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N-Arylmethyl-7-azabicyclo[2.2.1]heptane derivatives: synthesis and reaction mechanisms

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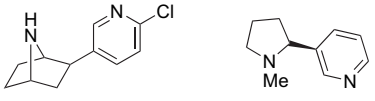
ABSTRACT

N-Arylmethyl-7-azabicyclo[2.2.1]heptane (**I**) derivatives have been synthesized by deprotection of *N*-protected, *N*-(arylmethyl)cyclohex-3-enamines, bromination of the resulting secondary cyclohex-3-enamines, followed by base-promoted cyclization (route a), or by bromination of *N*-protected, *N*-(arylmethyl)cyclohex-3-enamines followed by deprotection and base-mediated cyclization (route b). In these protocols we have observed that the bromination of the key intermediates (**12**, **13**, and **19**) is stereoselective leading to major *trans*-3-*cis*-4-dibromides (**14**, **17**, and **20**), whose mild base-mediated heterocyclization (on compound **14**), or the two-step acid hydrolysis plus base-promoted cyclization (on compounds **17** and **20**), gave products **6** and **7** in good yield. A mechanistic investigation using DFT has been carried out to explain the results observed in this work.

1. Introduction

Epibatidine (**1**)[1] (Fig. 1), an alkaloid isolated from the skin of the Ecuadorian poison frog *Epipedobates tricolor*,[2] is a powerful analgesic agent 200 times more potent than morphine, with high affinity for the nicotinic acetylcholine receptor (nAChR).[3] Epibatidine strongly binds at α4β2 subtype nAChRs, showing a K_i value about two orders of magnitude lower than nicotine (**2**)[2] (Fig. 1). However, the toxic effects associated with its low subtype selectivity have hampered its clinical application.[4]



Epibatidine (**1**) Nicotine (**2**)

Figure 1. Structure of epibatidine (**1**) and nicotine (**2**).

In the last years a number of methodologies have been reported for the total synthesis of epibatidine and 7-azabicyclo[2.2.1]heptane derivatives.[5a] In the search for epibatidine-type compounds devoid of secondary effects, a number of structure–activity relationship studies have been reported. Thus, a great attention has been paid to the synthesis and biological evaluation of epibatidine analogues,[5b] either heterocyclic[6] or conformationally constrained.[7]

In this context, Trudell and co-workers reported the synthesis and biological evaluation of a series of *N*-arylalkyl- and *N*-aryl-7-azabicyclo[2.2.1]heptanes,[8] among which, two new nAChR agonists (**3** and **4**; Fig. 2) have been identified. In the in vitro [^{3}H]cytisine binding assay, *N*-(3-pyridylmethyl)-7-azabicyclo[2.2.1]heptane (**4**) showed a potent affinity (K_i=98 nM), and both compounds (**3** and **4**) were found to elicit moderately potent nicotinic agonist activity in α4β2 subtype nACRs; in addition, and like epibatidine, these compounds produced dose-dependent analgesic activity in the tail-flick and hotplate tests. Conversely, compounds belonging to the *N*-aryl-7-azabicyclo[2.2.1]heptane family showed low binding affinities, probably due to the reduced basicity of the bridging nitrogen atom of the 7-azabicyclo[2.2.1]heptane moiety.[8] Consequently, compounds bearing the *N*-arylalkyl-7-azabicyclo[2.2.1]heptane and the *N*-aryl-7-azabicyclo[2.2.1]heptane skeleton are of interest, and have been synthesized by N-alkylation of 7-azabicyclo[2.2.1]heptane (**5**) with arylalkyl halides,[8] and by palladium-bisimidazol-2-ylidene complex catalyzed amination reactions on halogenated heteroaryl derivatives, respectively.[9] The synthesis of precursor **5** (Fig. 2) has been described several times.[10]

On the other hand, the synthesis of conformationally constrained epibatidine analogues has been approached by intramolecular reductive Heck reaction,[6b,7a] intramolecular S_N2

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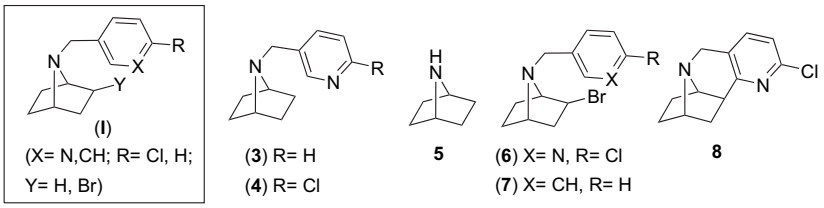
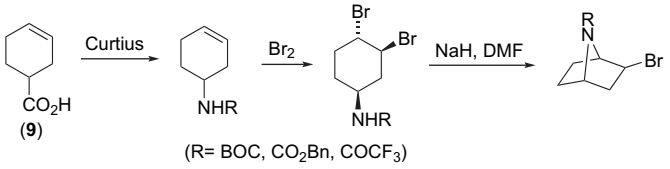


Figure 2. Structure of the target molecules (**I**), the reference products (**3**, **4**, **6**–**8**), and compound (**5**).

reactions,[7b] or by intramolecular 5-*exo* or 6-*endo* free radical cyclizations from suitable 7-azanorbornene precursors.[7c]

We have recently described the synthesis of 7-substituted *exo*-2-bromo-7-azabicyclo[2.2.1]heptane derivatives[11,12] following a potent method based on a four-step synthetic sequence, starting from readily available cyclohex-3-enecarboxylic acid (**9**), Curtius reaction, stereoselective bromination leading to major 7-*trans*-butyl (benzyl) 7-(*cis*-3,*trans*-4-dibromocyclohex-1-yl)carbamates (or 2,2,2-trifluoroacetamides), followed by NaH-mediated intramolecular cyclization (Scheme 1).[12,13]



Scheme 1.

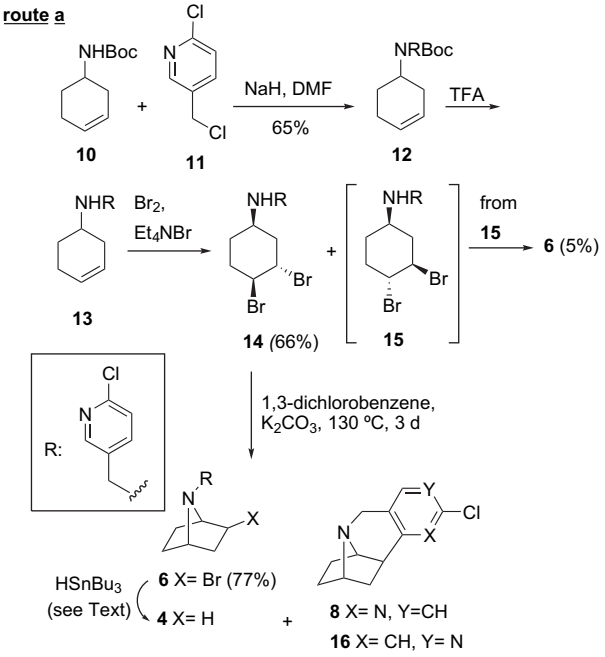
Our current interest in the synthesis and biological evaluation of new epibatidine analogues,[14] prompted us to apply this strategy to prepare epibatidine analogues of type **I** (*N*-arylmethyl-7-azabicyclo[2.2.1]heptanes) (Fig. 2). Here we are reporting the synthesis of *N*-arylmethyl-7-azabicyclo[2.2.1]heptanes **4**, **6**–**8** (Fig. 2). In addition, we include DFT-based studies aimed at explaining the observed stereoselectivities during the bromination reactions, as well as the mechanism of the heterocyclization.

2. Results and discussion

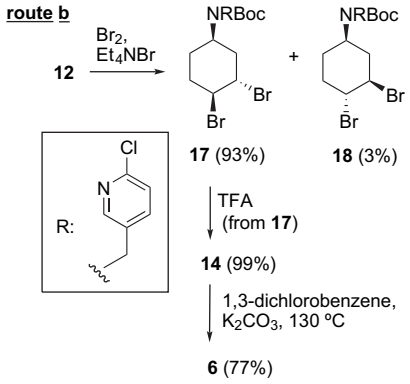
2.1. Synthesis and reactivity

According to our plan, we selected the Boc-carbamate **10**,[12,13] and submitted it to N-alkylation with 2-chloro-5-(chloromethyl)pyridine (**11**) to give carbamate **12** in 65% yield (Scheme 2). At this point two routes have been investigated in order to obtain compound **6** (Fig. 2): (route a) Boc-deprotection on carbamate **12**, followed by bromination and ring closure (Scheme 2), and (route b) bromination of compound **12** followed by Boc-deprotection and heterocyclization (Scheme 3).

