High 1,4-*syn*-induction in the addition of chiral allyltrichlorostannanes to chiral aldehydes

Luiz C. Dias,* Rosana Giacomini, Paulo R. R. Meira, Edílson Ferreira, Andréa A. Ferreira, Gaspar Diaz, Débora R. dos Santos, and Leonardo J. Steil

Instituto de Química, Universidade Estadual de Campinas, UNICAMP
C.P. 6154, 13084-971, Campinas, SP, Brazil
E-mail: ldias@iqm.unicamp.br

Dedicated to Prof. Edmundo A. Ruveda on the occasion of his 70th birthday

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Abstract

Chiral and achiral allyltrichlorostannanes reacted with chiral aldehydes to give the corresponding homoallylic alcohols with good to high diastereoselectivities. This approach has been applied to the synthesis of hydroxyethylene dipeptide isosteres L-682, 679, L-684,414, L-685,434 and L-685,458.

Keywords: Allylsilanes, allyltrichlorostannanes, chiral aldehydes, ligand exchange reactions

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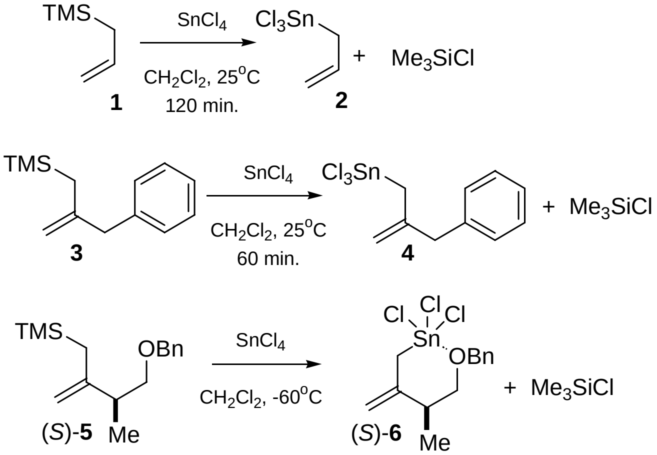
Introduction

The Lewis-acid mediated reaction of allylsilanes and allylstannanes with aldehydes is a well-known procedure for the preparation of homoallylic alcohols.[1,2] The stereochemical outcome of this reaction has on occasion been explained by considering Lewis acid-carbonyl complexation. This type of complexation mainly occurs by two discrete pathways, chelation and non-chelation controlled, depending on the nature of the Lewis acid and on the steric requirements of the carbonyl ligand. Condensation of allylic metals (e.g M: Si, Ti, Sn. B, Cr) with various carbonyl compounds can be used to achieve acyclic stereoselection, and has been applied to the synthesis of natural products.[3,4] Chiral allylmetal reagents may be thought of as acetate-enolate equivalents for diastereoselective construction of stereochemically well-defined homoallylic alcohols. As these reactions complement the aldol reactions, allylsilanes and allylstannanes are among the most important groups of organometallic type reagents available for the control of acyclic stereochemistry.[1,4] Many methods can be used to control the configurations of stereogenic centers that are close to each other. However, relatively few methods are available for control of the stereochemistry of more remote stereocenters.

This account focuses on our recent work on the chemistry of allylsilanes and allyltrichlorostannanes. We believe this chemistry may be very useful for the synthesis of compounds with remote stereogenic centers and is reviewed in this article.

NMR study on ligand exchange reactions between allylsilanes and $SnCl_4$

We began this work a few years ago, with a spectroscopic study (^{1}H, ^{13}C, and ^{119}Sn NMR) of the reactions of allylsilanes **1**, **3** and **5** with $SnCl_4$ (Scheme 1).[5,6] Allylsilanes **1**, **3** and **5** and $SnCl_4$ (0.5 M solution in $CDCl_3$) were mixed in order to promote ligand exchange, leading to the corresponding allyltrichlorostannanes **2**, **4** and **6**, respectively.[6-10]



Scheme 1

For allyltrimethylsilane **1** the ligand exchange producing allyltrichlorostannane **2** and Me_3SiCl is complete after 120 minutes at room temperature (Scheme 1). For allylsilane **3** the metathesis to give **4** and Me_3SiCl is faster, as expected for a 1,1-disubstituted olefin, being complete after 60 minutes at room temperature.[6] Upon addition of $SnCl_4$ to a solution of allylsilane (*S*)-**5** in $CDCl_3$, at −60 °C, as well as at room temperature, a slightly yellow homogeneous solution was obtained. The resulting NMR spectrum at −60 °C showed formation of Me_3SiCl and complete consumption of the allylsilane (*S*)-**5** within 1 minute to give allyltrichlorostannane (*S*)-**6**. It appears that the oxygen functionality is responsible for the rapid ligand exchange reaction observed even at low temperatures for this particular allylsilane and $SnCl_4$. The ligand exchange reaction is probably facilitated by coordination of tin to this oxygen followed by cleavage of the carbon-silicon bond by a free chloride ion.

Most diagnostics is the deshielding of the hydrogens H1 to H6 in the ^{1}H NMR spectrum of (*S*)-**6** (Figure 1). The methylenic hydrogens H3 and H4 as well as the benzylic hydrogens H5 and H6 are too far away from trichlorotin group to suffer from inductive effects. We believe that the deshielding observed for these hydrogens is due to the internal coordination of this oxygen to tin, as proposed in Figure 1.[6]

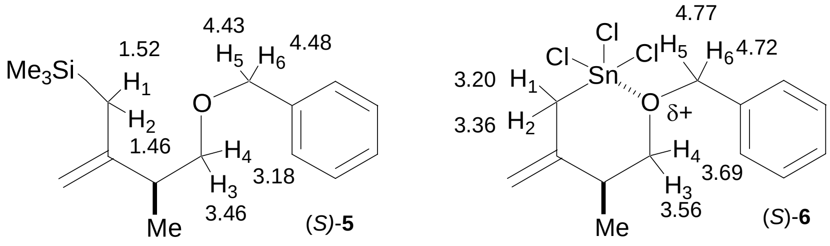


Figure 1

Analysis of the ^{13}C NMR spectrum showed a deshielding for most carbons of (*S*)-**6** when compared to allylsilane (*S*)-**5** (Figure 2). Most diagnostic is the chemical shift of 39.95 ppm for the carbon attached to tin in the new species, compared to 26.63 ppm for the same carbon in the allylsilane.[6]

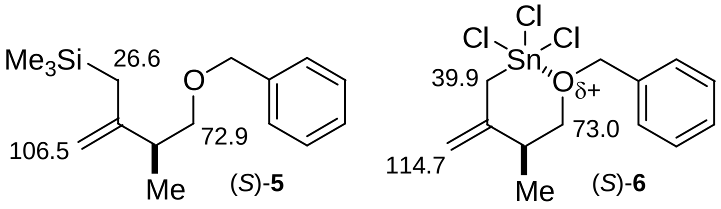


Figure 2

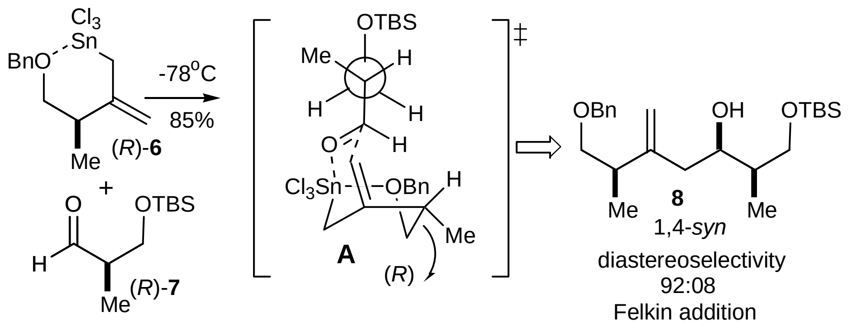
The ^{13}C NMR spectra proved less useful than the ^{1}H NMR spectra in establishing complexation to the benzyl oxygen, as there was no significant difference between the chemical shifts for methylenic carbons in both species.

We have observed ^{119}Sn resonance signals at −27 ppm for allylstannanes **2** and **4**.[6] The tin chemical shift for allylstannane **6** appeared at −187 ppm. We believe that tin chemical shifts are highly sensitive to oxygen bonding, and this is strong evidence in favor of the complexed intermediate.

