α-(DISILYLALLENYL) α-AMINO ACID DERIVATIVES FROM THE CLAISEN REARRANGEMENT OF PROPARGYL GLYCINATES

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Dedicated to Dr. Alfred Bader on the occasion of his 85th birthday.
Alfred Bader is probably not aware of the impact he had on my development as a chemist: he played a seminal role. Through several "Please Bother Us" interactions I had with him as a graduate student and then Assistant Professor, I learned as enormous amount about the chemistry enterprise – both the academic life and the industrial counterpart from someone who saw chemistry holistically. I thank him for sharing his vision and enthusiasm for chemistry with me then and many times since and I wish him the very best on this birthday and beyond.

Silylpropargyl glycinate esters undergo [3,3]-sigmatropic rearrangements to give 2-(disilylallenyl)glycine derivatives, interesting highly functional synthons, in moderate to good yield (30 to 85%) and in high diastereoselectivity when directed by a large silylpropargyl group (9:1 to 22:1). The highly functional amino acid, methyl (*R*)-2-(Boc-amino)-3,5-bis-(trimethylsilyl)hexa-3,4-dienoate was isolated and characterized by X-ray crystal structure analysis.

Keywords: Allenes; [3,3]-Sigmatropic rearrangements; Claisen rearrangement; Amino acids; Propargyl esters.

Aminoallenes can exhibit interesting biological activities, and they are also versatile intermediates for the synthesis of azacycles[1], as demonstrated by several groups[2]. For example, both the Ibuka and Hiemstra groups have developed synthetic strategies for the preparation of aminoallenes and further demonstrated that Pd-catalyzed intramolecular cyclizations of aminoallenes lead to substituted pyrrolines in high yields and with good enantioselect-

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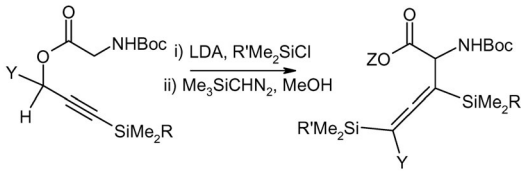
ivity[3]. The compounds can also be starting materials for unnatural amino acids. Kazmaier and co-workers have reported a variation of the ester Claisen rearrangement that they developed using $ZnCl_2$ and other chelating metal salts, which led to 2-allenylglycines[4].

Having previously synthesized allylsilane-modified amino acids via the Claisen rearrangement[5], we sought to develop analogous synthetic routes to aminoallenes which additionally contained a silyl group that could be subsequently exploited synthetically[6]. It was envisaged that the compounds could be interesting in their own right, lead to functional heterocycles or be converted into highly functional, unnatural amino acids. Initially, the method of Kazmaier was employed to effect the Claisen rearrangement of propargyl glycinates **1** and **2** (Table I). The starting glycine esters were accessible from the condensation of *N*-protected amino acid and the corresponding propargyl alcohol using DCC and DMAP[7]. Ester **1** was added to a freshly prepared solution of LDA, followed by the addition of $MgBr_2$ in THF solution. Reactions were sluggish at –78 °C, and even after warming to room temperature overnight, a very low product yield was obtained due to

TABLE I
Rearrangements of propargyl glycinates to 2-allenylglycinates



1, **2**, **5**, **8** **3**, **4**, **6**, **7**, **8**

Propargyl glycinate	Y	R	Z	LDA equiv.	R′[a]	2-Allenyl glycinate (yield), *syn*:*anti*
1[b]	H	Me	H	2.5	Me	**3** (10 %)
2[b]	H	i-Pr	H	3.0	Me	**4** (30 %)
5[c]	Me	Me	Me	2.5	Me	complex mixture
	Me	Me	Me	3.5	Me	**6** (85 %), 12:1 (**6a**:**6b**)
	Me	Me	Me	3.5	i-Pr	**7** (72 %), 22:1
8[c]	i-Pr	Me	Me	3.5	Me	**9** (78 %), 9:1

[a] Of the trapping reagent, R′Me_2SiCl. [b] Step (i) only, Y, Z = H. [c] Steps (i) and (ii), Y, Z = Me.

competing deprotection of the Boc group. Other groups have also reported a lack of success in the Ireland–Claisen rearrangement of propargylic esters[8] due to competitive deprotonation of the propargylic proton.

