Articles

Stereoselective "Ene" Reaction of Allylsilanes with Amino Aldehydes. An Application to the Synthesis of Potential HIV-1 Protease Inhibitors

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2-Substituted 3-(trimethylsilyl)-1-propenes react with *N*-Boc-α-amino aldehydes in the presence of BF_3·OEt_2 to give homoallylic alcohols, potential intermediates for the synthesis of hydroxyethylene peptide isosteres. The reaction gives a predominance of the syn products, but 2-(chloromethyl)-3-(trimethylsilyl)-1-propene (**5**) exhibits a higher stereoselectivity with respect to other analogous allylsilanes. We hypothesize that this selectivity is due to an "ene" reaction followed by desilylation in the reaction medium (BF_3·OEt_2, $CHCl_3$). This reaction shows applicability to the synthesis of potential HIV-1 protease inhibitors. The preparation of compound **3**, which has a structure related to the potent inhibitor L-682,679, is described.

The rapid spread of the acquired immunodeficiency syndrome (AIDS) epidemic has stimulated a world-wide search for therapeutic agents to stop the replication of the causative virus, human immunodeficiency virus (HIV).[1] The efforts to elucidate the mechanism of HIV proliferation led to the identification of several specific viral targets.[2] One promising possibility to interrupt the viral life cycle is the use of inhibitors of the virally encoded protease responsible for viral maturation. The HIV protease has been shown to belong to the class of aspartyl proteases that act at post integration steps of HIV replication. A number of paradigms have been developed for designing inhibitors of aspartyl proteases. These strategies generally involve the incorporation of a dipeptide isostere that resembles the tetrahedral intermediate for peptide bond hydrolysis. Peptide-based substrate analogues were the first inhibitors of protease reported to be active in vitro[3] and were the first to enter clinical trials. The inserts used in place of the P_1 and P'_1 residues of the substrate peptides include hydroxyethylene ($CH(OH)CH_2$), hydroxyethylamine ($CH(OH)CH_2N$), and dihydroxyethylene ($CH(OH)CH(OH)$) moieties.[4]

We recently described the stereoselective synthesis of the core of potent HIV-1 protease inhibitor **1** through the reaction between 2-(chloromethyl)-3-(trimethylsilyl)-1-propene and *N*-Boc-phenylalaninal.[5] At the same time, a structure–activity study showed that compounds related to structure **2** have higher activity;[6] interestingly, structures **1** and **2** differ only by a vinyl group. In our continuing effort to design and synthesize useful amino alcohols as potential inhibitors for the viral encoded protease, we decided to prepare compound **3**, which could be also considered as a new building block for the synthesis of efficacious modified peptides acting as HIV-1 protease inhibitors.

The Lewis acid-mediated reaction of allylsilanes with aldehydes is a well-known procedure for the preparation of homoallylic alcohols.[7] Protected α-amino aldehydes derived from α-amino acids have been used as electrophiles to prepare enantiomerically pure amino alcohol derivatives.[5,8,9] The stereochemistry of this reaction is reported to follow Cram's rules and to give generally good levels of stereocontrol.[9,10]

For these reasons we decided to follow the retrosynthetic analysis described in Scheme 2. This approach is versatile because allylsilanes with various substituents on the aromatic ring could be prepared from the corresponding substituted cinnamoyl ethyl esters and [(tri-

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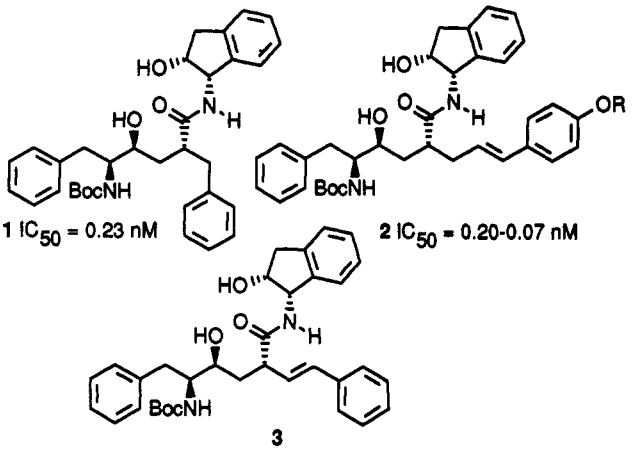
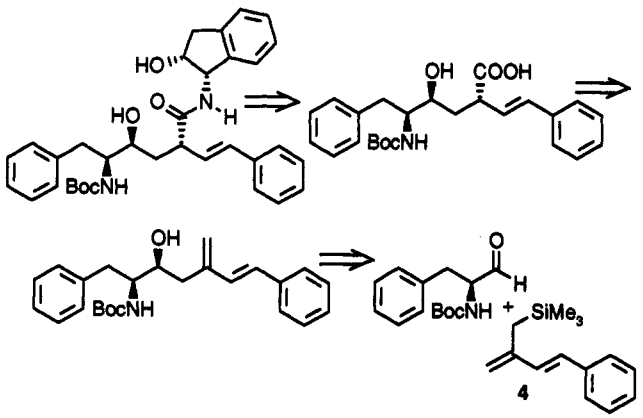
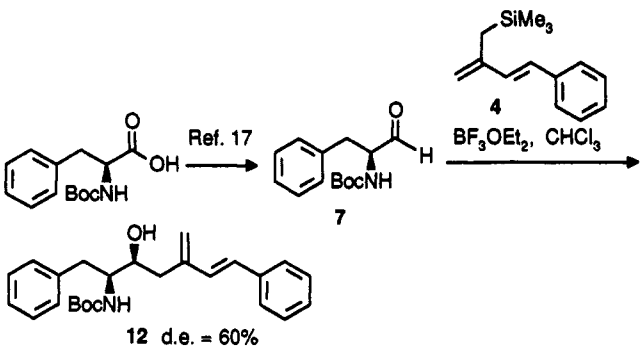
Scheme 1



Scheme 2



Scheme 3

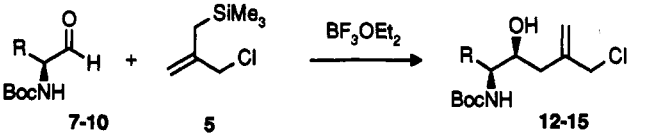


methylsilyl)methyl]magnesium chloride in the presence of anhydrous $CeCl_3$.[11]

Allylsilane **4** was obtained by means of this procedure and was allowed to react with *N*-Boc-phenylalaninal (**7**) in the presence of BF_3·OEt_2 to give homoallylic alcohol **12** in 76% yield. As was immediately clear from the ^1H NMR of the crude product, a mixture of diastereoisomers was obtained in a 4:1 ratio in favor of the syn product (see below and Experimental Section). This result was rather disappointing because we had previously observed high diastereoselectivity in a similar reaction with 2-(chloromethyl)-3-(trimethylsilyl)-1-propene (**5**), an allylsilane with a structure similar to that of **4**.[5]

