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Synthesis of Alkene Dipeptide Isosteres employing the Wittig-Still Rearrangement

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Abstract: A new approach to the synthesis of alkene dipeptide isosteres is reported which features the use of the [2,3]-Wittig-Still rearrangement, carried out in hexanes. Employing this rearrangement alkene dipeptide isosteres of "Gly-Xxx" are accessible starting from an α-β-unsaturated carbonyl compound. This is illustrated with the synthesis of the alkene dipeptide isostere of Gly-Ala as part of the tripeptide isostere Cbz-Phe-Glyψ[E-CH=CH]-(R,S)Ala-OH **20**, starting from crotonaldehyde. Alkene dipeptide isosteres of "Xxx-Gly" are accessible starting from an α-amino aldehyde derivative. As an example the synthesis of the dipeptide isostere of Phe-Gly as part of the tripeptide isostere Cbz-Phe-Pheψ[E-CH=CH]-Gly-OH **28** is described for which N-Tr-phenylalaninal was used as a starting material.

INTRODUCTION

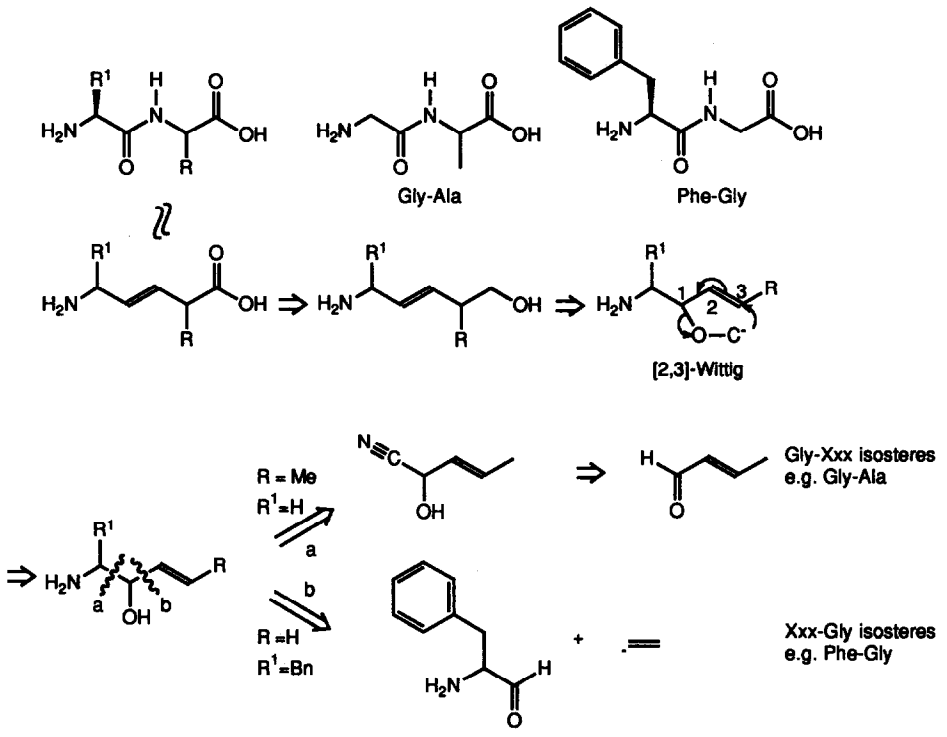
Peptide analogues containing isosteric replacements of the amide bond are of increasing importance[1]. By virtue of a close stereochemical resemblance to the parent peptide their biological activity is retained while they are inert to enzymatic hydrolysis[2]. In addition, peptide analogues in which replacement of the amide bond led to transition-state analogues have found a widespread use in the development of protease inhibitors[1,3] and -more recently- in the development of catalytic antibodies ("abzymes")[4].

The trans-alkene moiety[5,6] is a very suitable amide bond surrogate in terms of mimicking the rigidity, bond angles and bond length of the amide bond. Moreover, the trans carbon-carbon double bond locks the molecule in a trans-geometry whereas the amide bond can also exist in a cis-geometry. The importance of this particular isosteric replacement is also underlined by the considerable attention[7,8] it has received since the appearance of the seminal papers by Sammes et al.[5] and Cox et al.[6].

We are engaged in a program towards the design and synthesis of transition-state analogues[9], peptide isosteres and (rigid) secondary structure mimetics of the reverse turn. For this purpose we are interested in the development of new methods for the synthesis of alkene dipeptide isosteres.

A number of successful approaches towards the synthesis of alkene dipeptide isosteres has been reported[5-7]. Recently[10], we reported the clearly advantageous approach (retrosynthesis: scheme 1) in which a [2,3]-Wittig rearrangement[11,12] is employed to shift the double bond to the location corresponding to that of the amide bond in the parent peptide and, simultaneously, to introduce the carbon atom which will become the carboxylic acid functionality in the isostere. Another advantage of this approach is the possibility to transfer the chirality effectively from carbon-1 to carbon-3 when a homochiral reactant is used[11,13]. The Wittig rearrangement variant of Still[14], denoted as the Wittig-Still rearrangement[15-19], is excellently suited for the preparation of alkene dipeptide isosteres, because the generated carbanion (scheme 1) does not contain an anion stabilizing group[20], which would have to be removed ultimately, in order to obtain the carboxylic acid function of the isostere.

Two possible synthetic approaches of the amino alcohol necessary for the Wittig-rearangement are shown in scheme 1. The retrosynthetic route involving disconnection **a** ends at an α-β unsaturated carbonyl compound and is employed for the preparation of "Gly-Xxx" alkene dipeptide isosteres e.g. Gly-Ala (R=Me, R^1=H). The retrosynthetic route involving disconnection **b** ends at an α-amino aldehyde and a vinylic anion and is employed for the preparation of "Xxx-Gly" alkene dipeptide isosteres e.g. Phe-Gly (R=H, R^1=Bn).

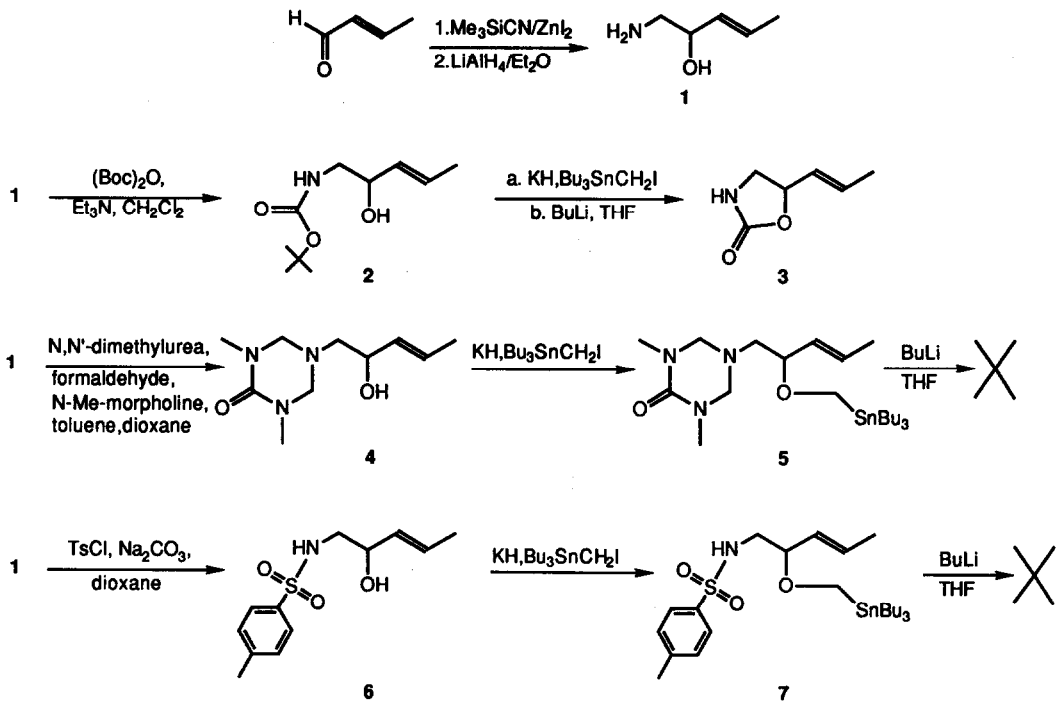


Scheme 1. Retrosynthesis of alkene dipeptide isosteres employing a [2,3]-Wittig rearrangement

In this paper we describe in detail the synthesis of alkene dipeptide isosteres of Gly-Ala and Phe-Gly to demonstrate the versatility of the [2,3]-Wittig-Still rearrangement for the preparation of dipeptide isosteres as is shown in scheme 3-5 and scheme 6, respectively.

