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Synthesis of nitrogen-containing heterocycles using exo- and endo-selective radical cyclizations onto enamides

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Abstract—The effect of positional change of the carbonyl group of enamides on Bu₃SnH-mediated alkyl radical cyclization leading to five-, six-, seven-, and eight-membered nitrogen-containing heterocycles was examined. A 5-exo cyclization is generally preferred over a 6-endo ring closure in systems having an alkyl radical center on the enamide-acyl side chain, whereas enamides having an alkyl radical center opposite to the acyl side chain predominantly gave 6-endo cyclization products. These results suggest that the exo or endo selectivity of radical cyclization onto the alkenic bond of enamides can be controlled by positional change of the carbonyl group. For an understanding of these selectivities, heat of formation for each transition state was calculated. 6-Endo-selective radical cyclization was applied to the radical cascade, enabling a concise synthesis of a cylindricine skeleton. A 7- or 8-endo alkyl radical cyclization, however, predominated over a corresponding 6- or 7-exo ring closure regardless of the positional change of the carbonyl group of enamides.

1. Introduction

In recent years, radical cyclization has emerged as a valuable tool for the construction of carbo- and heterocyclic compounds, including natural products.¹ It has been recognized that a 5-exo cyclization is generally preferred over a 6-endo ring closure in systems having an
alkenic bond at the 5-position relative to the radical center. For example, enamide 1, upon treatment with Bu₃SnH in the presence of azobis(cyclohexanecarbonitrile) (ACN), exclusively gave the 5-exo cyclization product 2 (Scheme 1).²

Formation of 2 was of particular interest since the primary alkyl radical 3 was formed from 1 as an intermediate, though 6-endo cyclization of 1 might produce the more stable secondary α-acylamino radical 4. We previously reported, however, that similar treatment of enamide 5 exclusively gave the 6-endo cyclization product 6 (Scheme 1).³ We also found that enamide 7 predominantly gave the 6-exo cyclization product 8, whereas enamide 10 afforded the 7-endo cyclization product 11 (Scheme 2).⁴ These results strongly suggest that exo and endo selectivities of radical cyclization onto the alkenic bond of enamides can be controlled by positional change of the carbonyl group.
In this paper, we describe the effect of positional change of the carbonyl group of enamides on the mode of Bu$_3$SnH-mediated alkyl radical cyclization leading to five-, six-, seven-, and eight-membered nitrogen-containing heterocycles. An application of the 6-endo-selective cyclization to a concise synthesis of a cylindricine skeleton is also described.$^5$

2. Results and discussion

2.1. 5-Exo versus 6-endo alkyl radical cyclizations onto enamide

Condensation of butylamine and acetaldehyde followed by treatment of the resulting imine with acryloyl chloride and successive treatment with diphenyl diselenide/sodium borohydride gave enamide 12 (Scheme 3). Treatment of enamide 12 with Bu$_3$SnH in the presence of ACN in boiling toluene resulted in alkyl radical cyclization of enamide 12 to afford the 5-exo cyclization product $^6$13 in 78% yield. On the other hand, similar treatment of enamide 14, prepared from 3-(phenylseleno)propylamine and acetaldehyde, gave the 6-endo cyclization product $^7$15 (61%) along with the 5-exo cyclization product $^8$16 (29%). Similar treatment of enamide 17 exclusively afforded the 5-exo cyclization product 18, whereas enamide 19 gave the 6-endo cyclization product $^9$20 (73%) as a 1.5:1 mixture of trans and cis-isomers, along with a small quantity of the 5-exo cyclization product 21 (15%). $^{13}$C NMR spectra of 18 and 21 showed the presence of a quaternary carbon atom at 64.0 and 66.3 ppm, respectively. These results clearly indicated that the mode of alkyl radical cyclization of enamides could be altered by changing the position of the carbonyl group of the enamides as in the cases of compounds 1 and 5.
Enamide 22, which was prepared from the corresponding ethyl ester, underwent acyl radical cyclization to afford also the 6-endo cyclization product 23 (97%) as a 1:1.5 mixture of trans and cis isomers.¹⁰

