SYNTHESIS OF 1-HYDROXY-7-AZATRICYCLO[6.3.1.0^{2,7}]DODECAN-9-ONES: POTENTIAL INTERMEDIATES FOR THE TOTAL SYNTHESIS OF SECURININES

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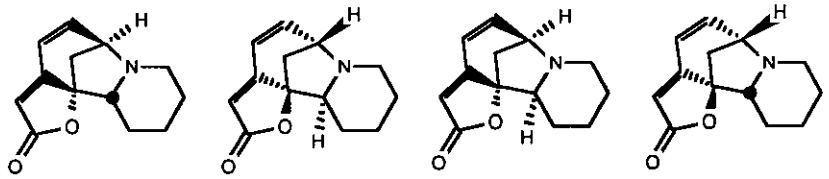
This paper is dedicated to Professor Sir Derek Barton on the occasion of his 70th birthday.

Abstract-A synthesis of epimeric 1-hydroxy-7-azatricyclo [6.3.1.0^{2,7}] dodecan-9-ones (3 and 4), in ten steps from p-methoxyphenol, is described. They have been converted to the corresponding 9(10)-olefinic derivatives 22 and 23.

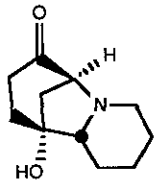
Securinine (1A) was first described in 1956 and its structure was established in 1962.[1] The total synthesis was published in 1967 by Horii et al.[2] Since then, other approaches have met with little success. [3,4] The enantiomers of securinine, virosecurinine (1B) and the epimers at C-2 of 1A and 1B, allosecurinine (2A) and allovirosecurinine (2B) respectively, have also been isolated from natural sources and their structure was determined.[1]



1A 1B 2A 2B

In this paper, we describe the synthesis of racemic tricyclic ketones 3 and 4 (one enantiomer is illustrated) from a common precursor, p-methoxyphenol (5), in ten steps with overall yields of 6% and 6.5% respectively. The relative stereochemistry of tricyclic ketone 3 corresponds to that of securinines (1A, 1B) and the relative stereochemistry of ketone 4 to that of allosecurinines (2A, 2B).

The synthetic sequence leading to a one-to-one mixture of diastereoisomeric 4-hydroxy-1-methoxy-4-(2'-piperidyl)-cyclohex-1-enes (14 and 15), in a 42% overall yield, is summarized in Scheme 1. The conversion of the known hydroxy-enol ether 6,[5] prepared by Birch reduction of p-methoxyphenol (5)



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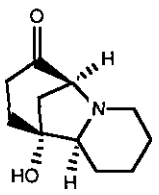

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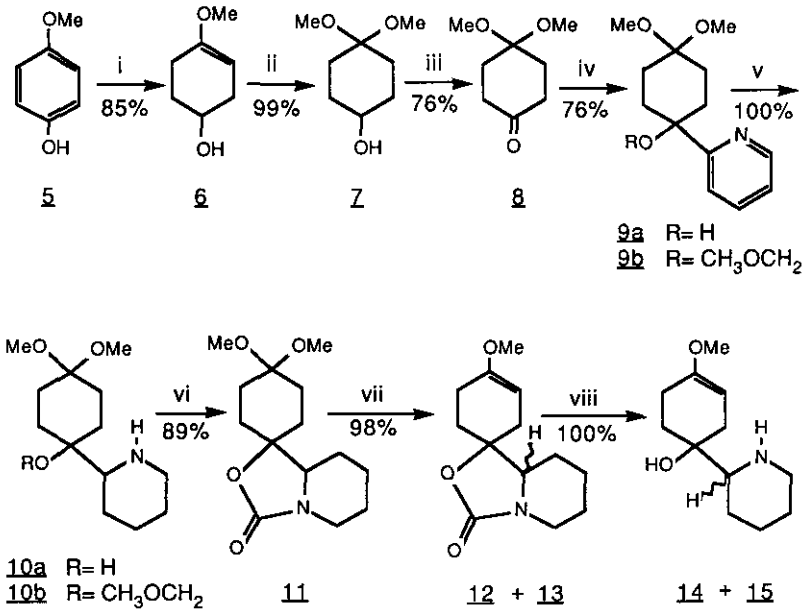
to the ketal-pyridine-alcohol 9a in four steps (49% overall yield) is straightforward. Reduction of 9a with sodium in boiling alcohol gave a complex mixture of products from which ketal-piperidine-alcohol 10a could not be isolated. The latter was obtained in a quantitative yield, thus without any hydrogenolysis of the tertiary benzylic alcohol, by catalytic hydrogenation over ruthenium. Attempts to convert ketal-piperidine-alcohol 10a directly to the diastereoisomeric mixture of the corresponding enol ethers 14 and 15 were unsuccessful. The elimination of methanol from the methoxymethyl ether derivative 10b was unsuccessful also. Both the hydroxy and amino groups were protected as the corresponding carbamate 11 by treatment with phosgene and an excess of triethylamine in methylene chloride. Pyrolysis of ketal-carbamate 11 in the presence of a catalytic amount of anhydrous potassium hydrogen sulfate (or thoroughly dried triethylammonium chloride) gave the desired mixture of enol ether-carbamates 12 and 13 in 95% (or 98%) yield, in a one-to-one ratio according to the ^{1}Hnmr and ^{13}Cnmr spectra (see the Experimental); they could not be separated. The carbamate group was then removed quantitatively by heating the mixture of 12 and 13 with potassium hydroxide in aqueous methanol. The resulting enol ether-piperidyl-alcohols 14 and 15 could not be separated either.