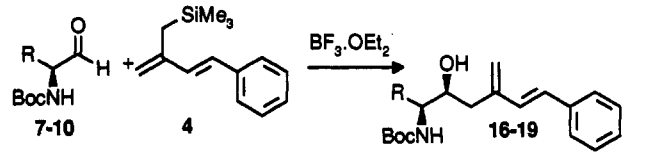
The differing diastereoselectivity observed with allylsilanes **4** and **5** could be linked to the steric bulk of the substituents attached to the double bond and/or to the

Scheme 4



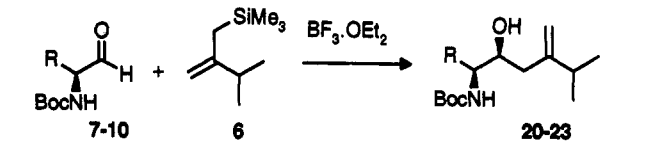
Starting AA	R =		Yield	d.e
Phe	$PhCH_2$	**7, 12**	72%	> 95 %
Leu	$(CH_3)_2CHCH_2$	**8, 13**	67%	> 95 %
Ile	$C_2H_5(CH_3)CH$	**9, 14**	62%	92 %
Ala	CH_3	**10, 15**	66%	93 %

Scheme 5



Starting AA	R =		Yield	d.e.
Phe	$PhCH_2$	**7, 16**	73%	60%
Leu	$(CH_3)_2CHCH_2$	**8, 17**	65%	60%
Ile	$C_2H_5(CH_3)CH$	**9, 18**	70%	50%
Ala	CH_3	**10, 19**	73%	60%

Scheme 6



Starting AA	R =		Yield	d.e.
Phe	$PhCH_2$	**7, 20**	61%	50 %
Leu	$(CH_3)_2CHCH_2$	**8, 21**	65%	40 %
Ile	$C_2H_5(CH_3)CH$	**9, 22**	61%	50 %
Ala	CH_3	**10, 23**	67%	20 %

coordination to the Lewis acid.[12] Therefore, we decided to examine the stereochemistry of the products obtained from allylsilanes **4**–**6** with different *N*-Boc-amino aldehydes **7**–**10** in the presence of Lewis acids. Results of this screening are reported in Schemes 4–6.

The ratios between the diastereomers described in Schemes 4–6 were determined from the ^1H NMR spectra of the crude products by integration of the NH signals, which always differed by 0.2–0.4 ppm, and the ratios were confirmed (when possible) with the integration of other well-separated signals. Products **12**–**23** were further purified by column chromatography on silica gel and fully characterized. The *syn/anti* stereochemistry was determined on the corresponding oxazolidinones **24**–**35** by comparison of the coupling constants J_{4-5} with those reported in the literature (see supplementary material).[13]

A comparative analysis of the stereochemistry of the products was also performed on representative products **12**, **15**, **16a**, **16b**, **20a**, and **20b**. They were transformed

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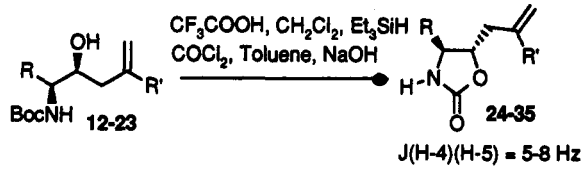
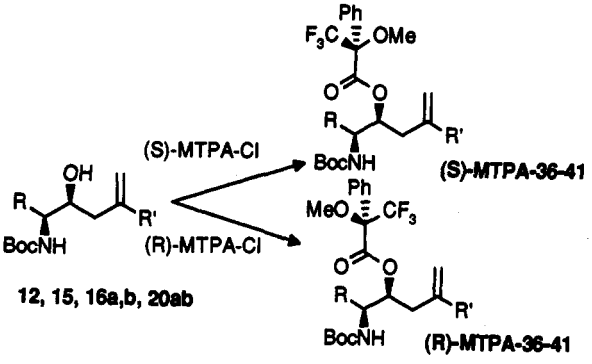
Scheme 7



Scheme 8



into the (*R*)- and the (*S*)-MTPA esters (Scheme 8) in order to verify the enantiomeric integrity of the products and to assign the absolute stereochemistry of the newly formed stereogenic centers (see the δ values in the supplementary material).[14]

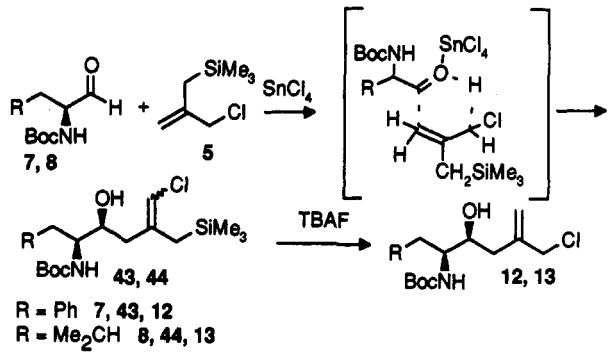
We also investigated the influence of the solvent and the Lewis acid on the diastereoisomeric ratio of the products obtained. We observed that the combination $BF_3{\cdot}OEt_2/CHCl_3$ gave the best results in terms of chemical yields and diastereomeric excesses. Only aldehydes **8** and **10** gave the expected products (namely, products **21** and **22**) when allowed to react with allylsilane **6** in the presence of $TiCl_4$ or $SnCl_4$ at −63 °C in $CHCl_3$ or at −78 °C in CH_2Cl_2; but the yields ranged from 10 to 35%, and the stereoselectivity was improved only modestly with respect to that of the reaction performed in the presence of $BF_3{\cdot}OEt_2$.

The diastereomeric composition of the product mixture was influenced by the nature of the substituent on the allylsilane. The rank order observed was **5** > **4** > **6**, and the diastereomeric composition was independent of the nature of the R group of the amino aldehyde. Nevertheless, only reaction with allylsilane **5** gave a high level of stereoselectivity, giving the syn product (*S*,*S*). According to the models proposed for the transition state of the reaction between allylsilanes and aldehydes (antiperiplanar or synclinal),[7] the substituents on the double bond are far away from the reacting center and should not influence the selectivity.

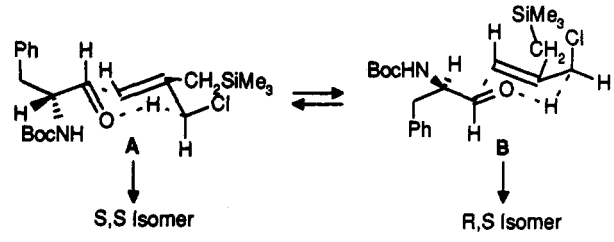
On the basis of all the above considerations, another proposal could be put forward to account for the difference observed between allylsilane **5** and the two others (**4** and **6**). We hypothesize that allylsilane **5** reacts through a different mechanism, an "ene" mechanism, to give an intermediate substituted allylsilane (**43** or **44** in Scheme 9), which can be further desilylated (in situ) by $BF_3{\cdot}OEt_2$ in $CHCl_3$ to give the final product.

