PRELIMINARY STUDY OF THE TOTAL SYNTHESIS OF BAO GONG TENG A ANALOGS USING 8-BENZYL-2-OXO-8-AZABICYCLO[3.2.1]-OCT-3-ENE-6-*ENDO/EXO*- AND 7-*ENDO/EXO*-CARBONITRILE

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Abstract - The use of four cycloadducts from the Katritzky reaction for subsequent preparation of Bao Gong Teng A analogs was studied. We show that the reduction of 2-oxo-8-azabicyclo[3.2.1]octanes (**1-4**) to alcohols allows the 2-*exo/endo* isomerism to be exploited. The 7-*endo* compound (**4**) also yielded azatricyclo[5.2.1.$0^{4,8}$]decanone (**12**) from alcohol (**11**). When the nitrile was converted into an acetyl group, 6-*endo* products (**13**) and (**14**) were isomerized to 6-*exo*. Trimethylsilyloxy derivatives (**13-18**) ultimately yielded 2-hydroxy-azabicyclooctethanone (**22-24**). These results afford an approach to the synthesis of the 6-*exo* 2-*endo*, 7-*exo* 2-*exo* and 7-*exo* 2-*endo* isomers of Bao Gong Teng A.

Bao Gong Teng A (6-*exo*-acetyloxy-8-azabicyclo[3.2.1]octan-2-*exo*-ol) is an alkaloid isolated from the Chinese herb *Erycibe obtusifolia* (Figure 1).[1-3] It has a hypotensive and myotic action and so is of interest

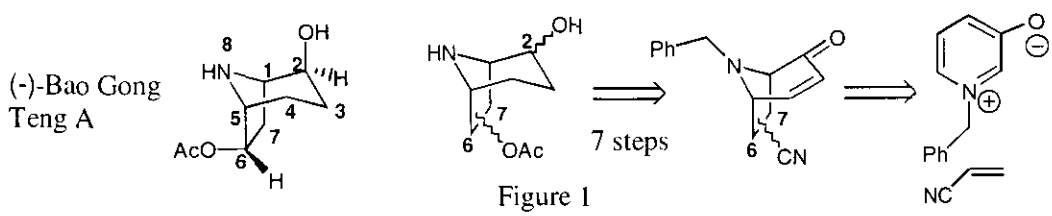
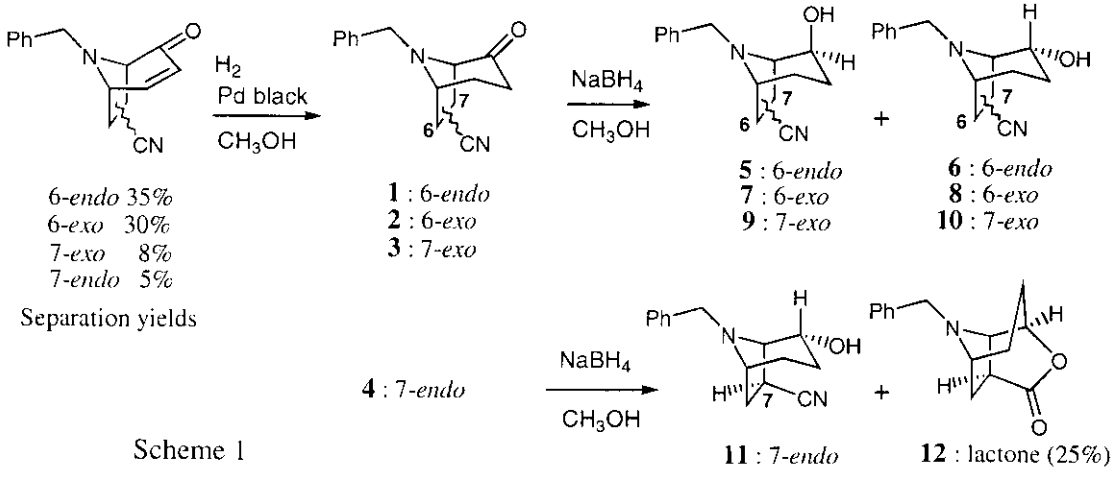


Figure 1

for the treatment of glaucoma.[4,5] In a previous study showed that the use of rhenium and technetium radioligands offers a powerful tool for the study of tropane derivative receptors.[6] Tropane derivatives can bind to monoaminergic transporters, in particular those of dopamine, and may be implicated in neurodegenerative processes.[7,8] Total syntheses of Bao Gong Teng A, both racemic[9] and asymmetric,[10] and of its 6-*endo* diastereoisomer,[11] have already been achieved. The main step is the Katritzky reaction,[12] i.e., the 1,3-dipolar cycloaddition of a dipolarophile onto the betaine of a 3-hydroxypyridinium salt (Figure 1), first reported to yield only the 6-*exo*, 6-*endo* and occasionally 7-*endo* isomers.[13-15] The recent isolation of the 7-*exo* and 7-*endo* cyclo-adducts from this reaction,[16] led us to consider using them to obtain Bao Gong Teng A analogs for pharmacological screening. As conditions for separating 6- and 7-carbonitrile isomers were also established, we applied to them the operating conditions of the Jung-Longmei synthesis.[9] In the carbonyl reduction step, we improved the separation yields of the two alcohols (2-*endo*/*exo*), enabling us to use them for the synthesis of new Bao Gong Teng A analogs (Figure 1). The synthetic scheme in Figure 1 was applied to all the isomer combinations. Yields after chromatographic work-up of the four cycloadducts are given in Scheme 1. Catalytic hydrogenation on palladium black gave saturated ketones (**1-4**) in quantitative yields. Reduction of the carbonyl function with sodium borohydride gave 2-*exo* and 2-*endo* alcohols (**5-10**) for the 6-*endo*, 6-*exo* and 7-*exo* isomers (Scheme 1).



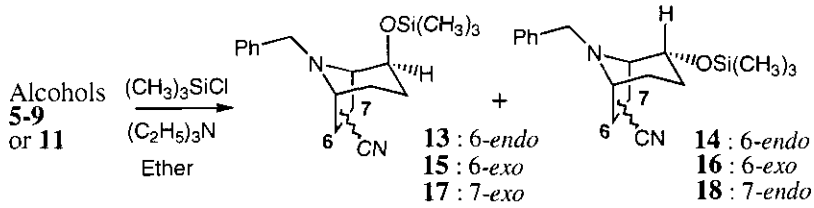
Scheme 1

These were then separated by elution with dichloromethane on an alumina column. Their formation ratio and separation yields are given in Table 1. The reduction of 7-*endo* ketone (**4**) afforded novel tricyclic lactone (**12**) in addition to 2-*endo* alcohol (**11**) (Scheme 1). This tropane lactone results from basic hydrolysis of the cyano function by the newly formed 2-*endo* hydroxyl group.[17] Only the 7-*endo* ketone gives this lactone because it is the only isomer in which the positions of the cyano and hydroxyl groups are favorable. For the 7-*exo* isomer the synthesis was continued on 2-*exo* compound (**9**), given a small amount of 2-*endo* alcohol (**10**) (Table 1). The hydroxyl groups of compounds (**5-9**) and (**11**) were

protected by silylation (yields: 67-88%) before undergoing a Grignard reaction on their cyano function (Scheme 2).

