JOC Article

Stereoselective Synthesis of Tetrahydropyrans via Formal [4 + 2]-Cycloaddition: A Comparison of Allylsilane and Crotylsilane

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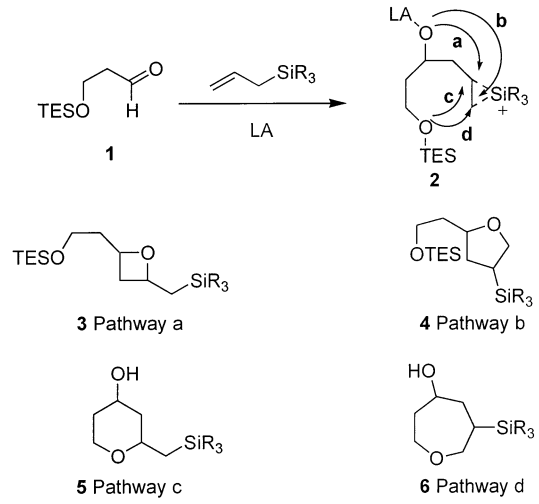
The reaction of a series of β-(triethylsilyloxy)aldehydes with several allylsilanes and crotyldimethylphenylsilane is described. Aldehydes possessing an α-stereocenter afforded tetrahydropyrans as mixtures of two diastereomers with allylsilane, but only a single diastereomer was observed in the case of crotylsilanes. The reaction time for crotylsilanes was longer than that for allylsilanes likely due to the increased steric hindrance. Allylsilanes afforded tetrahydropyrans in 34−67% yields, and crotylsilanes provided products in 0−62% yields.

Introduction

The use of allylsilanes as reagents in organic synthesis has seen an increase in recent years, particularly for the regioselective and stereoselective formation of carbon−carbon bonds.[1,2] The introduction of an allyl group by conjugate addition to α,β-unsaturated carbonyl compounds (Hosomi−Sakurai reaction) is a well-known reaction that has seen broad application.[1] More recently, the formal cycloaddition of allylsilanes with carbonyl compounds, electron-deficient alkenes, and imines has been used to great advantage by a number of research groups.[3,4] Allylsilanes function as the synthetic equivalent of a silyl-substituted 1,2- and/or 1,3-dipole,[3,4] which results in the formation of a variety of carbocycles and heterocycles.

SCHEME 1



The reaction of aldehydes and ketones with allylsilanes under Lewis acid-promoted conditions involves activation of the carbonyl group by the Lewis acid followed by addition of the allylsilane to afford a β-silylcation/siliranium ion[5] intermediate (**2**, Scheme 1). This intermediate is normally trapped via pathway "a" or "b" (Scheme 1) to afford oxetane **3** or tetrahydrofuran **4**, depending on the Lewis acid used. [4]

Previous work from our laboratory has shown triethylsilyl ethers to be excellent oxygen nucleophiles toward reactive electrophiles derived from substituted diazomethanes under Lewis acid conditions.[6] In a preliminary communication, we reported a new method for the synthesis of tetrahydropyrans by the formal [4 + 2]-cycloaddition of allylsilanes and β-triethylsilyloxyalde-

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(1) (a) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1−22. (b) Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200−206. (c) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673−1675.

(2) (a) Fleming, I.; Dunogues, J.; Smithers, R. *Org. Reac.* **1989**, *37*, 57−575. (b) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375−1408. (c) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063−2192. (d) Colvin, E. W. *Silicon in Organic Synthesis*; Butterworth: London 1981. (e) Tietze, L. F.; Schünke, C. *Eur. J. Org. Chem.* **1998**, 2089−2099.

(3) For leading references see, recent reviews: (a) Danheiser, R. L.; Dixon, B. R.; Gleason, R. W. *J. Org. Chem.* **1992**, *57*, 6094−6097. (b) Danheiser, R. L.; Takahashi, T.; Bertók, B.; Dixon, B. R. *Tetrahedron Lett.* **1993**, *34*, 3845−3848. (c) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1316. (d) Knölker, H. J. *J. Prakt. Chem.* **1997**, *339*, 304−314. (e) Akiyama, T.; Yasusa, T.; Ishikawa, K.; Ozaki, S. *Tetrahedron Lett.* **1994**, *35*, 8401−8404. (f) Akiyama, T.; Hoshi, E.; Fujiyoshi, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2121−2122. (g) Akiyama, T.; Ishida, Y. *Synlett* **1998**, 1150−1152. (h) Knölker, H. J.; Jones, P. G.; Wanzl, G. *Synlett* **1998**, 613−616. (i) Knölker, H. J.; Foitzik, N.; Gabler, C.; Graf, R. *Synthesis* **1999**, 145−151. (j) Knölker, H. J.; Foitzik, N.; Schmitt, O. *Tetrahedron Lett.* **1999**, *40*, 3557−3560. (k) Meyers, A. I.; Brengel, G. P. *J. Org. Chem.* **1996**, *61*, 3230−3231. (l) Roberson, C. W.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1434−1435. (m) Dussault, P. H.; Zope, U. *Tetrahedron Lett.* **1995**, *36*, 3655−3658. (n) Angle, S. R.; Boyce, J. P. *Tetrahedron Lett.* **1994**, *35*, 6461−6464. (o) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1994**, *59*, 2674−2675.

(4) For leading references, see: (a) Akiyama, T.; Kirino, M. *Chem. Lett.* **1995**, 723−724. (b) Akiyama, T.; Yamanaka, M. *Synlett* **1996**, 1095−1096. (c) Akiyama, T.; Nakano, M.; Kanatani, J.; Osaki, S. *Chem. Lett.* **1997**, 385−386, and references therein. (d) Akiyama, T.; Ishikawa, K.; Osaki, S. *Chem. Lett.* **1994**, 627−630.

(5) Lambert and co-workers have shown that these intermediates are properly viewed as β-silylcations (Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X. Y.; So, J. H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183−190 and references therein). Intermediate **2**, Scheme 1, is depicted as a siliranium ion rather than a β-silylcation to clearly show the relationships between products **3**−**6**.