To gain experimental support for this hypothesis, we tried to detect the assumed intermediate (**43** or **44**) through analysis of the reaction mixture via gas chromatography/mass spectroscopy. However, when the reaction was carried out in the presence of $BF_3{\cdot}OEt_2$ we were not able to detect these products. On the other hand, when the reaction of aldehyde **7** or **8** with allylsilane **5** was carried out using $SnCl_4$ as the Lewis acid and was quenched with Na_2CO_3 at −60 °C, we isolated product **43** or **44** in 20−30% yield. Treatment of these allylsilanes with TBAF in THF afforded products **12** and **13**, which were identical to the products obtained through the $BF_3{\cdot}OEt_2$-mediated reaction. This experiment could confirm our assumption that allylsilane **5** reacts through an ene mechanism. The high level of stereoselectivity obtained in this reaction could be interpreted as reflecting the preference of the chlorine for an equatorial position in model A, shown in Scheme 10.[15]

Scheme 9



Scheme 10



2-(Chloromethyl)-3-(trimethylsilyl)-1-propene (**5**) is more inclined to react with activated aldehydes as an electron-rich olefin. In this case, **5** stereoselectively gives the product coming from an "ene" reaction. This intermediate allylsilane is desilylated directly in the reaction mixture to give the homoallylic alcohol. The other allylsilanes employed in this work (**4** and **6**), structurally similar to **5**, react by the "normal" mechanism of nucleophilic displacement of the silicon via an acyclic transition state and give the same kind of final products but with lower stereoselectivity.

On the basis of those results, we decided to modify the planned strategy to prepare diene **3** using the more stereoselective reagent **5** instead of allylsilane **4**. First we transformed **12** into phosphonate **47** and attempted to perform an Emmons−Horner reaction with benzaldehyde. After protection of the NH and OH groups of **12** as the dimethyloxazolidine and transformation of chloride **45** into iodide **46**, reaction with triethyl phosphite at 140 °C for 2 h followed by removal of iodoethane and the excess of triethylphosphite under vacuum gave phosphonate **47**. Unfortunately, several attempts to generate the ylide from compound **47** were unsuccessful (we tried NaH/THF, LDA/THF, $LiN(SiMe_3)_2$/THF/toluene, DBU/LiCl/THF), generally giving unchanged starting materials and several byproducts.

We decided to invert the sequence in the carbon−carbon double bond formation. Therefore, allylic chloride

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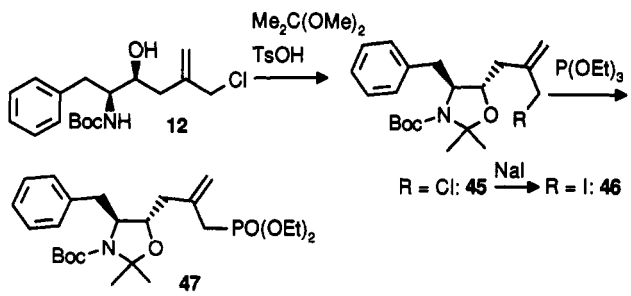
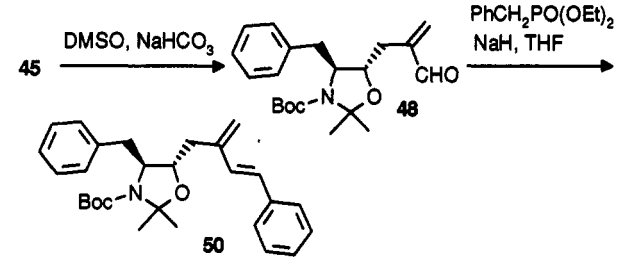
Scheme 11



Scheme 12



45 was transformed into α,β-unsaturated aldehyde **48** by means of the Kornblum oxidation (DMSO and $NaHCO_3$ at 90 °C for 12 h).[16] Reaction of **48** with diethyl benzylphosphonate in the presence of NaH gave product **50**, which was isolated by column chromatography on silica gel in 67% yield. Product **50** was a single isomer by HPLC analysis. The ^1H NMR spectrum suggested the formation of the *E* isomer, but the assignment of this stereochemistry was not verified until a later step of the synthesis.

Oxidative hydroboration with BH_3·THF selectively gave primary alcohol **51** as a mixture of diastereomers (**51a** and **51b** in a 55:45 ratio). The use of the more hindered dicyclohexylborane gave excellent results in terms of stereoselectivity, giving product **51a** in 60% yield with a de of 80%. At this stage we were not able to establish the configuration of the newly formed stereogenic center. Nevertheless, we carried out the synthesis on the major isomer (**51a**), purified by column chromatography, postponing the determination of its structure until a later step.

Alcohol **51a** was oxidized to aldehyde **52** by means of the typical Swern oxidation conditions and then oxidized to acid **53** with $NaClO_2$/2-methyl-2-propene. This two-step procedure gave better results than direct oxidation of the alcohol with the Jones reagent. Oxazolidinone **53a** was transformed into *N*-Boc-amino alcohol **54a** with BF_3·CH_3COOH in MeOH. Product **54a** cyclized to lactone **55a** with triflic anhydride and pyridine at −30 °C. The structure of lactone **55a** was determined by comparison of the NOE spectrum with that of lactone **55b**. Product **55a** did not show any NOE effect between the protons in positions 3 and 5 of the lactone, whereas in the spectrum of product **55b** there was a significant NOE (about 10%) between the same protons. This result is consistent with *trans* relationship in the lactone ring for the major isomer **55a**. The trans stereochemistry of the double bond was determined by the value of the $J_{(trans)}$ (17 Hz) shown after selective decoupling on the proton in position 3 of the lactone.

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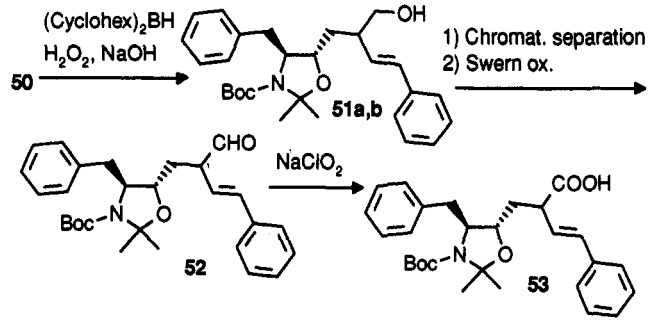
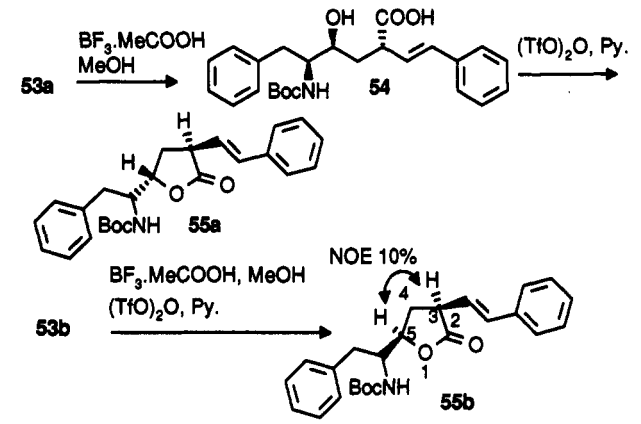
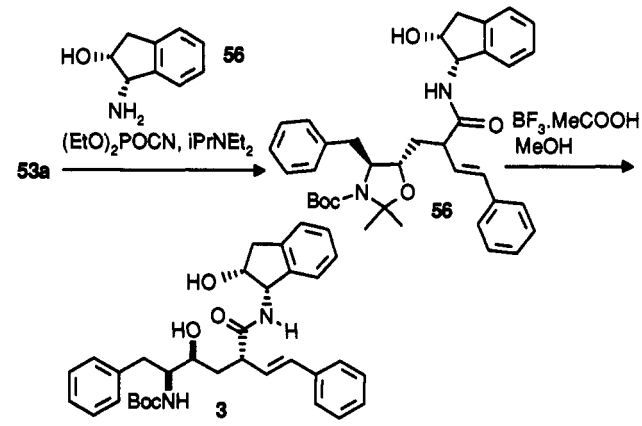
Scheme 13



