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Asymmetric Synthesis of α-Allenylglycines

Carmen Bucuroaia,[a] Ulrich Groth,*[a] Thomas Huhn,[a] and Michael Klinge[b]

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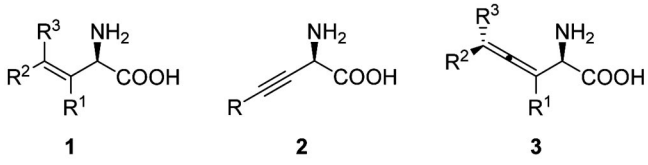
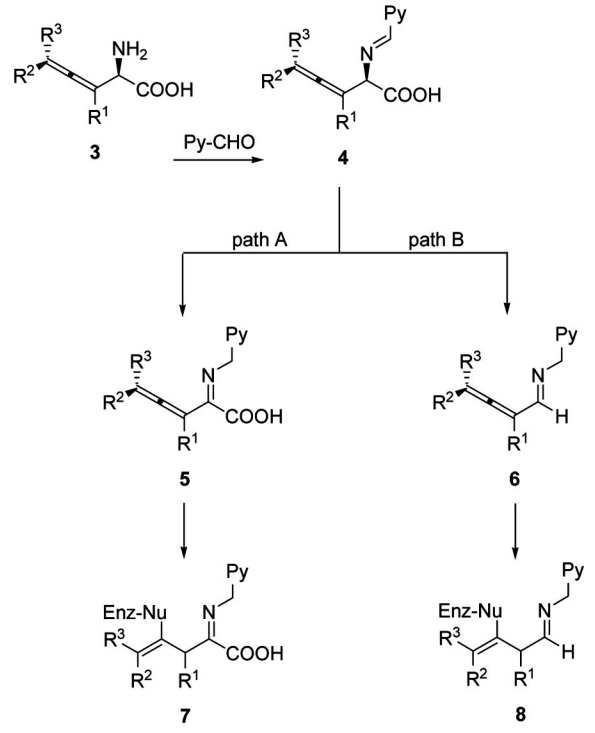
The coupling of the homocuprate of the bislactim ether of *cyclo*-(-L-Val-Gly-) (**9**) with primary propargyl halides produces the allenyl-substituted bislactim ethers **11** in a highly diastereoselective manner, whereas the alkylation of the lithiated bislactim ether of *cyclo*-(-L-Val-Gly-) yields the propargyl-substituted bislactim ethers **12**. Subsequent hydrolysis affords, after protection of the amino group, the methyl α-allenylglycinates **15**, the α-allenylglycines **16**, and the methyl α-propargylglycinates **17**.

I. Introduction

β,γ-Unsaturated α-amino acids such as vinylglycines **1** and alkynylglycines **2** have attracted considerable attention because of their potential biological activity.[1,2] α-Allenylic α-amino acids such as allenylglycines **3** are attractive candidates for the specific inhibition of vitamin B6-linked (pyridoxal-linked) enzyme systems;[3] α-allenyl DOPA, for example, rapidly inactivates porcine kidney aromatic amino acid decarboxylase.[4]



These kinds of unsaturated amino acids are challenging target molecules in asymmetric synthesis because of their known tendency towards racemization and their tautomerization to unstable α,β-dehydro amino acids.[5] Together with a few methods for the synthesis of racemic α-alkynylglycines[6,7] and α-allenylphenylalanines,[8] efficient methods for the asymmetric construction of vinyl-[9–12] and alkynylglycines[13–15] have already been developed, but asymmetric syntheses for allenyl amino acids are still lacking. While studying asymmetric syntheses of nonproteinogenic α-amino acids, we took special interest in α-allenyl amino acids **3**, because these amino acids have been recognized as irreversible enzyme inhibitors.[16,17] In the proposed mechanism (Scheme 1), an α-allenyl amino acid **3** reacts with the cofactor pyridoxalphosphate (Py-CHO) to give the Schiff base **4**. This Schiff base tautomerizes either with (path B) or without (path A) decarboxylation to afford the imines **5** or **6**. These imines act as Michael acceptors, which undergo irreversible Michael addition with a nucleophilic part of the enzyme to give the "inhibited" enzymes **7** or **8**.



Scheme 1. Proposed mechanism of pyridoxal phosphate-dependent decarboxylase inhibition by α-allenyl amino acids.

Krantz and Castelhano[8] prepared α-allenyl-α-benzyl amino acids by using oxazoles as intermediates; these underwent Claisen rearrangements to afford allenyl-substituted oxazolones. A four-step hydrolysis gave the corre-

[a] Fachbereich Chemie und Konstanz Research School Chemical Biology der Universität Konstanz, Fach 720, Universitätsstr. 10, 78457 Konstanz, Germany
Fax: +49-7531-884155
E-mail: Ulrich.Groth@uni-konstanz.de
[b] GIT Verlag GmbH & Co. KG, 64220 Darmstadt, Germany

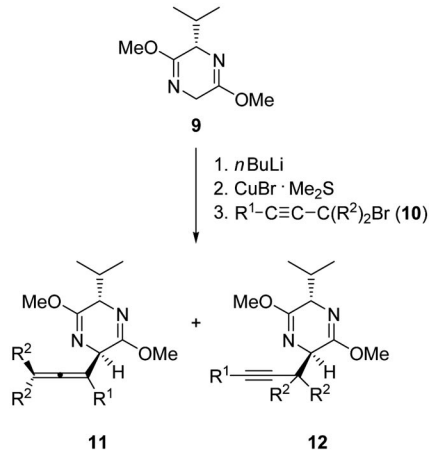
sponding α,α-disubstituted amino acids in about 70% yields. However, this method seems to be limited to the synthesis of racemic α-benzyl-α-allenylglycines, which obviously cannot act as suicide substrates as in path A because a rearrangement to imine **5** is impossible. Utilizing an allenylic *N*-benzoyl-protected amino acid ester, Casara et al. were able to obtain racemic α-allenylic amino acids by a cumbersome sequential five-step alkylation/deprotection sequence.[18] Kazmaier, employing a chelate-controlled ester enolate Claisen rearrangement, succeeded in the synthesis of α-H-allenyl amino acids.[19,20] With zinc(II) chloride as chelating agent rearrangements of amino acid propargylic esters proceeded in a highly diastereoselective fashion. In 1990, Doyle et al. reported on a synthesis of racemic *N*,*N*-dimethyl-α-allenylglycine.[21] The key step of their synthesis was a [2,3]-sigmatropic rearrangement of *N*,*N*-dimethylamino propyne.

Recently two different approaches towards enantiomerically enriched α-allenylglycines and α-alkynylglycines utilizing tin organyls have been published. Hamon et al. prepared 2-allenylglycinates by treatment of allenyltriphenylstannane with 8-phenylmenthyl *N*-Boc-2-bromoglycinate, albeit in 53% yield and with *ee*s of 86%.[22] Utilizing allenyltributylstannane, Akiyama et al. succeeded in the preparation of α-alkynylglycinates.[23] With catalytic amounts of a copper-based Lewis acid in conjunction with chiral diphosphanes, treatment of an α-iminoglycinate gave the corresponding α-alkynylglycinates under optimized reaction conditions in yields of up to 93% but with only 86% *ee*s. Both methods suffer from the limited availability of substituted allenyltin organyls and complicated starting material preparation.

II. Results and Discussion

The strategy employed here for the synthesis of enantiomerically pure α-H-allenyl amino acids is illustrated in Scheme 2. Allenes were synthesized by Crabbé et al.,[24] who treated propargylic acetates with homocuprates. The reaction sequence starts with an attack of the homocuprate at the triple bond to afford a copper-substituted allene, which then yields the allene with reductive elimination of alkylcopper.[25–27] We tried to apply this method for the synthesis of bislactim ethers **11**, which upon acidic hydrolysis should give the allenylglycine methyl esters **15**.

Because the synthetic value of alkyl, aryl, and alkenyl homocuprates is well established, only a very few azaenolate cuprates have been described.[28,29] The bislactim ether homocuprate was generated from two equivalents of the lithiated bislactim ether of *cyclo*-(-L-Val-Gly-) (**9**) and one equivalent of copper(I)bromide/dimethyl sulfide complex at –30 °C. This homocuprate is fairly stable at temperatures lower than –30 °C but decomposes rapidly at temperatures higher than –20 °C, as judged by strongly diminished yields. Under similar reaction conditions, mixed organocuprates were not obtainable. The first experiments carried out with this cuprate and propargylic acetates failed because of the



Scheme 2. Reactions between the bislactim ether homocuprate and different propargylic bromides.

low reactivities of the acetates. Despite these results, reactions between the bislactim ether homocuprate and the propargylic bromides **10** were investigated. The results are summarized in Table 1. Treatment of the bislactim ether homocuprate with primary propargylic bromides afforded the dihydropyrazines **11** with excellent diastereoselectivities (> 98% *de*s). As byproducts (11–30%, >98% *de*s) the dihydropyrazines **12** were formed by a simple alkylation of the homocuprate. The adduct **11a** obtained from propargyl bromide (**10a**) decomposed after chromatographic purification within a few hours. With tertiary propargylic bromides the corresponding dihydropyrazines **11** were obtained as the only products with low to reasonable diastereoselectivities (22–40% *de*s). As would be expected, no S_N2 alkylation of the cuprate took place with tertiary propargylic bromides. The yields are usually below 50% because only one equivalent of the bislactim ether from its homocuprate is consumed.

