Allylsilane-Modified Amino Acids from the *Claisen* Rearrangement

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It is an honour to dedicate this paper to *Dieter Seebach* on the occasion of his 65th birthday. He has been an exceptionally important presence in my professional life, both through his example of how to be a successful scientist and by the many doors he has opened for me. I am very grateful to have had the opportunity to be one of 'die Mitarbeiter'.

The *Claisen* rearrangement of the *N*-protected, silylated allyl glycinates **11** and **12** led to the formation of allyl/silyl-functionalized amino acids **13** and **14** in yields up to 80%. The diastereoisomer ratio varied from 2:1 to 29:1 for **11mb**, and from 2:1 to 46:1 (*syn*/*anti*) for **12mb**, depending on reaction conditions, as shown by X-ray crystallographic analysis of **14mb**. The relationship between the size of the alkyl groups on the chlorosilane reagent ($Me_2R''SiCl$, R'' = Cl, Me, *t*-Bu, Ph) used as an enolate trap and the observed stereoselectivity was investigated in the case of the *Ireland–Claisen* variant. Me_3SiCl gave the best results. However, the size of the alkyl groups on the silylated ester ($Me_2R''Si$, R = Me, *t*-Bu, Ph, i-Pr) did not exert a significant effect on the diastereoselectivity or yield of the rearrangement.

Introduction. – The *Claisen* rearrangement [1] and its variants provide a powerful means to effect stereocontrolled C–C bond formation. The highly-ordered transition state guarantees the reliable chirality transfer from starting materials to products. One of the most successful implementations of the many variants of the *Claisen* rearrangement is that of *Ireland* [2][3].

The *Ireland–Claisen* rearrangement has been used for crucial C–C bond-formation in the synthesis of many natural products and biologically important molecules, including steroids [4], macrocycles [5], polyether antibiotics [6], C-glycosides [7], terpenes [8], and iridoids [9]. Some noteworthy examples of stereoselective syntheses based on the *Ireland–Claisen* rearrangement include *Schreiber*'s preparation of the cyclohexyl moiety of FK-506 (**1**) [10], *Danishefsky*'s route to the C28–C49 unit of rapamycin (**2**) [11], and *Ireland*'s preparation of nonactic acid (**3**) [12] and the monensin c/d ring assembly (**4**) (*Scheme 1*) [6].

The preparation of natural and unnatural amino acids and peptides has captured the interest of the synthetic community. *Seebach*, among others, has devoted considerable attention to the stereoselective syntheses of this class of compounds [13]. γ,δ-Unsaturated amino acids have become the subject of intense investigation due to their biological activity [14]. We sought to synthesize such amino acids that, at the

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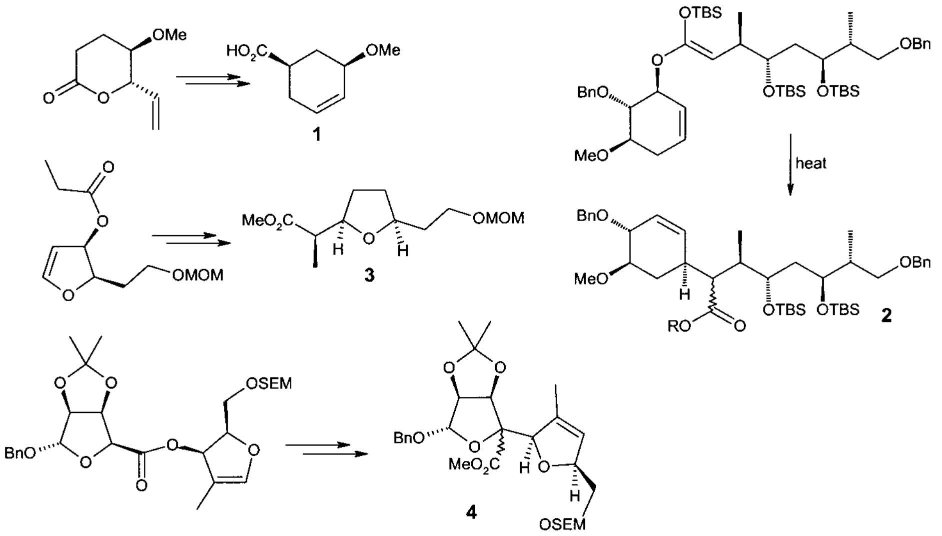
Scheme 1



same time, would possess allylsilane moieties for further functionalization, taking advantage of the well-documented allylsilane chemistry [15][16].

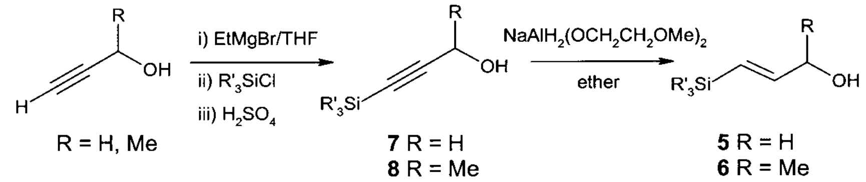
The *Ireland–Claisen* rearrangement occupies a prominent position among the available procedures for acyclic C–C bond-formation in a stereochemically-defined manner [1][17] and has been used for the preparation of amino acids [18]. We, thus, surmised that the *Ireland–Claisen* rearrangement with allylsilanes, described by *Panek* [19] and others for non-amino acids, might provide a new, generic entry to unnatural amino acids. To this end, we have investigated methods to facilitate the rearrangement of (substituted) 3-silylprop-2-enyl glycinates [20].

Results. – The silylated alcohols **5** and **6** were prepared according to literature procedures [21]. Treatment of either propargyl alcohol or but-3-yn-2-ol with 2.7 equiv. of EtMgBr followed by addition of silyl reagent (2.7 equiv.) and workup under acidic conditions gave **7** and **8**, respectively, in moderate to excellent yield, depending on the size of the silyl group (*Table 1*). Reduction with sodium bis(methoxyethoxy)aluminum hydride led to the *exclusive* formation of the (*E*)-configured vinylsilane allylic alcohols **5** and **6**, respectively.

Alternative methods for the synthesis of vinylsilanes, *e.g.*, hydrosilylation of the triple bond of a propargyl ester, were less convenient, since mixtures of (*Z*)- and (*E*)-configured products were obtained. The configuration at the double bond was determined by ^{1}H-NMR (coupling constants), and the presence of a single (*E*)-isomer was confirmed by GC.

The silylated allyl glycinate substrates for the *Claisen* rearrangement were prepared by esterification of the *N*-protected amino acids **9** and **10** with the appropriate alcohol (*Table 2*). Addition of dicyclohexylcarbodimide (DCC) at 0° to a solution of the alcohol and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in CH_2Cl_2 or DMF, depending

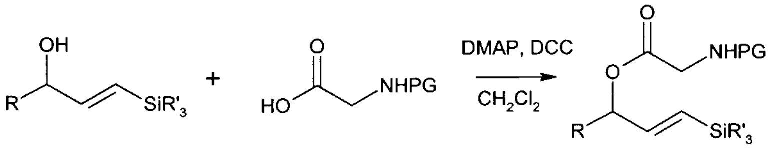
Table 1. *Preparation of Silylated Vinylsilane Alcohols*



R	R'$_3$Si	Product	Yield[a]) [%]	Product	Yield[a]) [%]
H	Me$_3$Si	**7m**	92	**5m**	77
H	(*t*-Bu)Me$_2$Si	**7b**	54	**5b**	58
H	Me$_2$(Ph)Si	**7a**	70	**5a**	65
Me	Me$_3$Si	**8m**	95	**6m**	72
Me	(i-Pr)Me$_2$Si	**8p**	82	**6p**	68

[a]) Isolated yield.

Table 2. *Esterification of* N*-Protected Glycine with Alcohols* **5** *and* **6**



R'$_3$Si	R	Solvent	PG[a])	Product	Yield [%]
Me$_3$Si	H	DMF	Boc	**11mb**	60
Me$_3$Si	H	CH$_2$Cl$_2$	Cbz	**11mc**	87
(*t*-Bu)Me$_2$Si	H	CH$_2$Cl$_2$	Boc	**11bb**	77
Me$_2$(Ph)Si	H	CH$_2$Cl$_2$	Boc	**11ab**	81
Me$_3$Si	H	CH$_2$Cl$_2$	Cbz	**11mc**	65
Me$_3$Si	H	DMF	Bz	**11mz**	60
Me$_3$Si	Me	CH$_2$Cl$_2$	Boc	**12mb**	82
Me$_3$Si	Me	DMF	Cbz	**12mc**	76
(i-Pr)Me$_2$Si	Me	CH$_2$Cl$_2$	Boc	**12pb**	80

[a]) Protecting groups: Boc = (*tert*-butoxy)carbonyl, Cbz = benzyloxycarbonyl, Bz = benzoyl.

on the specific amino-acid protecting group, followed by addition of the amino acid, resulted in formation of the esters **11** or **12** in good yield[2]).

