Novel Approach to the (–)-Sparteine-Mediated Synthesis of Kainoids: Total Synthesis of (–)-α-Kainic Acid by (–)-Sparteine-Mediated Deprotonation

M. Montserrat Martínez[a] and Dieter Hoppe*[a]

Keywords: Natural products / Asymmetric synthesis / Pyrrolidines / (–)-Sparteine / Allyl carbamates

We report a new synthesis of kainoids via allyllithium compounds using an intramolecular cycloalkylation as the key step. Preparation of different substituted pyrrolidines was carried out by using carbamates, that react with the chiral base *n*-BuLi/(–)-sparteine with strong selection between the diastereotopic protons adjacent to the carbamate group in favour for the *pro-S* proton. (–)-α-Kainic acid was synthetized from D-serine methyl ester hydrochloride, based on a (–)-sparteine-mediated asymmetric deprotonation of an intermediate carbamate that, by stereospecific *anti*-$S_N'S_E'$ intramolecular cycloalkylation, leads to the pyrrolidine ring precursor of (–)-α-kainic acid, in high yield and diastereoselectivity. Related approaches, starting from L-glutamic acid failed. The intermediate pyrrolidine was further transformed to (–)-α-kainic in three steps.

Introduction

Kainoids are an important class of natural non-proteinogenic amino acids which have a common characteristic structure consisting in a pyrrolidine nucleus with two carboxylic groups. Some of the members of this family like α-kainic acid,[1] domoic acid or acromelic acids A and B show interesting biological properties (Figure 1). The natural product (–)-α-kainic acid (**1**), which is the parent member of kainoids, shows a potent inhibitor neurotransmitting activity of the central nervous system.[2] In recent years, electrophysiologic studies about the mammalian CNS, show that the specific activity of these receptors is principally due to an unsaturated isopropylidene chain on C–4 of the pyrrolidine system.[3] Analogues with an unsaturated chain in this position with inverted configuration in C–4 or without substituent in C–4 have very low agonist activity.[4]

The importance of these natural products in pharmacological investigations has attracted the attention of number of synthetic groups. Synthesis of kainoids needs to address the formation of a pyrrolidine-2-carboxylic acid with defined stereochemistry at the three continuous chiral centers of the ring, where is essential to achieve a *cis* stereochemistry for the 3 and 4 positions. Since the first synthesis of (–)-α-kainic acid was carried out by Oppolzer,[5] several total syntheses of this compound have been published,[6] although only a few lead to the enantiopure product. Our diastereoselective approach to the pyrrolidine ring comprising the (–)-α-kainic acid relies on the (–)-sparteine-mediated asymmetric cycloalkylation. Past experience in our group has shown that (–)-sparteine-mediated carbocyclizations of allyllithium compounds lead to cyclopentanes with favored *cis*-stereochemistry.[7] This method was extended to the synthesis of a *cis*-3,4-divinylpyrrolidine with high enantio- and diastereoselectivity.[8] We suggested that this methodology could be well suitable for the synthesis of (–)-α-kainic acid and its analogues. Herein we report an alternative route for the synthesis of kainoids based on the (–)-sparteine-mediated carbocyclization of an allyllithium compound (**C**), following the strategy described in Scheme 1.

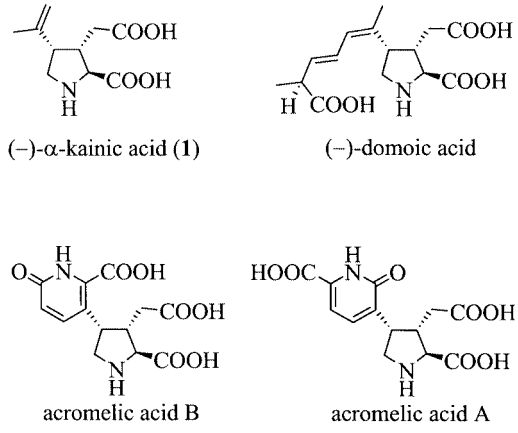


Figure 1. Structure of kainoids.

Results and Discussion

Synthetic Plan A by Cycloalkylation of Carbamate C

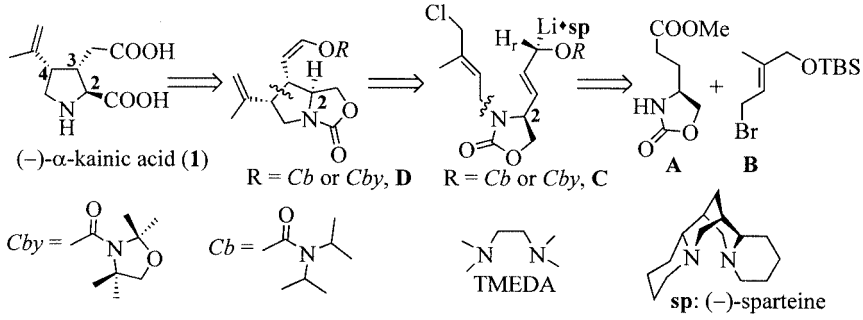
Our initial strategy was focused on the preparation of carbamate **C** (Scheme 1, R = *Cb* or *Cby*) as a late-stage

[a] Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster,
Corrensstrasse 40, 48149, Germany
Fax: +49-251-833-9772
E-mail: dhoppe@uni-muenster.de

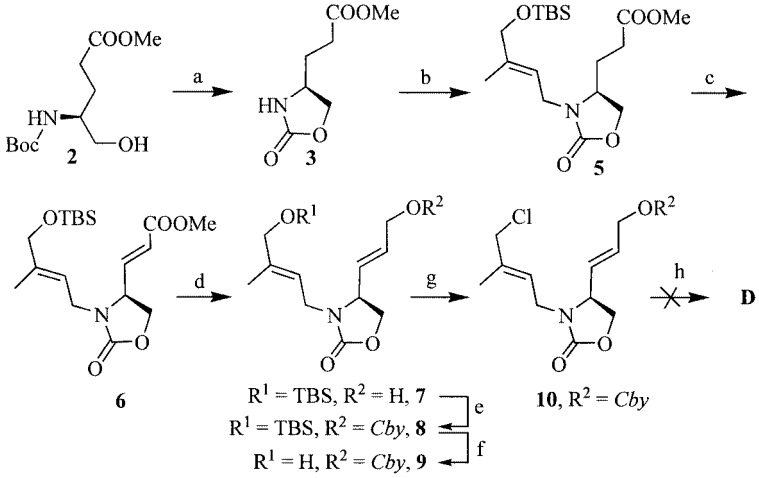
to the (–)-α-kainic acid synthesis. Asymmetric (–)-sparteine-mediated deprotonation, followed by an *anti*-$S_N'S_E'$ cycloalkylation of carbamate **C** (prepared starting from oxazolidinone **A** and isoprenoid **B**), would lead to bicycle **D** with the desired stereochemistry of (–)-α-kainic acid. After cleavage of carbamate moiety, followed by hydrolysis of the oxazolidinone ring and subsequent oxidation, intermediate **D** would be converted into (–)-α-kainic acid. The oxazolidinone ring was chosen because of promising C–2 stereochemical control during the synthesis of key intermediate **C** (Scheme 1).

Synthesis of Intermediate Carbamate C

The synthesis of key precursor **C** (Scheme 2, compound **10**) commenced with L-glutamic acid 5-methyl ester, which was transformed into the known alcohol **2** in good yield ($[\alpha]_D^{20}$ = –12.4, *c* = 1.20, $CHCl_3$) vs. ($[\alpha]_D^{20}$ = –13.2, *c* = 1.0, $CHCl_3$).[9] Formation of the oxazolidinone **3** ($[\alpha]_D^{20}$ = –29.3, *c* = 1.1, $CHCl_3$) was carried out without any racemization (as determined by ^1H NMR shift experiment) using thionyl chloride in 77% yield. Further synthesis required *N*-allylation of oxazolidinone **3** with (*E*)-4-bromo-1-(*tert*-butylsilyloxy)-2-methyl-2-butene (**4d**, Scheme 5).[10] The use of potassium *tert*-butoxide/18-crown-6 turned out to be the best method for deprotonation, compound **5** was obtained in 92% yield ($[\alpha]_D^{20}$ = –34, *c* = 1.0, $CHCl_3$). α,β-Unsaturated ester **6** ($[\alpha]_D^{20}$ = +19.9, *c* = 1.0, $CHCl_3$) was synthesized via silyl enol ether formation followed by oxidation with $Pd(OAc)_2$ in acetonitrile in 83%.[11] Both stereogenic double bonds in structure **6** were found in an *E*/*Z* ratio of > 99% as determined by NOE experiments. 1,2-Reduction of the ester moiety in compound **6** by treatment with DIBAL-H (for optimal result, Lewis acid must be added before introduction the metal hydride reagent) followed by carbamoylation with the oxazolidinecarbonyl chloride (*Cby*Cl, Scheme 1) by the sodium hydride method[12] furnished carbamate **8** ($[\alpha]_D^{20}$ = –6.9, *c* = 0.41, $CHCl_3$) in 76% overall yield. Therefore the reaction sequence was completed by deprotection with TBAF[13] providing the allylic alcohol **9** (98% yield, ($[\alpha]_D^{20}$ = +15.0, *c* = 0.80, $CHCl_3$) followed by dehydroxychlorination to the key precursor **10** ($[\alpha]_D^{20}$ = +9.2, *c* = 1.2, $CHCl_3$) in 47% yield (the low yield is presumably caused by the instability of the product).



Scheme 1. Retrosynthetic analysis of (–)-α-kainic acid.



Scheme 2. Reagents and conditions: (a) Cl_2SO, THF, room temp., 3 h, 77%; (b) KO*t*Bu, THF, 18-crown-6, 0 °C to room temp., 30 min, then **4d** (Scheme 5), 3 h, room temp., 92%; (c) TMSCl, THF, –78 °C, KHMDS, THF, 30 min, then $Pd(OAc)_2$, room temp., CH_3CN, 6 h, 83%; (d) $BF_3{\cdot}OEt_2$, –78 °C, CH_2Cl_2, 1 h, then DIBAL-H, 2 h, –78 °C, quant.; (e) NaH, THF, room temp., 30 min, then *Cby*Cl (Scheme 1), 70 °C, 12 h, 76% over two steps; (f) TBAF, Et_2O, room temp., 2 h, 98%; (g) NEt_3, CH_2Cl_2, –40 °C, CH_2Cl_2, MsCl, 1 h, then LiCl, THF, room temp., 12 h, 47%; (h) *n*BuLi, (–)-sparteine, toluene, 5 h, –90 °C, no products isolated.

Studies of Cyclization with the Carbamate 10

Subsequent formation of the pyrrolidine ring was investigated, but the resulting carbamate **10** failed to undergo the (–)-sparteine-mediated asymmetric cycloalkylation. When carbamate **10** was treated with the chiral base *n*BuLi/(–)-sparteine in toluene at –78 °C for 5 h, only a mixture of unidentified compounds was found. Different attempts by changing the solvent (e.g., Et_2O, pentane), temperature (–90 °C, –78 °C), pre-complexation of *n*BuLi and even high dilution conditions, were unsuccessful. The same negative result was obtained when *s*BuLi/(–)-sparteine was used, and even when TMEDA was used as a diamine no cycloalkylation products could be detected.

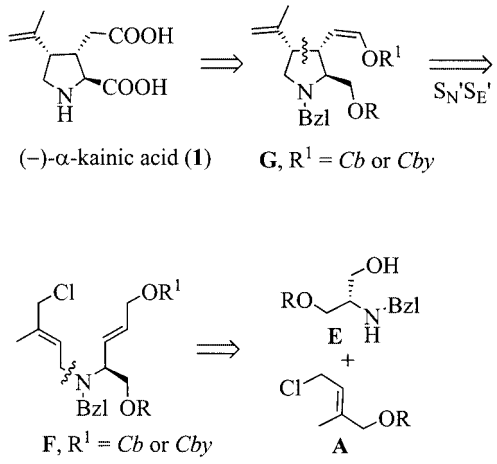
Although several side reactions are conceivable, these unsuccessful experiments can be understand as a consequence of the presence of oxazolidinone moiety: the α-protons closest to the carbonyl group of the oxazolidinone group have a similar kinetic acidity as the α-protons of the O*Cby* moiety (Scheme 1). This assumption is supported by Bertini–Gross and Beak[14] who demonstrated that conformationally restricted bicyclic carbamates undergo rapid diastereoselective deprotonation with *s*BuLi/TMEDA, where one of the methylene protons closest to the carbonyl group is preferentially removed. The installation of sterically bulky groups in the oxazolidinone ring was necessary, according to these authors to prevent addition of the *n*BuLi onto the carbamate carbonyl group.[14]

Synthetic Plan B by Cyclization of Carbamate F

Failing to provide a suitable substrate to synthesize (–)-α-kainic acid starting from oxazolidinone **C**, a different access was needed. In this new approach an *N*-benzyl group and a *O*-silyl group were selected as protecting group instead of an oxazolidinone moiety leading to key intermediate **F** (Scheme 3). We kept the same key step based on an asymmetric *anti*-$S_N'S_E'$ cycloalkylation reaction, to achieve the desired configuration of (–)-α-kainic acid in pyrrolidine **G**, but using key precursor **F**, synthesized from building blocks **A** and **E** as depicted in Scheme 3.

Synthesis of Intermediate Carbamates 19 and 20

The synthesis of the precursor **F** (Scheme 4, compound **19**) arising from D-serine methyl ester hydrochloride began with the *O*-silylation of *N*-benzyl-D-serine methyl ester **11**[15] using *tert*-butyldiphenylsilyl chloride (TBDPSCl) in 88% yield, followed by reduction of the ester moiety with $LiBH_4$ to afford alcohol **13** ($[\alpha]_D^{20}$ = –1.6, *c* = 1.90, $CHCl_3$) in 56% yield.[16] Best conditions for *N*-allylation of alcohol **13** with isoprenoid **4d** (Scheme 5) were heating at reflux in acetonitrile in the presence of $NaHCO_3$. Compound **14** was obtained in 81% yield ($[\alpha]_D^{20}$ = –11.8, *c* = 0.52, $CHCl_3$). Alcohol **14** was then subjected to Swern oxidation followed in situ by olefination employing (ethoxycarbonylmethylene) triphenylphosphorane in a single operation to afford α,β-unsaturated ester **15** ($[\alpha]_D^{20}$ = +9.7, *c* = 0.37, $CHCl_3$) as a single (*E,E*) stereoisomer (determined by ^1H NMR) in 70% overall yield. In the next step, selective removal of the TBS group in compound **15** could be only achieved by treatment of the bis-silyl ether **15** with pyridinium *p*-toluenesulfonate (PPTS)[17] in ethanol at 58 °C for several hours, furnishing allylic alcohol **16** ($[\alpha]_D^{20}$ = +6.8, *c* = 0.74, $CHCl_3$) in 100% yield. The conversion of the hydroxyl group into chloro **17** ($[\alpha]_D^{20}$ = +5.2, *c* = 0.64, $CHCl_3$) was carried out via the mesylate with LiCl in 83% yield.

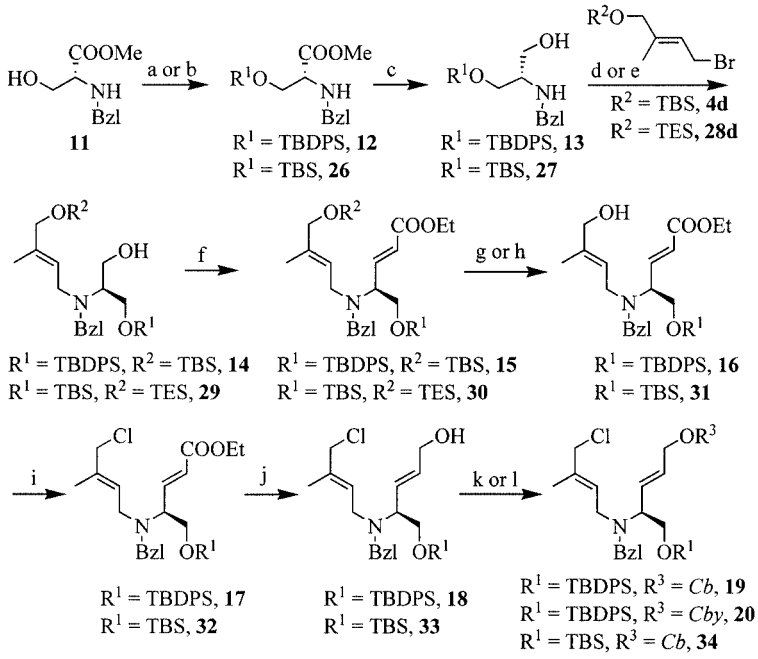


Scheme 3. Alternative retrosynthetic analysis of (–)-α-kainic acid by (–)-sparteine-mediated deprotonation.

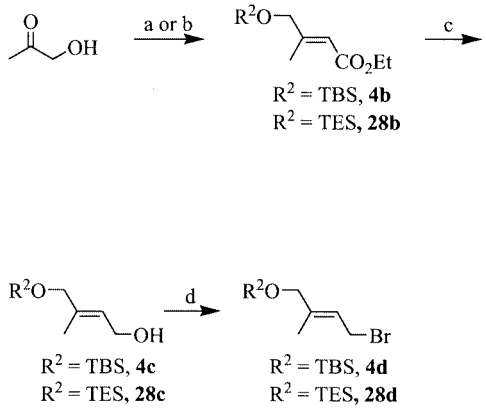
Subsequent chemoselective reduction of α,β-unsaturated ester **17** with diisobutylaluminium hydride (DIBAL-H) afforded the corresponding allylic alcohol, which was subjected without further purification to standard carbamoylation conditions[12] using *N,N*-diisopropylcarbamoyl chloride (*Cb*Cl, Scheme 1). The required carbamate **19** ($[\alpha]_D^{20}$ = +4.2, *c* = 0.45, $CHCl_3$) was obtained in 60% yield (over two steps). Carbamate **20** ($[\alpha]_D^{20}$ = +2.3, *c* = 1.9, $CHCl_3$) was also prepared in similar way in 68% yield (over two steps), but using *Cby*Cl instead of *Cb*Cl.

Synthesis of Trisubstituted Pyrrolidines

The crucial cyclization of carbamate (*E,E*)-**19** (Scheme 6) was carried out in toluene at –87 °Cby slow addition of 2.2 equivalents of *n*BuLi/(–)-sparteine, to furnish the expected cyclized product **21a** ($[\alpha]_D^{20}$ = –7.1, *c* = 0.52, $CHCl_3$) in 16% yield (entry 1, Table 1), with *cis* stereochemistry at positions 3 and 4 in a diastereomeric ratio of **21a:21b** nearly to 95:5. No *trans* products in respect to the C3–C4 bond were detected, as evidenced by ^1H NMR spectroscopy. A similar result was obtained by employing *s*BuLi/(–)-sparteine in toluene at –78 °C (entry 2, Table 1). The preference for the formation of one diastereoisomer (**21a**), demonstrates the effect of the kinetic control in the deprotonation step,[7,8] although yields of 16% to 27% were unsatisfying even if the starting material was recovered in high yield. These moderate yields prompted us to investigate the cyclization reaction of carbamate **19**, employing TMEDA as a ligand

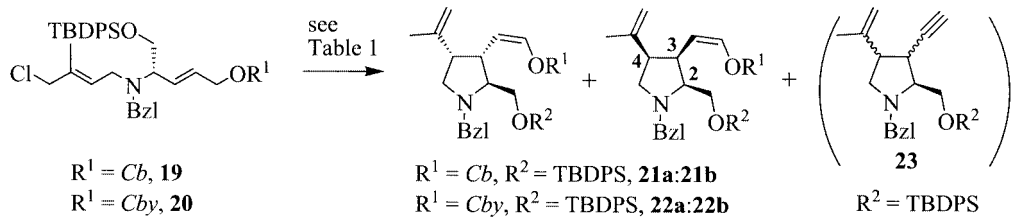


Scheme 4. Reagents and conditions: (a)TBDPSCl, NEt_3, DMAP, CH_2Cl_2, room temp., 12 h, 88% of **12**; (b) NEt_3, TBSCl, DMAP, CH_2Cl_2, room temp., 12 h, 89% of **26**; (c) $LiBH_4$, THF/toluene (4:1), reflux, 20 min, 56% of **13** and 47% of **27**; (d) $NaHCO_3$, CH_3CN, room temp., 30 min, then **4d** (Scheme 5), reflux, 3 h, 81% of **14**; (e) $NaHCO_3$, CH_3CN, room temp., 30 min, then **28d** (Scheme 5), reflux, 3 h, 82% of **29**; (f) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 20 min, then NEt_3, –78 to –15 °C, 1 h, then (ethoxycarbonylmethylene) triphenylphosphorane, –15 °C to room temp., 3 h, 70% overall yield of **15** and 75% overall yield of **30**; (g) PPTS, EtOH, 55 °C, 48 h, 100% of **16**; (h) TBAF, THF, 0 °C, 5 min, 81% of **31**; (i) NEt_3, CH_2Cl_2, –40 °C, MsCl, 1 h, then LiCl, THF, room temp., 3 h, 83% of **17** and 71% of **32**; (j) DIBAL-H, CH_2Cl_2, –78 °C, 2 h, quant. of **18** and 70% of **33**; (k) NaH, *Cb*Cl (Scheme 1), THF, reflux, 12 h, 60% (over two steps) of **19** and 53% of **34**; (l) NaH, THF, reflux, *Cby*Cl (Scheme 1), 12 h, 68% (over two steps) of **20**.



