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Stereoselective synthesis of 2-methylenepyrrolizidines by tandem cyclization of *N*-propargylaminyl radicals

Hikaru Hasegawa, Hisanori Senboku, Yoshinori Kajizuka, Kazuhiko Orito and Masao Tokuda*

Laboratory of Organic Synthesis, Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan

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Abstract—Tandem cyclization of *N*-propargylaminyl radicals, generated by N-chlorination of (*E*)-alk-4-enylamines **2a**–**d** and **2f** followed by treatment with tributyltin radical, afforded 2-methylenepyrrolizidines **3a**–**d** and **3f** in a highly stereoselective manner. A similar radical cyclization of (*Z*)-*N*-propargyl-1-methyl-5-phenylpent-4-enylamine (**2e**) gave pyrrolizidine **3b** having the same stereochemistry as that obtained from the *E* isomer **2b**.

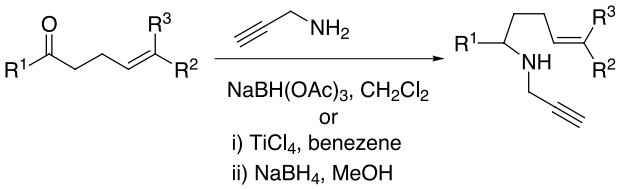
1. Introduction

Tandem radical cyclization has been widely investigated as a readily amenable method for the synthesis of polycarbocyclic as well as polyheterocyclic natural products.[1,2] Although various types of methods have been developed for synthesis of pyrrolizidine,[3] indolizidine[4] and quinolizidine alkaloids,[4] there are a few reports on the one-step synthesis of these bicyclic compounds using tandem radical cyclization.[5] On that account, nitrogen radical cyclization seems to be very useful for the synthesis of nitrogen heterocycles.[6] Especially, aminyl radical cyclizations are more feasible because of their high stereoselectivity,[7] although cyclization of other nitrogen radicals such as aminium[8] and amidyl radicals[9] and that of carbon radicals[10] usually gave a mixture of several stereoisomers. Furthermore, in aminyl radical cyclizations, there are several advantages such as an easy preparation of starting amines and a simple procedure without the use of syringe pump technique.[11] We have already reported an efficient and stereoselective synthesis of 1,2,5-trisubstituted pyrrolizidines by tandem cyclization of *N*-allylaminyl radicals.[12] In this paper, we report a stereoselective synthesis of 2-methylenepyrrolizidines by 5-*exo*, 5-*exo* tandem cyclization of aminyl radicals derived from *N*-propargylalk-4-enylamines.

2. Results and discussion

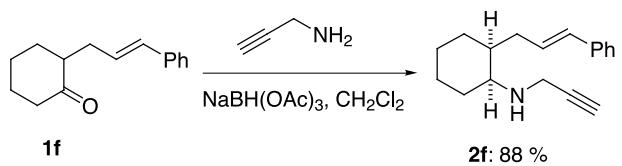
Starting *N*-propargylamines **2a**–**f** for aminyl radical cyclization were prepared according to our previously reported method.[12] Thus, reductive aminations of ketones **1a**,**b** and **1d**–**f** with propargylamine in the presence of $NaBH(OAc)_3$ in CH_2Cl_2[13] gave the corresponding amines **2a**,**b** and **2d**–**f** in 78–89% yields (Schemes 1 and 2). On the other hand, amine **2c** was prepared by the reaction of ketone **1c** with propargylamine in benzene in the presence of $TiCl_4$[14] followed by reduction of the resulting imine with $NaBH_4$ in MeOH (Scheme 1).

In the tandem cyclization of *N*-propargylaminyl radicals,



1a	$R^1 = CH_3$, $R^2 = C_3H_7$, $R^3 = H$	**2a**	89 %
1b	$R^1 = CH_3$, $R^2 = Ph$, $R^3 = H$	**2b**	78 %
1c	$R^1 = Ph$, $R^2 = Ph$, $R^3 = H$	**2c**	82 %
1d	$R^1 = CH_3$, $R^2 = Si(C_2H_5)_3$, $R^3 = H$	**2d**	87 %
1e	$R^1 = CH_3$, $R^2 = H$, $R^3 = Ph$	**2e**	78 %

Scheme 1.



1f **2f**: 88 %

Scheme 2.

Keywords: tandem radical cyclization; aminyl radical; pyrrolizidine; *N*-chloroamine.

* Corresponding author. Tel.: +81-11-706-6599; fax: +81-11-706-6598; e-mail: tokuda@org-mc.eng.hokudai.ac.jp

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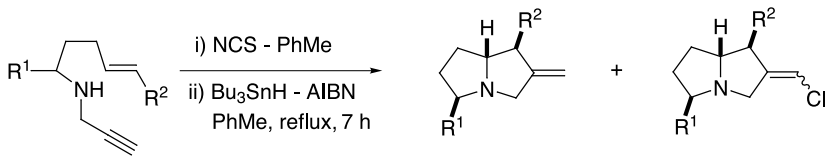


a	$R^1 = CH_3$, $R^2 = C_3H_7$	54 %	4 %
b	$R^1 = CH_3$, $R^2 = Ph$	63 %	6 %
c	$R^1 = Ph$, $R^2 = Ph$	43 %	0
d	$R^1 = CH_3$, $R^2 = Si(C_2H_5)_3$	52 %	0

Scheme 3.

