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Synthesis of 7-Azabicyclo[2.2.1]heptane and 2-Oxa-4-azabicyclo[3.3.1]non-3-ene Derivatives by Base-Promoted Heterocyclization of Alkyl *N*-(*cis*(*trans*)-3,*trans*(*cis*)-4-Dibromocyclohex-1-yl)carbamates and *N*-(*cis*(*trans*)-3,*trans*(*cis*)-4-Dibromocyclohex-1-yl)-2,2,2-trifluoroacetamides

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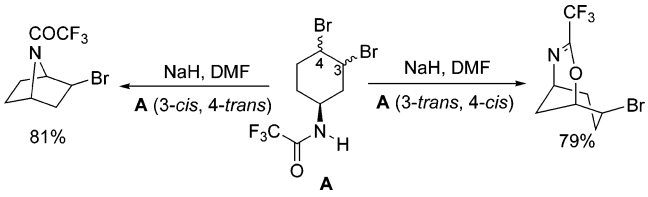

We have studied the base-promoted heterocyclization of alkyl *N*-(*cis*(*trans*)-3,*trans*(*cis*)-4-dibromocyclohex-1-yl)carbamates and *N*-(*cis*(*trans*)-3,*trans*(*cis*)-4-dibromocyclohex-1-yl)-2,2,2-trifluoroacetamides, investigating the effect of the nitrogen protecting group and the relative configuration of the leaving group at C3 and C4 on the outcome of this reaction. We have observed that the sodium hydride-promoted heterocyclization of alkyl *N*-(*cis*-3,*trans*-4-dibromocyclohex-1-yl)carbamates (**10**, **12**, **14**, **16**, **18**) is a convenient method for the synthesis of 7-azabicyclo[2.2.1]heptane derivatives. For instance, the reaction of *tert*-butyl *N*-(*cis*-3,*trans*-4-dibromocyclohex-1-yl)carbamate (**10**) with sodium hydride in DMF at room temperature provides 2-bromo-7-[(*tert*-butoxy)carbonyl]-7-azabicyclo[2.2.1]heptane (**2**) (52% yield), whose *t*-BuOK-promoted hydrogen bromide elimination affords 7-[(*tert*-butoxy)carbonyl]-7-azabicyclo[2.2.1]-hept-2-ene (**31**) in 78% yield, an intermediate in the total synthesis of epibatidine (**1**). However, the NaH/DMF-mediated heterocyclization of alkyl *N*-(*trans*-3,*cis*-4-dibromocyclohex-1-yl)carbamates (**11**, **13**) is a more structure dependent reaction, where the nucleophilic attack of the oxygen atom of the protecting group controls the outcome of the reaction, giving rise to benzooxazolone and 2-oxa-4-azabicyclo[3.3.1]non-3-ene derivatives, respectively, from low to moderate yields, in complex reaction mixtures. Conversely, the NaH/DMF heterocyclizations of *N*-(*cis*-3,*trans*-4-dibromocyclohex-1-yl)-2,2,2-trifluoroacetamide (**40**) or *N*-(*trans*-3,*cis*-4-dibromocyclohex-1-yl)-2,2,2-trifluoroacetamide (**42**) are very clean reactions giving 7-azabicyclo[2.2.1]heptane or 2-oxa-4-azabicyclo[3.3.1]non-3-ene derivatives, respectively, in good yields. Finally, a mechanistic investigation, based on DFT calculations, has been carried out to rationalize the formation of the different adducts.

Introduction

The 7-azabicyclo[2.2.1]heptane is a common structural motif in a number of natural or non-natural products with interesting biological and pharmacological properties. This is the case of epibatidine (**1**)[1] (Scheme 1), an alkaloid isolated from the Ecuadorian poison frog *Epipedobates tricolor*,[2] showing high

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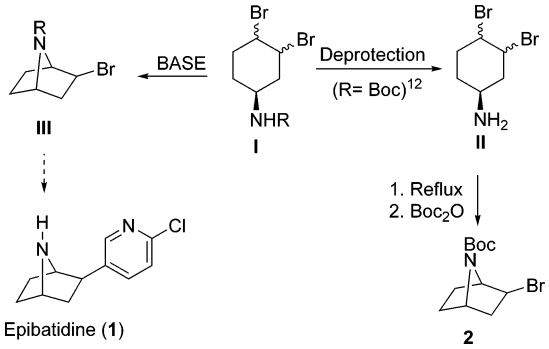
SCHEME 1



affinity for the nicotinic acetylcholine receptor.[3] Consequently, a series of methodologies have been reported for the preparation of 7-azabicyclo[2.2.1]heptane derivatives, mostly based on the Diels−Alder reaction, 1,3-dipolar cycloadditions, or in the ring contraction of tropinones.[4]

As a well-established synthetic strategy, the intramolecular substitution of a diverse array of free *trans*-4-cyclohexylamines substituted with different good leaving goups (cyclic sulfate, bromine, epoxide, methanosulfonates)[5−7] is known to provide the desired 7-azabicyclo[2.2.1]heptane derivatives in variable chemical yields. However, only sporadic examples have been reported describing the base-promoted intramolecular cyclization of related cyclohexylamines protected as the corresponding amides or carbamates, such as *trans*-*N*-benzoyl-*O*-methanosulfonyl-4-aminocyclohexanol,[8] *trans*-*N*-tosyl-1-chloro-4-aminocyclohexane,[9] or *trans*-*N*-Boc-*O*-methanosulfonyl-4-aminocyclohexanol,[10] for the synthesis of 7-azabicyclo[2.2.1]heptane derivatives.

In this context, and prompted by our current interest in the use of cyclohex-3-enecarboxylic acid for the synthesis of heterocycles,[11a,b] and particularly 7-azabicyclo[2.2.1]heptanes,[11c] our attention was recently caught by a dense and complete article published by Kapferer and Vasella[12] describing the synthesis of 2-bromo-7-[(*tert*-butoxy)carbonyl]-7-azabicyclo[2.2.1]heptane (**2**) by intramolecular ring closure of (*cis*-3,*trans*-4)- or (*trans*-3,*cis*-4)-dibromocyclohex-1-yl-amines (**II**) (Scheme 1). Based on these results, we were intrigued by the unexplored but seemingly possible synthesis of the same target molecules (**III**) by *direct base-catalyzed heterocyclization* on the readily available alkyl *N*-(*cis*-3,*trans*-4 or *N*-*trans*-3,*cis*-4)-dibromocyclohex-1-yl-carbamates or amides of type (**I**). If successful, this protocol would be simpler and more economic, resulting in a more efficient way to prepare compounds of type **III**[11c] (Scheme 1). These molecules are well-known intermediates for the synthesis of epibatidine or biologically active analogues.[13,14]

In this paper, we describe the results that we have obtained[11c] following this strategy, on various alkyl *N*-(*cis*-3,*trans*-4-dibromocyclohex-1-yl)-carbamates or *N*-(*cis*-3,*trans*-4-dibromocyclohex-1-yl)-2,2,2-trifluoroacetamides as well as alkyl *N*-(*trans*-3,*cis*-4-dibromocyclohex-1-yl)carbamates or *N*-(*trans*-3,*cis*-4-dibromocyclohex-1-yl)-2,2,2-trifluoroacetamides. As a result, we have noticed that the relative configuration of the bromine as the leaving group in the cyclohexane ring as well as the type of nitrogen protecting group determine the course of this base-mediated heterocyclization, leading either to 7-azabicyclo[2.2.1]heptane or to 2-oxa-4-azabicyclo[3.3.1]non-3-ene or benzooxazolone derivatives. Reaction mechanism studies based on DFT calculations have been also carried out in order to rationalize these results.

Results and Discussion

1. Synthesis of the Precursors and Heterocyclization Reaction. 1A. The 3-*cis*,4-*trans*-Dibromocarbamates (10, 12, 14, 16, 18, and 20). Starting from commercial (±)-cyclohex-3-enecarboxylic acid (**3**), *N*-(cyclohex-3-enyl)carbamates (**4**−**9**) (Scheme 2) were synthesized by Curtius reaction in good yields using the appropriate alcohol (*t*-butyl alcohol, benzyl alcohol, 2-chloro-5-hydroxymethylpyridine, methanol, 2-propyn-1-ol, 2-propen-1-ol), as described.[11,12]

Next, and after bromination, compound **4** gave known major *tert*-butyl *N*-(*cis*-3,*trans*-4-dibromocyclohex-1-yl)carbamate (**10**)[12] (50%) and minor *tert*-butyl *N*-(*trans*-3,*cis*-4-dibromocyclohex-1-yl)carbamate (**11**)[12] (38%) (Scheme 2). Similarly, compounds **5**−**9** provided the expected mixture of epimeric 3,4-dibromides which were readily separated and isolated by column chromatography to give pure 3-*cis*,4-*trans*- and 3-*trans*,4-*cis*-dibromocarbamates **12**, **14**, **16**, **18**, **20** and **13**, **15**, **17**, **19**, **21**, respectively.[11]

After some experimentation [(a) K_2CO_3 in dry acetone; (b) NaH in THF followed by treatment with Bu_4NI; (c) Bu_4NBr, in methylene chloride at 0 °C followed by treatment with 50% NaOH, (d) *t*-BuOK in dry THF at −78 °C[15,9b]], we found that

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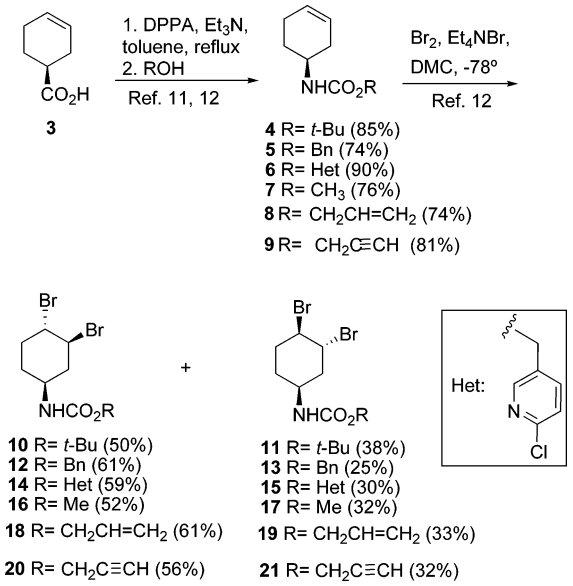
SCHEME 2



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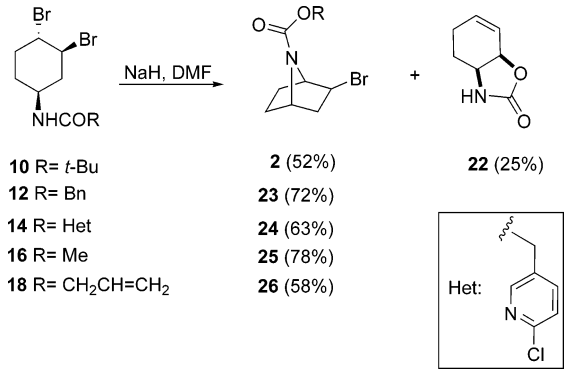
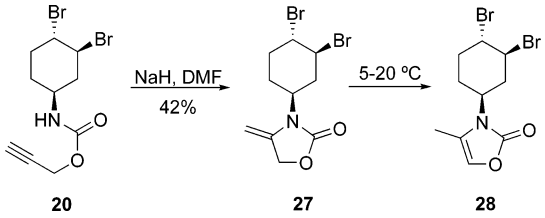


the reaction of 3-*cis*,4-*trans*-dibromo isomer **10** with sodium hydride in DMF, at room temperature (rt), gave the best results, affording 2-bromo-7-[(alkyloxy)carbonyl]-7-azabicyclo[2.2.1]-heptane (**2**)[12] (52%) and 3a,4,5,7a-tetrahydro-2(3*H*)-benzooxazolone (**22**)[16] (25%) (Scheme 3) in moderate total yield, but free of any azetidine resulting from the heterocyclization on C-3.[12,15] For comparative purposes, it is interesting to note that compound **2** has been prepared[12] from intermediate **10** in 83% yield, in three steps using long reaction times, while we have demonstrated that this synthetic operation is possible in one step only, in mild reaction conditions, and convenient chemical yield.

Very gratifyingly, carbamates **12**, **14**, **16**, and **18**, under the same experimental conditions, afforded only the expected 7-azabicyclo derivatives **23**−**26** (Scheme 3) cleanly and in good yield.

The NaH/DMF reaction of prop-2′-yn-1′-yl *N*-(3-*cis*,4-*trans*-dibromocyclohex-1-yl)carbamate (**20**) afforded 4-methylidene-2-oxazolidinone **27** (Scheme 4) as the result of the base-promoted formal 5-*exo*-*dig* heterocyclization onto the internal

SCHEME 4



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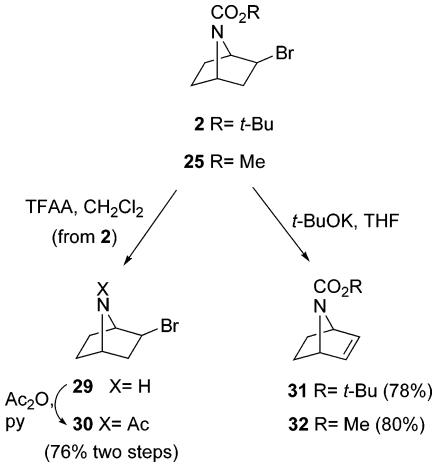

carbon of the alkyne. In fact, this reactivity was not surprising, as a similar type of transformation has been reported using other bases (*t*-BuOK, Et_3N)[17a,b] or transition-metal catalysts (AuCl)[17c] but shows a particular functional limitation regarding the generality of the present methodology for the synthesis of 7-azabicylo[2.2.1]heptanes. Compound **27** slowly isomerizes to 4-methyloxazol-2(3*H*)-one **28** (Scheme 4) on standing at 5−20 °C.

exo-2-Bromo-7-[(*tert*-butoxy)carbonyl]-7-azabicyclo[2.2.1]-heptane (**2**) was the expected compound after the NaH−DMF-promoted heterocyclization reaction of precursor **10**. Its structure has been confirmed by simple chemical manipulation and correlation with known compounds. As shown, acid hydrolysis of compound **2** gave the known free amine **29**,[12] which without isolation was acetylated to provide acetamide **30** in 76% overall yield (Scheme 5). In addition, the reaction of bromide **2** with *t*-BuOK in THF rendered product **31**[12,14] in 78% yield (Scheme 5). This 7-azanorbornene is an intermediate in the synthesis of epibatidine (**1**)[13a] and epibatidine analogues[13b,c] by Heck-type reactions with conveniently functionalized substrates; consequently, our new synthesis of compound **31** represents a new formal total synthesis of epibatidine. Similar treatment of compound **25** with *t*-BuOK in THF gave 7-carbomethoxy-7-azabicyclo[2.2.1]hept-2-ene (**32**) (Scheme 5), an intermediate that has also been converted in a number of epibatidine analogues.[18a] Compound **32** has been previously prepared by Diels−Alder reaction of *N*-carbomethoxypyrrole and phenyl vinyl sulfone at high pressure, followed by desulfonation, in

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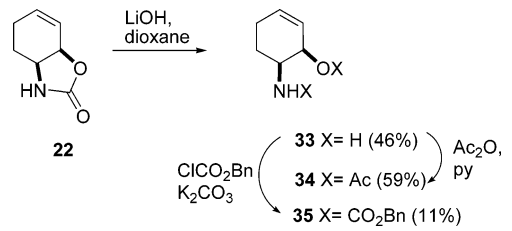
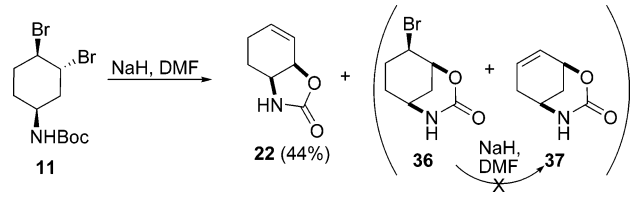
SCHEME 6



SCHEME 7

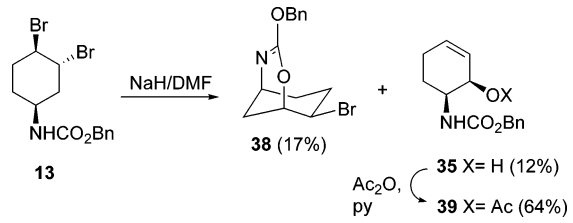


29% total yield.[18] Our approach leads to the same compound in a similar total yield (25%, four steps), requiring two steps more; however, we assume that the present method is easier, as no special experimental apparatus or device is necessary, and more flexible, as it gives potential useful intermediates such as **25** (Scheme 3). Another advantage is that the starting materials are less expensive. As a further comparison, an alternative method from *N*-carbomethoxypyrrole[18a] but not relying in a high-pressure step, provides **32** in a three-step sequence with a mere 10% yield.