Scheme 14



Scheme 15



Product **3** was prepared from acid **53a**. Condensation of **53a** with 1(*S*)-amino-2(*R*)-hydroxyindan[18] (**56**) (diethyl phosphorocyanidate, diisopropylethylamine) gave amide **56**, which was deprotected to give product **3**. When submitted to the HIV-1 protease inhibition tests, **3** gave an $IC_{50} = 1.2$ nM; this value was determined via a peptide hydrolysis assay. This result was encouraging when compared with the result obtained with product **2**,[6] and the activity may be improved by variation of the substituents on the phenyl ring or the introduction of this frame into a more complex peptidic sequence.

Experimental Section

^1H and ^{13}C NMR were obtained at 200 and 50 MHz, respectively, in $CDCl_3$. Mass spectra were recorded on a low-resolution instrument in the electron-impact mode (EI) at 70 eV. Air- and/or moisture-sensitive reactions were conducted

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Table 1. Spectroscopic Characterization of Products 12–23

product	^{1}H NMR	^{13}C NMR	MS (*m/z*)
12	1.40 (s, 9H), 2.2 (b, 1H, OH), 2.35 (m, 2H), 2.90 (m, 2H), 3.8 (m, 2H), 3.98 (m, 2H), 4.8 (bd, 1H), 5.03 (m, 1H), 5.25 (m, 1H), 7.2 (m, 5H)	28.8, 37.6, 37.9, 48.2, 56.4, 69.0, 79.9, 118.6, 126.9, 128.3, 129.9, 138.6, 142.1, 155.6	340 (M^+), 304, 248, 192, 120, 91, 57
13	0.92 (d, J = 7 Hz, 3H), 1.3–1.7 (bm, 3H), 1.44 (s, 9H), 2.15 (bd, 1H), 2.3 (AB part of a ABX system, 2H), 3.6 (m, 1H), 3.7 (m, 1H), 4.09 (s-like, 2H), 4.6 (bd, 1H, NH), 5.09 (s-like, 1H), 5.26 (s-like, 1H)	22.6, 23.7, 25.3, 28.8, 39.0, 42.0, 48.7, 52.9, 72.1, 79.8, 118.5, 142.6, 158.6	305 (M^+), 250, 186, 130, 86, 57
14	0.9 (m, 6H), 1.2 (m, 1H), 1.45 (s, 9H), 1.6 (m, 2H), 2.1 (bd, 1H), 2.3 (m, 2H), 3.3 (m, 1H), 3.9 (m, 1H), 4.1 (s-like, 2H), 4.75 (bd, 1H), 5.1 (s-like, 1H), 5.3 (s-like, 1H)	14.6, 18.6, 26.2, 28.0, 39.1, 40.1, 48.6, 58.6, 69.7, 79.7, 188.7, 143.6, 158.0	295 (M^+), 238, 233, 57
15	1.20 (d, 3H), 1.41 (s, 9H), 2.3 (8 lines, AB part of an ABX system, 2H), 2.5 (bd, 1H), 3.6 (m, 2H), 4.05 (s-like, 2H), 4.65 (bd, 1H), 5.05 (s-like, 1H), 5.26 (s-like, 1H)	19.0, 28.7, 38.9, 48.7, 50.1, 73.2, 79.8, 118.6, 142.4, 156.2	263 (M^+), 196, 171, 166, 57
16a	1.4 (s, 9H), 2.1 (bs, 1H), 2.5 (m, 2H), 2.9 (m, 2H), 3.8 (m, 2H), 4.9 (bs, 1H), 5.21 (s-like, 1H), 5.32 (s-like, 1H), 6.6 (d, J = 16 Hz, 1H), 6.82 (d, J = 16 Hz, 1H), 7.3 (m, 5H)	28.6, 37.9, 38.9, 54.5, 69.0, 79.6, 118.8, 128.5, 128.6, 129.2, 129.8, 129.9, 13.8, 138.4, 142.3, 156.9	393 (M^+), 378, 337, 322, 293, 246, 129, 115, 91, 57
16b	1.4 (s, 9H), 2.1 (bs, 1H), 2.5 (m, 2H), 2.9 (m, 2H), 3.8 (m, 2H), 4.5 (bs, 1H), 5.31 (s-like, 1H), 5.41 (s-like, 1H), 6.6 (d, J = 16 Hz, 1H), 6.82 (d, J = 16 Hz, 1H), 7.3 (m, 5H)	28.6, 37.9, 38.9, 56.5, 72.2, 79.6, 118.8, 128.5, 128.6, 129.2, 129.8, 129.9, 13.8, 138.4, 142.3, 156.9	393 (M^+), 378, 337, 322, 293, 246, 129, 115, 91, 57
17	0.89 (d, J = 7 Hz, 3H), 1.2–1.7 (bm, 3H), 1.4 (s, 9H), 2.2 (bd, 1H), 2.5 (m, 2H), 3.7 (m, 2H), 4.8 (bd, 1H), 5.2 (s-like, 1H), 5.4 (s-like, 1H), 6.6 (d, J = 17 Hz), 6.8 (d, J = 17 Hz), 7.3 (m, 5H)	25.7, 27.9, 28.4, 39.2, 39.7, 50.5, 70.1, 79.9, 118.6, 129.9, 128.5, 129.2, 136.8, 138.4, 142.2, 156.7	359 (M^+), 302, 225, 207, 91, 57
18	0.9 (m, 6H), 1.3 (m, 1H), 1.4 (s, 9H), 1.6 (m, 2H), 2.2 (bd, 1H), 2.4 (m, 2H), 3.7 (m, 1H), 3.8 (m, 1H), 4.7 (bd, 1H), 5.2 (s-like, 1H), 5.5 (s-like, 1H), 6.6 (d, J = 16 Hz), 6.8 (d, J = 16 Hz), 7.3 (m, 5H)	15.1, 18.9, 26.6, 28.4, 30.2, 39.8, 58.6, 70.2, 79.6, 118.9, 128.5, 129.2, 129.8, 136.4, 137.8, 142.4, 154.9	359 (M^+), 302, 225, 207, 91, 57
19	1.25 (d, J = 7 Hz, 3H), 1.40 (s, 9H), 2.4 (m, 2H), 2.5 (bd, 1H), 3.6 (m, 2H), 4.7 (bd, 1H), 5.2 (s-like, 1H), 5.5 (s-like, 1H), 6.6 (d, J = 16 Hz), 6.8 (d, J = 16 Hz), 7.3 (m, 5H)	18.0, 27.6, 28.9, 31.0, 39.8, 58.9, 71.0, 79.6, 118.9, 128.5, 129.2, 129.8, 136.4, 137.8, 142.4, 154.9	317 (M^+), 280, 245, 227, 91, 57
20a	1.1 (m, 3H), 1.4 (s, 9H), 2.15 (b, 1H), 2.22 (m, 1H), 2.31 (m, 1H), 2.95 (m, 2H), 3.70 (m, 1H), 3.9 (m, 1H), 4.75 (bd, 1H), 5.10 (m, 1H), 5.21 (m, 1H), 7.2 (m, 5H)	20.0, 22.6, 28.7, 37.6, 38.7, 39.9, 59.6, 69.3, 79.3, 118.9, 126.9, 128.9, 129.7, 142.1, 155.6	333 (M^+), 276, 216, 91, 57
20b	1.1 (m, 3H), 1.4 (s, 9H), 2.15 (b, 1H), 2.22 (m, 1H), 2.31 (m, 1H), 2.95 (m, 2H), 3.8 (m, 1H), 3.9 (m, 1H), 4.15 (bd, 1H), 5.10 (m, 1H), 5.26 (m, 1H), 7.2 (m, 5H)	20.0, 22.6, 28.7, 36.9, 37.9, 39.1, 58.9, 66.3, 79.3, 118.9, 126.9, 128.9, 129.7, 142.1, 155.6	333 (M^+), 276, 216, 91, 57
21	0.9 (m, 6H), 1.1 (m, 6H), 1.2–1.7 (bm, 3H), 1.45 (s, 9H), 2.35 (m, 2H), 2.48 (m, 1H), 2.9 (bd, 1H), 3.50 (t-like, 1H), 3.9 (m, 1H), 4.85 (bd, 1H), 5.10 (s-like, 1H), 5.30 (s-like, 1H)	20.2, 22.1, 22.6, 23.2, 25.2, 28.5, 36.9, 39.7, 39.1, 56.7, 56.7, 69.9, 79.3, 119.2, 142.1, 154.6	299 (M^+), 2452, 212, 57
22a	0.9 (m, 6H), 1.1 (m, 6H), 1.3 (m, 1H), 1.4 (s, 9H), 1.5 (m, 2H), 2.0 (bd, 1H), 2.3–2.5 (bm, 3H), 3.8 (m, 1H), 3.9 (m, 1H), 4.6 (bd, 1H), 5.1 (s-like, 1H), 5.3 (s-like, 1H)	14.8, 18.8, 20.4, 22.0, 24.8, 26.4, 28.4, 39.0, 39.7, 40.1, 58.5, 69.7, 79.3, 79.3, 118.9, 142.3, 154.9	299 (M^+), 2452, 212, 57
22b	0.9 (m, 6H), 1.1 (m, 6H), 1.3 (m, 1H), 1.4 (s, 9H), 1.5 (m, 2H), 2.0 (bd, 1H), 2.3–2.5 (bm, 3H), 3.7 (m, 1H), 3.9 (m, 1H), 4.4 (bd, 1H), 5.1 (s-like, 1H), 5.2 (s-like, 1H)	14.8, 18.8, 21.0.4, 22.8, 25.6, 26.4, 28.7, 39.0, 39.7, 40.1, 57.8, 69.7, 79.3, 79.3, 118.9, 142.3, 154.9	299 (M^+), 2452, 212, 57
23	1.0 (m, 6H), 1.2 (d, 3H), 1.4 (s, 9H), 2.1 (bd, 1H), 2.1–2.5 (m, 3H), 3.7 (m, 1H), 3.9 (m, 1H), 4.8 (bd, 1H), 5.1 (s-like, 1H), 5.3 (s-like, 1H)	19.7, 20.9, 22.1, 28.7, 39.1, 40.2, 51.2, 71.6, 79.9, 118.1, 143.0, 155.6	257 (M^+), 200, 170, 57

