Studies in the FR901483 tricyclic skeleton synthesis and a new approach to the perhydropyrrolo[2,1-*i*]indole ring system

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Dedicated with admiration to Professor Joan Bosch on his 60th anniversary

Abstract
Palladium- and radical-mediated cyclizations from *N*-(2-bromoprop-2-enyl)-1-azaspiro[4.5]decanes were studied, leading to the formation of azatricyclic derivatives embodying 7,10a-methanopyrrolo[1,2-*a*]azocine or a pyrrolo[2,3-*i*]indole framework depending on the reaction conditions

Key words: Palladium, radical cyclization, Heck reaction, nitrogen heterocycles, spirane derivatives

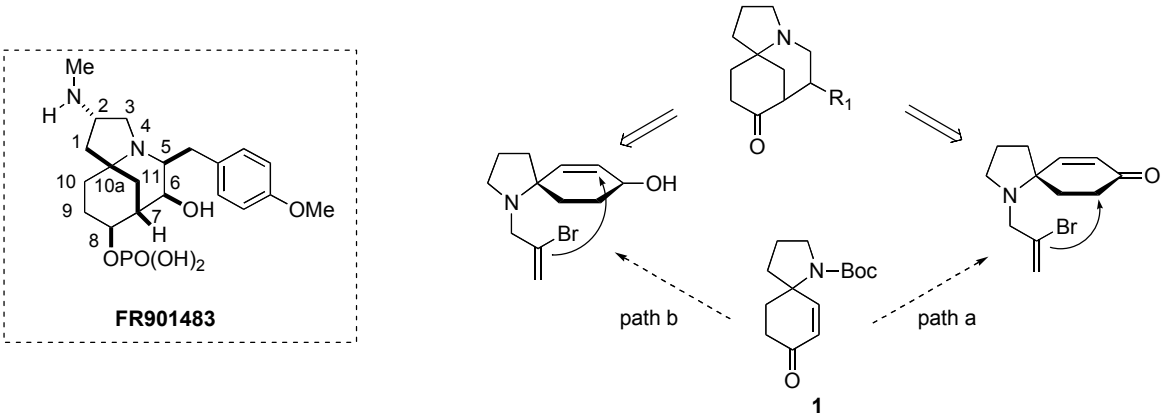
Introduction

The immunosuppressant FR901483 (Scheme 1) was isolated by a Fujisawa group in 1996,[1,2] who determined the structure by X-ray crystallography and the absolute configuration was eventually assigned when Snider achieved the enantiocontrolled total synthesis in 1999.[3] From a structural point of view, the most conspicuous feature of FR901483 is an azatricyclic ring system consisting of the combined morphan and indolizine nuclei sharing the piperidine ring.

In recent years several groups have succeeded in synthesizing the FR901483.[3-8] Four of them (Snider,[3] Sorensen,[4] Ciufolini,[5] and Brummond[6]) achieved the enantioselective synthesis of the natural enantiomer, while Funk's[7] and Fukuyama's[8] syntheses were developed in the racemic series. In all reported routes, a functionalized 1-azaspiro[4.5]decan-8-one was used as an intermediate to build the azatricyclic core of the target, using an aldol process whose regioselectivity is sensitive to the substitution pattern and reaction conditions.

With the aim of approaching the FR901483 framework[10] through a regioselective ring closure from an azaspiro[4.5]decan-8-one, we decided to prepare the azaspiranic enone **1** with the idea of forming the bridge either on the carbonyl α' position, the double bond acting as a blocking group (path a) or on the double bond, after reduction of the enone group, (path b) (Scheme 1). In the

former case we would explore our Pd(0)-catalyzed intramolecular coupling of amino-tethered vinyl halides and ketone enolates[11] as the methodology for the synthesis of the target nitrogen heterocycle using an enone as the substrate. Path b, on the other hand, would lead to a reversed regioselectivity, enabling us to study the feasibility of a radical cyclization either through a direct 6-*endo* or 5-*exo* process followed by a rearrangement of the initially-formed homoallyl radical, via a reversible 3-*exo*-*trig* cyclization, to give the corresponding six-membered ring.[12]