Allyltrichlorostannane additions to mono and disubstituted aldehydes

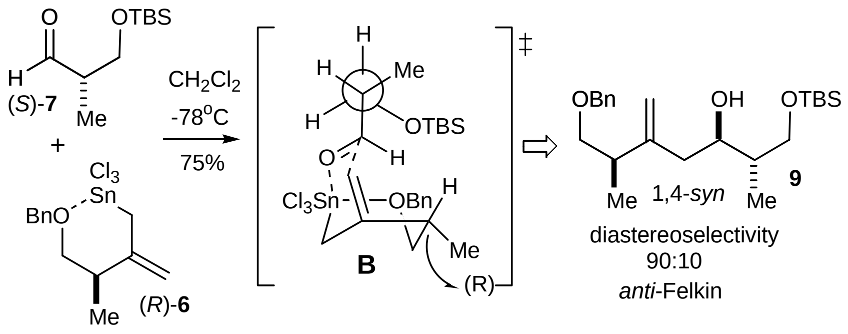
The next step involved the reaction between chiral α-substituted aldehydes and allylstannane (*R*)-**6** (Scheme 2). These substrates have been selected to be representative of the complex fragments that might be coupled in polyacetate and polypropionate-derived aldol-type reactions.[11]

The *in situ* prepared allylstannane (*R*)-**6** reacted with aldehyde (*R*)-**7** to give a mixture of 1,4-*syn* and 1,4-*anti*-diastereomers with 92:08 diastereoselectivity, favoring the 1,4-*syn*-isomer **8** with Felkin addition (Scheme 2).[11,12] It should be noted that this reaction gives a very important subunit with different protecting groups at both termini and a double bond that can be further manipulated to a carbonyl group and then selectively reduced to the 1,3-*syn* and 1,3-*anti* diol functionalities.



Scheme 2

Under the same conditions, allyltrichlorostannane (*R*)- **6** reacted with aldehyde (*S*)-**7** to give 1,4-*syn*-product **9** as the major isomer, with *anti*-Felkin addition (Scheme 3).[11,12]



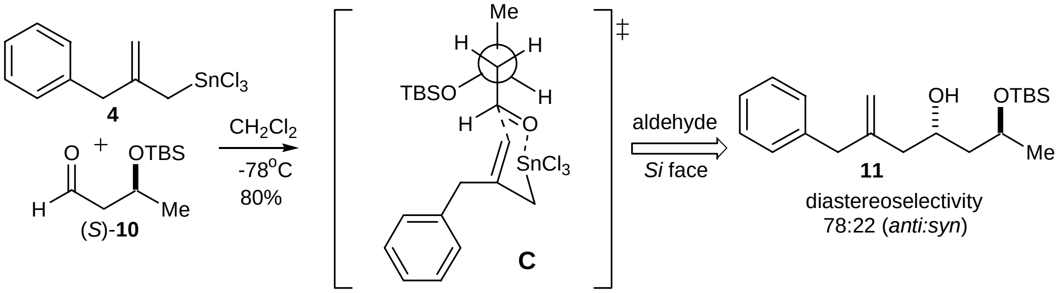
Scheme 3

The stereoselectivity of the reactions of allyltrichlorostannane (*R*)-**6** with aldehydes (*R*)-**7** and (*S*)-**7** is consistent with an intermediate allyltin trichloride, which is stabilized by tin-oxygen interaction. A boat-like arrangement is proposed, as it avoids steric interactions between the aldehyde substituents and the axial methyl group α to the double bond in the chair structure (transition states **A**, Scheme 2 and **B**, Scheme 3). This complex intermediate then reacts with the aldehyde via chair-like six-membered ring transition states (**A** and **B**) in which the aldehyde approaches the complex opposite to the methyl group. The preference of the alkyl group of the aldehyde to adopt an equatorial position controls the aldehyde facial selectivity, resulting in the favored 1,4-*syn* stereochemistry in the adduct, independent of the aldehyde absolute configuration.

These examples shown that the levels of π-facial selection are independent of the absolute stereochemistry of the α-methyl substituted aldehydes and support the notion that the stereocenter in allyltrichlorostannane is primarily responsible for the observed diastereoselection.[6]

We investigated the reaction between chiral β-alkoxy as well as α-methyl-β-alkoxy aldehydes with achiral and chiral allyltrichlorostannanes.[13] This study details our efforts to understand the double stereodifferentiating stereocontrol elements involved in chiral allyltrichlorostannane additions to chiral β- and α,β-disubstituted aldehydes. In this part of the investigation, we have examined the interplay between 1,2- (Felkin-Anh), 1,3- and 1,4-asymmetric induction in allyltrichlorostannane reactions with β-alkoxy and α-methyl-β-alkoxy aldehydes under conditions that preclude internal chelation with the aldehyde β-alkoxy substituent.

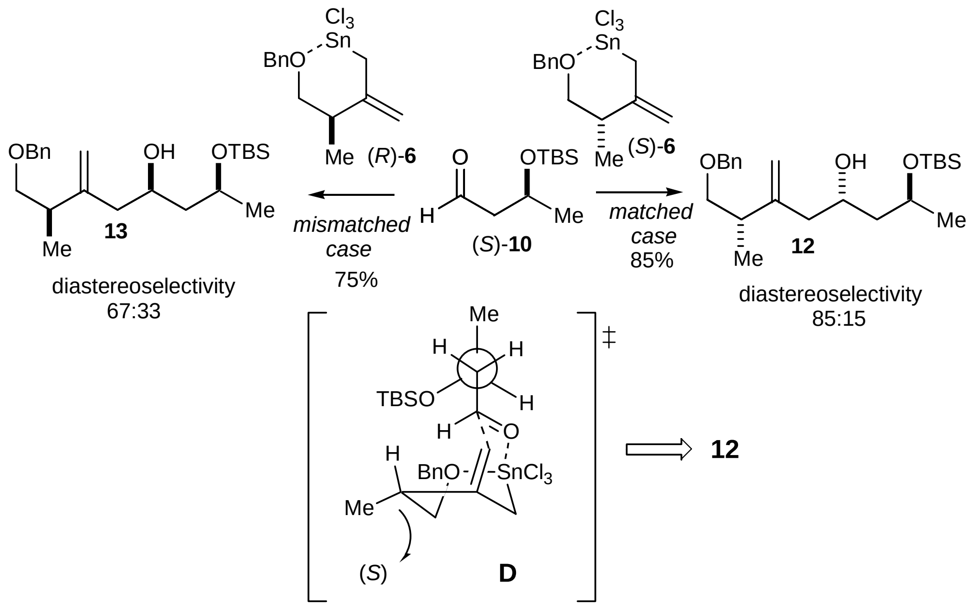
In order to check the facial selectivity of aldehyde (*S*)-**10** we reacted it first with achiral allyltrichlorostannane **4** (Scheme 4).[13]



Scheme 4

Achiral allyltrichlorostannane **4** reacted with chiral β-alkoxy aldehyde (*S*)-**10** in CH_2Cl_2 at –78 °C to give the corresponding 1,3-*anti* product **11** as the major product in good yield and with 78:22 diastereoselectivity (Scheme 4).[13] The stereoinduction observed in this reaction indicates that the intrinsic facial bias imposed by the resident β-OTBS substituent results in preferential formation of the 1,3-*anti* diastereomer, with a preference for aldehyde *si*-face attack. In the proposed transition state conformation (**C**), steric interactions are expected to be reduced when the β-Me substituent in this aldehyde is placed *anti* to the Cα-C=O bond (Scheme 4). In this conformation we might expect also minimization of destabilizing dipole interactions since the β-OTBS group and C=O are oriented in opposite directions. A chair-like transition state (**C**) with the alkyl group of the aldehyde in an equatorial position and with attack to the *si*-face of the aldehyde, explains the observed sense of induction.

Under the same conditions allyltrichlorostannane (*S*)-**6** reacted with aldehyde (*S*)-**10** to give 1,3-*anti*-1,4-*syn* product **12** as the major product (85:15 diastereoselectivity) (Scheme 5).[13] As we know from previous work that the facial bias of this chiral allyltrichlorostannane is dominated by the α-methyl stereocenter and tends to give the 1,4-*syn* isomer with *si*-face attack, and aldehyde (*S*)-**10** has a preference to give the 1,3-*anti* product, this is an example of a *matched* reaction.



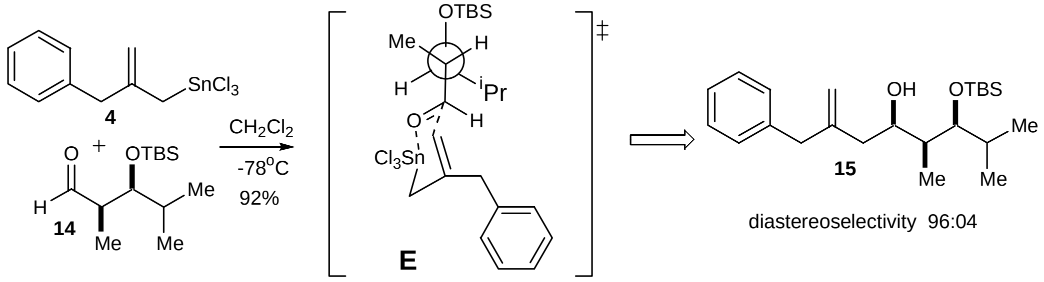
Scheme 5

The stereoselectivity of this reaction is consistent with an intermediate allyltin trichloride which is stabilized by tin-oxygen interaction, and which then reacts with the aldehyde via a chair-like six-member ring transition state (**D**) in which the aldehyde approaches the boat-like complex opposite to the methyl group (Scheme 5). Again, a boat-like arrangement is proposed, as it avoids steric interactions between the aldehyde substituents and the axial methyl group α to the double bond in the chair structure.

