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# STUDIES ON THE AZA-CLAISEN REARRANGEMENT OF 7 TO 9-MEMBERED VINYLAZACYCLES

**Seok-Ho Kim,[1,†] Won-Il Lee,[2,†] Seon-Mi Kim,[2] Jae-Kyung Jung,[3] Jaebong Jang,[2] Jaehoon Sim,[2] Jong-Wha Jung,[4,*] and Young-Ger Suh[2,*]**

[1] College of Pharmacy, Institute of Pharmaceutical Sciences, CHA University, Pocheon 487-010, Korea [2] College of Pharmacy, Seoul National University, Seoul 151-742, Korea; E-mail: ygsuh@snu.ac.kr [3] College of Pharmacy, Chungbuk National University, Cheongju 362-763, Korea [4] College of Pharmacy, Research Institute of Pharmaceutical Sciences, Kyungpook National University, Daegu 41566, Korea; E-mail: jungj@knu.ac.kr

**Abstract** – A systematic study on the amide enolate-induced aza-Claisen rearrangement (ACR) of 7 to 9-membered vinylazacycles has been carried out, resulting in an efficient synthetic method to prepare 11 to 13-membered macrolactams. Key feature includes introduction of electron-donating substituents at α-position of the amide substrates possessing 7 to 9-membered vinylazacycles to facilitate amide enolate-induced ACR. In addition, substituent effects on ACR has been discussed based on the experimental results. We believe this study would provide experimental evidences for the substituent effects and envision for the synthetic application of ACR-induced ring expansion.

## INTRODUCTION

Medium- and macrolactams as well as related azacyclic compounds[1] find widespread applications in the field of pharmaceutical research and the natural product synthesis.[2] Thus, the development of an efficient synthetic route to gain an access toward such ring systems has been a challenge. In an effort to expand the synthetic potential of the amide enolate-induced aza-Claisen rearrangement (ACR),[3] we have been interested in the syntheses of 11 to 13-memberd lactams from the corresponding 7 to 9-memberd precursors. This strategy share the defining characteristic of rapidly generating the medium-sized lactams starting from easily accessible 2-vinylazacycles (e.g. **1b-d**) with a pioneering lactam ring expansion

† These authors equally contributed to this work.

strategy that has been focused on the 3, 5, and 6-membered precursors.[4,5] Furthermore, highly reliable stereochemical outcome of [3,3]-sigmatropic rearrangement[6] due to the highly ordered transition state as well as advantages in entropic and enthalpic sense, promise an efficient chiral transfer to the ring-expanded lactams.[3]

Our research program has been focused on the synthesis of bioactive natural product via ACR, and we have reported a unique approach of lactam ring expansion for the synthesis of functionalized macrolactams.[3] Our previous studies involved the stereoselective lactam ring expansion and its applications. For instance, ACR of enol ethers has been reported as an intramolecular aldol equivalent, and utilized in several natural product synthesis programs.[3b-d] ACR of simple vinylazacycles, which has also been utilized in natural product synthesis, however, was only limited to deliver 10-membered lactam from the 6-membered azacycles.[3e-f] Thus, studies in the lactam ring expansion via ACR using medium- to macro-sized azacycles with a various functional groups are still in need to expand its synthetic utility of the strategy. Herewith, we report a systematic study for the preparation of the 11 to 13-memberd lactams from the 2-vinylazacycles via anionic ACR promoted by an introduction of electron-donating substituents at α-position of the amide substrate (Figure 1).

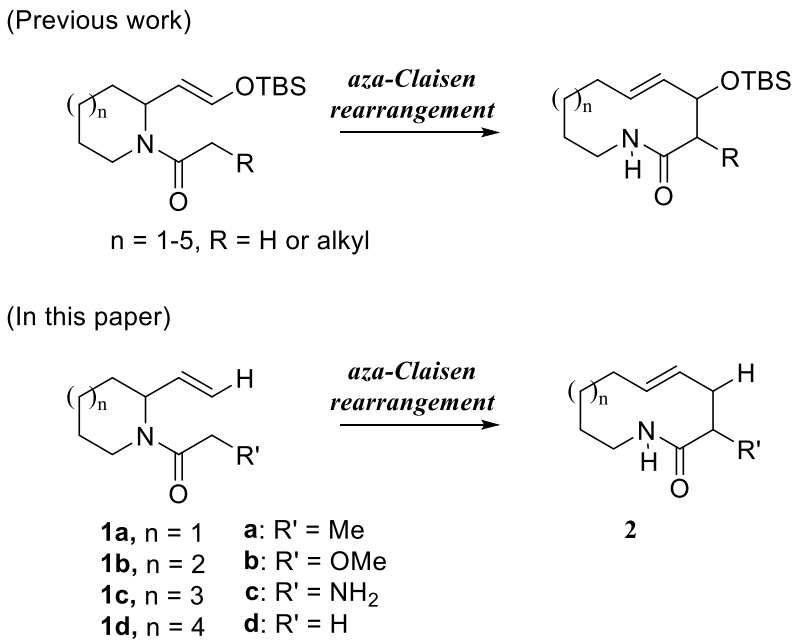
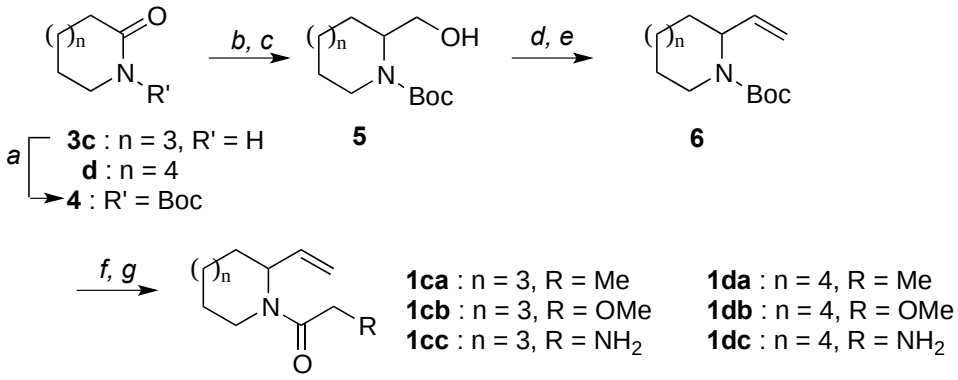



**Figure 1.** Strategies in ACR of 7 to 9-Membered Vinylazacycles

## RESULTS AND DISCUSSION

Our study commenced with the preparation of the requisite 8 and 9-membered azacycles as ACR precursors. As shown in Scheme 1, the Boc-protected lactam **4** were subjected to the Tebbe condition (Tebbe reagent, THF, 0 ºC)[7,8] to afford the enamines, which were then converted to the primary alcohols

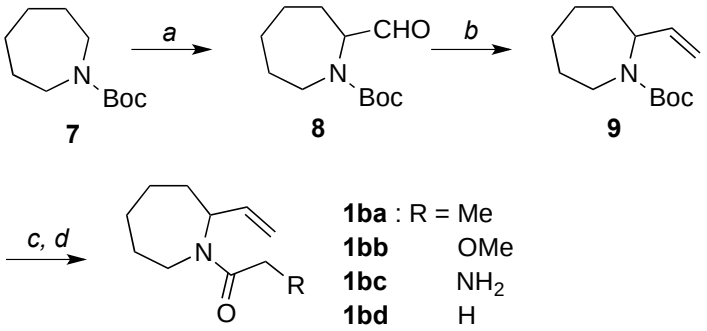
**5** by hydroboration in moderate yields. PDC oxidation of the alcohol **5** followed by Wittig reaction of the resulting aldehyde provided **6** in acceptable yields. Finally, Boc-deprotection of **6** and subsequent acylation with the various acid derivatives afforded the 2-vinyl amide **1c** and **1d**, requisite precursors of ACR.