under an atmosphere of dry nitrogen or argon using oven-dried glassware and standard syringe/septum techniques. Methylene chloride and chloroform were washed with water, dried over $CaCl_2$, and stored in the dark on molecular sieves (4 Å). THF and ether were distilled from Na and further distilled twice from $LiAlH_4$ just before use. The organic extracts of crude products were dried over anhydrous Na_2SO_4.

Reaction of Allylsilanes 4–6 with Aldehydes 7-10. General Procedure. (4*S*,5*S*)-5-((*tert*-Butoxycarbonyl)amino)-2-(chloromethyl)-6-phenyl-1-hexen-4-ol (12). To a stirred solution of aldehyde **7** (0.5 g, 2.2 mmol) in $CHCl_3$ (5 mL) cooled to −60 °C was added BF_3·OEt_2 (0.43 g, 3 mmol) followed by allylsilane **5** (0.73 g, 3.4 mmol) and $CHCl_3$ (3 mL). The reaction mixture was stirred at −60 °C for 5 h (until no more aldehyde was detected by TLC analysis). A saturated solution of $NaHCO_3$ (5 mL) and then ether (20 mL) were added, and the mixture was warmed to rt under vigorous stirring. The organic layer was separated, washed with 10% NH_4Cl solution and brine, and dried. After evaporation of the solvent, the crude was submitted to ^{1}H NMR analysis, which showed the presence of a single diastereoisomer. Product **12** was purified by column chromatography on silica gel (hexane/ethyl acetate, 1/1).

The characterization of product **12** (together with that of products **13-23**) is reported in Table 1.

(4*S*,5*S*)-5-((*tert*-Butoxycarbonyl)amino)-1-chloro-6-phenyl-2-((trimethylsilyl)methyl)-1-hexen-4-ol (43). To a stirred solution of aldehyde **7** (0.7 g, 2.8 mmol) and allylsilane **5** (0.77 g, 4.7 mmol) in $CHCl_3$ (10 mL) cooled to −60 °C was added $SnCl_4$ (0.78 g, 3 mmol). After 1 h at −60 °C, a saturated solution of $NaHCO_3$ (10 mL) and then ether (25 mL) were added. The mixture was warmed to rt under vigorous stirring, and the separated ethereal layer was dried. After evaporation of the solvent and column chromatography on silica gel (hexane/ethyl acetate, 4/1), four different fractions were collected. Product **43** was the compound with the higher R_f (0.2 g, 20% yield): ^{1}H NMR δ 0.06 (s, 9H), 1,4 (s, 9H), 2,1 (m, 2H), 2.3 (m, 3H), 2.9 (m, 2H), 3.85 (m, 1H), 4.01 (m, 1H), 4.7 (bd, 1H, NH), 6.0 (s, 1H), 7.2 (m, 5H); ^{13}C NMR δ -0.10 (3C), 24.2 (3C), 37.0, 37.9, 41.0, 59.0, 70.4, 78.1, 126.2 (2C), 127.2, 129.6 (2C), 129.7, 142.1, 148.0, 154.6. Anal. Calcd. for $C_{21}H_{34}ClNO_3Si$: C, 61.21; H, 8.32; N, 3.40; O, 11.65; Si, 6.82; Cl, 8.60. Found: C, 61.78; H, 8.44; N, 3.54.

