Synthesis of new 7-azabicyclo[2.2.1]heptane derivatives

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This manuscript is dedicated to Prof. Benito Alcaide on occasion of his 60th birthday

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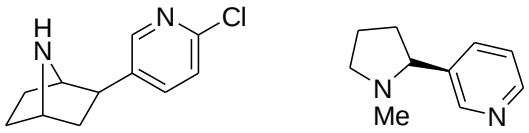
Abstract

The synthesis of new 7-azabicyclo[2.2.1]heptane derivatives has been achieved in a four-step synthetic sequence, starting from readily available cyclohex-3-enecarboxylic acid, Curtius reaction, stereoselective bromination leading to major benzyl(*cis*-3,*trans*-4-dibromocyclohex-1-yl)carbamates (amides or sulfonamides), followed by NaH-mediated intramolecular cyclization. The synthesis and free radical cyclization of precursors **4**-**7**, as well as the synthesis of a conformationally constrained epibatidine analogue **3** exploiting the reactivity of the 7-azabicyclo[2.2.1]hept-2-yl radical in intramolecular reactions, are described. The *N*-sulfonyl functional motif is the only one to afford a cyclized product when incorporated in the radical precursor.

Keywords: 7-Azabicyclo[2.2.1]heptane derivatives, conformationally constrained epibatidine analogues, *N*-(arylmethyl)cyclohex-3-enamines, 7-azabicyclo[2.2.1]hept-2-yl radical, intramolecular free radical reactions

Introduction

Epibatidine **1**,[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 values several times higher than nicotine (**2**)[2] (Figure 1). However, the toxic effects associated with this drug have hampered its clinical application.[4]

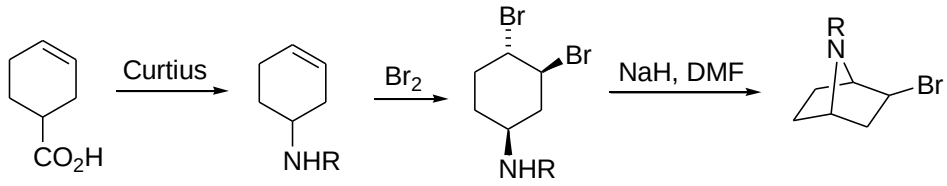


Epibatidine **1** Nicotine **2**

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, great attention has been paid to the synthesis and biological evaluation of epibatidine analogues,[5b] either heterocyclic[6] or conformationally constrained.[7]

We have recently described the synthesis of 7-substituted *exo*-2-bromo-7-azabicyclo[2.2.1]heptane derivatives[8,9] following a potent method based on a four-step synthetic sequence, starting from readily available cyclohex-3-enecarboxylic acid, Curtius reaction, stereoselective bromination leading to major *tert*-butyl (or benzyl) (*cis*-3,*trans*-4-dibromocyclohex-1-yl)carbamates (or 2,2,2-trifluoroacetamides),[10] followed by NaH-mediated intramolecular cyclization (Scheme 1).[11]



(R= BOC, CO_2Bn, $COCF_3$)

Scheme 1. General approach for the syntheis of 7-azabicyclo[2.2.1]heptane derivatives (ref. 9).

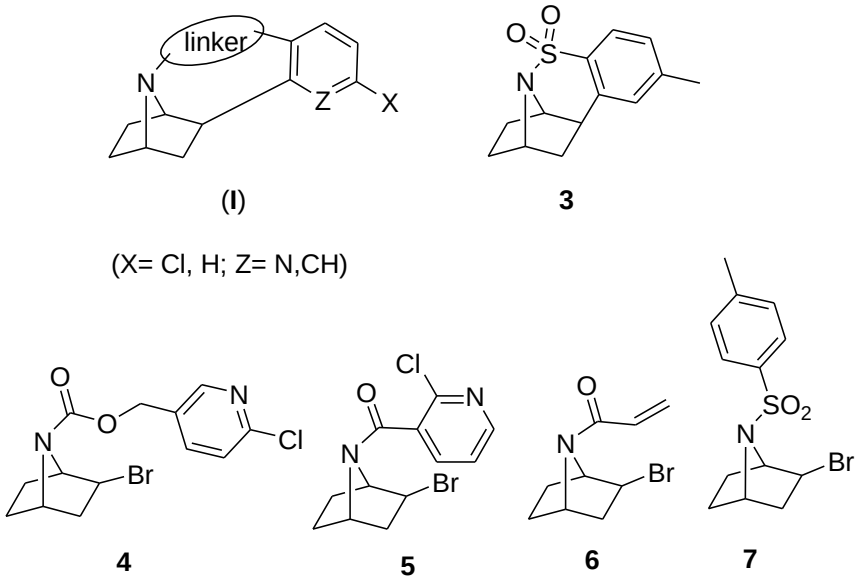
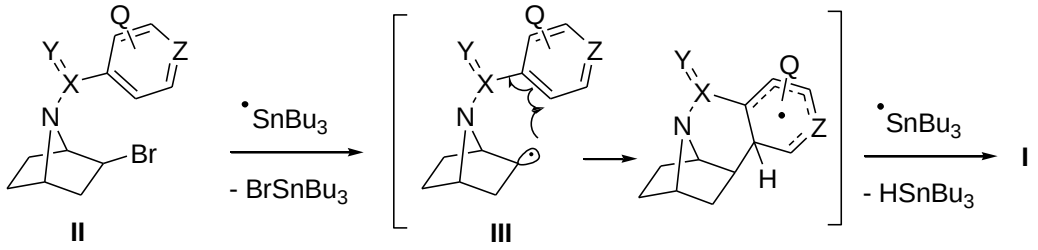


Figure 2. Structure of conformationally constrained epibatidine analogues (I), the target molecule 3, and the radical precursors 4-7.

Our current interest in the synthesis and biological evaluation of new epibatidine analogues using intermolecular free radical reactions exploiting the reactivity of the 7-azabicyclo[2.2.1]hept-2-yl radical,[12] prompted us to apply this strategy to prepare conformationally constrained epibatidine analogues of type **I** (Figure 2). In Scheme 2 we show our general approach for the synthesis of this type of compounds, based on the intramolecular free radical cyclization of species **II**, readily available from precursors **III** bearing convenient radical acceptors at C7 and good leaving groups at C2 (Scheme 2).

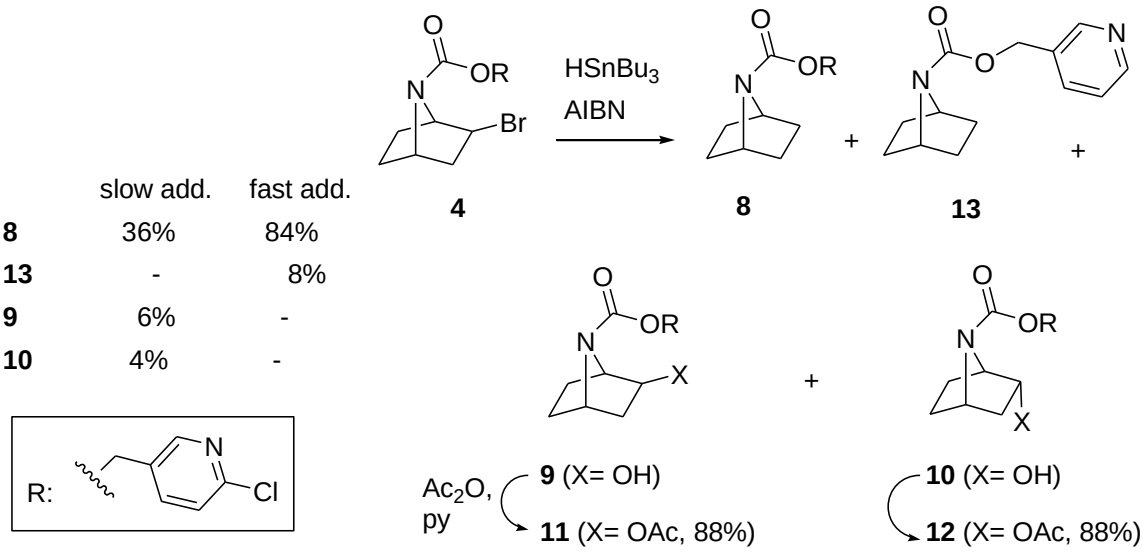


Scheme 2. Intramolecular free radical reaction for the preparation odf compounds I.