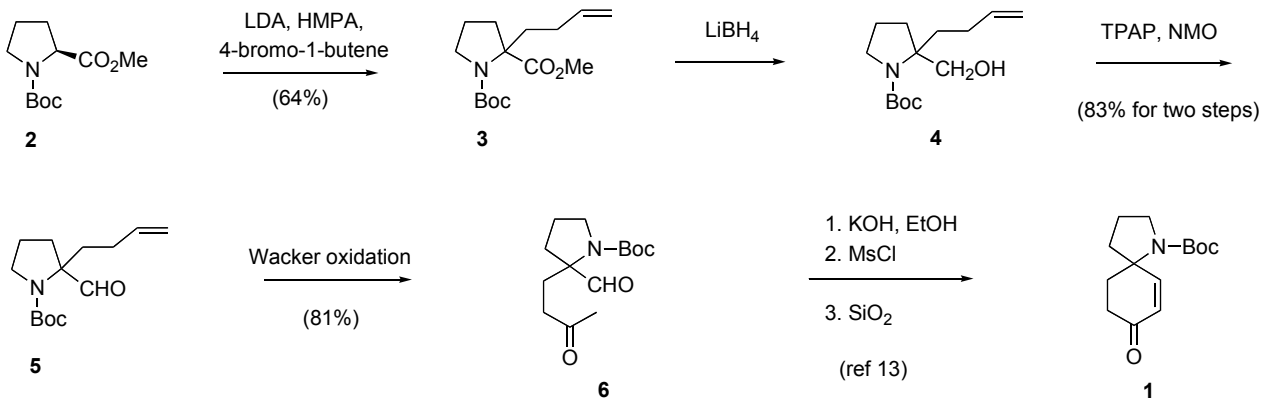


Scheme 1

Results and Discussion

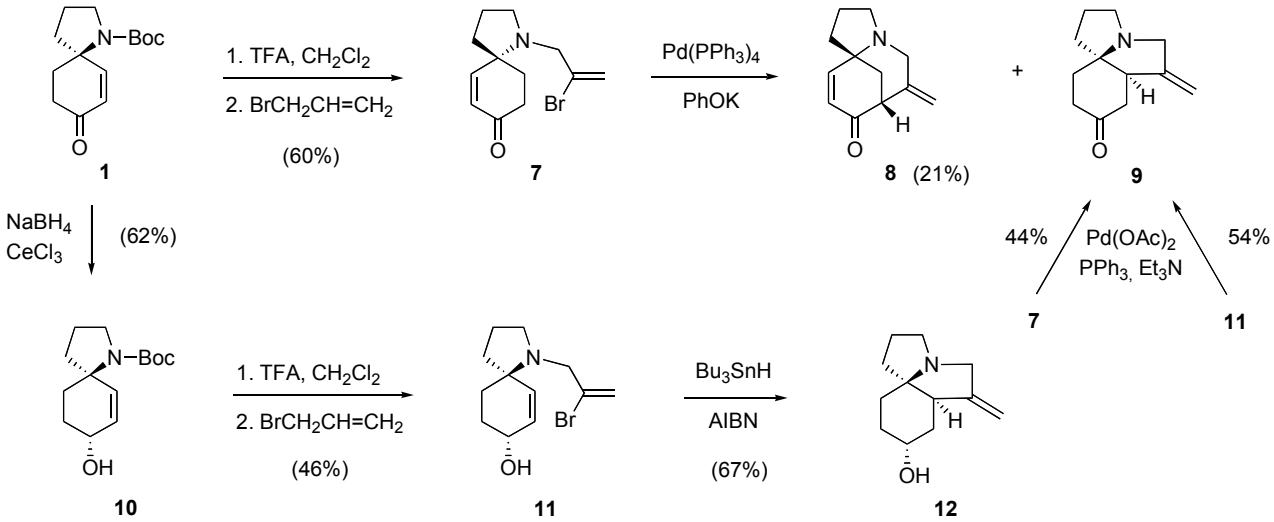
To access the tricyclic skeleton of FR901483 through the proposed methodology we required a cyclization precursor embodying the 1-azaspiro[4.5]dec-6-en-8-one framework (i.e. **1**). Although we have recently described an approach to obtain compounds of this type in their enantiopure form,[13] for this study we prepared compound **1** in its racemic form. Our protocol to assemble this azabicyclic system was inspired by Kawahara and Nagumo's procedure[14] for preparing spirolactams from proline derivatives, based on the alkylation of a proline derivative followed by some functional group interconversion steps and a final aldol cyclization step.

The synthesis (Scheme 2) starts with the alkylation of the L-proline derivative **2** with 4-bromo-1-butene using 1.15 eq of LDA to afford racemic **3** (64%).[15] The synthetic sequence **3** ∏ **6** involves conversion of ester **3** to aldehyde **5** through a reduction-oxidation process, followed by Wacker oxidation of the terminal alkene to give the keto aldehyde **6**. Aldol condensation and succesive elimination process in the ketol intermediate gave cyclohexenone **1**, in accordance with the recently reported protocol.[13]