Scheme 5. Reagents and conditions: (a) NEt_3, DMAP, TBSCl, CH_2Cl_2, room temp., 12 h, then KO*t*Bu, triethyl phosphonoacetate, 18-crown-6, CH_2Cl_2, 0 °C to room temp., 12 h, 76% over two steps of **4b**, (b) NEt_3, 0 °C, DMAP, TESCl, CH_2Cl_2, room temp., 12 h, then KO*t*Bu, triethyl phosphonoacetate, 18-crown-6, CH_2Cl_2, 0 °C to room temp., 12 h, 85% over two steps of **28b**, (c) DIBAL-H, –78 °C, CH_2Cl_2, 2 h, 96% of **4c** and 91% of **28c**, (d) NEt_3, MsCl, CH_2Cl_2, –40 °C, 1 h, then LiCl, THF, room temp., 12 h, quant.

for the *n*BuLi instead of the chiral diamine (–)-sparteine. The best conditions were the use of 2.2 equivalents of *n*BuLi/TMEDA in THF at –45 °C for 3 h, affording **21a** and **21b** in 88% yield with a diastereomeric ratio of 60:40 (entry 4, Table 1). Since the relative configuration of pyrrolidines **21a** and **21b** (separated by flash chromatography) could not be determined by NOE studies, the stereochemical assignment of structures to **21a** and **21b** is based on the fact that the two olefinic protons of the isopropenyl chain appear as two singlets in the ^1H NMR spectra, as is typical for similar kainoids[18] (see later for further discussion). The (*Z*)-geometry of the enol carbamate moiety is based on the small olefinic coupling constant (6.4 Hz) observed, in agreement with previous studies in our group.[7,8] A possible reason for why the cyclization is slower when using (–)-sparteine as diamine, might be either electrophile's reactivity dependence on the temperature or the fact the C–2 substituent influence the efficiency of the cyclization to produce the required 2,3-*trans* arrangement. To prove the first assumption, carbamate **19** was treated with *n*BuLi/(–)-sparteine in toluene at –78 °C, and through raising the temperature from –78 °C to –45 °C for 4 h,[19] an enhancement from 16% up to 45% yield was possible (entry 5, Table 1, *dr* = 95:5, by ^1H NMR). When Et_2O was used as solvent (entries 3 and 6, Table 1), at –78 °C or lower temperatures, the cyclization did not take place. The addition of 10% of THF to the solvent toluene led to higher yield (77%, entry 8, Table 1), but the diastereoselectivity decreased to 65:35. Finally, when carbamate **20** (*Cby* instead of *Cb*) was subjected under standard conditions (*n*BuLi/(–)-sparteine in toluene at –78–45 °C for 4 h), cyclized pyrrolidines **22a** and **22b** (Scheme 6) were furnished under these conditions in similar



Scheme 6. Asymmetric cycloalkylation of **19** by $S_N'S_E'$ substitution.

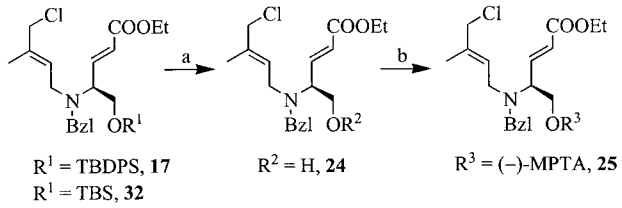
Table 1. Conditions employed in the cycloalkylation reaction on carbamate **19**.

Entry	Base	Solvent	*T* (°C)	Time (h)	**21** (%)	*dr* (**21a**:**21b**)
1	*n*BuLi/(–)-sp	toluene	–87	3	16	95:5
2	*s*BuLi/(–)-sp	toluene	–78	6	27	95:5
3	*n*BuLi/(–)-sp	Et_2O	–90	24	–	–
4	*n*BuLi/TMEDA	THF	–45	3	88	60:40
5	*n*BuLi/(–)-sp	toluene	–78–45	4	48	95:5
6	*n*BuLi/(–)-sp	Et_2O	–45	2	30	95:5
7	*n*BuLi/(–)-sp	toluene	–78–40	16	32[a,b]	95:5
8	*n*BuLi/(–)-sp	toluene/10%THF	–78–45	1	77	65:35

[a] Fritsch–Buttenberg–Wiechell rearrangement[19] to form alkyne **23** (Scheme 6) takes place in 25%. [b] 1 equiv. of LiCl was added.

yield (54%) and diastereoselectivity (*dr* = 95:5, by ^{1}H NMR).

The result of these experiments, together led to the following considerations: a) there is a risk of partial racemization on the stage of the α,β-unsaturated ester **17** (Scheme 4) which, in principle, would lead to *ent*-**21a** and *ent*-**21b** in the (–)-sparteine-mediated cyclization. Epimerization on the stage of the corresponding lithium compound of type **H·sp** (Scheme 8) most probably is the origin for the formation of **21b**, b) the ring closure of this functionalized cyclization precursors **19** and **20** provided preferentially one diastereomer although in lower to moderate yields, made us to prove the *ee* before the cycloalkylation reaction. Thus, the optical purity of ester **17** was determined to be 26% *ee* (by ^{1}H NMR), which was carried through the synthesis. Mosher ester **25** was derived from enantiomerically enriched and, as well, from racemic alcohol **24** by esterification using (–)-MPTA chloride in 65% overall yield (Scheme 7).



Scheme 7. Reagents and conditions: (a) TBAF, THF, 3 h, room temp., quant.; (b) Py, CCl_4, (–)-*R*-MPTACl, room temp., 4 h, 65% overall yield.

It was surprising that the problem of racemization emerged during the preparation of α,β-unsaturated ester **17** when TBDPS was used as a protecting group. However, this unsatisfactory result is supported by Hanessian et al.[20] who observed racemization as well during the formation of an oxazolidinone ring from D-serine alcohol derivative bearing a TBDPS group, most probably due to a 1,3-silyl shift.

We conclude that: a) in the cyclization reaction of the carbamates **19** and **20**, the major diastereomer was obtained from *pro-S*-proton abstraction in the presence of (–)-sparteine, but in lower yield as compared with TMEDA, b) a second diastereomer *all-cis*-substituted pyrrolidine **21b** was achieved when TMEDA was used instead of (–)-sparteine and when employing higher temperatures. Obviously, the enantiomeric carbamate *ent*-**19** has quite lower reactivity under the reaction conditions. If this is true, *rac*-**19** might be employed in a kinetic resolution.

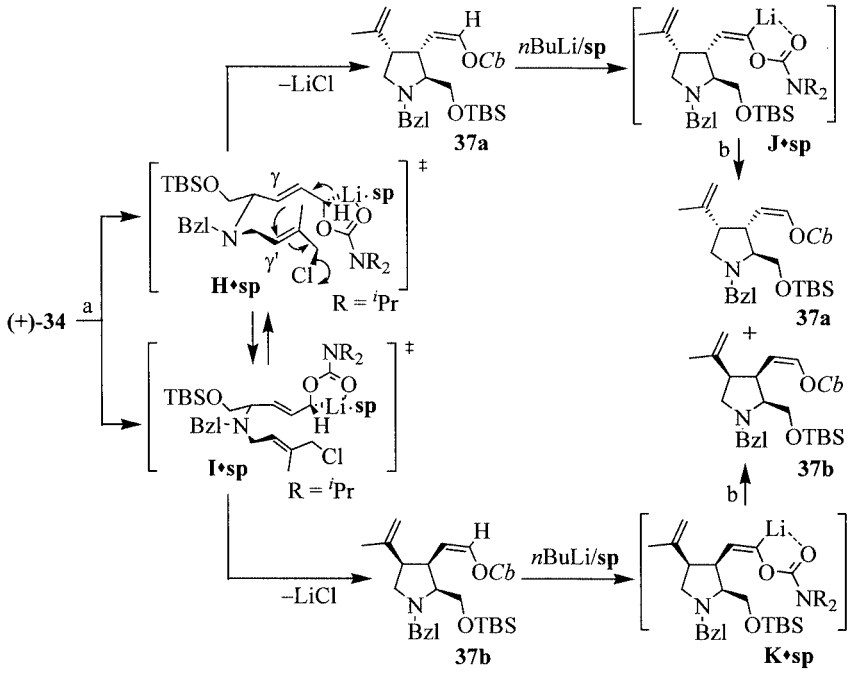
Total Synthesis of (–)-α-Kainic Acid

In the light of these results, an alternative plan was devised following the retrosynthetic analysis described in Scheme 3, in which TBS was chosen instead of TBDPS group. In the event precursor **34** was prepared using the established work on precursor **19** (Scheme 4). Thus, alcohol **11** was subjected to a) *O*-silylation (TBSCl, 89% yield, $[\alpha]_D^{20}$ = +3.9, *c* = 0.94, $CHCl_3$), b) reduction of ester moiety on **26** with $LiBH_4$ led to alcohol **27** in 47% (84% based on **26**, ($[\alpha]_D^{20}$ = –8.2, *c* = 1.10, $CHCl_3$), c) *N*-allylation of alcohol **27** was carried out by refluxing (*E*)-configured isoprenoid **28d** (prepared in a similar fashion of **4d**,

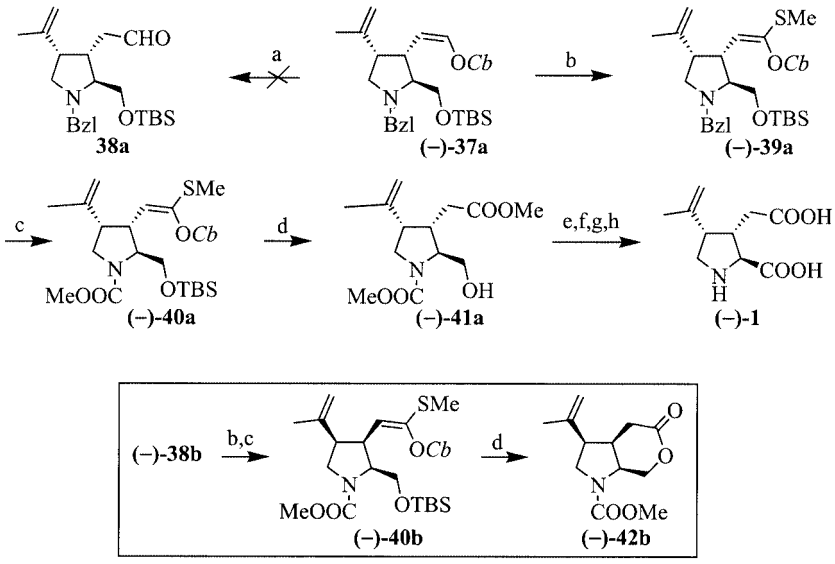
Scheme 5)[21] using $NaHCO_3$ in acetonitrile, yielding alcohol **29** ($[\alpha]_D^{20}$ = –3.6, *c* = 0.91, $CHCl_3$) in 82% yield, d) Swern oxidation followed by in situ olefination using (ethoxycarbonylmethylene)triphenylphosphorane, in a single operation to provide **30** ($[\alpha]_D^{20}$ = +8.2, *c* = 1.59, $CHCl_3$) in 75% overall yield with an *E*/*Z* ratio > 99% (determined by ^{1}H NMR). Then next step of the synthesis required selective removal of TES group in compound **30**, which was achieved with TBAF at low temperature in 81% yield. Allylic alcohol **31** ($[\alpha]_D^{20}$ = +14.7, *c* 0.61, $CHCl_3$) was then subjected to chlorine-substitution giving (*E,E*)-allylic chloride **32** ($[\alpha]_D$ = +22.0, *c* 0.78, $CHCl_3$) in 71% yield. An optical purity of > 95% enantiomeric excess was determined for **32** by ^{1}H NMR analysis of the corresponding (–)-MPTA ester **37** (Scheme 7). 1,2-Reduction of the ester moiety in compound **32** with DIBAL-H led to the allylic alcohol **33** in 70% yield ($[\alpha]_D^{20}$ = +7.2, *c* 0.76 $CHCl_3$). Carbamate **34** ($[\alpha]_D^{20}$ = +9.7, *c* 0.71, $CHCl_3$) was prepared from allylic alcohol **33** by using standard conditions[12] with *Cb*Cl (Scheme 1) in 53% yield.

Cyclization Mechanism of Carbamate 34 and Structure Determination

Intramolecular *anti*-$S_N'S_E'$ cycloalkylation of (*E,E*)-carbamate **34** (Scheme 8), the key step for the synthesis of (–)-α-kainic acid, commenced with α-deprotonation by means of *n*BuLi/(–)-sparteine at –78 °C in toluene.[22] After 1 h, a high C3–C4 *cis*-selectivity was achieved without formation of *trans* products in respect to the C3–C4 bond, giving the two separable diastereomers **37a** ($[\alpha]_D^{20}$ = –22.6, *c* = 0.57, $CHCl_3$) and **37b** ($[\alpha]_D^{20}$ = –6.4, *c* = 0.75, $CHCl_3$) in high yield (83%, **37a:37b**, *dr* 80:20, as determined by ^{1}H NMR). The stereochemical assignment of structures to **37a** and **37b** is based on the ^{1}H NMR spectra as was described before for pyrrolidines **21** and **22** (TBDPS instead of TBS group).[18] Further, experimental vicinal coupling constants ($^3J_{2,3}$ and $^3J_{3,4}$) observed for **37a** and **37b** were within the range of calculated ones by computational studies based on the Karplus–Conroy equation.[23] Further support to this assignment is provided by the conversion of **37a** to (–)-α-kainic acid (**1**). The stereochemical outcome of the asymmetric cycloalkylation reaction is supported by the following mechanistic considerations: 1) The chiral base *n*BuLi/(–)-sparteine stereoselectively removes the α-*pro*-*S*-proton[24] of carbamate **34**, generating the configurationally labile intermediate **H·sp**. Intramolecular cycloalkylation of **H·sp** occurs under regioselective C–C bond formation between both γ,γ′ positions, and simultaneous elimination of lithium chloride.[8] Although these (–)-sparteine-lithium ion pairs of primary allyl carbamates have been recognized to have limited configurational stability, the cycloalkylation is slightly more rapid than epimerization to form **I·sp**. 2) An *endo* conformation of the allylic moieties in an *anti*-mode is required for the $S_N'S_E'$ cycloalkylation.[25] The chair-like transition state **H·sp** allows the π–π* overlap of the electron-rich and electron-deficient allyl moieties, presumably being the origin of the high *cis*-diasteroselectivity. Compound **37b** is most probably formed by intramolecular cycloalkylation of the (*R*)-configured lithium derivative **I·sp**, formed by incomplete stereoselectivity of the deprotonation step and, as well, by competing epimerization. To confirm the proposed mechanism, knowledge of the configurations of pyrrolidines **37a** and **37b** is required. The configuration



Scheme 8. Mechanism of cycloalkylation. Reagents and conditions: (a) *n*BuLi/(–)-sparteine (sp) (2.2 equiv.), toluene, –78 °C, 1 h, then MeOH, 83%, *dr* = 80:20 (**37a**:**37b**).



Scheme 9. Reagents and conditions: (a) MeLi or TMSOTf; (b) *t*BuLi, THF, –78 °C, TMEDA, 1 h, MeSSMe,1 h, room temp., quant.; (c) MeOC(=O)Cl, $ClCH_2CH_2Cl$, reflux, 3 h, 84% overall yield of **40a** and 82% overall yield of **40b**; (d) $MeSO_3H$, MeOH, H_2O, reflux, 16 h, 55% overall yield of **41a** and 48% overall yield of **42b**; (e) Jones reagent; (f) 40% NaOH aq., reflux, 18 h; (g) Dowex 50WX-200 (elution with 1 N NH_4OH), Amberlite CG-50 (elution with H_2O); (h) recryst. EtOH aq., 38% overall yield.

of the latter has been determined by transformation of **37a** into the alcohol **41a** and subsequent conversion into (–)-α-kainic acid (Scheme 9), whereas **37b** was converted into the enantiomer of so-called β-kainic acid **42b** (see Scheme 9). By comparison of the sense of the optical rotations, **37a** and **37b** could be assigned the 2*S*,3*R*,4*S*-configuration and 2*S*,3*S*,4*R*-configuration, respectively.

To complete the synthesis of (–)-α-kainic acid, oxidative removal of the carbamate group in **37a** is necessary (Scheme 9). The usual oxidative methods[26] are not applicable to vinyl carbamates **37a** and **37b** due to the reactive additional trisubstituted double bond. Moreover, attempts to convert the vinyl carbamate **37a** into aldehyde **38a** by using methyllithium[27] or TMSOTf[28] failed. In light of these results, we used an indirect oxidation method consisting in a vinylic deprotonation by applying *tert*-BuLi followed by quench with MeSSMe.[29] The obtained ketene monothioacetal **39a** was submitted without further purification to *N*-debenzylation by treatment with methyl chloroformate,[30] providing **40a** ($[\alpha]_D^{20}$ = –19.0, *c* = 0.5, $CHCl_3$) in 84% overall yield. Treatment of monothioketene acetal **40a** with excess of methanesulfonic acid, resulted in the deprotection of the hydroxyl group and simultaneous hydrolysis of the ketene monothioacetal moiety giving alcohol **41a** in 55% overall yield. Eludicidation of the structure of **41a** was carried out by ^1H NMR spectra and NOE studies.[31] The absolute configuration was confirmed by comparing its respective $[\alpha]_D$ value with published one: **41a** ($[\alpha]_D^{20}$ = –41.2, *c* = 0.52, CH_2Cl_2) vs. ($[\alpha]_D^{20}$ = –43.0, *c* = 1.25, CH_2Cl_2).[6i] In a similar fashion, lactone **42b** ($[\alpha]_D^{20}$ = –28.1, *c* = 0.30, $CHCl_3$) in turn derived from **37b**, resulted by deprotection of silyl ether in **40b** followed by cyclization of both, C–2 and C–3 chains, in 48% yield (Scheme 9). The *all-cis*-relatioship of the C–2, C–3, and C–4 protons was unequivocally demonstrated by comparison of the ^1H NMR and optical rotation with the protected enantiomeric derivative of the so-called β-kainic acid **42b**, recently described by Campbell: **42b** ($[\alpha]_D^{20}$ = –28.1, *c* = 0.30, $CHCl_3$) vs. *ent*-**42b** ($[\alpha]_D^{20}$ = +32.1, *c* = 1.20, $CHCl_3$).[6j]

The final steps to the natural product were carried out following literature precedents:[6i] Jones oxidation of the primary alcohol **41a**, followed by hydrolysis with 40% aqueous sodium hydroxide, and purification by using ion-exchange chromatography afforded enantiopure (–)-α-kainic acid as colourless needles after recrystallization from aqueous ethanol (38% overall yield). Our final product possesses the same physical properties reported for (–)-α-kainic acid: m.p. 243–245 °C (dec.) vs. m.p.[6i] 241–244 °C (dec.); ($[\alpha]_D^{20}$ = –14.3, *c* = 0.40, H_2O) vs. ($[\alpha]_D^{20}$ = –14.6, *c* = 0.25, H_2O).[6i]

Conclusions

We provide a 7-step synthesis of the oxazolidinone **10** in 20.6% overall yield from L-glutamic acid methyl ester. An asymmetric deprotonation and cycloalkylation was planned as the key reaction, however it did not take place, presumably because of two functional groups (O*Cby* and oxazolidinone) are competing for the *n*BuLi.