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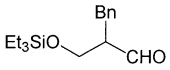
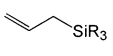
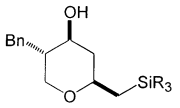
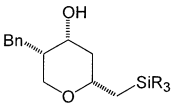
TABLE 1. Synthesis of Tetrahydropyrans Using Different Allylsilanes

	Aldehyde	Allylsilane	Tetrahydropyran (yield; diast. ratio)[a]				
							
1	**7**	**8**, SiR_3 = $SiMe_3$	**9a** (46%)	1	:	1	**9b**
2	**7**	**10**, SiR_3 = $Si(i\text{-}Pr)_3$	**11a** (67%)	1.7	:	1	**11b**
3	**7**	**12**, SiR_3 = $SiMe_2CPh_3$	**13a** (52%)[b]	3.4	:	1	**13b**

[a] Diastereomer ratio was determined by HPLC analysis. [b] Reaction mixture was stirred at −78 °C for 24 h, allowed to warm to 0 °C, and then stirred for an additional 1 h.

hydes. This methodology exploits the nucleophilicity of the triethylsilyl ether oxygen to suppress the normal aldehyde/allylsilane formal cycloaddition reaction.[7] Introduction of a triethylsilyloxy group β to the aldehyde provides an alternative to the normal reaction pathways a and b (Scheme 1). In this case, β-silylcation/siliranium ion[5] **2** reacts via pathway "c" to afford tetrahydropyran **5**. Oxepine **6** might have formed via pathway "d" but was not observed. This unusual reaction of β-siloxyaldehydes, where an atom other than the former carbonyl oxygen reacts with the β-silylcation intermediate, has few precedents in the literature.[4c, 8]

Results and Discussion

Synthesis of Tetrahydropyrans Using Different Allylsilanes. In an effort to investigate the scope and limitations of this methodology, α-benzyl-substituted aldehyde **7** was reacted with different allylsilanes: allyltrimethylsilane, allyltriisopropylsilane, and allyldimethyltritylsilane[9] (Table 1).

Preliminary studies using allyltriisopropylsilane established the optimal reaction conditions: 1.5 equiv of allylsilane, 2.0 equiv $BF_3{\cdot}OEt_2$, 1.0 equiv of 2,6-di-*tert*-butyl-4-methylpyridine (DBMP), −78 °C, 24 h of reaction time, and 0.10 M in CH_2Cl_2. When DBMP was omitted, the yield of the reaction decreased by at least 10%.

Aldehyde **7** possesses an α-stereocenter and afforded two diastereomeric tetrahydropyrans (Table 1). The diastereomer ratio was dependent upon the substituents on silicon, with bulkier substituents affording higher diastereomer ratios.

The successful formation of tetrahydropyrans shows that closure of the triethylsilyl ether on the cation via a six-membered transition state is more favorable than the attack of the Lewis acid-complexed alkoxide via a four- or five-membered transition state. This strategy relies on the triethylsilyl group hindering complexation of the ether oxygen with Lewis acids while still allowing the ether oxygen to function as a more potent nucleophile than the Lewis acid-complexed alkoxide ion.

Comparison of Allyl and Crotylsilanes. Crotylsilanes show higher stereoselectivity in reactions with aldehydes than allylsilanes. Thus, we sought to compare the reaction of a common set of aldehydes with allyldimethylphenylsilane (**14**)[10] and crotyldimethylphenylsilane (**16**)[11] in our tetrahydropyran synthesis.

Reaction of allyldimethylphenylsilane **14** with α-benzyl, α-isopropyl, and α-methyl aldehydes (**7**, **18**, and **23**, respectively) resulted in the formation of two diastereomeric tetrahydropyrans (Table 2; entries 1, 3, and 6). The additional methyl group of the crotylsilane should introduce additional steric bias in the transition state, thus allowing for the stereoselective addition to the aldehyde. On the other hand, there is a complication introduced because the methyl of the crotylsilane results in an additional stereocenter in the final product.

For crotylsilanes **16**, the optimum reaction conditions were: 1.5 equiv of silane, 5.0 equiv $BF_3{\cdot}OEt_2$, 1.0 equiv of 2,6-di-*tert*-butyl-4-methylpyridine (DBMP), −78 °C, 3.5 days of reaction time, and 0.10 M in CH_2Cl_2. The effect of the added methyl group of the crotylsilane on the stereoselectivity of the reaction was remarkable; only one diastereomer was obtained (Table 2; entries 2, 4, and 5).

The aldehydes used in these reactions were relatively unstable and had to be freshly synthesized and used immediately in the cycloaddition reaction. The α-methyl aldehyde proved to be the most difficult to work with. The reaction time was long (24 h), such that the decomposition of the aldehyde began before complete reaction with the allylsilane could occur. Thus, the yield of

(6) (a) Angle, S. R.; Bernier, D. S.; El-Said, N. A.; Jones, D. E.; Shaw, S. Z. *Tetrahedron Lett.* **1998**, *39*, 3919−3922. (b) Angle, S. R.; Bernier, D. S.; Chann, K.; Jones, D. E.; Kim, M.; Neitzel, M. L.; White, S. L. *Tetrahedron Lett.* **1998**, *39*, 8195−8198. (c) Angle, S. R.; Neitzel, M. L. *J. Org. Chem.* **1999**, *64*, 8754−8757. (d) Angle, S. R.; White, S. L. *Tetrahedron Lett.* **2000**, *41*, 8059−8062. (e) Angle, S. R.; Chann, K. *Tetrahedron Lett.* **2001**, *42*, 1819−1822. (f) Angle, S. R.; Shaw, S. Z. *Tetrahedron* **2001**, *57*, 5227−5232.

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

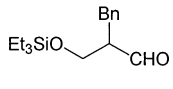
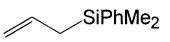
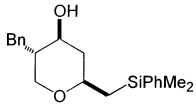
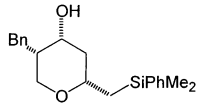
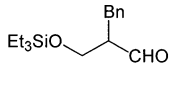
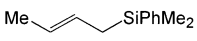
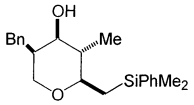
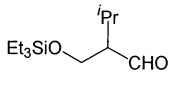
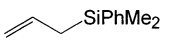
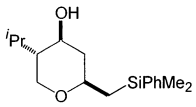
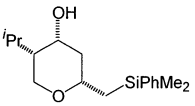
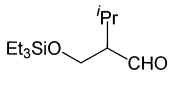
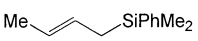
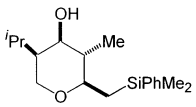
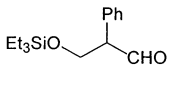
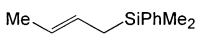
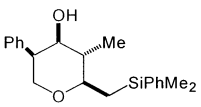
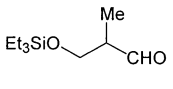
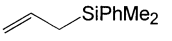
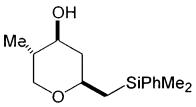
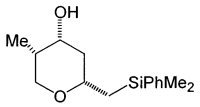
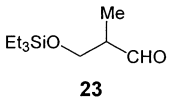
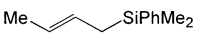
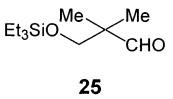
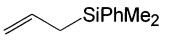
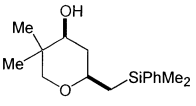
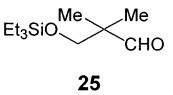
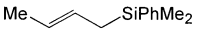
(8) (a) Banuls, V.; Escudier, J. M. *Tetrahedron* **1999**, *55*, 5831−5838. (b) Sugimura, H. *Tetrahedron Lett.* **1990**, *31*, 5909−5912. (c) Kiyooka, S.; Shiomi, Y.; Kira, H.; Kaneko, Y.; Tanimori, S. *J. Org. Chem.* **1994**, *59*, 1958−1960. (d) Brocherieux-Lanoy, S.; Dhimane, H.; Poupon, J. C.; Vanucci, C.; Lhommet, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2163−2165.