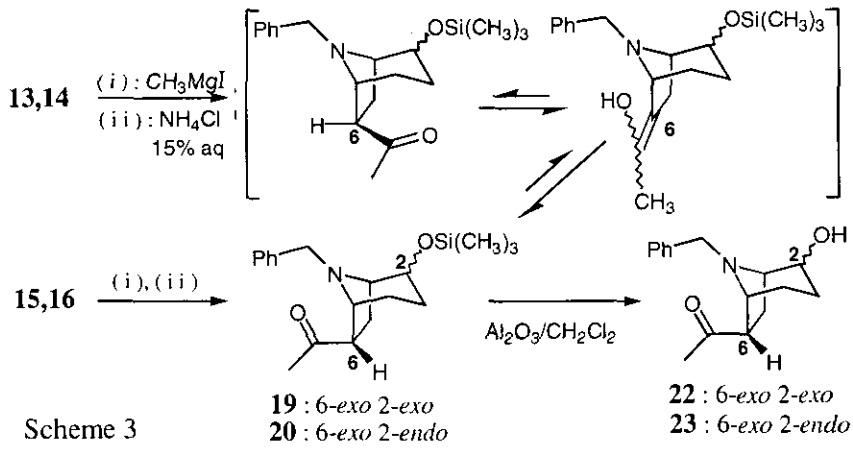
Isomer	Yield (%) 2-*exo*	Yield (%) 2-*endo*	Formation ratio[a] 2-*exo*/*endo*
6-*endo*	33 (**5**)	35 (**6**)	55/45
6-*exo*	39 (**7**)	28 (**8**)	60/40
7-*exo*	58 (**9**)	7 (**10**)	90/10
7-*endo*	-	31 (**11**)	-

Table 1 [a]: determined from NMR spectra



Scheme 2

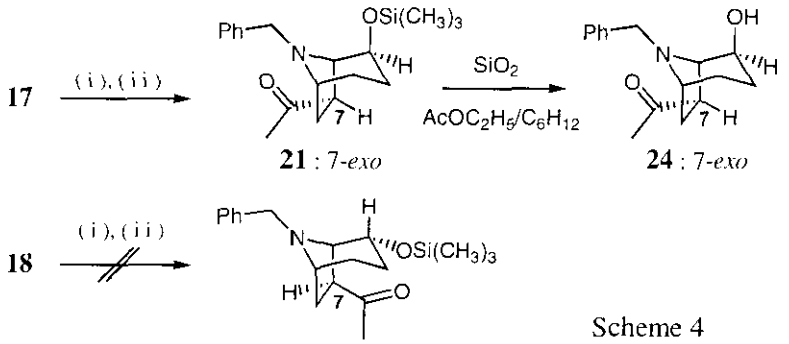
Protected compounds (**13-18**) were treated with methylmagnesium iodide (Scheme 3). Hydrolysis of the intermediate imines with aqueous ammonium chloride gave the acetylated derivatives, except for **18**, where steric hindrance at the 7-*endo* position apparently impedes the action of the Grignard reagent (Scheme 3). For 6-*endo* compounds (**13**) and (**14**), the carbonyl function formed is in equilibrium with its enol isomer. Reprotonation of the 6-carbon of the intermediate enols leads, for steric reasons, to the *thermodynamically more stable 6-exo* ketones (**19**) and (**20**).[18]



Scheme 3

The 7-*exo* 2-*exo* isomer (**17**) gave ketone (**21**). Silylated ketones (**19-21**) were obtained, showing that deprotection does not occur during hydrolysis, but during the chromatographic work-up, to give ketones (**22-24**). The partially hydrated stationary phase (silica or alumina) may replace the silicon in the

protected group, *via* a free hydroxyl function. In conclusion, from hydrogenated cycloadducts (**1-4**) we obtained 2-*exo* and 2-*endo* alcohols (**5-10**). From the 7-*endo* isomer we obtained tropane lactone (**12**). We also obtained 7-*exo* 2-*exo* ketone (**21**) and found that the 6-*endo* ketones isomerized to 6-*exo* ketones (**19**) and (**20**). In this step, 7-*endo* 2-*endo* nitrile (**18**) appears to be too sterically hindered to react (Scheme 4). We also show that cleavage of silylated ethers took place on a chromatographic stationary phase, affording ketones (**22-24**). This work should allow the subsequent synthesis of several Bao Gong Teng A analogs, in particular 6-*exo* 2-*endo*, 7-*exo* 2-*exo*, and 7-*exo* 2-*endo* isomers.



Scheme 4

ACKNOWLEDGEMENTS

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EXPERIMENTAL

General. TLC was carried out on Al_2O_3 (Neutral alumina 60 F_{254}, Merck, type E) or SiO_2 (Kieselgel 60 F_{254}), and the spots were located with UV light. Column chromatography was carried out on Al_2O_3 (Merck aluminium oxyde 90) and/or SiO_2 (Chromagel 60 ACC). Melting points were determined on a Kofler hot-plate melting point apparatus and are not corrected. IR spectra were obtained on a Beckman AccuLab 2 spectrophotometer. Absorption bands are expressed in cm^{-1} and only noteworthy absorptions are listed. ^1H and ^{13}C-NMR spectra were recorded on a Brüker AC-400 spectrometer working at 400 MHz (^1H-NMR) and 100 MHz (^{13}C-NMR) in $CDCl_3$. Chemical shifts are reported in ppm downfield δ from TMS. Coupling constants, J, are given in Hz. MS spectrometry was done on HEWLETT PACKARD 5985B - 5989A instruments. Elemental analyses were performed by Microanalytical Center, ENSCM, Montpellier (France). 8-Benzyl-2-oxo-8-azabicyclo[3.2.1]octane-6-*exo*-carbonitrile (**2**), 8-benzyl-2-*exo*-hydroxy-8-azabicyclo[3.2.1]octane-6-*exo*-carbonitrile (**7**), 8-benzyl-2-*endo*-hydroxy-8-azabicyclo[3.2.1] octane-6-*exo*-carbonitrile (**8**), 8-benzyl-2-*exo*-[(trimethylsilyl)oxy]-8-azabicyclo-[3.2.1]octane-6-*exo*-car-bonitrile (**15**) and 1-[8-benzyl-2-*exo*-hydroxy-8-azabicyclo[3.2.1]oct-6-*exo*-yl]-ethanone (**22**) are known compounds.[9]

General procedure (A) for preparation of 8-benzyl-2-oxo-8-azabicyclo[3.2.1]octane-6 (or 7)-carbonitrile (**1-4**) : To a solution of the corresponding 8-benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6 (or 7)-carbonitrile (20 mmol) in anhydrous methanol (40 mL) was added 106 mg (1 mmol) of black palladium. The mixture was subjected to catalytic hydrogenation at rt and at atmospheric pressure for 5 h. The black palladium was filtered off and washed with methanol and the filtrate evapored under reduced pressure to give the saturated ketone.

8-Benzyl-2-oxo-8-azabicyclo[3.2.1]octane-6-*endo*-carbonitrile (1) : This compound is obtained from the general procedure A with 8-benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6-*endo*-carbonitrile (6.9 g, 29 mmol) ; Yield : 94 % ; Oil ; Rf 0.77 (Al_2O_3, CH_2Cl_2) ; IR (CCl_4) ν 2250, 1726 ; ^{1}H NMR δ 2.09 (dd, 1H, $J_{7endo,7exo}$ = 14 Hz, $J_{7endo,6}$ = 6 Hz, H-7-*endo*), 2.26-2.76 (m, 5H, 2 x H-3, 2 x H-4, H-7-*exo*), 3.37 (td, 1H, $J_{6,7exo}$ = 12.5 Hz, $J_{6,5}$ = $J_{6,7endo}$ = 6 Hz, H-6), 3.43 (d, 1H, $J_{1,7exo}$ = 7.5 Hz, H-1), 3.60 (m, 1H, H-5), 3.69 (AB pattern, 2H, J = 13.5 Hz, NCH_2), 7.25-7.37 (m, 5H, Ph) ; ^{13}C NMR δ 26.14, 32.29 and 32.60 (C-3, C-4 and C-7), 28.75 (C-6), 54.34 (NCH_2), 59.15 (C-5), 68.67 (C-1), 120.34 (CN), 127.74 (1C, Ph), 128.46 (2C, Ph) 128.61 (2C, Ph), 137.06 (1C, Ph), 207.0 (C=O) ; MS (m/z, relative intensity) 240 ($M^{+\cdot}$, 2), 212 (17), 158 (21), 91 (100), 65 (24) ; Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97 ; H, 6.71 ; N, 11.66. Found : C, 74.88 ; H, 6.68 ; N, 11.90.

