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

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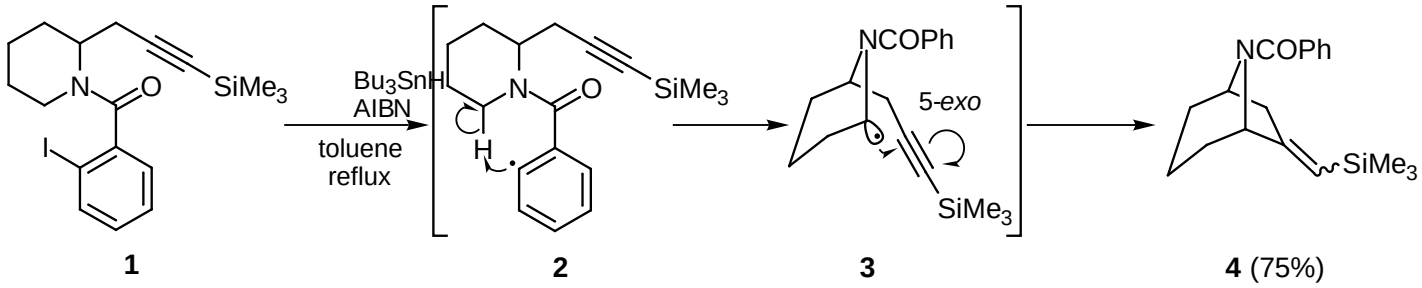
Abstract–Bu_3SnH-mediated radical translocation/cyclization reactionas of 4-alkynyl-1-(o-iodobenzoyl)piperidines were examined. The 4-[3-(trimethylsilyl)-prop-2-ynyl]- (12) and 4-[4-(trimethylsilyl)but-3-ynyl]piperidine derivatives (**16**), upon treatment with Bu3SnH in the presence of azobisisobutyronitrile 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 (morphan) (22) (20% yield as a diastereomeric mixture), respectively.

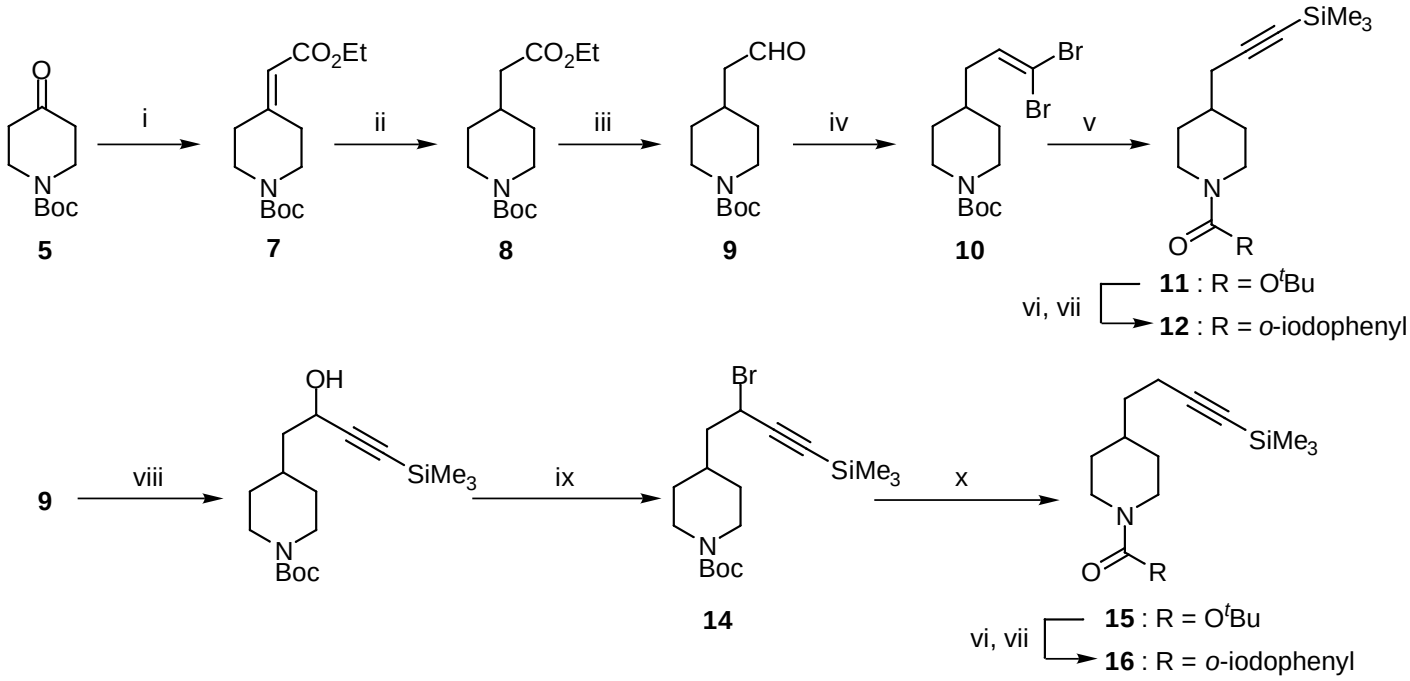
Previously we showed that 1-(*o*-iodobenzoyl)-2-(prop-2-ynyl)piperidine (**1**), upon treatment with tributyltin hydride (Bu_3SnH) in the presence of azobisisobutyronitrile (AIBN) in boiling toluene, gave regioselectively the 8-azabicyclo[3.2.1]octane (**4**).[1] A mechanistic rationalization for the formation of **4** would involve a 1,5-hydrogen transfer[2] 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]octane[3] and 2-azabicyclo[3.3.1]nonane (morphan)[4] ring systems.