Although the synthesis and reactivity of 7-norbornenyl,[13] norborn-5-en-2-yl,[14] norborn-2-yl[15,16] radicals is well known, the chemistry of 7-azabicyclo[2.2.1]hept-2-yl radicals has been scarcely investigated. Fraser and Swingle reported the chlorination of 7-trichloroacetyl-7-azabicyclo[2.2.1]heptane with sulfuryl chloride in the presence of benzoyl peroxide.[17] More recently, and when this work was in progress, Armstrong and co-workers reported what appears

to be the first intramolecular cyclization of a precursor in this series, namely *exo*-2-bromo-7-(toluene-4-sulfonyl)-7-azabicyclo[2.2.1]heptane.[18]

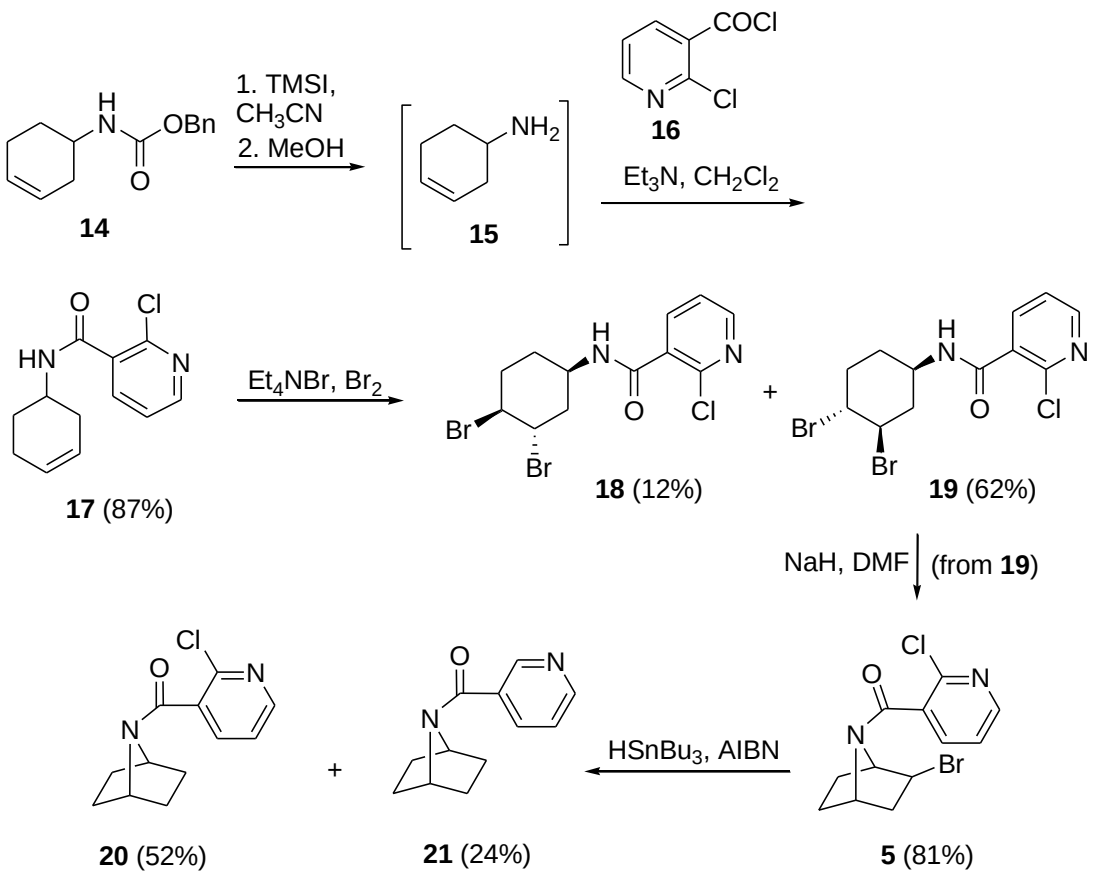
Here we report the synthesis of the conformationally constrained epibatidine analogues **3**, the preparation of radical precursors **4-7** and their intramolecular free radical reactions (Figure 2).



Scheme 3. Free radical cyclization of compound 4.

Results and Discussion

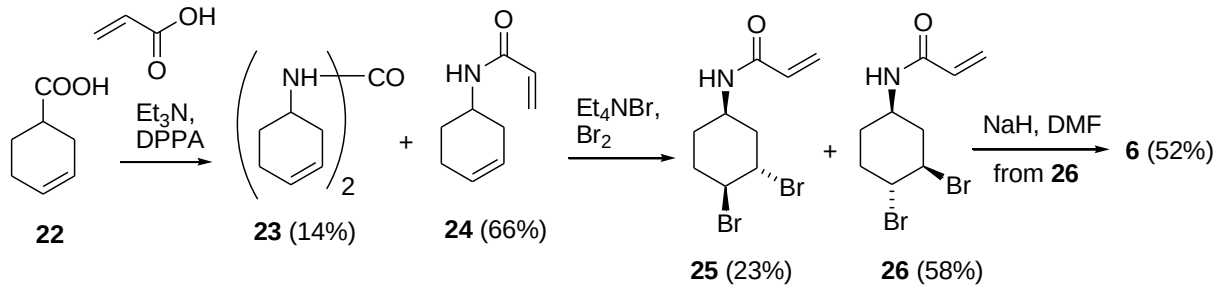
Under *slow addition* of $HSnBu_3$, radical precursor **4**[8,9] gave the reduced uncyclized product **8** in 36% yield, while small amounts of alcohols **9** and **10** (Scheme 3) were also isolated. The structure and relative configuration of the alcohols at C2 was easily established by NMR spectroscopic analysis on the corresponding acetates **11** and **12**. *Fast addition* of $HSnBu_3$ afforded a higher yield of **8** (84%), along with 8% of dechlorinated product **13** (Scheme 3). To sum up, from precursor **4**, no cyclized products were detected, regardless of the reaction conditions employed.



Scheme 4. Synthesis and free radical cyclization of compound 5.

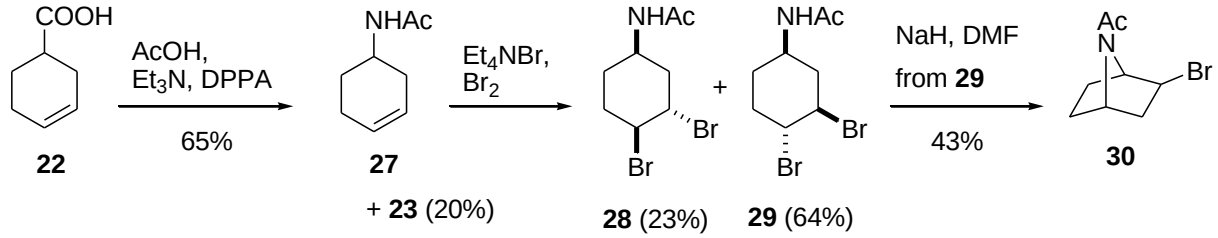
In order to prepare precursor **5**, our first choice was to apply our synthetic sequence[9] starting with cyclohex-3-enecarboxylic acid, and a Curtius type reaction with 2-chloronicotinic acid. Unfortunately, we were unable to obtain a convenient yield of the desired amide. Consequently, we were forced to use carbamate **14**,[9] promote the deprotection reaction, and transform the free, not isolated amine **15**[19] into amide **17** by simple amidation reaction with 2-chloronicotinic acid chloride **16**[20] (Scheme 4). As previously reported for analogous amides, bromination[11] of cyclohex-3-enamide **17** provided a mixture of minor 1,4-*cis*- and major 1,4-*trans*-3,4-dibromo derivatives, **18** and **19**, that were easily separated, and transformed (only for pure 1,4-*trans*-3,4-dibromo **19**) into precursor **5** by reaction with NaH in DMF[8] (Scheme 4). Free radical cyclization of compound **5** under slow addition gave the partially reduced, uncyclized derivative **20**, and the fully dehalogenated compound **21** (Scheme 4), as the only reaction products.

Next, precursor **6** was synthesized in good overall yield as shown in Scheme 5, from 3-cyclohex-3-enecarboxylic acid **22**, *via* intermediates **24**[21] and compound **26.** Unfortunately, the free radical cyclization of bromide **6** gave a complex reaction mixture, and no pure defined compound could be isolated and characterized.



Scheme 5. Synthetic pathway for the preparation of target compound 6.

