# Studies in the Synthesis and Reactivity of New Chiral 1-[(Trialkylsilyl)-methyl]propenamides

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**Abstract:** A very simple sequence of reactions such as cross-metathesis using two catalysts and allylation to give the chiral hydroxyamide is described.

**Key words:** amino acids, peptides, cross-metathesis, allylation

One of the challenging goals of synthetic chemistry is the development of new reactions and strategies that allow for the facile conversion of simple functionalized compounds into complex molecules. The 'ideal synthesis' of these functionalized compounds requires the development of simple reactions from commercially available and inexpensive starting materials.[1] In the past decade, olefin metathesis has emerged as a powerful tool for the formation of carbon–carbon bonds.[1] The development of the metathesis reaction greatly advanced the chemistry of natural product synthesis and facilitated the discovery of new methodologies.

This was made possible with the development of Ru-based catalysts, such as **I**[2] and **II**[3,4] (Figure 1), the former being used primarily for ring-closing metathesis. Recently catalyst **I** has been used in cross-metathesis reactions and was more reactive than catalyst **II**[5] (Figure 1).

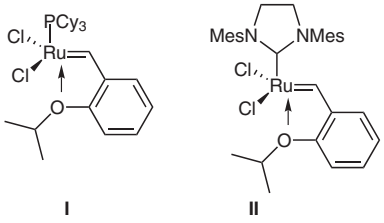
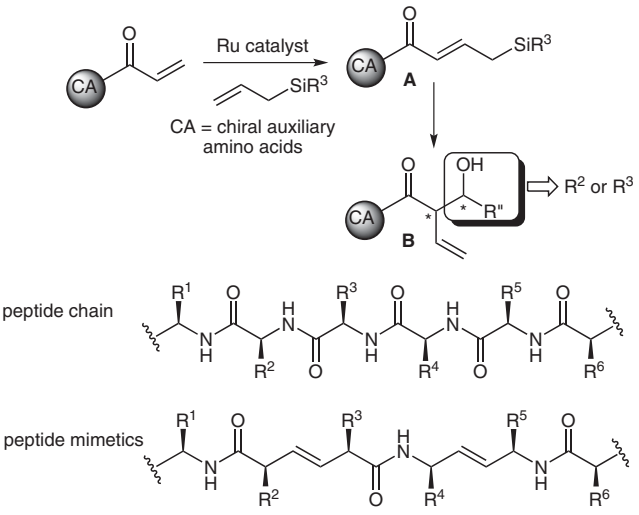



**Figure 1**

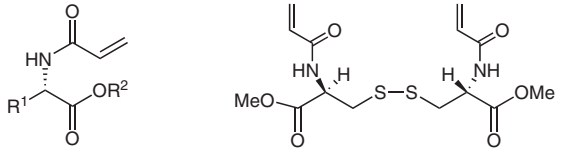
The stereogenic center of the amino acid subunit of allylsilane **A** can induce diastereoselectivity in the reaction mechanism. With the objective of synthesizing the peptide mimetics[6] shown in Scheme 1 via cross-metathesis reaction of hydroxyamide **B**, we chose to explore the auxiliary stereogenic center of amino esters derived from natural amino acids. Herein, we report a direct synthesis of allylsilanes **A** through a cross-metathesis of acryl amides and allyl trialkylsilanes via first-generation catalysts. The




**Scheme 1**

cross-metathesis reaction of acrylamides has been reported previously by exploiting Grubbs' second-generation catalysts.[7,8]

The synthesis of chiral acrylamides **1**–**4** was carried out by known procedures starting from commercially available (*S*)-amino esters. The acrylamide **5** was prepared in two steps from L-cystine [(*R*,*R*)-3,3′-dithiobis(2-aminopropionicacid, Figure 2].[9]




