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Sequential Mannich-Aza-Michael Reactions for the Stereodivergent Synthesis of Highly Substituted Pyrrolidines

Charlotte Enkisch[a] and Christoph Schneider*[a]

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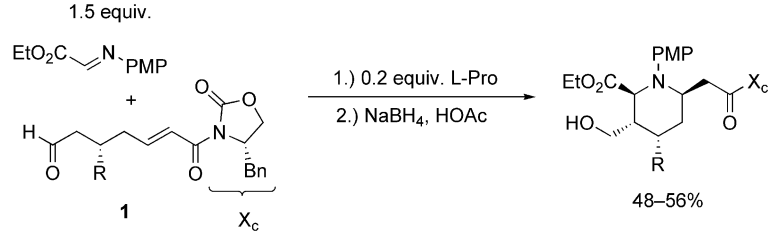
A stereodivergent synthesis of 2,3,5-trisubstituted pyrrolidines by an organocatalytic Mannich/aza-Michael addition sequence has been developed. Depending upon the choice of the base used in the intramolecular aza-Michael additions, 2,5-*trans*- or 2,5-*cis*-configured pyrrolidines were obtained in high yields and excellent diastereomeric ratios. Selective deprotection of the amino group and the side-chain hydroxy group proceeded without loss of diastereomeric purity. The stereodivergent outcome of the key aza-Michael reactions is the result of thermodynamically versus kinetically controlled cyclization.

Introduction

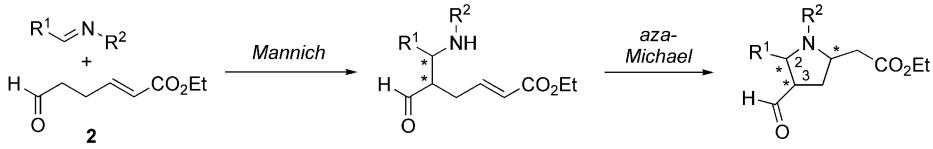
N-Heterocyclic compounds are common structural features in a variety of biologically active substances. In particular, substituted pyrrolidines are found in many natural products, such as kainic acid,[1] alkaloids such as (–)-codonopsinine,[2] and the family of the broussonetines,[3] as well as in a number of synthetic drugs that interact with a plethora of target enzymes such as acetylcholinesterase,[4] hepatitis C virus RNA polymerase,[5] influenza neuraminidase,[6] and HIV-1 protease.[7] The broad range of biological activity of highly functionalized pyrrolidines underlines the importance of having a broad range of versatile and efficient stereoselective preparation methods readily available. Two main strategies for the stereoselective preparation of highly substituted pyrrolidines have evolved:[8] either asymmetric 1,3-dipolar cycloadditions[9] or sequential approaches in which linear molecules containing the stereocenters are built up first, followed by cyclization.[2,10] Organocatalytic reactions that have emerged recently[11] facilitate the sequential approach, because they can be used to make the ring closures enantioselective[12] and/or help to achieve the efficient enantioselective preparation of the open-chain molecules.[13] For the diastereoselective ring-closure reactions, intramolecular aza-Michael additions have recently attracted considerable attention.[13b,14] An intramolecular aza-Michael addition, for instance, has been used as the key step in the synthesis of (3*R*,5*R*)-carbapenam-3-carboxylic acid.[14h] Moreover, it has been suggested that aza-Michael additions also occur in biosynthetic pathways, such as in the suggested biosynthesis of plakoridine A.[15]

We recently achieved the stereoselective synthesis of highly substituted piperidines by a similar approach (Scheme 1).[16] The functionalized aldehydes **1**, obtained in enantiomerically pure form through Cope rearrangements of silylated *syn*-aldol products,[17] were treated with glyoxyl imines and catalytic amounts of L-proline, resulting in a highly stereoselective domino-Mannich/aza-Michael reaction sequence and the formation of pipecolic esters in one step.



Scheme 1. Mannich/aza-Michael approach for the synthesis of functionalized piperidines (PMP: *p*-methoxyphenyl).[16]

[a] Institut für Organische Chemie, Universität Leipzig, Johannisallee 29, 04103 Leipzig, Germany
Fax: +49-341-9736599
E-mail: schneider@chemie.uni-leipzig.de



Scheme 2. Mannich/aza-Michael approach for the synthesis of highly functionalized pyrrolidines.

We have now extended this methodology to the highly diastereoselective preparation of trisubstituted pyrrolidines through a Mannich/aza-Michael sequence with the 6-oxo-2-enoate **2** as starting compound (Scheme 2). As a special bonus we can easily control the 2,5-*cis*/*trans* diastereoselectivity of the aza-Michael cyclizations by using the appropriate base under carefully optimized reaction conditions.

Results and Discussion

Asymmetric Organocatalytic Mannich Reactions

In the first step of the envisioned sequence, asymmetric proline-catalyzed Mannich reactions with *N*-Boc-imines according to the protocol developed by List et al.[18] were employed to establish the absolute and relative configurations at C2 and C3 (pyrrolidine numbering; Scheme 2). Thus, the aldehyde **2**, prepared by a Wittig reaction between succinaldehyde and ethoxycarbonyltriphenylphosphorane,[19] was treated with *N*-Boc-protected imines in the presence of L-proline (20 mol-%), followed by in situ reduction of the carbonyl group with sodium borohydride and acetic acid (Scheme 3). In order to achieve complete conversion, a second equivalent of the imine was added after 6–7 h.

By the above two-step sequence, a variety of aromatic *N*-Boc-protected imines were treated with aldehyde **2**, giving rise to the reduced Mannich products typically in good yields (Table 1). These products were generally obtained as single diastereomers with excellent enantioselectivities, the only exception being the 3-methylphenyl derivative **4f** (Entry 6), which was obtained in 44% yield and 82% *ee*. Silylation of the hydroxy group was achieved with *tert*-butyldimethylsilyl chloride (TBSCl), imidazole, and 4-(dimethylamino)pyridine (DMAP) in yields ranging from 70 to 99% (Scheme 4).

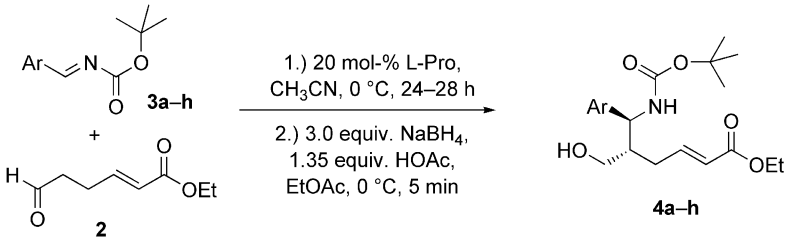
Table 1. L-Proline-catalyzed Mannich reactions with aldehyde **2** (Scheme 3).

Entry	Ar	Product	Yield [%][a]	*ee* [%][b]
1	Ph	**4a**	82	99
2	4-FC_6H_5	**4b**	80	99
3	4-ClC_6H_5	**4c**	83	99
4	4-$MeOC_6H_5$	**4d**	58	99
5	4-$CH_3C_6H_5$	**4e**	76	99
6	3-$CH_3C_6H_5$	**4f**	44	82
7	2-$CH_3C_6H_5$	**4g**	97	99
8	2-furyl	**4h**	63	98

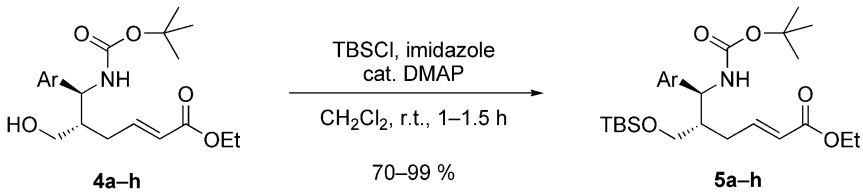
[a] Yield of isolated diastereomerically pure sample after flash column chromatography. [b] Determined by chiral HPLC analysis.

Base-Promoted Intramolecular Aza-Michael Additions

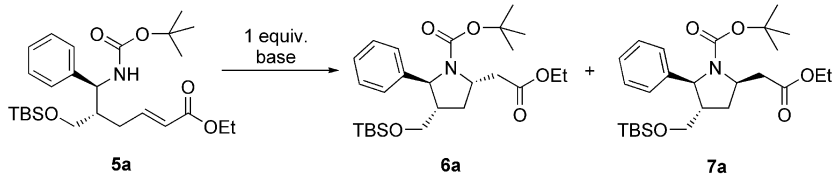
In an attempt to avoid the use of protecting groups, cyclization of the Mannich products was first attempted without prior protection of the hydroxy group. However, under various reaction conditions the formation of tetrahydrofurans resulting from the undesired oxa-Michael addition could not be suppressed completely. Accordingly the *O*-silylated Mannich products were used instead (Scheme 5 and Table 2).



Scheme 3. L-Proline-catalyzed Mannich reactions with aldehyde **2**.



Scheme 4. Silylation of the Mannich products.



Scheme 5. Intramolecular aza-Michael additions of the silylated Mannich products.

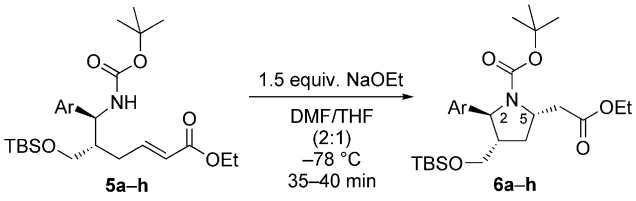
Table 2. Variation of base, solvent, and temperature in base-promoted intramolecular aza-Michael additions of the silylated Mannich product **5a** (Scheme 5).

Entry	Base	Solvent	*T* [°C]	*t* [min]	Yield [%][a]	**6a**/**7a**[b]
1	KO*t*Bu	THF	–78	30	86	80:20
2	KO*t*Bu	THF	room temp.	5	46	11:89
3	NaOEt	DMF	room temp.	5	59	20:80
4	NaH	DMF	room temp.	10	68	25:75
5	NaH	THF	–78 to 0	190	82	75:25
6	NaOEt[c]	DMF/THF (2:1)	–78	40	90	>95:5
7	KO*t*Bu	DMF/THF (2:1)	–78	40	88	6:94
8	NaOEt[d]	THF/EtOH (5:1)	–78	180	81[e]	
9	NaOEt	THF/EtOH (10:1)	room temp.	30	63	89:11

[a] Yield of isolated product after flash column chromatography. [b] Determined by ^{1}H NMR spectroscopy. [c] 1.5 equiv. [d] 10 equiv. [e] **5a**.

Treatment of the Mannich product **5a** with KO*t*Bu at –78 °C furnished **6a** with a diastereoselectivity of 80:20, whereas at room temp., an excess of **7a** was formed, albeit in only 46% yield (Table 2, Entries 1 and 2). The yield of **7a** was increased with use of NaOEt and NaH in DMF, but the selectivities were still only 80:20 and 75:25, respectively (Entries 3 and 4). Treatment of **5a** with NaH in THF at low temperatures led to an 82% yield of **6a** in a *dr* of 75:25 (Entry 5). Finally, use of a DMF/THF solvent mixture at –78 °C enabled us to perform highly diastereoselective aza-Michael additions. The 2,5-*trans*-configured pyrrolidine **6a** was selectively formed with NaOEt as base in 90% yield and with a diasteromeric ratio of >95:5 (Entry 6), whereas treatment of **5a** with KO*t*Bu under the same conditions gave an 88% yield of the 2,5-*cis*-configured pyrrolidine **7a** with a diastereoselectivity of 94:6 (Entry 7).

These optimized conditions were subsequently applied to the other Mannich products **5**. With NaOEt as base in DMF/THF (Scheme 6 and Table 3) the 2,5-*trans*-pyrrolidines **6** were obtained in generally excellent yields ranging between 81 and 94% and as single diastereomers according to ^{1}H NMR analysis. With KO*t*Bu as base (Scheme 7 and Table 4), on the other hand, the 2,5-*cis*-pyrrolidines **7** were prepared in 83–93% yields and with good diastereocontrol of at least 90:10.

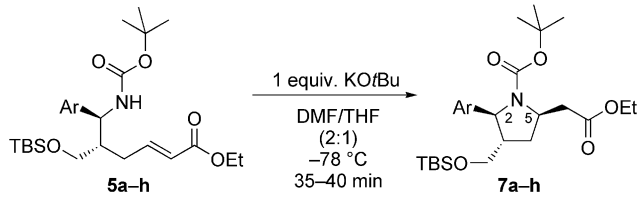


Scheme 6. Synthesis of the 2,5-*trans*-pyrrolidines **6a**–**h**.

Table 3. *trans*-Diastereoselective aza-Michael reactions (Scheme 6).

Entry	Ar	Product	Yield [%][a]	*trans*/*cis*[b]
1	Ph	**6a**	90	>95:5
2	4-FC_6H_5	**6b**	84	>95:5
3	4-ClC_6H_5	**6c**	88	>95:5
4	4-$MeOC_6H_5$	**6d**	85	>95:5
5	4-$CH_3C_6H_5$	**6e**	92	>95:5
6	3-$CH_3C_6H_5$	**6f**	94	>95:5
7	2-$CH_3C_6H_5$	**6g**	81	>95:5
8	2-furyl	**6h**	92	>95:5

[a] Yield of isolated product after flash column chromatography. [b] Determined by ^{1}H NMR spectroscopy.

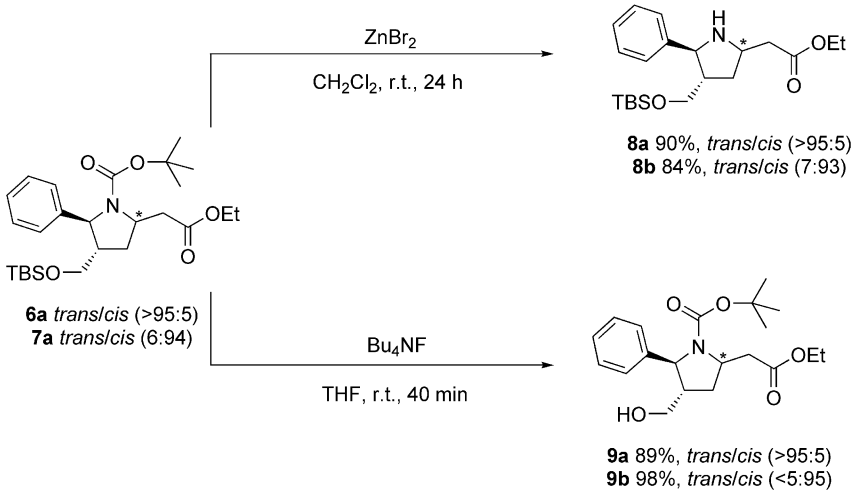


Scheme 7. Synthesis of 2,5-*cis*-pyrrolidines **7a**–**h**.

Table 4. *cis*-Diastereoselective aza-Michael reactions (Scheme 7).

Entry	Ar	Product	Yield [%][a]	*cis*/*trans*[b]
1	Ph	**7a**	88	94:6
2	4-FC_6H_5	**7b**	93	91:9
3	4-ClC_6H_5	**7c**	86	92:8
4	4-$MeOC_6H_5$	**7d**	83	>95:5
5	4-$CH_3C_6H_5$	**7e**	88	>95:5
6	3-$CH_3C_6H_5$	**7f**	89	>95:5
7	2-$CH_3C_6H_5$	**7g**	87	90:10
8	2-furyl	**7h**	88	>95:5

[a] Yield of isolated product after flash column chromatography. [b] Determined by ^{1}H NMR spectroscopy.



Scheme 8. Selective cleavage of the protecting groups.

Deprotection

Selective cleavage of the protecting groups was achieved for both diastereomers without affecting the diastereomeric ratio (Scheme 8). The amino groups in **6a** and **7a** were Boc-deprotected by treatment with $ZnBr_2$, furnishing **8a** and **8b** in 90% and 84% yields, respectively.[20] Cleavage of the silyl ethers with Bu_4NF proceeded smoothly, giving rise to **9a** and **9b** in yields of 89% and 98%, respectively.[21] Both deprotections proceeded without loss of diastereomeric purity.

Diastereoselectivities of the Aza-Michael Additions

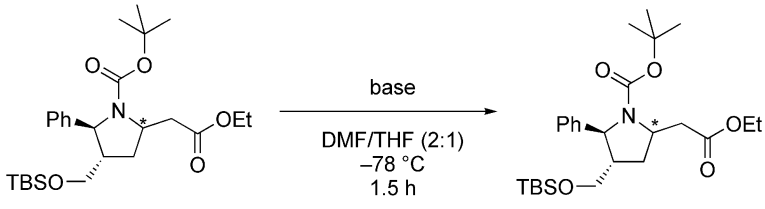
DFT calculations performed on the desilylated methyl esters **11** and **12** (Scheme 12, below) suggested that the 2,5-*cis*-pyrrolidine is thermodynamically more stable than the 2,5-*trans* isomer by 13 kJ mol^{-1}, whereas the activation energy for the formation of the latter is 3 kJ mol^{-1} less than for the 2,5-*cis*-pyrrolidine.[22] This is in accordance with the observation that **7a** is obtained at higher temperatures (Table 2, Entries 2–4), whereas the formation of **6a** is favored at lower temperatures (Table 2, Entries 1 and 5). In order to elucidate the influence of the base on the diastereoselectivity further, **6a** and **7a** were resubjected to the reaction conditions described above (Scheme 9).

Treatment of the kinetic product **6a** with KO*t*Bu in DMF/THF at –78 °C furnished the epimerized product **7a** with high stereoselectivity, whereas under the same reaction conditions the thermodynamic product **7a** was reisolated in 78% yield and unchanged diastereomeric ratio (Table 5, Entries 1 and 2). This suggests that **7a** is indeed the thermodynamically favored diastereomer. Upon treatment of **6a** and **7a** with NaOEt in DMF/THF at –78 °C, the substrates were isolated unchanged in almost quantitative yields (Entries 3 and 4). These findings imply that the deprotonation of the ethyl ester does not proceed in the presence of NaOEt (Scheme 10). In contrast, KO*t*Bu, being the stronger base, is able to generate the ester enolate of **6a**, thereby leading to a retro-aza-Michael reaction and accordingly to epimerization of the kinetically favored 2,5-*trans*-pyrrolidine **6a** to the thermodynamically favored 2,5-*cis*-pyrrolidine **7a**. In contrast, the basicity of NaOEt appears to be insufficient to deprotonate the ester. Hence the kinetically favored 2,5-*trans*-pyrrolidine **6a**, which is formed first, cannot be converted into the 2,5-*cis*-pyrrolidine **7a** when treated with NaOEt.

