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Asymmetric Synthesis of Homoallylic Amines and Functionalized Pyrrolidines via Direct Amino-Crotylation of In Situ Generated Imines

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Abstract—The asymmetric synthesis of functionalized homoallylic amines and silyl functionalized pyrrolidines through the Lewis acid promoted condensation of chiral (*E*)-crotylsilanes with sulfonyl imines and in situ generated *N*-acyl imines is described. We had anticipated that this bond construction could be used in the asymmetric synthesis of the N-terminal amino acid subunit of the nikkomycins. Aryl sulfonyl imines condense with chiral silane reagents in the presence of $BF_3{\cdot}OEt_2$ to form homoallylic arylsulfonyl amines with useful levels of *syn* selectivity. For cases involving aryl *N*-acyl imines we have learned that the temperature controls the course of the reaction. For instance, at temperatures of −78°C or below the major product is the pyrrolidine, while at higher temperatures (−30 to −20°C) the homoallylic amine is produced. For the cases studied, the [3+2]-annulation is limited to aryl imine derivatives, as alkyl- and branched- imines failed to produce the pyrrolidine derivatives: higher reaction temperatures promote the conversion of the annulation product to the homoallylic amines. In double stereodifferentiating reactions with in situ generated imines, good levels of selectivity were achieved in the formation of secondary amines bearing *syn–anti* and *syn–syn* stereochemical triads.

Introduction

The development of efficient, practical asymmetric syntheses of α- and β-amino acids has been an area of interest in the past several years.[1] The availability of these compounds in an enantiomerically enriched form is important due to their wide use as synthetic intermediates in the pharmaceutical and chemical industry. Various syntheses of natural and unnatural nonproteinaceous amino acid derivatives have already been established.[2] α-Amino acids are important pharmaceutical building blocks for their incorporation into enzyme inhibitors,[3] as well as conformational modifiers in physiologically active peptides.[4] The β-amino acids are potentially valuable for the chemical synthesis of peptidomimetics,[5] functionalized β-lactams, and some naturally occurring materials. Interest in biologically and synthetically important amines with well-defined stereochemistry has often contributed to the development of new reaction methodology for their synthesis. Methodology designed for the stereoselective synthesis of β-amino acid synthons has evolved from simple diastereoselective processes involving the use of enol derivatives and allylmetals in addition to chiral imines.[1a]

In studies directed toward the synthesis of nikkomycin B,[6] which belong to a group of potent chitin synthetase inhibitors with fungicidal, insecticidal, and acaricidal activity (Fig. 1).[7] We required the development of an efficient method for the synthesis of enantiomerically enriched homoallylic amines (β-amino acid synthons). These chiral amines can be obtained from the addition of chiral (*E*)-crotylsilane reagents to achiral and chiral in situ generated imines.[8] In this paper we report our results on the asymmetric synthesis of homoallylic amines via direct amino-crotylation of in situ generated *N*-acyl and *N*-sulfonyl imines. In certain cases, functionalized pyrrolidines are produced from these reactions through a [3+2]-annulation, which involves the internal trapping of the intermediate bridged-carbocation.

The retrosynthetic analysis of nikkomycin B, illustrated in Fig. 1, resulted in the disconnection of the amide bond, yielding two major fragments, the N-terminal amino-acid **3** and the polyoxin C **2**. Further disconnection of **3** produced homoallylic carbamate **4** where the trisubstituted olefin would serve as a precursor to an aryl ketone. This material could be derived from the crotylation of β-benzyloxy aldehyde **5** and (*R*)-β-aryl substituted crotylsilane **6j**. *Syn*homoallylic acylamine **4** possesses structural similarities to the 1,2-*syn*-stereochemistry of the nikkomycins and can serve as a precursor to the N-terminal amino acid subunit **3**. The versatility of these reagents has been

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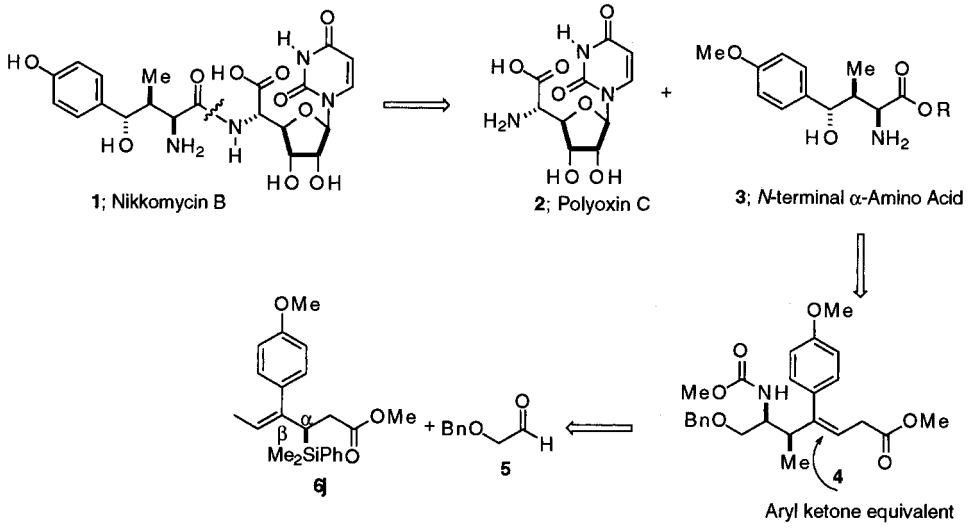


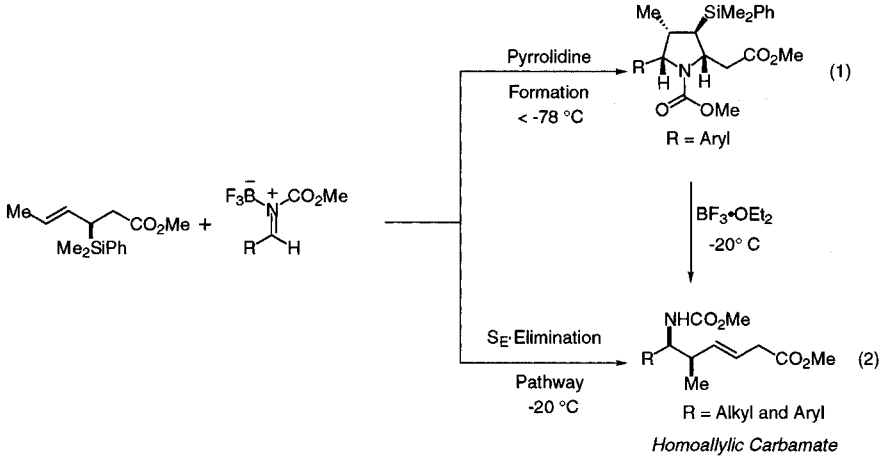
Figure 1. Retrosynthetic analysis of nikkomycin B.

illustrated by the synthesis of functionalized homoallylic ethers, homoallylic alcohols, tetrahydrofurans, cyclopentanes, Δ^2-isoxazolines, silylsubstituted pyrrolidines, allylic amines, and *C*-glycosides.[9] The application of chiral silanes in the synthesis of complex natural products has recently been demonstrated in our laboratories.[10]

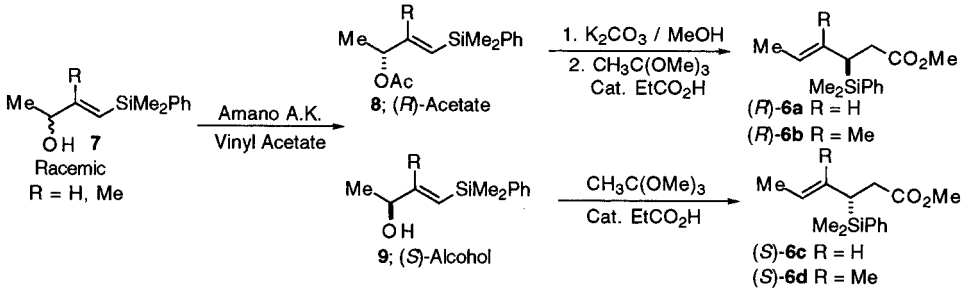
The Lewis acid promoted condensation between chiral (*E*)-crotylsilanes and in situ generated achiral *N*-acylimines produces the *syn* homoallylic *N*-acylamines or the *N*-acyl pyrrolidines through a [3+2] annulation. Both reactions occur with equally high levels of diastereoselectivity (Scheme 1, Eqs. (1) and (2)). Raising the temperature from −78 to −20°C can effect the opening of the resulting pyrrolidine product. However, for the cases examined, this annulation appears to be limited to aryl imine derivatives as the alkyl and branched imines failed to produce the pyrrolidine derivatives affording clean homoallylic amine products instead. Higher reaction temperatures resulted in a direct and efficient conversion to the homoallylic amines. The scope of this methodology was extended to produce homoallylic *N*-tosyl amines, and aryl imines, which should be applicable to the synthesis of the nikkomycins.

Synthesis of the chiral crotylsilanes

The synthesis of the silane reagents, summarized in Scheme 2, was initiated with an enzymatic resolution (*Pseudomonas* lipase)[11] of the racemic (*E*)-vinylsilanes which afforded the pure (*S*,*E*)-vinylsilane **9** and the (*R*,*E*)-vinyl acetate **8** in high enantiomeric purity after separation on SiO_2. In the course of our studies, we have learned that these (*E*)-vinyl silanes are excellent substrates for the enzymatic resolution; however, the corresponding (*Z*)-vinyl silanes showed no reactivity. A $LiAlH_4$ reduction or base catalyzed hydrolysis (K_2CO_3, MeOH) of the (*R*)-acetate provided the desired (*R*,*E*)-alcohol. The individual secondary allylic alcohols were subjected to an *ortho*-ester Claisen rearrangement to produce the chiral silane reagents (*R*)-**6a/6b** and (*S*)-**6c/6d**, respectively. As anticipated, the sigmatropic rearrangement was highly stereospecific (ee>96%) and highly stereoselective with respect to the configuration of the *trans*-double bond, which was exclusively produced.[12]



Scheme 1. Asymmetric addition to in situ generated iminium ions.