Accordingly, and following route a, the reaction of compound **12** with trifluoroacetic acid followed by treatment of the crude [(6-chloropyridin-3-yl)methyl]cyclohex-3-enamine (**13**), without isolation, with bromine, under the usual conditions,[13] gave (*trans*-3,*cis*-4)-dibromo-*N*-[(6-chloropyridin-3-yl)methyl]cyclohexanamine (**14**) (66% yield in two steps), and (*cis*-3,*trans*-4)-dibromo-*N*-[(6-chloropyridin-3-yl)methyl]cyclohexanamine (**15**), not detected, that most probably cyclized in situ once formed to give derivative **6** in 5% yield (Scheme 2). In these mild bromination reaction conditions, the alternative partial rearrangement of the major dibrominated intermediate **14** to give compound **6** (see below) can be excluded. Very interestingly, compound **6** was isolated in 77% yield by cyclization of (*trans*-3,*cis*-4)-dibromocyclohexylamine **14** upon reaction with potassium carbonate in 1,3-dichlorobenzene for 3 days at 130 °C. In view of the 1,4-*cis* arrangement between the nucleophile and the leaving group in



Scheme 2.



Scheme 3.

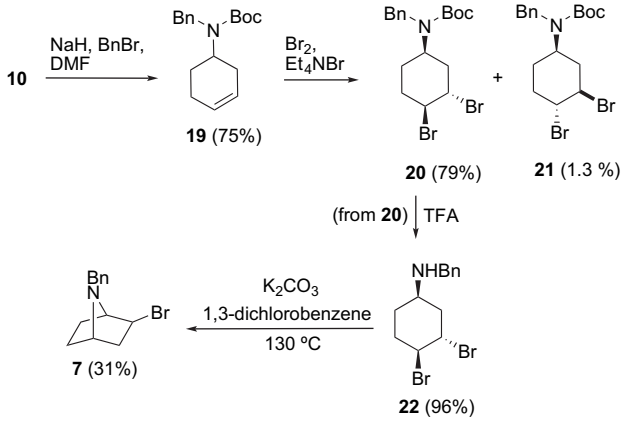
compound **14** during the intramolecular S_N2 reaction leading to compound **6**, this result was fortunate for our purposes, but surprising. However, this reactivity has precedent in the work of Kapferer and Vasella, who have shown that the base-catalyzed cyclization of *trans*-3,*cis*-4-dibromocyclohexan-1-amine is possible, yielding 2-bromo-7-*tert*-butoxy(carbonyl)-7-azabicyclo[2.2.1]heptane, upon N-carbonylation, in 62% yield.[13] The authors suggested that under the forcing experimental conditions (K_2CO_3, 1,3-dichlorobenzene, 130 °C) the diaxial dibromide rearranged to the diequatorial, which cyclized to the azanorbornane derivative.[13]

Finally, treatment of bromide **6** with tributyltin hydride (*slow addition*) gave a complex reaction mixture. In the GC/MS analysis of the reaction crude we detected unreacted starting material **6** and three new compounds (**4**/**8**/**16**[15]) (Scheme 2) in a 3:31:5 ratio. After chromatography we were only able to isolate and characterize an inseparable mixture of **4** and **8** in a 1:5.6 ratio (GC/MS). Alternatively, *the fast addition of HSnBu$_3$*, under otherwise identical reaction conditions, gave a mixture of compounds **4** and **8**, in a 1:1 ratio, as determined by GC/MS, and pure 7-[(6-chloropyridin-3-yl)methyl]-7-azabicyclo[2.2.1]heptane (**4**) (37%). Product **4** was known and showed spectroscopic data in good agreement with those reported in the literature.[8] The fact that the fast addition provided higher yields and less side products was an unexpected result but we have found no explanation for such outcome.

In conclusion, compounds **4** and **6** were obtained from carbamate **10** in four steps in 19%, and in three steps in 51% overall yield, respectively. In this sequence we observed that the bromination of *N*-[(6-chloropyridin-3-yl)methyl]cyclohex-3-enamine (**13**) gave mainly (*trans*-3,*cis*-4)-dibromo-*N*-[(6-chloropyridin-3-yl)methyl]-cyclohexanamine (**14**), whose base-mediated cyclization cleanly occurred to give e*xo*-2-bromo-7-[(6-chloropyridin-3-yl)methyl]-7-azabicyclo[2.2.1]heptane (**6**) in good yield.

Next we tested route b in order to improve the process. Bromination of carbamate **12** gave major 1,4-*cis*-dibromide **17** (93%), accompanied by minor 1,4-*trans*-dibromo **18** (3%) derivative. Acid hydrolysis of compound **17** quantitatively provided dibromide **14**, which smoothly cyclized to afford compound **6**, in three steps, in a 71% overall yield from carbamate **12** (Scheme 3). Thus, not only the yield was higher than in route a (Scheme 2), but the bromination reaction still afforded major *cis*-1,4-isomer **17**.

Thus, route b was used in further developments on this chemistry, and successfully applied for the synthesis of compound **7** (Fig. 2), bearing a *N*-benzyl moiety. Thus, starting from carbamate **10** NaH-mediated alkylation with benzyl bromide gave compound **19** in 75% yield,[16] whose bromination gave a mixture of dibromides **20** and **21**, where 1,4-*cis*-dibromide **20** prevailed (79% yield) (Scheme 4). Next, acid hydrolysis, to give amine **22**, followed by base-mediated cyclization, provided compound **7** in 30% yield (Scheme 4).



Scheme 4.

In conclusion, the bromination of compound **19** gave a mixture of dibromides **20** and **21**, where major 1,4-*cis*-dibromide **20** prevailed. We must conclude that this seems to be a general reactivity trend, as the bromination of related carbamate **23** afforded only *tert*-butyl allyl[(*trans*-3,*cis*-4)-dibromocyclohexyl]carbamate (**24**), easily transformed into secondary amine **25**[16,17] (Scheme 5) as usual (see Supplementary data).

In this context, it is interesting to note that related precursors substituted with a phenyl or aryl group at C2 give different stereochemical outcome depending on the *N*-protecting group, providing major 1,4-*cis*[18,19] and 1,4-*trans*-dibromides,[20–22] from amine and amide precursors, respectively. The reaction of *N*-methylcyclohex-3-enamine with chlorine gives a 1:1 mixture of the two *trans*-3,4-dichlorides,[23] and the bromination of carbamate **10** affords major 1,4-*trans*-dibromides.[12,13]

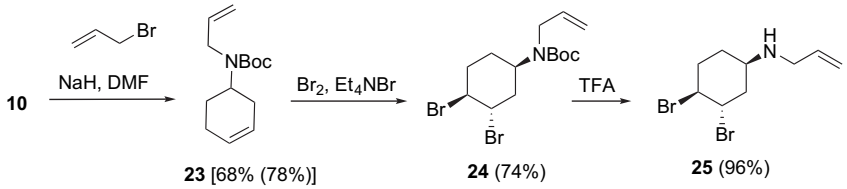
2.2. Computational chemistry: reaction mechanisms

To account for these experimental observations and get insights into the reaction pathways, we have carried a series of DFT calculations. We have first examined the mechanism of the bromination reaction. The results are used to discuss the factors that modulate the observed stereochemical outcome favoring the formation of major 1,4-*cis*-dibromides (Schemes 2–4). Next, a study on the mechanism of the base-mediated heterocyclization of 1,4-*cis*-dibromides is presented.