Scheme 2. Synthesis of the azaspiranic intermediate **1.**

Removal of the Boc group and alkylation of the secondary amine with 2,3-dibromopropene provided the aminotethered ketone vinyl halide **7**, which was submitted to the Pd promoted cyclization in presence of KOPh[11c] (Scheme 3). Treatment of vinyl halide **7** with 0.2 equiv of $Pd(PPh_3)_4$ and 2.5 equiv of KOPh in refluxing THF gave a mixture of tricyclic enone **8** (21% yield) and tricyclic ketone **9** (12%). It became clear from this result that the use of a base to form the enolate does not allow the regiocontrol in the cyclization step, since the vinylpalladium intermediate species reacted with both the enolate and enone double bonds.[16] In the latter case the reaction evolved through a Heck reductive process. The two compounds formed were separated and their structure elucidated by 2D NMR spectra (see Table 1). Compound **9** was obtained in better yield (44%) when the same precursor **7** was subjected to a classical Heck reaction conditions [$Pd(OAc)_2$, PPh_3, Et_3N]. Operating from the vinyl bromide **11** the yield increased to 54 %.



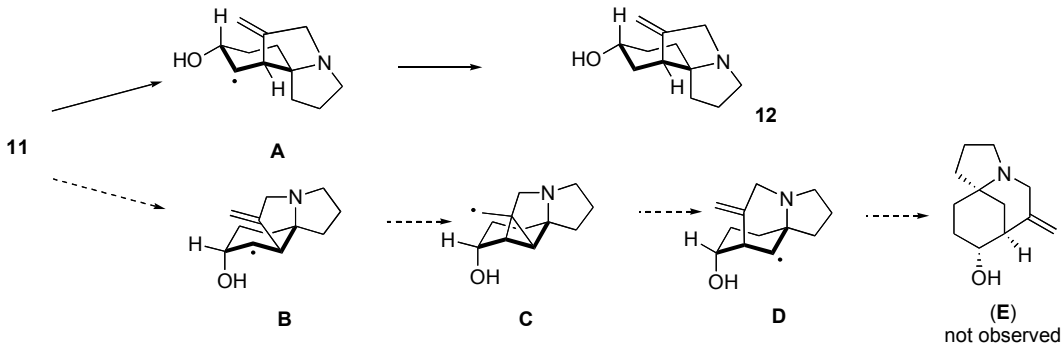
Scheme 3. Palladium- and tributylstannane-promoted cyclization of vinyl bromides **7** and **11**.

Although this ring-forming reaction led to the azatricyclic compound **8** and constitutes a novel approach to the heterocyclic system found in FR901483, the low regioselectivity (2 to 1) together with the poor yield in the synthesis of the bridged azatricyclic compound, via the intramolecular palladium-catalyzed enolate-driven cross coupling between the vinyl halide and the enone, induced us to discard this approach. Thus we turned our attention to Path b using the same azaspiranic intermediate **1**.

As we mentioned before, we were curious to see if a radical process from vinyl bromide **11** through a homoallyl-cyclopropylmethyl radical could be an entry to the FR901483 framework. Reduction of enone **1** with $NaBH_4/CeCl_3$ stereoselectively gave the allylic alcohol **10**, which after deprotection and alkylation with 2,3-dibromopropene provided the radical precursor **11**. Subjection of the vinyl bromide **11** to standard tin hydride conditions promoted only the 5-*exo* radical cyclization to give **12**, no bridged product **E** being observed (Scheme 4).

The course of the reaction may be influenced by steric factors. Indeed, the vinyl radical initially formed from the conformationally mobile **11** could lead to two conformationally different homoallyl radicals (**A** and **B**), but only homoallyl radical **B** could evolve to afford the cyclopropylmethyl radical (**B** ∏ **C** process) required for the formation of the six-membered ring intermediate **D**, from which **E** could be obtained.

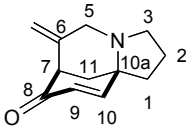
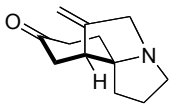
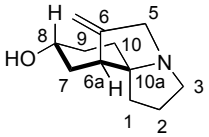
Considering that the only conformation detected for compound **12** was that corresponding to a trans-diequatorial conformational relationship between the hydroxyl group and the nitrogen atom, as suggested by the NMR experiments (Table 1), we assumed the same conformation for its radical precursor **A**. This may suggest that one of the reasons for the non-formation of compound **E** is the inaccessibility of the correct chair conformation **B** in the first radical formed. In turn, the lack of reactivity in the homoallyl radical **A** to the corresponding rearranged radical is due to steric reasons, as the conformation depicted in Scheme 4 shows, and to the fact that a conformational change to **B** is not available in the time-scale of the radical processes.



Scheme 4

Table 1 shows the NMR data of the three azatricyclic compounds reported here. Comparison of the NMR values of protons and carbons in the C(3)-C(5)-C(10a) domain reveals significant differences (Table 1). Most notably, the spirane carbon C-10a of the bridged compound **8** resonates at δ 58.3, whereas that of fused compounds **9** and **12** appears at δ 71.6.

