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

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 Bu_3SnH-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.

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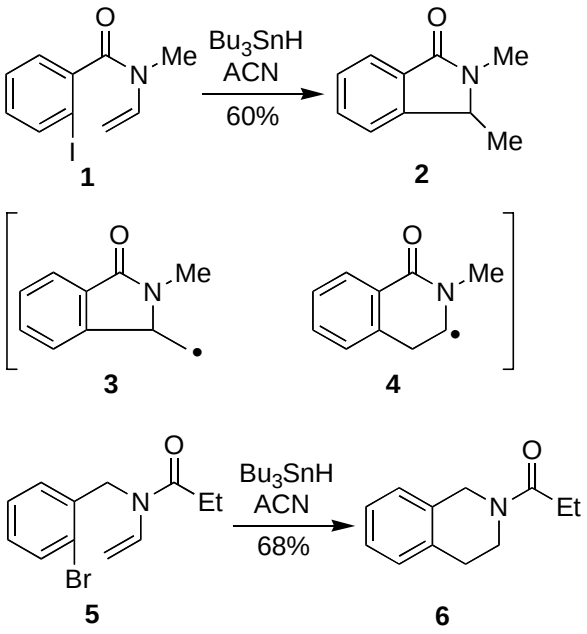
1. Introduction

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

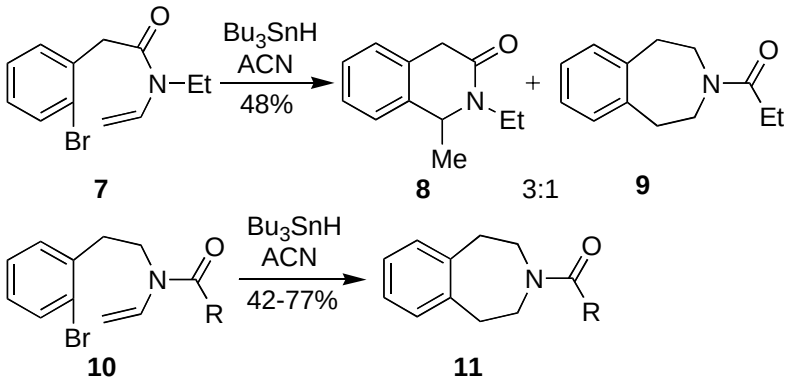
alkenic bond at the 5-position relative to the radical center. For example, enamide **1**, upon treatment with Bu_3SnH in the presence of azobis(cyclohexanecarbonitrile) (ACN), exclusively gave the 5-*exo* cyclization product **2** (Scheme 1).[2]



1 **2** **3** **4** **5** **6**

Scheme 1.

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.



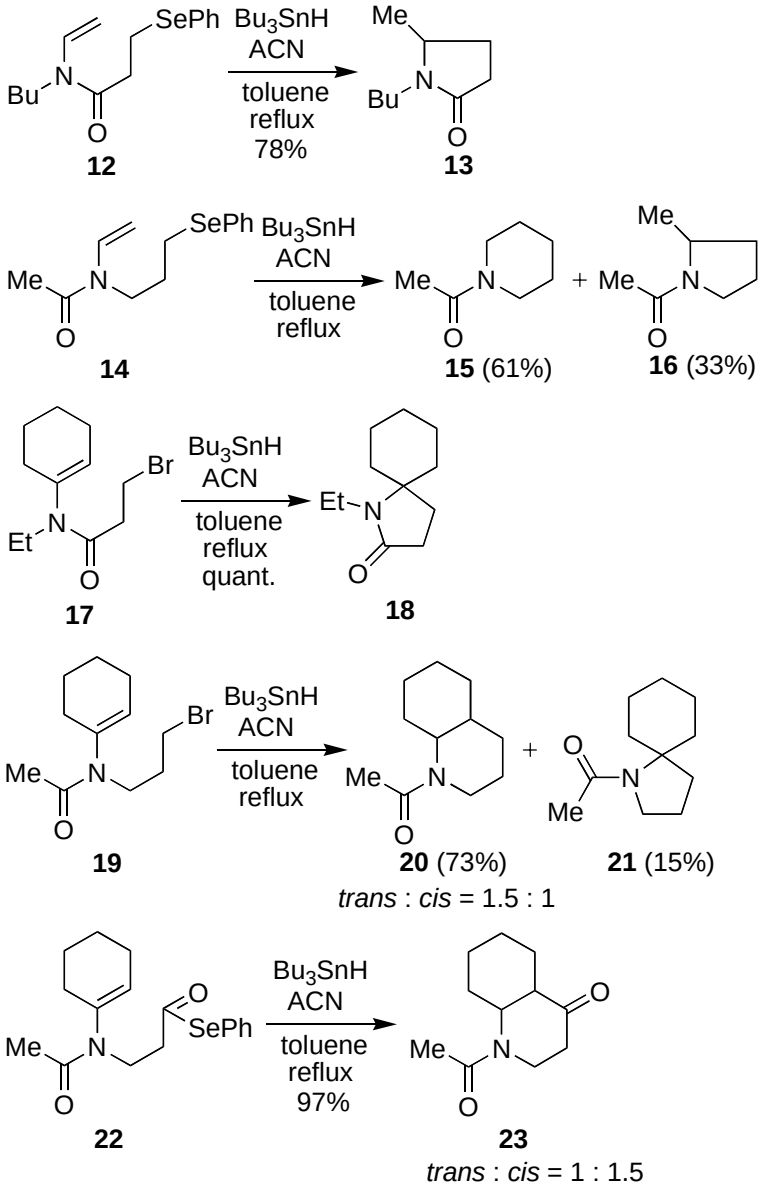
Scheme 2.

