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TETRAHEDRON

First Synthesis of (±)-10β-hydroxy-13β-methylcyclohexa[a]quinolizidine. A Convenient Route to the *ABC*-part of 8-Azasteroids.

Sylvain Célanire,[1] Isabelle Salliot-Maire,[2] Pierre Ribéreau,[1] Alain Godard[1] and Guy Quéguiner[1]*

UPRESA CNRS 6014, IRCOF/INSA de Rouen BP 08 76131 Mont Saint Aignan cedex - France

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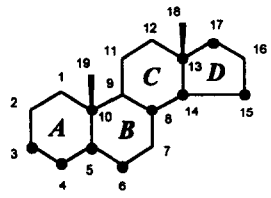
Abstract: The first synthesis of racemic 10β-hydroxy-13β-methylcyclohexa[a]quinolizidine is reported. Original construction of *AC*-bicyclic system is achieved by lateral metallation of 2-ethylpyridine followed by a Robinson annelation, with the creation of a quaternary picolinic carbon center. Functionalization of the *A*-ring and construction of the *B*-ring by a stereocontrolled reduction of the pyridinium salt and final hydrogenations afford the *ABC*-part of an 8-azasteroid.

INTRODUCTION

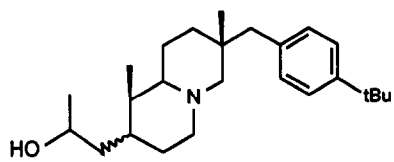
The inhibition of enzymatic reactions has received increasing attention in recent years and represents a high potential therapeutic target for the treatment of many diseases and human disorders. Heterocyclic compounds, and particularly azasteroids, are of continuing interest due to their large range of activity in the inhibition of steroid biosynthesis involved in benign prostatic hypertrophy,[3,4] hypocholesterolemia,[5] or fungal infections.[6] Other activities have also been attributed to azasteroids.[7]

In our search for new biologically active heterocyclic compounds, we directed our research program towards the synthesis of polycyclic analogues of such azasteroids including benzo-derivatives.[8] Considering that a wide variety of steroid-like compounds, with the nitrogen atom at a crucial position in the steroid skeleton (see numbering in figure 1), could mimic a high energy intermediate during the steroid biosynthesis[9] and consequently, inhibit the enzyme, we were interested in the development of new strategies towards such compounds.

In a preceding paper, we described the synthesis of a substituted quinolizidine **1**, which revealed an important antifungal activity.[10] Further potent biological activities could be attributed to this bicyclic system as in the azadecaline-type structure **2**[11] or other quinolizidine derivatives[12] which have been extensively studied as inhibitors of 2,3-oxidosqualene cyclase.[13]



Steroid numbering system



(+/-)-1

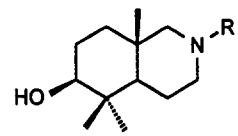


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Figure 1

E-mail: guy.queguiner@ircof.insa-rouen; Fax: (33) 02 35 52 29 62

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In this field, we decided to apply this strategy towards azasteroids with a bridgehead nitrogen atom, and particularly, 8-azasteroids. According to the literature, most of synthetic and semi-synthetic compounds are either benzo-fused *A*-ring[14] (also called 19-Nor-azasteroid,[15] such as (-)-8-azaestrone **3**; Figure 2)[16] or derivatives obtained by ring-cleavage / ring-closure strategy from natural steroids.[17] However, Guarna and co-workers recently reported the total synthesis and biological evaluation of a novel class of human 5α-reductase inhibitors such as compounds **4**.[18] To the best of our knowledge, no total synthesis have been early reported towards the real alicyclic structure of 8-azasteroids including 19-angular methyl group.

We wish to report here the first total synthesis of the 10β-hydroxy-13β-methylcyclohexa[a]quinolizidine **5** as a tricyclic model of an 8-azasteroid, which could be potent inhibitor in enzymatic processes according to its steroid-like configuration.

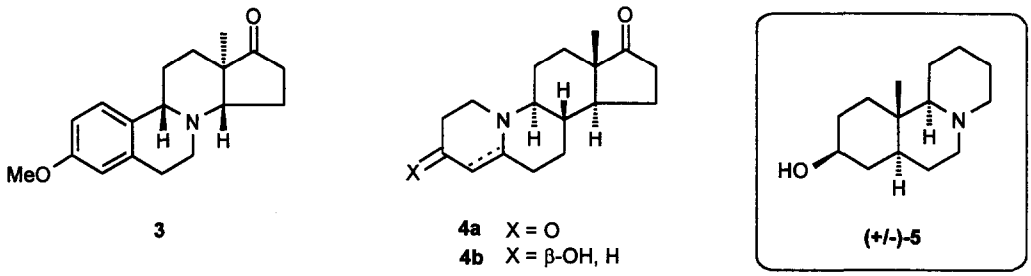
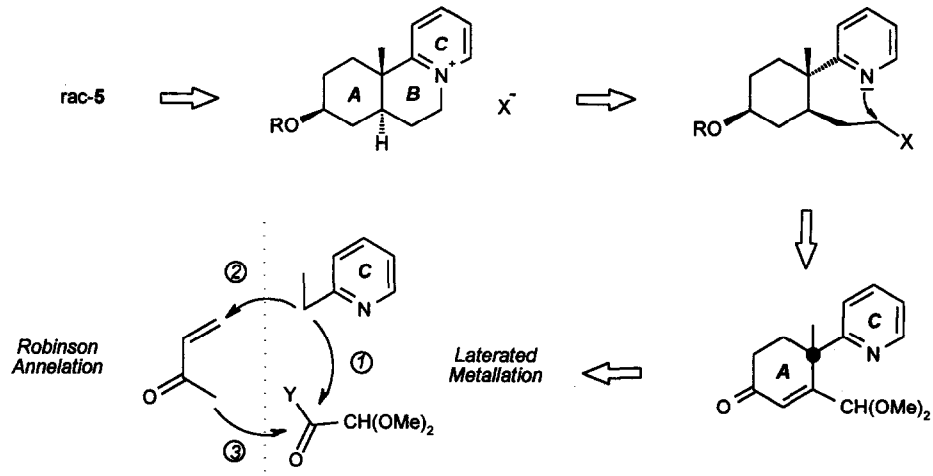


Figure 2

Retrosynthetic analysis

Elaboration of the target molecule rac-**5** was based on the retrosynthetic pathway described below. The first key steps are based on deprotonation reactions at the picolinic carbon of the 2-ethylpyridine, precursor of the *C*-ring: sequential laterated metallation / nucleophilic addition ① - Robinson annelation ②/③ reactions lead to the *AC*-bicyclic system with creation of a quaternary picolinic carbon center. Suitable functionalization of the *A*-ring followed by an intramolecular cyclization at the nitrogen atom of the pyridine provides the *B*-ring.