Table 1. Allenyl- and propargyl-substituted dihydropyrazines **11** and **12**.

10,**11**,**12**	R^1	R^2	**11** yield [%]	*de* [%]	**12** yield [%]	*de* [%]
a	H	H	38	98	6	98
a	H	H	–	–	88	54 [a]
b	*n*Bu	H	42	98	14	98
c	*t*Bu	H	37	98	11	98
d	*n*Hex	H	40	98	16	98
e	Ph	H	24	98	30	98
f	$SiMe_3$	H	–	–	91	38 [a]
g	*n*Bu	Me	59	40	–	–
h	*n*Hex	Me	50	32	–	–
i	Ph	Me	59	22	–	–

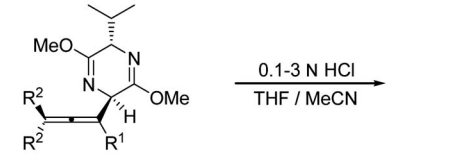
[a] These reactions were carried out with the lithiated bislactim ether of *cyclo*-(-L-Val-Gly-).

The isomers **11a**–**e** and **12a**–**e**, as well as the diastereomers of **11g**–**i**, were easily separated by flash chromatography on silica gel, so the allenyl-substituted bislactim ethers **11** can be obtained diastereomerically pure. The configurations of compounds **11** and **12** were estab-

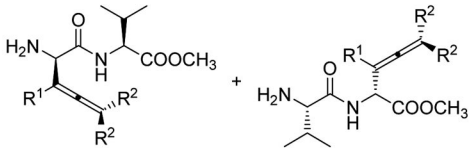
lished through their ^5J coupling constants. For *trans*-substituted dihydropyrazines ^5J constants of about 3.0–3.5 Hz are typical, whereas for the corresponding *cis* isomers ^5J constants of about 4.5–6.0 Hz were observed.

At this point it should be mentioned that α-propargylglycines are also obtainable by the bislactim ether method, because the lithiated bislactim ether reacts with primary propargyl bromides in a S_N2 fashion to yield the adducts **12a** and **12f**.

To our surprise the hydrolysis of the allenyl adducts **11** with HCl in THF/MeCN (0.1 N up to 3 N) did not afford the α-allenyl amino acid esters **15**. In these cases, the hydrolysis occurred only at one of the two imino ether functions, yielding 1:1 mixtures of dipeptide esters **13** and **14** in almost quantitative yield.

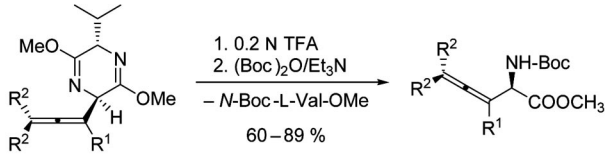


11



13 **14**

This result may be explained in terms of a nucleophilic attack of the chloride at the methyl imino ether group of the protonated bislactim ether.[30] Therefore, the hydrolysis of the bislactim ethers **11** with trifluoroacetic acid (TFA) was investigated. Unlike the chloride ion, the non-nucleophilic trifluoroacetate anion should not be able to cleave the imino ether bond. The results are summarized in Table 2.



(2*R*,5*S*)-**11** (*R*)-**15**

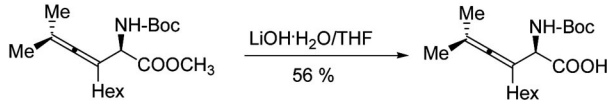
Table 2. Methyl α-allenylglycinates **15**.

11	**15**	R^1	R^2	Yield [%]	*Ee* [%]	$[\alpha]_D^{20}$[a]
b	**a**	*n*Bu	H	60	>95	–50.8
d	**b**	*n*Hex	H	83	>95	–28.4
g	**c**	*n*Bu	Me	68	>95	–36.3
h	**d**	*n*Hex	Me	77	>95	–24.2
h	*ent*-**d**	*n*Hex	Me	89	>95	+23.7[b]

[a] c = 1.0, $CHCl_3$. [b] Minor diastereomer (2*S*,5*S*)-**11h** was used to afford (*S*)-**15d**.

Hydrolysis of compounds **11** with TFA in THF (0.2 N) followed by protection of the amino group with $(Boc)_2O$/triethylamine afforded, besides methyl *N*-Boc-L-valinate, the hitherto unknown *N*-Boc-protected methyl α-allenylglycinates **15**. The crude methyl α-allenylglycinates, which were obtained after hydrolysis, were protected as their *N*-Boc derivatives because these compounds are more easily separable from methyl *N*-Boc-L-valinate by chromatography than the free amino acid esters.

In a model experiment it was demonstrated that the methyl α-allenylglycinates **15** can be hydrolyzed to the corresponding α-allenylglycines. Therefore, the *N*-Boc-protected methyl α-allenylglycinate **15d** was treated with 1.2 equiv. of lithium hydroxide in aqueous THF to afford, after aqueous workup and chromatographic purification, a 56% yield of the *N*-Boc-protected α-allenylglycine **16d**.

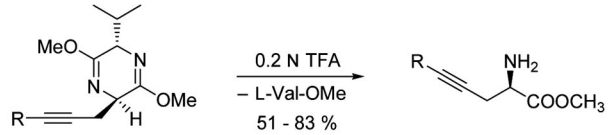


15d **16d**

As mentioned earlier, the lithiated bislactim ether of *cyclo*-(-L-Val-Gly-) (**9**) can be alkylated with primary propargyl bromides to afford the propargyl-substituted bislactim ethers **12**. Adducts **12a** and **12f** were isolated in 88 and 91% yields with *de*s of 54 and 38%, respectively. After chromatographic separation of diastereomers the propargyl-substituted bislactim ethers **12a** and **12f** were obtained diastereomerically pure. The configurations of the new stereogenic centers were once again established through the ^5J coupling constants.

This low diastereoselectivity for the alkylation step is somewhat surprising because the diastereoselectivity for the alkylation of the lithiated bislactim ether of *cyclo*-(-L-Val-Gly-) (**9**) usually varies between 75 and >95% *de*[31] Only for the alkylation with the relatively small methyl iodide and trimethylsilylmethyl iodide did the diastereoselectivity drop down to 43 and ca. 60% *de*.[32]

Hydrolysis of the diastereomerically pure progargyl-substituted bislactim ethers **12** afforded, besides methyl L-valinate, the methyl α-propargylglycinates **17**, which could usually be separated by bulb-to-bulb distillation (Table 3). Because methyl D-propargylglycinate (**17a**) and methyl L-valinate are not easily separable by distillation, **17a** can be prepared more conveniently through its trimethylsilyl derivative **17b** by simple desilylation.



(2*R*,5*S*)-**12** (*R*)-**17**

In this communication the asymmetric synthesis of enantiomerically pure (*R*)-allenylglycines and (*R*)-propargylglycines by use of the bislactim ether of *cyclo*-(-L-Val-Gly-) has

Table 3. Methyl α-propargyl glycinates **17**.

12	**17**	R	Yield [%]	*ee* [%]	$[\alpha]_D^{20}$
a	**a**	H	51	>95	+1.7[a]
f	**b**	$SiMe_3$	83	>95	–38.4[b]
f	*ent*-**b**	$SiMe_3$	78	>95	+38.1[b],[c]

[a] c = 1.0, EtOH. [b] c = 1.0, $CHCl_3$. [c] Minor diastereomer (2*S*,5*S*)-**12f** was used to afford (*S*)-**17b**.

been described. Likewise, (*S*)-α-allenylglycines can be obtained by use of the bislactim ether of *cyclo*-(-D-Val-Gly-). Both enantiomeric forms of the bislactim ether are commercially available.[33] Through the use of enantiomerically pure secondary propargyl bromides for this reaction enantio- and diastereomerically pure α-allenylglycines **3** should be obtainable.

