, Y.; Sawada, T.; Furukawa, H. *Tetrahedron Lett.* **1999**, *40*, 731. (f) Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Angew. Chem., Int. Ed.* **2000**, *39,* 3622. (g) Takahashi, S.; Nakata, T. *J. Org. Chem.* **2002**, *67,* 5739. (h) Maezaki, N.; Kojima, N.; Tominaga, H.; Yanai, M.; Tanaka, T. *Org. Lett.* **2003**, *5,* 1411. (i) Keum, G.; Kang, S. B.; Kim, Y.; Lee, E. *Org. Lett.* **2004**, *6,* 1895.

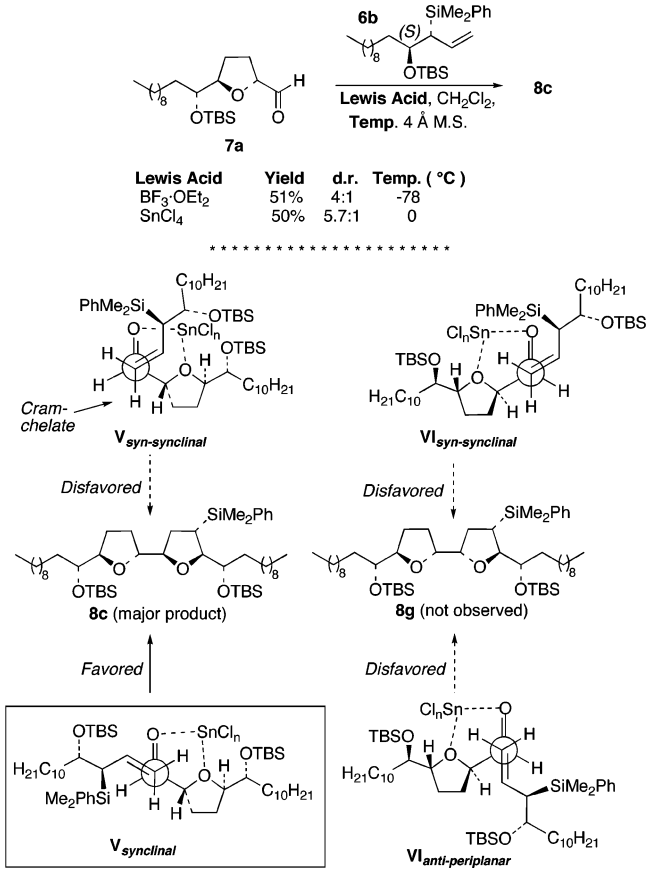


FIGURE 5. Proposed transition states for the $SnCl_4$–mediated [3 + 2]-annulation reaction of **6b** and 2,5-*trans*-tetrahydrofuryl aldehyde **7a**.