RESULTS AND DISCUSSION

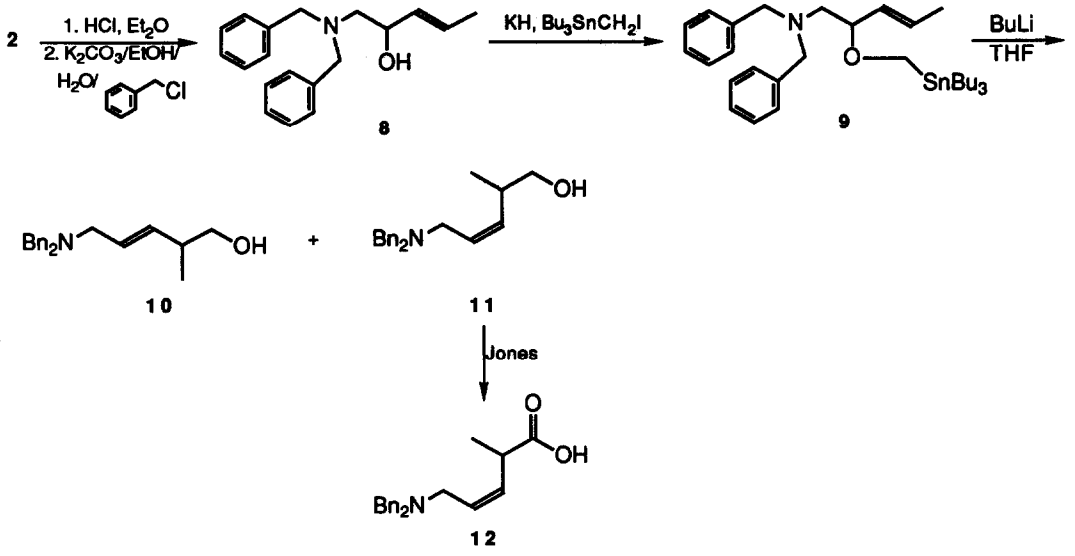
Starting from crotonaldehyde the amino alcohol **1** was prepared by treatment with trimethylsilylcyanide in the presence of ZnI_2 followed by reduction with lithiumaluminumhydride[21]. Choice of the proper amino protecting group turned out to be crucial (scheme 2). Originally, the amino alcohol **1** was converted to the Boc-protected amino alcohol **2**. After attempted formation of the tin compound followed by treatment with BuLi, only the oxazolidine derivative **3** could be isolated. Using the triazone[22] protective group, which has the electrodeficient carbonyl-carbon further removed from the OH- function prevented the intramolecular reaction of **4** and gave the Wittig precursor **5**. However, upon treatment with excess BuLi to effect the Wittig-Still rearrangement the protective group was removed leading to an intractable reaction mixture. Next, we prepared the Wittig precursor **7** of the tosyl protected amino alcohol **6**. Although the sulfonamide- sulfur is less susceptible to a nucleophilic attack, the tosyl protecting group was also removed upon treatment of the tin compound **7** with BuLi.



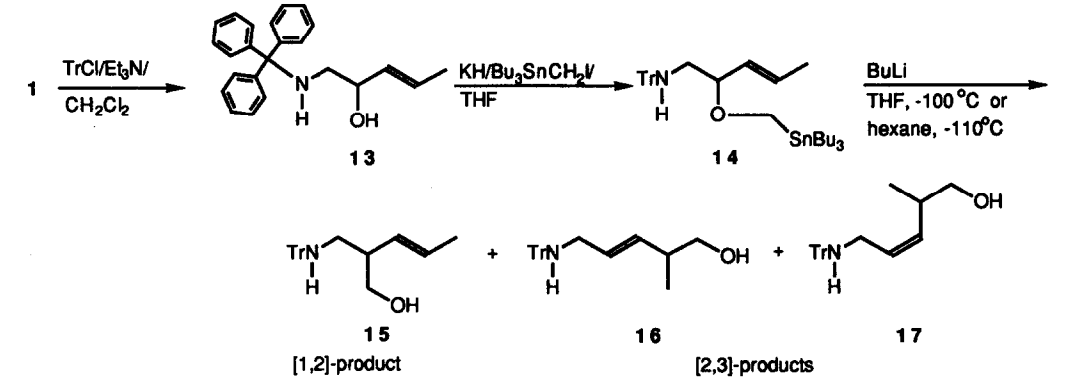
Scheme 2. Behaviour of protective groups containing an electrodeficient atom in theWittig-Still rearrangement

Thus, it was necessary to use a protective group without a electro deficient atom for a good preparation of the Wittig precursor and to be able to carry out the Wittig-Still rearangement. An obvious choice was therefore the use of two benzyl groups as a protection of the amino group as in compound **8**, prepared from the Boc-protected amino alcohol **2** (scheme 3). Indeed the Wittig precursor **9** could be prepared followed by the [2,3]-Wittig rearrangement to yield a difficult separable mixture of the trans and cis product **10** and **11**. Jones oxidation afforded the carboxylic acid **12**, but unfortunately removal of the benzyl groups could not be accomplished. Nevertheless, compound **8** was as useful model compound and proved our concept that a electrophilic site has to be absent in the protecting group.

We reasoned that the trityl group would have the same advantages as the benzyl groups with respect to preparation of the Wittig precursor and possibility of the Wittig-Still rearangement and, in addition, it is removable under mild acid conditions. Thus the amino group of **1** was protected with a trityl group to yield **13** (scheme 4). Subsequently the Wittig precursor **14** could be obtained in high yield (92%) after alkylation with tributyltinmethyleneiodide and KH. Surprisingly, after treatment of the Wittig precursor **14** in THF with excess of BuLi at low temperature, we found that the major product **15** (40%) was the result of a [1,2]-Wittig rearrangement instead of the desired [2,3]-Wittig-Still rearrangement[10]. The products **16** and **17** resulting from the [2,3]-Wittig-Still rearrangement were obtained in a combined yield of 35% (trans/cis ratio 0.8/1). However, when the solvent was changed from THF to hexanes we found that now the desired [2,3]-Wittig-Still rearrangement predominated leading to formation of products **16** and **17** in a combined yield of 80% (trans/cis ratio 1.5/1[23]) and only a small amount (3%) of the [1,2] product **15**. To our knowledge hexanes have not been used as a solvent in the [2,3]-Wittig-Still rearrangement, THF is the commonly used solvent. So far we have no satisfactory explanation for the observed solvent effect.



Scheme 3. Benzylgroups as amino-protecting groups for the Wittig-Still rearrangement



Scheme 4. Trityl group as a amino-protecting group for the Wittig-Still rearrangement

Preference for the formation of the trans product can be rationalized by examining the possible transition-states leading to the trans- and cis-product. In the former transition-state the methylene amino group bearing the trityl group assumes a pseudo equatorial position, whereas in the latter transition-state it has to assume the sterically less favorable pseudo axial position (figure 1).

Finally, completion of the synthesis of the alkene dipeptide isostere Gly-Ala and the simultaneous extension to the tripeptide isostere **20** is shown in scheme 5. Removal of the trityl group in **16** with TFA followed by coupling of the thus obtained amino alcohol **18** with Cbz-Phe-OH by the mixed anhydride method, gave -after Jones oxidation of **19**- Cbz-Phe-Glyψ[E-CH=CH]-(R,S)-Ala-OH **20** (overall yield 40%), i.e. the peptide isostere of Cbz-Phe-Gly-Ala-OH. Employing the DCC/HOBt-method, instead of the mixed anhydride method, for coupling of Cbz-Phe-OH gave a reaction mixture from which we were unable to obtain pure **19** although its presence is evident from NMR.

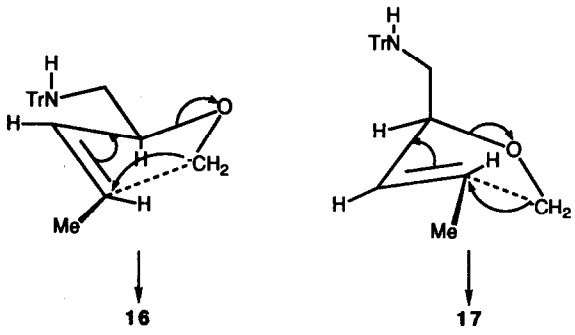
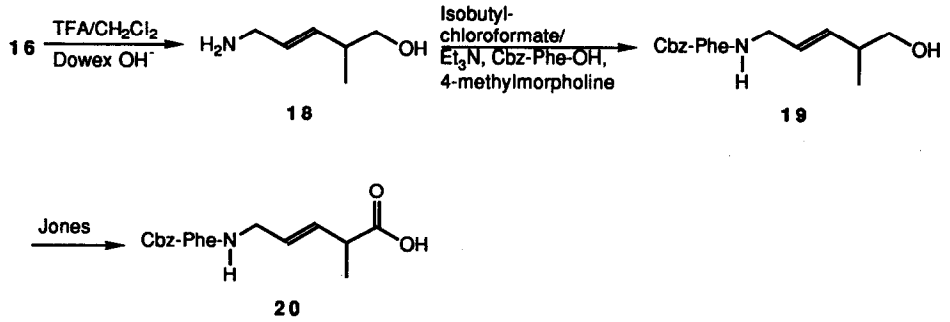