Scheme 2. Preparation of chiral (*E*)-crotylsilanes.

Direct amino crotylation reactions

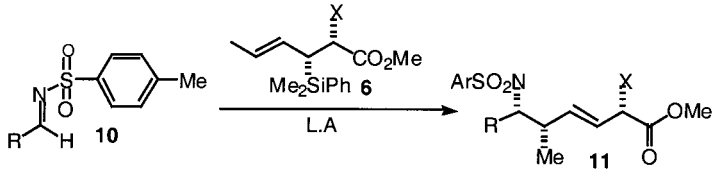
Our initial attempts at the synthesis of homoallylic amines was first studied in the Lewis acid catalyzed addition of chiral silane reagents to simple alkyl and aryl imines; however, their lack of reactivity toward the nucleophilic addition led to the examination of the more electrophilic *N*-tosylimines **10**.[13] The initial results of this study are summarized in Table 1.

In general, good to modest chemical yields were obtained (not optimized) and, except for one case (entry 2) only the unsubstituted silane reagents were examined.

The *N*-tosyl iminium ions were generated in situ from *p*-toluene-sulfonamide, the appropriate aldehyde, and silane **6c**. In the presence of $BF_3{\cdot}OEt_2$, the combination of reagents cleanly afforded the *N*-tosyl homoallylic amines **13** with high yields (71–90%) and high levels of diastereoselection (10:1 to 30:1 *syn–anti*) (see Table 2).

While attempting to expand the scope of these reagents in the synthesis of chiral amines, it was found that in situ generated acyliminium ions, formed from aldehydes and acetals with amines or carbamates, readily condensed with the silane reagents to form homoallylic amines and, in certain instances, pyrrolidines. Based on these results, an

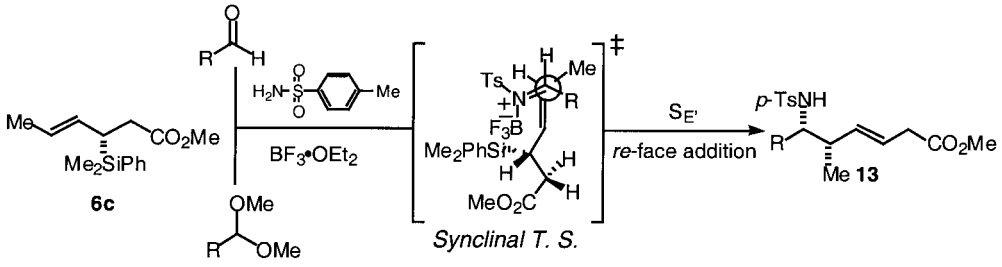
Table 1. Diastereoselective addition reactions of *N*-tosylimines with (*E*)-crotylsilane



Entry	Sulfonyl imine	Silane	Lewis acid/conditions	Yield(%)[a]	dr (*syn*/*anti*)[b]
1	**10a**; R=Ph	**6a**; (3*R*), X=H	$TiCl_4$/−78°C→rt 20 h	**11a**; 64	>30:1
2	**10b**; R=*p*-MeOPh	**6e;** (2*S*, 3*S*) X=OMe	$SnCl_4$/0°C→rt 24 h	**11b**; 82	5:1
3	**10b**	**6a**	$BF_3{\cdot}OEt_2$/−10°C→rt 16 h	**11c**; 42	10:1
4	**10b**	**6a**	$BF_3{\cdot}OEt_2$/−10°C→rt 40 h	**11d**: 67	10:1
5	**10c**; R=^{t}Bu	**6a**	TMSOTf/−20°C→rt 12 h	**11e**; 70	30:1

[a] Yield was based on the amount of major diastereomer obtained after SiO_2 chromatography.
[b] Ratios were determined by ^{1}H NMR.

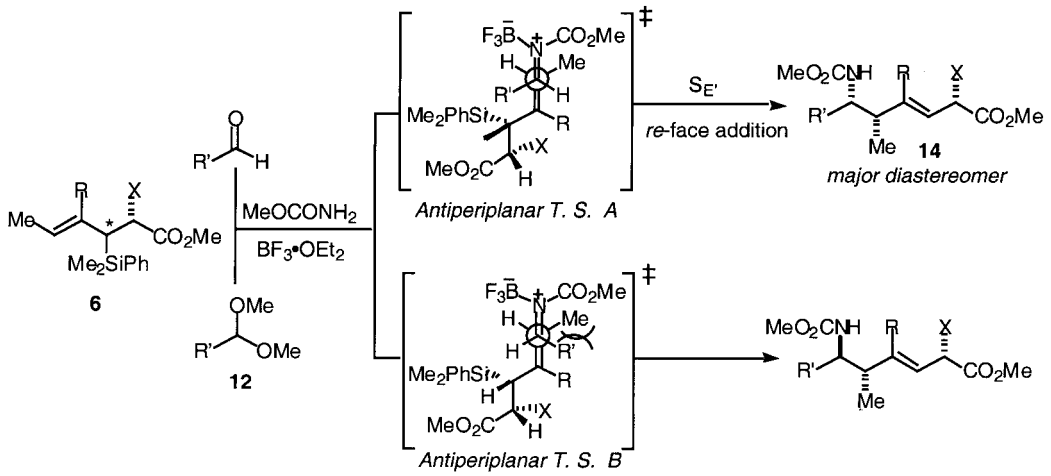
Table 2. Asymmetric synthesis of functionalized homoallylic *N*-tosyl imines



Entry[a]	Acetal/aldehyde	Yield (%)[b]	dr[c]
1	**12a**; R=Ph	**13a**; 80	20:1
2	**12b**; R=^{t}Bu	**13b**; 90	30:1
3	**12c**; R=$BnOCH_2$	**13c**; 71	10:1

[a] In all cases, silane **6c** was used.
[b] Yield was based on the amount of major diastereomer obtained after purification on SiO_2.

Table 3. Asymmetric synthesis of functionalized homoallylic carbamates



Entry	Silane	Acetal/aldehyde	Yield (%)[a]	dr (*syn*/*anti*)[b]
1	**6a**; (3*R*), R=H, X=H	**12a**; R′=Ph	**14a**; 87	30:1
2	**6e**; (2*S*,2*S*), R=H, X=OMe	**12a**	**14b**; 79	9:1
3	**6f**; (2*R*,2*S*), R=H, X=Me	**12a**	**14c**; 73	30:1
4	**6a**; (3*R*), R=H, X=H	**12d**; R′=$BnOCH_2CH_2$	**14d**; 65	30:1
5	**6a**; (3*R*), R=H, X=H	**12c**; R′=$BnOCH_2$	**14e**; 87	30:1
6	**6a**; (3*R*), R=H, X=H	**12e**; R′=Pr	**14f**; 68	30:1
7	**6a**; (3*R*), R=H, X=H	**12f**; R′=^{t}Bu	**14g**; 72	30:1
8	**6d**; (3*S*), R=Me, X=H	**12c**	**14h**; 77	24:1
9	**6d**; (3*S*), R=Me, X=H	**12f**	**14i**; 70	8:1
10	**6d**; (3*S*), R=Me, X=H	**12a**	**14j**; 89	1.2:1

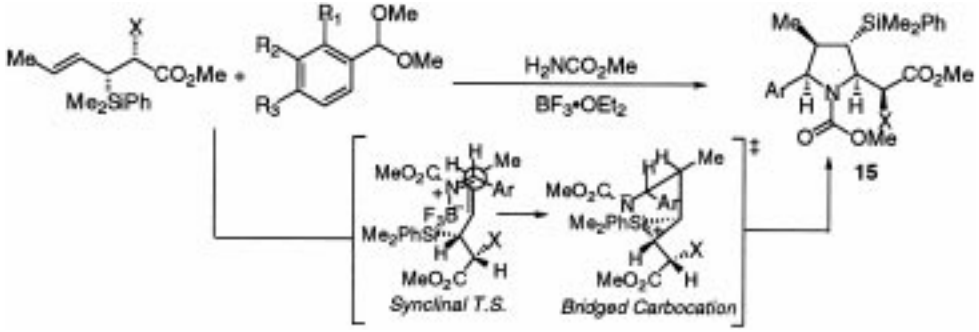
[a] Yield was based on the amout of major diastereomer obtained after SiO_2 chromatography.
[b] Ratios were determined by ^{1}H NMR.

efficient procedure for the direct asymmetric amino-crotylation and a [3+2]-pyrrolidine annulation was developed.[8]

Further efforts to probe the reactivity of in situ generated iminium ions in the condensation with (*E*)-crotylsilanes led us to investigate the use of *N*-acyl imine systems. We have learned that the silane reagents can reliably be used in highly diastereo- and enantioselective additions to in situ-generated *N*-acyl imines under mild conditions (−78⟶−20°C). It was shown that by lowering the reaction temperature the *N*-carbamoyl pyrrolidines are produced from aryl acetals or aldehydes. On the other hand, only acyclic homoallylic carbamates were detected and isolated when the reaction was warmed to −20°C. Based on these results, the scope of the reaction was extended to include the use of β-methyl substituted silane (Table 3, entries 8 through 10). Those reactions produced the amines with tri-substituted olefins.

