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Efficient Stereoselective Syntheses of Constrained Glutamates via Michael-Induced Ring Closing Reactions

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Dedicated to Prof. V. Jäger on the occasion of 65th birthday

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Zn-chelated glycine ester enolates are highly efficient nucleophiles for the synthesis of conformationally constrained glutamates via domino sequences of Michael additions and subsequent ring closures (MIRC). This protocol allows the generation of 3–6-membered ring systems in high yields and excellent diastereoselectivities. Depending on the reaction conditions either carbocyclic or heterocyclic ring systems are obtained.

Introduction

Cyclic amino acids, such as (2-carboxycyclopropyl)glycines **A** (Figure 1) or the many derivatives from the family of the kainoids have attracted interest due to their remarkable biological activity. These amino acids can be regarded as conformationally fixed analogues of the natural amino acid glutamate. It has been shown that these amino acids can interact very strongly and selectively with the metabotropic glutamate receptors in the mammalian central nervous systems.[1] (–)-Kainic acid (**B**), the parent member of the class of marine natural products, was first isolated in 1953 from *Digenea simplex*.[2] This alkaloid exhibits potent anthelmintic[3] properties but is used primarily as a neuroexcitatory agent[4] by the neuroscience community in modeling afflictions such as epilepsy,[5] Alzheimer's disease,[6] and Huntington's chorea.[7]

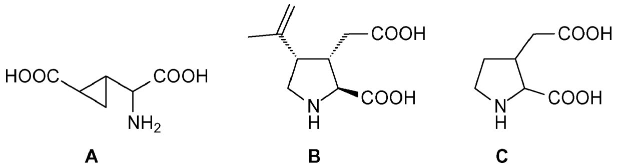

Figure 1. Conformationally constrained glutaminic acids.

Therefore, the interest in the stereoselective synthesis has increased considerably in recent years. Besides approaches to introduce the amino acid functionality via Strecker reaction,[8] several routes have been developed to construct the ring units.[1a,9] Joucla et al. were the first who reported on an approach based on the MIRC (Michael-induced ring closure) concept[10] to the desired cyclopropylic compounds by using lithium enolates of O'Donnell's phenylimino glycine esters[11] as nucleophiles.[12] Besides the imines, the Schöllkopf bislactime ethers can be used for an asymmetric approach of that kind as well.[13]

Prolineglutaminic acid (**C**), which can be seen as a chimera of proline and glutaminic acid, is a simplified analogue of kainic acid. Therefore it was the target of several synthetic approaches. Yoo et al. described an intramolecular Michael addition which provided a diastereomeric mixture of protected *cis*- and *trans*-**C**.[14] Correira et al. used a [2+2]-cycloaddition as key step in their synthesis, and therefore they were able to obtain the *cis*-isomer stereoselectively.[15] Enantioselective syntheses also of the *cis*-isomer were described by Sabol[16] and Karoyan et al.[17] The later ones used a zinc enolate cyclization of a chiral glycin derivative as key step (Scheme 1). The addition of zinc salts was essential for the success of this reaction.

In our group, metal-chelated glycine ester enolates also play a dominant role in the stereoselective synthesis of α-amino acids.[18] Therefore we tried to apply these nucleophiles also to domino reactions, such as conjugate additions and subsequent cyclizations.[19]

Due to very promising results in the field of the palladium-catalyzed allylic alkylations[20] we used the chelated zinc enolate of the trifluoroacetyl-protected glycine ester **1** as a nucleophile and commercially available methyl (2*E*)-4-bromo-but-2-enoate **2a** as a first acceptor (Scheme 2). The reaction gave a mixture of the desired cyclopropyl product

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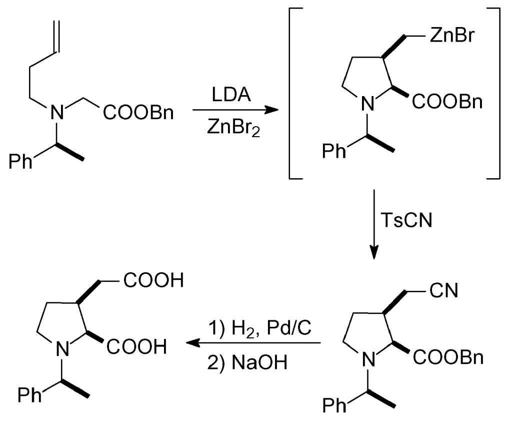
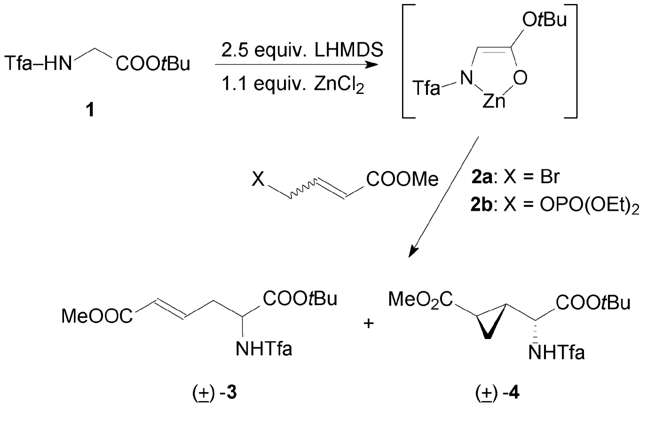


Scheme 1. Asymmetric synthesis of prolineglutaminic acid according to Karoyan et al.

