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Facile synthesis of substituted 2,3,4,7-tetrahydro-1*H*-azepines via ring-closing metathesis

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Abstract—A highly efficient synthesis based on inexpensive and readily available starting material towards the pharmacologically interesting class of substituted 2,3,4,7-tetrahydro-1*H*-azepines via a ring-closing metathesis (RCM) approach employing Grubbs catalysts 1 and 2 is described. The influence of the substituents R^1 and R^2 on the outcome of the RCM reaction is discussed. The seemingly first example of an RCM approach towards seven-membered azacycles bearing a substituent at the alkene moiety utilizing Grubbs catalyst 1 is presented.

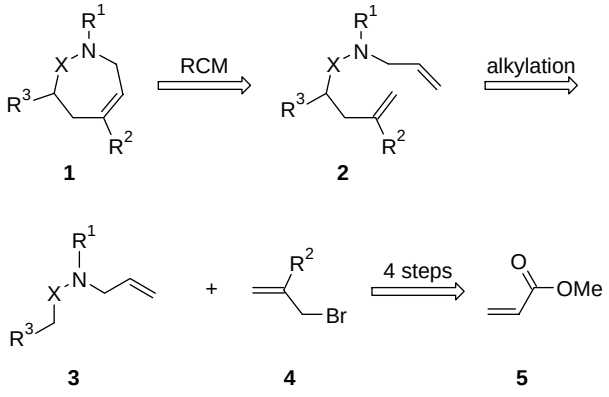
1. Introduction

During the last decade, ring-closing metathesis (RCM) has emerged as a powerful tool for the efficient synthesis of a plethora of carbo- and heterocycles of different size and substitution pattern.[1] In the case of nitrogen-containing heterocyles, the synthesis of five-, six-membered, and fused ringsystems bearing various substituents via RCM is well documented.[2,3]

However, the synthesis of medium-sized azacycles such as azepines and unsaturated seven-membered lactames has not been investigated in detail yet.[4] Moreover, medium-sized unsaturated azacycles bearing a substituent at the alkene moiety are hardly known in literature.[5]

Rising interest in these classes of azacycles as putative pharmaceuticals prompted us to develop a synthetic sequence leading to 3-substituted as well as 3,5-disubstituted azepines and 3,5-disubstituted azepine-2-ones, respectively, via an RCM approach.[6]

As outlined in Scheme 1, our straightforward convergent synthetic strategy towards these azacycles is mainly based on inexpensive and readily available starting material such as methyl acrylate, allylamine, allylbromide, and enables us to introduce a variety of different substituents at a later stage of the synthesis to optimize our preliminary synthesized lead structure.



for X: CH_2, C=O, R^1: Boc, Bn, R^2: H, CH_2OH, CH_2OTBS, R^3: CO_2Me

Scheme 1. Retrosynthetic analysis of the target structure.

For the key step of the synthetic approach only the commercially available Grubbs catalysts 1 and 2 were employed (Fig. 1).

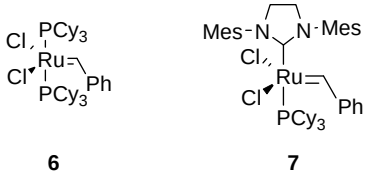


Figure 1. Grubbs catalysts 1 (**6**) and 2 (**7**).

Keywords: Azacycles; Lactames; β-Amino ester.
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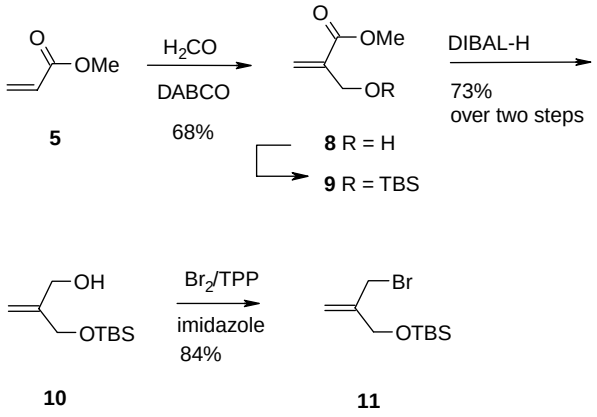
2. Results and discussion

2.1. Synthesis of the RCM precursors

As depicted in Scheme 1, we sought to synthesize our RCM precursors of type **2** via an alkylation of an appropriately functionalized allylamine derivative of type **3** with bromoallyl derivative **4**, each of them readily accessible from methyl acrylate. Starting with a Baylis–Hillmann reaction of methyl acrylate with formaldehyde, the α-hydroxymethylated ester **8** could easily be obtained in large quantities.[7,8] Conversion of **8** into its TBS–ether **9**, followed by subsequent reduction with DIBAL-H gave rise to the TBS-protected allylic alcohol **10** (Scheme 2).[9]

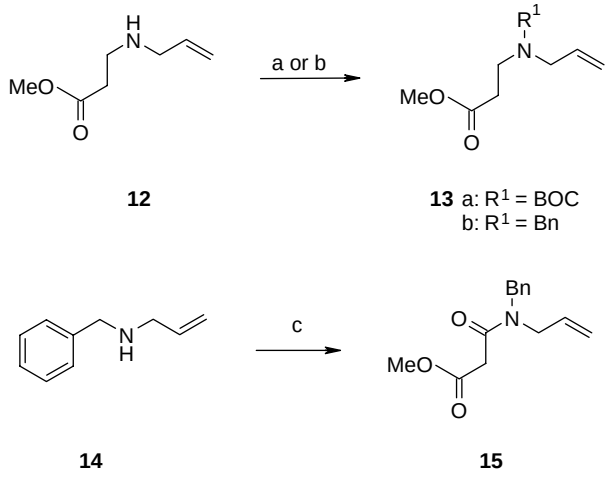


Scheme 2. Synthesis of the substituted allylic fragment **11**.

Following standard procedures for the required activation of the unprotected allylic alcohol functionality in the next step of our synthetic sequence, the corresponding mesylate as well as the trifluoroacetate were obtained in good yields. As we encountered difficulties in the following substitution reaction with these activated precursors, we switched to an alternative activation method such as the commonly used transformation of the alcohol into its halogenated derivative by means of a variety of reagents. For allylic alcohols, triphenylphosphine (TPP) and CCl_4 or TPP/CBr_4 are usually employed as they convert them into the corresponding halides in general without allylic rearrangement.[10]

However, in our case the usage of TPP/CBr_4 employing various reaction conditions surprisingly gave rise to a mixture of isomers and di-brominated derivatives as indicated by ^{1}H NMR. Moreover, the reaction proceeded only in moderate and varying yields and we were not able to isolate the desired product in appropriate purity. Nevertheless, conversion of the allylic alcohol to the corresponding bromide was successfully accomplished employing TPP/Br_2 as alternative brominating agent, even though it is known that trialkylsilyl ethers can directly be converted to alkyl bromides under these reaction conditions.[11,12] In order to prevent the cleavage of our protecting group we therefore added a slight excess of imidazole as a mild proton scavenger and were thus able to obtain our first building block, the desired bromide **11**, not only with excellent yield but also in high purity.[13]

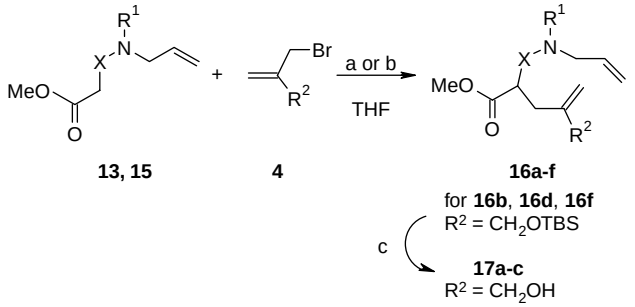
The syntheses of allylamines **13** and amide **15** being our second building blocks were carried out according to slightly modified literature procedures (Scheme 3). Addition of allylamine to methyl acrylate led to the corresponding β-amino ester **12**.[14] Subsequent reaction of ester **12** with benzyl chloride and di-*tert*-butyl-dicarbonate, respectively, furnished the *N*-protected-*N*-allyl-3-amino methyl propanoates **13** in excellent overall yield. Analogously, the corresponding 3-oxo-derivative of **13b**, methyl 3-[allyl(benzyl)amino]-3-oxopropanoate **15**, was prepared starting from allylbenzylamine and methyl malonyl chloride, which proceeded in high overall yield.[15]



Scheme 3. Synthesis of the allylamines **13** and **15**. Reagents and conditions: (a) $(Boc)_2O$, TEA, cat. DMAP, DCM, rt, 14 h, 93%; (b) BnCl, K_2CO_3, CH_3CN, reflux, 3 h, 89%; (c) $ClCOCH_2CO_2Me$, TEA, cat. DMAP, DCM, −30 °C to rt, 16 h, 86%.