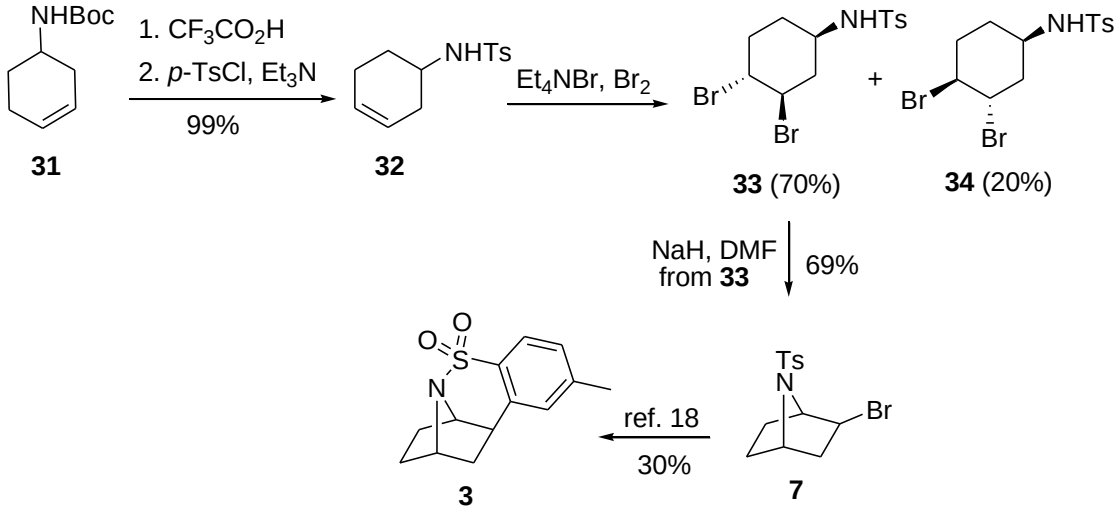
In retrospect, the success of the Curtius reaction of cyclohex-3-enecarboxylic acid **22** with acrylic acid (Scheme 5), and the failure to accomplish the same reaction with nicotinic acid (see above) was surprising, but we have no rationale for this behaviour. In fact, in this project we were able to carry out the same Curtius reaction with acetic acid to provide acetamide **27**,[22] that submitted to the standard protocol afford, *via* intermediate **29**, afforded bromide **30** (Scheme 6).



Scheme 6. Synthetic pathway for the preparation of compound 30.

The synthesis of precursor **7** was readily achieved from carbamate **31**[8,9] *via* intermediate **32**,[23] obtained after reaction with trifluoroacetic acid, and treatment with *p*-tosyl chloride (Scheme 7). At this point we considered the copper(II)-catalyzed oxidative cyclization of unsaturated sulfonylamides,[24] but our efforts to achieve a satisfactory result were fruitless, and we turned to our initial plan. Consequently, bromination of compound **32**, as usual[11] gave compounds **33** (70%) and **34** (20%). Then, major *N*-(*cis*-3-*trans*-4-dibromocyclohexyl)-4-methylbenzenesulfonamide **33**, submitted to NaH-mediated cyclization, gave precursor **7**. This compound was identical in its spectroscopic data to the compound reported by Armstrong,[18] but was prepared in four steps in 41% overall yield from cyclohex-3-ene carboxylic acid, a stable product, while the previously reported synthesis takes place in four steps also, but in 11% overall yield from 2-methoxy-3,4-dihydropyran, a flammable product that must be used with caution.[25] Finally, and as expected and reported, free radical cyclization of precursor **7** provided the ring

closure derivative **3** in 30% yield, a product which showed analytical and spectroscopic data in good agreement with its structure, and similar to those described.[18]



Scheme 7. Synthesis and free radical reaction of precursor 7.

Conclusions

We have reported the synthesis and reactivity of the 7-azabicyclo[2.2.1]hept-2-yl radicals in intramolecular reaction processes, and have shown the scope and limitations of this strategy for the synthesis of conformationally constrained epibatidine analogues. We have detailed the synthesis and free radical cyclization of radical precursors **4**-**7**. In overall, a carbonyl functional group as in a carbamate (precursor **4**), or in an amide (precursor **5** and **6**), to link the radical trap to the nitrogen at the C7 position, provides precursors that gave reduced, uncyclized reaction products. Conversely, the *N*-sulfonyl motif is the only ones able to afford a cyclized product in acceptable chemical yields. As a result we have described here the synthesis of the constrained epibatidine analogue **3**.

Experimental Section

General Procedures. 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. 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 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, 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).

Synthesis and intramolecular free radical reaction of precursor 4. A. Slow addition of $HSnBu_3$

To a deoxygenated solution of carbamate **4**[8,9] (58 mg, 0.17 mmol) in dry toluene (8 mL, 0.02 M) and AIBN (5 mg), $HSnBu_3$ (0.07 mL, 0.25 mmol, 1.5 equiv) in dry, deoxygenated toluene (2 mL) containing AIBN (5 mg) was slowly added in 14 h at 95 ºC. After the addition the mixture was heated at the same temperature for 10 h more. The reaction was cooled at rt, the solvent was removed, the residue was dissolved in ethyl ether, and washed with an aqueous saturated KF solution. The organic phase was dried over Na_2SO_4, filtered, and the solvent was evaporated. The crude was submitted to chromatography (20% → 50% hexane: AcOEt), to give compound **8** (16 mg, 36%), a mixture of compounds **4**/**8** (11 mg, 4:1) and alcohols **9** (2.6 mg, 6%) and **10** (2 mg, 4%). **8**: white solid; mp 87-9 ºC; IR (KBr) ν 3043, 2955, 1705, 1460, 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.39 (d, *J*= 2.4 Hz, 1H, H2’), 7.67 (dd, *J*= 2.4, 8.1 Hz, 1H, H4’), 7.32 (d, *J*= 8.1 Hz, 1H, H5’), 5.09 (s, 2H, CH_2O), 4.28 (s, 2H, H1, H4), 1.81-1.70 (m, 4H), 1.48-1.38 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.9 (NCOO), 151.2 (C6’), 149.4 (C2’), 138.8 (C4’), 131.6 (C3’), 124.3 (C5’), 63.4 (CH_2O), 56.4 (C1, C4), 29.8 (4xCH_2); MS (ES) *m*/*z* $[M+1]^+$ 267.3/269.2, $[M+23]^+$ 289.2/291.3, $[2M+23]^+$ 555.5/557.5. Anal. Calcd. for $C_{13}H_{15}ClN_2O_2$: C, 58.54; H, 5.67; N, 10.50. Found: C, 58.42; H, 5.60; N, 10.75.

(6-Chloropyridin-3-yl)methyl *exo*-2-hydroxy-7-azabicyclo[2.2.1]heptane-7-carboxylate 9. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.41 (d, *J*= 2.2 Hz, 1H), 7.69 (dd, *J*= 2.5, 8.2 Hz, 1H), 7.33 (d, *J*= 8.2 Hz, 1H), 5.12 (s, 2H), 4.34 (t, *J*= 4.7 Hz, 1H), 4.20 (d, *J*= 4.8 Hz, 1H), 3.95 (td, *J*= 1.8, 6.7 Hz, 1H), 1.88 (dd, *J*= 6.8, 13.1 Hz, 1H), 1.82-1.54 (m, 4H), 1.36-1.24 (m, 2H); MS (ES) *m*/*z* $[M+1]^+$ 283.0/285.0, $[M+23]^+$ 305.0/307.0.

(6-Chloropyridin-3-yl)methyl *endo*-2-hydroxy-7-azabicyclo[2.2.1]heptane-7-carboxylate 10. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.40 (d, *J*= 2.2 Hz, 1H), 7.68 (dd, *J*= 2.5, 8.2 Hz, 1H), 7.34 (d, *J*= 8.0 Hz, 1H), 5.10 (s, 2H), 4.42-4.31 (m, 1H), 4.28-4.18 (m, 2H), 2.30-2.15 (m, 2H), 1.88-1.72 (m, 1H), 1.72-1.50 (m, 3H), 1.11 (dd, *J*= 3.4, 12.7 Hz, 1H); MS (ES) *m*/*z* $[M+1]^+$ 283.0/285.0, $[M+23]^+$ 305.0/307.0.

Acetylation of alcohols 9 and 10. General Method

The alcohols were treated with a mixture of Ac_2O/ py (1: 1, vol), at rt for 21h. Then, the solvents and reagents were evaporated, and the residue was submitted to chromatography (25% hexane: AcOEt) to give the expected compounds.

(6-Chloropyridin-3-yl)methyl *exo*-2-acetoxy-7-azabicyclo[2.2.1]heptane-7-carboxylate (11). Following the **General Method** for acetylation compound **9** (14.9 mg, 0.05 mmol) was treated with Ac_2O/py (2 mL, 2 mL) to give compound **11** (15 mg, 88%): oil; IR (film) ν 3086, 2955, 1738, 1709, 1590, 1568, 1462, 1409, 1377, 1317, 1243, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.40 (d, *J*= 2.1 Hz, 1H, H2'), 7.68 (dd, *J*= 2.4, 8.2 Hz, 1H, H4'), 7.33 (d, *J*= 8.2 Hz, 1H, H5'), 5.11 (s, 2H, CH_2O), 4.73 (dd, *J*= 2.4, 7.0 Hz, 1H, H2), 4.42-4.30 (m, 2H, H1, H4), 2.03-1.87 (m, 4H, CH_3, $H3_{endo}$), 1.87-1.61 (m, 3H, $H3_{exo}$, $H5_{exo}$, $H6_{exo}$), 1.47-1.29 (m, 2H, $H5_{endo}$, $H6_{endo}$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9 (COO), 155.1 (NCOO), 151.4 (C6'), 149.5 (C2'), 138.8 (C4'), 131.5 (C3'), 124.3 (C5'), 76.5 (C2), 63.6 (CH_2O), 60.5, 55.4 (C1, C4), 39.0 (C3), 28.5, 24.7 (C5, C6), 21.2 (CH_3); MS (ES) *m*/*z* $[M+1]^+$ 325.3/327.2, $[M+23]^+$ 347.2/349.2. Anal. Calcd. for $C_{15}H_{17}ClN_2O_4$: C, 55.48; H, 5.28; N, 8.63. Found: C, 55.76; H, 5.19; N, 8.71.