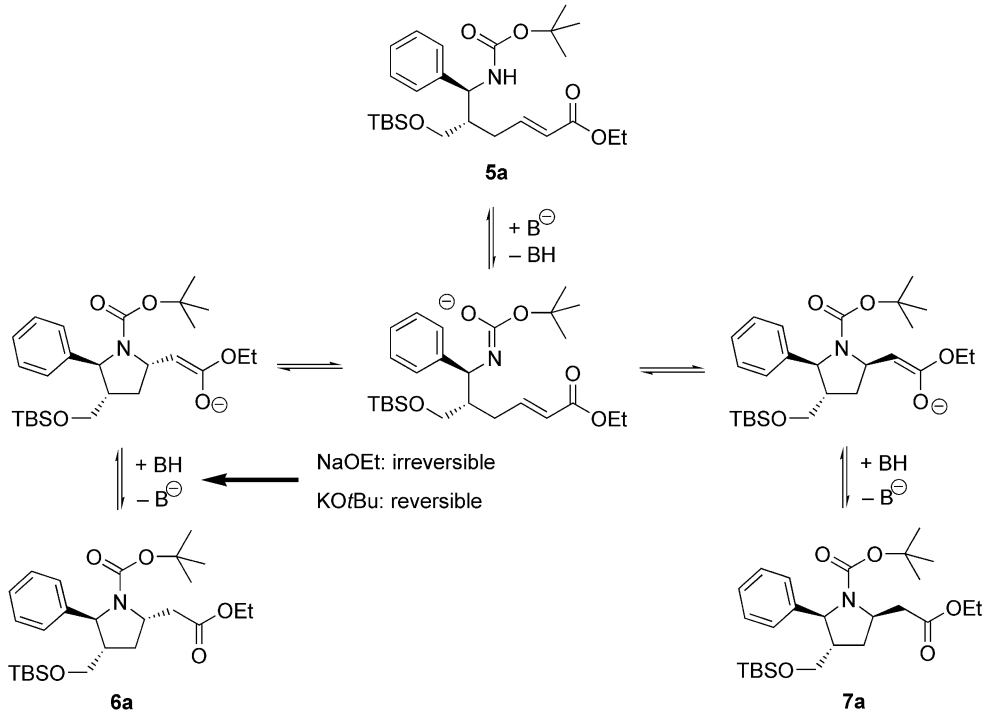
Table 5. Treatment of 2,5-*trans*- and 2,5-*cis*-pyrrolidines **6a** and **7a** with base (Scheme 9).

Entry	Substrate	Base	Product	Yield [%][a]	*trans*/*cis*[b]
1	**6a**	1 equiv. KO*t*Bu	**7a**	64	6:94
2	**7a**	1 equiv. KO*t*Bu	**7a**	78	<5:95
3	**6a**	1.5 equiv. NaOEt	**6a**	95	>95:5
4	**7a**	1.5 equiv. NaOEt	**7a**	94	6:94

[a] Yield of isolated product after flash column chromatography. [b] Determined by ^{1}H NMR spectroscopy.

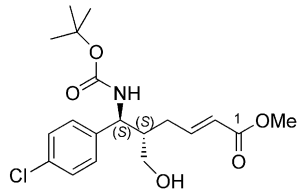


Scheme 9. Examination of the epimerization of 2,5-*trans*- and 2,5-*cis*-pyrrolidines **6a** and **7a** under the reaction conditions.



Scheme 10. Equilibria in the intramolecular base-promoted aza-Michael additions.

The 2,5-*trans* selectivity observed with the use of KO*t*Bu in THF at –78 °C can be explained by solvation effects (Table 2, Entry 1): DMF solvates the potassium ion much better than THF thereby increasing the basicity of the *t*BuO⁻ anion. Thus, in THF the ion pairing of KO*t*Bu is more pronounced, and the basicity of the *t*BuO⁻ anion is attenuated relative to the case of the DMF/THF solvent mixture. On the other hand, NaOEt is insoluble in THF, and addition of ethanol leads to reisolation of the substrate when the reaction is performed at –78 °C (Entry 8). Raising the temperature to room temperature under otherwise identical reaction conditions results in the diastereoselective formation of **6a** (Entry 9). Here, protonation of the formed ester enolate is accelerated by the addition of ethanol, whereas the ethoxide anion is less basic, due to solvation by ethanol. In summary, it can be concluded that the selectivity of the intramolecular aza-Michael addition is governed on one hand by the temperature and on the other by the actual basicity of the base, this being dependent on solvation effects.



Scheme 11. Structural formula of Mannich product **10**.

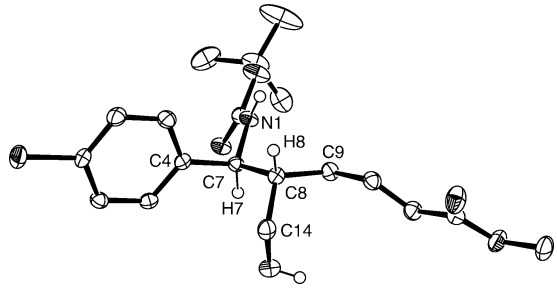


Figure 1. ORTEP[23] plot of the X-ray crystal structure of **10**.

Assignment of the Absolute and Relative Configurations

By analogy with known Mannich products[18] and according to the transition state[24] suggested for L-proline-catalyzed Mannich reactions the configuration of the Mannich products **4** was assigned as (5*S*,6*S*). This was confirmed by an X-ray crystal structure analysis of the 4-chlorophenyl derivative **10** (Scheme 11, Figure 1).

The assignment of the relative configuration of the pyrrolidines was derived from comparison of calculated conformations[22] with NOE measurements. According to the calculated structures of pyrrolidines **11** and **12**, NOEs would be expected to occur between H3/H5 and H5/H2′*o* in **11**, as well as between H3/H5′ and H5′/H2′*o* in **12** (Scheme 12, Figure 2, Table 6). Except for H3/H5 in the 2,5-*trans* isomer, all contacts were observed in the NOESY

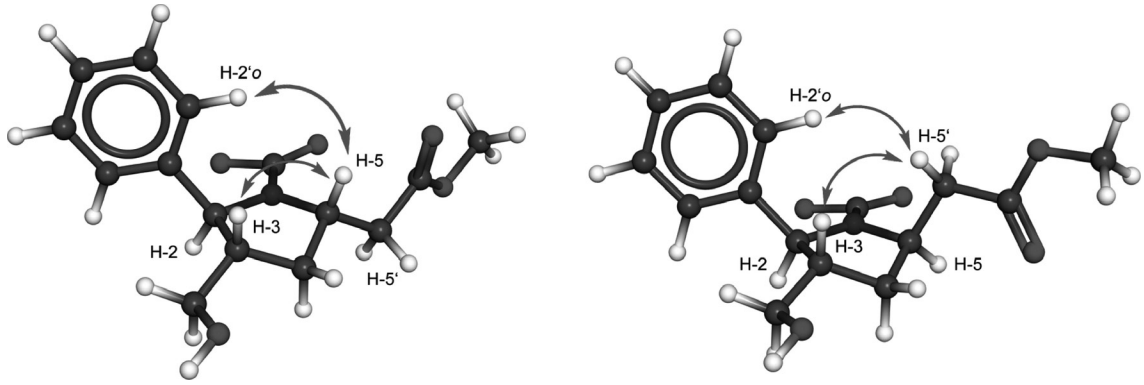
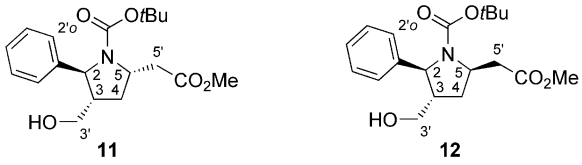


Figure 2. Geometries of **11** and **12** from DFT calculations (*t*Bu omitted for clarity).

spectra of **6a** and **7a**, so the (2*S*,3*S*,5*S*) configuration was assigned to **6a** and the (2*S*,3*S*,5*R*) configuration was assigned to **7a**. The assignment of the relative configuration was confirmed by X-ray crystal structure analysis of **12** (Figure 3).



Scheme 12. Structural formulae of **11** and **12**.

Table 6. Calculated distances and results from NOESY spectra of **6a** and **7a**.

2,5-*trans*	Distance [Å]	NOE	2,5-*cis*	Distance [Å]	NOE
H3 to H5	2.767	no	H3 to H5′	2.577	yes
H5 to H2′*o*	2.836	yes	H5′ to H2′*o*	2.614	yes

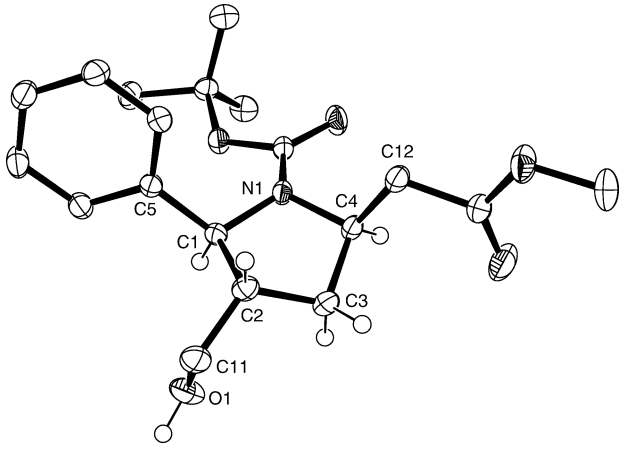


Figure 3. ORTEP[23] plot of the X-ray crystal structure of **12**.

Conclusions

A short and efficient reaction sequence for the stereodivergent synthesis of enantiomerically pure trisubstituted pyrrolidines has been developed. The stereocenters at C2 and C3 were established through L-proline-catalyzed Mannich reactions, whereas the configuration at C5 was controlled in base-promoted intramolecular aza-Michael additions. In these ring closures, variation of the base permitted the selective preparation either of 2,5-*trans*-pyrrolidines **6** or of 2,5-*cis*-pyrrolidines **7** with diastereomeric ratios between 90:10 and >95:5. Chemoselective deprotection of the amino group and the side-chain hydroxy group proceeded without loss of diastereomeric purity. The relative configuration in **6** and **7** was determined by NOE measurements in combination with conformational analysis by DFT methods. The assignments were confirmed by an X-ray crystal structure analysis of **12**. The absolute configuration was assigned by analogy with Mannich products known in the literature, and was confirmed by an X-ray crystal structure analysis of Mannich product **10**. Both the DFT calculations and the experimental results suggest that the 2,5-*trans* diastereomers represent the kinetically favored products, which, at higher temperatures or in the presence of a stronger base, can isomerize to the thermodynamically favored 2,5-*cis* diastereomers.

Experimental Section

General: All reactions were carried out with magnetic stirring under nitrogen. Dry solvents were distilled from the indicated drying agents: dichloromethane (CaH_2), tetrahydrofuran (K), *N*,*N*-dimethylformamide (CaH_2). Acetonitrile and chloroform were obtained from VWR in HPLC quality (HiPerSolvCHROMANORM). Diethyl ether and petroleum ether (PE) for chromatography were technical grade and distilled from KOH. Ethyl acetate was distilled from $CaCl_2$. All reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel plates (60 F_{254}, Merck KGaA); spots were visualized by treatment with a solution of vanillin (0.5 g), concd. acetic acid (10 mL), and concd. H_2SO_4 (5 mL) in methanol (90 mL), or with a solution of $KMnO_4$ (3.0 g), K_2CO_3 (20 g), and acetic acid (0.25 mL) in water (300 mL), or with a solution of phosphomolybdic acid hydrate (1.0 g) in ethanol (50 mL). Flash column chromatography was performed with Merck silica gel 60 (230–400 mesh, 0.040–0.063 mm). L-Proline was racemized,[25] and imines **3**[26] were prepared according to literature procedures. All other chemicals were used as received from commercial suppliers. ^1H and ^{13}C NMR spectra were recorded with

Varian Gemini 200 and 2000 (200 MHz), Varian Gemini 300 BB (300 MHz), and Bruker Avance DRX 400 (400 MHz) spectrometers. Chemical shifts are reported relative to tetramethylsilane as internal standard or to the residual solvent signals [tetrachloroethane: $\delta(^1H) = 6.00$ ppm, chloroform: $\delta(^{13}C) = 77.16$ ppm]. Melting points were determined with a Boetius heating table and are uncorrected. Elemental analyses were obtained from the microanalytical laboratory of the Department of Chemistry at the University of Leipzig. IR spectra were obtained with an FTIR spectrometer (Genesis ATI, Mattson/Unicam). ESI mass spectra were recorded with a Bruker APEX II FT-ICR (high resolution) and with a Bruker ESQUIRE instrument. Optical rotations were measured with a Schmidt & Haensch Polartronic D polarimeter. HPLC analyses were performed with a JASCO MD-2010 plus instrument with a chiral stationary-phase column (Chiralpak AD-H and Chiralcel OD purchased from Daicel Chemical Industries, Ltd.).

Ethyl (2*E*)-6-Oxohex-2-enoate (2):[19] 2,5-Dimethoxytetrahydrofuran (93 mL, 0.72 mol) was added to HCl (1 M, 360 mL), and the mixture was stirred at room temp. for 10 min. Solid $NaHCO_3$ (36.6 g, 0.43 mol) was added until pH = 6–6.5 was reached. The aqueous phase was extracted with ethyl acetate (6 × 350 mL), saturated with NaCl, and again extracted with ethyl acetate (3 × 300 mL). The combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was evaporated in vacuo. Distillation of the residue afforded succinaldehyde (36.71 g, 59%, b.p. 23 °C, 56–61 mbar). A solution of freshly prepared succinaldehyde (36.71 g, 0.426 mol) in dry CH_2Cl_2 (1.11 L) was cooled in an ice bath, and a solution of ethoxycarbonyltriphenylphosphorane (37.08 g, 0.107 mol) in dry CH_2Cl_2 (370 mL) was added dropwise. The reaction mixture was stirred at room temp. for 2 d. The solvent was evaporated, and the residue was stirred in diethyl ether/pentane (1:1, v/v; 3 × 100 mL) for 10 min and filtered, the solids being washed with a diethyl ether/pentane mixture (100 mL). The solvents were evaporated, and the residue was distilled to remove unchanged succinaldehyde (6.82 g, b.p. 50–60 °C, 15–20 mbar). The residue was purified by flash column chromatography on silica gel (1:20, w/w) with diethyl ether/petroleum ether [first 1:3, then 1:2 (v/v)] as eluent. The title compound was obtained as a colorless liquid (6.83 g, 41%). $R_f = 0.22$ (Et_2O/PE, 1:1). ^1H NMR (200 MHz, $CDCl_3$, 29 °C): $\delta = 1.3$ (t, $^3J_{H,H} = 7.0$ Hz, 3 H, OCH_2CH_3), 2.5–2.7 (m, 4 H, 4-CH_2, 5-CH_2), 4.2 (q, $^3J_{H,H} = 7.0$ Hz, 2 H, OCH_2CH_3), 5.9 (dt, $^4J_{H,H} = 1.5$, $^3J_{H,H} = 15.5$ Hz, 1 H, 2-CH), 6.9 (dt, $^3J_{H,H} = 6.5$, $^3J_{H,H} = 15.5$ Hz, 1 H, 3-CH), 9.8 (s, 1 H, CHO) ppm.

General Procedure for the L-Proline-Catalyzed Mannich Reactions: An imine **3** (1.0 equiv.) was added to a solution of the aldehyde **2** (0.1 M, 1.0 equiv.) in acetonitrile. The mixture was cooled in an ice bath under argon. L-Proline (0.2 equiv.) was added. After 6–7 h, a further solution of imine (1.0 equiv.) in acetonitrile (1 M) was added. After consumption of the aldehyde as monitored by TLC (after 24–28 h reaction time), the reaction mixture was transferred at 0 °C to a flask containing a freshly prepared solution of $NaBH_4$ (3.0 equiv.) and acetic acid (1.35 equiv.) in ethyl acetate (0.3 M with respect to $NaBH_4$). After 5 min at 0 °C, an equal volume of saturated NH_4Cl solution was added. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried with $MgSO_4$ and filtered, and the solvents were evaporated in vacuo. The residue was dissolved in a small amount of ethyl acetate and ethanol, adsorbed on silica gel, and purified by flash column chromatography on silica gel (1:50, w/w) with diethyl ether/petroleum ether as eluent. For purposes of authentication, the racemic products were prepared by use of DL-proline, and the HPLC retention times were compared with those for the enantioselective runs.

Ethyl (2*E*,5*S*,6*S*)-6-[(*tert*-Butoxycarbonyl)amino]-5-(hydroxymethyl)-6-phenylhex-2-enoate (4a): Yield: 502 mg, 82%, white solid. $R_f = 0.18$ (Et_2O/PE, 2:1). M.p. 120–123 °C. $[a]_D^{22} = +13$ ($c = 1.1$, $CHCl_3$). *ee* = 99%. Enantiomeric assay: Chiralpak AD-H, isocratic (*n*-hexane/*i*PrOH, 90:10; flow 1.0 mL min^{-1}), $\lambda_{max} = 208$ nm, $t_1 = 19.2$ min, $t_2 = 22.4$ min. ^1H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): $\delta = 1.3$ (t, $^3J_{H,H} = 7.0$ Hz, 3 H, OCH_2CH_3), 1.5 [s, 9 H, $C(CH_3)_3$], 2.1–2.3 (m, 4 H, 4-CH_2, 5-CH, OH), 3.5 (dd, $^3J_{H,H} = 7.0$, $^2J_{H,H} = 11.0$ Hz, 1 H, CH_2OH), 3.6 (dd, $^3J_{H,H} = 4.0$, $^2J_{H,H} = 11.0$ Hz, 1 H, CH_2OH), 4.2 (q, $^3J_{H,H} = 7.0$ Hz, 2 H, OCH_2CH_3), 5.0 (dd, $^3J_{H,H} = 5.0$, $^3J_{H,H} = 9.0$ Hz, 6-CH), 5.2 (d, $^3J_{H,H} = 9.0$ Hz, 1 H, NH), 5.9 (d, $^3J_{H,H} = 15.5$ Hz, 1 H, 2-CH), 6.9 (dt, $^3J_{H,H} = 7.0$, $^3J_{H,H} = 15.5$ Hz, 1 H, 3-CH), 7.1 (m, 3 H, ArH), 7.3 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 14.3$ (OCH_2CH_3), 28.4 [$C(CH_3)_3$], 29.7 (C4), 45.6 (C5), 54.7 (C6), 60.4 (OCH_2CH_3), 62.5 (CH_2OH), 80.1 [$C(CH_3)_3$], 123.1 (C2), 126.7 (C4′), 127.4 (C2′), 128.7 (C3′), 140.1 (C1′), 146.8 (C3), 156.3 (carbamate CO), 166.3 (C1) ppm. IR (KBr): $\tilde{\nu} = 3545$ (OH), 3379 (NH), 3066, 3033, 2982, 2937, 2907, 2878, 1703 (C=O), 1682 (C=O), 1652 (C=C), 1600 (C=C), 1580 (C=C), 1520 (C=O), 1500 (C=C), 1370, 1163, 758, 703 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 207 (11783), 212 (12837), 217 (13752 mol^{-1} dm^3 cm^{-1}) nm. HRMS-ESI: calcd. for $C_{20}H_{29}NO_5$ $[M + Na]^+$ 386.19379; found 386.19359.

