Diastereotopos-differentiating allylic alkylation as a key step in the synthesis of γ-glutamyl boletine

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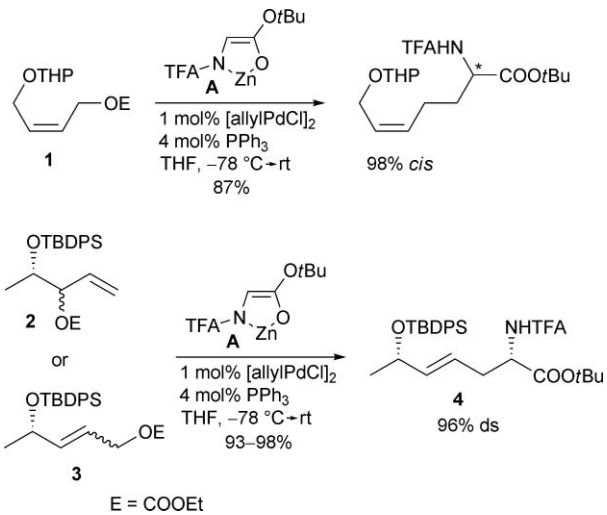
A straightforward approach towards γ-glutamyl boletine is described, based on a diastereotopos-differentiating allylic alkylation of chelated amino acid ester enolates. Independent of the configuration of the leaving group in the allylic substrate, the allylation product is obtained as a single stereoisomer. Its configuration is solely controlled by the stereogenic center adjacent to the π-allyl complex formed.

Introduction

π-Allyl palladium complexes play an important role in modern organic synthesis.[1] With respect to the different synthetic applications, the allylic alkylation is probably the most popular one.[2] Herein, a π-allyl complex is attacked by a nucleophile such as an amine or a stabilized carbanion (in general, a malonate). In contrast to the symmetrical malonates, reactions of β-keto esters, as well as all other unsymmetric nucleophiles, are more critical. Their reactions generate a stereogenic center that is configurationally labile (if α-CH is present), giving mixtures of stereoisomers.

Our group is investigating chelated enolates of amino acid esters (such as **A**, Scheme 1) as nucleophiles for the synthesis of unnatural amino acids.[3] Chelation causes a marked enhancement of thermal stability without having any negative influence on the reactivity of these enolates. In contrast to the generally used malonates, with our enolates, a stereogenic center is also formed at the α-position of the amino acid (Scheme 1).[4] Of course, the control of this stereogenic centre is not a trivial issue, but the products obtained are highly interesting structures, and therefore we decided to face this challenge. Efficient stereocontrol can be achieved by using chiral ligands[5] or chiral allylic substrates.[6] If peptide enolates are used as nucleophiles, the stereochemical outcome of the allylation can be controlled by the stereogenic information of the peptide chain.[7] The yields obtained are generally very high, even for very complex, or even stannylated, amino acids.[8] As a result of the high reactivity of the chelated enolates, the allylations already take place under very mild conditions at −78° C, which has an extremely positive effect on the selectivity of the reaction. In many cases, isomerization processes, such as π–σ–π-isomerizations, can be suppressed completely.[9] This allowed us for the first time to use C-nucleophiles in isomerization-free allylations of *cis*-configured substrates such as **1** (Scheme 1).

Under certain circumstances, this isomerization can even be suppressed for terminal π-allyl complexes, which are especially sensitive towards isomerization.[10] On the other hand, one can take also advantage of such a fast isomerization process. For example,



Scheme 1 Pd-catalyzed allylic alkylations of chelated enolates **A**

if chiral allylic substrates with a stereogenic center close to the allyl fragment, such as **2** or **3**, are used, this center can control the configuration of the π-allyl intermediate formed, giving rise to substitution product **4** in excellent yield and diastereoselectivity, independent of the substrate used.[11]

Herein, we describe an application of this diastereotopos-differentiating protocol towards the synthesis of γ-glutamyl boletine **5** (Fig. 1), a metabolite of the Japanese mushroom *Tylopilus* sp. (Boletaceae) showing antibiotic activity.[12]

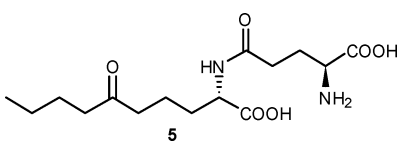


Fig. 1 γ-Glutamyl boletine.

