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Stereoselective Synthesis of Tetrahydrofurans via Formal [3+2]-Cycloaddition of Aldehydes and Allylsilanes. Formal Total Synthesis of the Muscarine Alkaloids (−)-Allomuscarine and (+)-Epimuscarine

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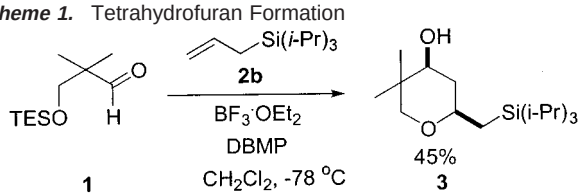
Abstract: The stereoselective synthesis of tetrahydrofurans was achieved by formal [3+2]-cycloaddition of allyl and crotylsilanes with α-triethylsilyloxy aldehydes. The scope of the reaction was examined by using different α-substituted aldehydes and different substituents on the silicon. Tamao oxidation of the products resulted in formation of diols that are easily functionalized allowing an entry to natural products synthesis. The formal total synthesis of the muscarine alkaloids (−)-allomuscarine and (+)-epimuscarine was achieved.

Introduction

Allylsilanes are excellent reagents for the regio- and stereoselective formation of carbon−carbon bonds.[1] The introduction of allyl groups by Lewis acid promoted conjugate addition of allyltrimethylsilane to α,β-unsaturated aldehydes or ketones (Hosomi−Sakurai reaction) has found many applications in stereoselective synthesis.[2] In addition, formal cycloaddition reactions of allylsilanes with carbonyls and imines have been developed into general methods for stereoselective annulation of four-, five-, and six-membered-ring systems.[3]

In cycloaddition reactions, the products retain the silicon group and the reaction may involve a 1,2 silyl shift depending on the nature of the Lewis acid used to catalyze the reaction.[4] In most of aldehyde−allylsilane reactions that are catalyzed by Lewis acids, the Lewis acid complexed alkoxide was the nucleophile that captured the β-silyl cation. There are a few exceptions in the literature where this was not the case and a nucleophile other than the alkoxide oxygen (or imine nitrogen) intercepted the β-silyl cation intermediate.[5]

Scheme 1. Tetrahydrofuran Formation



Previous work from our laboratory showed that the normal pathway of the cycloaddition reaction of aldehydes with allylsilanes could be diverted into another manifold by the use of a triethylsilyl ether as the nucleophile to trap the β-silyl cation/siliranium ion. We found that when the triethylsilyl protected β-hydroxy aldehyde **1** was treated with allyltriisopropylsilane **2b** in the presence of boron triflouride etherate and 2,6-di-*tert*-butyl-4-methylpyridine (DBMP), tetrahydropyran **3** was produced as a single diastereomer (Scheme 1).[6] This novel formal [4+2]-cycloaddition depends on the fact that the triethylsilyl group sterically hinders the complexation of the ether oxygen with the Lewis acid while still allowing it to function as a more potent nucleophile than the Lewis acid complexed alkoxide ion. The successful formation of tetrahydropyrans via this pathway led us to consider the synthesis of tetrahydrofurans from aldehydes containing one less carbon. Tetrahydrofurans are ubiquitous in nature, occurring in a wide range of biologically active substances such as C-nucleosides and ionophore antibiotics.[7] Preparation of substituted tetrahydrofurans in a stereoselective manner constitutes a significant challenge for synthetic

(1) (a) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57−575. (b) Hosomi, A. *Acc. Chem. Res*. **1988**, *21*, 200−206. (c) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1−22. (d) Colvin, E. W. *Silicon in Organic Synthesis*; Butterworth: London; Boston, 1981. (e) Langkopf, E.; Schinzer, D. *Chem. Rev*. **1995**, *95*, 1375−1408. (f) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063-2192.

(2) (a) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *16*, 1295−1298. (b) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc*. **1977**, *99*, 1673−1675.

(3) For leading references see the following and references therein: (a) Masse, C. E.; Panek, J. S. *Chem. Rev*. **1995**, *95*, 1293−1316. (b) Knolker, H. J. *J. Prakt. Chem.* **1997**, *339*, 304−314. (c) Knolker, H. J.; Foitzik, N.; Gabler, C.; Graf, R. *Synthesis* **1999**, 145−151. (d) Knolker, H. J.; Foitzik, N.; Schmitt, O. *Tetrahedron Lett.* **1999**, *40*, 3557−3560. (e) Knolker, H. J.; Baum, G.; Schmitt, O.; Wanzl, G. *Chem. Commun*. **1999**, 1737−1738.

(4) (a) Akiyama, T.; Kirino, M. *Chem. Lett*. **1995**, 723−724. (b) Akiyama, T.; Yasusa, T.; Ishikawa, k.; Ozaki, S. *Tetrahedron Lett*. **1994**, *35*, 8401−8404. (c) Akiyama, T.; Yamanaka, M. *Synlett* **1996**, 1095−1096.

(5) For three such exceptions see: (a) Sugimura, H. *Tetrahedron Lett*. **1990**, *31*, 5909−5912. (b) Escudier, J.; banuls, V. *Tetrahedron* **1999**, *55*, 5831−5838. (c) Puchot-Kadouri, C.; Agami, C.; Bihan, D.; Hamon, L. *Tetrahedron* **1998**, *54*, 10309−10316.