4 (with an exclusive *trans* orientation of the substituents at the cyclopropyl ring) and the direct substitution product **3** in a 7:3 ratio. To avoid the direct substitution, we switched to a weaker leaving group X, which should not react with the glycine enolate directly, but hopefully with the ester enolate formed in the Michael addition. And indeed, with phosphate **2b** we observed only the cyclopropyl products in 59% yield, but the α,β-diastereoselectivity was lower (*anti*/*syn* 79:21) than before. In palladium-catalyzed allylic alkylations the diastereoselectivities were raised significantly when (*Z*)-configured substrates were used instead of the (*E*)-isomers. A similar effect was also observed here. In the reaction of (*Z*)-**2b**, only one diastereomer was obtained (GC-analysis), which was identical to the major isomer in the previous reaction.[19a]

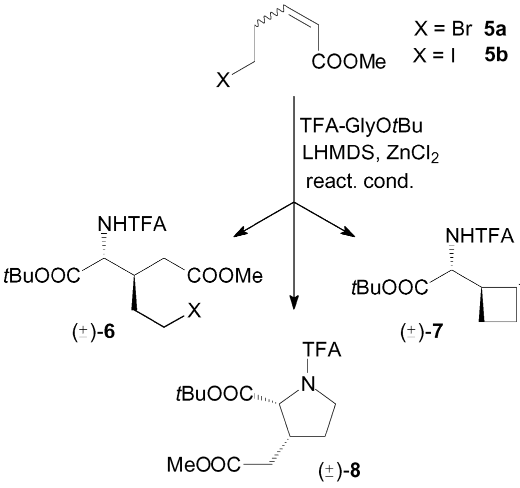


Acceptor	% Yield 3	 4	*ds* *anti*:*syn*
(*E*)-**2a**	16	36	92: 8
(*E*)-**2b**	–	59	79:21
(*Z*)-**2b**	–	82	>99:<1

Scheme 2. Reactions of chelated enolates with functionalized Michael acceptors.

Results and Discussion

To prove the generality of this domino reaction, we also synthesized the corresponding (*Z*)-substrates **5** with leaving groups in homoallylic position. For these molecules two different pathways concerning the second reaction are possible: either *C*-alkylation leading to a four-membered ring **7** or *N*-alkylation to give a five-membered heterocyclic ring **8**. (Scheme 3).[19a]



Scheme 3. Reactions of chelated enolates with homologated Michael acceptors **5**.

With brominated substrate **5a** we could isolate the Michael product **6a** (only the *anti*-diastereomer detectable) in 59% yield by quenching the reaction after 2.5 h at –78 °C (Table 1, entry 1). When the reaction mixture was warmed up to room temperature overnight the cyclized products were obtained in excellent yield (entry 2). Surprisingly, cyclobutane **7** was formed preferentially (52%) besides prolineglutaminic acid derivative **8** (39%). For both molecules only one diastereomer could be detected by GC-analysis. X-ray structure analysis of **7** confirmed the relative configuration to be *anti*,*trans*.[19a]

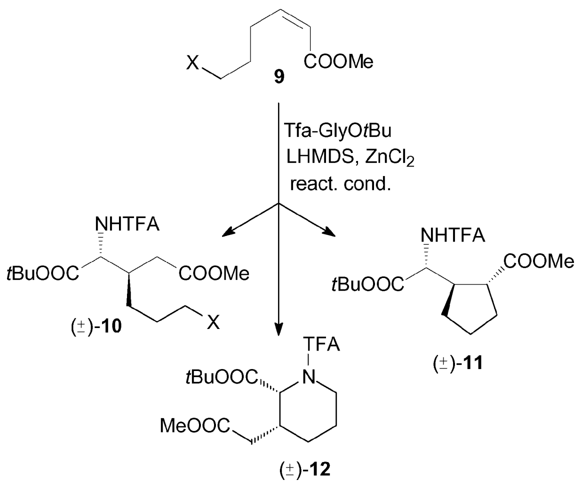
Table 1. Reactions of chelated enolates with homologated Michael acceptors **5**.

Entry	Substrate	Reaction conditions	% Yield[a]	Ratio **6**/**7**/**8**	% *ds*
1	(*Z*)-**5a**	THF, –78 °C, 2.5 h	59	100:0:0	>97
2	(*Z*)-**5a**	THF, –78 °C to r.t.	91	0:57:43	>97
3	(*Z*)-**5b**	THF, –78 °C to r.t.	90	0:87:13	>97
4	(*Z*)-**5a**	1) THF, –78 °C, 2 h 2) 1.5 equiv. *t*BuOH, –78 °C to r.t.	90	0:0:100	>98
5	(*E*)-**5a**	1) THF, –78 °C, 2 h 2) 1.5 equiv. *t*BuOH, –78 °C to r.t.	94	0:0:100	90

[a] Isolated yield.

Both cyclization products are interesting candidates as glutamate analogues, and therefore it is highly attractive to find selective protocols towards the one or the other. The product mixture obviously arises from a competitive cyclization either by the enolate formed in the addition step or the deprotonated amide. One might expect that the enolate intermediate is more reactive than the trifluoroacetamide, and should therefore react at lower temperature. To make the substrate more reactive we switched to the corresponding iodide (**5b**); and indeed, the yield of **7** could be increased to 78% and only 12% of **8** was formed (Table 1, entry 3). On the other hand, the higher acidity of the amide functionality can be used to get a clean *N*-cyclization. To avoid the enolate reaction we added *t*BuOH to the reaction mixture after 2 h at –78 °C. TLC control showed that after that time all Michael acceptor was consumed but no cyclization occurred. The mixture was warmed to room temperature overnight, and the *cis*-proline derivative **8** was obtained exclusively in 90% yield as a single diastereomer (entry 4). In previous work we observed that (*Z*)-configured Michael acceptors gave higher *anti*-selectivities in the addition step. To prove the generality of this observation, and to get also the *syn*-isomer for analytical purposes we also investigated the addition towards (*E*)-**5a**. And indeed, the selectivitiy dropped to 90% *ds*, although the yield was excellent (entry 5). The isomers could easily be separated by GC using the chiral column Chirasil-L-Val. To confirm the *cis*-orientation of the substituents at the proline ring, we compared the ^1H NMR coupling constants ($J_{\alpha,\beta}$ = 8.4 Hz) of the major isomer with those from the literature (*cis*: $J_{\alpha,\beta}$ = 8.3 Hz, *trans*: $J_{\alpha,\beta}$ = 7.5 Hz).[17]

Encouraged by these nice results we were interested to see if it is possible to get also the corresponding pipecolinic acid derivatives **12** from the ε-halogenated Michael acceptors **9** (Scheme 4). In principle three different products can be expected in this case: The Michael adduct **10**, the enolate cyclization product **11** and the *N*-alkylation product **12**. In our first experiment we used the (*Z*)-bromohexenoic acid ester **9a** (Table 2, entry 1).[21] Under the analogous reaction conditions as described before, addition products were obtained in 82%. The major product was the Michael adduct **10a**, followed by the enolate cyclization product **11**. The pipecolinic acid **12** was formed only as a side product.