**1** $R^1 = (CH_3)_2CHCH_2$, $R^2$ = Me
**2** $R^1 = (CH_3)_2CH$, $R^2$ = Me
**3** $R^1$ = 3-indolylCH$_2$, $R^2$ = Me
**4** $R^1 = PhCH_2$, $R^2$ = Et
**4'** $R^1 = PhCH_2$, $R^2$ = Me

**Figure 2**

Preliminary cross-metathesis studies were performed on acrylamides **1**–**4** with allyltrimethylsilane (3 equiv) in the presence of catalyst **II** (5 mol%) at a concentration of 0.2 M in $CH_2Cl_2$ for 16 h. Under these conditions, products **6**–**9** were obtained in moderate yields (48–65%, Table 1, entries 1–4). After purification, we obtained compounds in high *E*-stereoselectivity.[10] Some starting materials were

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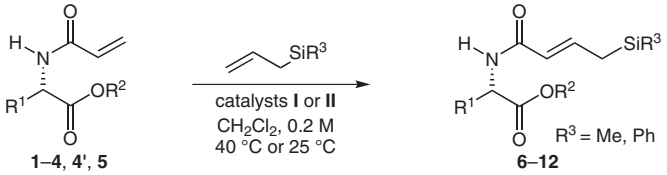
recovered. No reports detail the use of first-generation Hoveyda–Grubbs catalysts in cross-metathesis of acrylic amide to olefinic substrates. The comparison of two catalysts **I** and **II** was reported by Hoveyda.[3] The differences between these two catalytic systems are likely due to higher electron density at the transition-metal center of catalyst **II**, caused by the stronger electron donation by the heterocyclic ligand (relative to $PCy_3$).[3] In spite of these differences, we explored the potential of the more readily available catalyst **I** in cross-metathesis reactions.

When substrate **4** was treated with three equivalents of allyltrimethylsilane, the desired product **9** was obtained in acceptable yields depending on the reaction conditions. The methyl derivative product **9′** was obtained from **4′** under the same conditions, and the results are reported in Table 1 (entries 5–8). In order to examine fully the scope of this reaction, it was necessary to modify the allylsilane constituents, such as using allyltriphenylsilane, which has a different reactivity in allylation reactions than allyltrimethylsilane. These reactions were performed at reflux in dichloromethane ($CH_2Cl_2$) in the presence of 5 mol% of catalyst **I**. Several acrylamide compounds were tested in the cross-metathesis reaction with allylsilanes, and the results are reported in Table 1 (entries 9–11). The reaction of compound **1** with allyltriphenylsilane produced allylamide **10** in a disappointingly low yield of 43%. However, an excellent *E*/*Z* stereoselectivity of 20:1 was observed. When acrylamides **2** and **3** were likewise combined with allyltriphenylsilane, the corresponding allylamides **11** and **12** were obtained in 49% and 51% yields, respectively, with an *E*/*Z* stereoselectivity of greater than 20:1.