(6) Angle, S. R.; El-Said, N. E. *J. Am. Chem. Soc*. **1999**, *121*, 10211−10212.

(7) (a) *Polyether Antibiotics*; Westley, J. W., Ed.; Marcel Decker: New York, 1982; Vols. 1 and 2. (b) Garner, P. Nucleoside Antibiotics In *Studies in Natural Product Chemistry*; Atta-Yr-Rhaman, Ed.; Elsevier: Amsterdam, 1988; Vol. 1, Part A, pp 397−434.

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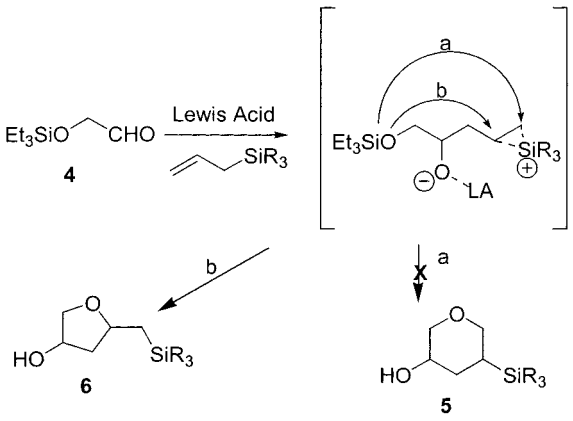
Scheme 2. Pathway for the Synthesis of Tetrahydrofurans



organic chemists.[8] In our previous work we had shown a single example of tetrahydrofuran formation.[6] This methodology has the potential to be a general approach for the stereoselective synthesis of tetrahydrofurans. The product from the reaction of aldehyde **4** and allylsilanes was the tetrahydrofuran **6** through pathway "b" (Scheme 2). No tetrahydropyran **5** (through pathway "a") was observed. We describe here the scope and limitations of this methodology for the synthesis of a variety of di-, tri-, and tetrasubstituted tetrahydrofurans.

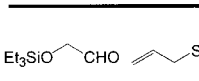
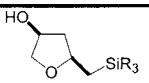
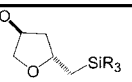
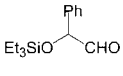
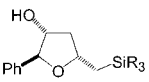
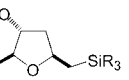
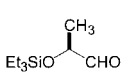
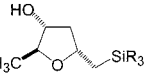
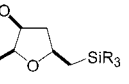
Results and Discussion

Reactions with Allylsilanes. The results of our study are summarized in Table 1. The allylsilanes were prepared following literature procedures[9a,b] except for triisopropylallylsilane, which was commercially available. The reaction was performed under boron trifluoride-mediated conditions for 24 h at low temperature (−78 °C) to ensure complete consumption of the aldehyde. The acid scavenger, 2,6-di-*tert*-butyl-4-methylpyridine, was added to minimize the decomposition of the aldehydes and allylsilanes under the long reaction times. The tetrahydrofurans were isolated in good to very good yields. The reaction of triethylsilyloxy acetaldehyde **4** with three different allylsilanes **2a**−**c** afforded tetrahydrofurans in 60−83% yield as a 12:1 mixture of diastereomers. The major diastereomer had a cis-relative stereochemistry of the hydroxyl group to the silyl methylene substituent (3,5-cis selectivity).

In the case of the protected mandelic aldehyde **7**, the product tetrahydrofurans were a mixture of two diastereomers (6:1 to 11:1 ratio) in 78−96% yield. In both diastereomers the phenyl group was trans to the hydroxyl group consistent with complete Felkin−Anh selectivity,[10] and the stereochemical difference arises from 3,5-selectivity in the addition to the β-silyl cation intermediate. The major diastereomers (**15**, **17**, and **19**) had 3,5-cis orientation and the minor diastereomers (**16**, **18**, and **20**) had 3,5-trans orientation. The stereochemical assignment of these diastereomers is described in a subsequent section.

The protected lactic aldehyde **8** provided tetrahydrofurans as a mixture of two diastereomers (1.3:1 to 2.2:1) in 41−80% yield.

Table 1. Reaction of Aldehydes with Allylsilanes

Aldehyde	Allylsilane	Tetrahydrofuran		Yield, Diast. ratio
				
4	**2a** SiR_3 = $SiPhMe_2$ **2b** SiR_3 = $Si(i\text{-}Pr)_3$ **2c** SiR_3 = $SiMe_2CHPh_2$	**9** **11** **13**	**10** **12** **14**	77% (12:1)[a] 83% (12:1)[a] 60% (12:1)[a]
				
7	**2a** SiR_3 = $SiPhMe_2$ **2b** SiR_3 = $Si(i\text{-}Pr)_3$ **2c** SiR_3 = $SiMe_2CHPh_2$	**15** **17** **19**	**16** **18** **20**	78% (7:1)[b] 96% (6:1)[b] 96% (11:1)[b]
				
8	**2a** SiR_3 = $SiPhMe_2$ **2b** SiR_3 = $Si(i\text{-}Pr)_3$ **2c** SiR_3 = $SiMe_2CHPh_2$	**21** **23** **25**	**22** **24** **26**	41% (1.7:1)[b] 58% (1.3:1)[b] 80% (2.2:1)[b]

[a] Diasteromeric ratios were dtermined by GC. [b] Diasteromeric ratios were determined by HPLC.