Scheme 4. Reactions of chelated enolates with Michael acceptors **9**.

The 5-ring cyclization is kinetically favoured over the 6-ring formation, and relatively fast even at low temperature. Obviously a significant amount of enolate had reacted before it was quenched by the alcohol added. In contrast, cyclization via the amide seems to be slow. Therefore, we decided to have a closer look to the Michael addition. Already after 4 h at –78 °C nearly half of the Michael adduct underwent cyclization (entry 2). Therefore it was relatively easy to get a clean conversion into **11** by simply warming up the

Table 2. Reactions of chelated enolates with homologated Michael acceptors **9**.

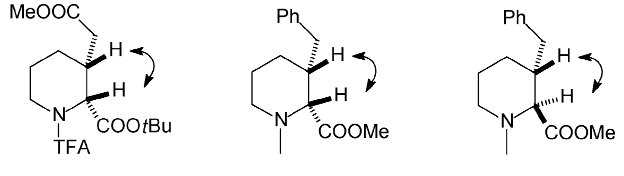
Entry	Substrate **9**	X	Reaction conditions	% Yield[a]	Ratio **10/11/12**	% *ds*
1	**9a**	Br	1) THF, –78 °C, 2 h 2) 1.5 equiv. *t*BuOH, –78 °C to r.t.	82	50:41:9	>97
2	**9a**	Br	THF, –78 °C, 4 h	95	55:45:0	>97
3	**9a**	Br	THF, –78 °C to r.t.	92	0:100:0	>97
4	**9b**	$OPO(OEt)_2$	THF, –78 °C to –60 °C	87	100:0:0	95
5	**9c**	Cl	THF, –78 °C to –60 °C	93	100:0:0	97
6	**9b**	$OPO(OEt)_2$	1) THF, –78 °C to –55 °C 2) 1.5 equiv. *t*BuOH, –55 °C to r.t.	81	100:0:0	95
7	**9c**	Cl	1) THF, –78 °C to –60 °C 2) 1.5 equiv. *t*BuOH, –60 °C to r.t. 3) 10 mol-% Bu_4NI, room temp., 24 h	n.d.[b]	>90:<5:<5	n.d.
8	**9c**	Cl	1) THF, –78 °C to –60 °C 2) 1.5 equiv. *t*BuOH, –60 °C to r.t. 3) 60 °C, 6 h	29	20:0:80	n.d.
9	**9c**	Cl	1) THF, –78 °C to –60 °C 2) 1.5 equiv. *t*BuOH, –60 °C to r.t. 3) HMPA, room temp., 12 h	n.d.[b]	25:0:76	n.d.
10	**9c**	Cl	1) THF, –78 °C to –60 °C 2) 1.5 equiv. *t*BuOH, –60 °C to r.t. 3) DMF, 40 °C, 12 h	64	0:0:100	> 95
11	**9c**	Cl	1) THF, –78 °C to –60 °C 2) 1.5 equiv. *t*BuOH, –60 °C to r.t. 3) DMPU, 10 mol-% Bu_4NI, room temp., 24 h	73	0:0:100	97

[a] Isolated yield. [b] Product ration determined by NMR spectroscopy.

reaction mixture to room temperature without the addition of *t*BuOH (entry 3). **11** was obtained as a single stereoisomer (as determined by GC) in 92%. While the two stereogenic centres at the α- and β-position of the amino acid result from the highly stereoselective *anti*-Michael addition, the third stereogenic centre is formed in the cyclization step. The expected *trans*-orientation of the substituents on the five-membered ring could be confirmed by X-ray structure analysis.

To suppress the enolate alkylation we switched to less reactive leaving groups such as phosphate (**9b**) and chloride (**9c**). And indeed, with both the corresponding Michael adduct was obtained in high yield and selectivity, and no cyclization was observed. With these leaving groups one might have a chance to protonate the enolate and to get the pipecolinic acid. The optimization of the reaction conditions is illustrated in Table 2. Unfortunately, the phosphate was a too weak leaving group to undergo any cyclization (entry 6) and therefore the optimization focused on the chloride **9c**. Even after warming up the reaction mixture to room temperature after the addition of alcohol and Bu_4NI (to generate a better leaving group via Finkelstein reaction) no significant improvement could be obtained (entry 7). Refluxing the reaction mixture caused several side reactions and the overall yield dropped, although the formation of some pipecolinic acid was observed (entry 8). Because alkylation reactions in general proceed well in dipolar aprotic solvents, we checked also the influence of these additives. HMPA and DMF both were suitable to increase the amount of cyclization product, and the best isolated yield of **12** (97% *ds*) was obtained by a combination of DMPU and Bu_4NI (entry 11).

According to the results obtained with the proline derivative **8** and the cyclization product **12** one can expect a *cis*-orientation of the substituents on the ring system. Nevertheless we compared the coupling constants of **12** with those of the closely related β-benzylated pipecolinic acid derivatives[22] **D** and **E**. A coupling constant of 4.7 Hz between the α- and β-proton clearly confirmed the *cis*-orientation (Figure 2).



cis-**12** $J_{\alpha,\beta}$ = 4.7 Hz

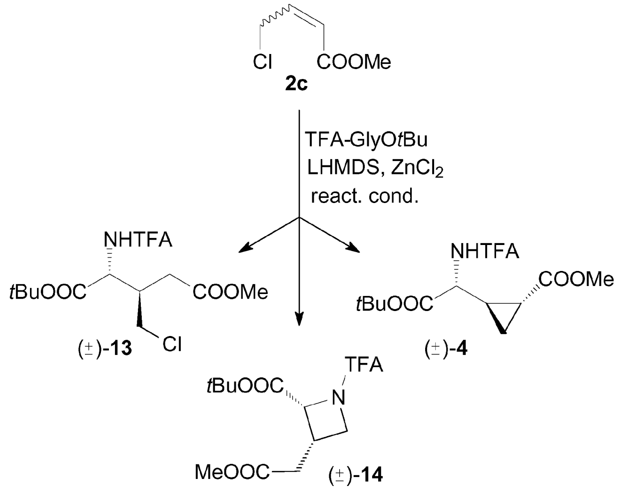
D $J_{\alpha,\beta}$ = 4.7 Hz

E $J_{\alpha,\beta}$ = 9.4 Hz

Figure 2. Determination of configuration by NMR.