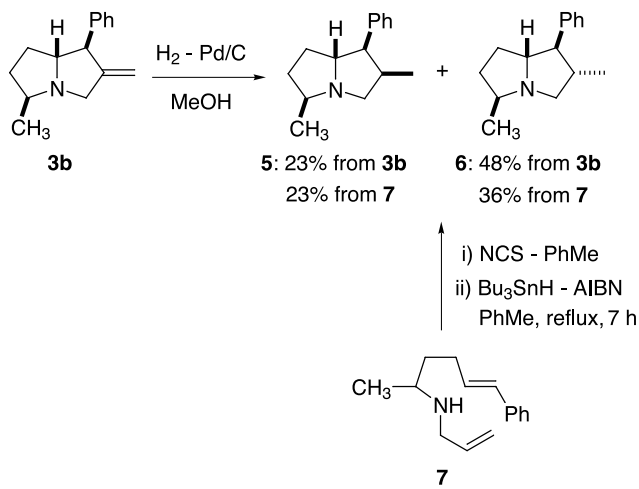
amine **2** was firstly treated with NCS (1.0 equiv.) in toluene to give the corresponding *N*-chloroamine, the precursor of aminyl radical, quantitatively. To this solution were added 1.0 equiv. of Bu_3SnH and catalytic amount of AIBN in one portion, and the solution was heated under reflux for 7 h. Purification of the crude product by preparative TLC (Al_2O_3) gave pyrrolizidines **3a–d** in 43–63% yields, and neither monocyclic pyrrolidine nor the starting amine **2** was obtained (Scheme 3). Atom transferred products **4a** and **4b** were also obtained in low yields in the case of **2a** and **2b**. Alkyl- and silyl-substituted C–C double bonds such as **2a** and **2d** were found to work effectively as an acceptor in the tandem cyclization of aminyl radicals, although phenyl-substituted double bond such as **2b** and **2c** is usually used as an acceptor of aminyl radicals.[5a,b]

The stereochemistry of the products **3** was determined by NOE or NOESY spectra. These spectral data show that all cyclization products **3a–d** have the same stereochemistries and that all of C1- and C5-substituent, and C7a–H in **3** are in *syn* relationships. Furthermore, the stereochemistry of the products was also confirmed by hydrogenation of the product **3**. Hydrogenation of **3b** over 10% Pd/C in methanol gave a mixture of two stereoisomeric pyrrolidines **5** and **6**, which were completely identical with known compounds that were previously provided by tandem radical cyclization of *N*-allylamine **7** in our group (Scheme 4).[12] These results show that both tandem radical cyclizations of *N*-propargylamine **3b** and *N*-allylamine **7** proceed via similar well-regulated transition states. In addition, it should be noted that only one stereoisomer was formed in the tandem radical cyclization of *N*-propargylamines **2a–d**, showing that these two consecutive cyclizations of aminyl radicals take place in completely stereoselective manner.

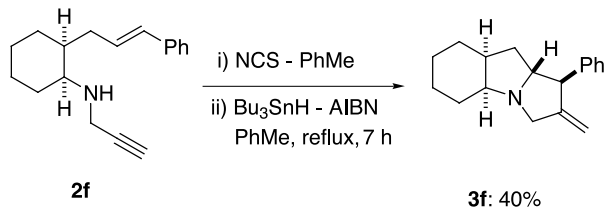
A tricyclic heterocycle was also obtained in one step by the tandem cyclization of *N*-propargylaminyl radical. *cis*-*N*-Propargyl-2-(3-phenyl-2-propenyl)cyclohexylamine (**2f**) was subjected to aminyl radical cyclization in a similar manner as those of **2a–d** to give perhydropyrrolo[1,2-*a*]indole **3f**, as a single diastereomer, in 40% yield together with the recovered starting amine **2f** (20%) (Scheme 5).

We next investigated an effect of the geometry of C–C double bond in the starting amine on the tandem radical cyclization. Aminyl radical cyclization of (*Z*)-alk-4-enylamine **2e** was carried out under the same conditions as those of **2b**. As a result, the radical reaction of **2e** gave the product **3b**, which was completely identical with the product obtained by the radical reaction of **2b** having *E* geometry (Scheme 6).[15]

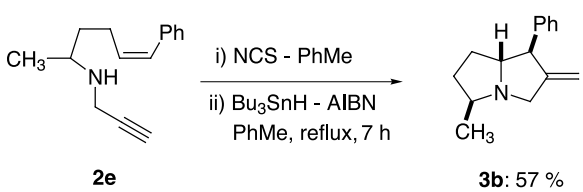
These results show that the present tandem cyclization of *N*-propargylaminyl radicals proceeds in highly stereoselective manner on each step. Proposed reaction pathways are shown in Scheme 7. Transition state **A** for aminyl radical cyclization would be a chair-like form, in which R^1 possesses a pseudo-equatorial position,[16] and the first ring