The next step of our synthetic approach (Table 1) was the formation of the α-substituted β-amino esters **16** and **17** as precursors for the subsequent RCM. The required substitution

Table 1. Synthesis of the RCM precursors **16** and **17**[a]



Entry	Substrate	R^1	R^2	X	Product (yield, %)
1	**13b**	Bn	H	CH_2	**16a** (96)
2	**13b**	Bn	CH_2OTBS	CH_2	**16b** (70)
3	**15**	Bn	H	C=O	**16c** (70)
4	**15**	Bn	CH_2OTBS	C=O	**16d** (65)
5	**13a**	Boc	H	CH_2	**16e** (62)
6	**13a**	Boc	CH_2OTBS	CH_2	**16f** (82)
7	**16b**	Bn	CH_2OH	CH_2	**17a** (65)
8	**16d**	Bn	CH_2OH	C=O	**17b** (79)
9	**16f**	Boc	CH_2OH	CH_2	**17c** (79)

[a] Reagents and conditions: (a) for **13**: LDA, HMPT, THF, −40 °C, 5 h; (b) for **15**: LiHMDS, THF, −50 °C to rt, 14 h; (c) HCl in THF, rt, 25 min.

at the α-carbon of esters **13** and **15** with bromoallyl precursor **4** turned out to be a crucial step in our reaction sequence. Deprotonation of **15** employing LiHMDS, followed by the addition of the appropriate electrophile **4** easily rendered the corresponding substitution products **16c** and **16d** in good yields. In case of **13**, however, generation of the intermediate carbanion utilizing a variety of commercially available bases such as LiHMDS or KHMDS, NaH, and LDA followed by the subsequent addition of allylbromide did not give rise to any of the desired product. Nevertheless, the use of HMPA as carbanion-stabilizing additive and freshly prepared LDA easily rendered the substituted β-amino esters **16** in high yields.[16,17]

Selective cleavage of the TBS group in **16b**, **d**, and **16f** proceeded smoothly and resulted in formation of the hydroxymethylated compounds **17a–c**.

2.2. Synthesis of the azepine core structure via RCM

With the acyclic diolefins **16** and **17** in hand, we then studied the outcome of the RCM reaction employing Grubbs catalysts 1 (**6**) and 2 (**7**) as outlined in Table 2. All RCM reactions were run with 1 mmol of the appropriate diolefinic precursor and 5 mol% of the corresponding catalyst in DCM at 40 °C for 8 h. Due to the rather sluggish reaction employing Grubbs catalyst 1, the reaction mixtures were stirred for an additional 12 h at room temperature.

In general, substrates bearing basic amine moieties are believed to be incompatible with ruthenium catalysts.[1] In contrast to that, the six-membered alkaloid coniine has recently been obtained in high yield via an RCM reaction employing a tertiary amine as precursor and Grubbs catalyst **6**.[18] Hence, we subjected diene **16a** to our standardized reaction conditions. However, the corresponding azepine **18a** was only formed in low yield applying **6** (Table 2, entry 1), whereas we observed decomposition of the second generation catalyst during this reaction.

In case of substrates **16c** and **16e**, in which the electronic environment of the nitrogen had been changed through implementation of neighboring electron withdrawing groups (amide vs carbamate), both catalysts rendered the desired azepines **18b** and **18e** in comparably high yields, indicating that the precursors bearing either an amide functionality (**16c**) or a Boc-protecting group at the nitrogen (**16e**) were suitable as starting material for the RCM reaction.

To investigate the dependency of the outcome of the RCM reaction on the presence of a substituent attached to one of the terminal alkene moieties, we exposed *gem*-disubstituted olefins (**16d**, **16f**, **17b**, and **17c**) to ruthenium catalysts **6** and **7**. It is remarkable that in all cases using catalyst **6**, the substituted azepines **18c**, **d**, **f**, and **18g** could be obtained in moderate yields. To the best of our knowledge, seven-membered azacycles bearing a substituent at the alkene moiety have not yet been successfully synthesized utilizing **6**. Moreover, yields even improved surprisingly applying **6** with increasing steric demand of the substituent at the alkene moiety (OH vs OTBS, Table 2, entries 3, 4, 6, and 7).

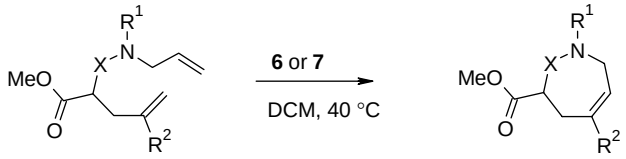
As expected, **7** overall performed significantly better giving rise to the desired azepines **18c**, **d**, **f**, and **18g** with yields ranging from 74–95%. However, yields dropped slightly for substrates bearing the bulkier TBS protecting group. Furthermore, we noticed that the *N*-Boc-protected substrates **16f** and **17c** in general gave higher yields in comparison to the analogous amide derivatives **16d** and **17b** employing either catalyst **6** or **7**.

These results clearly show that the outcome of the RCM reaction in case of these seven-membered azacycles is not only dependent on the substitution pattern of the alkene moieties, but also strongly depends upon the nature of the electron withdrawing group implemented in the RCM precursors (**16** and **17**) and thus on the concomitantly resulting geometry of the nitrogen atom (amide vs carbamate).

3. Conclusion

In summary we have developed a short and highly efficient synthetic strategy towards the hitherto hardly known

Table 2. Synthesis of substituted 2,3,4,7-tetrahydro-1*H*-azepines **18**



Entry	Substrate	R^1	R^2	X	Compound	Catalyst **6** yield (%)[a]	Catalyst **7** yield (%)[a]
1	**16a**	Bn	H	CH_2	**18a**	8[b]	0[c]
2	**16c**	Bn	H	C=O	**18b**	88	90
3	**17b**	Bn	CH_2OH	C=O	**18c**	16[b]	81
4	**16d**	Bn	CH_2OTBS	C=O	**18d**	23[b]	74
5	**16e**	Boc	H	CH_2	**18e**	87	86
6	**17c**	Boc	CH_2OH	CH_2	**18f**	37[b]	95
7	**16f**	Boc	CH_2OTBS	CH_2	**18g**	44[b]	87

[a] Reported yields refer to the analytically pure product obtained after column chromatography.
[b] Remaining starting material could be re-isolated.
[c] Decomposition of Grubbs 2 catalyst observed; starting material nearly quantitatively re-isolated.

substituted azepines of type **18** based on inexpensive and commercially available starting material. Derivative **18g** for example is accessible via a six-step sequence in 30% overall yield. This core structure can easily be modified by means of standard synthetic chemistry giving rise to a variety of putative pharmacologically active derivatives and thus enables us to probe structure–activity relationships in detail. To our knowledge, utilizing **6** in our reaction pathway represents the first synthesis of seven-membered azacycles bearing a substituent at the alkene moiety. Furthermore, we have presented a reliable large scale synthetic sequence towards bromide **11**, which serves as an interesting building block.