[a]Reagents and conditions: (a) LHMDS, $Boc_2O$, THF, -78 ºC, 93% for **4c**, 95% for **4d**; (b) Tebbe reagent, THF, 0 ºC; (c) $BH_3$-THF complex, THF, 0 ºC to rt, 54% for **5c** (2 steps), 60% for **5d** (2 steps); (d) PDC, $CH_2Cl_2$; (e) $Ph_3PMeI$, *n*-BuLi, THF, -78 ºC to rt, 72% for **6c** (2 steps), 63% for **6d** (2 steps); (f) TFA, $CH_2Cl_2$, 0 ºC to rt; (g) $Et_3N$, DMAP, $CH_2Cl_2$, propionic anhydride for R = Me, or methoxyacetyl chloride for R = OMe; $Et_3N$, DEPC, DMF, *N*-Boc-Gly-OH, then TFA, $CH_2Cl_2$, 0 ºC to rt for R = $NH_2$, 53-99% (2-3 steps).

**Scheme 1.** Preparation of 8 and 9-Membered Vinylazacycles[a]

For the synthesis of 7-membered azacyclic substrate, however, it was not successful to obtain the corresponding product in analogous to Scheme 1.[9] After an extensive efforts for the functionalization of the $\alpha$ position of nitrogen,[10] Beak's formylation protocol[11] was successfully employed after extensive efforts (Scheme 2).

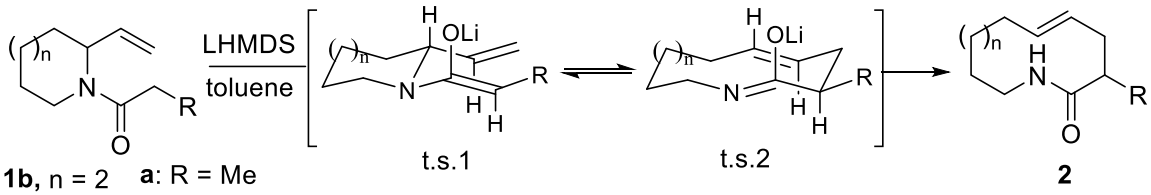



[a]Reagents and coditions: (a) *s*-BuLi, TMEDA, DMF, ether, -40 ºC, 65%; (b) $Ph_3PMeI$, *n*-BuLi, THF, -78 ºC to rt, 70%; (c) TFA, $CH_2Cl_2$, 0 ºC to rt; (g) $Et_3N$, DMAP, $CH_2Cl_2$, propionic anhydride for R = Me, acetic anhydride for R = H, or methoxyacetyl chloride for R = OMe; $Et_3N$, DEPC, DMF, *N*-Boc-Gly-OH, then TFA, $CH_2Cl_2$, 0 ºC to rt for R = $NH_2$, 69-98% (2-3 steps).

**Scheme 2.** Preparation of 7-Membered Vinylazacycle[a]

To this end, treatment of the Boc-protected azepine **7** with *s*-BuLi and subsequent formylation of the resulting metallated amine with DMF provided the desired aldehyde **8**. The aldehyde **8** was converted into the vinyl substituted 7-membered azacycle **1b** through a three-step sequence of Wittig olefination, deprotection of Boc group and acylation of the resulting amine by analogy to the synthesis of **1c** and **1d**.

**Table 1.** ACR of 2-Vinylazacycles[a]




**1b**, n = 2
**1c**, n = 3
**1d**, n = 4

**a**: R = Me
**b**: R = OMe
**c**: R = $NH_2$
**d**: R = H

| Entry | 2-Vinylazacycle (**1**) | n | R | Yield (%)[b] |
|---|---|---|---|---|
| 1 | **1ba** | 2 | Me | 69 |
| 2 | **1bb** | 2 | OMe | 75 |
| 3 | **1bc** | 2 | $NH_2$ | 82 |
| 4 | **1bd** | 2 | H | 31 |
| 5 | **1ca** | 3 | Me | 89 |
| 6 | **1cb** | 3 | OMe | 56 |
| 7 | **1cc** | 3 | $NH_2$ | 30 |
| 8 | **1da** | 4 | Me | 84 |
| 9 | **1db** | 4 | OMe | 49 |
| 10 | **1dc** | 4 | $NH_2$ | 31 |

[a]Reaction condition: LHMDS, toluene, reflux. [b]Isolated yields after $SiO_2$ chromatography.

With the desired 2-vinylazacycles **1** in hand, the objective ACR was attempted under the previously established reaction condition (LHMDS, toluene, reflux).[3] The result was summarized in Table 1. As expected, ACR of all substrates proceeded smoothly to afford the ring-expanded lactams **2** in moderate to high yields except for the acetylated vinylazacycles. The introduction of α-alkyl group or α-heteroatom facilitated ACR, and ACR of **1bb** and **1bc** were more efficient compared to the ACR of **1ba** and **1bd** in terms of both higher yield and shorter reaction time (69%, 1.5 h for entry 1 vs. 75-82%, 15 min for entry 2, 3). Considering factors affecting related [3,3]-sigmatropic rearrangements such as in Cope and Claisen rearrangement as well as other variants,[12] ACR induced ring expansion of azacycles containing