The use of a zinc-chelated enolate for the *Claisen* rearrangement [22] [23] was first examined (*Scheme 2*). *Kazmaier et al.* reported improved yields and better stereoselectivities in the rearrangement of glycinate esters in the presence of chelating salts such as ZnCl$_2$. The addition of lithium hexamethyldisilazide (LHMDS) to a solution of **11mb** at −78°, followed by addition of ZnCl$_2$ after 10 min, resulted in a clear yellow

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[2]) Designations for **11**–**14**: silyl group (first letter): **m** = SiMe$_3$, **b** = (*t*-Bu)Me$_2$Si, **p** = (i-Pr)Me$_2$Si, **a** = Me$_2$(Ph)Si; protecting group (second letter): **b** = Boc, **c** = Cbz, **z** = Bz; diastereoisomer (third letter): **a** = *anti*, **s** = *syn*. Thus, **13mba** is the *anti*-product **13** with the SiMe$_3$ and the *N*-Boc groups. For abbreviations, see *Table 2*.

solution. The rearrangement reaction was monitored by TLC. The formation of the product was observed after 4 h, at which point the temperature had reached – 20°. The mixture was allowed to warm to room temperature overnight. Workup under acidic conditions furnished **13mbs/13mba** in a *syn*/*anti* ratio of 25 : 1 (*Entry 1*, *Table 3*). However, a substantial amount of decomposition of the starting ester was associated with this procedure, and the combined yield of the two isomeric amino acids was only 30%. The yield could be improved to 50% when the reaction time was reduced and when the workup was performed at 5° (*Table 3*, *Entry 2*). However, the stereoselectivity was unaffected. Similar reaction conditions were used for the rearrangement of **12mb**. Addition of lithium diisopropyl amide (LDA) to a solution of the glycinate, followed by addition of $ZnCl_2$, led to **14mbs/14mba** in a *syn*/*anti* ratio of 28 : 1 in 57% yield (*Entry 3*). When $MgBr_2$ was employed as the enolate trap, only the *syn*-isomer was observed by GC. Unfortunately, the yield was relatively low at 46%. Thus, attractive diastereoselectivities were observed with the chelating *Lewis* acids $ZnCl_2$ and $MgBr_2$, but, in both cases, the yields were much lower than with the traditional *Ireland–Claisen* procedure [20].

Scheme 2

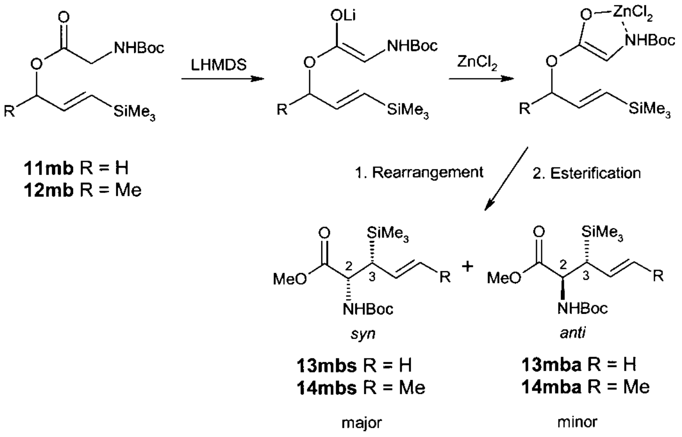


Table 3. Claisen *Rearrangement under Chelating Conditions*

Entry	Starting material	Condition[a])	Temp. [°]	Time [h]	Product	Yield [%]	*syn*/*anti*
1	**11mb**	LHMDS/$ZnCl_2$	– 78 → r.t.	24	**13mb**	30	25 : 1
2	**11mb**	LHMDS/$ZnCl_2$	– 78 → 5	10	**13mb**	50	25 : 1
3	**12mb**	LDA/$ZnCl_2$			**14mb**	57	28 : 1
4	**12mb**	LDA/$MgBr_2$			**14mb**	46	single isomer

[a]) LHMDS = lithium hexamethyldisilazide, LDA = lithium diisopropyl amide.

The *Ireland–Claisen* rearrangement of a series of glycinate esters with different silyl substituents and amine protecting groups was examined next. In general, good diastereoisomer selectivity (19 : 1) and high yields (*e.g.*, *Entry 7*, *Table 4*) were observed under standard conditions (sequential addition of the ester to LHMDS and quenching with Me_3SiCl) [6]. The resulting carboxylic acids were directly converted to the corresponding methyl esters by treatment with Me_3SiCHN_2 [24] to facilitate characterization. The major isomer in each case was purified by flash chromatography (FC). The products were formed in moderate to high stereoselectivity (3 : 1 – 29 : 1) and good yield (28 – 85%). Stereoselectivity and yield increased when Et_3N was used together with LDA (29 : 1, 85%) (*Entry 1*, *Table 4*), or upon reverse addition of the base to the ester (29 : 1, 82%) (*Entry 8*, *Table 4*).

Table 4. Claisen *Rearrangement of* **11mb** *to* **13mb** (*syn* and *anti*)

Entry	Conditions	Yield [%]	*syn*/*anti* (yield [%])
1	LDA (2.5 equiv.), Me_3SiCl (3 equiv.), Et_3N	85	29 : 1
2	LDA (3.5 equiv.), Me_3SiCl (3.5 equiv.)	50[a]	
3	LDA (2.5 equiv.), (*t*-Bu)Me_2SiCl	55	5 : 1
4	LDA, Ph_2SiCl_2	42	3 : 1
5	LDA, Cl_3SiH	40	5 : 1
6	LDA, $PhSiCl_3$	34	3 : 1
7	LHMDS (2.5 equiv.), Me_3SiCl	79	19 : 1
8	inverse addition	82	29 : 1
9	DMAP, TMSCl		9 : 1
10	$PhMe_2SiCl$, Et_3N		15 : 1
11	(*t*-Bu)Me_2SiCl, Et_3N	28	2.6 : 1

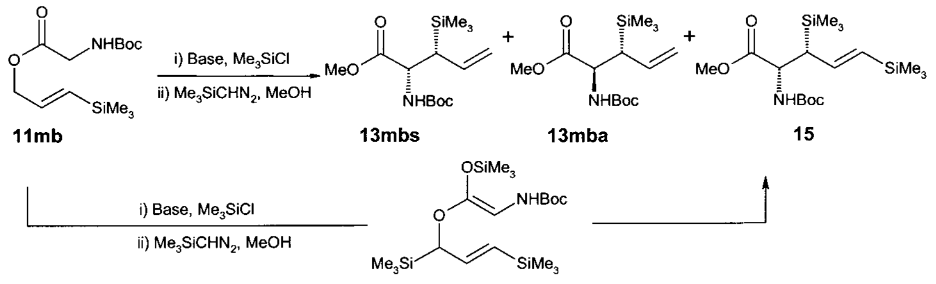
[a]) Plus 20% of **15** (*Scheme 3*).

Attempts to improve the reaction by changing the base/ester ratio in the enolization process proved to be difficult. Increasing the quantity of base led to severely diminished yields. In the case of **11mb**, excess base led to the formation of compound **15** in 20% yield (*Entry 2*, *Table 4*), which results from double deprotonation and silylation of **11mb** followed by rearrangement (*Scheme 3*). Compounds like **15** are *not* common side products in the *Ireland – Claisen* rearrangement; usually, silylation of the enolate carbon occurs, a process that was not observed in our reactions. Additional base (3.5 equiv.) led not only to **15**, but also to decomposition of the enolate intermediate *via* β-elimination (*Entry 2*, *Table 4*) [25]. Elimination of the allylic ether moiety has been reported to compete in certain cases with the rearrangement [26]. By using 2.5 equiv. of either LDA or LHMDS in the enolization process (*Entries 1* and *7*, *Table 4*), the formation of **15** could be suppressed. Under these conditions, the rearrangement took place at *ca.* -20°, and the yields of the esterified products were moderate to excellent (55 – 85%).

Next, we tried more-electrophilic dichloro- or trichlorosilanes as trapping agents to control product selectivity through N – Si – O cyclization. Alternatively, bulkier monochlorosilanes were tested to determine whether more steric congestion in the transition state would improve the stereoselectivity of the process. In neither case were these approaches successful with respect to yield or diastereoselectivity (*Entries 4 – 6*, *Table 4*).

The effect of different silyl groups (Me_3Si, (i-Pr)Me_2Si, Me_2(Ph)Si, (*t*-Bu)Me_2Si) on the starting allylic ester was studied next. It was expected that greater steric bulk on the silane would lead to an enhanced stereoselectivity due to fewer degrees of freedom in

Scheme 3



the transition state of the *Claisen* rearrangement (see below). In all cases examined, the reaction of Me_3Si-substituted **11mb** gave rise to both the highest stereoselectivity and yield. In general, the use of other silyl groups led either to lower yield or selectivity, or both. As the size of the silyl group increased, there was a dramatic decrease in yield, with the following trend: $Me_3Si > Me_2(Ph)Si > (t\text{-}Bu)Me_2Si$. A slight decrease in selectivity was noted, thus, with the larger silyl groups (*Table 5*).

Table 5. *Effect of the Silyl Group of* **11** *on the Stereoselectivity of the Rearrangement*

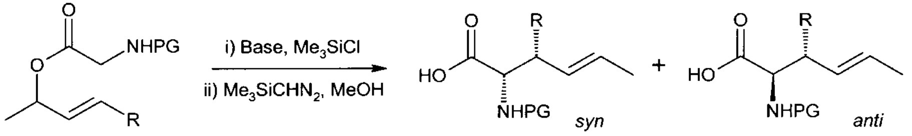
Entry	Compound	R'_3Si	Product	Yield [%]	*syn*/*anti*
1	**11mb**	Me_3Si	**13mbs/13mba**	85	29 : 1
2	**11bb**	$(t\text{-}Bu)Me_2Si$	**13bbs/13bba**	40	16 : 1
3	**11ab**	$Me_2(Ph)Si$	**13abs/13aba**	62	5.5 : 1

The optimized reaction conditions for **11mb** were used for the rearrangement of **12mb** and **12pb**, which bear an additional stereogenic center (*Table 6*). In the case of **12mb**, a notable increase in selectivity and yield resulted from introduction of the α-methyl substituent into the allylic system.