Although we knew from our previous work[19a] that shorter Michael acceptors with the leaving group in the allylic position (**2**) form the cyclopropyl amino acids **4** easily, we wondered, if we could not get also the corresponding *cis*-azetidine glutaminic acids **14** under our optimized reaction conditions (Table 3). Again, we chose the chloro derivative **2c** to avoid direct nucleophilic substitution at the allylic position. The Michael addition in this case was very fast, and a complete consumption of **2c** was observed after 10 min. The Michael adduct **13** could be obtained in high yield and excellent diastereoselectivity (98% *ds*) (entry 1). Again, with the corresponding (*E*)-isomer the selectivity was slightly worse (89% *ds*) (entry 2).

Table 3. Reactions of chelated enolates with Michael acceptors **2c** having an allylic leaving group.



Entry	Substrate	Reaction conditions	% Yield[a]	Ratio **13/4/14**	% *ds*
1	(*Z*)-**2c**	THF, –78 °C, 30 min	84	100:0:0	98
2	(*E*)-**2c**	THF, –78 °C, 30 min	86	100:0:0	89
3	(*Z*)-**2c**	THF, –78 °C to r.t.	77	0:100:0	>97
4	(*Z*)-**2c**	1) THF, –78 °C, 30 min 2) 1.5 equiv. *t*BuOH, –78 °C to r.t.	68	0:100:0	>97
5	(*Z*)-**2c**	1) THF, –78 °C, 30 min 2) 2.5 equiv. HOAc, –78 °C; 3) 2 equiv. KO*t*Bu, –78 °C to r.t.	n.d.[b]	0:95 5	>97
6	(*Z*)-**2c**	1) THF, –78 °C, 30 min 2) CF_3CH_2OH, –78 °C to r.t.	n.d.[b]	68:32:0	n.d.
7	(*Z*)-**2c**	1) THF, –78 °C, 30 min 2) 1.5 equiv. HOAc, –78 °C to r.t. 3) DMPU, 10 mol-% Bu_4NI, r.t., 5 d	75	16: 3:81	90

[a] Isolated yield. [b] Product ration determined by NMR spectroscopy.

If the reaction mixture was warmed up to room temperature, **4** was obtained in a clean reaction and good yield (entry 3). Attempts to quench the enolate by addition of *t*BuOH were unsuccessful in this case. Here, also only the cyclopropyl derivative **4** was obtained (entry 4). Obviously, *t*BuOH is not acidic enough to cause a complete protonation of the enolate, and the threering-cyclization is kinetically highly favoured removing irreversibly the enolate from the equilibrium. To prove this assumption we quenched the enolate with HOAc. Subsequent addition of KO*t*Bu again resulted in the formation of the cyclopropyl derivative **4** (entry 5). Therefore, because *t*BuOH obviously is unsuitable, we switched to more acidic proton donors such as trifluoroethanol (entry 6). Indeed, the amount of **4** could be reduced, but no *N*-alkylation was observed. A breakthrough was the combination of HOAc (to quench the enolate) and the addition of DMPU/Bu$_4$NI which proved superior in the pipecolinic acid case (entry 7). Although the cyclization was very slow, under these conditions the azetidine **14** could be obtained in 61% yield (90% *ds*). **4** was formed only in traces.

Conclusions

In conclusion we could show that Michael-induced ring closing reactions (MIRC) are excellently suited to generate conformationally constrained glutamates. By carefully optimizing the reaction conditions it is possible to get selectively the one or the other product. While three- and five-membered rings are formed easily, the selective synthesis of four- and six-membered products is more difficult.

Experimental Section

General Remarks: All reactions were carried out in oven-dried glassware (100 °C) under argon. All solvents were dried before use. THF was distilled from LiAlH$_4$ and stored over molecular sieves. The products were purified by flash chromatography on silica gel. Mixtures of EtOAc and hexanes were generally used as eluents. TLC: commercially precoated Polygram® SIL-G/UV 254 plates. Visualization was accomplished with UV-light and KMnO$_4$ solution. Melting points are uncorrected. NMR spectra were recorded in CDCl$_3$ using a Bruker DRX 500 or a Bruker AV 400 NMR spectrometer. The formation of rotamers causes broad signals in some cases and/or a second set of signals. Selected signals in the NMR spectra for the minor isomers are extracted from the spectra of the isomeric mixture. GC analyses were performed on a Varian 3400 GC and a chiral column Permabond Chirasil-L-Val (25m × 0.25 mm) from Macherey–Nagel. Melting points were determined on a Büchi melting point apparatus and are uncorrected. CI-MS analyses were performed using a Finnigan MAT 95. Elemental analyses were carried out at the department of chemistry, University of Saarbrücken.

Preparation of the Michael Acceptors: The required α,β-unsaturated esters were obtained either via Lindlar hydrogenation or via a *cis*-selective Horner–Wadsworth–Emmons reaction using the Ando protocol.[23]

General Procedure for Michael Additions: In a Schlenk flask hexamethyldisilazane (0.3 mL, 1.42 mmol) was dissolved in THF (2 mL). The solution was cooled to –78 °C before *n*-BuLi (1.6 M, 0.78 mL, 1.25 mmol) was added. The cooling bath was removed and the solution was warmed up for 15 min, before it was cooled again to –78 °C. In a second Schlenk flask ZnCl$_2$ (80 mg, 0.57 mmol) was dried with a heat gun in high vacuum, before it was dissolved in THF (3 mL). After addition of TFA-Gly-O*t*Bu (115 mg, 0.5 mmol) the solution was cooled to –78 °C, before the fresh prepared LHMDS solution was added. 15 Min later the Michael acceptor (0.5 mmol) was added in THF (2 mL). After complete consumption of the starting materials (TLC control) the solution was diluted with diethyl ether before 1 N KHSO$_4$ was added. The layers were separated, the aqueous phase was washed twice with CH$_2$Cl$_2$ and the combined organic layers were dried (Na$_2$SO$_4$). After evaporation of the solvent in vacuo the crude product was purified by flash chromatography.