electron-donating groups at α-position of the amide substrates are expected to have advantages in promoting ACR of azacycles as in the case of enol ethers. Previous studies also supported these trends in amide-enolate induced ACR involved in lactam ring expansion.[3] Especially, ACR of simple vinyl substituted 6-membered azacycles was found to be promoted by the introduction of electron-donating substituents at α-position.[3a,3e-f] The electronic effects of α-alkyl group or α-heteroatom shown in Table 1 might be understood by thermodynamic perturbation among the transition states (t.s.1 and t.s.2),[12a] whereas ACR-induced ring expansion might be promoted by anion effect as in the case of oxy-Cope rearrangement.[12b-c] In other words, weak forces including H-bonding, steric, electronic, and conjugation effects may affect the equilibrium between the transition states,[12a] and the anion effect introduced by the substitution of α-alkyl group or α-heteroatom seems to be one of the predominant factors for the acceleration of ACR. The remarkable anion effect in Cope rearrangement were widely used and discussed in synthetic applications since the oxy-Cope rearrangement reported,[12b-c] and the promotion of ACR-induced ring expansion in this study might also be attributed to the anion effect as well. The effects of α-heteroatom might also be interpreted with chelation-promoted or dianionic ACR (not shown.).[12d-e] For the ACR of 8 and 9-membered precursors, the corresponding substrates possessing α-heteroatom showed a somewhat different trend in terms of yield compared to the corresponding ACR of the corresponding 7-membered precursors (entry 5-10), and the reason is not clear at present. Nonetheless, it seems clear that the introduction of α-substituents facilitated ACR compared to the ACR of non-substituted acetamides in which the reaction of **1cb**, **1cc**, **1db**, and **1dc** completed faster than the ACR of **1ca** and **1da** in terms of the disappearance of corresponding substrates as in the case of ACR of 7-membered precursors. The (*E*)-stereochemistry of olefin in the ring expanded lactams is defined by coupling constant of ~15 Hz between two olefinic protons. The preference for (*E*)-olefin over (*Z*) might be contributed by the highly ordered chair-like transition state and exclusive formation of amide (*Z*)-enolate as proposed in Table 1.

## CONCLUSION

In summary, a systematic study on the ACR of 7 to 9-membered azacycles have been carried out, resulting in the efficient synthetic method to prepare the 11 to 13-membered lactams having internal (*E*)-olefins which has been synthetically inaccessible by the conventional methods.[13] Introduction of α-substituents facilitated ACR-induced ring expansion as in the case of enol ethers.[3b-d] We believe this study would provide experimental evidences and insights on the synthesis of natural products such as alkaloids and macrolactam antibiotics as well as bioactive small molecules via ACR-induced ring expansion.

## EXPERIMENTAL

Unless otherwise noted, all starting materials and solvents were used as obtained from commercial suppliers without further purification. Organic solvents used in this study were dried over appropriate drying agents and distilled prior to use. Thin layer chromatography was carried out using Merck silica gel 60 $F_{254}$ plates, and flash chromatography was performed using Merck silica gel 60 (0.040-0.063 mm, 230-400 mesh). NMR spectra were recorded in deuterated solvents on a Bruker 500 (500 MHz for $^1$H; 125 MHz for $^{13}$C), JEOL JNM-GCX 400 (400 MHz for $^1$H; 100 MHz for $^{13}$C), or JEOL JNM-LA 300 (300 MHz for $^1$H; 75 MHz for $^{13}$C) spectrometer. $^1$H- and $^{13}$C-NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Infrared spectra were recorded on a Perkin-Elmer 1710 FT-IR spectrometer. Low-resolution electrospray ionization (ESI) mass spectra were obtained with Finnigan LCQ mass spectrometer. Low and high-resolution fast atom bombardment (FAB) and electron impact (EI) mass spectra were obtained with JEOL JMS-700 instrument.

***tert*-Butyl 2-(hydroxymethyl)azocane-1-carboxylate (5c):** Tebbe reagent (1M in THF, 17.3 mL, 17.3 mmol) was added to a solution of **4c** (3.58g, 15.8 mmol) in THF (60 mL) at 0 °C. After stirring for 5 h, the reaction mixture was diluted with $Et_2O$, and quenched with MeOH. The suspension was filtered through a short plug of celite, and the filtrate was decanted with *n*-hexane and $Et_2O$. Volatiles were removed under the reduced pressure, and the residue containing *tert*-butyl 2-methyleneazocane-1-carboxylate was used without further purification: $^1$H-NMR ($CDCl_3$, 300 MHz) δ 4.94 (s, 1H), 4.80 (s, 1H), 3.56 (t, 2H, $J$ = 5.5 Hz), 1.92-1.89 (m, 2H), 1.14-0.72 (m, 17H).

To a solution of *tert*-butyl 2-methyleneazocane-1-carboxylate above in THF (30 mL), a solution of borane (1M $BH_3$·THF, 15.7 mL, 15.7 mmol) was added at 0 °C. After stirring for 9 h at rt, the solution was diluted with $Et_2O$, and then, 6N-NaOH (72 mL) and 30% $H_2O_2$ (72 mL) were added at 0 °C. The mixture was stirred for 5 h, and filtered with a short plug of celite. The filtrate was washed with water and brine, and dried over $MgSO_4$. Volatiles were removed under the reduced pressure, and the residue was purified with $SiO_2$ chromatography (40% EtOAc in *n*-hexane) to provide **5c** as a colorless oil (2.07 g, 54% for 2 steps): $^1$H-NMR ($CDCl_3$, 300 MHz) δ 4.07-2.94 (m, 7H), 1.81-1.24 (m, 17H).

***tert*-Butyl 2-vinylazocane-1-carboxylate (6c):** PDC (473 mg, 1.26 mmol) was added to a solution of alcohol **5c** (200 mg, 0.823 mmol) in $CH_2Cl_2$ (20 mL) at 0 °C. After stirring for 9 h at rt, the mixture was diluted with $Et_2O$, and filtered through a short plug of celite. Volatiles in the filtrate was removed under the reduced pressure, and the residue was purified by $SiO_2$ chromatography (15% EtOAc in *n*-hexane) to provide *tert*-butyl 2-formylazocane-1-carboxylate as a colorless oil (159 mg, 80%); $^1$H-NMR ($CDCl_3$, 300 MHz) δ 9.54 (d, $J$ = 12.2 Hz, 1H), 4.24 and 3.50 (m, 1H), 3.80 (m, 1H), 3.21 (m, 1H), 2.04-1.18 (m,

19H).

A solution of *n*-BuLi (1.6 M in hexane, 0.915 mL, 1.46 mmol) was added to the solution of methyltriphenylphosphonium iodide (650 mg, 1.60 mmol) in THF (10 mL) at -78 ºC. After stirring for 2 h, *tert*-butyl 2-formylazocane-1-carboxylate (324 mg, 1.34 mmol) in THF (5 mL) was added at -78 ºC, and the temperature was slowly elevated to rt. After stirring for 9 h, the reaction was quenched with aqueous $NH_4Cl$ solution. The organic phase was washed with water and brine, and dried over $MgSO_4$. Volatiles were removed under the reduced pressure, and the residue was purified with $SiO_2$ chromatography (10% EtOAc in *n*-hexane) to provide **6c** as a colorless oil (285 mg, 89%); $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.63 (ddd, 1H, *J* = 17.2, 10.4, 4.2 Hz), 4.96-4.85 (m, 2H), 4.54 and 4.30 (m, 1H), 2.82 (m, 1H), 1.91-1.41 (m, 19H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 155.7, 155.2, 138.7, 138.4, 113.1, 78.9, 78.8, 58.0, 56.7, 42.1, 41.7, 29.0, 28.4, 27.8, 26.9, 26.6, 26.6, 26.5, 26.1, 26.0, 25.9, 24.5, 24.1; FT-IR (thin film, neat) $\nu_{max}$ 2928, 1693, 1475, 1403 cm$^{-1}$; MS (ESI$^+$) *m/z* 240 (M+H$^+$), 262 (M+Na$^+$).