Fig. 1. Transition-states involved in formation of the cis- and trans product



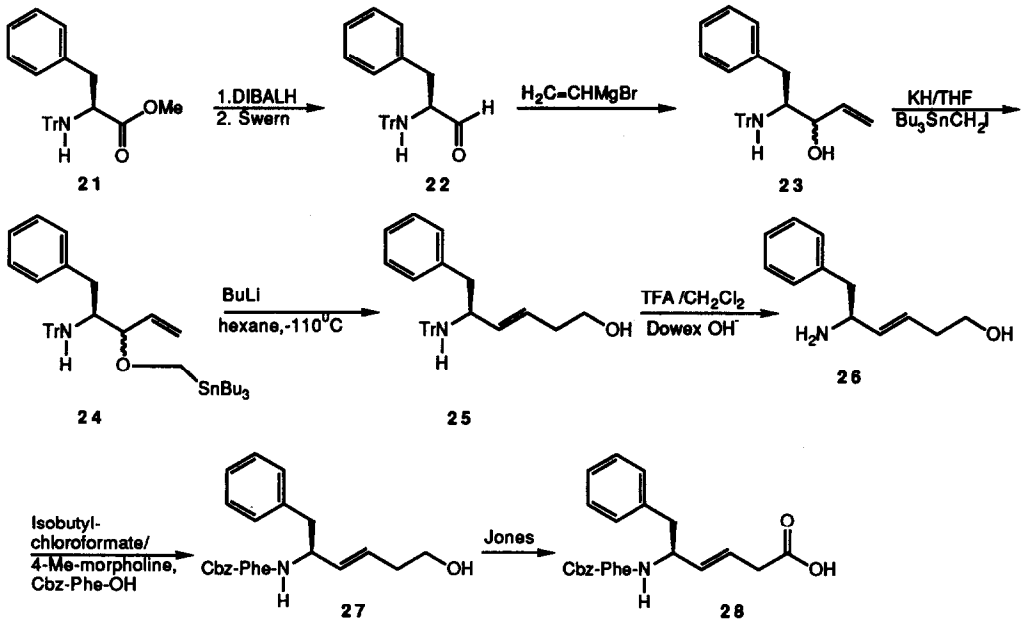
Scheme 5. Synthesis of the alkene dipeptide isostere of Gly-Ala as part of the tripeptide isostere Cbz-Phe-Glyψ[E-CH=CH]-(R,S)Ala-OH

As an example of the synthesis of "Xxx-Gly" alkene dipeptide isosteres (scheme 1), we choose the preparation of the dipeptide isostere of Phe-Gly. This sequence is present in the neuropeptide substance P (SP)[8,24] (figure 2) and replacement of the amide bond by the isosteric double bond prevents degradation by a peptidase capable of hydrolysing this amide bond[8].

H-Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2

Fig.2. Substance P (SP)

The synthesis of the Phe-Gly isostere (scheme 6) commenced with N-Tr-phenylalaninal **22** which was prepared by reduction of Tr-Phe-OMe **21** with DIBALH[25] followed by Swern oxidation. In an addition reaction with vinyl magnesium bromide the aldehyde was converted to a diastereomeric mixture of allylic alcohols **23**. Subsequently, the Wittig precursors **24** were prepared followed by the Wittig-Still rearrangement by treatment with excess BuLi to give the rearranged product **25**.
Remarkably, only the trans product **25** was formed in a good yield (80%) and only a trace of the [1,2]-product could be isolated. The exclusive formation of the trans product **24** can be explained by examing the transition-states. The transition-state leading to the trans product is even more favored, compared to the transition-state leading to the cis-product, than is the case in the formation of **16** (see figure 1), because of the presence of the additional benzyl group on the carbon next to the nitrogen atom. Finally, removal of the tritylgroup followed by coupling of the amino alcohol **26** and subsequent Jones oxidation of **27** afforded Cbz-Phe-Pheψ[E-CH=CH]-Gly (overall yield 28%) i.e. the peptide isostere of Phe(7)-Phe(8)-Phe(9) in substance P



Scheme 6. Synthesis of the alkene dipeptide isostere of Phe-Gly as part of the tripeptide isostere Cbz-Phe-Pheψ[E-CH=CH]-Gly-OH

In summary, we have shown that the Wittig-Still rearrangement, when carried out in hexanes, can be successfully employed for the synthesis of alkene peptide isosteres. By varying the α-β unsaturated carbonyl compounds a variety of natural and unnatural amino acids can be substituted for "Xxx" in the alkene dipeptide isosteres Gly-Xxx. In carrying out the Wittig rearrangement leading to these isosteres a remarkable solvent effect was observed. In addition, alkene dipeptide isosteres with a substituted double bond are accessible. This is presently applied to the development of reverse turn mimetics. Similarily, by varying the α-amino aldehyde - which are e.g. easily accessible from α-amino acids- a whole range of (unnatural) amino acids can be substituted for "Xxx" in the alkene dipeptide isosteres Xxx-Gly.
Under present investigation is the use of enzymatically synthesized[26] homochiral alcohols as well as amino alcohols derived from amino acids to prepare homochiral peptide isosteres using the above described methodology. In addition, we are investigating if the Wittig-Still rearrangement can be applied to the preparation of reverse turn mimetics. This work is in progress.

EXPERIMENTAL

General methods. Hexanes, pentane, petroleum ether 40-60 (pet-ether), ether, dioxane and THF were distilled from $LiAlH_4$. Acetone was distilled from $KMnO_4$ and N-methylmorpholine was distilled from CaH_2. Silica gel 60 (Merck 70-230 mesh) was used for column chromatography. Gel filtration was performed on Sephadex LH20 (Pharmacia). Thin layer chromatography (TLC) was carried out on Merck precoated silica gel F 254 plates (0.25 mm). Compounds were visualized by UV light, spraying with $KMnO_4$ (1%) in aqueous Na_2CO_3 (2%) or by dipping in a solution of ninhydrin followed by heating for a few minutes. NMR spectra were recorded with a Jeol JNM-FX200 (^1H and ^{13}C 200 MHz) or a Brucker WM-300 spectrometer equipped

with an Aspect-2000 computer (^{1}H 300 MHz). Chemical shifts are given in ppm (δ) relative to TMS as internal standard. $CDCl_3$ was used as a solvent unless stated otherwise. The compounds were homogeneous according to NMR and TLC.

E-1-amino-3-penten-2-ol (**1**)

The procedure described by *Evans et al.*[21] for the preparation of β-aminomethyl alcohols was used with some modifications. TMSCN (5.46 g, 7.33 mL, 55 mmol) was added dropwise to a homogeneous mixture of crotonaldehyde (3.5 g, 4.14 mL, 50 mmol) and a catalytic amount of ZnI_2 present in a dry 25 ml roundbottom flask. The reaction is exothermic and cooling -depending on the scale- may be necessary. The mixture was stirred for 0.5 h at rt. Reduction was carried out by adding the crude cyanohydrin ether dissolved in 14 mL ether to a mechanically stirred suspension of 2.09 g $LiAlH_4$ (55 mmol) in ether (41 mL) in a 100 mL three-necked flask, at a rate at which gentle reflux of the reaction mixture was maintained. Stirring and refluxing was continued for an additional h. Excess $LiAlH_4$ was destroyed by careful addition of a 2 mL water/2 mL THF mixture, followed by addition of a 2 mL 15% NaOH/2 mL THF mixture and a 6 mL water/6 mL THF mixture. Stirring was continued until a granular yellow precipitate was formed. Filtration, drying (Na_2SO_4) and evaporation of the ether solution gave a yellow oil which was distilled *in vacuo* to give 2.02 g (20.0 mmol, 40%) of the amino alcohol **1** (very hygroscopic crystals), bp 43 °C (0.5 mm); ^{1}H NMR (300 MHz, CD_3OD) δ 1.69 (dd, 3H, $C\underline{H}_3$, J_{vic} = 7.8 Hz, J_{allyl} = 1.2 Hz), 2.59 (m, 2H, $C\underline{H}_2NH_2$), 3.96 (4 lines, 1H, $C\underline{H}OH$, J_{vic} = 6.6 Hz and 6.2 Hz), 5.45 (16 lines, 1H, $C\underline{H}$=$CHCH_3$, J_{trans} = 15.4 Hz, J_{vic} = 6.7 Hz, J_{allyl} = 1.7 Hz), 5.73 (16 lines, 1H, CH=$C\underline{H}CH_3$, J_{trans} = 15.4 Hz, J_{vic} = 6.5 Hz, J_{allyl} = 1.2 Hz); ^{13}C NMR (CD_3OD) δ 18.0 ($\underline{C}H_3$), 74.6 ($\underline{C}HOH$), 128.4 and 133.3 ($\underline{C}H$=$\underline{C}H$), $\underline{C}H_2NH_2$ is masked by CD_3OD signals.