Addition of the enantiomeric allyltrichlorostannane (*R*)-**6** to aldehyde (*S*)-**10** led to a 67:33 mixture favoring the 1,4-*syn*-1,3-*syn* product **13**, in a *mismatched* case (Scheme 5).[13]

We next examined the stereochemical impact of both α and β-aldehyde substituents using chiral-*syn* and *anti* disubstituted α-methyl-β-alkoxy aldehydes. [13-15]

Achiral allyltrichlorostannane **4** reacted with chiral *syn*-α,β-disubstituted[14] aldehyde **14** to give the corresponding 1,2-*syn-1,3-syn* product **15** in 92% yield and with 96:04 diastereoselectivity (Scheme 6).

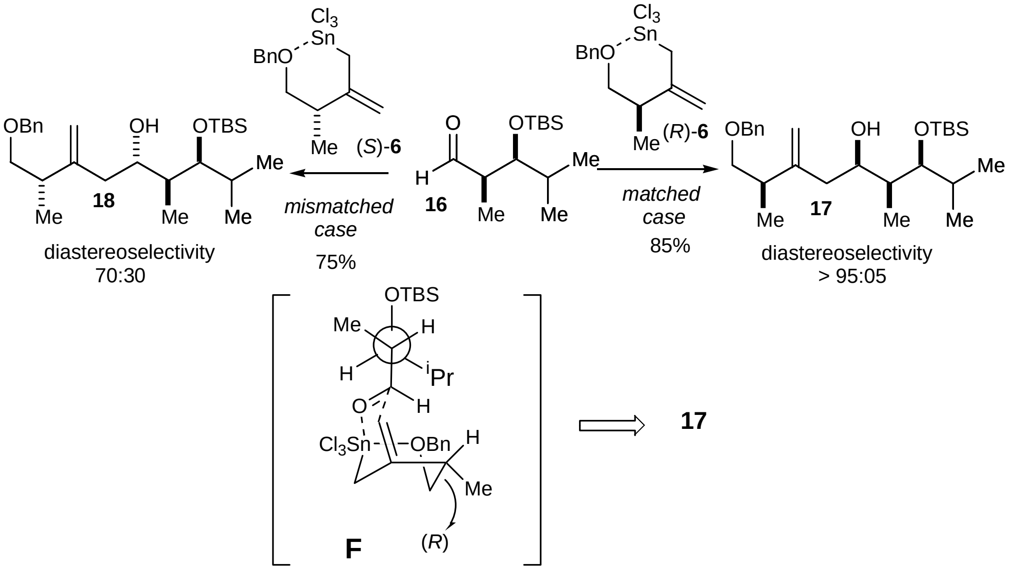


Scheme 6

This example shows that a 1,2-*syn* aldehyde has a preference to give the product with Felkin addition as well as 1,3-*syn* addition.[13] In the presence of an α-methyl stereocenter, 1,3-asymmetric induction imposes an intrinsic facial bias on the carbonyl that results in the formation of the 1,3-*syn*-dioxygen relationship.

A chair-like transition state (**E**) with attack to the *re*-face of the aldehyde (Felkin addition), explains the observed induction direction (Scheme 6).

The reaction of chiral allyltrichlorostannane (*R*)-**6** with aldehyde **16** gives homoallylic alcohol **17** (*all-syn* product) as the major isomer (Felkin addition, *matched case*) (Scheme 7).



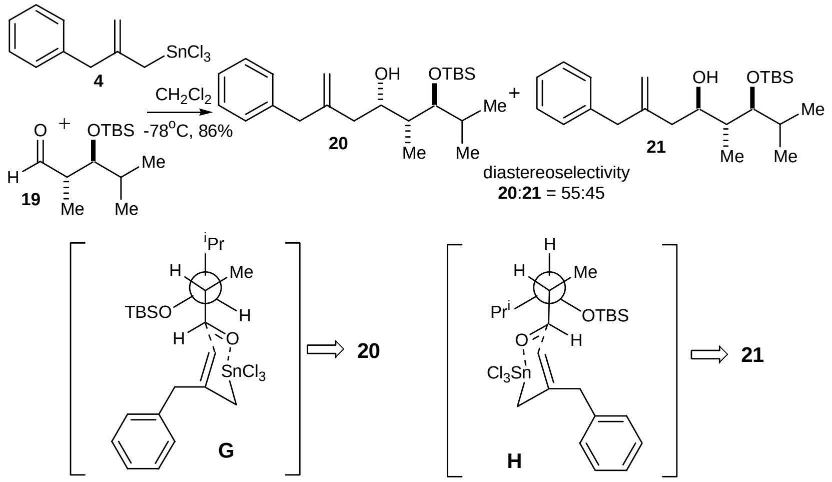
Scheme 7

The stereoselectivity of this reaction is consistent with a chair-like six-membered ring transition state (**F**) in which the aldehyde approaches the boat-like allyltin complex opposite to the methyl group (Scheme 7).

Allyltrichlorostannane (*S*)-**6** reacted with aldehyde **16** to give a 70:30 ratio favoring isomer **18**, in a *mismatched case* (Scheme 7). In this latter case, the α-methyl stereocenter in allyltrichlorostannane (propensity for 1,4-*syn* addition) exerts a dominant influence on aldehyde facial selectivity, by overriding the intrinsic bias imposed by the α and β stereocenters in the aldehyde, to give the 1,3-*syn* product.

Before starting the study described in Scheme 8, we expected that, under conditions that preclude internal chelation, the carbonyl facial bias of *anti*-disubstituted aldehyde **19** should be highly predictable, since the factors which favors both 1,2- and 1,3-asymmetric induction mutually reinforce nucleophilic addition to give 1,2-*syn*-1,3-*anti* diastereomer.[16] We have observed that this is not the case under the reaction conditions described here.

Achiral allyltrichlorostannane **4** additions to chiral *anti*-α,β-disubstituted aldehyde **19** gave the corresponding 1,2-*syn*-1,3-*anti*-product **20** as the major product in good yields, although with only 55:45 diastereoselectivity (Scheme 8).[13,15]



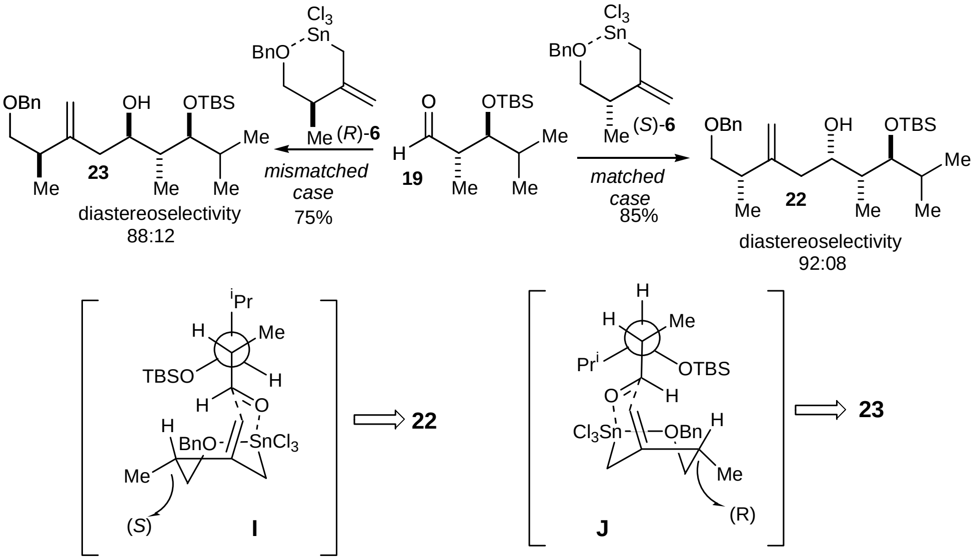
Scheme 8

This example shows that an *anti* aldehyde has no facial preference under these conditions, since the Felkin addition to give 1,2-*syn* isomer competes with the β-alkoxy stereocenter to give the 1,3-*syn* isomer. We believe that in this case, the corresponding transition states should be very similar in energy, with conformer **G** (which gives the 1,2-*syn* isomer) being destabilized by the gauche interaction ^{i}Pr/Me while conformer **H** (which gives the 1,2-*anti* isomer) being destabilized by the ^{i}Pr/C=O and Me/OTBS gauche interactions (Scheme 8).

Under the same conditions described before allyltrichlorostannane (*S*)-**6** reacted with aldehyde **19** to give 1,2-*syn*-1,3-*anti* isomer **22** with 92:8 diastereoselectivity (Scheme 9).[13]

The reaction of allyltrichlorostannane (*R*)-**6** with aldehyde **19** gave homoallylic alcohol **23** as the major isomer in 88:12 diastereoselectivity (*anti*-Felkin addition, partially *matched case*).