In this case, the Felkin−Anh selectivity was compromised, but the 3,5-cis selectivity was complete. Both diastereomers had the hydroxyl group in a cis orientation to the silyl methylene substituent. The difference in the stereochemistry between the major and the minor diastereomer was in the orientation of the methyl group relative to the hydroxyl group: trans in the major diastereomers (**21**, **23**, and **25**) and cis in the minor diastereomers (**22**, **24**, and **26**).

The change in Felkin−Anh selectivity combined with the expected C-3 to C-5 stereoselectivity (6:1 to 12:1 based on aldehydes **4** and **7**) led us to expect to isolate three and possibly four diastereomers for the tetrahydrofurans derived from aldehyde **8**. Consistent with this notion, careful analysis of the tail in the HPLC trace of the reaction products of aldehyde **8** with allylsilane **2c** showed trace amounts of a compound that was tentatively identified (^{1}H NMR, ^{13}C NMR, and MS) as a third tetrahydrofuran diastereomer. Due to the overlap in the HPLC separation, this third diastereomer was not analytically pure and could not be characterized; the ratio of this diastereomer to the major diastereomer **25** was <1:10 (HPLC, ^{1}H NMR).

The size of the substituents on silicon affected the diastereomer ratio of the tetrahydrofuran products; an increase in the size of the substituents on silicon resulted in an increase in the diastereomeric ratio of the products. This effect was also observed in our earlier work on tetrahydropyran synthesis.[6] Few accounts in the literature have recorded such an observation.[3c] In one such example, the [3+2]-cycloaddition of the allylsilane to cycloalkenyl methyl ketones reported by Knolker et al.,[3c] the size of the silicon substituent affected the diastereomeric ratio of products.

Reactions of Crotylsilanes. We next turned our attention to the use of crotylsilanes in this formal [3+2]-cycloaddition. The results showed that the selectivity of the reaction of the aldehydes and crotylsilanes depended on the stereochemistry of the crotylsilane.[11] Reactions of crotylsilanes **27**[12] and **28**[13] were slower than those of allylsilanes and the amount of the Lewis acid had to be increased to 5 equiv to achieve reasonable

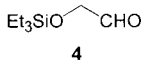
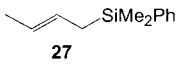
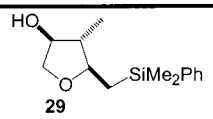
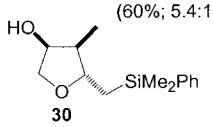
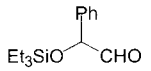
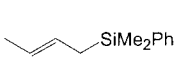
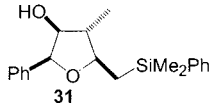
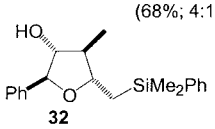
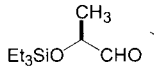
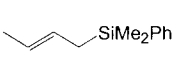
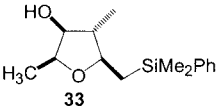
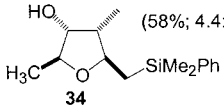
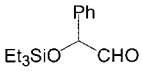
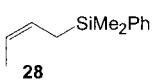
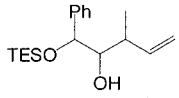
(8) For leading refrences and recent tetrahydrofuran syntheses see: (a) Aggarwal, V.; Eames, J.; Villa, M.-J.; McIntyre, S.; Sansbury, F.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 533−546. (b) Rodriguez, J.; Rumbo, A.; Castedo, L.; Mascarenas, J. *J. Org. Chem.* **1999**, *64*, 4560−4563. (c) Vares, l.; Rein, T. *Org. Lett.* **2000**, *2*, 2611−2614.

(9) (a) Knolker, H. J.; Foitzik, N.; Goesmann, H.; Graf, R.; Jones, P. G.; Wanzl, G. *Chem. Eur. J.* **1997**, *3*, 538−551. (b) Woerpel, K. A.; Peng, Z. H. *Org. Lett.* **2000**, *2*, 1379−1381.

(10) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18* 2199−2104 (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 335−348.

(11) (a) Panek, J. S.; Cirillo, P. F. *J. Org. Chem*, **1993**, *58*, 999−1002. (b) Denmark, S. E.; Almstead, N. G. *J. Org. Chem*, **1994**, *59*, 5130−5132.

Table 2. Reaction of Aldehydes with Crotylsilanes

Aldehyde	Allylsilane	Product (yield; diast.ratio)
 **4**	 **27**	 **29**
		(60%; 5.4:1)[a]
		 **30**
 **7**	 **27**	 **31**
		(68%; 4:1)[a]
		 **32**
 **8**	 **27**	 **33**
		(58%; 4.4:1)[a]
		 **34**
 **7**	 **28**	 **35** (56%; 1:1)[a]

[a] Diasteromeric ratios were determined by HPLC.

conversion in 24 h reaction time. The results are summarized in Table 2. *E*-Crotylsilane **27** provided tetrahydrofuran products in 58−68% yield as a mixture of two diastereomers in 4:1 to 5.4:1 ratios. In the case of aldehyde **4**, two diastereomeric trisubstituted tetrahydrofurans were obtained. The 3,5-cis selectivity was compromised. The major diastereomer **29** had the trans−trans orientation. The minor diastereomer **30**, on the other hand, had the cis−trans orientation. The stereochemical assignment of these two compounds is discussed below.