The *N*-protecting group had a significant impact on the stereoselectivity, Boc-protected esters performing much better than Bz- or Cbz-protected esters, as shown in the rearrangement of **12mb** (*Table 7*). *Bartlett* and co-workers reported similar results [18]. When more than 3 equiv. of base were employed in the enolization process, deprotection of the Boc group was observed at room temperature.

The configurations of the methyl glycinates were determined by two independent methods. First, the structure of the major isomer of **14mb** (*Figure*) was solved by X-ray crystallography (*Table 9* and *10*), which confirmed the assumed stereochemistry of the favored isomer. Second, the diastereoisomer ratios were determined by GC, and ^{1}H-NMR analyses were performed, correlating the coupling constants of the C(2) and C(3) protons (*Table 8*) [27]. For the remaining compounds, stereochemical assignment was based on ^{1}H-NMR chemical shifts of the C(3) methine proton, which distinguishes the *syn* and *anti* diastereoisomers (*Table 8*). In most cases, the vicinal coupling constants for the 2,3-*syn* diastereoisomer (zigzag conformation in *Scheme 2*) are larger than for those of the 2,3-*anti* counterpart and show a downfield shift. The resonance of the C(2) methine proton is not useful in this respect, since it overlaps with the signals of the vinylic protons.

Table 6. *Rearrangement Conditions for* **12mb** *and* **12pb**



	R	PG
12mb	Me_3Si	Boc
12mz	Me_3Si	Bz
12mc	Me_3Si	Cbz
12pb	$(i\text{-}Pr)Me_2Si$	Boc

	R	PG
14mb	Me_3Si	Boc
14mz	Me_3Si	Bz
14mc	Me_3Si	Cbz
14pb	$(i\text{-}Pr)Me_2Si$	Boc

Entry	Substrate	Condition[a])	Product	Yield [%]	*syn*/*anti*
1	**12mb**	*A* (reverse)	**14mb**	92	single isomer
2	**12mb**	*B*	**14mb**	65	46:1
3	**12mb**	*C*	**14mb**	50	46:1
4	**12mb**	THF/HMPA (23%)	**14mb**	72	23:1
5	**12pb**	THF/HMPA (23%)	**14pb**	65	2:1
6	**12pb**	(reverse addition)	**14pb**	78	25:1

[a]) For conditions *A*–*C*, see *Exper. Part* (*Sect. 4*).

Table 7. *Rearrangement of Differently* N-*Protected* **12**

Entry	Substrate	Condition	PG[a])	Product	Yield [%]	*syn*/*anti*
1	**12mb**	LDA, Me_3SiCl, Et_3N	Boc	**14mb**	92	32:1
2	**12mc**	LDA, Me_3SiCl	Cbz	**14mc**	80	12:1
3	**12mz**	LDA, Me_3SiCl	Bz	**14mz**	71	9:1

[a]) Protecting group.

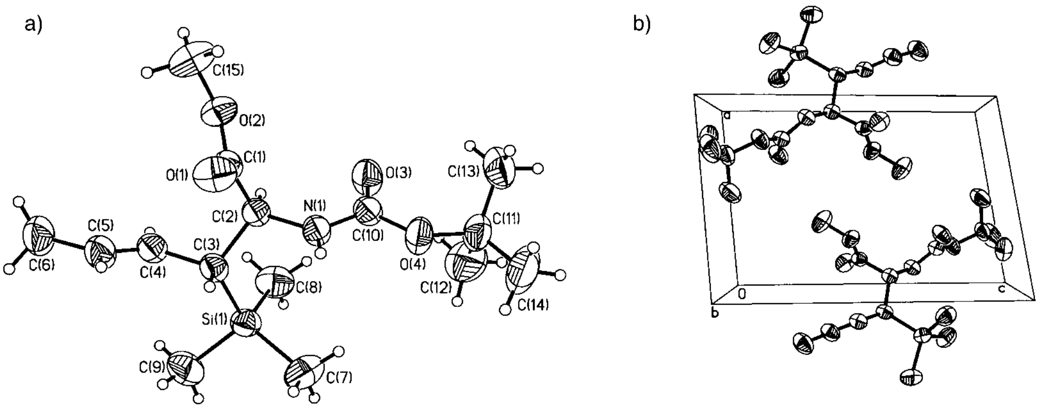


Figure. *a*) Thermal ellipsoids (50% probability) of **14mb**. *b*) Dimer in cell.

Table 8. *Vicinal* ^{1}*H-NMR Coupling Constants* (J [Hz]) *and Chemical Shifts* (δ [ppm]) *of Selected Compounds*

Compound	R_3Si	PG[a]	Product	δ(*syn*)	δ(*anti*)	$J_{2,3}$(*syn*)	$J_{2,3}$(*anti*)
11mb	Me_3Si	Boc	**13mb**	1.95	2.03	5.86	4.59
11bb	(*t*-Bu)Me_2Si	Boc	**13bb**	2.16	2.41	6.87	4.40
11ab	Me_2(Ph)Si	Boc	**13ab**	2.18	2.29	6.37	5.28
12mb	Me_3Si	Boc	**14mb**	1.83	–	5.65	–
12mc	Me_3Si	Cbz	**14mc**	1.81	–	5.34	–
12mz	Me_3Si	Bz	**14mz**	1.98	2.07	5.37	5.16
12pb	(i-Pr)Me_2Si	Boc	**14pb**	1.88	1.79	6.94	5.33

[a] Protecting group.

Table 9. *Bond Lengths* [Å] *and Angles* [°] *for* **14mb**

Bond lengths			
Si(1)–C(14)	1.857(3)	O(4)–C(9)	1.2084(19)
Si(1)–C(15)	1.857(3)	C(5)–C(7)	1.512(3)
Si(1)–C(13)	1.856(2)	C(5)–C(8)	1.544(2)
Si(1)–C(8)	1.905(2)	O(6)–C(7)	1.198(2)
O(1)–C(9)	1.345(2)	C(8)–C(10)	1.505(3)
O(1)–C(12)	1.467(2)	C(10)–C(11)	1.300(3)
O(2)–C(7)	1.3292(19)	C(11)–C(17)	1.490(3)
O(2)–C(16)	1.452(3)	C(12)–C(19)	1.509(4)
N(3)–C(9)	1.341(2)	C(12)–C(18)	1.511(3)
N(3)–C(5)	1.446(2)	C(12)–C(20)	1.511(4)
Bond angles			
C(14)–Si(1)–C(15)	108.74(15)	C(10)–C(8)–C(5)	110.89(13)
C(14)–Si(1)–C(13)	109.29(16)	C(10)–C(8)–Si(1)	111.39(13)
C(15)–Si(1)–C(13)	110.15(16)	C(5)–C(8)–Si(1)	113.09(13)
C(14)–Si(1)–C(8)	107.77(13)	O(4)–C(9)–N(3)	124.50(18)
C(15)–Si(1)–C(8)	111.91(11)	O(4)–C(9)–O(1)	125.84(17)
C(13)–Si(1)–C(8)	108.92(11)	N(3)–C(9)–O(1)	109.65(14)
C(9)–O(1)–C(12)	120.60(14)	C(11)–C(10)–C(8)	125.81(19)
C(7)–O(2)–C(16)	115.93(18)	C(10)–C(11)–C(17)	126.6(2)
C(9)–N(3)–C(5)	122.99(15)	O(1)–C(12)–C(19)	108.3(2)
N(3)–C(5)–C(7)	109.15(14)	O(1)–C(12)–C(18)	110.6(2)
N(3)–C(5)–C(8)	110.90(13)	C(19)–C(12)–C(18)	112.8(3)
C(7)–C(5)–C(8)	110.76(15)	O(1)–C(12)–C(20)	102.0(2)
O(6)–C(7)–O(2)	123.45(17)	C(19)–C(12)–C(20)	112.3(3)
O(6)–C(7)–C(5)	124.61(15)	C(18)–C(12)–C(20)	110.3(3)
O(2)–C(7)–C(5)	111.94(15)		

Discussion. – There are three structural elements that mainly determine the stereoselectivity of the ester enolate *Claisen* rearrangement: *1*) the chair or boat-like nature of the transition state, *2*) the geometry about the vinylic C=C bond, and *3*) the geometry about the allylic C=C bond.

In the case of simple allyl esters, the geometry of the silyl enolate formed during the first step of the *Ireland–Claisen* rearrangement can be controlled by the reaction

Table 10. *Selected Crystallographic Data for* **14mb**

Identification code	CCDC-186958	
Empirical formula	$C_{15}H_{29}NO_4Si$	
Formula weight	315.48	
Temperature	299(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	$a = 8.6830(8)$ Å	$\alpha = 97.131(2)°$
	$b = 10.3930(10)$ Å	$\beta = 94.114(2)°$
	$c = 11.9048(12)$ Å	$\gamma = 113.962(2)°$
Volume	965.25(16) Å^3	
Z	2	
Density (calc.)	1.085 Mg/m^3	
Absorption coefficient	0.135 mm^{-1}	
$F(000)$	344	
Crystal size	0.08 × 0.22 × 0.36 mm	
Theta range for data collection	1.74 to 27.52°	
Index ranges	$-11 \leq h \leq 9$, $-13 \leq k \leq 13$, $-14 \leq l \leq 15$	
Reflections collected	8800	
Independent reflections	4333 [R(int) = 0.0294]	
Completeness to theta	97.0%	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	4333/0/307	
Goodness-of-fit on F^2	0.986	
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0455$, $wR_2 = 0.1051$	
R indices (all data)	$R_1 = 0.0882$, $wR_2 = 0.1206$	
Extinction coefficient	0.009(3)	
Largest diff. peak and hole	0.190 and −0.157 e Å^{-3}	

conditions. The (*Z*)-configured ester enolate **16** was preferentially formed under kinetic control by LDA in THF and led, after silylation [28], to (*E*)-configured **17** (*Scheme 4*) [3]. The structures of such enolates have been established by X-ray crystal analysis [29]. In contrast, in the presence of solvents or additives that coordinate Li$^+$, *e.g.*, TMEDA, DMPU [30] or HMPA, the (*E*)-configured enolate **19** is preferentially formed and converted to the (*Z*)-oriented silyl ketene acetal **20**³)⁴). Note that the specific nature and concentration of the chelating molecules can strongly affect the degree of stereocontrol of enolates [31]. The ratio of the isomeric silyl ketene acetals can also be affected by the ratio of substrate to base. Higher mole ratios of base/ester slightly favor the formation of the (*E*)-configured silyl ketene acetal, whereas the (*Z*)-intermediate can be increased with a lower base/ester ratio. Deviations from a 1:1 base/ester ratio can, however, have a negative impact on isolated yields [31]. There is considerable discussion in the literature regarding the origin of this observation,