### 2.2. Calculation of heat of formation for transition state

For a better understanding of cyclization modes of 12, 14, 17, and 19, heat of formation for each transition state (TS) was calculated by using 6-31G*.¹¹ First, alkyl radical cyclization of model radical A was computed for the exclusive formation of 5-exo compound 13 from enamide 12 (Fig. 1). TS B was estimated to be more stable than TS C by ca. 4 kcal/mol, probably because TS B forms an ideal trajectory angle for radical approach to the double bond.
The planarity of the amide bond makes TS C a half-chair form which may result in considerable strain (see Supplementary data). The reason for the exclusive formation of 5-exo cyclization product 18 from 17 may be similar to that for the formation of 13. Calculation of TSs for cyclization of model radical D revealed that TS E for 5-exo cyclization is 3.38 kcal/mol more stable than is TS F for 6-endo cyclization.

\[
\begin{align*}
\Delta E &= +4.04 \text{ kcal/mol} \\
\Delta E &= 0.00 \text{ kcal/mol}
\end{align*}
\]

\[
\begin{align*}
\alpha &= 95.5^\circ \\
\alpha &= 109.3^\circ
\end{align*}
\]

Since the energy difference between TS H and TS J is only ca 0.3 kcal/mol, both 5-exo cyclization product 16 and 6-endo cyclization product 15 can be formed by cyclization of radical G (Fig. 2). In contrast to TS C, TS J (and also K) providing 15 is a chair-type transition state. The predominance of 15 might be partially due to the contribution of thermodynamic control (stabilities of product radicals).\textsuperscript{11c} The product radical J’ was calculated to be ca 39 kcal/mol more stable than TS J, whereas radical H’ was estimated to be only ca 31 kcal/mol more stable than H.
Calculation of TSs M-P for cyclization of radical L generated from 19 was also conducted (Fig. 3). Among them, TS O giving 6-endo cyclization product 20 exhibited the lowest heat of formation, and this supports the main formation of the 6-endo product 20. Perhaps owing to non-bonded interaction, the trajectory angles in M and N are different from ideal ones. For the formation of 5-exo cyclization product 21, the entropy effect might contribute to the distribution of products.
2.3. Synthesis of cylindricine skeleton using endo-selective cyclizations

The radical cascade consisting of 6-endo-trig and 5-endo-trig cyclizations was next examined. Treatment of enamide 24, prepared by bromination of the corresponding alcohol, with Bu$_3$SnH/ACN afforded the cis-fused tricyclic compound 25 in 30% yield (Scheme 4). The structure of 25 was confirmed by an X-ray crystallographic analysis of the picrate 26 (CCDC 262989) prepared by reduction of 25 with borane. Enamide 27, which was prepared by the corresponding ethyl ester, also gave the cis-fused compound 28 in 37% yield, the structure of which was again confirmed by an X-ray crystallographic analysis (CCDC 262990). Compound 28 is a basic structural element of cylindricines, which cause mortality in a brine shrimp bioassay.
The stereochemical outcome of the formation of the cis-fused compounds 25 and 28 from 24 and 27, respectively, can be explained by assuming their transition state for the cyclizations. As depicted in Figure 4, two transition states Q and R may be considered for the final step (5-endo-trig) of the radical cascade. The A ring of Q which provides 25 and 28 is a chair form and that of R leading to the trans-fused isomers 29 and 30 is a boat form. The 5-endo-trig cyclization may proceed through transition state Q, in which the A ring has a more favorable chair form, to give the observed cis-fused compound 25 or 28. Indeed, calculation of TS Q and R (transition state geometry by using 3-21G* followed by single point calculation by 6-31G*) revealed that TS Q is 5.89 kcal/mol more stable than is TS R.
2.4. **6-Exo versus 7-endo and 7-exo versus 8-endo alkyl radical cyclizations onto enamide**

Treatment of enamide 31 with Bu₃SnH/ACN afforded the 7-endo alkyl radical cyclization product 32 in 77% yield as a 1:1 mixture of trans and cis stereoisomers (Scheme 5). No expected 6-exo cyclization product was obtained. On the other hand, similar treatment of enamide 34 afforded the expected 7-endo cyclization product 35 in 73% yield as a 1:5.7 mixture of trans and cis stereoisomers.¹⁵