Results and discussion

We began our synthesis with the preparation of the required allylic substrate **10** (Scheme 2). Racemic allyl alcohol **6** was

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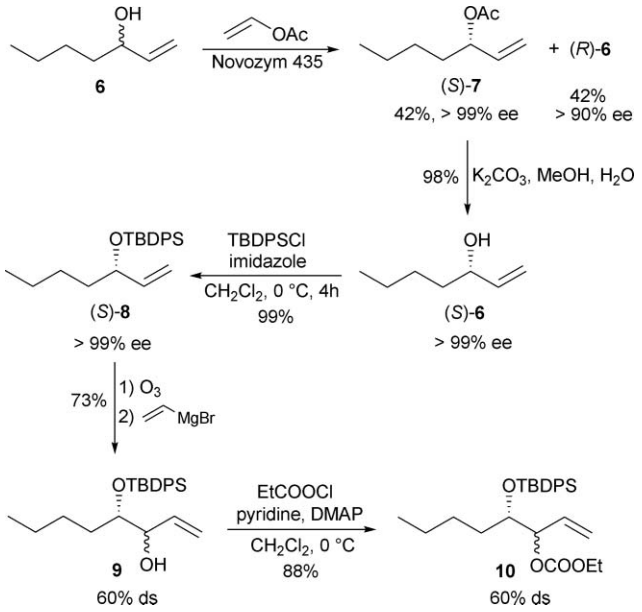


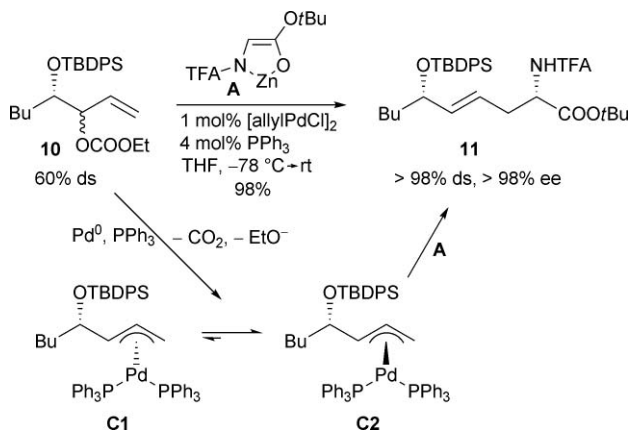
Scheme 2 Preparation of allylic substrate **10**

subjected to an enzymatic kinetic resolution using an immobilized *Candida antarctica* lipase (Novozym 435), giving rise to acetate **7** with excellent ee. Saponification and subsequent silyl protection provided silyl ether **8** in almost quantitative yield. Ozonolysis and subsequent Grignard addition towards the aldehyde obtained gave rise to allylic alcohol **9** as a diastereomeric mixture (60% ds). However, as already mentioned, the configuration of this newly formed stereogenic center does not play any role for our further synthesis. Esterification with ethyl chloroformate yielded the required allyl carbonate **10**.

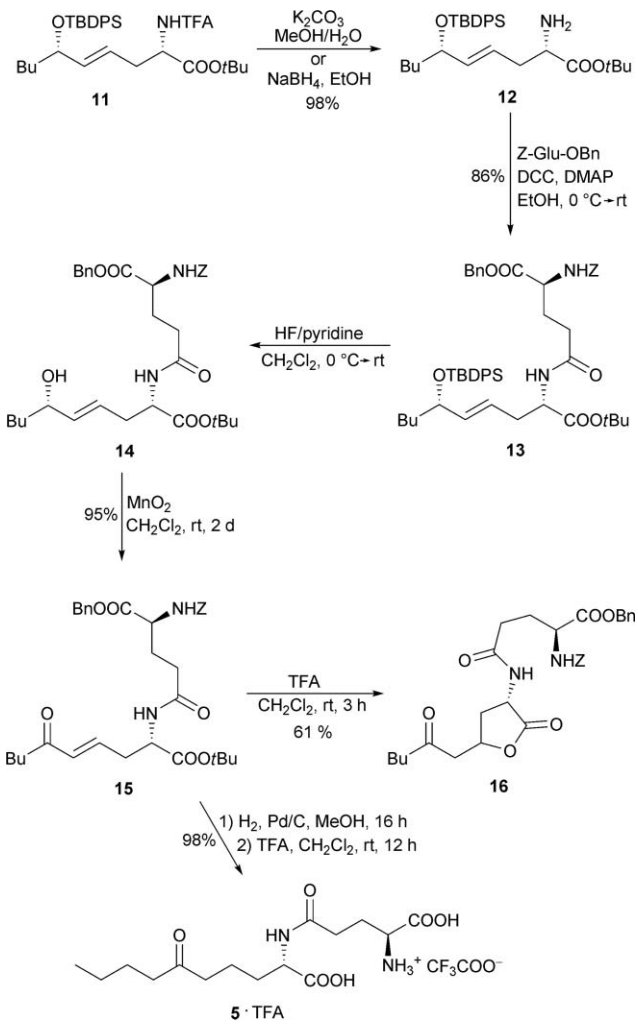
With this allylic substrate in hand, we next investigated the key step of our synthesis, the allylic alkylation (Scheme 3). The expected amino acid derivative **11** was obtained in excellent yield as a single stereoisomer. A perfect chirality transfer was observed from the allyl moiety towards the α-position of the amino acid. It should be mentioned that the corresponding allyl benzoate gave a slightly lower yield and selectivity, providing also the second diastereomer of **11**, which allowed us to verify our results. In addition, when stereoisomerically pure **11** was treated with LDA, a 1 : 1 diastereomeric mixture was formed by epimerization at the α-position, as distinguished from ^{13}C-NMR spectra.