(6-Chloropyridin-3-yl)methyl *endo*-2-acetoxy-7-azabicyclo[2.2.1]heptane-7-carboxylate (12). Following the **General Method** for acetylation compound **10** (6.8 mg, 0.02 mmol) was treated with Ac_2O/ py (2 mL, 2 mL) to give compound **12** (6.9 mg, 88%): white solid; mp 92-4 ºC; IR (KBr) ν 3023, 2963, 1732, 1704, 1590, 1571, 1465, 1412, 1376, 1308, 1264, 1240, 1116 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.40 (dd, *J*= 0.8, 2.3 Hz, 1H, H2'), 7.68 (dd, *J*= 2.7, 8.2 Hz, 1H, H4'), 7.34 (dd, *J*= 0.8, 8.2 Hz, 1H, H5'), 5.10 (s, 2H, CH_2O), 4.99-4.90 (m, 1H, H2), 4.48 (t, *J*= 4.7 Hz, 1H, H1), 4.31-4.24 (m, 1H, H4), 2.54-2.25 (m, 1H, $H3_{exo}$), 2.07 (s, 3H, CH_3), 1.96 (ddd, *J*= 3.9, 9.0, 12.7 Hz, 1H, $H6_{endo}$), 1.87-1.75 (m, 1H, $H5_{exo}$), 1.71-1.59 (m, 1H, $H6_{exo}$), 1.54 (ddd, *J*= 4.3, 9.0, 11.7 Hz, 1H, $H5_{endo}$), 1.24 (dd, *J*= 3.5, 13.3 Hz, 1H, $H3_{endo}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8 (COO), 154.8 (NCOO), 151.5 (C6'), 149.6 (C2'), 138.9 (C4'), 131.3 (C3'), 124.4 (C5'), 72.7 (C2), 63.7 (CH_2O), 58.2 (C1), 57.0 (C4), 37.0 (C3), 29.4 (C5), 22.2 (C6), 21.1 (CH_3); MS (ES) *m*/*z* $[M+1]^+$ 325.2/327.2, $[M+23]^+$ 347.2/349.2. Anal. Calcd. for $C_{15}H_{17}ClN_2O_4$: C, 55.48; H, 5.28; N, 8.63. Found: C, 55.76; H, 5.16; N, 8.91.

B. Fast addition of $HSnBu_3$. $HSnBu_3$ (0.07 mL, 0.25 mmmol, 1.7 equiv) in dry toluene (0.5 mL) was added to compound **4** (52 mg, 0.15 mmol) in toluene (0.02M) under reflux. After addition the mixture was heated at the same temperature for 3 h. The reaction was cooled at rt, the solvent was removed, and the residue was dissolved in ethyl ether and washed with an aqueous saturated KF solution. The organic phase was dried over Na_2SO_4, filtered and the solvent evaporated. The crude was submitted to chromatography (20% → 50% hexane: AcOEt) to yield **6-chloropyridin-3-yl) methyl-7-azabicyclo[2.2.1]heptane-7-carboxylate 8** (34 mg, 84%) and **pyridin-3-ylmethyl 7-azabicyclo[2.2.1]heptane-7-carboxylate 13** (2.6 mg, 8%). **13**: oil; IR (film) ν 2950, 1705, 1429 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.63 (d, *J*= 1.7 Hz, 1H, H2'), 8.57 (dd, *J*= 4.8 Hz, 1H, H6'), 7.70 (dm, *J*= 7.8 Hz, 1H, H4'), 7.30 (dd, *J*= 4.8, 7.7 Hz, 1H, H5'), 5.13 (s, 2H, CH_2O), 4.30 (s, 2H, H1, H4), 1.84-1.71 (m, 4H), 1.50-1.35 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.2 (c, NCOO), 149.6 (C2'), 149.5 (C6'), 135.9 (C4'), 132.7 (C3'), 123.6

(C5'), 64.3 (CH_2O), 56.4 (C1, C4), 29.9 (br, C2, C3, C5, C6); MS (ES) *m*/*z* $[M+1]^+$ 233.1, $[M+23]^+$ 255.1. HRMS calcd for $C_{13}H_{17}N_2O_2$ 233.1284 ($M + H^+$), found 233.1283 ($M + H^+$).

Synthesis and intramolecular free radical reaction of precursor 5. 2-Chloro-*N*-(cyclohex-3-enyl)nicotinamide (17)

To a solution of carbamate **14**[9] (795 mg, 3.44 mmol) in dry CH_3CN (44 mL, 0.1 M), TMSI (1.96 mL, 13.33 mmol, 3.88 equiv) was added at 0 ºC, and the mixture was stirred for 30 min under argon. Then, methanol (12.3 mL) was added, and the reaction was warmed at rt. After 30 min, the solvent was removed, and resulting **cyclohex-3-enamine 15**[19] was dissolved in dry CH_2Cl_2 (14 mL, 0.2 M). The solution was cooled at 0 ºC, Et_3N (1.20 mL, 8.62 mmol, 2.51 equiv) and acid chloride **16** (761 mg, 4.31 mmol, 1.26 equiv, prepared from commercial 2-chloronicotinic acid as described)[20] was added. The bath was removed and the reaction was warmed at rt for 17 h. Then, H_2SO_4 (8.8 mL, 2 M) was added. The resulting solution was neutralized with aqueous saturated $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2 (x3). The organic phases were dried over $MgSO_4$, filtered, and evaporated. The crude was submitted to chromatography (50% hexane: AcOEt), which gave

2-Chloro-*N*-(cyclohex-3-enyl)nicotinamide (17). (707 mg, 87%): white solid; 92-94 ºC; IR (KBr) ν 3470, 3268, 3062, 2920, 1635, 1585, 1543, 1397 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.46 (dd, *J*= 2.0, 4.7 Hz, 1H, H6'), 8.12 (dd, *J*= 2.0, 7.8 Hz, 1H, H4'), 7.35 (dd, *J*= 4.7, 7.4 Hz, 1H, H5'), 6.52 (br s, 1H, NH), 5.79-5.73 (m, 1H, H4), 5.70-5.63 (m, 1H, H3), 4.44-4.33 (m, 1H, H1), 2.52 (dm, *J*= 17.2 Hz, 1H, $H2_{eq}$), 2.30-2.13 (m, 2H, 2xH5), 2.13-1.93 (m, 2H, $H2_{ax}$, $H6_{eq}$), 1.85-1.74 (m, 1H, $H6_{ax}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.1 (NHCO), 150.1 (C6'), 147.2 (C2'), 140.0 (C4'), 131.6 (C3'), 127.4 (C4), 124.2 (C3), 123.0 (C5'), 45.5 (C1), 31.4 (C2), 27.6 (C6), 23.2 (C5); MS (ES) *m*/*z* $[M+1]^+$ 237.1/239.1, $[M+23]^+$ 259.0/261.0. Anal. Calcd. for $C_{12}H_{13}ClN_2O$: C, 60.89; H, 5.54; N, 11.84. Found: C, 60.68; H, 5.83; N, 11.55.