Ethyl (2*E*,5*S*,6*S*)-6-[(*tert*-Butoxycarbonyl)amino]-6-(4-fluorophenyl)-5-(hydroxymethyl)hex-2-enoate (4b): Yield: 494 mg, 80%, white solid. $R_f = 0.15$ (Et_2O/PE 2:1). M.p. 147–148 °C. $[a]_D^{22} = +18$ ($c = 1.09$, $CHCl_3$). *ee* = 99%. Enantiomeric assay: Chiralpak AD-H, isocratic (*n*-hexane/*i*PrOH, 90:10; flow 1.0 mL min^{-1}), $\lambda_{max} = 208$ nm, $t_1 = 16.5$ min, $t_2 = 21.7$ min. ^1H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): $\delta = 1.3$ (t, $^3J_{H,H} = 7.0$ Hz, 3 H, OCH_2CH_3), 1.5 [s, 9 H, $C(CH_3)_3$], 2.1–2.3 (m, 4 H, 4-CH_2, 5-CH, OH), 3.5 (dd, $^3J_{H,H} = 7.0$, $^2J_{H,H} = 11.0$ Hz, 1 H, CH_2OH), 3.6 (dd, $^3J_{H,H} = 4.0$, $^2J_{H,H} = 11.0$ Hz, 1 H, CH_2OH), 4.2 (q, $^3J_{H,H} = 7.0$ Hz, OCH_2CH_3), 5.0 (dd, $^3J_{H,H} = 4.5$, $^3J_{H,H} = 9.0$ Hz, 1 H, 6-CH), 5.2 (d, $^3J_{H,H} = 9.0$ Hz, 1 H, NH), 7.1 (m_c, 2 H, ArH), 7.3 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 14.3$ (OCH_2CH_3), 28.4 [$C(CH_3)_3$], 29.9 (C4), 45.4 (C5), 54.5 (C6), 60.5 (OCH_2CH_3), 62.5 (CH_2OH), 80.3 [$C(CH_3)_3$], 115.5 ($^2J_{C,F} = 21.0$ Hz, C3′, C5′), 123.3 (C2), 128.4 ($^3J_{C,F} = 7.5$ Hz, C2′, C6′), 135.9 (C1′), 146.5 (C3), 156.1 (carbamate CO), 162.1 ($^1J_{C,F} = 244$ Hz, C4′), 166.3 (C1) ppm. IR (KBr): $\tilde{\nu} = 3503$ (OH), 3381 (NH), 3010, 2981, 2939, 2907, 1698 (C=O), 1681 (C=O), 1653 (C=C), 1606 (C=C), 1517 (C=O), 1510 (C=C), 1368, 1292, 1226, 1177, 1159, 841 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 205 (13096), 210 (15793), 263 (444), 270 (309 mol^{-1} dm^3 cm^{-1}) nm. MS (ESI): $m/z = 404$ $[M + Na]^+$, 785 $[2M + Na]^+$. $C_{20}H_{28}FNO_5$ (381.44): calcd. C 62.98, H 7.40, N 3.67; found C 62.83, H 7.46, N 3.51.

Ethyl (2*E*,5*S*,6*S*)-6-[(*tert*-Butoxycarbonyl)amino]-6-(4-chlorophenyl)-5-(hydroxymethyl)hex-2-enoate (4c): Yield: 391 mg, 83%, white solid. $R_f = 0.16$ (Et_2O/PE, 2:1). M.p. 130–131 °C. $[a]_D^{22} = +13$ ($c = 1.04$, $CHCl_3$). *ee* = 99%. Enantiomeric assay: Chiralpak AD-H, isocratic (*n*-hexane/*i*PrOH, 90:10; flow 1.0 mL min^{-1}), $\lambda_{max} = 204$ nm, $t_1 = 17.2$ min, $t_2 = 23.2$ min. ^1H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): $\delta = 1.3$ (t, $^3J_{H,H} = 7.0$ Hz, 3 H, OCH_2CH_3), 1.5 [s, 9 H, $C(CH_3)_3$], 2.1–2.3 (m, 4 H, 4-CH_2, 5-CH, OH), 3.5–3.6 (m, 2 H, CH_2OH), 4.2 (q, $^3J_{H,H} = 7.0$ Hz, 2 H, OCH_2CH_3), 5.0 (dd, $^3J_{H,H} = 4.5$, $^3J_{H,H} = 9.0$ Hz, 1 H, 6-CH), 5.2 (d, $^3J_{H,H} = 9.0$ Hz, 1 H, NH), 5.9 (d, $^3J_{H,H} = 15.5$ Hz, 1 H, 2-CH), 6.9 (dt, $^3J_{H,H} = 7.5$, $^3J_{H,H} = 15.5$ Hz, 1 H, 3-CH), 7.3 (br. d, $^3J_{H,H} = 8.5$ Hz, 2 H, ArH), 7.4 (br. d, $^3J_{H,H} = 8.5$ Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz,

$CDCl_3$, 25 °C): δ = 14.3 (OCH_2CH_3), 28.4 [$C(CH_3)_3$], 30.0 (C4), 45.2 (C5), 54.6 (C6), 60.5 (OCH_2CH_3), 62.4 (CH_2OH), 80.4 [$C(CH_3)_3$], 122.3 (C2), 128.3, 128.8 (C2′, C3′, C5′, C6′), 133.2 (C4′), 138.7 (C1′), 146.4 (C3), 156.1 (carbamate CO), 166.3 (C1) ppm. IR (KBr): $\tilde{\nu}$ = 3495 (OH), 3370 (NH), 2980, 2935, 1720 (C=O), 1700 (C=O), 1681, 1651 (C=C), 1520 (C=O), 1493 (C=C), 1445, 1368, 1287, 1251, 1169, 1092, 1040, 1014 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 217 (17838 $mol^{-1}\,dm^3\,cm^{-1}$) nm. MS (ESI): *m*/*z* = 398 $[M + H]^+$, 420 $[M + Na]^+$. $C_{20}H_{28}ClNO_5$ (397.89): calcd. C 60.37, H 7.09, N 3.52; found C 60.24, H 7.16, N 3.35.

Ethyl (2*E*,5*S*,6*S*)-6-[(*tert*-Butoxycarbonyl)amino]-5-(hydroxymethyl)-6-(4-methoxyphenyl)hex-2-enoate (4d): Yield: 356 mg, 58%, white solid. R_f = 0.15 (Et_2O/PE, 2:1). M.p. 110–112 °C. $[\alpha]_D^{22}$ = +8 (*c* = 1.26, $CHCl_3$). *ee* = 99%. Enantiomeric assay: Chiralpak AD-H, isocratic (*n*-hexane/*i*PrOH, 90:10; flow 1.0 mL min^{-1}), λ_{max} = 204 nm, t_1 = 23.6 min, t_2 = 31.0 min. ^1H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): δ = 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.5 [s, 9 H, $C(CH_3)_3$], 2.1–2.3 (m, 4 H, 4-CH_2, 5-CH, OH), 3.5 (dd, $^3J_{H,H}$ = 7.0, $^2J_{H,H}$ = 11.5 Hz, 1 H, CH_2OH), 3.6 (dd, $^3J_{H,H}$ = 4.5, $^2J_{H,H}$ = 11.5 Hz, 1 H, CH_2OH), 3.9 (s, 3 H, OCH_3), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.9 (dd, $^3J_{H,H}$ = 5.0, $^3J_{H,H}$ = 9.0 Hz, 1 H, 6-CH), 5.1 (d, $^3J_{H,H}$ = 9.0 Hz, 1 H, NH), 5.9 (d, $^3J_{H,H}$ = 15.5 Hz, 1 H, 2-CH), 6.5–7.0 (m, 1 H, 3-CH), 6.9 (br. d, $^3J_{H,H}$ = 8.5 Hz, 2 H, ArH), 7.2 (br. d, $^3J_{H,H}$ = 8.5 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.3 (OCH_2CH_3), 28.4 [$C(CH_3)_3$], 29.9 (C4), 45.5 (C5), 54.3 (C6), 55.3 (OCH_3), 60.3 (OCH_2CH_3), 62.5 (CH_2OH), 80.0 [$C(CH_3)_3$], 114.0 (C3′), 123.0 (C2), 127.8 (C2′), 132.1 (C1′), 146.9 (C3), 156.2 (carbamate CO), 158.8 (C4′), 166.4 (C1) ppm. IR (KBr): $\tilde{\nu}$ = 3484 (OH), 3374 (NH), 3068, 2977, 2935, 2835, 1702 (C=O), 1681 (C=O), 1651 (C=C), 1614 (C=C), 1586 (C=C), 1514 (C=C, C=O), 1369, 1297, 1251, 1206, 1174, 1035, 1021, 835, 816 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 208 (17657), 211 (17653), 217 (17382), 221 (17106), 274 (1651), 282 (1342 $mol^{-1}\,dm^3\,cm^{-1}$) nm. HRMS-ESI: calcd. for $[M + Na]^+$ 416.20436; found 416.20399. HRMS-ESI: calcd. for $[2 M + Na]^+$ 809.41950; found 809.41973.

Ethyl (2*E*,5*S*,6*S*)-6-[(*tert*-Butoxycarbonyl)amino]-5-(hydroxymethyl)-6-(4-methylphenyl)hex-2-enoate (4e): Yield: 339 mg, 76%, white solid. R_f = 0.18 (Et_2O/PE, 2:1). M.p. 121–122 °C. $[\alpha]_D^{22}$ = +10 (*c* = 1.0, $CHCl_3$). *ee* = 99%. Enantiomeric assay: Chiralpak AD-H, isocratic (*n*-hexane/*i*PrOH, 90:10; flow 1.0 mL min^{-1}), λ_{max} = 212 nm, t_1 = 16.7 min, t_2 = 19.8 min. ^1H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): δ = 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.5 [s, 9 H, $C(CH_3)_3$], 2.1–2.3 (m, 4 H, 4-CH_2, 5-CH, OH), 2.4 (s, 3 H, CH_3), 3.5 (dd, $^3J_{H,H}$ = 7.0, $^2J_{H,H}$ = 11.5 Hz, 1 H, CH_2OH), 3.6 (dd, $^3J_{H,H}$ = 4.5, $^2J_{H,H}$ = 11.5 Hz, 1 H, CH_2OH), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 5.0 (dd, $^3J_{H,H}$ = 5.0, $^3J_{H,H}$ = 9.0 Hz, 1 H, 6-CH), 5.1 (d, $^3J_{H,H}$ = 9.0 Hz, 1 H, NH), 5.8 (d, $^3J_{H,H}$ = 15.5 Hz, 1 H, 2-CH), 6.9 (m_c, 1 H, 3-CH), 7.2 (m, 4 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3 (OCH_2CH_3), 21.1 (CH_3), 28.4 [$C(CH_3)_3$], 29.7 (C4), 45.6 (C5), 54.4 (C6), 60.3 (OCH_2CH_3), 62.6 (CH_2OH), 80.1 [$C(CH_3)_3$], 123.0 (C2), 126.6 (C2′), 129.4 (C3′), 137.0 (C1′, C4′), 146.9 (C3), 156.3 (carbamate CO), 166.3 (C1) ppm. IR (KBr): $\tilde{\nu}$ = 3500 (OH), 3379 (NH), 2980, 2934, 1717 (C=O), 1681 (C=O), 1651 (C=C), 1519 (C=C), 1368, 1251, 1172 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 211 (14427), 217 (14321), 264 (254 $mol^{-1}\,dm^3\,cm^{-1}$) nm. MS (ESI): *m*/*z* = 400 $[M + Na]^+$, 777 $[2 M + Na]^+$. $C_{21}H_{31}NO_5$ (377.47): calcd. C 66.82, H 8.28, N 3.71; found C 66.68, H 8.27, N 3.58.

Ethyl (2*E*,5*S*,6*S*)-6-[(*tert*-Butoxycarbonyl)amino]-5-(hydroxymethyl)-6-(3-methylphenyl)hex-2-enoate (4f): Yield: 268 mg, 44%, white solid. R_f = 0.21 (Et_2O/PE, 2:1). M.p. 57–58 °C. $[\alpha]_D^{22}$ = +7 (*c* = 1.46, $CHCl_3$). *ee* = 82%. Enantiomeric assay: Chiralcel OD, isocratic (*n*-hexane/*i*PrOH, 90:10; flow 0.5 mL min^{-1}), λ_{max} = 212 nm, t_1 = 14.4 min, t_2 = 15.9 min. ^1H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): δ = 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.5 [s, 9 H, $C(CH_3)_3$], 2.1–2.4 (m, 4 H, 4-CH_2, 5-CH, OH), 2.4 (s, 3 H, CH_3), 3.5 (dd, $^3J_{H,H}$ = 7.0, $^2J_{H,H}$ = 11.5 Hz, 1 H, CH_2OH), 3.6 (dd, $^3J_{H,H}$ = 4.5, $^2J_{H,H}$ = 11.5 Hz, 1 H, CH_2OH), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 5.0 (dd, $^3J_{H,H}$ = 5.0, $^3J_{H,H}$ = 9.0 Hz, 1 H, 6-CH), 5.1 (d, $^3J_{H,H}$ = 9.0 Hz, 1 H, NH), 5.8 (d, $^3J_{H,H}$ = 15.5 Hz, 1 H, 2-CH), 6.9 (dt, $^3J_{H,H}$ = 7.5, $^3J_{H,H}$ = 15.5 Hz, 1 H, 3-CH), 7.1–7.2 (m, 3 H, ArH), 7.3 (t, $^3J_{H,H}$ = 8.0 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3 (OCH_2CH_3), 21.6 (CH_3), 28.4 [$C(CH_3)_3$], 29.7 (C4), 45.8 (C5), 54.5 (C6), 60.4 (OCH_2CH_3), 62.6 (CH_2OH), 80.2 [$C(CH_3)_3$], 123.0 (C2), 123.6 (C6′), 127.4 (C4′), 128.1 (C5′), 128.6 (C2′), 138.3 (C3′), 140.0 (C1′), 146.9 (C3), 156.4 (carbamate CO), 166.3 (C1) ppm. IR (KBr): $\tilde{\nu}$ = 3558 (OH), 3384 (NH), 2977, 2910, 1708 (C=O), 1686 (C=O), 1651 (C=C), 1608 (C=C), 1519 (C=C), 1368, 1212, 1161 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 215 (20920 $mol^{-1}\,dm^3\,cm^{-1}$) nm. HRMS-ESI: calcd. for $C_{21}H_{31}NO_5$ $[M + Na]^+$ 400.20944; found 400.20913.

Ethyl (2*E*,5*S*,6*S*)-6-[(*tert*-Butoxycarbonyl)amino]-5-(hydroxymethyl)-6-(2-methylphenyl)hex-2-enoate (4g): Yield: 408 mg, 97%, viscous oil. R_f = 0.22 (Et_2O/PE, 2:1). $[\alpha]_D^{22}$ = –17 (*c* = 1.09, $CHCl_3$). *ee* = 99%. Enantiomeric assay: Chiralpak AD-H, isocratic (*n*-hexane/*i*PrOH, 90:10; flow 1.0 mL min^{-1}), λ_{max} = 208 nm, t_1 = 18.9 min, t_2 = 21.3 min. ^1H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): δ = 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.5 [s, 9 H, $C(CH_3)_3$], 2.1–2.5 (m, 4 H, 4-CH_2, 5-CH, OH), 2.5 (s, 3 H, CH_3), 3.5 (d, $^3J_{H,H}$ = 5.5 Hz, 2 H, CH_2OH), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 5.0 (d, $^3J_{H,H}$ = 9.0 Hz, 1 H, NH), 5.2 (dd, $^3J_{H,H}$ = 6.0, $^3J_{H,H}$ = 9.0 Hz,1 H, 6-CH), 5.9 (d, $^3J_{H,H}$ = 15.5 Hz, 1 H, 2-CH), 6.9 (m_c, 1 H, 3-CH), 6.9–7.3 (m, 4 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3 (OCH_2CH_3), 19.5 (CH_3), 28.4 [$C(CH_3)_3$], 29.3 (C4), 44.9 (C5), 50.5 (C6), 60.3 (OCH_2CH_3), 62.5 (CH_2OH), 80.1 [$C(CH_3)_3$], 122.9 (C2), 125.5 (C5′), 126.1 (C4′), 127.3 (C6′), 131.2 (C3′), 135.7 (C2′), 138.8 (C1′), 147.2 (C3), 156.4 (carbamate CO), 166.4 (C1) ppm. IR (film): $\tilde{\nu}$ = 3450 (OH), 3370 (NH), 2979, 2931, 1725 (C=O), 1698 (C=O), 1652 (C=C), 1600 (C=C), 1493 (C=C), 1385, 1367, 1169, 1044, 787, 762 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 202 (14995), 211 (19191), 216 (19551 $mol^{-1}\,dm^3\,cm^{-1}$) nm. HRMS-ESI: calcd. for $C_{21}H_{31}NO_5$ $[M + Na]^+$ 400.20944; found 400.20941.