The high diastereoselectivity obtained in the asymmetric cycloalkylation with carbamates **19** and **20**, supported the validity of the synthesis of stereochemically defined trisubstituted pyrrolidine systems and for the creation of two stereogenic centers in a single stage. This route proved to be inefficient as well, due to racemization before the key step.

A new and efficient asymmetric total synthesis of (–)-α-kainic acid, was accomplished in 12 steps (longest linear sequence) in 1.4% overall yield from alcohol **11**. Similar synthetic strategies might be useful for the preparation of other members of the kainic natural product family.

Experimental Section

General: All moisture-sensitive reactions were carried out under an atmosphere of argon in flame-dried glassware with dried solvents. The solvents (THF, toluene, CH_2Cl_2, CH_3CN, dimethyl sulfoxide, acetone, Et_2O, etc.) were dried according to standard procedures and distilled prior to use. Flash chromatography was performed using Merck silica gel 60 (particle size 0.040–0.055 mm, 230–400 mesh) at a pressure of about 1.5 bar. Solvents for chromatography, diethyl ether (Et_2O), petroleum ether (PE) and ethyl acetate (EtOAc), were distilled prior to use. For analytic thin-layer chromatography (TLC), Merck plastic sheets ($60F_{254}$ silica gel) were used. Visualization was accomplished with UV light or by staining with a basic I_2, permanganate, vanillin or cerium molydate solutions. NMR spectra were recorded on a Bruker ARX 300 and AMX 400 and on a Varian Unity plus (Varian Inc., Palo Alto, CA, USA) 600 spectrometer. Chemical shifts are given in ppm (δ) and *J* values are in Hz, with TMS (^1H) and $CDCl_3$ (^{13}C) as internal standards. Infrared (IR) spectra were recorded on a Nicolet FT-IR 5DXC spectrometer. Optical rotations were measured at 20 °C with a Perkin–Elmer 341 at the sodium D line. Mass spectra and elemental analyses were performed at the Department of the Organic Chemistry of the University of Münster. Exact mass determination (MS-ESI) was carried out with a Quattro LCZ (Waters-Micromass, Manchester, UK) with manospray inlet.

Ethyl (2*E*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-methyl-2-butenoate (4b): NEt_3 (11.5 mL, 81.8 mmol) was added to a stirred solution of α-hydroxyacetone (5.05 g, 68.2 mmol) in dry CH_2Cl_2 (75 ml). TBSCl (12.3 g, 81.8 mmol) and DMAP (0.42 g, 3.4 mmol) were then added. After 12 h at room temperature, the reaction mixture was diluted with H_2O (30 mL), the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and the solvents evaporated in vacuo; no further purification of the crude product. To a suspension of KO*t*Bu (7.51 g, 66.9 mmol) in CH_2Cl_2 (90 mL) was added at 0 °C, a solution of triethyl phosphonoacetate (13.8 g, 61.4 mmol) and 18-crown-6 (0.89 g, 3.4 mmol) in CH_2Cl_2 (70 mL). The reaction mixture was stirred at room temperature for 1 h. A solution of crude product *O*-TBS-α-hydroxyacetone (10.5 g, 55.8 mmol) in CH_2Cl_2 (100 mL) was added at 0 °C. After stirring at room temperature for 12 h, sat. aqueous NH_4Cl (200 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL), the combined organic phases were dried ($MgSO_4$), and the solvents evaporated in vacuo. The crude product was purified by flash chromatography, R_f = 0.61 (SiO_2, Et_2O/petroleum ether, 1:10) affording **4b** (13.4 g, 76% over two steps, *E*/*Z* 85:15) as a colorless oil. IR (film): $\tilde{\nu}$ (cm^{-1}) = 2967–2868, 1729 (CO), 1670, 1479. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 6 H, $Si(CH_3)_2$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 1.20 (t, 3 H, ^3J = 7.2 Hz, $CO_2CH_2CH_3$), 1.98 (s, 3 H, $C(CH_3)$=CH), 4.09 (m, 4 H, $CO_2CH_2CH_3$ and CH_2OSi), 5.88 (s, 1 H, $C(CH_3)$=C*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.1 ($Si(CH_3)_2$), 14.7, 15.8 ($C(CH_3)$=CH and $CO_2CH_2CH_3$), 18.7 ($SiC(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 59.9 ($CO_2CH_2CH_3$), 67.5 (CH_2OSi), 113.9 (CH=$C(CH_3)$), 157.4 (CH=$C(CH_3)$), 167.4 (CO). EI-MS, *m*/*z* (%) = 258 (8) [M^+], 243 (4) [$M^+ - CH_3$], 201 (100) [$M^+ - C(CH_3)_3$], 173 (36), 75 (73). $C_{13}H_{26}O_3Si$ (258.43): calcd. (%) C, 60.42, H 10.14; found: C 60.31, H 10.17.

(2*E*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-methyl-2-buten-1-ol (4c): To a 1 M solution of diisobutylaluminium hydride in heptane (87.1 mL, 87.1 mmol) at –78 °C was added a solution of (*E*)-**4b** (7.50 g, 29.0 mmol) in 50 mL of CH_2Cl_2. The reaction mixture was stirred at –78 °C for 2 h and then quenched with a 5 M solution of acetic acid in CH_2Cl_2 (50 mL). The solution was poured into a 10% aqueous solution of tartaric acid in CH_2Cl_2 (250 mL) and stirred at room temperature for 1 h. The aqueous phase was extracted with CH_2Cl_2 (3 × 250 mL), the organic phase dried ($MgSO_4$), and the solvents were evaporated. The crude product was purified by flash chromatography, R_f = 0.5 (SiO_2, Et_2O/petroleum ether, 90:10) affording **4c** (6.02 g, 96%, *E*/*Z* 100:0) as a colorless oil. IR (film): $\tilde{\nu}$ (cm^{-1}) = 3420–3300 (OH), 2959–2858, 1478, 1397, 1364. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 6 H, $Si(CH_3)_2$), 0.84 (s, 9 H, $SiC(CH_3)_3$), 1.58 (s, 3 H, $C(CH_3)$=CH), 3.96 (s, 2 H, CH_2OSi), 4.13 (d, 2 H, ^3J = 7.2 Hz, CH_2OH), 5.60 (t, 1 H, ^3J = 6.9 Hz, $C(CH_3)$=C*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.1 ($Si(CH_3)_2$), 13.3 ($C(CH_3)$=CH), 18.3 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 58.9 (CH_2OH), 67.6 (CH_2OSi), 122.6 ($C(CH_3)$=CH), 138.0 ($C(CH_3)$=CH). EI-MS, *m*/*z* (%) = 185 (2) [$M^+ - CH_2OH$], 159 (27) [$M^+ - C(CH_3)_3$], 75 (100). $C_{11}H_{24}O_2Si$ (216.39): calcd. (%) C 61.05, H 11.18; found: C 60.65, H 10.95.

{[(2*E*)-4-Bromo-2-methyl-2-butenyl]oxy}(*tert*-butyl)dimethylsilane (4d): To a solution of (*E*)-**4c** (6.80 g, 31.5 mmol) in 75 mL of CH_2Cl_2 at –40 °C NEt_3 (7.06 mL, 50.2 mmol) and methanesulfonyl chloride (3.17 mL, 40.9 mmol) were added. The reaction mixture was stirred at –40 °C for 1 h and then was added via cannula to a solution of dry LiBr (10.9 g, 126 mmol) in 50 mL of THF. The reaction mixture was allowed to warm to room temperature overnight and quenched by addition of H_2O (50 mL). The solution was poured into petroleum ether (100 mL) and washed several times with H_2O (5 × 70 mL). The organic phase was dried ($MgSO_4$) and the solvents were evaporated. Crude **4d** (8.65 g) was used freshly without further purification in *N*-allylation reaction of **3**. IR (film): $\tilde{\nu}$ (cm^{-1}) = 2963–2864, 1472, 1465, 1401. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 6 H, $Si(CH_3)_2$), 0.84 (s, 9 H, $SiC(CH_3)_3$), 1.61 (s, 3 H, $C(CH_3)$=CH), 3.97 (m, 4 H, CH_2Br and CH_2OSi), 5.74 (t, 1 H, ^3J = 8.8 Hz, $C(CH_3)$=C*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.2 ($Si(CH_3)_2$), 12.9 ($C(CH_3)$=CH), 18.2 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 28.4 (CH_2Br), 67.2 (CH_2OSi), 119.3 ($C(CH_3)$=CH), 141.7 ($C(CH_3)$=CH). EI-MS, *m*/*z* (%) = 220 (68) [$M^+ - C(CH_3)_3$], 199 (46) [M^+ – HBr], 137 (76), 73 (100). $C_{11}H_{23}BrOSi$ (279.29).

Methyl (*S*)-3-(2-Oxo-1,3-oxazolidin-4-yl)propanoate (3): Thionyl chloride (5.49 mL, 75.7 mmol) was added at room temperature to a solution of alcohol **2**[9] (6.24 g, 25.2 mmol) in THF (80 mL). The reaction mixture was stirred for 3 h and the excess of $SOCl_2$ removed in vacuo. The crude product was purified by flash chromatography, R_f = 0.34 (SiO_2, AcOEt), affording **3** (3.36 g, 77%) as a pale yellow solid which was crystallized from Et_2O: m.p. 63.8–63.5 °C. $[\alpha]_D^{20}$ = –29.3 (*c* = 1.1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3375 (NH), 2990–2934, 1752 (CO), 1710 (NCO), 1539, 1487, 1446. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.92 (m, 2 H, CH_2), 2.41 (t, 2 H, ^3J = 7.8 Hz, CH_2CO_2Me), 3.69 (s, 3 H, OMe), 3.96 (m, 1 H, $CHCH_2O$), 4.02 (t, 1 H, ^3J = 8.2 Hz, CH_2O), 4.51 (t, 1 H, ^3J = 7.8 Hz, CH_2O), 6.68 (br. s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.8, 30.3 (CH_2), 49.3 ($CHCH_2O$), 51.9 (OMe), 70.3 (CH_2O), 159.9 (NCO), 173.0 (CO). ESI-MS, *m*/*z* (%) = 196 (65) [M^+ + Na], 174 (100) [M^+ + H]. $C_7H_{11}NO_4$ (173.17): calcd. (%) C 48.55, H 6.40, N 8.09; found: C 48.51, H 6.23, N 8.08.

Methyl 3-[(4*S*)-3-((2*E*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-methyl-2-butenyl)-2-oxo-1,3-oxazolidin-4-yl]propanoate (5): To a solution of **3** (3.37 g, 19.5 mmol) in THF (50 mL) was added at 0 °C a solution of KO*t*Bu (2.62 g, 23.4 mmol) and 18-crown-6 (0.52 g, 1.9 mmol) in THF (20 mL). After stirring for 30 min at room temperature, a solution of freshly prepared crude isoprenoid **4d** (8.65 g, 31.0 mmol) in THF (30 mL) was added and the mixture was stirred for a further 3 h. The reaction was quenched with sat. aqueous NH_4Cl (80 mL) and the mixture extracted with AcOEt (3 × 80 mL).

The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to dryness. The crude product was purified by flash chromatography, R_f = 0.57 (SiO_2, AcOEt/petroleum ether, 70:30) affording **5** (6.67 g, 92%) as a colorless oil. $[\alpha]_D^{20}$ = –34.4 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2958–2864, 1764, 1731 (NCO and CO), 1444, 1419, 1370. ^1H NMR (600 MHz, $CDCl_3$): δ = 0.04 (s, 6 H, $Si(CH_3)_2$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 1.67 (s, 3 H, $CH{=}C(CH_3)$), 1.82 (m, 1 H, CH_2CO_2Me), 2.02 (m, 1 H, CH_2CO_2Me), 2.29 (m, 2 H, $CH_2CH_2CO_2Me$), 3.67 (s, 3 H, OMe), 3.71 (dd, 1 H, ^3J = 7.9, 15.0 Hz, CH_2N), 3.80 (m, 1 H, $CHCH_2O$), 3.93 (t, 1 H, ^3J = 8.7 Hz, CH_2O), 4.0 (s, 2 H, CH_2OSi), 4.11 (dd, 1 H, ^3J = 6.7, 15.1 Hz, CH_2N), 4.33 (t, 1 H, ^3J = 8.5 Hz, CH_2O), 5.42 (t, 1 H, ^3J = 6.7 Hz, $CH{=}C(CH_3)$). ^{13}C NMR (150 MHz, $CDCl_3$): δ = –5.3 ($Si(CH_3)_2$), 13.4 ($CH{=}C(CH_3)$), 18.2 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 26.7 ($CH_2CH_2CO_2Me$), 28.4 ($CH_2CH_2CO_2Me$), 39.3 (CH_2N), 51.8 (OMe), 53.6 ($CHCH_2O$), 66.5 (CH_2O), 67.4 (CH_2OSi), 116.9 ($C(CH_3){=}CH$), 139.9 ($C(CH_3){=}CH$), 157.8 (NCO), 172.5 (CO). EI-MS, m/z (%) = 356 (36) [$M^+ - CH_3$], 314 (100) [$M^+ - C(CH_3)_3$], 230 (25), 141 (69), 89 (44), 73 (56). $C_{18}H_{33}NO_5Si$ (371.54): calcd. (%) C 58.19, H 8.95, N 3.77; found: C 58.32, H 8.68, N 3.51.

Methyl (2*E*)-3-[(4*S*)-3-((2*E*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-methyl-2-butenyl)-2-oxo-1,3-oxazolidin-4-yl]-2-propenoate (6): To a solution of oxazolidinone **5** (3.45 g, 9.28 mmol) in THF (40 mL) freshly distilled TMSCl (2.37 mL, 18.6 mmol), followed by KHMDS (0.5 M *in* toluene) (37.2 mL, 18.6 mmol), were added at –78 °C and the mixture was stirred for further 30 min. To a stirred solution of $Pd(OAc)_2$ (2.29 g, 10.2 mmol) in CH_3CN (30 mL) at room temperature under argon was added via cannula the foregoing solution of **5**. After 6 h at room temperature the reaction was quenched by addition of sat. aqueous NH_4Cl (60 mL), and the salts were removed by filtration through Celite. The filtrate was washed with brine (3 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography, R_f = 0.47 (SiO_2, AcOEt/petroleum ether, 1:1), affording **6** (2.85 g, 83%) as a colorless oil. $[\alpha]_D^{20}$ = +19.9 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2956–2856, 1760, 1735 (CO and CON), 1478, 1441, 1403, 1360. ^1H NMR (600 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, $Si(CH_3)_2$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 1.57 (s, 3 H, $CH{=}C(CH_3)$), 3.61 (dd, 1 H, ^3J = 8.0, 16.0 Hz, CH_2N) 3.76 (s, 3 H, OMe), 3.95–3.99 (m, 3 H, $CHCH_2O$ and CH_2OSi), 4.10 (dd, 1 H, ^3J = 5.8, 15.4 Hz, CH_2N), 4.32 (m, 1 H, $CHCH_2O$), 4.41 (t, 1 H, ^3J = 11.5 Hz, $CHCH_2O$), 5.39 (t, 1 H, ^3J = 6.9 Hz, $C(CH_3){=}CH$), 5.99 (d, 1 H, ^3J = 15.8 Hz, $CHCH{=}CH$), 6.75 (dd, 1 H, ^3J = 7.5, 15.3 Hz, $CHCH{=}CH$). ^{13}C NMR (150 MHz, $CDCl_3$): δ = –5.3 ($Si(CH_3)_2$), 13.7 ($CH{=}C(CH_3)$), 18.2 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 39.6 (CH_2N), 52.0 (OMe), 56.4 ($CHCH_2O$), 66.1 (CH_2O), 67.2 (CH_2OSi), 116.3 ($C(CH_3){=}CH$), 125 ($CHCH{=}CH$), 140.6 ($C(CH_3){=}CH$), 143.0 ($CHCH{=}CH$), 165.4 (NCO), 174.8 (CO). EI-MS, m/z (%) = 312 (100) [$M^+ - C(CH_3)_3$], 228 (15), 141 (56), 89 (29), 73 (56). $C_{18}H_{31}NO_5Si$ (369.53): calcd. (%) C 58.51, H 8.46, N 3.79; found: C 58.30, H 8.80, N 3.65.

(2*E*)-3-[(4*S*)-3-((2*E*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-methyl-2-butenyl)-2-oxo-1,3-oxazolidin-4-yl]-2-propenyl 2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carboxylate (8): To a solution of **6** (1.18 g, 3.19 mmol) in CH_2Cl_2 (20 mL) at –78 °C, $BF_3{\cdot}OEt_2$ (0.44 mL, 3.51 mmol) was added and stirred for 1 h. A 1 M solution of DIBAL-H in hexane (9.57 mL, 9.57 mmol) was added dropwise. The mixture was stirred at –78 °C for 2 h before carefully quenching the reaction with 5 M acetic acid in CH_2Cl_2 (10 mL). The reaction was allowed to warm up to room temperature and poured into a 10% aqueous solution of tartaric acid (30 mL) and stirred at room temperature for 1 h. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic phases were washed with $NaHCO_3$ (3 × 25 mL), brine (3 × 25 mL), dried ($MgSO_4$), and the solvents evaporated in vacuo. The crude **7** was used without further purification. To a suspension of NaH (60% suspension mineral oil, 0.14 g, 3.6 mmol) in THF (10 mL), a solution of crude **7** (0.76 g, 2.2 mmol) in THF (10 mL) was added dropwise at room temperature. The mixture was stirred for 1 h and treated dropwise with a solution of *Cby*Cl (0.85 g, 4.5 mmol) in THF (5 mL). After being refluxed for 12 h, the reaction mixture was worked up by addition of sat. aqueous NH_4Cl (15 mL) and water (15 mL). The aqueous phase was extracted with AcOEt (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography, R_f = 0.46 (SiO_2, AcOEt/petroleum ether, 70:30) affording **8** (1.20 g, 76% over two steps) as a colorless oil. $[\alpha]_D^{20}$ = –6.9 (c = 0.41, $CHCl_3$). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2963–2864, 1742 (NCO), 1680, 1436. ^1H NMR (600 MHz, $CDCl_3$): δ = 0.04 (s, 6 H, $Si(CH_3)_2$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 1.35, 1.40, 1.50 and 1.54 (4 × s, 12 H, $CH_{3\,Cby}$), 1.60 (s, 3 H, $CH{=}C(CH_3)$), 3.56 (dd, 1 H, ^3J = 8.6, 16.9 Hz, CH_2N), 3.72 (s, 2 H, $CH_{2\,Cby}$), 3.91 (t, 1 H, ^3J = 9.3 Hz, $CHCH_2O$), 3.99 (s, 2 H, CH_2OSi), 4.08 (dd, 1 H, ^3J = 8.4, 16.5 Hz, CH_2N), 4.21 (m, 1 H, $CHCH_2O$), 4.39 (t, 1 H, ^3J = 9.4 Hz, $CHCH_2O$), 4.61 (m, 2 H, CH_2OCby), 5.39 (t, 1 H, ^3J = 6.4 Hz, $C(CH_3){=}CH$), 5.58–5.63 (m, 1 H, $CHCH{=}CH$), 5.83–5.88 (m, 1 H, $^3J_{(CH=CH)}$ = 15.6 Hz, $CHCH{=}CH$). ^{13}C NMR (150 MHz, $CDCl_3$): δ = –5.3 ($Si(CH_3)_2$), 13.6 ($CH{=}C(CH_3)$), 18.4 ($SiC(CH_3)_3$), 24.1, 25.2, 25.3 ($CH_{3\,Cby}$), 25.9 ($SiC(CH_3)_3$), 26.5 ($CH_{3\,Cby}$), 39.2 (CH_2N), 57.2 ($CHCH_2O$), 63.5 (CH_2OCby), 67.0, 67.5 ($CHCH_2O$), 76.0, 76.3 ($CH_{2\,Cby}$), 116.8 ($C(CH_3){=}CH$), 129.9 ($CHCH{=}CH$), 139.7 ($CHCH{=}CH$), 139.9 ($C(CH_3){=}CH$), 157.7 (NCO). ESI-MS, m/z (%): 519 (100) [M^+ + Na], 497 (30) [M^+ + H]. Daughter peaks resulting from m/z 497: 365 (100) [M^+ – OTBS]; 324 (12); 230 (10). $C_{25}H_{44}N_2O_6Si$ (496.71): calcd. (%) C 60.45, H 8.93, N 5.64; found: C 60.11, H 9.03, N 5.97.

