REGIOSELECTIVE SYNTHESIS OF BRIDGED AZABICYCLIC COMPOUNDS USING RADICAL TRANSLOCATION/CYCLIZATION REACTIONS OF 4-ALKYNYL-1-(O-IODOBENZOYL)PIPERIDINES

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Abstract—Bu₃SnH-mediated radical translocation/cyclization reactions of 4-alkynyl-1-(o-iodobenzoyl)piperidines were examined. The 4-[3-(trimethylsilyl)prop-2-ynyl]- (12) and 4-[4-(trimethylsilyl)but-3-ynyl]piperidine derivatives (16), upon treatment with Bu₃SnH in the presence of azobisisobutyronitrile in boiling toluene, gave the isomeric 2-azabicyclo[3.2.1]octanes (17a,b) (34 and 51% yields, respectively) and 2-azabicyclo[3.3.1]nonane (moran) (22) (20% yield as a diastereomeric mixture), respectively.

Previously we showed that 1-(o-iodobenzoyl)-2-(prop-2-ynyl)piperidine (1), upon treatment with tributyltin hydride (Bu₃SnH) in the presence of azobisisobutyronitrile (AIBN) in boiling toluene, gave regioselectively the 8-azabicyclo[3.2.1]octane (4).¹ A mechanistic rationalization for the formation of 4 would involve a 1,5-hydrogen transfer² of the initially formed aryl radical (2) to yield the α-acylamino radical (3), which undergoes a 5-exo-trig cyclization to lead to 4. We have now extended this reaction to the synthesis of the 2-azabicyclo[3.2.1]octane³ and 2-azabicyclo[3.3.1]nonane (moran)⁴ ring systems.

This paper is dedicated to Professor Shô Itô, Bunri University of Tokushima, on the occasion of his 77th birthday.
The radical precursor 4-[3-(trimethylsilyl)prop-2-ynyl]piperidine (12) was readily obtained as shown in Scheme 1. The Horner-Emmons reaction of tert-butyl 4-oxopiperidine-1-carboxylate (5)\textsuperscript{5} with 6 gave the α,β-unsaturated ester (7), which was subjected to catalytic hydrogenation over Pd-C followed by DIBAL-H reduction of the resulting ester (8) to give the aldehyde (9) in 67% overall yield. The aldehyde (9) was allowed to react with bromoform and triphenylphosphine in the presence of potassium tert-butoxide to give the dibromide (10), which was treated with butyllithium followed by quenching with chlorotrimethylsilane to give the 4-[3-(trimethylsilyl)prop-2-ynyl]piperidine (11). Replacement of the tert-butoxycarbonyl group of 11 by an o-iodobenzoyl group afforded the radical precursor (12). The 4-[4-(trimethylsilyl)but-3-ynyl]piperidine (16) was prepared starting from the aldehyde (9). Addition of trimethylsilylethynyllithium to 9 gave the ethynic alcohol (13), which was treated with carbon tetrabromide and triphenylphosphine followed by reduction of the resulting bromide (14) with Bu\textsubscript{3}SnH in the presence of a small amount of AIBN to give 15. The same sequence as that described for the conversion of 11 to 12 gave 16.

