Aza-[3,3]-Claisen Enolate Rearrangement in Vinylaziridines: Stereoselective Synthesis of Mono-, Di-, and Trisubstituted Seven-Membered Lactams

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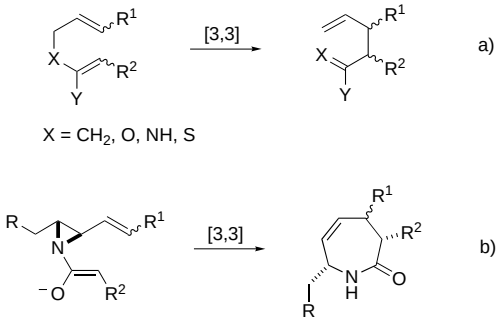
Dedicated to the memory of Tomas Jarevång

Abstract: Several 2,3-disubstituted vinylaziridines have been *N*-acylated and subjected to LiHMDS in THF at $-78\,^{\circ}C$. Upon warming to room temperature, the resulting amide enolates underwent a highly stereoselective [3,3]-sigmatropic rearrangement to give mono-, di-, and trisubstituted seven-membered lactams in good yields. The scope and limitations of the process have been investigated by using variously substituted vinylaziridines. A kinetically controlled process proceeding through a six-membered boatlike transition state assembly has been invoked to explain the stereochemical outcome of the reaction.

Keywords: C–C coupling · lactams · rearrangements · vinylaziridines

Introduction

Efficient methods for the stereoselective formation of C–C bonds are of importance in organic synthesis. For this reason, much effort has been, and still is, devoted to the development of such methodology. Frequently, these methods involve a reaction that proceeds through a cyclic transition state in a concerted bond reorganization, that is, a pericyclic reaction, which usually allows for accurate prediction of the stereochemical outcome of the reaction. Two well-known examples of this type are the sigmatropic [2,3]-Wittig[1–3] and [3,3]-Claisen rearrangements,[4–8] of which many variants have been explored. Those with an oxygen in the migrating σ-bond are the most frequently investigated, whereas the aza- or thia-analogues have received less attention. The rearrangement of allylic ester enolates (Scheme 1a, X = O, Y = O^-) known as the Ireland–Claisen rearrangement has found broad application in modern synthetic organic chemistry as a result of its relatively mild reaction conditions and the high degree of control it offers over the relative stereochemistry in the product. However, as with the regular Claisen rearrangement, the aza-analogue, that is, the amide enolate (Scheme 1a, X = N, Y = O^-), has received considerably less attention.



Scheme 1. a) Prototype of a [3,3]-rearrangement; b) Aza-[3,3]-Claisen enolate rearrangement of *N*-acyl vinylaziridines.

2-Vinylaziridines have been found useful for the synthesis of diverse compounds such as aza-heterocycles,[9–12] β-lactams,[13, 14] dipeptide isosteres,[15, 16] and sphingosines.[17] Analogously to vinylcyclopropanes and vinylepoxides, the inherent ring strain associated with vinylaziridines provides a thermodynamic driving force for efficient ring-opening or ring-expansion reactions.[18, 19] Vinylaziridines have mainly been associated with conjugate addition of organocuprates to produce allylamines,[20] sigmatropic [1,3]-rearrangements into pyrroline derivatives,[21] and aza-[2,3]-Wittig rearrangement of *N*-alkyl vinylaziridines to give di- and trisubstituted tetrahydropyridines.[10, 22–25] *N*-Alkyl vinylaziridines have also been shown to be viable substrates for a thermal [1,5]-hydrogen shift to give allylic amines.[26–28] Despite these

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Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the author. Experimental details of the acylation and rearrangement of vinylaziridines **3a–f** into lactams **5b–n** and of the preparation of vinylaziridines **3d** and **3f** (18 pages).