We further examined the mode of radical cyclization of enamides 37 and 40. Enamide 37 afforded the 8-endo cyclization product 38 (11%) along with the simple reduction product 39
(46%) (Scheme 6). No 7-exo cyclization product was formed.\textsuperscript{16} Enamide 40 gave the 8-endo cyclization product 41, but in low yield (7%) along with a considerable amount of the simple reduction product 42 (84%).\textsuperscript{17} Exo and endo selectivities were no longer observed for the alkyl radical cyclization of enamides 31, 34, 37 and 40 having an alkenic bond at the 6 or 7-position relative to the radical center. This was probably associated with an increase in the entropy effect.

\begin{center}
\textbf{Scheme 6.}
\end{center}

The aryl radical cyclization of enamide 7 gave the 6-exo cyclization product 8 in a high selectivity with reduction of the entropy effect (Scheme 2), and therefore the cyclization of 43 was examined in the hope that this compound might result in the selective formation of a 7-exo cyclization product. Enamide 43 was prepared by treatment of \textit{N}-ethyl-\textit{N}-[2-(phenylthio)ethyl]-\textit{o}-bromophenylpropionamide with \textit{m}-chloroperbenzoic acid (\textit{mCPBA}) followed by thermolysis of the resulting sulfoxide. Treatment of 43 with \textit{Bu}_3\textit{SnH}/ACN afforded the expected 7-exo cyclization product 44, but in low yield (6%) along with the 8-endo product 45 (5%) (Scheme 7).
3. Conclusions

We revealed that the 5-exo and 6-endo selectivity for alkyl radical cyclization onto the alkenic bond of enamide could be controlled by positional change of the carbonyl group. Calculation of heat of formation for each transition state (TS) supported these observations. 6-Endo-selective cyclization was applied to the radical cascade involving 5-endo trig cyclization, giving a concise synthesis of a cylindricine skeleton. A 7- or 8-endo alkyl radical cyclization predominated over a corresponding 6- or 7-exo cyclization regardless of the positional change of the carbonyl group of enamide. This was probably due to an increase in the entropy effect. An application of the endo-selective cyclization to the radical cascade would be highly promising in natural products synthesis. The results will be reported in due course.

4. Experimental

4.1. General.

Melting points are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrophotometer for solutions in CHCl₃. ¹H NMR and ¹³C NMR spectra were measured on a JEOL EX 500 (500 MHz) or a JEOL JNM-EX 270 (270 MHz) spectrometer. Chemical shifts (δ) quoted are relative to tetramethylsilane. High resolution mass spectra (HRMS) were obtained with a JEOL JMS-SX-102A mass spectrometer. Column chromatography was carried out on silica gel 60N (Kanto Kagaku Co., Ltd., spherical, neutral, 63–210 μm) under pressure.

4.1.1. 3-Bromo-N-cyclohex-1-en-1-yl-N-ethylpropanamide (17). To a solution of
cyclohexanone (785 mg, 8.00 mmol) in toluene (5 mL) was bubbled ethylamine at -78 °C for 5 min, and the mixture was heated in sealed tube at 110 °C for 2.5 h. After excess ethylamine was removed under reduced pressure, THF (10 mL), NaHCO₃ (1.00 g, 12.0 mmol) and 3-bromopropionyl chloride (1.37 g, 8.00 mmol) were added to the residue at 0 °C, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with water and extracted with AcOEt. The organic phase was washed brine, dried (MgSO₄), and concentrated. The residue was chromatographed on silica gel (benzene/Et₂O, 6:1) to give 17 (95.0 mg, 5%) as a colorless oil: IR (CHCl₃) ν 1635 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 1.11 (3H, t, J = 7.1 Hz), 1.57-1.66 (2H, m), 1.71-1.79 (2H, m), 2.05-2.19 (4H, m), 2.85 (2H, t, J = 6.9 Hz), 3.35-3.55 (2H, m), 3.64 (2H, t, J = 6.9 Hz), 5.61-5.64 (1H, m); ¹³C NMR (67.8 MHz, CDCl₃) δ 13.2, 21.42, 22.7, 24.7, 28.11, 28.13, 36.7, 40.3, 128.0, 137.8, 168.6. Anal. Calcd for C₁₁H₁₈BrNO: C, 50.78; H, 6.97; N, 5.38. Found: C, 50.91; H, 7.16; N, 5.56.