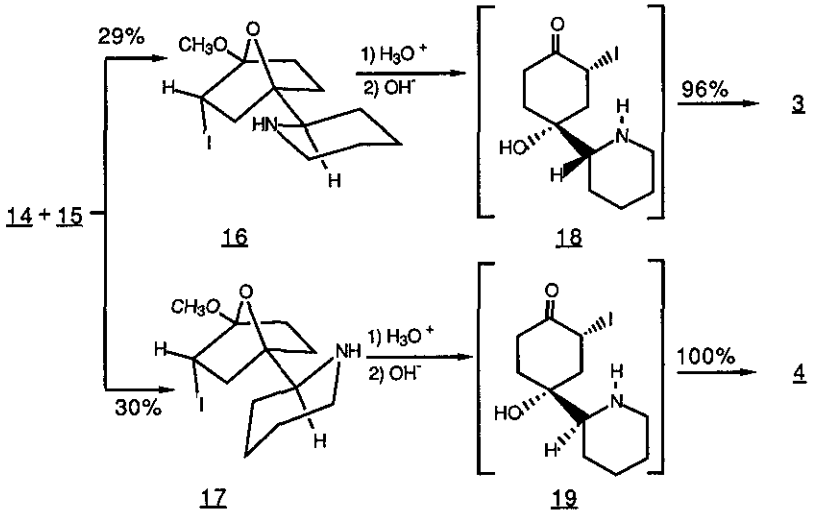
Furstoss et al.[7] have prepared the N-chloro derivatives of olefinic (enol ether) amines and cyclized them to azabycyclic ketones in good yields by solvolysis in trifluoroacetic acid followed by treatment with aqueous sodium carbonate. However this method was unsuccessful with the enol ether-piperidyl-alcohols 14 and 15. The tricyclic ketones 3 and 4 were obtained from 14 and 15 as outlined in Scheme 2.[8] The mixture of 14 and 15 was treated with one equivalent of acetic acid in methylene chloride at 0°C in order to convert the amine to its acetate. The addition of one equivalent of iodine monochloride followed by alkaline work-up gave a one-to-one mixture of the tricyclic iodo ketals 16 and 17 which were separated by flash chromatography (yields: 29% of pure 16 and 30% of pure 17). Each iodo ketal, dissolved in benzene, was treated, in one pot, under argon and at room temperature, first by one equivalent of aqueous hydrochloric acid and one equivalent of trifluoroacetic acid, then with an excess of aqueous potassium carbonate to afford the corresponding tricyclic ketones 3 (96% yield) and 4 (100% yield). The cis relationship of the iodine atom and the piperidine



SCHEME 1. *Reagents (see the Experimental for details)* i: Li/ NH_3 , then EtOH; [5] ii: $CH(OCH_3)_3$, p-TsOH/ C_6H_6-MeOH; ii. $CrO_3(C_5H_5N)_2$ /CH_2Cl_2[6] (yield after chromatographic purification); iv:2-pyridyllithium /THF (yield of recrystallized product); v: H_2, 5% Ru-C / THF-H_2O; vi: $COCl_2$, Et_3N (2 eq) / CH_2Cl_2, vii: Et_3NHCl (10-15% by weight), 180°C; viii: KOH/MeOH-H_2O, 110-120°C (sealed tube).

ring in 16 and 17 has no bearing on the outcome of the cyclization since the epimerization of the resulting α-iodo ketones in an alkaline medium should be relatively easy to give respectively 18 and 19 which then cyclize readily. This one-pot conversion has to be carried out in an inert atmosphere *because the azabicylcic ketones 3 and 4 decompose fairly quickly in the presence of oxygen* when in solution to give an intractable mixture of polar compounds soluble in polar solvents such as acetone, methanol, and water.

The structure of tricyclic iodo ketals 16 and 17 was established by ^1H *and* ^{13}C *nmr spectra* and two-dimensional correlated homonuclear and heteronuclear spectra (COSY ^1H-^1H and COSY ^1H-^{13}C). The proton at C2 (carbon bearing the iodine atom) of both isomers appears as a doublet of doublets of doublets at 4.1 ppm with coupling constants of 11.5 Hz (H3exo), 5.5 Hz (H3endo), and 2.9 Hz (H6exo) for 16 and 11.6 Hz, 5.5 Hz, and 3.0 Hz for 17. *The long range coupling with the exo* proton at C6 establishes the exo orientation of H2 and thus, the endo orientation of the iodine atom. The C2 carbon absorbs at 23 ppm, therefore is quite shielded and must bear the iodine atom; it correlates with the H2 proton at 4.1 ppm.



SCHEME 2

It was not possible to determine the relative stereochemistry at C2' (piperidine ring) from nmr data. This information was obtained from the X-ray crystalline structure of isomer 17[9] which confirms the endo orientation of the iodine atom and shows the relative stereochemistry of the four asymmetric centers. For instance, the configuration of C2' is S (or R) and that of C2 is S (or R). Then, for isomer 16, the configuration of C2' must be R (or S) and that of C2, S (or R). Therefore, the relative stereochemistry of tricyclic ketones 3 and 4 corresponds respectively to that of securinines (1A and 1B) and allosecurinines (2A and 2B).