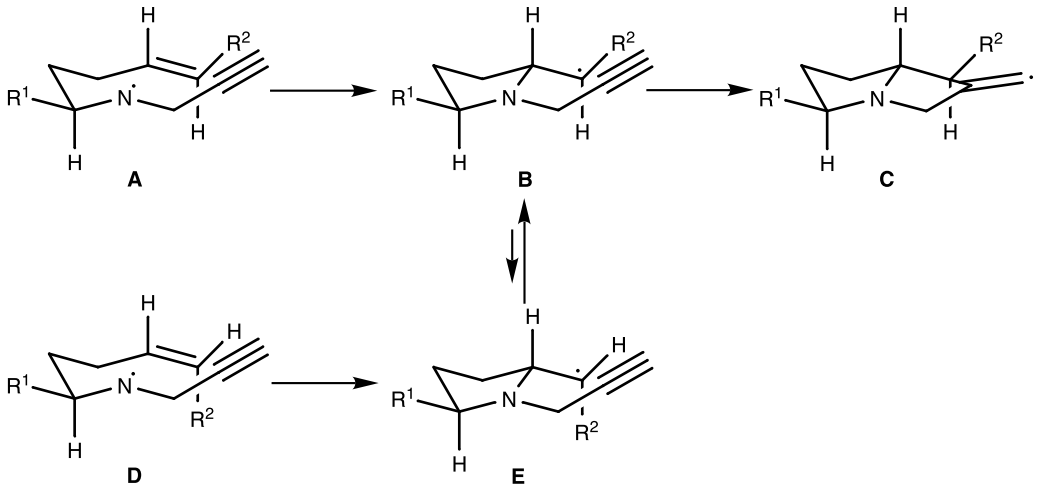
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

closure would give *trans*-2,5-disubstituted pyrrolidine intermediate **B**. Spontaneous cyclization of **B** would give the intermediate **C**, which abstracts a hydrogen atom from tributyltin hydride to give the product **3**. On the other hand, in the case of **2e**, the first cyclization of aminyl radical **D** would give the intermediate **E**. In the radical intermediate **E**, a rotation around the C–C single bond would occur to give a more sterically stable intermediate **B** probably due to a pseudo-axial substituent of R^2. 5-*exo* Cyclization would, then, occur onto the C–C triple bond efficiently to give pyrrolizidine intermediate **C** as a single diastereomer.

3. Conclusion

In conclusion, a tandem cyclization of *N*-propargylalk-4-enylaminyl radicals readily took place stereoselectively to give 2-methylenepyrrolizidines in moderate to good yields. These tandem cyclizations of *N*-propargylaminyl radicals gave only one stereoisomer. A similar reaction of aminyl radical having *Z* geometry in alk-4-enyl moieties afforded the same product as that obtained from (*E*)-alk-4-enyl-aminyl radicals. These results indicate that the present 5-*exo*, 5-*exo* tandem cyclization of aminyl radicals proceeds in highly stereoselective manner on each step.

4. Experimental

4.1. General

IR spectra were determined in a neat form with a JASCO IR-810 infrared spectrophotometer. The ^1H and ^{13}C NMR spectra were determined in $CDCl_3$ ($SiMe_4$ as an internal reference) with a JEOL JNM EX-270 high-resolution spectrometer. Mass spectra were recorded using a JOEL JMS-FABmate or JMS-700TZ spectrometer (70 eV). Measurement of mass spectra was performed by the staff of Center for Instrumental Analysis, Hokkaido University. Preparative TLC was carried out with Merck Silica gel 60 PF_{254} or Merck Aluminum oxide 60 PF_{254} or 60 $PF_{254+366}$ (Type E).

4.2. Preparation of ketones 1a–f

Ketones **1a–c** and **1f** were prepared according to our reported methods.[17]

4.2.1. (*E*)-6-Triethylsilylhex-5-en-2-one (1d). Hydrosilylation of hex-5-yn-2-one[18] with triethylsilane provided ketone **1d**. Thus, to a CH_2Cl_2 solution (1.6 ml, 1.0 M) ofhex-5-yn-2-one (150 mg, 1.56 mmol) were added triethylsilane (0.3 ml, 1.9 mmol) and $H_2PtCl_6{\cdot}H_2O$ (0.1 mg) as a catalyst, and the reaction mixture was stirred for 4 h at room temperature under an argon atmosphere. After evaporation of the solvent, a crude mixture was separated by preparative TLC (SiO_2, hexane+AcOEt 10:1) to give ketone **1d** (201 mg, 0.95 mmol, 61%): R_f=0.44; oil; ^1H NMR δ_H 0.54 (6H, q, *J*=7.9 Hz), 0.91 (9H, t, *J*=7.9 Hz), 2.15 (3H, s), 2.41 (2H, m), 2.55 (2H, m), 5.58 (1H, dt, *J*=1.7, 18.8 Hz), 6.02 (1H, dt, *J*=6.0, 18.8 Hz); ^{13}C NMR δ_C 3.43 [$(CH_2)\times3$], 7.35 [$(CH_3)\times3$], 29.99 (CH_3), 30.87 (CH_2), 42.71 (CH_2), 126.88 (CH), 146.13 (CH), 208.39 (C=O); IR 1717, 1657, 1239, 1017, 719 cm^{-1}; MS (EI) *m/z* 212 (M^+, 1.9), 183 [$(M-C_2H_5)^+$, 49.8], 103 (100%); HRMS calcd for $C_{12}H_{24}OSi$: *m/z* 212.1596. Found: *m/z* 212.1598.