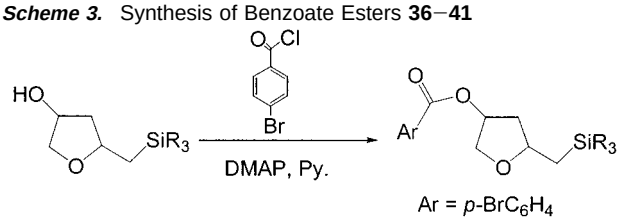
In case of α-phenyl aldehyde **7** and α-methyl aldehyde **8**, the major diastereomer had the same relative stereochemistry, cis−trans−trans. The minor diastereomers derived from aldehydes **7** and **8** had different relative stereochemistry of the substituents. In the case of α-phenyl aldehyde **7**, the 3,5-selectivity derived from addition to β-silyl cation was very high; however, the Felkin−Anh selectivity was only 4:1. In case of α-methyl aldehyde **8**, both the 3,5-slectivity and the Felkin−Anh selectivity were compromised. In the reactions of all of these aldehydes the trans orientation of the methyl and the silyl methylene substituent of the crotylsilane was retained in all of the tetrahydrofuran products.

Z-Crotylsilane **28** did not afford cyclization products. Upon reaction with aldehyde **7**, only allylation products **35** were obtained in 56% yield as a 1:1 mixture of diastereomers. At this point, it is not clear which one of the three stereocenters is epimeric resulting in the observed 1:1 diastereomer ratio. Generally in allylation reactions, *E*-crotylsilanes are highly selective and *Z*-crotylsilanes provided the same products as *E*-crotylsilanes but with less selectivity.[3a] To our knowledge *Z*-crotylsilanes have not seen use in the formal [3+2]-cycloaddition of crotylsilane with aldehydes to form tetrahydrofurans.[11]

Stereochemical Assignments

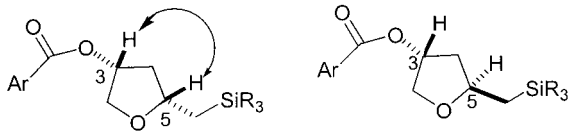
NOE Studies on the Allylsilane Adducts. The relative stereochemistry of substituents on the tetrahydrofuran ring was very challenging to prove and several different methods were required to unambiguously assign the relative stereochemistry of the substituents. In the case of tetrahydrofurans **9**−**14**, formed by the reaction of aldehyde **4** with allylsilanes **2a**−**c**, two diastereomeric tetrahydrofurans were obtained. The two diastereomers were not separable by HPLC, accordingly the hydroxyl group was derivatized as the *p*-bromobenzoyl ester[14] and the diastereomeric benzoate esters were separated by HPLC (Scheme 3). This was required for all the tetrahydrofurans

Scheme 3. Synthesis of Benzoate Esters **36**−**41**



9, 10 $SiR_3 = SiPhMe_2$ **36, 37** $SiR_3 = SiPhMe_2$ 97%
11, 12 $SiR_3 = Si(i\text{-}Pr)_3$ **38, 39** $SiR_3 = Si(i\text{-}Pr)_3$ 80%
13, 14 $SiR_3 = SiMe_2CHPh_2$ **40, 41** $SiR_3 = SiMe_2CHPh_2$ 90%

obtained from aldehyde **4**. The relative stereochemistry of each diastereomer was assigned by analysis of 2-D NOESY spectra. Figure 1 illustrates the key NOE between the hydrogens on C-3 and C-5, which were present in the major diastereomers (**36**, **38**, and **40**) and absent in the minor diastereomers (**37**, **39**, and **41**).



36 $SiR_3 = SiPhMe_2$ **37** $SiR_3 = SiPhMe_2$
38 $SiR_3 = Si(i\text{-}Pr)_3$ **39** $SiR_3 = Si(i\text{-}Pr)_3$
40 $SiR_3 = SiMe_2CHPh_2$ **41** $SiR_3 = SiMe_2CHPh_2$

Figure 1. NOE's for tetrahydrofurans **36**−**41**.

The tetrahydrofurans obtained from α-phenyl and α-methyl aldehydes were easily separated by HPLC, and 2-D NOESY spectra were obtained for both the major and the minor diastereomers (summarized in Figures 2 and 3**)**. The major 2-phenyl tetrahydrofuran diastereomer showed NOE for the hydrogens on C-3 and C-5 (Figure 2). No NOE was observed

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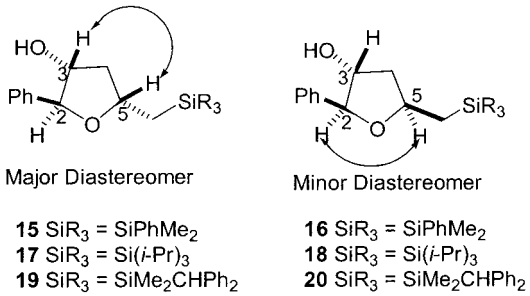


Figure 2. NOE's for tetrahydrofurans **15**−**20**.