In the first instance, from the two diastereomeric allyl carbonates, the two diastereomeric π-allyl complexes **C1** and **C2** are formed, which undergo a fast equilibration under the reaction conditions (*via* π–σ–π-isomerization). The sterically very demanding TBDPS-protecting group probably directs the Pd-fragment to the opposite face of the molecule, shifting the equilibrium strongly to the π-allyl complex **C2**. Nucleophilic attack of the chelated enolate on this complex then gives rise to the observed product.[11]

Next, the TFA-protecting group was removed by saponification in quantitative yield (Scheme 4). Alternatively, this protecting group can also be removed under reductive conditions[13] with comparable success. Coupling with benzyl-protected glutamate under standard conditions gave rise to dipeptide **13** in high yield. Because our aim was to remove the benzylic protecting group and the double bond in one final step, we next cleaved the silyl protecting group. This was not as trivial as expected. Under standard conditions the other protecting groups were also affected. With TBAF (THF, 0 °C), cleavage of the benzyl ester was also observed, and with HF in CH_3CN, cleavage of the *t*-butylester



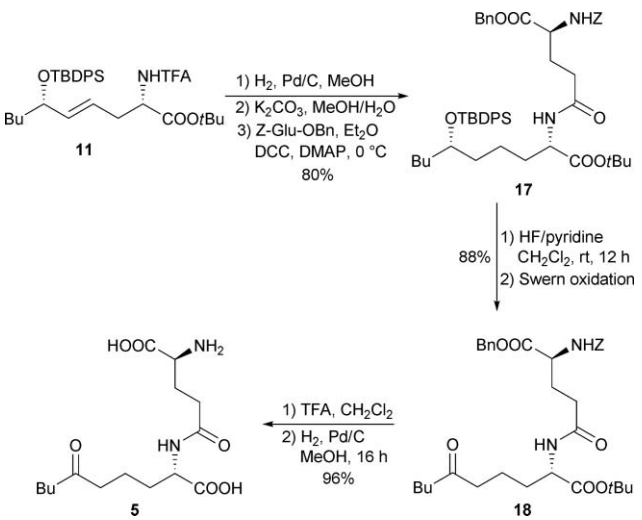
Scheme 3 Stereoselective allylic alkylation using **10**



Scheme 4 First attempts to synthesize **5**

also occurred, giving rise to a lactone derivative. Finally, the best results were obtained by using HF in pyridine. The allyl alcohol **14** obtained was then subjected to oxidation. Our first attempts were carried out with Dess–Martin periodinane (DMP). With four equivalents of DMP, a complete conversion was observed after twelve hours, but, unfortunately, the by-products formed from the DMP could not be separated by chromatography. Therefore, we switched to MnO_2 as the oxidizing agent. With freshly activated MnO_2, the oxidation was also complete after two days, and purification of **15** was not a problem in this case. Trifluoroacetic acid (TFA) was used to cleave the *t*-butylester. After three hours, a complete consumption of **15** was observed; however, the product formed was not the desired carboxylic acid, but rather the lactone **16**, resulting from a Michael addition of the carboxylic acid to the α,β-unsaturated ketone. Therefore, we decided to remove the double bond first, together with the benzylic protecting groups. Subsequent acidic cleavage of the *t*-butylester provided **5** as the corresponding TFA-salt.

Alternatively, for the preparation of the salt-free natural product, the double bond was removed at an earlier stage of the synthesis (Scheme 5). Hydrogenation of **11**, subsequent cleavage of the TFA-protecting group and coupling with protected glutamate provided **17**. Cleavage of the silyl protecting group was carried out as described before for the unsaturated analogue **13**. Subsequent Swern oxidation provided ketone **18**, which was easily converted into **5** by removing the protecting groups under standard conditions.