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\text{Scheme 1. Reagents and conditions: i, (EtO)}\textsubscript{2}P(O)CHNaCO\textsubscript{2}Et (6), \text{THF, quant.; ii, H}_2 (5 \text{ kg/cm}^2), 10\% \text{ Pd-C, AcOEt, quant.; iii, DIBAL-H, toluene, } -78^\circ\text{C, 67%; iv, CHBr}_3, \text{Ph}_3\text{P, tert-BuOK, toluene, 63%; v, BuLi, TMEDA, THF, } -78^\circ\text{C, and then Me}_3\text{SiCl, 83%; vi, 10\% aq. HCl, EtOH; vii, o-iodobenzoyl chloride, Et}_3\text{N, DMAP, CH}_2\text{Cl}_2; viii, Me}_3\text{SiCLi, THF, quant.; ix, CBr}_4, \text{Ph}_3\text{P, CH}_2\text{Cl}_2, 99%; x, Bu}_3\text{SnH, AIBN, toluene, reflux, 75%.}
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Treatment of 12 with Bu\textsubscript{3}SnH/AIBN in boiling toluene gave the isomeric 2-azabicyclo[3.2.1]octanes (17a) (less polar isomer) and (17b) (polar one) in 34 and 51% yields, respectively, along with a trace amount of the reduction product (18) whose structure was assumed by absorptions at 2160 (an acetylenic group) and 1630 cm\textsuperscript{-1} (an N-benzoyl group) in the IR spectrum. The structures of compounds (17a) and (17b) were confirmed by transformation into the ketone (20), which showed strong carbonyl absorptions at 1751 (a five-membered ketone) and 1631 cm\textsuperscript{-1} (an N-benzoyl group) in the IR spectrum. Cyclization of 16 proceeded more slowly to give the 2-azabicyclo[3.3.1]nonane (22) in 20% yield as a diastereomeric mixture. In this case, the reduction product (21) was obtained as a major product in 75%
yield. Compound (22) was converted into the methylene derivative, whose spectral data were in good agreement with those of an authentic sample synthesized from 24.\textsuperscript{6}

![Scheme 2](image_url)

Scheme 2. Reagents and conditions: i, Bu\textsubscript{3}SnH, AIBN, toluene, reflux; ii, CF\textsubscript{3}CO\textsubscript{2}H, CH\textsubscript{2}Cl\textsubscript{2}; iii, O\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, -78°C, and then NaI, AcOH, 53%; iv, Ph\textsubscript{3}P\textsubslash CH\textsubscript{2}, THF, 82%.

The low yield of 22 may be rationalized by considering the preferred conformation of the α-acylamino radical intermediates (A) derived from the 4-alkynyl-1-(o-iodobenzoyl)piperidines. The 4-alkynyl group adopts a more stable equatorial position, so that for the cyclization to take place the conformation of the 4-substituent must invert from the equatorial to the axial position. The distance of the 3-position of the 4-(but-3-ynyl) group and the radical center is still larger than that in the case of the 4-(prop-2-ynyl) group. Consequently, the reduction competes favorably with the cyclization.

\[ \alpha - \text{acylamino radical (A)} \]

In summary, we have shown that 4-alkynyl-1-(o-iodobenzoyl)piperidines undergo a 1,5-hydrogen transfer and cyclization to give the 2-azabicyclo[3.2.1]octane and 2-azabicyclo[3.3.1]nonane (morphan) ring systems.
EXPERIMENTAL

Mps are uncorrected. IR spectra were recorded on a JASCO-IR-A-100 or a JASCO FT/IR-410 spectrophotometer. $^1$H (60, 300 and 400 MHz) spectra were measured on a JEOL JNM-PMX 60, a Varian XL-300, or a Varian UNITY INOVA 400NB spectrometer for solutions in CDCl$_3$. \( \delta \) Values quoted are relative to tetramethylsilane (0 ppm) for $^1$H-NMR, and $J$ values are given in Hz. Column chromatography was performed on Silica gel 60 PF254 (Nacalai Tesque) under pressure.