**1-(2-Vinylazocan-1-yl)propan-1-one (1ca):** TFA (0.426 mL, 5.54 mmol) was added to a solution of **6c** (133 mg, 0.556 mmol) in $CH_2Cl_2$ (5 mL), and the solution was stirred for 2 h at rt. Volatiles were removed under the reduced pressure, and the residue was re-dissolved in $CH_2Cl_2$ (5 mL). DMAP (3.40 mg, 0.0279 mmol) and $Et_3N$ (1.54 mL, 11.1 mmol) were added at 0 ºC, and propionic anhydride (0.213 mL, 1.67 mmol) was added subsequently. After stirring for 3 h, water was added. The mixture was extracted with $CH_2Cl_2$, and the organic phase was dried over $MgSO_4$. Volatiles were removed under the reduced pressure, and the residue was purified with $SiO_2$ chromatography (33% EtOAc in *n*-hexane) to provide **1ca** as a yellow oil (107 mg, 99%): $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.67 (m, 1H), 5.06-4.89 (m, 2H), 3.85 (m, 1H), 3.46 (m, 1H), 3.16 (m, 1H), 2.73 (m, 1H), 2.34 (m, 1H), 2.03-0.75 (m, 13H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 177.4, 174.0, 138.1, 138.0, 114.2, 113.7, 59.6, 55.5, 42.5, 41.8, 29.5, 28.9, 27.7, 27.1, 26.7, 26.6, 26.0, 25.9, 24.5, 23.9, 9.7, 9.5; $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 174.4, 174.0, 138.1, 138.0, 114.2, 113.7, 59.6, 55.5, 42.5, 41.8, 29.5, 28.9, 27.7, 27.1, 26.7, 26.6, 26.0, 25.9, 24.5, 23.9, 9.7, 9.5; FT-IR (thin film, neat) $\nu_{max}$ 2930, 1734, 1642, 1417 cm$^{-1}$; MS (ESI$^+$) *m/z* 196 (M+H$^+$), 218.1 (M+Na$^+$).

**2-Methoxy-1-(2-vinylazocan-1-yl)ethan-1-one (1cb): 1cb** was synthesized by analogy to the synthesis of **1ca** except for using methoxyacetyl chloride instead of propionic anhydride; Yield 90%, a yellow oil; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.46 (ddd, 1H, *J* = 14.1, 10.5, 3.9 Hz), 4.86-4.70 (m, 2H), 3.85 (m, 1H), 3.21 (m, 1H), 2.86 (m, 1H), 2.53 (m, 1H), 3.22 (s, 3H), 1.66-0.55 (m, 10H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 169.2, 167.7, 139.6, 137.9, 137.7, 126.6, 114.4, 76.1, 71.6, 71.1, 69.5, 69.3, 60.5, 59.4, 59.3, 59.2, 58.6, 57.1, 56.0, 29.2, 28.9, 27.6, 26.9, 26.6, 26.2, 25.9, 25.7, 24.5, 24.1; FT-IR (thin film, neat) $\nu_{max}$ 1633, 1417 cm$^{-1}$; MS (EI$^+$) *m/z* 211 (M$^+$).

**2-Amino-1-(2-vinylazocan-1-yl)ethan-1-one (1cc):** TFA (0.209 mL, 2.73 mmol) was added to a solution of **6c** (65 mg, 0.273 mmol) in $CH_2Cl_2$ (3 mL), and the solution was stirred for 2 h at rt. Volatiles were removed under the reduced pressure, and the residue was re-dissolved in DMF (2 mL). DEPC (0.055 mL, 0.362 mmol), and $Et_3N$ (0.761 mL, 5.46 mmol) were added to a solution of *N*-Boc-glycine (57 mg, 0.327 mmol) in DMF (2 mL) in a separate flask, the resulting solution was added to the solution of Boc-deprotected amine after 30 min. The solution was stirred for 4 h at rt, and water was added. The mixture was extracted with $CH_2Cl_2$, and the organic phase was dried over $MgSO_4$. Volatiles were removed under the reduced pressure, and the residue was purified with $SiO_2$ chromatography (50% EtOAc in 1:1 solution of *n*-hexane and $CH_2Cl_2$) to provide *tert*-butyl (2-oxo-2-(2-vinylazocan-1-yl)ethyl)carbamate (102 mg, 89%) as a yellow oil; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.67 (m, 1H), 5.08-4.91 (m, 2H), 3.90 (m, 1H), 3.43 (m, 1H), 3.12 (m, 1H), 2.82 (m, 1H), 1.97-1.16 (m, 19H); $^{13}$C-NMR ($CDCl_3$, 125 MHz) δ 169.1, 168.4, 155.8, 137.5, 137.2, 79.5, 58.9, 56.7, 42.6, 42.4, 42.3, 29.3, 28.6, 28.4, 27.9, 27.1, 26.7, 26.2, 25.9, 24.5, 24.1; MS ($EI^+$) *m/z* 296 ($M^+$).

To a solution of the amide above (81 mg, 0.274 mmol) in $CH_2Cl_2$ (5mL), TFA was added at 0 ºC (0.210 mL, 2.37 mmol). After stirring for 2 h at rt, aqueous $NaHCO_3$ solution was added, and the mixture was extracted several times with $CH_2Cl_2$. The combined organic phases were dried over $MgSO_4$, and volatiles were removed under the reduced pressure. The resulting amine **1cc** was used as a substrate for aza-Claisen rearrangement without further purification.

***tert*-Butyl 2-oxoazonane-1-carboxylate (4d):** 9-Membered lactam **4d** was synthesized by analogy to the synthesis of 8-membered lactam **4c** except for using 2-azacyclononanone instead of 2-azacycloheptanone; Yield 91%, a colorless oil; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 3.78 (t, 2H, $J$ = 6.3 Hz), 2.87-2.83 (m, 2H), 1.83-1.75 (m, 2H), 1.69-1.61 (m, 2H), 1.51 (s, 9H), 1.52-1.25 (m, 6H).

***tert*-Butyl 2-(hydroxymethyl)azonane-1-carboxylate (5d):** 9-Membered azacycle **5d** was synthesized by analogy to the synthesis of 8-membered azacycle **5c** except for using 9-membered lactam **4d** instead of 8-membered lactam **4c** for *tert*-butyl 2-methyleneazonane-1-carboxylate, $^1$H-NMR ($CDCl_3$, 300 MHz) δ 4.87 (s, 1H), 4.77 (s, 1H), 3.60 (t, 2H, $J$ = 5.9 Hz), 2.47-2.33 (m, 2H), 1.73-1.23 (m, 19H); for *tert*-butyl 2-(hydroxymethyl)azonane-1-carboxylate (**5d**), yield 60% for 2 steps, a colorless oil; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 4.47-3.07 (m, 5H), 1.67-1.15 (m, 21H).