4.2.2. (*Z*)-6-Phenylhex-5-en-2-one (1e).[19] Ketone **1e** was prepared from hex-5-yn-2-one by the Sonogashira reaction and hydrogenation. Thus, to triethylamine solution (104 ml, 0.3 M) of hex-5-yn-2-one were added iodobenzene (3.5 ml, 31.2 mmol), dichlorobis(triphenylphosphine)palladium (365 mg, 0.52 mmol) and CuI (49 mg, 0.26 mmol), and the reaction mixture was stirred for 12 h at 45°C under nitrogen atmosphere. The mixture was diluted with Et_2O (100 ml) and then washed successively with water and 2N HCl. After concentration of the ethereal solution, the crude product was distilled in vacuo to give 6-phenylhex-5-yn-2-one (3.7 g, 21.8 mmol, 70%). This ketone (300 mg, 1.74 mmol) was hydrogenated in MeOH (20 ml) with Lindlar catalyst (5 mg), quinoline (0.1 ml) and H_2 (1 atom). After filtration and concentration of the solution, the crude product was purified by column chromatography (SiO_2, hexane+AcOEt 10:1, R_f=0.33) to give ketone **1e** (285 mg, 1.64 mmol, 94%). Oil; ^1H NMR δ_H 2.13 (3H, s), 2.5–2.6 (4H, m), 5.62 (1H, m), 6.45 (1H, d, *J*=11.5 Hz), 7.2–7.4 (5H, m); ^{13}C NMR δ_C 22.84 (CH_2), 29.90 (CH_3),

43.63 (CH_2), 126.74 (CH), 128.23 [(CH)×2], 128.71 [(CH)×2], 129.94 (CH), 130.64 (CH), 137.19 (C), 208.12 (C=O); IR 1713, 1160, 769, 700 cm^{-1}; MS (EI) *m/z* 174 (M^+, 100), 131 (88.9%); HRMS calcd for $C_{12}H_{14}O$: *m/z* 174.1045. Found: *m/z* 174.1045.

4.3. General procedure for the preparation of *N*-propargylamines 2a,b and 2d–f

N-Propargylamines **2a**,**b** and **2d**–**f** were prepared by reductive amination of the corresponding ketones **1a**,**b** and **1d**–**f** with propargylamine and $NaBH(OAc)_3$. Thus, a CH_2Cl_2 solution of ketone (0.3 M) was reacted with propargylamine (2.0 equiv.), AcOH (0.2 equiv.) and $NaBH(OAc)_3$ (1.5 equiv.) at room temperature under an argon atmosphere until the starting ketone had disappeared (monitored by TLC). The reaction mixture was quenched with 2N NaOH, and then the mixture was extracted with Et_2O. The combined organic layers were washed with water and brine, and it was dried over $MgSO_4$. After evaporation of the solvent, crude product was purified by preparative TLC (Al_2O_3) to give *N*-propargylamine **2a**,**b** and **2d**–**f** in 78–89% yields.

4.3.1. (*E*)-*N*-Propargyl-1-methyloct-4-enylamine (2a). Al_2O_3-TLC (hexane+AcOEt (30:1), R_f=0.33); oil; ^1H NMR δ_H 0.88 (3H, t, *J*=7.3 Hz), 1.03 (3H, t, *J*=6.3 Hz), 1.2–1.6 (5H, m), 1.9–2.1 (4H, m), 2.18 (1H, t, *J*=2.3 Hz), 2.86 (1H, sext, *J*=6.3 Hz), 3.39 (1H, dd, *J*=2.3, 17.2 Hz), 3.47 (1H, dd, *J*=2.3, 17.2 Hz), 5.42 (2H, m); ^{13}C NMR δ_C 13.66 (CH_3), 19.71 (CH_3), 22.68 (CH_2), 28.98 (CH_2), 34.68 (CH_2), 35.56 (CH_2), 36.64 (CH_2), 51.00 (CH), 70.96 (CH), 82.48 (C), 129.88 (CH), 130.62 (CH); IR 3306, 1459, 968 cm^{-1}; MS (EI) *m/z* 178 [$(M-H)^+$, 5], 164 [$(M-CH_3)^+$, 27], 137 (60), 82 (100%); HRMS calcd for $C_{12}H_{20}N$: *m/z* 178.1596. Found: *m/z* 178.1599.

4.3.2. (*E*)-*N*-Propargyl-1-methyl-5-phenylpent-4-enylamine (2b). Al_2O_3-TLC (hexane+AcOEt (10:1), R_f=0.43); oil; ^1H NMR δ_H 1.08 (3H, d, *J*=6.3 Hz), 1.49 (1H, m), 1.53 (1H, m), 2.18 (1H, t, *J*=2.6 Hz), 2.2–2.3 (2H, m), 2.93 (1H, m), 3.41 (1H, dd, *J*=2.6, 17.2 Hz), 3.48 (1H, dd, *J*=2.6, 17.2 Hz), 6.21 (1H, dd, *J*=6.6, 15.8 Hz), 6.41 (1H, d, *J*=15.8 Hz), 7.2–7.4 (5H, m); ^{13}C NMR δ_C 19.75 (CH_3), 29.34 (CH_2), 35.58 (CH_2), 36.24 (CH_2), 50.92 (CH), 71.10 (C), 82.39 (CH), 125.93 [(CH)×2], 126.88 (CH), 128.48 [(CH)×2], 130.06 (CH), 130.42 (CH), 137.72 (C); IR 3273, 1462, 699 cm^{-1}; MS (EI) *m/z* 213 (M^+, 4), 212 [$(M-H)^+$, 10], 129 (37), 82 (100%); HRMS calcd for $C_{15}H_{19}N$: *m/z* 213.1517. Found: *m/z* 213.1501.