To a boiling solution of 17 (90.0 mg, 0.346 mmol) in toluene (25 mL) was added dropwise a solution of Bu₃SnH (151 mg, 0.519 mmol) and ACN (17.0 mg, 0.0692 mmol) in toluene (25 mL) over 3 h and the mixture was further heated at reflux for 1 h. After evaporation of the solvent, the residue was chromatographed on silica gel containing KF (10%) (hexane/AcOEt, 2:1) to give 18 (66.0 mg, 100%) as a colorless oil: IR (CHCl₃) ν 1665 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 1.03-1.13 (1H, m), 1.15 (3H, t, J = 7.3 Hz), 1.25-1.76 (9H, m), 1.89 (2H, t, J = 8.1 Hz), 2.34 (2H, t, J = 8.1 Hz), 3.19 (2H, q, J = 7.3 Hz); ¹³C NMR (67.8 MHz, CDCl₃) δ 15.3, 22.9, 25.0, 29.0, 29.3, 33.9, 35.3, 64.0, 174.3; HRMS calcd for C₁₁H₁₉NO 181.1467, Found: 181.1471.

4.1.3. N-(3-Bromopropyl)-N-cyclohex-1-en-1-ylacetamide (19). A mixture of 3-(tert-butyldimethylsilyloxy)propylamine (2.50 g, 13.2 mmol) and cyclohexanone (1.30 g, 13.2 mmol) in benzene (30 mL) was heated under reflux with azeotropic removal of water for 1.5 h. Triethylamine (2.40 g, 23.8 mmol) and acetyl chloride (1.55 g, 19.8 mmol) were added at 0 °C, and the mixture was stirred at room temperature for 20 min. The reaction mixture was washed with brine, dried (MgSO₄), and concentrated. THF (50 mL) was added to the residue, a 1.0 M solution of tetrabutylammonium fluoride in THF (16 mL, 15.8 mmol) was
added to this solution, and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water and extracted with EtOAc, and the organic layer was washed with brine, dried (MgSO₄) and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to give N-cyclohex-1-en-1-yl-N-(3-hydroxypropyl)acetamide (1.40 g, 54%) as a colorless oil: IR (CHCl₃) ν 1625 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 1.57-1.81 (6H, m), 2.05 (3H, s), 2.07-2.17 (4H, m), 3.52-3.56 (4H, m), 4.12 (1H, br), 5.56-5.58 (1H, m); ¹³C NMR (67.8 MHz, CDCl₃) δ 21.26, 21.33, 22.6, 24.6, 27.4, 30.4, 41.2, 58.0, 127.8, 138.6, 171.4. Anal. Calcd for C₁₁H₁₉NO₂•½H₂O: C, 65.77; H, 9.73; N, 6.97. Found: C, 65.79; H, 9.88; N, 6.98.

To a solution of N-cyclohex-1-en-1-yl-N-(3-hydroxypropyl)acetamide (500 mg, 2.53 mmol) and triethylamine (617 mg, 6.08 mmol) in toluene (10 mL) was added a solution of methanesulfonyl chloride (348 mg, 3.04 mmol) in toluene (10 mL) at 0 °C, and the mixture was stirred at the same temperature for 1 h. The reaction mixture was washed with brine, dried (MgSO₄), and concentrated. DMF (10 mL) and LiBr (2.20 g, 25.3 mmol) were added to the residue and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with water and extracted with Et₂O. The organic layer was washed with brine, dried (MgSO₄), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 4:1) to give 19 (392 mg, 60%) as a colorless oil: IR (CHCl₃) ν 1680 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 1.57-1.65 (2H, m), 1.71-1.79 (2H, m), 2.01 (3H, s), 2.61-2.73 (2H, m), 3.44 (2H, t, J = 6.6 Hz); ¹³C NMR (67.8 MHz, CDCl₃) δ 23.0, 24.5, 25.3, 25.5, 33.2, 36.3, 49.9, 66.3.

4.1.4. 1-Acetyldecahydroquinoline (20) and 1-acetyl-1-azaspiro[4.5]decane (21).