The formation of 3a,4,5,7a-tetrahydro-2(3*H*)-benzooxazolone (**22**) in the heterocyclization of precursor **10** was totally unexpected (Scheme 3), but the structure of this compound has been unequivocally established by its spectroscopic data, and by comparison with those described in the literature for the same known product.[16] We have also confirmed the structure of oxazolone **22** by chemical transformations. As shown, basic hydrolysis gave 6-aminocyclohex-2-enol (**33**), whose acetylation furnished the peracetylated derivative **34** (Scheme 6). As an additional proof *N*-benzylcarbamate **35**[16c] was synthesized from intermediate **33** under the usual conditions (Scheme 6).

1B. The 3-*trans*,4-*cis*-Dibromocarbamates (11, 13). In view of the interesting results obtained with the 3-*cis*,4-*trans*-dibromide **10**, we turned our attention to the heterocyclization reaction of the 3-*trans*,4-*cis*-dibromide isomer **11** (Scheme 2). Vasella et al. have reported that this compound could be converted into the same 7-azabicyclo[2.2.1]heptane (**2**) (Scheme 1) in 62% overall yield, in three steps, in a time-consuming process that involved heating the free amine at 130 °C during 2 days.[12] These conditions (K_2CO_3, 1,2-dichlorobenzene, 3 days) applied to compound **11** yielded a complex reaction mixture, from which we could isolate unreacted compound **11** (25%), unsaturated carbamate **4** (15%), and 3-*cis*,4-*trans*-dibromide **10** (13%). When we submitted compound **11** to NaH/DMF, the reaction was also complex, affording in this case compound **22** (44%) and a mixture of (1*SR*,5*SR*,8*RS*)-8-bromo-2-oxa-4-azabicyclo[3.3.1]nonan-3-one (**36**) and (1*SR*,5*SR*)-2-oxa-4-azabicyclo[3.3.1]non-7-en-3-one (**37**) in a 3.6:1 ratio, as we could determine by GC/MS analysis (Scheme 7). After chromatography, we were able to obtain pure samples of compounds **36** and **37** (see the Experimental Section). Very interestingly, when the mixture **36**+**37** was further treated with NaH/DMF (or *t*-BuOK/THF) looking for a possible total transformation of bromide **36** into alkene **37**, the mixture was recovered unchanged, thus indicating that bromide **36** was not an intermediate in the formation of cyclohexene **37**.

SCHEME 8



From the results obtained in the heterocyclization of dibromides **10** and **11** (Schemes 3 and 7), it was apparent that the relative configuration at the different stereocenters was playing a major role in the chemical outcome of the heterocyclization reaction.

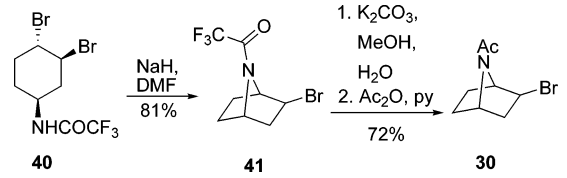
To confirm the scope and generality of these results and investigate the possible influence of the nitrogen protecting group, we next reacted benzyl *N*-(*trans*-3,*cis*-4-dibromocyclohex-1-yl)carbamate (**13**) (Scheme 2) under our usual heterocyclization reaction conditions. Similarly, a complex reaction mixture resulted, where we were able to isolate and characterize only compounds **38** and **35** in poor yields (Scheme 8). 3-(Benzyloxy)-8-bromo-2-oxa-4-azabicyclo[3.3.1]non-3-ene (**38**) is the *normal* heterocyclization product that results after a S_N2 intramolecular reaction between the oxygen of the benzyl carbamate at C-1 and the bromine atom at C-3, particularly favored due to the trans arrangement of these functional groups. In addition to the spectroscopic analysis, the structure of compound **35** has also been confirmed by acetylation to give 6-(benzyloxycarbonylamino)cyclohex-2-enyl acetate (**39**) in 64% yield (Scheme 8). Note that compound **35** is identical to the product obtained during the carbamoylation of aminoalcohol **33** (Scheme 6) (see the Experimental Section), and to the product reported by Bayer et al. following a different route.[16c] The formation of benzyl 2-hydroxycyclohex-3-enylcarbamate (**35**) is probably the result of a similar reaction mechanism that gives compound **22** from the parent precursor **11** (Scheme 7) and reflects the low stability of the presumed allylic 2-benzyloxy-2-oxazoline intermediate to the reaction conditions.[19]

1C. The 3,4-Dibromo-2,2,2-trifluoroacetamides (40, 42). It was evident that in order to have an efficient approach to 7-azabicyclo[2.2.1]heptane derivatives, the key point was the ready availability of appropriate (3-*cis*-4-*trans*-dibromocyclohex-1-yl)carbamate derivatives. Intermediates **10**, **12**, **14**, **16**, and **18** must be separated by chromatography from the corresponding 3-*trans*-4-*cis*-dibromo isomers (Scheme 2), always present in the reaction medium, and afford the corresponding 7-azabicyclo-[2.2.1]heptanes in moderate yields (52−78%) (Scheme 3). We next considered the readily available *N*-(3-*cis*,4-*trans*-dibromocyclohex-1-yl)-2,2,2-trifluoroacetamide, which we could isolate in 72% yield, accompanied by minor amounts of its *N*-(3-*trans*,4-*cis*-dibromocyclohex-1-yl)-2,2,2-trifluoroacetamide isomer during the bromination of *N*-(cyclohex-3-enyl)-2,2,2-trifluoroacetamide, as reported.[12]

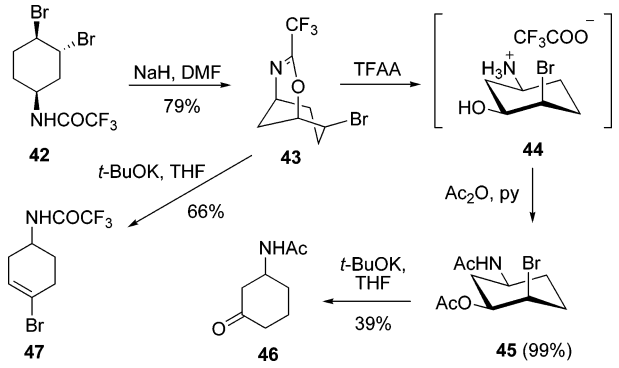
The NaH/DMF-promoted heterocyclization reaction of *N*-(3-*cis*,4-*trans*-dibromocyclohex-1-yl)-2,2,2-trifluoroacetamide (**40**) afforded the expected 7-azabicyclo[2.2.1]heptane derivative **41** in good yield (81%) (Scheme 9). Basic hydrolysis of compound

(19) In view of the reactivity observed with 3-*trans*,4-*cis*-dibromocarbamates **11** and **13**, similar analysis was not further investigated in related derivatives **15**, **17**, **19**, and **21**.

SCHEME 9



SCHEME 10

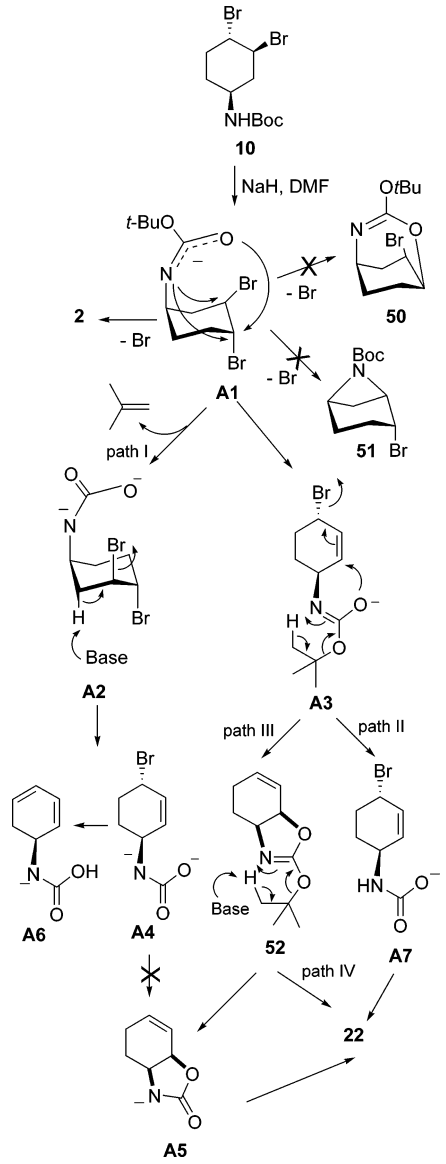


41 followed by acetylation gave product **30** in 72% yield (Scheme 9), identical in all analytical and spectroscopic data to the compound isolated in a related synthetic sequence starting from carbamate **2** (Scheme 5). For comparative purposes, it is interesting to note that Vasella has described the transformation of 2,2,2-trifluoroacetamide **40** (Scheme 9) into bromide **2** in good overall yield (93%), but in a time-consuming three-step synthetic sequence, as the first deprotection step required 13.5 h, the cyclization 13 days, and the reprotection 3 days,[12] while we have been able to obtain a similar *N*-protected, functionalized 7-azabicyclo[2.2.1]heptane such as **41** (Scheme 9) in one step only in 81% yield.

The clear advantage of the 2,2,2-trifluoroacetamide protecting group as stereodirecting and amide carbanion stabilizing group has also been observed in the base-promoted heterocyclization of *N*-(3-*trans*,4-*cis*-dibromocyclohex-1-yl)-2,2,2-trifluoroacetamide (**42**). As shown in Scheme 10, treatment of this dibromide with NaH/DMF afforded once more one compound only (**43**) in 79% yield, a relatively unstable product as we have observed that it slowly decomposes to the amino alcohol **44** (Scheme 10) on standing at 5−20 °C. The structure of bromide **43** has been confirmed by acid hydrolysis of the dihydro-1,3-oxazine moiety to provide 5-amino-2-bromocyclohexanol (**44**) as the corresponding trifluoroacetate, which on acetylation gave derivative **45** in 99% yield. *t*-BuOK/THF-promoted hydrogen bromide elimination on compound **45** provided ketone **46**[20] in low yield. The formation of ketone **46** is probably the result of the preferred capture of the hydrogen bonded to the carbon bearing the acetoxy group, located in a favorable *trans*-diaxial arrangement referring to the leaving group followed by bromide elimination, and aqueous hydrolysis of the intermediate enol ester during the workup. The same reaction conditions applied to bromide **43** afforded vinylic bromide **47** (Scheme 10), which is presumably formed after the capture of the hydrogen located in the carbon bearing the bromine atom, and double bond formation, followed by protonation.

In addition to the chemical manipulation and correlations with known compounds, all products described in this work showed analytical and spectroscopic data in good agreement with their structures, and when known, with the reported data[21−23] (see the Supporting Information).

SCHEME 11. Mechanism for the Formation of Compounds 2 and 22 from Dibromide 10



2. Mechanisms of the Heterocyclization Reactions. In this section, we present potential reaction mechanisms for the formation of the products obtained on the basis of a DFT study. We will focus on the precursor *tert*-butyl *N*-(*cis*-3,*trans*-4-dibromocyclohex-1-yl)carbamate (**10**) and on its isomer 3-*trans*,4-*cis*-dibromide (**11**) as models.[24]

We describe herein the reaction energy profiles from the reactive species **A1**, formed by abstraction of the carbamate proton in **10** by the strong base.[25] **A1** may evolve through

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(24) For the sake of brevity, the theoretical study on related processes (formation of **35** and **38** from **13**, and **47** from **43**) is shown in the Supporting Information.

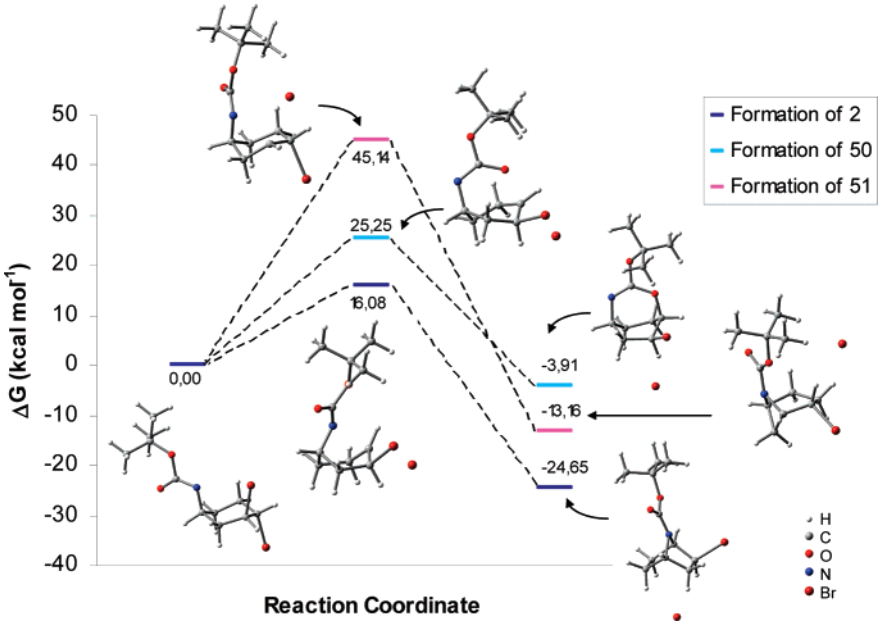


FIGURE 2. Free energy profiles in solution (DMF) and DFT-optimized geometries for direct cyclizaton routes of **A1**.