2.2.1. Computational analysis of the mechanism of the bromination reactions. We have established that major 1,4-*cis*-dibromides (**14**, **17**, and **20**, Schemes 2–4) are obtained in the bromination reactions of the corresponding cyclohex-3-enamine derivatives **12**, **13**, and **19**, respectively, by using Br$_2$/Et$_4$NBr as brominating system. As detailed above, under the same experimental conditions, related precursors substituted with a phenyl or aryl group at C2 give different stereochemical outcome depending on the *N*-group, providing major 1,4-*cis*[18,19] and 1,4-*trans*-dibromides,[20–22] from amine and amide precursors, respectively. Furthermore, the bromination of a Boc-carbamate (NHBoc) or trifluoroacetamide (NHCOCF$_3$) affords major 1,4-*trans*-dibromides.[12,13]

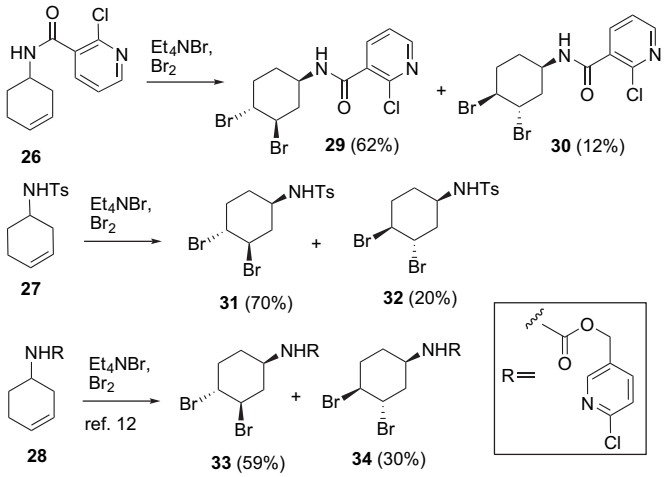
According to these results, the stereoselectivity of the bromination would be dependent on the nature of the *N*-protecting group: 1,4-*trans*-dibromides (i.e., 3*R*,4*S*-dibromides) are predominantly formed from amide and carbamate precursors [–NHCO(O)], while 1,4-*cis*-dibromides (i.e, 3*S*,4*R*-dibromides) result from other precursors, bearing bulky *N*-protecting groups (benzyl arylmethyl), and lacking acidic proton. As proposed by Vasella and Kapferer,[13] this stereoselectivity points to a key role of the –NHR moiety, which may act as hydrogen-bond donor and promote the nucleophilic attack by anchimeric assistance. This assistance between the brominating agent and the –NHR moiety can be envisioned to proceed by different modes:[13] (i) through the formation of H-bond with the nucleophilic Br^-;[24] (ii) H-bond with the Br_3^- formed;[25] (iii) H-bond with the leaving Br^-.[26] These hypotheses have been explored by computational methods in order to formulate a consistent reaction mechanism.

In addition, it should be expected that the effective formation of an H-bond, related with the pK_a value, would induce an efficient



Scheme 5.

bromination reaction. Hence, the estimation of theoretical descriptors related with the pK_a should provide insights into the strength of the H-bond, and thus, into the anchimeric assistance capability. Among others, the NPA charge has been shown to be an effective descriptor for the determination of pK_a.[27] The more positive the NPA charge on the proton atom, the more acidic (i.e., lower pK_a) the compound is, and as a result, the higher the tendency to bind one of the above-mentioned Br-species and promote the reaction. To cover a wide pK_a range, we have also considered the bromination of cyclohexenes **12** (Scheme 2), **13** (Scheme 2), **19** (Scheme 4), **26**,[28] **27**,[28] and **28**[12] (Scheme 6).

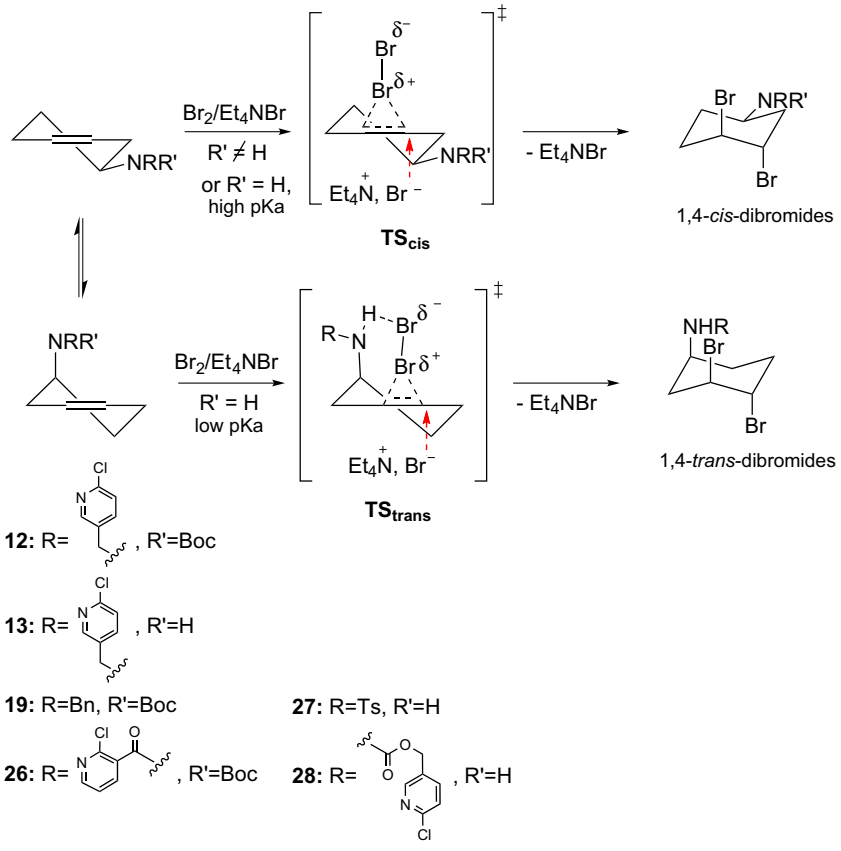


Scheme 6.

The calculations have shown that the H-bond inhibits the bromination when it engages the nucleophilic Br^- [mode (i)]: the Br–H electrostatic interaction stabilizes the bromide as anionic entity, consequently interfering with the nucleophilic addition. Similarly, the H-bond with Br_3^- [mode (ii)] promotes the Br_2 release, which then forms a stable π-complex with the alkene, rather than adding to the unsaturated moiety. Regarding both situations (i) and (ii) all our efforts to locate the pertinent transition structure, with or without explicit consideration of NEt_4^+ group, were unsuccessful, and instead π-complexes were found. So, after discarding modes (i) and (ii), we have effectively located an H-bonded transition structure driving concertedly to the dibromide product following mode (iii), i.e., formation of H-bond with the leaving Br^-. The ionization of the initially formed 1:1 alkene–Br_2 π-complex to a bromocarbenium bromide ion pair by formation of an H-bond with the leaving Br^-, assists an easier Br–Br bond breaking, which indeed promotes the rate-limiting Br^- backside nucleophilic attack on the π-complex.[26a,29]

According to the proposed model, the stereoselectivity can be rationalized as depicted in Scheme 7. For precursors lacking acidic proton, such as compounds **12** or **19**, the reaction would likely take place through diaxial bromination of the preferred pseudoequatorial conformer, lower in energy than the pseudoaxial conformer due to the steric hindrance, to yield preferentially the 1,4-*cis*-dibromides according to the Fürst–Plattner rule. On other hand, the presence of the –NHR fragment favors the pseudoaxial disposition by H-bond formation with Br_2 in the π-complex, which induces the Br_2 ionization. This complex would then be trapped by the nucleophilic Br^-, leading to the 1,4-*trans*-dibromide.

A close inspection of the transition structures provides further support for this different behavior. $\mathbf{TS_{trans}}$ for **27** shows a stronger H-bond (i.e., shorter bond) than $\mathbf{TS_{trans}}$ for **13** (2.318 vs 2.481 Å)



Scheme 7.

hence inducing a higher ionization of the Br^1–Br^2 bond, and the transition state is reached at a shorter Br^1–Br^2 bond length (3.567 vs 5.007 Å). The bromonium character is therefore achieved earlier for sulfonamide **27** than for amine **13**, promoting the backside nucleophilic attack, as suggests the larger asynchronicity of the Br–C forming bonds for **27**.

We have taken into account the difference between transition state free-energy for the formation of the 1,4-*cis* and 1,4-*trans*-dibromide adducts in solution ($\Delta\Delta G^{\#}_{(cis-trans)}$), and compared it with the experimental cis/trans ratio (Table 1).