In most cases high yields (ranging from 65 to 89%) and

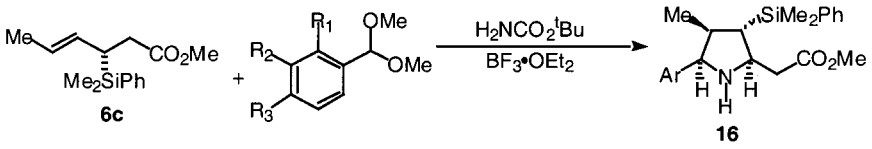
Table 4. Asymmetric synthesis of functionalized pyrrolidones with methyl carbamate



Entry	Silane	Acetal/aldehyde	Yield (%)[a]	dr[b]
1	**6a**; (3*R*) X=H	**12a**; R_1=R_2=R_3=H	**15a**; 68	30:1
2	**6e**; (2*S*,3*S*) X=OMe	**12a**	**15b**; 72	20:1
3	**6e**	**12g**; R_1=R_2=H, R_3=Cl	**15c**; 47	20:1
4	**6e**	**12h**; R_1=R_2=OMe, R_3=H	**15d**; 53	10:1

[a] Yield was based on the amount of major diastereomer obtained after SiO_2 chromatography.
[b] Ratios were determined by ^{1}H NMR.

Table 5. Asymmetric synthesis of functionalized pyrrolidines with *tert*-butyl carbamate



Entry[a]	Acetal/aldehyde	Yield (%)[b]	dr[c]
1	**12a**; R_1=R_2=R_3=H	**16a**; 89	30:1
2	**12g**; R_1=R_2=H, R_3=OMe	**16b**; 74	30:1
3	**12h**; R_1=R_2=OMe, R_3=H	**16c**; 78	30:1

[a] In all cases, silane **6c** was used.
[b] Yield was based on the amount of major diastereomer obtained after SiO_2 chromatography.
[c] Ratios were determined by ^{1}H NMR.

useful levels of diastereoselection were obtained, and often the *anti* diastereomer could not be detected by ^{1}H NMR (depicted in the table as dr=30:1). Only three cases did not exhibit useful selectivity (entries 2, 9 and 10). The difference in the level of selectivity observed in Table 3 is perhaps best explained based on the size of the aldehyde or acetal substituent used. For instance, this range can be rationalized using a steric argument based on the proposed open transition states (A and B). Thus, high levels of selectivity are observed for the sterically demanding substituents (entries 4 through 8) that preferentially react via transition state A. However, the planar nature of the phenyl ring allows for minimal interaction in either transition state A or B, thereby accounting for the low levels of facial bias with benzaldehyde (entries 2 and 10). The reaction was then studied for the formation of pyrrolidines **15** utilizing methyl carbamate; the results obtained are summarized in Table 4.

Based on the high levels of selectivity and on the high yields obtained in the pyrrolidine formation utilizing methyl carbamate, *tert*-butyl carbamate was used, anticipating this would be a more labile group, which would directly afford the free pyrrolidines **16** (see Table 5).

As anticipated, the annulation reaction with *tert*-butylcarbamate derived iminium ion took place with high levels of diastereoselection and in high yields. For the examples surveyed in this study, the deacylated pyrrolidines were isolated rather than the *N*-carbamoyl systems, as the intermediate product (amine or pyrrolidine) undergoes deacylation under the reaction conditions.

Double stereodifferentiating addition reactions

Lewis acid promoted allyl- and crotylation reactions of chiral α-substituted aldehydes have been extensively studied and continue to be an active area of research.[14] By analogy, these reagents may be thought of as propionate and acetate-enolate equivalents, for diastereo- and enantioselective construction of stereochemically well defined homoallylic alcohols (β-hydroxy carbonyl synthons). Because these reactions complement the enolate-based aldol and aldol surrogates they belong to an important group of organometallic reagents available for the control of acyclic stereochemistry. During the course of this Lewis acid catalyzed addition, the emerging hydroxyl bearing stereocenter is generally controlled by the inherent diastereofacial bias of the aldehyde.[15] This reaction is consistent with the stereochemical outcome of the Mukaiyama aldol.[16] In an earlier report, we described the results of double stereodifferentiating crotylation reactions with chiral silane reagents. We learned that there is considerable mechanistic homology with the Mukaiyama aldol; the stereochemical course of these double stereodifferentiating crotylation reactions is determined by the local chirality of the individual reaction partners. We have demonstrated that under non-chelation reaction conditions the diastereomeric relationships between α-methyl and β-alkoxy group of the chiral aldehyde does not reinforce carbonyl π-facial selectivity.[17]

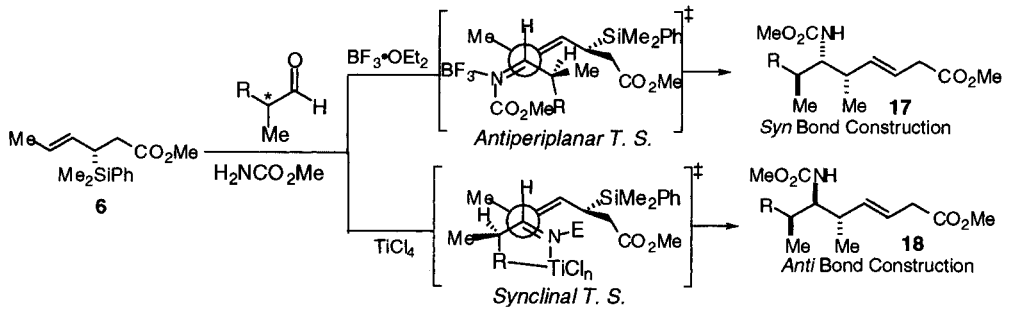
The addition of (*E*)-crotylsilanes to achiral in situ generated iminium ions proved efficient as well as highly diastereoselective. This led us to study the amino crotylation process with chiral imines. Based on the previous results with chiral aldehydes,[15b] the prediction was made that a *syn* crotylation will be favored when catalyzed with $BF_3{\cdot}OEt_2$ (a mono dentate Lewis acid), indicating that the silane reagent will override the chirality associated with the aldehyde (antiperiplanar transition state).

The reaction using methylcarbamate as the amine source was surveyed with the monodentate Lewis acid $BF_3{\cdot}OEt_2$ and three different chiral aldehydes **12i**–**12k** (Table 6). In general, the reactions were high yielding (73–85%) with levels of diastereoselectivity ranging from 4:1 to 30:1. Based on the results of these experiments and our previous efforts in this area with chiral α-substituted aldehydes,[18] and α-amino aldehydes,[19] *anti* crotylation products were obtained with $TiCl_4$ (a bidentate Lewis acid) and an oxygen protecting group that would enhance chelation (synclinal transition state). This concept is illustrated in with entries 6 and 7 (Table 6). Accordingly, the stereochemistry of the reaction of **12i** and **12j** are in expectation with previous observations with chiral aldehydes.[18,19]

Stereochemical assignment

The stereochemical assignment of the diastereomers was determined by measurement of the three-bond coupling constants ($^3J_{H4,\,H5}$) after conversion to their oxazolidinones (Scheme 3). Their individual synthesis required oxidative cleavage of the *trans* olefin of **17a**, **17b** and **17f**, and subsequent reduction of the intermediate aldehyde to the corresponding alcohol which was then cyclized in the presence of K_2CO_3 (refluxing toluene) to afford the oxazolidinones

Table 6. Representative double stereodifferentiating reactions



Entry	Silane	Lewis Acid	Aldehyde	Major Product [a]	Yield, % [b]	dr [c] (*syn / anti*)
1	**6c**; (3*S*)	BF_3•OEt_2	BnO, Me, **12i**	MeO$_2$CNH, BnO, Me, Me, CO_2Me	**17a**; 85	30 : 1
2	**6c**	BF_3•OEt_2	BnO, Me, **12j**	MeO$_2$CNH, BnO, Me, Me, CO_2Me	**17b**; 82	24 :1
3	**6c**	BF_3•OEt_2	BnO, Me, **12k**	MeO$_2$CNH, BnO, Me, Me, CO_2Me	**17c**; 87	5 :1
4	**6c**	BF_3•OEt_2	TBDPSO, Me, **12l**	MeO$_2$CNH, TBDPSO, Me, Me, CO_2Me	**17d**; 73	30 : 1
5	**6a**; (3*R*)	BF_3•OEt_2	**12j**	MeO$_2$CNH, TBDPSO, Me, Me, CO_2Me	**17e**; 80	8 : 1
6	**6c**	$TiCl_4$	**12i**	NH_2, BnO, Me, Me, CO_2Me	**17f**; 50	1 : 30
7	**6c**	$TiCl_4$	**12j**	MeO$_2$CN H, BnO, Me, Me, CO_2Me	**17g**; 35[d]	1 : 8

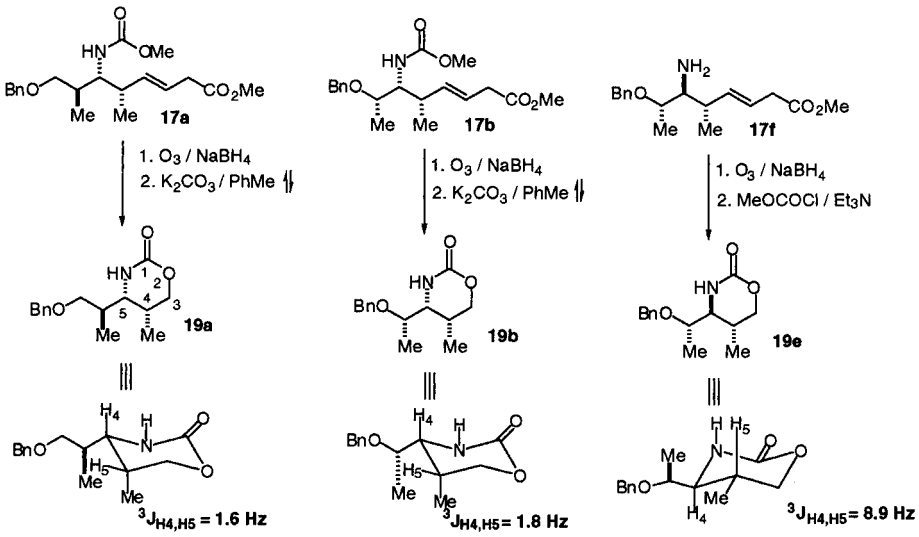
[a] All reactions were run in 0.1 M CH_2Cl_2 with BF_3·OEt_2 as the Lewis acid. The iminium ion was generated in situ at −78°C and the reaction was stirred at −35°C for 24 to 30 h before being diluted with saturated aqueous $NaHCO_3$.
[b] Yield was based on the amount of major diastereomer obtained after SiO_2 chromatography.
[c] Ratios determined by ^{1}H NMR.
[d] The reaction also provided the free amine (ca. 35%) and debenzylated material (ca. 10%).