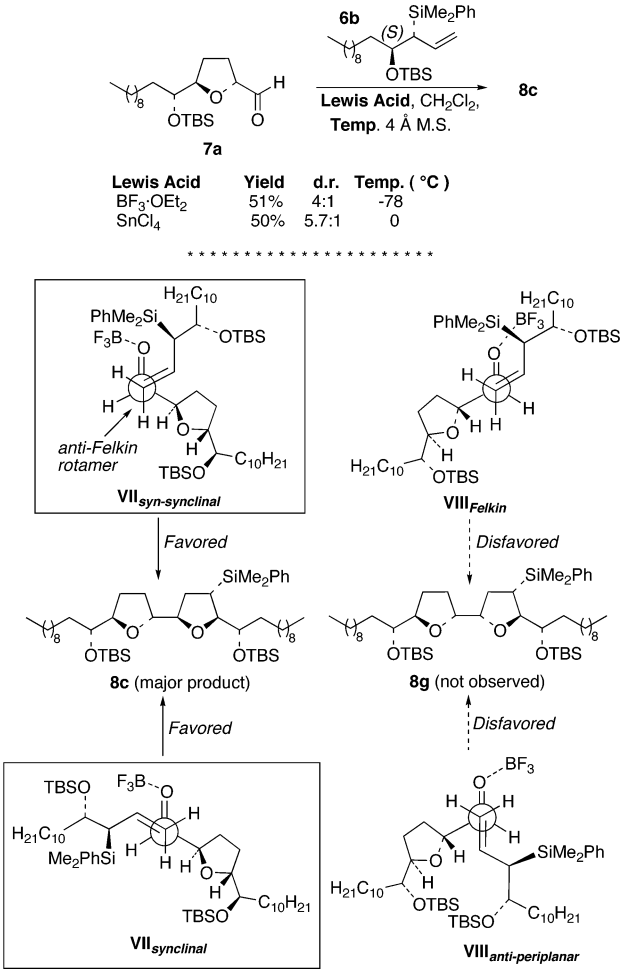


FIGURE 6. Proposed transition state for the $BF_3{\cdot}OEt_2$-catalyzed [3 + 2]-annulation reaction of **6b** and the 2,5-*trans*-disubstituted tetrahydrofuryl aldehyde **7a**.

observed that the nonchelate-controlled reaction gave a product consistent with addition to the anti-Felkin rotamer of the aldehyde, suggesting that the enantioselectivity of allylsilane **6b** overwhelms the intrinsic facial bias of aldehyde **7a**. A similar phenomenon was observed in our laboratory during studies of carbonyl addition reactions of a γ-[(diisopropylidine-α-D-mannopyranosyl)-oxy]allylstannane[21] and also in Ley's report of Mukaiyama aldol reactions involving chiral silyl enol ether substituted π-allyltricarbonyliron complexes.[22]

For the nonchelation-controlled reaction of **6b** with the 2,5-*cis*-tetrahydrofuryl aldehyde **7b**, *syn*-synclinal approach of the allylsilane to the *si* face of the aldehyde is preferred (transition state $\mathbf{IX}_{\text{Felkin}}$), and this trajectory does not exhibit significant steric crowding between allylsilane **6b** and BF_3 (Figure 7). Structure $\mathbf{IX}_{\text{Felkin}}$ which leads to **8d**, thus represents a matched transition state for the 2,5-*cis*-tetrahydrofuryl aldehyde. For the $SnCl_4$-mediated reaction, structure $\mathbf{X}_{\text{Cram}}$, in which the Cram chelate face of **7b** is approached by **6b,** was expected to be the major reaction pathway. However, the major product observed for the $SnCl_4$-catalyzed annulation, compound **8d**, does not arise from this transition state. Thus, aldehyde **7b** must react through a monodentate complex with $SnCl_4$, as shown by transition state $\mathbf{X}_{\text{Felkin}}$.

Our finding that the $SnCl_4$-catalyzed reaction of **6b** and **7b** favors the "anti-Cram" product **8d**, even for the "matched case", is consistent with other reports of Lewis acid catalyzed reactions of 2,5-*cis*-substituted tetrahydrofuran aldehydes with allylsilanes and allylstannanes.[20d,i] Stereoconvergence of $SnCl_4$- and $BF_3{\cdot}OEt_2$-catalyzed additions of group II allylmetal reagents to these substrates is a general phenomenon. In solution with $SnCl_4$, aldehyde **7b** must exist in a rapid equilibrium between the chelated structure $\mathbf{7b}_{\text{chelate}}$ and the nonchelated structure $\mathbf{7b}_{\text{nonchelate}}$ (Figure 8). The nonchelation-controlled transition state $\mathbf{X}_{\text{Felkin}}$ must be sufficiently low in energy so that product **8d** forms nearly exclusively.

Our proposal of a rapid equillibrium between $\mathbf{7b}_{\text{chelate}}$ and $\mathbf{7b}_{\text{non-chelate}}$ is in opposition to the conventional prediction of highly robust complexes forming between chelating Lewis acids and α- and β-alkoxy-substituted aldehydes.[23] However, spectroscopic evidence, crystallographic data, and experimental results have indicated that mixtures of $SnCl_4$- and β-alkoxy-substituted aldehydes can exist in equilibrium between the bidentate chelated aldehyde and the nonchelated aldehyde.[24] This equilibrium is highly dependent on the structure of the aldehyde substrate, and the extent to which the bidentate

(21) Roush, W. R.; VanNieuwenhze, M. S. *J. Am. Chem. Soc.* **1994**, *116*, 8536.