(9) Groaning, M. D.; Brengel, G. P.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 5517−5522.

(10) Knölker, H. J.; Foitzik, N.; Goesman, H.; Graf, R.; Jones, P. G.; Wanzl, G. *Chem. Eur. J.* **1997**, *3*, 538−551.

(11) (a) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527−2532. (b) Fleming, I.; Higgins, D.; Lawrence, N. J.; Thomas, A. P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3331−3349.

TABLE 2. Synthesis of Tetrahydropyrans

	Aldehyde	Allylsilane	Cond.	Tetrahydropyran (yield; diast. ratio)[a]
1	 **7**	 **14**	A	 **15a** (54%) 1.3 : 1  **15b**
2	 **7**	 **16**	B	 **17** (62%)
3	 **18**	 **14**	B	 **19a** (49%) 3.7 : 1  **19b**
4	 **18**	 **16**	B	 **20** (24%)
5	 **21**	 **16**	B	 **22** (14%)
6	 **23**	 **14**	A	 **24a** (34%) 1.7 : 1  **24b**
7	 **23**	 **16**	B	no product
8	 **25**	 **14**	A	 **26** (50%)
9	 **25**	 **16**	B	no product

[a] Diastereomer ratio was determined by HPLC analysis. A = 2.0 equiv of $BF_3{\cdot}OEt_2$; B = 5.0 equiv of $BF_3{\cdot}OEt_2$.

tetrahydropyran with allylsilane was low (Table 2; entry 6) and no tetrahydropyran product was observed upon reaction with crotylsilane (Table 2; entry 7). Reaction of α,α-dimethyl aldehyde **25** with allylsilane **14** afforded tetrahydropyran **26** in 50% yield (Table 2; entry 8). The steric bulk was apparently too great to allow addition of the crotylsilane to the aldehyde (Table 2; entry 9); no tetrahydropyran product was observed.

Stereochemistry and Mechanism. The stereoselectivity of the addition of allyl and crotylsilanes to aldehydes with different α-substituents could be rationalized in terms of three different levels of complexity. First, the reaction of allylsilanes with aldehydes with no α-stereocenter afforded only one diastereomer that possessed a cis orientation between the hydroxyl group and the silyl methylene substituent (Table 2; entry 8). This selectivity

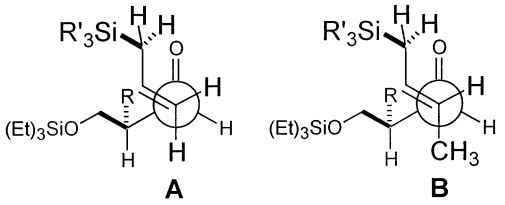


FIGURE 1. Proposed transition structures for THP formation.

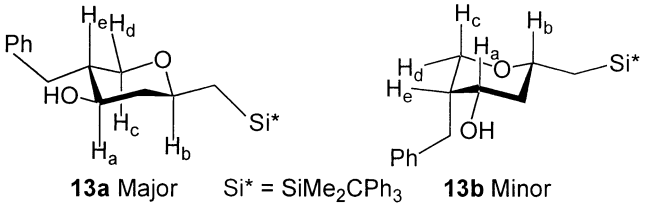


FIGURE 2. Stereochemistry for major and minor diastereomers of **13**.

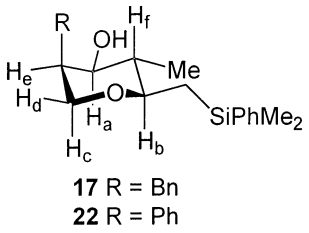


FIGURE 3. Stereochemistry of **17** and **22**.

is the result of an overall cis addition of the electrophile and nucleophile across the double bond of the alkene[12] and is well precedented.[3,4]

The second level of selectivity involves facial selectivity (Felkin−Ahn)[13] of addition to an aldehyde with an α-stereocenter. To our surprise, this selectivity was also affected by the size of the substituents on silicon (see Tables 1 and 2, entry 1). The larger dimethyltritylsilyl group provided a higher diastereomer ratio than the smaller trimethylsilyl group upon reaction with aldehyde **7** (Table 1, entries 1 and 3). In all cases examined, both tetrahydropyran diastereomers possessed a cis orientation of the hydroxyl group to the silyl methylene substituent. Keck and Roush have examined the stereoselective reaction of allylstannanes and allysilanes with aldehydes and provided arguments for these reactions proceeding through a syn synclinal transition state.[14c,f] The stereochemical outcome of our reactions are consistent with their proposals: an anti $S_{E'}$ addition of the allylsilane to the Lewis activated-aldehyde via the syn synclinal transition structure **A** (Figure 1).[14c,f]

The third level of selectivity involves the reaction of crotylsilane **16** with aldehydes that have an α-stereocenter. This reaction sets four contiguous stereocenters in remarkable stereoselectivity, albeit in modest yields (Table 2, entries 2, 4, and 5). In each case, the only diastereomer isolated (**17**, **20**, and **22**) had the cis−trans−trans orientation around the ring, with a cis orientation of the hydroxyl group to the silyl methylene substituent. The high level of stereoselectivity observed for the orientation of the new alcohol relative to the substituent α to the aldehyde (**7**, **18**, and **21**) results from a surprisingly high level of Felkin−Ahn selectivity. The observed anti orientation of the new hydroxyl relative to the methyl group derived from the allylsilane is well precedented in the reactions of crotylsilanes and crotylstannanes with aldehydes.[14a−e] The stereochemistry of tetrahydropyrans **17**, **20**, and **22** is consistent with these reactions proceeding through syn synclinal transition structure **B** (Figure 1).

Assignment of Relative Stereochemistry. The stereochemistry of the two diastereomers of **13** (Figure 2) was determined by analysis of the ^{1}H NMR spectrum. GOESY[15] experiments were used to establish the cis stereochemistry of the hydroxyl group relative to the silyl methylene group. For **13a** and **13b**, NOEs were observed between H_a, H_b, and H_c in both diastereomers. This indicates that these three hydrogens are all axial and on the same face of the molecule. The stereochemistry of the benzyl group was determined by analysis of the H−H coupling constants of the neighboring hydrogens. In the major diastereomer **13a**, the signal for H_d was a doublet of doublets (δ 3.72, J = 4.6, 11.7 Hz) and the signal for H_c was a triplet (δ 2.95, J = 11.4 Hz). Thus, H_e must be axial and trans to H_c leaving the benzyl group equatorial and cis to H_c. In the minor diastereomer **13b**, the signal for H_d was a doublet of doublets (δ 3.66, J = 1.5, 11.8 Hz) and the signal for H_c was a doublet of doublets (δ 3.16, J = 0.8, 11.9 Hz). Thus, the minor diastereomer must have H_e in an equatorial orientation cis to H_c, placing the benzyl group in an axial orientation, trans to H_c.