Table 1. NMR data of azatricyclic compounds **8**, **9**, and **12**

	 **8**		 **9**		 **12**	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	35.6	1.75 (m)/1.94 (m)	37.8	1.85-2.05 (m)	35.0	1.78-1.95 (m)
2	20.6	1.93-2.12 (m)	24.8	1.85-2.05 (m)	25.1	1.90-2.07 (m)
3	50.2	2.48 (td, 8.8, 6.4) 3.03 (td, 9.2, 3.6)	54.9	2.76(m) 3.17 (m)	55.5	2.61 (td, 9.6, 6.8) 3.24 (td, 9.6, 2.8)
5	51.7	3.16 (brd, 13.6) 3.46 (d, 13.6)	58.7	3.34 (d, 14.4) 3.80 (d, 14.4)	56.7	3.39 (dd, 15.6, 1.6) 3.79 (brd, 15.6)
6	140.1		151.6		152.1	
6a	---		47.0	2.77 (brs)	46.3	2.53 (brs)
7	53.3	3.24 (t, 2.6)	40.0	2.57 (dd, 16, 6.4) 2.64 (dd, 16, 4.8)	32.4	1.48-1.62 (m) 2.28 (ddt, 13.6, 4.4, 2.8)
8	198.2		211.4		65.9	3.76 (tt, 10.8, 4.4)
9	130.6	6.24 (dd, 10.4, 1.6)	37.0	2.24 (ddd, 17.2, 9.2, 4.8)	33.6	1.29 (tdd, 12.3, 10.8, 4.4)
				2.39 (ddd, 17.2, 8.4, 4.4)		1.81-1.92 (m)
10	148.6	6.57 (dd, 10.4, 2.0)	34.3	1.80 (ddd, 13.6, 8.4, 4.8) 1.85-2.05 (m)	33.5	1.47 -1.57 (m)
10a	58.3		71.6		71.6	
11	38.5	1.82 (ddd, 12.4, 3, 2) 2.37 (dd, 12.4, 3.2)		---		---
$=CH_2$	113.0	4.93 (brs) 5.02 (brs)	105.9	4.86 (brd, 1.6) 5.00 (brd, 1.6)	104.1	4.93 (q, 2.4) 4.97 (dt, 2.8, 2.0)

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 MHz and 100 MHz, respectively. Assignments were arded by gCOSY, gHSQC, and gHMBC spectra.

The relative configuration of **12** was inferred from the pattern of the two methine proton coupling constants of the stereogenic carbons at C-6a and C-8.

In summary, although the attempts to introduce a regioselective formation of the FR901483 azatricyclic framework have not been very fruitful, the easy formation of the tricyclic system of perhydropyrrolo[2,1-*i*]indole[17] could be useful in the development of new synthetic routes to cylindricine[18] and lepadiformine alkaloids[19] embodying the related azatricyclic framework of perhydropyrrolo[2,1-*j*]quinoline.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. Infrared spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck) or on Al_2O_3 (aluminium oxide 60 F254, Merck). The spots were located by UV light, a 1% $KMnO_4$ aqueous solution or a 1.5% K_2PtCl_6 aqueous solution. Unless otherwise noted chromatography refers to flash chromatography and was achieved on SiO_2 (silica gel 60, SDS, 230–400 mesh). All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents and under anhydrous conditions. Drying of the organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4.

***tert*-Butyl 2-methyl 2-(But-3-enyl)pyrrolidine-1,2-dicarboxylate (3)**. To a solution of diisopropylamine (4.21 mL, 30.1 mmol) in THF (100 mL) was added at -78 ºC *n*-BuLi (1.6 M in hexanes, 20 mL, 32.1 mmol) dropwise and the mixture was stirred at this temperature for 10 min. A solution of **2** (5.94 g, 25.9 mmol) and HMPA (20 mL, 129.6 mmol) in THF (30 mL) was added via cannula and stirring was continued for a further 30 min. 4-bromo-1-butene (7.2 g, 51.8 mmol) was added dropwise at -78 ºC and the mixture was allowed to reach rt while stirring overnight. The reaction mixture was quenched with a saturated aqueous NH_4Cl (50 mL) and extracted with ether (3×50 mL). The combined organic extracts were washed with brine (3×50 mL), dried, concentrated and purified by chromatography (hexane/EtOAc 4:1 to 1:1) yielding **3** as a viscous colorless oil (4.7 g, 64%). IR (neat) 3077, 2975, 2878, 1742, 1700, 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) 1.41 and 1.45 (2s, 9H, CH_3), 1.70-2.50 (m, 8H), 3.41 (m, 1H, H-5), 3.70 (m, 1H, H-5), 3.70 (s, 3H, CH_3O), 4.82-5.12 (m, 2H, $=CH_2$), 5.81 (m, 1H, =CH); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 22.6 and 23.2 (CH_2), 27.9 (CH_2), 28.2 and 28.3 (CH_3), 33.3 and 34.3 (CH_2), 36.1 and 37.3 (CH_2), 48.4 (CH_2N), 52.0 (CH_3O), 67.2 and 67.7 (C-2), 79.3 and 79.8 (C), 114.2 and 114.4 ($=CH_2$), 138.0 and 138.3 (=CH), 153.6 and 153.8 (CO), 175.1 (CO). Anal. Calcd for $C_{15}H_{25}NO_4.1/4H_2O$: C 62.59, H 8.93, N 4.87; found C 62.65, H 8.69, N 4.83.