Michael Acceptors (*Z*)-2c and (*E*)-2c: According to Pihko and Salo[24] fresh distilled α-chloroacetaldehyde (978 mg, 12.4 mmol) was treated with methyl diphenyloxyphosphorylacetate (3.14 g, 10.3 mmol) at –90 °C. After 2 h and warming the reaction mixture to –78 °C it was hydrolyzed with NH$_4$Cl solution. After separation of the layers, the aqueous phase was extracted three times with ether. The combined organic layers were dried (Na$_2$SO$_4$) and the solvent was evaporated in vacuo (40 °C, 330 mbar). After purification by flash chromatography (pentane/Et$_2$O, 97:3) the (*Z*)-isomer (902 mg, 6.70 mmol, 65%) and (*E*)-isomer (81 mg, 0.6 mmol, 6%) were obtained in pure form as colorless oils. $R_{\mathrm{f}(Z)\text{-}\mathbf{2a}}$ = 0.57, $R_{\mathrm{f}(E)\text{-}\mathbf{2a}}$ = 0.43 (hexanes/EtOAc, 7:3).

(*Z*)-2c: ^{1}H NMR (500 MHz): δ = 3.72 (s, 3 H), 4.64 (dd, *J* = 6.9, 1.7 Hz, 2 H), 5.86 (dt, *J* = 11.4, 1.6 Hz, 1 H), 6.30 (dt, *J* = 11.4, 6.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 39.7, 51.6, 121.3, 144.2, 165.8 ppm.

(*E*)-2c: ^{1}H NMR (500 MHz): δ = 3.74 (s, 3 H), 4.15 (dd, *J* = 6.1, 1.6 Hz, 2 H), 6.09 (dt, *J* = 15.4, 1.6 Hz, 1 H), 6.97 (dt, *J* = 15.4, 6.1 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 42.4, 51.8, 123.7, 141.9, 166.0 ppm. Based on the high volatility of **2c** we were not able to get elemental analysis and HRMS.

Cyclopropyl Amino Acids 4: According to the general procedure for Michael additions, TFA-Gly-O*t*Bu (82 mg, 0.36 mmol) was treated with (*Z*)-**2c** (66 mg, 0.49 mmol). The reaction mixture was warmed to room temperature overnight before hydrolysis. Flash chromatography (hexanes/EtOAc, 9:1) gave **4** (90 mg, 0.28 mmol, 77%) as a colorless solid, m.p. 44 °C. ^{1}H NMR (500 MHz): δ = 1.06 (ddd, *J* = 8.9, 5.7, 5.7 Hz, 1 H), 1.29 (ddd, *J* = 9.2, 5.2, 5.2 Hz, 1 H), 1.49 (s, 9 H), 1.73 (m, 1 H), 1.84 (ddd, *J* = 8.8, 4.6, 4.6 Hz, 1 H), 3.67 (s, 3 H), 4.10 (t, *J* = 7.9 Hz, 1 H), 6.98 (d, *J* = 7.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 12.7, 17.7, 23.6, 27.5, 51.8, 54.3, 83.8, 115.4 (*J* = 287.8 Hz), 156.6 (*J* = 37.6 Hz), 168.2, 173.0 ppm. GC (Chira-Si-L-Val, 100 °C, 10 min; 5°/min; 180 °C, 30 min): $t_{\mathrm{R}(2R)}$ = 23.55 min, $t_{\mathrm{R}(2S)}$ = 23.71 min. $C_{13}H_{18}F_3NO_5$ (325.28): calcd. C 48.00, H 5.58, N 4.31; found C 48.07, H 5.39, N 4.28. HRMS calcd. for $C_{13}H_{19}F_3NO_5$ $[M + H]^+$: 326.1215, found 326.1258.

Michael Acceptor (*Z*)-5a: According to a procedure described by de Meijere et al.[25] methyl 5-hydroxypentynoate (3.84 g, 30.0 mmol) was dissolved in CH$_2$Cl$_2$ (60 mL). Tetrabromomethane (7.86 g, 33.0 mmol) was added and after cooling to 0 °C PPh$_3$ (7.86 g, 30.0 mmol) was added in portions. Stirring was continued until no alcohol could be detected (4 h). PPh$_3$O was removed by filtration through silica using Et$_2$O as eluent. The solvent was removed in vacuo and the crude product was subjected to column chromatography. Elution with hexane allowed the removal of CBr$_4$ and CHBr$_3$, before the product was eluted with CH$_2$Cl$_2$. The 5-bromopentynoate (3.98 g, 20.8 mmol, 60%) was obtained as colorless liquid. ^{1}H NMR (500 MHz): δ = 2.90 (t, *J* = 7.3 Hz, 2 H), 3.44 (t, *J* = 7.1 Hz, 2 H), 3.75 (s, 3 H) ppm. ^{13}C NMR (125 MHz): δ = 23.0, 27.2, 52.7, 74.2, 85.3, 153.7 ppm. $C_6H_7BrO_2$ (191.02): calcd. C 37.73, H 3.69; found C 37.56, H 3.64.

This alkynoate (914 mg, 4.78 mmol) was dissolved in a mixture of hexanes (10 mL) and *t*BuOH (2.5 mL). Pd/BaSO$_4$ (5% Pd) and quinoline (80 mg) were added and the hydrogenation was carried out under typical Lindlar conditions. Samples were taken to control the process of the reaction (by GC). The crude product was purified by flash chromatography (hexanes/EtOAc, 95:5) giving rise to a colorless liquid (725 mg, 3.76 mmol, 79%). ^{1}H NMR (500 MHz): δ = 3.22 (dt, J = 6.8, 6.6 Hz, 2 H), 3.46 (t, J = 6.6 Hz, 2 H), 3.70 (s, 3 H), 5.90 (dt, J = 11.4, 1.6 Hz, 1 H), 6.27 (dt, J = 11.4, 7.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 31.7, 121.5, 146.2, 166.4 ppm. $C_6H_9BrO_2$ (193.04): calcd. C 37.33, H 4.70; found C 37.20, H 4.47.