**Table 1** Screening of Acrylamide, Olefin Partner, and Catalysts




**1–4, 4', 5** **6–12**

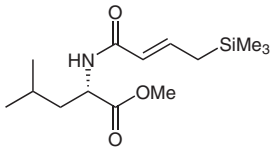
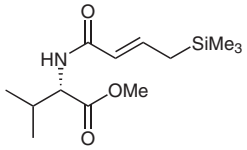
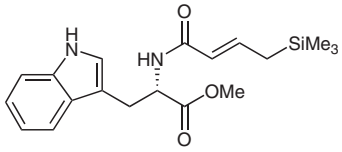
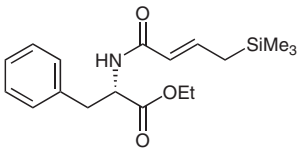
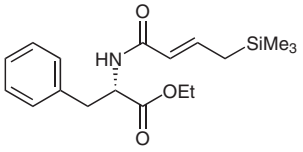
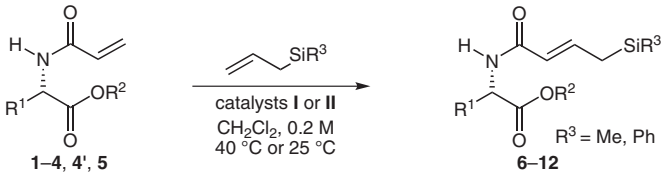
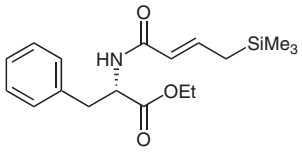
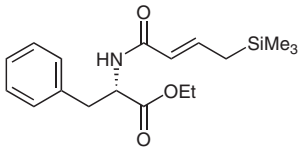
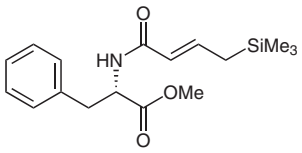
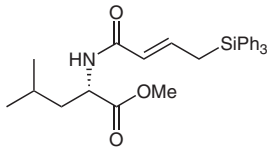
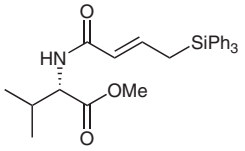
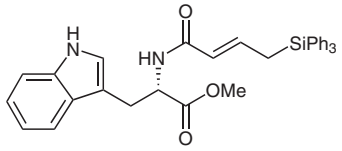
| Entry | Olefin | Product | Catalyst (mol%) | Temp (°C) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **1** |  **6** | **II** (5) | 25 | 48 |
| 2 | **2** |  **7** | **II** (5) | 25 | 65 |
| 3 | **3** |  **8** | **II** (5) | 25 | 55 |
| 4 | **4** |  **9** | **II** (5) | 25 | 60 |
| 5 | |  | **II** (2.5) | 25 | 62 |

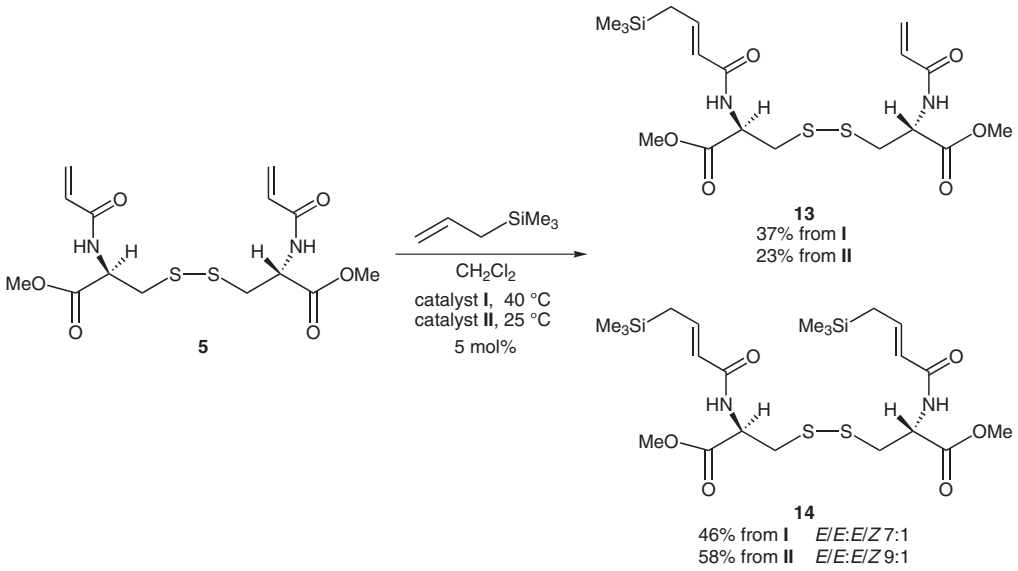
**Table 1** Screening of Acrylamide, Olefin Partner, and Catalysts (continued)




| Entry | Olefin | Product | Catalyst (mol%) | Temp (°C) | Yield (%)[b] |
|---|---|---|---|---|---|
| 6 | |  | **I** (5) | 40 | 67 |
| 7 | |  | **I** (2.5) | 25 | 24 |
| 8 | **4′** |  **9′** | **I** (5) | 40 | 69 |
| 9 | **1** |  **10** | **I** (5) | 40 | 43 |
| 10 | **2** |  **11** | **I** (5) | 40 | 49 |
| 11 | **3** |  **12** | **I** (5) | 40 | 51 |