E-1-(t-butyloxycarbonyl)-amino-3-penten-2-ol (**2**)

The crude amino alcohol **1** (1.0 g, 10 mmol) was converted to the corresponding amino protected derivative **2** using di-*t*-butyldicarbonate (2.4 g, 11.0 mmol) and Et_3N (2.0 g, 2.8 mL, 20 mmol) in CH_2Cl_2 (50 mL). After stirring the reaction mixture overnight, the solvent was evaporated, followed by column chromatography (eluent EtOAc/hexanes 2/3, v/v) to afford **2** as a pale yellow solid in 62% yield. R_f 0.29 (*ibid.*). ^{1}H NMR δ 1.44 (s, 9H, $C_4\underline{H}_9$), 1.69 (d, 3H, $C\underline{H}_3$, J_{vic}= 5.6 Hz), 2.98-3.36 (m, 2H, $C\underline{H}_2N$), 3.46 (s, 1H, $O\underline{H}$), 4.14 (4 lines, 1H, $C\underline{H}OH$), 5.23 (bs, 1H, $N\underline{H}$), 5.45 (8 lines, 1H, C(OH)-$C\underline{H}$=CH, J_{trans} = 15.4 Hz, J_{vic} = 6.4 Hz, J_{allyl} = 1.5 Hz), 5.74 (m, 1H, CH=$C\underline{H}CH_3$ J_{trans} = 15.4 Hz, J_{vic} = 6.1 Hz); ^{13}C NMR: δ 17.6 ($\underline{C}H_3$), 28.2 ($C(\underline{C}H_3)_3$), 46.3 ($\underline{C}H_2$), 71.7 ($\underline{C}(H)OH$), 79.3 ($O\underline{C}(CH_3)_3$), 127.7 and 130.9 ($\underline{C}H$=$\underline{C}H$), 156.5 ($\underline{C}$=O)

E-3-(2-oxazolidone)-2-propene (**3**)

In an attempt to prepare the tin compound (see preparation of **14**, *vide infra*) from **2** (301 mg, 3.0 mmol) followed by the Wittig-Still rearrangement, compound **3** was isolated in 44% yield after column chromatography (eluent EtOAc/hexanes 1/1 to 3/1 v/v). R_f 0.29 (EtOAc/hexanes 3/1, v/v); ^{1}H NMR δ 1.75 (bd, 3H, $C\underline{H}_3$), 3.32 and 3.70 (two t, 2H, $C\underline{H}_2N$), 4.99 (q, 1H, $C\underline{H}O$), 5.57 (8 lines, 1H, CO-$C\underline{H}$=CH), 5.88 (m, 1H, CH=$C\underline{H}CH_3$), 7.34 (b, 1H, $N\underline{H}$) ^{13}C NMR: δ 17.4 ($\underline{C}H_3$), 46.2 ($\underline{C}H_2$), 77.5 ($\underline{C}(H)O$), 127.5 and 131.6 ($\underline{C}H$=$\underline{C}H$), 160.4 ($\underline{C}$=O)

5-[1-(3-E-penten-2-ol)]-1,3-dimethyl-1,3,5-triazacyclohexan-2-one (**4**)

The triazone **4** was prepared from the amino alcohol **1** (436 mg, 4.3 mmol) according to procedure described by Knapp *et al.* [22] and obtained as a colorless oil in 46% after column chromatography (eluent MeOH/CH_2Cl_2 5/95 v/v). R_f 0.29 (MeOH/CH_2Cl_2, 1/9, v/v); ^{1}H NMR δ 1.72 (d, 3H, $C\underline{H}_3$, J = 7.6 Hz), 2.80 (m, 2H, $C\underline{H}_2N$), 2.87 (s, 6H, 2 x $NC\underline{H}_3$), 4.19 (m, 5H, 2 x $NC\underline{H}_2N$ and $C\underline{H}OH$), 5.42 (m, 1H, $C\underline{H}$=$CHCH_3$, J_{trans} = 15.3 Hz, J_{vic} = 6.7 Hz, J_{allyl} = 1.6 Hz), 5.75 (m, 1H, CH=$C\underline{H}CH_3$, J_{trans} = 15.3 Hz, J_{vic} = 6.7 Hz, J_{allyl} = 1.0 Hz);^{13}C NMR δ 17.2 ($\underline{C}H_3$), 32.0 ($N\underline{C}H_3$), 57.3 ($N\underline{C}H_2$), 68.5 ($N\underline{C}H_2N$), 69.6 ($\underline{C}HOH$), 127.1 and 130.8 ($\underline{C}H$=$\underline{C}H$), 155.5 ($\underline{C}$=O).

5-[1-(3-E-penten-2-O-methylenetributyltin)]-1,3-dimethyl-1,3,5-triazacyclohexan-2-one (**5**)
Compound **5** was prepared from **4** (639 mg, 3.0 mmol) according to the procedure described for the preparation of **14** and obtained as a yellow oil in 34% yield after column chromatography (eluent MeOH/CH_2Cl_2 4/96 v/v). To ensure completion of the reaction stirring overnight and addition of 18-crown-6 (793 mg, 3.0 mmol) were necessary. R_f 0.66 (MeOH/CH_2Cl_2 1/9 v/v); ^1H NMR δ 0.80-1.64 (m, 27H, 3 x Bu), 1.75 (d, 3H, CH=CHC$\underline{H}_3$, J = 6.5 Hz), 2.73 (m, 2H, C$\underline{H}_2$N), 2.84 (s, 6H, 2 x NC$\underline{H}_3$), 3.44 and 3.76 (two d, 2H, OC$\underline{H}_2$SnBu$_3$, J = 9.7 Hz), 4.17 (m, 5H, C$\underline{H}$OH and 2 x NC$\underline{H}_2$N), 5.31 (m, 1H, C$\underline{H}$=CHCH$_3$), 5.66 (m, 1H, CH=C$\underline{H}$CH$_3$).

E-1-Tosylamino-3-penten-2-ol (**6**)
To a cooled (0 °C) solution of the aminoalcohol **1** (0.41 g, 4 mmol) in dioxane (8 mL) 1 M Na_2CO_3 (4 mL) and TsCl (0.84 g, 4.4 mmol) were added. After stirring for 3 h, the mixture was concentrated under reduced pressure, dissolved in EtOAc and washed with 5% Na_2CO_3 and brine, respectively. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo*. Column chromatography using ether/pet-ether (4/1 v/v) as eluent gave 0.89 g **6** (3.47 mmol; 67%) as a colorless oil. R_f 0.51 (eluent EtOAc/hexanes 3/1 v/v); ^1H NMR δ 1.58 (d, 3H, CH=CHC$\underline{H}_3$, J_{vic} = 6.4 Hz), 2.38 (s, 1H, C$\underline{H}_3$, Ts), 2.83 and 2.93 (m, 2H, C$\underline{H}_2$NH), 4.11 (m, 1H, C$\underline{H}$OH), 5.35 (m, 1H, C$\underline{H}$=CHCH$_3$), 5.64 (m, 1H, CH=C$\underline{H}$CH$_3$), 5.86 (t, 1H, N$\underline{H}$, J_{vic} = 6.7 Hz) 7.27 and 7.73 (two d, 4H, C$_6\underline{H}_4$, J = 8.2 Hz); ^{13}C NMR δ 17.6 (CH=CH$\underline{C}$H$_3$), 21.4 ($\underline{C}$H$_3$, Ts), 48.5 ($\underline{C}$H$_2$NH), 71.0 ($\underline{C}$HOH), 127.0, 129.6, 136.2, 143.4 ($\underline{C}_6$H$_4$), 129.0 and 130.0 ($\underline{C}$H=$\underline{C}$H).

E-1-Tosylamino-3-penten-2-O-methylenetributyltin (**7**)
Compound **7** was prepared from **6** (399 mg, 1.6 mmol) according to the procedure described for the preparation of **14** and obtained as a colorless oil in 85% yield after column chromatography (eluent EtOAc/hexanes 1/9 v/v). To ensure completion of the reaction stirring overnight and addition of 18-crown-6 (415 mg, 1.6 mmol) were necessary. R_f 0.84 (EtOAc/hexanes, 3/1, v/v); ^1H NMR (300 MHz) δ 0.80-1.58 (m, 27 H, 3 x Bu), 1.71 (dd, 3H, C$\underline{H}_3$, J_{vic} = 6.5 Hz, J_{allyl} = 1.5 Hz), 2.41 (s, 3H, C$\underline{H}_3$, Ts), 2.94 and 3.27 (m, 2H, C$\underline{H}_2$NH), 3.26 and 3.66 (two d, 2H, J = 10.0 Hz, OC$\underline{H}_2$SnBu$_3$), 3.57 (m, 1H, C$\underline{H}$OH), 5.18 (8 lines, 1H, C$\underline{H}$=CHCH$_3$, J_{trans} = 15.4 Hz, J_{vic} = 8.0 Hz, J_{allyl} = 1.7 Hz), 5.64 (8 lines, 1H, CH=C$\underline{H}$CH$_3$, J_{trans} = 15.4 Hz, J_{vic} = 6.5 Hz, J_{allyl} = 1.2 Hz), 7.27 and 7.67 (two d, 4H, C$_6\underline{H}_4$, J = 9.3 Hz, J = 8.2 Hz); ^{13}C NMR δ 10.1, 13.6, 27.2, 29.0 (C 's Bu), 17.7 (CH=CH$\underline{C}$H$_3$), 21.3 (C$\underline{H}_3$, Ts), 55.7 ($\underline{C}$H$_2$NH), 58.5 (O$\underline{C}$H$_2$SnBu$_3$), 84.0 ($\underline{C}$HO), 129.4 and 130.1 ($\underline{C}$H=$\underline{C}$H), 127.3, 129.2, 136.1, 142.5 ($\underline{C}_6$H$_4$)