Table 1
Relationship between experimental cis/trans ratio of dibromide products and computed results (NPA charges, energy differences between precursor conformers, and relative activation barriers)

Precursor	–NRR′	cis/trans ratio	NPA charge on H[a]	$\Delta E_{(eq-ax)}$[b] (kcal mol^{-1})	$\Delta\Delta G^{\#}_{(cis-trans)}$[c] (kcal mol^{-1})
13	Secondary amine	66:5	0.4048	−1.04	−1.01
12	Carbamate; R,R′≠H	93:3	—	−2.12	−7.32
19	Carbamate; R,R′≠H	79:1.3	—	−2.36	−7.54
26	Amide; R=H	12:62	0.4411	+0.14	+3.29
27	Sulfonamide; R=H	20:70	0.4392	+0.92	+1.11
28	Carbamate; R=H	30:59	0.4376	−0.22	+1.48

[a] On the pseudoaxial conformer.
[b] Total energy difference between pseudoequatorial and pseudoaxial conformer precursors in solution ($\Delta E_{(eq-ax)}=E_{eq}-E_{ax}$).
[c] Free-energy difference between transition states for the formation of the 1,4-*cis* and 1,4-*trans*-dibromide adducts in solution ($\Delta\Delta G^{\#}_{(cis-trans)}=\Delta G^{\#}_{cis}-\Delta G^{\#}_{trans}$).

The results depicted in Table 1 clearly support the proposed key role of the acidic properties of the amine/amide proton and the conformational equilibrium of the precursor (governed by the bulkiness of the *N*-protecting groups) on the bromination stereoselectivity. Thus, the NPA charges on H plotted against experimental cis/trans ratio indicate a noteworthy linear dependence (R^2=0.997). Also, the conformational energy differences show a correlation with the experimental results (R^2=0.790). Whereas bulky protecting groups clearly favor a pseudoequatorial arrangement, the presence of a single functionality reduces the energy difference in relation to the pseudoaxial conformer.

With these results in hand, the computed energy differences between the stereoisomeric transition structures show the expected trend (Table 1). That is, the presence of only one protecting group and acidic proton reduces the preference for the pseudoequatorial conformer in relation to the pseudoaxial conformer ($\Delta E_{(eq-ax)}$, Table 1), where the formation of H-bond promotes the Br_2 ionization in the π-complex (**26**–**28**), which is then more easily trapped kinetically by the nucleophilic entity to afford major 1,4-*trans*-dibromides ($\Delta\Delta G^{\#}_{(cis-trans)}$>1 kcal mol^{-1}). Otherwise, precursors lacking acidic proton (**13**) or bearing two protecting groups (**12**, **19**) undergo bromination of the favored, less congested, pseudoequatorial conformer ($\Delta E_{(eq-ax)}$=−1 to −2.4 kcal mol^{-1}), yielding major 1,4-*cis*-dibromides ($\Delta\Delta G^{\#}_{(cis-trans)}$<−1 kcal mol^{-1}).

In summary, the stereoselectivity would be governed by the ability of the –NHR group to act as H-donor (pK_a value) and to provide anchimeric assistance, and also by the energy difference between pseudoaxial and pseudoequatorial conformers of the cyclohexene precursor. While these relationships are likely to fail to provide quantitative accuracy, the proposed model should supply reasonable results for qualitative purposes.

2.2.2. Computational analysis for the mechanism for the heterocyclization reaction. The base-mediated cyclization of the 1,4-*cis*-dibromides **14** and **22** to give the ring closure derivatives **6** and **7**, respectively (Schemes 2 and 4), was unexpected in view of the precedent for unsuccessful cyclization of the related 3-*trans*, 4-*cis*-dichloro-*N*-methylcyclohexanamine (3*S*,4*R* stereoisomer).[23] Conversely, Vasella and Kapferer have reported that both isomers, *tert*-butyl 3-*cis*,4-*trans*-dibromocyclohexylcarbamate (3*R*,4*S*-diastereoisomer) and *tert*-butyl 3-*trans*,4-*cis*-dibromocyclohexylcarbamate (3*S*,4*R*-diastereoisomer), can be transformed into a single *tert*-butyl-*exo*-2-bromo-7-azabicyclo[2.2.1]heptane-7-carboxylate, under the same basic conditions used by us.[13] These authors have assumed that at high temperature reaction (130 °C) the diaxial (3*S*,4*R*)-dibromide rearranges to the (3*R*,4*S*)-isomer that cyclizes to the corresponding 7-azanorbornane,[13] which is supported by previous results from our laboratory.[12]

Therefore, it may be supposed that dibromides **14** and **22** might undergo a similar rearrangement, justifying the formation of such reaction products **6** and **7** showing the *exo*-orientation of Br–C2. That is, the high temperature should allow the rearrangement from the 3*S*,4*R*-dibromide to the 3*R*,4*S*-isomer by passing through the cis–trans isomerization transition state. The ensuing cyclization of the 3*R*,4*S*-diastereomer should lead to the azabicyclic adducts **6** and **7**. Alternatively, the direct cyclization from the 3*S*,4*R*-dibromide would drive to the epimers **6′** and **7′**, showing *endo*-orientation of Br–C2. In order to account for the experimental observations, we have carried out a computational analysis.

The isomerization of 1,4-cis to 1,4-trans (that is, 3*S*,4*R*-→3*R*,4*S*-dibromide) proceeds through the transition structure **TS$_{isom}$** where the concerted bond forming/breaking at C3 and C4 takes place in a nearly synchronous mode (Fig. 3). This step involves a rather high free-energy barrier (27.03 kcal mol^{-1}), probably as a result of the steric distortion required to attain the transition state. However, alternative stepwise pathways have not been found.

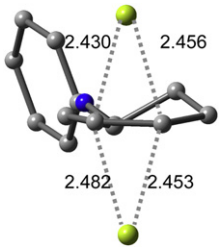


Figure 3. Transition structure for the 1,4-cis→1,4-trans isomerization, **TS$_{isom}$**, for **22**. Distances are shown in angstroms (Å).

The complete mechanistic scheme (isomerization+cyclization) to justify the stereochemistry shows some similarities with a pathway proposed by Fletcher and co-workers to account for the formation of the *exo*-7-benzyl-7-azabicyclo[2.2.1]heptan-2-ol from the *cis*-(*N*-benzylamino)cyclohexane 1,2-epoxide. They suggested[30] that the presence of a nucleophile in the reaction medium might cause initial 1,2-diaxial ring opening of the epoxide (dibromide isomerization), that after transannular displacement of this nucleophile by the amino substituent (1,4-*trans* cyclization) would lead to the azabicycle skeleton and regeneration of the nucleophile.

The calculations have revealed that the base-promoted heterocyclization proceeds through a barrierless proton abstraction by CO_3^{2-} followed by the intramolecular nucleophilic attack of the activated N to the C4 position.[12]

For the *syn*-nucleophilic attack, the free-energy barrier to reach the transition structure, **TS$_{1,4cis}$** (N–C=2.687 Å for **14**, 2.635 Å for **22**), is high and almost the same for both dibromides: 32.51 for **14** and 32.16 kcal mol^{-1} for **22**.

On the other hand, and as expected, the free-energy barrier to reach the transition structure **TS$_{1,4trans}$** (N–C=2.632 Å for **14**, 2.616 Å for **22**) is about 25 kcal mol^{-1}lower (6.68 Å for **14**, 6.53 kcal mol^{-1} for **22**) than that computed for the cyclization from the cis isomer.

In summary, according to these results, the most favorable heterocyclization pathway should lead to **6** and **7** through a mechanism

where the rate-determining step is the 3*S*,4*R*-→3*R*,4*S*-dibromide isomerization. This configurational change, nevertheless, requires a relatively high temperature to succeed. Other steps, such as cyclization or ring conformational interconversion,[31] are kinetically more accessible.

3. Conclusions

To sum up, in this manuscript we have reported two new methods for the synthesis of epibatidine analogues bearing the *N*-aryalkyl and the *N*-aryl-7-azabicyclo[2.2.1]heptane skeleton. Regarding the synthesis of *N*-arylalkyl-7-azabicyclo[2.2.1]heptanes we have explored two synthetic alternatives. Route a is based on the deprotection of *N*-protected, *N*-(arylmethyl)cyclohex-3-enamines, bromination of the resulting secondary cyclohex-3-enamines, followed by base-promoted cyclization, while route b proceeds by bromination of *N*-protected, *N*-(arylmethyl)cyclohex-3-enamines followed by deprotection and by base-mediated cyclization. Overall, the last approach is more efficient, and has been used for the synthesis of *exo*-2-bromo-7-azabicyclo[2.2.1]-heptanes **6** and **7**. In these processes we have observed that the highly stereoselective bromination of precursors **13**, **12**, and **19**, leads to major *trans*-3-*cis*-4-dibromides **14**, **17**, and **20**, whose base-mediated heterocyclization on compound **14**, or the two-step deprotection plus base-promoted cyclization on intermediates **17** and **20**, gave products **6** and **7** in good yield. Consequently, the *trans*-3-*cis*-4-dibromide intermediates **14** and **22** cleanly afforded the *exo*-2-bromo-7-azabicyclo[2.2.1]heptanes **6** and **7**. Compound **4** was obtained by tributyltin hydride reduction of bromide **6**.