(22) Ley, S. V.; Cox. L. R.; Worrall, J. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3349.

(23) Review of chelation-controlled carbonyl addition reactions: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

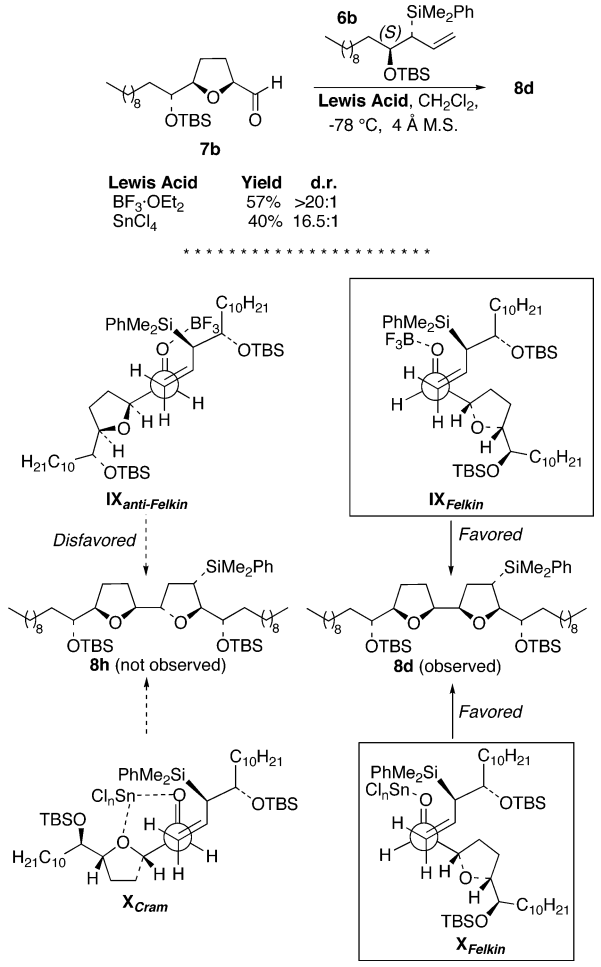


FIGURE 7. Proposed transition states for the $SnCl_4$- and $BF_3{\cdot}OEt_2$-catalyzed [3 + 2]-annulations of **6b** and the 2,5-*cis*-disubstituted tetrahydrofuryl aldehyde **7b**.

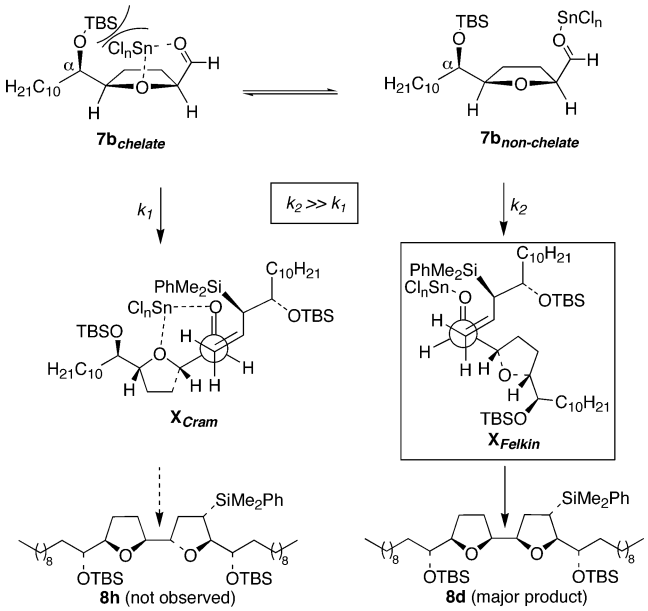


FIGURE 8. Proposed equilibration between bidentate chelated and nonchelated forms of 2,5-*cis*-disubstituted tetrahydrofuryl aldehyde **7b**.