(4*S*,5*S*)-5-((*tert*-Butoxycarbonyl)amino)-1-chloro-7-methyl-2-((trimethylsilyl)ethyl)-1-octen-4-ol (44): ^{1}H NMR δ 0.06 (s, 9H), 0.9 (d-like, 6H), 1.3–1.7 (m, 3H), 1.45 (s, 9H), 1.9 (bd, 1H, OH), 2.1 (m, 2H), 2.2 (m, 2H), 3.7 (m, 2H), 4.7 (bd, 1H, NH), 5.8 (s, 1H); ^{13}C NMR δ −0.10 (3C), 22.1, 23.2, 24.8 (3C), 26.4, 38.2, 39.1, 40.1, 54.4, 73.1, 78.6, 127.7, 148.3, 154.6. Anal. Calcd for $C_{18}H_{36}ClNO_3Si$: C, 57.19; H, 9.60; N, 3.71; O, 12.70; Si, 7.43; Cl, 9.38. Found: C, 56.98; H, 9.49; N, 3.66.

Transformation of Allylsilane 43 into Product 12.

Product **43** (0.20 g, 0.48 mmol) was dissolved in dry THF (5 mL), and TBAF (0.13 g, 0.5 mmol) was added. The mixture stirred for 2 h at room temperature, the solvent was evaporated, and the product was isolated by column chromatography on silica gel (hexane/ethyl acetate, 1/1). The product obtained from this column (0.10 g, 60% yield) was identical with the product obtained from **7** and allylsilane **5**.

(4*S*,5*S*)-4-Benzyl-3-(*tert*-butoxycarbonyl)-5-(2-(chloromethyl)-3-propenyl)-2,2-dimethyl-1,3-oxazolidine (45). A solution of amino alcohol derivative **3** (0.76 g, 2.2 mmol) and *p*-toluenesulfonic acid (16 mg) in 2,2-dimethoxyethane (3 mL) was stirred for 46 h at rt. Ether (10 mL) was added, and the organic layer was washed with 10% $NaHCO_3$ and dried. After evaporation of the solvent, column chromatography on silica gel (hexane/ethyl acetate, 6/1) gave product **45** (0.68 g, 84% yield) as an oil: ^1H NMR δ 1.52 (s, 9H), 1.58 (s, 6H), 2.1 (bm, 1H), 2.2 (m, 1H), 2.7 (bm, 1H), 3.25 (m, 1H), 3.8 (m, 3H), 4.05 (m, collapsing to a d upon strong irradiation at 2.5 ppm, J = 5 Hz, 1H), 4.6 (m, 1H), 5.0 (m, 1H), 7.2 (m, 5H); ^{13}C NMR δ 24.4, 27.5, 29.0, 38.4, 38.6, 48.4, 48.8, 63.5, 80.5, 92.5, 117.5, 127.1, 130,0, 130,2, 138.1, 141.9, 153.2; MS *m/z* 379 (M^+, 4), 290 (15), 288 (30), 232 (25), 190 (10), 188 (65), 57 (100). Anal. Calcd for $C_{21}H_{30}NO_3Cl$: C, 53.39; H, 7.96; N, 3.96; O, 12.63; Cl, 9.33. Found: C, 63.89; H, 7.87; N, 3.76.

(4*S*,5*S*)-4-Benzyl-3-(*tert*-butoxycarbonyl)-5-(2-iodo methyl)-3-propenyl)-2,2-dimethyl-1,3-oxazolidine (46). A mixture of product **45** (0.5 g, 3.2 mmol) and anhyd NaI (0.66 g, 3.2 mmol) in acetone (3 mL) was stirred in the dark for 12 h. Ether (20 ml) was added, the mixture was filtered through Celite, and the residue was washed several times with ether. The filtrate was concentrated, ether was added, and the mixture was filtered through a small sintered-glass funnel. The solvent was evaporated to give crude **46** as a yellow oil (0.55 g, 88% yield), which could be purified by column chromatography on silica gel (hexane/ethyl acetate, 10/1): ^1H NMR δ 1.52 (s, 9H), 1.58 (s, 6H), 2.2 (bm, 1H), 2.35 (m, 1H), 2.6 (m, 1H), 3.26 (m, 1H), 3.68 (m, 2H), 3.77 (m, 1H), 4.02 (m, 1H), 4.76 (m, 1H), 5.11 (m, 1H), 7.2 (m, 5H); ^{13}C NMR δ 11.0, 18.7, 24.7, 29.0, 39.5, 39.4, 48.4, 49.9, 80.5, 98.6, 116.7, 127.2, 129.9, 130.1, 138.1, 143.3, 158.6; MS *m/z* 471 (M^+, 10), 400 (15), 324 (25), 280 (30), 91 (60), 57 (100). Anal. Calcd for $C_{21}H_{30}NO_3I$: C, 53.51; H, 6.41; N, 2.97; O, 10.18; I, 26.92. Found: C, 53.01; 6.51; N, 2.89.

(4*S*,5*S*)-4-Benzyl-3-(*tert*-butoxycarbonyl)-5-(2-((diethylphosphono)methyl)-3-propenyl)-2,2-dimethyl-1,3-oxazolidine (47). Product **46** (0.55 g, 1.17 mmol) and triethyl phosphite (0.235 g, 1.52 mmol) were heated at 140 °C for 2 h. The mixture was cooled, and the flask was connected to a vacuum pump and maintained for 6 h under vacuum (0.1 mmHg). The crude material was purified by short-path column chromatography (hexane/ethyl acetate, 6/1) to give **47** (0.54 g, 96%): ^1H NMR δ 1.26 (t, 6H), 1.53 (s, 15H), 2.0–2.7 (m, 4H), 3.2 (m, 1H), 3.8 (bs, 1H), 4.05 (m, 6H), 4.75 (bs, 1H), 4.9 (bs, 1H), 7.2 (m, 5H); ^{13}C NMR δ 16.9, 17.2, 27.6, 27.9, 28.9, 35.2, 37.5, 40.0, 42.0, 62.2, 62.5, 63.5, 80.4, 95.0, 117.8, 127.0, 128.9, 129.9, 136.9, 138.6, 152.6; MS *m/z* 481 (M^+, 5), 395 (21), 280 (20), 91 (60), 57 (100). Anal. Calcd for $C_{25}H_{40}NO_6P$: C, 62.35; H, 8.37; N, 2.91; O, 19.93; P, 6.43. Found: C, 62.65; H, 8.45; N, 2.89.