(2*E*)-3-{(4*S*)-3-[(2*E*)-4-Hydroxy-3-methyl-2-butenyl]-2-oxo-1,3-oxazolidin-4-yl}-2-propenyl 2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carboxylate (9): To a solution of **8** (1.32 g, 2.66 mmol) in Et_2O (20 mL) was added dropwise a 1 M solution of tetrabutylammonium fluoride in THF (5.32 mL, 5.32 mmol). The reaction mixture was stirred at room temperature for 2 h, and quenched with H_2O (10 mL). The aqueous phase was extracted with EtO_2 (3 × 20 mL) and the combined organic phases were washed with brine (3 × 15 mL) and dried ($MgSO_4$). The solvent was removed by evaporation (bath temperature < 30 °C) affording **9** (1.00 g, 98%) as an oil. $[\alpha]_D^{20}$ = +15.0 (c = 0.80, $CHCl_3$). IR (film): $\tilde{\nu}$ (cm^{-1}) = 3560–3225 (OH), 2988–2871, 1756 and 1694 (NCO), 1412. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.35, 1.40, 1.51 and 1.54 (4 × s, 12 H, $CH_{3\,Cby}$), 1.58 (s, 3 H, $CH{=}C(CH_3)$), 3.71–3.79 (m, 3 H, CH_2N and $CH_{2\,Cby}$), 3.91 (t, 1 H, ^3J = 9.1 Hz, $CHCH_2O$), 4.02–4.08 (m, 3 H, CH_2N and CH_2OH), 4.25 (m, 1 H, $CHCH_2O$), 4.42 (t, 1 H, ^3J = 9.3 Hz, $CHCH_2O$), 4.63 (br. m, 2 H, CH_2OCby), 5.41 (t, 1 H, ^3J = 6.5 Hz, $C(CH_3){=}CH$), 5.55–5.62 (m, 1 H, $CHCH{=}CH$), 5.83–5.90 (m, 1 H, $CHCH{=}CH$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 ($CH{=}C(CH_3)$), 23.9, 24.5, 25.6 and 26.0 ($CH_{3\,Cby}$), 26.9 ($C(CH_3)_{2\,Cby}$), 39.9 (CH_2N), 60.2 ($CHCH_2O$), 63.8 (CH_2OCby), 67.3, 67.5 (CH_2O), 67.9 (CH_2OH), 76.5, 76.7 ($CH_{2\,Cby}$), 118.4 ($C(CH_3){=}CH$), 130.1 ($CHCH{=}CH$), 132.1 ($CHCH{=}CH$), 140.4 ($C(CH_3){=}CH$), 158.2 (NCO). EI-MS, m/z (%): 382 (2) [M^+], 367 (52) [$M^+ - CH_3$], 156 (32) [Cby^+], 126 (99). $C_{19}H_{30}N_2O_6$ (382.45): calcd. (%) C 59.67, H 7.91, N 7.32; found: C 59.27, H 7.75, N 7.06.

(2*E*)-3-{(4*S*)-3-[(2*E*)-4-Chloro-3-methyl-2-butenyl]-2-oxo-1,3-oxazolidin-4-yl}-2-propenyl 2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carboxylate (10): To a solution of **9** (0.86 g, 2.2 mmol) in CH_2Cl_2 (20 mL), NEt_3 (0.49 mL, 3.52 mmol), followed by methanesulfonyl chloride

(0.22 mL, 2.9 mmol), were added at –40 °C. After being stirred for 1 h at –40 °C, the reaction mixture was transferred via cannula to a suspension of anhydrous LiCl (0.37 g, 8.8 mmol) in THF (10 mL) at room temperature. The reaction mixture was stirred for 12 h. The resulting slurry was poured into pentane (20 mL) and washed several times with H_2O (5×15 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography, R_f = 0.43 (SiO_2, AcOEt/petroleum ether, 1:1) affording **10** (0.41 g, 47%) as a yellow oil. $[\alpha]_D^{20}$ = +9.2 (c = 1.2, $CHCl_3$). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2988–2871, 1763 and 1701 (NCO), 1446, 1412, 1371. ^1H NMR (600 MHz, $CDCl_3$): δ = 1.34, 1.39, 1.49, and 1.52 (4×s, 12 H, $CH_{3\,Cby}$), 1.75 (s, 3 H, CH=C(CH_3)), 3.58–3.64 (m, 1 H, CH_2N), 3.71 (s, 2 H, CH_{2Cby}), 3.87–3.90 (m, 1 H, CHCH_2O), 3.95–4.01 (m, 3 H, CH_2N and CH_2Cl), 4.18–4.21 (m, 1 H, CHCH$_2$O), 4.39 (t, 1 H, ^3J = 7.2 Hz, CHCH_2O), 4.60 (m, 2 H, CH_2OCby), 5.47–5.60 (m, 2 H, C(CH_3)=CH and CHCH=CH), 5.84–5.91 (m, 1 H, CHCH=CH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.5 (CH=C(CH_3)), 24.0, 25.2, 25.3 and 26.5 (4×CH_{3Cby}), 30.9 ($C(CH_3)_{2Cby}$), 39.6, 39.8 (CH_2N), 50.9 (CH_2Cl), 57.6 ($CHCH_2O$), 63.4 (CH_2OCby), 67.1 (CH_2O), 75.9, 76.2 (CH_{2Cby}), 123.5, 123.9 (C(CH_3)=CH), 129.3 ($CHCH$=CH), 132.2 (CHCH=CH), 136.7 ($C(CH_3)$=CH), 157.6 (NCO). EI-MS, m/z (%) = 385 (69) [M^+ – H – CH_3], 365 (100) [M^+ – HCl], 228 (15), 191 (16), 67 (81). $C_{19}H_{29}ClN_2O_5$ (400.90).

Methyl (2*R*)-2-(Benzylamino)-3-{[*tert*-butyl(diphenyl)silyl]oxy}propanoate (12): To a solution of *N*-benzoyl-D-serine methyl ester (**11**)[15] (8.47 g, 40.5 mmol) in CH_2Cl_2 (100 mL) at room temperature was added NEt_3 (6.83 mL, 48.6 mmol), followed by *tert*-butyldiphenylsilyl chloride (13.4 g, 48.6 mmol) and DMAP (0.25 g, 2.0 mmol). The reaction mixture was stirred at room temperature for 12 hours and then diluted with H_2O (50 mL). The mixture was then poured into a separating funnel containing CH_2Cl_2 (100 mL). The separated organic phase was washed with brine (3×75 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography, R_f = 0.55 (SiO_2, AcOEt/petroleum ether, 90:10) affording **12** (15.9 g, 88%) as a white solid: m.p. (recrystallized from CH_2Cl_2): 61.6–62.3 °C. $[\alpha]_D^{20}$ = +4.2 (c = 0.84, $CHCl_3$). *rac*-**12** (2.85 g, 95%) was obtained by the same procedure from *rac*-**11** (1.30 g, 6.70 mmol). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3346 (NH), 2961–2864, 1742 (CO), 1474, 1426. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.05 (s, 9 H, SiC(CH_3)$_3$), 3.41 (t, 1 H, ^3J = 3.7 Hz, CHCO$_2$Me), 3.71 (s, 3 H, OMe), 3.87–3.95 (m, 4 H, CH_2N and CH_2OSi), 7.29–7.43 (m, 11 H, ArH), 7.65–7.68 (m, 3 H, ArH), 7.71 (d, 1 H, ^3J = 8.1 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7 (SiC(CH_3)$_3$), 27.1 (SiC(CH_3)$_3$), 52.1 (OMe), 52.3 (NCH_2Ar), 62.6 ($CHCO_2Me$), 65.7 (CH_2OSi), 127.4, 128.1, 128.6, 128.8, 130.2, 130.1, 133.6, 135.2, 135.7, 136.0 and 140.3 (Ar), 174.2 (CO). EI-MS, m/z (%) = 447 (2) [M^+], 390 (60) [M^+ – C(CH_3)$_3$], 310 (13), 178 (22), 91 (100). $C_{27}H_{33}NO_3Si$ (447.64): calcd. (%) C 72.44, H 7.43, N 3.13; found: C 72.72, H 7.49, N 3.13.

(2*S*)-2-(Benzylamino)-3-{[*tert*-butyl(diphenyl)silyl}oxy}-1-propanol (13): To a 2 M solution of $LiBH_4$ (4.17 mL, 8.34 mmol) in THF (15 mL), a solution of *N*-benzyl-*O*-TBS-D-serine methyl ester (**12**) (6.72 g, 15.0 mmol) in THF/toluene (4:1) (50 mL) was slowly added. Toluene (12.5 mL) was added to avoid caking of the residue and to serve as a heat-transfer medium. The reaction mixture was heated at 100 °C for 20 min and then treated with sat. aqueous NH_4Cl (30 mL). The aqueous phase was extracted with AcOEt (3×50 mL), the combined organic phases were dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography, R_f = 0.36 (SiO_2, AcOEt/petroleum ether, 80:20) affording **13** (3.52 g, 56%) as a colourless oil. $[\alpha]_D^{20}$ = –1.6 (c = 1.9, $CHCl_3$). *rac*-**13** (970 mg, 42%) was obtained by the same procedure from *rac*-**12** (2.50 g, 5.60 mmol). IR (film): $\tilde{\nu}$ (cm^{-1}) = 3518–3263 (OH + NH), 2933–2864, 1475, 1410. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 9 H, SiC(CH_3)$_3$), 2.62 (br. s, 2 H, NH + OH), 3.10 (m, 1 H, CHCH$_2$OH), 3.75 (dd, 1 H, ^3J = 3.7, 10.4 Hz, CH_2OSi), 3.92 (dd, 1 H, ^3J = 3.8, 11.0 Hz, CH_2OSi), 4.01–4.07 (m, 4 H, CH_2OH and NCH_2Ar), 7.52–7.70 (m, 11 H, ArH), 7.91 (d, 4 H, ^3J = 8.1 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7 (SiC(CH_3)$_3$), 27.4 (SiC(CH_3)$_3$), 51.6 (NCH_2), 60.4 ($CHCH_2O$), 61.9 and 64.1 (CH_2OH, CH_2OSi), 127.5, 128.1, 128.2, 128.5, 128.6, 128.9, 129.4, 130.3, 133.6, 136.0 and 140.7 (Ar). EI-MS, m/z (%) = 418 (2) [M^+ – H], 404 (56) [M^+ – Me], 388 (46), 91 (100) [$PhCH_2^+$]. $C_{26}H_{33}NO_2Si$ (419.63): calcd. (%) C, 74.42, H 7.93, N 3.34; found: C 74.10, H 7.72, N 3.21.

(2*S*)-2-[Benzyl-((2*E*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-methyl-2-butenyl)amino]-3-{[*tert*-butyl(diphenyl)silyl]oxy}-1-propanol (14): To a suspension of $NaHCO_3$ (2.14 g, 25.4 mmol) in CH_3CN (30 mL) at room temperature was added over 5 min a solution of **13** (4.27 g, 10.2 mmol) in CH_3CN (30 mL). The reaction mixture was stirred for additional 30 min at room temperature. Freshly prepared isoprenoid **4d** (8.49 g, 30.4 mmol) in CH_3CN (50 mL) was added and the mixture was refluxed for 5 h. The reaction mixture was quenched with sat. aqueous NH_4Cl (50 mL) and the aqueous phase extracted with AcOEt (3×100 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography, R_f = 0.48 (SiO_2, AcOEt/petroleum ether, 5:95) affording **14** (5.10 g, 81%) as a colourless oil. $[\alpha]_D^{20}$ = –11.8 (c = 0.52, $CHCl_3$). *rac*-**14** (1.11 g, 84%) was obtained by the same procedure from *rac*-**13** (900 mg, 2.15 mmol). IR (film): $\tilde{\nu}$ (cm^{-1}) = 3538–3339 (OH), 2960–2857, 1481, 1432, 1310. ^1H NMR (600 MHz, $CDCl_3$): δ = 0.04 (s, 6 H, Si(CH_3)$_2$), 0.90 (s, 9 H, SiC(CH_3)$_3$), 1.06 (s, 9 H, SiC(CH_3)$_3$), 1.53 (s, 3 H, CH=C(CH_3)), 3.09 (m, 1 H, CHCH$_2$OH), 3.19–3.28 (m, 2 H, NCH_2), 3.45 (t, 1 H, ^3J = 10.1 Hz, CH_2OH), 3.53–3.57 (m, 3 H, NCH_2Ar and CH_2OSiPh$_2$), 3.67 (dd, 1 H, ^3J = 11.5 Hz, CH_2OH), 3.83 (dd, 1 H, ^3J = 10.1 Hz, CH_2OSiPh$_2$), 3.98 (s, 2 H, CH_2OSi(CH_3)$_2$), 5.44 (t, 1 H, ^3J = 6.2 Hz, C(CH_3)=CH), 7.22–7.30 (m, 5 H, ArH), 7.39–7.46 (m, 6 H, ArH), 7.66 (d, 4 H, ^3J = 5.6 Hz, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = –5.3 (Si(CH_3)$_2$), 13.6 (CH=C(CH_3)), 19.1, 19.5 (SiC(CH_3)$_3$), 25.9, 26.8 (SiC(CH_3)$_3$), 46.8 (NCH_2), 54.2 (CH_2OSiPh_2), 59.3 (NCH_2Ar), 60.9 ($CHCH_2OH$), 61.3 (CH_2OH), 68.2 ($CH_2OSi(CH_3)_2$), 122.3 (C(CH_3)=CH), 127.0, 127.8, 128.3, 128.8, 129.8, 129.9, 133.0, 133.1, 135.5, 135.6 and 137.6, 139.7 ($C(CH_3)$=CH). EI-MS, m/z (%) = 617 (1) [M^+ – H], 586 (89), 560 (5) [M^+ – C(CH_3)$_3$], 348 (100). ESI-HRMS $C_{37}H_{55}NO_3Si_2$ (618.01): [M^+ + H] calcd. 618.3799; found: 618.3817.

Ethyl (2*E*,4*S*)-4-[Benzyl-((2*E*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-methyl-2-butenyl)amino]-5-{[*tert*-butyl(diphenyl)silyl]oxy}-2-pentenoate (15): A solution of dimethyl sulfoxide (0.54 mL, 7.6 mmol) in dichloromethane (6 mL) was added to a solution of oxalyl chloride (0.30 mL, 3.5 mmol) in dichloromethane (15 mL) at –78 °C, and the reaction mixture was stirred for 5 more min at the same temperature. A solution of the alcohol **14** (1.80 g, 2.91 mmol) in dichloromethane (3 mL) was added over 5 min and stirring was continued for another 20 min after which NEt_3 (2.05 mL, 14.6 mmol) was added and the solution brought to –15 °C over 2 h. A solution of (ethoxycarbonylmethylene)triphenylphosphorane (2.95 g, 8.47 mmol) in dichloromethane (16 mL) was added to the reaction mixture and the temperature was allowed to reach at 25 °C over 3 h. The reaction mixture was poured into brine (25 mL) and the solution was extracted with dichloromethane (3×30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash

chromatography, R_f = 0.45 (SiO_2, AcOEt/petroleum ether, 10:90) affording **15** (1.40 g, 70%) as a pale yellow oil. $[\alpha]_D^{20}$ = +9.7 (*c* = 0.37, $CHCl_3$). *rac*-**15** (865 mg, 78%) was obtained by the same procedure from *rac*-**14** (1.00 g, 1.62 mmol). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2976–2856, 1728 (CO), 1474, 1447, 1370. ^1H NMR (600 MHz, $CDCl_3$): δ = 0.04 (s, 6 H, $Si(CH_3)_2$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 1.03 (s, 9 H, $SiC(CH_3)_3$), 1.30 (t, 3 H, ^3J = 7.2 Hz, $CO_2CH_2CH_3$), 1.53 (s, 3 H, $CH=C(CH_3)$), 3.12 (m, 1 H, NCH_2), 3.22 (m, 1 H, NCH_2), 3.50 (m, 1 H, C*H*CH=CH), 3.59 (d, 1 H, ^3J = 10.1 Hz, NCH_2Ar) 3.76 (m, 2 H, CH_2NAr and CH_2OSiPh_2), 3.88 (m, 1 H, CH_2OSiPh_2), 3.98 (s, 2 H, $CH_2OSi(CH_3)_2$), 4.22 (q, 2 H, ^3J = 7.1 Hz, 14.1 Hz, $CO_2CH_2CH_3$) 5.47 (t, 1 H, ^3J = 7.5 Hz, $C(CH_3)=CH$), 6.01 (d, 1 H, ^3J = 15.1 Hz, CHCH=C*H*), 7.01 (dd, 1 H, ^3J = 15.2, 7.5 Hz, CHC*H*=CH), 7.21 (t, 1 H, ^3J = 7.1 Hz, ArH), 7.22–7.42 (m, 10 H, ArH), 7.63 (d, 4 H, ^3J = 6.4 Hz, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = –5.3 ($Si(CH_3)_2$), 13.7 ($CH=C(CH_3)$), 14.3 (CH_2CH_3), 19.1, 19.5 ($SiC(CH_3)_3$), 25.9, 26.8 ($SiC(CH_3)_3$), 47.6 (NCH_2), 54.8 (NCH_2Ar), 60.3 (CH_2CH_3), 61.5 (C*H*CH=CH), 63.9 (CH_2OSiPh_2), 68.3 ($CH_2OSi(CH_3)_2$), 122.6 ($C(CH_3)=CH$), 123.7 (CHCH=*C*H), 126.7, 127.7, 128.2, 128.4, 129.7, 133.3, 135.6 and 137.2 (Ar), 140.1 ($C(CH_3)$=CH), 146.5 (CH*C*H=CH), 166.4 (CO). EI-MS, *m*/*z* (%) = 685 (8) [M^+ – H], 628 (3) [M^+ – H – $C(CH_3)_3$], 416 (100), 199 (26), 73 (35). ESI-MS, *m*/*z* (%) = 709 (10) [M^+ + Na], 686 (100) [M^+ + H]. $C_{41}H_{59}NO_4Si_2$ (686.08): calcd. (%) C, 71.78, H 8.67, N 2.04; found: C 71.39, H 8.61, N 1.93.