Experimental Section

General: Infrared (IR) spectra were obtained with a Perkin–Elmer 298 spectrometer. NMR spectra were obtained with a Varian XL 200 or VXR 200 spectrometer for ^1H and ^{13}C NMR spectroscopy. Chemical shifts are given in parts per million (δ) with tetramethylsilane as an internal standard for ^1H and ^{13}C NMR spectroscopy. A diastereomeric purity of >98% was assumed when only the signals of one isomer were detectable in the ^1H and ^{13}C NMR spectra or in the capillary GC. Optical rotations were measured with a Perkin–Elmer Mod. 141 polarimeter. TLC analyses were performed on Polygram Sil G/UV_{254} silica gel plates. Silica gel (0.030–0.060 mm) from Macherey & Nagel, Düren was used for flash chromatography. Combustion analyses were carried out by the microanalytical laboratory of the University of Konstanz. If required, reactions were carried out under dry argon or nitrogen. All reagents were purified and dried by standard protocols prior to use. The bislactim ether **9** was purchased from Merck,[33] or prepared according to ref.[34] The propargylic alcohols, necessary for the preparation of the propargylic bromides **10**, were prepared by deprotonation of the corresponding alkynes either with ethylmagnesium bromide or with *n*-butyllithium and subsequent addition of the corresponding aldehydes or ketones.[35] The transformation of the propargylic alcohols into their bromides was carried out by addition of phosphorus tribromide (0.35 equiv.) to ethereal solutions of these alcohols and pyridine (0.2 equiv.) at –70 °C.[36]

General Procedure for the Preparation of Allenyl-Substituted Bislactim Ethers 11: *n*-Butyllithium (2.6 mL, 4.1 mmol of a 1.58 N solution in hexane) was added dropwise at –70 °C to a solution of the bislactim ether **9** (0.74 g, 4.0 mmol) in THF (10 mL) and stirring was continued for 10 min. Separately, dimethyl sulfide was added at room temp. to a suspension of copper(I) bromide/dimethyl sulfide complex (0.41 g, 2.0 mmol) in THF (10 mL) until the copper(I) bromide complex was completely dissolved (ca. 3–4 mL). The resulting solution was cooled to –70 °C and the solution of the yellow lithiated bislactim ether, prepared as described above, was added by cannula at –70 °C. The resulting orange solution was stirred for 30 min at –30 °C. A solution of the propargyl bromide **10** (4.0 mmol) in THF (5 mL) was added at –70 °C and stirring was continued for 12 h at –70 °C. Over 5 h the solution was allowed to warm to room temp. The heterogeneous mixture was filtered through silica gel (30 g) and the solid material was washed with diethyl ether (300 mL). The filtrate was concentrated by rotary evaporation and the residue was purified by flash chromatography on silica gel (70 g).

(2*R*,5*S*)-5-Isopropyl-3,6-dimethoxy-2-(propa-1,2-dienyl)-2,5-dihydropyrazine (11a): Bislactim ether **9** (0.70 g, 3.8 mmol), copper(I) bromide/dimethyl sulfide complex (0.39 g, 1.9 mmol), and propargyl bromide **10a** (0.45 g, 3.8 mmol) were used to obtain allenyl-substituted bislactim ether **11a** (0.32 g, 38%) and propargyl-substituted bislactim ether **12a** (51 mg, 6%) after flash chromatography with diethyl ether/petroleum ether (1:20).

Compound 11a: R_f = 0.13; diastereomeric purity >98%. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.66, 1.03 [2 × d, J = 6.8 Hz, 6 H, CH-$(CH_3)_2$], 2.27 [dsp, J = 6.8 and 3.4 Hz, 1 H, $CH(CH_3)_2$], 3.69 (s, 6 H, OCH_3), 3.92 (dd, $^3J = {}^5J$ = 3.4 Hz, 1 H, 5-H), 4.55 (ddd, $^5J_1 = {}^5J_2 = {}^5J_3$ = 3.4 Hz, 1 H, 2-H), 4.72–4.90 (m, 2 H, C=C=CH_2), 5.32 (ddd, $^3J = {}^4J_1 = {}^4J_2$ = 6.6 Hz, 2 H, C=C=CH_2–H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.55, 19.11 [$CH(CH_3)_2$], 31.46 [$CH(CH_3)_2$], 52.70, 52.81 (OCH_3), 54.36, 60.52 (C-2,5), 77.91, 91.46 (C=C=C), 162.13, 164.70 (C=N), 208.47 (C=C=C) ppm. IR (neat): $\tilde{\nu}$ = 1960 (C=C=C), 1690 (C=N) cm^{-1}. MS: *m*/*z* (%) = 222 (31) $[M]^+$, 183 (23), 179 (46), 141 (100).

Compound 12a: R_f = 0.08; diastereomeric purity >98%; spectroscopic data see below.

(2*R*,5*S*)-2-(Hepta-1,2-dien-3-yl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (11b): Bislactim ether **9** (0.74 g, 4.0 mmol), copper(I) bromide/dimethyl sulfide complex (0.41 g, 2.0 mmol), and propargyl bromide **10b** (0.70 g, 4.0 mmol) were used to obtain allenyl-substituted bislactim ether **11b** (0.47 g, 42%) and propargyl-substituted bislactim ether **12b** (0.16 g, 14%) after flash chromatography with diethyl ether/petroleum ether (1:50).

Compound 11b: R_f = 0.13; diastereomeric purity >98%. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.69, 1.07 [2 × d, J = 7 Hz, 6 H, CH-$(CH_3)_2$], 0.88 [t, J = 7 Hz, 3 H, $(CH_2)_3CH_3$], 1.32 [m, 4 H, $(CH_2)_2$-CH_3], 1.88 (m, 2 H, C=C=C–CH_2), 2.31 [dsp, J = 7 and 3.5 Hz, 1 H, $CH(CH_3)_2$], 3.71 (s, 6 H, OCH_3), 3.95 (dd, $^3J = {}^5J$ = 3.5 Hz, 1 H, 5-H), 4.54 (dt, ^4J = 1.3, ^5J = 3.5 Hz, 1 H, 2-H), 4.81, 4.83 (2 × t, ^5J = 1.2 Hz, 2 H, C=C=CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.97, 16.49, 19.20 [$CH(CH_3)_2$, $(CH_2)_3CH_3$], 22.41, 27.70, 29.55 (CH_2), 31.39 [$CH(CH_3)_2$], 52.67, 52.81 (OCH_3), 59.18, 60.55 (C-2,5), 77.64, 104.14 (C=C=C), 162.49, 164.96 (C=N), 207.08 (C=C=C) ppm. IR (neat): $\tilde{\nu}$ = 1960 (C=C=C), 1690. (C=N) cm^{-1}. MS: *m*/*z* (%) = 278 (20) $[M]^+$, 263 (4), 235 (12), 183 (35), 141 (100). $C_{16}H_{26}N_2O_2$ (278.39): calcd. C 69.03, H 9.41; found C 69.22, H 9.35.

Compound 12b: R_f = 0.09; diastereomeric purity >98%. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.69, 1.06 [2 × d, J = 7 Hz, 6 H, CH-$(CH_3)_2$], 0.89 [t, J = 7 Hz, 3 H, $(CH_2)_3CH_3$], 1.38 [m, 4 H, $(CH_2)_2$-CH_3], 2.29 [dsp, J = 7 and 3.5 Hz, 1 H, $CH(CH_3)_2$], 2.68 (m, 4 H, CH_2-C≡C–CH_2), 3.72 (s, 6 H, OCH_3), 4.01 (dd, $^3J = {}^5J$ = 3.5 Hz, 1 H, 5-H), 4.10 ppm (m, 1 H, 2-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.57, 16.56, 19.11 [$CH(CH_3)_2$, $(CH_2)_3CH_3$], 18.38, 21.66, 25.37, 30.96 (CH_2), 31.60 [$CH(CH_3)_2$], 52.49, 52.56 (OCH_3), 54.82, 60.90 (C-2,5), 75.81, 82.23 (C≡C), 162.21, 164.71 ppm (C=N). IR (neat): $\tilde{\nu}$ = 2220 (C≡C), 1690 (C=N) cm^{-1}.

(2*R*,5*S*)-2-(2,2-Dimethyl-3,4-pentadien-3-yl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (11c): Bislactim ether **9** (0.74 g, 4.0 mmol), copper(I) bromide/dimethyl sulfide complex (0.41 g, 2.0 mmol), and propargyl bromide **10c** (0.70 g, 4.0 mmol) were used to obtain allenyl-substituted bislactim ether **11c** (0.41 g, 37%) and propargyl-substituted bislactim ether **12c** (0.12 g, 11%) after flash chromatography with diethyl ether/petroleum ether (1:50).