In this paper, we describe the effect of positional change of the carbonyl group of enamides on the mode of Bu_3SnH-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_3SnH in the presence of ACN in boiling toluene resulted in alkyl radical cyclization of enamide **12** to afford the 5-*exo* cyclization product **13**[6] 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 **15**[7] (61%) along with the 5-*exo* cyclization product **16**[8] (29%). Similar treatment of enamide **17** exclusively afforded the 5-*exo* cyclization product **18**, whereas enamide **19** gave the 6-*endo* cyclization product **20**[9] (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**.



Scheme 3.

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.

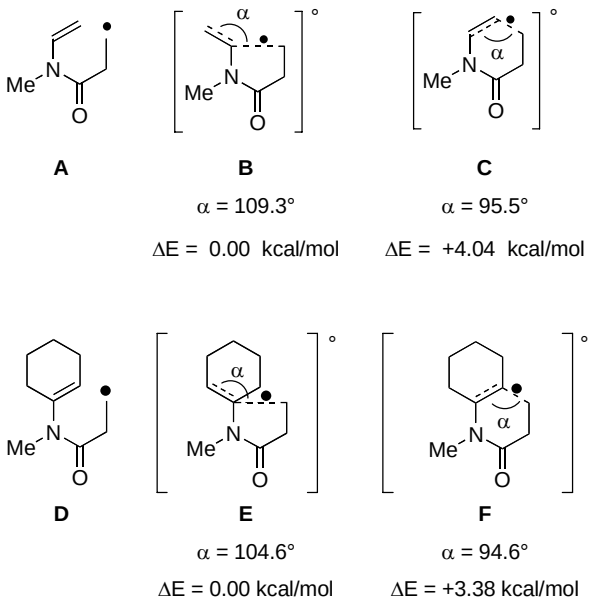


Figure 1.

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).[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**.

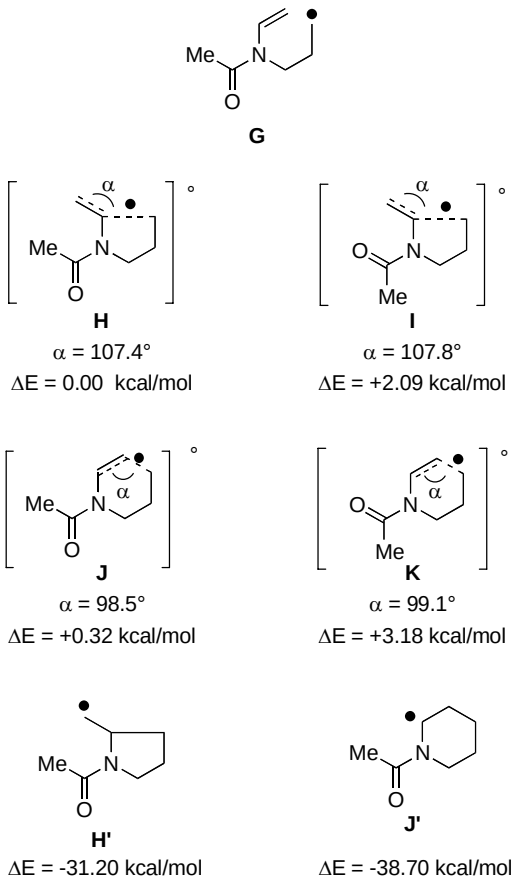


Figure 2.