19a,**19b**. Oxazolidinone **19f** was obtained directly from the amino alcohol **17f** in the presence of methylchloroformate and trimethylamine. Stereochemical assignment for the remaining crotylation products **17c**, **17d**, and **17e** was based on analogy with **17a** and **17b**, and with **17f** in the case of homoallylic carbamate **17g**.

The stereochemical assignment of the homoallylic carbamates was accomplished by homonuclear decoupling experiments on the individual diastereomeric oxazolidinones. The $J_{H4,\ H5}$ coupling constants were determined to be 1.6 and 1.8 Hz for the syn diastereomers **19a** and **19b** and 8.9 Hz for the anti crotylation product **19e**. Those *J* values are consistent with a 4,5-*syn* relationship between the emerging methyl group from the silane reagent and the C–N bond and a 4,5-*anti* relationship for **19e**.

Summary

Asymmetric synthesis of functionalized homoallylic amines



Scheme 3. Stereochemical assignment.

and silyl functionalized pyrrolidines through the Lewis acid promoted condensation of chiral (*E*)-crotylsilanes with in situ generated *N*-acyl imines were found to be highly diastereoselective. This methodology should be applicable to the preparation of a wide range of amino acid synthon equivalents, such as the one found in the nikkomycins. We anticipate that the enhanced selectivity exhibited by the chiral silane reagents in double stereodifferentiating reactions will prove useful in the synthesis of natural products bearing unusual amino acids.

Experimental

^{1}H NMR spectra were recorded on a Varian Unity (400 MHz) spectrometer at ambient temperature. Data are reported as follows: chemical shift in ppm from internal standard δ scale, multiplicity (b=broad, s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet), integration, and coupling constant (Hz). ^{13}C NMR were recorded on a Jeol (67.5 Hz) and Gemini Varian (150 Hz), spectrometers at ambient temperature. Chemical shifts are reported in ppm from tetramethylsilane on the δ scale, with the solvent resonance employed as the internal standard (deuterochloroform at 77.0 ppm). All ^{13}C spectra were recorded with complete proton decoupling. Difference NOE (DNOE) were recorded with 1024 accumulated transients each. The irradiation delay was set to 8 s. No special precautions were taken in sample preparation prior to recording the DNOE spectra (no degassing). Optical rotations were recorded on a AUTOPOL III digital polarimeter at 589 nm, and are reported as $[\alpha]_{23}^{D}$ (concentration in grams/100 mL solvent). High resolution mass spectra were obtained on a Finnegen MAT-90 spectrometer.

Analytical thin layer chromatography was performed on Whatman 0.25 mm silica gel 60-F plates. Flash chromatography was preformed as previously described.[20] When specified as 'anhydrous', solvents were distilled and/or stored over 4 Å sieves prior to use. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Unless otherwise noted, non aqueous reactions were carried out in oven dried glassware under a nitrogen atmosphere.

General procedure for the enzymatic resolution of the racemic (*E*)-vinylsilanes

The racemic vinyl silane **7** was dissolved in pentane. To this solution was added a crude extract of *Pseudomonas* lipase AK (0.5 wt. equiv.), and freshly distilled vinyl acetate (2.0 equiv.). The suspension was stirred at RT until the reaction came to 50% completion as determined by ^{1}H NMR analysis of reaction aliquots. The resolution afforded the pure (*S*,*E*)-vinylsilane alcohol and the (*R*,*E*)-vinyl acetate in high enantiomeric purity after chromatographic separation on SiO_2. The K_2CO_3-mediated hydrolysis of the (*R*)-acetate provided nearly enantiomerically pure (*R*,*E*)-alcohol. Finally, the β-substituted (*R*,*E*)- and (*S*,*E*)-crotylsilanes were produced in high yield by an *ortho*-ester Claisen rearrangement ($MeC(OMe)_3$, cat. propionic acid, PhMe, reflux) on the individual secondary allylic alcohols (see procedure below). The results of the resolution and Claisen rearrangements of the (*S*,*E*)- and (*R*,*E*)-vinylsilanes are summarized in Table 2.

General procedure for the *ortho*-ester Claisen rearrangement of enantiomerically pure (*E*)-vinylsilanes illustrated for (*3S*)-1-(dimethylphenyl)silyl-2-ethyl-1-buten-3-ol

To a toluene solution of the chiral secondary alcohol (5.0 g, 20.7 mmol, 0.25 M), trimethyl orthoacetate (82.8 mmol, 10.5 mL, 4.0 equiv.) and a catalytic amount of propionic acid (100 μL, 0.23 mmol) were added. The solution was warmed to reflux for 16 h before the reaction mixture was cooled to room temperature. The toluene was removed under reduced pressure and the products purified by flash chromatography on SiO_2 (100% hexanes→5% EtOAc–hexanes, gradient elution) to afford (*R*)-crotylsilane (5.34 g, 89% yield, 96% ee) as a colorless oil.

Representative procedure for the $BF_3{\cdot}OEt_2$ promoted

imine additions illustrated for the reaction of silane 6b to benzaldehyde dimethyl acetal and *p*-toluene sulfonamide. (5*R*,6*R*,3*E*)-Methyl-5-methyl-6-(*N*-tosylsulfonamide)-6-phenyl-hexenoate (13a). Table 2, entry 1. Into a dry 10 mL round bottom flask was dissolved benzaldehyde dimethyl acetal (171 mg, 1.12 mmol) and the *p*-toluene sulfonamide (202 mg, 1.18 mmol) in CH_2Cl_2 (1.1 mL, 1.0 M). The solution was cooled to −78°C and $BF_3{\cdot}OEt_2$ (208 μL, 2 equiv.) was added via microsyringe. The reaction mixture was stirred at −78°C for 30 min and the silane reagent **6a** (150 mg, 0.56 mmol) in CH_2Cl_2 (0.6 mL) was added. The reaction was then stirred at −35°C for 48 h before being diluted with saturated solution of $NaHCO_3$ (5 mL). The resulting solution was then extracted with $CHCl_3$ (3×3 mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The resulting clear yellow oil was flushed through a short plug of SiO_2, eluting with 20–30% EtOAc–hexanes, to yield the desired sulfonamide **13a** as a colorless oil (173 mg, 0.45 mmol, dr=20:1 *syn–anti*, 80%). ^{1}H NMR ($CDCl_3$) δ: 6.88–7.47 (m, 9H); 5.54 (m, 1H); 5.14 (m, 2H); 4.28 (dd, 1H, *J*=5.2 Hz, *J*=3.6 Hz); 3.71 (s, 3H); 2.79 (dd, 2H, *J*=1.2 Hz, *J*=2.0 Hz); 2.54 (m, 1H); 2.31 (s, 3H); 0.865 (d, 3H, *J*=6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 172.2; 142.7; 138.2; 137.7; 134.8; 129.1; 127.8; 127.4; 126.9; 124.2; 61.7; 51.9; 42.7; 37.5; 21.3; 16.4. IR (neat) cm^{-1}: 3289; 1736; 1456; 1437; 1326; 1160. MS: CIMS+NH_4 (NH_3 gas) 388, 260, 155, 91. CIHRMS+NH_4 calculated for $C_{21}H_{25}NO_4S$+H=388.15; found 388.1559. $[\alpha]_{23}^{D}$=+62.4° (CH_2Cl_2, *c*0.63).

(5*R*,6*R*,3*E*)-Methyl-5-methyl-6-(*N*-tosylsulfonamide)-6-trimethyl-hexenoate (13b). Table 2, entry 2, dr>30:1 *syn–anti*, 90% yield. ^{1}H NMR ($CDCl_3$) δ:7.71 (d, 2H, *J*=8.0 Hz); 7.26 (d, 2H, *J*=8.0 Hz); 5.32 (m, 1H); 5.09 (m, 1H); 4.35 (d, 1H, *J*=10.0 Hz); 3.66 (s, 3H); 3.06 (dd, 1H, *J*=2.0 Hz, *J*=8.4 Hz); 2.85 (m, 2H); 2.42 (m, 1H); 2.40 (s, 3H); 0.87 (d, 3H, *J*=6.8 Hz); 0.84 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 172.2; 142.7; 139.7; 139.2; 129.4; 127.1; 120.2; 66.1; 51.7; 37.5; 36.9; 36.2; 27.3; 21.4; 16.6. IR (neat) cm^{-1}: 3359; 2962; 1738; 1641; 1437; 1305; 1159; 1095. MS: CIMS+NH_4 (NH_3 gas) 368, 310, 240, 236, 155. CIHRMS+NH_4 calculated for $C_{13}H_{29}NO_4S$+H=368.1817; found 368.1920. $[\alpha]_{23}^{D}$=+14.2° (CH_2Cl_2, *c*0.96).

(5*R*,6*R*,3*E*)-Methyl-5-methyl-6-(*N*-tosylsulfonamide)-7-benzyloxy-heptenoate (13c). Table 2, entry 3, dr=10:1 *syn–anti*, 71% yield. ^{1}H NMR ($CDCl_3$) δ:7.67 (d, 2H, *J*=8.4 Hz); 7.26 (m, 7H); 5.36 (m, 2H); 4.82 (d, 1H, *J*=8.8 Hz); 4.29 (ABq, 2H, *J*=6.0 Hz); 3.66 (s, 3H); 3.40 (dd, 2H, *J*=6.4 Hz, *J*=2.8 Hz); 3.11 (m, 2H); 2.92 (d, 1H, *J*=6.8 Hz); 2.44 (m, 1H); 2.39 (s, 3H); 0.96 (d, 3H, *J*=7.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 172.1; 143.1; 138.0; 137.7; 135.9; 128.5; 128.3; 127.7; 127.7; 127.6; 123.2; 73.1; 68.9; 57.4; 51.8; 37.6; 36.9; 21.5; 16.7. IR (neat) cm^{-1}: 3422; 2100; 1643; 1454; 1437; 1330; 1162. MS: CIMS+NH_4 (NH_3 gas) 432, 354, 352, 260, 217, 91. CIHRMS+NH_4 calculated for $C_{23}H_{29}NO_5S$+H=432.55; found 432.2. $[\alpha]_{23}^{D}$=+12.2° (CH_2Cl_2, *c*0.90).