The results described in Scheme 9 can be rationalized with dominant acyclic 1,4-asymmetric induction from the chiral allyltrichlorostannane. These are examples of partially *matched* reactions, with the chiral allyltrichlorostannanes (*R*)-**6** and (*S*)-**6** being responsible for the control of the observed diastereoselectivities, through transition states analogous to **I** and **J**, respectively (Scheme 9). Poor levels of diastereoselectivity characterize this reaction with 1,2-anti β-OTBS aldehydes only when an achiral allyltrichlorostannane is used. This attenuated 1,3-*anti* selectivity for 1,2-*anti* aldehydes with the TBS protecting group appears to be general, as similar trends were observed for titanium and boron aldol reaction variants.[16] One might project that the transition states of these reactions exhibit less charge separation than the aldol processes, and are accordingly less subject to the electrostatic influence of the β-OTBS function.



Scheme 9

The examples presented in this work show that the levels of π-facial selection are dependent on the absolute stereochemistries of the disubstituted aldehydes as well as of the allyltrichlorostannane.

The results from these experiments suggest that the stereochemical relationships between the α and β aldehyde substituents may confer either a reinforcing (*matched*) or opposing (*mismatched*) facial bias on the carbonyl moiety. In this complex scenario, the chiral allyltrichlorostannane may adopt either a reinforcing or opposing relationship. One possible reason for this result could be attributed to the involvement of energetically similar chair and twist-boat pericyclic transition states which lead to diastereomeric product formation. Another possibility to consider in these reactions is that nonbonded interactions between the allyltrichlorostannane and aldehyde α substituents may not be significant in pericyclic transition states leading to either Felkin or *anti*-Felkin addition products.[13-17]

Allyltrichlorostannane additions to α-aminoaldehydes

In recent years there has been a major research effort towards the development of clinically useful inhibitors of aspartyl proteases.[18-21] This worldwide search has led to various peptide isosteres, wherein the scissile peptide bond is replaced by a hydrolytically more stable isosteric functional group. In this context, the hydroxyl amino acid framework **II** in Figure 3, where the peptidic linkage of the sequence in structure **I** is replaced by a CH(OH)CH$_2$ group, constitutes a useful class of aspartyl protease inhibitors.

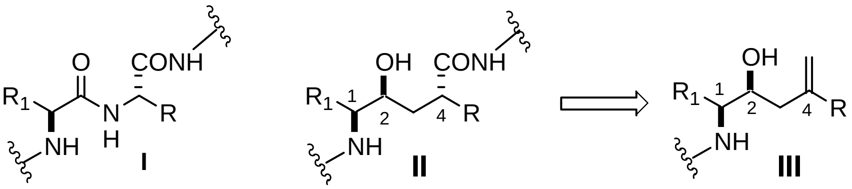
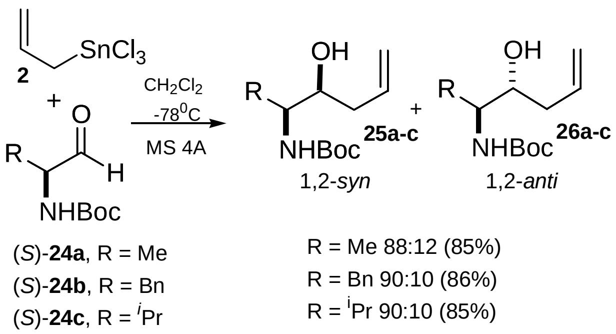


Figure 3

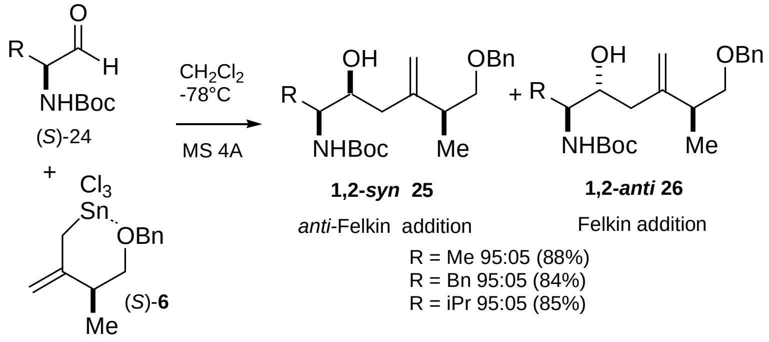
We were interested to investigate the allyltrichlorostannane additions to chiral aldehydes **24**. In order to confirm the facial selectivities of the (*S*)-*N*-Boc-α-aminoaldehydes **24**, we reacted them with allyltrichlorostannane **2** (Scheme 10).[22]



Scheme 10

In all cases, the major product results from a chelation controlled reaction that mainly gives the 1,2-*syn* isomers **25a-c**, showing that the (*S*)-α–aminoaldehydes **24a-c** have a preference for *anti*-Felkin addition (*si* face attack).[22]

Under the same conditions, chiral allyltrichlorostannane (*S*)-**6** reacted with (*S*)-α-aminoaldehydes **24** to give a mixture of 1,2-*syn* **25** and 1,2-*anti* **26** diastereomers with useful diastereoselectivities, favoring the 1,2-*syn*-isomer with *anti*-Felkin addition and aldehyde *si* face attack (Scheme 11).



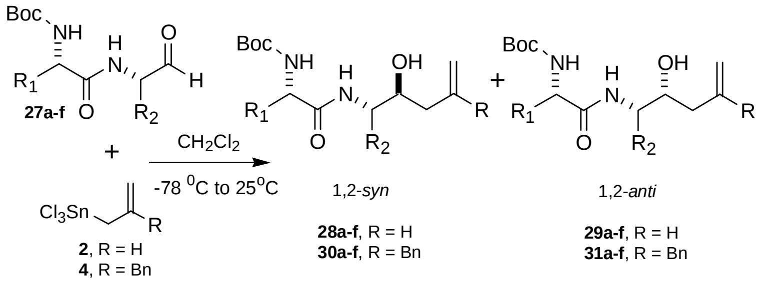
Scheme 11

As we are aware from previous work that the chiral allyltrichlorostannane (*S*)-**6** has a preference for *si* face approach, this is an example of a *matched* reaction. It should be noted that this reaction gives a very important subunit with a double bond and a benzyl protected primary alcohol that can be further manipulated.

A synthetic methodology, which allows compounds with programmed variations of substituents to be synthesized, is particularly important in the screening of the pharmacological activity and in a study of structure-activity relationships directed toward the design of the best substituents for positions 1 and 4 in structure **III** (R and R_1 groups in Figure 3).

Towards this end we initiated a study towards the synthesis of more complex dipeptide isosteres by reaction of allyltrichlorostannanes with dipeptide aldehydes.[23,24] The present methodology is useful for the preparation of molecules of type **III** and consists in the first step in the preparation of molecules of type **II** (Figure 3). To the best of our knowledge, these were the first examples of successfully allylsilane additions to chiral dipeptide aldehydes.

The results of allyltrichlorostannane additions to dipeptide aldehydes **27a-f** are shown in Scheme 12. In all cases, the major product results from a chelation controlled reaction that mainly gives the 1,2-*syn* isomer, showing that the (*S*)-α-amino dipeptide aldehydes have a preference for *anti*-Felkin addition (*si* face attack). Increased steric bulk of the R_2 group (R_2 = ^{i}Pr, ^{i}Bu) in the aldehydes gives better diastereoselection. With small R_2 groups (R_2 = Me, Bn, CH_2OTBS) the diastereoselectivity is poor, although the reaction occurs in very good yields. It is essential to promote the ligand exchange reaction before addition of the aldehyde in order to get good yields and selectivities.



Dipeptide Aldehydes **27**		R = H		R = Bn	
R_1	R_2	**28:29**	*Yield* (%)	**30:31**	*Yield* (%)
Bn	Me	78:22	87	68:32	80
Bn	^{i}Pr	95:05	89	95:05	89
Bn	^{i}Bu	90:10	83	90:10	83
Bn	Bn	60:40	79	60:40	70
^{i}Pr	Bn	53:47	74	60:40	75
Bn	CH_2OTBS	66:34	86	60:40	74

Scheme 12

Although the remote stereogenic center may influence the stereochemical course of C-C bond formation, we expect such reactions to be dominated by the stereogenic center next to the aldehyde function. We believe that the observed selectivity can be explained by an equilibrium between the intramolecular hydrogen bond conformer (**K**) and a not bonded conformer (**L**) (Figure 4).[22,23] When the form **K** predominates (bulkier R groups), the *syn* isomer is favored whereas the prevalence of the **L**-like conformer (smaller R groups) leads to the *anti* isomer. The nucleophile selects the less hindered *si*-face forming a six membered transition state **M** where the chiral residue of the aldehyde occupies a pseudo-equatorial position.[24-27]