Compound 11c: R_f = 0.11; diastereomeric purity >98%. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.70, 1.08 [2 × d, J = 7 Hz, 6 H, CH-(CH_3)$_2$], 1.19 [s, 9 H, C(CH_3)$_3$], 2.26 [dsp, J = 7 Hz and 3.5 Hz, 1 H, CH(CH_3)$_2$], 3.67, 3.69 (2 × s, 6 H, OCH_3), 3.95 (dd, ^3J = ^5J = 3.5 Hz, 1 H, 5-H), 4.57 (d, ^5J = 3.5 Hz, 1 H, 2-H), 4.72 ppm (m, 2 H, C=C=CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.23, 19.00 [CH(CH_3)$_2$], 27.48 [C(CH_3)$_3$], 29.55 [C(CH_3)$_3$], 32.05 [CH(CH_3)$_2$], 52.44, 52.53 (OCH_3), 54.38, 60.77 (C-2,5), 78.50, 104.33 (C=C=C), 163.20, 164.03 (C=N), 207.19 ppm (C=C=C). IR (neat): $\tilde{\nu}$ = 1955 (C=C=C), 1690 (C=N) cm^{-1}. MS: *m*/*z* (%) = 278 (6) [M]$^+$, 263 (3), 235 (1), 183 (37), 141 (100). $C_{16}H_{26}N_2O_2$ (278.39): calcd. C 69.03, H 8.41; found C 68.94, H 8.29.

Compound 12c: R_f = 0.07; diastereomeric purity >98%. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.68, 1.05 [2 × d, J = 7 Hz, 6 H, CH-(CH_3)$_2$], 1.13 [s, 9 H, C(CH_3)$_3$], 2.28 [dsp, J = 7 and 3.5 Hz, 1 H, CH(CH_3)$_2$], 2.59, 2.73 (2 × dd, AB part of ABX, J_{AB} = 11, J_{AX} = J_{BX} = 4 Hz, 2 H, CH_2), 3.71, 3.72 (2 × s, 6 H, OCH_3), 4.02 (dd, ^3J = ^5J = 3.5 Hz, 1 H, 5-H), 4.11 ppm (ddd, X part of ABX, J_{AX} = J_{BX} = 4, ^5J = 3.5 Hz, 1 H, 2-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.56, 19.17 [CH(CH_3)$_2$], 25.38 (CH_2), 27.25 [C(CH_3)$_3$], 31.18 [C(CH_3)$_3$], 31.56 [CH(CH_3)$_2$], 52.38, 52.45 (OCH_3), 54.91, 60.95 (C-2,5), 74.31, 91.07 (C≡C), 162.09, 164.51 ppm (C=N). IR (neat): $\tilde{\nu}$ = 2220 (C≡C), 1690 (C=N) cm^{-1}.

(2*R*,5*S*)-5-Isopropyl-3,6-dimethoxy-2-(nona-1,2-dien-3-yl)-2,5-dihydropyrazine (11d): Bislactim ether **9** (0.74 g, 4.0 mmol), copper(I) bromide/dimethyl sulfide complex (0.41 g, 2.0 mmol), and propargyl bromide **10d** (0.81 g, 4.0 mmol) were used to afford allenyl-substituted bislactim ether **11d** (0.49 g, 40%) and propargyl-substituted bislactim ether **12d** (0.20 g, 16%) after flash chromatography with diethyl ether/petroleum ether (1:20).

Compound 11d: R_f = 0.38; diastereomeric purity >98%. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.70, 1.09 [2 × d, J = 7 Hz, 6 H, CH-(CH_3)$_2$], 0.88 [t, J = 7 Hz, 3 H, (CH_2)$_5$$CH_3$], 1.35 [m, 8 H, ($CH_2$)$_4$-$CH_3$], 1.90 (m, 2 H, C=C=C–$CH_2$), 2.34 [dsp, J = 7 and 3.5 Hz, 1 H, CH(CH_3)$_2$], 3.72 (s, 6 H, OCH_3), 3.96 (dd, ^3J = ^5J = 3.5 Hz, 1 H, 5-H), 4.55 (dt, $^5J_1$ = 3.5, $^5J_2$ = 1.3 Hz, 1 H, 2-H), 4.84 ppm (dt, $^5J_1$ = 3.8, $^5J_2$ = 1.3 Hz, 2 H, C=C=CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.10, 16.47, 19.17 [CH(CH_3)$_2$, (CH_2)$_3$$CH_3$], 22.65, 27.31, 27.98, 29.01, 31.71 (CH_2), 31.35 [CH(CH_3)$_2$], 52.60, 52.73 (OCH_3), 59.13, 60.48 (C-2,5), 77.54, 104.08 (C=C=C), 162.29, 164.74 (C=N), 206.85 ppm (C=C=C). IR (neat): $\tilde{\nu}$ = 1960 (C=C=C), 1690 (C=N) cm^{-1}. MS: *m*/*z* (%) = 306 (11) [M]$^+$, 291 (5), 263 (33), 183 (41), 141 (100). $C_{18}H_{30}N_2O_2$ (306.45): calcd. C 70.55, H 9.87; found C 70.04, H 9.41.

Compound 12d: R_f = 0.24; diastereomeric purity >98%. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.71, 1.03 [2 × d, J = 7 Hz, 6 H, CH-(CH_3)$_2$], 0.87 [t, J = 7 Hz, 3 H, (CH_2)$_5$CH_3], 1.35 [m, 8 H, (CH_2)$_4$-CH_3], 2.29 [dsp, J = 7 and 3.5 Hz, 1 H, CH(CH_3)$_2$], 2.69 (m, 4 H, CH_2-C≡C–CH_2), 3.70, 3.71 (2 × s, 6 H, OCH_3), 4.02 (dd, ^3J = ^5J = 3.5 Hz, 1 H, 5-H), 4.08 ppm (m, 1 H, 2-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.88, 16.84, 19.45 [CH(CH$_3$)$_2$, (CH_2)$_3$$CH_3$], 18.35, 21.68, 25.36, 28.94, 29.72, 30.82 (CH_2), 31.55 [CH(CH_3)$_2$], 52.41, 52.55 (OCH_3), 54.70, 60.78 (C-2,5), 75.70, 82.11 (C≡C), 162.00, 164.39 (C=N) ppm. IR (neat): $\tilde{\nu}$ = 2220 (C≡C), 1690 (C=N) cm^{-1}.

(2*R*,5*S*)-5-Isopropyl-3,6-dimethoxy-2-(1-phenylpropa-1,2-dien-1-yl)-2,5-dihydropyrazine (11e): Bislactim ether **9** (0.74 g, 4.0 mmol), copper(I) bromide/dimethyl sulfide complex (0.41 g, 2.0 mmol), and propargyl bromide **10e** (0.78 g, 4.0 mmol) were used to obtain allenyl-substituted bislactim ether **11e** (0.29 g, 24%) and propargyl-substituted bislactim ether **12e** (0.36 g, 30%) after flash chromatography with diethyl ether/petroleum ether (1:5).

Compound 11e: R_f = 0.41; diastereomeric purity >98%. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.74, 1.06 [2 × d, J = 7 Hz, 6 H, CH-(CH_3)$_2$], 2.32 [dsp, J = 7 and 3.5 Hz, 1 H, CH(CH_3)$_2$], 3.66, 3.68 (2 × s, 6 H, OCH_3), 3.94 (dd, ^3J = ^5J = 3.5 Hz, 1 H, 5-H), 5.01 (m, 1 H, 2-H), 5.13 (m, 2 H, C=C=CH_2), 7.35 (m, 5H. C_6H_5) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.57, 19.19 [CH(CH$_3$)$_2$], 31.42 [CH(CH_3)$_2$], 52.56, 52.67 (OCH_3), 57.52, 60.56 (C-2,5), 79.46, 106.54 (*C*=C=*C*), 126.78, 126.89, 128.21, 134.73 (C_6H_5), 162.27, 164.61 (C=N), 209.40 (C=*C*=C) ppm. IR (neat): $\tilde{\nu}$ = 1955 (C=C=C), 1690 (C=N) cm^{-1}. MS: *m*/*z* (%) = 298 (40) [M]$^+$, 283 (5), 198 (4), 183 (32), 141 (100), 115 (30). $C_{18}H_{22}N_2O_2$ (298.38): calcd. C 72.46, H 7.43; found C 72.34, H 7.43.

Compound 12e: R_f = 0.31; diastereomeric purity >98%. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.68, 1.07 [2 × d, J = 7 Hz, 6 H, CH-(CH_3)$_2$], 2.30 [dsp, J = 7 and 3.5 Hz, 1 H, CH(CH_3)$_2$], 2.88, 2.99 (2 × dd, AB part of ABX, J_{AB} = 11.5, J_{AX} = J_{BX} = 4.5 Hz, 2 H, CH_2), 3.64 (s, 6 H, OCH_3), 4.05 (dd, ^3J = ^5J = 3.5 Hz, 1 H, 5-H), 4.22 (ddd, X part of ABX, J_{AX} = J_{BX} = 4.5, ^5J = 3.5 Hz, 1 H, 2-H), 7.27 (m, 5H. C_6H_5) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.53, 19.12 [CH(CH$_3$)$_2$], 26.13 (CH_2), 31.55 [CH(CH_3)$_2$], 52.56, 52.61 (OCH_3), 54.66, 60.87 (C-2,5), 82.40, 86.16 (C≡C), 123.78, 127.62, 128.16, 131.57 (C_6H_5), 161.93, 164.84 (C=N) ppm. IR (neat): $\tilde{\nu}$ = 2220 (C≡C), 1690 (C=N) cm^{-1}.