The stereochemistry of tetrahydropyran **17** was determined by analysis of the ^{1}H NMR spectrum and a gNOESY experiment. Figure 3 shows a conformational drawing of tetrahydropyran **17**, which is consistent with the observed H−H coupling constants. NOEs were observed between H_a, H_b, and H_c. This indicates that they are on the same face of the molecule and in an axial orientation. NOEs were also observed between H_f and the benzylic hydrogens, placing H_f and the benzyl group in a cis−axial orientation. The signal for H_a appeared as a doublet of doublets (δ 3.50, J = 10.3, 4.6 Hz) where the larger coupling constant is attributed to an axial−axial coupling constant, that of H_a−H_f, placing H_a in an axial orientation and thus trans to H_f. This requires the alcohol to be in an equatorial orientation, cis to the benzyl group. The smaller coupling constant, 4.6 Hz, is attributed to an axial−equatorial coupling constant H_a−H_e, indicating that H_e is in an equatorial orientation. The signal of H_b appeared as a doublet of triplets (δ 3.00, J = 3.6, 9.8 Hz), consistent with an axial benzyl group. The 9.8 Hz coupling constant is indicative of a diaxial

(12) Knölker, H. J.; Foitzik, N.; Graf, R.; Pannek, J. B. *Tetrahedron* **1993**, *49*, 9955−9972.

(13) (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.

(14) (a) Denmark, S. E.; Weber, E. J.; Wilson, T. M.; Willson, T. M.; *Tetrahedron* **1989**, *45*, 1053−1065. (b) Panek, J. S.; Cirillo, P. F. *J. Org. Chem.* **1993**, *58*, 999−1002. (c) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889−7896. (d) Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557−558. (e) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868−9870. (f) Micaliziao, G. C.; Roush, W. R. *Org. Lett.* **2000**, *2*, 461−464.

(15) Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 6037−6038.

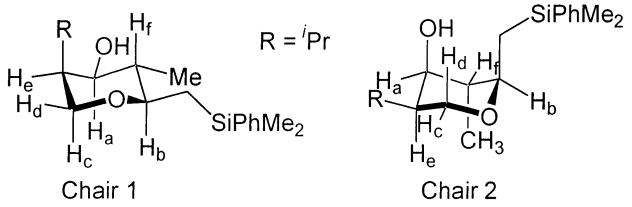


FIGURE 4. Stereochemistry of tetrahydropyran **20**.

orientation between H_b and H_f. There is a second 9.8 Hz coupling constant between H_b and one adjacent methylene hydrogen. The small coupling constant (3.6 Hz) is due to coupling of H_b and the other methylene hydrogen. Therefore, tetrahydropyran **17** must have substituents in a cis−trans−trans orientation about the ring. The relative stereochemistry of tetrahydropyran **22** is the same as the benzyl-substituted tetrahydropyran. The ^{1}H NMR signal of H_a was a doublet of doublets (δ 3.72, J = 10.5, 5.9 Hz). The larger coupling constant is attributed to an axial−axial coupling constant of H_a-H_f. The smaller coupling constant, 5.9 Hz, is attributed an axial−equatorial coupling constant, H_a-H_e. This places H_e in an equatorial position relative to the axial H_a, thus placing the substituents about the ring in a cis−trans−trans orientation. The signal of H_f was a multiplet and therefore could not be analyzed. It is well documented in the literature that crotylsilane addition to carbonyl compounds results in a trans−trans stereochemistry.[14b,e] This fact and the observed similarity of the NMR coupling constants with **17** provide a strong foundation for assigning H_b in **22** an axial orientation. Thus, tetrahydropyran **22** is assigned as having the same stereochemistry as the benzyl-substituted tetrahydropyran **17**. Stereochemical assignment of **20** proved to be difficult since ^{1}H NMR showed that it is not locked into a single conformer. The stereochemistry of **20** was determined by ^{1}H NMR using H−H coupling constants and gNOESY experiments in conjunction with molecular modeling to determine the preferred conformers. From NOE experiments, it was determined that H_a, H_b, H_c, and H_e are on the same face of the molecule. It was also determined that H_d and the hydroxyl group are on the same side. Molecular modeling (PC Model)[16] studies predict that tetrahydropyran **20** will be found 61% in Chair 1, 21% in Chair 2, and 18% in a twist boat conformation. Figure 4 shows the two chair conformers of tetrahydropyran **20**, where R = ^{i}Pr. This explains the ambiguity of the coupling constants obtained from the ^{1}H NMR. The signal of H_a appeared as a doublet of doublets (δ 3.55, J = 5.9, 3.8 Hz) with the larger coupling constant (5.9 Hz) due to coupling of H_a-H_f, while the smaller coupling constant (3.8 Hz) is derived from the coupling of H_a-H_e. The larger coupling constant places H_a in an axial orientation in the major chair conformer to the axial H_f, while the smaller coupling constant is indicative of an axial−equatorial orientation. Therefore, H_e must be in an equatorial orientation in the major conformer, Chair 1. While the values are not straightforward axial−axial and axial−equatorial orientation values, the molecular modeling studies support the discrepancies by predicting the percent distribution of the two chair conformers and the twist boat conformer and the relative magnitude of the observed coupling constants. The signal of H_b appears as a doublet of doublets (δ 3.04, J = 10.5, 7.7, 4.1 Hz). The coupling constant of H_b-H_f is 7.7 Hz, while the coupling constants to the exocyclic methylene hydrogens are 10.5 and 4.1 Hz. Molecular modeling has also correctly predicted the coupling constant attributed to H_b-H_f.

(16) Serena Software, Bloomington, IN.

Conclusion

In summary, we have developed a new route to tetrahydropyrans that exploits the nucleophilicity of a triethylsilyl ether toward a β-silylcation/siliranium ion intermediate. We have shown that using crotylsilane remarkably increases the stereoselectivity of the reaction. The limitation of this reaction is that increasing the steric bulk around the aldehyde carbonyl results in no reaction. Due to the long reaction times, the more stable aldehydes provide better yields. The application of this methodology to natural product synthesis will be reported in due course.

Experimental Section

General Information. All HPLCs were done on a high-performance silica column Si 83-121-c column (21.4 × 250 mm). Unless otherwise stated, the following parameters were used: flow rate = 9.9 mL/min; the appropriate mixture of hexanes/ethyl acetate was used. In all the cases, solvents were removed in a vacuum.

General Experimental Procedure for THP Synthesis. Boron trifluoride etherate (2.0 or 5.0 equiv, as appropriate) was added over 15 min to a −78 °C solution of protected β-hydroxy propanal (1.0 equiv), allylsilane or crotylsilane (1.5−2.0 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 for allylsilanes and 3.5 days for crotylsilanes. The reaction was then poured into a stirred solution of saturated $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2. Drying ($MgSO_4$) and concentration afforded crude product(s). Flash chromatography on silica gel (hexanes/ethyl acetate) gave product(s) in the yields indicated.

