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ARTICLE TYPE

Enantioselective, Protecting Group-Free Synthesis of 1*S*-Ethyl-4-Substituted Quinolizidines

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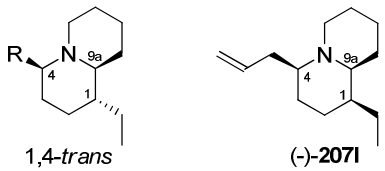
A practical enantioselective protecting group-free four-step route to the key quinolizidinone **6** from phenylglycinol-derived bicyclic lactam **1** is reported. The organometallic addition reaction upon **6** takes place stereoselectively to give 1-ethyl-4-substituted quinolizidines 4-*epi*-**207I** and **7**-**9**. Following a similar synthetic sequence, 9a-*epi*-**6** is also accessed. However, the addition of Grignard reagents upon 9a-*epi*-**6** proceeds in a non-stereoselective manner. In order to gain insight into the different stereochemical outcome in the two series, theoretical calculations on the iminium salts **A** and **B** have been performed. The study concludes that the addition of the hydride, which is the step that determines the configuration of the final products, occurs in a stereoelectronic controlled manner. The theoretical study is in agreement with the experimental results.

Introduction

The extracts from the skin of certain poisonous frogs and toads contain alkaloids showing promising biomedical activities. So far, none of these alkaloids has been reported from any other natural source. Most of them contain as a common structural feature an azabicyclic "izidine" nucleus, *e. g*. disubstituted pyrrolizidines, di- and trisubstituted indolizidines, or disubstituted quinolizidines.[1]

Among them, 1,4-disubstituted quinolizidines[2] are a relatively new class of alkaloids that have been isolated in minute quantities. Their structures have been partially elucidated based on the GC-MS and GC-FTIR spectra, the latter showing significant Bohlmann bands[3] indicating that the hydrogens at positions 4 and 9a are *cis*. The relative configuration at position 1 is only tentative and the absolute configuration of the stereocenters is unknown. As total synthesis is required for structural proof, it would be highly desirable to develop general asymmetric methodologies to easily access these biologically interesting compounds.

There are currently about 20 compounds assigned to this particular structural family of amphibian alkaloids[4] including seven 1-ethylquinolizidines representatives (Figure 1). Among them, six show a 1,4-*trans* relative configuration while alkaloid (**-**)**-207I** is unique, with substituents being 1,4-*cis*.



R = C_4H_7, **221X**
R = $CH_2CH{=}CHC{\equiv}CH$, **231A**
R = $(CH_2)_3C{\equiv}CH$, **233A**
R = $(CH_2)_3CH{=}CH_2$, **235U**
R = $(CH_2)_4C{\equiv}CH$, **247D**
R = n-C_6H_{13}, **251AA**

Figure 1 1-Ethyl-4-substituted quinolizidines.

The relative stereochemistry of natural quinolizidine (**-**)**-207I** was determined in 1997 by Momose's group by comparison of the GC-MS and GC-FIT spectra of the 1-*epi*-**207I** isomer synthesized by them and the natural alkaloid.[5] In 2003, Toyooka and co-workers published the first enantioselective synthesis of (+)**-207I**, the enantiomer of the alkaloid, thus determining the absolute stereochemistry of the natural product.[6] More recently, the same research team reported the synthesis of **233A**, **235U** and **251AA** alkaloids.[7] Although pioneering, these syntheses suffer from the drawback of requiring a considerable number of synthetic steps, leading to a low yield of the final product, partly due to the use of protecting groups. Therefore, a general and efficient procedure providing access to different 1,4-disubstituted quinolizidine alkaloids would be of interest.

Interestingly from the biological point of view, 1-*epi*-**207I** selectively blocks α7 nicotinic receptors (IC_{50} = 0.6μM).[8] In contrast, alkaloids **233A**, **235U** and **251AA** block the responses mediated by α7 and α4β2 nicotinic receptors without any

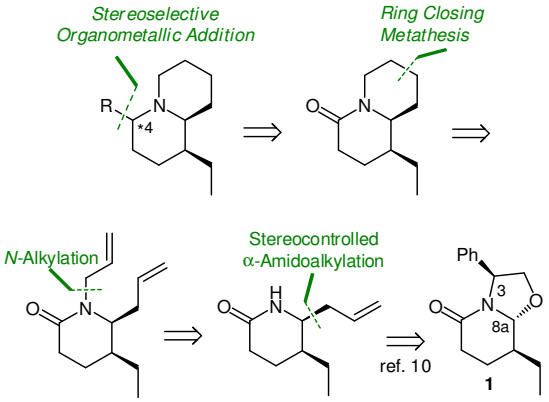
selectivity observed between both subtypes. Comparing the latter compounds with 1-*epi*-**207I** led the authors to conclude that the α7 subtype selectivity of 1,4-disubstituted quinolizidines is remarkably dependent on the structure of the C4 side chain. Increasing the length of the 4-moiety beyond three carbons appears to markedly reduce potency and selectivity at the α7 receptor.

In this paper we disclose a general protocol for the enantioselective construction of these biologically attractive structural motifs using chiral bicyclic lactams as enantiomeric scaffolds.[9] Taking into account the aforementioned biological studies, we planned to attach a 1 to 3 carbon chain at the C4 position of the azabicyclic nucleus.

Results and Discussion

Retrosynthetic analysis

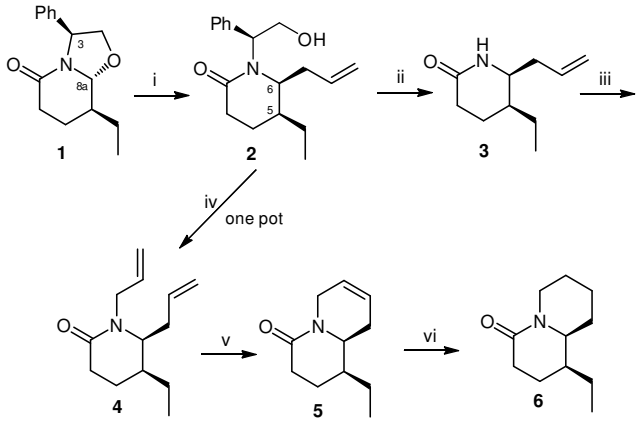
Our retrosynthetic analysis is briefly outlined in Scheme 1. We envisioned that the alkyl group at C-4 could be installed by a stereoselective addition of an organometallic reagent to the carbonyl amide group of a 1-ethyl quinolizidine derivative. This bicyclic lactam was surmised to be constructed by a ring-closing metathesis reaction of a monocyclic diallylated derivative. In turn, the required trisubstituted 2-piperidone would be obtained by alkylation of (5*S*,6*S*)-6-allyl-5-ethyl-2-piperidone, whose enantiomer had been previously synthesized by our group by an α-amidoalkylation reaction[10] of the enantiomer of the chiral bicyclic lactam **1**.[11]



Scheme 1 Retrosynthetic analysis.

Preparation of (5*S*,6*S*)-6-allyl-5-ethyl-2-piperidone (3)

As previously reported by our group in the enantiomeric series, the $TiCl_4$–promoted addition of allyltrimethylsilane to **1** occurs stereoselectively, with inversion of the configuration at the C8a to afford a 9:1 mixture of *cis*-6-allyl-5-ethyl disubstituted lactam **2** and its C6 epimer, 6-*epi*-**2**. The absolute stereochemistry of **2** was unambiguously confirmed by X-Ray crystallographic analysis (Figure 2). The configuration of the 5 and 6 stereocenters remains in the final product since both of them are configurationally stable in the subsequent synthetic transformations (Scheme 2).



Scheme 2 Reagents and conditions: (i) Allyltrimethylsilane (2.0 equiv), $TiCl_4$ (4.0 equiv), CH_2Cl_2, 0 ºC to rt, 16 h, **2** (77%) and 6-*epi*-**2** (7%); (ii) Na (metal), NH_3 (*l*), 30 min, –33 ºC, 81%; (iii) NaH (2.0 equiv), allyl bromide (1.1 equiv), THF, 0 ºC to rt, 24 h, 75%; (iv) (a) NaOH (10 equiv), O_2 (1 atm), MTBE, 40 ºC, 24 h; (b) Allyl bromide (1.25 equiv), rt, 19 h, 69% overall; (v) Second-generation Grubbs cat. (2.5 mol %), CH_2Cl_2, rt, 8 h, 87%; (vi) H_2 (1 atm), 10% Pd/C, MeOH, rt, 18 h, 87%.

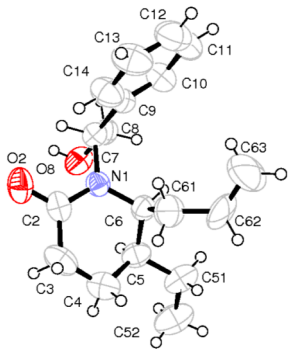


Figure 2 X-Ray structure of (5*S*,6*S*)-6-Allyl-5-ethyl-1-[(1*S*)-2-hydroxy-1-phenylethyl]-2-piperidone (**2**). Molecules are linked along the **a**-axis of the crystal through the hydrogen bond O8-H8···O2^{i} (d(O···O) = 2.722(3)Å, angle(O-H···O) = 171.2º, i=[x-½, ½-y, z]) forming zigzag motifs.