8-Benzyl-2-oxo-8-azabicyclo[3.2.1]octane-6-*exo*-carbonitrile (2) : This compound is obtained from the general procedure A with 8-benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6-*exo*-carbonitrile (6.25 g, 26.2 mmol) ; Yield : 98 % ; mp 82-84 °C (recrystallization solvent : CH_3OH) ; Rf 0.60 (Al_2O_3, CH_2Cl_2) ; IR (CCl_4) ν 2245, 1728 ; ^{1}H NMR δ 1.83 (m, 1H, H-7-*endo*), 2.19-2.44 (m, 4H, 2 x H-3, 2 x H-4), 2.62 (ddd, 1H, $J_{7exo,7endo}$ = 14 Hz, $J_{7exo,1}$ = 7.5 Hz, $J_{7exo,6}$ = 5.5 Hz, H-7-*exo*), 3.03 (dd, 1H, $J_{6,7endo}$ = 9.5 Hz, $J_{6,7exo}$ = 5.5 Hz, H-6), 3.57 (d, 1H, $J_{1,7exo}$ = 7.5 Hz, H-1), 3.76 (s, 1H, H-5), 3.86 (AB pattern, 2H, J = 13.5 Hz, NCH_2), 7.25-7.42 (m, 5H, Ph) ; ^{13}C NMR δ 28.76, 32.38 and 33.10 (C-3, C-4 and C-7), 30.42 (C-6), 54.14 (NCH_2), 62.20 (C-5), 69.53 (C-1), 122.54 (CN), 127.54 (1C, Ph), 128.47 (4C, Ph), 137.14 (1C, Ph), 206.71 (C=O) ; MS (m/z, relative intensity) 240 ($M^{+\cdot}$, 1), 212 (35), 131 (13), 91 (100), 65 (19) ; Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97 ; H, 6.71 ; N, 11.66. Found : C, 75.04 ; H, 6.94 ; N, 11.54.

8-Benzyl-2-oxo-8-azabicyclo[3.2.1]octane-7-*exo*-carbonitrile (3) : This compound is obtained from the general procedure A with 8-benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-7-*exo*-carbonitrile (1.9 g, 8 mmol) ; Yield : 84 % ; Oil ; Rf 0.69 (Al_2O_3, CH_2Cl_2) ; IR (CCl_4) ν 2245, 1728 ; ^{1}H NMR δ 1.77 (m, 1H, H-6-*endo*), 2.20-2.40 (m, 4H, 2 x H-3, 2 x H-4), 2.61 (ddd, 1H, $J_{6exo,6endo}$ = 13 Hz, $J_{6exo,5}$ = 6 Hz, $J_{6exo,7}$ = 5.5 Hz, H-6-*exo*), 3.05 (dd, 1H, $J_{7,6endo}$ = 10 Hz, $J_{7,6exo}$ = 5.5 Hz, H-7), 3.59 (m, 1H, $J_{5,6exo}$ = 6 Hz, H-5), 3.70 (s, 1H, H-1), 3.86 (AB pattern, 2H, J = 13.5 Hz, NCH_2), 7.29-7.42 (m, 5H, Ph) ; ^{13}C NMR δ 28.94, 32.56 and 33.44 (C-3, C-4 and C-6), 29.62 (C-7), 54.21 (NCH_2), 57.44 (C-5), 73.03 (C-1), 121.71 (CN), 127.36 (1C, Ph), 128.25 (2C, Ph), 128.33 (2C, Ph), 137.15 (1C, Ph), 204.69 (C=O) ; MS (m/z, relative intensity)

240 ($M^{+\cdot}$, 2), 212 (16), 183 (12), 91 (100), 65 (20) ; Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97 ; H, 6.71 ; N, 11.66. Found : C, 75.27 ; H, 6.64 ; N, 11.67.

8-Benzyl-2-oxo-8-azabicyclo[3.2.1]octane-7-*endo*-carbonitrile (4) : This compound is obtained from the general procedure A with 8-benzyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-7-*endo*-carbonitrile (1.64 g, 6.9 mmol) ; Yield : 99 % ; Oil ; Rf 0.82 (Al_2O_3, CH_2Cl_2) ; IR (CCl_4) ν 2240, 1720 ; ^{1}H NMR δ 1.88 (dd, 1H, J = 8.5 Hz, J = 10.5 Hz), 2.10 (dd, 1H, $J_{6endo,6exo}$ = 13 Hz, $J_{6endo,7}$ = 5.5 Hz, H-6-*endo*), 2.26 (m, 1H), 2.57 (m, 2H), 2.73 (ddd, 1H, $J_{6exo,6endo}$ = 13 Hz, $J_{6exo,7}$ = 12.5 Hz, $J_{6exo,5}$ = 7 Hz, H-6-*exo*), 3.38 (ddd, 1H, $J_{7,6exo}$ = 12.5 Hz, $J_{7,1}$ = 6 Hz, $J_{7,6endo}$ = 5.5 Hz, H-7), 3.50 (m, 1H, H-1), 3.61 (d, 1H, $J_{5,6exo}$ = 7 Hz, H-5), 3.67 (s, 2H, NCH_2), 7.26-7.43 (m, 5H, Ph) ; ^{13}C NMR δ 28.40 (C-7), 29.53, 32.47 and 33.54 (C-3, C-4 and C-6), 54.32 (NCH_2), 57.23 (C-5), 71.91 (C-1), 119.26 (CN), 127.59 (1C, Ph), 128.41 (2C, Ph), 128.50 (2C, Ph), 137.13 (1C, Ph), 204.47 (C=O) ; MS (m/z, relative intensity) 240 ($M^{+\cdot}$, 4), 212 (18), 158 (12), 91 (100), 65 (22) ; Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97 ; H, 6.71 ; N, 11.66. Found : C, 75.09 ; H, 6.70 ; N, 11.74.

General procedure (B) for preparation of 8-benzyl-2-hydroxy-8-azabicyclo[3.2.1]octane-6 (or 7)-carbonitrile (**5-12**) : Sodium borohydride (0.76 g, 20 mmol) was added at rt in portions with stirring to a solution of the corresponding 8-benzyl-2-oxo-8-azabicyclo[3.2.1]octane-6 (or 7)-carbonitrile (**1-4**) (10 mmol) in 100 mL of methanol, and the mixture was stirred for 3 h. Evaporation of the solvent under reduced pressure afforded a residue to which water (50 mL) was added. The mixture was extracted (CH_2Cl_2) and the organic extracts were dried (Na_2SO_4). After solvent removal, the mixture was chromatographed.

Compounds (**5**) and (**6**) : These compounds are obtained from the general procedure B with **1** (4 g, 16.6 mmol), and are isolated as a pure product by chromatography (Al_2O_3, CH_2Cl_2).

8-Benzyl-2-*exo*-hydroxy-8-azabicyclo[3.2.1]octane-6-*endo*-carbonitrile (5) : Yield : 33 % ; mp 73-74 °C (recrystallization solvent : CH_2Cl_2) ; Rf 0.70 (Al_2O_3, CH_2Cl_2) ; IR (CCl_4) ν 3508, 2240 ; ^{1}H NMR δ 1.65 (dd, 1H, $J_{7endo,7exo}$ = 13.5 Hz, $J_{7endo,6}$ = 5.5 Hz, H-7-*endo*), 1.77-2.00 (m, 4H, 2 x H-3, 2 x H-4), 2.55 (ddd, 1H, $J_{7exo,7endo}$ = 13.5 Hz, $J_{7exo,6}$ = 12.5 Hz, $J_{7exo,1}$ = 7.5 Hz, H-7-*exo*), 3.22-3.35 (m, 3H, H-5, H-6 and OH), 3.43 (m, 1H, H-1), 3.45 (s, 2H, NCH_2), 3.63 (m, 1H, H-2), 7.27-7.39 (m, 5H, Ph) ; ^{13}C NMR δ 24.21, 25.60 and 30.91 (C-3, C-4 and C-7), 26.51 (C-6), 57.84 (NCH_2), 62.20, 65.57 and 68.33 (C-1, C-2 and C-5), 120.92 (CN), 127.81 (1C, Ph), 128.66 (2C, Ph), 128.74 (2C, Ph), 137.70 (1C, Ph) ; MS (m/z, relative intensity) 242 ($M^{+\cdot}$, 4), 151 (17), 91 (100), 65 (27) ; Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35 ; H, 7.49 ; N, 11.56. Found : C, 74.48 ; H, 7.55 ; N, 11.68.