tert-Butyl 4-[(Ethoxycarbonyl)methylene]piperidine-1-carboxylate (7) To a suspension of NaH [60% dispersion in mineral oil (780 mg, 19.5 mmol), washed with dry pentane several times before use] in THF (30 mL) was added diethyl ethoxycarbonylmethylphosphonate (3.73 g, 16.5 mmol) at 0 °C and the mixture was stirred at the same temperature for 10 min. A solution of tert-butyl 4-oxopiperidine-1-carboxylate$^5$ (5) (3.00 g, 15.0 mmol) in THF (15 mL) was added to this mixture at 0 °C and the whole was stirred at rt for 1 h. The reaction mixture was diluted with a half-saturated aq. NaHCO$_3$, extracted with AcOEt. The extract was dried (MgSO$_4$) and concentrated to give 7 (4.05 g, quant.), which was used for the next step without further purification. $^1$H-NMR (60 MHz) \( \delta \): 1.26 (3 H, t, \( J = 7.0 \) Hz, CH$_2$C$_3$H$_3$), 1.46 (9 H, s, tBu), 2.1-2.4 (2 H, m), 2.8-3.1 (2 H, m), 3.1-3.6 (4 H, m), 4.12 (2 H, q, \( J = 7.0 \) Hz, CH$_2$CH$_3$), 5.68 (1 H, br s, C=CH).

tert-Butyl 4-(Ethoxycarbonylmethyl)piperidine-1-carboxylate (8) A solution of compound (7) (300 mg, 1.11 mmol) in AcOEt (10 mL) was hydrogenated in the presence of 10% Pd-C (50 mg) under pressure (5 kg/cm$^2$) over 3 h. After the catalyst had been removed by filtration, the filtrate was concentrated to give 8 (301 mg, quant.) as an oil, which was used for the next step without further purification. IR \( \nu_{\text{max}} \) (CCl$_4$) cm$^{-1}$: 1735, 1690; $^1$H-NMR (60 MHz) \( \delta \): 1.0-3.0 (9 H, m), 1.25 (3 H, t, \( J = 7.0 \) Hz, CH$_2$Ch$_3$), 1.46 (9 H, s, tBu), 2.1-2.4 (2 H, m), 2.8-3.1 (2 H, m), 3.1-3.6 (4 H, m), 4.12 (2 H, q, \( J = 7.0 \) Hz, CH$_2$CH$_3$).

tert-Butyl 4-(2-Oxoethyl)piperidine-1-carboxylate (9) A 1.00 mol/l solution of DIBAL-H in hexane (1.62 mL, 1.62 mmol) was added to a solution of 8 (400 mg, 1.47 mmol) in toluene (15 mL) at -78 °C under a nitrogen atmosphere and the mixture was stirred for 10 min. Methanol (2 mL) and sat. aq. NH$_4$Cl (1 mL) were added to this mixture and the whole was stirred at rt for 1 h then diluted with ether, dried (MgSO$_4$), and concentrated. The residue was chromatographed on silica gel [hexane-AcOEt (5:1)] to give 9 (224 mg, 67%) as an oil. IR \( \nu_{\text{max}} \)(film) cm$^{-1}$: 1724, 1691; $^1$H-NMR (400 MHz) \( \delta \): 1.18 (2 H, qd, \( J = 12.5, 4.4 \) Hz), 1.45 (9 H, s, tBu), 1.66-1.76 (2 H, m), 1.88-2.00 (0.3 H, m, 4-H), 2.00-2.11 (0.7 H, m, 4-H), 2.28 (2 H x 3/10, d, \( J = 7.0 \) Hz), 2.39 (2 H x 7/10, dd, \( J = 6.8, 1.8 \) Hz), 2.68-2.79 (2 H, br), 4.03-4.13 (2 H, br), 9.78 (1 H, t, \( J = 1.8 \) Hz, CHO); Exact MS \textit{m/z}: calcd for C$_{12}$H$_{21}$NO$_3$: 227.1521, found: 227.1530.