Ethyl (2*E*,5*S*,6*S*)-6-[(*tert*-Butoxycarbonyl)amino]-6-(2-furyl)-5-(hydroxymethyl)hex-2-enoate (4h): Yield: 372 mg, 63%, white solid. R_f = 0.17 (Et_2O/PE, 2:1). M.p. 60–64 °C. $[\alpha]_D^{22}$ = +7 (*c* = 1.13, $CHCl_3$). *ee* = 98%. Enantiomeric assay: Chiralpak AD-H, isocratic (*n*-hexane/*i*PrOH, 95:5; flow 0.5 mL min^{-1}), λ_{max} = 212 nm, t_1 = 91.3 min, t_2 = 96.6 min. ^1H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): δ = 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.5 [s, 9 H, $C(CH_3)_3$], 2.1–2.3 (m, 3 H, 4-CH_2, 5-CH), 3.5 (dd, $^3J_{H,H}$ = 7.5, $^2J_{H,H}$ = 11.5 Hz, 1 H, CH_2OH), 3.6 (dd, $^3J_{H,H}$ = 4.5, $^2J_{H,H}$ = 11.5 Hz, 1 H, CH_2OH), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 5.1 (m, 2 H, 6-CH, NH), 5.9 (dt, $^4J_{H,H}$ = 1.5 H, $^3J_{H,H}$ = 15.5 Hz, 1 H, 2-CH), 6.2 (d, $^3J_{H,H}$ = 3.0 Hz, 1 H, 3-furyl-H), 6.4 (dd, $^3J_{H,H}$ = 2.0, $^3J_{H,H}$ = 3.0 Hz, 1 H, 4-furyl-H), 6.9 (dt, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 15.5 Hz, 1 H, 3-CH), 7.4 (dd, $^4J_{H,H}$ = 1.0, $^3J_{H,H}$ = 2.0 Hz, 1 H, 5-furyl-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3 (OCH_2CH_3), 28.4 [$C(CH_3)_3$], 29.8 (C4), 45.0 (C5), 49.2 (C6), 60.3 (OCH_2CH_3), 62.5 (CH_2OH), 80.6 [$C(CH_3)_3$], 106.6 (C3′), 110.5 (C4′), 122.9 (C2), 141.9 (C5′), 146.5 (C3), 153.0 (C2′), 156.5 (carbamate CO), 166.3 (C1) ppm. IR (KBr): $\tilde{\nu}$ = 3537 (OH), 3367 (NH), 2985, 2936, 1708 (C=O), 1684 (C=O), 1652 (C=C), 1600 (C=C), 1518, 1367, 1322, 1266, 1252, 1210, 1161, 1010 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 215

(15493 $mol^{-1} dm^3 cm^{-1}$) nm. MS (ESI): *m*/*z* = 376 [M + Na]$^+$, 729 [2 M + Na]$^+$. $C_{18}H_{27}NO_6$ (353.41): calcd. C 61.17, H 7.70, N 3.96; found C 60.81, H 7.72, N 3.89.

General Procedure for the Silylation of the Mannich Products: *tert*-Butyldimethylsilyl chloride (1.5 equiv.), imidazole (2.0 equiv.), and 4-(dimethylamino)pyridine (0.19 equiv.) were added under nitrogen to a solution of the Mannich product **4** in dry dichloromethane (0.2 M, 1.0 equiv.). The reaction mixture was stirred at room temp. for 1–1.5 h. Water was added, and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried with $MgSO_4$ and filtered, and the solvents were evaporated in vacuo. The residue was dissolved in a small amount of diethyl ether, adsorbed on silica gel, and purified by flash column chromatography on silica gel (1:50, w/w) with mixtures of diethyl ether/petroleum ether as eluent.

Ethyl (2*E*,5*S*,6*S*)-6-[(*tert*-Butoxycarbonyl)amino]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-6-phenylhex-2-enoate (5a): Yield: 2.76 g, 96%, viscous oil. R_f = 0.61 (Et_2O/PE, 2:1). $[\alpha]_D^{22}$ = –8 (*c* = 1.32, $CHCl_3$). ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 3 H, $SiCH_3$), 0.1 (s, 3 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.4 [s, 9 H, $OC(CH_3)_3$], 2.1–2.4 (m, 3 H, 4-CH_2, 5-CH), 3.5 (dd, $^3J_{H,H}$ = 4.0, $^2J_{H,H}$ = 10.5 Hz, 1 H, CH_2OH), 3.5 (dd, $^3J_{H,H}$ = 6.0, $^2J_{H,H}$ = 10.5 Hz, 1 H, CH_2OH), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.8 (dd, $^3J_{H,H}$ = 5.0, $^3J_{H,H}$ = 8.5 Hz, 1 H, 6-CH), 5.7 (br., 1 H, NH), 5.9 (d, $^3J_{H,H}$ = 15.5 Hz, 1 H, 2-CH), 6.9 (dt, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 15.5 Hz, 1 H, 3-CH), 7.3–7.4 (m, 5 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = –5.6 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.2 [$C(CH_3)_3Si$], 26.0 [$SiC(CH_3)_3$], 28.5 [$OC(CH_3)_3$], 31.1 (C4), 44.7 (C5), 57.3 (C6), 60.3 (OCH_2CH_3), 63.0 (CH_2OTBS), 79.2 [$OC(CH_3)_3$], 123.3 (C2), 127.3 (C_{ar}), 128.4 (C_{ar}), 140.2 (q C_{ar}), 146.9 (C3), 155.3 (carbamate CO), 166.4 (C1) ppm. IR (film): $\tilde{\nu}$ = 3367 (NH), 3064, 3031, 2955, 2930, 2858, 1699 (C=O), 1653 (C=O), 1603 (C=C), 1496 (C=C), 1384, 1365, 1257, 1170, 1112, 1044, 837, 777, 757 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 210 (19731 $mol^{-1} dm^3 cm^{-1}$) nm. MS (ESI): *m*/*z* = 500 [M + Na]$^+$, 977 [2 M + Na]$^+$. $C_{26}H_{43}NO_5Si$ (477.77): calcd. C 65.37, H 9.07, N 2.93; found C 65.61, H 9.40, N 3.00.

Ethyl (2*E*,5*S*,6*S*)-6-[(*tert*-Butoxycarbonyl)amino]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-6-(4-fluorophenyl)hex-2-enoate (5b): Yield: 533 mg, 99%, viscous oil. R_f = 0.17 (Et_2O/PE, 1:2). $[\alpha]_D^{22}$ = –7 (*c* = 1.19, $CHCl_3$). ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 3 H, $SiCH_3$), 0.1 (s, 3 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.4 [s, 9 H, $OC(CH_3)_3$], 2.1–2.2 (m, 3 H, 4-CH_2, 5-CH), 3.5 (d, $^3J_{H,H}$ = 5.0 Hz, 2 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.8 (dd, $^3J_{H,H}$ = 5.0, $^3J_{H,H}$ = 8.0 Hz, 1 H, 6-CH), 5.7 (br., 1 H, NH), 5.9 (d, $^3J_{H,H}$ = 15.5 Hz, 1 H, 2-CH), 6.9 (dt, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 15.5 Hz, 1 H, 3-CH), 7.1 (br. t, $^3J_{H,H}$ = $^3J_{H,F}$ = 8.5 Hz, 2 H, 3′-CH, 5′-CH), 7.3 (m, 2 H, 2′-CH, 6′-CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –5.6 ($SiCH_3$), 14.3 (OCH_2CH_3), 18.1 [$SiC(CH_3)_3$], 26.0 [$SiC(CH_3)_3$], 28.4 [$OC(CH_3)_3$], 31.0 (C4), 44.5 (C5), 56.8 (C6), 60.4 (OCH_2CH_3), 63.0 (CH_2OTBS), 79.3 [$OC(CH_3)_3$], 115.2 ($^2J_{C,F}$ = 21.5 Hz, C3′, C5′), 123.5 (C2), 128.8 ($^3J_{C,F}$ = 8.0 Hz, C2′, C6′), 136.0 (C1′), 146.5 (C3), 155.2 (carbamate CO), 162.0 ($^1J_{C,F}$ = 245.0 Hz, C4′), 166.3 (C1) ppm. IR (film): $\tilde{\nu}$ = 3368, 3269 (NH), 3130, 2956, 2930, 2858, 1720 (C=O), 1700 (C=O), 1655 (C=C), 1606 (C=C), 1510 (C=C), 1385, 1367, 1258, 1225, 1172, 1113, 1144, 838, 787 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 208 (11508 $mol^{-1} dm^3 cm^{-1}$) nm. MS (ESI): *m*/*z* = 518 [M + Na]$^+$, 1013 [2 M + Na]$^+$. $C_{26}H_{42}FNO_5Si$ (495.70): calcd. C 63.00, H 8.54; found C 62.81, H 8.72.

Ethyl (2*E*,5*S*,6*S*)-6-[(*tert*-Butoxycarbonyl)amino]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-6-(4-chlorophenyl)hex-2-enoate (5c): Yield: 394 mg, 99%, viscous oil. R_f = 0.50 (Et_2O/PE, 2:1). $[\alpha]_D^{23}$ = –2 (*c* = 6.38, $CHCl_3$). ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 3 H, $SiCH_3$), 0.1 (s, 3 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.4 [s, 9 H, $OC(CH_3)_3$], 2.1–2.3 (m, 3 H, 4-CH_2, 5-CH), 3.5 (d, $^3J_{H,H}$ = 5.0 Hz, 2 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.8 (dd, $^3J_{H,H}$ = 5.0, $^3J_{H,H}$ = 8.0 Hz, 1 H, 6-CH), 5.7 (br., 1 H, NH), 5.9 (d, $^3J_{H,H}$ = 15.5 Hz, 1 H, 2-CH), 6.9 (dt, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 15.5 Hz, 1 H, 3-CH), 7.2 (br. d, 2 H, ArH), 7.4 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –5.6 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.1 [$SiC(CH_3)_3$], 26.0 [$SiC(CH_3)_3$], 28.4 [$OC(CH_3)_3$], 30.9 (C4), 44.3 (C5), 57.0 (C6), 60.4 (OCH_2CH_3), 63.1 (CH_2OTBS), 79.3 [$OC(CH_3)_3$], 123.5 (C2), 128.5, 128.7 (C2′, C3′, C5′, C6′), 133.1 (C4′), 138.8 (C1′), 146.4 (C3), 155.2 (carbamate CO), 166.2 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 3368, 3270, 3132, 2955, 2930, 2858, 1720 (C=O), 1699 (C=O), 1654 (C=C), 1597 (C=C), 1578 (C=C), 1492 (C=C), 1385, 1367, 1258, 1170, 1092, 837, 787 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 220 (36409 $mol^{-1} dm^3 cm^{-1}$) nm. HRMS-ESI: calcd. for $C_{26}H_{42}NO_5Si$ [M + Na]$^+$ 534.24130; found 534.24145.

Ethyl (2*E*,5*S*,6*S*)-6-[(*tert*-Butoxycarbonyl)amino]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-6-(4-methoxyphenyl)hex-2-enoate (5d): Yield: 369 mg, 88%, viscous oil. R_f = 0.43 (Et_2O/PE, 2:1). $[\alpha]_D^{23}$ = –8 (*c* = 1.30, $CHCl_3$). ^{1}H NMR (400 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 3 H, $SiCH_3$), 0.1 (s, 3 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.4 [s, 9 H, $OC(CH_3)_3$], 2.1–2.3 (m, 3 H, 4-CH_2, 5-CH), 3.5 (dd, $^3J_{H,H}$ = 4.0, $^2J_{H,H}$ = 10.5 Hz, 1 H, CH_2OTBS), 3.5 (dd, $^3J_{H,H}$ = 6.0, $^2J_{H,H}$ = 10.5 Hz, 1 H, CH_2OTBS), 3.9 (s, 3 H, OCH_3), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, OCH_2CH_3), 4.7 (dd, $^3J_{H,H}$ = 5.5, $^3J_{H,H}$ = 8.5 Hz, 1 H, 6-CH), 5.6 (br., 1 H, NH), 5.9 (d, $^3J_{H,H}$ = 15.5 Hz, 1 H, 2-CH), 6.9 (br. d, $^3J_{H,H}$ = 8.5 Hz, 2 H, ArH), 6.9 (dt, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 15.5 Hz, 1 H, 3-CH), 7.2 (br. d, $^3J_{H,H}$ = 8.5 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –5.6 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.2 [$SiC(CH_3)_3$], 26.0 [$SiC(CH_3)_3$], 28.5 [$OC(CH_3)_3$], 31.2 (C4), 44.7 (C5), 55.3 (OCH_3), 56.8 (C6), 60.4 (OCH_2CH_3), 63.1 (CH_2OTBS), 79.1 [$OC(CH_3)_3$], 113.8 (C3′, C5′), 123.3 (C2), 128.4 (C2′, C6′), 132.3 (C1′), 147.0 (C3), 155.3 (carbamate CO), 158.8 (C4′), 166.4 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 3370, 3130, 2955, 2930, 2858, 1719 (C=O), 1700 (C=O), 1654 (C=C), 1613 (C=C), 1586 (C=C), 1513 (C=O), 1500 (C=C), 1385, 1250, 1173, 836, 787 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 202 (21187), 213 (20725), 275 (2034 $mol^{-1} dm^3 cm^{-1}$) nm. HRMS-ESI: calcd. for $C_{27}H_{45}NO_6Si$ [M + Na]$^+$ 530.29084; found 530.290862.

Ethyl (2*E*,5*S*,6*S*)-6-[(*tert*-Butoxycarbonyl)amino]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-6-(4-methylphenyl)hex-2-enoate (5e): Yield: 364 mg, quant., viscous oil. R_f = 0.65 (Et_2O/PE, 2:1). $[\alpha]_D^{23}$ = –7 (*c* = 1.21, $CHCl_3$). ^{1}H NMR (400 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 3 H, $SiCH_3$), 0.1 (s, 3 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.4 [s, 9 H, $OC(CH_3)_3$], 2.1–2.3 (m, 3 H, 4-CH_2, 5-CH), 2.4 (s, 3 H, CH_3), 3.5 (dd, $^3J_{H,H}$ = 4.0, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 3.5 (dd, $^3J_{H,H}$ = 6.0, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.8 (dd, $^3J_{H,H}$ = 5.5, $^3J_{H,H}$ = 8.0 Hz, 1 H, 6-CH), 5.6 (br., 1 H, NH), 5.9 (d, $^3J_{H,H}$ = 15.5 Hz, 1 H, 2-CH), 6.9 (dt, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 15.5 Hz, 1 H, 3-CH), 7.2 (m, 4 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –5.6 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.2 [$SiC(CH_3)_3$], 21.2 (CH_3), 26.0 [$SiC(CH_3)_3$], 28.5 [$OC(CH_3)_3$], 31.2 (C4), 44.7 (C5), 57.1 (C6), 60.3 (OCH_2CH_3), 63.1 (CH_2OTBS), 79.0 [$OC(CH_3)_3$], 123.3 (C2), 127.3 (C2′, C6′), 129.1 (C3′, C5′), 136.8, 137.2 (q C_{ar}), 147.0 (C3), 155.3 (carbamate CO), 166.4 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 3368, 3271, 2956, 2929, 2858, 2739, 1720 (C=O), 1700 (C=O), 1654 (C=C), 1620 (C=C), 1575 (C=C), 1513 (C=O), 1500 (C=C), 1385, 1367, 1258, 1171, 1111, 1045, 837,

786 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 201 (22350), 208 (21476 mol^{-1} dm^3 cm^{-1}) nm. HRMS-ESI: calcd. for $C_{27}H_{45}NO_5Si$ [M + H]$^+$ 492.31398; found 492.31410.

Ethyl (2*E*,5*S*,6*S*)-6-[(*tert*-Butoxycarbonyl)amino]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-6-(3-methylphenyl)hex-2-enoate (5f): Yield: 246 mg, 84%, viscous oil. R_f = 0.67 (Et_2O/PE, 2:1). $[\alpha]_D^{23}$ = –10 (*c* = 1.46, $CHCl_3$). ^{1}H NMR (400 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 3 H, $SiCH_3$), 0.1 (s, 3 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.4 [s, 9 H, $OC(CH_3)_3$], 2.1–2.4 (m, 3 H, 4-CH_2, 5-CH), 2.4 (s, 3 H, CH_3), 3.5 (dd, $^3J_{H,H}$ = 4.0, $^2J_{H,H}$ = 10.5 Hz, 1 H, CH_2OTBS), 3.5 (dd, $^3J_{H,H}$ = 6.0, $^2J_{H,H}$ = 10.5 Hz, 1 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.7 (dd, $^3J_{H,H}$ = 5.5, $^3J_{H,H}$ = 8.5 Hz, 6-CH), 5.6 (br., 1 H, NH), 5.9 (d, $^3J_{H,H}$ = 15.5 Hz, 1 H, 2-CH), 6.9 (dt, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 15.5 Hz, 1 H, 3-CH), 7.1 (m, 3 H, ArH), 7.3 (t, $^3J_{H,H}$ = 7.5 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –5.6 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.2 [$SiC(CH_3)_3$], 21.6 (CH_3), 26.0 [$SiC(CH_3)_3$], 28.5 [$OC(CH_3)_3$], 31.2 (C4), 44.8 (C5), 57.3 (C6), 60.3 (OCH_2CH_3), 63.0 (CH_2OTBS), 79.1 [$OC(CH_3)_3$], 123.3 (C2), 124.3 (C6′), 128.1, 128.2, 128.3 (C2′, C4′, C5′), 137.9 (C3′), 140.2 (C1′), 147.0 (C3), 155.3 (carbamate CO), 166.4 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 3368, 3270, 3131, 2956, 2929, 2858, 1720 (C=O), 1700 (C=O), 1653 (C=C), 1608 (C=C), 1591 (C=C), 1495 (C=C), 1385, 1366, 1257, 1172, 838, 787 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 205 (30539), 213 (31290 mol^{-1} dm^3 cm^{-1}) nm. HRMS-ESI: calcd. for $C_{27}H_{45}NO_5Si$ [M + H]$^+$ 492.31398; found 492.31437.

Ethyl (2*E*,5*S*,6*S*)-6-[(*tert*-Butoxycarbonyl)amino]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-6-(2-methylphenyl)hex-2-enoate (5g): Yield: 356 mg, 93%, viscous oil. R_f = 0.55 (Et_2O/PE, 2:1). $[\alpha]_D^{23}$ = –29 (*c* = 1.10, $CHCl_3$). ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.0 (s, 3 H, $SiCH_3$), 0.1 (s, 3 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.4 [s, 9 H, $OC(CH_3)_3$], 2.1 (br., 1 H, 5-CH), 2.3–2.5 (m, 2 H, 4-CH_2), 2.4 (s, 3 H, CH_3), 3.5 (dd, $^3J_{H,H}$ = 4.5, $^2J_{H,H}$ = 10.5 Hz, 1 H, CH_2OTBS), 3.6 (dd, $^3J_{H,H}$ = 5.5, $^2J_{H,H}$ = 10.5 Hz, 1 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 5.0–5.1 (m, 2 H, 6-CH, NH), 5.9 (d, $^3J_{H,H}$ = 15.5 Hz, 1 H, 2-CH), 6.9 (dt, $^3J_{H,H}$ = 7.5, $^3J_{H,H}$ = 15.5 Hz, 1 H, 3-CH), 7.2 (m, 4 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –5.6 ($SiCH_3$), 14.5 (OCH_2CH_3), 18.3 [$SiC(CH_3)_3$], 19.7 (CH_3), 26.0 [$SiC(CH_3)_3$], 28.5 [$OC(CH_3)_3$], 30.1 (C4), 44.9 (C5), 52.4 (C6), 60.3 (OCH_2CH_3), 62.7 (CH_2OTBS), 79.3 [$OC(CH_3)_3$], 122.9 (C2), 126.0, 126.1 (C4′, C5′), 127.1 (C6′), 130.9 (C3′), 136.0 (C2′), 139.6 (C1′), 147.6 (C3), 155.4 (carbamate CO), 166.5 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 3367, 3275, 3132, 2956, 2930, 2858, 1720 (C=O), 1698 (C=O), 1653 (C=C), 1605 (C=C), 1495 (C=C), 1385, 1366, 1258, 1170, 838, 787 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 205 (23441), 210 (23358 mol^{-1} dm^3 cm^{-1}) nm. HRMS-ESI: calcd. for $C_{27}H_{45}NO_5Si$ [M + H]$^+$ 492.31398; found 492.31366.