(4*S*,5*S*)-4-Benzyl-3-(*tert*-butoxycarbonnyl)-5-(2-formyl-3-propenyl)-2,2-dimethyl-1,3-oxazolidine (48). Product **45** (0.22 g, 0.6 mmol) in toluene (1 mL) was heated at 110 °C for 20 h in the presence of $NaHCO_3$ (100 mg, 1.2 mmol) and DMSO (5 mL). The mixture was cooled to rt, and water (2 mL) and diethyl ether (5 mL) were added. The organic layer was separated, washed with 10% $NaHCO_3$ (5 mL) and brine (10 mL), and dried. After evaporation of the solvent, short path column chromatography on silica gel (hexane/ethyl acetate, 4/1) gave product **48** (0.175 g, 82% yield): ^1H NMR δ 1.53 (s, 15H), 2.4 (m, 1H), 2.8 (m, 2H), 3.2 (m, 1H), 3.6 (m, 1H), 4.1 (m, 1H), 5.9 (s-like, 1H), 6.1 (s-like, 1H) 7.3 (m, 5H), 9.3 (s, 1H); ^{13}C NMR δ 26.5, 26.3, 27.4, 37.6, 42.5; 63.4; 63.9, 79.4, 90.1, 126.4, 129.0, 129.4, 129.9, 136.0, 145.5, 193.3; MS *m/z* 359 (M^+, 10), 302 (15), 256 (10), 91 (80), 57 (100). An elemental analysis was determined on the phenylhydrazone of aldehyde **48** (mp 104–105 °C). Anal. Calcd for $C_{27}H_{35}N_3O_3$: C, 72.13; H, 7.85; N, 9.35; O, 10.68. Found: C, 72.10; H, 7.88; N, 9.39.

(4*S*,5*S*)-4-Benzyl-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-5-(2-methylene-4-phenyl-4(*E*)-butenyl)-1,3-oxazolidine (50). NaH (22.7 mg of a 60% dispersion in mineral oil, 0.49 mmol), previously washed with ether, and benzyl diethyl phosphite (0.11 g, 0.49 mmol) in ether (1 mL) were reluxed for 20 min. After mixture was cooled to rt, aldehyde **48** (0.17 g, 0.49 mmol) in dry Et_2O (2 mL) was added. After 2 h of stirring at rt, the mixture was hydrolyzed with a saturated solution of NH_4Cl. The organic layer was washed with brine and dried. After evaporation of the solvent, column chromatography on silica gel (hexane/ethyl acetate, 5/1) gave product **50** (0.15 g, 73% yield): ^1H NMR δ 1.5 (s, 15H), 2.3 (AB part of an ABX system, 4 lines, 1H), 2.6 (AB part of an ABX system, 4 lines, 1H), 2.8 (m, 1H), 3.2 (m, 1H), 4.0 (m, 1H), 4.2 (m, 1H), 5.0 (m, 2H), 6.3 (m, collapsing to a doublet upon irradiation at 5.0 ppm, J = 16 Hz), 6.6 (m, collapsing to a doublet upon irradiation at 5.0 ppm, J = 16 Hz), 7.1–7.3 (m, 10H); ^{13}C NMR δ 26.1, 26.3, 27.0, 37.6, 42.6, 44.6, 63.4, 90.7, 119.3, 126.0, 126.7, 129.4 (2C), 129.7, 129.9, 136.0, 140.0, 146.5; MS *m/z* 433 (M^+, 10), 376 (15) 332 (25), 91(100), 77 (80), 57 (60). Anal. Calcd for $C_{28}H_{35}NO_3$: C, 77.56; H, 8.14; N, 3.23; O, 11.07. Found: C: 77.39; H, 8.10; N, 3.20.

(4*S*,5*S*)-4-Benzyl-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-5-(2(*S*)-(hydroxymethyl)-4-phenyl-4(*E*)-butenyl)-1,3-oxazolidine (51a). In a vial sealed with a rubber septum and cooled to 0 °C, borane–methyl sulfide (0.2 mL of a 2 M solution in THF, 0.4 mmol) was mixed with cyclohexene (64 mg, 0.8 mmol). After 3 h of stirring, the mixture was added to a flask containing diene **50** (0.150 g, 0.36 mmol) in dry THF (1 mL) cooled to −30 °C. The mixture was warmed to rt and stirred overnight. The reaction mixture was cooled to 0 °C, and ETOH (0.5 mL), NaOH 3 M (0.9 mL), and hydrogen peroxide 30% (0.66 mL) were added sequentially. The mixture was warmed to rt and stirred for 4 h. After dilution with NaOH 1 M (3 mL) the mixture was extracted with ether (three portions of 5 mL), and the organic layer was washed with NaOH, water, and brine. After drying and evaporation of the solvent, short-path column chromatography (hexane/ethyl acetate 1.5/1) gave product **51a** (0.110 g, 71% yield) as single diastereoisomer: ^1H NMR δ 1.5 (s, 15H), 1.9-2.5 (m, 4H), 2.9 (m, 1H), 3.2 (m, 1H), 3.9–4.1 (m, 3H), 4.3 (m, 1H), 5.8 (d, J = 17 Hz, 1H), 6.3 (m, 1H), 7.1–7.3 (m, 10H); MS *m/z* 451 (M^+, 6) 394 (15), 376 (45), 350 (30), 91 (100), 77 (80), 57 (75). Anal. Calcd for $C_{28}H_{37}NO_4$: C, 74.47; H, 8.26; N, 3.10; O, 14.17. Found: C, 74.39; H, 8.25; N, 3.07.

(4*S*,5*S*)-4-Benzyl-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-5-(2(*R*)-(hydroxymethyl)-4-phenyl-4(*E*)butenyl)-1,3-oxazolidine (51b). From the above chromatography was isolated **51b** (11 mg, 7% yield): ^1H NMR δ 1.5 (s, 15H), 1.9-2.5 (m, 4H), 2.9 (m, 1H), 3.2 (m, 1H), 3.9–4.1 (m, 2H), 4.4 (m, 1H), 4.7 (m, 1H), 5.7 (d, J = 17 Hz, 1H), 6.3 (m, 1H), 7.1–7.3 (m, 10H); MS *m/z* 451 (M^+, 5) 394 (25), 376 (35), 350 (20), 91 (100), 77 (55), 57 (80).