Other features of the crystalline structure of 17 concern the conformational aspects (see Fig. 1 for a stereoscopic view).[9] The piperidine ring adopts a chair form with the C2'-C4 bond equatorial as expected. The orientation of the ring about the C2'-N1' bond is locked in such way to have the C2'-N1' bond oriented nearly perfectly antiperiplanar to the C4-C5 bond; this conformation corresponds to the rotamer having the lowest global strain energy, as calculated using MM2 program.[9] Finally, the methoxy group has one of its lone pair antiperiplanar to the C1-O7 bond as a result of the anomeric effect.[10,11].

A possible route to the securinines would be introduction of a double bond at C9, introduction of a carbonyl group at C11, addition of lithium ethoxyacetylide, hydrolysis to the α, β-unsaturated acid, and lactonization. So far, ketones 3 and 4 have been converted to olefins 22 and 23 as depicted in Scheme 3.

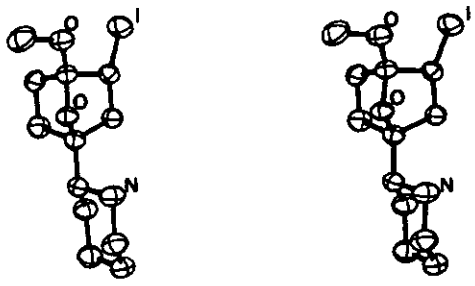
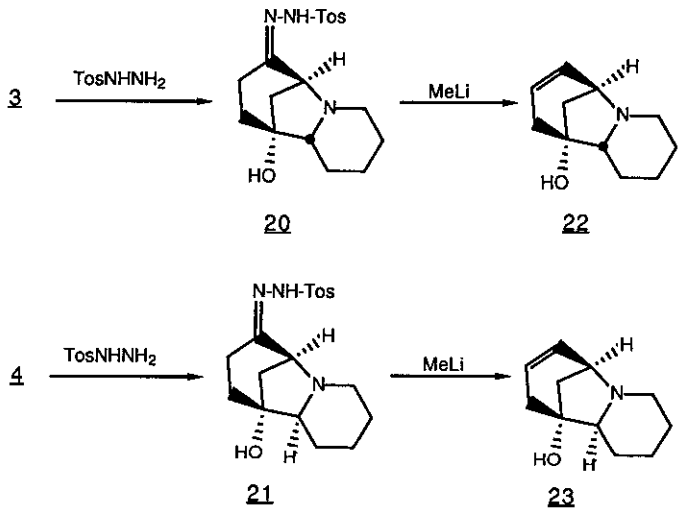


Fig. 1 Stereoscopic view of the crystalline structure of 17.[9]



SCHEME 3

EXPERIMENTAL

All solvents were distilled before use and, when necessary, dried according to described procedures. Melting points were determined on a Büchi apparatus and are uncorrected Infrared (ir) spectra were recorded on a Perkin-Elmer 781 spectrophotometer. Nuclear magnetic resonnance (nmr) spectra were recorded on a Bruker WP60 or on a Bruker WP80 or WM250 spectrometers both coupled with an ASPECT 2000 computer Mass spectra (ms) were taken on a VG ZAB-1F spectrometer. Thin layer chromatography (tlc) was carried out on Merck silica gel 60 F254 (0.25 mm) and flash chromatography on Merck silica gel 60 (230-400 mesh). Microanalyses were carried out by Mr. H. Seguin, National Research Council of Canada, Ottawa.

4-Hydroxy-1-methoxycyclohex-1-ene (6).[5] It was prepared by Birch reduction of p-methoxyphenol (5) in ether with 10 equivalents of Li in liquid ammonia at -50°C followed by the addition of anhydrous ethanol, as described by Radlick and Crawford.[5] Yield after distillation: 85%, bp 54-56°C (0.4 Torr), bp 84-86°C (1 Torr) (1 Torr = 133.3 Pa).

4,4-Dimethoxycyclohexanol (7). To a solution of enol ether-alcohol 6 (27.2 g, 0 21 mol) in dry benzene (100 ml) was added anhydrous methanol (12.6 ml, 0.31 mol) and trimethyl orthoformate (1.2 ml). The addition of a few crystals of p-toluenesulfonic acid caused heating of the solution which was stirred at room temperature for 1h. A few drops of ethylamine were added and the solvent was evaporated under reduced pressure to give 7 (33.7 g, 99%) as a pale yellow viscous oil, homogeneous by tlc. Ir (CCl_4) ν_{max}: 3600, 1100, 1050 cm^{-1}; ^{1}Hnmr ($CDCl_3$); δ: 1 2-2.1 (9H), 3.17 (6H, s, $(OCH_3)_2$), 3.75 ppm (1H, br s, OH).

4,4-Dimethoxycyclohexanone (8).- In a three necked one-liter flask, freshly distilled pyridine (105 ml, 1.3 mol) was dissolved in dry CH_2Cl_2 (450 ml). Under vigorous stirring (mechanical), dry celite (80 g) and then dry chromium trioxide (60 g, 0.6 mol) were added. When the suspension was homogeneous, ketal-alcohol 7 (15.8 g, 0.10 mol) was added all at once. The mixture turned from red-brown to black and was stirred at room temperature for 22 h. It was then filtered over Florisil to remove the chromium salt and the solvent was evaporated to a pale yellow liquid (13.2 g). The crude product still contained unreacted 7 (~5-10%) according to tlc and ^{1}Hnmr Chromatographic separation (ether-hexane-methanol 60:40:5) gave the known ketal-ketone 8[12] (11 4 g, 76%), homogeneous by tlc. It was used without further purification.