Scheme 5 Alternative approach towards **5**

Conclusion

In conclusion, we have shown that diastereotopos-differentiating allylic alkylations are a versatile tool for the synthesis of functionalized unusual amino acids. If isomeric mixtures of allylic substrates are used, a fast equilibration of the intermediate π-allyl-complexes results in the formation of only one allylation product in excellent yield and selectivity. Further applications of this straightforward protocol are currently under investigation.

Experimental

General remarks

All reactions were carried out in oven-dried glassware (100 °C) under nitrogen. All solvents were dried before use: THF was distilled from $LiAlH_4$, and CH_2Cl_2 from CaH_2. The products were purified by flash chromatography on silica gel (0.063–0.2 mm). Mixtures of ethyl acetate and hexanes were generally used as eluents. Analysis by TLC was carried out on commercially precoated Polygram SIL-G/UV 254 plates (Machery-Nagel, Dueren). Visualization was accomplished with UV light, $KMnO_4$ solution, Ce–Mo reagent or iodine. ^{1}H- and ^{13}C-NMR spectroscopic analysis was performed on Bruker AC-500 or Bruker DRX-500 spectrometers. Chemical shifts are reported on the δ (ppm) scale, and the coupling constants are given in Hz. The values for enantiomeric excess were determined by GCMS-QP2010 using a Chirasil–Dex-CB column. Optical rotations were measured on a Perkin–Elmer polarimeter PE 341. HRMS were measured with a Finnigan MAT 95S mass spectrometer. Elemental analyses were carried out at the Department of Chemistry at Saarland University.

(*S*)-Hept-1-en-3-ol acetate (7)[14]. To a solution of racemic alcohol **6** (22.8 g, 200 mmol) in vinyl acetate (330 mL), Novozym 435 (6.6 g) was added under stirring. The progress of the reaction was monitored by GC. After stirring vigorously at room temperature for 4 h, the enzyme was filtered off and was washed with diethyl ether. The organic phases were combined and evaporated to give approximately a 1 : 1 mixture of alcohol (*R*)-**6** and acetate (*S*)-**7** respectively. This mixture was separated by chromatography (silica, hexanes–ether, 100 : 0 to 95 : 5), which gave acetate (*S*)-**7** (12.48 g, 42%, > 99% ee) as colorless oil, $[\alpha]_D^{20} = +13.1°$ (*c* 1.1, $CHCl_3$); and unreacted alcohol (*R*)-**6** (9.12 g, 40%, > 90% ee) as colorless oil. (*S*)-**7**: ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 5.78–5.70$ (m, 1H), 5.21–5.11 (m, 3H), 2.03 (s, 3H), 1.65–1.22 (m, 6H), 0.86 (t, $J = 6.8$ Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 170.3$, 136.6, 116.4, 74.8, 33.9, 27.2, 22.4, 21.2, 13. 9; GC (Chirasil–Dex-CB, 1. 80 °C, 10 min; 2. 10 °C min^{-1}, 3. 100 °C, 5 min): (*S*)-(**7**): $t_R = 11.61$ min, (*R*)-(**7**): $t_R = 9.86$ min.

(*S*)-Hept-1-en-3-ol (6):[14]. To a stirred solution of acetate (*S*)-**7** (11.7 g, 75 mmol) in 80% MeOH (100 mL), K_2CO_3 (20.7 g, 150 mmol) was added. After completion of the reaction (as indicated by TLC) the solvent was evaporated *in vacuo*. Water was added to the residue, and the solution was extracted twice with diethyl ether. The combined organic layers were dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by flash chromatography (hexanes–diethyl ether, 90 : 10) to give alcohol (*S*)-**6** (8.38 g, 98%) as a colorless oil, $[\alpha]_D^{20} = +9.0°$ (*c* 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 5.85$ (ddd, $J =$ 16.9, 10.4, 6.2 Hz, 1H), 5.26–5.06 (dd, $J = 17.2$, 10.4 Hz, 2H), 4.06 (q, $J = 6.2$ Hz, 1H), 1.68 (s_{br}, 1H), 1.62–1.47 (m, 2H), 1.43–1.26 (m, 4H), 0.89 (t, $J = 7.1$, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta =$ 141.3, 114.4, 73.2, 36.7, 27.4, 22.6, 13.9. GC (Chirasil–Dex-CB, 1. 80 °C, 10 min; 2. 10 °C min^{-1}, 3. 100 °C, 5 min): (*S*)-(**6**): $t_R =$ 12.08 min, (*R*)-(**6**): $t_R = 12.33$ min.