E-1-dibenzylamino-3-penten-2-ol (**8**)
Boc protected amino alcohol **2** (2.02 g, 10 mmol) was dissolved in CH_2Cl_2 (10 mL) and treated with ether saturated with HCl (25 mL). After stirring for 1.25 h at rt, the reaction mixture was evaporated to dryness and coevaporated twice with ether. Subsequently, the amino group was dibenzylated analogous to a procedure described by Velluz *et al.* [27] by dissolving the residue in EtOH (25 mL) and water (15 mL) followed by treatment with BnCl (4.6 mL, 40 mmol) and K_2CO_3 (3.45 g, 25 mmol). After refluxing the mixture for 3.5 h an additional quantity of BnCl (1.15 mL, 10 mmol) and K_2CO_3 (1.38 g, 10 mmol) was added. After 4.5 h the reaction mixture was concentrated to a small volume, acidified with concentrated HCl and the resulting brown oil as well the aqueous layer washed with pet-ether to remove excess BnCl. Addition of concentrated NaOH, followed by extraction with ether (4 x 50 mL) gave after evaporation of the collected organic layers an oil which was chromatographed (eluent 150 mL pet-ether and ether/petroleumether 40-60/Et_3N 1/3/0.005 v/v). The dibenzylated product was obtained as a colorless oil in 59% yield (1.67 g). R_f 0.37 (eluent *ibid.*) ^1H NMR δ 1.63 (dd, 3H, C$\underline{H}_3$, J_{vic}= 6.4 Hz, J_{allyl}=1.5 Hz) 2.32-2.72 (m, 2H, C$\underline{H}_2$N), 3.39 and 3.81 (two d, 4H, 2 x PhC$\underline{H}_2$ J_{AB}=13.5 Hz) 3.60 (bs, 1H, O$\underline{H}$), 4.12 (m, 1H, C$\underline{H}$OH), 5.30 (m, 1H, COH-C$\underline{H}$=CH, J_{trans}=15 Hz, J_{vic}=6.5 Hz, J_{allyl}=1.5 Hz), 5.70 (m, 1H, CH=C$\underline{H}$CH$_3$, J_{vic}=6.4 Hz), 7.28 (m, 10H, 2 x Ph); ^{13}C

NMR δ 17.6 ($\underline{C}H_3$), 58.0 (Ph$\underline{C}H_2$) 59.5 ($\underline{C}H_2N$), 68.1 ($\underline{C}$(H)OH), 127.8 and 131.1 ($\underline{C}H$=$\underline{C}H$), 127.0, 128.2, 128.8 and 138.2 ($\underline{C}_6H_5$).

E-1-dibenzylamino-4-methyl-2-penten-5-ol (**10**), *Z-1-dibenzylamino-4-methyl-2-penten-5-ol* (**11**)
The Wittig precursor **9** was prepared according to the procedure described for the preparation of **14** (*vide infra*) from **8** (1.12 g, 4.0 mmol). However, **9** was not isolated but immediately subjected to treatment with excess of BuLi to effect the Wittig rearrangement as described for the preparation of **15-17** (*vide infra*). After column chromatography (eluent ether/pet-ether/Et3N 1/1/0.005 v/v) the trans-product **10** and cis-product **11** are obtained as a colorless oil in a combined yield of 70% (ratio ca. 1/1.9). Complete separation of the trans- and cis product was unsuccessful, invariably the trans-product **10** was contaminated with the cis-product **11**.
10: R_f 0.65 (ether/pet-ether/Et3N 1/3/0.005 to 1/1/0.005 v/v) ^{1}H NMR (only clearly distinguishable signals are given) δ 0.98 (d, 3H, $\underline{C}H_3$, J = 6.9 Hz), 2.34 (5 lines, 1H, $\underline{C}HCH_3$), 3.03 (2H, $\underline{C}H_2N$, J_{vic} = 6.2 Hz), 3.56 (s, 4H, 2 x Ph$\underline{C}H_2$), 7.10-7.50 (m, 10H, 2 x Ph) ^{13}C NMR δ 17.2 ($\underline{C}H_3$), 39.4 ($\underline{C}HCH_3$), 55.5 ($\underline{C}H_2N$), 57.8 (Ph$\underline{C}H_2$) 67.1 ($\underline{C}H_2OH$), 127.9, 135.7 ($\underline{C}H$=$\underline{C}H$), 127.0, 128.1, 128.5 and 139.6 ($\underline{C}_6H_5$).
11: R_f 0.73 (ether/pet-ether/Et3N 1/3/0.005 to 1/1/0.005 v/v); ^{1}H NMR δ 0.83 (d,3H, $\underline{C}H_3$, J = 6.7 Hz), 2.40 (m, 1H, $\underline{C}HCH_3$) 2.82 and 3.15 (m, 2H, $\underline{C}H_2N$, H_A: J_{AB} =13.5 Hz, J_{AX}= 7.2 Hz, H_B: J_{AB} =13.5, J_{BX}= 6.9 Hz, J_{allyl}= 1.5), 3.24 and 3.43 (m, 2H, $\underline{C}H_2OH$, H_A: J_{AB} =10.1 Hz, J_{AX}=5.4 Hz, H_B: J_{AB} =10.1, J_{BX}=9.1 Hz), 3.37 and 3.73 (two d, 4H, 2 x Ph$\underline{C}H_2$, J_{AB}=13.4 Hz), 5.35 (t, 1H, NCH=C$\underline{H}$, J_{cis} = 10.5 Hz, J_{vic} = 10.0 Hz), 5.73 (dt, 1H, NC$\underline{H}$=CH, J_{cis} = 10.8 Hz, J_{vic} = 6.9 Hz, J_{allyl} = 0.6 Hz), 7.12-7.50 (m, 10H, 2 x Ph) ^{13}C NMR δ 16.8 ($\underline{C}H_3$), 34.8 ($\underline{C}HCH_3$), 49.6 ($\underline{C}H_2N$), 58.1 (Ph$\underline{C}H_2$) 67.1 ($\underline{C}H_2OH$), 127.9, 137.1 ($\underline{C}H$=$\underline{C}H$), 126.9, 128.1, 129.1 and 138.6 ($\underline{C}_6H_5$).

Z-1-dibenzylamino-2-pentene-4-carboxylic acid (**12**)
The carboxylic acid **12** was obtained as a white foam in 75% yield (158 mg, 51 mmol) from the cis-alcohol **11** (200 mg, 0.68 mmol) by Jones' oxidation as described for the preparation of **20** (*vide infra*). ^{13}C NMR δ 17.1 ($\underline{C}H_3$), 39.2 ($\underline{C}HCH_3$), 48.9 ($\underline{C}H_2N$), 56.6 (Ph$\underline{C}H_2$), 119.8 and 139.0 ($\underline{C}H$=$\underline{C}H$), 129.0, 129.5, 129.7 and 131.0 ($\underline{C}_6H_5$), 175.8 ($\underline{C}OOH$)

(E)-1-tritylamino-3-penten-2-ol (**13**)
To a solution of of the amino alcohol **1** (1.11 g, 11.0 mmol) in CH_2Cl_2 (30 mL), TrCl (3.07 g, 11 mmol) and Et3N (8 mL, 22 mmol) were added. The mixture was stirred for 1 δ at rt, followed by concentration under reduced pressure. The residue was suspended in EtOAc and filtrated to remove Et3N·HCl. After column chromatography (eluent EtOAc/hexanes/Et3N 1/9/0.005, v/v) **13** was obtained as a colorless oil in 79% yield (2.99 g, 8.7 mmol). R_f 0.48 (EtOAc/hexanes 1/1, v/v); ^{1}H NMR (300 MHz) δ 1.65 (dd, 3H, $\underline{C}H_3$, J_{vic} = 6.5 Hz, J_{allyl} = 1.2 Hz), 2.26 (d, 2H, $\underline{C}H_2NH$, J_{vic} = 5.8 Hz), 4.11 (m, 1H, $\underline{C}HOH$), 5.39 (m, 1H, $\underline{C}H$=CHCH3, J_{trans} = 15.3 Hz, J_{vic} = 6.6 Hz, J_{allyl} = 1.6 Hz), 5.69 (m, 1H, CH=$\underline{C}H$CH3 J_{trans} = 15.3 Hz, J_{vic} = 6.5 Hz, J_{allyl} = 1.1 Hz), 7.18-7.53 (m, 15H, ($C_6\underline{H}_5$)3, Tr); ^{13}C NMR δ 17.7 ($\underline{C}H_3$), 49.4 ($\underline{C}H_2NH$), 72.2 ($\underline{C}HOH$), 126.3 and 131.7 ($\underline{C}H$=$\underline{C}H$), 74.1, 127.8, 128.6, 145.7 ($\underline{C}(C_6H_5)_3$, Tr).