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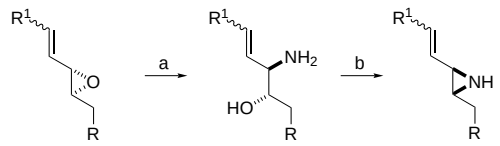
efforts, the more widespread use of vinylaziridines as intermediates in organic synthesis is hampered by the lack of efficient and general routes for their preparation. In an effort to alleviate this limitation, we recently developed a general and enantioselective synthesis of *N*–H vinylaziridines with the prospect that they would function as precursors for all types of *N*-substituted vinylaziridines (Scheme 2).[29]



1a R=OBn, R^1=H **2a-e** **3a-e**
b R=CH_2Ph, R^1=H
c R=H, R^1=(*E*)-CH_2OBn
d R=OBn, R^1=(*E*)-CH_3
e R=OBn, R^1=(*Z*)-CH_3 (*E*:*Z* 1:13)

Scheme 2. Reagents and conditions: a) NH_4OH, microwave irradiation, 30 W, 8 min, 86–93%; b) DEAD, Ph_3P, PhMe, Δ, 50–61%.

Vinylepoxides can easily be obtained in high enantiomeric excess by asymmetric epoxidation of allylic alcohols followed by a Swern–Wittig olefination procedure,[30] or by the recently disclosed regio- and enantioselective epoxidation of conjugated dienes.[31] Aminolysis of vinylepoxides **1a–e** by using a microwave-assisted protocol resulted in a stereospecific and highly regioselective ring opening to give amino alcohols **2a–e** (86–93%).[32] The subsequent ring closure of the amino alcohols **2a–e** by using standard Mitsunobu conditions [PPh_3, diethyl azodicarboxylate (DEAD)] afforded vinylaziridines **3a–e** (50–61%) with their configuration inverted compared with the starting vinylepoxides.[29] The added flexibility of this approach, compared with separate synthetic endeavors for each individual vinylaziridine target, should hopefully serve to establish vinylaziridines as useful intermediates in organic synthesis beyond their present scope. In a desire to increase the synthetic potential of vinylaziridines even further, we developed, and recently communicated, an aza-[3,3]-Claisen rearrangement in *N*-acyl vinylaziridines as a novel method to seven-membered lactams (Scheme 1b).[33] Although there are some elegant examples of stereocontrolled construction of seven-membered nitrogen heterocycles,[34–38] this is still an underdeveloped area in organic synthesis when one considers the potential these compounds have displayed as scaffolds for conformationally constrained peptidomimetics in drug design[39, 40] and as intermediates in the synthesis of natural products.[34]

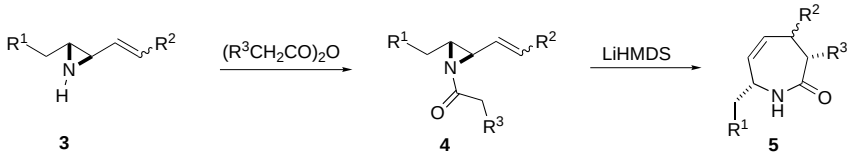
Herein is described the preparation of a number of *N*-acyl vinylaziridines and their base-induced ring expansions into seven-membered unsaturated lactams. Scope and limitations have been investigated by varying the substituents on the vinylaziridine.

Results and Discussion

Synthesis of *N*-acyl vinylaziridines: The *N*-acyl vinylaziridines **4a–4n** used in the present study were synthesized by treating the corresponding *N*–H vinylaziridines with acetic, propionic, benzyloxyacetic, *N*-Boc glycine, or *N*-Boc alanine anhydride in the presence of Et_3N and a catalytic amount of 4-dimethylaminopyridine (DMAP, Table 1). The *N*-acyl vinylaziridines were unstable to silica gel purification and were used directly in the subsequent Claisen rearrangements. Accordingly, all yields of tetrahydroazepinones reported herein refer to such two-step sequences.

Rearrangement in 2,3-disubstituted vinylaziridines: Variously substituted vinylaziridines have been prepared as described above and examined as substrates for the projected aza-[3,3]-

Table 1. Acylation and [3,3]-rearrangement of vinylaziridines **3a–e**.[a]