(3*S*)-3-*tert*-Butyldiphenylsilyloxy-1-heptene (8). To a stirred solution of alcohol (*S*)-**6** (2.51 g, 22.0 mmol) in CH_2Cl_2 (20 mL), imidazole (2.24 g, 33.0 mmol) was added at 0 °C. After 15 min, *tert*-butyldiphenylsilylchloride (7.23 g, 26.4 mmol) in CH_2Cl_2

(5mL) was added, and the reaction was allowed to warm up to room temperature. After completion of the reaction (as indicated by TLC), the salty mixture was diluted with water, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by chromatography (silica, hexanes–EtOAc) to afford (*S*)-**8** (7.69 g, 99%) as a colorless oil, $[\alpha]_D^{20} = +20.2°$ (*c* 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 7.72–7.34$ (m, 10H), 5.81 (ddd, $J = 16.9$, 10.4, 6.2 Hz, 1H), 4.98 (dd, $J = 17.1$, 11.1 Hz, 2H), 4.15 (q, $J = 6.3$ Hz, 1H), 1.52–1.36 (m, 2H), 1.28–1.12 (m, 4H), 1.08 (s, 9H), 0.80 (t, $J = 6.6$ Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta =$ 140.9, 136.0, 135.9 (2C), 134.6 (2C), 134.4, 129.5, 129.4, 127.4 (2C), 127.3 (2C), 114.1, 74.7, 37.3, 27.1 (3C), 26.6, 22.6, 19.4, 14.0. HPLC (Chiralcel OD-H, hexane, 100%, 1 mL min^{-1}): (*S*)-(**8**): $t_R = 3.92$ min, (*R*)-(**8**): $t_R = 4.80$ min. HRMS (EI) calcd for $C_{23}H_{32}OSi$ $[M]^+$: 352.2222. Found: 352.2219. Anal. calcd for $C_{23}H_{32}OSi$ (352.22): C, 78.35; H, 9.15. Found: C, 78.44; H, 8.78.

(4*S*)-4-(*tert*-Butyldiphenylsilyloxy)-1-octen-3-ol (9). To a solution of alkene **8** (2.82 g, 8.0 mmol) in CH_2Cl_2 (50 mL), ozone was passed through for 30 min at −78 °C. The reaction was allowed to warm up to room temperature before dimethylsulfide (0.99 g, 16 mmol) was added. After addition of water, the aqueous phase was washed twice with dichloromethane. The combined organic layers were dried over Na_2SO_4. After evaporating the solvent *in vacuo*, the crude product was dissolved in dry THF (2 mL), and the solution was added dropwise to a vinylmagnesium bromide solution (1.31 g, 10 mL 1.0 M solution in THF, 10 mmol) at −20 °C under nitrogen. The reaction mixture was allowed to warm up to room temperature for 2 h before it was quenched at 0 °C with aq. NH_4Cl. The aqueous phase was extracted three times with ethyl acetate (25 mL each) and the combined organic layers were dried over Na_2SO_4. After removing the solvents *in vacuo*, the crude product was purified by flash chromatography (hexanes–EtOAc, 70 : 30), which gave the desired allyl alcohol **9** (2.24 g, 5.86 mmol, 73%) as a colorless liquid (60% ds). Mixture of diastereomers: ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 7.70–7.36$ (m, 10H), 5.89–5.79 (m, 1H), 5.33–5.14 (m, 2H), 4.11–4.03 (m, 1H), 3.79–3.64 (m, 1H), 2.21 (d, $J = 5.3$ Hz, 1H), 1.56–0.97 (m, 15H), 0.73 (t, $J = 6.9$ Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 138.5$, 136.4, 135.9, 135.9, 134.0, 133.9, 133.8, 133.5, 129.8, 129.7, 129.6, 127.7, 127.6, 127.5, 127.4, 116.4, 116.0, 76.7, 76.6, 75.6, 74.2, 32.9, 31.7, 27.6, 27.1 (3C), 22.6, 22.5, 19.6, 19.5, 13.8. HPLC (Reprosil 100 Chiral-NR 8 µm, hexane–*i*PrOH, 99 : 1, 1 mL min^{-1}): $t_R = 9.14$ min (62%), 10.31 min (38%). HRMS (EI) calcd for $C_{24}H_{33}OSi$ $[M - OH]^+$: 365.2306. Found: 365.2306. Anal. calcd for $C_{24}H_{34}O_2Si$ (382.23): C, 75.34; H, 8.96. Found: C, 75.48; H, 8.41.