Preparation of azabicyclic compound 6

To construct the second six-membered ring from **2**, removal of the 2-phenylethanol moiety and installation of a second allyl moiety was required. To this end, treatment of **2** with Na/liquid NH_3 afforded **3** in 81% yield. Transformation of **3** into the diolefinic compound **4** was accomplished by deprotonation with NaH followed by alkylation with allyl bromide. More conveniently, we developed a one-pot two-step process from **2** to **4** involving removal of the 2-phenylethanol moiety and alkylation in the same vessel in basic media by sequential treatment with O_2 and allyl bromide (69% overall yield).[12] With all the carbon atoms installed in compound **4** a ring-closing metathesis reaction could be performed and the required six-membered piperidine ring accessed. A second-generation ruthenium Grubbs catalyst mediated this reaction from **4** to generate **5** (87%) under mild

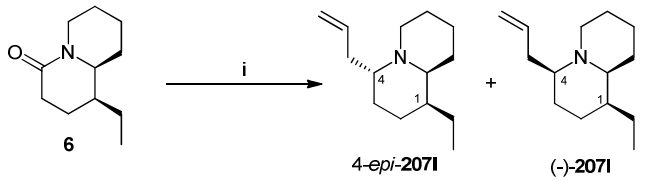
conditions.[13] Chemoselective reduction of **5** employing catalytic hydrogenation was accomplished to give **6**, which is a valuable synthetic intermediate for the formation of the targeted diversely 4-substituted 1-ethylquinolizidines.

Addition of Grignard reagents to azabicyclic compound 6

With bicyclic lactam **6** in hand, the stage was set to execute the installation of an alkyl substituent at carbon 4. To this end, a one-pot procedure, involving the reaction of **6** with Grignard reagents followed by dehydration to the corresponding iminium salts and reduction to the final products, was studied.

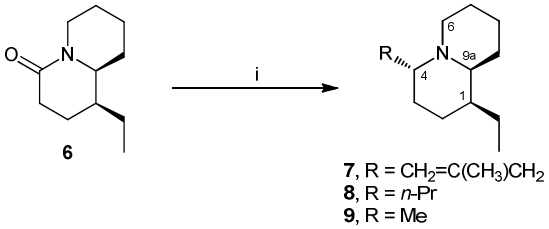
In order to access alkaloid (**-**)**-207I** we first considered the addition of allylmagnesium bromide. Interestingly, while there are several reports dealing with the addition of organometallic reagents to the 2-quinolizidinone nucleus,[14] to the best of our knowledge, the addition of an allylmetallic reagent is unprecedented.[15] Only after much experimentation did we find that the reaction indeed occurs using an excess of Grignard reagent (4 equiv) in the presence of anhydrous $CeCl_3$.[16]

Being aware that the reduction step would be responsible for the stereochemistry of the final product, different reducing agents were evaluated. While reduction with $NaBH_3CN$ or $NaBH(AcO)_3$ gave inseparable mixtures of (**-**)**-207I** and its C4-epimer, 4-*epi*-**207I**, (34:66 and 23:77, respectively), $NaBH_4$ and DIBAL-H furnished 4-*epi*-**207I** with a high degree of diastereoselectivity (3:97 and 4:96, respectively) (Scheme 3).[17]



Scheme 3 Reagents and conditions: (i) (a) $CeCl_3$ (4.0 equiv), allylmagnesium bromide (4.0 equiv), THF, rt, 18 h; (b) $NaBH_4$ (1.25 equiv), MeOH, AcOH, –78 ºC, 30 min, 58%, d.r. = 97:3.

In order to access C-4 analogues of the alkaloid (**-**)**-207I**, the addition of different Grignard reagents was studied. In all cases, the alkyl chain introduced was limited to a length of up to three carbon atoms, taking into account previous biological studies.[7,8] To this end, an excess of (2-methylallyl)magnesium bromide was added to **6**, followed by treatment with $NaBH_4$ to give **7** and 4-*epi*-**7** (96:4) in 56% yield. Following similar experimental conditions, a propyl and a methyl chain were also introduced to stereoselectively furnish **8** and **9** in 64 and 69% yield, respectively (Scheme 4).



Scheme 4 Reagents and conditions: (i) (a) $CeCl_3$ (2.0 equiv), 2-methylallylmagnesium chloride (8.0 equiv) or propylmagnesium bromide (4.0 equiv), THF, rt, 18 h; (b) $NaBH_4$ (1.25 equiv), MeOH, AcOH, –78 ºC, 30 min, 56%, **7**; 69%, **9**.

Structural elucidation of the final bicyclic amines

The absolute configuration of the C-4 stereogenic center in (**-**)**-207I** and 4-*epi*-**207I** was assigned by correlation of the NMR data of these two compounds with those reported for the previously synthesized enantiomer, (**+**)**-207I**.[6]

Worthy of note, in 4-*epi*-**207I** the peaks corresponding to C-6 and C-9a are about 5 and 3 ppm more shielded, respectively, than in (**-**)**-207I** (Table 1). This shielding probably reflects the γ-gauche effect due to an axial disposition of the allyl substituent in 4-*epi*-**207I**. Comparison of the ^{13}C NMR and ^{1}H NMR (Table 2) of compounds **7**-**9** with that of 4-*epi*-**207I** led to the depicted configuration being assigned to the C-4 stereocenter of these new products (Scheme 4).[18]

Table 1. Significant ^{13}C NMR data for bicyclic amines.

carbon	(-)-207I[a]	4-*epi*-207I	7	8	9
1	40.6	41.9	41.8	42.1	41.8
4	64.2	50.9	49.7	51.2	46.7
9a	66.7	61.1	61.1	61.2	60.8
6	53.1	50.1	50.3	50.2	50.1

[a] δ values from reference 6.

Table 2. Significant ^{1}H NMR data for bicyclic amines.

carbon	(-)-207I[a]	4-*epi*-207I	7	8	9
1	1.55	1.53	1.54	1.52	1.58
4	1.88	3.00	3.03	2.88	2.98
9a	1.96	2.93	2.94	2.93	2.92
6_{eq}	3.33	3.34	3.32	3.30	3.27
6_{ax}	1.54	2.71	2.69	2.66	2.67

[a] δ values from reference 6.

In fact, full geometry optimization of **9** and its hypothetical C4 epimer (4-*epi*-**9**), performed with the B3LYP density functional method using the 6-31G(d) basis set, revealed that while both compounds were in a chair-chair conformation, only **9** displayed its 4-methyl group in an axial valence (Figure 3), while the methyl group in 4-*epi*-**9** was in an equatorial disposition (Figure 4). Thus, theoretical calculations are in concordance with the ^{13}C-NMR observations.

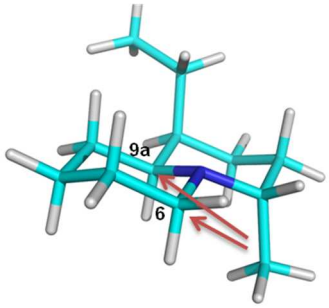


Figure 3 The most stable conformation of compound **9** (γ-gauche effects are indicated).

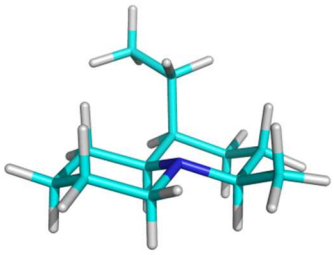
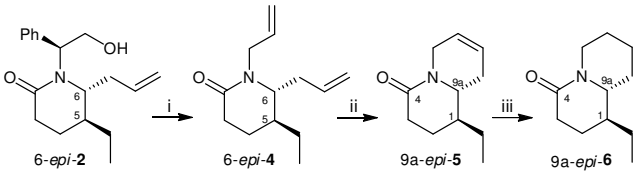


Figure 4 The most stable conformation of hypothetical compound 4-*epi*-**9**.

Synthesis of 9a-*epi* derivatives of 4-substituted 2-ethylquinolizidines

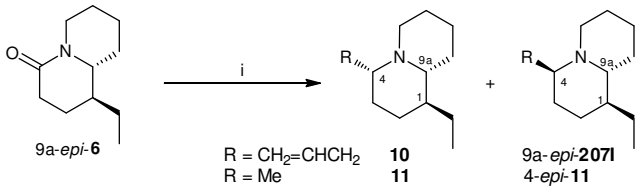
With compounds 6-*epi*-**2** in hand (Scheme 2), we decided to go a step further and apply the developed procedure to prepare 9a-*epi*-**6** to study the stereochemical outcome of the Grignard addition reactions in compounds with a C9a *R* configuration. Thus, the introduction of an allyl group on the piperidone nitrogen of 6-*epi*-**2** gave compound 6-*epi*-**4** in 56% yield. Subsequent treatment with Grubbs second-generation catalyst furnished 9a-*epi*-**5**, which was hydrogenated to give 9a-*epi*-**6** with yields comparable to those obtained in the previous series.