chelate structure dissociates greatly impacts the stereoselectivity of Lewis acid catalyzed carbonyl allylation reactions. In the case of **7b**, this equilibrium may allow $\mathbf{7b}_{\text{nonchelate}}$ to form due to ring strain associated with the bicyclo[3.3.0] ring system formed in structure $\mathbf{7b}_{\text{chelate}}$.[25] It may also be that $\mathbf{7b}_{\text{chelate}}$ is destabilized by interactions between the Cα side chain and the ligands on tin. The structure of the chelation-controlled transition state itself may be more complicated than is indicated by $\mathbf{X}_{\text{Cram}}$. The fact that the alkoxy group adjacent to the aldehyde in **7b** is tethered to the main chain through the tetrahydrofuran ring may prevent the bidentate chelate formed between the aldehyde and $SnCl_4$ from approaching planarity, as is normally expected for chelated α-alkoxy carbonyl compounds.[26] Thus, the ring oxygen of **7b** could effectively become an additional chiral center and diastereomeric forms of transition state structure $\mathbf{X}_{\text{Cram}}$ would result. It is important to note that the favored transition state $\mathbf{X}_{\text{Felkin}}$ is also likely more complex. Specifically, a 2:1 complex between **7b** and $SnCl_4$ should be expected based on Denmark's evidence of aldehydes forming such complexes in the absence of bidentate chelate formation.[17b,27]

For the $BF_3{\cdot}OEt_2$-catalyzed reaction of **7b** and **6a**, the Felkin *syn*-synclinal transition state $\mathbf{XII}_{\text{syn-synclinal}}$ again suffers from unfavorable steric congestion in the quadrant containing the Lewis acid (Figure 9). We therefore view **7b** and **6a** as another mismatched pair of reaction partners. Thus, the observed major product **8e** is proposed to form through the Felkin antiperiplanar structure $\mathbf{XII}_{\text{antiperiplanar}}$, the most sterically accessible transition state. The anti-Felkin transition states $\mathbf{XI}_{\text{syn-synclinal}}$ and $\mathbf{XI}_{\text{synclinal}}$ are apparently disfavored, consistent with our observations, and the observations of others,[20d,i] that additions to 2,5-*cis*-disubstituted tetrahydrofuryl aldehydes occur with a strong sense of Felkin induction.

The $SnCl_4$-mediated [3 + 2]-annulation reaction of **7b** and **6a** also furnished **8e** with moderate (8:1) diastereoselectivity (Figure 10). Addition to the Cram chelate face of **7b**, through transition state $\mathbf{XIII}_{\text{syn-synclinal}}$ or $\mathbf{XIII}_{\text{synclinal}}$ was initially expected. However, the observed product **8e** forms through addition to the Felkin face of aldehyde **7b**. The two proposed Felkin transition states, $\mathbf{XIV}_{\text{antiperiplanar}}$ and $\mathbf{XIV}_{\text{syn-synclinal}}$ both invoke simple coordination of **7b** by $SnCl_4$ without formation of a bidentate chelate structure. The antiperiplanar mode $\mathbf{XIV}_{\text{antiperiplanar}}$ is favored because it likely experiences fewer nonbonded interactions than the *syn*-synclinal transition state. Chelation control in the [3 + 2]-annulation reaction of **7b** with **6a** is disfavored for the same reasons explained above for the reaction of **7b** with **6b**. Comparison of the four proposed transition state models in Figure 10 reveals that the synclinal transition state $\mathbf{XIII}_{\text{synclinal}}$ might be favored. However, steric interactions between the *tert*-butyl dimethylsilyl ether of aldehyde **7b** and the chelated $SnCl_4$ must increase the energy of this pathway.

(24) (a) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281. (b) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5478.

(25) Chang, S.; McNally, D.; Shary-Tehrany, S.; Hickey, S. M. J.; Boyd, R. H. *J. Am. Chem. Soc.* **1970**, *92*, 3109.

(26) Reetz, M. T.; Harms, K.; Reif, W. *Tetrahedron Lett.* **1988**, *46*, 5881.

(27) (a) Denmark, S. E.; Henke, B. R.; Weber, E. *J. Am. Chem. Soc.* **1987**, *109*, 2512. (b) Keck, G. E.; Andrus, M. B.; Castellino, S. *J. Am. Chem. Soc.* **1989**, *111*, 8136.