8-Benzyl-2-*endo*-hydroxy-8-azabicyclo[3.2.1]octane-6-*endo*-carbonitrile (6) : Yield : 35 % ; mp 90-92

°C (recrystallization solvent : CH_2Cl_2) ; Rf 0.31 (Al_2O_3, CH_2Cl_2) ; IR (CCl_4) ν 3480, 2247 ; ^{1}H NMR δ 1.43-1.98 (m, 4H, 2 x H-3, 2 x H-4), 2.03 (s, 1H, OH), 2.18 (dd, 1H, $J_{7endo,7exo}$ = 14 Hz, $J_{7endo,6}$ = 6 Hz, H-7-*endo*), 2.34 (ddd, 1H, $J_{7exo,7endo}$ = 14 Hz, $J_{7exo,6}$ = 12 Hz, $J_{7exo,1}$ = 7 Hz, H-7-*exo*), 3.18 (m, 1H, H-1), 3.23 (ddd, 1H, $J_{6,7exo}$ = 12 Hz, $J_{6,7endo}$ = J_{6-5} = 6 Hz, H-6), 3.36 (m, 1H, H-5), 3.52 (AB pattern, 2H, J = 13.5 Hz, NCH_2), 3.89 (m, 1H, H-2), 7.25-7.38 (m, 5H, Ph) ; ^{13}C NMR δ 25.94, 27.40 and 27.52 (C-3, C-4 and C-7), 27.83 (C-6), 57.08 (NCH_2), 61.30, 64.91 and 69.10 (C-1, C-2 and C-5), 120.90 (CN), 127.36 (1C, Ph), 128.41 (2C, Ph), 28.44 (2C, Ph), 138.45 (1C, Ph) ; MS (m/z, relative intensity) 242 ($M^{+\cdot}$, 12), 151 (21), 91 (100), 65 (23) ; Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35 ; H, 7.49 ; N, 11.56. Found : C, 74.35 ; H, 7.50 ; N, 11.48.

Compounds (**7**) and (**8**) : These compounds are obtained from the general procedure B with **2** (5.2 g, 21.6 mmol), and are isolated as a pure product by chromatography (Al_2O_3, CH_2Cl_2).

8-Benzyl-2-*exo*-hydroxy-8-azabicyclo[3.2.1]octane-6-*exo*-carbonitrile (7) : Yield : 39 % ; mp 77-80 °C (recrystallization solvent : CH_2Cl_2) ; Rf 0.72 (Al_2O_3, CH_2Cl_2) ; IR (KBr) ν 3495, 2240 ; ^{1}H NMR δ 1.43 (m, 2H), 1.59 (m, 1H), 1.89 (m, 1H), 2.10 (dd, 1H, $J_{7endo,7exo}$ = 14 Hz, $J_{7endo,6}$ = 10 Hz, H-7-*endo*), 2.52 (ddd, 1H, $J_{7exo,7endo}$ = 14 Hz, $J_{7exo,1}$ = 7 Hz, $J_{7exo,6}$ = 5.5 Hz, H-7-*exo*), 2.87 (dd, 1H, $J_{6,7endo}$ = 10 Hz, $J_{6,7exo}$ = 5.5 Hz, H-6), 3.46 (m, 1H), 3.58 (m, 1H), 3.65 (s, 1H), 3.68 (d, 1H, J = 13 Hz, CH_2-N), 3.87 (d, 1H, J = 13 Hz, NCH_2), 7.30-7.47 (m, 5H, Ph) ; ^{13}C NMR δ 24.04, 28.44 and 31.81 (C-3, C-4 and C-7), 28.18 (C-6), 57.89 (NCH_2), 65.15, 66.59 and 67.79 (C-1, C-2 and C-5), 123.54 (CN), 127.51 (1C, Ph), 128.61 (2C, Ph), 128.90 (2C, Ph), 137.97 (1C, Ph) ; MS (m/z, relative intensity) 242 ($M^{+\cdot}$, 11), 151 (26), 91 (100), 65 (23) ; Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35 ; H, 7.49 ; N, 11.56. Found : C, 74.07 ; H, 7.46 ; N, 11.74.

8-Benzyl-2-*endo*-hydroxy-8-azabicyclo[3.2.1]octane-6-*exo*-carbonitrile (8) : Yield : 28 % ; mp 100-103 °C (recrystallization solvent : CH_2Cl_2) ; Rf 0.40 (Al_2O_3, CH_2Cl_2) ; IR (KBr) ν 3450, 2244 ; ^{1}H NMR δ 1.09, 1.52, 1.73 and 1.87 (m, 4H, 2 x H-3, 2 x H-4), 1.70 (s, 1H, OH), 2.30 (m, 1H, $J_{7exo,7endo}$ = 14 Hz, H-7-*exo*), 2.40 (dd, 1H, $J_{7endo,7exo}$ = 14 Hz, $J_{7endo,6}$ = 9.5 Hz, H-7-*endo*), 2.72 (dd, 1H, $J_{6,7endo}$ = 9.5 Hz, $J_{6,7exo}$ = 5.5 Hz, H-6), 3.30 and 3.59 (m, 2H, H-1, H-5), 3.83 (AB pattern, 2H, J = 13.5 Hz, NCH_2), 3.85 (ddd, 1H, $J_{2,3endo}$ = 9.5 Hz, $J_{2,1}$ = $J_{2,3exo}$ = 5.5 Hz, H-2), 7.25-7.43 (m, 5H, Ph) ; ^{13}C NMR δ 25.81, 28.88 and 30.00 (C-3, C-4 and C-7), 29.80 (C-6), 57.24 (NCH_2), 64.52, 65.86 and 68.79 (C-1, C-2 and C-5), 123.91 (CN), 127.26 (1C, Ph), 128.41 (2C, Ph), 128.65 (2C, Ph), 138.0 (1C, Ph) ; MS (m/z, relative intensity) 242 ($M^{+\cdot}$, 7), 151 (20), 91 (100), 65 (23) ; Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35 ; H, 7.49 ; N, 11.56. Found : C, 74.58 ; H, 7.45 ; N, 11.76.

Compounds (**9**) and (**10**) : These compounds are obtained from the general procedure B with **3** (1.5 g,

6.25 mmol), and are isolated as a pure product by chromatography (Al_2O_3, CH_2Cl_2). **8-Benzyl-2-*exo*-hydroxy-8-azabicyclo[3.2.1]octane-7-*exo*-carbonitrile (9) :** Yield : 58 % ; Oil ; Rf 0.69 (Al_2O_3, CH_2Cl_2) ; IR (CCl_4) ν 3500, 2250 ; ^{1}H NMR δ 1.38 (m, 2H), 1.60 (m, 1H), 1.89 (m, 1H), 2.20 (dd, 1H, $J_{6endo,6exo}$ = 13 Hz, $J_{6endo,7}$ = 9.5 Hz, H-6-*endo*), 2.52 (ddd, 1H, $J_{6exo,6endo}$ = 13 Hz, $J_{6exo,7}$ = $J_{6exo,5}$ = 6 Hz, H-6-*exo*), 2.77 (dd, 1H, $J_{7,6endo}$ = 9.5 Hz, $J_{7,6exo}$ = 6 Hz, H-7), 3.36 (m, 1H), 3.44 (m, 1H), 3.61 (s, 2H), 3.77 (s, 2H, NCH_2), 7.27-7.42 (m, 5H, Ph) ; ^{13}C NMR δ 24.13, 28.02 and 31.62 (C-3, C-4 and C-6), 28.84 (C-7), 57.94 (NCH_2), 61.02, 67.45 and 70.17 (C-1, C-2 and C-5), 123.70 (CN), 127.61 (1C, Ph), 128.65 (2C, Ph), 128.86 (2C, Ph), 138.5 (1C, Ph) ; MS (m/z, relative intensity) 242 ($M^{+\cdot}$, 16), 183 (15), 151 (15), 91 (100), 65 (18) ; Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35 ; H, 7.49 ; N, 11.56. Found : C, 74.28 ; H, 7.16 ; N, 11.30.

8-Benzyl-2-*endo*-hydroxy-8-azabicyclo[3.2.1]octane-7-*exo*-carbonitrile (10) : Yield : 7 % ; Oil ; Rf 0.10 (Al_2O_3, CH_2Cl_2) ; IR (CCl_4) ν 3450, 2240 ; ^{1}H NMR δ 1.06, 1.41, 1.70 and 1.82 (m, 4H, 2 x H-3, 2 x H-4), 2.03 (dd, 1H, $J_{6endo,6exo}$ = 13.5 Hz, $J_{6endo,7}$ = 10 Hz, H-6-*endo*), 2.46 (ddd, 1H, $J_{6exo,6endo}$ = 13.5 Hz, $J_{6exo,5}$ = $J_{6exo,7}$ = 6 Hz, H-6-*exo*), 3.10 (dd, 1H, $J_{7,6endo}$ = 10 Hz, $J_{7,6exo}$ = 6 Hz, H-7), 3.36 (m, 1H), 3.50 (m, 1H), 3.81 (s, 2H, NCH_2), 3.84 (m, 1H, H-2), 7.28 (t, 1H, J = 7 Hz, Ph), 7.35 (t, 2H, J = 7 Hz, Ph), 7.42 (d, 2H, J = 7 Hz, Ph) ; ^{13}C NMR δ 25.52, 29.58 and 32.97 (C-3, C-4 and C-6), 25.58 (C-7), 57.24 (NCH_2), 59.73, 68.63 and 70.61 (C-1, C-2 and C-5), 124.35 (CN), 127.17 (1C, Ph), 128.34 (2C, Ph), 128.63 (2C, Ph), 138.73 (1C, Ph) ; MS (m/z, relative intensity) 242 ($M^{+\cdot}$, 25), 183 (29), 151 (25), 91 (100), 65 (20) ; Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35 ; H, 7.49 ; N, 11.56. Found : C, 74.46 ; H, 7.38 ; N, 11.53.