Marginal improvements in the outcome were obtained when chlorosilane traps were utilized to capture the propargyl ion generated, following the precedent of Fujisawa et al.[9] (Table I). Treatment of ester **1** with 2.5 equivalents of freshly prepared LDA in THF at –78 °C, followed after 24 h by the addition of chlorotrimethylsilane to quench the dianion, gave a mixture of products that included 10% of the desired product **3**, and 30% of recovered starting ester. Increasing the amount of base used, from 2.5 to 3 equivalents, at –78 °C, then warming up to room temperature after 5 h gave a slightly improved yields of this mixture of starting materials and product **1**. The rearrangement of **2** to **4** occurred in marginally better yield, but was still unacceptable. Trying to increase the rate of these reactions by increasing reaction temperature or the amount of LDA led instead to extensive degradation.

On the assumption that degradation pathways were associated with secondary deprotonation at the propargylic site, the reaction was attempted with α-methyl-substituted propargyl glycinate esters **5** and **6**, respectively: the presence of the α-methyl group increased both reaction rate and yield. The Ireland–Claisen rearrangement was initiated by LDA addition, and the reaction was then quenched with trialkylchlorosilane at –78 °C. To facilitate isolation, the carboxylic acid product was converted to its methyl ester with diazotrimethylsilylmethane in MeOH prior to workup. GC analysis of the crude reaction mixture of **6**, derived from **5**, showed a 12:1 ratio of two

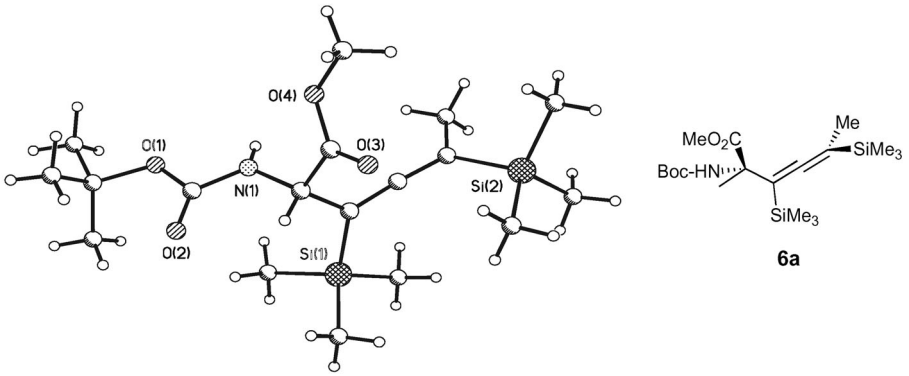


FIG. 1
X-ray crystal structure data for **6a**

diastereoisomeric products **6a** and **6b** (Scheme 1, Table I). The major isomer **6a**, after chromatographic purification, exhibited two distinct TMS groups in the ^{1}H NMR. Thus, deprotonation of the propargyl group had occurred and the resulting anion was trapped with chlorotrimethylsilane. While it was difficult to assign the relative stereochemistry and structure of the product from ^{1}H and ^{13}C NMR data alone, the structure of the major α-[bis(trimethylsilyl)allenyl] α-amino acid product **6a** was determined using X-ray single crystal analysis of colorless crystals after recrystallization from hexane (Tables I and II, Fig. 1)[10]. Very few allenes, and no disilyl-substituted allenes, have been crystallographically characterized.

The reaction likely proceeds via deprotonation of the amide, α-ester and propargyl sites (even with reduced amounts of LDA, ~2.0–2.5 equivalents, and low temperature) followed by silylation of all sites and then, on heating, the rearrangement (Scheme 1). Better proof that the propargyl anion was initially trapped by the chlorosilane came from two complementary reactions in which the terminal silyl group was distinct from the trapping silyl group. For example, trimethylsilyl-substituted ester **5**, when trapped with i-PrMe_2SiCl gave rearranged product **7** in 72% yield with 22:1 diastereoselectivity. However, attempts to further bias the reaction sterically, using bulkier chlorosilanes such a *t*-BuMe_2SiCl and PhMe_2SiCl as trapping agents, led to recovered starting material.