Following the general procedure, a boiling solution of 19 (150 mg, 0.577 mmol) in toluene (40 mL) was treated with a solution of Bu₃SnH (249 mg, 0.865 mmol) and ACN (28.0 mg, 0.115 mmol) in toluene (40 mL). After work-up, the residue was chromatographed on silica gel containing KF (10%) (hexane/AcOEt, 4:1). The first eluent gave 21 (15.3 mg, 15%) as a colorless needles, mp 95-96 °C (hexane): IR (CHCl₃) ν 1625 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 1.23-1.33 (4H, m), 1.57-1.91 (8H, m), 2.01 (3H, s), 2.61-2.73 (2H, m), 3.44 (2H, t, J = 6.6 Hz); ¹³C NMR (67.8 MHz, CDCl₃) δ 23.0, 24.5, 25.3, 25.5, 33.2, 36.3, 49.9, 66.3,
The second eluent gave a mixture of two stereoisomers (trans/cis = 1.5:1) of 20 (76.5 mg, 73%) as a colorless oil: IR (CHCl$_3$) $\nu$ 1620 cm$^{-1}$; $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 1.00-1.89 [(12 + 2/5)H, m], 2.05-2.12 (3/5H, m), 2.07 (3H x 4/5, s), 2.10 (3H x 1/5, s), 2.57 (1/5H, td, $J$ = 13.3, 2.6 Hz), 3.04-3.33 [(1 + 2/5)H, m], 3.53-3.74 (1H, m), 4.47-4.53 (1/5H, m), 4.63 (1/5H, dt, $J$ = 12.5, 3.8 Hz); HRMS calcd for C$_{11}$H$_{19}$NO 181.1467, found: 181.1475.

$^1$H NMR spectral data of 20 were identical with those reported in the literature.

### 4.1.5. Se-Phenyl N-acryloyl-3-(cyclohex-1-en-1-ylamino)selenopropanoate (27).

Using a procedure similar to that described for the preparation of 19, $\beta$-alanine ethyl ester hydrochloride (3.00 g, 19.5 mmol) was condensed with cyclohexanone (9.47 g, 97.7 mmol) and the mixture was treated with acryloyl chloride (2.67 g, 29.3 mmol) and triethylamine (3.56 g, 35.2 mmol). After work-up, the crude material was chromatographed (hexane/AcOEt, 6:1) to give ethyl N-acryloyl-3-(cyclohex-1-en-1-ylamino)propanoate (2.30 g, 47%) as a colorless oil: IR (CHCl$_3$) $\nu$ 1730, 1645, 1615 cm$^{-1}$; $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 1.22 (3H, t, $J$ = 7.3 Hz), 1.53-1.61 (2H, m), 1.67-1.75 (2H, m), 1.99-2.10 (4H, m), 2.55 (2H, t, $J$ = 7.3 Hz), 3.73 (2H, t, $J$ = 7.3 Hz), 4.09 (2H, q, $J$ = 7.3 Hz), 5.53-5.57 (2H, m), 6.29 (1H, dd, $J$ = 16.8, 3.0 Hz), 6.41 (1H, dd, $J$ = 16.8, 9.6 Hz); $^{13}$C NMR (67.8 MHz, CDCl$_3$) $\delta$ 14.1, 21.4, 22.6, 24.8, 28.0, 33.0, 41.3, 60.4, 127.0, 128.37, 128.43, 137.8, 165.1, 171.7. Anal. Calcd for C$_{14}$H$_{21}$NO$_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.85; H, 8.52; N, 5.19.

Ethyl $N$-acryloyl-3-($N$-cyclohex-1-en-1-ylamino)propanoate (1.13 g, 4.48 mmol) was hydrolyzed with NaOH (2 mL), and the resulting carboxylic acid was treated with sodium hydride (60% oil suspension, 214 mg, 5.37 mmol) to give sodium salt of the corresponding carboxylic acid. Diphenyl diselenide (2.80 g, 8.96 mmol) and tributylphosphine (1.81 g, 8.96 mmol) in THF (20 mL) were added to the solution at room temperature, and the mixture was stirred for 3 h.