1,1-Dimethoxy-4-hydroxy-4-(2'-pyridyl)cyclohexane (9a) - In a three necked 0.5 liter flask and under an argon atmosphere, n-butyllithium (31 ml of a 3.0 M solution in hexane, 93 mmol) was added to dry THF (200 ml) while stirring (magnetic stirrer) and the solution was cooled to -95°C. A solution of 2-bromopyridine (15.7 g, 100 mmol) in dry THF (20 ml) was added dropwise. The orange solution (a yellow precipitate was formed in some cases) was stirred at -78°C for 1h then cooled to -95°C. A solution of ketal-ketone 8 (10.2 g, 65 mmol) in dry THF (30 ml) was added slowly. The orange mixture was stirred at -78°C for 3 h then allowed to warm to -20°C and water (10 ml) was added slowly. The yellow solution was dried over K_2CO_3 and the solvent was evaporated under reduced pressure. Flash chromatography (hexane-ethyl acetate 60·40) gave unreacted 8 (1.6 g, 16%) and a crystalline fraction which gave pure 9a, mp 71-72°C (11.0 g, 76%) after recrystallization in ether. Ir ($CHCl_3$) ν_{max}:3450, 1600, 1580, 1080, 1040 cm^{-1}; ^{1}Hnmr ($CDCl_3$) δ. 1.5-1.7 (4H, m, H3 + H5) 1.8-2.1 (4H, m, H2 + H6), 3.22 (3H, s, OCH_3), 3.25 (3H, s, OCH_3), 5.14 (1H, br s, OH), 7.19 (1H, ddd, J=7.4, 4.9, 1.1 Hz, H5'), 7 38 (1H, dt, J=8.0, 1.1 Hz, H3'), 7.69 (1H, ddd, J=8.0, 7 4, 1 8 Hz, H4'), and 8.50 (1H, ddd, J=4.9, 1.7, 1.0 Hz, H6') ppm. Anal. calcd for $C_{13}H_{19}NO_3$: C 65 80, H 8.07, N 5 90; found. C 66.04, H 8.33, N 5.79.

Methoxymethyl ether of 1,1-dimethoxy-4-hydroxy-4-(2'-pyridyl)cyclohexane (9b). - To a solution of alcohol 9a (5.03 g, 21.2 mmol) in ahnydrous THF (125 ml) was added triethylamine (11.8 ml, 85 mmol) and chloromethyl methyl ether (4 84 ml, 63.7

mmol) The solution was refluxed under a nitrogen atmosphere for 29 days. The mixture was evaporated to dryness and the solid residue was washed with hot hexane-ether [1:5 (3 x 10 ml)]. *Removal of the solvent and recrystallization of the* solid residue (6.43 g) from hexane-ether (15:1) gave the pure ether 9b, mp 71-73°C (5.52 g, 92%). Ir ($CHCl_3$) ν_{max}: 1600, 1580, 1100, 1040 cm^{-1}; ^{1}Hnmr ($CDCl_3$) δ: 1.6-2.2 (8H), 3.20 (3H, s, OCH_3), 3.25 (3H, s, OCH_3), 3.40 (3H, s, OCH_3), 4 50 (2H, *s, OCH_2O), 7* 1-7.5 (3H, *aromatic* H), *8.55 (1H, m, H6') ppm.* Anal *calcd for* $C_{15}H_{23}NO_4$: H 64.03; C 8.24; N 4.92; found· C 64.32; H 8 24, N 4.97.

1,1-Dimethoxy-4-hydroxy-4-(2'-piperidyl)cyclohexane (10a) - The ketal-pyridyl-alcohol 9a (5.07 g, 21 mmol) in THF-water [1:1 (50 ml)] was hydrogenated over 5% Ru-C (5 g) in a Parr bomb at a H_2 pressure of 2000-2500 psi (13.5-17 MPa) for 24 h at room temperature The catalyst was removed by filtration and washed with THF-water [95:5 (3 x 10 ml)]. The solvent was evaporated under reduced pressure and the residual water was removed by azeotropic distillation with benzene using a Dean-Stark separator. The benzene solution was filtered through a short silica gel column. The benzene was allowed to evaporate slowly at room temperature to give crystalline 10, mp 81-83°C (5.30 g, 100%); mp 85°C after one recrystallization from benzene-hexane at -15°C. Ir ($CHCl_3$) ν_{max}: 3000, 1100, 1050 cm^{-1}; ^{1}Hnmr ($CDCl_3$) δ: 1.1-2.0 (14 H), 2.39 (1H, dd, J=11.2, 2.7 Hz, H2'ax), 2.63 (1H, dt, J=12.1, 3.0 Hz, H6'eq), 3.14 (3H, s, OCH_3), 3 16 (1H, br d, J=12.2 Hz, H6'ax), and 3.21 (3H, s, OCH_3) ppm. Exact mass calcd for $C_{13}H_{25}NO_3$. 244.1912 (M^+ + 1), 243.1834 (M^+); found (ms) . 244 1912 (M^+ + 1), 243.1834 (M^+). Anal. calcd for $C_{13}H_{25}NO_3.1/2H_2O$: C 61.67, H 10.38, N 5.55; found: C 62.60, H 10.65, N 5.51.