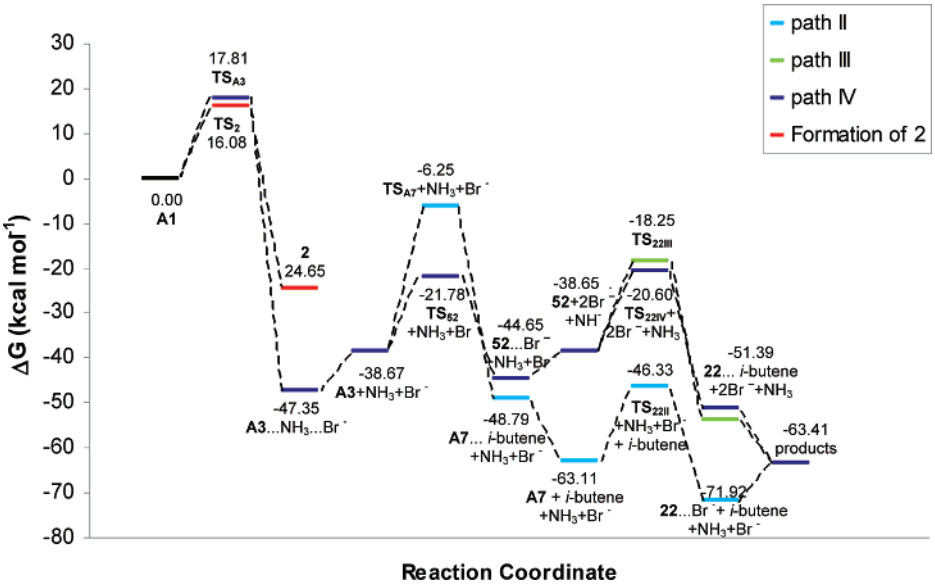


FIGURE 3. Free energy profiles in solution (DMF) for the formation of **22**.

different pathways (Scheme 11), and three direct cyclization routes may be envisaged: (1) to the expected product **2**, by intramolecular S_N2 displacement of the *trans*-bromine at C4; (2) to the bicyclo[3.2.2]nonene **50**, through nucleophilic attack of the carbamate oxygen at C4; and (3) to the bicyclo[3.1.1]-heptane **51**.

DFT calculations in solution[26] (Figure 2) show that formation of **2** is exothermic (−24.65 kcal mol^{-1}) and takes place with a reasonably low free-energy barrier (16.08 kcal mol^{-1}). In contrast, formation of **51** is predicted to involve a very high barrier (45.14 kcal mol^{-1}), prohibitive under the experimental conditions, probably due to steric hindrance induced by the *cis*-bromine and the strong steric strain of the forming cyclobutane framework. Cyclization to **50** takes place with a moderate energy barrier (25.25 kcal mol^{-1}) in a weakly exothermic step (−3.91 kcal mol^{-1}).

To summarize, the formation of **2** is kinetically and thermodynamically favored over other plausible direct heterocyclizations, in agreement with the experimental findings since **51** and **50** were not detected.

The competitive formation of **22** might imply that a secondary reaction involving elimination of the *tert*-butyl moiety in **A1** could take place in the strong basic medium, leading to species **A2**, which would then suffer a regioselective hydrogen bromide elimination and an intramolecular S_N2' displacement (Scheme 11, path I). This reactivity is very unusual, although it has been described.[27] Likewise, the Fmoc protecting group can be cleaved

(25) A scan of the potential energy surface (PES) for the system [**10** + NH_2^-] was performed (see Figure 1, Supporting Information), and the results reveal a double-well energy profile and a barrierless pathway for the formation of **A1**.

(26) The gas-phase results for the reactions evaluated are summarized in the Supporting Information.

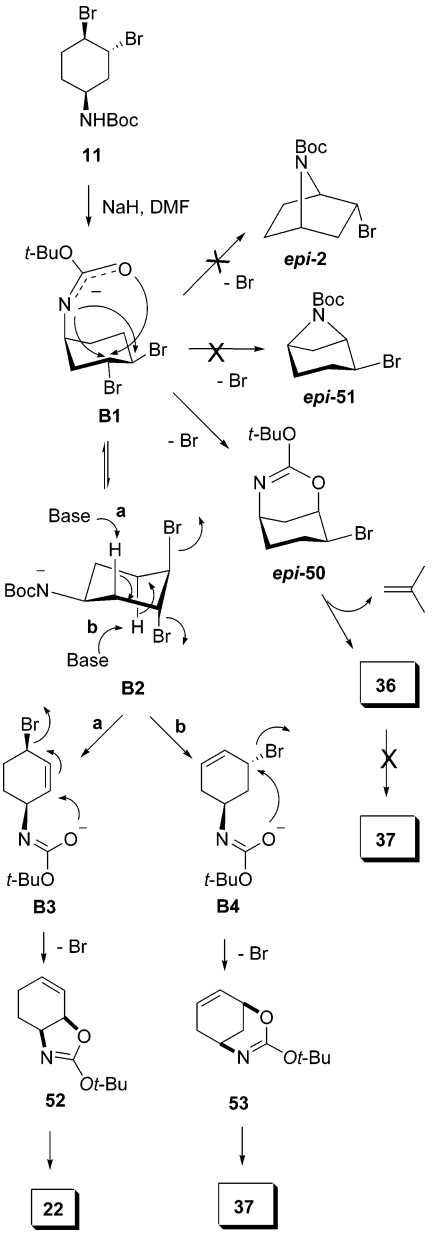
by ammonia and simple amines like triethylamine, DBU, or diisopropylamine,[28a] and di-Boc-protected α-amino acids can be selectively removed to give mono-Boc compounds.[28b]

The hydrogen bromide elimination must take place before the intramolecular S_N2' displacement, but the complete sequence of events is unknown. Thus, the fragmentation step may proceed before or after the elimination or cyclization process. The reductive elimination of the *tert*-butyl group to form **A2** (Scheme 11) seems doubtful because it is a dianionic structure and likely very high in energy. Moreover, the E_2 hydrogen bromide elimination to generate the conceivable intermediate **A3** should compete with this process. Computational results show that the base-assisted fragmentation to **A2** proceeds with an activation barrier significantly higher than the elimination to **A3** (33.67 vs 17.81 kcal mol^{-1} in solution, respectively). Additionally, we were unable to locate the cyclization transition structure connecting the intermediates **A4** and **A5** (path I); the reaction evolves instead through intramolecular proton abstraction by the carbamate, leading to diene **A6**. Although this result might be attributable to computational artifacts, the strong basic character of **A4** and the proximity of functional groups may induce an easier elimination toward **A6**. Hence, these findings suggest that path I may be discarded as an operating mechanism, and the formation of **A3** is probably the first step toward the formation of **22**.

The carbamate group in **A3** shows analogous electronic and steric properties to **A1**, so the base-promoted extrusion of alkene is expected to be as high in energy as from **A1** to **A2**. Alternatively, a deprotection via retro-ene reaction is also plausible (Scheme 11, path II). This is not necessarily a thermal process, and it can be accelerated at room temperature under basic conditions.[29] The retro-ene process of **A3** generates **A7** through the asymmetric transition structure $\mathbf{TS_{A7}}$ (C−H = 1.672 Å, N−H = 1.103 Å, C−O = 1.660 Å).[30] This step is highly exothermic but kinetically unfavored, as the activation energy to reach $\mathbf{TS_{A7}}$ is very high (41.10 kcal mol^{-1}; see Table 2, Supporting Information). Finally, **A7** would undergo an easy intramolecular S_N2' displacement to form **22** through $\mathbf{TS_{22II}}$ (activation barrier of 16.78 kcal mol^{-1}).

The high activation barrier computed for the fragmentation to **A7** prompted us to search for alternative paths. Thus, a mechanism where this step is the final event can be envisaged (Scheme 11, path III). **A3** may drive heterocyclization through $\mathbf{TS_{52}}$ to **52** by intramolecular *syn*-nucleophilic attack of the carbamate oxygen onto the cycloalkene. The barrier for this thermoneutral cyclization is 25.6 kcal mol^{-1}. At this point, the fragmentation of the alkyl chain might proceed, as proposed above, assisted by the base or via retro-ene reaction (Scheme 11, path IV). In the first case, **A5** is formed via $\mathbf{TS_{A5}}$ in a kinetically more favored fragmentation than from **A1** (barrier of 26.39 kcal mol^{-1}). The alternative [1,5]sigmatropic H-shift of **52** (Scheme 11, path IV) proceeds through a half-chair transition structure $\mathbf{TS_{22IV}}$. This step is thermodynamically favored (exothermic by 20 kcal mol^{-1}), and the activation barrier

SCHEME 12. Mechanism for the Formation of Compounds 22, 36, and 37 from Dibromide 11



is moderate (24.05 kcal mol^{-1}). It should be noted that $\mathbf{TS_{22IV}}$ is 2.35 kcal mol[1] more stable than $\mathbf{TS_{A5}}$, therefore supporting path IV; however, a competition between both fragmentation routes cannot be ruled out.

In total, these findings suggest path IV (Scheme 11) as the putative operative mechanism: this three-step route is thermodynamically feasible, involves moderate activation barriers, and is kinetically preferred over alternative paths. The rate-limiting step is the heterocyclization event, although the alkyl fragmentation involves a slightly lower barrier. The potential energy surfaces computed for paths II−IV are depicted in Figure 3.

According to these results, the formation of **22**, **36**, and **37** in the heterocyclization of *tert*-butyl *N*-(*trans*-3,*cis*-4-dibromocyclohex-1-yl)carbamate (**11**) (Scheme 7) could be explained as shown in Scheme 12. The reactive anion **B1**, probably because of stereochemical restrictions, does not cyclize to compounds *epi*-**51** or *epi*-**2**. In fact, the strong steric repulsion between the Boc group and the *cis*-bromine at C4 gives rise to

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(30) For some DFT studies of intramolecular retro-ene reactions, see: (a) Jabbari, A.; Sorensen, E. J.; Houk, K. N. *Org. Lett.* **2006**, *8*, 3105. (b) Yu, Z. X.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 13825. (c) Loncharich, R. J.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 6947.

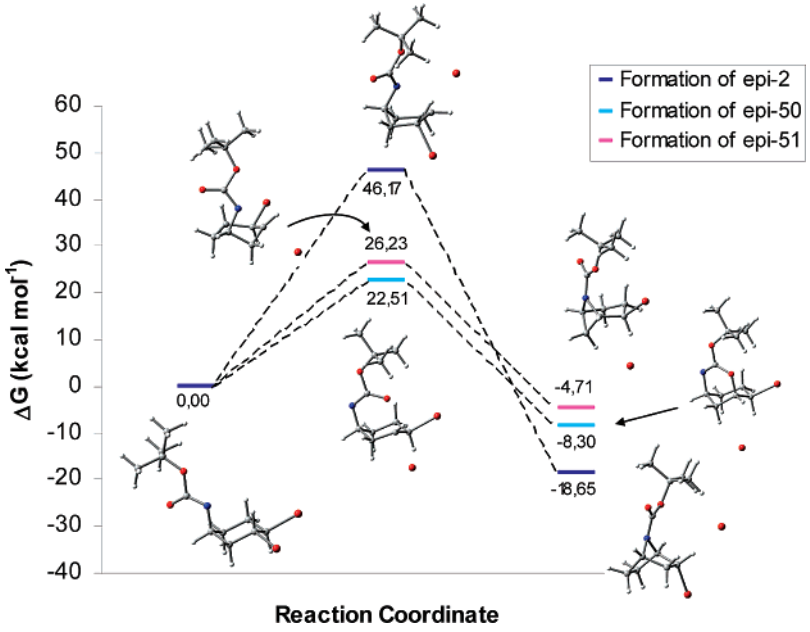

FIGURE 4. Free energy profiles in solution (DMF) for the direct cyclization of **B1**.

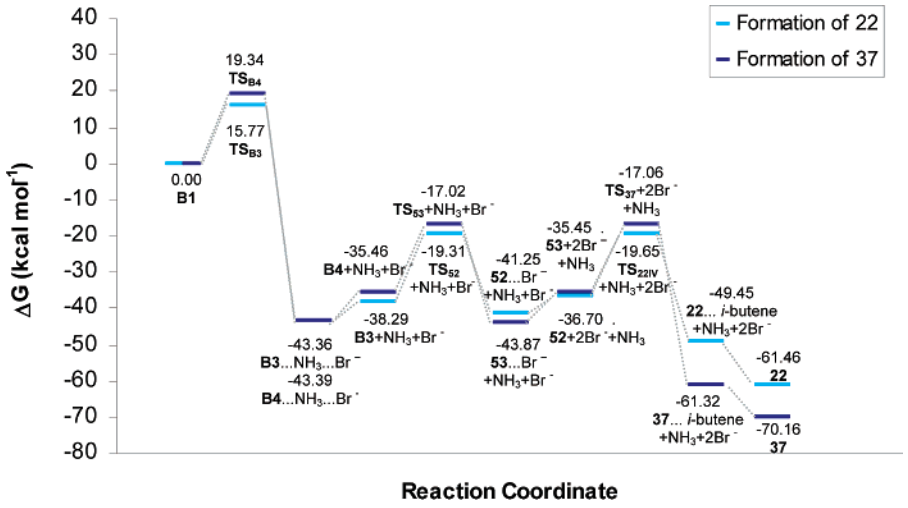

FIGURE 5. Free energy profiles in solution (DMF) computed for the formation of **22** and **37** from carbamate **11**.

a very high activation energy for the cyclization to *epi*-**2** (Figure 4). The steric tension involved in the N attack on C3 may account for the high barrier in the formation of *epi*-**51**. On the contrary, the unstrained oxygen attack to C3 justifies the low barrier, which points to a kinetically favored, selective, formation of the bicyclo[3.3.1]nonene *epi*-**50**.

In this context, formation of compound **36**, closely related with *epi*-**50**, might take place from this bicycle in a further retro-ene process (Scheme 12). The transition structure (**TS$_{36}$**) involves a moderate activation energy of 20.39 kcal mol^{-1}, thus supporting this hypothesis.

Compound **37** could be formed by a hydrogen bromide elimination from **36**. However, the inspection of **36** reveals that the pseudoequatorial orientation of the bromine should not be favored to undergo this process, a fact that has been experimentally confirmed as we could not transform **36** into **37** (Scheme 7). Although the pertinent transition structure could be successfully located and characterized, the activation energy was found to be high (33.61 kcal mol^{-1}), so we searched for other mechanistic proposals.

On the basis of the preferred pathway computed for **10**, we might speculate that transformation of **B1** into **22** follows an analogous three-step mechanism via E_2 elimination, heterocyclization through S_N2' and retro-ene processes. Whereas **B1** conformer (Scheme 12) is ideally functionalized to give compound **36**, the pseudoequatorial disposition of the bromine avoids the expected elimination. Conversely, the conformer **B2** displays pseudoaxial bromine disposition at C3, hence allowing the elimination to form **B3** (and finally **22**, Scheme 12, path **a**), and simultaneously at C4, thus giving intermediate **B4**, precursor of compound **37** (Scheme 12, path **b**). Note that conformer **B2** is 3.35 kcal mol^{-1} less stable than **B1**.

B2 keeps the main features of the model system **A1**, so the energy profile computed for the formation of **22** following path **a** is parallel, and only slight energy differences are observed (Table 3, Supporting Information).

Formation of **37** proceed through a competing elimination, affording intermediate **B4** (Scheme 12, path **b**). A comparison between the energetics for path **a** and **b** reveals a kinetic and thermodynamically favored base-assisted elimination of the

proton at C2. The following intramolecular S_N2' displacement to give **53** proceeds via **TS$_{53}$** with a higher energy barrier than that estimated for the related cyclization to *epi*-**50**, although **B4,** lacking *cis* bromine substituent would imply a lower steric hindrance. Finally, the alkyl chain fragmentation of **53** drives to **37**.

The rate-limiting step for the formation of **22** and **37** is the heterocyclization, as for the transformation of **10** into **22**. The high activation barrier and exothermicity for the first-step prevent the reverse process, making the product distribution dependent on the relative activation energies of the two competing paths **a** and **b**. Figure 5 shows the energy profiles computed for the transformation of **11** into **22** and **37**.