***tert*-Butyl 2-(But-3-enyl)-2-hydroxymethylpyrrolidine-1-carboxylate (4).** To a solution of **3** (4.17 g, 14.7 mmol) in toluene (100 mL) at -78 ºC was added dropwise a solution of DIBAL (1 M in CH_2Cl_2, 56.43 mL, 56.43 mmol). After being stirred at rt overnight, the reaction mixture was quenched with water (5 mL), filtered on a celite pad, dried and concentrated to yield alcohol **4** (3.5 g, 93%) pure enough to be used in the next step without further purification. An analytical

sample was obtained by chromatography (hexane/EtOAc 9:1) as a viscous colorless oil. IR (neat) 3400, 3076, 2974, 2877, 1692, 1667 cm^{-1}, ^1H NMR ($CDCl_3$, 200 MHz) 1.46 (s, 9H, CH_3), 1.65-2.38 (m, 8H), 3.23-3.55 (m, 2H, CH_2N), 3.65 (d, 2H, J = 5.4 Hz, CH_2OH), 4.85-5.15 (m, 2H, $=CH_2$), 5.36 (t, 1H, J = 5.4 Hz, OH), 5.82 (m,1H, =CH); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 22.0 (CH_2), 28.4 (CH_3), 28.8 (CH_2), 31.7 (CH_2), 34.0 and 34.7 (CH_2), 48.7 and 49.3 (CH_2N), 67.3 (C-2), 67.6 and 69.1 (CH_2OH), 79.9 (C), 114.2 ($=CH_2$), 138.4 (=CH), 155.9 (CO). Anal. Calcd for $C_{14}H_{25}NO_3$: C 65.85, H 9.87, N 5.49; found: C 65.93, H 9.91, N 5.43.

***tert*-Butyl 2-(But-3-enyl)-2-formylpyrrolidine-1-carboxylate (5).** To a solution of alcohol **4** (1.08 g, 4.24 mmol) in CH_2Cl_2 (80 mL) were added successively 4 Å molecular sieves (4.6 g), NMO (0.77 g, 6.37 mmol) and TPAP (0.077 g, 0.21 mmol) and the mixture was stirred at rt for 5 h. The reaction mixture was diluted with ether, filtered on florisil and concentrated yielding aldehyde **5** (0.95 g, 89%) as a viscous colorless oil. IR (neat) 3077, 2976, 2932, 2881, 2804, 2702, 1736, 1691, 1641 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) 1.42 and 1.46 (2s, 9H, CH_3), 1.70-2.20 (m, 8H), 3.32-3.80 (m, 2H, CH_2N), 4.90-5.15 (m, 2H, $=CH_2$), 5.82 (m, 1H, =CH), 9.41 and 9.51 (2s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 22.9 and 23.6 (CH_2), 28.0 (CH_2), 28.2 and 28.4 (CH_3), 31.3 and 31.9 (CH_2), 32.6 and 33.8 (CH_2), 48.2 and 48.3 (CH_2N), 70.6 and 70.9 (C-2), 80.0 and 80.9 (C), 114.5 and 114.7 ($=CH_2$), 137.8 and 138.1 (=CH), 153.3 (CO), 199.5 and 200.1 (CO). Anal. Calcd for $C_{14}H_{23}NO_3$: C 66.37, H 9.15, N 5.53; found: C 66.32, H 9.24, N 5.47.