Methoxymethyl ether of 1,1-dimethoxy-4-hydroxy-4-(2'-piperidyl)cyclohexane (10b). - The hydrogenation of the ketal-pyridyl-ether 9b was carried out as described above for 9a to give the ketal-piperidyl-ether 10b as an oil (93% yield). Ir ($CHCl_3$) ν_{max}. 3400, 1150, 1100, 1050, 1030 cm^{-1}; ^{1}Hnmr ($CDCl_3$) δ: 1.0-2 0 (14H), 2.50 (3H, m), 3.00 (1H, m), 3.15 (3H, s, OCH_3), 3 19 (3H, s, OCH_3), 3.40 (3H, s, OCH_3), 4.70 (2H, s, OCH_2O) ppm.

Carbamate of 1,1-dimethoxy-4-hydroxy-4-(2'-piperidyl)cyclohexane (11). - To a solution of triethylamine (26 g, 0.25 mol) in dry CH_2Cl_2 (70 ml) cooled to -78°C, phosgene (6 ml, 0.080 mol) was added at once. A yellow precipitate was formed. A solution of ketal-piperidyl-alcohol 10 (5.03 g, 0 021 mol) in CH_2Cl_2 (15 ml) was then added at once under vigorous stirring. The orange solution was allowed to warm to room temperature and stirred for 5 h. The resulting bronwish solution was treated with aqueous K_2CO_3 (10 ml, 5 M solution), water (10 ml), then stirred for ½ h. The organic layer was decanted and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic phases were dried over $MgSO_4$. Filtration *and solvent evaporation left a red-brown liquid consisting of 11 and N,N-diethylchloroformamide. Upon the addition of* hexane (100 ml) and cooling to 0°C, an orange solid (5.13 g) precipitated which, after chromatography on basic alumina Brockman, activity I (ethyl acetate-methanol 95:5 saturated with NH_3), gave the carbamate 11, mp 127-129°C (4.98g, 89%); *mp 129-130°C after one recrystallization from benzene-hexane.* Ir ($CHCl_3$) ν_{max}: 1740, 1110, 1080, 1055 cm^{-1}; ^{1}Hnmr 1 2-2.0 (14 H), 2.80 (1 H, dt, J=12.0, 3.0 Hz, H6'eq), 3.14 (3H, s, OCH_3), 3.18 (1H, m, H6'ax), 3.20 (3H, s, OCH_3), and 3.87

(1 H, dm, J=12.9 Hz, H2') ppm; ^{13}Cnmr ($CDCl_3$) δ: 23.0 (C4') 24.1 (C5'), 25.7 (C3'), 27.5 (C3), 27.8 (C2), 28 0 (C6), 33.3 (C5), 41.7 (C6'), 47 5 (OCH_3), 47.6 (OCH_3), 63.1 (C2'), 80.4 (C4), 99.0 (C1), 156.2 (C=O) ppm. Exact mass calcd for $C_{14}H_{23}NO_4$: 269.1627; found (ms). 269.1632.

Carbamates of 4-hydroxy-1-methoxy-4-(2'-piperidyl)cyclohex-1-enes (12 and 13). -

a) The ketal-carbamate 11 (~1g), a few drops of triethylamine, and a few crystals of freshly fused $KHSO_4$ were heated to 210°C in a bulb-to-bulb distillation apparatus at atmospheric pressure. Methanol distilled off rapidly then the product itself distilled slowly and crystallized in the second bulb The procedure was repeated 7 times (6.95 g of 11, 25.7 mmol) to give a 1:1 mixture of enol ether-carbamates 12 and 13, mp 102-104°C (5 86 g, 95%), contaminated by some (<5%) unreacted ketal-carbamate 11 according to the ^{1}Hnmr spectrum.

b) The ketal-carbamate 11 (1.455 g, 5.4 mmol) and thoroughly dried triethylamine hydrochloride (100-150 mg) were heated to 180°C in a bulb-to-bulb distillation apparatus Distillation of methanol at atmospheric pressure was followed by distillation of the product at 0.5 Torr to afford a 1:1 mixture of enol ether-carbamates 12 and 13, mp 102-104°C (1.272 g, 98%). Ir ($CHCl_3$) ν_{max}: 1740, 1670, 1180 cm^{-1}; ^{1}Hnmr ($CDCl_3$)δ; 1.25-2.55 (12 H), 2.81 (1H, m, H6'ax), 3.26 (1H, m, H6'eq), 3.49 and 3.50 (3H, two s, OCH_3), 3.88 (1H, m, H2'), 4.47 (1H, br t, J=3.6 Hz, H2) ppm; ^{13}Cnmr ($CDCl_3$) δ: 22.6, 22.8 (C4'), 23.8, 24.0 (C5'), 23.8, 24.4 (C3'), 24.9, 26.1 (C6), 26.6, 29.0 (C5), 32.2, 34.5 (C6), 41.3, 41.4 (C6'), 53.7, 53.8 (OCH_3), 62.2, 62.5 (C2'), 79.5, 79.6 (C4), 88.5, 88.8 (C2), 154.1, 154.5 (C1), 156.0, 156.2 (C7) ppm. Exact mass: calcd for $C_{13}H_{19}NO_3$: 237.1363; found (ms): 237.1372.