The formation of compounds **35** and **38** (Scheme 8) during the base-promoted heterocyclization of **13** follows a mechanism analogous to that discussed for the Boc-protected precursor **11**, so the interested reader is referred to the Supporting Information for deeper details.[24]

3. Conclusions

In this work, we have investigated the effect of the relative configuration as well as the influence of the nitrogen protecting group on the base-mediated heterocyclization of (3,4-dibromocyclohex-1-yl)amines. Consequently, the sodium hydride/DMF-promoted heterocyclization of alkyl *N*-(*cis*-3,*trans*-4-dibromocyclohex-1-yl)carbamates (**10**, **12**, **14**, **16**, **18**) is a convenient method for the synthesis of the 7-azabicyclo[2.2.1]-heptane derivatives. The NaH/DMF-mediated heterocyclization of alkyl *N*-(*trans*-3,*cis*-4-dibromocyclohex-1-yl)carbamates (**11**, **13**) is a more structure-dependent reaction, giving rise to 2-oxa-4-azabicyclo[3.3.1]non-3-ene derivatives from low to moderate yields, in complex reaction mixtures. Conversely, the NaH/DMF heterocyclization reactions of *N*-(*cis*-3,*trans*-4-dibromocyclohex-1-yl)-2,2,2-trifluoroacetamide (**40**) or *N*-(*trans*-3,*cis*-4-dibromocyclohex-1-yl)-2,2,2-trifluoroacetamide (**42**) are very clean, giving 7-azabicyclo[2.2.1]heptane or 2-oxa-4-azabicyclo[3.3.1]-non-3-ene derivatives, respectively, in good yields. In summary, the appropriate selection of the nitrogen protecting group on the easily available 3,4-dibromocyclohex-1-yl amines allowed us to control the type of final product obtained. As a practical application, the reaction of *tert*-butyl *N*-(*cis*-3,*trans*-4-dibromocyclohex-1-yl)carbamate (**10**) with sodium hydride in DMF at room temperature provided 2-bromo-7-[(*tert*-butoxy)carbonyl]-7-azabicyclo[2.2.1]heptane (**2**) in 52% yield. *t*-BuOK-promoted hydrogen bromide elimination in compound **2** afforded 7-[(*tert*-butoxy)carbonyl]-7-azabicyclo[2.2.1]hept-2-ene (**31**) in 78% yield, an intermediate in the total synthesis of epibatidine (**1**) (Scheme 1).[13]

In addition, compounds of type **2** or **41** are very well funtionalized in order to explore the synthesis of C-2 susbtituted epibatidine analogues, by simple bromine S_N2 nucleophilic displacements or intermolecular free radical reactions. Similarly, 2-oxa-4-azabicyclo[3.3.1]non-3-ene derivatives such as **43** have been easily transformed into 3-aminocyclohexane derivatives (**45**−**47**), a series of compounds of wide and potential synthetic interest. Finally, a DFT study has been carried out to investigate and rationalize the formation of the different cycloadducts. The evaluation of a variety of conceivable routes has allowed us to propose reasonable mechanistic pictures, which in general suggest a rate-limiting heterocyclization step.

Experimental Section

General Methods. Melting points were determined on a Kofler-type microscope 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, HMQC, HMBC). In the NMR spectra, values with (*) can be interchanged. Mass spectra were recorded on a LC/MS spectrometer with an API-ES ionization source. Elemental analyses were performed at CQO (CSIC, Spain). TLC was performed on silica F254 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, anhyd DMF was critical for the outcome of the cyclization reaction and was either distilled at reduced pressure, bought from Aldrich (99.8%), or purified through a Pure solv PS-400-3-MD model. Column chromatography was performed on silica gel 60 (230 mesh).

[(6′-Chloro-3′-pyridyl)methyl]-*N*-(cyclohex-3-enyl)carbamate (6). Following the general procedure for the Curtius reaction (method A), to a solution of cyclohex-3-enecarboxylic acid (**3**) (216 mg, 1.71 mmol) in 6 mL of dry toluene were added dropwise Et_3N (0.26 mL, 1.88 mmol, 1.1 equiv) and DPPA (0.44 mL, 2.05 mmol, 1.2 equiv). The reaction mixture was stirred for 20 min at rt and 60 min under reflux. 6-Chloropyridine-3-methanol (196 mg, 1.37 mmol, 0.8 equiv) was then added, and the resulting mixture was stirred under reflux for 17 h. Workup and flash chromatography (hexane/AcOEt, 32% to AcOEt) yielded compound **6** (329 mg, 90%) as a white solid: mp 82−4 °C; IR (KBr) ν 3428, 3310, 3029, 2920, 1687, 1537, 1461, 1239, 1111, 1048 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.40 (d, J = 2.3 Hz, 1H, H2′), 7.68 (dd, J = 2.3 and 8.1 Hz, 1H, H4′), 7.33 (d, J = 8.1 Hz, 1H, H5′), 5.65 (m, 2H, H3, H4), 5.09 (s, 2H, CH_2O), 4.79 (br s, 1H, NH), 3.86 (br s, 1H, C*H*NH), 2.41 (d, J = 17.2 Hz, 1H, H2A), 2.20−2.00 (m, 2H, 2H5), 2.00−1.80 (m, 2H, H2B, H6A), 1.70−1.50 (m, 1H, H6B); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.0 (NH*C*O$_2$CH$_2$Ar), 150.7 (C3′), 149.0 (C2′), 138.4 (C4′), 131.2 (C6′), 126.6 (CH=*C*H, C4), 124.0 (*C*H=CH, C3), 123.8 (C5′), 62.6 (NHCO$_2$*C*H$_2$Ar), 46.2 (C1), 31.5 (C2), 28.0 (C6), 23.3 (C5); MS (ES) m/z [M + 1]$^+$ 267.0, [M + 23]$^+$ 289.0. Anal. Calcd for $C_{13}H_{15}ClN_2O_2$: C, 58.54; H, 5.67; N, 10.50. Found: C, 58.76; H, 5.57; N, 10.43.

Methyl *N*-(Cyclohex-3-enyl)carbamate (7). Following the general procedure for the Curtius reaction (method A), a solution of cyclohex-3-enecarboxylic acid (**3**) (258 mg, 2.05 mmol) in dry toluene (6.4 mL, 0.32 M) was reacted with Et_3N (0.33 mL, 2.46 mmol, 1.2 equiv) and DPPA (0.46 mL, 2.15 mmol, 1.05 equiv). After the solution was refluxed for 4 h, dry methanol (0.4 mL, 10.24 mmol, 5 equiv) and CuCl (13.6 mg, 0.14 mmol, 0.067 equiv) were added, followed by warming at 70 °C for 4 h. Workup and flash chromatography (hexane/AcOEt, 10%) gave carbamate **7** (243 mg, 76%) which showed spectroscopic data [^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.74−5.64 (m, 1H), 5.64−5.55 (m, 1H), 4.69 (br s, 1H), 3.94−3.76 (m, 1H, HCN), 3.67 (s, 3H, OCH_3), 2.42 (m, 1H), 2.24−2.02 (m, 2H), 1.96−1.80 (m, 2H), 1.66−1.50 (m, 1H)] identical to those described[31] for the same compound.

Allyl *N*-(Cyclohex-3-enyl)carbamate (8). Following the general procedure for the Curtius reaction (method A**)**, to a solution of cyclohex-3-enecarboxylic acid (**3**) (309 mg, 2.45 mmol) in dry toluene (7.8 mL, 0.32 M) under argon were added recently distilled Et_3N (0.41 mL, 2.94 mmol, 1.2 equiv) and DPPA (0.56 mL, 2.55 mmol, 1.04 equiv). The mixture was stirred at rt for 30 min. After 4 h at reflux, the mixture was cooled at rt, and anhydrous allylic alcohol (0.83 mL, 12.20 mmol, 5 equiv) and CuCl (22.3 mg, 0.09

(31) Moriarty, R. M.; Chany, C. J., II; Vaid, R. K.; Prakash, O.; Tuladhar, S. M. *J. Org. Chem.* **1993**, *58*, 2478.

equiv, 99.99%) were added. Then, the reaction was warmed at 100 °C, for 2 h. The mixture was cooled, mixed with an aqueous saturated solution of $NaHCO_3$, and extracted with ethyl ether (4×). The organic phase was dried with Na_2SO_4, filtered, and evaporated. The crude was purified by column chromatography (14% hexane/AcOEt) to yield carbamate **8** (331 mg, 74%) as a colorless oil: IR (film) ν 3326, 3026, 2922, 1697, 1534, 1235, 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.94 (ddt, J = 17.2, 10.5 and 5.3 Hz, 1H, H2′), 5.72−5.66 (m, 1H, H4), 5.64−5.57 (m, 1H, H3, 5.32 (dc, J = 17.2 and 1.5 Hz, 1H, $H3'_{cis}$), 5.22 (dc, J = 10.4 and 1.4 Hz, 1H, $H3'_{trans}$), 4.75 (br s, 1H, NH), 4.57 (d, J = 5.2 Hz, 2H, CH_2O), 3.91−3.81 (m, 1H, H1), 2.40 (d J = 17.4 Hz, 1H, H2A), 2.19−2.10 (m, 2H, H5), 1.95−1.84 (m, 2H, H2B, H6A), 1.64−1.53 (m, 1H, H6B); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.6 (NHCO), 133.0 (C2′), 126.8 (CH═*C*H, C4), 124.3 (*C*H═CH, C3), 117.4 (C3′), 65.2 (C1′), 46.1 (C1), 31.8 (C2), 28.3 (C6), 23.6 (C5); MS (ES) m/z [M + 1]$^+$ 182.1, [M + 23]$^+$ 204.1, [2M + 1]$^+$ 363.3, [2M + 23]$^+$ 385.0. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.09; H, 8.25; N, 7.65.

(Prop-2′-yn-1′-yl) *N*-(Cyclohex-3-enyl)carbamate (9). Following the general procedure for the Curtius reaction (method A), a solution of cyclohex-3-enecarboxylic acid (**3**) (672 mg, 5.33 mmol) in dry toluene (16.6 mL, 0.32 M) was treated with Et_3N (0.89 mL, 6.38 mmol, 1.2 equiv) and DPPA (1.21 mL, 5.61 mmol, 1.05 equiv) at 80 °C for 5 h. Then, propargylic alcohol (1.55 mL, 26.63 mmol, 5 equiv) and CuCl (55.7 mg, 0.56 mmol, 0.1 equiv) were added, and the mixture was refluxed for 4 h. Workup and flash chromatography (hexane/AcOEt, 10%) afforded compound **9** (777.3 mg, 81%) as white crystals: mp 64−6 °C; IR (KBr) ν 3301, 2947, 2130, 1717, 1686, 1543, 1434, 1273, 1237, 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.74−5.52 (m, 2H, H3, H4), 4.85 (br s, 1H, NH), 4.68 (d, J = 2.4 Hz, 2H, CH_2O), 3.94−3.76 (m, 1H, H1, C*H*NH), 2.47 (t, J = 2.4 Hz, 1H, C≡CH), 2.40 (d, J= 17.1 Hz, 1H, H2), 2.26−2.02 (m, 2H, H5), 1.98−1.78 (m, 2H, H2′, H6), 1.70−1.50 (m, 1H, H6′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.8 (NH*C*O_2CH_2), 126.9, 124.2 (C3, C4), 78.4 (*C*≡CH), 74.5 (C≡*C*H), 52.2 (NHCO$_2$*C*H$_2$), 46.3 (CHN, C1), 31.7 (C2), 28.2 (C6), 23.5 (C5); MS (ES) m/z [M + 1]$^+$ 180.1, [M + 23]$^+$ 202.1. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.98; H, 7.24; N, 8.06.

Benzyl *N*-(*c*-3,*t*-4-Dibromocyclohex-1-yl)carbamate (12) and Benzyl *N*-(*t*-3,*c*-4-Dibromocyclohex-1-yl)carbamate (13). Following the general procedure for the bromination, a solution of benzyl *N*-(cyclohex-3-enyl)carbamate (**5**)[11] (1.30 g, 5.62 mmol) in dry DCM (65 mL 0.086 M) was reacted with Et_4NBr (11.97 g, 10 equiv) and Br_2 (0.58 mL, 11.32 mmol, 2 equiv) at −78 °C for 2 h. Workup and column chromatography (hexane/Et_2O, 10% to hexane/Et_2O, 30%) gave compounds **12** (1.35 g, 61%) and **13** (546 mg, 25%). **12**: mp 78−81 °C; IR (KBr) ν 3278, 3065, 2931, 1720, 1688, 1549, 1452, 1278, 1249, 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36 (s, 5H, C_6H_5), 5.10 (s, 2H, CH_2O), 4.94 (br s, 1H, NH), 4.2−4.0 (m, 2H, 2 × CHBr, H3, H4), 3.8−3.6 (m, 1H, H1, C*H*NH), 2.78 (br d, J = 13.5 Hz, 1H, H2), 2.5−2.4 (m, 1H, H5), 2.12−2.00 (m, 1H, H6), 2.0−1.8 (m, 2H, H5′, H2′), 1.5−1.3 (m, 1H, H6′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.5 (NH*C*O_2CH_2Ph), 136.4 (C_6H_5, C*ipso*), 128.7 (2 × CH, C_6H_5), 128.4 (2 × CH, C_6H_5), 128.2 (CH, C_6H_5), 67.0 (NHCO$_2$*C*H$_2$Ph), 55.1 (CHBr, C4),* 53.1 (CHBr, C3),* 48.5 (C1, CHN), 42.4 (br, C2), 33.9, 31.7 (br; C5, C6); MS (ES) m/z [M + 1]$^+$ 390.0/392.1/394.0, [M + 23]$^+$ 412.0/414.0/415.9. Anal. Calcd for $C_{14}H_{17}Br_2NO_2$: C, 42.99; H, 4.38; N, 3.58. Found: C, 42.61; H, 4.40; N, 3.72. **13**: oil; IR (film) ν 3322, 3033, 2950, 1695 (v br), 1533, 1454, 1279, 1234, 1043 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37 (s, 5H, Ar), 5.11 (s, 2H, CH_2O), 4.69 (br s, 1H, NH), 4.64 (m, 1H, CHBr, H3),* 4.60 (m, 1H, CHBr, H4),* 4.17−4.00 (m, 1H, H1, C*H*NH), 2.65−2.50 (m, 1H, H5), 2.39−2.19 (m, 2H, H2), 2.07−1.87 (m, 2H, H5′, H6), 1.84−1.67 (m, 1H, H6′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.6 (NH*C*O_2CH_2-Ph), 136.6 (C*ipso*), 128.6 (2xCH, C_6H_5), 128.2 (3xCH, C_6H_5), 66.8 (NHCO$_2$*C*H$_2$Ph), 52.2 (CHBr, C4),* 51.7 (CHBr, C3),* 45.6 (CHN, C1), 35.2 (br, C2), 28.4 (C5), 27.6 (C6); MS (ES) m/z [M + 23]$^+$ 412.0/414.0/416.0. Anal. Calcd for $C_{14}H_{17}Br_2NO_2$: C, 42.99; H, 4.38; N, 3.58. Found: C, 42.79; H, 4.40; N, 3.71.