***tert*-Butyl 2-Formyl-2-(3-oxobutyl)pyrrolidine-1-carboxylate (6).** A mixture of CuCl (0.29 g, 2.9 mmol), $PdCl_2$ (0.138 g, 0.78 mmol), water (1 mL) and DMF (15 mL) was stirred at rt and under an oxygen atmosphere for 1 h. To the resulting mixture was added a solution of aldehyde **5** (0.70 g, 2.8 mmol) in DMF (15 mL) and stirring at rt under oxygen was prolonged for a further 5 h. The mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL), saturated aqueous NH_4Cl (10 mL) and extracted with ether/hexane (1:1 300 mL). The organics were washed with brine, dried and concentrated to yield keto aldehyde **6** (0.6 g, 81%) pure enough to be used in the next step without further purification. An analytical sample was obtained by chromatography (hexane/AcOEt 9:1). The NMR data of **6** coincide with those reported for this compound when it was synthesized in an enantiopure form using another methodology.[13]

***tert*-Butyl 8-Oxo-1-azaspiro[4.5]dec-6-ene-1-carboxylate (1)** was prepared from **6** following our previously reported procedure.[13]

1-(2-Bromoprop-2-enyl)-1-azaspiro[4.5]dec-6-en-8-one (7). A mixture of **1** (0.23 g, 0.92 mmol) and TFA (2.87 mL, 37.2 mmol) in CH_2Cl_2 (9 mL) was stirred at rt for 2 h prior to solvent evaporation. The residue was taken up in 10 mL of CH_3CN and 2,3-dibromopropene (0.16 mL, 1.40 mmol), K_2CO_3 (0.39 g, 2.79 mmol) and LiI (0.013 g, 0.09 mmol) were added. The resulting mixture was heated overnight at 60 ºC, quenched with water (5 mL) and extracted with CH_2Cl_2 (5×25 mL). The organic extracts were dried, concentrated and the residue purified by chromatography (CH_2Cl_2) to give pure compound **7** as a viscous yellowish oil (0.147 g, 60%). IR (neat) 2948, 2809, 1681, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 1.80-2.16 (m, 6H), 2.40-2.59 (m, 2H), 2.82 and 2.95 (2m, 2H, H-2), 3.30 (d, 1H, J = 15 Hz, CH_2N), 3.35 (d, 1H, J = 15.3 Hz,

CH_2N), 5.52 (brs, 1H, $=CH_2$), 5.88 (brs, 1H, $=CH_2$), 5.98 (dd, 1H, *J* = 10.2, 0.6 Hz, H-7), 6.80 (dd, 1H, *J* = 10.2, 1.8 Hz, H-6); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 22.0 (C-3), 29.7 (CH_2), 34.8 (CH_2), 35.8 (CH_2), 50.5 (C-2), 57.8 (CH_2N), 63.5 (C-5), 117.0 ($=CH_2$), 129.6 (C-7), 132.6 (C-Br), 156.4 (C-6), 199.0 (C=O). Anal. Calcd for $C_{12}H_{16}BrNO$: C 53.35, H 5.97, N 5.18; found: C 53.73, H 6.21, N 4.44.

6-Methylene-2,3,4,5,6,7-hexahydro-1*H*,10a*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-8-one (8). To a solution of **7** (35 mg, 0.13 mmol) in THF (5 mL) were added phenol (37 mg, 0.39 mmol), *t*-BuOK solution (1 M in butanol, 0.32 mL, 0.32 mmol) and $Pd(PPh_3)_4$ (30 mg, 0.026 mmol). The resulting mixture was refluxed overnight, then diluted with CH_2Cl_2 (25 mL) and washed with saturated aqueous $NaHCO_3$, aqueous NaOH (2M) and brine. The organics were dried, concentrated and the residue purified by chromatography on Al_2O_3 (activity II-III, 70-230 mesh) eluting from hexane to 7:3 hexane/EtOAc to give **8** (5.1 mg, 21%) followed by **9** (3 mg, 12%). ^{1}H NMR ($CDCl_3$, 400 MHz) 1.75 (m, 1H, H-1), 1.82 (ddd, 1H, *J* = 12.4, 3, 2 Hz, H-11eq), 1.93-2.12 (m, 2H, CH_2-2), 1.94 (m, 1H, H-1), 2.37 (dd, 1H, *J* = 12.4, 3.2 Hz, H-11ax), 2.48 (td, 1H, *J* = 8.8, 6.4 Hz, H-3), 3.03 (td, 1H, *J* = 9.2, 3.6 Hz, H-3), 3.16 (brd, 1H, *J* = 13.6 Hz, H-5), 3.24 (t, 1H, *J* = 2.6 Hz, H-7), 3.46 (d, 1H, *J* = 13.6 Hz, H-5), 4.93 (brs, 1H, $=CH_2$), 5.02 (brs, 1H, $=CH_2$), 6.24 (dd, 1H, *J* = 10.4, 1.6 Hz, H-9), 6.57 (dd, 1H, *J* = 10.4, 2 Hz, H-10); ^{13}C NMR ($CDCl_3$, 100 MHz) 20.6 (C-2), 35.6 (C-1), 38.5 (C-11), 50.2 (C-3), 51.7 (C-5), 53.3 (C-7), 58.3 (C-10a), 113.0 ($H_2C=$), 130.6 (C-9), 140.1 (C-6), 148.6 (C-10), 198.2 (CO). HRMS (ESI) *m*/*z* calcd for $C_{12}H_{16}NO$ 190.1226 $[M+H]^+$; found 190.1222. For analytical data of **9**, see below.