(2*R*,5*S*)-5-Isopropyl-3,6-dimethoxy-2-(1-methylocta-2,3-dien-4-yl)-2,5-dihydropyrazine (11g): Bislactim ether **9** (0.74 g, 4.0 mmol), copper(I) bromide/dimethyl sulfide complex (0.41 g, 2.0 mmol), and propargyl bromide **10g** (0.81 g, 4.0 mmol) were used to obtain (2*R*,5*S*)-**11g** (0.51 g, 42%) and (2*S*,5*S*)-**11g** (0.22 g, 18%) after flash chromatography with diethyl ether/petroleum ether (1:10); the diastereomeric ratio was 70:30, 40% *de*.

Compound (2*R*,5*S*)-11g: R_f = 0.50. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.69, 1.08 [2 × d, J = 7 Hz, 6 H, CH(CH_3)$_2$], 0.89 [t, J = 7 Hz, 3 H, (CH_2)$_3$CH_3], 1.34 [m, 4 H, (CH_2)$_2$$CH_3$], 1.65, 1.67 [2 × s, 6 H, C=C=C-(CH_3)$_2$], 1.98 (m, 2 H, C=C=C–CH_2), 2.33 [dsp, J = 7 and 3.5 Hz, 1 H, CH(CH_3)$_2$], 3.70, 3.72 (2 × s, 6 H, OCH_3), 3.86 (dd, ^3J = ^5J = 3.5 Hz, 1 H, 5-H), 4.27 (d, ^5J = 3.5 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.05, 16.42, 19.29 [CH-(CH_3)$_2$, (CH_2)$_3$CH_3], 20.44, 20.64 [C=C=C-(CH_3)$_2$], 22.29, 29.36, 29.82 (CH_2), 30.88 [CH(CH_3)$_2$], 52.47, 52.62 (OCH_3), 59.33, 60.08 (C-2,5), 98.28, 102.61 (*C*=C=*C*), 163.19, 164.61 (C=N), 199.52 (C=*C*=C) ppm. IR (neat): $\tilde{\nu}$ = 1960 (C=C=C), 1690 (C=N) cm^{-1}. MS: *m*/*z* (%) = 306 (11) [M]$^+$, 263 (5), 249 (3), 183 (13), 141 (100), 70 (72). $C_{18}H_{30}N_2O_2$ (306.45): calcd. C 70.55, H 9.87; found C 69.94, H 9.29.

Compound (2*S*,5*S*)-11g: R_f = 0.27. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.79, 1.04 [2 × d, J = 7 Hz, 6 H, CH(CH_3)$_2$], 0.90 [t, J = 8 Hz, 3 H, (CH_2)$_3$CH_3], 1.35 [m, 4 H, (CH_2)$_2$$CH_3$], 1.67, 1.68 [2 × s, 6 H, C=C=C-(CH_3)$_2$], 2.08 [m, 3 H, C=C=C–CH_2, CH(CH_3)$_2$], 3.70, 3.71 (2 × s, 6 H, OCH_3), 3.85 (dd, ^3J = 6, ^5J = 4 Hz, 1 H, 5-H), 4.46 (d, ^5J = 4 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.08, 18.65, 19.97 [CH(CH$_3$)$_2$, (CH_2)$_3$$CH_3$], 20.38, 20.50 [C=C=C-($CH_3$)$_2$], 22.32, 29.91, 30.79 ($CH_2$), 32.71 [$C$H($CH_3$)$_2$], 52.32 ($OCH_3$), 59.09, 61.49 (C-2,5), 98.25, 103.58 (*C*=C=*C*), 162.85, 164.34 (C=N), 199.06 (C=*C*=C) ppm. IR (neat): $\tilde{\nu}$ = 2220 (C≡C), 1690 (C=N) cm^{-1}.

(2*R*,5*S*)-5-Isopropyl-3,6-dimethoxy-2-(1-methyldeca-2,3-dien-4-yl)-2,5-dihydropyrazine (11h): Bislactim ether **9** (0.74 g, 4.0 mmol), copper(I) bromide/dimethyl sulfide complex (0.41 g, 2.0 mmol), and propargyl bromide **10h** (0.92 g, 4.0 mmol) were used to obtain (2*R*,5*S*)-**11h** (0.44 g, 33%) and (2*S*,5*S*)-**11h** (0.23 g, 17%) after flash chromatography with diethyl ether/petroleum ether (1:20); the diastereomeric ratio was 66:34, 32% *de*.

Compound (2*R*,5*S*)-11h: R_f = 0.28. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.68, 1.08 [2 × d, J = 7 Hz, 6 H, CH(CH_3)$_2$], 0.88 [t, J = 8 Hz, 3 H, (CH$_2$)$_5$CH_3], 1.33 [m, 8 H, (CH_2)$_4$CH$_3$], 1.66, 1.68 [2 × s, 6 H, C=C=C-(CH$_3$)$_2$], 1.95 (m, 2 H, C=C=C–CH_2), 2.31 [dsp, J = 7 and 3.5 Hz, 1 H, CH(CH$_3$)$_2$], 3.68, 3.70 (2 × s, 6 H, OCH$_3$), 3.82 (dd, ^3J = ^5J = 3.5 Hz, 1 H, 5-H), 4.45 (d, ^5J = 3.5 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.14, 16.40, 19.29 (CH-(*C*H$_3$)$_2$, (CH$_2$)$_5$*C*H$_3$), 20.45, 20.65 [C=C=C-(*C*H$_3$)$_2$], 22.73, 27.61, 28.93, 29.64, 31.87 (CH$_2$), 30.86 [*C*H(CH$_3$)$_2$], 52.46, 52.60 (OCH$_3$), 59.35, 60.07 (C-2,5), 98.26, 102.64 (*C*=C=*C*), 163.17, 164.56 (C=N), 199.53 (C=*C*=C) ppm. IR (neat): $\tilde{\nu}$ = 1955 (C=C=C), 1690 (C=N) cm^{-1}. MS: *m*/*z* (%) = 334 (14) [M]$^+$, 291 (16), 264 (7), 249 (12), 183 (46), 141 (100). $C_{20}H_{34}N_2O_2$ (334.50): calcd. C 71.81, H 10.24; found C 71.70, H 10.10.

Compound (2*S*,5*S*)-11h: R_f = 0.05. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.83, 1.04 [2 × d, J = 7 Hz, 6 H, CH(CH_3)$_2$], 0.90 [t, J = 8 Hz, 3 H, (CH$_2$)$_5$CH_3], 1.33 [m, 8 H, (CH_2)$_4$CH$_3$], 1.63, 1.65 [2 × s, 6 H, C=C=C-(CH$_3$)$_2$], 2.07 [m, 3 H, C=C=C–CH_2, CH(CH$_3$)$_2$], 3.69, 3.71 (2 × s, 6 H, OCH$_3$), 3.84 (dd, ^3J = 6, ^5J = 4 Hz, 1 H, 5-H), 4.50 (d, ^5J = 4 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.15, 18.66, 19.96 (CH(*C*H$_3$)$_2$, (CH$_2$)$_5$*C*H$_3$), 20.38, 20.51 [C=C=C-(*C*H$_3$)$_2$], 22.74, 27.69, 28.95, 31.05, 31.90 (CH$_2$), 32.73 [*C*H(CH$_3$)$_2$], 52.33 (OCH$_3$), 59.08, 61.48 (C-2,5), 98.26, 103.61 (*C*=C=*C*), 162.86, 164.35 (C=N), 199.04 (C=*C*=C) ppm. IR (neat): $\tilde{\nu}$ = 2220 (C≡C), 1690 (C=N) cm^{-1}.

(2*R*,5*S*)-5-Isopropyl-3,6-dimethoxy-2-(3-methyl-1-phenylbuta-1,2-dien-1-yl)-2,5-dihydropyrazine (11i): Bislactim ether **9** (0.74 g, 4.0 mmol), copper(I) bromide/dimethyl sulfide complex (0.41 g, 2.0 mmol), and propargyl bromide **10i** (0.89 g, 4.0 mmol) were used to obtain (2*R*,5*S*)-**11i** (0.47 g, 36%) and (2*S*,5*S*)-**11i** (0.30 g, 23%) after flash chromatography with diethyl ether/petroleum ether (1:20); the diastereomeric ratio was 61:39, 22% *de*.