4. Experimental

4.1. General

Reported yields refer to the analytically pure product obtained by distillation or column chromatography. All proton and carbon nuclear magnetic resonance spectra were recorded on a 500 MHz spectrometer (^{1}H NMR: 500 MHz, ^{13}C NMR: 125 MHz). Chemical shifts are stated in parts per million (ppm) and were referenced to TMS at 0.00 ppm (^{1}H) except for compounds containing a silyl protecting group, which were referenced to the residual $CHCl_3$ in $CDCl_3$ at 7.24 ppm and to $CDCl_3$ at 77.0 ppm (^{13}C), respectively. NMR spectra were recorded in $CDCl_3$ unless otherwise indicated. Abbreviations: br dd=broad doublet of doublets, br m=broad multiplet, br s=broad singlet, d=doublet, m=multiplet, sm=symmetric multiplet, q=quartet, s=singlet, t=triplet, ps=pseudo, APT=attached proton test, COM=single pulse complete decoupling experiment. Mass spectra were obtained from a double-focussing sectorfield spectrometer. Combustion analyses were determined on a CH analyzer or a CHN autoanalyzer (only nitrogen). Flash column chromatography was performed using silica gel 60 (50–100 ASTM mesh) or silica gel 60 (40–63 ASTM mesh). TLC was carried out using 0.2 mm aluminium plates coated with silica gel 60 F_{254} and the products were visualized by UV detection, iodine or by utilization of phosphormolybdic acid ('blue stain'). Solvents and reagents that are commercially available were used without further purification unless otherwise noted. Tetrahydrofuran was dried by distillation from sodium/benzophenone. All moisture-sensitive reactions were carried out using oven-dried glassware under a positive pressure of argon. If necessary, solvents were deoxygenated by standard procedures. Grubbs catalysts 1 and 2 were purchased from Sigma-Aldrich.

4.1.1. 2-Hydroxymethyl-acrylic acid methyl ester (8). The title compound was prepared according to literature procedures.[8] Anal. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94. Found: C, 51.58; H, 6.86. Other spectral data were identical to those reported previously.

4.1.2. 2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-acrylic acid methyl ester (9). To a stirred solution of **8** (19.14 g, 165.0 mmol, 1.0 equiv) in DCM (420 mL) were added TEA (27.83 mL, 198.0 mmol, 1.2 equiv) and DMAP (2.02 g, 16.5 mmol, 0.1 equiv) followed by the dropwise addition of a solution of TBSCl (27.36 g, 181.5 mmol, 1.1 equiv) in DCM at 0 °C. The reaction mixture was allowed to reach room temperature and was stirred for 15 h at ambient temperature. After addition of *t*-BuOMe, the reaction mixture was filtered and the solvent removed under reduced pressure. The resulting slurry was re-dissolved in *t*-BuOMe and washed with a saturated NH_4Cl-solution. The aqueous layer was extracted twice with *t*-BuOMe. The combined organic layers were washed with saturated $NaHCO_3$-solution, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Bulb to bulb distillation (100°C/1.5 mbar) afforded 34.71 g (91%) of **9** as a colorless liquid: ^{1}H NMR δ 6.24 (dt, 1H, J=2.0, 2.0 Hz), 5.89 (dt, 1H, J=2.0, 2.0 Hz), 4.35 (t, 2H, J=2.0 Hz), 3.72 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR δ 166.2, 139.6, 123.7, 61.4, 51.5, 25.8, 18.2, −5.5; MS (ES+) *m/z* 231 (21 $[M+H]^+$), 253 (100, $[M+Na]^+$); HRMS (ES+) *m/z* calcd for $C_{11}H_{22}O_3SiNa$ $(M+Na)^+$: 253.123593 found 253.124812. Anal. Calcd for $C_{11}H_{22}O_3Si$: C, 57.35; H, 9.63. Found: C, 57.15; H, 9.28.

4.1.3. 2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-prop-2-en-1-ol (10).[9] DIBAL-H (115 mL of a 1.5 M solution in toluene, 172.5 mmol, 2.16 equiv) was added dropwise over a period of 45 min to a stirred solution of **9** (18.43 g, 80.0 mmol, 1.0 equiv) in THF (200 mL) at −78 °C. After 90 min the reaction mixture was slowly warmed to 0 °C, stirred for 30 min and then carefully quenched by addition of 4.5 mL H_2O in 10 mL of THF. Subsequent addition of 300 mL Et_2O and 200 mL of saturated Rochelle's solution produced a gelatin-like solid, which, after addition of 100 mL of a saturated NH_4Cl-solution, was stirred at room temperature until the slurry re-dissolved and a separation of the layers was observed (30 min). The aqueous layer was extracted three times with Et_2O and the combined organic layers were washed twice with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Bulb to bulb distillation (100 °C/0.3 mbar) yielded 12.99 g (80%) of **10** as a colorless liquid: ^{1}H NMR δ 5.08 (s, 1H), 5.06 (s, 1H), 4.22 (s, 2H), 4.15 (d, 2H, J=5.7 Hz), 2.00 (t, 1H, J=5.9 Hz), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR δ 147.5, 110.8, 64.9, 64.3, 25.8, 18.2, −5.5; MS (ES+) *m/z* 203 (18, $[M+H]^+$), 225 (100, $[M+Na]^+$). Anal. Calcd for $C_{10}H_{22}O_2Si$: C, 59.35; H, 10.96. Found: C, 59.48; H, 10.72.

4.1.4. (2-Bromomethyl-allyloxy)-*tert*-butyl-dimethyl-silane (11).[13] To a solution of triphenylphosphine (TPP, 7.68 g, 29.3 mmol, 1.1 equiv) in DCM (70 mL), a solution of bromine (4.68 g, 29.3 mmol, 1.1 equiv) in 10 mL of DCM was added dropwise at 0 °C. The reaction mixture was stirred until a colorless precipitate indicated the formation of the desired phosphonium salt, which was then added slowly to a solution of imidazole (2.18 g, 31.9 mmol, 1.2 equiv) and **10** (5.39 g, 26.6 mmol, 1.0 equiv) in 140 mL DCM at 0 °C. After stirring for 30 min maintaining the temperature at 0 °C, the reaction mixture was poured into an ice–water mixture and extracted twice with *t*-BuOMe. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual slurry was re-dissolved in a small amount of DCM and added dropwise into hexane giving rise to a suspension, which was filtered and the remaining residue was washed several times with hexane. After concentration under vacuum, hexane was added to the residual suspension,

which was filtered again and concentrated under reduced pressure. Column chromatography (hexane/*t*-BuOMe: 22:1) afforded 5.90 g (84%) of **11** as a colorless liquid: ^{1}H NMR δ 5.218 (d, 1H, J=1.4 Hz), 5.215 (d, 1H, J=1.4 Hz), 4.25 (s, 2H), 3.99 (s, 2H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR δ 144.8, 114.7, 63.5, 32.7, 25.9, 18.3, −5.4; MS (ES+) *m/z* 265 (100, $[M(^{79}Br)+H]^+$), 267 (85, $[M(^{81}Br)+H]^+$), 289 (22, $[M(^{81}Br)+Na]^+$). Anal. Calcd for $C_{10}H_{21}BrOSi$: C, 45.28; H, 7.98; Br, 30.12. Found: C, 45.50; H, 7.80; Br, 30.38.

4.1.5. 3-(Allylamino)-propionic acid methyl ester (12). The title compound was prepared according to a modified literature procedure.[14] A solution of methyl acrylate (17.2 g, 200 mmol, 1.0 equiv) and allylamine (11.7 g, 205 mmol, 1.03 equiv) in 250 mL of MeOH was stirred at 40 °C for 4 h. Removal of the solvent under reduced pressure followed by bulb to bulb distillation (105 °C/5 mbar) of the resulting residue gave rise to 21.40 g (75%) of **12** as a colorless oil: ^{1}H NMR δ 5.86 (ddt, 1H, J=17.2, 10.0, 6.0 Hz), 5.18 (ddt, 1H, J=17.2, 1.6, 1.6 Hz), 5.10 (ddt, 1H, J=10.2, 1.4, 1.4 Hz), 3.69 (s, 3H), 3.26 (dt, 2H, J=6.0, 1.4 Hz), 2.87 (t, 2H, J=6.5 Hz), 2.51 (t, 2H, J=6.5 Hz), 1.4 (br s, 1H); ^{13}C NMR δ 172.7, 136.4, 115.5, 51.8, 51.1, 44.2, 34.3; MS (EI) *m/z* 143 (13, M^+), 102 (11), 84 (14), 70 (100), 68 (18), 55 (43); HRMS (EI) *m/z* calcd for $C_7H_{13}NO_2$ 143.094629 found 143.096734. Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.55; H, 8.64; N, 9.99.