(4*S*)-4-(*tert*-Butyldiphenylsilyloxy)oct-1-en-3-yl ethyl carbonate (10). To a solution of alcohol **9** (2.10 g, 5.50 mmol) and ethyl chloroformate (0.89 g, 8.25 mmol) in CH_2Cl_2 (20 mL) at 0 °C, pyridine (0.65 g, 8.25 mmol) was added, as well as a catalytic amount of DMAP. The reaction was allowed to stir at this temperate until completion (TLC). The reaction mixture was neutralized with 1 N HCl solution, and the aqueous phase was extracted three times with CH_2Cl_2 (25 mL each). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexanes–EtOAc, 95 : 5) providing allyl substrate **10** (2.20 g, 4.85 mmol, 88%) as a colorless oil. Mixture of diastereomers: ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 7.75–7.34$ (m, 10H), 5.99–5.90 (m, 1H), 5.35–5.23 (m, 2H), 5.00–4.97 (m, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 3.84 (m, 1H), 1.48–1.38 (m, 2H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.14–1.03 (m, 4H), 1.08 (s, 9H), 0.72 (t, $J = 7.2$ Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 154.6$, 136.2 (2C), 136.0 (2C), 134.4, 133.4, 132.4, 129.6 (2C), 129.5 (2C), 127.4 (2C), 119.4, 81.4, 74.4, 63.7, 32.7, 27.4, 27.0 (3C), 22.4, 19.5, 14.3, 13.8). Selected signals of the minor diastereomer: ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 5.85–5.76$ (m, 1H), 5.13 (t, $J = 6.5$ Hz, 1H), 4.11–3.99 (m, 2H), 1.22 (t, $J = 7.1$ Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 154.5$, 136.1 (2C), 135.9 (2C), 133.9, 133.8, 132.8, 129.5 (2C), 129.4 (2C), 127.4 (2C), 118.7, 80.7, 73.9, 63.6, 32.4, 27.0 (3C), 26.4, 22.4, 19.5, 14.1, 13.8. HPLC (Reprosil 100 Chiral-NR 8 µm, hexane, 100%, 1 mL min^{-1}): $t_R = 8.65$ min (62%), 9.72 min (38%). HRMS (EI) calcd for $C_{27}H_{39}O_4Si$ $[M + H]^+$: 455.2618. Found: 455.2632.

(2*S*,6*S*,*E*)-*tert*-Butyl 6-(*tert*-butyldiphenylsilyloxy)-2-(trifluoroacetamido)dec-4-enoate (11). Hexamethyldisilazane (3.15 g, 19.5 mmol) was dissolved in THF (20 mL) in a Schlenk flask under argon. After the solution was cooled to −78 °C, *n*-BuLi (1.6 M, 10.9 mL, 17.4 mmol) was added slowly. The reaction mixture was stirred for 20 min at this temperature, and then the cooling bath was removed and the stirring was continued for a further 15 min. In a second Schlenk, TFA-Gly-O*t*Bu (1.59 g, 7.0 mmol) was dissolved in THF (40 mL). The solution was cooled to −78 °C, before the freshly prepared LHMDS was added. After 15 min, a solution of dried $ZnCl_2$ (1.05 g, 7.7 mmol) in THF (5 mL) was added, and stirring was continued for 30 min. A solution was prepared from $(allylPdCl)_2$ (12 mg, 0.033 mmol) and PPh_3 (34 mg, 0.13 mmol) in THF (5 mL), which was added to the chelated enolate at −78 °C. At the same temperature, the allyl substrate **10** (1.91 g, 4.2 mmol) was added in THF (5 mL), before the mixture was allowed to warm to room temperature overnight. The solution was diluted with ether before 1 M $KHSO_4$ was added. After separation of the layers, the aqueous layer was extracted three times with ether (20 mL each), and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated *in vacuo*, and the crude product was purified by flash chromatography (hexanes–EtOAc, 95 : 5) giving rise to the amino acid derivative **11** (2.43 g, 4.1 mmol, 98%) as a yellowish liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 7.67–7.33$ (m, 10H), 6.76 (d, $J = 7.1$ Hz, 1H), 5.52 (dd, $J = 15.4$, 6.4 Hz, 1H), 5.26–5.10 (m, 1H), 4.45 (q, $J = 7.1$ Hz, 1H), 4.12 (m, 1H), 2.59–2.38 (m, 2H), 1.45 (s, 9H), 1.43–1.07 (m, 6H), 1.05 (s, 9H), 0.79 (t, $J = 6.9$ Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 169.1$, 156.3, 138.8 (2C), 135.9 (2C), 135.8 (2C), 134.4, 134.2, 129.6, 129.5, 127.5 (2C), 127.4 (2C), 122.0, 83.3, 73.6, 52.4, 37.3, 33.9, 27.9 (3C), 27.0 (3C), 26.6, 22.5, 19.3, 13.8. HRMS (EI) calcd for $C_{32}H_{44}F_3NO_4Si$ $[M]^+$: 591.2922. Found: 591.2920. Anal. calcd for $C_{32}H_{44}F_3NO_4Si$ (591.29): C, 64.95; H, 7.49; N, 2.37. Found: C, 64.84; H, 7.72; N, 2.40.