Ethyl (2*E*,4*S*)-4-{Benzyl[(2*E*)-4-hydroxy-3-methyl-2-butenyl]amino}-5-{[*tert*-butyl(diphenyl)silyl]oxy}-2-pentenoate (16): Pyridinium *p*-toluenesulfonate (PPTS) (0.79 g, 3.0 mmol) was added with stirring at room temperature to a solution of **15** (1.30 g, 1.90 mmol) in absolute ethanol (20 mL). The reaction mixture was stirred for 48 h at 55 °C and the solvent was evaporated to dryness. The residue was purified by a short flash chromatography, R_f = 0.37 (SiO_2, AcOEt/petroleum ether, 20:80) affording **16** (1.08 g, 100%) as a colorless oil. $[\alpha]_D^{20}$ = +6.8 (*c* = 0.74, $CHCl_3$). *rac*-**16** (645 mg, 97%) was obtained by the same procedure from *rac*-**15** (800 mg, 1.16 mmol). IR (film): $\tilde{\nu}$ (cm^{-1}) = 3553–3298 (OH), 2961–2864, 1729 (CO), 1639, 1445, 1410, 1350. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.98 (s, 9 H, $SiC(CH_3)_3$), 1.21 (t, 3 H, ^3J = 7.0 Hz, $CO_2CH_2CH_3$), 1.48 (s, 3 H, $CH=C(CH_3)$), 3.11 (m, 2 H, NCH_2), 3.42 (m, 1 H, C*H*CH=CH), 3. 55 (d, 1 H, ^3J = 10.2 Hz, NCH_2Ar), 3.70–3.79 (m, 3 H, NCH_2Ar and CH_2OSiPh_2), 3.88 (m, 2 H, CH_2OH), 4.12 (q, 2 H, ^3J = 7.2 Hz, 14.0 Hz, $CO_2CH_2CH_3$) 5.38 (t, 1 H, ^3J = 7.3 Hz, $C(CH_3)=CH$), 5.91 (d, 1 H, ^3J = 15.0 Hz, CHCH=C*H*), 6.92 (dd, 1 H, ^3J = 15.0, 7.5 Hz, CHC*H*=CH), 7.19–7.40 (m, 11 H, ArH), 7.55 (d, 4 H, ^3J = 6.1 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.3 ($Si(CH_3)_2$), 13.5 ($CH=C(CH_3)$), 14.3 (CH_2CH_3), 19.6 ($SiC(CH_3)_3$), 27.2 ($SiC(CH_3)_3$), 48.4 (NCH_2), 55.8 (CH_2OH), 60.7 (CH_2CH_3), 62.7 (*C*HCH=CH), 64.5 (CH_2OSiPh_2), 68.9 (NCH_2Ar), 123.9 ($C(CH_3)=CH$), 124.6 (CHCH=*C*H), 127.2, 128.1, 128.6, 128.8, 129.2, 130.1, 133.7, 135.2, 136.0 and 137.5 (Ar), 140.6 ($C(CH_3)$=CH), 146.9 (CH*C*H=CH), 179.9 (CO). ESI-MS, *m*/*z* (%) = 572 (94) [M + H]. Daughter peaks resulting from *m*/*z* 572: 488 (10); 410 (30), 231 (42); 120 (40), 91 (100) [$PhCH_2^+$]. HRMS (TOF-CI) $C_{35}H_{45}NO_4Si$ (571.82): [M^+ + H] calcd. 572.3191; found: 572.3184.

Ethyl (2*E*,4*S*)-4-{Benzyl[(2*E*)-4-chloro-3-methyl-2-butenyl]amino}-5-{[*tert*-butyl(diphenyl)silyl]oxy}-2-pentenoate (17): Compound **16** (1.59 g, 2.78 mmol) was treated under the conditions described for **10** to produce **17** (1.36 g, 83%) as a colourless oil after flash chromatography, R_f = 0.47 (SiO_2, AcOEt/petroleum ether, 5:95). $[\alpha]_D^{20}$ = +5.2 (*c* = 0.64, $CHCl_3$, ≈26% *ee*). *rac*-**17** (365 mg, 71%) was obtained by the same procedure from *rac*-**16** (500 mg, 0.88 mmol). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2910–2833, 1707 (CO), 1442, 1407, 1368. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.09 (s, 9 H, $SiC(CH_3)_3$), 1.30 (t, 3 H, ^3J = 7.1 Hz, $CO_2CH_2CH_3$), 1.67 (s, 3 H, $CH=C(CH_3)$), 3.15–3.21 (m, 2 H, NCH_2), 3.48 (m, 1 H, C*H*CH=CH), 3. 61 (d, 1 H, ^3J = 10.1 Hz, CH_2Ar), 3.75–3.82 (m, 3 H, CH_2OSiPh_2 and CH_2Ar), 3.97 (s, 2 H, CH_2Cl), 4.21 (q, ^3J = 7.2 Hz, 2 H, 14.0 Hz, $CO_2CH_2CH_3$), 5.56 (t, 1 H, ^3J = 7.3 Hz, $C(CH_3)=CH$), 6.01 (d, 1 H, ^3J = 15.0 Hz, CHCH=C*H*), 7.00 (dd, 1 H, ^3J = 7.4, 15.1 Hz, CHC*H*=CH), 7.28–7.46 (m, 11 H, ArH), 7.61 (d, 4 H, ^3J = 6.1 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 ($CH=C(CH_3)$), 19.2 (CH_2CH_3), 22.4 ($SiC(CH_3)_3$), 26.9 ($SiC(CH_3)_3$), 44.6 (NCH_2), 51.8 (CH_2Cl), 60.4 (CH_2CH_3), 61.7 (*C*HCH=CH), 64.0 (CH_2OSiPh_2), 69.9 (NCH_2Ar), 116.2 ($C(CH_3)=CH$), 123.9 (CHCH=*C*H), 127.0, 127.8, 128.2, 128.3, 128.4, 128.9, 129.8, 133.2, 133.6, 135.6, 136.3 and 138.5 (Ar), 139.7 ($C(CH_3)$=CH), 145.8 (CH*C*H=CH), 179.6 (CO). ESI-MS, *m*/*z* (%) = 612 (50) [M^+ + Na], 590 (38) [M^+ + H]. HRMS (TOF-CI) $C_{35}H_{44}ClNO_3Si$ (589.28): [M^+ + H] calcd. 590.2852; found: 590.2844, [M^+ + Na] calcd. 612.2671; found 612.2659.

Ethyl (2*E*,4*S*)-4-{Benzyl[(2*E*)-4-chloro-3-methyl-2-butenyl]amino}-5-hydroxy-2-pentenoate (24): To a solution of **17** (50 mg, 0.08 mmol) in THF (10 mL) was added TBAF (0.17 mL, 0.17 mmol) at room temperature. After being stirred at the same temperature for 3 h, the reaction mixture was poured into ether (10 mL) and washed with H_2O several times (5 × 6 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The crude product **24** was used in next step without further purification. Crude product *rac*-**24** was obtained by the same procedure from *rac*-**17** (60 mg, 0.51 mmol). IR (film): $\tilde{\nu}$ (cm^{-1}) = 3526–3313 (OH), 2926–2852, 1717 (CO), 1647, 1447, 1365. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, 3 H, ^3J = 7.2 Hz, $CO_2CH_2CH_3$), 1.68 (s, 3 H, $CH=C(CH_3)$), 2.9 (br. s, 1 H, OH), 3.12–3.22 (m, 2 H, NCH_2), 3.35 (m, 1 H, C*H*CH=CH), 3.42–3.55 (m, 2 H, CH_2OH and NCH_2Ar), 3.58 (m, 1 H, CH_2OH), 3.82 (d, 1 H, ^3J = 10.6 Hz, NCH_2Ar), 3.90 (s, 2 H, CH_2Cl), 4.20 (q, 2 H, ^3J = 7.2 Hz, 14.0 Hz, $CO_2CH_2CH_3$), 5.60 (t, 1 H, ^3J = 7.3 Hz, $C(CH_3)=CH$), 5.98 (d, 1 H, ^3J = 15.0 Hz, CHCH=C*H*), 7.40 (dd, 1 H, ^3J = 6.8, 15.7 Hz, CHC*H*=CH), 7.48–7.67 (m, 5 H, ArH). HRMS (TOF-CI) $C_{19}H_{26}ClNO_3$ (351.87): [M^+ + H] calcd. 352.1674; found: 352.1667.

Ethyl (2*E*,4*S*)-4-{Benzyl[(2*E*)-4-chloro-3-methyl-2-butenyl]amino}-5-[(3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy]-2-pentenoate (25): To a solution of **24** (21 mg, 0.06 mmol) in CCl_4 (1 mL) were added three drops of pyridine followed by (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (14 μL, 0.07 mmol) at 0 °C. After being stirred at room temperature for 4 h, the reaction mixture was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography, R_f = 0.51 (1:1 Et_2O/petroleum ether) affording **25** and its epimer as a diastereomeric mixture, which could not be separated by flash chromatography (29 mg, 65% overall yield) as a pale colorless oil. *rac*-**25** (41 mg, 71%) was obtained by the same procedure from *rac*-**24** (33 mg, 0.94 mmol). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2917–2848, 1752 and 1721 (CO), 1656, 1456, 1374. ^1H NMR (600 MHz, $CDCl_3$): δ = 1.23 (t, 3 H, ^3J = 7.2 Hz, $CO_2CH_2CH_3$), 1.62 (s, 3 H, $CH=C(CH_3)$), 3.11–3.16 (m, 2 H, NCH_2), 3.42 (s, 3 H, OMe), 3.50 (d, 1 H, ^3J = 10.2 Hz, NCH_2Ar), 3.60–3.65 (m, 1 H, C*H*CH=CH), 3.70 (d, 1 H, ^3J = 10.2 Hz, NCH_2Ar), 3.96 (s, 2 H, CH_2Cl), 4.20 (q, 2 H, ^3J = 7.2 Hz, 14.0 Hz, $CO_2CH_2CH_3$), 4.30–4.37 (m, 1 H, $CHCH_2O$), 4.51–4.58 (m, 1 H, $CHCH_2O$), 5.48–5.55 (m, 1 H, $C(CH_3)=CH$), 5.86–5.91 (m, 1 H, CHCH=C*H*), 6.80–6.85 (m, 1 H, CHC*H*=CH), 7.20–7.50 (m, 10 H, ArH). HRMS $C_{29}H_{33}ClF_3NO_5$ (568.02): calcd. 568.2078; found: 568.2049.

In the ^{1}H NMR spectrum (600 MHz, $CDCl_3$) one of the CH_2O protons of **25** and its epimer could be detected separately at δ = 4.32 and 4.35 ppm (*dr* = 63:37 or 26% *ee*).

(2*E*,4*S*)-4-{Benzyl[(2*E*)-4-chloro-3-methyl-2-butenyl]amino}-5-{[*tert*-butyl(diphenyl)silyl]oxy}-2-penten-1-ol (18): To a solution of DIBAL-H (1 M *in* hexane) (8.29 mL, 8.29 mmol) in dichloromethane (40 mL) at –78 °C was added dropwise a solution of ester **17** (1.57 g, 2.76 mmol) in dichloromethane (25 mL) under an argon atmosphere. After being stirred at the same temperature for 3 h, a solution of AcOH (1 M *in* dichloromethane) (15 mL) was added and the reaction mixture was poured into a funnel containing a 10% solution of tartaric acid (30 mL), extracted with dichloromethane (3 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product **18** as a colourless oil was used in next step without further purification. $[\alpha]_D^{20}$ = +12.0 (*c* = 0.32, $CHCl_3$, ≈26% *ee*). IR (film): $\tilde{\nu}$ (cm^{-1}) = 3574–3254 (OH), 2963–2864, 1592, 1470, 1408. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (s, 9 H, $SiC(CH_3)_3$), 1.59 (s, 3 H, CH=C(CH_3)), 3.05–3.11 (m, 2 H, NCH_2), 3.29 (m, 1 H, C*H*CH=CH), 3.47 (d, 1 H, ^3J = 10.1 Hz, CH_2NAr), 3.65–3.82 (m, 3 H, CH_2OSiPh_2 and NCH_2Ar), 3.89 (s, 2 H, CH_2Cl), 4.08 (d, 2 H, ^3J = 4.9 Hz, CH_2OH), 5.48 (t, 1 H, ^3J = 7.3 Hz, C(CH_3)=C*H*), 5.61–5.69 (m, 2 H, CHC*H*=C*H*), 7.11–7.38 (m, 11 H, ArH), 7.55 (d, 4 H, ^3J = 6.2 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5 (CH=C(*C*H_3)), 18.2 (Si*C*$(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 47.1 (CH_2N), 51.0 (CH_2Cl), 54.0 (NCH_2Ar) 61.7 (*C*HCH=CH), 62.4 (CH_2OH), 64.1 (CH_2OSi), 125.7 (C(CH_3)=*C*H), 126.6 (CHCH=*C*H), 127.1, 127.5, 127.6, 128.7, 132.0, 132.3 and 132.6 (Ar), 132.7 (CH*C*H=CH), 134.6 (Ar), 139.4 (*C*(CH_3)=CH). EI-MS, *m*/*z* (%) = 529 (4) [$M^+ - H_2O$], 512 (7) [M^+ – HCl], 278 (100), 199 (15), 91 (100) [$PhCH_2^+$]. HRMS $C_{33}H_{42}ClNO_2Si$ (548.23): calcd. 548.274610; found: 548.272864.

Carbamoylation of Allylic Alcohol 18. General Procedures. Method A: To a suspension of sodium hydride (60% suspension in mineral oil) (0.13 g, 3.3 mmol) in THF (15 mL) was added over 10 min a solution of **18** (1.20 g, 2.19 mmol) in THF (25 mL). The reaction mixture was stirred at room temperature for 1 h, after which time a solution of *Cb*Cl (1.07 g, 6.57 mmol) in THF (15 mL) was added and the reaction mixture was heated to 70 °C for 12 h. The reaction mixture was allowed to chill to room temperature and treated with sat. aqueous NH_4Cl (30 mL) and H_2O (30 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo.

Method B: In Method B, *Cby*Cl (1.26 g, 6.57 mmol) was used instead of *Cb*Cl.

(2*E*,4*S*)-4-{Benzyl[(2*E*)-4-chloro-3-methyl-2-butenyl]amino}-5-{[*tert*-butyl(diphenyl)silyl]oxy}-2-pentenyl Diisopropylcarbamate (19): The crude product obtained by Method A was purified by flash chromatography, R_f = 0.36 (SiO_2, Et_2O/petroleum ether, 5:95) affording **19** (1.12 g, 60% overall yield) as a colourless oil. $[\alpha]_D^{20}$ = +4.2 (*c* = 0.45, $CHCl_3$, ≤ 26% *ee*). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2956–2865, 1658 (NCO), 1413, 1345. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (s, 9 H, $SiC(CH_3)_3$), 1.12 (s, 6 H, 2 × CH_{3Cb}), 1.13 (s, 6 H, 2 × CH_{3Cb}), 1.60 (s, 3 H, CH=C(CH_3)), 3.08 (m, 2 H, CH_2N), 3.29 (m, 1 H, C*H*CH=CH), 3.41 (d, 1 H, ^3J = 10.4 Hz, NCH_2Ar), 3.63–3.79 (m, 4 H, CH_2NAr, CH_2OSi and CH_{Cb}), 3.88 (m, 3 H, CH_2Cl and CH_{Cb}), 4.45 (br. s, 2 H, CH_2O*Cb*), 5.49 (t, 1 H, ^3J = 6.4 Hz, C(CH_3)=C*H*), 5.71 (br. s, 2 H, CHC*H*=C*H*), 7.10–7.23 (m, 11 H, ArH), 7.55 (m, 4 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.4 (CH=C(*C*H_3)), 18.2 (Si*C*$(CH_3)_3$), 19.9 (CH_{3Cb}), 25.8 ($SiC(CH_3)_3$), 28.7 (CH_{Cb}), 47.1 (CH_2N), 51.0 (CH_2Cl), 53.9 (NCH_2Ar), 61.5 (*C*HCH=CH), 63.9 (CH_2OSi), 64.1 (CH_2OCb), 125.7, 126.3, 127.1, 127.5, 128.1 (C(CH_3)=*C*H), 128.6 and 129.2 (CH*C*H=*C*H), 129.2, 129.6, 132.4, 132.6 and 134.6 (Ar), 139.3 (*C*(CH_3)=CH), 154.4 (NCO). EI-MS, *m*/*z* (%) = 674 (0.2) [M^+ – H], 639 (5) [M^+ – HCl], 405 (100), 320 (33), 91 (67). HRMS $C_{40}H_{55}ClN_2O_3Si$ (675.41): calcd. 675.374324; found: 675.373151.

(2*E*,4*S*)-4-{Benzyl[(2*E*)-4-chloro-3-methyl-2-butenyl]amino}-5-{[*tert*-butyl(diphenyl)silyl]oxy}-2-pentenyl 2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carboxylate (20): The crude product obtained by using Method B was purified by flash chromatography, R_f = 0.46 (SiO_2, Et_2O/petroleum ether, 5:95) affording **20** (1.32 g, 68% overall yield) as a colorless oil. $[\alpha]_D^{20}$ = +2.3 (*c* = 1.9, $CHCl_3$, ≤ 26% *ee*). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2922–2852, 1700 (NCO), 1456, 1404, 1343. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 9 H, $SiC(CH_3)_3$), 1.37, 1.57, 1.63 and 1.65 (4 × s, 12 H, CH_{3Cby}), 1.68 (s, 3 H, CH=C(CH_3)), 3.15 (m, 2 H, CH_2N), 3.34 (m, 1 H, C*H*CH=CH), 3.45–3.51 (m, 3 H, NCH_2Ar and CH_2OSi), 3.71–3.80 (m, 3 H, NCH_2Ar and CH_2OCby), 3.97 (s, 2 H, CH_2Cl), 4.60 (s, 2 H, CH_{2Cby}), 5.58 (t, 1 H, ^3J = 6.4 Hz, C(CH_3)=C*H*), 5.71 (br. m, 2 H, CHC*H*=C*H*), 7.10–7.23 (m, 11 H, ArH), 7.55 (m, 4 H, ArH). HRMS $C_{41}H_{55}ClN_2O_4Si$ (703.42): calcd. 703.3698; found: 703.3678.

Cyclization of Carbamates 19 and 20 with *n*BuLi/Diamine. General Procedures. Method A: The carbamate **19** or **20** (0.20 mmol) and (–)-sparteine (103 mg, 0.44 mmol) were dissolved in toluene (5 mL), cooled to –78 °C, and a 1.6 M solution of *n*BuLi in hexane (0.27 mL, 0.44 mmol) was added to the solution dropwise. The reaction mixture was stirred for 4 h at –45 °C. MeOH (1 mL) and sat. aqueous NH_4Cl (0.5 mL) were added, and the reaction mixture was allowed to warm to room temperature. The organic layer was separated and the aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), and concentrated in vacuo.

Method B: In Method B, THF was used instead of toluene. (–)-Sparteine was replaced by TMEDA (51 mg, 0.44 mmol) and the reaction mixture was stirred for 3 h.

(*Z*)-2-[(2*S*,3*R*,4*S*)- and (2*S*,3*S*,4*R*)-1-Benzyl-2-({[*tert*-butyl(diphenyl)-silyl]oxy}methyl)-4-isopropenylpyrrolidinyl]ethenyl Diisopropylcarbamate (21a and 21b): The crude product **21**, obtained from carbamate **19** (135 mg, 0.20 mmol) by Method A, was purified by flash chromatography, R_f = 0.33 (SiO_2, Et_2O/petroleum ether, 5:95) affording **21** (61 mg, 48%, *dr* = 95:5 by ^{1}H NMR) as a colorless oil.