To extend the scope of this reaction further, we examined other substrates, such as the bisacrylic amide derivative of L-cystine **5**, which contains a disulfide bond. Amide **5** was treated with allyltrimethylsilane (6 equiv) in the presence of catalyst **I** (5 mol%) at reflux in $CH_2Cl_2$. The mono-cross-metathesis product **13**[11] was isolated in 37% yield, and the bis-cross-metathesis product **14**[12] was produced in 46% yield with an (*E*,*E*)/(*E*,*Z*) ratio of 7:1. In the presence of catalyst **II** (5 mol%) at 25 °C in $CH_2Cl_2$, the mono-cross-metathesis product **13** was isolated in only 23% yield, while the bis-cross-metathesis product **14** was produced in 58% yield with a (*E*,*E*)/(*E*,*Z*) ratio of 9:1 (Scheme 2).

The reactivity of ally1silanes which incorporate interacting functional groups has received scant attention.[13] In particular the amide group that offers the possibility of introducing chirality by means of an amino acid as chiral ligand. To date no reactivity of chiral 1-[(trialkylsilyl)methyl]propenamides as nucleophiles has been described. These compounds in acid medium undergo deprotosilylation hence the importance of studying their reactivity in a basic medium in the presence of TBAF,[14] which would allow us to generate an allyl anion[15] to make a contribution to the area of diastereoselective C–C bond formation. With the chiral compounds **6** and **9** in hand, the envisaged fluoride-induced reaction with various aldehydes under kinetic conditions was investigated (Table 1). In the pres-