(E)-1-tritylamino-3-penten-2-O-methylenetributyltin (**14**)
After coevaporation twice with dry THF, the tritylated amino alcohol **13** (0.86 g, 2.5 mmol) was dissolved in THF (15 mL). In a separate flask, a KH suspension (1.00 g, 20-25%, 5 mmol) was washed under Ar with pentane (2 x 4 mL), to remove the mineral oil, followed by suspension in THF (5 mL) and addition to the solution of **13**. After stirring under Ar for 15 minutes at rt, Bu_3SnCH_2I[28] (1.62 g, 3.75 mmol) in THF (10 mL) was added. Stirring was continued for 1 h, after which the reaction mixture was poured in a saturated NH4Cl solution containing crushed ice. Organic and aqueous layers were separated and the aqueous layer was extracted four times with ether. The combined organic layers were dried (MgSO4), concentrated under reduced pressure and the resulting yellow oil was chromatographed on silica gel (eluent: EtOAc/hexanes/Et3N

1/9/0.005, v/v) to give the tin compound **14** as a colorless oil (1.31 g; 2.03 mmol, 82%). R_f 0.64 (EtOAc/hexanes, 1/1, v/v); ^{1}H NMR δ 1.64 (d, 3H, C<u>H</u>$_3$, J_{vic} = 6.5 Hz), 2.22 (d, 2H, C<u>H</u>$_2$NH, J_{vic} = 5.8 Hz), 3.41 and 3.75 (two d, 2H, OC<u>H</u>$_2$SnBu$_3$, J = 9.7 Hz), 3.54 (m, 1H, N<u>H</u>), 4.13 (m, 1H, C<u>H</u>OH), 5.22 (8 lines, 1H, C<u>H</u>=CHCH$_3$, J_{trans} = 15.3 Hz, J_{vic} = 6.6 Hz, J_{allyl} = 1.6 Hz), 5.60 (8 lines, 1H, CH=C<u>H</u>CH$_3$, J_{trans} = 15.3 Hz, J_{vic} = 6.5 Hz, J_{allyl} = 1.0 Hz), 7.10-7.51 (m, 15H, (C$_6$<u>H</u>$_5$)$_3$, Tr); ^{13}C NMR δ 8.9, 13.7, 27.2, 29.1 (C 's Bu), 17.8 (CH=CH<u>C</u>H$_3$), 48.2 (<u>C</u>H$_2$NH), 58.5 (O<u>C</u>H$_2$SnBu$_3$), 84.7 (<u>C</u>HOH), 129.1 and 130.6 (<u>C</u>H=<u>C</u>H), 70.4, 126.1, 127.7, 128.7, 146.3 (<u>C</u>(C$_6$H$_5$)$_3$, Tr).

E-1-aminotrityl-2-hydroxymethyl-3-pentene (**15**)

The [1,2]-product was synthesized analogous to the preparation of the [2,3]-products **16** and **17** (*vide infra*) and obtained in 40% yield as a colorless oil. However, THF was used to dissolve the tin derivative **14** (1.71 g, 1.81 mmol). The reaction mixture was cooled with pentane and liquid N_2 at -70 to -100 °C. The temperature at which the Wittig-Still rearrangement is carried out is less critical than is the case for the preparation of the [2,3]-products **16** and **17**. R_f 0.89 (EtOAc/hexanes, 1/1, v/v), ^{1}H NMR (300 MHz) δ 1.65 (d, 3H, C<u>H</u>$_3$, J = 6.4 Hz), 2.09 (broad, 1H, O<u>H</u>) 2.26 (m ,2H, NC<u>H</u>$_2$), 3.21 (d, 2H, C<u>H</u>$_2$OH, J = 4.0 Hz), 3.59 (6 lines, 1H, C<u>H</u>, J_{vic} = 7.6 Hz, J_{vic} = 7.9 Hz, J_{vic} = 5.2 Hz), 5.25 (m, 1H, C<u>H</u>=CHCH$_3$, J_{trans} = 15.3 Hz, J_{vic} = 8.1 Hz, J_{allyl} = 1.7 Hz), 5.64 (m, 1H, CH=C<u>H</u>CH$_3$, J_{trans} = 15.3 Hz, J_{vic} = 6.5 Hz), 7.13-7.57 (m, 15H, (C$_6$<u>H</u>$_5$)$_3$, Tr), ^{13}C NMR δ 17.7 (<u>C</u>H$_3$), 48.1 (<u>C</u>H$_2$N), 55.9 (<u>C</u>H), 70.5 (<u>C</u>H$_2$OH), 82.3 (<u>C</u>H), 128.9 and 130.1 (<u>C</u>H=<u>C</u>H), 126.1, 127.7, 128.7, 146.2 (<u>C</u>(C$_6$H$_5$)$_3$, Tr).

E-1-aminotrityl-4-methyl-2-penten-5-ol (**16**), *Z-1-aminotrityl-4-methyl-2-penten-5-ol* (**17**)

The tin derivative **14** (0.65 g; 1 mmol) was coevaporated three times with THF (3 x 10 mL) and dissolved in dry hexanes (13 mL). BuLi (1.6 N, 2 mmol; 1.25 mL) was added at -100 °C (pentane and liquid N_2), under Ar. The yellow- or red-colored reaction mixture was allowed to reach rt in the cooling bath and stirring was continued for 1 h. The mixture was quenched with saturated NH_4Cl solution (20 mL) containing crushed ice. The aqueous layer was extracted four times with ether. The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure and the resulting yellow oil was chromatographed using a gradient of ether/pet-ether (0/1 to 1/1, v/v), to give the [2,3]-trans-product **16** (0.161 g, 0.45 mmol, white solid) and the [2,3]-cis-product **17** (0.090 g, 0.25 mmol, light-yellow oil) in 45% and 25% yield respectively. In addition, 6% (0.021 g, 0.06 mmol) of the [1,2]-product (*vide supra*) was isolated.

16: R_f 0.60 (EtOAc/hexanes, 1/1, v/v); ^{1}H NMR (300 MHz) δ 0.97 (d, 3H, C<u>H</u>$_3$, J = 6.8 Hz), 1.78 (broad, O<u>H</u>), 2.38 (7 lines , 1H, C<u>H</u>CH$_3$, $J_{C=CH}$ = 7.5 Hz, J_{CH3} = 6.8 Hz, J_{CH2} = 6.7 Hz), 2.73 (dd, 2H, C<u>H</u>$_2$N, J_{vic} = 5.8 Hz, J_{allyl} = 1.1 Hz), 3.39 (m, 2H, C<u>H</u>$_2$OH J_{AB} = 10.5 Hz, J_{AX} = 5.7 Hz, J_{BX} = 7.4 Hz), 5.42 (12 lines, 1H, CH$_2$CH=C<u>H</u>, J_{trans} = 15.5 Hz, J_{vic} = 7.6 Hz, J_{allyl} = 1.5 Hz,), 5.67 (12 lines, 1H, CH$_2$C<u>H</u>=CH, J_{trans} = 15.5 Hz, J_{vic} = 5.8 Hz, J_{allyl} = 0.9 Hz), 7.13-7.49 (m, 15H, (C$_6$<u>H</u>$_5$)$_3$, Tr); ^{13}C NMR δ 16.4 (<u>C</u>H$_3$), 39.4 (<u>C</u>HCH$_3$), 45.9 (<u>C</u>H$_2$NH), 67.1 (<u>C</u>H$_2$OH), 130.1 and 133.3 (<u>C</u>H=<u>C</u>H), 70.8, 126.2, 127.7, 128.5, 145.9 (<u>C</u>(C$_6$H$_5$)$_3$, Tr); PDMS: m/z 357.3.

17: R_f 0.65 (EtOAc/hexanes, 1/1, v/v); ^{1}H NMR (300 MHz) δ 0.82 (d, 3H, C<u>H</u>$_3$, J = 6.8 Hz), 1.90 (broad, O<u>H</u>), 2.33 (24 lines, 1H, C<u>H</u>CH$_3$, J_{CH} =10.3 Hz, J_{CH3} = 6.7 Hz, J_{CH2} =6.4 Hz), 2.81 (16 lines, 2H, NC<u>H</u>$_2$, J_{AB} = 12.7 Hz, J_{AX}= J_{BX} = 7.1 Hz, J_{allyl} = 1.3 Hz), 3.29 (8 lines, 2H, C<u>H</u>$_2$OH, J_{AB} = 10.4 Hz, J_{AX} = 5.4 Hz, J_{BX} = 8.5 Hz,), 5.22 (9 lines, 1H, CH$_2$CH=C<u>H</u>, J_{cis} = 10.7 Hz, J_{vic} = 10.3 Hz, J_{allyl} = 1.3 Hz,), 5.68 (12 lines, 1H, CH$_2$C<u>H</u>=CH, J_{cis} = 10.7 Hz, J_{vic} = 7.3 Hz, J_{allyl} = 0.6 Hz), 7.14-7.50 (m, 15H, C$_6$<u>H</u>$_5$)$_3$, Tr), ^{13}C NMR δ 17.0 (<u>C</u>H$_3$), 34.9 (<u>C</u>HCH$_3$), 40.6 (<u>C</u>H$_2$N), 67.2 (<u>C</u>H$_2$OH), 129.5, 134.9 (<u>C</u>H=<u>C</u>H) 71.1, 126.3, 127.8, 128.6, 145.8 (<u>C</u>(C$_6$H$_5$)$_3$, Tr); PDMS: m/z 357.2.