tert-Butyl 4-(2,2-Dibromoprop-2-enyl)piperidine-1-carboxylate (10) Bromoform (2.22 g, 8.80 mmol) was added to a solution of triphenylphosphine (2.31 g, 8.80 mmol) and potassium tert-
butoxide (988 mg, 8.80 mmol) in toluene (10 mL) at −20 °C and the mixture was stirred at the same temperature for 15 min. A solution of the aldehyde (9) (500 mg, 2.2 mmol) in toluene (7 mL) was added to this mixture and the whole was stirred for 1 h at rt. The mixture was then diluted with ether (40 mL) and the resulting precipitate was filtered off. The filtrate was concentrated and the residue was chromatographed on silica gel [hexane-AcOEt (20:1)] to give 10 (530 mg, 63%) as an oil. IR ν_max (CCl_4) cm⁻¹: 1690; ^1^H-NMR (60 MHz) δ: 0.95-2.2 (7 H, m), 1.45 (9 H, s, tBu), 2.05-2.95 (2 H, m), 3.85-4.3 (2 H, m), 6.40 (1 H, t, J = 7.5 Hz, CH=C). Anal. Calcd for C_{13}H_{21}NO_2Br_2: C, 40.76; H, 5.52; N, 3.66. Found: C, 41.07; H, 5.72; N, 3.48.

**tert-Butyl 4-[3-(Trimethylsilyl)prop-2-ynyl]piperidine-1-carboxylate (11)**

TMEDA (385 mg, 3.31 mmol) and a 1.59 mol/l solution of butyllithium in hexane (2.42 mL, 3.85 mmol) were added to a solution of 10 (590 mg, 1.54 mmol) in THF (5 mL) at −78 °C under a nitrogen atmosphere and the mixture was stirred for 1 h. Chlorotrimethylsilane (225 mg, 2.07 mmol) was added to the reaction mixture at the same temperature and the whole was stirred at rt for 1 h. The mixture was diluted with sat. aq. NaHCO_3 and extracted with ether. The extract was washed with brine, dried (MgSO_4), and concentrated. The residue was chromatographed on silica gel [hexane-AcOEt (20:1)] to give 11 (341 mg, 83%) as an oil. IR ν_max (film) cm⁻¹: 2173, 1697; ^1^H-NMR (60 MHz) δ: 0.15 (9 H, s, SiMe_3), 0.8-2.95 (9 H, m), 1.47 (9 H, s, tBu), 3.85-4.3 (2 H, m); HR-MS (FAB) m/z calcd for C_{16}H_{30}NO_2Si: 296.2046, found: 296.2055 (MH^+).

**1-(o-Iodobenzoyl)-4-[3-(trimethylsilyl)prop-2-ynyl]piperidine (12)**

10% Aq. HCl (1 mL) was added to a solution of the carbamate (11) (700 mg, 2.37 mmol) in ethanol (5 mL) and the solution was stirred at rt for 2 days. After the solution had been concentrated to dryness, the residue was dissolved in dichloromethane (10 mL), then treated at 0 °C with triethylamine (718 mg, 7.11 mmol), DMAP (29 mg, 0.24 mmol), and o-iodobenzoyl chloride (820 mg, 3.08 mmol) and the whole was stirred at rt overnight. The reaction mixture was diluted with water and the organic layer was separated. The aqueous layer was extracted with AcOEt several times and the combined organic layer and the extracts were washed with 3% aq. HCl, sat. aq. NaHCO_3, and brine, dried (MgSO_4), and concentrated. The residue was chromatographed on silica gel [hexane-AcOEt (4:1)] to give 12 (735 mg, 73%) as an oil. IR ν_max (CCl_4) cm⁻¹: 2180, 1640; ^1^H-NMR (60 MHz) δ: 0.14 (9 H, s, SiMe_3), 1.5-3.6 (9 H, m), 4.5-4.95 (2 H, m), 6.75-7.45 (3 H, m, ArH), 7.68 (1 H, br d, J = 7.8 Hz, ArH). Anal. Calcd for C_{18}H_{24}NOI Si: C, 50.82; H, 5.69; N, 3.29. Found: C, 50.94; H, 5.91; N, 3.17.