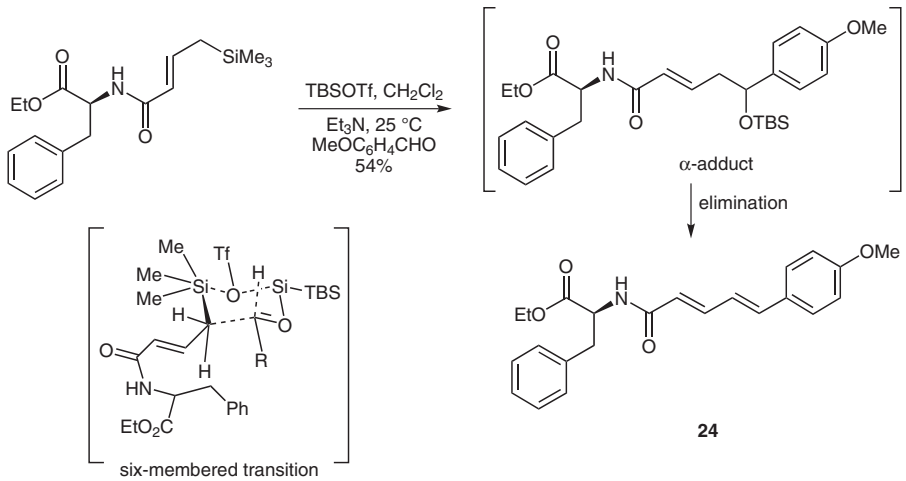

**Scheme 2**

ence of TBAF (1 equiv) at –70 °C, chiral **9** was transformed into hydroxamide **15**[16] (Table 2, entry 1) in 81% yield with a ratio of *syn*/*anti* diastereomers of 4:1.[17] The de of the *syn* major isomer was 60%.[18] Similar results were obtained with other aldehydes under the same conditions. The fluoride-induced reaction of silyl amide **9** and isovaleraldehyde was then carried out to obtain the hydroxyamide adduct **16** in 89% yield with a 4:1 *syn*/*anti* ratio (Table 2, entry 2). The reaction of **9** with isobutyraldehyde gave hydroxyamide **17** with a yield of 64% (Table 2, entry 3) as well as desilylation product.[19] This process was extended to other chiral 1-[(trialkylsilyl)methyl]propenamides and gave some similar results. The treatment of **6** with TBAF in the presence of acetaldehyde gave the hydroxyamide **18** in a yield of 80% (Table 2, entry 4). Fluoride-induced reaction of silyl amide **6** and isobutyraldehyde was then carried out to obtain the hydroxyamide adduct **19** in 71% yield with 4:1 *syn*/*anti* ratio (Table 2, entry 5) accompanied by desilylation product.

We examined the tandem-process method for the synthesis of hydroxyamide with THF as solvent, as this does not interfere with the cross-metathesis reaction. Moreover, the in situ formation of allyl anion by the introduction of TBAF is not compromised by the ligands of the catalyst.[20] The only problem arises if the conversion of the metathesis reaction is not complete, as this affects the final yield after two steps.

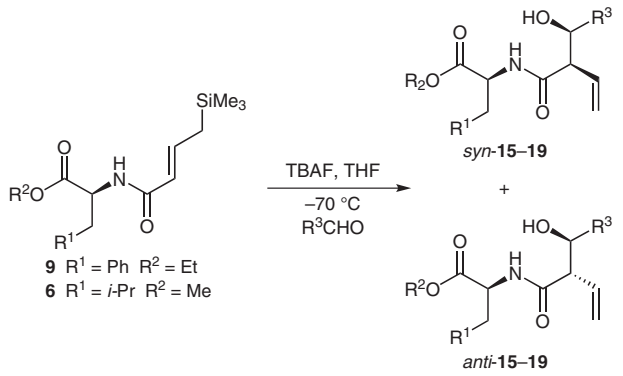
Three examples illustrate this process (Table 3). In the case of acrylamide esters **4** and **2** the *syn*/*anti* ratio of compounds **15** and **20** is 4:1 (Table 3, entry 1, 2); whereas acryamide **21** which has no ester function gave **22** with a 7:1 *syn*/*anti* ratio (Table 3, entry 3).

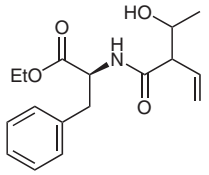
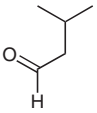
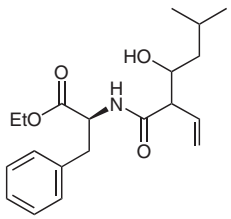
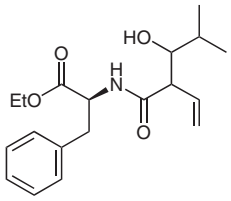
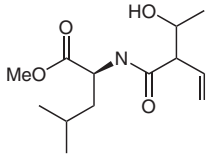
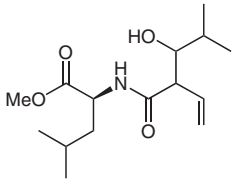
The reactivity of silylacrylamide **9** is completely different when reacted with a nonenolizable aldehyde in the pres-