To the reaction mixture was added sodium benzoate (1.94 g, 13.4 mmol), and the mixture was further stirred for 10 min. Phenylselenenyl chloride (1.72 g, 13.4 mmol) was added to the solution and the mixture was stirred for 1 h. The reaction mixture was diluted with a saturated aqueous solution of NaHCO$_3$ and extracted with AcOEt. The organic phase was washed with brine, dried (MgSO$_4$) and concentrated. The residue was
chromatographed on silica gel (benzene/Et₂O, 6:1) to give 27 (641 mg, 40%) as a colorless oil: IR (CHCl₃) ν 1715, 1645, 1610 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 1.55-1.64 (2H, m), 1.68-1.77 (2H, m) 2.07-2.17 (4H, m), 3.02 (2H, t, J = 7.3 Hz), 3.80 (2H, t, J = 7.3 Hz), 5.58-5.63 (2H, m), 6.34 (1H, dd, J = 16.8, 3.0 Hz), 6.44 (1H, dd, J = 16.8, 9.2 Hz), 7.33-7.43 (3H, m), 7.46-7.52 (2H, m); ¹³C NMR (67.8 MHz, CDCl₃) δ 21.3, 22.6, 24.8, 28.0, 41.3, 45.8, 126.1, 127.3, 128.2, 128.8, 129.3, 135.7, 137.7, 165.3, 198.5; HRMS (FAB) calcd for C₁₈H₂₂NO₂Se (MH⁺) 364.0816, found 364.0822.


Following the general procedure, a boiling solution of 27 (530 mg, 1.46 mmol) in toluene (70 mL) was treated with a solution of Bu₃SnH (649 mg, 2.20 mmol) and ACN (71.5 mg, 0.292 mmol) in toluene (70 mL). After work-up, the residue was chromatographed on silica gel containing KF (10%) (hexane/AcOEt, 1:1) to give 28 (113 mg, 37%) as colorless crystals, mp 106-107 °C (hexane): IR (CHCl₃) ν 1715, 1680 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 0.76-1.88 (2H, m), 0.92 (1H, tt, J = 13.4, 3.7 Hz), 1.02 (1H, td, J = 13.4, 3.7 Hz), 1.17-1.28 (3H, m), 1.31-1.42 (3H, m), 1.83 (1H, td, J = 14.0 and 7.9 Hz), 1.91 (1H, dd, J = 14.7, 4.3 Hz), 2.03 (2H, t, J = 7.3 Hz), 2.10-2.15 (1H, m), 2.49 (1H, td, 13.4 and 3.7 Hz), 4.26 (1H, ddd, 13.4, 7.9, 1.8 Hz); ¹³C NMR (67.8 MHz, CDCl₃) δ 20.5, 21.7, 22.8, 24.7, 29.0, 29.4, 32.4, 35.0, 39.7, 55.2, 64.6, 173.1, 207.3. Anal. Calcd for C₁₂H₁₇NO₂: C, 69.54, 8.27, N, 6.76. Found: C, 69.31, H, 8.42, N, 6.61.

4.1.7. 1-Ethyldecahydro-2H-1-benzazepin-2-one (32) and N-cyclohex-1-en-1-yl-N-ethylbutanamide (33). Following the general procedure, a boiling solution of 31 (180 mg, 0.346 mmol) in toluene (30 mL) was treated with a solution of Bu₃SnH (286 mg, 0.984 mmol) and ACN (32.0 mg, 0.131 mmol) in toluene (30 mL). After work-up, the residue was chromatographed on silica gel containing KF (10%) (hexane/AcOEt, 1:1). The first eluent gave 33 (30.0 mg, 23%) as a colorless oil: IR (CHCl₃) ν 1630 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.4 Hz), 1.15 (3H, t, J = 7.3 Hz), 1.60-1.78 (6H, m), 2.07-2.18 (4H, m), 2.22 (2H, t, J = 7.3 Hz), 3.42-3.63 (2H, m), 5.57-5.59 (1H, m); ¹³C NMR (67.8 MHz, CDCl₃) δ 13.4, 13.9, 19.2, 21.6, 22.8, 24.7, 28.3, 35.5, 40.2, 127.1, 138.5, 172.0; HRMS calcd for C₁₂H₂₁NO 195.1623, Found: 195.1622. The second eluent gave 32...
(98.0 mg, 77%) as a colorless oil: IR (CHCl₃) ν 1615 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.12 (3H x 1/2, t, J = 7.1 Hz), 1.13 (3H x 1/2, t, J = 7.1 Hz), 1.25-2.04 (13H, m), 2.42 (1/2H, t, J = 13.9 Hz), 2.53 (1/2H, ddd, J = 14.6, 10.0, 3.9 Hz), 2.58 (1/2H, dd, J = 14.6, 7.3 Hz), 2.75 (1/2H, ddd, J = 15.1, 9.8, 5.1 Hz), 3.18 (1/2H, dt, J = 13.0, 3.2 Hz), 3.21 (1/2H, dq, J = 13.9, 7.1 Hz), 3.27 (1/2H, td, J = 11.2, 3.2 Hz), 3.32 (1/2H, dq, J = 13.9, 7.1 Hz), 3.45 (1/2H, dq, J = 13.9, 7.1 Hz), 3.68 (1/2H, dq, J = 13.9, 7.1 Hz); ¹³C NMR (67.8 MHz, CDCl₃) δ 13.4, 14.9, 16.2, 19.8, 23.5, 25.8, 26.1, 26.7, 27.2, 29.5, 29.6, 30.3, 31.0, 34.1, 34.3, 36.2, 38.4, 39.1, 40.4, 44.7, 60.9, 63.2, 173.2, 174.6; HRMS calcd for C₁₂H₂₁NO 195.1623, Found: 195.1629.