4.1.6. 3-(Allyl-*tert*-butoxycarbonyl-amino)-propionic acid methyl ester (13a). To a solution of **12** (4.29 g, 30.0 mmol), TEA (5.06 mL, 36.0 mmol, 1.2 equiv) and a catalytic amount of DMAP in DCM at 0 °C, a solution of $(Boc)_2O$ (7.86 g, 36.0 mmol, 1.2 equiv) in DCM was added dropwise over a period of 30 min. The reaction mixture was allowed to reach room temperature and stirred for an additional 14 h. After addition of *t*-BuOMe, the organic layer was washed consecutively with 1% aqueous HCl, a saturated $NaHCO_3$-solution, brine, and finally dried over $MgSO_4$. Removal of the solvents under reduced pressure followed by column chromatography (hexane/ethyl acetate:9:1) gave rise to 6.75 g (93%) of **13a** as a colorless oil. For a large scale preparation, distillation (105 °C/0.6 mbar) of the resulting residue after extractive work up is preferable: ^{1}H NMR (CD_3OD, rotamers, ratio: ~1:1) δ 5.77 (br s, 1H), 5.14 (br s, 1H), 5.12 (br s, 1H), 3.84 (d, 2H, J=5.5 Hz), 3.65 (s, 3H), 3.46 (t, 2H, J=7.0 Hz), 2.56 (t, 2H, J=7.0 Hz), 1.45 (s, 9H); ^{13}C NMR (CD_3OD, rotamers) δ 173.9, 157.1, 135.6, 135.4, 117.4, 116.9, 81.4, 52.3, 51.7, 50.9, 44.4, 34.7, 34.3, 29.0; MS (EI) *m/z* 243 (2, M^+), 187 (100), 170 (90), 156 (96), 142 (96). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.30; H, 8.52; N, 5.48.

4.1.7. 3-(Allyl-benzyl-amino)-propionic acid methyl ester (13b).[19] A suspension of **12** (7.16 g, 50.0 mmol, 1.0 equiv), benzyl chloride (6.65 g, 52.5 mmol, 1.05 equiv), and K_2CO_3 (8.295 g, 60.0 mmol, 1.2 equiv) in CH_3CN was refluxed for 3 h, diluted with *n*-hexane (200 mL), and washed with water and brine. The aqueous layer was extracted twice with hexane, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Bulb to bulb distillation (150 °C/0.4 mbar) of the remaining oily residue afforded 10.38 g (89%) of **13b** as a colorless oil: ^{1}H NMR δ 7.32–7.21 (m, 5H), 5.85 (ddt, 1H, J=17.2, 10.3, 6.5 Hz), 5.18 (psdd, 1H, J=17.2, 1.6 Hz), 5.14 (psd, 1H, J=10.1 Hz), 3.65 (s, 3H), 3.60 (s, 2H), 3.08 (d, 2H, J=6.5 Hz), 2.81 (t, 2H, J=7.0 Hz), 2.49 (t, 2H, J=7.0 Hz); ^{13}C NMR δ 172.6, 139.1, 135.4, 128.5, 127.9, 126.7, 117.1, 57.8, 56.4, 51.1, 48.8, 32.4; MS (EI) *m/z* 233 (5, M^+), 192 (10), 160 (70), 142 (58), 91 (100). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.08; H, 7.99; N, 6.25.

4.1.8. Allylbenzylamine (14). The title compound was prepared according to a literature procedure.[15] ^{1}H NMR δ 7.35–7.23 (m, 5H), 5.94 (ddt, 1H, J=17.2, 10.3, 6.0 Hz), 5.20 (ddt, 1H, J=17.2, 1.6, 1.6 Hz), 5.12 (ddt, 1H, J=10.1, 1.7, 1.4 Hz), 3.80 (s, 2H), 3.28 (psdt, 2H, J=6.0, 1.4 Hz); ^{13}C NMR δ 140.2, 136.7, 128.2, 128.0, 126.8, 115.8, 53.1, 51.6; MS (EI) *m/z* 147 (38, M^+), 146 (61), 106 (28), 91 (100), 56 (12); HRMS (EI) calcd for $C_{10}H_{13}N$ 147.1048 found 147.1043.

4.1.9. *N*-Allyl-*N*-benzyl-malonamic acid methyl ester (15). To a solution of **14** (2.95 g, 20.0 mmol, 1.0 equiv), TEA (3.37 mL, 24.0 mmol, 1.2 equiv), and a catalytic amount of DMAP in DCM at −30 °C, a solution of methyl malonyl chloride (2.57 mL, 24.0 mmol, 1.2 equiv) in 70 mL of DCM was added dropwise maintaining the temperature. After additional stirring for 16 h at room temperature, the reaction mixture was diluted with Et_2O and consecutively washed once with 1% HCl, a saturated $NaHCO_3$-solution, three times with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (hexane/ethyl acetate: 2.5:1) of the oily residue gave rise to 4.25 g (86%) of **15** as a colorless oil: ^{1}H NMR (rotamers, ratio: 1.6:1) δ 7.39–7.17 (m, 5H), 5.83–5.69 (sm, 1H), 5.27–5.14 (m, 2H), 4.63 (s, 1.29H), 4.52 (s, 0.78H), 4.03 (psd, 0.79H, J=6.0 Hz), 3.82 (psd, 1.31H, J=5.5 Hz), 3.77 (s, 1.88H), 3.73 (s, 1.15H), 3.52 (s, 1.22H), 3.49 (s, 0.76H); ^{13}C NMR (rotamers) δ 167.9, 167.8, 166.3, 166.1, 136.7, 135.9, 132.1, 132.0, 128.8, 128.4, 128.14, 128.07, 127.9, 127.6, 127.3, 126.2, 117.6, 117.1, 52.2, 50.6, 49.5, 48.2, 48.0, 41.0, 40.7; MS (EI) *m/z* 248 (20, M^++H), 247 (85, M^+), 216 (37), 207 (59), 206 (100), 174 (28), 156 (37), 146 (53), 91 (49); HRMS (EI) *m/z* calcd for $C_{14}H_{17}NO_3$ 247.1208 found 247.1211.

4.2. General procedure for the synthesis of the RCM precursors 16a, 16b, 16e, and 16f

To a solution of *n*-BuLi (1.6 mol in hexane, 1.5 equiv) in THF, neat diisopropyl amine (1.5 equiv) was added at −78 °C. The reaction mixture was allowed to reach 0 °C, stirred for additional 15 min, and cooled again to −78 °C. A solution of the respective ester (**13a**, **b**, 1.5 equiv) dissolved in THF was added slowly. After stirring for 30 min, a solution of the respective allylbromide derivative (1.0 equiv) in HMPT (1.0 equiv) was then added slowly. The reaction mixture was warmed to −40 °C and kept at this temperature until TLC indicated the completion of the reaction (approx. 5 h). After subsequent addition of Et_2O and a saturated NH_4Cl-solution, the organic layer was separated and the aqueous layer was extracted twice with ether. The combined organic layers were washed with brine,

dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The remaining product was purified by flash chromatography.

4.2.1. 2-[(Allyl-benzyl-amino)-methyl]-pent-4-enoic acid methyl ester (16a).[19] The title compound was prepared according to the general procedure utilizing **13b** (2.80 g, 12.0 mmol, 1.5 equiv), and 0.968 g of allylbromide (8 mmol, 1.0 equiv). Column chromatography (hexane/ethyl acetate: 14:1) gave rise to 2.10 g (96%) of **16a** as colorless oil: ^{1}H NMR δ 7.31–7.20 (m, 5H), 5.81 (ddt, 1H, J=17.0, 10.6, 6.2 Hz), 5.70 (ddt, 1H, J=17.2, 10.3, 6.9 Hz), 5.17–5.11 (m, 2H), 5.03 (psdd, 1H, J=17.0, 1.6 Hz), 4.99 (psd, 1H, J=10.1 Hz), 3.67 (d, 1H, J=13.8 Hz), 3.66 (s, 3H), 3.47 (d, 1H, J=13.8 Hz), 3.10 (dd, 1H, J=14.2, 6.0 Hz), 2.98 (dd, 1H, J=14.2, 6.9 Hz), 2.80–2.71 (m, 2H), 2.55–2.46 (m, 1H), 2.32–2.21 (m, 2H); ^{13}C NMR δ 174.9, 139.2, 135.4, 135.1, 128.7, 128.0, 126.7, 117.2, 116.5, 58.3, 56.7, 55.4, 51.1, 44.5, 34.4; MS (EI) m/z 273 (25, M^+), 272 (33, M^+-H), 258 (44), 232 (32), 182 (68), 160 (100), 91 (66); HRMS (EI) m/z calcd for $C_{17}H_{23}NO_2$ 273.1729 found 273.1741. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.77; H, 8.38; N, 4.95.