Representative procedure for the $BF_3{\cdot}OEt_2$ promoted imine additions illustrated for the reaction of silane 6a to benzaldehyde dimethyl acetal and methyl carbamate. (5*R*,6*S*,3*E*)-Methyl-5-methyl-6-(*N*-methylcarbamate)-6-phenyl-hexenoate (14a). Table 3, entry 1, dr>30:1 *syn–anti*, 87% yield. A 25 mL round bottom flask equipped with a magnetic stir bar and rubber septum was charged with 4 mL dry CH_2Cl_2, benzaldehyde dimethyl acetal (350 mg, 2.3 mmol, 1 equiv.) and methylcarbamate (174 mg, 2.31 mmol, 1 equiv.). The resulting solution was cooled to −78°C. To this mixture, $BF_3{\cdot}OEt_2$ (572 μL, 4.638 mmol, 2.0 equiv.) was added under N_2 at −78°C. The reaction mixture was warmed to room temperature and stirred for 10 min (the reaction mixture becomes yellow and homogeneous). The reaction mixture was recooled to −78°C and a solution of (*E*)-crotylsilane (524.8 mg, 2 mmol, 0.863 equiv.) in CH_2Cl_2 (1 mL) was added to this dropwise over a period of 10 min. Then the reaction mixture was immediately warmed to −20°C while being monitored by TLC (20% EtOAc–petroleum ether). After 24 h the reaction mixture was diluted with a saturated solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and the solvent removed under reduced pressure to afford crude **14a** as light yellow oil. Chromatography on silica gel using 20% EtOAc–petroleum ether as the eluant afforded pure **14a** as a colorless oil (483.6 mg, 87% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.15–7.31 (m, 5H), 5.56 (m, 1H), 5.40 (bd, 1H, *J*=8.4 Hz), 5.30 (dd, 1H, *J*=8.4 Hz, *J*=15.6 Hz), 4.64 (t, 1H, *J*=8.4 Hz), 3.68 (s, 3H), 3.62 (s, 3H), 3.01 (d, 2H, *J*=10.8 Hz), 2.61 (m, 1H), 0.96 (d, 4H, *J*=7 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.1, 156.2, 139.9, 135.4, 128.0, 127.2, 127.1, 127.0, 123.5, 58.9, 52.0, 51.8, 41.9, 37.6, 16.5; IR (neat) cm^{-1}: 3325, 2980, 1710, 1540, 1480, 1360, 1250, 1180, 1020, 810; MS: CIMS+NH_4 (NH_3 gas) 309, 293, 292, 217, 164, 84, 82, 64; CIHRMS+NH_4 calculated for $C_{16}H_{22}NO_4$=292.1548; found: 292.1569. $[\alpha]_{23}^{D}$=−104° (CH_2Cl_2, *c* 0.85).

(2*S*,5*R*,6*S*,3*E*)-Methyl-5-methyl-6-(*N*-methylcarbamate)-2-methoxy-6-phenyl-hexenoate (14b). Table 3, entry 2, dr=9:1 *syn–anti*, 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.1–7.3 (m, 5H), 5.61 (dd, 1H, *J*=5.3, 15.6 Hz), 5.4 (m, 2H), 4.6 (b t, 1H, *J*=7.4 Hz), 4.1 (d, 1H, *J*=7.2 Hz), 3.65 (s, 3H), 3.54 (s, 3H), 3.25 (s, 3H), 2.6 (m, 1H), 0.9 (d, 3H, *J*=7 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.3, 156.6, 140.4, 137.9, 128.7, 128.5, 127.5, 127.5, 126.4, 81.3, 59.53, 57.3, 52.5, 52.3, 42.2, 16.7; IR (neat) cm^{-1} 3360, 2960, 1720, 1530, 1470, 1440, 1350, 1305, 1240, 1180, 1080, 1040, 1020, 880, 820; CIMS (NH_3 gas) 339, 322, 290, 215, 165, 164; CIHRMS+NH_4 calculated for $C_{17}H_{24}NO_5$=322.1654; found 322.1666. $[\alpha]_{23}^{D}$=−70° (CH_2Cl_2, *c* 5.4).

(2*S*,5*R*,6*S*, 3*E*)-Methyl-2, 5-dimethyl-6-phenyl-6-(*N*-methylcarbamate)hexenoate (14c). Table 3, entry 3, dr>30:1 *syn–anti*, 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.1–7.3 (m, 5H), 5.46 (dd, 1H, *J*=7.3 Hz, *J*=15.6 Hz), 5.25 (m, 2H), 4.58 (t, 1H, *J*=7.3 Hz), 3.63 (s, 3H), 3.60 (s, 3H), 3.04 (m, 1H), 2.53 (m, 1H), 1.12 (d, 3H, *J*=7 Hz), 0.95 (d, 3H, *J*=6.7 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 175.0, 156.2, 140.2, 132.6, 130.5, 128.06, 128.0, 127.1, 59.2, 52.0, 51.8, 42.3, 42.0, 17.1, 16.6; IR (neat) cm^{-1} 3360, 2960, 1723, 1530, 1475, 1460, 1350, 1305, 1240, 1180, 1080, 1040, 1020, 880, 820. MS: CIMS+NH_4 (NH_3 gas) 306.2, 232, 231, 199, 171, 165, 164, 144, 121, 120, 106, 77, 59, 42.

CIHRMS+NH_4 calculated for $C_{17}H_{23}NO_{4+}H$=306.1705, found 306.1733. $[\alpha]_{23}^{D}$=−13.3° (CH_2Cl_2, *c*1.5).

(5*R*,6*S*,3*E*)-Methyl-9-benzyloxy-5-methyl-6-(*N*-methylcarbamate)octenoate (14d). Table 3, entry 4, dr>30:1 *syn–anti*, 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3 (m, 5H), 5.53 (m, 1H), 5.42 (dd, 1H, *J*=8.3, 15.5 Hz), 4.92 (d, 1H, *J*=9.7 Hz), 4.46 (s, 2H), 3.66 (s, 3H), 3.63 (s, 3H), 3.53 (m, 3H), 3.02 (d, 2H, *J*=6.73 Hz), 2.34 (m, 1H), 1.95 (m, 1H), 1.5 (m, 1H), 1.01 (d, 3H, *J*=6.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.7, 157.2, 138.6, 136.5, 128.7, 128. 127.9, 123.4, 73.6, 68.1, 53.4, 52.3, 52.1, 41.8, 38.1, 31.9. 17.1; IR (neat) cm^{-1} 3340, 2980, 1720, 1520, 1440, 1340, 1250, 1160, 1100, 1090, 1010, 980; MS: CIMS+NH_4 (NH_3 gas) 350, 318, 292, 242, 164, 117, 116, 91; CIHRMS+NH_4 calculated for $C_{19}H_{27}NO_{5+}H$= 350.1967; found 350.2000. $[\alpha]_{23}^{D}$=+27° (CH_2Cl_2, *c*1.5).

(5*R*,6*S*,3*E*)-Methyl-9-benzyloxy-5-methyl-6-(*N*-methylcarbamate)heptenoate (14e). Table 3, entry 5, dr>30:1 *syn–anti*, 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 5H), 5.51 (m,1H), 5.4 (dd, 1H, *J*=6.9 Hz, *J*=15.2 Hz), 4.96 (d, 1H, *J*=8.5 Hz), 4.43 (ABq, 2H, *J*=11.7 Hz), 3.6 (s, 6H), 3.52 (m, 3H), 2.97 (d, 4H, *J*=6.7 Hz), 2.47 (m, 1H), 0.99 (d, 3H, *J*=6.9 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.3, 156.8, 138.0, 136.6, 128.3, 127.6, 122.7, 70.0, 54.7, 52.0, 51.7, 38.9, 37.7, 16.9. IR (neat) cm^{-1}: 3325, 2960, 1710, 1550, 1480, 1360, 1250, 1180, 1030, 810. $[\alpha]_{23}^{D}$=−7.5° (CH_2Cl_2, *c*0.6).

(5*R*,6*S*,3*E*)-Methyl-5,7-dimethyl-6-(*N*-methylcarbamate)-octenoate (14f). Table 3, entry 6, dr>30:1 *syn–anti*, 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53 (m, 1H), 5.42 (dd, 1H, *J*=8, 15.4 Hz), 4.42 (d, 1H, *J*=10.3 Hz), 3.65 (s, 3H), 3.64 (s, 3H), 3.34 (m, 1H), 3.02 (d, 2H, *J*=6.5 Hz), 2.24 (m, 1H), 1.8 (m, 1H), 0.97 (d, 3H, *J*=6.7 Hz), 0.88 (d, 3H, *J*=6.7 Hz), 0.78 (d, 3H, *J*=6.7 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.3, 157.43, 137.2, 121.6, 59.8, 52, 51.7, 39.8, 37.7, 29.4, 20.4, 16.5, 16.0; IR (neat) cm^{-1} 3340, 2980, 1740, 1520, 1240, 1180, 1110, 910, 740; MS: CIMS+NH_4 (NH_3 gas) 258, 202, 174, 130, 84, 64; CIHRMS+NH_4 calculated for $C_{13}H_{23}NO_4$+H=258.1705; found: 258.1690. $[\alpha]_{23}^{D}$=+19.0° (CH_2Cl_2, *c*1.0).