***tert*-Butyl 2-vinyl-1-azonanecarboxylate (6d):** 9-Membered azacycle **6d** was synthesized by analogy to the synthesis of 8-membered azacycle **6c** except for using 9-membered alcohol **5d** instead of 8-membered alcohol **5d** for, *tert*-butyl 2-formylazonane-1-carboxylate, $^1$H-NMR ($CDCl_3$, 300 MHz) δ 9.50 (d, 1H, $J$ = 10.0 Hz), 4.08-3.01 (m, 3H), 2.13-1.37 (m, 21H); for *tert*-butyl 2-vinyl-1-azonanecarboxylate (**6d**), yield 60% for 2 steps, oil; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.72 (m, 1H), 5.05-4.97 (m, 2H), 4.68 and 4.36 (m, 1H), 3.37 (m, 1H), 2.80 (m, 1H), 1.83-1.27 (m, 12H), 1.48 and 1.46 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 100 MHz)

δ 156.3, 155.8, 138.7, 138.6, 113.9, 113.8, 79.0, 60.1, 58.7, 57.4, 44.2, 43.3, 29.5, 28.3, 28.3, 28.0, 27.1, 26.8, 26.7, 25.5, 25.2, 24.0, 23.7, 23.5, 20.8, 14.0; FT-IR (thin film, neat) $\nu_{max}$ 2924, 1692, 1455, 1403 $cm^{-1}$; MS ($ESI^+$) *m/z* 254 ($M+H^+$), 276 ($M+Na^+$).

**1-(2-Vinylazonan-1-yl)propan-1-one (1da):** 9-Membered vinylazacycle **1da** was synthesized by analogy to the synthesis of 8-membered vinylazacycle **1ca** using 9-membered azacycle **6d** instead of 8-membered azacycle **6c**. Yield 99%, a colorless oil; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.66 (ddd, 1H, *J* = 17.3, 10.5, 3.9 Hz), 5.08-4.92 (m, 2H); 4.22-2.33 (m, 5H), 1.88-1.05 (m, 15H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 175.3, 174.7, 138.2, 137.9, 114.8, 114.2, 60.2, 60.0, 44.7, 43.8, 29.2, 28.3, 28.0, 27.7, 27.0, 26.9, 26.8, 26.5, 25.7, 24.9, 23.4, 23.0, 9.5, 9.3; FT-IR (thin film, neat) $\nu_{max}$ 2923, 1734, 1643, 1416 $cm^{-1}$; MS ($ESI^+$) *m/z* 210 ($M+H^+$), 232 ($M+Na^+$).

**2-Methoxy-1-(2-vinylazonan-1-yl)ethan-1-one (1db):** 9-Membered vinylazacycle **1db** was synthesized by analogy to the synthesis of 8-membered vinylazacycle **1cb** using 9-membered azacylcle **6d** instead of 8-membered azacycle **6c**: Yield 85%; a colorless oil; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.66 (ddd, 1H, *J* = 17.3, 10.5, 3.9 Hz), 5.09-4.94 (m, 2H), 4.16 (m, 1H), 3.73 (m, 1H), 3.39 (m, 1H), 3.01 (m, 1H), 2.69 (m, 1H), 3.44 (s, 3H), 2.11-0.76 (m, 12H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 170.2, 169.9, 150.5, 138.1, 115.2, 114.9, 71.9, 71.3, 69.2, 62.3, 59.3, 51.9, 43.7, 29.7, 29.0, 27.9, 26.7, 26.2, 25.8, 24.8, 23.8, 23.4; MS ($ESI^+$) *m/z* 226 ($M+H^+$).

**2-Amino-1-(2-vinylazonan-1-yl)ethan-1-one (1dc):** 9-Membered vinylazacycle **1dc** was synthesized by analogy to the synthesis of 8-membered vinylazacycle **1cc** using 9-membered azacylcle **6d** instead of 8-membered azacycle **6c**. For *tert*-butyl (2-oxo-2-(2-vinylazonan-1-yl)ethyl)carbamate; Yield 88%, a yellow oil; $^1$H-NMR ($CDCl_3$, 500 MHz) δ 5.74-5.61 (m, 2H), 5.07 (m, 1H), 4.97 (d, 1H, *J* = 17.3 Hz), 4.08-3.78 (m, 3H), 3.38, 3.09 and 2.74 (m, 1H), 1.93-1.36 (m, 12H), 1.43 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 125 MHz) δ 169.7, 168.9, 155.8, 155.7, 137.8, 137.3, 115.5, 115.1, 79.4, 59.4, 44.2, 42.9, 29.3, 28.4, 27.9, 27.2, 26.7, 26.0, 25.1, 23.6, 23.3; MS ($ESI^+$) *m/z* 310 ($M+H^+$).

***tert*-Butyl 2-formyl-1-azepanecarboxylate (8):** Formylazapane **8** was synthesized according to the literature.[11] Briefly, *N*-Boc-azapane **7** was treated with *s*-BuLi in the presence of TMEDA in $Et_2O$ at low temperature, and then formylated by the addition of DMF: Yield 40%, oil; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 9.55 (d, 1H, *J* = 4.1 Hz), 4.36 and 4.02 (dd, 1H, *J* = 11.1, 6.3 Hz), 3.7 and 3.65 (m, 1H), 3.28 and 2.99 (dd, 1H, *J* = 14.6, 9.8 Hz), 2.21 (m, 1H), 1.80-1.24 (m, 7H), 1.45 (s, 9H); MS ($EI^+$) *m/z* 228 ($M+H^+$).

***tert*-Butyl 2-vinyl-1-azepanecarboxylate (9):** 7-Membered azacycle **9** was synthesized by analogy to the synthesis of 8-membered azacycle **6c** except for using 7-membered formylazacycle **8** instead of 8-membered formylazacycle, *tert*-butyl 2-formylazocane-1-carboxylate: Yield 66%, oil; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.71 (m, 1H), 5.01-4.93 (m, 2H), 4.57 and 4.36 (m, 1H), 3.83 and 3.66 (m, 1H), 2.65 (dd, 1H, *J* = 14.1, 11.4 Hz), 2.04 (m, 1H), 1.79-1.20 (m, 7H), 1.45 and 1.36 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 100 MHz)

δ 155.5, 155.4, 138.2, 137.9, 112.5, 112.5, 78.8, 78.7, 77.1, 57.6, 56.2, 42.0, 41.4, 33.6, 33.3, 29.4, 29.4, 28.3, 28.2, 25.0, 24.6; FT-IR (thin film, neat) $\nu_{max}$ 2927, 1692, 1408 $cm^{-1}$; MS ($ESI^+$) *m/z* 226 ($M+H^+$), 248 ($M+Na^+$).