(2*S,4*S**,5*S**)- and (2*S**,4*S**,5*R**)-4-Hydroxy-5-phenylmethyl-2-[(trimethylsilyl)methyl]tetrahydropyran (9a and 9b).** Following the general procedure and allowing the reaction mixture to warm 0 °C and stir for 1 h, aldehyde **7**[17] (0.79 mmol) and $BF_3{\cdot}OEt_2$ (2.0 equiv) provided tetrahydropyran **9a** and **9b** (102 mg, 46%; flash chromatography 3:1 hexanes/ethyl acetate) as a 1:1 mixture of diastereomers (HPLC). Analytical samples of each diastereomer were obtained by preparative HPLC (4:1 hexanes/ethyl acetate); **9a** t_R = 26 min and **9b** t_R = 31 min. **High R_f Diastereomer 9a (2*S**,4*S**,5*S**):** white solid; mp 52−53 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.15 (m, 5H), 3.76 (dd, J = 11.7, 4.5 Hz, 1H), 3.48 (dt, J = 4.7, 10.3 Hz, 1H), 3.43−3.38 (m, 1H), 3.10 (dd, J = 13.8, 4.3 Hz, 1H), 3.02 (t, J = 11.4 Hz, 1H), 2.33 (dd, J = 13.8, 9.3 Hz, 1H), 1.99 (ddd, J = 12.5, 4.7, 1.9 Hz, 1H), 1.85−1.76 (m, 1H), 1.63 (s, 1H), 1.31 (q, J = 11.0 Hz, 1H), 0.93 (dd, J = 14.5, 7.7 Hz, 1H), 0.76 (dd, J = 14.5, 6.5 Hz, 1H), 0.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 128.9, 128.4, 126.1, 74.8, 72.4, 69.9, 45.7, 44.4, 35.0, 24.8, −0.8; IR ($CDCl_3$) 3632, 3504, 2247, 1224, 1211 cm^{-1}; MS (EI) m/z 278 (M^+, 20), 171 (46), 129 (100), 117 (69), 105 (70), 91 (95), 73 (77); HRMS (EI) m/z calcd for $C_{16}H_{26}O_2Si$ (M^+) 278.1702, found 278.1712. **Low R_f Diastereomer 9b (2*S**,4*S**,5*R**):** white solid; mp 79−80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.19 (m, 5H), 4.02 (dt, J = 11.5, 4.8 Hz, 1H), 3.72 (dd, J = 11.9, 1.7 Hz, 1H), 3.46−

(17) El-Said, N. A. Ph.D. Dissertation, University of California−Riverside, Riverside, CA, 2001.

3.43 (m, 1H), 3.25 (dm, J = 11.9 Hz, 1H), 2.92 (dd, J = 13.3, 3.4 Hz, 1H), 2.72 (dd, J = 13.2, 11.0 Hz, 1H), 1.95−1.91 (m, 1H), 1.79 (dm, J = 12.4 Hz, 1H), 1.73(br s, 1H), 1.55 (q, J = 11.3 Hz, 1H), 1.05 (dd, J = 14.3, 6.4 Hz, 1H), 0.91 (dd, J = 14.3, 7.7 Hz, 1H), 0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 129.4, 128.3, 125.7, 74.9, 70.5, 67.2, 43.2, 39.2, 29.5, 25.1, −0.7; IR ($CDCl_3$) 3610, 3029, 2360, 2247, 1559, 1447 cm^{-1}; MS (EI) m/z 277 (MH^+, 5), 171 (36), 129 (100),118 (56), 105 (70), 91 (99), 73 (85); HRMS (EI) m/z calcd for $C_{16}H_{25}O_2Si$ (MH^+) 277.1623, found 277.1615.

(2*S,4*S**,5*S**)- and (2*S**,4*S**,5*R**)-4-Hydroxy-5-phenylmethyl-2-(triisopropylsilyl)methyltetrahydropyran (11a and 11b).** Following the general procedure, aldehyde **7** (0.25 mmol) and BF_3·OEt_2 (2.0 equiv) provided tetrahydropyrans **11a** and **11b** (61 mg, 67%; flash chromatography 9:1 followed by 1:1 hexanes/ethyl acetate) as a 1.7:1 mixture of diastereomers (HPLC). Analytical samples of each diastereomer were obtained by preparative HPLC (9:1 hexanes/ethyl acetate); **11a** t_R = 19 min and **11b** t_R = 24 min. **Major Diastereomer 11a (2*S**,4*S**,5*S**):** white solid; mp 86−87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.16 (m, 5H), 3.75 (dd, J = 11.7, 4.6 Hz, 1H), 3.52−3.43 (m, 2H), 3.11 (dd, J = 13.8, 4.3 Hz, 1H), 2.98 (t, J = 11.4 Hz, 1H), 2.31 (dd, J = 13.8, 9.3 Hz, 1H), 2.04 (ddd, J = 12.4, 4.6, 1.7 Hz, 1H), 1.81−1.77 (m, 1H), 1.51 (s, 1H), 1.33 (q, J = 11 Hz, 1H), 1.06−0.93 (s broad, 22H), 0.81 (dd, J = 14.9, 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 128.9, 128.4, 126.0, 74.4, 72.5, 69.8, 45.7, 45.1, 35.0, 18.79, 18.78, 17.6, 11.3; IR ($CDCl_3$) 3616, 3610, 3029, 2247, 1382 cm^{-1}; MS (DCI/NH_3) m/z 363 (MH^+, 80), 171 (100), 136 (24), 129 (33), 91 (21); HRMS (CI/NH_3) m/z calcd for $C_{22}H_{39}O_2Si$ (MH^+) 363.2719, found 363.2726. **Minor Diastereomer 11b (2*S**,4*S**,5*R**):** clear oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.16 (m, 5H), 4.01 (dt, J = 11.6, 4.8 Hz, 1H), 3.68 (d, J = 11.9 Hz, 1H), 3.51−3.43 (m, 1H), 3.19 (d, J = 11.9 Hz, 1H), 2.91 (dd, J = 13.2, 3.4 Hz, 1H), 2.72 (t, J = 13.1 Hz, 1H), 1.94−1.82 (m, 2H), 1.61−1.44 (m, 1H), 1.58 (s, 1H), 1.06 (s broad, 22H), 0.91 (dd, J = 14.5, 6.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 129.4, 128.3, 125.7, 74.6, 70.5, 67.0, 43.1, 40.2, 29.5, 18.9, 17.9, 11.5; IR (neat) 3392, 3382, 2956, 2890, 1145 cm^{-1}; MS (DCI/NH_3) m/z 363 (MH^+, 21), 171 (100), 91 (40); HRMS (CI/NH_3) m/z calcd for $C_{22}H_{39}O_2Si$ (MH^+) 363.2719, found 363.2726.