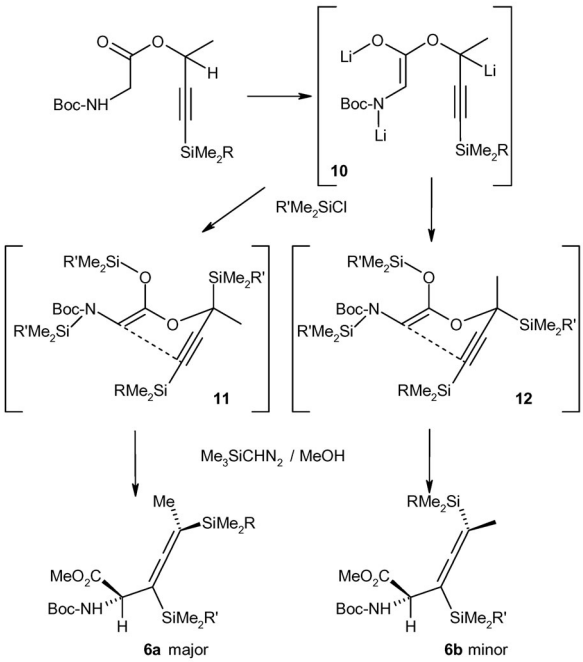
The dominant controlling feature in this reaction is the difference in bulkiness between the methyl and silyl groups at the propargylic site adjacent to oxygen (Scheme 1). The larger the difference, the higher the diastereoselectivity. By contrast, increasing the bulkiness of the silyl group at the alkynyl carbon led to a decrease in diastereoselectivity: isopropylsilyl-

TABLE II
Key bond lengths (in Å) and angles (in °) for **6a** [12]

Si(1)–C(9)	1.8821(14)
C(9)–C(13)	1.3127
C(13)–C(14)	1.3052
Si(2)–C(14)	1.8712(15)
C(14)–C(15)	1.522(2)
C(13)–C(9)–Si(1)	117.92(11)
C(14)–C(13)–C(9)	176.19(15)
C(13)–C(14)–Si(2)	118.74

substituted ester **8** rearranged to **9**, when trapped with Me_3SiCl, giving a good yield (78%, diastereoselectivity 9:1) (Table I). Compounds **7** and **9** have identical GC retention times and almost superimposable NMR spectra. Changes in the nature of the nitrogen protecting group were unhelpful in enhancing diastereoselectivity: attempts to perform the Ireland–Claisen rearrangement on Cbz- and Bz-protected glycinate esters led only to recovery of starting materials.

The observed high diastereoselectivity of the product can be explained by comparison of the likely transition states for the rearrangement. The stereoselectivity is dependent on the configuration of the enolate double bond[11]. Formation of the (*Z*)-silylketene acetal is facilitated by chelating ability of the amine group. Assuming that rearrangement occurs after silylation at the α position, one would anticipate that the most sterically demanding substituents, the α-silyl group ($SiMe_2R'$), would adopt a pseudoequatorial position in a chair-like transition state **12** (Scheme 1). However, the major product derives from the axial (*Z*)-silylketene acetal transition state, where



SCHEME 1
Rearrangement of propargyl glycinates

the R_3Si group is axially disposed **11**. The preferential formation of this isomer can similarly be ascribed to chelation, by enolate oxygen of the α-alkyllithium in the lithiated precursor **10**.

The key attraction of the preparation of compounds such as **6**, **7**, and **9** is the high degree of functionality in very compact structures. It should be possible to discriminate on steric grounds between the two different silyl groups in compounds such as **7** and **9** and sequentially elicit reactivity. Moreover, the established regio- and stereochemical control in the reaction of allenylsilanes should be applicable to the synthesis of a variety of complex unnatural amino acids[13]. Examination of such possibilities will form the basis of future work.

EXPERIMENTAL

Synthesis of Propargyl Glycinates. General Procedure

An oven-dried 250-ml round-bottomed flask equipped with a magnetic stirring bar was charged with silylated propargyl alcohol (20 mmol) and DMAP (0.24 g, 2.0 mmol). The flask was sealed with a rubber septum and dry dichloromethane CH_2Cl_2 (20 ml) was added. The resulting clear solution was allowed to stir at room temperature for 15 min. DCC (4.1 g, 20 mmol) in CH_2Cl_2 (10 ml) was added via syringe. The mixture was allowed to stir at 0 °C for 15 min before *N*-Boc-glycine (3.78 g, 20 mmol) in CH_2Cl_2 (10 ml) was added via syringe. The mixture was allowed to warm up to room temperature overnight. The precipitated urea was filtered off and the resulting clear yellow solution was washed with saturated $NaHCO_3$. After drying with anhydrous $MgSO_4$, the solvent was removed in vacuo. The crude product was purified by flash chromatography.