**1-(2-Vinylazepan-1-yl)propan-1-one (1ba):** 7-Membered vinylazacycle **1ba** was synthesized by analogy to the synthesis of 8-membered vinylazacycle **1cb** using 7-membered azacylcle **9** instead of 8-membered azacycle **6c**; Yield 78% for 2 steps; a colorless oil; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.71 (ddd, 1H, *J* = 17.0, 10.4, 4.1 Hz), 5.07-4.91 (dd, 2H, *J* = 19.9, 10.4 Hz), 4.18 (m, 1H), 3.56 and 2.95 (m, 1H), 2.56 (m, 1H), 2.49-2.01 (m, 3H), 1.85-1.19 (m, 7H), 1.12 (t, 3H, *J* = 7.4 Hz); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 174.1, 174.0, 136.9, 136.8, 113.2, 112.7, 58.6, 54.8, 42.3, 40.7, 33.8, 32.2, 29.6, 29.1, 28.8, 27.9, 26.9, 25.9, 25.8, 24.5, 24.1, 9.2, 9.1; FT-IR (thin film, neat) $\nu_{max}$ 1644, 1417 $cm^{-1}$; MS ($EI^+$) *m/z* 181 ($M^+$).

**2-Methoxy-1-(2-vinylazepan-1-yl)ethan-1-one (1bb):** 7-Membered vinylazacycle **1bb** was synthesized by analogy to the synthesis of 8-membered vinylazacycle **1cb** using 7-membered azacylcle **9** instead of 8-membered azacycle **6c**; Yield 98% for 2 steps; a colorless oil; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.67 (ddd, 1H, *J* = 17.0, 10.2, 4.1 Hz), 5.04-4.91 (dd, 2H, *J* = 17.0, 10.5 Hz), 4.19-3.84 (m, 4H), 3.38 (s, 3H), 2.91 and 2.57 (dd, 1H, *J* = 12.2, 12.1 Hz), 2.07 (m, 1H), 1.78-1.18 (m, 7H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 169.0, 167.7, 139.6, 137.4, 126.6, 113.8, 113.6, 71.3, 71.2, 69.5, 69.4, 60.5, 59.3, 59.2, 59.1, 57.9, 57.2, 55.5, 42.0, 41.1, 34.2, 32.5, 30.4, 29.7, 29.4, 28.4, 24.9, 24.7; FT-IR (thin film, neat) $\nu_{max}$ 1650, 1428, 1122 $cm^{-1}$; MS ($EI^+$) *m/z* 197 ($M^+$).

**2-Amino-1-(2-vinylazepan-1-yl)ethan-1-one (1bc):** 7-Membered vinylazacycle **1bc** was synthesized by analogy to the synthesis of 8-membered vinylazacycle **1cc** using 7-membered azacylcle **9** instead of 8-membered azacycle **6c**. For *tert*-butyl (2-oxo-2-(2-vinylazepan-1-yl)ethyl)carbamate, a yellow oil; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.65 (ddd, 1H, *J* = 21.4, 10.5, 6.1 Hz), 5.51 (bs, H), 5.05-4.89 (dd, 2H, *J* = 17.0, 10.5 Hz), 4.14 and 3.44 (m, 1H), 3.96 (m, 1H), 3.72 (m, 1H), 2.95 and 2.62 (dd, 1H, *J* = 13.3, 12.1 Hz), 2.10 (m, 1H), 1.76-1.17 (m, 8H), 1.38 (m, 9H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 168.5, 168.3, 155.9, 155.8, 137.0, 136.7, 114.3, 113.8, 79.5, 79.4, 58.3, 56.2, 42.4, 42.3, 42.1, 41.6, 34.3, 32.7, 30.1, 29.6, 29.3, 28.5, 28.4, 25.0, 24.7; FT-IR (thin film, neat) $\nu_{max}$ 3417, 3329, 1714, 1650 $cm^{-1}$; MS ($EI^+$) *m/z* 282 ($M^+$).

**1-(2-Vinylazepan-1-yl)ethan-1-one (1bd):** 7-Membered vinylazacycle **1bd** was synthesized by analogy to the synthesis of 7-Membered vinylazacycle **1ba** except for using acetic anhydride instead of propionic anhydride; Yield 69% for 2 steps; a colorless oil; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.72 (ddd, 1H, *J* = 17.0, 10.5, 4.4 Hz), 5.01 (dd, 2H, *J* = 20.4, 10.4 Hz), 4.16 (m, 1H), 3.60 and 3.03 (m, 1H), 2.58 (m, 1H), 2.09 (s, 3H), 2.14-1.20 (m, 8H); $^{13}$C-NMR ($CDCl_3$, 125 MHz) δ 171.0, 170.7, 137.5, 137.3, 113.8, 113.3, 60.2, 55.1, 43.7, 41.0, 34.5, 32.8, 29.9, 29.7, 29.4, 28.5, 25.1, 24.6, 21.7, 21.6; FT-IR (thin film, neat) $\nu_{max}$ 1633, 1417 $cm^{-1}$; MS ($EI^+$) *m/z* 167 ($M^+$).

**Typical Procedure of the Aza-Claisen Rearrangement for the Preparation of Lactam (2).**

**(*E*)-3-Methylazacycloundec-5-en-2-one (2ba):** To a solution of **1ba** (36.2 mg, 0.2 mmol) in refluxing toluene (2 mL) was added dropwise LHMDS (1.0 M solution in hexane, 0.4 mL, 0.4 mmol). The resulting mixture was refluxed for 1.5 h, and cooled to rt, then quenched with $NH_4Cl$ (aq). The resulting mixture was extracted with EtOAc. Volatiles removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (40% EtOAc in hexane) to afford the compound **2ba** (25.0 mg, 69%) as a white solid; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.47 (bs, 1H), 5.38-5.34 (m, 2H), 3.66 (m, 1H), 2.64 (m, 1H), 2.24-2.13 (m, 4H), 1.75 (m, 1H), 1.58-1.44 (m, 4H), 1.15-1.11 (m, 2H), 1.14 (d, 3H, *J* = 6.1 Hz); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 176.1, 132.2, 128.3, 42.1, 39.5, 39.1, 33.8, 28.8, 25.4, 22.6, 16.6; FT-IR (thin film, neat) $\nu_{max}$ 3261, 1643, 1556 cm$^{-1}$; HRMS (FAB$^+$) calculated for $C_{11}H_{20}NO$ (M+H$^+$) 182.1546, found 182.1548.