Michael Acceptor (*Z*)-5b: According to the literature[26] **5a** (514 mg, 2.66 mmol) was dissolved in acetone (2.2 mL). NaI (481 mg, 3.21 mmol) was added and the mixture was refluxed for 6 h. After cooling to room temperature CH_2Cl_2 (10 mL) and H_2O (10 mL) were added. After separation of the layers, the aqueous phase was extracted twice with CH_2Cl_2 (10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. Flash chromatography (hexanes/EtOAc, 96:4) provided (*Z*)-**5b** (225 mg, 2.05 mmol, 78%) as a clear, pale red liquid and in addition (*E*)-**5b** (52 mg, 0.22 mmol, 8%) as minor product.

[(*Z*)-5a]: ^{1}H NMR (500 MHz): δ = 3.20–3.28 (m, 4 H), 3.70 (s, 3 H), 5.90 (d, J = 11.7 Hz, 1 H), 6.19 (dt, J = 11.4, 6.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 3.8, 32.5, 51.2, 121.2, 147.9, 166.4 ppm. $C_6H_9IO_2$ (240.04): calcd. C 30.02, H 3.78; found C 30.07, H 3.76.

[(*E*)-5a]: ^{1}H NMR (500 MHz): δ = 2.76 (tdd, J = 7.1, 7.1, 1.6 Hz, 2 H), 3.18 (t, J = 7.1 Hz, 2 H), 3.71 (s, 3 H), 5.87 (d, J = 15.4 Hz, 1 H), 6.82 (dt, J = 15.8, 6.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 1.5, 35.7, 51.6, 122.9, 146.3, 166.4 ppm. HRMS calcd. for $C_6H_{10}IO_2$ $[M + 1]^+$: 239.9726, found 240.9722.

Michael Addition Product 6: According to the general procedure for Michael additions TFA-Gly-O*t*Bu (120 mg, 0.48 mmol) was treated with (*Z*)-**5a** (81 mg, 0.42 mmol). After 2 hours and warming the reaction mixture to –70 °C 1 N $KHSO_4$ (5 mL) was added to quench the reaction. Flash chromatography (hexanes/EtOAc, 1:1) gave rise to **6** (138 mg, 0.38 mmol, 91%) as a colorless oil. ^{1}H NMR (500 MHz): δ = 1.47 (s, 9 H), 1.93 (m, 2 H), 2.37 (dd, J = 16.3, 5.6 Hz, 1 H), 2.45 (dd, J = 16.3, 6.2 Hz, 1 H), 2.79 (m, 1 H), 3.41–3.52 (m, 2 H), 3.69 (s, 3 H), 4.58 (dd, J = 8.3, 4.1 Hz, 1 H), 7.79 (d, J = 8.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 28.0, 30.0, 33.0, 34.3, 35.6, 52.3, 54.6, 83.9, 115.7 (J = 287.7 Hz), 157.4 (J = 37.6 Hz), 168.7, 172.8 ppm. $C_{14}H_{21}BrF_3NO_5$ (420.22): calcd. C 40.02, H 5.04, N 3.33; found C 40.31, H 5.18, N 3.48. HRMS calcd. for $C_{14}H_{22}Br^{79}F_3NO_5$ $[M]^+$: 420.0633, found 420.0446.

Cyclobutyl Amino Acids 7: The reaction was carried out as described for **6**. The reaction mixture was warmed to room temperature before hydrolysis. ^{1}H NMR (500 MHz): δ = 1.43 (s, 9 H), 1.98 (m, 2 H), 2.14 (m, 2 H), 2.78 (m, 1 H), 3.03 (dt, J = 9.4 Hz), 3.66 (s, 3 H), 4.32 (dd, J = 10.1, 6.9 Hz, 1 H), 7.33 (s, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 21.7, 22.4, 27.9, 40.7, 41.7, 52.0, 57.4, 83.1, 115.7 (J = 286.9 Hz), 157.2 (J = 37.1 Hz), 168.2, 174.6 ppm. GC (Chirasil-Val, 135 °C, isothermic): $t_{R(R)}$ = 37.41 min, $t_{R(S)}$ = 38.55 min. $C_{14}H_{20}F_3NO_5$ (339.31): calcd. C 49.55, H 5.94, N 4.13; found C 49.30, H 5.96, N 4.27.

Proline Derivative 8: According to the general procedure for Michael additions TFA-Gly-O*t*Bu (127 mg, 0.56 mmol) was treated with (*Z*)-**5a** (100 mg, 0.52 mmol). After 2 hours *t*BuOH (68 mg, 0.92 mmol) was added to the reaction mixture and the solution was warmed to room temperature over 12 h. Flash chromatography (hexanes/EtOAc, 8:2) provided **8** (156 mg, 0.46 mmol, 90%) as a colorless oil. Diastereomeric ratio 98:2.

***cis*-8:** Major rotamer: ^{1}H NMR (500 MHz): δ = 1.44 (s, 9 H), 1.89 (m, 1 H), 2.16 (m, 1 H), 2.39 (dd, J = 17.1, 7.3 Hz, 1 H), 2.51 (dd, J = 17.1, 7.9 Hz, 1 H), 2.80 (m, 1 H), 3.62 (m, 1 H), 3.70 (s, 3 H), 3.96 (m, 1 H), 4.53 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 27.9, 29.9, 34.2, 36.2, 46.2 (J = 3.5 Hz), 51.9, 63.1, 82.9, 116.1 (J = 287.1 Hz), 155.8 (J = 37.1 Hz), 168.2, 171.4 ppm. Minor rotamer (selected signals): ^{1}HNMR (500 MHz): δ = 1.42 (s, 9 H), 1.73 (m, 1 H), 2.09 (m, 1 H), 2.89 (m, 1 H), 3.71 (s, 3 H), 3.80 (m, 1 H), 4.62 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 26.6, 27.8, 34.5, 39.3, 47.2, 51.9, 62.0 (J = 2.9 Hz), 83.3, 116.0 (J = 287.9 Hz), 155.4 (J = 37.1 Hz), 168.5, 171.3 ppm.