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.

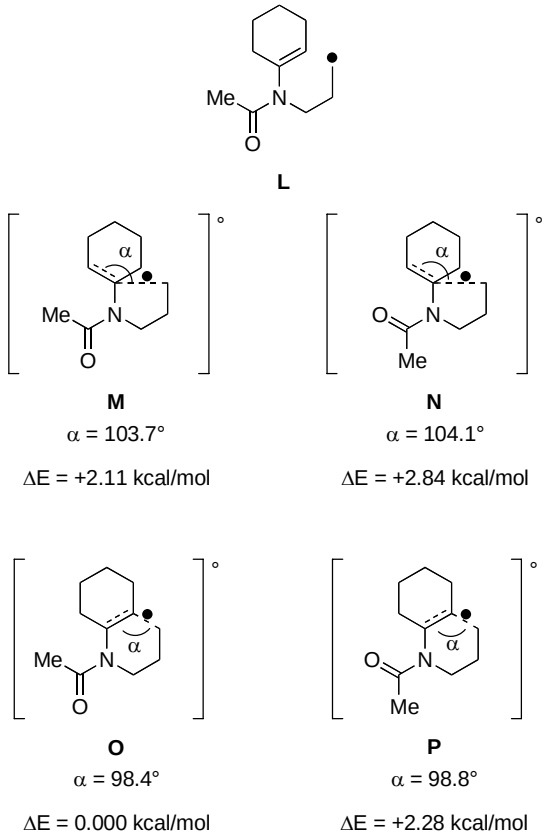
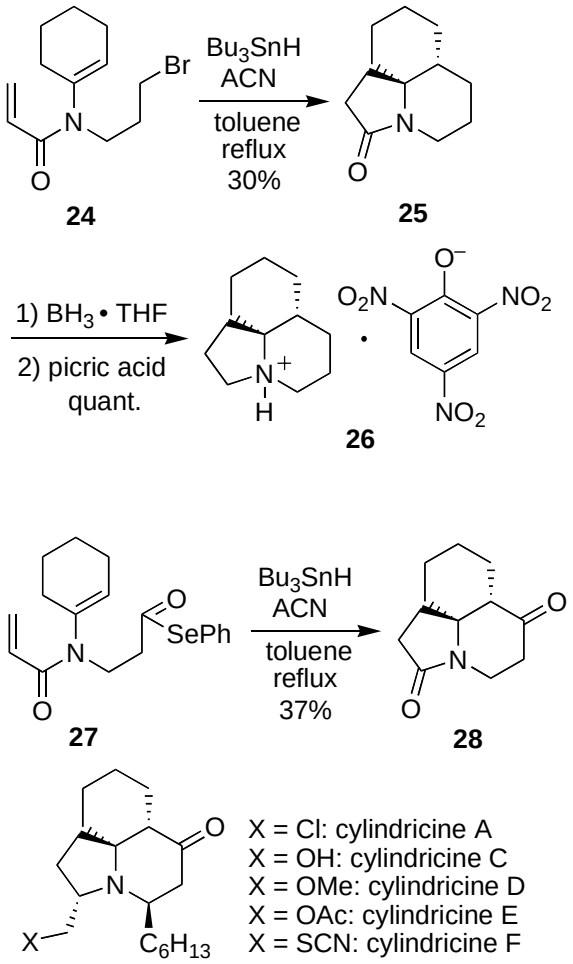


Figure 3.

2.3. Synthesis of cyclindricine skeleton using *endo*-selective cyclizations

The radical cascade consisting of 6-*endo-trig* and *5-endo-trig* cyclizations was next examined.[12] Treatment of enamide **24**, prepared by bromination of the corresponding alcohol, with Bu_3SnH/ACN afforded the *cis*-fused tricyclic compound **25**[13] 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.[14]



Scheme 4.

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**.