**tert-Butyl 4-[2-Hydroxy-4-(trimethylsilyl)but-3-ynyl]piperidine-1-carboxylate (13)**

To a solution of 2-(trimethylsilyl)ethynyllithium in THF [prepared from trimethylsilylacetylene (860 mg, 8.8 mmol) and a 1.59 mol/l solution of butyllithium in hexane (5.54 mL) in THF (5 mL)] was added a solution of 12 (1.00 g, 4.40 mmol) in THF (5 mL) at −78 °C under a nitrogen atmosphere and the mixture was stirred at the same temperature for 1 h. The reaction mixture was then diluted with sat. aq. NH_4Cl and extracted with ether. The extract was dried (MgSO_4) and concentrated. The residue was chromatographed
on silica gel [hexane-AcOEt (6:1)] to give 13 (1.40 g, quant.) as an oil. IR $\nu_{\text{max}}$(film) cm$^{-1}$: 3415, 2170, 1697, 1671; $^1$H-NMR (60 MHz) $\delta$: 0.17 (9 H, s, SiMe$^3$), 0.9-2.95 (10 H, m), 1.46 (9 H, s, tBu), 3.85-4.6 (3 H, m); HR-MS (FAB) m/z calcd for C$_{17}$H$_{32}$NO$_3$Si: 326.2151, found: 326.2156 (MH$^+$).

**tert-Butyl 4-[4-(Trimethylsilyl)but-3-ynyl]piperidine-1-carboxylate (15)** Carbon tetrabromide (3.20 g, 9.65 mmol) and triphenylphosphine (2.50 g, 9.53 mmol) were added to a solution of 13 (2.10 g, 6.45 mmol) in dichloromethane (15 mL) at 0°C and the whole was stirred at rt for 1 h. After evaporation of the solvent, the residue was dissolved in acetone and the resulting precipitate was filtered off. The filtrate was concentrated and the residue was chromatographed on silica gel [hexane-AcOEt (15:1)] to give tert-butyl 4-[2-bromo-4-(trimethylsilyl)but-3-ynyl]piperidine-1-carboxylate (14) (2.56 g, quant.) as an oil. IR $\nu_{\text{max}}$(film) cm$^{-1}$: 2171, 1697; $^1$H-NMR (60 MHz) $\delta$: 0.19 (9 H, s, SiMe$^3$), 0.9-2.1 (7 H, m), 1.47 (9 H, s, tBu), 2.4-3.0 (2 H, m), 3.9-4.3 (2 H, m), 4.53 (1 H, $\text{t, } J = 7.2$ Hz). To a solution of the bromide thus obtained (1.00 g, 2.57 mmol) in toluene (30 mL) was added dropwise a solution of Bu$_3$SnH (1.12 g, 3.85 mmol) and AIBN (42 mg, 0.26 mmol) in toluene (20 mL) under reflux and the whole was further refluxed for 1 h. After cooling and concentration of the mixture, ether (20 mL) and 8% aq. KF (20 mL) were added to the residue, and the mixture was vigorously stirred for 30 min. The organic layer was separated, dried (MgSO$_4$), and concentrated. The residue was chromatographed on silica gel [hexane-AcOEt (20:1)] to give 15 (594 mg, 75%) as an oil. IR $\nu_{\text{max}}$(film) cm$^{-1}$: 2173, 1697; $^1$H-NMR (60 MHz) $\delta$: 0.14 and 0.17 (total 9 H, both s, SiMe$^3$), 0.9-3.0 (11 H, m), 1.45 (9 H, s, tBu), 3.85-4.3 (2 H, m); HR-MS (FAB) m/z calcd for C$_{17}$H$_{32}$NO$_2$Si: 310.2203, found: 310.2192 (MH$^+$).