Scheme 5 Reagents and conditions: (i) (a) NaOH (10 equiv), O_2 (1 atm.), MTBE, 40 ºC, 24 h; (b) allyl bromide (1.25 equiv), rt, 19 h, 56% overall; (ii) Second-generation Grubbs cat. (3 mol %), CH_2Cl_2, rt, 6 h, 90%; (iii) H_2 (1 atm.), 10% Pd/C, MeOH, rt, 16 h, 98%.

The addition reaction of allylmagnesium bromide in the presence of anhydrous $CeCl_3$ to 9a-*epi*-**6** followed by $NaBH_4$ reduction occurs in a non steroselective manner to give a 1:1 mixture of **10** and 9a-*epi*-**207I**. Similar results were observed in the reaction of 9a-*epi*-**6** with methylmagnesium bromide, yielding an equimolecular mixture of the two possible products. These results are in striking contrast with the stereochemical behaviour of the additions previously studied in **6**, which occurred with very high stereoselectivity.

The structural assignation of these quinolizidines was done by comparison with the spectroscopic data of compound **10** whose enantiomer had been previously described in the literature.[5,19]



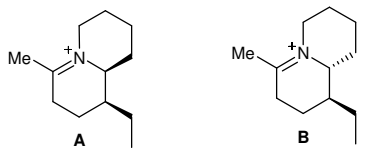
Scheme 6 Reagents and conditions: (i) (a) $CeCl_3$ (2.0 equiv), allylmagnesium bromide or methylmagnesium bromide (4.0 equiv), THF, rt, 18 h; (b) $NaBH_4$ (1.25 equiv), MeOH, AcOH, –78 ºC, 30 min, **10** and 9a-*epi*-**207I** (54%); **11** and 4-*epi*-**11** (48%).

Theoretical considerations of the stereochemical outcome in the introduction of the C-4 substituent

As previously mentioned, the stereochemistry of the organometallic addition reaction is determined by the attack of the hydride to the iminium salt. In order to gain insight into the stereochemistry of the final products, studies on the relative stability of different conformers of the iminium ion intermediates when a methyl substituent is attached were considered (Scheme 7). Indeed, exploration of the different conformational states for the iminium salts **A** and **B**, at the B3LYP/6-31 (G) level, gave two main possible conformations, depending on the disposition adopted by the ethyl substituent. Starting from **A**, the non substituted six-membered ring of the quinolizidine adopts a chair conformation in both iminium forms. As expected, the substituted ring adopts a half-chair conformation with the C3, C4, N and C9a atoms in the same plane, with the ethyl group either in an equatorial, **AI**, or axial disposition, **AII** (Figures 5 and 6), **AI** being more stable by 3.1 Kcal/mol. This fact could be ascribed to a 1,3-diaxial destabilizing interaction in **AII** between the axial ethyl substituent and the axial protons at positions 3 and 9. On the basis of these findings, the stereochemical outcome of the addition reaction can be explained considering an axial attack of the hydride, under stereoelectronic control,[20] at the electrophilic carbon of the lowest-energy iminium ion intermediate, **AI**. This directed nucleophile attack dictates an *S* configuration in the newly created stereocenter, as depicted in Figure 5.

In a similar fashion, in the two possible conformations of the iminium salt **B**, the non-substituted ring adopts a chair conformation, whereas the substituted ring shows a half-chair conformation with the C3, C4, N and C9a atoms in the same plane. However, in the iminium salt **B** both possible conformations, **BI**, with the ethyl group in an equatorial disposition, and **BII**, with the ethyl group in an axial disposition, are energetically similar ($\Delta E <$ 1 Kcal/mol) (Figures 7 and 8). The smaller energy gap between both conformations may be indicative of a relative stabilization of the conformation **BII** in comparison with **AII** because only one

1,3-diaxial destabilizing interaction (ax-Et/ax-H_3) is found in the former. Consequently, as both conformations are of similar energies, the stereoelectronic controlled addition of the hydride upon the iminium salt can occur on both **BI** and **BII**, yielding compounds **11** and 4-*epi*-**11** in nearly equal amounts.



Scheme 7 Intermediate iminium salts.

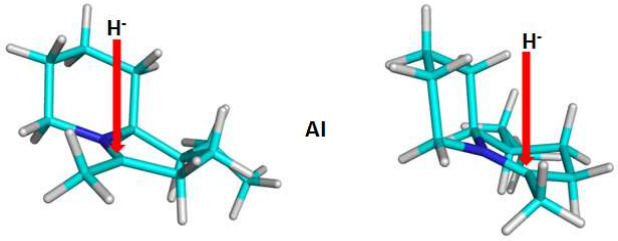


Figure 5 Two views of the most stable conformation of the iminium salt intermediate **AI** and indication of the hydride stereocontrolled addition.

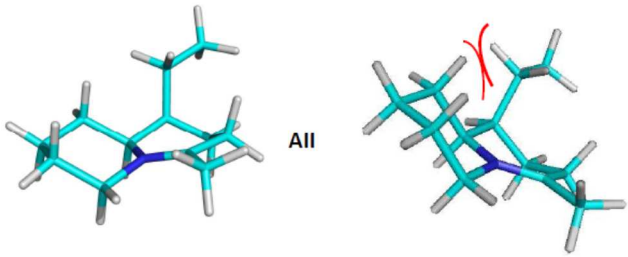


Figure 6 Two views of the most stable conformation of the iminium salt intermediate **AII**. 1,3-Diaxial destabilizing interactions are indicated.

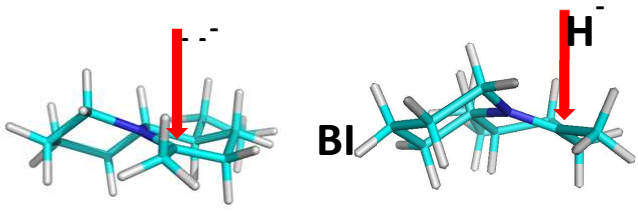


Figure 7 Two views of the most stable conformation of the iminium salt intermediate **BI** and indication of the hydride stereocontrolled addition.

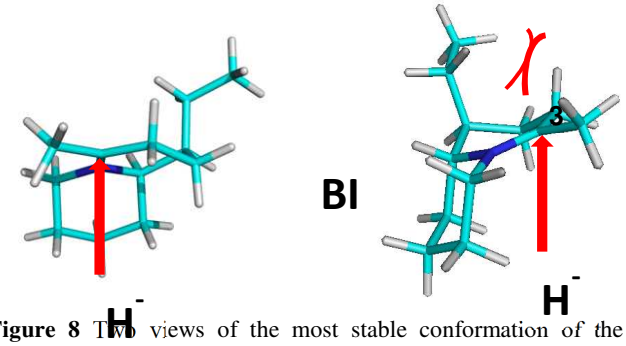


Figure 8 Two views of the most stable conformation of the iminium salt intermediate **BII** and indication of the hydride stereocontrolled addition. 1,3-Diaxial destabilizing interaction is indicated.

Conclusions

In conclusion, we have developed a straightforward enantioselective synthesis of potentially biologically interesting 1-ethyl-4-substituted quinolizidines without using protecting groups. The stereochemistry of the stereocenters is defined by the use of (*S*)-phenylglycinol as the source of chirality and by two stereocontrolled reactions, an α-amidoalkylation and an organometallic addition. Compounds in the 9a-*epi* series have been efficiently obtained following the synthetic sequence developed in the original series. However, the final organometallic addition reaction proved to be not stereoselective. In order to rationalize the different stereochemical outcome in the Grignard addition reactions in the two series, theoretical calculations on the iminium salts were performed indicating that the addition of the hydride occurs in a stereoelectronic controlled fashion.

Experimental Section

General Methods

NMR spectra were recorded in $CDCl_3$ at 300 or 400 MHz (^1H) and 75.4 or 100.6 MHz (^{13}C), and chemical shifts are reported in δ values downfield from TMS or relative to residual chloroform (7.26 ppm, 77.0 ppm) as an internal standard. Data are reported in the following manner: chemical shift, multiplicity, coupling constant (*J*) in hertz (Hz), integrated intensity. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet; br s, broad signal, app, apparent. Evaporation of solvents was accomplished with a rotatory evaporator. Melting points were determined in a capillary tube and are uncorrected. Thin-layer chromatography was done on SiO_2 (silica gel 60 F_{254}), and the spots were located by UV, 1% aqueous $KMnO_4$ or iodoplatinate (for tertiary amines). Chromatography refers to flash column chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230-400 mesh) or Al_2O_3 (Aluminium oxide 90 active basic, Merck). Mass spectra were recorded on a LTQ spectrometer using electrospray (ES^+) ionization techniques.

(5*S*,6*S*)-6-Allyl-5-ethyl-1-[(1*S*)-2-hydroxy-1-phenylethyl]-2-piperidone, (2).