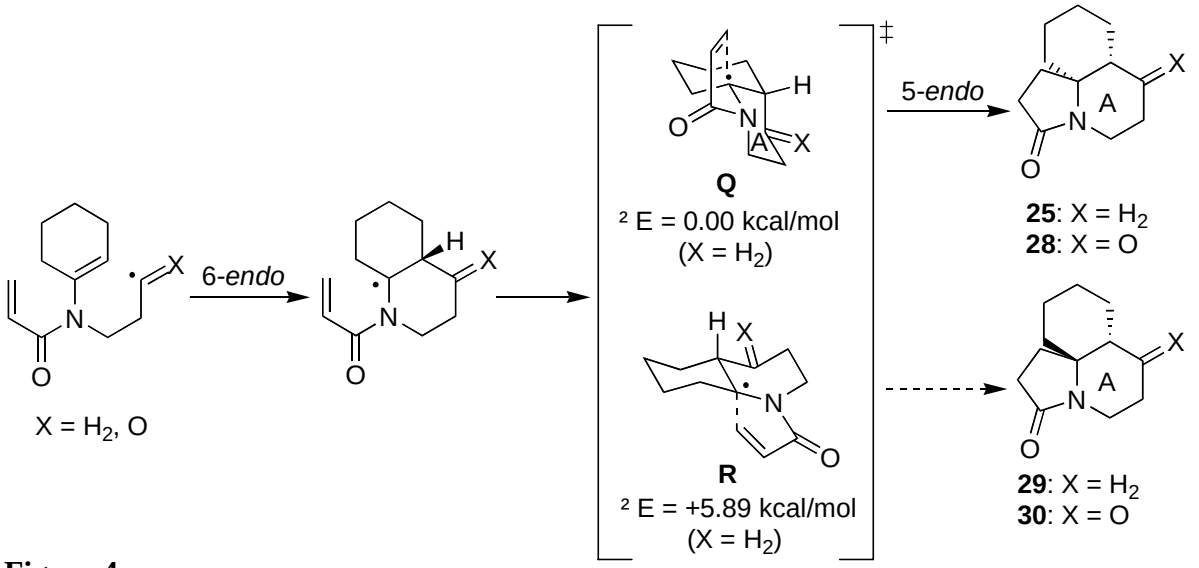
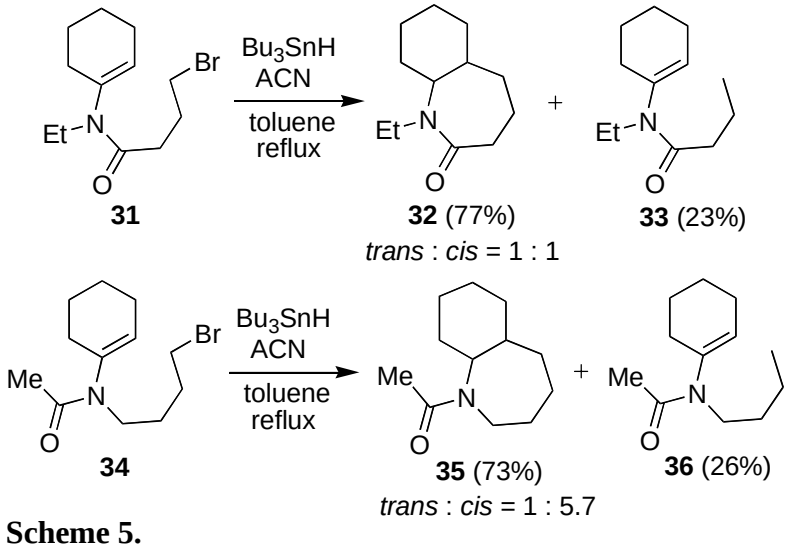


Figure 4.

2.4. 6-*Exo* versus 7-*endo* and 7-*exo* versus 8-*endo* alkyl radical cyclizations onto enamide