**1-(o-Iodobenzoyl)-4-[4-(trimethylsilyl)but-3-ynyl]piperidine (16)** Following the procedure described for the preparation of 12, 16 (594 mg, 77%) was obtained from 15 (543 mg, 1.75 mmol) and o-iodobenzoyl chloride (610 mg, 2.29 mmol) as an oil. IR $\nu_{\text{max}}$(film) cm$^{-1}$: 2171, 1637; $^1$H-NMR (400 MHz) $\delta$: 0.143 (9 H x 1/2, s), 0.145 (9 H x 1/2, s), 0.97-1.09 (0.5 H, m), 1.16-1.74 (5.5 H, m), 1.79-1.90 (1 H, m), 2.26 (2 H, td, $J = 7.3$, 1.1 Hz), 2.78 (1 H, tdd, $J = 12.9$, 8.4, 2.9 Hz), 2.93 (0.5 H, ddd, $J = 13.2$, 12.2, 3.1 Hz), 3.07 (0.5 H, ddd, $J = 13.2$, 12.2, 2.9 Hz), 3.32-3.39 (0.5 H, m), 3.37-3.44 (0.5 H, m), 4.71-4.77 (0.5 H, m), 4.75-4.81 (0.5 H, m), 7.06 (1 H, td, $J = 7.5$, 1.6 Hz), 7.15 (0.5 H, dd, $J = 7.5$, 1.6 Hz), 7.21 (0.5 H, dd, $J = 7.5$, 1.6 Hz), 7.37 (0.5 H, td, $J = 7.5$, 1.1 Hz), 7.38 (0.5 H, td, $J = 7.5$, 1.1 Hz), 7.82 (0.5 H, dd, $J = 7.5$, 1.1 Hz), 7.84 (0.5 H, dd, $J = 7.5$, 1.1 Hz); Exact MS m/z: calcd for C$_{19}$H$_{26}$NOISi: 439.0829, found: 439.0827.

**Radical Cyclization of 12** A solution of Bu$_3$SnH (359 mg, 1.23 mmol) and AIBN (13 mg, 0.08 mmol) in toluene (35 mL) was added dropwise to a solution of 12 (350 mg, 0.82 mmol) in boiling toluene (25 mL) over a period of 1 h and the whole was refluxed for additional 1 h. After evaporation of the solvent, ether (20 mL) and 8% aq. KF (20 mL) were added and the whole was vigorously stirred at rt for 30 min. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layer and extracts were dried (MgSO$_4$) and concentrated. The residue was chromatographed on
The first fraction gave a diastereomer of 2-benzyol-7-(trimethylsilyl)methylene-2-azabicyclo[3.2.1]octane (17a) (84 mg, 34%), mp 93-94 °C [from light petroleum (bp 30-70 °C)]; IR νmax(CCl4) cm⁻¹: 1625; ¹H-NMR (300 MHz, for a mixture of two conformers in the ratio of ca. 4:1) δ: -0.24 (9 H x 1/5, s), 0.15 (9 H x 4/5, s), 1.32-1.43 (1 H, m), 1.55-1.68 (1 H, m), 1.71-2.02 (2 H, m), 2.29-2.61 (3 H, m), 3.02 (0.2 H, td, J = 13.2, 4.4 Hz), 3.40 (0.8 H, J = 13.2, 4.4 Hz), 3.49 (0.8 H, dd, J = 13.2, 6.8 Hz), 4.45 (0.2 H, dd, J = 13.2, 6.8 Hz), 4.59 (0.2 H, br d, J = 4.0 Hz), 5.39 (0.8 H, br d, J = 3.3 Hz), 5.67 (0.2 H, br s), 5.79 (0.8 H, br s), 7.35 (5 H, s, ArH); Exact MS m/z: calcd for C18H25NOSi: 299.1705, found: 299.1708. The second fraction gave another diastereomeric 2-benzyol-7-(trimethylsilyl)methylene-2-azabicyclo[3.2.1]octane (17b) (99 mg, 51%), mp 74.5-75.5 °C [from light petroleum (bp 30-70 °C)]; IR νmax(CCl4) cm⁻¹: 1625; ¹H-NMR (300 MHz, for a mixture of two conformers in the ratio of ca. 2:1) δ: 0.09 (9 H x 2/3, s), 0.15 (9 H x 1/3, s), 1.34-1.44 (0.3 H, m), 1.52-1.76 (2.7 H, m), 1.78-1.91 (1 H, m), 2.24-2.59 (3 H, m), 2.97 (0.7 H, td, J = 13.9, 5.1 Hz), 3.26 (0.3 H, td, J = 13.2, 4.9 Hz), 3.43 (0.3 H, dd, J = 13.2, 6.6 Hz), 4.28 (0.7 H, br s), 4.32 (0.7 H, dd, J = 13.9, 6.8 Hz), 5.29 (0.3 H, br s), 5.44 (0.7 H, br t, J = 2.4 Hz), 5.88 (0.3 H, br s), 7.24-7.47 (5 H, m, ArH); Exact MS m/z: calcd for C18H25NOSi: 299.1705, found: 299.1703. The third fraction gave a trace amount of 18 [IR νmax(CCl4) cm⁻¹: 2160, 1630], which was not fully characterized.