Ester **1**. The compound was purified on silica gel (EtOAc/pentane 1:5) yielding 4.33 g (15 mmol, 75%) of the ester. ^{1}H NMR (200 MHz, $CDCl_3$): 5.08 b, 1 H; 4.66 s, 2 H; 3.86 d, J = 5.5 Hz; 1.37 s, 9 H; 0.095 s, 9 H. ^{13}C NMR (50 MHz, $CDCl_3$): 169.88, 155.87, 98.47, 92.82, 80.18, 53.55, 42.50, 28.44, –0.21. IR, ν_{max} (cm^{-1}): 3384, 2943, 1722, 1517. EIMS: 286 $(M + H)^+$, 214 (10), 111 (41), 91 (30), 73 (100), 59 (5).

Ester **2**. The compound was purified on silica gel (EtOAc/hexanes 1:5) yielding 4.38 g (14 mmol, 80%) of the ester. ^{1}H NMR (200 MHz, $CDCl_3$): 5.00 bs, 1 H; 4.75 s, 2 H; 3.94 d, $_3J$ = 4.2 Hz, 2 H; 1.44 s, 9 H; 0.98 d, $_3J$ = 7.1 Hz, 6 H; 0.88–0.77 m, 1 H; 0.11 s, 9 H. ^{13}C NMR (50 MHz, $CDCl_3$): 169.66, 155.58, 98.81, 91.32, 80.10, 53.44, 42.37, 28.27, 17.16, 13.64, –4.11. IR, ν_{max} (cm^{-1}): 3385, 2943, 1722, 1522. CIMS (NH_3): 331 $(M + NH_4^+)$, 314 (12), 275 (2), 258 (20), 214 (100), 170 (40), 93 (40), 76 (3).

Ester **5**. The compound was purified on silica gel (EtOAc/pentane 1:6) yielding 4.66 g (15 mmol, 82%) of the ester. ^{1}H NMR (200 MHz, $CDCl_3$): 5.49 q, $_3J$ = 6.4 Hz, 1 H; 4.62 b, 1 H; 3.99 bd, 2 H; 1.41 s, 9 H; 0.03 s, 9 H. ^{13}C NMR (50 MHz, $CDCl_3$): 169.20, 155.67, 102.82, 90.18, 80.0, 61.68, 42.54, 28.28, 21.45, –0.31. IR, ν_{max} (cm^{-1}): 3379, 2935, 2120, 1722. CIMS: 317 $(M + NH_4^+)$, 261 (8), 244 (2), 200 (5), 192 (5), 148 (3), 192 (20), 73 (46), 57 (100).

Ester **8**. The compound was purified on silica gel (EtOAc/pentane 1:5) yielding 4.25 g (13 mmol, 78%) of the ester. ^{1}H NMR (200 MHz, $CDCl_3$): 5.48 q, J = 6.6 Hz, 1 H; 5.01 b,

1 H; 3.88 d, *J* = 5.2 Hz, 1 H; 1.44 s, 9 H; 0.93 d, *J* = 6.7 Hz, 6 H; 0.90 m, 1 H. ^{13}C NMR (50 MHz, $CDCl_3$): 169.36, 155.80, 103.64, 88.80, 80.07, 61.80, 42.62, 28.40, 21.65, 17.31, 13.82, –3.93. IR, ν_{max} (cm^{-1}): 3384, 2943, 1722.

Propargyl Glycinate Rearrangement. General Procedure

In a typical experiment, freshly distilled diisopropylamine (1.72 ml, 12 mmol) was added to BuLi (7.50 ml of a 1.6 M solutions in hexanes, 12 mmol) in THF (2.0 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min, the cooling bath was removed and the reaction was stirred at room temperature for further 15 min. A solution of 1.3 M lithium diisopropylamide was cooled at –78 °C, and a solution of the ester (1.0 g, 3.5 mmol) in THF (1.0 ml) was added dropwise via syringe. After 3 min, trialkylchlorosilane (1.55 ml, 12.25 mmol) was added. The solution was stirred for 6 h and the cooling bath was removed. The solution was diluted with ethyl acetate (2 ml) and saturated $NaHCO_3$ solution (4 ml), and the mixture was stirred vigorously for 10 min. The aqueous layer was extracted with ethyl acetate (2 × 5 ml). Combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed in vacuo.