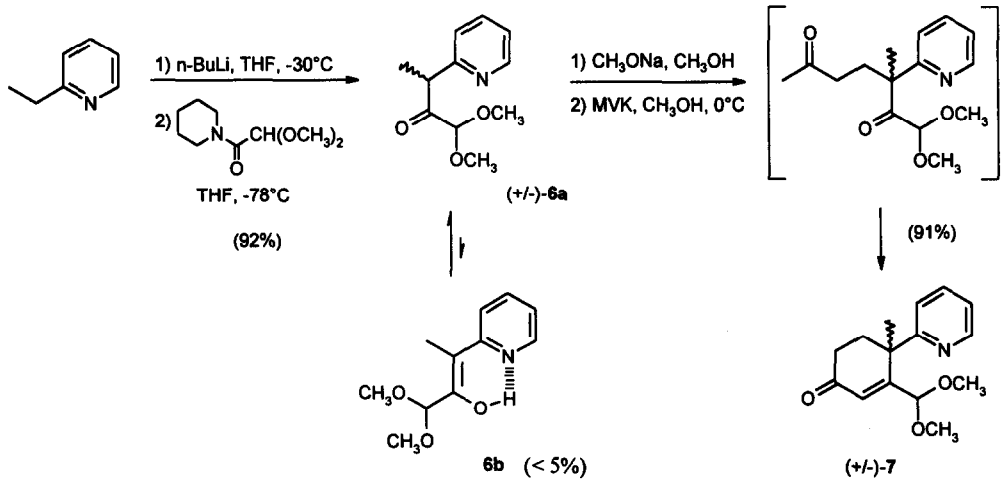


Scheme 1

RESULTS AND DISCUSSION

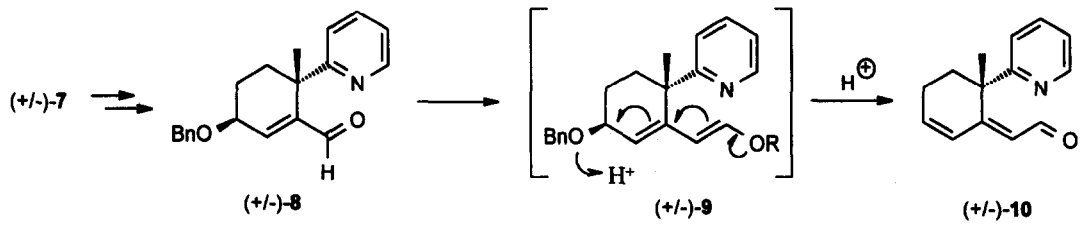
Elaboration of the AC-bicyclic system

According to our continuing interest in the chemistry of π-deficient heterocycles,[19] and more recently, in the laterated side chain metallation of alkylpyridines,[20] we focussed on the hydrogen abstraction at the picolinic carbon of the 2-ethylpyridine.[21] Thus, treatment of the commercially available 2-ethylpyridine with n-butyllithium at -30°C,[22] and subsequent addition of N-(2,2-dimethoxyacetyl)piperidine[23] gave the ketoacetal **6a** in 92% yield (Scheme 2). It is noteworthy that enol-form **6b** was present less than 5% as showed by NMR integration.[24] Robinson annelation applied to the tautomeric compound **6** with methyl vinyl ketone (MVK) in the presence of sodium methoxide afforded the trisubstituted cyclohexenone **7** in 91% yield, without isolating the supposed intermediate diketone.[25]



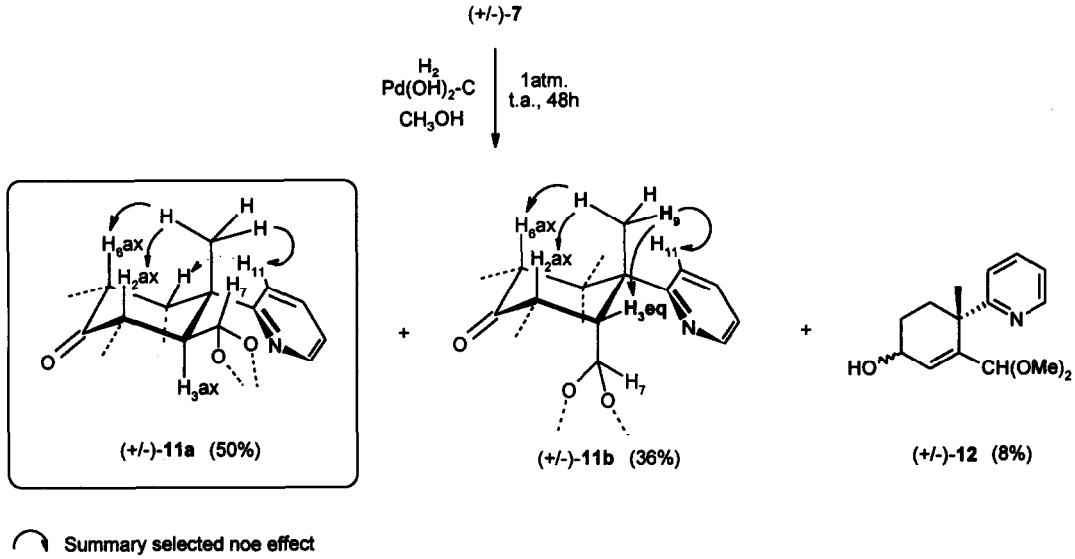
Scheme 2

Among the different ways encountered for the synthesis of the target molecule, the first one we used relies on the 1,2-reduction of the enone **7** by borohydride followed by sequential alcohol protection and acetal deprotection providing aldehyde **8**.[26] Unfortunately, the necessary homologation of the aldehyde realized by a Wittig reaction[27] results, after enol ether hydrolysis, in the loss of benzyl ether group to produce the highly conjugated aldehyde **10**. All attemps to avoid this side-reaction were unsuccessful and all other strategies to homologate the conjugated aldehyde were discouraging.



Scheme 3

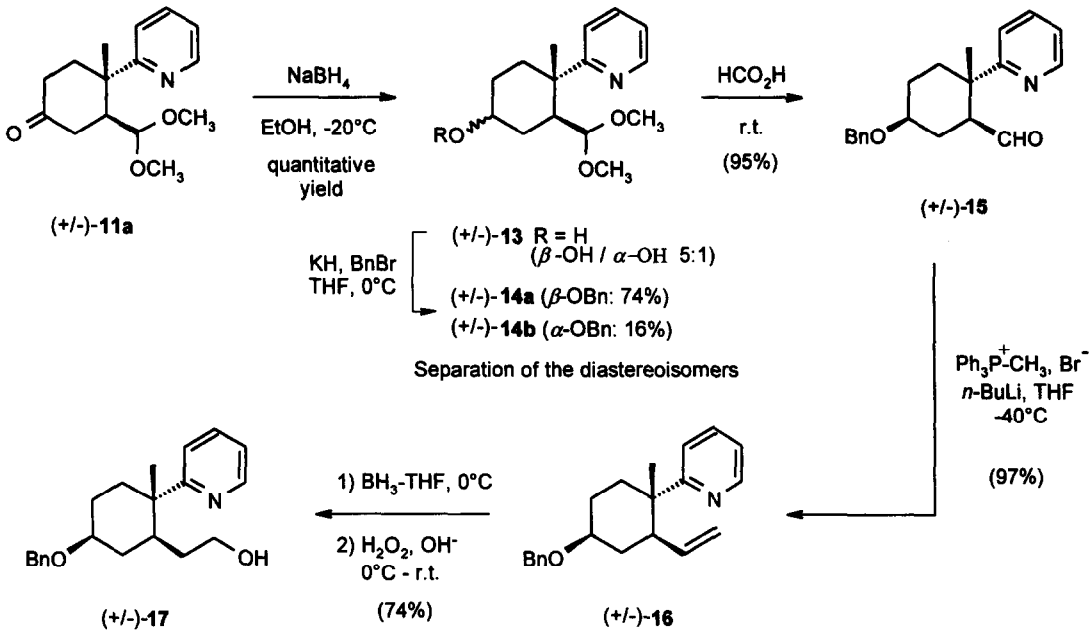
Taking account of the above failure, the second method relies on the preliminary α,β-double-bond hydrogenation of the enone. Unfortunatly, most of the hydrogenation systems using classic catalysts (Pd/C, Rh/C, Pd Black, PtO_2)[28] were unable to reduce chemo- or stereo-selectively the conjugated ketone. Partial or total reduction of the pyridine nucleus was observed as well as the carbonyl reduction into the corresponding allylic alcohol. Others attempts by homogeneous catalytic hydrogenation or hydride reduction were unsuccessful. Nevertheless, reduction with hydrogen using Pearlman's catalyst[29] in methanol afforded pure cyclohexanone **11** in good yield as two diastereoisomers in a 3:2 ratio (Scheme 4). The corresponding undesired allylic alcohol **12** was also isolated in less than 8% yield. After an efficient purification process,[30] the stereochemistry of the hydrogenated compounds **11a** and **11b** was assigned by 2D NMR experiments (NOESY and HMBC).