4.3.3. (*E*)-*N*-Propargyl-1-methyl-5-triethylsilylpent-4-enylamine (2d). Al_2O_3-TLC (hexane+AcOEt (10:1), R_f=0.67); oil; ^1H NMR δ_H 0.54 (6H, q, *J*=7.9 Hz), 0.92 (9H, t, *J*=4.0 Hz), 1.04 (3H, t, *J*=4.0 Hz), 1.4–1.6 (3H, m), 2.1–2.2 (2H, m), 2.18 (1H, t, *J*=2.6 Hz), 2.88 (1H, sext, *J*=6.3 Hz), 3.39 (1H, dd, *J*=2.6, 17.2 Hz), 3.47 (1H, dd, *J*=2.6, 17.2 Hz), 5.58 (1H, dt, *J*=1.3, 18.8 Hz), 6.04 (1H, dt, *J*=6.3, 18.8 Hz); ^{13}C NMR δ_C 3.45 [(CH_2)×3], 7.39 [(CH_3)×3], 19.68 (CH_3), 33.35 (CH_2), 35.54 (CH_2), 35.74 (CH_2), 50.91 (CH), 71.01 (C), 82.37 (CH), 126.20 (CH), 147.92 (CH); IR 3386, 1618, 1460, 1237, 1016 cm^{-1}; MS (EI) *m/z* 250 [$(M-H)^+$, 3.1], 236 [$(M-CH_3)^+$, 7.6], 222 [$(M-C_2H_5)^+$, 11.7], 82 (100%); HRMS calcd for $C_{15}H_{28}NSi$: *m/z* 250.1991. Found: *m/z* 250.1991.

4.3.4. (*Z*)-*N*-Propargyl-1-methyl-5-phenylpent-4-enylamine (2e). Al_2O_3-TLC (hexane+AcOEt (10:1), R_f=0.54); oil; ^1H NMR δ_H 1.03 (3H, d, *J*=6.3 Hz), 1.4–1.7 (3H, m), 2.17 (1H, t, *J*=2.3 Hz), 2.3–2.4 (2H, m), 2.90 (1H, sext, *J*=6.3 Hz), 3.38 (1H, dd, *J*=2.3, 17.2 Hz), 3.45 (1H, dd, *J*=2.3, 17.2 Hz), 5.65 (1H, dt, *J*=7.3, 11.9 Hz), 6.43 (1H, d, *J*=11.9 Hz); ^{13}C NMR δ_C 19.68 (CH_3), 24.94 (CH_2), 35.54 (CH_2), 36.82 (CH_2), 51.03 (CH), 71.09 (C), 82.30 (CH), 126.56 (CH), 128.16 [(CH)×2], 128.71 [(CH)×2], 129.16 (CH), 132.38 (CH), 137.55 (C); IR 3296, 1495, 768, 699 cm^{-1}; MS (EI) *m/z* 212 [$(M-H)^+$, 10.5], 198 [$(M-CH_3)^+$, 7.4], 82 (100%); HRMS calcd for $C_{15}H_{18}N$: *m/z* 212.1439. Found: *m/z* 212.1431.

4.3.5. *cis*-*N*-Propargyl-2-(3-phenylprop-2-enyl)cyclohexylamine (2f). Al_2O_3-TLC (hexane+AcOEt (10:1), R_f=0.56); oil; ^1H NMR δ_H 1.3–1.5 (4H, m), 1.5–1.7 (4H, m), 1.78 (1H, m), 2.16 (1H, m), 2.16 (1H, t, *J*=2.3 Hz), 2.32 (1H, m), 2.94 (1H, m), 3.38 (1H, dd, *J*=2.3, 17.2 Hz), 3.48 (1H, dd, *J*=2.3, 17.2 Hz), 6.20 (1H, ddd, *J*=6.6, 7.6, 15.8 Hz), 6.40 (1H, d, *J*=15.8 Hz), 7.2–7.4 (5H, m); ^{13}C NMR δ_C 22.27 (CH_2), 23.47 (CH_2), 27.28 (CH_2), 28.43 (CH_2), 33.03 (CH_2), 35.65 (CH_2), 39.73 (CH), 55.47 (CH), 70.93 (C), 82.71 (CH), 125.89 [(CH)×2], 126.77 (CH), 128.43 [(CH)×2], 129.83 (CH), 130.87 (CH), 137.83 (C); IR 3302, 1601, 1450, 966, 735 cm^{-1}; MS (EI) *m/z* 253 (M^+, 8.8), 252 [$(M-H)^+$, 18.2], 124 (100%); HRMS calcd for $C_{18}H_{23}N$: *m/z* 253.1830. Found: *m/z* 253.1818.