1 **2** **3** **4** (75%)

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**)[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_3SnH 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**.

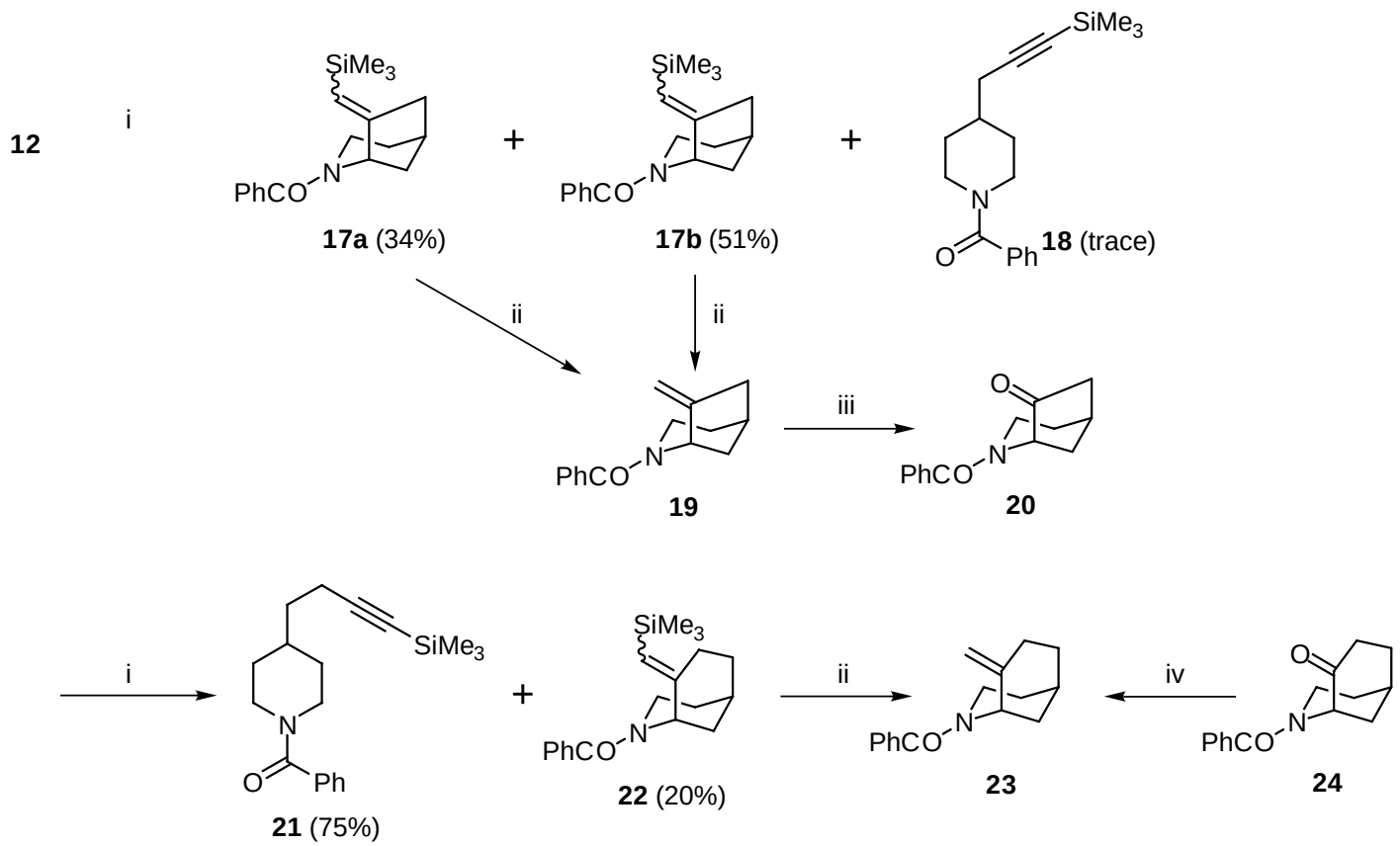


Scheme 1. *Reagents and conditions :* i, $(EtO)_2P(O)CHNaCO_2Et$ (**6**), THF, quant.; ii, H_2 (5 kg/cm^2), 10% Pd-C, AcOEt, quant.; iii, DIBAL-H, toluene, –78 ˚C, 67%; iv, $CHBr_3$, Ph_3P, *tert*-BuOK, toluene, 63%; v, BuLi, TMEDA, THF, –78 ˚C, and then Me_3SiCl, 83%; vi, 10% aq. HCl, EtOH; vii, *o*-iodobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2; viii, $Me_3SiC{\equiv}CLi$, THF, quant.; ix, CBr_4, Ph_3P, CH_2Cl_2, 99%; x, Bu_3SnH, AIBN, toluene, reflux, 75%.

Treatment of **12** with Bu_3SnH/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^{-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^{-1} (an *N*-benzoyl group) in the IR spectrum.

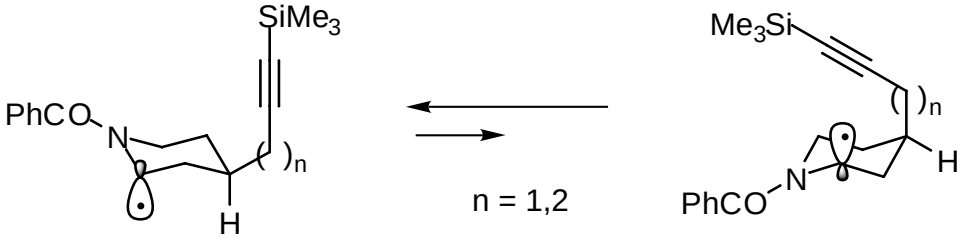
Cyclization of **16** proceeded more slowly to give the 2-azabicyclo[3.3.1]nonane (**22**) in 20% yield as a diastereomeric mixture. In this case, the reduction product (**21**) was obtained as a major product in 75%

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**.[6]



Scheme 2. *Reagents and conditions:* i, Bu_3SnH, AIBN, toluene, reflux; ii, CF_3CO_2H, CH_2Cl_2; iii, O_3, CH_2Cl_2, -78°C, and then NaI, AcOH, 53%; iv, $Ph_3P{=}CH_2$, 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.



α-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 $CDCl_3$. δ 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 PF_{254} (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**[7] (4.05 g, quant.), which was used for the next step without further purification. ^{1}H-NMR (60 MHz) δ: 1.26 (3 H, t, *J* = 7.0 Hz, $CH_2C\mathit{H}_3$), 1.46 (9 H, s, ^{t}Bu), 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, $C\mathit{H}_2CH_3$), 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**[7] (301 mg, quant.) as an oil, which was used for the next step without further purification. IR ν_{max} (CCl_4) cm^{-1}: 1735, 1690; ^{1}H-NMR (60 MHz) δ: 1.0-3.0 (9 H, m), 1.25 (3 H, t, *J* = 7.0 Hz, $CH_2C\mathit{H}_3$), 3.9-4.3 (2 H, m), 4.12 (2 H, q, *J* = 7.0 Hz, $C\mathit{H}_2CH_3$).