(5*R*,6*S*,3*E*)-Methyl-6-(*N*-methyl carbamate)-5, 7, 7-trimethyloctenoate (14g). Table 3, entry 7, dr>30:1 *syn–anti*, 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (m, 2H), 4.58 (d, 1H, *J*=11 Hz), 3.66 (s, 3H), 3.65 (s, 3H), 3.44 (dd, 1H, *J*=4, 11 Hz), 3.01 (m, 2H), 2.53 (m, 1H), 0.97 (d, 3H, *J*=6.89 Hz), 0.92 (s, 9H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.9, 157.7, 140.1, 132.1, 120.6, 62.4, 52.5, 52.2, 38.1, 37.9, 36.2, 27.8, 27.7, 16.9; IR (neat) cm^{-1} 3325, 2960, 1720, 1540, 1360, 1260, 1190, 1080, 1000, 805, 760; MS: CIMS+NH_4 (NH_3 gas) 289, 272, 240, 214, 144, 85; CIHRMS+NH_4 calculated for $C_{14}H_{25}NO_{4+}H$=272.2861; found: 272.2818. $[\alpha]_{23}^{D}$=+29.0° (CH_2Cl_2, *c* 0.2).

(5*R*,6*R*,3*E*)-Methyl-5-methyl-6-(*N*-methylcarbamate)-4-methyl-7-benzyloxy-heptenoate (14h). Table 3, entry 8, dr=24:1 *syn–anti*, 77% yield. ^{1}H NMR ($CDCl_3$) δ: 7.25–7.34 (m, 5H); 5.40 (t, 1H); 4.93 (b, 1H); 4.46 (m, 2H); 3.74 (d, 2H, *J*=2.8 Hz); 3.68 (s, 6H); 3.42 (m, 1H); 6.03 (d, 2H, *J*=4.8 Hz); 2.50 (m, 1H); 1.58 (s, 3H); 1.07 (d, 3H, *J*=4.4 Hz). dr>12:1 ^{13}C NMR ($CDCl_3$) δ: 172.4; 157.0; 140.4; 138.1; 128.9; 128.3; 127.7; 127.6; 117.8; 73.2; 70.4; 53.4; 52.0; 51.7; 44.3; 33.2; 15.8; 12.4. IR (neat) cm^{-1}: 3437, 2253, 1723, 1507, 1456, 1257, 909. MS: CIMS+NH_4 (NH_3 gas) 91, 105, 208, 242, 350. CIHRMS+NH_4 calculated for $C_{20}H_{26}NO_5$=361.1889; found: 361.1832. $[\alpha]_{23}^{D}$=+10.7° (CH_2Cl_2, *c*1.6).

(5*R*,6*R*,3*E*)-Methyl-5-methyl-6-(*N*-methylcarbamate)-4-methyl-7-trimethyl-heptenoate (14i). Table 3, entry 9, dr=8:1 *syn–anti*, 70% yield. ^{1}H NMR ($CDCl_3$) δ: 5.31 (t, 1H); 4.56 (br, 1H); 3.65 (s, 3H); 3.62 (s, 3H); 3.50 (dd, 1H, *J*=4.0, 6.0 Hz); 3.00 (d, 2H, *J*=6.8 Hz); 2.45 (m, 1H); 1.60 (s, 3H); 2.45 (m, 1H); 1.60 (s, 3H); 0.97 (d, 3H, *J*=2.8 Hz); 0.95 (s, 9H) dr>8:1 ^{13}C NMR ($CDCl_3$) δ: 172.7, 157.1, 143.2, 116.0, 60.1, 52.0, 51.6, 42.3, 33.4, 29.7, 27.2, 15.6, 14.3. IR (neat) cm^{-1}: 3055, 2987, 1727, 1517, 1435, 1422, 1266. MS: CIMS+NH_4 (NH_3 gas) 69, 76, 144, 154, 228, 286. CIHRMS+NH_4 calculated for $C_{15}H_{27}NO_4$+H= 286.1940; found 286.1980. $[\alpha]_{23}^{D}$=+8.9° (CH_2Cl_2, *c*1.0).

(5*R*,6*R*,3*E*)-Methyl-5-methyl-6-(*N*-methylcarbamate)-4-methyl-6-phenyl-hexenoate (14j). Table 3, entry 10, dr=1.2:1 *syn–anti*, 89% yield. ^{1}H NMR ($CDCl_3$) δ: 7.08–7.32 (m, 5H); 5.27 (t, 1H); 4.73 (t, 1H); 3.61 (s, 3H); 3.55 (s, 3H); 3.09 (d, 1H, *J*=7.2 Hz); 2.96 (dd, 2H, *J*=28.8, 2.8 Hz); 2.55 (t, 1H); 1.53 (s, 3H); 1.06 (d, 3H, *J*=6.8 Hz). dr>2:1. ^{13}C NMR ($CDCl_3$) δ: 182.7; 172.3; 156.5; 141.4; 139.6; 128.3; 128.2; 127.0; 126.9; 118.4; 57.8; 51.7; 47.9; 33.3; 16.6; 15.0; 14.2; 12.1. IR (neat) cm^{-1}: 3333; 2953; 1725; 1534; 1455; 1437; 1259; 1018. MS: CIMS+NH_4 (NH_3 gas) 59, 121, 164, 194, 306, 327. CIHRMS+NH_4 calculated for $C_{17}H_{23}NO_4$+H=306.1627; found 306.1713. $[\alpha]_{23}^{D}$=+15.5° (CH_2Cl_2, *c*1.3).

Representative experimental procedure for the $BF_3{\cdot}OEt_2$ promoted pyrrolidine annulation for the addition of silane 6a to benzaldehyde dimethyl acetal and methyl carbamate as illustrated for 15a. (2*S*,3*R*,4*S*,5*S*)-3-(Dimethylphenyl)silane-4-methyl-5-phenyl-pyrrolidine-*N*-methylcarbamate-2-acetic acid methyl ester (15a). Table 4, entry 1. A 25 mL round bottom flask equipped with magnetic stir bar and rubber septum was charged with 2 mL dry CH_2Cl_2, benzaldehyde dimethyl acetal (350 mg, 2.297 mmol, 1.0 equiv.) and methylcarbamate (174 mg, 2.31 mmol, 1.0 equiv.). The resulting solution was cooled to −78°C, and $BF_3{\cdot}OEt_2$ (572 μL, 4.638 mmol, 2.01 equiv.) was added under N_2. The reaction mixture was warmed to room temperature and stirred for 10 min (the reaction mixture became yellow and homogeneous). The reaction mixture was recooled to −100°C and a solution of (*E*)-crotylsilane (524.8 mg, 2 mmol, 0.863 equiv.) in CH_2Cl_2 was added to this dropwise over a period of 10 min (20% EtOAc–petroleum ether). After 10 min the reaction mixture was warmed to −85°C while being monitored by TLC (20% EtOAc–petroleum ether). After 12 h the reaction mixture was diluted with a saturated solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and the solvent removed under reduced pressure to afford crude **15a** as light yellow oil. Chromatography on silica gel using 20% EtOAc–petroleum

ether as the eluant afforded pure **15a** (579.5 mg, theoretical 852 mg, dr>30:1 *syn–anti*, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39(d, 2H, J=7.3 Hz), 7.15 (m, 6H), 6.86 (d, 2H, J=7.3 Hz), 4.57 (d, 1H, J=4.4 Hz), 4.16 (dd, 1H, J=5.5, 7.4 Hz) 3.68 (s, 3H), 3.33 (s, 3H), 2.52 (m, 2H), 1.85 (m, 2H), 0.51 (d, 3H, J=6.8 Hz), 0.30 (s, 3H), 0.22 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 174.1, 153.1, 141.1, 137.2, 133.8, 129.3, 128.0, 127.6, 127.4, 126.4, 81.2, 57.1, 54.3, 51.6, 32.4, 30.5, 25.4, 12.8, −2.9, −4.63. IR (neat) cm^{-1} 2905, 1715, 1655, 1420, 1300, 1210, 1190, 1080, 1000, 920, 880, 820; MS: CIMS+NH_4 (NH_3 gas) 426, 309, 292, 183, 164, 152, 106; CIHRMS+NH_4 calculated for $C_{24}H_{31}NSiO_{4+}H$=426.2100; found 426.2092. $[\alpha]_{23}^{D}$=+60.6° (CH_2Cl_2, *c*3.5).

(1′*S*,2*S*,3*R*, 4*S*,5*S*)-3-(Dimethylphenyl)silane-4-methyl-2-(1′-methoxy)-5-phenyl-pyrrolidine-*N*-methyl carbamate-2-acetic acid methyl ester (15b). Table 4, entry 2, dr=20:1 *syn–anti*, 72% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, 2H, J=7 Hz), 7.25 (m, 6H), 6.83 (d, 2H, J=7 Hz) 4.73 (d, 1H, J=4.5 Hz), 4.71 (d, 1H, J=2.5 Hz), 4.55 (dd, 1H, J=2.8, 10.5 Hz), 3.77 (s, 3H), 3.51 (s, 3H), 3.42 (s, 3H), 2.75 (dd, 1H, J=2.5, 10.5 Hz), 2.18 (m, 1H), 0.68 (d, 3H, J=7 Hz), 0.54 (s,3H), 0.49 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 173.7, 152.6, 142.6, 139.4, 134.1, 129.3, 128.5,128.4, 127.4, 126.4, 80.9, 79.4, 59.7, 55.2, 54.2, 51.3, 35.2, 32.9, 13.3, −4.0, −0.5; IR (neat) cm^{-1} 2900, 1710, 1650, 1420, 1300, 1210, 1190, 1080, 1000, 920, 880, 820; MS: CIMS+NH_4 (NH_3 gas) 456, 424, 384, 314, 292, 290, 215, 164, 135, 111; CIHRMS+NH_4 calculated for $C_{25}H_{33}NSiO_5$+H456.2206; found 456.2208. $[\alpha]_{23}^{D}$=+24.9° (CH_2Cl_2, *c*0.4).