Bromination of 2-chloro-*N*-(cyclohex-3-enyl)nicotinamide 17. To a solution of compound **17** (506 mg, 2.14 mmol) in dry CH_2Cl_2 (25 mL, 0.09 M), Et_4NBr (4.51 g, 21.4 mmol, 10 equiv) was added and the mixture was stirred 5 min at rt, under argon. Then, Br_2 (0.12 mL, 2.35 mmol, 1.1 equiv) was added at -78 ºC. After 1 h stirring, the mixture was warmed at rt, and an aqueous saturated $Na_2S_2O_5$ solution was added until the color disappeared. The mass was extracted with AcOEt (x3), and the organic phase was dried over Na_2SO_4, filtered, and evaporated. The crude was submitted to chromatography (silica gel, 0.2% CH_2Cl_2: MeOH) affording **2-chloro-*N*-(*trans*-3,*cis*-4-dibromocyclohexyl)nicotinamide 18** (102 mg, 12%) and 2-chloro-*N*-(*cis*-3,*trans*-4-dibromocyclohexyl]nicotinamide **19** (530 mg, 62%). **18:** white solid; 164-6 ºC; IR (KBr) ν 3270, 3071, 2950, 1644, 1544, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.46 (dd, *J*= 2.0, 4.7 Hz, 1H, H6'), 8.08 (dd, *J*= 2.0, 7.6 Hz, 1H, H4'), 7.35 (dd, *J*= 4.8, 7.6 Hz, 1H, H5'), 6.43 (d, *J*≈ 7.1 Hz, 1H, NH), 4.73-4.50 (m, 3H, H1, H3, H4), 2.75-2.58 (m, 1H, $H5_{ax}$), 2.48 (ddd, *J*= 3.2, 11.2, 14.3 Hz, 1H, $H2_{ax}$), 2.35 (dm, *J*= 14.3 Hz, 1H, $H2_{eq}$), 2.15-2.00 (m, 2H, $H5_{eq}$, $H6_{ax}$), 2.00-1.82 (m, 1H, $H6_{eq}$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.1 (NCO), 151.2 (C6'), 147.2 (C2'), 139.9 (C4'), 131.3 (C3'), 123.0 (C5'), 52.0, 51.3 (C3, C4), 45.0 (C1), 34.6 (C2*), 28.3 (C5*),

27.1 (C6*); MS (ES) *m*/*z* $[M+1]^+$ 395.0/397.0/398.9. Anal. Calcd. for $C_{12}H_{13}Br_2ClN_2O$: C, 36.35; H, 3.30; N, 7.07. Found: C, 36.34; H, 3.27; N, 7.04. **19**: white solid; 161-3 ºC; IR (KBr) ν 3436, 3263, 3071, 2934, 1638, 1551, 1398 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.48 (dd, *J*= 2.0, 4.8 Hz, 1H, H6'), 8.09 (dd, *J*= 2.0, 7.6 Hz, 1H, H4'), 7.35 (dd, *J*= 4.8, 7.6 Hz, 1H, H5'), 6.76 (br s, 1H, NH), 4.34-4.16 (m, 3H, H1, H3, H4), 2.91 (dtd, *J*= 1.9, 4.1, 13.8 Hz, 1H, $H5_{ax}$), 2.58 (ddt, *J*= 3.7, 6.1, 14.4 Hz, 1H, $H2_{ax}$), 2.26-2.12 (m, 1H, $H2_{eq}$), 2.11-1.94 (m, 2H, $H5_{eq}$, $H6_{eq}$), 1.68-1.53 (m, 1H, $H6_{ax}$); ^{13}C NMR ($CDCl_3$, 75 MHz) □δ□ 164.0 (NCO), 151.3 (C6'), 147.2 (C2'), 140.0 (C4'), 131.3 (C3'), 123.0 (C5'), 54.5, 52.6, 47.2 (C3, C4, C1), 40.3, 32.6, 30.5; EM (ES) *m*/*z* $[M+1]^+$ 395.0/397.0/399.0. Anal. Calcd. for $C_{12}H_{13}Br_2ClN_2O$: C, 36.35; H, 3.30; N, 7.07. Found: C, 36.51; H, 3.32; N, 6.89.

(2-Bromo-7-azabicyclo[2.2.1]heptan-7-yl)(2-chloropyridin-3-yl)methanone (5). To a solution of compound **19** (117 mg, 0.30 mmol) in dry DMF (3 mL, 0.1 M) under argon and at 0 ºC, NaH (15 mg, 0.38 mmol, 1.27 equiv, 60% in oil) was added. The mixture was stirred at rt for 24 h. Then, the flask was cooled, water was added, the mixture was extracted with ethyl ether (x4) and the organic layer was washed with brine. The organic phase was dried over $MgSO_4$, filtered and evaporated. The crude was submitted to column chromatography (silica gel, 1% CH_2Cl_2: MeOH) to yield radical precursor **5** (76 mg, 81%): white solid 173-6 ºC; IR (KBr) ν 3062, 2950, 1634, 1579, 1459, 1432, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.47-8.46 (m, H6', minor invertomer), 8.44 (dd, *J*= 2.0, 4.9 Hz, H6', major invertomer), 7.94 (dd, *J*= 1.9, 7.6 Hz, H4', major invertomer), 7.76 (dd, *J*= 1.8, 7.5 Hz, H4', minor invertomer), 7.32 (dd, *J*= 4.8, 7.6 Hz, 1H, H5'), 5.01 (d, *J*= 5.4 Hz, H1, minor invertomer), 4.94 (t, *J*= 4.6 Hz, H4, major invertomer), 4.15-4.09 (m, H2, minor invertomer), 4.04 (dd, *J*= 3.4, 7.0 Hz, H2, major invertomer), 3.88 (d, *J*= 5.3 Hz, H1, major invertomer), 3.82 (t, *J*= 4.5 Hz, H4, minor invertomer), 2.44-2.25 (m, 2H, 2xH3), 2.24-2.06 (m, 1H, $H6_{exo}$), 2.06-1.79 (m, 1H, $H5_{exo}$), 1.64-1.35 (m, 2H, $H5_{endo}$, $H6_{endo}$); ^{13}C NMR ($CDCl_3$, 75 MHz) □δ □162.8 (NCO, major invertomer), 162.6 (NCO, minor invertomer), 150.5 (C6'), 147.5 (C2'), 139.2 (C4', major invertomer), 137.4 (C4', minor invertomer), 132.5 (C3', minor invertomer), 132.1 (C3', major invertomer), 122.7 (C5', minor invertomer), 122.5 (C5', major invertomer), 65.4/65.3 (C1, major invertomer; presence of rotamers), 61.5/61.4 (C1, minor invertomer; presence of rotamers), 57.7 (C4, minor invertomer), 53.8/53.7 (C4, major invertomer), 49.9/49.8 (C2, major invertomer), 47.9 (C2, minor invertomer), 44.2 (C3, minor invertomer), 42.9 (C3, major invertomer), 29.7 (C5*, minor invertomer), 28.6 (C5*, major invertomer), 28.2 (C6*, major invertomer), 27.2 (C6*, minor invertomer); MS (ES) *m*/*z* $[M+1]^+$ 315.0/317.0/319.0, $[M+23]^+$ 336.9/339.0/341.0. Anal. Calcd. for $C_{12}H_{12}BrClN_2O$: C, 45.67; H, 3.83; N, 8.88. Found: C, 45.38; H, 3.79; N, 8.85.

Intramolecular free radical reaction of precursor 5. To a deoxygenated solution of carbamate **43** (40 mg, 0.13 mmol) in dry toluene (6 mL, 0.02 M), AIBN (2 mg) was added. Then, a solution of $HSnBu_3$ (0.05 mL, 0.19 mmol, 1.5 equiv) in dry, deoxygenated toluene (1.4 mL) was slowly added in 6 h, at 120 ºC. The mixture was cooled, and the solvent was evaporated. The residue was dissolved in ethyl ether, and treated with a 10% aqueous KF solution for12 h. The organic

layer was separated, and the aqueous layer was extracted with ethyl ether (x3). The organic phases were dried over $MgSO_4$, filtered, and evaporated. The crude was submitted to chromatography (0.5% → 1% CH_2Cl_2: MeOH) to give **7-azabicyclo[2.2.1]heptan-7-yl(2-chloropyridin-3-yl)methanone** (**20)** (15.7 mg, 52%) and **7-azabicyclo[2.2.1]heptan-7-yl(pyridin-3-yl)methanone (21)** (6.1 mg, 24%). **20**: white solid; 132-4 ºC; IR (KBr) ν 3038, 2954, 1623, 1581, 1399, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 4.8, 2.0 Hz, 1H,), 7.68 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.30 (dd, *J* = 7.5, 4.8 Hz, 1H), 4.84 (t, *J* = 4.7 Hz, 1H), 3.70 (t, *J* = 4.6 Hz, 1H), 2.03-1.80 (m, 4H), 1.63-1.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1 (NCO), 150.3 (C6'), 147.7 (C2'), 137.1 (C4'), 132.9 (C3'), 122.6 (C5'), 58.0 (C1*), 53.6 (C4*), 30.7 (2C), 29.2 (2C) (C2, C3, C5, C6); MS (ES) *m/z* $[M+1]^+$ 237.1, $[M+23]^+$ 259.0. Anal. Calcd. for $C_{12}H_{13}ClN_2O$: C, 60.89; H, 5.54; N, 11.84. Found: C, 60.65; H, 5.36; N, 11.71. **21**: white solid; 58-60 ºC; IR (KBr) ν 3018, 2950, 1620, 1413, 1140 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.80 (s, 1H, H2'), 8.69 (d, *J*= 3.9 Hz, 1H, H6'), 7.90 (dm, *J*= 7.8 Hz, 1H, H4'), 7.37 (dd, *J*= 5.0, 7.7 Hz, 1H, H5'), 4.78 (br s, 1H, H1*), 4.11 (br s, 1H, H4*), 2.08-1.70 (m, 4H), 1.61-1.46 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.1 (NCO), 151.5 (C6'), 148.8 (C2'), 135.7 (C4'), 132.2 (C3'), 123.6 (C5'), 59.2 (C1*), 54.2 (C4*), 30.8 (2xCH_2), 28.9 (2xCH_2); MS (ES) *m/z* $[M+1]^+$ 203.1, $[M+23]^+$ 225.1. Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.98; H, 7.10; N, 13.56.