***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_4Cl (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 ν_{max}(film) cm^{-1}: 1724, 1691; ^{1}H-NMR (400 MHz) δ: 1.18 (2 H, qd, *J* = 12.5, 4.4 Hz), 1.45 (9 H, s, ^{t}Bu), 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 *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 $\nu_{max}(CCl_4)$ cm^{-1}: 1690; ^{1}H-NMR (60 MHz) δ: 0.95-2.2 (7 H, m), 1.45 (9 H, s, ^{t}Bu), 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, ^{t}Bu), 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 $\nu_{max}(CCl_4)$ 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 $C_{18}H_{24}NOISi$: 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 ν_{max}(film) cm^{-1}: 3415, 2170, 1697, 1671; ^{1}H-NMR (60 MHz) δ: 0.17 (9 H, s, $SiMe_3$), 0.9-2.95 (10 H, m), 1.46 (9 H, s, ^{t}Bu), 3.85-4.6 (3 H, m); HR-MS (FAB) *m/z* calcd for $C_{17}H_{32}NO_3Si$: 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 ν_{max}(film) cm^{-1}: 2171, 1697; ^{1}H-NMR (60 MHz) δ: 0.19 (9 H, s, $SiMe_3$), 0.9-2.1 (7 H, m), 1.47 (9 H, s, ^{t}Bu), 2.4-3.0 (2 H, m), 3.9-4.3 (2 H, m), 4.53 (1 H, 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_3SnH (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 ν_{max}(film) cm^{-1}: 2173, 1697; ^{1}H-NMR (60 MHz) δ: 0.14 and 0.17 (total 9 H, both s, $SiMe_3$), 0.9-3.0 (11 H, m), 1.45 (9 H, s, ^{t}Bu), 3.85-4.3 (2 H, m); HR-MS (FAB) *m/z* calcd for $C_{17}H_{32}NO_2Si$: 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 ν_{max}(film) cm^{-1}: 2171, 1637; ^{1}H-NMR (400 MHz) δ: 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_3SnH (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

silica gel [hexane-AcOEt (20:1)]. The first fraction gave a diastereomer of 2-benzoyl-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 $\nu_{max}(CCl_4)$ cm^{-1}: 1625; ^{1}H-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), 7.38 (5 H, s, ArH); Exact MS *m/z*: calcd for $C_{18}H_{25}NOSi$: 299.1705, found: 299.1708. The second fraction gave another diastereomeric 2-benzoyl-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 $\nu_{max}(CCl_4)$ cm^{-1}: 1625; ^{1}H-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 $C_{18}H_{25}NOSi$: 299.1705, found: 299.1703. The third fraction gave a trace amount of **18** [IR $\nu_{max}(CCl_4)$ 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. $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel [hexane-AcOEt (5:1)] to give 2-benzoyl-7-methylene-2-azabicyclo[3.2.1]octane (**19**) (19 mg, 83%) as an oil. IR $\nu_{max}(CCl_4)$ cm^{-1}: 1625; ^{1}H-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 $C_{15}H_{17}NO$: 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. $Na_2S_2O_3$ 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. $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel [hexane-AcOEt (1:1)] to give **20** (40 mg, 53%) as an oil. IR $\nu_{max}(CCl_4)$ cm^{-1}: 1751, 1632; ^{1}H-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 $C_{14}H_{15}NO_2$: 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 Bu_3SnH (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 ^{1}H-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 ν_{max}(film) cm^{-1}: 2171, 1635; ^{1}H-NMR (400 MHz) δ: 0.15 (9 H, s, $SiMe_3$), 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 $C_{19}H_{28}NOSi$: 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 ν_{max}(film) cm^{-1}: 1630; ^{1}H-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 $C_{16}H_{19}NO$: 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**[6] (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 ($MgSO_4$) and concentrated to give the crude product which was chromatographed on silica gel [hexane-AcOEt (8:1)] affording **23** (81 mg, 82%).

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