Furthermore, mechanistic DFT-based studies have been carried out on the bromination and heterocyclization reactions to explain the observed results. The calculations have allowed us to propose a reasonable pathway for the bromination by the Br_2/NEt_4Br system to account for the stereochemical outcome. The stereoselectivity can be rationalized by an anchimeric assistance of the NHR substituent. The presence of an acidic H gives rise to the effective formation of an H-bond of the pseudoaxial conformer with Br_2, thus promoting the Br_2 ionization in the 1:1 π-complex, which is then more easily trapped by the nucleophile to yield *cis*-3-*trans*-4-dibromides in a concerted mechanism; otherwise, the bromination takes place on the preferred pseudoequatorial conformation of the precursor, hence affording *trans*-3-*cis*-4-dibromides. On other hand, our results suggest that the cyclization of the 1,4-*cis*-dibromides proceeds by an initial, rate-determining, isomerization of the diaxial conformer of the *trans*-3-*cis*-4-dibromide.

4. Experimental part

4.1. General methods

Melting points were determined on a microscope type apparatus, and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at rt in $CDCl_3$, at 300, 400 or 500 MHz and at 75, 100 or 125 MHz, respectively, using solvent peaks ($CDCl_3$: 7.27 (D), 77.2 (C) ppm; D_2O: 4.60 ppm) as internal reference. The assignment of chemical shifts is based on standard NMR experiments (^{1}H, ^{13}C-DEPT, ^{1}H,^{1}H-COSY, gHSQC, gHMBC). In the NMR spectra values with (*) can be interchanged. Values with (′) show the invertomers, when distinguishable. For compounds **14**, **17**, **18**, and **20** the conformation and relative configuration were determined at 55 °C from ^{1}H,^{1}H-COSY and NOESY spectra (see Supplementary data). Two-dimensional [^{1}H, ^{1}H] NMR experiments (COSY and NOESY) were carried out with the following parameters: a delay time of 1 s, a spectral width of 3000 Hz in both dimensions, 4096 complex points in *t*2 and 4 transients for each of 256 time increments, and linear prediction to 512. The data were zero-filled to 4096×4096 real points. NOESY experiments were acquired with a mix time of 300 ms. Mass spectra were recorded on a GC/MS spectrometer with an API-ES ionization source. Elemental analyses were performed at CQO (CSIC, Spain). TLC was performed on silica F_{254} and detection by UV light at 254 nm or by charring with either ninhydrin, anisaldehyde or phosphomolybdic/H_2SO_4 dyeing reagents. Where anhydrous solvents were needed, they were purified following the usual procedures. In particular, dry DMF was critical for the outcome of the cyclization reaction, and was either distilled at reduced pressure or bought from commercial sources. Column chromatography was performed on silica gel 60 (230 mesh).

*4.1.1. tert-Butyl (6-chloropyridin-3-yl)methyl(cyclohex-3-enyl)carbamate (**12**).* To a solution of carbamate **10**[12,13] (908 mg, 4.60 mmol) in dry DMF (54 mL, 0.09 M), NaH (415 mg, 10.38 mmol, 2.2 equiv, 60% in oil) was added, and the mixture was stirred for 15 min at 0 °C. Then, halide **11** (1.0 g, 6.02 mmol, 1.3 equiv) was added and the mixture was stirred for 54 h at rt. Water was added, and the mixture was extracted with ethyl ether (×4). The organic phase was washed with brine, dried with $MgSO_4$, filtered, and evaporated. The crude was submitted to chromatography (10% hexane/AcOEt) to give recovered unreacted starting material **10** (120 mg) and compound **12** [959 mg, 65% (74%)]: white solid; 71–73 °C; IR (KBr) ν 3035, 2977, 1691, 1588, 1567, 1461, 1415, 1164 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.26 (dd, *J*=0.6, 2.6 Hz, 1H, H2′), 7.63–7.47 (m, 1H, H4′), 7.26 (d, *J*=8.1 Hz, 1H, H5′), 5.64–5.52 (m, 2H, H3, H4), 4.50–4.20 (m, 3H, CH_2N, H1, invertomer **I**), 4.05–3.87 (m, invertomer **II**), 2.26–1.95 (m, 4H, 2×H2, 2×H5), 1.74–1.56 (m, 2H, 2×H6), 1.56–1.21 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.2, 155.4 (NCOO), 149.9 (C2′, invertomer **I**), 148.4 (C6′, C2′, invertomer **II**), 138.2, 137.2 (C4′), 135.0 (C3′), 126.7 (2×CH, C3, C4), 125.2, 124.0 (C5′), 80.5 (C–O), 53.6, 52.0 (C1), 43.8 (CH_2N), 30.0, 29.6 (C2*), 28.5 [$(CH_3)_3$], 27.9, 27.6 (C6), 25.9 (C5*); MS (ES) *m*/*z* $[M+1]^+$ 323.0/325.0, $[M+23]^+$ 345.0/347.0. Anal. Calcd for $C_{17}H_{23}ClN_2O_2$: C, 63.25; H, 7.18; N, 8.68. Found: C, 62.96; H, 7.47; N, 8.76.

*4.1.2. Acid hydrolysis and bromination of tert-butyl (6-chloropyridin-3-yl)methyl(cyclohex-3-enyl)carbamate (**12**).* To a solution of carbamate **12** (144 mg, 0.45 mmol) in dry CH_2Cl_2 (9 mL, 0.05 M) at rt, under argon, trifluoroacetic acid (0.64 mL, 8.60 mmol, 19.3 equiv) was added. The mixture was stirred for 3 h. Then, the solvent was removed, and an aqueous saturated K_2CO_3 solution and $CHCl_3$ (×4) were added. The combined organic phase was dried over K_2CO_3, filtered, and evaporated. The crude intermediate **13** (110 mg, 0.49 mmol) was submitted to bromination as follows. To a solution of this amine in dry CH_2Cl_2 (6 mL, 0.08 M), Et_4NBr (1.04 g, 4.93 mmol, 10.0 equiv) was added at rt under argon. After stirring for 5 min, the mixture was cooled at −78 °C, and bromine (0.1 mL, 1.95 mmol, 4.0 equiv) was added, the mixture was stirred at this temperature for 20 min, and warmed at rt. Then, an aqueous saturated $Na_2S_2O_5$ solution was added, and extracted with AcOEt (×4); the organic phase was dried over Na_2SO_4, and evaporated, giving a crude that was purified by chromatography (10% hexane/AcOEt), affording *(trans-3,cis-4)-dibromo-N-[(6-chloropyridin-3-yl)methyl]-cyclohexanamine (**14**)* (125 mg, 66%) and *exo-2-bromo-7-[(6-chloropyridin-3-yl)methyl]-7-azabicyclo[2.2.1]heptane (**6**)* (7.5 mg, 5%). Compound (**14**): white solid; 67–69 °C; IR (KBr) ν 3450, 3280, 2956, 2918, 1585, 1568, 1428, 1108 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.33 (d, *J*=2.2 Hz, 1H, H2′), 7.68 (dd, *J*=2.4, 8.3 Hz, 1H, H4′), 7.29 (d, *J*=8.3 Hz, 1H, H5′), 4.60 (td, *J*=3.4, 3.7 Hz, 1H, H3), 4.50 (ddd, *J*=3.6, 3.7, 3.9 Hz, 1H, H4), 3.82 (d, *J*=2.2 Hz, 2H, CH_2N), 3.06 (tt, *J*=3.9, 10.4 Hz, 1H, H1), 2.46 (dddd, *J*=3.7, 4.3, 12.0, 15.4 Hz, 1H, $H5_{ax}$), 2.27 (ddd, *J*=3.4, 10.4, 14.4 Hz, 1H, $H2_{ax}$), 2.21 (ddd, *J*=3.7, 3.9, 14.4 Hz, 1H, $H2_{eq}$), 1.99 (m, 1H, $H5_{eq}$), 1.78 (m, 1H, $H6_{eq}$), 1.64 (m, 1H, $H6_{ax}$), 1.33 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.2 (C6′), 149.4 (C2′), 138.9 (C4′), 135.0 (C3′), 124.2 (C5′), 53.1 (C4), 52.6 (C3), 51.3