Dipeptide 13. K_2CO_3 (2.346 g, 17.0 mmol) was added to a solution of TFA-protected amino acid **11** (2.0 g, 3.4 mmol) in 90% MeOH (20 mL) at room temperature. The reaction was stirred (36 h) until the removal of the TFA-group was complete (TLC). The solvent was removed *in vacuo* and the crude product was dissolved in water. The aqueous phase was extracted three times with $CHCl_3$ (25 mL each). The combined organic layers were dried

over Na_2SO_4. After removing the solvent *in vacuo*, the primary amine **12** was obtained in 98% yield (1.64 g, 3.3 mmol). This crude amine **12** was used directly without further purification for the subsequent peptide coupling.

To a solution of amine **12** (1.64 g, 3.3 mmol), *Z*-L-Glu-OBn (1.22, 3.3 mmol) and DMAP (40 mg, 0.33 mmol) in dry CH_2Cl_2 (20 mL), DCC (0.75 g, 3.63 mmol) was added at 0 °C. The reaction was stirred at this temperature for 15 min and was allowed to warm to room temperature. After 3 h the solvent was removed by evaporation, and the crude product was dissolved in Et_2O. The white precipitate formed was filtered off and the filtrate was washed with 1 N HCl, followed by sat. $NaHCO_3$. The organic layer was dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography (hexanes–EtOAc, 75 : 25), giving rise to the desired dipeptide **13** (2.41 g, 2.75 mmol, 86%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67–7.27 (m, 20H), 5.93 (d, J = 7.4, 1H), 5.72 (d, J = 7.8 Hz, 1H), 5.47 (dd, J = 15.3, 6.4 Hz, 1H), 5.21–5.05 (m, 5H), 4.50–4.30 (m, 2H), 4.15–4.07 (m, 1H), 2.45–2.28 (m, 2H), 2.24–1.90 (m, 4H), 1.53–1.31 (m, 2H), 1.41 (s, 9H), 1.23–1.09 (m, 4H), 1.04 (s, 9H), 0.78 (t, J = 6.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.7, 171.1, 170.7, 156.1, 137.5, 136.2, 135.9 (2C), 135.8 (2C) 135.2, 134.3, 134.2, 129.5, 129.4, 129.3, 128.6 (2C), 128.5 (2C), 128.4 (2C), 128.3, 128.1, 128.0, 127.4 (2C), 127.3 (2C), 123.5, 82.1, 73.7, 62.2, 67.0, 53.6, 52.2, 37.3, 34.6, 31.9, 27.9 (3C), 27.8, 27.0 (3C), 26.7, 22.5, 19.3, 14.0. HRMS (EI) calcd for $C_{50}H_{64}N_2O_8Si$ $[M]^+$: 848.4432. Found; 848.4454.

Dipeptide 14. Dipeptide **13** (2.12 g, 2.5 mmol) in CH_2Cl_2 (5 mL) was added to a solution of HF·pyridine (65–75%) (2.47 g, 3.8 mL, 2.5 mmol) and pyridine (1.9 mL) in CH_2Cl_2 (20 mL) at 0 °C. After stirring the reaction mixture at room temperature for 24 h, the solvent was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with sat. $NaHCO_3$, H_2O and brine, and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography (hexanes–EtOAc, 6 : 4) to provide allyl alcohol **14** (1.25 g, 2.05 mmol, 82%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.58–7.08 (m, 10H), 6.24 (d, J = 6.8 Hz, 1H), 5.8 (d, J = 7.6 Hz, 1H), 5.61–5.45 (m, 2H), 5.21–5.02 (m, 4H), 4.53 (q, J = 6.7 Hz, 1H), 4.40 (t_{br}, J = 7.8 Hz, 1H), 4.06–3.92 (m, 1H), 2.64–2.32 (m, 2H), 2.30–1.87 (m, 4H), 1.54–1.21 (m, 6H), 1.45 (s, 9H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.8, 171.3, 170.8, 156.3, 137.7, 136.1, 135.2, 128.6 (2C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 128.1, 128.0, 124.5, 82.2, 72.2, 67.3, 67.1, 53.4, 52.3, 36.7, 35.1, 31.9, 28.2, 28.0 (3C), 27.6, 22.6, 14.0. HRMS (EI) calcd for $C_{34}H_{46}N_2O_8$ $[M]^+$: 610.3254. Found; 610.3222.