(6a*RS*,10a*RS*)-6-Methylene-2,3,5,6,6a,7,9,10-octahydro-1*H*-pyrrolo[2,1-*i*]indol-8-one (9). From 7. Palladium acetate (43 mg, 0.19 mmol) was added to a solution of **7** (51 mg, 0.19 mmol), PPh_3 (0.22 g, 0.83 mmol) and Et_3N (0.2 mL, 1.43 mmol) in CH_3CN (5 mL) and the mixture was refluxed for 4 h. Saturated aqueous Na_2CO_3 was added and the mixture extracted with $CHCl_3$ (5×25 mL). The combined organic extracts were dried, concentrated and purified by chromatography (CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to give pure **9** (16 mg, 44%). IR (neat): 2949, 2866, 1717, 1666 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) 1.80 (ddd, 1H, *J* = 13.6, 8.4, 4.8 Hz, H-10), 1.85-2.05 (m, 5H), 2.24 (ddd, 1H, *J* = 17.2, 9.2, 4.8 Hz, H-9), 2.39 (ddd, 1H, *J* = 17.2, 8.4, 4.4 Hz, H-9), 2.57 (dd, 1H, *J* = 16.0, 6.4 Hz, H-7), 2.64 (dd, 1H, *J* = 16.0, 4.8 Hz, H-7), 2.76 (m, 1H, H-3), 2.77 (brs, 1H, H-6a), 3.17 (m, 1H, H-3), 3.34 (d, 1H, *J* = 14.4 Hz, H-5), 3.80 (d, 1H, *J* = 14 Hz, H-5), 4.86 (brd, 1H, *J* = 1.6 Hz, $H_2C=$), 5.00 (brd, 1H, *J* = 1.6 Hz, $=CH_2$); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 24.8 (C-2), 34.3 (C-10), 37.0 (C-9), 37.8 (C-1), 40.0 (C-7), 47.0 (C-6a), 54.9 (C-3), 58.7 (C-5), 71.6 (C-10a), 105.9 ($H_2C=$), 151.6 (C-6), 211.4 (CO). HRMS (ESI) *m*/*z* calcd for $C_{12}H_{18}NO$ 192.1383 $[M+H]^+$; found 192.1377.

From 11. Operating as above from **11** (26 mg, 0.095 mmol), $Pd(OAc)_2$ (6 mg, 0.029 mmol), PPh_3 (16 mg, 0.062 mmol) and Et_3N as solvent (4.3 mL). After 1.5 h of reflux **9** was isolated (9.8 mg, 54%).

***tert*-Butyl (5*RS*,8*RS*)-8-Hydroxy-1-azaspiro[4.5]dec-6-ene-1-carboxylate (10).** To a solution of enone **1** (100 mg, 0.40 mmol) in THF (10 mL) at 0 ºC was added $CeCl_3$ (125 mg, 0.5 mmol) and the mixture was stirred for 5 min. $NaBH_4$ (20 mg, 0.5 mmol) was added and stirring was

continued for 5 min at 0 ºC and 10 min at rt. The reaction mixture was evaporated to dryness, water (10 mL) was added and the mixture extracted with $CHCl_3$. The combined organic extracts were dried and concentrated. After chromatography (CH_2Cl_2/MeOH 99.5:0.5) **10** (63 mg, 62%) was obtained as a viscous colorless oil. IR (neat) 3416, 2972, 2870, 1683 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 1.42 and 1.43 (2s, 9H, CH_3), 1.46-1.67 (m, 2H), 1.77 (m, 3H), 1.98 (m, 1H), 2.12 (m, 1H), 2.21 and 2.41 (2t, 1H, *J* = 13.6 Hz), 3.35 (m, 1H, H-2), 3.49 and 3.56 (2m, 1H, H-2), 4.26 and 4.44 (2brs, 1H, H-8), 5.45 and 5.53 (2d, 1H, *J* = 10 Hz, H-7), 5.63 and 5.72 (2d, 1H, *J* = 10 Hz, H-6);^{13}C NMR ($CDCl_3$, 100 MHz) 22.2 and 22.7 (C-3), 28.4 and 28.6 (CH_3), 30.8 (C-10), 32.0 and 32.3 (C-9), 38.6 and 39.5 (C-4), 47.5 and 47.8 (C-2), 61.9 and 62.0 (C-5), 67.0 and 67.4 (C-8), 79.0 and 79.4 (C), 130.3 and 130.7 (C-6), 136.0 and 135.5 (C-7), 153.2 (CO). HRMS (ESI) *m*/*z* calcd for $C_{14}H_{23}NNaO_3$ 276.1570 $[M+Na]^+$; found 276.1565.