4.2.2. 2-[(Allyl-benzyl-amino)-methyl]-4-(*tert*-butyl-dimethyl-silanyloxymethyl)-pent-4-enoic acid methyl ester (16b). The title compound was prepared according to the general procedure utilizing **13b** (2.1 g, 9.0 mmol, 1.5 equiv) and 1.59 g (6.0 mmol, 1.0 equiv) of bromide **11**. Column chromatography (hexane/ethyl acetate: 10:1) gave rise to 1.75 g (70%) of **16b** as colorless oil: ^{1}H NMR δ 7.27–7.24 (m, 5H), 5.83–5.75 (sm, 1H), 5.15–5.10 (m, 2H), 5.01 (d, 1H, J=1.3 Hz), 4.80 (s, 1H), 4.03 (d, 1H, J=15.5 Hz), 4.00 (d, 1H, J=14.9 Hz), 3.69 (d, 1H, J=13.8 Hz), 3.62 (s, 3H), 3.43 (d, 1H, J=13.8 Hz), 3.09 (dd, 1H, J=14.0, 5.8 Hz), 2.95 (dd, 1H, J=14.2, 7.1 Hz), 2.88 (br dd, 1H, J=15.4, 7.1 Hz), 2.77 (dd, 1H, J=12.6, 9.7 Hz), 2.46 (dd, 1H, J=12.6, 5.7 Hz), 2.20 (d, 2H, J=7.6 Hz), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR δ 175.2, 145.7, 139.2, 135.5, 128.7, 128.0, 126.8, 117.3, 110.4, 65.6, 58.4, 56.7, 56.1, 51.2, 43.5, 33.5, 25.8, 18.3, −5.4; MS (EI) m/z 417 (17, M^+), 402 (12), 376 (17), 326 (40), 284 (41), 160 (100), 91 (37); HRMS (EI) m/z calcd for $C_{24}H_{39}NO_3Si$ 417.2699 found 417.2703. Anal. Calcd for $C_{24}H_{39}NO_3Si$: C, 69.02; H, 9.41; N, 3.35. Found: C, 69.07; H, 9.38; N, 3.25.

4.2.3. 2-[(Allyl-*tert*-butoxycarbonyl-amino)-methyl]-pent-4-enoic acid methyl ester (16e). The title compound was prepared according to the general procedure utilizing **13a** (2.55 g, 10.5 mmol, 1.5 equiv), and 0.85 g (7.0 mmol, 1.0 equiv) allylbromide. Column chromatography (hexane/ethyl acetate: 14:1) yielded 1.20 g (62%) of **16e** as colorless oil: ^{1}H NMR (CD_3OD, rotamers, ratio: 1:1) δ 5.75 (sm, 2H), 5.17–4.98 (m, 4H), 3.94–3.80 (br t, 1H), 3.79–3.69 (br s, 1H), 3.65 (s, 3H), 3.36 (d, 1H, J=6.2 Hz), 3.35 (d, 1H, J=8.5 Hz), 2.34–2.27 (m, 1H), 2.23–2.15 (m, 2H), 1.46 (s, 4.5H), 1.44 (s, 4.5H); ^{13}C NMR (rotamers) δ 174.3, 155.1, 155.0, 134.4, 133.7, 116.8, 116.2, 115.7, 79.5, 79.4, 51.3, 50.5, 49.7, 48.5, 48.0, 44.5, 44.1, 34.1, 28.0; MS (ES+) m/z 306 (100, $[M+Na]^+$), 589 (18, $[2M+Na]^+$); HRMS (ES+) m/z calcd for $C_{15}H_{25}NO_4Na$ 306.168128 found 306.166972. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.10; H, 8.54; N, 4.84.

4.2.4. 2-[(Allyl-*tert*-butoxycarbonyl-amino)-methyl]-4-(*tert*-butyl-dimethyl-silanyloxymethyl)-pent-4-enoic acid methyl ester (16f). The title compound was prepared according to the general procedure employing **13a** (1.82 g, 7.5 mmol, 1.5 equiv), and 1.33 g of bromide **11** (5.0 mmol, 1.0 equiv). Column chromatography (hexane/ethyl acetate: 14:1) afforded 1.76 g (82%) of **16f** as colorless oil: ^{1}H NMR (DMSO-d_6) δ 5.72 (br s, 1H), 5.09 (dd, 1H, J=10.0, 1.5 Hz), 5.05 (d, 1H, J=17.0 Hz), 4.99 (s, 1H), 4.78 (s, 1H), 4.03 (s, 2H), 3.84–3.73 (br s, 1H), 3.64 (dd, 1H, J=16.0, 5.0 Hz), 3.55 (s, 3H), 3.30–3.24 (br m, 2H), 2.88 (sm, 1H), 2.20 (dd, 1H, J=14.3, 9.0 Hz), 2.09 (dd, 1H, J=14.3, 6.0 Hz), 1.37 (s, 9H), 0.89 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (DMSO-d_6, rotamers) δ 174.8, 155.3, 145.3, 133.9, 133.7, 116.5, 116.0, 110.8, 110.7, 79.9, 79.5, 65.5, 51.6, 50.7, 49.9, 49.1, 48.9, 43.6, 43.2, 33.2, 28.3, 25.8, 18.3, −5.5; MS (ES+) m/z 428 (43, $[M+H]^+$), 450 (100, $[M+Na]^+$), 877 (70, $[2M+Na]^+$); HRMS (ES+) m/z calcd for $C_{22}H_{41}NO_5NaSi$ 450.265172 found 450.265767. Anal. Calcd for $C_{22}H_{41}NO_5Si$: C, 61.79; H, 9.66; N, 3.28. Found: C, 61.71; H, 9.51; N, 3.13.

4.3. General procedure for the synthesis of the RCM precursors 16c and 16d

To a solution of LiHMDS (1.0 mol in THF, 1.1 equiv) in THF, *N*-allyl-*N*-benzyl-malonamic acid methyl ester **15** in THF (1.0 equiv) was added at −50 °C, and gently warmed to −10 °C. After stirring for additional 30 min, the reaction mixture was cooled again to −50 °C and a solution of the respective allylbromide derivative (1.0 equiv) in THF was added slowly. The reaction mixture was warmed to room temperature and stirred for an additional 14 h at ambient temperature, diluted with Et_2O and washed with NH_4Cl-solution. The aqueous layer was extracted twice with Et_2O and the combined organic layers were washed with water, twice with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The remaining product was purified by flash chromatography.

4.3.1. 2-(Allyl-benzyl-carbamoyl)-pent-4-enoic acid methyl ester (16c). The title compound was prepared according to the general procedure employing **15** (1.38 g, 5.6 mmol), and 0.71 g of allylbromide (5.9 mmol, 1.06 equiv). Column chromatography (hexane/ethyl acetate: 3:1) furnished 1.11 g (70%) of **16c** as colorless oil: ^{1}H NMR (rotamers, ratio: 1.6:1) δ 7.38–7.18 (m, 5H), 5.83–5.67 (m, 4ddt overlapping, 2H), 5.26–5.05 (m, 4ddt overlapping, 4H), 4.79 (d, 0.66H, J=14.7 Hz), 4.68 (d, 0.40H, J=17.2 Hz), 4.51 (d, 0.41H, J=17.2 Hz), 4.47 (d, 0.64H, J=14.7 Hz), 4.13 (psdd, 0.41H, J=15.4, 5.5 Hz), 3.99 (psdd, 0.68H, J=17.9, 4.1 Hz), 3.91 (psdd, 0.44H, J=15.4, 5.8 Hz), 3.81 (psdd, 0.77H, J=17.7, 4.6 Hz), 3.73 (s, 1.9H), 3.69 (s, 1.2H), 3.67 (t, 1H, J=7.2 Hz), 2.79–2.63 (sm, 2H); ^{13}C NMR (rotamers) δ 169.6, 169.5, 168.4, 168.2, 136.9, 136.1, 134.5, 134.4, 132.3, 132.2, 128.6, 128.3, 127.8, 127.4, 127.1, 126.2, 117.3, 117.21, 117.19, 116.97, 52.1, 50.1, 49.0, 48.5, 48.4, 48.3, 48.1, 33.3; MS (EI) m/z 288 (75, M^++H), 287 (100, M^+), 256 (62), 246 (74), 228 (70), 196 (48), 174 (37), 146 (55),

91 (42); HRMS (EI) *m/z* calcd for $C_{17}H_{21}NO_3$ 287.1521 found 287.1525. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.86; H, 7.37; N, 4.73.