(1′*S*,2*S*,3*R*,4*S*,5*S*)-5-(*p*-Chloro-phenyl)-3-dimethylphenyl-silane-4-methyl-2-(1′methoxy)-pyrrolidine-*N*-methyl carbamate-2-acetic acid methyl ester (15c). Table 4, entry 3, dr=20:1 *syn–anti*, 47% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.5 (m, 5H), 7.0 (d, 2H, J=8.2 Hz), 6.31 (d, 2H, J=8.4 Hz), 4.38 (d, 1H, J=2.5 Hz), 4.28 (m, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 3.57 (s, 3H), 2.35 (dd, 1H, J=2.5, 10.7 Hz), 1.8 (m, 1H), 0.45 (d, 3H, J=7 Hz), 0.41 (s, 3H), 0.2 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 174, 152.3, 140.3, 139.2, 133.8, 129.33, 128.3, 128.1, 127.7, 81.0, 79.0, 60.1, 54.4, 54.1, 51.9, 34.7, 32.4, 13.0, −0.46 −0.7; IR (neat) cm^{-1} 2900, 1710, 1650, 1420, 1300, 1210, 1190, 1080, 1000, 920, 880, 820; MS: CIMS+NH_4 (NH_3 gas) 492, 490, 458, 332, 324, 249, 198, 135, 111, 89; CIHRMS+NH_4 calculated for $C_{25}H_{33}ClNSiO_5$=491.1894; found 491.1879. $[\alpha]_{23}^{D}$=+56.8° (CH_2Cl_2, *c*2.5).

(1′*S*,2*S*,3*R*, 4*S*,5*S*)-5-(2,3-Dimethoxy-phenyl)-3-(dimethyl-phenyl)silane-4-methyl-2-(1′methoxy)-pyrrolidin-*N*-methyl carbamate-2-acetic acid methyl ester (15d). Table 4, entry 4, dr=10:1 *syn–anti*, 53% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23–7.55 (m, 5H), 6.94 (t, 1H, J=7.8 Hz), 6.77 (d, 1H, J=7.8 Hz), 6.65 (d, 1H, J=7.8 Hz), 4.96 (d, 1H, J=5 Hz), 4.12 (d, 1H, 4.3 Hz), 4.05 (dd, 1H, J=4.4, 8.2 Hz), 3.84 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 3.62 (s, 3H), 3.42 (s, 3H), 2.17 (m, 1H), 2.1 (dd, 1H, J=4.3, 8.2 Hz), 0.47 (s, 3H), 0.40 (s, 3H), 0.33 (d, 3H, J=7 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 173.7, 153.1, 152.2, 146.25, 137.2, 135.3, 134.6, 134.5, 133.0, 127.6, 127.5, 123.4, 123.3, 120.9, 110.6, 79.9, 79.1, 60.3, 59.0, 55.7, 55.6, 54.3, 51.7, 51.3, 34.6, 31.7, 12.9, −1.85; IR (neat) cm^{-1} 2905, 1719, 1645, 1420, 1305, 1210, 1190, 1180, 1000, 920, 880, 820; MS: CIMS+NH_4 (NH_3 gas) 516, 350, 275, 224, 148; CIHRMS+NH_4 calculated for $C_{27}H_{37}NSiO_{7+}H$= 516.2416; found 516.2396. $[\alpha]_{23}^{D}$=+75.4° (CH_2Cl_2, *c*1.1).

Representative experimental procedure for the BF_3·OEt_2 promoted pyrrolidine annulations for the addition of silane 6a to benzaldehyde dimethyl acetal and *tert*-butyl carbamate as illustrated for 16a. (2*S*,3*R*,4*S*,5*S*)-3-(dimethylphenyl)silane-4-methyl-5-phenyl-pyrrolidine-2-acetic acid methyl ester (16a). Table 5, entry 1. In a dry 10 mL round bottom flask, 2,3-dimethoxy benzaldehyde (34 mg, 0.21 mmol) and the *tert*-butylcarbamate (24 mg, 0.21 mmol) were taken up in dry CH_2Cl_2 (0.2 mL, 1.0 M). The solution was cooled to −78°C before addition of BF_3·OEt_2 (47 μL, 2 equiv.). The reaction mixture was then pulled out of the dry ice/acetone bath and stirred for 10 min. The reaction is then cooled again to −100°C and a solution of silane (50 mg, 0.188 mmol) in CH_2Cl_2 (0.2 mL, 1.0 M) was added dropwise. The solution was then stirred overnight at −85°C before being diluted with a saturated solution of $NaHCO_3$ (3 mL) and extracted with $CHCl_3$ (3×1 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification on SiO_2, eluting with 30⟶40% EtOAc–hexanes, afforded the desired pyrrolidine as a colorless oil (67 mg, 0.15 mmol, dr>30:1 *syn–anti*, 78%). ^{1}H NMR ($CDCl_3$) δ: 7.16–7.55 (m, 10H); 6.72 (d, 1H, J=6.0 Hz); 5.15 (br, 1H); 4.60 (dd, 1H, J=4.4, 7.2 Hz); 3.62 (s, 3H); 2.57 (dd, 2H, J=10.4, 26.8 Hz); 2.13 (m, 1H); 1.83 (m, 1H); 0.59 (d, 3H, J=7.2 Hz); 0.45 (s, 3H); 0.34 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 201.4; 174.2; 153.6; 140.8; 138.3; 137.0; 133.9; 129.4; 127.0; 126.1; 80.2; 78.4; 56.7; 52.9; 51.8; 42.0; 32.5; 29.5; 29.3; 25.2; 24.7; 12.8. IR (neat) cm^{-1}: 3408; 2977; 1702; 1456; 1411; 1309; 1119. MS: CIMS+NH_4 (NH_3 gas) 352, 334, 284, 240, 143, 135. CIHRMS+NH_4 calculated for $C_{22}H_{29}NO_2Si$+H368.1967; found 368.2066. $[\alpha]_{23}^{D}$=−36.1° (CH_2Cl_2, *c*1.65).

(2*S*,3*R*,4*S*,5*S*)-3-(Dimethylphenyl)silane-4-methyl-5-(*p*-methoxy-phenyl)-pyrrolidine-2-acetic acid methyl ester (16b). Table 5, entry 2, dr>30:1 *syn–anti*, 74% yield. ^{1}H NMR ($CDCl_3$) δ: 7.36–7.56 (m, 7H); 6.70 (dd, 2H, J=2.0, =6.4 Hz); 5.10 (br, 1H); 4.38 (m, 1H); 4.11 (m, 1H); 3.77 (s, 3H); 3.62 (s, 3H); 2.56 (ABx, 2H, J=6.4, 10.0, 6.4, 27.2 Hz); 2.08 (m, 1H); 1.80 (m, 1H); 0.58 (d, 3H, J=6.8 Hz); 0.45 (s, 3H); 0.34 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 201.4; 174.2; 153.6; 138.3; 137.0; 129.3; 129.0; 128.4; 128.2; 128.0; 127.7; 127.0; 126.1; 80.2; 56.7; 52.9; 51.8; 42.0; 32.5; 29.6; 29.4; 25.2; 24.7; 12.8; −3.1. IR (neat) cm^{-1}: 3427; 1702; 1456; 1360; 1268; 1026. MS: CIMS+NH_4 (NH_3 gas) 68, 135, 207, 270, 314, 396, 426. CIHRMS+NH_4 calculated for $C_{23}H_{31}NO_3Si$+H397.2073; found 398.2151. $[\alpha]_{23}^{D}$=−47.2° (CH_2Cl_2, *c*1.15).

(2*S*,3*R*,4*S*,5*S*)-3-(Dimethylphenyl)silane-4-methyl-5-(2,3-dimethoxy-phenyl)-pyrrolidine-2-acetic acid methyl ester (16c). Table 4, entry 3, dr>30:1 *syn–anti*, 78% yield. ^{1}H NMR ($CDCl_3$) δ: 6.80–7.53 (m, 8H); 6.48 (d, 1H, J=7.6 Hz); 5.02 (br, 1H; 4.15 (dd, 1H, J=5.2 Hz, J=2.8 Hz); 3.86 (s, 3H); 3.84 (s, 3H); 3.80 (s, 3H); 2.49 (ABx, 2H, J=6.4, 9.6, 6.8, 39.2 Hz); 2.32 (m, 1H); 1.78

(m, 1H); 0.60 (d, 3H, J=7.2 Hz); 0.45 (s, 3H); 0.40 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 202.6; 202.5; 174.4; 153.7; 125.3; 134.0; 132.1; 129.3; 127.9; 123.8; 119.5; 111.8; 80.2; 60.6; 55.7; 51.8; 50.7; 32.3; 29.5; 24.7; 11.9. IR (neat) cm^{-1}: 3406; 1707; 1480; 1354; 1268; 1169; 1123; 1006. MS: CIMS+NH_4 (NH_3 gas) 83, 85, 135, 206, 292, 300, 344. CIHRMS+NH_4 calculated for $C_{24}H_{33}NO_4Si$= 427.2179; found 427.2150. $[\alpha]_{23}^{D}$=−53.7° (CH_2Cl_2, c0.6).

(5*S*,6*S*,7*S*,3*E*) Methyl-8-benzyloxy-5-methyl-6-(*N*-methyl carbamate)-7-methyl-hexenoate (17a). Table 6, entry 1, dr>30:1 *syn–anti*, 85% yield. ^{1}H NMR ($CDCl_3$) δ: 7.25–7.35 (m, 5H), 5.41 (m, 2H), 4.45 (s, 2H), 3.65 (s, 3H). 3.63 (s, 3H), 3.42 (m, 1H), 3.32 (m, 2H). 2.98 (d, 2H, J=7.6 Hz), 2.24 (m, 1H), 1.89 (m, 1H); 1.05 (d, 3H, J=7.2 Hz), 0.97 (d, 3H, H=7.2).