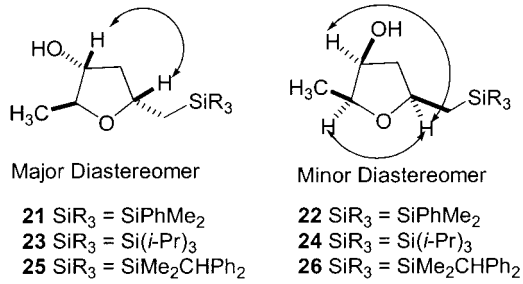


Figure 3. NOE's for tetrahydrofurans **21**−**26**.

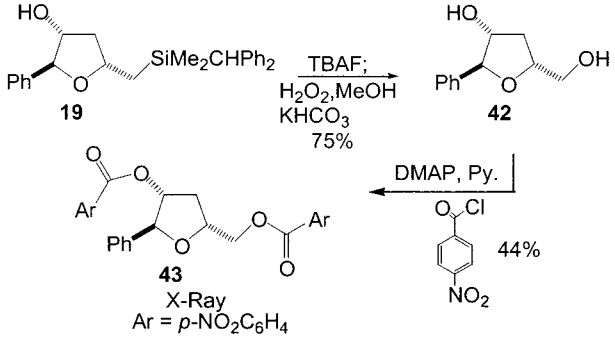
for the hydrogens on C-2 and C-5. Thus, the major 2-phenyl tetrahydrofurans **15**, **17**, and **19** must have a trans−cis arrangement of substituents about the tetrahydrofuran ring. The minor 2-phenyl diastereomer showed a NOE between the hydrogens on C-2 and C-5 and the absence of a NOE between the hydrogens on C-3 and C-5 (Figure 2).

The major 2-methyl tetrahydrofuran diastereomer showed cross-peaks in the 2-D NOESY spectrum for hydrogens on C-3 and C-5 (Figure 3). No NOE was observed between hydrogens on C-2 and C-5. The minor 2-methyl tetrahydrofuran diastereomer showed cross-peaks indicating NOE's for the hydrogens on C-2 and C-5 and also for the hydrogens on C-3 and C-5. Unambiguous proof of stereochemistry is provided by the formal synthesis of two muscarine alkaloids in a later section.

Tamao−Fleming Oxidation. The dimethylphenylsilyl group is a synthon for a hydroxyl group upon Tamao−Fleming oxidation. A variety of procedures have been developed to convert the dimethylphenylsilyl group to a hydroxyl group,[15] but with our substrates all of these methods either failed completely or provided low yields of alcohol products. Using **15** as a substrate, oxidation with $Hg(OAc)_2$/peracetic acid[16] provided alcohol **42** in 25% yield. The KBr reaction conditions[16] which have been reported to work for β-hydroxysilyl compounds afforded **42** in 14% yield. Oxidation under basic conditions with DMSO/*t*-BuOK[17] failed to afford any alcohol product whatsoever. In all of these cases no unreacted starting material was observed.

We were able to circumvent this problem using Woerpel's dimethylbenzhydryl group on silicon,[9b] which was easily oxidized under modified Tamao oxidation conditions. Treatment of tetrahydrofuran **19** with TBAF followed by H_2O_2/MeOH, afforded diol **42** in 75% yield (Scheme 4). The stereochemistry

Scheme 4. Proof of Stereochemistry of Tetrahydrofuran **19**



of this compound was confirmed by single-crystal X-ray crystal analysis of its *p*-nitrobenzoyl[18] derivative **43**. This crystal structure confirms the stereochemical assignment of **19** based on 2-D NOESY spectra.

Crotylsilane adduct **31** was treated under the $Hg(OAc)_2$/peracetic acid protocol to afford diol **44** in 36% yield. Alternative oxidation conditions afforded **44** in lower yields. The stereochemistry of diol **44** was determined by single-crystal X-ray crystallographic analysis.

The tetrahydrofurans **32**, **33**, and **34** (obtained by HPLC separation) were separately subjected to Tamao−Fleming oxidation using $Hg(OAc)_2$/peracetic acid, and provided diols **45**, **47**, and **49** in 37%, 59%, and 59% yield. Derivatization of both hydroxyl groups as their *p*-nitrobenzoyl esters **46**, **48**, and **50** provided crystalline solids, which were subjected to X-ray crystal analysis to provide the stereochemical assignments.

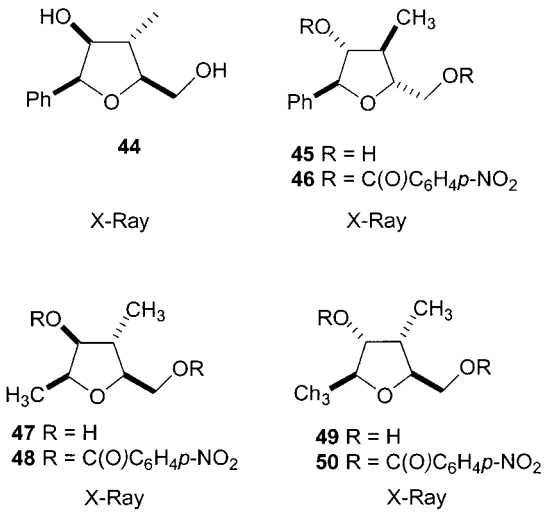


Figure 4. Stereochemical proof of tetrahydrofuran **31**, **32**, **33**, and **34**.