4.3.6. (*E*)-*N*-Propargyl-1,5-diphenylpent-4-enylamine (2c). This amine was prepared by reduction of the corresponding imine, prepared from (*E*)-1,5-diphenylpent-4-en-1-one (**1c**) according to a literature.[12] Thus, to a benzene (4.2 ml) solution of ketone **1c** (200 mg, 0.85 mmol) and propargylamine (0.58 ml, 8.5 mmol) was slowly added a benzene (1 ml) solution of $TiCl_4$ (0.06 ml, 0.51 mmol) at 0°C and the reaction mixture was stirred at room temperature for 12 h. After usual work-up, the crude product was dissolved in EtOH (3 ml) and then treated with $NaBH_4$ until the starting imine had disappeared (monitored by TLC). Usual work-up and purification by preparative TLC (Al_2O_3) afforded the corresponding *N*-propargylamine **2c** (193 mg, 0.70 mmol, 82%). Al_2O_3-TLC (hexane+AcOEt (10:1), R_f=0.47); oil; ^1H NMR δ_H 1.8–1.9 (2H, m), 2.1–2.2 (2H, m), 2.18 (1H, t, *J*=2.3 Hz), 3.10 (1H, dd, *J*=2.3, 17.2 Hz), 3.34 (1H, dd, *J*=2.3, 17.2 Hz), 3.88 (1H, m), 6.15 (1H, dt, *J*=6.6, 15.8 Hz), 6.33 (1H, d, *J*=15.8 Hz), 7.1–7.4 (10H, m); ^{13}C NMR δ_C 29.67 (CH_2), 35.83 (CH_2), 37.23 (CH_2), 61.01 (CH), 71.28 (C), 82.26 (CH), 125.93 [(CH)×2], 126.90 (CH), 127.38 (CH), 127.62 [(CH)×2], 128.48 [(CH)×4], 130.03 (CH), 130.28 (CH), 137.68 (C), 142.62 (C); IR 3274, 1461, 738, 700 cm^{-1}; MS (EI) *m/z* 274 [$(M-H)^+$, 13.8], 220 (16.5), 144 (100%); HRMS calcd for $C_{20}H_{20}N$: *m/z* 274.1596. Found: *m/z* 274.1601.

4.4. General procedure for the tandem cyclization of aminyl radicals

To a toluene solution of *N*-propargylamines **2a**–**f** (0.02 M)

was added *N*-chlorosuccinimide (1.0 equiv.) under nitrogen atmosphere at room temperature. After stirring for 30 min, Bu_3SnH (1.0 equiv.) and AIBN (0.2 equiv.) were added and the solution was heated under reflux for 7 h. After evaporation of toluene, the residue was diluted with 5 ml of ethyl acetate and stirred vigorously with 10%-KF aqueous solution for several hours to remove tin by-product. The precipitate (Bu_3SnF) was filtered off, and the aqueous phase was made basic by 2N NaOH and was extracted with Et_2O. The combined organic layers were washed with water and brine, and dried over $MgSO_4$. After evaporation of the solvent, the resultant crude product was purified with TLC (Al_2O_3) to give 2-methylenepyrrolizidines **3a**–**f** and **4a**,**b**.

4.4.1. Radical cyclization of 2a; 5-methyl-2-methylene-1-propylpyrrolizidine (3a) and 2-chloromethylene-5-methyl-1-propylpyrrolizidine (4a). Compound **3a**. Al_2O_3-TLC (hexane+AcOEt (10:1), R_f=0.44); oil; ^{1}H NMR δ_H 0.92 (3H, t, *J*=6.9 Hz), 1.08 (3H, d, *J*=6.3 Hz), 1.3–1.4 (3H, m), 1.5–1.6 (3H, m), 1.97 (1H, m), 2.1–2.2 (2H, m), 2.63 (1H, m), 3.26 (1H, m), 3.29 (1H, dt, *J*=1.7, 14.8 Hz), 3.61 (1H, ddd, *J*=1.7, 3.6, 14.8 Hz), 4.83 (1H, ddd, *J*=0.7, 2.0, 4.3 Hz), 4.89 (1H, dd, *J*=2.0, 3.6 Hz); ^{13}C NMR δ_C 14.47 (CH_3), 20.59 (CH_3), 20.81 (CH_2), 31.03 (CH_2), 35.04 (CH_2), 35.25 (CH_2), 49.51 (CH), 57.25 (CH_2), 60.66 (CH), 71.61 (CH), 104.24 (CH_2), 155.00 (C); IR 1457, 1376 cm^{-1}; MS (EI) *m*/*z* 179 (M^+, 44), 164 [$(M-CH_3)^+$, 100], 150 [$(M-C_2H_5)^+$, 87], 136 [$(M-C_3H_7)^+$, 54%]; HRMS calcd for $C_{12}H_{21}N$: *m*/*z* 179.1674. Found: *m*/*z* 179.1681.

Compound **4a**. R_f=0.50; oil; ^{1}H NMR δ_H 0.92 (3H, t, *J*=7.3 Hz), 1.10 (3H, d, *J*=6.3 Hz), 1.2–1.4 (3H, m), 1.5–1.6 (3H, m), 1.98 (1H, m), 2.12 (1H, m), 2.31 (1H, m), 2.61 (1H, m), 3.31 (1H, dt, *J*=4.3, 7.6 Hz), 3.52 (1H, dd, *J*=2.3, 16.8 Hz), 3.68 (1H, dt, *J*=2.3, 16.8 Hz), 5.83 (1H, dd, *J*=2.3, 4.6 Hz); ^{13}C NMR δ_C 14.38 (CH_3), 20.56 (CH_3), 20.59 (CH_2), 30.17 (CH_2), 34.45 (CH_2), 35.56 (CH_2), 49.38 (CH_2), 54.64 (CH), 60.32 (CH), 72.18 (CH), 108.91 (CH), 148.82 (C); IR 1650, 1458, 1377, 734 cm^{-1}; MS (EI) *m*/*z* 213 (M^+, 19), 198 [$(M-CH_3)^+$, 32], 184 [$(M-C_2H_5)^+$, 36], 178 [$(M-Cl)^+$, 100%]; HRMS calcd for $C_{12}H_{20}N$: *m*/*z* 178.1596. Found: *m*/*z* 178.1612.