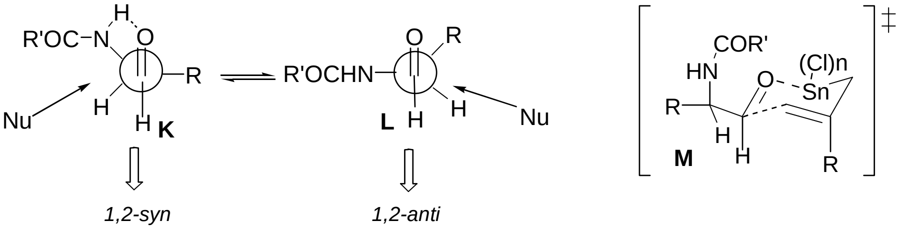
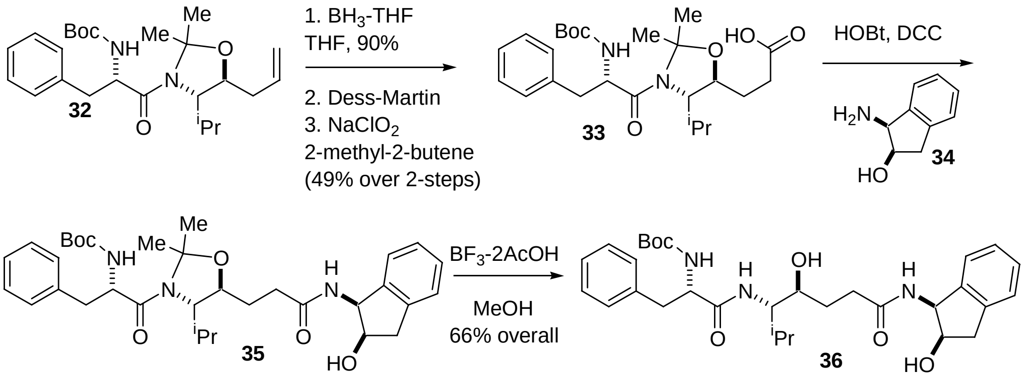


Figure 4

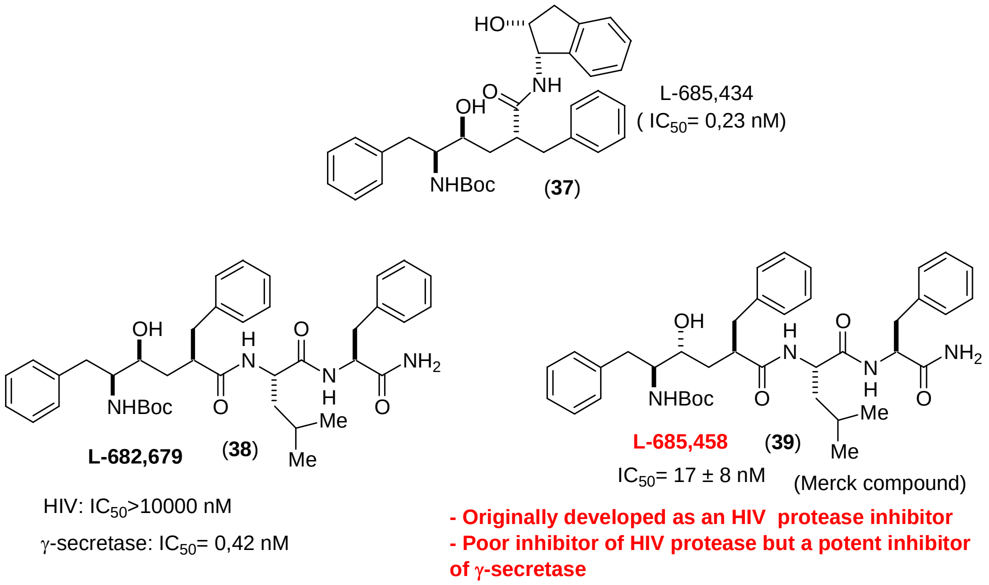
We have applied this protocol to the synthesis of tripeptide **36** (Scheme 13). Acetonide formation from **28b** followed by hydroboration with BH_3-THF followed by Dess-Martin and Pinnick oxidation gave carboxylic acid **33** in 44% overall yield. Coupling of **33** with **34** using standard conditions gave **35** that was treated with the complex BF_3-2AcOH in MeOH to give tripeptide **36** in 66% overall yield.



Scheme 13

Total synthesis of aspartyl protease inhibitors

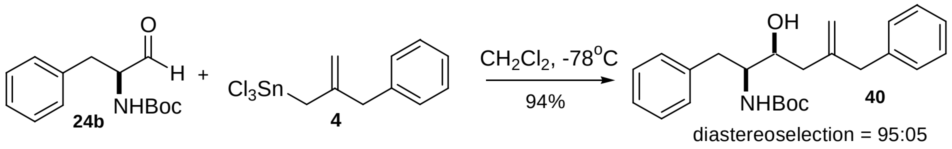
Based on our initial results on allyltrichlorostannane additions to *N*-Boc-α-aminoaldehydes and attracted by the HIV inhibitory potency of L685,434 (**37**), L-682,679 (**38**) as well as by the highly potent inhibition of AβPP γ-secretase activity of L-685,458 (**39**), we initiated a project directed towards their total synthesis (Figure 5). The approach described here to L685,434 (**37**), L-682,679 (**38**), and L-685,458 (**39**) might also give access to additional derivatives with potential relevance for biological evaluation.[28-30]



- Originally developed as an HIV protease inhibitor
- Poor inhibitor of HIV protease but a potent inhibitor of γ-secretase

Figure 5

Addition of the aldehyde **24b** to a CH_2Cl_2 solution of allyltrichlorostannane **4** at −78°C gave the 1,2-*syn* aminoalcohol **40** in 94% yield and 95:5 diastereoselectivity (Scheme 14).[31,32]

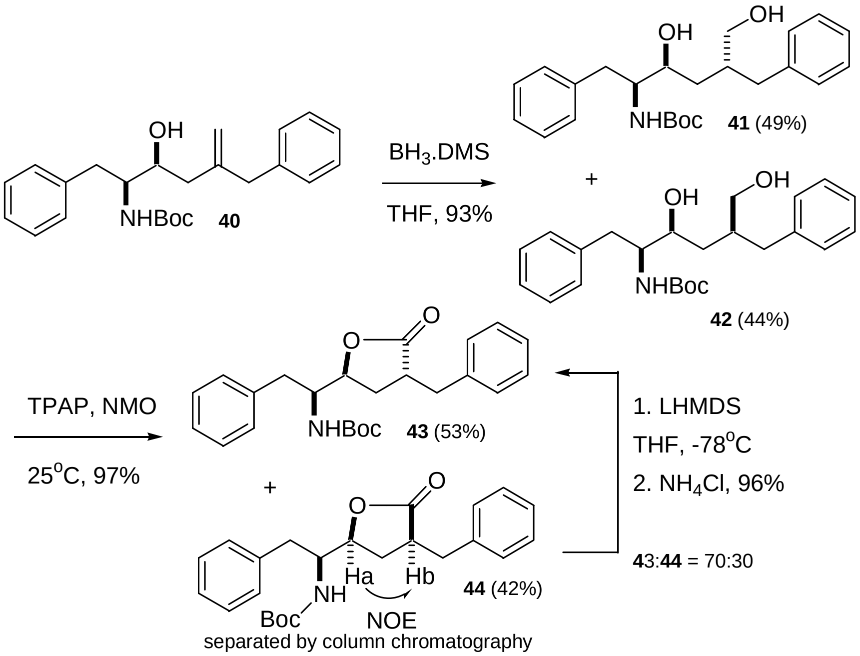


Scheme 14

Direct hydroboration of the unprotected homoallylic alcohol **40** with BH_3.DMS in THF at 0°C gave a mixture of diols **41** and **42**, in 93% yield (Scheme 15).