Ethyl (2*E*,5*S*,6*S*)-6-[(*tert*-Butoxycarbonyl)amino]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-6-(2-furyl)hex-2-enoate (5h): Yield: 344 mg, 70%, viscous oil. R_f = 0.67 (Et_2O/PE, 2:1). $[\alpha]_D^{24}$ = –21 (*c* = 1.15, $CHCl_3$). ^{1}H NMR (400 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 6 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.5 [s, 9 H, $OC(CH_3)_3$], 2.2–2.4 (m, 3 H, 4-CH_2, 5-CH), 3.5 (dd, $^3J_{H,H}$ = 4.0, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 3.6 (dd, $^3J_{H,H}$ = 6.0, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.9 (dd, $^3J_{H,H}$ = 5.0, $^3J_{H,H}$ = 9.0 Hz, 1 H, 6-CH), 5.5 (br., 1 H, NH), 5.9 (dt, $^4J_{H,H}$ = 1.5, $^3J_{H,H}$ = 15.5 Hz, 1 H, 2-CH), 6.2 (d, $^3J_{H,H}$ = 3.0 Hz, 1 H, 3-furyl-H), 6.4 (dd, $^3J_{H,H}$ = 2.0, $^3J_{H,H}$ = 3.0 Hz, 1 H, 4-furyl-H), 7.0 (dt, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 15.5 Hz, 1 H, 3-CH), 7.4 (dd, $^4J_{H,H}$ = 0.5, $^3J_{H,H}$ = 2.0 Hz, 1 H, 5-furyl-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –5.6 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.2 [$SiC(CH_3)_3$], 25.9 [$SiC(CH_3)_3$], 28.4 [$OC(CH_3)_3$], 31.3 (C4), 43.9 (C5), 51.0 (C6), 60.3 (OCH_2CH_3), 63.4 (CH_2OTBS), 79.4 [$OC(CH_3)_3$], 107.2 (C3′), 110.2 (C4′), 123.3 (C2), 141.7 (C5′), 146.7 (C3), 153.3 (C2′), 155.2 (carbamate CO), 166.4 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 3369, 3120, 2956, 2930, 2858, 1720 (C=O), 1700 (C=O), 1655 (C=C), 1596 (C=C), 1499 (C=C), 1385, 1367, 1257, 1172, 838, 786 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 211 (17233 mol^{-1} dm^3 cm^{-1}) nm. HRMS-ESI: calcd. for $C_{24}H_{41}NO_6Si$ [M + H]$^+$ 468.27759; found 468.27783.

General Procedure for the Aza-Michael Additions Furnishing 2,5-*trans*-Pyrrolidines: NaOEt (1.5 equiv.) was added under nitrogen at –78 °C to a solution of the silylated Mannich product **5** in dry DMF/THF (2:1, v/v; 0.1 M). After 40 min, a saturated NH_4Cl solution was added. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed twice with water and once with brine, dried with $MgSO_4$, and filtered, and the solvents were evaporated in vacuo. The residue was dissolved in a small amount of diethyl ether, adsorbed on silica gel and purified by flash column chromatography on silica gel (1:100, w/w) with diethyl ether/petroleum ether (1:5, v/v) as eluent.

***tert*-Butyl (2*S*,3*S*,5*S*)-3-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-(2-ethoxy-2-oxoethyl)-2-phenylpyrrolidine-1-carboxylate (6a):** Yield: 75 mg, 90%, oil. R_f = 0.38 (Et_2O/PE, 1:2). $[\alpha]_D^{22}$ = –41 (*c* = 1.23, $CHCl_3$). ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 6 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.2 [br., 9 H, $OC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.7 (dt, $^3J_{H,H}$ = 4.5, $^2J_{H,H}$ = 15.0 Hz, 1 H, 4-CH_2), 2.2 (m_c, 1 H, 3-CH), 2.4–2.5 (m, 2 H, 4-CH_2, CH_2CO_2Et), 3.4 (br. d, $^2J_{H,H}$ = 15.5 Hz, 1 H, CH_2CO_2Et), 3.6 (dd, $^3J_{H,H}$ = 6.0, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 3.7 (dd, $^3J_{H,H}$ = 7.0, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.5 (m_c, 1 H, 5-CH), 4.7 (d, $^3J_{H,H}$ = 4.0 Hz, 1 H, 2-CH), 7.2 (br. d, $^3J_{H,H}$ = 7.5 Hz, 2 H, 2′-CH, 6′-CH), 7.2 (br. t, $^3J_{H,H}$ = 7.5 Hz, 1 H, 4′-CH), 7.3 (br. t, $^3J_{H,H}$ = 7.5 Hz, 2 H, 3′-CH, 5′-CH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = –5.2 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.4 [$SiC(CH_3)_3$], 26.0 [$SiC(CH_3)_3$], 28.1 [$OC(CH_3)_3$], 31.6 (C4), 39.7 (CH_2CO_2Et), 50.1 (C3), 55.3 (C5), 60.4 (OCH_2CH_3), 64.5 (CH_2OTBS), 65.2 (C2), 79.5 [$OC(CH_3)_3$], 125.6 (C4′), 126.7 (C2′, C6′), 128.4 (C3′, C5′), 145.3 (C1′), 154.4 (carbamate CO), 171.9 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 3064, 3030, 2955, 2930, 2858, 1735, 1694, 1604, 1495, 1472, 1455, 1385, 1306, 1255, 1162, 1127, 838, 786, 700 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 207 (13151), 260 (1002), 280 (710 mol^{-1} dm^3 cm^{-1}) nm. HRMS-ESI: calcd. for $C_{26}H_{43}NO_5Si$ [M + H]$^+$ 478.29833; found 478.29821.

***tert*-Butyl (2*S*,3*S*,5*S*)-3-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-(2-ethoxy-2-oxoethyl)-2-(4-fluorophenyl)pyrrolidine-1-carboxylate (6b):** Yield: 65 mg, 84%, oil. R_f = 0.33 (Et_2O/PE, 1:2). $[\alpha]_D^{22}$ = –40 (*c* = 1.01, $CHCl_3$). ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 3 H, $SiCH_3$), 0.1 (s, 3 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.2 [s, 9 H, $OC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.7 (dt, $^3J_{H,H}$ = 4.5, $^2J_{H,H}$ = 13.5 Hz, 1 H, 4-CH_2), 2.2–2.3 (m, 1 H, 3-CH), 2.4–2.5 (m, 2 H, 4-CH_2, CH_2CO_2Et), 3.4 (dd, $^3J_{H,H}$ = 3.0, $^2J_{H,H}$ = 15.5 Hz, 1 H, CH_2CO_2Et), 3.6 (dd, $^3J_{H,H}$ = 6.0, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 3.7 (dd, $^3J_{H,H}$ = 7.0, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.4 (m_c, 1 H, 5-CH), 4.7 (d, $^3J_{H,H}$ = 4.0 Hz, 1 H, 2-CH), 7.0 (br. t, $^3J_{H,H}$ = $^3J_{H,F}$ = 8.5 Hz, 2 H, 3′-CH, 5′-CH), 7.1 (m, 2′-CH, 6′-CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = –5.2 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.4 [$SiC(CH_3)_3$], 26.0 [$SiC(CH_3)_3$], 28.1 [$OC(CH_3)_3$], 31.6 (C4), 39.6 (CH_2CO_2Et), 50.2 (C3), 55.2 (C5), 60.4 (OCH_2CH_3), 64.4 (CH_2OTBS), 64.5 (C2), 79.7 [$OC(CH_3)_3$], 115.2 ($^2J_{C,F}$ = 21.0 Hz, C3′, C5′), 127.1 ($^3J_{C,F}$ = 8.0 Hz, C2′, C6′), 141.1

(C1′), 154.2 (carbamate CO), 161.7 ($^1J_{C,F}$ = 242.5 Hz, C4′), 171.8 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 3050, 3025, 2955, 2930, 2896, 2859, 1735 (C=O), 1695 (C=O), 1606 (C=C), 1510 (C=C), 1472, 1385, 1255, 1226, 1156, 837, 785 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 201 (9041), 265 (1103), 271 (1018 mol^{-1} dm^3 cm^{-1}) nm. HRMS-ESI: calcd. for $C_{26}H_{42}FNO_5Si$ [M + H]$^+$ 496.28895; found 496.28895.

***tert*-Butyl (2*S*,3*S*,5*S*)-3-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-2-(4-chlorophenyl)-5-(2-ethoxy-2-oxoethyl)pyrrolidine-1-carboxylate (6c):** Yield: 59 mg, 88%, oil. R_f = 0.33 (Et_2O/PE, 1:2). $[\alpha]_D^{24}$ = –35 (*c* = 1.13, $CHCl_3$). ^{1}H NMR (400 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 3 H, $SiCH_3$), 0.1 (s, 3 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.3 [br., 9 H, $OC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.7 (dt, $^3J_{H,H}$ = 4.5, $^2J_{H,H}$ = 13.5 Hz, 1 H, 4-CH_2), 2.2 (m, 1 H, 3-CH), 2.4–2.5 (m, 2 H, 4-CH_2, CH_2CO_2Et), 3.4 (br. d, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 3.6 (dd, $^3J_{H,H}$ = 6.0, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 3.7 (dd, $^3J_{H,H}$ = 7.5, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.4 (m_c, 1 H, 5-CH), 4.7 (br. d, $^3J_{H,H}$ = 3.5 Hz, 1 H, 2-CH), 7.1 (br. d, $^3J_{H,H}$ = 8.5 Hz, 2 H, ArH), 7.3 (br. d, $^3J_{H,H}$ = 8.5 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = –5.3 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.4 [$SiC(CH_3)_3$], 26.0 [$SiC(CH_3)_3$], 28.1 [$OC(CH_3)_3$], 31.5 (C4), 39.6 (CH_2CO_2Et), 50.1 (C3), 55.2 (C5), 60.4 (OCH_2CH_3), 64.4 (CH_2OTBS), 64.6 (C2), 79.8 [$OC(CH_3)_3$], 127.0 (C3′, C5′), 128.5 (C2′, C6′), 132.3 (C4′), 143.9 (C1′), 154.2 (carbamate CO), 171.8 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2858, 1735 (C=O), 1600 (C=C), 1580 (C=C), 1697 (C=O), 1492 (C=C), 1388, 1366, 1255, 1163, 1093, 838, 777 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 201 (17044), 222 (14340), 267 (1106 mol^{-1} dm^3 cm^{-1}) nm. HRMS-ESI: calcd. for $C_{26}H_{42}ClNO_5Si$ [M + H]$^+$ 512.29530; found 512.25892.

***tert*-Butyl (2*S*,3*S*,5*S*)-3-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-(2-ethoxy-2-oxoethyl)-2-(4-methoxyphenyl)pyrrolidine-1-carboxylate (6d):** Yield: 62 mg, 85%, oil. R_f = 0.33 (Et_2O/PE, 1:2). $[\alpha]_D^{24}$ = –37 (*c* = 1.19, $CHCl_3$). ^{1}H NMR (400 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 6 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.2 [br. s, 9 H, $OC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.7 (dt, $^3J_{H,H}$ = 4.5, $^2J_{H,H}$ = 13.5 Hz, 1 H, 4-CH_2), 2.2 (m_c, 1 H, 3-CH), 2.4 (m, 2 H, 4-CH_2, CH_2CO_2Et), 3.4 (br. d, $^2J_{H,H}$ = 15.5 Hz, 1 H, CH_2CO_2Et), 3.6 (dd, $^3J_{H,H}$ = 6.5, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 3.7 (dd, $^3J_{H,H}$ = 7.5, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 3.8 (s, 3 H, OCH_3), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.4 (m_c, 1 H, 5-CH), 4.7 (d, $^3J_{H,H}$ = 2.5 Hz, 1 H, 2-CH), 6.9 (br. d, $^3J_{H,H}$ = 8.5 Hz, 2 H, ArH), 7.1 (br. d, $^3J_{H,H}$ = 8.5 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = –5.3 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.4 [$SiC(CH_3)_3$], 26.0 [$SiC(CH_3)_3$], 28.1 [$OC(CH_3)_3$], 31.6 (C4), 39.7 (CH_2CO_2Et), 50.1 (C3), 55.1 (C5), 55.4 (OCH_3), 60.4 (OCH_2CH_3), 64.5 (CH_2OTBS), 64.6 (C2), 79.4 [$OC(CH_3)_3$], 113.7 (C3′, C5′), 126.7 (C2′, C6′), 137.5 (C1′), 154.4 (carbamate CO), 158.4 (C4′), 171.9 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2858, 1735 (C=O), 1694 (C=O), 1614 (C=C), 1590 (C=C), 1513 (C=C) 1389, 1366, 1250, 1174, 1111, 837, 787 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 226 (17250), 277 (2987 mol^{-1} dm^3 cm^{-1}) nm. HRMS-ESI: calcd. for $C_{27}H_{45}NO_6Si$ [M + H]$^+$ 508.30889; found 508.30840.

***tert*-Butyl (2*S*,3*S*,5*S*)-3-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-(2-ethoxy-2-oxoethyl)-2-(4-methylphenyl)pyrrolidine-1-carboxylate (6e):** Yield: 66 mg, 92%, oil. R_f = 0.33 (Et_2O/PE, 1:2). $[\alpha]_D^{24}$ = –42 (*c* = 1.24, $CHCl_3$). ^{1}H NMR (400 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 6 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.2 [br., 9 H, $OC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.7 (dt, $^3J_{H,H}$ = 4.5, $^2J_{H,H}$ = 13.5 Hz, 1 H, 4-CH_2), 2.2 (m_c, 1 H, 3-CH), 2.4 (m, 2 H, 4-CH_2, CH_2CO_2Et), 2.4 (s, 3 H, CH_3), 3.4 (br. d, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 3.6 (dd, $^3J_{H,H}$ = 6.5, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 3.7 (dd, $^3J_{H,H}$ = 7.0, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.4 (m_c, 1 H, 5-CH), 4.7 (br., 1 H, 2-CH), 7.0 (br. d, $^3J_{H,H}$ = 8.0 Hz, 2 H, ArH), 7.1 (br. d, $^3J_{H,H}$ = 8.0 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = –5.3 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.4 [$SiC(CH_3)_3$], 21.1 (CH_3), 26.0 [$SiC(CH_3)_3$], 28.1 [$OC(CH_3)_3$], 31.5 (C4), 39.7 (CH_2CO_2Et), 50.1 (C3), 55.1 (C5), 60.4 (OCH_2CH_3), 64.5 (CH_2OTBS), 64.9 (C2), 79.4 [$OC(CH_3)_3$], 125.5 (C2′, C6′), 129.0 (C3′, C5′), 136.1 (C4′), 142.2 (C1′), 154.5 (carbamate CO), 171.9 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2858, 1736 (C=O), 1695 (C=O), 1514 (C=C), 1388, 1366, 1254, 1161, 1112, 838, 778 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 216 (10264), 266 (456), 273 (376 mol^{-1} dm^3 cm^{-1}) nm. HRMS-ESI: calcd. for $C_{27}H_{45}NO_5Si$ [M + H]$^+$ 492.31398; found 492.31408.

***tert*-Butyl (2*S*,3*S*,5*S*)-3-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-(2-ethoxy-2-oxoethyl)-2-(3-methylphenyl)pyrrolidine-1-carboxylate (6f):** Yield: 48 mg, 94%, oil. R_f = 0.33 (Et_2O/PE, 1:2). $[\alpha]_D^{24}$ = –45 (*c* = 1.16, $CHCl_3$). ^{1}H NMR (400 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 6 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.2 [br., 9 H, $OC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.7 (dt, $^3J_{H,H}$ = 4.5, $^2J_{H,H}$ = 13.5 Hz, 1 H, 4-CH_2), 2.2 (m_c, 1 H, 3-CH), 2.4 (s, 3 H, CH_3), 2.4–2.5 (m, 2 H, 4-CH_2, CH_2CO_2Et), 3.4 (br. d, $^2J_{H,H}$ = 15.5 Hz, 1 H, CH_2CO_2Et), 3.6 (dd, $^3J_{H,H}$ = 6.0, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 3.7 (dd, $^3J_{H,H}$ = 7.0, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.5 (m_c, 1 H, 5-CH), 4.7 (br., 1 H, 2-CH), 7.0 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, 4′-CH), 7.0 (s, 1 H, 2′-CH), 7.1 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, 6′-CH), 7.2 (t, $^3J_{H,H}$ = 7.5 Hz, 1 H, 5′-CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = –5.2 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.4 [$SiC(CH_3)_3$], 21.6 (CH_3), 26.0 [$SiC(CH_3)_3$], 28.1 [$OC(CH_3)_3$], 31.7 (C4), 39.7 (CH_2CO_2Et), 50.1 (C3), 55.3 (C5), 60.4 (OCH_2CH_3), 64.5 (CH_2OTBS), 65.1 (C2), 79.5 [$OC(CH_3)_3$], 122.8, 126.3, 127.3, 128.3 (C_{ar}), 137.9 (C3′), 145.2 (C1′), 154.5 (carbamate CO), 171.9 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2858, 1736 (C=O), 1695 (C=O), 1609 (C=C), 1389, 1366, 1255, 1175, 1126, 838, 777 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 265 (852 mol^{-1} dm^3 cm^{-1}) nm. HRMS-ESI: calcd. for $C_{27}H_{45}NO_5Si$ [M + H]$^+$ 492.31398; found 492.31382.