Treatment of 17a with TFA  Trifluoroacetic acid (25.3 mg, 0.22 mmol) was added to a solution of 17a (30 mg, 0.10 mmol) in dichloromethane (3 mL) at 0 °C and the whole was stirred at rt for 30 min. The mixture was diluted with AcOEt (20 mL), washed with sat. aq. NaHCO₃, dried (MgSO₄), and concentrated. The residue was chromatographed on silica gel [hexane-AcOEt (5:1)] to give 2-benzyol-7-methylene-2-azabicyclo[3.2.1]octane (19) (19 mg, 83%) as an oil. IR νmax(CCl4) cm⁻¹: 1625; ¹H-NMR (300 MHz, for a mixture of two conformers in the ratio of ca. 1:1) δ: 1.08-1.92 (4 H, m), 2.25-2.56 (3 H, m), 3.02 (0.5 H, td, J = 13.6, 5.2 Hz), 3.32 (0.5 H, td, J = 13.1, 4.5 Hz), 3.44 (0.5 H, dd, J = 13.1, 6.8 Hz), 4.33 (0.5 H, dd, J = 13.6, 7.0 Hz), 4.38 (0.5 H, br s), 4.96 (0.5 H, br s), 5.05 (0.5 H, br s), 5.17 (0.5 H, br s), 5.34 (0.5 H, br s), 5.40 (0.5 H, br s), 7.38 (5 H x 1/2, br s), 7.42 (5 H x 1/2, br s). Anal. Calcd for C15H17NO: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.13; H, 7.81; N, 5.83.

Treatment of 17b with TFA  Following the procedure described for 17a, 17b (31 mg, 0.10 mmol) was treated with trifluoroacetic acid (26.1 mg, 0.23 mmol) at rt for 16 h to give 19 (21 mg, 89%).

2-Benzoyl-2-azabicyclo[3.2.1]octan-7-one (20)  A stream of ozone was passed through a solution of 19 (75 mg, 0.33 mmol) in dichloromethane (5 mL) at −78 °C for 5 min. To this solution were added acetic acid (105 mg, 1.75 mmol) and NaI (148 mg, 0.99 mmol) and the whole was stirred for 30 min at rt and 10% aq. Na₂S₂O₃ was added to the mixture. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with sat. aq. NaHCO₃, dried (MgSO₄), and concentrated. The residue was chromatographed on silica gel [hexane-AcOEt (1:1)] to give 20 (40 mg, 53%) as an oil. IR νmax(CCl4) cm⁻¹: 1751, 1632; ¹H-NMR (400 MHz, for a mixture
of two conformers in the ratio of ca. 3:2) δ: 1.52-2.14 (4 H, m), 2.18 (0.4 H, d, J = 3.3 Hz), 2.23 (0.6 H, d, J = 3.3 Hz), 2.32-2.49 (1 H, br), 2.79-2.85 (1 H, m), 2.95-3.07 (0.6 H, br), 3.21-3.37 (0.4 H, br), 3.59-3.73 (0.4 H, br), 4.05 (0.6 H, br s), 4.46-4.58 (0.6 H, br), 4.96 (0.4 H, br s), 7.27 (5 H x 3/5, br s), 7.42 (5 H x 2/5, br s); Exact MS m/z: calcd for C14H15NO2: 229.1103, found: 229.1098.