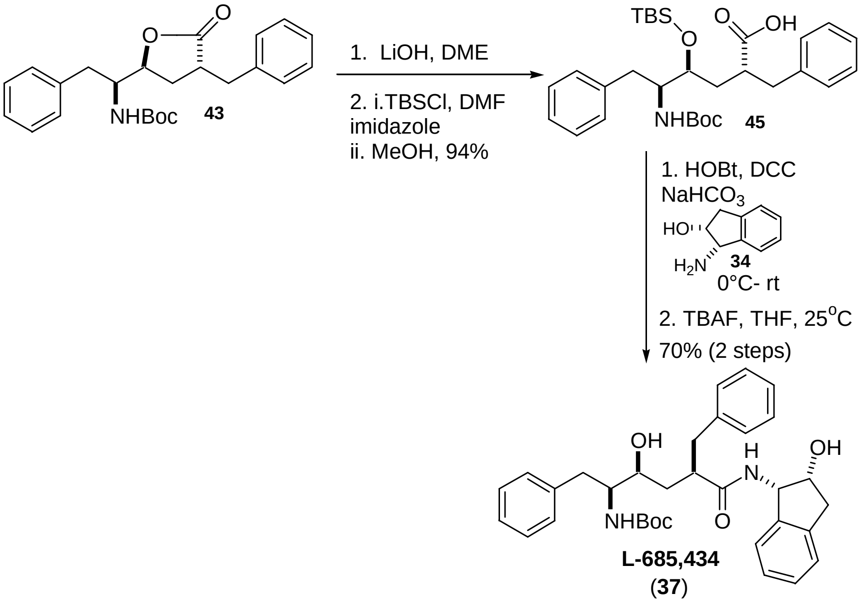
These diols were not separated but were converted directly to a mixture of lactones **43** and **44** (95% yield) by treatment with TPAP and NMO in the presence of molecular sieves at room temperature.[31,32] These lactones were readily separated by flash column chromatography. Although these lactones have been prepared earlier by others, the relative stereochemistry for *cis*-lactone **44** was ascertained by NOESY experiments (observed interaction between Ha and

Hb). Attempts to obtain more of the desired *trans*-lactone **43** by a deprotonation and reprotonation sequence of *cis*-lactone **44** led to a 70:30 mixture of lactones **43:44** in 96% yield (Scheme 15). It is interesting to point out that *cis*-lactone **44** is also an important intermediate for the synthesis of other potent HIV-1 protease inhibitors.[31,32]



Scheme 15

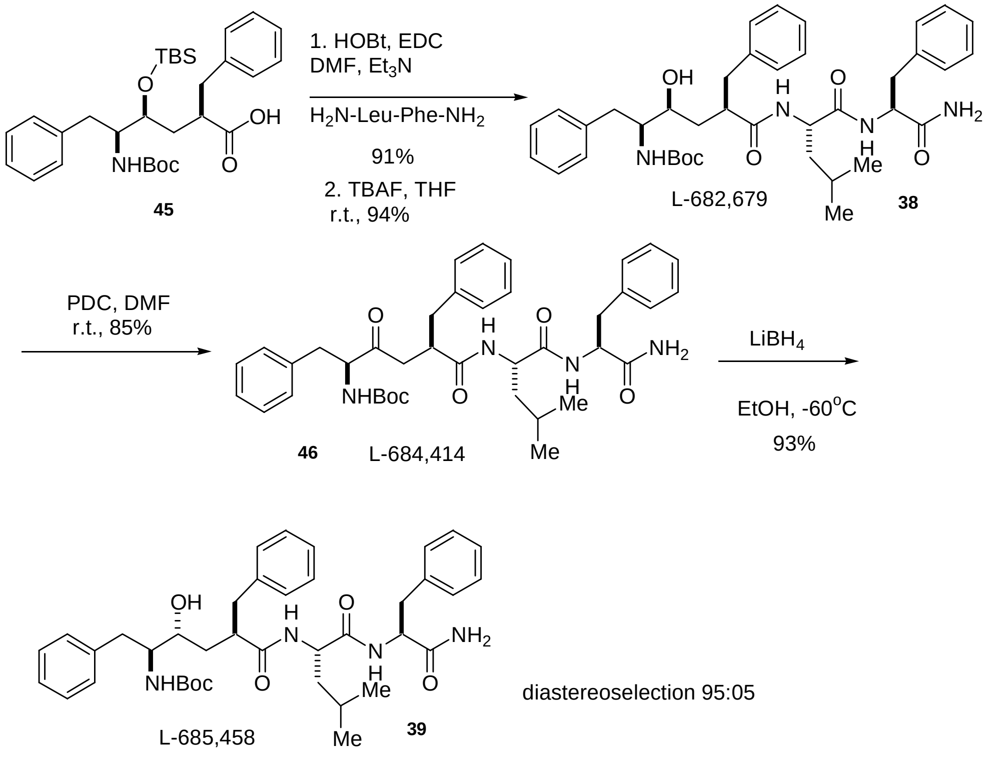
Basic hydrolysis of desired *trans*-lactone **43** (LiOH, 1,2-dimethoxyethane), silylation (TBSCl, imidazole, DMF, room temperature, 12h) of the resulting carboxylate, and selective desilylation of the acylsiloxy moiety (MeOH) cleanly provided **45** in excellent yield after purification by silica-gel flash chromatography (Scheme 16).



Scheme 16

Compound L-685,434 (**37**) was readily prepared from carboxylic acid **45** by a simple peptide coupling reaction with 1(*S*)-amino-2(*R*)-hydroxyindane **34** followed by TBS removal with TBAF in 70% yield for the 2-step sequence (Scheme 16).

Compound L-682,679 (**38**) is also prepared from carboxylic acid **45** and dipeptidic amine NH_2-Leu-Phe-NH_2 by a simple peptide coupling reaction followed by TBS deprotection with TBAF in 86% overall yield (Scheme 17).[31,32]



Scheme 17

Oxidation of the hydroxyl function in **38** with PDC in DMF gave inhibitor L-684,414 (**46**) in 85% isolated yield. Selective reduction of L-684,414 (**46**) with $LiBH_4$ gave γ-secretase inhibitor L-685,458 (**39**) in 93% yield and 95:5 diastereoselection (Scheme 17).[31,32]

Conclusions

We believe that this chemistry is truly significant in the context of acyclic diastereoselection and will prove to be useful in the synthesis of more complex molecules like polyacetate and polypropionate-derived natural products as well as in the synthesis of a variety of dipeptide isosteres with promising pharmacological activity.

Experimental Section

General Procedures. All reactions were carried out under an atmosphere of argon or nitrogen in flame-dried glassware with magnetic stirring. Dichloromethane, triethylamine, cyclohexane, and dimethylformamide were distilled from CaH_2. Tin tetrachloride was distilled from P_2O_5 and stored in a Schlenk flask. Dimethyl sulfoxide was distilled under reduced pressure from calcium hydride and stored over molecular sieves. THF, diethyl ether and toluene were distilled from sodium/benzophenone ketyl. Oxalyl chloride, dimethoxypropane, isobutyraldehyde, trimethylsilylmethyl chloride and $(c\text{-Hex})_2BCl$ were distilled immediately prior to use. MeOH was distilled from $Mg(OMe)_2$. TLC plates were silica gel 60 (GF 5-40-μm). Visualization was accomplished with either a UV lamp or I_2 staining. Chromatography on silica-gel (230-400mesh) was performed using forced-flow of the indicated solvent system (flash chromatography). Visualization was accomplished with UV light and an anisaldehyde, ceric ammonium nitrate stain, a heated phosphomolybdic acid or by I_2 staining. ^1H NMR spectra were recorded on either a Varian Gemini 300 (300MHz) or a Varian Inova 500 (500MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm or C_6D_6 at 7.15 ppm) unless otherwise indicated. Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, st = sextet, apt = apparent triplet, m = multiplet, b = broad, brs = broad singlet, brd = broad doublet, dq = doublet of quartets, dt = doublet of triplets, td = triplet of doublets, apqt = apparent quintet, apdt = apparent doublet of triplets, number of hydrogens, coupling constant(s) in Hz. Proton-decoupled ^{13}C NMR spectra were recorded on either a Varian Gemini 300 (75 MHz) or Bruker AC 300/P (75 MHz) spectrometers and are recorded in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm or C_6D_6 at 128 ppm) unless otherwise indicated. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded on a HP-5988-A GC-MS. Optical rotations were measured on a Polamat A polarimeter from Carl Zeiss Jen, using a 1 mL quartz cell, with mercury or sodium lamps, and are reported as follows: $[a]^{t(oC)}_{\lambda}$, (c g/100mL, solvent).

General procedure for the preparation of homoallylic alcohols 11-13, 15, 17, 20-22-23

To a solution of allylsilane **5** (1.5 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added $SnCl_4$ (1.5 mmol). The resulting solution was stirred at 0 °C for 5 min and then cooled to –78 °C when a solution of the corresponding aldehyde (1.5 mmol) in CH_2Cl_2 (2 mL) was added. This mixture was stirred for 2 h at –78 °C and quenched by the slow addition of a saturated aqueous solution of $NaHCO_3$ (5 mL) followed by CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10% EtOAc/hexane) gave the corresponding homoallylic alcohols.

(2*S*,4*S*)-6-Benzyl-2-[*tert*-butyl(dimethyl)silyloxy]-6-octen-4-ol (11). TLC: R*f* 0.20 (5% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.10 (s, 3H), 0.11 (s, 3H), 0.92 (s, 9H), 1.17 (d, *J* 6.2 Hz, minor isomer) + 1.20 (d, 3H, *J* 6.2 Hz), 1.45-1.63 (m, 2H), 2.04-2.26 (m, 2H), 3.39 (s, 2H), 3.86-4.06 + 4.08-4.26 (m, 2H), 4.88 (s, 1H), 4.94 (s, 1H), 7.16-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ -4.8, -4.6, -4.3, -3.8, 18.0, 18.1, 23.3, 24.5, 25.9, 43.1, 43.2, 44.0, 44.1, 44.6, 45.5, 65.9, 67.1, 68.9, 69.6, 113.9, 114.0, 126.0, 128.2, 128.9, 139.2, 145.6, 145.8.