(6′-Chloro-3′-pyridyl)methyl *N*-(*c*-3,*t*-4-Dibromocyclohex-1-yl)carbamate (14) and (6′-Chloro-3′-pyridyl)methyl *N*-(*t*-3,*c*-4-Dibromocyclohex-1-yl)carbamate (15). Following the general procedure for the bromination, to a solution of compound **6** (1.12 g, 4.23 mmol) in dry CH_2Cl_2 (50 mL) was added Et_4NBr (9.05 g, 43.06 mol, 10.2 equiv). After being stirred for some minutes at rt, the reaction vessel was placed in a dry ice−acetone bath at −78 °C. Then, bromine (0.44 mL, 8.59 mol, 2.03 equiv) was added. The reaction was pursued for 3 h stirring at −78 °C. Workup and flash chromatography (hexane/AcOEt, 30% to AcOEt) gave products **14** (1.06 g, 59%) and **15** (537 mg, 30%), both isolated as white crystalline solids. **14**: mp 107−9 °C; IR (KBr) ν 3358, 3045, 2939, 1693, 1531, 1463, 1276, 1107, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.39 (d, J = 2.4 Hz, 1H, H2′), 7.67 (dd, J = 2.4 and 8.1 Hz, 1H, H4′), 7.34 (d, J = 8.1 Hz, 1H, H5′), 5.09 (s, 2H, CH_2O), 5.05−4.95 (br s, 1H, NH), 4.24−4.0 (m, 2H, H3, H4, CHBr), 3.8−3.6 (m, 1H, C*H*NH), 2.78 (d, J = 13.5 Hz, 1H, H2A), 2.5−2.4 (m, 1H, H5A), 2.1−1.8 (m, 3H, H2B, H5B, H6A), 1.7−1.5 (m, 1H, H6B); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.8 (NH*C*O_2CH_2Ar), 151.0 (C3′), 149.2 (C2′), 138.8 (C4′), 130.9 (C6′), 124.1 (C5′), 63.1 (NHCO$_2$*C*H$_2$Ar), 54.7 (C3, CHBr),* 52.9 (C4, CHBr),* 48.3 (C1, CHNH), 42.1 (br, C2), 33.7 (br, C5), 31.5 (C6); MS (ES) m/z [M + 1]$^+$ 426.9. Anal. Calcd for $C_{13}H_{15}Br_2ClN_2O_2$: C, 36.61; H, 3.54; N, 6.57. Found: C, 37.17; H, 3.69; N, 6.23. **15**: mp 92−95 °C; IR (KBr) ν 3312, 3040, 2949, 1703, 1534, 1461, 1235, 1104, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.40 (d, J = 1.8 Hz, 1H, H2′), 7.68 (dd, J = 8.0, 1.9 Hz, 1H, H4′), 7.34 (d, J = 8.1 Hz, 1H, H5′), 5.09 (s, 2H, CH_2O), 4.80−4.67 (br s, 1H, NH), 4.68−4.56 (m, 2H, H3, H4, C*H*-Br × 2), 4.17−3.95 (m, 1H, H1, C*H*-NH), 2.65−2.49 (m, 1H, H5A), 2.0−2.18 (m, 2H, 2 × H2) , 2.08−1.97 (m, 1H, H5B), 1.97−1.85 (m, 1H, H6A), 1.76 (qd, J = 12.4, 3.6 Hz, 1H, H6B); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.9 (NH*C*O_2CH_2-Ar), 151.2 (C3′), 149.4 (CH, C2′), 138.8 (CH, C4′), 131.0 (C6′), 124.1 (CH, C5′), 63.1 (NHCO$_2$*C*H$_2$Ar), 51.8 (*C*HBr, C3),* 51.3 (CHBr, C4),* 45.5 (*C*H−N, C1), 34.8 (*C*H$_2$, C2), 28.1 (*C*H$_2$, C5), 27.3 (*C*H$_2$, C6); MS (ES) m/z [M + 1]$^+$ 426.9. Anal. Calcd for $C_{13}H_{15}Br_2ClN_2O_2$: C, 36.61; H, 3.54; N, 6.57. Found: C, 36.35; H, 3.69; N, 6.34.

Methyl *N*-(3-*c*,4-*t*-Dibromocyclohex-1-yl)carbamate (16) and Methyl *N*-(3-*t*,4-*c*-Dibromocyclohex-1-yl)carbamate (17). Following the general procedure for the bromination, a solution of compound **7** (362 mg, 2.34 mmol) in dry CH_2Cl_2 (27 mL, 0.09 M) was treated with Et_4NBr (4.92 g, 23.36 mmol, 10 equiv) and Br_2 (0.24 mL, 4.67 mmol, 2 equiv) for 3 h at −78 °C. Workup and flash chromatography (hexane/AcOEt, 15%) gave compound **16** (382 mg, 52%) and its isomer **17** (221 mg, 30%). **16**: white solid; mp 97−9 °C; IR (KBr) ν 3301, 2947, 1719, 1692, 1548, 1447, 1278, 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.83 (br s, NH), 4.16 (td, J = 9.4, 3.9 Hz, 1H, H3), 4.09 (td, J = 9.5, 3.9 Hz, 1H, H4), 3.78−3.60 (m, 1H, H1), 3.67 (s, 3H, OCH_3), 2.78 (dm, 1H, J = 13.5 Hz, 1H, $H2_{eq}$), 2.56−2.45 (m, 1H, $H5_{eq}$), 2.12−2.00 (m, 1H, $H6_{eq}$), 2.00−1.90 (m, 1H, $H5_{ax}$), 1.90−1.78 (m, 1H, $H2_{ax}$), 1.49−1.30 (m, 1H, $H6_{ax}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.1 (NH*C*O_2CH_3), 55.2 (CHBr, C3), 53.3 (CHBr, C4), 52.2 (OCH_3), 48.4 (CHN, C1), 42.5 (br, C2), 34.1 (br, C5), 31.8 (C6); MS (ES) m/z [M + 1]$^+$ 315.9, [M + 23]$^+$ 337.9. Anal. Calcd for $C_8H_{13}Br_2NO_2$: C, 30.50; H, 4.16; N, 4.45. Found: C, 30.42; H, 3.95; N, 4.50. **17**: white solid; mp 104−6 °C; IR (KBr) ν 3340, 2951, 1694, 1542, 1434, 1320, 1059 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.94 (br s, NH), 4.64−4.59 (m, 1H, H3), 4.58−4.53 (m, 1H, H4), 4.12−3.92 (m, 1H, H1), 3.64 (s, 3H, OCH_3), 2.55 (ddt, J = 15.2, 12.1, 3.4 Hz, 1H, $H5_{ax}$), 2.38−2.24 (m, 1H, $H2_{ax}$), 2.18 (d, J = 14.4 Hz, 1H, $H2_{eq}$), 2.04−1.94 (m, 1H, H $H5_{eq}$), 1.88 (br d, J = 11.6 Hz, 1H, $H6_{eq}$), 1.73 (dtd, J = 12.4, 12.3, 3.3 Hz, 1H, $H6_{ax}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.3 (NH*C*O_2CH_3), 52.3 (OCH_3), 52.2 (CHBr, C4), 51.7 (CHBr, C3), 45.4 (CHN, C1), 35.2 (C2), 28.3

(C5), 27.6 (C6); MS (ES) *m*/*z* [M + 1]$^+$ 315.9, [M + 23]$^+$ 337.9. Anal. Calcd for $C_8H_{13}Br_2NO_2$: C, 30.50; H, 4.16; N, 4.45. Found: C, 30.21; H, 4.07; N, 4.32.

Allyl *N*-(3-*c*,4-*t*-Dibromocyclohex-1-yl)carbamate (18) and Allyl *N*-(3-*t*,4-*c*-Dibromocyclohex-1-yl)carbamate (19). Following the general procedure for the bromination, to a solution of compound **8** (114 mg, 0.63 mmol) in dry CH_2Cl_2 (7.5 mL, 0.08 M) was added Et_4NBr (1.33 g, 6.31 mmol, 10 equiv), and the resulting solution was stirred under argon at rt. After 30 min, the solution was cooled at −78 °C, and then Br_2 (0.04 mL, 0.69 mmol, 1.1 equiv) was added. After 70 min, the temperature was allowed to rise, and workup was performed as usual. Flash chromatography (hexane/AcOEt, 10%) gave 3-*cis*,4-*trans*-dibromide **18** (130 mg, 61%) and 3-*trans*,4-*cis*-dibromide **19** (71 mg, 33%). **18**: oil; IR (film) ν 3323, 3080, 2948, 1701, 1530, 1274, 1047 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.98−5.86 (m, 1H, H2′), 5.31 (dq, J = 17.2 and 1.5 Hz, 1H, H3′$_{cis}$), 5.23 (dm, J = 10.4 Hz, 1H, H3′$_{trans}$), 4.87 (br s, 1H, NH), 4.56 (d, J = 5.5 Hz, 2H, CH_2O), 4.21−4.05 (m, 2H, H3, H4), 3.77−3.66 (m, 1H, H1), 2.79 (dm, J = 13.5 Hz, 1H, H2A), 2.55−2.48 (m, 1H, H5A), 2.11−2.04 (m, 2H, H6A), 2.00−1.82 (m, 2H, H5B, H2B), 1.46−1.34 (m, 1H,H6B); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.3 ($NHCO_2$), 132.8 (C2′), 118.2 (C3′), 65.9 (C1′), 55.0, 53.1 (C3, C4), 48.4 (C1), 42.2 (C2), 33.7 (C5), 31.7 (C6); MS (ES) *m*/*z* [M + 1]$^+$ 339.9/341.9/343.9, [M + 23]$^+$ 361.9/363.9/365.9. Anal. Calcd for $C_{10}H_{15}Br_2NO_2$: C, 35.22; H, 4.43; N, 4.11. Found: C, 34.94; H, 4.31; N, 4.02. **19**: oil; IR (KBr) ν 3322, 3080, 2950, 1700, 1533, 1278, 1235, 1044 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.00−5.85 (m, 1H, H2′), 5.32 (d, J = 17.1 Hz, 1H, H3′$_{cis}$), 5.22 (d, J = 10.4 Hz, 1H, H3′$_{trans}$), 4.68 (br s, 1H, NH), 4.64 (s with multiplicity, 1H, H3*), 4.62−4.54 (m, 3H, CH_2O + H4*), 4.14−4.00 (m, 1H, H1), 2.58 (ddt, J = 15.5, 12.3, and 3.4 Hz, 1H, H5A), 2.38−2.29 (m, 1H, H2A), 2.24 (dm, J = 14.4 Hz, 1H, H2B), 2.02 (dm, J = 15.4 Hz, 1H, H5B), 1.98−1.88 (m, 1H, H6A), 1.76 (dc, J = 12.4 and 3.5 Hz, 1H, H6B); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5 ($NHCO_2$), 133.0 (−*C*H═CH_2), 118.0 (−CH═*C*H_2), 65.8 (*C*H_2−O), 52.2, 51.7 (C3, C4), 45.6 (C1), 35.3 (C2), 28.4 (C5), 27.7 (C6); MS (ES) *m*/*z* [M + 1]$^+$ 339.9/341.9/343.9, [M + 23]$^+$ 361.9/363.9/365.9. Anal. Calcd for $C_{10}H_{15}Br_2NO_2$: C, 35.22; H, 4.43; N, 4.11. Found: C, 35.40; H, 4.28; N, 4.25.

Prop-2′-yn-1′-yl *N*-(3-*c*,4-*t*-Dibromocyclohex-1-yl)carbamate (20) and Prop-2′-yn-1′-yl *N*-(3-*t*,4-*c*-Dibromocyclohex-1-yl)-carbamate (21). Following the general procedure for the bromination, a solution of compound **9** (330 mg, 1.84 mmol) in dry CH_2Cl_2 (21 mL, 0.09 M) was reacted with Et_4NBr (3.88 g, 18.5 mmol, 10 equiv) and Br_2 (0.19 mL, 3.71 mmol, 2 equiv) at −78 °C for 2.5 h. Workup and flash chromatography (hexane/AcOEt, 13%) gave 3-*cis*,4-*trans*-dibromide **20** (349 mg, 56%) and 3-*trans*,4-*cis*-dibromide **21** (201 mg, 32%). **20** (white solid): mp 81−2 °C; IR (KBr) ν 3413, 3240, 2957, 2134, 1716, 1519, 1452, 1276, 1220, 1053 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.08 (br s, 1H, NH), 4.66 (d, J = 1.8 Hz, 2H, CH_2O), 4.20−4.12 (m, 1H, H3), 4.12−4.04 (m, 1H, H4), 3.76−3.65 (m, 1H, H1), 2.80−2.73 (dm, J = 13.6 Hz, 1H, H2$_{eq}$), 2.53−2.46 (m, 2H, HC≡C, H5$_{eq}$), 2.09−2.02 (m, 1H, H6$_{eq}$), 1.99−1.83 (m, 2H, H5$_{ax}$, H2$_{ax}$), 1.46−1.35 (m, 1H, H6$_{ax}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.6 ($NHCO_2CH_2$), 78.2 (*C*≡CH), 75.0 (C≡*C*H), 54.9 (*C*HBr, C4), 53.0 (*C*HBr, C3), 52.7 ($NHCO_2CH_2$), 48.5 (CHN, C1), 41.9 (br, C2), 33.5 (br, C5), 31.5 (C6); MS (ES) *m*/*z* [M + 1]$^+$ 337.9/339.9/341.9, [M + 23]$^+$ 359.9/361.9/363.9. Anal. Calcd for $C_{10}H_{13}Br_2NO_2$: C, 35.43; H, 3.86; N, 4.13. Found: C, 35.40; H, 3.69; N, 4.13. **21**: oil; IR (film) ν 3402, 3298, 2949, 2125, 1702, 1537, 1435, 1279, 1236, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.82 (br d, J = 6.4 Hz, 1H, NH), 4.65 (d, J = 2.1 Hz, 2H, CH_2O), 4.63−4.59 (m, 1H, H3), 4.58−4.53 (m, 1H, H4), 4.09−3.96 (m, 1H, H1), 2.58−2.48 (m, 1H, H5$_{eq}$), 2.47 (t, J = 2.4 Hz, 1H, HC≡C), 2.32 (ddd, J = 14.3, 11.1, 3.2 Hz, 1H, H2$_{ax}$), 2.19 (dm, J = 14.4 Hz, 1H, H2$_{eq}$), 1.98 (dm, J = 13.8 Hz, 1H, H5$_{ax}$), 1.93−1.84 (m, 1H, H6$_{eq}$), 1.74 (dtd, J = 12.4, 12.2, 3.7 Hz, 1H, H6$_{ax}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.6 ($NHCO_2CH_2$), 78.3 (*C*≡CH), 74.8 (C≡*C*H), 52.5, 52.2 (2 C, C3, C4), 51.6 ($NHCO_2CH_2$), 45.6 (CHN, C1), 35.0 (C2), 28.3 (C5), 27.4 (C6); MS (ES) *m*/*z* [M + 1]$^+$ 337.9/339.9/341.9, [M + 23]$^+$ 359.9/361.9/363.9. Anal. Calcd for $C_{10}H_{13}Br_2NO_2$: C, 35.43; H, 3.86; N, 4.13. Found: C, 35.60; H, 3.83; N, 4.08.