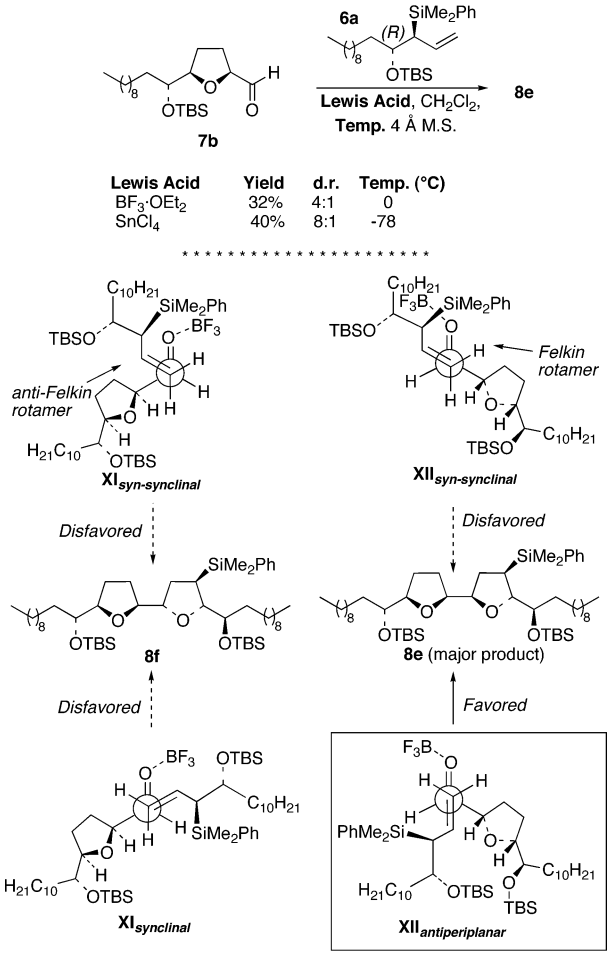
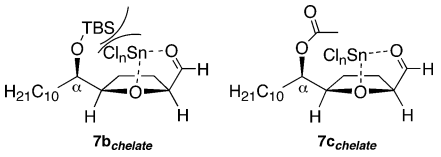


FIGURE 9. Proposed transition states for the $BF_3{\cdot}OEt_2$-catalyzed [3 + 2]-annulation reaction of **6a** and the 2,5-*cis*-disubstituted tetrahydrofuryl aldehyde **7b**.

Our finding that $SnCl_4$ annulation reactions of the acetate protected 2,5-*cis*-tetrahydrofuryl aldehyde **7c** with **6a** resulted in a reversal in stereoselectivity was intriguing. Formation of the *cis-threo-cis* structure **8f** likely occurs through a synclinal transition state structure **XIII**$_{\text{synclinal}}$ (Figure 10). Such a dramatic change in the preferred reaction pathway must result from reduction of the steric bulk of the protecting group α to the tetrahydrofuran ring, as shown by **7b**$_{\text{chelate}}$ and **7c**$_{\text{chelate}}$. This altered steric environment, or possibly a distorted conformation, of **7c** relative to **7b** likely translates into changes in the relative energy of possible transition states available to **7c** and **6a**.



Our results indicate that the discreet interplay of steric effects in the [3 + 2]-annulation reaction can modify the stereoselectivity of reactions involving double stereodifferentiation. In the case of **8c**, we have used this to our advantage by employing a modest structural change in our substrate to synthesize a bis-tetrahydrofuran diastereomer which we were not otherwise able to access. It is possible that additional modifications to **7a** or **7b** might lead to further diversity in the bis-tetrahydrofuran structures available from our [3 + 2]-annulation approach.