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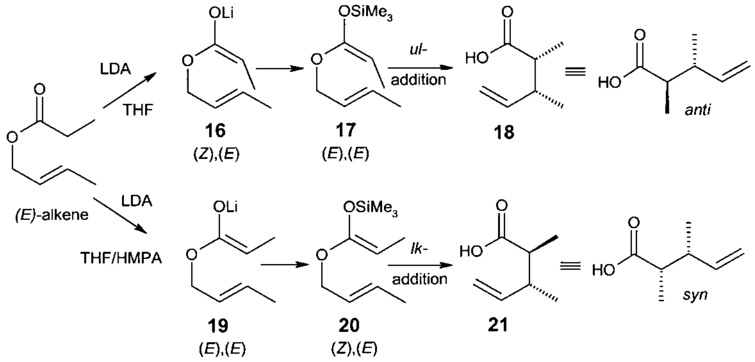
³) The (*E*)/(*Z*) notation is adopted from the definition of the geometries of silyl ketene acetal as well as metal enolates; the configurations are opposite due to the priority of Si over Li [3].

⁴) Note that, because of *CIP* priorities, the α-heteroatom-substituted, (*Z*)-configured silyl ketene acetals (*Scheme 5,a*) have the same relative configuration during the bond-forming process as **19** (*Scheme 4*), but the addition is *ul* in this case (see *Footnote 5*), while, with two heteroatom substituents (*Scheme 5,b*), it returns to *lk* addition.

including formation of the thermodynamically more stable enolate, change of transition-state geometry after deprotonation, and kinetic resolution of the intervening lithium enolates. The situation is somewhat different with α-heteroatom-substituted esters, where internal chelation constrains the deprotonation geometry. Preferential formation of the (*E*)-configured ester enolate **22** has been observed by *Bartlett* [32], *Fujisawa* [33], *Burke* [34], *Panek* [27], and *Kazmaier* [23] (*Scheme 5,a*).

Scheme 4



The *Ireland–Claisen* rearrangement is predetermined by the pericyclic transition state. In our case, the starting allylic esters **11** and **12** are (*E*)-configured vinyl silanes and, thus, the impact on stereoselectivity should be the same for both types of compound (the distal stereogenic center bearing the Me group in **12** is considered separately below). Thus, much of the battle for stereoselectivity in the rearrangement rides on the ability to control the enolate geometry. With (*E*)-allyl groups, (*E*)-configured silyl ketene acetals preferentially undergo *ul* addition⁵) to the *anti* product **18**, and (*Z*)-configured silyl ketene acetals *lk* addition to the *syn* product **21** – a typical trend in many related addition reactions⁶).

The preferred stereochemical outcome of the rearrangement of **11** can be explained by invoking the generally favored chair-like over the boat-like transition state [37]. The selectivity in the *Claisen* rearrangement of esters containing α-heteroatom substituents has been attributed to the formation of five-membered chelates, which lead to the

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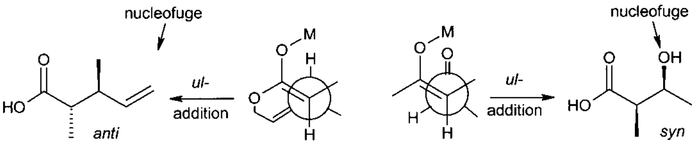
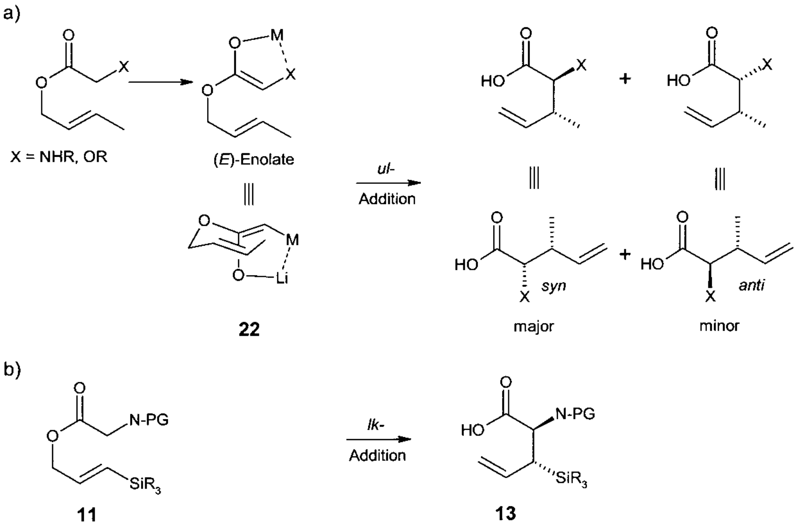
⁵) For a definition of the stereodescriptors *lk* ('*like*') and *ul* ('*unlike*') for bond-forming reactions between trigonal centers, see [35].

⁶) There is a disconnect between the *syn* and *anti* stereochemical descriptors used here and those more generally used for aldol condensations. In the latter, the nucleofuge is found on the side chain, thus *ul* aldol addition gives a *syn*-adduct. In the case of the *Claisen* rearrangement, however, the alignment of the C chain puts the nucleofugal allyl group on the chain end, such that *lk*-addition produces the *syn*-adduct. In both cases, however, the relative stereochemistry of the addition process is the same:



Note that *Lewis* acid catalyzed addition frequently favor *ul*-additions irrespective of the enolate geometry [36].

Scheme 5

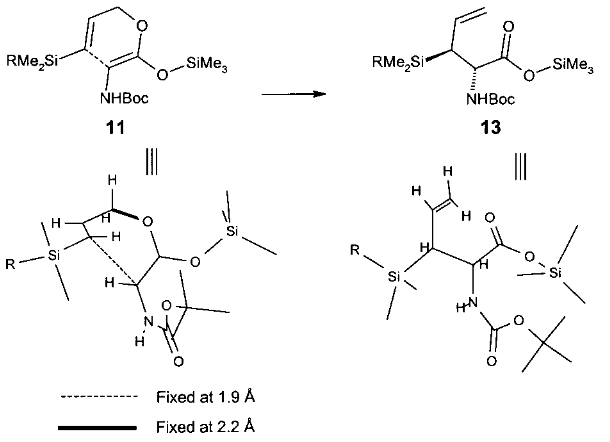


(*Z*)-configured silyl ketene acetal and, finally, to the *syn*-isomer **13** as the major product (*Scheme 5*) [38]. The low stereoselectivity observed with the Cbz- and Bz-protected compounds **11mc** and **11mz** may have its origin in the presence of the aromatic ring in the protecting groups, which may simply adopt a conformation that prevents chelation. Alternatively, it is conceivable that the ring affects the nucleophilicity of the N-atom, reducing its ability to coordinate to the Si. Similarly, it is well-known that certain amines coordinate to tetravalent Si to produce hypervalent silane species [39][40]. A Si–N interaction cannot be excluded as an additional (unhelpful) stereocontrol element in the rearrangement.

The best yields and stereoselectivities in the rearrangement of **11** occurred with an excess of 2 equiv. of both base and chlorosilane. The active silyl enolate that undergoes the *Ireland–Claisen* rearrangement should, thus, be silylated on N as well as O. Multifunctional silanes were used in the hope that the resulting cyclic 5-ring, analogous to **22** (M = Si; *Scheme 5*), would cooperatively direct the rearrangement, thereby improving selectivity. Alternatively, larger chlorosilanes were used as trapping agents, but did not prove helpful. The structures of the silylated enolates were apparently distorted away from the transition state that leads to the *syn* diastereoisomer (*Table 4*).

Attempts were also made to bias the relative formation of the (*E*)- and (*Z*)-configured silyl enolates by adding larger silyl moieties to the allyl group, which, however, decreased the selectivity. Simple molecular modelling [41] of the transition state (lengthening of the C–O bond, shortening of the $=C\cdots C=$ distance: dotted line = 1.9 Å, bold line = 2.2 Å in *Scheme 6*), following the work of *Houk* and co-workers [42], showed that, first, the silyl group is somewhat remote from the reaction centre and, second, that the large group R can avoid the reaction centre by simple rotation. This suggests that size may not be the only significant factor in controlling the stereoselectivity of the reaction. Irrespective, this simple expedient

Scheme 6



could not be productively exploited to improve the stereoselectivity of the rearrangement.

Finally, we found that another stereoelement, the additional Me group in **12**, gave rise to both higher yields and stereoselectivities in the formation of **14** compared to **13**. The stereotransfer of the allyl group was extremely efficient. We were unable to detect any (*Z*)-alkene at all [38]. It remains to be established whether the (*Z*)-crotyl analogue of **12** will behave similarly and what the stereochemical outcome in these systems would be. Similarly, the utility of allylsilanes as nucleophiles for the preparation of new, unnatural amino acids must be examined and will form the basis of future reports.