NOE Studies on Crotylsilane Adducts. The stereochemical assignment of the tetrahydrofuran diastereomers **29** and **30** was extremely difficult. HPLC separation of these two compounds followed by analysis of the 2-D NOESY spectra provided inconclusive results.

Due to the inconclusive stereochemical assignment for tetrahydrofuran **30** using NOE enhancements, we decided to pursue the proof of stereochemistry by derivatization of the hydroxyl group on C-3. The mixture of diastereomers of tetrahydrofurans **29** and **30** was treated with *p*-nitrobenzoyl

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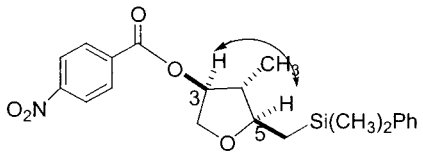
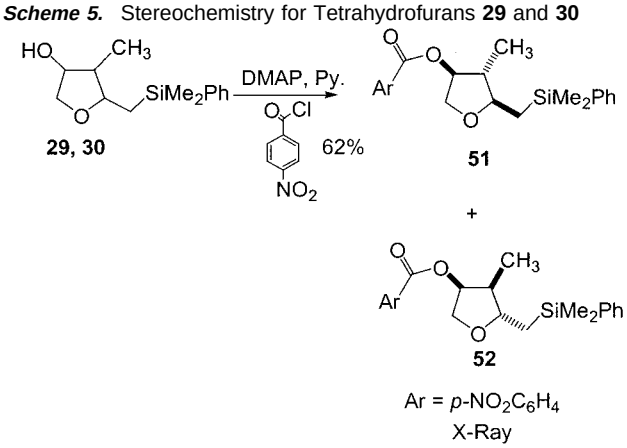
(18) Kolar, C.; Dehmel, K.; Moldenhauer, H.; Gerken, M. *J. Carbohydr. Chem.* **1990**, *9*, 873−890.



51

Figure 5. NOE's for tetrahydrofuran **51**.

Scheme 5. Stereochemistry for Tetrahydrofurans **29** and **30**



chloride to provide a mixture of diastereomers **51** and **52** in 62% (Scheme 5). Separation of the **51**/**52** mixture by HPLC afforded analytical samples for characterization. The minor diastereomer **52** was a crystalline solid and the structure was determined by single-crystal X-ray determination. The major diastereomer **51** showed cross-peaks in the 2-D NOESY spectra indicating a NOE between the hydrogens on C-3 and C-5, thus a cis orientation of the substituents on C-3 and C-5.

Mechanism and Stereochemistry. The mechanism of this reaction involves the addition of the allylsilane to the Lewis acid activated aldehyde (Scheme 9). Our results indicate that the triethylsilyl ether oxygen is more nucleophilic than the Lewis acid complexed alkoxide and thus it is the internal nucleophile that participates in the cyclization.

The stereoselectivity of tetrahydrofuran formation has several levels of complexity. The simplest case is the addition of allylsilanes to nonsubstituted aldehyde **4**. Additional complexity is introduced for the reaction of allylsilanes with aldehydes possessing an α-stereocenter (**7** and **8**). The use of crotylsilane introduces another stereochemical factor. In our earlier work on tetrahydropyran synthesis,[6] which also involved reactions of aldehydes with allylsilanes, only one diastereomer was isolated and it had a cis orientation between the hydroxyl group and the silyl methylene substituent. In this work on tetrahydrofurans both diastereomers were observed with the major isomer having the same cis orientation between the C-3 hydroxyl and C-5 silyl methylene substituent that was seen in the case of tetrahydropyrans. This selectivity can be explained by an overall cis addition of the electrophile and nucleophile across the double bond of the olefin.[19] It is possible, albeit unlikely,[1f,11b] that the minor products (**10**, **12**, and **14**) arise via cyclization syn to the silicon. This proposal is consistent with our experimental results that increasing the size of the substituent on silicon afforded higher selectivity. The introduction of an α-substituent on the

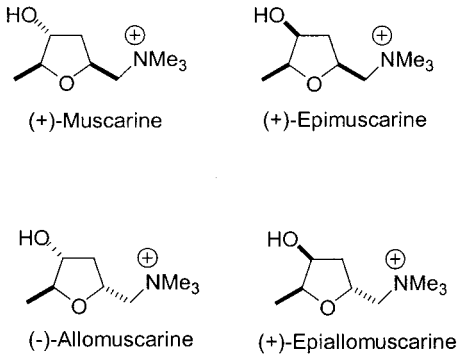
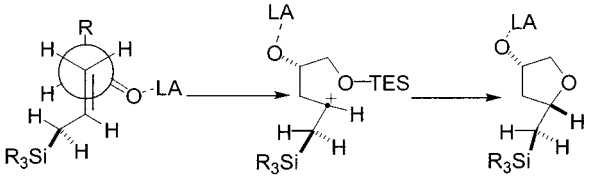


Figure 6. Diastereoisomers of muscarine.