Synthesis of radical precursor 6. *N*-(Cyclohex-3-enyl)acrylamide 24.[21] To a solution of 3-cyclohex-3-enecarboxylic acid (**22**) (240 mg, 1.91 mmol) in dry toluene (6 mL, 0.32 M), Et_3N (0.32 mL, 2.29 mmol, 1.2 equiv) and DPPA (0.43 mL, 2.00 mmol, 1.05 equiv) were added, and the mixture was stirred at rt for 30 min, and at 80 ºC for 4 h. The mixture was cooled, and acrylic acid (0.65 mL, 9.53 mmol, 5.0 equiv) and CuCl (22 mg, 0.22 mmol, 0.1 equiv) were added. The mixture was refluxed for 2 h, and then cooled. An aqueous saturated $NaHCO_3$ solution was added, and extracted with ethyl ether (x3). The organic phase was dried over Na_2SO_4, filtered, and evaporated. The crude obtained was submitted to column chromatography (silica gel, 1% CH_2Cl_2: MeOH), to give 1,3-di(cyclohex-3-enyl)urea **23** (28 mg, 14%),[10] and compound **24**[21] (189 mg, 66%): white solid; 95-7 ºC; IR (KBr) ν 3429, 3285, 3024, 2920, 1656, 1624, 1552 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.24 (dd, *J*= 1.6, 16.8 Hz, 1H, H3'$_{cis}$), 6.10 (dd, *J*= 10.3, 17.0 Hz, 1H, H2'), 5.89 (br s, 1H, NH), 5.68 (dm, *J*= 9.8 Hz, 1H, H4), 5.63-5.56 (m, 1H, H3), 5.58 (dd, *J*= 1.6, 10.2 Hz, 1H, H3'$_{trans}$), 4.22-4.12 (m, 1H, H1), 2.40 (dm, *J*= 17.4 Hz, 1H, H2A), 2.23-2.01 (m, 2H, 2xH5), 1.96-1.83 (m, 2H, H2$_{ax}$, H6$_{eq}$), 1.67-1.55 (m, 1H, H6$_{ax}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.1 (NCO), 131.5, 131.4 (C2'), 127.2 (C4), 126.0 (C3'), 124.5 (C3), 44.8, 44.7 (C1), 31.7 (C2), 28.1 C6, 29.6 (C5); MS (ES) *m/z* $[M+1]^+$ 152.1, $[M+23]^+$ 174.1, $[2M+1]^+$ 303.2; $[2M+23]^+$ 325.2. Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.28; H, 8.61; N, 9.44.

Bromination of *N*-(cyclohex-3-enyl)acrylamide 24. To a solution of compound **24** (136 mg, 0.90 mmol) in dry CH_2Cl_2 (10 mL, 0.09 M), at rt and under argon, Et_4NBr (1.89 g, 8.98 mmol, 10 equiv) was added. The mixture was cooled at -78 ºC, and bromine (0.05 mL, 0.99 mmol, 1.1

equiv) was added. After 1.5 h, the reaction was warmed at rt and aqueous saturated $Na_2S_2O_5$ was added. The mixture was then stirred until total decoloration, and extracted with AcOEt (x3). The organic phases were dried over Na_2SO_4, filtered, evaporated, and the crude submitted to chromatography (35% hexane: AcOEt), giving ***N*-(*trans*-3,*cis*-4-dibromocyclohexyl)acrylamide (25)** (63 mg, 23%) and ***N*-(*cis*-3,*trans*-4-dibromocyclohexyl)acrylamide (26)** (163 mg, 58%). **25**: white solid; 142-4 ºC; IR (KBr) ν 3264, 3062, 2951, 1658, 1629, 1544, 1434, 1409 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.31 (dd, *J*= 1.4, 17.0 Hz, 1H, H3', 6.08 (dd, *J*= 10.3, 17.0 Hz, 1H, H2'), 5.67 (dd, *J*= 1.4, 10.3 Hz, 1H, H3'), 5.50 (br s, 1H, NH), 4.71-4.57 (m, 2H, H3, H4), 4.51-4.39 (br s, 1H, H1), 2.62 (ddt, *J*= 3.1, 12.5, 15.6 Hz, 1H, $H5_{ax}$), 2.38 (ddd, *J*= 3.1, 11.3, 14.4 Hz, 1H, $H2_{ax}$), 2.26 (dm, *J*= 14.1 Hz, 1H, $H2_{eq}$), 2.09-1.92 (m, 2H, $H5_{eq}$, $H6_{eq}$), 1.78 (qd, *J*= 3.5, 12.4 Hz, 1H, $H6_{ax}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.9 (C1'), 130.8 (C2'), 127.1 (C3'), 52.4 (C4), 51.4 (C3), 43.9 (C1), 34.8 (C2), 28.3 (C5), 27.3 (C6); MS (ES) *m*/*z* $[M+1]^+$ 309.9/311.9/313.9, $[M+23]^+$ 331.9/333.9/335.9. Anal. Calcd. for $C_9H_{13}Br_2NO$: C, 34.76; H, 4.21; N, 4.50. Found: C, 34.95; H, 4.33; N, 4.71. (**26**): white solid; 119-121 ºC; IR (KBr) ν 3422, 3260, 3071, 2947, 1655, 1624, 1552, 1410 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.28 (dd, *J*= 1.3, 17.0 Hz, 1H, H3'), 6.06 (dd, *J*= 10.2, 17.0 Hz, 1H, H2'), 5.94 (br s, 1H, NH), 5.67 (dd, *J*= 1.4, 10.3 Hz, 1H, H3'), 4.24 (td, *J*= 4.2, 9.1 Hz, 1H, H3), 4.20-4.30 (m, 2H, H1, H4), 2.80 (ddt, *J*= 2.0, 4.2, 13.7 Hz, 1H, $H2_{ec}$), 2.52 (ddt, *J*= 3.9, 5.7, 14.3 Hz, 1H, $H5_{eq}$), 2.09 (dm, *J*= 13.3 Hz, 1H, $H6_{eq}$), 2.04-1.93 (m, 1H, $H5_{ax}$), 1.91 (dt, *J*= 9.7, 13.7 Hz, 1H, $H2_{ax}$), 1.53-1.41 (m, 1H, $H6_{ax}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.8 (C1'), 130.8 (C2'), 127.2 (C3'), 54.8 (C4), 52.1 (C3), 46.3 (C1), 41.0 (C2), 33.1 (C5), 30.9 (C6); MS (ES) *m*/*z* $[M+1]^+$ 309.9/311.9/313.9, $[M+23]^+$ 331.9/333.9/335.9. Anal. Calcd. for $C_9H_{13}Br_2NO$: C, 34.76; H, 4.21; N, 4.50. Found: C, 34.80; H, 4.45; N, 4.60.

1-(2-Bromo-7-azabicyclo[2.2.1]heptan-7-yl)prop-2-en-1-one (6). To a solution of compound **26** (50 mg, 0.16 mmol) in dry DMF (2 mL, 0.09 M), NaH (8 mg, 0.20 mmol, 1.2 equiv, 60% in oil) was added at 0 ºC. The resulting mixture was stirred at rt for 14 h. The addition of NaH (4 mg, 0.09 mmol, 0.6 equiv) was repeated, and the reaction stirred for 7 h more; then, water was added, and extracted with ethyl ether (x4). The organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated. The residue was submitted to chromatography (0.5% CH_2Cl_2: MeOH) to give precursor **6** (19 mg, 52%): oil; IR (film) ν 2951, 1651, 1614, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.46 (dd, *J*= 9.8, 16.9 Hz, 1H, H2'), 6.39 (br d, *J*= 16.6 Hz, 1H, $H3'_{cis}$), 5.72 (br d, *J*= 10.0 Hz, 1H, $H3'_{trans}$), 4.90 (br s, H1, minor invertomer), 4.82 (s, H4, major invertomer), 4.44 (d, *J*= 4.6 Hz, H1, major invertomer), 4.40 (br s, H4, minor invertomer), 4.14-4.07 (m, H2, major invertomer), 4.04 (br s, H2, minor invertomer), 2.38-2.19 (m, 2H, 2xH3), 1.98-1.88 (m, 1H, $H6_{exo}$), 1.85-1.66 (m, 1H, $H5_{exo}$), 1.61-1.33 (m, 2H, $H5_{endo}$, $H6_{endo}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.8 (NCO, C1'), 128.6 (C2'), 127.9 (C3'), 64.3, 61.5 (C1), 56.3, 53.6 (C4), 50.2, 47.8 (C2), 44.6, 42.7 (C3), 29.8, 29.1 (C6), 27.5, 26.8 (C5); MS (ES) *m*/*z* $[M+1]^+$ 230.1/232.1, $[M+23]^+$ 252.1/254.1, $[2M+23]^+$ 481.0/483.0/485.0. Anal. Calcd. for $C_9H_{12}BrNO$: C, 46.98; H, 5.26; N, 6.09. Found: C, 46.79; H, 5.31; N, 6.32.