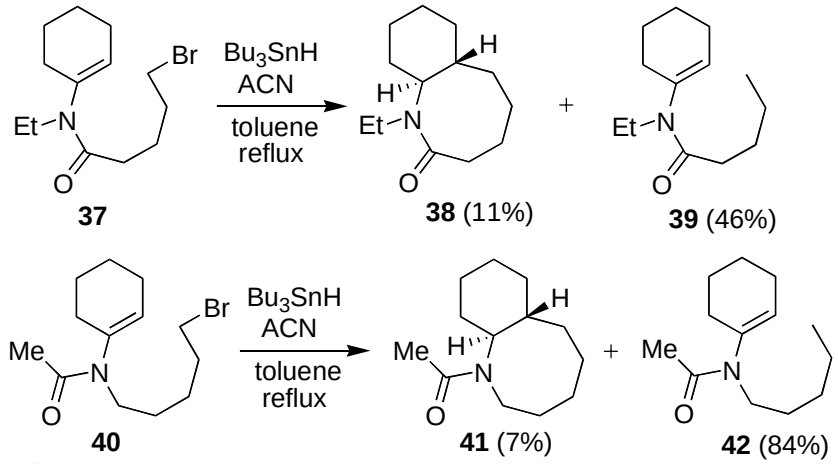
Treatment of enamide **31** with Bu_3SnH/ACN afforded the 7-*endo* alkyl radical cyclization product **32** in 77% yield as a 1:1 mixture of *trans* and *cis* stereoisomers (Scheme 5). No expected 6-*exo* cyclization product was obtained. On the other hand, similar treatment of enamide **34** afforded the expected 7-*endo* cyclization product **35** in 73% yield as a 1:5.7 mixture of *trans* and *cis* stereoisomers.[15]



Scheme 5.

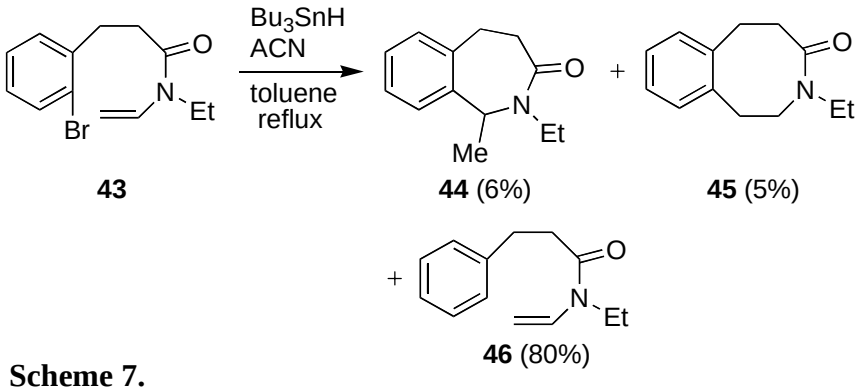
We further examined the mode of radical cyclization of enamides **37** and **40**. Enamide **37** afforded the 8-*endo* cyclization product **38** (11%) along with the simple reduction product **39**

(46%) (Scheme 6). No 7-*exo* cyclization product was formed.[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%).[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.



Scheme 6.

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 *N*-ethyl-*N*-[2-(phenylthio)ethyl]-*o*-bromophenylpropionamide with *m*-chloroperbenzoic acid (*m*CPBA) followed by thermolysis of the resulting sulfoxide. Treatment of **43** with Bu_3SnH/ACN afforded the expected 7-*exo* cyclization product **44**, but in low yield (6%) along with the 8-*endo* product **45** (5%) (Scheme 7).



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 $CHCl_3$. ^1H NMR and ^{13}C 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), $NaHCO_3$ (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 ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (benzene/Et_2O, 6:1) to give **17** (95.0 mg, 5%) as a colorless oil: IR ($CHCl_3$) υ 1635 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 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); ^{13}C NMR (67.8 MHz, $CDCl_3$) 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 $C_{11}H_{18}BrNO$: C, 50.78; H, 6.97; N, 5.38. Found: C, 50.91; H, 7.16; N, 5.56.

4.1.2. 1-Ethyl-1-azaspiro[4.5]decan-2-one (18). General procedure for radical reaction. To a boiling solution of **17** (90.0 mg, 0.346 mmol) in toluene (25 mL) was added dropwise a solution of Bu_3SnH (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%)[18] (hexane/AcOEt, 2:1) to give **18** (66.0 mg, 100%) as a colorless oil: IR ($CHCl_3$) υ 1665 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 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); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 15.3, 22.9, 25.0, 29.0, 29.3, 33.9, 35.3, 64.0, 174.3; HRMS calcd for $C_{11}H_{19}NO$ 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[19] (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 ($MgSO_4$), 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 ($MgSO_4$) 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 ($CHCl_3$) υ 1625 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 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); ^{13}C NMR (67.8 MHz, $CDCl_3$) 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 $C_{11}H_{19}NO_2 \cdot 1/5H_2O$: 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 ($MgSO_4$), 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 Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 4:1) to give **19** (392 mg, 60%) as a colorless oil: IR ($CHCl_3$) υ 1680 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.57-1.65 (2H, m), 1.71-1.79 (2H, m), 2.01 (3H, s), 2.05-2.17 (6H, m), 3.41 (2H, t, *J* = 7.0 Hz), 3.50 (2H, t, *J* = 7.3 Hz), 5.59-5.63 (1 H, m). It was used in the next step without further purification.