**(*E*)-3-Methoxyazacycloundec-5-en-2-one (2bb):** a white solid; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 6.49 (bs, 1H), 5.40-5.34 (m, 2H), 3.78-3.73 (m, 2H), 3.39 (s, 3H), 2.67-2.53 (m, 4H), 1.83 (m, 1H), 1.60-1.46 (m, 5H), 1.11 (m, 1H); FT-IR (thin film, neat) $\nu_{max}$ 3294, 1650, 1106 cm$^{-1}$; $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 172.2, 133.8, 124.6, 82.4, 57.8, 39.1, 35.3, 33.8, 28.7, 25.4, 22.5; HRMS (FAB$^+$) calculated for $C_{11}H_{20}NO_2$ (M+H$^+$) 198.1494, found 198.1492.

**(*E*)-3-Aminoazacycloundec-5-en-2-one (2bc):** a dark yellow oil; $^1$H-NMR ($CD_3OD$, 300 MHz) δ 6.97 (bs, 1H), 5.44-5.38 (m, 2H), 3.30 (m, 1H), 2.92 (m, 1H), 2.50 (m, 1H), 2.49 (m, 1H), 2.15 (m, 1H), 2.09 (m, 1H), 1.89 (m, 1H), 1.40-1.15 (m, 6H); FT-IR (thin film, neat) $\nu_{max}$ 3286, 2852, 1647 cm$^{-1}$; HRMS (FAB$^+$) calculated for $C_{10}H_{19}N_2O$ (M+H$^+$) 183.1497, found 183.1501.

**(*E*)-Azacycloundec-5-en-2-one (2bd):** a white solid; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.39 (bs, 1H), 5.33 (m, 1H), 5.24 (m, 1H), 3.09-3.06 (m, 2H), 2.29-2.26 (m, 2H), 2.08-2.05 (m, 2H), 2.00-1.96 (m, 2H), 1.46-1.18 (m, 6H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 174.1, 132.9, 128.4, 40.6, 34.0, 30.4, 29.7, 29.0, 25.6, 22.7; FT-IR (thin film, neat) $\nu_{max}$ 3296, 1645 cm$^{-1}$; HRMS (FAB$^+$) calculated for C10H18NO (M+H$^+$) 168.1388, found 168.1389.

**(*E*)-3-Methylazacyclododec-5-en-2-one (2ca):** a white solid; $^1$H-NMR ($CD_3OD$, 300 MHz) δ 7.69 (bs, 1H), 5.37 (m, 1H), 5.20 (ddd, 1H, *J* = 15.4, 10.2, 3.2 Hz), 3.75 (m, 1H), 2.73 (m, 1H), 2.35 (m, 1H), 2.11-1.92 (m, 4H), 1.67-1.34 (m, 8H), 1.08 (d, 3H, *J* = 6.6 Hz); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 175.4, 132.4, 128.0, 43.0, 38.7, 36.3, 30.2, 26.5, 25.0, 23.8, 21.0, 17.4; FT-IR (thin film, neat) $\nu_{max}$ 3286, 2932, 1638, 1556 cm$^{-1}$; HRMS (FAB$^+$) calculated for $C_{12}H_{22}NO$ (M+H$^+$) 196.1702, found 196.1706.

**(*E*)-3-Methoxyazacyclododec-5-en-2-one (2cb):** a white solid; $^1$H-NMR ($CD_3OD$, 300 MHz) δ 7.67 (bs, 1H), 5.41 (ddd, 1H, *J* = 15.1, 5.9, 9.2 Hz), 5.26 (ddd, 1H, *J* = 15.6, 5.3, 8.5 Hz), 3.75 (m, 1H), 3.56 (m, 1H), 3.37 (s, 3H), 3.03 (m, 1H), 2.49 (m, 1H), 2.37 (m, 1H), 2.09-2.01 (m, 2H), 1.66-1.11 (m, 8H);

$^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 171.1, 133.8, 124.0, 82.3, 57.6, 35.7, 34.4, 30.4, 26.4, 24.9, 23.8, 20.9; FT-IR (thin film, neat) $\nu_{max}$ 3307, 2913, 1641 $cm^{-1}$; HRMS ($FAB^+$) calculated for $C_{12}H_{22}NO_2$ ($M+H^+$) 212.1651, found 212.1650.

**(*E*)-3-Aminoazacyclododec-5-en-2-one (2cc):** a yellow sticky oil; $^1$H-NMR ($CD_3OD$, 300 MHz) δ 5.39 (ddd, 1H, *J* = 15.1, 9.5, 4.6 Hz), 5.25 (ddd, 1H, *J* = 15.1, 9.3, 4.9 Hz), 3.60 (m, 1H), 2.93 (m, 1H), 2.38 (m, 1H), 2.20-1.97 (m, 4H), 1.66-0.91 (m, 8H); HRMS ($FAB^+$) calculated for $C_{11}H_{21}N_2O$ ($M+H^+$) 197.1654, found 197.1659.

**(*E*)-3-Methylazacyclotridec-5-en-2-one (2da):** a white solid; $^1$H-NMR ($CD_3OD$, 300 MHz) δ 7.99 (bs, 1H), 5.53-5.34 (m, 2H), 3.55 (m, 1H), 2.72 (m, 1H), 2.40 (m, 1H), 2.21 (m, 1H), 2.13-1.97 (m, 3H), 1.67-1.15 (m, 10H), 1.09-1.07 (d, 3H, *J* = 6.2 Hz); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 175.7, 133.0, 128.1, 42.2, 39.4, 37.3, 31.3, 27.3, 26.8, 26.6, 26.1, 25.4, 18.4; FT-IR (thin film, neat) $\nu_{max}$ 3301, 2928, 1642, 1549 $cm^{-1}$; HRMS ($FAB^+$) calculated for $C_{13}H_{24}NO$ ($M+H^+$) 210.1858, found 210.1857.

**(*E*)-3-Methoxyazacyclotridec-5-en-2-one (2db):** a white solid; $^1$H-NMR ($CD_3OD$, 300 MHz) δ 7.98 (bs, 1H), 5.57-5.39 (m, 2H), 3.73 (m, 1H), 3.45 (m, 1H), 3.39 (s, 3H), 2.98 (m, 1H), 2.78 (m, 1H), 2.44 (m, 1H), 2.06-2.00 (m, 2H), 1.66-1.17 (m, 10H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 171.5, 134.9, 81.6, 57.4, 39.2, 33.2, 31.2, 27.3, 27.0, 26.8, 26.2, 25.7; FT-IR (thin film, neat) $\nu_{max}$ 3325, 2917, 1646 $cm^{-1}$; HRMS ($FAB^+$) calculated for $C_{13}H_{24}NO_2$ ($M+H^+$) 226.1807, found 210.1815.

**(*E*)-3-Aminoazacyclotridec-5-en-2-one (2dc):** a dark yellow oil; $^1$H-NMR ($CD_3OD$, 300 MHz) δ 5.57-5.36 (m, 2H), 3.49 (m, 1H), 3.33 (m, 1H), 2.89 (m, 1H), 2.37-2.22 (m, 2H), 2.07-2.03 (m, 2H), 1.59-1.31 (m, 10H); HRMS ($FAB^+$) calculated for $C_{12}H_{23}N_2O$ ($M+H^+$) 211.1810, found 211.1816.