4.4.2. Radical cyclization of 2b; 5-methyl-2-methylene-1-phenylpyrrolizidine (3b) and 2-chloromethylene-5-methyl-1-phenylpyrrolizidine (4b). Compound **3b**. Al_2O_3-TLC (hexane+AcOEt (4:1), R_f=0.63); oil; ^{1}H NMR δ_H 1.14 (3H, d, *J*=6.3 Hz), 1.5–1.7 (2H, m), 2.0–2.1 (2H, m), 2.80 (1H, m), 3.33 (1H, d, *J*=9.2 Hz), 3.54 (1H, d, *J*=15.5 Hz), 3.62 (1H, m), 3.85 (1H, dd, *J*=1.7, 15.5 Hz), 4.58 (1H, d, *J*=2.0 Hz), 5.00 (1H, d, *J*=1.3 Hz), 7.2–7.3 (5H, m); ^{13}C NMR δ_C 21.08 (CH_3), 28.93 (CH_2), 34.63 (CH_2), 57.27 (CH), 57.77 (CH_2), 61.01 (CH), 74.77 (CH), 107.24 (CH_2), 126.88 (CH), 128.88 [(CH)×2], 129.13 [(CH)×2], 141.85 (C), 156.17 (C); IR 1661, 1454, 748, 700 cm^{-1}; MS (EI) *m*/*z* 213 (M^+, 99.7), 198 [$(M-CH_3)^+$, 100], 136 [$(M-C_6H_5)^+$, 11.0%]; HRMS calcd for $C_{15}H_{19}N$: *m*/*z* 213.1517. Found: *m*/*z* 213.1531.

Compound **4b**. R_f=0.55; oil; ^{1}H NMR δ_H 1.10 (3H, d, *J*=5.9 Hz), 1.5–1.7 (2H, m), 1.9–2.1 (2H, m), 2.73 (1H, m), 3.36 (1H, d, *J*=9.9 Hz), 3.5–3.6 (2H, m), 3.89 (1H, dt, *J*=2.6, 17.2 Hz), 5.47 (1H, dd, *J*=2.6, 5.3 Hz), 7.1–7.3 (5H, m); ^{13}C NMR δ_C 20.47 (CH_3), 27.46 (CH_2), 33.69 (CH_2), 55.04 (CH_2), 56.30 (CH), 60.16 (CH), 75.29 (CH), 111.91 (CH), 126.94 (CH), 128.50 [(CH)×2], 128.73 [(CH)×2], 140.32 (C), 149.76 (C); IR 1650, 1458, 1377, 700 cm^{-1}; MS (EI) *m*/*z* 247 (M^+, 72), 212 [$(M-Cl)^+$, 51], 129 (100%); HRMS calcd for $C_{15}H_{18}NCl$: *m*/*z* 247.1128. Found: *m*/*z* 247.1164.

4.4.3. Radical cyclization of 2c; 1,5-diphenyl-2-methylenepyrrolizidine (3c). Al_2O_3-TLC (hexane+AcOEt (10:1), R_f=0.83); oil; ^{1}H NMR δ_H 1.8–2.0 (2H, m), 2.16 (1H, m), 2.35 (1H, m), 3.4–3.6 (2H, m), 3.8–3.9 (3H, m), 4.61 (1H, dd, *J*=2.0, 4.3 Hz), 4.97 (1H, dd, *J*=2.0, 4.3 Hz), 7.2–7.4 (10H, m); ^{13}C NMR δ_C 29.15 (CH_2), 36.39 (CH_2), 57.25 (CH), 57.68 (CH_2), 69.70 (CH), 74.12 (CH), 107.04 (CH_2), 126.54 (CH), 126.97 (CH), 127.17 [(CH)×2], 128.37 [(CH)×2], 128.53 [(CH)×2], 128.73 [(CH)×2], 141.49 (C), 143.84 (C), 155.70 (C); IR 1458, 1378, 699 cm^{-1}; MS (EI) *m*/*z* 275 (M^+, 100%); HRMS calcd for $C_{20}H_{21}N$: *m*/*z* 275.1674. Found: *m*/*z* 275.1672.

4.4.4. Radical cyclization of 2d; 1-triethylsilyl-5-methyl-2-methylenepyrrolizidine (3d). Al_2O_3-TLC (hexane+AcOEt (30:1), R_f=0.44); oil; ^{1}H NMR δ_H 0.61 (6H, q, *J*=7.6 Hz), 0.97 (9H, t, *J*=7.6 Hz), 1.07 (3H, t, *J*=5.9 Hz), 1.48 (2H, m), 1.81 (1H, m), 1.97 (1H, m), 2.17 (1H, m), 2.55 (1H, m), 3.31 (1H, d, *J*=15.2 Hz), 3.47 (1H, dd, *J*=2.3, 15.2 Hz), 3.70 (1H, dt, *J*=3.0, 7.6 Hz), 4.74 (1H, s), 4.82 (1H, s); ^{13}C NMR δ_C 2.32 [(CH_2)×3], 7.60 [(CH_3)×3], 20.20 (CH_3), 31.81 (CH_2), 34.09 (CH_2), 38.11 (CH), 57.68 (CH), 58.38 (CH_2), 67.69 (CH), 102.87 (CH_2), 152.94 (C); IR 1647, 1240, 867 cm^{-1}; MS (EI) *m*/*z* 251 (M^+, 33.2), 236 (55.5), 222 (58.3), 136 (100%); HRMS calcd for $C_{15}H_{29}NSi$: *m*/*z* 251.2069. Found: *m*/*z* 251.2061.