Compound (2*R*,5*S*)-11i: R_f = 0.13. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.72, 1.09 [2 × d, J = 7 Hz, 6 H, CH(CH_3)$_2$], 1.74, 1.77 [2 × s, 6 H, C=C=C-(CH$_3$)$_2$], 2.35 [dsp, J = 7 and 3.5 Hz, 1 H, CH(CH$_3$)$_2$], 3.67, 3.68 (2 × s, 6 H, OCH$_3$), 3.88 (dd, ^3J = ^5J = 3.5 Hz, 1 H, 5-H), 5.05 (d, ^5J = 3.5 Hz, 1 H, 2-H), 7.32 (m, 5 H, C$_6$H$_5$) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.45 19.30 [CH(*C*H$_3$)$_2$], 19.80, 20.25 [C=C=C-(*C*H$_3$)$_2$], 30.91 [*C*H(CH$_3$)$_2$], 52.47, 52.59 (OCH$_3$), 57.40, 60.11 (C-2,5), 100.79, 105.29 (*C*=C=*C*), 126.33, 126.90, 128.10, 136.66 (C$_6$H$_5$), 162.95, 164.23 (C=N), 202.17 (C=*C*=C) ppm. IR (neat): $\tilde{\nu}$ = 1955 (C=C=C), 1690 (C=N) cm^{-1}. MS: *m*/*z* (%) = 326 (27) [M]$^+$, 311 (2), 183 (25), 141 (100), 128 (15). $C_{20}H_{26}N_2O_2$ (326.44): calcd. C 73.59, H 8.03; found C 73.62, H 8.11.

Compound (2*S*,5*S*)-11i: R_f = 0.38. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.82, 1.07 [2 × d, J = 7 Hz, 6 H, CH(CH_3)$_2$], 1.71, 1.78 [2 × s, 6 H, C=C=C-(CH$_3$)$_2$], 2.12 [dsp, J = 7 and 4 Hz, 1 H, CH(CH$_3$)$_2$], 3.66, 3.67 (2 × s, 6 H, OCH$_3$), 3.90 (dd, ^3J = 4, ^5J = 5 Hz, 1 H, 5-H), 5.12 (d, ^5J = 5 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.32, 19.88 [CH(*C*H$_3$)$_2$], 20.01, 20.03 [C=C=C-(*C*H$_3$)$_2$], 32.40 [*C*H(CH$_3$)$_2$], 52.29, 52.36 (OCH$_3$), 57.26, 61.17 (C-2,5), 100.72 105.41 (*C*=C=*C*), 126.32, 126.86, 128.08, 137.25 (C$_6$H$_5$), 162.18, 163.67 (C=N), 202.06 (C=*C*=C) ppm. IR (neat): $\tilde{\nu}$ = 2220 (C≡C), 1690 (C=N) cm^{-1}.

General Procedure for Hydrolysis of Allenyl-Substituted Bislactim Ethers 11 to Afford Methyl α-Allenyl-*N*-Boc-glycinates 15: Trifluoroacetic acid (0.2 N, 15 mL, 3.0 mmol) was added at 0 °C to a stirred solution of the bislactim ether **11** (1.0 mmol) in THF (10 mL) and stirring was continued at room temp. until the bislactim ether **11** was no longer detectable by TLC analysis (22–36 h). The reaction mixture was concentrated to dryness and the residue was dissolved in dichloromethane (15 mL). A solution of di-*tert*-butyl dicarbonate [(Boc)$_2$O, 0.65 g, 3.0 mmol] in dichloromethane (5 mL) was added at room temp., and subsequently triethylamine (0.35 mL, 2.5 mmol) was added at –5 °C. After stirring at room temp. for 12 h the reaction mixture was extracted with HCl (0.1 N, 20 mL). The aqueous layer was reextracted with dichloromethane (20 mL), the combined organic layers were dried with $MgSO_4$, and the solvent was evaporated in vacuo. The residue – the crude methyl *tert*-butyloxycarbonyl-α-allenyl glycinates **15** and methyl *N*-*tert*-butyloxycarbonyl-L-valinate – was purified by chromatography on silica gel (70 g).

Methyl (2*R*)-3-Butyl-2-[(*tert*-butyloxycarbonyl)amino]penta-3,4-dienoate (15a): Compound **11b** (0.28 g, 1.0 mmol) was used to obtain **15a** (0.17 g, 60%) after flash chromatography with diethyl ether/petroleum ether (1:5). R_f = 0.32. $[\alpha]_D^{20}$ = –50.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 [t, J = 7 Hz, 3 H, (CH$_2$)$_3$CH_3], 1.28 [m, 4 H, (CH_2)$_2$CH$_3$], 1.42 [s, 9 H, C(CH$_3$)$_3$], 2.02 (m, 2 H, C=C=C–CH_2), 3.71 (s, 3 H, OCH$_3$), 4.64 (d, J = 8 Hz, 1 H, 2-H), 4.86, 4.91 (AB signal, $^2J_{AB}$ = 3 Hz, 2 H, C=C=CH$_2$), 5.16 (br d, J = 8 Hz, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.99 [(CH$_2$)$_3$*C*H$_3$], 22.51, 27.54, 30.92 (CH$_2$), 28.20 [C(*C*H$_3$)$_3$], 52.30 (OCH$_3$), 55.35 (C-2), 79.80, 101.92 (*C*=C=*C*), 79.98 [*C*(CH$_3$)$_3$], 155.03 [(CH$_3$)$_3$CO-*C*=O], 171.40 (*C*OOCH$_3$), 206.00 (C=*C*=C) ppm. IR (neat): $\tilde{\nu}$ = 3420–3200 (NH), 1960 (C=C=C), 1740 (C=O) cm^{-1}. MS: *m*/*z* (%) = 226 (1) [M – C$_4$H$_9$]$^+$, 209 (1), 172 (12), 158 (2), 116 (21), 72 (28), 57 (100). $C_{15}H_{25}NO_4$ (283.37): calcd. C 63.56, H 8.89; found C 63.34, H 8.62.

Methyl (2*R*)-2-[(*tert*-Butyloxycarbonyl)amino]-3-hexylpenta-3,4-dienoate (15b): Compound **11d** (0.31 g, 1.0 mmol) was used to obtain **15b** (0.26 g, 83%) after flash chromatography with diethyl ether/petroleum ether (1:5). R_f = 0.45. $[\alpha]_D^{20}$ = –28.4 (c = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86 [t, J = 7 Hz, 3 H, (CH$_2$)$_5$CH_3], 1.28 [m, 8 H, (CH_2)$_4$CH$_3$], 1.44 [s, 9 H, C(CH$_3$)$_3$], 2.02 (m, 2 H, C=C=C–CH$_2$), 3.65 (s, 3 H, OCH$_3$), 4.67 (d, J = 8.5 Hz, 1 H, 2-H), 4.89, 4.94 (AB signal, $^2J_{AB}$ = 3 Hz, 2 H, C=C=CH$_2$), 5.18 (br d, J = 8.5 Hz, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.97 [(CH$_2$)$_5$*C*H$_3$], 22.51, 27.20, 28.72, 29.21, 31.53 (CH$_2$), 28.21 [C(*C*H$_3$)$_3$], 52.24 (OCH$_3$), 55.26 (C-2), 79.62, 101.89 (*C*=C=*C*), 79.93 [*C*(CH$_3$)$_3$], 154.99 [(CH$_3$)$_3$CO-*C*=O], 171.24 (*C*OOCH$_3$), 205.16 (C=*C*=C) ppm. IR (neat): $\tilde{\nu}$ = 3420–3200 (NH), 1960 (C=C=C), 1740 (C=O) cm^{-1}. MS: *m*/*z* (%) = 255 (38) [M – C$_4$H$_8$]$^+$, 240 (5), 223 (21), 196 (43), 170 (54), 57 (100). $C_{17}H_{29}NO_4$ (311.42): calcd. C 65.55, H 9.39; found C 65.17, H 9.07.

Methyl (2*R*)-3-Butyl-2-[(*tert*-butyloxycarbonyl)amino]-5-methylhexa-3,4-dienoate (15c): Compound **11g** (0.31 g, 1.0 mmol) was used to obtain **15c** (0.21 g, 68%) after flash chromatography with diethyl ether/petroleum ether (1:15). R_f = 0.17. $[\alpha]_D^{20}$ = –36.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 [t, J = 7 Hz; 3 H, (CH$_2$)$_3$CH_3], 1.40 [m, 4 H, (CH_2)$_2$CH$_3$], 1.45 [s, 9 H, C(CH$_3$)$_3$], 1.68, 1.69 [2 × s, 6 H, C=C=C(CH$_3$)$_2$], 2.03 (t, J = 7 Hz, 2 H, C=C=C–CH$_2$), 3.71 (s, 3 H, OCH$_3$), 4.61 (d, J = 8.5 Hz, 1 H, 2-H), 5.09 (br d, J = 8.5 Hz, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.11 [(CH$_2$)$_3$*C*H$_3$], 20.37, 20.51 [C=C=C(*C*H$_3$)$_2$], 22.55, 27.29, 30.99 (CH$_2$), 28.29 [C(*C*H$_3$)$_3$], 52.10 (OCH$_3$), 56.14 (C-2), 79.91 [*C*(CH$_3$)$_3$], 100.49, 100.69 (*C*=C=*C*), 155.39 [(CH$_3$)$_3$-CO-*C*=O], 171.91 (*C*OOCH$_3$), 198.50 (C=*C*=C) ppm. IR (neat): $\tilde{\nu}$ = 3420–3200 (NH), 1960 (C=C=C), 1740 (C=O) cm^{-1}. MS: *m*/*z* (%) = 255 (19) [M – C$_4$H$_8$]$^+$, 238 (5), 198 (14), 123 (31), 81 (52), 57 (100). $C_{17}H_{29}NO_4$ (311.42): calcd. C 65.55, H 9.39; found C 65.23, H 9.02.