(2*S*,4*S*)-6-[(*S*)-2-Benzyloxy-1-methylethyl]-2-[*tert*-butyl(dimethyl)silyloxy]-6-hepten-4-ol (12). TLC: R*f* 0.22 (10% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.05 (d, 3H, *J* 7.0 Hz), 1.19 (d, 3H, *J* 6.2 Hz), 1.58 (m, 2H), 2.18 (d, 2H, *J* 5.5

Hz), 2.49 (m, 1H), 3.23 (br s, 1H), 3.37 (dd, 1H, *J* 9.2 and 6.4 Hz), 3.49 (dd, 1H, *J* 9.2 and 7.7 Hz), 4.08 (m, 1H), 4.15 (m, 1H), 4.52 (s, 2H), 4.93 (s, 2H), 7.25-7.40 (m, 5H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ -4.8, -4.3, 17.6, 18.1, 23.8, 26.0, 39.2, 44.4, 45.3, 65.9, 66.6, 73.1, 74.7, 111.7, 127.5, 127.6, 128.2, 138.1, 149.1.

(2*S*,4*R*)-6-[(*R*)-2-Benzyloxy-1-methylethyl]-2-[*tert*-butyl(dimethyl)silyloxy]-6-hepten-4-ol (13). TLC: R*f* 0.24 (10% EtOAc/hexanes); ^{1}H NMR (CDCl$_3$, 300 MHz): δ 0.09 + 0.10 + 0.11 + 0.12 (s, 6H), 0.90 (s) + 0.91 (s, 9H), 1.07 (d, *J* 7.0 Hz) + 1.10 (d, 3H, *J* 7.0 Hz), 1.18 (d, *J* 5.9 Hz) + 1.20 (d, 3H, *J* 6.2 Hz), 1.50-1.65 (m, 2H), 2.16-2.24 (m, 2H), 2.49 (m, 1H), 3.30-3.45 (m, 2H), 3.51 (m, 1H), 3.90-4.22 (m, 2H), 4.52 (s, 2H), 4.93 (s, 2H), 7.25-7.40 (m, 5H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ -4.6, -3.9, 17.5, 18.1, 23.5, 24.3, 25.9, 29.8, 39.2, 43.9, 44.2, 45.1, 45.7, 66.5, 66.8, 68.3, 68.8, 71.1, 73.0, 74.6, 74.7, 111.7, 111.8, 125.9, 126.3, 127.5, 128.7, 130.2, 138.2, 148.8, 149.0.

(4*R*,5*S*,6*S*)-2-Benzyl-6-O-*tert*-butyldimethylsilyloxy-5,7-dimethyl-1-octen-4-ol (15). TLC R*f*: 0.48 (10% EtOAc/hexanes); [α]$^{20}_{D}$: +5.0 (*c* 2.18, EtOAc); ^{1}H RMN (CDCl$_3$, 300 MHz): δ 0.13 (s, 6H), 0.92 (d, 3H, *J* 7.0 Hz), 0.97 (br s, 15H, *J* 5.5 Hz), 1.69 (m, 1H), 1.89 (m, 1H), 1.96 (br s, 1H), 2.22 (d, 2H, *J* 6.6 Hz), 3.45 (br s, 2H), 3.58 (t, 1H, *J* 3.7 Hz), 3.85 (br s, 1H), 4.96 (br s, 1H), 5.02 (br s, 1H), 7.25-7.39 (m, 5H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ -3.6, -3.1, 9.6, 18.6, 18.8, 19.6, 26.5, 33.1, 40.5, 42.2, 43.4, 71.9, 79.8, 114.8, 126.7, 128.8, 129.4, 139.7, 146.6; IR (film): ν 3571, 3480, 3063, 3027, 3480, 2959, 2922, 2858, 1645, 1602, 1496, 1471, 1259, 1091, 1027, 826 cm^{-1}.

(2*S*,3*R*,4*R*)-6-[(1*R*)-2-Benzyloxy-1-methylethyl]-3-methyl-6-hepten-2,4-diol (17). TLC R*f*: 0.40 (10% EtOAc/hexanes); [α]$_D$: + 20.7 (*c* 0.42, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.87 (d, 3 H, *J* 6.8 Hz), 0.91 (d, 3H, *J* 6.3 Hz), 0.92 (s, 9H), 0.94 (d, 3H, *J* 6.8 Hz), 1.04 (d, 3H, *J* 6.8 Hz), 1.67 (m, 1H), 1.84 (m, 1H), 2.15 (dd, 1H, *J* 9.4 and 14.0 Hz), 2.23 (dd, 1H, *J* 3.7 and 13.9 Hz), 2.47 (m, 1H), 3.37 (dd, 1H, *J* 6.1 and 9.0 Hz), 3.48 (dd, 1H, *J* 8.1 and 9.0 Hz), 3.55 (t, 1H, *J* 4.1 Hz), 3.81 (m, 1H), 4.50 (s, 2H), 4.94 (s, 1H), 4.95 (s, 1H), 7.26–7.36 (m, 5H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ -3.9, -3.6, 9.8, 17.6, 18.1, 18.4, 19.5, 26.1, 32.6, 39.0, 40.6, 41.7, 71.0, 73.1, 74.6, 78.9, 111.9, 127.6, 127.7, 128.3, 138.1, 149.4; IR (film): ν 3471, 3065, 3025, 2963, 2922, 2854, 1641, 1464, 1258, 1105, 1047, 841, 773, 738, 698 cm^{-1}; HRMS Calcd. for C$_{26}$H$_{46}$O$_3$Si: 434,3216; found: 373.2499; MS (70 eV): m/z: 373 (3%), 305 (2%), 269 (5%), 245 (9%), 223 (4%), 187 (77%), 147 (43%), 115 (7%), 91 (100%).

(3*S*,4*R*,5*S*)-7-[(*S*)-2-Benzyloxy-1-methylethyl]-3-[*tert*-butyl(dimethyl)silyloxy]-2,4-dimethyl-7-octen-5-ol (22). TLC: R*f* 0.20 (5% EtOAc/hexanes); ^{1}H NMR (CDCl$_3$, 300 MHz): δ 0.11 (s, 3H), 0.13 (s, 3H), 0.91 (d, 3H, *J* 7.0 Hz), 0.93 (d, 3H, *J* 6.6 Hz), 0.94 (s, 9H), 0.99 (d, 3H, *J* 7.0 Hz), 1.10 (d, 3H, *J* 7.0 Hz), 1.70 (ddd, 1H, *J* 7.0, 3.7 and 1.8 Hz), 1.92 (m, 1H), 2.13 (dd, 1H, *J* 14.0 and 6.0 Hz), 2.29 (dd, 1H, *J* 14.0 and 7.7 Hz,), 2.49 (m, 1H), 3.30 (s, 1H), 3.33 (m, 1H), 3.48 (dd, 1H, *J* 6.2 and 3.7 Hz), 3.53 (dd, 1H, *J* 9.2 and 5.9 Hz,), 4.25 (ddd, 1H, *J* 7.7, 6.2 and 1.8 Hz), 4.52 (s, 2H), 4.91 (s, 1H), 4.95 (s, 1H), 7.20-7.40 (m, 5H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ -3.6, -3.5, 11.8, 17.4, 18.5, 19.1, 19.9, 26.3, 32.2, 38.0, 39.3, 41.0, 68.7, 73.0, 74.7, 83.1, 111.3, 127.3, 127.5, 128.2, 138.3, 148.9.

(3*S*,4*R*,5*R*)-7-[(*R*)-2-Benzyloxy-1-methylethyl]-3-[*tert*-butyl(dimethyl)silyloxy]-2,4-dimethyl-7-octen-5-ol (23). TLC: R*f* 0.24 (5% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.91 (d, 3H, *J* 7.0 Hz), 0.92 (d, 3H, *J* 6.6 Hz), 0.93 (d, 3H, *J* 7.0 Hz), 0.94 (s, 9H), 1.08 (d, 3H, *J* 7.0 Hz), 1.75-1.90 (m, 2H), 2.00 (dd, 1H, *J* 14.3 and 10.3 Hz), 2.42 (br d, 1H, *J* 14.3 Hz), 2.50 (m, 1H), 2.55 (brs, 1H), 3.40 (dd, 1H, *J* 9.0 and 6.6 Hz), 3.53 (dd, 1H, *J* 9.0 and 7.5 Hz), 3.60 (ap t, 1H, *J* 4.6 Hz), 3.76 (ddd, 1H, *J* 10.3, 8.4 and 2.6 Hz), 4.52 (s, 2H), 4.94 (s, 1H), 4.98 (s, 1H), 7.25-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ -4.1, -3.7, 14.1, 17.9, 18.4, 18.5, 20.6, 26.2, 32.1, 39.0, 41.4, 43.2, 70.6, 73.0, 74.7, 79.8, 111.4, 127.4, 127.5, 128.2, 138.1, 149.4.