3 **4** **5**

	N–H Vinylaziridine	R^1	R^2	R^3	*N*-Acyl Vinylaziridine[b]	Lactam	R^2	Yield [%][c]
1	**3a**	OBn	H	H	**4a**	**5a**	H	83
2	**3b**	CH_2Ph	H	H	**4b**	**5b**	H	83
3	**3b**	CH_2Ph	H	CH_3	**4c**	**5c**[d]	H	85
4	**3b**	CH_2Ph	H	OBn	**4d**	**5d**	H	81
5	**3b**	CH_2Ph	H	NHBoc	**4e**	**5e**	H	76
6	**3c**	H	(*E*)-CH_2OBn	H	**4f**	**5f**	α-CH_2OBn	73
7	**3d**	OBn	(*E*)-CH_3	H	**4g**	**5g**	α-CH_3	71
8	**3e**	OBn	(*Z*)-CH_3 (*E*:*Z* 1:13)	H	**4h**	**5h**	β-CH_3[e]	73
9	**3c**	H	(*E*)-CH_2OBn	CH_3	**4i**	**5i**	α-CH_2OBn	60
10	**3d**	OBn	(*E*)-CH_3	CH_3	**4j**	**5j**	α-CH_3	64
11	**3e**	OBn	(*Z*)-CH_3 (*E*:*Z* 1:13)	CH_3	**4k**	**5k**	β-CH_3[e]	61
12	**3c**	H	(*E*)-CH_2OBn	NHBoc	**4l**	**5l**	α-CH_2OBn	63

[a] All acylation reactions were run in CH_2Cl_2 at −78 °C with 1.1 equiv anhydride, 2 equiv Et_3N, and DMAP (cat.). The rearrangements were performed in THF at −78 °C → RT using 2 equiv LiHMDS. [b] The crude *N*-acyl vinylaziridines were not subjected to further purification after work up. [c] Isolated yields after SiO_2 chromatography using 2–3% *i*$PrNH_2$ in the eluent. The yields refer to two steps from the corresponding *N*–H vinylaziridine. [d] (α/β 22:1). [e] The isomeric ratio of **4h** (*E*:*Z* 1:13) was retained in the rearrangement.

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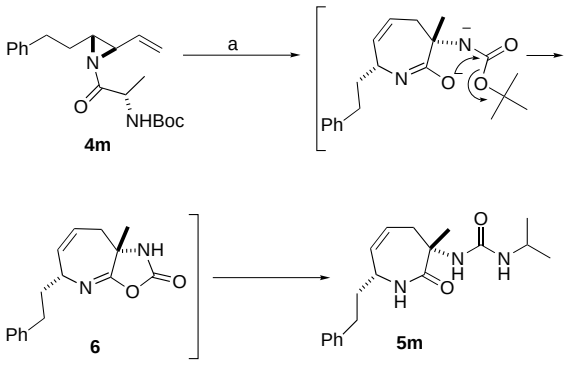
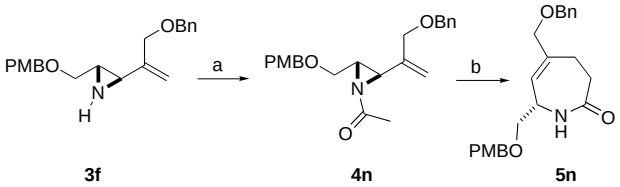
Claisen enolate rearrangement. The results from the rearrangements of all *trans*-2,3-disubstituted vinylaziridines are collected in Table 1. When *N*-acetyl vinylaziridine **4a** was treated with LiHMDS (lithium bis(trimethylsilyl)amide) in THF at $-78\,^{\circ}C$ and warmed to room temperature, the C7-substituted lactam **5a** was formed in 83% yield over two steps from *N*–H vinylaziridine **3a** (Table 1, entry 1). Repetition of the procedure with **4b** gave **5b** in equally good yield (83%, entry 2).

Much of the synthetic utility of the Claisen rearrangement arises from its high degree of control over the stereochemical outcome. To investigate whether this would apply to the present rearrangements, several more highly substituted vinylaziridines (**4c–4l**) were synthesized, which after ring expansion should give 3,7-di-, 4,7-di-, and 3,4,7-trisubstituted lactams. Indeed, deprotonation of **4c**, the α-benzyloxy derivative **4d**, and the glycine amide **4e**, which are known to give preferentially the corresponding (*Z*)-enolates,[41, 42] and rearrangement gave the *cis*-3,7-disubstituted tetrahydroazepinones **5c** (85%, α/β 22:1, entry 3), **5d** (81%, entry 4), and **5e** (76%, entry 5), respectively. The last two products gave only single detectable diastereomers. Similarly, (*Z*)-alkenyl derivative **4h** and (*E*)-alkenyl derivatives **4f** and **4g** were rearranged into *trans*-4,7-disubstituted lactam **5h** (73%, entry 8) and *cis*-4,7-disubstituted lactams **5f** (73%, entry 6) and **5g** (71%, entry 7), respectively, as single detectable diastereomers in each case. This indicates that the stereochemistry of the olefin is retained throughout the reaction. Trisubstituted lactams were obtained by rearranging vinylaziridines **4i** through to **4l** (entries 9–12). Once again only single diastereomers were detected, although the yields dropped to around 60%.