21a: $[\alpha]_D^{20}$ = –7.1 (*c* = 0.52, $CHCl_3$, *ee* unknown). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2916–2850, 1686 (NCO), 1420, 1365. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.03 (s, 9 H, $SiC(CH_3)_3$), 1.12 (s, 6 H, 2 × CH_{3Cb}), 1.13 (s, 6 H, 2 × CH_{3Cb}), 1.64 (s, 3 H, CH=C(CH_3)), 2.49 (dd, 1 H, ^3J = 6.0, 10.8 Hz, CH_2N), 2.65 (m, 1 H, C*H*CH_2OSi), 2.89 (m, 1 H, C*H*C(CH_3)=CH_2), 2.97 (dd, 1 H, ^3J = 10.8, 6.0 Hz, CH_2N), 3.26 (m, 1 H, C*H*CH=CH), 3.41 (d, 1 H, ^3J = 11.3 Hz, NCH_2Ar), 3.76 (br. s, 2 H, CH_2OSi), 3.98–4.11 (br. m, 2 H, CH_{Cb}), 4.21 (d, 1 H, ^3J = 11.3 Hz, NCH_2Ar), 4.54 (s, 1 H, C(CH_3)=CH_2), 4.58 (dd, 1 H, ^3J = 11.6, 8.2 Hz, C*H*=CHO*Cb*), 4.73 (s, 1 H, C(CH_3)=CH_2), 7.00 (d, 1 H, ^3J = 6.4 Hz, CH=C*H*O*Cb*), 7.23–7.40 (m, 11 H, ArH), 7.70 (m, 4 H, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 19.4 (Si*C*$(CH_3)_3$), 20.6, 23.2 (CH_{3Cb}), 23.2 (CH=C(*C*H_3)), 26.8 ($SiC(CH_3)_3$), 27.1 (CH_{Cb}), 39.8 (*C*HCH=CHO*Cb*), 47.6 (*C*HC(CH_3)=CH_2), 56.1 (CH_2N), 60.6 (NCH_2Ar), 67.6 (*C*H_2OSi), 72.8 (*C*HCH_2OSi), 110.4 (C(CH_3)=*C*H_2), 111.0 (*C*H=CHO*Cb*), 126.9, 127.8, 127.9, 128.0, 128.4, 128.9, 129.0, 129.8, 129.9, 133.8, 134.0, 134.6 and 135.0 (Ar), 135.9 (CH=*C*HO*Cb*), 140. 0 (Ar), 144.1 (*C*(CH_3)=CH_2), 153.8 (NCO). EI-MS, *m*/*z* (%) = 638 (0.6) [M^+], 581 (2) [M^+ – C$(CH_3)_3$], 369 (100) [M^+ – OTPS], 128 (12),

86 (43). ESI-HRMS $C_{40}H_{54}N_2O_3Si$ (638.95): [M^+ + H] calcd. 639.3982; found: 639.3972.

The crude **21** obtained from carbamate **19** (140 mg, 0.21 mmol) by Method B was purified by flash chromatography, affording a separable mixture of diastereomers **21a** and **21b** (118 mg, 88%, *dr* = 60:40) as a colourless oil. R_f = 0.33 and 0.18 (SiO_2, Et_2O/petroleum ether, 5:95).

21b: $[\alpha]_D^{20}$ = –3.2 (*c* = 0.91, $CHCl_3$, *ee* unknown), **21a**: $[\alpha]_D^{20}$ = –4.8 (*c* = 0.42, $CHCl_3$, *ee* unknown). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.03 (s, 9 H, $SiC(CH_3)_3$), 1.12 (s, 6 H, 2×CH_{3Cb}), 1.13 (s, 6 H, 2×CH_{3Cb}), 1.63 (s, 3 H, CH=C(C*H*$_3$)), 2.56 (m, 1 H, CH_2N), 2.82 (m, 1 H, C*H*C(CH_3)=CH_2), 3.18–3.23 (m, 2 H, C*H*CH_2OSi and C*H*$_2$N), 3.45–3.52 (m, 2 H, NC*H*$_2$Ar and C*H*CH=CH), 3.71–3.79 (m, 2 H, C*H*$_2$OSi), 3.9–3.97 (br. m, 2 H, CH_{Cb}), 4.21 (d, 1 H, ^3J = 11.1 Hz, NC*H*$_2$Ar), 4.54 (s, 1 H, C(CH_3)=C*H*$_2$), 4.65 (dd, 1 H, ^3J = 6.8, 11.6 Hz, C*H*=CHO*Cb*), 4.73 (s, 1 H, C(CH_3)=C*H*$_2$), 7.05 (d, 1 H, ^3J = 6.3 Hz, CH=C*H*O*Cb*), 7.23–7.40 (m, 11 H, ArH), 7.68 (m, 4 H, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 19.1 (Si*C*(CH_3)$_3$), 20.4, 21.8 (CH_{3Cb}), 22.8 (CH=C(*C*H$_3$)), 26.5 (CH_{Cb}), 26.8 ($SiC(CH_3)_3$), 41.0 (*C*HCH=CH), 47.2 (*C*HC(CH_3)=CH_2), 54.5 (CH_2N), 60.1 (NCH_2Ar), 65.9 (CH_2OSi), 69.7 (*C*HCH_2OSi), 106.7 (*C*H=CHO*Cb*), 110.4 (C(CH_3)=*C*H$_2$), 126.5, 127.5, 127.6, 127.7, 128.1, 128.3, 129.4, 129.5, 129.6, 133.6, 135.6, 135.7 and 135.8 (Ar), 136.3 (CH=*C*HO*Cb*), 140.6 (Ar), 143.7 (*C*(CH_3)=CH_2), 157.0 (NCO).

(*Z*)-2-[(2S,3*R*,4*S*)- and (2*S*,3*S*,4*R*)-1-Benzyl-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-isopropenylpyrrolidinyl]ethenyl 2,2,4,4-Tetramethyl-1,3-oxazolidine-3-carboxylate (22a and 22b): The crude product **22** obtained from carbamate **20** (141 mg, 0.20 mmol) by Method A was purified by flash chromatography, affording **22a** (72 mg, 54%, *dr* = 95:5) as a colorless oil. R_f = 0.43 (SiO_2, AcOEt/petroleum ether, 5:95). $[\alpha]_D^{20}$ = –5.4 (*c* = 0.73, $CHCl_3$, *ee* unknown). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2965–2856, 1695 (NCO), 1457, 1400, 1387. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.12 (s, 9 H, $SiC(CH_3)_3$), 1.40, 1,43, 1.55 and 1.58 (4×s, 12 H, CH_{3Cby}), 1.62 (s, 3 H, CH=C(C*H*$_3$)), 2.44 (m, 1 H, CH_2N), 2.65 (m, 1 H, C*H*CH_2OSi), 2.78 (m, 2 H, C*H*C(CH_3)=CH_2 and C*H*$_2$N), 2.96 (m, 1 H, C*H*CH=CH), 3.42 (d, 1 H, ^3J = 11.0 Hz, NCH_2Ar), 3.63 (m, 2 H, CH_2OSi), 3.77 (s, 2 H, CH_{2Cby}), 4.03 (d, 1 H, ^3J = 11.1 Hz, NCH_2Ar), 4.52 (s, 1 H, C(CH_3)=C*H*$_2$), 4.71 (s, 1 H, C(CH_3)=C*H*$_2$), 5.18 (m, 1 H, C*H*=CHO*Cby*), 7.00 (d, 1 H, ^3J = 6.2 Hz, CH=C*H*O*Cby*), 7.21–7.40 (m, 11 H, ArH), 7.70 (m, 4 H, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 19.2 (CH=C(*C*H$_3$)), 23.1 (Si*C*(CH_3)$_3$), 23.9, 25.1, 25.2 and 25.5 (CH_{3Cby}), 26.9 ($SiC(CH_3)_3$), 42.1 (CH_2N), 47.1 (*C*HC(CH_3)=CH_2), 55.4 (*C*HCH=CH), 60.1 (NCH_2Ar), 66.3 (CH_2OSi), 72.1 (*C*HCH_2OSi), 73.3 (CH_{2OCby}), 110.3 (C(CH_3)=*C*H$_2$), 111.9 (*C*H=CHO*Cby*), 126.7, 127.7, 127.7, 128.1, 128.4, 128.5, 128.7, 129.5, 129.6, 133.7, 134.8 and 135.6 (Ar), 135.7 (CH=*C*HO*Cby*), 135.7, and 139.7 (Ar), 143.5 (*C*(CH_3)=CH_2), 152.8 (NCO). ESI-HRMS $C_{41}H_{54}N_2O_4Si$ (666.96): [M^+ + H] calcd. 667.3931; found: 667.3954.

Methyl (2*R*)-2-(Benzylamino)-3-{[*tert*-butyl(dimethyl)silyl]-oxy}-propanoate (26): *N*-Benzyl-D-serine methyl ester (**11**) (6.00 g, 28.7 mmol) was treated under the same conditions as described for **12**, but using TBSCl (5.18 g, 34.4 mmol) instead of TPSCl, to produce **26** (8.36 g, 90%) as a colourless oil after flash chromatography, R_f = 0.42 (SiO_2, AcOEt/petroleum ether, 1:1). $[\alpha]_D^{20}$ = +3.9 (*c* = 0.94, $CHCl_3$). *rac*-**26** (848 mg, 91%) was obtained by the same procedure from *rac*-**11** (602 mg, 2.88 mmol). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2910–2840, 1721 (CO), 1442, 1231. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 6 H, $Si(CH_3)_2$), 0.81 (s, 9 H, $Si(CH_3)_3$), 2.10 (br. s, 1 H, NH) 3.38 (m, 1 H, C*H*CO_2Me), 3.69 (s, 3 H, OMe), 4.78–4.90 (m, 4 H, NCH_2Ar and CH_2OSi), 7.21–7.32 (m, 5 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.1 ($Si(CH_3)_2$), 18.6 (Si*C*(CH_3)$_3$), 26.1 ($SiC(CH_3)_3$), 52.0 (OMe), 52.3 (NCH_2Ar), 62.7 (*C*HCO_2Me), 65.0 (CH_2OSi), 127.4, 128.6, 128.7 and 140.3 (Ar), 174.2 (CO). EI-MS, *m*/*z* (%) = 308 (2) [M^+ – CH_3], 264 (36) [M^+ – CO_2CH_3], 234 (12), 178 (36), 106 (34), 91 (100) [$PhCH_2^+$]. $C_{17}H_{29}NO_3Si$ (323.50): calcd. (%) C, 63.12, H 9.04, N 4.33; found: C 62.90, H 9.26, N 4.20.

(2*S*)-2-Benzylamino-3-{[*tert*-butyl(dimethyl)silyl]oxy}-1-propanol (27): Compound **26** (10.6 g, 32.8 mmol) was treated under the conditions described for **13** to produce **27** (4.55 g, 47%) as an oil after flash chromatography, R_f = 0.23 (SiO_2, AcOEt). $[\alpha]_D^{20}$ = –8.2 (*c* = 1.1, $CHCl_3$). *rac*-**27** (346 mg, 48%) was obtained by the same procedure from *rac*-**26** (790 mg, 2.44 mmol). IR (film): $\tilde{\nu}$ (cm^{-1}) = 3245–3503 (OH), 2790–2986, 1448, 1231. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.02 (s, 6 H, $Si(CH_3)_2$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 2.20 (br. s, 1 H, NH), 3.75 (m, 1 H, C*H*CH_2OH), 3.41 (dd, 1 H, ^3J = 4.7, 10.8 Hz, CH_2OSi), 3.55 (m, 3 H, C*H*$_2$OH and C*H*$_2$OSi), 3.69 (s, 2 H, NCH_2Ar), 7.20–7.30 (m, 5 H, ArH). ^{13}C NMR ($CDCl_3$): δ = –5.2 ($Si(CH_3)_2$), 18.1 (Si*C*(CH_3)$_3$), 25.8 ($SiC(CH_3)_3$), 51.1 (NCH_2), 59.1 (*C*HCH_2O), 61.4, 63.0 (CH_2OH and CH_2OSi), 126.9, 127.9, 128.4 and 140.2 (Ar). ESI-MS, *m*/*z* (%) = 318 (10) [M^+ + Na], 296 (100) [M^+ + H]. $C_{16}H_{29}NO_2Si$ (295.49): calcd. (%) C, 65.03, H 9.89, N 4.74; found: C 64.75, H 9.85, N 4.55.

Ethyl (2*E*)-3-Methyl-4-[(triethylsilyl)oxy]-2-butenoate(28b): α-Hydroxyacetone (2.95 g, 39.8 mmol) was treated under the conditions described for **4b** to produce **28b** (8.74 g, 85% over two steps, *E*/*Z* 85:15) as a colorless oil after flash chromatography, R_f = 0.53 (SiO_2, Et_2O/petroleum ether, 2:8). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2910–2861, 2343, 1693 (CO), 1630, 1309. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.61 (q, 6 H, ^3J = 7.4 Hz, 13.8 Hz, Si(C*H*$_2$$CH_3$)$_3$), 0.98 (t, 9 H, ^3J = 7.6 Hz, Si(CH_2C*H*$_3$)$_3$), 1.30 (t, 3 H, ^3J = 7.2 Hz, $CO_2CH_2CH_3$), 2.19 (s, 3 H, C(C*H*$_3$)=CH), 4.11–4.20 (m, 4 H, $CO_2CH_2CH_3$ and C*H*$_2$OSi), 6.08 (s, 1 H, C(CH_3)=C*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 5.1 (Si(*C*$H_2$$CH_3$)$_3$), 7.0 (Si($CH_2$C*H*$_3$)$_3$), 14.6 (C(*C*H$_3$)=CH), 15.7 ($CO_2CH_2CH_3$), 59.9 ($CO_2CH_2CH_3$), 67.1 ($CH_2OSi$), 113.8 (*C*H=C($CH_3$)), 157.3 (CH=*C*($CH_3$)), 167.4 (CO). EI-MS, *m*/*z* (%) = 258 (14) [M^+], 229 (100) [M^+ – CH_2CH_3], 201 (32), 131 (81), 103 (71), 75 (42). $C_{13}H_{26}O_3Si$ (258.43): calcd. (%) C, 60.42, H 10.14; found: C 60.08, H 10.37.

(2*E*)-3-Methyl-4-[(triethylsilyl)oxy]-2-buten-1-ol (28c): Compound (*E*)-**28b** (6.07 g, 23.5 mmol) was treated under the conditions described for **4c** to produce **28c** (4.62 g, 91%, *E*/*Z* 100:0) as a colorless oil after flash chromatography, R_f = 0.48 (SiO_2, Et_2O/petroleum ether, 2:8). IR (film): $\tilde{\nu}$ (cm^{-1}) = 3434–3161 (OH), 2890–2855, 1428. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.49–0.68 (q, 6 H, ^3J = 6.9 Hz, 13.4 Hz, Si(C*H*$_2$$CH_3$)$_3$), 0.91–1.00 (t, 9 H, ^3J = 7.4 Hz, Si(CH_2-C*H*$_3$)$_3$), 2.67 (s, 3 H, C(C*H*$_3$)=CH), 3.38 (s, 2 H, CH_2OSi), 4.10 (d, 1 H, ^3J = 8.7 Hz, CH_2OH), 4.19 (d, 1 H, CH_2OH), 5.63 (m, 1 H, C(CH_3)=C*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.8 (Si(*C*$H_2$$CH_3$)$_3$), 6.2 (Si($CH_2$C*H*$_3$)$_3$), 14.0 (C(*C*H$_3$)=CH), 59.9 (*C*$H_2$OH), 67.8 (*C*$H_2$OSi), 124.4 (*C*H=C($CH_3$)), 138.2 (CH=*C*($CH_3$)). EI-MS, *m*/*z* (%) = 217 (100) [M^+], 189 (49), 161 (27), 105 (13). ESI-HRMS $C_{11}H_{24}O_2Si$ (216.39): [M^+ + Na] calcd. 239.143778; found: 239.142952.

{[(2*E*)-4-Bromo-2-methyl-2-butenyl]oxy}(triethyl)silane (28d): Compound (*E*)-**28c** (5.89 g, 27.2 mmol) was treated under the conditions described for **4d** to produce **28d** (6.81 g). The freshly prepared crude product **28d** was used in the *N*-allylation of **27** without further purification. IR (film): $\tilde{\nu}$ (cm^{-1}) = 2928–2865, 1675, 1339. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.61 (q, 6 H, Si(C*H*$_2$$CH_3$)$_3$), 0.98 (t,

9 H, ^3J = 7.3 Hz, Si(CH_2CH_3)$_3$), 1.70 (s, 3 H, C(CH_3)=CH), 4.13–4.29 (m, 4 H, CH_2OSi and CH_2OH), 5.63 (m, 1 H, C(CH_3)=C*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.1 (Si(*C*H_2CH$_3$)$_3$), 8.2 (Si(CH_2*C*H$_3$)$_3$), 14.8 (C(*C*H_3)=CH), 30.1 (*C*H_2Br), 68.7 (*C*H_2OSi), 121.2 (*C*H=C(CH_3)), 143.4 (CH=*C*(CH_3)). EI-MS, *m*/*z* (%) = 249 (25) [M$^+$ – CH_2CH_3]; 199 (55) [M$^+$ – Br], 165 (100), 115 (46). $C_{11}H_{23}$BrOSi (279.29).

(2*S*)-2-(Benzyl{(2*E*)-3-methyl-4-[(triethylsilyl)oxy]-2-butenyl}amino]-3-{[*tert*-butyl(dimethyl)silyl]oxy}-1-propanol (29): Compound **28** (6.02 g, 20.4 mmol) was treated under the same conditions described for **13**, but refluxing with freshly prepared isoprenoid **28d** instead of **4d** (6.81 g, 24.5 mmol) for 3 h, to produce **29** (8.25 g, 82%) as a colourless oil after flash chromatography, R_f = 0.42 (SiO_2, Et_2O/petroleum ether, 1:1). $[\alpha]_D^{20}$ = –3.6 (*c* = 0.91, $CHCl_3$). *rac*-**29** (431 mg, 86%) was obtained by the same procedure from *rac*-**28** (300 mg, 1.02 mmol). IR (film): $\tilde{\nu}$ (cm^{-1}) = 3553–3343 (OH), 2916–2890, 1441, 1238. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 6 H, Si(CH_3)$_2$), 0.55 (q, 6 H, ^3J = 7.1 Hz, 14.2 Hz, Si(CH_2CH$_3$)$_3$), 0.81 (s, 9 H, SiC(CH_3)$_3$), 0.90 (t, 9 H, ^3J = 7.3 Hz, Si(CH_2CH_3)$_3$), 1.49 (s, 3 H, CH=C(CH_3)), 2.92 (m, 1 H, C*H*CH$_2$OH), 3.18 (m, 2 H, NCH_2), 3.37 (dd, 1 H, ^3J = 3.7, 10.1 Hz, CH_2OH), 3.51 (m, 3 H, CH_2OSi and CH_2OH), 3.60 (d, 1 H, ^3J = 7.2 Hz, NCH_2Ar), 3.81 (d, 1 H, ^3J = 7.2 Hz, NCH_2Ar), 3.91 (s, 2 H, CH_2OSi(Et)$_3$), 5.41 (t, 1 H, ^3J = 6.1 Hz, C*H*=C(CH_3)), 7.11–7.20 (m, 5 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.2 (Si(CH_3)$_2$), 4.9 (Si(*C*H_2CH$_3$)$_3$), 7.15 (Si(CH_2*C*H$_3$)$_3$), 14.1 (CH=C(*C*H_3)), 18.5 (Si*C*(CH_3)$_3$), 26.4 (SiC(*C*H_3)$_3$), 47.4 (NCH_2), 54.6 (*C*H_2OSi), 59.8 (N*C*H_2Ar), 60.0 (*C*HCH$_2$OH), 61.2 (CH_2OH), 68.4 (*C*H_2OSi), 122.9 (C(CH_3)=*C*H), 127.3, 128.7, 129.2, 137.9 and 140.3 (CH=*C*(CH_3) and Ar). EI-MS, *m*/*z* (%) = 493 (0.5) [M$^+$]; 478 (2) [M$^+$ – CH_3]; 462 (66); 348 (100) [M$^+$ – OTES], 199 (47), 91 (70). HRMS (TOF-CI) $C_{27}H_{51}NO_3Si_2$ (493.87): [M$^+$ + H] calcd. 494.348024; found 494.346344. $C_{27}H_{51}NO_3Si_2$ (493.87): calcd. (%) C, 65.66, H 10.41, N 2.84; found: C 65.63, H 10.52, N 2.72.