Conclusions. – The *Ireland–Claisen* rearrangement of silylated allyl glycinates provides allyl/silyl-functionalized glycines in good yield with moderate to high stereoselectivity, favoring the *syn*-diastereoisomer. Replacing the intermediate Me$_3$Si enolate with either bulkier or more electrophilic silanes did not improve the outcome in terms of selectivity or yield. The stereochemical outcome was mainly determined by the size of the silyl substituent of the substrate. Thereby, best results were obtained with the smallest substituent, *i.e.*, the Me$_3$Si group.

We gratefully acknowledge the financial support of the *Natural Sciences and Engineering Research Council of Canada* and thank *Jim Britten* (McMaster) for obtaining the X-ray structure.

Experimental Part

1. *General.* ^{1}H- and ^{13}C-NMR Spectra were recorded on a *Bruker AC-200* spectrometer in CDCl$_3$ or C$_6$D$_6$, δ in ppm, *J* in Hz. IR Spectra were recorded on a *Biorad* spectrometer; in cm^{-1}. Electron-impact (EI) and chemical-ionization (CI) mass spectra were recorded at 70 eV with a source temp. of 200° on a *VG Instruments* analytical *ZAB-R* mass spectrometer equipped with a *VG 11-250* data system; *m/z* (rel. [%]). Gas chromatographic (GC) analyses were run on a *Hewlett-Packard 5890A* gas chromatograph equipped with a conventional heated injector, a flame ionization detector, a *Hewlett-Packard 3393A* integrator, and a *DB-1* megabore capillary column (30 m × 0.54 mm) from *Chromatographic Specialties, Inc.* GC/MS Analyses were recorded on a *Hewlett-Packard 5890II* gas chromatograph equipped with a *HP-5971A* mass selective detector and a *DB-5* fused-silica capillary column (30 m × 0.25 mm; *Chromatographic Specialties, Inc.*).

All reactions were performed with dried glassware under an atmosphere of anh. N_2. The following reagents were purchased from *Aldrich* and used without further purification: *N*-protected glycines, sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH), dicyclohexylcarbodiimide (DCC), 4-(*N*,*N*-dimethylamino)pyridine (DMAP), $ZnCl_2$, $MgBr_2$. Et_3N and hexamethylphosphortriamide (HMPA) were distilled from CaH_2. Diisopropylamine was distilled from NaOH. Propargyl alcohol and but-3-yn-2-ol were distilled from flame-dried glass ware prior to use. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under N_2 just before use. Silica-coated aluminium TLC plates (*60 F_{254}*) were purchased from *Merck*.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as depositon No. CCDC-186958. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

2. *Synthesis of Silylated Alcohols* [21]. 2.1. *3-(Trimethylsilyl)prop-2-yn-1-ol* (**7m**). A three-neck, round-bottomed flask equipped with a magnetic stirring bar and dry N_2 inlet was fitted with a reflux condenser, a thermometer, and a septum. The apparatus was flushed with N_2 and charged with Mg turnings (12.2 g, 50 mmol) and dry THF (50 ml). To the stirred suspension was added dropwise bromoethane (37.3 ml, 50 mmol) over 1 h *via* a syringe, while the temp. was kept at 37 – 47°. After complete addition, the grey suspension was heated at 50° for 1 h and then cooled to 5°. A soln. of propargyl alcohol (10.47 ml, 18.50 mmol) in THF (20 ml) was cautiously added dropwise to the grey suspension over 1 h at a const. temp. of 10°. When the grey suspension became very viscous, an additional 60 ml of THF was added and the mixture was stirred overnight. The resulting soln. was cooled to 5°, and 1.0 equiv. of Me_3SiCl (6.35 ml, 50 mmol) was added dropwise over 1 h at 25° or less (external cooling with ice). The mixture was heated to reflux for 2 h, the suspension was cooled to r.t. and carefully quenched with H_2SO_4 (300 ml, 1.4M) over 1 h and below 40°. The resulting soln. was stirred for 5 min, the org. layer was extracted with Et_2O (3 × 100 ml), the etheral layer was washed with 2 × 100 ml of H_2O. The combined org. extracts were dried over $MgSO_4$, and the solvent was removed *in vacuo*. The yellow-brown residue was purified by short-path distillation to afford a colourless oil (21.5 g, 16.8 mmol, 90%). IR: 3331 (br., OH), 2961, 2866, 2177, 1446, 1413, 1252, 1045, 983, 844, 761. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.23 (*s*, 2 H–C(1)); 1.97 (*s*, OH); 0.14 (*s*, Me_3Si).

2.2. *3-[(*tert*-Butyl)dimethylsilyl]prop-2-yn-1-ol* (**7b**). Prepared according to *2.1.* Yield: 54%. IR: 3331 (br., OH), 2961, 2866, 2177. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.4 (*s*, 2 H); 1.2 (*s*, 1 H); 0.98 (*s*, 9 H); 0.20 (*s*, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 108.3; 87.0; 58.8; 16.3; 13.9; –3.8.

2.3. *3-[(Dimethyl)phenylsilyl]prop-2-yn-1-ol* (**7a**). Prepared according to *2.1.* Yield: 70%. IR: 3331 (br., OH), 2961, 2866, 2177, 1720, 740. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.66 (*m*, 2 H); 7.41 (*m*, 3 H); 4.28 (*s*, 2 H); 2.48 (br. *s*, 1 H); 0.46 (*s*, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 133.6; 133.3; 129.0; 128.8; 127.9; 107.9; 88.4; 58.90; –4.1.

2.4. *4-(Trimethylsilyl)but-3-yn-2-ol* (**8m**). Prepared according to *2.1.* Yield: 95%. IR: 3330 (br., OH), 2961, 2866, 2177. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.38 (*q*, *J* = 6.6, H–C(2)); 3.79 (*s*, OH); 1.30 (*d*, *J* = 6.6, 3 H–C(1)); 0.02 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 107.1; 87.5; 58.1; 24.0; –0.3.

2.5. *3-[(Isopropyl)dimethylsilyl]but-3-yn-2-ol* (**8p**). Prepared according to *2.1.* Yield: 80% ^{1}H-NMR (200 MHz, $CDCl_3$): 4.51 (*q*, *J* = 6.6, 1 H); 2.08 (*s*, 1 H); 1.44 (*d*, *J* = 6.6, 3 H); 0.98 (*d*, *J* = 6.6, 6 H); 0.90 (*m*, 1 H); 0.09 (*s*, 6 H, $SiMe_3$). ^{13}C-NMR (50 MHz, $CDCl_3$): 108.50; 86.92; 58.86; 24.47; 16.94; 13.91; –3.78.

2.6. *(*E*)-3-(Trimethylsilyl)prop-2-en-1-ol* (**5m**). A two-neck, 500 ml round-bottomed flask fitted with a thermometer, septum, N_2 inlet, and magnetic stirring bar was charged with SMEAH (47 ml, 3.4M soln., 160 mmol) and Et_2O (65 ml). The soln. was cooled to 0° and treated dropwise *via* syringe with a soln. of 3-(trimethylsilyl)prop-2-yn-1-ol (12.78 g, 100 mmol) in Et_2O (60 ml) over 30 min at 5° or less. After complete addition, the cooling bath was removed. The reaction was complete within 1 h. The mixture was cooled to 0° and quenched with aq. H_2SO_4 (200 ml, 3.6M). The org. layer was extracted with Et_2O (2 × 100 ml). The org. extract was dried over $MgSO_4$, the solvent was removed *in vacuo*, and the remaining yellow oil was purified by FC (SiO_2; AcOEt/pentane 1:3) to afford a colorless oil (9.1 g, 70 mmol, 77%). ^{1}H-NMR (200 MHz, $CDCl_3$): 6.12 (*dt*, *J* = 4, 18, 1 H); 5.86 (*d*, *J* = 18, 1 H); 4.12 (*dd*, *J* = 4, 6, 2 H); 0.18 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 144.8; 129.2; 65.1; –1.45.

2.7. *(*E*)-3-[(*tert*-Butyl)dimethylsilyl]prop-2-en-1-ol* (**5b**). Prepared according to *2.6.* Yield: 58%. IR: 3335 (br., OH), 1645, 1120, 750. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.9 (*dt*, *J* = 12.2, 3.2, 1 H); 5.8 (*d*, *J* = 12.2, 1 H); 3.9 (*d*, *J* = 5.4, 2 H); 1.3 (*s*, 1 H); 0.9 (*s*, 9 H); 0.2 (*s*, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 139.3; 131.6; 67.5; 26.41; 17.23; –6.4.

2.8. *(*E*)-3-[(Dimethyl)phenylsilyl]prop-2-en-1-ol* (**5a**). Prepared according to *2.6.* Yield: 65%. IR: 3335 (br., OH), 1645. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.4 (*m*, 3 H); 7.3 (*m*, 2 H); 6.1 (*dt*, *J* = 18.1, 3.9, 1 H); 5.9 (*d*,

$J = 18.1$, 1 H); 4.1 (*d*, $J = 4.0$, 2 H); 1.6 (*s*, 1 H); 0.3 (*s*, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 133.6; 133.4; 129.1; 128.9; 128.0; 126.5; 64.6; -4.0.

2.9. *(*E*)-4-(Trimethylsilyl)but-3-en-2-ol* (**6m**). Prepared according to *2.6.* Yield: 95%. IR: 3330 (br., OH). ^{1}H-NMR (200 MHz, $CDCl_3$): 4.38 (*dd*, $J = 4.6$, 18.8, 1 H); 5.6 (*d*, $J = 18.6$, 1 H); 2.18 (*s*, 1 H); 1.30 (*d*, $J = 6.7$, 3 H); 0.01 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 140; 131.1; 67.1; 19.7; -0.9.