4-Hydroxy-1-methoxy-4-(2'-piperidyl)cyclohex-1-enes (14 and 15). - To a mixture of enol ether-carbamates 12 and 13 (1.251 g, 5.28 mmol) in methanol (3 ml) in a heavy walled tube (inner diameter: 1 cm) was added potassium hydroxide (4 ml of a 6 M solution in CH_3OH-H_2O 1:1). The tube was sealed off under reduced pressure (0.01 to 0.02 Torr), placed in a steel mantle, and heated to 110-120°C in an oil bath for 88 h. After the addition of water (~20 ml), the mixture was extracted with CH_2Cl_2 (4 x 10 ml). The combined organic phases were dried over anhydrous K_2CO_3 then filtered. Evaporation to dryness under vacuum gave a 1:1 mixture of enol ether-piperidyl-alcohols 14 and 15 as a light orange viscous oil (1 110 g, 100%) homogenous by tlc and spectroscopically pure. Ir ($CHCl_3$) ν_{max}: 3600, 3400, 1670, 1170 cm^{-1}; ^{1}Hnmr ($CDCl_3$) δ· 1.10-2.45 (12 H), 2.46 (1 H, m, H2'), 2.63 (1 H, dt, J=12 5, 2.9 Hz, H6'ax), 3.14 (1 H, br d, J=11.7 Hz, H6'eq), 3.51 (s, OCH_3), and 4.47 (1H, dd, J=4.5, 2.3 Hz, H2) ppm , no detectable signal for OH and NH; ^{13}Cnmr ($CDCl_3$) δ: 24.1 (C4'), 24 7 (C5'), 26 4 (C3'), 26.5 (C6), 28.6, 30 9 (C3), 31 2, 33.9 (C5), 47.1 (C6'), 53.8 (OCH_3) 63.5, 64.3 (C2'), 70.6, 71.0 (C4), 89.5 (C2), 154.6 (C1) Exact mass. calcd for $C_{12}H_{21}NO_2$: 212.1650; found (ms). 212.1644.

2-Endo-Iodo-1-methoxy-7-oxa-4-(2'-piperidyl)bicyclo [2.2.1] heptanes (16 and 17). - To a vigorously stirred solution of a 1:1 mixture of enol ether-piperidyl-alcohols 14 and 15 (1.366 g, 6.45 mmol) in dry CH_2Cl_2 (40 ml) under argon at 0°C, was added slowly a 1 M solution of acetic acid in dry CH_2Cl_2 (6.5 ml) then, dropwise, a solution of ICl (recrystallized twice) (1.155 g, 6.46 mmol) in dry CH_2Cl_2 (10 ml). The solution became orange and was stirred at 0°C for 45 min. Potassium carbonate

(10 ml of a 5 M aqueous solution) was added, followed by sodium thiosulfate (2 ml of a 1 M aqueous solution) and water (20 ml). The mixture was allowed to warm to room temperature and vigorous stirring was maintained for 90 min The organic layer was decanted. The aqueous phase was saturated with NaCl and extracted with CH_2Cl_2 (4 x 10 ml). The combined organic phases were dried over anhydrous K_2CO_3 and filtered. Evaporation to dryness gave a reddish oil (1.938 g) which after chromatographic separation (ether-methanol 99:1 saturated with NH_3) gave three fractions. Fraction 1 (less polar) consisted of 17, mp 62-64°C (0.604 g, 28%), fraction 2 of a 3:1 mixture of 16 and 17 (0.171 g, 8%), and fraction 3 of 16 (0.502 g, 23%), a viscous oil. Further and complete separation of the second fraction was achieved by preparative layer chromatography.

16. ir (CCl_4) ν_{max}: 3340, 1210, 1120, 1020 cm^{-1}; ^{1}Hnmr ($CDCl_3$) δ: 1.00-1.85 (7H), 1.96 (1 H, dddd, J=12.8, 12.7, 4.7, 2.9 Hz, H6 exo), 1.98 (1 H, dd, J= 12.8, 5.5 Hz, H3 endo), 2.13 (1 H, dddd, J= 12 8, 12.7, 5.3, 3.1 Hz, H5 exo), 2.38 (1 H, ddd, J= 12 8, 11.5, 3.1 Hz, H3 exo), 2.54 (1 H, ddd, J= 12 8, 9.0, 5.3 Hz, H6 endo), 2.64 (1 H, dt, J= 11.2, 2.4 Hz, H6'ax), 2.76 (1 H, dd, J= 11.4, 3.4 Hz, H2'), 3.08 (1 H, dm, J= 11.4 Hz, H6'eq), 3.46 (3 H, s, OCH_3), 4.14 (1 H, ddd, J= 11.5, 5.5, 2.9 Hz, H2 exo) ppm, no detectable NH absorption; ^{13}Cnmr ($CDCl_3$) δ: 22.8 (C2), 24.5 (C4'), 25.9 (C5'), 26.5 (C3'), 28.6 (C6), 29.2 (C5), 46.2 (C3), 46.7 (C6'), 52.3 (C7), 60.2 (C2'), 84.1 (C4), 111.5 (C1) ppm. Exact mass calcd for $C_{12}H_{20}INO_2$: 337.0540; found (ms): 337 0546

17: ir ($CHCl_3$) ν_{max}: 3340, 1220, 1130, 1020 cm^{-1}; ^{1}Hnmr ($CDCl_3$) δ: 1.02 (1 H, dq, J= 12.1, 4.0 Hz), 1.05-1.85 (8 H), 1.97 (1 H, dddd, J=12 8, 12.7, 4.7, 3.0 Hz, H6 exo), 2.54 (1 H, ddd, J=12.8, 9.0, 5.3 Hz, H6 endo), 2.64 (1 H, dt, J= 11.6, 2 8 Hz, H6'ax), 2.80 (1 H, dd, J= 11.4, 3.4 Hz, H2'), 2.90 (1 H, ddd, J=12.9, 11.6, 3.2 Hz, H3 exo), 3.06 (1 H, br d, J= 11.1 Hz, H6'eq), 3.46 (3H, s, OCH_3), 4.12 (1 H, ddd, J= 11.6, 5.5, 3.0 Hz, H2) ppm, no detectable NH absorption; ^{13}Cnmr ($CDCl_3$) δ: 22 7 (C2), 24.5 (C4'), 25.8 (C5'), 26.4 (C3'), 29.2 (C6), 34.2 (C5), 41.4 (C3), 46.6 (C6'), 52.2 (C7), 60.4 (C2'), 84.3 (C4), 111.5 (C1) ppm. Exact mass calcd for $C_{12}H_{20}INO_2$: 337.0540; found (ms): 337.0546. For X-ray crystalline structure, see ref. 9.