4.3.2. 2-(Allyl-benzyl-carbamoyl)-4-(*tert*-butyl-dimethyl-silanyloxymethyl)-pent-4-enoic acid methyl ester (16d). The title compound was prepared according to the general procedure utilizing 1.484 g (6.0 mmol, 1.0 equiv) of **15** and 1.687 g (6.36 mmol, 1.06 equiv) of bromide **11** to furnish 1.69 g (65%) of **16d** as colorless oil after column chromatography (hexane/ethyl acetate: 4:1): ^{1}H NMR (rotamers, ratio: 1.6:1) δ 7.35–7.15 (m, 5H), 5.72 (sm, 1H), 5.23–5.08 (m, 2H, 4ddt, overlapping), 5.06 (br d, 0.66H, J=1.2 Hz), 5.03 (br d, 0.42H, J=1.4 Hz), 4.85 (br d, 0.64H, J=1.2 Hz), 4.78 (br d, 0.39H, J=1.0 Hz), 4.67 (d, 0.63H, J=14.9 Hz), 4.62 (d, 0.41H, J=17.0 Hz), 4.54 (d, 0.40H, J=17.2 Hz), 4.50 (d, 0.66H, J=14.9 Hz), 4.10–3.91 (m, 3.4H), 3.91–3.80 (m, 1.7H), 3.69 (s, 1.9H), 3.65 (s, 1.2H), 2.76–2.57 (sm, 2H), 0.87 (s, 5.68H), 0.84 (s, 3.77H), 0.03 (s, 3.64H), −0.02 (s, 2.44H); ^{13}C NMR (rotamers) δ 169.7, 169.6, 168.5, 168.4, 145.0, 144.8, 137.0, 136.1, 132.5, 132.3, 128.6, 128.3, 127.8, 127.4, 127.1, 126.3, 117.2, 117.1, 111.2, 111.0, 65.9, 65.7, 52.0, 50.1, 49.0, 48.3, 48.1, 47.8, 47.6, 32.0, 25.6, 18.04, 18.01, −5.69, −5.72; MS (EI) *m/z* 431 (10, M^+), 375 (60), 374 (100), 91 (17); HRMS (EI) *m/z* calcd for $C_{24}H_{37}NO_4Si$ 431.2492 found 431.2503. Anal. Calcd for $C_{24}H_{37}NO_4Si$: C, 66.78; H, 8.64; N, 3.24. Found: C, 66.64; H, 8.84; N, 3.17.

4.4. General procedure for the synthesis of hydroxymethylated compounds 17a–c

The respective TBS-protected derivative (**16b**, **16d**, or **16f**) was dissolved in a 30:1 mixture of THF and aqueous HCl 32% and stirred at room temperature for 25 min. After addition of a saturated $NaHCO_3$-solution, the reaction mixture was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. Column chromatography of the oily residue afforded the corresponding hydroxymethyl derivative **17a–c**.

4.4.1. 2-[(Allyl-benzyl-amino)-methyl]4-hydroxymethyl-pent-4-enoic acid methyl ester (17a). According to the general procedure utilizing 1.286 g (3.1 mmol) of **16b**, 0.610 g (65%) of 2-[(allyl-benzyl-amino)-methyl]-4-hydroxymethyl-pent-4-enoic acid methyl ester (**17a**) was obtained after column chromatography (hexane/ethyl acetate: 3:1) as colorless oil: ^{1}H NMR δ 7.32–7.22 (m, 5H), 5.87–5.78 (sm, 1H), 5.16 (d, 1H, J=17.4 Hz), 5.15 (d, 1H, J=9.6 Hz), 5.02 (s, 1H), 4.86 (s, 1H), 4.04 (s, 2H), 3.69–3.62 (sm, 1H), 3.66 (s, 3H), 3.51 (br d, 1H, J=13.5 Hz), 3.10 (dd, 1H, J=14.2, 6.0 Hz), 3.02 (dd, 1H, J=14.0, 6.4 Hz), 2.97–2.89 (sm, 1H), 2.77 (dd, 1H, J=12.6, 12.4 Hz), 2.53 (dd, 1H, J=12.4, 6.0 Hz), 2.36–2.25 (m, 2H), 2.07 (br s, 1H); ^{13}C NMR δ 175.3, 146.0, 138.8, 135.1, 128.8, 128.0, 126.8, 117.5, 111.5, 65.4, 58.2, 56.6, 55.8, 51.3, 43.4, 33.7; MS (EI) *m/z* 303 (3, M^+), 230 (64), 212 (13), 180 (95), 161 (61), 160 (100), 91 (61); HRMS (EI) *m/z* calcd for $C_{18}H_{25}NO_3$ 303.1834 found 303.1800. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.05; H, 8.78; N, 4.57.

4.4.2. 2-(Allyl-benzyl-carbamoyl)-4-hydroxymethyl-pent-4-enoic acid methyl ester (17b). According to the general procedure employing 1.530 g (3.5 mmol) of **16d**, 0.871 g (79%) of 2-(allyl-benzyl-carbamoyl)-4-hydroxymethyl-pent-4-enoic acid methyl ester (**17b**) was obtained as colorless oil after column chromatography (hexane/ethyl acetate: 1:1): ^{1}H NMR (rotamers, ratio: ~1.6:1) δ 7.38–7.17 (m, 5H), 5.80–5.70 (m, 1H), 5.24 (dd, 0.66H, J=10.3, 1.2 Hz), 5.20 (psdd, 0.53H, J=5.4, 0.9 Hz), 5.17 (pst, 0.47H, J=1.4 Hz), 5.12 (psdd, 0.45H, J=17.2, 1.4 Hz), 5.08 (d, 0.60H, J=0.9 Hz), 5.03 (d, 0.40H, J=0.9 Hz), 4.91 (s, 0.63H), 4.81 (s, 0.36H), 4.80 (d, 0.64H, J=14.7 Hz), 4.69 (d, 0.38H, J=17.2 Hz), 4.53 (d, 0.39H, J=17.0 Hz), 4.44 (d, 0.64H, J=14.9 Hz), 4.19 (dd, 0.42H, J=15.4, 4.8 Hz), 4.07 (s, 1.2H), 4.01 (sm, 0.76H), 3.96 (s, 0.70H), 3.93–3.80 (sm, 2.20H), 3.73 (s, 1.89H), 3.68 (s, 1.16H), 2.83–2.68 (m, 2H), 2.20 (br s, 1H); ^{13}C NMR (rotamers) δ 170.0, 169.8, 168.8, 168.7, 145.6, 145.4, 136.8, 136.1, 132.2, 132.1, 128.7, 128.4, 127.9, 127.6, 127.3, 126.4, 117.5, 117.3, 112.5, 112.3, 65.8, 65.7, 52.3, 50.2, 49.2, 48.6, 48.5, 48.2, 48.0, 31.9; MS (EI) *m/z* 317 (15, M^+), 286 (19), 285 (55), 245 (33), 244 (100), 194 (60), 147 (36), 146 (75), 106 (54), 91 (44); HRMS (EI) *m/z* calcd for $C_{18}H_{23}NO_4$ 317.1627 found 317.1589. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 67.88; H, 7.63; N, 4.43.