(5*R*,6*S*,7*S*,3*E*) Methyl-7-benzyloxy-5-methyl-6-(*N*-methyl carbamate)-7-methyl-heptenoate (17b). Table 6, entry 2, dr=24:1 *syn–anti*, 82% yield. ^{1}H NMR ($CDCl_3$) δ: 7.22–7.34 (m, 5H); 5.40–5.57 (m, 2H); 4.63 (br, 1H); 4.50 (m, 4H); 3.79 (m, 1H); 3.66 (s, 3H); 3.63 (s, 3H); 3.61 (m, 1H); 2.99 (d, 3H, J=6.4 Hz); 2.45 (m, 1H); 1.15 (d, 3H, J=6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 182.7, 157.2, 137.0, 128.3, 127.7, 121.8, 74.8, 70.5, 57.2, 52.1, 37.8, 15.9, 15.3. IR (neat) cm^{-1}: 3428, 2113, 1646, 1540. MS: CIMS+NH_4 (NH_3 gas) 49, 91, 132, 140, 214, 228, 242, 260, 350. CIHRMS+NH_4 calculated for $C_{19}H_{27}NO_5$+ H=350.1889; found 350.1999. $[\alpha]_{23}^{D}$=+2.3° (CH_2Cl_2, c0.7).

(5*S*,6*R*,7*R*,3*E*) Methyl-8-benzyloxy-5-methyl-6-(*N*-methyl carbamate)-7-methyl-hexenoate (17c). Table 6, entry 3, dr=5:1 *syn–anti*, 87% yield. ^{1}H NMR ($CDCl_3$) δ: 7.25–7.35 (m, 5H), 5.38 (m, 1H), 4.97 (d, 1H J=9.6 Hz), 4.63 (d, 1H, J=11.6 Hz), 4.47 (d, 1H, J=11.6 Hz), 3.68 (m, 1H), 3.65 (s, 3H), 3.64 (s, 3H), 3.32 (t, 1H, J=9.6 Hz), 2.44 (m, 1H), 1.16 (d, 3H, J=8 Hz), 0.99 (d, 3H, J=8 Hz).). ^{13}C NMR ($CDCl_3$) δ: 172.25, 157.6, 137.3, 128.4, 128.3, 127.8, 127.7, 127.6, 122.6, 75.5, 73.2, 70.7, 66.3, 60.0, 52.1, 37.7, 17.7, 16.6, 15.8. IR (neat) cm^{-1}: 3450, 2133, 1655, 1530 MS: CIMS+NH_4 (NH_3 gas) 91, 132, 140, 228, 260, 350

(5*R*,6*S*,7*S*,3*E*) Methyl-8-*t*-butyldimethylphenyloxy-5-methyl-6-(*N*-methyl carbamate)-7methyl-heptanoate (17d). Table 6, entry 4, dr>30:1 *syn–anti*, 73% yield. ^{1}H NMR ($CDCl_3$) δ: 7.34–7.65 (m, 10H); 5.61 (br, 1H); 5.34 (m, 2H); 3.80 (dd, 1H, J=3.2, 7.2 Hz); 3.64 (s, 3H); 3.59 (s, 3H); 3.45 (m, 2H); 2.92 (d, 2H, J=5.2 Hz); 2.29 (m, 1H); 1.77 (m, 1H); 1.06 (s, 9H); 1.01 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 172.2, 157.8, 137.5, 135.7, 132.8, 129.8, 127.8, 121.8, 65.5, 58.9, 51.9, 51.7, 41.2, 37.7, 35.2, 26.9, 19.1, 17.6, 15.9. IR (neat) cm^{-1}: 3428, 2961, 1727, 1643. MS: CIMS+NH_4 (NH_3 gas) 256, 384, 434, 454, 480, 512. CIHRMS+ NH_4 calculated for $C_{29}H_{42}NO_5Si$+H512.2754; found 512.2824. $[\alpha]_{23}^{D}$=−8.6° (CH_2Cl_2, c1.7).

(5*R*,6*R*,7*R*,3*E*) Methyl-8-*t*-butyldimethylphenyloxy-5-methyl-6-(*N*-methyl carbamate)-7methyl-heptanoate (17e). Table 6, entry 5, dr=8:1 *syn–anti*, 80% yield. ^{1}H NMR ($CDCl_3$) δ: 7.35–7.65 (m, 10H); 5.46 (m, 1H); 5.36 (m, 1H); 4.53 (broad d, 1H); 3.65 (s, 3H); 3.62 (s, 3H); 3.55 (m, 2H); 3.43 (m, 1H); 3.01 (d, 2H, J=6.8 Hz), 2.27 (m, 1H), 1.92 (m, 1H), 1.03 (m, 9H), 0.976 (d, 3H, J=6.8 Hz), 0.77 (d, 3H, J=6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 172.2, 157.0, 137.3, 135.7, 135.6, 135.5, 133.7, 127.8, 127.7, 127.6, 121.8, 66.6, 55.5, 52.0, 51.6, 40.1, 37.7, 37.1, 36.7, 26.8, 16.7, 19.2, 17.0, 11.2. IR (neat) cm^{-1}: 3432, 2958, 1750, 1635. MS: CIMS+NH_4 (NH_3 gas) 256, 384, 434, 455, 480, 512. CIHRMS+NH_4 calculated for $C_{29}H_{42}NO_5Si$+H= 512.2754; found 512.2826.

(5*S*,6*R*,7*S*,3*E*) Methyl-8-benzyloxy-5-methyl-6-amino-7-methyl-hexenoate (17f). Table 6, entry 6, dr>1:30 *syn–anti*, 63% yield. ^{1}H NMR ($CDCl_3$) δ: 7.29–7.34 (m, 5H), 5.58 (m, 2H), 4.49 (s, 2H), 3.65 (s, 3H), 3.55 (m, 1H), 3.46 (m, 1H), 3.05 (m, 2H, J=6 Hz), 2.34 (m, 1H), 1.89 (m, 1H); 1.05 (d, 3H, J=6.8 Hz), 0.97 (d, 3H, J=6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 172.6, 135.5, 128.4, 127.7, 127.6, 122.4, 79.9, 75.4, 73.5, 51.7, 39.9, 37.9, 36.2, 17.9, 13.4. IR (neat) cm^{-1}: 3460, 2964, 2931, 1737, 1454, 1275.

(5*R*,6*R*,7*S*,3*E*) Methyl-7-benzyloxy-5-methyl-6-(*N*-methyl carbamate)-7-methyl-heptenoate (17g). Table 6, entry 7, dr=1:8 *syn–anti* 35% yield. ^{1}H NMR ($CDCl_3$) δ: 7.27–7.48 (m, 5H); 5.56 (m, 2H); 4.63 (d, 1H, J=11.6 Hz); 4.38 (d, 1H, J= 11.6 Hz), 3.66 (s, 3H), 3.62 (s, 3H), 3.50 (m, 1H), 3.27 (m, 1H), 3.04 (2H, d, J=6 Hz), 2.37 (m, 1H), 1.18 (d, 3H, J=6 Hz), 1.12 (d, 3H, J=6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 171.2, 135.8, 133.4128.6, 127.2, 121.9, 99.470.8, 67.3, 51.2, 41.0, 38.3, 37.1, 19.5, 17.2, 14.9. IR (neat) cm^{-1}: 3433, 1653, 1457, 1252, 1018.

General procedure for the cyclization of the homoallylic amine illustrated with 3-benzyloxy-2-(*S*)-methyl-propionyaldehyde

Cleavage of olefin **18a** by ozonolysis and reduction of the crude aldehyde yielded the corresponding crude alcohol (20 mg, 0.067 mmol) which was taken up in toluene (1.5 mL) and excess K_2CO_3 was added. The solution was then heated until all the toluene evaporated followed by an additional heating for 10 min. The residue was the diluted in CH_2Cl_2 (2 mL) and filtered through a pad of Celite®. After concentration under reduced pressure and purification on SiO_2, the desired oxizolidinone **19a** was obtained as a colorless oil (12 mg, 0.045 mmol, 68%).

Oxazolidinone (19a). ^{1}H NMR ($CDCl_3$) δ: 7.25–7.37 (m, 5H), 6.63 (b, 1H), 4.52 (s, 2H), 4.27 (dd, 1H, J_1=2.4 Hz, J_2=8.4 Hz), 4.08 (dd, 1H, J_1=2.0 Hz, J_2=8.8 Hz), 3.49 (dd, 1H, J_1=3.2 Hz, J_2=6.4 Hz), 3.35 (m, 2H), 1.96 (m, 1H), 1.85 (m, 1H), 1.05 (d, 3H, J=6.8 Hz), 0.80 (d, 3H, J=7.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 169.3; 128.6; 128.0; 127.8; 75.9; 73.6; 72.5; 60.5; 34.3; 27.6; 13.0; 9.4.

Oxazolidinone (19b). ^{1}H NMR ($CDCl_3$) δ: 7.33 (m, 5H); 5.55 (br, 1H); 4.50 (ABq, 2H, J_1=11.2 Hz, J_2=10.8 Hz); 4.23 (ABq, 2H, J_1=10.8 Hz, J_2=10.8 Hz); 3.40 (m, 2H); 2.03 (m, 1H); 1.21 (d, 3H, J=2.0 Hz); 1.03 (d, 3H, J=6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 169.3; 128.7; 128.1; 127.8; 75.6; 72.4; 70.9; 58.8; 29.8; 26.7; 14.9; 10.2.

Oxazolidinone (19e). ^{1}H NMR ($CDCl_3$) δ: 7.53 (m, 5H); 4.68 (d, 1H, J=12 Hz), 4.4 (d, 1H, J=12 Hz), 4.24 (m, 1H),

3.94 (m, 2H), 3.75 (m, 1H), 2.37 (m, 1H), 1.33 (d, 3H, J=6.4 Hz), 0.85 (d, 3H, J=6.8 Hz).

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