**Scheme 3**

**Table 2** Fluoride-Induced Reaction of **6** and **9** with Various Aldehydes

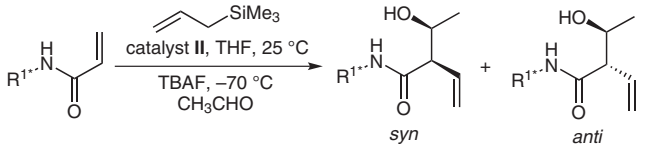


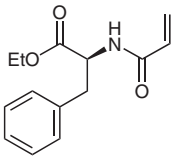
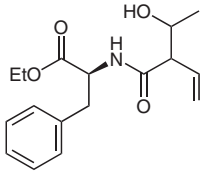
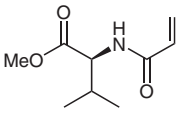
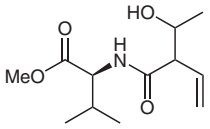
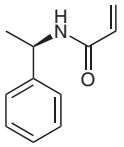
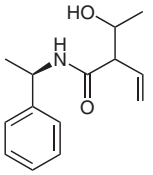

| Entry | Olefin | Aldehyde | Hydroxyamide | Yield (%) | *syn*/*anti* |
|---|---|---|---|---|---|
| 1 | **9** |  |  **15** | 81 | 4:1 |
| 2 | **9** |  |  **16** | 89 | 4:1 |
| 3 | **9** |  |  **17** | 64 | 4:1 |
| 4 | **6** |  |  **18** | 80 | 4:1 |
| 5 | **6** |  |  **19** | 71 | 4:1 |

ence of TBSOTf and triethylamine. We obtained the protected hydroxyamide which underwent concomitant elimination to formation of diene **24** (Scheme 3).[21] This result can possibly be explained by the Lewis acid being involved in the formation of a six-membered transition state to afford the α-adduct directly.

In conclusion, a very simple one-pot cross-metathesis methodology between chiral acrylamides and silylalkenes followed by the addition of electrophiles leads to a diversity of functionalized chiral hydroxyamide compounds in satisfactory yields. Extension to other electrophiles and the use of this one-pot methodology to synthesize a library of biologically active compounds analogues of the inhibitor of MMP marimastat[22] is under way in our laboratory and will be reported in due course.

**Table 3** One-Pot Process Cross-Metathesis–Allylation of Various Acrylamides




| Entry | Acrylamide | Hydroxyamide | Yield (%) | *syn*/*anti* |
|---|---|---|---|---|
| 1 |  **4** |  **15** | 48 | 4:1 |
| 2 |  **2** |  **20** | 43 | 4:1 |
| 3 |  **21** |  **22** | 25 | 7:1 |

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Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8. (i) Brümmer, O.; Rückert, A.; Blechert, S. *Chem. Eur. J.* **1997**, *3*, 441. (j) Vernall, A. J.; Abell, A. D. *Aldrichimica Acta* **2003**, *36*, 93. (k) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

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(3) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

(4) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973.

(5) Rothman, J. H. *J. Org. Chem.* **2009**, *74*, 925.

(6) Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, *63*, 6088.

(7) Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1277.

(8) Streuff, J.; Nieger, M.; Muñiz, K. *Chem. Eur. J.* **2006**, *12*, 4362.

(9) Compounds **1**–**4**, and **4′** were prepared from commercially available chiral L-amino esters and acryloyl chloride in the presence of $Et_3N$ at 0 °C

(10) Two separated spots appear corresponding to the two isomers *E* and *Z*. The *E*/*Z* ratio is greater than 14:1.

(11) **Spectroscopic Data for Compound 13**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 6.95 (td, *J* = 8.8, 15.1 Hz, 1 H), 6.87 (d, *J* = 8.3 Hz, 1 H, NH), 6.45 (d, *J* = 7.2 Hz, 1 H, NH), 6.36 (d, *J* = 16.9 Hz, 1 H), 6.23 (m, 1 H), 5.73 (d, *J* = 14.9 Hz, 1 H), 5.68 (d, *J* = 9.8 Hz, 1 H) 4.95 (m, 2 H), 3.72 (s, 6 H), 3.37–3.11 (m, 4 H), 1.70 (d, *J* = 8.8 Hz, 4 H), 0.01 (s, 9 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 171.2 (s), 170.9 (s), 165.9 (s), 165.3 (s), 145.1 (d), 130.2 (d), 127.8 (t), 120.6 (d), 52.9 (2 q), 51.8 (d), 51.7 (d), 41.2 (t), 41.0 (t), 24.7 (t), –1.7 (3 q). IR (neat): ν = 3320, 2955, 2890, 1741, 1659, 1214, 1186 cm$^{-1}$. MS: *m/z* = 463 (23)[M$^+$ + 1], 405 (64), 391 (100) [M – $SiMe_3$], 377 (17), 313 (9), 276 (20), 242 (7), 204 (56), 190 (25), 170 (20), 156 (7), 142 (1.6), 86 (2). HRMS: *m/z* calcd for $C_{18}H_{31}N_2O_6S_2Si$ [M]: 463.1393 [M + H$^+$]; found: 463.1404.