Compounds (**11**) and (**12**) : These compounds are obtained from the general procedure B with **4** (1.56 g, 6.5 mmol), and are isolated as a pure product by chromatography (SiO_2, ethyl acetate/hexanes, 9/1, v/v).

8-Benzyl-2-*endo*-hydroxy-8-azabicyclo[3.2.1]octane-7-*endo*-carbonitrile (11) : Yield : 31 % ; Oil ; Rf 0.64 (SiO_2, ethyl acetate/hexanes, 9/1, v/v) ; IR (CCl_4) ν 3350, 2240 ; ^{1}H NMR δ 1.53 (m, 1H, H-4), 1.69 (m, 1H, H-3-*endo*), 1.78 (m, 1H, H-4), 1.90 (dd, 1H, $J_{6endo,6exo}$ = 13.5 Hz, $J_{6endo,7}$ = 5.5 Hz, H-6-*endo*), 2.06 (m, 1H, H-3-*exo*), 2.17 (m, 1H, OH), 2.58 (ddd, 1H, $J_{6exo,6endo}$ = 13.5 Hz, $J_{6exo,7}$ = 12.5 Hz, $J_{6exo,5}$ = 6.5 Hz, H-6-*exo*), 3.20 (ddd, 1H, $J_{7,6exo}$ = 12.5 Hz, $J_{7,1}$ = 6.5 Hz, $J_{7,6endo}$ = 5.5 Hz, H-7), 3.24 (dd, 1H, $J_{5,6exo}$ = 6.5 Hz, $J_{5,4}$ = 3 Hz, H-5), 3.41 (dd, 1H, $J_{1,7}$ = 6.5 Hz, $J_{1,2}$ = 3 Hz), 3.50 (AB pattern, 2H, J = 13.5 Hz, NCH_2), 3.96 (ddd, 1H, $J_{2,3endo}$ = 11 Hz, $J_{2,3exo}$ = 5.5 Hz, $J_{2,1}$ = 3 Hz, H-2), 7.25-7.40 (m, 5H, Ph) ; ^{13}C NMR δ 24.85 (C-7), 26.02, 29.94 and 32.28 (C-3, C-4 and C-6), 56.78 (NCH_2), 58.77, 66.82 and 70.57 (C-1, C-2 and C-5), 121.16 (CN), 126.95 (1C, Ph), 128.10 (4C, Ph), 138.32 (1C, Ph) ; MS (m/z, relative intensity) 242 ($M^{+\cdot}$, 10), 151 (23), 91 (100), 65 (21) ; Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35 ; H, 7.49 ; N, 11.56. Found : C, 74.28 ; H, 7.16 ; N, 11.33.

9-Benzyl-5-oxa-9-azatricyclo[5.2.1.0^{4,8}]decan-6-one (12) : Yield : 25 % ; Oil ; Rf 0.77 (SiO_2, ethyl

acetate/hexanes, 9/1, v/v) ; IR (CCl_4) ν 2870, 1777 ; ^{1}H NMR δ 1.25 (m, 1H, H-4-*endo*), 1.62 (dd, 1H, $J_{3endo,3exo}$ = 14.5 Hz, $J_{3endo,4endo}$ = 6.5 Hz, H-3-*endo*), 1.78 (dd, 1H, $J_{6endo,6exo}$ = 13.5 Hz, $J_{6endo,7}$ = 1.5 Hz, H-6-*endo*), 1.93 (m, 1H, H-3-*exo*), 2.19 (ddd, 1H, $J_{4exo,4endo}$ = 14 Hz, $J_{4exo,5}$ = 9.5 Hz, $J_{4exo,3exo}$ = 9 Hz, H-4-*exo*), 2.58 (ddd, 1H, $J_{6exo,6endo}$ = 13.5 Hz, $J_{6exo,7}$ = 12.5 Hz, $J_{6exo,5}$ = 6 Hz, H-6-*exo*), 3.08 (ddd, 1H, $J_{7,6exo}$ = 12.5 Hz, $J_{7,1}$ = 7.5 Hz, $J_{7,6endo}$ = 1.5 Hz, H-7), 3.40 (dd, 1H, $J_{5,4exo}$ = 9.5 Hz, $J_{5,6exo}$ = 6 Hz, H-5), 3.47 (AB pattern, 2H, J = 13.5 Hz, NCH_2), 3.94 (ddd, 1H, $J_{1,2}$ = 8.5 Hz, $J_{1,7}$ = 7.5 Hz, $J_{1,5}$ = 1 Hz, H-1), 4.92 (dd, 1H, $J_{2,1}$ = 8.5 Hz, $J_{2,3exo}$ = 3.5 Hz, H-2), 7.26-7.37 (m, 5H, Ph) ; ^{13}C NMR δ 22.50 (C-3), 26.29 (C-4), 37.91 (C-6), 40.16 (C-7), 57.39 (C-5), 57.48 (NCH_2), 64.50 (C-1), 80.45 (C-2), 127.25 (1C, Ph), 128.34 (2C, Ph), 128.41 (2C, Ph), 138.92 (1C, Ph), 179.68 (CO_2) ; MS (m/z, relative intensity) 243 ($M^{+\cdot}$, 19), 199 (5), 152 (7), 91 (100), 65 (26) ; Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05 ; H, 7.04 ; N, 5.76. Found : C, 74.06 ; H, 7.08 ; N, 5.73.

General procedure (C) for preparation of 8-benzyl-2-[(trimethylsilyl)oxy]-8-azabicyclo[3.2.1]octane-6(or 7)-carbonitrile (**13-18**) : To a solution of alcohol (**5-9** or **11**) (10 mmol) in anhydrous ether (50 mL) were added dropwise, at 25 °C and with stirring, a solution of trimethylsilyl chloride (3.2 g, 30 mmol) in anhydrous ether (50 mL) and a solution of triethylamine (6 g, 60 mmol) in anhydrous ether (100 mL). After the mixture had stirred for several hours at rt, water was added (50 mL) and the aqueous layer was extracted with dichloromethane. The organic layer was separated and dried (Na_2SO_4). The solvant and triethylamine were evaporated at 70 °C under reduced pressure to give the protected alcohol.

8-Benzyl-2-*exo*-[trimethylsilyloxy]-8-azabicyclo[3.2.1]octane-6-*endo*-carbonitrile (13) : This compound is obtained from the general procedure C (reaction time : 1.5 h) with **5** (1.65 g, 6.8 mmol) ; Yield : 84 % ; mp 97-99 °C (recrystallization solvent : CH_2Cl_2) ; Rf 0.85 (Al_2O_3, CH_2Cl_2) ; IR (KBr) ν 2240, 1253 ; ^{1}H NMR δ 0.09 (s, 9H, $(CH_3)_3Si$), 1.56 (dd, 1H, J = 14 Hz, J = 5 Hz), 1.75 (m, 2H), 1.98 (m, 1H), 2.20 (m, 1H), 2.45 (m, 1H), 3.18 (m, 2H), 3.49 (m, 1H), 3.55 (d, 1H, J = 14 Hz, NCH_2), 3.66 (m, 1H), 3.74 (d, 1H, J = 14 Hz, NCH_2), 7.22-7.47 (m, 5H, Ph) ; ^{13}C NMR δ -0.13 ($(CH_3)_3Si$), 24.00, 24.7 and 30.89 (C-3, C-4 and C-7), 26.93 (C-6), 56.30 (NCH_2), 62.06, 63.96 and 69.49 (C-1, C-2 and C-5), 121.35 (CN), 126.82 (1C, Ph), 128.05 (2C, Ph), 128.19 (2C, Ph), 138.81 (1C, Ph) ; MS (m/z, relative intensity) 314 ($M^{+\cdot}$, 7), 223 (23), 185 (11), 91 (100), 73 (22) ; Anal. Calcd for $C_{18}H_{26}N_2OSi$: C, 68.74 ; H, 8.33 ; N, 8.91. Found : C, 68.68 ; H, 8.32 ; N, 9.04.