Scheme 4

Functionalization of the A-ring

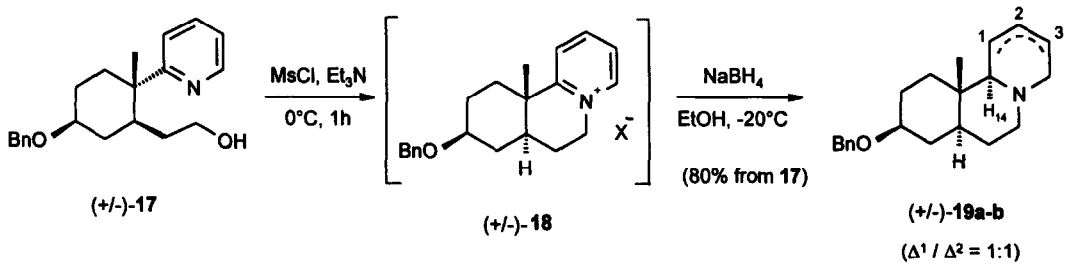
Cyclohexanone **11a** was choosen according to its steroid-like conformation, confirmed by the CH_3 / H_{3ax} *trans*-conformation. The ketone was reduced by sodium borohydride in ethanol to afford in quantitative yield the alcohols **13a-b**. (Scheme 5). The β-OH/α-OH ratio (5:1) determined by ^{1}H NMR and 2D-NMR experiments confirmed the stereoselective α-attack of the hydride from the lower face of the cyclohexanone.[31] *o*-Benzyl protection[32] of the mixture of alcohol **13** allowed an efficient separation of the two diastereoisomers **14a** and **14b**. Acetal hydrolysis using formic acid of the isolated β-benzyloxy compound **14a** (74% yield from **11a**) afforded the required aldehyde **15** in excellent yield (95%); the presence of the formyl group was confirmed by the association of spectral data as caracteristic singlet at 9.47 ppm on the ^{1}H NMR spectrum and a strong C=O absorption in its infra-red spectra. Subsequent Wittig reaction applied to aldehyde **15** with methylenetriphenylphosphorane in THF produced the vinylic compound **16** in nearly quantitative yield. Regioselective hydroboration on the terminal carbon with BH_3•THF complex followed by oxidation in a one-pot procedure gave the primary alcohol **17** in 74% yield.



Scheme 5

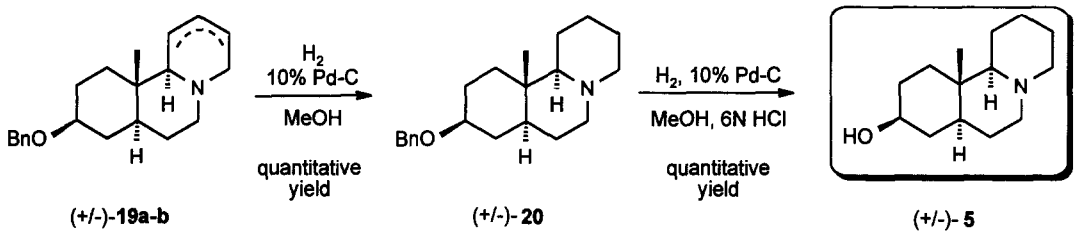
Creation of the B-ring by alcohol activation - cyclization - reduction procedure

The last key-step in this total synthesis relies on an intramolecular cyclization with the nitrogen atom of the pyridine nucleus.[33] Thus, displacement of the alcohol function by mesylate with MsCl at 0°C induced the intramolecular ring-closure affording compound **18** (Scheme 6). The pyridinium salt (not isolated; counter-ion could be either Cl^- or MsO^-) was directly reduced by sodium borohydride in ethanol to afford tricyclic compound (80% overall yield from **17**) as a mixture of two compounds **19a-b** in a 1:1 ratio as showed by NMR analyses. A pure sample of **19a** could be isolated by chromatography and studied by high-field NMR. The position of the endocyclic double-bond in the quinolizidine nucleus was determinated by association of 2D experiments (NOESY, HMBC, HMQC, COSY): the structure of Δ^1-derivative **19a** was deduced from the disymmetry (H_1/H_{14ax} and $H_2/H_{3ax\text{-}eq}$) and the mutiplicity of the signal of the two ethylenic hydrogens in association with coupling constants; Δ^2-derivative **19b** was defined from the NMR spectra of the mixture by a symmetric and complex signal including $^2J_{cis}$, allylic and homoallylic coupling constants.



Scheme 6

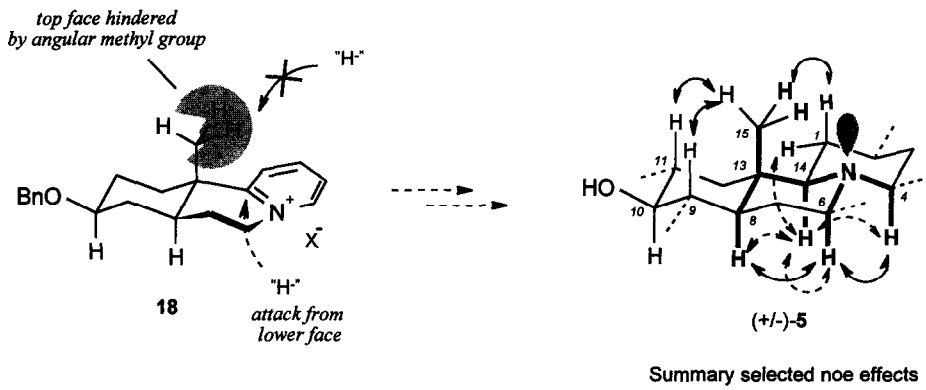
The mixture of **19a-b** was then subject to hydrogenation. Selective reduction of the double bond occured in the presence of the potentially reactive benzyl ether to provide compound **20** (Scheme 7). A similar chemoselective inhibition has been recently reported and performed by the simple addition of a nitrogen-containing base (triethylamine or pyridine).[34] Thus, the nitrogen atom of the quinolizidine skeleton is supposed to poison the Pd-catalyst and inhibited the hydrogenolys of the benzyl ether protecting group. Finally, deprotection was achieved by a second hydrogenation in the presence of hydrochloric acid to give the target molecule rac-**5** in quantitative yield from the mixture **19a-b**. It is noteworthly that a tandem ethylenic reduction - deprotection reaction in acidic conditions failed.