1-Hydroxy-7-azatricyclo [6.3.1.$0^{2,7}$] dodecan-9-one (3). - To a solution of iodo-ketal 16 (502 mg, 1.49 mmol) in benzene (50 ml) under argon, at room temperature, was added rapidly, with vigorous stirring, 1 M aqueous HCl (1.50 ml, 1.50 mmol) then trifluoroacetic acid (115 µl, 4.49 mmol). The solution was stirred for 20 min. Aqueous K_2CO_3 (4 ml of a 5 M solution) was then added quickly followed by the addition of water (5 ml) The mixture was stirred vigorously for 90 min and the organic phase was decanted The aqueous phase was extracted with benzene (3 x 10 ml). The combined organic phases were dried over anhydrous K_2CO_3 and filtered. All the work-up operations were carried out under argon as much as possible. The solvent was evaporated under vacuum to give ketone 3, mp 64-70°C dec. (179 mg, 96%) as a pale yellow solid. It was stored under argon. Ir (CCl_4) ν_{max}: 3610, 3450, 1710, 1140, 1080 cm^{-1}; ^{1}Hnmr (C_6D_6) δ: 0.90-1.38 (3H), 1.38-1.80 (6H), 1.90-2.20 (3H), 2.32 (1H, dd, J=10.7, 2.9 Hz, H2), 2.44 (1H, m, H6ax), 2.67 (1H, ddd, J=12.3, 5.0, 3.4 Hz, H6eq), 3.12 (1H, d, J=5.9 Hz, H8) ppm, OH absorption not detected; ^{13}Cnmr (C_6D_6) δ: 24.5 (C4), 25.8 (C3), 28.1 (C5), 34.5 (C11), 37.1 (C10), 41.1 (C12), 47.8 (C6), 65.3 (C2), 69.2 (C8), 76.8 (C1), 206.2 (C9) ppm. Exact mass calcd for $C_{11}H_{17}NO_2$: 195.1251; found (ms): 195.1257.

1-Hydroxy-7-azatricyclo[6.3.1.$0^{2,7}$]dodecan-9-one (4). - It was prepared from iodo-ketal 17 (1.584 g, 4.70 mmol) as described above: benzene (50 ml), 1 M HCl (4.70 ml, 4.70 ml), trifluoroacetic acid (360 µl, 4.70 mmol), 5 M K_2CO_3 (10 ml), H_2O (15 ml). Ketone 4 was isolated (0.918 g, 100 %) as a pale yellow liquid which was stored under argon. Ir (CCl_4) ν_{max}: 3600, 3440, 1720, 1150, 1100 cm^{-1}; ^{1}Hnmr (C_6D_6) δ: 0.90-1 15 (2H), 1.15-1.40 (2H), 1.40-1.70 (4H), 1.80-2.10 (3H), 2.35 (1H, m, H6), 2.50 (1 H, br d, J=9 0 Hz, H2), 2.69 (1H, dt, J= 10 5, 3.6 Hz, H6), 2.88 (1 H, dt, J= 16.8, 9.6 Hz, H10), 2.97 (1 H, d, J= 7 2 Hz, H8) ppm, OH absorption not detectable, ^{13}Cnmr (C_6D_6) δ:24.6 (C4), 25.1 (C5), 27.0 (C3), 30.6 (C11), 33 5 (C10), 42.3 (C12), 50.9 (C6), 67.2 (C8), 70.4 (C2), 75.9 (C1), 207.1 (C9) ppm. Exact mass calcd for $C_{11}H_{17}NO_2$: 195.1251; found (ms) 195.1257.

Tosylhydrazone of 1-hydroxy-7-azatricyclo[6.3.1.$0^{2,7}$]dodecan-9-one (20). - To a solution of ketone 3 (0.646 g, 3.31 mmol) in methanol (35 ml) at 50°C were added tosylhydrazine (620 mg, 3.32 mmol) in hot methanol (3.5 ml) and trimethyl orthoformate (3.6 ml, 33 mmol). The mixture was stirred at 50°C for 16 h then evaporated to dryness to leave crystalline *tosylhydrazone 20 which decomposed with gas evolution upon heating at 65°C* (1.210 g, ~100%). It did not contain any unreacted ketone 3 according to tlc and was used without further purification. Ir ($CHCl_3$) ν_{max}: 3600, 3300, 3200, 1600, 1170, 1095,815 cm^{-1};^{1}Hnmr ($CDCl_3$) δ: 1.1-1.9 (9H), 2.0-2.2 (2H), 2.3-2.7 (3H, 2m), 2.42 (3H, s, CH_3), 3.41 (1H, br d, J= 6.1 Hz, NH), 7.31 (2H, d, J= 8.0 Hz, aromatic H3' and H5'), 7.81 (2H, d, J= 8.4 Hz, aromatic H2' and H6') ppm