(4*S*,5*S*)-4-Benzyl-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-5-(2(*S*)-carboxy-4-phenyl-4(*E*)-butenyl)-1,3-oxaozolidine (53). Oxalyl chloride (36 mg, 0.29 mmol, 0.5 mL) and DMSO (46 mg, 0.6 mmol) were stirred in CH_2Cl_2 at −60 °C for 20 min. Alcohol **51a** (0.1 g, 0.22 mmol) in CH_2Cl_2 (0.5 mL) was added, and the mixture was stirred for 20 min. Triethylamine (60 mg, 0.6 mmol) was added, and the mixture was warmed to rt. CH_2Cl_2 (5 mL) and then HCl 1 M (2 mL) were added. The organic layer was wahed with brine, and after it was dried the solvent was evaporated. The crude product was dissolved in 2-methyl-2-propanol (2 mL) and 2-methylbutene (1 mL), and then a solution of $NaClO_2$ (0.17 g, 1.9 mmol) and NaH_2PO_4 (0.174 g, 1,3 mmol) in water (3 mL) were added. After 4 h of stirring at 40 °C, the volatile components of the mixture were removed under vacuum, $NaHCO_3$ (0.4 g) was added to the aqueous residue, and the solution was washed with hexane. The aqueous phase was acidified to pH 3 with HCl 3 M and extracted with ethyl acetate (two portions of 5 mL). After drying and evaporation of the solvent, product **53** was obtained as a solid sufficiently pure to be used in the next step (64 mg, 63% yield). The analytical sample was crystallied

from benzene: mp 76–78 °C; ^{1}H NMR δ 1.5 (s, 15H), 1.9–2.5 (m, 3H), 2.9 (m, 1H), 3.2 (m, 1H), 3.8 (m, 1H), 4.3 (m, 1H), 5.7 (d, J = 17 Hz, 1H), 6.2 (m, 1H), 7.1–7.3 (m, 10H), 10.6 (bs, 1H): MS m/z 465 (M^+, 12), 435 (18), 390 (60), 91 (100). Anal. Calcd for $C_{28}H_{35}NO_5$: C, 72.23; H, 7.58; N, 3.01; O, 17.18. Found: C, 72,39; H, 7.63, N, 3.11.

(3*S*,5*S*,6*S*)-6-((*tert*-butoxycarbonyl)amino)-3-carboxy-1,7-diphenyl-1(*E*)-hepten-5-ol (54). BF_3·MeCOOH (0.2 mL) and acid **53** (55 mg, 0.11 mmol) were stirred in MeOH (1 mL) at rt for 5 h. Solid $NaHCO_3$ (0.1 g) was added, and the mixture was stirred for 30 min. After filtration through Celite and evaporation of the solvent, column chromatography on silica gel (hexane/ethyl acetate, 2/1) gave product **53** (40 mg, 86% yield): ^{1}H NMR δ 1.5 (s, 9H), 1.9–2.5 (m, 4H), 2.9 (m, 1H), 3.2 (m, 1H), 3.8 (m, 1H), 4.3 (m, 1H), 5.4 (m, 1H), 5.7 (d, J = 17 Hz, 1H), 6.2 (m, 1H), 7.1–7.3 (m, 10H), 9.6 (bs, 1H); MS m/z 407 (M^+ – 18), 350 (20), 91 (100), 57 (80). Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34; N, 3.29; O, 18.80. Found C, 70.61; H, 7.39; N, 3.36.

3(*S*)-2(*E*)-Phenylethenyl)-5(*S*)-(1-((*tert*-butoxycarbonyl)amino)-2-phenethyl)tetrahydrofuran-2-one (55a). Product **54** (40 mg, 0.09 mmol) and trifluoromethanesulfonic anhydride (10 μL) were stirred at –20 °C for 2 h. Ether was added, and the mixture was washed with HCl 1 N. The organic layer was dried, and the solvent was evaporated to give product **55a** as a solid, which was crystallized from hexane: mp 81–83 °C (31 mg, 84% yield): ^{1}H NMR δ 1.5 (s, 9H), 1.9–2.3 (m, 2H), 2.9 (m, 1H), 3.2 (m, 2H), 3.8 (m, 1H), 4.8 (m, 1H), 5.4 (m, 1H), 5.7 (d, J = 17 Hz, 1H), 6.2 (m, 1H), 7.1–7.3 (m, 10H); MS m/z 407 (M^+, 10), 350 (25), 91 (40), 57 (100). Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.69; H, 7.17; N, 3.44; O, 15.70. Found: C, 73.73; H, 7.20; N, 3.49.

3(*R*)-(2(*E*)-Phenylethenyl)-5(*S*)-(1-((*tert*-butoxycarbonyl)amino)-2-phenethyl)tetrahydrofuran-2-one (55b): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.5 (s, 9H), 1.9–2.3 (m, 2H), 2.8 (m, 1H), 3.1 (m, 2H), 3.8 (m, 1H), 4.7 (m, 1H), 5.4 (m, 1H), 5.7 (d, J = 17 Hz, 1H), 6.3 (m, 1H), 7.1–7.3 (m, 10H); MS m/z 407 (M^+, 5), 350 (20), 91 (65), 57 (100).

1(*S*)-((5(*S*)-((*tert*-Butoxycarbonyl)amino)-4(*S*)-hydroxy-6-phenyl-2(*S*)-(2-phenylethenyl)esanoyl)amino)-2(*R*)-hydroxyindan (3). A solution of acid **53a** (55 mg 0.11 mmol), 1(*S*)-amino-2(*R*)-hydroxyindan[18] (**56**) (17 mg, 0.12 mmol), and diisopropylethylamine (20 μL, 0.13 mmol) in dichloromethane (1 mL) was cooled to 0 °C, and diethyl phosphorocyanidate (20 μL, 0.13 mmol) was added. The reaction mixture was stirred at rt overnight, and then CH_2Cl_2 (5 mL) and a saturated solution of NH_4Cl were added. The organic layer was dried, and the solvent was evaporated to give crude product **56**. This product was dissolved in MeOH (2 mL), and BF_3·CH_3COOH (10 μL) was added. The mixture was stirred 3 h at rt. Ether (5 mL) and then a saturated solution of $NaHCO_3$ (1 mL) were added. The organic layer was washed with brine and dried. Evaporation of the solvent and column chromatography on silica gel (ethyl acetate/hexane, 5/1) gave product **3** as a white solid: mp 176–178 °C; ^{1}H NMR δ 1.4 (s, 9H), 1.8 (m, 2H), 2.02 (d, J = 6Hz, 1H), 2.4 (m, 1H), 2.6 (m, 1H), 2.7 (m, 1H), 2.8–2.9 (m, 2H), 3.10 (m, 1H), 3.8 (bs, 1H), 4.4 (m, 1H), 4.9 (d, J = 10 Hz, 1H), 5.4 (m, 1H), 6.20 (dd, J = 7, 17 Hz, 1H), 6.45 (d, J = 17 Hz, 1H), 6.7 (b, 1H), 7.1–7.4 (m, 14H); MS m/z 556 (M^+, 5), 91 (15), 71 (40), 57 (100). Anal. Calcd for $C_{34}H_{40}N_2O_5$: C, 73.36; H, 7.24; N, 5.03. Found: C, 73.46; H, 7.22; N, 5.10.

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Supplementary Material Available: The general procedures for the preparation of oxazolidinones **24-35** and for the preparation of the MTPA esters of alcohols **12**, **15**, **16a,b**, and **20a,b**; a listing of the diagnostic ^{1}H NMR signals of products **24–35b** and **(*R*)-MTPA–** and **(S)-MTPA–36-4a**; and analytical data for compounds **12-35** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.