When vinylaziridine **4m**, obtained by acylating **3b** with the anhydride of *N*-Boc-L-alanine, was subjected to standard rearrangement conditions, the result was only unchanged starting material. However, refluxing for one hour following deprotonation at $-78\,^{\circ}C$ gave the rearranged product in 58% yield, surprisingly not as the *tert*-butyl carbamate but as the urea derivative **5m** (Scheme 3). Standard isolation procedure for all the lactams described herein includes doping the solvent used for chromatography with 2–3% iPrNH$_2$ to avoid minor decomposition and accompanying lower yields. It is assumed that the unexpected formation of **5m** is most likely to be the result of intramolecular nucleophilic attack by the anionic amide oxygen on the carbamate, and this leads to the formation of the 5,7-fused bicyclic oxazolidinone **6**, which should be susceptible to nucleophilic ring opening by iPrNH$_2$ on silica gel. In line with this, rearrangement of **4m** followed by flash chromatography and excluding the addition of iPrNH$_2$ to the eluent gave only unidentifiable material and none of **5m**. Finally, the 5,7-disubstituted lactam **5n** was obtained in 85% yield by acetylation and rearrangement of *N*–H vinylaziridine **3f** (Scheme 4).



Scheme 3. Reagents and conditions: LiHMDS (2 equiv), THF, $-78\,^{\circ}C \rightarrow \Delta$; SiO_2 chromatography (EtOAc/pentane 8:1 + 3% iPrNH$_2$), 58%.



Scheme 4. Reagents and conditions: a) 1.1 equiv Ac_2O, 2 equiv Et_3N, cat. DMAP, CH_2Cl_2, $-78\,^{\circ}C$; b) 2 equiv LiHMDS, THF, $-78\,^{\circ}C \rightarrow$ RT, 85% for two steps.

Conformational studies: Molecular modeling[43] indicated that the seven-membered ring preferably adopts a conformation, in which the β-C3 proton and the C7 methine proton are in close proximity. This was confirmed by NOE experiments, and revealed significant NOE's between these two protons in all of the lactams. This corroborates the *cis*-relation between the substituents of the 3,7-disubstituted lactams **5c–e** (Figure 1). Determination of relative configuration of the 4,7-disubstituted and the 3,4,7-trisubstituted lactams also required additional inspection of the relevant proton couplings. For the 3,3,7-trisubstituted lactam **5m**, strong NOEs were observed between the protons of the β-C3 methyl and the C7 proton.

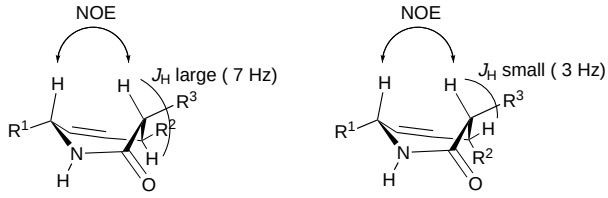


Figure 1. Conformational analysis of the seven-membered unsaturated lactams.

Mechanistic considerations: The high selectivities observed in the [3,3]-rearrangements of this investigation suggest that the reaction follows a highly ordered, probably concerted reaction pathway, in which the relative stereochemistry of the substrate is effectively communicated to the product, as is often described for other rearrangements of this kind. All of the results from the rearrangements of vinylaziridines **4** can be rationalized by assuming that the reaction proceeds through the six-membered boatlike transition state assembly **7** (Scheme 5). It should be noted that boatlike transition states have been invoked previously to explain the outcome in Claisen-type rearrangements of certain cyclic substrates, while the acyclic cases are generally believed to involve