Methyl (2*R*)-2-[(*tert*-Butyloxycarbonyl)amino]-3-hexyl-5-methyl-3,4-hexadienoate (15d): Compound (2*R*,5*S*)-**11h** (0.33 g, 1.0 mmol) was used to obtain (2*R*)-**15d** (0.26 g, 77%) after flash chromatog-

raphy with diethyl ether/petroleum ether (1:10). R_f = 0.17. $[\alpha]_D^{20}$ = –24.2 (*c* = 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.88 [t, *J* = 7 Hz, 3 H, $(CH_2)_5CH_3$], 1.38 [m, 8 H, $(CH_2)_4CH_3$], 1.45 [s, 9 H, $C(CH_3)_3$], 1.68, 1.71 [2 × s, 6 H, C=C=C$(CH_3)_2$], 2.02 (t, *J* = 7 Hz, 2 H, C=C=C–CH_2), 3.70 (s, 3 H, OCH_3), 4.61 (d, *J* = 8.5 Hz, 1 H, 2-H), 5.09 (br d, *J* = 8.5 Hz, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.10 [$(CH_2)_5CH_3$], 20.35, 20.52 [C=C=C$(CH_3)_2$], 22.68, 27.50, 28.77, 30.37, 31.77 (CH_2), 28.34 [$C(CH_3)_3$], 52.13 (OCH_3), 56.08 (C-2), 79.85 [$C(CH_3)_3$], 100.49, 100.76 (C=C=C), 155.21 [$(CH_3)_3CO$-C=O], 171.86 ($COOCH_3$), 198.40 (C=C=C) ppm. IR (neat): $\tilde{\nu}$ = 3420–3200 (NH), 1960 (C=C=C), 1740 (C=O) cm^{-1}. MS: *m*/*z* (%) = 283 (11) [M – C_4H_8]$^+$, 268 (5), 250 (18), 225 (18), 57 (100). $C_{19}H_{33}NO_4$ (339.47): calcd. C 67.21, H 9.81; found C 66.96, H 9.64.

Methyl (2*S*)-2-[(*tert*-Butyloxycarbonyl)amino]-3-hexyl-5-methylhexa-3,4-dienoate (15d): Compound (2*S*,5*S*)-**11h** (0.33 g, 1.0 mmol) was used to obtain (2*S*)-**15d** (0.30 g, 89%) after flash chromatography with diethyl ether/petroleum ether (1:10). R_f = 0.18. $[\alpha]_D^{20}$ = +23.7 (*c* = 1.0, $CHCl_3$); Spectroscopic data were identical with those obtained for (2*R*)-**15d**.

(2*R*)-2-[(*tert*-Butyloxycarbonyl)amino]-3-hexyl-5-methylhexa-3,4-dienoic Acid (16d): Lithium hydroxide monohydrate (30 mg, 0.71 mmol) was added at 0 °C to a stirred solution of (2*R*)-**15d** (200 mg, 0.59 mmol) in THF (15 mL) and H_2O (5 mL) and stirring was continued at room temp. for 48 h. The solvent was evaporated in vacuo to dryness and the residue was dissolved in phosphate buffer solution (20 mL, pH 7) and dichloromethane (20 mL). The aqueous layer was extracted with dichloromethane (2 × 20 mL), the combined organic layers were dried with $MgSO_4$, and the solvent was removed in vacuo. The residue was purified by chromatography on silica gel (70 g) with diethyl ether/petroleum ether (1:1) to yield α-allenylglycine **16d** (106 mg, 56%). R_f = 0.30. $[\alpha]_D^{20}$ = –34.6 (*c* = 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.88 [t, *J* = 7 Hz, 3 H, $(CH_2)_5CH_3$], 1.32 [m, 8 H, $(CH_2)_4CH_3$], 1.45 [s, 9 H, $C(CH_3)_3$], 1.69, 1.70 [2 × s, 6 H, C=C=C$(CH_3)_2$], 2.07 (t, *J* = 7.5 Hz, 2 H, C=C=C–CH_2), 4.59 (d, *J* = 8 Hz, 1 H, 2-H), 5.09 (br d, *J* = 8 Hz, 1 H, NH), 9.30 (broad, 1 H, COOH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.09 [$(CH_2)_5CH_3$], 20.16, 20.53 [C=C=C$(CH_3)_2$], 22.67, 27.46, 28.77, 30.42, 31.78 (CH_2), 28.32 [$C(CH_3)_3$], 55.87 (C-2), 80.09 [$C(CH_3)_3$], 100.27, 101.46 (C=C=C), 155.27 [$(CH_3)_3CO$-C=O], 176.73 (COOH), 198.49 (C=C=C) ppm. IR (neat): $\tilde{\nu}$ = 3400–3200 (OH, NH), 1955 (C=C=C) cm^{-1}. MS: *m*/*z* (%) = 269 (9) [M – C_4H_8]$^+$, 252 (5), 225 (6), 208 (32), 110 (33), 57 (39), 41 (100). $C_{18}H_{31}NO_4$ (325.45): calcd. C 66.41, H 9.61; found C 66.05, H 9.83.

General Procedure for Preparation of Propargyl-Substituted Bislactim Ethers 12: *n*-Butyllithium (7.0 mL, 11 mmol of a 1.58 N solution in hexane) was added dropwise at –70 °C to a solution of bislactim ether **9** (1.84 g, 10 mmol) in THF (25 mL) and stirring was continued for 10 min. A solution of the propargyl bromide **10** (12 mmol) in THF (10 mL) was added at –70 °C and stirring was continued for 4 h at –70 °C. The solution was allowed to warm to room temp. over 1 h, the solvent was removed in vacuo, and the residue was dissolved in diethyl ether (50 mL) and H_2O (50 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 30 mL). The combined organic layers were dried with $MgSO_4$, the diethyl ether was removed in vacuo, and the residue was purified by bulb-to-bulb distillation. The diastereomers (2*R*,5*S*)-**12** and (2*S*,5*S*)-**12** were separated by flash chromatography on silica gel.

5-Isopropyl-3,6-dimethoxy-2-propargyl-2,5-dihydropyrazine (12a): Bislactim ether **9** (1.84 g, 10 mmol) and propargyl bromide **10a** (1.43 g, 12 mmol) were used to obtain **12a** (1.95 g, 88%) after bulb-to-bulb distillation; b.p. 70–80 °C/0.1 Torr; the diastereomeric ratio was 77:23, 54% *de*. After chromatographic separation with diethyl ether/petroleum ether (1:8) the diastereomers (2*R*,5*S*)-**12a** (1.45 g, 65%) and (2*S*,5*S*)-**12a** (0.41 g, 18%) were obtained as colorless oils that crystallized upon refrigeration.

Compound (2*R*,5*S*)-12a: R_f = 0.20; m.p. 38 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.66; 1.04 [2 × d, *J* = 7 Hz, 6 H, CH-$(CH_3)_2$], 1.87 (t, ^4J = 2.5 Hz, 1 H, C≡C–H), 2.26 [dsp, *J* = 3,5 and 7 Hz, 1 H, $CH(CH_3)_2$], 2.58–2.82 (m, 2 H, C≡C–CH_2), 3.69, 3.70 (2 × s, 6 H, OCH_3), 4.02 (dd, ^3J = ^5J = 3.5 Hz, 1 H, 5-H), 4.08 (dt, ^3J = 2.5, ^5J = 3.5 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.48, 19.09 [$CH(CH_3)_2$], 25.01 (C≡C–CH_2), 31.56 [$CH(CH_3)_2$], 52.41, 52.47 (OCH_3), 54.39 (C-5), 60.89 (C-2), 70.14 (C≡C–H), 80.46 (C≡C–H), 161.79, 164.70 (C=N) ppm. IR (neat): $\tilde{\nu}$ = 3290 (C≡C–H), 2100 (C≡C), 1690 (C=N) cm^{-1}. MS: *m*/*z* (%) = 222 (8) [M]$^+$, 183 (70) [M – C_3H_3]$^+$, 141 (100) [M – C_3H_3 – C_3H_6]$^+$. $C_{12}H_{18}N_2O_2$ (222.29): calcd. C 64.84, H 8.16; found C 64.55, H 8.19.