Heterocyclization of *tert*-Butyl *N*-(*c*-3,*t*-4-Dibromocyclohex-1-yl)carbamate (10). Following the general procedure for the heterocyclization reaction, dibromide **10**[12] (304 mg, 0.85 mmol) in DMF (9 mL) was reacted with NaH (52 mg, 1.30 mmol). After 1 h at 0 °C and 1 h at rt, more NaH (69 mg, 1.72 mmol, 2.0 equiv) was added. After 5 h, the reaction was complete. Workup and column chromatography (hexane/Et_2O, 15%, and AcOEt) afforded 2-*exo*-bromo-7-[(*tert*-butoxy)carbonyl]-7-azabicyclo[2.2.1]heptane (**2**) [^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.38, 4.31 (2 br s, 2H, H1, H4), 3.99 (dd, J = 7.4, 3.4 Hz, 1H, H2), 2.28 (dm, J = 13.8 Hz, 1H, H3$_{exo}$), 2.18 (dd, J = 13.9, 7.4 Hz, 1H, H3$_{endo}$), 1.96−1.77 (m, 1H), 1.77−1.68 (m, 1H), 1.47 (s, 9H, *t*-Bu), 1.44−1.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.0, 79.9 (C−O), 63.9, 55.7 (br) (C1, C4), 49.7 (br, C2), 43.6 (C3), 28.3 (*t*-Bu, C5, C6)][12] (122 mg, 52%) and 3a,4,5,7a-tetrahydro-2(3*H*)-benzooxazolone (**22**) [^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.14−6.20 (m, 2H, NH, H6), 5.84−5.80 (m, 1H, H7), 4.92−4.89 (m, 1H, H7a), 4.02−3.95 (td, J = 7.6, 4.0 Hz, 1H, H3a), 2.27−2.20 (m, 1H, H5), 2.03−1.82 (m, 2H, H4, H5′), 1.75−1.63 (m, 1H, H4′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.4, 134.3, 122.6, 72.4, 51.1, 25.6, 20.7][16] (30 mg, 25%).

7-[(Benzyloxy)carbonyl]-*exo*-2-bromo-7-azabicyclo[2.2.1]heptane (23). Following the general procedure for the heterocyclization reaction, dibromide **12** (385 mg, 0.99 mmol) in dry DMF was reacted with NaH (55 mg, 1.38 mmol, 1.40 equiv) and stirred for 31 h. Then, more NaH (22.8 mg, 0.57 mmol, 0.56 equiv) was added, and after 18 h, the reaction was complete. Workup and column chromatography (CH_2Cl_2) gave compound **23** (220 mg, 72%): white solid; mp 50−53 °C; IR (KBr) ν 3436, 3032, 2955, 1690, 1434, 1318, 1158, 1103 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41−7.28 (m, 5H, C_6H_5), 5.16 (s, 2H, CH_2O), 4.52 (br s, 1H, CH−N, H1),* 4.40 (br s, 1H, CHN, H4),* 4.02 (dd, J = 7.3, 3.3 Hz, 1H, H2), 2.33 (dm, J = 13.8 Hz, 1H, H3$_{exo}$), 2.22 (dd, J = 13.8, 7.3 Hz, 1H, H3$_{endo}$), 1.99−1.83 (m, 1H, H6), 1.83−1.66 (m, 1H, H5), 1.50−1.41 (m, 1H, H6′), 1.39−1.28 (m, 1H, H5′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.5 ($NHCOOCH_2Ph$), 136.7 (C_6H_5, C*ipso*), 128.6 (2 × CH, C_6H_5), 128.2 (CH, C_6H_5), 128.1 (2 × CH, C_6H_5), 67.2 ($NHCOOCH_2Ph$), 64.2 (C1), 56.2 (C4), 49.7 (br, C2), 43.5 (br, C3), 28.3 (br, 2C, C5, C6); MS (ES) *m*/*z* [M + 1]$^+$ 309.9/311.9, [M + 23]$^+$ 331.9/333.9. Anal. Calcd for $C_{14}H_{16}BrNO_2$: C, 54.21; H, 5.20; N, 4.52. Found: C, 54.05; H, 5.08; N, 4.64.

***exo*-2-Bromo-7-[(6′-chloropyridin-3′-yl)methyloxycarbonyl]-7-azabicyclo[2.2.1]heptane (24).** Following the general procedure for the heterocyclization reaction, to a solution of carbamate **14** (263 mg, 0.617 mmol) in dry DMF (13 mL, 0.049 M) cooled at 0 °C was added NaH (51.9 mg, 1.30 mmol, 2.1 equiv, 60% dispersion in oil) in portions, and then the temperature of the bath was allowed to reach rt. After 27 h, usual workup and column chromatography (hexane/AcOEt, 25%) yielded compound **24** (133 mg, 63%) as a white solid: mp 78−80 °C; IR (KBr) ν 2953, 1709, 1461, 1315, 1097 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.42 (d, J = 2.3 Hz, 1H, H2′), 7.71 (dd, J = 8.2, 2.3 Hz, 1H, H4′), 7.33 (d, J = 8.2 Hz, 1H, H5′), 5.14 (s, 2H, CH_2O), 4.48 (br s, 1H, CHN, H1),* 4.42 (br s, 1H, CHN, H4),* 4.02 (dd, J = 7.1, 3.5 Hz, 1H, H2), 2.35−2.15 (m, 2H, H3), 2.01−1.82 (m, 1H, H6A) 1.81−1.62 (m, 1H, H5A), 1.53−1.41 (m, 1H, H6B), 1.40−1.37 (m, 1H, H5B); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.6 ($NHCO_2CH_2Ar$), 151.2 (C3′), 149.4 (C2′), 138.9 (C4′), 131.2 (C6′), 124.2 (C5′), 64.1 (C1), 63.6 ($NHCO_2CH_2Ar$), 56.1 (C4), 49.6 (C2), 43.3 (C3), 28.3 (C6),* 28.1 (C5);* MS (ES) *m*/*z* 265.0 [M − 79], 345.0/347.0 [M + 1]$^+$, 367.0/368.9 [M + 23]$^+$. Anal. Calcd for $C_{13}H_{14}BrClN_2O_2$: C, 45.18; H, 4.08; N, 8.11. Found: C, 45.40; H, 4.08; N, 8.34.

***exo*-2-Bromo-7-[(methoxy)carbonyl]-7-azabicyclo[2.2.1]heptane (25).** Following the general procedure for the heterocyclization reaction, a solution of compound **16** (341 mg, 1.08 mmol) in dry

DMF (22 mL, 0.05 M) was reacted with NaH (55 mg, 1.37 mmol, 1.26 equiv) for 25 h at rt. Workup and column chromatography (hexane/AcOEt, 15%) afforded recovered starting material **16** (10 mg) and **25** [197 mg, 78% (80%, taking into account the unreacted starting material)]: oil; IR (film) ν 2953, 1707, 1447, 1369, 1319, 1235, 1190, 1158, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.46 (d, J = 4.0 Hz, 1H, H1), 4.40 (t, J = 4.5 Hz, 1H, H4), 4.01 (dd, J = 7.4, 4.5 Hz, 1H, H2), 3.72 (s, 3H, OCH_3), 2.31 (dm, J = 14.0 Hz, 1H, $H3_{exo}$), 2.21 (dd, J = 14.0, 7.4 Hz, 1H, $H3_{endo}$), 1.90 (tdd, J = 12.1, 5.2, 3.7 Hz, 1H, $H6_{exo}$), 1.83−1.68 (m, 1H, $H5_{exo}$), 1.51−1.40 (m, 1H, $H6_{endo}$), 1.39−1.28 (m, 1H, $H5_{endo}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2 ($NHCO_2CH_3$), 64.2 (CHN, C1), 56.2 (CHN, C4), 52.7 (OCH_3), 49.4 (CHBr, C2), 43.7 (C3), 28.4 (2 C, C5, C6); MS (ES) m/z $[M + 1]^+$ 234.1, $[M + 23]^+$ 256.0, $[2M + 23]^+$ 491.0. Anal. Calcd for $C_8H_{12}BrNO_2$: C, 41.05; H, 5.17; N, 5.98. Found: C, 40.89; H, 5.12; N, 5.75.

***exo*-2-Bromo-7-(allyloxycarbonyl)-7-azabicyclo[2.2.1]heptane (26).** Following the general procedure for the heterocyclization reaction, dibromide **18** (108 mg, 0.32 mmol) in DMF (6.5 mL) was reacted with NaH (14 mg, 0.36 mmol). After 1 h at 0 °C and 20 h at rt, more NaH (7.8 mg, 0.19 mmol, 0.61 equiv) was added. After 22 h, starting material was still visible by NMR, so more NaH was added (7.8 mg, 0.19 mmol, 0.61 equiv), after which time the reaction had finished within 2 h. Workup as usual and column chromatography (hexane/AcOEt, 10%) afforded 2-*exo*-bromo-7-(allyloxycarbonyl)-7-azabicyclo[2.2.1]heptane **26** (48 mg, 58%). **26**: oil; IR (film) ν 3015, 2950, 1707, 1441, 1312, 1091 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.99−5.89 (m, 1H, H2′), 5.32 (dm, J = 17.2 Hz, 1H, $H3'_{cis}$), 5.21 (dm, J = 10.4 Hz, 1H, $H3'_{trans}$), 4.60 (dm, J = 5.6 Hz, 2H, 2 × H1′), 4.48 (d, J = 4.7 Hz, 1H, H1), 4.43−4.38 (m, 1H, H4), 4.01 (dd, J = 7.4, 3.0 Hz, 1H, H2), 2.30 (dm, J = 13.9 Hz, 1H, $H3_{exo}$), 2.21 (dd, J = 14.0, 7.5 Hz, 1H, $H3_{endo}$), 1.94−1.85 (m, 1H, $H6_{exo}$), 1.81−1.70 (m, 1H, $H5_{exo}$), 1.48−1.41 (m, 1H, $H6_{endo}$), 1.38−1.30 (m, 1H, $H5_{endo}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.3 ($NHCO_2$), 133.0 (C2′), 117.6 (C3′), 66.0 (C1′), 64.1 (C1), 56.1 (C4), 49.4 (C2), 43.5 (C3), 28.2 (2 C, C5, C6); MS (ES) m/z $[M + 1]^+$ 260.0/262.0, $[M + 23]^+$ 282.0/284.0, $[2M + 23]^+$ 541.0/543.0/545.0. Anal. Calcd for $C_{10}H_{14}BrNO_2$: C, 46.17; H, 5.42; N, 5.38. Found: C, 46.35; H, 5.31; N, 5.24.

3-((1*SR*,3*SR*,4*SR*)-3,4-Dibromocyclohexyl)-4-methyleneoxazolidin-2-one (27). Following the general procedure for the heterocyclization reaction, a solution of dibromide **20** (30 mg, 0.09 mmol) in dry DMF (0.9 mL, 0.1 M) was reacted with NaH (4.3 mg, 0.11 mmol, 1.2 equiv) at rt for 4.5 h, until starting material disappeared (TLC). Workup and column chromatography (hexane/AcOEt, 15%) yielded compound **27** (12.6 mg, 42%): oil; IR (film) ν 3150, 2953, 1740, 1662, 1377, 1235 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.82 (t, J = 2.3 Hz, 2H, CH_2O), 4.24 (dt, J = 3.3, 2.6 Hz, 1H, =CHA), 4.15 (dt, J = 3.4, 2.1 Hz, 1H, =CHB), 4.06−4.01 (m, 2H, H3, H4), 3.65 (tt, J = 12.4, 3.9 Hz, 1H, H1), 2.79 (dt, J = 13.1, 12.2 Hz, 1H, $H2_{ax}$), 2.60 (dc, J = 13.9, 3.7 Hz, 1H, $H5_{ec}$), 2.50 (dtd, J = 13.1, 3.9, 2.8 Hz, 1H, $H2_{eq}$), 2.35 (dtd, J = 12.5, 13.3, 3.7 Hz, 1H, $H6_{ax}$), 2.04−1.90 (m, 1H, $H5_{ax}$), 1.82 (dm, J = 13.2 Hz, 1H, $H6_{eq}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2 (NCO_2CH_2), 140.2 (C=CH_2), 81.3 (C=$C$$H_2$), 66.9 ($NCO_2CH_2$), 55.0, 53.9 (2 C, C3, C4), 51.4 (C1), 39.3 (C2), 36.4 (C5), 28.1 (C6); MS (ES) m/z $[M + 1]^+$ 337.9/339.9/341.9, $[M + 23]^+$ 359.9/361.9/363.7, $[2M + 23]^+$ 698.7/700.7/702.8. Anal. Calcd for $C_{10}H_{13}Br_2NO_2$: C, 35.43; H, 3.86; N, 4.13. Found: C, 35.54; H, 3.90; N, 3.97. Compound **27** slowly isomerizes to **3-[(1*SR*,3*SR*,4*SR*)-3,4-dibromocyclohexyl]-4-methyloxazol-2(3*H*)-one** (**28**) as detected after storage for 5 months at 5−20 °C and isolation by flash chromatography (1% CH_2Cl_2/MeOH): oil; IR (film) ν 2926, 2342, 2360, 1738, 1444 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.54 (q, J = 1.6 Hz, 1H, H5′), 4.06−4.01 (m, 2H, H3, H4), 3.66 (tt, J = 12.4, 4.0 Hz, 1H, H1), 2.90−2.80 (m, 1H, $H2_{ax}$), 2.61 (dm, J = 14.0 Hz, 1H, $H5_{ec}$), 2.55−2.49 (dm, J = 13.1 Hz, 1H, $H2_{eq}$), 2.47−2.34 (m, 1H, $H6_{ax}$), 2.02 (d, J = 1.6 Hz, 3H, CH_3); 2.00−1.90 (m, 1H, $H5_{ax}$), 1.84 (dm, J = 13.3 Hz, 1H, $H6_{eq}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.1 (NCO_2), 124.0 (C5′), 123.4 (C4′), 54.7 (C3*), 53.6 (C4*), 52.0 (C1), 40.8 (C2), 36.4 (C5), 29.6 (C6), 9.7 (CH_3); MS (ES) m/z 255.9/257.9/259.9, $[M + 1]^+$ 337.6/339.6/341.9, $[M + 23]^+$ 359.9/361.6/363.6, $[2M + 23]^+$ 696.5/698.5/700.5/702.5/704.7. Anal. Calcd for $C_{10}H_{13}Br_2NO_2$: C, 35.43; H, 3.86; N, 4.13. Found: C, 35.18; H, 3.89; N, 3.94.