Scheme 7

Stereochemical study of the pyridinium salt reduction step

The total stereoselectivity in the reduction step of the pyridinium salt was somewhat unexpected: a hypothesis could be that the methyl group sterically hindered the upper face of the tricyclic pyridinium salt **18** and, consequently, directed efficiently the α-attack of the hydride from the lower face (Scheme 8). The structure of final product was established by ^{1}H and ^{13}C NMR experiments on a Bruker Avance DMX 500 Spectrometer: NOESY spectra analysis indicated the absence of correlation between hydrogens of the axial methyl group and H_{14} whereas strong correlations H_{15} / H_{1ax}, H_{9ax} and H_{11ax}, and H_{14} / H_{4ax}, H_{6ax} and H_{8ax} were clearly observed. Furthemore, coupling constants H_{14} / H_{1ax} (J = 10.3 Hz) and H_{14} / H_{1eq} (J = 6.5Hz) confirmed the axial position of H_{14} and subsequently, the *trans*-diaxial conformation of tricyclic compound **5** with H_{8ax} - Me_{13ax} - H_{14ax} - N_5 - H_{4ax} system as in steroid-like structures.[35] Finally, FTIR spectra of compounds **19**, **20** and **5** showed an intense (and sharp) Bohlmann band in the 2800-2600 cm^{-1} region, which proved that all the isolated tricyclic compounds have the *trans* relationship between nitrogen lone-pair and α-axial hydrogens.[36]



Scheme 8

CONCLUSION

In summary, we have reported here a convenient and efficient route for the synthesis of a new hydroxy-cyclohexa[a]quinolizidine[37] (12 steps, 17% overall yield), tricyclic model of an 8-azasteroidal system. The lateral metallation of 2-ethylpyridine step followed by a Robinson annelation reaction allowed the preparation of a highly functionalized intermediate with creation of a quaternary carbon center. Despite the poor stereoselectivity in the enone hydrogenation stage, the following steps are realised with high stereoselectivity, and particularly the cyclization pathway to build the quinolizidine skeleton in the strictly steroid-like structure configuration. It is noteworthy that the major advantage relies on the presence of the axial methyl group in the first key-steps of the synthesis.

Synthesis of new tricyclic compounds from the diastereoisomer **11b** is in current investigation in our laboratory as well as applications to the total synthesis of a 10-methyl-8-azasteroid and related compounds. Biological activity tests of the original pyridine substructures and tricyclic adducts are planned.

ACKNOWLEDGEMENT

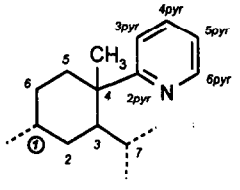
We thank the Région Haute-Normandie for financial support and the Centre Européen de Bioprospective for its collaboration.

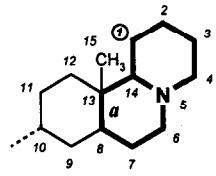
EXPERIMENTAL

General

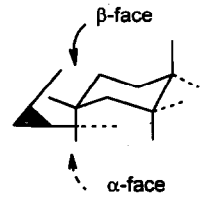
All materials were obtained from commercial suppliers and used without further purification. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from benzophenone / sodium prior to use. Commercial 2.5 M solutions of *n*-butyllithium (*n*-BuLi) in hexanes were stored under an argon atmosphere. Reactions were monitored by thin-layer chromatography (TLC) with silica gel Geduran SI 60 (70-230 Mesh ASTM). Infra-Red spectra were recorded on a Perkin-Elmer FTIR 1600. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-200 (200 MHz) or Bruker Avance DMX-500 (500 MHz). Chemical shifts are given in parts per million from Me_4Si in $CDCl_3$ and coupling constant (*J*) were reported in hertz (Hz). Mass spectra were carried out by the Centre Régional Universitaire de Spectroscopie, IRCOF, Mont-St-Aignan and were taken on a JEOL AX500 (IC positive, 200eV). Melting points were measured on a Kofler apparatus. Elemental analyses were performed on a Carlo Erba 1160 CHN apparatus.

For a comprehensive experimental part, all the bicyclic and tricyclic structures have the following numbering system as well as steroid-faces differentiation on the α- and β- terminology.





cyclohexa-[a]-**quinolizidine**



1,1-Dimethoxy-3-(2-pyridyl)butan-2-one (6) To a stirred solution of commercial 2-ethylpyridine (16.2 ml, 141.9 mmol) in THF (100 ml) was added dropwise *n*-BuLi (2.5 M/hexanes; 60.3 ml, 150.8 mmol) at -20°C. After 1 h at -30°C, the solution was cooled to -70°C and treated dropwise with a solution of N-(2,2-dimethoxyacetyl)piperidine (20.87 g, 111.6 mmol) in THF (20 ml). The mixture was stirred 2h at -70°C, 4h -20°C and finally overnight at room temperature. After hydrolysis with saturated NH_4Cl solution and extraction with diethyl ether, the combined organic layers are washed with saturated NaCl solution, dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by distillation (83°C/0.1 mmHg) and yielded 23.33 g (92%) of pure **6** as a red oil. IR (film) υ 3052, 2977, 2935, 2833, 1735, 1589, 1570, 1472, 1434, 1193, 1078; ^{1}H NMR ($CDCl_3$) δ 1.42 (d, 3H, J = 7 Hz; CH_3), 3.21 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 4.34 (q, 1H, J = 7 Hz; C*H*-CH_3), 4.57 (s, 1H, C*H*-$(OCH_3)_2$), 7.13 (td, 1H, J = 1.8, 4.0 Hz; H_{5pyr}), 7.2 (d, 1H, J = 7.8 Hz; H_{3pyr}), 7.62 (td, 1H, J = 1.8, 7.8 Hz; H_{4pyr}), 8.49 (dd, 1H, J = 1.8, 4.0 Hz; H_{6pyr}); ^{13}C NMR ($CDCl_3$) δ 16.4, 50.1, 54.1, 54.4, 102.5, 121.8, 122.3, 136.7, 149.3, 159.8, 204.2; Anal. calcd. for $C_{11}H_{15}NO_3$: C, 63.14; 7.23; 6.69; found: C, 63.24; H, 7.05; N, 6.69.