2.10. *(*E*)-4-[(Isopropyl)dimethylsilyl]but-3-en-2-ol* (**6p**). Prepared according to *2.6.* Yield: 68%. IR: 3331 (br., OH), 1645. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.0 (*dd*, $J = 6.0$, 18.8, 1 H); 5.9 (*d*, $J = 18.8$, 1 H); 3.9 (*m*, $J = 5.5$, 1 H); 2.0 (*s*, 1 H); 0.83 (*d*, $J = 6.5$, 1 H); 0.78 (*d*, $J = 6.5$, 6 H); 0.67 (*m*, 1 H); 0.3 (*s*, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 139.2; 131.4; 67.3; 24.2; 17.3; 13.3.

3. *General Procedure for the Synthesis of Silylated Allyl Glycinates.* An oven-dried 250 ml round-bottomed flask, equipped with a magnetic stirring bar, was charged with **5m** (2.6 g, 20 mmol) or **6m** (2.9 g, 20 mmol) and DMAP (0.20 g, 2.0 mmol). The flask was sealed with a rubber septum, and anh. CH_2Cl_2 (20 ml) was added. The resulting clear soln. was stirred for 15 min at r.t. DCC (4.1 g, 20 mmol) in CH_2Cl_2 (10 ml) was added *via* syringe. The mixture was stirred at 0° for 15 min before the *N*-protected glycine (20 mmol) in CH_2Cl_2 (10 ml) was added *via* syringe. The mixture was allowed to warm to r.t. overnight. The precipitated urea was filtered off, the resulting yellow soln. was washed with sat. $NaHCO_3$, dried ($MgSO_4$), and the solvent was removed *in vacuo.*

3.1. *(*E*)-3-(Trimethylsilyl)prop-2-en-1-yl* N-*(*tert*-Butoxycarbonyl)glycinate* (**11mb**). FC (SiO_2; AcOEt/pentane 1 : 4) afforded a colorless oil (5.0 g, 17.4 mmol, 87%). IR (neat): 3376, 2967, 1763, 1701, 1625, 1519, 1509, 1166. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.98 – 5.86 (*m*, 2 H); 4.99 (br., 1 H); 4.63 (*d*, $J = 3.9$, 2 H); 3.92 (*d*, $J = 6.5$, 2 H); 1.42 (*s*, 9 H); 0.06 (*s*, 9 H). ^{13}C-NMR (50.32 MHz, $CDCl_3$): 169.99; 155.58; 138.47; 134.19; 79.96; 67.50; 42.43; 28.28; -1.55. CI-MS (NH_3): 305 ($M + NH_4^+$), 288 (M^+), 249 (3), 232 (14), 188 (2), 176 (30), 144 (29), 130 (5), 90 (40), 73 (85), 57 (100). HR-MS: 288.163 ($[M + 1]^+$, $C_{13}H_{25}NO_4Si$; calc. 288.165).

3.2. *(*E*)-3-[(*tert*-Butyl)dimethylsilyl]prop-2-en-1-yl* N-*(*tert*-Butoxycarbonyl)glycinate* (**11bb**). FC (SiO_2; AcOEt/pentane 1 : 4) afforded a colorless oil (5.89 g, 18 mmol, 77%). R_f 0.68 (AcOEt/pentane 1 : 4). IR: 3385, 2955, 2931, 1755, 1722, 1514. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.01 (*td*, $J = 3.2$, 12.5, 1 H); 5.86 (*d*, $J = 12.5$, 1 H); 5.14 (br. *s*, 1 H); 4.60 (*d*, $J = 4.2$, 2 H); 3.87 (*d*, $J = 3.2$, 2 H); 1.38 (*s*, 9 H); 0.80 (*s*, 9 H); -0.38 (*s*, 6 H). ^{13}C-NMR (50.32 MHz, $CDCl_3$): 169.97; 155.68; 139.85; 131.27; 79.78; 67.47; 42.32; 27.75; 26.33; 16.25; -6.41. EI-MS: 330 (11, $[M + H]^+$), 289 (5), 274 (20), 216 (40), 116 (4), 73 (60), 57 (100).

3.3. *(*E*)-[(Dimethyl)phenylsilyl]prop-2-en-1-yl* N-*(*tert*-Butoxycarbonyl)glycinate* (**11ab**). FC (SiO_2; AcOEt/pentane 1 : 4) afforded a colorless oil (5.90 g, 17 mmol, 81%). IR: 3380, 2977, 1719, 1167. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.48 (*m*, 2 H); 7.34 (*m*, 3 H); 6.10 (*dt*, $J = 3.4$, 18.8, 1 H); 5.94 (*d*, $J = 18.8$, 1 H); 5.06 (br. *s*, 1 H); 4.68 (*d*, $J = 2.1$, 2 H); 3.93 (*d*, $J = 3.4$, 2 H); 1.43 (*s*, 9 H); 0.32 (*s*, 6 H). ^{13}C-NMR (50.32 MHz, $CDCl_3$): 169.97; 155.65; 140.31; 137.80; 133.73; 131.68; 129.11; 127.78; 79.93; 67.24; 42.37; 28.24; -2.86. CI-MS (NH_3): 350 (12, $[M + H]^+$), 278 (5), 216 (23), 176 (45), 57 (100).

*(*E*)-3-[(Trimethylsilyl)prop-2-en-1-yl* N-*(Benzyloxycarbonyl)glycinate* (**11mc**). FC (SiO_2; AcOEt/pentane 1 : 4) gave **11mc** (6.42 g, 20 mmol, 65%). R_f 0.52 (AcOEt/pentane 3 : 7). IR: 3360, 2956, 1777, 1529, 1249, 1193. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.26 (*s*, 5 H); 5.99 (*dt*, $J = 4.3$, 18.8, 1 H); 5.89 (*d*, $J = 18.8$, 1 H); 5.33 (br. *s*, 1 H); 5.06 (*s*, 2 H); 4.60 (*d*, $J = 4.2$, 2 H); 3.94 (*d*, $J = 5.4$, 2 H); 0.02 (*s*, 9 H). ^{13}C-NMR (50.32 MHz, $CDCl_3$): 169.68; 156.27; 138.43; 136.26; 134.37; 128.50; 128.14; 128.06; 67.63; 67.06; 42.76; -1.53. CI-MS: (NH_3): 339 (6, $[M + H]^+$), 322 (25), 278 (22), 131 (12), 91 (100).

3.4. *(*E*)-3-(Trimethylsilyl)prop-2-en-1-yl* N-*(Benzoyl)glycinate* (**11mz**). FC (SiO_2; AcOEt/pentane 1 : 4) gave **11mz** (5.2 g, 18 mmol, 60%). R_f 0.38 (AcOEt/pentane 3 : 7). IR: 3343, 2957, 1751, 1651, 1539. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.36 – 7.22 (*m*, 5 H); 7.19 (br., 1 H); 5.94 (*dt*, $J = 4.3$, 18.8, 1 H); 5.84 (*d*, $J = 18.8$, 1 H); 4.54 (*d*, $J = 4.3$, 2 H); 4.10 (*d*, $J = 5.3$, 2 H); 0.04 (*s*, 9 H). ^{13}C-NMR (50.32 MHz, $CDCl_3$): 169.72; 167.66; 138.46; 134.11; 133.66; 131.59; 128.41; 127.11; 67.52; 41.74; -1.58. CI-MS (NH_3): 292 (10, $[M + H]^+$), 276 (5), 236 (8), 206 (19), 162 (41), 105 (21), 73 (100).

3.5. *(*E*)-1-Methyl-3-(trimethylsilyl)prop-2-en-1-yl* N-*(*tert*-Butoxycarbonyl)glycinate* (**12mb**). FC (SiO_2; AcOEt/pentane 1 : 4) gave a colorless oil (9.0 g, 30 mmol, 82%). IR: 3375, 2959, 2980, 1753, 1721, 1518, 1170. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.91 (*dd*, $J = 4.3$, 18.9, 1 H); 5.77 (*d*, $J = 18.9$, 1 H); 5.31 (*m*, 1 H); 5.18 (br. *s*, 1 H); 3.84 (*d*, $J = 5.5$, 2 H); 1.37 (*s*, 9 H); 1.24 (*d*, $J = 6.5$, 3 H); 0.01 (*s*, 9 H). ^{13}C-NMR (50.32 MHz, $CDCl_3$): 169.49; 155.61; 143.86; 131.09; 79.70; 73.35; 42.52; 28.19; 19.66; -1.57. CI-MS (NH_3): 214 (8), 120 (42), 73 (100), 57 (71).

3.6. *(*E*)-1-Methyl-3-(trimethylsilyl)prop-2-en-1-yl* N-*(Benzyloxycarbonyl)glycinate* (**12mc**). FC (SiO_2; AcOEt/pentane 1.4) gave a colorless oil (8.71 g, 26 mmol, 76%). ^{1}H-NMR: 7.32 – 7.24 (5 H); 5.96 (*dd*, $J = 4.8$, 18.8, 1 H); 5.83 (*d*, $J = 18.8$, 1 H); 5.06 (*s*, 2 H); 5.3 (br. *s*, 1 H); 5.38 (*m*, 1 H); 3.94 (*d*, $J = 5.4$, 2 H); 1.28 (*d*, $J = 6.5$, 3 H); 0.49 (*s*, 9 H). ^{13}C-NMR (50.32 MHz, $CDCl_3$): 169.13; 156.20; 143.81; 136.24; 131.33; 128.41;

128.04; 127.95; 73.59; 66.92; 42.89; 19.67; -1.57. CI-MS (NH$_3$): 353 (10, $[M+\mathrm{NH_4}]^+$), 336 (20, $[\mathrm{M}+\mathrm{H}]^+$), 291 (18), 268 (42), 227 (6), 210 (40), 108 (28), 91 (45), 73.