$TiCl_4$ (20 mL, 182.12 mmol) was slowly added to a cooled (0 ºC) solution of **1** (11.17 g, 45.53 mmol) in anhyd CH_2Cl_2 (90 mL) and the mixture was stirred for 15 min. Allyltrimethylsilane (14.5 mL, 91.06 mmol) was added in 3 portions and the resulting mixture was warmed at rt and stirred for 16 h. The mixture was poured onto ice and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered and concentrated to give a 90:10 (^{1}H NMR) mixture of **2** and 6-*epi*-**2**, which was purified by column chromatography (Biotage Si 40M 2197-1, CH_2Cl_2-MeOH 99.5:0.5 to 97:3) to yield **2** (10.02 g, 77%) and C6-*epi*-**2** (0.87 g, 7%). **2**:[10] m.p 75.0-76.0 ºC (cyclohexane/pentane); $[\alpha]^{22}_D$ = +21.3 (c 0.45, $CHCl_3$). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.29; H, 8.68; N, 4.94 %. **(5*S*,6*R*)-6-Allyl-5-ethyl-1-[(1*S*)-2-hydroxy-1-phenylethyl]-2-piperidone, (6-*epi*-2).** IR (NaCl) 3383, 2958, 1624 (s, NCO), 1452 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.62 (t, *J* = 8.2 Hz, 3H, CH_2CH_3), 1.01 (m, 1H, CH_2CH_3), 1.17 (m, 1H, CH_2CH_3), 1.51 (m, 1H, H-4), 1.61 (m, 1H, H-5), 1.99 (m, 1H, H-4), 2.28 (m, 1H, CH_2CH=), 2.41-2.46 (m, 3H, H-3, CH_2CH=), 3.06 (dm, *J* = 10.5 Hz, 1H, H-6), 3.96 (br s, 1H, OH), 4.16 (m, 1H, H-2'), 4.24 (m, 1H, H-2'), 5.01 (d, *J* = 4.5 Hz, 1H, CH=CH_2), 5.05 (m, 1H, CH=CH_2), 5.41 (dd, *J* = 8.1, 5.1 Hz, 1H, H-1'), 5.57 (m, 1H, CH=CH_2), 7.26-7.37 (m, 5H, H-Ar); ^{13}C NMR (100.6 MHz) δ 11.3 (CH_2CH_3), 22.2 (C-4), 24.3 (CH_2CH_3), 28.5 (C-3), 35.4 (C-5), 39.3 (CH_2CH=), 59.1 (C-6), 62.7 (C-1'), 63.6 (C-2'), 117.7 (CH=CH_2), 127.8 (CHAr),128.3 (2CHAr), 128.5 (2CHAr), 134.0 (CH=CH_2), 136.9 (CAr), 172.4 (NCO); $[\alpha]^{22}_D$ –19.6 (c 1.0, $CHCl_3$); HRMS $C_{18}H_{26}NO_2$ $[M+H]^+$ 288.1958; found, 288.1958.

(5*S*,6*S*)-6-Allyl-5-ethyl-2-piperidone, (3).

Into a three-necked, round-bottomed flask equipped with a cold-finger condenser charged with dry ice-acetone was condensed NH_3 (ca. 150 mL) at –78 °C. The temperature was allowed to rise to –33 °C and a solution of alcohol **2** (1.00 g, 3.48 mmol) in THF (5 mL) was added, followed by the addition of sodium metal in small portions until the blue colour persisted. After the mixture was stirred at –33 °C for 30 min, the reaction was carefully quenched by the addition of solid NH_4Cl until the blue colour disappeared. The mixture was stirred at rt overnight, the residue was partitioned between H_2O and CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered and concentrated. The resulting residue was chromatographed (SiO_2, hexane-EtOAc 1:1 to 1:2) to give **3** as a white solid (0.47 g, 81 %) and **2** (0.07 g, 7%). IR (NaCl) 3208, 2959, 1664 (s, NCO) cm^{-1}; ^{1}H NMR (300 MHz, COSY) δ 0.96 (t, *J* = 7.4, 3H, (CH_2CH_3), 1.52–1.24 (m, 2H, CH_2CH_3), 1.70–1.86 (m, 3H, H-4, H-5), 2.02–2.12 (m, 1H, CH_2CH=), 2.21–2.40 (m, 3H, CH_2CH=, H-3), 3.39-3.50 (m, 1H, H-6), 5.16 (d, *J* = 7.6, 1H, CH=CH_2), 5.20 (d, *J* = 0.7, 1H, CH=CH_2), 5.65–5.82 (m, 1H, CH=CH_2), 5.83 (br s, 1H, NH); ^{13}C NMR (75.4 MHz) δ 11.6 (CH_2CH_3) 20.7 and 22.7 (C-4/CH_2CH_3), 29.1 (C-3), 36.3 (CH_2CH=), 37.3 (C-5), 54.8 (C-6), 119.1 (CH=CH_2), 134.0 (CH=CH_2), 172.0 (NCO); $[\alpha]^{22}_D$ = –66.32 (c 1.03, MeOH); HRMS $C_{10}H_{18}NO$ $[M+H]^+$ 168.1383; found, 168.1382.

(5*S*,6*S*)-1,6-Diallyl-5-ethyl-2-piperidone, (4).

Method A. A solution of **3** (656 mg, 3.93 mmol) in THF (20 mL) was added via cannula to NaH (320 mg, 7.85 mmol, 60% dispersion in mineral oil). After 15 min, the reaction mixture was cooled (0 ºC) and allyl bromide (380 µL, 4.32 mmol) was added with a syringe pump over 60 min. Then, the mixture was warmed up at rt and stirred for 24 h. The reaction mixture was cooled (0 ºC), quenched by the addition of water (10 mL), and extracted with EtOAc. The combined organic extracts were dried and concentrated to give a residue, which was chromatographed (hexane-EtOAc 4:1) to furnish **4** (613 mg, 75%) as a yellow oil.

Method B. In a round-bottomed flask equipped with a 1 gallon gas bag of O_2, an excess of freshly ground NaOH (2.78 g, 69.6 mmol) was added to a solution of **2** (2.00 g, 6.96 mmol) in MTBE (20 mL). The mixture was heated at 40 ºC and stirred slowly at this temperature for 24 h. The progress of reaction was monitored by TLC and, when **2** was consumed, the gas bag was disconnected and the reaction mixture was cooled to rt. Allyl bromide (0.75 mL, 8.70 mmoL) was slowly added and stirring was continued for additional 19 h at rt. The solvent was removed, the residue was partitioned between H_2O and CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2. The organic extracts were washed with saturated NH_4Cl solution, dried and concentrated to give a residue, which was purified by column chromatography (hexane-EtOAc 4:1) to yield **4** (994 mg, 69%) as a yellow oil. IR (NaCl film) 2932, 1642 (s, NCO) cm^{-1}; ^{1}H NMR (300 MHz, COSY, HSQC) δ 0.93 (t, *J* = 7.4 Hz, 3H CH_2CH_3), 1.31-1.42 (m, 2H, -CH_2CH_3), 1.58-1.83 (m, 3H, H-4 and H-5), 2.23 (m, 1H, H-1'), 2.36-2.49 (m, 3H, H-3 and H-1'), 3.35 (m, 1H, H-1''), 3.40 (m, 1H, H-6), 4.71 (dddd, *J* = 15.3, 4.2, 1.5, 1.5 Hz, 1H, H-1''), 5.04-5.16 (m, 4H, H-3', H-3''), 5.69-5.90 (m, 2H, H-2', H-2''); ^{13}C NMR (100.6 MHz) δ 11.8 (CH_2CH_3), 22.6 (CH_2CH_3), 25.4 (C-4), 30.6 (C-3), 34.1 (C-1'), 40.6 (C-5), 49.0 (C-1''), 58.7 (C-6), 116.9 (=CH_2), 117.4 (=CH_2), 133.2 (CH=CH_2), 135.7 (CH=CH_2), 170.0 (CON); $[\alpha]^{22}_D$ = –95.56 (c 1.0, MeOH); HRMS $C_{13}H_{22}NO$ $[M+H]^+$ 208.1696; found, 208.1696. Anal. Calcd for $C_{13}H_{21}NO$.¼ H_2O: C, 73.72; H, 10.23; N, 6.61. Found: C, 73.96; H, 10.18; N, 6.18 %. Note: Trace amounts of **(5*S*,6*S*)-6-allyl-1-[(*S*)-2-(allyloxy)-1-phenylethyl)]-5-ethylpiperidin-2-one** were also isolated. IR (NaCl) 2961, 1641 (s, NCO), 1452 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, HSQC, COSY) δ 0.88 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 1.24-1.37 (m, 2H, CH_2CH_3), 1.60 (m, 1H, H-4), 1.73-1.87 (m, 2H, H-4, H-5), 1.96 (dddt, *J* = 14.6, 7.2, 4.5, 1.3 Hz, 1H, CH_2CH=), 2.21 (m, 1H, CH_2CH=), 2.45-2.54 (m, 2H, H-3), 3.46 (m, 1H, H-6), 4.01 (ddt, *J* = 7.0, 5.5, 1.4 Hz, 2H, OCH_2CH=), 4.08 (dd, *J* = 6.1, 1.6 Hz, 2H, H-2'), 4.83 (m, 1H, C6-CH_2CH=CH_2), 4.87 (app t, *J* = 1.4 Hz, 1H, C6CH_2CH=CH_2), 5.16 (m, app dq, *J* = 10.4, 1.3 Hz, 1H, OCH_2CH=CH_2), 5.23-5.28 (m, 2H, H-1', OCH_2CH=CH_2), 5.48 (m, 1H, CH_2CH=), 5.89 (ddt, *J* = 17.2, 10.4, 5.5 Hz, 1H, OCH_2CH=CH_2), 7.24-7.36 (m, 5H, H-Ar); ^{13}C NMR (100.6 MHz) δ 11.9 (CH_2CH_3), 22.2 (C-4), 25.7 (CH_2CH_3), 30.6 (C-3), 34.8 (CH_2CH=), 41.3 (C-5), 58.8 (C-6), 60.1 (C-1'), 70.6 (C-2'), 71.9 (OCH_2CH=CH_2), 116.5 (CH=CH_2), 116.8 (OCH_2CH=CH_2), 127.6 (CHAr), 128.4 (4CHAr), 134.6 (CH_2CH=), 135.6 (C6CH_2CH=CH_2), 138.4 (CAr), 171.0 (NCO); HRMS $C_{21}H_{30}NO_2$ $[M+H]^+$ 328.2271; found, 328.2270.