Radical Cyclization of 16  Following the same procedure described for the cyclization of 12, 16 (233 mg, 0.53 mmol) was treated with Bu3SnH (232 mg, 0.79 mmol) and AIBN (9 mg, 0.05 mmol) and the residue was chromatographed on silica gel [hexane-AcOEt (8:1)]. The first fraction gave a diastereomeric mixture of the cyclized products (22) (33 mg, 20%) as an oil, whose 1H-NMR spectrum could not be analyzed due to its complexity, and this was directly protodesilylated to 23 (vide infra). The second fraction gave 21 (124 mg, 75%) as an oil. IR νmax (film) cm⁻¹: 2171, 1635; 1H-NMR (400 MHz) δ: 0.15 (9 H, s, SiMe3), 1.03-1.33 (2 H, br), 1.51 (2 H, br q, J = 7.3 Hz), 1.61-1.90 (3 H, m), 2.27 (2 H, t, J = 7.3 Hz), 2.70-2.85 (1 H, br), 2.90-3.05 (1 H, br), 3.67-3.82 (1 H, br), 4.63-4.79 (1 H, br), 7.36-7.42 (5 H, m, ArH); HR-MS (FAB) m/z calcd for C19H28NOSi: 314.1940, found: 314.1946 (MH⁺).

Treatment of 22 with TFA  Following the procedure described for 17a, 22 (33 mg, 0.11 mmol) was treated with trifluoroacetic acid (604 mg, 5.3 mmol) in dichloromethane (5 mL) and the crude product was chromatographed on silica gel [hexane-AcOEt (8:1)] to give 2-benzoyl-8-methylene-2-azabicyclo[3.3.1]nonane (23) (20 mg, 75%), mp 107-108 °C (from hexane); IR νmax (film) cm⁻¹: 1630; 1H-NMR (400 MHz, for a mixture of two conformers in the ratio of ca. 1:1) δ: 1.56-2.08 (6 H, m), 2.09-2.18 (1 H, br), 2.28-2.43 (1 H, m), 2.51-2.65 (1 H, m), 3.38-3.58 (1.5 H, m), 4.25 (0.5 H, br s), 4.31 (0.5 H, br s), 4.40 (0.5 H, dd, J = 14.4, 7.6 Hz), 4.70 (0.5 H, br s), 4.93 (0.5 H, br s), 5.11 (0.5 H, br s), 5.31 (0.5 H, br s), 7.34-7.40 (5 H, m, ArH). Anal. Calcd for C16H19NO: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.55; H, 7.92; N, 6.00.

Synthesis of 23 from 24  To a solution of methyltriphenylphosphonium bromide (292 mg, 0.82 mmol) in THF (5 mL) was added a 1.6 mol/L solution of butyllithium in hexane (0.51 mL, 0.82 mmol) at −78 °C under a nitrogen atmosphere and the mixture was stirred at the same temperature for 1 h. A solution of 24 (100 mg, 0.41 mmol) in THF (5 mL) was added to the above mentioned mixture and the whole was stirred at rt for 1 h. The reaction mixture was poured into water and extracted with ether. The extract was dried (MgSO4) and concentrated to give the crude product which was chromatographed on silica gel [hexane-AcOEt (8:1)] affording 23 (81 mg, 82%).

ACKNOWLEDGEMENT  This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan.