(C1), 47.6 (CH_2N), 36.1 (C2), 28.6 (C5), 28.1 (C6); MS (ES) *m/z* $[M+1]^+$ 380.9/382.9/384.9. Anal. Calcd for $C_{12}H_{15}Br_2ClN_2$: C, 37.68; H, 3.95; N, 7.32. Found: C, 37.84; H, 4.06; N, 7.31.Compound (**6**): white solid; 154–156 °C; IR (KBr) ν 3044, 2967, 1586, 1567, 1458, 1324, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.39 (br s, 1H, H2′), 7.96 (dm, *J*=8.1 Hz, 1H, H4′), 7.32 (d, *J*=8.1 Hz, 1H, H5′), 3.94 (dd, *J*=3.3, 7.8 Hz, 1H, H2), 3.84 (d, *J*=14.2 Hz, 1H, CH_2), 3.52 (d, *J*=14.2 Hz, 1H, CH_2), 3.44–3.34 (m, 2H, H1, H4), 2.30 (dm, *J*=13.5 Hz, 1H, $H3_{endo}$), 2.30 (dd, *J*=7.8, 13.8 Hz, 1H, $H3_{exo}$), 1.59–1.55 (m, 2H, $H5_{exo}$, $H6_{exo}$), 1.49–1.45 (m, 2H, $H5_{endo}$, $H6_{endo}$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.2 (C6′), 149.3 (C2′), 139.1 (C4′), 134.5 (C3′), 124.2 (C5′), 67.2, 60.6 (C1, C4), 50.4 (C2), 48.2 (CH_2N), 43.9 (C3), 26.0, 25.7 (C5, C6); MS (ES) *m/z* $[M+1]^+$ 301.0/303.0. Anal. Calcd for $C_{12}H_{14}Br_2BrClN_2$: C, 47.79; H, 4.68; N, 9.29. Found: C, 47.56; H, 4.51; N, 9.24.

*4.1.3. exo-2-Bromo-7-[(6-chloropyridin-3-yl)methyl]-7-azabicyclo[2.2.1]heptane (**6**) from amine **14**.* To a solution of compound **14** (347 mg, 0.91 mmol) in 1,3-dichlorobenzene (40 mL, 0.023 M) at rt, under argon, dry K_2CO_3 (129 mg, 0.93 mmol, 1.0 equiv) was added, and the mixture was heated at 130 °C for 3 days. Then, more K_2CO_3 (34 mg, 0.24 mmol, 0.27 equiv) was added, and after 7 h at the same temperature the solvent was removed, and the crude submitted to chromatography (0.5%→1% CH_2Cl_2/MeOH) to give compound **6** (211 mg, 77%).

*4.1.4. Reaction of exo-2-bromo-7-[(6-chloropyridin-3-yl)methyl]-7-azabicyclo[2.2.1]heptane (**6**) with $HSnBu_3$*

4.1.4.1. Slow addition of $HSnBu_3$. To a deoxygenated solution of product **6** (48.4 mg, 0.160 mmol) in dry toluene (8 mL, 0.02 M), under argon, AIBN (3 mg) was added. Then, a solution of tributyltin hydride (0.07 mL, 0.252 mmol, 1.57 equiv), AIBN (5 mg) in deoxygenated toluene (1.6 mL) was slowly added in 6 h at 120 °C. After the addition, the reaction mixture was heated at the same temperature for 18 h. Then, the mixture was cooled, and the solvent was removed. The residue was dissolved in ethyl ether, treated with iodine, until persistent color, washed with an aqueous saturated KF solution, and the organic phase was dried with $MgSO_4$, filtered, and evaporated. The residue was submitted to chromatography (0.1% CH_2Cl_2/MeOH to 0.5% CH_2Cl_2/MeOH) giving recovered compound **6** (7.6 mg) and a inseparable mixture of compounds *(2-chloro-5,7,8,9,9a,10-hexahydro-7,10-methanopyrrolo[1,2-g]-1,6-naphthyridine) (**8**)* and *7-[(6-chloropyridin-3-yl)methyl]-7-azabicyclo[2.2.1]heptane (**4**)* (14.8 mg). Analysis by coupled GC/MS of the mixture showed two compounds (**8** and **4**) in a 5.6:1 ratio, respectively. Compound **8** (t_R 26.99 min): MS *m/z* 222 (34), 220 (100), 205 (76), 152 (77). Compound **4** (t_R 26.04 min): MS *m/z* 224 (10), 222 (32), 193 (77), 166 (69), 126 (100). Compounds **8**+**4**: (see text for discussion: assignments with *, ♦, † could be interchanged within each set of symbols) ^1H NMR ($CDCl_3$, 500 MHz) δ 8.34 (d, *J*=1.7 Hz, 1H, H2′, **4**), 7.88 (br s, 1H, H4′, **4**), 7.33 (d, *J*=7.8 Hz, 1H, H3*, **8**), 7.12 (d, *J*=8.0 Hz, 1H, H4*, **8**), 4.36 (d, *J*=18.3 Hz, 1H, H5A, **8**), 3.92 (d, *J*=18.3 Hz, 1H, H5B, **8**), 3.61 (br s, 2H, CH_2N, **4**), 3.51 (t, *J*=4.4 Hz, 1H, H7, **8**), 3.30 (br s, 2H, H1, H4, **4**), 3.22 (d, *J*=4.9 Hz, 1H, H9a♦, **8**), 3.11 (d, *J*=7.1 Hz, 1H, H10♦, **8**), 2.01–1.34 (m, 6H, **1**; 8H, **4**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.9 (**8**), 149.8 (C2′, C6′, **4**), 147.7 (**8**), 139.8 (C4′, **4**), 136.6 (C3*, **8**), 134.1 (C3′, **4**), 127.4 (**8**), 124.4 (C5′, **4**), 121.8 (C4*, **8**), 64.7 (C7, **8**), 61.6 (C9a♦, **8**), 59.9 (C1, C4, **4**), 49.4 (C5, **8**), 48.5 (CH_2N, **4**), 46.0 (C10♦, **8**), 39.4 (C8†, **8**), 30.9 (C9†, **8**), 27.0 (4C, **4**), 26.6 (C11†, **8**).

4.1.4.2. Fast addition of $HSnBu_3$. To a deoxygenated solution of bromide **6** (33.5 mg, 0.11 mmol) and AIBN (5 mg) in dry toluene (2 mL, 0.45 M), $HSnBu_3$ (0.04 mL, 0.14 mmol, 1.3 equiv) was added, and the mixture was refluxed for 24 h. Then, the solvent was removed, the residue was dissolved in ethyl ether and iodine was added until a persistent color was observed. The mixture was washed with an aqueous saturated KF solution, and the organic phase was dried over $MgSO_4$, filtered, and evaporated. The crude was purified by chromatography (CH_2Cl_2→0.5% CH_2Cl_2/CH_3OH→1% CH_2Cl_2/CH_3OH) to give an unseparable mixture of 7-[(6-chloropyridin-3-yl)methyl]-7-azabicyclo[2.2.1]heptane (**4**) and **8** (14.2 mg; analysis by coupled GC/MS of the mixture showed two compounds (**8** and **4**) in a 1:1 ratio, respectively), and pure *7-[(6-chloropyridin-3-yl)methyl]-7-azabicyclo[2.2.1]heptane (**4**)* (9.1 mg, 37%) {^1H NMR ($CDCl_3$, 500 MHz) δ 8.34 (d, *J*=2.3 Hz, 1H, H2′), 7.87 (br s, 1H, H4′), 7.32 (d, *J*=8.1 Hz, 1H, H5′), 3.59 (br s, 2H, CH_2N), 3.28 (br s, 2H, H1, H4), 1.93–1.78 (m, 4H), 1.46–1.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.8 (C2′, C6′), 139.7 (C4′), 134.6 (C3′), 124.3 (C5′), 59.8 (C1, C4), 48.5 (CH_2N), 28.4 (br, 4×CH_2); MS (ES) *m/z* $[M+1]^+$ 223.3/225.3} that showed spectroscopic data identical to those described by Trudell and co-workers.[8]