2-(Boc-amino)-5-(dimethylisopropylsilyl)-3-(trimethylsilyl)penta-3,4-dienoic acid **4**. ^{1}H NMR (300 MHz, $CDCl_3$): 5.29 s, 1 H; 4.99 bs, 1 H; 3.94 s, 1 H; 3.92 s, 1 H; 1.45 s, 9 H; 0.98 d, 6 H; 0.7–0.8 m, 1 H; 0.14 s, 9 H; 0.09 s, 6 H. ^{13}C NMR (75 MHz, $CDCl_3$): 206.05, 172.06, 154.97, 88.73, 86.21, 79.87, 53.28, 51.88, 28.45, 17.64, 14.72, 13.49, –1.82, –5.10. IR, ν_{max} (cm^{-1}): 3440, 2951, 1910, 1749. CIMS: 358 $(M + H)^+$ (3), 319 (22), 248 (12), 200 (17), 90 (100), 73 (78), 57 (13), 41 (21).

Methyl Esters

The crude carboxylic acid in methanol was treated with diazo(trimethylsilyl)methane until the yellow color persisted and the evaluation of N_2 gas stopped.

Methyl 2-(Boc-amino)-3,5-bis(trimethylsilyl)hexa-3,4-dienoate **6**. The product was purified on silica gel (EtOAc/pentane 1:5) yielding 1.1 g (2.84 mmol, 85%) of the ester. ^{1}H NMR (300 MHz, $CDCl_3$): 4.93 d, $_3J$ = 7.9 Hz, 1 H; 4.57 d, $_3J$ = 8.7 Hz, 1 H; 3.59 s, 3 H; 1.57 s, 3 H; 1.34 s, 9 H; 0.04 s, 9 H; –0.03 s, 3 H. ^{13}C NMR (75 MHz, $CDCl_3$): 205.39, 172.16, 155.06, 89.10, 87.90, 79.96, 53.19, 52.0, 28.56, 14.60, –0.77, –1.74. IR, ν_{max} (cm^{-1}): 3444, 2960, 1913, 1711. HRMS, *m/z*: found 385.21044, required 385.21034. R_F 0.7 (20% ethyl acetate/pentane).

Methyl 2-(Boc-amino)-5-(isopropyldimethylsilyl)-3-(trimethylsilyl)hexa-3,4-dienoate **7** *and methyl 2-(Boc-amino)-3-(isopropyldimethylsilyl)-5-(trimethylsilyl)hexa-3,4-dienoate* **9**. ^{1}H NMR (300 MHz, $CDCl_3$): 4.96 d, $_3J$ = 8.1 Hz, 1 H; 4.54 d, $_3J$ = 8.6 Hz; 3.58 s, 3 H; 1.57 s, 3 H; 1.33 s, 9 H; 0.63 s, 9 H. ^{13}C NMR (75 MHz, $CDCl_3$): 171.90, 154.94, 88.57, 86.02, 79.71, 53.09, 51.70, 28.28, 17.44, 14.55, 13.22, –2.00, –4.87, –5.28. IR, ν_{max} (cm^{-1}): 3448, 2957, 1913, 1747. EIMS: 414 $(M + H)^+$, 371 (13), 343 (2), 315 (9), 165 (6), 118 (20), 73 (100).

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12. The crystal data of **6a**: $C_{18}H_{35}NO_4Si_2$, MW = 385.65, monoclinic, P 1 21/*c* 1, *a* = 11.2578(7)Å, *b* = 22.0766(14)Å, *c* = 9.8463(6)Å, β = 116.480(1)°, *V* = 6181.7(1)Å^3, *Z* = 4, D_c = 1.312 g cm^{-3}, μ(Mo-Kα) = 0.083 mm^{-1}, *F*(00 0) = 2592, rectangular block, yellow, size = 0.5 × 0.16 × 0.345 mm, 6350 reflections measured (R_{int} = 0.0187), 5445 unique, *w*R2 = 0.1448 for all data, conventional *R* = 0.0501 [$(\Delta/\sigma)_{max}$ = 000)] on *F*-values of 8642 reflections with $I > 2\sigma(I)$, *S* = 0.944 for all data and 415 parameters. Unit cell determination and intensity data collection (2θ = 50 °C) were performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: XSCANS [Siemens Analytical X-ray Instrument Inc.: Madison, Wisconsin, USA 1996], SHELXTL-NT [Bruker AXS Inc.: Madison, Wisconsin, USA 1997]. CCDC (Deposit No: 620682) contains the supplementary crystallographic data. These data can be obtained free of charge from www.ccdc.cam.uk/conts/retrieving.html
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