(1*S*,9a*S*)-1-Ethyl-4-oxo-1,2,3,6,9,9a-hexahydro-4*H*-quinolizine, (5).

Ruthenium catalyst (Grubbs 2nd generation, 245 mg, 0.29 mmol) was added to a solution of **4** (2.40 g, 11.58 mmol) in CH_2Cl_2 (300 mL) and the solution was stirred at rt for 8 h. The mixture was concentrated and the resulting residue was purified by column chromatography (Al_2O_3, hexane-EtOAc 3:1 to 3:2) to afford **5** (1.80 g, 87%), which revealed to be unstable. IR (NaCl) 2960, 2932, 1662 (s, NCO), 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, COSY, HSQC) δ 0.96 (t, 3H, *J* = 7.4 Hz, -CH_2CH_3), 1.36 (m, 2H, -CH_2CH_3), 1.50-1.75 (m, 3H, 2xH2 and H-1), 1.80-2.22 (m, 2H, H-9), 2.30-2.55 (m, 2H, H-3), 3.39 (app d, *J* = 18.0 Hz, 1H, H-6), 3.58 (td, *J* = 11.6, 4.5 Hz, 1H, H-9a), 4.95 (app d, *J* = 18.0 Hz, 1H, H-6), 5.68 (m, 1H, H-7), 5.73 (m, 1H, H-8); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 11.8 (CH_2CH_3), 22.1 (C-2), 24.3 (CH_2CH_3), 26.3 (C-9), 32.3 (C-3), 38.3 (C-1), 43.1 (C-6), 55.9 (C-9a), 124.8 and 125.0 (C-7/C-8), 168.8 (NCO); $[\alpha]^{22}_D$ = –44.3 (c = 1.20, MeOH); HRMS $C_{11}H_{18}NO$ $[M+H]^+$ 180.1383; found, 180.1379.

(1*S*,9a*S*)-1-Ethyl-4-oxo-1,2,3,6,7,8,9,9a-octahydro-4*H*-quinolizine, (6).

10% Pd/C (60 mg) was added to a solution of **5** (1.20 g, 6.69 mmol) in MeOH (20 mL) and the mixture was stirred under hydrogen atmosphere for 18 h. Then, the crude mixture was filtered through a Celite® and the solvent was evaporated to afford a residue, which was purified by bulb-to-bulb distillation (6 Torr, 160-170 ºC) to obtain **6** (1.05 g, 87%) as a colourless liquid. IR (NaCl) 2934, 2863, 1642 (s, NCO), 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 0.87 (t, 3H, *J* = 7.4 Hz, CH_2CH_3), 1.16-1.64 (m, 9H, CH_2CH_3, H-2, H-7, H-8, H-9), 1.78 (m, 1H, H-1), 1.87 (m, H7), 2.27 (m, 1H, H-3), 2.30-2.41 (m, 2H, H-3, H-6), 3.24 (dd, 1H, *J* = 11.8, 5.1 Hz, H-9a), 4.65 (ddd, 1H, *J* = 12.8, 3.9, 1.9Hz, H-6); ^{13}C NMR (100.6 MHz) δ 11.7 (CH_2CH_3), 22.9 (C-8), 24.1 (CH_2CH_3), 25.1 (C-7), 25.7 (C-2), 26.2 (C-9), 32.3 (C-3), 38.7 (C-1), 44.6 (C-6), 60.6 (C-9a), 168.6 (NCO); $[\alpha]^{22}_D$ = –49.1 (c 2.0, $CHCl_3$); MS-EI *m/z* 181 M^+ (37), 125 (51), 97 (100), 83 (43), 55 (30); HRMS $C_{11}H_{20}NO$ $[M+H]^+$, 182.1539; found, 182.1541. Anal. Calcd for $C_{11}H_{19}NO{\cdot}1/3\ H_2O$: C, 70.57; H, 10.58; N, 7.48. Found: C, 70.23; H, 10.14; N, 7.32 %.

(5*S*,6*R*)-1,6-Diallyl-5-ethyl-2-piperidone, (6-*epi*-**4**).

Following the procedure for the preparation of **4** (method B), from lactam 6-*epi*-**2** (2.10 g, 7.27 mmol), NaOH (2.91 g, 72.7 mmol), MTBE (25 mL), and allyl bromide (0.79 mL, 9.09 mmol), compound 6-*epi*-**4** (0.84 g, 56%) was obtained after column chromatography (hexane-EtOAc 4:1). IR (NaCl) 2932, 1642 (s, NCO) cm^{-1}; ^1H NMR (400 MHz, COSY, HSQC) δ 0.91 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 1.32-1.43 (m, 2H, CH_2CH_3), 1.58 (m, 1H, H-4), 1.69 (m, 1H, H-5), 1.98 (m, 1H, H-4), 2.22-2.51 (m, 4H, 2xH-3 and 2xH-1'), 3.20 (dt, *J* = 9.3, 3.3 Hz, 1H, H-6), 3.37 (dd, *J* = 15.0, 7.7 Hz, 1H, H-1''), 4.67 (ddt, *J* = 15.0, 4.7, 1.6 Hz, 1H, H-1''), 5.07-5.21 (m, 4H, H-3' and H-3''), 5.62-5.82 (m, 2H, H-2' and H-2''); ^{13}C NMR (100.6 MHz) δ 11.3 (CH_2CH_3), 20.3 (C-4), 24.1 (-CH_2CH_3), 27.9 (C-3), 35.4 (C-5), 37.3 (C-1'), 47.5 (C-1''), 59.3 (C-6), 117.3 (C-3' or C-3''), 117.8 (C-3' or C-3''), 133.2 (C-2'' or C-2'), 135.9 (C-2'' or C-2'), 169.6 (CON); $[\alpha]^{22}_D$ = +44.1 (c 1.0, $CHCl_3$); HRMS calcd for $C_{13}H_{22}NO$ $[M+H]^+$, 208.1696; found, 208.1695. Anal. Calcd. for $C_{13}H_{21}NO.1/5\ H_2O$: C, 74.07; H, 10.23; N, 6.64. Found: C, 74.07; H, 10.40; N, 6.42 %.

(1*S*,9a*R*)-1-Ethyl-4-oxo-1,2,3,6,9,9a-hexahydro-4*H*-quinolizine, (9a-*epi*-**5**).

Following the procedure for the preparation of **5**, from lactam 6-*epi*-**4** (0.62 g, 2.99 mmol) and 2nd generation Grubbs catalyst (76 mg, 0.09 mmol, 0.03 equiv) in CH_2Cl_2 (100 mL), compound 9a-*epi*-**5** (0.48 g, 90%) was obtained after column chromatography (Al_2O_3, hexane-EtOAc 1:1 to 0:1). 9a-*Epi*-**5** revealed to be unstable. ^1H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 0.96 (t, 3H, *J* = 7.3 Hz, CH_2CH_3), 1.36 (m, 1H, CH_2CH_3), 1.45-1.55 (m, 2H, H-1, H-2), 1.60 (m, 1H, CH_2CH_3), 1.92 (m, 1H, H-2), 2.11 (m, 1H, H-9), 2.26 (m, 1H, H-9), 2.32 (m, 1H, H-3), 2.45 (m, 1H, H-3), 3.21 (ddd, *J* = 9.9, 5.8, 3.8 Hz, 1H, H-9a), 3.40 (app d, *J* = 18.5 Hz, 1H, H-6), 4.83 (app d, *J* = 18.5 Hz, 1H, H-6), 5.68 (m, 1H, H-7), 5.77 (m, 1H, H-8); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.3 (CH_2CH_3), 22.9 (C-2), 25.1 (CH_2CH_3), 30.7 (C-3), 32.5 (C-9), 40.4 (C-1), 42.5 (C-6), 57.7 (C-9a), 124.1 and 124.3 (C-7/C-8), 169.5 (NCO); HRMS calcd for $C_{11}H_{18}NO$ $[M+H]^+$, 180.1383; found, 180.1380.

(1*S*,9a*R*)-1-Ethyl-4-oxo-1,2,3,6,7,8,9,9a-octahydro-4*H*-quinolizine, (9a-*epi*-**6**).