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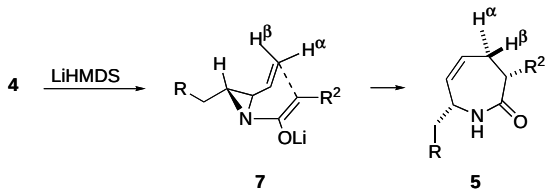
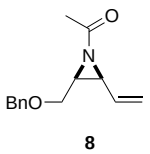


Scheme 5. Proposed transition state structure (**7**).

chairlike transition state structures.[6, 7] The main features of **7** are the olefin and enolate moieties, which are *cis*-related in order to facilitate bond formation. Both these groups adopt an *endo* conformation, which projects over the three-membered ring. Bond formation between the enolate and the alkene and concomitant opening of the aziridine give the observed products. This model correctly accounts for i) the formation of α-C3 isomers **5c–e** and **i–l** when deprotonating and rearranging **4c–e** and **i–l**; the sound assumption is that (*Z*)-enolates are involved in each case,[41, 42] and ii) the stereochemical outcome when using the alkenyl derivatives **4f–l**. It is also presumed that the ease with which these transformations occur is a consequence of the considerable relief of ring strain when one goes from a three- to a seven-membered ring.[18] Some additional support for the above was obtained when we tried to rearrange vinylaziridine **8**. Deprotonation followed by warming to room temperature and quenching with D_2O gave completely deuterated starting material (10%), along with decomposed material; this indicated that for steric reasons the enolate derived from **8** is not capable of attaining the required transition state structure to participate in the [3,3]-rearrangement.



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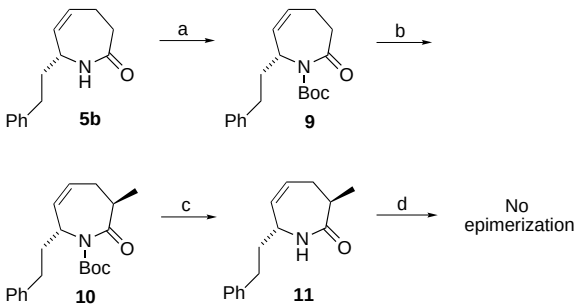
In order to verify that the observed high selectivities of the rearrangements were actually the result of a kinetically controlled process and not due to a base-promoted equilibration of an initially formed mixture, the β-C3 methyl substituted lactam **11**, the C3-epimer of **5c**, was synthesized. Starting from lactam **5b**, deprotonation using BuLi followed by quenching with Boc-anhydride gave *N*-Boc protected lactam **9** in 95% yield (Scheme 6).[44] Methylation was best



Scheme 6. Reagents and conditions: a) BuLi (1.1 equiv), $(Boc)_2O$ (2 equiv), THF, $-78\,^{\circ}C \rightarrow 0\,^{\circ}C$, 95%; b) LiHMDS (2 equiv), MeI (2 equiv), THF, $-78\,^{\circ}C \rightarrow 0\,^{\circ}C$, 76%; c) trifluoroacetic acid (TFA, 1.5 equiv), CH_2Cl_2, RT, 82%; d) LiHMDS (2 equiv), THF, $-78\,^{\circ}C \rightarrow$ RT; phosphate buffer, recovered **11**.

effected using LiHMDS and methyl iodide in THF, and this furnished, as a single diastereomer, the *trans*-3,7-disubstituted lactam **10** in 76% yield. The reason for the high diastereoselectivity observed in this alkylation is not clear but may be rationalized by assuming that the enolate derived from **9** will adopt a conformation, in which the *N*-Boc moiety will be oriented on the α-face of the ring to minimize unfavorable allylic strain with the C7-substituent. This would favor electrophilic attack from the less hindered β-face. Standard deprotection of **10** then gave amide **11** in 82% yield. This simple synthetic route towards the epimer of **5c** is gratifying as it complements the [3,3]-rearrangement to provide access to both α- and β-C3-substituted lactams. When **11** was subjected to rearrangement conditions, standard isolation procedures gave only unchanged starting material. Apparently, epimerization does not occur under these conditions, which indicates that the reaction is kinetically controlled and strongly supports the initial assumption that our postulated transition state assembly can be used to predict the stereochemical outcome of these rearrangements.