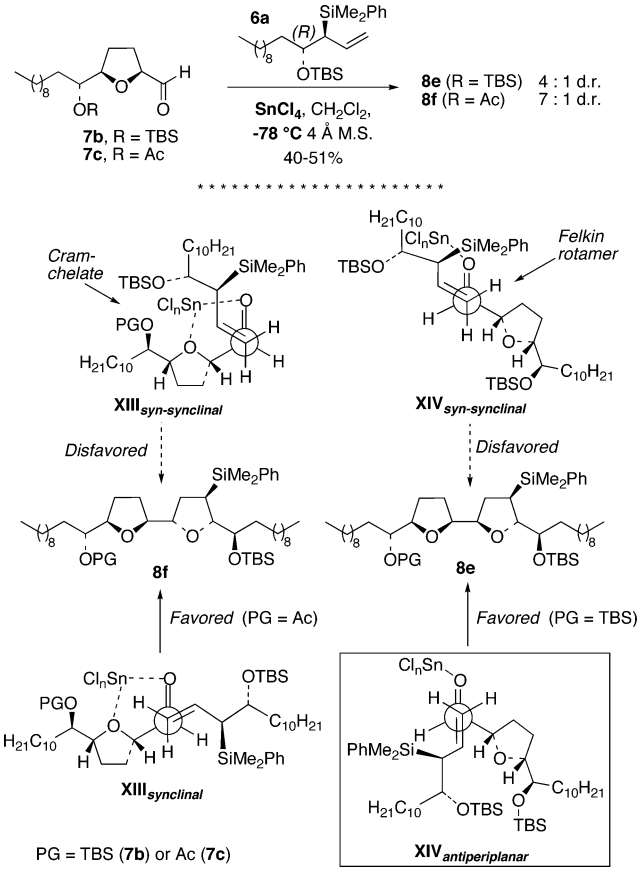


FIGURE 10. Proposed transition states for the $SnCl_4$-catalyzed [3 + 2]-annulation reaction of **6a** and the 2,5-*cis*-tetrahydrofuryl aldehydes **7b** and **7c**.

In conclusion, we have obtained a better understanding of the scope of double stereodifferentiating [3 + 2]-annulation reactions of chiral allylsilanes with 2-tetrahydrofuryl aldehydes. Our iterative approach provides access to six diastereomeric bis-tetrahydrofuran structures **8a**−**f** related to the core subunits of several bis-tetrahydrofuran Annonaceous acetogenins, including the *trans-threo-trans* series (e.g., asimicin and bullatacin), the *trans-erythro-cis* series (e.g., trilobacin and trilobin), and the *cis-threo-cis* series (e.g., squamocin N). The [3 + 2]-annulation reactions of the 2,5-*trans*-tetrahydrofuryl aldehyde **7a** with a stereochemically matched allylsilane **6a** was stereodivergent with respect to $SnCl_4$ and $BF_3{\cdot}OEt_2$ Lewis acids, in accordance with our previous results involving achiral aldehydes. The other [3 + 2]-annulation reactions, including all reactions involving the 2,5-*cis*-tetrahydrofuryl aldehyde **7b** were stereoconvergent with respect to Lewis acid. These results serve to highlight the challenge of reagent versus substrate control in double stereodifferentiating reactions as well as the importance of the aldehyde structure in bidentate chelation-controlled carbonyl additions. Applications of these results to the total synthesis of other members of the Annonaceous acetogenin family will be reported in due course.

Experimental Section[28]

Representative Procedure for the Chelate-Controlled ($SnCl_4$-Promoted) Double-Asymmetric [3 + 2]-Annulation Reaction: (2*R*,2′*R*,4′*R*,5*R*,5′*S*)-4′-(Dimethylphenylsilanyl)-5,5′-bis[(1*R*)-1-(*tert*-butyldimethylsilanyloxy)-undecyl]octahydro-2,2′-bifuran (8a). To a 0 °C solution of **7a** (87 mg, 0.23 mmol), **6a** (189 mg, 0.41 mmol), 4 Å molecular sieves (5 mg), and CH_2Cl_2 (0.80 mL) was added tin(IV) tetrachloride (0.040 mL, 0.22 mmol). The mixture was stirred at 0 °C for 3 h. The yellow-orange reaction mixture was quenched at 0 °C by dropwise addition of Et_3N (0.20 mL), and the resulting mixture was warmed to room temperature. EtOAc (5 mL) and 5 mL of saturated aqueous $NaHCO_3$ were added to form a cloudy white suspension which was stirred at room temperature for 12 h. The organic layer was removed, and the aqueous layer was extracted with 5 mL of EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a yellow oil. Purification of the crude product by silica gel chromatography (2.5% Et_2O−hexanes stepped to 5% Et_2O−hexanes) provided **8a** (98 mg, 51%) as a clear oil: $[\alpha]^{23.0}_D = +2.0$ (*c* 1.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.37−7.31 (m, 3H), 3.91 (dd, J = 8.8, 1.8 Hz, 1H), 3.91 (m, 1H), 3.80 (m, 2H), 3.61 (m, 1H), 3.29 (ddd, J = 7.3, 5.9, 1.8 Hz, 1H), 1.84 (m, 3H), 1.68−1.54 (m, 5H), 1.46 (m, 4H), 1.35−1.16 (m, 42H), 0.89 (m, 6H), 0.88 (s, 19H), 0.321 (s, 3H), 0.316 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 134.0, 129.3, 128.0, 83.0, 82.3, 81.3, 75.0, 74.9, 34.7, 32.5, 31.8, 30.1, 29.9, 29.6, 28.8, 26.5, 26.3, 26.2, 26.1, 22.9, 18.5, 18.4, 14.3, −3.7, −3.8, −3.9, −4.1, −4.3; IR (thin film, NaCl) 2955, 2855, 1463, 1251, 1111, 1070, 835, 774 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{50}H_{96}O_4Si_3$ $(M + Na)^+$ 867.6514, observed 867.6539.