Following the procedure for the preparation of **6**, from lactam 6-*epi*-**5** (315 mg, 1.76 mmol), 10% Pd/C (32 mg) and MeOH (9.0 mL), compound 9a-*epi*-**6** (310 mg, 98%) was obtained as a colourless liquid after bulb-to-bulb distillation (6 Torr, 160-170 ºC). IR (NaCl) 2933, 1643 (s, NCO), 1463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 0.95 (t, 3H, *J* = 7.4 Hz, CH_3CH_2-), 1.14-1.47 (m, 6H, CH_2CH_3), H-1, H-2, H-8, H-9), 1.55-1.68 (m, 2H, CH_2CH_3, H-9), 1.83-1.97 (m, 3H, H-2, H-7, H-8), 2.23 (m, 1H, H-3), 2.35 (td, 1H, *J* = 12.8, 2.9 Hz, H-6), 2.44 (dt, 1H, *J* = 17.3, 4.4 Hz, H-3), 2.89 (ddd, 1H, *J* = 11.3, 6.9, 2.4 Hz, H-9a), 4.81 (ddt, 1H, *J* = 12.8, 4.0, 2.9 Hz, H-6); ^{13}C NMR (100.6 MH) δ 11.3 (CH_2CH_3), 23.5 (C-2*), 24.7 (C-8*), 25.3 (CH_2CH_3), 25.4 (C-9*), 31.4 (C-3), 33.0 (C-7), 41.4 (C-1), 42.9 (C-6), 61.9 (C-9a), 169.0 (NCO); $[\alpha]^{22}_D$ = –27.5 (c 1.0, $CHCl_3$); HRMS calcd for $C_{11}H_{20}NO$ $[M+H]^+$ 182.1539; found, 182.1538. Anal. Calcd for $C_{11}H_{19}NO{\cdot}1/4\ H_2O$: C, 71.12; H, 10.58; N, 7.54. Found: C, 71.36; H, 10.49; N, 6.94 %.

General procedure for the addition of organometal reagents.

Anhydrous $CeCl_3$[21] (2.0 equiv) was added to a solution of **6** (1 equiv) in anhyd THF. The resulting suspension was vigorously stirred at rt for 1 h. Grignard reagent was added dropwise (4.0-8.0 equiv) over 30 min and the mixture was stirred for additional 18 h. MeOH was added to quench the reaction and the mixture was cooled at -78 ºC. $NaBH_4$ (1.25 equiv) and AcOH (0.3 mL) were added and the mixture was stirred at –78 ºC for 30 min. The mixture was concentrated and the residue was partitioned between Et_2O and 1N HCl solution. Then, the acidic aqueous phase was washed with Et_2O and basified with 4N NaOH solution (pH=12-14). The resulting suspension was centrifuged (800 *g* for 30 min at rt) and the supernatant was extracted with CH_2Cl_2.[22] The combined

organic extracts were dried, filtered, concentrated and analysed by GC-MS. The crude product was purified by flash chromatography (Al_2O_3).

(1*S*,4*R*,9a*S*)-4-Allyl-1-ethylquinolizidine, (4-*epi*-207I), (1*S*,4*S*,9a*S*)-4-allyl-1-ethylquinolizidine, (-)-**207I and (1*S*,9a*S*)-4,4-diallyl-1-ethylquinolizidine.**

Following the general procedure, from lactam **6** (300 mg, 1.66 mmol), $CeCl_3$ (1.63 g, 6.62 mmol), allylmagnesium bromide (7.0 mL, 7.0 mmol, 1.0 M solution in Et_2O), THF (7 mL), and $NaBH_4$ (78 mg, 2.7 mmol), a 97:3 diastereomeric mixture of 4-*epi*-**207I** and (-)-**207I** (GC-MS) was obtained. Traces of diallylated quinolizidine were also detected. 4-*epi*-**207I** (198 mg, 58%) was obtained after column chromatography (Al_2O_3, hexanes-EtOAc 95:5 to 85:15). 4-*epi*-**207I**. IR (NaCl) 2957, 2928, 2856, 1456, 908 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 0.87 (t, 3H, *J* = 7.4 Hz, CH_3), 1.13-1.74 (m, 12H, C*H*$_2$CH$_3$, H-1, H-2, H-3, H-7, H-8, H-9), 1.88 (m, app dd, 1H, *J* = 12.7, 2.5 Hz, H-7), 2.14 (m, 1H, C*H*$_2$CH=), 2.37 (m, 1H, C*H*$_2$CH=), 2.71 (td, 1H, *J* = 13.6, 2.5 Hz, H-6$_{ax.}$), 2.93 (m, 1H, H-9a), 3.00 (m, 1H, H-4), 3.34 (app d 1H, *J* = 13.6 Hz, H-6$_{eq.}$), 4.98-5.10 (m, 2H, -CH=C*H*$_2$), 5.83 (dddd, *J* = 16.8, 10.2, 7.7, 6.6 Hz, 1H, C*H*=CH$_2$); ^{13}C NMR (75.4 MHz) δ 11.8 (CH_3), 18.0 (CH_2), 19.3 (CH_2), 25.2 (CH_2), 25.7 (C-7), 29.7 (CH_2), 31.3 (CH_2), 36.9 (*C*H$_2$CH=), 41.9 (C-1), 50.1 (C-6), 50.9 (C-4), 61.1 (C-9a), 116.5 (CH=*C*H$_2$), 135.7 (*C*H=CH$_2$); $[\alpha]^{22}_D$ = +14.4 (c 0.5, CH_2Cl_2); MS-EI *m*/*z* 206 (1), 167 (14), 166 (100), 110 (12), 55 (3); HRMS calcd for $C_{14}H_{26}N$ $[M+H]^+$ 208.2060; found, 208.2061. (-)-**207I**. ^{13}C NMR spectra of (-)-**207I** (from a mixture of 4-*epi*-**207I** and (-)-**207I**) was coincident with that described previously in the literature;[6] MS-EI *m*/*z* 206 M^+ (1), 167 (12), 166 (100), 136 (4), 110 (8), 55 (3). **(1*S*,9a*S*)-4,4-diallyl-1-ethylquinolizidine**. ^1H NMR (300 MHz, $CDCl_3$, COSY) δ 0.89 (t, 3H, *J* = 7.4 Hz, CH$_2$C*H*$_3$), 1.12-1.94 (m, 13H, C*H*$_2$CH$_3$, H-1, H-2, H-3, H-7, H-8, H-9), 2.24 (app d, 4H, *J* = 7.4 Hz, C*H*$_2$CH=), 2.54 (m, 1H, H-9a), 2.61 (app t, 1H, *J* = 11.4 Hz, H-6$_{ax.}$), 3.12 (app d, 1H, *J* = 11.4 Hz, H-6$_{eq.}$), 5.03-5.19 (m, 4H, CH$_2$CH=C*H*$_2$), 5.86 (m, 2H, CH$_2$C*H*=CH$_2$); ^{13}C NMR (75.4 MHz) δ 12.0 (CH$_2$*C*H$_3$), 22.7 (CH_2), 25.1 (CH_2), 26.5 (CH_2), 28.7 (CH_2), 36.9 (CH_2), 43.6 (2x*C*H$_2$CH=), 44.1 (CH_2), 45.5 (C-1), 47.5 (C-6), 59.1 (C-9a), 73.5 (C-4), 118.3 (2xCH=*C*H$_2$), 134.0 (2x *C*H=CH$_2$); MS-EI *m*/*z* 224 (34), 110 (3), 85 (6), 84 (100), 69 (5), 56 (6), 55 (6); HRMS calcd for $C_{14}H_{32}NO$ $[M+H_2O]^+$ 266.2478; found, 266.2478.

(1*S*,4*R*,9a*S*)-1-Ethyl-4-(2-methylallyl)quinolizidine, (7).

Following the general procedure, from lactam **6** (50 mg, 0.28 mmol), $CeCl_3$ (140 mg, 0.55 mmol), 2-methylallylmagnesium chloride (3 mL, 2.20 mmol, 0.7 M solution in THF), THF (1.5 mL), and $NaBH_4$ (14 mg, 0.35 mmol), a 96:4 diastereomeric mixture of **7** and 4-*epi*-**7** (GC-MS) was obtained. Pure **7** (34 mg, 56%) was obtained after column chromatography (Al_2O_3, hexane-EtOAc 90:10 to 75:25). **7**. IR (NaCl) 2956, 2926, 2855, 1734, 1460, 1377 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 0.87 (t, 3H, *J* = 7.4 Hz, CH$_2$C*H*$_3$), 1.10-1.70 (m, 12H, C*H*$_2$CH$_3$, H-1, H-2, H-3, H-7, H-8, H-9), 1.73 (s, 3H, CC*H*$_3$), 1.81-1.90 (m, 2H, H-7, C*H*$_2$C), 2.52 (dd, 1H, *J* = 13.0, 3.7 Hz, C*H*$_2$C), 2.69 (td, 1H, *J* = 13.6, 2.6 Hz, H-6$_{ax.}$), 2.94 (app d, 1H, *J* = 12.7 Hz, H-9a), 3.03 (m, 1H, H-4), 3.32 (app d, *J* = 13.6 Hz, H-6$_{eq.}$), 4.71 (br s, 1H, =C*H*$_2$), 4.77 (br s, 1H, =C*H*$_2$); ^{13}C NMR (100.6 MHz) δ 11.9 (CH$_2$*C*H$_3$), 19.7 (CH_2), 22.7 (C*C*H$_3$), 24.8 (CH_2), 25.4 (CH_2), 25.6 (C-7), 29.7 (CH_2), 30.3 (CH_2), 40.7 (*C*H$_2$C), 41.8 (C-1), 49.7 (C-4), 50.3 (C-6), 61.1 (C-9a), 112.5 (=*C*H$_2$), 143.7 (CH$_2$*C*); MS-EI *m*/*z* 220 (1), 167 (13), 166 (100), 110 (10), 55 (3); HRMS calcd for $C_{15}H_{27}N$ $[M+H]^+$, 222.2216; found, 222.2219. 4-*epi*-**7**: MS-EI *m*/*z* 221 (13), 220 (12), 206 (10), 192 (18), 167 (12), 166 (100), 164 (16), 136 (11), 110 (14), 84 (35), 83 (11), 82 (15), 67 (10), 55 (10).