***tert*-Butyl (2*S*,3*S*,5*S*)-3-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-(2-ethoxy-2-oxoethyl)-2-(2-methylphenyl)pyrrolidine-1-carboxylate (6g):** Yield: 59 mg, 81%, oil. R_f = 0.33 (Et_2O/PE, 1:2). $[\alpha]_D^{24}$ = –23 (*c* = 1.11, $CHCl_3$). ^{1}H NMR (400 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 6 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.2 [br. s, 9 H, $OC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.8 (dt, $^3J_{H,H}$ = 3.5, $^2J_{H,H}$ = 13.5 Hz, 1 H, 4-CH_2), 2.2 (m, 1 H, 3-CH), 2.4–2.5 (m, 2 H, 4-CH_2, CH_2CO_2Et), 2.4 (s, 3 H, CH_3), 3.4 (br. d, $^2J_{H,H}$ = 15.5 Hz, CH_2CO_2Et), 3.7 (dd, $^3J_{H,H}$ = 6.0, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 3.8 (dd, $^3J_{H,H}$ = 7.5, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.5 (m_c, 1 H, 5-CH), 5.0 (d, $^3J_{H,H}$ = 3.0 Hz, 1 H, 2-CH), 7.0 (br. d, $^3J_{H,H}$ = 7.0 Hz, 1 H, ArH), 7.1–7.2 (m, 3 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°): δ = –5.3 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.5 [$SiC(CH_3)_3$], 19.6 (CH_3), 26.1 [$SiC(CH_3)_3$], 28.0 [$OC(CH_3)_3$], 31.2 (C4), 39.9 (CH_2CO_2Et), 48.8 (C3), 55.3 (C5), 60.4 (OCH_2CH_3), 61.7 (C2), 65.0 (CH_2OTBS), 79.4 [$OC(CH_3)_3$], 124.4 (C5′), 126.2 (C4′), 126.5 (C6′), 130.2 (C3′), 134.6 (C2′), 143.2 (C1′), 154.5 (carbamate CO), 171.9 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 2956, 2930, 2858, 1736 (C=O), 1695 (C=O), 1605 (C=C), 1389, 1366, 1255, 1164, 1129, 1104, 838, 787 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 202 (17167), 263 (418 mol^{-1} dm^3 cm^{-1}) nm. HRMS-ESI: calcd. for $C_{27}H_{45}NO_5Si$ [M + H]$^+$ 492.31398; found 492.31368. HRMS-ESI: calcd. for [M + Na]$^+$ 514.29592; found 514.29617.

***tert*-Butyl (2*S*,3*S*,5*S*)-3-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-(2-ethoxy-2-oxoethyl)-2-(2-furyl)pyrrolidine-1-carboxylate (6h):** Yield:

65 mg, 92%, oil. R_f = 0.33 (Et_2O/PE, 1:2). $[\alpha]_D^{24}$ = –44 (*c* = 1.26, $CHCl_3$). ^1H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 6 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.3 [s, 9 H, $OC(CH_3)_3$], 1.7 (dt, $^3J_{H,H}$ = 4.0, $^2J_{H,H}$ = 13.0 Hz, 1 H, 4-CH_2), 2.4 (dd, $^3J_{H,H}$ = 10.0, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 2.4–2.5 (m, 2 H, 3-CH, 4-CH_2), 3.4 (dd, $^3J_{H,H}$ = 3.5, $^2J_{H,H}$ = 15.5 Hz, 1 H, CH_2CO_2Et), 3.6 (dd, $^3J_{H,H}$ = 6.0, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 3.7 (dd, $^3J_{H,H}$ = 7.0, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, OCH_2CH_3), 4.8 (m, 1 H, 5-CH), 4.8 (d, $^3J_{H,H}$ = 3.0 Hz, 1 H, 2-CH), 6.1 (d, $^3J_{H,H}$ = 3.0 Hz, 1 H, 3′-CH), 6.3 (dd, $^3J_{H,H}$ = 2.0, $^3J_{H,H}$ = 3.0 Hz, 1 H, 4′-CH), 7.3 (dd, $^3J_{H,H}$ = 2.0, $^4J_{H,H}$ = 0.5 Hz, 1 H, 5′-CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –5.3 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.4 [Si*C*$(CH_3)_3$], 26.0 [SiC(*C*$H_3)_3$], 28.2 [OC(*C*$H_3)_3$], 31.8 (C4), 39.8 (*C*H_2CO_2Et), 46.7 (C3), 54.3 (C5), 58.4 (C2), 60.4 (O*C*H_2CH_3), 64.1 (*C*H_2OTBS), 79.7 [O*C*$(CH_3)_3$], 105.4 (C3′), 110.2 (C4′), 141.1 (C5′), 154.5 (carbamate CO), 156.2 (C2′), 171.8 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 2956, 2930, 2858, 1736 (C=O), 1699 (C=O), 1366, 1255, 1162, 1121, 838, 786, 763 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 217 (19373), 297 (2461), 310 (2590), 355 (1906 $mol^{-1}\,dm^3\,cm^{-1}$) nm. HRMS-ESI: calcd. for $C_{24}H_{41}NO_6Si$ [M + H]$^+$ 468.27759; found 468.27723.

General Procedure for the Aza-Michael Additions Furnishing 2,5-*cis*-Pyrrolidines: KO*t*Bu (1.0 equiv.) was added under nitrogen at –78 °C to a solution of the silylated Mannich product **5** in dry DMF/THF (2:1, v/v; 0.1 M). After 40 min, a saturated NH_4Cl solution was added. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed twice with water and once with brine, dried with $MgSO_4$, and filtered, and the solvents were evaporated in vacuo. The residue was dissolved in a small amount of diethyl ether, adsorbed on silica gel, and purified by flash column chromatography on silica gel (1:100, w/w) with diethyl ether/petroleum ether (1:5, v/v) as eluent.

***tert*-Butyl (2*S*,3*S*,5*R*)-3-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-(2-ethoxy-2-oxoethyl)-2-phenylpyrrolidine-1-carboxylate (7a):** Yield: 64 mg, 88%, oil. R_f = 0.47 (Et_2O/PE, 1:2). $[\alpha]_D^{24}$ = +20 (*c* = 1.21, $CHCl_3$). ^1H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 3 H, $SiCH_3$), 0.1 (s, 3 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.3 [s, 9 H, $OC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.9 (ddd, $^3J_{H,H}$ = 4.0, $^3J_{H,H}$ = 7.0, $^2J_{H,H}$ = 13.0 Hz, 1 H, 4-CH_2), 2.1 (dt, $^3J_{H,H}$ = 8.0, $^2J_{H,H}$ = 13.0 Hz, 1 H, 4-CH_2), 2.3–2.4 (m, 1 H, 3-CH), 2.5 (dd, $^3J_{H,H}$ = 10.0, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 3.2 (dd, $^3J_{H,H}$ = 4.0, $^2J_{H,H}$ = 15.0 Hz, CH_2CO_2Et), 3.6 (dd, $^3J_{H,H}$ = 5.5, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 3.7 (dd, $^3J_{H,H}$ = 5.5, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.4 (m_c, 1 H, 5-CH), 4.7 (d, $^3J_{H,H}$ = 6.5 Hz, 1 H, 2-CH), 7.2–7.3 (m, 3 H, ArH), 7.3–7.4 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –5.3 ($SiCH_3$), 14.3 (OCH_2CH_3), 18.4 [Si*C*$(CH_3)_3$], 26.0 [SiC(*C*$H_3)_3$], 28.2 [OC(*C*$H_3)_3$], 32.7 (C4), 40.4 (*C*H_2CO_2Et), 49.3 (C3), 55.1 (C5), 60.5 (O*C*H_2CH_3), 62.6 (*C*H_2OTBS), 64.3 (C2), 79.7 [O*C*$(CH_3)_3$], 126.0 (C4′), 126.7 (C2′, C6′), 128.3 (C3′, C5′), 144.0 (C1′), 154.7 (carbamate CO), 171.5 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 3065, 3030, 2955, 2929, 2857, 1736, 1694, 1604, 1495, 1455, 1385, 1253, 1157, 1135, 837, 787, 699 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 202 (9157), 207 (8295), 232 (4418), 269 (2966 $mol^{-1}\,dm^3\,cm^{-1}$) nm. HRMS-ESI: calcd. for $C_{26}H_{43}NO_5Si$ [M + H]$^+$ 478.29833; found 478.29821.

***tert*-Butyl (2*S*,3*S*,5*R*)-3-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-(2-ethoxy-2-oxoethyl)-2-(4-fluorophenyl)pyrrolidine-1-carboxylate (7b):** Yield: 67 mg, 93%, oil. R_f = 0.38 (Et_2O/PE, 1:2). $[\alpha]_D^{22}$ = +19 (*c* = 0.93, $CHCl_3$). ^1H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.10 (s, 3 H, $SiCH_3$), 0.1 (s, 3 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.3 [s, 9 H, $OC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.9 (ddd, $^3J_{H,H}$ = 4.0, $^3J_{H,H}$ = 7.0, $^2J_{H,H}$ = 13.0 Hz, 1 H, 4-CH_2), 2.1 (dt, $^3J_{H,H}$ = 8.0, $^2J_{H,H}$ = 13.0 Hz, 1 H, 4-CH_2), 2.3–2.4 (m, 1 H, 3-CH), 2.5 (dd, $^3J_{H,H}$ = 10.0, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 3.2 (dd, $^3J_{H,H}$ = 4.0, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 3.6 (dd, $^3J_{H,H}$ = 5.5, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 3.7 (dd, $^3J_{H,H}$ = 5.5, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.4 (m_c, 1 H, 5-CH), 4.7 (d, $^3J_{H,H}$ = 6.5 Hz, 1 H, 2-CH), 7.1 (br. t, $^3J_{H,H}$ = $^3J_{H,F}$ = 8.5 Hz, 2 H, 3′-CH, 5′-CH), 7.2 (m, 2′-CH, 6′-CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = –5.3 ($SiCH_3$), 14.3 (OCH_2CH_3), 18.4 [Si*C*$(CH_3)_3$], 26.0 [SiC(*C*$H_3)_3$], 28.3 [OC(*C*$H_3)_3$], 32.6 (C4), 40.5 (*C*H_2CO_2Et), 49.4 (C3), 55.2 (C5), 60.6 (O*C*H_2CH_3), 62.6 (*C*H_2OTBS), 63.8 (C2), 79.9 [O*C*$(CH_3)_3$], 115.1 ($^2J_{C,F}$ = 20.5 Hz, C3′, C5′), 127.5 ($^3J_{C,F}$ = 7.5 Hz, C2′, C6′), 139.8 (C1′), 154.7 (carbamate CO), 161.8 ($^1J_{C,F}$ = 244.0 Hz, C4′), 171.4 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 3040, 3020, 2955, 2930, 2858, 1736 (C=O), 1697 (C=O), 1606 (C=C), 1510 (C=C), 1384, 1253, 1225, 1155, 1134, 837, 787 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 265 (1460), 271 (1283 $mol^{-1}\,dm^3\,cm^{-1}$) nm. HRMS-ESI: calcd. for $C_{26}H_{42}FNO_5Si$ [M + H]$^+$ 496.28895; found 496.28895.

***tert*-Butyl (2*S*,3*S*,5*R*)-3-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-2-(4-chlorophenyl)-5-(2-ethoxy-2-oxoethyl)pyrrolidine-1-carboxylate (7c):** Yield: 63 mg, 86%, oil. R_f = 0.38 (Et_2O/PE, 1:2). $[\alpha]_D^{24}$ = +17 (*c* = 1.05, $CHCl_3$). ^1H NMR (400 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 3 H, $SiCH_3$), 0.1 (s, 3 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.3 [br., 9 H, $OC(CH_3)_3$], 1.9 (ddd, $^3J_{H,H}$ = 4.0, $^3J_{H,H}$ = 7.0, $^2J_{H,H}$ = 13.0 Hz, 1 H, 4-CH_2), 2.1 (dt, $^3J_{H,H}$ = 8.0, $^2J_{H,H}$ = 13.0 Hz, 1 H, 4-CH_2), 2.3 (m, 1 H, 3-CH), 2.5 (dd, $^3J_{H,H}$ = 10.0, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 3.2 (dd, $^3J_{H,H}$ = 4.0, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 3.7 (d, $^3J_{H,H}$ = 6.0 Hz, 2 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.4 (m, 1 H, 5-CH), 4.7 (d, $^3J_{H,H}$ = 6.5 Hz, 1 H, 2-CH), 7.2 (br. d, $^3J_{H,H}$ = 8.5 Hz, 2 H, ArH), 7.3 (br. d, $^3J_{H,H}$ = 8.5 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –5.3 ($SiCH_3$), 14.3 (OCH_2CH_3), 18.4 [Si*C*$(CH_3)_3$], 26.0 [SiC(*C*$H_3)_3$], 28.3 [OC(*C*$H_3)_3$], 32.6 (C4), 40.5 (*C*H_2CO_2Et), 49.4 (C3), 55.2 (C5), 60.6 (O*C*H_2CH_3), 62.6 (*C*H_2OTBS), 63.8 (C2), 80.0 [O*C*$(CH_3)_3$], 127.4 (C3′, C5′), 128.5 (C2′, C6′), 132.4 (C4′), 142.7 (C1′), 154.7 (carbamate CO), 171.4 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 2956, 2930, 2858, 1736 (C=O), 1698 (C=O), 1492 (C=C), 1383, 1367, 1253, 1159, 1092, 837, 786, 763 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 222 (9152), 267 (404 $mol^{-1}\,dm^3\,cm^{-1}$) nm. HRMS-ESI: calcd. for $C_{26}H_{42}ClNO_5Si$ [M + H]$^+$ 512.29530; found 512.25892.

***tert*-Butyl (2*S*,3*S*,5*R*)-3-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-(2-ethoxy-2-oxoethyl)-2-(4-methoxyphenyl)pyrrolidine-1-carboxylate (7d):** Yield: 66 mg, 83%, oil. R_f = 0.38 (Et_2O/PE, 1:2). $[\alpha]_D^{24}$ = +24 (*c* = 1.23, $CHCl_3$). ^1H NMR (400 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 3 H, $SiCH_3$), 0.1 (s, 3 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.3 [br. s, 9 H, $OC(CH_3)_3$], 1.9 (ddd, $^3J_{H,H}$ = 4.5, $^3J_{H,H}$ = 6.5, $^2J_{H,H}$ = 13.0 Hz, 1 H, 4-CH_2), 2.1 (dt, $^3J_{H,H}$ = 8.0, $^2J_{H,H}$ = 13.0 Hz, 1 H, 4-CH_2), 2.3–2.4 (m, 1 H, 3-CH), 2.5 (dd, $^3J_{H,H}$ = 10.0, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 3.21 (dd, $^3J_{H,H}$ = 4.0, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 3.6 (m_c, 2 H, CH_2OTBS), 4.2 (q, ^3J = 7.0 Hz, 2 H, OCH_2CH_3), 4.3–4.4 (m, 1 H, 5-CH), 4.6 (d, $^3J_{H,H}$ = 6.0 Hz, 1 H, 2-CH), 6.9 (br. d, $^3J_{H,H}$ = 8.5 Hz, 2 H, ArH), 7.2 (br. d, $^3J_{H,H}$ = 8.5 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = –5.3 ($SiCH_3$), 14.3 (OCH_2CH_3), 18.4 [Si*C*$(CH_3)_3$], 26.0 [SiC(*C*$H_3)_3$], 28.3 [OC(*C*$H_3)_3$], 32.6 (C4), 40.5 (*C*H_2CO_2Et), 49.3 (C3), 55.1 (C5), 55.4 (OCH_3), 60.5 (O*C*H_2CH_3), 62.7 (*C*H_2OTBS), 63.7 (C2), 79.6 [O*C*$(CH_3)_3$], 113.7 (C3′, C5′), 127.1 (C2′, C6′), 136.1 (C1′), 154.8 (carbamate CO), 158.5 (C4′), 171.5 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 2955, 2931, 2857, 1736 (C=O), 1694 (C=O), 1614 (C=C), 1586 (C=C), 1513

(C=C), 1388, 1366, 1249, 1175, 1112, 1036, 836, 777 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 226 (11735), 276 (2010 $mol^{-1} dm^3 cm^{-1}$) nm. HRMS-ESI: calcd. for $C_{27}H_{45}NO_6Si$ [M + H]$^+$ 508.30889; found 508.30840.

***tert*-Butyl (2*S*,3*S*,5*R*)-3-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-(2-ethoxy-2-oxoethyl)-2-(4-methylphenyl)pyrrolidine-1-carboxylate (7e):** Yield: 67 mg, 88%, oil. R_f = 0.38 (Et_2O/PE, 1:2). $[\alpha]_D^{24}$ = +20 (*c* = 1.02, $CHCl_3$). ^{1}H NMR (400 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 3 H, $SiCH_3$), 0.1 (s, 3 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.3 [br., 9 H, $OC(CH_3)_3$], 1.9 (ddd, $^3J_{H,H}$ = 4.5, $^3J_{H,H}$ = 7.0, $^2J_{H,H}$ = 13.0 Hz, 1 H, 4-CH_2), 2.1 (dt, $^3J_{H,H}$ = 8.0, $^2J_{H,H}$ = 13.0 Hz, 1 H, 4-CH_2), 2.1–2.8 (m, 1 H, 3-CH), 2.4 (s, 3 H, CH_3), 2.5 (dd, $^3J_{H,H}$ = 10.0, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 3.2 (dd, $^3J_{H,H}$ = 4.0, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 3.6 (m_c, 2 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.3–4.4 (m, 1 H, 5-CH), 4.7 (d, $^3J_{H,H}$ = 6.0 Hz, 1 H, 2-CH), 7.0–7.1 (m, 4 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –5.3 ($SiCH_3$), 14.3 (OCH_2CH_3), 18.4 [Si*C*-$(CH_3)_3$], 21.2 (CH_3), 26.0 [SiC(CH_3)$_3$], 28.3 [OC(CH_3)$_3$], 32.6 (C4), 40.4 (CH_2CO_2Et), 49.3 (C3), 55.1 (C5), 60.5 (OCH_2CH_3), 62.7 (CH_2OTBS), 64.0 (C2), 79.7 [O*C*(CH_3)$_3$], 125.9 (C2′, C6′), 129.0 (C3′, C5′), 136.2 (C4′), 141.0 (C1′), 154.8 (carbamate CO), 171.5 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2858, 1736 (C=O), 1694 (C=O), 1514 (C=C), 1388, 1366, 1252, 1157, 1112, 836, 776 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 212 (9874), 218 (9781), 266 (551), 273 (467 $mol^{-1} dm^3 cm^{-1}$) nm. HRMS-ESI: calcd. for $C_{27}H_{45}NO_5Si$ [M + H]$^+$ 492.31398; found 492.31408.