Dipeptide 15. MnO_2 (1.56 g, 18.0 mmol) was added to a solution of alcohol **14** (1.10 g, 1.8 mmol) in CH_2Cl_2 (20 mL). The solution was stirred at room temperature for 2 d. The mixture was filtered through Celite, and the filtrate was evaporated. After purification by flash chromatography (hexanes–EtOAc, 70 : 30), unsaturated ketone **15** (1.04, 1.71 mmol, 95%) was obtained as a white solid, mp. 58 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.44–7.24 (m, 10H), 6.72–6.63 (m, 1H_2), 6.36 (s_{br}, 1H), 6.10 (d, J = 15.8 Hz, 1H), 5.70 (s_{br}, 1H), 5.24–5.06 (m, 4H), 4.65–4.33 (m, 2H), 2.77–2.55 (m, 2H), 2.50 (t, J = 7.6 Hz, 2H), 2.30–1.87 (m, 4H), 1.55 (quin, J = 7.7 Hz, 2H), 1.44 (s, 9H), 1.35–1.23 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.2, 171.6, 171.3, 170.1, 156.1, 140.2, 136.1, 135.1, 133.2, 128.6 (2C), 128.4 (2C), 128.3 (2C), 128.2, 128.1, 128.0 (2C), 82.8, 67.3, 67.0, 53.4, 51.8, 39.6, 35.4, 32.0, 28.2, 27.9 (3C), 26.1, 22.3, 13.8; HRMS (EI) calcd for $C_{34}H_{44}N_2O_8$ $[M]^+$: 608.3098. Found: 608.3048. Anal. calcd for $C_{34}H_{44}N_2O_8$ (608.30): C, 67.09; H, 7.29; N, 4.60. Found: C, 66.75; H, 7.08; N, 4.35.

γ-Glutamyl boletine TFA-salt (5·TFA). A solution of compound **15** (304 mg, 0.5 mmol) in MeOH (10 mL) was continuously stirred in the presence of 10 mol% Pd/C (30 mg) at room temperature, under an atmosphere of hydrogen overnight. The reaction mixture was filtered through a pad of Celite, which was washed with methanol (20 mL). The solvent was evaporated *in vacuo*, and the crude product obtained was dissolved in CH_2Cl_2 (10 mL) and treated with trifluoroacetic acid (57 mg, 2.5 mmol). After stirring the reaction mixture for 12 h the solvent was removed *in vacuo*, and the TFA salt of **5** (217 mg, 98%) was obtained in excellent yield, mp. 72 °C. ^{1}H-NMR (500 MHz, CD_3OD): δ = 4.15 (s_{br}, 1H), 3.98 (s_{br}, 1H), 2.66–2.35 (m, 4H), 2.32–2.03 (m, 2H), 1.95–1.24 (m, 10H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C-NMR (125 MHz; CD_3OD): δ = 212.7, 174.2, 173.5, 171.2, 162.1, 117.13, 53.0, 52.4, 42.2, 41.1, 31.4, 30.6, 26.2, 25.7, 22.1, 19.7, 13.0.

γ-Glutamyl boletine (5)[12]. The free natural product **5** was obtained in an analogous manner from **11**. ^{1}H-NMR (500 MHz, CD_3OD): δ = 4.38 (1H, br s, C*H*NH), 4.24 (1H, br s, C*H*NH), 2.49–2.39 (2H, m, COCH_2), 2.34 (2H, t, J 7.4, COCH_2), 2.32–2.21 (2H, m, COCH_2), 2.20–1.81 (2H, m, CH_2), 1.79–1.47 (4H, m, 2 × CH_2), 1.52 (2H, quint., J 7.1, $CH_2CH_2CH_2$), 1.36–1.25 (2H, m, CH_3CH_2), 0.90 (3H, t, J 7.3, CH_3CH_2); ^{13}C-NMR (125 MHz; CD_3OD): δ = 212.4, 175.1, 174.0, 173.5, 52.4, 50.8, 41.6, 40.9, 31.2, 30.3, 27.4, 25.4, 21.7, 19.4, 12.6.

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