(12) **Spectroscopic Data for Compound 14**
*E*/*E*-Isomers: $^1$H NMR (300 MHz, $CDCl_3$): δ = 6.92 (td, *J* = 8.8, 14.9 Hz, 2 H), 6.60 (d, *J* = 7.5 Hz, 2 H, NH), 5.71 (d, *J* = 15.0 Hz, 2 H), 4.92 (m, 2 H), 3.71 (s, 6 H), 3.15 (ddd, *J* = 5.9, 14.1, 21.8 Hz, 4 H), 1.65 (d, *J* = 8.7 Hz, 4 H), 0.01 (s, 18 H). *E*/*E*-Isomers: $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 171.1 (2 s), 165.8 (2 s), 144.7 (2 d), 120.6 (2 d), 52.7 (2 q), 51.5 (2 d), 41.1 (2 t), 24.5 (2 t), –1.8 (6 q). *E*/*Z*-Isomers: $^1$H NMR (300 MHz, $CDCl_3$): δ = 6.92 (td, *J* = 8.7, 15.1 Hz, 1 $H_E$), 6.51 (d, *J* = 7.5 Hz, 1 H, NH), 6.49 (d, *J* = 7.3 Hz, 1 H, NH), 6.26 (dd, *J* = 9.6, 10.7 Hz, 1 $H_Z$), 5.70 (d, *J* = 15.1 Hz, 1 $H_E$), 5.62 (d, *J* = 11.3 Hz, 1 $H_Z$), 3.73 (s, 6 H), 3.15 (m, 4 H), 2.35 (m, 2 H), 1.65 (d, *J* = 8.8 Hz, 2 H), 0.01 (s, 18 H). *E*/*Z*-Isomers: $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 171.2 (s), 171.1 (s), 166.6 (s), 165.8 (s), 146.2 (d), 144.9 (d), 120.6 (d), 117.7 (d), 120.6 (d), 52.8 (q), 52.7 (q), 51.6 (d), 51.2 (d), 41.1 (2 t), 24.6 (t), 22.7 (t), –1.6 (3 q), –1.7 (3 q). IR (neat): ν = 3320, 2955, 2890, 1745, 1656, 1214, 1186 cm$^{-1}$. MS: *m/z* = 549 (100)[M$^+$ + 1], 477 (8), 276 (22), 242 (6), 204 (2), 170 (1.6), 142 (3), 73 (3). HRMS: *m/z* calcd for $C_{22}H_{41}N_2O_6S_2Si_2$ [M]: 549.1945 [M + H$^+$]; found: 549.1976.