*4.1.5. Bromination of tert-butyl (6-chloropyridin-3-yl)methyl(cyclohex-3-enyl)carbamate (**12**).* Following the same method as described for the bromination of amine **13** (see above), carbamate **12** (459 mg, 1.42 mmol) in dry CH_2Cl_2 (17 mL, 0.08 M) was reacted with Et_4NBr (3.00, 14.2 mmol, 10.0 equiv) and bromine (0.08 mL, 1.56 mmol, 1.1 equiv) for 2.5 h. Work-up and chromatography (10% hexane/AcOEt) gave *tert-butyl (6-chloropyridin-3-yl)methyl[(trans-3,cis-4)-dibromocyclohexyl]carbamate (**17**)* (639 mg, 93%), and *tert-butyl (6-chloropyridin-3-yl)methyl[(cis-3,trans-4)-dibromocyclohexyl]carbamate (**18**)* (20 mg, 3%). Compound (**17**): white solid; 87–89 °C; IR (KBr) ν 3086, 2975, 1735, 1694, 1586, 1568, 1462, 1367, 1254, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.37–8.30 (m, 1H, H2′), 7.68–7.55 (m, 1H, H4′), 7.30 (d, *J*=8.1 Hz, 1H, H5′), 4.58 (q, *J*=2.6 Hz, 1H, H3), 4.49 (ddd, *J*=2.6, 2.9, 3.5 Hz, 1H, H4), 4.50–4.35 (m, 2H, CH_2N), 4.26 (br s, 1H, H1), 2.56–2.47 (m, 2H, $H2_{ax}$, $H5_{ax}$), 2.25–1.95 (m, 1H, $H6_{ax}$), 1.80 (dm, *J*=15.0 Hz, 1H, $H2_{eq}$), 1.95–1.80 (m, 1H, $H5_{eq}$), 1.57 (s, 1H, $H6_{eq}$), 1.50 [br s, 9H, $(CH_3)_3$]; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.8 (NCOO), 150.3 (C6′), 148.7 (C2′), 138.3 (C4′), 134.4 (C3′), 124.2 (C5′), 81.0 (C–O), 52.6, 51.8 (C3, C4), 50.4 (C1), 45.1 (CH_2N), 32.8 (C5*), 28.6 [$(CH_3)_3$, C2*], 25.2 (C6); MS (ES) *m/z* $[M+1]^+$ 481.0/483.0/485.0. Anal. Calcd for $C_{17}H_{23}Br_2ClN_2O_2$: C, 42.31; H, 4.80; N, 5.80. Experimental: C, 42.60; H, 5.01; N, 5.80. Compound (**18**): white solid; IR (KBr) ν 2931, 1691, 1460, 1366, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.26 (d, *J*=2.1 Hz, 1H, H2′), 7.59–7.46 (m, 1H, H4′), 7.30 (d, *J*=8.2 Hz, 1H, H5′), 4.50–4.18 (m, 2H, CH_2N), 4.18–3.94 (m, 2H, H1, H3), 3.88 (td, *J*=4.4, 11.3 Hz, 1H, H4), 2.56–2.40 (m, 2H, $H2_{eq}$, $H5_{eq}$), 2.09 (q, *J*=12.3 Hz, 1H, $H2_{ax}$), 1.91 (q, *J*=12.7 Hz, 1H, $H5_{ax}$), 1.78–1.50 (m, 2H, 2×H6), 1.42 [br s, 9H, $(CH_3)_3$]; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.2 (NCOO), 150.5 (C6′), 148.4 (C2′), 137.4 (C4′), 134.1 (C3′), 124.4 (C5′), 81.5 (C–O), 55.3 (C4), 54.2 (2×CH, C1, C3), 44.6 (CH_2N), 42.4 (C2), 36.4 (C5), 31.2 (C6), 28.5 [$(CH_3)_3$]; MS (ES) *m/z* $[M+1]^+$ 481.0/483.0/485.0. Anal. Calcd for $C_{17}H_{23}Br_2ClN_2O_2$: C, 42.31; H, 4.80; N, 5.80. Found: C, 42.60; H, 4.91; N, 5.76.

*4.1.6. Deprotection of tert-butyl (6-chloropyridin-3-yl)methyl[(trans-3,cis-4)-dibromocyclohexyl]carbamate (**17**).* To an argonized solution of carbamate **17** (122 mg, 0.25 mmol) in anhyd CH_2Cl_2 (6 mL, 0.04 M) TFA was added (0.36 mL, 4.89 mmol, 19.3 equiv). The resulting solution was reacted at rt for 5 h, and then evaporated under pressure. Then, K_2CO_3, aqueous saturated solution was added, and extracted with $CHCl_3$ (×5). The organic phases were dried over K_2CO_3, thus obtaining the free amine **14** (96 mg, 99%).

*4.1.7. tert-Butyl benzyl(cyclohex-3-enyl)carbamate (**19**).* Following the same method as described for the synthesis of carbamate **12** (see above), compound **10** (840 mg, 4.26 mmol) in dry DMF (36 mL, 0.19 M) was reacted with NaH (454 mg, 11.36 mmol, 2.67 equiv) and benzyl bromide (1.24 mL, 10.22 mmol, 2.4 equiv) for 22 h at rt.

Work-up and chromatography (4% hexane/AcOEt) gave recovered starting material (**10**) (57 mg) and compound **19** (916 mg [75% (80%)]): oil; IR (KBr) ν 3026, 2974, 1692, 1454, 1408, 1365, 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.19 (m, 5H, Ph), 5.58 (s, 2H, H3, H4), 4.40 (br s, 3H, H1, CH_2N), 2.12 (br s, 4H, 2×H2, 2×H5), 1.80–1.70 (m, 2H, 2×H6), 1.40 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.0 (NCOO), 140.5 (C_{ipso}, Ph), 128.3 (2×CH, Ph), 126.7 (3×CH, Ph), 126.6, 125.6 (C3, C4), 79.8 [$OC(CH_3)_3$], 52.3 (br, C1), 47.0 (CH_2N), 29.0 (C2*), 28.5 [$OC(CH_3)_3$], 27.7 (C6), 26.1 (C5*); MS (ES) *m*/*z* $[M-55]^+$ 232.1, $[M+1]^+$ 288.0, $[M+23]^+$ 310.0, $[2M+23]^+$ 597.3. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.41; H, 8.52; N, 4.85.