(1*S*,4*S*,9a*S*)-1-Ethyl-4-propylquinolizidine, (8).

Following the general procedure, from lactam **6** (90 mg, 0.50 mmol), $CeCl_3$ (250 mg, 1.0 mmol), propylmagnesium bromide (1.0 mL, 2.0 mmol, 2.0 M solution in Et_2O), THF (2.5 mL) and $NaBH_4$ (25 mg, 0.63 mmol), a 99:1 diastereomeric mixture of **8** and 4-*epi*-**8** (GC-MS) was obtained. Pure amine **8** (67 mg, 64%) was isolated after column chromatography (Al_2O_3, hexane-EtOAc 95:5 to 80:20). **8**. IR (NaCl) 2958, 2928, 2858, 1461, 1276 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$, COSY, HSQC) δ 0.86 (t, 3H, *J* = 7.4 Hz, C*H*$_3$CH$_2$), 0.91 (t, 3H, *J* = 7.1 Hz, C*H*$_3$CH$_2$CH$_2$C4), 1.10-1.30 (m, 10H), 1.36-1.75 (m, 6H), 1.87 (app d, 1H, *J* = 14.6, H-7), 2.66 (td, 1H, *J* = 13.5, 2.7, H-6$_{ax.}$), 2.88 (m, 1H, H-4), 2.93 (app d, 1H, *J* = 14.1, H-9a), 3.30 (app d, 1H, *J* = 13.5, H-6$_{eq.}$); ^{13}C NMR (100.6 MHz) δ 11.8 (CH$_2$*C*H$_3$), 14.7 (CH$_2$CH$_2$*C*H$_3$), 18.5 (CH_2), 18.5 (CH_2), 19.3 (CH_2), 25.3 (CH_2), 25.8 (C-7), 25.9 (CH_2), 29.7 (CH_2), 31.3 (CH_2), 34.6 (CH_2), 42.0 (C-1), 50.0 (C-6), 50.8 (C-4), 61.1 (C-9a); MS-EI *m*/*z* 209 M^+ (2), 167 (13), 166 (100), 110 (7), 84 (4); $[\alpha]^{22}_D$ = +22.2 (*c* 1.0, $CHCl_3$); HRMS calcd for $C_{14}H_{27}N$ $[M+H]^+$ 210.2216; found, 210.2218. 4-*epi*-**8**. MS-EI *m*/*z* 209 (2), 167 (21), 166 (100), 138 (6), 110 (12), 84 (5), 55 (6).

(1*S*,4*S*,9a*S*)-1-Ethyl-4-methylquinolizidine, (9).

Following the general procedure, from lactam **6** (90 mg, 0.50 mmol), $CeCl_3$ (250 mg, 1.0 mmol), methylmagnesium bromide (0.7 mL, 2.0 mmol, 3.0 M solution in Et_2O), THF (2.5 mL) and $NaBH_4$ (25 mg, 0.63 mmol), only one diastereomer (**9**) was detected by GC-MS. Pure **9** (62 mg, 69%) was obtained after filtration thought a pad of Al_2O_3 (hexane-EtOAc 95:5). IR (NaCl) 2958, 2935, 2877, 1665, 1463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, COSY, HSQC) δ 0.82 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$), 1.02 (d, *J* = 6.2 Hz, 3H, C*H*$_3$C4), 1.07 – 1.31 (m, 6H, CH$_3$C*H*$_2$, H-3, H-8, H-9), 1.36-1.66 (m, 6H, H-1, H-2, H-7, H-8, H-9), 1.83 (app d, *J* = 12.7 Hz, 1H, H-7), 2.67 (td, *J* = 13.7, 2.7 Hz, 1H, H-6$_{ax.}$), 2.92 (app d, *J* = 12.6 Hz, 1H, H-9a), 2.98 (m, 1H, H-4), 3.27 (app d, *J* = 13.7 Hz, 1H, H-6$_{eq.}$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.7 (CH$_2$*C*H$_3$), 17.8 (CH_2), 18.8 (CH_2), 19.3 (*C*H$_3$C4), 25.2 (CH_2), 25.4 (CH_2), 25.8 (CH_2), 34.8 (CH_2), 41.8 (C-1), 46.7 (C-4), 50.1 (C-6), 60.8 (C-9a); MS-EI *m*/*z* 181 M^+ (10), 167 (13), 166 (100), 152 (13), 110 (11), 83 (17); $[\alpha]^{22}_D$ = –23.8 (c 1.0, $CHCl_3$); HRMS calcd for $C_{12}H_{24}N$ $[M+H]^+$ 182.1903; found, 182.1907.

(1*S*,4*R*,9a*R*)-4-Allyl-1-ethylquinolizidine, (10) and (1*S*,4*S*,9a*R*)-4-allyl-1-ethylquinolizidine, (9a-*epi*-**207I**).

Following the general procedure, from lactam 9a-*epi*-**6** (124 mg, 0.6840 mmol), $CeCl_3$ (340 mg, 1.37 mmol), allylmagnesium bromide (2.75 mL, 2.75 mmol, 1.0 M solution in Et_2O), THF (3.0 mL) and $NaBH_4$ (33 mg, 0.86 mmol), a 1:1 diastereomeric mixture

of **10** and 9a-*epi*-**207I** (GC-MS) was obtained (75 mg, 54%). Compound 9a-*epi*-**207I** was isolated by column chromatography (Al_2O_3, hexane-EtOAc 95:5). **10**:[5] MS-EI *m*/*z* 206 (1), 167 (42), 166 (100), 110 (54), 84 (20), 67 (23), 55 (42), 54 (20). 9a-*epi*-**207I**. IR (neat) 2958, 2928, 2856, 1450, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS, NOE, COSY, HSQC) δ = 0.86 (t, 3H, *J* = 7.3 Hz, CH_2), 1.13-1.74 (m, 13H, C*H*$_2$CH$_3$, H-1, H-2, H-3, H-7, H-8, H-9), 2.04 (td, 1H, *J* = 9.6, 3.0 Hz, 1H, H-9a), 2.17 (m, 1H, C*H*$_2$CH=), 2.42 (m, 1H, C*H*$_2$CH=), 2.50 (td, 1H, *J* = 11.3, 3.7 Hz, H-6$_{ax.}$), 2.66 (m, app dt, 1H, *J* = 11.3, 4.4 Hz, H-6$_{eq.}$), 2.81 (m, 1H, H-4), 4.97-5.06 (m, 2H, CH=C*H*$_2$), 5.71 (dddd, *J* = 17.0, 10.1, 8.4, 6.1 Hz, 1H, CH$_2$C*H*=); ^{13}C NMR (100.6 MHz) δ 10.8 (CH$_2$*C*H$_3$), 23.4 (CH_2), 24.9 (CH_2), 25.0 (CH_2), 26.1 (C-7), 27.3 (CH_2), 27.4 (*C*H$_2$CH=), 31.1 (CH_2), 43.2 (C-1), 52.9 (C-6), 58.4 (C-4), 59.8 (C-9a), 115.8 (=*C*H$_2$), 137.5 (-CH$_2$*C*H=); $[\alpha]^{22}_D$ = +57.5 (c 0.75, $CHCl_3$); MS-EI *m*/*z* 206 M (1), 167 (27), 166 (100), 110 (55), 84 (17), 67 (21), 55 (37), 54 (20). HRMS calcd for $C_{14}H_{26}N$ $[M+H]^+$, 208.2060; found, 208.2058.

(1*S*,4*S*,9a*R*)-1-Ethyl-4-methylquinolizidine, (11) and (1*S*,4*R*,9a*R*)-1-ethyl-4-methylquinolizidine, (4-*epi*-**11**).

Following the general procedure, from lactam 9a-*epi*-**6** (90 mg, 0.50 mmol), $CeCl_3$ (250 mg, 1.0 mmol), methylmagnesium bromide (0.70 mL, 2.0 mmol, 3.0 M solution in Et_2O), THF (3.0 mL) and $NaBH_4$ (25 mg, 0.63 mmol), a 1:1 diastereomeric mixture of **11** and 4-*epi*-**11** (GC-MS) was obtained (46 mg, 48%). The amines proved to be unstable under chromatography conditions. **11***. MS-EI: *m*/*z* 181 M^+ (34), 180 (29), 166 (100), 152 (46), 138 (35), 124 (47), 110 (48), 96 (49), 83 (90), 67 (30), 55 (74). C4-*epi*-**11***. MS-EI *m*/*z* 181 M^+ (29), 180 (30), 166 (100), 152 (47), 138 (37), 124 (46), 110 (42), 96 (50), 83 (88), 67 (32), 55 (78). Dimethylated product was detected in the GC-MS MS-EI *m*/*z* 195 M (17), 181 (16), 180 (100), 124 (20), 110 (20), 84 (43), 83 (43), 82 (21), 56 (23), 55 (37).