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(16) **Spectroscopic Data for Compound 15**
Major isomer(*syn*): $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.08 (m, 10 H), 6.31 (d, *J* = 7.5 Hz, 1 H, NH amide), 5.90 (m, 1 H), 5.27 (d, *J* = 10.2 Hz, 1 H), 5.17 (d, *J* = 17.1 Hz, 1 H), 4.79 (m, 1 H), 4.17–4.10 (m, 3 H), 3.31 (br s, 1 H, OH), 3.15 (m, 2 H), 2.82 (dd, *J* = 7.5, 3.2 Hz, 1 H), 1.28 (t, *J* = 7.2 Hz, 1 H), 1.12 (d, *J* = 6.4 Hz, 1 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 171.7 (s), 171.5 (s), 135.9 (s), 132.1 (d), 129.3 (2 d), 128.6 (2 d), 127.2 (d), 121.0 (t), 67.5 (d), 61.7 (q), 57.5 (d), 53.1 (d), 37.8 (t), 19.9 (q),14.2 (q). IR (neat): ν = 3367, 3306, 2978, 2929, 1724, 1632, 1545, 1279, 1180 cm$^{-1}$. HRMS: *m/z* calcd for $C_{17}H_{24}NO_4$ [M]: 306.1705 [M + H$^+$]; found: 306.1711.

(17) The identities of the *syn* and *anti* products were readily established from their $^1$H NMR spectra. The α-products were distinguished by virtue of the larger vicinal coupling constant of the α-methine proton in the *anti* diastereomer (*J* = 7–8 Hz) relative to the s*yn* diastereomer (*J* = 3.2 Hz, Figure 3).

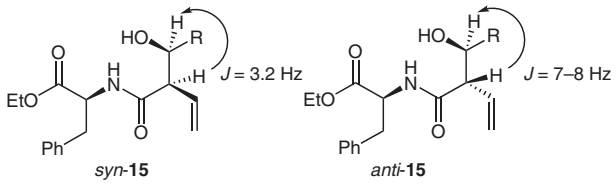



**Figure 3**

(18) Separation of *syn* and *anti* isomers was achieved by Supercritical Fluid Chromatography (column: AD-H21 × 250, mobile phase 15% EtOH, parameters: F = 50 mL/min, nozzle pressure: 100 bar).

(19) When the reaction is not complete and when the aldehyde contains traces of water, protodesilylation product **23** is formed (Figure 4).

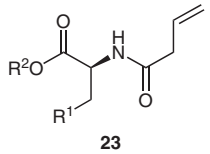



**Figure 4**

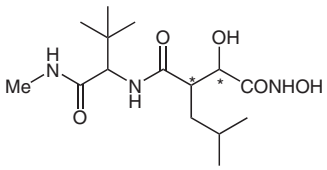
(20) **General Procedure for the One-Pot Process**
To a solution of allyltrimethylsilane (1.1 equiv) and acrylamide **1** (1 mmol) in dry THF (5 mL/mmol) under an argon atmosphere was added Hoveyda–Grubbs catalyst **II**. After 2 h at r.t. the aldehyde was introduced (1.3 equiv), the temperature reduced to –78 °C, and TBAF (1.1 equiv) was added. After 10 min, the reaction mixture was washed with $NH_4Cl$, dried over $MgSO_4$, and concentrated carefully at r.t.

under reduced pressure. The residue was purified by a silica gel chromatography to give the desired hydroxyamide.

(21) **Spectral Data for Compound 24**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.36–6.65 (m, 12 H), 6.07 (d, *J* = 7.5 Hz, 1 H, NH amide), 5.87 (d, *J* = 14.9 Hz, 1 H), 4.92 (m, 1 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 3.77 (s, 3 H), 3.14 (m, 2 H), 1.25 (t, *J* = 7.2 Hz, 1 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 171.8 (s), 165.8 (s), 160.1 (s), 142.0 (d), 139.3 (d), 136.0 (s), 129.4 (d), 129.0 (s), 128.5 (d), 127.0 (d), 124.1 (d), 122.0 (d), 114.1 (d), 61.5 (t), 55.3 (q), 53.3 (d), 37.9 (t), 14.1 (q). HRMS (EI$^+$): *m/z* calcd for $C_{23}H_{26}NO_4$ [M]: 380.1862; found: 380.1857.

(22) Marimastat is a drug that acts on the $Zn^{2+}$ ion at the active site of the matrix metalloproteinase (MMP, Figure 5).




marimastat

**Figure 5**