3-Dimethoxymethyl-4-methyl-4-(2-pyridyl)cyclohex-2-en-1-one (7) To a stirred solution of sodium methylate, prepared from sodium metal (2.2 g, 1.3 eq) in MeOH (180 ml), was added dropwise ketone **6** (15.0 g, 71.7 mmol) in MeOH (60 ml) at -5°C. The solution was stirred 2h at 0°C and freshly distilled methyl vinyl ketone (7.2 ml, 1.2 eq) in MeOH (40 ml) was added dropwise. The mixture was stirred 2h at 0°C and at room temperature, sheltered from light for 7 days. The black-red solution was finaly heated 1h at 40°C to complete dehydratation. The solution was cooled before hydolysis with saturated NH_4Cl solution. After evaporation of the methanol, Et_2O was added and the organic layer was washed with saturated NH_4Cl solution. The combined organic extract was washed with saturated NaCl solution, dried ($MgSO_4$) and evaporated *in vacuo* to give the crude product. Purification by distillation (180°C/0.2 mmHg) afforded cyclic enone as a red oil which crystallized (17.16 g, 91%). mp 70-71°C. IR (film) υ 2937, 2830, 1666, 1587, 1431, 1135, 1077; ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 3H, CH_3), 2.03-2.53 (m, 4H), 3.14 (s, 3H, OCH_3), 3.25 (s, 3H, OCH_3), 4.71 (s, 1H, C*H*-$(OCH_3)_2$), 6.41 (s, 1H, C*H*=C), 7.18 (td, 1H, J = 4.7, 7.8 Hz; H_{5pyr}), 7.34 (d, 1H, J = 7.8 Hz; H_{3pyr}), 7.67 (td, 1H, J = 1.5, 7.8 Hz; H_{4pyr}), 8.59 (dd, 1H, J = 1.5, 4.7 Hz; H_{6pyr}); ^{13}C NMR ($CDCl_3$) δ 23.6, 34.4, 39.1, 44.6, 52.9, 54.4, 101.7, 120.7, 121.5, 127.5, 136.4, 149.0, 161.5, 164.3, 199.6. Anal. calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36; found: C, 68.47; H, 7.35; N, 5.32.

3-Dimethoxymethyl-4-methyl-4-(2-pyridyl)cyclohexan-1-one (11) To a stirred solution of the enone **7** (1g, 3.83 mmol) in MeOH (20 ml) was added Pearlman's catalyst 20% $Pd(OH)_2$/C (204 mg, 0.38 mmol, 10mol.%) under argon. After three vacuum / H_2 cycles to remove air from the reaction vessel, the solution was stirred under hydrogen atmosphere (balloon) (TLC: complete reaction) at room temperature for 24 h. The hydrogen was evacuated and the catalyst was removed by centrifugation. The resulting solution was filtered through celite® and washed with MeOH. The solvent was evaporated *in vacuo* to give the crude product as a red oil.

Purification process: a first flash chromatography (silica gel, eluent: petroleum ether-ethyl acetate (1:1 + 6% triethylamine) allowed the separation of the undesired allylic alcohol **12** (8 mg, 8%) as an oil; IR (film) υ 3378 (OH), 1077 (C-O); ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 3H, CH_3), 1.57-2.2 (m, 4H), 3.11 (s, 3H, OCH_3), 3.15 (s, 3H, OCH_3), 4.30 (m, 2H, C*H*-OH / C*H*-$(OCH_3)_2$), 6.28 (d, 1H, J = 3.6 Hz; C*H*=C), 7.13 (tdd, 1H, J = 2.0, 5.9, 8.0 Hz; H_{5pyr}), 7.39 (dd, 1H, J = 2.0, 8.0 Hz; H_{3pyr}), 7.64 (td, 1H, J = 1.0, 8.0 Hz; H_{4pyr}), 8.59 (dd, 1H, J = 1.0, 5.9

Hz; H_{6pyr}). A second column chromatography (silica gel, eluent: CH_2Cl_2-MeOH 95:5) of the above purified mixture provided compound **11a** (504 mg, 50%) as a red oil and **11b** (362 mg, 36%) as a white crystalline solid.

3β-Dimethoxymethyl-4β-methyl-4α-(2-pyridyl)cyclohexan-1-one **(11a)**: b.p. 150°C / 0.2 mmHg (Kügelrhor); IR (film) υ 3051, 2934, 2831, 1713, 1587, 1466-1431, 1109, 1071; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 3H, CH_3), 1.72 (m, 1H), 2.23-2.50 (m, 5H), 2.98 (s, 3H, OCH_3), 3.05-3.10 (m, 1H, H_{3ax}), 3.16 (s, 3H, OCH_3), 3.78 (d, 1H, J = 2.9 Hz; C*H*-$(OCH_3)_2$), 7.05 (td, 1H, J = 1.0, 8.0 Hz; H_{5pyr}), 7.30 (d, 1H, J = 7.9 Hz; H_{3pyr}), 7.60 (dt, 1H, J = 1.8, 7.9 Hz; H_{4pyr}), 8.50 (d, 1H, J = 3.9 Hz; H_{6pyr}); ^{13}C NMR ($CDCl_3$) δ 19.4, 37.4, 37.9, 38.4, 41.6, 45.9, 54.8, 55.1, 105.9, 120.0, 121.2, 136.40, 146.8, 166.4, 211.4. Anal. calcd. for $C_{15}H_{21}NO_3$: C, 68.52; H, 8.04; N, 5.32; found: C, 68.41; H, 7.95; N, 5.40.

3α-Dimethoxymethyl-4β-methyl-4α-(2-pyridyl)cyclohexan-1-one **(11b)**: mp: 82-83°C; IR (film) υ 3051, 2936, 2832, 1712, 1588, 1470-1431, 1370, 1186, 1121-1196, 1069; ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 3H, CH_3), 1.90 (m, 1H), 2.35-2.60 (m, 4H), 2.64-2.70 (m, 2H), 3.02 (s, 3H, OCH_3), 3.07 (s, 3H, OCH_3), 3.48 (d, 1H, J = 2.2 Hz; C*H*-$(OCH_3)_2$), 7.09 (td, 1H, J = 1.1, 5 Hz; H_{5pyr}), 7.26 (d, 1H, J = 7.9 Hz; H_{3pyr}), 7.61 (td, 1H, J = 1.8, 7.9 Hz; H_{4pyr}), 8.53 (dd, 1H, J = 1.0, 3.0 Hz; H_{6pyr}). ^{13}C NMR ($CDCl_3$) δ 26.2, 31.7, 36.4, 40.2, 47.5, 55.2, 55.4, 102.7, 106.5, 119.6, 121.3, 136.7, 148.0, 166.0, 210.0. Anal. calcd. for $C_{15}H_{21}NO_3$: C, 68.52; H, 8.04; N, 5.32; found: C, 68.22; H, 8.04; N, 5.59.