8-Benzyl-2-*endo*-[trimethylsilyloxy]-8-azabicyclo[3.2.1]octane-6-*endo*-carbonitrile (14) : This compound is obtained from the general procedure C (reaction time : 3 h) with **6** (1.99 g, 8.2 mmol) ; Yield : 88 % ; Oil ; Rf 0.86 (Al_2O_3, CH_2Cl_2) ; IR (CCl_4) ν 2235, 1245 ; ^{1}H NMR δ 0.05 (s, 9H, $(CH_3)_3Si$), 1.55 (m, 1H), 1.74 (m, 1H), 1.87 (m, 2H), 2.28 (m, 2H, H-7), 3.08 (m, 1H), 3.21 (ddd, 1H, $J_{6,7exo}$ = 12 Hz, $J_{6,7endo}$ = $J_{6,5}$ = 6.5 Hz, H-6), 3.33 (m, 1H), 3.53 (s, 2H, NCH_2), 3.84 (ddd, 1H, $J_{2,3endo}$ = 10.5 Hz, $J_{2,1}$ = 6

Hz, $J_{2,3exo}$ = 4 Hz, H-2), 7.25-7.38 (m, 5H, Ph) ; ^{13}C NMR δ 0.16 ($(CH_3)_3Si$), 26.75, 27.53 and 27.56 (C-3, C-4 and C-7), 27.76 (C-6), 57.04 (NCH_2), 61.30, 65.51 and 69.61 (C-1, C-2 and C-5), 121.00 (CN), 127.31 (1C, Ph), 128.32 (2C, Ph), 128.41 (2C, Ph), 138.54 (1C, Ph) ; MS (m/z, relative intensity) 314 ($M^{+\cdot}$, 6), 223 (33), 185 (16), 133 (13), 91 (100), 73 (34) ; Anal. Calcd for $C_{18}H_{26}N_2OSi$: C, 68.74 ; H, 8.33 ; N, 8.91. Found : C, 68.95 ; H, 8.11 ; N, 9.06.

8-Benzyl-2-*exo*-[trimethylsilyloxy]-8-azabicyclo[3.2.1]octane-6-*exo*-carbonitrile (15) : This compound is obtained from the general procedure C (reaction time : 4 h) with **7** (2.57 g, 10.6 mmol) ; Yield : 84 % ; mp 99-100 °C (recrystallization solvent : $CHCl_3$) ; Rf 0.82 (Al_2O_3, CH_2Cl_2) ; IR (KBr) ν 2235, 1250 ; ^{1}H NMR δ 0.07 (s, 9H, $(CH_3)_3Si$), 1.39 (m, 1H), 1.51 (m, 2H), 1.93 (dd, 1H, $J_{7endo,7exo}$ = 14 Hz, $J_{7endo,6}$ = 9.5 Hz, H-7-*endo*), 2.15 (m, 1H), 2.37 (ddd, 1H, $J_{7exo,7endo}$ = 14 Hz, $J_{7exo,1}$ = 7 Hz, $J_{7exo,6}$ = 5.5 Hz, H-7-*exo*), 2.86 (dd, 1H, $J_{6,7endo}$ = 9.5 Hz, $J_{6,7exo}$ = 5.5 Hz, H-6), 3.30 (dd, 1H, $J_{1,7exo}$ = 7 Hz, $J_{1,2}$ = 3 Hz, H-1), 3.56 (m, 1H), 3.68 (s, 1H), 3.88 (d, 1H, J = 14 Hz, NCH_2), 4.03 (d, 1H, J = 14 Hz, NCH_2), 7.24 (t, 1H, J = 7.5 Hz, Ph), 7.32 (t, 2H, J = 7.5 Hz, Ph), 7.51 (d, 2H, J = 7.5 Hz, Ph) ; ^{13}C NMR δ 0.00 ($(CH_3)_3Si$), 25.02, 26.55 and 32.02 (C-3, C-4 and C-7), 29.01 (C-6), 56.31 (NCH_2), 64.73, 65.22 and 69.26 (C-1, C-2 and C-5), 124.06 (CN), 126.78 (1C, Ph), 128.11 (2C, Ph), 128.29 (2C, Ph), 139.30 (1C, Ph) ; MS (m/z, relative intensity) 314 ($M^{+\cdot}$, 1), 223 (11), 91 (100), 73 (19), 65 (17) ; Anal. Calcd for $C_{18}H_{26}N_2OSi$: C, 68.74 ; H, 8.33 ; N, 8.91. Found : C, 68.89 ; H, 8.54 ; N, 8.73.

8-Benzyl-2-*endo*-[trimethylsilyloxy]-8-azabicyclo[3.2.1]octane-6-*exo*-carbonitrile (16) : This compound is obtained from the general procedure C (reaction time : 3.5 h) with **8** (1.96 g, 8.1 mmol) ; Yield : 86 % ; Oil ; Rf 0.86 (Al_2O_3, CH_2Cl_2) ; IR (CCl_4) ν 2240, 1247 ; ^{1}H NMR δ 0.04 (s, 9H, $(CH_3)_3Si$), 1.08 (m, 1H), 1.41 (m, 1H), 1.68 (m, 1H), 1.76 (m, 1H), 2.26 (m, 1H), 2.44 (dd, 1H, $J_{7endo,7exo}$ = 14 Hz, $J_{7endo,6}$ = 10 Hz, H-7-*endo*), 2.69 (dd, 1H, $J_{6,7endo}$ = 10 Hz, $J_{6,7exo}$ = 5.5 Hz, H-6), 3.21 (dd, 1H, $J_{1,7exo}$ = 6.5 Hz, $J_{1,2}$ = 4 Hz, H-1), 3.55 (s, 1H, H-5), 3.76 (m, 1H, H-2), 3.83 (AB pattern, 2H, J = 13.5 Hz, NCH_2), 7.26 (t, 1H, J = 7 Hz, Ph), 7.33 (t, 2H, J = 7 Hz, Ph), 7.42 (d, 2H, J = 7 Hz, Ph) ; ^{13}C NMR δ 0.12 ($(CH_3)_3Si$), 26.83, 29.07 and 30.20 (C-3, C-4 and C-7), 29.67 (C-6), 57.19 (NCH_2), 64.51, 66.42 and 69.33 (C-1, C-2 and C-5), 124.15 (CN), 127.17 (1C, Ph), 128.35 (2C, Ph), 128.57 (2C, Ph), 138.87 (1C, Ph) ; MS (m/z, relative intensity) 314 ($M^{+\cdot}$, 3), 223 (27), 91 (100), 73 (21), 65 (13) ; Anal. Calcd for $C_{18}H_{26}N_2OSi$: C, 68.74 ; H, 8.33 ; N, 8.91. Found : C, 68.53 ; H, 8.27 ; N, 9.09.

8-Benzyl-2-*exo*-[trimethylsilyloxy]-8-azabicyclo[3.2.1]octane-7-*exo*-carbonitrile (17) : This compound is obtained from the general procedure C (reaction time : 3.5 h) with **9** (800 mg, 3.3 mmol) ; Yield : 85 % ; mp 101-103 °C (recrystallization solvent : $CHCl_3$) ; Rf 0.95 (Al_2O_3, CH_2Cl_2) ; IR (KBr) ν 2235, 1250 ; ^{1}H NMR δ 0.06 (s, 9H, $(CH_3)_3Si$), 1.24 (m, 1H), 1.53 (m, 2H), 2.12 (m, 1H), 2.14 (dd, 1H, $J_{6endo,6exo}$ = 13 Hz, $J_{6endo,7}$ = 9.5 Hz, H-6-*endo*), 2.43 (ddd, 1H, $J_{6exo,6endo}$ = 13 Hz, $J_{6exo,5}$ = $J_{6exo,7}$ = 6.5 Hz, H-6-*exo*), 2.65 (dd, 1H, $J_{7,6endo}$ = 9.5 Hz, $J_{7,6exo}$ = 6.5 Hz, H-7), 3.44 (m, 1H), 3.49 (m, 1H), 3.61 (m, 1H),

3.94 (AB pattern, 2H, J = 14 Hz, NCH_2), 7.26 (t, 1H, J = 7 Hz, Ph), 7.32 (t, 2H, J = 7 Hz, Ph), 7.50 (d, 2H, J = 7 Hz, Ph) ; ^{13}C NMR δ -0.03 ($(CH_3)_3Si$), 25.05, 25.66 and 32.55 (C-3, C-4 and C-6), 28.81 (C-7), 56.07 (NCH_2), 59.53, 68.82 and 68.92 (C-1, C-2 and C-5), 123.61 (CN), 126.88 (1C, Ph), 128.15 (2C, Ph), 128.63 (2C, Ph), 139.16 (1C, Ph) ; MS (m/z, relative intensity) 314 ($M^{+\cdot}$, 7), 223 (16), 133 (33), 91 (100), 73 (24) ; Anal. Calcd for $C_{18}H_{26}N_2OSi$: C, 68.74 ; H, 8.33 ; N, 8.91. Found : C, 68.89 ; H, 8.54 ; N, 8.73.