(2*S,4*S**,5*S**)- and (2*S**,4*S**,5*R**)-2-(Dimethyltritylsilyl)methyl-4-hydroxy-5-(phenyl)methyltetrahydropyran (13a and 13b).** Following the general procedure, aldehyde **7** (0.19 mmol) and BF_3·OEt_2 (2.0 equiv) provided tetrahydropyran **13a** and **13b** (49 mg, 52%; flash chromatography 9:1 followed by 1:1 hexanes/ethyl acetate) as a 3.4:1 mixture of diastereomers (HPLC). Analytical samples of each diastereomer were obtained by preparative HPLC (4:1 hexanes/ethyl acetate); **13a** t_R = 19 min and **13b** t_R = 27 min. **Major Diastereomer 13a (2*S**,4*S**,5*S**):** clear oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−6.98 (m, 20H), 3.72 (dd, J = 11.7, 4.6 Hz, 1H), 3.43 (m, 1H), 3.31−3.24 (m, 1H), 3.08 (dd, J = 4.2, 13.7 Hz, 1H), 2.95 (t, J = 11.4 Hz, 1H), 2.30 (dd, J = 13.7, 9.3 Hz, 1H), 1.84 (ddd, J = 12.5, 4.7, 1.8 Hz, 1H), 1.80−1.73 (m, 1H), 1.43 (d, J = 1.2 Hz, 1H), 1.29−1.18 (m, 1H), 0.97 (dd, J = 15.0, 9.2 Hz, 1H), 0.76 (dd, J = 15.0, 4.5 Hz, 1H), 0.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.5, 139.4, 130.0, 128.9, 128.4, 127.8, 126.1, 125.4, 74.7, 72.3, 69.8, 54.0, 45.6, 44.7, 34.9, 24.9, 1.4, −0.4; IR ($CDCl_3$) 3608, 3031, 2247, 1342 cm^{-1}; MS (FAB, NBA/NaCl) m/z 529 (MNa^+, 9), 301 (29), 243 (100), 171 (23), 129 (23); HRMS (FAB, NBA/NaCl) calcd for $C_{34}H_{38}O_2NaSi$ (MNa^+) 529.2539, found 529.2513. **Minor Diastereomer 13b (2*S**,4*S**,5*R**):** clear oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.02 (m, 20H), 3.97−3.93 (m, 1H), 3.66 (dd, J = 11.8, 1.5 Hz, 1H), 3.31−3.27 (m, 1H), 3.16 (dd, J = 11.9, 0.8 Hz, 1H), 2.88 (dd, J = 13.3, 3.5 Hz, 1H), 2.66 (dd, J = 13.0, 11.0 Hz, 1H), 1.92−1.88 (br m, 1H), 1.68−1.62 (m, 1H), 1.56 (s, 1H), 1.53−1.39 (m, 1H), 1.12 (dd, J = 14.9, 8.3 Hz, 1H), 0.86 (dd, J = 14.9, 5.5 Hz, 1H), 0.20 (s, 3H), 0.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.5, 141.1, 130.1, 129.4, 128.3, 127.9, 125.7, 125.4, 74.9, 70.4, 67.2, 54.0, 43.0, 39.7, 29.3, 25.1, 1.1, 0.1; IR ($CDCl_3$) 3510, 3063, 3030, 1397 cm^{-1}; MS (FAB, NBA/NaCl) m/z 529 (MNa^+, 17), 301 (43), 243 (100), 171 (44), 129 (42); HRMS (FAB, NBA/NaCl) calcd for $C_{34}H_{38}O_2NaSi$ (MNa^+) 529.2539, found 529.2556.

(2*S,4*S**,5*S**)- and (2*S**,4*S**,5*R**)-2-(Dimethylphenylsilyl)methyl-4-hydroxy-5-phenylmethyltetrahydropyran (15a and 15b).** Following the general procedure, aldehyde **7** (0.76 mmol) and BF_3·OEt_2 (2.0 equiv) provided tetrahydropyrans **15a** and **15b** (140 mg, 54%; flash chromatography 3:1 hexanes/ethyl acetate) as a 1.3:1 mixture of diastereomers (HPLC). Analytical samples of each diastereomer were obtained by preparative HPLC (4:1 hexanes/ethyl acetate); **15a** t_R = 24 min and **15b** t_R = 26 min. **Major Diastereomer 15a (2*S**,4*S**,5*S**):** white solid; mp 76−77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.15 (m, 10H), 3.76 (dd, J = 11.7, 4.5 Hz, 1H), 3.47−3.31 (m, 2H), 3.10 (dd, J = 13.8, 4.3 Hz, 1H), 2.97 (t, J = 11.4 Hz, 1H), 2.29 (dd, J = 13.8, 9.4 Hz, 1H), 1.93 (ddd, J = 12.5, 4.7, 1.9 Hz, 1H), 1.84−1.74 (m, 1H), 1.52 (s, 1H), 1.30 (q, J = 11.0 Hz, 1H), 1.16 (dd, J = 14.7, 8.2 Hz, 1H), 1.00 (dd, J = 14.7, 5.8 Hz, 1H), 0.30 (s, 3H), 0.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 139.0, 133.5, 128.9, 128.8, 128.4, 127.7, 126.1, 74.5, 72.3, 69.8, 45.6, 44.4, 34.9, 24.0, −1.8, −2.4; IR ($CDCl_3$) 3615, 3055, 1434, 1320, 1276 cm^{-1}; MS (CI/NH_3) m/z 358 (MNH_4^+, 10), 171 (100), 129 (37), 91 (42); HRMS (CI/NH_3) m/z calcd for $C_{21}H_{32}NO_2Si$ (MNH_4^+) 358.2202, found 358.2220. **Minor Diastereomer 15b (2*S**,4*S**,5*R**):** white solid; mp 66.4−66.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57−7.52 (m, 2H), 7.39−7.17 (m, 8H), 3.95 (dt, J = 11.5, 4.9 Hz, 1H), 3.70 (dd, J = 11.9, 1.7 Hz, 1H), 3.43−3.38 (m, 1H), 3.18 (dt, J = 11.9, 0.8 Hz, 1H), 2.89 (dd, J = 13.2, 3.4 Hz, 1H), 2.70 (dd, J = 13.1, 11.1 Hz, 1H), 1.92−1.88 (m, 1H), 1.73 (dm, J = 12.6 Hz, 1H), 1.58 (s, 1H), 1.50 (q, J = 11.4 Hz, 1H), 1.27 (dd, J = 14.5, 7.1 Hz, 1H), 1.13 (dd, J = 14.5, 7.0 Hz, 1H), 0.35 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 139.2, 133.6, 129.4, 128.8, 128.3, 127.7, 125.7, 74.7, 70.3, 67.1, 43.0, 39.3, 29.5, 24.2, −1.8, −2.1; IR ($CDCl_3$) 3610, 3070, 1442, 1350, 1146 cm^{-1}; MS (CI/NH_3) m/z 258 (MNH_4^+, 13), 171 (100), 129 (33), 91 (45); HRMS (CI/NH_3) m/z calcd for $C_{21}H_{32}NO_2Si$ (MNH_4^+) 358.2202, found 358.2195.