4.4.3. 2-[(Allyl-*tert*-butoxycarbonyl-amino)-methyl]-4-hydroxymethyl-pent-4-enoic acid methyl ester (17c). The title compound was prepared according to the general procedure employing 4.786 g (11.19 mmol) of **16f**. After column chromatography (hexane/ethyl acetate: 2:1) 2.77 g (79%) of **17c** were obtained as colorless oil: ^{1}H NMR (rotamers, ratio: ~1:1) δ 5.80–5.67 (br s, 1H), 5.09 (psddd, 2H, J=17.7, 10.3, 1.6 Hz), 4.97 (d, 1H, J=1.6 Hz), 4.82 (t, 1H, J=5.5 Hz), 4.75 (s, 1H), 3.84 (d, 2H, J=5.5 Hz), 3.83–3.75 (br s, 1H), 3.69–3.61 (br s, 1H), 3.57 (s, 3H), 3.31–3.21 (sm, 2H), 2.90 (br s, 1H), 2.21 (dd, 1H, J=14.7, 9.3 Hz), 2.08 (dd, 1H, J=14.7, 5.7 Hz), 1.38 (s, 9H); ^{13}C NMR (rotamers) δ 175.0, 174.9, 155.5, 155.2, 145.6, 133.7, 116.5, 116.0, 112.2, 111.7, 79.9, 65.4, 51.7, 50.9, 49.9, 48.9, 43.7, 43.3, 33.6, 28.2; MS (ES+) *m/z* 336 (100, $[M+Na]^+$), 649 (28, $[2M+Na]^+$); HRMS (ES+) *m/z* calcd for $C_{16}H_{27}NO_5Na$ 336.178693 found 336.178391. Anal. Calcd for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.38; H, 8.44; N, 4.98. Anal. Calcd for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.01; H, 8.68; N, 4.48.

4.5. General procedure for the synthesis of 18a–g

Method A. A solution of the corresponding precursor (**16a**, **16c–f**, and **17b**, **c**) in 90 mL of thoroughly degassed DCM was heated to 40 °C and bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride **6** (Grubbs 1 catalyst, 5 mol%), dissolved in 5 mL of degassed DCM, was added to the reaction mixture. After stirring for 8 h at 40 °C, the reaction mixture was allowed to reach room temperature and stirred for an additional 12 h. After quenching the reaction through addition of 20 mL of DMSO and subsequent stirring for 12 h, the reaction mixture was extracted three times with diluted NaCl-solution, twice with brine, dried over $MgSO_4$, and filtered.[20] Removal of the solvent under reduced pressure followed by column

chromatography of the oily residue gave rise to the corresponding azepines **18**.

Method B. A solution of the corresponding precursor (**16a**, **16c–f**, and **17b**, **c**) in 90 mL of thoroughly degassed DCM was heated to 40 °C and benzyliden-[1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]-dichloro-(tricyclohexylphosphine)-ruthenium **7** (Grubbs 2 catalyst, 5 mol%), dissolved in 5 mL of degassed DCM, was added to the reaction mixture. After stirring for 8 h at 40 °C, the reaction mixture was allowed to reach room temperature. After quenching the reaction through addition of 20 mL of DMSO and subsequent stirring for 12 h, the reaction mixture was washed three times with diluted NaCl-solution, twice with brine, dried over $MgSO_4$, and filtered.[20] Removal of the solvent under reduced pressure followed by column chromatography of the oily residue gave rise to the corresponding azepines **18**.

4.5.1. 1-Benzyl-2,3,4,7-tetrahydro-1*H*-azepine-3-carboxylic acid methyl ester (18a). The title compound was prepared according to the general procedure (Method A) employing 0.311 g (1.14 mmol) of **16a** and 47 mg (0.057 mmol, 5 mol%) of **6**. Column chromatography (hexane/ethyl acetate: 14:1) gave rise to 0.235 g (76%) of the recovered starting material and to 0.023 g (8%) of **18a** as colorless oil: ^{1}H NMR δ 7.35–7.21 (m, 5H), 5.86 (psquint, 1H, J=11.0, 5.5 Hz), 5.66 (sm, 1H), 3.68 (s, 2H), 3.63 (s, 3H), 3.28–3.20 (m, 3H), 3.07 (dd, 1H, J=13.1, 9.1 Hz), 2.88–2.81 (sm, 1H), 2.62–2.53 (m, 1H), 2.53–2.46 (m, 1H); ^{13}C NMR δ 174.8, 138.7, 130.0, 129.7, 128.9, 128.3, 127.1, 60.2, 58.9, 53.6, 51.7, 41.8, 29.5; MS (EI) *m/z* 246 (15, M^++H), 245 (71, M^+), 244 (18), 214 (30), 186 (30), 158 (25), 155 (31), 154 (100), 121 (31), 120 (27), 119 (35), 94 (27), 91 (54), 88 (57), 84 (88); HRMS (EI) *m/z* calcd for $C_{15}H_{19}NO_2$ 245.1416 found 245.1413.

4.5.2. 1-Benzyl-2-oxo-2,3,4,7-tetrahydro-1*H*-azepine-3-carboxylic acid methyl ester (18b). According to the general procedure (Method A) utilizing 0.339 g (1.18 mmol) of **16c** and 49 mg (0.059 mmol, 5 mol%) of **6**, 0.268 g (88%) of **18b** was obtained after column chromatography (hexane/ethyl acetate: 2:1) as colorless oil: ^{1}H NMR δ 7.34–7.21 (m, 5H), 5.77–5.72 (sm, 1H), 5.63–5.58 (sm, 1H), 4.75 (d, 1H, J=14.9 Hz), 4.54 (d, 1H, J=14.9 Hz), 4.18 (sm, 1H), 4.14 (dd, 1H, J=12.2, 3.7 Hz), 3.80 (s, 3H), 3.42 (dd, 1H, J=17.7, 7.1 Hz), 2.83–2.72 (sm, 1H), 2.62–2.53 (sm, 1H); ^{13}C NMR δ 170.7, 169.8, 136.7, 129.4, 128.3, 127.6, 127.2, 124.1, 51.9, 51.1, 48.4, 44.9, 27.2; MS (EI) *m/z* 260 (36, M^++H), 259 (100, M^+), 228 (42), 200 (14), 168 (66), 146 (63), 136 (31), 108 (28), 101 (32), 91 (41); HRMS (EI) *m/z* calcd for $C_{15}H_{17}NO_3$ 259.1208 found 259.1213. Following the general procedure (Method B) employing 0.287 g (1.00 mmol) of **16c** and 42 mg (0.05 mmol, 5 mol%) of **7**, 0.233 g (90%) of **18b** was obtained after column chromatography (hexane/ethyl acetate: 2:1) as colorless oil. The isolated product exhibited identical spectroscopic data to those obtained using Method A.

4.5.3. 1-Benzyl-5-hydroxymethyl-2-oxo-2,3,4,7-tetrahydro-1*H*-azepine-3-carboxylic acid methyl ester (18c). According to the general procedure (Method B) utilizing 0.331 g (1.04 mmol) of **17b** and 44 mg (0.052 mmol, 5 mol%) of **7**, 0.243 g (81%) of **18c** was obtained after column chromatography (hexane/ethyl acetate: 3:1) as colorless oil: ^{1}H NMR δ 7.35–7.21 (m, 5H), 5.69–5.65 (sm, 1H), 4.62 (s, 2H), 4.16 (br d, 1H, J=17.9 Hz), 4.12 (dd, 1H, J=12.1, 3.7 Hz), 3.98 (s, 2H), 3.81 (s, 3H), 3.48 (dd, 1H, J=17.9, 7.3 Hz), 2.77–2.69 (sm, 1H), 2.58 (d, 1H, J=18.3 Hz), 1.70 (s, 1H); ^{13}C NMR δ 170.8, 170.0, 140.6, 136.6, 128.4, 127.7, 127.3, 118.8, 66.5, 52.2, 51.1, 48.0, 44.7, 27.5; MS (ES+) *m/z* 290 (11, $[M+H]^+$), 312 (100, $[M+Na]^+$), 601 (85, $[2M+Na]^+$), 890 (17, $[3M+Na]^+$); HRMS (ES+) *m/z* calcd for $C_{16}H_{19}NO_4Na$ 312.121178 found 312.120229. According to the general procedure (Method A) employing 0.331 g (1.04 mmol) of **17b** and 43 mg (0.052 mmol, 5 mol%) of **6**, 0.048 g (16%) of **18c** was obtained as a colorless oil, which exhibited identical spectroscopic data to those obtained using Method B.