General procedure for the preparation of homoallylic alcohols 28a-c-30b-c

To a solution of allylsilane (1.5 mmol) in CH_2Cl_2 (5 mL) at r.t. was added $SnCl_4$ (1.4 mmol). The resulting solution was stirred at rt for 2 h and then cooled to –78 °C when a solution of the corresponding aldehyde (1.4 mmol) in CH_2Cl_2 (2 mL) was added. This mixture was stirred for 2 h at –78 °C and quenched by the slow addition of a saturated aqueous solution of $NaHCO_3$ (5 mL) followed by CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (20-30% EtOAc/hexane) gave the corresponding homoallylic alcohols.

(4*S*,5*S*)-5-[*N*-(*tert*-Butoxycarbonyl-(*S*)-phenylalanyl)amino]-1-hexenyl-4-ol (28a). TLC: R*f* 0.21 (35% EtOAc/hexane); mp 100.3-101.9 ^{O}C; [α]$^{20}_{D}$: -17.8 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.96 (d, *J* 6.9 Hz, minor isomer) and 1.06 (d, 3H, *J* 6.9 Hz), 1.39 (s, 9H), 1.84 (m, 1H, minor isomer), 1.96 (m, 2H), 2.52 (br s, 1H), 2.97 (d, 2H, *J* 6.9 Hz), 3.41 (m, 1H), 3.84 (m, 1H), 4.26 (m, 1H), 5.02 (m, 2H), 5.18 (m, 1H), 5.60 (m, 1H), 6.22 (m, minor isomer) and 6.29 (m, 1H), 7.13-7.24 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.5 (minor isomer), 17.8, 28.2, 38.4 (minor isomer), 38.5, 48.6, 49.0 (minor isomer), 56.0, 72.5 (minor isomer), 72.9, 80.1, 117.6 (minor isomer), 117.9, 126.8, 128.5, 129.3, 134.4 (minor isomer), 136.6, 155.4, 170.7, 171.1; IR (KBr): ν 3351, 3072, 2980, 1682, 1641, 1549, 1520, 1457, 1369, 1293, 1247, 1165, 987, 755, 703 cm^{-1}; Elemental analysis calcd. for $C_{20}H_{30}N_2O_4$: C 66.27,H 8.34, N 7.73, found: C 65.60; H 8.17, N 7.74; HRMS calcd. for $C_{20}H_{30}N_2O_4$: 362.2206; found: 362.2206.

(4*S*,5*S*)-5-[*N*-(*tert*-Butoxycarbonyl-(*S*)-phenylalanyl)amino]-6-methyl-1-heptenyl-4-ol (28b). TLC: R*f* 0.22 (35% EtOAc/hexane); mp148.6-150.8 ^{O}C; [α]$^{20}_{D}$: -40,0 (c 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84 (d, 3H, *J* 6.9 Hz), 0.93 (d, 3H, *J* 6.6 Hz), 1.41 (s, 9H), 1.83 (m, 2H), 1.93 (m, 1H), 3.08 (m, 2H), 3.46 (ap t, 1H), 3.76 (m, 1 H), 4.35 (ap q, 1H, *J* 7.3 Hz), 5.10 (m, 2H), 5.18 (br d, 1H, *J* 8,8 Hz), 5.75 (m, 1H), 6.32 (br d, *J* 9,5 Hz), 7.18-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.3 19.7, 28.2, 30.0, 37.9, 39.2, 56.3, 58.1, 69.4, 80.2, 118.2, 126.9, 128.6, 129.3, 134.0, 136.6, 155.0, 171.6; IR (KBr): ν 3345, 3078, 2963, 2933, 1682, 1635, 1549, 1514, 1422, 1369, 1299, 1165, 1038, 703 cm $^{-1}$; HRMS calcd. 390.2519; found:390.2512.

(4*S*,5*S*) 5-[*N*-(*tert*-Butoxycarbonyl -(*S*) -phenylalanyl) amino]7methyl1octenyl4-ol (28c). TLC: R*f* 0.23

(35% EtOAc/hexane); mp 143.8-145.2 ^{O}C; $[\alpha]^{20}_{D}$: -34.0 (c 1.0, EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.87 (d, 3H, *J* 6.6 Hz), 0.90 (d, 3H, *J* 6.6 Hz), 1.37 (m, 2H), 1.42 (s, 9H), 1.87 (m, 1H), 2.07 (br s, 2H), 3.09 (br d, 2H, *J* 6.2 Hz), 3.53 (m, 1H), 3.92 (m, 1H), 4.32 (ap q, 1H, *J* 7.3 Hz), 5.02 (m, 2H), 5.14 (br s, 1H), 5.77 (m, 1H), 6.06 (d, 1H, *J* 9.5 Hz), 7.18-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.0, 23.2, 24.5, 28.2, 37.7, 38.8, 41.5, 50.8, 56.2, 72.2, 80.3, 118.2, 126.9, 128.7, 129.3, 134.5, 136.6, 155.4, 171.1; IR (KBr): ν 3438, 3351, 3078, 2951, 1775, 1687, 1641, 1555, 1520, 1363, 1293, 1241, 1178, 1120, 900, 870, 703 cm $^{-1}$; Elemental analysis calcd. for $C_{23}H_{36}N_2O_4$: C 68.29, H 8.97, N 6.92; found: C 68.47, H 8.97, N 6.92; HRMS calcd. for $C_{23}H_{36}N_2O_4$: 404.2675; found: 404.2601.

(4*S*,5*S*)-5-[*N*-(*tert*-Butoxycarbonyl-(*S*)-phenylalanyl)amino]-6-methyl-2-benzyl-1-heptenyl-4-ol (30b). TLC: R*f* 0.23 (35% EtOAc/hexane); mp 132.5-134.3 ^{O}C; $[\alpha]^{20}_{D}$: -26.3 (c 0.76, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.81 (d, 3H, *J* 6.6 Hz), 0.87 (d, 3H, *J* 6.6 Hz), 1.40 (s, 9H), 1.76 (m, 2H), 1.87 (m, 2H), 3.05 (m, 2H), 3.31 (br d, 2H, *J* 3.7 Hz), 3.41 (ap t, 1H, *J* 8.8 Hz), 3.74 (br d, 1H, *J* 7.7 Hz), 4.33 (ap q, 1H, *J* 7.3 Hz), 4.8 (br s, 1H), 4.87 (br s, 1H), 5.00 (br d, 1H, *J* 8.1 Hz), 6.20 (br d, 1H, *J* 9.5 Hz), 7.24 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.3, 19.6, 28.2, 30.3, 37.9, 41.2, 42.8, 56.3, 58.2, 67.2, 80.2, 115.2, 126.3, 126.9, 128.4, 128.6, 128.9, 129.3, 136.6, 138.9, 145.2, 155.4, 171.2; IR (KBr): ν 3351, 3084, 3031, 2974, 2933, 2869, 1682, 1641, 1549, 1520, 1450, 1363, 1293, 1241, 1165, 1044, 870, 755, 703 cm $^{-1}$; Elemental analysis calcd. for $C_{29}H_{40}N_2O_4$: C 72.47, H 8.39, N 5.83; found: C 71.37, H 8.42, N 5,95; HRMS calcd. for $C_{29}H_{40}N_2O_4$: 480.2988; found: 480.2912.

(4*S*,5*S*)-5-[*N*-(*tert*-butoxycarbonyl-(*S*)-phenylalanyl)amino]-7-methyl-2-benzyl-1-octenyl-4-ol (30c). TLC: R*f* 0.25 (35% EtOAc/hexane); mp 127.8-131.5 ^{O}C; $[\alpha]^{20}_{D}$: -15.7 (c 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85 (d, 3H, *J* 6.2 Hz), 0.88 (d, 3H, *J* 6.2 Hz), 1.42 (s, 9H), 1.80 (m, 1H), 1.99 (m, 2H), 3.03 (d, 2H, *J* 7.3 Hz), 3.30 (ap q, 2H, *J* 8.2 Hz), 3.55 (br d, 1H, *J* 8.1 Hz), 3.85 (m, 1H), 4.32 (ap q, 1H, *J* 6.6 Hz), 4.83 (br s, 1H), 4.85 (br s, 1H), 4.98 (br d, 1H, *J* 7.3 Hz), 6.0 (br d, 1H, *J* 9.1 Hz), 7.16-7,30 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.1, 23.1, 24.6, 28.2, 38.0, 40.7, 41.8, 42.7, 50.9, 56.1, 70.1, 80.2, 115.0, 126.3, 126.9, 128.4, 128.6, 128.9, 129.3, 136.6, 138.9, 145.3, 155.3, 170.9; IR (KBr): ν 3348, 3062, 3022, 2974, 2918, 1655, 1500, 1457, 1374, 1252, 1164, 1047, 740, 700 cm $^{-1}$; Elemental analysis calcd. for $C_{30}H_{42}N_2O_4$: C 72.84, H 8.56, N 5.66; found: C 72.69, H 8.40, N 5.58; HRMS calcd. for $C_{30}H_{42}N_2O_4$: 494.3144; found: 494.3138.

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