(2*S,3*S**,4*S**,5*R**)-2-(Dimethylphenylsilyl)methyl-4-hydroxy-3-methyl-5-(phenylmethyl)tetrahydropyran (17).** Following the general procedure, aldehyde **7** (0.72 mmol) and BF_3·OEt_2 (5.0 equiv) provided tetrahydropyran **17** (168 mg, 62%; flash chromatography 4:1 hexanes/ethyl acetate) as a white solid; mp 80−83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.35 (m, 3H), 7.29 (m, 2H), 7.20 (m, 3H), 3.68 (dd, J = 11.8, 1.5 Hz, 1H), 3.50 (dd, J = 10.3, 4.6 Hz, 1H), 3.15 (br d, J = 11.8 Hz, 1H), 3.00 (dt, J = 3.6, 9.8 Hz, 1H), 2.90 (dd, J = 13.3 3.3 Hz, 1H), 2.72 (dd, J = 13.3, 11.3 Hz, 1H), 1.90 (m, 1H), 1.63−1.49 (m, 1H), 1.54 (partially obscured m and H_2O, 1H), 1.22 (dd, J = 14.9, 10.3 Hz, 1H), 1.04 (dd, J = 14.9, 10.3 Hz, 1H), 0.93 (d, J = 6.7 Hz, 3H), 0.34 (s, 3H), 0.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 140.2, 133.7, 129.5, 128.6, 128.3, 127.5, 125.8, 80.5, 75.9, 66.9, 43.6, 42.1, 30.2, 21.3, 13.7, −1.5, −2.2; IR (KBr) 3429, 3371, 3019, 2957, 2909, 2860, 1458, 1247, 1150, 1104 cm^{-1}; MS (CI/NH_3) m/z 372 (MNH_4^+, 3), 337 (4), 277 (15), 221 (13), 186 (21), 185 (100), 152 (25), 143 (44), 129 (27), 91 (34); HRMS (CI/NH_3) m/z calcd for $C_{22}H_{34}NO_2Si$ (MNH_4+) 372.2359, found 372.2343.

(2*S,4*S**,5*S**)- and (2*S**,4*S**,5*R**)-2-(Dimethylphenylsilyl)methyl-4-hydroxy-5-methylethyltetrahydropyran (19a and 19b).** Following the general procedure, aldehyde **18**[6c] (0.87 mmol) and BF_3·OEt_2 (5.0 equiv) provided tetrahydropyran **19a** and **19b** (122 mg, 49%; flash chromatography 4:1 hexanes/ethyl acetate) as a 3.7:1 mixture of diastereomers (HPLC). Analytical samples of each diastereomer were obtained by preparative HPLC (4:1 hexanes/ethyl acetate); **19b** t_R = 23 min and **19a** t_R = 25 min. **Major Diastereomer 19a (2*S**,4*S**,5*S**):** clear oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.35 (m, 3H), 3.89 (dd, J = 11.5, 4.4 Hz, 1H), 3.56 (dt, J = 4.6, 10.5 Hz, 1H), 3.34 (m, 1H), 3.08 (t, J = 11.5 Hz, 1H), 2.08 (doublet of pentuplets, J = 3.1, 6.9 Hz, 1H), 1.94

(ddd, J = 12.3, 4.6, 2.1 Hz, 1H) 1.56 (br s, 1H), 1.42 (m, 1H), 1.32−1.13 (m, 2H), 1.05−0.95 (m, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.85 (d, J = 7.2 Hz, 3H), 0.32 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 133.6, 128.9, 127.7, 74.4, 69.6, 66.4, 49.1, 44.8, 24.9, 24.1, 20.8, 17.3, −1.8, −2.3; IR (neat) 3390, 1427, 1248, 1113, 836 cm^{-1}; MS (EI/NH_3) m/z 310 (MNH_4^+, 11), 146 (15), 123 (100), 92 (59); HRMS (EI/NH_3) m/z calcd for $C_{17}H_{32}NO_2Si$ (MNH_4^+) 310.2202 found 310.2210. **Minor Diastereomer 19b (2*S**,4*S**,5*R**):** clear oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (m, 3H), 7.35 (m, 2H), 3.98 (m, 1H), 3.89 (dd, J = 11.8, 5.1 Hz, 1H), 3.59−3.49 (m, 1H), 3.37 (dd, J = 11.8, 3.6 Hz, 1H), 1.86 (m, 1H), 1.75 (dt, J = 13.3, 4.4 Hz, 1H), 1.70−1.50 (partially obscured br m, 1H), 1.55 (dt, J = 13.3, 8.5 Hz, 1H), 1.32 (m, 2H), 1.15 (dd, J = 14.4, 7.2 Hz, 1H), 1.02 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.32 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 133.6, 128.8, 127.7, 72.7, 69.8, 65.5, 45.9, 39.8, 25.2, 23.8, 22.7, 21.3, −1.9, −2.4; IR (neat) 3424, 2954, 2871, 1247, 1112, 836 cm^{-1}; MS (EI/NH_3) m/z 310 (MNH_4^+, 16), 293 (MH^+, 9), 152 (9), 123 (100), 92 (56); HRMS (EI/NH_3) m/z calcd for $C_{17}H_{32}NO_2Si$ (MNH_4^+) 310.2202, found 310.2210.

(2*S,3*S**,4*S**,5*R**)-2-(Dimethylphenylsilyl)methyl-4-hydroxy-3-methylethyl-5-methyltetrahydropyran (20).** Following the general procedure, aldehyde **18** (0.87 mmol) and BF_3·OEt_2 (5.0 equiv) provided tetrahydropyran **20** (62 mg, 24%; flash chromatography 4:1 hexanes/ethyl acetate) as a clear oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.35 (m, 3H), 3.81 (dd, J = 11.5, 5.9 Hz, 1H), 3.55 (dd, J = 5.9, 3.8 Hz, 1H), 3.42 (dd, J = 11.5, 4.9 Hz, 1H), 3.04 (ddd, J = 10.5, 7.7, 4.1 Hz, 1H), 1.87 (m, 1H), 1.65 (m, 1H), 1.55 (s, 1H), 1.36 (m, 1H), 1.22 (dd, J = 14.9, 4.1 Hz, 1H), 1.08 (dd, J = 14.6, 10.0 Hz, 1H), 1.02 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 7.2 Hz, 3H), 0.31 (s, 3H), 0.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 133.6, 128.7, 127.6, 78.6, 77.2, 74.8, 66.1, 26.2, 22.4, 21.9, 21.0, 15.0, −1.7, −2.5; IR (neat) 3440, 2957, 1426, 1388, 1246, 1129 cm^{-1}; MS (CI/NH_3) m/z 324 (MNH_4^+), 307 (MH^+, 1) 229 (25), 173 (10), 152 (16), 137 (100), 92 (15); HRMS (CI, NH_3) m/z calcd for $C_{18}H_{34}NO_2Si$ (MNH_4^+) 324.2359, found 324.2358.