8-Benzyl-2-*endo*-[trimethylsilyloxy]-8-azabicyclo[3.2.1]octane-7-*endo*-carbonitrile (18) : This compound is obtained from the general procedure C (reaction time : 16 h) with **11** (450 mg, 1.86 mmol) ; Yield : 67 % ; Oil ; Rf 0.94 (SiO_2 / ethyl acetate, 9/1, v/v) ; IR (CCl_4) ν 2240, 1248 ; ^1H NMR δ 0.10 (s, 9H, $(CH_3)_3Si$), 1.49 (m, 1H), 1.75 (m, 2H), 1.88 (m, 1H), 1.90 (dd, 1H, $J_{6endo,6exo}$ = 12.5 Hz, $J_{6endo,7}$ = 7 Hz, H-6-*endo*), 2.57 (ddd, 1H, $J_{6exo,6endo} = J_{6exo,7}$ = 12.5 Hz, $J_{6exo,5}$ = 7 Hz, H-6-*exo*), 3.14-3.26 (m, 3H, H-1, H-5 and H-7), 3.51 (AB pattern, 2H, J = 13.5 Hz, NCH_2), 3.93 (m, 1H, H-2), 7.23-7.40 (m, 5H, Ph) ; ^{13}C NMR δ 0.16 ($(CH_3)_3Si$), 25.53 (C-7), 26.99, 30.32 and 32.69 (C-3, C-4 and C-6), 57.15 (NCH_2), 59.05, 67.38 and 70.76 (C-1, C-2 and C-5), 120.35 (CN), 127.29 (1C, Ph), 128.31 (2C, Ph), 128.40 (2C, Ph), 138.62 (1C, Ph) ; MS (m/z, relative intensity) 314 ($M^{+\cdot}$, 7), 223 (30), 185 (19), 91 (100), 73 (28) ; Anal. Calcd for $C_{18}H_{26}N_2OSi$: C, 68.74 ; H, 8.33 ; N, 8.91. Found : C, 68.81 ; H, 8.30 ; N, 8.85.

General procedure (D) for preparation of 1-[8-benzyl-2-[(trimethylsilyl)oxy]-8-azabicyclo[3.2.1]oct-6 (or 7)-yl]ethanone (**19-21**) : A solution of iodomethane (5.7 g, 40 mmol) in anhydrous ether (100 mL) was added with stirring to magnesium ribbon (2.4 g, 0.1 mol), a small amount of iodine and 30 mL of sodium dried ether. When the mixture had lost color, a solution of protected compound (**13-17**) (10 mmol) in anhydrous ether (30 mL) was added dropwise. After the mixture had stirred for 24 h, 100 mL of 15 % NH_4Cl was added dropwise and the mixture stirred for 2 h. After that time, the mixture was extracted with ether and then with dichloromethane. The combined organic extract was dried over sodium sulfate and the solvent evaporated under reduced pressure to give the corresponding compound as crude product.

1-[8-Benzyl-2-*exo*-[trimethylsilyloxy]-8-azabicyclo[3.2.1]oct-6-*exo*-yl]ethanone (19) : This compound is obtained from the general procedure D, as crude product with **13** (1.44 g, 4.58 mmol) and as pure product with **15** (1.19 g, 3.78 mmol, Yield : 83 %) ; Oil ; Rf 0.76 (Al_2O_3, CH_2Cl_2) ; ^1H NMR δ 0.10 (s, 9H, $(CH_3)_3Si$), 1.36 (m, 1H), 1.56 (m, 2H), 1.77 (m, 1H), 2.21 (s, 3H, CH_3CO), 2.24 (m, 1H), 2.46 (m, 1H), 2.88 (dd, 1H, $J_{6,7endo}$ = 9 Hz, $J_{6,7exo}$ = 6 Hz, H-6), 3.23 (m, 1H), 3.50 (s, 1H), 3.62 (s, 1H), 3.74 (AB pattern, 2H, J = 14.5 Hz, NCH_2), 7.15-7.45 (m, 5H, Ph) ; ^{13}C NMR δ 0.05 ($(CH_3)_3Si$), 25.71, 26.41 and 27.21 (C-3, C-4 and C-7), 28.66 (CH_3), 54.84 (C-6), 55.37 (NCH_2), 61.83, 64.67 and 70.01 (C-1, C-2 and C-5), 126.43 (1C, Ph), 127.96 (2C, Ph), 128.33 (2C, Ph), 140.22 (1C, Ph), 209.76 (C=O) ; Anal. Calcd for $C_{19}H_{29}NO_2Si$: C, 68.84 ; H, 8.82 ; N, 4.22. Found : C, 68.71 ; H, 8.99 ; N, 4.14.

1-[8-Benzyl-2-*endo*-[trimethylsilyloxy]-8-azabicyclo[3.2.1]oct-6-*exo*-yl]ethanone (20) : This compound is obtained from the general procedure D, as crude product with **14** (2 g, 6.36 mmol) and as pure product with (**16**) (1 g, 3.18 mmol, Yield : 76 %) ; Oil ; Rf 0.84 (Al_2O_3, CH_2Cl_2) ; IR (CCl_4) ν 1705, 1248 ; ^{1}H NMR δ 0.06 (s, 9H, $(CH_3)_3Si$), 1.32 (m, 1H), 1.47 (m, 1H), 1.78 (m, 2H), 2.08 (dd, 1H, $J_{7endo,7exo}$ = 13.5 Hz, $J_{7endo,6}$ = 10 Hz, H-7-*endo*), 2.19 (s, 3H, CH_3CO), 2.34 (ddd, 1H, $J_{7exo,7endo}$ = 13.5 Hz, $J_{7exo,6}$ = $J_{7exo,1}$ = 6.5 Hz, H-7-*exo*), 2.78 (dd, 1H, $J_{6,7endo}$ = 10 Hz, $J_{6,7exo}$ = 6.5 Hz, H-6), 3.12 (dd, 1H, $J_{1,7exo}$ = 6.5 Hz, $J_{1,2}$ = 3.5 Hz, H-1), 3.44 (s, 1H, H-5), 3.53 (AB pattern, 2H, J = 14 Hz, NCH_2), 3.82 (m, 1H, H-2), 7.20-7.35 (m, 5H, Ph) ; ^{13}C NMR δ 0.25 ($(CH_3)_3Si$), 24.22 (C-7), 27.48 (C-3), 30.63 (C-4), 28.97 (CH_3), 56.17 (C-6), 56.39 (NCH_2), 61.23 (C-2), 66.24 (C-1), 69.66 (C-5), 126.81 (1C, Ph), 128.21 (2C, Ph), 128.45 (2C, Ph), 139.85 (1C, Ph), 209.69 (C=O) ; MS (m/z, relative intensity) 331 ($M^{+\cdot}$, 6), 288 (28), 240 (5), 91 (100), 73 (29) ; Anal. Calcd for $C_{19}H_{29}NO_2Si$: C, 68.84 ; H, 8.82 ; N, 4.22. Found : C, 68.92 ; H, 8.82 ; N, 4.16.