4.1.8. (6αR*,10αS*)-1-Ethylodecahydro-1-benzazocin-2(1H)-one (38) and N-cyclohex-1-en-1-yl-N-ethylpentanamide (39). Following the general procedure, a boiling solution of 37 (200 mg, 0.694 mmol) in toluene (30 mL) was treated with a solution of Bu₃SnH (303 mg, 1.04 mmol) and ACN (34.0 mg, 0.139 mmol) in toluene (30 mL). After work-up, the residue was chromatographed on silica gel containing KF (10%) (hexane/AcOEt, 2:1). The first eluent gave 39 (67.0 mg, 46%) as a colorless oil: IR (CHCl₃) ν 1625 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 0.90 (3H, t, J = 7.3 Hz), 1.09 (3H, t, J = 7.3 Hz), 1.31 (2H, sextet, J = 7.3 Hz), 1.57-1.79 (6H, m), 2.06-2.15 (4H, m), 2.24 (2H, t, J = 7.4 Hz), 3.39-3.47 (2H, m), 5.57-5.60 (1H, m); ¹³C NMR (67.8 MHz, CDCl₃) δ 13.4, 13.8, 21.6, 22.5, 22.8, 24.7, 28.1, 28.3, 33.3, 40.2, 127.1, 138.5, 172.4; HRMS calcd for C₁₃H₂₃NO 209.1780, Found: 209.1773.

The second eluent gave 38 (16.0 mg, 11%) as a colorless oil: IR (CHCl₃) ν 1615 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 1.14 (3H, t, J = 7.1 Hz), 1.22-1.94 (15H, m), 2.37 (1H, ddd, J = 13.2, 5.9, 2.0 Hz), 2.61 (1H, td, J = 13.0, 2.5 Hz), 2.97 (1H, dq, J = 13.8, 7.1 Hz), 3.49 (1H, td, J = 10.4, 3.5 Hz), 3.58 (1H, dq, J = 13.8, 7.1 Hz); ¹³C NMR (67.8 MHz, CDCl₃) δ 15.0, 22.3, 25.7, 26.1, 29.4, 30.3, 30.9, 31.2, 35.5, 36.0, 41.2, 59.3, 174.6; HRMS calcd for C₁₃H₂₃NO 209.1780, Found: 209.1776.