(5*RS*,8*RS*)-1-(2-Bromoprop-2-enyl)-1-azaspiro[4.5]dec-6-en-8-ol (11). Operating as in the preparation of **7**, from allylic alcohol **10** (0.273 g, 1.08 mmol), TFA (3.35 mL, 40.1 mmol) and CH_2Cl_2 (10 mL). The mixture was concentrated and the residue was treated with 2,3-dibromopropene (0.186 mL, 1.62 mmol), K_2CO_3 (0.3 g, 2.16 mmol) and LiI (0.015 g, 0.108 mmol) in CH_3CN (10 mL). After chromatography (CH_2Cl_2-CH_2Cl_2/MeOH 98:2) pure **11** (0.134 g, 46%) was isolated as a viscous yellowish oil: ^1H NMR ($CDCl_3$, 400 MHz) 1.10-1.64 (m, 3H), 1.71-1.90 (m, 4H), 2.11 (m, 1H), 2.77 and 2.84 (2m, 2H, CH_2-2), 3.20 (d, 1H, *J* = 15.6 Hz, CH_2N), 3.26 (d, 1H, *J* = 15.2 Hz, CH_2N), 4.23 (m, 1H, H-8), 5.48 (brs, 1H, $=CH_2$), 5.53 (d, 1H, *J* = 10 Hz, H-6), 5.77 (dt, 1H, *J* = 10, 1.6 Hz, H-7), 5.88 (brs, 1H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 21.8 (C-3), 28.5 (C-10), 31.6 (C-9), 37.8 (C-4), 50.5 (C-2), 57.7 (CH_2N), 63.5 (C-5), 67.3 (C-8), 116.3 ($H_2C=$), 133.0 (C-6), 133.3 (C-Br), 134.8 (C-7). Anal. Calcd for $C_{12}H_{18}BrNO$: C 52.95, H 6.67, N 5.15; found: C 52.58, H 6.65, N 4.91.

(6a*RS*,8*RS*,10a*RS*)-6-Methylene-2,3,6,6a,7,8,9,10-octahydro-1*H*,5*H*-pyrrolo[2,1-*i*]indol-8-ol (12). A mixture of **11** (21 mg, 0.077 mmol), Bu_3SnH (0.034 mL, 0.123 mmol) and catalytic amount of AIBN (3 mg, 0.018 mmol) in benzene (15 mL) was refluxed for 4 h. The solvent was removed under reduced pressure and the residue purified by chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 97:3 saturated with NH_3) to provide pure **12** as a white solid (10 mg, 67%): mp 108-109 ºC (CH_2Cl_2/hexane). IR (NaCl, neat) 3358, 3068, 2926, 2855, 1663 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 1.29 (tdd, 1H, *J* = 12.3, 10.8, 4.4 Hz, H-9ax), 1.45-1.57 (m, 2H, CH_2-10), 1.48-1.62 (m, 1H, H-7ax), 1.78-1.95 (m, 2H, CH_2-1), 1.81-1.92 (m, 1H, H-9eq), 1.90-2.07 (m, 2H, CH_2-2), 2.28 (ddt, 1H, *J* = 13.6, 4.4, 2.8 Hz, H-7eq), 2.53 (brs, 1H, H-6a), 2.61 (td, 1H, *J* = 9.6, 6.8 Hz, H-3), 3.24 (td, 1H, *J* = 9.6, 2.8 Hz, H-3), 3.39 (dd, 1H, *J* = 15.6, 1.6 Hz, H-5), 3.76 (tt, 1H, *J* = 10.8, 4.4 Hz, H-8ax), 3.79 (brd, 1H, *J* = 15.6 Hz, H-5), 4.93 (q, 1H, *J* = 2.4 Hz, $=CH_2$), 4.97 (dt, 1H, *J* = 2.8, 2 Hz, $=CH_2$); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 25.1 (C-2), 32.4 (C-7), 33.5 (C-10), 33.6 (C-9), 35.0 (C-1), 46.3 (C-6a), 55.5 (C-3), 56.7 (C-5), 65.9 (C-8), 71.6 (C-10a), 104.1 ($=CH_2$), 152.1 (C-6). HRMS (ESI) *m*/*z* calcd for $C_{12}H_{20}NO$ 194.1539 $[M+H]^+$; found 194.1538.

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