Ethyl (2*E*,4*S*)-4-(Benzyl{(2*E*)-3-methyl-4-[(triethylsilyl)oxy]-2-butenyl}amino)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-2-pentenoate (30): Compound **29** (3.18 g, 6.44 mmol) was treated under the conditions described for **15** to produce **30** (2.71 g, 75%) as a pale yellow oil after flash chromatography, R_f = 0.58 (SiO_2, Et_2O/petroleum ether, 5:95). $[\alpha]_D^{20}$ = +8.2 (*c* = 1.6, $CHCl_3$). *rac*-**30** (295 mg, 68%) was obtained by the same procedure from *rac*-**29** (380 mg, 0.77 mmol). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2930–2833, 1693 (CO), 1441, 1246. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 6 H, Si(CH_3)$_2$), 0.55 (q, ^3J = 7.0 Hz, 6 H, 13.6 Hz, Si(CH_2CH$_3$)$_3$), 0.86 (s, 9 H, SiC(CH_3)$_3$), 0.92 (t, 9 H, ^3J = 7.1 Hz, Si(CH_2CH_3)$_3$), 1.26 (t, 3 H, ^3J = 7.2 Hz, $CO_2CH_2CH_3$), 1.52 (s, 3 H, CH=C(CH_3)), 3.11 (m, 1 H, NCH_2), 3.21 (m, 1 H, NCH_2), 3.40 (m, 1 H, C*H*CH=CH), 3.62 (d, 1 H, ^3J = 7.2 Hz, NCH_2Ar), 3.79–3.88 (m, 3 H, CH_2OSi(CH_3)$_2$ and NCH_2Ar), 4.11 (s, 2 H, CH_2OSi(Et)$_3$), 4.21 (q, 2 H, ^3J = 7.1 Hz, 14.1 Hz, $CO_2CH_2CH_3$) 5.55 (t, 1 H, ^3J = 7.5 Hz, C*H*=C(CH_3)), 6.05 (d, 1 H, ^3J = 15.1 Hz, CHCH=C*H*), 7.03 (dd, 1 H, ^3J = 6.0, 15.6 Hz, CHC*H*=CH), 7.21–7.35 (m, 5 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.1 (Si(CH_3)$_2$), 4.9 (Si(*C*H_2CH$_3$)$_3$, 7.2 (Si(CH_2*C*H$_3$)$_3$, 14.1 (CH=C(*C*H_3)), 14.6 ($CO_2CH_2CH_3$), 18.6 (Si*C*(CH_3)$_3$), 26.2 (SiC(*C*H_3)$_3$), 48.2 (NCH_2), 55.3 (N*C*H_2Ar), 60.6 ($CO_2CH_2CH_3$), 61.9 (*C*HCH=CH), 63.9 and 68.4 (*C*H_2OSi), 123.2 (*C*H=C(CH_3)), 123.9 (CHCH=*C*H), 127.1, 128.5, 128.8, 137.6 and 140.6 (Ar and CH=*C*(CH_3), 147.1 (CH*C*H=CH), 166.8 (CO). EI-MS, *m*/*z* (%) = 561 (3) [M$^+$]; 532 (4) [M$^+$ – CH_2CH_3]; 416 (100), 199 (27), 115 (40), 91 (35). $C_{31}H_{55}NO_4Si_2$ (561.94): calcd. (%) C, 66.26, H 9.87, N 2.49; found: C 65.90, H 10.04, N 2.35.

Ethyl (2*E*,4*S*)-4-{Benzyl[(2*E*)-4-hydroxy-3-methyl-2-butenyl]amino}-5-{[*tert*-butyl(dimethyl)silyl]oxy}-2-pentenoate (31): A 1 M solution of tetrabutylammonium fluoride (3.01 mL, 3.01 mmol) in THF (10 mL) was added with stirring at 0 °C to a solution of **30** (1.54 g, 2.74 mmol) in THF (10 mL). The reaction mixture was stirred an additional 5 min, diluted with H_2O (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and the solvents evaporated to dryness. The residue was purified by a flash chromatography, R_f = 0.35 (SiO_2, AcOEt/petroleum ether, 1:1) on a short column affording **31** (1.00 g, 81%) as a pale yellow oil oil. $[\alpha]_D^{20}$ = +14.7 (*c* = 0.61, $CHCl_3$). *rac*-**31** (182 mg, 85%) was obtained by the same procedure from *rac*-**30** (270 mg, 0.48 mmol). IR (film): $\tilde{\nu}$ (cm^{-1}) = 3526–3318 (OH), 2952–2851, 1721 (CO), 1650, 1470, 1369. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 6 H, Si(CH_3)$_2$), 0.86 (s, 9 H, SiC(CH_3)$_3$), 1.29 (t, 3 H, ^3J = 7.4 Hz, $CO_2CH_2CH_3$), 1.59 (s, 3 H, CH=C(CH_3)), 3.19 (m, 2 H, NCH_2), 3.40 (m, 1 H, C*H*CH=CH), 3.60 (d, 1 H, ^3J = 7.1 Hz, NCH_2Ar), 3.70–3.82 (m, 3 H, CH_2OSi and NCH_2Ar), 3.91 (s, 2 H, CH_2OH), 4.19 (q, 2 H, ^3J = 7.5 Hz, 14.8 Hz, $CO_2CH_2CH_3$), 5.45 (t, 1 H, ^3J = 7.3 Hz, C(CH_3)=C*H*), 5.98 (d, 1 H, ^3J = 14.9 Hz, CHCH=C*H*), 6.98 (dd, 1 H, ^3J = 6.2, 15.7 Hz, CHC*H*=CH), 7.19–7.31 (m, 5 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –3.7 (Si(CH_3)$_2$), 13.8 (CH=C(*C*H_3)), 14.2 ($CO_2CH_2CH_3$), 18.1 (Si*C*(CH_3)$_3$), 25.7 (SiC(*C*H_3)$_3$), 48.0 (NCH_2), 55.3 (N*C*H_2Ar), 60.2 ($CO_2CH_2CH_3$), 61.9 (*C*HCH=CH), 63.4 and 68.4 (*C*H_2OSi and *C*H_2O), 123.3 (*C*H=C(CH_3)), 124.2 (CHCH=*C*H), 126.7, 128.1, 128.3, 137.0 and 140.2 (CH=*C*(CH_3) and Ar), 146.6 (CH*C*H=CH), 166.4 (CO). ESI-MS, *m*/*z* (%) = 917 (10) [2 M$^+$ + Na], 448 (100) [M$^+$ + H]. ESI-HRMS $C_{25}H_{41}NO_4Si$ (447.68): [M$^+$ + H] calcd. 448.2883; found: 448.2913.

Ethyl (2*E*,4*S*)-4-{Benzyl[(2*E*)-4-chloro-3-methyl-2-butenyl]amino}-5-{[*tert*-butyl(dimethyl)silyl]oxy}-2-pentenoate (32): Compound **31** (3.77 g, 8.42 mmol) was treated under the conditions described for **17** to produce **32** (2.68 g, 71%) as a colourless oil after flash chromatography, R_f = 0.48 (SiO_2, Et_2O/petroleum ether, 5:95). $[\alpha]_D^{20}$ = +22.0 (*c* = 0.78, $CHCl_3$). *rac*-**32** (103 mg, 80%) was obtained by the same procedure from *rac*-**31** (130 mg, 0.29 mmol). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2956–2857, 1687 (CO), 1426, 1385. ^{1}H NMR (300 Mz, $CDCl_3$): δ = 0.03 (s, 6 H, Si(CH_3)$_2$), 0.84 (s, 9 H, SiC(CH_3)$_3$), 1.26 (t, 3 H, ^3J = 8.5 Hz, $CO_2CH_2CH_3$), 1.67 (s, 3 H, CH=C(CH_3)), 3.12 (dd, 1 H, ^3J = 6.8, 14.7 Hz, NCH_2), 3.24 (dd, 1 H, ^3J = 6.8, 14.4 Hz, NCH_2), 3.37 (m, 1 H, C*H*CH=CH), 3.59 (d, 1 H, ^3J = 14.0 Hz, NCH_2Ar), 3.69–3.83 (m, 3 H, CH_2OSi and NCH_2Ar), 3.94 (s, 2 H, CH_2Cl), 4.18 (q, 2 H, ^3J = 7.0 Hz, 15.0 Hz, $CO_2CH_2CH_3$), 5.61 (t, 1 H, ^3J = 6.0 Hz, C*H*=C(CH_3)), 5.97 (d, 1 H, ^3J = 16.3 Hz, CHCH=C*H*), 6.92 (dd, 1 H, ^3J = 16.7 Hz, 6.9 Hz, CHC*H*=CH), 7.18–7.32 (m, 5 H, ArH). ^{13}C NMR (75 Mz, $CDCl_3$): δ = –3.0 (Si(CH_3)$_2$), 16.7 (CH=C(*C*H_3)), 16.9 (CH_2CH_3), 20.6 (Si*C*(CH_3)$_3$), 28.2 (SiC(*C*H_3)$_3$), 50.6 (NCH_2), 54.2 (NCH_2Ar), 57.6 ($CO_2CH_2CH_3$), 62.7 (CH_2Cl), 64.2 (*C*HCH=CH), 65.9 (CH_2OSi), 126.1 (*C*H=C(CH_3)), 129.3 (CHCH=*C*H), 130.6, 130.8, 131.6 and 136.4 (Ar), 142.3 (CH=*C*(CH_3)), 148.7 (CH*C*H=CH), 168.7 (CO). HRMS $C_{25}H_{40}ClNO_3Si$ (446.13): calcd. 466.2544; found: 466.2551.

Ethyl (2*E*,4*S*)-4-{Benzyl[(2*E*)-4-chloro-3-methyl-2-butenyl]amino}-5-[(3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy]-2-pentenoate (36): Compound **32** (40 mg, 0.09 mmol) was treated under the conditions described for **25** to produce **36** (36 mg, 70%, *dr* = 100:0) as a pale colorless oil.

(2*E*,4*S*)-4-{Benzyl[(2*E*)-4-chloro-3-methyl-2-butenyl]amino}-5-{[*tert*-butyl(dimethyl)silyl]oxy}-2-penten-1-ol (33): Compound **32** (2.30 g, 5.16 mmol) was treated under the conditions described for **18** to produce **33** (1.53 g, 70%) as a colourless oil after flash chromatography, R_f = 0.27 (SiO_2, Et_2O/petroleum ether, 4:6). $[\alpha]_D^{20}$ = +7.2 (*c* = 0.76, $CHCl_3$). IR (film): $\tilde{\nu}$ (cm^{-1}) = 3491–3226

(OH), 2956–2856, 1461, 1426, 1365. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 6 H, $Si(CH_3)_2$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 1.66 (s, 3 H, $CH=C(CH_3)$), 3.05–3.26 (m, 3 H, NCH_2 and $CHCH=CH$), 3.53 (d, 1 H, ^3J = 13.4 Hz, NCH_2Ar), 3.64–3.78 (m, 3 H, CH_2OSi and NCH_2Ar), 3.94 (s, 2 H, CH_2Cl), 4.14 (m, 2 H, CH_2OH), 5.57 (t, 1 H, ^3J = 6.8 Hz, $CH=C(CH_3)$), 5.64–5.81 (m, 2 H, $CHCH=CH$), 7.15–7.33 (m, 5 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.6 ($Si(CH_3)_2$), 14.4 ($CH=C(CH_3)$), 18.1 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 48.1 (NCH_2), 51.4 (CH_2Cl), 54.9 (CH_2NAr), 62.3 ($CHCH=CH$), 63.4 (CH_2OH), 64.1 (CH_2OSi), 126.6 ($CH=C(CH_3)$), 126.9 ($CHCH=CH$), 128.0, 128.4, 128.7, 129.6 and 132.7 (Ar and $CH=C(CH_3)$), 133.3 ($CHCH=CH$). ESI-MS, *m*/*z* (%) = 446 (5) [M^+ + Na], 424 (100) [M^+ + H]. $C_{23}H_{38}ClNO_2Si$ (424.09): calcd. (%) C. 65.14, H. 9.03, N. 3.30; found C. 64.85, H. 9.34, N. 2.99.

(2*E*,4*S*)-4-{Benzyl[(2*E*)-4-chloro-3-methyl-2-butenyl]amino}-5-{[*tert*-butyl(dimethyl)silyl]oxy}-2-pentenyl Diisopropylcarbamate (34): Compound **33** (1.30 g, 3.07 mmol) was treated under the conditions described for **19** to produce **34** (0.89 g, 53%) as a colourless oil after flash chromatography, R_f = 0.44 (SiO_2, Et_2O/petroleum ether, 2:8). $[\alpha]_D^{20}$ = +9.7 (*c* = 0.71, $CHCl_3$). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2952–2852, 1721 (NCO), 1469, 1430, 1365. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6 H, $Si(CH_3)_2$), 0.90 (s, 9 H, $SiC(CH_3)_3$), 1.19 (s, 6 H, $2\times CH_{3Cb}$), 1.21 (s, 6 H, $2\times CH_{3Cb}$), 1.70 (s, 3 H, $CH=C(CH_3)$), 3.09–3.28 (m, 2 H, NCH_2), 3.29 (m, 1 H, $CHCH=CH$), 3.50 (d, 1 H, ^3J = 13.0 Hz, NCH_2Ar), 3.68–3.80 (m, 4 H, NCH_2Ar, CH_2OSi and CH_{Cb}), 3.97 (br. s, 3 H, CH_2Cl and CH_{Cb}), 4.60 (s, 2 H, CH_2OCb), 5.68 (t, 1 H, ^3J = 6.1 Hz, $CH=C(CH_3)$), 5.69–5.80 (m, 2 H, $CHCH=CH$), 7.26–7.48 (m, 5 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.2 ($Si(CH_3)_2$), 14.3 ($CH=C(CH_3)$), 18.1 ($SiC(CH_3)_3$), 21.0 (CH_{3Cb}), 25.8 ($SiC(CH_3)_3$), 28.7 (CH_{Cb}), 48.1 (NCH_2), 51.9 (CH_2Cl), 54.9 (NCH_2Ar), 62.3 ($CHCH=CH$), 64.6 (CH_2OSi), 64.8 (CH_2OCb), 126.6, 128.0, and 128.4 (Ar), and 128.9 ($CHCH=CH$), 129.6 ($CH=C(CH_3)$), 130.8 ($CHCH=CH$), 133.3 and 140.3 ($CH=C(CH_3)$ and Ar), 155.3 (NCO). ESI-MS, *m*/*z* (%) = 551 (100) [M^+]. $C_{30}H_{51}ClN_2O_3Si$ (551.28): calcd. (%) C, 65.36, H 9.32, N 5.08; found: C 65.38, H 9.35, N 4.89.

(1*Z*)-2-[(2*S*,3*R*,4*S*)- and (2*S*,3*S*,4*R*)-1-Benzyl-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4-isopropenylpyrrolidinyl]ethenyl Diisopropylcarbamate (37a and 37b): The chloride **34** (116 mg, 0.21 mmol) and (–)-sparteine (114 mg, 0.46 mmol) were dissolved in toluene (10 mL) and cooled to –78 °C. After slow addition of *n*BuLi (1.6 M *in* hexane) (0.30 mL, 0.46 mmol), the solution was stirred for 90 min at –78 °C. MeOH (1 mL) and NH_4Cl (0.5 mL) were added, and the reaction mixture was allowed to warm to room temperature. The organic layer was separated and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic phases were dried ($MgSO_4$), and concentrated in vacuo. The crude product was separated by flash chromatography, R_f = 0.48 and 0.33 (SiO_2, Et_2O/petroleum ether, 20:80) affording **37a** and **37b**, respectively (90 mg, 83%, *dr* 80:20) as a colourless oil.

37a: $[\alpha]_D^{20}$ = –22.6 (*c* = 0.57, $CHCl_3$). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2960–2852, 1713 (NCO), 1465, 1430, 1365. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.01 (s, 6 H, $Si(CH_3)_2$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 1.23–1.25 (m, 12 H, CH_{3Cb}), 1.62 (s, 3 H, $CH=C(CH_3)$), 2.46–2.50 (m, 1 H, CH_2N), 2.57 (m, 1 H, $CHCH_2OSi$), 2.81–2.85 (m, 1 H, $CHC(CH_3)=CH_2$), 2.95 (d, 1 H, ^3J = 8.7 Hz, CH_2N), 3.17–3.21 (m, 1 H, $CHCH=CH$), 3.46 (d, 1 H, ^3J = 13.2 Hz, NCH_2Ar), 3.61–3.63 (m, 2 H, CH_2OSi), 3.89 (br. s, 1 H, CH_{Cb}), 3.98 (br. s, 1 H, CH_{Cb}), 4.19 (d, 1 H, ^3J = 13.4 Hz, NCH_2Ar), 4.53 (br. s, 1 H, $C(CH_3)=CH_2$)), 4.60 (dd, 1 H, ^3J = 11.9 Hz, $CH=CHOCb$), 4.71 (br. s, 1 H, $C(CH_3)=CH_2$), 6.97 (d, 1 H, ^3J = 5.6 Hz, $CH=CHOCb$), 7.22–7.35 (m, 5 H, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = –5.4 ($Si(CH_3)_2$), 19.1 ($SiC(CH_3)_3$), 20.6, 21.3 (CH_{3Cb}), 22.9 ($CH=C(CH_3)$), 25.9 ($SiC(CH_3)_3$), 27.9 (CH_{Cb}), 39.4 ($CHCH=CH$), 47.0 ($CHC(CH_3)=CH_2$), 56.1 (NCH_2), 60.4 (NCH_2Ar), 66.6 (CH_2OSi), 72.4 ($CHCH_2OSi$), 110.1 ($C(CH_3)=CH_2$), 111.0 ($CH=CHOCb$), 126.7, 128.1 and 128.8 (Ar), 134.4 ($CH=CHOCb$), 139.8 (Ar), 143.9 ($C(CH_3)=CH_2$), 153.6 (NCO). ESI-MS, *m*/*z* (%) = 515 (100)[M^+ + H]. ESI-HRMS $C_{30}H_{50}N_2O_3Si$ (514.82): [M^+ + H] calcd. 515.3669 found: 515.3658.

37b: $[\alpha]_D^{20}$ = –6.4 (*c* = 0.75, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.00 (s, 6 H, $Si(CH_3)_2$), 0.83 (s, 9 H, $SiC(CH_3)_3$), 1.18–1.24 (m, 12 H, CH_{3Cb}), 1.632 (s, 3 H, $CH=C(CH_3)$), 2.52–2.56 (d, 1 H, ^3J = 11.0 Hz, CH_2N), 2.77 (dd, 1 H, ^3J = 8.7, 14.9 Hz, $CHC(CH_3)=CH_2$), 3.07 (m, 1 H, $CHCH_2OSi$), 3.18 (d, 1 H, ^3J = 11.0 Hz, CH_2N), 342–3.47 (m, 2 H, $CHCH=CH$ and NCH_2Ar), 3.61–3.68 (m, 2 H, CH_2OSi), 3.89–4.07 (br. s, 2 H, CH_{Cb}), 4.22 (d, 1 H, ^3J = 14.2 Hz, NCH_2Ar), 4.52 (br. s, 1 H, $C(CH_3)=CH_2$), 4.66 (dd, 1 H, ^3J = 11.3 Hz, $CH=CHOCb$), 4.72 (br. s, 1 H, $C(CH_3)=CH_2$), 7.09 (d, 1 H, ^3J = 5.6 Hz, $CH=CHOCb$), 7.20–7.36 (m, 5 H, ArH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = –5.3 ($Si(CH_3)_2$), 16.1 ($SiC(CH_3)_3$), 17.4, 19.5 (CH_{3Cb}), 23.1 ($CH=C(CH_3)$), 26.3 ($SiC(CH_3)_3$), 32.1 (CH_{Cb}), 41.1 ($CHCH=CH$), 47.2 ($CHC(CH_3)=CH_2$), 54.8 (NCH_2), 60.3 (NCH_2Ar), 65.7 (CH_2OSi), 69.6 ($CHCH_2OSi$), 107.2 ($C(CH_3)=CH_2$), 110.6 ($CH=CHOCb$), 126.7, 128.1 and 128.8 (Ar), 136.5 ($CH=CHOCb$), 139.8 (Ar), 140.9 ($C(CH_3)=CH_2$), 153.6 (NCO).