3β-Dimethoxymethyl-4β-methyl-4β-(2-pyridyl)cyclohexan-1β-ol (13) To a stirred solution of ketone **11a** (6.5 g, 24.68 mmol) in absolute EtOH (100 ml) at -20°C was added portionwise sodium borohydride (2.3 g, 61.7 mmol). The mixture was stirred overnight and the ethanol was evaporated. The residue was treated with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic extract was washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was chromatographed on silica gel. Elution with petroleum ether-ethyl acetate (1:1) + 6% Et_3N gave unseparable compounds **13a** and **13b** (6.54 g, 100%) as a colorless oil. IR (film) υ 3387, 3058, 2937, 2830, 1588, 1570, 1468, 1431, 1377, 1126, 1061; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 3H, CH_3), 1.46-2.20 (m, 6H), 2.72-2.90 (m, 1H), 2.82-2.90 (m, 1H), 2.95 (s, 3H, OCH_3), 3.23 (s, 3H, OCH_3), 3.60-3.82 (m, 2H, OH and C*H*-$(OCH_3)_2$), 3.78-3.90 (m, 1H, H_1, C*H*-OH), 7.07-7.15 (m, 1H, H_{5pyr}), 7.30-7.39 (m, 1H, H_{3pyr}), 7.58-7.65 (m, 1H, H_{4pyr}), 8.56-8.58 (m, 1H, H_{6pyr}); ^{13}C NMR ($CDCl_3$) δ 18.0, 26.0, 39.5, 42.0, 45.0, 54.0, 70.2, 83.7, 102.7, 106.4, 120.1, 120.5, 135.9, 148.3, 168.2; Anal. calcd. for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28; found C, 67.81; H, 8.56; N, 5.14.

1β-Benzyloxy-3β-dimethoxymethyl-4β-methyl-4α-(2-pyridyl)cyclohexane (14) To a stirred solution of KH (35% in oil, 1.12 g, 9.80 mmol, 2.6 eq; the hydride was washed three time with pentane prior to use) in THF (20 ml) under argon was added dropwise a solution of alcohol **13** (1 g, 3.77 mmol) in THF (10 ml) at 0°C. The solution was gently heated 20 min and allowed at room temperature for 1h. A solution of benzyl bromide (98%, 464 µl, 3.82 mmol, 1.15 eq) in THF (10 ml) was then added dropwise and allowed to stand at room temperature overnight. Ether was added before cautious hydrolysis at 0°C with saturated NH_4Cl solution. The resulting mixture was extracted with Et_2O. The ethereal layer was washed with saturated NaCl solution, dried ($MgSO_4$) and evaporated to afford an oil, which was chromatographed on silica gel. Elution with petroleum ether-ethyl acetate (3:1) gave two diastereoisomeric benzylic ether **14a** (1.02 g, 74%) and **14b** (214 mg, 16%) in a 5:1 ratio. IR (film) υ 2937, 2860, 2830, 2360, 1586, 1466, 143, 1113, 1071.

1β-Benzyloxy-3β-dimethoxymethyl-4β-methyl-4α-(2-pyridyl)cyclohexane **14a** ^{1}H NMR ($CDCl_3$) δ 1.20-1.31 (m, 3H), 1.39 (s, 3H, CH_3), 1.58-1.90 (m, 3H), 2.02-2.10 (m, 2H), 2.28-2.40 (m, 1H), 3.04 (s, 3H, OCH_3), 3.24 (s, 3H, OCH_3), 3.50 (m, 1H, C*H*-OBn), 3.79 (d, 1H, H_7, J = 4.1 Hz; C*H*-$(OCH_3)_2$), 4.57 (dd, 2H, *AB*-signal, J = 11.9 Hz; O-CH_2-Ph), 7.07 (td, 1H, J = 1.7, 5.0 Hz; H_{5pyr}), 7.25-7.38 (m, 6H, Ph and H_{3pyr}), 7.60 (td, 1H, J = 1.7, 7.5 Hz; H_{4pyr}), 8.58 (dd, 1H, J = 3.6 Hz; H_{6pyr}). ^{13}C NMR ($CDCl_3$) δ 17.5, 25.4, 26.6, 35.5, 40.1, 42.3, 54.5, 54.6, 69.4, 72.3, 106.9, 120.2, 120.5, 127.1, 127.3, 128.2, 135.8, 139.4, 148.3, 168.7; Anal. calcd. for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94; found C, 74.11; H, 7.98; N, 3.78.

1α-Benzyloxy-3β-dimethoxymethyl-4β-methyl-4α-(2-pyridyl)cyclohexane **(14b)** ^{1}H NMR (CDCl3) δ 1.38 (s, 3H, CH_3), 1.41-1.50 (m, 3H), 1.90-2.10 (m, 2H), 2.22-2.29 (m, 1H), 2.71-2.81 (m, 1H), 2.93 (s, 3H, OCH_3), 3.23 (s, 3H, OCH_3), 3.56 (m, 1H, C*H*-OBn), 3.73 (d, 1H, H_7, J = 4.0 Hz; C*H*-$(OCH_3)_2$), 4.62 (dd, 2H, *AB*-signal, , J = 11.9 Hz; O-CH_2-Ph), 7.07 (td, 1H, J = 1.7, 4.9 Hz; H_{5pyr}), 7.25-7.38 (m, 6H, Ph and H_{3pyr}), 7.63 (td, 1H, J = 1.7, 7.9 Hz; H_{4pyr}), 8.56 (d, 1H, J = 3.6 Hz; H_{6pyr}). ^{13}C NMR ($CDCl_3$) δ 17.0, 27.9, 28.6, 39.8, 42.0, 44.6, 54.0, 54.6, 69.8, 77.2, 106.6, 120.2, 120.6, 127.3, 127.5, 128.3, 135.9, 139.0, 148.4, 168.4. Anal. calcd. for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94; found C, 74.01; H, 8.07; N, 3.86.

1β-(5β-Benzyloxy-2β-methyl-2α-[2-pyridyl])cyclohexanecarboxaldehyde (15) To a stirred solution of benzylic ether **14a** (1.76 g , 4.11 mmol) in pentane (2 ml) was added pure formic acid in excess (99%, 8 ml). The resulting mixture was allowed to stand 48h at room temperature. Water was then added and the solution was basified with aqueous NaOH until pH>10. After several extraction with CH_2Cl_2, the combined organic extracts were dried ($MgSO_4$) and the solvent evaporated to afford aldehyde **15** (1.45g, 95%) as a colorless oil, which used without purification. IR (film) υ 3061, 2940, 2865, 1715, 1587, 1467, 1431, 1360, 1203, 1096, 1074; ^{1}H NMR (300MHz, $CDCl_3$) δ 1.42 (s, 3H, CH_3), 1.50-2.10 (m, 5H, $H_{5\ ax/eq}$, $H_{6\ ax/eq}$, H_{2ax}), 2.20-2.38 (m, 1H, H_{2eq}), 3.41 (dd, 1H, J = 3.6, 9.8 Hz; H_{3ax}), 3.4-3.50 (m, 1H, H_{1ax}, C*H*-OBn), 4.58 (dd, 2H, J_{gem} = 11.9 Hz; O-CH_2-Ph), 7.13 (tdd, 1H, J = 1.9, 5.9, 7.5 Hz; H_{5pyr}), 7.26-7.37 (m, 6H, Ph and H_{3pyr}), 7.65 (tdd, 1H, J = 2.0, 7.5, 7.8 Hz; H_{4pyr}), 8.56 (dd, 1H, J = 2.0, 5.9 Hz; H_{6pyr}), 9.47 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 18.7, 27.8, 28.0, 37.9, 42.1, 53.6, 69.9, 76.2, 120.0, 121.3, 127.4, 128.2, 136.6, 138.5, 148.5, 166.2, 202.9; Anal. calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53; found: C, 77.45; H, 7.62; N, 4.63.