Representative Procedure for the BF_3·OEt_2-Promoted Double-Asymmetric [3 + 2]-Annulation Reactions: (2*R*,2′*S*,4′*R*,5*R*,5′*S*)-4′-(Dimethylphenylsilanyl)-5,5′-bis-[(1*R*)-1-(*tert*-butyldimethylsilanyloxy)undecyl]octahydro-2,2′-bifuran (8b). To a −78 °C solution of **7a** (90 mg, 0.234 mmol), **6a** (160 mg, 0.35 mmol), 4 Å molecular sieves (5 mg), and CH_2Cl_2 (0.65 mL) was added BF_3·OEt_2 (0.030 mL, 0.24 mmol). The mixture was stirred at −78 °C for 6 h. The yellow-orange reaction mixture was quenched cold by dropwise addition of Et_3N (0.150 mL), and the resulting mixture was warmed to room temperature. EtOAc (10 mL) and 10 mL of saturated aqueous $NaHCO_3$ were added to form a suspension which was stirred at room temperature for 12 h. The organic layer was removed, and the aqueous layer was extracted with 5 mL of EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a yellow oil. Purification of the crude product by silica gel chromatography (10% Et_2O−hexanes stepped to 15% Et_2O−hexanes) provided **8b** (126 mg, 64%) as a clear oil: $[\alpha]^{24.0}_D = -2.5$ (*c* 2.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.37−7.31 (m, 3H), 3.87 (dd, J = 9.8, 1.7 Hz, 1H), 3.83 (q, J = 8.0 Hz, 1H), 3.73 (td, J = 8.1, 6.1 Hz, 1H), 3.64 (td, J = 5.4, 2.7 Hz, 1H), 3.48 (m, 1H), 3.28 (ddd, J = 8.3, 5.1, 1.5 Hz, 1H), 2.07 (ddd, J = 12.5, 8.3, 2.9 Hz, 1H), 1.99 (m, 1H), 1.86 (m, 2H), 1.72 (m, 2H), 1.66 (m, 1H), 1.54 (m, 1H), 1.40−1.17 (m, 1H), 0.89 (t, J = 6.8 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.332 (s, 3H), 0.330 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H), −0.03 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 134.1, 129.4, 128.1, 83.2, 82.8, 81.2, 80.4, 75.5, 73.4, 35.2, 32.9, 32.8, 32.3, 30.1, 30.1, 29.9, 29.86, 29.81, 29.6, 27.8, 26.3, 26.2, 26.0, 25.8, 24.4, 22.9, 18.6, 18.4, 14.3, −3.8, −3.9, −4.0, −4.0, −4.1, −4.5; IR (thin film, NaCl) 2927, 2855, 1472, 1472, 1251, 1073, 835, 774 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{50}H_{96}O_4Si_3$ $(M + Na)^+$ 867.6514, obsd 867.6509. Anal. Calcd for $C_{50}H_{96}O_4Si_3$: C, 71.02; H, 11.44. Found: C, 71.13; H, 11.56.

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Supporting Information Available: Experimental details and ^1H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) Complete experimental details are provided in the Supporting Information.