***trans*-8** (selected signals): ^{1}H NMR (500 MHz): δ = 1.43 (s, 9 H), 2.66 (m, 1 H), 3.70 (s, 3 H) ppm. GC (Chirasil-Val, 135 °C, isothermic): $t_{R(trans\text{-}\mathbf{8})}$ = 50.99 min, $t_{R(cis\text{-}\mathbf{8})}$ = 61.31 min. $C_{14}H_{20}F_3NO_5$ (339.31): calcd. C 49.55, H 5.94, N 4.13; found C 49.78, H 5.93, N 4.11. HRMS calcd. for $C_{14}H_{21}F_3NO_5$ $[M + H]^+$: 340.1372, found 340.1365.

Michael Acceptor 9c: According to the preparation of **2c**, **9c** was obtained from γ-chlorobutyraldehyde (989 mg, 9.29 mmol) and methyl 2-(diphenyloxyphosphoryl)acetate (4.24 g, 13.9 mmol) in 69% yield (1.04 g, 6.41 mmol, 95%). ^{1}H NMR (500 MHz): δ = 1.91 (dt, J = 6.9 Hz, 2 H), 2.78 (tdd, J = 7.6, 6.9, 1.6 Hz, 2 H), 3.54 (t, J = 6.9 Hz, 2 H), 3.69 (s, 3 H), 5.82 (dt, J = 11.5, 1.6 Hz, 1 H), 6.20 (dt, J = 11.5, 7.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 26.4, 31.9, 44.3, 51.1, 120.5, 148.2, 166.6 ppm. HRMS calcd. for $C_7H_{11}Cl^{35}O_2$ $[M]^+$: 162.0448, found 162.0418.

Michael Addition Product 10a: According to the general procedure for Michael additions TFA-Gly-O*t*Bu (90 mg, 0.40 mmol) was treated with methyl (*Z*)-6-bromo-2-hexenoate[21] (76 mg, 0.37 mmol). After 4.5 h at –78 °C the reaction was quenched with HOAc (1 mL). Flash chromatography (hexanes/EtOAc, 9:1) provided **10a** (72 mg, 0.16 mmol, 52%) and **11** (46 mg, 0.13 mmol, 43%). ^{1}H NMR (500 MHz): δ = 1.47 (s, 9 H), 1.53 (m, 2 H), 1.92 (m, 2 H), 2.36 (dd, J = 16.0, 5.5 Hz, 1 H), 2.44 (dd, J = 16.0, 6.5 Hz, 1 H), 2.48 (m, 1 H), 3.37 (m, 2 H), 3.69 (s, 3 H), 4.57 (dd, J = 8.3, 4.2 Hz, 1 H), 7.76 (d, J = 8.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 27.9, 29.4, 29.8, 32.8, 35.0, 36.5, 52.2, 55.1, 83.7, 115.7 (J = 288.0 Hz), 157.5 (J = 37.4 Hz), 168.9, 173.0 ppm. HRMS (CI) calcd. for $C_{15}H_{24}Br^{79}F_3NO_5$ $[M + H]^+$: 434.0790, found 434.0756.

Michael Addition Product 10b: According to **10a**, **10b** was obtained in 78% yield as colorless oil. ^{1}H NMR (500 MHz): δ = 1.30 (m, 6 H), 1.43 (m, 1 H), 1.45 (s, 9 H), 1.53 (m, 1 H), 1.72 (m, 2 H), 2.36 (dd, J = 15.8, 4.9 Hz, 1 H), 2.45 (dd, J = 15.8, 5.0 Hz, 1 H), 2.48 (m, 1 H), 3.67 (s, 3 H), 4.0 (dt, J = 6.3 Hz, 2 H), 4.07 (m, 4 H), 4.55 (dd, J = 8.2, 3.9 Hz, 1 H), 7.97 (d, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 16.0, 16.1, 26.8, 27.6 (J = 6.8 Hz), 27.9, 34.9, 36.5, 52.2, 55.2, 63.8 (J = 5.8 Hz), 66.7 (J = 5.8 Hz), 83.5, 115.8 (J = 287.8 Hz), 157.5 (J = 37.5 Hz), 168.9, 173.1 ppm.

Michael Addition Product 10c: According to **10a**, **10c** was obtained in 94% yield as a colorless oil. ^{1}H NMR (500 MHz): δ = 1.47 (s, 9 H), 1.53 (m, 2 H), 1.84 (m, 2 H), 2.36 (dd, J = 16.0, 5.4 Hz, 1 H), 2.44 (dd, J = 16.0, 6.1 Hz, 1 H), 2.48 (m, 1 H), 3.46–3.56 (m, 2 H), 3.69 (s, 3 H), 4.57 (dd, J = 8.4, 4.2 Hz, 1 H), 7.76 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 27.8, 28.1, 29.7, 34.9, 36.5, 44.3, 52.2, 55.1, 83.6, 115.7 (J = 287.7 Hz), 157.4 (J = 37.6 Hz), 168.9, 173.0 ppm. HRMS calcd. for $C_{15}H_{24}Cl^{35}F_3NO_5$ $[M + H]^+$: 390.1295, found 390.1334.

Cyclopentyl Amino Acids 11: According to the general procedure for Michael additions TFA-Gly-O*t*Bu (108 mg, 0.48 mmol) was treated with methyl (*Z*)-6-bromo-2-hexenoate (78 mg, 0.38 mmol). The reaction mixture was warmed to room temperature overnight, before it was hydrolyzed with 1 N $KHSO_4$. Flash chromatography (hexanes/EtOAc, 95:5) provided **11** (138 mg, 0.39 mmol, 92%) as a colorless oil, which solidified on standing, m.p. 43–44 °C. ^{1}H NMR

(500 MHz): δ = 1.45 (s, 9 H), 1.56 (m, 1 H), 1.62–1.75 (m, 2 H), 1.82–1.90 (m, 2 H), 1.97 (m, 1 H), 2.53–2.65 (m, 2 H), 3.68 (s, 3 H), 4.26 (dd, J = 8.5 Hz, 1 H), 7.37 (d, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 25.1, 27.9, 29.9, 30.4, 45.1, 47.3, 52.2, 57.4, 83.2, 118.4 (J = 287.6 Hz), 156.9 (J = 37.8 Hz), 169.1, 176.4 ppm. $C_{15}H_{22}F_3NO_5$ (354.15): calcd. C 50.99, H 6.28, N 3.96; found C 51.24, H 6.31, N 4.00. HRMS calcd. for $C_{15}H_{23}F_3NO_5$ [M + H]$^+$: 354.1528, found 354.1503.