1β-Benzyloxy-4β-methyl-4α-(2-pyridyl)-3β-vinylcyclohexane (16) To a stirred solution of methyltriphenylphosphonium bromide (214 mg, 0.6 mmol) in THF (4 ml) was added dropwise *n*-BuLi (2.5M in hexanes, 240 µl, 0.6 mmol) at -40°C. The resulting mixture was stirred 40 min at -10°C, then cooled at -30°C and treated by the dropwise addition of a solution of aldehyde **15** (62 mg, 0.2 mmol) in THF (4 ml). The solution was allowed at room temperature overnight. Water and ethyl acetate were added successively and the organic layer was washed with saturated NaCl solution, dried ($MgSO_4$) and evaporated to afford an oil, which was chromatographed on silica gel. Elution with petroleum ether-ethyl acetate (4:1) gave vinylic compound **16** (75 mg, 97%) as a colorless oil. IR (film) υ 3062, 3029, 2978, 2935, 2863, 1586, 1570, 1466, 1431, 1095; ^{1}H NMR (300MHz, $CDCl_3$) δ 1.33 (s, 3H, CH_3), 1.50-1.72 (m, 3H, H_{2ax}, H_{5ax}, H_{6ax}), 2.03-2.23 (m, 3H, H_{2eq}, H_{5eq}, H_{6eq}), 3.05 (ddd, 1H, J = 3.4, 6.4, 12.6 Hz; H_{3ax}), 3.63 (dd, 1H, J = 9.6, 10.1 Hz; H_{1ax}), 4.69-4.83 (m, 2H, J_{cis} = 10.6 Hz, J_{trans} = 17.1 Hz, J_{gem} = 1.9 Hz; $H_{8-8'}$, CH=CH_2), 4.63 (s, 2H, OCH_2-Ph), 5.45 (ddd, 1H, J = 6.4 Hz, J_{cis} = 10.6 Hz, J_{trans} = 17.1 Hz; H_7, C*H*=CH_2), 7.08 (td, 1H, J = 4.7, 7.8 Hz; H_{5pyr}), 7.34 (m, 6H, Ph and H_{3pyr}), 7.60 (td, 1H, J = 1.6, 7.8 Hz; H_{4pyr}), 8.60 (ddd, 1H, J = 0.8, 1.6, 4.7 Hz; H_{6pyr}); ^{13}C NMR ($CDCl_3$) δ 16.1, 28.1, 32.5,

37.7, 43.3, 45.9, 69.9, 77.0, 114.3, 120.7, 120.5, 127.3, 127.5, 128.2, 135.9, 138.8, 139.2, 148.5, 167.3; Anal. calcd. for $C_{21}H_{25}NO$: C, 82.05; H, 8.20; N, 4.56; found: C, 82.01; H,8.12 ; N,4.65 .

2-(1β-(5β-Benzyloxy-2β-methyl-2α-[2-pyridyl])cyclohexyl)ethanol (17) To a stirred solution of alkene **16** (1 g, 3.26 mmol) in THF (10 ml) under argon was added dropwise a solution of BH_3-THF complex (1M in THF, 19 ml, 19.57 mmol, 6 eq) at 0°C. The solution was stirred 1h at 0°C and then at room temperature for 48h. The mixture was cooled to 0°C and was added successively with water (2 ml), aqueous NaOH (3N, 8 ml) and H_2O_2 (35%, 8 ml); CAUTION!, strong gas evolution. The resulting mixture was stirred 1 h at 0°C and 48h at room temperature. Water, saturated Na_2CO_3 solution and ethyl acetate were added successively. The organic layer was washed with saturated NaCl solution, dried ($MgSO_4$) and the solvent evaporated to afford an oil, which was chromatographed on silica gel. Elution with petroleum ether–ethyl acetate-triethylamine (72:24:4) gave alcohol **17** (787 mg, 74%) as a colorless oil. IR (film) υ 3362, 3061, 2932, 2861, 1587, 1430, 1407, 1099, 1066; ^{1}H NMR (300MHz, $CDCl_3$) δ 1.34 (s, 3H, CH_3), 1.10-1.71 (m, 6H, H_{2ax}, $H_{5ax/eq}$, H_{6ax}, H_7), 1.92-2.05 (m, 1H, H_{6eq}), 2.10-2.35 (m, 1H, H_{2eq}), 2.50-3.51 (m, 1H, H_{3ax}), 3.43-3.54 (m, 3H, C*H*$_2$-OH and H_{1ax}), 3.80 (brs, 1H, OH), 4.59 (s, 2H, OC*H*$_2$-Ph), 7.10 (td, 1H, J = 0.9, 7.8 Hz; H_{5pyr}), 7.26-7.37 (m, 6H, Ph and H_{3pyr}), 7.64 (td, 1H, J = 1.9, 7.8 Hz; H_{4pyr}), 8.50 (dd, 1H, J = 1.0, 4.8 Hz; H_{6pyr}); ^{13}C NMR ($CDCl_3$) δ 16.5, 28.3, 34.9, 34.2, 36.8, 39.6, 43.1, 60.7, 70.0, 77.1, 121.3, 121.6, 127.4, 127.6, 128.3, 136.6, 138.6, 146.2, 166.1; Anal. calcd. for $C_{21}H_{27}NO_2$: C, 77.51; H, 8.36; N, 4.30; found: C, 77.38; H, 8.52; N, 4.41.

Δ^1- and Δ^2-10β-Benzyloxy-13β-methylcyclohexa[a]quinolizidine 19a-b To a stirred solution of alcohol **17** (100 mg, 0.31 mmol) in CH_2Cl_2 (5 ml) was added triethylamine (128 µl, 0.92 mmol, 3 eq) at 0°C and dropwise methanesulfonylchloride (48 µl, 0.62 mmol, 2 eq) under argon. After 1h (TLC: no starting material), the mixture was concentrated *in vacuo* and taken up with EtOH (10 ml). The solution was refluxed 30 min to complete cyclization and then cooled to -20°C. Sodium borohydride (117 mg, 3.2 mmol, 10 eq) was added portionwise (CAUTION!, strong gas evolution) and allowed 12 h at room temperature.The mixture was refluxed 30 min before cooled (0°C), poored into aqueous NaOH (10%) and extracted with CH_2Cl_2. The organic layer was washed with saturated NaCl solution, dried ($MgSO_4$) and evaporated to afford, after purification by chromatography on silica gel (with petroleum ether-ethyl acetate-triethylamine (47:47:6)), the alkenyl compounds **19a-b** (77 mg, 80 %) in a 1:1 NMR ratio. It is noteworthy that compound **19b** could not be well separated from the mixture. However, the first chromatographic fraction allows the analysis of pure compound **19a**.