3.7. *(*E*)-3-[(Isopropyl)dimethylsilyl]prop-2-en-1-yl* N-*(*tert-*Butoxycarbonyl)glycinate* (**12pb**). FC (SiO$_2$; AcOEt/pentane 1:4) gave a colorless oil (7.2 g, 22 mmol, 80%). IR: 3377, 1722, 1514, 1250, 1171. ^{1}H-NMR (200 MHz, CDCl$_3$): 5.98 (*dd*, $J=5.0$, 18.8, 1 H); 5.82 (*d*, $J=18.8$, 1 H); 5.41 – 5.33 (*m*, 1 H); 5.02 (br., 1 H); 3.90 (*d*, $J=3.4$, 2 H); 1.44 (*s*, 9 H); 1.30 (*d*, $J=6.5$, 3 H); 0.92 (*d*, $J=7.1$, 6 H); 0.81 – 0.72 (*m*, 1 H); 0.01 (*s*, 6 H). ^{13}C-NMR (50.32 MHz, CDCl$_3$): 169.79; 155.93; 145.24; 129.39; 80.13; 73.91; 42.91; 28.54; 20.12; 17.67; 13.68; -5.22. EI-MS: 330 (22, $[M+\mathrm{H}]^+$), 274 (11), 230 (95), 176 (78), 73 (30), 57 (100). CI-MS: 347, ($[M+\mathrm{NH_4}]^+$).

4. *Ester Enolate* Claisen *Rearrangement*. *Method A*. The silylated allyl ester (1 mmol) was added to a freshly prepared soln. of LDA (2.5 mmol) in THF (5 ml). Me$_3$SiCl (0.38 ml, 3 mmol) was added after 3 min. The resulting yellow soln. was diluted with AcOEt and hydrolyzed with 1N aq. HCl soln. The aq. layer was extracted with AcOEt (2 × 5 ml), the combined org. layers were dried (MgSO$_4$), and the solvent was removed *in vacuo*.

Method B. To a soln. of potassium hexamethyldisilazide (KHMDS) in anh. THF (25 ml) at $-78°$ was added Me$_3$SiCl. After 5 min, a soln. of the ester in THF (2 ml) was added dropwise. The mixture was allowed to warm to r.t. overnight, mixed with 1N aq. HCl soln., stirred for 10 min, and extracted with sat. NaHCO$_3$ soln. (2 ×).

Method C. A soln. of lithium hexamethyldisilazide (LHMDS) in hexanes (1.0M, 3.3 ml, 3.3 mmol) in anh. THF (2 ml) at $-78°$ was added to the allyl ester (0.37 g, 1.3 mmol). After 3 min, Me$_3$SiCl (0.49 ml, 0.39 mmol) was added, followed by Et$_3$N (0.54 ml, 0.39 mmol). The soln. was stirred for 10 min, the cooling bath was removed, the soln. was diluted with AcOEt (2 ml) and 1N HCl soln. (4 ml), and stirred vigorously for 10 min. The aq. layer was extracted with AcOEt (2 × 5 ml). The combined org. layers were dried over MgSO$_4$, and the solvent was removed *in vacuo*.

Esterification of Crude Products. To a soln. of the crude carboxylic acid in MeOH (10 ml), obtained by *Methods A – C*, was slowly added Me$_3$SiCHN$_2$ [24] *via* syringe until the yellow color persisted and evolution of N$_2$ gas stopped.

4.1. *Methyl (*E*)-2-[(*tert-*Butoxycarbonyl)amino]-3-(trimethylsilyl)pent-4-enoate* (**13mb**). FC (SiO$_2$; AcOEt/pentane 1:3 gave a colorless oil (0.35 g, 1.1 mmol, 85%). IR: 3443, 2957, 1741, 1251. ^{1}H-NMR (300 MHz, CDCl$_3$): 5.55 (*m*, 1 H); 5.12 (*s*, 1 H); 4.97 (*dd*, $J=16.8$, 10.7, 2 H); 4.37 (*m*, 1 H); 3.65 (*s*, 3 H); 1.91 (*dd*, $J=8.6$, 16.0, 1 H); 1.38 (*s*, 9 H); 0.03 (*s*, 9 H). ^{13}C-NMR (75 MHz, CDCl$_3$): 172.68; 154.98; 134.05; 116.79; 79.86; 53.75; 51.77; 39.75; 28.30; -2.54. CI-MS (NH$_3$): 318 (5, $[M+\mathrm{NH_4}^+]$), 302 (5), 246 (14), 202 (4), 186 (27), 112 (92), 73 (94), 57 (100). HR-MS: 302.1775 ($\mathrm{C_{14}H_{28}NO_4Si^+}$; calc. 302.1788).

4.2. *Methyl (*E*)-2-[(*tert-*Butoxycarbonyl)amino]-3-[(*tert-*butyl)dimethylsilyl]pent-4-enoate* (**13bb**). FC (SiO$_2$; AcOEt/pentane 1:3) gave a colorless oil (0.14 g, 0.40 mmol, 40%). IR: 3444, 2957, 1718, 1491, 1366. ^{1}H-NMR (300 MHz, CDCl$_3$): 5.60 (*m*, 1 H); 5.32 (br., 1 H); 4.77 (*m*, 3 H); 3.25 (*s*, 3 H); 2.16 (*dd*, $J=6.9$, 16.8, 1 H); 1.42 (*s*, 9 H); 0.90 (*s*, 9 H); 0.12 (*s*, 3 H); 0.01 (*s*, 3 H). ^{13}C-NMR (75 MHz, CDCl$_3$): 172.11; 155.11; 135.81; 117.59; 79.44; 54.60; 51.17; 37.16; 27.46; 27.28; 18.56; -6.80; -7.79. EI-MS: 344 ($[M+\mathrm{H}]^+$), 287 (2), 270 (3), 230 (32), 170 (21), 154 (16), 118 (44), 81 (53), 73 (100), 57 (89), 41 (33). HR-MS: 344.2257 ($[M+\mathrm{H}]^+$, $\mathrm{C_{17}H_{34}NO_4Si}$; calc. 344.1762).

4.3. *Methyl (*E*)-2-[(*tert-*Butoxycarbonyl)amino]-3-[(dimethyl)phenylsilyl]pent-4-enoate* (**13ab**). FC (SiO$_2$; AcOEt/pentane) gave a colorless oil (0.62 g, 0.25 mmol, 65%). IR: 3441, 2984, 1742, 1373, 1242. ^{1}H-NMR (300 MHz, CDCl$_3$): 7.50 (*d*, $J=3.4$, 2 H); 7.19 (*m*, 3 H); 5.59 (*m*, 1 H); 5.02 (*dd*, $J=1.6$, 10.1, 1 H); 4.90 (br., 1 H); 4.90 (*dd*, $J=1.2$, 16.9, 1 H); 4.37 (br. *m*, 1 H); 3.53 (*s*, 3 H); 2.18 (*dd*, $J=6.4$, 10.3, 1 H); 0.98 (*s*, 9 H); 0.04 (*s*, 6 H). ^{13}C-NMR (75 MHz, CDCl$_3$): 172.54; 154.87; 137.01; 134.07; 129.24; 127.78; 117.04; 79.78; 54.01; 51.64; 39.40; 28.30; -3.85; -4.19. EI-MS: 364 (32, $[M+\mathrm{H}]^+$), 308 (26), 264 (54), 230 (100), 186 (15), 170 (66), 135 (142), 81 (17), 69 (9). HR-MS: 364.1944 ($\mathrm{C_{17}H_{33}NO_4Si^+}$; calc. 364.1589).

4.4. *Methyl (*E*)-2-[(*tert-*Butoxycarbonyl)amino]-3-(trimethylsilyl)hex-4-enoate* (**14mb**). FC (SiO$_2$; AcOEt/pentane 1:3) gave a colorless oil (0.43 g, 1.4 mmol, 92%). IR: 3439, 2980, 1710, 1497, 1250, 842. ^{1}H-NMR (75 MHz, CDCl$_3$): 5.39 (*m*, 1 H); 5.17 (*m*, 1 H); 5.02 (br., 1 H); 4.35 (br., 1 H); 3.70 (*s*, 3 H); 1.83 (*dd*, $J=5.7$, 10.6, 1 H); 1.67 (*d*, $J=6.3$, 3 H); 1.43 (*s*, 9 H); 0.05 (*s*, 9 H). ^{13}C-NMR (75 MHz, CDCl$_3$): 169.49; 155.61; 143.85; 131.09; 79.70; 73.35; 51.81; 53.52; 28.20; 19.66; -1.57. EI-MS: 316 (2, $[M+\mathrm{H}]^+$), 198 (6), 156 (5), 134 (21), 111 (82), 95, 73 (80), 57 (100). HR-MS: 316.1638 ($\mathrm{C_{15}H_{23}NO_4Si^+}$; calc. 316.1688).