1-[8-Benzyl-2-*exo*-[trimethylsilyloxy]-8-azabicyclo[3.2.1]oct-7-*exo*-yl]ethanone (21) : This compound is obtained from the general procedure D with **17** (800 mg, 2.54 mmol) as crude product ; Oil ; Rf 0.64 (Al_2O_3, CH_2Cl_2) ; IR (CCl_4) ν 1700, 1240 ; ^{1}H NMR δ 0.07 (s, 9H, $(CH_3)_3Si$), 1.25 (m, 1H), 1.53 (m, 2H), 1.74 (dd, 1H, $J_{6endo,6exo}$ = 13 Hz, $J_{6endo,7}$ = 9 Hz, H-6-*endo*), 1.76 (m, 1H), 2.14 (s, 3H, CH_3CO), 2.53 (ddd, 1H, $J_{6exo,6endo}$ = 13 Hz, $J_{6exo,5}$ = 6.5 Hz, $J_{6exo,7}$ = 6 Hz, H-6-*exo*), 2.68 (dd, 1H, $J_{7,6endo}$ = 9 Hz, $J_{7,6exo}$ = 6 Hz, H-7), 3.33 (m, 1H, H-1), 3.60-3.90 (m, 4H, H-2, H-5 and NCH_2), 7.26-7.50 (m, 5H, Ph) ; ^{13}C NMR δ 0.04 ($(CH_3)_3Si$), 25.46, 25.69 and 27.60 (C-3, C-4 and C-6), 28.86 (CH_3), 54.94 (C-7), 55.32 (NCH_2), 59.54, 66.34 and 70.25 (C-1, C-2 and C-5), 126.64 (1C, Ph), 128.04 (2C, Ph), 128.65 (2C, Ph), 139.8 (1C, Ph), 209.5 (C=O).

General procedure (E) for preparation of 1-[8-benzyl-2-hydroxy-8-azabicyclo[3.2.1]oct-6-yl]ethanone (**22-24**) : The trimethylsilyl ether was chromatographed with neutral alumina (CH_2Cl_2, (**19-20**)) or with silica gel (ethyl acetate/hexanes, 9/1, v/v, (**21**)). This supported reaction yields the corresponding alcohol.

1-[8-Benzyl-2-*exo*-hydroxy-8-azabicyclo[3.2.1]oct-6-*exo*-yl]ethanone (22) : This compound is obtained from the general procedure E with **19** (990 mg, 2.99 mmol, Yield : 50 %) and from the general procedures D and E with **13** (1.44 g, 4.58 mmol, Yield : 32 %) ; mp 103-106 °C (recrystallization solvent : $CHCl_3$) ; Rf 0.70 (Al_2O_3, CH_2Cl_2) ; IR (CCl_4) ν 3480, 1710 ; ^{1}H NMR δ 1.45 (m, 1H), 1.61 (m, 2H), 1.70 (dd, 1H, $J_{7endo,7exo}$ = 14 Hz, $J_{7endo,6}$ = 9.5 Hz, H-7-*endo*), 1.88-2.00 (m, 1H), 2.20 (s, 3H, CH_3CO), 2.67 (ddd, 1H, $J_{7exo,7endo}$ = 14 Hz, $J_{7exo,1}$ = $J_{7exo,6}$ = 6 Hz, H-7-*exo*), 2.90 (dd, 1H, $J_{6,7endo}$ = 9.5 Hz, $J_{6,7exo}$ = 6 Hz, H-6), 3.32 (m, 1H), 3.40 (AB pattern, 2H, J = 13 Hz, NCH_2), 3.52 (s, 1H), 3.58 (s, 1H), 7.25-7.40 (m, 5H, Ph) ; ^{13}C NMR δ 24.85, 26.68 and 29.56 (C-3, C-4 and C-7), 26.51 (CH_3), 54.43 (C-6), 57.44 (NCH_2), 62.55, 67.02 and 68.39 (C-1, C-2 and C-5), 127.22 (1C, Ph), 128.45 (2C, Ph), 128.82 (2C, Ph),

139.05 (1C, Ph), 209.16 (C=O) ; MS (m/z, relative intensity) 259 ($M^{+\cdot}$, 2), 216 (43), 168 (13), 91 (100), 65 (18) ; Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10 ; H, 8.16 ; N, 5.40. Found : C, 73.98 ; H, 8.29 ; N, 5.40.

1-[8-Benzyl-2-*endo*-hydroxy-8-azabicyclo[3.2.1]oct-6-*exo*-yl]ethanone (23) : This compound is obtained from the general procedure E with **20** (700 mg, 2.11 mmol, Yield : 55 %) and from the general procedures *D* and *E* with (**14**) (2 g, 6.36 mmol, Yield : 39 %) ; *Oil* ; *Rf 0.19* (Al_2O_3, CH_2Cl_2) ; *IR* (CCl_4) ν 3400, 1700 ; ^{1}H NMR δ 1.21 (m, 1H), 1.53 (m, 1H), 1.81 (m, 1H), 1.91 (m, 1H), 2.05 (dd, 1H, $J_{7endo,7exo}$ = 13.5 Hz, $J_{7endo,6}$ = 9.5 Hz, H-7-*endo*), 2.21 (s, 3H, CH_3CO), 2.42 (ddd, 1H, $J_{7exo,7endo}$ = 13.5 Hz, $J_{7exo,1}$ = $J_{7exo,6}$ = 6 Hz, H-7-*exo*), 2.79 (dd, 1H, $J_{6,7endo}$ = 9.5 Hz, $J_{6,7exo}$ = 6 Hz, H-6), 3.22 (dd, 1H, $J_{1,7exo}$ = 6 Hz, $J_{1,2}$ = 3.5 Hz, H-1), 3.46 (s, 1H, H-5), 3.54 (AB pattern, 2H, J = 13.5 Hz, NCH_2), 3.87 (m, 1H, H-2), 7.25-7.40 (m, 5H, Ph) ; ^{13}C NMR δ 23.70, 26.28 and 30.29 (C-3, C-4 and C-7), 28.84 (CH_3), 56.04 (C-6), 56.21 (NCH_2), 61.19, 65.66 and 68.78 (C-1, C-2 and C-5), 126.78 (1C, Ph), 128.13 (2C, Ph), 128.42 (2C, Ph), 139.50 (1C, Ph), 209.68 (C=O) ; MS (m/z, relative intensity) 259 ($M^{+\cdot}$, 4), 216 (22), 168 (10), 91 (100), 65 (18) ; Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10 ; H, 8.16 ; N, 5.40. Found : C, 73.88 ; H, 8.32 ; N, 5.30.

1-[8-Benzyl-2-*exo*-hydroxy-8-azabicyclo[3.2.1]oct-7-*exo*-yl]ethanone (24) : This compound is obtained from the general procedures D and E with **17** (800 mg, 2.54 mmol, Yield : 25 %) ; Oil ; Rf 0.50 (SiO_2 / ethyl acetate/hexanes, 9/1, v/v) ; IR (CCl_4) ν 3400, 1707 ; ^{1}H NMR δ 1.37 (m, 1H, H-4), 1.59 (m, 2H, H-3), 1.76 (dd, 1H, $J_{6endo,6exo}$ = 13 Hz, $J_{6endo,7}$ = 9 Hz, H-6-*endo*), 1.89 (m, 1H, H-3), 2.23 (s, 3H, CH_3CO), 2.62 (ddd, 1H, $J_{6exo,6endo}$ = 13 Hz, $J_{6exo,5}$ = $J_{6exo,7}$ = 6.5 Hz, H-6-*exo*), 2.83 (dd, 1H, $J_{7,6endo}$ = 9 Hz, $J_{7,6exo}$ = 6.5 Hz, H-7), 3.32 (m, 1H, H-5), 3.42 (AB pattern, 2H, J = 14 Hz, NCH_2), 3.47 (m, 1H, H-1), 3.67 (m, 1H, H-2), 7.25-7.40 (m, 5H, Ph) ; ^{13}C NMR δ 24.73 (C-3), 26.50 (C-6), 28.32 (C-4), 29.14 (CH_3), 55.21 (C-7), 57.49 (NCH_2), 61.13 (C-5), 67.84 (C-1), 68.60 (C-2), 127.17 (1C, Ph), 128.45 (2C, Ph), 128.69 (2C, Ph), 139.07 (1C, Ph), 208.24 (C=O) ; MS (m/z, relative intensity) 259 ($M^{+\cdot}$, 2), 168 (9), 91 (100), 65 (19) ; Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10 ; H, 8.16 ; N, 5.40. Found : C, 73.86 ; H, 8.17 ; N, 5.36.

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