In conclusion, we have shown that *N*-acylated vinylaziridines are excellent substrates in the base-induced aza-[3,3]-Claisen enolate rearrangement to furnish, highly stereoselectively, mono-, di-, or trisubstituted seven-membered lactams. A kinetically controlled, concerted reaction pathway, proceeding through a six-membered boatlike transition state assembly, is proposed and supported by experimental results. This reaction should serve to make vinylaziridines more attractive as precursors for the synthesis of larger *N*-heterocycles. Work is now in progress to apply this reaction for the synthesis of natural products and peptidomimetics.

Experimental Section

General: For general experimental details, see Supporting Information.

Typical procedure for the *N*-acylation and rearrangement of vinylaziridines 3a–f

(*7R*)-*7-Benzyloxymethyl-1,3,4,7-tetrahydroazepin-2-one* (***5a***): Ac_2O (0.011 mL, 0.117 mmol) was added to a solution of vinylaziridine **3a** (0.0201 g, 0.106 mmol), Et_3N (0.030 mL, 0.212 mmol), and a few crystals of DMAP in CH_2Cl_2 (2 mL) at $-78\,^{\circ}C$. After 20 min, the reaction was quenched with phosphate buffer (pH 7), diluted with Et_2O, and washed with water, $NaHCO_3$ (sat. aq), and brine. Drying (Na_2SO_4) and concentration gave the crude *N*-acyl vinylaziridine **4a**, which was taken on to the next step without further purification. ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.39–7.24 (m, 5H), 5.54–5.28 (m, 3H), 4.59 (s, 2H), 3.71 (dd, $J = 10.9$, 4.1 Hz, 1H), 3.67 (dd, $J = 10.9$, 4.6 Hz, 1H), 3.08 (dd, $J = 7.6$, 2.7 Hz, 1H), 2.75 (ddd, $J = 4.5$, 2.8, 2.7 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 181.5$, 138.1, 134.3, 132.6, 132.5, 128.9, 128.3, 120.5, 73.4, 68.4, 43.3, 42.9, 24.7; IR (neat): $\tilde{\nu} = 3400$, 3060, 3030, 2980, 2920, 2860, 1680 cm^{-1}.

The crude aziridine **4a** from above was dissolved in THF (1 mL) and added to a solution of LiHMDS (1.0 M in hexanes; 0.236 mL, 0.236 mmol) in THF (1 mL) at $-78\,^{\circ}C$. After 20 min, the cooling bath was removed, and after an additional 0.5 h at RT, the reaction was quenched with phosphate buffer (pH 7). The mixture was diluted with Et_2O and then washed with water and brine. Drying (Na_2SO_4), concentration, and flash chromatography (heptane/EtOAc 2:1, 3% $iPrNH_2$) furnished lactam **5a** (0.0202 g, 83%). $[\alpha]_D = -9.5$ ($c = 1.31$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.40$–7.29 (m, 5H), 6.14 (br s, 1H), 5.79 (m, 1H), 5.42 (dd, $J = 11.6$, 2.4 Hz, 1H), 4.56 (s, 2H), 4.39 (br m, 1H), 3.52 (dd, $J = 9.5$, 4.4 Hz, 1H), 3.43 (dd, $J = 9.5$, 8.5 Hz, 1H), 2.90 (ddd, $J = 5.1$, 4.1, 3.1 Hz, 1H), 2.52–2.30 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 176.5$, 137.6, 131.9, 129.0, 128.5, 128.3, 126.6, 73.7,

72.2, 50.3, 34.3, 25.0; IR (neat): $\tilde{\nu}$ = 3360, 2910, 2860, 1660 cm^{-1}; HRMS (CI+): calculated for $C_{14}H_{18}NO_2$ $[M+H]^+$: 232.1337; found: 232.1335.