***tert*-Butyl (2*S*,3*S*,5*R*)-3-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-(2-ethoxy-2-oxoethyl)-2-(3-methylphenyl)pyrrolidine-1-carboxylate (7f):** Yield: 42 mg, 89%, oil. R_f = 0.38 (Et_2O/PE, 1:2). $[\alpha]_D^{24}$ = +20 (*c* = 1.08, $CHCl_3$). ^{1}H NMR (400 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 3 H, $SiCH_3$), 0.1 (s, 3 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.3 [br., 9 H, $OC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.9 (ddd, $^3J_{H,H}$ = 4.0, $^3J_{H,H}$ = 7.0, $^2J_{H,H}$ = 13.0 Hz, 1 H, 4-CH_2), 2.1 (dt, $^3J_{H,H}$ = 8.0, $^2J_{H,H}$ = 13.0 Hz, 1 H, 4-CH_2), 2.3–2.4 (m, 1 H, 3-CH), 2.4 (s, 3 H, CH_3), 2.5 (dd, $^3J_{H,H}$ = 10.0, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 3.2 (dd, $^3J_{H,H}$ = 4.0, $^3J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 3.7 (m_c, 2 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.4 (m, 1 H, 5-CH), 4.6 (d, $^3J_{H,H}$ = 6.5 Hz, 1 H, 2-CH), 7.0–7.1 (m, 3 H, ArH), 7.2 (t, $^3J_{H,H}$ = 7.5 Hz, 1 H, 5′-CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –5.3 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.4 [Si*C*(CH_3)$_3$], 21.6 (CH_3), 26.0 [SiC(CH_3)$_3$], 28.2 [OC(CH_3)$_3$], 32.7 (C4), 40.4 (CH_2CO_2Et), 49.2 (C3), 55.1 (C5), 60.6 (OCH_2CH_3), 62.7 (CH_2OTBS), 64.3 (C2), 79.6 [O*C*(CH_3)$_3$], 123.1, 126.8, 127.5, 128.2 (C_{ar}), 137.8 (C3′), 143.9 (C1′), 154.8 (carbamate CO), 171.6 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 2956, 2930, 2858, 1736 (C=O), 1695 (C=O), 1608 (C=C), 1389, 1366, 1254, 1175, 1135, 837, 787 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 264 (677 $mol^{-1} dm^3 cm^{-1}$) nm. HRMS-ESI: calcd. for $C_{27}H_{45}NO_5Si$ [M + H]$^+$ 492.31398; found 492.31382.

***tert*-Butyl (2*S*,3*S*,5*R*)-3-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-(2-ethoxy-2-oxoethyl)-2-(2-methylphenyl)pyrrolidine-1-carboxylate (7g):** Yield: 65 mg, 87%, oil. R_f = 0.38 (Et_2O/PE, 1:2). $[\alpha]_D^{24}$ = +47 (*c* = 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 3 H, $SiCH_3$), 0.1 (s, 3 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.3 [s, 9 H, $OC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.9 (dt, $^3J_{H,H}$ = 6.0, $^2J_{H,H}$ = 12.5 Hz, 1 H, 4-CH_2), 2.2 (dt, $^3J_{H,H}$ = 7.5, $^2J_{H,H}$ = 13.0 Hz, 1 H, 4-CH_2), 2.2–2.3 (m, 1 H, 3-CH), 2.4 (s, 3 H, CH_3), 2.6 (dd, $^3J_{H,H}$ = 10.0, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 3.4 (dd, $^3J_{H,H}$ = 4.0, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 3.7 (m_c, 2 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.3–4.9 (m, 1 H, 5-CH), 4.9 (d, $^3J_{H,H}$ = 5.5 Hz, 1 H, 2-CH), 7.1–7.3 (m, 4 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = –5.4 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.5 [Si*C*(CH_3)$_3$], 19.6 (CH_3), 26.0 [SiC(CH_3)$_3$], 28.1 [OC(CH_3)$_3$], 32.4 (C4), 40.1 (CH_2CO_2Et), 49.1 (C3), 55.1 (C5), 60.4 (C2), 60.5 (OCH_2CH_3), 62.3 (CH_2OTBS), 79.6 [O*C*(CH_3)$_3$], 125.0 (C5′), 126.1 (C4′), 126.5 (C6′), 130.1 (C3′), 135.3 (C2′), 142.3 (C1′), 154.8 (carbamate CO), 171.6 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 2956, 2930, 2858, 1736 (C=O), 1695 (C=O), 1390, 1366, 1254, 1158, 1133, 837, 786 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 264 (491 $mol^{-1} dm^3 cm^{-1}$) nm. HRMS-ESI: calcd. for $C_{27}H_{45}NO_5Si$ [M + H]$^+$ 492.31398; found 492.31368. HRMS-ESI: calcd. for [M + Na]$^+$ 514.29592; found 514.29617.

***tert*-Butyl (2*S*,3*S*,5*R*)-3-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-(2-ethoxy-2-oxoethyl)-2-(2-furyl)pyrrolidine-1-carboxylate (7h):** Yield: 66 mg, 88%, oil. R_f = 0.38 (Et_2O/PE, 1:2). $[\alpha]_D^{22}$ = +7 (*c* = 1.20, $CHCl_3$). ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): δ = 0.1 (s, 6 H, $SiCH_3$), 1.0 [s, 9 H, $SiC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.4 [s, 9 H, $OC(CH_3)_3$], 2.0 (ddd, $^3J_{H,H}$ = 5.0, $^3J_{H,H}$ = 7.0, $^2J_{H,H}$ = 13.0 Hz, 1 H, 4-CH_2), 2.1 (dt, $^3J_{H,H}$ = 7.0, $^2J_{H,H}$ = 13.0 Hz, 1 H, 4-CH_2), 2.5 (dd, $^3J_{H,H}$ = 10.0, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 2.6 (m, 1 H, 3-CH), 3.1 (dd, $^3J_{H,H}$ = 4.0, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 3.6 (d, $^3J_{H,H}$ = 6.0 Hz, 2 H, CH_2OTBS), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.3–4.4 (m, 1 H, 5-CH), 4.8 (d, $^3J_{H,H}$ = 5.0 Hz, 1 H, 2-CH), 6.2 (d, $^3J_{H,H}$ = 3.0 Hz, 1 H, 3′-CH), 6.3 (dd, $^3J_{H,H}$ = 2.0, $^3J_{H,H}$ = 3.0 Hz, 1 H, 4′-CH), 7.4 (m_c, $^3J_{H,H}$ = 1.0 Hz, 1 H, 5′-CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –5.3 ($SiCH_3$), 14.3 (OCH_2CH_3), 18.4 [Si*C*(CH_3)$_3$], 26.0 [SiC(CH_3)$_3$], 28.4 [OC(CH_3)$_3$], 32.7 (C4), 39.9 (CH_2CO_2Et), 45.7 (C3), 54.7 (C5), 57.4 (C2), 60.4 (OCH_2CH_3), 63.4 (CH_2OTBS), 79.9 [O*C*(CH_3)$_3$], 106.2 (C3′), 110.2 (C4′), 141.4 (C5′), 154.2 (carbamate CO), 155.6 (C2′), 171.7 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 2955, 2931, 2896, 2858, 1736 (C=O), 1697 (C=O), 1600 (C=C), 1506 (C=C), 1389, 1367, 1253, 1175, 1115, 838, 778 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 217 (11508 $mol^{-1} dm^3 cm^{-1}$) nm. HRMS-ESI: calcd. for $C_{24}H_{41}NO_6Si$ [M + H]$^+$ 468.27759; found 468.27723.

General Procedure for the Removal of the *tert*-Butoxycarbonyl Group: Anhydrous $ZnBr_2$ (6.2 equiv.) was added under nitrogen at room temp. to a solution of the appropriate pyrrolidine in dry dichloromethane (0.1 M, 1 equiv.). After 24 h, a saturated NH_4Cl solution was added. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried with $MgSO_4$ and filtered, and the solvents were evaporated in vacuo. The residue was dissolved in a small amount of diethyl ether, adsorbed on silica gel, and purified by flash column chromatography on silica gel (1:100, w/w) with diethyl ether/petroleum ether (1:5, v/v; containing 2% Et_3N) as eluent.

Ethyl (2′*S*,4′*S*,5′*S*)-(4-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-phenylpyrrolidin-2-yl)acetate (8a): Yield: 38 mg, 90%, oil. R_f = 0.22 (Et_2O/PE, 1:1 + 2% Et_3N). $[\alpha]_D^{23}$ = +14 (*c* = 1.16, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.0 (s, 3 H, $SiCH_3$), 0.0 (s, 3 H, $SiCH_3$), 0.9 [s, 9 H, $SiC(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.4 (dt, $^3J_{H,H}$ = 9.0, $^2J_{H,H}$ = 12.0 Hz, 1 H, 3′-CH_2), 2.1 (br., 1 H, NH), 2.2–2.4 (m, 2 H, 3′-CH_2, 4′-CH), 2.5 (dd, $^3J_{H,H}$ = 8.0, $^2J_{H,H}$ = 15.5 Hz, 1 H, 2-CH_2), 2.6 (dd, $^3J_{H,H}$ = 5.5, $^2J_{H,H}$ = 15.5 Hz, 1 H, 2-CH_2), 3.6 (dd, $^3J_{H,H}$ = 5.5, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 3.6 (dd, $^3J_{H,H}$ = 5.0, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 3.9 (m_c, 1 H, 2′-CH), 4.1 (d, $^3J_{H,H}$ = 7.0 Hz, 1 H, 5′-CH), 4.1 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 7.2–7.4 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –5.3 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.4 [Si*C*(CH_3)$_3$], 26.0 [SiC(CH_3)$_3$], 35.9 (C3′), 41.6 (C2), 51.0 (C4′), 54.5 (C2′), 60.5 (OCH_2CH_3), 63.7 (C5′), 64.3 (CH_2OTBS), 126.8 (*p*-C_{ar}), 127.0 (*o*-C_{ar}), 128.6 (*m*-C_{ar}), 145.2 (q C_{ar}), 172.5 (C1) ppm. IR (film): $\tilde{\nu}$ = 3450, 3356, 3062, 3028, 2955,

2929, 2895, 2857, 1734 (C=O), 1602 (C=C), 1492 (C=C), 1471, 1255, 1183, 1095, 1029, 837, 776, 701 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 206 (9937 $mol^{-1} dm^3 cm^{-1}$) nm. HRMS-ESI: calcd. for $C_{21}H_{35}NO_3Si$ $[M + H]^+$ 378.24590; found 378.24566.

Ethyl (2′*R*,4′*S*,5′*S*)-(4-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5-phenylpyrrolidin-2-yl)acetate (8b): Yield: 32 mg, 84%, oil. R_f = 0.35 (Et_2O/PE, 1:1 + 2% Et_3N). $[\alpha]_D^{23}$ = –5 (c = 1.10, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.0 (s, 3 H, $SiCH_3$), 0.0 (s, 3 H, $SiCH_3$), 0.9 [s, 9 H, $C(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.7 (ddd, $^3J_{H,H}$ = 8.0, $^3J_{H,H}$ = 9.5, $^2J_{H,H}$ = 12.5 Hz, 1 H, 3′-CH_2), 1.9 (ddd, $^3J_{H,H}$ = 3.5, $^3J_{H,H}$ = 5.5, $^2J_{H,H}$ = 12.5 Hz, 1 H, 3′-CH_2), 2.1–2.2 (m, 1 H, 4′-CH), 2.5 (dd, $^3J_{H,H}$ = 8.0, $^2J_{H,H}$ = 16.0 Hz, 1 H, 2-CH_2), 2.6 (dd, $^3J_{H,H}$ = 5.5, $^2J_{H,H}$ = 16.0 Hz, 1 H, 2-CH_2), 3.5 (dd, $^3J_{H,H}$ = 5.5, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 3.6 (dd, $^3J_{H,H}$ = 5.0, $^2J_{H,H}$ = 10.0 Hz, 1 H, CH_2OTBS), 3.6–3.7 (m, 1 H, 2′-CH), 4.0 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, 5′-CH), 4.4 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OC$H_2$$CH_3$), 7.2 ($m_c$, 1 H, ArH), 7.3 ($m_c$, 2 H, ArH), 7.4 ($m_c$, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = –5.3 ($SiCH_3$), 14.4 (OCH_2CH_3), 18.4 [SiC(CH_3)$_3$], 26.0 [SiC(CH_3)$_3$], 34.5 (C3′), 41.7 (C2), 49.3 (C4′), 53.9 (C2′), 60.4 (OCH_2CH_3), 63.9 (CH_2OTBS), 64.7 (C5′), 127.0 (p-C_{ar}), 127.3 (o-C_{ar}), 128.3 (m-C_{ar}), 144.5 (q C_{ar}), 172.8 (C1) ppm. IR (film): $\tilde{\nu}$ = 3450, 3350, 3062, 3028, 2954, 2929, 2886, 2856, 1735 (C=O), 1603 (C=C), 1492 (C=C), 1471, 1256, 1189, 1162, 1101, 836, 776, 701 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 205 (8277), 210 (8216 $mol^{-1} dm^3 cm^{-1}$) nm. MS (ESI): m/z = 378 $[M + H]^+$.

General Procedure for the Removal of the *tert*-Butyldimethylsilyl Group: Tetrabutylammonium fluoride (1 M in THF, 5.0 equiv.) was added under nitrogen at room temp. to a solution of the appropriate pyrrolidine in dry THF (0.02 M). After 40 min, a saturated NH_4Cl solution was added. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried with $MgSO_4$ and filtered, and the solvents were evaporated in vacuo. The residue was dissolved in a small amount of ethyl acetate, adsorbed on silica gel, and purified by flash column chromatography on silica gel (1:100, w/w) with diethyl ether/petroleum ether (3:1, v/v) as eluent.

***tert*-Butyl (2*S*,3*S*,5*S*)-5-(2-Ethoxy-2-oxoethyl)-3-(hydroxymethyl)-2-phenylpyrrolidine-1-carboxylate (9a):** Yield: 49 mg, 89%, oil. R_f = 0.33 (Et_2O/PE, 5:1). $[\alpha]_D^{23}$ = –69 (c = 1.33, $CHCl_3$). ^1H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): δ = 1.2 [s, 9 H, OC$(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 1.7 (dt, $^3J_{H,H}$ = 5.5, $^2J_{H,H}$ = 13.5 Hz, 1 H, 4-CH_2), 2.2–2.3 (m, 1 H, 3-CH), 2.4–2.5 (m, 1 H, 4-CH_2), 2.5 (dd, $^3J_{H,H}$ = 9.5, $^2J_{H,H}$ = 15.5 Hz, 1 H, CH_2CO_2Et), 3.4 (dd, $^3J_{H,H}$ = 3.5, $^2J_{H,H}$ = 15.5 Hz, 1 H, CH_2CO_2Et), 3.7 (dd, $^3J_{H,H}$ = 6.0, $^2J_{H,H}$ = 10.5 Hz, 1 H, CH_2OH), 3.8 (dd, $^3J_{H,H}$ = 7.0, $^2J_{H,H}$ = 10.5 Hz, 1 H, CH_2OH), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.5 (m_c, 1 H, 5-CH), 4.7 (d, $^3J_{H,H}$ = 4.0 Hz, 1 H, 2-CH), 7.2 (br. d, $^3J_{H,H}$ = 7.0 Hz, 2 H, 2′-CH, 6′-CH), 7.3 (m_c, 1 H, 4′-CH), 7.3 (br. t, $^3J_{H,H}$ = 7.0 Hz, 2 H, 3′-CH, 5′-CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3 (OCH_2CH_3), 28.0 [OC(CH_3)$_3$], 31.9 (C4), 39.5 (CH_2CO_2Et), 50.0 (C3), 55.4 (C5), 60.5 (OCH_2CH_3), 64.3 (CH_2OH), 65.4 (C2), 79.7 [OC(CH_3)$_3$], 125.6 (C4′), 126.8 (C2′, C6′), 128.5 (C3′, C5′), 145.1 (C1′), 154.3 (carbamate CO), 172.0 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 3448 (OH), 2978, 1733, 1692, 1477, 1455, 1392, 1367, 1254, 1167, 1133, 788, 763, 701 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 201 (14064), 259 (281 $mol^{-1} dm^3 cm^{-1}$) nm. HRMS-ESI: calcd. for $C_{20}H_{29}NO_5$ $[M + Na]^+$ 386.19379; found 386.19407.

***tert*-Butyl (2*S*,3*S*,5*R*)-5-(2-Ethoxy-2-oxoethyl)-3-(hydroxymethyl)-2-phenylpyrrolidine-1-carboxylate (9b):** Yield: 54 mg, 98%, oil. R_f = 0.25 (Et_2O/PE, 5:1). $[\alpha]_D^{23}$ = –0.7 (c = 5.62, $CHCl_3$). ^1H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): δ = 1.3 [s, 9 H, OC$(CH_3)_3$], 1.3 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 2.0 (ddd, $^3J_{H,H}$ = 3.5, $^3J_{H,H}$ = 7.0, $^2J_{H,H}$ = 13.0 Hz, 1 H, 4-CH_2), 2.1 (ddd, $^3J_{H,H}$ = 8.0, $^3J_{H,H}$ = 9.0, $^2J_{H,H}$ = 13.0 Hz, 1 H, 4-CH_2), 2.3–2.4 (m, 1 H, 3-CH), 2.6 (dd, $^3J_{H,H}$ = 10.0, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 3.2 (dd, $^3J_{H,H}$ = 4.0, $^2J_{H,H}$ = 15.0 Hz, 1 H, CH_2CO_2Et), 3.7 (dd, $^3J_{H,H}$ = 6.0, $^2J_{H,H}$ = 11.0 Hz, 1 H, CH_2OH), 3.8 (dd, $^3J_{H,H}$ = 5.5, $^2J_{H,H}$ = 11.0 Hz, 1 H, CH_2OH), 4.2 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 4.4–4.5 (m, 1 H, 5-CH), 4.6 (d, $^3J_{H,H}$ = 7.0 Hz, 1 H, 2-CH), 7.3–7.4 (m, 5 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3 (OCH_2CH_3), 28.2 [OC(CH_3)$_3$], 32.8 (C4), 40.2 (CH_2CO_2Et), 49.3 (C3), 55.1 (C5), 60.6 (OCH_2CH_3), 62.6 (CH_2OH), 64.7 (C2), 79.9 [OC(CH_3)$_3$], 126.0 (C4′), 126.9 (C2′, C6′), 128.4 (C3′, C5′), 143.9 (C1′), 154.7 (carbamate CO), 171.5 (ester CO) ppm. IR (film): $\tilde{\nu}$ = 3459 (OH), 3031, 2978, 2932, 1735, 1692, 1604, 1477, 1455, 1392, 1367, 1304, 1253, 1177, 787, 700 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 201 (7684), 259 (79 $mol^{-1} dm^3 cm^{-1}$) nm. MS (ESI): m/z = 386 $[M + Na]^+$, 749 $[2 M + Na]^+$.