Scheme 6. Synclinal Arrangement of the Aldehyde and Allylsilane



aldehyde provides another factor, facial selectivity (Felkin−Anh) of the addition of the allylsilane. As expected α-phenyl aldehyde **7** shows higher Felkin−Anh selectivity than the α-methyl aldehyde **8** (Table 1). Only the Felkin−Anh addition products were observed in the case of the α-phenyl aldehyde **7**, whereas a mixture of products was observed in the case of α-methyl aldehyde **8**. It is possible that there is more to the stereoselectivity than just simple Felkin−Anh selectivity.

The addition of crotylsilanes to the α-substituted aldehydes adds a third element of complexity to the problem: the orientation of approach of the crotylsilane. Panek[3a] and Roush[20] have discussed these types of reactions for allylsilanes and Keck[21] has examined them for allylstannanes. There are several potential transition states that could afford the observed products and at the present time it is impossible to determine which transition state is responsible for product formation.

Synthesis of Muscarine Alkaloids. The success of Tamao oxidation of the benzhydryldimethylsilyl substituent provided us with the means to apply our methodology to natural product synthesis and prove the stereochemistry of tetyrahydrofurans **25** and **26**. Our target was the muscarine alkaloids[22] which were first isolated from *Amanita muscaria*, a mushroom found in pinewoods. There are three stereocenters in these compounds, thus there are four possible pairs of enanatiomers. All four diastereomers (Figure 6) occur in nature and have been isolated and prepared by total synthesis.[23]

The naturally occurring diastereomers of Muscarine are (+)-(2*S*,3*R*,5*S*)-muscarine, (−)-(2*S*,3*R*,5*R*)-allomuscarine, (+)-(2*S*,3*S*,5*S*)-epimuscarine, and (+)-(2*S*,3*S*,5*R*)-epiallomuscarine. Their physiological effects are on the peripheral nervous system causing lowering of blood pressure, slowing of heart rate, miosis,and bronchoconstriction. They resemble acetylcholine in

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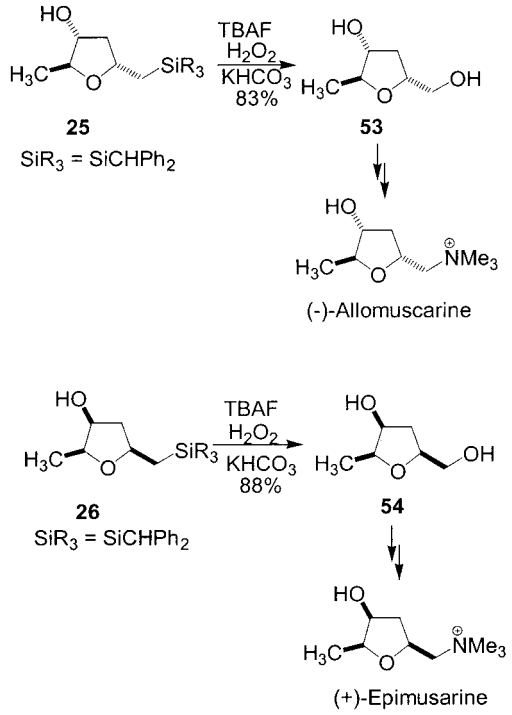
(23) For recent syntheses see: (a) Ogasawara, K.; Ohshiba, Y.; Yoshimitsu, T. *Chem. Pharm. Bull*. **1995**, *43*, 1067−1069. (b) Norrild, J. C.; Pedersen, C. *Synthesis* **1997**, 1128−1130. (c) Popsavin, V.; Beric, O.; Popsavin, M.; Radic, L.; Csanadi, J.; Cirin-Novta, V. *Tetrahedron* **2000**, *56*, 5929−5940. (d) Hartung, *J. Eur. J. Org. Chem*. **2001**, 619−632.

Scheme 7. Synthesis of Intermediates to (−)-Allomuscarine and (+)-Epimuscarine



their action and have been used in clinical research as an acetylcholine substitute. This cholinomimetic activity and their simple but challenging structure has interested chemists over the years.

Our methodology provided a concise route to an advanced intermediate in two steps from aldehyde **8** and in very good yield. Formal cycloaddition of aldehyde **8** with allylsilane **2c** afforded the cycloadducts **25** and **26** in 80% yield and 2.2:1 ratio. Preparative HPLC separation of the mixture provided quantities of each diastereomer. Fleming−Tamao oxidation of **25** provided the known diol **53**[24] in 83% yield and ≥92% ee. The minor diastereomer **26** was converted to the known[25] diol **54** in 88% yield and ≥96% ee. This constitutes a formal total synthesis of (−)-allomuscarine and (+)-epimuscarine since both compounds have been converted to the corresponding natural products upon treatment with TsCl and Me_3N.[26]

Conclusion

A fundamentally new approach to the cycloaddition reactions of allylsilanes with aldehydes has been developed. This method assembles tetrahydrofuran ring systems from allylsilanes and aldehydes and diverts the normal reaction pathway to another manifold. The triethylsilyl ether oxygen is a more potent nucleophile than the Lewis acid complexed alkoxide resulting in novel cyclization products. It is important to note that no 1,2 silyl shift was observed and only five-membered-ring cyclization products were isolated.