4.1.9. 2-Ethyl-1-methyl-1,2,4,5-tetrahydro-3H-2-benzazepin-3-one (44), 3-ethyl-2,3,5,6-tetrahydro-3-benzazocin-4(1H)-one (45) and N-ethenyl-N-ethyl-3-phenylpropanamide (46). Following the general procedure, a boiling solution of 43 (150 mg, 0.531 mmol) in toluene was treated with a solution of Bu₃SnH (232 mg, 0.794 mmol) and ACN (26.0 mg, 0.106 mmol) in toluene. After work-up, the crude
material was chromatographed on silica gel containing KF (10%) (hexane/AcOEt, 1:1). The first eluent gave 46 (86.2 mg, 80%) as a colorless oil. \(^{1}\)H NMR and \(^{13}\)C NMR spectra of 46 showed it to contain two rotamers: IR (CHCl\(_3\)) \(\nu\) 1620, 1665 cm\(^{-1}\); \(^{1}\)H NMR (270 MHz, CDCl\(_3\)) \(\delta\) 1.12 (3 H, t, \(J = 7.1\) Hz), 2.73 (2 H, t, \(J = 7.3\) Hz), 2.99 (2 H, t, \(J = 7.3\) Hz), 3.53 (2H \(x\), q, \(J = 7.1\) Hz), 3.70 (2H \(x\), q, \(J = 7.1\) Hz), 4.31 (3/4H, d, \(J = 9.2\) Hz), 4.42 (1/4H, d, \(J = 9.2\) Hz), 4.46 (1/4H, d, \(J = 15.3\) Hz), 4.48 (3/4H, d, \(J = 15.3\) Hz), 6.74 (3/4H, dd, \(J = 15.3, 9.2\) Hz), 7.20-7.40 (5H, m), 7.45 (1/4 H, dd, \(J = 15.3, 9.2\) Hz); \(^{13}\)C NMR (67.8 MHz, CDCl\(_3\)) \(\delta\) 11.8, 12.8, 21.9, 24.3, 31.0, 33.8, 35.7, 36.7, 93.1, 93.4, 126.1, 128.3, 128.4, 130.8, 132.1, 140.9, 170.3; HRMS calcd for C\(_{13}\)H\(_{17}\)NO 203.1310, found: 203.1303. The second eluent gave 44 (6.0 mg, 6%) as a colorless oil: IR (CHCl\(_3\)) \(\nu\) 1670, 1630 cm\(^{-1}\); \(^{1}\)H NMR (270 MHz, CDCl\(_3\)) \(\delta\) 1.11, 1.13 (total 3 H, t, \(J = 7.1\) Hz), 1.25 (3 H x 9/20, d, \(J = 7.4\) Hz), 1.52 (9/20H, dd, \(J = 6.6, 4.3\) Hz), 1.71 (3 H x 11/20, d, \(J = 7.4\) Hz), 2.54 (11/20H, dd, \(J = 16.8, 8.7\) Hz), 2.74-2.87 (1H, m), 2.93-3.14 [(2 + 11/20)H, m], 3.29-3.42 (11/20H, m), 3.60-3.77[(1 + 9/20)H, m], 4.63 (9/20H, q, \(J = 7.4\) Hz), 7.09-7.37 (4H, m); \(^{13}\)C NMR (67.8 MHz, CDCl\(_3\)) \(\delta\) 12.7, 13.7, 18.6, 23.6, 29.4, 34.9, 35.5, 39.1, 42.8, 46.8, 59.0, 60.7, 126.1, 127.1, 127.3, 128.28, 128.33, 128.4, 128.5, 128.8, 130.6, 137.7, 139.4, 141.8, 173.1, 173.2; HRMS calcd for C\(_{13}\)H\(_{17}\)NO 203.1310, Found: 203.1307. The third eluent gave 45 (5.0 mg, 5%) as colorless oil: IR (CHCl\(_3\)) \(\nu\) 1630 cm\(^{-1}\); \(^{1}\)H NMR (270 MHz, CDCl\(_3\)) \(\delta\) 0.93 (3H, t, \(J = 7.1\) Hz), 2.82-2.88 (2H, m), 2.97-3.08 (2H, m), 3.10 (2H, t, \(J = 6.8\) Hz), 3.14 (2H, q, \(J = 7.1\) Hz), 3.70 (2H, t, \(J = 6.8\) Hz), 7.02-7.31 (4H, m); \(^{13}\)C NMR (67.8 MHz, CDCl\(_3\)) \(\delta\) 12.7, 30.5, 34.7, 37.0, 41.5, 46.2, 126.9, 127.3, 130.1, 130.5, 136.4, 138.5, 172.4; HRMS calcd for C\(_{13}\)H\(_{17}\)NO 203.1310, Found: 203.1304.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:

References and notes


11. For recent studies on the regioselectivity in radical cyclizations, see: (a) Pintér, B.; De


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