4.5.4. 1-Benzyl-5-(*tert*-butyl-dimethyl-silanyloxymethyl)-2-oxo-2,3,4,7-tetrahydro-1*H*-azepine-3-carboxylic acid methyl ester (18d). The title compound was prepared according to the general procedure (Method B) employing 0.432 g (1.00 mmol) of **16d** and 42 mg (0.05 mmol, 5 mol%) of **7**. Column chromatography (hexane/ethyl acetate: 3:1) gave rise to 0.29 g (74%) of **18d** as colorless oil: ^{1}H NMR δ 7.31–7.19 (m, 5H), 5.66–5.62 (sm, 1H), 4.61 (s, 2H), 4.18–4.11 (sm, 1H), 4.08 (dd, 1H, J=12.4, 3.7 Hz), 3.94 (s, 2H), 3.78 (s, 3H), 3.46 (dd, 1H, J=17.7, 7.6 Hz), 2.68–2.59 (br m, 1H), 2.47 (br d, 1H, J=18.3 Hz), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR δ 170.8, 170.0, 140.3, 136.8, 128.5, 127.8, 127.4, 117.8, 66.8, 52.3, 51.3, 48.2, 44.8, 27.5, 25.8, 18.2, −5.5; MS (EI) *m/z* 403 (23, M^+), 388 (19), 346 (100), 271 (69), 258 (23), 213 (51), 91 (33); HRMS (EI) *m/z* calcd for $C_{22}H_{33}NO_4Si$ 403.2179 found 403.2181. Following the general procedure (Method A) employing 0.432 g (1.00 mmol) of **16d** and 41 mg (0.05 mmol, 5 mol%) of **6**, 0.093 g (23%) of **18d** was obtained after column chromatography (hexane/ethyl acetate: 2:1) as colorless oil. The isolated product exhibited identical spectroscopic data to those obtained using Method B.

4.5.5. 2,3,4,7-Tetrahydro-1*H*-azepine-1,3-dicarboxylic acid-1-*tert*-butyl ester 3-methyl ester (18e). According to the general procedure (Method A) utilizing 0.340 g (1.20 mmol) of **16e** and 49 mg (0.06 mmol, 5 mol%) of **6**, 0.265 g (87%) of **18e** was obtained after column chromatography (hexane/ethyl acetate: 14:1) as colorless oil: ^{1}H NMR (rotamers, ratio: ~1.2:1) δ 5.76–5.61 (m, 2H), 4.20 (br d, 0.56H, J=17.4 Hz), 4.10 (br d, 0.47H, J=15.8 Hz), 4.00 (br dd, 0.43H, J=14.0, 6.2 Hz), 3.84 (br dd, 1.12H, J=14.4, 6.7 Hz), 3.75 (br d, 0.56H, J=17.4 Hz), 3.70 (s, 1.63H), 3.69 (s, 1.36H), 3.58–3.49 (m, 1H), 2.99–2.91 (m, 1H), 2.50–2.40 (m, 2H) 1.46 (s, 5H), 1.45 (s, 4H); ^{13}C NMR (rotamers) δ 173.9, 155.1, 155.0, 129.2, 128.8, 128.1, 126.9, 51.6, 48.0, 47.8, 47.3, 47.1, 43.5, 42.9, 28.2, 28.1, 27.2, 26.5; MS (ES+) *m/z* 278 (100, $[M+Na]^+$), 533 (13, $[2M+Na]^+$); HRMS (ES+) *m/z* calcd for $C_{13}H_{21}NO_4Na$ 278.136828 found 278.135883. According to the general procedure (Method B) employing 0.340 g (1.20 mmol) of **16e** and 51 mg (0.06 mmol, 5 mol%) of **7**, 0.263 g (86%) of **18e** was obtained as a colorless oil, which exhibited identical spectroscopic data to those obtained using Method A.

4.5.6. 5-Hydroxymethyl-2,3,4,7-tetrahydro-1*H*-azepine-1,3-dicarboxylic acid-1-*tert*-butyl ester 3-methyl ester (18f). The title compound was prepared according to the general procedure (Method B) employing 0.313 g (1.00 mmol) of **17c** and 42 mg (0.05 mmol, 5 mol%) of **7**. Column chromatography (hexane/ethyl acetate: 3:2) gave rise to 0.271 g (95%) of **18f** as colorless oil: ^{1}H NMR (rotamers, ratio: ~1.5:1) δ 5.67 (s, 0.4H), 5.64 (s, 0.6H), 4.28 (d, 0.6H, J=17.6 Hz), 4.17 (d, 0.4H, J=17.2 Hz), 4.06–3.95 (m, 2.46H), 3.88–3.74 (m, 1.59H), 3.70 (s, 1.79H), 3.69 (s, 1.31H), 3.52 (sm, 1H), 3.09–2.98 (m, 1H), 2.52–2.41 (sm, 2H), 2.13 (br s, 1H), 1.47 (s, 5.40H), 1.45 (s, 4.18H); ^{13}C NMR (rotamers) δ 174.4, 174.3, 155.0, 139.5, 138.3, 123.0, 122.8, 79.9, 79.7, 67.8, 67.6, 51.8, 47.9, 47.6, 46.9, 46.7, 42.8, 42.1, 28.2, 27.9, 27.4; MS (ES+) m/z 286 (56, $[M+H]^+$), 308 (67, $[M+Na]^+$), 593 (100, $[2M+Na]^+$); HRMS (ES+) m/z calcd for $C_{14}H_{23}NO_5Na$ 308.147393 found 308.150227. Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.60; H, 7.90; N, 5.16. Following the general procedure (Method A) employing 0.313 g (1.00 mmol) of **17c** and 41 mg (0.05 mmol, 5 mol%) of **6**, 0.105 g (37%) of **18f** was obtained after column chromatography (hexane/ethyl acetate: 2:1) as colorless oil. The isolated product exhibited identical spectroscopic data to those obtained using Method B.

4.5.7. 5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2,3,4,7-tetrahydro-1*H*-azepine-1,3-dicarboxylic acid-1-*tert*-butyl ester 3-methyl ester (18g). According to the general procedure (Method A) utilizing 0.658 g (1.54 mmol) of **16f** and 63 mg (0.077 mmol, 5 mol%) of **6**, 0.267 g (44%) of **18g** was obtained after column chromatography (hexane/ethyl acetate: 10:1) as colorless oil: ^{1}H NMR (rotamers, ratio: ~1.1:1) δ 5.68 (s, 0.5H), 5.61 (s, 0.5H), 4.16 (d, 0.5H, J=17.9 Hz), 4.10 (d, 0.5H, J=16.7 Hz), 4.04–3.93 (m, 2.6H), 3.86 (d, 0.5H, J=17.1 Hz), 3.79 (dd, 0.5H, J=14.5, 6.8 Hz), 3.71 (br d, 0.5H, J=19.5 Hz), 3.67 (s, 1.50H), 3.65 (s, 1.50H), 3.52 (dd, 0.50H, J=14.3, 8.3 Hz), 3.44 (dd, 0.5H, J=14.0, 8.8 Hz), 2.91–2.83 (m, 1H), 2.32 (s, 1H), 2.31 (s, 1H), 1.43 (s, 4.6H), 1.42 (s, 4.4H), 0.88 (s, 4.9H), 0.87 (s, 4.5H), 0.04 (s, 6H); ^{13}C NMR (rotamers) δ 174.0, 155.2, 155.0, 139.6, 138.0, 121.7, 121.3, 79.8, 79.6, 67.3, 67.1, 51.7, 48.4, 47.8, 46.7, 46.6, 42.7, 42.3, 28.3, 28.2, 27.4, 25.8, 18.2, −5.4, −5.5; MS (ES+) m/z 422 (100, $[M+Na]^+$); HRMS (ES+) m/z calcd for $C_{20}H_{37}NO_5SiNa$ 422.233872 found 4222.229903. According to the general procedure (Method B) employing 0.460 g (1.08 mmol) of **16f** and 46 mg (0.054 mmol, 5 mol%) of **7**, 0.375 g (87%) of **18g** was obtained as a colorless oil, which exhibited identical spectroscopic data to those obtained using Method A.

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