Tosylhydrazone of 1-hydroxy-7-azatricyclo[6.3.1.$0^{2,7}$]dodecan-9-one (21). - It was prepared from ketone 4 (0.918 g, 4 70 mmol) in methanol (50 ml) as described above: toshylhydrazine (0.876 g, 4.70 mmol) in hot methanol (5 ml), trimethyl orthoformate (5.1 ml, 47 mmol). Toshylhydrazone 21 (1.709 g, ~100%) was obtained as a solid which decomposed with gas evolution upon heating at 65-70°C. It did not contain any unreacted ketone 4 and was used without further purification. Ir ($CHCl_3$) ν_{max}: 3600, 3350, 3200, 1600, 1180, 1095, 810 cm^{-1}; ^{1}Hnmr ($CDCl_3$) δ· 1 1-2.2 (11H), 2 40 (1H, m), 2 41 (3H, s, CH_3), 2.56 (2H, m), 3.50 (1H, br d, J= 5 0 Hz, NH), 7.30 (2H, d, J= 8.0 Hz, aromatic H3' and H5'), 7.81 (2H, d, J= 8.4 Hz, aromatic H2' and H6') ppm.

1-Hydroxy-7-azatricyclo[6.3.1.$0^{2,7}$]dodec-9-ene (22). - To a solution of tosylhydrazone 20 (500 mg, 1.38 mmol) in anhydrous THF (30 ml) under argon, N-methylmorpholine (3.5 ml, 31.7 mmol) was added and the mixture was cooled to -78°C. Methyllithium (6.1 ml of a 1.37 M solution in ether, 8.33 mmol) was added dropwise (Shapiro's conditions[13]). The orange solution was stirred at -78°C for 2 h, then allowed to warm at room temperature and stirred for an additional 2 h Water (10 ml) and ether (20 ml) were added and the aqueous phase was separated. It was saturated with NaCl and extracted with ether (5 x 10 ml). The combined organic phases were dried over anhydrous K_2CO_3 and the solvent was evaporated Microdistillation of the crude product (184 mg) at 140°C (2 Torr) gave olefin 22, mp 109-112°C (133 mg, 54%) Another microdistillation at 85°C (0.25 Torr) gave pure 22, mp 115-117°C It decomposed on tlc plates. Ir ($CHCl_3$) ν_{max}: 3600, 3400, 3010, 1630(w), 1140 cm^{-1}; ^{1}Hnmr ($CDCl_3$) δ: 1.15-1.40 (2H), 1.50-1 70 (3H), 1.75 (1H, dd, J= 9.3, 0.6 Hz, H12), 1.80-2.00 (3H), 2.14 (1H, ddt, J= 14 3, 4.5, 1.6 Hz, H11), 2.35 (2H, m), 2.86 (1H, ddd, J= 10.5, 4.2, 3.2 Hz, H6), 3.39 (1H, t, J= 4.5 Hz,

H8), 5 67 (1H, dddd, J=9.6, 5.0, 2.4, 1.2 Hz, H9), 5.78 (1H, dddd, J= 9.6, 4.5, 2.1, 1.0 Hz, H10) ppm, no OH absorption was detected; ^{13}Cnmr ($CDCl_3$) δ:25.2 (C4), 25.8 (C3), 26.6 (C5), 43.0 (C12), 44.7 (C11), 48.7 (C6), 58.3 (C8), 68.4 (C2), 77.3 (C1), 126.3 (C9), 128.6 (C10) ppm. Exact mass calcd for $C_{11}H_{17}NO$:179.1310; found (ms): 179.1306.

1-Hydroxy-7-azatricyclo[6.3.1.0^{2,7}]dodec-9-ene (23). - It was prepared from tosylhydrazone 21 (505 mg, 1.39 mmol) as described above. Microdistillation of the crude product (190 mg) at 170°C (2 Torr) gave olefin 23, mp 132-140°C (144 mg, 58%) Another microdistillation at 95°C (0.25 Torr) gave pure 23, mp 144-146°C. Ir ($CHCl_3$) ν_{max}: 3600, 3350, 3010(w), 3030(w), 1630(w), 1150, 1125, 1075 cm^{-1}; ^{1}Hnmr ($CDCl_3$) δ: 1.40-1.65 (3H), 1.65-1.85 (3H), 1.90 (1H, d, J= 9.9 Hz, H12), 2 10 (1H, m, OH), 2.26 (1H, ddt, J= 9.9, 4.5, 0.8 Hz, H12), 2.44 (2H, m), 2.56 (1H, dt, J= 10.3, 3.6 Hz, H6), 2 80 (1H, m, H6), 3 10 (1H, dd, J = 12.2, 4.4 Hz, H2), 3.44 (1H, t, J= 5.6 Hz, H8), 5.76 (1H, dddd, J= 9.4, 4.8, 3.0, 1.1 Hz, H10), 5 91 (1H, ddd, J= 9 4, 5.2, 3.0 Hz, H9) ppm; ^{13}Cnmr ($CDCl_3$) δ: 18 9 (C4), 20.9 (C3), 21.7 (C5), 38.6 (C11), 41.9 (C6), 42.2 (C12), 57 8 (C8), 66.4 (C2), 77 3 (C1), 128.6 (C10), 132.1 (C9) ppm. Exact mass calcd for $C_{11}H_{17}NO$: 179 1310; found (ms) 179.1306.

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