4.4.5. Radical cyclization of 2f; perhydro-2-methylene-1-phenylpyrrolo[1,2-*a*]indole (3f). Al_2O_3-TLC (hexane+AcOEt (10:1), R_f=0.50); oil; ^{1}H NMR δ_H 1.1–1.9 (10H, m), 2.16 (1H, m), 2.89 (1H, d, *J*=3.6 Hz), 3.34 (1H, d, *J*=9.6 Hz), 3.45 (1H, dd, *J*=1.0, 14.8 Hz), 3.73 (1H, m), 3.86 (1H, d, *J*=14.8 Hz), 4.50 (1H, d, *J*=2.0 Hz), 4.97 (1H, d, *J*=2.0 Hz), 7.2–7.3 (5H, m); ^{13}C NMR δ_C 20.58 (CH_2), 24.69 (CH_2), 27.82 (CH_2), 28.79 (CH_2), 36.89 (CH_2), 39.73 (CH), 57.79 (CH), 57.92 (CH_2), 64.85 (CH), 71.99 (CH), 106.34 (CH_2), 127.39 (CH), 128.43 [(CH)×2], 128.82 [(CH)×2], 140.72 (C), 155.29 (C); IR 1659, 1454, 746, 700 cm^{-1}; MS (EI) *m*/*z* 253 (M^+, 100), 210 (51), 129 (40%); HRMS calcd for $C_{18}H_{23}N$: *m*/*z* 253.1830. Found: *m*/*z* 253.1834.

References

1. Reviews: (a) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286. (b) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103–13159. (c) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195–206. (d) Malacria, M. *Chem. Rev.* **1996**, *96*, 289–306. (e) Dhimane, A.-L.; Fensterbank, L.; Malacria, M. In *Polycyclic Compounds via Radical Cascade Reactions. Radicals in Organic Synthesis*;

Renaud, P., Sibi, M. P., Eds.; Wiley/VCH: Weinheim, 2001; Vol. 2, pp 350–382.
2. Recent examples: (a) Zhou, S.; Bommezijn, S.; Murphy, J. A. *Org. Lett.* **2002**, *4*, 443–445. (b) Njardarson, J. T.; McDonald, I. M.; Spiegel, D. A.; Inoue, M.; Wood, J. L. *Org. Lett.* **2001**, *3*, 2435–2438. (c) Toyota, M.; Yokota, M.; Ihara, M. *J. Am. Chem. Soc.* **2001**, *123*, 1856–1861. (d) Hilton, S. T.; Ho, T. C. T.; Pljevaljcic, G.; Schulte, M.; Jones, K. *Chem. Commun.* **2001**, 209–210.
3. Reviews for pyrrolizidine alkaloids: (a) Robins, D. J. *Nat. Prod. Rep.* **1993**, 487–496. (b) Liddell, R. *Nat. Prod. Rep.* **1997**, 653–660.
4. Reviews for indolizidine and quinolizidine alkaloids: (a) Michael, J. P. *Nat. Prod. Rep.* **1995**, 535–552. (b) Michael, J. P. *The Alkaloids*; Brossi, A., Ed.; Academic Press Inc: New York, 2001; Vol. 55, pp 91–267, Chapter 2.
5. (a) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1295–1310. (b) Bowman, W. R.; Stephenson, P. T.; Young, A. R. *Tetrahedron Lett.* **1995**, *36*, 5623–5626. (c) Smaele, D. D.; Bogaert, P.; Kimpe, N. D. *Tetrahedron Lett.* **1998**, *39*, 9797–9800. (d) Baker, S. R.; Burton, K. I.; Parsons, A. F.; Pons, J.-F.; Wilson, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 427–436.
6. Reviews for nitrogen radical: (a) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337–422. (b) Esker, J. L.; Newcomb, M. *Adv. Heterocycl. Chem.* **1993**, *58*, 1–45. (c) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543–17594. (d) Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1–14.
7. Tokuda, M.; Fujita, H.; Suginome, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 777–778.
8. Clark, A. J.; Deeth, R. J.; Samuel, C. J.; Wongtap, H. *Synlett* **1999**, 444–446.
9. Newcomb, M.; Marquardt, D. J.; Deeb, T. M. *Tetrahedron* **1990**, *46*, 2329–2344.
10. Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959–974.
11. Senboku, H.; Hasegawa, H.; Orito, K.; Tokuda, M. *Heterocycles* **1999**, *50*, 333–340.
12. Senboku, H.; Kajizuka, Y.; Hasegawa, H.; Fujita, H.; Suginome, H.; Orito, K.; Tokuda, M. *Tetrahedron* **1999**, *55*, 6465–6474.
13. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.
14. Moretti, I.; Torre, G. *Synthesis* **1970**, 141.
15. A similar result was shown in Ref. 5a.
16. (a) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073–3100. (b) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925–3941. (c) Broeker, J. L.; Houk, K. N. *J. Org. Chem.* **1991**, *56*, 3651–3655, and also see: Ref. 7d.
17. For ketones **1b**, **1c** and **1f**: Tokuda, M.; Miyamoto, T.; Fujita, H.; Suginome, H. *Tetrahedron* **1991**, *47*, 747–756, and also see Ref. 8. For ketone **2a**, see: Ref. 11.
18. Davies, L. B.; Greenberg, S. G.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1909–1912.
19. Condon-Gueugnot, S.; Dupré, D.; Nédélec, J.-Y.; Périchon, J. *Synthesis* **1997**, 1457–1460.