7-Acetyl-*exo*-2-bromo-7-azabicyclo[2.2.1]heptane (30). (A) From Compound 2. To a solution of bromide **2** (50 mg, 0.18 mmoles) in dry CH_2Cl_2 (4 mL) was added TFA (0.27 mL, 3.63 mmol, 20 equiv). The mixture was allowed to react at rt during 6 h, and then the solvent was evaporated at reduced pressure, avoiding warming over 35 °C. The residue was dissolved in a satd aq K_2CO_3 solution and extracted with $CHCl_3$ (3×). The organic phases were then dried over K_2CO_3 and the solvents evaporated at T < 35 °C. The resulting crude, showing spectroscopic data [^1H NMR ($CDCl_3$, 300 MHz) δ 4.12 (dd, J = 6.9, 2.7 Hz, 1H, H2), 3.78−3.71 (m, 2H, H1, H4), 2.20 (dd, J = 14.4, 6.9 Hz, 1H, H3-*endo*), 2.04 (ddt, J = 14.4, 5.2, 2.7 Hz, 1H, H3-*exo*), 1.91 (br s, 1H, NH), 1.78 (tdd, J = 12.2, 5.2, 3.2 Hz, 1H), 1.69−1.56 (m, 1H), 1.34−1.13 (m, 2H)] identical to those described in the literature for *exo*-2-bromo-7-azabicyclo[2.2.1]heptane **(29)**,[12] was then submitted to standard acetylation conditions [pyridine (2 mL), Ac_2O (2 mL)] during 17 h. The reagents were then coevaporated with toluene at reduced pressure, and the crude was purified by chromatographic column using silica gel and AcOEt/MeOH/NH_3 (6:94:0.3) as eluent, yielding compound **30** (30 mg, 76%) of as a white solid: mp 64−6 °C; IR (KBr) ν 2952, 1643, 1449, 1419 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.79 (d, J = 5.6 Hz, 1H, H1) (minor invertomer), 4.72 (t, J = 4.6 Hz, 1H, H4) (major invertomer), 4.27 (d, J = 5.2 Hz, 1H, H1) (major invertomer), 4.21 (t, J = 4.2 Hz, 1H, H4) (minor invertomer), 4.07 (dd, J = 3.6, 6.8 Hz, 1H, H2) (major invertomer), 4.03 (dd, J = 3.8, 6.6 Hz, 1H, H2) (minor invertomer), 2.31−2.26 (m, 2H, H3) (minor invertomer), 2.23−2.17 (m, 2H, H3) (major invertomer), 2.11 (s, 3H, $COCH_3$) (major invertomer), 2.07 (s, 3H, $COCH_3$) (minor invertomer), 1.96−1.83 (m, H6 *exo*, both invertomers), 1.78−1.65 (m, 1H, H5 *exo*, both invertomers), 1.56−1.47 (m, 1H, H6 *endo*, major invertomer), 1.45−1.39 (m, H6 *endo*, H5 *endo*, minor invertomer), 1.35−1.27 (m, 1H, H5 *endo*, major invertomer); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.7 ($NCOCH_3$), 64.7 (C1, major invertomer), 61.1 (C1, minor invertomer), 56.7 (C4, minor invertomer), 53.0 (C4, major invertomer), 50.4 (C2, major invertomer), 48.2 (C2, minor invertomer), 44.5 (C3, minor invertomer), 42.8 (C3, major invertomer), 29.5 (C6, minor invertomer), 28.9 (C6, major invertomer), 27.7 (C5, major invertomer), 27.0 (C5, minor invertomer), 21.7 (major invertomer) and 21.5 (major invertomer) ($COCH_3$); MS (ES) m/z $[M + 1]^+$ 218.1/220.1, $[M + 23]^+$ 240.1/242.1. Anal. Calcd for $C_8H_{12}BrNO$: C, 44.06; H, 5.55; N, 6.42. Found: C, 43.78; H, 5.40; N, 6.33. **(B) From Compound 41.** To a solution of 2,2,2-trifluoroacetamide **41** (161 mg, 0.59 mmol) in MeOH/H_2O (7:3, 10 mL) was added K_2CO_3 (416 mg, 3.00 mmol, 5 equiv), and the mixture was stirred for 21 h at rt. The solvent was removed, and the residue was suspended in an aqueous saturated solution of K_2CO_3, and extracted with $CHCl_3$ (5×). The organic phase was dried, filtered, and evaporated. The crude was acetylated under the usual conditions [pyridine (2 mL), Ac_2O (2 mL), rt, 50 h). After solvent removal, the crude was purified by flash chromatography (AcOEt/MeOH/NH_3, 94:6:4) giving compound **30** (93 mg, 72%).

7-[(*tert*-Butoxy)carbonyl]-7-azabicyclo[2.2.1]hept-2-ene (31). To a solution of bromide **2** (175 mg, 0.63 mmol) in dry THF (8 mL, 0.08 M) under argon, at rt, was added *t*-BuOK (84 mg, 0.71 mmol, 1.12 equiv), and the suspension was refluxed for 3.5 h. Then, further *t*-BuOK (38 mg, 0.32 mmol, 0.5 equiv) was added, and the reflux was continued for 1.5 h. The mixture was cooled at rt, brine was added, and the mass was extracted with ethyl ether (3×). The organic layer was dried (Na_2SO_4), filtered, and evaporated. The crude was submitted to column chromatography (hexane/AcOEt, 5%), to give compound **31** (96 mg, 78%) [^1H NMR ($CDCl_3$, 300

MHz) δ 6.22 (s, 2H, H2, H3), 4.65 (s, 2H, H1, H4), 1.84 (d, J = 9.3 Hz, 2 H), 1.42 [s, 9H, OC(CH_3)$_3$], 1.09 (d, J=7.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.3 (NHCOO), 134.8 (2C, C2, C3), 79.8 [O*C*(CH_3)$_3$], 59.7 (2C, C1, C4), 28.4 [OC(*C*H_3)$_3$], 24.0 (2C, C5, C6)] identical to those described in the literature for the same compound.[14]

7-Carbomethoxy-7-azabicyclo[2.2.1]hept-2-ene (32). To a solution of bromide **25** (100 mg, 0.43 mmol) of in dry THF (7 mL, 0.06 M) was added *t*-BuOK (68 mg, 0.60 mmol, 1.40 equiv) in small portions. The resulting solution was then heated under reflux during 4 h, after which 25 mg more of *t*-BuOK (0.22 mmol, 0.5 equiv) was added. After 1 h, the starting material was no longer detectable by TLC analysis, and the mixture was allowed to reach rt and then added to 5 mL of a satd aq solution of NaCl. The aqueous solution was extracted with ether (3×), and the organic phases were dried over Na_2SO_4 and evaporated to afford **32** (80%), which showed spectroscopic data [^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.23 (s, 2H, H2, H3), 4.72 (s, 2H, H1, H4), 3.63 (s, 3H, OCH_3), 1.91−1.80 and 1.18−1.04 (m, 4, 2H5, 2H6) ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.1 (NH*C*O_2CH_3), 134.9 (br s, 2 C, *C*2, C3), 59.7 (2 C, C1, C4), 52.6 (NHCO$_2$*C*H_3), 24.0 (2 C, C5, C6)] similar to the same product previously described in the literature.[18b]

6-Aminocyclohex-2-enol (33). To a solution of 3a,4,5,7a-tetrahydro-2(3*H*)-benzooxazolone (**22**) (70 mg, 0.5 mmol) in 1,4-dioxane (12.5 mL, 0.04 M) was added an aqueous solution of LiOH 2N (1.25 mL, 2.5 mmol, 5 equiv). The mixture was stirred ar rt for 68 h, 29 h at 60 °C, and 7 days at reflux. The crude was cooled, the solvent removed, and the residue suspended in brine and extracted with AcOEt. The organic layer was dried (Na_2SO_4) and filtered, and the solvents were evaporated. The resulting crude was purified by column chromatography (CH_2Cl_2/MeOH, 1% to CH_2Cl_2/MeOH/NH_3, 85: 15: 4) to give starting material **22** (18 mg, 26%) and compound **33** [(26 mg, 46% (63% taking into account the recovered starting material)]: red solid; mp 66−70 °C; IR (KBr) ν 3435, 3026, 2920, 1631, 1462, 1382, 1068, 1000 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.88−5.72 (m, 2H, H2, H3), 4.02 (br s with multiplicity, 1H, H1), 2.97 (dt, J = 9.3, 3.9 Hz, 1H, H6), 2.28 (br s, 3H, NH_2, OH), 2.24−1.96 (m, 2H, 2xH4), 1.75−1.55 (m, 2H, 2xH5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 130.4, 128.4 (C2, C3), 66.0 (C1), 50.1 (C6), 26.6 (C5), 24.0 (C4); MS (ES) m/z [M + 1]$^+$ 114.1. Anal. Calcd for $C_6H_{11}NO$: C, 63.68; H, 9.80; N, 12.38. Found: C, 63.51; H, 9.70; N, 12.24.

6-Acetamidocyclohex-2-enyl Acetate (34). Amino alcohol **33** (19 mg, 0.17 mmol) was treated with Ac_2O (2 mL) and pyridine (2 mL) for 83 h at rt. The solvents were removed in vacuo and the residue purified by column chromatography (CH_2Cl_2/MeOH, 1%), affording compound **34** (24.7 mg, 74%): mp 86−8 °C; IR (KBr) ν 3440, 3319, 3031, 2908, 1729, 1643, 1541, 1237 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.96 (dt, J = 10.0, 3.4 Hz, 1H, H3), 5.81 (ddt, J = 9.8, 4.4, 2.2 Hz, 1H, H2), 5.70 (br d, J = 7.1 Hz, 1H, NH), 5.19−5.15 (m, 1H, H1), 4.28−4.19 (m, 1H, H6), 2.23−2.17 (m, 2H, 2 × H4), 2.08 (s, 3H, OCOCH_3), 1.99 (s, 3H, NHCOCH_3), 1.80−1.74 (m, 2H, 2 × H5); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.5 (O*C*OCH_3), 169.6 (NH*C*OCH_3), 133.3 (C3), 124.0 (C2), 68.3 (C1), 46.8 (C6), 24.6 (C4), 24.0 (C5), 23.7 (NHCO*C*H_3), 21.4 (OCO*C*H_3); MS (ES) m/z [M − 59]$^+$ 138.1, [M + 1]$^+$ 198.1, [M + 23]$^+$ 220.1, [2M + 1]$^+$ 395.2, [2M + 23]$^+$ 417.1. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.75; H, 7.65; N, 7.09.

Benzyl (1*SR*,2*RS*)-2-Hydroxycyclohex-3-enylcarbamate (35). To a solution of amino alcohol **33** (5.9 mg, 0.05 mmol) in anhyd CH_2Cl_2 (0.1 mL) was added dimethylaminopyridine (26.4 mg, 0.21 mmol, 4.1 equiv) and then benzyloxycarbonyl chloride (8.2 μL, 0.06 mmol, 1.05 equiv) at 0 °C. After 20 h, distilled water was added, and the aqueous phase was extracted with CH_2Cl_2. The organic phases were dried over Na_2SO_4, and the residue, after distillation at reduced pressure, was purified by silica gel column chromatography (1.2% CH_2Cl_2/MeOH), which yielded product **35** (1.4 mg, 11%) showing good correlation with the spectroscopic data [^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41−7.29 (m, 5H, C_6H_5), 5.91 (dt, J = 10.0, 3.6 Hz, 1H, H4), 5.82 (ddt, J = 10.0, 4.4, 2.1 Hz, 1H, H3), 5.34 (br d, J = 6.8 Hz, 1H, NH), 5.12 (s, 2H, CH_2O), 4.14 (br s, 1H, C*H*OH, H2), 3.85−3.75 (m, 1H, CHN, H1), 2.21−2.12 (m, 2H, H5), 2.10−1.98 (br s, OH), 1.85−1.76 (m, 1H, H6), 1.72−1.58 (m, 1H, H6′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2 (N*C*$O_2CH_2C_6H_5$), 136.7 (C*ipso*, C_6H_5), 132.0 (C4), 128.7 (3xCH, C_6H_5), 128.3 (2xCH, C_6H_5), 127.3 (C3), 66.9 (NCO$_2$*C*$H_2C_6H_5$), 65.3 (CHOH, C2), 50.8 (CHN, C1), 24.9 (CH_2, C5), 23.6 (CH_2, C6)] previously described in the literature.[16c]

Heterocyclization of *tert*-Butyl *N*-(*t*-3,*c*-4-Dibromocyclohex-1-yl)carbamate (11). Following the general procedure for the heterocyclization reaction, dibromide **11**[12] (219.7 mg, 0.62 mmol) in dry DMF (6.4 mL) was reacted with NaH (37.1 mg, 0.928 mmol). Three hours after the first addition, a further portion of NaH was added (50.8 mg, 1.27 mmol). After 4 h, workup, column chromatography (hexane/Et_2O, 10% to hexane/Et_2O, 60%) gave compound **22** (37.4 mg, 44%) and a mixture of compounds **36** + **37** {33.8 mg, in a 3.6: 1 ratio, as determined by GC/MS analysis [column (methylsilicon as stationary phase, 0.2 mm internal diameter, 25 m long, and 0.33 μ width), He as transporter gas, 70−270 °C at 4 °C/min]}: **36** 34.65 min (MS m/z 219, 221 (3, 3), 98 (100), 68 (8), 41 (17); **37** 24.60 min (MS m/z 139 (M$^+$, 19), 94 (100), 80 (46), 67 (60), 39 (33). After careful chromatography, we could isolate only small amounts of the pure components. **36**: white solid; mp 133−5 °C; IR (KBr) ν 3262, 2953, 1698, 1445, 1268, 1115, cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.28 (br s, 1H, NH, H4), 4.74−4.71 (m, $W_{h/2}$ = 8.0 Hz, 1H, H1), 4.11 (ddd, J = 10.0, 8.3, 2.0 Hz, 1H, H8), 3.74−3.71 (m, $W_{h/2}$ = 10.0 Hz, 1H, H5), 2.31−2.22 (m, 3 H, 2H7, H9), 1.96−1.88 (m, 2H, H9′, H6), 1.60−1.74 (m, 1H, H6′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.2 (NHCOO, C3), 76.7 (CHO, C1), 50.5 (CHBr, C8), 44.5 (CHN, C5), 33.2 (C6), 30.3 (C9), 27.9 (C7); MS (ES) m/z [M + 1]$^+$ 219.9/221.9, [M + 23]$^+$ 241.9/243.9, [2M + 1]$^+$ 439.0/441.0/442.9, [2M + 23]$^+$ 460.9/462.9/465.0. Anal. Calcd for $C_7H_{10}BrNO_2$: C, 38.20; H, 4.58; N, 6.36. Found: C, 38.09; H, 4.32; N, 6.09. **37**: white solid; mp 185−7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.12−6.04 (m, 1H, H8),* 6.00−5.92 (m, 1H, H7),* 5.33 (br s, 1H, NH), 4.75−4.73 (m, $W_{h/2}$ = 12.1 Hz, 1H, H1), 3.89−3.83 (m, $W_{h/2}$ = 11.0 Hz, 1H, H5), 2.39−2.31 (m, 2H, 2H6), 2.29−2.18 (m, 1H, H9), 1.92 (dm, J = 13.2 Hz, 1H, H9′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (C=O signal hidden by noise), 129.6, 125.8 (C7, C8), 68.0 (CHO, C1), 44.8 (CHN, C5), 35.0 (C6), 26.9 (C9); MS (ES) m/z [M + 1]$^+$ 140.1, [M + 23]$^+$ 162.1, [2M + 1]$^+$ 279.0, [M + 23]$^+$ 301.0; HRMS calcd for $C_7H_9NO_2$ 162.0525 (M + Na$^+$), found 162.0530 (M + Na$^+$).