4.5. *Methyl (*E*)-2-[(*tert-*Butoxycarbonyl)amino]-3-[(isopropyl)dimethylsilyl)hex-4-enoate* (**14pb**). FC (SiO$_2$; AcOEt/pentane 1.3) gave a colorless oil (0.41 g, 1.2 mmol, 78%). ^{1}H-NMR (300 MHz, CDCl$_3$): 5.38 – 2.24 (*m*, 1 H); 5.17 – 5.08 (*m*, 1 H); 5.02 – 4.49 (*m*, 1 H); 4.26 (br., 1 H); 3.61 (*s*, 3 H); 1.88 (*dd*, $J=6.0$, 10.8, 1 H); 1.60 (*d*, $J=5.1$, 3 H); 1.36 (*s*, 9 H); 0.86 (*d*, $J=6.5$, 6 H); 0.74 (*m*, 1 H); 0.03 (*s*, 6 H). ^{13}C-NMR (75 MHz, CDCl$_3$): 172.79; 154.94; 127.72; 126.36; 79.70; 53.93; 51.59; 35.71; 28.27; 17.62; 17.47; 12.00; -6.64. EI-MS: 344

(6, $[M+H]^+$), 288 (22), 270 (7), 244 (24), 126 (43), 95 (100), 73 (70), 57 (100). HR-MS: 344.225 ($[M+H]^+$, $C_{17}H_{34}NO_4Si$; calc. 344.224).

4.6. *Methyl (*E*)-2-[Benzyloxycarbonyl)amino]-3-(trimethylsilyl)hex-4-enoate* (**14mc**). FC (SiO_2; AcOEt/pentane 1:3) gave a colorless oil (0.36 g, 1.0 mmol, 80%). IR: 3351, 2955, 1726, 1503, 1250, 842. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.25 (*m*, 5 H); 5.36 (*m*, 2 H); 5.08 (*m*, 3 H); 4.35 (br., 1 H); 3.64 (*s*, 3 H); 1.81 (*dd*, $J = 5.4$, 10.6, 1 H); 1.61 (*dd*, $J = 1.4$, 6.4, 3 H); 0.05 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.29; 155.48; 136.29; 128.41; 128.18; 128.07; 125.67; 66.83; 54.29; 51.73; 38.03; 29.60; 16.40; −2.54. EI-MS: 350 (4, M^+), 290 (3), 258 (5), 199 (3), 91 (100), 73 (51).

4.7. *Methyl (*E*)-2-[(Benzoyl)amino]-3-(trimethylsilyl)hex-4-enoate* (**14mz**). FC (SiO_2; AcOEt/pentane 1:3) gave a colorless oil (0.22 g, 0.71 mmol, 71%). IR: 3351, 2955, 1744, 1652, 1526, 1249. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.29 (*m*, 5 H); 5.33 (*m*, 1 H); 5.23 (*m*, 1 H); 5.06 (*m*, 2 H); 4.37 (br. *m*, 1 H); 3.65 (*s*, 1 H); 1.80 (*dd*, $J =$ 5.4, 10.7, 1 H); 1.61 (*dd*, $J = 1.2$, 6.3, 3 H); −0.03 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.20; 166.39; 133.90; 131.50; 128.44; 128.15; 127.89; 126.88; 125.95; 52.85; 51.78; 37.92; 17.99; −2.52.

REFERENCES

[1] G. B. Bennett, *Synthesis* **1977**, 589; S. Pereira, M. Srebnik, *Aldrichimica Acta* **1993**, *26*, 17.

[2] R. E. Ireland, R. H. Mueller, *J. Am. Chem. Soc.* **1972**, *94*, 5897.

[3] R. E. Ireland, A. K. Willard, *Tetrahedron Lett.* **1975**, *16*, 3975.

[4] H. Nemoto, A. Satoh, M. Ando, K. Fukumoto, *J. Chem. Soc., Chem. Commun.* **1990**, 1001.

[5] A. Y. Mohammed, D. L. J. Clive, *J. Chem. Soc., Chem. Commun.* **1986**, 588; A. G. Cameron, D. W. Knight, *J. Chem. Soc., Perkin Trans. 1* **1986**, 161.

[6] R. E. Ireland, D. W. Norbeck, *J. Am. Chem. Soc.* **1985**, *107*, 3279.

[7] R. E. Ireland, C. S. Wilcox, S. Thaisrivongs, N. R. Vanier, *Can. J. Chem.* **1979**, *57*, 1743.

[8] Z. Wang, *Tetrahedron Lett.* **1989**, *30*, 6611; S. D. Burke, K. Takeuchi, C. W. Murtiashaw, D. W. M. Liang, *Tetrahedron Lett.* **1989**, *30*, 6299.

[9] M. M. Abelman, R. L. Funk, J. D. Munger Jr., *J. Am. Chem. Soc.* **1982**, *104*, 4030.

[10] S. L. Schreiber, D. B. Smith, *J. Org. Chem.* **1989**, *54*, 9.

[11] M. J. Fisher, C. D. Myers, J. Jogler, S.-H. Chen, S. J. Danishefsky, *J. Org. Chem.* **1991**, *56*, 5826.

[12] R. E. Ireland, J. P. Vervet, *J. Org. Chem.* **1980**, *45*, 4259.

[13] D. Seebach, A. R. Sting, M. Hoffmann, *Angew. Chem., Int. Ed.* **1997**, *35*, 2708.

[14] M. Johnston, R. Raines, M. Chang, N. Esaki, K. Soda, C. Walsh, *Biochemistry* **1981**, *20*, 4325; T. Wirth, in 'Organic Synthesis Highlight IV', Ed. H.-G. Schmalz, Wiley, Weinheim, 2000, p. 26–33.

[15] I. Fleming, A. Barbero, D. Walter, *Chem. Rev.* **1997**, *97*, 2063.

[16] M. A. Brook, 'Silicon in Organic, Organometallic, and Polymer Chemistry', Wiley, New York, 2000, Chapt. 16, p. 552–607.

[17] R. E. Ireland, R. H. Mueller, A. K. Willard, *J. Am. Chem. Soc.* **1976**, *98*, 2868.

[18] P. A. Bartlett, J. F. Barstow, *J. Org. Chem.* **1982**, *47*, 3933.

[19] J. S. Panek, N. F. Jain, *J. Org. Chem.* **1994**, *59*, 2674; J. S. Panek, M. Yang, J. S. Solomon, *J. Org. Chem.* **1993**, *58*, 1003; J. S. Panek, M. Yang, *J. Am. Chem. Soc.* **1991**, *113*, 6594.

[20] M. Mohamed, M. A. Brook, *Tetrahedron Lett.* **2001**, *42*, 191.

[21] S. E. Denmark, T. K. Jones, *J. Org. Chem.* **1982**, *47*, 4595.

[22] U. Kazmaier, *Angew. Chem., Int. Ed.* **1994**, *33*, 998; U. Kazmaier, *Amino Acids* **1996**, *11*, 283; U. Kazmaier, in 'Bioorganic Chemistry', Ed. U. Diederichsen, Wiley-VCH, Weinheim, 1999, p. 201–206; U. Kazmaier, S. Maier, F. L. Zumpe, *Synlett* **2000**, 1523.

[23] U. Kazmaier, *Liebigs Ann./Recl.* **1997**, 285.

[24] A. Plazonnet, W. J. Vandenheuvel, *J. Chromatogr.* **1977**, *142*, 587.

[25] E. Vedejs, M. Gingras, *J. Am. Chem. Soc.* **1994**, *116*, 579.

[26] H. M. Hull, D. W. Knight, *J. Chem. Soc., Perkin Trans. 1* **1997**, 857.

[27] M. A. Sparks, J. S. Panek, *J. Org. Chem.* **1991**, *56*, 3431.

[28] C. S. Wilcox, R. E. Babston, *Tetrahedron Lett.* **1989**, *30*, 447.

[29] D. Seebach, R. Amstutz, T. Laube, W. B. Schweizer, J. D. Dunitz, *J. Am. Chem. Soc.* **1985**, *107*, 5403.

[30] T. Mukhopadhyay, D. Seebach, *Helv. Chim. Acta* **1982**, *65*, 385.

[31] R. E. Ireland, P. Wipf, J. D. Armstrong III, *J. Org. Chem.* **1991**, *56*, 650.

[32] P. A. Bartlett, D. J. Tanzella, J. F. Bastrow, *J. Org. Chem.* **1982**, *47*, 3941.

[33] T. Sato, K. Tajima, T. Fujisawa, *Tetrahedron Lett*. **1983**, *24*, 729.
[34] S. D. Burke, W. F. Forbare, G. Pacofsky, *J. Org. Chem*. **1983**, *48*, 5221.
[35] D. Seebach, W. Prelog, *Angew. Chem., Int. Ed*. **1982**, *21*, 654.
[36] M. A. Brook, D. Seebach, *Can. J. Chem*. **1987**, *65*, 836.
[37] R. K. Hill, 'Asymmetric Synthesis: Stereodifferentiating Addition Reactions', Part B, Ed. J. D. Morrison, Academic Press, New York, 1984, Vol. 3, Chapt. 8, p. 503.
[38] T. J. Gould, M. Balestra, M. D. Wittman, J. A. Gary, T. Lucius, T. Rossano, J. Kallmerten, *J. Org. Chem*. **1987**, *52*, 3889.
[39] M. A. Brook, 'Silicon in Organic, Organometallic, and Polymer Chemistry', Wiley, New York, 2000, Chapts. 4, 5, p. 97 – 141.
[40] R. J. P. Corriu, J. C. Young, in 'The Chemistry of Organosilicon Compounds', Eds. S. Patai, Z. Rappoport, Wiley, Chichester, 1989, Chapt. 20.
[41] MM2, using *Hyperchem 5.01*, Gainesville, Florida.
[42] V. Aviyente, H. Y. Yoo, K. N. Houk, *J. Org. Chem*. **1997**, *62*, 6121; H. Y. Yoo, K. N. Houk, *J. Am. Chem. Soc*. **1994**, *116*, 12047.

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