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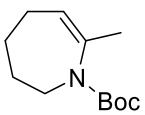
## REFERENCES AND NOTES

1. (a) U. Nubbemeyer, *Top. Curr. Chem.*, 2001, **216**, 125; (b) P. A. Evans and A. B. Holmes, *Tetrahedron*, 1991, **47**, 9131.
2. (a) V. R. Hedge, M. G. Patel, V. P. Gullo, A. K. Ganguly, O. Sarre, M. S. Puar, and A. T. McPhail, *J. Am. Chem. Soc.*, 1990, **112**, 6403; (b) H. Ui, M. Imoto, and K. Umezawa, *J. Antibiot.*, 1995, **48**, 387; (c) M. V. D'Auria, C. Giannini, L. Minale, A. Zampella, C. Debitus, and M. Frostin, *J. Nat. Prod.*, 1997, **60**, 814; (d) A. Groweiss, J. J. Newcomer, B. R. O'Keefe, A. Blackman, and M. R. Boyd, *J. Nat. Prod.*, 1997, **62**, 1691; (e) K. Shindo, M. Kamishohara, A. Odagawa, M. Matsuoka, and H.

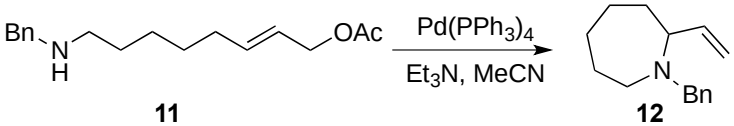
Kawai, *J. Antibiot.*, 1993, **46**, 1076.

3. (a) Y.-G. Suh, S.-A. Kim, J.-K. Jung, D.-Y. Shin, K.-H. Min, B.-A. Koo, and H.-S. Kim, *Angew. Chem. Int. Ed.*, 1999, **38**, 3545; (b) Y.-S. Lee, J.-W. Jung, S.-H. Kim, J.-K. Jung, S.-M. Paek, N.-J. Kim, D.-J. Chang, J. Lee, and Y.-G. Suh, *Org. Lett.*, 2010, **12**, 2040; (c) S.-M. Paek, N.-J. Kim, D. Shin, J.-K. Jung, J.-W. Jung, D.-J. Chang, H. Moon, and Y.-G. Suh, *Chem. Eur. J.*, 2010, **16**, 4623; (d) Y.-G. Suh, Y.-S. Lee, S.-H. Kim, J.-K. Jung, H. Yun, J. Jang, N-.J. Kim, and J.-W. Jung, *Org. Biomol. Chem.*, 2012, **10**, 561; (e) J. Jang, J.-W. Jung, J. Ahn, J. Sim, D.-J. Chang, D.-D. Kim, and Y.-G. Suh, *Org. Biomol. Chem.*, 2012, **10**, 5202; (f) J. Sim, H. Yun, J.-W. Jung, S. Lee, N.-J. Kim, and Y.-G. Suh, *Tetrahedron Lett.*, 2012, **53**, 4813.
4. (a) U. Nubbemeyer, *Top. Curr. Chem.*, 2005, **244**, 149; (b) K. C. Majumdar, T. Bhattacharyya, B. Chattopadhyay, and B. Sinha, *Synthesis*, 2009, 2117; (c) T. Tsunoda and S. Ito, *J. Synth. Org. Chem. Jpn.*, 1994, **52**, 113.
5. (a) E. D. Edstrom, *J. Am. Chem. Soc.*, 1991, **113**, 6690; (b) E. Vedejs and M. Gingras, *J. Am. Chem. Soc.*, 1994, **116**, 579; (c) M. Diederich and U. Nubbemeyer, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1026; (d) U. M. Lindstro and P. Somfi, *J. Am. Chem. Soc.*, 1997, **119**, 8385; (e) A. Sudau and U. Nubbemeyer, *Angew. Chem. Int. Ed.*, 1998, **37**, 1140; (f) See also ref. 1.
6. (a) A. M. Martin Castro, *Chem. Rev.*, 2004, **104**, 2939; (b) H. Ito and T. Taguchi, *Chem. Soc. Rev.*, 1999, **28**, 43; (b) M. Hiersemann and L. Abraham, *Eur. J. Org. Chem.*, 2002, 1461; (c) Y. H. Chai, S. P. Hong, H. A. Lindsay, C. McFarland, and M. C. MacIntosh, *Tetrahedron*, 2002, **58**, 2905; (d) U. Nubbemeyer, *Synthesis*, 2003, 961.
7. Other synthetic approaches involving Stille coupling of the corresponding enol phosphate followed by chemoselective reduction of the resulting enamine were also investigated with little success.
8. (a) F. N. Tebbe, G. W. Parshall, and G. S. Reddy, *J. Am. Chem. Soc.*, 1978, **100**, 3611; (b) S. H. Pine, R. Zahler, D. A. Evans, and R. H. Grubbs, *J. Am. Chem. Soc.*, 1980, **102**, 3270.
9. The major byproduct of the Tebbe reaction in the 7-membered lactam **4b** was olefin-isomerized product **10**.




**10**

10. Pd(0)-Catalyzed allylic cyclization of **11** gave the desired vinyl-substituted product **12** in satisfactory yield; however, selective debenzylation in the presence of olefin proved to be of problem.




**11** **12**

11. P. Beak and W. K. Lee, *J. Org. Chem.*, 1993, **58**, 1109.
12. (a) S. M. So, L. Mui, H. Kim, and J. Chin, *Acc. Chem. Res.*, 2012, **45**, 1345 and references therein; (b) D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, 1975, **97**, 4765; (c) H. Baumann and P. Chen, *Helv. Chim. Acta*, 2001, **84**, 124; (d) T. Tsunoda, S. Tatsuki, Y. Shiraishi, M. Akasaka, and S. Ito, *Tetrahedron Lett.*, 1993, **34**, 3297; (e) R. M. Coates, B. D. Rogers, S. J. Hobbs, D. R. Peck, and D. P. Curran, *J. Am. Chem. Soc.*, 1987, **109**, 1160.
13. Conventional ring-closing reaction of amides via metathesis generates medium- to macrolactams suffers from a resulting mixture of *E/Z*-internal olefins, often *Z*-isomer dominates: for example, (a) T. Matsumura, M. Akiba, S. Arai, M. Nakagawa, and A. Nishida, *Tetrahedron Lett.*, 2007, **48**, 1265; (b) S. Dandapani, J. T. Lowe, E. Comer, and L. A. Marcaurelle, *J. Org. Chem.*, 2011, **76**, 8042; (c) H. M. Hassan, *Chem. Commun.*, 2010, **46**, 9100.