Compound (2*S*,5*S*)-12a: R_f = 0.17; m.p. 32 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.72, 1.06 [2 × d, *J* = 7 Hz, 6 H, $CH(CH_3)_2$], 1.92 (t, ^4J = 2.5 Hz, 1 H, C≡C–H) 2.24 [dsp, *J* = 3.5 and 7 Hz, 1 H, $CH(CH_3)_2$], 2.48–2.82 (m, 2 H, C≡C–CH_2), 3.63, 3.66 (2 × s, 6 H, OCH_3), 3.88 (dd, ^3J = 3.5, ^5J = 4.5 Hz, 1 H, 5-H), 4.10 (dt, ^3J = 2.5, ^5J = 4.5 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.41, 19.67 [$CH(CH_3)_2$], 25.11 (C≡C–CH_2), 30.85 [$CH(CH_3)_2$], 52.42, 52.47 (OCH_3), 54.52 (C-5), 60.83 (C-2), 70.13 (C≡C–H), 81.23 (C≡C–H), 161.40, 163.97 (C=N) ppm. IR (neat): $\tilde{\nu}$ = 3295 (C≡C–H), 2100 (C≡C), 1685 (C=N) cm^{-1}. $C_{12}H_{18}N_2O_2$ (222.29): calcd. C 64.84, H 8.16; found C 65.00, H 7.99.

5-Isopropyl-3,6-dimethoxy-2-(trimethylsilyl)propargyl-2,5-dihydropyrazine (12f): Bislactim ether **9** (1.84 g, 10 mmol), and propargyl bromide **10f** (2.30 g, 12 mmol) were used to obtain **12f** (2.68 g, 91%) after bulb-to-bulb distillation; b.p. 100–110 °C/0.1 Torr. Ratio of diastereomers = 69:31, 38% *de*. After chromatographic separation with diethyl ether/petroleum ether (1:8) the diastereomers (2*R*,5*S*)-**12f** (1.65 g, 56%) and (2*S*,5*S*)-**12f** (0.76 g, 26%) were obtained as pale yellow oils.

Compound (2*R*,5*S*)-12f: R_f = 0.29. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.08 [s, 9 H, $Si(CH_3)_3$], 0.67 and 1.04 [2 × d, *J* = 7 Hz, 6 H, $CH(CH_3)_2$], 2.26 {dsp, *J* = 3.3 and 7 Hz, 1 H, [$CH(CH_3)_2$]}, 2.65, 2.76 (AB part of ABX, J_{AB} = 16.9, J_{AX} = 4.6, J_{BX} = 4.4 Hz, 2 H, C≡C–CH_2), 3.69, 3.70 (2 × s, 6 H, OCH_3), 3.98 (dd, ^3J = ^5J = 3.3 Hz, 1 H, 5-H), 4.09 (X part of ABX, J_{AX} = 4.6, J_{BX} = 4.4, ^5J = 3.3 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –0.34 [$Si(CH_3)_3$], 16.23, 18.92 [$CH(CH_3)_2$], 26.12 (CH_2), 31.52 [$CH(CH_3)_2$], 52.07, 52.14 (OCH_3), 54.37 (C-5), 60.67 (C-2), 86.23 (C≡C-Si) 103.15 (C≡C-Si), 161.52, 164.42 (C=N) ppm. IR (neat): $\tilde{\nu}$ = 2160 (C≡C–Si), 1690 (C=N) cm^{-1}. $C_{15}H_{26}N_2O_2Si$ (294.47): calcd. C 61.18, H 8.90; found C 61.15, H 8.89.

Compound (2*S*,5*S*)-12f: R_f = 0.22. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.09 [s, 9 H, $Si(CH_3)_3$], 0.67, 1.07 [2 × d, *J* = 7 Hz, 6 H, $CH(CH_3)_2$], 2.25 [dsp, *J* = 3.9 and 7 Hz, 1 H, $CH(CH_3)_2$], 2.67, 2.80 (AB part of ABX, J_{AB} = 16.1, J_{AX} = 6.1, J_{BX} = 4.9 Hz, 2 H, C≡C–CH_2), 3.67, 3.68 (2 × s, 6 H, OCH_3), 3.89 (dd, ^3J = 3.9, ^5J = 5.7 Hz, 1 H, 5-H), 4.10 (X part of ABX, J_{AX} = 6.1, J_{BX} = 4.9, ^5J = 5.7 Hz, 1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –0.08 [$Si(CH_3)_3$], 17.78, 19.63 [$CH(CH_3)_2$], 26.21 (CH_2), 30.99 [$CH(CH_3)_2$], 52.36, 52.41 (OCH_3), 54.39 (C-5), 60.74 (C-2), 86.41 (C≡C-Si), 103.61 (C≡C-Si), 161.48, 163.86 (C=N) ppm. IR (neat): $\tilde{\nu}$ = 2160 (C≡C–Si), 1690 (C=N) cm^{-1}. $C_{15}H_{26}N_2O_2Si$ (294.47): calcd. C 61.18, H 8.90; found C 61.07, H 8.82.

General Procedure for Hydrolysis of Propargyl-Substituted Bislactim Ethers 12 to Afford Methyl α-Propargylglycinates 17: Trifluoroacetic acid (0.2 N, 75 mL, 15 mmol) was added at 0 °C to a stirred solution of the bislactim ether **12** (5 mmol) in THF (30 mL) and stirring was continued at room temp. until the bislactim ether **12** was no longer detectable by TLC analysis (8 –12 h). Most of the solvent was removed in vacuo and the remaining aqueous solution (≈10 mL) was diluted with dichloromethane (50 mL). Conc. aqueous ammonia was added until pH 10, the layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried with $MgSO_4$, and the solvent was evaporated in vacuo (0 °C/20 Torr). Methyl L-valinate was removed by bulb-to-bulb distillation (50 °C/10 Torr) and the residue – the crude methyl α-propargylglycinate **17** – was purified by bulb-to-bulb distillation.

Methyl (*R*)-α-Propargylglycinate (17a): Compound **12a** (1.10 g, 5 mmol) was used to obtain **17a** (0.32 g, 51%) after bulb-to-bulb distillation. In order to obtain analytically pure **17a** the bulb-to-bulb distillation was repeated twice; b.p. 80–85 °C/10 Torr. $[\alpha]_D^{20}$ = 1.7 (*c* = 1.0, EtOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.73 (s, 2 H, NH_2), 2.04 (t, ^4J = 3 Hz, 1 H, C≡C–H), 2.59 (dd, *J* = 6, ^4J = 3 Hz, 2 H, CH_2C≡C–H), 3.60 (t, *J* = 6 Hz, 1 H, α-H), 3.72 (s, 3 H, OCH_3) ppm. IR (neat): ṽ = 3400–3200 (NH_2 and C≡C–H), 2100 (C≡C), 1730 (C=O) cm^{-1}. $C_6H_9NO_2$ (127.14): calcd. C 56.68, H 7.13; found C 56.67, H 7.18.

Methyl (*R*)-α-(Trimethylsilyl)propargylglycinate (17b): Compound (2*R*,5*S*)-**12f** (1.47 g, 5 mmol) was used to obtain (*R*)-**17b** (0.83 g, 83%) after bulb-to-bulb distillation; b.p. 115–120 °C/10 Torr. $[\alpha]_D^{20}$ = –38.4 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.12 [s, 9 H, $Si(CH_3)_3$], 1.69 (s, 2 H, NH_2), 2.57, 2.68 (AB part of ABX, J_{AB} = 16.9, J_{AX} = 6.5, J_{BX} = 6.4 Hz, 2 H, C≡C–CH_2), 3.59 (X part of ABX, J_{AX} = 6.5, J_{BX} = 6.4 Hz, 1 H, α-H), 3.72 (s, 3 H, OCH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –0.12 [$Si(CH_3)_3$], 26.31 (CH_2), 52.07 (C-2), 53.22 (OCH_3), 87.89 (*C*≡C–Si), 101.68 (C≡*C*-Si), 174.09 (*C*$OOCH_3$) ppm. IR (neat): ṽ = 3400–3200 (NH_2), 2160 (C≡C–Si), 1730 (C=O) cm^{-1}. MS: *m*/*z* (%) = 199 (1) $[M]^+$, 184 (3) $[M - CH_3]^+$, 140 (56) $[M - COOCH_3]^+$, 73 (100) $[Si(CH_3)_3]$. $C_9H_{17}NO_2Si$ (199.32): calcd. C 54.21, H 8.60; found C 54.36, H 8.55.

Methyl (*S*)-α-(Trimethylsilyl)propargylglycinate (*ent*-17b): Compound (2*S*,5*S*)-**12f** (0.59 g, 2 mmol) was used to obtain (*S*)-**17b** (0.31 g, 78%) after bulb-to-bulb distillation; b.p. 115–120 °C/10 Torr. $[\alpha]_D^{20}$ = +38.1 (*c* = 1.0, $CHCl_3$); spectroscopic data identical with those obtained for (2*R*)-**17b**.

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