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Experimental Section

General Procedure for Tetrahydrofuran Cyclization Reaction Using Allylsilanes. Boron trifluoride etherate (2.0 equiv) was added over 15 min to a −78 °C solution of protected α-hydroxy aldehydes (1.0 equiv), allylsilane (1.2−1.5 equiv), and 2,6-di-*tert*-butyl-4-methylpyridine (1.0 equiv) in CH_2Cl_2 (0.1 M). The reaction was stirred at −78 °C for 24 h. The reaction mixture was then poured into a stirred solution of saturated $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried ($MgSO_4$) and concentrated to afford the crude product(s). Flash chromatography on silica gel (7:1 to 3:1 hexanes/EtOAc) gave product(s) in the yields shown.

General Procedure for Tetrahydrofuran Cyclization Reaction Using Crotylsilanes. Boron trifluoride etherate (5.0 equiv) was added over 30 min to a −78 °C solution of protected α-hydroxy aldehydes (1.0 equiv), allylsilane (1.2 equiv), and 2,6-di-*tert*-butyl-4-methylpyridine (1.0 equiv) in CH_2Cl_2 (0.1 M). The reaction was left to stir at −78 °C for 24 h. The reaction mixture was then poured into a stirred solution of saturated $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to afford crude product(s). Flash chromatography on silica gel (7:1 then 3:1 hexanes/EtOAc) gave product(s) in the yields shown.

(2*S*,3*R*,5*R*)-5-Hydroxymethyl-2-methyltetrahydrofuran-3-ol (53). A solution of *n*-Bu_4NF (0.68 mL of a 1 M solution in THF, 0.68 mmol) was added dropwise to a 0 °C solution of **25** (144 mg, 0.43 mmol) in THF (5 mL). After 30 min, MeOH (1.2 mL) was added to the reaction mixture followed by $KHCO_3$ (70 mg, 0.69 mmol) and H_2O_2 (30%, 0.5 mL, 4.9 mmol). The ice bath was removed and the reaction mixture was allowed to warm to room temperature. After 12 h the reaction mixture was refluxed for 1 h, then it was cooled to room temperature and diluted with MeOH and stirred then filtered through silica plug. The resulting mixture was concentrated and purified by flash chromatography (1:1 MeOH:ether) to provide **53** (47 mg, 83%) as a colorless oil: $[\alpha]_D$ −41.5 (*c* 0.065, $CHCl_3$) (lit.[24] (+) enantiomer $[\alpha]_D$ +45.0 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.27 (m, 1H), 4.12 (dq, J = 6.7, 1.6 Hz, 1H), 3.97 (dt, J = 5.7, 2.1 Hz, 1H), 3.80 (dq, J = 9.3, 2.6 Hz, 1H), 3.53 (dd, J = 11.8, 3.1 Hz, 1H), 3.12 (s, 2H), 2.41 (ddd, J = 13.9, 9.2, 6.2 Hz, 1 H), 1.81 (ddd, J = 13.9, 3.1, 2.1 Hz, 1H), 1.11 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.1, 77.4, 76.1, 64.2, 35.1, 18.8; IR ($CDCl_3$) 3619, 3386, 2972, 1456, 1375 cm^{-1}; MS (DEI) *m*/*z* 133 (MH^+, 19), 101(81); HRMS (DEI) *m*/*z* calcd for $C_6H_{13}O_3$ (MH^+) 133.0865, found 133.0861.

(2*S*,3*S*,5*S*)-5-Hydroxymethyl-2-methyl-tetrahydrofuran-3-ol (54). The same procedure used for the conversion of **25** to the diol **53** was carried out with **26** (289 mg, 0.85 mmol). Flash chromatography (3:1 EtOAc/hexanes) provided **54** (99 mg, 88%) as a white solid: mp 66−67 °C; $[\alpha]_D$ +45.3 (*c* 0.088, $CHCl_3$) (lit.[25] $[\alpha]_D$ +47.0 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, CD_3OD) δ 4.02 (m, 2H), 3.80 (dq, J = 6.7, 3.6 Hz, 1H), 3.62 (dd, J = 11.3, 3.6 Hz, 1H), 3.52 (dd, J = 11.8, 4.6 Hz, 1H), 2.34 (ddd, J = 14.9, 8.7, 5.6 Hz, 1H), 1.72 (ddd, J = 13.9, 5.1, 1.5 Hz, 1 H), 1.21 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 80.7, 79.3, 73.5, 65.4, 38.3, 14.4; IR ($CDCl_3$) 3626, 3410, 2937, 2882, 2678, 2533 cm^{-1}; MS (DEI) *m*/*z* 133 (MH^+, 17), 115(26), 101(87), 83(12), 69(26), 57(100); HRMS (DEI) *m*/*z* calcd for $C_6H_{13}O_3$ (MH^+) 133.0865, found 133.0868.

Acknowledgment. We thank NSF (CHE-9528266) for partial support of this research. We would like to also thank Dr. Fook Tham at the UCR X-ray facility for the X-ray structures.

Supporting Information Available: ^1H NMR and ^{13}C NMR spectra of all new compounds, X-ray crystallographic files (CIF) for compounds where X-ray data were collected. This material is available free of charge via the Internet at http://pubs.acs.org.

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