E-1-amino-(Cbz-Phe)-4-methyl-2-penten-5-ol (**19**)

The [2,3]-trans-product **16** (0.36 g, 1.0 mmol) was detritylated in a 10% solution of TFA in CH_2Cl_2 (20 mL) by stirring for 30 min at rt. Subsequently, the solvent was evaporated and the residue coevaporated twice with

ether (10 mL).The TFA-salt was then dissolved in 10 mL MeOH/water (1/1, v/v) and 2mL Et_2O. The free amine **18** was obtained after adding excess Dowex^R (OH^- form) followed by filtration and evaporation, as a colorless oil, which was used withhout further purification. After coevaporation with THF **18** was dissolved in DMF (2 mL). A solution of dry Cbz-Phe-OH (0.30 g, 1.0 mmol) in THF (1 mL) was cooled to -15 °C and neutralized with N-methylmorpholine; isobutylchloroformate (0.14 mg, 130 mL, 1.0 mmol) was added, followed by addition of the DMF solution of **18**. The reaction mixture was stirred for 2 h at rt, filtrated and concentrated under reduced pressure using the oilpump to remove DMF. The resulting oil was redissolved in EtOAc. The solution was washed with 1 N $KHSO_4$, 5% $NaHCO_3$, brine and dried ($MgSO_4$). After evaporation and gel filtration over Sephadex LH-20 (eluent: MeOH/H_2O 1/1, v/v) **19** was obtained as a white solid in 55% yield (0.259 g, 0.65 mmol). ^1H NMR δ 0.94 (d, 3H CH_3, J = 6.8 Hz), 2.28 (m, 1H, $CHCH_3$, J = 6.3 Hz), 2.34 (s, 1H, OH), 3.05 (m, 2H, CH_2Phe), 3.35 and 3.46 (12 lines, 2H, CH_2OH , J_{AB} = 10.6 Hz, J_{AX} = 7.5 Hz, J_{BX} = 5.4 Hz, J_{allyl} = 1.5 Hz), 3.72 (t, 2H, NCH_2, J = 5.2 Hz), 4.39 (m, 1H, $CHCH_2$Ph), 5.02 and 5.07 (two d, 2H, OCH_2, Cbz, J = 12.3 Hz) 5.35 (m, 2H, CH=CH), 5.60 (d, 1H, NHPhe, J = 7.8 Hz), 6.17 (s, 1H, NH), 7.17-7.38 (m, 10H, Ph(Phe), Ph(Cbz)); ^{13}C NMR δ 16.1 (CH_3), 38.7 (CH_2Phe), 38.9 ($CHCH_3$), 41.2 (CH_2N), 56.2 ($CHCH_2$Phe), 66.8 (CH_2OH and $CH_2OC(O)$), 125.7-135.4 and 136.0, 136.4 (CH=CH and C_6H_5), 156.0 (C=O, Cbz), 170.9 (C=O, amide).

Cbz-Phe-Glyψ[E-CH=CH]-(R,S)Ala-OH (**20**)

To a cooled (0 °C) solution of the alcohol **19** (405 mg, 1.02 mmol) in acetone (5 mL, distilled from $KMnO_4$), Jones' reagent (2.8 M CrO_3)[29] 1.33 mL (3.6 mmol) was added. The reaction mixture was stirred for 0.5 h at 0 °C, and an additional 3.5 h at rt. Excess Jones' reagent was destroyed by addition of *i*-PrOH (5 mL), followed by stirring for 0.5 h. After evaporation, water (2.5 mL) and EtOAc (10 mL) were added. The aqueous layer was extracted with EtOAc (4 x 10 mL) and the combined organic layers were washed with brine (2.5 mL), dried ($MgSO_4$), and evaporated to dryness. The resulting solid was purified by gel filtration over Sephadex LH-20 (eluent MeOH/H_2O 85/15, v/v) yielding 0.131 g (0.35 mmol; 35%) of the acid **20** (white solid). ^1H NMR δ 1.23 (d, 3H, CH_3, J = 6.9 Hz), 3.04 (m, 3H, $CHCH_2$Ph and $CHCH_3$), 3.76 (m, NCH_2), 4.34 (t, 1H, $CHCH_2$Ph, J = 5.3 Hz), 5.04 and 5.08 (two d, 2H, OCH_2, Cbz, J = 12.3 Hz), 5.41 (dt, 1H, CH=CH, J_{trans} = 15.3 Hz, J_{vic} = 5.6 Hz), 5.58 (dd, 1H, CH=CH, J_{trans} = 15.3 Hz, J_{vic} = 6.8 Hz), 7.16-7.36 (m, 10H, Ph(Phe), Ph (Cbz)); ^{13}C NMR δ 16.9 (CH), 38.7 (CH_2Phe), 41.0 (CH_2N), 42.6 (CH_3CH), 56.3 ($CHCH_2$Ph), 66.8 ($CH_2OC(O)$), 125.9-129.2, 131.8 and 136.5 (CH=CH, C_6H_5), 156.1 (C=O, Cbz), 171.4 (C=O, amide), 178.7 (C=O, acid); PDMS of the corresponding methylester, obtained by treatment with diazomethane: m/z 425.3.

N-tritylphenylalaninemethylester (**21**)

HCl·H-Phe-OMe was prepared using $SOCl_2$/MeOH[30]. The trityl group was introduced and purification of **21** was carried out as described for **13** (*vide supra*) to yield 17.57 g of a white solid (41.7 mmol, 92%) after column chromatography (eluent). R_f 0.61 (EtOAc/hexanes 1/3, v/v); ^1H NMR δ 2.85 (s, 1H, NH), 2.85-3.02 (8 lines, J_{vic} = 6.3 Hz, 2H, CH_2Ph), 3.02 (s, 3H, CH_3), 3.55 (t, 1H, CH, J = 6.8 Hz), 7.08-7.42 (m, 20H, Ph, Tr); ^{13}C NMR δ 42.2 (CH_2Ph), 51.0 (OCH_3), 58.2 (CHPh), 70.8, 126.1, 129.7, 137.3, 145.7 (aromatic C's), 174.7 (C=O).

N-tritylphenylalaninal (**22**)

To a cooled (-78 °C) solution of Tr-Phe-OMe **21** (15.22 g; 36.2 mmol) in toluene (75 mL) under an argon atmosphere, was added a 1.0 M solution of DIBALH in hexane (72.3 mL) over a period of 30 min. After additional stirring for 0.5 h the mixture was quenched with MeOH (7 mL) followed by addition of 1 M Rochelle's salt solution (100 mL) and ether (50 mL). Organic and aqueous layers were separated and the aqueous layer was extracted three times with ether. Combined organic layers were dried ($MgSO_4$) and evaporated. The resulting oil was chromatographed on silica gel (eluent: EtOAc/hexanes/Et_3N 1/9/0.005, v/v) to

give 13.79 g of N-tritylphenylalaninol (35.1 mmol; 97%) as a colorless oil. R_f 0.49 (EtOAc/hexanes 1/9 v/v); ^{1}H NMR δ 2.21 (s, 2H, OH and NH), 2.45 and 2.64 (8 lines, 2H, CH_2Ph J_{AB} = 13.0 Hz, J_{AX}= 4.7 Hz, J_{BX} = 9.1 Hz,), 2.93 (m, 1H, CH), 2.99 and 3.23 (8 lines, 2H, CH_2OH, J_{AB}= 10.6 Hz, J_{AX} = 4.1 Hz, J_{BX} = 2.5 Hz), 7.05-7.72 (m, 20H, Ph, Tr); ^{13}C NMR : δ 39.0 (CH_2Ph), 55.3 ($CHCH_2$Ph), 62.2 (CH_2OH), 71.1, 125.9-129.3, 139.0, 146.5 (aromatic C's).

Oxidation of the thus obtained N-tritylphenylalaninol (9.75 g; 24.8 mmol) to the aldehyde **22** was carried out by the method of Swern[31] using oxalylchloride and DMSO. The aldehyde **22** was obtained as a colorless oil, which slowly crystallizes, and used without further purification. R_f 0.68 (EtOAc/hexanes 1/9 v/v); ^{1}H NMR : δ 2.60 (d, 2H, CH_2Phe, J = 6.7 Hz and s, 1H, NH), 3.44 (t, 1H, $CHCH_2$Ph, J = 6.7 Hz), 6.97-7.28 (m, 20H, Ph, Tr), 8.70 (s, 1H, CHO); ^{13}C NMR δ 38.5 (CH_2Phe), 62.8 ($CHCH_2$Ph), 70.8, 126.5-129.7, 136.6, 145.7 (aromatic C's), 202.8 (CHO); Anal Calcd for $C_{28}H_{25}NO$ (391.52): C, 85.90; H, 6.44; N, 3.58. Found: C, 85.41; H, 6.65; N, 3.63.