(2*S,3*S**,4*S**,5*R**)-2-(Dimethylphenylsilyl)methyl-4-hydroxy-3-methyl-5-phenyltetrahydropyran (22).** Following the general procedure, aldehyde **21**[18] (0.57 mmol) and BF_3·OEt_2 (5.0 equiv) provided tetrahydropyran **22** (26 mg, 14%; flash chromatography 4:1 hexanes/ethyl acetate) as a clear oil and a single diastereomer (^{1}H NMR): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (m, 4H), 7.39−7.24 (m, 6H), 4.25 (dd, J = 11.8, 1.0 Hz, 1H), 3.72 (dd, J = 11.8, 3.1 Hz, 1H), 3.50 (dd, J = 10.5, 5.9 Hz, 1H), 3.11 (m, 1H), 2.99 (m, 1H), 1.46−1.32 (m, 2H), 1.25 (dd, J = 14.4, 3.6 Hz, 1H), 1.05 (dd, J = 14.4, 10.8 Hz, 1H), 0.89 (d, J = 6.2 Hz, 3H), 0.38 (s, 3H), 0.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0, 139.4, 133.6, 130.5, 128.6, 128.2, 127.6, 126.9, 80.4, 74.8, 69.6, 46.3, 42.5, 21.3, 13.2, −1.5, −2.4; IR (neat) 3384, 2956, 1426, 1245, 1103 cm^{-1}; MS (CI/NH_3) m/z 358 (MNH_4^+, 53), 341 (MH^+, 1), 325 (1), 263 (8), 171 (100), 104 (26), 91 (17); HRMS (CI/NH_3) m/z calcd for $C_{21}H_{32}NO_2Si$ (MNH_4^+) 358.2202, found 358.2191.

(18) White, S. L. Ph.D. Dissertation, University of California−Riverside, Riverside, CA, 2001.

(2*S,4*S**,5*S**)- and (2*S**,4*S**,5*R**)-2-(Dimethylphenylsilyl)methyl-4-hydroxy-5-methyltetrahydropyran (24a and 24b).** Following the general procedure, aldehyde **23**[6c] (0.64 mmol) and BF_3·OEt_2 (2.0 equiv) provided tetrahydropyrans **24a** and **24b** (58 mg, 34%; flash chromatography 3:1 hexanes/ethyl acetate) as a 1.7:1 mixture of diastereomers (HPLC). Analytical samples of each diastereomer were obtained by preparative HPLC (3:1 hexanes/ethyl acetate); **24a** t_R = 52 min and **24b** t_R = 56 min. **Major Diastereomer 24a (2*S**,4*S**,5*S**):** clear oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.50 (m, 2H), 7.37−7.35 (m, 3H), 3.81 (dd, J = 11.8, 4.6 Hz, 1H), 3.43−3.35 (m, 1H), 3.22 (td, J = 10.3, 4.6 Hz, 1H), 2.93 (t, J = 11.3 Hz, 1H), 1.91 (dm, J = 12.8 Hz, 1H), 1.61 (s, 1H), 1.57−1.47 (m, 1H), 1.32−1.16 (m, 2H), 1.03 (dd, J = 14.9, 6.7 Hz, 1H), 0.90 (d, J = 6.7 Hz, 3H), 0.33 (s, 3H), 0.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 133.5, 128.8, 127.6, 74.7, 74.0, 71.8, 44.1, 39.2, 24.2, 13.0, −1.7, −2.2; IR ($CDCl_3$) 3607, 3069, 1601, 2912 cm^{-1}; MS (CI/NH_3) m/z 282 (MNH_4^+, 28), 265 (10), 187 (54), 154 (22), 95 (100), 92 (58); HRMS (CI/NH_3) m/z calcd for $C_{15}H_{25}O_2Si$ (MH^+) 265.1623, found 265.1620. **Minor Diastereomer 24b (2*S**,4*S**,5*R**):** clear oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.49 (m, 2H), 7.40−7.33 (m, 3H), 3.85−3.78 (m, 1H), 3.72 (dd, J = 11.8, 1.5 Hz, 1H), 3.42 (dd, J = 11.8, 2.6 Hz, 1H), 3.37−3.28 (m, 1H), 1.87−1.82 (m, 1H), 1.65−1.59 (m, 1H), 1.44−1.33 (m, 2H), 1.22 (dd, J = 14.9, 7.2 Hz, 1H), 1.07−1.02 (m, 1H), 1.01 (d, J = 7.2 Hz, 3H), 0.32 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 133.5, 128.8, 127.7, 74.7, 71.2, 70.1, 38.7, 34.9, 24.2, 9.9, −1.7, −2.1; IR ($CDCl_3$) 3609, 2955, 2359, 1426 cm^{-1}; MS (DCI/NH_3) m/z 265 (MH^+, 3), 135 (14), 95 (100), 92 (14); HRMS (DCI/NH_3) m/z calcd for $C_{15}H_{25}O_2Si$ (MH^+) 265.1623, found 265.1611.

(2*S,4*S**)-5,5-Dimethyl-2-(dimethylphenylsilyl)methyl-4-hydroxytetrahydropyran (26).** Following the general procedure, aldehyde **25**[6c] (0.56 mmol) and BF_3·OEt_2 (2.0 equiv) provided tetrahydropyran **26** (78 mg, 50%; flash chromatography 3:1 hexanes/ethyl acetate) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.33 (m, 5H), 3.43 (d, J = 11.5 Hz, 1H), 3.39−3.33 (m, 2H), 3.00 (d, J = 11.5 Hz, 1H), 1.68 (ddd, J = 12.7, 4.7, 2.2 Hz, 1H), 1.47 (br s, 1H), 1.37 (apparent q, J = 11.3 Hz, 1H), 1.23 (dd, J = 14.5, 7.0, Hz, 1H), 1.05 (dd, J = 14.5, 7.0 Hz, 1H), 0.94 (s, 3H), 0.85 (s, 3H), 0.32 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 133.5, 128.8, 127.7, 76.6, 75.3, 39.8, 35.6, 24.1, 23.0, 16.9, −1.8, −2.2; IR (neat) 3453, 3396, 2871, 1192 cm^{-1}; MS (CI/NH_3) m/z 279 (MH^+, 7), 201 (38), 159(12), 109 (100); HRMS (CI/NH_3) m/z calcd for $C_{16}H_{30}NO_2Si$ (MNH_4^+) 296.2046, found 296.2032.

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Supporting Information Available: Copies of ^{1}H NMR, ^{13}C NMR, GOESY, COSEY, and gNOESY (where applicable) for compounds **9**, **11**, **13**, **15**, **17**, **19**, **20**, **22**, **24**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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