Heterocyclization of Benzyl *N*-(*t*-3,*c*-4-Dibromocyclohex-1-yl)carbamate (13). Following the general procedure for the heterocyclization reaction, dibromide **13** (203 mg, 0.52 mmol) in dry DMF (11 mL) was reacted with NaH (31 mg, 0.77 mmol, 1.49 equiv), at rt for 72 h; then, more NaH (31 mg, 0.78 mmol, 1.5 equiv) was added. After 24 h at rt, workup and column chromatography (hexane/AcOEt, 20%; CH_2Cl_2/MeOH, 1−5%) provided compounds **38** (27 mg, 17%) and **35** (15 mg, 12%).[16c] **3-(Benzyloxy)-8-bromo-2-oxa-4-azabicyclo[3.3.1]non-3-ene (38):** white solid; mp 122−4 °C; IR (KBr) ν 3026, 2938, 1685, 1448, 1233, 1123 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.46 (m, 5H, C_6H_5), 5.15 (s, 2H, OC$H_2C_6H_5$), 4.74−4.68 (m, 1H, CHO, H1), 4.13 (ddd, J = 11.8, 5.6, 1.8 Hz, 1H, CHBr, H8), 3.77 (br s, 1H, CHN, H5), 2.24−1.88 (m, 4H, 2H7, H6, H9), 1.82 (br d, J = 13.5 Hz, 1H, H9ax), 1.76−1.50 (m, 1H, H6); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.1 [N=C(O C$H_2C_6H_5$)O], 136.4 (C *ipso*), 128.6 (2 × CH, C_6H_5), 128.1 (CH, C_6H_5), 128.0 (2xCH, C_6H_5), 76.5 (CHO, C1), 69.2 (O*C*$H_2C_6H_5$), 52.3 (CHBr, C8), 45.3 (CHN, C5), 32.6 (CH_2, C6), 30.0 (CH_2, C9), 28.3 (*C*H_2, C7); MS (ES) m/z [M + 1]$^+$ 309.9/311.9, [M + 23]$^+$ 331.9/333.9. Anal. Calcd for $C_{14}H_{16}BrNO_2$: C, 54.21; H, 5.20; N, 4.52. Found: C, 53.98; H, 5.05; N, 4.73.

6-(Benzyloxycarbonylamino)cyclohex-2-enyl acetate (39). Benzyl 2-hydroxycyclohex-3-enylcarbamate (**35**) (11.6 mg, 0.046

mmol) was treated with Ac_2O (2 mL) and pyridine (2 mL) at rt for 85 h. Evaporation of solvents and column chromatography of the residue (hexane/AcOEt, 25%) furnished acetate **39** (8.5 mg, 64%) as a white solid: mp 64−6 °C; IR (KBr) ν 3428, 3363, 3038, 2938, 1721, 1683, 1525, 1301, 1252, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42−7.30 (m, 5H, C_6H_5), 5.96 (dt, J = 9.9, 3.5 Hz, 1H, H3), 5.84−5.76 (m, 1H, H2), 5.22 (t, J = 4.0 Hz, 1H, H1), 5.11 (s, 2H, CH_2O), 4.98 (br d, J = 8.4 Hz, 1H, NH), 4.07−3.97 (m, 1H, CHN, H6), 2.24−2.17 (m, 2H, H4), 2.05 (s, 3H, $OCOCH_3$), 1.86−1.74 (m, 2H, H5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3 ($OCOCH_3$), 155.7 ($NCO_2CH_2C_6H_5$), 136.3 (*Cipso*), 132.9 (C3), 128.5, 128.3, 128.2 (5xCH, C_6H_5), 123.9 (C2), 68.4 (CHO, C1), 66.8 ($NCO_2CH_2C_6H_5$), 48.4 (CHN, C6), 24.3, 24.2 (2 C, C4, C5), 21.1 ($OCOCH_3$); MS (ES) *m*/*z* [M + 23]$^+$ 312.0. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.35; H, 6.71; N, 4.74.

***exo*-2-Bromo-7-(2,2,2-trifluoroacetyl)-7-azabicyclo[2.2.1]heptane (41).** Following the general procedure for the heterocyclization reaction, a solution of compound **40**[12] (4.61 g, 13.06 mmol) in dry DMF (150 mL, 0.087 M), was reacted with NaH (629 mg, 15.72 mmol, 1.20 equiv). After 22 h, workup and column chromatography (hexane/AcOEt, 20%) gave product **41** (2.86 g, 81%): mp 45−8 °C; IR (KBr) ν 2961, 1690, 1475, 1244, 1191, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.92 (d, J = 5.6 Hz, 1H, H1), 4.86−4.83 (m, 1H, H4), 4.13−4.05 (m, 1H, H2), 2.33−2.29 (m, 2H, 2H3), 2.06−1.93 (m, 1H, H6 *exo*), 1.91−1.79 (m, 1H, H5 *exo*), 1.69−1.43 (m, 2H, H5 *endo*, H6 *endo*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.7 (q, $^2J_{C-F}$ = 37.2 Hz, N*C*OCF$_3$), 116.6 (q, $^1J_{C-F}$ = 288.2 Hz, NCO*C*F$_3$), 63.0 (C1), 55.3 (C4), 48.0 (*C*2), 42.4 (C3), 27.3 (C5), 26.6 (C6); MS (ES) *m*/*z* [M + 1]$^+$ 272.0/274.0, [M + 23]$^+$ 294.0/296.0, [2M + 23]$^+$ 565.0/567.0/569.0. Anal. Calcd for $C_8H_9BrF_3NO$: C, 35.32; H, 3.33; N, 5.15. Found: C, 35.39; H, 3.41; N, 5.12.

8-Bromo-3-(trifluoromethyl)-2-oxa-4-azabicyclo[3.3.1]non-3-ene (43). Following the general procedure for the heterocyclization reaction, a solution of compound **42**[12] (328.9 mg, 0.932 mmol) in dry DMF (16 mL) was treated with NaH (46 mg, 1.15 mmol, 1.23 equiv). After 22 h, workup and flash chromatography (hexane/AcOEt, 30%) provided compound **43** (201 mg, 79%): mp 130−2 °C; IR (film) ν 2950, 1688, 1450, 1392, 1321, 1276, 1208, 1133 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.83−4.76 (m, 1H, H1), 4.15 (ddd, J = 12.2, 5.6, 2.1 Hz, 1H, H8), 4.00−3.93 (m, 1H, H5), 2.29−2.16 (m, 1H, H7), 2.14−1.99 (m, 2H, H9, H6), 1.98−1.94 (m, 1H, H9′), 1.94−1.86 (m, 1H, H7′), 1.86−1.70 (m, 1H, H6′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.4 [q, $^2J_{C-F}$ = 153.8 Hz, N=*C*(O)CF$_3$], 116.8 (q, $^1J_{C-F}$ = 1100.8 Hz, CF_3), 76.1 (CHO, C1), 51.0 (CHBr, C8), 45.4 (CHN, C5), 31.0 (C6), 28.9 (C9), 28.0 (C7); MS (ES) *m*/*z* [M + 1]$^+$ 272.0/274.0. Anal. Calcd for $C_8H_9BrF_3NO$: C, 35.32; H, 3.33; N, 5.15. Found: C, 35.12; H, 3.39; N, 4.98.

5-Acetamido-2-bromocyclohexyl Acetate (45). To a solution of compound **43** (91 mg, 0.33 mmol) in THF/H_2O [21 mL:7 mL (3:1), 0.012 M] was added trifluoroacetic acid (0.5 mL, 6.73 mmol, 20 equiv) at rt. After 2.5 h, the solvents were evaporated, and the crude amino alcohol **44** [^1H NMR (D_2O, 300 MHz) δ 4.42−4.37 (m, 1H), 3.53 (dt, J = 10.9 and 3.6 Hz, 1H), 3.11 (tt, J = 15.6, 10.4 and 4.7 Hz, 1H), 2.01 (dq, J = 15.1 and 3.6 Hz, 1H), 1.85−1.54 (m, 5H); ^{13}C NMR (D_2O, 75 MHz) δ 162.7 (q, J = 36.1 Hz), 116.2 (q, J = 291.2 Hz), 68.3, 58.0, 47.6, 32.8, 29.1, 24.0] was acetylated as usual [pyridine (2 mL), Ac_2O (2 mL), 27 h, rt]. After evaporation of the solvents, the residue was purified by column chromatography (DCM/MeOH, 5%) to give compound **45** (92 mg, 100%): white solid; mp 122−4 °C; IR (KBr) ν 3428, 3290, 2932, 1741, 1650, 1555, 1367, 1234, 1038 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.58 (d, J = 6.5 Hz, 1H, NH), 4.71 (dt, J = 11.0, 3.6 Hz, 1H, H1), 4.65−4.60 (m, $W_{h/2}$ = 7.9 Hz, 1H, H2), 4.02−3.91 ($W_{h/2}$ = 23.7 Hz, 1H, H5), 2.16 (dq, J = 15.2, 3.9 Hz, 1H, $H3_{eq}$), 2.10 (s, 3H, $OCOCH_3$),* 2.04−1.94 (m, 2H, $H3_{ax}$, H6), 1.98 (s, 3H, $NHCOCH_3$),* 1.87−1.75 (m, 2H, H6′, $H4_{eq}$), 1.68 (qd, J = 12.1, 3.9 Hz, 1H, $H4_{ax}$) [deuterium exchange with D_2O shows that the multiplet at 4.02−3.91 is simplified (3.97, tt, J = 11.2, 4.4 Hz)]; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1 ($OCOCH_3$), 169.3 (NH-*C*OCH_3), 71.2 (C1), 53.6 (C2), 45.9 (C5), 33.0 (C6), 30.4 (C3), 26.9 (C4), 23.6 ($NHCOCH_3$), 21.2 ($OCOCH_3$); MS (ES) *m*/*z* [M + 1]$^+$ 278.0/230.0, [M + 23]$^+$ 300.0/302.0, [2M + 1]$^+$ 555.0/557.0/559.0. Anal. Calcd for $C_{10}H_{16}BrNO_3$: C, 43.18; H, 5.80; N, 5.04. Found: C, 43.40; H, 5.99; N, 5.02.

***N*-(3-Oxocyclohexyl)acetamide (46).**[20] To a solution of compound **45** (157 mg, 0.56 mmol) in dry THF (7.5 mL, 0.075 M), *t*-BuOK (73 mg, 0.64 mmol, 1.13 equiv) was added at rt, under argon. The mixture was refluxed for 23 h. Then, more *t*-BuOK (36 mg, 0.31 mmol, 0.56 equiv) was added; after 5 h, a similar aliquot of *t*-BuOK (36 mg, 0.31 mmol, 0.56 equiv) was added again. After 2 h at reflux, the mixture was cooled, brine was added, and the reaction was extracted with ethyl ether (4×). The organic phase was dried (Na_2SO_4), filtered, and the solvent removed. The crude was submitted to chromatography (hexane/AcOEt, 1:1 to AcOEt), yielding compound **46** (34.3 mg, 39%): viscous oil; IR (film) ν 3292, 2941, 1709, 1655, 1549, 1223 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.49 (br s, 1H, NH), 4.35−4.20 (tt, J = 12.6, 4.0 Hz, 1H, $H1_{ax}$), 2.71 (dd, J = 14.0, 4.8 Hz, 1H, $H2_{eq}$), 2.47−2.20 (m, 3H, $H2_{ax}$, 2H4), 2.14−1.91 (m, 2H, H5, H6), 2.00 (s, 3H, CH_3), 1.87−1.58 (m, 2H, H5′, H6′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.1 (C3), 169.4 ($NHCOCH_3$), 48.7 (C1), 47.8 (C2), 41.1 (C4), 30.9 (C6), 23.6 (CH_3), 22.3 (C5); MS (ES) *m*/*z* [M + 1]$^+$ 156.1, [M + 23]$^+$ 178.1, [2M + 23]$^+$ 333.3. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.75; H, 8.15; N, 8.79.

Reaction of 8-Bromo-3-(trifluoromethyl)-2-oxa-4-azabicyclo-[3.3.1]non-3-ene (43) with Potassium *tert*-Butoxide. To a solution of dihydro-1,3-oxazine **43** (106 mg, 0.39 mmol) in dry THF (5.5 mL, 0.076 M) was added *t*-BuOK (53 mg, 0.46 mmol, 1.18 equiv) at rt, under argon. The resulting mixture is then heated under reflux for 3 h, and more *t*-BuOK (23 mg, 0.20 mmol, 0.52 equiv) was added. After 1 h more at reflux, the reaction was cooled, brine was added, and extracted with ethyl ether (3×). The organic phase was dried (Na_2SO_4), filtered, and evaporated. The crude was purified by column chromatography (hexane/AcOEt, 15% → 30%) providing *N*-(4-bromocyclohex-3-enyl)-2,2,2-trifluoroacetamide (**47**) (70 mg, 66%): white solid; mp 120−2 °C; IR (KBr) ν 3416, 3294, 3103, 2935, 1702, 1562, 1248, 1203, 1184, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.28 (br s, 1H, NH), 6.02−5.97 (m, $W_{h/2}$ = 8.9 Hz, 1H, H3), 4.25−4.15 (m, $W_{h/2}$ = 18.5 Hz, 1H, H1), 2.70−2.58 (m, 1H, H2), 2.58−2.48 (m, 2H, H5, H6), 2.13−1.97 (m, 2H, H2′, H5′), 1.93−1.82 (m, 1H, H6′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.0 (q, $^2J_{C-F}$ = 36.9 Hz, *C*OCF$_3$), 125.5 (BrC=*C*H, C3), 121.8 (Br*C*=CH, C4),116.0 (q, $^1J_{C-F}$ = 288.1 Hz, NHCO*C*F$_3$), 44.5 (d, $^4J_{C-F}$=3.6 Hz, C1), 33.0, 32.9 (C2, C5), 29.1 (C6); MS (ES) *m*/*z* [M + 1]$^+$ 272.0/274.0, [M + 23]$^+$ 293.9/296.0. Anal. Calcd for $C_8H_9BrF_3NO$: C, 35.32; H, 3.33; N, 5.15. Found: C, 35.07; H, 3.42; N, 5.35.

Computational Methods. All of the calculations were carried out using the Gaussian98 and Gaussian03 packages.[32] In the gas phase, all structures were fully optimized at the mPW1PW91 level.[33] Despite the most popular version of a hybrid DFT method is B3LYP, which provides excellent low-cost performance for geometry optimizations, the hybrid mPW1PW91 functional, which uses the modified Perdew−Wang exchange functional that has improved the long-range behavior, has been reported to give better results in some cases. DFT models may substantially underestimate the activation energies for SN_2 substitution reactions, a kind of process present in this study, and where the mPW1PW91 functional has shown good performance.[34]

As the present study involves anions, which have a more spread-out electron density than neutral atoms, it is essential to add diffuse

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functions in the basis set,[35] and the 6-31+G(d,p) basis sets was used, except for Br atom which was described by means of the 3-21G(d) basis set. Zero-point energies (ZPEs) and thermal contributions to thermodynamic functions and activation parameters were computed at the same level on the optimized structures, and harmonic frequencies by using the rigid rotor/harmonic oscillator approximation and the standard expressions for an ideal gas in the canonical ensemble at 298.15 K and 1 atm. The transition states were verified to have only one imaginary frequency and hence correspond to a first-order saddle point on the potential energy surface.

In some cases, the whole step path was traced by using the intrinsic reaction coordinate (IRC) at the optimization level. The IRC calculation started from the optimized transition structure and followed the reaction path in both directions, toward the two minima it connects.

In order to simulate the strong base, NH_2^- was selected instead of H^- to avoid computational artifacts, since both species exhibit a similar pK_a value.[36]

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 39.0 was assumed to simulate DMF as solvent, and 7.58 for THF. After some tests, we observed that for transition structures involving hydrogen shift it is necessary to add an explicit sphere on the transferring atom in order to obtain reliable results. Therefore, the solute cavity was built up with UA0 radii and explicitly placing an individual sphere on the hydrogen of interest.

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Supporting Information Available: NMR spectra for all new compounds, general experimental methods, structural and stereochemical assignments (Charts 1−4), theoretical scan of the PES for the proton abstraction step to **A1** (Figure 1), computed data in the gas-phase and in solution (Tables 1−3), DFT-based study of the formation of compounds **35**, **38**, and **47**, complete ref 32, and atomic coordinates for the computed structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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