(2S,3RS)-1-phenyl-2-aminotrityl-1-penten-3-ol (**23**)

Reaction of the aldehyde **22** with vinylmagnesiumbromide was carried out analogous to a procedure described by Shue *et al.* [7n]. To a cooled (-78 °C) solution of the crude **22** (7.88 g, 20 mmol) in THF (100 mL) stirred under Ar , 1 M vinylmagnesiumbromide in THF (80 mL) was added over a period of 15 min. The reaction mixture was stored overnight at -20 °C, quenched with saturated NH_4Cl solution (50 mL) containing crushed ice and extracted with ether. After drying ($MgSO_4$) and evaporation of the solvent, the resulting oil was chromatographed (eluent EtOAc/hexanes/Et_3N 1/9/0.005 v/v) yielding 7.31 g (overall yield starting from N-tritylphenylalaninol: 17.4 mmol; 87%) of the adduct **23** as a non-separable mixture of diastereomers. R_f 0.60 (EtOAc/hexanes 1/9 v/v); ^{1}H NMR δ 2.30-2.90 (m, 5H, OH, CH_2Ph and $CHCH_2$Ph), 3.45 and 3.86 (s of each diastereomer, 1H, CHOH), 5.08-5.40 (m, 3H, $CH=CH_2$ and NH), 5.57 and 5.85 (8 lines of each diastereomer, 1H, $CH=CH_2$, J_{trans} = 17 Hz, J_{cis} = 10 Hz, J_{vic} = 4 Hz), 6.77-7.57 (m, 20H, Ph, Tr); ^{13}C NMR δ 36.5 and 37.6 (CH_2Ph), 59.0 ($CHCH_2$Ph), 71.6 and 72.1 (CHOH), 115.5 and 115.6 ($CH=CH_2$), 137.8 and 139.7 ($CH=CH_2$), 70.4, 70.6, 125.9-129.3, 139.1, 139.3, 146.3, 146.5 (aromatic C's).

(2S,3RS)-1-phenyl-2-aminotrityl-1-penten-3-O-methylenetributyltin (**24**)

The tin compound **24** was prepared from **23** (6.84 g, 16 mmol) as was described for the preparation of **14** and obtained as a colorless oil in a yield of 76% after chromatography (eluent). R_f 0.75 (EtOAc/pet-ether 1/1 v/v); δ ^{13}C NMR : δ 8.9, 10.7, 13.7, 27.3, 29.2 (C's Bu), 38.4 (CH_2Ph), 58.6 ($CHCH_2$Ph), 59.2 (OCH_2SnBu_3), 85.6 ($CHOCH_2SnBu_3$), 118.1 ($CH=CH_2$), 136.3 ($CH=CH_2$), 70.6, 125.5-129.6, 140.9, 147.1 (aromatic C's).

(2S)-1-phenyl-2-aminotrityl-3-hexen-6-ol (**25**)

The Wittig-Still rearrangement of **24** (856 mg, 1.1 mmol)was carried out as described above for the preparation of **16**. However, stirring overnight was necessary for completion of the reaction and only the trans-produkt could be isolated in 80% yield as a white solid after column chromatography using EtOAc/pet-ether (1/1 v/v) as an eluent. R_f 0.21 (EtOAc/pet-ether 1/1 v/v); ^{1}H NMR δ 1.94 (dt, 2H, $CH=CHCH_2$, J_{vic} = 6.2 Hz, J_{allyl} = 1.2 Hz), 2.30 and 2.48 (8 lines, 2H, CH_2Ph, J_{AB} = 13.0 Hz, J_{AX} = 8.4 Hz, J_{BX} = 5.4 Hz), 3.16 (6 lines, 1H, $CHCH_2$Ph, J_{AX} = 5.4 Hz, J_{BX} = 8.2 Hz), 3.26 and 3.33 (dt, 2H, CH_2OH, J_{AB} = 10.7 Hz, J_{AX} = 6.2 Hz, J_{BX} = 6.0 Hz), 4.78 (dt, 1H, $CH=CH$, J_{trans} = 15.5 Hz, J_{vic} = 7.1 Hz), 5.19 (12 lines, 1H, $CH=CH$, J_{trans} = 15.5 Hz, J_{vic} = 8.0 Hz, J_{allyl} = 1.3 Hz), 6.83-7.61 (m, 20H, Tr, Ph); ^{13}C NMR δ 35.6 (CH_2Ph), 43.9 ($CH=CHCH_2$), 57.2 ($CHCH_2$Ph), 61.5 (CH_2OH), 71.4, 125.5-129.5, 138.8, 146.6 (aromatic C's and $CH=CH$), 136.7 ($CH=CH$).

Cbz-Phe-Pheψ[E-CH=CH]-Glycinol (**27**)

Analogous to the preparation of isostere **19**, compound **25** (2.04 g; 4.7 mmol) was detritylated to afford the amine **26** which was coupled without further purification to give **27** as a white solid in 41% yield. R_f 0.70 (EtOAc); ^{1}H NMR δ 1.58 (s, 1H, $CH_2O\underline{H}$), 2.17 (4 lines, 2H, CH=CHC$\underline{H}_2$, J_{vic} = 5.0 Hz), 2.72 (7 lines, 2H, CHC$\underline{H}_2$Phe, J_{AB} = 13.1 Hz, J_{AX} = J_{BX} = 6.0 Hz), 3.01 (7 lines, 2H, CHC$\underline{H}_2$Phe, J_{AB} = 14.0 Hz, J_{AX} = 7.2 Hz, J_{BX} = 6.0 Hz), 3.51 (4 lines, 2H, C$\underline{H}_2$OH, J_{vic} =5.0 Hz), 4.30 (4 lines, 1H, C$\underline{H}$CH$_2$Phe), 4.82 (5 lines, 1H, C$\underline{H}$CH$_2$Phe), 5.08 (s, 2H, C$\underline{H}_2$OC(O)), 5.23 (m, 3H, N$\underline{H}$ and C$\underline{H}$=C$\underline{H}$), 5.59 (d, 1H, N$\underline{H}$, J_{vic} = 7.8 Hz), 7.02-7.36 (m, 15H, Ph(Phe), Cbz); ^{13}C NMR δ 35.6 and 38.5 (2 x $\underline{C}H_2$Phe), 41.1 (CH=CH$\underline{C}H_2$), 52.1 and 56.5 (2 x $\underline{C}$HCH$_2$Phe), 61.4 ($\underline{C}H_2$OH), 67.1 ($\underline{C}H_2$OC(O)), 126.6 and 131.8 ($\underline{C}$H=$\underline{C}$H), 127.0-129.3, 135.8, 136.3, 137.0 ($\underline{C}_6H_5$), 155.8 ($\underline{C}$=O, Cbz), 169.8 ($\underline{C}$=O, amide).

Cbz-Phe-Pheψ[E-CH=CH]-Gly-OH(**28**)

Alcohol **27** (421 mg, 0.88 mmol) was oxidized to the corresponding carboxylic acid according to the procedure described for the preparation of compound **20**. Gel filtration using MeOH/CH_2Cl_2 (1/1, v/v) as an eluent yielded **28** (291 mg, 0.60 mmol, 68%) as a white solid. R_f 0,42 (EtOAc); ^{1}H NMR (300 MHz) δ 2.77 (m, 3H, C$\underline{H}_2$Ph and C$\underline{H}$HPh(Phe)), 2.95 (4 lines, 3H, CH=CHC$\underline{H}_2$ and C$\underline{H}$HPh(Phe)), 4.31 (3 lines, 1H, C$\underline{H}$CH$_2$Ph(Phe)), 4.54 (4 lines, 1H, C$\underline{H}$CH$_2$Ph), 5.03 (s, 2H, C$\underline{H}_2$OC(O)), 5.34 (5 lines, 1H, CH=C$\underline{H}$CH$_2$, J_{trans} = 15.8 Hz, J_{vic} = 6.5 Hz), 5.44 (dd, 1H, C$\underline{H}$=CHCH$_2$, J_{trans} = 15.7 Hz, J_{vic} = 5.5 Hz), 7.08-7.36 (m, 15H, Ph); ^{13}C NMR δ 38.3 and 39.5 ($\underline{C}H_2$Ph, $\underline{C}H_2$Ph(Phe)), 41.9 (CH=CH$\underline{C}H_2$), 53.2 and 58.0 ($\underline{C}$HCH$_2$Ph, $\underline{C}$HCH$_2$Ph(Phe)), 67.6 ($\underline{C}H_2$OC(O)), 124.7, 133.8 ($\underline{C}$H=$\underline{C}$H), 127.3-130.5, 138.2, 139.1 ($\underline{C}_6H_5$), 157.8 ($\underline{C}$=O, Cbz), 167.6 ($\underline{C}$=O, Phe), 172.9 ($\underline{C}$=O, Gly); PDMS: m/z 487.7 $(M+H)^+$.

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