Theoretical calculations.

Initial geometries were obtained using the PCMODEL program.[23] Further geometry optimizations were carried out using the Gaussian 03 suite of programs on an Compaq HPC320 computer,[24] at the Hartree-Fock (HF) level,[25] and at the Becke's three-parameter hybrid functional with the Lee, Yang and Parr correlation functional (B3LYP) level,[26] using the 6-31G(d) basis set.[27] Analytical energy second derivatives were calculated at all optimized structures to confirm that these were minima.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Additional experimental information. Copies of ^1H and ^{13}C NMR spectra of new products. Cartesian coordinates and total energies for compounds **9**, 4-*epi*-**9** and iminium salts **A** and **B**. CCDC reference number 861638. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

1 a) J. W. Daly and T. F. Spande, in *Alkaloids: Chemical and Biological Perspectives*; S. W. Pelletier, Ed.; Wiley: New York, 1986; Vol. 4, pp 1-274. b) J. W. Daly, H. M. Garraffo and R. F. Spande. In The Alkaloids, G. A. Cordell, Ed.; Academic Press: San Diego, 1993; Vol. 43, pp 185-288. c) J. Daly, in *The Alkaloids*, G. A. Cordell, Ed.; Academic Press: New York 1997; Vol. 50. For a review on the indolizidine and quinolizidine alkaloids, see: d) J. P. Michael, *Nat. Prod. Rep*., 2008, **25**, 139-165, and other reviews in these series.

2 1,4-Disubstituted quinolizidines occur in the dendrobatid frogs of the genera *Dendrobates*, *Minyobates*, and *Epipedobates* (ref. 1b); in Martelline frogs of genus *Mantella*, H. M. Garrafo, J. Caceres, J. W. Daly, T. F. Spande, N. R. Andriamahavaravo and M. Andriantsiferana, *J. Nat. Prod*., 1993, **56**, 1016-1038, and in bufonid toads of the genus *Melanophryniscus*, H. M. Garraffo, T. F. Spande, J. W. Daly, F. Baldessari and E. G. Gros, *J. Nat. Prod*., 1993, **56**, 357-373. For the racemic synthesis of 1,4-disubstituted quinolizidines found in poison frog skins, see: P. Michel, A. Rassat, J. W. Daly and T. F. Spande, *J. Org. Chem.,* 2000, **65**, 8908-8918.

3 H. M. Garraffo, L. D. Simon, J. W. Daly, T. F. Spande and T. H. Jones, *Tetrahedron*, 1994, **50**, 11329-11338.

4 J. W. Daly, T. F. Spande and H. M. Garraffo, *J. Nat. Prod*., 2005, **68**, 1556-1575.

5 a) N. Toyooka, K. Tanaka, T. Momose, J. W. Daly and H. M. Garraffo, *Tetrahedron*, 1997, **53**, 9553-9574. b) For the racemic synthesis of alkaloid **207I**, see: P. Michel and A. Rassat, *Chem. Commun*., 1999, 2281-2282.

6 N. Toyooka and H. Nemoto, *Tetrahedron Lett*., 2003, **44**, 569-570.

7 N. Toyooka, S. Kobayashi, D. Zhou, H. Tsuneki, T. Wada, H. Sakai, H. Nemoto, T. Sasaoka, H. M. Garraffo, T. F. Spande and J. W. Daly, *Bioorg. Med. Chem. Lett*., 2007, **17**, 5872-5875.

8 H. Tsuneki, Y. You, N. Toyooka, S. Kagawa, S. Kobayashi, T. Sasaoka, H. Nemoto, I. Kimura and J. A. Dani, *Mol. Pharmacol*., 2004, **66**, 1061-1069.

9 a) T. C. Coombs, M. D. Lee, IV, H. Wong, M. Armstrong, B. Cheng, W. Chen, A. F. Moretto and L. S. Liebeskind, *J. Org. Chem*., 2008, **73**, 882-888. b) H. Wong, E. C. Garnier-Amblard and L. S. Liebeskind, *J. Am. Chem. Soc*., 2011, **133**, 7517–7527.

10 M. Amat, C. Escolano, A. Gómez-Esqué, O. Lozano, N. Llor, R. Griera, E. Molins and J. Bosch, *Tetrahedron: Asymmetry*, 2006, **17**, 1581-1588.

11 M. Amat, N. Llor, J. Hidalgo and J. Bosch, *Tetrahedron: Asymmetry*, 1997, **8**, 2237-2240.

12 V. Semak, C. Escolano, C. Arróniz, J. Bosch and M. Amat, *Tetrehedron: Asymmetry*, 2010, **21**, 2542-2549.

13 For some representative examples in the formation of the second ring of the quinolizidine skeleton by RCM, see: a) N. Diedrichs and B. Westermann, *Synlett*, 1999, **7**, 1127-1129. b) C. A. Tarling, A. B. Holmes, R. E. Markwell and N. D. Pearson, *J. Chem. Soc., Perkin Trans 1*, 1999, 1695-1701. c) S. S. Kinderman, R. Gelder, J. H. Van Maarseveen, H. E. Schoemaker, H. Hiemstra and F. P. J. T. Rutjes, *J. Am. Chem. Soc*., 2004, **126**, 4100-4101. d) M. Katoh, H. Mizutani and T. Honda, *Tetrahedron Lett*., 2005, **46**, 5161-5163. e) T. L. Suyama and W. H. Gerwick, *Org. Lett*., 2006, **8**, 4541-4543. f) G. Cheng, X. Wang, D. Su, H. Liu, F. Liu and Y. Hu, *J. Org. Chem*., 2010, **75**, 1911-

1916. g) For a review on the RCM as key reaction to access to piperidine alkaloids, see: F.-X. Felpin and J. Lebreton, *Eur. J. Org. Chem*., 2003, **68**, 3693-3712.
14 For some representative examples in the addition of organometal reagents to the 2-quinolizidinone nucleus, see: a) D. L. Comins, X. Zheng and R. R. Goehring, *Org. Lett*., 2002, **4**, 1611-1613. b) V. Gracias, Y. Zeng, P. Desai and J. Aube, *Org. Lett.*, 2003, **5**, 4999-5001. c) B. B. Snider and J. G. Grabowski, *J. Org. Chem*., 2007, **72**, 1039-1042. d) See ref. 13f. e) S.-S. P. Chou, Y.-Ch. Chung, P.-A. Chen, S.-L. Chiang and Ch.-J. Wu, *J. Org. Chem*., 2011, **76**, 692-695.
15 A single report on the addition of allyl Grignard derivatives to an *N*-methyl protected δ-valerolactam, furnishing 2,2-disubstituted piperidine and 2-substituted piperideine derivatives, was found: Lukeš, R and Černý, M. *Collect. Czech. Chem. Commun.*, 1959, **24**, 3596-3600.
16 Noteworthy, larger excess of the Grignard reagent led to considerable amounts of the diallylated derivative.
17 All ratios were determined by GC-MS chromatography.
18 T. A. Crabb, R. F. Newton, and D. Jackson, *Chem. Rev.*, 1971, **71**, 109-126. For comments on mass spectrometry and IR Bohlmann bands of new compounds, see supporting information.
19 For comments on NOE experiments of compound 9-*epi*-**207I**, see supporting information.
20 a) Deslongchamps, P. In Stereoelectronic Effects in Organic Chemistry; Pergamon Press: Oxford, UK, 1983; Chapter 4, pp. 101-162; b) Stevens, R. V. *Acc. Chem. Res*., 1984, **17**, 289-296 and references therein.
21 a) V. Dimitrov, K. Kostova, and M. Genov, *Tetrahedron Lett*., 1996, **37**, 6787-6790. b) D. A. Conlon, D. Kumke, Ch. Moeder, M. Hardiman, G. Hutson, and L. Sailer, *Adv. Synth. Catal*., 2004, **346**, 1307 –1315
22 Purification protocol inspired by a) W. Wysocka and A. K. Przybyl, *The Science of Legumes*, 1994, **1**, 37-50; b) T. Aniszewski, In *Alkaloids Secrets of Life*; Elsevier, Amsterdam, 2007, pp 235.
23 PCMODEL, Version 8.00.1 for Windows, Serena Software.
24 Theoretical calculations were carried out using Gaussian 03, Revision B.01. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E.; Scuseria, M. A. Robb, J. R. Cheeseman, Jr., J. A. Montgomery, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh PA, 2003.
25 P. Echenique and J. L. Alonso, *Mol. Phys*., 2007, **105**, 3057-3098.
26 (*a*) A. D. Becke, *J. Chem. Phys*., 1993, **98**, 5648-5652; (*b*) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785-789.
27 P. A. Hariharan and J. A. Pople, *Theor. Chim. Acta*, 1973, **28**, 213-222.