Pipecolinic Acid Derivative 12: According to the general procedure for Michael additions TFA-Gly-O*t*Bu (86 mg, 0.38 mmol) was treated with **9c** (29 mg, 0.18 mmol). After stirring for 2 h and warming the reaction mixture to –60 °C *t*BuOH (41 mg, 0.55 mmol) in THF (0.5 mL) was added. After 15 min DMPU (2 mL) and NaI (10 mg, 0.07 mmol) were added. The reaction mixture was warmed to room temperature over 24 h. Flash chromatography (hexanes/EtOAc, first 9:1, then 8:2) gave rise to **12** (46 mg, 0.13 mmol, 73%, 98% *ds*) as a colorless oil. ^{1}H NMR (500 MHz): δ = 1.43 (s, 9 H), 1.48–1.88 (m, 4 H), 2.26 (m, 1 H), 2.43 (dd, J = 16.8, 8.2 Hz, 1 H), 2.64 (dd, J = 16.8, 6.8 Hz, 1 H), 3.51 (ddd, J = 13.4, 13.4, 3.2 Hz, 1 H), 3.67 (s, 3 H), 3.87 (d, J = 13.4 Hz, 1 H), 5.16 (d, J = 5.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 25.1, 26.3, 27.9, 35.0, 37.5, 42.9 (J = 3.7 Hz), 51.7, 56.3, 82.9, 116.1 (J = 287.1 Hz), 156.7 (J = 37.1 Hz), 167.9, 171.9 ppm. Minor rotamer (selected signals): ^{1}H NMR (500 MHz): δ = 1.45 (s, 9 H), 3.21 (ddd, J = 13.4, 13.2, 2.9 Hz, 1 H), 3.68 (s, 3 H), 4.42 (d, J = 13.4 Hz, 1 H), 4.82 (d, J = 5.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 25.1, 26.4, 27.8, 35.8, 37.3, 40.3, 52.2, 58.2 (J = 3.1 Hz), 83.1, 167.7, 171.8 ppm. $C_{15}H_{22}F_3NO_5$ (354.15): calcd. C 50.99, H 6.28, N 3.96; found C 51.40, H 6.34, N 3.56. HRMS calcd. for $C_{15}H_{23}F_3NO_5$ [M + H]$^+$: 354.1528, found 354.1570.

Michael Addition Product 13: According to the general procedure for Michael additions TFA-Gly-O*t*Bu (136 mg, 0.60 mmol) was treated with **2c** (67 mg, 0.50 mmol) at –90 °C. After 30 min and warming the reaction mixture to –78 °C the reaction was quenched by 1 N $KHSO_4$ (1 mL). Flash chromatography (hexanes/EtOAc, 9:1) provided **13** (151 mg, 0.38 mmol, 84%, 98% *ds*) as a colorless oil.

***anti*-13:** ^{1}H NMR (500 MHz): δ = 1.47 (s, 9 H), 2.85 (m, 1 H), 3.58 (dd, J = 11.5, 6.4 Hz, 1 H), 3.63 (dd, J = 11.5, 6.2 Hz, 1 H), (m, 1 H), 3.70 (s, 3 H), 4.72 (dd, J = 8.2, 4.9 Hz, 1 H), 7.62 (d, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 27.9, 33.0, 39.6, 44.5, 52.3, 54.1, 84.2, 115.7 (J = 287.7 Hz), 157.4 (J = 37.6 Hz), 168.2, 172.4 ppm.

***syn*-13:** Selected signals. ^{1}H NMR (500 MHz): δ = 1.48 (s, 9 H), 3.71 (s, 3 H), 4.76 (dd, J = 8.3, 4.7 Hz, 1 H), 7.48 (d, J = 8.3 Hz, 1 H) ppm. HRMS calcd. for $C_{13}H_{20}ClF_3NO_5$ [M + H]$^+$: 362.0937, found 362.1010.

Azetidine Derivative 14: According to the general procedure for Michael additions TFA-Gly-O*t*Bu (125 mg, 0.55 mmol) was treated with **2c** (54 mg, 0.40 mmol) at –78 °C. After 15 min HOAc (57 mg, 0.95 mmol) was added. DMPU (2 mL) and NaI (10 mg, 0.07 mmol) were added after further 15 min, and the cooling bath was removed. After stirring for 5 d and flash chromatography (hexanes/EtOAc first 9:1, then 8:2) **14** (79 mg, 0.24 mmol, 61%, 90% *ds*) was obtained as colorless oil. ^{1}H NMR (400 MHz): δ = 1.46 (s, 9 H), 2.38 (dd, J = 16.9, 8.9 Hz, 1 H), 2.47 (dd, J = 16.9, 5.1 Hz, 1 H), 2.58 (m, 1 H), 3.68 (s, 3 H), 4.01 (dd, J = 4.6, 1.5 Hz, 1 H), 4.15 (ddd, J = 11.2, 5.3, 1.5 Hz, 1 H), 4.43 (dd, J = 11.2, 3.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 27.8, 29.7, 33.9, 52.0, 59.0, 66.8, 82.7, 116.3 (J = 287.1 Hz), 148.4 (J = 39.0 Hz), 168.9, 171.1 ppm. Minor rotamer (selected signals): ^{1}H NMR (400 MHz): δ = 1.45 (s, 9 H), 2.22 (dd, J = 17.0, 8.5 Hz, 1 H), 2.38 (dd, J = 17.0, 6.3 Hz, 1 H), 2.66 (m, 1 H), 3.70 (s, 3 H), 4.23–4.34 (m, 3 H) ppm. ^{13}C NMR (100 MHz): δ = 27.9, 29.2, 31.7, 52.1, 57.3, 66.5, 83.0, 168.2, 170.8 ppm. $C_{14}H_{20}F_3NO_5$ (325.28): calcd. C 48.00, H 5.58, N 4.31; found C 48.07, H 5.39, N 4.28. HRMS calcd. for $C_{13}H_{19}F_3NO_5$ [M + H]$^+$: 326.1215, found 326.1193.

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