Methyl (2*S*,3*R*,4*S*)-2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3-[(*E*)-2-{[(diisopropylamino)carbonyl]oxy}-2-(methylsulfanyl)ethenyl]-4-isopropenyl-1-pyrrolidinecarboxylate (40a): To a solution (pre-cooled to –78 °C) of **37a** (110 mg, 0.21 mmol) and TMEDA (55 mg, 0.47 mmol) in THF (10 mL), a solution of *t*BuLi (1.7 M *in* pentane) (0.28 mL, 0.47 mmol) was added dropwise. The reaction mixture was then quenched with MeSSMe (75 µL, 0.86 mmol) at –78 °C. Aqueous workup was performed of the resulted solution after stirring for 1 h at –78 °C and 30 min at room temperature. The aqueous phase was extracted with Et_2O (3×10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo affording the crude product **39a** as a yellow oil which was used in the next step without further purification. To a solution of crude product **39a** in dry 1,2-dichloroethane (10 mL), methyl chloroformate (81 µL, 1.1 mmol) was added dropwise at room temperature. The resulted solution was refluxed for 3 h, after that, the solvent was evaporated in vacuo. The crude product was purified by flash chromatography, R_f = 0.48 (SiO_2, Et_2O/petroleum ether, 1:1) affording **40a** (93 mg, 84%). $[\alpha]_D^{20}$ = –19.0 (*c* = 0.57, $CHCl_3$). IR (film): $\tilde{\nu}$ (cm^{-1}) = 2952–2856, 1708 (NCO), 1447, 1382. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 6 H, $Si(CH_3)_2$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 1.20–1.23 (m, 12 H, CH_{3Cb}), 1.50 (s, 3 H, $CH=C(CH_3)$), 2.20 (s, 3 H, SMe), 2.40–2.45 (m, 1 H, $CHCH_2OSi$), 3.32–3.40 (m, 2 H, $CHCH=C(SMe)$ and NCH_2), 3.61 (s, 3 H, NCO_2Me), 3.65 (m, 2 H, NCH_2, $CHC(CH_3)=CH_2$), 3.85 (m, 2 H, CH_2OSi), 3.88–3.99 (br. s, 2 H, CH_{Cb}), 4.60 (br. s, 1 H, $C(CH_3)=CH_2$)), 4.80 (br. s, 1 H, $C(CH_3)=CH_2$), 5.55 (d, 1 H, ^3J = 10.3 Hz, $CH=C(SMe)$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.6 ($Si(CH_3)_2$), 17.1 (SMe), 18.0 ($SiC(CH_3)_3$), 20.3, 21.5 (CH_{3Cb}), 22.8 ($CH=C(CH_3)$), 25.8 ($SiC(CH_3)_3$), 45.9 (CH_{Cb}), 46.7 (NCH_2), 47.6 (CH_2OSi), 48.5 ($CHCH=C(SMe)$), 52.0 (OMe), 61.7 ($CHCH_2OSi$), 110 ($C(CH_3)=CH_2$), 120.4 ($CH=C(SMe)$), 142.2 ($C(CH_3)=CH_2$), 144.4 ($CH=C(SMe)$), 152.3 (NCO). ESI-MS, *m*/*z* (%) = 1080 (80) [2 M^+ + Na], 551 (68) [M^+ + Na], 529 (75) [M^+ + H]. ESI-HRMS $C_{26}H_{48}N_2O_5SSi$ (528.82): [M^+ + H] calcd. 529.312596; found: 529.310321; [M^+ + Na] calcd. 551.294541; found: 551.292223.

Methyl (2*S*,3*S*,4*S*)-2-(Hydroxymethyl)-4-isopropenyl-3-(2-methoxy-2-oxoethyl)-1-pyrrolidinecarboxylate (41a): To a solution of **40a** (109 mg, 0.21 mmol) in MeOH (10 mL), methanesulfonic acid (54 μL, 0.82 mmol) and 3 drops of water were added. The reaction mixture was refluxed for 16 h. The mixture was diluted with H_2O (5 mL) and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic phase was washed with saturated $NaHCO_3$ (3 × 5 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography, R_f = 0.39 (SiO_2, AcOEt/Et_2O, 70:30) affording **41a** (31 mg, 55%) as a colourless oil which was identical spectroscopically (NMR) with the product obtained by Chevliakov et al.[6i] $[\alpha]_D^{20}$ = –41.2 (*c* = 0.52, CH_2Cl_2); {ref.[6i] $[\alpha]_D^{20}$ = –43.0 (*c* = 1.25, CH_2Cl_2)}. IR (film): $\tilde{\nu}$ (cm^{-1}) = 3578–3283 (OH), 2952–2883, 1739 and 1686 (NCO, CO), 1452, 1346, 1330. ^1H NMR (600 Mz, $CDCl_3$): δ = 1.67 (s, 3 H, CH=C(CH_3)), 2.13–2.27 (m, 2 H, C$H_2$$CO_2$Me), 2.50–2.54 (m, 1 H, C$H$$CH_2CO_2$Me), 2.90–2.94 (m, 1 H, CHC(CH_3)=CH_2), 3.41–3.49 (m, 2 H, CH_2N), 3.52–3.64 (m, 5 H, CO_2Me and CH_2OH), 3.67 (s, 3 H, NCO_2Me), 3.81 (m, 1 H, C$H$$CH_2OH$), 4.62 (br. s, 1 H, C($CH_3$)=C$H_2$), 4.87 (br. s, 1 H, C($CH_3$)=C$H_2$). ^{13}C NMR (150 Mz, $CDCl_3$): δ = 22.8 (CH=C(*C*H_3)), 32.9 (*C*H_2CO_2Me), 38.8 (*C*HCH_2CO_2Me), 45.5 (*C*HC(CH_3)=CH_2), 48.3 (CH_2N), 52.4 (CO_2Me), 53.4 (NCO_2Me), 65.5 (*C*HCH_2OH), 66.5 (CH_2OH), 113.3 (C(CH_3)=*C*H_2), 141.6 (*C*(CH_3)=CH_2), 158.0 (NCO), 173.3 (CO). ESI-MS, *m*/*z* (%) = 294 (100) [M^+ + Na], 272 (5) [M^+ + H]. HRMS (TOF-CI) $C_{13}H_{21}NO_5$ (271.31): [M^+ + Na] calcd. 294.130890; found: 294.131194.

Methyl (3*R*,3a*R*,7a*S*)-3-Isopropenyl-5-oxohexahydropyrano[3,4-*b*]pyrrole-1(2*H*)-carboxylate (42b): To a solution of **40b** (80 mg, 0.68 mmol, obtained from **37b** using the same procedure described for **40a**) in MeOH (8 mL), methanesulfonic acid (18 μL, 2.7 mmol) and 2 drops of water were added. The reaction mixture was refluxed for 15 h. The mixture was diluted with H_2O (4 mL) and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic phase was washed with saturated $NaHCO_3$ (3 × 5 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography, R_f = 0.20 (SiO_2, AcOEt/petroleum ether, 1:2) affording **42b** (17 mg, 48%) as a colourless oil which was identical NMR spectroscopically with the product obtained by Campbell et al.[6j] $[\alpha]_D^{20}$ = –28.1 (*c* = 0.30, $CHCl_3$); {ref.[6j] *ent*-**42b** $[\alpha]_D^{20}$ = +32.1 (*c* = 1.20, CH_2Cl_2)}. IR (film): $\tilde{\nu}$ (cm^{-1}) = 2952–2926, 1748 and 1704 (NCO, CO), 1456, 1383. ^1H NMR (400 Mz, $CDCl_3$): δ = 1.70 (s, 3 H, CH=C(CH_3)), 2.34 (d, 2 H, ^3J = 7.0 Hz, CHCH_2CO), 2.79–2.83 (m, 1 H, CHC(CH_3)=CH_2), 2.92–2.98 (m, 1 H, C$H$$CH_2$CO), 3.25–3.30 (m, 1 H, CH_2N), 3.70–3.76 (m, 4 H, NCO_2Me and CH_2N), 4.33–4.36 (m, 1 H, NC$H$$CH_2O$), 4.39–4.53 (m, 2 H, NCHCH_2O), 4.71 (br. s, 1 H, C(CH_3)=CH_2), 5.02 (br. s, 1 H, C(CH_3)=CH_2). ^{13}C NMR (100 Mz, $CDCl_3$): δ = 23.1 (CH=C(*C*H_3), 28.4 (*C*HCH_2CO), 36.5 (CH*C*H_2CO), 47.2 (CH_2N), 52.8 (NCO_2Me), 55.2 (N*C*HCH_2O), 67.9 (NCH*C*H_2O), 113.6 (C(CH_3)=*C*H_2), 139.7 (*C*(CH_3)=CH_2), 172.7 (CO). ESI-MS, *m*/*z* (%) = 501 (10) [2 M^+ + Na], 262 (100) [M^+ + Na], 240 (40) [M^+ + H]. HRMS (TOF-CI) $C_{12}H_{17}NO_4$ (239.27): [M^+ + Na] calcd. 262.1050; found: 262.1039; [M^+ + H] calcd. 240.1230; found: 240.1221.

(–)-α-Kainic Acid(1): A 8 N solution of Jones reagent (141 μL, 1.1 mmol) was added to solution of **41a** (27 mg, 0.11 mmol) in acetone (2 mL) at 0 °C. After stirring for 5 min at 0 °C the reaction mixture was allowed to warm to room temperature, and 0.1 mL of water was added. The resulted mixture was stirring at room temperature for 2 h, diluted with water (2 mL) and extracted with diethyl ether (3 × 5 mL). The organic phase was washed with brine, dried ($MgSO_4$) and the solvents evaporated in vacuo to afford the crude acid which was used without purification. The crude acid was dissolved in MeOH (1 mL) and was refluxed with 1 mL of a 40% aqueous NaOH solution for 18 h. The reaction mixture was diluted with water (1 mL) and was extracted with CH_2Cl_2 (3 × 5 mL). Water was removed under reduced pressure, and the residue was first passed through an ion-exchange DOWEX 50WX8-200 column, eluting with 1 N NH_4OH. Water was removed under reduced pressure, and the residue was then passed through a short Amberlite CG-50 ion-exchange column, eluting with water. Water evaporation and recrystalization from aqueous EtOH afforded 8.0 mg (38% overall yield) of a (–)-α-kainic acid (**1**). m.p. 243–245 °C (dec.); [ref.[6i] 241–244 °C (dec.)]. $[\alpha]_D^{20}$ = –14.3 (*c* = 0.40, H_2O); {ref.[6i] $[\alpha]_D^{20}$ = –14.6 (*c* = 0.25, H_2O)}. ^1H NMR (D_2O, 500 Mz): δ = 1.65 (s, 3 H, CH=C(CH_3)), 2.25 (dd, 1 H, ^3J = 7.6, 15.0 Hz, CH_2CO_2 H), 2.30 (dd, 1 H, ^3J = 15.3, 8 Hz, CH_2CO_2 H), 2.88–2.94 (m, 2 H, CHC(CH_3)=CH_2 and C$H$$CH_2CO_2$ H), 3.33 (dd, 1 H, ^3J = 13.2, 8.0 Hz, CH_2N), 3.52 (dd, 1 H, ^3J = 12.6, 8.0 Hz, CH_2N), 3.94 (d, 1 H, ^3J = 2.5 Hz, $CHCO_2$ H), 4.66 (br. s, 1 H, C(CH_3)=CH_2), 4.94 (br. s, 1 H, C(CH_3)=CH_2). ESI-MS, *m*/*z* (%) = 427 (90) [2 M^+ + H], 214 (45) [M^+ + H]. HRMS (TOF-CI) $C_{10}H_{15}NO_4$ (213.23): [M^+ – H] calcd. 212.0928; found: 212.0920.

Acknowledgments

This work was supported by the Deutsche Forschunsgemeinschaft (Sonderforschungsbereich 424), the Fonds der Chemischen Industrie and the Alexander von Humboldt Foundation. M. M. M. thanks the Spanish "Ministerio de Educación Cultura y Deporte" for a grant. We thank Mrs. E. Izgorodina for theoretical calculations of NMR coupling constants.

[1] For a preliminary communication of our work see: M. M. Martínez, D. Hoppe, *Org. Lett.* **2004**, *6*, 3743–3746.
[2] a) L. Rodney, J. Johnson, F. Koerner, *J. Med. Chem.* **1988**, *31*, 2057–2062 and references cited therein; b) J. C Watkins, P. Krogsgaard-Larsen, P. Honoré, *Trends Pharmacol. Sci.* **1990**, *11*, 25–33; c) J. C. Watkins, in: *Kainic Acid as a Tool in Neurobiology* (Eds.: E. G. McGeer, J. W. Olney, P. L. McGeer), Raven Press, New York, **1978**, pp. 26–69.
[3] K. Hashimoto, Y. Ohfune, H. Shirahama, *Tetrahedron Lett.* **1995**, *36*, 6235–6238.
[4] J. C. Watkins, R. H. Evans, *Annu. Pharmacol. Toxicol.* **1981**, *21*, 165–166.
[5] W. Oppolzer, K. Thirring, *J. Am. Chem. Soc.* **1982**, *104*, 4978–4979.
[6] a) For review see: A. F. Parsons, *Tetrahedron* **1996**, *52*, 4149–4174.<lit6b>For review see: R. M. Williams in: *Synthesis of Optically Active a-Amino Acids*, *Pergamon Press*, Oxford, **1989**, pp. 306–320; c) For selected syntheses of (–)-α-kainic acid see: K. Hashimoto, H. Shirahama, *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 212–223; d) H. Nakagawa, T. Sugahara, K. Ogasawara, *Org. Lett.* **2000**, *2*, 3181–3183; e) Q. Xia, B. Ganem, *Org. Lett.* **2001**, *3*, 485–487; f) J. Clayden, C. J. Menet, K. Tchabanenko, *Tetrahedron* **2002**, *58*, 4727–4733; g) O. Miyata, Y. Ozawa, I. Ninomiya, T. Naito, *Tetrahedron* **2000**, *56*, 6199–6207; h) B. M. Trost, M. T. Rudd, *Org. Lett.* **2003**, *5*, 1467–1470; i) M. V. Chevliakov, J. Montgomery, *J. Am. Chem. Soc.* **1999**, *121*, 11139–11143; j) A. D. Campbell, T. M. Raynham, R. J. K. Taylor, *J. Chem. Soc. Perkin Trans. 1* **2000**, *19*, 3194–3204; k) H. Hirasawa, T. Taniguchi, K. Ogasawara, *Tetrahedron Lett.* **2001**, *42*, 7587–7590; l) S. E. Yoo, S. H. Lee, N. Jeong, I. Cho, *Tetrahedron Lett.* **1993**, *34*, 3435–3438; m) S. Takano, T. Sugihara, S. Satoh, K. Ogasawara, *J. Am. Chem. Soc.* **1988**, *110*, 6467–6471.
[7] A. Deiters, D. Hoppe, *J. Org. Chem.* **2001**, *66*, 2842–2849.

[8] A. Deiters, B. Wibbeling, D. Hoppe, *Adv. Synth. Catal.* **2001**, *1*, 181–183.
[9] K. Shimamoto, M. Ishida, H. Shinozaki, Y. Ohfune, *J. Org. Chem.* **1991**, *56*, 4167–4176.
[10] See experimental section for more details.
[11] J. Tsuji, I. Minami, I. Shimizu, H. Kataoka, *Chem. Lett.* **1984**, 1133–1136.
[12] a) F. Hintze, D. Hoppe, *Synthesis***1992**, 1216–1218; b) P. Michan, A. Rassat, *Bull. Soc. Chim. Fr.* **1971**, 3561–3562; c) D. Hoppe, F. Hintze, P. Tebben, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1422–1423.
[13] E. Corey, A. Venkateswarlu, *J. Am. Chem. Soc.* **1972**, *94*, 6190–6192.
[14] K. M. Bertini Gross, P. Beak, *J. Am. Chem. Soc.* **2001**, *123*, 315–321.
[15] *N*-Benzylation was carried out by reductive amination, see: A. Barco, S. Benetti, G. Spalluto, *J. Org. Chem.* **1992**, *57*, 6279–6286.
[16] Moderate yields were obtained due to deprotection of silyl ether takes place at the same time. Other reducing agents were checked ($LiAlH_4$, $NaBH_4$) unsuccessfully.
[17] C. Prakash, S. Saleh, I. A. Blair, *Tetrahedron Lett.* **1989**, ***30***, 19–22.
[18] a) K. Kondo, Y. Kondo, T. Takemoto, T. IKenoue, *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1899–1900; b) For a discusion the rotameric distribution of several kainoids, see: G. A. Conway, J. S. Park, L. Maggiora, M. P. Mertes, N. Galton, E. K. Michaelis, *J. Med. Chem.* **1984**, *27*, 52–56; c) A. P. Kozikowski, A. H. Fauq, *Tetrahedron Lett.* **1990**, *31*, 2967–2970, and references therein.
[19] a) P. Kocienski, N. J. Dixon, *Synlett* **1989**, 52–54; b) P. Kocienski, C. Barber, *Pure Appl. Chem.* **1990**, *62*, 1933–1940.
[20] S. Hanessian, S. Ninkovic, *J. Org. Chem.* **1996**, *61*, 5418–5424.
[21] Synthesized from α-hydroxyacetone in 67% overall yield over four steps: silylation followed by Horner–Wadsworth–Emmons reaction, 1,2-reduction of ester moiety and bromination.
[22] A. Deiters, C. Mück-Lichtenfeld, R. Fröhlich, D. Hoppe, *Org. Lett.* **2000**, *2*, 2415–2418.
[23] H. Günther in: *NMR-Spektroskopie*, Georg Thieme Verlag, Stuttgart, New York, **1992**. The coupling constants were obtained with the use of packet of programs TURBOMOLE (vers 5.6), University of Karlsruhe, **2003**. The structures were obtimized with the theoretical function at the DFT level using the pure B-P functional [DFT(B-P)] and the basis set TZVP (triple-valence-polarized).
[24] a) In all known examples, deprotonation of *O*-allylic carbamates with *n*-BuLi/(–)-sparteine led to the (*S*)-configured organo-lithium compound. For review see: D. Hoppe, T. Hense, *Angw. Chem. Int. Ed. Engl.* **1997**, *36*, 2282–2316, and references therein; b) D. Hoppe, F. Marr, M. Brüggemann in: *Organolithiums in Enantioselective Synthesis* in *Topics in Organometallic Chemistry* (Ed.: D. M. Hodgson), Springer-Verlag, Berlin, Heidelberg, **2003**, vol. 5, pp. 61–67.
[25] a) D. Hoppe, A. Brönneke, *Tetrahedron Lett.* **1983**, *24*, 1687–1693; b) For review about S_N-reactions, see: M. R. Magid, *Tetrahedron* **1980**, *36*,1901–1930.
[26] a) F. Rehders, D. Hoppe, *Synthesis* **1992**, 859–864; b) A. P. Grieco, T. Oguri, Y. Yokoyama, *Tetrahedron Lett.* **1978**, *19*, 419–420.
[27] D. Madec, V. Henryon, P. J. Férézou, *Tetrahedron Lett.* **1999**, *40*, 8103–8107.
[28] M. Seppi, R. Kalkofen, J. Reupohl, R. Fröhlich, D. Hoppe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1423–1427.
[29] H. Paulsen, D. Hoppe, *Tetrahedron* **1992**, *48*, 5667–5670.
[30] A. D. Campbell, T. M. Raynham, R. J. K. Taylor, *Chem. Commun.* **1999**, 245–246.
[31] The ^{1}H NMR exhibits two broad singlets at δ = 4.62 and 4.91 ppm for the alkene protons, indicating the C3–C4 *cis*-relationship (see refs.[6i,6j]). The NOE studies were carried out at low temperature because of the broad signals.

Received: November 19, 2004