Δ^1-10β-Benzyloxy-13β-methylcyclohex[a]quinolizidine **(19a)**: white crystalline solid; mp 64-65°C; IR (film) υ 3034, 2937, 2742, 2684, 1454, 1349, 1287, 1104, 1069, 1028; ^{1}H NMR (300MHz, $CDCl_3$) δ 0.87 (s, 3H, CH_3), 0.88-1.08 (m, 2H, H_{12} and H_{8ax}), 1.15-1.31 (m, 2H, H_7 and H_9), 1.34-1.45 (m, 1H, H_{11}), 1.48-1.67 (m, 3H, H_9 , H_{12} and H_7), 1.75-1.90 (m, 2H, H_{3ax} and H_{11}), 2.07-2.16 (m, 2H, H_{14ax} and H_{6ax}), 2.21-2.30 (m, 2H, H_{4ax} and H_{3eq}), 2.67 (dd, 1H, J = 4.1, 9.4 Hz; H_{4eq}), 2.78 (ddd, 1H, J = 1.9, 3.9, 11.1 Hz; H_{6eq}), 3.35 (m, 1H, J= 4.9, 10.9 Hz; H_{10ax}), 4.54 (s, 2H, OC*H*$_2$-Ph), 5.49 (dd, 1H, J = 0.9, 10.3 Hz; H_1), 5.67 (ddd, 1H, J = 2.7, 6.0, 10.3 Hz; H_2), 7.21-7.23 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 13.1 (C_{15}), 26.3 (C_3), 28.2 (C_{11}), 29.1 (C_7), 34.6 (C_9), 34.7 (C_{12}), 36.9 (C_{13}), 43.7 (C_8), 52.8 (C_4), 57.2 (C_6), 70.2 (C_{16}; CH_2-Ph), 72.1 (C_{14}), 78.0 (C_{10}), 125.7 (C_1), 126.9 (C_2), 127.8-127.9-128.7-139.4 (C_{phenyl}, 6C); MS (EI) m/z (rel. intensity) 311 ($M^{+\cdot}$, 38), 310 (42), 296 (59), 220 (52), 205 (76), 108 (100), 96 (59), 91 (42), 81 (38); Anal. calcd. for $C_{21}H_{29}NO$: C, 80.95; H, 9.38; N, 4.49; found: C, 80.86; H, 9.46; N, 4.31.

10β-Benzyloxy-13β-methylcyclohexa[a]quinolizidine (20) To a solution of alkenes **19a-b** (100 mg, 0.32 mmol) in MeOH (5 ml) was added 10% Pd/C (34mg, 0.032mmol, 10 mol.%) under argon. After three vacuum / H_2 cycles to remove air from the reaction vessel, the solution was stirred under hydrogen atmosphere (balloon) at room temperature for 24 h (TLC: complete reaction). The hydrogen was evacuated and the catalyst was removed by centrifugation. The resulting mixture was filtered through celite® and washed with MeOH. The solvent was evaporated *in vacuo* to give the crude product as a yellow oil, which was chromatographed on silica gel. Elution with petroleum ether-ethyl acetate-triethylamine (47:47:6), gave benzylic ether **20** (100.2 mg, 100%) as a white crystalline solid; mp 90-91°C; IR (film) υ 2924, 2850, 2767, 1498, 1448, 1360, 1252, 1107, 1071; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (s, 3H, CH_3), 0.85-1.74 (m, 15H, H_1, H_2, H_3, H_7, H_9, H_{11}, H_{12} (ax/eq) and H_{8ax}), 1.87-2.10 (m, 3H, H_{4ax}, H_{5ax} and H_{13ax}), 2.79-2.84 (m, 2H, H_{4eq} and H_{5eq}), 4.50 (s, 2H, OCH_2-Ph), 3.20-3.40 (m, 1H, H_{10ax}), 7.21-7.30 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 13.1 (C_{15}), 24.6-24.8-25.5-27.7-28.2 (C_1, C_2, C_3, C_7, C_{12}), 35.0-34.0 (C_{11}, C_9), 35.8 (C_{13}), 43.2 (C_8), 57.3-57.5 (C_6, C_4), 69.6 (C_{Bn}), 72.8 (C_{14}), 77.4 (C_{10}), 127.1-127.3-128.1-138.8 (C_{Phenyl}); MS (EI) m/z (rel intensity) 313 ($M^{+\cdot}$, 37), 206 (65), 111 (100), 98 (84), 91 (42), 83 (67). Anal. calcd. for $C_{21}H_{31}NO$: C, 80.43; H, 9.96; N, 4.47; found: C, 80.35; H, 9.98; N, 4.39.

10β-Hydroxy-13β-methylcyclohexa[a]quinolizidine (5) To a stirred solution of ether **20** (873 mg, 2.78 mmol) in MeOH (10 ml) was added few drops of 6N HCl and 10% Pd/C (296 mg, 0.27 mmol, 10 mol.%) under argon. The flask was evacuated by aspiration and purged with hydrogen three times. The solution was stirred 24h under hydrogen atmosphere (TLC: complete reaction). The hydrogen was evacuated and the catalyst was separated by centrifugation. The resulting solution was filtered through celite and the filter washed with MeOH. The solvent was evaporated *in vacuo*, the residue taken up with CH_2Cl_2 and the solution with aqueous $NaHCO_3$, saturated NaCl solution, dried ($MgSO_4$) and evaporated to afford the crude product, which was chromatographed on silica gel. Elution with petroleum ether-ethyl acetate-triethylamine (47:47:6) gave the racemic hydroxy cyclohexaquinolizidin-10β-ol **5** (620 mg, 100%) as a yellow oil; IR (film) υ 3342, 2926, 2854, 2803, 2756, 2678, 2598, 14664, 1445, 1362, 1334, 1290, 1130, 1053; ^{1}H NMR (500MHz, $CDCl_3$) δ 0.75 (s, 3H, CH_3), 0.80-1.41 (m, 2H, H_{8ax} and H_{12ax}), 1.05-1.07 (m, 2H, H_{7ax} and H_{2ax}), 1.06-1.08 (m, 1H, H_{1ax}), 1.16-1.20 (m, 1H, H_{9ax}), 1.23-1.30 (m, 1H, H_{11ax}), 1.30-1.34 (m, 1H, H_{14ax}), 1.40-1.42 (m, 2H, $H_{3ax/eq}$), 1.40-1.45 (m, 2H, H_{7eq} and H_{12eq}), 1.42-1.45 (m, 1H, H_{9eq}), 1.48-1.52 (m, 1H, H_{1eq}), 1.57-1.60 (m, 1H, H_{2eq}), 1.60-1.65 (m, 1H, H_{11eq}), 1.75-1.82 (m, 1H, H_{4ax}), 1.85-1.93 (m, 1H, H_{6ax}), 2.69-2.72 (m, 2H, H_{4eq} and H_{6eq}), 3.35-3.40 (m, 1H, H_{10ax}); 4.00 (brs, 1H, O*H*); ^{13}C NMR ($CDCl_3$) δ 13.5 (C_{15}), 25.0 (C_2), 25.2 (C_1), 26.0 (C_3), 28.5 (C_7), 31.5 (C_{11}), 35.0 (C_{13}), 35.5 (C_{12}), 37.8 (C_9), 44.0 (C_8), 58.0 (C_4 and C_6), 71.0 (C10), 74.0 (C14); MS (EI) m/z (rel intensity) 223 ($M^{+\cdot}$, 28); 111 (95); 98 (100); 83 (98); Anal. calcd. for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27; found: C, 75.15; H, 11.16; N, 6.19.

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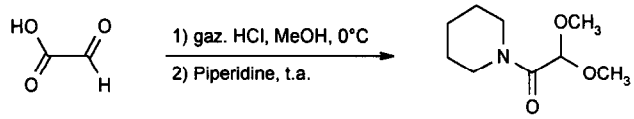

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