(7*R*)-1-*N*-*tert*-Butylcarbonate-7-phenethyl-1,3,4,7-tetrahydroazepin-2-one (9): BuLi (1.6 M in hexanes, 0.314 mL, 0.502 mmol) was added to a solution of lactam **5b** (0.090 g, 0.418 mmol) in THF (5 mL) at −78 °C. After 10 min, $(Boc)_2O$ (0.115 mL, 0.502 mmol) was added. The mixture was allowed to attain −45 °C over 2 h, after which the reaction was quenched with NH_4Cl (sat. aq). The mixture was poured into Et_2O and water. The organic phase was washed with water, $NaHCO_3$ (sat. aq), and brine, sequentially. Drying (Na_2SO_4) and removal of the solvent at reduced pressure furnished the spectroscopically pure lactam **9** (0.125 g, 95%). $[\alpha]_D$ = −127.1 (c = 0.96 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.16 (m, 5H), 5.82 (m, 1H), 5.72 (m, 1H), 4.87 (q, J = 7.0 Hz, 1H), 2.91 (m, 1H), 2.72 (m, 2H), 2.48 (m, 2H), 2.24 (m, 1H), 2.11 (m, 1H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.4, 141.2, 129.9, 128.7, 128.7, 128.5, 126.3, 83.2, 55.0, 39.3, 38.4, 33.5, 28.4, 24.5; IR ($CDCl_3$): $\tilde{\nu}$ = 3210, 2910, 2860, 1700, 1670 cm^{-1}; HRMS (CI+): calculated for $C_{19}H_{26}NO_3$ $[M+H]^+$: 316.1913; found: 316.1895.

(3*R*,7*R*)-1-*N*-*tert*-Butylcarbonate-3-methyl-7-phenethyl-1,3,4,7-tetrahydroazepin-2-one (10): LiHMDS (1.0 M in hexanes, 0.057 mL, 0.057 mmol) was added to a solution of lactam **9** (0.015 g, 0.048 mmol) in THF (2 mL) at −78 °C. After 25 min, MeI (0.009 mL, 0.144 mmol) was added at −50 °C. The reaction mixture was allowed to attain RT, and after 4 h at RT, NH_4Cl (sat. aq) was added. The mixture was poured into Et_2O and water. The organic phase was washed with water and brine, sequentially. Drying (Na_2SO_4) and removal of the solvent at reduced pressure furnished the crude lactam **10** as a single diastereomer. Purification by flash column chromatography (pentane/EtOAc 25:1 → 15:1) afforded pure lactam **10** (0.012 g, 76%). $[\alpha]_D$ = −100.4 (c = 0.56 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.16 (m, 5H), 5.77 (m, 2H), 4.88 (m, 1H), 2.98 (m, 1H), 2.73 (m, 2H), 2.37–2.24 (m, 2H), 2.14 (m, 2H), 2.10 (dd, J = 8.0, 1.1 Hz, 1H), 1.51 (s, 9H), 1.20 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 154.3, 141.0, 129.5, 128.4, 128.3, 128.1, 126.0, 82.7, 55.1, 40.4, 38.9, 33.3, 33.1, 28.1, 17.5; IR ($CDCl_3$): $\tilde{\nu}$ = 3220, 2930, 2910, 2860, 1690, 1670 cm^{-1}; HRMS (CI+): calculated for $C_{20}H_{28}NO_3$ $[M+H]^+$: 330.2069; found: 330.2065.

(3*R*,7*R*)-3-Methyl-7-phenethyl-1,3,4,7-tetrahydroazepin-2-one (11): Trifluoroacetic acid (0.006 mL, 0.072 mmol) was added to a solution of lactam **10** (0.012 g, 0.036 mmol) in CH_2Cl_2 (2 mL) at RT. The solution was stirred overnight, after which it was poured into Et_2O and water. The organic phase was washed with NaOH (0.5 M), water, and brine, sequentially. Drying (Na_2SO_4) and removal of the solvent at reduced pressure furnished the crude lactam. Purification by flash column chromatography (heptane/EtOAc 4:1, 1% iPrNH$_2$) afforded pure lactam **11** (0.0068 g, 82%). $[\alpha]_D$ = −44.7 (c = 0.42 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.16 (m, 5H), 6.04 (brs, 1H), 5.77 (m, 1H), 5.62 (ddt, J = 11.8, 6.0, 2.2 Hz, 1H), 3.61 (m, 1H), 2.96–2.62 (m, 3H), 2.20 (m, 2H), 2.06 (m, 2H), 1.19 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.5, 128.8, 128.5, 128.2, 126.2, 51.8, 38.4, 37.9, 32.9, 32.5, 16.8; IR ($CDCl_3$): $\tilde{\nu}$ = 3210, 2910, 2860, 1670 cm^{-1}; HRMS (CI+): calculated for $C_{15}H_{20}NO$ $[M+H]^+$: 230.1545; found: 230.1550.

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