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 Bu_3SnH (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 ($CHCl_3$) υ 1625 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 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); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 23.0, 24.5, 25.3, 25.5, 33.2, 36.3, 49.9, 66.3,

169.2; HRMS calcd for $C_{11}H_{19}NO$ 181.1467, found: 181.1475. 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 ($CHCl_3$) υ 1620 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 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: 181.1471. ^1H NMR spectral data of **20** were identical with those reported in the literature.[9]

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**, β-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 ($CHCl_3$) υ 1730, 1645, 1615 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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-ylamimo)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, 5.37mmol) 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.[20] 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/Et_2O, 6:1) to give **27** (641 mg, 40%) as a colorless oil: IR ($CHCl_3$) υ 1715, 1645, 1610 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 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); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.3, 22.6, 24.8, 28.0, 41.3, 45.8, 126.1, 127.3, 128.2, 128.8, 128.9, 129.3, 135.7, 137.7, 165.3, 198.5; HRMS (FAB) calcd for $C_{18}H_{22}NO_2Se$ (MH^+) 364.0816, found 364.0822.

4.1.6. (7a*R,11a*R**)-hexahydro-1*H*-pyrrolo[2,1-j]quinoline-3,7(2*H*,7a*H*)-dione (28).** Following the general procedure, a boiling solution of **27** (530 mg, 1.46 mmol) in toluene (70 mL) was treated with a solution of Bu_3SnH (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 ($CHCl_3$) υ 1715, 1680 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) 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): ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.5, 21.7, 22.3, 29.0, 29.4, 32.4, 35.0, 39.7, 55.2, 64.6, 173.1, 207.3. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54, 8.27, N, 6.76. Found: C, 69.31, H, 8.42, N, 6.61.

4.1.7. 1-Ethyldecahydro-2*H*-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 Bu_3SnH (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 ($CHCl_3$) υ 1630 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 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); ^{13}C NMR (67.8 MHz, $CDCl_3$) 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 $C_{12}H_{21}NO$ 195.1623, Found: 195.1622. The second eluent gave **32**

(98.0 mg, 77%) as a colorless oil: IR ($CHCl_3$) υ 1615 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (67.8 MHz, $CDCl_3$) 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 $C_{12}H_{21}NO$ 195.1623, Found: 195.1629.

4.1.8. (6a*R,10a*S**)-1-Ethyldodecahydro-1-benzazocin-2(1*H*)-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 Bu_3SnH (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 ($CHCl_3$) υ 1625 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 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 (6 H, 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); ^{13}C NMR (67.8 MHz, $CDCl_3$) 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 $C_{13}H_{23}NO$ 209.1780, Found: 209.1773. The second eluent gave **38** (16.0 mg, 11%) as a colorless oil: IR ($CHCl_3$) υ 1615 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 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); ^{13}C NMR (67.8 MHz, $CDCl_3$) 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 $C_{13}H_{23}NO$ 209.1780, Found: 209.1776.

4.1.9. 2-Ethyl-1-methyl-1,2,4,5-tetrahydro-3*H*-2-benzazepin-3-one (44), 3-ethyl-2,3,5,6-tetrahydro-3-benzazocin-4(1*H*)-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 Bu_3SnH (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 ($CHCl_3$) υ 1620, 1665 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 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 1/4, q, *J* = 7.1 Hz), 3.70 (2H x 3/4, 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, $CDCl_3$) δ 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 ($CHCl_3$) υ 1670, 1630 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 ($CHCl_3$) υ 1630 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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

Experimental procedures and compound characterization data for compounds **12-16**, **22-26**, **31**, **34-37** and **40-43**. Calculation for transition states **B-C**, **E-F**, **H-K**, **H'**, **J'** and **M-R**. Supplementary data associated with this article can be found in the online version, at doi:

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