*4.1.8. Bromination of tert-butyl benzyl(cyclohex-3-enyl)carbamate (**19**).* Following the same method as described for the bromination of amine **13** (see above), to a solution of carbamate **19** (804 mg, 2.80 mmol) in 33 mL of anhyd DCM (0.09 M) under argon, Et_4NBr (5.891 g, 28.0 mmol, 10 equiv) was added. The solution was left stirring at rt for some minutes. The temperature was then lowered to −78 °C and Br_2 was added (0.16 mL, 3.08 mmol, 1.1 equiv). The temperature was maintained for 3 h and then allowed to reach rt. A saturated aqueous solution of $Na_2S_2O_5$ was added until lack of color, and the resulting solution was extracted with AcOEt (×4). The organic phases were dried over Na_2SO_4, and the solvents were evaporated under reduced pressure. The crude thus obtained was purified by chromatography (silica gel, 2%→4% hexane/AcOEt), obtaining *tert-butyl benzyl[(trans-3,cis-4)-dibromocyclohexyl]carbamate (**20**)* (984 mg, 79%) and *tert-butyl benzyl[(cis-3,trans-4)-dibromocyclohexyl]carbamate (**21**)* (16.8 mg, 1.3%). Compound (**20**): white solid; 85–87 °C; IR (KBr) ν 3056, 2976, 1676, 1366, 1241, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.19 (m, 5H, Ph), 4.56 (q, *J*=2.7 Hz, 1H, H3), 4.47 (ddd, *J*=2.7, 3.0, 3.2 Hz, 1H, H4), 4.51–4.34 (m, 2H, CH_2N), 4.25 (br s, 1H, H1), 2.70–2.35 (m, 2H, $H2_{ax}$, $H5_{ax}$), 2.11 (m, 1H, $H6_{ax}$), 2.05–1.75 (m, 2H, $H2_{eq}$, $H5_{eq}$), 1.50 [s, 10H, $C(CH_3)_3$, $H6_{eq}$]; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.7, 154.7 (NCOO), 139.8, 138.8 (C_{ipso}, CH), 128.4 (2×CH, Ph), 127.5, 127.0, 126.0 (3×CH, Ph), 80.2, 79.2 (C–O), 53.0 (b, C3*), 52.1, 51.1 (C4*), 50.2 (C1), 48.4, 47.5 (CH_2N), 32.6, 31.7 (CH_2), 28.6 (*t*-Bu), 27.6 (CH_2), 24.9, 23.9 (CH_2); MS (ES) *m*/*z* $[M-55]^+$ 390.0/392.0/394.0, $[M+23]^+$ 468.0/470.0/472.0. Anal. Calcd for $C_{18}H_{25}Br_2NO_2$: C, 48.34; H, 5.63; N, 3.13. Found: C, 48.48; H, 5.60; N, 3.36. Compound (**21**): oil; IR (KBr) ν 3026, 2968, 1689, 1452, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39–7.11 (m, 5H, Ph), 4.70–4.15 (m, 2H, CH_2N), 4.15–3.75 (m, 3H, H1, H3, H4), 2.56–2.30 (m, 2H, $H2_{eq}$, $H5_{eq}$), 2.23–2.02 (m, 1H, $H2_{ax}$), 1.97–1.77 (m, 1H, $H5_{ax}$), 1.77–1.48 (m, 2H, 2×H6), 1.41 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.4 (NCOO), 139.5 (C_{ipso}, CH), 128.7 (2×CH, Ph), 127.2, 126.8 (3×CH, Ph), 80.7 (C–O), 55.8 (C1*), 54.8 (2×CH, C3*, C4*), 47.8 (CH_2N), 42.2 ($C2^{\blacklozenge}$), 36.6 ($C5^{\blacklozenge}$), 31.0 ($C6^{\blacklozenge}$), 28.5 (*t*-Bu); MS (ES) *m*/*z* $[M-55]^+$ 390.0/391.9/393.9, $[M+23]^+$ 467.9/470.0/472.0. Anal. Calcd for $C_{18}H_{25}Br_2NO_2$: C, 48.34; H, 5.63; N, 3.13. Found: C, 48.18; H, 5.67; N, 3.22.

*4.1.9. (trans-3,cis-4)-N-Benzyl-3,4-dibromocyclohexanamine (**22**).* Following the same method as described for the acid hydrolysis of carbamate **17** (see above), compound **20** (199 mg, 0.45 mmol) in dry CH_2Cl_2 (9 mL, 0.05 M) was reacted with TFA (0.64 mL, 8.62 mmol, 19.3 equiv) at rt for 7 h. Work-up and chromatography as usual gave amine **22** (149 mg, 96%): 34–35 °C; IR (film) ν 3155, 3026, 2944, 1452, 1429, 1176 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.24 (m, 5H, Ph), 4.71–4.66 (m, $W_{total}\approx 19$ Hz, 1H, H3), 4.59–4.53 (m, $W_{total}\approx 20$ Hz, 1H, H4), 3.82 (d, *J*=1.6 Hz, 2H, CH_2N), 3.11 (tt, *J*=4.0, 10.0 Hz, 1H, H1), 2.46 (ddt, *J*=3.7, 11.5, 15.1 Hz, 1H, $H5_{ax}$), 2.31 (ddd, *J*=3.4, 9.9, 14.4 Hz, 1H, $H2_{ax}$), 2.20 (dm, *J*=14.5 Hz, 1H, $H2_{eq}$), 2.12–2.03 (m, 1H, $H5_{eq}$), 1.90–1.81 (m, 1H, $H6_{ax}$), 1.80–1.68 (m, 1H, $H6_{eq}$), 1.43 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.6 (C_{ipso}), 128.7 (2×CH, Ph), 128.3 (2×CH, Ph), 127.2 (CH, Ph), 53.6 (C4), 52.9 (C3), 51.4 (CH_2N), 51.3 (C1), 36.5 (C2), 28.9 (C5), 28.4 (C6); MS (ES) *m*/*z* $[M+1]^+$ 345.9/347.9/349.9. Anal. Calcd for $C_{13}H_{17}Br_2N$: C, 44.99; H, 4.94; N, 4.04. Found: C, 44.70; H, 5.05; N, 4.26.

*4.1.10. 7-Benzyl-exo-2-bromo-7-azabicyclo[2.2.1]heptane (**7**).* Following the same method as described for the cyclization of amine **14** (see above), compound **22** (117 mg, 0.34 mmol) in 1,3-dichlorobenzene (18 mL, 0.02 M) was reacted with K_2CO_3 (49.1 mg, 0.36 mmol, 1.0 equiv) at 140 °C for 2 days. Work-up and chromatography (12% hexane/AcOEt) gave recovered starting material **38** (13 mg) and compound **7** [28 mg, 31% (35%)]: oil; IR (film) ν 3026, 2965, 1452, 1233 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.56–7.46 (m, Ph), 7.38–7.30 (m, Ph), 7.29–7.22 (m, Ph), 4.37–4.28 (m, H2, minor invertomer), 3.93 (dd, *J*=3.5, 7.8 Hz, H2, major invertomer), 3.87 (d, *J*=13.9 Hz, 1H, CH_2N, major invertomer), 3.52 (d, *J*=13.9 Hz, 1H, CH_2N, major invertomer), 3.62 (s, CH_2N, minor invertomer), 3.50–3.44 (d, *J*=4.3 Hz, H1*, major invertomer), 3.43–3.36 (d, *J*=4.3 Hz, H1*, H4*), 3.26 (t, *J*=4.5 Hz, H4*, minor invertomer), 2.60–2.48, 2.36–2.26 (m, 1H), 2.08 (dd, *J*=8.0, 13.8 Hz, 1H), 1.98–1.82 (m, 2H), 1.53–1.44 (m, 1H), 1.38–1.23 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.9 (C_{ipso}), 128.6, 128.4, 128.3, 127.0 (5×CH, Ph); 67.2 (C1*, major invertomer), 64.5 (C1*, minor invertomer), 60.5 (C4*, minor invertomer), 60.2 (C4*, major invertomer), 52.2 (CH_2N), 51.5 (C2, major invertomer), 50.8 (C2, minor invertomer), 44.1 ($C3^{\blacklozenge}$, major invertomer), 41.1 ($C3^{\blacklozenge}$, minor invertomer), 27.9 ($C5^{\blacklozenge}$, minor invertomer), 26.0 ($C5^{\blacklozenge}$, major invertomer), 25.7 ($C6^{\blacklozenge}$, major invertomer), 22.8 ($C6^{\blacklozenge}$, minor invertomer); MS (ES) *m*/*z* $[M+1]^+$ 266.0/268.0. Anal. Calcd for $C_{13}H_{16}BrN$: C, 58.66; H, 6.06; N, 5.26. Found: C, 58.40; H, 6.22; N, 5.37.

4.2. Computational methods

All calculations were carried out with Gaussian98 and Gaussian03 packages.[32] All the minima and transition states were fully optimized at the mPW1PW91 level,[33] which has a similar form to the B3LYP functional[34] but has been proved more accurate.[35] This model uses the modified Perdew–Wang exchange functional that has improved long-range behavior, has been reported to give better results in some cases, usually for negatively charged species. The standard 6-31G(d) basis set has been applied for all the atoms. To get reliable energy values, single-point-energy calculations have been carried out with the extended 6-311G(2d,p) basis set on the optimized structures. Zero-point energies (ZPEs) and thermal contributions to thermodynamic functions and activation parameters, as well as harmonic frequencies were computed at the same level of theory on the optimized structures. Intrinsic reaction coordinate, IRC, calculations[36] at the optimization level of theory were carried out on the transition structures to obtain the two minima on the potential energy surface, PES, connected by each transition state.

Solvent effects have been taken into account by the self-consistent reaction field (SCRF) method using the so-called conductor polarizable continuum model (CPCM)[37] as implemented in Gaussian03, in which the solvent is represented by an infinite dielectric medium characterized by the relative dielectric constant of the bulk. A relative permittivity of 8.93 and 2.8 was assumed to simulate DCM and 1,3-dichlorobenzene, respectively, as solvents. Natural bond orbital (NBO) analyses[38] have been performed by the module NBO v.3.1 implemented in Gaussian03 to evaluate the NPA charges and hyperconjugation effects on the optimized structures.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.09.013.

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