***N*-(Cyclohex-3-enyl)acetamide (27).** To a solution of cyclohex-3-en carboxylic acid **22** (156 mg, 1.23 mmol) in dry toluene (6 mL, 0.21 M), dry Et_3N (0.21 mL, 1.51 mmol, 1.22 equiv) and DPPA (0.29 mL, 1.30 mmol, 1.06 mmol) were added, and the mixture was stirred at rt for 30 min. Then, the reaction was refluxed for 5 h, the flask was cooled, and acetic acid (0.35 mL, 6.17 mmol, 5 equiv) and CuCl (9.3 mg, 0.09 mmol, 0.08 equiv) were added. The mixture was refluxed again for 2 h. Then, the flask was cooled, aqueous saturated $NaHCO_3$ was added, and the solution was extracted with ethyl ether (x4). The organic phase was dried over Na_2SO_4, filtered, and evaporated. The residue was submitted to chromatography (30% → 50% hexane: AcOEt) giving 1,3-di(cyclohex-3-enyl)urea **23**[10] (27.5 mg, 20%), and compound **27**[22] (111 mg, 65%): white solid; 75-7 ºC; IR (KBr) ν 3298, 3079, 3032, 2928, 2840, 1645, 1554, 1311, 655 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.72-5.66 (m, 1H, H4), 5.64-5.54 (m, 2H, H3, NH), 4.16-4.06 (m, 1H, H1), 2.38 (dm, *J*=17.3 Hz, 1H, $H2_{ax}$), 2.23-2.04 (m, 2H, 2xH5), 1.98 (s, 3H, CH_3), 1.92-1.81 (m, 2H, $H2_{eq}$, $H6_{ax}$), 1.63-1.52 (m, 1H, $H6_{eq}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.6 (NHCO), 127.2 (C4), 124.5 (C3), 44.6 (C1), 31.8 (C2), 28.1 (C6), 23.7 (CH_3), 23.6 (C5); MS (ES) *m*/*z* $[M+1]^+$ 140.1, $[M+23]^+$ 162.1, $[2M+1]^+$ 279.3, $[2M+23]^+$ 301.2. Anal. Calcd. for $C_8H_{13}NO \cdot 1/3H_2O$: C, 66.17; H, 9.49; N, 9.65. Found: C, 65.86; H, 9.22; N, 9.92.

Bromination of *N*-(cyclohex-3-enyl)acetamide (27). To a solution of compound **27** (220 mg, 1.58 mmol) in dry CH_2Cl_2 (19 mL, 0.08 M), Et_4NBr (3.34 g, 0.016 mol, 10 equiv) was added, and the mixture was stirred under argon for some minutes. After cooling at -78 ºC, Br_2 (0.16 mL, 3.1 mmol, 2.0 equiv) was added, and the mixture was stirred for 2 h. The reaction was warmed at rt, and then an aqueous saturated $Na_2S_2O_5$ solution was added until the colour was quenched. The mass was extracted with AcOEt (x3), and the organic phase was dried over Na_2SO_4, filtered, and evaporated. The crude was submitted to chromatography (75% hexane: AcOEt) affording *N*-(*trans*-3,*cis*-4-dibromocyclohexyl)acetamide **28** (108 mg, 23%), and *N*-(*cis*-3,*trans*-4-dibromocyclohexyl]acetamide **29** (306 mg, 64.5%). **28**: white solid; 118-120 ºC; IR (KBr) ν 3257, 2953, 1635, 1566, 1310, 545 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.55 (br s, 1H, NH), 4.66-4.58 (m, 2H, H3, H4), 4.40-4.28 (m, $W_{full} \approx 45$ Hz, 1H, H1), 2.59 (ddt, *J*= 3.5, 12.6, 15.6 Hz, 1H, $H5_{eq}$), 2.33 (ddd, *J*= 3.2, 11.2, 14.4 Hz, 1H, $H2_{ax}$), 2.20 (dm, *J*= 14.2 Hz, 1H, $H2_{ec}$), 1.99 (s, 3H, CH_3), 2.05-1.88 (m, 2H, $H5_{ax}$, $H6_{eq}$), 1.79-1.66 (m, 1H, $H6_{ax}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.5 (NHCO), 52.4 (C3*), 51.5 (C4*), 43.8 (C1), 34.8 (C2), 28.3 (C5), 27.4 (C6), 23.7 (CH_3); MS (ES) *m*/*z* $[M-Br]^+$ 218.1/220.1; $[M+1]^+$ 298.0/300.0/302.0, $[M+23]^+$ 320/322/324. Anal. Calcd. for $C_8H_{13}Br_2NO$: C, 32.14; H, 4.38; N, 4.68; O, 5.35. Found: C, 32.32; H, 4.14; N, 4.74. **29**: white solid; 106-8 ºC; IR (KBr) ν 3255, 2951, 1636, 1579, 1373, 1168, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.73 (br s, 1H, NH), 4.19 (td, *J*= 4.2, 9.6 Hz, 1H, H3), 4.11 (td, *J*= 4.0, 9.7 Hz, 1H, H4), 4.04-3.93 (m, $W_{full} \approx$ 43 Hz, 1H, H1), 2.76 (dtd, *J*= 2.1, 4.2, 13.6 Hz, 1H, $H2_{eq}$), 2.50 (dm, *J*= 14.3 Hz, 1H, $H5_{ec}$), 2.09-1.99 (m, 1H, $H6_{eq}$), 1.99-1.96 (m, 1H, $H5_{ax}$), 1.97 (s, 3H, CH_3), 1.85 (dt, *J*= 9.8, 13.5 Hz, 1H, $H2_{ax}$), 1.40 (m, 1H, $H6_{ax}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.5 (NHCO), 55.1 (C4), 53.5 (C3), 46.8 (C1), 42.0 (C2), 34.0 (C5), 31.4 (C6), 23.4 (CH_3); MS (ES) *m*/*z* $[M+1]^+$ 298.0/300.0/302.0, $[M+23]^+$ 320.0/322.0/324.0. Anal. Calcd. $C_8H_{13}Br_2NO$: C, 32.14; H, 4.38; N, 4.68. Experimental: C, 31.89; H, 4.31; N, 4.69.

1-(2-Bromo-7-azabicyclo[2.2.1]heptan-7-yl)ethanone (30). To a solution of compound **29** (109 mg, 0.36 mmol) in dry DMF, under argon and at 0 ºC, NaH (16 mg, 0.4 mmol, 1.1 equiv, 60% dispersion in oil) was added. After 40 min, the mixture was stirred at rt for 19 h; then, NaH (8.0 mg, 0.2 mmol, 0.55 equiv) was added again, and the stirring was maintained for 24 h at rt. The mixture was cooled, water was added, extracted with ethyl ether (x4), and the organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The crude was submited to chromatography (1% → 2% CH_2Cl_2: MeOH) giving compound **30** (34.3 mg, 43%), identical in all its analytical and spectroscopic data for the same compound obtained by a different route in our laboratory.[9]