Crystal Data for Methyl (2*E*,5*S*,6*S*)-6-[(*tert*-Butoxycarbonyl)-amino]-6-(4-chlorophenyl)-5-(hydroxymethyl)hex-2-enoate (10): Empirical formula $C_{19}H_{26}ClNO_5$, M = 383.86, T = 293(2) K, λ = 71.073 pm, crystal system: triclinic, space group $P1$, unit-cell dimensions: a = 533.96(2), b = 1153.10(4), c = 1690.32(6) pm, α = 78.826(3), β = 86.028(2), γ = 88.086(2)°, V = 1.01835(6) nm^3, Z = 2. ρ(calcd.) = 1.252 $g cm^{-3}$, absorption coefficient 0.215 mm^{-1}, F(000) = 408, crystal size: 0.4 × 0.1 × 0.1 mm, Θ = 3.32–30.50°; index ranges: $-7 \le h \le 7$, $-16 \le k \le 16$, $-24 \le l \le 24$, reflections collected: 21296, independent reflections: 12362 (R_{int} = 0.0237), completeness to Θ = 30.50°: 99.9%, refinement method: full-matrix least squares on F^2, data/restraints/parameters: 12362/3/677, goodness-of-fit on F^2: 0.817, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0327, wR_2 = 0.0479, R indices (all data): R_1 = 0.0517, wR_2 = 0.0503, absolute structure parameter: 0.01(2).

***tert*-Butyl (2*S*,3*S*,5*R*)-3-(Hydroxymethyl)-5-(2-methoxy-2-oxoethyl)-2-phenylpyrrolidine-1-carboxylate (12):** A solution of the appropriate Mannich product (226 mg, 0.647 mmol) in dry THF (6.5 mL) was treated with KO*t*Bu (74 mg, 0.647 mmol) at 0 °C for 15 min. Yield: 88 mg, 39%, white solid, dr >95:5. R_f = 0.10 (Et_2O/PE, 5:1). M.p. 80–82 °C. $[\alpha]_D^{22}$ = –2 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $C_2D_2Cl_4$, 90 °C): δ = 1.3 [s, 9 H, C$(CH_3)_3$], 1.9 (ddd, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 3.5 Hz, 1 H, 4-CH_2), 2.1–2.2 (m, 1 H, 4-CH_2), 2.3–2.4 (m, 1 H, 3-CH), 2.6 (dd, $^2J_{H,H}$ = 15.0, $^3J_{H,H}$ = 9.5 Hz, 1 H, CH_2CO_2Me), 3.2 (dd, $^2J_{H,H}$ = 15.0, $^3J_{H,H}$ = 4.0 Hz, 1 H, CH_2CO_2Me), 3.7 (dd, $^2J_{H,H}$ = 10.5, $^3J_{H,H}$ = 6.0 Hz, 1 H, CH_2OH), 3.8 (s, 3 H, OCH_3), 3.7–3.8 (m, 1 H, CH_2OH), 4.4 (m_c, 1 H, 5-CH), 4.6 (d, $^3J_{H,H}$ = 7.0 Hz, 1 H, 2-CH), 7.3–7.4 (m, 5 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 28.2 [C(CH_3)$_3$], 32.9 (C4), 40.1 (CH_2CO_2Me), 49.3 (C3), 51.8 (OCH_3), 55.2 (C5), 62.6 (CH_2OH), 64.7 (C2), 79.9 [C(CH_3)$_3$], 126.0 (C4′), 127.0 (C2′, C6′), 128.5 (C3′, C5′), 143.8 (C1′), 154.7 (carbamate CO), 171.9 (ester CO) ppm. IR (KBr): $\tilde{\nu}$ = 3572, 3501, 3030, 3012, 2979, 2904, 2873, 1732, 1724, 1692, 1674, 1604, 1493, 1476, 1458, 1445, 1400, 1382, 1365, 1313, 1179, 1155, 1136, 1074, 1059, 972, 772, 702 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) = 205 (11184), 252 (402), 258 (422 $mol^{-1} dm^3 cm^{-1}$) nm. MS (ESI): m/z = 350 $[M + H]^+$, 372 $[M + Na]^+$.

Crystal Data for *tert*-Butyl (2*S*,3*S*,5*R*)-3-(Hydroxymethyl)-5-(2-methoxy-2-oxoethyl)-2-phenylpyrrolidine-1-carboxylate (12): Empirical formula $C_{19}H_{27}NO_5$, M = 349.42, T = 130(2) K, λ = 71.073 pm, crystal system: monoclinic, space group: $P2(1)$, unit-cell dimensions: a = 1565.12(2), b = 592.100(10), c = 2011.51(3) pm, α = γ = 90°, β = 94.6290(10)°, V = 1.85800(5) nm^3, Z = 4, ρ(calcd.)

= 1.249 g cm^{-3}, absorption coefficient 0.090 mm^{-1}, $F(000)$ = 752, crystal size: 0.4 × 0.3 × 0.1 mm, Θ = 2.88–30.51°, index ranges: $-22 \le h \le 22$, $-8 \le k \le 8$, $-28 \le l \le 27$, reflections collected: 31243, independent reflections: 11279 (R_{int} = 0.0265), completeness to Θ = 30.51°: 99.7%, refinement method: full-matrix least squares on F^2, data/restraints/parameters: 11279/1/667, goodness-of-fit on F^2: 0.950, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0356, wR_2 = 0.0730, R indices (all data): R_1 = 0.0484, wR_2 = 0.0759, absolute structure parameter: –0.2(4).

CCDC-739483 (**10**) and CCDC-739484 (**12**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[1] A. F. Parsons, *Tetrahedron* **1996**, *52*, 4149–4174.
[2] a) H. Yoda, T. Nakajima, K. Takabe, *Tetrahedron Lett.* **1996**, *37*, 5531–5534; b) E. A. Severino, C. R. G. Correia, *Org. Lett.* **2000**, *2*, 3039–3042.
[3] D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435–446.
[4] M. M. Murphy, J. R. Schullek, E. M. Gordon, M. A. Gallop, *J. Am. Chem. Soc.* **1995**, *117*, 7029–7030.
[5] M. Slater, E. Amphlett, D. Andrews, G. Bravi, G. Burton, A. Cheasty, J. Corfield, M. Ellis, R. Fenwick, S. Fernandes, R. Guidetti, D. Haigh, C. Hartley, P. Howes, D. Jackson, R. Jarvest, V. Lovegrove, K. Medhurst, N. Parry, H. Price, P. Shah, O. Singh, R. Stocker, P. Thommes, C. Wilkinson, A. Wonacott, *J. Med. Chem.* **2007**, *50*, 897–900.
[6] G. T. Wang, Y. Chen, S. Wang, R. Gentles, T. Sowin, W. Kati, S. Muchmore, V. Giranda, K. Stewart, H. Sham, D. Kempf, W. G. Laver, *J. Med. Chem.* **2001**, *44*, 1192–1201.
[7] A. Blum, J. Böttcher, A. Heine, G. Klebe, W. E. Diederich, *J. Med. Chem.* **2008**, *51*, 2078–2087.
[8] Other methodologies employed for the synthesis of highly substituted pyrrolidines: a) F. A. Davis, J. Zhang, H. Qiu, Y. Wu, *Org. Lett.* **2008**, *10*, 1433–1436; b) R. Kuwano, M. Kashiwabara, M. Ohsumi, H. Kusano, *J. Am. Chem. Soc.* **2008**, *130*, 808–809; c) H. Sakaguchi, H. Tokuyama, T. Fukuyama, *Org. Lett.* **2007**, *9*, 1635–1638; d) C. Liu, J. Gao, G. Yang, R. H. Wightman, S. Jiang, *Lett. Org. Chem.* **2007**, *4*, 556–558; e) P. Merino, I. Delso, T. Tejero, F. Cardona, A. Goti, *Synlett* **2007**, 2651–2654; f) H.-U. Reissig, K. Homann, F. Hiller, R. Zimmer, *Synthesis* **2007**, 2681–2689; g) P. Restorp, M. Dressel, P. Somfai, *Synthesis* **2007**, 1576–1583; h) A. Ghosh, S. Kulkarni, C.-X. Xu, P. Fanwick, *Org. Lett.* **2006**, *8*, 4509–4511; i) M. Buchholz, H.-U. Reissig, *Eur. J. Org. Chem.* **2003**, 3524–3533; j) T. A. Johnson, D. O. Jang, B. W. Slafer, M. D. Curtis, P. Beak, *J. Am. Chem. Soc.* **2002**, *124*, 11689–11698; k) D. A. DeGoey, H.-J. Chen, W. J. Flosi, D. J. Grampovnik, C. M. Yeung, L. L. Klein, D. J. Kempf, *J. Org. Chem.* **2002**, *67*, 5445–5453.
[9] Review articles: a) H. Pellissier, *Tetrahedron* **2007**, *63*, 3235–3285; b) G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484–4517; c) C. Nájera, J. M. Sansano, *Angew. Chem.* **2005**, *117*, 6428–6432; *Angew. Chem. Int. Ed.* **2005**, *44*, 6272–6276; d) S. Husinec, V. Savic, *Tetrahedron: Asymmetry* **2005**, *16*, 2047–2061; recent research: e) J. Hernández-Toribio, R. Gómez Arrayás, B. Martín-Matute, J. C. Carretero, *Org. Lett.* **2009**, *11*, 393–396; f) A. López-Pérez, J. Adrio, J. Carretero, *Angew. Chem.* **2009**, *121*, 346–349; *Angew. Chem. Int. Ed.* **2009**, *48*, 340–343; g) Y.-K. Liu, H. Liu, W. Du, L. Yue, Y.-C. Chen, *Chem. Eur. J.* **2008**, *14*, 9873–9877; h) C.-J. Wang, G. Liang, Z.-Y. Xue, F. Gao, *J. Am. Chem. Soc.* **2008**, *130*, 17250–17251; i) X.-H. Chen, W.-Q. Zhang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 5652–5653; j) T. Tsubogo, S. Saito, K. Seki, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2008**, *130*, 13321–13332; k) C. Nájera, M. Retamosa, J. Sansano, *Angew. Chem.* **2008**, *120*, 6144–6147; *Angew. Chem. Int. Ed.* **2008**, *47*, 6055–6058; S.-I. Fukuzawa, H. Oki, *Org. Lett.* **2008**, *10*, 1747–1750; l) J. Xie, K. Yoshida, K. Takasu, Y. Takemoto, *Tetrahedron Lett.* **2008**, *49*, 6910–6913; m) A. A. Agbodjan, B. E. Cooley, R. C. B. Copley, J. A. Coreld, R. C. Flanagan, B. N. Glover, R. Guidetti, D. Haigh, P. D. Howes, M. M. Jackson, R. T. Matsuoka, K. J. Medhurst, A. Millar, M. J. Sharp, M. J. Slater, J. F. Toczko, S. Xie, *J. Org. Chem.* **2008**, *73*, 3094–3102; n) M.-X. Xue, X.-M. Zhang, L.-Z. Gong, *Synlett* **2008**, 691–694.
[10] a) S. G. Davies, R. L. Nicholson, P. D. Price, P. M. Roberts, A. J. Russell, E. D. Savory, A. D. Smith, J. E. Thomson, *Tetrahedron: Asymmetry* **2009**, *20*, 758–772; b) S. Jackson, A. Karadeolian, A. Driega, M. Kerr, *J. Am. Chem. Soc.* **2008**, *130*, 4196–4201; c) M. E. Scott, M. Lautens, *J. Org. Chem.* **2008**, *73*, 8154–8162; d) S. Saito, T. Tsubogo, S. Kobayashi, *J. Am. Chem. Soc.* **2007**, *129*, 5364–5365; e) C. Taillier, M. Lautens, *Org. Lett.* **2007**, *9*, 591–593; f) F. A. Davis, M. Song, A. Augustine, *J. Org. Chem.* **2006**, *71*, 2779–2786; g) M. M. Martínez, D. Hoppe, *Eur. J. Org. Chem.* **2005**, 1427–1443; h) F. A. Davis, J. Deng, *Tetrahedron* **2004**, *60*, 5111–5115; i) H. Ohno, Y. Takeoka, Y. Kadoh, K. Miyamura, T. Tanaka, *J. Org. Chem.* **2004**, *69*, 4541–4544; j) F.-X. Felpin, J. Lebreton, *Eur. J. Org. Chem.* **2003**, 3693–3712; k) B. M. Trost, D. B. Horne, M. J. Woltering, *Angew. Chem.* **2003**, *115*, 6169–6172; *Angew. Chem. Int. Ed.* **2003**, *42*, 5987–5990; l) I. C. Baldwin, P. Briner, M. D. Eastgate, D. J. Fox, S. Warren, *Org. Lett.* **2002**, *4*, 4381–4384; m) D. Díez, M. T. Beneitez, I. S. Marcos, N. M. Garrido, P. Basabe, J. G. Urones, *Synlett* **2001**, 655–657; n) J. V. Schaus, N. Jain, J. S. Panek, *Tetrahedron* **2000**, *56*, 10263–10274; o) G. Revial, S. Lim, B. Viossat, P. Lemoine, A. Tomas, A. F. Duprat, M. Pfau, *J. Org. Chem.* **2000**, *65*, 4593–4600; p) E. Lorthiois, I. Marek, J. F. Normant, *J. Org. Chem.* **1998**, *63*, 2442–2450; q) J. Fitremann, A. Duréault, J.-C. Depezay, *Synlett* **1995**, 235–237; r) S. Choi, I. Bruce, A. J. Fairbanks, G. W. J. Fleet, A. H. Jones, R. J. Nash, L. E. Fellows, *Tetrahedron Lett.* **1991**, *32*, 5517–5520.
[11] a) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716–4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660; b) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; c) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840–3864; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748.
[12] a) H. Li, L. Zu, H. Xie, J. Wang, W. Wang, *Chem. Commun.* **2008**, 5636–5638; b) I. Kumar, S. Bhide, C. Rode, *Tetrahedron: Asymmetry* **2007**, *18*, 1210–1216.
[13] a) Y.-G. Wang, T. Kumano, T. Kano, K. Maruoka, *Org. Lett.* **2009**, *11*, 2027–2029; b) N. Ruiz, E. Reyes, J. Vicario, D. Badía, L. Carrillo, U. Uria, *Chem. Eur. J.* **2008**, *14*, 9357–9367.
[14] a) V. D. Chaudhari, K. S. A. Kumar, D. D. Dhavale, *Tetrahedron Lett.* **2004**, *45*, 8363–8366; b) J. Perron, B. Joseph, J.-Y. Mérour, *Tetrahedron Lett.* **2003**, *44*, 6553–6556; c) S. K. Verma, M. N. Atanes, J. H. Busto, D. L. Thai, H. Rapoport, *J. Org. Chem.* **2002**, *67*, 1314–1318; d) A. D. Borthwick, S. J. Angier, A. J. Crame, A. M. Exall, T. M. Haley, G. J. Hart, A. M. Mason, A. M. K. Pennell, G. G. Weingarten, *J. Med. Chem.* **2000**, *43*, 4452–4464; e) S. J. F. Macdonald, *J. Med. Chem.* **1998**, *41*, 3919–3922; f) M. Reggelin, T. Heinrich, *Angew. Chem.* **1998**, *110*, 3005–3008; *Angew. Chem. Int. Ed.* **1998**, *37*, 2883–2886; g) J. C. Carretero, R. G. Arrayás, I. Storch de Gracia, *Tetrahedron Lett.* **1996**, *37*, 3379–3382; h) B. W. Bycroft, S. R. Chhabra, *J. Chem. Soc., Chem. Commun.* **1989**, 423–425; i) K. Shishido, Y. Sukegawa, K. Fukumoto, T. Kametani, *J. Chem. Soc. Perkin*

Trans. 1 **1987**, 993–1004; j) S. Saito, S. Matsumoto, S. Sato, M. Inaba, T. Moriwake, *Heterocycles* **1986**, *24*, 2785–2789.
[15] a) J. R. Doncaster, L. L. Etchells, N. M. Kershaw, R. Nakamura, H. Ryan, R. Takeuchi, K. Sakaguchi, A. Sardarian, R. C. Whitehead, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2877–2881; b) S. Takeuchi, T. Kikuchi, S. Tsukamoto, M. Ishibashi, J. Kobayashi, *Tetrahedron* **1995**, *51*, 5979–5986.
[16] S. Khaliel, M. V. Nandakumar, H. Krautscheid, C. Schneider, *Synlett* **2008**, 2705–2707.
[17] a) C. Schneider, M. Rehfeuter, *Synlett* **1996**, 212–214; b) C. Schneider, M. Rehfeuter, *Tetrahedron* **1997**, *53*, 133–144; c) C. Schneider, *Synlett* **2001**, 1079–1091; d) C. Schneider, S. Khaliel, *Synlett* **2006**, 1413–1415.
[18] J. W. Yang, M. Stadler, B. List, *Angew. Chem.* **2007**, *119*, 615–617; *Angew. Chem. Int. Ed.* **2007**, *46*, 609–611.
[19] a) E. L. Richards, P. J. Murphy, F. Dinon, S. Fratucello, P. M. Brown, T. Gelbrich, M. B. Hursthouse, *Tetrahedron* **2001**, *57*, 7771–7784; b) H. O. House, T. H. Cronin, *J. Org. Chem.* **1965**, *30*, 1061–1070.
[20] T. Ashton, K. M. Aumann, S. P. Baker, C. H. Schiesser, P. J. Scammells, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6779–6784.
[21] D. L. Boger, R. M. Borzilleri, S. Nukui, R. T. Beresis, *J. Org. Chem.* **1997**, *62*, 4721–4736.
[22] Conformational analysis of pyrrolidines **11** and **12**, as well as the transition-state search for the anionic cyclisation (cf. Scheme 10) were carried out by DFT calculations at the B3LYP/6-31G(d) level. All structures were further refined by the standard B3LYP/6-311G(d,p) protocol with Gaussian03. Energy minimum structures and transitions states were verified by frequency analysis and normal-mode visualization; energies reported are the calculated Gibbs free energies after zero-point correction and extrapolation to standard conditions (298 K).
[23] ORTEP3: L. J. Farrugia, *J. Appl. Crystallogr.* **1999**, *32*, 837–838.
[24] C. Allemann, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong, K. N. Houk, *Acc. Chem. Res.* **2004**, *37*, 558–569.
[25] I. Chibata, S. Yamada, C. Hongo, R. Yoshioka (Tanabe Seiyaku), *Eur. Pat. Appl.* **1982**, EP57092A1.
[26] A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.

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