***N*-(Cyclohex-3-enyl)-4-methylbenzenesulfonamide (32).** To a solution of carbamate **31**[9] (726 mg, 3.68 mmol) in dry CH_2Cl_2 (52 mL, 0.07 M) under argon and at rt, trifluoroacetic acid (5.28 mL, 71.07 mmol, 19.3 equiv) was added, and the mixture was stirred for 2.5 h. The solvent was evaporated to give pure primary amine[15] as its trifluoroacetate salt [white solid; 121-3 ºC; IR (KBr) ν 3430, 3038, 1699, 1178, 724 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.73-5-65 (m, 1H, H4), 5.61-5.53 (m, 1H, H3), 3.35-3.24 (m, 1H, H1), 2.38 (dm, *J*= 17.0 Hz, 1H, H2A), 2.19-2.11 (m, 2H, 2xH5), 2.09-1.91 (m, 2H, H2B, H6A), 1.68-1.55 (m, 1H, H6B); 5.68-5.58 (m, 1H, H4), 5.53-5.45 (m, 1H, H3), 4.87 (d, *J*= 8.1 Hz, 1H, NH), 3.49-3.37 (m, 1H, H1), 2.43 (s, 3H, CH_3), 2.19 (dm, *J*= 17.4 Hz, 1H, H2A), 2.13-1.95 (m, 2H, 2xH5), 1.84 (dm, *J*= 17.4 Hz, 1H, H2B), 1.74 (dm, *J*= 12.8 Hz, 1H, H6A), 1.60-1.47 (m, 1H, H6B); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 128.1 (C4), 123.7 (C3), 48.3 (C1), 30.4 (C2), 27.6 (C6), 24.4 (C5). Anal. Calcd. for $C_6H_{11}N{\cdot}5CF_3COOH$: C, 28.80; H, 2.42; N, 2.10. Found: C, 28.17; H, 2.95; N, 2.97]. The resulting crude was dissolved in dry CH_2Cl_2 (20mL, 0.18 M) under argon and at 0 ºC. Then, Et_3N (1.3 mL, 9.33 mmol, 2.5 equiv) and *p*-TsCl (878 mg, 4.60 mmol, 1.25 equiv) were added. The mixture was stirred at rt for 48 h. An aqueous H_2SO_4 (9.39 mL, 2 M) solution was then added, followed by an aqueous saturated $NaHCO_3$ solution (until pH 7), and the mixture was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered, and evaporated to give a crude that was submitted to chromatography (20% hexane: AcOEt) giving sulfonamide **32**[23] (916 mg, 99%): oil; IR (KBr) ν 3273, 3022, 2918, 1438, 1323, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, *J*= 8.5 Hz, 2H, H2', H6'), 7.30 (d, *J*= 8.6 Hz, 2H, H3', H5'), 5.68-5.58 (m, 1H, H4), 5.53-5.45 (m, 1H, H3), 4.87 (d, *J*= 8.1 Hz, 1H, NH), 3.49-3.37 (m, 1H, H1), 2.43 (s, 3H, CH_3), 2.19 (dm, *J*= 17.4 Hz, 1H, $H2_{ax}$), 2.13-1.95 (m, 2H, 2xH5), 1.84 (dm, *J*= 17.4 Hz, 1H, $H2_{eq}$), 1.74 (dm, *J*= 12.8 Hz, 1H, $H6_{eq}$), 1.60-1.47 (m, 1H, $H6_{ax}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.4 (C4'), 138.4 (C1'), 129.8 (2xCH, C3', C5'), 127.2 (C4), 127.1 (2xCH, C2', C6'), 124.0 (C3), 49.0 (C1), 32.5 (C2), 28.9 (C6), 23.5 (C5), 21.7 (CH_3); MS (ES) *m*/*z* $[M+1]^+$ 252.1, $[M+23]^+$ 274.0, $[2M+23]^+$ 525.3. Calcd. for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57, S, 12.76. Found: C, 61.98; H, 6.99; N, 5.33; S, 12.52.

Bromination of *N*-(cyclohex-3-enyl)-4-methylbenzenesulfonamide (32). To a solution of compound **32** (475 mg, 1.89 mmol) and Et_4NBr (3.974 g, 18.89 mmol, 10 equiv) in dry CH_2Cl_2 (22 mL, 0.086 M) at -78 ºC and under argon, bromine (0.11 mL, 2.08 mmol, 1.1 equiv) was added. The mixture was stirred for 4 h, and then warmed at rt. An aqueous saturated $Na_2S_2O_5$

solution was then added until total decolouration. The solution was extracted with AcOEt (x4), the organic phase was dried over Na_2SO_4, filtered, and evaporated. The crude was submitted to chromatography (10% hexane: AcOEt) giving ***N*-(*cis*-3,*trans*-4-dibromocyclohexyl)-4-methylbenzenesulfonamide** (**33)** (546 mg, 70%) and ***N*-(*trans*-3,*cis*-4-dibromocyclohexyl)-4-methylbenzenesulfonamide (34)** (154 mg, 20%). **33**: White solid; 137-9 ºC; IR (KBr) ν 3436, 3226, 3057, 2952, 1450, 1330, 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, *J*= 8.2 Hz, 2H, H2', H6'), 7.32 (d, *J*= 8.1 Hz, 2H, H3', H5'), 5.41 (d, *J*= 7.9 Hz, 1H, NH), 4.05-3.92 (m, 2H, H3, H4), 3.30-3.18 (br s, 1H, H1), 2.56 (dm, *J*= 13.7 Hz, 1H, $H2_{eq}$), 2.44 (s, 3H, CH_3), 2.45-2.36 (m, 1H, $H5_{eq}$), 1.92-1.74 (m, 3H, $H2_{ax}$, $H5_{ax}$, $H6_{eq}$), 1.44-1.30 (m, 1H, $H6_{ax}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.9 (C4'), 137.7 (C1'), 130.0 (2xCH, C3', C5'), 127.0 (2xCH, C2', C6'), 54.6, 52.9 (C3, C4), 50.8 (C1), 42.6 (br, C2), 33.8 (br, C5), 32.4 (C6), 21.7 (CH_3); MS (ES) *m*/*z* $[M+1]^+$ 410.0/412.0/414.0, $[M+23]^+$ 432.0/434.0/436.0. Anal. Calcd. for $C_{13}H_{17}Br_2NO_2S$ C, 37.98; H, 4.17; N, 3.41; S, 7.81. Found: C, 38.20; H, 4.35; N, 3.27; S, 7.76. **34**: White solid; 104-6 ºC; IR (KBr) ν 3436, 3250, 3060, 2945, 1442, 1330, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, *J*= 8.3 Hz, 2H, H2', H6'), 7.33 (d, *J*= 8.4 Hz, 2H, H3', H5'), 4.53-4.43 (m, 3H, NH, H3, H4), 3.77-3.66 (m, 1H, H1), 2.52-2.42 (m, 1H, $H5_{ax}$), 2.45 (s, 2H, CH_3), 2.28 (ddd, *J*= 3.1, 11.1, 14.4 Hz, 1H, H, $H2_{ax}$), 2.02-1.92 (m, 2H, H, $H2_{eq}$, $H5_{eq}$), 1.80-1.72 (m, 2H, 2xH6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.8 (C4'), 138.1 (C1'), 130.0 (2xCH, C3', C5'), 127.2 (2xCH, C2', C6'), 51.5, 51.4 (C3, C4), 48.2 (C1), 35.8 (C2), 28.5 (C6), 28.4 (C5), 21.8 (CH_3); MS (ES) *m*/*z* $[M+23]^+$ 432.0/434.0/436.0. Anal. Calcd. for $C_{13}H_{17}Br_2NO_2S$ C, 37.98; H, 4.17; N, 3.41. Found: C, 38.11; H, 4.06; N, 3.24.

2-Bromo-7-tosyl-7-azabicyclo[2.2.1]heptane (**7).** To a solution of compound **33** (146 mg, 0.356 mmol) in dry DMF (3.4 mL, 0.097 M), NaH (17 mg, 0.42 mmol, 1.2 equiv, 60% in oil) was added at 0 ºC. After stirring for 1 h, the mixtured was warmed at rt for 17 h. Then, more NaH (7.3 mg, 0.182 mmol, 0.51 equiv) was added, and the mixture was reacted for 6 h. Then, water was added, and the mixture extracted with ethyl ether (x4). The organic phases were washed with brine, dried over $MgSO_4$, filtered, and evaporated. The crude was submitted to chromatography (hexane: AcOEt 15%) to give recovered compound **33** (20.8 mg), and product **7**[18] {81.6 mg [69% (81%)]}: white solid; 107-9 ºC; IR (KBr) ν 3049, 2958, 1595, 1335, 1155, 1092, 1058 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, *J*= 8.2 Hz, 2H, H2', H6'), 7.31 (d, *J*= 7.9 Hz, 2H, H3', H5'), 4.28 (t, *J*= 4.7 Hz, 1H, H4), 4.24 (d, *J*= 5.1 Hz, 1H, H1), 3.93 (dd, *J*= 3.1, 7.5 Hz, 1H, H2), 2.43 (s, 3H, CH_3), 2.27 (dm, *J*= 13.7 Hz, 1H, $H3_{exo}$), 2.16 (dd, *J*= 7.5, 13.7 Hz, 1H, $H3_{endo}$), 2.13-2.04 (m, 1H, $H6_{exo}$), 2.03-1.93 (m, 1H, $H5_{exo}$), 1.53-1.45 (m, 1H, $H6_{endo}$), 1.43-1.15 (m, 1H, $H5_{endo}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.8 (C4'), 137.4 (C1'), 129.6 (2xCH, C3', C5'), 127.9 (2xC, C2', C6'), 67.2 (C1), 59.4 (C4), 48.4 (C2), 44.5 (C3), 29.0 (C5), 28.2 (C6), 21.8 (CH_3); MS (ES) *m*/*z* $[M+1]^+$ 330.0/332.0, $[M+23]^+$ 350.0/352.0, $[2M+23]^+$ 681.0/683.2/685.0. Anal. Calcd. for $C_{13}H_{16}BrNO_2S$: C, 47.28; H, 4.88; N, 4.24; S, 9.71. Found: C, 47.31; H, 4.93; N, 4.18; S, 9.60.

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